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CONCEPTS AND CLINICAL PRACTICE

Marx Hockberger Walls

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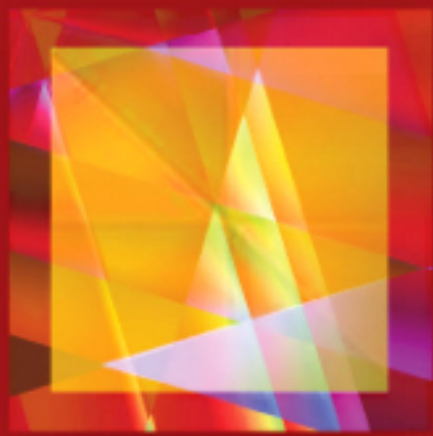

VOLUME 1

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ROSEN'S EMERGENCY MEDICINE

CONCEPTS AND CLINICAL PRACTICE

Volume 1

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ROSEN'S EMERGENCY MEDICINE: CONCEPTS AND CLINICAL PRACTICE, 7TH EDITION

ISBN-13: 978-0-323-05472-0
Volume 1 Part Number: 9996073467
Volume 2 Part Number: 9996073521

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The Publisher

Library of Congress Cataloging-in-Publication Data

Rosen's emergency medicine : concepts and clinical practice / editor-in-chief, John A. Marx ; senior editors, Robert S. Hockberger, Ron M. Walls ; editors, James G. Adams ... [et al.].—7th ed.
p. ; cm.
Includes bibliographical references and index.
ISBN 978-0-323-05472-0
1. Emergency medicine. I. Marx, John A. II. Hockberger, Robert S. III. Walls, Ron M. IV. Adams, James, 1962 May 8– V. Rosen, Peter, 1935– Emergency medicine. VI. Title: Emergency medicine.
[DNLM: 1. Emergencies. 2. Emergency Medicine. WB 105 R815 2010]
RC86.7.E5784 2010
616.02′5—dc22

2008037485

Acquisitions Editor: Stefanie Jewell-Thomas
Developmental Editor: Dee Simpson
Cover Design Direction: Steven Stave
Interior Design: Steven Stave

Printed in China

Last digit is the print number: 9 8 7 6 5 4 3 2

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We wish to dedicate this 7th edition to Peter Rosen, MD, the founder of this textbook and its Editor-in-Chief through the first four editions. Thirty-one years ago, in 1978, Peter came to the belief that an emergency medicine textbook should be written by emergency physicians, and 5 years later, in 1983, he was the first to carry out that mission when the inaugural edition of this textbook was published. While this eponymous work is significant, Peter is more widely acknowledged as one of the true fathers of academic emergency medicine. He continues to leave his imprimatur on numerous programs and innumerable medical students, residents, and faculty members throughout the country and indeed the world. Many of these individuals, like ourselves, have tried to emulate his unbending leadership, his passion for teaching, and his reverence for emergency medicine and the patients we have the great privilege to serve.

This textbook represents just one of many exemplary accomplishments of one extraordinary man. We are indebted to Peter for his vision and his wisdom. We are unspeakably grateful for the honor of continuing this work, ever humbled by the responsibility of carrying his legacy forward, and beholden to him for helping craft our specialty into what it is today.

John A. Marx
Robert S. Hockberger
Ron M. Walls

How this Medical Textbook Should Be Viewed by the Practicing Clinician and the Judicial System

The editors and authors of this textbook strongly believe that the complex practice of medicine, the vagaries of human diseases, the unpredictability of pathologic conditions, and the functions, dysfunctions, and responses of the human body cannot be defined, explained, or rigidly categorized by any written document. *Therefore, it is neither the purpose nor intent of our textbook to serve as an authoritative source on any medical condition, treatment plan, or clinical intervention, nor should our textbook be used to rigorously define a standard of care that should be practiced by all clinicians.*

Our written word provides the physician with a literature-referenced database, and a reasonable clinical guide, which is combined with practical suggestions from individual experienced practitioners. We offer a general reference source and clinical roadmap on a variety of conditions and procedures that may confront clinicians who are experienced in emergency medicine practice. This text cannot replace physician judgment; cannot describe every possible aberration, nuance, clinical scenario, or presentation; and cannot define rigid standards for clinical actions or procedures. *Every medical encounter must be individualized, and every patient must be approached on a case-by-case basis.* No complex medical interaction can possibly be reduced to the written word. The treatments, procedures, and medical conditions described in out textbook do not constitute the total expertise or knowledge base expected to be possessed by all clinicians. Finally, many of the described complications and adverse outcomes associated with implementing or withholding complex medical and surgical interventions may occur, even when every aspect of the intervention has been standard or performed correctly.

The editors and authors of *Rosen's Emergency Medicine: Concepts and Clinical Practice*, 7th Edition

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From Roberts JR, Marx JA: Position Statement: Use of Medical Textbooks in Malpractice Claims. Emerg Med News, Vol. XXXI, 2:3, February 2009.

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Preface to the Seventh Edition

We are pleased to provide this 7th edition of *Rosen's Emergency Medicine: Concepts and Clinical Practice*, now in its 28th year of existence, and wish to recite several changes intended to enhance its content, readability, and purpose. The textbook has been converted into two volumes and reduced in size by more than 500 pages. This was accomplished with judicious editing but mostly through the transfer of the entire bibliography onto the book's website at expertconsult.com, where the full text is available online, along with an image library, Q&A, and updates. The number of chapters is virtually unchanged while the number of annotations per chapter has been expanded. More importantly, we have strived to render the textbook as strongly evidenced based as possible through reliance on the vigilant selection of high-quality and recent references. We will continue to add online updates, wherein recent journal articles selected by the senior editors are abstracted and electronically plugged into the margins of the relevant area of the existing web-based version of the book. We also have the good fortune of adding numerous authors who are authoritative in the subjects about which they write as well as a new team that has composed a Question and Answer compendium. Much of the artwork and the format have been reworked and many of the photographs, including radiographs, have been updated.

We are grateful to many. The authors have committed their many hours and substantive expertise to lay the foundation. The editors have performed yeoman's work to maintain consistency in templating each chapter and to help assure accuracy and clarity. We thank Judy Fletcher, our Publishing Director; Stefanie Jewell-Thomas, our Acquisitions Editor; and Dee Simpson, our Developmental Editor; for listening thoroughly and suggesting wisely and for all their work behind the scenes. We are most appreciative for the terrific support from our administrative assistants, Tricia Wyatt and Gail Franklin (JAM), Maria Figueroa (RSH), and Diane Pugh and Janice Bingham (RMW). We could not have committed the requisite time and energy to this labor of great love were we without the encouragement and buoying up from our families. Finally, we thank you, Peter, for making all this possible just because you chased a dream three decades ago.

John A. Marx
Robert S. Hockberger
Ron M. Walls

Preface to the First Edition

From the vision and foresight of a few physicians who perceived the need for a unique, disciplined, sensitive approach to the identification and stabilization of patients threatened with loss of life or limb, emergency medicine has rapidly developed into an exciting, academically recognized medical specialty. This textbook is dedicated to those who have accepted its responsibilities, challenges, and excitements.

We have attempted to define in depth the material on which our practice is based. There have been a number of efforts to write about emergencies, but we believe that this is the first to call solely on those people who themselves practice the specialty. In every chapter theory and knowledge pertinent to the practice of emergency medicine are presented.

This book is not an easy one; it was written based on published literature, not anecdote or prejudice. In many instances where the data are not available, both sides are presented with a suggested practice. The book is intended for all with a serious interest in or a need to know emergency medicine, including those who do not practice full-time emergency medicine, as well as the dedicated specialists who do.

The book is organized into two main sections—trauma and nontrauma. This division is artificial but does correspond to the first major decisions made in patient evaluations, because trauma usually affects individual anatomic structures, whereas nontrauma is more likely to affect systems.

Despite this artificial separation, long and detailed discussion and instruction to authors concerning content and style ensued. We realize that we could not tap all available talent for contributions to the book, but we have made an effort to represent different schools of thought and regions of the country.

There are deliberate omissions; for example, we elected not to include any procedures. There was not enough room to create an atlas, but it was our desire to cover the chosen topics in detail. No effort has been made to address administration, management, disaster planning, or technical requirements of emergency medicine supplies or design. Prehospital care has been included only as it related to individual topics, not as suggested protocol or from the vantage point of technician training programs.

It would be impossible to write a book this long and present nothing controversial. In fact we ourselves find sections we cannot totally accept, but in the process of working with multiple authors, we cannot with intellectual honesty put ideas into their material. We have, however, achieved our goal of presenting an in-depth vision of emergency medicine. We hope you will find the reading of this book as stimulating and enjoyable as we have found in its creation.

Peter Rosen
Frank J. Baker II
G. Richard Braen
Robert H. Dailey
Richard C. Levy

Acknowledgments

To all my editorial colleagues, especially Ron and Bob, as well as our authors, all of whose extraordinary and collective efforts created this edition; to my wife, Karin, for her immeasurable love and support; and to my children, Conner and Shelby, who have enriched my heart and soul beyond description.

JAM

To my mentors, my colleagues, and my students, who together comprised my professional family over the past 30 years, for their inspiration, friendship, and support; and to Patty, who brought beauty, love, and balance to my life.

RSH

With humble thanks to Peter, for his enduring friendship, for his great vision in the creation of an extraordinary specialty, and for his selfless mentorship of so many of its present and future leaders; to John and Bob, for being the engine of this amazing and rewarding collaboration; to the editors and authors, who give so freely of their precious time to help to bring so much to so many; to my amazingly resilient, loving, and supportive wife, Barb, and to my children, Andrew, Blake, and Alexa, whose love and intellectual energy inspire me.

RMW

To my father, James J. Adams, whose strength will forever inspire me; to my mother, Rita A. Adams, whose devotion to family will forever guide me; and to the many other members of my family: Cecelia, Joe, Jeff, Liz, Rob, David, Nicholas, Gregory, Leah, Katherine, Sydney, and Trent, whose support I rely on.

JGA

To all my former residents over the past 28 years from both Cincinnati and Michigan. I have been privileged to work with the best and I have learned a lot from all of you. I have to thank my children, David, Blake, and Anna, for keeping me thinking young and teaching me lots about life and family. Most of all, thanks to my wife and best friend, Mary, for her love and support over the past 33 years. She makes it all worthwhile.

WGB

To my family, friends, students, and teachers. I am continuously amazed, grateful, and humbled by your support and encouragement. Thank you.

MHB

To Joanna, Megan, and Julia and our dual-phase marriage; kind of "pre-Rosen" and now four editions together. May you never be tempted to join the literary "first-wives club."

DFD

I dedicate this book to my husband, David, and our children, Sarah, Jeremiah, and Katie—for their patience, love, and support.

MGH

To emergency medicine residents and faculty everywhere in their constant pursuit of knowledge but especially those at Hennepin County Medical Center for continuing to teach me. I am grateful to my parents, Rose and Joseph, for their commitment to education. Special thanks to Eric, Ali, Amanda, and, most of all, Beth for their love, patience, and understanding.

LJL

I would like to thank my teachers—my parents and my children, professors and patients, colleagues and students—who have patiently taught me about medicine and life; and my steadfast companion and wife, Lynda, who has made the pursuit of wisdom possible.

EJN

PART I

Fundamental Clinical Concepts

CHAPTER 1 Airway

Ron M. Walls

PERSPECTIVE

Airway management is the cornerstone of resuscitation and is a defining skill for the specialty of emergency medicine. The emergency physician has primary responsibility for management of the airway. All techniques of airway management lie within the domain of emergency medicine. Rapid sequence intubation (RSI) with direct laryngoscopy is the most commonly used method for emergency intubation, but emergency airway management includes various intubation maneuvers, use of ancillary devices, approaches to the difficult airway, and rescue techniques when intubation fails.

Since the first reported use of neuromuscular blocking agents (NMBAs) in the emergency department (ED) by emergency personnel in 1971, there has been progressive sophistication of emergency airway techniques, pharmacologic agents, and special devices used to facilitate intubation.[1,2] In the 1990s, RSI was widely adopted as the method of choice for most emergency intubations in the ED, and increasing attention has focused on identification and management of anticipated difficult intubation.[3,4]

PATHOPHYSIOLOGY

Decision to Intubate

A decision to intubate should be based on careful assessment of the patient with respect to three essential criteria: (1) failure to maintain or protect the airway, (2) failure of ventilation or oxygenation, and (3) the patient's anticipated clinical course and likelihood of deterioration.[5]

Failure to Maintain or Protect the Airway

A patent airway is essential for adequate ventilation and oxygenation. If the patient is unable to maintain the airway, patency must be established by artificial means, such as repositioning, chin lift, jaw thrust, or insertion of an oral or nasal airway. Likewise, the patient must be able to protect against aspiration of gastric contents, which carries significant morbidity and mortality. Traditionally, the presence or absence of a gag reflex has been advocated as a reliable indicator of the patient's ability to protect the airway, but the gag reflex is absent in 12 to 25% of normal adults, and there is no evidence that its presence or absence corresponds to airway protective reflexes or the need for intubation.[6] Testing the gag reflex in an obtunded, supine patient is unlikely to yield useful information with respect to the need to intubate and may precipitate vomiting. The patient's ability to swallow or handle secretions is a more reliable indicator of airway protection.[5] The recommended approach is to evaluate the patient's ability to phonate in response to voice command or query (which provides information about level of consciousness and voice quality), level of consciousness, and ability to manage his or her own secretions (e.g., pooling of secretions in the oropharynx, absence of swallowing spontaneously or to command.) In general, a patient who requires a maneuver to establish a patent airway or who easily tolerates an oral airway probably requires intubation for protection of that airway, unless a temporary or readily reversible condition, such as opioid overdose, is present.

Failure of Ventilation or Oxygenation

Ventilatory failure that is not reversible by clinical means or increasing hypoxemia that is not adequately responsive to supplemental oxygen is a primary indication for intubation. This assessment is clinical and includes evaluation of the patient's general status, oxygenation by pulse oximetry, and changes in the ventilatory pattern. Continuous capnography also can be helpful, but is not essential if oximetry readings are reliable. Arterial blood gases (ABGs) generally are not required to determine the patient's need for intubation. In most circumstances, clinical assessment, including pulse oximetry with or without capnography, and observation of improvement or deterioration lead to a correct decision. ABG results are rarely helpful, may cause delay in intubating a deteriorating patient, and may be misleading, so, if obtained, they must be interpreted carefully in the context of the patient's clinical status. Patients who are clinically improving despite severe or worsening ABG alterations may not require intubation, whereas a rapidly tiring patient may require intubation when ABG values are only modestly disturbed or even improving.

Regardless of the underlying cause, the need for mechanical ventilation generally mandates intubation. External mask devices increasingly have been used to provide assisted mechanical ventilation without intubation (see Chapter 2), but despite these advances, most patients who need assisted ventilation or positive pressure to improve oxygenation require intubation.[7]

Anticipated Clinical Course

Certain conditions indicate the need for intubation even in the absence of frank airway, ventilatory, or oxygenation failure. These conditions are characterized by a moderate to high likelihood of predictable deterioration that would require airway intervention. Intubation may be indicated relatively early in the course of severe cyclic antidepressant overdose. Although the patient is awake, protecting the airway, and exchanging gas well, intubation is advisable to guard against the strong likelihood of clinical deterioration, which can occur relatively abruptly and includes coma, seizure, cardiac dysrhythmia or arrest, and possible aspiration of activated charcoal or gastric contents.

Significant multiple trauma, with or without head injury, may be an indication for intubation.[8,9] Many of these patients are ventilating normally through a patent airway, and oxygen levels frequently are normal or supernormal with supplemental oxygen. Despite this, anticipated deterioration, loss of the ability to protect the airway, the need for invasive and painful procedures, or the need for studies outside the ED (e.g., computed tomography, angiography) may mandate intubation.[10] A patient with penetrating neck trauma may present with a patent airway and adequate gas exchange. Nevertheless, early intubation is advisable with any evidence of vascular or direct airway injury because these patients tend to deteriorate and because increasing hemorrhage or swelling in the neck tends to both compromise the airway and confound later attempts at intubation.[11,12]

Although these indications for intubation may seem quite different and individualized, the common thread is the anticipated clinical course over time. In each circumstance, it can be anticipated that future events will compromise either the patient's ability to maintain and protect the airway or the patient's ability to oxygenate and ventilate. A similar thought process is applied to any patient who will be leaving the ED for diagnostic studies (e.g., angiography) or who may be transported to another facility. If it seems clinically likely that the patient may deteriorate, then "preemptive" intubation is the prudent course.

CLINICAL FEATURES

Identification of the Difficult Airway

In most patients, even in the ED's dynamic and unpredictable environment, intubation is technically easy and straightforward. In large ED studies, overall intubation failure rates are less than 1% for medical intubations and less than 3% in trauma patients.[1,13,14] Intubation failure occurs in approximately 1 in 200 to 1 in 2000 elective general anesthesia cases.[3,15,16] Bag-mask ventilation (BMV) is difficult in approximately 1 in 50 general anesthesia patients, and impossible in approximately 1 in 600.[17,18] BMV is difficult, however, in up to one third of patients in whom intubation failure occurs, and difficult BMV-makes the likelihood of difficult intubation four times greater and the likelihood of impossible intubation 12 times greater.[17,18] The combination of failure of intubation and failure of BMV in elective anesthesia practice is estimated to be exceedingly rare: 1 in 5000 to 1 in 20,000 elective anesthesia patients.[16,18] These numbers cannot be applied directly to the ED situation, where patient selection cannot occur (as with a preanesthetic visit), but are reassuring in that they indicate a high degree of safety if a preintubation analysis of factors predicting difficult intubation is undertaken.[19]

The emergency nature of the patient's presentation often precludes postponement of the intubation, even for a short time, but knowledge of the difficulties presented by the patient's airway permits thoughtful planning and preparation for possible intubation failure. Preintubation assessment should evaluate the patient for difficult intubation, difficult BMV, difficult ventilation using an extraglottic device (EGD, such as a laryngeal mask airway, see later discussion) and difficult cricothyrotomy. Knowledge of all four domains is crucial to successful planning.[3,4]

Neuromuscular paralysis should be avoided in patients for whom a high degree of intubation difficulty is predicted, unless the administration of the NMBA is part of a planned approach to the difficult airway. This approach may include use of a *double setup*, in which an alternative approach, such as cricothyrotomy, is simultaneously prepared.

Preintubation evaluation should be as comprehensive as clinical circumstances permit. A systematic approach to the patient is required.

Difficult Direct Laryngoscopy: LEMON

Most of the difficult airway markers discussed in the anesthesia and emergency medicine literature have not been scientifically validated.[20] Nevertheless, a methodical approach can be used to evaluate the patient, based on the accepted markers of difficult intubation by direct laryngoscopy. One such approach uses the mnemonic *LEMON* (Box 1-1).[3,21]

L—Look Externally. The patient first should be examined for external markers of difficult intubation, which are determined based simply on the intubator's clinical impression. For example, the severely bruised and bloodied face of a combative trauma patient, immobilized in a cervical collar on a spine board, might (correctly) invoke an immediate appreciation of anticipated difficult intubation. Subjective clinical judgment can be highly specific (>90%), but insensitive and so must be augmented by other evaluations.[18]

E—Evaluate 3-3-2. The second step in the evaluation of the difficult airway is to assess the patient's anatomy to determine his or her suitability for direct laryngoscopy. Direct laryngoscopy requires the ability to visualize the glottis by direct vision through the mouth, using alignment of the oral, pharyngeal, and laryngeal axes. Visualization requires that the mouth open adequately, that the submandibular space be adequate to accommodate the tongue, and that the larynx be positioned low enough in the neck to be accessible. These relationships have been explored in various studies by external measurement of mouth opening, oropharyngeal size, neck movement, and thyromental distance.[22] The "3-3-2 rule" is an effective summary of these geometric evaluations.[3,21] The 3-3-2 rule requires that the patient be able to place 3 of his or her own fingers between the open incisors, 3 of his or her own fingers along the floor of the mandible beginning at the mentum, and 2 fingers from the laryngeal prominence to the floor of the

BOX 1-1 "LEMON" APPROACH FOR EVALUATION OF DIFFICULT DIRECT LARYNGOSCOPY

Look externally for signs of difficult intubation (by gestalt)
Evaluate the "3-3-2 rule"
Mallampati
Obstruction/**O**besity
Neck mobility

Adapted with permission from The Difficult Airway Course: Emergency and Walls RM and Murphy MF [eds]: Manual of Emergency Airway Management, 3rd ed, Philadelphia, Lippincott Williams & Wilkins, 2008.

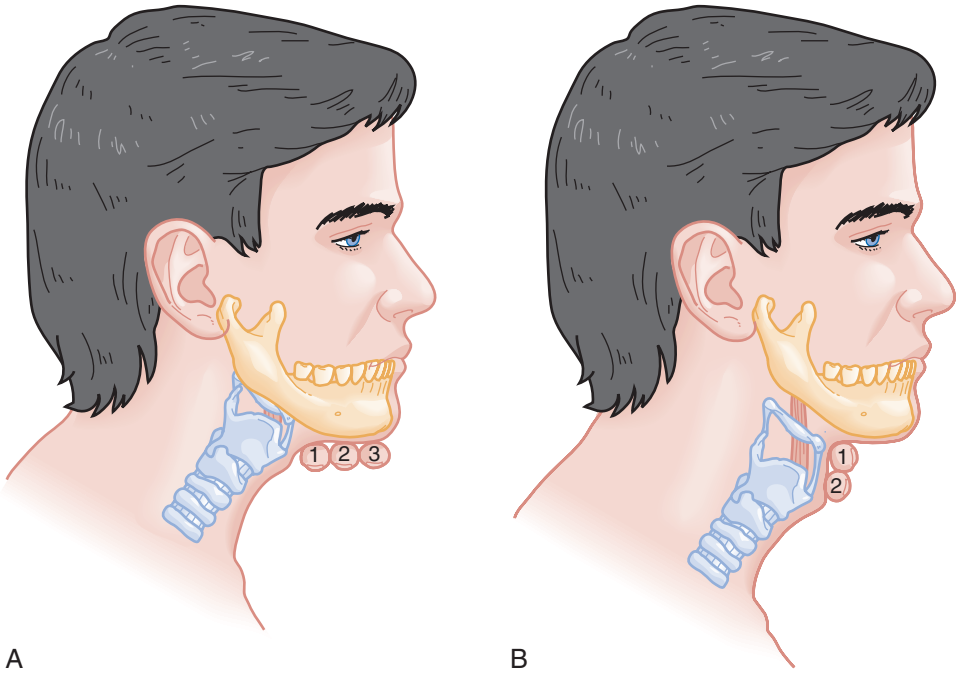

Figure 1-1. Final two steps of the 3-3-2 rule. **A,** Three fingers are placed along the floor of the mouth beginning at the mentum. **B,** Two fingers are placed in the laryngeal prominence (Adam's apple). (Adapted from Murphy MF, Walls RM: Identification of difficult and failed airways. In Walls RM and Murphy MF [eds]: Manual of Emergency Airway Management, 3rd ed. Philadelphia, Lippincott Williams & Wilkins, 2008, pp. 81–91. The 3-3-2 Rule is copyrighted © 2004 by The Airway Course and Lippincott Williams & Wilkins, publishers of The Manual of Emergency Airway Management.)

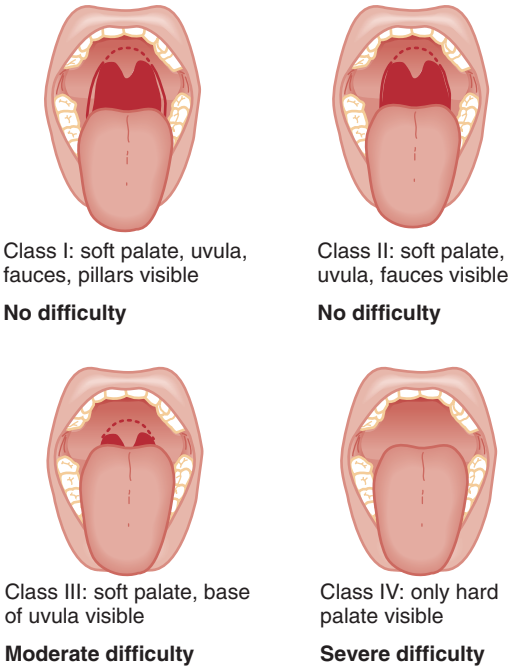

Figure 1-2. The Mallampati scale assesses oral access for intubation. (From Whitten CE: Anyone Can Intubate, 4th ed. San Diego, KW Publications, 2004, with permission.)

mandible (Fig. 1-1). A patient with a receding mandible and high-riding larynx can be impossible to intubate using direct laryngoscopy. Most patients are not sufficiently cooperative for such an evaluation, and the operator compares his or her fingers with the patient's fingers to estimate the sizes for the three tests.

M—Mallampati Scale. Oral access is assessed using the Mallampati scale (Fig. 1-2). Visibility of the oral pharynx ranges from complete visualization, including the tonsillar pillars (class I), to no visualization at all, with the tongue pressed against the hard palate (class IV). Class I and class II predict adequate oral access, class III predicts moderate difficulty, and class IV predicts a high degree of difficulty.[22,23] A recent meta-analysis confirmed that the four-class Mallampati score performs well as a predictor of difficult laryngoscopy (and, less so, difficult intubation), but that the Mallampati score, alone, is not a sufficient assessment tool.[24]

O—Obstruction or Obesity. Upper airway (supraglottic) obstruction may make visualization of the glottis, or intubation itself, mechanically impossible. Conditions such as epiglottitis, laryngeal tumor, Ludwig's angina, neck hematoma, or glottic polyps can compromise laryngoscopy, passage of the endotracheal tube (ETT), BMV, or all three. Physical examination for airway obstruction is combined with assessment of the patient's voice to satisfy this evaluation step. There is conflicting evidence regarding whether obesity is itself an independent marker of difficult intubation or whether patients with obesity simply are more likely to have other markers of difficult intubation.[25,26] Regardless, obese patients generally are more difficult to intubate than their non-obese counterparts, and preparations must account both for this, and for the more rapid oxyhemoglobin desaturation and increased difficulty with ventilation using bag and mask or an EGD (see below) that will occur.

N—Neck Mobility. Neck mobility is essential for the repositioning of the angled axes of the upper airway in order to permit direct visualization of the glottis. Neck mobility is assessed by having the patient flex and extend the head and neck through a full range of motion. Neck extension is the most important motion, and simple extension may be as effective as the "sniffing" position in achieving an optimal laryngeal view.[27] A recent study also found that the "extension-extension" position, in which the neck is extended on the body (opposite of the sniffing position) with the head extended on the neck, provides superior laryngeal views to the sniffing position.[28] Modest limitations of motion do not seriously impair laryngoscopy, but severe loss of motion, as can occur in ankylosing spondylitis or rheumatoid arthritis, for example, may render laryngoscopy impossible. Cervical spine immobilization in trauma artificially reduces cervical spine mobility and predicts a more difficult laryngoscopy, but direct laryngoscopy is still highly successful in this group of patients.[1]

Identification of a difficult intubation does not preclude use of an RSI technique (see Fig. 1-7). The crucial determination is whether the clinician judges that the patient has a reasonable likelihood of intubation success, despite the difficulties identified, and that ventilation with a bag and mask or an EGD will be successful in the event that intubation fails (hence the value of the BMV and EGD assessments; see Boxes 1-2 and 1-3).

Difficult Bag-mask Ventilation: MOANS

Attributes of difficult BMV have largely been validated and can be summarized with the mnemonic *MOANS* (see Box 1-2).[3,17,18]

Difficulty with mask seal; obstruction (particularly supraglottic obstruction, but can be present anywhere in the airway) or obesity (because of redundant upper airway tissues, chest wall weight, and resistance of abdominal mass); advanced age (best judged by the physiologic appearance of the patient, but age older than 55 years increases risk); edentulousness ("no teeth"), which independently interferes with mask seal; and stiffness or resistance to ventilation (e.g., asthma, chronic obstructive pulmonary disease, pulmonary edema, restrictive lung disease, term pregnancy) all cause or contribute to increased difficulty with BMV. The difficulty with BMV of the edentulous patient is the basis of the adage: "Remove dentures to intubate, leave them in to bag-mask ventilate." The wisdom of this approach recently was validated yet again.[29]

Difficult Extraglottic Device Placement: RODS

Placement of an EGD, such as a laryngeal mask airway, a Combitube, or a similar upper airway device often can facilitate ventilation, and convert a "**can't** intubate, **can't** oxygenate" situation to a "**can't** intubate, **can** oxygenate" situation, which allows time for more careful planning of the rescue of a failed airway (see following section.) Difficulty achieving placement or ventilation using an EGD is predicted by the mnemonic "RODS." Fortunately, if the clinician has already performed the LEMON and MOANS assessments, only the "D" for distorted anatomy remains to be evaluated (see Box 1-3).

BOX 1-2 MOANS MNEMONIC FOR EVALUATION OF DIFFICULT BAG-MASK VENTILATION

Mask seal
Obstruction or obesity
Aged
No teeth
Stiffness (resistance to ventilation)

Adapted with permission from The Difficult Airway Course: Emergency and Walls RM and Murphy MF [eds]: Manual of Emergency Airway Management, 3rd ed, Philadelphia, Lippincott, Williams & Wilkins, 2008.

BOX 1-3 RODS MNEMONIC FOR EVALUATION OF DIFFICULT EXTRAGLOTTIC DEVICE PLACEMENT

Restricted mouth opening
Obstruction or obesity
Distorted anatomy
Stiffness (resistance to ventilation)

Adapted with permission from The Difficult Airway Course: Emergency and Walls RM and Murphy MF [eds]: Manual of Emergency Airway Management, 3rd ed, Philadelphia, Lippincott, Williams & Wilkins, 2008.

Difficult Cricothyrotomy

Difficult cricothyrotomy can be anticipated whenever there is disturbance of the ability to locate and access the landmarks of the anterior airway via the neck. Prior surgery; the presence of hematoma, anatomic disruption, tumor, or abscess; scarring (as from radiation therapy or prior injury); or obesity, edema, or subcutaneous air each has the potential to make cricothyrotomy more difficult. The landmarks for cricothyrotomy are sought and identified as part of the preintubation assessment of the patient.

Measurement of Intubation Difficulty

The actual degree to which an intubation is "difficult" is highly subjective, and quantification is challenging. Research has relied on laryngoscopic view to characterize the intubation difficulty, and the most widely used system is that of Cormack and Lehane, which grades laryngoscopy according to the extent to which laryngeal and glottic structures can be seen. In grade 1 laryngoscopy, the entire glottic aperture is seen. Grade 2 laryngoscopy visualizes only a portion of the glottis (arytenoid cartilages alone or arytenoid cartilages plus part of the vocal cords). Grade 3 laryngoscopy visualizes only the epiglottis. In grade 4 laryngoscopy, not even the epiglottis is visible.

Research conducted on elective anesthesia patients suggests that true grade 4 laryngoscopy, which is associated with impossible intubation, occurs in less than 1% of patients. Grade 3 laryngoscopy, which represents extreme intubation difficulty, is found in less than 5% of patients. Grade 2 laryngoscopy, which occurs in 10 to 30% of patients, can be subdivided further into grade 2a, in which arytenoids and a portion of the vocal cords are seen, and grade 2b, in which only the arytenoids are seen. Intubation failure occurs in 67% of grade 2b cases but in only 4% of grade 2a cases.[30] Approximately 80% of all grade 2 laryngoscopies are grade 2a; the rest are grade 2b. A grade 1 view is associated with virtually 100% intubation success. An alternative system, the POGO (percentage of glottic opening) also has been proposed and validated, but is not widely used or studied.[31]

Confirmation of Endotracheal Tube Placement

The most serious complication of endotracheal intubation is unrecognized esophageal intubation with resultant hypoxic brain injury. Although direct visualization of the ETT passing through the vocal cords generally is a reliable indicator of tracheal intubation, such clinical anatomic observations are fallible, and additional means are required to ensure correct placement of the tube within the trachea. Traditional methods, such as chest auscultation, gastric auscultation, bag resistance, exhaled volume, visualization of condensation within the ETT, and chest radiography, all are prone to failure as means of confirming tracheal intubation.[32] Other clinical techniques are readily available for detecting tracheal or esophageal intubation.

Immediately after intubation, the intubator should apply an end-tidal carbon dioxide ($ETCO_2$) detection device to the ETT and assess it through six manual ventilations. Disposable, colorimetric $ETCO_2$ detectors are highly reliable, convenient, and easy to interpret, indicating adequate CO_2 detection by color change (Figs. 1-3 and 1-4) (see Chapter 3). $ETCO_2$ detection is highly reliable in determining tracheal and esophageal intubation in patients with spontaneous circulation.[33] These devices indicate the carbon dioxide content in exhaled

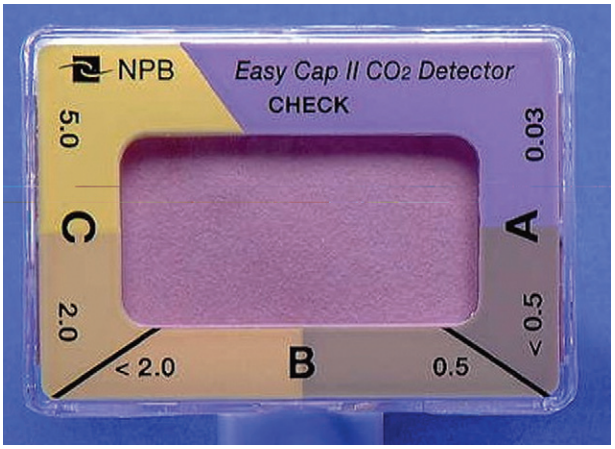

Figure 1-3. End-tidal CO_2 detector before application. The indicator is purple, which indicates failure to detect CO_2. This also is the appearance when the esophagus is intubated.

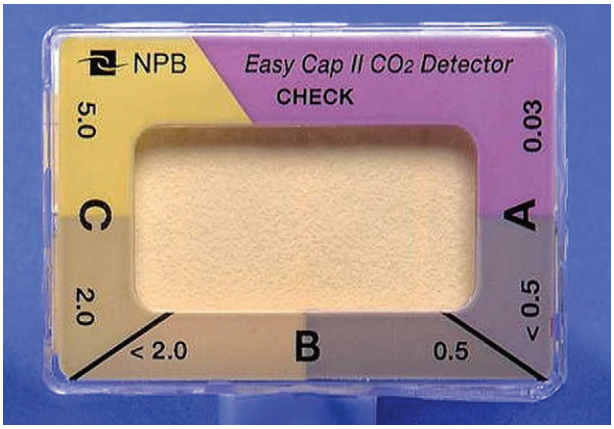

Figure 1-4. Positive detection of CO_2 turns the indicator yellow, indicating tracheal placement of the endotracheal tube.

air either qualitatively or quantitatively. The persistence of detected CO_2 after six manual breaths indicates that the tube is within the airway, although not necessarily within the trachea. Gas exchange is detected with the tube in the mainstem bronchus, the trachea, or the supraglottic space. Correlation of $ETCO_2$ detection with the depth markings on the endotracheal tube (particularly important in pediatric patients) confirms tracheal placement. Rarely, BMV before intubation or ingestion of carbonated beverages may lead to release of CO_2 from the stomach after esophageal intubation, causing a transient false indication of tracheal intubation. Washout of this phenomenon occurs within six breaths, however, so persistence of CO_2 detection after six breaths indicates tracheal intubation.

Although colorimetric $ETCO_2$ measurement is highly sensitive and specific for detecting esophageal intubation, caution is required for patients with cardiopulmonary arrest. Insufficient gas exchange may hamper CO_2 detection in the exhaled air, even when the tube is correctly placed within the trachea.[33] In patients with cardiopulmonary arrest, a CO_2 level greater than 2%, which is the threshold for color change on colorimetric capnometers, should be considered definitive evidence of correct ETT placement, but the absence of such CO_2 cannot be used reliably as an indicator of esophageal intubation. This circumstance arises in approximately 25 to 40% of intubated cardiac arrest patients.[33,34] In all other patients, absence of CO_2 detection indicates failure to intubate the trachea, and rapid reintubation is indicated. When possible, continuous quantitative capnography is more accurate and yields more information than capnometry (including colorimetric devices; see Chapter 3).

The other method of tube placement confirmation is the aspiration technique, which is based on the anatomic differences between the trachea and the esophagus. The esophagus is a muscular structure with no support within its walls. The trachea is held patent by cartilaginous rings. Vigorous aspiration of air through the ETT with the ETT cuff deflated results in occlusion of the ETT orifices by the soft walls of the esophagus, whereas aspiration after tracheal placement of the tube is easy and rapid.

Bulb or syringe aspiration devices may be used in patients with cardiac arrest who have no detectable CO_2, but although such devices are highly reliable at detecting esophageal intubation (sensitivity > 95%), false-positives, in which a correctly placed tracheal tube is incorrectly identified as esophageal, can occur in up to 25% of cardiac arrest patients.[33] Aspiration devices may be useful in the out-of-hospital setting when poor lighting hampers colorimetric $ETCO_2$ determination. They also are good backup devices when cardiac arrest confounds attempts to assess placement using $ETCO_2$. Detection of expired CO_2 is more reliable and should be considered the standard for confirmation of tracheal placement of an ETT and for early detection of accidental esophageal intubation. Aspiration devices have a valuable, but secondary role.

Repeat laryngoscopy generally is insufficient to "confirm" that the tube is through the glottis because error and misinterpretation can occur, especially if the clinician confirming the intubation is the same person who intubated in the first place. The objective instrument ($ETCO_2$) should be considered correct. Complete obstruction of the trachea or both main stem bronchi, which prevents ventilation of the patient with even small tidal volumes, can lead to failure to detect CO_2 even when the tube is in the trachea. In the absence of known or suggested complete large airway obstruction, however, failure to detect CO_2 should not be ascribed to other causes, such as severe asthma, in which the physician might postulate that adequate CO_2 exchange is not occurring for physiologic reasons. Absent equipment failure, this generally does not occur, and detection failure should be equated with intubation failure.

Accordingly, $ETCO_2$ detection, with aspiration as backup, should be considered the primary means of ETT placement confirmation. Secondary means include physical examination findings, oximetry, and radiography. The examiner should auscultate both lung fields and the epigastric area. Auscultation of typical hollow, gurgling, gastric sounds in the epigastrium is highly suggestive of esophageal intubation and should prompt consideration of immediate reintubation. Diminished or absent breath sounds on one side (usually the left side) indicate main stem bronchus intubation, in the absence of pneumothorax or an alternative cause of unilateral loss of breath sounds. Persistent, obvious leak despite positive $ETCO_2$ detection indicates cuff malfunction or supraglottic placement of the ETT, such that the tube is in the airway, detecting CO_2, but above the vocal cords. In either case (main stem bronchus intubation or supraglottic intubation), tube malpositioning can be confirmed by inspection of the depth of insertion of the tube, supplemented by chest radiography when needed. If malpositioning is detected, repositioning is indicated.

Pulse oximetry is indicated as a monitoring technique in all critically ill patients, not just those who require intubation. Oximetry is useful in detecting esophageal intubation, but

may not show a decreasing oxygen saturation for several minutes after a failed intubation because of the oxygen reservoir (preoxygenation) created in the patient before intubation.[35] Oximetry may be particularly misleading in a spontaneously breathing patient who has had an inadvertent nasoesophageal intubation and did not have the $ETCO_2$ measured. In this case, oxygen saturation may be preserved because of spontaneous respirations, but catastrophe can ensue if the patient is later paralyzed or heavily sedated in the mistaken belief that the tube is in the trachea.

Although chest radiography is universally recommended after ETT placement, its primary purpose is to ensure that the tube is well positioned below the cords and above the carina. A single anteroposterior chest radiograph is not sufficient to detect esophageal intubation, although esophageal intubation may be detected if the ETT is clearly outside the air shadow of the trachea. In cases where doubt persists, a fiberoptic scope can be passed through the ETT to identify tracheal rings, a "gold standard" for confirmation of tracheal placement.

MANAGEMENT

Approach to Intubation

After it is determined that the patient requires intubation, an approach must be planned. Algorithms for emergency airway management have been developed and provide a useful guide, both for planning intubation and for rescue in the event of intubation failure.[4] The algorithm in Figure 1-5 assumes that a decision to intubate has been made and outlines such an approach. The approach is predicated on two key determinations that must be made before active airway management is begun (see Fig. 1-5). The first determination is whether the patient is in cardiopulmonary arrest or a state near to arrest and is predicted to be unresponsive to direct laryngoscopy. Such a patient (agonal, near death, circulatory collapse) is called a "crash airway" patient for the purposes of emergency airway management and is treated using the crash airway algorithm by immediate intubation without use of drugs, supplemented by a single dose of succinylcholine if the attempt to intubate fails and the patient is felt not to be sufficiently relaxed (Fig. 1-6). Next, it must be determined whether the patient represents a difficult intubation as determined by the LEMON, MOANS, and RODS evaluations. If so, the difficult airway algorithm is used (Fig. 1-7).

For all other cases, that is, for all patients who require emergency intubation but who have neither a crash airway nor a difficult airway, RSI is recommended. RSI provides the safest and quickest method of achieving intubation in such

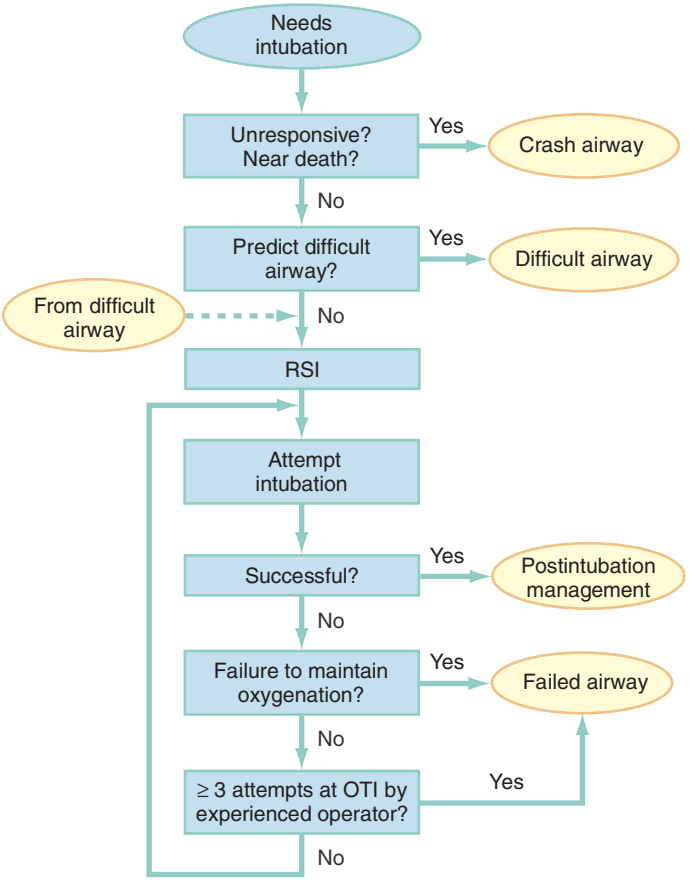

Figure 1-5. Main emergency airway management algorithm. OTI, orotracheal intubation; RSI, rapid sequence intubation. (Adapted from Walls RM: The emergency airway algorithms. In Walls RM, Murphy MF [eds]: Manual of Emergency Airway Management, 3rd ed. Philadelphia, Lippincott Williams & Wilkins, p. 11, 2008. Copyright © 2008 The Difficult Airway Course: Emergency and Lippincott Williams & Wilkins.)

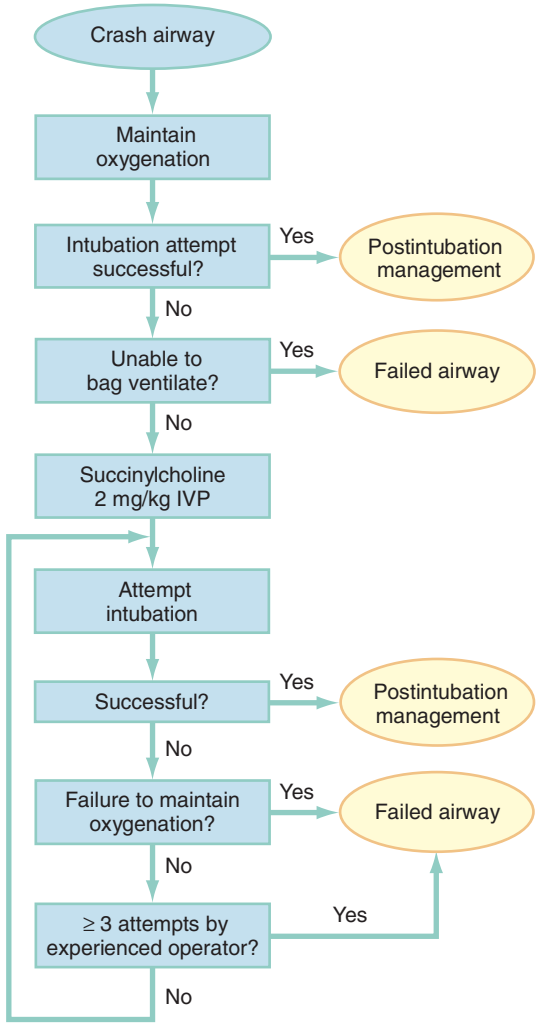

Figure 1-6. Crash airway algorithm. IVP, intravenous push. (Adapted from Walls RM: The emergency airway algorithms. In Walls RM, Murphy MF [eds]: Manual of Emergency Airway Management, 3rd ed. Philadelphia, Lippincott Williams & Wilkins, p. 14, 2008. Copyright © 2008 The Difficult Airway Course: Emergency and Lippincott Williams & Wilkins.)

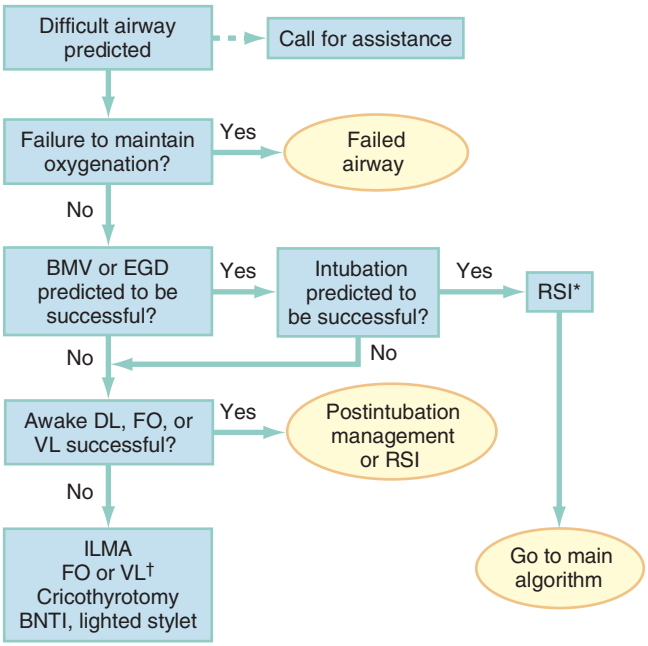

Figure 1-7. Difficult airway algorithm. BMV, bag-mask ventilation; BNTI, blind nasotracheal intubation; DL, direct laryngoscopy; EGD, extraglottic device; FO, fiberoptic laryngoscopy; ILMA, intubating laryngeal mask airway; RSI, rapid sequence intubation; VL, video laryngoscopy. (Adapted from Walls RM: The emergency airway algorithms. In Walls RM, Murphy MF [eds]: Manual of Emergency Airway Management, 3rd ed. Philadelphia, Lippincott Williams & Wilkins, p. 15, 2008. Copyright © 2008 The Difficult Airway Course: Emergency and Lippincott Williams & Wilkins.)
*May require double set-up.
†If not done earlier.

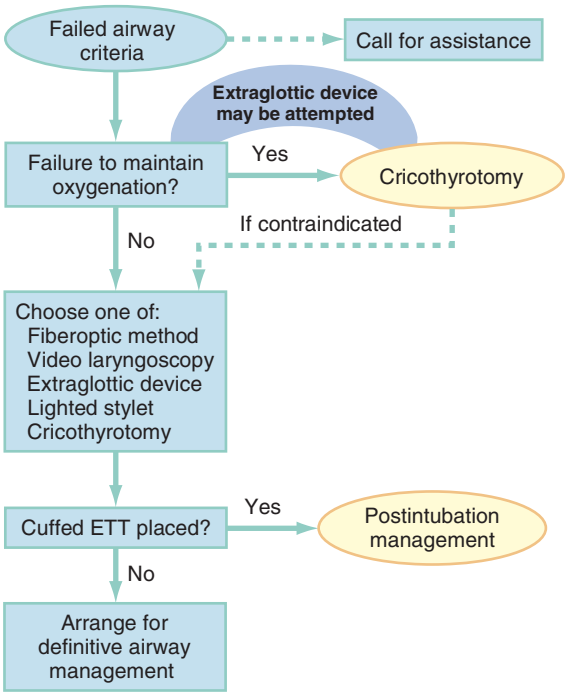

Figure 1-8. Failed airway algorithm. ETT, endotracheal tube. (Adapted from Walls RM: The emergency airway algorithms. In Walls RM, Murphy MF [eds]: Manual of Emergency Airway Management, 3rd ed. Philadelphia, Lippincott Williams & Wilkins, p. 18, 2008. Copyright © 2008 The Difficult Airway Course: Emergency and Lippincott Williams & Wilkins.)

patients.[1,20,36,37] After administration of the RSI drugs, intubation attempts are repeated until the patient is intubated or a failed intubation is identified. If more than one intubation attempt is required, oxygen saturation is monitored continuously, and if saturation falls to 90% or less, BMV is performed until saturation is recovered for another attempt. If the clinician cannot maintain oxygen saturation with BMV, despite optimal use of a two-person, two-handed technique with an oral airway in place, a failed airway exists. This is referred to as a "**can't** intubate, **can't** oxygenate" situation. In addition, if three attempts at direct laryngoscopy have been unsuccessful, a failed airway exists because subsequent attempts at laryngoscopy by the same clinician are unlikely to succeed. The three failed laryngoscopy attempts are defined as attempts by an experienced clinician, using best possible patient positioning and technique. A further attempt at direct laryngoscopy by the same clinician or one of equivalent experience is inadvisable, unless the clinician identifies a specific situation on the third laryngoscopy that is amenable to correction, justifying a fourth attempt. Also, if the clinician ascertains after even a single attempt that intubation will be impossible (e.g., grade IV laryngoscopic view despite optimal patient positioning), a failed airway is present. The failed airway is managed according to the failed airway algorithm (Fig. 1-8).

Difficult Airway

When preintubation evaluation has identified a potentially difficult airway, a different approach is used (see Fig. 1-7).[3,4] The approach is based on the fact that NMBAs should not be administered to a patient for intubation unless the clinician believes that (1) intubation is likely to be successful and (2) oxygenation via BMV or EGD is likely to be successful if a first intubation attempt does not succeed and oxygenation is required.

The perception of a difficult airway is relative, and many emergency intubations could be considered "difficult." The judgment regarding whether to treat the airway as a typical emergency airway or whether to use the difficult airway algorithm is based on the degree of perceived difficulty and the individual circumstances of the case.[38] The LEMON, MOANS, and RODS assessments provide a systematic framework to assist in identifying the potentially difficult airway.

When a difficult airway is identified, the first step is to ensure that oxygenation is sufficient to permit a planned, orderly approach (see Fig. 1-7). If oxygenation is inadequate and cannot be made adequate by supplementation with bag and mask, the airway should be considered a failed airway. The failed airway algorithm should be used because the predicted high degree of intubation difficulty combined with failure to maintain oxygen saturation is analogous to the "**can't** intubate, **can't** oxygenate" situation. When oxygenation is adequate, the next consideration is whether RSI is appropriate, based on the operator's assessment of the likelihood of (1) successful ventilation using a bag and mask or an EGD in the event intubation is unsuccessful, and (2) the likelihood of successful intubation by direct laryngoscopy. In some cases, a double setup can be used in which RSI is performed, but all preparations are undertaken for rescue cricothyrotomy before the drugs are administered. If RSI is not advisable, an "awake" technique can be used. In this context, *awake* means that the patient continues to breathe and is able to respond to caregivers. Usually the technique involves sedation and topical anesthesia, often preceded by a drying agent, such as glycopyrrolate.

The awake technique often is direct laryngoscopy, assisted by topical anesthesia and sedation (comparable to that for a painful procedure), with the purpose of ascertaining whether intubation using direct laryngoscopy is possible. If the glottis is adequately visualized, the patient can be intubated at that time, or, in a stable difficult airway situation, the clinician may proceed with planned RSI, now assured of intubation success. Awake laryngoscopy can be performed using a direct laryngoscope, a flexible fiberoptic scope, a videolaryngoscope, or a rigid fiberoptic scope. If the awake laryngoscopy determines that oral intubation using a standard laryngoscope would likely be unsuccessful, the patient is intubated using any of numerous techniques shown in the last box in Figure 1-7. For each of these methods, the patient is kept breathing but variably sedated and anesthetized and each of the methods results in placement of a cuffed ETT in the trachea. The choice among these methods depends on clinician experience and preference, device availability, and patient attributes.

Failed Airway

Management of the failed airway is dictated by an assessment of whether the patient can be oxygenated.[3,4] If adequate oxygenation cannot be maintained, the rescue technique of first resort is cricothyrotomy (see Fig. 1-8). Multiple attempts at other methods in the context of failed oxygenation delay cricothyrotomy and place the patient at increased risk for hypoxic brain injury. If an alternative device (i.e., an EGD such as a laryngeal mask airway or Combitube) is readily at hand, however, an attempt can be made to use it simultaneously with preparations for immediate cricothyrotomy, as long as initiation of cricothyrotomy is not delayed. Only a single attempt with the EGD is recommended in this circumstance.

If adequate oxygenation is possible, several options are available for the failed airway. In almost all cases, cricothyrotomy is the definitive rescue technique for the failed airway if time (i.e., preservation of oxygenation) does not allow for other approaches or if they fail. The fundamental difference in philosophy between the difficult airway and the failed airway is that the difficult airway is planned for, and the standard is to place a cuffed ETT in the trachea. The failed airway is *not* planned for, and the standard is to achieve an airway that provides adequate oxygenation to avert the immediate problem of hypoxic brain injury. Some of the devices used in the failed airway (e.g., EGDs) are temporary and do not provide airway protection.

THERAPEUTIC MODALITIES

Methods of Intubation

Although many techniques are available for intubation of the emergency patient, four methods are most common, with RSI being the most frequently used in nonarrested patients.[1,13,14,39]

Rapid Sequence Intubation

RSI is the cornerstone of modern emergency airway management and is defined as the virtually simultaneous administration of a potent sedative (induction) agent and an NMBA, usually succinylcholine, for the purpose of endotracheal intubation. This approach provides optimal intubating conditions and has long been believed to minimize the risk of aspiration of gastric contents. A systematic review of the literature in 2007 failed to prove that rapid sequence intubation results in a lower incidence of aspiration than other techniques, but the authors correctly noted that virtually no studies have ever been designed to measure this precise endpoint.[40] RSI is nevertheless the most widely used technique by far for emergency intubation of patients without identifiable difficult airway attributes.[1,13,14]

The central concept of RSI is to take the patient from the starting point (e.g., conscious, breathing spontaneously) to a state of unconsciousness with complete neuromuscular paralysis, then to achieve intubation *without* interposed assisted ventilation. The risk of aspiration of gastric contents is felt to be significantly higher for patients who have not fasted before induction. Application of positive-pressure ventilation can cause air to pass into the stomach, resulting in gastric distention and likely increasing the risk of regurgitation and aspiration.[41] The purpose of RSI is to avoid positive-pressure ventilation until the ETT is placed correctly in the trachea with the cuff inflated. This requires a preoxygenation phase, during which the nitrogen reservoir in the functional residual capacity in the lungs is replaced with oxygen, permitting at least several minutes of apnea (see later discussion) in the normal adult before oxygen desaturation to 90% ensues (Fig. 1-9).[35]

Use of RSI also facilitates successful endotracheal intubation by causing complete relaxation of the patient's musculature, allowing better access to the airway.[19,36,37,42] Finally, RSI permits pharmacologic control of the physiologic responses to laryngoscopy and intubation, mitigating potential adverse effects. These effects include further intracranial pressure (ICP) increase in response to the procedure and to the sympathetic discharge resulting from laryngoscopy (Box 1-4).[43] RSI is a series of discrete steps, and every step should be planned (see Box 1-5).[5]

Preparation. In the initial phase, the patient is assessed for intubation difficulty (unless this has already been done), and the intubation is planned, including determining dosages and

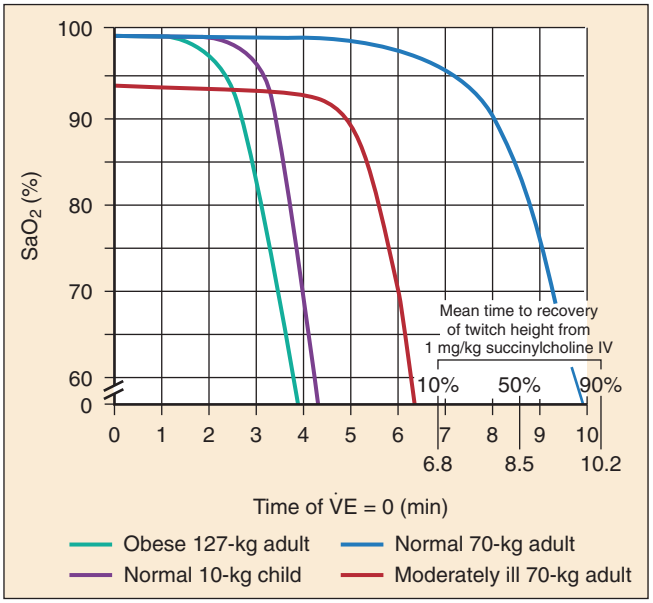

Figure 1-9. Desaturation time for apneic, fully preoxygenated patients. Children, patients with comorbidity, and obese patients desaturate much more rapidly than healthy, normal adults. The box on the lower right-hand side of the graph depicts time to recovery from succinylcholine, which in almost all cases exceeds safe apnea time. Note also the precipitous decline of oxygen saturation from 90% to 0% for all groups. Modified from Benumof J, et al: Critical hemoglobin desaturation will occur before return to unparalyzed state following 1 mg/kg intravenous succinylcholine. Anesthesiology 87:979, 1997.

BOX 1-4 PRETREATMENT AGENTS FOR RAPID SEQUENCE INTUBATION*

Reactive airways disease: Lidocaine: 1.5 mg/kg IV, to mitigate bronchospasm. Albuterol 2.5 mg by nebulizer (if time permits and not already given).
Cardiovascular disease: Fentanyl: 3 µg/kg to mitigate sympathetic discharge.
Elevated ICP: Lidocaine: 1.5 mg/kg IV to mitigate ICP increase in response to airway manipulation. Fentanyl 3 µg/kg to mitigate sympathetic discharge and attendant rise in ICP.

*Given 3 minutes before induction and paralysis.
ICP, intracranial pressure.

BOX 1-5 THE SEVEN "PS" OF RSI

1. **P**reparation
2. **P**reoxygenation
3. **P**retreatment
4. **P**aralysis with induction
5. **P**ositioning
6. **P**lacement of tube
7. **P**ostintubation management

sequence of drugs, tube size, and laryngoscope type, blade and size. Drugs are drawn up and labeled. All necessary equipment is assembled. All such patients require continuous cardiac monitoring and pulse oximetry. At least one and preferably two good-quality intravenous (IV) lines should be established. Redundancy is always desirable in case of equipment or IV access failure.

Preoxygenation. Administration of 100% oxygen for 3 minutes of normal, tidal volume breathing in a normal, healthy adult establishes an adequate oxygen reservoir to permit 8 minutes of apnea before oxygen desaturation to less than 90% occurs (see Fig. 1-9).[35] The time to desaturation to less than 90% in children, obese adults, late-term pregnant women, and patients with significant comorbidity is considerably less. Desaturation time also is reduced if the patient does not inspire 100% oxygen.[44] Nevertheless, adequate preoxygenation usually can be obtained, even in ED patients, to permit several minutes of apnea before oxygen desaturation to less than 90% occurs. In children and adults, preoxygenation is essential to the "no bagging" approach of RSI. If time is insufficient for a full 3-minute preoxygenation phase, eight vital capacity breaths using high-flow oxygen can achieve oxygen saturations and apnea times that match or exceed those obtained with traditional preoxygenation.[45] Preoxygenation of obese patients in the head up position results in significantly longer (approximately 45 seconds) apnea time before critical saturation.[46] Preoxygenation should be done in parallel with the preparation phase and can be started in the field for high risk patients. Oxygen saturation monitors permit earlier detection of desaturation during laryngoscopy, but preoxygenation remains an essential step in RSI.

Pretreatment. During this phase, drugs are administered 3 minutes before administration of the succinylcholine and induction agent to mitigate the effects of laryngoscopy and intubation on the patient's presenting or comorbid conditions. Intubation is intensely stimulating and results in sympathetic discharge (the reflex sympathetic response to laryngoscopy), elevation of ICP in patients with ICP disturbance, and reactive bronchospasm. Bradycardia often occurs in children, particularly young children, but appears multifactorial, likely involving both parasympathetic discharge in response to airway instrumentation and perhaps some contributory effect of succinylcholine.

Pretreatment focuses on three main objectives, in certain at-risk patients. The three groups of patients at risk are those with reactive airways disease, elevated ICP, or a cardiovascular or neurovascular condition or acute event for which an acute elevation in blood pressure and heart rate might be hazardous. Patients with reactive airways disease often experience a worsening of their bronchospasm when intubated. Controversy exists regarding whether albuterol alone, lidocaine alone, or both drugs together are effective in reducing this intubation-related bronchospasm.[47-49] Asthmatic patients being intubated in the ED for status asthmaticus will have received albuterol before intubation, and, pending larger studies, it is reasonable also to administer lidocaine (1.5 mg/kg) as a pretreatment drug in these cases. When an asthmatic patient is being intubated for a condition (e.g., trauma) other than acute asthma, nebulized albuterol and IV lidocaine should be given before intubation, if possible. Patients with significant cardiovascular disease (e.g., ischemic coronary disease) who are being intubated in the ED may benefit from the administration of the synthetic opioid, fentanyl, in a dose of 3 µg/kg to mitigate the release of catecholamines in response to airway manipulation. Similarly, patients with intracranial hemorrhage, elevated ICP, or marked hypertension may benefit from pretreatment with fentanyl.[49] Finally, there is some evidence that patients with elevated ICP may experience less exacerbation of the ICP during intubation if they are pretreated with lidocaine (1.5 mg/kg). These patients, unless hypotensive, should also receive fentanyl (3 µg/kg) to mitigate blood pressure surges that might translate to further increases in ICP. There is evidence supporting the physiologic effects of these agents, but outcome data are lacking. Individualization is necessary, and critical time should not be lost administering pretreatment drugs if the patient requires immediate intubation. Despite the lack of outcome studies, considerable inferential evidence supports this approach, and these agents probably provide protection for vulnerable patients against the adverse hemodynamic and intracranial effects of laryngoscopy and intubation.[49] Although many variations are possible for pretreatment regimens in various conditions, pretreatment can be simplified to these three basic indications (see Box 1-4).

When possible, 3 minutes should elapse between the administration of the pretreatment drug and the administration of the induction drug and NMBA. If time is insufficient to wait 3 minutes, even a reduced time may provide some benefit.

Paralysis with Induction. In this phase, a potent sedative agent is administered by rapid IV push in a dose capable of rapidly producing unconsciousness. This is immediately followed by rapid administration of an intubating dose of an NMBA, usually succinylcholine. It is usual to wait 45 seconds from the time the succinylcholine is given to allow sufficient paralysis to occur. (See later discussion of drugs and doses.)

Positioning. The patient should be positioned for intubation as consciousness is lost. Usually, positioning involves head extension, often with flexion of the neck on the body, but there is evidence that simple extension of the head alone, or extension of both the head and neck (the extension-extension position) are equivalent or superior.[27,28] (See earlier discussion.) Sellick's maneuver (application of firm backward-directed pressure over the cricoid cartilage) has long been recommended to minimize the risk of passive regurgitation and, hence, aspiration, but two recent reviews have challenged this premise.[50-52] In addition, there is evidence that Sellick's maneuver may make laryngoscopy or intubation more difficult

in some patients.[51] Accordingly, Sellick's maneuver should be considered optional, applied selectively, and released or modified to improve laryngeal view or tube passage, as indicated. During this phase after administration of the induction agent and NMBA, although the patient becomes unconscious and apneic, BMV should not be initiated unless the oxygen saturation falls to 90%.

Placement of Tube. Approximately 45 seconds after the administration of succinylcholine, the patient is relaxed sufficiently to permit laryngoscopy; this is assessed most easily by moving the mandible to test for absence of muscle tone. The ETT is placed under direct visualization of the glottis. If the first attempt is unsuccessful, but oxygen saturation remains high, it is not necessary to ventilate the patient with a bag and mask between intubation attempts. If the oxygen saturation is approaching 90%, the patient may be ventilated briefly with a bag and mask between attempts to reestablish the oxygen reservoir. When BMV is performed, Sellick's maneuver is advisable to minimize passage of air into the stomach.[41] Sellick's maneuver may be continued or released during repeat laryngoscopy, according the judgment of the clinician and the glottic view obtained. As soon as the ETT is placed, the cuff should be inflated and its position confirmed as described earlier.

Postintubation Management. A chest radiograph should be obtained to confirm that main stem intubation has not occurred and to assess the lungs. There is a trend away from the use of long-acting NMBAs (e.g., pancuronium, vecuronium) toward optimal management using opioid analgesics and sedative agents to facilitate mechanical ventilation.[50] (See Chapter 3.) An adequate dose of a benzodiazepine (e.g., midazolam 0.1–0.2 mg/kg, IV) and an opioid analgesic (e.g., fentanyl, 3–5 µg/kg, IV, or morphine, 0.2–0.3 mg/kg, IV) is given to improve patient comfort and decrease sympathetic response to the ETT. Appropriate use of sedation and analgesia often obviates the need for an NMBA. Table 1-1 presents a sample RSI protocol using etomidate and succinylcholine. "Zero" refers to the time at which the induction agent and succinylcholine are pushed.

Table 1-1 Sample Rapid Sequence Intubation Using Etomidate and Succinylcholine

TIME	STEP
Zero minus 10 min	**Preparation**
Zero minus 5 min	**Preoxygenation** 100% oxygen for 3 min *or* eight vital capacity breaths
Zero minus 3 min	**Pretreatment** as indicated
Zero	**Paralysis with induction** Etomidate, 0.3 mg/kg Succinylcholine, 1.5 mg/kg
Zero plus 30 sec	**Positioning** Sellick's maneuver optional
Zero plus 45 sec	**Placement** Laryngoscopy and intubation End-tidal carbon dioxide confirmation
Zero plus 2 min	**Postintubation management** Sedation and analgesia as indicated Initiate mechanical ventilation NMBA only if needed after adequate sedation/analgesia

Blind Nasotracheal Intubation

Historically, blind nasotracheal intubation (BNTI) was used extensively in the ED and out-of-hospital setting, but has fallen out of favor largely because of the superiority of RSI.[11,53] Success rates have been about 80 to 90%, and high complication rates are reported, most often epistaxis or delayed or incorrect tube placement.[53] Long-term complications (e.g., sinusitis, turbinate destruction, laryngeal perforation) are uncommon and related to multiple attempts or prolonged intubation. Basilar skull fracture and facial trauma have been considered contraindications to nasotracheal intubation because of the risk of entering the cranial vault or increasing the incidence of intracranial infection. These contraindications are not based on scientific study, however, and two small studies failed to detect a difference in complications between orally and nasally intubated facial trauma patients.[54,55] Two other studies compared the success rates of RSI and BNTI performed by physicians or paramedics on helicopter services. Results differed, with one study showing essentially equivalent success rates and the other showing a significant advantage for neuromuscular blockade over BNTI.[56,57] ED studies have shown superiority of RSI over BNTI.[11,39] Also, the incidence and severity of oxygen desaturation are greater in BNTI than with RSI.[58]

BNTI is a valid and useful method of intubation in the out-of-hospital setting and is still widely used by paramedics and other out-of-hospital first responders. In the ED, where NMBAs and RSI are available, BNTI should be considered a second-line approach and reserved for patients in whom the presence of a difficult airway makes RSI undesirable or contraindicated and alternatives (e.g., fiberoptics) are not available. Interestingly, the old recommendation that refrigeration of the tube before use increases success of nasotracheal intubation probably is not true. To the contrary, warming the tube to 40° before use appears to facilitate easy tube passage and reduce the incidence of epistaxis.[59] Similarly, maintaining the head in a neutral position and inflating the ETT cuff to 15 mL in the oropharynx or hypopharynx before attempting to traverse the glottis also improves the success rate.[60] Use of BNTI in the ED has declined sufficiently, and it is doubtful that emergency medicine residents will be adequately trained in the technique.[53]

Awake Oral Intubation

Awake oral intubation is a technique in which sedative and topical anesthetic agents are administered to permit management of a difficult airway. Sedation and analgesia are achieved in a manner analogous to that for painful procedures in the ED. Topical anesthesia may be achieved by spray, nebulization, or local anesthetic nerve block. After the patient is sedated and topical anesthesia has been achieved, gentle direct, video, or fiberoptic laryngoscopy is performed to determine whether the glottis is visible and intubation possible. The patient may be intubated during the laryngoscopy, or the laryngoscopy may show that oral intubation is possible, permitting safe use of RSI (see earlier discussion).

Awake oral intubation is distinct from the practice of oral intubation using a sedative or opioid agent to obtund the patient for intubation without neuromuscular blockade, which had been a typical ED practice. This latter technique can be referred to as "intubation with sedation alone" or, paradoxically, "nonparalytic RSI." Proponents of intubation with sedation alone argue that administration of a benzodiazepine, opioid, or both provides improved access to the airway, decreases patient resistance, and avoids the risks inherent

in neuromuscular blockade. This technique actually is more hazardous than RSI, however. Intubating conditions achieved even with deep anesthesia are significantly inferior to the conditions achieved when neuromuscular blockade is used.[36,37,61] The same superiority of neuromuscular blockade-assisted intubation over intubation with sedation alone has been observed in pediatric emergency medicine and in EMS care.[62,63] In general, the technique of administering a potent sedative agent to obtund the patient's responses and permit intubation in the absence of neuromuscular blockade is ill-advised and inappropriate for ETI in the ED, unless it is performed as part of an "awake" intubation as described earlier.

Oral Intubation without Pharmacologic Agents

The unconscious, unresponsive, near death patient may not require pharmacologic agents for intubation. If the patient is essentially dead, administration of any pharmacologic agent, including an NMBA, may needlessly delay intubation. Even an unconscious patient may retain sufficient muscle tone to render intubation difficult, however. If the glottis is not adequately visualized, administration of a single dose of succinylcholine alone may facilitate laryngoscopy. Success rates for intubating unconscious, unresponsive patients are comparable to those achieved with RSI, presumably because the patient is in a similar physiologic state (i.e., muscle relaxation, no ability to react to laryngoscopy or tube insertion).[1]

Pharmacologic Agents

Neuromuscular Blocking Agents

Muscle contraction is the result of membrane depolarization, which causes massive intracellular release of calcium ions from the sarcoplasmic reticulum, leading to active contraction of myofibrils. The inciting incident is the depolarization of portions of the myocyte membrane, called the motor endplates, which are adjacent to the innervating axons. Action potentials conducted down the innervating axons cause release of the neurotransmitter acetylcholine (ACh) from the terminal axon. The ACh traverses the synaptic cleft, binds reversibly to receptors on the motor endplate, and opens channels in the membrane to initiate depolarization.

NMBAs are highly water-soluble, quaternary ammonium compounds that mimic the quaternary ammonium group on the ACh molecule. Their water solubility explains why these agents do not readily cross the blood-brain barrier or placenta. The NMBAs are divided into two main classes. The *depolarizing* agent, succinylcholine, exerts its effects by binding noncompetitively with ACh receptors on the motor endplate and causing sustained depolarization of the myocyte. The other major class of NMBA comprises the *competitive*, or *nondepolarizing*, agents, which bind competitively to ACh receptors, preventing access by ACh and preventing muscular activity. The competitive agents are of two pharmacologically distinct types, steroid-based agents (aminosteroid compounds) and benzylisoquinolines. Each of these basic chemical types has distinct properties, but only the aminosteroid compounds are used in the ED.

Succinylcholine. Succinylcholine is a combination of two molecules of ACh. Succinylcholine is rapidly hydrolyzed by plasma pseudocholinesterase to succinylmonocholine, which is a weak NMBA, then to succinic acid and choline, which have no NMBA activity. Pseudocholinesterase is not present at the motor endplate and exerts its effects systemically before the succinylcholine reaches the ACh receptor.[64] Only a small amount of the succinylcholine that is administered survives to reach the motor endplate. When attached to the ACh receptor, succinylcholine is active until it diffuses away. Decreased plasma pseudocholinesterase activity can increase the amount of succinylcholine reaching the motor endplate, prolonging succinylcholine block, but this is of little significance in the emergency setting because the prolongation of action is rarely significant, reaching only 23 minutes at the extreme.[64,65]

Uses. Succinylcholine is rapidly active, typically producing intubating conditions within 60 seconds of administration by rapid IV bolus injection.[37,66] The clinical duration of action before spontaneous respiration is 6 to 10 minutes (see Fig. 1-9).[35] Full recovery of normal neuromuscular function occurs within 15 minutes. The combination of rapid onset, complete reliability, short duration of action, and absence of serious side effects maintains succinylcholine as the drug of choice for most ED intubations.[1,13,50,62] The use of a competitive, or nondepolarizing, NMBA for RSI may be desirable when succinylcholine is contraindicated and in certain other settings.

Cardiovascular Effects. As an ACh analogue, succinylcholine binds to ACh receptors throughout the body, not just at the motor endplate. It is difficult to separate the effects of succinylcholine on the heart that are caused by direct cardiac muscarinic stimulation from those caused by stimulation of autonomic ganglia by succinylcholine and from the effects induced by the autonomic responses to laryngoscopy and intubation. Succinylcholine can be a negative chronotrope, especially in children, and sinus bradycardia may ensue after succinylcholine administration. Sinus bradycardia is treated with atropine, if necessary, but is often self-limiting. Some pediatric practitioners recommend pretreatment with atropine for children younger than 1 year old, but there is no evidence for benefit.[67] Other cardiac dysrhythmias, including ventricular fibrillation and asystole, have been reported with succinylcholine, but it is impossible to distinguish the effects of the drug itself from those caused by the intense vagal stimulation and catecholamine release that accompany laryngoscopy and intubation. In addition, many of these catastrophic complications occur in critically ill patients, further confounding attempts to identify whether the illness or any particular drug or procedure is the cause.

Fasciculations. The depolarizing action of succinylcholine results in fine, chaotic contractions of the muscles throughout the body for several seconds at the onset of paralysis in over 90% of patients. Muscle pain occurs in approximately 50% of patients who receive succinylcholine. Although it is widely believed that muscle pains are reduced or abolished by prior administration of a defasciculating dose of a competitive NMBA, the evidence is not conclusive.[68] Use of 1.5 mg/kg of succinylcholine results in both less fasciculation and less myalgia than occur with 1 mg/kg.[68]

Hyperkalemia. Succinylcholine has been associated with severe, fatal hyperkalemia when administered in specific clinical circumstances (Table 1-2).[69] Although the hyperkalemia occurs within minutes after administration of succinylcholine and may be severe or fatal, the patient's vulnerability to succinylcholine-induced hyperkalemia does not become significant until at least 5 days after the inciting injury or burn. Succinylcholine remains the agent of choice for RSI in acute burn, trauma, stroke, spinal cord injury, and intra-abdominal sepsis if intubation occurs less than 5 days after onset of the condition. If doubt exists regarding the onset time, succinylcholine should be replaced with a competitive NMBA, usually rocuronium. Denervation syndromes (e.g., multiple sclerosis, amyotrophic lateral sclerosis) can be particularly troubling, however, because the risk begins with the onset of the disease and continues indefinitely, regardless of the apparent stability of the symptoms. Patients who have denervation caused by

stroke or spinal cord injury are stabilized after 6 months, and thereafter can receive succinylcholine safely.[65] Potassium release does not occur to any significant extent in the general population. Succinylcholine is not contraindicated in renal failure but probably should not be used in patients with known or presumed hyperkalemia sufficient to manifest on the electrocardiogram. The only published series of patients with hyperkalemia, many of whom had renal failure, failed to show a single adverse event related to succinylcholine administration.[70]

Increased Intraocular Pressure. Succinylcholine may cause a modest increase in intraocular pressure and historically has been considered relatively to absolutely contraindicated in penetrating globe injury. There is no published evidence to support this view, however, and several large series show safety when succinylcholine is used in patients with open globes. The admonition to avoid succinylcholine in open globe injuries is unjustified and should be abandoned.[71]

Masseter Spasm. Succinylcholine has been reported rarely to cause masseter spasm, primarily in children.[64] The clinical significance of this phenomenon is unclear, but administration of a competitive NMBA terminates the spasm. Severe, persistent spasm should raise suspicion of malignant hyperthermia.

Malignant Hyperthermia. Succinylcholine has been associated with malignant hyperthermia, a perplexing syndrome of rapid temperature rise and aggressive rhabdomyolysis. Malignant hyperthermia occurs in genetically predisposed individuals who receive certain volatile anesthetic agents or succinylcholine. The condition is extremely rare and has not been reported in the context of ED intubation. Treatment consists of cessation of any potential offending agents, administration of dantrolene (2 mg/kg IV every 5 min to a maximum dose of 10 mg/kg), and attempts to reduce body temperature by external means.[72] A national malignant hyperthermia hotline is available for emergency consultation at 1-800-644-9737 (then dial zero).

Refrigeration. The standard recommendation to keep succinylcholine refrigerated creates problems related to its storage, timely retrieval, and ready availability on intubation carts or kits in the ED. Succinylcholine undergoes degradation beginning at the time of manufacture, and the rate of this degradation is much lower when the drug is refrigerated. Succinylcholine retains more than 90% of its original activity when stored at room temperature for 3 months; it retains even more if protected from light.[73] Succinylcholine may be kept at room temperature in the ED or EMS setting, provided that a proper inventory control system ensures that all supplies are replaced not more than 3 months after introduction.

Competitive Agents. Competitive NMBAs are classified according to their chemical structure. The aminosteroid agents include pancuronium, vecuronium, and rocuronium. Vecuronium neither releases histamine nor exhibits cardiac muscarinic blockade and is an excellent agent for maintenance of neuromuscular blockade when this is desirable. Rocuronium is the best agent for use in RSI when succinylcholine is contraindicated.

Rapid Sequence Intubation with a Competitive Agent. Competitive agents, especially vecuronium and rocuronium, have been studied extensively for RSI. Although vecuronium was the first competitive NMBA to establish a role in RSI, it works best when given as a split dose. First, 0.01 mg/kg is administered as a "priming" dose. Three minutes later, 0.15 mg/kg is given for paralysis, which is achieved in about 75 to 90 seconds. Rocuronium bromide (1 mg/kg IV) achieves intubating conditions closely approaching those of succinylcholine, lasts approximately 50 minutes, and has been used in the ED with success (Table 1-3).[61,74]

Paralysis after Intubation. After intubation, prolonged paralysis may be desired to optimize mechanical ventilation; however, current management trends are away from the use of prolonged paralysis in favor of deep sedation with analgesia. If neuromuscular blockade is desired, vecuronium (0.1 mg/kg IV) can be given. Longer term neuromuscular blockade must not be undertaken without attention to appropriate sedation and analgesia of the patient.[50] An adequate dose of a benzodiazepine, such as midazolam (0.1–0.2 mg/kg IV), and an opioid analgesic, such as fentanyl (3–5 µg/kg IV) or morphine (0.2–0.3 mg/kg IV), is required to improve patient comfort and decrease sympathetic response to the ETT. Appropriate use

Table 1-2 Conditions Associated with Hyperkalemia after Succinylcholine Administration

CONDITION	PERIOD OF CONCERN
Burns >10% BSA	>5 days until healed
Crush injury	>5 days until healed
Denervation (stroke, spinal cord injury)	>5 days until 6 months postinjury
Neuromuscular disease (ALS, MS)	Indefinitely
Intra-abdominal sepsis	>5 days until resolution

ALS, amyotrophic lateral sclerosis; BSA, body surface area; MS, multiple sclerosis.

Table 1-3 Sample Rapid Sequence Intubation Using Etomidate and Rocuronium

TIME	STEP
Zero minus 10 min	**Preparation**
Zero minus 5 min	**Preoxygenation** 100% oxygen for 3 min *or* eight vital capacity breaths
Zero minus 3 min	**Pretreatment** As indicated
Zero	**Paralysis with induction** Etomidate, 0.3 mg/kg Rocuronium, 1.0 mg/kg
Zero plus 30 sec	**Positioning**
Zero plus 60 sec	**Placement** Laryngoscopy and intubation End-tidal carbon dioxide confirmation
Zero plus 2 min	**Postintubation management** Sedation and analgesia mandatory because of prolonged (45 min) duration of paralysis with rocuronium

of sedation and analgesia often obviates the need for an NMBA. Additional medication may be required if the patient's blood pressure and heart rate indicate excessive sympathetic tone.

Induction Agents

A patient who presents with any degree of clinical responsiveness, including reactivity to noxious stimuli, requires a sedative or induction agent at the time of administration of any NMBA. Patients who already are deeply unconscious and unresponsive may not require a full dose of an induction agent if the unconscious state is caused by drugs or alcohol (themselves general anesthetic agents.) Patients who are unconscious because of a central nervous system insult should receive an induction agent to attenuate adverse responses to airway manipulation. Induction agents also enhance the effect of the NMBA and improve intubation conditions because the intubation is done at the earliest phase of neuromuscular blockade, and the relaxation effects of the induction agent are additive to those of the NMBA.[75]

Etomidate. Etomidate is an imidazole derivative that has been in use since 1972. Its activity profile is similar to that for thiopental, with rapid onset, rapid peak activity, and brief duration, but it is remarkably hemodynamically stable.[76,77] Etomidate has emerged as the agent of choice for ED RSI, and numerous reports attest to its effectiveness and safety.[1,14] The induction dose is 0.3 mg/kg IV. Because etomidate is able to decrease ICP, cerebral blood flow, and cerebral metabolic rate without adversely affecting systemic mean arterial blood pressure and cerebral perfusion pressure, it is an excellent induction agent for patients with elevated ICP, even in cases of hemodynamic instability.[77,78] Etomidate may cause brief myoclonus, but this is of no clinical significance. Etomidate by continuous infusion has been reported to cause suppression of endogenous cortisol production. Recently, controversy has emerged regarding the role of etomidate for intubation of patients with septic shock.[79-81] Several retrospective studies have claimed to demonstrate that etomidate, used in a single dose for intubation, causes suppression of the adrenal response to exogenously administered adrenocorticotropic hormone, and have attempted to link this to increased mortality.[82,83] Other retrospective studies have shown the opposite.[84,85] Ironically, much of the original criticism of etomidate arose from the belief that adrenocortical response to exogenous corticotropin predicts outcome in patients with septic shock, a belief that has since been abandoned.[86] Also, the most recent and comprehensive study of the role of corticosteroids in septic shock failed to show any benefit, casting further doubt about any possible mortality effect of a single dose of etomidate.[87] Pending a properly constructed, prospective, randomized clinical trial, there is not sufficient evidence to support a recommendation that etomidate not be used in patients with septic shock.[81,88] In fact, etomidate's superior hemodynamic profile makes it an excellent choice in these generally unstable patients.

Barbiturates. Although both the thiobarbiturate, sodium thiopental, and the methylated oxybarbiturate, methohexital, have been used as induction agents for RSI, thiopental has been used more widely. The use of these agents has declined significantly, however, with the adoption of newer agents, particularly etomidate and propofol. The rapidly acting barbiturates are highly lipid-soluble and readily cross the blood-brain barrier, acting on the γ-aminobutyric acid receptor neuroinhibitory complex to rapidly depress central nervous system activity. A single dose of 3 mg/kg of thiopental produces loss of consciousness in less than 30 seconds, has a peak effect at 1 minute, and has a clinical duration of 5 to 8 minutes. Methohexital may have a slightly shorter duration of action but is more prone to cause central nervous system excitatory side effects, such as myoclonus. Thiopental is a negative inotrope and a potent venodilator and should be used with caution in patients whose cardiovascular reserve is diminished. For the same reason, thiopental should be avoided in a hypotensive patient who would not tolerate further compromise of circulation. Thiopental can release histamine and probably should not be used in asthmatic patients.

Benzodiazepines. Of the benzodiazepines, only midazolam is suited to use as an induction agent, with a normal induction dose of 0.2 to 0.3 mg/kg IV.[77] In a dose of 0.3 mg/kg IV, midazolam produces loss of consciousness in about 30 seconds and has a clinical duration of 15 to 20 minutes.[89] Midazolam is a negative inotrope comparable to thiopental and should be used with caution in hemodynamically compromised and elderly patients, for whom the dose can be reduced to 0.1 mg/kg or 0.05 mg/kg. Onset is slower at these reduced doses. Much lower doses than indicated are often used in ED intubations, perhaps because practitioners are familiar with the sedation doses, but not the anesthetic induction doses, of midazolam.[90] These inadequate doses reduce the effectiveness of laryngoscopy, do not provide optimal blunting of adverse physiologic effects of laryngoscopy and intubation, and may compromise the patient's amnesia for the intubation. Midazolam may be cerebroprotective, but less so than etomidate or thiopental.

Ketamine. Ketamine, a phencyclidine derivative, has been widely used as a general anesthetic agent since 1970. After an IV dose of 1 to 2 mg/kg, ketamine produces loss of awareness within 30 seconds, peaks in approximately 1 minute, and has a clinical duration of 10 to 15 minutes. As a dissociative anesthetic agent, ketamine induces a cataleptic state rather than a true unconscious state. The patient has profound analgesia but may have open eyes. Many protective reflexes, including airway reflexes, are preserved.

The principal uses of ketamine in emergency airway management are for the induction of patients with acute, severe asthma and for hemodynamically unstable trauma patients. Ketamine is exceptionally hemodynamically stable, more so than etomidate, so although either drug is a good choice in the trauma patient, ketamine is probably superior in terms of preserving precarious cardiovascular stability.[89] In patients with status asthmaticus, etomidate or any of most of the other induction agents is acceptable, with the notable exception of sodium thiopental, which releases histamine. Ketamine is a direct bronchodilator and releases catecholamines, so may be useful both for intubation and for intermittent administration as part of sedation for mechanical ventilation in patients with severe asthma, although no outcome studies clearly demonstrate its superiority.

Controversy exists regarding the use of ketamine in patients with elevated ICP because ketamine has been believed to increase cerebral metabolic rate, ICP, and cerebral blood flow.[91] The evidence that ketamine can produce harm in this way is conflicting, however, and its role as an induction agent in trauma is significant because of its superior hemodynamic stability.[10] Because of its tendency to release catecholamines and increase blood pressure, ketamine should probably be avoided in head trauma patients with normal or elevated blood pressure. However, in the hypotensive head trauma patient, ketamine is a reasonable choice for induction.[77] Ketamine tends to produce unpleasant emergence phenomena, especially disturbing or frightening dreams in the first 3 hours after awakening. These reactions, which are more prominent in

adults than in children, in women than in men, in patients receiving larger doses, and in certain personality types, are mitigated by benzodiazepine administration. Patients (e.g., with asthma) who undergo RSI with ketamine should receive a sufficient dose of a benzodiazepine (e.g., 0.05 mg/kg of lorazepam) as part of postintubation management.

Special Clinical Circumstances

Status Asthmaticus

Status asthmaticus with supervening respiratory failure is a preterminal event. Respiratory failure in the asthmatic patient is not caused primarily by progressive worsening of the bronchospasm, but rather by eventual exhaustion and fatigue secondary to the effort of breathing against severe airway resistance. All patients who are intubated for status asthmaticus are heavily sedated and receive mechanical ventilation. RSI permits the most rapid attainment of intubation, protects against aspiration, and induces the unconsciousness and motor paralysis necessary for optimal initiation of mechanical ventilation; it is the recommended technique for intubation of a patient in status asthmaticus. Difficult airway considerations are complex in an asthmatic patient because of impending respiratory arrest and the patient's inability to tolerate attempts at awake intubation. Even when a difficult airway is identified in an asthmatic patient, RSI is usually the intubation method of choice, with a double setup for rescue cricothyrotomy when indicated.

The asthmatic patient has highly reactive airways, and steps should be taken to minimize any additional bronchospasm that may occur during intubation. Lidocaine has been shown to suppress the coughing that occurs in response to airway manipulation and may improve ETT tolerance and reduce reactive bronchospasm in asthmatic patients.[48] The balance of evidence suggests that lidocaine (1.5 mg/kg) is indicated as a pretreatment drug before intubation in status asthmaticus and in asthmatic patients being intubated for reasons other than their asthma. High-dose, inhaled beta-agonists may provide maximal protection against reactive bronchospasm during intubation in asthmatics without active bronchospasm, and lidocaine may provide little additional benefit in this setting.[47] This approach has not been tested in patients in status asthmaticus, however. Ketamine has been shown to produce bronchodilation in humans and animal models and may be the ideal induction agent in asthma. Although reports to date have been limited, there is a growing body of experience with ketamine as an induction agent for the emergency intubation of patients with status asthmaticus. Ketamine also has been reported to mitigate bronchospasm in patients who are not intubated and in patients who are already intubated and who are not improving with mechanical ventilation (Table 1-4).

Table 1-4 Rapid Sequence Intubation for Status Asthmaticus

TIME	STEP
Zero minus 10 min	**Preparation**
Zero minus 5 min	**Preoxygenation** (as possible) Continuous albuterol nebulizer 100% oxygen for 3 min *or* 8 vital capacity breaths
Zero minus 3 min	**Pretreatment** Lidocaine, 1.5 mg/kg
Zero	**Paralysis with induction** Ketamine, 1.5 mg/kg Succinylcholine, 1.5 mg/kg
Zero plus 30 sec	**Positioning**
Zero plus 45 sec	**Placement** Laryngoscopy with intubation End-tidal carbon dioxide confirmation
Zero plus 2 min	**Postintubation management** Sedation and analgesia NMBA only if required after adequate sedation/analgesia In-line albuterol nebulization Additional ketamine as indicated

Hemodynamic Consequences of Intubation

Laryngoscopy and intubation are potent stimuli for the reflex release of catecholamines.[92] This reflex sympathetic response to laryngoscopy (RSRL) produces only modest increases in blood pressure and heart rate and is of little consequence in otherwise healthy patients. The RSRL is of potential clinical significance in two settings: acute elevation of ICP and certain cardiovascular diseases (e.g., intracerebral hemorrhage, subarachnoid hemorrhage, aortic dissection or aneurysm, and ischemic heart disease). In these settings, the reflex release of catecholamines, increased myocardial oxygen demand, and attendant rise in mean arterial blood pressure and heart rate may produce deleterious effects. The synthetic opioids (e.g., fentanyl) and beta-adrenergic blocking agents (e.g., esmolol) are capable of blunting the RSRL and stabilizing heart rate and blood pressure during intubation.[92] Lidocaine also has been studied, but the results are contradictory and inconclusive.[93] In patients at risk from acute blood pressure elevation, administration of fentanyl (3 µg/kg) during the pretreatment phase of RSI attenuates the heart rate and blood pressure increase. The full sympatholytic dose of fentanyl is 5 to 9 µg/kg, but if this dose is administered as a single pretreatment bolus, hypoventilation or apnea can occur. The administration of 3 µg/kg is safer and can be supplemented with an additional 3 µg/kg immediately after intubation if full sympathetic blockade is desired or if hypertension and tachycardia ensue, providing evidence of excessive sympathetic activity. Fentanyl should be given as the last pretreatment drug over 60 seconds to prevent hypoventilation or apnea.

Elevated Intracranial Pressure

When ICP is elevated as a result of head injury or acute intracranial catastrophe, maintenance of cerebral perfusion pressure and avoidance of further increases in ICP are desirable.[43] Significant reductions in mean arterial blood pressure decrease cerebral perfusion pressure by reducing the driving gradient between arterial pressure and ICP, leading to increased cerebral ischemia. Maintenance of the systemic mean arterial blood pressure at 100 mm Hg or greater supports the cerebral perfusion pressure and reduces the likelihood of secondary injury. In addition, cerebral autoregulation may be lost, and increases in systemic blood pressure may lead to corresponding increases in cerebral blood flow and ICP. With elevated ICP, control of the reflex hemodynamic stimulation resulting from intubation is desirable to avoid further elevation of ICP. Fentanyl (3 µg/kg) given as a pretreatment drug is the best choice for this purpose in the emergency setting.[43,94]

Evidence suggests a separate reflex that increases ICP in response to laryngoscopy and intubation, although the precise mechanism is not understood. IV lidocaine reduces ICP and

Table 1-5 Rapid Sequence Intubation for Elevated Intracranial Pressure

TIME	STEP
Zero minus 10 min	**Preparation**
Zero minus 5 min	**Preoxygenation** (as possible) 100% oxygen for 3 min *or* 8 vital capacity breaths
Zero minus 3 min	**Pretreatment** Lidocaine, 1.5 mg/kg Fentanyl, 3 µg/kg (slowly)
Zero	**Paralysis with induction** Etomidate, 0.3 mg/kg Succinylcholine, 1.5 mg/kg*
Zero plus 30 sec	**Positioning**
Zero plus 45 sec	**Placement** Laryngoscopy with intubation End-tidal carbon dioxide confirmation
Zero plus 2 min	**Postintubation management** Sedation and analgesia, consider propofol to permit frequent reexamination NMBA only if required after adequate sedation/analgesia

*May substitute rocuronium, 1 mg/kg, for succinylcholine.

blunts the ICP response to laryngoscopy and intubation. Lidocaine (1.5 mg/kg IV), administered during the pretreatment phase of RSI, is desirable to blunt the ICP response to laryngoscopy and intubation. Similarly, RSRL and ICP response to laryngoscopy and intubation relatively contraindicate BNTI, which should be undertaken only if RSI is impossible and fiberoptic intubation is not an option.

The physician should choose an induction agent that balances a favorable effect on cerebral dynamics and ICP with a stable systemic hemodynamic profile. At present, etomidate (0.3 mg/kg) probably is the best choice for patients with elevated ICP, although thiopental also is an excellent choice when hypotension is not present (Table 1-5).

Potential Cervical Spine Injury

Historically, it was believed that oral endotracheal intubation carried an unacceptably high risk of injury to the cervical spinal cord in patients with blunt cervical spine injury and was relatively contraindicated, but this assertion was never subjected to scientific scrutiny. Numerous studies and reports have asserted the safety and effectiveness of controlled, oral intubation with in-line cervical spine immobilization, whether done as an awake procedure or with neuromuscular blockade.[95,96] The evidence favors RSI with in-line stabilization, which provides maximal control of the patient, the ability to mitigate adverse effects of the intubation, and the best conditions for laryngoscopy. In-line stabilization also seems to improve the laryngoscopic view of the larynx compared with conventional tape/collar/sandbag immobilization. The intubating laryngeal mask airway (ILMA) also has been compared with conventional laryngoscopy and may result in less movement of the cervical spine during intubation than that caused by direct laryngoscopy.[97] A comparison of methods on a cadaver model of unstable injury of the third cervical vertebra reinforced the potential role for fiberoptic intubation and raised questions about the safety of the Combitube because of significant cervical spine movement during its placement.[98] Newer devices have also shown promise for safe intubation of patients with cervical spine injury. A fluoroscopic study comparing intubation using the Shikani optical stylet (SOS) to that done with direct laryngoscopy showed significantly less cervical spine movement with the SOS, but a slightly longer time (28 sec vs. 17 sec) to achieve intubation.[99] The Airtraq, a single-use intubation device, resulted in better glottic views and more rapid intubation of patients with cervical spine immobilization than direct laryngoscopy using a Macintosh blade.[100] The Glidescope, a video laryngoscope, provides superior glottic views with reduced or comparable cervical spine movement when compared with conventional direct laryngoscopy using the Macintosh blade.[101,102]

Cervical spine immobilization of patients with penetrating head and neck trauma is poorly addressed in the literature. It is not proven whether patients with gunshot or shotgun injuries to the head or neck are at risk of exacerbation of cervical cord injury during intubation, but there is no report of such a patient, with or without clinical evidence of spinal cord injury, who was injured by intubation. If the path of the missile is felt not to involve the bony spinal column and there is no evidence of spinal cord injury, prudence would dictate immobilization of patients with gunshot wounds to the head or neck with a secondary injury mechanism (e.g., fall from height) or with neurologic deficit suggesting spinal involvement.[103] Immobilization for intubation of patients with penetrating injury elsewhere in the body should be directed by the likelihood of secondary injury to the spine from a fall or other event distinct from the wounding.

Pediatric Intubation

Although many considerations in pediatric intubation are the same as for adults, a few differences exist in regard to airway management. The larynx is higher in the child's neck, causing a more acute angle between the oral pharynx and the larynx. Visualization is aided by gentle posterior pressure on the anterior aspect of the thyroid cartilage. The epiglottis is high and soft, making visualization of the cords more difficult. If the child is very small, the prominent occiput brings the mouth to a position far anterior to the larynx; an assistant can lift the chest gently by grasping both shoulders, immobilizing the head at the same time. The airway in the small child is short, and care must be taken not to intubate either bronchus.[67]

A straight laryngoscope blade is desirable to displace the floppy epiglottis, especially in young children, and positioning for intubation may be different. BNTI is relatively contraindicated in children younger than 12 years old. Although the product insert for succinylcholine now advises against its routine use in pediatric anesthesia because of the risk of hyperkalemia in children with undiagnosed congenital neuromuscular disorders (e.g., muscular dystrophy), it remains the drug of choice for emergency RSI of infants and children.[62] Rocuronium has been used in children, but experience is too limited to recommend that it replace succinylcholine for pediatric RSI in the ED. RSI may be used in children in a similar manner to adults, with two important differences. Excessive bradycardia may be seen with succinylcholine in children younger than 1 year old, but it is not known whether administration of atropine (0.02 mg/kg) during the pretreatment phase prevents any possible adverse outcome. The dose of succinylcholine in infants is 2 mg/kg. Induction agents may be selected using similar criteria as for adults. The major difficulty in intubating children and infants is choosing the correct size of equipment and the correct drug doses for age or size. These obstacles can be overcome by use of a length-based system (Broselow-Luten Color Coding Kids; Vital Signs, Inc., Totowa, NJ), which provides dosing and equipment sizes based on the length of the child. Cricothyrotomy is impossible

in small children, and alternative rescue airway devices (e.g., percutaneous oxygenation via the cricothyroid membrane) are required.

Other Airway Devices and Techniques

Regardless of the care taken by the intubator and the detailed assessment of the patient before intubation, some intubations are simply unsuccessful or impossible. In most circumstances when intubation is not possible, BMV or ventilation using an EGD provides adequate ventilation and oxygenation until a rescue airway can be established. This underscores the importance of evaluating the patient for ease of intubation, ventilation, and EGD use before deciding on the best approach and initiating the intubation sequence. Over the past 10 years, there has been a revolution in airway management, based primarily on the incorporation of video and fiberoptic technology into laryngoscopes and stylets. In addition, increasing experience with extraglottic devices and other approaches has proved useful both for routine and difficult or failed airways.

Extraglottic Devices

Laryngeal Mask Airway. The laryngeal mask airway (LMA) is an irregular, ovoid, silicone mask with an inflatable rim, connected to a tube that allows ventilation (Fig. 1-10). It is available in both reusable and single-use configurations; single-use models are offered by several manufacturers and are probably equivalent.[104] The mask is inserted blindly into the pharynx, then inflated, providing a seal that permits ventilation of the trachea with minimal gastric insufflation. In elective anesthesia, the LMA has an extremely high insertion success rate and low complication rate, including a low incidence of tracheal aspiration.[105,106] In the emergency setting, studies to date have focused on use during resuscitation from cardiopulmonary arrest, although data are beginning to emerge for use of the LMA as a rescue device in the event of failed intubation and as an alternative to direct laryngoscopy for intubation or a bag-valve-mask for ventilation.[107] Evaluations of LMA insertion by experienced and inexperienced personnel consistently have shown ease of insertion, high insertion success rates, and successful ventilation.[108] Novice users appear to be able to both ventilate and intubate more easily and successfully with the intubating LMA (ILMA) than by bag-mask ventilation and direct laryngoscopy.[108] The LMA may be a viable alternative to endotracheal intubation for in-hospital or out-of-hospital treatment of cardiac arrest, particularly when responders are inexperienced airway managers. At a minimum, the device may serve a temporizing role equal or superior to BMV until definitive airway management can be achieved. A new form of LMA, the iGel, has a viscous gel within the cuff, so does not require inflation. Initial experience with the device, even with minimally trained novice users, is promising, with high insertion success rates and short insertion times.[109]

The ILMA is designed to facilitate intubation through the mask after correct placement (Fig. 1-11). It differs from the LMA in two main ways: The mask is attached to a rigid, stainless steel ventilation tube that is bent almost to a right angle, and the mask incorporates an epiglottic elevator at its distal end. Placement of the ILMA results in successful ventilation in almost 100% of cases and successful subsequent intubation in 95%.[97,110-112] The ILMA can also be used for both ventilation and intubation in obese patients with similarly high success rates.[113] The ILMA has a special ETT and a stabilizer rod to remove the mask over the ETT after intubation is accomplished, but intubation can be comparably successful with a conventional polyvinylchloride (PVC) endotracheal tube.[114]

The ILMA is a better device than the standard LMA for use in the ED because it facilitates both rescue ventilation and intubation. Intubation through the ILMA has compared favorably in terms of success with direct laryngoscopy and is superior in the hands of relatively novice intubators.[108,110] When the ILMA is placed, intubation can be performed blindly or guided by a lighted stylet or a fiberoptic scope. The ILMA comes only in sizes 3, 4, and 5 and so is not suitable for use in patients weighing less than about 30 kg. For smaller patients, the standard LMA, which has sizes down to size 1 (infant), should be used. Intubation can be achieved through the standard LMA,

Figure 1-10. The standard laryngeal mask airway (LMA Classic) is available in sizes from infant to large adult. (Courtesy LMA North America, Inc., San Diego.)

Figure 1-11. The intubating laryngeal mask airway is modified to facilitate insertion of an endotracheal tube after placement and ventilation are achieved. The epiglottic elevator (*triangle*) lifts the epiglottis to allow passage of the special ETT (*arrow*).

but the success rate is significantly less than with the ILMA. As experience with both the LMA and ILMA grows, it is likely that there will be increasing adoption of the LMA as a primary airway management technique by nonhospital first-responders, and the ILMA is gaining attention as a primary rescue device in the ED.

A new version of the ILMA, the CTrach incorporates fiberoptic bundles and a detachable viewing screen to provide a view of the glottis during intubation. The device performs better than the standard ILMA for first attempt intubation, where it achieves almost 93% success versus approximately 80% for the ILMA in one well-conducted study.[115] Ultimately, though, the ILMA's intubation success rate is so high (on three or fewer attempts) that it is not clear that the CTrach provides additional benefit overall. The view can uncommonly be obscured by secretions, but this is easily solved by removing and reinserting the device, or cleaning it with a swab through the airway lumen.[116] The greatest issue is cost, with the CTrach priced almost five times higher than the corresponding set of standard ILMAs. Whether the additional cost provides additional benefit for application in the ED remains to be seen.

In the ED, the primary use of the LMA or ILMA is as a rescue technique to provide a temporary airway when intubation has failed, bag ventilation is satisfactory, and the patient has been paralyzed or is otherwise in need of immediate airway management. In such cases, the LMA is one of numerous acceptable devices. In the "**can't** intubate, **can't** ventilate" situation, cricothyrotomy is indicated, but an ILMA may be placed rapidly in an attempt to achieve ventilation (converting the situation to "**can't** intubate, **can** ventilate") as long as this is done in parallel with preparations for cricothyrotomy and does not delay the initiation of a surgical airway.[107] Availability of the LMA and adequate prior training of the clinician offer a legitimate option for the management of the failed airway, and the ILMA compares well with fiberoptic intubation in terms of successful intubation of difficult airways.[112] The standard LMA may also offer advantages for providing ventilation in unconventional positions, such as when the patient is lying on his or her side.[117] In the out-of-hospital setting, where concerns about esophageal placement of ETTs have focused interest on methods used for airway management, the LMA and Combitube offer excellent placement and ventilation characteristics and may be preferable to endotracheal intubation in this setting, especially when intubation is relatively infrequently performed.[118] If the patient is in a difficult position in terms of intubation access, the LMA may facilitate more rapid ventilation.[119] New LMA devices, from a number of manufacturers, are now available.

Esophagotracheal Combitube. The Combitube is a plastic double-lumen tube with one lumen functioning as an airway after esophageal insertion and the other lumen functioning as a tracheal airway (Fig. 1-12). The tube is placed blindly into the esophagus, and proximal and distal balloons are inflated to prevent escape of ventilatory gases through the pharynx to the mouth or nose or down the esophagus. The tube is placed into the esophagus, as designed, almost 100% of the time, but both lumens are patent, so ventilation is still possible if the tube has been placed inadvertently into the trachea.

The Combitube is primarily a substitute for endotracheal intubation for non-ETT-trained personnel, but it also has a role as a primary airway device in place of endotracheal intubation in the out-of-hospital setting.[120] It has been used as a rescue device or as a primary intubating device in difficult airways that have precluded endotracheal intubation or successful LMA placement, both in patients with and those without cardiac arrest.[121,122] Serious complications attributable

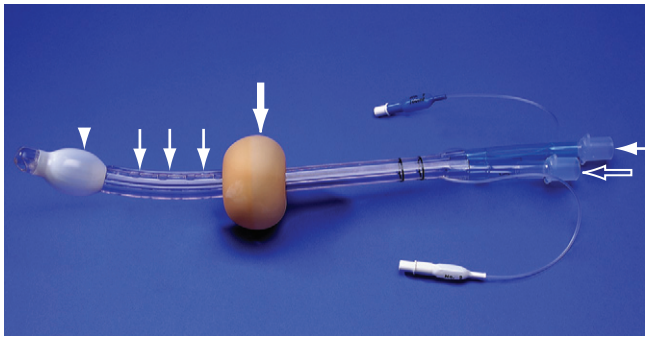

Figure 1-12. The Combitube is inserted through the mouth blindly, although a laryngoscope can be used, if desired. It seats itself in the esophagus more than 95% of the time, and ventilation is performed through the proximal lumen and side ports (*white arrows*) after inflation of the two balloons. The lower balloon (*triangle*) occludes the esophagus. The upper (large) balloon (*thick arrow*) occludes the oropharynx. If the tube is in the trachea, the alternate lumen (*clear arrow*) is used for ventilation.

to Combitube use are uncommon.[123] The tube may be difficult to insert blindly when the patient is in cervical spine precautions, raising concerns about first-responder use in trauma patients, but results have been conflicting.[124,125] Standard methods for confirming tube placement, using $ETCO_2$, seem to be reliable in identifying whether the tube has been passed into the esophagus or trachea and in confirming the correct ventilation port.

Although the Combitube has provided successful ventilation for several hours, it should be considered a temporizing measure only. Current use in the ED should be restricted to rescue placement after failed oral intubation with adequate BMV or a quick maneuver in the "**can't** intubate, **can't** oxygenate" patient simultaneous with preparation for a cricothyrotomy (analogous to the use of the ILMA in this situation). The Combitube has virtually no role in the ED as a primary airway management device except in cases of cardiopulmonary arrest when expertise for endotracheal intubation is not available.

Video Laryngoscopes

New devices incorporate video imaging into modified laryngoscopes to allow superior visualization of the glottis without the need to create a straight-line visual axis through the mouth. The Glidescope uses an extended Macintosh blade with a sharply angulated tip to direct the video camera at the glottis, even in patients with difficult airways (Fig. 1-13). When compared with direct laryngoscopy, the Glidescope provides an equivalent or superior glottic view, and has a very high intubation success rate.[126,127] The Glidescope appears to cause less cervical spine movement than conventional direct laryngoscopy with a Macintosh blade.[101] The C-MAC video laryngoscope (Fig. 1-14) incorporates a complementary-metal-oxide-semiconductor (CMOS) video chip into otherwise conventional laryngoscope blades, to enhance glottic view. Other videolaryngoscopes are available or under development. Overall, videolaryngoscopy offers the promise of transforming laryngoscopy and has the potential to render conventional, direct laryngoscopy obsolete.[128]

Fiberoptic Intubating Stylets

Several rigid fiberoptic intubating stylets have also been approved and adopted into clinical use.[129] The Shikani Optical Stylet (SOS—Clarus Medical, Minneapolis, Minn.) is the most studied of these. The endotracheal tube is placed over the

Figure 1-13. The GlideScope (Verathon, Inc.) is a video laryngoscope that uses a 50° deflection of the distal tip of the blade (which is otherwise similar to an extended MAC-3 blade) to direct the video camera and light source directly at the glottis without repositioning the head. The endotracheal tube insertion is done under direct vision via the video screen. (From Walls RM, Murphy MF [eds]: Manual of Emergency Airway Management, 3rd ed. Philadelphia, Lippincott Williams & Wilkins, p. 171, 2008, with permission.)

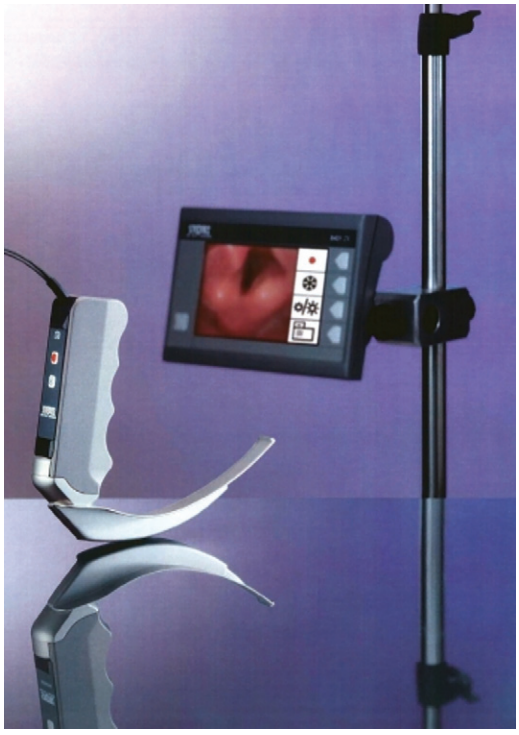

Figure 1-14. The C-MAC video laryngoscopy (Karl Storz Endoscopy) uses an integrated CMOS video chip to capture a video image from near the distal tip of an otherwise conventional laryngoscope blade. The image is conveyed to a video screen where it is viewed by the intubator. (From Walls RM, Murphy MF [eds]: Manual of Emergency Airway Management, 3rd ed. Philadelphia, Lippincott Williams & Wilkins, p. 173, 2008, with permission.)

malleable stylet, then advanced through the mouth in the midline and into the trachea using built-in fiberoptic visualization (Fig. 1-15). The SOS appears to cause less movement of the cervical spine than conventional laryngoscopy during intubation with in-line stabilization.[99] A simpler version, the Levitan scope, uses an LED-illuminated fiberoptic stylet to facilitate intubation by direct laryngoscopy.[128] The device is recommended by the manufacturer to facilitate first-pass success when a limited glottic view is obtained by direct laryngoscopy. In the only study comparing the Levitan scope to the gum-elastic bougie, however, the two devices performed

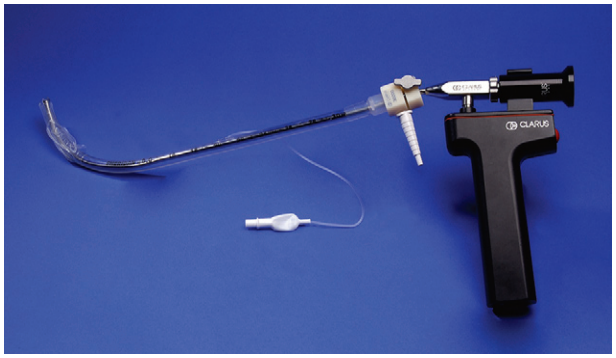

Figure 1-15. The Shikani optical stylet (SOS, Clarus Optical) with endotracheal tube mounted. The eyepiece and battery pack are at the right.

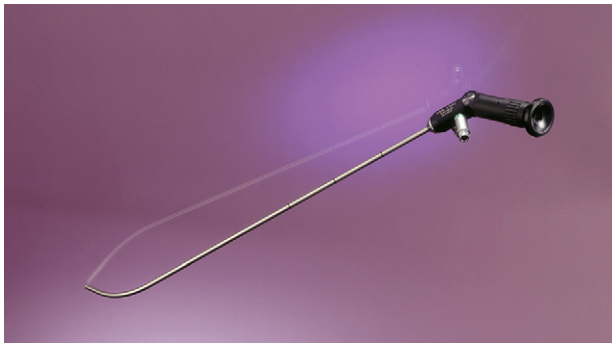

Figure 1-16. The Bonfils intubating fiberscope (Karl Storz). The endotracheal tube is mounted on the stylet, and intubation is facilitated through the eyepiece at right.

similarly.[130] The Bonfils intubating fiberscope (Karl Storz Endoscopy of America, Culver City, Calif.) functions as a retromolar intubating stylet (Fig. 1-16). The ETT is loaded directly onto the nonmalleable fiberoptic stylet, then guided along the cheek and directed around posterior to the back molar, then through the glottic aperture by direct fiberoptic visualization.[128,129]

Flexible Fiberoptic Scopes

Intubation using a flexible fiberoptic scope is increasingly applied to difficult airways in the ED, after many years of use for similar applications in the operating room. The intubating fiberoptic bronchoscope can be passed through the vocal cords under fiberoptic visualization, then can serve as an introducer over which the ETT is passed. Fiberoptic examination facilitates airway assessment for the need for intubation, without definitely committing the patient to intubation, as is the case when an NMBA is administered for RSI. For example, in a patient with smoke inhalation, examination with the fiberoptic scope might identify that intubation is not required, but will also facilitate intubation when it is indicated. Intubation of morbidly obese patients, those with distorted airway anatomy (e.g., penetrating or blunt anterior neck injury), or those with fixed cervical spine deformity, can be achieved using the fiberoptic scope, topical anesthesia, and moderate (procedural level) sedation, thus preserving the patient's ability to breathe until intubation is achieved. The fiberoptic scope also has been used successfully in concert with the ILMA to achieve intubation in difficult cases, including when the cervical spine is immobilized, where it significantly outperforms conventional laryngoscopy.[131]

There is a significant learning curve for flexible fiberoptic intubation, and fiberoptic examination of the upper airway in

patients with pharyngitis or odynophagia, for example, is helpful, as it requires the same "navigation skills" as are required for intubation. Use of a video attachment for instruction, so that the instructor and learner can simultaneously see the same image appears to enhance learning.[132] Models have been created to allow learners to navigate through a series of openings and around barriers, which also increases subsequent intubation performance.[133]

The role of flexible fiberoptic intubation in the ED is greatly expanding, as obesity increases in the population, and, increasingly, difficult airways are handled in the ED without backup. The transition from fiberoptic to CMOS video technology should make these flexible scopes more durable, less prone to fogging, and less expensive—all desirable attributes for emergency intubation. Emergency physicians should have immediate access to fiberoptic scopes and should endeavor to acquire training and practice in their use. Fiberoptic scopes are of great value in the patient with predicted difficulty in direct laryngoscopy, EGD use, and BMV. The expanding use of video laryngoscopy will redefine the role of flexible fiberoptic scopes, as video laryngoscopy solves many of the difficulties that occur with direct laryngoscopy.

Other Intubation Techniques

Retrograde Intubation. In retrograde intubation, a flexible wire is passed in retrograde fashion through a cricothyroid membrane puncture. The wire is retrieved through the mouth, then used to facilitate intubation by serving as a guide over which the ETT is passed. Purported advantages of retrograde intubation include ease of learning and application to the difficult airway. Although retrograde intubation theoretically may be useful when the upper airway is disrupted by trauma, rendering oral intubation difficult or impossible, it is unlikely to be used in the ED except in circumstances in which alternative devices, such as fiberoptic intubation, Trachlight, Combitube, and cricothyrotomy, are unavailable. Published reports of its use in emergency circumstances have been limited to case reports, very small series, and review articles. It is doubtful whether retrograde intubation would ever be the airway maneuver of first choice in the ED, but it may be a useful consideration in rare, unique difficult airway cases.

Lighted Stylet. The lighted stylet is a device that incorporates a handle, a fitting for mounting an ETT, and an intubating stylet with a fiberoptic light mounted on the end (Fig. 1-17). The ETT is mounted as on a conventional intubating stylet, but transillumination of the soft tissues from within the neck permits identification of tracheal entry by the stylet and ETT. The lighted stylet has been used for oral and nasal intubation and has an excellent success rate.[134] The lighted stylet is less stimulating to the heart rate and blood pressure than conventional laryngoscopy and may be useful when sympathetic stimulation is not desirable.[135] Although overall success rates with the Trachlight lighted stylet have been high, it may be more difficult for novice intubators to learn than conventional laryngoscopy, if only minimal manikin training is used.[136] The Trachlight can be used as a primary intubating device or as a rescue device in the "**can't** intubate, **can** ventilate" failed airway. It is not appropriate for the "**can't** intubate, **can't** ventilate" failed airway, when cricothyrotomy is indicated. As a device for a difficult airway, the lighted stylet can be used as the intubating stylet for a standard oral intubation. The direct illumination by the stylet can aid in visualization during intubation. If direct laryngoscopy is unsuccessful, the first rescue procedure could be an immediate attempt at blind, oral intubation using the lighted stylet, as long as ventilation is possible. There is also some evidence that the Trachlight produces less cervical spine motion than does direct laryngoscopy.[102]

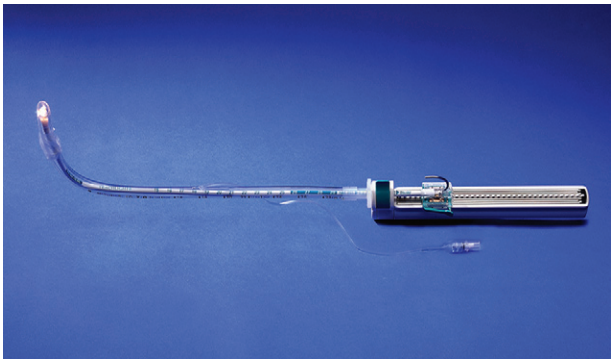

Figure 1-17. The Trachlight lighted stylet facilitates placement of the endotracheal tube when the glottis cannot be visualized by direct laryngoscopy. It also is used as a primary intubation device. Here the endotracheal tube is correctly mounted on the stylet.

Surgical Airway Management

Needle Cricothyrotomy with Transtracheal Jet Ventilation

Needle cricothyrotomy involves the insertion of a large needle (ideally 10-gauge) through the cricothyroid membrane into the airway. When inserted, the needle is used to ventilate the patient with a standard wall oxygen source. Because of the high-velocity ventilation that ensues through the narrow catheter, this procedure is called *transtracheal jet ventilation*. Transtracheal jet ventilation has been used successfully in humans and has been subjected to various animal experiments to determine its uses and limitations. It rarely has been used in patients in EDs, however, where its role as a rescue device in the "**can't** intubate, **can't** ventilate" situation is vastly inferior to cricothyrotomy.

The jet ventilator should include a regulator and gauge so that pressures can be monitored and reduced, especially in children (Fig. 1-18). Upper airway obstruction has been considered a contraindication to transtracheal jet ventilation, but ventilation still can be successful, although at the cost of higher intrapleural pressure and possibly pulmonary barotrauma. In general, when upper airway obstruction is present in adults, percutaneous or surgical cricothyrotomy is preferred.

The primary indication for transtracheal ventilation in the ED is the initiation of emergency oxygenation for a pediatric patient who is apneic (either because of the presenting condition or because of administration of an NMBA) and in whom intubation and BMV are impossible. Cricothyrotomy is extremely difficult or impossible in children younger than 10 years old, and transtracheal ventilation should be considered the surgical rescue modality of choice in this age group. For children younger than 5 years old, bag ventilation is used with the percutaneous catheter, and pressurized devices are avoided.[67]

Cricothyrotomy

Cricothyrotomy is the creation of an opening in the cricothyroid membrane through which a cannula, usually a cuffed tracheostomy tube, is inserted to permit ventilation. The techniques, and variations thereof, are well described elsewhere.[137] When surgical airway management is required, cricothyrotomy is the procedure of choice in the emergency setting, where it is faster, more straightforward, and more likely to be successful than tracheotomy.

Cricothyrotomy is indicated when oral or nasal intubation is impossible or fails and when BMV cannot maintain adequate oxygen saturation (the "**can't** intubate, **can't** ventilate" situation). Several large series have established that the incidence of cricothyrotomy is approximately 1% of all ED intubations.[1,39]

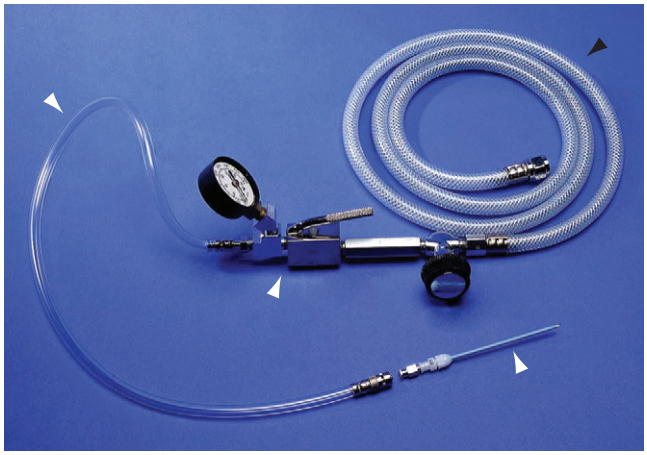

Figure 1-18. Transtracheal jet ventilation. High-pressure ventilation tubing (*black triangle*) attaches to standard wall oxygen outlet at 55 psi. Ventilation block (*middle white triangle*) is used to control oxygen flow through tubing (*top left white triangle*) to catheter (*lower right triangle*), which is inserted in the airway.

Cricothyrotomy is relatively contraindicated by distorted neck anatomy, preexisting infection, and coagulopathy; these contraindications are relative, however, and the establishment of the airway takes precedence over all other considerations. Successful cricothyrotomy after systemic fibrinolytic therapy has been reported.[138] The procedure should be avoided in children younger than 10 years old, in whom anatomic considerations make it exceedingly difficult.[67] Studies suggest that approximately five "practice" cricothyrotomies on a simulator or animal model are sufficient to achieve at least baseline capability with the procedure.[139]

Cricothyrotomes are devices used to perform percutaneous cricothyroidotomy. Percutaneous cricothyrotomy using the Seldinger technique appears comparable to formal open cricothyrotomy in terms of ease of learning and success rates.[140] The safety and effectiveness of other cricothyrotomes are not clearly established. A recently released kit by Portex offers a small red flag indicator to warn when the posterior tracheal wall is touched, but a cadaver study showed that, although the device resulted in somewhat faster placement of an airway than did a Seldinger technique, the incidences of both failure and major complications (posterior airway wall laceration) were unacceptably high, so the device cannot be recommended.[141] Only two percutaneous cricothyrotomy sets on the market currently have the ability to place a cuffed tracheostomy tube. One is a dedicated Seldinger cricothyrotomy set; the other is a combination set that has all necessary equipment for either a Seldinger percutaneous cricothyrotomy or a standard surgical cricothyrotomy (Melker universal cricothyrotomy kit; Cook Critical Care, Bloomington, Ind.) (Fig. 1-19).

OUTCOMES

Few studies of emergency airway management have characterized complications and outcomes. The largest single-institution series reported a success rate for ED RSI of 99% and a complication rate of 9.3%; most complications were minor.[14] Phase II of the large National Emergency Airway Registry Study (NEAR II) of almost 9000 ED intubations reported success rates of approximately 97% for RSI. The NEAR classification system characterizes potentially adverse occurrences during intubation as "adverse events."[1,39,142] In the NEAR study, the observed rate of adverse events was approximately

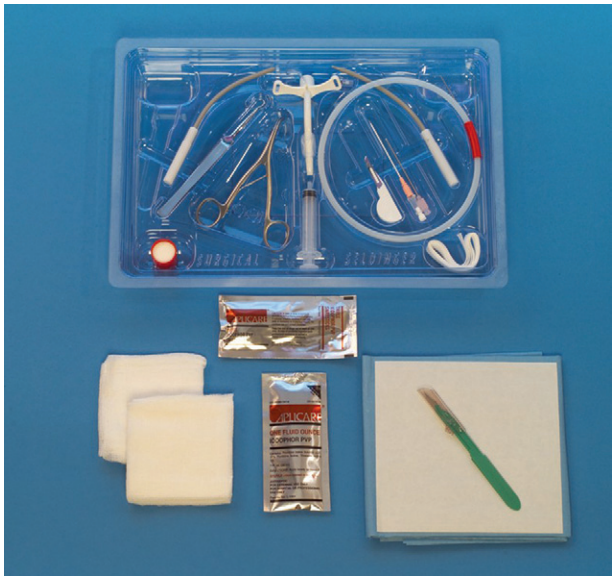

Figure 1-19. Melker universal cricothyrotomy kit. (Courtesy of Cook Critical Care.) (Disclosure: The author assisted in the design of this kit and receives a 10–35% royalty on its sales.)

9% in medical patients and 8% in trauma patients, and most of these were minor.[1] No studies have evaluated the long-term outcome of intubated ED patients.

KEY CONCEPTS

- Knowledge of the clinical course of the patient's condition and anticipation of possible deterioration are crucial to the decision to intubate, especially if the patient is to leave the ED for a time (e.g., interfacility transfer, diagnostic testing).
- Assessment of the patient for potential difficulty with intubation, bag-mask ventilation (BMV), ventilation using an extraglottic device (EGD), and cricothyrotomy is an essential step in planning airway management. The mnemonics LEMON, MOANS, and RODS can serve as useful aids.
- In the absence of a "crash" patient (agonal, unresponsive to laryngoscopy) or a difficult airway, RSI is the airway management method of choice for ED patients.
- Succinylcholine is the NMBA of choice for ED RSI, but it should be avoided in certain patient groups because of risk of significant hyperkalemia.
- Pretreatment drugs given during RSI can mitigate adverse responses to intubation and improve the patient's clinical condition.
- Tube placement confirmation using end-tidal CO_2 ($ETco_2$) is essential after intubation, and failure to detect adequate quantities of exhaled CO_2 is evidence of esophageal intubation until proven otherwise.
- Videolaryngoscopy is transforming intubation by eliminating the traditional anatomic barriers to direct laryngoscopy. Emergency practitioners should evaluate video laryngoscopes for incorporation into their practice, both for difficult and routine intubations.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 2

Mechanical Ventilation and Noninvasive Ventilatory Support

Megan L. Anderson and John G. Younger

PERSPECTIVE

Invasive and noninvasive ventilation are essential tools for treatment of critically ill patients. The indications for endotracheal intubation (ETT) and for assisted ventilation in the emergency department (ED) are not always the same. Some patients require support for respiratory failure or as part of comprehensive management of critical illness, while others' cardiopulmonary function may be preserved and assistance is needed primarily for airway protection.

The decision to intubate is discussed in Chapter 1 and in various other places throughout this textbook in the context of individual conditions. This chapter describes the modalities and techniques of mechanical ventilation.

FUNDAMENTALS

Invasive Techniques

Once the need for ventilatory support has been identified, three questions must be answered to initiate support: (1) What will constitute a breath—a delivered tidal volume or a delivered airway pressure? (2) To what extent will the patient be allowed to participate in breathing? (3) How will the support be delivered—by endotracheal tube or by some noninvasive means? These three are typically referred to, in order, as the *cycle* or *limit*, the *mode*, and the *method* of mechanical ventilation. Regardless of the specific method used, an oxygenated mixture of gases, usually warmed and humidified, is cyclically forced into the lungs under supra-atmospheric pressure during the inspiratory phase and allowed to exit passively during expiration.

In pressure-limited, or cycled, ventilation, a breath is defined by the peak inspiratory pressure (PIP) that is achieved each cycle. When that pressure is reached, gas insufflation ends, and passive exhalation is permitted; the delivered tidal volume is thus a function of dynamic lung compliance. An advantage of pressure-cycled ventilation is that it serves as an explicit safeguard against iatrogenic, injurious high airway pressures. A significant disadvantage is the possibility of hyper- or hypoventilation in the event of an acute change in lung compliance during therapy.

In volume-cycled ventilation, inhalation ends when a preset tidal volume has been delivered, and inspiratory pressure varies with the inverse of lung compliance. The benefit to this method is the ability to control tidal volume; the risk is potentially high peak pressures when compliance is poor. There is no consensus regarding which approach to positive-pressure ventilation is better; pressure- and volume-cycling are opposite sides of the same coin, and both strategies are used clinically.

The most commonly available modes of positive-pressure ventilation are (1) controlled mechanical ventilation (CMV), (2) assist/control (A/C) ventilation, and (3) synchronized intermittent mandatory ventilation (SIMV), all of which can be supplied through either pressure-cycled or volume-cycled ventilators. Two main factors differentiate these modes from one another: (1) how a breath is *triggered* (at a preset fixed rate or by a patient's inspiratory effort sensed by the ventilator), and (2) the target capacity (pressure or volume) for each breath.

During CMV, the ventilator delivers breaths at a preset rate, regardless of any ventilatory effort made by the patient. A person receiving CMV can neither trigger a breath nor inspire gas spontaneously through the ventilator circuit, so this mode is appropriate only for apneic, pharmacologically paralyzed, and deeply sedated patients. In contrast, a ventilator applying A/C mode continuously monitors the ventilator circuit for either negative pressure or air flow deflections (generated by spontaneous inspiratory effort) and responds with a full breath. In the absence of any such patient effort, the device automatically cycles at a preset minimum "backup" rate. For example, if an A/C ventilator is set to deliver 12 breaths per minute, a breath is provided every 5 seconds in the absence of spontaneous inspiratory effort. Should a patient attempt to inspire, an additional breath is provided and the ventilator's timer resets for another 5 seconds. Thus a patient can breathe at a higher rate than the programmed A/C rate, with an attendant increase in work of breathing. A/C ventilation is a useful initial mode of mechanical ventilation in many ED patients. Commonly encountered disadvantages of this mode include poor tolerance in awake patients (often resulting in frequent elevated airway pressure alarms and underventilation) and worsening of intrathoracic air trapping in patients with chronic obstructive pulmonary disease (COPD).[1]

SIMV is a more complex mode developed to improve patient comfort by facilitating patient-device synchrony. The delivery of a mandatory breath is synchronized as much as possible with a patient's spontaneous respirations, preventing breath *stacking* (i.e., the delivery of a mechanical breath before the previous breath has been completely exhaled). Stacking may result in hyperinflation and barotrauma.[2] If spontaneous breathing occurs at a rate equal to or lower than the preset ventilator rate,

the patient's inspiration, or an elapsed time, triggers the next breath delivery. If the patient's spontaneous breathing is faster than the established SIMV rate, the patient breathes gas from the ventilator circuit and receives a volume consistent with his or her inspiratory effort, in addition to regular breaths at the set tidal volume and rate, which are triggered by the patient and delivered by the ventilator.

Regardless of the ventilatory mode chosen, additional refinements are available and commonly used. The most important of them is positive end-expiratory pressure, or PEEP. PEEP and continuous positive airway pressure (CPAP), a closely related entity, refer to the maintenance of positive airway pressure after the completion of passive exhalation. By convention, PEEP refers to pressure applied during invasive mechanical ventilation, whereas CPAP is the application of positive pressure (invasively or noninvasively) during spontaneous breathing. The terms are occasionally used interchangeably. Acute lung injury and cardiogenic pulmonary edema are characterized by loss of surfactant function. The chief beneficial effect of PEEP or CPAP is to increase functional residual capacity (FRC) by maintaining patency of injured or flooded alveoli that would otherwise collapse at the end of exhalation. Increasing the FRC may improve both oxygenation and lung compliance. One of the potential adverse effects of PEEP is decreased cardiac output.

Pressure support ventilation (PSV) is another adjunct in which breathing is controlled by the patient, and peak pressures are controlled by the ventilator. The primary goal of PSV is to support the patient's spontaneous breathing effort while providing satisfactory oxygenation. PSV provides for the prompt attainment of a preset PIP each time the patient initiates inspiratory effort. Inspiratory time, inspiratory flow rate, and tidal volume (TV) are augmented, whereas inspiratory work of breathing is reduced. The machine likewise senses the end of inspiration or initiation of exhalation, at which time the pressure support ceases, and exhalation is allowed to proceed spontaneously. Increasing levels of PSV decrease the work of breathing.[1] PEEP may be added to PSV, and a mandatory ventilation rate can be set in case spontaneous respirations deteriorate, typically using SIMV.

PSV first was used as a weaning tool, but some authorities now recommend it as a primary means of ventilatory support. Careful monitoring is necessary during its use because TV is uncontrolled. Invasive ventilation with PSV is rarely used in the ED, but PSV may be applied noninvasively.

Applied PEEP must be differentiated from *intrinsic* PEEP (iPEEP, or auto-PEEP), which may result from improper assisted ventilation when adequate time is not allowed between breaths for complete exhalation. This circumstance is discussed later.

Noninvasive Techniques

Noninvasive positive-pressure ventilation (NPPV) includes CPAP or biphasic positive airway pressure (BiPAP) and is applied with a face or nose mask. CPAP provides constant pressure throughout the respiratory cycle, and its benefits were discussed earlier in relation to PEEP. BiPAP alternates between higher pressure during inspiration (IPAP) and lower pressure during expiration (EPAP). The machine senses and responds to the patient's respiratory efforts. EPAP splints airways open and prevents alveolar collapse and atelectasis. IPAP decreases the work of breathing and improves TV (Fig. 2-1).

MANAGEMENT

Invasive versus Noninvasive Approach

Alert patients with a patent airway and an intact respiratory drive, even if that drive is insufficient, may be candidates for NPPV. Patients most likely to respond to NPPV in the ED are those with more readily reversible causes of their distress, such as COPD exacerbation or cardiogenic pulmonary edema, in which fatigue is a significant factor.[3-6] Patient selection, comprehensive management of the underlying condition, and ongoing monitoring are essential for successful NPPV. NPPV

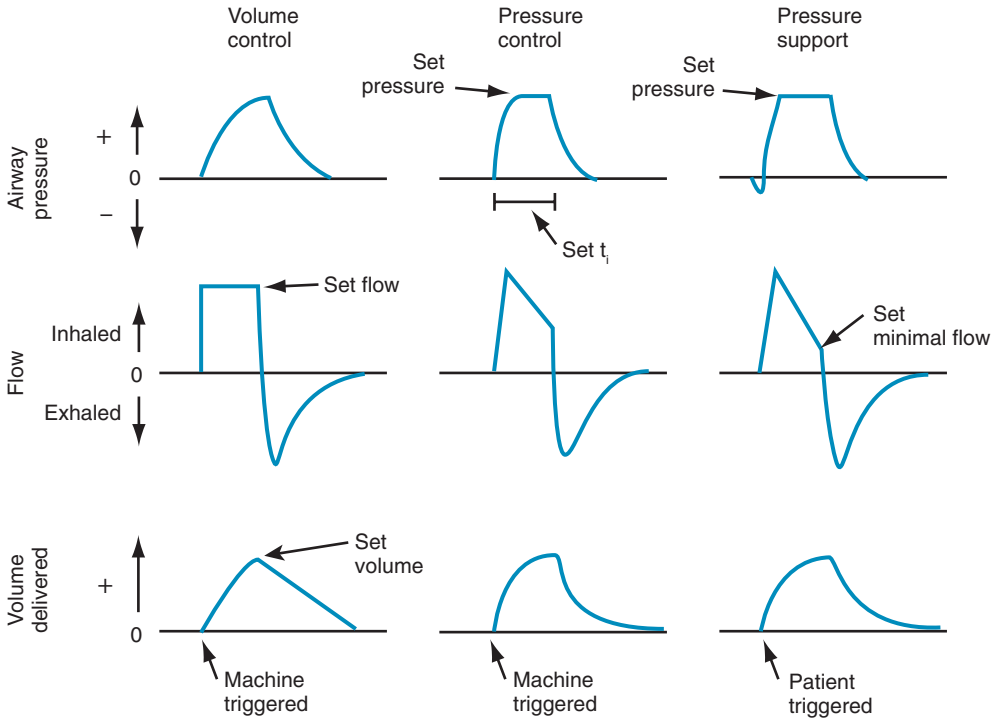

Figure 2-1. Pressure, flow, and waveforms typically encountered during mechanical ventilation in the emergency department. The nature of fresh gas delivery during mechanical ventilation is in part a function of the definition of "breath" (i.e., a delivered volume or delivered pressure) and the means by which that breath is initiated (i.e., by the patient or by a timing decision made by the ventilator). In practice, only a handful of ventilator parameters commonly are managed in the emergency department (the mode, the magnitude of the delivered breath, the rate of delivery, and FiO_2). However, as this figure shows, a number of additional features can be fine-tuned to optimize the effectiveness and comfort of mechanical ventilation in critically ill patients. (Modified from Mason RJ: Murray and Nadel's Textbook of Respiratory Medicine, 4th ed. Philadelphia: Elsevier, 2005.)

has been shown to be a beneficial initial intervention for both congestive heart failure (CHF) and COPD.[7,8] Although studies have significant flaws, they have consistently demonstrated reduced need for intubations in both conditions, as well as a mortality benefit in COPD patients. In COPD, NPPV decreases the work of breathing and splints airways open, improving ventilation-perfusion matching.[7] Predictors for success in COPD include younger age, unimpaired consciousness, less severe acidemia, and prompt response (less than 2 hours), as measured by heart rate, respiratory rate, and gas exchange. Predictors for failure in COPD include a Glasgow Coma Score less than 11, an arterial pH less than 7.25, and tachypnea greater than 30 breaths per minute.[9] In CHF, NPPV reduces work of breathing, improves cardiac output by decreasing preload and afterload, redistributes lung water, and improves ventilation-perfusion matching thereby reducing shunt. However, although symptoms during acute exacerbations of CHF are improved, a mortality benefit has not been detected.[10] Some trials have used NPPV for hypoxemic respiratory failure such as in pneumonia; however, the results are not clearly beneficial.[8,11]

Contraindications to NPPV include severely impaired level of consciousness, cardiac arrest, acute MI, inability to protect airway, apnea, copious secretions, uncontrolled vomiting, upper airway obstruction and facial trauma.[11]

Patients in whom NPPV is initially chosen should be reassessed frequently for progress of therapy, tolerance of the mode of support, and any signs of clinical deterioration that indicate a need for intubation. NPPV is an attractive alternative to ETT because it reduces the risks of airway trauma and ventilator-acquired pneumonia and may be helpful in patients who decline intubation. NPPV also may be considered for a patient whose advanced directives proscribe intubation. An individualized approach is important, and discussion with the patient and family members may be helpful.[12]

Initial Settings and Ongoing Monitoring

Recommended initial settings for BiPAP ventilators are an IPAP of 8 cm H_2O and an EPAP of 3 cm H_2O. Either a face mask or a nose mask can be used. The flow of supplemental oxygen bled into the circuit should be governed by pulse oximetry, as corroborated by arterial blood gas (ABG) results; it is appropriate to initiate therapy with 3 to 5 L/min of supplemental oxygen, but this should be adjusted with each titration of IPAP or EPAP. The ventilator should be in spontaneous mode to support the patient's respiratory effort.

As the patient's response to NPPV and other therapy is monitored (using cardiac and blood pressure monitors, ABGs, and oximetry, and the patient's own voiced assessment of tolerance and progress), support pressures are adjusted. Although this adjustment must be individualized, a reasonable approach for BiPAP support in hypoxemic patients is to increase EPAP in 2-cm H_2O increments, with IPAP maintained at a fixed interval higher. Hypercapnia can be managed by increasing IPAP in 2-cm H_2O increments, with EPAP being increased in approximately a 1:2.5 ratio to IPAP.[6,13]

For the intubated patients, initial ventilator settings depend on the goal of the ventilatory intervention (mechanical ventilation, assisted ventilation, or PSV) and on the underlying cause of respiratory insufficiency. The basic parameters to be set in volume-cycled ventilators in CMV, A/C, IMV, and SIMV modes are fraction of inspired oxygen (Fio_2), TV, rate, and inspiratory/expiratory (I/E) ratio. (The I/E ratio reflects the duration of machine insufflation and the rest periods between them.) If atelectasis is a problem, PEEP should be added; the addition of PEEP may permit the use of more physiologic Fio_2 values as well. For an apneic or paralyzed patient, CMV, A/C, or IMV mode may be used. For a breathing patient with inadequate ventilatory effort, A/C is usually the best initial approach.

Reasonable initial ventilator settings are a TV of 6 to 8 mL/kg body mass and a rate of 12 to 14 breaths/min. Initial Fio_2 should be set at 1.0 but generally can be adjusted down quickly to maintain an oxygen saturation of 90% or greater. Ventilator settings are adjusted dynamically using pulse oximetry, end-tidal carbon dioxide monitoring, ventilation pressures, clinical status, and ABGs as a guide. PEEP, if indicated, should be initiated at 2.5 to 5 cm H_2O.

In pressure-cycled ventilators, the rate and Fio_2 are set as described earlier. An inspiratory pressure should be chosen that results in a TV of 6 to 8 mL/kg, usually 25 to 40 cm H_2O. There are additional specific considerations for many particular conditions (see section on Special Clinical Circumstances).

Mechanical ventilation is a dynamic process that requires constant monitoring and regular adjustment of these parameters. Tachycardia and hypertension can indicate ventilator intolerance and a need for increased sedation or adjustment of the ventilator settings. Bradycardia and ventricular irritability represent hypoxemia until this is disproved. Unless capnometry and pulse oximetry are in use, an ABG should be measured approximately 20 minutes after initiating support. These results indicate the sufficiency of ventilation (using the pH and arterial partial pressure of carbon dioxide, $Paco_2$) and oxygenation (using arterial oxygen partial pressure, Pao_2). Adjustments in minute volume (the product of TV and rate) and Fio_2 can be guided by baseline measurements supplemented by ongoing monitoring. To avoid oxygen toxicity, Fio_2 should be reduced to the lowest level that provides acceptable (≥90%) oxygen saturation. In many instances PEEP will allow better oxygenation for a given Fio_2.

Important ventilator readouts include the PIP and expiratory volume. PIP is among the most frequently referenced measures of ventilatory function during mechanical ventilation. It reflects lung compliance and airway resistance; changes in the magnitude of PIP may reflect any of several potentially detrimental problems related to ventilation.[14] In a practical sense, PIP can be considered an additional vital sign for patients on a ventilator. Acute decreases in PIP reflect inadequate volume delivery to the patient, which may be caused by insufficient gas supply to the ventilator, inadvertent change in settings, a leak in the breathing circuit, unintended extubation, or failure of the ventilator. Increases in PIP may indicate ETT occlusion by secretions in or kinking of the tube, acute bronchospasm, pneumothorax, or conditions causing decreased lung compliance such as the development of worsening pulmonary edema. PIP can serve as a useful measure of effectiveness of therapy in patients with asthma or COPD; as airway resistance lessens, the PIP decreases. High PIP may cause barotrauma and other acute lung injury.[15,16]

Measurement of expiratory volume and expiratory flow allows estimation of the effectiveness of spontaneous respiratory efforts and, by comparing expiratory volume with the set TV, assessment of the effectiveness of ventilation and the integrity of the breathing circuit. The expiratory volume measurement is particularly important in assessing mechanical ventilation in children, who often have air leaks around an uncuffed ETT.

Patient Treatment

Even if a mechanically ventilated patient's stay in the ED is brief, attention must be paid to ventilatory management. Routine concerns are sedation, neuromuscular paralysis if

necessary, analgesia, and suctioning. Sedation and analgesia should be titrated to provide the greatest patient comfort and ventilation performance. In addition, a rapid and systematic approach should be taken to manage the patient who becomes suddenly difficult to oxygenate or ventilate.

An opioid (e.g., fentanyl or morphine) and a sedative agent (e.g., midazolam by intermittent bolus or infusion, or propofol by infusion) are commonly used for analgesia and sedation. Ketamine can provide both sedation and analgesia and is often used for children and patients with reactive airways disease. Prolonged neuromuscular paralysis can usually be avoided by the use of adequate sedation and analgesia (see Chapter 1). If neuromuscular blockade is required, a competitive, nondepolarizing agent, such as pancuronium, vecuronium, or rocuronium, is often selected.

Endotracheal suctioning should be performed regularly. The appropriate frequency is a balance between the need for clearing secretions (especially in pulmonary edema or asthma) and the disadvantage of interrupting ventilation, which can sacrifice gains in alveolar recruitment by allowing airway pressures to fall, even very briefly, to atmospheric levels. Orally intubated patients should have a bite-block placed to protect the endotracheal tube.

Complications

PPV is a lifesaving therapy. However, its use is associated with complications that can become quickly life-threatening, and it is important for emergency physicians to be familiar with common problems associated with PPV. Most of these result from changes in thoracic physiology when positive pressure is present for part or all of the respiratory cycle and are outlined in Box 2-1. Many of these are discussed elsewhere in this text.

Acute difficulty with oxygenation or ventilation, or the development of high airway pressures in a previously calm patient, may indicate undersedation or inadequate analgesia. Additional sedation is administered in concert with a systematic search for patient or device-associated abnormalities. The differential diagnosis, after initial acclimatization, includes ETT migration, ETT occlusion, pneumothorax, bronchospasm, pulmonary edema, acute pulmonary embolism, dynamic hyperinflation, abdominal distention, mechanical failure of the ventilator, and patient-ventilator asynchrony.[17] ETT placement can be checked by capnometry, physical examination, and chest radiography. ETT patency should be assessed by passing a suction catheter. In patients with copious secretions, the existence of a mucous plug acting as a "ball valve" in the endotracheal tube must be considered. This phenomenon presents as a sudden decrease in exhaled volume and elevated PIP, which responds immediately to suctioning but then quickly recurs.

The diagnoses of pulmonary edema, pneumothorax, and bronchospasm can be made clinically, with chest radiography used as an adjunct. Pulmonary embolism in a ventilated patient may be an even more elusive diagnosis than in other ED patients. Abdominal distention should be apparent on physical examination and is relieved by passage of a nasogastric or orogastric tube. Dynamic hyperinflation and ventilator malfunction may be diagnosed by momentarily disconnecting the ventilator. In the former circumstance, allowing full exhalation results in improvement; in the latter, the patient can be ventilated satisfactorily with a bag and 100% oxygen.

Patient-ventilator asynchrony may indicate incorrect ventilator mode selection, improper flow trigger sensitivity for A/C or SIMV modes, dynamic hyperinflation, or poor tolerance of mechanical ventilation despite sedation. In the last case, there is an indication for increased sedation and, if necessary, neuromuscular blockade.

Patients treated in the ED with NPPV generally should not be given sedatives or major analgesics because preservation of respiratory drive is essential to the use of this technique. Small, incremental doses of benzodiazepines for patients who have difficulty tolerating the face mask or nose mask may be useful.[18] Successful application of noninvasive methods is an acquired skill that takes advantage of not just drugs but of a calming bedside approach to frequently terrified patients. The authors' experience suggests that allowing family members to stay at the bedside to offer reassurance is often very helpful during the use of NPPV.

Intrinsic PEEP is an important issue, usually in patients with obstructive lung disease. In these cases, the expiratory flow rate is less than normal because of diminished elastic recoil from small airway obstruction (in emphysema) or because of dynamic airflow obstruction during exhalation (in reactive airway disease), or both. The time needed for intrapulmonary pressures to fall to ambient levels at the end of exhalation is prolonged. In spontaneously breathing intubated patients, iPEEP contributes to respiratory failure because this pressure must be matched by deep negative pressures generated by the respiratory bellows in order to initiate inhalation.[19] In mechanically ventilated patients, failure to anticipate prolonged expiration in patients with chronic obstructive or severe reactive lung disease risks setting a respiratory rate too high to allow complete exhalation. Breath stacking results, and unexpectedly high PIPs, patient distress, and hypotension can occur. In patients with chronic lung disease or severe asthma exacerbations who suddenly develop hypotension or become difficult to mechanically ventilate, an appropriate measure is to temporarily discontinue mechanical ventilation by switching to bag-valve breathing with deliberately prolonged exhalation. If this corrects the problem, then mechanical ventilation can be resumed by either using a slower respiratory rate or often with the aid of a respiratory therapist, customizing the inspiratory/expiratory duty cycle to allow the patient more time to exhale.

BOX 2-1 POTENTIAL ADVERSE EFFECTS OF POSITIVE-PRESSURE VENTILATION

- Increased intrathoracic pressure, leading to
  - Decreased venous return to the heart and decreased cardiac output
  - Increased ventilation/perfusion ratio
  - Air trapping and intrinsic positive end-expiratory pressure (iPEEP)
  - Barotrauma
- Nosocomial infections of the lungs and sinuses
- Respiratory alkalosis
- Agitation and increased respiratory distress
- Increased work of breathing due to asynchrony or improperly set triggers

Special Clinical Circumstances

In the following five common clinical indications for mechanical ventilation in the ED, special fine-tuning adjustments to the guidelines offered previously may be appropriate (Table 2-1).

Table 2-1 General Guidelines for Initial Invasive Ventilator Settings in Various Clinical Settings

	MODE*	Fio_2 (%)	TV (ML/KG)	RATE (BREATHS/MIN)	I/E RATIO	PEEP (CM H_2O)
Overdose in otherwise healthy patient	CMV, A/C, IMV, SIMV	100	8–10	10–12	1:2	0–5
Status asthmaticus	CMV, A/C, IMV, SIMV	100	5–10	8–12	1:4	2.5–10†
	PHC‡, CMV, IMV, SIMV	100	5–8	6–10	1:4	2.5–10†
COPD exacerbation, respiratory acidosis	CMV, A/C, IMV, SIMV	100	5–10	10–12	1:3–1:4	2.5–10†
	PHC‡, CMV, IMV, SIMV	100	5–8	8–12	1:3–1:4	2.5–10†
Cardiogenic pulmonary edema	CMV, A/C, IMV, SIMV	100	8–10	10–12	1:2	2.5–15
ARDS	CMV, A/C, IMV, SIMV	100	6–8	20–25	1:2	2.5–10
	Inverse ratio	100	6–8	8–12	1:1–1:2.1	2.5–5
Hypovolemic shock	CMV, A/C, IMV, SIMV	100	8–10	§	1:2	0–5

*CMV is the appropriate mode when the patient is apneic or paralyzed.
†PEEP in air-trapping diseases should not exceed measured intrinsic PEEP.
‡PHC is *permissive hypercapnia*, a ventilatory strategy that can be employed in multiple modes.
§Rate should be set based on desired $Paco_2$.
A/C, assist/control (ventilation); ARDS, acute respiratory distress syndrome; CMV, controlled mechanical ventilation; Fio_2, fraction of inspired oxygen; I/E, inspiratory/expiratory (ratio); IMV, intermittent mandatory ventilation; PEEP, positive end-expiratory pressure; SIMV, synchronized intermittent mandatory ventilation; TV, tidal volume.
When using a pressure-cycled ventilator, set pressures to deliver desired TV. After 20 minutes on initial settings, arterial blood gases should be checked so that settings and down-titrations of Fio_2 can be modified appropriately.

Acute Exacerbation of Chronic Obstructive Pulmonary Disease

In treating patients with COPD on the ventilator, respiratory acidosis should be corrected gradually over hours. Overcorrection or too-rapid correction of hypercapnia and acidosis may result in metabolic alkalosis, hypokalemia, and hypophosphatemia.[20] Hypoxemia usually is easily correctable by increasing Fio_2. Target values for Pao_2, $Paco_2$, and pH should reflect the patient's predicted (or known) baseline function rather than usual "normal" values.

The other major goal in the mechanical ventilation of patients with COPD is normalization of lung volume. Air trapping and resultant iPEEP in a patient with COPD increase the work of breathing and the likelihood of barotrauma with mechanical ventilation. Strategies used to address this problem center on reducing iPEEP. When inadequate expiratory time is allowed in the COPD patient, air trapping is exacerbated with each inspiration; this *dynamic hyperinflation* eventually results in a sufficiently high iPEEP that any additional breath necessarily overinflates the thorax. The immediate remedy for this problem is to disconnect the patient from the ventilator momentarily, allowing complete exhalation. The ongoing solution is to build adequate expiratory time into the ventilator settings. The rate should be kept as low as possible for patients with COPD, and the expiratory time should be maximized by increasing the I/E ratio to 1:3 or 1:4. The TV also should be minimized to reduce exhaled volumes. Often patients with COPD require higher flow rates (≥100 L/min) during inspiration to minimize inspiratory time. This approach allows more of the ventilatory cycle to be spent in exhalation. Each of these modifications in the settings reduces iPEEP.

The iPEEP also may be reduced by the use of bronchodilators and corticosteroids. These agents increase inspiratory muscle strength and reduce the amount of secretions in the bronchial lumen, both of which decrease the work of breathing. Finally, iPEEP can be replaced in part by extrinsic PEEP. PEEP at a level of no more than the measured iPEEP (some authors suggest no more than 85% of iPEEP) unloads the work required to maintain iPEEP and allows the recruitment of the muscles providing the inspiratory effort. A consensus statement has suggested that BiPAP should be the initial ventilatory assistance modality of choice in COPD exacerbation.[19]

Status Asthmaticus

Interventions aimed at reducing hypercapnia in ventilated patients with status asthmaticus may result in dynamic hyperinflation and barotrauma. The best approach in these patients, similar to that used in COPD, is small TV and high inspiratory flow rates to reduce inspiratory time and peak airway pressures. Airway pressures also can be lowered by *permissive hypercapnia*, which uses a low TV (5–8 mL/kg) *and* relatively low rates (8–10 breaths/min) to prevent excessive alveolar distention. $Paco_2$ is allowed to remain at supranormal values without ventilatory correction. The primary goal of permissive hypercapnia is the reduction of lung volume (and iPEEP) and the risk of barotrauma, while maintaining adequate oxygenation. This approach has not been studied thoroughly under controlled conditions, but permissive hypercapnia has potential applicability in status asthmaticus, acute respiratory distress syndrome, and severe COPD exacerbations.[21] Occasional external chest compression also may be useful in assisting exhalation in asthma. This concept has shown promise in animal and uncontrolled human trials.[22]

Acute Lung Injury

Acute lung injury (ALI) typically develops over several hours but may become evident in the ED. Pathophysiologically it is characterized by heterogeneous noncardiogenic pulmonary edema and surfactant failure that produces poor lung compliance and hypoxia. Pressure-limited special modes may be the optimal means of ventilating patients with ALI, but these techniques are often unavailable in the ED. On standard ventilators, settings should be adjusted to keep PEEP and Fio_2 as low as possible. Small TV (6–8 mL/kg) and fast rates (20–25 breaths/min) are indicated.[23] Although PEEP is considered primary therapy for ALI, these patients are highly susceptible to barotrauma. The risk of oxygen toxicity in ALI also is high and can be minimized by reducing the inspired oxygen concentration to the lowest level that maintains safe hemoglobin saturation levels. Sustained supraphysiologic oxygen tensions worsen inflammation. Iatrogenic barotrauma includes both mechanically induced tissue injury and the introduction of extrapulmonary air, such as pneumothorax or

BOX 2-2 VENTILATOR RECOMMENDATIONS FOR ACUTE LUNG INJURY (ARDSNET REFERENCE)

A/C, volume-cycled ventilation
Reduce TV to 6–8 mL/kg ideal body weight
Plateau pressures < 30 cm H_2O (2.9 kPa); may require reducing TV as low as 4 mL/kg
Wean Fio_2 to maintain a saturation of 88–95%
Strategic use of PEEP to permit lower Fio_2 and reduce risk of oxygen toxicity[24]

A/C, assist/control (ventilation); Fio_2, fraction of inspired oxygen; PEEP, positive end-expiratory pressure; TV, tidal volume.

pneumomediastinum, due to airspace rupture. Repetitive opening and closing of alveoli lead to shear stress and worsening inflammation. Box 2-2 lists recommendations for minimizing the potential complications of PPV in the setting of ALI; these settings are often appropriate for other applications of mechanical ventilation as well. Collectively, this is often referred to as open lung approach.[25]

Cardiogenic Shock and Pulmonary Edema

The ventilatory management of pulmonary edema with cardiogenic shock is complicated by the adverse effect of applied PEEP, which is ordinarily a primary mode of therapy for pulmonary edema, on cardiac output. A reasonable compromise is to use only sufficient PEEP to allow titration of the inspired oxygen concentration. Patients in cardiogenic shock require invasive hemodynamic monitoring. Hemodynamic and ventilatory parameters must be followed in tandem to achieve optimal benefit.

Patients with less severe pulmonary edema secondary to CHF often may benefit from noninvasive ventilatory support while receiving appropriate pharmacologic therapy. CPAP and BiPAP have been studied in this setting, and one study indicated that there may be little difference between the two modes in either safety or efficacy.[26]

Hypovolemic Shock

Appropriate volume resuscitation is the optimal means of managing respiratory compromise after trauma or with other causes of hypovolemic shock (e.g., massive gastrointestinal hemorrhage). PPV may exacerbate hypotension in hypovolemic patients. Patients in shock should be ventilated with 100% oxygen at a rate and TV predicted to produce near-physiologic $Paco_2$. PEEP generally should be avoided until circulating volume is restored.

OUTCOMES

When NPPV is successful (i.e., when ETT-mechanical ventilation is avoided), several potential therapeutic, patient comfort, and fiscal benefits are derived. The advantages of NPPV over ETT-mechanical ventilation include (1) preservation of speech, swallowing, and physiologic airway defense mechanisms; (2) reduced risk of airway injury; (3) reduced risk of nosocomial infection; and (4) decreased length of stay in, and reduced need for admission to, the intensive care unit (ICU) because less weaning and less intensive monitoring are necessary.[18,27-30]

Patients treated with NPPV have an increased risk of pulmonary barotrauma, aerophagia, and pressure stress to the face compared with intubated and ventilated patients. (BiPAP is a leak-tolerant system so that pressure sores are a much less common complication of extended BiPAP support than of CPAP.) In two series, patients successfully supported in the ED with NPPV usually could be admitted to a telemetry unit instead of an ICU, with significant cost savings.[13,29] Uncontrolled studies without definitive inclusion criteria found NPPV successful in avoiding ETT-mechanical ventilation in 60 to 90% of patients.[3,4] One study[31] showed increased mortality rates from the use of NPPV, which was attributed to a delay in necessary intubation; the study suffered from selection bias, however, and its results have not been corroborated.[6] In a prospective trial of NPPV in acute cardiogenic pulmonary edema, NPPV produced more improvement in subjective dyspnea, tachycardia, and acidosis at 1 hour compared to standard oxygen therapy, but did not produce a difference in mortality at 30 days.[10]

Treatment of mechanically ventilated patients usually extends beyond the ED. Adequate resuscitation and stabilization are the primary ED goals so that more focused therapy of the underlying problems can be pursued in the ICU. Occasionally, patients are extubated in the ED, most often those intubated solely for airway protection when the initial insult has been reversed or adequately tolerated. Adequate ventilatory drive and oxygen must be confirmed before ED extubation; before attempting to discontinue mechanical ventilation, patients should have a respiratory rate less than 30 breaths/minute, PEEP 5 cm H_2O or less, and Pao_2 greater than 60 mm Hg with Fio_2 less than 60%. NPPV may serve as a bridge between mechanical and spontaneous ventilation.

KEY CONCEPTS

- Not all patients who require intensive ventilatory support in the ED require endotracheal intubation-mechanical ventilation. Careful patient selection for noninvasive ventilatory support may spare some patients invasive therapy and its attendant risk of complications.
- TV of 6 to 8 mL/kg, rate of 12 to 14 breaths/minute, Fio_2 of 1.0 is a reasonable starting point for mechanical ventilator settings for patients whose primary pathology is not pulmonary. For patients with pulmonary pathology, settings specific for the cause of the patient's respiratory failure should be used, then carefully adjusted based on clinical response.
- Sudden difficulty in the treatment of patients receiving NPPV is usually the result of intolerance, inadequate ventilation or oxygenation, or air trapping. Intolerance should not be assumed until other causes are excluded.
- Sudden difficulty in the treatment of patients receiving mechanical ventilation should prompt a quick and systematic evaluation for tube, ventilator, airway pressures, and physiologic problems; such difficulties must not be automatically assumed to result from undersedation. This frequently starts with disconnecting the ventilator from the tube and temporarily bagging with Fio_2 of 1.0.
- The goal of therapy in many patients is *not* prompt normalization of blood gas parameters but may be relief of significant work of breathing. Slow correction to a patient-specific baseline likely results in significantly better clinical outcomes.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 3

Monitoring the Emergency Patient

Michael F. Murphy and Baruch Krauss

PERSPECTIVE

To *monitor* means to measure or observe a physiologic parameter either continuously or intermittently. Monitoring devices provide a "snapshot in time" and a window into the clinical status of the patient, detecting deterioration, tracking improvement, or measuring the effects of interventions. Monitoring parameters such as clinical observation, routine vital sign measurement, and electrocardiographic monitoring are basic tools in the practice of emergency medicine.

This chapter focuses on the following monitoring modalities: oxygenation monitoring with pulse oximetry, ventilation monitoring with end-tidal carbon dioxide ($ETCO_2$) measurement and waveform analysis, and hemodynamic monitoring with noninvasive blood pressure (BP) measurement. Fetal monitoring immediately after maternal trauma is also briefly discussed.

NONINVASIVE BLOOD PRESSURE MEASUREMENT

Automatic noninvasive BP measurement has become a popular and, if applied appropriately, an accurate method of determining BP. Advantages include more time for staff to attend to other tasks, timed repetition of BP measurements, continuous display of the systolic pressure, and a multiparameter display (e.g., systolic, diastolic, and mean BP; pulse rate).

Two types of noninvasive BP measurement devices are currently available:

1. Cuff-type
2. Radial arterial noninvasive waveform analysis

The noninvasive cuff-type devices use a detection system based on auscultatory, oscillometric, or Doppler principles.[1,2] Automatic oscillometric devices determine BP by electronically determining the pulse amplitude. This method and Doppler are the most accurate of the indirect methods. The cuff is automatically inflated at predetermined intervals to a preset level. As the machine gradually deflates the cuff, it senses the amplitude of the oscillations (pulsations) transmitted to the cuff by movement of the arterial wall under the cuff. An abrupt increase in the magnitude of the oscillation signals an opening of the artery and an increase in volume under the cuff; this is the *systolic pressure*. The magnitude of the oscillation increases to a peak and then falls rapidly. The point where there is no longer an alteration in the magnitude of the oscillation is the *diastolic pressure*. Some devices calculate the *mean arterial pressure* (MAP); others identify it as the cuff pressure at the point of largest oscillation.[1]

Noninvasive cuff-type oscillometric devices can be cycled every 15 to 20 seconds in the "STAT" mode when necessary to provide rapid but intermittent BP readings.[3] Accuracy during rapid cycling is the same as during less frequent sampling, but to prevent pressure injury from the high frequency of cycling, most cuff-type automatic BP devices revert to the intermittent mode after a brief period of rapid cycling.

The shortcomings of cuff-based noninvasive BP monitoring are those of any cuff measurement technique; patients with obese arms, uncooperative moving patients, and patients with very high or very low BP. Even with these limitations, automatic devices are more accurate and reliable than manual auscultation in patients with very low or high BP because the sensing devices are more sensitive than the human ear.[2] The cycle length of the inflation-deflation sequence of the older devices was exceedingly long and led to frequent failure. The newer devices have rectified this problem.

A newer method of continuous, noninvasive BP monitoring measures radial artery BP and pulse rate every 12 to 15 beats. The Vasotrac (Medwave Inc., Arden Hills, St. Paul, MN) device measures BP and pulse rate and displays a radial arterial pressure waveform.[4] It consists of a reusable circular sensor (diameter 1.20″; width 0.35″) which is strapped over the radial artery at the wrist. The wrist sensor module is designed to measure only the pulsatile energy perpendicular to the artery, using cyclical compression and decompression. The processor requires 12 to 15 consecutive beats without interference (movement artifacts) to obtain adequate energy information to generate the pulsatile calibrated beat.[4]

Although the device is expensive and requires the patient to remain relatively still, a limited number of studies have demonstrated that this noninvasive method of continuous BP measurement is comparable to that provided by an invasive arterial catheter.[4-6]

The most accurate method of measuring BP is with an intra-arterial catheter transduced to an electronic display. The ability to identify beat-to-beat variability, respiratory variation, and longer trends is unsurpassed. In addition, arterial catheter placement enables frequent sampling of arterial blood without additional arterial punctures. Arterial pressure monitoring is

used increasingly in EDs, particularly as lack of available beds in the intensive care unit mandates longer stays in the emergency department (ED) for critically ill patients. The risk of arterial injury or thrombosis related to arterial line insertion is low, but real, and can result in vascular compromise.

Situations when noninvasive BP measurement may prove inadequate and invasive monitoring via an arterial catheter should be considered include

1. Exceedingly high (>250 mm Hg systolic) or low (<80 mm Hg systolic) pressures. Although the invasive methods are also less accurate at these extremes, the error is significantly less than with noninvasive methods.
2. Patients requiring continuous BP monitoring (e.g., rapid antihypertensive therapy with sodium nitroprusside) due to the potential for rapid fluctuations in BP.
3. In impending shock states, the best chance to insert an arterial line may be in the ED while the arterial pulse is still readily palpable, although this should not delay transferring the patient to a more appropriate location for definitive care.
4. Patients with anatomic abnormalities (e.g., no suitable limb to undertake noninvasive measurement, morbidly obese patient).
5. Conditions where frequent arterial sampling is required. The requirement in such cases is for vascular access rather than the monitoring per se. Patients who are ill enough to require frequent arterial sampling usually benefit from continuous arterial BP monitoring.

BLOOD GAS MONITORING

Although the ability to monitor oxygen utilization at the cellular level might be considered ideal, current technology permits less precise measures of performance. Transcutaneous oxygen and CO_2 monitoring, conjunctival oxygen pressure, pulse oximetry, and $ETCO_2$ monitoring (capnography, capnometry) are all used to indicate the adequacy of pulmonary gas exchange and arterial blood gas [ABG] tensions and to assess ventilatory efficacy.

Pulse Oximetry

The pulse oximeter provides a rapid, noninvasive, and continuous measurement of arterial oxygen saturation that has become a uniform standard for patient monitoring throughout medicine. Oximeters are easy to use and interpret, pose no risk to the patient, and are relatively inexpensive, although reliable interpretation of the information given by these devices requires an appreciation of the limitations of the technology.[7,8]

Transmission oximetry is the most common type of oximetry used in clinical practice. Transmission oximetry is based on differences in the optical transmission spectrum of oxygenated and deoxygenated hemoglobin. In addition to arterial hemoglobin, other absorbers in the light path include skin, soft tissue, and venous and capillary blood. Pulse oximeters measure the pulse variations in red and infrared (IR) light transmitted through a tissue bed.[9] Data averaged over several arterial pulse cycles are then presented as oxygen saturation as measured using pulse oximetry (SpO_2).[9] Studies have shown an excellent correlation between arterial hemoglobin oxygen saturation and SpO_2 in patients with normal perfusion.[9,10]

The limitations of oximetry technology are related to alterations in local or systemic perfusion and severe vasoconstriction (e.g., shock, hypothermia), excessive movement, interference with transfer through the nail bed (e.g., from synthetic fingernails or nail polish), and alterations in hemoglobin (e.g., severe anemia, abnormal hemoglobins). Carboxyhemoglobin (COHb) and methemoglobin (MetHb) contribute to light absorption and cause errors in oximetry readings.[10] The pulse oximeter senses COHb as though it were mostly oxyhemoglobin and provides a falsely high reading. MetHb produces a large pulsatile absorbance signal at both the red and IR wavelengths, which forces the absorbance ratio toward unity, corresponding to an SpO_2 of 85%.[10] Thus, with high levels of MetHb, the SpO_2 is erroneously low when the arterial saturation is above 85% and erroneously high when the arterial saturation is below 85%. Erroneously high readings (about 3–5%) and a higher incidence of failure to detect signals have been reported in dark-skinned races.[9]

Signals tend to be weaker from ears than from fingers, except in hypotension or peripheral vasoconstriction, but ear responses are faster.

Pulse oximetry is particularly useful in the ED evaluation of patients with acute cardiopulmonary disorders such as bronchiolitis, asthma, heart failure, and chronic obstructive pulmonary disease (COPD) and in patients with drug-induced or traumatic alterations in consciousness. It is mandatory in patients undergoing procedural or deep sedation and in those requiring definitive airway management.[11,12] However, it is valuable in any patient for whom continuous knowledge of oxygen levels is helpful in their treatment.[11] Pulse oximetry decreases the frequency with which ABG sampling is required.[11] Continuous monitoring may indicate the insidious development of shock as vasoconstriction and deterioration of signal detection develop. Improvements in pulse oximeter technology have resulted in improved accuracy and reliability during patient motion. In short, this valuable device has become an established component of the monitoring armamentarium of emergency medicine.[13,14]

However, adequate oxygen saturation does not ensure adequate *ventilation*, particularly in patients with decreased levels of consciousness. $ETCO_2$ monitoring is required for accurate assessment of ventilation.

End-Tidal Carbon Dioxide Monitoring

The concentration of CO_2 in an exhaled breath is intrinsically linked to tissue metabolism, systemic circulation, and ventilation.[15] *Capnography* is the graphic record, represented as a waveform, or *capnogram*, of the instantaneous CO_2 concentrations in respired gases during a respiratory cycle.[16,17] Capnography provides continuous, real-time, breath-to-breath feedback on the clinical status of the patient, allows the clinician to determine the baseline ventilatory status and to track changes over time.[18] Capnography is also a diagnostic monitoring modality because certain disease conditions are associated with characteristic waveforms.[18,19] Although the concentrations of CO_2 *can* be displayed continuously through the respiratory cycle, by convention only the maximum CO_2 concentration at the end of each tidal breath, the $ETCO_2$, is ordinarily displayed. *Capnometry* is the quantitative measurement of $ETCO_2$ displayed as a number without a waveform. *Colorimetric* detectors use color scales to estimate ranges of $ETCO_2$, but are not sufficiently accurate to give quantitative measurements. Their use is therefore limited to confirmation of correct endotracheal tube (ETT) placement and its continuous location in the trachea.

Although originally used during general anesthesia in the operating room, $ETCO_2$ monitoring has become a standard monitoring modality in the ED and nonhospital medical setting.[20,21]

Carbon dioxide monitors are configured as either sidestream or mainstream, depending on the location of the photoelectric

detector or sensor. Mainstream devices measure CO_2 directly from the airway, with the sensor attached directly to the ETT. Sidestream devices, more commonly used by emergency medical service (EMS) personnel and in the ED, aspirate a sample of gas through tubing into a sensor located inside the monitor, and are used for both intubated and nonintubated patients. They are lightweight and may be integrated into special nasal-oral cannulae that simultaneously sample CO_2 and deliver low-flow oxygen, allowing for continuous oxygen delivery during procedural sedation and analgesia.

Colorimetric CO_2 detectors use pH-sensitive filter paper impregnated with metacresol purple, which changes color from purple (<4 mm Hg CO_2) to tan (4–15 mm Hg CO_2) to yellow (>20 mm Hg CO_2) depending on the concentration of CO_2.[15,22,23] (See Chapter 1, Figs. 1-3 and 1-4.) The indicator, housed in a plastic casing, is inserted between the ETT and the ventilator bag and detects changes on a breath-by-breath basis.[16] They are also inexpensive and easy to use, and should be available in every ED and on every EMS unit that performs intubation for confirmation of ETT placement if capnography or capnometry is not available.

In patients with normal cardiopulmonary function, there is a close correlation between alveolar CO_2 (P_{ACO_2}) and arterial CO_2 (P_{aCO_2}). The $ETCO_2$ is usually 2 to 5 mm Hg less than the P_{aCO_2} because of the contribution of physiologic dead space gas to the end-tidal gases.[24] Conditions that affect ventilation-perfusion ratios (including pulmonary embolism), cardiac arrest, hypovolemia, obstructive lung disease, and the lateral decubitus position, can widen the Pa- $ETCO_2$ gradient.[25,26,48] Several recent studies, however, have shown high concordance between $ETCO_2$ and P_{ACO_2} in adult asthmatics and in children with moderate and severe respiratory distress from bronchiolitis, asthma, and pneumonia.[27] Although $ETCO_2$ may not always accurately reflect the absolute P_{ACO_2} in critically ill patients, it is still valuable in detecting ventilatory trends and identifying sudden airway events.

Analysis of the shape of the capnogram can yield valuable diagnostic information.[19] A normal capnogram has four phases (Fig. 3-1A). Phase 1-2 represents a CO_2-free portion of the respiratory cycle. Most often this is the inspiratory phase, although it may represent apnea or a disconnection of the device from the patient. An elevation of this baseline above zero implies rebreathing of CO_2, as in increased dead space in the circuit or contamination of the sensor.[18]

Phase 2-3, the *rapid upstroke* of the curve, represents the transition from inspiration to expiration and the mixing of dead space and alveolar gas. Prolongation of phase 2-3 (Fig. 3-1B) occurs with obstruction to expiratory gas flow (e.g., obstructive lung disease, bronchospasm, kinked ETT) or leaks in the breathing system.

Phase 3-4, the *alveolar plateau*, represents the predominance of CO_2-rich alveolar gas in the breath stream and tends to slope gently upward with the uneven emptying of alveoli. *Point 4* (the $ETCO_2$) represents the maximum CO_2 concentration in each breath and is the number that appears on the monitor. The slope of this phase can be increased by the same obstructive factors that increase the slope of phase 2-3 and is also a normal physiologic variation in pregnancy.[16] A dip in the plateau indicates a spontaneous respiratory effort during mechanical ventilation, as in hypoxia, hypercarbia, or inadequate anesthesia (Fig. 3-1C).[19,21]

Phase 4-5, the *inspiratory downstroke*, is a nearly vertical drop to baseline. This slope can be prolonged and blend in with the expiratory phase in endotracheal cuff leaks (Fig. 3-1D). Abnormal respiratory patterns that are fast or chaotic limit the usefulness of $ETCO_2$ monitoring because characteristic waveform patterns are difficult to discern.

Capnography is used in the ED in many intubated and nonintubated clinical scenarios. It can confirm ETT placement in the trachea, continuously monitor tube position in the trachea during transport, provide qualitative and quantitative methods of assessing cardiac output, gauge effectiveness of cardiopulmonary resuscitation (CPR) during cardiac arrest, determine prognosis in CPR and in trauma, maintain appropriate $ETCO_2$ levels in patients with elevated intracranial pressure, estimate P_{ACO_2} in patients with normal lung function, aid in the detection and diagnosis of pulmonary embolism, assess response to treatment in patients with acute respiratory distress, determine adequacy of ventilation in patients with altered mental status (including drug-induced alterations in consciousness during procedural sedation and analgesia), assess ventilatory status of actively seizing patients, and help detect metabolic acidosis.

Along with visualizing tracheal rings on bronchoscopy, capnography is *the* other "gold standard" used to confirm intubation of the trachea (see Chapter 1). Misleading $ETCO_2$ readings can occur with esophageal intubation after bag or mask ventilation and ingestion of carbonated beverages or antacids.

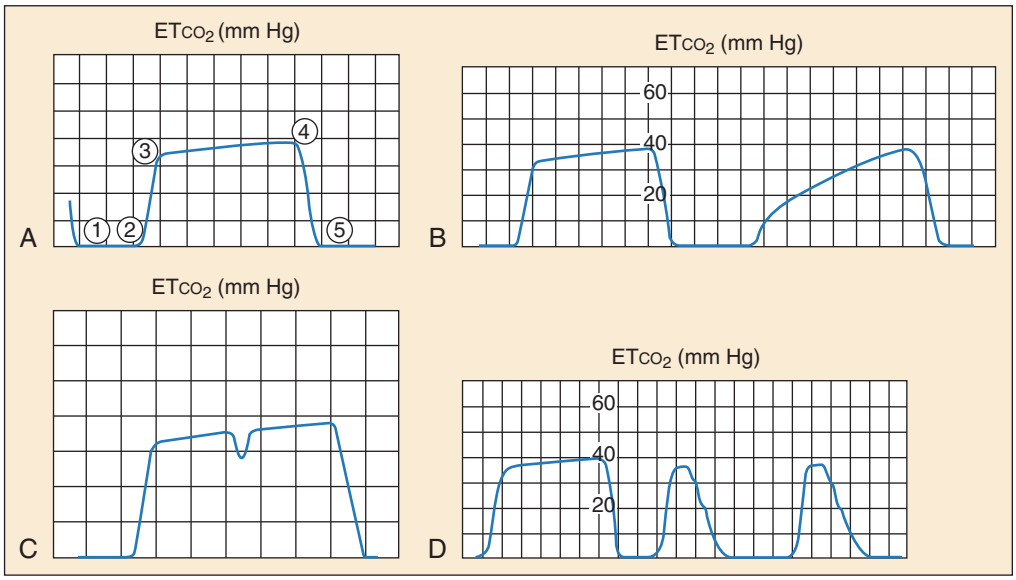

Figure 3-1. **(A)** Four phases of a normal capnogram. **1-2,** The carbon dioxide-free portion of the respiratory cycle. **2-3,** The rapid upstroke of the curve, representing the transition from inspiration to expiration and the mixing of dead space and alveolar gas. **3-4,** The alveolar plateau, representing the alveolar gas rich in carbon dioxide and tending to slope gently upward with the uneven emptying of the alveoli. **4-5,** The respiratory downstroke, which is a nearly vertical drop to baseline. $ETCO_2$, end-tidal carbon dioxide (concentration). **(B-D)** See text for explanation.

However, detection of $ETCO_2$ usually ceases after six breaths and, if capnography is used, the tracings look abnormal.[28] $ETCO_2$ is also falsely elevated for 5 to 10 minutes after injection of sodium bicarbonate.[29] In nonarrest settings the $ETCO_2$ approaches 100% sensitivity and specificity in confirming correct tube placement and is also useful for monitoring for accidental extubation.

Airway, breathing, and circulatory assessment of critically ill or injured patients can be rapidly determined using $ETCO_2$ values and the capnogram.[30] The presence of a normal capnogram denotes a patent airway and spontaneous breathing, and normal $ETCO_2$ levels indicate adequate ventilation and perfusion. Capnography can therefore be used to assess critically ill patients (including victims of chemical terrorism with nerve gas exposure) and patients who are actively seizing.[30,31] Unlike pulse oximetry and electrocardiography, capnographic measurement is airway-based and therefore is not subject to motion artifact. It also provides reliable readings in low perfusion states.[32]

Animal and human studies have shown that $ETCO_2$ is a useful noninvasive measurement that is highly correlated with cardiac output and is the earliest indicator of return of spontaneous circulation (ROSC) in CPR.[33-35,40] ROSC is heralded by an almost immediate increase in $ETCO_2$ from baseline. Multiple studies showed that $ETCO_2$ has prognostic value in terms of mortality during CPR.[35-39] No patient with a mean $ETCO_2$ less than 10 mm Hg after 20 minutes of CPR survived, giving $ETCO_2$ measurement a high negative predictive value for failure of resuscitation. Despite these promising findings, capnography requires further prospective validation to confirm its utility as a prognostic tool in cardiac arrest.

Capnography is the only ventilation monitoring modality that is accurate and reliable in actively seizing patients.[30,31] Capnographic data (capnogram, $ETCO_2$, respiratory rate) can be used to distinguish among actively seizing patients with apnea (flatline waveform, no $ETCO_2$ readings, and no chest wall movement), ineffective ventilation with low tidal volume breathing (small capnograms, low $ETCO_2$), and effective ventilation (normal capnogram, normal $ETCO_2$).

Capnography can also rapidly detect the common airway, respiratory, and central nervous system complications associated with the nerve agents in chemical terrorism, including apnea, upper airway obstruction, laryngospasm, bronchospasm, and respiratory failure.[17,30]

Capnography provides dynamic monitoring of ventilatory status in patients with acute respiratory distress, such as from asthma, bronchiolitis, COPD, congestive heart failure, croup, and cystic fibrosis. By measuring $ETCO_2$ and respiratory rate with each breath, capnography provides instantaneous feedback on the clinical status of the patient. Respiratory rate is measured directly from the airway by nasal-oral cannulae, providing a more reliable reading than impedance respiratory monitoring. In upper airway obstruction and laryngospasm, for example, impedance monitoring detects chest wall movement, interprets this as a valid breath, and displays a respiratory rate, even though the patient is not ventilating. In contrast, capnography detects no ventilation and shows a flatline capnogram.

Bronchospasm in obstructive lung disease leads to upward slanting of the expiratory plateau of the capnogram (Fig. 3-2, *middle panel*). Changes in $ETCO_2$ over time and the slope of this phase of the capnogram have been shown to correlate well with spirometric measurements (forced expiratory volume in 1 second [FEV_1] and peak expiratory flow rate [PEFR]).[41-43] Capnography has the advantage of being independent of effort, gender, age, and height and is a useful objective measure in asthmatic patients who are unwilling or unable to cooperate with spirometry (e.g., young children, ventilated patients, and patients in acute respiratory distress). Capnography can also be used to distinguish obstructive from restrictive lung disease.[41] Characteristic capnographic patterns associated with restrictive and obstructive lung disease are shown in Figure 3-2 (*bottom panel*).

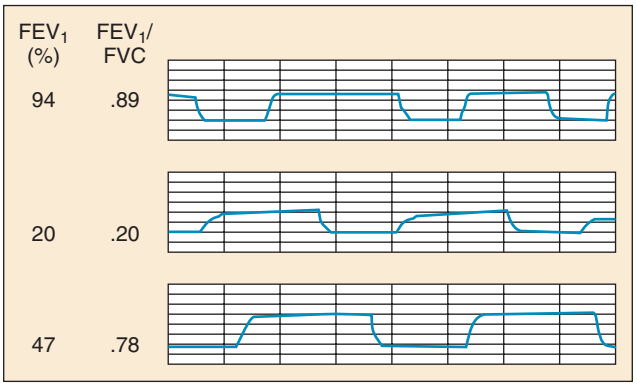

Figure 3-2. Capnogram shape in normal subjects (*top panel*), patients with bronchospasm (*middle panel*), and those with obstructive and restrictive (*bottom panel*) lung disease. FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

Capnography can also detect the common adverse airway and respiratory events associated with procedural sedation and analgesia.[17] Capnography is the earliest indicator of airway or respiratory compromise and displays an abnormally high or low $ETCO_2$ before pulse oximetry detects a falling oxyhemoglobin saturation, especially in patients receiving supplemental oxygen. Both central and obstructive apnea can be almost instantaneously detected by capnography. Capnography may be more sensitive than clinical assessment of ventilation in the detection of apnea. In a recent study, 10/39 (26%) of patients experienced 20-second periods of apnea during procedural sedation and analgesia. All ten episodes of apnea were detected by capnography but not by the anesthesia providers.[44]

Obtunded or unconscious patients, including those with alcohol intoxication, intentional or unintentional drug overdose, and postictal patients (especially those treated with benzodiazepines), may have impaired ventilation. Capnography can differentiate between postictal patients with effective ventilation and those with ineffective ventilation as well as provide continuous monitoring of ventilatory trends over time to identify those patients at risk for respiratory depression and respiratory failure.

In addition to its established uses for assessment of ventilation and perfusion, capnography is a valuable tool for assessing metabolic status. Recent studies have shown that $ETCO_2$ and serum bicarbonate (HCO_3) are linearly correlated in diabetes and in pediatric gastroenteritis, and $ETCO_2$ can be used as an indicator of metabolic acidosis in these patients (Figs. 3-3 and 3-4, respectively).[45,46] As a patient becomes acidotic, HCO_3 decreases and a compensatory respiratory alkalosis develops with an increase in minute ventilation and a resultant decrease in $ETCO_2$. The more acidotic, the lower the HCO_3; the higher the respiratory rate, the lower the $ETCO_2$. Furthermore, $ETCO_2$ can be used to distinguish diabetics in ketoacidosis (metabolic acidosis, compensatory tachypnea, low $ETCO_2$) from those who are not (nonacidotic, normal respiratory rate, normal $ETCO_2$). A similar association between $ETCO_2$ and HCO_3 was demonstrated in children with gastroenteritis, in whom an $ETCO_2$ = 31 mm Hg is 76% sensitive and 96% specific for the presence of metabolic acidosis (Fig. 3-4).[47]

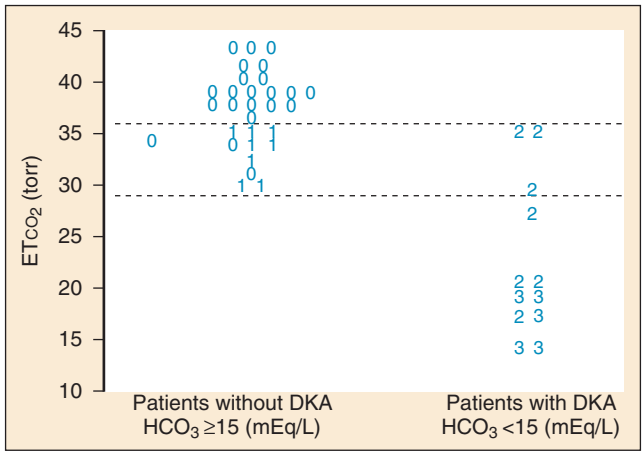

Figure 3-3. Predictive value of end-tidal carbon dioxide ($ETCO_2$) in detecting metabolic acidosis in diabetics. DKA, diabetic ketoacidosis; HCO_3, bicarbonate ion.

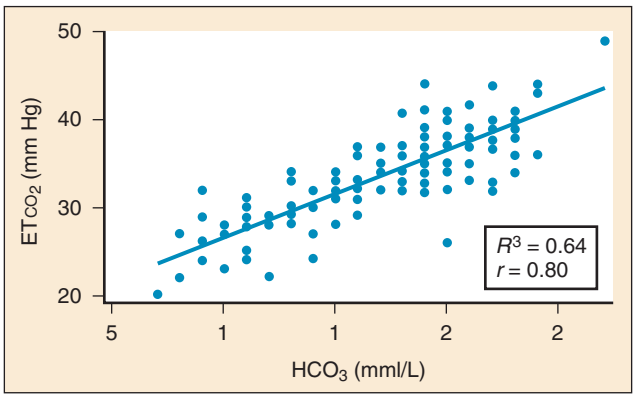

Figure 3-4. End-tidal carbon dioxide ($ETCO_2$)/serum bicarbonate (HCO_3) correlation in gastroenteritis. *r*, correlation coefficient; R^2, coefficient of determination for multivariate analysis.

FETAL MONITORING

Trauma occurs in about 7% of pregnant females.[49] Although maternal mortality rates in trauma do not differ from those for nonpregnant females with comparably severe injury, fetal mortality rates increase over those for pregnant women who have not suffered a traumatic injury. The American College of Obstetricians and Gynecologists recommends that the pregnant patient with a viable fetus undergo fetal monitoring for 2 to 6 hours after an injury characterized with any degree of abdominal jarring.[50]

Fetal monitoring is used by emergency physicians to detect occult fetal distress and inform therapy and referral. Persistent fetal tachycardia, bradycardia, loss of baseline variability or decelerations following uterine contractions (e.g., Braxton Hicks contractions), and uterine hyperactivity require urgent obstetric consultation. Although most emergency medicine residents are trained to recognize the cardiotocographic findings indicative of fetal distress, most EDs do not have this monitoring equipment available. Ultrasound machines are used widely to measure and monitor fetal heart rate.[49]

CEREBRAL FUNCTION MONITORING

The Bispectral index (BIS) monitors analyses and processes a patient's electroencephalogram during sedation to produce a single number—the Bispectral index. This unitless number, ranging from 0 to 100, is used as an indicator of the depth of sedation, with 0 representing EEG silence and 100 a fully awake adult.[51]

BIS monitoring has been studied in the ED in an attempt to objectify sedation endpoints by titrating to a target BIS score.[52,53] The evidence of its ability to reliably reflect depth of sedation is conflicting, however. More importantly, the threshold beyond which ventilatory compromise occurs has not been determined, further limiting the usefulness of routine BIS monitoring for sedation in the ED.[53-57] Gill and colleagues found that BIS monitoring reliably distinguished patients undergoing procedural sedation and analgesia who were sedated to the point of general anesthesia from those with lesser degrees of sedation but did not discriminate mild-to-moderate sedation or moderate-to-deep sedation.[57] The findings of Miner and coauthors supported this contention in that the assignment of a preprocedural BIS target sedation level of moderate or deep procedural sedation did not influence the level of sedation achieved, the rate of respiratory depression, the occurrence of complications, the time to return of baseline mental status, or the success of the procedure. They concluded that the assignment of a preprocedural target sedation level was not an effective means of changing the outcome of procedural sedation in the ED.[56]

In small pediatric ED studies, however, Agrawal and coworkers[54] and Overly and associates[55] found BIS monitoring correlated with clinical sedation scores. Determination of utility and effectiveness on outcome for children undergoing procedural sedation and analgesia awaits larger trials.

KEY CONCEPTS

1. Monitoring modalities, when used appropriately, help to identify the effectiveness of interventions, predict deterioration, track the patient's clinical course, and inform clinical decision-making.
2. $ETco_2$ monitoring, especially capnography, supplements oximetry by providing useful information regarding pathologic conditions and response to therapy.
3. Alarm limits should be adjusted to ensure reasonable warnings are delivered, optimally reducing the number of false alarms. Disabling alarms is dangerous.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 4 Shock

Alan E. Jones and Jeffrey A. Kline

PERSPECTIVE

In philosophic terms, shock can be viewed as a transition between life and death. Whether shock results from hemorrhage, sepsis, or cardiac failure, mortality rates exceed 20%.[1-3] In scientific parlance, shock results from the widespread failure of the circulatory system to oxygenate and nourish the body adequately. In the laboratory the scientist defines the metabolic effect of shock quantitatively, by examining the mechanisms by which shock alters mitochondrial energy transfer, evokes the production of toxic chemicals, and reduces their removal. At the bedside, however, the clinician identifies shock by linking the clinical impression, synthesized from the patient's history of present illness, age, underlying health status, and general appearance, with quantitative data, including vital signs, blood chemistry, urine output, and direct measurements of oxygenation. When the clinical impression and the quantitative data suggest widespread organ hypoperfusion, emergent resuscitation must restore normal tissue oxygenation and substrate delivery to prevent deterioration into systemic inflammation, organ dysfunction, and death.

At the subcellular level, shock first affects the mitochondria. Mitochondria function at the lowest oxygen tension in the body, but paradoxically, they consume almost all the oxygen used by the body. More than 95% of aerobic chemical energy comes from mitochondrial combustion of fuel substrates (fats, carbohydrates, ketones) plus oxygen (O_2) into carbon dioxide (CO_2) and water (H_2O). Mitochondria therefore have been referred to as the "canaries in the coal mine" because they are affected first in conditions of inadequate tissue perfusion.[4,5] When mitochondria have inadequate oxygen, the cell catabolizes fuels to lactate, which inexorably accumulates and diffuses into the blood.

Classification

For years, shock has been classified into four broad categories based on Blalock's 1940 description: hematologic, neurologic, vasogenic, and cardiogenic.[6] This basic organization scheme remains useful today. Box 4-1 outlines five categories of shock that generally have specific mechanisms and treatments.

Epidemiology

The epidemiology of shock in the emergency department (ED) context remains speculative because shock is rarely listed as a primary coding diagnosis and depends on defining criteria. Arterial hypotension, defined as a systolic blood pressure less than 100 mm Hg, is measured at least one time in 19% of ED patients[7]; however, diagnosed traumatic, cardiogenic, or septic shock is less common, constituting about 1 to 3% of all ED visits.

This chapter reviews the metabolic, systemic, and inflammatory responses that occur in all types of circulatory shock and discusses specific pathophysiology of the major causes of shock.

Specific Causes

Hemorrhagic Shock

Hemorrhagic shock results from a rapid reduction in blood volume, which causes baroreceptor activation and leads to vasoconstriction, increased strength of cardiac contraction, and increased heart rate (HR). Cardiovascular response to hemorrhage can vary with underlying cardiopulmonary status, age, and presence of ingested drugs. Responses of HR and blood pressure (BP) are notoriously variable in hemorrhage, so no firm conclusion can be made at the bedside about the presence or absence of hemorrhagic shock simply by evaluating HR and BP.[8] In general, hemorrhage first increases pulse and cardiac contraction, then increases vasoconstriction. Blood loss causes an elevated pulse rate with a slight increase in the diastolic BP, causing the pulse pressure (difference between systolic and diastolic BP) to narrow. As blood loss continues ventricular filling decreases, and cardiac output drops, followed by a reduction in systolic BP. Before the total cardiac output begins to decrease, blood flow to noncritical organs and tissues begins to decrease, and their cells produce and release lactic acid.

Consequently, acidemia often precedes any significant decrease in cardiac output with hemorrhage.[9] However, the blood contains bicarbonate ions that buffer the blood pH, keeping it near neutral, even as lactic acid accumulates in blood. The base *deficit*, defined as the amount of strong base that would have to be added to a liter of blood to normalize the pH, represents an index of how far the bloodstream has dipped into its reserve of bicarbonate buffer. A normal base deficit is more positive than −2 mEq/L. Accordingly, the arterial and venous blood base deficit can become more negative early in hemorrhage even while blood pH and BP remain in the normal range. The base deficit, therefore, crudely represents the physiologic endpoint that distinguishes trivial blood loss from clinically significant hemorrhage. In addition to

BOX 4-1 CATEGORIES OF SHOCK ACCORDING TO PRIMARY TREATMENT

Causes That Require Primarily the Infusion of Volume
Hemorrhagic shock
- Traumatic
- Gastrointestinal
- Body cavity

Hypovolemia
- Gastrointestinal losses
- Dehydration from insensible losses
- Third-space sequestration from inflammation

Causes That Require Improvement in Pump Function by Either Infusion of Inotropic Support or Reversal of the Cause of Pump Dysfunction
Myocardial ischemia
- Coronary artery thrombosis
- Arterial hypotension with hypoxemia

Cardiomyopathy
- Acute myocarditits
- Chronic diseases of heart muscle (ischemic, diabetic, infiltrative, endocrinologic, congenital)

Cardiac rhythm disturbances
- Atrial fibrillation with rapid ventricular response
- Ventricular tachycardia
- Supraventricular tachycardia

Hypodynamic septic shock
Overdose of negative inotropic drug
- Beta-blocker
- Calcium channel antagonist overdose

Structural cardiac damage
- Traumatic (e.g., flail mitral valve)
- Ventriculoseptal rupture
- Papillary muscle rupture

Causes That Require Volume Support and Vasopressor Support
Hyperdynamic septic shock
Anaphylactic shock
Central neurogenic shock
Drug overdose

Problems That Require Immediate Relief from Obstruction to Cardiac Output
Pulmonary embolism
Cardiac tamponade
Pneumothorax
Valvular dysfunction
- Acute thrombosis of prosthetic valve
- Critical aortic stenosis

Congenital heart defects in newborn (e.g., closure of patent ductus arteriosus with critical aortic coarctation)
Critical idiopathic subaortic stenosis (hypertrophic obstructive cardiomyopathy)

Cellular Poisons That Require Specific Antidotes
Carbon monoxide
Methemoglobinemia
Hydrogen sulfide
Cyanide

chemical buffering, the body responds to small reductions in arterial pH by activating brainstem chemoreceptors, which increase minute ventilation, leading to reduced partial pressure of carbon dioxide in arterial gas ($Paco_2$).

After approximately one third of the total blood volume is acutely lost, cardiovascular reflexes can no longer sustain adequate filling of the arterial circuit, and frank hypotension supervenes. Arterial hypotension is generally and arbitrarily defined as an arterial BP below 90 to 100 mm Hg. Usually coincident with the development of hypotension, bicarbonate buffers become overwhelmed, and increased alveolar ventilation becomes ineffective, culminating in reduced arterial pH. Hemorrhagic shock causes an activation of the hypothalamic-pituitary-adrenomedullary axis, with release of stress hormones that cause glycogenolysis, lipolysis, and mild hypokalemia. Therefore, in the ED, patients sustaining traumatic hemorrhage generally have an arterial lactate concentration greater than 4.0 mmol/L, a $Paco_2$ less than 35 mm Hg, and mild hyperglycemia (150–170 mg/dL) and hypokalemia (3.5–3.7 mEq/L). Although hemorrhagic hypotension reduces lung perfusion, arterial hypoxemia should not be attributed simply to blood loss, but instead should prompt investigation for aspiration, airway obstruction, alveolar consolidation, or lung injury.

The second phase of organ injury from hemorrhagic shock occurs during resuscitation. It has been said that the acute phase of hemorrhage "cocks the gun," and resuscitation "pulls the trigger" to cause organ injury from hemorrhagic shock. During resuscitation, neutrophils become most aggressive, binding to the lung endothelium and causing capillary leaks that characterize the adult respiratory distress syndrome (ARDS). Inflammatory cytokines are liberated during resuscitation, and membrane injury occurs in many cells. In the liver, damage from inflammation and reactive oxygen species from neutrophils is compounded by persistent microischemia. During resuscitation from hemorrhagic shock, the normal balance of vasodilation by nitric oxide (NO) versus vasoconstriction by endothelins becomes distorted, producing patchy centrilobular ischemic damage in the liver, which may produce an immediate rise in blood transaminase levels. A growing body of evidence suggests that resuscitation from hemorrhage exerts greater injury to the heart than the actual hypotensive insult.[10,11] Depending on the degree of hypotensive insult, the kidney may manifest acute spasm of the preglomerular arterioles, causing acute tubular necrosis. Systemic metabolic changes can impair fuel delivery to the heart and brain, secondary to depressed hepatic glucose output, impaired hepatic ketone production, and inhibited peripheral lipolysis.[12]

Septic Shock

Septic shock can be produced by infection with any microbe, although in as many as half of the cases of septic shock, no organism is identified. One of the most well-studied mediators of sepsis is lipopolysaccharide, contained in the outer cell membrane of gram-negative bacteria. Infusion of lipopolysaccharide into humans or animals produces cardiovascular, immunologic, and inflammatory changes identical to those observed with microbial infection. In recent years, multicenter trials of sepsis have suggested the emergence of gram-positive organisms as the chief cause of sepsis in hospitalized patients.[13] Two lines of reasoning imply that gram-positive sepsis will continue to increase in prevalence:

1. More patients are being treated at home for chronic immunocompromising diseases with indwelling catheters, which serve as excellent portals of entry into the vascular space for *Staphylococcus aureus* and coagulase-negative staphylococci.
2. The frequency of community-acquired infections caused by antibiotic-resistant gram-positive organisms has greatly increased in recent years, including infections caused by *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Streptococcus pyogenes*.

Septic shock causes three major effects that must be addressed during resuscitation: relative hypovolemia, cardiovascular depression, and induction of systemic inflammation. Septic shock produces relative hypovolemia from increased venous capacitance, which reduces right ventricular filling. Septic shock often causes absolute hypovolemia from gastrointestinal volume losses, tachypnea, sweating, and decreased ability to drink during development of the illness. Sepsis also induces capillary leak, which leads to relative loss of intravascular volume into third spaces. Recent evidence has shown that septic shock causes myocardial depression simultaneously with vasodepression and capillary leak. Direct measurements of cardiac contractility have shown that cardiac mechanical function becomes impaired early in the course of septic shock, even in the hyperdynamic stages.[14] Multiple mechanisms may explain depressed heart function in sepsis, including actions of specific cytokines (most notably tumor necrosis factor alpha [TNF-α] and interleukin 1 beta [IL-1β]),[15] overproduction of NO by nitric oxide synthase (iNOS),[16] and possibly impairment in mitochondrial oxidative phosphorylation[17] coincident with reduced mechanical efficiency.[18] Evidence indicates that circulating mediators, myocardial cellular injury from inflammation, and deranged metabolism interact synergistically to injure the heart during septic shock. Systemic inflammation causes capillary leak in the lung, which may cause alveolar infiltration characteristic of ARDS early in the treatment of septic shock in up to 40% of patients.[13] With the potential for early development of ARDS, more profound ventilation/perfusion $(\dot{V}/\dot{Q})$ mismatching, and pneumonia or pulmonary aspiration, hypoxemia is more severe with septic shock than hemorrhagic shock.

Cardiogenic Shock

Cardiogenic shock (myocardial pump failure) results when more than 40% of the myocardium undergoes necrosis from ischemia, inflammation, toxins, or immune destruction. Otherwise, cardiogenic shock essentially produces the same circulatory and metabolic alterations observed with hemorrhagic shock. Undoubtedly, impaired baseline cardiac function can contribute to the development of circulatory shock secondary to infection, hemorrhage, or vasodilatory drug overdose. However, when shock results from a pure cardiac cause, severe left ventricular dysfunction is evident on echocardiography early in the course. Patients with severe dysfunction are far more likely to have a cardiogenic cause of shock than patients with normal or moderate left ventricular dysfunction.[19]

CLINICAL FEATURES

Patients frequently present to the ED in shock with no obvious cause. Rapid recognition of shock requires the integration of information from immediate history and physical examination, and a diagnosis of shock can be strongly supported by the presence of a worsening base deficit or lactic acidosis. In general, patients with shock exhibit a stress response: they appear ill, pale, often sweating, usually tachypneic or grunting, and often with a weak and rapid pulse (Box 4-2). HR can be normal or low in cases of shock, especially when the patient is taking prescribed drugs that depress HR or the circumstance is complicated by profound hypoxemia. BP initially can be normal because of adrenergic reflexes. Although arterial BP as a sole measurement remains an unreliable marker of circulatory status, the finding of a single systolic BP less than 100 mm Hg in the ED is associated with a threefold increase in in-hospital mortality and a tenfold increase in sudden and unexpected death.[7] The HR/systolic BP ratio may provide a better marker of shock than either measurement alone; a normal ratio is less than 0.8.[20] Urine output provides an excellent indicator of organ perfusion and is readily available with insertion of a Foley catheter. Measuring urine output, however, requires at least 30 minutes to accurately determine if output is normal (>1.0 mL/kg/hr), reduced (0.5–1.0 mL/kg/hr), or severely reduced (<0.5 mL/kg/hr). Point measurements of the arterial lactate concentration and the base deficit can be rapidly performed and provide accurate assessment of global perfusion status. A lactate concentration greater than 4.0 mM or a base deficit more negative than –4 mEq/L predicts the presence of circulatory insufficiency severe enough to cause subsequent multiple organ failure.[21] Once the empirical criteria for circulatory shock are discovered, the next step is to consider the cause of shock. Figure 4-1 is an algorithm of potential decisions to facilitate diagnosis in a patient with undifferentiated shock.

BOX 4-2 EMPIRICAL CRITERIA FOR DIAGNOSIS OF CIRCULATORY SHOCK*

Ill appearance or altered mental status
Heart rate >100 beats/min
Respiratory rate >20 breaths/min or $Paco_2$ <32 mm Hg
Arterial base deficit <–4 mEq/L or lactate >4 mM/L
Urine output <0.5 mL/kg/hr
Arterial hypotension >20 minutes duration

*Regardless of cause. Four criteria should be met.

Use of the history, vital signs and physical examination documented by outside providers represents a valuable insight into a patient's physiologic status prior to any medical intervention and can be useful in ED management. Studies suggest that both medical and trauma patients with hypotension prior to being seen in the ED have a three- to fourfold higher in-hospital mortality rate than patients without hypotension.[22,23]

The primary survey must ensure presence of a patent airway as well as sufficient respiratory effort for adequate oxygenation and ventilation. The physical examination should be performed on an undressed patient and should begin with a quick head-to-toe inspection. Dry mucous membranes suggest dehydration, whereas distended jugular veins suggest cardiac failure or obstruction from pulmonary embolism (PE) or cardiac tamponade. Muffled heart sounds suggest cardiac tamponade, whereas a loud machine-like systolic murmur indicates acute rupture of a papillary muscle or rupture of the interventricular septum. Bilateral pulmonary rales in a patient with a normal rectal temperature help to define the presence of primary left ventricular failure. Wheezing suggests bronchospasm from anaphylaxis or, less likely, cardiac failure or PE. Abdominal tenderness may indicate peritoneal inflammation or occult trauma. Rectal examination may disclose occult gastrointestinal hemorrhage. Rectal temperature should be performed as early as is reasonable on every patient with suspected shock.

The neurologic examination documents responsiveness, cognition, and the presence of any focal deficits. In children, documentation should include level of alertness, response to parents, appropriateness of crying, pupillary function, symmetry of grimace, symmetry of extremity movements, and motor tone in infants.

Laboratory, radiographic, and other ancillary data should be ordered to assess tissue and vital organ perfusion and to diagnose injury from trauma, find the source of infection with sepsis, or identify the cause of cardiac failure. A chest radiograph, electrocardiogram, finger-stick glucose measurement,

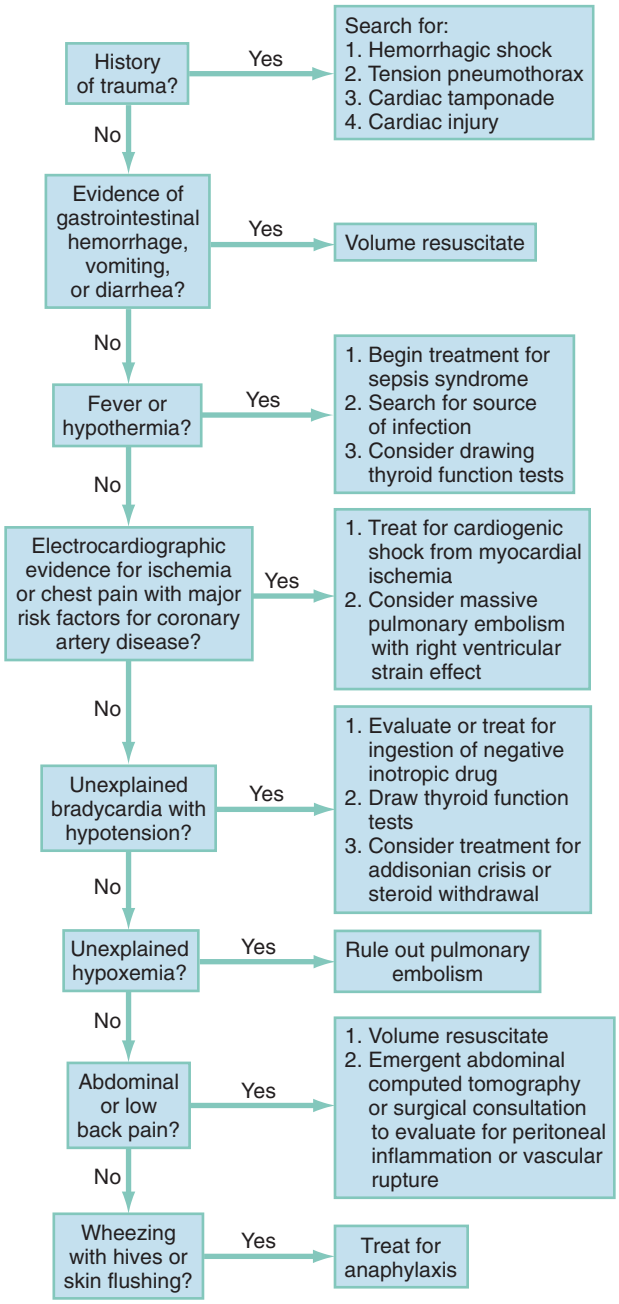

Figure 4-1. Flow diagram to classify undifferentiated shock.

complete blood count (CBC), urinalysis, serum electrolytes, and kidney and liver function tests are all indicated in the ED assessment. Arterial blood gases are ordered for a base deficit calculation and to correlate arterial oxygen partial pressure (Pao_2) with that measured by pulse oximetry, when the latter is deemed unreliable. Serum lactate measurement should be performed as early as possible in patients with suspected shock. Either venous or arterial lactate concentrations can be used.[24-27] If peripheral venous lactate is used, time, storage temperature, and tourniquet use have no significant effect on in vitro lactate production by erythrocytes if the measurement is done within 15 minutes after the sample is obtained.[28] Some EDs have bedside ultrasound capability, and both cardiac and abdominal scanning can be rapidly performed at the bedside to screen for inadequate central venous volume, occult hemoperitoneum, abdominal aortic aneurysm, left ventricular failure, and cardiac tamponade. A systematic ultrasound protocol can significantly improve the physician's ability to accurately diagnose the cause of undifferentiated shock in ED patients,[29] and the finding of hyperdynamic left ventricular function in patients with undifferentiated shock strongly suggests sepsis as the cause.[30]

BOX 4-3 Definitions and Criteria for Septic, Hemorrhagic, and Cardiogenic Shock

Septic Shock

Systemic Inflammatory Response Syndrome (SIRS)

Two or more of the following:

1. Temperature >38°C or <36°C
2. Heart rate >90 beats/min
3. Respiratory rate >20 breaths/min or $Paco_2$ <32 mm Hg
4. While blood cell count >12,000/mm^3, <4000/mm^3, or >10% band neutrophilia

Severe Sepsis

SIRS with suspected or confirmed infection and associated with organ dysfunction or hypotension; organ dysfunction may include presence of lactic acidosis, oliguria, or altered mental status

Septic Shock

SIRS with suspected or confirmed infection with hypotension despite adequate fluid resuscitation; septic shock should still be diagnosed if vasopressor therapy has normalized blood pressure

Hemorrhagic Shock

Simple Hemorrhage

Suspected bleeding with pulse <100 beats/min, normal respiratory rate, normal blood pressure, and normal base deficit

Hemorrhage with Hypoperfusion

Suspected bleeding with base deficit <–4 mEq/L *or* persistent pulse >100 beats/min

Hemorrhagic Shock

Suspected bleeding with at least four criteria listed in Box 4-2

Cardiogenic Shock

Cardiac Failure

Clinical evidence of impaired forward flow of the heart, including presence of dyspnea, tachycardia, pulmonary edema, peripheral edema, or cyanosis

Cardiogenic Shock

Cardiac failure plus four criteria listed in Box 4-2

Consensus definitions of shock show the spectrum of hypoperfusion for the following three common causes of shock (Box 4-3):

1. *Septic shock.* The American College of Chest Physicians, European Society of Intensive Care Medicine, Society for Critical Care Medicine, American Thoracic Society, and the Surgical Infection Society[31] developed international consensus definitions for distinguishing septic shock from its precursor conditions, the systemic inflammatory response syndrome (SIRS), sepsis, and severe sepsis. Although this particular consensus requires persistent hypotension after fluid resuscitation to strictly define septic shock, initiation of treatment for empirically diagnosed severe sepsis or septic shock should not await the onset of hypotension.
2. *Hemorrhagic shock.* The American College of Surgeons has divided hemorrhagic shock into four stages, depending on

the severity of blood loss and the physiologic response to this loss, but such arbitrary divisions are of little value. A more useful approach defines hemorrhagic shock as being present when systemic hypoperfusion manifests as lactic acidosis with organ dysfunction.

3. *Cardiogenic shock*. Cardiogenic shock should be thought to be present whenever cardiac failure (ischemic, toxic, or obstructive) causes systemic hypoperfusion that manifests as lactic acidosis with organ dysfunction.

MANAGEMENT

Monitoring Perfusion Status

In the effort to resuscitate a patient with circulatory shock, the clinician must follow specific indices of systemic perfusion and organ function to know if the resuscitation effort is working. In all patients with shock, circulation must be monitored by continuous electrocardiography and pulse oximetry. Cuff sphygmomanometer measurement of BP should be performed frequently during resuscitation. Because cuff sphygmomanometer measurement may be inaccurate in severe hypotensive states, the use of an arterial pressure monitoring line should be considered, especially if vasoactive medications are being administered. BP and HR correlate poorly with cardiac index (CI) in shock and often underestimate the severity of systemic hypoperfusion.[8] Moreover, children with hypovolemic shock frequently demonstrate a normal BP until they rapidly deteriorate.[32] Urine output should be measured as an index of vital organ perfusion (about 1 mL/kg/hr in persons without renal disease). A downward trend of the serum lactate concentration or upward trend of the base deficit, when observed with improving vital signs and urine output, is a reliable gauge of the adequacy of resuscitation and prognosis in shock from any cause.[21,33] A rising lactate concentration (or refractory hypotension with worsening base deficit) despite ongoing resuscitation is a portent of imminent death, and vigorous resuscitation efforts or specific procedural intervention should be instituted.

Most patients with shock can be fully resuscitated with peripheral venous access established with two catheters of at least a size 18 gauge. Monitoring of central venous pressure (CVP) as part of a goal-directed resuscitation may improve outcome in patients with septic shock.[34] Patients with cardiac failure or renal failure may benefit from closer measurement of the CVP and insertion of a central venous catheter. An 8.5-French catheter (Cordis Sheath) allows for accurate measurement of the CVP and insertion of a pulmonary artery catheter or other monitoring device if needed. In children a 3- or 5-French bilumen catheter can be placed in the femoral vein with few complications.[35] To reduce the potential for limb damage from extravasation from a peripheral IV, vasoactive medications are optimally administered through a central venous catheter. If vasoactive medications are administered, additional peripheral intravenous catheters are required for infusion of crystalloid and other treatments. Many patients with renal disease or cancer have indwelling catheters. In patients with empirical criteria for shock, this catheter should be used for IV access, unless satisfactory access has already been established at other anatomic sites. In EDs where the standard practice is not to use these ports at the request of other physicians, a specific hospital policy and training session should be developed to make an exception in the case of circulatory shock. In general, failure to administer fluids rapidly and in sufficient quantity outweighs considerations about preservation of the line for future therapy.

Quantitative Resuscitation

Quantitative resuscitation (also called goal-directed therapy, goal-oriented resuscitation, or hemodynamic optimization) was first described in 1988 and refers to the practice of resuscitating patients to predefined physiologic endpoints indicating that systemic perfusion and vital organ function have been restored.[36] Since that time many studies have evaluated the efficacy of such a therapeutic approach to shock, and a meta-analysis of these studies confirms its benefit for reducing mortality rates.[37] For many years in the intensive care unit (ICU), physicians have relied on the use of the pulmonary artery catheter (PAC) to help optimize left ventricular filling indices. At present the use of the PAC remains controversial. In the last 5 years, five randomized controlled trials investigating the management of critically ill patients with a PAC have been published.[38-42] None have found a benefit in terms of survival or length of stay. Insufficient data have been published to support the use or avoidance of PACs in ED populations; however, extrapolating from ICU studies, PACs have no role in the management of shock in the ED.

Several alternative methods to the PAC have been proposed as endpoints to resuscitation in the ED. The *lactate clearance* index refers to serial measurements of venous or arterial lactate.[33,43] Lactate clearance involves measuring the blood lactate concentration at two or more times. If the lactate concentration has not decreased by 10% two hours after resuscitation has begun, additional steps must be undertaken to improve systemic perfusion.[43] Resuscitation should continue until the lactate concentration drops below 2 mM/L. Clinical trials are presently investigating the utility of lactate clearance as an endpoint of resuscitation, which will have ramifications for the increasing use of point-of-care lactate testing platforms in the ED.

Mixed venous oxygen saturation (Svo_2) measurements reflect the balance between oxygen delivery and oxygen consumption. Previous studies have suggested that the Svo_2 can be used as a surrogate to CI when targeting normalization of endpoints ($Svo_2 = 65\%$ or CI 2.5–3.5 L/min/m^2) for therapeutic intervention in critically ill patients.[44] Although Svo_2 requires the use of a PAC, the central venous oxygen saturation ($Scvo_2$) drawn from the central circulation has been shown to closely parallel the Svo_2, especially when tracking changes or trends in the values.[45]

Early quantitative resuscitation, which incorporates multiple indices of circulatory and oxygenation status, was shown in one randomized controlled trial to significantly reduce mortality and morbidity rates in ED patients with severe sepsis or septic shock.[34] Patients are resuscitated within the first 6 hours of care to achieve normalization of CVP and mean BP and to maintain a $Scvo_2$ greater than or equal to 70% (Fig. 4-2). The decrease in mortality rate from this new treatment strategy, termed *early goal-directed therapy*, has been found effective in smaller prospective before-and-after studies of patients with sepsis.[46,47] Large multicenter validation of this resuscitation strategy in sepsis is underway. However, it has not been tested in other causes of shock but shows the value of using defined physiologic endpoints to measure systemic perfusion during resuscitation from shock in the ED. This approach also further substantiates the importance of the first 6 hours of resuscitation.

Ventilation

Rapid sequence intubation is the preferred method of airway control in most patients with shock (see Chapter 1). Intubation

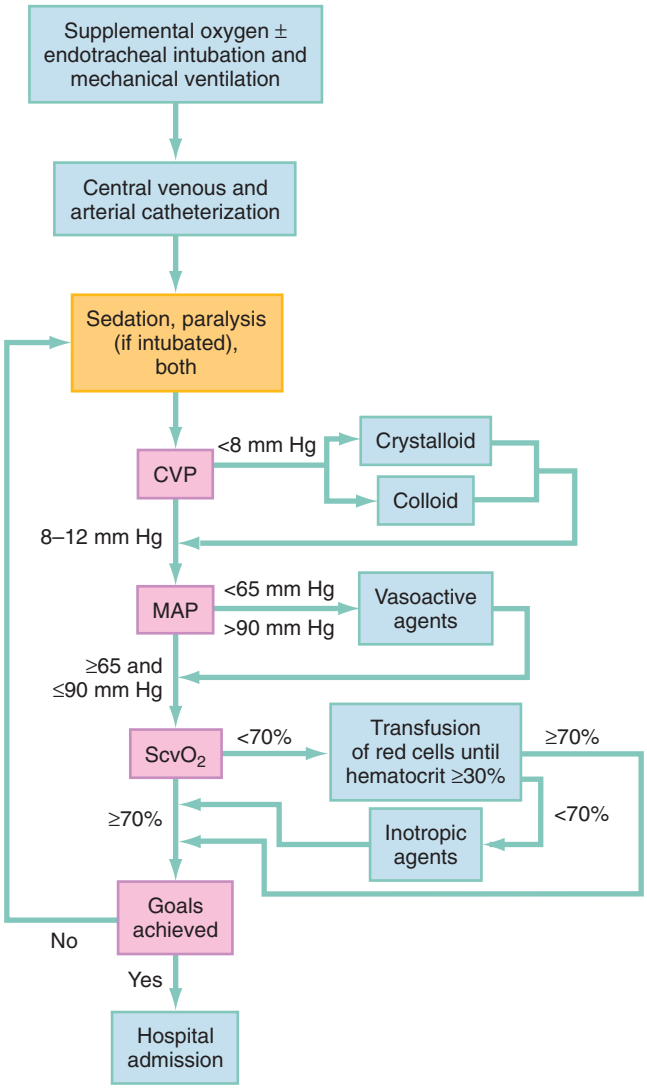

Figure 4-2. Flow diagram outlining the protocol for quantitative resuscitation when treating patients with severe sepsis or septic shock. This protocol outlines specific hemodynamic and physiologic parameters the clinician should seek to achieve within the first 6 hours of care. This protocol is focused on resuscitation and should be used in conjunction with standard clinical care for patients with suspected infection, such as appropriate diagnostic studies to determine the focus of infection and appropriate antimicrobial agents to treat the infection. CVP, central venous pressure; MAP, mean arterial pressure; $ScvO_2$, central venous oxygen saturation. (Redrawn from Rivers E, et al: Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 345:1368, 2001.)

prevents aspiration, increases oxygenation, treats acute respiratory failure, provides initial treatment for metabolic or hypercarbic acidemia, and protects the patient who will be sent to an uncontrolled environment (e.g., for tests). Intubation also reduces the work of breathing, which, in the hypoperfused patient, further exacerbates lactic acidemia. Strenuous use of accessory respiratory muscles can increase oxygen consumption by 50 to 100% and decrease cerebral blood flow by 50%.[48,49] More importantly, if the patient has increased airway resistance (e.g., bronchospasm with anaphylaxis) or a decrease in lung compliance (e.g., pulmonary edema, ARDS), a more negative intrathoracic pressure must be generated to fill the lungs with each inspiration. The greater suction effect is also exerted on the left ventricle, impeding its ability to eject and increasing functional afterload. Positive pressure ventilation removes this impedance and can improve ventricular function and cardiac output up to 30%.[48]

BOX 4-4 CLINICAL MANAGEMENT GUIDELINES FOR FOUR COMMON CAUSES OF SHOCK

Hemorrhagic Shock

Ensure adequate ventilation/oxygenation
Provide immediate control of hemorrhage, when possible (e.g., traction for long bone fractures, direct pressure)
Initiate judicious infusion of isotonic crystalloid solution (10–20 mL/kg)
With evidence of poor organ perfusion and 30-minute anticipated delay to hemorrhage control, begin packed red blood cell (PRBC) infusion (5–10 mL/kg)
With suspected central nervous system trauma or Glasgow Coma Scale score <9, immediate PRBC transfusion may be preferable as initial resuscitation fluid
Treat coincident dysrhythmias (e.g., atrial fibrillation with synchronized cardioversion)

Cardiogenic Shock

Ameliorate increased work of breathing; provide oxygen and positive end-expiratory pressure (PEEP) for pulmonary edema
Begin vasopressor or inotropic support; norepinephine (0.5 µg/min) and dobutamine (5 µg/kg/min) are common empirical agents
Seek to reverse the insult (e.g., initiate thrombolysis, arrange percutaneous transluminal angioplasty)
Consider intra-aortic balloon pump counterpulsation for refractory shock

Septic Shock

Ensure adequate oxygenation; remove work of breathing
Administer 20 mL/kg of crystalloid or 5 mL/kg of colloid, and titrate infusion to adequate central venous pressure and urine output
Begin antimicrobial therapy; attempt surgical drainage or débridement
Begin PRBC infusion for hemoglobin < 8 g/dL
If volume restoration fails to improve organ perfusion, begin vasopressor support; initial choice includes dopamine, infused at 5–15 µg/kg/min, or norepinephrine, infused at 0.5 µg/min

Volume Replacement

The next imperative in shock is to decide when "the tank is full." The goal in volume replacement is slightly elevated left ventricular end-diastolic *volume*, which is a difficult measurement to make in the ED. The CVP is most often used to estimate right ventricular filling pressure and is used in some quantitative resuscitation algorithms. Because both ventricles tend to stiffen during shock, a high CVP (10–15 cm H_2O) is often needed to produce adequate filling volume. It is a long way, however, from the CVP measurement to actual knowledge of left ventricular end-diastolic volume; a presumed adequate CVP must be substantiated by increases in urine output and BP and decreasing lactate concentrations.[50]

Treating Specific Causes

Box 4-4 presents the general treatment approach for the four common causes of shock.

Hemorrhagic Shock

Standard treatment for hemorrhagic shock consists of rapidly infusing several liters of isotonic crystalloid in adults or three successive 20-mL/kg boluses in children. Colloids, including albumin and hydroxyethyl hetastarch (Hespan), can be used as well but at considerable increase in cost and without effect on morbidity or mortality rates.[51] Colloids offer the theoretic advantage of a high osmotic pressure, which should help to maintain a normal intravascular volume after retransfusion from hemorrhage. If criteria for shock persist despite crystalloid infusion (see Box 4-2), packed red blood cells (PRBCs) should be infused (1–2 units in adults or 5–10 mL/kg in children). Type-specific blood should be used when the clinical scenario permits, but uncrossmatched blood should be used at the earliest opportunity for patients with arterial hypotension and uncontrolled hemorrhage. O-negative blood is used in women of childbearing age and O-positive blood in all others (see Chapter 5). Substantial evidence supports the use of leukodepleted blood, which has been filtered to remove donor neutrophils.[52] Leukodepleted blood is used in countries outside the United States because it produces less retransfusion-related organ damage.[53]

The infusion of hemoglobin-based oxygen carriers as alternatives to PRBCs for resuscitation of hemorrhagic shock have been extensively studied. In a large randomized controlled trial, diaspirin cross-linked hemoglobin, a purified and chemically modified human hemoglobin substrate, was compared with crystalloid for initial resuscitation in the critically injured, and its use resulted in a higher mortality rate at interim analysis, resulting in termination of the trial.[54] Other artificial hemoglobin substitutes may be available in the future but at present show no benefit over PRBCs.

Recent studies have endorsed the concept of either delayed resuscitation or hypotensive resuscitation for hemorrhagic shock. This is discussed in Chapters 34, 42, and 43. Controlling hemorrhage remains the cornerstone of treating hemorrhagic shock, and evidence continues to support immediate surgery when direct vascular control cannot otherwise be obtained (see Chapter 34).

Septic Shock

Septic shock begins as an infectious nidus, which triggers a domino effect of cellular, microvascular, hematologic, and cardiovascular dysfunction. Treatment begins by establishing adequate ventilation to correct hypoxia and acidosis and to reduce systemic oxygen consumption and left ventricular work. This often requires endotracheal intubation and sedation for mechanical ventilation. The controversy regarding the use of etomidate in patients with septic shock is discussed in Chapter 1.

The second goal is to achieve adequate ventricular filling. The choice of fluids in treating septic shock is probably less important than scrupulous monitoring for adequate tissue perfusion. However, choices for fluid resuscitation should involve consideration of availability and the cost-benefit ratio. Initial volume replacement should include rapid infusion of 20 to 25 mL/kg of crystalloid. If hypoperfusion is persistent, 5- to 10-mL/kg boluses of a colloid should be considered. Blood should be transfused in the ED to restore hematocrit to at least 30 to 35%.

The third directive is to eradicate the infection with antimicrobial therapy and, where necessary, surgical drainage. A recent study reported that in adult patients with septic shock, effective antimicrobial administration within the first hour of documented hypotension was associated with increased survival to hospital discharge and that each hour delay in antimicrobial administration over the first 6 hours after recognition was associated with an average decrease in survival of 7.6% per hour.[55] The choice of antimicrobial agent can be directed by clinician experience and institutional minimal infective concentration (MIC) data. When no focus can be found in septic shock, a semisynthetic penicillin with a β-lactamase inhibitor, in combination with an aminoglycoside plus vancomycin is a rational empirical choice. When neutropenia is suspected in a patient with sepsis syndrome, the progression to refractory, fatal septic shock can be cataclysmic. Neutropenia is suggested in patients who have recently undergone chemotherapy. Chemotherapy patients with sepsis represent a special challenge because the pathophysiology may be complicated by anemia, thrombocytopenia, dehydration from vomiting, and the effect of adjunctive steroid therapy. Chemotherapy patients often have indwelling catheters, which predisposes them to more unusual causes of sepsis, including gram-positive bacteria and fungi[56] (see Chapter 143).

Septic shock refractory to volume restoration (urine output or BP remains low; lactate increases) requires vasopressor support. The primary goal of vasopressor support is to increase cardiac output and oxygen delivery to vital organs. Norepinephrine (0.5–30 μg/min) or dopamine (5–20 μg/kg/min) are the first-choice vasopressors for correcting hypotension in septic shock. Norepinephrine is more potent than dopamine and thus may be more effective at reversing hypotension; however, dopamine may be preferred in the setting of inadequate systolic heart function.[57] Dobutamine may also be used with norepinephrine to increase cardiac output and maintain adequate oxygen delivery. A recent multicenter randomized controlled trial of 330 subjects reported that, when simultaneous blood pressure and inotropic support were necessary, there is not a difference in safety or efficacy between epinephrine (0.2 μg/kg/min starting dose) alone and norepinephrine plus dobutamine.[58] Many other studies of different vasopressor regimens are ongoing; however, to date there is no definitive evidence to clearly support the use of one vasopressor over another in septic shock.[59]

Drotrecogin alfa activated (or activated protein C), a recombinant human activated protein with anti-inflammatory, antithrombotic, and profibrinolytic properties, has been investigated in large multicenter trials for the treatment of patients with systemic inflammation and organ failure from acute infection.[60] The institution of activated protein C therapy is not part of the routine ED management of sepsis as there is a large window of time for treatment initiation (within 24 hours of meeting criteria). If this therapy is considered, consultation with the ICU physician who will assume care of the patient is recommended because the therapy is continued for 96 hours.

The use of corticosteroids in the treatment of sepsis and septic shock has been investigated with mixed results. The results of two large randomized controlled trials confirm that there is no role for high-dose, short-course corticosteroid therapy in septic shock.[61,62] Recently, two large multicenter randomized trials of low-dose hydrocortisone treatment failed to show survival benefit among all patients with septic shock.[63,64] One of the studies did show a survival benefit to use of low-dose hydrocortisone among patients who did not adequately respond to a corticotropin stimulation test[64]; however, the larger study did not find this survival benefit.[63] Most current guidelines recommend that low-dose hydrocortisone should only be administered to patients receiving chronic steroid replacement and in patients with refractory shock despite adequate fluid and vasopressor support, and corticotropin stimulation testing is no longer considered of value.[57]

Cardiogenic Shock

The immediate treatment of cardiogenic shock focuses on improving myocardial contractility and pump function. Cardiogenic shock is traditionally defined as the combination of systemic signs of hypoperfusion with arterial systolic BP less than 90 mm Hg (or 30% below a known baseline). If the work of breathing is tiring the patient, if severe pulmonary edema is causing significant hypoxemia, or if respiratory failure is imminent, intubation and mechanical ventilation should be initiated, followed by emergent treatment of bradydysrhythymias or tachydysrhythmias and inotropic support. Barbiturates are not recommended for sedation or anxiety in the intubated patient, because they may have exaggerated negative inotropic effects. Cautious use of benzodiazepines, supplemented by fentanyl for analgesia, is the best approach. Improving perfusion often ameliorates the anxiety and restlessness that accompanies shock states. Etomidate and ketamine have the least risk for hemodynamic compromise and should be used (but in reduced doses) for intubation, accompanied by a full dose of succinylcholine. Prior to administration of vasoactive medications, if hypovolemia is present, it should be corrected by infusing crystalloid or blood products. To improve myocardial contractility, vasopressors or inotropic agents should be administered. The choice of which agent to use depends on signs and symptoms and on the systolic blood pressure (SBP). If the SBP is less than 70 mm Hg and the signs and symptoms of shock are present, norepinephrine is the agent of choice. If the SBP is between 70 and 100 mm Hg and the signs and symptoms of shock are present, dopamine should be used. However, if the SBP is 70 to 100 mm Hg and there are no signs or symptoms of shock, dobutamine is the agent of choice.[3] All of these agents should be started at the same doses used for septic shock. For refractory hypotension and shock, amrinone or milrinone may improve cardiac output, although no empirical evidence is available to support their routine use. Amrinone and milrinone are biperidin derivatives that increase cyclic adenosine monophosphate (cAMP) by inhibiting phosphodiesterase (complex F-III). A loading dose of 0.75 mg/kg for amrinone or 50 µg/kg for milrinone is necessary, followed by a titrated constant infusion for either drug (5–10 µg/kg/min for amrinone and 0.5 µg/kg/min for milrinone).

When pharmacologic support fails to improve indices of perfusion, the next step is to initiate intra-aortic balloon pump counterpulsation (IABPC). This requires the facilities and personnel of a high-level ICU or coronary care unit (CCU). Controlled trials have shown IABPC to improve short-term survival, improve post-thrombolytic patency rates, and reduce stroke morbidity. IABPC increases cardiac output by a mean of 30% in refractory cardiogenic shock and can prolong survival until interventional procedures can be performed. IABPC may be contraindicated in patients with aortic insufficiency or severe peripheral vascular disease.

The dismal outcome of cardiogenic shock complicating acute myocardial infarction (MI) has been improved in recent years. Evidence suggests that emergent revascularization is not superior to medical management in reducing mortality rates in the short term; however, significant improvements in general mortality rates are seen at both 6 months and 1 year[65,66] (see Chapter 77). At present the management of acute MI with cardiogenic shock proceeds as follows and constitutes optimal therapy: (1) ensure adequate ventilation and oxygenation, (2) treat emergent dysrhythmias, (3) initiate vasopressor/inotropic support, (4) administer aspirin if the patient is not allergic, and (5), heparin anticoagulation and arrangement for emergent percutaneous coronary intervention.

KEY CONCEPTS

- Circulatory shock can occur with normal arterial blood pressure, and not all patients with arterial hypotension have circulatory shock.
- A base deficit more negative than –4 mEq/L or a serum lactate > 4.0 mmol/L indicates the presence of widespread circulatory insufficiency in suspected shock.
- Urine output is a reliable index of vital organ perfusion in patients with suspected shock.
- Ill patients with tachycardia, a worsening base deficit, and low urine output should be diagnosed with circulatory shock.
- Use of defined physiologic endpoints to measure systemic perfusion during resuscitation (quantitative resuscitation) is a valuable approach to optimal resuscitation in ED patients with shock.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 5

Blood and Blood Components

Matt Emery

PERSPECTIVE

The era of modern blood transfusion began in the early 1900s with discovery of the ABO red cell antigen system. By World War I it was known that adding citrate enabled the storage of anticoagulated blood. Blood banking in the United States began during the 1930s. Energetic pioneers such as John Lundy of the Mayo Clinic gained a wealth of clinical experience, prompting dissemination of expert-based advice, such as Lundy's recommendation that blood transfusion was appropriate when a patient's hemoglobin (Hgb) was less than 10 g/dL or when a patient lost more than 15% of circulating blood volume. These recommendations were not, however, based on rigorous controlled trials. Rapid expansion of blood banking occurred after World War II, and in subsequent decades research focused on such critical issues as prolonging the storage life of blood products, component therapy, and reducing the risk of transfusion reactions and transfusion-related infections.[1,2]

More recently, at a time when nearly 14 million units of packed red blood cells (PRBCs) are transfused yearly in the United States, attention has turned toward evaluating the efficacy of more restrictive transfusion policies, rethinking the overall risk-benefit ratio of blood products, and developing bloodless alternatives.[1,3-7]

PATHOPHYSIOLOGIC PRINCIPLES

Blood Banking[3]

Blood centers, such as those of the American Red Cross and America's Blood Centers, process more than 90% of the units collected in the United States. Traditional allogenic donation methods still predominate, but increasing use is being made of red cell apheresis technology, by which red cells are separated from the blood at the time of collection, with the rest returned to circulation. This allows collection of about two transfusable units during a single donation.

Blood collection bags contain an anticoagulant-preservative of citrate, phosphate, dextrose, and adenine (CPDA-1), ensuring a shelf life (viability of at least 70% of the RBCs 24 hours after infusion) of 35 days and hematocrit of 70 to 80% for PRBCs.[8] Additive solutions (Adsol, Nutricel, Optisol) provide additional nutrients, extending maximum storage to 42 days and lowering viscosity, which makes infusion easier.[9,10]

Storage impairs red cell function. Transfused blood delivers oxygen to the tissues less efficiently. Even though blood is refrigerated at 1 to 6° C (usually 4° C), cell metabolism continues and changes occur (collectively referred to as the *storage lesion*). Documented alterations are numerous and include a decrease in pH and in the level of 2,3-diphosphoglycerate (2,3-DPG). In addition, the deformability of RBCs makes them, over time, more spherical and rigid, thereby increasing resistance to capillary flow. With time, many of these changes are reversed in vivo. The decrease in 2,3-DPG, for example, results in a left shift in the hemoglobin-oxygen dissociation curve (less oxygen is released at a given partial pressure of oxygen [Po_2]), but the ability to synthesize 2,3-DPG is regained over the first 24 hours after transfusion.[10] The relationship between overall oxygen transport and oxygen delivery to tissues is complex. Depletion of S-nitrosohemoglobin during storage alters oxygen-dependent regulation of microcirculatory blood flow ("hypoxic vasodilation").[11] There is ongoing debate about whether and when these and other changes are clinically significant, and how they might be overcome.[12-16]

Additional well-established changes include cell leakage of potassium, although the amount (≈ 6 mEq/U[17]) is readily tolerated by most otherwise healthy patients. PRBCs contain essentially no functional platelets or granulocytes.

Blood Typing

A basic knowledge of compatibility testing allows emergency physicians to order blood bank products and services appropriately. Identified red blood cell (RBC) antigens include the ABO and related carbohydrate antigens (H, P, I, and Lewis), the 48 Rh system antigens, and more than 200 non-ABO/Rh antigens. When a clinician anticipates that transfusion might be indicated, a "type and screen" can be ordered, and a blood specimen from the patient is sent for the following tests: ABO grouping, Rh typing, and an antibody screen for unexpected (non-ABO/Rh) antibodies. Completion of these steps speeds the delivery of crossmatched blood if it is subsequently required.

ABO incompatibility results in acute hemolysis, the most serious transfusion reaction. ABO grouping requires that the recipient's red cells be tested with anti-A and anti-B serum, and that their serum be tested with A and B red cells.[8] Patients form antibodies at about 6 months of age against the A and B antigens they lack. Those with type AB blood form no ABO group antibodies. Patients who are type O have antibodies against both. The major clinically

significant Rh antigen is the D antigen. Rh typing can usually be determined by adding a commercial reagent (anti-D) to recipient RBCs.

The antibody screen identifies clinically significant "unexpected antibodies" in the patient's serum. These antibodies form when a patient responds to a foreign RBC antigen, usually due to prior exposure, such as with allogenic transfusion, pregnancy, or organ transplant. The antibody screen is performed by mixing commercial RBC reagents (mixtures of red cells expressing clinically significant antigens) with the patient's serum. The incidence of these unexpected antibodies in the general population is low (<1–2%), but a positive screen mandates further compatibility testing.[10,17]

The type and screen allows quicker selection of appropriate banked blood for complete crossmatch if a transfusion is ordered. Ideally, blood identical to the patient's own ABO and Rh group is used. Local blood supplies, however, might dictate that a nonidentical, but compatible, unit be used. Patients with blood group AB, for example, can receive blood from any of the ABO groups. Men, and women beyond childbearing age, who are Rh-negative and have no preformed Rh (anti-D) antibodies may receive either Rh+ or Rh− blood. When a blood transfusion is ordered, a formal crossmatch is done by mixing recipient serum with donor RBCs as a final compatibility test prior to transfusion. This can be done using a Coombs test (with serum incubated to 37° C), or the more rapid "immediate spin crossmatch" at room temperature, which will detect only ABO incompatibility. The more thorough Coombs' test can detect incompatibilities that were missed with the antibody screen.[17]

Special Clinical Circumstances

To select the most appropriate blood product in the emergency setting, clinicians must consider the patient's hemodynamic stability and the amount of time available to intervene.[17]

Universal Donor Group O

Universal (group O) blood is used when RBCs must be given at once to hemorrhaging, unstable patients. Premenopausal females (adults *and* children) need group O Rh-negative blood, whereas men and all other women may receive O Rh-positive blood, which is more common. Conversely, the "universal" type for fresh frozen plasma (FFP) is type AB, since it contains no antibodies to either A or B antigens.

If the patient's condition can be initially stabilized with crystalloid infusion, type-specific blood (using ABO and Rh testing) should be available within 15 minutes of receiving a sample of the patient's blood.

An antibody screen and immediate spin crossmatch take approximately 45 to 60 minutes. The recipient's serum is screened for unexpected antibodies as described earlier. An "immediate spin crossmatch" is then performed at room temperature if the antibody screen is negative.

If the antibody screen is positive, however, the antibody is identified using more elaborate procedures, and a complete crossmatch (using a Coombs test with incubated serum) is required. This process can take up to several hours.[17]

Massive Transfusion

Abnormalities from massive transfusion are rarely seen during a patient's initial resuscitation in the emergency department, but the physician should be aware of potential problems. Massive transfusion has been defined as transfusion equivalent to the patient's blood volume with stored RBCs within a 24-hour period.[8]

In addition to storage lesion problems, hypothermia can result when patients receive more than 100 mL/min of cold blood for 30 minutes. This can be prevented by warming the blood to 37° C with a blood warmer. Transiently decreased levels of ionized calcium may result from the citrate preservative. Clinical signs of hypocalcemia include circumoral tingling, skeletal muscle tremors, and QT segment prolongation. Calcium administration is guided by determination of ionized calcium levels and clinical findings.[18]

Dilutional thrombocytopenia may result, but platelet concentrate is not indicated unless there is evidence of microvascular bleeding. If disseminated intravascular coagulation (DIC) develops, platelet concentrate, FFP, and cryoprecipitate may be required.[18]

Administration

Legal Aspects

Before a blood product can be infused, two qualified personnel check it at the bedside to prevent a potentially fatal clerical error. This check includes recipient and unit identification, as well as confirmation of compatibility, and the expiration date.[8]

At times a patient may arrive from a transferring facility with typed and crossmatched blood. If the blood is administered immediately in the emergency department, the hospital blood bank is not involved and accepts no responsibility for the blood. If the blood is not used immediately and the blood bank is asked to hold the blood for the patient, it is processed and crossmatched as for other issued blood and quarantined for 24 hours. It can be sent back to the blood bank to have this done only if (1) it has been constantly maintained at a temperature between 1 and 6° C, (2) all container seals are intact, and (3) tubing segments have remained attached to the blood container.[8]

Infusion Adjuncts

Urgent transfusion situations require flow rates faster than gravity can provide. An administration set with an in-line pump that is squeezed by hand is the simplest method to speed infusion. Pressure bags are also available that completely encase the blood bag and apply pressure evenly to the blood bag surface. If external pressure is anticipated, large-bore needles are recommended for venous access to prevent hemolysis.[8]

If only a small-gauge needle is available, the transfusion may be diluted with normal saline, but this may cause unwanted volume expansion. In elective transfusions, no significant hemolysis occurs when small-gauge needles are used and when the maximum rate of infusion is less than 100 mL/hr.[8]

MANAGEMENT

Decision-Making

When considering the use of blood component therapy, the patient's age, severity of symptoms, cause of the deficit, underlying medical condition, ability to compensate for decreased oxygen-carrying capacity, and tissue oxygen requirements are all considered. Clinical evaluation, including appearance (pallor, diaphoresis), mentation (alert, confused), heart rate, blood pressure, and the nature of the bleeding (active,

controlled, uncontrolled), can be supplemented by laboratory evaluation of Hgb, hematocrit, platelets, and clotting functions.

A review of relevant literature underscores the difficulty of making firm recommendations. Only recently[5,7,19,20] have randomized controlled trials investigated the efficacy of various transfusion triggers in the critical care and surgical setting. The largest randomized trial in adult patients to date, the TRICC (Transfusion Requirements in Critical Care) trial,[5] demonstrated that in the critical care setting, a transfusion threshold of 7 g/dL was as safe as a threshold of 10 g/dL, although subgroup analysis generated some concern that patients with ischemic heart disease may benefit from a higher transfusion threshold.[21] In a large, retrospective analysis of patients hospitalized with acute myocardial infarction, anemia appeared to raise the risk of death, and transfusion for a hematocrit of 33% or less improved overall mortality rates.[22] It is debatable, however, whether these results can be generalized to the emergency department setting. Further research is urgently needed.[1] The list of known and suspected risks associated with transfusion, on the other hand, is long and growing. Recent concerns include Transfusion Related Acute Lung Injury (TRALI) and immune modulation.[23] As a result, recent guidelines generally recommend a "restrictive strategy" for most patients, utilizing transfusion triggers more stringent than those traditionally followed.[24] Recommendations for the use of FFP likewise have long been more expert-based than evidence-based.[25,26]

Whole Blood

Whole blood is not as economical as component therapy, although there has recently been renewed interest in the benefits of using fresh whole blood in military field hospitals.[16] In the United States it is rarely used.

Packed Red Blood Cells

PRBCs are given to improve oxygen delivery to tissues at the microvascular level. Controversies regarding efficacy were discussed earlier; absent further research, the recommendations of the American Society of Anesthesiologists seem reasonable: transfusion is rarely needed with a Hgb concentration greater than 10 g/dL and almost always needed when the Hgb is less than 6 g/dL.[27] Patients with a Hgb between 6 and 10 mg/dL require careful clinical judgment. Ischemic heart disease may render patients more intolerant of anemia, although more research is needed to clarify whether transfusion benefits these patients. Lastly, most emergency physicians would still transfuse a patient with ongoing hemorrhage and unstable vital signs despite adequate fluid resuscitation, and would occasionally consider withholding transfusion for Hgb levels even lower than 6 g/dL in a young, healthy, asymptomatic patient without ongoing hemorrhage.

Artificial Oxygen Carriers

Research into both hemoglobin-based oxygen carriers and perfluorocarbon emulsions is ongoing, but as yet none are approved for general clinical use in the United States. Several problems remain unsolved. Hemoglobin-based carriers, for example, have been found to cause vasoconstriction through nitric oxide (NO) scavenging,[19] endothelin release, and peripheral alpha-adrenergic receptor sensitization. Perfluorocarbon emulsions require relatively high partial pressure of oxygen (Po_2) levels. When used clinically, pure oxygen is usually administered to patients.[6]

Fresh Frozen Plasma

Current practice dictates that FFP be given to patients with evidence of coagulopathy (international normalized ratio [INR] >1.5–2.0) who are either actively bleeding (absolute indication) or require an invasive procedure (relative indication).[28,29] Most clinicians consider active bleeding to include clinically significant hemorrhage, not minor degrees of oozing. If a specific factor deficiency is identified (e.g., hemophilia), targeted replacement of that factor, if available, is more practical. FFP should not be used for volume expansion.

Platelets

Platelet transfusion is indicated prophylactically when the count is less than 10,000/mL, and this includes a margin of safety, as it appears that hemostasis is well-maintained even at counts of 5000/mL. Platelet counts of 40,000 to 50,000/mL are sufficient to perform invasive procedures.[30] Platelets have traditionally been given to adults in a dose of 6 U of platelet concentrate (i.e., a "six-pack" of platelets), which typically raises the platelet count about 40,000 to 60,000/mL. This practice is not, however, evidence-based.[30] Because hemostasis is maintained with platelet counts as low as 5000/mL, it seems likely that smaller, more frequent platelet transfusions should be equally efficacious, but more cost-effective in hospitalized patients. This may be impractical, of course, in outpatients. An ongoing randomized trial addresses this issue by assigning patients to low-, medium-, and high-dose platelet regimens.[31] Lastly, if immune-mediated consumption is the cause of thrombocyopenia, transfusion is generally ineffective.

Autotransfusion

Autotransfusion may be used in the emergency setting in the event of severe chest trauma. This strategy has numerous advantages: immediate availability, blood compatibility, elimination of patient-to-patient disease transmission, avoidance of the storage lesion, less risk of circulatory overload, and fewer direct complications (e.g., hyperkalemia, hypothermia, hypocalcemia, and metabolic acidosis). There is also greater acceptability to some patients whose religious convictions prohibit transfusions.[31,33] Widespread use has not occurred, however, because of the limited number of appropriate trauma patients, the training required to operate the equipment, and the time required for equipment setup.[34]

Therapeutic Modalities

Packed Red Blood Cells

In acute hemorrhage, PRBCs are used to supplement initial crystalloid replacement. In an average adult, 1 U of PRBCs increases the Hgb by about 1 g/dL or the hematocrit by about 3%.[35] A similar increase in pediatric patients is obtained by administering 3 mL/kg. PRBCs are run through a filter with a large-bore intravenous line with normal saline. Lactated Ringer's solution can lead to clotting secondary to the added calcium, and hemolysis may result with a hypotonic solution. Medications should not be added to the unit or pushed through the transfusion line unless it has been thoroughly flushed. Most transfusions are given over 60 to 90 minutes (not longer than 4 hours). Unused blood should be returned promptly to the blood bank because any units unrefrigerated for more than 30 minutes are discarded.[8]

Fresh Frozen Plasma

A unit of FFP typically has a volume of 200 to 250 mL, is ABO compatible, and is given through blood tubing within 2 to 6 hours of thawing.[8] It contains all clotting factors. One unit of activity for any coagulation factor is equal to the clotting activity found in 1 mL of FFP. It should be given in doses calculated to achieve a minimum of 30% of plasma factor concentration, traditionally calculated as 10 to 15 mL/kg of FFP. When used for the urgent reversal of warfarin anticoagulation, 5 to 8 mL/kg of FFP is considered sufficient.[29] Recent research, however, has questioned this,[36] and indicates that screening tests such as INR and activated partial thromboplastin time (aPTT) do not correlate well with clinical risk of bleeding, and large amounts of FFP (possibly as high as 30 mL/kg) may be needed to raise factor levels adequately to achieve hemostasis.[37] The need to correct the INR for invasive procedures such as central line placement has also been questioned.[38]

Platelets

Crossmatching is unnecessary, but Rh-negative patients should receive Rh-negative platelets because there may be enough cells in the platelet concentrate to cause Rh sensitization. In adults the traditional dose has been 4 to 6 U (a "six pack" of platelets), and in children it is 1 U/10 kg body weight. As noted earlier, however, consider giving smaller, more frequent transfusions in hospitalized patients. In frequently transfused patients it is often desirable to reduce human leukocyte antigen (HLA) sensitization. The use of leukoreduced, HLA-matched, cellular products decreases the risk of HLA antibody-induced immune destruction.[8]

OUTCOMES

Adverse effects of RBC transfusion can be divided into immune-mediated and non-immune-mediated categories, as well as acute, delayed, and chronic effects.

Immune-Mediated Adverse Effects

Acute

Intravascular Hemolytic Transfusion Reaction. Intravascular hemolytic transfusion reaction is the most serious transfusion reaction. It is usually the result of ABO incompatibility, most often due to error. The resulting antigen-antibody reaction leads to the intravascular destruction of transfused red cells, producing hemoglobinemia and hemoglobinuria. The onset of symptoms is immediate and may include fever, chills, headache, nausea, vomiting, a sensation of chest restriction, severe joint or low back pain, and a burning sensation at the site of the infusion.[17,39] Clinical effects can include hypotension, DIC, and acute tubular necrosis. Treatment includes stopping the transfusion immediately, replacing all old tubing with new, and initiating vigorous crystalloid fluid therapy. Diuretic therapy should be used to maintain urine output at 1 to 2 mL/kg/hr. Pressor agents may be needed to sustain the blood pressure and protect the kidneys. Blood and urine specimens should be sent to the laboratory, as well as the remainder of the transfusion and the blood tubing. Detecting free Hgb (blood and urine) and a positive Coombs test on post-transfusion, but not pretransfusion specimens confirms the diagnosis.[17]

Febrile Transfusion Reaction. This is the most common and least serious transfusion reaction and is defined as a 1°C temperature elevation associated with transfusion that has no other medical explanation. Reactions are believed to result from antileukocyte antibodies, most commonly as a result of prior transfusion. Treatment is symptomatic with an analgesic-antipyretic and an antihistamine. The use of leukoreduced RBCs can decrease, but not eliminate, the risk of this reaction.[10,17] If a febrile reaction occurs in a first-time transfusion, it should be treated in the same way as an intravascular hemolytic reaction until proven otherwise.

Allergic Reactions (Urticaria to Anaphylaxis). Urticaria, or hives, may occur during a transfusion without other signs or symptoms and with no serious sequelae. It is generally attributed to an allergic, antibody-mediated response to a donor's plasma proteins. The transfusion does not need to be stopped, and treatment with an antihistamine is usually sufficient. If the patient has a known history of urticaria, the antihistamine should be administered before the transfusion. Occasionally, full anaphylaxis may be caused by an anti-immunoglobulin A (IgA) reaction to IgA in the donor's blood components. The patient is likely to have a genetic IgA deficiency and display hypotension, respiratory and gastrointestinal symptoms, but no fever. Treatment is with epinephrine and corticosteroids. Future transfusions should be with washed RBCs, and plasma products should be from other IgA-deficient individuals.[10]

Transfusion-Related Acute Lung Injury. TRALI, now considered the leading cause of transfusion-related mortality,[40] presents abruptly during, or within 6 hours of, the transfusion of plasma-containing blood products. These include PRBCs, FFP, platelets, and cryoprecipitate. The initial clinical presentation is that of a noncardiogenic pulmonary edema, with dyspnea, hypoxemia, and bilateral infiltrates on chest radiograph. Fever, hypotension, and transient leukopenia may also be seen. Other causes of acute lung injury should be ruled out. The underlying pathophysiologic mechanism is a subject of continuing debate and could involve multiple insults. Proposed theories include a reaction between transfused antibodies and granulocytes in the recipient, as well as the effects of biologically active factors that accumulate in stored blood such as cytokines and lipids.[41] One strategy suggested for reducing TRALI has been to use only male donors for plasma in order to avoid allotypic leukocyte antibodies which can occur in women as a result of prior pregnancies.[42]

Appropriate treatment consists of stopping the transfusion, notifying the blood bank, and providing respiratory support, which may include intubation and mechanical ventilation. It is safe to continue transfusion of blood products from a different donor, if necessary.[43] Complete resolution is typically seen within 48 to 96 hours. Overall prognosis is better than would be expected with many other causes of acute lung injury, with a reported mortality rate of 6% in one series.[44] Survivors rarely show long-term adverse effects.

Delayed

Extravascular Hemolytic Transfusion Reaction. These result from a non-ABO-mediated immune reaction, most often due to an anamnestic response in a patient previously sensitized to red cell antigens by transfusion, pregnancy, or transplant. This prior exposure may result in antibody levels that are too low to detect with the antibody screen. Following repeat exposure from transfusion, however, antibody levels rise, and extravascular hemolysis occurs days to weeks later. Less commonly, primary alloimmunization can occur after transfusion. The patient may have fever, anemia, and jaundice. Symptoms are not usually severe. Rare cases of oliguria or DIC can occur, however. Because the hemolysis is extravascular, hemoglobinemia and hemoglobinuria are typically not present.[10] Many

cases are subclinical, but management may require monitoring of hematologic and renal labs, maintenance of urine output, and additional red cell transfusions. Care is needed for subsequent transfusions to provide antigen-negative blood, which can be discussed with the blood bank.[45]

Transfusion-Associated Graft-Versus-Host Disease. This rare, but life-threatening, complication results when transfused lymphocytes proliferate and attack the recipient. Cell-mediated immunodeficiency puts the patient at risk, as does having an HLA type that is identical between donor and recipient (most often among first-degree relatives). Symptoms, which begin 3 to 30 days following transfusion, include fever, erythematous skin rash, diarrhea, elevated liver enzymes, and pancytopenia. The only effective treatment is bone marrow transplant, and most deaths result from coagulopathy or infection. Efforts are therefore directed at prevention by using gamma irradiation of all cellular components, which renders the donor lymphocytes incapable of proliferating. The use of leukocyte-poor components is also advocated. This condition should be kept in mind when considering transfusion in anemic leukemia or lymphoma, especially in patients who have recently received chemotherapy.[10] Consultation with an oncologist prior to transfusion should be strongly considered in these complex cases.

Non-Immune-Mediated Adverse Effects

Acute

Circulatory Overload. Chronically anemic, normovolemic elderly patients are at greatest risk for developing congestive heart failure with the rapid infusion of blood. Taking 4 hours to infuse a unit and using diuretics (if needed) should prevent this complication.[10]

Bacterial Contamination. Bacterial contamination, most commonly with *Yersinia enterocolitica* (which grows well in cool, iron-rich environments), occurs in fewer than 1 per million units of stored RBCs, but typically results in symptoms during the transfusion, and carries a 60% mortality rate.[23] Risk is higher, however, with platelets, which are stored at a higher temperature, and may occur as frequently as 1 per 1000 to 2000 U.[23] During or after the transfusion, the patient may develop rigors, vomiting, abdominal cramps, fever, shock, renal failure, and DIC. When a septic transfusion reaction is considered, vigorous resuscitative therapy and broad-spectrum antibiotics should be started and the transfusion stopped.[10]

Other Effects. Although infrequent, the following complications can occur secondary to multiple-unit transfusions: hypocalcemia, hyperkalemia and acidosis, hypothermia, microembolization, and coagulopathies. Treatment is specific to the symptom and problem.

Chronic

Risk of Transmission-Transmitted Viruses. Improved techniques for selecting and testing blood donors have dramatically reduced the risk of viral transmission of disease by transfusion. The blood supply in the United States has never been safer.[23] Current estimates for the risk of acquiring hepatitis C and HIV from transfusion are approaching 1 in 2 million. The risk of hepatitis B infection, however, remains closer to 1 in 200,000 to 500,000.[46] Cytomegalovirus (CMV) can be transmitted by blood transfusion as well. Those at risk include recipients of allogeneic stem cell or solid-organ transplantation, and neonates. CMV-negative blood products should be considered in these patients.[18,23] Recently, West Nile virus has emerged as a risk, although one that varies considerably by geography and season (as high as 1233 per million units in one metropolitan area during the epidemic of 2002).[23] Transfusion-related infection with West Nile virus, however, has been virtually eliminated by the use of system-wide nucleic acid amplification testing.[46]

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 6 Brain Resuscitation

Robert Silbergleit

PERSPECTIVE

Recognition of the dominant role of the brain in determining the quality of human life dates back to the dawn of recorded medical history. Until recently, however, medical efforts after cardiac arrest have focused exclusively on cardiac resuscitation. Recent advances in the understanding of the pathophysiologic mechanisms of brain ischemia have encouraged attention to cerebral resuscitation. This chapter reviews the pathophysiology of postischemic encephalopathy and discusses therapies for improving neurologic recovery after cardiac arrest.

PATHOPHYSIOLOGY

The human brain consists of 10 billion neurons, each with multiple connections to other cells, totaling an estimated 500 trillion synapses. Although the brain constitutes only 2% of body weight, it receives 15% of the body's cardiac output and accounts for 20% of the body's overall oxygen use because of its high metabolic activity. Although no mechanical or secretory work is performed by the brain, energy expenditures include the synthesis of cellular constituents (e.g., an estimated 2000 mitochondria are reproduced each day by each cell) and neurotransmitter substances, the axoplasmic transport of these substances, and the transmembrane pumping of ions.

When the brain is deprived of adequate blood flow, the resulting ischemia is characterized by a bewildering array of inter-related physiologic and cellular responses that ultimately result in neuronal cell death (Fig. 6-1).[1,2] Although this complex cascade of events can be triggered by periods of ischemia lasting only a few minutes, the resulting neuronal death is usually delayed by hours or days. Furthermore, the biology of cerebral cell death after global cerebral ischemia follows (with slight variations) the pattern of delayed cerebral cell death that follows stroke, traumatic brain injury, and other forms of hypoxic or toxic brain injury. Increased understanding of the brain's response to injury during the period between insult and neuronal cell death will eventually allow more specific brain resuscitation therapies.

MANAGEMENT

Standard management of cardiac arrest and subsequent ischemic brain damage involves restoring cerebral blood flow (CBF) and preventing secondary insult. These treatments have generally not been studied in prospective, randomized controlled trials, but are supported by clinical experience and limited experimental data. Although proposed and experimental therapies are generally aimed at specific molecular interventions in the pathophysiology of ischemic brain injuries, none of these as yet have proven effective in clinical trials.

Standard Strategies

Return of Spontaneous Circulation

Cardiac resuscitation is the first priority in cerebral resuscitation. The degree of brain injury after cardiac arrest depends on both the duration of complete cerebral ischemia (the "down time," or time before the initiation of cardiopulmonary resuscitation [CPR]) and the duration of relative ischemia that occurs during CPR and that may occur from cardiogenic shock preceding or subsequent to the period of cardiac arrest.[3] Extensive clinical evidence on hospital discharge rates and neurologic recovery rates supports the concept first proposed nearly 100 years ago that success in resuscitation is inversely proportional to the duration of cardiac arrest. Although duration of arrest generally predicts outcome in the population of patients with sudden cardiac death, it cannot be used reliably to predict the outcome of individual patients. The epidemiology of neurologic outcome of survivors is described in detail in the following section and is influenced by patient comorbidity and other individual characteristics. Depending on their timing and severity, low-flow states, hypotension, or hypoxia preceding cardiac arrest may provide protective preconditioning or may increase the risk of poor neurologic outcome.

The efficacy of closed-chest CPR in generating adequate cerebral perfusion is somewhat controversial. Cardiac output during optimal standard closed-chest CPR has previously been estimated to be only 20 to 30% of normal, but more recent data suggest that higher cardiac outputs are possible in clinical practice.[4] Experimental measurement of CBF during CPR has led to estimates ranging from 1 to 60% of prearrest CBF, depending on the experimental model and technique and on the duration of arrest.[5] Furthermore, the CBF achieved with standard closed-chest CPR is inversely proportional to the duration of cardiac arrest preceding the initiation of CPR.[6] Researchers have obtained 50% of normal (prearrest) CBF in animals when CPR was started within 2 minutes of the onset of ventricular fibrillation, but they obtained only 28% of normal CBF if the circulatory arrest persisted for 5 minutes before

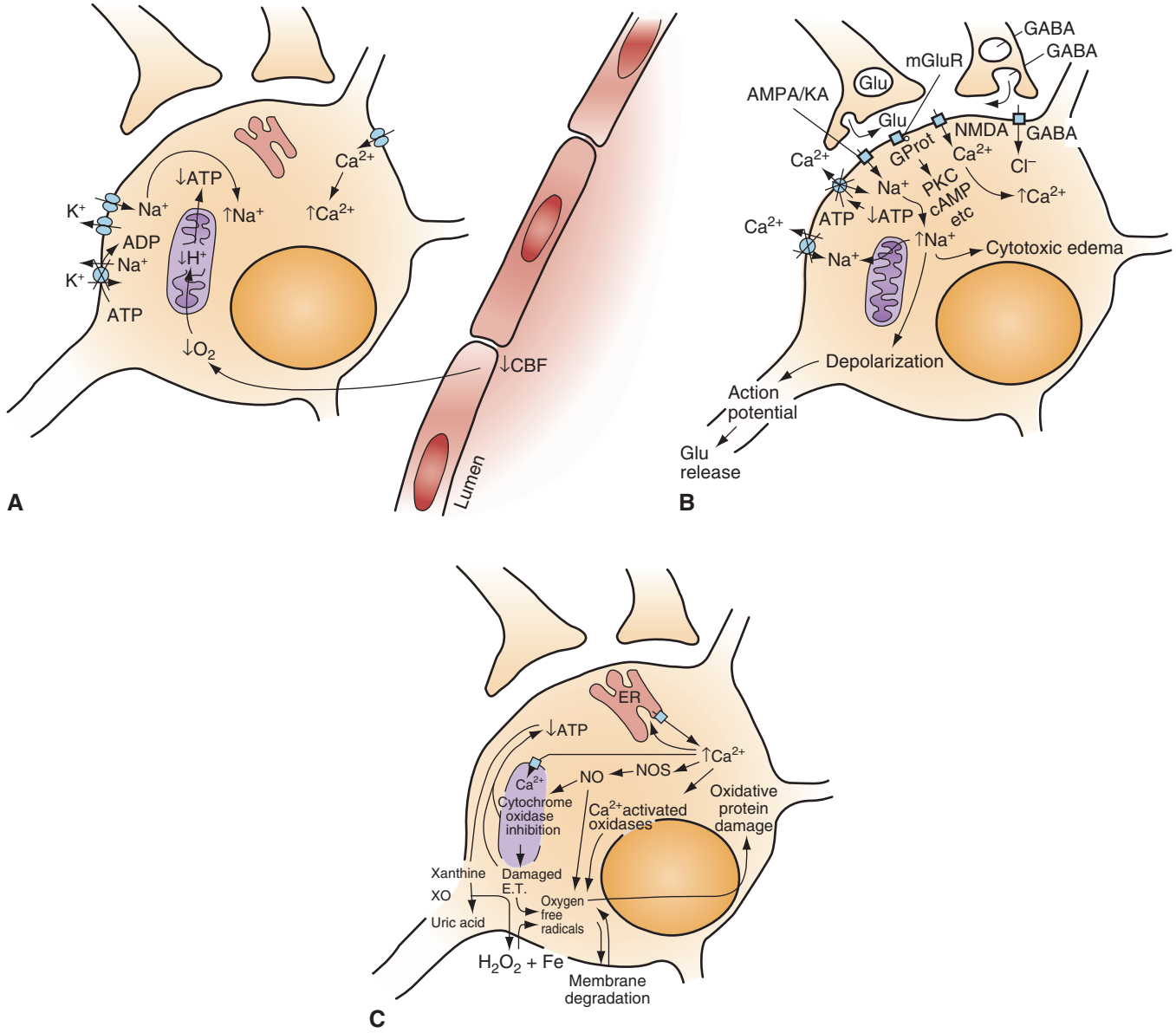

Figure 6-1. Synopsis of events contributing to neuron cell death cascade after ischemia. **A,** Decreased cerebral flow (CBF) and arterial oxygen content during ischemia cause decreased adenosine triphosphate (ATP) production, failure of ATP-driven ion pump efflux of potassium ions (K^+), and influx of sodium ions (Na^+) and calcium ions (Ca^{2+}) through voltage-gated channels. ADP, adenosine diphosphate. **B,** Na^+ influx causes depolarization and glutamate (Glu) release, opening Glu receptor α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) and kainate (KA) channels and exacerbating intracellular Na^+ overload. Increased Na^+ concentration ([Na^+]i) leads to cytotoxic edema. Glu-mediated *N*-methyl-D-aspartate (NMDA) channels allow intracellular Ca^{2+} overload. Insufficient ATP causes failure of energy-dependent Ca^{2+} pumps, and high [Na^+]i prevents removal of Ca^{2+} by Na^+/Ca^{2+} exchange pumps. γ-Aminobutyric acid (GABA) release can attenuate excitatory changes by opening a receptor-gated Cl^-. [Ca^{2+}]i, Ca^{2+} concentration; cAMP, cyclic adenosine monophosphate; PKC, protein kinase C. **C,** Increased [Ca^{2+}]i is amplified by calcium-induced release of Ca^{2+} from the endoplasmic reticulum (ER). Mitochondria may be injured attempting to buffer increasing [Ca^{2+}]i, resulting in further metabolic failure and diminished ATP. Ca^{2+} activates nitric oxide synthase (NOS), transforming it to nitric oxide (NO), which is amplified by NO activation of NOS. NO contributes to the formation of damaging oxygen free radicals and inhibits mitochondrial cytochrome oxidase function. ATP degradation to xanthine and then uric acid by xanthine oxidase (XO) yields hydrogen peroxide (H_2O_2), which reacts with iron to form dangerous oxygen radicals. Oxygen free radicals react with lipids in the cell membrane, which produces membrane degradation and more free radicals. Oxygen free radicals also can damage proteins.

CPR was started. After 10 minutes of arrest, CBF was zero with standard CPR. Although some experimental work suggests that about 20% of normal CBF is necessary to maintain neuronal viability, the real issue is not the degree of biochemical, electric, or physiologic abnormality measured in animal experiments of brain ischemia, but whether functional recovery will occur . Approached from this perspective, clinical evidence overwhelmingly confirms the beneficial effects of CPR in terms of improvement in survival and neurologic recovery.[7,8] Considerable effort has been directed toward the investigation of improved CPR techniques that will prove to be even more effective for longer periods (see Chapter 7).

Treatment of Hypotension, Hypoperfusion, and Hypoxia

Maintaining cerebral oxygen delivery after cardiac resuscitation is a mainstay of therapy. Oxygen delivery requires a sufficiently high cerebral perfusion pressure, a sufficiently low

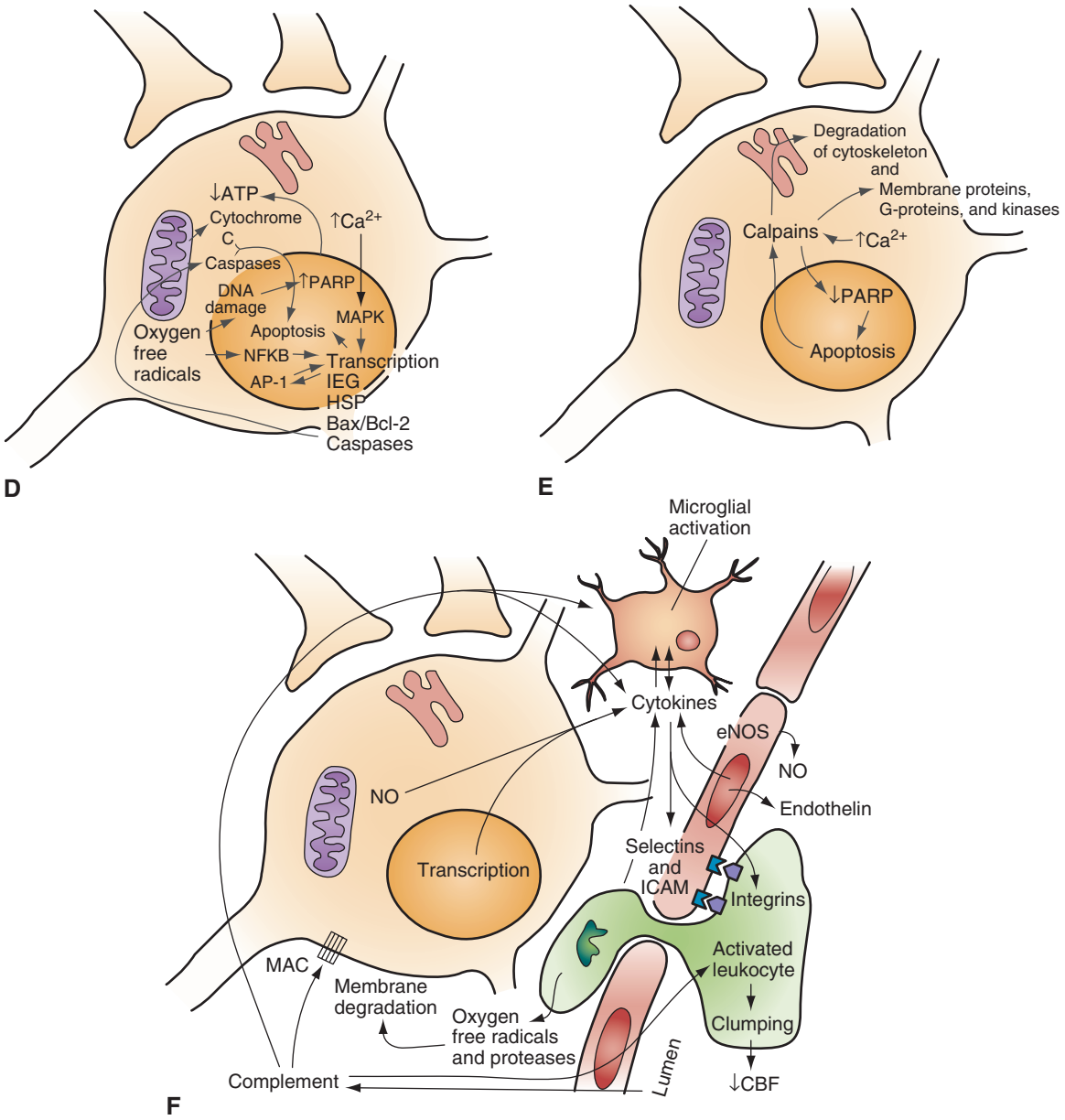

Figure 6-1—cont'd **D,** Ca^{2+} also activates kinase transcription factors, such as mitogen-activated protein kinase (MAPK). Oxygen radicals trigger nuclear factor κ B (NFκB), another transcription factor. Many genes, including immediate early genes (IEG), heat-shock protein (HSP) genes, genes for caspases, and the *Bax/Bcl-2* systems, are activated. IEG products include AP-1, another transcription factor. Mitochondrial release of cytochrome *c,* existing and newly formed caspases, and other factors trigger apoptosis. DNA is damaged by oxygen free radicals and by endonucleases formed in apoptosis. DNA damage activates poly(ADP-ribose) polymerase (PARP), which further depletes ATP stores. **E,** Ca^{2+} and apoptosis activate calpains, proteases that degrade a variety of structural elements (e.g., cytoskeletal and membrane proteins), signaling elements (e.g., G-proteins, kinases), and PARP. **F,** Transcription and NO contribute to neuronal expression of cytokines, chemokines, and growth factors. These intercellular signals activate complement, epithelial cells, leukocytes, and microglia. Complement can amplify chemotactic signals, activate microglia directly, or cause cellular damage by creation of the membrane attack complex (MAC). Leukocyte integrins, epithelial cell selectins, and intercellular adhesion molecules (ICAM) allow demargination. Activated leukocytes cause neuronal injury by releasing potent oxidants and protease. Cerebrovascular resistance may be affected by epithelial release of NO and endothelin and by leukocyte clumping. eNOS, endothelial nitric oxide synthase.

cerebrovascular resistance (CVR), and adequate blood oxygen saturation.

Hypotension in the postarrest period can dangerously lower cerebral perfusion pressure. Although CBF is normally independent of perfusion pressure over a wide range of arterial blood pressure, such autoregulation is often lost in the injured brain. As a result, perfusion of ischemic tissue becomes passively dependent on arterial pressure, and hypotension can compromise CBF and result in significant additional brain damage.[3] Therefore, after return of spontaneous circulation (ROSC), low arterial pressures should be rapidly normalized, using intravascular volume administration and vasopressors as needed. Because elevated arterial pressures may be needed to provide sufficient CBF, hypertension usually should not be treated in the postresuscitation period. Very high blood pressures may require treatment, but specific cutoffs are controversial. Generally, diastolic pressures may be allowed to run as high as 120 mm Hg without requiring treatment. In fact, hypertension is sometimes induced clinically or experimentally with vasopressors in an attempt to raise cerebral perfusion

pressure and improve neurologic recovery.[9] Because it is unproved, and because risks of this therapy include blood-brain barrier disruption and worsening of vasogenic edema, induced hypertension is not currently a standard therapy.

CVR after resuscitation from cardiac arrest is another determinant of CBF and may be affected by hyperventilation and microvascular patency. Although the cerebral circulation may lose its ability to adjust to blood pressure changes after ischemia, attenuated responsiveness to carbon dioxide and oxygen levels in arterial blood can still be present.[10,11] Carbon dioxide is a potent vasoactive agent, and lowering of the arterial carbon dioxide partial pressure ($Paco_2$) by hyperventilation results in rapid reduction of CBF. Because reductions in CBF reduce total cerebral blood volume, hyperventilation may transiently abort brainstem herniation in the presence of critically elevated intracranial pressure (ICP) until osmotherapy or ventriculostomy can be initiated. When ICP is not elevated, however, the vasoconstriction and increased CVR caused by hyperventilation can cause potentially dangerous reductions in CBF. Although controversy surrounds whether increases in ICP are clinically significant after global ischemia, the measurement of ICP is generally not recommended in the management of adult cardiac arrest survivors.[12] Generally, ventilation to maintain a $Paco_2$ between 35 and 40 mm Hg is safe and appropriate. CVR may also be elevated after cardiac arrest by endothelin-induced vasospasm or microvascular occlusion by leukocyte clumping or coagulation. Hemodilution, anticoagulation, and antiplatelet agents have been studied in animals for effectiveness in mitigating microvascular occlusion with mostly negative results.[13] Acute use of these agents to improve microcirculatory flow has not been studied in human cerebral ischemia.

Normal arterial oxygen saturation should be maintained after resuscitation from cardiac arrest. Because the injured brain may not be able to compensate for hypoxia by augmenting CBF, cerebral oxygen delivery may diminish rapidly as the oxygen content of blood decreases. Hyperoxia secondary to the use of 100% oxygen in the immediate postarrest period, however, has also been shown to increase oxidative brain injury in animal models of cardiac arrest and resuscitation.[14] Normoxia or mild hyperoxia (Pao_2 of 80–120 mm Hg) should be maintained using the lowest fraction of inspired oxygen (Fio_2) possible. The use of 100% oxygen is appropriate during cardiac arrest, but Fio_2 should be titrated downward shortly after the ROSC. An important clinical trial to compare earlier use of normoxia after ROSC to the more typical prolonged period of postresuscitative hyperoxia has been proposed. Because hypoxia and hypercapnia must be avoided, controlled ventilation is appropriate in the period after resuscitation, with muscle relaxation and sedation if needed.

Maintenance of Body Temperature

Hyperthermia (or fever) exacerbates brain injury and worsens neurologic outcome.[15,16] Elevated body temperature increases cerebral metabolic demand by 8 to 13% per degree Celsius, escalates glutamate release, increases oxygen free radical production, and increases cytoskeletal and blood-brain barrier breakdown with increased vasogenic edema.[17,18] Core body temperature (usually rectal, bladder, or esophageal) should be accurately measured in patients resuscitated from cerebral ischemia.[19] Hyperthermia may be treated with antipyretics, circulating air or water cooling systems, or evaporative cooling using water mist and fans.[19] Aggressive treatment should, at a minimum, be used to prevent temperature increases in the postischemic period in all patients, and the practice of inducing therapeutic hypothermia is now emerging as a therapy for comatose survivors of cardiac arrest.

Resuscitative Mild Hypothermia

Hypothermia was first reported more than 50 years ago to have a protective effect in global and focal brain ischemia[20] and ranges from mild (32–34° C) to profound (5°). The mechanism by which hypothermia conveys protection is uncertain, but several possibilities have been suggested. Hypothermia reduces glutamate release, metabolic demand, free radical formation, and production of inflammatory cytokines.[17] Cell-signaling and genetic responses to cellular injury are also affected by hypothermia, and hypothermia may protect the brain from programmed neuronal cell death.[21,22]

Mild hypothermia is easier to achieve and has fewer adverse effects than lower temperatures, and has consistently been found to be neuroprotective in experimental cerebral ischemia.[21,23] Two multicenter prospective, randomized, controlled trials of mild hypothermia have now shown marked improvements in neurologic outcome in comatose survivors of out-of-hospital cardiac arrest.[24,25] The improvements in neurologic outcome (recovery with minimal or no neurologic deficits at hospital discharge) and in mortality in patients treated with hypothermia in these trials are shown in Table 6-1. In these trials, the number needed to treat in order to have one additional patient with a good neurologic outcome was only about seven. The 2005 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care and the International Liaison Committee on Resuscitation now recommend cooling unconscious adult patients after cardiac arrest to 33° C for 12 to 24 hours.[26,27] Implementation of these guidelines has been slow and represents a failure of clinical translation. Barriers to adoption and the public health impact of widespread use have been reported.[28]

Table 6-1 Clinical Outcomes in Randomized Controlled Trials of Hypothermia in Comatose Survivors of Cardiac Arrest

CLINICAL TRIAL	HYPOTHERMIA, *N* (%)	NORMOTHERMIA, *N* (%)	*P* VALUE
HACA[24]	*N* = 137	*N* = 138	
Good Neurologic Outcome*	75 (55)	54 (39)	<0.01
Death	56 (41)	76 (55)	0.02
Bernard et al.[25]	*N* = 43	*N* = 34	
Good Neurologic Outcome†	21 (49)	9 (26)	0.05
Death	22 (51)	23 (68)	0.14

*Good neurologic outcome defined as recovery with no neurologic deficits or with moderate disability but living independently and working at least part time at 6 months.

†Good neurologic outcome defined as recovery with moderate, minimal, or no neurologic deficits at hospital discharge and discharge to home or acute rehabilitation facility.

Mild hypothermia can be induced through a variety of techniques. In both clinical trials of hypothermia after cardiac arrest, hypothermia was achieved by cooling the body surface with ice packs and cooling blankets. Surface cooling is noninvasive, and a variety of specialized devices have been developed to make it less labor intensive and faster,[29,30] but some difficulties inherent with surface cooling are well described.[31] These include slower than desired rates of cooling (0.3–0.6° C/hr ± SD 0.3° C/hr),[24,25] overshooting and undershooting the temperature target (SD usually > 1° C),[32,33] and uncontrolled rewarming with very frequent rebound hyperthermia.[31] Alternative core cooling methods have been investigated. A promising technique using infusions of ice cold intravenous fluids has been demonstrated and is more effective than would be expected based on the transfer of heat content alone.[34] Although more invasive, endovascular cooling with a heat exchange catheter provides the most rapid cooling (1.4–6.3° C/hr ± SD 0.3° C/hr) and offers the tightest control of body temperature (SD usually < 0.3° C) at the target temperature and during controlled rewarming.[32,35-37] Designed to induce hypothermia or maintain normothermia in surgical patients, this new type of commercially available device is placed in the inferior vena cava through a femoral introducer and cools or heats passing blood. Endovascular systems promise to be far less nursing labor-intensive than surface cooling because they monitor core temperature and are automatically controlled through a feedback loop. Although temperature control can also be achieved by extracorporeal bypass devices, this is not pragmatic in most circumstances and does not offer the same promise as simpler core cooling techniques. The optimal method of cooling patients resuscitated from cardiac arrest has not been established.

The rate of cooling needed for effective neuroprotection, the optimal duration of cooling, and the best process for rewarming after hypothermia are all unknown.[38] Animal experimentation and the consensus recommendations suggest that cooling should be initiated as early and as rapidly as possible.[26] Cooling may begin during the out-of-hospital phase of resuscitation, and may even be initiated prior to ROSC. In the positive clinical trials, hypothermia at 33 ±1° C was achieved by 2 hours[25] or 8 hours[24] after ROSC and was maintained for either 12 hours[25] or 24 hours.[24] Patients were then allowed to rewarm passively[24] or with a combination of passive and active rewarming.[25] Rebound hyperthermia is common with passive rewarming and must be avoided.[31] Although the clinical trials only enrolled patients resuscitated from cardiac arrest caused by ventricular fibrillation, there is clinical experience with resuscitative hypothermia in patients with cardiac arrest from other causes,[39] and consensus recommendations support its use in such cases.[26]

Cooling of comatose survivors of out-of-hospital cardiac arrest requires a multidisciplinary hospital policy, and should be initiated as early as possible. In hospitals capable of hypothermic resuscitation, cooling is optimally started in the ED and maintained in the ICU.[12] Regardless of cooling technique, patients cooled after cardiac arrest require pharmacologic therapy to prevent shivering because shivering effectively warms the patient. In the two clinical trials, shivering was prevented with a nondepolarizing paralytic, and sedation was maintained with midazolam with or without fentanyl.[24,25] When paralysis is not clinically desirable, it may be possible to sufficiently lower the shivering threshold in awake patients with meperidine, buspirone, dexmedetomidine, or a combination of these.[40,41] Shivering can sometimes also be reduced in a patient cooled by an endovascular catheter even when the core temperature is 33° C by applying a warming blanket, since surface temperature receptors control thermoregulation to a much greater extent than core temperature receptors. Other pharmacologic treatments that may be used during induced hypothermia include antipyretics, which lower the core body temperature set point, even in normothermic patients, although to such a small degree that the effect is unlikely to be clinically relevant.[42] More effective pharmacologic lowering of core body temperature is, however, being investigated. Neurotensin is an endogenous neuropeptide involved in thermoregulation that can induce hypothermia and neuroprotection in experimental models of cerebral ischemia.[43]

Clinical trials of mild hypothermia in the resuscitation of patients with acute ischemic stroke,[44] and two new clinical trials of mild hypothermia in adult and pediatric patients with traumatic brain injury[45] are being performed and may expand the indications of this therapy in the future. Ongoing efforts to develop feasible methods of selective cooling of the brain after cardiac arrest,[46,47] and studies of profound systemic hypothermia are still experimental.

Treatment of Hyperglycemia

Postischemic hyperglycemia has detrimental effects on CBF, metabolism, edema formation, and neurologic outcome. In experimental focal cerebral ischemia, profound hyperglycemia (>500 mg/dL) causes a more pronounced decrease in intracellular pH, increases brain lactate levels, and increases neuronal loss. Increased neuronal damage from hyperglycemia in global cerebral ischemia may also be glutamate-mediated. Observational studies in patients with stroke and survivors of cardiac arrest have shown that hyperglycemia after brain ischemia is strongly associated with worse outcomes in both diabetics and nondiabetics.[48,49] In experimental studies, normoglycemia and mild insulin-induced hypoglycemia have been shown to improve neurologic function after focal and global ischemia. Interestingly, insulin itself may have a neuronal growth-factor-like effect that may theoretically also be neuroprotective. Thus, the best available evidence supports active treatment of hyperglycemia after global brain ischemia, and the administration of glucose should be avoided except in verified hypoglycemia.[50]

Seizure Management

Seizures may result from global cerebral ischemia and may exacerbate the underlying brain injury. Seizure activity can increase brain metabolism by 300 to 400%, worsening the mismatch between oxygen delivery and demand in the post-arrest period, with greater metabolic failure and neuronal loss and worsened neurologic outcome. Although prevention of seizures has not been proved to improve neurologic recovery, seizures are clearly not desirable in the postischemic period.[12] The prophylactic use of anticonvulsant drugs in patients resuscitated from cardiac arrest is controversial and is not standard care, but it is generally agreed that seizures should be quickly and effectively treated. Common therapeutic agents include benzodiazepines, phenytoin, and barbiturates. Each of these anticonvulsant drugs has also been considered as specific therapy for cerebral ischemia because of the antagonism of excitatory amino acids, sodium channel blockade, or effects on cerebral metabolism. Although these drugs are of proven value as anticonvulsants, other uses in cerebral ischemia are experimental and unproved.

Immobilization, Sedation, and Head Position

The comatose brain responds to external stimuli (e.g., physical examination, airway suctioning) with increases in cerebral

metabolism. This elevation of regional brain metabolism requires increased regional CBF at a time when the oxygen demand/perfusion ratios may be precariously balanced. Protection from afferent sensory stimuli with administration of titrated doses of sedative-anesthetic drugs and muscle relaxants may prevent oxygen supply/demand imbalance and improve the chances for neuronal recovery.

All activity that increases ICP (e.g., straining, coughing) should be restricted, and tracheal suction should be performed only when necessary and with care. There is no evidence to support the commonly recommended practice of elevating the head of the bed to reduce intracranial venous pressure, and this practice may even be harmful.[51] Torsion or compression of neck veins should be avoided by eliminating compressive dressings and not rotating or flexing the head.[52]

CLINICAL OUTCOMES

Global cerebral ischemia resulting from a period of cardiac arrest is a frequently fatal and highly morbid condition, but the prognosis for its victims is not universally poor. An increasing body of data is providing more complete and precise estimates of the functional outcomes and quality of life of survivors of cardiac arrest, and the results are better than many physicians assume.

The published experience in Olmsted County, Minnesota, between 1990 and 2000 may represent the best possible outcomes with currently available therapy.[53] First-responders (including police and firefighters) with automated external defibrillators in that county responded to 330 patients with cardiac arrest, 200 (61%) of whom had ventricular fibrillation at presentation. The majority of patients with ventricular fibrillation (145 patients, 44% of all arrests) survived to hospital admission, and 84 patients (25%) were discharged alive. Remarkably, among these 84 survivors, 79 (24% of all arrests) left the hospital neurologically intact.[53]

More typical outcomes were identified by a recent very large cohort study of outcomes in 8091 patients with cardiac arrest in Ontario, Canada.[54] Survival was 5.2% at hospital discharge, and was 4.0% at 1 year. The vast majority of 1-year survivors (3% of all those with cardiac arrest), however, had no or minimal neurologic deficits, and the average quality of life indices of all survivors were as good as those for patients without a history of cardiac arrest.[54] The Ontario experience echoes that of a Portuguese study,[55] but other recent data on 6240 patients from studies in the Netherlands,[56] Norway,[57] and Switzerland[58] all confirm a rate of survival to discharge home with minimal or no deficit of 8% in all out-of-hospital cardiac arrests. Quality of life among long-term survivors of cardiac arrest is consistently high in all of these studies, with low rates of patients in persistent vegetative states or requiring skilled nursing care. Overall, among those surviving to hospital admission, between 14 and 55% of patients will have good long-term neurologic outcomes.[53,55]

Despite these data, nihilism is common among physicians treating patients with cardiac arrest and ischemic brain injury. This may be due, in part, to the fact that most survivors of cardiac arrest are comatose at the time of admission and are without early prognostic findings suggesting which patients will have a favorable outcome. Although predicting the outcome of coma is difficult, a recent meta-analysis suggests that the absence of pupillary and corneal reflexes at 24 hours and the absence of motor responses at 72 hours on physical examination are the best predictors of a poor neurologic outcome.[59] Nihilism is of particular concern, however, and should be avoided because of the potential for poor prognoses to be self-fulfilling.[59] In the near future, serum biomarkers of brain injury may identify the potential for neurologic recovery early in a patient's course and help guide therapy. Until early predictions of outcome can be accurately made, the emergency physician should consider every survivor of cardiac arrest as having a significant chance of full recovery (14–55%), and should know that bad neurologic outcomes are usually fatal rather than chronically debilitating.

SUMMARY

Rapidly expanding knowledge about the pathophysiology of postischemic brain injury has stimulated the search for effective cerebral resuscitation therapies. Newly proven therapies like resuscitative hypothermia will continue to be developed and will improve the outcomes of patients with ischemic brain injury in future years. Although experimental work suggests many potentially promising brain resuscitation therapies, attention should also be paid to determining the benefits of existing "standard" therapies.

Because of the complexity and interconnectedness of the pathophysiologic cascades that occur after global cerebral ischemia, it is likely that a multifaceted therapeutic approach or "cocktail," rather than a single pharmacologic agent, is needed to reduce neurologic damage after cardiac arrest.

It is crucial that the emergency physician recognize that the patient resuscitated from cardiac arrest is, contrary to outward appearance, in a dynamic stage of brain injury. At present, patients must be protected from further brain injury caused by hypotension, hypoperfusion, hypoxia, hyperthermia, hyperglycemia, or seizures. Comatose survivors of out-of-hospital cardiac arrest should now also undergo resuscitative hypothermia. In the future, cerebral resuscitation may also involve other specific pharmacologic interventions to derail the process by which brain cells slowly die after ischemic brain injury.

KEY CONCEPTS

- Neuronal injury is a dynamic process that continues for hours or days after an ischemic insult to the brain.
- Hypotension, hypoperfusion, and hypoxia must be avoided during brain resuscitation.
- Hyperthermia, hyperglycemia, and seizures should be treated promptly during brain resuscitation.
- Comatose survivors of out-of-hospital cardiac arrest should be rapidly cooled in the ED and maintained at 33°C in an ICU setting for 12 to 24 hours after resuscitation.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 7 Adult Resuscitation

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PERSPECTIVE

Epidemiology

It is estimated that between 77,000 and 174,000 patients are treated for out-of-hospital cardiac arrest each year in the United States.[1] The incidence of ventricular fib2rillation as the initial rhythm has declined over time and is now estimated to be between 20 and 38%.[1] Epidemiologic data from studies of out-of-hospital cardiac arrest show a wide range of outcomes. Return of spontaneous circulation (ROSC) that takes long enough to result in hospital admission ranges from 9 to 65%, whereas only 1 to 31% (median 6.4%) of patients survive to hospital discharge.[1,2] Of patients surviving to hospital discharge, one third have persistent neurologic deficits, and less than half return to prearrest function. In patients meeting the inclusion criteria of clinical hypothermia trials, favorable outcome was reported in approximately 50% of cardiac arrest survivors who were admitted comatose and treated with hypothermia.[3,4]

PRINCIPLES OF DISEASE

Etiology

Understanding the causes of cardiac arrest directs therapy and diagnostic testing during resuscitation and in the immediate postarrest period (Table 7-1). Cardiac arrest from a primary cardiac origin typically presents as ventricular fibrillation (VF) or less often as pulseless ventricular tachycardia (VT). Coronary artery disease is the most common pathologic condition found in patients who die suddenly from VF; autopsy studies show a 75% incidence of previous myocardial infarction (MI) and a 20 to 30% incidence of acute MI.[5] Other anatomic abnormalities associated with sudden cardiac death caused by VF or VT include myocardial hypertrophy, cardiomyopathy, and specific structural abnormalities. Pulseless electrical activity (PEA) and asystole are less common initial presenting rhythms in patients with a cardiac cause of arrest. These rhythms most often occur as a deterioration of VF or VT or develop in response to resuscitation treatments, such as defibrillation.

Primary respiratory failure generally causes initial hypertension and tachycardia, followed by hypotension and bradycardia and progressing to PEA, VF, or asystole. Circulatory obstruction (e.g., tension pneumothorax, pericardial tamponade) and hypovolemia generally present with initial tachycardia and hypotension, progressing through bradycardia to PEA, but also may deteriorate to VF or asystole.

The most common metabolic cause of cardiac arrest is *hyperkalemia*, which is seen most frequently in patients with renal failure. Hyperkalemia results in progressive widening of the QRS complex, which can deteriorate to VT, VF, asystole, or PEA. Other electrolyte abnormalities (e.g., hypomagnesemia, hypermagnesemia, hypokalemia) may lead to significant dysrhythmias, but the frequency with which they cause cardiac arrest is not documented.

Cardiac arrest from drug toxicity has specific characteristics depending on the drug involved. Specific therapy directed at drug toxicity is essential but may not be immediately effective. Prolonged resuscitation efforts may be needed using a method that provides adequate perfusion.

Electrocution causes cardiac arrest through primary dysrhythmias or apnea. Alternating current in the range of 100 mA to 1 A generally causes VF, whereas currents greater than 10 A can cause ventricular asystole. Lightning produces a massive direct current electrocution that can result in asystole and prolonged apnea.

Hypothermia-induced cardiac arrest can present with any electrocardiogram (ECG) rhythm, and successful resuscitation depends on rapid rewarming, which often requires aggressive and invasive measures (e.g., peritoneal lavage, cardiopulmonary bypass [CPB], open-chest cardiac massage [OCCM]). Drowning is a form of asphyxia usually resulting in bradyasystolic arrest. Because drowning often is accompanied by hypothermia, the victim may benefit from prolonged resuscitation efforts similar to resuscitation efforts for hypothermia.

CLINICAL FEATURES AND MANAGEMENT

Most cardiac arrest cases managed in the emergency department (ED) initially occur outside the hospital. An increasing number of first responders, nontraditional providers, and public venues are being equipped with automated defibrillators. Dramatic resuscitation rates have been achieved when these programs enable providers to deliver countershock within less than 4 to 5 minutes of arrest onset.[6-9] Programs that fail to enable a significant number of patients to be defibrillated within this critical time window have limited or no effect on survival.[10,11]

Advanced life support (ALS) units staffed by paramedics often have standing orders to follow advanced protocols. Because quality of cardiopulmonary resuscitation (CPR) and

Table 7-1 Common Causes of Nontraumatic Cardiac Arrest

GENERAL	SPECIFIC	DISEASE/AGENT
Cardiac		Coronary artery disease
		Cardiomyopathies
		Structural abnormalities
		Valve dysfunction
Respiratory	Hypoventilation	CNS dysfunction
		Neuromuscular disease
		Toxic and metabolic encephalopathies
	Upper airway obstruction	CNS dysfunction
		Foreign body
		Infection
		Trauma
		Neoplasm
	Pulmonary dysfunction	Asthma, COPD
		Pulmonary edema
		Pulmonary embolus
		Pneumonia
Circulatory	Mechanical obstruction	Tension pneumothorax
		Pericardial tamponade
		Pulmonary embolus
	Hypovolemia	Hemorrhage
	Vascular tone	Sepsis
		Neurogenic
Metabolic	Electrolyte abnormalities	Hypokalemia or hyperkalemia
		Hypermagnesemia
		Hypomagnesemia
		Hypocalcemia
Toxic	Prescription medications	Antidysrhythmics
		Digitalis beta-blockers
		Calcium channel blockers
		Tricyclic antidepressants
	Drugs of abuse	Cocaine
		Heroin
	Toxins	Carbon monoxide
		Cyanide
Environmental		Lightning
		Electrocution
		Hypothermia or hyperthermia
		Drowning/near-drowning

CNS, central nervous system; COPD, chronic obstructive pulmonary disease.

time to defibrillation are the two most important determinants of outcome, there is no evidence to support interrupting properly performed advanced measures to transport a patient who is still in cardiac arrest. In cases of cardiac arrest refractory to properly performed advanced measures, the patient may be pronounced dead at the scene if appropriate protocols have been outlined within the system.[12]

Simultaneous assessment and management of cardiac arrest must occur in an orchestrated effort by a health care team led by an emergency physician who can make the ongoing assessment and monitor the efficacy and response to therapeutic interventions. It is often difficult or impossible to determine the cause of cardiac arrest at presentation. Although a differential diagnosis can be formulated based on history, physical examination, and ECG rhythm on arrival, key information often is not available or is unreliable.[13] The differential diagnosis potentially can be narrowed by the patient's age, underlying diseases, and medications.

History and Physical Examination

Historical information from the family, bystanders, and emergency medical services (EMS) personnel provides key information regarding cause and prognosis. Information surrounding the event includes whether the arrest was witnessed, the time of arrest, what the patient was doing (e.g., eating, exercising, trauma), the possibility of drug ingestion, time of initial CPR, initial ECG rhythm, and interventions by EMS providers. Important past medical history includes baseline health and mental status; previous heart, lung, renal, or malignant disease; hemorrhage; infection; and risk factors for coronary artery disease and pulmonary embolism. The patient's current medications and allergies also should be obtained, if possible.

Physical examination of a cardiac arrest patient is necessarily focused on a few key goals: (1) ensure adequacy of airway maintenance and ventilation, (2) confirm the diagnosis of cardiac arrest, (3) find evidence of cause, and (4) monitor for complications of therapeutic interventions. This examination must occur in descending order of importance, simultaneous with therapeutic interventions, and must be repeated frequently to assess for response to therapy and occurrence of complications (Table 7-2).

Cardiopulmonary arrest is defined by the triad of unconsciousness, apnea, and pulselessness. The pulse must be palpated for in a large artery (carotid or femoral). If any question exists as to the diagnosis of pulselessness, CPR should be initiated and pulselessness confirmed by such methods as handheld vascular Doppler ultrasound or end-tidal carbon dioxide monitoring. Rapid bedside ultrasound may confirm loss of cardiac activity, but CPR should not be interrupted to determine this, except in the very late phases of the resuscitation, when termination of resuscitative efforts is contemplated. With sudden onset of circulatory arrest, as in VF, loss of consciousness occurs within 15 seconds, although agonal gasping respirations may persist for several minutes. A brief seizure may result from cessation of cerebral blood flow. Primary respiratory arrest results in transient tachycardia and hypertension that progress to loss of consciousness, bradycardia, and pulselessness, usually within 5 minutes.

After the initial minutes of cardiac arrest, physical examination may provide little evidence of the duration of arrest. Pupils dilate within 1 minute but constrict if CPR is initiated immediately and performed effectively. Dependent lividity and rigor mortis develop after hours of cardiac arrest. Temperature is an unreliable predictor of duration of cardiac arrest because it does not decrease significantly during the first hours of arrest. Moderate to severe hypothermia may cause cardiac arrest or may be caused by prolonged arrest, with opposite prognostic implications.

Monitoring

Traditional monitoring during CPR has relied on evaluation of the ECG in one or more leads and palpation of carotid or femoral artery pulses. Although the lack of a palpable pulse during CPR may indicate inadequate forward flow, the degree of forward flow cannot be estimated accurately in the presence of a palpable pulse because pressures generated during CPR may be transmitted equally to the venous and the arterial vasculatures. In addition, myocardial blood flow does not depend on the palpated arterial systolic pressure, but rather on the difference between aortic diastolic pressure and right atrial diastolic pressure (coronary perfusion pressure). ECG monitoring during cardiac arrest indicates the presence or absence of electrical but not mechanical activity. Although these two monitoring modalities may be the best attainable in

Table 7-2 Physical Examination Findings Indicating Potential Cause of Cardiac Arrest and Complications of Therapy

PHYSICAL EXAMINATION	ABNORMALITIES	POTENTIAL CAUSES
General	Pallor	Hemorrhage
	Cold	Hypothermia
Airway	Secretions, vomitus, or blood	Aspiration
		Airway obstruction
	Resistance to positive-pressure ventilation	Tension pneumothorax
		Airway obstruction
		Bronchospasm
Neck	Jugular venous distention	Tension pneumothorax
		Cardiac tamponade
		Pulmonary embolus
	Tracheal deviation	Tension pneumothorax
Chest	Median sternotomy scar	Underlying cardiac disease
Lungs	Unilateral breath sounds	Tension pneumothorax
		Right main stem intubation
		Aspiration
	Distant or no breath sounds or no chest expansion	Esophageal intubation
		Airway obstruction
		Severe bronchospasm
	Wheezing	Aspiration
		Bronchospasm
		Pulmonary edema
	Rales	Aspiration
		Pulmonary edema
		Pneumonia
Heart	Audible heart tones	Hypovolemia
		Cardiac tamponade
		Tension pneumothorax
		Pulmonary embolus
Abdomen	Distended and dull	Ruptured abdominal aortic aneurysm or ruptured ectopic pregnancy
	Distended, tympanitic	Esophageal intubation
		Gastric insufflation
Rectal	Blood, melena	Gastrointestinal hemorrhage
Extremities	Asymmetrical pulses	Aortic dissection
	Arteriovenous shunt or fistula	Hyperkalemia
Skin	Needle tracks or abscesses	Intravenous drug abuse
	Burns	Smoke inhalation
		Electrocution

certain circumstances, they do not provide reliable information regarding the effectiveness of CPR and interventions or prognosis.

Unfortunately, no ideal monitoring technique provides all the information that might be desired during resuscitation, and even the modalities discussed next are often difficult or impossible to establish or interpret during CPR. A brief overview is provided of coronary perfusion pressure (CPP), end-tidal carbon dioxide ($ETco_2$), and central venous oxygen saturation ($Scvo_2$) monitoring, which if available can be used to detect inadequate CPR with high specificity (Table 7-3). In addition, several of these techniques are useful in the immediate post-arrest period.

Table 7-3 Indicators of Inadequate Blood Flow During Cardiopulmonary Resuscitation

MONITORING TECHNIQUE	INDICATOR
Carotid or femoral pulse	Not palpable
CPP	<15 mm Hg
$ETco_2$	<10 mm Hg (before vasopressor)
$Scvo_2$	<40%

CPP, coronary perfusion pressure; $ETco_2$, end-tidal carbon dioxide partial pressure; $Scvo_2$, central venous oxygen saturation.

Arterial Blood Pressure and Coronary Perfusion Pressure

Successful resuscitation of the arrested heart depends on generating adequate CPP during CPR, which has been directly correlated with myocardial blood flow.[14] Animal and human studies indicate that a minimum CPP of 15 mm Hg is necessary to achieve ROSC if initial defibrillation attempts have failed.[14,15] Unfortunately, CPP monitoring is rarely feasible in ED resuscitations of cardiac arrest patients, because it requires both an indwelling arterial pressure catheter and a central venous catheter, both transduced properly to provide simultaneous readings.

Invasive arterial blood pressure monitoring alone also may be helpful, but again, establishment of an indwelling arterial pressure catheter often is not feasible during cardiac arrest resuscitation in the ED. Studies have indicated that achievement of an arterial diastolic pressure of 40 mm Hg is highly predictive of ROSC and this relates to the CPP achieved at

such a diastolic pressure.[16] Invasive, arterial pressure monitoring during CPR may also be useful to facilitate distinguishing electromechanical dissociation (EMD) from pseudo-EMD, provide immediate confirmation of ROSC, and assist in serial arterial blood gas monitoring. Although arterial and central venous catheters are most often placed in the postresuscitation phase of care, a significant number of patients initially achieving ROSC will rearrest in the ED, making these modalities helpful at this time in the patient's subsequent resuscitation.

End-tidal Carbon Dioxide

Experimental and clinical studies have shown that $ETCO_2$ is a reliable indicator of cardiac output during CPR, but this depends on achieving several conditions during CPR in the out-of-hospital setting or in the ED. $ETCO_2$ depends on CO_2 production, alveolar ventilation, and pulmonary blood flow (i.e., cardiac output). If ventilation and CO_2 production are held constant, an increase or decrease in $ETCO_2$ reflects an increase or decrease in cardiac output, respectively. Although CO_2 production during cardiac arrest and CPR probably is not constant, small changes in CO_2 production are not likely to cause appreciable changes in $ETCO_2$ because of the extremely high mixed-venous CO_2 levels and large dead space created by cardiac arrest and CPR. Administration of sodium bicarbonate ($NaHCO_3$) during CPR may cause a sudden large increase in mixed-venous CO_2, however, which may produce a variable but transient increase in $ETCO_2$. Otherwise, with minute ventilation held constant (a desirable but often unmet goal,) only increased cardiac output during CPR and ROSC significantly increases $ETCO_2$.

In addition to correlations with cardiac output, animal and human studies show that $ETCO_2$ correlates with CPP and cerebral perfusion pressure during CPR.[17,18] This correlation would be predicted based on the known relationship between mean arterial pressure and cardiac output when peripheral vascular resistance (PVR) is constant. With dramatic increases in PVR, however, as may occur with high-dose vasopressor therapy, cardiac output and $ETCO_2$ may decrease despite increased CPP.

$ETCO_2$ has the potential to guide adjustments in compression force and rate, maximize forward flow, and to detect CPR provider fatigue (Fig. 7-1).[19] Resuscitation after cardiac arrest is likely to fail if $ETCO_2$ values are less than 10 mm Hg.[20,21] In the absence of high-dose vasopressor therapy, $ETCO_2$ values less than 10 mm Hg should prompt the clinician to enhance the quality of CPR (either rate or force of compression) or consider more invasive maneuvers such as OCCM if the situation warrants and a good neurologic outcome is believed to be possible.

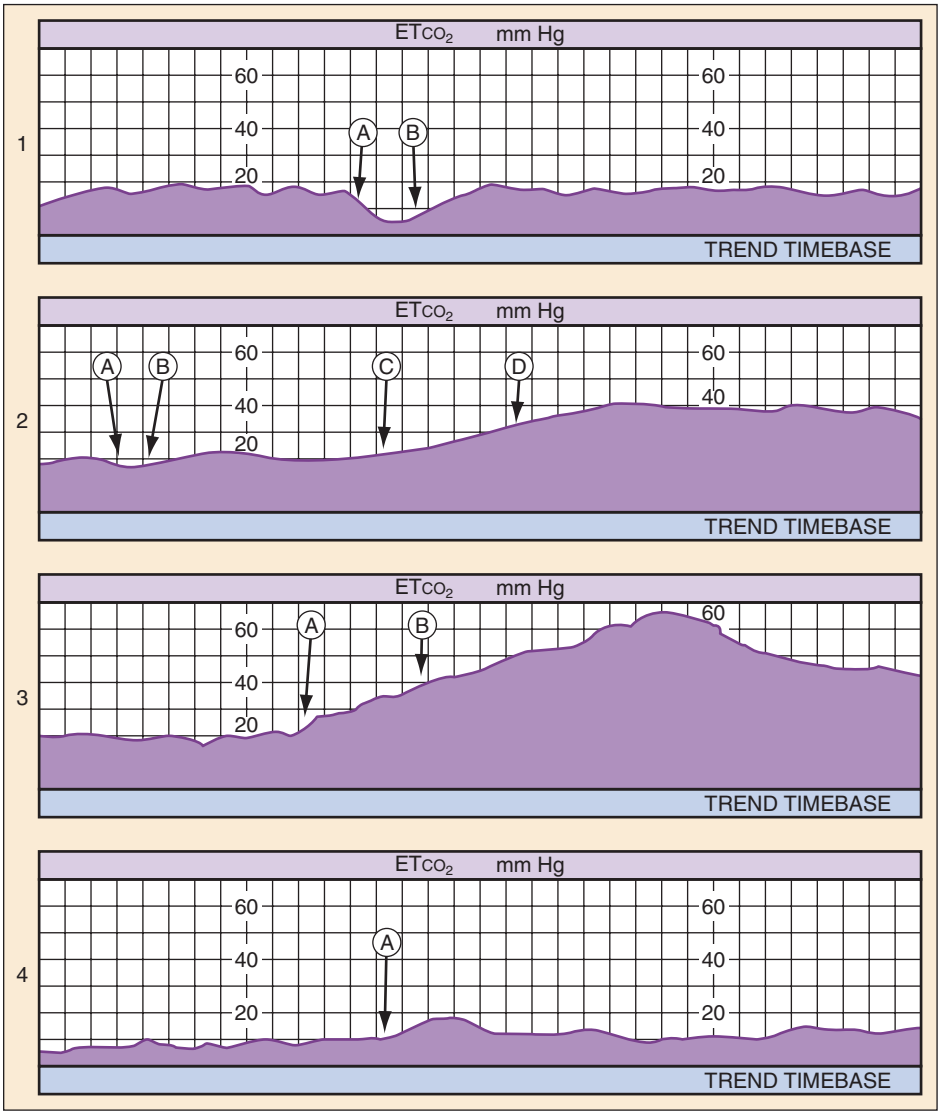

Figure 7-1. Capnogram tracings of end-tidal carbon dioxide pressure ($ETCO_2$) during human cardiopulmonary resuscitation (CPR). **1,** Effect of rescuer fatigue is shown at point *A*. Point *B* shows the effect of changing to a fresh rescuer. **2,** Patient with pseudoelectromechanical dissociation. At point *A,* the patient is pulseless but has a persistent $ETCO_2$ value of 20 mm Hg without CPR; at point *B,* CPR is restarted; at point *C,* dopamine infusion is started; and at point *D,* CPR is stopped, and a pulse is palpated. **3,** Sudden increase in $ETCO_2$ (point *A*) heralds the return of spontaneous circulation; pulses are palpated at point *P*. **4,** Point *A* shows a transient increase in $ETCO_2$ such as occurs during bolus administration of sodium

$ETCO_2$ monitoring also can aid in the diagnosis and treatment of PEA. Patients in a state of pseudo-EMD (cardiac contraction that does not generate a pulse) may have pulsatile flow that simply cannot be detected by palpation of a pulse. In such circumstances, $ETCO_2$ levels may be elevated even without compressions. If, for example, the $ETCO_2$ is 10 mm Hg without compressions, consideration should be given to the possibility the patient has spontaneous circulation but is profoundly hypotensive. In such cases, volume expansion or the use of vasopressors should be considered. $ETCO_2$ monitoring also is useful in rapidly detecting success of tension pneumothorax decompression, pericardiocentesis for pericardial tamponade, and fluid resuscitation for hypovolemia. ROSC causes immediate and significant increases in $ETCO_2$ before detection of a pulse by palpation. With the use of $ETCO_2$ monitoring, interruption of CPR is never necessary except to look for changes in the patient's rhythm.

Finally, $ETCO_2$ monitoring is valuable in patients after cardiac arrest to detect sudden hemodynamic deterioration. Undetectable $ETCO_2$ during CPR indicates failure to intubate the trachea, massive pulmonary embolism, or inadequate chest compressions. Undetectable $ETCO_2$, even after prolonged cardiac arrest, cannot be attributed to cessation of CO_2 production.

Central Venous Oxygen Saturation

$ScvO_2$, when available, provides an additional method to monitor adequacy of resuscitative measures.[22] The mixed-venous blood oxygen saturation in the pulmonary artery (SvO_2) represents the oxygen remaining in the blood after systemic extraction. Studies have shown a close correlation between $ScvO_2$ and SvO_2 during CPR.[23] Because oxygen consumption remains relatively constant during CPR, as does arterial oxygen saturation (SaO_2) and hemoglobin, changes in $ScvO_2$ reflect changes in oxygen delivery by means of changes in cardiac output.

Although used primarily in the ICU setting, multilumen oximetric $ScvO_2$ catheters are placed in the same manner as regular central venous catheters and can be used to monitor $ScvO_2$ continuously in real time. $ScvO_2$ values normally range from 60 to 80%. During cardiac arrest and CPR, these values range from 25 to 35%, indicating the inadequacy of blood flow produced during CPR. Failure to achieve a $ScvO_2$ of 40% or greater has a negative predictive value for ROSC of almost 100%.[22] $ScvO_2$ also helps to rapidly detect ROSC without interruption of chest compressions. $ScvO_2$ monitoring also is useful in the postarrest period to help titrate therapy and recognize any sudden deterioration in the patient's clinical condition.

Echocardiography

The main usefulness of echocardiography is diagnostic, especially in patients with PEA. Echocardiography distinguishes EMD from pseudo-EMD. It also may be helpful in diagnosing mechanical causes of PEA, such as tension pneumothorax, pericardial tamponade, and pulmonary embolism. Echocardiography also is useful in guiding pericardiocentesis. In the postarrest period, echocardiography could prove to be valuable in determining the need for postarrest cardiac intervention or mechanical assistance of the failing heart.

Laboratory Testing

Intermittent arterial and venous blood sampling for gas or chemistry analysis is of limited utility during CPR. Typical blood gas findings during CPR are venous respiratory acidosis and arterial respiratory alkalosis. SaO_2 is usually greater than 94% during CPR and of little value in titrating resuscitation therapy except in the case of massive pulmonary embolism or unrecognized esophageal intubation. Although $ScvO_2$ indicates adequacy of CPR, a single measurement may not be as useful as continuous oximetric $ScvO_2$ monitoring.

Other laboratory studies during CPR serve more to confirm a diagnosis rather than guide therapy because results are usually available too late to make a difference. Serum electrolytes may be ordered to rule out hyperkalemia, hypokalemia, hypomagnesemia, hypercalcemia, and hypocalcemia; however, empiric therapy should be initiated immediately if a high clinical probability exists. Hemoglobin levels may indicate hemorrhage, but initial hemoglobin may be normal even in acute exsanguinating hemorrhage.

Resuscitation

Restoration of adequate cardiac function is the defining factor of ROSC, but restoration of normal brain function is the defining factor of successful resuscitation. The likelihood of achieving both of these goals decreases with every minute the patient remains in cardiac arrest. Although many interventions are specific to the presenting ECG rhythm, most therapeutic modalities and monitoring techniques are used in all rhythms, making separate algorithms redundant. In addition, a patient rarely remains in one ECG rhythm during the course of prolonged resuscitation.

Interventions must be performed rapidly and efficiently to maximize the chances of a good neurologic outcome. The quality of CPR is perhaps the most underappreciated component of the resuscitation effort.[24] Important quality performance measures include compression rate (at least 100 per minute), compression depth (4–5 cm), duty cycle (50% of time in compression), full relaxation, and minimum pauses especially before and after defibrillation.[25] Furthermore hyperventilation has been shown to be common and reduces cardiac output during CPR.[26,27] A 30:2 compression-to-ventilation ratio is currently recommended for health care professionals in all adult resuscitation scenarios.[25] Although recent evidence suggests chest-compression-only CPR is effective when performed by bystanders in the out-of-hospital setting, there is inadequate evidence to recommend this as an alternative strategy for heath care professionals, except when inadequate personnel are present to provide compressions, ventilation, and other resuscitative activites.[28] Intubation should be performed only when capable personnel are available and without interruption of chest compressions. Use of supraglottic airway adjuncts such as the esophageal tracheal Combitube and laryngeal mask airways may be good alternatives for airway management in the out-of-hospital phase of resuscitation with the main disadvantage being the inability to use the trachea as a route of drug administration. In addition to monitoring specific CPR performance parameters, physiologic monitoring, if available, can help optimize CPR quality for the individual patient (see Table 7-3). If the inadequacy of CPR is recognized early in the resuscitation despite optimized therapy, the physician in charge may consider more invasive measures such as OCCM if ROSC and a good neurologic outcome are possible. After prolonged arrest, however, clear indications that CPR is inadequate (based on appropriate monitoring techniques) should prompt cessation of resuscitation efforts. Figure 7-2 is an algorithm for management of cardiac arrest. Interventions specific to each rhythm are discussed in the following sections.

EMERGENCY DEPARTMENT ALGORITHM FOR TREATMENT OF CARDIAC ARREST

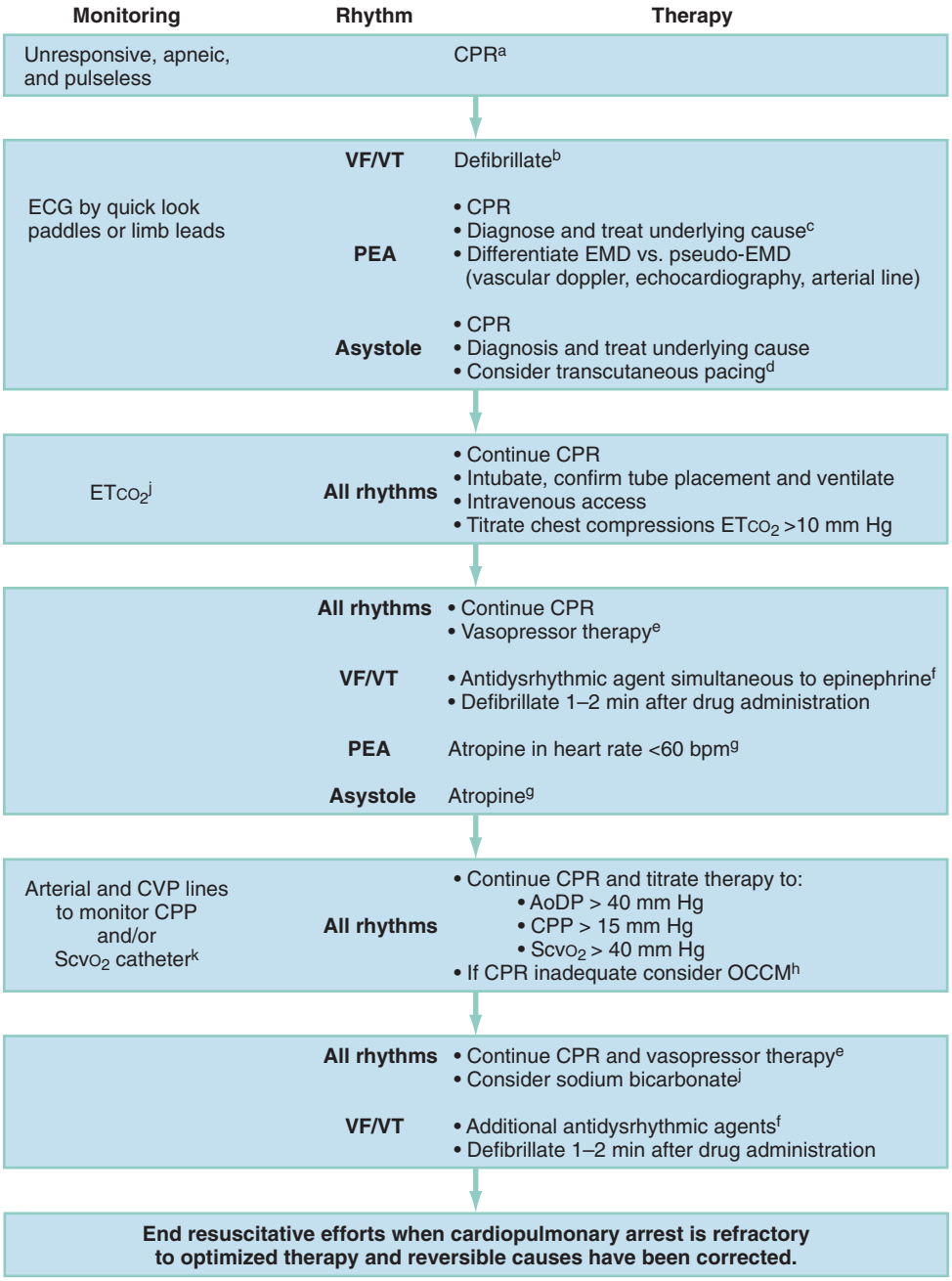

Figure 7-2. Emergency treatment algorithm for treatment of cardiac arrest. [a]If arrest is witnessed and known to be of short duration, immediate rhythm assessment and defibrillation or ventricular fibrillation/ventricular tachycardia (VF/VT) precede cardiopulmonary resuscitation (CPR). In cases of prolonged untreated VF/VT, 1 to 2 minutes of CPR before defibrillation may enhance the ability to achieve return of spontaneous circulation. EMD, electromechanical dissociation; PEA, pulseless electrical activity. [b]Consider using biphasic defibrillation (120–150 J) vs. monophasic defibrillation (360 J). [c]See Table 7-4. [d]Generally ineffective unless initiated immediately after onset of asystole. [e]Epinephrine, initial dose of 1 mg intravenous (IV) or intraosseous (IO) or 2.5 mg by endotracheal tube (ETT). Repeat every 3 to 5 minutes. Subsequent doses may be increased up to 0.1 mg/kg. An alternative to epinephrine is vasopressin, 40 U IV push. Vasopressin is potentially more effective if the presenting rhythm is asystole. The dose (40 U) can be repeated once in 3 minutes, followed by administration of epinephrine every 3 to 5 minutes. [f]Amiodarone, 300 mg IV push followed by 150 mg every 30 minutes. Alternative antidysrhythmics include lidocaine and bretylium. Magnesium sulfate, 1 to 2 g IV push in torsades de pointes or known hypomagnesemia. [g]Atropine, 1 mg IV push or 2.5 mg by ETT. Repeat dose every 3 to 5 minutes to a total dose of 0.04 mg/kg. [h]Open chest cardiac massage (OCCM) should be considered if (1) there are clear indications of inadequate blood flow during standard CPR, (2) duration of arrest is less than 20 minutes, and (3) the clinician judges that a potential exists for good neurologic outcome. AoDP, aortic diastolic pressure; CPP, coronary perfusion pressure; CVP, central venous pressure; $ScvO_2$, central venous oxygen saturation. [i]Sodium bicarbonate, 1 mEq/kg after prolonged rest or high dose of epinephrine. [j]Changes in end-tidal carbon dioxide partial pressure ($ETCO_2$) may not be predictive of myocardial blood flow after high-dose vasopressor therapy. [k]Invasive monitoring should be performed only if adequate personnel are available and if it would not delay therapeutic interventions.

Ventricular Fibrillation and Pulseless Ventricular Tachycardia

VF and pulseless VT are treated identically because they are generally caused by the same mechanisms and respond to the same interventions. Traditional monophasic defibrillators using either a monophasic truncated exponential (MTE) or a monophasic dampened sinusoidal (MDS) waveform are rapidly being replaced by defibrillators that use biphasic waveforms. With biphasic defibrillation, the energy required for successful defibrillation, or the "defibrillation threshold," is less than with monophasic defibrillation. This translates into an increased likelihood of initial defibrillation success and a decreased likelihood of postcountershock myocardial dysfunction. Despite documented advantages of lower defibrillation threshold and reduced myocardial injury using biphasic defibrillation, the data are currently inadequate to conclude that any specific waveform (biphasic or monophasic) is superior in achieving ROSC or survival to hospital discharge. New defibrillation technologies have stimulated reevaluation of optimal defibrillation strategies. Current consensus suggests that the most effective strategy is delivery of single countershocks at optimal energy levels with minimal pauses in CPR both before and immediately afterward.[29] This is facilitated by placement of defibrillation pads early in the resuscitation sequence, thus not requiring a pause while defibrillation paddles and gel pads are placed for each shock. Recommended countershock energies range from 150 to 200 J for biphasic truncated exponential (BTE) waveforms and 120 J for rectilinear biphasic waveforms.[29] Health professionals should be familiar with the manufacturer-recommended countershock energies of the biphasic defibrillator(s) available in their practice setting. The recommended energy for single monophasic defibrillation is 360 J.[29]

A patient who develops VF or pulseless VT while on a cardiac monitor may remain conscious for 15 to 30 seconds. The patient should be encouraged to cough vigorously until a defibrillator is available. If the patient is unresponsive, chest compressions should be initiated immediately and continued until a defibrillator is available. Defibrillation without antecedent CPR is most likely to result in ROSC when administered in the early minutes of arrest. If the duration of untreated arrest is prolonged (>4–5 minutes), a brief period of chest compressions and ventilations (90–180 seconds) before defibrillation has been shown to improve the likelihood of ROSC and survival.[24,30,31] The current consensus favors delivering a single countershock with minimal pause in chest compressions prior to defibrillation.[32] Defibrillation is followed immediately by resumption of chest compressions for 2 minutes prior to rhythm check.[32]

VF and pulseless VT refractory to initial defibrillation should be treated with assisted ventilation and chest compression. Intravenous (IV) access and vasopressor therapy (epinephrine or vasopressin) should be administered and repeated every 3 to 5 minutes. Simultaneous administration of epinephrine and vasopressin does not improve outcome relative to epinephrine alone regardless of presenting rhythm.[33]

Defibrillation attempts should be preceded and followed by minimal interruptions of chest compression.[32] Subsequent therapy for refractory VF and pulseless VT includes continued administration of vasopressors and antidysrhythmic agents, followed by repeated countershocks. Antidysrhythmics should be administered up to their maximum loading dose. The use of magnesium sulfate during VF and pulseless VT is of no proven efficacy except in torsades de pointes and possible hypomagnesemia. Specific indications for $NaHCO_3$ therapy include hyperkalemia and tricyclic antidepressant overdose. There is no evidence to support use of $NaHCO_3$ or other buffers as empiric treatment for metabolic acidosis during cardiac arrest. If a patient is defibrillated into a different pulseless rhythm, such as PEA or asystole, subsequent treatment should be modified to address those specific rhythms.

Pulseless Electrical Activity

PEA is defined as coordinated electrical activity of the heart (other than VT/VF) without a palpable pulse. This group of dysrhythmias includes EMD, in which no myocardial contractions occur, and pseudo-EMD, in which myocardial contractions occur but no pulse can be palpated. Although distinguishing EMD from pseudo-EMD may be useful in determining cause and guiding treatment, in most cases of primary PEA there is a natural progression from hypotension to pseudo-EMD to EMD.

True EMD is the result of a primary disorder of electromechanical coupling in myocardial cells. It often is associated with abnormal automaticity and conduction resulting in bradycardia and a wide QRS complex. Although the mechanism of uncoupling is unclear, it most often is associated with global myocardial energy depletion and acidosis resulting from ischemia or hypoxia. True EMD typically occurs after defibrillation following prolonged VF and is associated with hyperkalemia, hypothermia, and drug overdose.

Pseudo-EMD caused by global myocardial dysfunction is a transient state in the progression to EMD and has the same etiology. An additional cardiac cause of pseudo-EMD is papillary muscle and myocardial wall rupture, in which the ventricle continues to contract, but forward flow is greatly diminished. Pseudo-EMD also may be caused by primary supraventricular tachycardia Additional extracardiac causes of pseudo-EMD include hypovolemia, tension pneumothorax, pericardial tamponade, and massive pulmonary embolism. Pseudo-EMD of extracardiac origin most often has narrow-complex tachycardia initially, which can progress to bradycardia with conduction abnormalities and QRS widening.

Treatment of PEA requires all general resuscitation measures, including CPR, intubation with assisted ventilation, IV access, and repeated administration of vasopressors. Initial assessment also should include vascular Doppler ultrasound, echocardiography, or $ETCO_2$ monitoring to distinguish EMD from pseudo-EMD. This is important since volume loading or continuous vasopressor infusion, which is not typically used in routine cardiac arrest resuscitation, may be helpful in cases of pseudo-EMD. PEA thought to result from supraventricular tachycardia should be immediately cardioverted. Atropine should be administered if the heart rate is less than 60 beats/min. These interventions alone are generally inadequate, unless the underlying cause of PEA is primary respiratory arrest or supraventricular tachycardia. Successful resuscitation of patients with PEA hinges on rapid diagnosis and treatment of the underlying cause. Physical examination may provide valuable clues to the underlying cause (Table 7-4). In hypoxia and hypovolemia, the diagnosis is based on response to empirical therapy, whereas other causes, such as pericardial tamponade, tension pneumothorax, and hypothermia, can be definitively diagnosed during resuscitation. Physical examination and monitoring are used to guide ongoing resuscitation efforts.

Asystole

Asystole represents complete cessation of myocardial electrical activity. Although asystole may occur early in cardiac arrest as a consequence of progressive bradycardia, asystole generally represents the end-stage rhythm after prolonged cardiac arrest caused by VF or PEA. Because the potential exists for an

Table 7-4 Diagnosis and Treatment of Common Causes of Pulseless Electrical Activity

CAUSE	DIAGNOSIS	PALLIATIVE THERAPY	DEFINITIVE THERAPY
Hypovolemia	Response to volume infusion	Volume infusion, consider OCCM	Hemostasis if hemorrhage
Hypoxia	Response to oxygenation	Oxygenation, assisted ventilation	Treat underlying cause
Cardiac tamponade	Echocardiogram, pericardiocentesis	Pericardiocentesis	Thoracotomy and pericardiotomy
Tension pneumothorax	Asymmetrical breath sounds, tracheal deviation	Needle thoracostomy	Tube thoracostomy
Hypothermia	Rectal temperature		Warm peritoneal or thoracic lavage, OCCM or CPB
Pulmonary embolus	Risk factors or evidence of deep venous thrombosis	OCCM or CPB	Lytic therapy, pulmonary embolectomy
Drug overdose	History of drug ingestion	Drug-specific	Drug-specific
Hyperkalemia	History of renal failure or elevated serum potassium	Calcium chloride, insulin and glucose, sodium bicarbonate	Hemodialysis
Acidosis	Arterial blood gas	Hyperventilation, sodium bicarbonate	Treat underlying cause

CPB, cardiopulmonary bypass; OCCM, open-chest cardiac massage.

organized rhythm or VF to appear as asystole in a single lead (if the rhythm vector is completely perpendicular to the lead vector), asystole always should be confirmed in at least two limb leads. It may be difficult to distinguish between extremely fine VF and asystole. Routine countershock of asystole to treat possible fine VF has not been shown to improve outcome, however.

Treatment of asystole requires all general resuscitation measures, including CPR, intubation with assisted ventilation, IV access, and repeated administration of vasopressors. In one randomized prospective out-of-hospital trial, improved survival to hospital admission and discharge was observed in patients presenting in asystole when two doses of vasopressin (40 IU) were given initially during resuscitation compared with standard-dose epinephrine (1 mg) followed by additional epinephrine if needed.[34] In a more recent study, simultaneous administration of epinephrine and vasopressin did not improve outcome relative to epinephrine alone, regardless of presenting rhythm.[33] Atropine should be administered with the first dose of vasopressor and repeated to a total dose of 0.04 mg/kg. Extensive research has shown that asystole in the out-of-hospital setting seldom responds to pacing. To be effective, pacing must be initiated within several minutes of arrest.

Postarrest

Resuscitation of a cardiac arrest victim does not end with ROSC. Management includes rapid diagnosis and treatment of the disorders that caused the arrest and the complications of prolonged global ischemia. Simultaneous management of these two entities makes caring for a postarrest patient particularly challenging.

Induction of prolonged therapeutic hypothermia in comatose survivors of cardiac arrest has been shown to improve survival and functional outcome in two prospective randomized clinical trials.[3,4] Both studies enrolled only out-of-hospital patients with witnessed arrest and an initial rhythm of VF. The time to achieve target temperature (32–34° C) ranged from less than 2 hours[3] to a median of 8 hours (interquartile range 4–16 hours),[4] suggesting a broad therapeutic window. Hypothermia was maintained for 12 to 24 hours followed by gradual rewarming over 12 to 24 hours. Although these parameters provide guidelines within which postarrest hypothermia is effective, additional preclinical and clinical data are needed to determine the optimal temperature, time to achieve target temperature, and duration of therapy. In both studies, the rates of complications were not statistically different between groups. Although there are no absolute contraindications, relative contraindications include severe cardiogenic shock, life-threatening dysrhythmias, uncontrolled bleeding, preexisting coagulopathy, pregnancy, another obvious reason for coma (i.e., drug overdose or status epilepticus), known end-stage terminal illness, and a preexisting do-not-resuscitate status. Thrombolytic therapy does not preclude the use of hypothermia.[4] Finally, although the current data are limited to patients with witnessed VF out-of-hospital cardiac arrest, induced postarrest hypothermia potentially should be effective in patients with other presenting rhythms and cardiac arrest presentations.

When the decision is made to treat the patient with therapeutic hypothermia, cooling efforts should be initiated as soon as possible. Practical methods of rapidly inducing hypothermia include ice packs (applied to the neck, inguinal areas, and axilla), fan cooling of dampened exposed skin, cooling blankets underneath and on top of the patient, and disabling of ventilator warming circuits. Rapid IV infusion of limited volumes (1–2 L) of 4° C saline facilitates rapid cooling, but additional measures are needed to maintain hypothermia. A number of automated surface cooling devices are now available that use chest and thigh pads and continuous temperature feedback from bladder or esophageal temperature probes. More invasive methods, including endovascular venous catheters, are also available and allow for rapid and precise control of temperature, but they require time and additional resources to institute. Shivering, which inhibits cooling, can be prevented with sedation and pharmacologic paralysis. However, prolonged paralysis should be avoided due to the risk of unrecognized seizure activity in postarrest patients. Target core body temperature should be 32 to 34° C and is best monitored by an indwelling temperature-sensitive bladder catheter or esophageal temperature probe.[35]

When the patient is stabilized and cooling efforts are initiated, transfer to a critical care unit should occur as soon as possible. Although the optimal duration of postarrest hypothermia is unknown, target temperature should be actively maintained for 12 to 24 hours followed by gradual rewarming over 8 to 12 hours.[36] Effective application of therapeutic hypothermia in comatose cardiac arrest survivors requires a coordi-

nated interdisciplinary effort and is best carried out using a predetermined goal-directed algorithm developed with input from emergency medicine, cardiology, and critical care physicians and nurses.

A simultaneous immediate concern in a comatose cardiac arrest survivor is whether the patient has an acute coronary syndrome. Diagnosing acute coronary syndrome in an unconscious patient after cardiac arrest presents a unique challenge. A standard 12-lead ECG should be obtained as soon as feasible after ROSC, with a right-sided 12-lead ECG, as indicated. In one study, 50% of patients achieving ROSC after out-of-hospital cardiac arrest were found to have acute coronary occlusion on cardiac catheterization, 10% of whom did not have ST segment elevation.[13]

Immediate percutaneous coronary intervention (PCI) is indicated in patients with ST segment elevation myocardial infarction or new left bundle branch block (LBBB) and can be performed during therapeutic hypothermia.[36-39] Given the potentially high incidence of occult critical coronary stenosis and myocardial ischemia, patients without ECG criteria for PCI represent a greater dilemma. Angioplasty of acute coronary lesions regardless of history or initial postarrest ECG has been shown to be an independent predictor of survival after cardiac arrest.[13] When PCI is indicated but not available, either early transfer of postarrest patients to a center capable of PCI or fibrinolytic therapy should be considered.[40] Relative exclusion criteria for fibrinolytic therapy unique to the postarrest patient include CPR duration greater than 10 minutes and evidence of significant CPR trauma (e.g., pneumothorax, flail chest, pulmonary contusion with hemorrhage). The effects of therapeutic hypothermia on the efficacy and complications of fibrinolytic therapy in postarrest patients have not been formally studied.

Antiplatelet and anticoagulant therapy should be administered to all patients after ROSC, whether or not therapeutic hypothermia is induced, if no evidence of hemorrhage exists and profound hypertension is absent. The choice of antiplatelet and anticoagulant therapy depends in part on the presence of active ischemia, renal function, and plans for acute angioplasty.[41] Although there is no proven benefit from prophylactic antiarrhythmic therapy in postarrest patients, it may be reasonable to continue an infusion of an antiarrhythmic drug that was associated with restoration of a stable rhythm during CPR. Concomitant therapies (e.g., nitrates, beta-blockers) are best performed in conjunction with careful hemodynamic monitoring. If indicated, IV preparations of nitrates and short-acting beta-blockers (e.g., esmolol) should be used because they have a brief duration of action and are easily titrated. Patients with new LBBB, right bundle branch block with left anterior or posterior hemiblock, second-degree type II block, or third-degree block should have transthoracic pacing pads immediately applied if needed. Placement of transvenous pacing catheters also can be considered, but is less often done since transthoracic pacing came into common use.[42]

Inadequate oxygen delivery (Do_2) causes cells to convert to anaerobic metabolism, resulting in increased lactate production (dysoxia). Continued resuscitation efforts to optimize Do_2 may help to stabilize the patient and potentially prevent subsequent multiorgan dysfunction and recurrent arrest.

During cardiac arrest and CPR, Do_2 is well below necessary levels. On ROSC, resuscitation efforts should continue to establish adequate Do_2. Serum lactate levels provide an indirect measure of whether Do_2 is adequate to prevent anaerobic metabolism. A single lactate level is almost universally elevated after resuscitation from cardiac arrest. Detection of ongoing lactate production requires following serial lactate levels. Insufficient Do_2 also causes increased oxygen extraction, resulting in decreased Svo_2. Low Svo_2 coupled with persistently elevated lactate levels indicates inadequate Do_2. Patients subjected to prolonged CPR times or high-dose vasopressor therapy during CPR may develop impaired tissue oxygen extraction.[43] In such patients, Svo_2 is abnormally high (venous hyperoxia) in the face of inadequate Do_2 and likely represents a state of severe systemic shunting resulting in an increase in non-nutritive blood flow. Lactate levels in these circumstances continue to be elevated. Thus the combination of sustained elevated lactate levels along with normal or elevated $Scvo_2$ levels indicate severe systemic shunting. Treatments for this would include carefully reducing any continuous infusion of vasopressors, more aggressive volume loading, and possibly the use of guided vasodilator therapy to open up underperfused tissue beds.

The use of combined hemodynamic and metabolic endpoints to guide resuscitation in the ED has been shown to improve the outcome of patients with septic shock states, but has not been evaluated in the postarrest situation.[44] This strategy may be helpful in this setting, however. It is relatively straightforward and requires only the insertion of a supradiaphragmatic central venous catheter. $Scvo_2$ can be used as a reliable surrogate for Svo_2, which eliminates the need for a pulmonary artery catheter.[23] If $Scvo_2$ is abnormally low (<65%), but hemoglobin and Sao_2 values are normal, cardiac output is insufficient. Central venous pressure (CVP) should be used to deduce whether inadequate cardiac output is secondary to hypovolemia or impaired myocardial function. Augmenting CVP to levels between 10 and 15 mm Hg ensures adequate preload in most patients. If CVP is adequate and the patient has a mean arterial pressure of at least 70 mm Hg, therapy with an inotropic agent, such as dobutamine, should be initiated while considering reperfusion strategies. CVP measurements may decrease rapidly on initiation of dobutamine therapy. Additional volume expansion while maintaining a hemoglobin value of at least 10 g/dL should be provided as needed to maintain an adequate CVP.

The response to Do_2-optimizing interventions can be monitored by continuous or serial $Scvo_2$ measurements and serial lactate levels. An increase in $Scvo_2$ coupled with a decrease in lactate levels indicates improved Do_2. An unchanging $Scvo_2$ level indicates the need to continue to increase delivery. Persistently elevated lactate levels and low $Scvo_2$ despite maximum pharmacologic support and volume management signal the need for additional interventions to optimize Do_2 to prevent accumulation of oxygen debt, which will lead to either death or the development of multisystem organ failure. Options to consider include revascularization or mechanical assistance in the form of intra-aortic balloon pulsation or extracorporeal support. The induction of mild hypothermia may assist in lowering the metabolic demands of tissues in the postarrest state. Figure 7-3 provides a goal-directed guide to care of the postarrest patient. Similar options should be considered in a patient with venous hyperoxia and elevated levels of lactate because the combination of these findings indicate severe microvascular dysfunction, which also leads to the accumulation of oxygen debt incompatible with survival. The incidence of this condition may increase with the increased use of potent vasopressors, such as vasopressin.

Systems should ensure prompt transfer of postarrest patients from the ED to the cardiac catheterization laboratory or an intensive care unit, where intensive monitoring can guide subsequent therapy to achieve the optimal patient outcome. Family members should be fully informed of the circumstances and the patient's transfer. Unless prompt transfer to the ICU is anticipated and achieved, postarrest care should begin in the ED.

GOAL-DIRECTED POST ARREST TREATMENT ALGORITHM

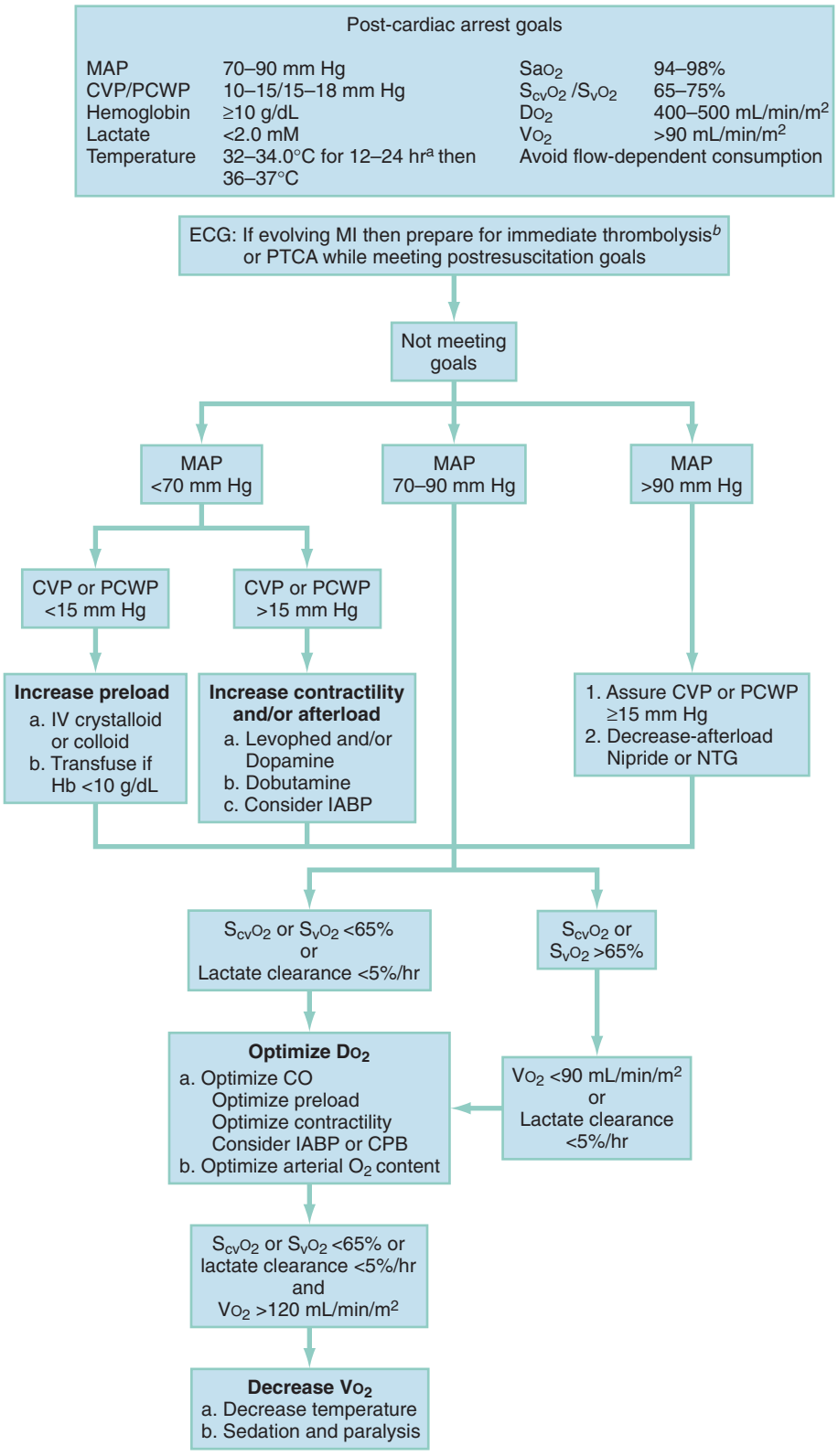

Figure 7-3. Goal-directed postarrest treatment algorithm. [a]Therapeutic hypothermia is indicated in comatose survivors of witnessed cardiac arrest that had a presenting rhythm of ventricular fibrillation. It may also be effective in patients resuscitated from other cardiac arrest presentations. Relative contraindications include an unwitnessed cardiac arrest, severe cardiogenic shock, life-threatening dysrhythmias, uncontrolled bleeding, preexisting coagulopathy, pregnancy, another obvious reason for coma (i.e., drug overdose or status epilepticus), known end-stage terminal illness, and a preexisting do-not-resuscitate status. [b]Initiation of therapeutic hypothermia is not a contraindication to thrombolytic therapy. CPB, cardiopulmonary bypass; CVP, central venous pressure; D_{O_2}, oxygen delivery; ECG, electrocardiogram; Hb, hemoglobin; IABP, intra-aortic balloon pulsation; MAP, mean arterial pressure; PCWP, pulmonary capillary wedge pressure; PTCA, percutaneous transluminal angioplasty; Sa_{O_2}, mixed-venous oxygen saturation; V_{O_2}, oxygen consumption.

KEY CONCEPTS

- CPR quality, including minimizing chest compression pauses, is critical to successful resuscitation from cardiac arrest.
- Restoration of adequate cardiac function is the defining factor of ROSC. Restoration of normal brain function is the defining factor of successful resuscitation.
- Resuscitation of a cardiac arrest victim does not end with ROSC. Rapid diagnosis and proper management of the pathologic conditions that precipitated and resulted from the arrest as well as goal-directed hemodynamic management can improve outcome.
- Induced prolonged hypothermia (32–34°C for 12–24 hours) is the first and only post-ROSC intervention shown to improve survival and functional outcome of comatose cardiac arrest survivors.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 8 Pediatric Resuscitation

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CARDIAC ARREST

Perspective

Cardiac arrest is not rare in pediatric patients, occurring in 2 to 6% of children admitted to a pediatric intensive care unit (PICU)[1,2] and about 16,000 children per year out-of-hospital in the United States (i.e., ≈8-20/100,000 children/year).[3,4] These data suggest that the rate of in-hospital cardiac arrest is about 100-fold higher than that for out-of-hospital arrest.[5]

Although outcomes from pediatric cardiac arrest were once considered dismal,[6,7] more recent data indicate that pediatric cardiopulmonary resuscitation (CPR) is saving lives. As many as two thirds of in-hospital pediatric cardiac arrest patients can be initially resuscitated,[8-12] and over 25% survive to hospital discharge. For out-of-hospital pediatric cardiac arrests, 30% attain return of spontaneous circulation, 24% survive to hospital admission, and 12% survive to discharge.[4] In contrast to previous assertions in the literature, performing CPR in children is not an exercise in futility.[13]

Etiologic and Pathophysiologic Categories of Cardiac Arrest

Cardiac arrests can result from many pathophysiologic processes. Three common pathways to arrest have been identified: asphyxial, ischemic, and arrhythmogenic. Asphyxial cardiac arrests are precipitated by acute hypoxia or hypercarbia and are the most common in children.[3,10,12] Ischemic arrests are precipitated by inadequate myocardial blood flow, in children most commonly due to shock from hypovolemia, sepsis, or myocardial dysfunction. Finally, arrhythmogenic arrests are precipitated by ventricular fibrillation (VF) or ventricular tachycardia (VT). The immediate cause of arrest in two recent in-hospital studies was arrhythmogenic for 10%, asphyxial for 67%, and ischemic for 61% (many had both asphyxia and ischemia).[10,12] The vast majority of out-of-hospital arrests are also either asphyxial or ischemic, and 5 to 20% are arrhythmogenic.[4,14]

Distinguishing Principles of Disease

Children Are Different

Appropriate pediatric CPR differs from that for adults due to children's differences in anatomy and physiology, as well as the differences in the pathogenesis of cardiac arrest and the common rhythm disturbances for children. In contrast to adults, children rarely suffer sudden VF cardiac arrest from coronary artery disease. The causes of pediatric arrests are more diverse and are usually secondary to profound hypoxia or asphyxia due to respiratory failure or circulatory shock. Prolonged hypoxia and acidosis impair cardiac function and ultimately lead to cardiac arrest. By the time the arrest occurs, all organs of the body have generally suffered significant hypoxic-ischemic insults.

The use of closed-chest cardiac massage to provide adequate circulation during cardiac arrest was initially demonstrated in small dogs with compliant chest walls.[15] Based on reasonable extrapolation, these investigators felt that closed-chest cardiac massage would be effective with children, but might not be with adults. Therefore, the first patients successfully treated with this technique were children. The presumed mechanism of blood flow was direct compression of the heart between the sternum and the spine in these children with compliant chest walls. Later investigations indicated that blood could also be circulated during CPR by the thoracic pump mechanism. That is, chest compression-induced increases in intrathoracic pressure can generate a gradient for blood to flow from the pulmonary vasculature, through the heart, and into the peripheral circulation. Regardless of mechanism, cardiac output during CPR seems to be greater in children (and immature animals) with compliant chest walls than in adults with less compliant chest walls.[16,17] Interestingly, recent American Heart Association (AHA) National Registry of CPR data indicate that outcomes from in-hospital cardiac arrest are substantially better in infants than older children, perhaps because of superior perfusion during CPR.[9]

The Four Phases of Cardiac Arrest

Cardiac arrest may be categorized into four "phases," each with unique physiology and treatment strategies: (1) prearrest, (2) no flow (untreated cardiac arrest), (3) low flow (CPR), and (4) postresuscitation.

The Prearrest Phase. The *prearrest phase* is the period before the arrest. Because most out-of-hospital pediatric cardiac arrests are due to progressive asphyxia or ischemia, they can often be prevented by avoiding the precipitating insult. For example, infant and child car seats, and seat belts for older children, can prevent cardiac arrests resulting from motor vehicle collisions. Similarly, fences around swimming pools with self-closing gates can prevent drownings.

Both the BRESUS study in the United Kingdom and the AHA's National Registry of Cardiopulmonary Resuscitation

(NRCPR) data clearly demonstrate that most in-hospital cardiac arrests are asphyxial or ischemic rather than sudden arrhythmia-induced events.[10,18,19] Most importantly, many of these arrests could be prevented by early recognition and treatment of respiratory failure and shock. This information has fueled interest in the development of medical emergency teams (aka rapid response teams) to recognize and treat respiratory failure and circulatory shock before progression to cardiac arrest.[20,21] These issues were appreciated by the founders of the Pediatric Advanced Life Support (PALS) course, which was therefore designed to prevent cardiac arrests by early recognition and treatment of respiratory failure and shock in children.[7] In the *prearrest phase*, hospitalized children at high risk for a cardiac arrest should be in a monitored unit, where prompt diagnosis and treatment is available for respiratory failure, circulatory shock, and life-threatening arrhythmias.

The No-Flow Phase (Untreated Cardiac Arrest). Interventions during the *no-flow* phase of untreated pulseless cardiac arrest focus on early recognition of cardiac arrest and initiation of basic and advanced life support. Yet only a third of children with an out-of-hospital cardiac arrest are provided with bystander CPR.[4,14]

According to NRCPR data, 83% of pediatric in-hospital arrests were witnessed, and the children were on monitors.[10] It is becoming increasingly clear that any in-hospital pediatric cardiac arrest that does not occur in a monitored unit should be evaluated as a sentinel event or potentially an avoidable death.

The Low-Flow Phase (Resuscitation). During untreated cardiac arrest, circulation has stopped (i.e., the *no-flow* phase). Blood flow during CPR is generated by chest compressions. For children the main mechanism of blood flow is from cardiac compression. The cardiac output depends on the product of the stroke volume and heart rate. The force of compressions is a major determinant of stroke volume, and the rate of compressions is the sole determinant of heart rate. Stroke volume also depends on preload. Therefore, patients with cardiac arrests precipitated by circulatory shock (e.g., hypovolemic or septic shock) may need additional intravascular volume to generate an adequate stroke volume with chest compressions. Notably, excellent CPR can result in a cardiac output 10 to 25% of that in normal sinus rhythm.

Adequate myocardial blood flow is necessary for return of spontaneous circulation. During CPR, myocardial blood flow depends on coronary perfusion pressure or the "driving pressure" of blood into the coronary arteries from the aorta (i.e., the difference between the aortic and right atrial pressures during the relaxation phase). If the coronary perfusion pressure falls below 15 mm Hg during CPR in adults, the likelihood for a return of spontaneous circulation is substantially decreased.[22] Animal data suggest that outcomes improve as coronary perfusion pressure increases above 25 mm Hg.[23] Moreover, even relatively brief interruptions to chest compressions (e.g., 4-second pauses for two rescue breaths) lead to substantial decreases in the aortic relaxation pressure and coronary perfusion pressure, thereby resulting in inadequate myocardial perfusion[24,25] (Fig. 8-1).

Circumferential Versus Focal Sternal Compressions

In adults and animal models of cardiac arrest, circumferential CPR (e.g., vest CPR) provides better CPR hemodynamics than two-finger compressions. In smaller infants, the recommended CPR technique is to encircle the chest with both hands and depress the sternum with the thumbs, while compressing the thorax circumferentially (when the resuscitator's hands are relatively large enough to do so; Fig. 8-2).[14] This "two-thumb" circumferential compression technique results in higher systolic and diastolic blood pressures and a higher pulse pressure than traditional two-finger compression of the sternum.[26,27]

Chest Compression Rate

Another important determinant of myocardial blood flow is the chest compression rate. Although the optimal chest compres-

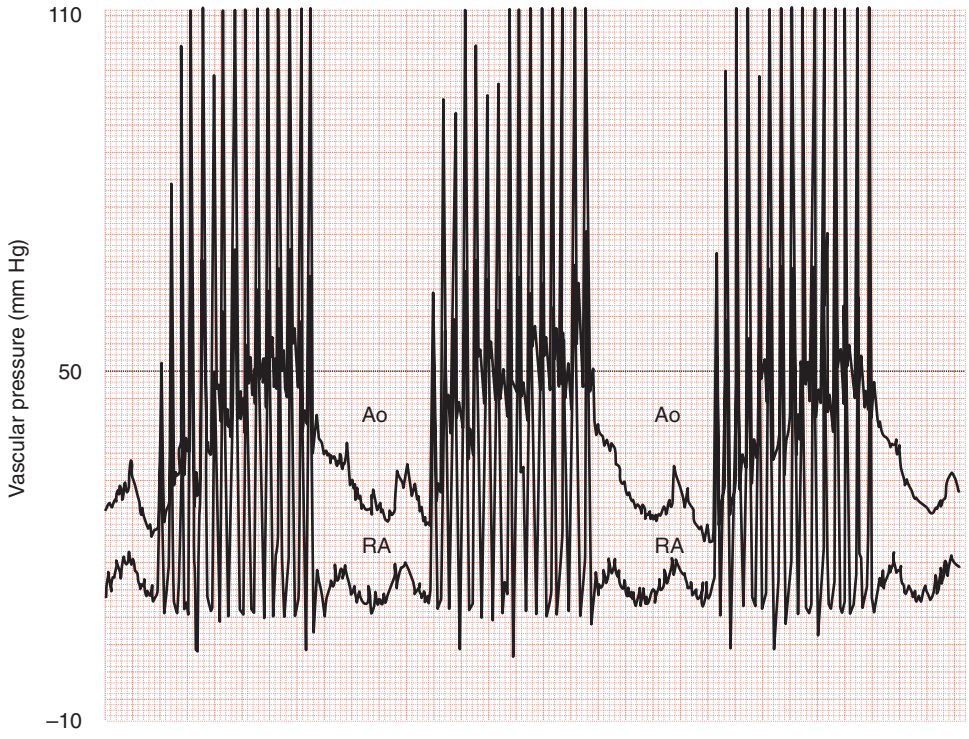

Figure 8-1. Cerebral perfusion pressure with cardiopulmonary resuscitation. Ao, aorta; RA, right atrium. (Courtesy of University of Arizona, Department of Pediatrics, Division of Pediatric Critical Care.)

Figure 8-2. Hand-thumbs encircling technique for chest compression in infants with cardiopulmonary failure. (Reprinted with permission from BLS for Healthcare Providers. Copyright ©2006, American Heart Association, Inc.)

sion rate is unknown, data from large studies of animals have shown that coronary perfusion pressure, cardiac output, and survival are substantially superior, with chest compression rates of 100/minute compared with rates of less than 80/minute.[28,29] In addition, clinical studies in adults have shown that end-tidal carbon dioxide levels, a marker of cardiac output during CPR, were significantly higher with chest compressions at 120/minute versus 80/minute.[30] Because of preferential blood flow to the myocardium and cerebrum compared with the rest of the body during CPR, excellent CPR can provide myocardial blood flow greater than 50% of that in normal sinus rhythm.

Although restoration of coronary perfusion during CPR is critical for successful return of spontaneous circulation, adequate cerebral perfusion is important for mitigating the injurious effects of cerebral anoxia during cardiac arrest. Unlike myocardial blood flow, cerebral blood flow is generated during the compression phase of CPR. Forceful, uninterrupted chest compressions at a rate of 120/minute compared with 60/minute improves both cerebral and coronary perfusion pressures compared with less forceful compressions or compressions at a lower rate.[28,29] In addition, vasoconstrictors, such as epinephrine or vasopressin, preferentially direct the cardiac output during CPR to the coronary and cerebral circulations.

The ultimate goal of CPR is to provide coronary and cerebral perfusion pressure and blood flow to critical organs during the low-flow phase. Excellent quality basic life support with continuous effective chest compressions is the emphasis in this low-flow phase. During this phase, the *only* source of coronary and cerebral perfusion comes from the blood pressure generated by good chest compressions. Providing adequate coronary and cerebral perfusion pressure is critical for successful resuscitation. Any interruption, whether to perform procedures, analyze rhythms, check for pulses, or to change rescuer position for ventilation is potentially harmful.[24] For VF and pulseless VT, rapid determination of electrocardiographic rhythm and prompt defibrillation when appropriate are important. For cardiac arrests due to asphyxia or ischemia, adequate myocardial perfusion and myocardial oxygen delivery with ventilation to match blood flow is important.

Despite evidence-based guidelines, extensive provider training, and provider credentialing in resuscitation medicine, the quality of CPR is typically poor. Slow compression rates, inadequate depth of compression, and substantial pauses are the norm.[31-33] Moreover, observed ventilation rates during professional rescuer CPR are often too high, potentially leading to deleterious effects on venous return and outcome.[33,34] The resuscitation mantra must be: *Push hard, push fast, minimize interruptions, allow full chest recoil, and don't overventilate.* This approach can markedly improve myocardial, cerebral, and systemic perfusion, and will likely improve outcomes.[35]

Chest Compression to Ventilation Ratios

Ideal compression-to-ventilation ratios for pediatric patients are unknown. Physiologic estimates suggest that the amount of ventilation needed during CPR is much less than the amount needed during a normal perfusing rhythm because the cardiac output (and therefore pulmonary blood flow) during CPR is only 10 to 25% of that during normal sinus rhythm.[36] The best ratio of compressions to ventilations depends on many factors, including the compression rate, the tidal volume, the blood flow generated by compressions, and the time that compressions are interrupted to perform ventilations. In a manikin model of pediatric CPR, a chest compression-to-ventilation (CC:V) ratio of 15:2 delivered the same minute ventilation as CPR with a CC:V ratio of 5:1, but the number of chest compressions delivered was 48% higher with the 15:2 ratio.[37,38] The benefits of positive pressure ventilation (increased arterial oxygen content and carbon dioxide elimination) must be balanced against the adverse consequence of impeding circulation because of increases in intrathoracic pressure and venous return to the heart.

For adults, mathematical models of oxygen delivery during CPR suggest the optimal CC:V ratio is approximately 30:2 for two-rescuer health care provider CPR and is closer to 50:2 for single-lay rescuers.[39] Similar mathematical models adjusted to the known physiologic variables in children indicate that CC:V ratios from 10:2 to 30:2 would be reasonable to optimize tissue oxygen delivery during CPR.[40]

The present recommendations for CC:V ratios during CPR are based on rational conjecture from animal, manikin, and mathematical models, as well as educational theory on the retention of skills in adult learners. In the 2005 AHA Guidelines, a universal CC:V ratio of 30:2 is recommended for single-person bystander CPR. For two-rescuer CPR, a 15:2 ratio is recommended for all children beyond the newly born period. For the newly born, a ratio of 3:1 is recommended, resulting in a greater number of ventilations per minute, but nearly the same number of compressions (100/min vs. 90/min).[41] This recommended ratio was arrived at by consensus to balance educational issues (i.e., the benefit to single-rescuer bystanders of remembering only one compression to ventilation ratio of 30:2) with what is known about the physiology of the cardiac and pulmonary circulations of children during cardiac arrest.

Leaning

Along with the increased recognition that chest compressions are often too slow and too shallow (i.e., not forceful enough), investigators have focused on the problem of leaning during CPR. Leaning, or incomplete decompression of the chest during the relaxation phase of chest compressions, is a well-recognized phenomenon.[42-44] In a manikin study of CPR-trained lay volunteers, Aufderheide observed incomplete chest wall decompression in 6 of 13 resuscitations.[42-44] In a larger observational study of out-of-hospital cardiac arrests, incomplete release in greater than 10% of compressions was observed in 16 of 173 (9%) CPR episodes.[43] Observations during in-hospital pediatric CPR indicate that "leaning" is a common phenomenon, occurring in 23% of chest compressions.[45]

"Leaning" pressures of approximately 15% of body weight may affect intrathoracic pressure and theoretically affect the hemodynamics of CPR.[45-48]

Real-Time Cardiopulmonary Resuscitation Feedback

In an effort to optimize CPR quality, new technology has been developed that monitors CPR through a force sensor and accelerometer on the chest. This information is transmitted to a defibrillator monitor to provide quantitative verbal feedback to the rescuer on the rate and force of compressions as well as the frequency and volume of ventilations. Recent studies document that poor-quality CPR, as analyzed by a feedback device, reduces the likelihood of defibrillation success,[35] and rescuers can use this type of automated feedback to improve CPR quality and compliance with current guidelines.[49] A recent pilot study suggests that real-time corrective feedback during pediatric CPR can improve CPR performance, but more information on the accuracy and appropriateness of CPR performance targets is warranted.[50] The optimal goals for aortic pressures during pediatric CPR are unknown. Animal data and adult data suggest that a reasonable goal for the aortic diastolic (or relaxation) pressure is greater than 20 to 30 mm Hg.[22,23] Similarly, a reasonable goal for the aortic systolic (or compression) pressure is greater than 50 mm Hg for a newborn, 60 mm Hg for an infant, 70 to 80 mm Hg for a child, and 80 to 90 mm Hg for an adolescent.

"Hands Only" Bystander Cardiopulmonary Resuscitation

There has been increasing interest in chest compressions alone, or "hands-only" CPR for sudden cardiac arrest. The AHA recently issued a science advisory statement recommending hands-only CPR for adult sudden cardiac arrest.[51] This recommendation specifically excludes pediatric cardiac arrests and arrests secondary to progressive respiratory failure and hypoxia (i.e., asphyxial arrests). Hands-only bystander CPR is the treatment of choice for a bystander without formal CPR training and a CPR-trained bystander who "is not confident in his or her ability to provide rescue breaths with minimal interruptions to chest compressions." For a CPR-trained bystander who "is confident in his or her ability to provide rescue breaths with minimal interruptions to chest compressions, the bystander should provide either conventional CPR using a 30:2 compression-to-ventilation ratio or hands-only CPR." Finally, because mouth-to-mouth rescue breathing is a complex psychomotor task that is difficult to teach by telephone, the simpler technique of hands-only CPR is the recommended technique for telephone-directed CPR.

Many animal studies have established that continuous chest compressions without rescue breathing is as effective as chest compressions with rescue breathing for the first several minutes of CPR for VF.[25,52-55] Since oxygenation and ventilation are clearly important for survival from any cardiac arrest, why is rescue breathing not initially necessary for VF? Immediately after an acute fibrillatory cardiac arrest, aortic oxygen and carbon dioxide concentrations do not vary from the prearrest state because there is no blood flow and aortic oxygen consumption is minimal. Therefore, when chest compressions are initiated, the blood flowing from the aorta to the coronary and cerebral circulations provides adequate oxygenation at an acceptable pH. At that time, myocardial and cerebral oxygen delivery is limited more by blood flow than oxygen content. Adequate oxygenation and ventilation can continue without rescue breathing because the lungs serve as a relatively high oxygen/low carbon dioxide reservoir during the low-flow state of CPR. In addition, ventilation can occur due to chest compression-induced gas exchange and spontaneous gasping during CPR in victims of sudden cardiac arrest. Therefore, arterial oxygenation and pH can be adequate with chest compressions alone in VF arrests.[52,53,56]

Six clinical out-of-hospital studies in adults found that outcomes were as good or better after hands-only bystander CPR as with standard bystander CPR.[57-63] One of these studies was a randomized, controlled prospective study of telephone-directed CPR, whereas the other five were observational studies of outcomes after bystander CPR.[57-63]

Asphyxia and Pediatric Cardiac Arrest

Chest compression (i.e., hands-only) CPR for children is not recommended. Foregoing ventilation in the pediatric patient is not prudent because respiratory arrest and asphyxia generally precede pediatric cardiac arrest. During asphyxia, blood continues to flow to tissues; therefore, arterial and venous oxygen saturations decrease while carbon dioxide and lactate continue to increase for many minutes before progression to cardiac arrest. In addition, continued pulmonary blood flow before the cardiac arrest depletes the pulmonary oxygen reservoir. In this circumstance, rescue breathing can be life-saving.

Not surprisingly, animal studies of bystander CPR for asphyxia-precipitated cardiac arrests demonstrate that the addition of rescue breathing to compressions results in much better outcomes than chest compressions alone.[64,65] Chest compressions alone, however, were superior to no CPR at all, even with hypoxia-induced cardiac arrest. These studies support the need for rescue breathing as a critical component of CPR for pediatric asphyxia-precipitated cardiac arrests. However, approximately 10% of both in-hospital and out-of-hospital pediatric cardiac arrests are arrhythmogenic arrests precipitated by VF or VT. For an older child with a sudden collapse from cardiac arrest (i.e., presumed VF or VT), hands-only CPR is a reasonable choice for bystander CPR.

Advanced Life Support Medications During the Low-Flow Phase of Cardiopulmonary Resuscitation

Figure 8-3 demonstrates a simplified algorithm for pediatric pulseless cardiac arrest. In addition, Table 8-1 lists medicines commonly used during CPR. Table 8-1 also includes the dosage and appropriate indications for these medications.

Although animal studies indicate that epinephrine can improve initial resuscitation success after both asphyxial and VF cardiac arrests, no single medication has been shown to improve survival to hospital discharge outcome from pediatric cardiac arrests. Medications commonly used for CPR in children are vasopressors (epinephrine or vasopressin), calcium chloride, sodium bicarbonate, and antiarrhythmics (amiodarone or lidocaine). During CPR, epinephrine's alpha-adrenergic effect increases systemic vascular resistance, increasing diastolic blood pressure, which in turn increases coronary perfusion pressure and blood flow and increases the likelihood of the return of spontaneous circulation (ROSC). Epinephrine also increases cerebral blood flow during CPR because peripheral vasoconstriction directs a greater proportion of flow to the cerebral circulation. The beta-adrenergic effect increases myocardial contractility and heart rate and relaxes smooth muscle in the skeletal muscle vascular bed and bronchi, although this effect is of less importance. Epinephrine also changes the character of VF (i.e., higher amplitude, more "coarse"), increasing the likelihood of successful defibrillation.

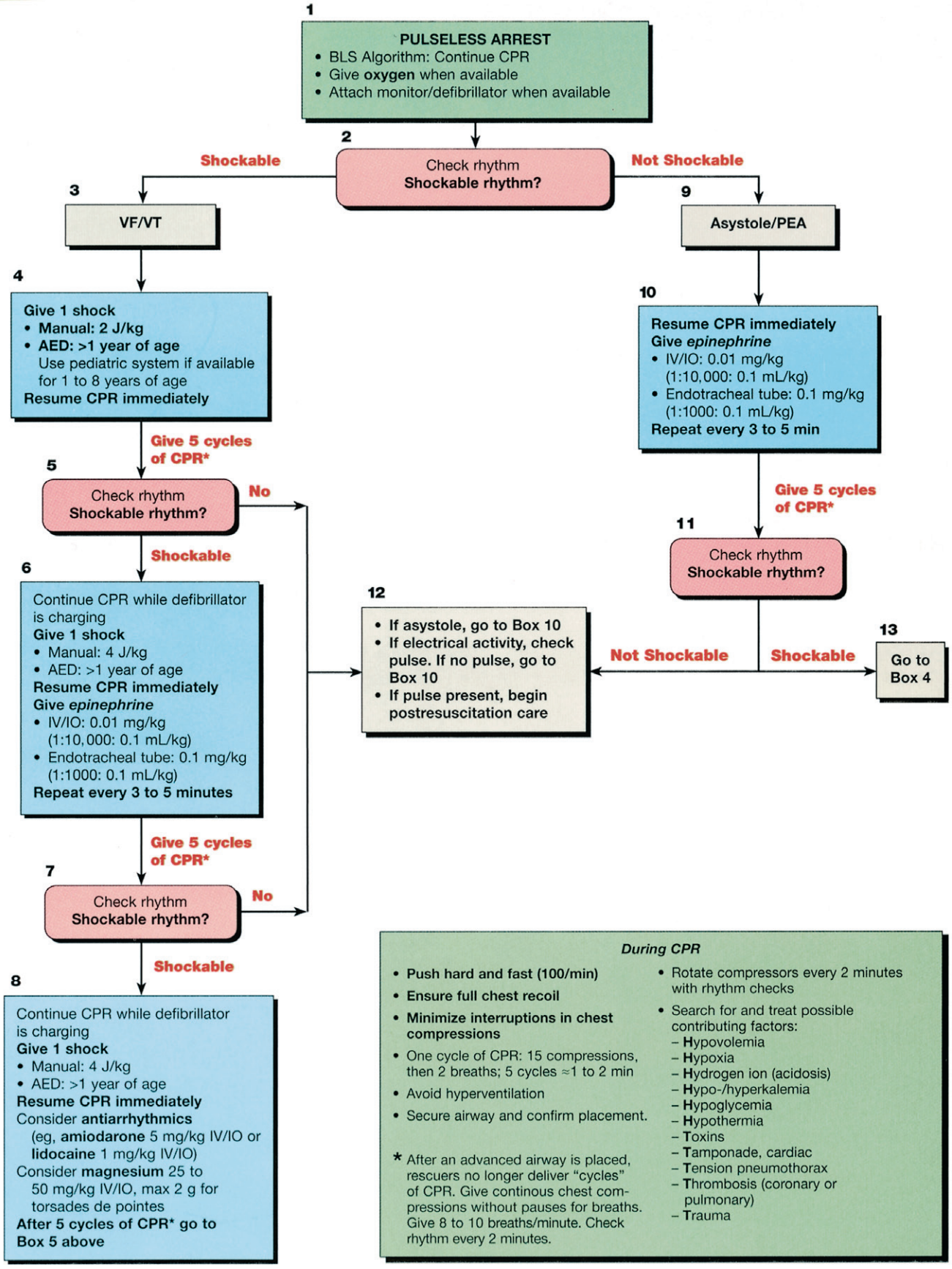

Figure 8-3. Management algorithm for infants and children with cardiopulmonary arrest. AED, automated external defibrillator; CPR, cardiopulmonary resuscitation; IO, intraosseous; IV, intravenous; PEA, pulseless electrical activity; VF, ventricular fibrillation; VT, ventricular tachycardia. Reprinted with permission from Pediatric Advanced Life Support Course Guide. Copyright ©2006, American Heart Association, Inc.

Table 8-1 Medications Used in the Treatment of Pediatric Patients in Cardiopulmonary Arrest

DRUG	INDICATIONS/DOSAGE
Adenosine	SVT 0.1 mg/kg IV/IO *rapid* push (max 6 mg), 2nd dose 0.2 mg/kg IV/IO *rapid* push (max 12 mg)
Albumin	Shock, trauma, burns 0.5–1 g/kg (10–20 mL/kg of 5% solution) IV/IO *rapid* infusion
Albuterol	Asthma, anaphylaxis (bronchospasm), hyperkalemia MDI: 4 to 8 puffs INH q 20 min PRN with spacer (*OR* ETT if intubated) Nebulizer: 2.5 mg/dose (wt < 20 kg) *OR* 5 mg/dose (wt > 20 kg) INH q 20 min PRN Continuous nebulizer: 0.5 mg/kg/hr INH (max 20 mg/hr)
Alprostadil (PGE_1)	Ductal-dependent congenital heart disease (all forms) 0.05–0.1 µg/kg/min IV/IO infusion initially, then 0.01–0.05 µg/kg/min IV/IO
Amiodarone	SVT, VT (with pulses) 5 mg/kg IV/IO *load* over 20–60 min (*max* 300 mg), repeat to daily max 15 mg/kg (or 2.2 g) Pulseless arrest (ie, VF/pulseless VT) 5 mg/kg IV/IO *bolus* (max 300 mg), repeat to daily max 15 mg/kg (or 2.2 g)
Atropine sulfate	Bradycardia (symptomatic) 0.02 mg/kg IV/IO (min dose 0.1 mg, max single dose child 0.5 mg, max single dose adolescent 1 mg), may repeat dose once, max total dose child 1 mg, max total dose adolescent 2 mg 0.04–0.06 mg/kg ETT Toxins/overdose (eg, organophosphate, carbamate) 0.02–0.05 mg/kg (<12 years) *OR* 0.05 mg/kg (>12 years) IV/IO initially, repeat q 20–30 min until atropine effect (dry mouth, tachycardia, mydriasis) is observed or symptoms reverse
Calcium chloride 10%	Hypocalcemia, hyperkalemia, hypermagnesemia, calcium channel blocker overdose 20 mg/kg (0.2 mL/kg) IV/IO *slow* push during arrest or if severe hypotension, repeat PRN
Dexamethasone	Croup 0.6 mg/kg PO/IM/IV (max 16 mg)
Dextrose (Glucose)	Hypoglycemia 0.5–1 g/kg IV/IO ($D_{25}W$ 2–4 mL/kg; $D_{10}W$ 5–10 mL/kg)
Diphenhydramine	Anaphylactic shock 1–2 mg/kg IV/IO/IM q 4–6 hr (max 50 mg)
Dobutamine	Congestive heart failure, cardiogenic shock 2–20 µg/kg/min IV/IO infusion; titrate to desired effect
Dopamine	Cardiogenic shock, distributive shock 2–20 µg/kg/min IV/IO infusion; titrate to desired effect
Epinephrine	Pulseless arrest, bradycardia (symptomatic) 0.01 mg/kg (0.1 mL/kg) 1:10,000 IV/IO q 3–5 min (max 1 mg; 1 mL) 0.1 mg/kg (0.1 mL/kg) 1:1000 ETT q 3–5 min Hypotensive shock 0.1–1 µg/kg/min IV/IO infusion (consider higher doses if needed) Anaphylaxis 0.01 mg/kg (0.01 mL/kg) 1:1000 IM in thigh q 15 min PRN (max 0.5 mg) *OR* Auto-injector 0.3 mg (wt ≥ 30 kg) IM or Child Jr auto-injector 0.15 mg (wt 10–30 kg) IM 0.01 mg/kg (0.1 mL/kg) 1:10,000 IV/IO q 3–5 min (max 1 mg) if hypotension 0.1–1 µg/kg/min IV/IO infusion if hypotension despite fluids and IM injection Asthma 0.01 mg/kg (0.01 mL/kg) 1:1000 SQ q 15 min (max 0.5 mg; 0.5 mL) Croup 0.25–0.5 mL *racemic* solution (2.25%) mixed in 3 mL NS INH *OR* 3 mL 1:1000 INH Toxins/Overdose (e.g., beta-adrenergic blocker, calcium channel blocker) 0.01 mg/kg (0.1 mL/kg) 1:10,000 IV/IO (max 1 mg); if no response, consider higher doses up to 0.1 mg/kg (0.1 mL/kg) 1:1000 IV/IO 0.1–1 µg/kg/min IV/IO infusion (consider higher doses)
Furosemide	Pulmonary edema, fluid overload 1 mg/kg IV/IM (usual max 20 mg if not chronically on loop diuretic)
Hydrocortisone	Adrenal insufficiency 2 mg/kg IV bolus (max 100 mg)
Inamrinone	Myocardial dysfunction and increased SVR/PVR Loading dose: 0.75–1 mg/kg IV/IO slow bolus over 5 min (may repeat twice to max 3 mg/kg), then 5–10 µg/kg/min IV/IO infusion
Ipratropium bromide	Asthma 250–500 µg INH q 20 min PRN × 3 doses

Table 8-1 Medications Used in the Treatment of Pediatric Patients in Cardiopulmonary Arrest—cont'd

DRUG	INDICATIONS/DOSAGE
Lidocaine	VF/Pulseless VT, wide-complex tachycardia (with pulses) 1 mg/kg IV/IO bolus Maintenance: 20–50 µg/kg/min IV/IO infusion (repeat bolus dose if infusion initiated >15 min, after initial bolus) 2–3 mg/kg ETT
Magnesium sulfate	Asthma (refractory status asthmaticus), torsades de pointes, hypomagnesemia 25–50 mg/kg IV/IO *bolus* (pulseless VT) *OR* over 10–20 min (VT with pulses) *OR slow* infusion over 15–30 min (status asthmaticus); (max 2 g)
Methylprednisolone	Asthma (status asthmaticus), anaphylactic shock Load: 2 mg/kg IV/IO/IM (max 80 mg); use acetate salt IM Maintenance: 0.5 mg/kg IB/IO q 6 hr (max 120 mg/d)
Milrinone	Myocardial dysfunction and increased SVR/PVR Loading dose: 50–75 µg/kg IV/IO over 10–60 min followed by 0.5–0.75 µg/kg/min IV/IO infusion
Naloxone	Narcotic (opiate) reversal Total reversal required (for narcotic toxicity secondary to overdose): 0.1 mg/kg IV/IO/IM/SQ bolus q 2 min PRN (max 2 mg) Total reversal not required (eg, for respiratory depression associated with therapeutic narcotic use): 1–5 µg/kg IV/IO/IM/SQ; titrate to desired effect Maintain reversal: 0.002–0.16 mg/kg/hr IV/IO infusion
Nitroglycerin	Congestive heart failure, cardiogenic shock 0.25–0.5 µg/kg/min IV/IO infusion, may increase by 0.5–1 µg/kg/min q 3–5 min PRN to 1–5 µg/kg/min (max 10 µg/kg/min) Adolescents: 10–20 µg/min, increase by 5–10 µg/min q 5–10 min PRN to max 200 µg/min
Norepinephrine	Hypotensive (usually distributive) shock (ie, low SVR and fluid refractory) 0.1–2 µg/kg/min IV/IO infusion; titrate to desired effect
Oxygen	Hypoxia, hypoxemia, shock, trauma, cardiopulmonary failure, cardiac arrest Administer 100% O_2 via high-flow O_2 delivery system (if spontaneous ventilations) or ETT (if intubated); titrate to desired effect
Procainamide	SVT, atrial flutter, VT (with pulses) 15 mg/kg IV/IO load over 30–60 min (do not use routinely with amiodarone)
Sodium bicarbonate	Metabolic acidosis (severe), hyperkalemia 1 mEq/kg IV/IO *slow* bolus Sodium channel blocker overdose (eg, tricyclic antidepressant) 1–2 mEq/kg IV/IO bolus until serum pH is >7.45 (7.50–7.55 for severe overdose) followed by IV/IO infusion of 150 mEq $NaHCO_3$/L solution to maintain alkalosis
Sodium nitroprusside	Cardiogenic shock (i.e., associated with high SVR), severe hypertension 1–8 µg/kg/min (wt < 40 kg) *OR* 0.1 to 5 µg/kg/min (wt > 40 kg) IV/IO infusion
Terbutaline	Asthma (status asthmaticus), hyperkalemia 0.1–10 µg/kg/min IV/IO infusion; consider 10 µg/kg IV/IO load over 5 min 10 µg/kg SQ q 10–15 min until IV/IO infusion is initiated (max 0.4 mg)

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Prospective and retrospective studies indicate that use of high-dose epinephrine in adults or children (0.05–0.2 mg/kg) does not improve survival and may be associated with a worse neurologic outcome.[66-69] A randomiz, blinded, controlled trial of rescue high-dose epinephrine versus standard-dose epinephrine following failed initial standard-dose epinephrine for pediatric in-hospital cardiac arrest demonstrated a worse 24-hour survival rate in the high-dose epinephrine group (1/27 vs. 6/23, $P < 0.05$).[70] High-dose epinephrine cannot be recommended for routine use during CPR.

The Postresuscitation Phase. The postarrest syndrome is a unique and complex combination of pathophysiologic processes that occurs after successful resuscitation. This postarrest syndrome includes (1) postarrest brain injury, (2) postarrest myocardial dysfunction, (3) systemic ischemia-reperfusion response, and (4) the unresolved pathologic process that caused the cardiac arrest.

Clinical manifestations of postarrest brain injury include coma, seizures, myoclonus, varying degrees of neurocognitive dysfunction (ranging from memory deficits to persistent vegetative state), and brain death. Mild induced hypothermia is the most well-established postresuscitation therapy for adult postarrest brain injury. Two seminal articles established that induced hypothermia (32–34° C) could improve outcome for comatose adults after resuscitation from VF cardiac arrest.[71,72] In both randomized controlled trials, the inclusion criteria were patients *older* than 18 years who were persistently comatose after successful resuscitation from nontraumatic VF. Interpretation and extrapolation of these studies to children are difficult. Fever following cardiac arrest, brain trauma, stroke, and other ischemic conditions is associated with poor neurologic outcome. Hyperthermia following cardiac arrest is common in children.[73] It is reasonable to believe that mild induced systemic hypothermia may benefit children resusci-

tated from nontraumatic cardiac arrest. However, benefit from this treatment has not been rigorously studied and reported in children or in any patients with non-VF arrests. Multicenter trials of induced hypothermia after both in-hospital cardiac arrest and traumatic arrest are ongoing. Emerging neonatal trials of selective brain cooling and systemic cooling show promise for this therapy in neonatal hypoxic-ischemic encephalopathy, suggesting that induced hypothermia may improve outcomes.[74]

Postarrest myocardial dysfunction and hypotensive shock are very common among human survivors of cardiac arrest. For example, Laurent and colleagues reported that 90 of 165 consecutive patients admitted to the ICU after successful resuscitation following an out-of-hospital cardiac arrest needed vasoactive infusions for hypotensive shock.[75] Other studies have similarly demonstrated that left ventricular dysfunction and hypotension are common among adult and pediatric survivors following cardiac arrests and are generally reversible among long-term survivors.[71,72,76-80] Interestingly, postarrest myocardial dysfunction appears to be pathophysiologically similar to sepsis-related myocardial dysfunction, including increases in inflammatory mediator and nitric oxide production.[75,77,78,81,82] Although the optimal management of postarrest hypotension and myocardial dysfunction have not been defined, data suggest that aggressive hemodynamic support may improve outcomes. Controlled trials in animal models have shown that dobutamine, milrinone, or levosimendan can effectively ameliorate postarrest myocardial dysfunction.[83-87] In clinical observational studies, fluid resuscitation has been provided for patients with hypotension and concomitant low central venous pressure, and various vasoactive infusions, including epinephrine, dobutamine, and dopamine, have been provided for the myocardial dysfunction.[71,72,76-80]

How should patients be treated in the postarrest setting? An organized multidisciplinary postresuscitation protocol begins before the patient arrives at the hospital, continues in the emergency department (ED), and is tailored in the intensive care unit (ICU). Such a protocol that includes hemodynamic support, induced hypothermia, and percutaneous coronary intervention where indicated appears to improve outcomes in adults.[80] Postarrest myocardial dysfunction and hemodynamic instability are common and should be anticipated. Therefore, continuous electrocardiographic and hemodynamic monitoring should be provided for all patients following successful resuscitation from a cardiac arrest. Furthermore, postarrest echocardiography should be considered for monitoring myocardial function. Reasonable interventions for vasodilatory shock with low central venous pressure include fluid resuscitation and vasoactive infusions. Appropriate considerations for left ventricular myocardial dysfunction include inotropic infusions and afterload reduction.

Pediatric Ventricular Fibrillation and Ventricular Tachycardia

Although asystole and pulseless electrical activity (PEA) are the most common rhythms seen with in-hospital pediatric cardiac arrest, VF or pulseless VT are not rare.[10] VF/VT may occur as the primary inciting arrest rhythm (i.e., arrhythmogenic arrest) due to a variety of underlying myocardial pathologies (acute infectious cardiomyopathies, congenital heart disease, Wolff-Parkinson-White syndrome, etc.) or electrolyte derangements. Of 1005 pediatric in-hospital cardiac arrests in the NRCPR database, 27% had VF/VT at some point during the resuscitation, 10% as an initial rhythm, an additional 15% as subsequent VF/VT (i.e., some time later during the resuscitation effort), and the timing could not be determined for 2%.[12] Among pediatric cardiac ICU patients, as many as 41% of the arrests have been associated with VF/VT.[88] Asphyxia-associated VF (presumably subsequent VF) is also well documented in pediatric drowning patients.[89]

Traditionally, VF and VT have been considered "good" cardiac arrest rhythms, resulting in much better outcomes than after asystole and PEA. However, NRCPR data establish that survival to discharge was more common among children with *initial* VF/VT than among children with *subsequent* VF/VT (35% vs. 11%; odds ratio 2.6, 95% confidence interval 1.2–5.8).[12] Surprisingly, the subsequent VF/VT group had worse outcomes than children with asystole/PEA (11% vs. 27% survival). These data suggest that outcomes after *initial* VF/VT in children (an arrhythmogenic arrest) are "good," but outcomes after *subsequent* VF/VT (i.e., VF/VT in the setting of an asphyxial or ischemic arrest) are worse, even compared with initial asystole/PEA without subsequent VF/VT.

Defibrillation

Defibrillation, defined as termination of VF, is necessary for successful resuscitation from VF cardiac arrest. The goal of defibrillation is return of an organized electrical rhythm with a palpable pulse. When prompt defibrillation is provided soon after the induction of VF in a cardiac catheterization laboratory, the rates of successful defibrillation and survival approach 100%. When automated external defibrillators are used within 3 minutes of adult-witnessed VF, long-term survival can occur in more than 70% of cases.[90,91] In general, the mortality rate increases by 5 to 10% per minute of delay to defibrillation.[92] Provision of high-quality CPR can improve outcomes and save lives. Because pediatric cardiac arrests are commonly due to progressive asphyxia or shock (or both), the initial treatment of choice is prompt CPR, not defibrillation. Therefore, rhythm recognition has been deemphasized in the latest PALS guidelines compared with adult cardiac arrests.[14] This historical emphasis must be balanced against the increasing evidence that VF in children is not rare, outcomes from arrhythmogenic VF arrests are superior to those from other types of cardiac arrests, and that early rhythm diagnosis is necessary for optimal care.

Because of the increasing awareness that "shockable" rhythms are not uncommon in children, greater attention has been focused on the dose for pediatric defibrillation. The recommended shock dose is 2 to 4 J/kg, which is based on animal studies of short-duration VF and a single retrospective study of in-hospital (short duration) VF with 91% (52/57) defibrillation success.[93] More recent piglet and out-of-hospital pediatric data indicate that 2 J/kg is often ineffective at terminating fibrillation.[94,95] In-hospital pediatric defibrillation data also suggest that 2 J/kg is often ineffective at terminating fibrillation.[96] Animal and clinical data suggest that a single pediatric dose of 50 J (i.e., the dose in pediatric AEDs) can be quite effective at terminating fibrillation.

SPECIAL CONSIDERATIONS: APPARENT LIFE-THREATENING EVENT, SUDDEN INFANT DEATH SYNDROME, AND DISCONTINUATION OF CARDIOPULMONARY RESUSCITATION

Sudden Infant Death Syndrome

Perspective

Passed in 1974, the Sudden Infant Death Syndrome (SIDS) Act assigned the responsibility for SIDS research to the National Institute of Child Health and Human Development (NICHD)

and provided focus for public information.[97,98] The NICHD established the first nationally recognized definition of SIDS as well as other terms describing infants who present with apnea, periodic breathing, and cardiopulmonary distress.[99]

Apnea is a cessation of airflow. The respiratory pause may be central or diaphragmatic (i.e., no respiratory effort), obstructive (usually caused by upper airway obstruction), or mixed. Short (<15 sec) periods of central apnea can be normal at all ages.

Pathologic Apnea is an abnormal respiratory pause that is prolonged (>20 sec), or is associated with cyanosis, marked pallor, hypotonia, or bradycardia.

Apnea of Prematurity (AOP) is periodic breathing with pathologic apnea in a premature infant. AOP usually ceases by 37 weeks' gestation (menstrual dating) but occasionally persists past term.

Apnea of Infancy (AOI) is an unexplained episode of cessation of breathing for 20 seconds or longer or a shorter respiratory pause associated with bradycardia, cyanosis, pallor, or marked hypotonia. This generally refers to infants who are older than 37 weeks' gestational age at the onset of pathologic apnea.

Periodic Breathing (PB) is a breathing pattern in which three or more respiratory pauses occur of greater than 3 seconds' duration with less than 20 seconds of respiration between the pause. Periodic breathing may be a normal event.

Breath-holding Spells occur when infants perform a Valsalva maneuver in response to pain, fright, crying, coughing, or defecation. During the spell, minute ventilation decreases without any adverse effects. Breath-holding spells, however, if severe and prolonged, may result in cyanosis, unconsciousness, and seizures.

Apparent Life-threatening Event (ALTE) is an episode that is frightening to the observer and is characterized by some combination of apnea (central or occasionally obstructive), color change (usually cyanotic or pallid but occasionally erythematous or plethoric), marked change in muscle tone (usually marked limpness), choking, or gagging. Often the observer fears that the infant has died. Terms for apparent life-threatening events, such as *near-miss SIDS* or *aborted crib death* are no longer used because they imply an unproven, misleading association between an ALTE and SIDS.

Sudden Infant Death Syndrome (SIDS) is "the sudden death of an infant under one year of age, which remains unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene, and review of the clinical history."

The National Center for Health Statistics reports that SIDS is the third leading cause of death in infants, accounting for 8% of deaths in children younger than 1 year of age.[100] SIDS may occur at any time during the first 2 years of life, but it is rare (1%) in children younger than 1 month of age and in those older than 1 year of age (2%). Ninety-five percent of SIDS infants die before 6 to 8 months, with a peak occurring between 2 and 4 months of age.[101-104] Some epidemiologic variation occurs among different racial and ethnic groups, with black, Native American, and Alaskan Native infants having rates two to three times higher than the national average.[105-107] Other epidemiologic risk factors include male sex and multiple births.[99,108]

Distinguishing Principles of Disease

Risk Factors for Sudden Infant Death Syndrome. Although a number of risk factors have been studied; the following factors have been consistently associated with an increased risk of SIDS: maternal smoking during pregnancy, preterm or low birth weight, male gender, prone sleep position, and overheating.[105,108-112]

Approximately 20% of all SIDS cases occur in the preterm population. Compared with age-matched controls, infants born at less than 37 weeks' and less than 33 weeks' gestation are 5 and 16 times, respectively, more likely to die of SIDS.[112]

The most important modifiable *risk factor* for SIDS is prone sleeping. In 1992, the American Academy of Pediatrics (AAP) recommended that infants be placed to sleep in a nonprone position to reduce the risk of SIDS.[113] The "Back to Sleep" (BTS) campaign was initiated in 1994 under the leadership of the NICHD, as a collaborative effort of the U.S. Public Health Service, the AAP, the SIDS Alliance, and the Association of SIDS and Infant Mortality Programs. Since then, the frequency of prone sleeping has decreased 50 to 90% worldwide as has the rate of SIDS.[105,108,109,114-119]

The prevalence of prone sleeping in the United States decreased from 70% in 1992 to 13% in 2004.[105,120] Racial disparities in rates of SIDS deaths have been noted as well as in the prevalence of prone positioning; blacks have a 2.5 times greater risk of SIDS and a prevalence of prone positioning of 21% compared with white infants who have a prone positioning rate of 11%.[105,121,122] Despite the association between prone sleeping and SIDS, some parents continue to place their infant to sleep in the prone position. Many parents and health practitioners do not realize that the supine sleeping position is also associated with other health benefits, such as decreased rates of nasal congestion, otitis media, and fever before the age of 1 month.[123]

The original 1992 recommendation from the AAP identified any nonprone position (supine or side) as reducing the risk for SIDS. Since then, however, studies have demonstrated that side sleeping is less stable, and has a higher risk for SIDS than the supine position.[105,109,124]

Other postnatal factors associated with SIDS include soft sleep surfaces and loose bedding, overheating, and bed sharing.[125-129] Polystyrene bead-filled pillows, soft pillows, quilts, comforters, sheepskin, and porous mattresses have been identified as risk factors for SIDS, particularly when placed under the sleeping infant.[125] Overheating with clothing and blankets, as well as higher room temperatures also increase the risk. Bed sharing may lead to suffocation of an infant by an overlying adult, and the risk of SIDS associated with cosleeping is greater when the adult is under the influence of alcohol or other mind-altering drugs.[129]

Possible protective factors against SIDS have also been identified. A few retrospective studies have demonstrated a protective effect of breast-feeding; however, other analyses have failed to confirm the association after adjustment for confounding variables. Thus, the Task Force on Infant Sleep Position and Sudden Infant Death Syndrome does not recommend breast-feeding as a strategy for reducing SIDS.[130] Other studies have demonstrated a lower incidence of SIDS among infants who use pacifiers, possibly by stinting of the airway. Conversely, the use of pacifiers is associated with an increased susceptibility to otitis media, an increased rate of dental malocclusion, and a shorter duration of breast-feeding. Additional outcome studies are therefore required before specific recommendations regarding pacifiers can be made.[108,109]

The AAP Task Force on SIDS has made the following recommendations to reduce the risk of SIDS in the general population: (1) parents should place infants in the supine position for sleep (wholly on the back), and side sleeping is no longer recommended; (2) parents should not place infants to sleep on waterbeds, sofas, soft mattresses, or other soft surfaces; (3) soft

materials should not be placed in the infant's sleeping environment; (4) smoking in pregnancy should be discontinued as smoking has proven to be a major risk factor for SIDS; (5) bed sharing and co-sleeping may be hazardous and should be avoided; (6) parents should consider offering a pacifier at nap time and bed time; (7) overheating should be avoided; (8) parents should avoid using commercially available devices to prevent SIDS as none of the devices has been adequately safety tested; (9) parents should not use home monitors to reduce the risk of SIDS as home monitoring has no effect on the incidence of SIDS; and (10) parents should place the infant in the non-prone position while the infant is awake to prevent positional plagiocephaly.[109]

Pathophysiology and Etiology of Sudden Infant Death Syndrome. The pathophysiology of SIDS is multifactorial and includes genetic factors that may change an infant's response to environmental or infectious stressors, maturational factors that affect the infant's control of homeostatic mechanisms, and environmental factors, such as exposure to infection or being placed in the prone position.[105,108,131] This construct has been termed "the triple-risk theory,"[105,132,133] which suggests that when these factors combine, selected infants succumb to SIDS.

Genetic factors have not been fully defined, but recent data suggest multiple polymorphisms influence autonomic nervous system development and the ability of SIDS infants to respond to infectious or environmental stressors.[105,131] These reports suggest that SIDS infants have a delayed or deficient arousal response. Arousability is affected by gestational and postnatal age, and the arousal threshold is significantly elevated at 2 to 3 months, when the rate of SIDS is highest.[134]

Prone sleeping may further impair arousability. Prone sleep positions also cause a reduction in vasomotor tone with a lower resting blood pressure, a higher peripheral skin temperature, and a faster heart rate. A combination of sleep-induced reduction in vasomotor control with a reduction in central venous return and cardiac distension may trigger a brainstem-mediated bradycardia. Decreased central venous return compromises pulmonary perfusion and causes worsening hypoxia.[135,136] Prone positioning may exacerbate the rebreathing of exhaled gases trapped in soft bedding material, leading to hypercarbia and worsening hypoxia.[137,138]

Diagnosis of Sudden Infant Death Syndrome. The diagnosis of SIDS is made at autopsy after postmortem evaluation fails to reveal another cause of death. Autopsies of SIDS victims demonstrate the effects of chronic hypoxemia, but no specific findings are pathognomonic of SIDS.[108,139-141]

Guidelines are available for the diagnosis of SIDS by autopsy as well as for the on-scene investigation.[141-144] If a suspected SIDS death has occurred, a thorough investigation of the death scene may identify contributing factors, such as accidental asphyxiation or hyperthermia. Any findings suggestive of child abuse should be reported, although fewer than 5% of SIDS victims are discovered to have died of child abuse. However, in families with recurrent unexpected deaths, the estimated association increases to 55%.[103,145] Most investigations of the history, home circumstances, and postmortem examination are negative for child neglect or abuse. Child protection is rarely needed, but an investigation should be initiated if there is a recurrence of SIDS or an ALTE with a second baby.[103]

Management of Sudden Infant Death Syndrome. In the management of a SIDS case, the death scene investigation should delineate the location and position of the infant, the room temperature, type of surface, presence of soft toys, pillows, bedding materials, and the general condition of the house.

Nonhospital Medical Considerations and Emergency Department Management of Sudden Infant Death Syndrome. Nonhospital medical care providers and emergency physicians may be involved in the resuscitation of infants who are apparent SIDS victims. In a study of apparent SIDS victims (cardiopulmonary arrest after being placed to nap by a caregiver) in Los Angeles and Orange Counties, California, all 113 infants with apparent SIDS ultimately died,[146] including the 30% of infants whose final diagnosis was not SIDS. Nonhospital management centers on the delivery of cardiopulmonary life support and rapid transport to the ED. These nonhospital providers may be faced with the complex decision to begin resuscitation and transport infants with possible SIDS or declare the infant with signs of death in the field.[146,147] Currently, no national guidelines are available for termination of resuscitation in the field for children; local practices dictate declaration of death without resuscitation as well as termination of resuscitation. Nonhospital providers generally feel uncomfortable in making the decision to terminate resuscitation, and patients are often transported to the ED for care.

Because CPR is unsuccessful in the majority of cases, the emergency physician must provide supportive care for the family. When the cause of death is unknown, appropriate samples (blood, urine, etc.) should be obtained. An autopsy should be performed on all SIDS deaths by a competent and experienced pathologist.[52]

Psychosocial Considerations for Sudden Infant Death Syndrome. The emergency physician and pediatrician must address psychosocial considerations in any SIDS case. The physician should be direct when informing parents that their child has died. The word *dead* or *died* should be used instead of confusing euphemisms as *passed on*.[148-151] Parents universally experience intense guilt, and siblings may also have guilt over the loss of their brother or sister. Additionally, parents may further intensify the guilt by accusing one another of not taking adequate care of the infant. The police investigation may arouse suspicion in neighbors and friends and leave the parents and caretakers socially alienated. The overall toll of guilt and social alienation is enormous, and the effects are manifested in increased rates of miscarriage, divorce, and infertility after a SIDS death. The outcome of SIDS for the family depends on the support they receive. Thus, the team approach, which includes the nurse, social worker, chaplain, emergency physician, and pediatrician, may provide comfort and information to the grieving family. The emergency physician and the pediatrician must recognize that they can play a pivotal role in helping the family to adjust to their loss, initiate the process of grieving, and educate the family about SIDS prevention.[152,153] The AAP and the American College of Emergency Physicians have outlined recommendations for emergency physicians in a joint policy statement entitled "Death of a child in the emergency department." Recommendations for emergency physicians caring for families can be found in Table 8-2.[151]

Health care providers may also experience guilt, self-reproach, and sadness after a SIDS death. Although the likelihood of survival for infants who present with SIDS is infinitesimally small, health care providers may require opportunities to openly express and work through these tumultuous emotions.

APPARENT LIFE-THREATENING EVENTS

Perspective

Epidemiology of Apparent Life-Threatening Event

Children with ALTE account for 0.8% of all ED visits of those younger than 1 year of age, and 2% of pediatric hospitalizations. Generally, children with ALTE are younger than 1 year, with a median age of 2 to 3 months. Most studies also demonstrate a male predominance as high as 2:1.[154,155]

Table 8-2 Recommendation for Emergency Physicians in Caring for Families of Children Who Have Died in the Emergency Department

Use a family-centered and team-oriented approach when a child dies in the ED.
Provide personal, compassionate, and individualized support to families while respecting social, religious, and cultural diversity.
Notify the child's primary care physician of the death and, as appropriate, work with the primary care physician in follow-up of postmortem examination results.
Organize resources and staff to provide a coordinated response to a child's death, such as working with the primary care physician to notify subspecialty physicians of the death of their patient; identifying and reporting cases of child maltreatment; working with staff to provide resources to families for follow-up care and grief counseling; facilitating organ procurement; and assisting in critical stress management for prehospital and ED staff.

ED, emergency department.
Adapted from The American College of Emergency Physicians and the American Academy of Pediatrics Policy recommendations in the policy statement "Death of a child in the emergency department." Ann Emerg Med 40:409, 2004.

Distinguishing Principles of Disease

Pathophysiology and Etiology of an Apparent Life-Threatening Event

ALTE is a description of a characteristic clinical presentation; therefore, the pathophysiology of an ALTE has not been clearly defined. Children with ALTE pose a diagnostic and therapeutic challenge to emergency physicians because the cause of such events is diverse and ranges from minor to life-threatening. In addition, studies of children with ALTE reveal that in 50% of the cases, a definitive diagnosis will not be made.[156,157]

The etiology of ALTE is extensive (Table 8-3) and includes infection (sepsis, respiratory syncytial virus, or other respiratory viruses, pertussis, or central nervous system infection), gastroesophageal reflux disease (GERD) with or without obstructive apnea, congenital malformations (tracheomalacia, vascular rings, pulmonary slings), seizure disorder, cardiac dysrhythmias, congenital cardiac malformations, metabolic derangements (hypoglycemia), and child abuse.[157] A number of authors suggest clues to the various categories of diagnoses; however, many of the signs and symptoms of these conditions overlap.

ALTE may be a manifestation of child abuse, possibly from a smothering attempt, an intentional poisoning, or "shaken baby" syndrome.[158,159] The AAP Committee on Child Abuse and Neglect outlines certain circumstances that should alert the emergency physician to the possibility of intentional suffocation in children with ALTE (Table 8-4).[103] Injury associated with head trauma or child abuse may be difficult to distinguish in the absence of a reliable history. Intoxication, either accidental or intentional, as in Munchausen syndrome by proxy, can produce subsequent hypoventilation, hypoxia, cardiopulmonary arrest, and death.

In a retrospective study of 196 infants that presented with an ALTE, the discharge diagnoses included seizure (25%), GERD (18%), febrile convulsion (12%), bronchiolitis (9%), apnea (9%), pertussis (6%), choking (5%), upper respiratory tract infections (4%), cyanotic episode (2%), gastroenteritis (2%), asthma (1%), head injury (1%), feeding difficulties (1%), urinary tract infection (1%), and breath-holding (1%).[160]

Since GERD is physiologic and occurs in most infants, establishing the diagnosis of GERD does not prove that it is the cause of an ALTE.

An ALTE may be the first manifestation of an epileptic seizure, but the diagnosis is often difficult. A transient episode of apnea may be the only manifestation of a partial seizure, and the interictal electroencephalogram is characteristically normal. Seizures may be the cause for up to 11% of ALTEs, and a normal interictal electroencephalogram does not exclude seizures as the precipitating factor.[161]

Table 8-3 Etiologies of Apparent Life-Threatening Event

Cardiac
Dysrhythmias
Congenital heart disease
Child Abuse
Physical abuse
Munchausen syndrome by proxy
Gastrointestinal
GERD
Congenital malformations
Infectious
Meningitis/encephalitis
Pertussis
Respiratory syncytial virus
Sepsis
Metabolic
Hypoglycemia
Hypocalcemia
Hyponatremia
Inborn errors of metabolism
Neurologic
Seizure
CNS tumor
Arnold-Chiari malformations
Subdural or epidural hematoma
Respiratory
Foreign body aspiration
Obstructive sleep apnea
Respiratory infection
Other
Breath-holding spells
Vasovagal syncope
Drug/toxin exposure

CNS, central nervous system; GERD, gastroesophageal reflux disease.

QT prolongation has been associated with ALTE. Thus, an electrocardiogram is often recommended as an initial screen for differentiating an ALTE in the ED.[162]

Overall, the most common causes include GERD, seizure, and lower respiratory tract infection, accounting for 50% of the diagnoses associated with ALTE.

Management of an Apparent Life-Threatening Event

The infant who presents with a history of an ALTE may look well and act normally at the time of the evaluation by the nonhospital medical provider or the emergency physician. However, infants who are judged by nonhospital personnel to have choked, turned blue, or are showing other signs suggestive of a possible ALTE should be considered seriously ill and transported to the ED for evaluation.[157] Fifty percent of children who present to the ED after an ALTE have an entirely

Table 8-4 American Academy of Pediatrics Recommendations for Circumstances That Could Indicate Intentional Suffocation Versus Sudden Infant Death Syndrome

Previous recurrent cyanosis, apnea or ALTE, while in care of the same person
Age at death greater than 6 months
Previous unexpected or unexplained deaths of one or more siblings
Simultaneous or nearly simultaneous death of twins
Previous death of infants, under the care of the same unrelated person
Discovery of blood on the infant's nose or mouth in association with ALTE

ALTE, apparent life-threatening event.
Adapted from Hymel KP and the American Academy of Pediatrics Committee on Child Abuse and Neglect and National Association of Medical Examiners: Distinguishing sudden infant death syndrome from child abuse fatalities. Pediatrics 118:421, 2006.

normal clinical examination, and the final diagnosis often correlates poorly with the presenting signs and symptoms, which often includes cyanosis, breathing difficulties, abnormal movements, loss of consciousness, vomiting, pallor, and choking.[157]

In the ED, resuscitation must be the initial focus. Airway, breathing, and circulation should be stabilized. A complete history should be taken and a physical performed. If possible, the physician should obtain a detailed description of the infant at the time of discovery (especially the color and muscle tone of the infant), the duration of the episode, the resuscitation measures used, and the infant's response to the resuscitation measures. Other questions that may be pertinent include the following: Was the infant awake or sleeping? Were there symptoms of airway obstruction? Does the infant have any history or symptoms suggestive of GERD? Did the event occur after feeding? Did the episode occur after vigorous crying (suggestive of breath-holding)? Is there any family history of SIDS, apnea, or unexplained sibling death?

During the physical exam, the physician should note the presence of stridor or wheezing. The skin should be examined for suspicious bruising (patterned bruises or truncal bruising suggestive of child abuse), the extremities for abnormalities (fractures, burns, healing wounds, or other signs of unusual injury), and the eyes for pupillary changes or retinal hemorrhages (shaken baby syndrome). A recent study demonstrated that a dilated fundoscopic examination in 128 patients who presented with an ALTE-detected retinal hemorrhages in 1.4% of the patients and helped detect child abuse in 2.3% of the patients.[159] Thus, in addition to obtaining a detailed family and social history, it may be prudent to conduct a dilated fundoscopic exam in children who present to the ED after an ALTE.

The ED evaluation of children presenting with ALTE must be tailored to the child's history and physical examination but often includes laboratory and radiographic studies. Laboratory evaluation may include complete blood count, serum glucose, electrolytes, blood and urine cultures if the child is younger than 1 month of age or febrile, a toxicology screen, and an electrocardiogram.[163] The infants may also undergo a screen for inborn errors of metabolism, chest radiograph, computed tomographic scan of the head, and lumbar puncture depending on signs and symptoms at presentation, although few diagnostic tests are positive.[163-165]

Inpatient evaluation often includes electroencephalogram, an evaluation for GERD (24-hour pH probe and barium esophagram), polysomnography for sleep disorders, and possibly flexible and rigid laryngoscopy.

The outcome of an ALTE depends on the underlying cause. In a retrospective patient review of 196 ALTE patients, there were no deaths.[160] The follow-up revealed a high percentage of asthma and seizures, as well as GERD requiring Nissen fudoplication. Infants who survive an ALTE generally do well in follow-up. However, some rare complications do occur, including pulmonary edema, aspiration pneumonia, and neurologic sequelae secondary to hypoxia.[166]

Based on the results of a study of 59 infants with ALTE, Claudius and Keens developed a clinical decision rule suggesting that infants younger than 1 month of age and those with recurrent ALTE should be admitted for evaluation, but other well-appearing children with ALTE may be discharged with close follow-up.[167] Fu and Moon suggest other conditions under which it may be safe to discharge a patient with an ALTE, and these include the following: (1) the episode is brief, nonsevere, and self-resolving; (2) the cause is probably a nonprogressive condition such as GERD; and (3) the infant has no comorbidities and is well-appearing.[154] It should be noted, however, that none of these proposed criteria has been adequately validated in clinical trials to determine which patients may be safely discharged from the ED. Multiple studies show that 84% of cases of ALTE are admitted for evaluation and monitoring.

Home Monitoring. Monitoring devices measure chest wall movement and heart rate. Parents must learn about equipment maintenance, interpretation of alarms, and CPR. Technical support should be available to the parents 24 hours a day. Parents may misinterpret alarms when they sound, and the majority of alarms that parents felt required resuscitation were associated with normal electrocardiograms. Due to the lack of demonstrated efficacy and the frequency of false alarms, a great deal of controversy is associated with the use of home monitoring. In fact, the AAP Committee on Fetus and Newborn SIDS and home monitoring does not recommend home cardiorespiratory monitoring to prevent SIDS, since studies show that SIDS death is not reduced by home monitor use. Home monitors, however, may be warranted for premature infants with an ALTE, especially those younger than 43 weeks postmenstrual age or those with extreme episodes.[168] Both pediatricians and emergency physicians should be consulted about monitor alarms. Admission to the hospital for further care may be prudent if the event was associated with the infant changing color or the infant required vigorous resuscitation.

When Should Cardiopulmonary Resuscitation Be Discontinued? Several factors determine the likelihood of survival after cardiac arrest, including the mechanism of the arrest (e.g., traumatic or asphyxial), location (out-of-hospital vs. in-hospital, ward vs. PICU), response (e.g., monitored vs. unmonitored, witnessed vs. unwitnessed), and underlying pathophysiology (e.g., cardiomyopathy, congenital defect, single-ventricle physiology, drug toxicity or metabolic derangement). Additionally, discontinuation of resuscitation in the nonhospital setting is further complicated because emergency medical service providers are not comfortable making this decision before transport to the hospital.[97] These factors should all be considered before deciding to terminate resuscitative efforts.

Continuation of CPR has been considered futile beyond 15 to 20 minutes of CPR or when more than two doses of epinephrine are needed.[169-181]

Future Directions. New epidemiologic initiatives, such as the National Registry for Cardiopulmonary Resuscitation for in-hospital cardiac arrests and the large-scale, multicenter National Heart, Lung, and Blood Institute Resuscitation Outcome Consortium for out-of-hospital arrests, are providing new data to guide our resuscitation practices and generate hypotheses for new approaches. Innovative technical advances, such as directive and corrective real-time feedback, can increase the likelihood of effective basic life support and skill sorely lacking in many resuscitative efforts today. In addition, team dynamic training and debriefing can rapidly identify weaknesses and improve operational performance.[182] Simulation technology will be increasingly used for effective team training to provide excellent resuscitations[183] and improve outcomes.

KEY CONCEPTS

- Excellent CPR is the foundation for successful resuscitation from cardiac arrest; without it all other subsequent interventions are rendered meaningless. The mantra for excellent CPR is: "Push Hard, Push Fast, Allow Full Chest Recoil, and Minimize Interruptions." This "new emphasis" on CPR is intended to enhance CPR performance so that more lives can be saved.
- The thumb-encircling technique is recommended over the two-finger technique for chest compression in infants.
- Prospective and retrospective studies indicate that use of high-dose epinephrine in adults or children does not improve survival and may be associated with a worse neurologic outcome.
- Despite the dramatic decline in the incidence of SIDS in the past several decades, SIDS remains the leading cause of postneonatal mortality in the United States, accounting for one-third of all such deaths and is the third most common cause of infant deaths.
- Emergency physicians may play a key role in SIDS education and prevention. Parents must be taught the importance of the supine sleeping position, smoking cessation, and the elimination or avoidance of co-sleeping, overheating, and soft or loose bedding material.
- The team approach that combines the efforts of the nurse, social worker, chaplain, emergency physician, and pediatrician may help the family to adjust to their loss, initiate the process of grieving, and counsel the family about SIDS.
- Although the infant who presents with a history of an ALTE may look well and act normally at the time of the evaluation by the nonhospital medical provider or the emergency physician, these infants and children generally require admission and monitoring, as the final diagnosis and the presenting symptoms often correlate poorly.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 9 Neonatal Resuscitation

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PERSPECTIVE

Approximately 10% of newborns require some resuscitative assistance at birth, and approximately 1% require extensive resuscitative measures.[1] Appropriate equipment and preparation, knowledge of neonatal physiology and response to stress, and skill in performing the necessary procedures are essential to successful resuscitation. Preparation for neonatal resuscitation requires an understanding of how it differs from pediatric and adult resuscitation, as follows:

1. Newborns have rapidly changing cardiopulmonary physiology, their own range of normal vital signs (Table 9-1), and unique responses to stress.[2,3]
2. The approach to newborn resuscitation focuses almost *entirely* on respiratory, not cardiac, management.
3. Because of their small size, infants require special equipment.

PATHOPHYSIOLOGY

Transition from Fetal to Extrauterine Life

The successful transition from the fetal to the extrauterine environment requires two major cardiorespiratory changes: (1) removal of fluid from unexpanded alveoli to allow ventilation and (2) redistribution of cardiac output to provide lung perfusion. Failure of the development of either adequate ventilation or adequate perfusion leads to shunting, hypoxia, and ultimately reversion to fetal physiology.[2]

In utero, the pulmonary alveoli are filled with pulmonary fluid. Removal of this fluid is partially accomplished by vaginal delivery, which compresses the fluid into the bronchi, trachea, and pulmonary capillary bed. Most pulmonary fluid is removed by the first few breaths; the amount of fluid removed depends on the forcefulness of these breaths. Expansion of alveoli requires the generation of high intrathoracic pressures and the presence of surfactant to maintain alveolar patency. The quality of the first few breaths is crucial to the establishment of adequate ventilation.

The fetal lung is poorly perfused. Because the pulmonary arterial bed is intensely vasoconstricted, the fetal lung receives only 40% of the right ventricular cardiac output; most of the right ventricular output is shunted from the pulmonary artery through the ductus arteriosus to the descending aorta. After the first few breaths, with exposure to diffused alveolar oxygen, pulmonary vascular resistance decreases. The fetal shunt through the ductus arteriosus reverses as systemic vascular resistance increases; then the shunt ceases by 15 hours of age as the ductus also constricts. This reversal of flow allows all right ventricular output to perfuse the lungs. If hypoxia or severe acidosis occurs, however, the muscular pulmonary vascular bed constricts again, and the ductus may reopen. The reinstitution of fetal circulation, with its attendant shunting, leads to ongoing hypoxia and is termed *persistent fetal circulation*. Resuscitation facilitates the first few breaths, prevents and reverses ongoing hypoxia and acidosis, and assists the newborn in the transition to extrauterine life.

Neonatal Responses

Hypoxia

The newborn's clinical response to severe hypoxia is unique.[4] In utero or intrapartum asphyxia (pathologic lack of oxygen to the fetus before or during delivery) precipitates a sequence of events termed *primary apnea* and *secondary apnea*. After initial hypoxia, the infant gasps rapidly, followed by cessation of respirations (primary apnea) and a decreasing heart rate (HR). At this point, only simple stimulation and oxygen are needed to reverse bradycardia and assist the development of ventilation. With ongoing asphyxia, however, the infant takes several final deep, gasping respirations, followed by secondary apnea, worsening bradycardia, and decreasing blood pressure; in this case more vigorous and prolonged resuscitation is needed to restore ventilation and an adequate circulation. Apnea in the newborn should be assumed to be secondary apnea and treated rapidly with ventilatory assistance.

The presence of respirations *may not* ensure adequate ventilation. In addition, signs of hypoxia (e.g., cyanosis, lethargy, unresponsiveness) may have other causes. Bradycardia in the newborn (HR < 100 beats/min) almost always reflects inadequate ventilation and oxygenation. *Bradycardia is a major indicator of hypoxia.*[5-7]

Hypothermia

The newborn's inability to maintain body temperature (36.5–37° C) has severe physiologic consequences. The newborn cannot generate heat by shivering, cannot retain heat because of low fat stores, and has a relatively large surface-to-volume area. In addition, the newborn is at risk for heat loss because of a high metabolic rate, wet amniotic fluid covering, and exposure to a relatively cool environment, especially in contrast to intrauterine temperature. The body temperature easily decreases, and low body temperatures can lead to meta-

Table 9-1 Normal Vital Signs in the Newborn

WEIGHT	HEART RATE (BEATS/MIN)	RESPIRATORY RATE (BREATHS/MIN)	SYSTOLIC BLOOD PRESSURE (MM HG, MEAN)
≥3 kg (full term)	>100 (100–180)	40–80	60–70 (45–55)
<3 kg (premature)	>100 (100–180)	40–80	40–60 (35–45)

bolic acidosis, increased oxygen consumption, hypoglycemia, and apnea.[2,8] Some studies have suggested that selective cerebral hypothermia in asphyxiated infants may protect against brain injury, but there is not enough evidence to implement such a therapy until further study is performed.[9-13] Currently there is insufficient data to recommend routine use of hypothermia after resuscitation of infants with possible asphyxia.[1]

Hypoglycemia

The newborn is at risk for developing hypoglycemia (defined as glucose level < 40 mg/dL if the newborn weighs > 2.5 kg or < 30 mg/dL if < 2.5 kg) when stressed because of poor glycogen stores and immature liver enzymes. Hypoglycemia is common in premature or small-for-gestational-age infants and in infants born to diabetic mothers. It also develops in response to respiratory illness, hypothermia, asphyxia, and sepsis. Hypoglycemia may be asymptomatic or may cause an array of symptoms, including apnea, color changes, respiratory distress, lethargy, jitteriness, seizures, acidosis, and poor myocardial contractility.[14] Low blood glucose has been associated with adverse neurologic outcomes in both animal and clinical studies.[15,16]

INDICATIONS FOR RESUSCITATION

Any infant born outside of the controlled environment of the delivery room should be considered in need of resuscitation.[17] Minimal intervention may be required, but a standardized approach as described in this chapter should be followed. Some specific conditions increase the likelihood that resuscitation will be required. Premature infants pose a special problem because of their immature lungs and susceptibility to hypothermia. Adequate ventilation and warming are essential to a successful resuscitation.

The presence of meconium in the amniotic fluid at delivery indicates that the infant has been stressed before delivery and warrants special consideration in resuscitation. When delivered, a nonvigorous infant with meconium in the amniotic fluid must have the trachea suctioned before other steps in resuscitation to prevent aspiration of meconium.

Medications given to the mother or illicit drugs taken before delivery can lead to respiratory depression in the newborn. Maternal opioid administration or opioid use should be considered in any newborn with isolated respiratory depression. Naloxone reverses respiratory depression caused by opioids. Naloxone may have a shorter half-life than the original maternal opioid; so the neonate should therefore be monitored closely for recurrent apnea or hypoventilation, and subsequent doses of naloxone may be required.[1] Use of naloxone may precipitate acute withdrawal in infants who have prolonged intrauterine opioid exposure.[18,19] Therefore, in infants whose mothers may have had long-term opioid exposure, support of ventilation may be preferable to reversal using naloxone.

Hemorrhage caused by abruptio placentae, placenta previa, trauma, or other complications can lead to respiratory depression and shock. Hemorrhage is one of the few situations in which fluid resuscitation is required.

No reliable set of parameters has been identified for newborns who should not receive resuscitative efforts.[20] Currently, resuscitation is not recommended for neonates with confirmed gestational age less than 23 weeks; those with birth weight less than 400 g; and those with confirmed anencephaly, trisomy 13, or trisomy 18.[1,21,22] In the out-of-hospital setting or in the emergency department, every attempt should be made to stabilize the neonate until it is clear that attempted or continued resuscitation would not improve the patient's chance of survival. Infants with no signs of life (no heart beat and no respiratory effort) after 10 minutes of resuscitation show either a high mortality or severe developmental delay. After 10 minutes of continuous and adequate resuscitative efforts, discontinuation may be justified if there are no signs of life.[23,24]

Few situations require deviations from the approach described here. The presence of meconium may require intervention after delivery. Other anatomic anomalies require special care and include diaphragmatic hernia, meningomyelocele, abdominal anomalies (e.g., gastroschisis, omphalocele), and upper airway obstructive lesions (e.g., bilateral choanal atresia, Pierre Robin sequence).

SPECIFIC DISORDERS

Meconium Aspiration

Meconium in the amniotic fluid is a sign of in utero distress, and the presence of thick or particulate meconium before or at delivery should raise concern about the potential for aspiration. Aspiration of meconium and its consequences can be avoided by rapid intervention to avoid aspiration. Previous recommendations included suctioning meconium from the infant's airway after delivery of the head but before delivery of the shoulders (intrapartum suctioning). However, evidence from a large multicenter trial did not show benefit from intrapartum suctioning.[25] Therefore, current recommendations no longer advise routine intrapartum suctioning for infants born to mothers with meconium-stained fluid. Decision to perform endotracheal intubation with tracheal suctioning after delivery of the infant should be made based on the vigor of the infant, rather than on the consistency of the meconium (e.g., thick or particulate vs. thin). Infants with meconium-stained fluid and with any of the following are candidates for tracheal suctioning: (1) absent or depressed respirations, (2) poor muscle tone, or (3) HR less than 100 beats/min.[21,22,26] In such newborns, a meconium aspirator should be attached to the endotracheal tube (ETT) and connected to wall suction at 100 mm Hg or less. The ETT is withdrawn as suction is being applied. The ETT with meconium aspirator serves as the ideal suction catheter. Because of its narrower width, a suction catheter placed in the ETT does *not* suction meconium effectively. Reintubation and suction should be repeated until the meconium clears. Two passes are usually sufficient. When these steps are completed, the resuscitation should continue, beginning with the steps at the top of the neonatal flow algorithm (Fig. 9-1).

Anatomic Anomalies

The neonate should be intubated as soon as possible if a prenatal diagnosis of diaphragmatic hernia was made or if a diaphragmatic hernia is diagnosed on chest radiograph. Bag-mask

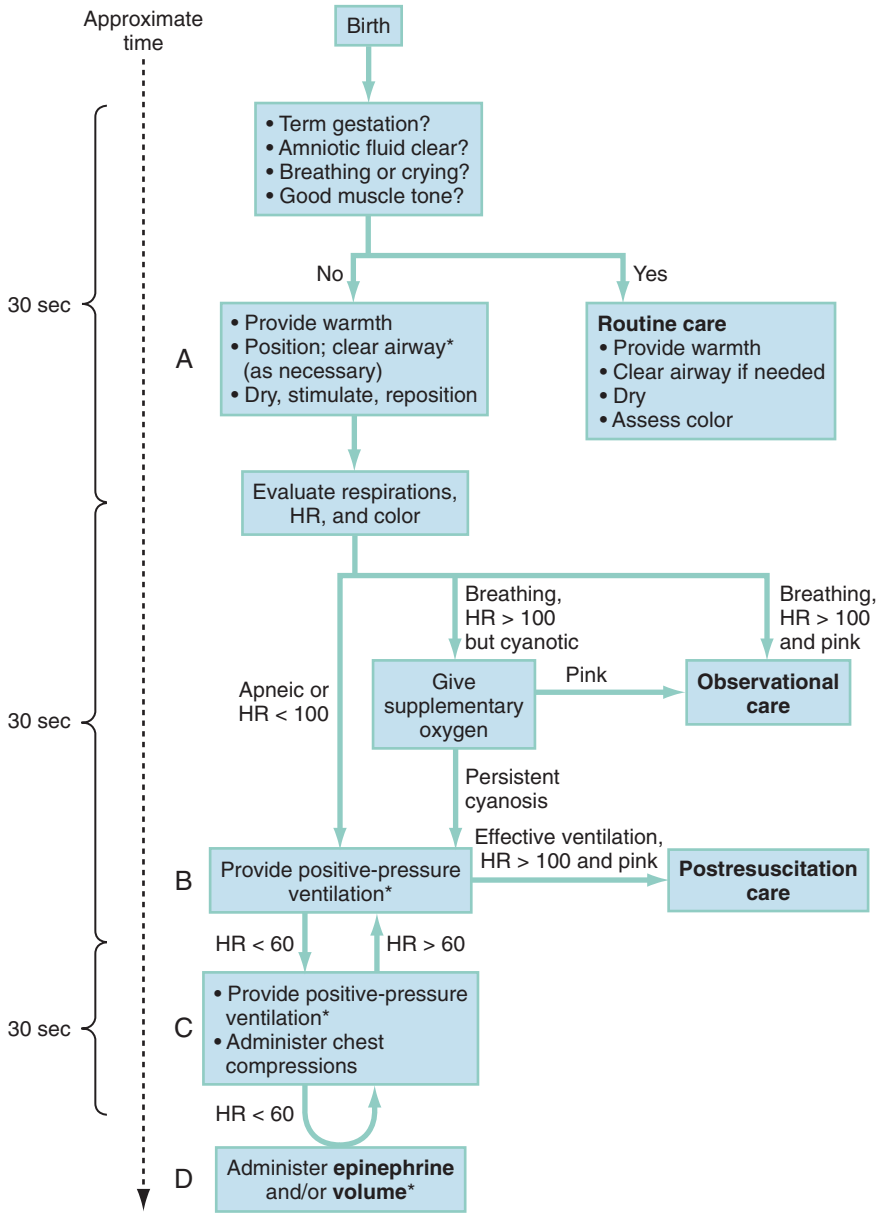

Figure 9-1. Neonatal flow algorithm. *Endotracheal intubation may be considered at several steps. (From American Heart Association, American Academy of Pediatrics, Pediatrics 117:e1029, 2006. © Copyright 2006 American Academy of Pediatrics.)

ventilation distends the stomach and worsens respiratory distress because of the presence of the stomach in the chest cavity.

Infants with meningomyelocele should not be placed on their backs to avoid pressure on the defect, but on their stomachs or sides. The resuscitation should be conducted in this position if possible. The spinal defect should be covered with warm sterile gauze pads soaked in warm sterile saline and covered with a plastic covering. Infants with gastroschisis or omphalocele should be resuscitated as needed; in the same manner as for patients with meningomyelocele, the defect should be covered with an occlusive plastic covering to decrease water and heat loss.

Because newborns are obligate nose breathers, bilateral choanal atresia causes upper airway obstruction and respiratory distress. It is diagnosed by the inability to pass a catheter through either nare into the oropharynx. An oral airway bypasses the obstruction. Patients with Pierre Robin sequence have small jaws and large tongues leading to upper airway obstruction. A nasal or oral airway should be able to bypass the obstruction; if not, intubation may be necessary. It is technically difficult to intubate a patient with Pierre Robin sequence, so a laryngeal mask airway (LMA) may be placed instead.[27] Consultation with anesthesiology may be needed.

PREPARATION

To maximize the effectiveness of resuscitation, the emergency department should have a prestocked drug pack, standardized equipment (Box 9-1), and staff familiar with newborn resuscitation.[4,22,20,28] The pediatric Broselow Emergency Tape has a section that can be used to determine equipment size and drug dosages for newborn resuscitation for infants weighing greater than or equal to 3 kg.[29,30]

It is crucial to use universal precautions and to wear gown, gloves, and eye protection during neonatal resuscitation. For adequate preparation, the heat source must be turned on early, and the resuscitation table must be warm when the newborn is placed on it. Equipment of proper size is essential, especially respiratory equipment because it is most likely to be

BOX 9-1 EQUIPMENT NEEDED FOR NEONATAL RESUSCITATION

1. Gown, gloves, and eye protection (universal precautions)
2. Blankets (to warm and dry infant)
3. Radiant warmer
4. Bulb syringe
5. Suction and suction catheters (French #5, #8, and #10)
6. Self-inflating bags (450 and 750 mL)
7. Masks (premature, newborn, and infant sizes)
8. Laryngoscope with straight blades (No. 0 and 1)
9. Endotracheal tubes with stylets (2.5, 3, and 3.5 mm)
10. Scissors and tape to stabilize endotracheal tube
11. Meconium aspirator
12. Umbilical catheters (French #3.5 and #5)
13. Hemostats, sterile drapes and gloves, povidone-iodine solution, scalpel, umbilical tape, suture, and three-way stopcock for umbilical vessel catheterization

BOX 9-2 MATERNAL HISTORY QUESTIONS

1. What is the estimated gestational age?
2. Is this a multiple gestation?
3. Is meconium present?
4. Is there a history of vaginal bleeding?
5. Were medications given or drugs taken?

used, and ventilation is the key to most resuscitative efforts. Appropriately sized self-inflating devices and ventilation masks decrease complications from overventilation and prevent injury or inability to ventilate because of improper mask fit.

If available, additional information may be helpful in preparing for resuscitation (Box 9-2). The estimated gestational age provides information about possible prematurity and associated complications. Multiple births require more equipment and personnel, and the newborns are at greater risk for prematurity and its complications. Meconium present in the amniotic fluid may require suctioning of the neonate's trachea after delivery. A history of maternal vaginal bleeding increases the likelihood of hypovolemic shock and respiratory distress in the newborn. A history of medication administration or drug use may provide clues to the cause of respiratory depression in the neonate.

MANAGEMENT

An organized approach is key to successful resuscitation outside and inside the delivery room. The American Heart Association and the American Academy of Pediatrics have published a neonatal flow algorithm (see Fig. 9.1)—a stepwise approach to neonatal resuscitation. These steps are discussed in this section.[1]

Dry, Warm, Position, Suction, Stimulate, Assess Need for Further Intervention

To prevent complications caused by hypothermia, all newborns should be dried off as soon as possible after delivery and placed under a radiant heat source. Wet blankets should be replaced after drying with dry, preferably warm blankets. Next, the neonate should be positioned to maximize air entry and avoid obstruction of airflow. Because of the infant's relatively large occiput and anterior airway, an open airway is best achieved with the neck in slight extension. The slightly extended position is best accomplished by placing a rolled diaper or small towel *under the infant's shoulders*. Placement under the neck is not useful, and a towel that is too large and under the shoulders leads to hyperextension at the neck and possible airway occlusion.

If meconium is present and the newborn has poor respirations, poor tone, or bradycardia (HR < 100 beats/min), the trachea should be suctioned with an ETT before any other intervention. If no meconium is present, the newborn may be suctioned with bulb or mechanical suction (<100 mm Hg wall suction). The mouth should be suctioned first, followed by the nose. The mouth is suctioned first to avoid aspiration of material if the infant takes in a breath after suctioning of the nose. Vigorous or deep suctioning can lead to a vagal response, with subsequent bradycardia, or to apnea, and should be avoided.[31]

Usually these measures adequately stimulate the infant to breathe effectively and may be the only measures needed to resuscitate a newborn. If adequate respirations are not present at this point, stimulation of the infant is needed; this is best done by flicking the soles of the feet and rubbing the back. It is important to avoid stimulation that is too vigorous because it does not aid in initiation of respirations and may stress the newborn. If stimulation is not effective in initiating respirations, bag-mask ventilation is required followed by intubation if necessary.

The Apgar score, comprising HR, respiratory effort, muscle tone, reflex irritability, and color, has been used as a prognostic indicator in newborns (Table 9-2). The Apgar score is not useful in resuscitation management, however.[32] Muscle tone and reflex irritability do not aid in the assessment of the newborn during resuscitation.[32] HR, respiratory effort, and color are the important indicators of hypoxia and should be monitored continuously. Further resuscitative efforts are required if respiratory effort is insufficient, HR is less than 100 beats/min, or central cyanosis is present.

Table 9-2 Apgar Score

SIGN	0	1	2
Heart rate (beats/min)	Absent	Slow (<100)	>100
Respirations	Absent	Slow, irregular	Good, crying
Muscle tone	Limp	Some flexion	Active, good flexion
Reflex irritability	No response	Grimace	Cough, sneeze
Color	Blue, pale	Pink body, blue hands/feet	Pink

Oxygen, Ventilation, Intubation

Any infant who is cyanotic or appears to be in respiratory distress (grunting, nasal flaring, tachypnea) should be given 100% oxygen. If the infant is apneic, appears to be in severe respiratory distress, has an HR of less than 100 beats/min, or has central cyanosis despite oxygen administration, bag-mask ventilation (with a manometer, if available) should be initiated. Although resuscitation with 100% oxygen is recommended, especially for hypoxia, more recent studies support the effectiveness of room air if 100% oxygen is not available for bag-mask ventilation.[21,22,33-36] The initial breaths require higher pressure (30–40 mm Hg) to remove lung fluid and to get the chest to rise. Subsequent breaths generally require 20 mm Hg.

Excessive pressures, more than is needed to achieve chest rise should be avoided since barotraumas may result. The primary measure of adequate initial ventilation is a prompt improvement in HR. An appropriately sized mask with a good seal (covering the mouth and nose, but not the eyes), proper positioning of the infant, and use of appropriate pressure to attain chest wall movement are essential for effective ventilation. The newborn should be ventilated at 40 to 60 breaths/min, unless blood gases dictate otherwise. If bag-mask ventilation is required for more than 2 minutes, an orogastric tube should be placed to prevent respiratory compromise from stomach distention.[4]

Endotracheal intubation may be indicated at several points during neonatal resuscitation: when tracheal suctioning for meconium is needed, if bag-mask ventilation is ineffective or prolonged, when chest compressions are performed, and for extremely low-birth-weight infants or infants with anatomic anomalies (e.g., diaphragmatic hernia). Box 9-1 lists the equipment needed for endotracheal intubation. Confirmation of proper ETT placement should include detection of expired carbon dioxide.[37-40]

Acute deterioration (bradycardia, decreased oxygen saturation) after intubation should suggest one of the following problems (*DOPE*)[41]:

1. *D*islodgment: The ETT is no longer in the trachea (right main stem bronchus or esophagus).
2. *O*bstruction: Secretions are obstructing airflow through the ETT.
3. *P*neumothorax
4. *E*quipment: Oxygen is not being delivered to the patient (check equipment).

If the patient acutely deteriorates after intubation, the equipment should be checked quickly; if no explanation is obvious, the patient should be extubated and ventilated with a self-inflating resuscitator (bag-mask ventilation device). Time should not be wasted adjusting or suctioning the ETT if the patient is bradycardic. If unequal breath sounds are present after extubation, or if the patient is not improving with effective ventilation, needle aspiration of the chest should be considered for treatment of a possible pneumothorax.

The LMA has been shown effective for ventilating full-term newborns[42-44]; however, there are limited data on LMA use in preterm infants.

Chest Compressions

Bradycardia (HR < 100 beats/min) is the major indicator of hypoxia. Most infants respond promptly to effective ventilation with 100% oxygen. If a neonate has an HR of less than 60 beats/min despite oxygen and adequate ventilation (good air movement and chest rise) for at least 30 seconds, chest compressions should also be provided.[1,22] Chest compressions should be performed at a rate of 90/min, with 30 breaths/min for a total of 120 events/min. The preferred method for performing chest compressions is as follows:

The fingers of both hands encircle the chest and support the back. The thumbs of both hands are placed side by side or one over the other on the sternum just below the nipple line. The depth of compression is one third the anteroposterior diameter of the chest.

Respirations, HR, and color should be reassessed about every 30 seconds, and coordinated chest compressions and ventilation should continue until the spontaneous HR is greater than or equal to 60 beats/min.[1]

Medications

Few neonates require the use of medications during resuscitation.[45] Medications are indicated for bradycardia or asystole that does not respond to effective ventilation and chest compressions, and for hemorrhage (maternal, fetal, or placental) that requires fluid resuscitation.[46] Naloxone may be needed for respiratory depression caused by maternal ingestion of opioids before delivery.

The only medications that should be used during the early phase of neonatal resuscitation are oxygen, epinephrine, and volume expanders (Table 9-3). Albumin has been removed as an initial resuscitation drug but may be used in the postresuscitation phase. Dopamine should be reserved for prolonged resuscitation. Naloxone should be used only after the neonate is adequately ventilated. Sodium bicarbonate should not be used in most resuscitations; it may be beneficial in the rare instance of a prolonged resuscitation when metabolic acidosis has been documented and ventilation is adequate.[47] No current evidence supports the use of atropine or calcium in neonatal resuscitation.

Vascular access is a challenge in neonatal resuscitation. The preferred route of immediate vascular access is the umbilical vein because it is easily identified and cannulated. Because of

Table 9-3 Resuscitation Medications

MEDICATION	CONCENTRATION	DOSE	ROUTE	CONSIDERATIONS
Oxygen	100%		Blowby, ET	
Epinephrine	1:10,000	0.01–0.03 mg/kg (0.1–0.3 mL/kg)	IV (preferred), ET	
Naloxone	0.4 mg/mL	0.1 mg/kg (0.25 mL/kg)	IV, IM, IO, SQ	
Glucose	$D_{10}W$	2–4 mL/kg	IV	Avoid higher concentrations
Volume expanders*	Whole blood	10 mL/kg	IV	Give over 5–10 min; repeat as needed
	Normal saline	10 mL/kg	IV	
	Ringer's lactate	10 mL/kg		
Dopamine	Concentration varies among institutions.	Continuous IV infusion at 5 µg/kg/min Increase to 20 µg/kg/min as needed		

*5% albumin/saline no longer recommended for use during initial resuscitation efforts.

$D_{10}W$, 10% dextrose in water; ET, endotracheal; IM, intramuscular; IV, intravenous; SQ, subcutaneous.

potentially serious complications (infection, portal vein thrombosis), the umbilical vein cannula should be removed immediately after stabilization after other access (e.g., umbilical artery catheterization) has been attained. Other routes include peripheral veins and the femoral vein. Intraosseous access can be problematic in neonates (especially premature infants) because of bone fragility and the small size of the intraosseous space.[22] If vascular access cannot be achieved, some drugs (e.g., lidocaine, epinephrine, atropine) can be given through the ETT. The medication should be injected directly into the ETT, followed by several positive-pressure ventilations.[4,41]

Oxygen

The first resuscitation medication that should be used is 100% oxygen. Indications for oxygen use include central cyanosis and respiratory distress (nasal flaring, grunting, tachypnea, apnea).

Epinephrine

Epinephrine is indicated for asystole, and for an HR less than 60 beats/min despite effective ventilation with 100% oxygen and chest compressions. Although epinephrine may be given by ETT, the preferred administration route is intravenous (IV). The IV dose is 0.01 to 0.03 mg/kg or 0.1 to 0.3 mL/kg of 1:10,000 solution. Repeat doses may be given every 3 to 5 minutes.[22,48,49] If the endotracheal route is used, doses of 0.01 or 0.03 mg/kg will likely be ineffective. While access is being obtained, administration of up to 0.1 mg/kg through the ETT may be considered, but the safety and efficacy of this practice have not been evaluated.[1]

Naloxone

Respiratory depression induced by opioids given or taken within 3 to 4 hours of delivery can be reversed with naloxone. If respiratory depression is present, and if it is unclear whether the mother took opioids before delivery, reversal with naloxone may be attempted. The dose is 0.1 mg/kg IV, IO, SQ, or intramuscularly (IM). Administration of naloxone by ETT is not recommended in newborn resuscitation.[1] The duration of action of naloxone is 1 to 4 hours, depending on route of administration. Repeat dosing may be necessary, and the patient should be monitored carefully. Naloxone is not always needed in a newborn with respiratory depression. It may precipitate withdrawal seizures in an infant born to a drug-addicted mother.[19,49] The priority of care is support of ventilation with bag-mask device and intubation, if necessary. Naloxone should be considered only after ventilatory support is achieved.

Glucose

Hypoglycemia should be considered in a neonate undergoing resuscitation. Hypoglycemia is diagnosed with a rapid bedside glucose or serum glucose measurement. Treatment is indicated only for documented hypoglycemia: glucose less than 40 mg/dL in a full-term infant (>2.5 kg) and less than 30 mg/dL in a premature infant (<2.5 kg). Hypoglycemia is treated with 2 to 4 mL/kg of 10% dextrose in water ($D_{10}W$). Higher concentrations of glucose (e.g., 25% dextrose in water, $D_{25}W$) are hyperosmolar and should be avoided. Repeat glucose measurement should be obtained 10 to 20 minutes after glucose administration.

Volume Expanders

Volume expanders are indicated when acute bleeding is evident with signs of hypovolemia (pallor despite oxygenation, weak pulses with a good HR, poor response to resuscitation), or the newborn appears to be in shock.[21,22] Volume expanders include whole blood (Rh-negative type O blood crossmatched with the mother's blood), normal saline, or Ringer's lactate solution. Whole blood is preferred in the setting of significant blood loss but may be difficult to obtain quickly. Normal saline and Ringer's lactate (e.g., isotonic crystalloid solutions) should be readily available and may be considered the fluid of choice overall for volume expansion. Expanders are given in small IV boluses of 10 mL/kg over 5 to 10 minutes. When resuscitating premature infants, rapid administration of volume expanders should be avoided, as this has been associated with intraventricular hemorrhage.[1] Higher volume (e.g., 20 mL/kg) fluid boluses are recommended for older infants. Boluses may be repeated several times, guided by patient assessment. The use of albumin 5% with saline is currently not recommended for the initial resuscitation.

Dopamine

Dopamine is indicated only when signs of shock (e.g., poor peripheral perfusion, thready pulses) are still present despite adequate volume replacement. Given as a continuous infusion beginning at 5 µg/kg/min, dopamine may be increased to 20 µg/kg/min as necessary.

DISPOSITION

Early consultation with a neonatologist can assist in the resuscitation and postresuscitation phases of care. When the neonate has been stabilized, monitoring of oxygenation, ventilation, perfusion, temperature, and glucose must continue. Preparations should be made for transport of the newborn to a neonatal intensive care unit. A transport team with personnel skilled in neonatal resuscitation should be employed. Ideally, before transport, parents should see and touch (and hold if medically appropriate) their newborn.

KEY CONCEPTS

- The necessary equipment must be readily available for neonatal resuscitation in the emergency department.
- Preparation is most effective with an adequate maternal and prenatal history.
- The neonatal flow algorithm provides a guide for management.
- Drying, warming, positioning, and stimulating the infant are usually sufficient resuscitative measures in most deliveries.
- Endotracheal suctioning for neonates at risk for meconium aspiration is reserved for nonvigorous infants.
- Transport of the neonate to a neonatal intensive care unit allows continued treatment.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 10 Fever in the Adult Patient

Frederick C. Blum

PERSPECTIVE

Epidemiology

Fever is part of the presenting complaint in 6% of all adult (aged 18–65) visits to the emergency department (ED), 10 to 15% of all elder (older than 65 years) patient visits, and 20 to 40% of all pediatric visits.[1,2] Morbidity and mortality rates vary dramatically with age. Younger adults with fever usually have benign self-limited disease with less than 1% mortality. The challenge in this group is to identify the rare meningitis or septic conditions when confronted with a predominance of self-limited viral and focal bacterial diseases. Patients older than 65 years, or those with chronic disease who present with fever, represent a group at high risk for serious disease. Morbidity and mortality rates in this group are significant. Between 70 and 90% are hospitalized, and 7 to 9% die within 1 month of admission. Infection is the most common cause of fever in these patients, and most of these infections are bacterial in nature. Three body systems: the respiratory tract, the urinary tract, and the skin and soft tissue, are the target for more than 80% of these infections.[3] The relative mortality and morbidity for any given infection are much higher in the geriatric population. For example, elders are at 5 to 10 times greater risk for urinary tract infections and 15 to 20 times for appendicitis.[4,5] Even viral illnesses that are generally not fatal, such as influenza, can be highly lethal in elder persons.

Pathophysiology

Body temperature is normally controlled within a narrow range by the preoptic area of the hypothalamus. This range is usually between 36.0 and 37.8° C (96.8–100.4° F). There is a circadian rhythm within this range, with lower temperatures in the morning and higher temperatures in the late afternoon. Fever occurs when this normal range is reset to a higher value. Fever is typically defined as a core temperature greater than 38.0° C (100.4° F). Fever should not be confused with hyperthermia. Hyperthermia is an elevation of the temperature related to the inability of the body to dissipate heat. Almost all cases of temperatures higher than 41.0° C (105.8° F) are due to hyperthermia rather than to fever.

In the anterior hypothalamus, neurons directly sense the blood temperature. Temperature is subsequently controlled by a combination of vasomotor changes, shivering, changes in metabolic heat production, and behavioral changes.

Fever may be produced by a number of endogenous and exogenous substances referred to as *pyrogens*. Endogenous pyrogens include a variety of cytokines released by leukocytes in response to infectious and inflammatory and neoplastic processes. Exogenous pyrogens include a large number of bacterial and viral products and toxins. Toxins induce fever by stimulating cells of the immune system to release endogenous pyrogens. These cytokines, such as interleukin-1 (IL-1), IL-6, tumor necrosis factor, and interferon, travel to the hypothalamus and induce the production of prostaglandin E_2 (PGE_2).

PGE_2 raises the set point of the temperature range by a combination of effects including peripheral vasoconstriction, increased metabolic heat production, shivering, and behavioral changes that conserve heat. Fever is maintained as long as the levels of endogenous pyrogens and PGE_2 are high. Cyclooxygenase inhibitors, such as aspirin, decrease fever by blocking the production of PGE_2. Age, malnutrition, and chronic disease may also blunt the febrile response.

Moderate elevations of the body temperature may serve to aid the host defense by increasing chemotaxis, decreasing microbial replication, and improving lymphocyte function. Elevated temperatures directly inhibit the growth of certain bacteria and viruses.[5]

Fever also results in certain increased costs to the host including increased oxygen consumption, metabolic demands, protein breakdown, and gluconeogenesis. These costs are particularly problematic in elders, who typically have a smaller margin of reserve for any given body system. It is well established that the ability to develop fever in elders is somewhat impaired. Older individuals also are known to have lower baseline temperatures than younger adults.[6] It has not been proved that treatment of fever with antipyretics has a beneficial effect on outcome or prevents complications.

The initial step in the process of fever is the resetting of the thermostatic set point in the hypothalamus to a higher temperature while actual body temperature remains normal. This mismatch of the thermostat with the "sensed" body temperature causes the patient to feel chilled (chills). If the chills are reported to a caregiver and the skin is touched or the temperature is taken, it is usually noted to be normal or minimally elevated. The patient remains chilled until the body temperature rises. At this point, the patient feels euthermic (but may feel fatigued or ill), but to the caregiver, the skin temperature or thermometer reading is now elevated. This sequence of chills followed by febrile illness is the basis of the (incorrect) popular belief that getting chilled leads to infection (classically pneumonia). When the thermostatic set point is reduced to normal, the patient suddenly feels hot and

Table 10-1 Differential Diagnoses—Infectious Causes

ORGAN SYSTEM	CRITICAL DIAGNOSES	EMERGENT DIAGNOSES	NONEMERGENT DIAGNOSES
Respiratory	Bacterial pneumonia with respiratory failure	Bacterial pneumonia, peritonsillar abscess, retropharyngeal abscess, epiglottitis	Otitis media, sinusitis, pharyngitis, bronchitis, influenza, tuberculosis
Cardiovascular		Endocarditis, pericarditis	
Gastrointestinal	Peritonitis	Appendicitis, cholecystitis, diverticulitis, intra-abdominal abscess	Colitis/enteritis
Genitourinary		Pyelonephritis, tubo-ovarian abscess, pelvic inflammatory disease	Cystitis, epididymitis, prostatitis
Neurologic	Meningitis, cavernous sinus, thrombosis	Encephalitis, brain abscess	
Skin and soft tissue		Cellulitis, infected decubitus ulcer, soft tissue abscess	
Systemic	Sepsis/septic shock, meningococcemia		

sweats until the body temperature falls to match the (now normal) set point.

DIAGNOSTIC APPROACH

Differential Considerations

The complete differential diagnosis for the patient presenting to the ED with fever is extensive. The major infectious and noninfectious causes are summarized in Table 10-1 and Box 10-1, respectively. The vast majority of serious causes are infectious in origin. Immediate threats to life result from decompensated shock (usually septic), respiratory failure (related to shock or pneumonitis), or central nervous system infection (meningitis). Some critical noninfectious causes of fever also exist (see Box 10-1), but these are relatively rare and frequently do not occur with fever as the primary symptom.

BOX 10-1 DIFFERENTIAL DIAGNOSIS—NONINFECTIOUS CAUSES OF FEVER

Critical Diagnoses
Acute myocardial infarction
Pulmonary embolism/infarction
Intracranial hemorrhage
Cerebrovascular accident
Neuroleptic-malignant syndrome
Thyroid storm
Acute adrenal insufficiency
Transfusion reaction
Pulmonary edema

Emergent Diagnoses
Congestive heart failure
Dehydration
Recent seizure
Sickle cell disease
Transplant rejection
Pancreatitis
Deep vein thrombosis

Nonemergent Diagnoses
Drug fever
Malignancy
Gout
Sarcoidosis
Crohn's disease
Postmyocardiotomy syndrome

Rapid Assessment and Stabilization

Patients with life-threatening signs and symptoms, including significant alterations in mental status, respiratory distress, and cardiovascular instability, may require rapid, vigorous treatment. Prompt airway management and initiation of monitoring, intravenous access, fluid resuscitation, supplemental oxygen, and respiratory support are often necessary despite incomplete information concerning the cause of the fever. Sustained temperatures above 41.0°C are rare but can be damaging to neural tissue and require rapid cooling (e.g., misting, fans, cooling blankets).

In the younger, otherwise healthy patient with fever, immediate threats to life such as toxic or septic shock, meningitis, meningococcemia, and peritonitis should be considered and treated empirically.

In the older, chronically ill population with fever, most of the serious illnesses originate from infections in the respiratory tract, the genitourinary tract, and the skin and soft tissues. Meningitis, although less common, can also be a significant cause of morbidity and mortality in this group.

Pivotal Findings

Although the differential diagnosis of fever is broad, most of the treatable causes are of infectious origin. Up to 85% of these may be diagnosed by careful history and physical examination alone. Age and the presence of underlying medical conditions can substantially influence the evaluation and subsequent decision-making regarding management.

In younger and otherwise healthy adults, self-limited, localized bacterial infections or benign systemic viral infections are usually the cause of their fever. The challenge with this group is to identify the rare life-threatening illness, such as meningococcemia, meningitis, or systemic methicillin-resistant *Staphylococcus aureus* (MRSA) infection.

In the older or chronically ill population, fever is frequently a sign of severe illness. Usually, the cause is infectious. Eighty percent have respiratory infections, urinary tract infections, or soft tissue infections as the cause. Infections such as meningitis, cholecystitis, appendicitis, and diverticulitis may arise with atypical signs and symptoms in elderly or immunosuppressed patients. In this population, subtle changes in behavior may be the only sign of severe infection. Abnormal vital signs, especially significant tachypnea and hypotension, may portend a complicated and severe course. Seventy-five percent of the cases of functional decline in nursing home patients are due to infection.[6,7]

History

The *onset* of the fever, its *duration* and *magnitude,* and any *associated symptoms* help identify possible causes and severity of illness. Localizing symptoms such as dysuria or productive cough are especially helpful. The *timing* of the fever and its *patterns* may implicate certain diseases (e.g., malaria). *Recent or remote travel*, *chronic illnesses*, past surgeries, hospitalizations, and treatment modalities may raise the suspicion of exotic or nosocomial infections. The presence of cardiac valves or any prosthetic or indwelling device may be critical to the diagnosis.[8] With the emergence of community-acquired MRSA, it is important to seek a history of skin infections in close family members or other close contacts. MRSA should also be considered in military personnel, prisoners, and persons involved in competitive sports that involve close contact.[9,10]

Also important is a list of all the patient's medications, including any antipyretic medication. Family members are frequently an important source of information in elder and very young patients. They are often the first to notice a functional decline in the patient, such as difficulty ambulating, anorexia, decreased activity, or new urinary incontinence. A decline in mental status in the older patient may be the only clue to the presence of significant infection. The patient's baseline mental function must rely on the reports of others who know the patient well.

Atypical symptoms are common in elder patients. Pneumonia or urinary tract infection in the older patient may be heralded by only a change in mental status, difficulty ambulating, or some other functional decline. Dysuria, frequency, and flank pain often are absent entirely in elders with urinary tract infection. Patients with pneumonia may inconsistently present with productive cough or shortness of breath. Other frequent but nonspecific symptoms include anorexia, weight loss, weakness, lethargy, nausea, and recurrent falls.[8,9] A history of cancer with recent chemotherapy or radiation therapy may be a clue to leukopenia or other immunodepressed states.[4]

Physical Examination

The presence and magnitude of fever is an important element of the examination, but the elder, very young, or chronically ill patient may not mount a febrile response to significant infection. Temperatures may fluctuate, and rechecks may be necessary.

Rectal temperatures are the most accurate. Axillary and tympanic temperatures often are unreliable. Oral temperatures may be transiently distorted by recent ingestion of hot or cold liquids, smoking, or hyperventilation. Rectal temperatures are typically 0.7 to 1.0°C higher than oral temperatures.

Fever is inconsistently associated with tachycardia and tachypnea. The heart rate may increase by 10 beats/min for each 0.55°C (1°F) degree rise in temperature. Relative bradycardia may be caused by medication such as beta-blockers, but can suggest factitious or drug-related fevers, typhoid fever, brucellosis, or leptospirosis. Frank bradycardia may occur with rheumatic fever, Lyme disease, viral myocarditis, and endocarditis. The respiratory rate may increase 2 to 4 breaths per minute per degree Celsius. More significant tachypnea may be due to respiratory infection or the acidosis related to shock.

In many patients, the examination is directed by the patient's localization of symptoms. The head and neck examination focuses on treatable foci of infection such as otitis media, sinusitis, pharyngitis, peritonsillar abscess, retropharyngeal abscess, and dental infections. A muffled, "hot potato" voice with severe sore throat may be a clue to adult epiglottitis or upper airway abscess. Funduscopy rarely may reveal evidence of disseminated candidiasis, miliary tuberculosis, endocarditis, toxoplasmosis, or leukemia.

The neck is examined for lymphadenopathy, masses, or thyroid pathology (thyromegaly or mass). Nuchal rigidity or pain on forward flexion of the neck is assessed but may not be prominent in the very young, or in a debilitated or elder patient, even if meningitis is present. Conversely, cervical arthritis or Parkinson's disease may cause preexisting nuchal rigidity.

The lungs are examined for rales, pleural rubs, or dullness to percussion. Localized rales or rhonchi may be more subtle clues to the presence of pneumonia. The presence of concomitant chronic obstructive pulmonary disease or congestive heart failure, as well as poor respiratory effort, may hamper the diagnosis of pneumonia in elders. The heart is examined for pericardial rubs or new murmurs.

The abdominal examination may be deceptively benign in older patients, patients with diabetes, or patients taking immunosuppressives or steroids.[10] When indicated by history or other findings, a rectal examination is performed to check for evidence of enteritis, perirectal abscess, or prostatitis. The external genitalia examination may reveal evidence of Bartholin's abscess, urethral or vaginal discharge, or evidence of epididymitis or orchitis.

Females with appropriate symptoms should have a pelvic examination to evaluate for pelvic inflammatory disease or tubo-ovarian abscess. The skin and extremities should be evaluated for rash, petechiae, joint inflammation, or evidence of soft tissue infection. In the absence of trauma, tenderness over the long bones or the spine may be evidence of osteomyelitis or neoplastic processes. Elders and bedridden patients should be checked for the presence of pressure sores or decubitus ulcers.[3]

Ancillary Testing

The two most important ancillary tests, especially in elder patients, are urinalysis and chest radiography. Chest radiographs are often helpful in the diagnosis of pulmonary infection but may be difficult to interpret in the patient with concurrent chronic obstructive pulmonary disease, congestive heart failure, dehydration, or other chronic lung disease. The urinalysis, although not foolproof, is highly accurate for urinary tract infection, especially in men. Although the white blood cell count is almost universally used in the evaluation of febrile patients, it lacks the sensitivity and specificity to be of discriminatory value. The white blood cell count may incorrectly indicate serious infection when none is present or may be normal in the presence of life-threatening infection.[11] Other indirect tests of infection and inflammation, such as the erythrocyte sedimentation rate, are also plagued with irregular sensitivity and poor specificity and should be used sparingly. Gram's stain of appropriate specimens may be helpful, and cultures may be ordered, although the results do not influence emergency evaluation and treatment. With the emergence of MRSA, it has become increasingly important to obtain cultures from soft tissue skin abscesses in patients considered at risk for MRSA infection. In elder or chronically ill patients with fever of unknown source, blood and urine cultures are frequently appropriate. Outpatient blood cultures should rarely, if ever, be done. A patient ill enough to require blood cultures generally requires hospitalization and empirical antibiotic coverage. Cerebrospinal fluid evaluation should be considered when mental status changes or if headache, meningismus, or other unexplained neurologic symptoms are present and cannot be clearly accounted for by infection outside the central

nervous system. Thyroid function studies may be helpful when thyroid storm is suspected.

Plain films of the abdomen are rarely indicated or helpful. Abdominal computed tomography (CT) is helpful if appendicitis, diverticulitis, cholecystitis, or intra-abdominal abscess is suspected. Ultrasonography may be helpful in the patient with potential cholecystitis.

Cranial CT scanning may be indicated prior to lumbar puncture in patients with focal neurologic findings or an embolic source, such as suspected endocarditis, to exclude mass lesions such as tumor or brain abscess. This test should not delay antibiotics in patients with suspected meningitis.

Other ancillary testing is directed by the findings of the history and physical examination.

DIFFERENTIAL DIAGNOSIS

The differential diagnoses of infectious causes of fever are summarized in Table 10-1. The differential diagnoses of noninfectious causes of fever are listed in Box 10-1.

EMPIRICAL MANAGEMENT

Patients with temperatures greater than 41.0° C require prompt and vigorous treatment with antipyretics and possibly external cooling measures. Temperatures above this range can result in damage to neuronal tissue. There is no evidence for improved outcome by routine use of antipyretic therapy, such as acetaminophen, in patients without extreme temperature elevation, but it is not harmful, and patients often feel better when their temperature declines. Achieving a normal or near-normal temperature is not necessary as a criterion for discharge, however. Patients with signs and symptoms of shock require prompt and vigorous treatment (see Chapter 4). Patients with evidence of respiratory failure from shock or pneumonia require ventilatory support. Soft tissue infections of the head and neck may compromise the airway because of mechanical obstruction. These may require acute intervention to provide a secure airway.

In many cases, early empirical antibiotic therapy is appropriate. The choice of antibiotics is based on the likely cause of the fever as well as concomitant conditions such as absolute neutropenia and end-stage renal disease. If a specific infection is identified, antibiotic therapy should be specific to that infection. In the absence of a clear source of infection, broad-spectrum coverage of gram-positive and gram-negative aerobic and anaerobic bacteria is indicated.

DISPOSITION

Localized bacterial infections can most frequently be treated with outpatient oral antibiotics. Relatively young, healthy patients with systemic viral illness can be treated as outpatients. These illnesses are often accompanied by vomiting and poor oral intake, and treatment in the ED with antipyretics, antinausea medications, and intravenous hydration may help prepare the patient for a successful outpatient course.

When no clear infection is identified in older patients or those with chronic illness such as diabetes or chronic renal failure, admission to the hospital often is necessary to further elucidate the possible causes of the presentation. In this subset of patients, a diligent search for evidence of bacterial infection is required. Also, admission to an inpatient unit or ED observation unit may be advisable when fever or other systemic symptoms accompany a suspected MRSA infection. In patients with unexplained severe febrile illness, blood and urine cultures and broad-spectrum antibiotics are indicated to treat possible life-threatening infection, until a specific disease process or pathogen is identified. Indwelling devices, such as percutaneous intravenous access ports, frequently require culture and may need to be removed. Neutropenic patients with fever require prompt treatment with broad-spectrum parenteral antibiotics pending results of cultures. Patients with unstable vital signs or life-threatening infections may require admission to a special care unit if they cannot be adequately stabilized in the ED prior to admission.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 11 Weakness

Eve D. Losman

PERSPECTIVE

Weakness is a subjective term that can be used to describe many symptoms that can relate to a variety of disease states. *Webster's Dictionary* definition for *weak* is "lacking strength, deficient in physical vigor, not able to sustain or exert much weight, pressure, or strain." However, when a patient uses the term *weakness*, he or she might be describing symptoms beyond the loss of muscle power. Malaise, frailty, fatigue, pain, dizziness, and alteration of mental status might all be described as weakness.

This chapter focuses on the evaluation and treatment of patients complaining of the acute onset of generalized, diffuse, and symmetrical weakness. Discussion regarding chronic neurologic conditions, localized weakness, space-occupying lesions, and traumatic injury can be found elsewhere.

Epidemiology

No research data are currently available specifically related to the presenting complaint of "weakness" in the emergency department (ED). Because this complaint can originate from derangements in multiple organ systems, it is difficult to get a true estimate of its frequency in the ED setting.

Acute neuromuscular weakness is a relatively rare entity. Poliomyelitis has been eradicated in Western Europe and North America, and there has been a dramatic decrease in the incidence of this disease worldwide (1187 cases in 2007 per the World Health Organization).[1] The most common cause of acute symmetrical weakness in industrialized countries is Guillian-Barré syndrome, with an annual incidence of 2 cases per 100,000 in the United States. To put this in perspective, the incidence of diabetes mellitus is 740 cases per 100,000.[2] New infectious causes of acute symmetrical weakness have emerged in the past few decades including West Nile virus and HIV.

Pathophysiology

The key differentiation is whether the patient has actual, quantitative, muscle weakness. If so, the nervous system is involved, often with dysfunction of the motor unit. In contrast, the complaint of weakness in the absence of decreased strength on examination suggests a disease process outside of the nervous system. These two broad categories of weakness will be examined in turn.

Neuromuscular Weakness

Muscle contraction is the result of a series of signals that originate in the cerebral cortex. Upper motor neurons (UMN) originate in the motor strip, anterior to the central sulcus, and travel in the pyramidal system. They descend the spinal column in the lateral corticospinal tract on the side opposite their origin in the brain. The UMN then synapses with the lower motor neuron (LMN) in the anterior horn of the spinal cord, which in turn carries the signal to the muscle bundle. The LMN (peripheral nerve) releases acetylcholine into the synaptic cleft, which then depolarizes the motor endplate and results in muscle contraction. This series of events depends on the presence of myelin insulating the nerves, the function of calcium and sodium channels, and the presence of acetylcholinesterase. Neuromuscular weakness can be caused by lesions or derangements at any level of this cascade of events.

Non-neuromuscular Weakness

A patient's complaint of weakness often stems from a non-neuromuscular cause. The patient's age, underlying health status, current symptom complex, and examination findings help narrow the differential diagnosis. Infectious, cardiovascular, endocrine, metabolic, and toxicologic causes of the patient's complaint need to be considered.

DIAGNOSTIC APPROACH

Pivotal Findings

History

A clear description of the symptoms is crucial to clarifying whether the patient is experiencing neuromuscular weakness. Does the patient describe a decrement in function? For example, is the patient unable to climb stairs because of leg weakness or because of shortness of breath and fatigue? The former case is likely to be due to neuromuscular weakness; the latter may be related to compromised cardiovascular function or another systemic process.

It is important to obtain the time course of symptoms, severity, and their progression or worsening. The distribution (proximal, distal, generalized) of weakness, fluctuations in function, and alleviating or aggravating factors (activity, rest) are also

important factors. The presence or absence of bladder and bowel dysfunction, sexual dysfunction, paresthesias or altered sensation, and muscle pain or spasm should also be elicited. Recent history of infectious illness, trauma, new medications, exposure to toxins, alcohol and drug use should also be considered. Table 11-1 lists a few of the serious causes of acute neuromuscular weakness with their distinguishing characteristics and management.

The patient's age, comorbidities, and overall vigor or frailty should be taken into account. A thorough review of organ systems should be performed. The presence or absence of fever, infectious symptoms, fatigue, chest discomfort, dyspnea, malaise, abdominal discomfort, alteration of bowel habits, especially melena or hematochezia, and headache should be elicited. Careful medication review, especially of diuretics, beta-blockers, and psychotropic medications, may suggest

Table 11-1 Neuromuscular Diseases: A Brief Description

DISEASE	MECHANISM	HISTORICAL FEATURES/EXAM FINDINGS	ED MANAGEMENT
Botulism Toxin 12–72 hr postingestion	Neurotransmission Toxin prevents release of acetylcholine at the neuromuscular junction	Ingestion of contaminated canned goods 50% have GI symptoms Postural hypotension Diplopia, blurred vision, ptosis, facial weakness, dysphagia, respiratory compromise, then limb weakness	Supportive care, ICU admission Notify Health Dept/CDC Trivalent antitoxin (May try guanidine hydrochloride, facilitates release of acetylcholine from nerve endings; anticholinesterase drugs not helpful)
Myasthenia Gravis Idiopathic	Neurotransmission Decreased number of functioning acetylcholine receptors	Mild infection may exacerbate symptoms Fluctuating weakness; easy fatigability of voluntary muscles; cranial nerves involved with ptosis and diplopia in >25%; normal pupillary responses; normal sensation; normal reflexes Improves with rest May have a coexisting thymoma (CXR, chest CT)	Supportive care, ICU admission Neurology consult Edrophonium/neostigmine test Bedside spirometry Measure serum acetylcholine receptor antibody levels Tx: Anticholinesterase drugs—neostigmine; pyridostigmine
Organophosphate/ Carbamante Poisoning Immediate–3 wk	Neurotransmission Cholinergic crisis from inhibition of acetylcholine Neuropathy (weeks after exposure)	History of insecticide exposure Gastrointestinal symptoms, agitation, miosis, paralysis, diaphoresis, muscle weakness, bradycardia Cramping muscle pain, distal numbness and paresthesias, progressive muscle weakness; decreased reflexes; can develop flaccid/ wasted leg muscles	Decontamination Supportive care, ICU admission Atropine Pralidoxime (2-Pam)
Tetanus Toxin 3 wk 10–60% fatality	Neurotransmission Toxin interferes with release of inhibitory transmitters including GABA; results in motor nerve hyperactivity	Immunization status History of cutaneous infection Trismus, laryngospasm, painful muscle spasms and rigidity (opisthotonos), autonomic instability	Supportive care, ICU admission Débridement of wounds Tetanus immunoglobulin Penicillin for the infection High-dose benzodiazapines Neuromuscular blockade
Tick Paralysis Toxin 2–7 days Rocky Mountain wood tick and the American dog tick are most common in the USA	Neurotransmission Toxin reduces motor neuron action potential and the action of acetylcholine	History of outdoor activities/tick bite Progressive, ascending, flaccid weakness over several hours may lead to respiratory failure; may present as acute ataxia without muscle weakness; decreased or absent reflexes; ophthalmoplegia and bulbar palsy can occur	Removal of the embedded tick (look at the hairline/in the scalp) Supportive care Full recovery if tick removed; 10% fatality if not recognized
Ciguatoxin Toxin 12–24 hr; neurologic symptoms can last months	Neuropathy Toxin causes cell membrane excitability and instability	History of ingestion of large, tropical fish Diarrhea, abdominal pain, nausea, and vomiting are followed by painful paresthesias, ataxia, altered hot/cold perception, myalgias, bradycardia, and hypotension Rarely, death occurs through respiratory failure	Supportive care, ICU admission Atropine for bradycardia Hydration IV mannitol can be helpful
Diphtheria Toxin 2 wk–3 mo after infection	Neuropathy Lower motor neuron	Immunization status History of throat infection with pseudomembrane; cutaneous infection Palatal weakness, impaired pupillary responses, generalized sensorimotor polyneuropathy; respiratory failure; motor weakness of the proximal muscle groups and extending distally	Supportive care, ICU admission Equine diphtheria antitoxin Erythromycin or penicillin G for 14 days to halt toxin production, treat localized infection and prevent transmission of organisms Immunization

Table 11-1 Neuromuscular Diseases: A Brief Description—cont'd

DISEASE	MECHANISM	HISTORICAL FEATURES/EXAM FINDINGS	ED MANAGEMENT
Gullian-Barré Syndrome Idiopathic 1–4 wk 75% recover 5% fatality	Neuropathy Lower motor neuron Immune-mediated polyneuropathy Multiple variants	May have a history of infection; viral infection; *Campylobacter jejuni* in 15–40% Symmetrical ascending motor neuropathy; decreased/absence reflexes; mild sensory involvement; autonomic dysfunction; can progress to respiratory compromise	Lumbar puncture: CSF with elevated protein but normal WBC Bedside spirometry Plasmapheresis and IVIG Consider ICU admission Neurology consult
Transverse Myelitis Idiopathic, postinfectious, autoimmune Rapid onset (hours–days)	Neuropathy Upper motor neuron Axonal demyelination	Loss of spinal cord functions with symptoms depending on the level of the lesion; thoracic is most common Acute, focal back pain; distal muscle weakness; abnormal sensation; urinary retention/loss of bowel control; muscles may be flaccid; decreased or absent reflexes initially Differentiate from spinal cord compression, trauma or infarct; may be the first sign of multiple sclerosis	Supportive care, ICU admission if C-spine level for respiratory support Spine radiograph to evaluate for boney lesion Stat MRI/CT myelogram Decompress bladder
Electrolyte Imbalance	Myopathy	History of nausea/vomiting/diarrhea History of renal failure, alcohol dependence, new medication Ascending symmetric muscle weakness with normal to diminished reflexes	ECG Electrolyte panel: Na, K, Cl, PO_4, Ca, and Mg Renal function Correct the abnormality; close hemodynamic monitoring
Polymyositis Autoimmune	Myopathy	History of connective tissues disorders or cancer Progressive at a variable rate; muscle weakness and wasting; ascending pattern with proximal limb and girdle muscle involvement; muscle pain; dysphagia; respiratory difficulty; can have an erythematous periorbital and eyelid rash (dermatomyositis)	Elevated CPK, rhabdomyolysis rare Normal ESR Supportive care Corticosteroids

Adapted and expanded from LoVecchio, et al: Approach to generalized weakness and peripheral neuromuscular disease. Emerg Med Clin North Am 15:605, 1997.
CDC, Centers for Disease Control and Prevention; CPK, creatine phosphokinase; CSF, cerebrospinal fluid; CT, computed tomography; CXR, chest radiograph; ESR, erythrocyte sedimentation rate; GABA, γ-aminobutyric acid; GI, gastrointestinal; ICU, intensive care unit; IVIG, intravenous immunoglobulin; MRI, magnetic resonance imaging; WBC, white blood cell count.

electrolyte disturbances or generalized medication side effects.

In adults older than age 50, particularly women, the complaint of generalized weakness should prompt consideration of cardiac ischemia.

In adults older than age 65, a complaint of weakness may be the only symptom of a serious infection, electrolyte disturbance, or cardiovascular compromise. When this complaint is combined with a recent fall, altered mental status, or urinary incontinence, urosepsis should be considered. When this complaint is accompanied by the report of poor sleep, dyspnea, or decreased exercise tolerance, acute coronary syndrome or heart failure should be considered. Consideration should be given to situational orthostasis resulting in a sensation of weakness accompanied by a presyncopal feeling; examples include postparandial hypotension and post-tussive or micturition near-syncope.

Examination

Fever, hypotension, tachycardia, or tachypnea may provide clues regarding the source of the patient's complaint (Table 11-2). If severe weakness is present, an assessment of the patient's ability to maintain the airway and the adequacy of respiration is indicated (Fig. 11-1).

The neurologic exam should focus on clarifying if the patient is experiencing true loss of strength along with the distribution of the deficits (Table 11-3). A complete examination, including cranial nerves, and gait, where possible, is helpful. The motor exam should be systematic and thorough. Muscle bulk, strength, tone, and the presence or absence of abnormal movements should be noted. Sarcopenia (age-associated loss of muscle mass and function) is normal in the older adult. In this situation, the loss of power is uniform in all limbs. Walking on heels, toes, and in tandem is a good test of strength as well as coordination and proprioception. Gait apraxia has a wide differential and should prompt investigation for cerebellar abnormality; normal pressure hydrocephalus should be considered in the patient who has simultaneous incontinence and decreased cognitive function. Fine muscle fasciculations typically point to an LMN disorder, whereas spasticity, greater in the flexors than extensors, is seen in UMN lesions.

Ancillary Testing

Patients presenting with weakness can have myriad underlying abnormalities. Although testing will be guided by the history and exam, virtually all patients require a complete blood count to evaluate for anemia or blood loss and serum electrolytes, glucose, and creatinine. An electrocardiogram

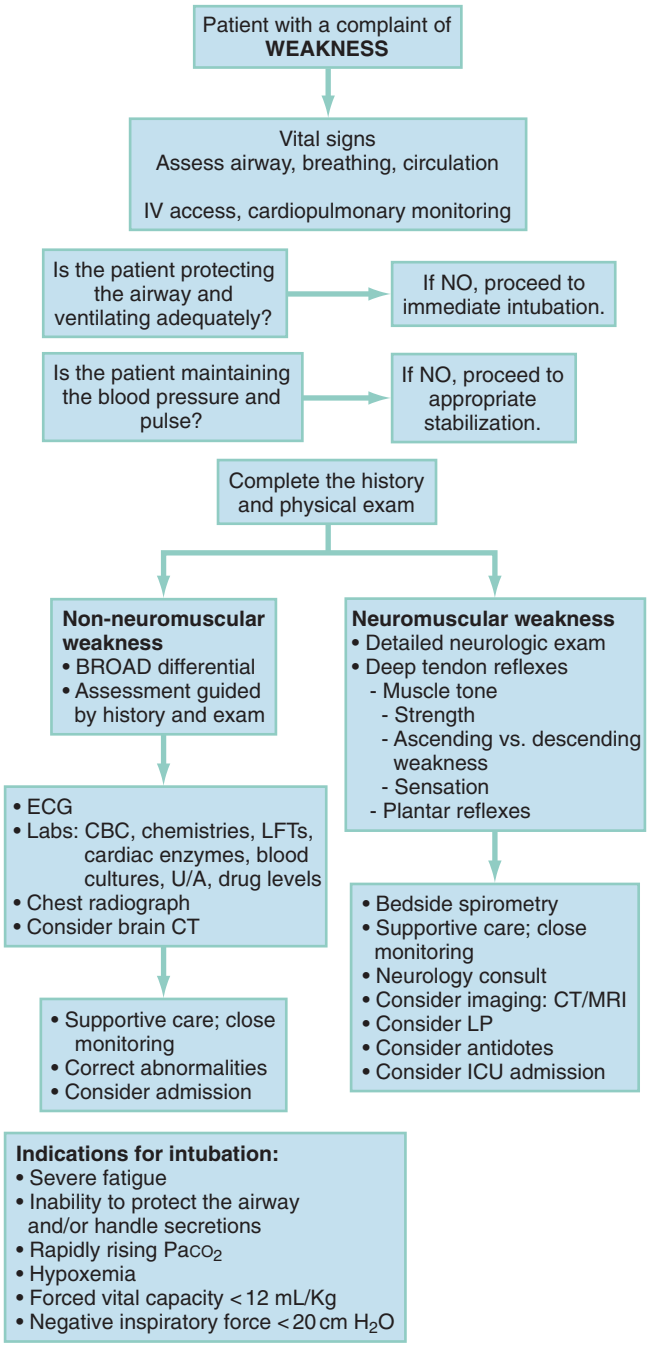

Figure 11-1. Diagnostic management algorithm. CBC, complete blood count; CT, computed tomography; ECG, electrocardiogram; ICU, intensive care unit; LFTs, liver function tests; LP, lumbar puncture; MRI, magnetic resonance imaging; $Paco_2$, arterial partial pressure of carbon dioxide; U/A, urinalysis.

may indicate cardiac ischemia or hypo- or hyperkalemia. In patients with infectious symptoms and in elders with nonlocalized symptoms, a chest radiograph and urinalysis are helpful. Computed tomography or magnetic resonance imaging of the brain or spine are not generally indicated in the absence of focal findings, altered mental status, history of cancer, or anticoagulation with (even minor) trauma. Lumbar puncture can help confirm central nervous system infection when suggested, or Guillian-Barré syndrome when protein levels are elevated and a white blood cell count of 10 or fewer per milliliter strongly supports the diagnosis.

Any patient who appears to have respiratory compromise or for whom Guillian-Barré syndrome or myasthenia gravis is possible should undergo bedside spirometry. A forced vital capacity (FVC) of less than 10 to 12 mL/kg or a negative inspiratory force (NIF) of less than 20 cm H_2O is an indication for respiratory support. An arterial blood gas test for carbon dioxide tension or capnography may also be helpful.

DIFFERENTIAL DIAGNOSIS AND INITIAL MANAGEMENT

The differential diagnosis of weakness is very broad, and at times, a definitive diagnosis is impossible in the span of an ED visit. Ensuring appropriate disposition and follow-up is particularly important in these patients.

In a patient with neuromuscular weakness, the respiratory drive is preserved, but the ability to ventilate adequately can be impaired and the patient may complain of dyspnea. Patients with rapid progression of weakness may require early airway intervention and mechanical ventilation. Warning signs of worsening respiratory status include the inability to lift the head, ineffective cough, alteration of the voice, and difficulty controlling secretions. As a crude measure of vital capacity, the patient's inability to count to 20 in a single exhalation suggests that the FVC is compromised; when the patient can only count to 10, the FVC can be estimated at 1 L and preparations to intubate should be made. About 30% of patients with Guillian-Barré syndrome require mechanical ventilation, and several studies have demonstrated that an elective, controlled intubation leads to better outcomes in terms of ventilation-associated pneumonia and total time on the ventilator[3] (Fig. 11-2).

Patients with neuromuscular weakness increase their respiratory rate to compensate for low tidal volumes, and the $Paco_2$ is maintained within the normal range. If the patient develops muscle fatigue or increased muscle weakness, the $Paco_2$ will rise and respiratory failure can occur quickly. In this situation, intubation, usually using a rapid sequence technique, is indicated. Succinylcholine should be avoided when a progressive denervation syndrome is suggested.[4] The up-regulation and redistribution of acetylcholine receptors on denervated myocytes that occurs with succinylcholine can lead to significant hyperkalemia with administration of this drug (see Chapter 1). In addition, autonomic instability in these patients can make intubation challenging; the physician should anticipate the possibility of labile blood pressures and bradycardia.[5] Bradycardia responds to atropine administration, and the blood pressure should be closely monitored but not necessarily treated as it can fluctuate rapidly.

Special Situations

Myasthenia Gravis: Myasthenic Crisis versus Cholinergic Crisis

Myasthenia gravis is discussed in detail in Chapter 106. *Myasthenic crisis* refers to a rapid worsening of neuromuscular function with respiratory compromise. It occurs in approximately 15% of patients with this disease and can be triggered by infection (≈ 30% of cases), change in medications, metabolic derangement, or physical stress; a third of the time no cause is found.[6] A crisis can be precipitated by a recent change in the dose of the patient's anticholinesterase inhibitor, recent initiation or tapering of corticosteroids, and recent initiation of several commonly used medications (aminoglycoside and quinolone antibiotics, beta-blockers, and antiarrhythmic agents). Myasthenic crisis is associated with prolonged hospitalization and intubation periods of 1 to 3 weeks.

Table 11-2 Vital Signs: Weakness

VITAL SIGNS	ELEVATED	DECREASED	POTENTIAL INTERVENTIONS / ANCILLARY TEST
Heart rate	Arrhythmia Blood loss Dehydration Hyperthyroidism Pain Serious infection	Electrolyte imbalance Medication effect (BB, CCB)	ECG Fluid bolus and reevaluate Orthostatic blood pressure/pulse Rate control based on ECG findings Antibiotics if infection suspected
Blood pressure	Hyperthyroidism Medication noncompliance Pain	Arrhythmia Blood loss Dehydration Medication effect (BB, CCB) Serious infection	ECG Fluid bolus and reevaluate Orthostatic blood pressure/pulse Pressors
Respiratory rate	Serious infection COPD/Asthma	Impending respiratory failure	Bronchodilators CXR Respiratory support: oxygen, BiPAP, intubation
Temperature	Serious infection Medication effect	Serious infection Environmental exposure	Antipyretics/cooling measures Passive rewarming ECG Infectious workup
Oxygen saturation	N/A	Serious infection COPD/asthma Impending respiratory failure	Bronchodilators CXR Respiratory support: oxygen, BiPAP, intubation

BB, beta-blocker; BiPAP, Bi-level positive airway pressure; CCB, calcium channel blocker; COPD, chronic obstructive pulmonary disease; CXR, chest radiograph, ECG, electrocardiogram.

Table 11-3 Physical Examination: Localizing Neuromuscular Lesions

LOCATION OF LESION	DEEP TENDON REFLEXES	MUSCLE TONE	PLANTAR REFLEXES	STRENGTH
Upper motor neuron	Increased	Normal (Increased/spastic as disease progresses)	Upgoing	Weak/paralysis
Lower motor neuron	Decreased or absent	Decreased/flaccid (may see fasciculations)	Normal or absent	Weak/paralysis
Neuromuscular junction	Normal or decreased	Decreased/flaccid	Normal or absent	Variable weakness pattern
Muscle	Normal or decreased	Decreased/flaccid	Normal or decreased	Constant/progressive Proximal > distal

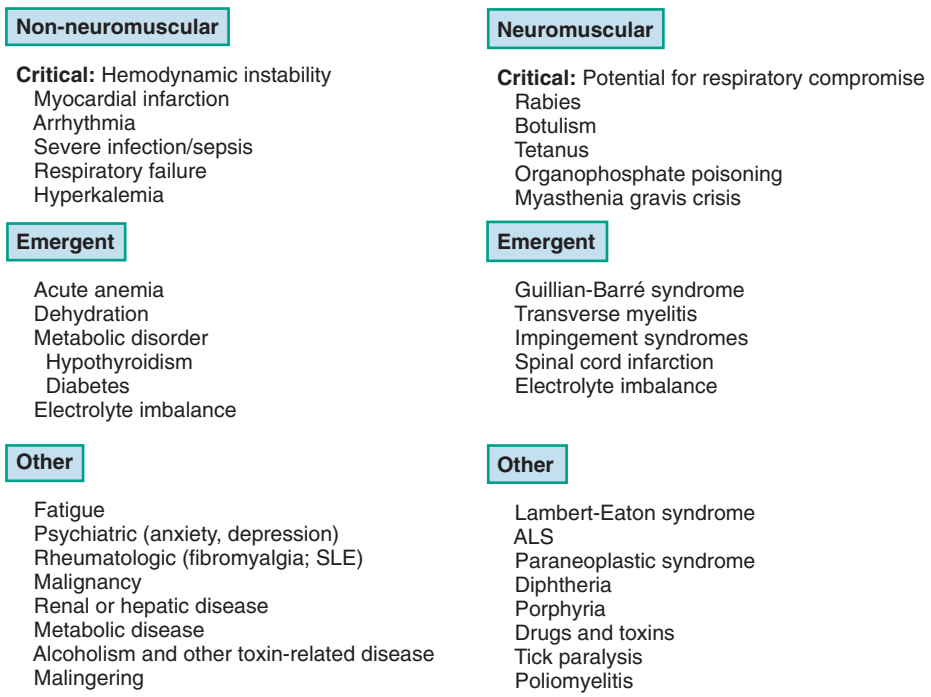

Figure 11-2. Differential diagnosis algorithm: Weakness.

Cholinergic crisis results from an excess of cholinesterase inhibitor medication that produces a flaccid muscle paralysis and generalized weakness. Respiratory failure may be present with or without other cholinergic symptoms.

These two forms of crisis can be difficult to distinguish but are managed similarly with a focus on airway protection and ensuring adequate ventilation. Potential triggers for the crisis should be sought, and because many of these patients are on immunosuppressive medications, infection should be strongly considered. An urgent neurology consultation may be helpful, and an edrophonium challenge test may be performed if a myasthenic crisis is suggested (see Chapter 106).

Older Adults and Frailty

In the older adult with a complaint of weakness, an accurate history can be difficult to obtain. In addition, comorbidities and polypharmacy can often complicate the presentation in these patients.

Frailty is a biologic syndrome defined by decreased reserve and resistance to stressors and is an independent predictor of future functional decline, falls, hospitalization, and mortality.[7,8] Hallmarks of this syndrome include generalized muscle weakness, poor endurance, weight loss, low physical activity, and slow gait speed. The prevalence of frailty in community-dwelling persons older than age 65 is approximately 7% and it increases with age and female gender.

Older adults with disability, frailty (as measured by their functional status, grip strength, and ability to ambulate), and comorbid chronic illness are at high risk for poor outcome after the ED visit.[9] A thorough evaluation with attention to potential life-threatening conditions and a low threshold for admission and further evaluation is warranted in this population.

One year post-ED visit with hospitalization, mortality in this population is in the range of 25%.

DISPOSITION

Most patients presenting to the ED with a complaint of weakness have a non-neuromuscular cause for their complaint. The history, exam, and results of ancillary testing dictate treatment and disposition of these patients.

Those patients who present with acute symmetrical neuromuscular weakness require a thorough evaluation with particular attention to their airway and ventilation. Disposition decisions should be made in conjunction with neurology consultation, and admission to the intensive care unit for close respiratory monitoring should be considered.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 12 Dizziness and Vertigo

Jonathan S. Olshaker

PERSPECTIVE

An estimated 7.5 million patients with dizziness are seen each year in ambulatory care settings. It is one of the most common principal complaints in the emergency department.[1] Benign paroxysmal positional vertigo, felt to be caused by loose particles in the semicircular canals, is the most common cause of vertigo with an incidence estimated to be 107 cases per 100,000 population per year.[2] Dizziness in older persons is associated with a variety of cardiovascular, neurosensory, and psychiatric conditions and with the use of multiple medications.[3] Among patients older than 60 years, 20% have experienced dizziness severe enough to affect their daily activity.[4] In a study of 1000 outpatients, dizziness was the third most common complaint. *Vertigo* is defined more clearly as a sensation of disorientation in space combined with a sensation of motion. In 1921, Bárány published the first detailed description of benign paroxysmal positional vertigo.

A complaint of "dizziness" is an imprecise term. The emergency department physician may believe that the patient will be difficult to interview and that the condition will be problematic to diagnose and treat. But in reality, most of these patients have an organic basis for symptoms that can be successfully identified and treated. The diagnostic process is consistently based on two basic concepts: deciding whether the patient has true vertigo and, if vertigo exists, deciding whether the cause is central or peripheral.[5]

Pathophysiology

The maintenance of equilibrium and awareness of the body in relationship to its surroundings depend on the interaction of three systems: visual, proprioceptive, and vestibular. The eyes, muscles, joints, and otic labyrinths continuously supply information about the position of the body. Visual impulses, mediated through the higher brain centers, provide information about body position in space. Impulses from proprioceptors of the joints and muscles supply data about the relative positions of the parts of the body. Impulses from the neck are of special importance in relating the position of the head to the rest of the body. The sense organs of the visual, vestibular, and proprioceptive systems are connected with the cerebellum by way of the vestibular nuclei in the brainstem. Any disease that interrupts the integration of these three systems may give rise to symptoms of vertigo and disequilibrium.

The vestibular apparatus helps maintain head position and stabilize head movement. It is housed in the inner ear, or labyrinth, which lies embedded in the petrous portion of the temporal bone, where it is vulnerable to trauma; blood-borne toxins; and infections in nearby structures, including the middle ear and meninges. The vestibular apparatus consists of three semicircular canals with their cristae and two otolithic structures: the utricle and saccule. The semicircular canals provide information about movement and angular momentum; the otoliths provide information about the orientation of the body with respect to gravity.

The semicircular canals are paired structures that normally respond to motion in a symmetrical manner. With inner ear disease, the resting discharge or the discharge stimulated by motion can be altered in one ear. This alteration produces asymmetrical responses and results in the perception of vertigo. Freely moving debris within the semicircular canals can produce positional vertigo as the debris moves under the influence of gravity.

Impulses leave the vestibular apparatus by the vestibular part of the acoustic nerve (cranial nerve VIII), enter the brainstem just below the pons and anterior to the cerebellum, and proceed to the four vestibular nuclei of the brainstem and to the cerebellum. From there, impulses travel along two pathways that contribute to the clinical manifestations of vertigo: the medial longitudinal fasciculus and the vestibulospinal tract. In individuals with healthy vestibular systems, these connections allow the eyes to compensate for body movement in different directions and to maintain a visual axis that is stable with respect to the environment.

Nystagmus occurs when the synchronized vestibular information becomes unbalanced. Typically, it results from unilateral vestibular disease, which causes asymmetrical stimulation of the medial and lateral rectus muscles. This unopposed activity causes a slow movement of the eyes toward the side of the stimulus, regardless of the direction of deviation of the eyes. The cerebral cortex then corrects for these eye movements and rapidly brings the eyes back to the midline, only to have the process repeated.

By convention, the direction of nystagmus is denoted by the direction of the fast "cortical" component. Nystagmus caused by vestibular disease tends to be unidirectional and horizontorotary. If the nystagmus is vertical, a central lesion (either brainstem or cerebral) is usually the cause.

The vestibular nuclei send information to the lateral vestibulospinal tract, where they connect with motor neurons that supply the muscles of the extremities. This phenomenon explains the false steps or other body movements made by people with a defective vestibular apparatus who are

attempting to correct for an imagined change in position. Connections between the vestibular nuclei and the autonomic system account for the perspiration, nausea, and vomiting that commonly accompany an attack of vertigo. Connections between the vestibular nuclei and the cerebellum account for the modulating influence of this organ on motor activity.

■ DIAGNOSTIC APPROACH

Differential Considerations

Patients use the term *dizzy* to describe a variety of experiences, including sensations of motion, weakness, fainting, light-headedness, unsteadiness, and depression. To clarify the picture, it is often helpful to have patients describe the sensation without using the word *dizzy*. True vertigo may be defined as a sensation of disorientation in space combined with a sensation of motion. There is a hallucination of movement either of the self (subjective vertigo) or the external environment (objective vertigo). Descriptions of light-headedness or feeling faint are more consistent with presyncope. The differential diagnosis for these patients should include dysrhythmias, myocardial infarction, sepsis, hypovolemia, drug side effects, and pulmonary embolism. For some patients, dizziness is simply a metaphor for malaise, representing a variety of other causes, such as anemia, viral illness, or depression. The primary focus of this chapter is to review the evaluation of the vertiginous patient.

If the patient has true vertigo, the clinician must determine whether the cause is a peripheral lesion (e.g., of the inner ear) or a central process, such as cerebrovascular disease or a neoplasm. In most cases, peripheral disorders are benign, and central processes have more serious consequences. Occasionally, as in the case of a cerebellar hemorrhage, immediate therapeutic intervention is indicated. Acute suppurative labyrinthitis is the only cause of peripheral vertigo that requires urgent intervention. Box 12-1 lists causes of vertigo and identifies the peripheral, central, and systemic diagnoses. Table 12-1 summarizes the different characteristics of peripheral and central vertigo.

Pivotal Findings

History

The medical history is the most important source of information. A first key question is, "Does true vertigo exist?" Does the patient have a sensation of disorientation in space or a sensation of motion? The sensation of spinning usually indicates a vestibular disorder. Some nausea, vomiting, pallor, and perspiration accompany almost all but the mildest forms of vertigo. The presence of these symptoms without vertigo should suggest a different cause. The labyrinth has no effect on the level of consciousness. The patient should not have an associated change in mentation or syncope. A sensation of imbalance often accompanies vertigo, but true instability, disequilibrium or ataxia makes a higher likelihood of a central process.[6]

Because nystagmus accompanies acute vertigo, it is often helpful to ask members of the patient's family if they have noted any unusual eye movements during the dizzy spells. This question is especially important in children unable to offer a concise history.[7] Occasionally, the patient may be able to describe a flickering or oscillating visual field immediately after a change in position, such as rolling over in bed. In addition, interviewing family and other witnesses can often uncover evidence suggesting seizures, syncope, or imbalance unrelated to feelings of vertigo.

The *time of onset* and the *duration of vertigo* are important clues to the cause. Episodic vertigo that is severe, lasts several hours, and has symptom-free intervals between episodes sug-

BOX 12-1 CAUSES OF VERTIGO

Peripheral Causes
Foreign body in ear canal
Cerumen or hair against tympanic membrane
Acute otitis media
Labyrinthitis (suppurative, serous, toxic, chronic)
Benign positional vertigo
Ménière's disease
Vestibular neuronitis
Perilymphatic fistula
Trauma (labyrinth concussion)
Motion sickness
Acoustic neuroma*

Central Causes
Infection (encephalitis, meningitis, brain abscess)
Vertebral basilar artery insufficiency
Subclavian steal syndrome
Cerebellar hemorrhage or infarction
Vertebral basilar migraine
Post-traumatic injury (temporal bone fracture)
Postconcussive syndrome
Temporal lobe epilepsy
Tumor
Multiple sclerosis
Cervical spine muscle and ligamentous injury

Systemic Causes
Diabetes mellitus
Hypothyroidism

*Cause of peripheral vertigo that proceeds centrally.

Table 12-1 Characteristics of Peripheral and Central Vertigo

CHARACTERISTIC	PERIPHERAL	CENTRAL
Onset	Sudden	Gradual or sudden
Intensity	Severe	Mild
Duration	Usually seconds or minutes; occasionally hours, days (intermittent)	Usually weeks, months (continuous) but can be seconds or minutes with vascular causes
Direction of nystagmus	One direction (usually horizontorotary), never vertical	Horizontal, rotary, or vertical (different directions in different positions)
Effect of head position	Worsened by position, often single critical position	Little change, associated with more than one position
Associated neurologic findings	None	Usually present
Associated auditory findings	May be present, including tinnitus	None

gests a peripheral labyrinth disorder. Vertigo produced primarily by a change in position also suggests a peripheral disorder. Vestibular neuronitis and benign positional vertigo fit this pattern.

The presence of *auditory symptoms* suggests a peripheral cause of the vertigo, as in middle and inner ear problems, or a peripheral cause that progresses centrally, such as an acoustic neuroma. The abnormally hearing ear is usually the side of end-organ disturbance. Progressive unilateral hearing loss of several months' duration may be the earliest symptom of an acoustic neuroma. Tinnitus occurs in most patients with acoustic neuroma and, along with vertigo, is what often prompts patients to seek medical attention. Hearing loss, vertigo, and tinnitus form the characteristic triad of Ménière's disease.

Are there associated neurologic symptoms? The patient or family members should be questioned about the time of onset of ataxia or gait disturbances. Ataxia of recent and relatively sudden onset suggests cerebellar hemorrhage or infarction in the distribution of the posterior inferior cerebellar artery or the superior cerebellar artery. The salient feature of chronic cerebellar disorders is a slowly progressive ataxia. True ataxia may be difficult to discern from the unsteadiness that occurs when a patient with significant vertigo attempts to walk.

Vertiginous symptoms are common after head injury. The presence of recent head or neck trauma should be explored because vertiginous symptoms are common after both.[8,9] Head injury can cause vertigo occasionally from intercerebral injury and more commonly from labyrinth concussion. Neck injury can cause vertigo from strain of muscle proprioceptors. In addition, vertebral artery injury has been seen resulting from activities such as chiropractic manipulation and even hair shampooing with marked hyperextension in a salon.[10]

It has clearly been shown that isolated vertigo can be the only initial symptom of cerebellar and other posterior circulation bleeds, transient ischemic attacks (TIAs), and infarction.[11-13] One study showed that emergency physicians often did not make the correct diagnosis in patients with validated strokes or TIAs that presented with only vertigo.[6] Risk factor assessment and symptom patterns can be extremely helpful in deciding which patients warrant imaging and admission. Older age, male sex, hypertension, coronary artery disease, diabetes mellitis, and atrial fibrillation put patients at higher risk. In addition, frequent episodes lasting only minutes or prolonged episodes of a day or more are more often associated with central processes.[6,11,12] A recent retrospective study showed emergency physicians often failed to chart triggers and duration of dizziness, information that could potentially lead to increased likelihood of a more serious cause of symptoms.[14]

Past Medical History. Many medications have direct vestibulotoxicity. The most commonly encountered are the aminoglycosides, anticonvulsants, alcohols, quinine, quinidine, and minocycline. In addition, caffeine and nicotine can have wide-ranging autonomic effects that may exacerbate vestibular symptoms. The history of past and present illnesses should be explored, with specific questioning about the existence of diabetes, drug or alcohol use, and the risk factors mentioned earlier.

Physical Examination

Vital Signs. In some cases, pulses and blood pressure should be checked in both arms. Most patients with subclavian steal syndrome, which also can cause vertebrobasilar artery insufficiency, have pulse or systolic blood pressure differences between the two arms.

Head and Neck. Carotid or vertebral artery bruits suggest atherosclerosis. The neck is auscultated along the course of the carotid artery from the supraclavicular area to the base of the skull.

Vertigo can be caused by impacted cerumen or a foreign object in the ear canal. Accumulation of fluid behind the eardrum as a result of a middle ear infection may cause mild vertigo, as can occlusion of the eustachian tubes associated with an upper respiratory tract infection. A perforated or scarred eardrum may indicate a perilymphatic fistula, especially if the history includes previous trauma.

Examination of the eyes is key in assessing a patient with vertigo or disequilibrium. The focus is on any pupillary abnormalities indicating third cranial nerve or descending sympathetic tract involvement or optic disk signs of early increased intracranial pressure. Extraocular movements should be assessed carefully. Relatively subtle ocular movement abnormalities can be the only clue to a cerebellar hemorrhage. A sixth cranial nerve palsy ipsilateral to the hemorrhage may result from early brainstem compression by the expanding hematoma. Internuclear ophthalmoplegia is recognized when the eyes are in a normal position on straight-ahead gaze, but on eye movement the adducting eye (cranial nerve III) is weak or shows no movement while the abducting eye (cranial nerve VI) moves normally, although often displaying a coarse nystagmus. This finding indicates an interruption of the medial longitudinal fasciculus on the side of the third cranial nerve weakness. It indicates brainstem pathology and is virtually pathognomonic of multiple sclerosis.

Abnormal nystagmus is the cardinal sign of inner ear disease and the principal objective evidence of abnormal vestibular function. In nystagmus, the patient has difficulty maintaining the conjugate deviation of the eyes or has a postural control imbalance of eye movements.

The abnormal jerk nystagmus of inner ear disease consists of slow and quick components. The eyes slowly "drift" in the direction of the diseased, hypoactive ear, then quickly jerk back to the intended direction of gaze. Positional nystagmus, induced by rapidly changing the position of the head, strongly suggests an organic vestibular disorder. The characteristics of nystagmus are one of the most valuable tools for distinguishing peripheral from central causes of vertigo (Table 12-2).

Positional Testing. If nystagmus is not present at rest, positional testing can be helpful in determining its existence and characteristics. In the Hallpike maneuver, the patient is moved quickly from an upright seated position to a supine position, and the head is turned to one side and extended (to a head-down posture) approximately 30° from the horizontal plane off the end of the stretcher. The eyes should be observed for nystagmus and the patient queried for the occurrence of symp-

Table 12-2 Distinguishing Characteristics of Nystagmus with Central and Peripheral Vertigo

CHARACTERISTIC	CENTRAL	PERIPHERAL
Direction	Any direction	Horizontal or horizontorotary
Laterality	Unilateral or bilateral	Bilateral
Position testing effects:		
Latency	Short	Long
Duration	Sustained	Transient
Intensity	Mild	Mild to severe
Fatigability	Nonfatigable	Fatigable
Effect of visual fixation	Not suppressed, may be enhanced	Suppressed

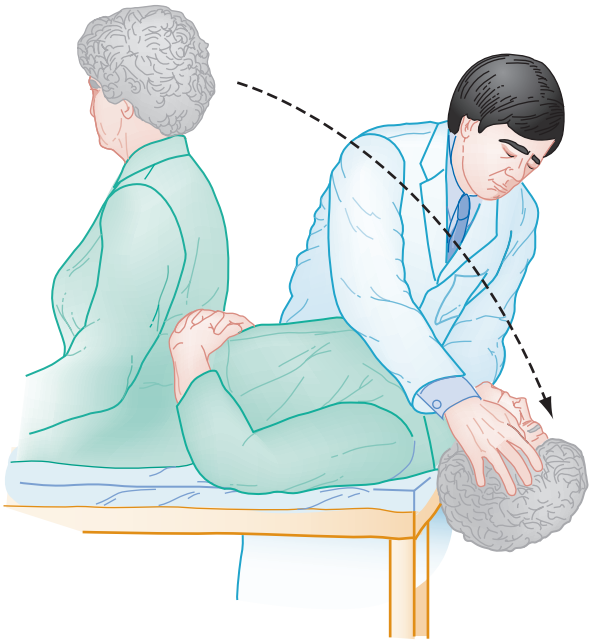

Figure 12-1. Testing for positional vertigo and nystagmus.

toms. This test should be repeated with the head turned to the other side. Positive elicitation of symptoms and signs to one side or the other generally indicates vestibular pathology on that same side. This test should be performed with caution if vertebrobasilar insufficiency (VBI) is suggested because sudden twisting movements theoretically might dislodge atheromatous plaques (Fig. 12-1).

Neurologic Examination. The presence of cranial nerve deficits suggests a space-occupying lesion in the brainstem or cerebellopontine angle. The corneal reflex is a sensory cranial nerve V and motor cranial nerve VII circuit. Its diminution or absence can be one of the early signs of an acoustic neuroma. Vertigo caused by eighth cranial nerve involvement is likely to be accompanied by a unilateral hearing loss. Patients cannot hear a tuning fork when it is held alongside the affected ear, but they can hear it when it is held against the mastoid process. Involvement of the eighth cranial nerve suggests an acoustic tumor. Seventh cranial nerve involvement causes facial palsy that affects the entire side of the face. In supranuclear facial paralysis, the forehead is spared because these muscles receive bilateral cortical innervation.

The patient should be evaluated specifically for evidence of cerebellar dysfunction. This examination must be performed in bed and standing because truncal ataxia may be occult on testing of limbs in bed and may become obvious only when the patient has to sit, stand, or walk unaided. Dysmetria is the inability to arrest a muscular movement at the desired point. Dysmetria should be assessed using finger-to-finger/finger-to-nose pointing, and dysdiadochokinesia (an inability to perform coordinated muscular movement smoothly) is assessed with rapid alternating movements. The gait must be evaluated when the patient gives a history suggesting ataxia, although examination may be impossible during an attack of vertigo. Any marked abnormality (e.g., consistent falling or a grossly abnormal gait) should suggest a central lesion, especially in a patient whose vertiginous symptoms have subsided. The main features of a cerebellar gait are a wide base (separation of legs), unsteadiness, irregularity of steps, tremor of the trunk, and lurching from side to side. The unsteadiness is most prominent on arising quickly from a sitting position, turning quickly, or stopping suddenly while walking. Patients with gait ataxia cannot perform heel-to-toe walking.

Ancillary Testing

Most routine laboratory testing is not helpful in the evaluation of a vertiginous patient. A finger-stick blood glucose test should be performed in most cases because hypoglycemia can present as vertigo.[15] Blood counts and blood chemistries are sometimes helpful when it is difficult to distinguish whether "dizziness" is vertigo or near-syncope. An electrocardiogram should be obtained if there is any possibility of myocardial ischemia.

Radiologic Imaging. If cerebellar hemorrhage, cerebellar infarction, or other central lesions are suggested, emergent computed tomography (CT) or magnetic resonance imaging (MRI) of the brain is indicated. MRI, when available, has become the diagnostic modality of choice when cerebellar processes other than acute hemorrhage are possible. MRI is particularly useful for the diagnosis of acoustic neuromas and for sclerotic and demyelinating lesions of the white matter, as seen in multiple sclerosis. Acute vertigo by itself does not usually warrant urgent CT or MRI in all patients, particularly patients in whom a clear picture of peripheral vertigo emerges. But as mentioned earlier, many studies strongly support the use of imaging in patients of advanced age or at risk for cerebrovascular disease.[6,11,12,16]

Conventional angiography or magnetic resonance angiography can be used in cases of suspected VBI to document the presence of vascular disease. It is used most often in patients with changing neurologic signs and symptoms, suggesting impending posterior circulation occlusion.

Audiology and electronystagmography are helpful in the follow-up evaluation of a vertiginous patient. Audiology can locate the anatomic site of a lesion causing vertigo. Electronystagmography is a collection of examinations that, when abnormal, suggest vestibular dysfunction but do not yield the specific diagnosis.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for other peripheral, central, and systemic causes of vertigo is large (see Box 12-1). More detailed information is given on selected causes in Table 12-3, including the most common peripheral causes of true vertigo: benign positional vertigo, labyrinthitis, Ménière's disease, and vestibular neuronitis.

Diagnostic Algorithm

Most cases of vertigo are of peripheral origin and are not usually life-threatening. The diagnostic approach must focus on identifying entities that either immediately or in the near future can lead to death or significant morbidity (Fig. 12-2).

MANAGEMENT

Management is based on an accurate diagnosis that distinguishes the serious central causes of vertigo from the less serious, albeit more debilitating, peripheral causes (Fig. 12-3). Any suggestion of cerebellar hemorrhage should warrant immediate imaging with CT or MRI and neurosurgery consultations. VBI should be considered in any patient of advanced age or at high risk of cerebrovascular disease with isolated, new-onset vertigo without an obvious cause.[6,11,17,18] Because of the possibility of progression of new-onset VBI in the first 24 to 72 hours, hospital or observation unit admission and consid-

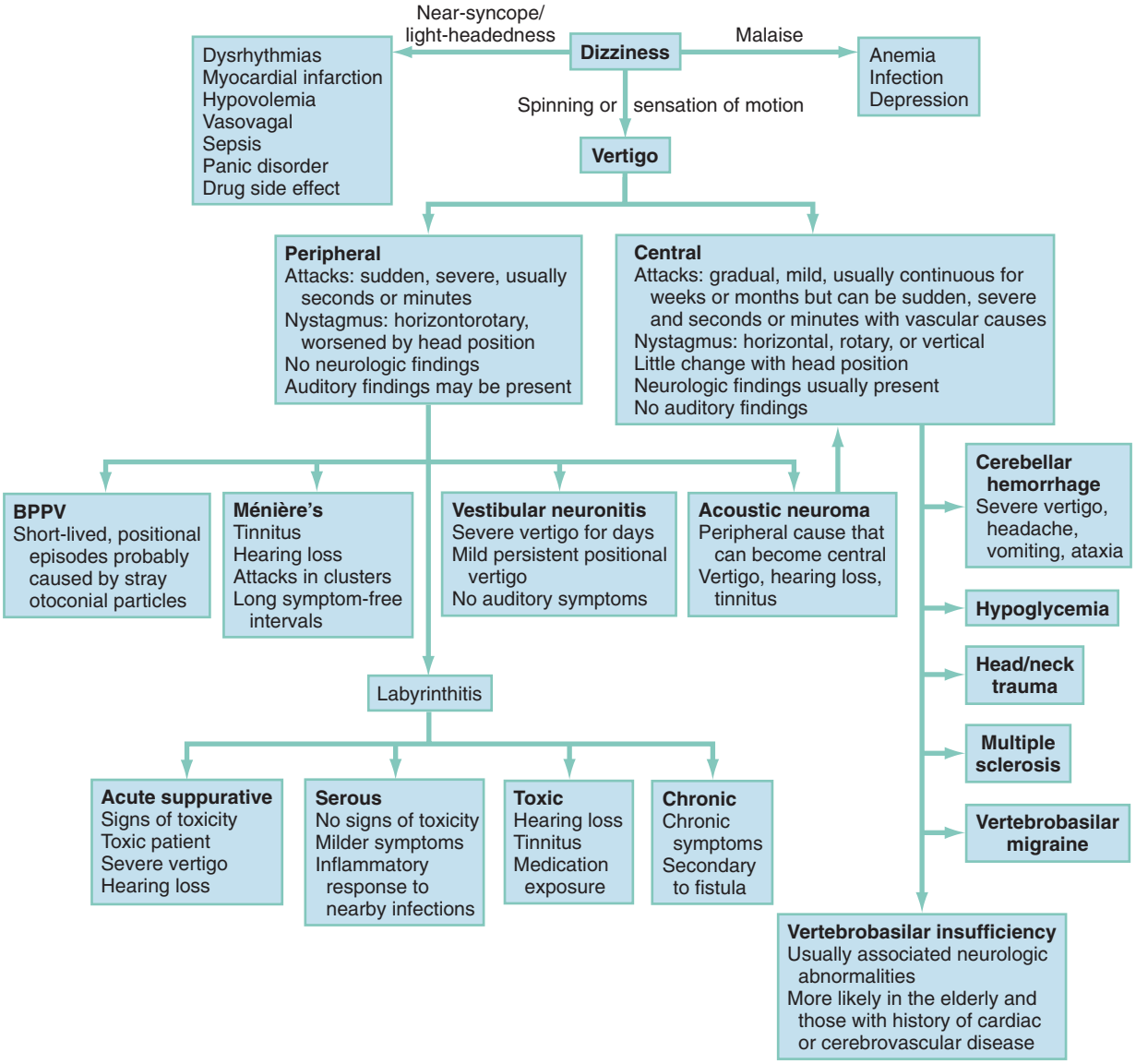

Figure 12-2. Diagnostic algorithm for dizziness and vertigo. BPPV, benign paroxysmal positional vertigo.

eration of early magnetic resonance angiography probably are warranted, even in a stable patient. Changing or rapidly progressive symptoms should raise awareness of impending posterior circulation occlusion. If CT or MRI excludes hemorrhage as the source of the patient's symptoms, an immediate neurologic consultation, emergency angiography, and possibly anticoagulation are indicated.

Acute bacterial labyrinthitis requires admission, intravenous antibiotics, and, occasionally, surgical drainage and débridement. In cases of toxic labyrinthitis, the offending medication should be discontinued immediately.

Some cases of Ménière's disease have been treated successfully by vasodilation and diuretic therapy. Diets low in sodium and caffeine and cessation of smoking also have been helpful. Chemical ablation of vestibular function with gentamicin and streptomycin is an option in severe Ménière's disease. In one small controlled study, corticosteroids were more effective than placebo in treating the acute symptoms of vestibular neuritis.

The treatment of acute attacks of vertigo caused by peripheral disorders is symptomatic. Intravenous diazepam in 2- to 5-mg doses is extremely effective in stopping vertigo. It has a sedative effect that acts on the limbic system, the thalamus, and the hypothalamus. Outpatient treatment with diazepam can be continued at doses of 5 to 10 mg three times daily.

The neurons involved in vestibular reactions are mediated by acetylcholine. Anticholinergic drugs or antihistamines with anticholinergic activity are extremely useful in treating vertigo. Meclizine hydrochloride (Antivert) is usually prescribed as 25 mg every 8 hours, but has a wide therapeutic margin and can be taken much more frequently to control symptoms. Diphenhydramine hydrochloride (Benadryl), 25 to 50 mg every 6 to 8 hours, and dimenhydrinate (Dramamine, Gravol) are also effective, but are more sedating than meclizine. Either drug also can be given intravenously. Transdermal scopolamine has shown disappointing results for treatment of peripheral vertigo but may be considered a third-line or fourth-line option. Promethazine hydrochloride (Phenergan), 25 mg orally or rectally every 6 to 8 hours, is effective because of its strong antiemetic and mild anticholinergic properties; it also can be used intravenously in doses of 12.5 to 25 mg. Buccal

Table 12-3 Differential Diagnosis of Patients with True Vertigo

CAUSE	HISTORY	ASSOCIATED SYMPTOMS	PHYSICAL
Peripheral			
1. Benign paroxysmal positional vertigo	Short-lived, positional, fatigable episodes	Nausea, vomiting	Single position can precipitate vertigo. Horizontorotary nystagmus often can be induced at bedside.
2. Labyrinthitis			
A. Serous	Mild to severe positional symptoms. Usually coexisting or antecedent infection of ear, nose, throat, or meninges	Mild to severe hearing loss can occur	Usually nontoxic patient with minimal fever elevation
B. Acute suppurative	Coexisting acute exudative infection of the inner ear. Severe symptoms	Usually severe hearing loss, nausea, vomiting	Febrile patient showing signs of toxicity. Acute otitis media
C. Toxic	Gradually progressive symptoms: Patients on medication causing toxicity	Hearing loss that may become rapid and severe, nausea and vomiting	Hearing loss. Ataxia common feature in chronic phase
3. Ménière's disease	Recurrent episodes of severe rotational vertigo usually lasting hours. Onset usually abrupt. Attacks may occur in clusters. Long symptom-free remissions	Nausea, vomiting, tinnitus, hearing loss	Positional nystagmus not present
4. Vestibular neuronitis	Sudden onset of severe vertigo, increasing in intensity for hours, then gradually subsiding over several days. Mild positional vertigo often lasts weeks to months. Sometimes history of infection or toxic exposure that precedes initial attack. Highest incidence is found in third and fifth decades	Nausea, vomiting. Auditory symptoms do not occur	Spontaneous nystagmus toward the involved ear may be present.
5. Acoustic neuroma	Gradual onset and increase in symptoms. Neurologic signs in later stages. Most occur in women between 30 and 60	Hearing loss, tinnitus. True ataxia and neurologic signs as tumor enlarges	Unilateral decreased hearing. True truncal ataxia and other neurologic signs when tumor enlarges. May have diminution or absence of corneal reflex. Eighth cranial nerve deficit may be present.
Central			
1. Vascular disorders			
A. Vertebrobasilar insufficiency	Should be considered in any patient of advanced age with isolated new-onset vertigo without an obvious cause. More likely with history of atherosclerosis. Initial episode usually seconds to minutes	Often headache. Usually neurologic symptoms including dysarthria, ataxia, weakness, numbness, double vision. Tinnitus and deafness uncommon	Neurologic deficits usually present, but initially neurologic examination can be normal.
B. Cerebellar hemorrhage	Sudden onset of severe symptoms	Headache, vomiting, ataxia	Signs of toxicity. Dysmetria, true ataxia. Ipsilateral sixth cranial nerve palsy may be present.
C. Occlusion of posterior inferior cerebellar artery (Wallenberg's syndrome)	Vertigo associated with significant neurologic complaints	Nausea, vomiting, loss of pain and temperature sensation, ataxia, hoarseness	Loss of pain and temperature sensation on the side of the face ipsilateral to the lesion and on the opposite side of the body, paralysis of the palate, pharynx, and larynx. Horner's syndrome (ipsilateral ptosis, miosis, and decreased facial sweating)
D. Subclavian steal syndrome	Classic picture is syncopal attacks during exercise, but most cases present with more subtle symptoms.	Arm fatigue, cramps, mild light-headedness may be only other symptoms than vertigo	Diminished or absent radial pulses in affected side or systolic blood pressure differentials between the two areas occur in most patients.

Table 12-3 Differential Diagnosis of Patients with True Vertigo—cont'd

CAUSE	HISTORY	ASSOCIATED SYMPTOMS	PHYSICAL
2. Head trauma	Symptoms begin with or shortly after head trauma. Positional symptoms most common type after trauma. Self-limited symptoms that can persist weeks to months	Usually mild nausea	Occasionally, basilar skull fracture
3. Neck trauma	Usual onset 7–10 days after whiplash injury. Symptoms may last weeks to months. Episodes seconds to minutes when turning head	Neck pain	Neck tenderness, pain on movement, and positional nystagmus and vertigo when head is turned to side of the whiplash
4. Vertebrobasilar migraine	Vertigo almost always followed by headache. Patient has usually had similar episodes in past. Most patients have a family history of migraine. Syndrome usually begins in adolescence	Dysarthria, ataxia, visual disturbances, or paresthesias usually precede headache	No residual neurologic or otologic signs are present after attack.
5. Multiple sclerosis	Vertigo presenting symptoms in 7–10% and appears in the course of the disease in a third. Onset may be severe and suggest labyrinth disease. Disease onset usually between ages 20 and 40. Often history of other attacks with varying neurologic signs or symptoms	Nausea and vomiting, which may be severe	May have horizontal, rotary, or vertical nystagmus. Nystagmus may persist after the vertiginous symptoms have subsided. Bilateral internuclear ophthalmoplegia and ataxic eye movements suggest multiple sclerosis.
6. Temporal lobe epilepsy	Can be initial or prominent symptom in some patients with the disorder	Memory impairment, hallucinations, trancelike states, seizures	May have aphasia or convulsions
7. Hypoglycemia	Should be considered in diabetics and any other patient with unexplained symptoms	Sweating, anxiety	Tachycardia, mental status change may be present.

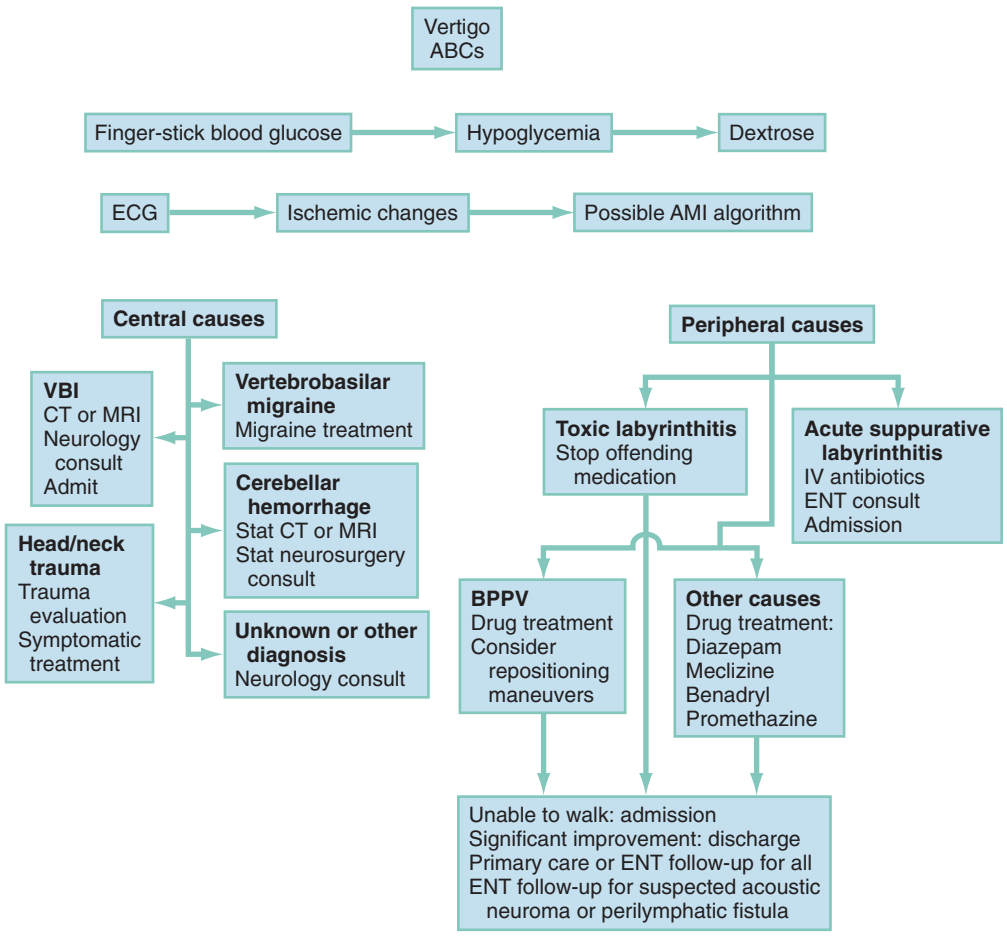

Figure 12-3. Management algorithm for vertigo. AMI, acute myocardial infarction; BPPV, benign paroxysmal positional vertigo; CT, computed tomography; ECG, electrocardiogram; ENT, ear, nose, and throat; MRI, magnetic resonance imaging.

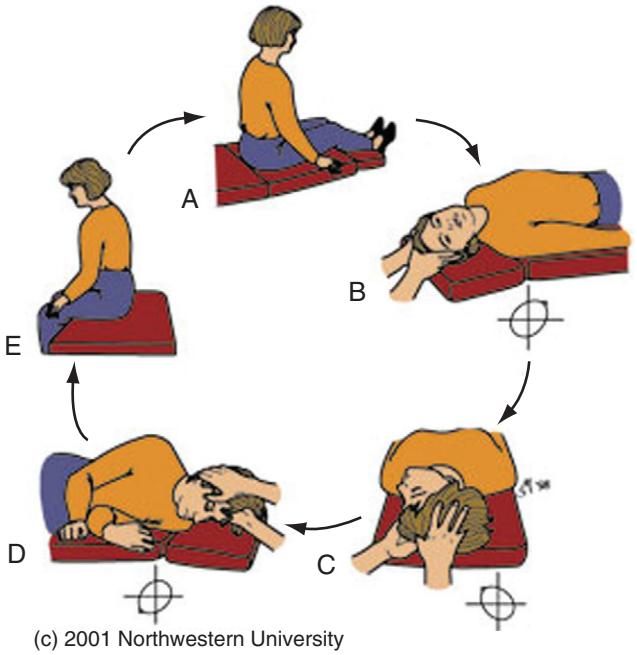

Figure 12-4. The Epley maneuver for benign paroxysmal peripheral vertigo, also known as the particle repositioning or canalith repositioning procedure. Image used with permission of ⟨http://www.dizziness-and-balance.com/disorders/bppv/bppv.html⟩ Timothy C. Hain, Professor of Neurology, Feinberg School of Medicine, Northwestern University, http://www.dizziness-and-balance.com/disorders/bppv/bppv.html.

prochlorperazine (Compazine, Stemetil) also has been shown to be a safe and effective treatment for vertigo. Avoidance of stimulants (e.g., caffeine, pseudoephedrine, nicotine) may ease symptoms in some cases. In addition, canalith repositioning procedures, such as the Epley and Semont maneuvers, have been shown to be extremely effective in treating benign paroxysmal positional vertigo.[19-21] The Epley maneuver involves sequential movement of the head into four positions, staying in each position for approximately 30 seconds, as demonstrated in Figure 12-4. One study has even shown these maneuvers have resulted in long-term efficacy in successful symptom treatment.[22]

One of the most useful tools the physician has is patient reassurance. Most patients with vertigo have self-limited disease processes that have a specific organic cause. By combining patient education and reassurance with judicious use of medications, the treatment of a dizzy patient can be rewarding for the patient and the physician.

DISPOSITION

Documented or suggested cerebellar hemorrhage or infarction, VBI, and acute bacterial labyrinthitis require workup and hospitalization. In patients older than age 55 years, particularly patients with vascular disease, admission for observation and imaging of cerebral vasculature is often warranted. Most younger patients with peripheral causes of vertigo can be discharged from the emergency department after symptoms are controlled. Some patients may have such severe symptoms (e.g., vomiting, inability to walk) despite a trial of medication that they require admission for intravenous hydration and observation. All discharged patients should receive primary care; neurology; or a follow-up consult with an ear, nose, and throat specialist. This follow-up is especially important for possible cases of acoustic neuroma and toxic labyrinthitis.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 13 Confusion

J. Stephen Huff

PERSPECTIVE

The term *confusion* connotes an alteration in higher cerebral functions, such as memory, attention, or awareness. Confusion is a symptom, not a diagnosis. Clinical jargon includes "altered mental status," "delta MS" (change in mental status), "altered mentation," and "change from baseline." Additionally, the ability to sustain and focus attention is impaired. Symptoms of confusion may fluctuate, as may the level of consciousness. Implicit in the definition is a recent change in behavior. Chronic mental status changes such as dementia typically have a different clinical chronology. Other forms of altered mentation include states of diminished alertness on the coma spectrum; these presentations may result from some of the same pathophysiologic processes causing confusion and are discussed in Chapter 15. Confusion may range in severity from a mild disturbance of short-term memory to a global inability to relate to the environment and process sensory input. This extreme state is termed *delirium*. Delirium has two subtypes: hyperactive and hypoactive.[1] Hyperactive delirium is characterized as an acute confusional state associated with increased alertness, increased psychomotor activity, and disorientation and is often accompanied by hallucinations. In hypoactive delirium (sometimes referred to as quiet delirium), the confusional state is present but the patient has a reduction in alertness and behavior. Confusion has many causes, and an orderly approach is necessary to discover the causative diagnosis.

Epidemiology

Physicians underestimate the incidence of confusion in patients.[2,3] Often, confusion is accepted as an incidental or secondary component of another condition. A patient with injuries from a motor vehicle crash or with dyspnea may be confused, but the primary condition overshadows the underlying abnormal mental status. When confusion exists as an isolated or unexplained finding, it is more likely to receive full and immediate consideration by the clinician. Confusion is estimated to occur in 2% of emergency department (ED) patients, 10% of all hospitalized patients, and 50% of elderly hospitalized patients.[2,4]

Pathophysiology

Conceptually, consciousness may be divided into elements of alertness or arousal and elements constituting content of consciousness. Confusion is largely a problem of the content portion of consciousness. Many different clinical processes may disrupt optimal cortical functioning and result in confusion. The pathophysiology is not straightforward. Widespread cortical dysfunction is thought to result from substrate deficit (hypoglycemia or hypoxemia), neurotransmitter dysfunction, or circulatory dysfunction. Compounding this problem is the idea that the reserve of central nervous system (CNS) function varies from individual to individual; individuals with a preexisting impairment may become confused after even minor changes in their normal state.

DIAGNOSTIC APPROACH

Differential Considerations

The observation of acute confusion prompts a search for an underlying cause. Four groups of disorders encompass most causes of diffuse cortical dysfunction: (1) systemic diseases secondarily affecting the CNS, (2) primary intracranial disease, (3) exogenous toxins, and (4) drug withdrawal states (Box 13-1).[1] Focal cortical dysfunction, such as from tumor or stroke, typically does not cause confusion, although exceptions are encountered. Likewise, subcortical or brainstem dysfunction most frequently results in a diminished level of alertness and consciousness, not confusion.

Rapid Assessment and Stabilization

Most patients with acute confusion do not require immediate interventions. Three crucial exceptions are hypoglycemia, hypoxemia, and shock. A complete set of vital signs, including temperature and oxyhemoglobin saturation, and a bedside blood glucose level should be determined promptly for all confused patients. Oral or intravenous glucose therapy is indicated if low blood glucose is discovered. Supplemental oxygen and intravenous fluid are administered as necessary.

Patients should be protected from harming themselves or others. Close observation may need to be supplemented by medications or physical restraint. Family members may offer valuable assistance in observing and comforting the patient.

In a patient with abnormal or unstable vital signs, initial diagnostic and management efforts are directed toward treatment of the systemic condition. A confused patient with acute pulmonary edema, hypoxia, and confusion obviously requires evaluation and treatment of the pulmonary edema, not a screening test for cognitive functioning.

BOX 13-1 MAJOR CATEGORIES: DIFFERENTIAL CONSIDERATIONS

Primary intracranial disease
Systemic diseases secondarily affecting the central nervous system
Exogenous toxins
Drug withdrawal

BOX 13-2 FINDINGS THAT MAY HELP DIFFERENTIATE BETWEEN ORGANIC AND FUNCTIONAL CAUSES OF CONFUSION

Organic	Functional (psychiatric)
History	History
Acute onset	Onset over weeks to months
Any age	Onset ages 12 to 40 years
Mental status examination	Mental status examination
Fluctuating level of consciousness	Alert
Disoriented	Oriented
Attention disturbances	Agitated, anxious
Poor recent memory	Poor immediate memory
Hallucinations: visual, tactile, auditory	Hallucinations: most commonly auditory
Cognitive changes	Delusions, illusions
Physical examination	Physical examination
Abnormal vital signs	Normal vital signs
Nystagmus	No nystagmus
Focal neurologic signs	Purposeful movement
Signs of trauma	No signs of trauma

Generally, in patients with schizophrenia and other psychiatric disorders, tests of cognition, orientation, and attention are normal unless the condition is severe. The term *psychosis* implies a disorder of reality testing and thought organization severe enough to interfere with normal daily functioning. Psychosis is a nonspecific syndrome, and careful evaluation is required to differentiate between psychiatric and organic origins (e.g., drug intoxication or other systemic process) (Box 13-2).

Pivotal Findings

A patient with an altered state of consciousness including confusion is evaluated by taking a focused history and conducting a pertinent examination, performing rapid bedside screening investigations, and observing the response to certain therapies (e.g., dextrose or naloxone). Additional evaluation may include laboratory testing and diagnostic imaging with various modalities. Useful information that provides the diagnosis or strongly suggests the etiology is found roughly in descending order from the patient's history, the examination including results of rapid bedside testing, and the response to ED therapies; the results of laboratory testing and diagnostic imaging are less often useful.[5]

History

Confusion is often reported by family members or caregivers; frequently the patient is not aware of the confusion and seemingly glosses over problems. Families may articulate the complaint as confusion but also may describe rambling, disorientation, speaking to persons not there, the patient's inability to find his or her way around familiar surroundings, or simply "not being right." An essential goal of the history is to determine when the patient last exhibited "normal" thinking and behavior.

Attention deficit is the common denominator in confusional states. The initial task in evaluating the patient is to define the symptoms and severity of confusion. The specific behaviors that are of concern to the patient or caregivers should be defined. Often, the family is the most valuable source for information; a physician or other caregiver with an established relationship with the patient also may be helpful. The duration of the confusion, any recent changes in medications, and recent illnesses are important points in the clinical history. Hallucinations are not unique to psychiatric illness and can commonly occur in confusion states, especially delirium. Hallucinations in delirium tend to be visual (with or without auditory components), powerful, fleeting, and poorly organized. A history of medication or substance abuse and any recent changes, especially cessation of benzodiazepines or ethanol, should be sought.

ORIENTATION TO TIME
"What is the date?"

REGISTRATION
"Listen carefully. I am going to say three words.
You say them back after I stop.
Ready? Here they are . . .
HOUSE (pause), CAR (pause), LAKE (pause).
Now repeat those words back to me."
[Repeat up to 5 times, but score only the first trial.]

NAMING
"What is this?" [Point to a pencil or pen.]

READING
"Please read this and do what it says."
[Show examinee the words on the stimulus form.]
CLOSE YOUR EYES

Figure 13-1. Mini-mental state examination sample items. (Reproduced by special permission of the Publisher, Psychological Assessment Resources, Inc., 16204 North Florida Avenue, Lutz, Florida 33549, from the Mini Mental State Examination, by Marshal Folstein and Susan Folstein. Copyright © 1975, 1998, 2001 by Mini Mental LLC, Inc. Published 2001 by Psychological Assessment Resources, Inc. Further reproduction is prohibited without permission of PAR, Inc. The MMSE can be purchased from PAR, Inc., by calling (800) 331-8378 or (813) 968-3003.)

Physical Examination

The patient's confusion may be obvious at the bedside. In other cases, confusion may be subtle, and informal assessment of mental status and cognitive abilities may fail to detect it. The mini-mental state examination (MMSE) (Fig. 13-1) commonly is recommended as a screening instrument but is used infrequently in the ED because of the time required to administer it.[6,7] A more rapidly performed screening tool, the Quick Confusion Scale (QCS; Fig. 13-2), has been developed and tested in ED patients.[8-10] This tool objectively measures elements of the patient's mental status in 2 to 3 minutes and correlates well with the MMSE.[9,11] The tasks measured by either the MMSE or the QCS require adequate attention on

ITEM	SCORE (highest number in category indicates correct response; decreased scoring indicates increased number of errors)	WEIGHT	SCORE
What year is it now?	0 or 1 (score 1 if correct; 0 if incorrect)	x2	
What month is it?	0 or 1 (score 1 if correct; 0 if incorrect)	x2	
Repeat phrase and remember it: "John Brown, 42 Market Street, New York"			
About what time is it? (answer correct if within the hour)	0 or 1 (score 1 if correct; 0 if incorrect)	x2	
Count backwards from 20 to 1	0, 1, or 2 (score 2 if correct; 1 if 1 error; score 0 if more than 2 errors)	x1	
Say the months in reverse	0, 1, or 2 (score 2 if correct; 1 if 1 error; score 0 if more than 2 errors)	x1	
Repeat the memory phrase (each underlined portion is worth 1 point)	0, 1, 2, 3, 4, 5 (score 5 if correctly performed; each error drops score by one)	x1	
		TOTAL	_____

Final score is sum of the totals; score less than 15 suggests the presence of altered cognition and need for further assessment.

Figure 13-2. Quick Confusion Scale.

the part of the patient. If the patient's attention span is greatly impaired, detailed testing may be impossible. Digit repetition forward (five or six digits) and backward (four digits) is a brief screen for attention function. Alternatively, spelling a commonly used word backward ("world" is frequently used) measures a patient's ability to concentrate. Screening tests may detect confusion not obvious in casual conversation, identifying the need for further investigations.[12,13]

The physical examination may suggest a cause for confusion such as congestive heart failure or pneumonia. A fever suggests an infection as the cause of altered mental status and should prompt a search for the source, particularly urinary tract infection in the elder patient. Any new focal neurologic findings suggest a possible mass lesion or stroke and should trigger neuroimaging. In this regard, testing of gait and tandem gait, if possible, may be invaluable. Aphasia, fluent or nonfluent, is a focal sign suggesting a lesion in the dominant cerebral hemisphere. In confusional states, speech may be abnormal and is often incoherent, and the rate of speech may be either rapid or slowed. Involuntary movements, such as asterixis or tremor, may be present. The various toxidromes may assist in the identification of an intoxication or drug effect as the cause of confusion.

Laboratory Tests

The results of the history and physical examination frequently guide the clinician in the choice of laboratory tests most likely to yield valuable diagnostic information. Pulse oximetry may reveal hypoxia, or bedside glucose testing may reveal hypoglycemia or hyperglycemia. In the presence of a fever, chest radiography and urinalysis often reveal the source of the infection causing the altered mentation. In elder patients, urinalysis should be performed whether or not fever is present. Other tests commonly available in the ED and useful in the evaluation of a confused patient are serum electrolyte testing (especially sodium) and electrocardiography. Electrocardiography is indicated in elderly patients because myocardial infarction may present as confusion. The complete blood count, although commonly performed, is unlikely to provide useful diagnostic clues. Arterial blood gas testing is rarely indicated or useful, unless pulse oximetry is not reliable.

If common and simple tests do not suggest a solution, more complex testing should be initiated in the ED, observation unit, or inpatient service. The clinical situation and overall condition of the patient determine the speed and direction of evaluation. Additional laboratory work is often of decreasing yield but may reveal the cause of confusion. Serum ammonia, calcium, thyroid function, and selected drug and toxicologic testing may be ordered in this second tier of evaluation. Blood and urine cultures should be obtained in the febrile patient when hospital admission is anticipated and a clear infectious source is not evident. Paracentesis or thoracentesis may be appropriate if ascites or pleural effusion is present. Cranial computed tomography (CT) scanning is usually done to screen for CNS lesions in the absence of another identified source for the confusion. Focal findings on CT increase the yield of this test, but unanticipated abnormalities are often found on neuroimaging. Lumbar puncture may discover or exclude CNS infection if no other source has been identified. Cerebrospinal fluid examination may clarify a diagnosis of bacterial meningitis, encephalitis, aseptic meningitis, or subarachnoid hemorrhage. If the cause of confusion remains unclear or if the patient is unable to function safely in his or her current environment, admission may be necessary for additional ongoing assessment, including diagnostic testing not usually available in the ED, such as magnetic resonance imaging or electroencephalography.[5]

BOX 13-3 CRITICAL AND EMERGENT DIAGNOSES

Critical

Hypoxia/diffuse cerebral ischemia
- Respiratory failure
- Congestive heart failure
- Myocardial infarction
- Shock

Systemic processes
- Hypoglycemia

CNS infections

Hypertensive encephalopathy

Elevated intracranial pressure—medical and surgical origin

Emergent

Hypoxia/diffuse cerebral ischemia
- Severe anemia

Systemic diseases
- Electrolyte and fluid disturbance
- Endocrine disease
  - Thyroid
  - Adrenal
- Hepatic failure
- Nutrition/Wernicke's encephalopathy
- Sepsis, infection

Intoxications and withdrawal
- CNS sedatives
- Ethanol
- Other medication side effects, particularly anticholinergics

CNS disease
- Trauma
- Infections
- Stroke
- Subarachnoid hemorrhage
- Epilepsy/seizures
  - Postictal state
  - Nonconvulsive status epilepticus
  - Complex partial status epilepticus

Neoplasm

Note: These represent a partial diagnosis; causes are myriad. "Critical" in this case means conditions that need immediate assessment and correction within moments, such as oxygenation and ventilation problems or hypoglycemia. Because confusion represents CNS failure, other problems may be considered critical as well and may require intensive care unit admission, depending on severity.
CNS, central nervous system.

DIFFERENTIAL DIAGNOSIS

Certain critical and emergent diagnoses require prompt recognition to prevent morbidity or mortality (Box 13-3). The diagnosis of confusion implies the exclusion of other states of altered mental status, such as coma and decompensated psychiatric syndromes. A new focal neurologic deficit points to a focal defect of the CNS, which is less likely to cause the global cortical dysfunction necessary for confusion. Stroke rarely causes confusion, but resulting disturbances in speech or understanding may mimic a confusional state. The diagnosis of stroke is relatively straightforward if a new motor deficit is present. Occasionally, other focal neurologic abnormalities may mimic a confusional state. A person with a new visual field deficit and visual neglect may have difficulty ambulating in familiar surroundings and be labeled as confused, but this

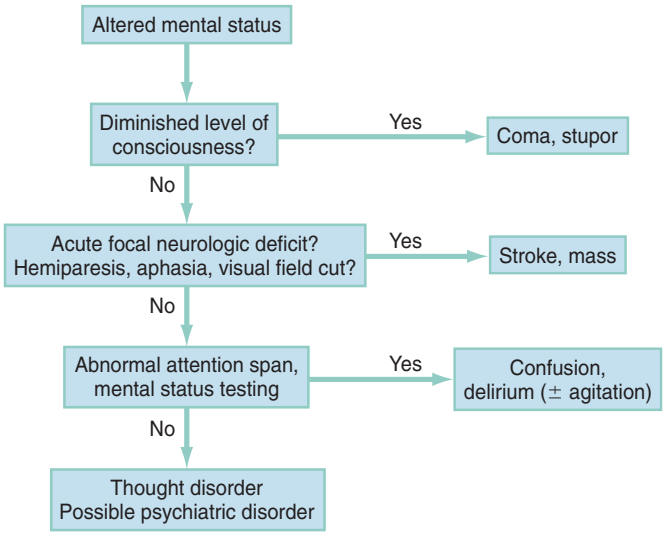

Figure 13-3. Diagnostic algorithm for confusion.

reflects focal neurologic injury and not a confusional state from global CNS dysfunction. Careful assessment of mental status assists in resolving the diagnostic dilemma. Frontal lobe dysfunction from stroke, subdural hematoma, or tumor may result in personality changes and the report of "confusion" by family or friends.

Altered mental status may be divided into three different categories depending on the findings of diminished level of consciousness, acute focal neurologic deficit, or abnormal attention span. Placement into one of these categories may guide the differential assessment and therapy (Fig. 13-3).

EMPIRICAL MANAGEMENT

Ideally, treatment is directed at the underlying cause of the confusion. Investigations continue until a likely diagnosis is discovered or consultation and admission are deemed necessary (Fig. 13-4). Many febrile patients are found to have a systemic infectious cause of the confusion. Urinary tract infections and pneumonia are the more common sources, but soft tissue infections also warrant consideration. CNS infections are encountered less frequently but have potentially devastating consequences if not recognized promptly. Antibiotic treatment for coverage of common causes of meningitis may be considered in ill febrile patients while definitive evaluation is in progress.

Postictal confusion is common in patients with seizures but should improve within 20 to 30 minutes. If the patient remains unconscious or confused after a seizure, the possibility of ongoing or intermittent seizure activity (i.e., nonconvulsive seizures) should be considered. Nonconvulsive status epilepticus, an epileptic twilight state, is unusual but does occur, and may be particularly difficult to recognize in the elderly[14] (see also Chapter 15).

Sometimes it may be necessary to treat confusion or agitation for patient safety. Environmental manipulations, such as dim lighting or psychosocial support, may be helpful. Confinement or physical restraint may be necessary at times for patient safety; institutional guidelines should be followed. Benzodiazepines or butyrophenones may be used if necessary to decrease agitation. These medications may alter mental status further, making evaluation more difficult.

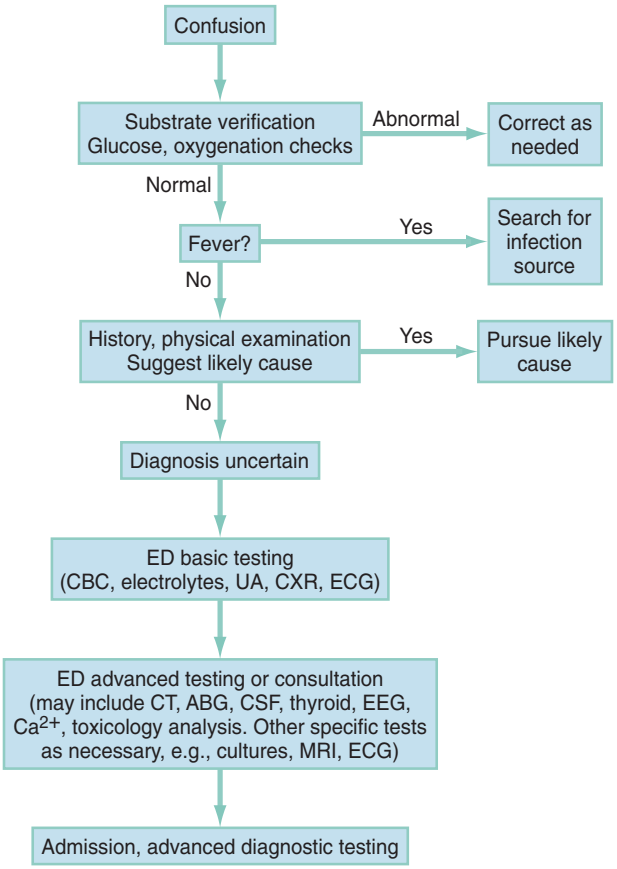

Figure 13-4. Management algorithm for confusion. ABG, arterial blood gas; CBC, complete blood count; CT, computed tomography; CSF, cerebrospinal fluid; CXR, chest x-ray; ECG, electrocardiogram; MRI, magnetic resonance imaging; UA, urinalysis.

DISPOSITION

Most patients presenting with confusion are admitted to the hospital or ED observation unit for additional diagnostic procedures, extended observation, and treatment. Exceptions include patients with rapidly resolved confusional states after treatment for insulin-induced hypoglycemia, after generalized seizures of known origin, or after recovering from self-limiting intoxicants or withdrawal states, such as those related to ethanol or recreational drugs. These patients may be observed and then discharged after successful identification and resolution of acute confusional state. Unresolved confusion or unexplained findings on repeat mental status screen should prompt admission or careful reevaluation before considering discharge.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 14 Depressed Consciousness and Coma

Jeremy L. Cooke

PERSPECTIVE

Epidemiology

Depressed consciousness is a common presenting complaint in the emergency department (ED). It represents a spectrum of disease that ranges from sleepiness or decreased alertness to frank coma. The majority of cases of depressed consciousness and coma are caused by metabolic or systemic derangements, and the remainder are caused by structural lesions.[1] The differential diagnosis for depressed level of consciousness often overlaps that for confusion (see Chapter 13).

Pathophysiology

Consciousness includes the properties of *arousal*, which is defined as the awareness of one's self or surroundings, and cognition. *Cognition* is the combination of *orientation*, the accurate perception of what is experienced, *judgment*, the ability to process input data to generate more meaningful information, and *memory*, the ability to store and retrieve information. The *ascending reticular activating system* (ARAS) is the neuroanatomic structure primarily responsible for arousal. It is located in the paramedian tegmental zone in the dorsal part of the brainstem (Fig. 14-1). The input of somatic and sensory stimuli to the cerebral cortex is controlled by the ARAS and functions to initiate arousal from sleep. The brain's cognition centers are located primarily in the cerebral cortex.

Insults to the cerebral cortex or brainstem can each independently cause depressed consciousness or coma. These structures are vulnerable to metabolic derangements, toxins, or mechanical injury. Typically, both cerebral hemispheres need to be affected to induce coma and this also depends on the size and speed of progression of the insult. Localized, unilateral lesions in the cerebral cortex usually do not induce depressed consciousness or coma even if other cognitive functions are impaired. In contrast, a completely intact brainstem is necessary for arousal. Small focal lesions in the brainstem can affect the ARAS. If the ARAS is impaired, the cerebral cortex cannot be aroused and depressed consciousness or coma occurs.

Potential causes of depressed consciousness can be broken down into a few general categories. Metabolic or systemic causes of coma can include hypoxia, hypoperfusion, infection, toxic drug effects, or electrolyte disturbances. Hypoxia can be the result of congestive heart failure (CHF), pulmonary embolism, carbon monoxide poisoning, or severe pulmonary compromise such as occurs in chronic obstructive pulmonary disease (COPD), cystic fibrosis, and asthma. The various causes of shock can result in hypoperfusion states leading to depression of consciousness. These include anaphylactic, septic, hypovolemic, cardiogenic, and neurogenic origins of shock. Each type of shock has its own special characteristics, which are detailed in other chapters. Infection, both systemic (sepsis) and focal, can be another general cause of depressed consciousness. This is particularly true if central nervous system (CNS) structures are involved as in meningitis, encephalitis, or CNS abscess. Toxic drug effects ranging from recreational drug use and intentional overdoses to therapeutic doses with adverse side effects are common general causes of depressed consciousness seen in the ED. In the elderly, adverse side effects from prescription medications are common. In addition, electrolyte and glucose abnormalities can be caused by multiple conditions, including diabetes, renal dysfunction, malignancy, and medication interactions or dosing errors.

Structural causes of coma and depressed consciousness are those most commonly arising from head trauma, stroke, tumor, or infection. Traumatic causes can include subdural and epidural hematomas, intraparenchymal or subarachnoid hemorrhage, or simply contusion or concussion. Strokes occur with embolic, thrombotic, or hemorrhagic mechanisms, but it is extremely unusual for ischemic (i.e., nonhemorrhagic) stroke to depress consciousness unless a massive insult to both hemispheres has occurred (e.g., diffuse, severe cerebral edema after a massive infarct). Depression of consciousness with CNS infections may be caused by mass effect and is common with severe bacterial meningitis, cerebral abscess or empyema, or parasitic mass. Malignancies, whether primary or metastatic, can cause depressed consciousness if their mass effect is sufficient or if surrounding edema develops rapidly.

Special consideration should be given to specific populations of patients. The elderly, in particular, are susceptible to alterations in therapeutic medication dosage and drug-drug interactions. Even seemingly minor infections, such as urinary tract infections, upper respiratory infections, or viral gastroenteritis, may cause altered mental status (see Chapter 13), depressed consciousness, or coma. In addition, immunocompromised patients such as those with AIDS or those undergoing chemotherapy treatment for transplants, malignancy, or immunologic disease are vulnerable to a multitude of opportunistic infections not commonly seen in the general patient population.

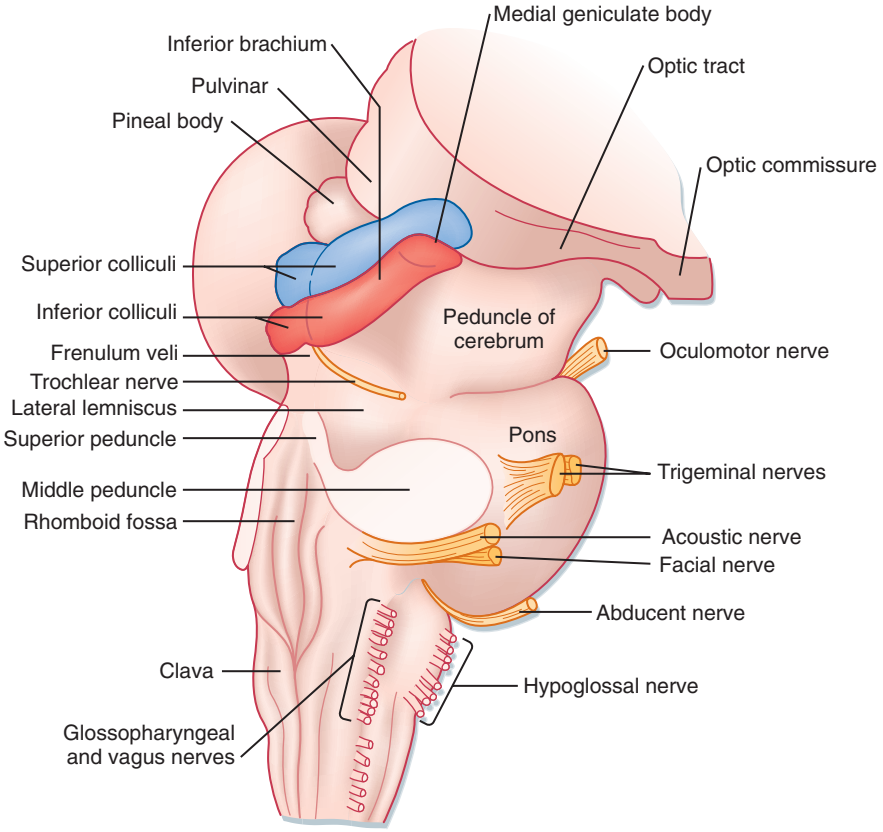

Figure 14-1. Brainstem anatomy. (Adapted from Adams J: Emergency Medicine. Fig. 89-1. Philadelphia, Elsevier. Copyright © 2008.)

Clinical Evaluation

The clinical evaluation and stabilization of patients with depressed consciousness occur simultaneously with the diagnosis in the ED. The differential diagnosis of depression of consciousness is extensive but can be greatly simplified by focusing attention on the distinguishing characteristics of the available patient history and physical examination (Boxes 14-1 and 14-2).[2] Approaching the patient's presentation systematically, beginning with a broad differential diagnosis, usually allows development of a short list of likely diagnoses early in the encounter.

History

Chief complaints relating to depressed consciousness vary widely. Family members may report the patient as being more difficult to arouse from sleep or less interactive. Often, family members or friends have alerted emergency medical services after the patient is "found down" and unarousable even with vigorous stimulation.

Family members, caregivers, or friends often can provide information that is unobtainable or unreliable from the patient who presents with depressed consciousness. They usually have some knowledge regarding the patient's past medical history, which may include diabetes, liver or renal disease, vascular disease such as hypertension, stroke or transient ischemic attacks, malignancy, seizures, immunocompromised states such as HIV, sickle cell disease or a history of organ transplant, or psychiatric illness. Symptoms in the hours to days preceding the occurrence of depressed consciousness are important. Specifically, the patient may have complained of headache, focal weakness or numbness, incoordination, or vision disturbances. The patient may have experienced nausea, vomiting, or fever. There may be a history of a traumatic fall or exposure to drugs or toxins. Family members may also be able to relay additional diagnostic clues such as rate of onset or waxing-waning characteristics of the patient's symptoms.

Causes of depression of consciousness vary with patient age (Box 14-3). The elderly are particularly vulnerable to infec-

BOX 14-1 Structural Etiology of Altered Mental Status and Coma

Trauma
Subdural hematoma
Epidural hematoma
Cerebral concussion/contusion

Stroke Syndromes
Embolism
- Cardiac (atrial fibrillation, endocarditis)
- Paradoxical (fat embolus)

Thrombosis
- Cerebral venous sinus thrombosis

Hemorrhage
- Subarachnoid hemorrhage (SAH)
- Pontine hemorrhage
- Cerebellar hemorrhage
- Intracerebral hemorrhage

Tumor
Brainstem tumors
Metastatic disease
Angiomas
Pituitary apoplexy
Acute hydrocephalus

Infection
Subdural empyema/abscess

BOX 14-2 METABOLIC/SYSTEMIC ETIOLOGY OF ALTERED MENTAL STATUS AND COMA

Hypoxia
- Severe pulmonary disease (hypoventilation)
- Severe anemia
- Environmental/toxin
  - Methemoglobinemia
  - Cyanide
  - Carbon monoxide
  - Decreased atmospheric oxygen (high altitude)
  - Near-drowning

Disorders of Glucose
- Hypoglycemia
  - Chronic alcohol abuse and liver disease
  - Excessive use of insulin or other hypoglycemic agents
  - Insulinoma
- Hyperglycemia
  - Diabetic ketoacidosis
  - Nonketotic hyperosmolar coma

Decreased Cerebral Blood Flow
- Hypovolemic shock
- Cardiac
  - Vasovagal syncope
  - Arrhythmias
  - Myocardial infarction
  - Valvular disorders
  - Congestive heart failure
  - Pericardial effusion/tamponade
  - Myocarditis
- Infectious
  - Septic shock
  - Bacterial meningitis
- Vascular/hematologic
  - Hypertensive encephalopathy
  - Pseudotumor cerebri
  - Hyperviscosity (sickle cell, polycythemia)
  - Hyperventilation
  - Cerebral lupus vasculitis
  - Thrombotic thrombocytopenic purpura
  - Disseminated intravascular coagulation

Metabolic Cofactor Deficiency
- Thiamine (Wernicke-Korsakoff syndrome)
- Pyridoxine (isoniazid overdose)
- Folic acid (chonic alcohol abuse)
- Cyanocobalamine
- Niacin

Electrolyte/pH Disturbances
- Acidosis/alkalosis
- Hypernatremia/hyponatremia*
- Hypercalcemia/hypocalcemia
- Hypophosphatemia
- Hypermagnesemia/hypomagnesemia

Endocrine Disorders
- Myxedema coma, thyrotoxicosis
- Hypopituitarism
- Addison's disease (primary or secondary)
- Cushing's disease
- Pheochromocytoma
- Hyperparathyroidism/hypoparathyroidism

Endogenous Toxins
- Hyperammonemia (liver failure)
- Uremia (renal disease)
- Carbon dioxide narcosis (pulmonary disease)
- Porphyria

Exogenous Toxins
- Alcohols
  - Ethanol, isopropyl alcohol, methanol, ethylene glycol
- Acid poisons
  - Salicylates
  - Paraldehyde
  - Ammonium chloride
- Antidepressant medications
  - Lithium
  - Tricyclic antidepressants (TCAs)
  - Selective serotonin reuptake inhibitors (SSRIs)
  - Monamine oxidase inhibitors (MAOIs)
- Stimulants
  - Amphetamines/methamphetamines
  - Cocaine
  - Over-the-counter sympathomimetics
- Narcotics/opiates
  - Morphine
  - Heroin
  - Codeine, oxycodone, meperidine, hydrocodone
  - Methadone
  - Fentanyl
  - Propoxyphene
- Sedative-hypnotics
  - Benzodiazepines
  - Barbiturates
  - Rohypnol
  - Bromide
- Hallucinogens
  - Lysergic acid diethylamide (LSD)
  - Marijuana
  - Mescaline, peyote
  - Mushrooms
  - Phencyclidine (PCP)
- Herbs/plants
  - Aconite
  - Jimson weed
  - Morning glory
- Volatile substances
  - Hydrocarbons (gasoline, butane, toluene, benzene, choroform)
  - Nitrites
  - Anesthetic agents (nitrous oxide, ether)
- Other
  - γ-Hydroxybutyrate (GHB)
  - Ketamine
  - Penicillin
  - Cardiac glycosides
  - Anticonvulsants
  - Steroids
  - Heavy metals
  - Cimetidine
  - Organophosphates

Disorders of Temperature Regulation/Environmental
- Hypothermia
- Heat stroke
- Malignant hyperthermia
- Neuroleptic malignant syndrome
- High-altitude cerebral edema (HACE)
- Dysbarism

Primary Glial or Neuronal Disorders
- Adrenoleukodystrophy
- Creutzfeldt-Jakob disease
- Progressive multifocal leukoencephalopathy
- Marchiava-Bignami disease
- Gliomatosis cerebri
- Central pontine myelinolysis

Other Disorders of Unknown Etiology
- Seizures
- Postictal states
- Reye's syndrome†
- Intussuception†

*Can be associated with dilution of formula in infant feeding.
†Prominent in the pediatric population.

tious etiologies, medication changes, and alterations in their living environments. Young adults and adolescents are more likely to present after recreational drug use or trauma. Accidental toxic ingestions are often seen in younger children. In infants, infectious causes of depressed consciousness are most common; however, trauma secondary to physical abuse and metabolic derangements from inborn errors of metabolism can be seen.[3]

Physical Examination

The severity of presenting symptoms dictates the speed needed for stabilization and diagnosis. After necessary stabilization measures have been instituted (e.g., intubation of the frankly comatose patient), a systematic examination is conducted. Level of consciousness is determined by the patient's ability to speak in full, coherent sentences and to respond

BOX 14-3 Common Age-Related Etiology of Altered Mental Status

Infant
Infection
Trauma/abuse
Metabolic

Child
Toxic ingestion

Adolescent/Young Adult
Toxic ingestion
Recreational drug use
Trauma

Elderly
Medication changes
Over-the-counter medications
Infection
Alterations in living environment
Stroke

BOX 14-4 Glascow Coma Scale

		Score
Eye Opening	Spontaneous	4
	To voice	3
	To pain	2
	None	1
Verbal Response		
Adult	Oriented	5
	Confused	4
	Inappropriate words	3
	Incomprehensible words	2
	None	1
Pediatric	Appropriate	5
	Cries, consolable	4
	Persistently irritable	3
	Restless, agitated	2
	None	1
Motor Response	Obeys commands	6
	Localizes pain	5
	Withdraws to pain	4
	Flexion to pain	3
	Extension to pain	2
	None	1

appropriately to the examiner. A rapid, directed neurologic screening examination can determine whether the patient has a significant focal motor deficit. The presence of a distinctive odor on the breath, although uncommon, can cue the examiner to the presence of alcohol, ketones (diabetic/alcoholic ketoacidosis), or bitter almonds (cyanide toxicity). Undressing the patient promptly and completely permits evaluation for signs of trauma or skin lesions suggesting overwhelming infection.

Vital signs are paramount in the initial assessment of all patients. Significant hypotension with depressed consciousness suggests shock, and both causes and therapy should be addressed immediately. Late-stage, severe elevation in intracranial pressure (ICP) can cause bradycardia and hypertension. Tachycardia and hypotension can be the result of primary cardiac, infectious, or toxic/metabolic causes. Both hypothermia and hyperthermia can result in altered mental status whether from infectious, structural, or toxic/metabolic causes. Hyperventilation, Kussmaul's or Cheyne-Stokes breathing, agonal breathing, apnea, or other alterations in respiratory patterns can suggest primary CNS abnormalities or toxic/metabolic derangements.

Immediately after an assessment of the patient's vital signs, a head-to-toe physical examination is performed.[4] A methodical and complete head and neck examination is conducted, with particular emphasis on examination of the papillary reflexes and eye movements (see later discussion) and any indications of head trauma (hemotympanum, scalp hematoma). The mucous membranes may suggest specific toxidromes.

Examination of the neck should focus on evidence of infection, including nuchal rigidity, lymphadenopathy, or fluctuance. The cervical spine should be immobilized if there are signs of neck trauma, such as cervical spine tenderness, or evidence of blunt external trauma. Stridor indicates respiratory distress typically from infection, edema, or foreign body aspiration.

Chest examination focuses on pulmonary function, infection, cardiac output, and the presence of injury. Potentially helpful abdominal findings include ascites, hepatosplenomegaly, ecchymosis, or striae. Gross blood, purulent drainage, or retained foreign bodies should be sought on genitourinary and rectal examination. In the absence or presence of signs of trauma, lesions on the skin such as rashes, signs of drug use (needle "tracks" or medication patches), or embolic phenomena can be differential clues.

A systematic neurologic examination, with particular attention paid to the eyes, is the most useful tool in differentiating a structural from a systemic or metabolic etiology of depressed consciousness or coma. A head-to-toe approach is a proven strategy. This should include evaluation of the patient's Glasgow Coma Scale (GCS) (Box 14-4), level of alertness, cranial nerves, strength, reflexes, and cerebellar functions with emphasis on gait, pronator drift, finger-to-nose, heel-to-shin, rapid alternating movements, and Romberg testing. A change of two or more points in serial GCS testing represents a significant change in the patient's level of consciousness.

Discovery of a focal neurologic deficit is suggestive of a structural etiology. Particular attention should be paid to a focused eye examination during which a helpful amount of information can be obtained. Unilateral dilatation of a pupil ("blown pupil") and loss of reactivity in a comatose patient are ominous signs of uncal herniation requiring immediate neurosurgical consultation and intervention. Papilledema in the setting of increased ICP or retinal hemorrhage associated with trauma can be found on funduscopic examination. The eye examination should also include testing of eye movements, which are coordinated by the medial longitudinal fasciculus located in the brainstem and ocular centers located in the cerebral cortex. Cranial nerves III, IV, and VI are responsible for control of the extraocular muscles. Cranial nerve III paralysis results in a persistently abducted eye, whereas a persistently adducted eye is caused by paralysis of cranial nerve VI. In the setting of trauma, a unilateral third cranial nerve palsy suggests an ipsilateral compressive lesion such as seen with epidural hematoma. Cranial nerve VI palsies are often nonlocalizing as the nerve has a long intracranial course and compressive forces from intracranial mass effects (tumor, traumatic hematoma, increased ICP, etc.) may compromise cranial nerve function anywhere in its course. Horizontal disconjugate gaze is an important finding and is commonly seen in patients who are sedated, drowsy, or intoxicated. Disconjugate gaze found

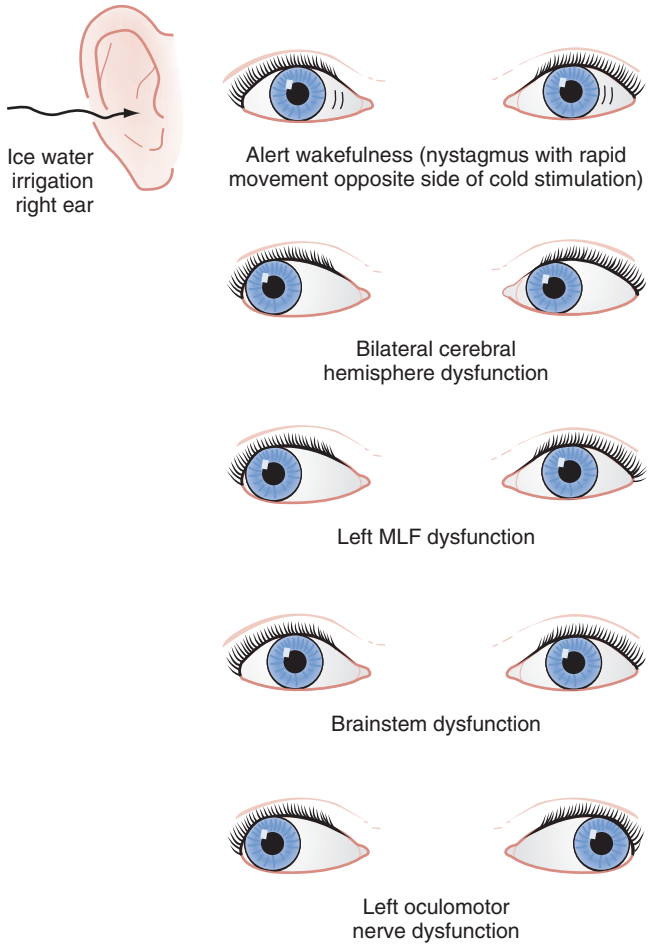

Figure 14-2. Oculocephalogyric (caloric) responses to various central nervous system pathologic conditions. MLF, medial longitudinal fasciculus.

in the vertical plane is usually more serious and suggests cerebellar or pontine dysfunction.

Oculocephalic (doll's eyes) and oculovestibular reflex testing are useful in looking at the functional integrity of the brainstem. These tests, if negative, make structural lesions in the brainstem very unlikely as the source of the patient's altered mental status.

If there are no contraindications, such as suspected cervical spine injury, oculocephalic testing is accomplished by observing the patient's eye movements while the head is turned from side to side. Patients who exhibit a maintained forward gaze despite head turning ("doll's eyes reflex") are unlikely to have a brainstem-mediated cause of coma. If the eyes remain in a fixed position within the orbits, turning in unison with the head, brainstem dysfunction is suggested. Oculovestibular or "cold water caloric" testing is a more sensitive test for brainstem involvement and cannot voluntarily be resisted (Fig. 14-2). After elevation of the patient's head to 30° (this can be done in patients whose cervical spine is not cleared by placing the bed in the reverse Trendelenburg position), 10 to 30 mL of ice water is used to irrigate the external auditory canal. Tympanic membrane perforation and cerumen impaction should be ruled out prior to performing this test. In patients who have an intact brainstem, the response is a slow conjugate deviation of gaze toward the side of the cold water stimulus lasting 30 to 120 seconds. The reflex is short-lived and followed by corrective fast beats of nystagmus toward the midline. This corrective nystagmus is described by the mnemonic COWS, which stands for "cold-opposite, warm-same." If there is no response to the irrigation, brainstem dysfunction is possible.

Diagnostic Algorithm

Information gathered from the history and physical examination of the patient with depressed consciousness must be used to direct the approach to diagnostic testing (Fig. 14-3). Most often, this information points toward a systemic or metabolic rather than a structural etiology. Neuroimaging studies are performed early in patients with suggested structural causes, but should not precede treatment of quickly reversible conditions such as possible opioid overdose or hypoglycemia.

Systemic or metabolic causes of depressed consciousness and coma are most often found on analysis of laboratory studies. Bedside glucose testing definitively confirms or excludes hypoglycemia. Serum electrolytes identify derangements in sodium, CO_2, or the anion gap. Changes in serum calcium can be a marker for metastatic disease. A urine dip test is a quick way to identify infection, ketones, or spilling of glucose. Urinalysis itself provides valuable information regarding volume status (specific gravity), infection, and the possible presence of calcium oxalate crystals in the setting of ethylene glycol ingestion. Urine drug testing may be helpful if another cause is not forthcoming.

Although an elevated white blood cell count can be a marker for infection, it is nonspecific and rarely helpful. An abnormally low white blood cell count, however, suggests an immunocompromised state and should urgently direct clinical investigation toward an infectious etiology. Thrombocytopenia can be a marker for sepsis or intracranial hemorrhage and may sound a cautionary note against an invasive procedure such as obtaining central venous access or performing a lumbar puncture. Elevated results from serum coagulation studies can be a marker for bleeding tendencies or liver disease. Serum ammonia levels are controversial and have not been shown to be a reliable marker in the setting of depressed consciousness. Thyroid function studies can reveal myxedema coma from hypothyroidism. When CNS pathology such as infection or hemorrhage is suggested but not seen on neuroimaging studies, cerebrospinal fluid analysis is undertaken.

Noncontrast computed tomography (CT) of the brain is the preliminary imaging modality of choice in the setting of depressed consciousness and coma. In the majority of ED settings, it is quickly available, making it more suitable for the patient with borderline stability. It is sufficiently sensitive to detect most intracranial hemorrhages that are large enough to cause coma. Contrast-enhanced CT may be used if a tumor or infection is possible. Linear artifacts created by the thick skull base can limit the view of the posterior fossa on CT. For this reason, magnetic resonance imaging of the brain is generally more useful for identifying structural lesions in this region; however, this modality is less feasible in most ED settings due to its cost and limited availability. Angiography may be available in larger tertiary care centers for use in the diagnosis or treatment of intracerebral aneurysms or arteriovenous malformations after initial identification of an intracranial hemorrhage on noncontrast CT.

Plain radiography may identify severe pneumonia or acute respiratory distress syndrome, or it may rarely reveal specific types of heavy-metal ingestions such as mercury, iron, or lead in the pediatric population. Electrocardiograms can point to certain ingestions (tricyclic antidepressants, etc.), electrolyte abnormalities (potassium, calcium, etc.), or hypothermia. If nonconvulsive status epilepticus is suggested, or if a patient with status epilepticus has required neuromuscular blockade,

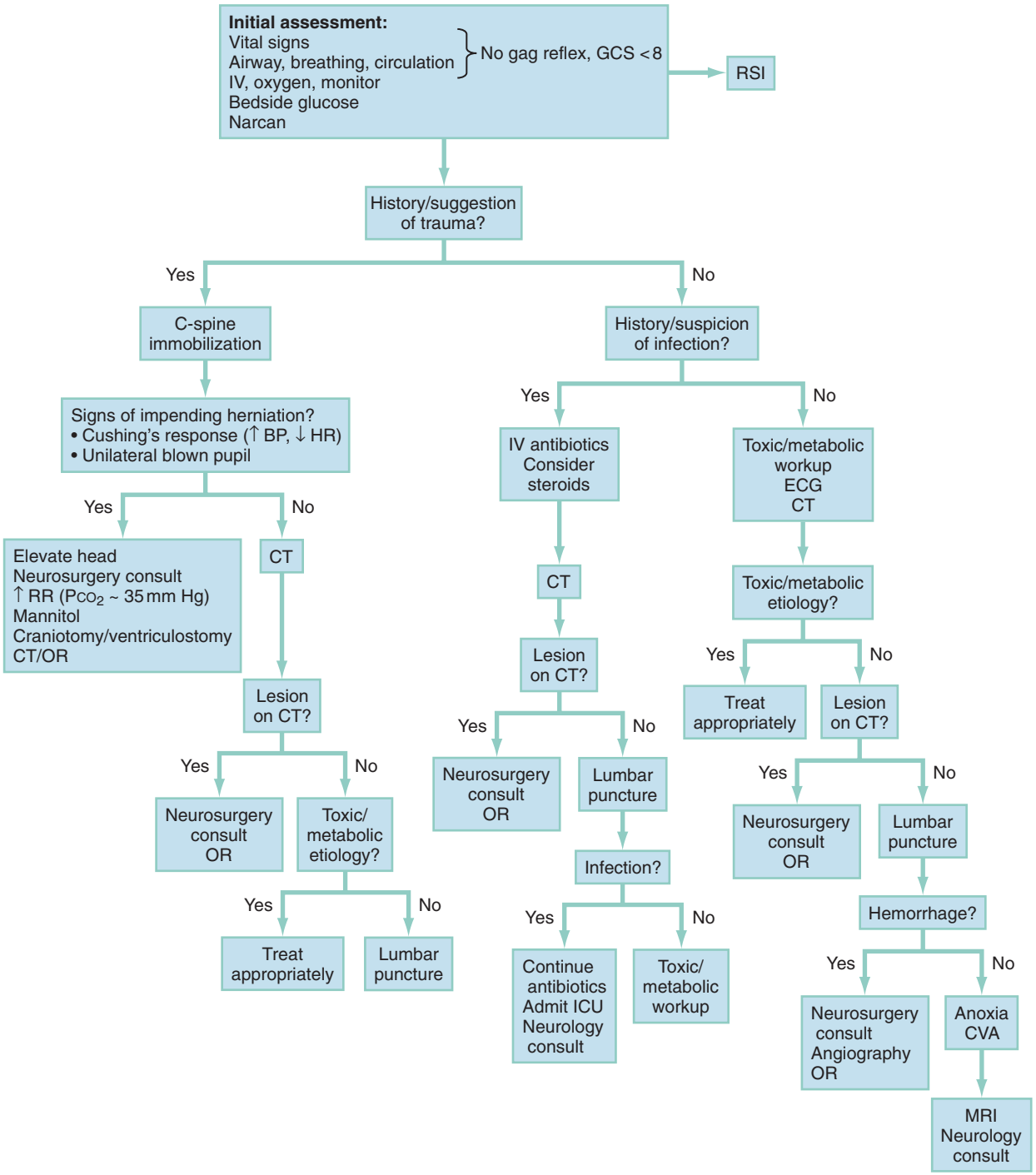

Figure 14-3. Algorithm for diagnostic approach to altered mental status and coma. BP, blood pressure; C-spine, cervical spine; CT, computed tomography; CVA, cerebrovascular accident, HR, heart rate; ICU, intensive care unit; IV, intravenous; OR, operating room; RR, respiration rate; RSI, rapid sequence intubation. (Adapted from Adams J: Emergency Medicine. Fig. 89-2. Philadelphia, Elsevier. Copyright ©2008.)

continuous electroencephalographic monitoring, if available, can provide key information about the patient's status and guide therapy.

Empirical Management

Initial establishment of airway, breathing, and circulation (ABCs) is of primary importance in stabilizing the patient with altered mental status. Initiation of IV access combined with the administration of oxygen and continuous telemetry monitoring should happen concomitantly within the first few minutes of the patient's arrival.[5] In patients with a GCS score lower than 8, definitive airway control should be obtained unless the coma is readily reversible (e.g., hypoglycemia, opioid overdose). Patients with possible increased ICP should receive lidocaine prior to rapid sequence intubation (see

Chapter 1). Trauma patients require spinal immobilization in addition to indicated fluid resuscitation.

Reversible causes of the patient's condition should be sought concomitantly with initial stabilization. Administration of the components of the "GI cocktail," which include dextrose, nalaxone, and thiamine, can quickly reverse the alterations in mental status caused by hypoglycemia, narcotic overdose, and thiamine deficiency, respectively. Further therapy and workup will be dictated by the patient's history and physical examination. Specific attention should be given to identifying the focal neurologic abnormalities, including pupillary reflexes and pathologic eye movements that suggest mass effect or depressed brainstem function, prompting neuroimaging and evaluation by a neurosurgeon. Empirical administration of mannitol is indicated when there is evidence of transtentorial herniation in this setting. Ventriculostomy and ICP monitoring are commonly performed by the neurosurgeon in the ED. In trauma patients with suspected epidural hematoma who have evidence of brain herniation, the use of burr holes in the skull on the side of the dilated pupil may be a last resort. In patients with compromised brainstem function who lack evidence of herniation, a workup to investigate possible exposure to toxins or metabolic imbalances should proceed while supportive care is provided. Brain tissue is considered to be unsalvageable in patients who have not received sedative medications, are normothermic, and demonstrate lack of brainstem reflex activity.

In patients who demonstrate normal brainstem function, the workup proceeds as supportive care is provided. When an infectious cause is suggested, empirical administration of a broad-spectrum antibiotic should not be delayed for lumbar puncture or other diagnostic tools. Lesions or masses found on brain imaging should prompt evaluation by a neurosurgeon and, if indicated, early operative intervention. In patients in whom a toxic ingestion is possible, activated charcoal is of no proven benefit in most cases and gastric emptying is rarely indicated (see Chapter 145). Specific toxin antidotes, if indicated, can be given, with consultation with a local or regional poison center when required. Early hemodialysis after consultation with a nephrologist should also be considered in patients who have toxic or metabolic abnormalities amenable to this therapy.

The vast majority of patients who present with depressed consciousness or coma require admission to the hospital for further treatment and workup. Some patients who have returned to their baseline mental status after reversal of hypoglycemia or opioid overdose may be suitable for discharge directly from the ED or ED observation unit after a period of observation. Patients with alcohol or recreational drug intoxication and no other discernible cause of altered mental status can be discharged when they are clinically sober.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 15 Seizures

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PERSPECTIVE

Seizure is defined as abnormal neurologic functioning caused by abnormally excessive activation of neurons, either in the cerebral cortex or in the deep limbic system. *Epilepsy* is defined as recurrent unprovoked seizures due to a genetically determined or acquired brain disorder[1]; it is not an appropriate term for seizures that occur intermittently and predictably after a known insult, such as alcohol intoxication and withdrawal.

Presentation to the emergency department (ED) with a generalized convulsive seizure prompts immediate concern for airway protection and stabilization, followed by a focused search for the cause. Nonconvulsive seizures, which are much less common, may be relatively obscure in their presentation, more diverse in their etiology, and are sometimes more difficult to recognize and control acutely.

Epidemiology and Classification

It is estimated that 6% of the U.S. population experience at least one nonfebrile seizure during their lifetime; the annual incidence among adults is 84 per 100,000 population, and more than half of these individuals develop epilepsy.[2] In one study, approximately 1% of ED visits were for seizure-related complaints.[3] Nearly half of these patients had alcohol or low antiepileptic drug levels implicated as contributing factors.

Seizures can be classified as primary or secondary (the latter also termed *reactive*), as generalized or focal (partial), or as convulsive or nonconvulsive. Table 15-1 shows the distribution of seizures in a typical population of patients. A generalized seizure is defined as abnormal neuronal activity in both cerebral hemispheres. Seizues may be divided into tonic-clonic, absence, and myoclonic. Partial seizures or focal seizures usually involve one hemisphere. They are divided into simple partial (in which consciousness is maintained), complex partial (in which consciousness is lost), and those that become secondarily generalized. Some seizures are impossible to classify because of inadequate or inaccurate description of the ictal activity.[2,3]

Status epilepticus is defined as at least 30 minutes of persistent seizures or a series of recurrent seizures without intervening return to full consciousness,[4] although several authors have proposed shortening the time criterion from 30 minutes to 5 minutes.[5]

Secondary seizures may occur as a result of a vast array of injuries and of illnesses such as intoxication or poisoning, encephalitis, encephalopathy, organ failure, other metabolic disturbances, infections of the central nervous system, cerebral tumors, pregnancy, and, paradoxically, supratherapeutic levels of anticonvulsants.

Seizures in children follow a different distribution, primarily because of the relatively high incidence of febrile seizures and the frequently uncertain observational history of possible ictal activity. Febrile seizure is the most common pediatric seizure, occurring in 2 to 5% of children between 6 months and 5 years of age; 20 to 30% of those children have at least one recurrence. It is important to differentiate between febrile seizure and seizure with fever.[6] First-time seizures in infants younger than 6 months may indicate significant underlying pathology and warrant a full assessment.[7]

Pathophysiology

Seizures occur when the abnormal increased electrical activity of the initiating neurons activates adjacent neurons and propagates until the thalamus and other subcortical structures are similarly stimulated. At a cellular level, the pathophysiology is not well understood, although recent research in specific epilepsy syndromes is elucidating possible mechanisms. Investigation of rare inherited epilepsy syndromes has identified mutations in neuronal ion channel proteins, limiting intracellular passage of potassium. Given that the potassium current is the primary force behind repolarization of membranes, depolarization is prolonged in these patients, leading to an increase in neuronal hyperexcitability.[1] Other studies have found that malformations of cortical development and glial cells may play a role in epileptogenesis.[1]

Clinical seizure activity typically, but not always, reflects the initiating focus. When the ictal discharge extends below the cortex to deeper structures, the reticular activating system in the brainstem may be affected, altering consciousness. In generalized seizures, the focus is often deep and midline, which explains the prompt loss of consciousness and bilateral involvement. Seizures are typically self-limited; at some point the hyperpolarization subsides and the bursts of electrical discharges from the focus terminate. This cessation may be related to reflex inhibition, neuronal exhaustion, or alteration of the local balance of neurotransmitters.

Partial seizures may represent a similar pathophysiologic process in which less recruitment occurs and the ictal activity does not cross the midline. Because of the more limited focus of abnormal activity, convulsive motor activity may not be the predominant clinical manifestation.[3]

■ DIAGNOSTIC APPROACH

Differential Considerations

Because an incorrect diagnosis is expensive and involves loss of driving privileges and exposure to potentially toxic medicines, the first diagnostic task is to determine whether the patient is having a "true" seizure.[8] Ictal activity can be irrefutably verified only by electroencephalography (EEG). Other abnormal movements and states of consciousness, including pseudoseizures, can be confused with ictal activity. Other disorders mimicking seizures are listed in Table 15-2.[7]

Syncope, whether vasodepressive (vagal syncope), orthostatic, or dysrhythmia related, can be confused with seizures by observers. A sudden loss of consciousness followed by abnormal movements can be ictal or syncopal in origin, hence the consideration "fit versus faint." One video analysis of 56 brief syncopal episodes showed myoclonic activity in 90% of patients, together with frequent head turns, upward gaze, oral automatisms, and righting movements. These are likely a transient response by the brain to sudden deprivation of blood flow. Generally, ictal tonic-clonic movements are more forceful and prolonged than the "twitches" sometimes associated with fainting. In addition, most generalized seizures are characterized by a postictal state (an important exception being atonic drop attack ictus), which syncope patients do not manifest.[9]

The cause of an unwitnessed, unprovoked loss of consciousness with a fall, after which the patient presents to the ED, may be difficult to determine. Suggestions of an ictal diagnosis include retrograde amnesia, loss of continence, and evidence of tongue biting.[10] If blood was drawn by emergency medical service personnel soon after a true seizure, it often demonstrates a metabolic acidosis that has resolved by the time a repeat analysis is performed in the ED.

Table 15-1 Classification of Seizures in a General Adult Population

SEIZURE TYPE	PERCENTAGE
Generalized	
Tonic-clonic	35
Absence	1
Myoclonic	<1
Others	2–3
Partial	
Simple partial	3
Complex partial	11
Secondarily generalized	27
Mixed partial	12
Unclassified	9

Rapid Assessment and Stabilization

The patient who arrives with a history of possible seizure activity should be placed in a monitored area of the ED and prepared for prompt physician examination.[4] An IV line or saline lock catheter should be placed in case anticonvulsants are emergently indicated. Blood glucose is checked at the bedside, and a thorough list of all medications currently being used by the patient is obtained.

If the patient is seizing in the ED, the first step is to confirm that a pulse is present and that the "seizure" activity is not the result of cerebral hypoxia from lack of blood flow. After this, attention is paid to protecting and maintaining the airway, including use of a nasopharyngeal airway and ready availability of oxygen and suction. The patient should be protected from self-injury during this time.[11]

Table 15-2 Differential Considerations for the Diagnosis of Seizure*

DISORDER	CLASSIFICATION	ICTAL-LIKE MANIFESTATIONS
Syncope	Vasodepressive vs dysrhythmogenic (including long QT syndrome) vs orthostatic Preictal or postictal twitching	"Fit vs. faint"
Hyperventilation syndrome		Mood disturbances Posturing of extremities
Prolonged breath-holding	More typical in children	Tonic-clonic movements Loss of urinary continence
Toxic and metabolic disorders	Alcohol abuse/withdrawal Hypoglycemia Phencyclidine Tetanus Strychnine and camphor Extrapyramidal reactions	Delirium tremens, blackout Abnormal behavior Buccolingual spasms Myotonic spasms Myotonic spasms Posturing, deviation of eyes
Nonictal CNS events	Transient ischemic attacks Transient global amnesia Hemiparetic migraine Carotid sinus hypersensitivity Narcolepsy	Drop attacks, "fit vs. faint" Similar to postictal state, absence status Todd's paralysis Drop attacks, "fit vs. faint" Drop attacks, "fit vs. faint"
Movement disorders	Hemiballismus, tics	Convulsions
Psychiatric disorders	Fugue state Panic attacks	Similar to postictal state, absence status Twitching, altered mental state
Functional disorders	Pseudoseizure	May closely resemble ictal activity; patients may have both true seizures and pseudoseizures

*Electroencephalography provides the definitive diagnosis in unclear cases.
CNS, central nervous system.

A pulse oximeter should be applied and oxygen administered as necessary. Optimally, the patient is turned on his or her side to protect the airway from aspiration. If the patient is immobilized on a spine board after trauma, the entire board is tipped up to one side. Preparation should be made for endotracheal intubation in case anticonvulsant drugs fail to terminate the seizure. While these procedures are accomplished, an assistant should be establishing IV access.[11]

Hypoglycemia is the most common metabolic cause of seizure activity. The only treatment required for the patient may be administration of IV glucose. *Prolonged* seizure activity may also *cause* hypoglycemia, so that the cause-and-effect relationship may sometimes be reversed and further therapy is required. Benzodiazepines are the optimal first-line agents for stopping seizure activity in patients of all ages. Available agents include lorazepam (Ativan), diazepam (Valium), and midazolam (Versed). All three are efficacious in terminating seizure activity (see Table 15-3 for doses), but if IV access cannot be achieved, diazepam may be given rectally, endotracheally, or intraosseously; rectal diazepam stops seizures in 70% of patients, compared with 60 to 80% for IV dosing.[12] Midazolam can be given intramuscularly, and recent research shows that buccal midazolam works in children.[13] If IV access is obtained, however, lorazepam is the agent of choice for initial management of status epilepticus, particularly because its longer half-life leads to less recurrence of seizures.[14] Lorazepam is also specifically recommended for alcohol withdrawal seizures, again due to its longer duration of action.[15]

If benzodiazepines do not abort seizure activity, the airway should be reevaluated. If the patient's ability to protect the airway is compromised or oxygen saturation remains persistently below 90%, emergent intubation should be performed. If the seizure has not terminated 5 to 7 minutes after benzodiazepine administration, or if the maximum dose of lorazepam (0.1 mg/kg) or diazepam (0.15 mg/kg)[16] has been reached, a second drug should be given.[16] Use of maximal doses of benzodiazepines may require intubation and ventilatory support. Phenytoin is recommended as second-line therapy for adults with persistent seizure activity.[16] The prodrug, fosphenytoin, can be administered more quickly, can be given intramuscularly, and has less tendency to cause hypotension, but is significantly more expensive.[17] (See Table 15-3).[18,19] Second-line therapy for children is phenobarbital. Third-line therapy is phenytoin for children and phenobarbital for adults.[20-23] IV valproic acid is safe[24] and should be considered for patients who are on chronic valproic therapy and whose levels are subtherapeutic.[25] If a patient's seizures are refractory to benzodiazepines, consider isoniazid overdose as the cause. Pyridoxine

Table 15-3 Drugs and Dosages for Abortive Treatment of Seizures in the Emergency Department*

DRUG	ADULT DOSE	PEDIATRIC DOSE	COMMENTS
Glucose	50 mL of 50% glucose	0–1 month: 2 mL/kg IV of D10W 1 month–2 years: 2 mL/kg IV of D25W >2 years: 2 mL/kg IV of D50W	1 month–2 years: 2 mL/kg IV of D25W
Magnesium sulfate		6 g over 15–20 min followed by 2 g/hr	First-line therapy for eclamptic seizures
Diazepam	0.2 mg/kg IV at 2 mg/min up to 20 mg	0.2–0.5 mg/kg IV/IO/ET *or* 0.5–1.0 mg/kg PR up to 20 mg	Monitor airway protection and respiratory drive
Lorazepam	0.1 mg/kg IV at 1–2 mg/min to up to 10 mg	0.05–0.1 mg/kg IV	Monitor airway protection and respiratory drive
Midazolam	0.1 mg/kg given at 1 mg/min up to 10 mg IV 0.2 mg/kg IM 0.5 mg/kg buccal	0.15 mg/kg IV, then 2–10 mcg/kg/min	Monitor airway protection and respiratory drive
Phenytoin	20 mg/kg IV at ≤40 mg/min	20 mg/kg IV at 1 mg/kg/min	During infusion patient should have continuous cardiac and blood pressure monitoring
Fosphenytoin	15–20 mg/kg IV at 100–150 mg/min *or* 20 mg/kg IM	20–25 mg/kg IV, then up to 3 mg/kg/min IV up to 159 mg/min IV	Level of monitoring directed by patient's status, not drug use
Propofol	3–5 mg/kg initial dose, then 1–15 mg/kg/hr infusion		Used for status epilepticus; intubation required
Phenobarbital	20–30 mg/kg IV at 60–100 mg/min or as single IM dose		Intubation may be required
Valproate	20 mg/kg PR or 10–15 mg/kg IV (initial dose)		Maximum dosage 60 mg/kg/day Dilute 1:1 with water; onset is slow
Pentobarbital	5 mg/kg IV at 25 mg/min, then titrate to EEG		Intubation, ventilation, and pressor support are required
Isoflurane	Via general endotracheal anesthesia		Monitor with EEG

*Although alternative routes of administration (e.g., IO, PR) have not all been studied in adults, appropriate weight or length based on dosing by pediatric guidelines can be used when the clinical situation dictates.

EEG, electroencephalogram; ET, endotracheal; IM, intramuscular; IO, intraosseous; IV, intravenous; PR, rectal administration.

is the only fully effective pharmacologic treatment for toxic isoniazid seizures, although benzodiazepines have been shown to suppress seizure activity in some cases.[26] In seizing females of childbearing age, eclampsia should be considered; in this case, intravenous magnesium (6 g) is the drug of choice. (See Chapter 177.) Approximately 10% of patients will have a second seizure despite magnesium; these patients should get a second 2-g bolus of magnesium.[27] If the eclamptic patient continues seizing, magnesium dosing should be repeated; refractory eclamptic seizures can also respond to benzodiazepines or barbiturates with or without phenytoin. Children and psychiatric patients at risk for water intoxication should be considered potential candidates for hypertonic saline therapy, after laboratory confirmation of hyponatremia.

Patients who remain unresponsive to the third-level choice of pharmacologic intervention are by definition in *refractory* status epilepticus. Further choices for therapy at that juncture are general anesthetic doses of midazolam or propofol, barbiturate coma and isoflurane anesthesia; all of which mandate endotracheal intubation.[22,23,29] A neuromuscular blocking agent is administered concomitantly to reduce the metabolic burden and potential hyperthermia that can ensue from prolonged status seizures. Anesthetic dosing of midazolam is 0.2 to 0.3 mg/kg bolus, then 0.05 to 2.0 mg/kg/hr, and for propofol it is 2 to 4 mg/kg, then 1 to 15 mg/kg/hr. Both drugs are usually well-tolerated and can be titrated to effect, although propofol is preferable because of its rapid onset and offset of action, which allows the patient to be "awakened" intermittently for examination in the event that continuous EEG monitoring is not available.[16]

Pivotal Findings

When the patient is stabilized with a secure airway and ictal activity is controlled, attention is turned to gathering more complete data.

History

History taking in the patient with seizure is directed by two main questions. First, "Was the incident truly a seizure?" This is important because of the broad differential diagnosis for seizures (see Table 15-2) and the notoriously inaccurate descriptions of seizure-like activity from laypersons.[10] In general, however, ictal events have six properties:

1. *Abrupt onset*: Generalized seizures typically occur without an aura.
2. *Brief duration*: Seizures rarely last longer than 90 to 120 seconds, although bystanders typically overestimate the duration.
3. *Altered mental status*: Present by definition, except for simple partial seizures.
4. *Purposeless activity*: For example, automatisms and undirected tonic-clonic movements.
5. *Unprovoked*: Especially with regard to emotional stimuli; fever in children and substance withdrawal in adults are notable exceptions.
6. *Postictal state*: An acute confusional state that typically occurs with all seizures except simple partial and absence.

Information regarding focality of onset, loss of bowel or bladder control, or tongue biting should also be elicited.

The second question to direct the history is, "Does this patient have a history of seizures?" If he or she does have a documented history of seizures, ED evaluation may be limited to a thorough history and consideration of measurement of anticonvulsant drug levels. History should focus on intercurrent illness or trauma, drug or alcohol use, potential adverse drug-drug interactions with anticonvulsants, medication compliance, a recent change in anticonvulsant dosing regimens, or a change in ictal pattern or characteristics.[2,11]

Supratherapeutic and toxic levels of some anticonvulsants such as phenytoin and carbamazepine, whether attained chronically or after acute overdose, may *cause* seizures. If empiric anticonvulsant therapy is indicated before the serum level is available, only 50% of a full loading dose should be given unless the patient is known reliably not to be taking anticonvulsant medication.

If the patient does not have a history of seizures and the description of the event is truly consistent with a seizure, the history should focus on potential underlying medical, toxicologic, or neurologic causes.

A personal history from the patient, close friend, relative, or medical record may reveal potential ictogenic factors such as recent or remote head trauma, developmental abnormalities, metabolic diseases, drug or alcohol abuse, sleep deprivation, pregnancy, recent travel, previous seizures, or use of herbal supplements. When no witness or family member is available, extensive questioning must await clearance of the postictal confusional state.

Physical Examination

The physical manifestations of convulsive ictal activity include hypertension, tachycardia, and tachypnea from sympathetic stimulation. These signs typically resolve quickly after the seizure activity ceases. With more prolonged convulsions, skeletal muscle damage, lactic acidosis, and, rarely, frank rhabdomyolysis may ensue. Autonomic discharges and bulbar muscle involvement may result in urinary or fecal incontinence, vomiting (with significant aspiration risk), tongue biting, and airway impairment. All of these signs are helpful discriminators in the differential evaluation of seizure-like spells.

After the seizure activity has ceased, resting vital signs should be evaluated. Fever and underlying infection can cause seizures, although there may be a low-grade temperature elevation immediately after a convulsive generalized seizure. Tachypnea, tachycardia, or an abnormal blood pressure that persists beyond the immediate postictal period may indicate toxic exposure, hypoxia, or a central nervous system lesion. Pertinent physical findings may include nuchal rigidity, stigmata of substance abuse, lymphadenopathy suggestive of HIV disease or malignancy, dysmorphic features, or skin lesions. The examination should also focus on potential adverse sequelae of convulsive seizures, such as head trauma, tongue injury, posterior shoulder dislocation, or back pain.

Finally, a complete neurologic examination must be performed. A persistent focal deficit after a seizure (e.g., Todd's paralysis) often indicates the focal origin of the event but also can be evidence of an underlying stroke. The patient should be carefully examined for papilledema; elevated intracranial pressure can both cause and result from ictal activity. Failure to note steady improvement of postictal depression of consciousness suggests the possibility of an underlying encephalopathy or nonconvulsive status epilepticus.

Ancillary Testing

Laboratory. Routine screening studies such as a complete blood count and chemistry profile have little use in the neurologically normal, otherwise healthy, postictal patient with a known seizure disorder for whom a reliable history can be obtained.

Table 15-4 Indications for Emergent Head CT for New-Onset Seizure Patients

Acute intracranial process is suspected
History of acute head trauma
History of malignancy
Immunocompromise
Fever
Persistent headache
History of anticoagulation
New focal neurologic examination
Age older than 40 years
Focal onset before generalization
Persistently altered mental status

CT, computed tomography.

Bedside blood glucose is measured early. Anticonvulsant levels are appropriate in patients known or thought to be taking anticonvulsant medication. Febrile patients are evaluated for the source of the fever. For medically ill adults (e.g., diabetic patients, cancer patients, patients with liver disease, patients taking medications that can affect serum electrolyte levels) and in those presenting with a first-time seizure, appropriate chemistry studies are ordered, including electrolytes and liver function tests.[8] Directed toxicologic screens should be obtained if substance abuse is possible. Serum sodium should be evaluated, particularly if mental status remains altered after apparent recovery from the postictal state. Pregnancy testing is useful if eclampsia is possible. If there is *any* suggestion of meningitis or subarachnoid hemorrhage, lumbar puncture should be performed, with a preceding cranial computed tomography (CT) scan.[30]

Imaging. In the fully recovered patient without headache and with fully normal mental status and neurologic examination who has had a single, brief seizure, a cranial CT scan can be obtained in the ED or at a follow-up visit at the discretion of the treating physician.[4,29] Table 15-4 lists the circumstances under which a head CT is recommended in the ED due to a higher likelihood of discovering an acute abnormality.[4]

The literature on this issue for first-time nonfebrile seizures in children is also inconclusive.[31] Cranial CT is indicated in any age group when there is a possibility of head trauma, elevated intracranial pressure, intracranial mass, persistently abnormal mental status or focal neurologic abnormality, or HIV disease.

Electroencephalography. EEG is not consistently available in the ED. It may be particularly useful in specific cases, such as the diagnosis of nonconvulsive status epilepticus, to monitor seizure activity after intubation and neuromuscular blockade, and to help differentiate seizures from other similar presentations. In general, EEGs are most appropriate for the follow-up evaluation of first-time seizures without clear cause after a complete ED evaluation.[19]

MANAGEMENT

Usually, an acute seizure self-terminates or can be pharmacologically terminated before a need arises for active airway management. Rapidly reversible ictal insults (e.g., hypoglycemia, hypoxemia, isoniazid ingestion) should be considered and, if found, treated. Primary abortive therapy in the ED is accomplished as described earlier. Although a number of newer antiepileptic medications have become available, their therapeutic purpose is directed toward chronic rather than acute seizures.[32]

Identifying a new-onset seizure in the ED generates consideration for further management. The choice to initiate anticonvulsant therapy depends on the risk of seizure recurrence and any underlying predisposing disease, and the risk of initiating anticonvulsant therapy is typically not made by the emergency physician. The initiation of anticonvulsant therapy after a single seizure is an issue of considerable controversy and should be undertaken in consultation with the neurologist who will be following the patient after discharge from the ED.[33,34] Prompt treatment of any apparent ictal source discovered in the ED, however, is always appropriate.

DISPOSITION

Disposition plans must be individualized according to the findings of the ED evaluation and the presence or absence of underlying disease. One quarter of adult patients presenting with seizure-related complaints have new-onset seizures.[3] Almost half of them require admission, most because of abnormal CT scans or persistent focal abnormalities; 95% of those who retrospectively required admission were correctly identified by using an ED evaluation consistent with that recommended previously. Patients may be discharged home with early referral to a neurologist if they have a normal neurologic exam, no comorbidities, no known structural brain disease, do not require the use of an antiepileptic drug in the ED, and are felt to be sufficiently resourceful and reliable to comply with follow-up instructions.[4] Patients discharged home from the ED should receive appropriate state-specific guidance regarding driver's license privileges and information for prompt follow-up with a neurologist.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 16 Headache

Christopher S. Russi

PERSPECTIVE

Epidemiology

Up to 85% of the U.S. adult population complains of significant headaches at least occasionally, and 15% does so on a regular basis. Headache as a primary complaint represents between 3 and 5% of all emergency department (ED) visits. The vast majority of patients who have the primary complaint of headache do not have a serious medical cause for the problem. Tension headache accounts for approximately 50% of patients presenting to the ED, another 30% have headache of unidentified origin, 10% have migraine-type pain, and 8% have headache from other potentially serious causes (e.g., tumor, glaucoma). It is estimated that less than 1% of patients who present to the ED with headache have a life-threatening organic disease.[1] The percentages can create a false sense of security, and headache is disproportionately represented in emergency medicine malpractice claims. Although still rare, the most commonly encountered life-threatening cause of severe sudden head pain is subarachnoid hemorrhage (SAH); approximately 20,000 potentially salvageable cases of SAH present to EDs each year. It is estimated that between 25 and 50% of these are missed on the first presentation to a physician.[2] The other significant, potentially life-threatening causes of headache occur even less frequently. Meningitis, carbon monoxide poisoning, temporal arteritis, acute angle-closure glaucoma, intracranial hemorrhage (ICH), cerebral venous sinus thrombosis, and increased intracranial pressure can often be linked with specific historical elements and physical findings that facilitate their diagnosis.

Pathophysiology

The brain parenchyma is insensitive to pain. The pain-sensitive areas of the head include the coverings of the brain—the meninges—and the blood vessels, both arteries and veins supplying the brain, and the various tissues lining the cavities within the skull. The ability of the patient to specifically localize head pain is often poor. Much of the pain associated with headache, particularly with vascular headache and migraines, is mediated through the fifth cranial nerve. Such pain may proceed back to the nucleus and then be radiated through various branches of the fifth cranial nerve to areas not directly involved. A specific inflammation in a specific structure (e.g., periapical abscess, sinusitis, or tic douloureux) is much easier to localize than the relatively diffuse pain that may be generated by tension or traction headaches. Pains in the head and neck may easily overlap. They should be thought of as a unit when considering complaints of headache.

DIAGNOSTIC APPROACH

Differential Considerations

The differential diagnosis of headache is complex because of the large number of potential disease entities and the diffuse nature of many types of pain in the head and neck region (Table 16-1). However, in evaluating the patient with a headache complaint, the top priority is to exclude intracranial hemorrhage (SAH and ICH), meningitis, encephalitis, and mass lesions. Carbon monoxide is an exogenous toxin, the effects of which may be reversible by removing the patient from the source and administering oxygen. Carbon monoxide poisoning is a rare example of a headache in which a simple intervention may quickly improve a critical situation. On the contrary, returning the patient to the poisoned environment without a diagnosis could be lethal.

Rapid Assessment and Stabilization

If the patient presents in a critical or comatose state, initial stabilization, including airway management, is undertaken as indicated, preceded by a neurologic examination if at all possible. For purposes of the initial assessment, headache can be divided into two categories: accompanied by altered mental status and without altered mental status. Whenever a patient's mental status is impaired, brain tissue is initially assumed to be compromised. The principles of care centered on cerebral resuscitation address the seven major causes of evolving brain injury: lack of substrate (glucose, oxygen), cerebral edema, intracranial mass lesion, endogenous or exogenous toxins, metabolic alterations (fever, seizure), ischemia, or elevated intracranial pressure.

Pivotal Findings

History

The history is the pivotal part of the workup for the patient with headache (Table 16-2).

1. The patient should be asked to describe the *pattern and onset of the pain*. Patients often relate frequent and recurrent headaches similar to the one they have

Table 16-1 Differential Diagnosis

ORGAN SYSTEM	CRITICAL DIAGNOSES	EMERGENT DIAGNOSES	NONEMERGENT DIAGNOSES
Neurologic, CNS, vessels	Subarachnoid hemorrhage	Shunt failure Traction headaches Tumor/other masses Subdural hematomas	Migraine, various types Vascular, various types Trigeminal neuralgia Post-traumatic Postlumbar puncture Headaches
Toxic/metabolic Environmental	Carbon monoxide poisoning	Mountain sickness	
Collagen vascular disease	Temporal arteritis		
Eye/ENT		Glaucoma/sinusitis	Dental problems/temporomandibular joint disease
Musculoskeletal			Tension headaches Cervical strain
Allergy			Cluster/histamine headaches
Infectious disease	Bacterial meningitis/encephalitis	Brain abscess	Febrile headaches/nonneurologic source of infection
Pulmonary/O_2		Anoxic headache Anemia	
Cardiovascular		Hypertensive crisis	Hypertension (rare)
Unspecified			Effort-dependent/coital headaches

CNS, central nervous system; ENT, ear, nose, and throat.

Table 16-2 Significant Symptoms

SYMPTOM	FINDING	POSSIBLE DIAGNOSES
Sudden onset of pain	Lightning strike or thunder clap with any decreased mentation, any positive focal finding or intractable pain	Subarachnoid hemorrhage
"Worst headache of their life"	Associated with sudden onset	Subarachnoid hemorrhage
Near syncope or syncope	Associated with sudden onset	Subarachnoid hemorrhage
Increase with jaw movement	Clicking or snapping. Pain with jaw movement	Temporomandibular joint disease
Facial pain	Fulminant pain of the forehead and area of maxillary sinus. Nasal congestion	Sinus pressure or dental infection
Forehead or temporal area pain (or both)	Tender temporal arteries	Temporal arteritis
Periorbital or retro-orbital pain	Sudden onset with tearing	Temporal arteritis or acute angle-closure glaucoma

on this ED visit. A marked variation in headache pattern can signal a new or serious problem. The rate of onset of pain may have significance. Pain with rapid onset of a few seconds to minutes is more likely to be vascular in origin than pain that developed over several hours or days.

Almost all studies dealing with subarachnoid bleeding report that patients moved from the pain-free state to severe pain within seconds to minutes. The "thunder clap" or "lightning strike" headache is a real phenomenon, and this response to questioning may lead to the correct diagnosis of subarachnoid hemorrhage, even if the pain is improving at the time of evaluation.[3]

2. The patient's *activity at the onset of the pain* may be helpful. Certainly, headaches that come on during severe exertion have a relationship to vascular bleeding, but again, there is enough variation to make assignment to any specific cause highly variable. The syndrome of coital or postcoital headache is well known, but coitus is also a common time of onset for SAH. These headaches require the same evaluation on initial presentation as any other exertion-related head pain. If the patient can recall the precise activity in which he or she was engaging at the time of the onset of the headache (e.g., "I was just getting up out of the chair to answer the doorbell"), sudden onset is extremely likely and evaluation for SAH is warranted.
3. If the patient or nonhospital medical personnel can relate a *history of head trauma*, the differential diagnosis and emergent causes have narrowed significantly. The considerations now focus on epidural and subdural hematoma, traumatic SAH, skull fracture, and closed-head injury (i.e., concussion and diffuse axonal injury).
4. Toxoplasmosis, cryptococcal meningitis, and abscess are considered higher in the differential in patients with a *history of HIV or immunocompromised state*. Although such entities are rare, it is important to remember that this subset of patients may have serious disease without typical signs or symptoms of systemic illness (e.g., fever and meningismus).
5. The *intensity of head pain* is difficult to quantify objectively. Almost all patients who present to the ED consider their headache to be "severe." Use of a pain scale of 1 to 10 may help differentiate patients initially but has more value in monitoring their response to therapy.

6. The *character of the pain* (i.e., throbbing, steady), although sometimes helpful, may not be adequate to differentiate one type of headache from another.
7. The *location of head pain* is helpful when the patient can identify a specific area. It is useful to have the patient point or try to indicate the area of pain and the emergency physician to then properly examine that area. Unilateral pain is more suggestive of migraine or a localized inflammatory process in the skull (e.g., sinus) or soft tissue.[4] Occipital headaches are classically associated with hypertension. Certainly, temporal arteritis, temporomandibular joint disease, dental infections, and sinus infections frequently have a highly localized area of discomfort. Meningitis, encephalitis, SAH, and even severe migraine, although intense in nature, are usually more diffuse in their localization.
8. *Exacerbating* or *alleviating factors* may be important. Patients whose headaches rapidly improve when they are removed from their environment may have carbon monoxide poisoning. Most other severe causes of head pain are not rapidly relieved or improved when patients get to the ED. Headaches on awakening are typically described with brain tumors. Intracranial infections, dental infections, and other regional causes of head pain tend not to be improved or alleviated before therapy is given.
9. *Associated symptoms and risk factors* may relate to the severity of headache but rarely point to the specific causes (Box 16-1). Nausea and vomiting are completely nonspecific. Migraine headaches, increased intracranial pressure, temporal arteritis, and glaucoma can all manifest with severe nausea and vomiting, as can some systemic viral infections with headache. Such factors may point toward the intensity of the discomfort but are not specific in establishing the diagnosis.
10. A *prior history of headache*, although helpful, does not rule out current serious problems. It is extremely helpful, however, to know that the patient has had a workup for severe disease. Previous ED visits, computed tomography (CT) magnetic resonance imaging, and other forms of testing should be inquired about. Patients with both migraine and tension headaches tend to have a stereotypical recurrent pattern. Adherence to these patterns is also helpful in deciding the degree to which a patient's symptoms are pursued.

Physical Examination

Physical findings associated with various forms of headache are listed in Table 16-3.

Ancillary Testing

The vast majority of headache patients do not require additional testing (Table 16-4). The single largest consistent mistake made by emergency physicians in the workup of the headache patient is believing a single CT scan clears the patient of the possibility of SAH or other serious intracranial disease. The CT scan can miss 6 to 8% of patients with SAH, especially in patients with minor (grade I) SAH, who are most treatable.[5] The sensitivity of CT for identifying SAH is reduced by nearly 10% for symptom onset greater than 12 hours and by almost 20% at 3 to 5 days. The basic approach to integrating CTs and lumbar puncture in the assessment of headache is outlined in Figure 16-1.[6,8,9]

BOX 16-1 RISK FACTORS ASSOCIATED WITH POTENTIALLY CATASTROPHIC ILLNESS

1. Carbon monoxide poisoning
   a. Breathing in enclosed or confined spaces with engine exhaust or ventilation of heating equipment
   b. Multiple family members with the same symptoms
   c. Pattern of recurrence in one setting (where the exposure is occurring), relief when not in that setting
   d. Wintertime and working around machinery or equipment producing carbon monoxide (furnaces, etc.)
2. Meningitis/encephalitis/abscess
   a. History of sinus or ear infection or recent surgical procedure
   b. Immunocompromised state
   c. General debilitation with decreased immunologic system function
   d. Acute febrile illness—any type
   e. Extremes of age
   f. Impacted living conditions (e.g., military barracks, college dormitories)
   g. Lack of primary immunizations
3. Temporal arteritis
   a. Age > 50
   b. Females > males 4:1
   c. History of other collagen vascular diseases (e.g., systemic lupus)
   d. Previous chronic meningitis
   e. Previous chronic illness such as tuberculosis, parasitic infection, fungi
4. Glaucoma—sudden angle-closure
   a. Not associated with any usual or customary headache pattern
   b. History of previous glaucoma
   c. Age >30
   d. History of pain increasing in a dark environment
5. Increased intracranial pressure
   a. History of previous benign intracranial hypertension
   b. Presence of a cerebrospinal fluid shunt
   c. History of congenital brain or skull abnormalities
6. Cerebral venous sinus thrombosis
7. Intracranial hemorrhage (ICH)
   a. Subarachnoid hemorrhage (SAH)
      i. Sudden severe pain. "Worst headache of life."
      ii. Acute severe pain following sexual intercourse or straining (i.e., heavy lifting)
      iii. History of SAH or cerebral aneurysm
      iv. History of polycystic kidney disease
      v. Family history of subarachnoid hemorrhage
      vi. Hypertension—severe
      vii. Previous vascular lesions in other areas of the body
      viii. Young and middle-aged
   b. Subdural hematoma (SDH)
      i. History of alcohol dependency with or without trauma
      ii. Current use of anticoagulants
   c. Epidural hematoma (EDH)
      i. Traumatic injury
      ii. Lucid mentation followed by acute altered mentation or somnolence
      iii. Anisocoria on physical examination

Table 16-3 Pivotal Findings on Physical Examination

SIGN	FINDING	POSSIBLE DIAGNOSES
General appearance	Alteration of mental status—nonfocal	Meningitis/encephalitis Subarachnoid hemorrhage Anoxia Increased CSF pressure
	Alterations of mental status with focal findings	Intraparenchymal bleed Tentorial herniation Stroke
	Severe nausea/vomiting	Increased CSF pressure Acute angle-closure glaucoma Subarachnoid hemorrhage
Vital signs	Hypertension with normal heart rate or bradycardia	Increased CSF pressure Subarachnoid hemorrhage Tentorial herniation Intraparenchymal bleed
	Tachycardia	Anoxia/anemia Febrile headache Exertional/coital headaches
	Fever	Febrile headaches Meningitis/encephalitis
HEENT	Tender temporal arteries	Temporal arteritis
Fundi—loss of spontaneous venous pulsations or presence of papilledema	Increased CSF pressure	Mass lesions
	Subhyaloid hemorrhage	Subarachnoid hemorrhage
	Acute red eye (severe ciliary flushing) and poorly reactive pupils	Acute angle-closure glaucoma
	Enlarged pupil with third nerve palsy	Tentorial pressure cone Mass effect (i.e., subdural, epidural, tumor, intraparenchymal hemorrhage)
Neurologic	Lateralized motor or sensory deficit	Stroke (rare) Subdural hematoma, epidural hematoma, hemiplegic or anesthetic migraine (rare)
	Acute cerebellar ataxia	Acute cerebellar hemorrhage Acute cerebellitis (mostly children) Chemical intoxication—various types

CSF, cerebrospinal fluid; HEENT, head, eyes, ears, nose, and throat.

Table 16-4 Diagnostic Adjuncts in Headache Assessment

TEST	FINDING	DIAGNOSIS
Erythrocyte sedimentation rate (ESR)	Significant elevation	Temporal arteritis
ECG	Nonspecific ST-T wave changes	Subarachnoid hemorrhage Increased CSF pressure
CBC	Severe anemia	Anoxia
CT—head	Increased ventricular size	Increased CSF pressure
	Blood in subarachnoid space	Subarachnoid hemorrhage
	Blood in epidural or subdural space	Epidural/subdural hematoma
	Bleeding into parenchyma of brain	Intraparenchymal hemorrhage
	Areas of poor vascular flow	Pale infarct
	Structural/mass lesion	Traction headache secondary to mass effect
Lumbar puncture/CSF analysis	Increased pressure	Pseudotumor cerebri Mass lesions Shunt failure
	Increased protein	Tumor/other structural lesions
	Increased RBCs	Subarachnoid hemorrhage
	Increased WBCs	Infection
	Positive Gram's stain	Infection
	Decreased glucose	Infection

CBC, complete blood count; CSF, cerebrospinal fluid; CT, computed tomography; ECG, electrocardiogram; RBC, red blood cell; WBC, white blood cell.

Table 16-5 Causes and Differentiation of Potentially Catastrophic Illness Presenting with Nontraumatic Headache

DISEASE ENTITIES	PAIN HISTORY	ASSOCIATED SYMPTOMS	SUPPORT HISTORY	PREVALENCE	PHYSICAL EXAMINATION	USEFUL TESTS	ATYPICAL OR IMPORTANT ASPECTS
Carbon monoxide poisoning	Usually gradual, subtle, dull, nonfocal throbbing pain	May wax and wane as they leave and enter the involved area of carbon monoxide. Throbbing may vary considerably	Exposure to engine exhaust, old or defective heating systems, most common in winter months	Rare	No focal neurologic findings. May need cognitive testing	Carbon monoxide level, cognitive testing	May improve on the way to the hospital. Occurs in groups, may involve entire families or groups of people exposed to the carbon monoxide
Subarachnoid hemorrhage	Sudden onset, "thunder clap" or "lightning strike," severe throbbing	Whenever altered mental status is present, the outcome is decidedly worse	History of polycystic kidney disease. History of chronic hypertension	Uncommon	Frequently decreased mentation—meningismus, increased blood pressure, decreased pulse, decreased spontaneous venous pulsations, rarely subhyaloid hemorrhage	CT. Lumbar puncture	If CT positive, immediate involvement of neurosurgery. If CT negative, lumbar puncture
Meningitis/ encephalitis/ abscess	Gradual—as general symptoms increase, headache increases—nonfocal	Decreased mentation prominent, irritability prominent. With abscess, focal neurologic findings may be present	Recent infection Recent facial or dental surgery or other ENT surgery	Uncommon	Fever—late in course, decreased spontaneous venous pulsations	CT. Lumbar puncture	When such infection suspected, treat. Do not delay antibiotics and steroids awaiting laboratory results
Temporal arteritis	Often pain developing over a few hours from mild to severe. Virtually always focal in nature	Decreased vision, nausea, vomiting intense—may confuse diagnosis	Age over 50. Other collagen vascular diseases or inflammatory diseases	Uncommon	Tender temporal arteries	Sedimentation rate	Usually unrelated and rapidly progressive
Acute angle-closure glaucoma	Sudden in onset	Nausea, vomiting, decreased vision	History of glaucoma. History of pain going into dark area	Rare	"Steamy" cornea. Midposition pupil poorly reactive. Acute red eye	Measurement of intraocular pressure	Rapid intervention with medications required—if no relief, immediate surgery may be required
Increased intracranial pressure syndromes	Gradual, dull, nonfocal	Vomiting, decreased mentation	History of CSF shunt or other congenital brain or skull abnormality	Uncommon	Papilledema. Loss of spontaneous venous pulsations	CT. Shunt function study. If OK, lumbar puncture	Shunt failure or other cause of significant increased CSF pressure requires involvement of neurosurgery

CSF, cerebrospinal fluid; CT, computed tomography; ENT, ear, nose, and throat.

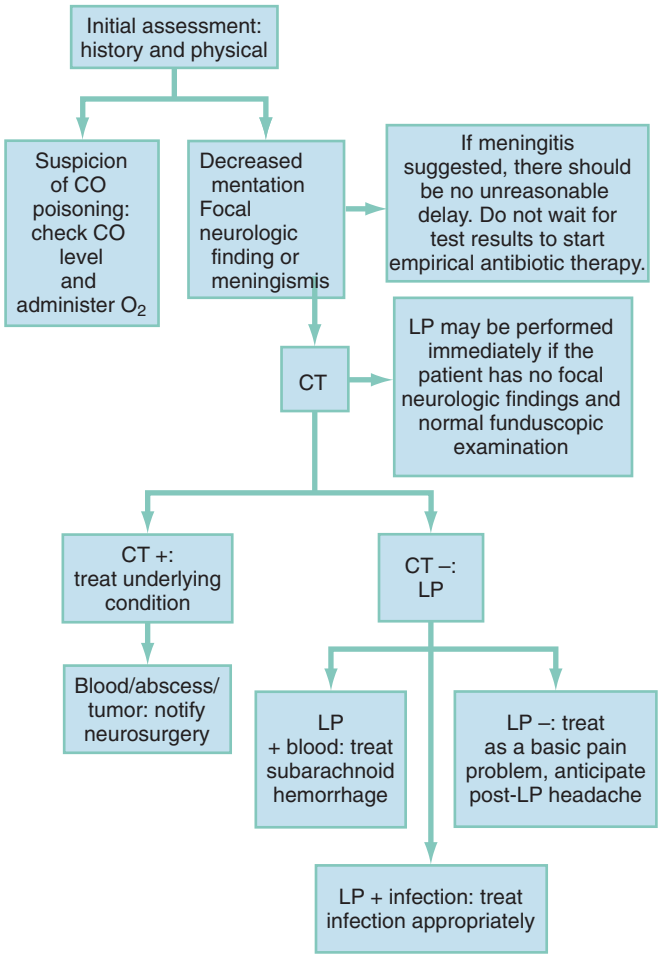

Figure 16-1. Initial assessment and treatment of headache. CO, carbon monoxide; CT, computed tomography; LP, lumbar puncture.

Obtaining cerebrospinal fluid should not delay antimicrobial treatment if intracranial infection is suggested. Intravenous antibiotics should precede lumbar puncture. Abnormal mental status, signs of increased intracranial pressure, papilledema focal findings on the neurologic examination, or any other indication suggestive of focal intracranial lesion requires CT before lumbar puncture.

DIFFERENTIAL CONSIDERATIONS

Certain historical and physical findings can help the emergency physician decide whether the patient falls into an "all clear" or a "warning signal" group. In the warning group, further investigation and testing should be performed on all patients who present with any of the following: (1) sudden onset of headache, (2) "the worst headache ever," (3) decreased or altered mental status, (4) true meningismus, (5) unexplained fever or bradycardia, (6) focal neurologic deficits on examination, (7) symptoms refractory to treatment or worsening under observation, (8) new onset of headache with exertion, or (9) history of HIV. These patients have the highest risk for significant disease.

In addition, a group of reliable "all clear signals" indicates patients who do not require further investigation when *all* are present: (1) previous identical headaches, (2) normal alertness and cognition by both examination and history of the event, (3) normal examination of the neck showing no meningismus, (4) normal vital signs, (5) normal or nonfocal neurologic examination, and (6) improvement under observation or with treatment.

Sequential evaluation and assessment of data are ongoing processes. Patients should be reevaluated while in the ED, and inconsistent findings may require a rapid review of the situation and rethinking of the diagnosis (Table 16-5).[7]

MANAGEMENT

Empirical

Patients with headache represent a spectrum of disease. Patients with headache need to receive triage for evaluation according to their symptoms. Clearly, patients with abnormal vital signs or altered mental status require evaluation before patients with less severe symptoms. If history and physical examination point toward potentially lethal causes, however, effort should be made to establish the diagnosis rapidly with ancillary testing. Pain treatment should be started early. The pain medication of choice depends on the particular patient, underlying vital signs, allergies, and general condition; but relief of pain is still an essential part of the physician's job and should have little effect on the diagnostic workup.

Specific

Specific management for headache is described in Chapter 101. The challenge in emergency medicine, however, is to eliminate life-threatening causes of headache and to treat the patient's pain.

DISPOSITION

Most patients presenting with headache are discharged from the ED with appropriate analgesia and follow-up. These represent patients in the all-clear category or those found to have no serious disease after a careful evaluation and testing. Any patients in whom warning findings are noted require more extensive assessment.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 17 Dyspnea

Sabina Braithwaite and Debra Perina

PERSPECTIVE

Dyspnea is the term applied to the sensation of breathlessness and the patient's reaction to that sensation. It is an uncomfortable awareness of breathing difficulties that in the extreme manifests as "air hunger." Dyspnea is often ill defined by patients, who may describe the feeling as shortness of breath, chest tightness, or difficulty breathing. Dyspnea results from a variety of conditions, ranging from nonurgent to life-threatening. Neither the clinical severity nor the patient's perception correlates well with the seriousness of underlying pathology and may be affected by emotions, behavioral and cultural influences, and external stimuli.[1,2]

The following terms may be used in the assessment of the dyspneic patient:

Tachypnea: A respiratory rate greater than normal. Normal rates range from 44 cycles/min in a newborn to 14 to 18 cycles/min in adults.

Hyperpnea: Greater than normal minute ventilation to meet metabolic requirements.

Hyperventilation: A minute ventilation (determined by respiratory rate and tidal volume) that exceeds metabolic demand. Arterial blood gases (ABG) characteristically show a normal partial pressure of oxygen (Po_2) with an uncompensated respiratory alkalosis (low partial pressure of carbon dioxide [Pco_2] and elevated pH).

Dyspnea on exertion: Dyspnea provoked by physical effort or exertion. It often is quantified in simple terms, such as the number of stairs or number of blocks a patient can manage before the onset of dyspnea.

Orthopnea: Dyspnea in a recumbent position. It usually is measured in number of pillows the patient must use to lie in bed (e.g., two-pillow orthopnea).

Paroxysmal nocturnal dyspnea: Sudden onset of dyspnea occurring while reclining at night, usually related to the presence of congestive heart failure.

Epidemiology

Dyspnea is a common presenting complaint among emergency department patients of all ages. Causes vary widely and may be due to a benign, self-limited condition or significant pathology that can produce long-term morbidity and premature mortality.

Pathophysiology

The actual mechanisms responsible for dyspnea are unknown. Normal breathing is controlled both centrally by the respiratory control center in the medulla oblongata, as well as peripherally by chemoreceptors located near the carotid bodies, and mechanoreceptors in the diaphragm and skeletal muscles.[3] Any imbalance between these sites is perceived as dyspnea. This imbalance generally results from ventilatory demand being greater than capacity.[4]

The perception and sensation of dyspnea are believed to occur by one or more of the following mechanisms: increased work of breathing, such as the increased lung resistance or decreased compliance that occurs with asthma or chronic obstructive pulmonary disease (COPD), or increased respiratory drive, such as results from severe hypoxemia, acidosis, or centrally acting stimuli (toxins, central nervous system events). Pulmonary stretch receptors also are thought to play a role.

DIAGNOSTIC APPROACH

Differential Considerations

Dyspnea is subjective and has many different potential causes.[5] The differential diagnosis list can be divided into acute and chronic causes, of which many are pulmonary. Other etiologies include cardiac, metabolic, infectious, neuromuscular, traumatic, and hematologic (Table 17-1).

Pivotal Findings

History

Duration of Dyspnea. Chronic or progressive dyspnea usually denotes primary cardiac or pulmonary disease.[6] Acute dyspneic spells may result from asthma exacerbation; infection; pulmonary embolus; intermittent cardiac dysfunction; psychogenic causes; or inhalation of irritants, allergens, or foreign bodies.

Onset of Dyspnea. Sudden onset of dyspnea should lead to consideration of pulmonary embolism (PE) or spontaneous pneumothorax. Dyspnea that builds slowly over hours or days may represent a flare of asthma or COPD; pneumonia; recurrent, small pulmonary emboli; congestive heart failure; or malignancy.

Table 17-1 Differential Diagnoses for Acute Dyspnea

ORGAN SYSTEM	CRITICAL DIAGNOSES	EMERGENT DIAGNOSES	NONEMERGENT DIAGNOSES
Pulmonary	Airway obstruction Pulmonary embolus Noncardiogenic edema Anaphylaxis Ventilatory failure	Spontaneous pneumothorax Asthma Cor pulmonale Aspiration Pneumonia	Pleural effusion Neoplasm Pneumonia (CAP score < = 70) COPD
Cardiac	Pulmonary edema Myocardial infarction Cardiac tamponade	Pericarditis	Congenital heart disease Valvular heart disease Cardiomyopathy
Primarily Associated with Normal or Increased Respiratory Effort			
Abdominal		Mechanical interference Hypotension, sepsis from ruptured viscus, bowel obstruction, inflammatory/infectious process	Pregnancy Ascites Obesity
Psychogenic			Hyperventilation syndrome Somatization disorder Panic attack
Metabolic/endocrine	Toxic ingestion DKA	Renal failure Electrolyte abnormalities Metabolic acidosis	Fever Thyroid disease
Infectious	Epiglottitis	Pneumonia (CAP score < = 70)	Pneumonia (CAP score < = 70)
Traumatic	Tension pneumothorax Cardiac tamponade Flail chest	Simple pneumothorax, hemothorax Diaphragmatic rupture	Rib fractures
Hematologic	Carbon monoxide poisoning Acute chest syndrome	Anemia	
Primarily Associated with Decreased Respiratory Effort			
Neuromuscular	CVA, intracranial insult Organophosphate poisoning	Multiple sclerosis Guillain-Barré syndrome Tick paralysis	ALS Polymyositis Porphyria

ALS, amyotrophic lateral sclerosis; CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; DKA, diabetic ketoacidosis.

Positional Changes. Orthopnea can result from left-sided heart failure, COPD, or neuromuscular disorders. One of the earliest symptoms seen in patients with diaphragmatic weakness from neuromuscular disease is orthopnea.[7] Paroxysmal nocturnal dyspnea is most common in patients with left-sided heart failure,[6] but also can be found in COPD. Exertional dyspnea commonly is associated with COPD, but also can be seen with poor cardiac reserve and abdominal loading. Abdominal loading, caused by ascites, obesity, or pregnancy, leads to elevation of the diaphragm, resulting in less effective ventilation and dyspnea.

Trauma. Dyspnea can result from trauma, causing fractured ribs, flail chest, hemothorax, pneumothorax, diaphragmatic rupture, pericardial effusion, cardiac tamponade, or neurologic injury.

Symptoms

Patient descriptions of dyspnea vary significantly and generally correlate poorly with severity. Fever suggests an infectious cause. Anxiety may point to panic attack or psychogenic dyspnea, if no organic cause can be isolated. PE or myocardial infarction may present with isolated dyspnea or with associated chest pain, particularly if the pain is constant, dull, or visceral.[8,9] If the pain is sharp and worsened by deep breathing but not by movement, pleural effusion and pleurisy or pleural irritation from pneumonia or PE are possible. Spontaneous pneumothorax also may produce sharp pain with deep breathing that is not worsened by movement.

Signs

Physical signs in dyspneic patients may be consistent with specific illnesses (Table 17-2). Physical findings found in specific diseases also can be grouped as presenting patterns (Table 17-3).

Ancillary Studies

Specific findings obtained from the history and physical examination should be used to determine which ancillary studies are needed (Table 17-4). Bedside oxygen saturation determinations, or selective use of ABGs when oximetry is not reliable, are useful in determining the degree of hypoxia and the need for supplemental oxygen or assisted ventilation. An additional resource for quickly assessing ventilatory status is noninvasive waveform capnography. Using both the end-tidal CO_2 value and the shape of the waveform itself can be helpful in assessing the adequacy of ventilations as well as potential causes of the dyspnea (See Chapter 3). An electrocardiogram may be useful if the etiology is cardiac or suggests acute pulmonary hypertension.

Serum electrolytes may suggest less common possible causes, such as hypokalemia, hypophosphatemia, diabetic ketoacidosis, or hypocalcemia. A complete blood count may identify severe anemia or thrombocytopenia associated with sepsis. The white blood cell count is not sufficiently sensitive or specific to be of discriminatory value. Cardiac markers and D-dimer assay may be useful in pursuing etiologies such as

Table 17-2 Pivotal Findings in Physical Examination

SIGN	PHYSICAL FINDING	DIAGNOSES TO CONSIDER
Vital signs	Tachypnea	Pneumonia, pneumothorax
	Hypopnea	Intracranial insult, drug/toxin ingestion
	Tachycardia	PE, traumatic chest injury
	Hypotension	Tension pneumothorax
	Fever	Pneumonia, PE
General appearance	Cachexia, weight loss	Malignancy, acquired immune disorder, mycobacterial infection
	Obesity	Hypoventilation, sleep apnea, PE
	Pregnancy	PE
	Barrel chest	COPD
	"Sniffing" position	Epiglottitis
	"Tripoding" position	COPD/asthma with severe distress
	Traumatic injury	Pneumothorax (simple, tension), rib fractures, flail chest, hemothorax, pulmonary contusion
Skin/nails	Tobacco stains/odor	COPD, malignancy, infection
	Clubbing	Chronic hypoxia, intracardiac shunts or pulmonary vascular anomalies
	Pallid skin/conjunctivae	Anemia
	Muscle wasting	Neuromuscular disease
	Bruising	Chest wall: rib fractures, pneumothorax
		Diffuse: thrombocytopenia, chronic steroid use, anticoagulation
	Subcutaneous emphysema	Rib fractures, pneumothorax, tracheobronchial disruption
	Hives, rash	Allergic reaction, infection, tick-borne illness
Neck	Stridor	Upper airway edema/infection, foreign body, traumatic injury, anaphylaxis
	JVD	Tension pneumothorax, COPD or asthma exacerbation, fluid overload/CHF, PE
Lung examination	Wheezes	CHF, anaphylaxis
		Bronchospasm
	Rales	CHF, pneumonia, PE
	Unilateral decrease	Pneumothorax, pleural effusion, consolidation, rib fractures/ contusion, pulmonary contusion
	Hemoptysis	Malignancy, infection, bleeding disorder, CHF
	Sputum production	Infection (viral, bacterial)
	Friction rub	Pleurisy
	Abnormal respiratory pattern (e.g., Cheyne-Stokes)	Intracranial insult
Chest examination	Crepitance or pain on palpation	Rib or sternal fractures
	Subcutaneous emphysema	Pneumothorax, tracheobronchial rupture
	Thoracoabdominal desynchrony	Diaphragmatic injury with herniation; cervical spinal cord trauma
	Flail segment	Flail chest, pulmonary contusion
Cardiac examination	Murmur	PE
	S_3 or S_4 gallop	PE
	S_2 accentuation	PE
	Muffled heart sounds	Cardiac tamponade
Extremities	Calf tenderness, Homans' sign	PE
	Edema	CHF
Neurologic examination	Focal deficits (motor, sensory, cognitive)	Stroke, intracranial hemorrhage causing central abnormal respiratory drive; if long-standing, risk of aspiration pneumonia
	Symmetrical deficits	Neuromuscular disease
	Diffuse weakness	Metabolic or electrolyte abnormality (hypocalcemia, hypomagnesemia, hypophosphatemia), anemia
	Hyporeflexia	Hypermagnesemia
	Ascending weakness	Guillain-Barré syndrome

CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; JVD, jugular venous distention; PE, pulmonary embolism.

cardiac ischemia or PE. Amino-terminal pro-B-type natriuretic peptide (NT-proBNP) analysis adds both diagnostic and prognostic value for several causes of dyspnea, including heart failure, PE, and ischemic cardiac disease.[9-11] Combinations of specific serum markers can also help define pathology.[12-14] Specialized tests, such as ventilation-perfusion scans, chest computed tomography, pulmonary angiography, or, rarely, conventional pulmonary angiography, may confirm the diagnosis of PE.[15] If dyspnea is believed to be upper airway in origin, direct or fiberoptic laryngoscopy or a soft tissue lateral radiograph of the neck may be useful.

DIFFERENTIAL DIAGNOSIS

The range and diversity of pathophysiologic states that produce dyspnea make a simple algorithmic approach difficult.[16] After initial stabilization and assessment, findings from the history, physical examination, and ancillary testing are collated to match patterns of disease that produce dyspnea. This process is updated periodically as new information becomes available. Table 17-3 presents recognizable patterns of disease for common dyspnea-producing conditions, along with specific associated symptoms.

Table 17-3 Diagnostic Table: Patterns of Diseases Often Resulting in Dyspnea

DISEASE	HISTORY: (DYSPNEA)	ASSOCIATED SYMPTOMS	SIGNS AND PHYSICAL FINDINGS	TESTS
Pulmonary embolism	HPI: abrupt onset, pleuritic pain, immobility (travel, recent surgery) PMH: malignancy, DVT, PE, hypercoagulability, oral contraception, obesity	Diaphoresis, exertional dyspnea	Tachycardia, tachypnea, low-grade fever	ABG (A-a gradient), D-dimer ECG (dysrhythmia, right heart strain) CXR (Westermark sign, Hampton's hump) $\dot{V}/\dot{Q}$, spiral CT, MRV Pulmonary angiogram Ultrasound positive for DVT
Pneumonia	Fever, productive cough, chest pain	Anorexia, chills, nausea, vomiting, exertional dyspnea, cough	Fever, tachycardia, tachypnea, rales or decreased breath sounds	CXR, CBC, sputum and blood cultures
Bacterial	SH: tobacco use			ABG if hypoxia suspected Waveform capnography if altered mental status
Viral	Exposure (e.g., influenza, varicella)			
Opportunistic	Immune disorder, chemotherapy			
Fungal/parasitic	Exposure (e.g., birds), indolent onset	Episodic fever, nonproductive cough		
Pneumothorax	Abrupt onset ± trauma, chest pain, thin males more likely to have spontaneous pneumothorax	Localized chest pain	Decreased breath sounds, subcutaneous emphysema, chest wall wounds or instability	CXR: pneumothorax, rib fractures, hemothorax
Simple				Ultrasound positive for pneumothorax
Tension	Decompensation of simple pneumothorax	Diaphoresis	Above JVD, tracheal deviation, muffled heart sounds, cardiovascular collapse	Clinical diagnosis: requires immediate decompression. May verify using bedside ultrasound
COPD/asthma	Tobacco use, medication noncompliance, URI symptoms, sudden weather change PMH: environmental allergies FH: asthma	Air hunger, diaphoresis	Retractions, accessory muscle use, tripoding, cyanosis	CXR: rule out infiltrate, pneumothorax, atelectasis (mucus plug) Waveform capnography
Malignancy	Weight loss, tobacco or other occupational exposure	Dysphagia	Hemoptysis	CXR, chest CT: mass, hilar adenopathy, focal atelectasis
Fluid overload	Gradual onset, dietary indiscretion or medication noncompliance, chest pain PMH: recent MI, diabetes, CHF	Worsening orthopnea, PND	JVD, peripheral edema, S_3 or S_4 gallop, new cardiac dysrhythmia, hepatojugular reflux	CXR: pleural effusion, interstitial edema, Kerley B lines, cardiomegaly ECG: ischemia, dysrhythmia NT-proBNP
Anaphylaxis	Abrupt onset, exposure to allergen	Dysphagia	Oral swelling, stridor, wheezing, hives	

ABG, arterial blood gas; CBC, complete blood count; CHF, congestive heart failure; CT, computed tomography; CXR, chest x-ray; DVT, deep vein thrombosis; ECG, electrocardiogram; FH, family history; HPI, history of present illness; JVD, jugular venous distention; MI, myocardial infarction; MRV, magnetic resonance venography; NT-proBNP, amino-terminal pro-brain natriuretic peptide; PE, pulmonary embolism; PMH, past medical history; PND, paroxysmal nocturnal dyspnea; SH, social history; URI, upper respiratory infection.

Table 17-4 Ancillary Testing in the Dyspneic Patient

CATEGORY	TEST	FINDINGS/POTENTIAL DIAGNOSES
Laboratory	Pulse oximetry, selective ABG use	Hypoxia, hyperventilation (muscular weakness, intracranial event)
	Waveform capnography	CO_2 retention (COPD, sleep apnea), obstructive or restrictive pulmonary pattern Metabolic versus respiratory acidosis (DKA, ingestions) A-a gradient (PE) Elevated carboxyhemoglobin (inhalation injury or CO poisoning)
	Complete blood count	WBC Increase: infection, stress demargination, hematologic malignancy Decrease: neutropenia, sepsis Hgb/Hct: anemia, polycythemia Smear: abnormal Hgb (i.e., sickling), inclusions Platelets: thrombocytopenia (marrow toxicity)
	Chemistry	BUN/Cr: acute/chronic renal failure K/Mg/Phos: low levels resulting in muscular weakness Glucose: DKA D-dimer: abnormal clotting activity NT-proBNP: heart failure, PE Troponin: cardiac ischemia or infarct
Cardiac	ECG	Ischemia, dysrhythmia, $S_1Q_3T_3$ (PE), right heart strain
	Echocardiogram	Pulmonary hypertension, valvular disorders Wall motion abnormalities related to ischemia, intracardiac shunts
Radiologic	Chest radiograph	Bony structures: fractures, lytic lesions, pectus, kyphoscoliosis Mass: malignancy, cavitary lesion, infiltrate, foreign body Diaphragm: eventration, elevation of hemidiaphragm, bowel herniation Mediastinum: adenopathy (infection, sarcoid), air Cardiac silhouette: enlarged (cardiomyopathy, fluid overload) Soft tissue: subcutaneous air Lung parenchyma: blebs, pneumothorax, effusions (blood, infectious), interstitial edema, local consolidation, air bronchograms, Hampton's hump, Westermark's sign
	$\dot{V}/\dot{Q}$ scan	PE
	Pulmonary angiogram	PE, intervention (thrombolysis)
	CT	Mass lesion, adenopathy, trauma, PE
	MRI	PE, bony and soft tissue lesions, vascular abnormality
	Soft tissue neck radiograph	Epiglottitis, foreign body
	Ultrasound	Pneumothorax, pleural effusion, impaired cardiac function or pericardial effusion
Fiberoptic	Bronchoscopy	Mass lesion, foreign body Intervention (stenting, biopsy)
	Laryngoscopy	Mass lesion, edema, epiglottitis, foreign body

A-a, alveolar-arterial; ABG, arterial blood gas; BUN, blood urea nitrogen; CHF, congestive heart failure; CO, carbon monoxide; COPD, chronic obstructive pulmonary disease; Cr, creatinine; CT, computed tomography; DKA,.diabetic ketoacidosis; ECG, electrocardiogram; MRI, magnetic resonance imaging; NT-proBNP, amino-terminal pro-brain natriuretic peptide; PE, pulmonary embolism; V/Q, ventilation-perfusion; WBC, white blood cell.

Critical Diagnoses

Several critical diagnoses should be promptly considered to determine the best treatment options to stabilize the patient. Tension pneumothorax is such a critical diagnosis. If a dyspneic patient has diminished breath sounds on one side, ipsilateral hyper-resonance, severe respiratory distress, hypotension, and oxygen desaturation, prompt decompression of presumptive tension pneumothorax is necessary. Bedside ultrasonography may assist in confirming pneumothorax. If obstruction of the upper airway is evidenced by dyspnea and stridor, early, definitive assessment and intervention must occur in the emergency department or operating room. Complete obstruction by a foreign body warrants the Heimlich maneuver until the obstruction is relieved or the patient is unconscious, followed rapidly by direct laryngoscopy. Congestive heart failure and pulmonary edema can produce dyspnea and respiratory failure and should be treated as soon as possible if severe.[17] Significant dyspnea and wheezing can be seen in anaphylaxis and must be treated promptly to prevent further deterioration. Severe bronchospastic exacerbations of asthma at any age may lead rapidly to respiratory failure and arrest and should receive vigorous attention, including continuous or frequent administration of a beta-agonist aerosol.[18] As mentioned earlier, waveform capnography is a valuable tool for assessing the severity and determining the cause of respiratory distress.

Emergent Diagnoses

Asthma and COPD exacerbations can result in marked dyspnea with bronchospasm and decreased ventilatory volumes.[19] Sudden onset of dyspnea with a decreased oxygen saturation on room air accompanied by sharp chest pain may represent PE.[15] Dyspnea accompanied by decreased breath sounds and tympany to percussion on one side is seen with spontaneous pneumothorax. Dyspnea associated with decreased respiratory effort may represent a neuromuscular process, such as multiple sclerosis, Guillain-Barré syndrome, or myasthenia gravis.[14] Unilateral rales, cough, fever, and dyspnea usually indicate pneumonia.

Figure 17-1 provides an algorithm for assessment and stabilization of a dyspneic patient. The initial division is based on the degree of breathing effort associated with the symptoms.

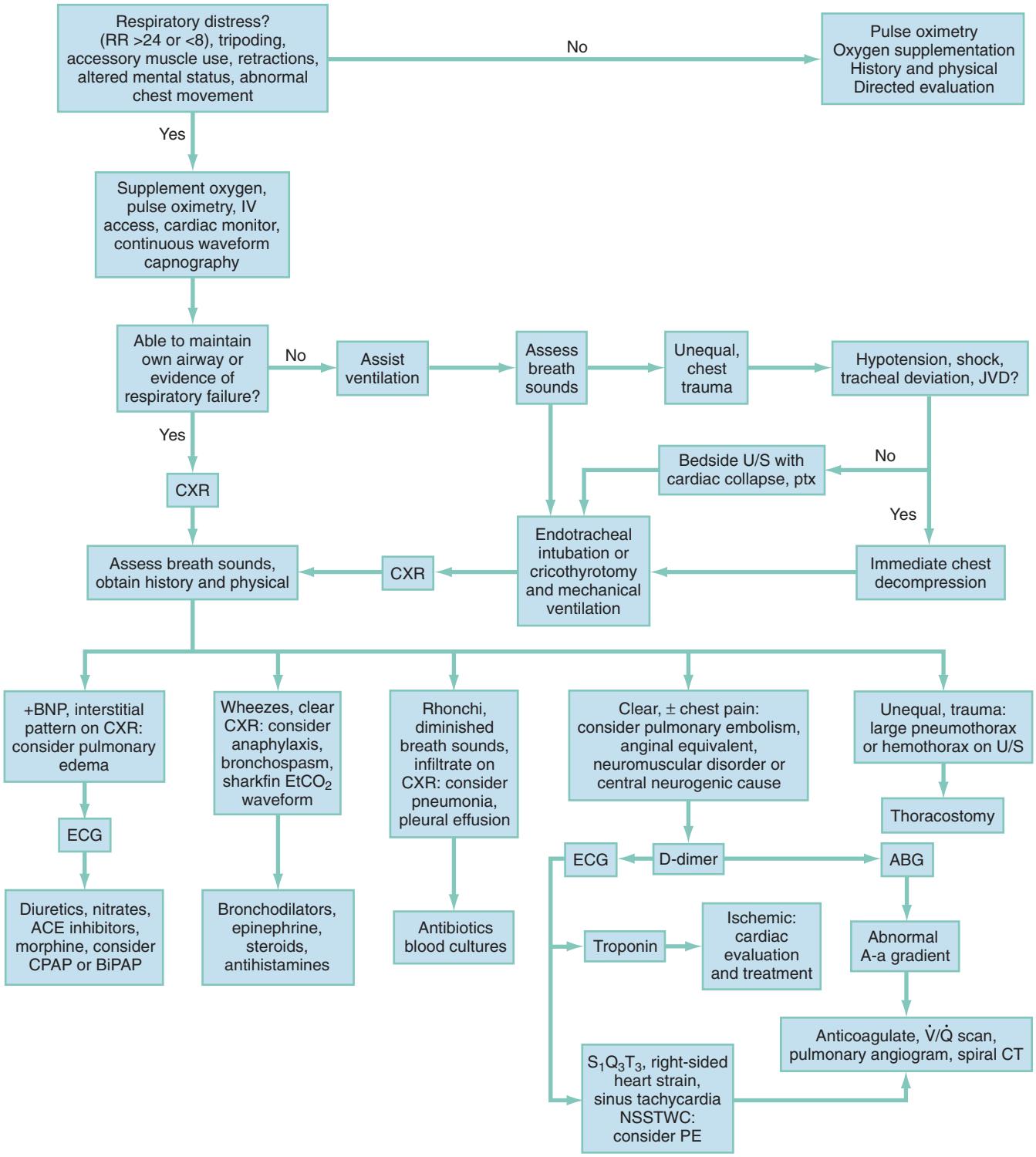

Figure 17-1. Rapid assessment and stabilization of a dyspneic patient. ABG, arterial blood gas; ACE, angiotensin-converting enzyme; BiPAP, biphasic positive airway pressure; BNP, B-type natriuretic peptide; CO, carbon monoxide; CPAP, continuous positive airway pressure; CT, computed tomography; CXR, chest x-ray; ECG, electrocardiogram; $EtCO_2$, end-tidal carbon dioxide; IV, intravenous; JVD, jugular venous distention; NSSTWC, nonspecific ST wave changes (on ECG); PE, pulmonary embolism; RR, respiratory rate; $\dot{V}/\dot{Q}$, ventilation-perfusion ratio; U/S, ultrasound.

The most critical diagnoses must be considered first and appropriate intervention taken as necessary.

All patients experiencing dyspnea, regardless of possible cause, should be promptly transported to the treatment area. Bedside pulse oximetry should be obtained, and the patient should be placed on a cardiac monitor. If the pulse oximetry is less than 98% saturated on room air, the patient should be placed on supplemental oxygen either by nasal cannula or mask depending on the degree of desaturation detected. If necessary, the patient should be intubated, and breathing should be assisted with manual or mechanical ventilation.

When the airway has been secured, rapid assessment of the patient's appearance and vital signs can help determine the need for further stabilization. Decreased mental alertness, inability to speak in more than one-word syllables, or certain types of body positioning, signal the presence of significant

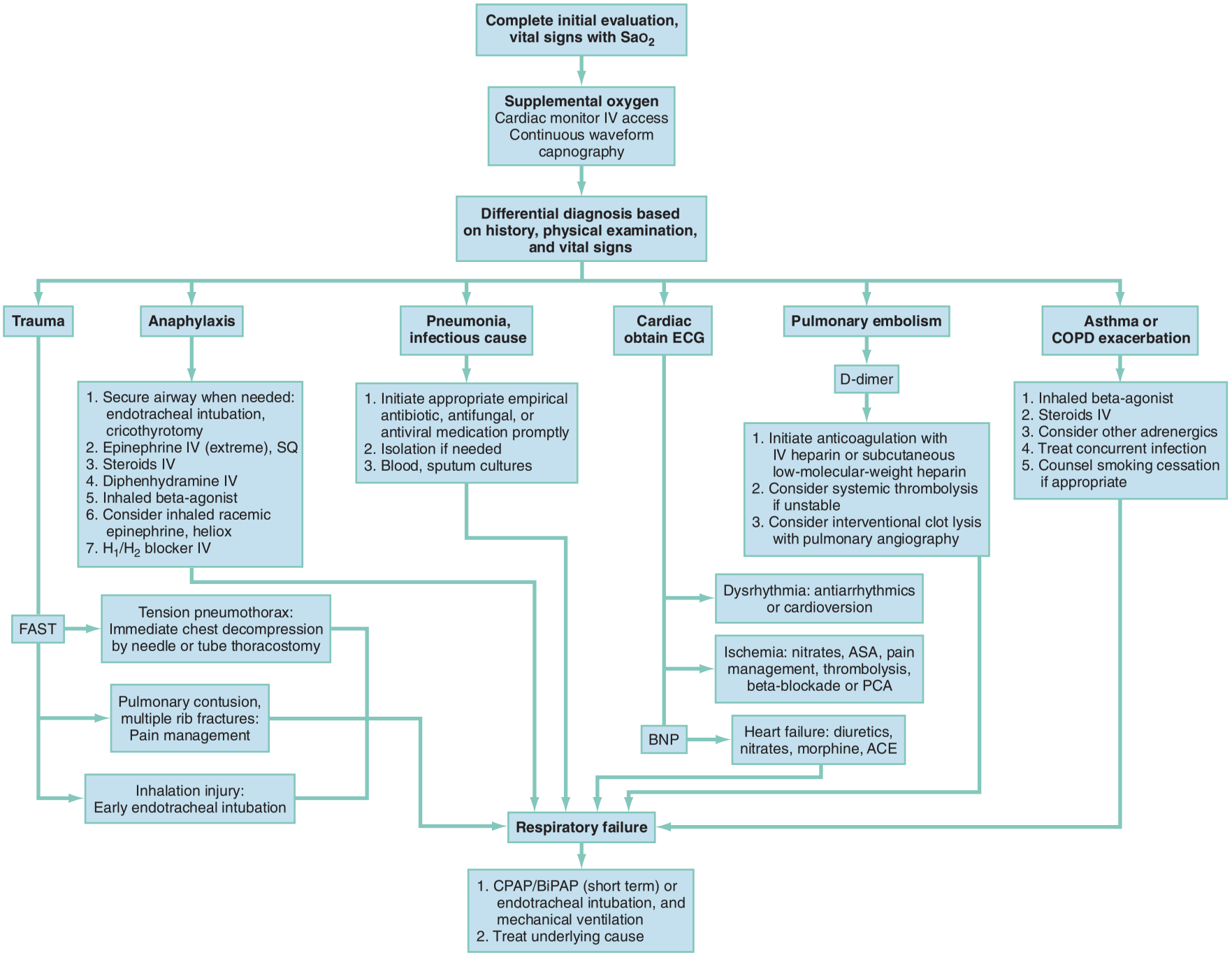

Figure 17-2. Clinical guidelines for emergency department management of dyspnea. ACE, angiotensin-converting enzyme; ASA, acetylsalicylic acid; COPD, chronic obstructive pulmonary disease; CPAP/BiPAP, continuous positive airway pressure/biphasic positive airway pressure; ECG, electrocardiogram; IV, intravenous; PCA, patient-controlled analgesia; SQ, subcutaneous.

respiratory distress and the need for rapid intervention. After stabilization has occurred, the cause of the dyspnea can be further investigated.

EMPIRICAL MANAGEMENT AND DISPOSITION

The management algorithm for dyspnea (Fig. 17-2) outlines the approach to treatment for most identifiable diseases. Unstable patients or patients with critical diagnoses must be stabilized and may require admission to an intensive care unit. Emergent patients who have improved in the emergency department may be admitted to an intermediate care unit. Patients diagnosed with urgent conditions in danger of deterioration without proper treatment or patients with severe comorbidities, such as diabetes, immunosuppression, or cancer, may also require admission for observation and treatment.

Most patients in the nonurgent category can be treated as outpatients if good medical follow-up can be arranged. If dyspnea persists despite therapy and no definitive cause has been delineated, the best course of action is hospitalization for observation and ongoing evaluation. If no definitive diagnosis can be obtained and the symptoms have abated, the patient may be discharged with good medical follow-up and instructions to return if symptoms recur.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 18 Chest Pain

James E. Brown and Glenn C. Hamilton

PERSPECTIVE

Nearly 6 million patients present to the emergency department (ED) each year with complaints of chest pain, constituting 5% of all patients seen in EDs in the United States.[1] Chest pain is a symptom caused by several life-threatening diseases and has a broad differential diagnosis. It is complicated by a frequent disassociation between intensity of symptoms and signs and seriousness of underlying pathology.

Epidemiology

The epidemiology of the critical diagnoses causing chest pain varies widely. Acute coronary syndromes (ACS), aortic dissection, pulmonary embolism (PE), pneumothorax, pericarditis with tamponade, and esophageal rupture are potentially catastrophic causes of chest pain. Due to its high incidence and potential lethality, ACS is the most significant potential diagnosis in the ED. Of all deaths in the United States, 36% are attributed to cardiovascular diseases; these account for approximately 870,000 deaths per year.[2] Historically, emergency physicians misdiagnose 3 to 5% of myocardial infarctions (MIs), accounting for 25% of malpractice losses in emergency medicine.[3,4] Thoracic aortic dissection has an incidence of 0.5 to 1 per 100,000 population with a mortality rate exceeding 90% if misdiagnosed. The true incidence of PE is unclear, with estimates of 70 per 100,000. This equates to approximately 100,000 PE cases per year in the United States.[5] Although the incidence of tension pneumothorax is also unclear, the incidence of spontaneous pneumothorax ranges from 2.5 to 18 per 100,000 total patients. The total incidence of esophageal rupture is 12.5 cases per 100,000 persons. The true incidence of pericarditis is unknown, but is diagnosed in 1 of every 1000 hospital admissions.[6] Up to 5% of ED chest pain patients without acute ST elevation MI may have pericarditis.[7]

Pathophysiology

Afferent fibers from the heart, lungs, great vessels, and esophagus enter the same thoracic dorsal ganglia. Through these visceral fibers, each organ produces the same indistinct quality and location of pain. The quality of visceral chest pain varies widely and is described as "burning," "aching," "stabbing," or "pressure." Since dorsal segments overlap three segments above and below a level, disease of a thoracic origin can produce pain anywhere from the jaw to the epigastrium. Radiation of pain is caused by somatic afferent fibers synapsing in the same dorsal root ganglia as the thoracic viscera. This stimulation can "confuse" the patient's central nervous system into misperceiving that the pain originates in the arms or shoulders.

DIAGNOSTIC APPROACH

Differential Considerations

Due to the indistinct nature of visceral pain, the differential diagnosis of chest pain is broad and includes many of the most critical diagnoses in medicine and many nonemergent conditions (Table 18-1).

Rapid Stabilization and Assessment

The initial questions are, "Must I intervene immediately?", and "What are the life-threatening possibilities in this patient?" The answers are usually apparent within the first few minutes after assessing the patient's appearance and vital signs. One of the critical diagnoses is tension pneumothorax. If a patient presents with chest pain, respiratory distress, shock, and unilateral reduction or absence of breath sounds, immediate intervention with needle or tube thoracostomy is required. Additionally, patients with severe derangements in vital signs require stabilizing treatment during a search for the precipitating cause. Patients who present with respiratory distress require immediate intervention and lead the emergency physician to consider a more serious cause of the pain (Fig. 18-1; also see Chapter 17).

All patients, except those with obvious benign causes of chest pain, must have an electrocardiogram (ECG) within minutes of reporting their pain. This ECG should be read for acute MI by the emergency physician as soon as it is completed. Patients with positive ECG findings and those considered at high risk are triaged directly to the treatment area and monitored. Symptomatic derangements in vital signs are addressed. If vital signs are stable, a focused history and physical examination are performed. Most patients also require a chest radiograph to evaluate the chest pain. If a cardiac cause is suggested and vital signs are stable, pain relief with nitroglycerin (0.4 mg sublingual every 3–5 minutes) may be appropriate. Aspirin (81–325 mg) is a consideration for patients without hemorrhagic disorders, known allergies, or vascular dissections. Clopidogrel (loading dose 300 mg) or other anti-

Table 18-1 Differential Diagnosis of Chest Pain

ORGAN SYSTEM	CRITICAL DIAGNOSES	EMERGENT DIAGNOSES	NONEMERGENT DIAGNOSES
Cardiovascular	Acute myocardial infarction Acute coronary ischemia Aortic dissection Cardiac tamponade	Unstable angina Coronary spasm Prinzmetal's angina Cocaine-induced pericarditis or myocarditis	Valvular heart disease Aortic stenosis Mitral valve prolapse Hypertrophic cardiomyopathy
Pulmonary	Pulmonary embolus Tension pneumothorax	Pneumothorax Mediastinitis	Pneumonia Pleuritis Tumor Pneumomediastinum
Gastrointestinal	Esophageal rupture (Boerhaave)	Esophageal tear (Mallory-Weiss) Cholecystitis Pancreatitis	Esophageal spasm Esophageal reflux Peptic ulcer Biliary colic
Musculoskeletal			Muscle strain Rib fracture Arthritis Tumor Costochondritis Nonspecific chest wall pain
Neurologic			Spinal root compression Thoracic outlet Herpes zoster Postherpetic neuralgia
Other			Psychologic Hyperventilation

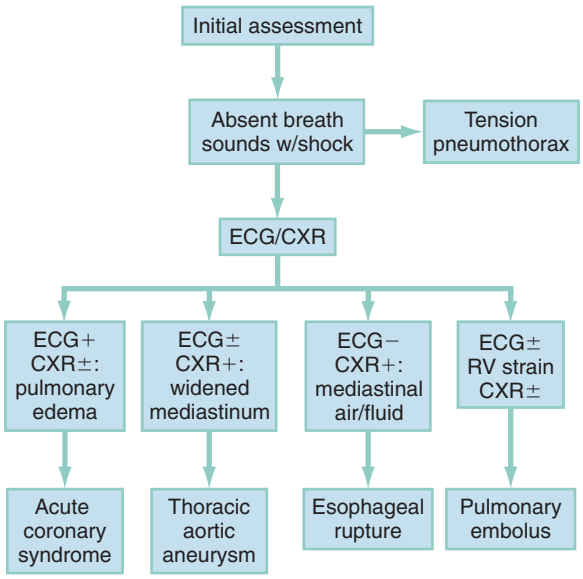

Figure 18-1. Initial assessment of critical diagnoses. CXR, chest x-ray; ECG, electrocardiogram; RV, right ventricular.

platelet agents may also be an alternative. Patients with low voltage on the ECG, diffuse ST segment elevation, elevated jugular venous pressure on examination,[8] and signs of shock should undergo prompt bedside cardiac ultrasound.

Pivotal Findings

The broad and complex nature of chest pain defies application of a simple algorithm. An organized approach to a patient with chest pain is essential, however, to ensure that all causes are evaluated appropriately. The history and physical examination are key to diagnosis. Information pertinent to the differential diagnosis is obtained by the history, physical examination, and ECG in 80 to 90% of patients.

History

1. The patient is asked to describe the character of the pain or discomfort. Descriptions such as "squeezing," "crushing," or "pressure" lead the emergency physician to suspect a cardiac ischemic syndrome, although cardiac ischemia can also be characterized by nonspecific discomfort, such as "bloating" or "indigestion." "Tearing" pain that may migrate from the front to back or back to front is the classic description in aortic dissection. "Sharp" or "stabbing" pain is seen more in pulmonary and musculoskeletal diagnoses. Patients complaining of a "burning" or "indigestion" type of pain may initially be thought to have a gastrointestinal etiology, but due to the visceral nature of chest pain, all causes of pain may present with any of the preceding descriptions. Of note, descriptors may vary among ethnic groups, and, for example, "sharp" may mean "severe."
2. Additional history about the patient's activity at the onset of pain may be helpful. Pain occurring during exertion suggests an ischemic coronary syndrome, whereas progressive onset of pain at rest suggests acute MI. Pain of sudden onset is more typical with aortic dissection, PE, or pneumothorax. Pain after meals is more indicative of a gastrointestinal cause.
3. The severity of pain is commonly quantified using a 1-to-10 pain scale. Alterations in pain severity are documented at times of onset, peak, present, and after intervention.
4. The location of the discomfort is described. Pain that is localized to a small area is more likely to be somatic versus visceral in origin. Pain localized at the periphery of the

chest is more likely with a pulmonary rather than cardiac etiology. Lower chest or upper abdominal pain may be of cardiac or gastrointestinal origin.

5. Any description of radiation of pain should be noted. Transthoracic pain through to the back should suggest aortic dissection or gastrointestinal causes, especially pancreatitis or posterior ulcer. Inferioposterior myocardial ischemia may also present primarily as thoracic back pain. Radiation to the arms, neck, or jaw increases the likelihood of cardiac ischemia.[9,10] Pain located primarily in the back, especially interscapular back pain that migrates to the base of the neck, suggests aortic dissection.[11]
6. Duration of pain is another important historical factor. Pain that lasts a few seconds is rarely of cardiac origin.[12] Pain that is exertional but lasts for only a few minutes after rest may be a manifestation of cardiac ischemia.[9] Pain that is maximal at onset may be due to aortic dissection.[11] Pain that is not severe and persists over the course of days is less likely to be of serious origin than pain that is severe or has a stuttering or fluctuating course.
7. The clinician should consider aggravating or alleviating factors. Pain that worsens with exertion and improves with rest is more likely related to coronary ischemia.[9] Pain related to meals is more suggestive of a gastrointestinal cause. Pain that worsens with respiration is seen more often with pulmonary, pericardial, and musculoskeletal causes.
8. Other associated symptoms may suggest the visceral nature of the pain (Table 18-2). Diaphoresis should lead to an increased clinical suspicion for a serious or visceral cause. Hemoptysis, a classic PE sign, is rarely seen.[13] Near-syncope and syncope lead to higher likelihood of a cardiovascular cause or PE. Dyspnea is seen in cardiovascular and pulmonary disease. Nausea and vomiting may be seen in cardiovascular and gastrointestinal complaints.
9. A history of prior pain and the diagnosis of that episode can facilitate the diagnostic process, but the physician must be wary of prior presumptive diagnoses that may be misleading. A prior history of cardiac testing, such as stress testing, echocardiography, or angiography, may be useful in determining if the current episode is suggestive of cardiac disease. Similarly, patients with previous spontaneous pneumothorax or PE[14] are at increased risk of recurrence.
10. The presence of risk factors for a particular disease is primarily of value as an epidemiologic marker for large population studies (Box 18-1). In the ED, presence of risk factors in an individual patient without established disease has minimal or no effect on the clinical likelihood (pretest probability) of a specific disease process.

Table 18-2 Significant Symptoms of Chest Pain

SYMPTOM	FINDING	DIAGNOSIS
Pain	Severe, crushing, pressure, substernal, exertional, radiation to jaw, neck, shoulder, arm	Acute MI Coronary ischemia Unstable angina Coronary spasm
	Tearing, severe, radiating to or located in back, maximum at onset, may migrate to upper back or neck	Aortic dissection
	Pleuritic	Esophageal rupture Pneumothorax Cholecystitis Pericarditis Myocarditis
	Indigestion or burning	Acute MI Coronary ischemia Esophageal rupture Unstable angina Coronary spasm Esophageal tear Cholecystitis
Associated syncope/ near-syncope		Aortic dissection PE Acute MI Pericarditis Myocarditis
Associated dyspnea (SOB, DOE, PND, orthopnea)		Acute MI Coronary ischemia PE Tension pneumothorax Pneumothorax Unstable angina Pericarditis
Associated hemoptysis		PE
Associated nausea/ vomiting		Esophageal rupture Acute MI Coronary ischemia Unstable angina Coronary spasm Esophageal tear Cholecystitis

DOE, dyspnea on exertion; MI, myocardial infarction; PE, Pulmonary embolism; PND, paroxysmal nocturnal dyspnea; SOB, shortness of breath.

Physical Examination

Specific findings may be found in a variety of causes (Table 18-3).

Ancillary Studies

The two most commonly performed studies in patients with chest pain are the chest radiograph and 12-lead ECG (Table 18-4). An ECG should be performed within 10 minutes of arrival in all patients with chest pain in whom myocardial ischemia is a possibility.[15,16] This generally includes all male patients 33 years old and older and female patients over the age of 39 who complain of pain from the umbilicus to the mandible unless a noncardiac cause is readily apparent. Rapid acquisition of the ECG facilitates the diagnosis of acute MI and expedites the National Heart, Lung, and Blood Institute's recommended "door to treatment" times from arrival to percutaneous coronary intervention (PCI) or thrombolytic therapy in acute MI. Patients with a new injury pattern on ECG (Table 18-5) or new ischemic ECG changes should have appropriate therapy instituted at this point (Fig. 18-2; see also Chapter 77). An ECG showing right ventricular strain pattern, in the appropriate setting, should raise the clinical suspicion for PE. Diffuse ST segment elevation helps make the diagnosis of pericarditis.

A chest radiograph is performed for patients with a possibly serious cause of chest pain. Pneumothorax is definitively diagnosed at this point. A wide mediastinum or ill-defined aortic knob increases the clinical suspicion for acute aortic dissection. Pleural effusion, subcutaneous air, or mediastinal air-fluid

Table 18-3 Pivotal Findings in Physical Examination

SIGN	FINDING	DIAGNOSES
Appearance	Acute respiratory distress	PE Tension pneumothorax Acute MI Pneumothorax
	Diaphoresis	Acute MI Aortic dissection Coronary ischemia PE Esophageal rupture Unstable angina Cholecystitis Perforated peptic ulcer
Vital signs	Hypotension	Tension pneumothorax PE Acute MI Aortic dissection (late) Coronary ischemia Esophageal rupture Pericarditis Myocarditis
	Tachycardia	Acute MI PE Aortic dissection Coronary ischemia Tension pneumothorax Esophageal rupture Coronary spasm Pericarditis Myocarditis Mediastinitis Cholecystitis Esophageal tear (Mallory-Weiss)
	Bradycardia	Acute MI Coronary ischemia Unstable angina
	Hypertension	Acute MI Coronary ischemia Aortic dissection (early)
	Fever	PE Esophageal rupture Pericarditis Myocarditis Mediastinitis Cholecystitis
	Hypoxemia	PE Tension pneumothorax Pneumothorax
Cardiovascular examination	Significant difference in upper extremity blood pressures	Aortic dissection
	Narrow pulse pressure	Pericarditis (with effusion)
	New murmur	Acute MI Aortic dissection Coronary ischemia
	S_3/S_4 gallop	Acute MI Coronary ischemia
	Pericardial rub	Pericarditis
	Audible systolic "crunch" on cardiac auscultation (Hamman's sign)	Esophageal rupture Mediastinitis
	JVD	Acute MI Coronary ischemia Tension pneumothorax PE Pericarditis
Pulmonary examination	Unilateral diminished/absent breath sounds	Tension pneumothorax Pneumothorax
	Pleural rub	PE
	Subcutaneous emphysema	Tension pneumothorax Esophageal rupture Pneumothorax Mediastinitis
	Rales	Acute MI Coronary ischemia Unstable angina
Abdominal examination	Epigastric tenderness	Esophageal rupture Esophageal tear Cholecystitis Pancreatitis
	Left upper quadrant tenderness	Pancreatitis
	Right upper quadrant tenderness	Cholecystitis
Extremity examination	Unilateral leg swelling, warmth, pain, tenderness, or erythema	PE
Neurologic examination	Focal findings Stroke	Aortic dissection Acute MI Coronary ischemia Aortic dissection Coronary spasm

JVD, jugular venous distention; MI, myocardial infarction; PE, pulmonary embolism.

BOX 18-1 RISK FACTORS ASSOCIATED WITH POTENTIALLY CATASTROPHIC CAUSES OF CHEST PAIN

- Acute coronary syndromes
  - Past or family history of coronary artery disease
  - Age
    - Men >33 years
    - Women >40 years
  - Diabetes mellitus
  - Hypertension
  - Cigarette use/possible passive exposure
  - Elevated cholesterol (LDL)/triglycerides
  - Sedentary lifestyle
  - Obesity
  - Postmenopausal
  - Left ventricular hypertrophy
  - Cocaine abuse
- Pulmonary embolism
  - Prolonged immobilization
  - Surgery >30 minutes in last 3 mo
  - Prior deep vein thrombosis or pulmonary embolus
  - Pregnancy or recent pregnancy
  - Pelvic or lower extremity trauma
  - Oral contraceptives with cigarette smoking
  - Congestive heart failure
  - Chronic obstructive pulmonary disease
  - Obesity
  - Past medical or family history of hypercoagulability
- Aortic dissection
  - Hypertension
  - Congenital disease of the aorta or aortic valve
  - Inflammatory aortic disease
  - Connective tissue disease
  - Pregnancy
  - Arteriosclerosis
  - Cigarette use
- Pericarditis or myocarditis
  - Infection
  - Autoimmune disease (e.g., systemic lupus erythematosus)
  - Acute rheumatic fever
  - Recent myocardial infarction or cardiac surgery
  - Malignancy
  - Radiation therapy to mediastinum
  - Uremia
  - Drugs
  - Prior pericarditis
- Pneumothorax
  - Prior pneumothorax
  - Valsalva's maneuver
  - Chronic lung disease
  - Cigarette use

Table 18-4 Ancillary Testing of Patients with Chest Pain

TEST	FINDING	DIAGNOSIS
ECG	New injury	Acute MI Aortic dissection
	New ischemia	Coronary ischemia Coronary spasm
	RV strain	PE
	Diffuse ST segment elevation	Pericarditis
CXR	Pneumothorax with mediastinal shift	Tension pneumothorax
	Wide mediastinum	Aortic dissection
	Pneumothorax	Esophageal rupture Pneumothorax
	Effusion	Esophageal rupture
	Increased cardiac silhouette	Pericarditis
	Pneumomediastinum	Esophageal rupture Mediastinitis
ABG	Hypoxemia, A-a gradient	PE
$\dot{V}/\dot{Q}$ scan or spiral CT	High probability or any positive in patient with high clinical suspicion	PE

ABG, arterial blood gas; CT, computed tomography; ECG, electrocardiogram; MI, myocardial infarction; RV, right ventricular.

Table 18-5 Electrocardiogram Findings in Ischemic Chest Pain

Classic myocardial infarction	ST segment elevation (>1 mm) in contiguous leads; new LBBB; Q waves ≥0.04 sec duration
Subendocardial infarction	T wave inversion or ST segment depression in concordant leads
Unstable angina	Most often normal or nonspecific changes; may see T wave inversion
Pericarditis	Diffuse ST segment elevation; PR segment depression

LBBB, left bundle-branch block.

level may be seen in esophageal rupture. Increased cardiac silhouette may indicate pericarditis or cardiomyopathy.

Pneumomediastinum is seen with esophageal rupture and mediastinitis. A serum D-dimer assay may help discriminate patients with PE from those with a possible gastrointestinal cause. A low serum D-dimer in a patient without a high pretest probability of PE effectively excludes the diagnosis.[13,17,18] (see Chapter 87.)

Patients at high pretest probability for PE should undergo diagnostic imaging (multidetector computed tomography [CT], or, less commonly, pulmonary angiography or a ventilation-perfusion lung scan).[19] High pretest probability warrants initiation of anticoagulation (heparin or low-molecular-weight heparin) therapy in the ED before the imaging study, in the absence of a contraindication.

Patients with suspected thoracic aortic dissection may be evaluated by CT angiography, transesophageal echocardiography, or magnetic resonance imaging. Selection of imaging modality depends on patient status and availability of the testing equipment.[20]

CT with a 64 or higher detector scanner has the potential to rule out all of the life-threatening causes of chest pain. Although the "triple rule out" of ACS, PE, and thoracic dissection are the causes most commonly discussed, pneumothorax, mediastinitis, and pericardial effusions are also diagnosed with CT.[21,22]

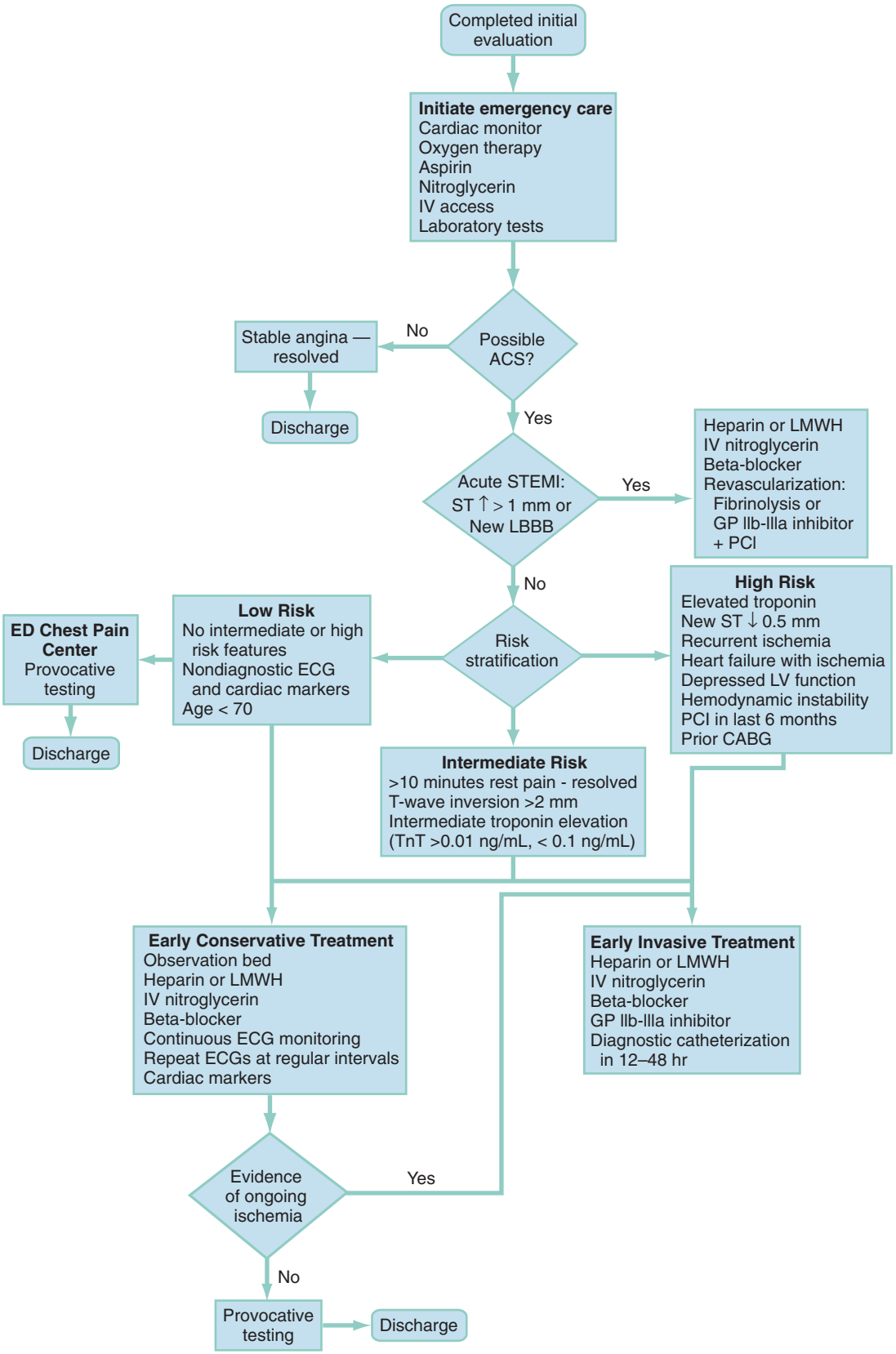

Figure 18-2. Clinical guidelines for emergency department management of chest pain of myocardial ischemic origin. ACS, acute coronary syndrome; CABG, coronary artery bypass graft; ECG, electrocardiogram; GP, glycoprotein; IV, intravenous; LBBB, left bundle-branch block; LMWH, low-molecular-weight heparin; LV, left ventricular; MI, myocardial infarction; PCI, percutaneous coronary intervention; ST, echocardiographic peak; STEMI, ST segment evaluation myocardial infarction; TnT, troponin T. (Adapted from Gibler WB, Cannon CP, Blonikalns AL, et al: Practical implementation of the guidelines for unstable angina/non-ST-segment elevation myocardial infarction in the emergency department: A scientific statement from the American Heart Association Council on Clinical Cardiology (Subcommittee on Acute Cardiac Care), Council on Cardiovascular Nursing, and Quality of Care and Outcomes Research Interdisciplinary Working Group, in Collaboration with the Society of Chest Pain Centers. Circulation 111:2699, 2005.)

Table 18-6 Causes and Differentiation of Potentially Catastrophic Illness Presenting with Central Chest Pain or Discomfort

	PAIN HISTORY	ASSOCIATED SYMPTOMS	SUPPORTING HISTORY	PREVALENCE IN EMERGENCY DEPARTMENT	PHYSICAL EXAMINATION	USEFUL TESTS	ATYPICAL OR ADDITIONAL ASPECTS
Myocardial Infarction	Discomfort is usually moderately severe to severe and rapid in onset. May be more "pressure" than pain. Usually retrosternal, may radiate to neck, jaw, both arms, upper back, epigastrium, and sides of chest (left more than right). Lasts more than 15–30 min and is unrelieved by NTG	Diaphoresis, nausea, vomiting, dyspnea	May be precipitated by emotional stress or exertion. Often comes on at rest. May come on in early awakening period. Prodromal pain pattern often elicited. Previous history of MI or angina. Age >40 years, positive risk factors, and male sex increase possibility	Common	Patients are anxious and uncomfortable. Blood pressure usually is elevated, but normotension and hypotension are seen. The heart rate is usually mildly increased, but bradycardia can be seen. Patients may be diaphoretic and show peripheral poor perfusion. There are no diagnostic examination findings for MI, although S_3 and S_4 heart sounds and new murmur are supportive	ECG changes (new Q waves or ST segment–T wave changes) occur in 80% of patients. CK-MB and troponins are helpful if elevated, but may be normal	Pain may present as "indigestion" or "unable to describe." Other atypical presentations include altered mental status, stroke, angina pattern without extended pain, severe fatigue, syncope. Elderly may present with weakness, congestive heart failure, or chest tightness. 25% of nonfatal MIs are unrecognized by patient. The pain may have resolved by the time of evaluation
Unstable Angina	Changes in pattern of preexisting angina with more severe, prolonged, or frequent pain (crescendo angina). Pain usually lasts >10 min. Angina at rest lasting 15–20 min or new-onset angina (duration <2 mo) with minimal exertion. Pattern of pain change important in gauging risk for AMI. Unpredictable responses to NTG and rest	Often minimal. May have mild diaphoresis, nausea, dyspnea with pain. Increasing pattern of dyspnea on exertion	Not clearly related to precipitating factors. May be a decrease in amount of physical activity that initiates pain. Previous history of MI or angina. Over 40 years old, presence of risk factors, and male sex increase probability	Common	Nonspecific findings of a transient nature, may have similar cardiac findings as in MI, especially intermittent diaphoresis	Often no ECG or enzyme changes. Variant angina (Prinzmetal's) has episodic pain, at rest, often severe, with prominent ST segment elevation	May be pain-free at presentation. Full history is essential. Fewer than 15% of patients hospitalized for unstable angina go on to acute MI. May respond to NTG. May manifest similarly to non–Q wave infarction

Aortic Dissection	90% of patients have rapid-onset severe chest pain that is maximal at beginning. Radiates anteriorly in chest to the back interscapular area or into abdomen. Pain often has a "tearing" sensation, and may migrate	Neurologic complications of stroke, peripheral neuropathy, paresis or paraplegia, abdominal and extremity ischemia possible	Median age 59 years. History of hypertension in 70–90% of patients. 3:1 ratio males to females. Marfan's syndrome and congenital bicuspid aortic valves have increased incidence	Rare	Often poorly perfused peripherally but with elevated BP. In 50–60% of cases, there is asymmetrical decrease or absence of peripheral pulses. 50% of proximal dissections cause aortic insufficiency. Other vascular occlusions: coronary (1–2%), mesentery, renal, spinal cord. New-onset pericardial friction rub or aortic insufficiency murmur supportive of diagnosis	ECG usually shows left ventricular hypertrophy, nonspecific changes. Chest film shows abnormal aortic silhouette (90%). Aortic angiography has diagnostic accuracy of 95–99%. Transesophageal echocardiogram, CT, MRI most useful in screening	Rare for patient to present pain-free. May present with neurologic complications. Physical examination findings may be minimal. Dissection into coronary arteries can mimic MI Ascending aortic aneurysms are more often approached surgically. Descending are generally managed medically
Pulmonary Embolism	Pain is more often lateral-pleuritic. Central pain is more consistent with massive embolus. Abrupt in onset and maximal at beginning. May be episodic or intermittent	Dyspnea and apprehension play a prominent role, often more than pain. Cough accompanies about half the cases Hemoptysis occurs in <20%. Angina-like pain may occur in 5%	Often some period of immobilization has occurred, e.g., postoperative. Pregnancy, oral contraceptives, heart disease, and cancer are all risk factors. Previous DVT or PE is the greatest risk factor	Uncommon in ambulatory patients, but common in departments with high volumes of elderly or medically complex patients	Patients are anxious and often have a respiratory rate >16/min. Tachycardia, inspiratory rales, and an increased pulmonic second sound are common. Fever, phlebitis, and diaphoresis are seen in 30–40% of patients. Wheezes and peripheral cyanosis are less common	Arterial blood gases show Po_2 < 80 mm Hg in 90%. Widened A-a gradient is helpful. Chest film is usually normal, although 40% show some volume loss, oligemia, or signs of consolidation due to pulmonary infarction. Lung perfusion scan rules out, if truly negative	Patients may present with dyspnea with or without bronchospasm. Acute mortality rate is 10%. Emboli usually from lower extremities above knee, prostate/pelvis venous plexus, right heart. May be subtle cause of COPD exacerbation

Table 18-6 Causes and Differentiation of Potentially Catastrophic Illness Presenting with Central Chest Pain or Discomfort—cont'd

	PAIN HISTORY	ASSOCIATED SYMPTOMS	SUPPORTING HISTORY	PREVALENCE IN EMERGENCY DEPARTMENT	PHYSICAL EXAMINATION	USEFUL TESTS	ATYPICAL OR ADDITIONAL ASPECTS
Pneumothorax	Pain is usually acute and maximal at onset. Most often lateral-pleuritic, but central pain can occur in large pneumothorax	Dyspnea has a prominent role. Hypotension and altered mental states occur in tension pneumothorax	Chest trauma, previous episode, or asthenic body type	Infrequent	Decreased breath sounds, increased resonance on percussion. Elevated pressure in neck veins occurs in tension pneumothorax	Chest film definitive. Inspiratory and expiratory films may enhance contrast between air and lung parenchyma. Tension pneumothorax should be diagnosed on physical examination	May be subtle in COPD, asthma, cystic fibrosis. Can be complicated by pneumomediastinum
Esophageal Rupture	Pain usually is preceded by vomiting and is abrupt in onset. Pain is persistent and unrelieved, localized along the esophagus, and increased by swallowing and neck flexion	Diaphoresis, dyspnea (late), shock	Older individual with known gastrointestinal problems. History of violent emesis, foreign body, caustic ingestion, blunt trauma, alcoholism, esophageal disease	Rare	Signs of lung consolidation, subcutaneous emphysema may be present	Chest film usually has mediastinal air, a left-sided pleural effusion, pneumothorax, or a widened mediastinum. pH of pleural effusion is <6.0. Diagnosis supported by water-soluble contrast esophagram or esophagoscopy	Patient may present in shock state. This entity often considered late in differential diagnostic process
Pericarditis	Dull, aching recurrent pain unrelated to exercises or meals. Or it may be a sharp, stabbing, pleuritic-type pain that does not change with chest wall motion. May be severe. Not relieved by NTG	Dyspnea, diaphoresis	Pain is often worse when supine, but improves sitting up. Often preceded by viral illness or underlying disease (SLE or uremia)	Rare Tamponade even more rare complication	Friction rub may be heard, often fleeting, position-dependent (50% of patients).	ECG pattern typical for ST segment elevation across the precordial leads. Erythrocyte sedimentation rate may be elevated	More common in 20- to 50-year-olds. May have associated tachycardias, ventricular dysrhythmias. Idiopathic most common (80%). Treated with aspirin, NSAID

AMI, acute myocardial infarction; CK-MB, an isoform of creatine kinase; COPD, chronic obstructive pulmonary disease; CT, computed tomography; DVT, deep vein thrombosis; ECG, electrocardiogram; MRI, magnetic resonance imaging; NSAID, nonsteroidal anti-inflammatory drug; NTG, nitroglycerin; PE, pulmonary embolus; SLE, systemic lupus erythematosus.

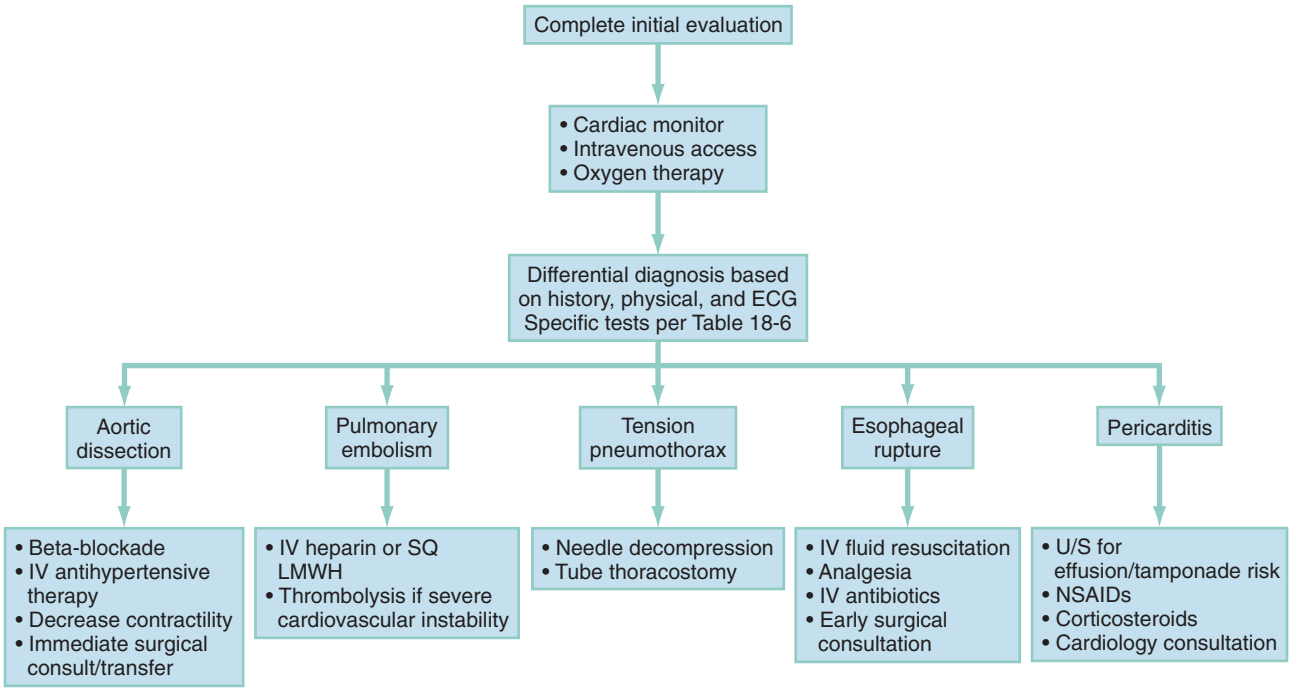

Figure 18-3. Clinical guidelines for emergency department management of chest pain from potentially catastrophic nonmyocardial origins. ECG, electrocardiogram; IV, intravenous; NSAIDs, nonsteroidal anti-inflammatory drugs; SQ, subcutaneous; LMWH, low-molecular-weight heparin; U/S, ultrasound.

Laboratory testing is useful in the evaluation of ACS. Creatine kinase (CK) is associated with multiple false-positive results and has no use in the evaluation of unstable angina. CK-MB, an isoform of CK, is more specific for cardiac ischemia. Evaluating this enzyme produces fewer false-positive results, and peak sensitivity approaches 98%. Sensitivity at 4 hours is, however, only about 60%. CK-MB isoforms improve sensitivity at 4 hours to 80%, approaching 93% at 6 hours. The current universal definition of MI places CK and CK-MB in a secondary role to troponins.[23]

Troponins (I and T), when elevated, identify patients with ACS who have the highest risk for an adverse outcome.[23,24] Sensitivity for acute MI at 4 hours is 60%, rising to nearly 100% by 12 hours.[25,26] Elevated troponin in the correct clinical setting is synonymous with acute MI and is embedded in the universal definition of MI.

DIAGNOSTIC TABLE

After the patient is stabilized and assessment has been completed, the findings are matched to the classic and atypical patterns of the seven potentially critical diseases causing chest pain. This matching process is continual while evaluating the patient and monitoring the response to therapy. Any inconsistency in findings with the primary working diagnoses requires a rapid review of the pivotal findings and the potential diagnoses (Table 18-6).

MANAGEMENT AND DISPOSITION

The management of ACS is discussed in Chapter 76. Figure 18-3 outlines the approach to treatment of critical noncardiac diagnoses. Patients with critical diagnoses generally are admitted to the intensive care unit. Patients with emergent diagnoses typically are admitted to the hospital, most often on telemetry units. Patients with nonemergent diagnoses are most frequently treated as outpatients. Hospitalization is required in certain circumstances, particularly when patients have other comorbid conditions.

Frequently, no definitive diagnosis is established. Any patient with almost any type of chest pain may be having coronary ischemia, PE, or aortic dissection. When a clear pattern does not emerge to allow the emergency physician to make an alternative diagnosis confidently, continued evaluation, hospitalization, or observation admission may be the best course.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 19 Syncope

Robert A. De Lorenzo

PERSPECTIVE

Syncope is the sudden transient loss of consciousness with a loss of postural tone. It is a common presenting complaint in the emergency department (ED). Despite improved understanding of risk and outcomes, consensus on diagnostic approach and disposition remains elusive. This is in part due to its varied causes and lack of definitive diagnostic studies, and in part because of confusion and lack of standard terminology to describe the disorder.[1] Diagnostic accuracy relies largely on the synthesis of patient risk factors and reported symptoms, with limited reliance on the physical examination and ancillary testing.

Epidemiology

The prevalence of syncope in the general population is approximately 19%.[2] Patients present to the ED at a rate of 2.8 visits per 1000 population, which accounts for 0.8% of ED visits.[2,3] Approximately 32% of these patients are admitted, and syncope accounts for 1 to 6% of all hospitalized patients.[2,4] Persons aged 65 years and older account for 80% of such admissions.[5] In the pediatric population, 15% experience at least one episode of syncope.[6]

Risk factors for syncope include cerebrovascular disease, cardiac medications, and hypertension.[7] Most causes of syncope are benign and have favorable outcomes. Patients with preexisting cardiovascular disease and syncope from any cause are at the greatest short- and long-term risk of mortality.[4,8] Syncope from cardiovascular causes carries a long-term hazard ratio of death of 2.41 when adjusted for age and sex.[8] In contrast, there is no increased risk of cardiovascular morbidity or mortality associated with syncope from neurocardiogenic, orthostatic, and medication-related syncope.[8] Recurrence of syncope may be as high as 50% and is not correlated with age or sex.[2]

Benign causes of syncope predominate in adolescents and young adults. Approximately 30% of athletes dying during exercise, however, have had a prior episode of syncope as a sentinel event.[9] Prospective outcome studies in children are lacking, but most reports suggest that mortality rates are very low.[9] Significant trauma may result from syncope and can contribute to increased risk of mortality and morbidity, particularly in the elderly.[10,11] The overall U.S. medical cost of syncope is estimated at $2.4 billion annually.[12]

Pathophysiology

The final common pathway resulting in syncope is dysfunction of either both cerebral hemispheres or the brainstem (reticular activating system), usually from acute hypoperfusion. Reduced blood flow may be regional (cerebral vasoconstriction) or systemic (hypotension).[13] Loss of consciousness results in loss of postural tone, with the resulting syncopal episode. Less severe derangements may result in sensations of presyncope or light-headedness. In this fashion, presyncope and syncope may be considered on a continuum with shared etiologies and mechanisms. By definition, syncope is transient; therefore, the cause of central nervous system (CNS) dysfunction must likewise be transient.[8,14] Persistent causes of significant CNS dysfunction result in coma or depressed consciousness (See Chapter 14).

Hypoperfusion resulting in approximately 35% or more reduction in cerebral blood flow usually produces unconsciousness, and any mechanism that adversely affects the components of perfusion (cardiac output, systemic vascular resistance, blood volume, regional vascular resistance) can cause or contribute to syncope. Other mechanisms of CNS dysfunction resulting in syncope include hypoglycemia, toxins, metabolic abnormalities, failure of autoregulation, and primary neurologic derangements.

DIAGNOSTIC APPROACH

Differential Considerations

The potential causes of syncope are numerous and can be categorized according to their primary mechanism (Box 19-1). The first differential diagnostic consideration is to distinguish syncope from other causes of an apparent sudden loss of consciousness, especially seizure and uncommon disorders such as cataplexy. When syncope has been established as the working diagnosis, the life-threatening causes, primarily cardiovascular in origin, are considered first. The principal serious causes of syncope are dysrhythmias and myocardial ischemia.[15] Cerebrovascular disease, principally subarachnoid hemorrhage, is less frequently encountered, but equally serious. Toxic-metabolic abnormalities may induce syncope through alterations in blood pressure or cardiac rhythm. Structural cardiac lesions, such as critical aortic stenosis, and sudden

BOX 19-1 CAUSES OF SYNCOPE

Focal Hypoperfusion of CNS Structures
- Cerebrovascular disease
- Hyperventilation
- Subclavian steal
- Subarachnoid hemorrhage
- Basilar artery migraine
- Cerebral syncope

Systemic Hypoperfusion Resulting in CNS Dysfunction
- Outflow obstruction
  - Mitral, aortic, or pulmonic stenosis
  - Hypertrophic cardiomyopathy
  - Atrial myxoma
  - Pulmonary embolism
  - Pulmonary hypertension
  - Cardiac tamponade
  - Congenital heart disease
- Reduced cardiac output
  - Tachycardia
    - Supraventricular tachycardia
    - Ventricular tachycardia
    - Ventricular fibrillation
    - Wolff-Parkinson-White syndrome
    - Torsades de pointes
  - Bradycardia
    - Sinus node disease
    - Second-degree and third-degree A-V block
    - Prolonged Q-T syndrome
    - Pacemaker malfunction
    - Implanted cardioverter-defibrillator malfunction
  - Other cardiovascular disease
    - Aortic dissection
    - Myocardial infarction
    - Cardiomyopathy
- Vasomotor—neurally mediated (reflex vasodepressor)
  - Neurocardiogenic (vasovagal)
    - Emotion
    - Pain
    - Situational
  - Carotid sinus sensitivity
    - Necktie syncope
    - Shaving syncope
  - Miscellaneous reflex
    - Tussive, sneeze
    - Exercise/postexercise
    - Gastrointestinal—swallowing, vomiting, defecation
    - Postmicturition
    - Elevated intrathoracic pressure (weightlifting)
- Other causes of hypoperfusion
  - Orthostatic hypotension—volume depletion
  - Anemia
  - Drug-induced

CNS Dysfunction with Normal Cerebral Perfusion
- Hypoglycemia
- Hypoxemia—asphyxiation
- Seizure
- Narcolepsy
- Psychogenic
  - Anxiety disorder
  - Conversion disorder
  - Somatization disorder
  - Panic disorder
  - Breath-holding spells
- Toxic
  - Drugs
  - Carbon monoxide
  - Other agents
  - Undetermined causes

CNS, central nervous system.

interruption of right ventricular outflow by pulmonary embolism can also cause sudden loss of consciousness.[14] Dissection of the thoracic aorta rarely manifests primarily as syncope, but is potentially catastrophic.[15]

Pivotal Findings

The majority of cases of syncope arise from benign causes, so the evaluation is largely focused on excluding serious pathology. Young, healthy patients with clearly benign syncope may require no formal diagnostic evaluation other than a thorough history and physical examination.[16,17] The yield of an electrocardiogram (ECG) is generally low; however, it is recommended because it is noninvasive and relatively inexpensive.[18] The clinical examination alone can suggest the diagnosis in 45% of cases.[19] Nevertheless, up to 50% of patients may not have a clear diagnosis for their syncope after an initial evaluation in the ED.[19]

Symptoms

Symptoms can often suggest the diagnosis, although the value of the history diminishes in older patients.[20] The patient is asked to describe the *character* of the syncopal event.[14] Witnesses may be able to supplement and corroborate the patient's incomplete recall, and that history should be solicited. Key characteristics include the rate of onset (gradual or abrupt), position on symptom onset (e.g., standing, sitting, or supine), and duration and rate of recovery. Abrupt onset, occurrence while sitting or supine, and duration of more than a few seconds are usually ascribed to serious, often cardiac, causes of syncope.[15] Similarly, incomplete or near-syncope may be less serious, but at least one study suggests that onset associated with a prodrome or presyncope may herald cardiac origin.[20] The diagnostic approach to presyncope, however, is the same as for syncope.

Additional history regarding the events *preceding* the syncope is helpful.[14] Occurrence during significant exertion suggests outflow obstruction, whereas after exercise or a prolonged exposure to heat stress suggests orthostasis. The myriad mechanisms that may mediate a neurocardiogenic response (e.g., vagal stimulation), including significant emotional events, micturition, eating, bowel movements, emesis, and movement or manipulation of the neck causing stimulation of the carotid sinus, must be addressed. Occurrence in supine position or the presence of acute palpitations is relatively specific for syncope of cardiac origin.[20] Seizures may be preceded by an aura.

Events *during* the syncopal episode do not usually clarify the cause.[14] Tonic-clonic movements, related to inadequate cerebral perfusion, can occur in any form of syncope, including benign neurocardiogenic syncope, and must be differentiated from the prolonged activity with subsequent postictal depression of consciousness seen in seizure disorders (see Chapter

15). Trauma from a fall or other mechanism may mask the underlying syncope that caused the incident.[11]

The postsyncopal events should be queried. Symptoms consistent with a postictal state are characteristic of seizures. Initial vital signs and cardiac monitoring by nonhospital medical providers may provide clues to primary cardiac dysrhythmias.

Associated symptoms can offer potentially important clues.[15] Chest pain or shortness of breath can suggest myocardial ischemia, aortic dissection, or pulmonary embolism. Diaphoresis and light-headedness are nonspecific, but if prominent and accompanied by a graying of vision may suggest orthostasis or vasovagal causes. Tongue biting and incontinence of urine or stool suggest seizures.

The *past medical history* is critical in stratifying risk.[4,20] Prior coronary artery or cerebrovascular disease, diabetes, hypertension, or other significant chronic disease increases the risk of mortality after syncope.[7]

Certain *medications* are well established to be associated with syncope (Box 19-2). QT interval-prolonging agents, beta-blockers, insulin, and oral hypoglycemics, in particular, deserve attention because of the likelihood of repeated syncope without careful medication monitoring.[7]

Signs

The physical examination focuses primarily on the elements affecting the cardiovascular and neurologic systems.[20] Specific findings are detailed in Table 19-1. Signs of orthostasis should be sought in all cases where this mechanism is suggested.[21] Carotid massage to detect carotid sinus hypersensitivity is both safe and occasionally revealing; it is probably underutilized. Rectal examination for gross blood or melena is recommended if anemia or gastrointestinal bleed is possible.

Ancillary Studies

The chief diagnostic adjunct in evaluating syncope is the 12-lead ECG (Table 19-2). It is warranted in all cases of syncope except in young, otherwise healthy patients with a clear history and setting for benign neurocardiogenic (vasovagal) syncope.[16,17] Although the yield is low, the ECG is noninvasive and relatively inexpensive, and may be revealing.[18] New ischemic ECG changes are indicative of acute coronary ischemia and

BOX 19-2 MEDICATIONS THAT MAY INDUCE SYNCOPE

Cardiovascular
β-Blockers
Vasodilators (α-blockers, calcium channel blockers, nitrates, hydralazine, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, phenothiazines, phosphodiesterase inhibitors)
Diuretics
Central antihypertensives (clonidine, methyldopa)
Other antihypertensives (guanethidine)
Q-T prolonging (amiodarone, disopyramide, flecainide, procainamide, quinidine, sotalol)
Other antidysrhythmics
Psychoactive
Anticonvulsants (carbamazepine, phenytoin)
Antiparkinsonian agents
Central nervous system depressants (barbiturates, benzodiazepines)
Monoamine oxidase inhibitors
Antidepressants
Narcotic analgesics
Sedating and nonsedating antihistamines
Cholinesterase inhibitors (donepezil, tacrine, galantamine)
Drugs with other mechanisms
Drugs of abuse (cannabis, cocaine, alcohol, heroin)
Digitalis
Insulin and oral hypoglycemics
Neuropathic agents (vincristine)
Nonsteroidal anti-inflammatory drugs
Bromocriptine

Table 19-1 Directed Physical Examination in Syncope

SYSTEM	PIVOTAL FINDING	SIGNIFICANCE
Vital signs	Pulse rate and rhythm	Tachycardia, bradycardia, other dysrhythmias
	Respiratory rate and depth	Tachypnea suggests hypoxia, hyperventilation, or pulmonary embolus
	Blood pressure	Shock may cause decreased cerebral perfusion; hypovolemia or medication use may lead to orthostasis
	Temperature	Fever from sepsis may cause volume depletion and orthostasis
Skin	Color, diaphoresis	Signs of decreased organ perfusion
HEENT	Tenderness and deformity	Signs of trauma
	Papilledema	Increased intracranial pressure, head injury
	Breath	Ketones from ketoacidosis
Neck	Bruits	Identify presence of cerebrovascular disease
	Jugular venous distention	Right heart failure from myocardial ischemia, tamponade, pulmonary embolism
Lungs	Breath sounds, crackles, wheezes	Infection, left heart failure from myocardial ischemia, rarely pulmonary embolism
Heart	Systolic murmur	Aortic stenosis, hypertrophic cardiomyopathy
	Rub	Pericarditis, tamponade
Abdomen	Pulsatile mass	Abdominal aortic aneurysm
Rectum	Stool for gross blood or melena	Anemia, GI bleed
Pelvis	Uterine bleeding, adnexal tenderness	Anemia, ectopic pregnancy, hypovolemia
Extremities	Pulse equality in upper extremities	Subclavian steal, thoracic aortic dissection
Neurologic	Mental status, focal neurologic findings	Seizure, stroke, or other primary neurologic disease

HEENT, head, eyes, ears, nose, and throat.

Table 19-2 Ancillary Studies in Syncope

STUDY	INDICATION
12-Lead ECG/limb-lead ECG monitoring	Cardiac dysrhythmia, ischemia, cardiomyopathy
Orthostatic vital signs	Orthostatic hypotension or bradycardia
Hemogram	Anemia
Electrolytes, serum	Metabolic abnormality, especially hyponatremia, hyper- or hypokalemia
Glucose, serum or blood	Hypoglycemia
D-dimer, serum	Pulmonary embolism
Cardiac enzymes, serum	Myocardial infarction
β-hCG	Pregnancy
Toxicologic screen	Drug-related syncope
Arterial blood gas	Acid-base disturbance
Chest x-ray	Thoracic aortic dissection
Cranial CT/MRI	New-onset or focal seizure, trauma, intracranial hemorrhage
Echocardiogram	Cardiac outflow obstruction, tamponade, thoracic dissection
Ventilation-perfusion scan	Pulmonary embolism
CT pulmonary angiogram	Pulmonary embolism, thoracic aortic dissection
Abdominal ultrasound /CT	Abdominal aortic aneurysm
Pelvic ultrasound	Ectopic pregnancy
Tests Usually Performed as Part of an Inpatient or Outpatient Evaluation	
Holter or loop ECG	Dysrhythmia
Echocardiogram	Cardiomyopathy, valvular disease
Exercise/^{99m}Tc sestamibi ECG	Myocardial ischemia
Electrophysiologic study	Dysrhythmia
Carotid ultrasound	Stroke, TIA
Head-up tilt-table test	Orthostatic hypotension
Electroencephalogram	Seizures

CT, computed tomography; ECG, electrocardiogram; hCG, human chorionic gonadotropin; MRI, magnetic resonance imaging; TIA, transient ischemic attack.

warrant appropriate therapy. Dysrhythmias and shortened PR or prolonged QT intervals may be identified on the 12-lead ECG. A right bundle branch block in association with ST elevation in leads V_1 through V_3 suggests Brugada's syndrome.[22] Unanticipated cardiac hypertrophy may be revealed. Continuous limb-lead ECG monitoring in the ED may also identify transient dysrhythmias. An ECG showing right ventricular strain pattern may suggest pulmonary embolism, whereas diffuse ST elevation or electrical alternans help diagnose pericarditis associated with pericardial tamponade.

Routine blood, serum, and urine studies have limited utility in the evaluation of syncope and are generally unrewarding.[23] When suggested by the history and physical examination, however, selective use of the hemogram, serum electrolytes and glucose, urine drug screen, and pregnancy test may identify or exclude some uncommon causes of syncope. Radiographic studies including cranial computed tomography offer limited yield in most cases of syncope, and unless abnormalities are identified on neurological examination, are not routinely indicated.[24]

In otherwise healthy patients for whom a benign dysrhythmia, such as rapid supraventricular tachycardia or atrial fibrillation, is suggested, Holter or preferably event ECG monitoring may be helpful. In patients with significant underlying cardiac disease or when a significant dysrhythmia is a possible cause of the syncope, echocardiography, continuous monitoring, or cardiovascular stress-testing may be helpful in the inpatient or ED observation unit setting. Depending on the results of initial evaluation, electrophysiologic studies, or magnetic resonance imaging may be indicated. Electroencephalography has a low yield unless seizure is suggested. Tilt table testing, although infrequently used in the United States, may have diagnostic value in elderly patients and children in whom chronic orthostatic hypotension is possible.

Table 19-3 Critical Diagnoses to Consider in Syncope

Myocardial infarction
Life-threatening dysrhythmias
Thoracic aortic dissection
Critical aortic stenosis
Hypertrophic cardiomyopathy
Pericardial tamponade
Abdominal aortic aneurysm
Pulmonary embolism
Subarachnoid hemorrhage
Stroke
Toxic-metabolic derangements
Severe hypovolemia or hemorrhage

Although not technically an ancillary study, formal psychiatric evaluation deserves mention as a potential diagnostic tool in syncope.[25] In patients with compatible symptoms and signs or negative medical evaluation and recurrent episodes of syncope, psychiatric evaluation may be revealing.

DIAGNOSTIC ALGORITHM

The critical diagnoses to consider are listed in Table 19-3.

The emergent causes of syncope are protean and are included in Box 19-1. Many other causes such as neurocardiogenic and reflex-mediated syncope have benign mechanisms.

After stabilization and assessment, the clinical features coupled with onset and recovery suggest the cause (Table 19-4). A logical approach to the history, physical examination, and diagnostic testing is depicted in Figure 19-1. The emphasis is on risk stratification since short-term mortality risk in syncope

Table 19-4 Clinical Features of Common and Serious Causes of Syncope

CAUSE	ONSET AND RECOVERY	FEATURES
Dysrhythmia	Abrupt onset; rapid recovery	Past cardiac history, risk factors for CAD more common in elderly; implanted pacemaker or cardioverter-defibrillator
Cardiac outflow obstruction	Exertion causes abrupt symptoms; rapid recovery with rest	Murmurs not always audible; mechanical valves warrant close monitoring
Myocardial infarction	Exertion or at rest; recovery often incomplete with chest pain persisting	Past cardiac history, risk factors for CAD; chest pain and shortness of breath common but frequently absent in diabetics and the elderly
Pulmonary embolism	Abrupt onset; recovery often incomplete with dyspnea persisting	Chest pain, dyspnea, hypercoagulable state, DVT, pregnancy
Thoracic aortic dissection	Spontaneous; recovery often incomplete with chest or upper back pain persisting	Tearing chest pain; associated with hypertension, Marfan syndrome, cystic medial necrosis
Abdominal aortic aneurysm	Spontaneous onset; recovery often incomplete with abdominal pain persisting	Abdominal or low back pain; associated with peripheral vascular disease
Pericardial tamponade	Penetrating chest trauma or thoracic cancers	Beck's triad of hypotension, JVD, muffled heart sounds
Anomalous left coronary artery	Onset with exercise, Valsalva maneuver	Left coronary artery arises from pulmonary artery; usually detected in childhood
Subarachnoid hemorrhage	Rapid onset; sentinel event may resolve	Focal neurologic findings; "thunderclap" worst headache; nuchal rigidity
Vertebrobasilar insufficiency	Posture change or neck movement	Vertigo, nausea, dysphagia, dysarthria, blurry vision common associated symptoms
Hypovolemia	Bleeding, emesis, heat stress, dehydration; gradual onset	Orthostatic hypotension
Anemia	Bleeding, often occult or gradual from menses or gastrointestinal sources; iron deficiency or decreased red blood cell production	Orthostatic hypotension commonly associated
Hypoglycemia	Gradual onset; incomplete spontaneous recovery common	Diabetes, ingestion or injection of hypoglycemics or insulin; diaphoresis, anxiety, jitteriness
Hypoxemia	Usually gradual onset; spontaneous recovery if asphyxiating circumstance is reversed	Carbon monoxide, natural gas, sewer gas, bleach-ammonia mix
Subdural hematoma	Onset with or after trauma (which may be trivial in high-risk patients)	Elderly, alcoholics, patients on anticoagulants at greater risk
Air embolus	Diving	Hyperbaric oxygen a key treatment
Pulmonary hypertension	Associated with myocardial infarction or pulmonary embolus	Risk factors for myocardial infarction or pulmonary embolism
Drug syncope	Medication associated with syncope	Consider illicit and alternative drug use; elderly at risk for polypharmacy and drug interactions
Ruptured ectopic pregnancy	Patient often unaware of pregnancy	Abdominal pain, abnormal tenderness; positive β-hCG test
Seizure	Abrupt or with aura; postictal state common	Past history common
Carotid sinus sensitivity	Carotid sinus sensitivity; rapid onset and recovery	Shaving, necktie, sudden neck movement; carotid massage may provoke symptoms
Reflex syncope	Gastrointestinal, genitourinary, or thoracic stimulation	Urination, defecation, cough, eating, swallowing, weightlifting
Neurocardiogenic (vasovagal)	Emotion, pain are common triggers; upright posture; gradual onset; rapid recovery once supine	Prodrome of light-headedness, graying or blurring of vision, nausea, sweats common
Hyperventilation	Emotion, pain; gradual onset; patient often unaware of rapid respirations	Perioral tingling, carpopedal spasms, extremity numbness
Narcolepsy	Often spontaneous	Known history
Basilar artery migraine	Specific triggers often known to patient	Visual prodrome often absent; more common in young women; vertigo and nausea common
Trigeminal or glossopharyngeal neuralgia	Sudden onset; specific triggers often known to patient	Lancinating pain in characteristic location
Subclavian steal	Moving affected arm	Thoracic outlet syndrome
Psychogenic	Variable	Anxiety or psychiatric history; diagnosis by examining symptom pattern and excluding organic cause
Breath-holding	Deliberate breath-holding	Usually toddlers or young children
Drop attack	Unpredictable	Not true syncope—no loss of consciousness; usually elderly; loss of tone, ataxia, vertigo

CAD, coronary artery disease; DVT, deep vein thrombosis; hCG, human chorionic gonadotropin; JVD, jugular venous distention; TIA, transient ischemic attack.

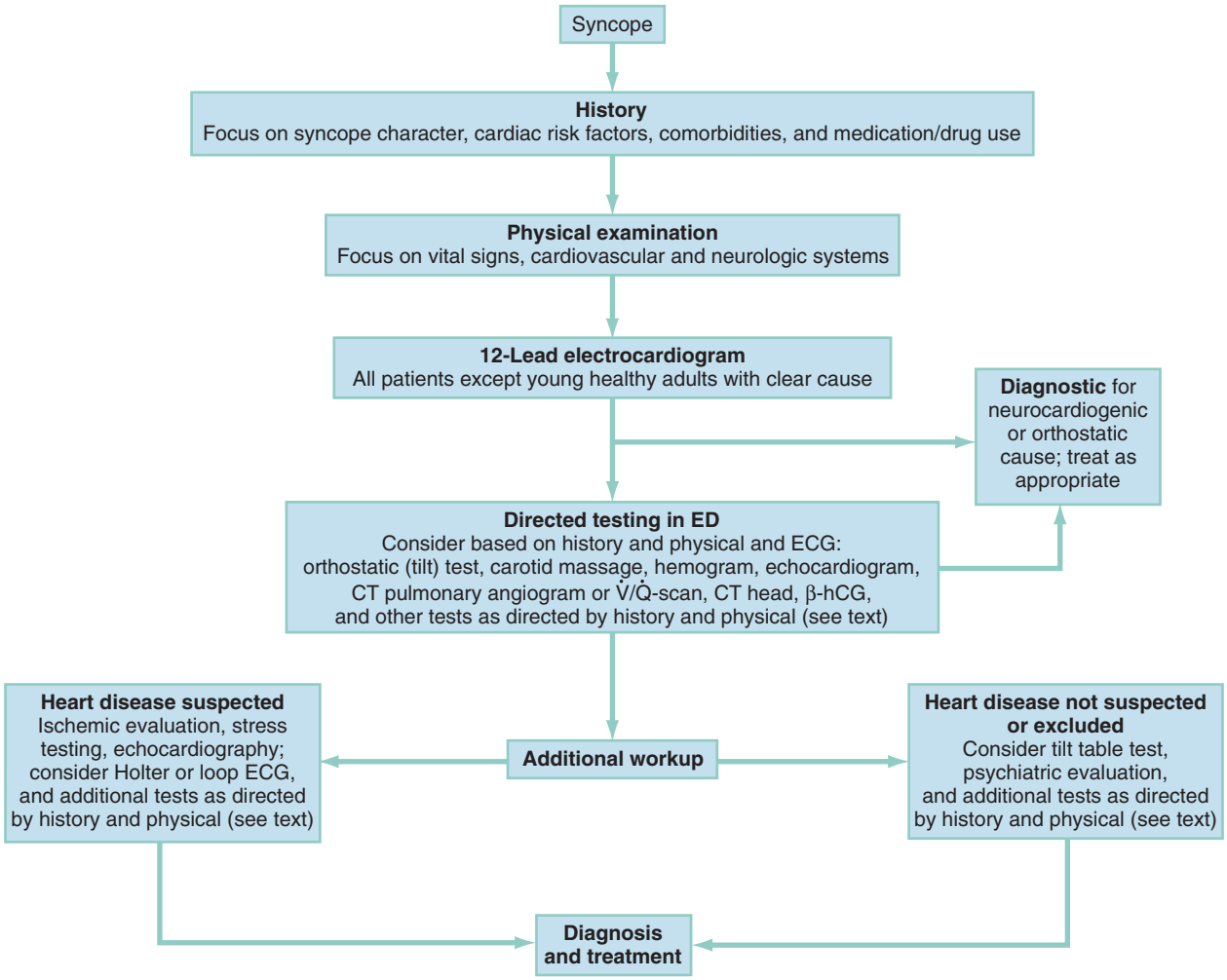

Figure 19-1. Management algorithm for patients with syncope.

is related to structural cardiac disease, heart failure, and dysrhythmias.[26]

EMPIRICAL MANAGEMENT

Rapid Assessment and Stabilization

Syncope is by definition a transient event so most patients are asymptomatic on presentation. Patients with significantly abnormal vital signs, recurrent syncope, or associated symptoms of a concerning nature such as chest pain or shortness of breath should undergo rapid evaluation.

Diagnosis and Management

Most patients presenting with syncope require confirmatory bedside diagnostic evaluation. The 12-lead ECG is the principal tool for evaluating cardiac causes of syncope. Orthostatic vital signs, although unreliable as an evaluation of volume status, may be helpful when positional changes are accompanied by typical presyncopal symptoms and a significant fall in heart rate or blood pressure.[23] A schematic of selected diagnostic testing strategies for syncope is depicted in Figure 19-2.

Patients with critical diagnoses are generally admitted to the intensive care unit (ICU). Those with emergent diagnoses are typically admitted to telemetry units. Patients with nonemergent diagnoses can be treated as outpatients.

Several scoring systems aid in the admission decision-making process, most notably the San Francisco Syncope Rule.[27] In essence, this guideline suggests that in the absence of abnormal ECG findings, shortness of breath, hypotension (systolic < 90 mm Hg), anemia (hematocrit < 30%), or a history of congestive heart failure, the patient is at sufficiently low risk to consider outpatient disposition. The San Francisco Syncope Rule as well as other proposed rules, however, require external validation before widespread application.[4,28-31]

Hospitalization is required for patients with chest pain, unexplained shortness of breath, a history of significant congestive heart failure, or valvular disease.[14,18,32] Patients with ECG evidence of ventricular dysrhythmias, ischemia, significantly prolonged QT interval, or new bundle branch block are also admitted.[14,17,18] The clinician should consider monitoring patients with any of the following indications: age older than 45 years, preexisting cardiovascular or congenital heart disease, family history of sudden death, serious comorbidities such as diabetes, or exertional syncope.[17,18,23,32]

The ED evaluation of syncope is often inconclusive. After a history, physical examination, and 12-lead ECG, up to 50% of patients do not have a firm diagnosis.[19,32] Patients younger than 45 years and without worrisome symptoms, signs, or ECG findings are generally at lower risk for adverse outcome and may often be treated as an outpatient. Discharged patients should be warned of the hazards of recurrent syncope occurring during activities such as driving or working at heights.[17]

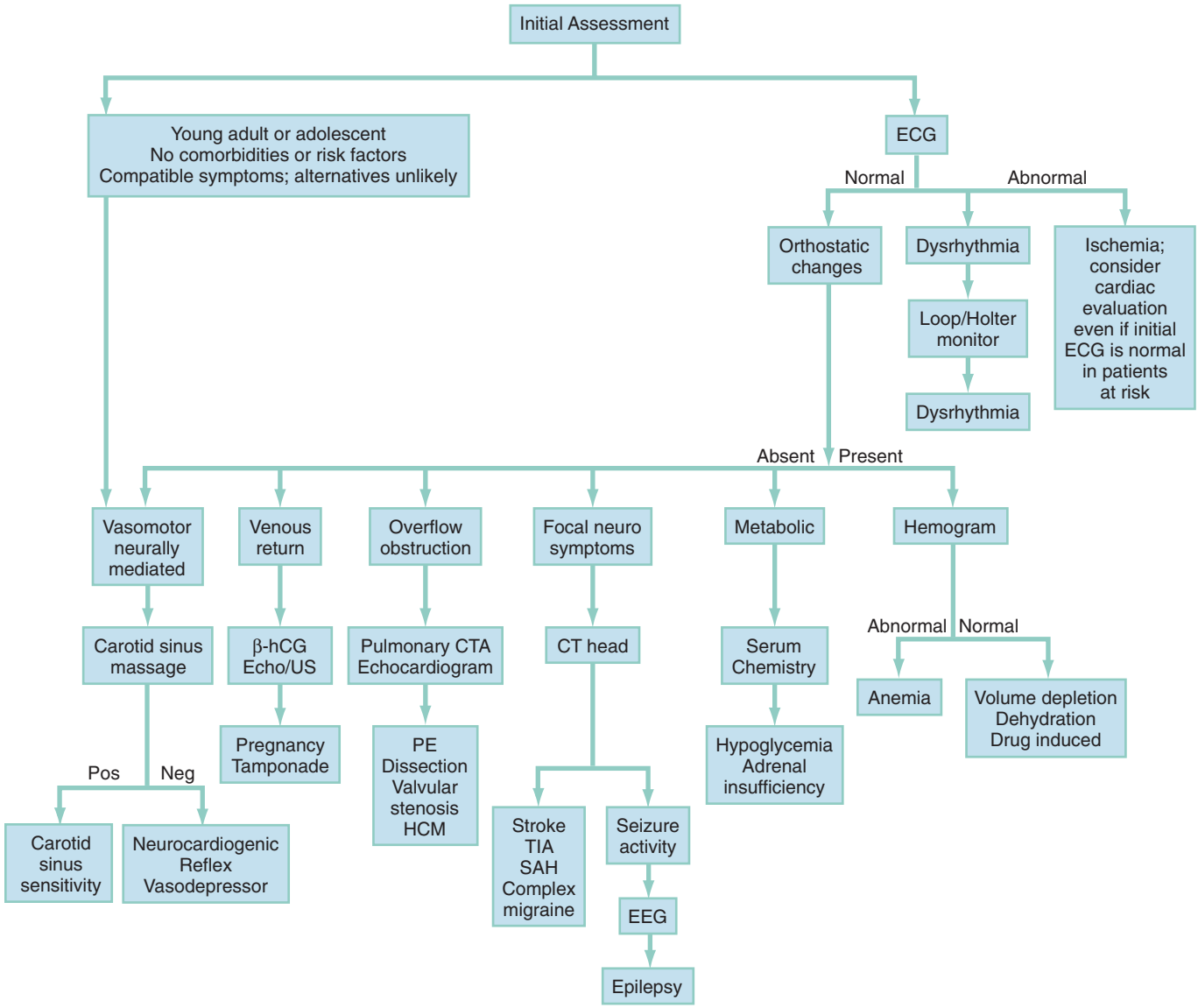

Figure 19-2. Diagnosis algorithm for syncope.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 20 Nausea and Vomiting

Leslie S. Zun and Amardeep Singh

PERSPECTIVE

Nausea and vomiting may constitute the primary presentation of many gastrointestinal (GI) disorders (e.g., bowel obstruction, gastroenteritis) or the secondary presentation of numerous systemic conditions (1) caused by severe pain, especially visceral pain; (2) caused by or related to severe systemic illness, such as myocardial infarction, sepsis, or shock; or (3) related to definitive conditions by specific mechanisms, such as pregnancy (hormones), increased intracranial pressure (central mechanism), toxins (homeostatic response), motion sickness (neuroendocrine), and chemotherapy (chemoreceptor trigger zone [CTZ]). Additionally, vomiting may cause serious sequelae, such as aspiration pneumonia, Mallory-Weiss syndrome, esophageal rupture, volume depletion, and metabolic derangement. Classification by duration and frequency of the vomiting (acute, recurrent, chronic, or cyclic) may assist in determination of the underlying cause.[1]

Epidemiology

The most common causes of nausea and vomiting are acute gastroenteritis, febrile systemic illnesses, and drug effects. Acute viral gastroenteritis is the most common GI disease in the United States. In adult medicine, nausea and vomiting are caused most often by medications. Emesis associated with pregnancy is common, especially in the first trimester, but hyperemesis gravidarum is not. Although the scope of the differential diagnosis in the pediatric population is broad, acute vomiting is commonly seen with infectious disorders affecting the gastrointestinal tract as well as with infections in other areas of the body.[2]

Pathophysiology

The act of vomiting can be divided into three distinct phases: nausea, retching, and actual vomiting[3,4] (Fig. 20-1). Nausea may occur without retching or vomiting, and retching may occur without vomiting. *Nausea* is defined as a vague and extremely unpleasant feeling that often precedes vomiting. The exact neural pathways mediating nausea are not clear, but they are likely to be the same pathways that mediate vomiting. Mild activation of the pathways may result in nausea, whereas more intense stimulation results in vomiting. During nausea, there is an increase in tone in the musculature in the duodenum and jejunum, with a concomitant decrease in gastric tone; this leads to reflux of intestinal contents into the stomach. There is often associated hypersalivation, repetitive swallowing, and tachycardia.

Retching is characterized as rhythmic, synchronous contractions of the diaphragm, abdominal muscles, and intercostals that occur against a closed glottis. There is a resultant increase in abdominal pressure with a concurrent decrease in intrathoracic pressure. This pressure gradient causes gastric contents to move up into the esophagus. The mouth is usually closed.

Vomiting is the forceful expulsion of gastric contents through the mouth. There is contraction of the external oblique and abdominal rectus muscles, and the hiatal portion of the diaphragm relaxes; this increases the pressure in the abdominal and the thoracic compartments. There is contraction of the pyloric portion of the stomach. Simultaneously, there is relaxation of the gastric fundus, cardia, and upper esophageal sphincter as the vomitus is brought up and out the mouth. The glottis closes to prevent aspiration.

The complex act of vomiting is not completely understood but is thought to be coordinated by a *vomiting center* located in the lateral reticular formation of the medulla (Fig. 20-2). The efferent pathways from the vomiting center are mainly through the vagus, phrenic, and spinal nerves. These pathways are responsible for the integrated response of the diaphragm, intercostals, abdominal muscles, stomach, and esophagus. The vomiting center is activated by afferent stimuli from a variety of sources. These include vagal and sympathetic impulses directly from the GI tract. Direct irritation of the stomach lining causes vomiting in this way. Other GI sources of afferent impulses include the pharynx, small bowel, colon, biliary system, and peritoneum. Receptors also are found outside the GI tract in the vestibular system, heart, and genitalia.

The other major source of impulses to the vomiting center is the CTZ. The CTZ is located in the area postrema, the floor of the fourth ventricle. Part of this area is located outside of the blood-brain barrier, enabling it to respond to endogenous and exogenous substances that activate vomiting. It is activated by hormones, peptides, medications, or toxins in the circulation, including opiates, digitalis, chemotherapy agents, salicylate, syrup of ipecac, and dopamine neurotransmitters.

The discovery of various neurotransmitters and their receptor sites within the medulla has improved the understanding and development of therapeutic agents. The CTZ area is rich in dopamine D_2 receptors, which are antagonized by drugs such as prochlorperazine, metoclopramide, and droperidol. The serotonin receptor has been found widely in the area postrema and the GI tract. It may act directly and through the release of dopamine. The serotonin receptor antagonists ondansetron and granisetron have been shown to be effective in preventing chemotherapy-induced nausea and vomiting. Concentrations of cholinergic and histamine receptors are found in the lateral vestibular nucleus and are important in

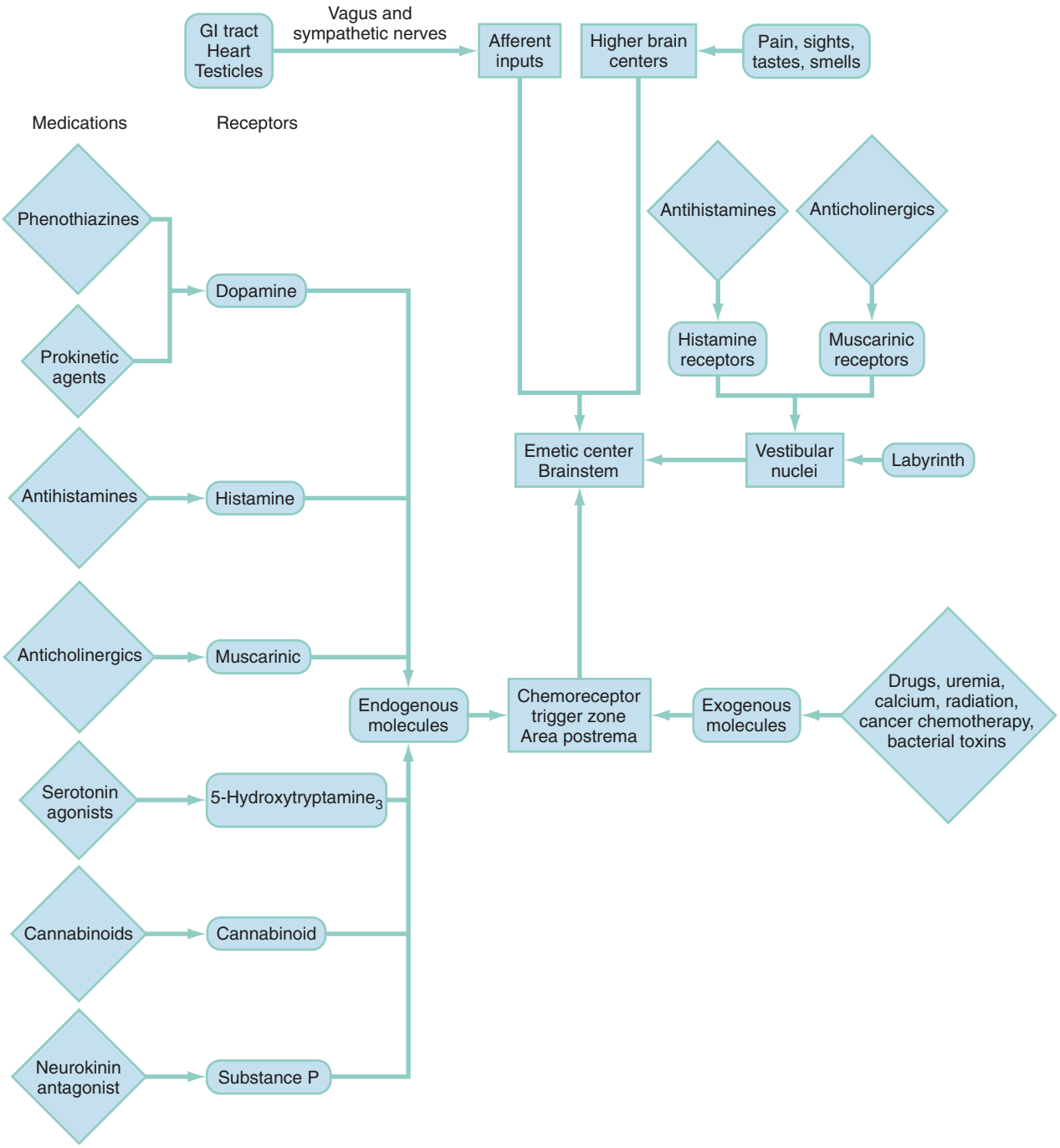

Figure 20-1. Pathophysiology of nausea and vomiting.

motion sickness. Meclizine, diphenhydramine, and scopolamine act by antagonizing these receptors. Cannabinoid receptors have been found to inhibit the emetic reflex.

Rumination is regurgitation of ingested food that subsequently is reswallowed or ejected. Rumination syndrome is found in infants, children, and mentally challenged adults, but rarely in adults with normal intelligence.

■ DIAGNOSTIC APPROACH

Differential Considerations

The differential diagnosis for nausea and vomiting is particularly broad in scope; almost any organ system can be involved (Table 20-1). Vomiting also can result in complications, which must be considered in addition to the causes. The sequelae of vomiting may include the following various metabolic and traumatic lesions.

Hypovolemia is caused by loss of water and sodium chloride in the vomitus. The contraction of the extracellular fluid space leads to activation of the renin-angiotensin-aldosterone system.

Metabolic alkalosis is produced by loss of hydrogen ions in the vomitus. Many factors serve to maintain the alkalosis, including volume contractions, hypokalemia, chloride depletion, shift of extracellular hydrogen ions into cells, and increased aldosterone.

Hypokalemia is produced primarily by loss of potassium in the urine. The metabolic alkalosis leads to large amounts of sodium bicarbonate being delivered to the distal tubule. Secondary hyperaldosteronism from volume depletion causes

reabsorption of sodium and excretion of large amounts of potassium in the urine.

Mallory-Weiss tears typically result from a forceful bout of retching and vomiting. The lesion itself is a 1- to 4-cm tear through the mucosa and submucosa; 75% of cases occur in the stomach, with the remainder near the gastroesophageal junction. Bleeding usually is mild and self-limited; however, 3% of deaths from upper GI bleeds are due to Mallory-Weiss tears.

Boerhaave's syndrome refers to a perforation of all layers of the esophagus occurring as a result of forceful retching or vomiting. The overlying pleura is torn so that there is free passage of esophageal contents into the mediastinum and thorax; 80% of cases involve the posterolateral aspect of the distal esophagus. Boerhaave's syndrome constitutes a surgical emergency. The mortality rate is 50% if surgical repair is not performed within 24 hours.

Aspiration of gastric contents is a concern in patients who have altered mental status or pulmonary findings after an episode of vomiting. Patients with pulmonary findings after vomiting need further evaluation for aspiration.

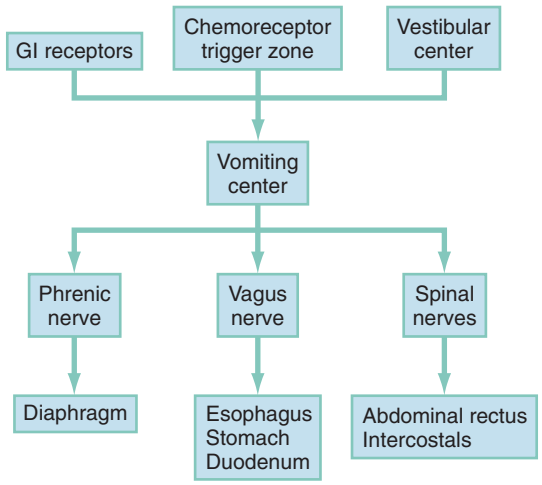

Figure 20-2. Vomiting process. GI, gastrointestinal.

Rapid Assessment and Stabilization

The initial assessment is directed toward the patient's hemodynamic status and identifying the critical causes or sequelae of vomiting (see Table 20-1). Data gathered include duration of vomiting, whether blood is in the vomitus, symptoms of volume depletion, and associated symptoms pointing to serious underlying disease. Physical findings include level of consciousness, abdominal examination, rapid neurologic screen for focality, and serial vital signs. Initial stabilization may include establishing intravenous access and fluid resuscitation in patients with signs of volume depletion, cardiac monitoring, and therapeutic measures directed toward specific underlying diseases (e.g., blood pressure control in severe hypertension).

Pivotal Findings

A thorough history and physical examination usually yield the underlying cause of nausea and vomiting.

Table 20-1 Differential Diagnosis of Nausea and Vomiting

ETIOLOGIC CATEGORY	CRITICAL DIAGNOSES	EMERGENT DIAGNOSES	NONEMERGENT DIAGNOSES
Gastrointestinal (GI)	Boerhaave's syndrome Ischemic bowel GI bleeding	Gastric outlet obstruction Pancreatitis Cholecystitis/cholangitis Bowel obstruction/ileus Ruptured viscus Appendicitis Peritonitis Spontaneous bacterial peritonitis	Gastritis Gastroparesis Peptic ulcer disease Inflammatory bowel disease Biliary colic Hepatitis Gastroenteritis
Neurologic	Intracerebral bleed Meningitis	Migraine CNS tumor Raised ICP	
Endocrine	DKA	Adrenal insufficiency Uremia	Thyroid
Pregnancy		Hyperemesis gravidarum	Nausea and vomiting of pregnancy
Drug toxicity		Acetaminophen Digoxin Aspirin Theophylline	
Therapeutic drug use			Aspirin Antibiotics Erythromycin Ibuprofen Chemotherapy
Drugs of abuse			Narcotics Narcotic withdrawal Alcohol
Genitourinary		Gonadal torsion	Urinary tract infection Poisoning Nephrolithiasis
Miscellaneous	Myocardial infarction Sepsis	Carbon monoxide Electrolyte disorders Organophosphate poisoning	Motion sickness Labyrinthitis

CNS, central nervous system; DKA, diabetic ketoacidosis; ICP, intracranial pressure.

History

Duration of the vomiting can lead to a diagnosis. *Acute* vomiting is vomiting occurring for less than 1 week and is associated with obstructive, ischemic, toxic, metabolic, infectious, neurologic, and postoperative causes. *Chronic* vomiting occurs with partial obstructions, motility disorders, and neurologic conditions or may be pregnancy-related or functional in origin.

Timing of the vomiting may be important. An acute onset of nausea and vomiting suggests gastroenteritis, pancreatitis, cholecystitis, or a drug-related side effect. Symptoms occurring primarily in the morning suggest pregnancy, although this pattern also may be seen with uremia, alcohol ingestion, or increased intracranial pressure. Delayed vomiting more than 1 hour after eating suggests gastric outlet obstruction or gastroparesis. Vomiting of material eaten more than 12 hours previously is pathognomonic for outlet obstruction. Nausea and vomiting for more than 1 month are considered chronic. Discrete episodes of intractable vomiting with intervening asymptomatic periods are considered cyclic.

Content of the vomitus may provide clues. The presence of bile indicates a patent connection between the duodenum and the stomach and essentially rules out a gastric outlet obstruction. Regurgitation of undigested food can suggest achalasia, esophageal stricture, or Zenker's diverticulum. Feculent material usually suggests a distal bowel obstruction but also may be seen with gastrocolic fistula or bacterial overgrowth of stomach contents in long-standing outlet obstruction.

Associated symptoms and signs may be helpful. Hypersalivation, defecation, tachycardia, bradycardia, atrial fibrillation, and termination of ventricular tachyarrhythmias are associated phenomena with nausea and vomiting. Chronic headaches with nausea and vomiting should raise the index of suspicion for an intracranial lesion. Also, vomiting without preceding nausea is typical of central nervous system pathology. The *social history* should include inquiries about alcohol or other substance abuse. The *past medical history* will reveal the presence of any GI disease or previous surgeries. Nutritional history is valuable in the consideration of failure to thrive in infancy. Finally, a thorough *medication list*, including over-the-counter drugs, should be included.

Physical Examination

The important physical examination findings are outlined in Table 20-2. During evaluation, findings of jaundice, lymphadenopathy, vertigo, fever, and goiter can help determine the etiology of the disease. Oral examination may reveal loss of dental enamel commonly seen with bulimia. Abdominal examination may reveal ascites, distention, hernias, abdominal tenderness and masses, organomegaly, or hyper- or hypoactive bowel sounds, with appropriate laboratory testing for occult blood in the stool. Determination of orthostatic vital signs may be valuable in patients with signs of dehydration, lightheadedness, generalized weakness, or toxic appearance. It also is important to evaluate neurologic status to rule out a central cause of a patient's symptoms, which includes cranial nerves, funduscopic examination, and gait observation. Provocative testing for vertigo such as with the Nylan-Bárány test may elicit nausea and vomiting. Attentive physicians may elicit evidence of depression or anxiety that may lead to a psychiatric diagnosis.

In children, the examination should search for other diagnostic clues. A bulging fontanelle (meningitis), projective vomiting (pyloric stenosis), unusual odors (metabolic), visible bowel loops (obstruction), enlarged parotid, and loss of dental enamel (bulimia) point to specific etiologic disorders. Most of these disorders are age-dependent.

Ancillary Studies

Because of the broad differential diagnosis for nausea and vomiting, there is no standard panel of laboratory tests. Appropriate testing is determined by the specifics of the history and

Table 20-2 Physical Examination of the Patient with Nausea and Vomiting

ORGAN SYSTEM	FINDING	SUGGESTED DIAGNOSES
General	Poor skin turgor Dry mucous membranes	Dehydration
Vital signs	Fever	Gastroenteritis, cholecystitis, appendicitis, hepatitis Bowel perforation
	Tachycardia/orthostatic changes	Dehydration
HEENT	Nystagmus	Labyrinthitis Vertebrobasilar insufficiency Cerebellar infarct or bleed CPA tumor
	Papilledema	Increased ICP from CNS tumor or bleeding
Neck	Goiter	Thyroid disease
Lungs	Rales	Pneumonia
Heart	Arrhythmia Murmur	Acute myocardial infarction
Abdomen	Abdominal distention Peristaltic waves High-pitched bowel sounds Decreased bowel sounds Hernias or surgical scars Peritoneal signs	Bowel obstruction, gastroparesis Gastric outlet obstruction Bowel obstruction Ileus Possible bowel obstruction Appendicitis, cholecystitis Perforated viscus
Neurologic	Abnormal mental status Cerebellar findings Cranial nerve findings	CNS pathology

CNS, central nervous system; CPA, cerebellopontine angle; HEENT, head, eyes, ears, nose, throat; ICP, intracranial pressure.

physical examination. The following general guidelines regarding specific tests are useful.

Complete blood count: Most patients do not require a complete blood count. Elevated hemoglobin may suggest dehydration, but other tests are better for this purpose. An elevated white blood count is entirely nonspecific and of no discriminatory value.

Serum electrolytes: Measurement of serum electrolytes is not indicated in most cases of vomiting. Severe, protracted vomiting can cause a hypochloremic, hypokalemic metabolic alkalosis. Patients with this history or with clinical evidence of dehydration should undergo electrolyte testing. In general, serum electrolyte testing is indicated only in patients with symptoms lasting longer than 3 days or signs of significant dehydration who require intravenous fluid to replenish vascular volume.

Blood urea nitrogen and creatinine: Classically a blood urea nitrogen-to-creatinine ratio greater than 20:1 implies significant dehydration.

Serum lipase: Lipase determination is indicated in cases of suspected pancreatitis.

Urine tests: A urine pregnancy test should be performed in all women of childbearing age. Nitrites, leukocyte esterase, white blood cells, and bacteria indicate a urinary tract infection. Ketones may support a diagnosis of diabetic ketoacidosis or prolonged starvation state. Hematuria indicates a possible renal calculus.

Cultures: Blood cultures may be indicated in the fever patient with nausea and vomiting. Urine cultures may be necessary to determine an underlying cause, and stool cultures looking for enteric pathogens, parasites, or leukocytes may be valuable.

Liver function and ammonia tests: Liver function tests are indicated in cases of suspected hepatitis or biliary disease. Ammonia testing is useful if liver failure is suspected.

Serum drug levels: Serum drug levels may be important in patients on theophylline, digoxin, or salicylates, especially in elderly patients who are taking medication without supervision.

Abdominal imaging: Flat and upright plain radiographs are indicated only in cases of suspected bowel obstruction or ileus. Computed tomography (CT) scan of the abdomen has supplanted plain radiography for the evaluation of many patients with suspected obstruction because of the improved ability to discern the cause of the problem in addition to the presence of obstruction. An abdominal ultrasound study is indicated in cases of suspected choledocholithiasis or cholecystitis in adults, and suspected pyloric stenosis and intussusception in children. Imaging studies such as cranial CT scan or magnetic resonance imaging (MRI) may be needed for evaluation for possible central nervous system (CNS) trauma, tumor, or infectious causes.

Electrocardiogram: An electrocardiogram (ECG) is indicated in cases of suspected coronary artery ischemia.

Thyroid function tests: Although not usually available during the patient's stay in the emergency department (ED), thyroid function tests may indicate a thyroid cause for the vomiting.

DIFFERENTIAL DIAGNOSIS

Clinical and diagnostic findings are helpful in differentiating among the common and catastrophic causes of nausea and vomiting (Table 20-3). The differential diagnosis in adults is extensive; etiologic categories include medication-induced, infectious and toxic causes, disorders of the gastrointestinal tract, CNS causes, pregnancy-related, endocrine and metabolic disorders, radiation-induced, postoperative, unknown (as in cyclic vomiting), psychogenic, and other causes such as acute myocardial infarction and acute graft-versus-host disease.

PEDIATRIC CONSIDERATIONS

The evaluation and management of pediatric patients with nausea and vomiting depend on age and likely causative disorders[5] (Table 20-4). Mild degrees of reflux and associated regurgitation are common in the first few months of life, but vomiting in infancy can be associated with life-threatening illness. In the first week of life, obstructive lesions of the alimentary tract, inborn errors of metabolism, and serious infectious processes are associated with vomiting. After the first week of life, pyloric stenosis needs to be considered. The diagnosis of "feeding problems" should be considered a diagnosis of exclusion. After the first month of life, infections, metabolic diseases, cow's milk intolerance, failure to thrive, and subdural hematoma from abuse should be prime considerations. Thereafter, various disorders are associated with vomiting, including recurrent cyclic vomiting, acute surgical emergencies, food poisoning, toxic ingestion, Henoch-Schönlein purpura, pneumonia, and diabetic ketoacidosis. Anorexia nervosa and bulimia should be considered in teenagers with recurrent vomiting.[5]

MANAGEMENT

If an underlying cause for the nausea and vomiting is discovered, treatment of this disorder would take precedence. Decreased oral intake is a major cause of dehydration and malnutrition. If the patient is able to take oral liquids, sports drinks are preferred while avoiding citrus and highly sweetened drinks.[6] Patients who are dehydrated and in whom intake of oral fluids is not possible or is contraindicated should be given intravenous fluids. Hypokalemia is rarely of clinical significance but may be found with profound vomiting secondary to contraction metabolic alkalosis. Treatment of the underlying condition with administration of intravenous fluids is indicated. Placement of a nasogastric tube is an option in cases such as persistent vomiting, gastroparesis, pancreatitis, and bowel obstruction.

Pharmacologic management of patients with nausea and vomiting is outlined in Figure 20-2. To allow the physician to make an appropriate choice for each patient, the pharmacologic therapies available may be classified into histamine antagonists, muscarinic antagonists, dopamine antagonists, and serotonin antagonists.

The phenothiazines are widely used as general-purpose antiemetics. These agents have multiple complex mechanisms of action. The antiemetic effect is apparently through blockade of the dopamine D_2 receptor in the CTZ. Prochlorperazine (Compazine), droperidol (Inapsine), haloperidol (Haldol), and promethazine (Phenergan) are commonly used medications in this class. Mild to moderate side effects are fairly common and include dystonic reactions and feelings of restlessness. These side effects may be treated with diphenhydramine (Benadryl) or benztropine (Cogentin). Although prochlorperazine was found to be more effective in reducing vomiting than promethazine, use of prochlorperazine has been reported to be associated with a 16% incidence of akathisia and a 4% incidence of dystonia, so patients should be advised about this potential and its mitigation with diphenhydramine or benztropine. Neuroleptic malignant syndrome, blood dyscrasias, and cholestatic jaundice have been documented rarely with use of phenothiazines.

The serotonin receptor antagonists, such as ondansetron, granisetron, and tropisetron, are a class of agents that have

Table 20-3 Disorders Commonly Associated with Vomiting

DISORDER	HISTORY	PREVALENCE	PHYSICAL EXAMINATION	USEFUL TESTS	COMMENTS
Nausea and vomiting of pregnancy (NVP)	Vomiting occurs predominantly in the morning. Associated breast tenderness. NVP typically starts in weeks 4–7, peaks in weeks 10–16, and disappears by week 20. Vomiting that begins after week 12 or continues past week 20 should prompt a search for another cause.	Very common Affects 75% of all pregnancies	Benign abdomen	Urine pregnancy test Serum electrolytes, urine ketones to exclude hyperemesis gravidarum	Consider NVP in all females of childbearing age. Prognosis for mother and infant is excellent. NVP is associated with a decreased risk of miscarriage, fetal growth retardation, and fetal mortality.
Hyperemesis gravidarum	Severe, protracted form of NVP. No universally accepted definition of the disease. Generally accepted hallmarks include 5% weight loss, ketonuria, and disturbance. Hyperemesis is associated with multiple gestation, molar pregnancy, and nulliparity.	Uncommon Affects <1% of pregnancies	Signs of dehydration Benign abdomen	β-hCG Urinalysis for ketones Serum electrolytes Ultrasound exam to exclude molar pregnancy or multiple gestation	Most studies have found no adverse outcomes for the fetus. A few studies, however, have shown a correlation with fetal growth retardation.
Gastroenteritis	Fever, diarrhea, and crampy abdominal pain. Vomiting and pain occur early, usually followed by diarrhea within 24 hr.	Very common	Benign abdomen	Usually not necessary	Early gastroenteritis, when only vomiting and periumbilical pain are present, may be confused with early appendicitis. Diarrhea is usually in the diagnosis of gastroenteritis.
Gastritis	Epigastric pain, belching, bloating, fullness, heartburn, and food intolerance. Use of NSAIDs or ETOH common.	Very common	Mild epigastric tenderness may be present.	Lipase and pregnancy test may be necessary to exclude other diagnoses.	Removal of inciting agent along with antacid therapy will resolve symptoms in most patients.
Peptic ulcer disease (PUD)	Epigastric pain present in 90% of cases. Classically, duodenal ulcer pain is relieved by food while gastric ulcer pain is made worse. Presence of severe pain should raise suspicion of perforation.	Very common	Mild epigastric tenderness	Hemoglobin if bleeding is suspected Heme-positive stool Upright abdominal film if perforation is suspected	Three major causes of PUD are NSAIDs, *H. pylori* infection, and hypersecretory states.

Biliary disease	Abdominal pain may be midepigastric or right upper quadrant (RUQ). Onset frequently after a fatty meal. May have history of similar episodes in the past.	Very common	RUQ tenderness present in most cases. If instructed to breathe deeply during palpation in the RUQ, the patient experiences heightened tenderness and inspiratory arrest (Murphy's sign).	WBC Lipase Serum bilirubin Alkaline phosphatase RUQ ultrasound exam	Normal temperature, WBC, and spontaneous resolution of symptoms suggest biliary colic. Fever, Murphy's sign, elevated WBC, and suggestive ultrasound indicate cholecystitis.
Myocardial infarction	Patients typically have substernal chest pain that may radiate to left arm or jaw. Often associated with dyspnea, diaphoresis, or dizziness.	Common	Patients often are anxious and in distress from pain. No diagnostic examination findings.	ECG (new Q waves, ST segment changes, or T wave inversions) CPK-MB/troponin	Not all patients present with chest pain. A subset of patients, particularly diabetics and the elderly, may present with only nausea, vomiting, and epigastric discomfort.
Diabetic ketoacidosis (DKA)	Polydipsia and polyuria occur early. Without treatment, altered mental status and coma may develop. In long-standing diabetics, DKA may be triggered by infection, trauma, MI, or surgery.	Common	"Fruity" breath odor results from serum acetone. Tachypnea occurs with attempts to "blow off" carbon dioxide to compensate for metabolic acidosis. Signs of dehydration may be present. Severe cases often manifest with altered mental status or coma.	Serum glucose, urine ketones, ABGs	DKA may be the first manifestation of diabetes in some patients. These patients often do not recognize the importance of polydipsia and polyuria. They often present complaining only of nausea, vomiting, and epigastric pain.
Pancreatitis	Patients present with epigastric pain, which often radiates to the back. Most cases are caused by gallstones or alcoholism. Other causes include hypercalcemia, hyperlipidemia, drugs (sulfas and thiazides), ERCP.	Common	Epigastric tenderness is present. Associated paralytic ileus may cause abdominal distention and decreased bowel sounds. Frank shock may be present in severe cases.	Lipase WBC, serum glucose, LDH, AST Hematocrit, BUN, calcium, ABGs	Criteria correlating with higher mortality: *At admission*—Age >55 yr, WBC >16,000/mm^3, glucose >200 dL, base deficit >4, LDH >350 IU/L, AST >250 F Units *Within 48 hours*—Hct drop of 10%, BUN >2 mg/dL, Po_2 < 60 mm Hg, calcium <8 mg, fluid sequestration >4 L
Appendicitis	Abdominal pain classically begins in periumbilical region and later moves to right lower quadrant. Anorexia is common.	Common	Localized tenderness over right lower quadrant. Low-grade fever may be present.	WBC Abdominal CT	Early appendicitis can be a difficult diagnosis to make. It is still frequently missed on the first physician encounter.

Continued

Table 20-3 Disorders Commonly Associated with Vomiting—cont'd

DISORDER	HISTORY	PREVALENCE	PHYSICAL EXAMINATION	USEFUL TESTS	COMMENTS
Bowel obstruction	Classically, abdominal pain consists of intermittent cramps occurring at regular intervals. The frequency of the cramps varies with the level of the obstruction; the higher the level, the more frequent the cramps. The location of the pain also varies with the level of the obstruction; high obstruction causes epigastric pain, mid-level obstruction causes periumbilical pain, colonic obstruction causes hypogastric pain.	Common	Abdominal distention, mild diffuse tenderness, and high-pitched "tinkling" bowel sounds may be present. Thorough search for hernias should be performed.	Supine and upright plain abdominal films Abdominal CT	Adhesions, hernias, and tumors account for 90% of bowel obstructions. Other causes include intussusception, volvulus, foreign bodies, gallstone ileus, inflammatory bowel disease, stricture, cystic fibrosis, and hematoma.
Carbon monoxide (CO) poisoning	Headache is usually present. CO poisoning often occurs during winter months when furnaces are turned on. Family members may have similar symptoms if they also have been exposed.	Uncommon	No reliable signs of early CO poisoning	CO level	Because CO is a tasteless, odorless gas, patients may not realize they have been exposed. It is important to keep a high index of suspicion during the winter months.
Boerhaave's syndrome	Patients may have neck, chest, or epigastric pain. Forceful, protracted vomiting usually causes the tear. Most cases follow a bout of heavy eating and drinking. Other reported causes include childbirth, defecation, seizures, and heavy lifting.	Uncommon	Tachypnea, tachycardia, and hypotension may be present. Escaped air from the esophagus may produce subcutaneous emphysema. Air in the mediastinum produces a "crunching" sound as the heart beats (Hamman's sign).	CXR may show pleural effusion, widened mediastinum, pneumothorax, or pneumomediastinum. Esophagogram using water-soluble contrast is definitive.	The classic presentation includes forceful vomiting, severe chest pain, subcutaneous emphysema, and multiple CXR findings. There is a growing body of evidence that most cases do not have this "classic" picture. In more subtle presentations, the diagnosis can be difficult to make.

ABGs, arterial blood gases; AST, aspartate aminotransferase; β-hCG, β-human chorionic gonadotropin; BUN, blood urea nitrogen; CK, creatine kinase; CT, computed tomography; CXR, chest radiography; DKA, diabetic ketoacidosis; ECG, electrocardiogram; ERCP, endoscopic retrograde cholangiopancreatography; ETOH, ethyl alcohol; LDH, lactate dehydrogenase; MI, myocardial infarction; NSAID, nonsteroidal anti-inflammatory drug; PUD, peptic ulcer disease; WBC, white blood cell.

Table 20-4 Etiology of Nausea and Vomiting in Pediatric Age Groups

ETIOLOGIC CATEGORY	NEWBORN	INFANT	CHILD	ADOLESCENT
Infectious	Sepsis, meningitis, UTI, thrush	Pneumonia, otitis media, thrush	Gastroenteritis	Gastroenteritis, URI
Anatomic	Atresia and webs, malrotation, stenosis, meconium ileus, Hirschsprung's disease	Pyloric stenosis, intussusception, Hirschsprung's disease	Bezoars, chronic granulomatous disease	PUD, superior mesenteric syndrome
Gastrointestinal	Reflux, overfeeding, gastric outlet obstruction, volvulus	Reflux, gastritis, milk intolerance	Appendicitis, pancreatic, hepatitis, other food intolerance	Achalasia, hepatitis
Neurologic	Subdural hematoma, hydrocephalus	Subdural hematoma	Neoplasia, migraine, Reye's syndrome, motion sickness, hypertension	Neoplasia, migraine, motion sickness, hypertension
Metabolic	Organic or amino acidemias, urea cycle defects, galactosemia, hypercalcemia, phenylketonuria, kernicterus	Hereditary fructose intolerance, disorders of fatty acid metabolism, uremia, adrenal hyperplasia, kernicterus	Diabetes, vitamin A excess	Diabetes, pregnancy, acute intermittent porphyria
Other	Idiopathic, cardiac failure	Rumination, cardiac failure	Cyclic vomiting syndrome, toxins, food poisoning, Munchausen syndrome by proxy	Psychogenic, anorexia

PUD, peptic ulcer disease; URI, upper respiratory infection; UTI, urinary tract infection.
Adapted from Li HK, Sunku BK: Vomiting and nausea. In Wyllie R, Hyams JS (eds): Pediatric Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, Management. Philadelphia, Saunders, 2005, pp 127–149.

Table 20-5 Commonly Used Medications for the Treatment of Nausea and Vomiting

MEDICATION	DOSE	COMMENTS
Promethazine (Phenergan)	*Adult*: 12.5–25 mg IV, IM, PO, or by rectum *Pediatric*: 0.25–1 mg/kg/dose q4–6 h prn IV, IM, PO, or by rectum; max 25 mg/dose	May be repeated every 4-6 hr, until cessation of vomiting. Dry mouth, dizziness, blurred vision. Boxed warning for use under 2 yrs old
Prochlorperazine (Compazine)	*Adult*: 5–10 mg IM, or PO; 2.5–10 mg IV; 25 mg by rectum *Pediatric*: 0.4 mg/kg/24 hr tid-qid PO or by rectum; 0.1–0.15 mg/kg/dose tid-qid IM; max 40 mg/24 hr	May be repeated every 4 hr by IV or IM or every 12 hr by rectum, until cessation of vomiting. Lethargy, hypotension, extrapyramidal effects
Metoclopramide (Reglan)	*Adult*: 10 mg IM or IV, may repeat q6 h *Pediatric*: 1–2 mg/kg/dose q2–6 h IV q2–3 hr	Dystonic reactions, tardive dyskinesia, neuroleptic malignant syndrome
Ondansetron (Zofran)	*Adult*: 4 mg IV single dose *Pediatric*: up to 40 kg: 0.1 mg/kg; >40 kg: 4 mg/dose IV single dose	Headache, dizziness, and musculoskeletal pain

IM, intramuscular; IV, intravenous.

generated much interest because of their beneficial effect in chemotherapy-induced emesis. Their principal site of action is the area postrema, although they also affect receptors in the GI tract. Several studies in small series of patients have looked at their effect in overdose of theophylline and acetaminophen. With both of these agents, overdose causes vomiting, and oral intake is required as part of therapy (multiple-dose charcoal and *N*-acetylcysteine). It is well documented that the vomiting often prevents effective oral therapy in patients with overdose of these agents. These studies showed that ondansetron stopped the vomiting and allowed oral therapy to proceed. The dose was 8 mg given intravenously over 20 minutes. The side effects of the serotonin receptor antagonists are mild and include headache and constipation.[7,8]

The prokinetic agents are useful in patients with gastroparesis, gastroesophageal reflux disease, and other putative dysmotility syndromes. Metoclopramide (Reglan) has the most applicability in the ED. It has dopamine antagonist activity at the CTZ and exerts anticholinergic and antiserotonin effects. The primary effect is increased gastric emptying; the exact mechanism for this is not understood. Metoclopramide has multiple antiemetic actions and may be used as a general-purpose agent. Other prokinetic agents, such as cisapride (Propulsid), do not cross the blood-brain barrier. They are not useful as general-purpose antiemetics. Prokinetic agents are used in patients with isolated gastric motility disorders. The most common side effects of metoclopramide are restlessness, drowsiness, and diarrhea. These effects are usually mild and transient.

Antihistamines are useful in nausea and vomiting associated with motion sickness and vertigo. Agents such as dimenhydrinate (Gravol, Dramamine) and meclizine (Antivert) directly inhibit vestibular stimulation and vestibular-cerebellar pathways. Their anticholinergic effect also may contribute to their effectiveness in vertigo and motion sickness. Antihistamines have some role as general antiemetics but are better used in the prevention of motion sickness; for nausea and vomiting, they are less effective than the phenothiazines. The most common side effects of antihistamines are drowsiness, blurred vision, dry mouth, and hypotension. The newer, less-sedating antihistamines are thought to be less effective as antiemetics.

The anticholinergic agent scopolamine in a transdermal patch (Transderm Scō p) or hyoscine (Buscopan) in an oral form may be used for prophylaxis and treatment of motion sickness. These agents also have mild efficacy in preventing cytotoxic chemotherapy-related nausea and vomiting but are not useful in the emergency department.

Benzodiazepine medications have been used for nausea and vomiting, with variable results. Limited studies have evaluated the efficacy of benzodiazepines in the treatment of hyperemesis gravidarum, in prophylaxis for emetogenic chemotherapy, and preoperatively for minor gynecologic surgery. Although this aspect was not directly measured in these studies, the studies inferred that part of the response may be related to the anxiolytic component. No studies have addressed the use of benzodiazepines to treat nonspecific nausea and vomiting in an ED population.

Many of the new medications for nausea and vomiting are first tested as agents for prevention and treatment related to chemotherapy and postoperative nausea and vomiting (PONV). A new oral neurokinin-1 antagonist, aprepitant (Emend), has been found to be an effective adjunctive agent for use in patients receiving cancer chemotherapy.[9] Aprepitant blocks the effects of substance P in the brain. Currently, it is not indicated for use in patients with established nausea and vomiting.

The medication choice is directed at the underlying cause of the nausea and vomiting, if known, such as motion sickness, PONV, or nausea and vomiting related to cancer chemotherapy. For all other patients, the choice of antiemetic agent has not been well studied in emergency medicine. One study found droperidol to be more effective than prochlorperazine or metoclopramide as compared with placebo for moderate to severe nausea of any cause.[10] The same limitation is true of preferred agents used in the field. One study found that ondansetron was moderately effective in the treatment of nausea and vomiting in this setting.[11]

As with adults, the underlying cause of nausea and vomiting is first addressed in determining treatment choices.[6] Most of the same agents used in adults are recommended for children in a weight-based dosing regimen. Ondansetron and metoclopramide have value for antiemetic treatment to reduce nausea and vomiting in pediatric patients. These agents are particularly effective in improving gastroenteritis patients' ability to maintain oral hydration.[12]

Special Situations

Medications such as antihistamines are frequently used to reduce the incidence of nausea and vomiting when opioid analgesics are administered in the ED for pain control. Studies have demonstrated that the incidence of nausea and vomiting related to opioid administration in the ED is low and that these medications have little efficacy in reducing nausea and vomiting.[13,14]

Many agents have been advocated for the treatment of nausea and vomiting in pregnancy (NVP). The treatments include *nonpharmacologic*—avoiding triggers, dietary changes, acupuncture acupressure, ginger, and behavioral therapy—and *pharmacologic*—pyridoxine, antihistamines, metoclopramide, ondansetron, or prochlorperazine. Hyperemesis gravidarum is treated essentially as for NVP. For mild symptoms, pyridoxine (vitamin B_6), acupressure, ginger, and administration of antiemetics including antihistamines, metoclopramide, ondansetron, prochorperazine, and phenothiazines may be used. Pyridoxine, acupressure, and ginger are thought to be of benefit but are not commonly used in the ED. For severe symptoms, hospitalization, fluids, corticosteroids, and electrolyte replacement may be needed. No specific medication has been shown to be superior in the treatment of hyperemesis gravidarum.[15]

Treatment of PONV is well known. Approximately one third of the patients undergoing surgery may experience nausea and vomiting unless they receive appropriate prophylactic treatment, and the incidence is surgical procedure–dependent. Droperidol, metoclopramide, ondansetron, and dexamethasone have been used to reduce PONV.[16] However, the need for antiemetic therapy during procedural sedation in the ED is not well studied. Many of the same drugs associated with PONV used by anesthesiologists in the operating room are used in the ED for procedural sedation. Nitrous oxide and propofol have been associated with a higher incidence of nausea and vomiting. Although the optimal medication for PONV has yet to be determined, ondansetron is considered a first-line agent in some studies; this recommendation could be extended to postprocedural sedation–related nausea and vomiting in the ED.

Chemotherapy-related nausea and vomiting may be seen in the ED. The chemotherapy-induced nausea and vomiting may be acute (up to 24 hours) or delayed (after 24 hours).[17] The incidence of nausea and vomiting is correlated with the emetic potential of the chemotherapeutic agents, the patient's risk factors and other comorbid disorders, and antiemetic treatment. Patients commonly are given the serotonin antagonists dexamethasone and aprepitant for both immediate and delayed prophylaxis. Cannabinoids also have been used to control chemotherapy-induced nausea and vomiting. Choice of agents for treatment in the ED has not been studied, but for this indication the serotonin antagonists and aprepitants are used.

DISPOSITION

Hospital admission is appropriate when the patient has a significant underlying disease, has an unclear diagnosis and responds poorly to fluid and antiemetic therapy, continues to experience uncontrolled emesis refractory to medication, or is at the extremes of age with poor response to treatment. A category subject to broad interpretation is patients in whom the diagnosis is unclear and prospects for timely follow-up are poor (e.g., the patient has no family physician, lacks transportation, is indigent, habitually abuses drugs or alcohol, or has a language barrier). Discharge may be considered if no serious underlying illness is present, the response to fluid and antiemetic therapy is good, the patient is able to take clear liquids before discharge, and the prospects for follow-up and observation at home are favorable.

Close follow-up is arranged for most discharged patients, preferably with their primary care physician, in 24 to 48 hours. At discharge, the patient is prescribed medications as needed and is advised to restart oral intake with small feedings of a liquid diet with gradual return to a normal diet. Some experts have recommended the nausea and vomiting diet, which requires the least amount of gastric neuromuscular work. It is a three-step diet: Sports drinks and bouillon are recommended in step 1; soups are recommended in step 2; and foods that require the least amount of gastric "work" are recommended in step 3, such as meals high in protein and low in lipids.[16] Clear instructions are given to return to the emergency department if there is a recurrence, change, or deterioration in symptoms.

Causes for nausea and vomiting frequently remain undiagnosed. Some cases declare themselves or resolve over time; reevaluation and close follow-up are imperative for patients with continuing symptoms. In patients with persistent or recurring symptoms, psychogenic causes or cyclic vomiting syndrome should be considered.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 21 Abdominal Pain

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PERSPECTIVE

Abdominal pain is a common emergency department (ED) complaint but, for many reasons, is often diagnostically challenging. The nature and quality of abdominal pain may be difficult for the patient to convey. Physical examination findings with this complaint are variable and can be misleading. The location and severity of the pain may change over time. Benign-appearing symptoms and presentations may evolve into life-threatening conditions. Conversely, patients presenting with severe symptoms may carry a relatively benign diagnosis. All of these factors make evaluation of patients with acute abdominal pain challenging in the ED setting.

Epidemiology

Abdominal pain is a common presenting complaint, accounting for up to 10% of all ED visits. Some of the most common causes of acute abdominal pain are listed in Table 21-1. Many patients present with pain and other symptoms that are not typical of any specific disease process. A specific diagnosis may not be possible in about one in every four individuals presenting with this chief complaint.[1] In addition, several adult groups deserve special consideration: the elderly (older than 65 years of age), the immunocompromised, and women of reproductive age.

Elderly patients with acute abdominal pain are more likely to have a life-threatening process as the cause of their pain. Conditions such as diverticulitis, ruptured abdominal aneurysm, or mesenteric ischemia may manifest atypically and be rapidly progressive. Decreased diagnostic accuracy, coupled with increased probability of severe disease, results in increased mortality in elderly patients with abdominal pain.[2]

Increasingly, emergency physicians are seeing patients in immunocompromised states secondary to HIV/AIDS, chemotherapy, and immunosuppressive drugs. For many reasons, these patients also prove challenging. Their clinical presentation can be misleading owing to atypical physical and laboratory findings, such as lack of fever or elevated white count. In regard to infection, the scope of the differential diagnosis also should be broader than usual.[3–7] Presentations in the immunocompromised patient may be highly variable and subtle and are discussed in Chapter 181.

The evaluation of abdominal pain in women involves a differential diagnosis of considerable extent and often requires a more in-depth physical exam and further diagnostic testing. Pelvic organs may be the source of significant pathology in both the pregnant and the nonpregnant patient. The possibility of ectopic pregnancy in women of reproductive age greatly increases the risk of serious disease with a high potential for misdiagnosis. During pregnancy the uterus becomes an abdominal rather than a pelvic organ and may displace the normal intraperitoneal contents, adding complexity to the evaluation of these patients.[8] Nonpregnant patients require evaluation for various ovarian and uterine pathology states.

Pathophysiology

Pathology in the gastrointestinal and genitourinary tracts remains the most common source of pain perceived in the abdomen. Also, pain can arise from a multitude of other intra-abdominal and extra-abdominal locations (Box 21-1). Abdominal pain is derived from one or more of three distinct pain pathways: visceral, somatic, and referred.

Visceral pain results from stimulating autonomic nerves invested in the visceral peritoneum surrounding internal organs. It is often the earliest manifestation of a particular disease process. Distention of hollow organs by fluid or gas and capsular stretching of solid organs from edema, blood, cysts, or abscesses are the most common stimuli. This discomfort is poorly characterized and difficult to localize. If the involved organ is affected by peristalsis, the pain often is described as intermittent, crampy, or colicky. In general, visceral pain is perceived from the abdominal region that correlates with the embryonic somatic segment:

- *Foregut* structures (stomach, duodenum, liver, and pancreas) are associated with *upper abdominal pain*.
- *Midgut* derivatives (small bowel, proximal colon, and appendix) are associated with *periumbilical pain*.
- *Hindgut* structures (distal colon and genitourinary tract) are associated with *lower abdominal pain*.

Visceral pain can be perceived in a location remote from the actual disease process. Localization occurs with the extension of the disease process beyond the viscera. A classic example is that of the early periumbilical pain of appendicitis (midgut). When the parietal peritoneum becomes involved, the pain localizes to the right lower quadrant of the abdomen, the usual location of the appendix.

Somatic pain occurs with irritation of the parietal peritoneum. This is usually caused by infection, chemical irritation, or another inflammatory process. Sensations are conducted by

Table 21-1 Common Causes of Abdominal Pain

CAUSATIVE DISORDER/CONDITION	EPIDEMIOLOGY	ETIOLOGY	PRESENTATION	PHYSICAL EXAMINATION	USEFUL TEST(S)
Gastric, esophageal, or duodenal inflammation	Occurs in all age groups.	Caused by gastric hypersecretion, breakdown of mucoprotective barriers, infection, or exogenous sources.	Epigastric radiating or localized, associated with certain foods. Pain may be burning. In some cases, exacerbation in supine position.	Epigastric tenderness without rebound or guarding. Perforation or bleeding leads to more severe clinical findings.	Uncomplicated cases are treated with antacids or histamine H_2 blockers before invasive studies are contemplated. Gastroduodenoscopy is valuable in diagnosis and biopsy. Testing for *H. pylori* with blood or biopsy specimens. If perforation is suspected, an upright chest radiograph is obtained early to rule out free air. CT may be beneficial.
Acute appendicitis	Peak age in adolescence and young adulthood; less common in children and elders. Higher perforation rate in women, children, and elders and in pregancy. Mortality rate is 0.1% but increases to 2–6% with perforation.	Appendiceal lumen obstruction leads to swelling, ischemia, infection, and perforation.	Epigastric or periumbilical pain migrates to RLQ over 8–12 hr (50–60%). Later presentations associated with higher perforation rates. Pain, low-grade fever (15%), and anorexia (80%) common; vomiting less common (50–70%).	Mean temperature 38° C (100.5° F). Higher temperature associated with perforation. RLQ tenderness (90–95%) with rebound (40–70%) in majority of cases. Rectal tenderness in 30%.	Leukocyte count usually elevated or may show left shift. Urinalysis may show sterile pyuria. CT is sensitive and specific. US may have use in women, pregnancy, and children with RLQ pain.
Biliary tract disease	Peak age 35–60 yr; rare in patients younger than 20. Female-to-male ratio of 3:1. Risk factors include multiparity, obesity, alcohol intake, and use of birth control pills.	Passage of gallstones causes biliary colic. Impaction of a stone in cystic duct or common duct causes choecystitis or cholangitis.	Crampy RUQ pain radiates to right subscapular area. Prior history of pain is common. May have nausea or postprandial pain. Longer duration of pain favors diagnosis of cholecystitis or cholangitis.	Temperature normal in biliary colic, elevated in cholecystitis and cholangitis. RUQ tenderness, rebound, and jaundice (less common) may be present.	WBC count elevated in cholecystitis and cholangitis. Lipase and liver function tests may help differentiate this from gastritis or ulcer disease. Ultrasound shows wall thickening, pericholecystic fluid, stones, or duct dilatation. Hepatobiliary scintigraphy diagnoses gallbladder function.
Ureteral colic	Average age 30–40 yr, primarily in men. Prior history or family history of stones is common.	Family history, gout, *Proteus* infection. Renal tubular acidosis and cystinuria lead to stone formation.	Acute onset of flank pain radiating to groin. Nausea, vomiting, and pallor are common. Patient usually writhing in pain.	Vital signs usually normal. Tenderness on CVA percussion with benign abdominal examination.	Urinalysis usually shows hematuria. Noncontrast CT is sensitive and specific. US with fluid bolus useful diagnostically.

Diverticulitis	Incidence increases with advancing age, affects males more often than females. Recurrences are common. Often called "left-sided" appendicitis.	Colonic diverticula may become infected or perforated or cause local colitis. Obstruction, peritonitis, abscesses, fistulas result from infection or swelling.	Change in stool frequency or consistency commonly reported. LLQ pain is common. Associated with fever, nausea/vomiting; rectal bleeding may be seen.	Fever usually of low grade. LLQ pain without rebound is common. Stool may be heme-positive.	Results on most tests usually normal. Plain radiographs may show obstruction or mass effect. CT is often diagnostic.
Acute gastroenteritis	Common diagnosis. Seasonal. Most common misdiagnosis of appendicitis. May be seen in multiple family members. History of travel or immune compromise.	Usually viral. Consider invasive bacterial or parasitic in prolonged cases, in travelers, or immune-compromised patients.	Pain usually poorly localized, intermittent, crampy, and diffuse. Diarrhea is key element in diagnosis; usually large-volume, watery. Nausea and vomiting usually begin before pain.	Abdominal examination usually nonspecific without peritoneal signs. Watery diarrhea or no stool noted on rectal examination. Fever is usually present.	Usually symptomatic care with antiemetics and volume repletion. Heme-positive stools may be a clue to invasive pathogens. Key is not using this as a "default" diagnosis and missing more serious disease.
Constipation and obstipation	More common in females, the elderly, the very young, and patients on narcotics.	Idiopathic or hypokinesis secondary to disease states (low motility) or exogenous sources (diet, medications).	Abdominal pain; change in bowel habits.	Variable, nonspecific without peritoneal signs. Rectal exam may reveal hard stool or impaction.	Radiographs may show large amounts of stool. This is a diagnosis of exclusion.
Nonspecific abdominal pain	More common in persons of young and middle age, women of childbearing age or persons of low socioeconomic status, and patients with psychiatric disorders. Up to 10% of patients older than 50 years of age will have intra-abdominal cancer.	Unknown. Early or undiagnosed presentation of pathologic conditions.	Variable but tends to be chronic or recurrent.	Variable but no peritoneal signs. Rectal exam should be done to evaluate for subtle signs of pathology, including heme-positive stool, fistulas, and fissures.	Variable and often can be done on an outpatient basis.

CT, computed tomography; CVA, costovertebral angle; LLQ, left lower quadrant; LUQ, left upper quadrant; RLQ, right lower quadrant; RUQ, right upper quadrant; US, ultrasonography; WBC, white blood cell.

BOX 21-1 IMPORTANT EXTRA-ABDOMINOPELVIC CAUSES OF ABDOMINAL PAIN

Thoracic
Myocardial infarction/unstable angina
Pneumonia
Pulmonary embolism
Herniated thoracic disk (neuralgia)
Pericarditis/myocarditis

Genitourinary
Testicular torsion

Abdominal Wall
Muscle spasm
Muscle hematoma
Herpes zoster

Infectious
Streptococcal pharyngitis (more often in children)
Rocky Mountain spotted fever
Mononucleosis

Systemic
Diabetic ketoacidosis
Alcoholic ketoacidosis
Uremia
Sickle cell disease
Porphyria
Systemic lupus erythematosus
Vasculitis
Glaucoma
Hyperthyroidism

Toxic
Methanol poisoning
Heavy metal toxicity
Scorpion bite
Snake bite
Black widow spider bite

Adapted from Purcell TB: Nonsurgical and extraperitoneal causes of abdominal pain. Emerg Med Clin North Am 7:721, 1989.

the peripheral nerves and are better localized than the visceral pain component. Figure 21-1 illustrates some more typical pain locations corresponding to specific disease entities. Somatic pain is often described as intense and constant. As disease processes evolve to peritoneal irritation with inflammation, better localization of the pain to the area of pathology generally occurs.

Referred pain is defined as pain felt at a distance from its source because peripheral afferent nerve fibers from many internal organs enter the spinal cord through nerve roots that also carry nociceptive fibers from other locations, as illustrated in Figure 21-2. This makes interpretation of the location of noxious stimuli difficult for the brain. Both visceral pain and somatic pain can manifest as referred pain. Two examples of referred pain are the epigastric pain associated with an inferior myocardial infarction and the shoulder pain associated with blood in the peritoneal cavity irritating the diaphragm.

Gynecologic and obstetric presentations are discussed in other chapters. Notably, any abdominal pain in a female may represent referred pain from pelvic structures or an extension of a pelvic process, as in the case of perihepatic inflammation with pelvic inflammatory disease.

DIAGNOSTIC APPROACH

The clinical approach should focus on early stabilization, history, physical examination, and any ancillary tests collectively facilitating appropriate management and disposition plans.

Differential Considerations

Classically, potential diagnoses are divided into intra-*abdominopelvic* (intraperitoneal, retroperitoneal, and pelvic) causes (e.g., appendicitis, cholecystitis, pancreatitis) and extra-*abdominopelvic* processes (e.g., pneumonia, myocardial infarction, ketoacidosis).

Although significant morbidity and mortality can result from many disorders causing abdominal pain, a few processes warrant careful consideration in the ED. Table 21-2 lists important potentially life-threatening nontraumatic causes of abdominal pain. This group represents the major etiologic disorders likely to be associated with hemodynamic compromise and for which early therapeutic intervention is critical.

Rapid Assessment and Stabilization

As with any complaint, triage is the first critical step in management. Most patients presenting with abdominal pain do not have hemodynamic instability, but up to 7% of these patients may have a life-threatening process. This percentage is higher in elders and immunocompromised patients.[1]

Physiologically compromised patients should be brought to a treatment area immediately and resuscitation initiated. Profound shock or protracted emesis can lead to airway compromise necessitating intubation. These patients are often severely volume depleted and require rapid intravenous access and volume resuscitation with an isotonic crystalloid solution, titrated to a physiologic endpoint.

Extreme conditions such as ruptured abdominal aortic aneurysm, massive gastrointestinal hemorrhage, ruptured spleen, and hemorrhagic pancreatitis may require blood or blood product replacement. Bedside ultrasonography can be used to quickly evaluate patients for free intraperitoneal fluid, volume status, and presence of aortic pathology. Ultrasound assessment should be part of the initial physical examination and can be invaluable in guiding treatment and disposition. Because any of the immediately life-threatening entities may necessitate surgical intervention or management, early surgical consultation is indicated.

Pivotal Findings

History

A careful and focused history is central to unlocking the puzzle of abdominal pain. Box 21-2 lists some historical questions with high yields for serious pathology. Language and cultural differences may influence accurate communication and mutual understanding.

Abrupt onset often is indicative of a more serious cause; however, delayed presentations also may represent a surgical condition. Surgical causes of abdominal pain are more likely to manifest with pain first, followed by nausea and vomiting, rather than with nausea and vomiting followed by pain. Localization and pain migration also are helpful components of the pain history. Diffuse pain generally is nonsurgical, but it may represent the early visceral component of a surgical process. Colicky pain is indicative of hollow viscus distention, and

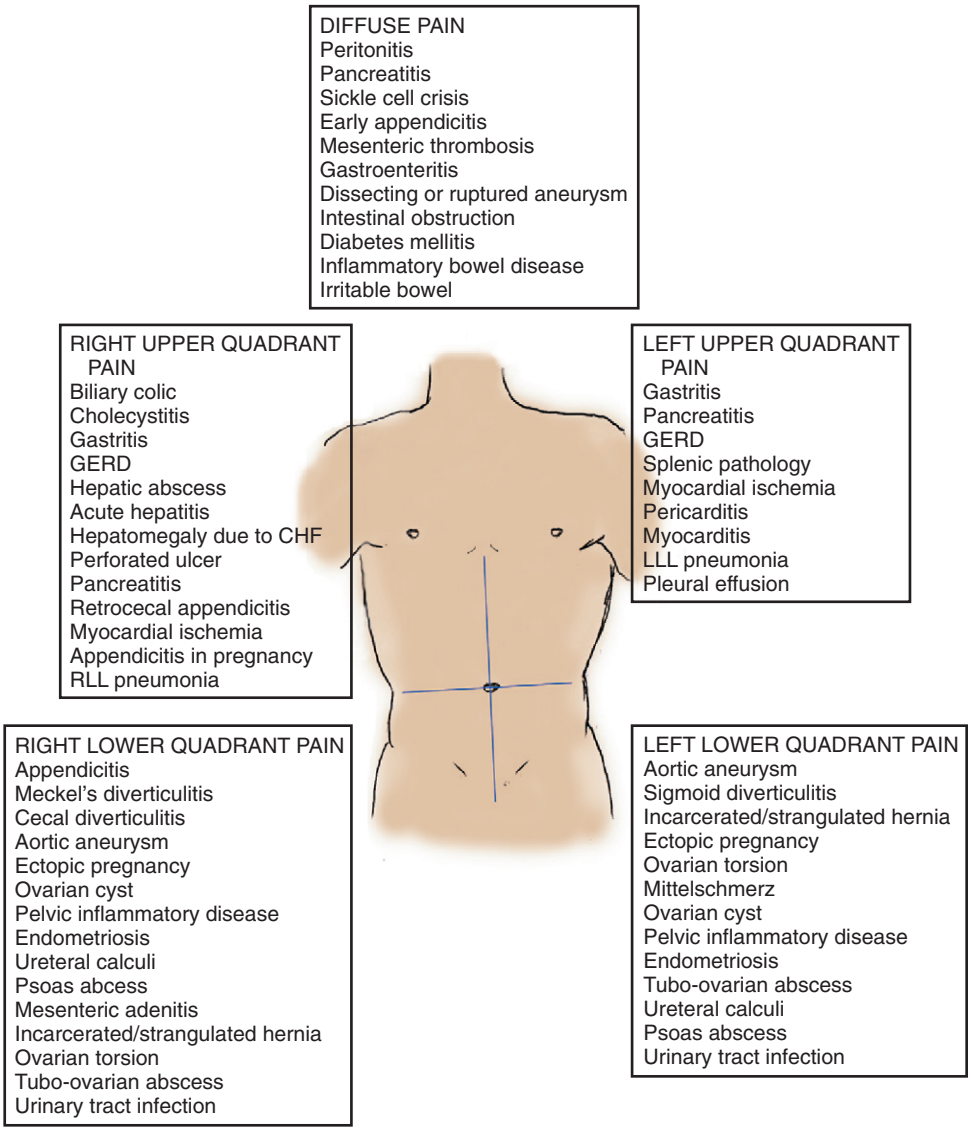


Figure 21-1. Differential diagnosis of acute abdominal pain. CHF, congestive heart failure; GERD, gastroesophageal reflux disease; LLL, left lower lobe; RLL, right lower lobe.

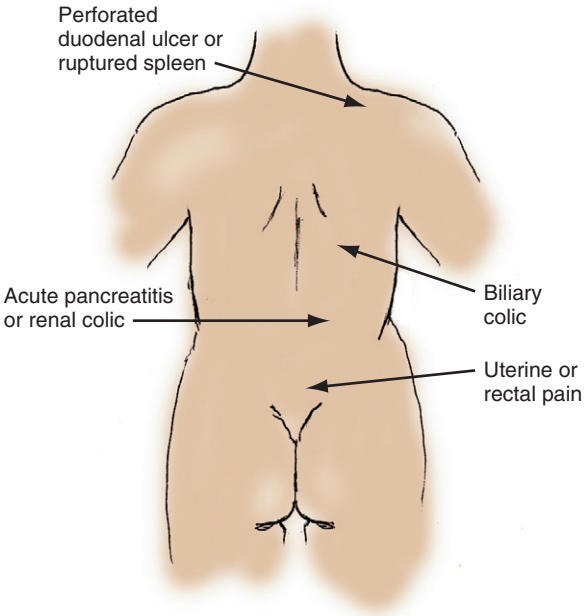


Figure 21-2. Common locations of referred pain from abdominal etiology.

duration and time of colic may give clues to the identity of the culprit organ, as displayed in Figure 21-3.

The severity and descriptive nature of the pain are the most subjective aspects of the pain history, but a few classical descriptions are recognized, such as the following:

- The diffuse, severe, colicky pain of bowel obstruction
- The "pain out of proportion to examination" observed in patients with mesenteric ischemia
- The radiation of pain from the epigastrium straight through to the midback associated with pancreatitis, either related to primary organ inflammation or secondary to a penetrating ulcer
- The radiation of pain to the left shoulder or independent pain in the left shoulder associated with splenic pathology, diaphragmatic irritation, or free intraperitoneal fluid
- The onset of pain associated with syncope seen in perforation of gastric or duodenal ulcer, ruptured aortic aneurysm, or ruptured ectopic pregnancy

Physical Examination

The objective evaluation begins with measurement of the vital signs. Significant tachycardia and hypotension are indicators that hypovolemia or sepsis may be present. Tachypnea

Table 21-2 Potentially Life-threatening Causes of Abdominal Pain

CAUSE	EPIDEMIOLOGY	ETIOLOGY	PRESENTATION	PHYSICAL EXAMINATION	USEFUL TOOL(S)
Ruptured ectopic pregnancy	Occurs in females of childbearing age. No method of contraception prevents ectopic pregnancy. Approximately 1 in every 100 pregnancies.	Risk factors include nonwhite race, older age, history of STD or PID, infertility treatment, intrauterine contraceptive device placed within the past year, tubal sterilization, and previous ectopic pregnancy.	Severe, sharp constant pain localized to the affected side. More diffuse abdominal pain with intraperitoneal hemorrhage. Signs of shock may be present. Midline pain tends not to be ectopic pregnancy.	Shock or evidence of peritonitis may be present. Lateralized abdominal tenderness. Localized adnexal tenderness or cervical motion tenderness increase the likelihood of ectopic pregnancy. Vaginal bleeding does not have to be present.	β-hCG testing necessary in all females of childbearing age (10–55 yr); combined with ultrasonography, preferably transvaginal in early pregnancy, usually is diagnostic. FAST exam is useful in evaluating for free fluid in patients with shock or peritonitis.
Ruptured or leaking abdominal aneurysm	Incidence increases with advancing age. More frequent in men. Risk factors include HTN, DM, smoking, COPD, and CAD.	Exact etiology is undetermined. Contributing factors include atherosclerosis, genetic predisposition, HTN, connective tissue disease, trauma, and infection.	Patient often asymptomatic until rupture. Acute epigastric and back pain often associated with or followed by syncope or signs of shock. Pain may radiate to back, groin, or testes.	Vital signs may be normal (in 70%) to severely hypotensive. Palpation of a pulsatile mass is usually possible in aneurysms 5 cm or greater. The physical examination may be nonspecific. Bruits or inequality of femoral pulses may be evident.	Abdominal plain films abnormal in 80% of cases. Ultrasound can define diameter and length but can be limited by obesity and bowel gas. FAST exam can be helpful in evaluating for leak by looking for free fluid. Spiral CT test of choice in stable patients.
Mesenteric ischemia	Occurs most commonly in elders with CV disease, CHF, cardiac dysrhythmias, DM, sepsis, and dehydration. Responsible for 1 of 1000 hospital admissions. Mortality 70%. Mesenteric venous thrombosis associated with hypercoagulable states, hematologic inflammation, and trauma.	20–30% of lesions are nonocclusive. The causes of ischemia are multifactorial, including transient hypotension in the presence of preexisting atherosclerotic lesion. The arterial occlusive causes (65%) are secondary to emboli (75%) or acute arterial thrombosis (25%).	Severe pain, colicky, that starts in periumbilical region and then becomes diffuse. Often associated with vomiting and diarrhea. Sometimes postprandial. "Mesenteric or abdominal angina."	Early examination results can be remarkably benign in the presence of severe ischemia. Bowel sounds often still present. Rectal examination important because mild bleeding with positive guaiac stools can be present.	Often a pronounced leukocytosis is present. Elevations of amylase and creatine kinase levels are seen. Metabolic acidosis due to lactic acidemia is often seen with infarction. Plain radiographs of limited benefit. CT, MRI, and angiography are accurate to varying degrees.

Intestinal obstruction	Peaks in infancy and older age. More common with history of previous abdominal surgery.	Adhesions, carcinoma, hernias, abscesses, volvulus, and infarction. Obstruction leads to vomiting, "third spacing" of fluid, or strangulation and necrosis of bowel.	Crampy diffuse abdominal pain associated with vomiting.	Vital signs usually normal unless dehydration or bowel strangulation has occurred. Abdominal distention, hyperactive bowel sounds, and diffuse tenderness. Local peritoneal signs indicate strangulation.	Elevated WBC count suggests strangulation. Electrolytes may be abnormal if associated with vomiting or prolonged symptoms. Abdominal radiographs and CT are useful in diagnosis.
Perforated viscus	Incidence increases with advancing age. History of peptic ulcer disease or diverticular disease common.	More often a duodenal ulcer that erodes through the serosa. Colonic diverticula, large bowel, and gallbladder perforations are rare. Spillage of bowel contents causes peritonitis.	Acute onset of epigastric pain is common. Vomiting in 50%. Fever may develop later. Pain may localize with omental walling off of peritonitis. Shock may be present with bleeding or sepsis.	Fever, usually of low grade, is common; worsens over time. Tachycardia is common. Abdominal examination reveals diffuse guarding and rebound. "Boardlike" abdomen in later stages. Bowel sounds are decreased.	WBC count usually elevated due to peritonitis. Amylase may be elevated; LFT results are variable. Upright radiographic view reveals free air in 70–80% of cases with perforated ulcers.
Acute pancreatitis	Peak age in adulthood; rare in children and elders. Male preponderance. Alcohol abuse and biliary tract disease are risk factors.	Alcohol, gallstones, hyperlipidemia, hypercalcemia, or endoscopic retrograde pancreatography causing pancreatic damage, saponification, and necrosis. ARDS, sepsis, hemorrhage, and renal failure are secondary.	Acute onset of epigastric pain radiating to the back. Nausea and vomiting are common. Pain disproportionate to physical findings. Adequate volume repletion is important in the initial therapy.	Low-grade fever common. Patient may be hypotensive or tachypneic. Some epigastric tenderness usually present. Because pancreas is retroperitoneal organ, guarding or rebound not present unless condition is severe. Flank ecchymosis or periumbilical ecchymosis may be seen if process is hemorrhagic.	Lipase determination is test of choice. Ultrasound exam may show edema, pseudocyst, or biliary tract disease. CT scan may show abscesses, necrosis, hemorrhage, or pseudocysts. CT is ordered if severe acture pancreatitis is suspected. Rule out gallstones with ultrasound exam.

ARDS, acute respiratory distress syndrome; β-hCG, β human chorionic gonadotropin; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CT, computed tomography; CV, cerebrovascular; DM, diabetes mellitus; FAST, focused assessment with sonography in trauma; HTN, hypertension; LFT, liver function test; MRI, magnetic resonance imaging; PID, pelvic inflammatory disease; STD, sexually transmitted disease; WBC, white blood cell.

BOX 21-2 HIGH-YIELD HISTORICAL QUESTIONS

1. *How old are you?* Advanced age means increased risk.
2. *Which came first—pain or vomiting?* Pain first is worse (i.e., more likely to be caused by surgical disease).
3. *How long have you had the pain?* Pain for less than 48 hours is worse.
4. *Have you ever had abdominal surgery?* Consider obstruction in patients who report previous abdominal surgery.
5. *Is the pain constant or intermittent?* Constant pain is worse.
6. *Have you ever had this before?* A report of no prior episodes is worse.
7. *Do you have a history of cancer, diverticulosis, pancreatitis, kidney failure, gallstones, or inflammatory bowel disease?* All are suggestive of more serious disease.
8. *Do you have human immunodeficiency virus (HIV)?* Consider occult infection or drug-related pancreatitis.
9. *How much alcohol do you drink per day?* Consider pancreatitis, hepatitis, or cirrhosis in patients with history or signs of significant intake.
10. *Are you pregnant?* Test for pregnancy—consider ectopic pregnancy.
11. *Are you taking antibiotics or steroids?* Effects of these drugs may mask infection.
12. *Did the pain start centrally and migrate to the right lower quadrant?* High specificity for appendicitis.
13. *Do you have a history of vascular or heart disease, hypertension, or atrial fibrillation?* Consider mesenteric ischemia and abdominal aneurysm.

From Colucciello SA, Lukens TW, Morgan DL: Abdominal pain: An evidence-based approach. Emerg Med Pract 1:2, 1999.

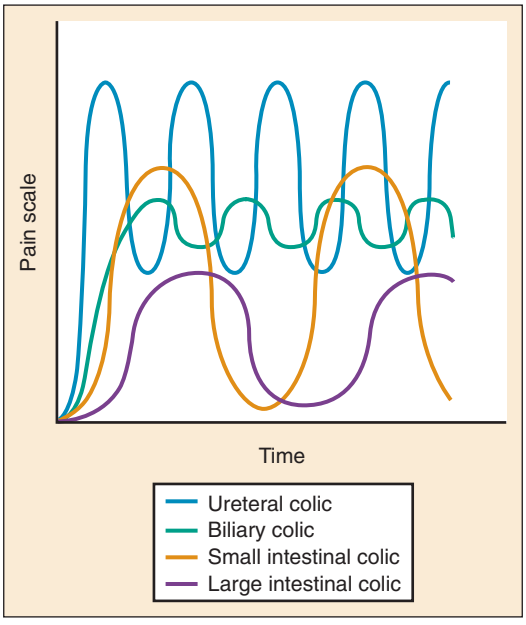


Figure 21-3. The characteristics of colicky abdominal pain.

may be an indication of metabolic acidosis from gangrenous viscera or sepsis, hypoxemia from pneumonia, or simply a catecholamine-induced reaction to pain. Elevated temperature often is associated with intra-abdominal infections. Although important, vital signs may be misleading and should be interpreted in the context of the entire presentation. Tachycardia may develop late for various reasons in hypovolema. Temperature often is normal in elderly patients with laparotomy-proven intraperitoneal infections.[9] Septic elderly patients also may present with hypothermia.

A thorough abdominal examination is an essential part of evaluation of the patient with abdominal pain. This requires properly positioning the patient supine and exposing the abdomen. The examination should begin with inspection for any signs of trauma, bruising, or skin lesions. The patient should be asked to localize the area of maximal tenderness by pointing with one finger. The abdomen can be mentally divided into four quadrants: right upper, right lower, left upper, and left lower; each area is then examined individually. Tenderness in one quadrant often corresponds with the location of the diseased organ, which will direct the workup (see Fig. 21-1). Some disease processes may manifest with pain that is not exclusively within one specific quadrant, such as the suprapubic pain of a urinary tract infection or the midepigastic pain of a gastric ulcer. Although 80% of patients with suspected appendicitis present with right lower quadrant abdominal tenderness, 20% of patients with proven appendicitis do not.[10]

Rectal examination may have limited use in the evaluation of abdominal pain, except that associated with intraluminal gastrointestinal hemorrhage, prostatitis, or perirectal disease. The main utility of the rectal examination is in the detection of heme-positive stool, anal fissures or fistulas, or stool impaction. Rectal examination has not been shown to increase diagnostic accuracy for appendicitis when added to external physical examination of the abdomen.[11]

The abdominal evaluation should include a pelvic examination in female patients with lower abdominal pain or an otherwise uncertain diagnosis. The pelvic exam should be done early in the evaluation of the female patient with abdominal pain to help differentiate an abdominal from a pelvic source. This information is helpful in choosing an imaging modality. Pelvic ultrasound exam is helpful in evaluating uterine and ovarian pathology, whereas computed tomography (CT) is more beneficial in evaluation of suspected intra-abdominal pathology. Although the pelvic exam may guide the initial choice of imaging modality, overlap in exam findings is common. For example a patient with right lower quadrant tenderness may have both right adnexal tenderness and tenderness over McBurney's point—necessitating exclusion of both appendicitis and ovarian torsion. The diagnosis highest on the differential list should be ruled out first using the corresponding imaging modality.

In the male patient with abdominal pain, the urogenital system should be examined. Diseases such as prostatitis, orchitis, and epididymitis commonly cause abdominal pain in males. Furthermore, inguinal hernias are more common in males, with the possibility of strangulation or incarceration in the inguinal canal making a thorough genitourinary examination mandatory.

In view of the evolving nature of abdominal pain, repetitive examinations may be useful. This is common practice with respect to suspected appendicitis and has improved the diagnostic accuracy in patients whose presentations were atypical.[2]

Ancillary Testing

Urinalysis and testing for pregnancy are perhaps the most time- and cost-effective adjunctive laboratory tests available. Results often can be obtained quickly, so the former can lead to an early diagnosis and the latter may significantly affect

further evaluation and management approaches. It is necessary to interpret urinalysis results within the context of the patient's clinical picture. Pyuria, with or without bacteriuria, often is present in a variety of conditions besides a simple urinary tract infection. For example, appendicitis may feature sterile pyuria.[12] Similarly, hematuria usually is present with the relatively benign condition of nephrolithiasis but also may indicate an abdominal aortic aneurysm.

Complete blood counts frequently are ordered for patients with abdominal pain, but findings seldom are contributory to a diagnosis. Despite the association of elevated white blood cell (WBC) counts with many infectious and inflammatory processes, the WBC count is neither sufficiently sensitive nor specific to be considered a discriminatory test to help establish or rule out a serious cause for the pain. Even serial WBC counts have failed to differentiate surgical from nonsurgical conditions. The WBC count is therefore not helpful for diagnosis. Serum electrolytes, even in the presence of protracted emesis or diarrhea, are abnormal in less than 1% of patients. These studies are not indicated for most patients in the absence of another indication. Blood urea nitrogen concentrations can be elevated in gastrointestinal hemorrhage and dehydration, but such conditions are better detected and quantified by history and physical examination. Increased serum creatinine usually is indicative of renal dysfunction. Blood glucose, anion gap, and serum ketone determinations are useful in diabetic ketoacidosis, one cause of acute abdominal pain and tachypnea.

Liver enzymes and coagulation studies are helpful only in a small subset of patients with suspected liver disease.[13] If pancreatitis is suspected, the most useful diagnostic result is serum lipase elevated to at least double the normal value, because it is more specific and more sensitive than serum amylase for this process. Measurement of serum amylase is of no value if a serum lipase level is available.[14] Serum phosphate and serum lactate levels are elevated late in bowel ischemia, and such determinations may be useful if this entity is suspected but cannot be considered either sufficiently sensitive or specific to establish or exclude the diagnosis on their own.

Plain radiography of the abdomen has limited usefulness in the evaluation of acute abdominal pain. Suspected bowel obstruction, foreign body, and perforated viscus are the main indications. CT of the abdomen has become the imaging modality of choice with nonobstetric abdominal pain. It allows visualization of both intraperitoneal and extraperitoneal structures and has a high degree of accuracy, establishing a diagnosis in more than 95% of cases in one study[15] and increasing the confidence in diagnosis in another.[16] Incidental findings are common on CT scans and may lead to a diagnosis. Patients who undergo CT have a change in diagnosis more often than those who do not.[17] The proper execution and interpretation of CT studies will reduce morbidity, mortality, and medical expenses.[18,19]

CT has increased diagnostic utility in elderly patients for several reasons. Older people with abdominal pain may have twice the rate of surgery[20-22] and a six- to eight-fold increase in mortality compared with younger adults.[20,21] Furthermore, evaluation of abdominal pain in the elderly often is more challenging owing to unreliable findings on physical examination including vital signs, difficulties in history taking, physiologic age-related changes, and comorbid conditions. In the elderly population, CT results change management or disposition decisions in a significant proportion of patients.[23] Table 21-3 lists the most common findings on CT scans in elderly patients with abdominal pain.

Some controversy surrounds the use of oral contrast in abdominal CT in the critically ill ED patient. Technologic advances have improved image acquisition and resolution, and preliminary studies have shown that intravenous contrast alone may now be adequate in the evaluation of certain suspected pathologic processes, such as solid organ or bowel wall disease.[24] CT with intravenous contrast alone also has been shown to be sensitive and specific for the confirmation or exclusion of acute appendicitis.[25] The exclusion of oral contrast in these patients significantly decreases ED time to disposition and improves patient satisfaction.

Bedside transabdominal and transvaginal ultrasonography have emerged as extremely useful adjuncts, decreasing time to diagnosis of life-threatening abdominopelvic conditions. Useful indications include the following:

- Identification of an intrauterine pregnancy, effectively lowering the chances of an ectopic pregnancy to less than 1 in 20,000 (In women using fertility aids, however, identification of intrauterine pregnancy does not exclude ectopic pregnancy, in keeping with an increased incidence of heterotopic pregnancy.)
- Measurement of the cross-sectional diameter of the abdominal aorta to determine whether an abdominal aortic aneurysm exists
- Detection of free intraperitoneal fluid indicating hemorrhage, pus, or extrusion of gut contents
- Use as a diagnostic aid for detection of the following non–life-threatening conditions:
  - Gallstones or a dilated common bile duct, which may be a clue to the presence of choledocholithiasis
  - Pericholecystic fluid or gallbladder wall thickening, which may be indicative of cholecystitis
  - Free intraperitoneal fluid indicating ascites
  - Hydronephrosis indicating possible obstructive uropathy
  - Inferior vena cava distention or collapse as an indicator of volume status

Table 21-3 Most Common Diagnostic Computed Tomography (CT) Findings in Older Patients Presenting to the Emergency Department with Acute Abdominal Pain

FINDING	PERCENT OF ABDOMINAL CT SCANS
Small bowel obstruction or ileus	18%
Diverticulitis	18%
Urolithiasis	10%
Cholelithiasis	10%
Abdominal mass/neoplasm	8%
Pyelonephritis	7%
Pancreatitis	6%

From Hustey FM, Meldon SW, et al: The use of abdominal computed tomography in older ED patients with acute abdominal pain. Am J Emerg Med 23:259–265, 2005.

The results of sonographic examinations are operator-dependent, and misdiagnosis can occur because of failure to detect or identify pathology, incorrect identification of normal anatomy as pathologic, or overinterpretation of correctly identified findings (e.g., the mere presence of gallstones does not indicate that cholelithiasis is the cause of the pain). The emergency physician must be properly trained in image acquisition and interpretation, and ultrasound evaluation in the radiology department should be sought if there is ambiguity or uncertainty in findings.

DIFFERENTIAL DIAGNOSIS

The differential considerations with abdominal pain include a significant number of potentially life- or organ-threatening entities, particularly in the setting of a hemodynamically unstable or toxic-appearing patient. Severely ill patients require timely resuscitation and expeditious evaluation for potentially life-threatening conditions. A focused history and exam should be performed, and the patient should be placed in a monitored acute care area well equipped for airway control, quick intravenous access, and fluid administration. Only then should appropriate diagnostics be initiated (bedside focused assessment with sonography in trauma [FAST] and aorta ultrasound assessment and radiographic, electrocardiographic, and laboratory studies). This approach is particularly important in dealing with elderly or potentially pregnant patients (see Tables 21-1 and 21-2).

Women of reproductive age who present with abdominal pain should undergo pregnancy testing early, and a known pregnancy or a positive result on urine or serum pregnancy testing associated with abdominal pain in the ED should be considered to represent an ectopic pregnancy until proved otherwise. If evidence of blood loss is present, early obstetric consultation and diagnostic ultrasonography should be promptly sought. Bedside transabdominal sonography may identify free intraperitoneal fluid during the evaluation of shock, which may be sufficient evidence to justify operative intervention in the context of a positive pregnancy test and appropriate history and physical findings.

Despite the limitations already described, the approach to the differential diagnosis of abdominal pain generally is based on the location of maximum tenderness. Figure 21-1 shows locations of subjective pain and maximal tenderness on palpation related to various underlying causes. In women of childbearing age, a positive result on pregnancy testing may indicate ectopic pregnancy, but the entire spectrum of intra-abdominal conditions remains in the differential diagnosis, as for the nonpregnant patient. When the very broad differential list is compartmentalized by both history and physical examination, ancillary testing should proceed to either confirm or support the clinical suspicion.

Despite the significant variety of tests available, close to one half of the patients presenting to the ED with acute abdominal pain will have no conclusive diagnosis. It is incumbent on the clinician to reconsider the extra-abdominal causes of abdominal pain (see Box 21-1), with special consideration in elderly and immunocompromised patients, before arriving at the diagnosis of "nonspecific abdominal pain."

EMPIRICAL MANAGEMENT

The main therapeutic goals in managing acute abdominal pain are physiologic stabilization, mitigation of symptoms (e.g., emesis control, pain relief), and expeditious diagnosis, with consultation, if required.

There is no evidence to support withholding analgesics from patients with acute abdominal pain to preserve the accuracy of subsequent abdominal exams; in fact, the preponderance of evidence supports the opposite. Pain relief may facilitate the diagnosis in patients ultimately requiring surgery.[26-28] In the acute setting, analgesia usually is accomplished with intravenously titrated opioids. Meperidine (Demerol) has an unfavorable side effect profile and should be avoided. Intravenous ketorolac, the only parenteral nonsteroidal anti-inflammatory drug available in North America, is useful for both ureteral and biliary colic,[29,30] as well as some gynecologic conditions, but is not indicated for general treatment of undifferentiated abdominal pain. Among patients with gastrointestinal hemorrhage and potential surgical candidates, ketorolac has been shown to increase bleeding times in healthy volunteers.[31]

Aside from analgesics, a variety of other medications may be helpful to patients with abdominal pain. The burning pain caused by gastric acid may be relieved by antacids.[32] Intestinal cramping may be diminished with oral anticholinergics such as the combination agent atropine-scopolamine-hyoscyamine-phenobarbital (Donnatal), although evidence for this is scant and highly variable.

Antiemetics such as promethazine, prochlorperazine, ondansetron, granisetron, or inapsine can be useful for nausea and vomiting. Gastric emptying by nasogastric tube with suction is appropriate for suspected small bowel obstruction and intractable pain or vomiting.

If intra-abdominal infection is suspected, broad-spectrum antibiotic therapy should be initiated promptly. Abdominal infections are often polymicrobial and coverage for enteric gram-negative, gram-positive, and anaerobic bacteria must be included. In the choice of antibiotic or combination, the following should be considered:

- Unless local antibiotic resistance surveillance indicates otherwise, second-generation cephalosporins (e.g., cefamandole, cefotetan, cefoxitin) or quinolone (ciprofloxacin, levofloxacin) may be combined with metronidazole for the initial dose of antibiotics in the ED. Other noncephalosporin, β-lactam agents with β-lactamase antagonists (e.g., ampicillin-sulbactam, piperacillin-tazobactam, ticarcillin-clavulanate) are alternatives.
- Many enteric gram-negative bacilli mutate rapidly to produce β-lactamases that are poorly antagonized by specific drug combinations containing clavulanate, sulbactam, or tazobactam. A carbapenem (e.g., imipenem, meropenem) or cefepime is an alternative for patients who may have recently received other antibiotics.[10,33]

Whether to provide coverage for *Enterococcus* species is still a subject of debate, and the decision to treat for these bacteria specifically can be made after consultation. Immunocompromised patients may require antifungal agents.

DISPOSITION

Because up to 40% of patients presenting with acute abdominal pain receive the diagnosis of nonspecific abdominal pain, the disposition can be as difficult as the diagnosis in these patients. Categories for disposition may include surgical versus nonsurgical consultation and management, admission for observation, and discharge to home with follow-up evaluation.[34] The decision to admit a patient to an observation unit or a hospital bed must factor in the following:

- Information gained from the history, physical examination, and test results
- The likelihood of any suspected disease
- Any potential ramifications of progression of a known disease, or of incorrect diagnosis or management
- The likelihood of appropriate (or any) and timely follow-up after hospital discharge

Clinically stable patients may be discharged from the ED with appropriate follow-up care, possibly to include repeated physical exam or additional diagnostic imaging if indicated.

In the case of nonspecific abdominal pain that is considered potentially worrisome, it is prudent to have the patient reevaluated after 8 to 12 hours. This can be done through a return visit to the ED, an appointment with a primary care physician, or an observation unit protocol.

Before discharge of a patient with an undiagnosed cause of nonspecific abdominal pain, several conditions should be met: The abdominal examination findings should be benign overall, with normal vital signs. Pain and nausea should be controlled, and the patient should be able to eat and drink. If a patient is to be discharged home without a specific diagnosis, clear instructions to the patient must include the following information:

- What the patient has to do for relief of symptoms or to maximize chances of resolution of the condition (e.g., avoiding exacerbating food or activities, taking medications as prescribed)
- Under what circumstances, with whom, and in what time frame to seek follow-up evaluation, if all goes as desired on the basis of what is known when the patient is in the ED
- Under what conditions the patient should seek more urgent care because of unexpected changes in his or her condition (such as with natural progression of the process before improvement, incorrect diagnosis made in the ED, or untoward reactions to medications)

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 22 Gastrointestinal Bleeding

Philip L. Henneman

PERSPECTIVE

Epidemiology

Gastrointestinal (GI) bleeding is a relatively common problem encountered in emergency medicine that often requires early consultation and hospital admission. The overall mortality rate for GI bleeding is approximately 10% and has not changed significantly since the 1960s. Diagnostic modalities have improved much more than therapeutic techniques. GI bleeding is often easy to identify when there is clear evidence of vomiting blood or passing blood in the stool, but the clinical presentation may be subtle, with signs and symptoms of hypovolemia, such as dizziness, weakness, or syncope.

The approach to GI bleeding depends on whether the hemorrhage is located in the proximal or the distal segment of the GI tract (i.e., upper or lower GI bleeding). These segments are anatomically defined by the ligament of Treitz in the fourth section of the duodenum. In the United States, upper GI bleeding (UGIB) affects 50 to 150 people per 100,000 population each year and results in more than 300,000 admissions and about 30,000 deaths per year at an estimated annual cost of almost $1 billion. Lower GI bleeding (LGIB) affects a smaller portion of patients and results in proportionally fewer hospital admissions than UGIB.[1]

GI bleeding can occur in persons of any age but most commonly affects people in their 40s through 70s (mean age, 59 years). Most deaths caused by GI bleeding occur in patients older than 60 years. UGIB is more common in men than in women (in a 2:1 ratio), whereas LGIB is more common in women. Significant UGIB requiring admission is more common in adults, whereas LGIB requiring admission is more common in children.[2]

DIAGNOSTIC APPROACH

Differential Considerations

Peptic ulcer disease, gastric erosions, and varices account for approximately three fourths of adult patients with UGIB (Box 22-1). Diverticulosis and angiodysplasia account for approximately 80% of adults with LGIB. In children, esophagitis, gastritis, and peptic ulcer disease are the most common causes of UGIB, and infectious colitis and inflammatory bowel disease are the most common causes of LGIB (Box 22-2). In children younger than 2 years of age, massive LGIB is most often a result of Meckel's diverticulum or intussusception. At all ages, anorectal abnormalities are the most common cause of minor LGIB. Despite improved diagnostic techniques, no source of bleeding is identified in approximately 10% of patients with GI bleeding. In patients with abdominal aortic grafts who present to the emergency department (ED) with GI bleeding, the possibility of aortoenteric fistula should be considered. Prompt surgical consultation in the ED should be obtained if this is suspected, because bleeding can be massive and fatal.

Rapid Assessment and Stabilization

Most patients with GI bleeding are easy to diagnose because they present to the ED complaining of vomiting blood or passing black or bloody stool. The diagnosis is confirmed quickly by examination of the stool for the presence of blood.

Patients with suspected GI bleeding who are hemodynamically unstable should undergo rapid evaluation and resuscitation. They should be undressed quickly to permit placement of cardiac and oxygen saturation monitors, and supplemental oxygen should be given as needed. At least two large-bore peripheral intravenous lines should be placed (minimum 18-gauge); blood should be drawn for hemoglobin or hematocrit, platelet count, prothrombin time (PT), and type and screen or type and crossmatch studies; and crystalloid resuscitation should be initiated. Intravenous crystalloid fluid should be given as a 2-L bolus in adults or 20 mL/kg in children until the patient's vital signs have stabilized or the patient has received 40 mL/kg of crystalloid in an adult or 60 mL/kg as a child. Patients who remain unstable after 40 to 60 mL/kg of crystalloid should be given type O, type-specific, or crossmatched blood, depending on availability. Persistently unstable patients should receive immediate consultation with a gastroenterologist for UGIB and with a surgeon for LGIB.[3]

Pivotal Findings

History, physical examination, testing a stool sample for blood, and measuring hemoglobin or hematocrit are the keys to diagnosing GI bleeding in most patients.

History

Patients typically complain of vomiting red blood or coffee grounds–like material, or passing black or bloody stool. *Hematemesis* (vomiting blood) occurs with bleeding of the esophagus, stomach, or proximal small bowel. Approximately

BOX 22-1 Etiology of Significant Gastrointestinal (GI) Bleeding in Adults*

Upper	Lower
Peptic ulcer disease	Diverticulosis
Gastric erosions	Angiodysplasia
Varices	Upper GI bleeding
Mallory-Weiss tear	Cancer/polyps
Esophagitis	Rectal disease
Duodenitis	Inflammatory bowel disease

*Potential causes listed in decreasing frequency.

BOX 22-2 Etiology of Gastrointestinal Bleeding in Children*

Upper	Lower
Esophagitis	Anal fissure
Gastritis	Infectious colitis
Ulcer	Inflammatory bowel
Esophageal varices	Polyps
Mallory-Weiss tear	Intussusception

*Potential causes listed in decreasing frequency.

50% of patients with UGIB present with this complaint. Hematemesis may be bright red or darker (i.e., coffee grounds–like) as a result of the conversion of hemoglobin to hematin or other pigments by hydrochloric acid in the stomach. The color of vomited or aspirated blood from the stomach does not differentiate between arterial and venous bleeding.

Melena, or black tarry stool, will result from the presence of approximately 150 to 200 mL of blood in the GI tract for a prolonged period. Melena is seen in approximately 70% of patients with UGIB and in one third of patients with LGIB. Black stool that is not tarlike may result from presence of 60 mL of blood from the upper GI tract. Blood from the duodenum or jejunum must remain in the GI tract for approximately 8 hours before turning black. Occasionally, black stool may follow bleeding into the lower portion of the small bowel and ascending colon. Stool may remain black and tarry for several days, even though bleeding has stopped. Black stool also may be seen after ingestion of bismuth (e.g., Pepto-Bismol), which can confuse the situation because such preparations often are taken for UGI distress. In contrast with melena, stool rendered black by bismuth is not positive on Hemoccult testing.

Hematochezia, or bloody stool (bright red or maroon), most often signifies LGIB but may be due to a brisk UGIB with rapid transit time through the bowel in 10 to 15% of patients. Because UGIB is much more common than LGIB, a more proximal source of significant bleeding must be excluded before assuming the bleeding is from the lower GI tract. Approximately two thirds of patients with LGIB present with red blood from bleeding per rectum. Small amounts of red blood (e.g., 5 mL) from rectal bleeding, such as bleeding due to hemorrhoids, may cause the water in the toilet bowl to appear bright red. Bright red stools also can be seen after ingestion of a large quantity of beets; in this case, Hemoccult testing would be negative and the patient also will report pink-colored water in the toilet bowl.

In taking the history, specific questions should address the duration and quantity of bleeding, associated symptoms, previous history of bleeding, current medications, alcohol, nonsteroidal anti-inflammatory drug use and long-term aspirin ingestion, allergies, associated medical illnesses, previous surgery, treatment by nonhospital personnel, and the response to that treatment.[4,5] Patients with GI bleeding may report symptoms of hypovolemia, such as dizziness, weakness, or loss of consciousness, most often after standing up. Other nonspecific complaints include dyspnea, confusion, and abdominal pain. Rarely an elderly patient may present with ischemic chest pain precipitated by significant anemia due to a GI bleed. One in five patients with GI bleeding may have only nonspecific complaints.

The history is of limited help in predicting the site or quantity of bleeding. Patients with a previously documented GI lesion bleed from the same site in only 60% of cases. Gross estimates of blood loss based on the volume and color of the vomitus or stool (e.g., brown or black, pink or red) or the number of episodes of hemorrhage are notoriously inaccurate.

Physical Examination

Vital Signs Vital signs and postural changes in heart rate and blood pressure have been used to assess the amount of blood loss in patients with GI bleeding but are insensitive and nonspecific, with the exception of significant, sustained heart rate increase and hypotension. All patients with a history suggesting GI bleeding who are hypotensive, are tachycardic, or experience sustained posture-induced changes in heart rate of greater than 20 beats per minute should be assumed to have a significant hemorrhage. Normal vital signs do not exclude a significant hemorrhage, and postural changes in heart rate and blood pressure may occur in individuals who are not bleeding (e.g., elderly patients, many normal individuals, individuals on certain medications such as beta-blockers, individuals with hypovolemia from other causes).

General Examination The physical examination is valuable in establishing a specific diagnosis and assessing the severity of blood loss and the physiologic response to that loss. Careful attention is given to the patient's general appearance, vital signs, mental status (including restlessness), skin signs (e.g., color, warmth, and moisture to assess for shock, or presence of lesions such as telangiectasia, bruises, or petechiae to assess for vascular diseases or hypocoagulable states), pulmonary and cardiac findings, abdominal examination, and rectal and stool examination. Frequent reassessment is important because a patient's status may change quickly.

Rectal Examination Rectal and stool examinations are often key to making or confirming the diagnosis of GI bleeding. The finding of red, black, or melenic stool early in the assessment is helpful in prompting early recognition and management of patients with GI bleeding. The absence of black or bloody stool, however, does not exclude the diagnosis of GI bleeding. Regardless of the apparent character and color of the stool, occult blood testing is indicated.

Ancillary Testing

Tests for Occult Blood The presence of hemoglobin in occult amounts in stool is confirmed by tests such as guaiac assays (e.g., Hemoccult, HemaPrompt). Stool tests for occult blood may have positive results 14 days after a single, major episode of UGIB. False-positive results have been associated with the ingestion of certain fruits (e.g., cantaloupe, grapefruit, figs), uncooked vegetables (e.g., radish, cauliflower, broccoli) and red meat, methylene blue, chlorophyll, iodide, cupric sulfate, and bromide preparations. False-negative results are uncommon but can be caused by bile or ingestion of magnesium-containing antacids or ascorbic acid. Tests to evaluate gastric contents for occult blood (e.g., Gastroccult) can be unreliable

and should not be used for this purpose. In newborns, maternal blood that is swallowed may cause bloody stools; the Apt test may show that it is maternal in origin.

Clinical Laboratory Tests Blood should be drawn for evaluation of baseline hematocrit or hemoglobin, coagulation studies (PT and platelet count), and type and crossmatch studies (or type and screen studies if the patient is stable). The initial hematocrit may be misleading in patients with preexisting anemia or polycythemia. Changes in the hematocrit may lag significantly behind actual blood loss. Infusion of normal saline speeds equilibration of the hematocrit; however, rapid infusion of crystalloid in nonbleeding patients also may cause a decrease in hematocrit by hemodilution. The optimal hematocrit with respect to oxygen-carrying capacity and viscosity in critically ill patients has been reported to be 33%. In general, patients with a hemoglobin concentration of 8 g/dL or less (hematocrit <25%) from acute blood loss usually require blood therapy. After transfusion and in the absence of ongoing blood loss, the hematocrit can be expected to increase approximately 3% for each unit of blood administered (hemoglobin level increases by 1 mg/dL).

The PT should be used to determine whether a patient has a preexisting coagulopathy. An elevated PT may indicate vitamin K deficiency, liver dysfunction, warfarin therapy, or consumptive coagulopathy. Patients receiving therapeutic anticoagulants or patients with an elevated PT and evidence of active bleeding should receive sufficient fresh frozen plasma to correct the PT. Serial platelet counts are used to determine the need for platelet transfusions (i.e., less than 50,000/mm^3).

Blood Bank Blood should be sent for "type and hold" or type and crossmatch studies early in the patient's care. Immediate transfusion needs in unstable patients can be met with O-positive packed red blood cells (O-negative packed red blood cells in women of childbearing age whose Rh status is unknown). Type-specific blood is usually available within 10 to 15 minutes. Group O blood and type-specific blood are safe for patients and cause few transfusion reactions. Fully crossmatched blood may take 60 minutes to prepare. Stable patients can be managed more cost-effectively by ordering "type and hold" without crossmatching for units of blood.

Other Laboratory Tests Electrolytes usually are normal in patients with GI bleeding. However, determination of electrolytes, blood urea nitrogen, and creatinine may be useful in a small percentage of patients with GI bleeding when indicated. For example, in patients with repeated vomiting, hypokalemia, hyponatremia, and metabolic alkalosis may develop, which usually correct with adequate hydration and the resolution of vomiting. Patients with shock often have metabolic acidosis from lactate accumulation. The blood urea nitrogen is elevated in many patients with UGIB as a result of the absorption of blood from the GI tract and hypovolemia causing prerenal azotemia. After 24 hours, hypovolemia probably is the sole determinant of azotemia unless there has been recurrent bleeding or there is baseline renal insufficiency.

Electrocardiogram An electrocardiogram (ECG) should be obtained in all patients with a GI bleed who are older than 50 years of age or have preexisting ischemic cardiac disease, significant anemia, or chest pain, shortness of breath, or persistent hypotension. Asymptomatic myocardial ischemia (ST segment depression greater than 1 mm) or injury (ST segment elevation greater than 1 mm) may develop in the setting of GI bleeding. Patients with GI bleeding and clinical or ECG evidence of myocardial ischemia should receive packed red blood cells as soon as possible, as well as appropriate treatment for myocardial ischemia.

Imaging GI hemorrhage is not an indication for plain abdominal radiography. An upright chest radiograph should be obtained in patients with UGIB suspected of aspiration or with signs and symptoms of bowel perforation (shock with significant abdominal or peritoneal tenderness). Subdiaphragmatic air consistent with bowel perforation is a rare finding with UGIB, but it is an indication for immediate surgical consultation and operative repair.

DIFFERENTIAL DIAGNOSIS

Not all patients complaining of vomiting blood or passing blood in the stool have GI bleeding. Swallowing blood during epistaxis or from the oral cavity may cause hematemesis or melena. Red vomitus may be due to food products (e.g., Jell-O, tomato sauce, wine), and black stool may be due to iron therapy or bismuth (e.g., Pepto-Bismol). Hypovolemia (and its symptoms) may be due to vomiting and diarrhea without bleeding. Poor oral intake with or without fever also may result in hypovolemia. Usually the patient's hemoglobin or hematocrit is normal or elevated until hemodilution can occur. There are many causes of anemia other than GI bleeding. In the absence of suggestive symptoms or blood in the stool, GI bleeding is less likely to be the cause of observed anemia.[3]

MANAGEMENT

Quick identification, aggressive resuscitation, risk stratification, and prompt consultation are the keys to appropriate emergency management. When the diagnosis of GI bleeding is made, emergency management of patients can proceed (Fig. 22-1).

Reassurance

Patients who present to the ED with symptoms and signs of GI bleeding are often frightened by their symptoms. They may be concerned about the possibility of painful procedures and of the real or perceived risk of death. These patients and their families should be treated in a supportive and reassuring manner. They should be provided with accurate information about their problem, and all aspects of the care they are receiving should be explained in a way that they understand.

Nasogastric Tube and Gastric Lavage

After initial resuscitation of the patient, it is important to identify whether the hemorrhage is proximal or distal to the ligament of Treitz (i.e., UGIB or LGIB). If the patient's vomitus demonstrates blood, then the diagnosis of UGIB is confirmed. If a patient reports bloody or "coffee grounds" emesis or if melenic stool is present, an upper GI bleed is more likely. Placement of a nasogastric (NG) tube formerly was widely undertaken in the belief that it had both diagnostic and therapeutic benefit. Although in some cases, an NG tube may help to establish or confirm the diagnosis of UGIB, it is not useful for risk stratification. Aspiration of bloody contents from the NG tube diagnoses UGIB (or bleeding from nasal or oral passageways), but it does not determine if the bleeding is ongoing or has already stopped. Earlier assertions that gastric lavage "until clear" demonstrated that the bleeding had stopped have been refuted by findings at endoscopy. There is a 10% incidence of failure to aspirate blood through the NG tube in established UGIB. False-negative results are possible if the bleeding is intermittent or has already stopped and the stomach is cleared, or if the bleeding is in the duodenum, and edema or spasm of the pylorus has prevented reflux of

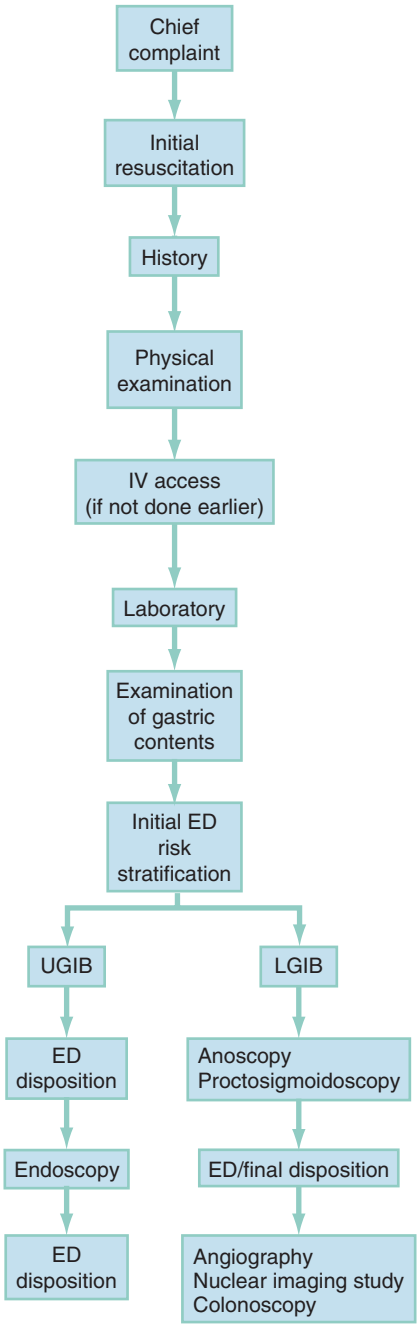


Figure 22-1. Emergency management of patients with gastrointestinal bleeding. ED, emergency department; IV, intravenous; LGIB, lower gastrointestinal bleeding; UGIB, upper gastrointestinal bleeding.

blood into the stomach. The presence of bile in an otherwise clear aspirate excludes the possibility of active bleeding above the ligament of Treitz, but should not be used to exclude UGIB in a patient with documented melena.

False-positive results may occur from nasal bleeding. Gastric contents should not be tested for occult blood; visual inspection of the vomitus or aspirate is insufficient to diagnose subtle bleeding, and testing is unreliable. In patients who have hematochezia, an upper GI origin for the bleeding often is associated with signs and symptoms of shock, because rapid transit time of large quantities of blood is producing the hematochezia. Because up to 10 to 15% of patients with hematochezia have UGIB, it has been recommended that an NG tube be inserted in most cases of LGIB, but there is no evidence to support an improved outcome related to this practice.[2,6] Typically, a clinical decision is made regarding the likelihood of an upper versus lower GI origin for the bleeding, and endoscopy is then performed based on that determination. If the first endoscopy approach fails to identify the bleeding site, often endoscopy of the other end of the GI tract is necessary.

Gastric tubes are safe in most patients, but pharyngeal and esophageal perforation, cardiac arrest, ethmoid sinus fracture with brain trauma, and bronchial intubation have been reported. No evidence exists that gastric tube placement aggravates hemorrhage from varices or Mallory-Weiss tears.

Gastric lavage may be helpful to prepare a patient for endoscopy. Before gastric lavage, patients with evidence of a possible perforated viscus (e.g., severe pain, peritoneal signs) should undergo radiologic assessment looking for free air. Lavage should not be performed in the presence of pneumoperitoneum. Gastric lavage does not reduce blood loss in patients with UGIB, and use of iced lavage fluid is not recommended. Gastric lavage in preparation for endoscopy is best performed with a large-bore Ewald tube, passed orally while the patient is in the left lateral decubitus position with the bed in Trendelenburg position. Additional holes may be cut in the distal portion of the Ewald tube to improve aspiration of blood and clots. Clots that cannot be aspirated continue to cause pink return, giving the false impression of continued bleeding. The irrigant need not be sterile; regular tap water may be used. The irrigant should be delivered and removed by gravity in volumes of 200 to 300 mL until the return is clear. Little irrigant is absorbed by the patient. Gastric rupture has been reported as a rare complication of gastric lavage.[7,8]

Anoscopy/Proctosigmoidoscopy

Patients with mild rectal bleeding who do not have obviously bleeding hemorrhoids should undergo anoscopy or proctosigmoidoscopy. If bleeding internal hemorrhoids are discovered, and the patient does not have portal hypertension, the patient may be discharged with appropriate treatment and follow-up evaluation for hemorrhoids. If hemorrhoids are not detected, it is important to determine if the stool above the rectum contains blood. The absence of blood above the rectum in a patient who is actively bleeding indicates that the source of bleeding is in the rectum. The presence of blood above the anoscope or sigmoidoscope does not invariably indicate a proximal source of bleeding, because retrograde passage of blood into the more proximal colon commonly occurs. Such patients need further evaluation.

Endoscopy

Endoscopy is the most accurate diagnostic tool available for the evaluation of UGIB. It identifies a lesion in 78% to 95% of patients with UGIB if it is performed within 12 to 24 hours of the hemorrhage. Accurate identification of the bleeding site allows for risk stratification with respect to predicting rebleeding and mortality. Endoscopy-based triage significantly reduces hospitalization rates and costs of treating upper GI bleeding.[8,9] Significant advances in endoscopic hemostasis also make it of therapeutic value in select patients (e.g., for banding or sclerosing of varices). Colonoscopy is an effective tool for diagnosis and selected treatment of LGIB.[10,11]

Angiography and Tagged Red Blood Cell Scan

Angiography can detect the location of UGIB in two thirds of patients studied. Since the advent of endoscopy, however, the use of angiography has decreased significantly, and today angiography is used in only 1% of patients with UGIB. Angiography is used more commonly in patients with LGIB and usually in consultation with a general surgeon. Although angiography rarely diagnoses the cause of bleeding, it does identify the site of bleeding in approximately 40% of patients who have LGIB and in 65% of patients who eventually require surgical intervention. Angiography ideally is performed during active bleeding; this may be apparent from persistently unstable vital signs or continued transfusion requirements to establish or maintain an optimal hemoglobin or hematocrit level. Arterial embolization can be used in selected cases of LGIB.[12] In some patients with more indolent or elusive bleeding, a nuclear isotope–tagged red blood cell scan, usually performed from the inpatient unit, may identify the bleeding site.

Gastric Acid Secretion Inhibition

All patients with peptic ulcer disease documented by endoscopy should receive therapy with a proton-pump inhibitor (e.g., omeprazole).[13–15] There is no documented benefit to initiating this therapy or administering H_2 antihistamines in the ED for patients with UGIB, however.

Octreotide (Somatostatin Analogues)

Patients with documented esophageal varices and acute upper GI bleeding should receive an intravenous infusion of octreotide at 25–50 µg/hour for a minimum of 24 hours while being observed in the intensive care unit (ICU). Octreotide is a useful addition to endoscopic sclerotherapy and decreases rebleeding occurrences.[16,17] (See Chapter 87.) Octreotide may also reduce the incidence of lower GI rebleeding secondary to angiodysplasia.[18]

Vasopressin

Intravenous vasopressin has been used in the treatment of UGIB, most commonly in patients with variceal hemorrhage. Controlled studies have not shown a positive effect of vasopressin on overall mortality, however. These results, combined with a relatively high rate of serious complications (9% major and 3% fatal), suggest that use of vasopressin should be limited. A trial of vasopressin may be warranted in an exsanguinating patient with suspected variceal bleeding, especially if endoscopy is not immediately available. The recommended dose of vasopressin is 20 units given intravenously over 20 minutes and then 0.2 to 0.4 unit per minute. Consultation with a gastroenterologist is advisable.

Sengstaken-Blakemore Tube

Placement of a Sengstaken-Blakemore tube stops hemorrhage in approximately 80% of patients bleeding from esophageal varices. The Linton tube may be superior to the Sengstaken-Blakemore tube in patients with bleeding gastric varices; however, either of these tubes is rarely used. In general, these tubes should not be used without endoscopic documentation of the source of bleeding because complications are common and significant (14% major, 3% fatal). A trial of balloon tamponade should be considered, however, in an exsanguinating patient with probable variceal bleeding in whom endoscopy is not immediately available and vasopressin has not slowed the hemorrhage. Consultation with a surgeon or gastroenterologist is advisable.

Surgery

Surgery is indicated for all hemodynamically unstable patients with active bleeding who do not respond to appropriate intravascular volume replacement, correction of any coagulopathy, and endoscopic intervention (if available). The mortality rate for patients undergoing emergency procedures for GI bleeding is approximately 23%. Generally, surgery is indicated whenever the risk of ineffective medical therapy and continued hemorrhage outweighs that of surgical morbidity and mortality.[19] Emergency surgical consultation should be considered when blood replacement exceeds 5 units within the first 4 to 6 hours or when 2 units of blood is needed every 4 hours (after replacement of initial losses) to maintain normal cardiac output.

DISPOSITION

Risk Stratification

Risk stratification involves combining historical, clinical, and laboratory data to determine the risk of death and rebleeding in patients presenting to an ED with GI bleeding. Patients can be sorted into four risk categories: very low, low, moderate, and high risk. Some patients present to the ED with a vague complaint of vomiting blood or passing blood from the rectum in whom detailed history and examination allows a diagnosis of hemorrhoid, or anal fissure, or there may be little or no objective evidence of significant GI bleeding. These patients can be categorized as very low risk and can be sent home without further diagnostic tests[2,7,20] (Box 22-3).

Before discharge, patients should be educated about the signs and symptoms of significant GI bleeding and when to return to the ED or when to call their primary care physician. They should be given specific education about the possible or actual cause of the bleeding and specific treatment for that disorder. They should be educated about the side effects of any medications. Patents should undergo specific follow-up evaluation within 24 to 36 hours. They should be instructed to avoid aspirin, nonsteroidal anti-inflammatory drugs, and alcohol.[2,21,22]

Patients with low-risk, moderate-risk, and high-risk criteria are more complicated and require further assessment. Historically, nearly all patients with significant GI bleeding were admitted to the hospital. As health care has changed, a greater emphasis has been placed on outpatient management of select

BOX 22-3 VERY-LOW-RISK CRITERIA FOR PATIENTS COMPLAINING OF GASTROINTESTINAL BLEEDING WHO CAN BE DISCHARGED HOME

- No comorbid diseases
- Normal vital signs
- Normal or trace positive result on stool guaiac testing
- Negative findings on gastric aspiration, if done
- Normal or near-normal hemoglobin/hematocrit
- Good support systems
- Proper understanding of signs and symptoms of significant bleeding
- Immediate access to emergent care if needed
- Follow-up arranged within 24 hr

Table 22-1 Initial Emergency Department Risk Stratification for Patients with Gastrointestinal Bleeding

LOW RISK	MODERATE RISK	HIGH RISK
Age < 60 yr	Age > 60 yr	
Initial SBP ≥ 100 mm Hg	Initial SBP < 100 mm Hg	Persistent SBP < 100 mm Hg
Normal vital signs for 1 hr	Mild ongoing tachycardia for 1 hr	Persistent moderate/severe tachycardia
No transfusion requirement	Transfusions required, ≤4 units	Transfusion required, >4 units
No active major comorbid diseases	Stable major comorbid diseases	Unstable major comorbid diseases
No liver disease	Mild liver disease—PT normal or near-normal	Decompensated liver disease—e.g., coagulopathy, ascites, encephalopathy
No moderate-risk or high-risk clinical features	No high-risk clinical features	

PT, prothrombin time; SBP, systolic blood pressure.
Data from Terdiman JP, Lindenauer GF: Acute gastrointestinal bleeding. In Wachter RM, Goldman L, Hollander H (eds): Hospital Medicine. Philadelphia, Lippincott Williams & Wilkins, 2005, pp. 767–779.

Table 22-2 Management by Risk Category for Patients with Upper Gastrointestinal Bleeding after Endoscopy

RISK STRATIFICATION	Recommended Management		
	LOW RISK	MODERATE RISK	HIGH RISK
Low risk	Immediate discharge*	23-hr observation (floor)†	ICU monitoring for 24 hr‡ (48- to 72-hr hospitalization)
Moderate risk	48-hr inpatient stay†	48- to 72-hr inpatient stay (floor)†	ICU monitoring for 24 hr (48- to 72-hr hospitalization)
High risk	ICU monitoring for 48 hr (48- to 72-hr hospitalization)	ICU monitoring for 24 to 48 hr (72-hr hospitalization)	ICU monitoring for 72 hr (≥72-hr hospitalization)

*Patients with low-risk clinical and endoscopic findings can be discharged home with appropriate treatment based on diagnosis, scheduled follow-up evaluation within 24 hours, and proper patient education to ensure immediate return if signs of rebleeding appear.
†Patients may be discharged after 24 to 48 hours of in-hospital observation if there is no evidence of rebleeding, vital signs are normal, there is no need for further transfusion, and the hemoglobin or hematocrit has remained stable. They should be provided with appropriate treatment based on diagnosis, scheduled follow-up evaluation within 24 hours, and proper patient education to ensure immediate return if signs of rebleeding appear.
‡Patients with high-risk clinical or endoscopic findings should be hospitalized and monitored closely for evidence of rebleeding.
Data from Terdiman JP, Lindenauer GF: Acute gastrointestinal bleeding. In Wachter RM, Goldman L, Hollander H (eds): Hospital Medicine. Philadelphia, Lippincott Williams & Wilkins, 2005, pp. 767–779.

low-risk patients with GI bleeding. Studies have shown that combining clinical and endoscopic criteria provides an accurate estimation of the risk of rebleeding and mortality in patients with UGIB. These combined criteria have been used to identify patients with UGIB at low risk, who can be discharged home, and patients at moderate or high risk, who need to be admitted to an appropriate care site in the hospital. Risk stratification for patients with LGIB is less well studied, so nearly all patients with significant LGIB are admitted. Risk stratification can be used for patients with LGIB, however, to decide an appropriate inpatient care site.

Table 22-1 presents an initial risk stratification tool for patients with upper and lower GI bleeding. Combining clinical and endoscopic findings allows for final risk stratification, as shown in Table 22-2, to decide disposition, inpatient care site, and treatment.[1,2,6,20,23-25]

Patients with clinical evidence of GI bleeding should undergo endoscopy as soon as it is available for final risk stratification, inpatient triage, and determination of appropriate treatment (see Table 22-2). If endoscopy is not immediately available, patients with low clinical risk may be admitted to an ED observation unit or short-stay hospital bed until endoscopy can be performed. Patients with moderate clinical risk criteria may be admitted to an inpatient floor, intermediate care unit, or ICU, as indicated by specific patient management needs and depending on the capabilities of the institution. Patients with high clinical risk should be admitted to a closely monitored step-down unit or an ICU. The timing of endoscopy depends on availability, the acuity of the patient, the need for emergent therapy, the need to determine final care site, and the need to minimize length of stay.[3,26]

Patients with LGIB that is not clearly due to hemorrhoids, fissure, or proctitis should be admitted to an inpatient bed. Patients with low risk may be admitted to an inpatient floor bed and prepared for a nuclear medicine imaging study (e.g., red blood cell–labeled study) or colonoscopy. Patients with high-risk criteria should be admitted to a step-down unit or ICU and considered for angiography to identify the site of LGIB. Patients with moderate-risk criteria require individualized determination of the most appropriate inpatient care site (floor, intermediate care bed, or ICU) and the most useful diagnostic studies (nuclear imaging or angiography).

Consultation with a surgeon should be obtained if it appears that more than 5 units of blood is required to achieve hemodynamic stability or if there is reasonable suspicion that operative intervention may be needed. This is especially true of patients older than 65 years of age. In general, the older the patient, the more aggressive the surgical management ought to be. Patients with a history of varices, persistent postural changes in heart rate, or significant bleeding of bright red blood per rectum are more likely to require surgery than are patients without these findings. Emergent vascular surgical consultation is needed for patients who have abdominal aortic grafts who present to the ED with GI bleeding, because of the possibility of an aortoenteric fistula.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 23 Diarrhea

Robert E. Collier, John E. Gough, and Philip A. Clement

PERSPECTIVE

Diarrhea is a common presenting complaint in the emergency department (ED) and can account for up to 5% of all visits. Most cases of diarrhea are self-limited and require only supportive care. Conversely, patients with more serious infection and associated comorbidity may present with life-threatening dehydration and shock. There may be an associated sepsis and septic shock component. Numerous but relatively rare, noninfectious causes of diarrhea should also be considered.

Incidence

Worldwide, diarrhea remains a major health problem, accounting for approximately 4% of all deaths each year, which is estimated by the World Health Organization (WHO) to be 2.2 million victims (World Health Report, 2000).[1] A large proportion of these deaths occur in small children in developing countries. Rotavirus causes 25% to 65% of childhood-associated diarrheal illnesses (3.5 million cases per year in the United States), whereas adults experience 74 million episodes of diarrhea annually. In the United States, 90% of diarrheal illnesses are caused by noroviruses (caliciviruses), of which more than 100 different strains are recognized.[2] Patients at the extremes of age, those with significant comorbidity, those who are immunologically compromised, and those with iatrogenic illness are most vulnerable to significant morbidity and mortality. An estimated 60% of patients infected with human immunodeficiency virus (HIV) experience significant diarrhea during the course of their illness.[3]

Most adults experience diarrhea many times during their lifetime. Diarrhea illnesses are the primary cause of many hospitalizations and hours of lost work.

Definition and Categorization

The term *diarrhea* is derived from the Greek words *dia* ("through") and *rhein* ("to flow"). The two main categories of diarrhea-associated illness are infectious and noninfectious. Infectious causes represent about 85% of cases, whereas noninfectious causes account for only 15% of the total. Infectious diarrhea may be divided into viral, bacterial, and parasitic causes (Box 23-1), with estimates of their relative contributions being 70% for viral, 24% for bacterial, and 6% for parasitic infections.[4]

Definitions for diarrhea have been proposed to standardize nomenclature, help the clinician determine a probable etiology, and direct empirical therapy if indicated[5]:

- *Acute* diarrhea is defined as lasting for 14 days or less.
- *Persistent* diarrhea lasts for longer than 14 days.
- *Chronic* diarrhea lasts 30 days or longer.

Acute diarrhea presentations usually will be infectious. A majority of these cases are self-limited and caused by viral and bacterial pathogens. Persistent diarrhea suggests an enteric pathogen other than viral, such as bacterial or protozoan. Chronic diarrhea usually is associated with noninfectious causes and requires further testing to determine the etiology.

Normally, the small and large bowel absorb 99% of gastrointestinal tract secretions produced and liquids ingested each day. Any pathologic state that reduces water absorption by 1% can cause diarrhea.[6] Diarrhea results from one or more of four different pathologic processes that are characteristic of the primary cause and that contribute to the decreased absorption of the gut.

Secretory diarrhea is caused by pathogens that produce cytotoxins that increase cellular permeability and cause the oversecretion of water and electrolytes. Most cases of diarrhea encountered in the ED are secretory. Noninfectious causes of secretory diarrhea include medications, toxic substances, endocrine disorders, and neoplasias (Box 23-2).

Inflammatory diarrhea, also described as invasive or severe diarrhea, or dysentery, results from cellular damage to the intestinal mucosa, leading to the hypersecretion of water, electrolytes, blood, mucus, and plasma proteins. This diarrhea most commonly is caused by invasive bacterial and parasitic pathogens that produce dysenteric illnesses (see Box 23-1). Some noninfectious causes of inflammatory diarrhea include chemotherapy, radiation therapy, hypersensitivity reactions, autoimmune disorders, ischemic colitis, and inflammatory bowel disease. With inflammatory diarrhea, fecal leukocytes and erythrocytes typically are present, as are systemic symptoms, and the diarrhea continues despite fasting.

Osmotic diarrhea occurs with the ingestion or malabsorption of osmotically active solutes. These solutes cause the osmotic movement of water into the intestinal lumen, which then overwhelms the gut's ability to reabsorb it. Examples include the effects of osmotic laxatives and carbohydrate malabsorption. Steatorrhea results from osmotic effects of lipids not absorbed in malabsorption and maldigestion syndromes.

Abnormal motility generally is seen in patients with chronic diarrhea but is always a component of acute diarrhea. Hypermotility decreases contact time between luminal contents and the absorbing mucosa, limiting water and electrolyte absorption.

BOX 23-1 ETIOLOGIC AGENTS OF INFECTIOUS DIARRHEA

Viral (60% of cases)
Astrovirus
Calicivirus
Coronavirus
Cytomegalovirus*
Enteric adenovirus
Hepatitis A through G
Herpes simplex virus
HIV enteropathy
Norwalk-like agents
Norwalk virus
Pararotavirus
Picornavirus
Rotavirus
Small round viruses

Bacterial (20% of cases)
Invasive*
Aeromonas spp.
Campylobacter spp.
Clostridium difficile
Enteroinvasive *E. coli*
Mycobacterium spp.
Plesiomonas shigelloides
Salmonella spp.
Shigella spp.
Vibrio fluvialis
Vibrio parahaemolyticus
Vibrio vulnificus
Yersinia enterocolitica
Yersinia pseudotuberculosis

Toxigenic
FOOD POISONING WITH PREFORMED TOXINS
Bacillus cereus
Clostridium botulinum
Staphylococcus aureus
TOXIN FORMATION AFTER COLONIZATION
Aeromonas hydrophila
Clostridium perfringens
Enterohemorrhagic *E. coli** O157:H7
Enterotoxigenic *E. coli*
Klebsiella pneumoniae
Shigella spp.
Vibrio cholerae

Other bacteria

Parasitic (5% of cases)
Protozoa
*Balantidium coli**
Blastocystis hominis
Cryptosporidium
Cyclospora
Dientamoeba fragilis
*Entamoeba histolytica**
Entamoeba polecki
Enteromonas hominis
Giardia lamblia
Isospora belli
Microsporidia
Sarcocystis hominis

Helminths
Angiostrongylus costaricense
Anisakiasis
Ascaris lumbricoides
Diphyllobothrium latum
Enterobius vermicularis
Hookworms
Schistosoma spp.
Strongyloides stercoralis
Taenia spp.
Trichinella spiralis
Trichuris trichiura

*Associated with fever, abdominal pain, and fecal red blood cells or white blood cells. % indicates the estimated contribution to total cases.

CLINICAL APPROACH

Emergency Assessment and Stabilization

An immediate assessment should be made of the patient's stability, including maintenance of the airway, adequacy of oxygenation and ventilation, and circulation, with particular attention to volume status. Tachycardia, orthostatic hypotension, poor skin turgor and color, diaphoresis, and mental status changes all are characteristic of hypovolemia and hypoperfusion. Associated septic shock may contribute to the hypotension and general organ hypoperfusion, and diarrhea may be a manifestation of toxic shock syndrome. A diarrhea-associated acid-base disorder should be suspected in patients with Kussmaul respirations, a significant anion gap on basic metabolic panel reflecting a lactic acidosis from significant volume loss, or a non–anion gap metabolic acidosis associated with massive bicarbonate loss. After stabilization, a secondary survey may elucidate the potential cause of the diarrhea and direct further evaluation and treatment.

Secondary Survey

The physical examination should assess the patient's overall health, toxicity, fever, volume status, signs of a surgical abdomen, and determine the presence of blood in the stool. Young healthy adults may maintain a normal blood pressure and heart rate even with significant dehydration. In patients who are taking antiarrhythmic or beta-blocker medications or have conduction disease or fixed-pace rhythms, heart rate may not be a reliable indicator of volume status. Signs of volume depletion and impending shock include dry mucosa, poor skin turgor, decreased urine output, and mental status changes. Children will present with sunken eyes, depression of the fontanel, decrease in urine output (number of wet diapers), and decrease in alertness and activity.[7]

Particular attention should be given to the abdominal examination. Focal abdominal pain with peritoneal findings may be due to an acute surgical abdomen with symptoms mimicking those of severe gastroenteritis. A rectal examination should be performed to detect fecal impaction, melena, or hematochezia.

BOX 23-2 CAUSES OF NONINFECTIOUS DIARRHEA

Toxins

Drugs
ACE inhibitors
Alprazolam (Xanax)
Antacids (Mg)
Antibiotics
Antidepressants
Antiepileptic drugs
Antihypertensives
Antiparkinson drugs
Beta-blockers
Caffeine
Cardiac antiarrhythmics
Chemotherapy agents
Cholesterol-lowering drugs
Cholinergic agents
Cholinesterase inhibitors
Colchicine
Digitalis
Diuretics
Fluorouracil
Fluoxetine (Prozac)
Histamine H_2-receptor antagonists
Hydralazine
Lactulose
Laxatives/cathartics
Levodopa
Lithium
NSAIDs
Neomycin
Podophyllin
Procainamide
Prostaglandins
Quinidine
Ricinoleic acid
Theophylline
Thyroid hormone
Valproic acid

Dietetic Foods
Mannitol
Sorbitol
Xylitol

Fish-Associated Toxins
Amnestic shellfish poisoning
Ciguatera
Echinoderms
Neurotoxic shellfish poisoning
Paralytic shellfish poisoning
Scombroid
Tetroton

Plant-Associated Toxins
Herbal preparations
Horse chestnut
Mushrooms—*Amanita* spp.
Nicotine
Other plant toxins
  Pesticides—organophosphates
  Pokeweed
  Rhubarb
Miscellaneous
  Allergic reactions
  Carbon monoxide poisoning
  Ethanol
  Heavy metals
  Monosodium glutamate (MSG)
  Opiate withdrawal

Gastrointestinal Pathology
Appendicitis
Autonomic dysfunction
Bile acid malabsorption
Blind loop
Bowel obstruction
Celiac disease
Cirrhosis
Defects in amino acid transport
Diverticular disease
Familial dysautonomia
Fecal impaction
Fecal incontinence
GI bleed
GI cancer
Hirschsprung's disease
Inflammatory bowel disease (ulcerative colitis, Crohn's disease)
Intussusception
Irritable bowel syndrome
Ischemic bowel
Lactose/fructose intolerance
Malabsorption syndromes
Malrotation
Postsurgical
Postvagotomy
Radiation therapy
Short gut syndrome
Small bowel resection
Strictures
Toxic megacolon
Tropical sprue
Volvulus
Whipple's disease

Endocrine-Related
Carcinoid syndrome (serotonin)
Hormonal hypersecretion
Hyperthyroidism (thyroid hormone)
Medullary carcinoma of the thyroid (calcitonin)
Pancreatic cholera (VIP)
Somatostatinoma (somatostatin)
Systemic mastocytosis (histamine)
Zollinger-Ellison syndrome (gastrin)

Endocrine Pathology
Adrenal insufficiency
Diabetes enteropathy
Hypoparathyroidism
Pancreatic insufficiency

Systemic Illness/Other
Alcoholism
Amyloidosis
Connective tissue disease
Cystic fibrosis
Ectopic pregnancy
Hemolytic-uremic syndrome
Henoch-Schönlein purpura
Lymphoma
Otitis media—infants
Pelvic inflammatory disease
Pneumonia/sepsis
Pyelonephritis
Scleroderma/SLE
Severe malnutrition
Stevens-Johnson syndrome
Toxic shock syndrome
Wilson's disease
Miscellaneous
  Factitious diarrhea
  Runner's diarrhea

ACE, angiotensin-converting enzyme; GI, gastrointestinal; NSAIDs, nonsteroidal anti-inflammatory drugs; SLE, systemic lupus erythematosus; VIP, vasoactive intestinal polypeptide.

Gross blood may be consistent with invasive, infectious diarrhea but may be the harbinger of many other pathologic states that manifest with gastrointestinal bleeding. Histamine-induced skin changes may be indicative of an intestinal parasitic infection. The patient should be assessed for specific toxidromes, such as cholinergic or sympathomimetic states that may be clues to a noninfectious cause.

Characterization of the Diarrheal Syndrome

Acute Infectious Diarrhea Most viral and many bacterial agents cause a self-limited, secretory diarrhea that lasts less than 14 days and causes only mild dehydration and minimal systemic symptoms. These infections do not require extensive testing and are treated symptomatically. In the United States, monitoring of pathogens causing this type of acute gastroenteritis demonstrates that 90% of the infections are caused by norovirus species.[8] All other potential causes of diarrhea are highly improbable unless certain historical and clinical findings are present. Bacterial and protozoan agents less commonly cause diarrhea syndromes indistinguishable from norovirus infection with a nontoxic, self-limited course. A Bayesian approach to diagnosing and treating acute diarrhea has been proposed.[8] The clinical evaluation should screen for all factors (Table 23-1) that may change the probability of "not norovirus" from 10% to 50% or greater.[8] With one or more of these findings

Table 23-1 Factors Increasing Probability of Nonbenign Diarrhea

FACTOR	SPECIFIC PATHOGEN(S)/OTHER CONSIDERATIONS
Presentation to a health care facility	Degree of illness overall greater in patients presenting for evaluation; increased probability of "not norovirus" etiology to 50%
Travel history	Especially foreign travel and to endemic areas of dysenteric disease
Recent hospitalization	C. *difficile* from antibiotic exposure
Day care attendance	Rotavirus, *Shigella*, *Giardia*
Nursing home residence	C. *difficile*, medication side effects, tube feedings, ischemic colitis, fecal impaction, and overflow diarrhea
Wilderness exposure	*Giardia* or *Cryptosporidium*
Antibiotic therapy	C. *difficile*, antibiotic side effects
Raw shellfish, farm animals and fair livestock, pet reptiles or amphibians, petting zoos	*Salmonella* spp., *E. coli* O157:H7 and non-O157 Shiga toxin–producing *E. coli*, *Vibrio* spp.
Epidemic of multiple patients with a short time of onset	Norovirus; less commonly, *Campylobacter jejuni*, *Salmonella* spp., *Cryptosporidium*
Acute vomiting and diarrhea after suspected contaminated food	*Bacillus cereus*, *Clostridium botulinum*, *Staphylococcus aureus*
Epidemic of severe gastroenteritis traced to eggs, poultry, meat, or dairy products	*Campylobacter jejuni*, *Salmonella* spp.
Homosexual lifestyle (males)	*Giardia lamblia*, *Entamoeba hystolytica*
Abdominal pain Nausea, vomiting Bloody stool Fever Rectal pain Tenesmus	Severe bacterial infections: *Salmonella*, *Campylobacter*, *Shigella*, EPEC, *Yersinia* or *Vibrio* spp. Also consider surgical abdomen, GI bleeding Inflammatory bowel disease
Diarrhea >7–14 days' duration	Protozoa and microsporidia, *Clostridium difficile*, *Campylobacter*, Shiga toxin–producing *E. coli*
Hemolytic uremic syndrome	*E. coli* O157:H7 or other species
Stool WBC count	Not reliable for diagnosis of bacterial etiology
Colonic ulcerations	Inflammatory bowel disease
Proctitis	Bacterial etiology highly probable
Pseudomembranes	Toxic megacolon, *Clostridium difficile*
Chronic disease (e.g., cirrhosis, DM)	Complicated course expected with any form of diarrheal illness
Organ transplantation	Abnormally severe illness from rotavirus and adenovirus Increased frequency of cytomegalovirus Severe illness from dysenteric diarrhea Spore-forming protozoa and microsporidia
HIV infection, other immunodeficiency disorders	Severe illness from common bacteria/spore-forming protozoa and microsporidia Increased frequency of cytomegalovirus and *Mycobacterium avium* complex

DM, diabetes mellitus; EPEC, enteropathogenic *E. coli*; WBC, white blood cell.

present, empirical antibiotic or other specific therapy may be indicated, as well as clinical testing to determine the exact etiologic disorder.

Chronic Infectious Diarrhea *Persistent* diarrhea is defined as that lasting for more than 14 days, and *chronic* diarrhea, more than 30 days.[5] Infectious agents of persistent and chronic diarrhea include bacteria, parasites, and rarely viruses.[9] Common bacterial pathogens include *Aeromonas*, *Plesiomonas*, *Campylobacter*, *Clostridium difficile*, *Salmonella*, and *Mycobacterium tuberculosis*. Parasites causing chronic diarrhea are colonic forms such as *Amoeba*, *Trichuris*, *Yersinia*, and *Schistosoma* species or small intestinal pathogens such as *Giardia*, *Cryptosporidium*, *Cyclospora*, *Isospora*, and *Strongyloides*.[9] In developing countries, chronic diarrhea is more likely to have a bacterial cause. In developed countries, chronic diarrhea is caused by noninfectious disorders such as irritable bowel syndrome, malabsorption syndromes, laxative abuse, and inflammatory bowel disease.[6] Categorization of the stool type as watery, inflammatory, or fatty may assist in proper classification of the chronic diarrhea syndrome as infectious and noninfectious. Testing for HIV or immune deficiency is important because these patients commonly present with chronic diarrhea. Evaluation should include testing for cryptosporidia, microsporidia, mycobacteria (i.e., *Mycobacterium avium* complex), herpes simplex virus (HSV), *Isospora*, *Cyclospora*, and cytomegalovirus. In addition, parasitic and helminthic infections should be ruled out.

Noninfectious Diarrhea Noninfectious causes of diarrhea (see Box 23-2) are responsible for approximately 15% of all cases of diarrheal illness. The distinction between infectious and noninfectious causes may not be clinically apparent. A complete evaluation should consider possible surgical pathology of the abdomen, including gastrointestinal bleeding, ischemic bowel, acute appendicitis, intussusception, ectopic pregnancy, and partial bowel obstruction.[7] The differential diagnosis also includes possible toxic exposures or ingestions, such as heavy metal poisoning, or ingestion of plant-borne or fish-borne toxins. Endocrine pathology, such as adrenal insufficiency, hyperthyroidism, diabetic enteropathy, and

hormone-secreting tumors, and other systemic illnesses should be considered, and special attention should be directed at underlying medical conditions, medication use, and past surgical history.

Ancillary Testing

Most cases of acute diarrhea are self-limited, and laboratory and diagnostic tests should be kept to a minimum unless required for epidemiologic studies. Testing is indicated in patients who have a high probability of a "non-norovirus" clinical picture and have worrisome historical data, signs, and symptoms associated with an increased probability of those causes. Ancillary testing should never compromise empirical treatment when indicated (as discussed later on). Fever with a toxic appearance and volume depletion, blood- or mucus-containing stools, frequent voluminous stools, and other risk factors (Table 23-1) should prompt a diligent search for a specific causative disorder in order to guide appropriate therapy.[8,10] A white blood cell count is rarely helpful and not sensitive or specific enough to aid in diagnostic decision-making, although hemoglobin determination is useful to screen for anemia from blood loss, and abnormalities in platelet and coagulation parameters may contribute to identification of a cause for gastrointestinal bleeding. A comprehensive chemistry panel including renal function tests can be important when significant volume loss is suspected, or when significant diarrhea has been present for 48 to 72 hours. Liver function studies, thyroid tests, serum lipase assay, and a pregnancy test may be helpful in selected cases.

Hemoccult and fecal cell count: The presence of fecal leukocytes is not specific or sensitive enough to use as the sole criterion to decide which patients with presumed bacterial gastroenteritis should be treated empirically with antibiotics. With inflammatory diarrhea of various causes, red and white blood cells are seen on stool examination. Included are bacterial, parasitic, and noninfectious causes, such as chemotherapy, radiation therapy, hypersensitivity reactions, autoimmune disorders, and inflammatory bowel disease. The presence of fecal leukocytes does not delineate which patients would benefit from empirical antimicrobial therapy. The presence of blood does not always correlate with the presence of fecal leukocytes, so reliance on positive stool guaiac test result alone as a rationale for antibiotic therapy is not recommended. The presence of blood without fecal leukocytes may indicate amebiasis, malignancies, heavy metal poisoning, fissures, hemorrhoids, bowel ischemia, or primary gastrointestinal bleeding.

Assays for calprotectin and lactoferrin, produced by leukocytes, are sensitive and specific and may be more useful than microscopic examination of the stool, but these tests are rarely, if ever, of use in the ED.[6]

Clostridium difficile *toxin assay:* This test is indicated if the patient reports recent antibiotic use. *C. difficile*–associated diarrhea most commonly occurs during or shortly after the antibiotic course. In 25% to 40% of cases, however, onset of the diarrhea may be delayed as long as 12 weeks after antibiotic therapy. The most commonly implicated antibiotics are cephalosporins, penicillins, and clindamycin. Although *C. difficile* accounts for only 10% to 20% of antibiotic-associated diarrhea, an assay for *C. difficile* toxin gives a positive result in nearly all cases of antibiotic-associated pseudomembranous colitis.[11] Approximately 3% of adult patients and 65% of newborns may be colonized with *C. difficile*.

E. coli *O157:H7 toxin assay:* This test is considered in endemic areas and in patients with suspected hemolytic-uremic syndrome.[12]

Stool culture for bacteria: Stool cultures may be warranted in patients who are febrile, toxic-appearing, immunocompromised, at the extremes of age, experiencing a prolonged course, or not responding to conventional treatment. Studies have shown a 2% positive rate, thus proving that routine cultures are of limited value.[12]

Stool examination for ova and parasites: The assessment of stool for ova and parasites is not routinely recommended. This study is used in patients with chronic diarrhea (*E. histolytica*, *Cryptosporidium*); patients with a history of travel to developing countries, particularly to Nepal or areas of Russia (*Cryptosporidium*, *Giardia*, *Cyclospora*)[13]; patients with exposure to infants in day care centers (*Cryptosporidium*, *Giardia*); and patients with HIV infection (*E. histolytica*, *Giardia*).[14]

Giardia *antigen assay* and serologic testing for amebiasis may be considered in patients exposed to poor sanitation, HIV-infected patients, patients with a history of travel to developing countries, patients with a history of backpacking, and patients with day care exposures.

Urinalysis: A urinalysis and a urine pregnancy test should be obtained only when urinary tract infection is a possibility, a gastrointestinal origin for the symptoms is not clear, or pregnancy is suspected.

Radiographic studies: Plain radiographs and contrast computed tomography (CT) may be indicated for patients thought to have a surgical abdomen and to identify pathologic abnormalities, such as tumor, obstruction, free air, fistulas, blind loops, and those associated with Crohn's disease.

Gastrointestinal referral: Referral may be indicated in the evaluation of chronic diarrhea and for workup beyond the scope of the ED (e.g., endoscopy, further stool studies, biopsy).

EMPIRICAL MANAGEMENT

Oral rehydration is the treatment of choice for mild to moderate fluid losses (Fig. 23-1). Oral rehydration can be accomplished using sports beverages, commercial rehydration solutions, or a balanced clear liquid diet in the home (e.g.,

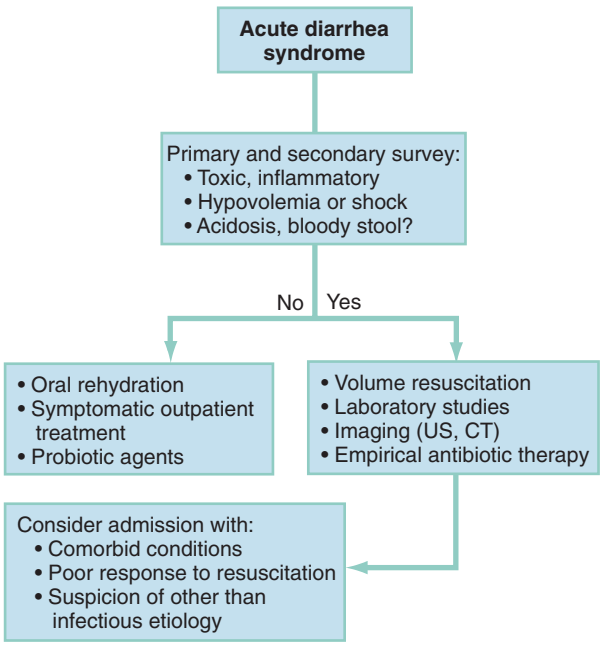


Figure 23-1. Approach to the patient with acute diarrhea. CT, computed tomography; US, ultrasonography.

consisting of water, salt-containing liquids such as canned soups, and potassium from oranges or bananas). The WHO has defined an oral rehydration solution (WHO-ORS) that can be made by dissolving the following in 1 liter of clean water:

3.5 g of sodium chloride
2.9 g of trisodium citrate or 2.5 g of sodium bicarbonate
1.5 g of potassium chloride
20 g of glucose or 40 g of sucrose

Replacement of micronutrients, particularly copper and zinc, has been recommended, especially in developing countries.[15] The concept of bowel rest has been abandoned because it may worsen diarrhea and lead to more severe dehydration. The choice of oral rehydration fluids depends on the extent of dehydration and the underlying health of the patient. In otherwise healthy patients with mild to moderate dehydration, fluids such as sports drinks, diluted fruit juices, and soft drinks supplemented with soups, broths, or crackers may be sufficient to replace the fluid and sodium losses associated with acute diarrhea. Such frequently used "clear liquids" may contain excess sugars and insufficient sodium content, however, leading to an osmotic diarrhea. Beverages containing caffeine should be avoided because caffeine increases cyclic adenosine monophosphate levels and may cause a secretory diarrhea. Milk and other products containing lactose also should be avoided because viral and bacterial pathogens, responsible for many cases of diarrhea, may cause a transient lactase deficiency, leading to malabsorption and osmotic diarrhea. Food intake is encouraged, but foods high in simple sugars should be avoided because the osmotic effect is counterproductive. Foods with a high fat content may delay gastric emptying and should be avoided. The *BRAT* (bananas, rice, apples, and toast) *diet* has long been recommended, particularly with pediatric patients. Although no controlled studies have examined the efficacy of the BRAT diet, it remains a commonly recommended strategy. The pectin in the peel of apples is constipating (pectin, found in fruit peel, is the "pectate" in Kaopectate), and bananas provide potassium. If this diet is used for extended periods, adequate provision of protein and energy needs of the patient becomes a concern.

In patients with evidence of more severe dehydration, intravenous fluid resuscitation with normal saline or lactated Ringer's solution is the preferred treatment. Pediatric patients should receive a bolus of 20 mL/kg of normal saline, which may be repeated as indicated. Specific treatment for diarrhea should be directed toward the suspected cause. In patients with suspected surgical pathology, further diagnostic testing and surgical consultation may be required. With toxic exposures, treatment consists of early decontamination, supportive care, and, if appropriate, administration of specific antidotes. Other noninfectious causes of diarrhea are treated as indicated.

Because the specific pathogen causing infectious diarrhea is rarely identified in the ED, and the results of cultures are usually unavailable, any antimicrobial treatment must be empirical and guided by knowledge of the common causes of infectious diarrhea (see Box 23-1). Viral and noninvasive bacterial gastroenteritis tend to be self-limiting and require only supportive therapy. Empirical antibiotic treatment is directed against invasive bacterial and parasitic organisms that cause the greatest harm. Antibiotic treatment is initiated in patients with a suspected invasive process and severe diarrhea, systemic symptoms, fever, or abdominal pain and in patients who appear toxic. The current recommendation for empirical treatment of a systemically ill–appearing adult is ciprofloxacin, 500 mg orally twice a day, or levofloxacin, 500 mg orally every 24 hours for 3 to 5 days.[16] Fluoroquinolones are efficacious against most organisms that cause dysenteric illnesses and have been shown to be more effective than trimethoprim-sulfamethoxazole.[13,17] Fluoroquinolones should not be administered to pregnant patients or children younger than 18 years of age. The antibiotic treatment of severe gastroenteritis in children has been associated with the development of hemolytic-uremic syndrome and thrombotic thrombocytopenic purpura if the bacterial cause is enterohemorrhagic *E. coli* O157:H7, although *Salmonella*, *Shigella*, and *Campylobacter* also have been implicated. If possible, treatment for pediatric patients should be based on culture results with supportive care initially.

If amebic dysentery is of concern in high-risk patients (see Table 23-1), treatment with metronidazole after stool analysis for ova and parasites is recommended. In patients with a history of recent antibiotic use suspected of having *C. difficile* colitis, a *C. difficile* toxin assay followed by vancomycin or metronidazole is appropriate.[18]

The use of antimotility agents in the treatment of acute enteritis has been controversial, with the literature divided over this issue. Patients with simple, acute viral gastroenteritis benefit from antimotility agents and often obtain significant relief of symptoms, with less fluid loss and without significant complications. Loperamide is the safest and most effective medication. Relief of symptoms is achieved much more rapidly than with bismuth subsalicylate (Pepto-Bismol) in patients with inflammatory diarrhea or antibiotic-associated colitis. In pediatric age groups, the use of opioids, loperamide, or diphenoxylate with atropine rarely has been associated with the precipitation of toxic megacolon and hemolytic-uremic syndrome. Because the beneficial effects of these medications are modest, they should be avoided or used with extreme caution in these high-risk patients.

Probiotics have been used as an alternative to traditional antibiotic therapy for diarrhea. *Lactobacillus* and other bacteria have proved to be effective in restoring the normal gastrointestinal flora that is disrupted during diarrhea illness. This approach has been most effective with traveler's diarrhea and nonspecific diarrhea in children.

DISPOSITION

Most patients with uncomplicated, acute diarrhea can be discharged home after assessment and symptomatic relief. Hospitalization rarely is required for diarrhea secondary to viral and many forms of bacterial gastroenteritis, which tend to be self-limiting. Often the exact etiologic agent of diarrhea is not identified in the ED. An understanding of common causes and their treatment and recognition of patients at risk for a more severe clinical course are essential to make the appropriate disposition. In patients with severe dehydration, hemodynamic instability, or a toxic appearance and in high-risk groups, hospital admission is warranted for continuous monitoring, further treatment, and definitive management when initial evaluation and stabilization are complete.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 24 Constipation

Jan M. Shoenberger

PERSPECTIVE

Constipation is a symptom, not a disease. Patients and doctors often define constipation differently. Patients often use the term *constipation* to describe a broad set of complaints including straining, hard or infrequent stools, feeling of incomplete evacuation, and abdominal discomfort. Constipation may be acute (new for the patient) or chronic. Chronic constipation is defined as the presence of symptoms for at least 3 months. The Rome III criteria constitute a consensus definition of functional chronic constipation often used in research (Table 24-1).[1] Attempting to identify the cause of this symptom will often result in the best chance of effective treatment and will help determine disposition. A definitive diagnosis often is not possible in the emergency department, and appropriate follow-up evaluation should be arranged in those cases. When constipation becomes severe with constant pain, some clinicians use the term *obstipation*. Obstipation represents the progression of the symptom of constipation toward bowel obstruction.

In the emergency department (ED), the complaint of constipation should be of concern when it represents a significant change from a patient's own normal pattern that is creating discomfort for the patient. This change may manifest as a decrease in frequency of defecation, sudden and persistent change in the character or amount of stools (especially decrease in stool caliber), blood in the stool, or problems expelling the stool.[2]

Epidemiology

The prevalence of constipation in North America is approximately 15%. Constipation is more common in women than in men, in nonwhites than in whites, and in the elderly. A consistent trend of increasing prevalence of constipation is observed with age, with significant increases after the age of 70 years. The high prevalence among elderly patients is multifactorial and related to a diet low in fiber, sedentary habits, multiple medications, and various disease processes that impair neurologic and motor control. Constipation also is common with patients who are institutionalized, debilitated, or neurologically impaired.[3]

Pathophysiology

Normally the gastrointestinal tract is presented with 9 to 10 L/day of secretions and ingested fluids. The small intestine usually absorbs all of this except for approximately 500 mL. The colon mixes the ileal effluent, ferments and salvages the unabsorbed carbohydrate residues, and desiccates the contents to form stool. The process of stool transport and evacuation is complex and is regulated by neurotransmitters, intrinsic colonic reflexes, and a multitude of learned and reflex mechanisms that are not fully understood. Constipation may result from structural, metabolic, mechanical, neurologic, or behavioral disorders that affect the colon or anorectum either directly or indirectly.[4-6]

DIAGNOSTIC APPROACH

Differential Considerations

The causes of constipation are numerous. Causes of constipation can be divided into *primary* (no apparent external cause) and *secondary* causes (summarized in Table 24-2). These two groupings have some overlap. In the ED, patients commonly present with acute constipation due to side effects of medications or avoidance of defecation secondary to presence of painful perianal lesions such as fissures, hemorrhoids, or perirectal abscesses.[6]

Pivotal Findings

History

A thorough, detailed history usually identifies the most likely cause of the patient's constipation. Defining what the patient means by "constipation" is a good starting point. Essential information includes the presence or absence of alarming signs or symptoms. These include fevers, anorexia, nausea, vomiting, new onset or worsening of constipation, blood in the stool, weight loss, and a family history of inflammatory bowel disease or colon cancer.

Additional elements of the history are directed toward elucidating a possible cause. Questions about the character of the stools may reveal a decrease in caliber of the stool, suggesting possible mass lesion, or diarrhea alternating with constipation, which may indicate irritable bowel syndrome. Frequency of stools and what the patient considers "normal" should be assessed.

The review of systems may need to include questions regarding associated symptoms if no obvious cause is elicited in the cursory history. Questions directed at associated neuro-

Table 24-1 Rome III Criteria for Functional Constipation

(1) At least 2 of the following for a minimum of 3 months, with symptom onset at least 6 months before diagnosis:
  (a) Straining during ≥25% of bowel movements
  (b) Lumpy or hard stools for ≥25% of bowel movements
  (c) Sensation of incomplete evacuation for ≥25% of bowel movements
  (d) Manual maneuvers to facilitate ≥25% of bowel movements (e.g., digital evacuation, support of the pelvic floor)
  (e) <3 bowel movements per week
(2) Loose stools rarely present without use of laxatives
(3) Insufficient criteria for irritable bowel syndrome

logic symptoms, activity level, and status of comorbid diseases may provide clues to contributing factors.[7]

A medication history is essential and should include any recent changes in dosing of any prescription medications, herbal agents, and over-the-counter (OTC) medications. Many patients experience constipation as a side effect of medication. Drugs of abuse also may cause changes in bowel patterns. Opiates are the most common cause of constipation among medications and drugs of abuse.

Physical Examination

The physical examination should initially focus on two major aspects: the abdominal and rectal portions of the physical examination. The abdominal examination usually yields normal findings but may reveal tenderness, a mass, distention, or possibly evidence of obstruction. Bowel sounds should be auscultated.

The anorectal examination and an evaluation of the stool are the most important parts of the physical assessment. Anorectal inspection may reveal fissures, skin excoriations, hemorrhoids, or rectal prolapse. The digital rectal examination should include careful palpation for masses, and the presence or absence of pain should be noted. Other possible findings include strictures, high sphincter tone, and the presence of blood. Having the patient bear down may be helpful in assessing sphincter function and may reveal milder forms of prolapse. The quantity and the characteristics of the stool should be recorded. Testing the stool for occult blood may yield additional information, although straining at stool can produce local anal lesions and bleeding. If results of occult blood testing are positive, diverticular disease, carcinoma, and simply trauma from repeated attempts at straining all are possibilities. Patients with acute constipation who present to the ED most commonly have large amounts of hard stool in the rectum. Results of rectal examination have not been shown, however, to correlate with complaints of constipation or with evidence of colonic loading on abdominal radiographs. The rectal examination alone should not be used to confirm or exclude the presence of constipation.[8]

Ancillary Testing

A majority of patients who present to the ED with a chief complaint of constipation do not need any testing. Plain radiographs may provide information about extent of stool retention but also may suggest emergent diagnoses such as megacolon or volvulus. Although constipation can cause cramping and abdominal pain, plain radiographs documenting an increased stool load in the constipated patient cannot be used to rule out more serious underlying etiologic disorders, especially if the

Table 24-2 Causes of Constipation

Primary Causes

Functional Disorders
Idiopathic
Irritable bowel syndrome
Pelvic dyssynergia (anismus)
Slow-transit constipation

Neuropathic
Congenital anal sphincter myopathy
Hirschsprung's disease
Spinal cord injury

Obstructive
Anal stenosis
Crohn's disease
Colon cancer
Stricture
Rectal prolapse

Gynecologic
Large rectocele
Pelvic relaxation

Secondary Causes

Lifestyle/General Condition
Dehydration
Inadequate dietary fiber
Sedentary
Voluntary suppression of defecation

Medications
Antacids
Anticholinergics
Anticonvulsants
Antidepressants
Antihistamines
Antiparkinsonian drugs
Antipsychotics
Calcium channel blockers
Calcium supplements
Diuretics
Iron supplements
Laxatives (chronic abuse)
Nonsteroidal anti-inflammatory drugs
Opiates

Metabolic/Endocrine
Diabetes mellitus
Hypercalcemia
Hypokalemia
Hypothyroidism
Hypomagnesemia
Porphyria
Uremia

Myopathic
Scleroderma
Amyloidosis
Neurologic
Cerebrovascular accident
Autonomic neuropathy
Mutiple sclerosis
Paraneoplastic neuropathy
Parkinson's disease
Amyotrophic lateral sclerosis

Psychological
Anxiety
Depression
Eating disorders
Situational stress
Sexual abuse

Adapted from Swegle JM, Logemann C: Management of common opioid-induced adverse effects. Am Fam Physician 74:1347, 2006.

patient has a significant amount of abdominal pain or tenderness on examination.

Clinical laboratory studies are not routinely indicated in the workup for constipation. When blood is found in the stool, a hemoglobin level may reveal an accompanying anemia, which may suggest an occult carcinoma. The white blood cell count is nonspecific and not helpful.

Patients with acute constipation for which the cause is not readily apparent should receive symptomatic treatment, with referral for outpatient evaluation and reassessment as needed. The patient who presents to the ED with chronic constipation and no alarming signs or symptoms should receive empirical treatment without any ancillary testing. Outpatient tests may eventually include blood tests to investigate metabolic or endocrine causes and possibly specialized tests such as colonic transit studies, defecography, and anorectal manometry with balloon expulsion. Consensus recommendations state that the routine use of colonoscopy to exclude organic disorders in patients with chronic constipation symptoms is not indicated, although it is still recommended for colon cancer screening in all patients older than 50 years of age.[9,10]

DIAGNOSTIC ALGORITHM

The approach to the patient with constipation starts with assessing whether or not this symptom is accompanied by the additional symptom of abdominal pain. If such pain is present, the workup should be geared toward this symptom, which may ultimately reveal the cause of the constipation. Constipation may itself cause abdominal pain; however, this should be a diagnosis of exclusion once other, more serious potential etiologic disorders are ruled out.

Figure 24-1 presents a diagnostic algorithm. If the physical examination reveals a structural or mechanical cause, such as

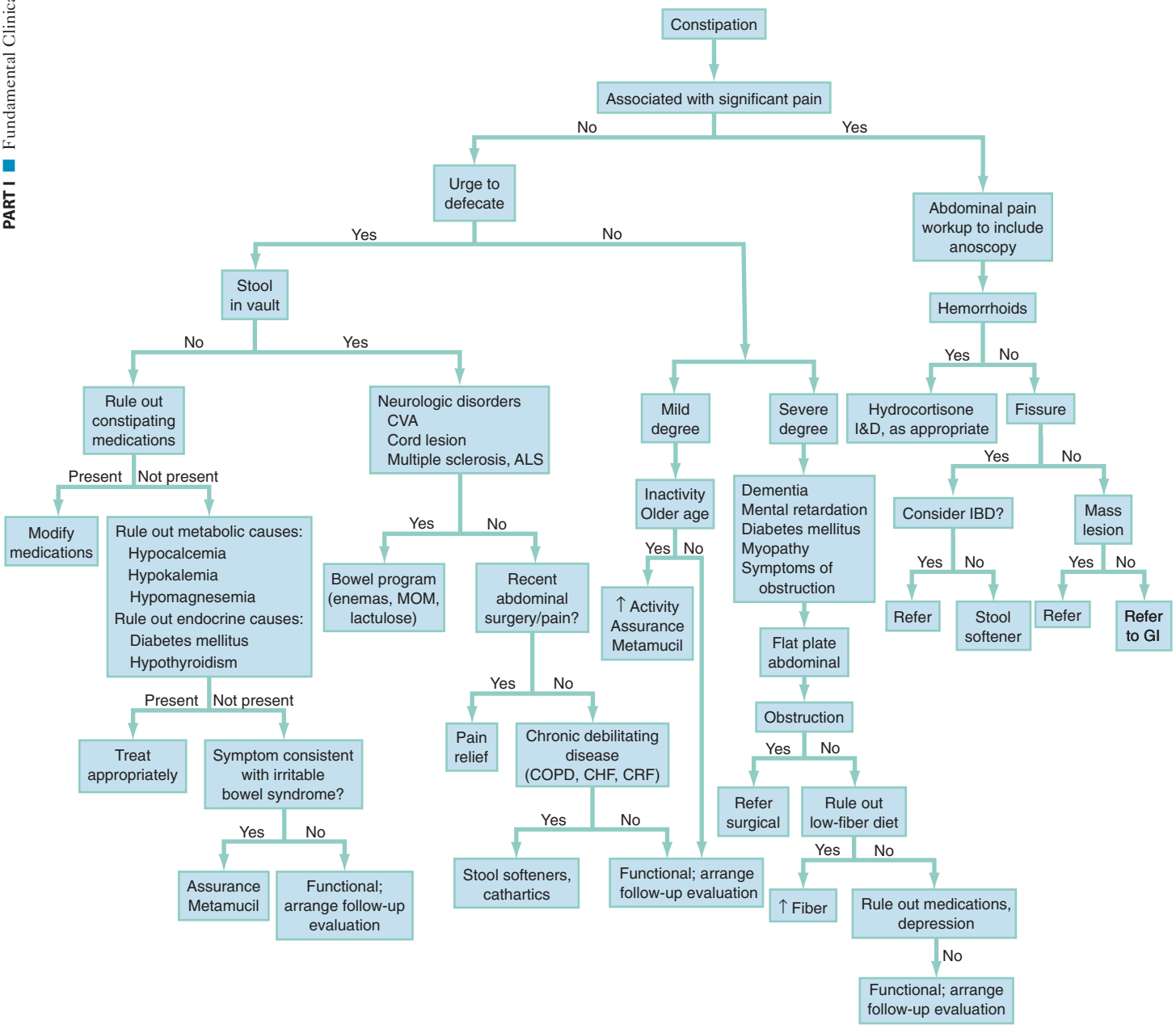


Figure 24-1. Algorithmic approach to the diagnosis of constipation. ALS, amyotrophic lateral sclerosis; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; IBD, inflammatory bowel disease; I&D, incision and drainage; MOM, milk of magnesia.

pain from hemorrhoids, fissures, or mass lesion, the appropriate treatment or referral is indicated; the constipation will resolve once the cause is addressed. If no obvious cause is found on examination, then determination of the presence or absence of stool in the rectal vault may be helpful. History will be very helpful in differentiating between causes such as medication side effect and possible neurologic disease.

Constipation is rarely associated with morbidity or mortality. Most bad outcomes are due to missed diagnosis of bowel obstruction or perforation. These conditions are diagnosed with physical examination, plain radiographs, and computed tomography (CT) scan if needed. Surgical consultation is needed for suspected perforation and obstruction.

EMPIRICAL MANAGEMENT

Treatment of acute constipation is directed toward eradicating the underlying cause and providing symptom relief. Prevention of further episodes of constipation may include recommending increased fluid intake, increased dietary fiber, and, if necessary, additional sources of bulk in the form of synthetic bulk agents. These interventions will not usually help the acutely constipated patient in the short term.[10] Laxatives often will be required[11] (see Table 24-3). Specific therapy also may include actions such as withholding a causal medication, management of an anal fissure, or draining of a perirectal abscess. Stool softeners have not been shown to be any more effective than placebo at relieving acute constipation, although they may be somewhat helpful in patients with anal fissures or hemorrhoids, which can make defecation painful.[4,12]

Specific agents for symptomatic treatment of constipation are listed in Table 24-4. Most of these agents are designated category B or C as determined by the U.S. Food and Drug Administration (FDA). A consensus panel recently concluded that polyethylene glycol (category C) was the optimal laxative for pregnant women because it is effective and minimally absorbed, has few side effects, and is low risk.[13] Patients who are on chronic, medically necessary medications that cause constipation (e.g., opioids in patients with chronic pain or cancer) should be on so-called bowel regimens. These regimens usually include preventive measures such as high levels of dietary fiber (e.g., in prunes or figs) as well as stimulant laxatives. Patients on chronic opioids with acute constipation may also respond to naloxone although precipitating withdrawal symptoms are possible.[14] The new specific peripheral opioid receptor agents on the horizon may prove to be very useful in treating the constipation associated with chronic opioid use without reversing central actions.[15] Elderly patients who are prescribed opiates from the ED for home use should be warned about constipation and given instructions to prevent and treat it.

Enemas are sometimes necessary if laxatives have failed to provide relief or if the patient has a large volume of stool in the lower colon or rectum that cannot be expelled. Warm tap-water enemas probably are the safest. For immediate relief, manual disimpaction may be necessary in some patients, especially in elderly persons with large amounts of stool present in the rectal vault. In the rare case, disimpaction may need to be performed with procedural sedation.

There are alternatives to the traditional laxatives and enemas for patients who suffer from chronic constipation. Patients with recalcitrant constipation may benefit from interventions such as acupuncture, biofeedback, and bowel training.[16,17]

Table 24-3 General Approach to Treatment of Constipation

For specific agents, dosages, and precautions, see Table 24-4.

I. Core program for all patients
   - A. Adequate intake of fluid and fiber is one key to preventing constipation. Fiber is available primarily from grains and bran cereals. Flatulence, bloating, and cramps are common side effects encountered when bran fiber is introduced.
   - B. Another source of bulk is from synthetic bulk agents (e.g., psyllium). Bulk agents require an adequate amount of fluid intake; otherwise, they may worsen constipation.
   - C. Avoid irritant laxatives as part of a core program because long-term use may decrease bowel motility. Encourage the patient to exercise and respond promptly to the urge to defecate.

II. Individualized program—specific indications and general comments
   - A. *Stimulant laxatives*: Many believe that long-term use of these agents leads to dependency and habituation, but this is not substantiated. When used appropriately, these medications are not harmful and are very effective. Senna is probably the first-line choice among this class of laxatives.
   - B. *Osmotic laxatives*: These agents are most commonly used for colonic preparation before bowel procedures. This class of drugs includes magnesium-containing laxatives, polyethylene glycol (PEG), and nonabsorbable sugars such as lactulose and sorbitol. These agents are safe and well tolerated. PEG has been shown to be slightly more effective than lactulose and causes less bloating and flatus.
   - C. *Lubricants*: Oral mineral oil lubricants are particularly helpful in patients who have acute painful perianal lesions. The softening and coating of the stool can make passage much easier and less painful, preventing constipation. It is also helpful in elderly patients who have chronically hard stools and usually is well tolerated. Mineral oil is contraindicated in patients with swallowing problems or in those who are particularly debilitated, to prevent aspiration leading to lipid pneumonia.
   - D. *Stool softeners*: Stool softeners are wetting agents believed to enhance the moisture content of fecal material. Evidence exists that stool softeners are no more effective than placebo and certainly not any better than other agents available.
   - E. *Suppositories and enemas*: These agents are especially helpful in patients who tend to have trouble expelling soft stool from the rectum. Glycerin suppositories may have a soothing effect and be helpful in patients with constipation caused by local, painful perianal lesions. Tap-water enemas or soapsuds enemas are helpful when disimpaction is necessary.

DISPOSITION

Constipation is appropriately treated at home, and only the most severe cases require disimpaction or enema treatment in the ED. With complications or presence of a serious disorder as a cause for the constipation, such as fecal impaction beyond that able to be resolved by digital disimpaction, megacolon, volvulus, or bowel obstruction, the patient should be admitted to the hospital for further evaluation and treatment.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

Table 24-4 Preparations Used in the Symptomatic Treatment of Constipation

MEDICATION	MAXIMAL RECOMMENDED DOSE	ONSET OF ACTION	COMMENTS
Bulk laxatives			Increases colonic residue, stimulates peristalsis.
Psyllium (Metamucil)	Titrate up to 20 g	12–72 hr	Natural fiber that undergoes bacterial degradation, which may contribute to bloating and flatus. Should be taken with plenty of water to avoid intestinal obstruction.
Methylcellulose (Citrucel)	Titrate up to 20 g		Semisynthetic cellulose fiber that is relatively resistant to colonic bacterial degradation.
Polycarbophil (Fibercon)	Titrate up to 20 g		Synthetic fiber of polymer of acrylic acid, resistant to bacterial degradation.
Osmotic laxatives			Draws water into the intestines along osmotic gradient.
Magnesium/sodium salts			
Magnesium hydroxide (Milk of Magnesia)	15–30 mL once or twice daily	0.5–3 hr	A small percentage of magnesium is absorbed—caution in renal insufficiency and in children.
Magnesium citrate	150–300 mL as needed		
Sodium phosphate (Fleet phospho-soda)	20–45 mL with 12 oz of water as needed		Hyperphosphatemia may result if patient has renal insufficiency. Commonly used before colonoscopy.
Poorly absorbed sugars			
Lactulose	15–30 mL once or twice a day	24–72 hr	Synthetic disaccharide not absorbed by the small intestine. Gas and bloating common.
Sorbitol	15–30 mL once or twice a day		Poorly absorbed by small intestine.
Polyethylene glycol and electrolytes (GoLYTELY, Miralax)	17–36 g once or twice a day	1–24 hr	Organic polymers that are poorly absorbed and not metabolized by bacteria, thus may cause less bloating and cramping. Can be mixed with noncarbonated beverages.
Stimulant laxatives			Stimulate intestinal motility or secretion.
Senna (Senokot, Ex-lax)	8–34 mg daily	6–12 hr	Stimulates secretion and motility of small intestine and colon.
Bisacodyl (Dulcolax, Correctol)	5–10 mg daily		
Castor oil	15–30 mL daily		Causes cramping and severe diarrhea.
Stool softeners			
Docusate sodium (Colace)	100 mg twice a day; some use higher doses	6–8 hr	In many studies, no better than placebo.
Mineral oil (Fleet mineral oil)	5–15 mL orally at night		Provides lubrication for the passage of stool. Long-term use is not recommended. Lipid pneumonia can occur in patients predisposed to aspiration.
Enterokinetic agents			
Lubiprostone (Amitiza)	24 μg once or twice per day	1 hr	A chloride channel activator. Approved for treatment of chronic idiopathic constipation in adults. Headache, nausea, possible diarrhea.

CHAPTER 25 Jaundice

Matthew A. Wheatley and Katherine L. Heilpern

PERSPECTIVE

Epidemiology and Pathophysiology

Jaundice affects patients of all ages, from neonates to the elderly. It is not a common chief complaint; however, the jaundiced patient may present with a related symptom such as abdominal pain, pruritus, or substance ingestion. Jaundice is the manifestation of elevated serum bilirubin, so an understanding of the metabolism of bilirubin is crucial for the emergency evaluation and management of jaundice.

Bilirubin Metabolism

Bilirubin is generated from heme products, primarily senescent red blood cells. A small portion is derived from myoglobin and maturing erythroid cells. Within the reticuloendothelial system, heme is oxidized to biliverdin, which is then converted to bilirubin. Bilirubin forms a tight but reversible bond with albumin in circulation. It is passively taken into the hepatocytes, where it undergoes glucuronidation. This conjugated fraction is secreted into the biliary system and emptied into the gut. Colonic bacteria metabolize the major portion of the bilirubin to urobilinogen and stercobilin. Stercobilin is excreted in the stool and urobilinogen is reabsorbed and excreted in the urine. The remaining conjugated bilirubin is deconjugated and reenters the portal circulation to be taken up again by the liver (enterohepatic circulation).

In the laboratory, conjugated bilirubin is the fraction that reacts directly with reagents whereas unconjugated bilirubin requires the addition of an accelerator compound. They are reported as direct and indirect fractions, respectively.

Pathophysiology

Clinical jaundice usually is not evident until the serum bilirubin concentration rises above 2.5 mg/dL. It is observed in tissues with high albumin concentrations, for example, the skin and eyes. It is absent in albumin-poor fluids, such as tears or saliva. The physiology of bile metabolism may be altered on four principal levels: overproduction of heme products, failure of the hepatocyte to take up the bilirubin for processing, failure of the hepatocyte to conjugate or excrete bilirubin, or an obstruction of biliary excretion into the intestine. Unconjugated bilirubin that is not bound to albumin can cross the blood-brain barrier, causing adverse neurologic effects ranging from subtle developmental abnormalities to encephalopathy and death. The risk of neurotoxicity is increased by conditions that favor the unbound fraction of unconjugated bilirubin, including hemolysis, hypoalbuminemia, acidemia, and drugs that bind competitively to albumin. Conjugated bilirubins are not neurotoxic, although they may indicate serious disease.

DIAGNOSTIC APPROACH

Differential Considerations

The three major diagnostic categories to consider as causes of jaundice are biliary obstructive disorders, liver injury or dysfunction, and hematologic disorders. Figure 25-1 outlines a laboratory-based approach to differentiating among these three categories.

Pivotal Findings

The pivotal findings related to history, physical examination, and ancillary testing are listed in Figure 25-2.

History

Patients may be asymptomatic at presentation or have nonspecific symptoms, such as pruritus, malaise, or nausea. There are a few symptom complexes that, if present, can help narrow the differential diagnosis. Jaundice with abdominal pain suggests significant hepatic inflammation. New-onset painless jaundice is the classic presentation for a neoplasm involving the head of the pancreas. Patients may complain of ill-fitting clothing because of weight loss or increasing abdominal girth related to ascites. The patient or caregiver may note personality changes or confusion, suggestive of hepatic encephalopathy. Unexplained liver failure and jaundice may be the downstream sequelae of an intentional overdose of acetaminophen taken 48 to 72 hours (or more) earlier.

Physical Examination

A thorough examination should be performed in patients presenting with jaundice, because the physical findings can help narrow the differential diagnosis. Pertinent examination findings are summarized in Figure 25-2. Jaundice is first apparent sublingually, on the hard palate, and in the conjunctiva. From there, it spreads caudally. Studies in both adults and neonates suggest that the "level" of cephalocaudal progression of jaundice cannot accurately estimate the serum bilirubin concentration.[1,2]

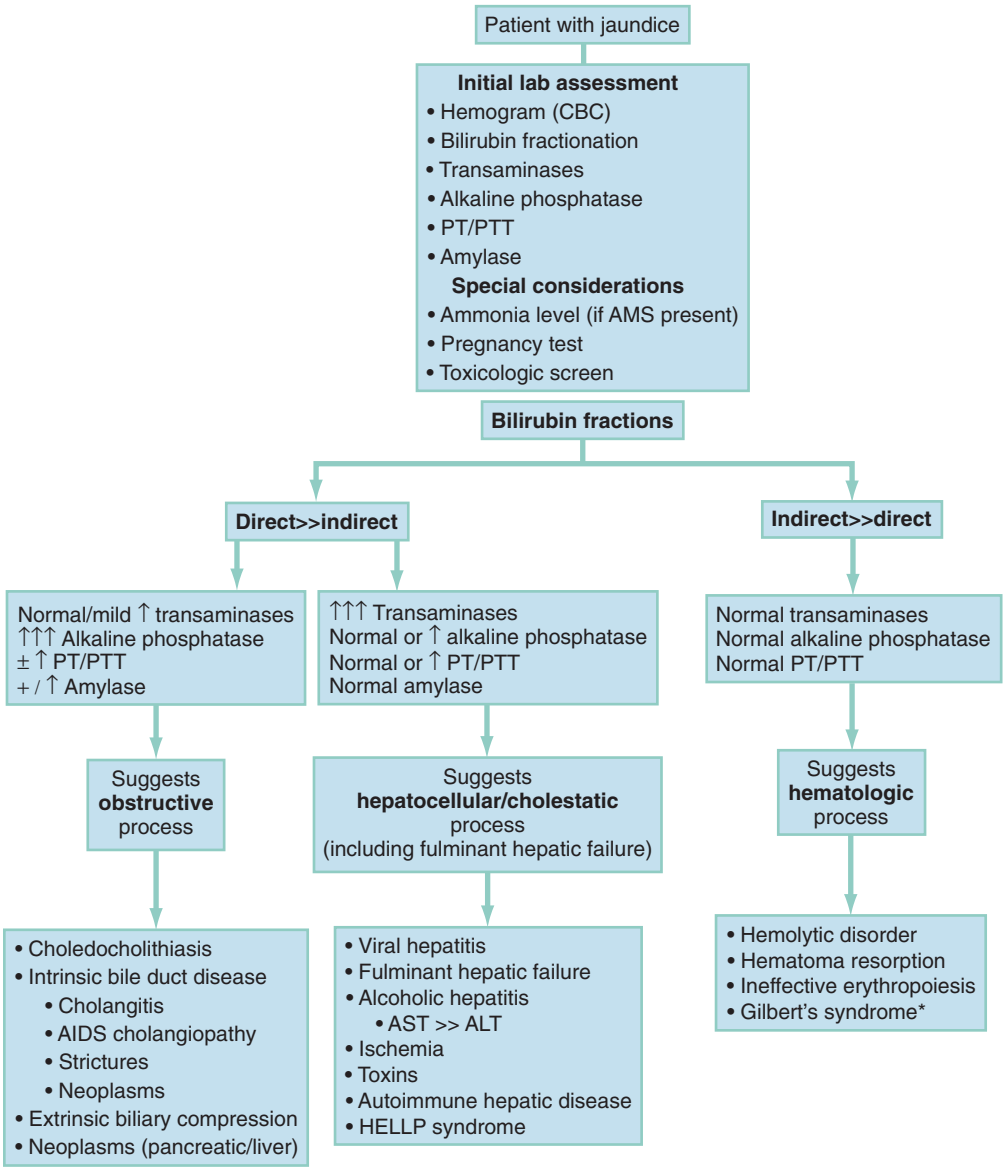


Figure 25-1. Laboratory approach to differential diagnosis of jaundice. AIDS, acquired immunodeficiency syndrome; ALT, alanine aminotransferase; AMS, altered mental status; AST, aspartate aminotransferase; CBC, complete blood count; HELLP, hemolysis, elevated liver enzymes, and low platelets; PT, prothrombin time; PTT, partial thromboplastin time.

*A benign hereditary condition characterized by hyperbilirubinemia and jaundice due to inadequate hepatic conjugation of bilirubin.

Fever with right upper quadrant tenderness suggests cholangitis.[3] In this clinical scenario, the liver should not be engorged. A large tender liver may represent an exacerbation of acute or chronic hepatitis or malignant infiltration. A palpable gallbladder, a rare finding, suggests chronic cholestasis or malignancy. The presence of splenomegaly suggests hemolysis, malignancy, or portal hypertension. Ascites may be associated with acute or chronic liver disease. Ascites associated with abdominal tenderness raises suspicion for spontaneous bacterial peritonitis. Rapid onset of hepatomegaly and ascites may indicate portal vein thrombosis (Budd-Chiari syndrome).[4] Jaundice associated with a large pulsatile abdominal mass may indicate a rapidly enlarging or ruptured abdominal aortic aneurysm. The patient's mental status should be assessed for evidence of hepatic encephalopathy.

Physical examination findings associated with chronic liver disease and cirrhosis include spider angiomas, gynecomastia, testicular atrophy, and caput medusae. Excoriations from scratching in attempts to relieve pruritus suggest chronic liver disease. Asterixis, a sign of hepatic encephalopathy, usually is found only in patients with chronic liver disease. Table 25-1 summarizes the clinical stages of hepatic encephalopathy.

Ancillary Testing

Figure 25-1 lists the laboratory tests that should be considered in the evaluation of the patient with jaundice. Alkaline phosphatase (AP) also can be elevated in diseases affecting bone or the placenta in the first trimester. In the setting of isolated elevated AP, increased serum gamma-glutamyl transpeptidase (GGT) or 5′-nucleotidase points to a hepatic source. A reticulocyte count and evaluation of the peripheral blood smear may identify hemolysis. In the setting of toxic ingestion or unexplained hepatocellular injury, serum acetaminophen concentration level is indicated. Rapid stool guaiac testing should be performed to assess for the presence of gastrointestinal bleeding. Patients with altered mental status should have a rapid bedside glucose assessment in addition to determination of

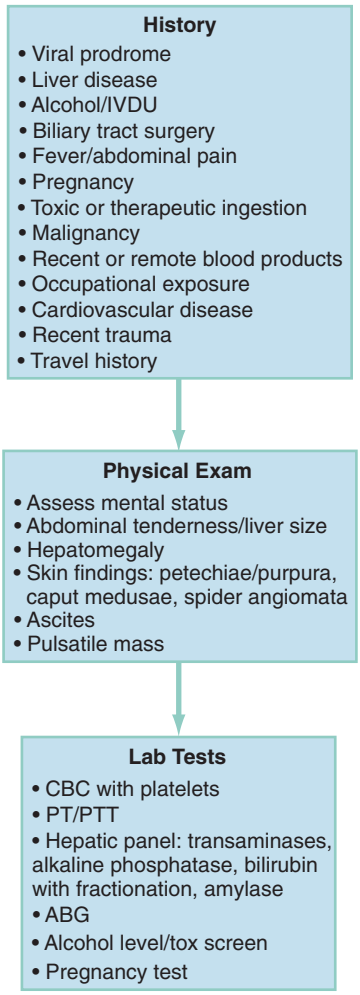


Figure 25-2. Pivotal points in the assessment of the jaundiced patient. ABG, arterial blood gas (analysis); Alk phos, alkaline phosphatase; CBC, complete blood count; IVDU, intravenous drug use; PT, prothrombin time; PTT, partial thromboplastin time.

Table 25-1 Clinical Stages of Hepatic Encephalopathy

CLINICAL STAGE	INTELLECTUAL FUNCTION	NEUROMUSCULAR FUNCTION
Subclinical	Normal examination findings, but work or driving may be impaired	Subtle changes in psychometric testing
Stage 1	Impaired attention, irritability, depression, or personality changes	Tremor, incoordination, apraxia
Stage 2	Drowsiness, behavioral changes, poor memory, disturbed sleep	Asterixis, slowed or slurred speech, ataxia
Stage 3	Confusion, disorientation, somnolence, amnesia	Hypoactive reflexes, nystagmus, clonus, muscular rigidity
Stage 4	Stupor and coma	Dilated pupils and decerebrate posturing, oculocephalic reflex

From Fitz G: Hepatic encephalopathy, hepatopulmonary syndromes, hepatorenal syndrome and other complications of liver disease. In Feldman M, Friedman L (eds.): Gastroenterology and Liver Disease, 8th ed., Philadelphia, WB Saunders, 2006, p 1966.

serum ammonia concentration. Although elevated serum ammonia may aid in diagnosis, the degree of hyperammonemia has not been shown to correlate with the degree of encephalopathy.[5] In the presence of abdominal tenderness and ascites, ascitic fluid should be tested for cell count, Gram staining, culture, and protein.[6] Two sets of blood cultures should be obtained in patients with fever and jaundice. If the patient appears ill or there is evidence of gastrointestinal bleeding, type and screen or type and crossmatch studies should be performed.

Imaging

The best radiologic study for the emergent evaluation of obstructive biliary disease remains somewhat controversial. Both ultrasonography (US) and computed tomography (CT) are available in the emergency department (ED), and each has its advantages. The choice of imaging procedure depends on the pretest probability of biliary obstruction and on the index of suspicion of malignancy. In cases in which the probability of malignant obstruction is high, CT is the preferred imaging methodology. It is more sensitive than US in locating the site of the obstruction. Additionally, it is 70% accurate in staging disease and determining resectable versus unresectable disease.[7] Patients with a high likelihood of benign obstruction are best screened with US. It is safe, rapid, and less expensive and less invasive than CT. Some common duct stones may be missed with US, but it is as sensitive as CT in determining the presence of obstruction. US with Doppler flow can detect obstruction of the hepatic, portal, and splenic veins. Sonographic features that suggest acute cholecystitis include presence of pericholecystic fluid and gallbladder wall thickening.[8] If gallstones are present on ultrasound images, a sonographic Murphy sign has a positive predictive value of 90% for acute cholecystitis. In patients with low or intermediate clinical likelihood of mechanical obstruction, US is the preferred modality to evaluate whether or not biliary obstruction is present. CT is preferred if the entire abdomen needs to be evaluated.

DIFFERENTIAL DIAGNOSIS

Using a systems approach, jaundice can be classified into critical, emergent, and nonemergent categories (Table 25-2). Patients are considered to be critically ill if they present with jaundice and any of the following: altered level of consciousness, hypotension, fever with abdominal pain, or active bleeding. Any patient with a *new* triad of jaundice, encephalopathy, and coagulopathy is considered to have fulminant hepatic failure.[9] In general, these patients have no previous history of liver disease and experience sudden onset of illness or toxic exposure that leads to hepatic necrosis. The time course from insult to fulminant hepatic failure ranges from 1 to 8 weeks. Patients with fulminant hepatic failure require aggressive stabilization, consideration for toxic exposures, and admission to an intensive care unit or possible transfer to a center with liver transplantation capabilities.

Table 25-2 Causes of Jaundice Grouped by Level of Urgency

ETIOLOGIC CATEGORY	CRITICAL	EMERGENT	NONEMERGENT
Hepatic	Fulminant hepatic failure Toxin Virus Alcohol Ischemic insult Reye's syndrome	Hepatitis of any etiology with confusion, bleeding, or coagulopathy Wilson's disease* Primary biliary cirrhosis Autoimmune hepatitis Liver transplant rejection Infiltrative liver disease Drug-induced (isoniazid, phenytoin, acetaminophen, ritonavir, halothane, sulfonamides) Toxin ingestion or exposure	Hepatitis with normal mental status, normal vital signs, and no active bleeding
Biliary	Cholangitis	Bile duct obstruction (stone, inflammation, stricture, neoplasm)	
Systemic	Sepsis Heatstroke	Sarcoidosis Amyloidosis Graft-versus-host disease	Post-traumatic hematoma resorption Total parenteral nutrition
Cardiovascular	Obstructing AAA Budd-Chiari syndrome Severe congestive heart failure	Right-sided congestive heart failure Veno-occlusive disease	
Hematologic-oncologic	Transfusion reaction	Hemolytic anemia Massive malignant infiltration Inborn error of metabolism Pancreatic head tumor Metastatic disease	Gilbert's syndrome Physiologic neonatal jaundice
Reproductive	Preclampsia/HELLP syndrome Acute fatty liver of pregnancy	Hyperemesis gravidarum	Cholestasis of pregnancy

*In Wilson's disease, hereditary deficiency of ceruloplasmin causes copper to accumulate in the liver, leading to fulminant hepatic failure.
AAA, abdominal aortic aneurysm; HELLP, hemolysis, elevated liver enzymes, low platelets.

EMPIRICAL MANAGEMENT AND DISPOSITION

Specific therapies depend on the likely clinical entity causing the jaundice (Fig. 25-3). The patient with depressed mental status should have bedside glucose testing. If mental status remains significantly depressed, endotracheal intubation for maintaining airway patency or protection may be required.

Intravenous access should be obtained immediately, and crystalloid infusion may be indicated in the hypotensive patient. A quick assessment of volume status is required because hepatic congestion with jaundice can occur in the setting of congestive heart failure. Owing to the risk of coagulopathy, compressible sites should be used for central venous access. Significant bleeding from any source requires aggressive management. Crystalloid infusion is initiated and continued until blood products become available. Coagulopathy should be corrected with fresh frozen plasma and blood volume repleted with packed red blood cells.

If ascites is present, diagnostic paracentesis should be considered to rule out spontaneous bacterial peritonitis (SBP). This disease can have a subtle presentation and may be missed without a diagnostic paracentesis. The presence of more than 250 polymorphonuclear cells per cm^3 of ascitic fluid is diagnostic for SBP. The empiric antibiotic of choice is a third-generation cephalosporin.[6]

Patients with jaundice and elevated transaminase levels out of proportion to the elevation of alkaline phosphatase have a hepatocellular injury pattern. Liver failure with hepatic encephalopathy, if present, can be treated with lactulose, either 60 mg orally or 300 mg by retention enema. Patients with fulminant hepatic failure should be admitted to the intensive care unit or possibly transferred to a liver transplantation center.

Even in the absence of acute liver failure, patients with encephalopathy or unstable vital signs should be hospitalized. On the basis of laboratory data alone, patients with new-onset jaundice should be hospitalized if transaminases are greater than 1000 IU/L, the bilirubin exceeds 10 mg/dL, or there is evidence of coagulopathy. Any of these laboratory abnormalities suggests significant hepatic dysfunction. Patients with hepatitis or cholestatic jaundice may be managed as outpatients if they have a normal mental status and stable vital signs, are able to tolerate oral fluids, have no evidence of acute bleeding, and have no complicating infectious process. Intravenous fluids and antiemetics may be required in the ED. Medications with potential hepatotoxicity, particularly acetaminophen, should be avoided.

If the laboratory evaluation and diagnostic imaging point to an obstructive picture, ascending cholangitis must be ruled out. If it is suspected, blood cultures should be obtained, followed by prompt administration of broad-spectrum antibiotics with coverage for gram-negative aerobes and anaerobes. Patients with this disorder usually require emergent decompression by means of endoscopic retrograde cholangiopancreatography (ERCP) or cholecystostomy, which dramatically improves survival.[10] Some stable patients can undergo a trial of antibiotics and have drainage performed subacutely.[11] However, conservative treatment is more likely to fail in patients older than 75 years or chronic smokers.[12]

Patients with extrahepatic obstructive jaundice without cholangitis should be admitted for drainage. ERCP is therapeutic for benign obstructions such as gallstones or strictures. Patients with obstructive jaundice due to malignancy also benefit from biliary decompression, whether operative, endoscopic, or palliative. Once jaundice develops, malignancy is associated with more advanced disease and increased morbid-

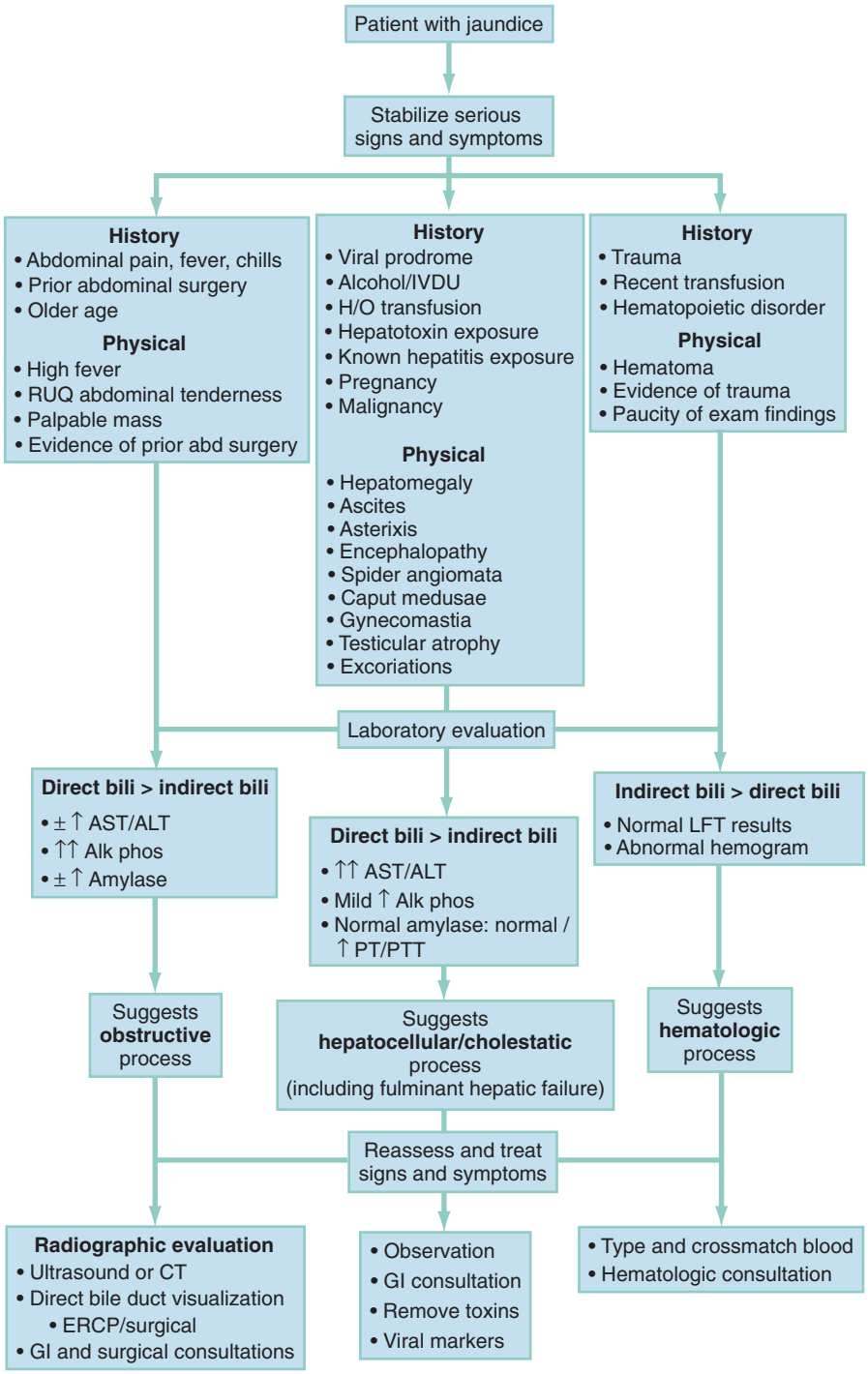


Figure 25-3. Management of the patient with jaundice. Alk phos, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; bili, bilirubin; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; GI, gastrointestinal; H/O, history of; IVDU, intravenous drug use; LFT, liver function test; PT, prothrombin time; PTT, partial thromboplastin time; RUQ, right upper quadrant.

ity and mortality.[13,14]. Biliary drainage has been correlated with improvements in cardiac function[15] and, not insignificantly, food intake.[16] In patients with obstructive jaundice secondary to malignancy, preoperative drainage is not beneficial in those undergoing surgery.[17] Palliative biliary drainage is recommended for patients who are not surgical candidates. Endoscopic drainage with biliary stenting has been found to result in fewer complications, although the rate of recurrent obstruction is higher[18] than with percutaneous drainage.

In general, patients with uncomplicated cholecystitis should receive intravenous fluids in the ED, parenteral analgesics, and antiemetics as needed and should be hospitalized. For uncomplicated cholecystitis, antibiotic therapy usually is not indicated. Patients with temperature greater than 38.8°C (102°F), a toxic appearance, or frank sepsis should receive broad-spectrum antibiotic therapy with coverage for enteric pathogens, streptococcal species, and anaerobes. These patients should undergo emergent imaging and consultation with a surgeon or gastroenterologist.[8]

Choledocholithiasis, presence of a stone in the common bile duct, may not be as easily visualized by sonography but is suggested by significant obstructive signs and symptoms and dilation of the common bile duct beyond 6 mm. Affected patients require hospitalization for possible ERCP and cholecystectomy.[19-21]

In immune-mediated hemolytic anemia, appropriate crossmatching may be difficult and fatal if not done properly. The decision to transfuse should be based on the achievable level

of oxygenation and the feasibility of instituting alternative treatments. An urgent hematology consultation is recommended. In the case of drug-induced hemolytic anemia, the mainstay of treatment is removal of the offending agent. For patients with glucose-6-phosphate deficiency, blood transfusions are rarely indicated, and the focus of management should be on maintaining urine output to prevent renal failure. Patients with hemoglobinopathies rarely require transfusion therapy unless they present with severe anemia without evidence of reticulocytosis. Fluids, oxygen, and analgesics can be given for an acute crisis.

SPECIAL POPULATIONS

One specific presentation that warrants discussion is the pregnant patient who presents with jaundice. Normal physiologic changes in pregnancy have little effect on the liver, so jaundice always indicates serious pathology. Jaundice can occur in pregnancy as a result of any of the conditions discussed earlier, as well as conditions specific to pregnancy, such as hyperemesis gravidarum, acute fatty liver of pregnancy, and intrahepatic cholestasis of pregnancy.

Hyperemesis gravidarum usually manifests in the first trimester and, in severe cases, can be associated with elevated serum bilirubin. The exact mechanism for jaundice is unknown but is likely to be related to malnutrition and impaired excretion of bilirubin. ED treatment is unchanged in these cases: hydration and antiemetics. Patients with hyperemesis and jaundice should be admitted for intravenous hydration.

Intrahepatic cholestasis of pregnancy is an idiopathic cause of jaundice that occurs early in the third trimester. It manifests with pruritus mainly on the trunk, extremities, palms, and soles, followed by jaundice after 1 to 4 weeks. Other features of obstructive jaundice such as acholic stools and dark urine may be present. Laboratory analysis reveals a cholestatic picture. Affected patients are at increased risk for preterm delivery and intrauterine fetal demise and should therefore be managed in conjunction with the obstetric team or transferred to a center capable of caring for premature neonates. Specific treatments include cholestyramine for pruritus and vitamin K.

Acute fatty liver of pregnancy (AFLP) occurs in the third trimester and is characterized by accumulation of microvesicular fat within hepatocytes. It is rare, occurring in 1 in 13,000 deliveries. There is a slight predilection toward primiparous and multiple gestation pregnancies. Clinical manifestations include nausea, vomiting, right upper quadrant or epigastric pain, malaise, anorexia, and jaundice progressing to fulminant hepatic failure and encephalopathy. Treatment consists of prompt delivery. Jaundice and liver dysfunction may progress after delivery but generally resolve. AFLP generally does not recur in subsequent pregnancies. Liver transplantation has been successful for this condition.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 26

Acute Pelvic Pain in Women

Ari Lipsky

PERSPECTIVE

Women of childbearing age who present with low abdominal pain often have pathologic conditions related to the female reproductive system or bladder, although additional causes must also be considered. Potential etiologic disorders range from the very benign to the immediately life-threatening. Pregnancy presents its series of considerations, and pregnancy status should be determined in all patients.

Epidemiology

Acute pain due to pelvic pathology is common, although the presenting complaint is often abdominal pain or lower abdominal pain; a complaint of low back pain may also signal pelvic pathology. A flare of chronic pelvic pain may manifest as an acute process.

In a survey of reproductive-age adult women, 39% reported that they experience nonmenstrual pelvic pain at least sometimes.[1] Among women who present to an emergency department (ED) and receive a gynecologic diagnosis, 24% of those diagnoses are for pelvic inflammatory disease (PID), 23% for lower genital tract infections (e.g., cervicitis, candidiasis, Bartholin's abscess), 12% for menstrual disorders, 12% for noninflammatory ovarian and tubal pathology (including cysts and torsion), and 4.3% for ectopic pregnancy.[2] In the general population, annually 5.8 of every 1000 women present to an ED and receive a diagnosis of PID, and 1.1 of every 1000 women are diagnosed with an ectopic pregnancy.[2]

Younger patients and those with multiple sexual partners are more likely to have PID, and a previous episode increases the likelihood of a subsequent episode.[3] The risk of ectopic pregnancy is higher in women who have had PID, pelvic surgery, or an intrauterine device. Heterotopic pregnancy is of special concern in women undergoing fertility treatment.[4] Common nongynecologic diseases, such as appendicitis, diverticulitis, urinary tract infection, and urolithiasis, remain important considerations in the woman with acute pelvic pain. Box 26-1 lists conditions accounting for pelvic pain in most women.[5,6]

Some causes of pelvic pain may lead to serious sequelae. PID carries the short-term risk of tubo-ovarian abscess, and the long-term risks of impaired fertility, chronic pelvic pain, and increased predisposition to ectopic pregnancy.[3] Rupture of an ectopic pregnancy or a hemorrhagic ovarian cyst may be acutely life-threatening. Unrecognized abuse may have serious or lethal consequences as well.

Pathophysiology

The female pelvis contains the vagina, uterus, fallopian tubes and ovaries, ureters and urinary bladder, and sigmoid colon and rectum, as well as components of the musculoskeletal system. Although pelvic pain often originates from the reproductive organs, it may arise from any structures that lie adjacent to or course through the pelvis. Visceral pain afferents supplying the pelvic organs have common innervation with the appendix, ureters, and colon. Their significant overlap makes accurate localization difficult for both patient and clinician. Pain may be initiated by inflammation, distention, or ischemia of an organ, or by spillage of blood, pus, or other material into the pelvis. Parietal pain develops when the afferent nerves in the parietal peritoneum adjacent to an affected organ are stimulated.

DIAGNOSTIC APPROACH

Differential Considerations

The differential diagnosis of pelvic pain is broad in scope (see Box 26-1). Most causes of pelvic pain fit into three categories, however: (1) those that originate in the reproductive tract, (2) those that originate in the urinary tract, and (3) those that originate in the intestinal tract. Within the reproductive tract, a subset of causes of pelvic pain is only found in pregnancy; the pregnancy test is therefore a key branch point in the diagnostic process. Potential pregnancy-related disorders can be divided into complications of early pregnancy and complications that occur further along in pregnancy. Although the specific cause of pelvic pain is not always determined at the initial ED visit, an organized approach usually leads to the confirmation or exclusion of disorders most likely to result in significant morbidity.

Pivotal Findings

It is rare that any particular finding on history or physical examination (summarized in Table 26-1) is reliable enough to conclusively make or exclude a particular diagnosis, so ancillary testing (beyond a simple pregnancy test) is commonly required in the evaluation of patients with acute pelvic pain.

The bimanual examination may at times provide important and convincing information. Unfortunately, however, findings on pelvic examination are somewhat subjective and unreliable,[7,8] and the test may be more helpful to localize the process to one side or the other, or to help focus the workup of the

BOX 26-1 POTENTIAL CAUSES OF PELVIC PAIN IN WOMEN

Reproductive Tract
Ovarian torsion
Ovarian cyst
Salpingitis/tubo-ovarian abscess
Septic pelvic thrombophlebitis
Endometritis
Endometriosis
Uterine perforation
Uterine fibroids
Dysmenorrhea

Pregnancy-Related
First Trimester
Ectopic pregnancy
Threatened abortion
Nonviable pregnancy
Ovarian hyperstimulation syndrome

Second and Third Trimesters
Placenta previa
Placental abruption
Round ligament pain

Intestinal Tract
Appendicitis
Diverticulitis
Ischemic bowel
Perforated viscus
Bowel obstruction
Incarcerated/strangulated hernia
Inflammatory bowel disease
Gastroenteritis

Urinary Tract
Pyelonephritis
Cystitis
Ureteral stone

pathologic process to the reproductive organs. For instance, tenderness on examination that seems to arise from the right ovary may be appropriately used to guide the subsequent workup, perhaps the ordering of a pelvic ultrasound study. The lack of certainty of the findings on the bimanual examination, however, do not allow the examiner to completely exclude appendicitis, especially if the pelvic ultrasound study fails to identify a clear explanation for the pain.

A sequential approach, as outlined next, allows the clinician to progressively limit the diagnostic possibilities until a sound provisional diagnosis is reached.

Symptoms

The location of *pain* and the *radiation* pattern often are helpful in focusing the differential diagnosis toward a specific cause or group of causes. Lateral pelvic pain usually is related to a process in the tube or ovary. In right-sided pain, appendicitis is considered, and in left-sided pain (especially in patients older than 40 years of age), the differential diagnosis includes diverticulitis and colitis. Urolithiasis may also manifest as lateral pelvic pain, especially when the stone is impacted at the ureterovesicular junction. Central pelvic pain usually is due to processes involving the uterus or bladder, or involving both adnexae. Pain radiating to the rectum may be secondary to pooling of fluid or blood in the cul-de-sac. Diffuse pain may occur with a bilateral process, such as PID, or with diffuse peritonitis secondary to infection or intra-abdominal hemorrhage.

Information regarding the *onset* and *duration* of pain may also be useful. Patients with uncomplicated appendicitis (without perforation or abscess) typically present within 48 hours of symptom onset. Sudden-onset pain suggests acute intrapelvic hemorrhage, cystic rupture, or ovarian torsion. Gradual-onset pain is more consistent with inflammation (such as in PID) or obstruction. Chronic or recurrent pain is consistent with endometriosis, recurrent ovarian cysts, or a persistent ovarian mass. The quality of pain may differentiate the crampy, intermittent pattern of muscular contractions along a hollow viscus (arising from, e.g., uterine, ureteral, or bowel pathology) from the steady, progressive pain associated with inflammatory or neoplastic causes, but this finding is highly variable. Pain associated with PID often manifests at the end of menses. Ovarian cyst pain may fluctuate through several menstrual cycles, finally manifesting as rupture, which often occurs in the middle of the menstrual cycle.

A complaint of fever and chills is more common with an infectious process. Nausea and vomiting occur more frequently when the process originates within the gastrointestinal tract but also may accompany ovarian torsion, ureteral colic, other causes of severe pain, and pregnancy. Dysuria and frequency occur in many local vulvar and vaginal processes, such as herpesvirus infection, candidiasis, and other types of vulvovaginitis, but urgency typically signals an irritated bladder or urethra, focusing attention on the urinary tract.

Information about the patient's last menstrual period, pattern of menses, and sexual activity pattern is useful, although such data cannot be used to rule out pregnancy. Accordingly, a pregnancy test is always indicated except in women who have had a hysterectomy or are clearly postmenopausal. In a pregnant patient, the obstetric history may provide some helpful diagnostic clues. Recurrent spontaneous abortion or previous ectopic pregnancy increases the likelihood of these conditions, respectively. Patients who are actively undergoing infertility treatment are at increased risk for ectopic pregnancy, heterotopic pregnancy, ovarian torsion, and ovarian hyperstimulation syndrome. Round ligament pain usually is noted in the second trimester. Postpartum patients are at increased risk for endometritis.

The presence, quantity, and duration of associated vaginal bleeding should be ascertained. (See also Chapters 27 and 176.) In a nonpregnant patient, bleeding may be associated with PID, trauma, dysfunctional uterine bleeding, or cervical or uterine cancer. In a pregnant patient, bleeding may be associated with a subchorionic hemorrhage in an otherwise viable pregnancy or with an ectopic pregnancy or a nonviable intrauterine pregnancy (which may continue to cause bleeding after expulsion of the uterine contents, especially if any products of conception are retained), or later in pregnancy with placenta previa or abruption. In some cases, the amount of bleeding may be substantial enough to necessitate blood transfusion and surgical intervention.

As part of the past medical history, any recent procedures should be ascertained. All women are interviewed in private to permit disclosure of sensitive information, such as a known pregnancy or recent abortion. The onset of pelvic pain shortly after uterine instrumentation increases the possibility of uterine perforation or infection. Sexual history is important, with an emphasis on recent sexual contact and previous history of sexually transmitted diseases.

Signs

The physical examination is directed toward the abdomen and pelvis. Pelvic examination is performed in virtually all patients, including pregnant patients at less than 20 weeks of gestation.

Table 26-1 Differentiation of Common or Potentially Catastrophic Causes of Pelvic Pain

CAUSATIVE DISORDER/CONDITION	PAIN HISTORY	ASSOCIATED SYMPTOMS	SUPPORTING HISTORY	PREVALENCE IN ED	PHYSICAL EXAMINATION	USEFUL TESTS	ATYPICAL OR ADDITIONAL ASPECTS
Ectopic pregnancy (critical if ruptured)	Classically severe, sharp, lateral pelvic pain, but severity, location, and quality highly variable	Vaginal bleeding	Missed period; history of previous ectopic pregnancy, infertility, tubal ligation, PID, or IUD use	Common	Classically unilateral adnexal tenderness, adnexal mass, and CMT	Pelvic US, quantitative β hCG, T&C progesterone?, laparoscopy	Cannot reliably exclude diagnosis based on history and physical; severe pain, hypotension, or peritonitis suggests rupture.
Ruptured corpus luteum cyst (emergent-critical with significant hemorrhage; otherwise, urgent)	Abrupt moderate to severe lateral pain	Light-headedness if bleeding is severe; rectal pain arises from fluid in cul-de-sac.		Uncommon	Hypotension and tachycardia if blood loss is significant; possible peritonitis	Pelvic US, CBC, T&C	Physical examination findings often do not correlate with volume of blood in pelvis at US.
Ovarian torsion (emergent)	Acute onset of moderate to severe lateral pain	Nausea and vomiting	History of ovarian mass	Uncommon	Adnexal mass and tenderness, possible peritonitis	US with Doppler flow studies, laparoscopy	Torsion can be intermittent.
Appendicitis (emergent)	Duration often <48 hr, generalized followed by localized RLQ	Low-grade fever, nausea, anorexia	Migration of pain to RLQ from center, abdominal pain before vomiting	Common	RLQ tenderness, possible peritonitis	US or CT in unclear cases	Early in course, tenderness may be minimal or poorly localized.
PID/TOA (TOA: emergent; PID: urgent-emergent)	Without TOA, pain usually bilateral. May present acutely within 48 hr, or subacutely with up to 3 wk of pain.	Fever, vaginal discharge	Vaginal discharge, history of PID, history of unprotected intercourse/ multiple partners	PID: common TOA: uncommon	Pus from cervical os, (+) CMT, adnexal tenderness. Peritonitis suggests severe PID or TOA.	CBC, ESR, CRP, pelvic US, laparoscopy, cervical cultures, cervical smear for WBCs	History and physical may be inaccurate for diagnosis, particularly in patients presenting subacutely.
UTI (urgent)	Pain with urination usually is not severe unless patient has flank pain from associated pyelonephritis.	Urinary urgency and frequency; fever and vomiting if patient has associated pyelonephritis	Recent urologic procedure, prior history of UTI	Common	Suprapubic tenderness, flank tenderness, and fever with pyelonephritis	Urinalysis, urine culture	WBC can be present in urine with PID and appendicitis.
Ureteral colic (urgent)	Acute onset, presents within hours. Pain is lateral, usually moderate to severe. Often radiates into the groin.	Nausea and vomiting	Prior history of stones	Common	Patient often appears uncomfortable, but physical examination can be otherwise unremarkable	Urinalysis: hematuria present in ~80% of cases; abdominal CT	If stone is at junction of ureter and bladder, can have localized pain that can mimic appendicitis or other acute pelvic pathology
Nonruptured ovarian cyst/tumor	Lateral ache, gradual onset	Often minimal	Prior history of similar pain	Common	Lateral pelvic tenderness, with or without a mass	Pelvic US, CBC	
Endometriosis	Unilateral or bilateral pelvic pain, often recurrent	Dysmenorrhea, dyspareunia	Prior history of same type of pain in association with menstrual cycle	Common	Unilateral or bilateral adnexal tenderness, occasionally pelvic mass present, peritoneal findings uncommon	Pelvic US, laparoscopy	Symptoms can mimic other types of pelvic pathology; laparoscopy often is needed for confirmation.

CBC, complete blood count; CMT, cervical motion tenderness; CRP, C-reactive protein; CT, computed tomography; ED, emergency department; ESR, erythrocyte sedimentation rate; β hCG, β human chorionic gonadotropin; IUD, intrauterine device; PID, pelvic inflammatory disease; RLQ, right lower quadrant; T&C, type and crossmatch; TOA, tubo-ovarian abscess; US, ultrasonography; UTI, urinary tract infection.

Pregnant patients beyond 20 weeks of gestation with complaints of vaginal bleeding undergo transabdominal pelvic ultrasound study for placental localization before the pelvic examination (see Chapter 27). Timely obstetric consultation should be obtained for patients beyond 20 weeks of gestation.

Abnormal vaginal discharge may be seen in a variety of conditions, including vaginitis, cervicitis, endometritis, and PID more generally, as well as retained foreign body. Cervical motion tenderness most commonly indicates reproductive tract inflammation, but irritation of adjacent structures (e.g., cystitis, appendicitis) also may give rise to this finding. Although an open os is most consistent with an incomplete or inevitable abortion, it does not definitively exclude an ectopic pregnancy. A large uterus in a nonpregnant patient may indicate fibroids. Fundal tenderness often is difficult to distinguish from cystitis but could suggest endometritis or necrotic fibroids. Adnexal masses and tenderness suggest cystic disease, as well as ectopic pregnancy, tubo-ovarian abscess, and torsion, especially if these findings are unilateral.

The constellation of bilateral lower abdominal tenderness, bilateral adnexal tenderness, and cervical motion tenderness is classically associated with PID, particularly when onset of the pain occurs during or just after menstruation, although the diagnosis may (and often should) be made without the presence of all three signs.

Laboratory Tests

A pregnancy test is required in almost all patients. A positive test may indicate intra- or extrauterine pregnancy or, rarely, molar pregnancy or cancer. Urine dipstick testing of a clean-catch specimen can be used to identify pyuria, typically seen in the setting of urinary tract infection, or hematuria, which is consistent with urolithiasis and also hemorrhagic cystitis. The absence of hematuria does not rule out a ureteral stone, although it lowers the likelihood. Urinalysis should be performed in all pregnant patients, even if their symptomatology does not include urinary tract complaints.

Patients who may be hemorrhaging either internally or externally should have blood drawn for a hemoglobin and hematocrit, as well as for typing and crossmatching.

Patients with a positive pregnancy test should undergo formal ultrasound assessment or bedside ED ultrasound examination to evaluate for ectopic pregnancy.[9,10] Identification of an intrauterine pregnancy by ultrasound imaging excludes ectopic pregnancy with a high degree of certainty. Heterotopic pregnancy is exceedingly rare in patients who are not undergoing assisted reproduction. Conversely, a patient with a positive pregnancy test result in whom a definite intrauterine pregnancy cannot be seen is presumed to have an ectopic pregnancy until proved otherwise. Furthermore, presence of free intra-abdominal fluid on ultrasound images is consistent with hemorrhage from either an ectopic pregnancy or a ruptured ovarian cyst and must be addressed expediently.

DIAGNOSTIC ALGORITHM

The algorithm in Figure 26-1 is designed to help focus further testing and progress to a rational provisional diagnosis. It is not unusual, however, for common diseases to present in uncommon ways or for more than one disease to be present, and tests

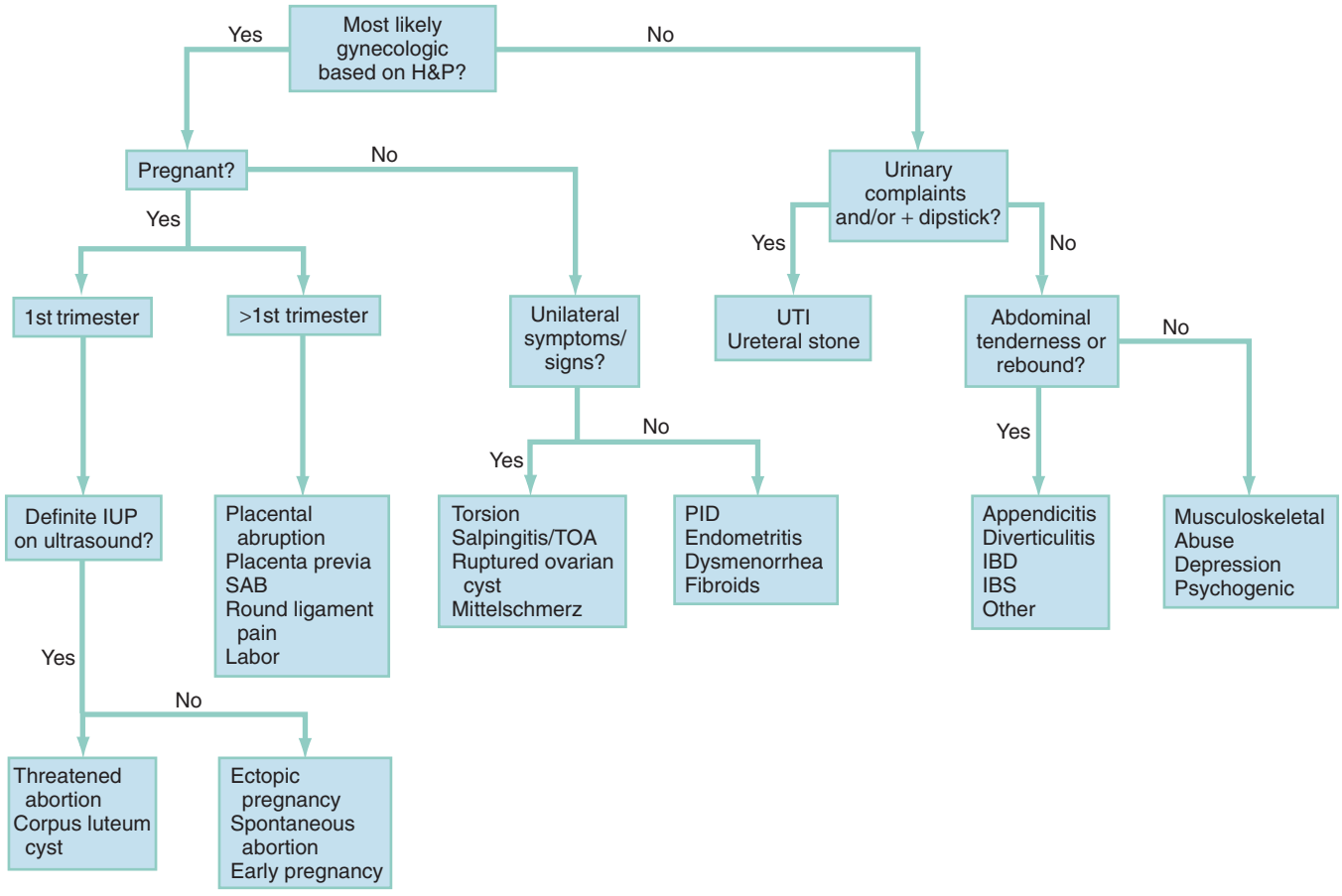


Figure 26-1. Diagnostic algorithm for acute pelvic pain. H&P, history and physical; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; IUP, intrauterine pregnancy; PID, pelvic inflammatory disease; SAB, spontaneous abortion; TOA, tubo-ovarian abscess; UTI, urinary tract infection.

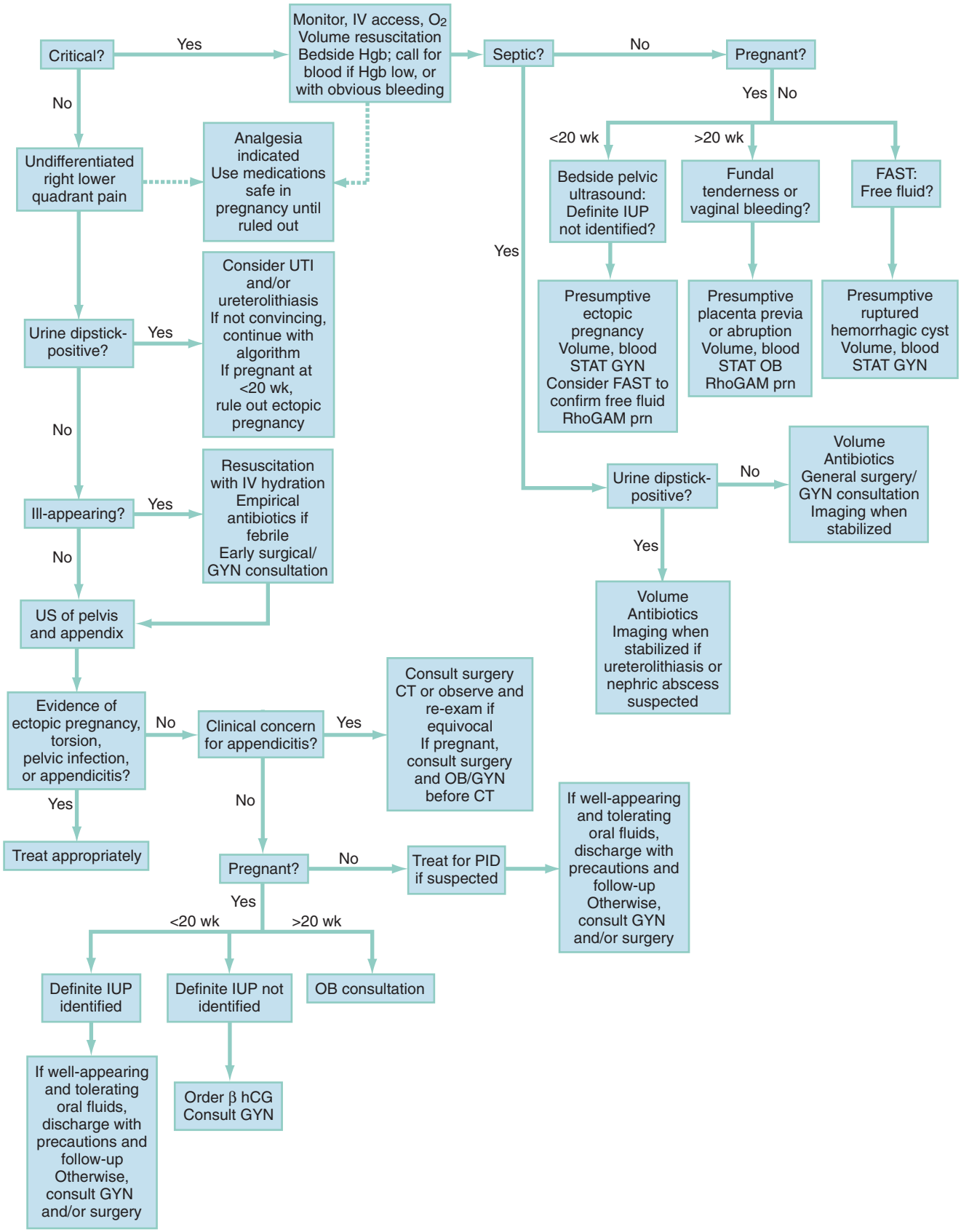


Figure 26-2. Management algorithm for acute pelvic pain: critical patients and right lower quadrant pain presentations. CT, computed tomography; FAST, focused assessment with sonography for trauma; GYN, gynecology; β hCG, β human chorionic gonadotropin; Hgb, hemoglobin; IUP, intrauterine pregnancy; IV, intravenous; OB, obstetrics; PID, pelvic inflammatory disease; US, ultrasound; UTI, urinary tract infection.

must be interpreted carefully in the context of the individual patient's presentation. As examples, patients with a positive result on urine dipstick testing may have appendicitis, and pregnant patients may suffer from ovarian torsion. With certain diseases, such as endometriosis, definitive testing is not available in the ED, and the patient's history may become the most important discriminator.

After an initial history and physical examination, the pregnancy test determines the subsequent priorities. If the patient is in early pregnancy, an ectopic pregnancy is the most emergent diagnosis to consider. Bedside or formal ultrasound assessment may rapidly confirm an intrauterine pregnancy, in which case a threatened abortion is most likely, although unilateral pain may prompt further evaluation for torsion. An empty uterus on ultrasound imaging (or any ultrasound study that cannot confirm a definite intrauterine pregnancy) is consistent with both an ectopic pregnancy and a spontaneous abortion; a very normal pregnancy is also possible. Later in pregnancy, formal ultrasound study often is indicated, and many women whose pregnancies are past 20 weeks' gestation will require observation with monitoring.

Nonpregnant patients with pain that seems to be gynecologic in nature must be assessed for hemorrhage from a ruptured ovarian cyst; for ovarian torsion; and for infection, including cervicitis, endometritis, salpingitis, and tubo-ovarian abscess. Although the history and physical examination often are sufficient to diagnose infection, formal ultrasound assessment usually is required if torsion or tubo-ovarian abscess is suspected. Ultrasound findings also may support a diagnosis of PID if evidence of salpingitis is noted, or of a ruptured cyst if a characteristic ovarian appearance is combined with presence of a small amount of free fluid. Although not as reliable as CT scanning, the ultrasound study also may be used to examine the appendix.

Because in practice it is difficult to differentiate some gynecologic origins of pain from classic intra-abdominal causes (such as right ovarian pathology from appendicitis), the workup often will require an ultrasound study or a CT scan, or both. If the cause appears to be most likely gynecologic, then an ultrasound exam of both the ovary and the appendix is more reasonable, followed by a CT scan if the ultrasound findings are negative and the presentation is possibly consistent with (say) appendicitis. Patients whose pain does not seem to be from the reproductive tract usually are found to have urinary infections or stones, abdominal sources of pain (see Chapter 21), or musculoskeletal pathology, or may be suffering from abuse or depression.

If the available data either do not make sense or conflict with the clinical gestalt, execution of the following three steps should be considered: (1) Ensure that emergent, life-threatening diagnoses have been addressed (e.g., is a reliable, negative pregnancy test recorded, so that ectopic pregnancy is ruled out?). (2) Move back up the algorithm and reassess whether the presentation may be atypical (e.g., is the examiner confident that appendicitis is not a consideration?). (3) If it seems reasonable that emergent causes are unlikely and sufficient consideration was given to less likely etiologic disorders without uncovering an apparent cause, review the possibility of depression or abuse before disposition. Follow-up planning for all patients is recommended.

EMPIRICAL MANAGEMENT

An algorithm for management of patients with acute pelvic pain is presented in Figure 26-2. Patients who are in extremis are most likely to be hemorrhaging, although on occasion their critical condition arises from septic shock. Presentations related to vaginal bleeding are discussed in Chapter 27. Ectopic pregnancy, placental abruption, and hemorrhagic ovarian cyst also may cause life-threatening hemorrhage with no or minimal vaginal bleeding. Patients with these disorders need rapid treatment with fluid and blood products and may require surgical intervention before stabilization can be achieved. A bedside ultrasound assessment by an appropriately trained operator may help the clinician reach the presumptive diagnosis expediently. The obstetric-gynecologic service should be consulted promptly. Septic shock may be a consequence of abdominal or pelvic processes and may require both general surgical and gynecologic consultations, as well as admission to an intensive care setting.

In both critical and noncritical patients, early administration of analgesia is advisable, both for patient comfort and to improve the yield of examinations. Intravenous opioids, such as morphine, are rapid and effective, titratable, and safe in pregnancy. Patients who do not appear ill and for whom a sound provisional diagnosis is reached may be discharged with close follow-up and appropriate precautions. However, pregnant patients who are at more than 20 weeks of gestation should be referred to the obstetrics service for observation. Abdominal trauma in pregnancy, especially in patients who present later in pregnancy, arouses additional concerns not addressed in this chapter.

The author would like to thank Robert Dart, MD, the previous author for this chapter.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 27 Vaginal Bleeding

Hilarie Cranmer and Mark Foran

PERSPECTIVE

Vaginal bleeding is one of the most frequent chief complaints of women presenting for emergency care. Normal vaginal bleeding occurs cyclically in women who have achieved menarche, mean age 12.5 years, until menopause, mean age 51 years, in North America. The normal cycle, defined as the first day of bleeding of one cycle to the first day of bleeding of the next cycle, lasts 28 days, plus or minus 7 days, and average volume of blood loss is 60 mL. Vaginal bleeding is defined temporally as midcycle (ovulatory), premenstrual, menstrual, and postmenstrual. Abnormal vaginal bleeding is classified on the basis of the duration, amount, and frequency of bleeding (Table 27-1). It occurs in women of all ages, and it can result from a number of causes, including anatomic abnormalities, complications of pregnancy, malignancies, infections, systemic diseases, and endocrinologic imbalances. Typically, premenarchal or postmenopausal vaginal bleeding is rarely life-threatening, but bleeding as a complication of pregnancy has a significantly increased risk of morbidity and mortality for the mother and fetus.[1,2]

Epidemiology

Approximately 5% of women aged 30 to 45 years will see a physician for vaginal bleeding. Nonpregnancy causes are classified as ovulatory, anovulatory, and nonuterine. Menorrhagia secondary to anovulation is seen in 10 to 15% of all gynecologic patients. It is common in perimenarchal and perimenopausal women, as well as in patients with endocrine disorders, polycystic ovary syndrome, exogenous hormone use, and liver or renal disease. Nonuterine bleeding must also be considered.[3] Approximately 20% of all pregnant patients have vaginal bleeding before the 20th week of gestation; more than 50% of these women spontaneously abort. Vaginal bleeding is reported in 50 to 80% of ectopic pregnancies. Ectopic pregnancy is the most common cause of maternal death in the first trimester of pregnancy, accounting for 9% of pregnancy-related maternal deaths in the United States, and the second leading cause for maternal mortality overall, after postpartum hemorrhage. Teenagers and women of color have the highest risk of death related to ectopic pregnancy. Vaginal bleeding after the 20th week of gestation occurs in approximately 4% of pregnancies; approximately 30% of cases are due to placental abruption (abruptio placentae), and 20% are due to placenta previa. Postpartum hemorrhage accounts for nearly 30% of pregnancy-related maternal deaths. The most common cause of postpartum hemorrhage in the first 24 hours is uterine atony. After 24 hours, retained products of conception are frequently the etiology.[4]

Pathophysiology

Pregnant Patients

The differential diagnosis of vaginal bleeding in early pregnancy (before the 20th week of gestation) includes ectopic pregnancy; threatened, inevitable, missed, or incomplete abortion; implantation bleeding; cervicitis; cervical conditions such as polyp or ectropion; bleeding from the urinary or gastrointestinal tract; and cervical carcinoma. Risk factors for ectopic pregnancy should increase clinical suspicion but are often absent. These include tubal abnormalities due to past infection or surgical scarring and assisted reproductive techniques. Disruption of the blood supply to the ectopic gestational sac can cause hemorrhage into the fallopian tube, or the size of the developing sac fetus can lead to rupture through the tubal wall.[5]

Spontaneous abortion is the most common complication of pregnancy and is defined as the passing of a pregnancy prior to completion of the 20th gestational week. It implies delivery of all or any part of the products of conception, with or without a fetus weighing less than 500 g. Threatened abortion is bleeding of intrauterine origin occurring before the 20th completed week, with or without uterine contractions, without dilatation of the cervix, and without expulsion of the products of conception. Complete abortion is the expulsion of all of the products of conception before the 20th completed week of gestation, whereas incomplete abortion is the expulsion of some, but not all, of the products of conception. Inevitable abortion refers to bleeding of intrauterine origin before the 20th completed week, with dilatation of the cervix without expulsion of the products of conception. In missed abortion, the embryo or fetus dies, but the products of conception are retained in utero. In septic abortion, infection of the uterus and sometimes surrounding structures occurs.[6]

Placental abruption can occur spontaneously or secondary to abdominal trauma with transmission of forces to the uterus. An increased incidence is seen in association with cocaine use, hypertension, preeclampsia, HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome, smoking, increased maternal age, and abnormal implantation of the placenta (e.g., placenta previa, accreta, increta, or percreta). Placenta previa

occurs when the implanted placenta overlays the cervical os. Bleeding is due to partial separation of the placenta from the uterine wall. Uterine atony occurs when myometrial dysfunction prevents the uterine corpus from contracting, allowing continued bleeding at the placental site. Atony is more likely to occur with conditions that overdistend the uterus, such as polyhydramnios, multiparity, prolonged labor, induced labor, high pitocin usage during labor, precipitous labor, magnesium therapy, or intrauterine infection (chorioamnionitis).[7]

Nonpregnant Patients

The pathophysiology of nonpregnant vaginal bleeding varies with age group. Children may present with foreign bodies, genital trauma, or severe vulvovaginitis causing mucosal breakdown and hemorrhage. Sexual abuse must always be considered. In adolescent girls and women, anovulatory uterine bleeding occurs when estrogen stimulates endometrium proliferation without the stabilizing effect of progesterone, causing spontaneous sloughing of the endometrium. Submucosal leiomyomas cause hemorrhage by disrupting the endometrial vascular supply and the ability of the uterus to contract to stop bleeding. Cervical and endometrial polyps have vascular pedicles and are prone to bleed.

Table 27-1 Definitions of Vaginal Bleeding

Polymenorrhea	Abnormally shortened cycle, with bleeding occurring every 21 days or sooner
Oligomenorrhea	A cycle duration of 35 days or longer
Menorrhagia	Cycle occurs at regular intervals but lasts for more than 7 days and involves the loss of more than 80 mL of blood
Hypomenorrhea	Cycle occurs at regular intervals but has a decrease in monthly blood loss
Intermenstrual bleeding	Bleeding that occurs between regular periods
Metrorrhagia	Bleeding that is frequent and irregular
Menometrorrhagia	When metrorrhagia becomes prolonged
Dysfunctional uterine bleeding	Abnormal vaginal bleeding due to anovulation
Postcoital bleeding	Bleeding after sexual intercourse, suggesting cervical pathology
Postmenopausal bleeding	Any bleeding that occurs more than 6 months after the cessation of menstruation

DIAGNOSTIC APPROACH

Differential Considerations

The differential diagnosis can be categorized by age of presentation and frequency of cause (Table 27-2). Primary coagulation disorders account for almost 20% of acute menorrhagia in adolescents. Von Willebrand's disease is the most common; however, myeloproliferative disorders and immune thrombocytopenia are also possibilities.[8] After immediate resuscitation and stabilization of unstable patients, pregnancy status is determined. Patients presenting with hemodynamic instability require intravenous access, fluid resuscitation, stabilization with blood components, and consultation with obstetrics/gynecology (or, less often, surgery). Concurrently, steps must be taken to prevent further vaginal bleeding. In hemodynamically unstable patients, surgical intervention is often necessary to control bleeding effectively. Ectopic pregnancy should be considered in all women of childbearing age who present with abdominal or pelvic complaints or with unexplained signs or symptoms of hypovolemia.

Nonuterine causes of vaginal bleeding must be included in the differential diagnosis, systematically addressed during the history taking and physical examination, and pursued with relevant investigations and consultations, if indicated. Potential sources of nonuterine bleeding include the cervix, vagina, lower urinary tract, and lower gastrointestinal tract. Cervical causes include carcinoma, polyps, condylomata, eversion of squamocolumnar junction associated with oral contraceptive use or pregnancy, trauma, and some infections. Vaginal sources of bleeding include carcinoma, sarcoma, adenosis, lacerations, infections, and retained foreign bodies. Lower urinary tract lesions, such as urethral faruncles and infected urethral diverticula, may also mimic vaginal bleeding.

Pivotal Findings (Symptoms, Signs, and Laboratory)

Symptoms

The volume, duration, and timing of bleeding should be ascertained. The average tampon or pad absorbs 20 to 30 mL of

Table 27-2 Causes of Vaginal Bleeding by Age in Descending Order of Frequency

	PREPUBERTAL	ADOLESCENT	REPRODUCTIVE	PERIMENOPAUSAL	POSTMENOPAUSAL
Most common	Vaginitis	Anovulation	Pregnancy	Anovulation	Endometrial lesions, including cancer (30%)
	Anovulation	Pregnancy	Anovulation	Uterine leiomyomas	Exogenous hormone use (30%)
	Genital trauma or foreign bodies	Exogenous hormone use	Exogenous hormone use	Cervical and endometrial polyps	Atrophic vaginitis (30%)
		Coagulopathy (von Willebrand's disease)	Uterine leiomyomas	Thyroid dysfunction	Other tumor: vulvar, vaginal, cervical (10%)
			Cervical and endometrial polyps		
Least common			Thyroid dysfunction		

vaginal effluent, although the number of pads or tampons used is unreliable because personal habits vary greatly among women. Amenorrhea may not indicate pregnancy, and bleeding during approximately the time of the last expected period does not exclude pregnancy. Bleeding during or after intercourse may indicate a cervical lesion and is more common in pregnancy because of increased blood flow to the cervix. Abdominal pain may indicate critical, emergent, or noncritical causes, depending on the severity of pain, bleeding, and hemodynamic state. During active labor, a history of previous cesarean section, cocaine abuse, or high doses of oxytocin or prostaglandins should raise the suspicion of uterine rupture. A history of trauma should be considered in an adolescent with bleeding, and sexual assault should be considered in an adult in whom abuse is present. In the pregnant patient, there is significant increased risk of maternal and fetal morbidity and mortality after blunt trauma, such as motor vehicle accident, interpersonal violence, or falls. Associated symptoms of nausea, breast tenderness, urinary frequency, and fatigue may indicate that the patient is pregnant. In the absence of pregnancy, vaginal discharge, pelvic pain, and fever may suggest pelvic inflammatory disease. Pelvic inflammatory disease is very rare during pregnancy.

Signs

A thorough evaluation includes recording and interpreting vital signs, abdominal and pelvic examinations, and, in the pregnant patient of sufficient gestational age, fetal heart tones and fundal height. Vaginal bleeding associated with hemodynamic shock alerts the clinician to ruptured ectopic pregnancy. Fetal heart tones that are diminished to less than 100 or that are absent in a gravid female may indicate fetal distress. Pelvic examination may reveal the source of bleeding; however, after the 20th week of gestation, ultrasound should precede pelvic examination to avoid disruption of a possible placenta previa. Bedside transabdominal ultrasound imaging may reveal free intraperitoneal fluid in an unstable patient, which should lead to immediate gynecologic or surgical evaluation.

Uterine size, measured from the symphysis pubis to the fundus, is the quickest means of roughly estimating gestational age. This distance in centimeters equals the gestational age in weeks (e.g., 24 cm = 24 weeks), which allows some early indication of fetal viability if delivery is necessary. Usually, 24 or 25 weeks is used as the cutoff point for fetal viability. As a rough guide, the fetus is potentially viable when the dome of the uterus extends beyond the umbilicus. Fetal heart tones can be detected by auscultation at 20 weeks of gestation or by Doppler probe at 10 to 14 weeks. If either the uterus is less than 24 cm in size or fetal heart tones are absent, the pregnancy is probably too early to be viable, and treatment is directed solely at the mother.

Ancillary Testing

In hemodynamically compromised patients, blood is obtained for hematocrit, platelet count, prothrombin time, partial thromboplastin time, ABO and Rh typing, and cross-matching of blood. Ultrasound is the imaging modality of choice for simultaneous assessment of the mother and the fetus. In the pregnant trauma patient, it is useful in the detection of major abdominal injury (sensitivity 80%, specificity 100%) and for establishing fetal well-being or demise, gestational age, and placental location.[9] Computed tomography and magnetic resonance imaging are rarely indicated in the evaluation of vaginal bleeding, except in the case of pregnant trauma patients to diagnose potentially life-threatening injuries in those patients not proceeding directly to surgical intervention.

Qualitative pregnancy tests in clinical use are typically reported as positive when the β-hCG concentration is 20 mIU/mL or higher in urine and 10 mIU/mL or higher in serum. At this level of detection, the false-negative rate for detection of pregnancy will not be more than 1% for urine and 0.5% or less for serum. In clinical use, the performance of urine qualitative testing has been found to be 95 to 100% sensitive and specific compared with serum testing. When a bedside urine test is negative and ectopic pregnancy is still being considered, a quantitative serum test should be performed. The sensitivity of quantitative serum testing for the diagnosis of pregnancy is virtually 100% when an assay capable of detecting 5 mIU/mL or more of β-hCG is used.[10] The discriminatory level of serum β-hCG for ectopic pregnancy is 1500 to 2000 mIU/mL.[11] Below this level, with no evidence of an intrauterine pregnancy (IUP) on transvaginal ultrasound, ectopic pregnancy as well as normal IUP are still possible. Above this level, ectopic pregnancy is diagnosed by the absence of an IUP on transvaginal ultrasound. In stable patients with minimal symptoms who are below the discriminatory level, serial quantitative β-hCG levels every 48 hours may distinguish ectopic pregnancy from IUP and spontaneous abortion in pregnancies less than 5 to 7 weeks of gestation. A system for close follow-up with gynecology is essential to an outpatient strategy for such patients. Additional testing such as progesterone level may help to distinguish normal verses abnormal pregnancy. A progesterone level of less than or equal to 5 ng/mL indicates a nonviable pregnancy, ectopic pregnancy, or IUP and excludes normal pregnancy with 100% sensitivity (Figs. 27-1 and 27-2).[12]

EMPIRICAL MANAGEMENT

All patients who present in shock with a surgical abdomen or evidence of intra-abdominal free fluid should be resuscitated and promptly evaluated with immediate consideration of operative intervention in consultation with obstetrics/gynecology and surgery.

Pregnant Patients

If ectopic pregnancy is suspected and the serum or urine β-hCG is positive, and the patient is hemodynamically unstable, immediate surgical consultation is indicated. If bleeding presents with shock after the 20th week of pregnancy, stabilization is performed while obtaining a transabdominal ultrasound to evaluate the placenta (location in placenta previa and separation and hemorrhage in placentae abruptio). In the presence of vaginal bleeding in these patients, bimanual or speculum vaginal examination or transvaginal ultrasound should not be undertaken until placenta previa is excluded. High-grade third-trimester bleeding should prompt immediate obstetric consultation, even before diagnostic studies elucidate the possible cause. Vaginal delivery is the preferred management of third-trimester vaginal bleeding in the absence of placenta previa, but cesarean section is indicated if (1) fetal distress is present and vaginal delivery is not imminent, (2) there is severe abruption with a viable fetus, (3) life-threatening hemorrhage exists, or (4) the patient has failed a trial of labor.

Uterine rupture may present with excessive vaginal bleeding, uterine pain, and a change in abdominal contour. A soft horizontal lump often appears below a hard fundus, representing expanding hematoma and a retracting uterus, respectively. Emergent surgical delivery is indicated.

Urgent cesarean section is performed if excessive vaginal bleeding accompanies the rupture of membranes and the fetus

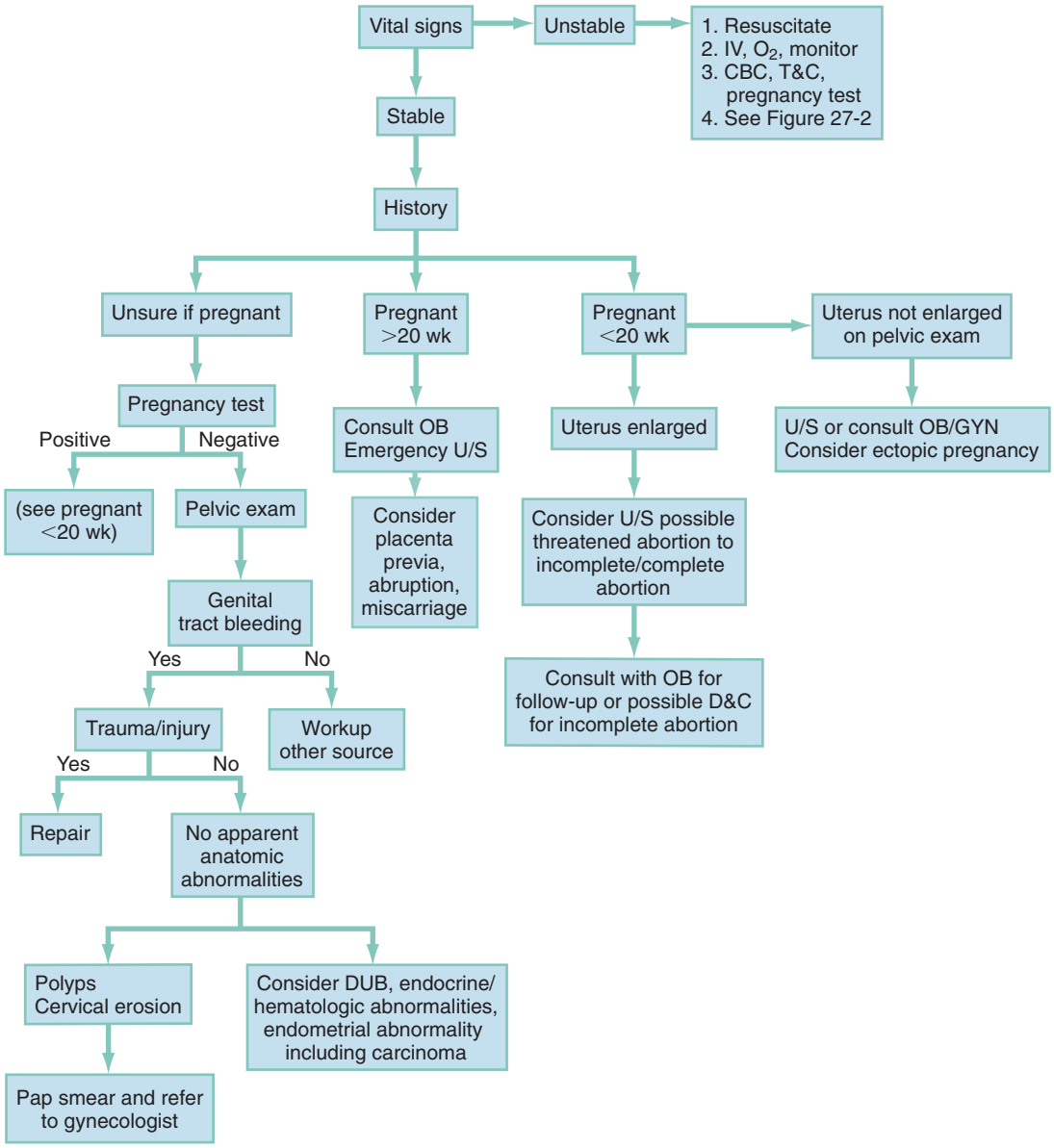


Figure 27-1. Diagnostic approach to patient with vaginal bleeding.

shows signs of distress. Painless vaginal bleeding with rupture of membranes classically suggests vasa previa; it indicates fetal bleeding and requires emergent cesarean section. If after delivery of the fetus the placenta adheres abnormally and has difficulty separating, placenta accreta is likely present and may require urgent hysterectomy to prevent life-threatening hemorrhage. If available, interventional radiology for thromboembolization may be considered. Firm bimanual compression of the uterus or insertion and inflation of a Foley catheter with a 30-mL balloon may limit hemorrhage until surgery is arranged. Uterine atony often responds to vigorous uterine massage and intravenous oxytocin.[13]

Evidence for the administration of anti-D immunoglobulin (Rhogam) for the prevention of Rh seroconversion in pregnant women is limited. Nevertheless, it is recommended to administer anti-D immunoglobulin to Rh-negative women in all cases of documented first-trimester loss of established pregnancy, including threatened abortion, incomplete abortion, and ectopic pregnancy. One may consider administration of anti-D immunoglobulin in cases of minor trauma in Rh-negative pregnant women.[14]

Nonpregnant Patients

In nonpregnant patients, heavy vaginal bleeding may be under ovulatory control or related to anovulatory dysfunctional uterine bleeding. Nonsteroidal anti-inflammatory drugs are the mainstay of treatment for both conditions, although the exact mechanism of action is not clearly understood.[15] In nonpregnant hemodynamically unstable patients, consider administering IV conjugated estrogen (Premarin) 25 mg and repeat doses if necessary until bleeding stops, usually within 1 to 5 hours. If bleeding continues after IV estrogen, insert a pediatric Foley catheter into the cervical os and inflate to tamponade the bleeding. Distend the balloon with saline until the bleeding stops. A larger balloon may be needed and this can be left in place for 12 to 24 hours.[16] Hemodynamically stable patients can be referred for outpatient ultrasound and/or endometrial biopsy. All patients with abnormal uterine bleeding should receive close follow-up from a primary care physician or gynecologist. Outpatient treatment with oral contraceptives can arrest bleeding. Patients older than 35 years or with risk factors for endometrial cancer should have an endometrial

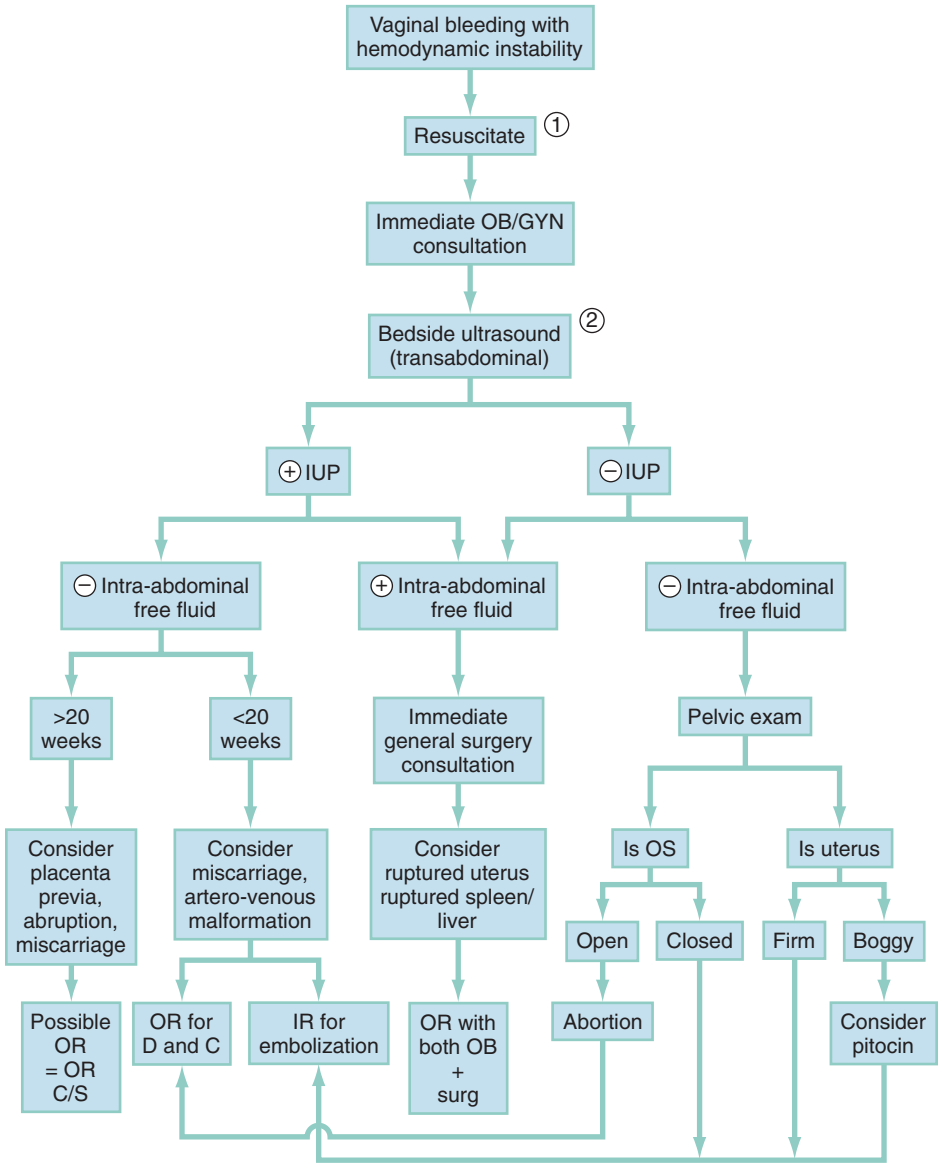


Figure 27-2. Diagnostic approach to unstable patient with vaginal bleeding.

① Consider immediate transfusion with RH negative blood products

② Transvaginal ultrasound is ideal for diagnosis but may not be available at bedside for unstable patients

IR = interventional radiology
D and C = dilitation and curretage
C/S = cesarean section
OR = operating room
IuP = intrauterine pregnancy

biopsy within one week of starting hormonal manipulation. A baseline hemoglobin/hematocrit is recommended. Finally, other medical causes, such as hypothyroidism, hemostasis disorders, or anticoagulant therapy, must be considered and appropriate outpatient consultation obtained.

DISPOSITION

In a patient with postpartum uterine atony or coagulopathy, medical management is often sufficient. Obstetrics consultation is rarely indicated. In a preadolescent patient, abuse must be ruled out before the patient is discharged to her current environment. In a nonpregnant stable patient, malignancy always should be suspected, and additional inpatient or timely outpatient gynecologic workup is indicated. Laboratory studies such as thyroid function and prolactin levels may be helpful to the consultant or in the initial outpatient workup of dysfunctional uterine bleeding, but they are not required in the emergency department setting.[17]

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 28 Back Pain

Brian D. Mahoney, Kevin G. Rodgers, and James B. Jones*

PERSPECTIVE

Back pain is a common symptom causing patients to seek care in the emergency department (ED). It accounts for 2.3% of all physician visits,[1] and 84% of the adult population have experienced low back pain in their lifetime.[2] Forty-nine percent have suffered low back pain in the last 6 months[2] and 26% in the last 3 months.[1] Total costs of low back pain in the United States exceed $100 billion per year.[3] Although mechanical or nonspecific low back is the most common cause, the differential diagnosis includes several life-threatening and disabling conditions (see Box 28-2). Developing a systematic approach that screens all the potential causes of back pain is the key to accurate clinical decision-making.

Epidemiology

Ninety-seven percent of patients presenting to a physician for evaluation of acute back pain, defined as lasting less than 6 weeks, are finally diagnosed with mechanical or nonspecific low back pain.[4] Most will recover but many will have a recurrence within a year.[5] For those with chronic back pain, defined as lasting longer than 3 months, persistence or a recurrence within 12 months is very common.[5] About 1% of all patients with back pain have true sciatica.[5] Back pain is the second most common cause of lost time in the workplace and an enormous source of health care expenditures and lost productivity.[6,7]

Before considering these common mechanical causes, several emergent diagnoses must be excluded, including aortic dissection, abdominal aortic aneurysm, cauda equina syndrome, epidural abscess, osteomyelitis, and tumor. The presence of "red flags" (Box 28-1) should prompt a more thorough examination of these possibilities. Visceral causes constitute about 2% of the diagnoses in patients presenting with back pain.[4] Aortic dissection is a rare but catastrophic event, with mortality rates exceeding 90% if it is not diagnosed. Cauda equina syndrome (bilateral leg pain and weakness, urinary retention with overflow incontinence, fecal incontinence or decreased rectal tone, and "saddle anesthesia") is a rare but disabling complication usually due to a large central herniated disk, and less often to tumor or infection. Epidural abscess and vertebral osteomyelitis comprise 0.01% of the diagnoses in patients complaining primarily of back pain.[4] Spinal carcinoma is uncommon (0.7%) in the general population presenting with back pain.[4] Of cancer patients, 80% who present with back pain have spinal metastases. Metastasis to bone is seen commonly in breast, lung, prostate, kidney, and thyroid carcinomas. Inflammatory arthritis is the diagnosis for 0.3% of patients presenting with back pain.[4]

Pathophysiology

The pathophysiology of back pain is diverse. Sources of pain include vascular, visceral, infectious, mechanical, and rheumatologic causes. Pain may originate in the spinal column, cord or root, or musculature or may be referred from thoracic or abdominal organs.

The gelatinous nucleus pulposus is surrounded by the tough anulus fibrosus. The anulus thins posteriorly, creating the opportunity for the nucleus pulposus to herniate. This varies from bulging, to protrusion, to extrusion, to sequestration. Ninety-five percent of herniations occur at the L4-5 and L5-S1 disk spaces, causing radicular pain in the L5 and S1 dermatomes.[4] Sciatica radiates below the knees, causing focal motor and sensory loss. It worsens with bending, sitting, coughing, sneezing, and straining. Involvement of the L5 nerve root presents with decreased sensation in the first web space, weakness with extension of the great toe, and normal reflexes. An S1 radiculopathy is characterized by diminished sensation of the lateral small toe, impaired plantar flexion, and a decreased or absent ankle jerk. Disk bulging (52–81%) and anular tears with focal disk protrusion (32–67%) are commonly found in asymptomatic patients, whereas disk extrusion (0–18%) is not.[8-11] Serial magnetic resonance imaging (MRI) studies show that two thirds of herniated disks regress or resolve over 6 months.[4] The fact that so many patients with herniated disk improve over time, and the high incidence of findings in asymptomatic patients argues against early MRI or computed tomography (CT). This natural resolution of symptoms in disk disease is in contrast to spinal stenosis, which tends to remain the same or worsen over time.[4]

The spinal cord ends at L1 in the adult where it gives rise to the cauda equina. Compressive lesions above the cauda equina cause upper motor neurologic signs. Compression of the cauda equina leads to lower motor neurologic findings. The ligamentum flavum can thicken with age and along with degenerative changes contributes to spinal stenosis.

DIAGNOSTIC APPROACH

Differential Considerations

The emergency physician must first rule out life-threatening and disabling causes of back pain, including thoracic aortic dissection, ruptured abdominal aortic aneurysm, epidural

*I gratefully acknowledge the work of Kevin G. Rodgers and James B. Jones on this chapter in the last edition and who figure so prominently in this new edition.

BOX 28-1 Common Historical and Physical Examination "Red Flags"

Historical Information
Recent significant trauma
Recent mild trauma in patients older than 50 years
History of prolonged steroid use
History of osteoporosis
Patients older than 70 years
Syncope
Acute onset of back, flank, or testicular pain
Diaphoresis or nausea associated with pain
History of cancer
Low back pain worse at rest or night pain
Unexplained weight loss
Recent bacterial infection
Unexplained fever > 38° C (>100° F)
Intravenous drug use
Immunocompromised status

Physical Examination
Abnormal vital signs—hypotension, tachycardia, fever
Unequal blood pressure readings in the upper extremities
Pulse deficit or circulatory compromise of the lower extremities
Pulsatile abdominal mass
Loss of rectal sphincter tone, urinary retention, or focal lower extremity weakness
Focal back pain with fever

BOX 28-2 Differential Considerations in Acute Low Back Pain

Emergent
Aortic dissection
Cauda equina syndrome
Epidural abscess or hematoma
Meningitis
Ruptured/expanding aortic aneurysm
Spinal fracture or subluxation with cord or root impingement

Urgent
Back pain with neurologic deficits
Disk herniation causing neurologic compromise
Malignancy
Sciatica with motor nerve root compression
Spinal fractures without cord impingement
Spinal stenosis
Transverse myelitis
Vertebral osteomyelitis

Common or Stable
Acute ligamentous injury
Acute muscle strain
Ankylosing spondylitis
Degenerative joint disease
Intervertebral disk disease without impingement
Pathologic fracture without impingement
Seropositive arthritis
Spondylolisthesis

Referred or Visceral
Cholecystitis
Esophageal disease
Nephrolithiasis
Ovarian torsion, mass, or tumor
Pancreatitis
Peptic ulcer disease
Pleural effusion
Pneumonia
Pulmonary embolism
Pyelonephritis
Retroperitoneal hemorrhage or mass

abscess or compressive mass, spinal column injury with cord or root compression, and cauda equina syndrome. An accurate history and physical examination guides the investigation of possible more serious underlying pathologic process (Boxes 28-1 and 28-2).[4,12] Laboratory and imaging are needed in some cases, but it is usually possible to rule out significant pathology without recourse to extensive testing.

Rapid Assessment and Stabilization

If the initial history and physical examination identify any suggestion of serious disease, rapid stabilization measures should ensue consistent with the cause of concern (Fig. 28-1). Management of aortic dissection, ruptured abdominal aortic aneurysm, and spinal cord and column injuries are covered in other chapters. If epidural abscess or cauda equina syndrome is suggested, emergent MRI and neurosurgical consultation then should be obtained based on the results of the scan. For epidural abscess, blood cultures are obtained followed by intravenous (IV) administration of antibiotics against *Staphylococcus aureus*. For cauda equina syndrome, an urgent neurosurgical consultation is required. Although the evidence supporting steroid use is conflicting, dexamethasone is commonly used with the hope of decreasing compression from inflammation or to shrink tumor mass. For all patients with significant pain, including patients with "benign" causes for back pain, effective analgesia should be provided early in the evaluation.

Pivotal Findings

History

History of Present Illness. The history helps to localize pain to the most likely structure and mechanism. The following questions are useful in differentiating between mechanical and nonmechanical causes and will help guide appropriate management.

Where is the pain? The patient is asked to point with one finger to the one spot where it hurts the most. Does the pain radiate to the legs and, if so, specifically where in the legs? Does the pain conform to a specific dermatomal area? Radicular pain, particularly extending below the knee in a dermatomal distribution, implies nerve root involvement. Pain mainly in the paralumbar musculature without dermatomal radiculopathy implies nonspecific low back pain. Any associated chest or abdominal pain may indicate a possible visceral cause. Flank location implies a renal origin, and a higher location can be from the chest or pleura.

When did the pain start? The patient should describe in detail what he or she was doing when the pain started. Has there been a recent change in type or intensity of physical activity? Is there any past history of back pain, and what therapeutic modalities were used to treat it? If there is a history of back pain, is there any difference between present and past pain? Acute onset associated with a specific task suggests a mechanical cause. Sudden-onset, severe back pain suggests aortic dissection. Slow onset or onset unrelated to activity suggests a nonmechanical cause (e.g., tumor). Non-

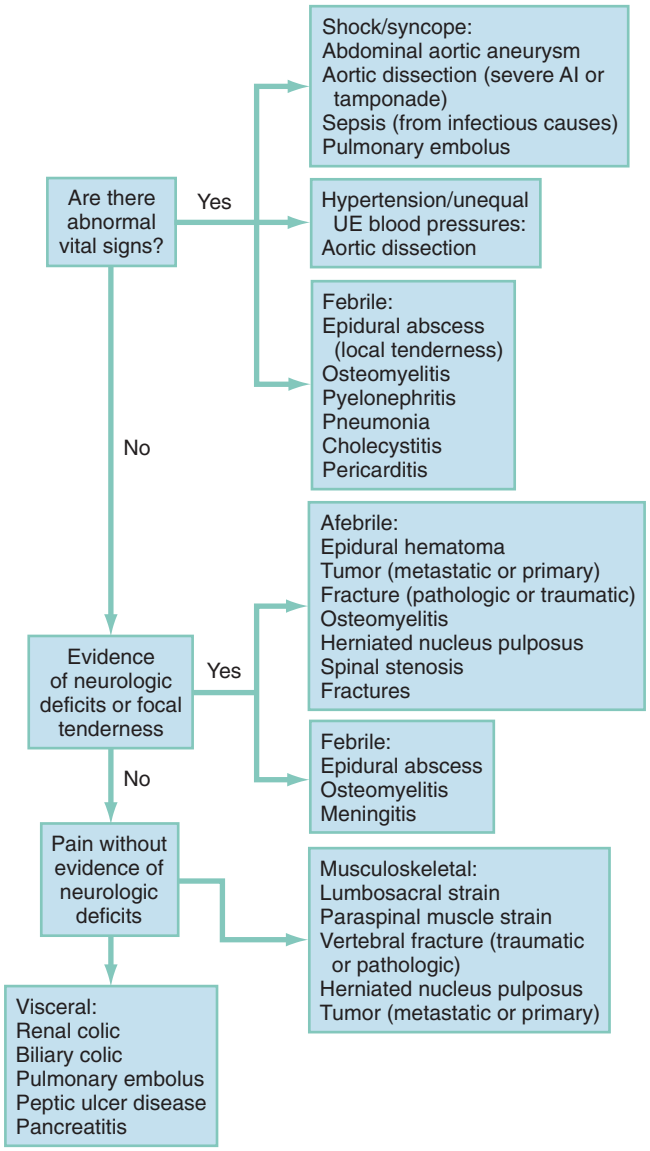


Figure 28-1. Rapid assessment of acute low back pain. AI, aortic insufficiency; UE, upper extremity.

mechanical pain may improve then recur, but the trend is progressive worsening.

Are there any aggravating or alleviating factors? Cough or Valsalva maneuver that aggravates the pain in general favors a mechanical cause and may point specifically to a herniated disk. Patients with back pain associated with tumors and infectious causes often present with nighttime pain and persistent pain unrelieved by rest and analgesics. Spinal stenosis presents with diffuse back pain, numbness, and tingling in one or both legs (pseudoclaudication). Symptoms are aggravated by ambulation (especially "downhill") and relieved with spinal flexion, which increases spinal canal diameter, temporarily relieving the stenosis. Direct trauma may suggest contusion, strain or fracture, while deceleration may suggest aortic dissection.

Is there motor or sensory loss, bowel or bladder dysfunction? Back pain associated with progressive or severe neurologic symptoms, motor loss, or urinary retention or bowel incontinence requires MRI or CT, which may indicate the need for emergent decompression.

Is there other pertinent history? Other pertinent history should include work history, past and present (a history of repeated loading would suggest mechanical cause); fever (suggesting infectious cause); medications (anticoagulants associated with epidural hematomas, steroids associated with infection and compression fractures); hematuria (suggest nephrolithiasis or pyelonephritis); and pending litigation or worker's compensation status (possible secondary gains).

Past Medical History. In addition to any history of back disorders, a thorough inquiry about any systemic disease is important. Ask if there is a history of (1) cancer (metastatic disease), (2) inflammatory disease, (3) IV drug abuse (diskitis), (4) arthropathies, (5) endocrinopathies (hyperparathyroidism), (6) bleeding disorders, (7) osteoporosis, or (8) sickle cell disease. Previous atherosclerotic or vascular disease suggests aortic disease; previous kidney stones or alcohol-related disease may suggest related disease. Knowledge of medications or other modalities used to treat present and past symptoms informs direct treatment decisions. Knowledge of current medications used by the patient gives clues about the presence of other systemic disease. The family history also is assessed. Diseases such as spondyloarthropathies (e.g., ankylosing spondylitis) have a familial component.

Physical Examination

Vital Signs. Vital signs are important because alterations may suggest a life-threatening process (e.g., hypotension and tachycardia with ruptured abdominal aortic aneurysm, hypertension with aortic dissection, fever with abscess, osteomyelitis, or diskitis).

Lower Back Inspection.

1. Observe the patient's gait and movement in the examining room. Does the patient move cautiously, protecting himself or herself, or freely and appear to be in little pain?
2. Examine the patient while standing, searching for scoliosis (may be structural or secondary to muscle spasm), increase or decrease of lumbar lordosis or thoracic kyphosis (may predispose to mechanical pain), or pelvic obliquity (may indicate muscle spasm, leg-length discrepancy, or uncompensated scoliosis).
3. Assess the range of motion for the low back. Patients with significant mechanical pain usually flex without reversing the normal lumbar lordosis, and extension may aggravate facet causes or nerve root impingement.
4. Perform the palpation in an orderly fashion with the fingertips to localize the area of greatest tenderness (e.g., specific spinous process, paravertebral musculature).

Other Examinations, Including Neurologic Examination.

1. The neurologic assessment evaluates the asymmetry of reflexes (clinically, reflexes diminish with age, and uncovering asymmetry is key), dermatomal sensory loss, and focal muscle weakness (suggests nerve root impingement). If possible, motor testing of the legs is best done with the patient standing. Heel-walking and toe-walking indicate normal plantar and dorsiflexion strength, and a partial knee bend while bearing weight on one leg, then the other, indicate normal hip, buttock, and thigh muscle strength. A patient with a long history of back pain should be asked about previous motor, sensory, or reflex abnormality. The presence of clonus, hyper-reflexia, or upgoing toes (Babinski's sign) indicate an upper motor neuron lesion.
2. A rectal examination can assess sphincter tone and anal wink. Testing for perianal sensation is necessary if there is any history of bowel or bladder dysfunction.

3. A head-to-toe examination looking for signs of systemic disease should include cardiac and pulmonary auscultation; abdominal examination for tenderness, aneurysm, or masses; and palpation of peripheral pulses.
4. The hips are examined for a musculoskeletal or inflammatory focus other than the back.

Straight Leg Raise. The straight leg raise is the classic test for sciatic nerve root irritation. It is sensitive but not specific for disk disease.[4] This test is often negative in patients with spinal stenosis. With the knee extended, the leg is elevated until pain is elicited. A positive result is pain radiating down the leg below the knee in a dermatomal distribution when the leg is elevated to less than 90° (not back, buttocks, or thigh pain). Pain referred to an affected leg ("crossover pain") with straight leg raise of the unaffected leg is insensitive but highly specific for nerve root irritation. In a patient who may be malingering, the straight leg raise can be done with the patient sitting with the knees flexed at the side of the bed and then passively straightening the legs. If there is true nerve root irritation, results should be similar in the sitting and the supine positions.

Ancillary Testing

Laboratory Tests. For mechanical causes of back pain, laboratory studies are of little use. For nonmechanical causes, erythrocyte sedimentation rate and complete blood count may be useful if inflammatory disease is suggested, but are rarely of use in the ED. Urinalysis is helpful in possible cases of renal disease with referred back pain (nephrolithiasis, pyelonephritis, urinary tract infection).

Imaging. Although patient satisfaction is reportedly improved when imaging is performed,[13] plain radiographs are not useful in uncomplicated mechanical low back pain of less than 6 weeks duration.[12] If the patient has a history of trauma with bony tenderness or focal signs of trauma, neurologic deficit, cancer, unexplained weight loss, pain that persists at rest or at night, advanced age, osteoporosis, prolonged glucocorticoid use, or fever, plain radiographs may be helpful.[13] Plain radiographs should not be obtained, however, if advanced imaging (e.g., CT, MRI) is planned. Most patients do not require radiographic evaluation while in the ED.[14]

Emergency MRI, CT, or myelogram (in order of preference) is indicated if an acute, significant neurologic deficit such as motor loss or cauda equina syndrome is present. For patients with acute back and radicular pain but no motor weakness, and for those with chronic low back pain without neurologic deficit, obtaining MRI and CT does not improve outcome.[15-17] Eighty-four percent of patients with sciatica will recover without surgery.[18] For patients in whom infection or tumor is suggested, MRI (or bone scan followed by MRI) is the diagnostic test of choice.[19] The degree of neurologic impairment and patient stability dictates whether these tests are obtained on an emergent or urgent basis.

DIFFERENTIAL DIAGNOSIS

After stabilization and assessment, the clinical findings aid in narrowing the differential diagnosis (Table 28-1). An algorithm

Table 28-1 Classic Findings in Selected Serious Causes of Acute Back Pain

	DIAGNOSES	HISTORY	IMPORTANT PHYSICAL EXAMINATION FINDINGS	ANCILLARY TESTING	COMMENTS
Critical					
Vascular	Aortic dissection	Often sudden-onset, "tearing" severe pain. Associated nausea, vomiting, acute anxiety are common. Syncope can occur	Associated diaphoresis, unstable vital signs. Hypertension is common. Unequal upper extremity blood pressure. New-onset aortic insufficiency murmur. Central and peripheral neurologic deficits secondary to ischemia	Choice of CT, MRI, aortogram depends on patient stability and availability of equipment	More common as a chest pain cause, but low back pain may be only complaint
	Abdominal aortic aneurysm (ruptured/expanding)	Pain may radiate to back, flank, or testicle. Patient may present with syncope	Pulsatile abdominal mass (especially if right of midline), abdominal bruits. Diminished lower extremity pulses or hypoperfusion or both	Bedside US. If "stable," abdominal CT with contrast. Plain films may show a calcified enlarged aortic contour	Can also mimic renal colic, GI bleeding, diverticulitis, and myocardial infarction. 30% of signs are misdiagnosed
Infectious	Spinal epidural abscess	At-risk population with diabetes, chronic renal failure, intravenous drug use, alcoholism, cancer, or recent spinal surgery or trauma. Sepsis-linked history is common	Fever, reproducible radicular pain, other signs of sepsis. Localized body tenderness along spine Focal neurologic deficits are late findings (<50% patients). Rare cauda equina–like syndrome	CBC, blood cultures useful but nonspecific. MRI modality of choice. CT or myelography can be used. Search for source of infection. *Staphylococcus aureus* common cause (70%)	Presents as mass-occupying lesion compressing spinal cord; may be hematoma, malignancy, disk. Often begins as focal pyogenic infection in disk. Biopsy may be necessary

Table 28-1 Classic Findings in Selected Serious Causes of Acute Back Pain—cont'd

	DIAGNOSES	HISTORY	IMPORTANT PHYSICAL EXAMINATION FINDINGS	ANCILLARY TESTING	COMMENTS
Mechanical	Cauda equina syndrome	Usually a history of back pain. Symptoms may develop over hours	Urinary retention and fecal incontinence. Saddle anesthesia, bilateral leg pain. Lower extremity weakness with hypo-reflexia	CT with or without contrast, MRI useful	Can result in severe dysfunction. An emergent condition caused by compression of lumbosacral nerve roots
	Spinal fracture with cord impingement	Acute onset, localized pain. Usually trauma history. Older population with osteoporosis also at risk	Bone tenderness, radicular, or cord compression findings	Plain films initially, then CT or MRI	Symptoms/signs depend on level
	Epidural hematoma	Usually patient with coagulation disorder, hereditary or acquired (e.g., anticoagulants). May occur after epidural anesthesia	Radicular findings (neurologic defects). Neurologic pattern similar to abscess	MRI, CT, or myelography	Can also occur in AV malformations
Emergent					
Infectious	Vertebral osteomyelitis	At-risk group similar to that for epidural abscess. Onset may be insidious. Back pain, tenderness, and stiffness may precede neurologic findings by significant time period	Fever and other constitutional symptoms. Localized body tenderness of two adjacent vertebrae	CBC, blood cultures generally low yield. Plain films diagnostic 80–95%, but MRI more accurate and detailed	Biopsy may be necessary for diagnosis. *S. aureus* most common
Immune	Transverse myelitis	Back pain and neurologic deficits. Almost 50% of patients worsen maximally in 24 hr	Partial/total loss sensory, motor, autonomic, and sphincter function below the level of the lesion. Leg weakness more common; arm involvement is rare. Bladder (bowel control) involved in most patients	Goal is to rule out mass lesion compressing the cord. Thought to be autoimmune origin. MRI is imaging modality of choice. Contrast CT and CT myelogram may be obtained	May be associated with multiple sclerosis, SLE, sarcoidosis. Also associated with Lyme disease. Epstein-Barr virus, and other viral (herpes, enterovirus) or bacterial (tuberculosis syphilis) infections
Mechanical	Back pain with neurologic deficits Intervertebral disk herniation Spinal stenosis Spinal fractures without cord impingement Malignancy Sciatica with potential of nerve root compression	Most patients recall atraumatic mechanisms (lifting, twisting). Common complaints are stiffness, tenderness, decreased range of motion	Positive straight leg raise test. Muscular weakness. Potential for sensory deficits. Absent or diminished deep tendon reflexes	Selective use of plain films. CT or MRI performed for complete assessment when "red flag" present	Search for "red flags" (see Box 28-1) to rule out serious underlying disease

AV, arteriovenous; CBC, complete blood count; CT, computed tomography; GI, gastrointestinal; MRI, magnetic resonance imaging; SLE, systemic lupus erythematosus.

(see Fig. 28-1) that takes into account important differential considerations, such as abnormal vital signs, the presence of fever, and an abnormal neurologic examination, is a useful tool. After collecting this information the emergency physician should be able to answer two additional key questions. *Does the patient need emergent, urgent, or more routine treatment? Does the patient need surgical or medical treatment?* Young children for whom there is no clear explanation of their back pain warrant earlier and more extensive evaluation for infection and tumor.

EMPIRICAL MANAGEMENT

The initial empirical management of acute back pain depends on the presenting vital signs and the patient's overall appearance. Figure 28-2 details the specific management considerations for treating unstable patients.[20-26] For a stable patient, early effective pain management can be of significant value. The choice of analgesic is dictated by the patient's and physician's perception of the degree of pain. Physicians notoriously underestimate and undertreat pain, especially acute and chronic low back pain. If the pain is severe, IV opioids are the preferred analgesic and should be given in a titrated fashion. Frequent reassessment of the patient for an adequate response is required. After adequate response to the initial IV opioid, an oral agent can be administered in preparation for discharge. For patients with less acute symptoms, an oral opioid or a nonsteroidal anti-inflammatory drug (NSAID) is appropriate. NSAIDs are effective for short-term relief of acute low back pain but are not superior to acetaminophen.[27] Their safety profiles must be considered in patients with acid peptic disease, renal insufficiency, diabetes, and liver pathology. NSAIDs are routinely used for chronic back pain, but evidence for their effectiveness is lacking.[28] Muscle relaxants such as

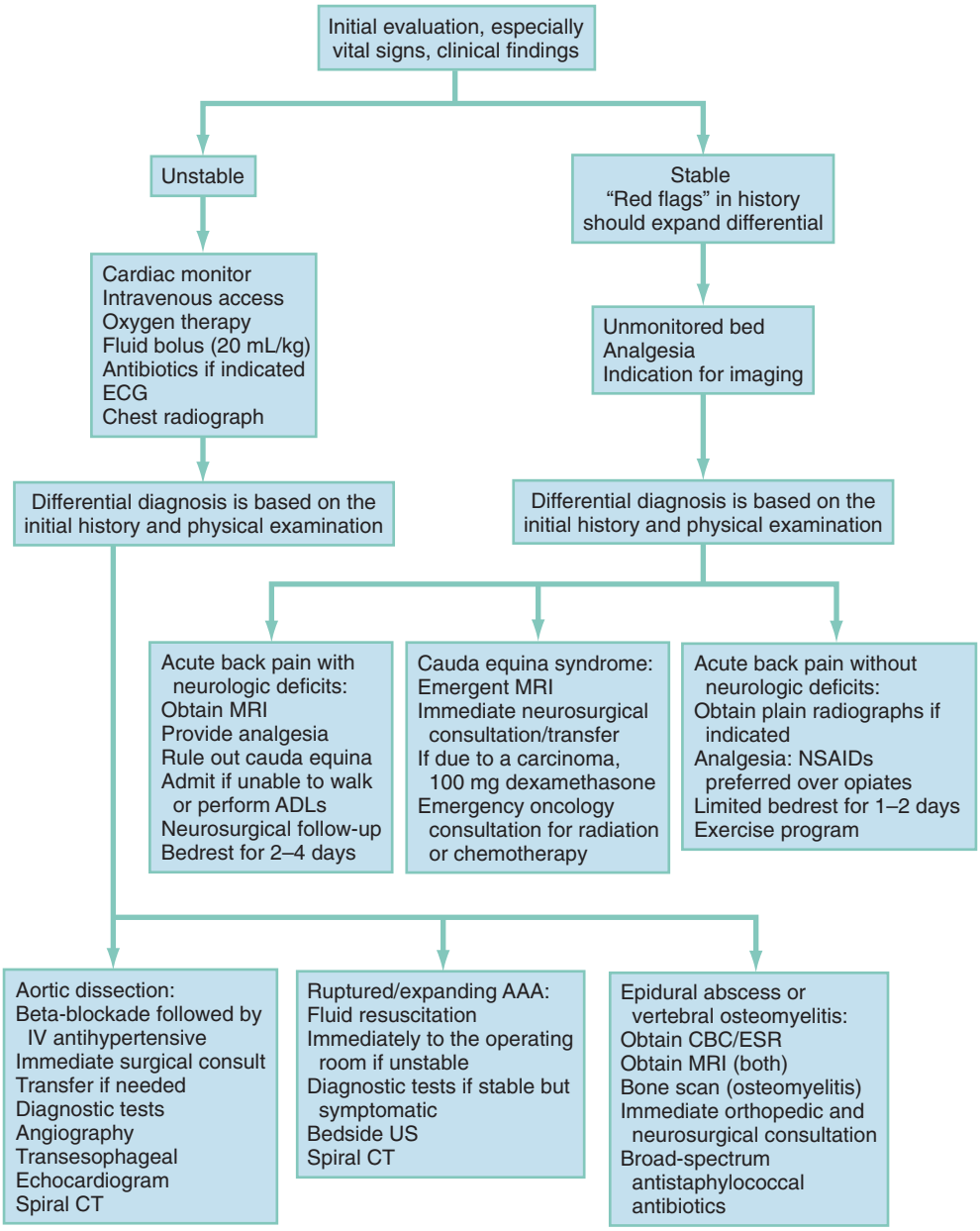


Figure 28-2. Management of acute low back pain. AAA, abdominal aortic aneurysm; ADLs, activities of daily living; CBC, complete blood count; CT, computed tomography; ECG, electrocardiogram; ESR, erythrocyte sedimentation rate; IV, intravenous; MRI, magnetic resonance imaging; NSAIDs, nonsteroidal anti-inflammatory drugs; US, ultrasound.

benzodiazepines and cyclobenzaprine (Flexeril) may be effective adjuncts for acute low back pain, but their significant adverse side effects require they be used with caution.[29,30]

For some patients, chronic recurrent mechanical back pain is a long-term issue. Such patients need support, and often a multidisciplinary approach to help manage their chronic pain or recurrent flare-ups. Management and follow-up require referral to primary care or a pain clinic. Tools that may be tried by their primary care or pain clinic may include lumbar supports,[31,32] traction,[33] acupuncture,[34] spinal manipulative therapy,[35] physical therapy or chiropractic therapy,[36] back education,[37] massage,[38] exercise therapy,[39] transcutaneous electrical nerve stimulation (TENS),[40] heat therapy,[41] epidural injection of methylprednisolone,[42–44] and tricyclic or tetracyclic antidepressant therapy.[45] ED treatment is directed to relief of their current exacerbation.

DISPOSITION

The disposition of patients with back pain depends on their diagnosis. Patients with one of the life-threatening or disabling causes require admission and further emergent treatment. Patients with acute cord compression from a fracture, disk protrusion, abscess, or hematoma require urgent neurosurgical evaluation.

Patients who are unable to walk or require IV analgesics for adequate pain control should be considered for admission to hospital or the ED observation unit. If pain can be controlled using oral analgesics, patients can be discharged with appropriate follow-up. Reassure the patient with acute mechanical back pain that the vast majority of patients eventually experience spontaneous relief of pain. Prescribe NSAIDs, supplemented with oral opioids for moderate to severe pain, and refer the patient for primary care. Oral opioids may be effective for short-term relief, but long-term efficacy is less clear and aberrant medication taking occurs in up to 24% of cases of chronic back pain.[46,47] Repeat visits to the ED for chronic back pain can be a source of frustration for the physician and the patient. Patients frequently receive prescriptions for pain relief and referral for primary care but for many reasons do not complete this referral. For such a chronic, recurring, painful condition, repeat visits to the doctor are to be expected. Short-term oral opioids plus NSAIDs or acetaminophen may be what the patient needs. Rather than a consistent relationship with a primary care provider, repeat visits to the ED raise the possibility of drug seeking. For those patients, it may become necessary for the ED physician to prescribe simple analgesics such as NSAIDs instead of narcotics. Encourage patients to maintain activities as their pain allows, avoiding heavy lifting or twisting during the acute phase. Advise patients to avoid strict or prolonged bedrest as it is no more effective and may be worse than maintaining reasonable activities.[48,49]

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 29 Cyanosis

Madonna Fernández-Frackelton and Jennifer Bocock

PERSPECTIVE

Epidemiology

Cyanosis is a blue or purple appearance of the skin or mucous membranes. This clinical finding is secondary to inadequately oxygenated blood perfusing peripheral tissues or the presence of abnormal hemoglobin forms unable to bind oxygen or to supply adequate oxygen to end organs and tissues. Cyanosis is a relatively rare presenting chief complaint in the emergency department (ED) and is most commonly noted in patients with a hypoperfused state or known cardiopulmonary disease, including congenital heart disease.[1] Although carbon monoxide poisoning and cyanide toxicity result in difficulty with hemoglobin oxygenation or tissue hypoxia, these entities typically do not present with the clinical finding of cyanosis and are discussed in other chapters.

Pathophysiology

Cyanosis is evident on physical examination when the absolute amount of desaturated (unoxygenated) hemoglobin in the circulating capillary blood (>4–5 g/dL in whole blood) is elevated. It is not a percent of desaturated total hemoglobin mass or a decreased amount of oxyhemoglobin. For this reason patients with a relatively low hemoglobin exhibit cyanosis at a much lower partial pressure of oxygen (Pao_2) and arterial oxygen saturation (Sao_2) than those with normal hemoglobin levels. Cyanosis is an insensitive indicator of tissue oxygenation.[2] Its presence suggests hypoxia, buts its absence does not exclude it.

Abnormal hemoglobin forms contribute significantly to cyanotic disease. Under normal conditions, red blood cells (RBCs) contain hemoglobin with iron in the reduced ferrous state (Fe^{2+}). The iron molecule may be oxidized to the ferric state (Fe^{3+}) to produce methemoglobin. This reaction impairs the ability of hemoglobin to transport oxygen to and carbon dioxide from the tissues. The oxygen dissociation curve is shifted to the left, resulting in tissue hypoxia and lactic acid production (Fig. 29-1). Methemoglobin normally accounts for less than 1% of total hemoglobin.[3] Cyanosis results when greater than 10 to 15% of the total hemoglobin is methemoglobin (≥1.5 g/dL) that has a dark purple-brown color, even when exposed to room air. Methemoglobin is reduced to ferrous hemoglobin primarily by nicotinamide adenine dinucleotide (NADH) cytochrome-b_5 reductase, an enzyme system present within RBCs. A secondary NADPH-dependant system uses glutathione production and glucose-6-phosphate dehydrogenase (G6PD) to reduce methemoglobin to hemoglobin. This secondary pathway normally plays a minor role, but is accelerated by methylene blue.[3]

Primary methemoglobinemia is a congenital error of enzyme metabolism, with either diminished levels of NADH reductase or an abnormally functioning enzyme. Patients may present with cyanosis in a stable compensated state. Acquired methemoglobinemia occurs when methemoglobin production (hemoglobin oxidation) is accelerated beyond the capacity of NADH reductase activity. This usually occurs as a drug reaction. (See Box 29-1 for common causes.) Newborns are at risk for methemoglobinemia because their NADH reductase activity is relatively low.[3]

DIAGNOSTIC APPROACH

Differential considerations for patients presenting with cyanosis are listed in Box 29-2.

Pivotal Findings

Symptoms

The onset, duration, and time of day of symptoms, and any previous episodes should be noted. Precipitating factors may include exposure to cold air or water, high altitude, or exercise in patients with a history of cardiopulmonary disease. Additional history should include known congenital heart disease or cardiopulmonary disease, hypercoagulable states, and any family history of cyanotic disease or hematologic illness. A history of home or occupational exposures to fumes or chemicals should be obtained, including aniline, azo dyes (pyridium), phenacetin, and nitrates.[4] A drug history should be reviewed, including use of prescription and over-the-counter medications, health food supplements, and herbal or alternative preparations.[5] The potential of pseudocyanosis resulting from exposure to dyes, heavy metals, or topically absorbed pigments should be explored.[2]

In infants, congenital heart disease is suggested by difficulty feeding, sweating, lethargy, poor weight gain, or respiratory distress. Episodic cyanotic events, or "Tet spells," may be seen in children with tetralogy of Fallot (ventricular septal defect, overriding aorta, pulmonary stenosis or atresia, and right ventricular hypertrophy with outlet obstruction). These patients present with cyanosis, tachypnea, and anxiety due to

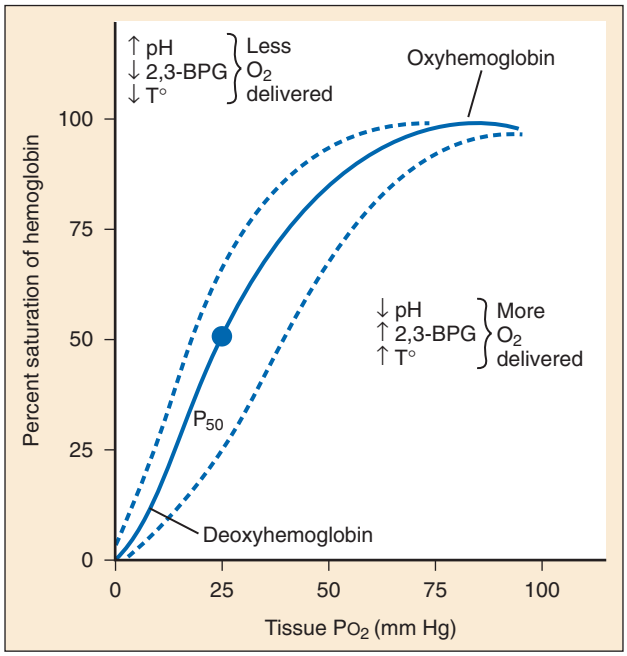


Figure 29-1. Hemoglobin-oxygen dissociation curve. Deoxyhemoglobin does not bind oxygen efficiently. Methemoglobin has a high affinity for oxygen molecules and does not readily release oxygen to the peripheral tissues. This shifts the normal oxygen dissociation curve to the left, resulting in hypoxia and lactic acid production. Typically, when acid is produced in the tissues, the dissociation curve shifts back to the right, facilitating oxygen release; however, the high affinity of methemoglobin prevents this normal process. (Redrawn from Benz EJ Jr: Hemoglobinopathies. In Harrison's online.) 2,3-BPG, 2,3-bisphosphoglycerate; P_{O_2}, partial pressure of oxygen; P-50, oxygen half saturation pressure of hemoglobin; T°, temperature.

BOX 29-1 COMMON CAUSES OF METHEMOGLOBINEMIA

Hereditary
Hemoglobin M
NADH methemoglobin reductase deficiency (homozygote and heterozygote)

Acquired
Medications
Amyl nitrite
Antineoplastics (cyclophosphamide, ifosfamide, flutamide)
Celecoxib
Dapsone
Local anesthetics (benzocaine, lidocaine, prilocaine)
Nitroglycerin
Nitroprusside
Phenacetin
Phenazopyridine (pyridium)
Quinones (chloroquine, primaquine)
Sulfonamides (sulfanilamide, sulfathiazide, sulfapyridine, sulfamethoxazole)

Chemical Agents
Aniline dye derivatives (shoe dyes, marking inks)
Butyl nitrite
Chlorobenzene
Fires (heat-induced denaturation)
Food adulterated with nitrites
Food high in nitrates
Isobutyl nitrite
Naphthalene (mothballs)
Nitrophenol
Nitrous gases (seen in arc welders)
Paraquat
Silver nitrate
Trinitrotoluene
Well water (nitrates)

Pediatric
Reduced NADH methemoglobin reductase activity in infants (4 mo)
Seen in association with low birth weight, prematurity, dehydration, acidosis, diarrhea, and hyperchloremia

NADH, reduced nicotinamide adenine dinucleotide.
Modified from Goldfrank LR: Toxicologic Emergencies, 6th ed. Stamford, Conn, Appleton and Lange, 1998.

decreased pulmonary blood flow with shunting of unoxygenated blood into the peripheral circulation.[6,7]

Signs

There is significant interobserver variability in detecting cyanosis on physical examination. Room lighting and temperature may affect examination of the skin and mucous membranes. A patient's natural skin tone, thickness, and pigmentation also may alter findings.

Central cyanosis is often secondary to the shunting of venous unsaturated hemoglobin into the arterial circulation or the presence of abnormal hemoglobin. A bluish discoloration of the skin and mucous membranes is best seen on perioral skin, oral mucosa, or conjunctivae.

Peripheral cyanosis is secondary to vasoconstriction and slow flow of normally oxygenated hemoglobin in arterial blood, allowing for greater oxygen extraction by the tissues. Peripheral cyanosis affects capillary beds and typically is seen in the extremities and nail beds. Differential cyanosis may occur in either the upper or lower (or the right or the left) half of the body, with the remainder appearing well oxygenated. This form of cyanosis usually is seen in cases of cyanotic heart disease with multiple anomalies.

Vital signs should be obtained on all patients. Temperature is typically normal. Blood pressure and heart rate may be high, normal, or low depending on the underlying cause. Upper airway obstruction and other signs of respiratory insufficiency should be sought. Intermittent apnea in infants suggests central nervous system immaturity or a central lesion. Infants with cyanosis, increased respiratory depth, periodic apnea episodes, or diaphoresis with feeding may have congenital heart disease.[6] Tachypnea (>60 breaths/min) in a newborn may indicate a pulmonary disorder, congenital heart disease, infection, a metabolic disorder, or central nervous system pathology.[8]

General appearance and mental status should be evaluated. The head, eyes, ears, nose, and throat examination may reveal central cyanosis. Funduscopic examination may detect dilated tortuous veins and papilledema in patients with cyanotic congenital heart disease.[9] Jugular venous distention may be seen on the neck examination in patients with pulmonary edema.

The chest examination may reveal crackles, wheezing, or inadequate ventilation. Heart sounds should be assessed for tachycardia, abnormal rhythm, or gallops, and the presence and quality of murmurs, especially in newborns. Central pulse strength should be noted. The abdomen should be examined for the presence of hepatosplenomegaly, a pulsatile mass, or abdominal bruit.

Extremity examination includes evaluation of nail beds for peripheral cyanosis, strength and symmetry of distal pulses,

BOX 29-2 DIFFERENTIAL DIAGNOSIS OF CYANOSIS

I. Peripheral cyanosis
  A. Low cardiac output states
    1. Shock
    2. Left ventricular failure
    3. Hypovolemia
  B. Environmental exposure (cold)
    1. Air or water
  C. Arterial occlusion
    1. Thrombosis
    2. Embolism
    3. Vasospasm (Raynaud's phenomenon)
    4. Peripheral vascular disease
  D. Venous obstruction
  E. Redistribution of blood flow from extremities
II. Central cyanosis
  A. Decreased arterial oxygen saturation
    1. High altitude (>8000 ft)
    2. Impaired pulmonary function
      a. Hypoventilation
      b. Impaired oxygen diffusion
      c. Ventilation-perfusion mismatching
        (1) Pulmonary embolism
        (2) Acture respiratory distress syndrome
        (3) Pulmonary hypertension
      d. Respiratory compromise
        (1) Upper airway obstruction
        (2) Pneumonia
        (3) Diaphragmatic hernia
        (4) Tension pneumothorax
        (5) Polycythemia
  B. Anatomic shunts
    1. Pulmonary arteriovenous fistulae and intrapulmonary shunts
    2. Cerebral, hepatic, peripheral arteriovenous fistulae
    3. Cyanotic congenital heart disease
      a. Endocardial cushion defects
      b. Ventricular septal defects
      c. Coarctation of aorta
      d. Tetralogy of Fallot
      e. Total anomalous pulmonary venous drainage
      f. Hypoplastic left ventricle
      g. Pulmonary vein stenosis
      h. Tricuspid atresia and anomalies
      i. Premature closure of foramen ovale
      j. Dextrocardia
      k. Pulmonary stenosis of atrial septal defect
      l. Patent ductus arteriosis with reversed shunt
  C. Abnormal hemoglobin
    1. Methemoglobinemia
      a. Hereditary
      b. Acquired
    2. Sulfhemoglobinemia
    3. Mutant hemoglobin with low oxygen affinity (e.g., hemoglobin Kansas)

and capillary refill. Evidence of chronic vascular disease, such as hair loss and temperature difference, should be noted. Clubbing of the nails may occur due to increased soft tissue and expansion of the capillary beds (Fig. 29-2). Clubbing may be idiopathic or hereditary, but is usually the result of chronic hypoxemic states, such as cyanotic heart disease, infective endocarditis, pulmonary disease (chronic obstructive pulmonary disease, cystic fibrosis), and some gastrointestinal disorders (cirrhosis, Crohn's disease, and regional enteritis). Thrombotic events should also be considered with findings of skin and nail bed hemorrhages or end-organ damage (eye, kidney).

Figure 29-2. Symmetrical cyanosis. Equal cyanosis and clubbing of hands and feet resulting from transposition of great vessels and a ventricular septal defect without patent ductus arteriosus.

A neurologic examination should be performed focusing on mental status, symmetry of motor and sensory function, and any gross deficit.

Laboratory and Ancillary Testing

The complete blood count should be checked to assess for polycythemia or anemia.[10] Peripheral smear assesses RBC morphology and fragments, as well as white blood cell differential count.

Interpretation of pulse oximetry is problematic in the setting of cyanosis (see Chapter 3). Assessment of distal perfusion usually determines if poor circulation is a cause of low pulse oximetry. Pulse oximetry measures light absorbance of tissue at 660 nm (red reduced hemoglobin) and 940 nm (infrared oxyhemoglobin). The ratio of these two readings is the basis of the pulse oximetry calculation. Methemoglobin absorbs well at both wavelengths, resulting in a saturation approximation of 85%, regardless of the actual Pao_2 and Sao_2.[11]

Arterial blood gas testing assesses Sao_2, often sampled when the patient is breathing room air (see Fig. 29-1). Co-oximetry measurements should be specifically ordered if carbon monoxide exposure or methemoglobinemia is suspected. Sulfhemoglobin is reported as methemoglobin on co-oximetry, so if sulfhemoglobinemia is possible, measured oxygen saturation should be specifically requested.[12]

Imaging

A chest radiograph should be ordered to evaluate lung fields for consolidation, infiltrates, and increased vasculature or pulmonary edema. The cardiac silhouette and mediastinum may suggest congenital heart disease. In patients thought to have pulmonary embolism, imaging may include lower extremity venous Doppler ultrasound (if deep venous thrombosis

symptoms are present), ventilation-perfusion scanning or computerized tomography pulmonary angiogram.

Electrocardiogram and Echocardiogram

An electrocardiogram should be performed on all patients with cyanosis to assess for arrhythmias and acute ischemic changes. Right-axis deviation or right ventricular hypertrophy may be seen with significant cardiopulmonary disease (e.g., cor pulmonale, acute pulmonary hypertension). An echocardiogram may be helpful in detecting septal defects in infants or valvular disease in infants and adults.

DIFFERENTIAL ALGORITHMS

Figures 29-3 and 29-4 outline the differential diagnosis and treatment for peripheral and central cyanosis, respectively. After the initial assessment is completed, and the distribution of cyanosis is noted, the clinician should begin 100% oxygen therapy and follow steps to determine the cause of cyanosis. Clinical improvement with oxygen suggests diffusion impairment. Patients who do not respond to oxygen are more likely to have ventilation-perfusion ratio abnormalities, such as shunting from a consolidated pulmonary lobule, or congenital heart disease with right-to-left shunting. Cardiac size and silhouette on chest radiograph may provide a clue to the presence of congenital cardiac disease. If heart size is normal, impaired pulmonary function, pulmonary embolus, or other noncardiac causes should be considered. If no improvement occurs with 100% oxygen therapy, the patient's respiratory status should be reassessed, and tension pneumothorax or upper airway obstruction considered. Pulmonary embolus should be considered and a ventilation-perfusion scan or spiral computed tomography pulmonary angiogram performed. If a patient exhibits no respiratory distress and remains resistant to oxygen therapy, cardiac shunting or abnormal hemoglobin forms should be considered and treated accordingly.

Critical Diagnoses

Acute cardiovascular and respiratory compromise must be considered in a patient presenting with cyanosis and symptoms or signs of shock. The differential diagnosis for these critical presentations includes acute congestive heart failure, acute coronary syndromes, hypovolemic or cardiogenic shock, acute respiratory insufficiency or failure, massive pulmonary embolism, an exacerbation or decompensation in a patient with known congenital heart disease, or the first presentation of pediatric congenital heart disease. These patients require emergent treatment, critical therapeutic intervention, and admission to the intensive care unit.

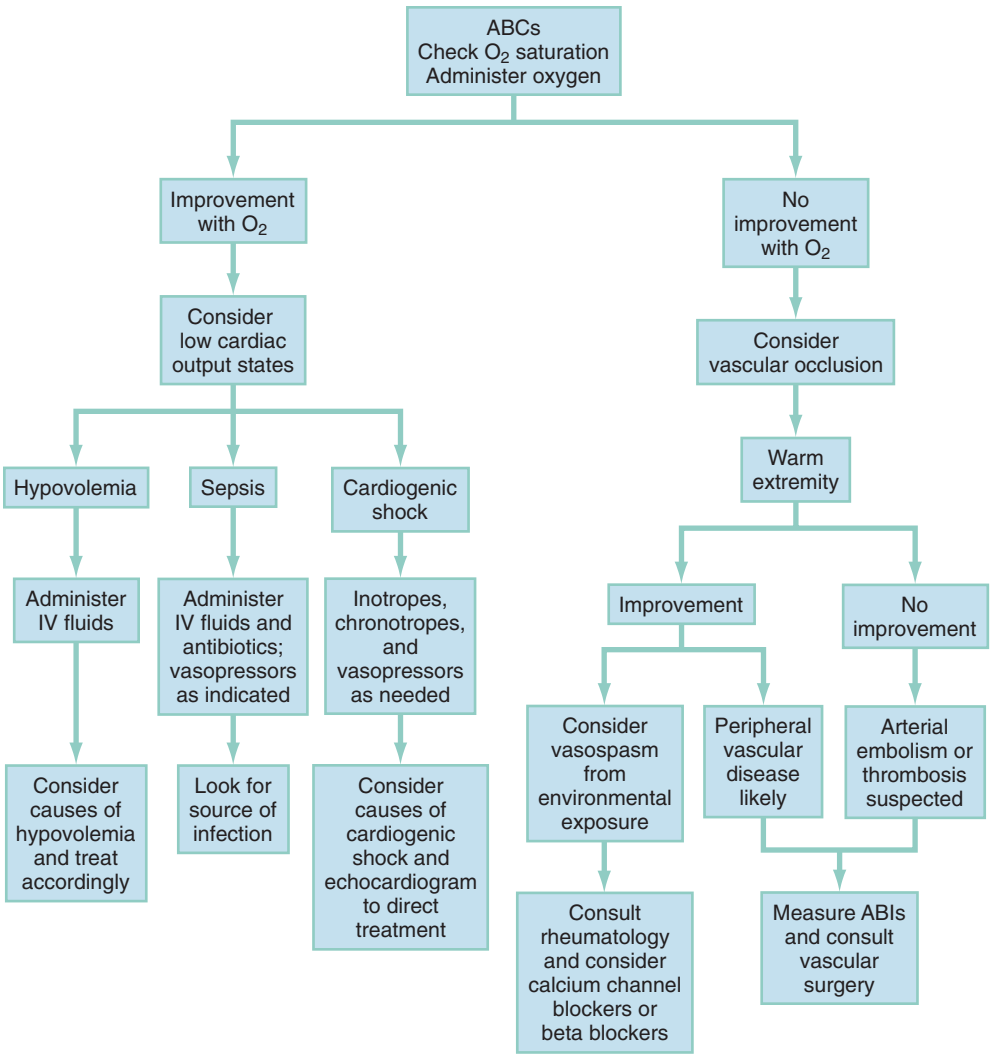


Figure 29-3. An algorithmic approach to peripheral cyanosis. ABCs, airway, breathing, circulation; ABI, ankle brachial index; IV, intravenous.

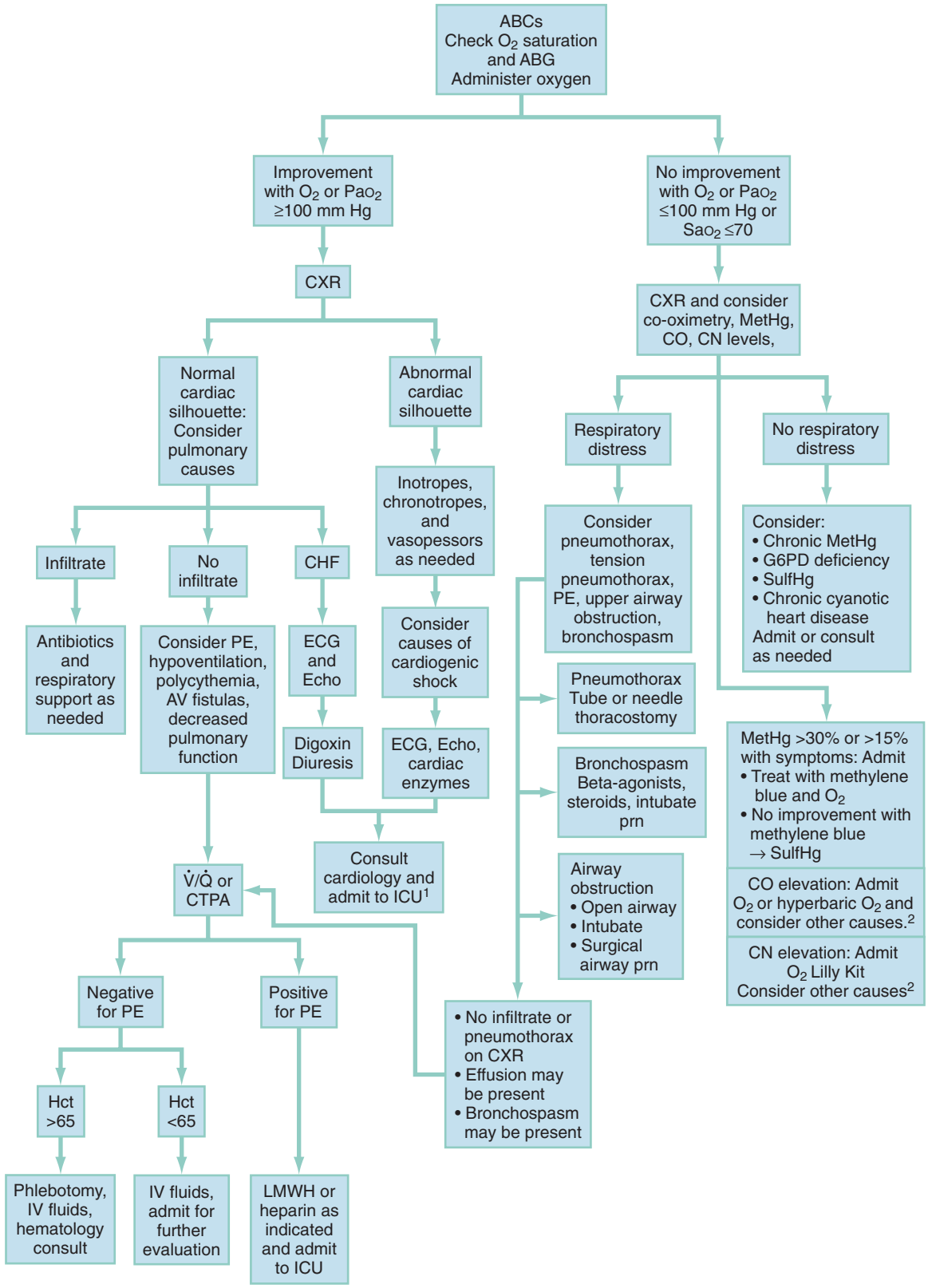


Figure 29-4. An algorithmic approach to central cyanosis. ABCs, airway, breathing, circulation; ABG, arterial blood gas; AV, arteriovenous; CHF, congestive heart failure; CN, cyanide; CO, carbon monoxide; CTPA, computed tomography pulmonary angiography; CXR, chest radiograph; ECG, electrocardiogram; Echo, echocardiogram; G6PD, glucose-6-phosphate dehydrogenase; Hct, hematocrit; ICU, intensive care unit; IV, intravenous; LMWH, low-molecular-weight heparin; MetHgb, methemoglobin; Pao_2, partial pressure of arterial oxygen; PE, pulmonary embolus; prn, as needed; RA, room air; Sao_2, arterial oxygen saturation; SulfHg, sulfhemoglobin; V̇/Q̇, ventilation-perfusion scan.
[1] Patients with chronic cyanotic heart disease may not require ICU care or even admission. Disposition should be discussed with patient's cardiologist.
[2] Cyanide and carbon monoxide toxicity do not present with cyanosis. If either of these is present, consider coexisting diagnosis.

Emergent Diagnoses

Methemoglobinemia is an infrequent cause of cyanosis, but should be considered in patients presenting without a history or physical findings suggestive of cardiovascular or pulmonary disease.

Sulfhemoglobinemia is a rare cause of cyanosis, most commonly occurring after exposure to hydrogen sulfide from organic sources, medications that are sulfonamide derivatives, or gastrointestinal sources (bacterial overgrowth). Strong consideration should be given to sulfhemoglobin toxicity in patients with cyanotic findings and methemoglobin on co-oximetry, but who do not improve with methylene blue treatment.

Polycythemia is defined as an elevated RBC mass due to one of three causes. Polycythemia vera is a disorder of bone marrow stem cells with increased RBC mass, cyanosis, and splenomegaly. Patients may present with hyperviscosity syndrome. Secondary polycythemia occurs with either an appropriate or inappropriate increase of erythropoietin, a physiologic response to chronic hypoxemia (≤92% oxygen saturation), cyanotic congenital heart disease, cigarette smoking, or high altitude exposures. Relative polycythemia is an increased RBC mass, often due to dehydration or reduced plasma volumes.

Finally, vascular disease, such as Raynaud's phenomenon, may present with a cyanotic appearance. Raynaud's phenomenon occurs in 15% of the population and has a female predominance. Patients have an abnormal response to excessive cold or emotional stress and report vasoconstriction, profound cold sensitivity, and recurrent events of sharply demarcated pallor or cyanosis of the digits. Most commonly, the cutaneous arterial capillary beds of the fingers and toes are affected, but tongue, ear, and other distal areas are sometimes also affected.[13]

EMPIRICAL MANAGEMENT

Administration of high-flow oxygen is the first therapy for patients with cyanosis. Any clinical improvement, or lack thereof, should be noted. At this point, consideration of abnormal hemoglobin and toxin-induced cyanosis is crucial because the administration of appropriate antidotes and systemic therapies may decrease morbidity and improve outcome.

Intravenous fluid resuscitation should be initiated in patients with hypovolemia. Treatment of congestive heart failure, arrhythmia, or poor cardiac output should occur as clinical conditions indicate. Cardiology consultation is recommended in patients thought to have congenital or ischemic heart disease. Although several specific treatments are discussed here, the cause of the cyanosis may be elusive, and hospitalization is required to determine it.

Specific Strategies

Methemoglobinemia and Sulfhemoglobinemia

If cutaneous exposure with an inciting agent occurred (i.e., aniline dyes), complete decontamination with soap and water is recommended. The staff should use appropriate protective equipment. Urgent treatment with oxygen and methylene blue (1–2 mg/kg IV over 5 minutes)[14] is indicated for patients with symptomatic hypoxia (dysrhythmias, angina, respiratory distress, seizures, or coma) and methemoglobin levels greater than 30%. Sulfhemoglobinemia is suggested when the laboratory reports an elevated methemoglobin level and the patient does not respond to methylene blue. Treatment of sulfhemoglobinemia is supportive in addition to removing the causative agent.

Other Causes of Cyanosis

Acute therapy for patients with symptomatic hyperviscosity syndrome and secondary polycythemia includes phlebotomy and volume expansion with isotonic crystalloid. The goal of therapy is a normal hematocrit (45% in men and 42% in women). Long-term therapy is focused on the underlying cause, and patients may require referral to a hematologist.[10,15]

Raynaud's phenomena is treated with warming the affected digits and extremities. Systemic vasodilating agents (e.g., calcium channel blockers [nifedipine] or nitrates) may be useful in the acute setting.[16] If there is no improvement of peripheral cyanosis with warming and administration of 100% oxygen, arterial insufficiency or occlusion may be present. In cases of critical limb ischemia, intravenous heparin should be considered in consultation with a vascular surgeon. Embolic sources, such as endocarditis and abdominal aortic aneurysms should be considered. Vascular bypass, intra-arterial thrombolysis, or stenting may be indicated.

Carbon monoxide and cyanide poisoning do not typically present with cyanosis and are covered elsewhere.

PATIENT DISPOSITION

Admission

All patients with a first episode of cyanosis or an uncertain cause require admission. Cardiology consultation and referral is recommended for children with a first episode of congestive heart failure and newly diagnosed or suggested congenital heart disease. Surgical consultation and intervention are indicated for acute arterial occlusion from embolic or thrombotic sources.

Discharge

Patients with peripheral cyanosis from vasospasm, asymptomatic methemoglobinemia less than 15%, and stable patients with primary pulmonary disease may be treated as outpatients, after several hours of monitoring in the ED. Unless the patient has a previous diagnosis of chronic cyanosis, follow-up must be arranged within 24 hours. Instructions should clearly state that if the cyanosis worsens, or if dyspnea, altered mentation, or chest pain occur after discharge, the patient must return immediately to the ED.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 30 Sore Throat

Amy V. Kontrick, Jonathan I. Singer, and Mark E. Gebhart

PERSPECTIVE

Epidemiology

Sore throat is a frequent complaint among patients presenting to the emergency department (ED). The National Health Care Survey in 2001–2002 reported more than 2.4 million ED visits with complaints relating to the throat and acute pharyngitis diagnosed in more than 1.9 million patients.[1] The chief complaint of sore throat is seen in every age group and has no sex predilection. Sore throat and other upper respiratory tract infections are some of the most common diseases for which care is sought and for which antibiotics are prescribed.[1,2]

Pathophysiology

Sore throat results from irritation or inflammation of any anatomic surface within the oropharynx. The oropharynx is defined by the following borders: (1) posteriorly by the prevertebral fascia, (2) laterally by the buccinator muscle groups, (3) superiorly by the base of the skull, and (4) inferiorly by the vocal cords (Fig. 30-1). Pain may originate within the buccal mucosa, tongue, palatine tonsils, lingual tonsils, adenoids, soft palate, and posterior pharyngeal wall. In addition, pain may result from infection, inflammation, or invasive diseases of the potential spaces within and surrounding the oropharynx—the peritonsillar, retropharyngeal, sublingual, submental, lateral pharyngeal, parotid, buccal, and pretracheal spaces. Sore throat also occurs with inflammatory changes of the epiglottis, aryepiglottic folds, vocal cords, and subglottic region. Infectious diseases of dental structures and cervical nodes and the presence of middle ear fluid may cause sore throat through referred pain. The 9th and 10th cranial nerves provide sensory input from the oropharynx, larynx, middle ear, and external auditory canal.[3] Many systemic diseases, including hepatitis, infectious mononucleosis, retroviral disease, and neutropenia, may also have sore throat as part of their symptom complex or initial presentation.

Sore throat commonly results from infections within the oropharynx, and the majority of these illnesses are self-limited. Table 30-1 lists common infectious and noninfectious causes of sore throat. Although the majority of infections are mild and not associated with serious complications, several infections may result in airway compromise, systemic disease, or sepsis.

Viruses cause the majority of cases of sore throat—up to 80% by some reports.[2,4] Enterovirus infection accounts for the majority of sore throats in all age groups from late spring through autumn. Adenovirus, rhinovirus, parainfluenza virus, influenza virus, and respiratory syncytial virus predominate during winter months. Epstein-Barr virus (EBV), herpes simplex, and varicella-zoster virus have less seasonal predilection.

Acute pharygitis due to bacterial infection is much less common than viral infection, and the cause can usually be discerned by a combination of clinical evaluation and rapid strep testing, because group A β-hemolytic streptococcus (GABHS) is the most common bacterial pathogen.[2,4,5] Aerobes such as GABHS with anaerobes or anaerobes alone cause infection in the deeper planes of the pharynx and neck. GABHS is isolated as the offending pathogen in 10 to 15% of all patients with sore throat. The incidence of GABHS in school-age children with sore throat may reach 15 to 30%, and some studies have reported the incidence as high as 50%.[2,5-8] GABHS is implicated in as few as 5% of adults with sore throat, but 47 to 73% of adults with pharyngitis are prescribed antibiotics.[2,9] GABHS is most often isolated from patients between late winter and spring. GABHS infection may cause coinfection with other viral agents, but distinguishing acute infection from carrier state is difficult.

Fungal colonization and systemic infection with *Candida albicans* may occur throughout the oral cavity. Immunocompromised patients may present with severe infections or repeated infections. Recent antibiotic therapy, chemotherapy, and radiation therapy increase the risk for fungal colonization with *Candida* species.

Sore throat may be a manifestation of noninfectious systemic disease, trauma, tumor, or congenital anomaly. Additional systemic complaints or physical findings will often accompany these diseases.

DIAGNOSTIC APPROACH

Differential Considerations

The stable patient should receive a directed history and physical examination followed by judicious use of ancillary testing. Table 30-1 lists the possible causes of acute sore throat.

Pivotal Findings

History

Characteristic of Pain. Rapidly progressing symptoms, high fever, or severe pain suggest the possibility of invasive disease.[10,11] A duration of several days accompanied by fever suggests deeper plane infection or systemic disease. Inflam-

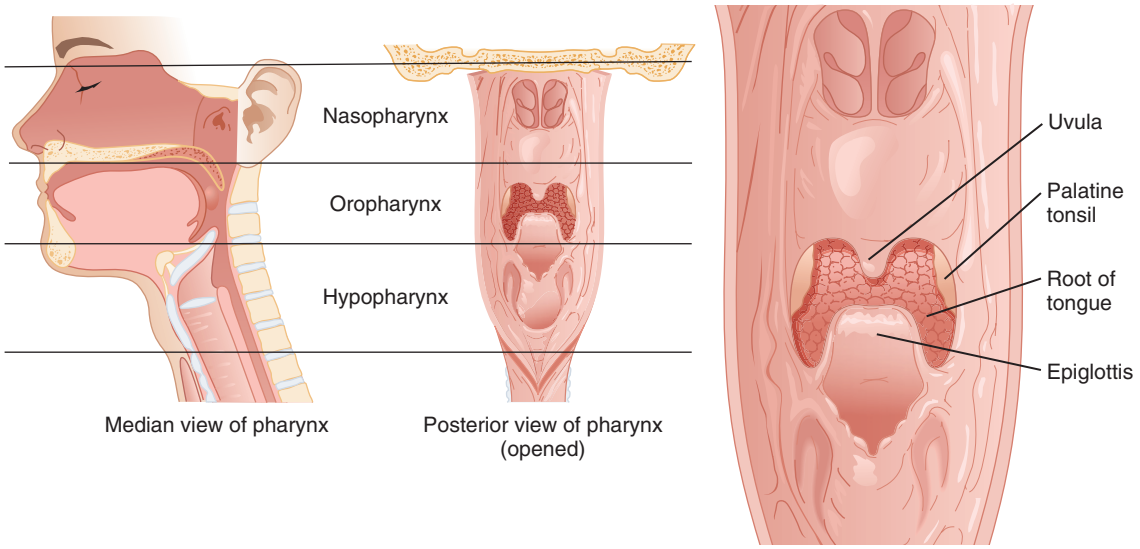


Figure 30-1. Anatomy of the nasopharynx, oropharynx, and hypopharynx.

Table 30-1 Differential Diagnosis for Sore Throat

INFECTIOUS CAUSES				
	AEROBES			
VIRAL	COMMON	UNCOMMON	ANAEROBES	OTHER
Rhinovirus	*Streptococcus pyogenes* (GABHS)	*Haemophilus influenzae*	*Bacteroides* sp.	*Candida* sp.
Adenovirus	GABHS *Peptostreptococcus* sp.	*Haemophilus parainfluenzae* *Coccidioides* sp.		
Coronavirus	Non–group A streptococcus	*Corynebacterium diphtheriae*	*Peptococcus* sp.	
Herpes simplex 1, 2	*Neisseria gonorrhoeae*	*Streptococcus pneumoniae*	*Clostridium* sp.	
Influenza A, B	*Neisseria meningitides*	*Yersinia enterocolitica*	*Fusobacterium* sp.	
Parainfluenza	*Mycoplasma pneumoniae*	*Treponema pallidum*	*Prevotella* sp.	
Cytomegalovirus	*Arcanobacterium hemolyticum*	*Francisella tularensis*		
Epstein-Barr	*Chlamydia trachomatis*	*Legionella pneumophila*		
Varicella-zoster	*Staphylococcus aureus*	*Mycobacterium* sp.		
Hepatitis virus				

NONINFECTIOUS CAUSES		
SYSTEMIC	TRAUMA, MISCELLANEOUS	TUMOR
Kawasaki disease	Penetrating injury Angioneurotic edema	Tongue
Stevens-Johnson syndrome	Retained foreign body Anomalous aortic arch	Larynx
Cyclic neutropenia	Laryngeal fracture Calcific retropharyngeal tendinitis	Thyroid
Thyroiditis	Retropharyngeal hematoma	Leukemia
Connective tissue disease	Caustic exposure	

GABHS, group A beta-hemolytic streptococcus.

mation or infection within Waldeyer's ring is accompanied by pain localized to the oropharynx. Pain that radiates to the back of the neck or between the shoulder blades suggests prevertebral or retropharyngeal pathology (abscess or calcific tendinitis). Sore throat with radiation to the jaw or ear may be seen with dental abscess or deeper tissue plane infection.[1,2]

Associated Complaints. Odynophagia is almost universal, and many viral infections can cause a raspy dysphonia (laryngitis). The presence of severe pain or significant dysphagia, drooling, voice muffling ("hot potato" voice), or difficulty breathing, however, may indicate serious infection and potential for airway compromise. In the febrile patient, these symptoms suggest glossal abscess, severe infection of the lingual tonsils or palatine tonsils (peritonsillar cellulitis or abscess), epiglottitis, or Ludwig's angina (submental or sublingual space infection).[3,12]

Systemic Symptoms. Prolonged fever (more than 5 to 7 days) may be seen in Kawasaki disease. Cough, myalgia, and arthralgia are seen with influenza A and B, parainfluenza, *Neisseria meningitidis*, and *Mycoplasma pneumoniae* infection. Hepatitis,

infectious mononucleosis, cytomegalovirus (CMV), and human herpesvirus 6 are associated with fatigue, malaise, and loss of appetite.[13,14] Retroviral disease may present with similar symptoms and will often be accompanied by a rash.[13]

Epidemiology. For children, sick contacts within a daycare or school setting may provide important clues to infectious causes of sore throat. Secondary spread of disease is common for persons exposed to *M. pneumoniae*, GABHS, *Haemophilus influenzae*, *N. meningitides*, and many viruses. Among adults, intrafamilial spread is common with viruses, *Mycoplasma* sp., and GABHS. A history of recent orogenital contact may point to gonococcal or herpetic infection.

Trauma. Blunt or penetrating trauma to the oropharynx can result in deep space infections. Recent medical or dental procedures may increase the likelihood of certain infections. Potential exposures to caustics or foreign body ingestions should be sought, especially in young children.

Immunizations/Specific GABHS History. The patient's immunization status is assessed for diphtheria, pertussis, *H. influenza*, and tetanus vaccines. The presence of previous GABHS infections should be ascertained.

Immune Status. The immune status of the patient should be assessed, including (1) the presence of diabetes, (2) known immune disorders, or (3) recent chemotherapeutic or radiation therapy. Underlying alcoholism or malnutrition may place the patient at risk for more serious infections. Recent antibiotic use may indicate the presence of resistant organisms or atypical pathogens.

Physical Examination

Assessing for airway compromise or potential airway compromise is the critical first step in the approach to the patient with sore throat (Fig. 30-2). Rapid assessment of the patient can be accomplished by observing the patient's posture, color, level of consciousness, and phonation. Observation alone is especially important in the pediatric patient with potential airway compromise because attempts at a more thorough physical examination may result in agitation and progression to complete airway obstruction. The presence of air hunger, stridor, drooling, or toxic appearance may indicate pending airway obstruction.[3,4] A complete ear, nose, and throat (ENT) and general examination will help narrow the differential diagnosis (Table 30-2).

A reduced functional caliber of the airway may occur acutely, subacutely, or insidiously, depending on the cause of the disease process.[10,11,15,16] Pending airway loss leads to air-preserving posturing especially in children. Infants unable to sit without support choose the lateral decubitus position with the neck hyperextended when partial obstruction occurs. Children capable of sitting may support their heads with their hands. Airway obstruction in an older child is typically associated with fixed upright posturing. The patient has forced flexion at the waist and maintains the neck flexed and the head extended with an open mouth. Alternatively, patients may assume tripod posturing, in which additional support is gained by hands held on a surface.

Ancillary Testing

Laboratory procedures, other than rapid group A strep testing or throat culture, generally are not necessary to develop a working diagnosis of viral pharyngitis or GABHS pharyngitis (Table 30-3). Use of the Centor criteria, with or without rapid antigen detection test or culture, is a rational but not universally accepted approach.[8,17-19] Patients with a score of 0 or 1 do not require treatment or additional testing. The goal is to

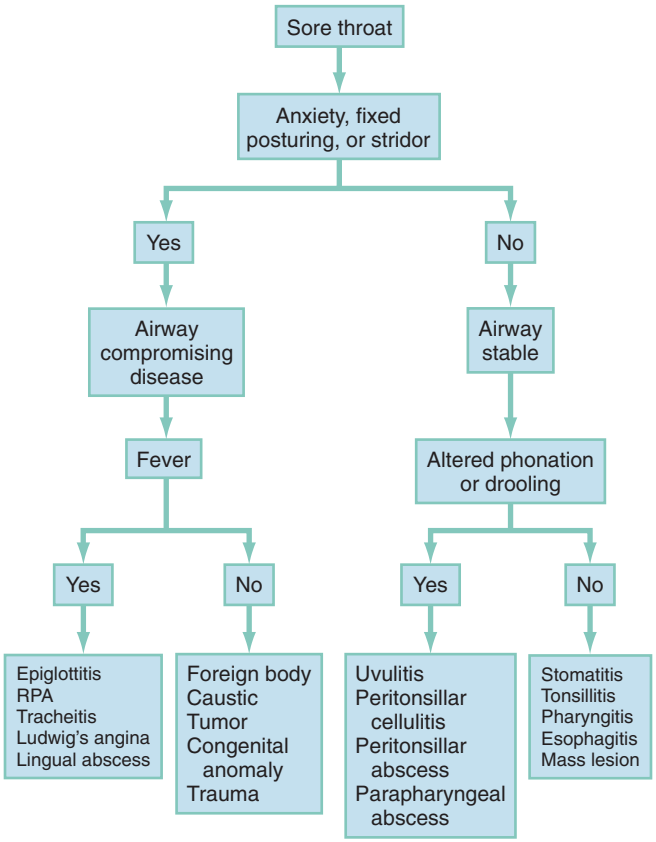


Figure 30-2. Diagnostic alogorithm for the patient with a sore throat. RPA, retropharyngeal abscess.

decrease the cost of additional testing and decrease the inappropriate use of antibiotics while still treating those with GABHS to prevent suppurative and nonsuppurative complications.

A complete blood count is rarely helpful but may be used, along with serologic test for EBV, for the patient with a compatible presentation—severe sore throat, fever, and lymphadenopathy. Hematologic findings of leukocytosis, relative and absolute lymphocyte predominance, and the presence of atypical lymphocytes constituting more than 10% of the total leukocyte count suggest EBV. A serologic test such as the heterophile antibody screen (Monospot) may provide evidence of primary EBV infection.[13] Patients with a negative serologic test but with compatible symptom complex should be retested a week later because heterophile antibodies may not be present in the first week in 10% of patients.[13,14] In addition, CMV, acute retroviral illness, herpes simplex virus, and human herpes 6 viral infections should be considered.

A lateral portable upright neck radiograph may be used in the pediatric patient to narrow the differential diagnosis of infectious conditions associated with potential airway obstruction. The lateral neck film may demonstrate swelling in the prevertebral soft tissue in a patient with a retropharyngeal abscess (RPA).[4] Plain radiographic imaging is rarely warranted in the adult patient with an acute sore throat. The adult with severe symptoms should be considered for direct nasopharyngoscopy to search for epiglottitis. Use of the *H. influenza* b vaccine in children has resulted in a dramatic decrease in the incidence of epiglottitis, but the incidence in adults has not changed.[10,11,16,20] Ultrasonography may be a useful tool in the diagnosis and treatment of some deep space infections. The advantages of ultrasound are as follows: (1) It can be used at the bedside, (2) it can be used to guide incision and drainage

Table 30-2 Pivotal Findings in Physical Examination

SIGN	FINDING	DIAGNOSES
Appearance	Toxic	Epiglottitis RPA Bacterial tracheitis Kawasaki disease
Posturing	Fixed, upright, leaning forward	Epiglottitis RPA Tracheitis Laryngotracheobronchitis
	Torticollis	Parapharyngeal abscess
Phonation	Absent Muffled	Epiglottitis RPA Peritonsillar cellulitis Peritonsillar abscess
Stridor, drool	Either present	Epiglottitis RPA Tracheitis Peritonsillar abscess
Noninvasive ENT	Conjunctivitis	Kawasaki disease Stevens-Johnson syndrome Adenovirus
	Mucous membrane sore	Stevens-Johnson syndrome Behçet disease Enterovirus Herpes simplex
	Submental, sublingual mass Adenopathy	Ludwig's angina Adenovirus EBV *Mycobacterium* sp. HIV
	Tender hyoid Tender thyroid	Epiglottitis Thyroiditis Thyroglossal duct cyst infection
Augmented ENT findings	Trismus	Parapharyngeal abscess Peritonsillar abscess
	Tongue coating	Kawasaki disease GABHS
	Palatal petechiae Pharyngeal hyperemia	GABHS Infectious tonsillopharyngitis Caustic Trauma
	Exudative tonsillitis	GABHS *Corynebacterium diphtheriae* *Fusobacterium* sp. EBV Adenovirus
	Bulged retropharynx Uvular erythema Displaced uvula	RPA Uvulitis Peritonsillar abscess Parapharyngeal abscess
	Inflamed epiglottis	Epiglottitis
Abdomen	Hepatosplenomegaly	EBV, hepatitis
Joint examination	Arthritis	Lemierre's syndrome
Rash	Scarlatiniform	GABHS *Arcanobacterium* sp. EBV Kawasaki disease

EBV, Epstein-Barr virus; ENT, ear, nose, throat; GABHS, group A beta-hemolytic streptococcus; HIV, human immunodeficiency virus; RPA, retropharyngeal abscess.

of peritonsillar abscesses (PTAs), and (3) it decreases the exposure to ionizing radiation in computed tomography (CT) scans.[4] CT scanning defines the extent of infection and is superior to ultrasonography for this purpose. It can also help distinguish cellulitis from abscess.[4,21] Magnetic resonance imaging provides superior resolution of deep tissue planes and may supplant the use of CT scanning in the future.

Table 30-3 **Centers for Disease Control and Prevention: Practice Guidelines for Acute Pharyngitis in Adults**

Population: Adults (patients older than 15 years)
Patients with viral symptoms: Do not test or treat
Patients with symptoms of GABHS: Use Centor criteria*
Centor score = 4: Perform RADT or treat presumptively
Centor score = 3: Perform RADT or treat presumptively
Centor score = 2: Perform RADT or do not test or treat
Centor score = 1 or 0: Do not test or treat
In all cases in which an RADT is performed, only those with positive results are treated.
Culture after negative RADT: No
Recommended antibiotic: Penicillin (erythromycin if penicillin allergic)

*Centor criteria history of fever; absence of cough; swollen, tender anterior cervical lymph nodes; and tonsillar exudate.
GABHS, group A beta-hemolytic streptococcus; RADT, rapid antigen detection test.

DIFFERENTIAL DIAGNOSIS

Table 30-1 lists the infectious and noninfectious causes of sore throat.

EMPIRICAL MANAGEMENT

The management of the patient presenting with a sore throat begins with a rapid assessment for potential airway compromise (Figs. 30-2 and 30-3). If the patient is in extremis, immediate airway control is obviously necessary. If the airway is patent and ventilation is adequate, diagnostic and therapeutic efforts may simultaneously commence. Infections within the parotid, buccal, parapharyngeal, submental, and sublingual spaces create masses that are readily apparent.[3,12,21,22] The purulent material rapidly expands the tissues but rarely occludes the airway. A thorough head and neck examination accompanied by fiberoptic nasopharyngoscopy, ultrasonography, or CT scan may be necessary to identify the severity and extent of the process. Needle aspiration of a PTA can be both diagnostic and therapeutic. Intravenous antibiotics are administered to treat mixed infection with aerobic and anaerobic organisms. ENT consultation is often necessary for definitive management of PTA, RPA, and other infectious or mass lesions, and early consultation is often warranted.

The patient who is febrile and appears toxic, is in respiratory distress, has an abnormal voice or prefers not to speak, or is drooling through a persistently open mouth may require emergent airway management before any other diagnostic

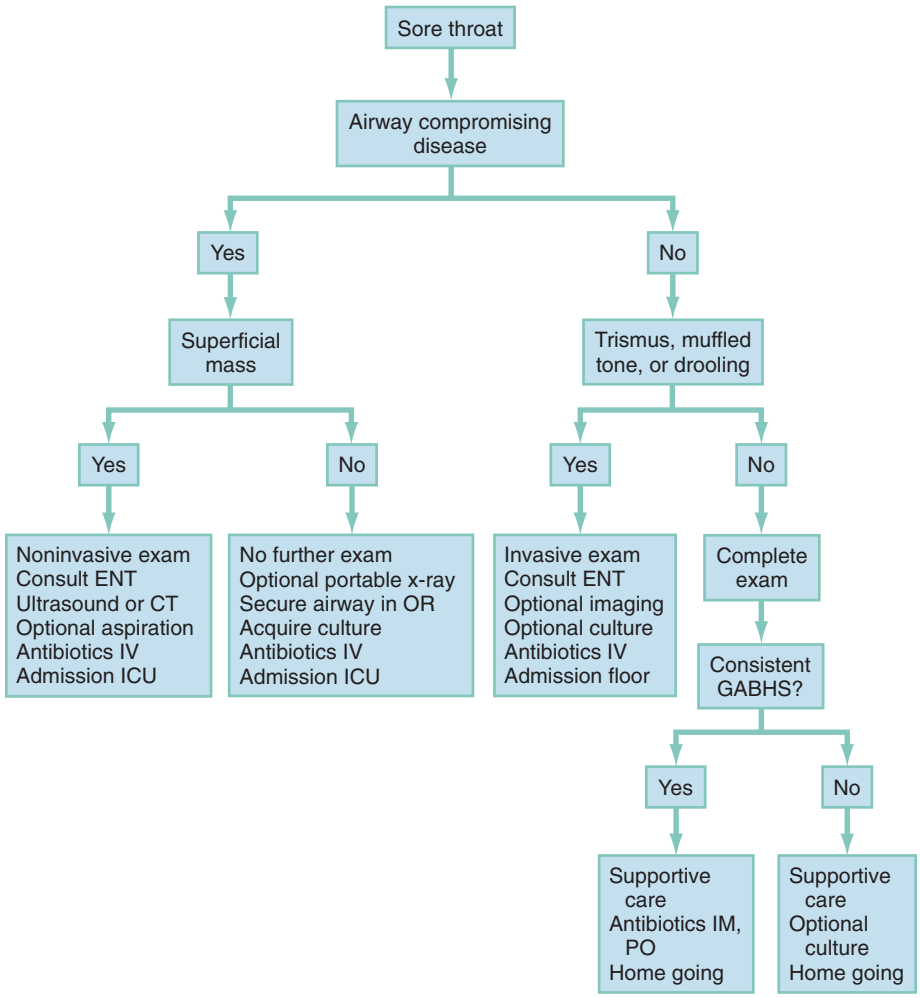


Figure 30-3. Management algorithm for the patient with a sore throat. CT, computed tomography, ENT, ear, nose, and throat; GABHS, group A beta-hemolytic streptococcus.

maneuvers are attempted due to impending airway compromise. If time permits, immediate transfer to the operating room may be warranted, with ENT and anesthesiology consultation. This requires that the operating room be ready to receive the patient and the patient be accompanied by a physician or surgeon capable of surgical cricothyrotomy. If the patient cannot be transported, then fiberoptic intubation (nasal or oral) is the preferred route, with light sedation and topical anesthesia (see Chapter 1). Equipment for cricothyrotomy should be readily available because instrumentation can lead to airway obstruction or laryngospasm. After the airway is secured, the infected surface and secretions can be swabbed for culture; tissue aspiration and blood culture specimens can be submitted for culturing.[15] Broad-spectrum parenteral antibiotics are begun for mixed aerobic and anaerobic infection, and the patient should be admitted to the intensive care unit.

If the febrile patient does not have evidence of airway compromise but has vocal changes (e.g., muffled or "hot potato" voice), epiglottitis, peritonsillar cellulitis, or abscess may be present. If examination of the oropharynx does not identify the offending condition, then fiberoptic examination of the upper airway for epiglottitis is indicated. ENT need not be consulted for peritonsillar cellulitis or uvulitis. ENT may be consulted for peritonsillar abscess, even after needle aspiration, for incision and drainage. Intravenous antibiotics are provided to cover *Streptococcus pyogenes*, non-group A streptococci, and *Staphylococcus aureus*. The patient may require admission for further care if he or she has severe symptoms or is unable to tolerate liquids by mouth.

In the patient with a sore throat who has no evidence of airway compromise, the pain may be a problem within the oropharynx, referred from another location, or part of a systemic illness. Further workup may continue in the ED or on an outpatient basis. The patient with presumed or proven GABHS should be treated with antibiotics. Penicillin remains the drug of choice.[7-9,23] Details of treatment are provided in Chapter 73.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 31 Hemoptysis

Calvin A. Brown III

PERSPECTIVE

Epidemiology

Hemoptysis is defined as the expectoration of blood from the respiratory tract that originates below the vocal cords. Most cases are mild and consist of blood-tinged sputum or minute amounts of frank blood. The most common cause of small-volume hemoptysis is bronchitis. Rarely, hemoptysis is accompanied by massive blood loss, generally accepted as 100 to 600 mL of blood loss in any 24-hour period. In addition to manifesting as hemoptysis, endobronchial bleeding may impair alveolar oxygen exchange and cause significant morbidity and mortality. Rapid blood loss can also result in hemodynamic instability and shock.

Although hemoptysis is a common complaint in emergency populations, only 1 to 5% of hemoptysis patients have massive or life-threatening hemorrhage, with mortality rates approaching 80%.[1] Large, contemporary series of patients with massive hemoptysis are lacking. Most etiologic data originate from small, often rural studies where tuberculosis (TB) and bronchiectasis are responsible for the vast majority of cases.[2,3] In developed nations, cancer, cystic fibrosis, arteriovenous malformations, and postprocedural complications play a more prominent role. Pediatric hemoptysis is rare but can be caused by infection, congenital heart disease, cystic fibrosis, or bleeding from a preexisting tracheostomy.[4]

Pathophysiology

Trace hemoptysis typically originates from tracheobronchial capillaries that become disrupted with vigorous coughing or minor bronchial infections. Massive hemoptysis almost exclusively involves one of the two sets of vessels that constitute the lung's dual blood supply. Bronchial arteries, direct branches from the thoracic aorta, are responsible for supplying oxygenated blood to lung parenchyma. Disruption of these vessels from arteritis, trauma, or bronchiectasis or erosion from an adjacent malignancy can result in sudden and profound hemorrhage. Although small in caliber, the bronchial circulation is a high-pressure system and the culprit in nearly 90% of the cases of massive hemoptysis requiring embolization. Pulmonary arteries, although transmitting large volumes of blood, are at much lower pressure and, unless affected at a very central location, are less likely to cause massive hemoptysis.

Nearly all causes of hemoptysis have a common mechanism—vascular disruption within the trachea, bronchi, small-caliber airways, or lung parenchyma. Modes of vessel injury include acute and chronic inflammation (from bronchitis and arteritis), local infection (especially lung abscesses, TB, and aspergillosis), trauma, invasion from a growing tumor, infarction following a pulmonary embolus and fistula formation (specifically aortobronchial fistulae).

Bronchiectasis, a chronic necrotizing infection resulting in bronchial wall inflammation and dilation, is one of the most common causes of massive hemoptysis. As tissue destruction and remodeling continue, rupture of nearby bronchial vessels results in bleeding. Brochiectasis can complicate chronic airway obstruction, necrotizing pneumonia, TB, or cystic fibrosis. Broncholithiasis, the formation of calcified endobronchial lesions following a wide array of granulomatous infections, is an uncommon problem with a propensity to erode nearby vessels. Hemorrhage control often requires surgical intervention.[5-7]

Iatrogenic hemoptysis may complicate 2 to 10% of all endobronchial procedures, especially percutaneous lung biopsies.[8,9] Additionally, bleeding can be exacerbated by coagulopathy and thrombocytopenia. An uncommon cause includes ectopic endometrial tissue within the lung that can result in monthly catamenial episodes of hemoptysis. Diffuse alveolar hemorrhage can be seen with autoimmune vasculitides such as Wegener's granulomatosis, systemic lupus erythematosus, and Goodpasture's syndrome. Still others include pulmonary hereditary telangectasias and hydatiform infections.

DIAGNOSTIC APPROACH

Differential Considerations

When a patient presents with apparent hemoptysis, two other potential sources of bleeding should be investigated. Nasal, oral, or hypopharyngeal bleeding sometimes inadvertently contaminates the tracheobronchial tree and can mimic true hemoptysis. The clinician should closely inspect the nasopharynx and oral cavity to exclude this possibility. Differentiating hemoptysis from a gastric or proximal duodenal source of bleeding is the principle diagnostic dilemma, since further evaluation and management follow divergent pathways. Usually, this can be done by the patient and physician discriminating coughing from vomiting. In unclear cases, inspection and pH testing may help to distinguish gastrointestinal from tracheobronchial hemorrhage. Unless an active, brisk upper GI hemorrhage is present, the acidification of blood in the stomach results in fragmentation and

darkening of its color. This produces specks of brown or black material often referred to as "coffee-grounds" emesis. Pulmonary blood appears bright red or as slightly darker clots and is alkaline.

Rapid Assessment and Stabilization

Although hemodynamic instability can occur as a result of hemorrhage, the most lethal sequela of massive hemoptysis is hypoxia resulting from the ventilation-perfusion mismatch that occurs as small airways and alveoli are submerged with blood. The clinician should consider the standard indications for emergency airway management in such cases.

As a mitigating maneuver in patients with a known lateralizing source of bleeding, the "lung down" position can be employed in which the patient is positioned so the bleeding lung is more dependent. This position can promote continued protection and ventilation of the unaffected lung and improve oxygenation.[10,11] Large-bore (8.0) endotracheal tubes should be used to facilitate emergent fiberoptic bronchoscopy. In selected cases of confirmed left-sided bleeding, a single-lumen right-mainstem intubation can be successfully performed by advancing the tube in either the neutral position or by using a 90° rotational technique.[12] Left-mainstem intubations are more difficult and should be attempted with caution.

The use of double-lumen endotracheal tubes for lung isolation should be reserved for dire circumstances and usually requires an experienced anesthetist. The correct positioning of blindly placed double-lumen tubes is difficult and requires confirmation by auscultation and fiberoptic bronchoscopy, both of which have severely impaired accuracy in massive hemoptysis. Complications of double-lumen tubes include unilateral and bilateral pneumothorax, pneumomediastinum, carinal rupture, lobar collapse, and tube malposition.[13]

Pivotal Findings

History

Although patient reports of bleeding severity are historically inaccurate, a rough estimate of the rate, volume, and appearance of expectorated blood should be obtained.

Any history of parenchymal pulmonary disorders should be obtained, including the presence of bronchiectasis, recurrent pneumonia, chronic obstructive pulmonary disease, bronchitis, TB, and fungal infection. Inflammatory disorders that secondarily involve the lungs or pulmonary vasculature include Wegener's granulomatosis, Goodpasture's syndrome, and systemic lupus erythematosus. Risk factors for platelet dysfunction, thrombocytopenia, and coagulopathy may be present. Hypercoagulable states can contribute to deep venous thrombi and pulmonary embolism.

The presence of primary or metastatic cancer can cause hemoptysis by erosion into pulmonary and bronchial vessels. Recent percutaneous or transbrochial procedures can cause immediate or delayed postprocedural bleeding, and any recent history of trauma should also be noted. A pertinent travel history to areas endemic with TB or pulmonary paragonimiasis is crucial.

Physical Examination

After a primary survey and stabilization, a targeted examination may suggest the location and etiology of bleeding, but does so in less than 50% of cases.[14] Focal adventitious breath sounds may indicate pneumonia or pulmonary abscess. A new heart murmur, especially in a febrile patient, might reflect endocarditis causing septic pulmonary emboli. Symptoms and signs of deep venous thrombosis should suggest pulmonary embolism. Ecchymoses and petechiae can indicate coagulopathy and thrombocytopenia, respectively.

Ancillary Testing

Initial laboratory studies include a complete blood count, coagulation tests, and a type and screen or crossmatch. Renal function tests should be obtained if vasculitis is suggested or contrast computed tomography (CT) is planned. Plain chest radiography should be ordered, although its sensitivity is marginal. A prospective study of 184 consecutive patients with varying degrees of hemoptysis reveals that more than 40% of patients with a normal chest radiograph have a positive chest CT.[15]

In patients with massive hemoptysis, plain films may localize the site of hemorrhage in as many as 80% of patients.[6] High-resolution multidetector CT of the chest is the principle diagnostic test for investigating both bronchial and nonbronchial arterial causes of massive hemoptysis. CT is diagnostically comparable, yet less invasive, than conventional angiography, which is now done primarily as a combined diagnostic-therapeutic modality.[16-18] A chest CT should be obtained in the high risk patient (smokers, oncology patients) or in any patient with moderate to severe bleeding even if the initial chest radiography is normal. CT localization of hemorrhage can expedite bronchoscopic evaluation or guide subsequent interventional procedures.

DIFFERENTIAL DIAGNOSIS

Potential causes of hemoptysis vary and include systemic illnesses as well as pulmonary parenchymal disease. Box 31-1 includes the most common causes.

MANAGEMENT

Since the advent of high-resolution CT, radiologic evaluation has had an integral role in the evaluation and treatment of patients with hemoptysis. The challenge to the emergency physician is to rapidly assess the need for airway control prior to hemodynamic stabilization. Unless the initial chest radiograph is diagnostic or the patient is hemodynamically unstable, a chest CT should be obtained in most cases. Further management strategy should be developed in conjunction with pulmonary and thoracic surgery consultants, guided by the CT results (Fig. 31-1).

Bronchoscopy

Early bronchoscopy facilitates both localization of bleeding and therapeutic intervention. Balloon and topical hemostatic tamponade, thermocoagulation, and injection of vasoactive agents can all control arterial bleeding. Optimal timing for bronchoscopy remains conjectural. Stable patients with mild to moderate bleeding may benefit from early bronchoscopy. In unstable patients or those with brisk hemorrhaging, bronchoscopy sometimes can facilitate airway management, but is less likely to control bleeding.

Chest CT is as diagnostically accurate as bronchoscopy in locating peripheral vessels not accessible by a flexible bronchoscope.[19] Chest CT is used to identify the bleeding site and to determine whether angiography is indicated. There may be little benefit to bronchoscopy prior to interventional angiography if a CT scan has accurately identified a bleeding source.[20]

BOX 31-1 DIFFERENTIAL DIAGNOSIS: HEMOPTYSIS

Airway Disease
Bronchitis (acute or chronic)
Bronchiectasis
Neoplasm (primary and metastatic)
Trauma
Foreign body

Parenchymal Disease
Tuberculosis
Pneumonia/lung abscess
Fungal infection
Neoplasm

Vascular Disease
Pulmonary embolism
Arteriovenous malformation
Aortic aneurysm
Pulmonary hypertension
Vasculitis (Wegener's granulomatosis, SLE, Goodpasture's syndrome)

Hematologic Disease
Coagulopathy (cirrhosis or warfarin therapy)
Disseminated intravascular coagulation
Platelet dysfunction
Thrombocytopenia

Cardiac Disease
Congenital heart disease (especially in children)
Valvular heart disease
Endocarditis

Miscellaneous
Cocaine
Post-procedural injury
Tracheal-arterial fistula

SLE, systemic lupus erythematosus.

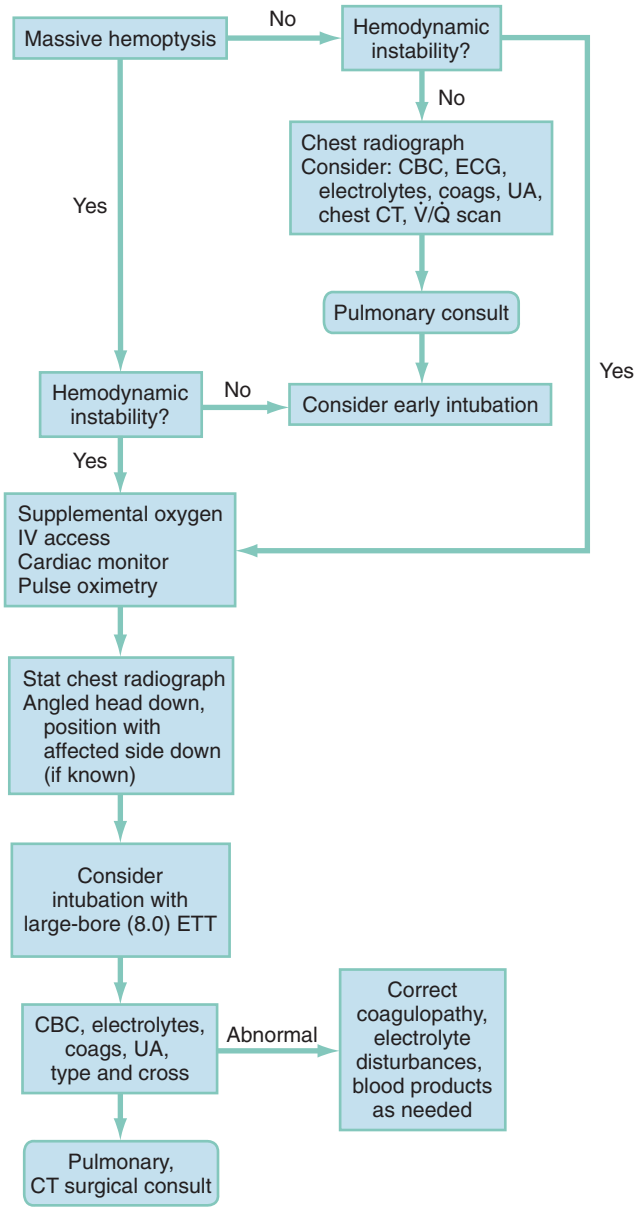


Figure 31-1. Emergency department management of hemoptysis. CBC, complete blood count; coags, coagulation studies; CT, computed tomography; ECG, electrocardiogram; ETT, endotracheal tube; IV, intravenous; UA, urinalysis; V/Q, ventilation-perfusion.

Interventional Angiography

Bronchial arterial embolization is an effective first-line therapy and is the procedure of choice for patients unable to tolerate surgery, or those in whom bronchoscopy was unsuccessful. Hemostatic rates range from 91 to 98%, but as many as 20 to 50% of patients have early episodes of repeat bleeding. The risk of delayed bleeding may exist for up to 36 months.[21-24] In order to guide therapy, initial localization of bleeding by bronchoscopy or CT is preferred. Rare complications include arterial perforation and dissection.

Surgery

Emergency thoracotomy is reserved for life-threatening hemoptysis or for persistent, rapid bleeding that is uncontrolled by bronchoscopy and percutaneous embolization. Pulmonary arterial hemorrhage from tumor necrosis represents a surgical emergency.[25]

DISPOSITION

Healthy patients with blood-streaked sputum and normal vital signs do not require imaging beyond plain chest radiography and can be discharged with follow-up. High risk patients with minor hemoptysis and all patients with moderate or large amounts of hemoptysis should undergo plain chest radiography followed by emergent chest CT. Brief hospitalization or admission to an observation unit for bronchoscopy should be considered. All patients with massive hemoptysis require admission to an intensive care unit and expedited multidisciplinary treatment involving the emergency physician, pulmonologist, and thoracic surgeon.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 32 Red and Painful Eye

Joshua L. Wright and John M. Wightman

PERSPECTIVE

Epidemiology and Pathophysiology

Most eye complaints are not immediately sight-threatening and can be managed by an emergency physician. Nontraumatic diseases, such as glaucoma and peripheral vascular disease leading to retinal ischemia, are more common with advancing age. Ocular injuries are the leading cause of visual impairment and blindness in the United States.[1] More patients with postoperative complications can be expected to present to the emergency department as more vision correction surgeries are performed.

The external and internal anatomy of the eye is depicted in Figure 32-1A and B. The globe has a complex layer of blood vessels in the conjunctiva, sclera, and retina. Redness reflects vascular dilation and may occur with processes that produce inflammation of the eye or surrounding tissues. Eye pain may originate from the cornea, conjunctiva, iris, or vasculature. Each is sensitive to processes causing irritation or inflammation.

DIAGNOSTIC APPROACH

Rapid and accurate triage is the most critical consideration in the approach to the red and painful eye. The first question should be, "Did anything get in your eye?" If so, the second question should be, "What do you think it is?" This helps separate trauma from nontrauma, but, more importantly, seeks to identify quickly eyes that may have been exposed to a caustic substance. Patients exposed to caustic substances require rapid decontamination to prevent permanent loss of visual acuity.

Differential Considerations

Diagnoses are classically divided into traumatic and nontraumatic. Traumatic pain and redness can be caused by caustic fluids and solid materials, low-velocity contact with a host of materials that can fall or be rubbed into the eye, higher velocity blunt-force impacts to the orbit or globe, or potentially penetrating injuries. Causes of nontraumatic pain and redness require a more detailed history, including contact lens use and questions directed toward determining the likelihood of systemic illnesses.

Pivotal Findings

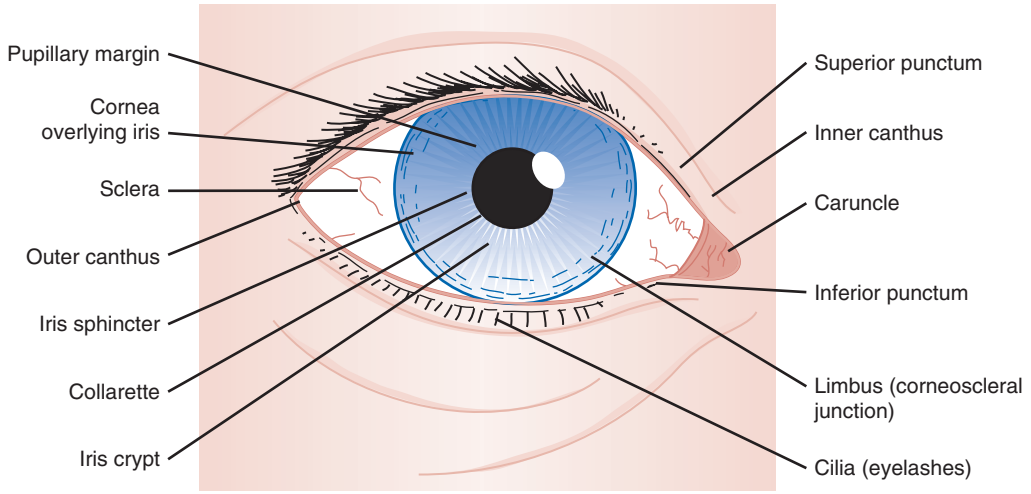
Measurement of the patient's best corrected visual acuity (i.e., with glasses on, if available) with each eye individually and with both eyes provides vital information when evaluating eye complaints. Only a few situations preclude early and accurate visual acuity testing. Eyes exposed to caustic materials should be decontaminated as soon as possible. Patients with sudden and complete visual loss in one eye require prompt funduscopic examination to determine the possibility of acute central retinal artery occlusion. This condition is readily apparent as a diffusely pale retina with indistinct or unseen retinal arteries (Fig. 32-2).

Other pivotal findings, which are more likely to be associated with a serious diagnosis, in patients with a red or painful eye are listed in Box 32-1.

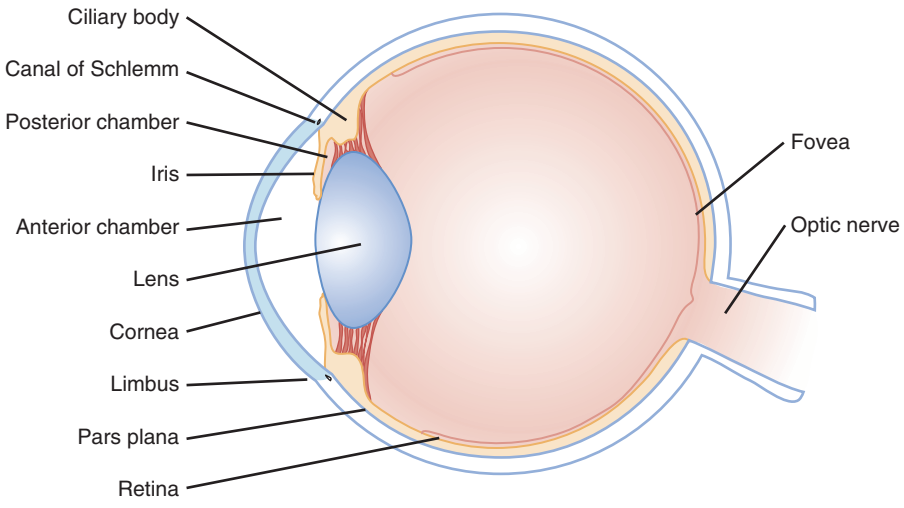
History

Chief complaints of pain can be manifestations of a variety of sensations. When carefully questioned, some patients may differentiate between itching, burning, dull pain, sharp pain, and perception of a foreign body. Itching tends to be more often due to blepharitis, conjunctivitis, or dry eye syndrome. Burning is associated with these conditions and with other mostly extraocular problems such as irritation of a pterygium or pinguecula, episcleritis, or limbic keratoconjunctivitis. Dull pain may be a manifestation of increased intraocular pressure (IOP) or referred from an extraorbital process such as sinusitis, migraine headache, or temporal arteritis. Sharp pain generally results from abnormalities of the anterior eye, such as keratitis, uveitis, and acute angle-closure glaucoma. A foreign body sensation is more typical of corneal irritation or inflammation.

A chief complaint of redness commonly results from palpebral or limbal injection of the conjunctiva. However, free blood can be noted behind the bulbar conjunctiva (i.e., subconjunctival hemorrhage) or in the anterior chamber (i.e., hyphema). Both of these can be spontaneous or post-traumatic. Spontaneous subconjunctival hemorrhages may follow coughing or straining or may be due to systemic hypertension. Often, it occurs without any identifiable precipitating incident and is simply noticed by the patient when looking in the mirror. Spontaneous subconjunctival hemorrhage is painless, and the presence of pain raises concern for a more serious cause of the hemorrhage, such as direct globe injury. Hyphema of



A External appearance of the eye



B Cross section of the eye

Figure 32-1. External (**A**) and internal (**B**) anatomy. (From Ragge NK, Easty DL: Immediate Eye Care. St. Louis, Mosby-Year Book, 1990.)

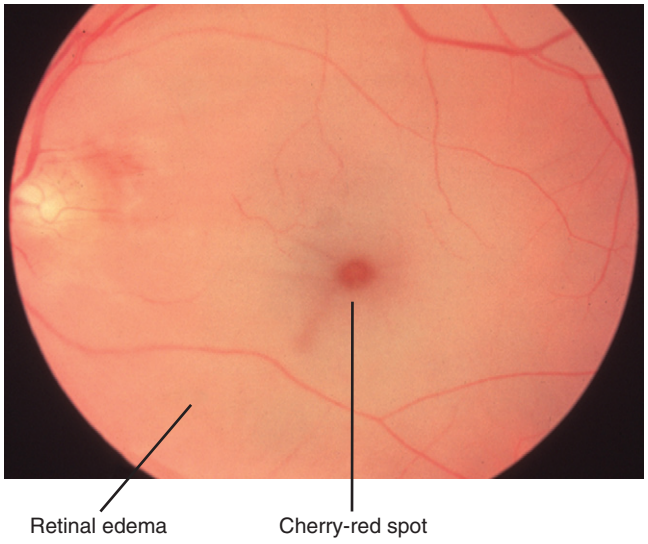


Figure 32-2. Key funduscopic findings in acute central retinal artery occlusion include general pallor of the retina (except for a characteristic cherry-red spot where the perfused choroid shows through the thinner fovea) and attenuation of retinal arteries (possibly with retinal veins preserved as in the photograph). (From Kaiser PK, Friedman NJ, Pineda R, II: The Massachusetts Eye and Ear Infirmary Illustrated Manual of Ophthalmology, 2nd ed. Philadelphia, WB Saunders, 2004, p 297.)

BOX 32-1 PIVOTAL FINDINGS MORE LIKELY ASSOCIATED WITH A SERIOUS DIAGNOSIS IN PATIENTS WITH A RED OR PAINFUL EYE

Severe ocular pain
Persistently blurred vision
Proptosis
Reduced ocular light reflection
Corneal epithelial defect or opacity
Limbal injection (i.e., ciliary flush)
Pupil unreactive to a direct light stimulus
Wearer of soft contact lenses
Neonate
Immunocompromised host
Worsening signs after 3 days of pharmacologic treatment

Adapted and reprinted, with permission, from Trobe JD: The Physician's Guide to Eye Care. San Francisco, Foundation of the American Academy of Ophthalmology, 2001.

sufficient size to be noted by the patient or bystander usually arises with pain and blurred vision.

Other subjective findings may be transient and detected only by history. The patient may relate lid swelling, tearing, discharge, crusting, or sensitivity to light. Lid swelling can be caused by inflammatory and noninflammatory processes. Concurrent erythema of the lid favors the former. In the absence of trauma or other external irritant (e.g., contact dermatitis), inflammatory processes include primary lid problems such as hordeolum (i.e., stye) or blepharitis as well as extension from concomitant conjunctivitis or cellulitis in orbital or periorbital structures. When pain is present, tearing is usually secondary. Discharge and crusting are most commonly associated with conjunctivitis, whether allergic, viral, or bacterial. Blepharitis, dacryocystitis, and canaliculitis are other inflammatory processes that may create a discharge and subsequent crusting.

Other eye status review questions include the following:

- Are contact lenses used? If so, what type, how are they cleaned, and how old are the lenses? Has there been a change in the pattern of use (especially increased use)? Were the lenses worn for a particularly long period recently? Are there problems with the lenses drying out? Does insertion of the lenses worsen or relieve the symptoms?
- Are glasses worn? If so, when was the last assessment for adequate refraction?
- Has previous eye surgery or injury occurred?
- What is the patient's usual state of health?
- What medications are being taken? Are there any allergies, including environmental allergies?

Physical Examination

A complete eye examination usually includes eight components, although many patients require only a limited or directed eye examination, depending on the presentation.[2] The mnemonic VVEEPP (pronounced "veep") plus slit-lamp and funduscopic examinations represent these components (Box 32-2).[3] Slit-lamp examination is recommended for any complaint involving trauma and for any medical presentation involving foreign body sensation or alteration of vision.

BOX 32-2 COMPLETE EYE EXAMINATION

Visual acuity (best possible using correction)
Visual fields (tested by confrontation)
External examination
  Globe position in orbit
  Conjugate gaze
  Periorbital soft tissues, bones, and sensation
Extraocular muscle movement
Pupillary evaluation (absolute and relative)
Pressure determination (tonometry)
Slit-lamp examination
  Lids and lashes
  Conjunctiva and sclera
  Cornea (with fluorescein in some cases)
  Anterior chamber
  Iris
  Lens
Funduscopic examination

Adapted from Wightman JM, Hurley LD: Emergency department management of eye injuries. Crit Decis Emerg Med 12:1, 1998.

Funduscopic examination is usually pursued if there is visual loss, visual alteration, or suggestion of serious pathology in the history and initial physical examination. A thorough physical examination can be conducted in the following order.

Visual Acuity

The initial determination of a patient's visual acuity provides a baseline from which deterioration or improvement may be followed. It is also predictive of functional outcome after ocular trauma. Visual acuity is quantitatively assessed by use of a Snellen chart test at a distance of 20 feet (6 m) or a Rosenbaum chart at a distance of 14 inches. Young patients who cannot yet read letters and numbers should be tested with an Allen chart that depicts easily recognizable shapes. Each eye is tested separately with the opposite eye carefully covered. Patients who present without their prescribed corrective lenses may be evaluated by having them view the chart through a pinhole eye cover, which negates most refractive errors in vision.

If the patient cannot distinguish letters or shapes on a chart, visual acuity must be determined qualitatively. Any printed material suffices. The result may be recorded as, for example, "patient able to read newsprint at 3 feet." If this is not possible, visual acuity is recorded as:

- Unable/able to count fingers (CF)
- Unable/able to perceive hand motion (HM)
- Unable/able to perceive light (LP)

Visual Field Testing

Confrontation is the most common method of testing visual fields in the emergency department.[4] Detection of a scotoma usually represents a retinal problem. However, glaucoma may cause scotomata that can be crescent-shaped, involve just the binasal visual fields, or affect all peripheral vision. Hemi- or quadrantanopia is more commonly a problem of the neural pathways to the brain.

External Examination

Gross abnormalities are assessed by a visual inspection of both eyes simultaneously. Findings may be more apparent if compared with the opposite side. Fractures of facial bones are associated with ocular injuries, some of which require immediate intervention by an ophthalmologist.[5]

Globe position is part of the external examination. Subtle exophthalmos and enophthalmos are rare, and are best detected by looking inferiorly, tangentially across the forehead, from over the patient's scalp.[6] Exophthalmos may have traumatic or nontraumatic causes, but is due to increased pressure or a space-occupying lesion within the orbit, which may manifest as pain. Medical causes include cellulitis or intraorbital or lacrimal tumors. Hyperthyroidism may cause enlargement of extraocular muscles. The most important cause of exophthalmos in the emergency department is retrobulbar hematoma, a condition characterized by hemorrhage within the bony orbit, behind the globe. Orbital compartment syndrome pushes the globe forward, stretching the optic nerve and retinal artery and increasing IOP. The resulting microvascular ischemia is sight-threatening if sufficiently severe and persistent. Orbital emphysema and inflammation caused by a retained foreign body behind the eye are other causes of exophthalmos. The discovery of exophthalmos should prompt ocular tonometry measurements to determine the urgency of intervention. Trauma, particularly penetrating globe injury with extrusion

of vitreous, can cause the globe to recede into the orbit, but the most common cause of enophthalmos is actually pseudoenophthalmos when the contralateral globe is proptotic.

Inspection also involves examination of the upper and lower palpebral sulci for foreign bodies or other abnormalities. The lower sulcus is easily viewed after manual retraction of the lower lid toward the cheek and having the patient gaze upward. The upper sulcus is inspected by pulling its lashes directly forward and looking under the lid with white light. The lid can then be everted by pressing a cotton-tipped applicator in the external lid crease and folding the lid margin over the applicator.

Extraocular Muscle Function

Limitation of ocular movement in one eye may be detected by having the patient follow the examiner's finger or a bright light through the cardinal movements of gaze. The eyes may move in a disconjugate fashion, or the patient may admit to diplopia if asked. Diplopia on extreme gaze in one direction may indicate entrapment of one of the extraocular muscles within a fracture site, but more often is caused simply by edema or hemorrhage related to the injury and is functional rather than actual entrapment. In the absence of trauma, diplopia is rarely associated with redness or pain.

Pupillary Evaluation

The pupils are inspected for abnormalities of shape, size, and reactivity. These examinations are conducted with light specifically directed into the pupil and by means of the swinging flashlight test.

Previous surgery (e.g., iridotomy for cataract extraction) and synechiae from prior iritis or other inflammatory condition are the most common causes of irregularly shaped pupils. Asymmetrically sized pupils may represent normal or pathologic conditions. Physiologic anisocoria is a slight difference in pupil size that occurs in up to 10% of the population. Topical or systemic medications, drugs, and toxins may cause abnormal pupillary constriction or dilation.

Pathologic reasons for failure of one pupil to constrict with a direct light stimulus include globe injury, abnormalities of afferent or efferent nerves, and paralysis of the ciliaris or sphincter pupillae muscles in the iris. Potentially serious problems, which also cause pain and redness, include uveitis and acute angle-closure glaucoma.

The swinging flashlight test is used to determine whether a relative afferent pupillary defect (RAPD) exists.[4] The patient fixes the gaze on a distant object and the examination room is darkened. The size of the pupils in lowered light is noted, and unless there is physiologic anisocoria, the pupils should be equal in size. The direct and consensual light responses of the eyes are compared as a light source, angled into the pupil from in front of the cheeks, is swung back and forth between the two. When the light source shines into an eye with an RAPD, the pupil dilates because the consensual response from withdrawal of light from the opposite eye with normal afferent activity is stronger than the direct constrictive response to light in the affected eye with inhibited afferent activity. It is termed "relative" because the response is compared with that of the opposite side as the light source is alternated between eyes. An RAPD may be partial or complete and due to inhibition of light transmission to the retina because of vitreous hemorrhage, loss of some or all of the retinal surface for light contact because of ischemia or detachment, or the presence of lesions affecting the prechiasmal optic nerve (e.g., optic neuritis).

Pressure Determination

Ocular tonometry is usually the last examination performed in the emergency department. Common methods of determining the IOP in the emergency department include use of electronic, manual (e.g., Schiøtz), or applanation tonometers. IOPs in the 10- to 20-mm Hg range are considered normal. Causes of intraocular hypertension include glaucoma in its many forms, suprachoroidal hemorrhage, and space-occupying retrobulbar pathology. Patients presenting with IOPs exceeding 20 mm Hg should have ophthalmologic consultation. Rapid treatment is usually not necessary until the pressure exceeds 30 mm Hg.

Slit-Lamp Examination

The slit lamp permits a magnified, binocular view of the conjunctivae and anterior globe for diagnostic purposes and to facilitate delicate procedures. It allows depth perception in otherwise clear structures, such as the cornea, aqueous humor, and lens. The slit-lamp examination can include the following:

- Lids and lashes may be inspected for blepharitis and pointing of a lid abscess (i.e., hordeolum). The inner canthus and lacrimal punctum may be better viewed for evidence of dacryocystitis.
- Punctures, lacerations, and inflammatory patterns of the conjunctiva or sclera may be discovered with magnification.
- Corneal abrasions, ulcers, foreign bodies, and other abnormalities may be seen. The depth of these lesions may be accurately assessed with an angled beam. Edema, which appears as a white haze or cloudiness within clear structures, can be differentiated within the epithelium or deeper stroma.
- The anterior chamber may be examined for cells (e.g., red and white blood cells) and "flare." Cells are seen as small floating objects caught in the beam of a highly angulated slit-lamp light, as dust floating in the movie theater glows from the reflected light of the projector beam. Flare is a diffuse haziness, related to cells and proteins suspended in the aqueous humor, and is often visible only when illuminated directly (Fig. 32-3). It usually represents deep

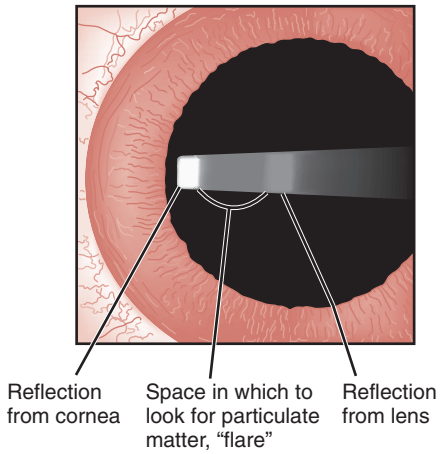


Figure 32-3. Technique of slit-lamp examination with a short, narrow light beam projected from an extreme temporal angle across the contrasting black pupil to better find cells or "flare" indicative of acute anterior uveitis. (From Ragge NK, Easty DL: Immediate Eye Care. St. Louis, Mosby-Year Book, 1990.)

inflammation of the eye and is often seen in iritis. Collections of layered blood or pus in the dependent portions of the anterior chamber are called hyphema or hypopyon, respectively, and are graded by the percentage of the vertical diameter of the visible iris when the head is upright. Foreign bodies that have penetrated the cornea may be found floating in the anterior chamber.

- The trabeculated pattern of the iris can be seen in detail. Spiraling muscle fibers may be seen in acute angle-closure glaucoma. If the beam is shown almost coaxially with the examiner's line of sight such that the red reflex is elicited, tears in the iris may be seen by light returning through the iris itself instead of just through the pupil.
- The lens should be examined for position, general clarity, and the presence of opacities or foreign bodies. The type and position of any lens implants can also be better assessed during a slit-lamp examination.

Direct Funduscopic Examination

Emergency physicians most commonly perform a nondilated funduscopic examination because there are several eye conditions in which dilation may be harmful (e.g., glaucoma). Iridodialysis, lens dislocation, and conditions requiring early intervention are usually identifiable along the visual axis.

Inability to obtain a red reflex or visualize the fundus of the eye can be due to:

- Opacification of the cornea, most commonly by edema secondary to injury or infection
- Hyphema or hypopyon within the anterior chamber
- Extremely miotic pupil
- Cataract of the lens
- Blood in the vitreous or posterior eye wall
- Retinal detachment

In the absence of trauma, few posterior findings are associated with chief complaints of external redness. Findings associated with visual loss include pallor of the retina indicating ischemia, "cupping" of the optic disk indicating glaucoma, indistinctness of disk margins indicating papilledema or optic neuritis or neuropathy, air or plaque emboli in retinal arteries, and a host of other signs indicating more chronic ocular or systemic pathology not normally amenable to management in the emergency department.

Bedside Testing

Fluorescein solution and the cobalt blue lamp are the best means for identifying damage to the corneal epithelium, including that which cannot be seen with conventional slit-lamp examination. Fluorescein highlights defects, making them easy to identify, because the fluorescing liquid is thicker in defects than it is across the normally smooth corneal surface. Use of fluorescein may reveal corneal abrasions and ulcers as well as damage from keratitides related to chemicals, ultraviolet light, or infections (e.g., herpes).

Relief of discomfort after instillation of a topical anesthetic can be used as a diagnostic test for an external source of pain. In general, abolition of pain by local anesthetic drops indicates pain of corneal origin. Modest but incomplete relief suggests a conjunctival process. Intraocular pain is not diminished by local anesthetic solution.[7] When ocular penetration is suggested, Seidel's test can be used. This test involves placing a fluorescein strip directly over an area of possible corneal disruption. The high localized concentration of fluorescein may facilitate identification of the corneal defect with a slit lamp by allowing visualization of leaking aqueous fluid diluting the fluorescein. This test does not work on the conjunctiva overlying the sclera, and a negative test result does not rule out a full-thickness corneal injury.

Ancillary Testing

An erythrocyte sedimentation rate may be used to evaluate for temporal arteritis, which may arise with eye pain and decreased visual acuity.

Infections are usually evident by examination, and laboratory tests such as a complete blood count are not necessary. Microbiologic cultures are rarely ordered in the emergency department.

Plain radiography is used to identify facial fractures associated with facial or ocular trauma or indirectly by detecting an air-fluid level in the orbit or fluid in the paranasal sinuses. Computed tomography (CT), using 1.5-mm axial and coronal cuts, provides superior imaging, but is not necessary in many cases.

CT also reliably localizes metal and many nonradiopaque foreign bodies in the globe and orbit. It can also detect small amounts of intraocular air following penetrating trauma. Magnetic resonance imaging (MRI) clearly delineates the orbital and retro-orbital structures, but cannot be employed with metallic (magnetic) foreign bodies, which can migrate to cause additional damage.[8] It is less often used in emergency eye assessment, for which, in general, CT is the initial imaging modality of choice.[9] Ultrasonography is more sensitive for detecting intraocular foreign bodies, but CT is better at delineating the damage caused by them, so they are complementary tests.[10]

DIFFERENTIAL DIAGNOSIS

Clinical findings most indicative of serious eye disorder are listed in Box 32-1.

Critical Diagnoses

Caustic injury to the eye can rapidly lead to a destructive keratoconjunctivitis (Fig. 32-4A and B) if the agent is not removed immediately. The diagnosis is made on history alone, before any other examination is performed. Early and copious irrigation is indicated. Many patients have already undergone extensive irrigation at the job site, but when the exposure has occurred in the home, irrigation prior to arrival in the emergency department is uncommon. Alkaline caustic agents cause a liquefactive necrosis of the cornea by progressively reacting with the corneal layers, and destruction is severe and relentless. Continuous irrigation is the only effective method to terminate the reaction and should be continued for at least 30 minutes. Acid injury is much less severe and requires less irrigation than alkaline exposures, but irrigation should continue until the pH of the tears is neutral or the patient is essentially asymptomatic.

Acute angle-closure glaucoma is a relatively rare but important critical diagnosis to make in the emergency department. Patients present with pain, the onset of which is often sudden in low-light conditions requiring pupillary dilation through contraction and thickening of the iris peripherally. The iris becomes immobile and often irregular, and the pupil is commonly fixed at 5 to 6 mm in diameter. Inability of the pupil to constrict may result in photophobia, and accommodation may be affected. These reactions and the increased IOP can lead to frontal headache, nausea, and vomiting. As inflammation progresses, limbal injection of the conjunctiva is almost universally seen. Figure 32-5 demonstrates many of these findings. Immediate medical intervention in the emergency

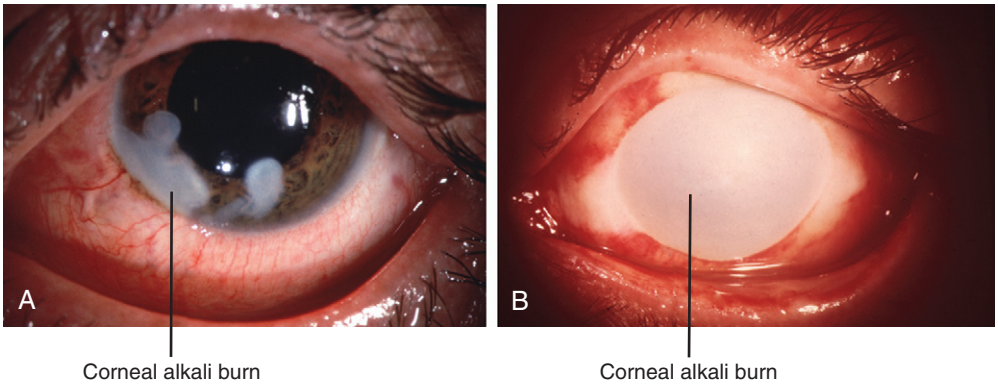


Figure 32-4. **A,** Alkali burn demonstrating corneal burns and conjunctival injection on the day of the accident. **B,** Complete corneal tissue destruction 7 days after alkali burn. (From Kaiser PK, Friedman NJ, Pineda R, II: The Massachusetts Eye and Ear Infirmary Illustrated Manual of Ophthalmology, 2nd ed. Philadelphia, WB Saunders, 2004.)

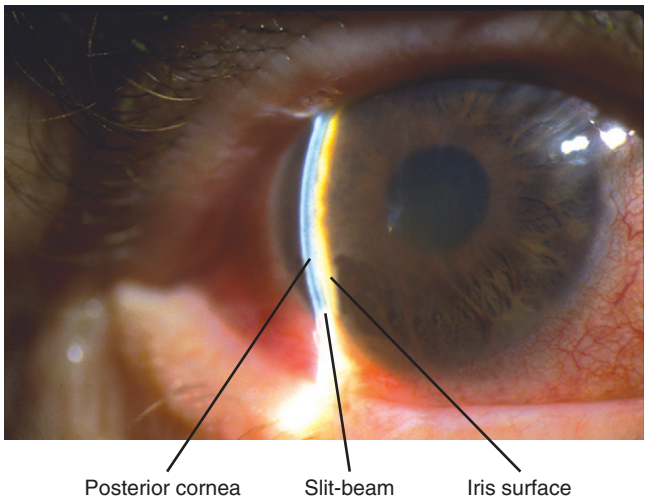


Figure 32-5. Primary angle-closure glaucoma with very shallow anterior chamber and iridocorneal touch (no space between slit-beam view of cornea and iris). (From Kaiser PK, Friedman NJ, Pineda R, II: The Massachusetts Eye and Ear Infirmary Illustrated Manual of Ophthalmology, 2nd ed. Philadelphia, WB Saunders, 2004.)

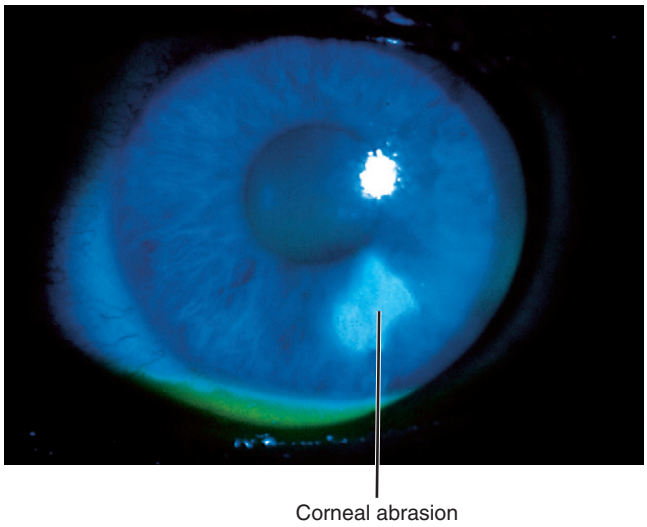


Figure 32-6. Corneal abrasion demonstrating fluorescein pooling of a small inferior epithelial defect. (From Kaiser PK, Friedman NJ, Pineda R, II: The Massachusetts Eye and Ear Infirmary Illustrated Manual of Ophthalmology, 2nd ed. Philadelphia, WB Saunders, 2004.)

department and urgent ophthalmologic consultation are warranted.

Retrobulbar hematoma (blood) is usually caused by orbital trauma, but it can also occur spontaneously in patients with coagulopathy. Retrobulbar abscess (pus) or emphysema (air) can also occur.[11,12] Elevated IOP in any of these conditions constitutes orbital compartment syndrome and a surgical emergency. Emergency intervention is to decompress the orbit by performing lateral canthotomy and cantholysis.[13,14]

Emergent Diagnoses

Most emergent diagnoses involve some kind of inflammation secondary to trauma, infection, or systemic disease. These include keratitis, anterior uveitis, scleritis, and endophthalmitis. Any of these may be complications of surgical procedures, and an appropriate ophthalmologic history must be obtained.

Keratitis, or inflammation of the cornea, is most commonly viral in origin but can also be caused by exposure to intense ultraviolet light (e.g., snow blindness, arc welder's blindness), various chemicals, or ischemia related to contact lens use. Patients present with an intense foreign-body sensation, ciliary spasm causes photophobia that is often severe, and the affected eyes are often clenched shut. Topical anesthesia provides immediate (but temporary) relief of pain, thus reinforcing the corneal origin of the process and facilitating examination and definitive diagnosis.[6] Corneal abrasions are very common and may be identified by white light or fluorescein-facilitated blue light using a slit lamp or any other magnification (Fig. 32-6). Following thorough irrigation, thermal and chemical burns must receive a careful slit-lamp examination for potential full-thickness injury. If this is not found, the corneal injury may be treated similarly to an abrasion.

In immunocompetent hosts, corneal ulcerations are most commonly due to overuse of contact lenses. They are seen as a denuding of epithelium with surrounding edema, the increased interstitial water of which is seen as whitish clouding of the normally clear tissue (Fig. 32-7). Almost all ulcerations require same-day evaluation by an ophthalmologist. Infections of the cornea with herpes simplex virus can rapidly lead to opacification and significant visual loss. It is most commonly recognized by a characteristic dendritic pattern of fluorescein pooling under blue light (Fig. 32-8). Anterior uveitis, which includes iritis and iridocyclitis, often occurs secondary to a traumatic injury or infectious process or can be associated with serious systemic immune diseases, such as adult and juvenile rheumatoid arthritis, sarcoidosis, and ankylosing spondylitis.

Scleritis is rare and may be difficult to differentiate from episcleritis, which is somewhat more common and a more

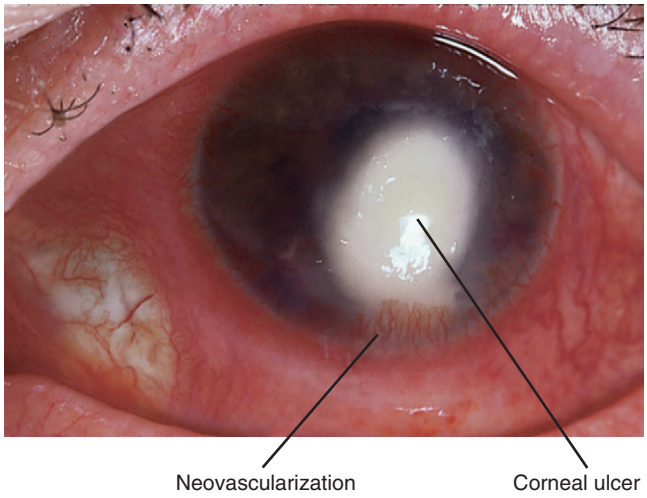


Figure 32-7. Bacterial keratitis demonstrating large, central *Streptococcus pneumoniae* corneal ulcer. Note the dense, white corneal infiltrate and the extreme conjunctival injection. (From Kaiser PK, Friedman NJ, Pineda R, II: The Massachusetts Eye and Ear Infirmary Illustrated Manual of Ophthalmology, 2nd ed. Philadelphia, WB Saunders, 2004.)

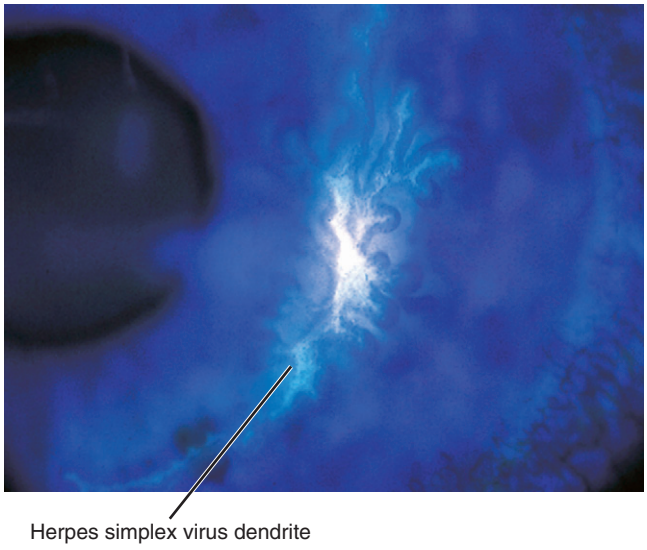


Figure 32-8. Patient demonstrating fluorescein pooling of herpes simplex virus dendrite. (From Kaiser PK, Friedman NJ, Pineda R, II: The Massachusetts Eye and Ear Infirmary Illustrated Manual of Ophthalmology, 2nd ed. Philadelphia, WB Saunders, 2004.)

benign inflammation. The former is commonly idiopathic but may be associated with a systemic inflammatory process, such as a connective tissue disease, gout, or infection (e.g., Lyme disease, syphilis, tuberculosis). Eye redness in episcleritis results from dilation of the episcleral blood vessels just underneath the conjunctiva, usually in a small sector of the visible portion of the globe. If the location of the involved layer is in doubt, a topical anesthetic allows the examiner to move the conjunctiva and its contained vessels with a cotton-tipped applicator, thus differentiating between vessels of scleral or conjunctival origin. The pain of scleritis is typically slower in onset but is often described as a severe "boring" pain that radiates to the ipsilateral forehead, cheek, or jaw. Engorgement of scleral vessels is usually more prominent and more diffuse than that of the episcleral vessels in episcleritis. A bluish hue may be seen as the underlying pigmented epithelium shows through the edematous, and hence more

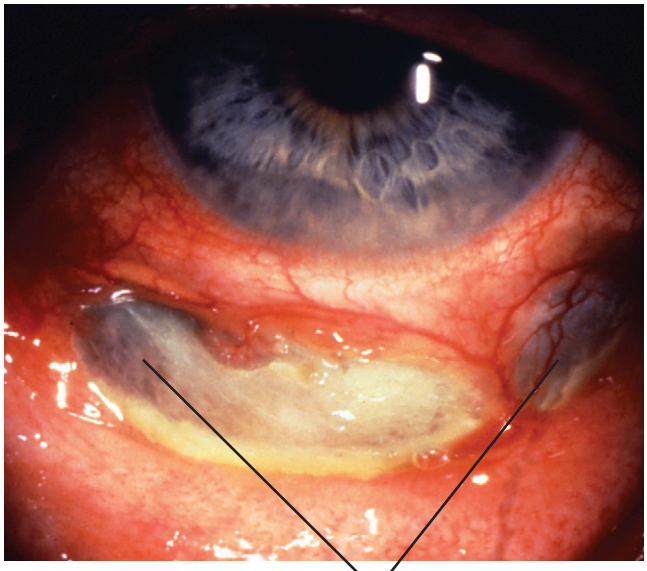


Figure 32-9. Diffuse scleritis with slight bluish region in addition to injection of scleral, episcleral, and conjunctival vessels. (From Kaiser PK, Friedman NJ, Pineda R, II: The Massachusetts Eye and Ear Infirmary Illustrated Manual of Ophthalmology, 2nd ed. Philadelphia, WB Saunders, 2004.)

translucent, sclera (Fig. 32-9). Scleritis may be associated with anterior uveitis, cataract, and secondary glaucoma.

Endophthalmitis usually results from an infection of structures inside the globe. It is most common following penetrating trauma but may begin after hematogenous seeding from a remote or systemic infection, particularly in immunocompromised hosts. Unless it is detected early, and is responsive to aggressive antimicrobial therapy, endophthalmitis is a devastating process that frequently requires enucleation.

Urgent Diagnoses

Penetrating ocular trauma is evaluated by history (e.g., working with high-speed grinding equipment), examination (extrusion of aqueous humor or other globe content; direct visualization of a foreign body in the anterior chamber, vitreous, or retina), or identification of the offending object by biplanar plain radiography, thin-cut CT, or ultrasonography. MRI should not be used if there is any possibility that the foreign object may be metallic. Indirect indicators of globe penetration are hyphema, an irregularly shaped pupil from traction on or injury to the iris' attachments, or lack of a red reflex. If penetrating ocular injury is confirmed or if the possibility persists after evaluation, an ophthalmologic consultation is indicated.[4]

Spontaneous or traumatic hyphema is often managed conservatively. Blood in the anterior chamber is usually the result of direct ocular trauma and may be associated with traumatic mydriasis or an obvious tear of the iris. If penetration and rupture can be reasonably excluded, the hyphema should be graded and IOP determined. Intraocular hypertension (or hypotension in the case of occult globe rupture) following trauma must also be evaluated by an ophthalmologist urgently. Inability to view posterior structures through the anterior blood may necessitate radiologic or ultrasonographic imaging.

Diagnostic Algorithm

A recommended algorithmic approach to the patient with an acute red eye is provided in Figure 32-10.

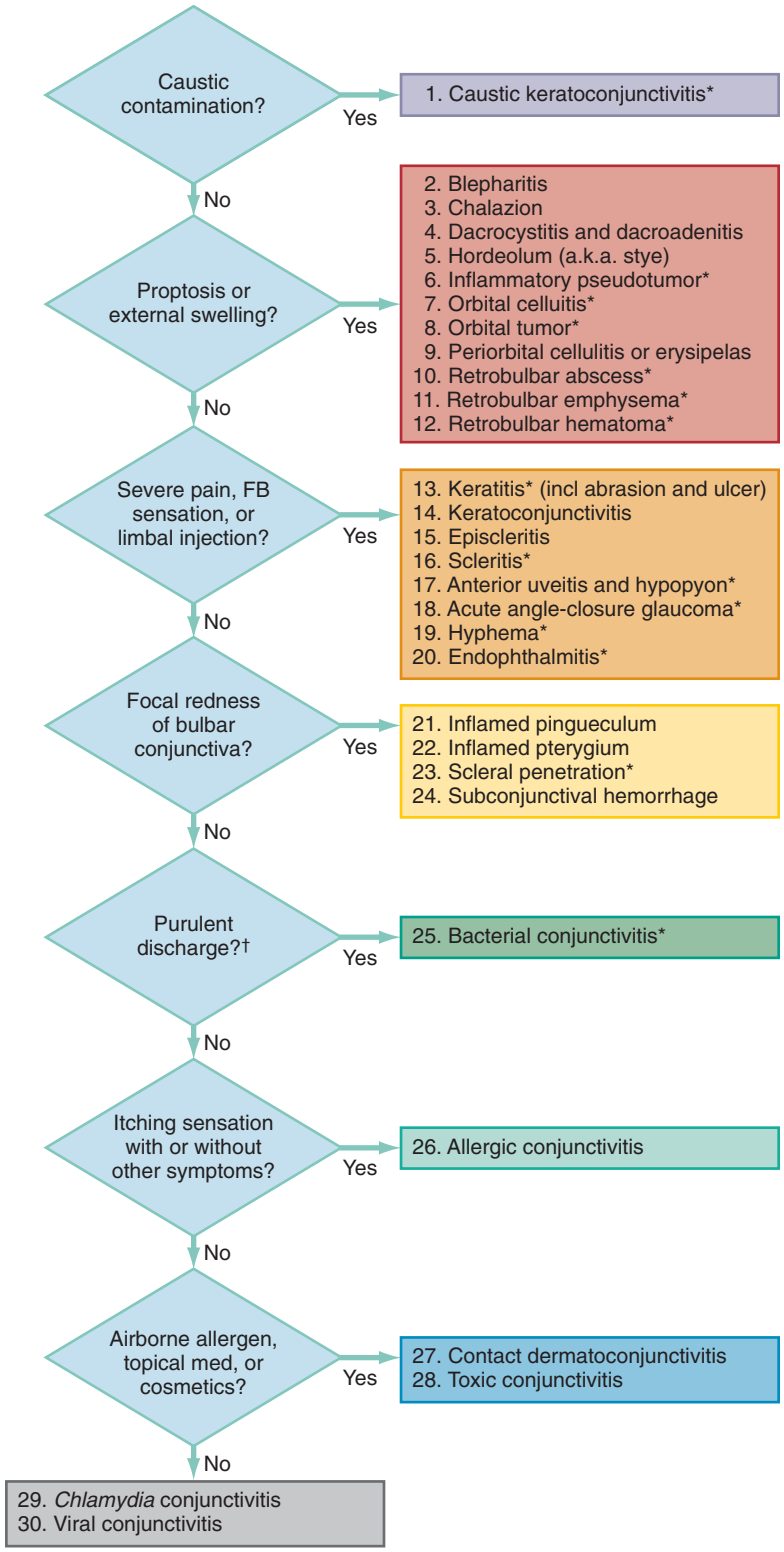


Figure 32-10. Diagnostic algorithm for red eyes. *Indicates potentially serious diagnoses if not identified on initial emergency department evaluation. †Purulent implies true pus, as opposed to the mucoid discharge more commonly associated with nonbacterial causes of conjunctivitis. a.k.a., also known as; FB, foreign body; incl, including. (Modified from Trobe JB: The Physician's Guide to Eye Care. San Francisco, Foundation of the American Academy of Ophthalmology, 2001.)

EMPIRICAL MANAGEMENT

Irrigation

Any clean water is appropriate for irrigation, and prompt initiation takes precedence over procurement of a particular irrigating solution. The most important principles are *rapid and copious* dilution and removal of the offending material. An eyewash station or faucet with tap water may be employed. Normal saline may be instilled through the end of macrodrip intravenous administration tubing. If there is no gross eye injury, a Morgan lens may be attached to this tubing, but emergency department staff do not have to help the patient hold the eye open. Quickly administering two drops of topical anesthetic and allowing 30 seconds or so for the anesthetic to become effective greatly facilitates patients' tolerance of the prolonged irrigation required. It is recommended that the first 500 to 1000 mL of irrigation fluid be

administered while examining the eye; then the Morgan lens may be placed.

Pain Relief

Pain often interferes with obtaining an adequate assessment. A topical anesthetic, such as proparacaine 0.5%, may facilitate cooperation in patients with possible injury or inflammation of the anterior eye by reducing pain and blepharospasm long enough to obtain a targeted history and focused examination. Topical anesthetic agents should not be given to patients to use at home. Parenteral or oral analgesics can be used for severe deep pain not amenable to topical relief in the emergency department, or for outpatient management of discomfort after discharge.

Mydriatic and Cycloplegic Agents

Dilation of the pupil is not usually necessary in the emergency department for funduscopic examination, but may relieve pain associated with ciliary spasm in anterior uveitis. Mydriatic agents (e.g., phenylephrine, tropicamide) merely prevent constriction of the pupil by paralyzing the sphincter pupillae muscle of the iris. Cycloplegic agents (e.g., cyclopentolate, homatropine) paralyze the ciliaris muscle, with an accompanying mydriatic effect. The agent chosen should be guided by the desired length of time of mydriasis for the particular condition being treated (Table 32-1). Mydriatic agents are contraindicated in patients with narrow-angle glaucoma.

Antimicrobial Agents

Most conjunctivitis is viral in origin, but it is often difficult to distinguish bacterial from viral types of conjunctivitis based solely on clinical grounds.[15,16] Although no definitive empirical evidence dictates the use of antibiotic solutions or ointments for surface infections, the use of broad-spectrum topical antibiotics in cases of proven bacterial conjunctivitis is associated with benefit showing significantly higher clinical remission rates.[17] Antimicrobial prophylaxis should be used for penetrating wounds to prevent bacterial keratitis or endophthalmitis.

Antibiotics are typically used to treat identified or suggested bacterial infections, even if the exact bacterial agent has not been determined. The most common causes of bacterial conjunctivitis are nontypable *Haemophylis influenzae*, *Streptococcus pneumoniae*, and *Staphylococcus aureus*.[18,19] Trachoma, a chronic keratoconjunctivitis caused by *Chlamydia trachomatis*, is the most common infectious cause of blindness.[20] Bacterial keratitis is usually seen in contact lens wearers, particularly those who wear them overnight.[21] In descending order of frequency of cultured organisms, microbial keratitis is caused by *Pseudomonas aeruginosa*, streptococcal or staphylococcal species, filamentous fungi, nonpseudomonal gram-negative rods, *Acanthamoeba*, other bacteria, and yeast.[22]

The most common organisms cultured from deeper eye structures, particularly following open-globe injuries, are *Bacillus cereus*, *Propionibacterium acnes*, and various species of *Bacillus*, *Streptococcus*, and *Staphylococcus*.[23,24] While awaiting emergent ophthalmologic consultation for possible vitrectomy, empirical parenteral antibiotic combinations include cefazolin plus gentamicin or vancomycin plus cefotaxime, ceftazidime, or ceftriaxone. Possible cases of mycotic endophthalmitis have historically been treated with amphotericin B,[23] though voriconazole has been shown to have good intraocular penetration, broad-spectrum activity, and relatively low systemic toxicity.[25]

Open wounds also require tetanus prophylaxis, if the patient's immunization status is not up to date. There is no current evidence supporting the practice of administering tetanus immunization to patients with superficial corneal abrasions.

Other Protective Interventions

Significantly increased IOP must be reversed as rapidly as possible, often before the specific cause is known. After placing the patient in at least a 30° head-up position, two drops of timolol 0.5%, a topical beta-adrenergic blocking medication, should be administered as a first-line agent to decrease the production of aqueous humor. This may be followed by two drops of dorzolamide 2%, a topical carbonic anhydrase inhibitor, to reduce aqueous humor production further. If not available, 500 mg of acetazolamide may be given orally or intravenously. If the patient has sickle cell disease or trait, oral methazolamide 50 mg must be used instead. Patients with suggested intraocular hypertension who also have nausea or vomiting should receive a parenteral antiemetic so that they do not gag or vomit, which may further increase IOP.

Specific Management

Management of the specific entities listed in the diagnostic algorithm presented in Figure 32-10 is presented in Table 32-2. Specific management of ophthalmologic conditions is also discussed in Chapter 69.

Table 32-1 Duration of Action for Common Mydriatic and Cycloplegic Medications

NAME	CONCENTRATION (%)	COMMON DURATION	MAXIMUM DURATION
Ephedrine*	5.0	0.5–1 hr	3 hr
Phenylephrine*	2.5	0.5–1 hr	3 hr
Tropicamide	0.5	3–4 hr	6 hr
Cyclopentolate	0.5	12–18 hr	24 hr
Homatropine	1.0	1–2 days	3 days
Scopolamine	0.5	2–5 days	7 days
Atropine	0.5	5–10 days	14 days

*Mydriatic action only, no cycloplegic effect. Combination products such as Cyclomydril, which is cyclopentolate 0.2% and phenylephrine 10%, are also available.

SPECIAL CONSIDERATIONS

Pediatrics

A red eye in a neonate or infant is always abnormal. It is usually caused by corneal abrasion or infection. Corneal abrasions can also be a cause of inconsolable crying in an infant. Fluorescein examination helps to identify abrasions and herpes keratitis, acquired from the birth canal. *Chlamydia* infections may also be acquired during vaginal deliveries but may not arise for weeks. These infections should be treated with oral azithromycin as well as parenteral ceftriaxone to cover *Neisseria gonorrhoeae*. Conjunctivitis associated with respiratory symptoms or infiltrates on a chest radiograph in an infant younger than 3 months should be treated with an oral macrolide. Oral antibiotics are also indicated for conjunctivitis associated with otitis media. *Mycoplasma* is a common infectious agent in these cases, and a macrolide is indicated.[14]

Table 32-2 Management Algorithm for Red Eyes Extended from Diagnostic Algorithm in Figure 32-10

DIAGNOSIS FROM FIGURE 32-10	MANAGEMENT	CONSULTATION	DISPOSITION
1. Caustic keratoconjunctivitis	Immediate and copious irrigation with tap water or sterile normal saline until tear-film pH = 7. *Solids*: lift particles out with dry swab before irrigation *Acids*: minimum of 2 L *and* 20 min *Alkalis*: minimum of 4 L *and* 40 min	Ophthalmologist must come to ED if there is any abnormal visual acuity or objective finding on examination after sufficient irrigation, with exception of expected injection of conjunctiva secondary to treatment.	May discharge only if tear film pH = 7 *and* no findings on examination except conjunctival injection *and* ophthalmologist can reevaluate next day.
2. Blepharitis Inflammation of eyelid margins often a/w crusts on awakening, FB sensation, and tearing.	None except artificial tears for dry eye.	Outpatient referral only for treatment failure after 2 wk.	Discharge with instructions to apply warm compresses to eyelids for 15 min qid and scrub lid margins and lashes with mild shampoo on washcloth bid.
3. Chalazion Inflammation of meibomian gland causing subcutaneous nodule within the eyelid.	None.	Outpatient referral only for treatment failure after 2 wk.	Discharge with instructions to apply warm compresses to eyelids for 15 min and gently massage nodule qid.
4. Dacrocystitis and dacroadenitis Eye tearing and inflammation of lower eyelid inferior to lacrimal punctum finding redness and tenderness over nasal aspect of lower lid and adjacent periorbital skin.	First r/o periorbital cellulitis (#9) and orbital cellulitis (#7). Inspect for obstruction of punctum by SLE, may express pus by pressing on sac, PO Rx for nasal and skin flora if not admitting.	Ophthalmologist may admit if systemically ill, case is moderate or severe, or no social support for patient. Ask about culturing before Rx if admitting, then Rx same as for periorbital cellultitis (#9).	May discharge mild cases with PO analgesics and antibiotics (e.g., amoxicillin/clavulanate), and instructions to apply warm compresses to eyelids for 15 min and gently massage inner canthal area qid.
5. Hordeolum (a.k.a. stye) Abscess in eyelash follicle or modified sebaceous gland at lid margin: *external* or *internal* based on side of lid margin that abscess is pointing.	*External*: Warm compresses often all that is needed, may Rx anti-*Staph* ointment bid. *Internal*: PO Rx for β-lactamase *Staph*.	Outpatient referral only for treatment failure after 2 wk.	Discharge with instructions to apply warm compresses to eyelids for 15 min and gently massage abscess qid.
6. Inflammatory pseudotumor* Nonspecific idiopathic retrobulbar inflammation with eyelid swelling, palbebral injection of conjunctiva, chemosis, proptosis, blurred vision, painful or limited ocular mobility, binocular diplopia, edema of optic disk, or venous engorgement of retina.	Measure IOP. Evaluate for infection, diabetes mellitus, and vasculitis with CBC, BMP, UA, and ESR. Obtain axial CT of brain and axial and coronal CT of orbits and sinuses.	IOP > 20 mm Hg may be surgical emergency, Rx to decrease IOP in ED.	May discharge if no systemic problems, no findings of particular concern on CT, and IOP > 20 mm Hg. Start high-dose PO steroids after discussion with ophthalmologist and ensure reevaluation in 2–3 days.
7. Orbital cellulitis* Eyelid swelling, redness and warmth of skin overlying orbit, tenderness of skin overlying bone palbebral injection of conjunctiva, and chemosis. Differentiated from periorbital cellulitis by *presence* of any finding of fever, ill appearance, blurred vision, proptosis, painful or limited ocular mobility, binocular diplopia, edema of optic disk, or venous engorgement of retina.	Measure IOP. Start IV Rx with second-generation cephalosporin (e.g., cefuroxime, cefoxitin, or cefotetan) or with ampicillin/sulbactam to cover sinus and skin flora. Alternative Rx is ticarcillin/clavulanate, piperacillin/tazobactam, vancomycin, or clindamycin + third-generation cephalosporin (e.g., cefotaxime or ceftriaxone).	IOP > 20 mm Hg may be surgical emergency, Rx to decrease IOP in ED. Obtain blood cultures and start antibiotics. Axial and coronal CT of orbits and sinuses to r/o FB, retrobulbar abscess, orbital gas, subperiosteal abscess, osteomyelitis, and changes in cavernous sinus. Consider LP.	Admit all cases of orbital cellulitis.
8. Orbital tumor* Blurred vision, proptosis or other displacement of globe, painful or limited ocular mobility, or binocular diplopia (but can be asymptomatic).	Measure IOP. Evaluate for extraocular signs of malignancy. Obtain axial CT of brain and axial and coronal CT of orbits and sinuses.	IOP > 20 mm Hg may be surgical emergency, Rx to decrease IOP in ED. Ophthalmologist may want MRI, MRA, or orbital US.	Based on findings and discussion with consultant.

Continued

Table 32-2 Management Algorithm for Red Eyes Extended from Diagnostic Algorithm in Figure 32-10—cont'd

DIAGNOSIS FROM FIGURE 32-10	MANAGEMENT	CONSULTATION	DISPOSITION
9. Periorbital cellulitis or erysipelas Eyelid swelling, redness and warmth of skin overlying orbit, tenderness of skin overlying bone, palbebral injection of conjunctiva, and chemosis. Differentiated from orbital cellulitis by *absence* of any other finding listed in #7.	First r/o orbital cellulitis (#7). PO Rx for sinus and skin flora if not admitting.	Ophthalmologist may admit if systemically ill, case is moderate or severe, or no social support for patient.	May discharge mild cases with PO antibiotics. Ophthalmologist must reevaluate next day to ensure no orbital extension.
10. Retrobulbar abscess* Findings of orbital cellulitis (#7) but a/w increased IOP.	Measure IOP unless possibility of ruptured globe. IOP > 30 mm Hg may require emergent needle aspiration or lateral canthotomy and cantholysis in ED.	IOP > 20 mm Hg may be surgical emergency, Rx to decrease IOP in ED. Obtain axial CT of brain and axial and coronal CT of orbits and sinuses.	Admit all cases of retrobulbar pathology causing increased IOP. Others might be candidates for discharge depending on cause of problem.
11. Retrobulbar emphysema* Findings of pseudotumor (#6) but a/w increased IOP.	*Abscess*: Antibiotics as in orbital cellulitis (#7). *Emphysema*: Prophylax with antibiotics to cover sinus flora. *Hematoma*: Correct any coagulopathy or thrombocytopenia.		
12. Retrobulbar hematoma* Findings of pseudotumor (#6) but occurs due to trauma, coagulopathy, or thrombocytopenia and a/w diffuse subconjunctival hemorrhage anteriorly and extending posteriorly as well as increased IOP.			
13. Keratitis (abrasion or UV injury) Pain, FB sensation, blepharospasm, tearing, photophobia, epithelial disruption on inspection under white light or fluorescein pooling under blue light. SPK appears as stippling of corneal surface [often lower 2/3 of cornea if due to light exposure].	First r/o corneal penetration either grossly or employing Seidel's test. Relieve pain and blepharospasm with topical anesthetic. Inspect all conjunctival recesses and superficial cornea for any foreign material that can be removed by irrigation or manually lifted from surface. Tetanus prophylaxis is standard of care even if cornea not penetrated.	Ophthalmologist must come to ED if there is any concern for globe penetration. Otherwise consult for follow-up examination in 1–2 days. One-time administration of cycloplegic agent may limit photophobia until follow-up examination.	May discharge cases not infected or ulcerated on topical antibiotic prophylaxis using polymyxin B combinations with bacitracin (ointment) or trimethoprim (solution). Gentamicin and sulfacetamide are less desirable single-agent alternatives. PO NSAIDs or narcotics for analgesia. Patching not necessary.
Keratitis (ulceration)* Symptoms and signs as above. Ulceration from complications of contact wear or neglected corneal abrasion has "scooped out" epithelium with surrounding edema appearing as white "cloudiness" in clear tissue.	Relieve pain and blepharospasm with topical anesthetic. *Staph.* and *Strep.* species still most common organisms, but *Pseudomonas* greater percentage in existing infections (especially contact lens wearer), so Rx with topical fluoroquinolone is preferred.	Discuss any potential need to débride or culture before starting antibiotic.	Based on findings and discussion with consultant. Typical ciprofloxacin dosing is 1 gt. q 15 min for 1 hr, then 1 gt. q hr for 8 hr, then 1 gt. q 4 hr until seen by consultant next day. PO NSAIDs or narcotics for analgesia. No patch.
Keratitis (herpetic infection)* Symptoms and signs as above. Look for other signs of herpes, varicella, zoster (or CMV infection in immunocompromised patient). Look for "dendritic" defects of cornea with fluorescein under blue light.	Relieve pain and blepharospasm with topical anesthetic. Rx with trifluridine 1% solution, vidarabine ointment, or acyclovir ointment. Varicella-zoster and CMV not normally given antivirals if immunocompetent.	Discuss with ophthalmologist any potential need to débride or culture before starting antiviral.	Based on findings and discussion with consultant. Typical trifluridine dosing is 1 gt. q 2 hr for 7 days, then taper over 2 more wk. Typical vidarabine or acyclovir dosing is five times a day for 7 days, then taper over 2 more wk. PO NSAIDs or narcotics for analgesia. No patch.

14.	Keratoconjunctivitis Conjunctivitis with subepithelial infiltrates in cornea causing pain and decreased vision, possibly with halos reported.	Treat for conjunctivitis by likely etiologic category (#25–30).	Discuss findings and use of prednisolone acetate 1% (frequency determined by ophthalmologist).	May discharge patient with medications recommended by ophthalmologist and ensure reevaluation in 2–3 days.
15.	Episcleritis Rapid onset of localized pain, injection of episcleral vessels, and localized tenderness.	Relieve irritation with artificial tears and decrease inflammation with ketorolac gtt.	Outpatient referral only for treatment failure after 2 wk.	May discharge patient with PO NSAIDs alone or in combination with topical ketarolac gtt.
16.	Scleritis* Progressively increasing eye pain with radiation to ipsilateral face and decreasing vision, photophobia, tearing, and possible pain with eye motion.	Decrease inflammation with PO NSAIDs.	Discuss findings and use of topical or PO steroids.	May discharge patient with medications recommended by ophthalmologist and ensure reevaluation in 2–3 days.
17.	Anterior uveitis and hypopyon* Eye pain, photophobia, tearing, limbal injection of conjunctiva, and cells or flare in anterior chamber. Hypopyon is layering of white cells (pus) in anterior chamber.	First r/o glaucoma with IOP measurement. Rx in ED if IOP > 20 mm Hg. Otherwise OK to dilate pupil with 2 gtt. of cyclopentolate 1%.	Discuss findings and use of prednisolone acetate 1% (frequency determined by ophthalmologist but range is q 1–6 hr).	May discharge patient with medications recommended by ophthalmologist and ensure reevaluation in 2–3 days. Patients with hypopyon are generally admitted.
18.	Acute angle-closure glaucoma Sudden-onset eye pain and blurred vision that may be a/w frontal headache, nausea, and vomiting. Anterior eye may manifest shallow or closed angle between iris and cornea, pupil fixed in mid-dilation, or limbal injection of conjunctiva. Rx in ED if IOP > 30 mm Hg.	Decrease production of aqueous humor. Timolol 0.5% 1 gt., then repeat in 30 min. Apraclonidine 1% 1 gt. once. Dorzolamide 2% 2 gtt. *or if sickle cell disease or trait* then methazolamide 50 mg PO. Decrease inflammation. Prednisolone 1% 1 gt. every 15 min four times. Constrict pupil. Pilocarpine 4% 1 gt., then repeat in 15 min Consider establishing osmotic gradient Mannitol 2 g/kg IV.	Discuss any IOP > 20 mm Hg with ophthalmologist.	Based on findings and discussion with consultant, which primarily depends on speed of onset and response to treatment.
19.	Hyphema* Pain, decreased visual acuity, gross or microscopic blood in anterior chamber, may be a/w dilated and fixed pupil following blunt trauma. Graded by amount of blood Percentage of vertical diameter of anterior chamber when blood layers with patient in upright position. Microhyphema shows no layering and only suspended red blood cells.	First r/o globe rupture. May require ultrasound if cannot visualize posterior structures. Measure IOP unless possibility of ruptured globe. IOP > 30 mm Hg may require acute treatment as in glaucoma (#18). If IOP > 20 mm Hg and no iridodialysis, may use cycloplegic to prevent iris motion.	Discuss findings and use of ε-aminocaproic acid and steroids, other medical therapy, best disposition, and follow-up examination by ophthalmologist within 2 days. Some patients may be admitted for observation, bed-rest, head elevation, and frequent medication administration.	Most patients can be discharged with careful instructions to return for any increased pain or change in vision. Patients should decrease physical activity and sleep with an eye shield in place. Eyes should be left open while awake, so any change in vision can be immediately recognized. PO NSAIDs or narcotics for analgesia.

Continued

Table 32-2 Management Algorithm for Red Eyes Extended from Diagnostic Algorithm in Figure 32-10—cont'd

DIAGNOSIS FROM FIGURE 32-10	MANAGEMENT	CONSULTATION	DISPOSITION
20. Endophthalmitis* Progressively increasing eye pain and decreasing vision, diminished red reflex, cells and flare (and possibly hypopyon) in anterior chamber, chemosis, and eyelid edema.	Empirical parenteral antibiotic administration with cefazolin + gentamicin *or* vancomycin + cefotaxime, ceftazidime, *or* ceftriaxone to cover *Bacillus*, *enterococcus*, and *Staphylococcus* spp.	Ophthalmologist must admit for parenteral and possibly intraocular antibiotics.	Admit all cases of endophthalmitis.
21. Inflamed pinguecula Inflammation of soft yellow patches in temporal and nasal edges of limbal margin.	Decrease inflammation with naphazoline or ketorolac gtt.	Outpatient referral only for treatment failure after 2 wk.	Discharge to follow-up with ophthalmologist for possible steroid therapy or surgical removal.
22. Inflamed pterygium Inflammation of firmer white nodules extending from limbal conjunctiva onto cornea.	Same as #21	Same as #21	Same as #21
23. Scleral penetration* Localized redness at site of entry, teardrop pupil, blood in anterior chamber or loss of red reflex.	Protect eye from further pressure, provide pain relief, and prevent vomiting. Tetanus prophylaxis.	Ophthalmologist must come to ED if there is any concern for globe penetration.	Admit for IV antibiotics and possible procedural intervention.
24. Subconjunctival hemorrhage Red blood beneath clear conjunctival membrane.	Exclude coagulopathy or thrombocytopenia, if indicated by history.	None required if no complications.	Reassure patient that red should resolve over 2–3 wk.
25. Bacterial conjunctivitis* Hyperpurulent discharge not typical of common "pink eye" and more commonly unilateral in adults. Inflammation of eyelid margins a/w lid edema, chemosis, and possibly subconjunctival hemorrhage, but usually no follicular "cobblestoning."	Topical polymyxin B trimethoprim in infants and children, because more *Staph.* spp. Topical sulfacetamide or gentamicin clinically effective in 90% of uncomplicated adult cases. Use topical fluoroquinolone if *Pseudomonas* possible.	Culture drainage and ophthalmology consult in all neonates and those at risk for vision loss or systemic sepsis. *Neisseria gonorrhoeae* can be rapidly sight-threatening.	Discharge uncomplicated cases with 10 days of topical antibiotics in both eyes, regardless of laterality of apparent infection. Use ointments in infants and gtt. in others.
26. Allergic conjunctivitis Often bilateral palpebral injection of conjunctiva and follicular cobblestoning of inner surface of lids that may be seasonal and a/w other allergic symptoms such as rhinitis.	Decrease irritation with naphazoline gtt.	Outpatient referral only for treatment failure after 2 wk.	Identify antigen if possible. Consider treating other allergic symptoms with PO antihistamines.
27. Contact dermatoconjunctivitis Localized lid and conjunctival redness and edema.	Irrigation with tap water or sterile normal saline. Decrease irritation with naphazoline gtt.	Outpatient referral only for severe cases or treatment failure after 2 wk.	Identify offending agent and avoid subsequent exposure. Discharge uncomplicated cases on continued naphazoline.
28. Toxic conjunctivitis Diffuse conjunctival injection, chemosis, and lid edema.	Same as #27	Same as #27	Same as #27
29. *Chlamydia* conjunctivitis Often bilateral palpebral injection of conjunctiva in neonate or other individual at risk for sexually transmitted disease.	Rx PO azithromycin for *Chlamydia*. Consider parenteral ceftriaxone for concurrent *Neisseria gonorrhoeae*.	Culture drainage and consult ophthalmology in all neonates and those at risk for vision loss or systemic sepsis.	Discharge uncomplicated cases on 5 days of PO azithromycin.
30. Viral conjunctivitis Often bilateral palpebral injection of conjunctiva and follicular cobblestoning of inner surface of lids. Inflammation of eyelid margins often a/w crusts on awakening, FB sensation, and tearing.	Decrease irritation with artifical tears, naphazoline, or ketorolac gtt.	Culture drainage and consult ophthalmology in all neonates and those at risk for vision loss or systemic sepsis.	Ask about pregnant mothers, infants, and immunocompromised individuals in close contact. Discharge uncomplicated cases with instructions on respiratory and direct-contact contagion for 2 wk.

*Potentially serious diagnoses if not identified on initial emergency department evaluation. Antibiotic choices should be based on current practice.

a.k.a., also known as; a/w, associated with; bid; twice daily; BMP, basic metabolic profile (includes electrolytes, glucose, and renal function tests); CBC, complete blood count; CMV, cytomegalovirus; CT, computed tomography; ED, emergency department; ESR, erythrocyte sedimentation rate; FB, foreign body; gt., drop; gtt. drops; IOP, intraocular pressure; LP, lumbar puncture; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; NSAIDs, nonsteroidal anti-inflammatory drugs; PO, oral; q, every; qid, 4 times a day; r/o, rule out; Rx, prescribe; SLE, slit-lamp examination; SPK, superficial punctuate keratitis; spp, species; *Staph.*, *Staphylococcus*; *Strep.*, *Streptococcus*; UA; urinalysis; US, ultrasonography; UV, ultraviolet.

Trauma

Blunt trauma is a common cause of a red and painful eye. Large hyphemas and those with clots are likely to require hospitalization for bedrest with 30° of head elevation. Systemic analgesia and, if required, antiemetics are indicated. Medications affecting platelet function should be avoided. Treatment may be indicated when the IOP exceeds 30 mm Hg, as it is in acute angle-closure glaucoma. If the iris is not injured, a long-acting cycloplegic agent (e.g., topical homatropine) may be recommended to prevent repetitive motion of the iris. Some reliable adult patients may be discharged with daily follow-up by a specialist. Strong analgesia and patching are not indicated, so that the patient may immediately identify increases in pain or decreases in visual acuity.

Corneal abrasions are common problems in the emergency department. When the emergency physician is convinced that the cornea has not received a full-thickness laceration or penetration by a foreign body, management is relatively simple. Foreign bodies (on or in the epithelium only) should be removed when possible. These may frequently adhere to a saline-moistened cotton-tipped applicator. Ones that do not may sometimes be lifted off with a blunt-tipped tool ("spud") under the binocular magnification of a slit lamp. The common use of hypodermic needle removal may damage surrounding cornea and is not recommended. Whether or not the object can be successfully removed, management is the same as for corneal abrasions. Rust staining of the corneal epithelium does not require removal in the emergency department, but patients are referred to a specialist for examination within 3 days. Prophylactic topical antibiotics are indicated for all epithelial defects of the cornea. Patching is not necessary and may be harmful. Systemic analgesia appropriate to the patient's level of pain should be provided. Larger lesions may require a prophylactic mydriatic or cycloplegic agent anticipating a secondary iritis. Topical anesthetics should not be given to the patient for home use.[4]

DISPOSITION

Most emergency department patients with eye complaints are candidates for discharge and, if indicated, follow-up in the emergency department or with an ophthalmologist in 1 to 2 days. Others may require referral only if there is lack of resolution or treatment fails. A few patients require admission for procedural intervention, parenteral antibiotic regimens, management of intractable pain, or further diagnostic evaluation. General consultation and disposition considerations for the most important entities are outlined in Table 32-2.

KEY CONCEPTS

- Prompt and prolonged irrigation is advised for patients who experience caustic injury to the eye.
- Headache and nausea may be prominent symptoms in patients with acute angle-closure glaucoma.
- Keratitis, inflammation of the cornea, is most commonly caused by a viral infection, but may also be caused by recent ultraviolet light exposure, chemical injury, or hypoxic injury from contact lens use.
- A localized corneal defect with edematous, inflammatory changes may signal corneal ulceration.
- A corneal dendritic pattern may signal a herpetic infection, which can progress to corneal opacification and visual loss.
- Pain, consensual photophobia, perilimbic conjunctivial infection, and a miotic pupil that is caused by ciliary spasm could signal iritis, which is inflammation of the iris and ciliary body, or uveitis, inflammation of the iris, ciliary body, and also choroids. The cause may be trauma or underlying autoimmune disease. The presence of cells and flare in the anterior chamber can help signal these conditions.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

PART II

Trauma

CHAPTER 33 Multiple Trauma

Eric Gross and Marc Martel

INTRODUCTION

The care of the injured patient remains one of the mainstays of emergency medicine practice. Emergency physicians play a vital role in the stabilization and diagnostic phases of trauma care. Management of these patients involves complex, time-dependent decision-making, leadership capability, and technical skill. Proper resuscitation can lead to functional outcomes, even in severely injured patients.[1]

EPIDEMIOLOGY

In 2004, there were 167,184 injury-related deaths, of which 73% were motor vehicle–related, firearms-related, or caused by poisonings or falls. Unintentional accidents were the leading cause of death in people ages 1 to 44 years. Motor vehicle collisions (MVCs) made up the largest percentage of those accidents, accounting for 26% of all injury-related deaths.[2] The number of motor vehicle deaths has remained relatively stable for the past decade. The number of people injured in motor vehicle crashes, however, has declined 22% during the same time period, to 2.7 million in 2005.[3] Homicide is one of the top five leading causes of death in people ages 1 to 44 years, with firearm injuries accounting for 17.7% of all injury deaths in 2004.[2]

The economic cost of traumatic injuries is staggering. It is estimated that the total cost of injuries that occurred in 2000 is $406 billion; this includes medical costs and lost productivity. Motor vehicle and fall injuries account for 22% ($89 billion) and 20% ($81 billion) of this total, respectively.[4]

Many of these injuries are avoidable. Proper use of lap/shoulder belts can reduce the risk of fatal injury by 45%.[5] Yet, in 2005, it is estimated that 55% of MVC occupant fatalities were unrestrained; this percentage increases to 65% for the 21- to 24-year-old age group.[5] Child safety seats reduce the risk of death in passenger cars by 71% for infants and by 54% for toddlers ages 1 to 4 years.[6] Educational and law enforcement initiatives addressing seat belts, proper child restraint, drinking and driving, gun safety, and fall prevention can assist in raising public awareness. The National Highway Traffic Safety Administration's (NHTSA) "Click-it or Ticket" campaign increased belt use in 41 of 50 states and the District of Columbia during a 2-month time period.[7] NHTSA has a similar program aimed at drunk driving called "Over the limit. Under arrest." The effect of firearm laws on decreasing firearm violence is less concrete (even though a decrease has been seen).[8] Further study is needed to determine the impact of legislation, public education, and prevention programs on firearm violence.

TRAUMA SYSTEMS

The first document to set criteria for categorizing hospitals as trauma centers was promulgated by the American College of Surgeons (ACS) Committee on Trauma in 1976.[9] As other groups recognized the importance of structured trauma care, legislation and funding to promote the development of trauma systems grew. In the early 1990s, the Health Resources and Services Administration developed the Model Trauma Care System Plan, a well-designed framework for progress measurement in trauma systems. Unfortunately, this program lost funding in 2006. As of 1998, 38 states and the District of Columbia had at least one critical element in place for a formal trauma system.[10] More up-to-date data are not readily available because the program was the main source for this information.

The benefit of regionalized trauma systems has been shown in multiple studies. A meta-analysis of 14 studies demonstrated an overall 15% decline in mortality due to the presence of a trauma system.[11] However, this apparent decline may be confounded by other factors. A nationwide study suggests that mortality reduction could not be solely attributed to the presence of a trauma system because its impact was small and statistically not significant. Rather, the presence of a primary seat belt law and mean per capita income were associated with a reduction in occupant mortality rates, whereas rural population and speed limits faster than 65 mph were associated with an increase in mortality rates.[12] As new trauma systems mature, more research will be needed to guide implementation of new system strategies to further reduce morbidity and mortality from traumatic injury.

One goal of the out-of-hospital trauma system is to transport the patient to the closest appropriate facility in a timely manner. Problems with over- and undertriage occur. Most efforts are aimed at reducing undertriage (transport of severely injured patients to lower level trauma centers), which may result in preventable morbidity and mortality from delay in definitive care. Overtriage (transport of minimally injured patients to higher level trauma centers) has no deleterious effects on patient care; however, it may contribute to unneces-

sary resource utilization and potential overcrowding in tertiary care, level 1 trauma centers. The ACS published a field triage decision scheme to assist in appropriate transport decisions (Fig. 33-1).[10]

Limitations to effective use of regionalized trauma systems remain. Hospital crowding, ambulance diversion, lack of specialist on-call availability, and reimbursement issues all contribute. In addition, from 1995 to 2005, the number of hospital emergency departments declined from 4176 to 3795.[13] Trends such as this increase the burden of emergency care on those remaining hospitals, potentially compromising care. Future funding and legislative decisions at the state and national levels will have a significant impact on the future of quality trauma care in the United States.

PRINCIPLES OF DISEASE

The emergency physician faces significant clinical uncertainty when a multiple trauma patient presents to the emergency department. Much of the diagnostic dilemma and subsequent evaluation can be directed based on knowledge of the mechanism of injury. Although mechanisms of injury alone are not good predictors of major trauma,[14] common patterns of injuries can be anticipated and specifically assessed in emergency department patients. Table 33-1 outlines several blunt trauma mechanisms of injury with potential associated clinical findings.

Basic anatomic principles are useful in the assessment of patients with penetrating trauma. In contrast to penetrating trauma from knife wounds, in which injuries can be expected along the track of the weapon, gunshot wounds depend on several factors. The amount of tissue damage is related to the kinetic energy of the bullet imparted to the patient. The bullet weight (caliber) and velocity (determined by the weapon) play a role in anticipating injuries. Gunshot wounds result in trauma to the surrounding tissue by direct laceration, crush injury, shock waves and cavitation—the displacement of tissue forward and radially. Because of these dynamic forces, the emergency physician should anticipate more widespread injuries from high-velocity weapons, such as rifles, than from low-velocity weapons, such as handguns. Similar to knife wounds, handguns generally cause injury based on direct laceration and crush generated by the missile along its track. Shotgun wounds from close range are characterized by massive tissue injury.

Injury patterns can differ significantly between adults and children subjected to similar mechanisms of trauma. The major anatomic distinctions relate to the smaller size and surface area, larger head-to-body ratio, and less protected abdominal cavity of the child. As a result, children are more vulnerable to multisystem injury in blunt trauma, more frequently sustain significant head and intra-abdominal injuries, and are more at risk for hypothermia.[15-18]

Trauma is the seventh leading cause of death in patients older than the age of 65 years.[19] Elder patients commonly sustain extremity, craniofacial, and closed head injuries. The majority of these occur as the result of a fall or an MCV. Elder trauma patients typically have normal, age-related changes in organ system function related to decreased cardiopulmonary functional reserve, decreased renal function, decreased bone density, and cerebral atrophy. These changes can increase susceptibility to sheer forces and other aspects of trauma.[20]

Comorbidities and preexisting medication use further complicate the management of elder trauma patients. Lower extremity weakness, gait disturbances, decreased visual acuity, and the use of psychotropics, antihypertensives, and sedatives have been associated with falls in elders, resulting in major injury.[21] The use of these medications, particularly antihypertensives, should not be considered causative in trauma patients with hypotension until acute hemorrhage is assessed and managed. In addition, anticoagulants, antiplatelet drugs, and aspirin are commonly prescribed, and their effects should be suspected and reversed if possible in elder trauma patients.

MANAGEMENT

Out-of-Hospital

Management of the trauma patient frequently begins prior to arrival in the emergency department by first responders. The goals of out-of-hospital care include intervening in immediately life-threatening injuries, preventing additional injury, and rapid transport to trauma centers for definitive care. Although accepted as tenets of out-of-hospital care, controversy exists regarding each of these goals.

The majority of life-threatening injuries that require intervention by out-of-hospital providers are related to airway, breathing, and circulation (the ABCs). Preventing aspiration of gastric contents and providing adequate tissue oxygenation are the primary goals of endotracheal intubation. Although controversy exists regarding the use of out-of-hospital rapid sequence induction,[22-27] securing an unprotected airway is essential in this phase of trauma management. Tension pneumothorax is the fundamental threat to adequate ventilation and requires immediate needle thoracostomy. Systemic hypotension with impaired end-organ perfusion mandates treatment in the trauma patient, despite the debate surrounding controlled hypotension versus aggressive fluid resuscitation.

Preventing additional injury requires an awareness of not only clinically evident abnormalities but also potentially more serious injuries. Coordinated extrication and transport with rigid cervical immobilization, complete spinal precautions, intensive hemodynamic monitoring, and stabilization of fractures to prevent neurovascular compromise are examples of assuming the most serious injuries exist in multiple trauma patients.

In the United States, rapid transport to the nearest appropriate facility is one of the fundamental concepts in trauma management. Much of the controversy regarding various out-of-hospital approaches to the ABCs is rooted in attempts to limit transport times and avoid further infringement on the "golden hour" of trauma care. In contrast, physician-operated emergency medical service (EMS) systems more aggressively manage airway and ventilatory issues and are more likely to commit out-of-hospital time resources to establishing hemodynamic stability prior to transport.[28,29] Rural EMS systems in the United States, where transport times may be prolonged because of the distance to a receiving facility, may benefit from more advanced interventions such as rapid sequence induction/intubation and more aggressive fluid resuscitative measures.

Emergency Department

General Principles

Care of the multiple trauma patient is complex and involves the coordination of multiple providers, including EMS personnel, emergency physicians, nurses, technicians, trauma surgeons, and subspecialists. A systematic and comprehensive approach to these patients is necessary, incorporating providers from each discipline. Advanced Trauma Life Support (ATLS) guidelines delineate the use of defined trauma response teams, with providers performing assessments, diagnostics, and interventions simultaneously. With this approach,

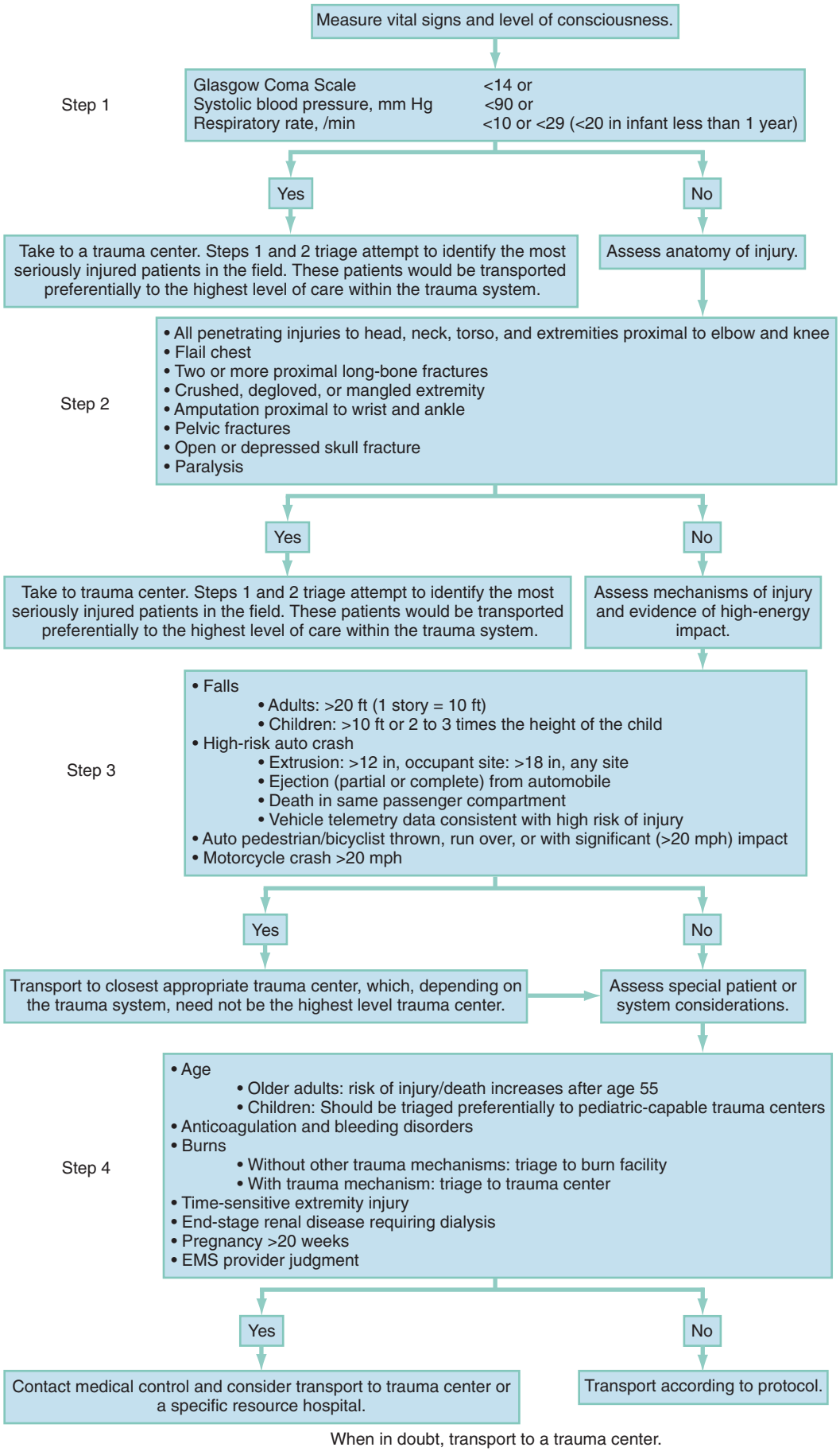


Figure 33-1. Triage decision scheme. Redrawn from American College of Surgeons, Committee on Trauma: Resources for the Optimal Care of the Injured Patient. Chicago, American College of Surgeons, 2006.

Table 33-1 Blunt Trauma Mechanisms and Associated Injuries

MECHANISM OF INJURY	ADDITIONAL CONSIDERATIONS	POTENTIAL ASSOCIATED INJURIES
Motor vehicle collisions		
Head-on collision		Facial injuries Lower extremity injuries Aortic injuries
Rear-end collision		Hyperextension injuries of cervical spine Cervical spine fractures Central cord syndrome
Lateral (T-bone) collision		Thoracic injuries Abdominal injuries—spleen, liver Pelvic injuries Clavicle, humerus, rib fractures
Rollover	Greater chance of ejection Significant mechanism of injury	Crush injuries Compression fractures of spine
Ejected from vehicle	Likely unrestrained Significant mortality	Spinal injuries
Windshield damage	Likely unrestrained	Closed head injuries, coup and countercoup injuries Facial fractures Skull fractures Cervical spine fractures
Steering wheel damage	Likely unrestrained	Thoracic injuries Sternal and rib fractures, flail chest Cardiac contusion Aortic injuries Hemo/pneumothoraces
Dashboard involvement/damage		Pelvic and acetabular injuries Dislocated hip
Restraint/seat belt use		
Proper three-point restraint	Decreased morbidity	Sternal and rib fractures, pulmonary contusions
Lap belt only		Chance fractures, abdominal injuries, head and facial injuries/fractures
Shoulder belt only		Cervical spine injuries/fractures, "submarine" out of restraint devices (possible ejection)
Airbag deployment	Front-end collisions Less severe head/upper torso injuries Not effective for lateral impacts More severe injuries in children (improper front seat placement)	Upper extremity soft tissue injuries/fractures Lower extremity injuries/fractures
Pedestrian versus automobile		
Low speed (braking automobile)		Tibia and fibula fractures, knee injuries
High speed		Waddle's triad—tibia/fibula or femur fractures, truncal injuries, craniofacial injuries "Thrown" pedestrians at risk for multisystem injuries
Bicycle		
Automobile related		Closed head injuries "Handlebar" injuries Spleen/liver lacerations Additional intra-abdominal injuries Consider penetrating injuries
Nonautomobile related		Extremity injuries "Handlebar" injuries
Falls	LD_{50} 36–60 ft	
Vertical impact		Calcaneal and lower extremity fractures Pelvic fractures Closed head injuries Cervical spine fractures Renal and renal vascular injuries
Horizontal impact		Craniofacial fractures Hand and wrist fractures Abdominal and thoracic visceral injuries Aortic injuries

Table 33-2 American College of Surgeons Requirements for the Presence of a Surgeon in Major Resuscitations

A surgeon should be present in the emergency department on trauma patient arrival or within 15 minutes if any of the following major criteria are found:
- Confirmed hypotension (systolic blood pressure < 90 mm Hg)
- Respiratory compromise requiring intubation
- Penetrating gunshot wound to the neck, chest, abdomen, or pelvis
- Glasgow Coma Scale score of <8 attributed to trauma
- Discretion of emergency physician

the physician team leader coordinates the management of the patient, considering the presence of life- or limb-threatening injuries in a sequential manner.

For level 1 trauma centers, the ACS mandates the presence of a surgeon or an appropriate representative (e.g., a fourth- or fifth-year surgery resident) to be present in the hospital 24 hours a day. The attending surgeon is expected to be present in the emergency department no later than 15 minutes after the emergency department arrival of trauma patients (Table 33-2).[10] As the specialty of emergency medicine has evolved and the number of residency-trained and board-certified emergency physicians has increased, the need for a surgeon for all trauma patients has been increasingly debated.[30-34] Optimal patient care is best provided in a collaborative, patient-centered manner.

The priorities in the treatment of trauma patients are similar to those for any other life-threatening condition. Securing the airway, maintaining ventilation, controlling hemorrhage, and treating shock are first priorities because of their crucial importance for survival. The emergency physician should give consideration to the worst possible injury and act accordingly until the diagnosis is confirmed or excluded. The consequences of an overzealous evaluation are more acceptable than those of a missed injury. Based on ATLS, the phases of emergency department care are divided into the primary survey with interventions, initial diagnostics and imaging, the secondary survey, and disposition.[35]

Primary Survey

Airway and Breathing. Proper assessment and management of airway, oxygenation, and ventilation in the trauma patient is of utmost importance but can be challenging. In a review of 44,404 trauma patient admissions and 2594 deaths, airway management was responsible for 16% of preventable errors likely contributing to trauma mortality.[36] The goals of airway management are threefold: airway protection, adequate oxygenation, and adequate ventilation.

Airway protection is necessary in a variety of trauma patients. Airway obstruction mandates immediate intervention. Obstruction from debris, blood, or vomitus may be easily removed with suction. Neck or facial trauma may be more problematic. Swelling, distorted anatomy, and hematoma formation may all contribute to impending obstruction. Early airway control is safest because these conditions may rapidly worsen. Inability to adequately protect the airway, such as in patients with depressed levels of consciousness, is another indication for intervention. Airway control is recommended in patients with significant head injury (GCS ≤ 8).[37]

As a general rule, all trauma patients should be placed on supplemental oxygen. Adequate oxygenation has a direct effect on outcome of many trauma patients. In head-injured patients, hypoxia in both out-of-hospital and hospital phases of resuscitation has been associated with poorer outcomes.[38-41] Hypoxia may also worsen outcome in spinal cord injury.[42] Maintenance of Pao_2 greater than 60 mm Hg has been recommended.[43] Inadequate ventilation, which may lead to respiratory acidosis, can be noted by the rate and quality of respirations. Signs of inadequate oxygenation may be more subtle and include agitation and restlessness. Assessment for injury that may compromise oxygenation, ventilation, or both requires careful inspection and auscultation of the chest. Signs of such compromising injury include increased work of breathing, tachypnea, penetrating wounds, flail segments, tracheal deviation, and distended neck veins. In determining the need for more aggressive airway management, these data are put into the context of the patient's overall presentation. Certain ventilatory problems, such as pneumothorax or hemothorax, may require tube thoracostomy in addition to intubation. Early intervention is preferable in the tenuous patient.

Once the decision to intubate the patient has been made, many considerations must be taken into account. If the patient's condition allows, a brief neurologic examination prior to paralytics can be helpful in determining the extent of injury. Also, cervical spine injury precautions should be considered for patients with blunt trauma and gunshot wounds to the neck. Rapid sequence induction and orotracheal intubation with in-line cervical stabilization provides a safe method. There have been no reported cases of spinal cord injury from orotracheal intubation if proper stabilization has been applied.[44] There are many approaches to airway control, and many alternative devices, such as the flexible fiberoptic scope, intubating laryngeal mask airway, and video-assisted laryngoscope, are now available to assist in intubation. The choice will be based on clinical scenario and physician comfort. A review of the literature did not reveal one superior modality for intubation of the patient with suspected spinal cord injury.[45] Nasotracheal intubation is generally undesirable in trauma patients due to the potential for abrupt rises in intracranial pressure, a higher complication rate than that for orotracheal intubation,[46] and relative contraindications of severe midface trauma or severe basilar skull fracture.

Surgical airways are indicated in cases of failure or contraindication to orotracheal or nasotracheal intubation. Cricothyrotomy is the preferred method. A variety of devices for percutaneous cricothyrotomy are available that show good success rates and are easy to use.[47-49] If there is any question of the ability to identify the cricothyroid membrane, the traditional surgical approach with a vertical incision should be used.

Circulation. Assessment of hemodynamics and circulatory status are of critical importance after the airway has been evaluated and controlled and adequate ventilation has been ensured. The assessment of circulation is multidimensional. Clinical indicators of adequate perfusion include mental status, skin color and temperature, heart rate, blood pressure, and capillary refill. A normal finding of any single sign does not rule out shock. Mental status changes associated with hypoperfusion can include anxiety, agitation, or sedation. Cool, pale skin or extremities with delayed capillary refill suggest inadequate perfusion and shock. A normal heart rate and/or blood pressure can be present despite significant hemorrhage. Conversely, tachycardia may be seen without evidence of significant volume loss.

Control of external hemorrhage is crucial. Traditionally, direct pressure to external bleeding sites has been advocated and the use of tourniquets has been discouraged. The use of direct pressure on bleeding remains first-line therapy; recent

data have suggested the more liberal use of tourniquets for massive extremity bleeding that is not easily controlled.[50-53] Similarly, recent studies of newer hemostatic agents have shown potential application both in combat and out-of-hospital settings.[54-57]

Intravenous access is required early in the assessment of circulation. Two large-bore (14- or 16-gauge) intravenous catheters are recommended. Routine intravenous access may be difficult or unobtainable in certain cases. Intraosseous vascular access can be obtained rapidly in both pediatric[58] and adult[59] patients and allows the safe infusion of large amounts of fluid or blood products. Compact, battery-operated intraosseous drills have recently been introduced. Ultrasound-guided peripheral venous access should be considered in patients when blind peripheral attempts are unsuccessful.[60-62] Central venous access may also be indicated in the appropriate clinical scenario or based on physician discretion. The use of ultrasound has been shown to increase successful vein cannulation and decrease complications in the placement of central venous lines.[63-67] Central venous pressure measurements may be used to direct resuscitative efforts but should not delay definitive care.

The choice of fluids for resuscitation includes crystalloid, colloid, and blood products. Fluid replacement is generally based on a 3:1 ratio of fluids to blood loss. There are few clinically significant differences between lactated Ringer's and normal saline. The debate regarding the choice of fluid for resuscitation is ongoing. No indisputable advantages of colloids have been demonstrated. Therefore, the less expensive and more readily available crystalloids are the routine mainstay as first line of therapy. No clear benefit to the use of hypertonic saline has been established.[68-71] Current ATLS guidelines standardize the ratio of replacement fluids to loss and recommend 2 L of crystalloid be infused in all patients in shock, followed by blood products. O-positive blood should be used except in women of childbearing age. Type-specific blood should be used when available, but emergent transfusion should not be delayed.

The concept of "permissive hypotension" is based on the concern that resuscitation to normal blood pressures may increase bleeding from a site that is contained and not actively hemorrhaging.[72] Clinically, restoration of normal blood pressure is delayed until active bleeding foci are ruled out. Although data exist to support this strategy,[72,73] a Cochrane review of the six available clinical trials meeting inclusion criteria did not support (or disprove) the use of early or larger volume intravenous fluids in uncontrolled bleeding.[74] Permissive hypotension is contraindicated in the management of traumatic brain injury because of the risk of hypoperfusion.[75,76]

The extended focused abdominal sonography in trauma (eFAST) examination should be performed on all patients as an adjunct to the assessment of circulation. The presence or absence of free intra-abdominal, -thoracic, or -pelvic hemorrhage or pneumothorax diagnosed by ultrasound will direct the management of trauma patients. Pericardial effusions or tamponade can be readily identified. In addition, ultrasound evaluation of the inferior vena cava may be useful in the overall assessment of fluid status in resuscitation.[77-81]

Disability. A rapid assessment of the patient's neurologic status is necessary early in the emergency department course. The Glasgow Coma Scale score is commonly employed (see Chapter 38).

Exposure. The final phase of the primary survey is completely undressing the patient in order to assess for inconspicuous injuries. Special attention to the axilla, perineum, and skin folds is needed. Preventing hypothermia is essential in this phase. Blankets, warming lights, and warm fluids may be used as indicated.

Secondary Survey

The goals of the secondary survey are to obtain pertinent historical data about the patient and injury as well as evaluate and treat injuries not found on the primary survey. An AMPLE (*a*llergies, *m*edications, *p*ast medical history, *l*ast meal, *e*nvironments and events) history should be obtained. Frequent reassessment of the ABCs throughout the emergency department phase of management is necessary. If deterioration occurs, a complete reevaluation of the primary survey should be initiated. Features of the secondary survey and management are listed in Table 33-3.

Table 33-3 Secondary Survey

REGION/SYSTEM	ASSESSMENT/EXAMINATION
General	Level of consciousness GCS score Specific complaints
Head	Pupils (size, shape, reactivity, visual fields) Contusions Lacerations Evidence of skull fracture (hemotympanum, Battle's sign, raccoon eyes, palpable defects)
Face	Contusions Lacerations Midface instability Malocclusion
Neck (maintain cervical immobilization)	Penetrating injury/lacerations Tracheal deviation Jugular venous distention Subcutaneous emphysema Hematoma Midline cervical tenderness
Chest	Respiratory effort/excursion Contusions Lacerations Focal tenderness/crepitus Subcutaneous emphysema Heart tones (muffled) Breath sounds (symmetrical)
Abdomen/flank	Contusions Penetrating injury/lacerations Tenderness Peritoneal signs
Pelvis/genitourinary	Contusions Lacerations Stability/symphyseal tenderness Blood (urethral meatus, vaginal bleeding, hematuria) Rectal examination
Neurologic/spinal cord	Midline bony spinal tenderness Mental status Paresthesias Sensory level Motor function, including sphincter tone
Extremities	Contusions Lacerations Deformity Focal tenderness Pulses Capillary refill Evaluation of compartments

Pitfalls

The goal of trauma management in the emergency department is to provide life-saving interventions and evaluate for injuries. The tenets of ATLS provide a structured approach to ensure a thorough assessment is performed. Because multiple trauma patients present with a variety of injuries from varying mechanisms, the initial focus is directed at defining the most serious pathology. The emergency physician must be aware of potential pitfalls. Studies from large trauma centers have shown that preventable deaths frequently result from human error and are related to the inability to intubate or secure the airway; delayed control of thoracic, abdominal, and pelvic hemorrhage; and several inpatient factors.[36,82] Head-injured, unconscious, and intubated patients frequently have injuries that are not identified early in their hospital course.[83-85] More aggressive diagnostics may be indicated in this subset of patients when history and patient-specific complaints are not obtainable. When cervical radiography is indicated, it is essential that the imaging obtained is complete and adequate. Limited radiographic series and inadequate cervical spine imaging have been shown to result in missed or delayed diagnosis of injuries.[86]

Radiographic Evaluation

The approach to radiographic evaluation of the trauma patient has changed in recent years. The mantra of C-spine, chest, and pelvis radiographs for all trauma patients has been challenged, and new recommendations continue to emerge. However, in the critically injured patient, imaging of the chest and pelvis and an eFAST exam should be obtained early in the evaluation. These studies provide essential information on possible sources of hemorrhage in either the chest or abdomen or from a pelvic fracture.

Imaging of the cervical spine can usually be delayed; however, in a patient with neurologic findings and persistent moderate hypotension (e.g., 70 mm Hg), neurogenic shock should be considered. A positive finding on C-spine imaging (e.g., fracture, soft tissue swelling, and subluxation) may confirm this if other causes of hypotension have been ruled out. A single cross-table lateral cervical radiograph is not adequate to fully assess the cervical spine; in trauma patients, the sensitivity is too low to rule out fracture.[87-90]

Cervical spine radiographs may not be necessary in all trauma patients. The NEXUS criteria allows clinical clearance of the cervical spine in patients without posterior midline tenderness, focal neurologic deficit, altered mental status, intoxication, or distracting injury.[91] The Canadian C-spine rule uses a different set of criteria and, although more complex, has higher specificity and therefore allows the elimination of a higher percentage of unnecessary x-rays.[92] In a patient with a concerning mechanism of injury or physical examination, computed tomography (CT) scanning is more efficient and effective than plain radiography[87] and should be considered the primary imaging modality. Plain C-spine radiographs are often inadequate to identify fractures and often miss secondary injury.[93] In the patient with a low-risk mechanism of injury and no neurologic findings on examination, plain radiography alone may be sufficient to rule out cervical fracture.[94] If this approach is used, three views of the cervical spine (lateral, anteroposterior, and odontoid) should be obtained.[95]

Imaging studies of the thoracolumbar spine and extremities can also be delayed until higher priority assessments and interventions are complete. Once the patient has been stabilized, the clinical examination can direct whether additional radiographic examinations are necessary.

Imaging of the thorax early in the evaluation of the trauma patient can give important information about potentially life-threatening injuries. However, the dogmatic "chest x-ray (CXR) for all trauma patients" approach to radiographic evaluation of the chest has undergone some recent challenges. Plain radiography of the chest is considered an acceptable first screening modality. However, in the patient with a significant blunt mechanism of injury, CT scanning may be considered the imaging modality of choice. The sensitivity of CXR alone, *even in patients with a normal physical exam*, may be too low for use as the primary screening tool to rule out injury to the mediastinum or a blunt aortic dissection,[96,97] and the results of those radiographs likely do not affect decision-making.[98] In patients with penetrating thoracic injury, primary CT scan, rather than repeat CXRs, can speed disposition.[99] Cost and radiation considerations must, of course, be taken into account. Other preliminary evidence suggests that some patients may not require chest imaging.[100] Ultrasound is gaining favor as the initial screening tool for pneumothorax and hemothorax because it shows better sensitivity and is more rapid than CXR.[101,102] One possible approach for initial screening of the blunt trauma patient with a significant mechanism of injury could be carried out by thoracic ultrasound to identify life-threatening pneumo- or hemothorax that must be immediately managed, followed by chest CT scan to further elucidate other injuries.

Pelvis radiographs are useful in the severely injured trauma patient. Pelvic fractures can account for significant hemorrhage, and early recognition of fracture and closure of the pelvic space can mitigate hypotension in these patients. Although not validated in large multicenter studies, evidence suggests that pelvic radiographs may be omitted in patients without altered level of consciousness, complaint of pelvic pain, pelvic tenderness on examination, distracting injury, or clinical intoxication.[103,104] Stable patients undergoing CT scan of the abdomen and pelvis can be further evaluated by bone windows of the CT scan.

As mentioned previously, the eFAST exam should take place early in the evaluation of the trauma patient, ideally as part of the primary survey. A positive scan in hypotensive patients can identify, with good sensitivity, those in need of emergent laparotomy.[52] In addition, valuable information regarding the presence or absence of pericardial effusion can be obtained. False-negative scans can occur with hollow viscous injuries or solid organ injuries without free fluid.[105] A normal scan does not necessarily eliminate the need for further abdominal imaging in significantly injured patients. Further discussion and suggested algorithms are found in Chapter 42.

Laboratory Evaluation

Laboratory evaluation of the trauma patient can provide an objective measure of the adequacy of resuscitation. It also provides much needed information for proper transfusion products and the onset of coagulopathy. Finally, it provides baseline information and values for follow-up studies (e.g., tracking hemoglobin values in a patient with a nonoperative splenic injury).

Lactate and base deficit have both been used to measure adequacy of resuscitation in the trauma patient.[106,107] New non-invasive devices, such as muscle tissue oxygenation and sublingual capnometry, have shown promise in assessing severity of shock and predicting multiorgan dysfunction and mortality.[108-110] Using one of these objective markers can assist in ensuring proper resuscitation of these patients.

All patients with potentially serious injuries should have blood type and screening done. Cross-matched blood should be immediately ordered for those with apparent serious hemorrhage. As transfusion requirements increase, attention should be paid to the development of coagulopathy. INR and fibrinogen should be followed in these patients. Routine electrolytes, blood urea nitrogen, creatinine, complete blood count, and pregnancy testing (when appropriate) should be obtained as well.

DISPOSITION

The emergency department management of the multiple trauma patient is but one critical phase of the spectrum of care. The decision to admit the patient or transfer to a tertiary care facility should be coordinated based on available resources, consultation with the trauma surgeon, and consideration of institutional and regional guidelines.

Ultimate disposition is dictated by a number of factors, including the patient's condition, the nature of the injury, and the availability of surgeons, subspecialists, and anesthesiologists. Possible dispositions include transfer to the operating room, admission to the surgical service, limited observation in the emergency department, or transfer to another hospital. The level of care and monitoring established in the emergency department should be maintained throughout transfer. All equipment and medications needed for resuscitation and maintenance of vital functions should be available during the transfer, as should qualified personnel to oversee the patient's care.

In cases of interhospital transfers, all arrangements should be carefully coordinated by physicians at the two institutions. Stabilizing measures are begun before the patient's transfer, but decompensation in transit should be anticipated. Qualified personnel and necessary resuscitative equipment must accompany the patient. The compelling reason for transferring a patient with life-threatening trauma is the lack of resources or personnel to care for the patient's particular injuries. Transfer should not be delayed for nonessential diagnostic procedures. All documentation and results of ancillary testing should accompany the patient in transfer.

In certain circumstances, the multiple trauma patient may not need admission or interhospital transfer. The decision to discharge these patients must be evaluated carefully because many traumatic injuries may present in a delayed manner. When discharge is considered, thorough emergency department evaluation is necessary with resources in place to ensure an optimal outcome: surgical consultation where appropriate, attending radiologist support for radiographic image interpretation, and timely, scheduled follow-up as an outpatient.

SPECIAL CONSIDERATIONS

The role of emergency department thoracotomy (EDT) has become more selective in order to limit futile resuscitation efforts and minimize risk to providers. Patients with penetrating trauma who have cardiac arrest while in transport or the emergency department are most likely to benefit from EDT. In contrast, cardiac arrest patients with blunt trauma, prolonged cardiopulmonary resuscitation (CPR), or delayed transport times generally have dismal outcomes not altered by EDT.[111-113] Most institutions have protocols in place outlining criteria for which EDT would be performed. The National Association of EMS Physicians and the ACS Committee on Trauma have published guidelines for withholding or terminating resuscitation efforts in out-of-hospital traumatic cardiac arrest patients. As a result, these guidelines often limit the transport of patients who would not likely benefit from EDT. Patients who may not be transported include any blunt trauma patient without vital signs at the scene, apneic or pulseless penetrating trauma victims without other signs of life, patients receiving more than 15 minutes of CPR, or patients with transport times of more than 15 minutes after arrest.[114] Suggested algorithms for the application of EDT are outlined in Figures 33-2 and 33-3.

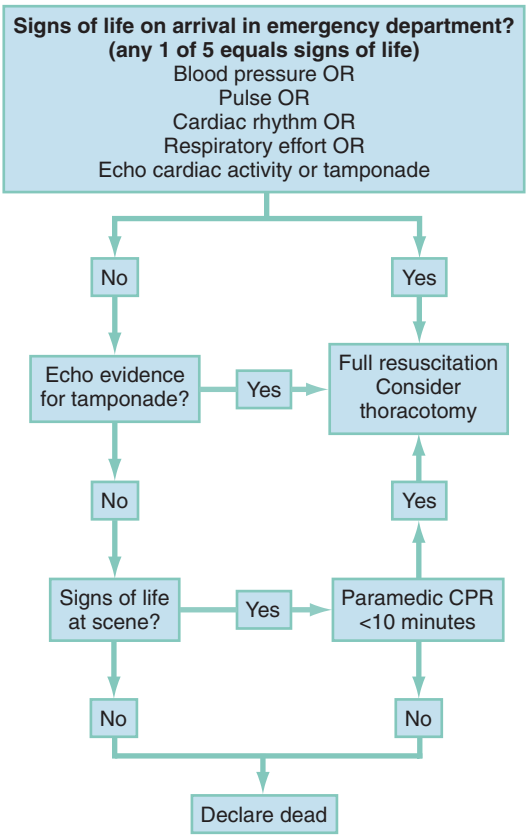


Figure 33-2. Penetrating trauma emergency department thoracotomy algorithm.

When performed, the goal of EDT is to manage rapidly correctable traumatic injuries and allow for transfer to definitive operative intervention. The use of ultrasound should be employed to assist in determining the presence or absence of pericardial effusions and tamponade. When the chest is open, a number of therapeutic measures can be undertaken, depending on the injuries present. After identifying the phrenic nerve, tamponade should be relieved by pericardotomy. Cardiac injuries are sutured or hemorrhage is controlled with digital pressure or placement of a Foley catheter balloon. Compressing or cross-clamping the pulmonary hilum can control major pulmonary bleeding, but damage to the bronchus is likely to occur and may require repair if the patient survives. The descending aorta is compressed to maximize coronary and cerebral perfusion. The aorta should remain clamped until hemorrhage has been controlled and volume replaced. Open cardiac massage can also be performed.

Acknowledgments

We acknowledge the previous authors of this chapter, Drs. Susan L. Gin-Shaw and Robert C. Jordan.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

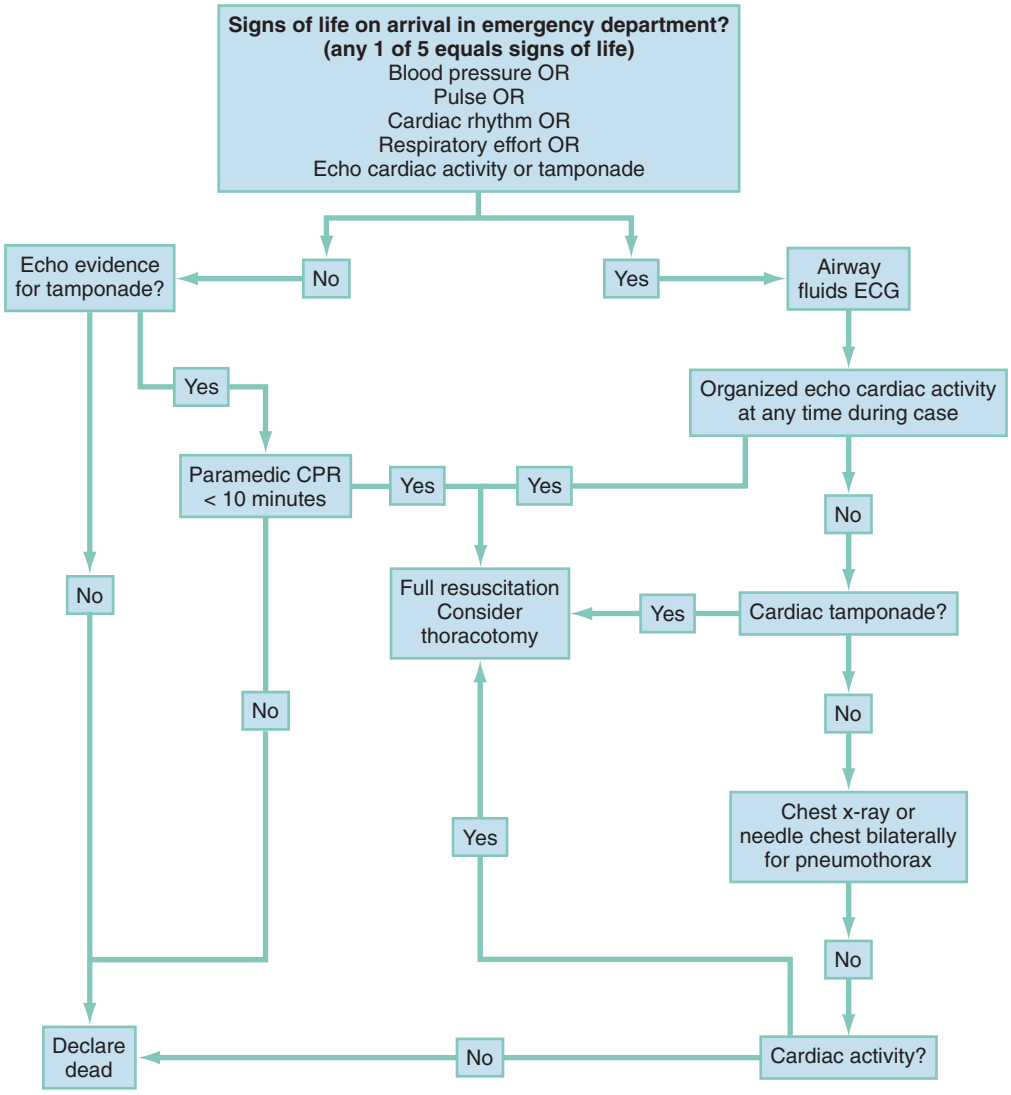


Figure 33-3. Blunt trauma emergency department thoracotomy algorithm.

CHAPTER 34

Trauma in Pregnancy

*Kriti Bhatia and Hilarie Cranmer**

PERSPECTIVE

Trauma occurs in 6 to 7% of all pregnancies. It is the leading cause of maternal death due to nonobstetric causes, accounting for close to 50% of fatalities in pregnant women.[1] The most common causes of injury in pregnancy, in order of frequency, that result in emergency department (ED) visits are motor vehicle crashes (MVCs), interpersonal violence, and falls.[2-6] Patients with penetrating injuries present more frequently to EDs in inner city medical centers.[7] Of note, 8% of women, aged 15 to 40, admitted to a trauma center do not yet know they are pregnant.[8] Commonly used thresholds of fetal viability are an estimated gestational age of 24 to 26 weeks or an estimated fetal weight of 500 g. Only viable fetuses are monitored, because no obstetric intervention will alter the outcome with a previable fetus.[9] Counseling on proper seatbelt and alcohol use and screening for interpersonal violence may help to reduce the morbidity and mortality rates for pregnant patients. Although the essential principles of trauma management remain unchanged in the pregnant patient, a number of special points need to be considered. Pregnancy causes alterations in physiology and anatomy that affect multiple organ systems. Although there are two lives involved, maternal life takes priority.

PRINCIPLES OF DISEASE—CHANGES OF PREGNANCY

Physiology

Cardiovascular

The normal cardiovascular changes of pregnancy can alter the presentation of shock and vascular events (Table 34-1).

Some Alterations Mimic Shock. Blood pressure declines in the first trimester, levels out in the second trimester, and then returns to nonpregnant levels during the third trimester. The decline in systole is small, 2 to 4 mm Hg, whereas diastole falls 5 to 15 mm Hg. Heart rate increases in pregnancy but does not rise by more than 10 to 15 beats per minute above baseline (mean of approximately 90 beats/min).[10]

A major contributor to maternal hypotension is the supine hypotensive syndrome. After 20 weeks' gestation, the uterus has risen to the level of the inferior vena cava, resulting in compression when the mother is supine. Such caval obstruction diminishes cardiac preload, which can decrease cardiac output 28%, resulting in reduced systolic blood pressure by 30 mm Hg.[10] In late pregnancy, it is common for the inferior vena cava to become completely occluded when the pregnant patient is supine. Attempts at resuscitation will be improved if compression is relieved. To determine whether observed hypotension is related to positioning, the pregnant woman's pelvis can be tilted so that the uterus is displaced from the inferior vena cava, which is to the patient's left, unless otherwise prevented due to other injuries (e.g., hip fracture). The uterus can also be manually pushed to the left by using two hands and pushing it toward the patient's head. One study found that tilting limited to only about 15 degrees may only partially resolve vena caval obstruction;[11]thus, maintaining a position between 15 and 30 degrees is optimal. Elevating the patient's legs, where blood may pool due to increased capacitance, will improve venous return.

Similarly, central venous pressure (CVP) measurements can be lowered in the last two trimesters by inferior vena caval compression. Normal CVP during pregnancy is approximately 12 mm Hg.

Alterations That May Mask Hypovolemic Shock. Blood volume gradually increases during pregnancy, starting at 6 to 8 weeks' gestation, to as much as 45% above normal, peaking at 32 to 34 weeks' gestation. Blood volumes become increasingly larger for multigravidas, twins, triplets, and quadruplets.[12] With this increased circulatory reserve, clinical signs of maternal hypotension from acute traumatic bleeding may be delayed.

Some Alterations Can Exacerbate Traumatic Bleeding. By the beginning of the second trimester and throughout the remaining pregnancy, cardiac output is increased 40%, to 6 L/min.[10] Blood flow to the uterus increases from 60 mL/min before pregnancy to 600 mL/min at term.[13] This hyperdynamic state is needed to maintain adequate oxygen delivery to the fetus. Because the mother's total circulating blood volume flows through the uterus every 8 to 11 minutes at term, this organ can be a major source of blood loss when injured. By the third trimester there is also marked venous congestion in the pelvis and lower extremities, increasing the potential for hemorrhage from both bony and soft tissue pelvic injuries.

Compression of the lower abdominal venous system by the gravid uterus increases peripheral venous pressure and volume in the legs, creating the potential for brisk blood loss from leg wounds.

This alteration can play an important role in procedures that may be necessary for maternal resuscitation, such as central venous catheter placement.

*The contributors would like to sincerely thank John D. G. Neufeld, MD, for his previous work on this chapter.

Table 34-1 Hemodynamic Changes of Pregnancy (Mean Values)

PARAMETER	NONPREGNANT	TRIMESTER 1	TRIMESTER 2	TRIMESTER 3
Heart rate (beats/min)	70	78	82	85
Systolic blood pressure (mm Hg)	115	112	112	114
Diastolic blood pressure (mm Hg)	70	60	63	70
Cardiac output (L/min)	4.5	4.5	6	6
Central venous pressure (mm Hg)	9.0	7.5	4.0	3.8
Blood volume (mL)	4000	4200	5000	5600
Hematocrit without iron (%)	40	36	33	34
Hematocrit with iron (%)	40	36	34	36
White blood cell (cell/mm^3)	7200	9100	9700	9800

Data from de Swiet M: The cardiovascular system. In Hytten F, Chamberlain G (eds): Clinical Physiology in Obstetrics. Oxford, UK. Blackwell Scientific Publications, 1980, pp 3–42: Colditz RB, Josey WE: Central venous pressure in supine position during normal pregnancy. Comparative determinations during first, second and third trimesters. Obstet Gynecol 36:769, 1970; Letsky E: The haematological system. In Hytten RF, Chamberlin G (eds): Clinical Physiology in Obstetrics. Oxford, UK. Blackwell Scientific Publications, 1980, pp 43–78; and Cruikshank DP: Anatomic and physiologic alterations of pregnancy that modify the response to trauma. In Buchsbaum HJ (ed): Trauma in Pregnancy. Philadelphia, WB Saunders, 1979, pp 21–39.

Pulmonary

The term pregnant woman has a significantly reduced oxygen reserve. This effect comes from a 20% reduction in functional residual capacity caused by diaphragm elevation and a 15% increase in oxygen consumption related to the growing fetus, uterus, and placenta.[14] Archer and Marx observed that mean arterial oxygen tension dropped by 29% in term pregnant women during 60 seconds of apnea but just 11% in nonpregnant women. Labor accelerates this decline by a further 7%.[15] Additionally, minute ventilation increases, leading to hypocapnea. Therefore, an arterial partial pressure of carbon dioxide ($Paco_2$) of 35 to 40 mm Hg may indicate inadequate ventilation and impending respiratory decompensation in the pregnant patient. At signs of respiratory compromise or hypoxia, endotracheal intubation should be considered, as maternal hypoxia rapidly leads to fetal hypoxia, distress, and possibly demise. There are no contraindications to rapid sequence intubation during pregnancy. Bag-valve-mask ventilation is more difficult in the pregnant patient.

Gastrointestinal

Gastroesophageal sphincter response is reduced in pregnancy and gastrointestinal motility is decreased, both of which increase the possibility of aspiration during reduced levels of consciousness and intubation.[16] The stomach's increased acid production in pregnancy makes aspiration more ominous than usual.[17] Therefore early gastric decompression should be considered under appropriate circumstances.

Anatomic Changes in Pregnancy

The uterus remains an intrapelvic organ until approximately the 12th week of gestation. It reaches the umbilicus by 20 weeks and the costal margins by 34 to 36 weeks. It grows from a 7-cm, 70-g organ to a 36-cm, 1000-g structure at term. As a result of this growing mass, the normal anatomic location and function of multiple structures are altered.

The diaphragm progressively rises an extra 4 cm in pregnancy with compensatory flaring of the ribs.[18] Pneumothorax may be exacerbated and tension pneumothorax can develop more quickly in pregnancy because of this diaphragm elevation, combined with pulmonary hyperventilation. For thoracostomies done in the third trimester, the chest tube should be placed one or two interspaces higher than the usual fifth interspace site to allow for diaphragm elevation.

Abdominal viscera are pushed upward by the enlarging uterus, resulting in altered pain location patterns. The gravid uterus itself tends to protect abdominal organs from trauma but substantially increases the likelihood of bowel injury with penetrating trauma to the upper abdomen. Conversely, the upward displacement of the bowel makes it less susceptible to blunt trauma. The stretching of the abdominal wall modifies the normal response to peritoneal irritation. Therefore, expected muscle guarding and rebound can be progressively blunted as pregnancy approaches term, despite significant intra-abdominal bleeding and organ injury, another factor that may lead to underestimation of the extent and gravity of maternal trauma.

Total weight for the gravid uterus and its contents typically reaches 4500 g.[13] In the first trimester, the bony pelvis shields the uterus. After the third month, the uterus rises out of the pelvis and becomes vulnerable to direct injury. The bladder is also displaced into the abdominal cavity beyond 12 weeks' gestation, thereby becoming more vulnerable to injury. Like the uterus, the bladder becomes hyperemic, and injury may lead to a marked increase in blood loss compared with similar injury in a nonpregnant patient.

Imaging studies may show ureteral dilation that can be physiologic secondary to smooth muscle relaxation or caused by compression from the gravid uterus. Thus hydronephrosis is not necessarily pathologic. The ligaments of the symphysis pubis and sacroiliac joints are loosened during pregnancy. As a result, a baseline diastasis of the pubic symphysis may exist that can be mistaken for pelvic disruption on a radiograph.

Changes in Laboratory Values with Pregnancy

The physiologic anemia of pregnancy, resulting from a 48 to 58% increase in plasma volume and only an 18% increase in red blood cells, causes hematocrits of 32 to 34% by the 32nd to 34th week. Despite the lower hematocrit, there is actually an overall increase in oxygen-carrying capacity because of an increased total red blood cell mass.

Placental progesterone directly stimulates the medullary respiratory center, producing a $Paco_2$ of 30 mm Hg from the second trimester until term. The subsequent compensatory lowering of serum bicarbonate to 21 mEq/L slightly reduces blood-buffering capacity for stress situations.[14] A $Paco_2$ of 40 mm Hg in the latter half of pregnancy reflects inadequate

ventilation and potential respiratory acidosis that could precipitate fetal distress.

Electrocardiographic changes include a left-axis shift averaging 15 degrees, caused by diaphragm elevation. Consequently, flattened T waves or Q waves in leads III and augmented voltage unipolar in left foot lead may be seen.

CLINICAL FEATURES OF TRAUMA IN PREGNANCY

Blunt and Penetrating Trauma

The findings of the physical examination in the pregnant woman with blunt trauma are not reliable in predicting adverse obstetric outcomes. However, risk factors that are significantly predictive of contractions or preterm labor include gestational age greater than 35 weeks, assaults, and pedestrian collisions. In gravid patients, penetrating trauma of the abdomen has an increased likelihood of causing injuries of the bowel, liver, or spleen.

Fetal mortality rates range between 4 and 40% after maternal trauma, with most likely causes of fetal death occurring from placental abruption, maternal shock, and maternal death, in order of decreasing incidence. Risk factors significantly predictive of fetal death included ejections, motorcycle and pedestrian collisions, maternal death, maternal tachycardia, abnormal fetal heart rate, lack of restraints, and an Injury Severity Score greater than 9.[9]

Unbelted or improperly restrained pregnant women are twice as likely to experience excessive maternal bleeding, and fetal death is three times more likely to occur.[19,20] For low- to moderate-severity crashes (constituting 95% of all MVCs), proper restraint use, with or without air bag deployment, generally leads to acceptable fetal outcomes. For high-severity crashes, even proper restraint does not improve fetal outcome.[21]

Pregnant crash-test-dummy trials show that improper placement of the lap belt over the pregnant abdomen causes a three- to fourfold increase in force transmission through the uterus. The lowest force transmission readings through the uterus occur when a three-point seat belt is used properly. For correct position, the lap belt should be placed under the gravid abdomen, snugly over the thighs, with the shoulder harness off to the side of the uterus, between the breasts and over the midline of the clavicle.[22] Women who receive information on seat belt use during pregnancy from a health care worker are statistically more likely to use seat belts and to use them properly than uninformed controls.[23]

Interpersonal Violence

Although it has been previously documented that intimate partner violence against women affects one in four U.S. women, and numerous health consequences have been associated with being a victim of such violence, a recent study by Silverman and colleagues conclusively demonstrates that physical abuse from husbands or boyfriends compromises a woman's health during pregnancy, as well as her likelihood of carrying a child to term and the health of her newborn.[24] Women experiencing abuse in the year prior to or during a recent pregnancy were 40 to 60% more likely than nonabused women to report high blood pressure, vaginal bleeding, severe nausea, kidney or urinary tract infections, and hospitalization during this pregnancy. Abused women were 37% more likely to deliver preterm, and children of abused women were 17% more likely to be born underweight. These conditions pose grave health risks to newborns, and children born to abused mothers were over 30% more likely than other children to require intensive care at birth.[24-27] Physicians detect only 4 to 10% of cases, which supports the need for routine screening for interpersonal violence in pregnant patients.[27]

Falls

Falls become more prevalent after the 20th week of pregnancy.[2] Protuberance of the abdomen, loosening of pelvic ligaments, strain on the lower back, and fatigability contribute to this problem. In a given pregnancy, about 2% of pregnant women sustain repeated direct blows to the abdomen because of falling more than once. Although repeated falls often trigger premature contractions, they seldom result in immediate labor and delivery.[28]

Penetrating Trauma

The gravid uterus alters injury patterns to the mother. There is an increased probability of harm (approaching 100%) to the bowel, liver, or spleen if the entrance of the penetrating object is in the upper abdomen. When the entry site is anterior and below the uterine fundus, visceral injuries are less likely Although the enlarging uterus can act as a shield against intra-abdominal injuries in the mother, it makes the fetus more susceptible to injury. Awwad and colleagues observed a 67% fetal death rate from penetrating trauma to the uterus but a lower fetal death rate (38%) for maternal injuries above the uterus.[29]

Fetal Injury

Pregnancy does not alter rates of maternal mortality caused by trauma. However, trauma is associated with a high risk for fetal loss. When the mother suffers a severe level of injury, poor fetal outcome is predicted by maternal hypotension and acidosis (hypoxia, lowered pH, lowered bicarbonate) and a fetal heart rate of less than 110 beats per minute.[6,7,30-34] When the mother suffers life-threatening injuries, there is a 40% chance of fetal demise, compared with a less than 2% chance in cases of non–life-threatening maternal injuries. Maternal age and gestational age may also be important factors in determining fetal outcome.[35]

For women with less severe trauma, fetal outcome is not predicted by maternal vital signs, abdominal tenderness, blood tests, or ultrasonography (US) results. Only cardiotocographic monitoring for a minimum of 4 hours is useful in predicting fetal outcome.[3]

Fatal in utero fetal injuries from blunt trauma usually involve intracranial hemorrhage and skull fractures. Such head injury is often secondary to fractured maternal pelvic bones striking the fetal skull due to vertex lie.[36,37] Pelvic and acetabular fractures during pregnancy are associated with a high maternal (9%) and a higher fetal (38%) mortality rate.[38] With penetrating trauma, gunshot wounds to the uterus are associated with a high incidence of fetal injury (59–89%) and fetal mortality (41–71%).[39] Stab wounds to the uterus can produce 93% morbidity and 50% mortality rates, respectively, to the fetus.[40]

Placental Injury

In blunt trauma, 50 to 70% of all fetal losses result from placental abruption.[41,42] It is the leading cause of fetal death after blunt trauma.

Placental separation results when the inelastic placenta shears away from the elastic uterus during sudden deformation of the uterus. Because deceleration forces can be as damaging

to the placenta as direct uterine trauma, abruption can occur with little or no external sign of injury to the abdominal wall.[43] Because all gas exchange between the mother and fetus occurs across the placenta, abruption inhibits the flow of oxygen to the fetus and causes in utero CO_2 accumulation. Such hypoxia and acidosis can lead to fetal distress.[13] Sustained uterine contractions induced by intrauterine hemorrhage also inhibit uterine blood flow, further contributing to fetal hypoxia.[44]

The diagnosis of abruption is a clinical one, and ultrasonography and the Kleihauer-Betke test are of limited value.[45] Classical clinical findings of abruption may include vaginal bleeding, abdominal cramps, uterine tenderness, maternal hypovolemia (up to 2 L of blood can accumulate in the gravid uterus), or a change in the fetal heart rate. However, in some trauma studies, as many as 63% of cases showed no evidence of vaginal bleeding.[46]

The most sensitive indicator of placental abruption is fetal distress. Hence, prompt fetal monitoring is a very important assessment technique in trauma during pregnancy. There is also a close linkage of abruption to uterine activity. One study reported that if 12 or more contractions occurred in any hour of a 4-hour cardiotocographic monitoring period, the risk of abruption was 14%; abruption did not occur in this study if contractions occurred less than once every 10 minutes.[3] Ultrasound (US) is less than 50% accurate as a first-line test in detecting placental abruption.[3,47] If the abruption bleeds externally, not enough blood collects to be seen sonographically. Even with significant intrauterine blood accumulation, accurate US diagnosis may be difficult because of placental position (i.e., posterior) and confounding uterine or placental structural conditions.[48]

Placental abruption is associated with an overall 8.9-fold increased risk of stillbirth (>20 weeks) and a 3.9-fold increased risk of preterm delivery (before 37 weeks). The extent of placental separation affects stillbirth rates. At 50% separation there is a fourfold increase of stillbirth and a more profound 31.5-fold increased risk of stillbirth at 75% separation. The risk of preterm delivery is substantially increased with even mild abruptions; a 25% separation carries a 5.5-fold increased risk of preterm.[49]

When mother and fetus are stable, expectant management can be tried for partial placental abruptions of less than 25%. This usually applies to fetuses of less than 32 weeks' gestation in whom the likelihood of morbidity and mortality associated with prematurity makes delivery management risky. Expectant care in stable patients may allow further fetal maturation and improved outcome. Metzger and associates recommended intervention if the fetus is older than 32 weeks' gestation because the risk of further placental separation outweighs the benefit of further fetal maturation.[50] If expectant management is pursued, close maternal and fetal monitoring is needed to ensure the well-being of both patients. The ability to perform an immediate cesarean section is necessary because there may be little time between the appearance of fetal distress from further placental separation and the occurrence of fetal death.[51]

Women with placental abruption are more likely to have coagulopathies than those without abruption.[51] The injured placenta can release thromboplastin into the maternal circulation, resulting in disseminated intravascular coagulation, whereas the damaged uterus can disperse plasminogen activator and trigger fibrinolysis.[52] The precipitation of disseminated intravascular coagulation is directly related to the degree of placental separation. Severe clotting disorders rarely occur unless separation of the placenta is significant enough to result in fetal demise.[53]

Uterine Injury

The most common obstetric problem caused by maternal trauma is uterine contractions.[3,4,54] Myometrial and decidual cells, irritated by contusion or placental separation, release prostaglandins that stimulate uterine contractions. Progression to labor depends on the extent of uterine damage, the amount of prostaglandins released, and the gestational age of the pregnancy. The routine use of tocolytics for premature labor has come under question because 90% of contractions stop spontaneously.[3] Contractions that are not self-limited are often induced by some pathologic condition, such as underlying placental abruption, which is a contraindication to tocolytic therapy. Others consider this contraindication relative and have used tocolysis successfully with careful evaluation and intensive monitoring to continue the pregnancy and enhance fetal maturity.[55] The option to use tocolytics ends when cervical dilation reaches 4 cm.

Uterine rupture is a rare event. It is most often caused by severe vehicular crashes in which pelvic fractures strike directly against the uterus. There have been a few reports of uterine rupture from stab wounds and gunshot injuries.[56] Maternal shock, abdominal pain, easily palpable fetal anatomy caused by extrusion into the abdomen, and fetal demise are typical findings on examination. Diagnosing uterine rupture can be difficult. A fractured liver or spleen can produce similar signs and symptoms of peritoneal irritation, hemoperitoneum, and unstable vital signs. Optimal treatment, between suturing the tear or performing a hysterectomy, depends on the extent of uterus and uterine vessel tears and the importance of future childbearing.

DIAGNOSTIC STRATEGIES

Radiography

Plain Radiographs

Adverse effects are unlikely at less than 5 to 10 radiation-absorbed doses (rad). Less than 1% of trauma patients are exposed to more than 3 rad. Sensitivity to radiation is greater during intrauterine development than at any other time of life, especially in the first trimester (i.e., when the embryo undergoes organogenesis in weeks 2–9). However, the risk to the fetus of a 1-rad (1000 mrad) exposure, approximately 0.003%, is thousands of times smaller than the spontaneous risks of malformations, abortions, or genetic disease.[57] Studies show that intrauterine exposure to 10 rad causes no significant increase in congenital malformations, intrauterine growth retardation, or miscarriage but is associated with a small increase in the number of childhood cancers.[58-60] Pathologic conditions more readily appear with intrauterine radiation doses of 15 rad. At 15 rad there is approximately a 6% chance that the fetus could experience severe mental retardation, a less than 3% chance of developing childhood cancer, and a 15% chance of the having a small head, although this does not necessarily affect normal cerebral function.[61]

Providing information on radiation exposure from diagnostic radiographs is difficult. The individual amount of fetal dosage may vary by a factor of 50 or more, depending on the equipment used, technique, number of radiographs done in a complete study, maternal size, and fetal-uterine size. In general, coned x-ray beams aimed more than 10 cm away from the fetus are not harmful.[62]

Diagnostic radiographic studies should be performed with regard for fetal protection, but necessary diagnostic studies should not be withheld out of concern for fetal radiation exposure. When appropriate, fetal irradiation should be minimized

Table 34-2 Estimated Radiation Dose to the Unshielded Ovaries/Pelvic Uterus

IMAGING STUDY	UTERINE RADIATION DOSE (MRAD)*
Plain-film Radiography	
Cervical spine	Undetectable
Thoracic spine	<1
Chest (PA)	<1
Chest (AP)	<5
Extremities (femur)	<50
Hip	10–210
Lumbar spine	31–400
Pelvis	140–2200
KUB	200–503
Intravenous pyelogram	503–880
Urethrocystogram	1500
Computed Tomography	
Head	<50
Thorax	10–590
Abdomen	2800–4600
Pelvis	1940–5000
Angiography	
Cerebral	<100
Cardiac catheterization	<500
Aortography	<100

*mrad, millirad; dose increases as the fetus grows to occupy more of the abdomen.

AP, anteroposterior; KUB, kidney, ureter, and bladder; PA, posteroanterior.

Data from Berlin L. Radiation exposure and the pregnant patient. AJR Am J Roentgenol 167:1377, 1996; North DL. Radiation doses in pregnant women. J Am Coll Surg 194:100, 2002; Damilakis J, Perisinakis K, Voloudaki A, Gourtsoyiannis N. Estimation of fetal radiation dose from computed tomography scanning in late pregnancy: Depth-dose data from routine examinations [published correction appears in Invest Radiol 2000;35:706]. Invest Radiol 35:527, 2000.

by limiting the scope of the examination and using technical means such as shielding and collimation.[58] Table 34-2 provides estimated radiation doses from various types of examinations.[63-65] For comparison, the amount of naturally occurring radiation that the fetus receives during 9 months of gestation is approximately 50 to 100 mrad.[61] If ionizing radiation is used, one must adhere to the principle of using a dose that is as low as reasonably achievable after a discussion of risks versus benefits with the patient.

Ultrasonography

US is the best modality for simultaneous assessment of both the mother and the fetus. It has a sensitivity of 88%, a specificity of 99%, and an accuracy of 97% for detecting intra-abdominal injuries in blunt trauma in all patients. In the pregnant patient, it is most useful in detecting major abdominal injury (sensitivity 80%, specificity 100%) and establishing fetal well-being or demise, gestational age, and placental location.[66,67]

Sonography is a safe and effective screening examination that can obviate more hazardous tests such as computed tomography (CT), cystography, and diagnostic peritoneal lavage (DPL) in most pregnant patients with trauma who require an objective evaluation of the abdomen. Limitations in accuracy include operator experience, patient obesity, the presence of subcutaneous air, and a history of multiple abdominal operations. If an ultrasound is equivocal and the patient is hemodynamically unstable, DPL performed in an open and suprauterine fashion is indicated.

Computed Tomography and Magnetic Resonance Imaging Scans

CT and, increasingly, magnetic resonance imaging (MRI) studies are used in evaluating abdominal trauma in pregnancy. If US is indeterminate and the patient's condition is stable, CT and MRI have the potential to identify specific organ damage.[68] They are particularly useful in assessing penetrating wounds of the flank and back. CT can miss diaphragm and bowel injuries.[69] Both of these studies generally lack portability, and trauma patients may have to be taken from the closely monitored environment of the ED to a distant room.

Radiation from CT is a concern in the pregnant trauma patient. However, with shielding, fetal exposure from head and chest CT scans can be kept below an acceptable 1-rad limit. CT of the abdomen above the uterus can be done with less than 3 rad of exposure to the fetus.[61] Pelvic CT, centered over the fetus, produces a more prohibitive 3- to 9-rad dose.[70] Fortunately, spiral CT can reduce radiation dosage by a further 14 to 30%.[71] Radiation exposure ultimately depends on the patient, scanner, and technique used in performing the study (see Table 34-2). MRI scanners use no radiation and cause no fetal disease or disability.[72]

SPECIAL PROCEDURES

Diagnostic Peritoneal Lavage

In unstable trauma patients with equivocal or negative findings on US, DPL can be done quickly and safely in any trimester by an open technique above the uterus. Blunt trauma studies indicate that the gravid uterus does not compartmentalize intraperitoneal hemorrhage and does not reduce the accuracy of DPL for selecting patients who need operative intervention for intra-abdominal bleeding.[73] DPL is limited in detecting bowel perforations and does not assess retroperitoneal and intrauterine pathology.

MANAGEMENT

As with any trauma, advance notification and preparation can be helpful. Depending on mechanism, maternal condition, and gestational age, the emergency physician should consider early notification or consultation with an obstetrician, neonatologist, or pediatrician (or all three). A fetal monitor, portable US, and neonatal resuscitation equipment should be available in the ED.[74]

Maternal Resuscitation

Primary Survey

The primary survey focuses on the mother. However, because two patients are present, it is reasonable also to gather preliminary information about the fetus in the primary survey (Fig. 34-1).

Airway and Breathing. Oxygen therapy should be instituted early. Because of reduced oxygen reserve and increased oxygen consumption, the traumatized pregnant woman can quickly become hypoxic. The fetus is very vulnerable to any reduction in oxygen delivery. Animal studies show that severe hypoxia causes a 30% reduction in uterine blood flow.[75] Therefore, supplemental oxygen should be continued throughout maternal resuscitation and evaluation.[74]

A secure airway is critical to an optimum outcome. Not only does it enable proper oxygenation but it negates the higher risk of aspiration in pregnancy. Rapid sequence intubation is

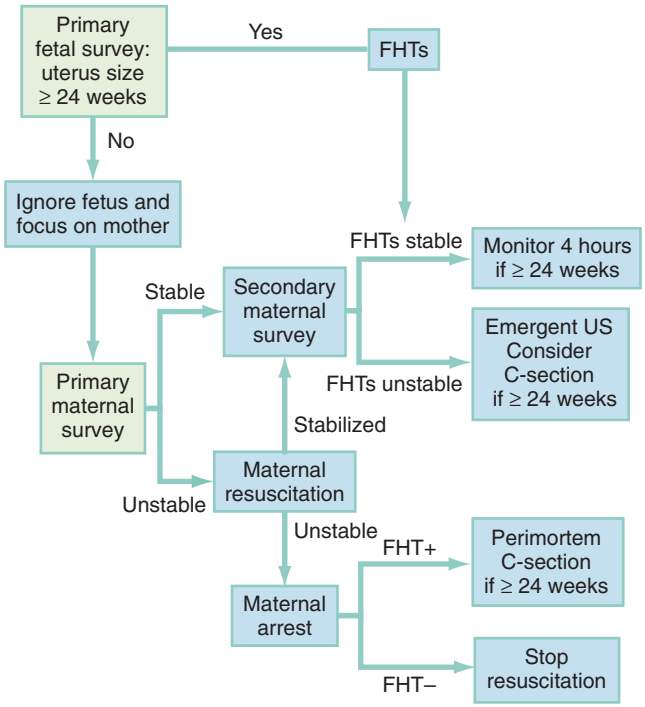


Figure 34-1. Decision-making algorithm in emergency obstetric care. C-section, cesarean section; FHTs, fetal heart tones; US, ultrasonography.

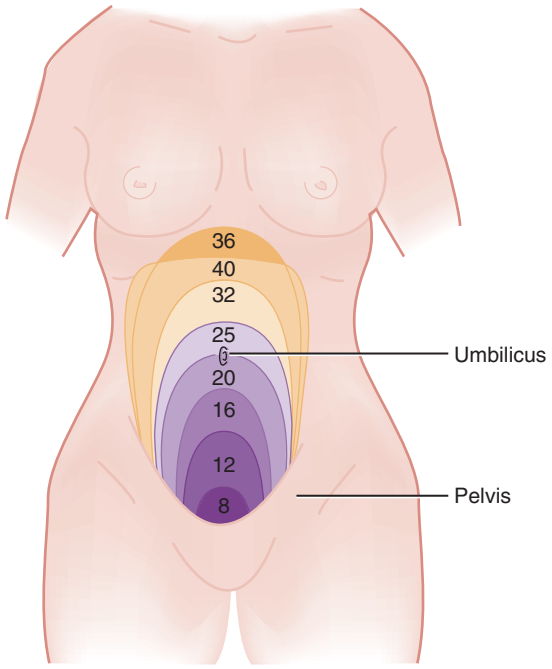


Figure 34-2. Uterine size at different weeks of gestation. (From Kravis TC, Warner CG [eds]: Emergency Medicine: A Comprehensive Review. Rockville, Md, Aspen Publishers, 1979.)

recommended when intubation is performed. Mechanical respirators need to be adjusted for increased tidal volumes and respiratory alkalosis consistent with the physiologic P_{ACO_2} of 30 mm Hg in the last stage of pregnancy.

Circulation. Any time significant maternal injury is suggested by the mechanism of injury or clinical findings, early IV access for volume resuscitation is indicated. Maternal blood pressure and heart rate are not consistently reliable predictors of fetal and maternal well-being.[74] Because of an expanded circulating volume, the mother can be bleeding but not show early signs of hypotension. The uterus is not a critical organ, and its blood flow is markedly reduced when the maternal circulation must be maintained. As a result, after an acute blood loss, uterine blood flow can be decreased 10 to 20% while maternal blood pressure remains normal.[76] Consequently, the mother who presents with borderline stability probably already has a jeopardized fetus. When traditional signs of shock appear, fetal compromise can be far advanced. Vasopressors should be avoided because they produce fetal distress by further decreasing uterine blood flow.

Beyond 20 weeks' gestation, the patient should be tilted to approximately 30 degrees to the left when on a backboard or should have the right hip elevated, unless otherwise precluded by right-sided injuries. This reduces the compression on the inferior vena cava caused by the gravid uterus. Tilting to the right is less effective in removing the uterus from the inferior vena cava; so consider manually displacing the uterus upward and leftward as discussed earlier.

For severe injuries, a CVP line is helpful in assessing cardiac preload. CVP pressures decline as pregnancy progresses because of inferior vena caval compression by the gravid uterus. Therefore, correction to nonpregnant normal pressures may be unnecessary. Instead, it is more valuable to focus on trends of how the CVP responds to fluid challenges. A Foley catheter for measuring urine output provides further information on circulatory volume status.

Table 34-3 Fetal Viability

WEEKS' GESTATION	6-MONTH SURVIVAL (%)	SURVIVAL WITH NO SEVERE ABNORMALITIES (%)
22	0	0
23	15	2
24	56	21
25	79	69

Data from Morris JA Jr et al: Infant survival after cesarean section for trauma. Ann Surg 223:481, 1996.

With trauma in pregnancy, the primary survey can be modified to assess uterine size and the presence of fetal heart tones. Uterine size, measured from the symphysis pubis to the fundus, is the quickest means of estimating gestational age. This distance in centimeters equals the gestational age in weeks (e.g., 24 cm = 24 weeks), which allows some early indication of fetal viability if delivery is necessary (Fig. 34-2). Usually, 24 to 26 weeks is used as the cutoff point for fetal viability (Table 34-3). As a rough guide, the fetus is potentially viable when the dome of the uterus extends beyond the umbilicus. Fetal heart tones can be detected by auscultation at 20 weeks' gestation or by Doppler probe at 10 to 14 weeks. If either the uterus is less than 24 cm in size or fetal heart tones are absent, the pregnancy is probably too early to be viable, and treatment is directed solely at the mother.

Secondary Survey

The secondary survey involves a detailed examination of the patient but is also modified to gather additional information about the maternal abdomen and the fetus. Physical examination of the abdomen, frequently unreliable in the nonpregnant patient, is more inaccurate with changing organ position, abdominal wall stretching in advancing pregnancy, and uterine

contraction pains. Still, information can be gathered about uterine tenderness, contraction frequency, and vaginal bleeding.

Pelvic examination begins with sterile speculum examination to allow direct visualization to enable detection of possible trauma in the genital tract, the degree of cervical dilation, and the source of any observed vaginal fluid. Vaginal bleeding suggests placental abruption, and a watery discharge suggests rupture of the membranes. If a vaginal fluid sample placed on a slide dries and crystallizes in a ferning pattern, it is amniotic fluid and not urine. Cervical cultures for group B streptococci, *Neisseria gonorrhoeae*, and *Chlamydia* should be obtained if there is evidence of amniotic fluid leak. Bimanual examination should be limited to assessing for pelvic bone injury or progression of advanced labor. This examination is preferably performed by an obstetrician. If the mechanism of injury is significant enough and the fetus is judged to be viable, it is strongly preferred that an obstetrician be involved in the treatment.

Fetal Evaluation

Fetal evaluation in the secondary survey focuses on the fetal heart rate and detection of fetal movement. When the presence of fetal heart tones has been confirmed, intermittent monitoring of fetal heart rate is sufficient for the previable fetus. If the fetus is viable (i.e., 24 weeks or more), continuous external monitoring should be initiated quickly and maintained throughout all diagnostic and therapeutic procedures. Such monitoring can also benefit the mother because fetal hemodynamics are more sensitive to decreases in maternal blood flow and oxygenation than are most measures of the mother. Fetal distress can be a sign of occult maternal distress. Signs of fetal distress include an abnormal baseline rate, decreased variability of heart rate, and fetal decelerations after contractions.

The normal fetal heart rate ranges between 120 and 160 beats per minute. Rates outside or trending toward these limits are ominous. Heart rate variability has two components. Beat-to-beat variability measures autonomic nervous function, whereas long-term variability indicates fetal activity. Heart rate variability increases with gestational age. The loss of beat-to-beat and long-term variability warns of fetal central nervous system depression and reduced fetal movement caused by fetal distress[74] (Fig. 34-3).

Late decelerations are an indication of fetal hypoxia. These decelerations are relatively small in amplitude and occur after the peak or conclusion of a uterine contraction. By comparison, early decelerations are larger, occur with the contraction, and recover to baseline immediately after the contraction. Early decelerations may be vagally mediated when uterine contractions squeeze the fetal head, stretch the neck, or compress the umbilical cord. Variable decelerations are large, occur at any time, and are possibly caused by umbilical cord compression[74] (Fig. 34-4).

Laboratory

Besides routine trauma blood work, emergency laboratory tests should include a blood type with Rh status. In apparently stable pregnant patients, a low serum bicarbonate level may indicate occult maternal shock.[77] Interpretation of bicarbonate results must consider that the normal bicarbonate level is 21 mEq/L in the later stages of pregnancy due to respiratory alkalosis. Arterial blood gases can allow detection of maternal hypoxia and acidosis, whereas pulse oximetry can be used to monitor oxygen saturation. Coagulation studies should be obtained for patients with multisystem trauma or when the diagnosis of placental abruption is considered. The main difference between the nonpregnant trauma patient and the pregnant trauma patient's laboratory workup is the need to determine Rh status and quantitative β-hCG, if indicated based on mechanism; besides this, the physician should order any and all laboratory tests that would be ordered for any trauma patient.

Kleihauer-Betke Test and Fetomaternal Hemorrhage

Fetomaternal hemorrhage (FMH), the transplacental bleeding of fetal blood into the normally separate maternal circulation, is a unique complication of pregnancy. The reported incidence

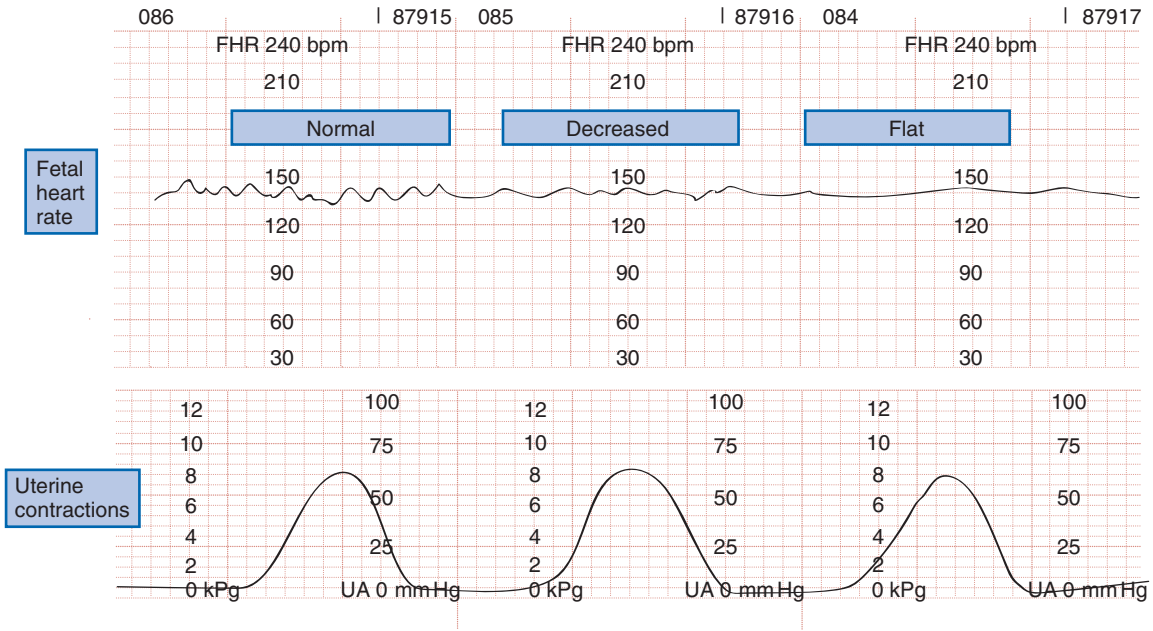


Figure 34-3. Types of fetal heart rate variability. bpm, beats per minute; FHR, fetal heart rate; UA, uterine activity.

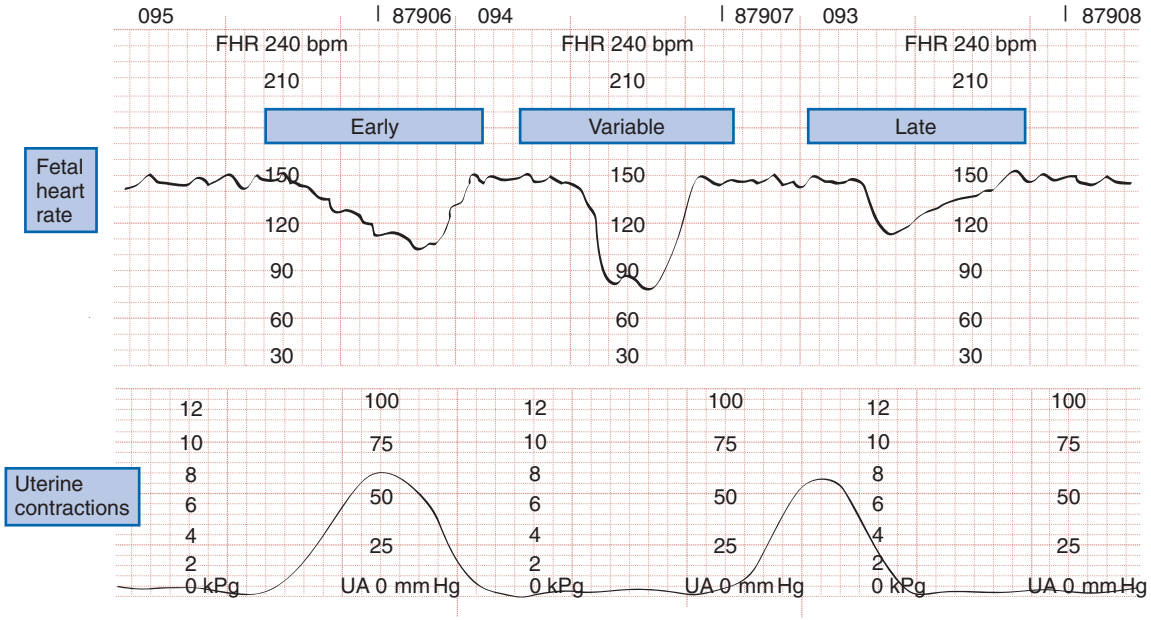


Figure 34-4. Types of fetal heart rate decelerations. bpm, beats per minute; FHR, fetal heart rate; UA, uterine activity.

of FMH after trauma is 8 to 30% (with a range of 2.5–115 mL of blood) compared with 2 to 8% (range of 0.1–8 mL) for control studies. MVCs, anterior placental location, and uterine tenderness are associated with an increased risk of FMH, but gestational age is not.[3,5,78] Massive fetomaternal transplacental hemorrhage causes alloimunization in Rh incompatibility but also endangers the fetus by severe fetal anemia and resulting fetal distress and possible exsanguination. ABO incompatibility causes less severe disease.

In theory, it is possible that trauma can result in FMH as early as the fourth week of gestation, when the fetal and placental circulations first form. In practice, FMH is usually of more concern after 12 weeks' gestation, when the uterus rises above the pelvis and becomes susceptible to direct trauma.[3]

The Kleihauer-Betke test identifies fetal cells in a maternal blood sample. Most laboratories screen for FMH of 5 mL or more. Unfortunately, the amount of FMH sufficient to sensitize most Rh-negative women is well below this 5-mL sensitivity level. Therefore, all Rh-negative mothers who have a history of abdominal trauma should receive one prophylactic dose of Rhesus immune globulin (RhIG). In the first trimester, one 50-µg dose is used because total fetal blood volume is only 4.2 mL by 12 weeks' gestation and a 50-µg dose covers 5 mL of bleeding. During the second and third trimesters, a 300-µg dose of RhIG is given, which protects against 30 mL of FMH. Beyond 16 weeks' gestation, the total fetal blood volume reaches 30 mL, so it is quite possible that massive FMH may exceed the efficacy of one 300-µg dose of RhIG. Therefore, it is unlikely that a Kleihauer-Betke test is useful in the treatment of severely injured pregnant trauma patients.

Trauma patients at risk for massive FMH present with major injuries or abnormal obstetric findings, such as uterine tenderness, contractions, or vaginal bleeding. Less than 1% of all pregnant trauma patients and only 3.1% of major trauma cases exceed the coverage of one 300-µg RhIG dose.[5]

Because RhIG can effectively prevent Rh isoimmunization when administered within 72 hours of antigenic exposure, the results of the Kleihauer-Betke test are not immediately needed in the ED.

Mother Stable, Fetus Stable

Minor trauma does not necessarily exempt the fetus from significant injury. It is estimated that 1 to 3% of all minor trauma results in fetal loss, typically from placental abruption.[79] Therefore, once the traumatized mother is stabilized, the focus of care is directed toward the fetus. For the viable fetus (greater than 24 weeks' gestation), monitoring is the next step. Monitoring must be continuous and should be maintained throughout all diagnostic and therapeutic actions. Because direct impact is not necessary for fetoplacental pathology to occur, the mother with no obvious abdominal injury still needs monitoring.

The recommended 4 hours of cardiotocographic observation of the viable fetus should be extended to 24 hours if, at any time during the first 4 hours, there are more than three uterine contractions per hour, uterine tenderness persists, results on a fetal monitor strip are worrisome, vaginal bleeding occurs, the membranes rupture, or if any serious maternal injury is present. In Pearlman's study, all cases of placental abruption after maternal trauma were detected within the first 4 hours of monitoring.[3] These mothers typically had more than 12 uterine contractions per hour. Although 70% of patients required admission beyond the 4-hour observation period, all patients who were discharged at the end of the 4-hour or 24-hour monitoring periods had subsequent live births.

On release from the hospital, the mother should be instructed to record fetal movements during the next week. If fewer than four movements per monitored hour are noted, the patient should see her obstetrician immediately and a nonstress test should be performed. The occurrence of preterm labor, membrane rupture, vaginal bleeding, or uterine pain also necessitates prompt reevaluation. Serial US and fetal heart rate tests should be performed on viable fetuses a few days after all trauma episodes and periodically throughout the remaining portion of the pregnancy to monitor fetal well-being.

Mother Stable, Fetus Unstable

Fetal death rates following maternal trauma are three to nine times higher than maternal death rates.[6] If a viable fetus

remains in distress despite optimization of maternal physiology, cesarean section should be performed.

Although fetal viability is first reached at 24 weeks, the ultimate determinant of the age of fetal viability is the level of neonatal care provided by the intensive care nursery unit in each hospital or accessible regional facility. Note that determining gestational age for fetuses less than 29 weeks is difficult. Even with the best US criteria, unless the time of conception is known exactly, the assignment of gestational age is subject to 1 to 2 weeks of uncertainty.[80] Emergency decisions on fetal viability are, therefore, made on the basis of the best gestational age information available.

Morris and colleagues found that the presence of fetal heart tones is an important survival marker for fetuses about to undergo emergency cesarean section.[81] No infant survives if there is no fetal heart tone before emergency cesarean section commences. If fetal heart tones are present and the gestational age is 26 weeks or more, then infant survival rate is 75%. Sixty percent of fetal deaths result from underuse of cardiotocographic monitoring and delayed recognition of fetal distress.

Besides fetal distress, other reasons for a cesarean section include uterine rupture, placental rupture with significant vaginal bleeding, fetal malpresentation during premature labor, and situations in which the uterus mechanically limits maternal repair. Fetal demise without any of the aforementioned conditions is not an indication for cesarean section because most will pass spontaneously within 1 week.

Mother Unstable, Fetus Unstable

If the mother's condition is critical, primary repair of her wounds is the best course. This may apply even when the fetus is in distress because a critically ill mother may not be able to withstand an additional operative procedure such as cesarean section, which prolongs laparotomy time and increases blood loss by at least 1000 mL. The best initial action on behalf of the fetus is early restoration of normal maternal physiology. If it is felt that the unstable mother can tolerate an emergency cesarean section, it can be attempted for the distressed, viable fetus.

As with nonpregnant patients, operative intervention for blunt trauma and above-the-uterus stab wounds is dictated by clinical findings and diagnostic testing results. Above-the-uterus intraperitoneal gunshot wounds should be explored.

There is little evidence to support a definitive management strategy for penetrating trauma to the gravid uterus. In situations of a hemodynamically stable mother, expectant management has been recommended. However, no prospective study has verified this. Damage to the uterus alone can be quite devastating because of its increased circulation. Meizner and Potashnik reported a shrapnel injury to only the uterus in a case in which an initially normal examination quickly changed to a hypotensive emergency.[82] At celiotomy, 1000 mL of blood was found in the abdomen from a perforated corner injury to the uterus. Without exploration it is impossible to know the occurrence, size, or depth of uterine penetration, and there are no guidelines indicating whether a uterine wound can be left unsutured without incurring an increased risk of infection or delayed uterine rupture. Laparotomy or laparoscopy seems to be the safest means of managing penetrating uterine wounds because missed maternal injuries can quickly compromise the fragile fetus.

Perimortem Cesarean Section

Restoration of maternal and thus fetal circulation is the optimal goal. However, extended and exclusive attention to the mother in cardiopulmonary arrest may prevent recovery of a potentially viable fetus. During maternal resuscitation, adequate oxygenation, fluid loading, and a 30-degree left tilting position should be tried to determine whether maternal circulation can be improved. If there is no response to advanced cardiac life support, a decision for perimortem cesarean section must be made. If there are no fetal heart tones, a cesarean section is not warranted.[83]

Perimortem cesarean section in the ED should be performed if uterine size exceeds the umbilicus and fetal heart tones are present. Time since maternal circulation ceased is the critical factor in fetal outcome. Published reports from more than 20 years ago support, but fall far from proving, that perimortem cesarean delivery should be initiated within 4 minutes if no pulse to obtain cardiac return by 5 minutes. Beyond 20 minutes, there is virtually never survival or favorable neurologic outcome for either mother or fetus.[84]

In the event of maternal cardiopulmonary arrest, perimortem cesarean section is indicated. The most experienced physician, preferably an obstetrician, should perform the procedure. However, this task ultimately may fall to the emergency physician or trauma surgeon, given the time constraints of the situation. A pediatric consultation should be obtained emergently. While continuing CPR, a "classic midline vertical incision is made, using a large scalpel, extending from the epigastrium to the symphysis pubis and carried through all layers to the peritoneal cavity. A vertical incision is then made in the anterior uterus from the fundus to the bladder reflection. Assistants and other surgical instruments (e.g., clamps, retractors) are helpful but not required. If, when the uterus is entered, an anterior placenta is encountered, it should be incised in order to reach the fetus. The cord should be promptly clamped and cut following delivery of the child."[84] Maternal revival after delivery of the fetus is reported in a few perimortem circumstances, presumably because vena caval compression is relieved.[85]

DISPOSITION

Any pregnant woman at 24 or more weeks of gestation who has suffered blunt body trauma should undergo at least 4 hours of fetal monitoring even if she looks well. Other admission and operative criteria are similar for pregnant and nonpregnant trauma patients. The emergency physician must always consider the stability of the mother and the viability of the growing fetus when making management and disposition decisions.

MISCELLANEOUS

Tetanus toxoid and immune globulin have no detrimental effect on the fetus. Proper immunization of pregnant women decreases the incidence of neonatal tetanus because the tetanus antibody crosses the placenta.

Electrical flow that bypasses the fetus has little effect on the pregnancy. Maternal elective and emergent cardioversion has been performed safely for cardiac dysrhythmias in all three stages of pregnancy. Energies up to 300 watt-seconds have been used without affecting the fetus or inducing premature labor. Cullhead reported no disruption of a monitored fetal heart rhythm during maternal cardioversion with 80 and 200 watt-seconds.[86]Although the amount of energy reaching the fetal heart is thought to be small, the fetal heart should be monitored during cardioversion.

KEY CONCEPTS

- Management of life- and limb-threatening injury in the mother comes first.
- Even in the noninjured pregnant patient, the fetus is at increased risk of morbidity and mortality.
- The fetus is viable at 24 weeks' gestation. A fetus is estimated to be viable if the fundus is at or above the umbilicus.
- When assessing the injured pregnant patient, it is important to keep in mind the alterations in anatomy and physiology that occur during pregnancy.
- Stable pregnancies with a viable fetus should be monitored after trauma continuously for a minimum of 4 hours.
- Keeping the mother tilted 30 degrees to the left or in the left lateral decubitus position may alleviate hypotension and improve perfusion for the mother and fetus.
- Perimortem cesarean section should be performed only for a viable fetus with signs of life.
- Minimize the use of ionizing radiation to the pregnant patient, including CT and plain radiography, but imaging should not be withheld if it may provide significant diagnostic information.
- Nonionizing radiation, including ultrasound and MRI, is preferred for pregnant patients.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 35 Pediatric Trauma

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PERSPECTIVE

Half of all deaths in children 1 to 14 years old are the result of trauma, and more than 15,000 traumatic deaths per year occur within this age group. More than half of these mortalities are directly related to motor vehicle collisions (MVCs). Injury accounts for approximately 30% of infant deaths as well.[1,2] In the United States, estimates of mortality for children hospitalized after injury are uniformly low; however, most fatalities occur in the field before arrival at a health care facility, which contributes to an underestimation of the magnitude of overall mortality figures.

The most common single organ system injury associated with death in injured children is head trauma.[3] Rates of 80% have been reported in patients with combined thoracoabdominal injuries.[1,4] Because multiple injuries are common in children, the emergency physician must evaluate all organ systems in any injured child, regardless of the actual mechanism of injury.

Within the subset of MVCs, death rates increase steeply in adolescents (>13 years old). MVC mortality statistics show that the youngest occupant in the vehicle is the most vulnerable to injury. Among school-age children (5–9 years old), pedestrian injuries and bicycle crashes predominate. Falls from heights account for 25 to 30% of injury; submersion injuries account for 10 to 15%, and burns account for 5 to 10%.[4,5] Throughout the United States, the number of children who are victims of violent acts has increased. Some children's hospitals report that 25 to 35% of all pediatric trauma deaths are related to child abuse.[6]

PRINCIPLES OF DISEASE

There are major anatomic and physiologic differences between pediatric and adult patients that play a significant role in the evaluation and management of a pediatric trauma patient (Box 35-1 and Table 35-1). Compared with adults, any given force is more widely distributed through the body of a child, making multiple injuries significantly more likely to occur in children. The proportionately large surface area of infants and children relative to weight predisposes them to greater amounts of heat loss as a result of evaporation. During resuscitation, even mild to moderate hypothermia has direct negative effects on cardiac function, inotropy, left-ventricular contractility, catecholamine responsiveness, platelet function, renal/hepatic drug clearance, and metabolic academia. Maintenance requirements for free water, trace metals, and minerals are therefore magnified compared to those for adults. Oxygen extraction and consumption, as well as glucose utilization, is much higher per kilogram in infants and small children than in adults. These factors contribute to a significantly higher energy and caloric requirement for an injured child compared with an injured adult. Finally, a child's physiologic response to injury is different from an adult's response, depending on the age and maturation of the child and the severity of the injury. In contrast to adults, children have a great capacity to maintain blood pressure despite significant acute blood losses comprising 25 to 30% of total blood volume. However, changes in heart rate, blood pressure, and extremity perfusion may precede cardiorespiratory failure and should not be overlooked. Small children respond to decreased cardiac output primarily through an increase in heart rate, not contractility. Similarly, children have decreased pulmonary reserve and respond differently to stress than do adults. Children are primarily diaphragmatic breathers dependent on the excursion of the diaphragm to increase the volume of the thoracic cage, thereby increasing the volume of air exchanged per breath. Unlike adults, children's elastic barrel-shaped chest wall prevents them from using their extrathoracic muscles to lift the ribs in order to generate an increase in intrathoracic volume and, hence, increased tidal volume. When infants create greater negative pressures in their pleural spaces, their more elastic chest wall caves inward, leading to chest wall retractions.

CLINICAL FEATURES

Initial Assessment Priorities and Primary Survey

The highest priority in the approach to the injured child is ruling out the presence of life-threatening or limb-threatening injury. Treatment of these injuries must occur before proceeding with the rest of the physical examination. This initial assessment (the primary survey) and necessary initial resuscitation efforts must occur simultaneously. In general, the assessment and resuscitation should be addressed within the first 5 to 10 minutes of evaluation. Any infant or child with a potentially serious or unstable injury requires continual reassessment. Vital signs should be repeated every 5 minutes during the primary survey and every 15 minutes thereafter until the patient is considered stable. The primary survey for pediatric trauma patients can be remembered by *A*, *B*, *C*, *D*, *E*, and *F*.

A—Airway and Cervical Spine Stabilization

Table 35-1 describes anatomic considerations that have implications in the management of the pediatric airway. The physi-

Table 35-1 Anatomic Differences in the Pediatric Airway—Implications in Pediatric Trauma Management

DIFFERENCES	IMPLICATIONS
Increased vagal response to laryngoscopy	Bradycardia during intubation; in infants and small children may be abated through the use of glycopyrrolate or atropine
Relatively larger tongue	Most common cause of airway obstruction in children May necessitate better head positioning or use of airway adjunct (oropharyngeal or nasopharyngeal airway)
Larger mass of adenoidal tissues may make nasotracheal intubation more difficult	Nasopharyngeal airways may also be more difficult to pass in infants
Epiglottis floppy and more U shaped	Necessitates use of a straight blade in young children
Larynx more cephalad and anterior	More difficult to visualize the cords; may need to get lower than the patient and look up at 45-degree angle or greater while intubating
Cricoid ring the narrowest portion of the airway	Allows for use of uncuffed tubes in children up to size 6 mm or approximately 8 years old Can use cuffed tube with or without balloon blown up; cuffed tube size typically (age/4) + 3
Narrow tracheal diameter and distance between the rings, making tracheostomy more difficult	Needle cricothyrotomy for the difficult airway versus a surgical cricothyrotomy for the same reason
Shorter tracheal length (4–5 cm in newborns and 7–8 cm in 18-month-olds)	Leads to intubation of right mainstem or dislodgment of the endotracheal tube Ensure tube position is checked before taping with head in neutral position or it can be driven into the right mainstem when the head is flexed or withdrawn when the head is extended to get to neutral
Large airways more narrow	Leads to greater airway resistance (R proportional to 1/radius^4)

BOX 35-1 Anatomic Differences in Adults and Children: Implications for Pediatric Trauma Management

- The child's body size allows for a greater distribution of traumatic injuries, so multiple trauma is common.
- The child's greater relative body surface area causes greater heat loss.
- The child's internal organs are more susceptible to injury based on more anterior placement of liver and spleen and less protective musculature and subcutaneous tissue mass.
- The child's kidney is less well protected and more mobile, making it susceptible to deceleration injury.
- Fifteen percent of pediatric patients presenting with hematuria after trauma have underlying congenital abnormalities.
- Growth plates are not yet closed in pediatric patients, leading to Salter-type fractures with possible limb-length resultant abnormalities.
- The child's head-to-body ratio is greater, the brain is less myelinated, and cranial bones are thinner, resulting in more serious head injury.

Table 35-2 Airway: Assessment and Treatment

ASSESSMENT PRIORITIES	INTERVENTIONS
Airway patency	Jaw thrust, suction, airway adjuncts Stabilize/remove loose teeth or other foreign bodies
Level of consciousness	Cervical spine immobilization
Maxillofacial injury	Apply 100% O_2 by mask Monitor patient closely for emesis
Stridor or cyanosis	Intubate for Glasgow Coma Scale ≤8 or absent gag reflex in a patient with a clinically concerning head injury or Po_2 < 50 mm Hg or Pco_2 > 50 mm Hg Needle cricothyrotomy if intubation impossible and cannot oxygenate and ventilate by bag-valve-mask until successful airway control by alternative method or provider

cian assesses for possible airway obstruction from injury, teeth, blood, constriction, or vomitus. The physician must know normal dental anatomy and development in order to better recognize the possibility of missing primary or secondary teeth. Efforts to perform cricoid pressure, or ligatures such as ties on gowns, can easily occlude the infant/child's airway with as little as 0.2 pounds of force. Excessive cricoid pressure is a preventable but common reason for difficulty passing the endotracheal tube once it has passed through the cords.[7] Gurgling or stridor may indicate upper airway obstruction. While stabilizing the neck, the airway is opened with a jaw-thrust maneuver. Efforts should be directed toward clearing the oropharynx of debris. The clinician must consider the possibility of cervical cord injuries in all seriously traumatized children. Evaluation of the cervical spine in children is discussed later: A gentle, developmentally appropriate approach must be used if reliable information is to be gained. Any complaint of past or current neurologic deficit, neck pain, or significant trauma to the head, chest, abdomen, or other spinal level injury should raise concern for a cervical spine injury. Repeatedly asking a toddler, "Does this hurt?" will typically lead to a response of, "No, No, No, Yes" as the child tries to accommodate to what he or she believes the examiner must want for an answer. It is often more useful to watch facial expression and for other cues of discomfort. Table 35-2 describes priorities in the assessment of the pediatric airway.

The physician assesses for adequacy of chest rise; in a young child, this occurs in the lower chest and upper abdomen. Both the chest and the abdomen should move concordantly. Discordant motion is referred to as *paradoxical breathing* and is a sign of impending respiratory failure. The respiratory rate is also assessed. Rates that are too fast or too slow can indicate impending respiratory failure. Treatment is assisted ventilation. If ventilation is necessary, a bag-valve-mask device is recommended initially. Only the volume necessary to cause the chest to rise should be provided because excessive volume or rate of ventilation can increase the likelihood of gastric distention (increasing the risk of vomiting and aspiration) and impair ventilation further. Cricoid pressure may help decrease the amount of air entering the esophagus during positive-pressure ventilation. A nasogastric/orogastric (NG/OG) tube should be placed during the first few minutes of bag-valve-mask ventilation and should be considered in all seriously injured children. Gastric distention due to bag-valve-mask and air swallowing often leads to respiratory embarrassment and potential hypotension due to decreased venous return. In conscious children, placement of an NG or OG should be preceded by local anesthesia, using agents such as atomized or nebulized lidocaine plus lidocaine jelly. The overall amount of lidocaine given should be closely monitored to prevent accidental overdose.

Indications for endotracheal intubation of a pediatric trauma patient include (1) any inability to ventilate by bag-valve-mask methods or the need for prolonged control of the airway, (2) Glasgow Coma Scale (GCS) score of less than 9 to secure the airway and provide controlled hyperventilation as indicated, (3) respiratory failure from hypoxemia (e.g., flail chest and pulmonary contusions) or hypoventilation (e.g., injury to airway structures or spinal cord injury), and (4) the presence of decompensated shock resistant to initial fluid administration.

Compared with adults, intubation of pediatric patients involves special considerations (see Table 35-1).

In children younger than age 8 years, the cricoid ring is the narrowest portion of the airway. For this reason, the cricoid ring often forms a physiologic cuff on uncuffed endotracheal tubes. In general, uncuffed tubes are used in children younger than age 8 years; cuffed tubes may be indicated when more airway protection than that from an uncuffed tube is necessary or when high-pressure or more precise ventilatory management is necessary. In general, the orotracheal approach to intubation is recommended. Problems associated with nasotracheal intubation in children include impairment of tube passage by the acute angle of the posterior pharynx, the potential for causing or worsening bleeding within the oral cavity, sinusitis, and increasing intracranial pressure (ICP) with insertion.

There are many limiting factors that compromise ventilatory function in an injured child, including depressed sensorium, occlusion of the airway, painful restriction of lung expansion, and direct pulmonary injury. Determination of adequate ventilation is possible only in the face of airway patency and adequate air exchange. As noted previously, the diaphragm plays a special role in the maintenance of proper ventilatory status in children. It is easily fatigued in a young child and often is displaced by any process that promotes distention of the stomach. As such, it is advisable to consider early placement of an NG/OG tube to facilitate decompression of the stomach.

To assess "ventilation," pulse oximetry is useful; however, pulse oximetry measures adequacy of oxygenation only. The measurement of exhaled CO_2 is useful to confirm endotracheal tube position. Historically, a colorimetric semiquantitative device was used to detect the presence of exhaled CO_2 in patients with perfusion. The use of continuous end-tidal CO_2 capnography provides far more information and continues to be underutilized. In addition to serving as an initial qualitative device to confirm successful intubation of the trachea, it may also provide an early warning of unintended extubation, tube kinking or partial occlusion, or ventilator malfunction. It also characterizes the response to therapeutic maneuvers instantaneously, provides a quantitative tool to manage the ventilatory aspects of respiration, and may provide prognostic information when used in patients with cardiac arrest. The lack of appropriate CO_2 production when the tube is in proper position often indicates poor perfusion. The use of end-tidal CO_2 capnography allows better ventilatory management during head injury resuscitation, and its values can be confirmed with a single venous or arterial blood gas. This can assist greatly with continuing ventilatory management without the need for recurrent blood draws and the inherent delays and discomfort of acquiring arterial blood gases. Table 35-3 describes priorities in the assessment of breathing in pediatric trauma patients.

Table 35-3 Breathing: Assessment and Treatment

ASSESSMENT PRIORITIES	INTERVENTIONS
Respiratory rate	100% O_2 by nonrebreather mask or intubate if in respiratory failure; fast rates may indicate shock (fluid resuscitation) or pain (parenteral analgesics).
Chest wall movements	For significant pneumothorax or hemothorax: Place chest tube. Small pneumothorax in a patient spontaneously breathing may only require close monitoring and/or oxygen washout. Transfer to operating room if initial drainage >20 cc/kg or subsequent output >2 mL/kg/hr.
Percussion	Open pneumothorax: Seal with three-sided occlusive dressing (Vaseline gauze) followed by tube thoracostomy and then seal remaining side of occlusive dressing.
Paradoxical breathing	Contusion/flail chest: Intubate if tachypneic or $Po_2 < 50$ mm Hg or $Pco_2 > 50$ mm Hg.
Tracheal deviation	Tension pneumothorax: Needle decompression at second intercostal space, midclavicular line, followed by placement of chest tube unless chest tube incision can be immediately placed, negating the necessity of needle decompression.
Flail segments	O_2 by nonrebreather mask or intubate if in respiratory failure.
Open wounds	Compress bleeding sites and cover as indicated. Consider use of hemostatic dressing.

Table 35-4 Circulation: Assessment and Treatment

ASSESSMENT PRIORITIES	INTERVENTIONS
Capillary refill	Oximeter and cardiac monitor, O_2 and fluid resuscitation 20 mL/kg. Consider intubation and ventilation to decrease workup breathing.
Heart rate	Monitor vital signs every 5 min.
Peripheral pulses	Two large-bore intravenous sites (above and below diaphragm when indicated).
Sensorium	Bolus with 20 mL/kg lactated Ringer's or normal saline solution (warm all intravenous fluids).
Pulse pressure increase	Repeat fluid bolus two times if necessary.
Skin condition/perfusion	Packed red blood cells, 10–20 mL/kg for decompensated shock secondary to blood loss.

Table 35-5 Disability: Assessment and Treatment

ASSESSMENT PRIORITIES	INTERVENTIONS
Level of consciousness	Maintain blood pressure and oxygenation and ventilation.
AVPU scale or GCS	If head injury with GCS <9: RSI and intubate; head computed tomography, neurosurgical consult. If normotensive, consider mannitol 0.25–0.5 g/kg. Maintain CO_2 at approximately 35 mm Hg. Maintain cerebral perfusion pressure of at least 50 mm Hg in children and 70 mm Hg in adults.
Pupil size and reactivity	Hyperventilate: P_{CO_2} to 30–35 mm Hg with signs of herniation. Consider alternative causes of pupillary dilatation, such as traumatic mydriasis or drug effect from atropine.
Extremity movement and tone	Stabilize spinal column. If blunt cord trauma, consider methylprednisolone sodium succinate (Solu-Medrol) 30 mg/kg IV bolus, then 5.4 mg/kg/hr for 23 hr IV.
Posturing	Hyperventilate: P_{CO_2} to 30–35 mm Hg.
Reflexes	Assess for signs of respiratory failure/bulbocavernosus reflex or anal wink for spinal injury "completeness."

AVPU, alert, verbal, painful, unresponsive; GCS, Glasgow Coma Scale; RSI, rapid sequence intubation.

BOX 35-2 AVPU System

A *A*lert
V Responds to *v*erbal stimuli
P Responds to *p*ainful stimuli
U *U*nresponsive

C—Circulation and Hemorrhage Control

Shock is not defined by any specific blood pressure but is instead a state in which the body is unable to maintain adequate tissue perfusion. Maintenance of systolic blood pressure does not ensure that the patient is not in shock. The pediatric vasculature has the ability to constrict and increase systemic vascular resistance in an attempt to maintain perfusion. Signs of poor perfusion, such as cool distal extremities, decreases in peripheral versus central pulse quality, and delayed capillary refill time, are signs of pediatric shock, even when blood pressure is maintained at normal levels. Palpable pulses are detectable at a systolic blood pressure greater than 80 mm Hg in children over approximately 10 years of age; however, it may be felt at lower pressures in infants and children younger than 10 years of age. Pulses can frequently be felt at lower systolic blood pressures in infants. Normal capillary refill time is less than 2 seconds; however, many variables affect this clinical finding. Alteration in a child's response to the environment or interaction with caregivers may indicate respiratory failure or shock. External hemorrhage should be sought and controlled with direct pressure. The assessment of circulation in pediatric trauma patients is described in Table 35-4.

D—Disability Assessment (Thorough Neurologic Examination)

The assessment of disability in pediatric trauma patients is described in Table 35-5. To assess patient disability, a rapid neurologic evaluation is needed. Many methods are available to the clinician, specifically the AVPU system (Box 35-2) and the modified GCS (Table 35-6).

E—Exposure and Thorough Examination

The final component of the primary survey involves fully undressing the patient to assess for hidden injury. Maintenance of normothermia is paramount in the undressed toddler and infant because metabolic needs are greatly increased by hypothermia. As soon as possible, in addition to increased ambient temperature, additional warming methods such as warmed humidified oxygen, warmed fluids and/or blood, head wraps, and convective warmers or radiant heat sources should be used. Preventing and treating hypothermia is not a matter of comfort for traumatized infants and children but, instead, one of survival (Table 35-7).

F—Family

In the management of children, the family could be added to the primary survey. Rapidly informing the family of what has happened and the evaluation that is proceeding helps lessen the stress of the caregivers. Allowing family members to be present during resuscitations is acceptable and often preferred by families. Some caregivers choose not to be present, but that choice should be given to them. If a caregiver is present, it is advisable to assign a staff member to be with him or her during the trauma resuscitation to explain the process.

Child life specialists and clergy are valuable members of the resuscitation team. They can not only serve the patient directly through their provision of comfort and developmentally appropriate explanations of medical activities but also serve as a single caring person for the child to focus on throughout their evaluation. They can also be instrumental in assisting the family to better understand what they may and may not do during and soon after the resuscitation. Families often wonder, but are afraid to ask, if they may touch the child, who can help with siblings, which siblings should be allowed to visit, what is the next step, and a myriad of other concerns. These special-

Table 35-6 Glasgow Coma Scale Modified for Pediatric Patients*

EYE OPENING RESPONSE		
SCORE	**>1 YR**	**<1 YR**
4	Spontaneous	Spontaneous
3	To verbal command	To shout
2	To pain	To pain
1	None	None
MOTOR RESPONSE		
SCORE	**>1 YR**	**<1 YR**
6	Obeys commands	Spontaneous
5	Localizes pain	Localizes pain
4	Withdraws to pain	Withdraws to pain
3	Abnormal flexion to pain (decorticate)	Abnormal flexion to pain (decorticate)
2	Abnormal extension to pain (decerebrate)	Abnormal extension to pain (decerebrate)
1	None	None

VERBAL RESPONSE			
SCORE	**>5 YR**	**2–5 YR**	**0–2 YR**
5	Oriented and converses	Appropriate words and phrases	Babbles, coos appropriately
4	Confused conversation	Inappropriate words	Cries but is consolable
3	Inappropriate words	Persistent crying or screaming to pain	Persistent crying or screaming to pain
2	Incomprehensible sounds	Grunts or moans to pain	Grunts or moans to pain
1	None	None	None

*Total score key: severe, <9; moderate, 9–13; mild, 14–15.

Table 35-7 Exposure: Assessment and Treatment

ASSESSMENT PRIORITIES	INTERVENTIONS
Undress Look under collar and splints	Trauma examination, including rectal examination when indicated.
Log roll and examine back	Remove from board when not contraindicated.
Radiology	Consider cervical spine, chest, and pelvis radiographs.
Laboratory	Complete blood cell count, type and crossmatch, amylase, urinalysis, urine pregnancy test.
Interventions	Place urinary catheter and nasogastric or orogastric tube as indicated.
Immunization	Appropriate tetanus vaccine if indicated. Consider tetanus immune globulin in appropriate cases.
Pelvic fracture	Consider binding pelvis to decrease pelvic volume and improve hemostasis.

ists can assist in all these areas. They are also expert in "playing"—the art of distraction and visual imagery. They may also play a role as the quintessential patient advocate, ensuring that the health care providers focus on the patient and not only on the individual medical issue at hand. Child life specialists should be viewed as part of the resuscitation team.

Secondary Survey

After completion of the primary survey and requisite procedures, the secondary survey is performed. The secondary survey is an organized complete assessment to detect additional injury not found on the primary survey. A more complete and detailed history is obtained at this time. Features of the history that need to be obtained can be remembered by the mnemonic *AMPLE* (Box 35-3). Ongoing assessment of the patient occurs after the secondary survey, and key points are summarized in Box 35-4.

MANAGEMENT AND DIAGNOSTIC STRATEGIES

General Management Principles

All pediatric patients who have sustained major trauma should be placed on a cardiac monitor; receive supplemental oxygen; and have constant reassessment of vital signs, oximetry, and, when possible, end-tidal CO_2. Vascular access is best obtained by accessing the upper extremity for the establishment of two large-bore intravenous lines. In the absence of available upper extremity peripheral sites, lower extremity sites could be used. Many clinicians favor the femoral vein as a safe site for insertion of a central line by use of a guidewire technique. A guide

BOX 35-3 AMPLE HISTORY

A *A*llergies
M *M*edications
P *P*ast medical history
L *L*ast meal
E *E*nvironments and events

BOX 35-4 TASKS TO BE COMPLETED AFTER THE SECONDARY SURVEY

- Complete head-to-toe examination
- Appropriate tetanus immunization
- Antibiotics as indicated
- Continued monitoring of vital signs
- Ensure urine output of 1 mL/kg/hr

BOX 35-5 FEMORAL LINE SIZING ESTIMATES

3 F	<3 kg
4 F	3–10 kg
5 F	10–20 kg
6 F	>20 kg

to suggested sizing of femoral catheters is shown in Box 35-5.

If cutdowns are necessary, the antecubital or saphenous sites are preferred; however, intraosseous access is typically a quicker and more reliable procedure to obtain access to the vascular space. Essentially all labs with the exception of the peripheral WBC and peripheral smear can be obtained from an intraosseous needle (including blood type and cross). Although most commonly started in the proximal medial tibia just below the growth plate, intraosseous access often can be obtained more easily in the flattened area of the anterior distal femur. The intraosseous route serves as an appropriate venous access site; however, the delivery rate of large amounts of crystalloid solutions is limited, based on maximal flow rate of approximately 25 mL/min.[8] More than one intraosseous needle may need to be placed (in separate bones), and a separate peripheral or a central line may be more easily obtained once fluids have been given via the intraosseous route. Intraosseous placement in a fractured extremity is contraindicated. Umbilical vein cannulation can be obtained in infants up to approximately 2 weeks of age. Three- and 5-F single and 5-F double-lumen catheters are available for use in the umbilical vein. If a specialized catheter is not available, a feeding tube or even a flexible intravenous catheter can be used for the infusion of crystalloid or blood. If vasopressors or highly osmotic agents are to be used, a more formal umbilical venous line placed above the liver should be considered to avoid hepatic injury.

Most hypovolemic pediatric trauma patients respond to 20 mL/kg boluses of isotonic crystalloid solutions. If 40 mL/kg has not reversed systemic signs of hypoperfusion, infusion of packed red blood cells at 10 mL/kg should be considered. In patients who present in decompensated shock or cardiopulmonary failure and occult bleeding is a potential cause for the shock, crystalloid and blood products may be administered simultaneously.

The use of blood products during trauma resuscitation is controversial. Although it is desirable to reduce risks of infectious disease and conserve precious resources, coagulopathy is to be expected after trauma and massive transfusion. When massive transfusion (>1 blood volume = approximately 80 mL/kg) is expected, most current guidelines appear to underutilize additional blood products. This leads to continued coagulopathy and likely contributes to unnecessary death and morbidity. Some experts now recommend, based predominantly on adult studies, that if massive transfusion is expected, blood and fresh frozen plasma (FFP) be given in a near 1:1 ratio, although other experts believe a ratio closer to 1:2.5 may suffice and decrease the risk of multiorgan failure. In general, FFP should be dosed at 15 to 25 mL/kg. Platelet transfusion dosing can be very confusing. Practically all platelet units currently used are apheresis packs from a single donor. Each apheresis unit roughly equates to six of the older concentrate units. The usual dose in trauma is 10 mL/kg; however, the response may be quite variable (i.e., it can vary by more than a factor of two) due partly to the heterogeneity of the concentration of platelets in an apheresis pack. A general goal in trauma patients is to raise the platelet count above 50×10^9/L. The platelet count should be rechecked at 1 and 24 hours after transfusion, more often if the patient has ongoing difficulties with hemostasis or need for recurrent transfusion of red blood cells. The primary goal of giving cryoprecipitate is to increase the fibrinogen to levels of 1 to 1.5 g/dL, especially after central nervous system trauma. Although dependent on the fibrinogen concentration in the individual cryoprecipitate bags, the dose is typically 0.1 to 0.2 bags/kg. Each bag of cryoprecipitate contains approximately 150 mg of fibrinogen and 80 units of factor VIII.

In contrast to adults, cardiogenic shock is a rare event in childhood injury.[3,9] However, any degree of chest trauma associated with the presence of shock must alert the clinician to the possibility of concomitant myocardial contusion or rupture. Myocardial rupture should be apparent during the focused abdominal sonography in trauma (FAST) exam. The classic presentation of neurogenic shock due to loss of sympathetic tone and contractility involves hypotension with a relative bradycardia. Vasodilatation leading to a suboptimal systemic vascular resistance is the root cause of this hypotension. These patients are often hypothermic. Neurogenic shock typically occurs after injury to the sympathetic outflow tracks between T1 and L2. Generally, dopamine is the first-line agent for treatment of neurogenic shock. The mechanism and clinical findings of neurogenic shock are distinct from those of spinal shock. Spinal shock often presents with decreased systemic vascular resistance, a relative hypovolemia, and tachycardia. It is often treated with fluids and, when necessary, pressors with primarily alpha vasoconstrictive effects, such as phenylephrine.

Specifics of the head examination include pupillary size and reactivity, funduscopic examination, and palpation of the skull. Assessment of the cervical spine must be done carefully, with the patient in full cervical spine immobilization. As soon as feasible, the patient should be removed from the backboard with cervical spine immobilization maintained. Backboards are not only uncomfortable but also often rapidly cause necrosis at pressure points. There are no common indications to justify leaving children on backboards after their initial evaluation.

Assessment of the chest and internal structures involves inspection for wounds and flail segments, palpation for tenderness and crepitus, and auscultation for asymmetry, poorly transmitted breath sounds, or cardiac impulses. When airbags have deployed, occult trauma (e.g., ocular injury) should be expected and specifically ruled out. Similarly, a seat belt sign across the abdomen is a significant harbinger of serious traumatic injury.

Examination of the pediatric abdomen is most reliable when performed on a cooperative patient. It is an insensitive screen-

BOX 35-6 Indications for Laparotomy

- Hemodynamic instability despite aggressive resuscitation and appropriate emergency department procedures (e.g., a decompression hemothorax or tension pneumothorax)
- Transfusion of ≥ 50% of total blood volume because of massive intraperitoneal bleeding
- Radiographic evidence of pneumoperitoneum, intraperitoneal bladder rupture, grade V renovascular injury
- Gunshot wound to the abdomen
- Evisceration of intraperitoneal or stomach contents
- Signs of peritonitis
- Evidence of fecal or bowel contamination on diagnostic peritoneal lavage

ing test for the presence of an injury, however. The diagnostic test of choice to assess intra-abdominal injury in stable trauma patients is rapid abdominal computed tomography (CT).[10] The role of diagnostic peritoneal lavage (DPL) and bedside ultrasonography is more limited. The finding of intraperitoneal hemorrhage alone is not necessarily an indication for surgery in a stable pediatric patient. The ultrasound FAST exam is a useful screen, however, because when positive, it will clarify the need for abdominal CT, close observation, and possible repeat ultrasound exams. In hemodynamically unstable children, FAST or DPL may point to the abdomen as the primary area in need of hemorrhage control. Because of the desire for splenic salvage to maintain immunocompetency, an injured spleen is often left in place as long as the patient can be resuscitated adequately with crystalloid and blood products. Indications for surgery are listed in Box 35-6. Whatever the surgical preference within a health care facility, it is important to establish a protocol for approaching these challenging patients. Patients who remain hypotensive after adequate crystalloid infusion, have active arterial bleeding on CT scan, or have consistent decreases in their hemoglobin level may be candidates for early operative intervention.

A rectal examination provides information concerning sphincter tone, prostatic position, and the presence of blood in the stool. Unfortunately, the rectal exam lacks sensitivity, so its findings, when negative, are often misleading. Studies have demonstrated that the rectal exam has a sensitivity of only approximately 33% for *any* injury, and it misses the majority of urethral injuries, rectal wall injuries, pelvic injuries, bowel injuries, and spinal injuries. In a subset analysis of children younger than age 18 years, it performed even more poorly. The rectal exam is not required in all cases and should only be performed when its result has a reasonable chance of meaningfully changing the patient's treatment.[11] Although urethral injury is rare in children, all trauma patients should be assessed for a perineal or lower abdominal hematoma and blood from the urethral meatus. A retrograde urethrogram should be completed to assess for urethral trauma prior to the insertion of a urinary catheter in cases with suggestive physical findings.

Examination of the extremities is directed toward the evaluation of any deformities, penetrations, and interruptions of perfusion. Most fracture sites may be stabilized with splinting until surgical intervention can be carried out. Careful neurologic examination and documentation should occur in all cases of significant extremity injury, with repeat assessments as indicated. Early orthopedic consultation is advisable.

The pediatric patient is at great risk for the development of hypothermia. This risk is based on the large amount of surface area relative to body weight as well as increased transcutaneous heat conductance, especially in neonates. As a major contributor to the "triad of death" (acidosis, coagulopathy, and hypothermia), the importance of maintaining normothermia in trauma patients cannot be overemphasized.[12] Core temperatures should be monitored in these vulnerable patients, typically with temperature-sensing urinary catheters. Supplemental external warming techniques should be employed when necessary to maintain normothermia.

Pain Control

Pain control is an essential part of any trauma patient's management. Pain control may include not only medications but also techniques designed to change the perception and attention of the patient away from noxious stimuli and toward more pleasant experiences. The mainstay of pain control is narcotic analgesics, which should be used appropriately. Fentanyl has an advantage over morphine due to its hemodynamic profile and should be used readily but appropriately. It does not cause the release of histamine with secondary hypotension. Initial orders should generally be for both a loading dose and a PRN dose so that the nurse can continue to adequately control and assess the patient's pain after the physician has left the bedside. In addition to narcotics for pain control, immobilization of fractures and extremities with significant soft tissue injury also helps control pain. Visual imagery and distraction techniques, as well as a consistent and calm approach to the patient, should be utilized. Child life specialists (when available), patient representatives, chaplaincy, and most parents can assist in this endeavor. When asked if they want pain medicine, many children will say "No," even when they are in pain, because they are afraid of getting a shot or they interpret "pain medicine" as medicine that will cause pain. Basing pain medication on pain scales and common sense seems to be most appropriate.

In head-injured patients, fentanyl has the additional advantage of a short duration of action. If the patient has a mental status change, fentanyl clears quickly, making it possible to differentiate worsening brain injury from side effects of the medication. This is generally a better option than reversing the pain medicine and pain control with a narcotic antagonist. It is not humane to withhold pain medication completely in a traumatized patient whose mental status is of concern; it is better to titrate with smaller doses of short-lived medications. If immediate concern arises, the narcotic can be reversed with very small doses of naloxone.

Diagnostic Evaluation

Laboratory Studies

Blood sampling for a pediatric trauma patient is no different than that for an adult trauma patient; however, use of smaller blood collection tubes and microtechnique by laboratory staff may be necessary in infants and small children. All older pediatric trauma patients should be assessed for the possible use of drugs or alcohol as contributing factors to the traumatic event. In patients with hypovolemic shock, the hemoglobin alone is unreliable because equilibration will not have occurred at the time of presentation to the emergency department.[13]

A bedside glucose should be obtained on all patients with significant trauma. Repeat testing 30 to 60 minutes after significant pediatric trauma may be indicated as well. Children's glucose utilization and metabolic rate per kilogram is much greater than that of an adult, and they have far less substrate reserve in the form of glycogen stores. Any child with a change in mental status after trauma should have a bedside glucose

checked immediately. Any child requiring dextrose due to hypoglycemia will likely need an ongoing dextrose supply to prevent recurrence of hypoglycemia. In patients who can eat, this may be a meal with starches, fats, and protein. In others, it may require intravenous dextrose.

Radiology

The most important "traditional" radiographs to obtain on moderately to severely injured children are of the chest and pelvis to assess for sites of blood loss or potential causes of shock. In stable, alert children without distracting injuries, the pelvic film may be eliminated if no suggestion of sacral or pelvic fracture is found on thorough clinical exam. The following seven criteria are required to rule out any relevant pelvic fracture: patient age older than 3 years, no impairment of consciousness, no other major distracting injury, no complaint of pelvic pain, no signs of fracture on inspection, no pain on iliac or pubic symphysis compression, and no pain on hip rotation or flexion.[14-17] In patients with remarkable sacral tenderness and negative plain films, a CT scan should be strongly considered. Sacral fractures can be difficult to discern reliably on plain films. The radiographs of the cervical spine may be delayed until after further diagnostic studies are obtained, depending on the clinical presentation of the patient.

Other radiographs are obtained based on the physical examination. For patients sustaining minor trauma, no radiographs may be needed. Children younger than 2 years with injuries consistent with child abuse should undergo a skeletal survey, including skull, chest, abdomen, and long bone radiographs. Generally, these should be completed on a nonemergent basis while in the hospital. In most cases, they can be scheduled in the inpatient radiology department with the pediatric radiologist or the most experienced radiologist on staff available to interpret the films.

Although not considered part of the primary survey, consideration of cervical spine CT instead of plain radiographs in those with mental status changes and significant trauma, those receiving a head CT scan for a head injury, and those at high clinical pretest likelihood for cervical fracture may be appropriate. Although the negative predictive value of plain radiographs in low-risk populations seems high, the sensitivity of plain films to detect fractures is far less impressive. The pretest likelihood of fracture must be considered when making decisions regarding the removal of cervical immobilization in children with apparently normal radiographs. Patients with continued neck pain despite negative radiographs and/or CT may require magnetic resonance imaging (MRI) evaluation, delayed flexion-extension views, or, in rare cases, evaluation by neurosurgery under fluoroscopy. The use of immediate flexion-extension views is rarely indicated or helpful.

Electrocardiogram after Electrical Injury

The majority of pediatric electrocution cases are due to household current (≤240 V). Asymptomatic patients who did not have ventricular tachydysrhythmias in the field or water contact at the time of their electrocution with household current and do not have dysrhythmias in the emergency department are at very low risk for significant arrhythmias. Current literature does not indicate a need for an electrocardiogram (ECG) or monitoring in these children.[18] Those patients with normal and nonspecific ECG changes, when one is performed, remain at low risk. Nonspecific changes generally resolve within 24 hours. ECGs are indicated, as is cardiac monitoring for at least 4 hours, in patients who experience high-voltage electrocution.

SPECIFIC DISORDERS/INJURIES

Head Injury

Perspective

Head trauma is the leading cause of death among injured children and is responsible for 80% of all trauma deaths.[3] Each year, 29,000 children younger than age 19 years experience permanent disability from traumatic brain injury. Falls account for 37% of pediatric head injuries,[19] MVCs account for 18%,[20] pedestrian injuries account for 17%, and falls from bicycles account for 10%. On an age-related basis, infants and toddlers are more prone to falls from their own height, school-age children are involved in sports injuries and MVCs, and all ages are subject to the sequelae of abuse.

Principles of Disease

An important anatomic difference of a pediatric patient compared with an adult is that the cranial vault of a child is larger and heavier in proportion to the total body mass. This anatomic characteristic predisposes children, specifically toddlers and infants, to high degrees of torque that are generated by any forces along the cervical spine axis. Sutures within the pediatric skull are both protective and detrimental to the outcome of head injury in these patients. Although the cranium may be more pliable relative to traumatic insult, forces are generated internally that predispose the pediatric patient to parenchymal injury in the absence of skull fractures. The pediatric brain is less myelinated, predisposing it to shearing forces and further injury.[3,21]

Clinical Features

The clinician must obtain as many details regarding the traumatic event as possible. The height of the fall or injury is particularly important with regard to the development of associated injury. Most children fall from their own height. It is important to consider the quality of the surface at the point of impact, specifically the presence or absence of carpeting within the home or location of injury. Impact with an object increases the localized force even after a short fall and may lead to increased risk for fracture and intraparenchymal injury. Children involved in MVCs are best evaluated by the degree of restraint that was present during the time of the accident. An infant in a properly installed car seat is likely to have a better outcome than an unrestrained infant. Unrestrained children involved in high-speed crashes are prone to serious injury.

In most cases, it is important to establish whether there was alteration of consciousness at the time of the injury event. With playground trauma, the history may be vague, and the interpretation of any change in consciousness of the child may be regarded as an actual loss of consciousness. The behavior of the child after the event should include questions related to the presence or absence of irritability, lethargy, personality change, abnormal gait, or other alterations in behavior. Any worsening of these symptoms since the injury should also be reported.

The prognostic significance of vomiting after pediatric head trauma is unclear. There is no adequate study defining an acceptable time frame in which vomiting after head injury is benign in nature. The development of seizures after head trauma, in contrast to vomiting, has been well studied.[21] A brief seizure that occurs immediately after the insult (with rapid return of normal level of consciousness) is commonly called an *impact seizure*. This seizure usually is not associated with intracranial parenchymal injury. A CT is not necessary if the only

concern is the impact seizure; the decision to scan should take into account the mechanism of injury and current neurological status of the child. An impact seizure does not mandate the institution of anticonvulsant therapy. Seizures that occur later (>20 minutes after the insult) portend the greater possibility of traumatic brain injury and the development of seizures at a later date. CT is indicated for children with late seizures after head injury. Patients who experience seizures later in the course of the posttraumatic event are best evaluated by the neurosurgical service. As in all instances of trauma, a careful history related to the possibility of substance abuse must be obtained.

The physical examination of a head-injured child must include strict attention to the ABCs of emergency care. Although internal injuries are important in the outcome of these patients, the maintenance of oxygenation and perfusion is paramount in eliminating further insult. Because the pediatric brain is sensitive to decreases in glucose, oxygen, and perfusion, their maintenance optimizes the chances of good recovery. Strict attention must be paid to the maintenance of euvolemia because cerebral perfusion pressure (CPP) is adequate only in the face of a normal mean arterial pressure (MAP). Conceptually, CPP is equal to MAP minus intracranial pressure (ICP): CPP = MAP − ICP. As the blood pressure is reduced, so is CPP. Localized cerebral perfusion pressure at the site of injury and in the areas surrounding it may vary greatly from that approximated by this formula. Pediatric patients with any form of head injury should be evaluated and protected from cervical spine injury.

Several methods are available for evaluating head-injured patients, including AVPU and the GCS. A commonly used modification of the GCS for children is shown in Table 35-6. Although widely utilized, none of the pediatric modifications of the GCS have been well verified.[22] However, studies on the reliability of the GCS in predicting the outcome in children with traumatic brain injury provide optimism compared with those on head-injured adults. In a study involving 80 children with traumatic brain injuries admitted to an intensive care unit (ICU), initial GCS scores were compared with eventual outcome.[23] ICU length of stay and time to cognition relative to GCS scores indicated that scores greater than or equal to 6 were associated with favorable outcomes and neurologic status. Although the number of patients in this study was small, the important message is that no matter how the patient presents neurologically, all efforts should be initiated to ensure survival and maintain stable neurologic status in the emergency department.

Examining a brain-injured child involves mental status testing, cranial nerve testing, motor testing, sensory testing, and short-term memory testing, with additional cognitive function testing under stress when indicated. The evaluation of cranial nerve function is essentially no different from that of an adult. The most important aspect of motor and cranial nerve evaluation involves ruling out the presence of increased ICP. Common symptoms and signs of increased ICP in infants and children should be sought (Boxes 35-7 and 35-8).

Minor injury to the scalp of infants and children involves the development of three common injury complexes.[24-27] In order to better understand these injury complexes, the layers of the "SCALP" (skin, connective tissue, aponeurosis, loose areolar tissue, and periosteum) must be considered. *Caput succedaneum* refers to injury with hematoma in the connective tissue layer. This is freely mobile and crosses suture lines. A *subgaleal hematoma* refers to a hematoma that is subgaleal within the loose areolar tissue above the periosteum. Lastly, *cephalohematoma* refers to a collection of blood under the periosteum. Since the periosteum is tightly adhered to the various suture lines, the cephalohematoma does not cross them. Bleeding from scalp wounds is often profuse and can lead to hemodynamic embarrassment in infants and small children if not quickly controlled. Although children may develop shock from a scalp injury, it is prudent to look elsewhere while controlling this bleeding.

BOX 35-7 COMMON SYMPTOMS AND SIGNS OF INCREASED INTRACRANIAL PRESSURE IN INFANTS

- Full fontanel
- Split sutures
- Altered state of consciousness
- Paradoxical irritability
- Persistent emesis
- "Setting sun" sign (bilateral downward gaze of the eyes with apparent inability to elevate the eyes superiorly in a normal manner leading to an area of sclera being seen between the iris and the upper palpebra when the child attempts to look upward). This finding can be a normal finding when intermittent in infants younger than 7 months of age, especially with the withdrawal of a light stimulus.

BOX 35-8 COMMON SYMPTOMS AND SIGNS OF INCREASED INTRACRANIAL PRESSURE IN CHILDREN

- Headache
- Stiff neck
- Photophobia
- Altered state of consciousness
- Persistent emesis
- Cranial nerve involvement
- Papilledema
- Hypertension, bradycardia, and hypoventilation
- Decorticate or decerebrate posturing

Skull fractures in children occur in many different configurations.[19,21,28] Linear fractures, the most common type of skull fracture, rarely require therapy and often are associated with good outcomes. Factors favoring a poor outcome include the presence of the fracture overlying a vascular channel, depression, a diastatic fracture, or a fracture that extends over the area of the middle meningeal artery. Diastatic fractures, or defects extending through suture lines, are different from linear fractures in that leptomeningeal cysts (growing fractures) may develop at these sites. Fractures of the basilar portions of the occipital, temporal, sphenoid, or ethmoid bones commonly occur in children. The presence of cerebrospinal fluid rhinorrhea and otorrhea has been associated with these injuries. Signs of basilar skull fractures in children are similar to signs in adults and include posterior auricular ecchymosis (Battle's sign) and raccoon eyes (the presence of periorbital subcutaneous hematoma).[29]

Strictly speaking, *concussion* is defined as a brain insult with transient impairment of consciousness. Amnesia is often involved. Patients who sustain concussive insults have anorexia, vomiting, or pallor soon after the insult. This transitional period is followed by rapid recovery to baseline. A CT scan is usually not indicated; if one is obtained, it is most often normal. In contrast, contusions are often the result of coup and contrecoup forces at work. Contusions may not be associated with

any loss of consciousness at the time of insult. Patients often present with associated symptoms, such as altered level of consciousness, severe headache, vomiting, or focal deficits on neurologic assessment. These injuries are clearly demonstrable on CT.

Traditional teaching regarding the development of epidural hematomas involves the typical triad of head injury followed by a lucid interval, followed by rapid deterioration as intracranial hemorrhage worsens. In contrast to epidural hematomas in adults, pediatric epidural hematomas may be the result of venous bleeding, which predisposes them to a delay in the development of symptoms. Guardians should always be informed of delayed signs and symptoms following head trauma that should prompt immediate reassessment. In any event, epidural hematomas are associated with a high incidence of overlying skull fractures (60–80% of cases). Patients with small fracture-related epidurals localized only to the site of the inner table fracture should be monitored closely in the hospital but often do not require surgical intervention.

Special attention should be directed toward infants and toddlers to rule out the presence of subdural hematomas. This clinical scenario is most often secondary to rupture of bridging veins and rarely is associated with the presence of overlying fractures (<30%). Subdural hematomas most commonly occur in patients younger than age 2 years, with 93% of cases involving children younger than age 1 year. Chronic subdural hematomas are most often encountered in patients who have been subjected to what has been termed the "shaken baby syndrome." This clinical complex involves forcible shaking of the child with accelerating and decelerating forces impacting the cranial vault.[30] This syndrome is most often due to child abuse; 22% of abused children have central nervous system injuries. Patients present with nonspecific findings, such as vomiting, failure to thrive, change in level of consciousness, or seizures. Retinal hemorrhages are present in the majority of cases, and all patients should have careful funduscopic examinations to rule out the presence of these nearly pathognomonic findings. Definitive exams should be performed by an ophthalmologist after pupil dilation to characterize the specific type of retinal hemorrhage. Those that occur in multiple retinal layers, are diffuse, and extend to the periphery are more likely secondary to abuse. Similarly, in less severe evident trauma, subdural hematomas at multiple sites, over areas other than the convexities, in the posterior fossa, or in the posterior interhemispheric fissure should strongly suggest the possibility of nonaccidental trauma.[31,32] Left to their own development, the worst cases may manifest with signs of increased ICP. Retinal hemorrhages are not observed in children with mild to moderate trauma from other causes and are not associated with a prior history of cardiopulmonary resuscitation; the presence of retinal hemorrhages suggests child abuse. Coagulation studies, platelet count, platelet function assays, and, when indicated, metabolic tests for glutaric aciduria should be performed in these cases as well.

Diagnostic Strategies and Management

As a basic rule, serial examinations are the most reliable indicators of clinical deterioration.[21,28] The presence of focality is a reliable indicator of a localized insult, whereas the absence of focality may be misleading. The signs of increased ICP usually develop late in the course of the process in infants. As in an adult, papilledema may require days to develop. The classic Cushing's response (bradycardia and hypertension) is also unreliable in children. If ICP elevation is suspected, emergency intervention must be initiated immediately (Table 35-8).

The Monroe-Kelly doctrine describes the contents of the skull to be made up of essentially three compartments: brain, cerebrospinal fluid, and blood. The volume of the skull is fixed. Although not a perfect model, this doctrine suggests the effects that changes in each compartment may have on the others. For example, in the presence of an intracerebral hemorrhage of significant volume, either cerebral spinal fluid or brain must leave the cranial vault. Similarly, if the brain swells, cerebral spinal fluid, blood, or both must leave the cranial vault. When this balance is disrupted, and the autoregulatory system's capacity to adapt is exceeded, the ICP rapidly increases. ICP can quickly reach a level that is not conducive to localized brain survival or continued blood flow to the brain. If left untreated, herniation may occur: An ICP over 20 to 25 mm Hg should be treated, but the absolute value less than this that should trigger treatment is unclear. From the standpoint of global cerebral perfusion, CPP is equated with MAP – ICP. However, this model does not allow the accurate prediction of CPP at the specific site of injury or within the ischemic penumbra. Measurement of oxygen extraction (using modifications of the Fick principle) and outcome studies have played a role in the following recommendations. In general, it is best to keep the cerebral perfusion pressure greater than 50 to 65 mm Hg in children and greater than 70 mm Hg in adults. There appears to be an age continuum with regard to necessary cerebral perfusion pressure. Hackbarth and coworkers demonstrated that the single greatest prognostic sign of outcome from traumatic brain injury in children was the ability to maintain a cerebral perfusion pressure greater than 50 mm Hg.[33] Many have adopted this as the minimum acceptable cerebral perfusion pressure.

The use of anticonvulsants after moderate to severe head injury in children is controversial. Early prophylaxis does not decrease the incidence of late seizures and is not recommended for this purpose. Clearly, the effects on temperature, intracranial oxygenation, and cerebral perfusion during an early seizure after trauma are discordant with the management principles of acute brain injury. In addition, early seizures often disrupt the evaluation and management of the patient's head and other trauma. However, the evidence for phenytoin effectiveness in preventing early seizures after trauma is weak at best. Also, Young and coauthors demonstrated that in moderate to severe head injury the incidence of early seizure was much lower than expected and that phenytoin did not substantially lower this risk.[34] Others have suggested that topiramate or levetiracetam may be more effective with decreased risks of side effects.[35,36] It may be prudent to treat seizures aggressively if they occur and to consider using sedative medications with anticonvulsant properties such as benzodiazepines while reserving the use of prophylactic phenytoin or fosphenytoin for the highest risk patients.

Most clinicians favor early and controlled intubation in pediatric patients with GCS scores that are deteriorating or are less than 9. However, in the out-of-hospital phase of care, or if the physician is not knowledgeable and experienced in pediatric rapid sequence induction, bag-valve-mask ventilation should be strongly considered during short transports and until additional, more experienced support personnel are available. An OG tube should be placed if bag-valve-mask ventilation is utilized to decrease the chance of emesis and to prevent respiratory embarrassment from gastric distension with air. Isolated head injury is uncommon; a careful search for other injuries should be made using meticulous and repetitive examinations as well as indicated laboratory and imaging tests.

Herniation syndromes in children are similar to those in adults. Uncal herniation is suggested early on by the presence of a unilaterally dilated pupil (compression of ipsilateral third

Table 35-8 Emergent Management of Increased Intracranial Pressure

THERAPY	DOSE	MECHANISM OF ACTION
Head elevation (30 degrees)		Lowers intracranial venous pressure
Head in midline		Prevents jugular vein compression
Hyperventilation	Maintenance $Paco_2$ 38–42 mm Hg If acute increase in ICP then reduce $Paco_2$ to 30–35 mm Hg	Promptly but temporarily decreases cerebral blood volume and thus intracranial pressure Only recommended for short-term treatment of acute ICP elevation
Mannitol	0.25–0.5 g/kg IV	Both agents effect rapid osmotic diuresis.
Hypertonic saline (HTS)	0.1–1 mL/kg of 3% Titrate to effect	Diuresis may decrease BP and CPP. Mannitol should be given through filter. HTS may require central line. Effect from osmotic and rheologic effects Avoid dehydration
Pentobarbital	5–10 mg/kg over 30 minutes, then 5 mg/kg/hr for 3 hours, then 1 mg/kg/hr Rarely indicated or started in emergency department	Thought to lower cerebral metabolism; also may have some effect on free radical formation. Other barbiturates (phenobarbital) also have been used. May decrease BP and CPP
Decompressive craniotomy		Allows more space for swelling and decreases ICP Potential value in children
Mild hypothermia (35° C)		Thought to decrease cerebral blood flow and metabolic rate Can cause cardiac dysrhythmias Is currently under investiagtion
Maintain euvolemia	Clinically or invasive monitoring	Maintenance of mean arterial pressure
Pressors if needed to maintain CBF	Depends on agent used	Maintain CBF and CPP by increasing MAP
Neuromuscular blockade	Depends on agent used	Helps maintain lower ICP
Sedation	Depends on agent used	Do not assume they are completely incapable of response to noxious stimuli or situation.
Prevent fever	Acetaminophen 15 mg/kg OG	Fever raises ICP and cardiac work.
Treat seizure aggressively	Depends on agent used	Prophylactic treatment controversial. Treatment of seizure not controversial and must be aggressive to prevent increased ICP, hypoxia, hyperpyrexia, and hypercarbia.

BP, blood pressure; CBF, cerebral blood flow; CPP, cerebral perfusion pressure; ICP, intracranial pressure; MAP, mean arterial pressure.

nerve parasympathetic fibers), contralateral hemiplegia (due to ipsilateral cerebral peduncle compression against the tentorium), and spontaneous hyperventilation. With progression, the ipsilateral eye may be noted to be looking downward and outward secondary to the loss of third nerve motor function but continued fourth and sixth cranial nerve function. Often, bilateral third nerve compression occurs very early, leading to bilateral "blown" pupils. In Kernohan's phenomena, the temporal lobe compresses the contralateral cerebral peduncle against the tentorium, leading to ipsilateral paresis, making localization of the lesion challenging without neuroimaging. Small, sluggish pupils, decorticate posturing, and Cheyne-Stokes respirations characterize early central diencephalic herniation. If this progresses and extends to the pons or medulla, the patient will present with fixed and dilated pupils, flaccid muscle tone, and slow or apneustic breathing or frank apnea and cardiorespiratory arrest. Management of suspected acute herniation begins with immediate controlled hyperventilation.[37,38] Clinical endpoints of hyperventilation are improved patient status or constriction of dilated pupils. End-tidal CO_2 capnography is used with arterial or venous blood gas correlation to assess adequacy of hyperventilation with a target partial pressure of carbon dioxide (Pco_2) of 30 to 35 mm Hg. Excessive hyperventilation can result in excessive cerebral vasoconstriction and secondary brain injury; ventilation is started at an age-appropriate rate, and then the rate is increased until pupillary function returns. Subsequent management of herniation includes hyperosmolar agents acutely, followed by other specific interventions in the ICU.[37-42]

Radiology

Skull Radiographs. Most clinicians agree that firm indications for skull radiographs alone include the skeletal survey involved with the evaluation of child abuse, establishment of a functioning ventricular peritoneal shunt, some penetrating wounds of the scalp, or the suspicion of foreign bodies underlying scalp lacerations. In children requiring neuroimaging due to concern for intracranial injury, plain skull radiography lacks sufficient sensitivity to be used as a screening tool and a noncontrast CT scan is the recommended test.

Computed Tomography of the Head. There has been a considerable amount of research on the indications and relative value of CT scanning in pediatric head-injured patients. A large study evaluated 185 children ages 2 to 17 years with loss of consciousness and GCS scores of 15 after mild head injury.[43] The children were grouped according to physical examination findings, neurologic status, and whether the head injury was isolated or nonisolated. Patients with obvious skull fractures were excluded. Two variables were highly associated with the presence of intracranial hemorrhage: the presenting neurologic status and the presence of multiple injuries. None of the 49

neurologically normal children with isolated head injury had intracranial hemorrhages. All patients with intracranial hemorrhages were noted to have other traumatic insults on physical examination. The authors concluded that after isolated head injury with any loss of consciousness, children older than 2 years of age who were neurologically normal could be discharged without a CT scan after careful physical examination alone.

Other studies contradict these findings, establishing a clear association with parenchymal injury and loss of consciousness.[43,44] Currently, recommendations for CT scanning include the presence of neurologic deficits, GCS scores of less than 14, and injury patterns that are the result of major forcible insults. Studies have shown various combinations of characteristics that make significant intracranial injury very unlikely but have provided less guidance in selection of which patients actually need a head CT (high negative predictive value but low positive predictive value). Studies have shown that if these rules are utilized, they must be used exactly as they were performed in the study to be effective. Dunning and coauthors' meta-analysis showed a statistically significant correlation of intracranial hemorrhage with focality (relative risk [RR] = 9.4), skull fracture (RR = 6.1), altered level of consciousness (RR = 2.23), and GCS scores greater than 15 (RR = 5.51).[36] Children younger than 1 year of age are a special challenge to the clinician because their neurologic milestones are more difficult to evaluate. Within this age group, any loss of consciousness, protracted vomiting, irritability, poor feeding, or suspicion of abuse should trigger strong consideration for CT scanning. The value of brief loss of consciousness and the determination of the need for CT in the child more than 1 year old are less clear, but loss of consciousness lasting longer than a minute is considered an indication for neuroimaging by many practitioners.

The evaluation of infants with minor closed-head injury was studied in a series of 668 infants younger than 2 years of age who underwent CT scanning, in which a subset of 92 infants younger than 2 months of age was further scrutinized. The presence of a significant scalp hematoma highly correlated with underlying parenchymal brain injury. The authors recommended CT scans for these patients.[45]

BOX 35-9 Anatomic Differences in the Pediatric Cervical Spine

- Cervical spine fulcrum changes from C2–C3 in toddlers to C5–C6 by age 8–12 years.
- Relatively larger head size, resulting in greater flexion and extension injuries.
- Relatively large occiput in children younger than age 2 years leads to flexion of cervical spine if they are laid flat on standard backboard without support under their scapula and pelvis.
- Smaller neck muscle mass with ligamentous injuries more common than fractures.
- Anterior wedge appearance of cervical vertebral bodies is common.
- Increased flexibility of interspinous ligaments.
- Flatter facet joints with a more horizontal orientation.
  - Upper 30→65 degrees and lower 55→70 degrees as one ages to adulthood.
- Incomplete ossification, making interpretation of bony alignment difficult (synchondrosis).
  - Uncinate processes do not calcify until approximately 7 years of age.
  - Basilar odontoid synchondrosis fuses at 3–7 years of age.
  - Apical odontoid epiphyses radiographically apparent at 7 years of age but may not fuse until approximately 12 years of age.
  - Posterior arch of C1 fuses at 4 years of age.
  - Anterior C1 arch may not be visible until one year of age and fuses at 7–10 years of age.
  - More inferior cervical vertebral segments.
    - Neural arches fuse to body by approximately 7 years of age.
    - Posterior arches fuse by 3–5 years of age.
- Epiphyses of spinous process tips may mimic fractures.
- Preodontoid space 4–5 mm in those <8 years of age and <3 mm in those 8 years or older.
- Pseudosubluxation of C2 on C3 seen in 40% of children <8–12 years of age.
- Prevertebral space size varies with phase of respiration.

Cervical Spine Injury

Perspective

In the United States, more than 1100 children sustain spinal injury annually.[46] Cervical injury patterns vary with the age of the patient. Fractures below the C3 level account for only 30% of spinal lesions in children younger than 8 years of age, which differs dramatically from the patterns seen in adults. Likewise, spinal cord injury (SCI) without radiographic abnormality (SCIWORA) has been found in 25 to 50% of spinal cord injuries in this same age group.[42-44] SCIWORA may be a misnomer in the era of MRI. Intra- or extraneural findings are usually seen immediately on MRI but may be delayed, necessitating immobilization and a follow-up MRI to prevent late or recurrent injury. Length of immobilization is controversial, but it may be up to 12 weeks.

Principles of Disease

Anatomic features of the cervical spine approach adult patterns between the ages of 8 and 10 years (Box 35-9).[2] Injury patterns identical to those of adults are often not fully manifested, however, until age 15 years. The pediatric spine has greater elasticity of the supporting ligamentous structures than the adult spine. The joint capsules of the child have greater elastic properties, and the cartilaginous structures are less calcified than in adults. In the spine, there is a relatively more horizontal orientation of the facet joints and uncinate processes, and the anterior surfaces of the vertebral bodies have a more wedge-shaped appearance. Compared to the adult, the child has relatively underdeveloped neck musculature and a head that is disproportionately large and heavy compared with the body. Both of these differences lead to an "anatomic fulcrum of the spine" in children that is at the level of the C2 and C3 vertebrae versus the lower cervical vertebrae as found in adults.

Clinical Features

Any patient with severe multiple injuries should be considered to have an SCI until proved otherwise. Likewise, significant head, neck, or back trauma and trauma associated with speed, MVCs, and falls from any height (especially those with associated head injury) should raise suspicions for SCI and be evaluated appropriately. The evaluation of a pediatric patient should begin with a primary survey to assess airway patency, ventilatory status, and perfusion. After initial evaluation and stabilization, the cervical region can be examined. Palpation

of the neck for pain and bony deformity should be performed. If the patient has pain or tenderness, closely watching his or her facial expression will generally indicate more than asking, "Do you have pain?" Any continued concern or perceived discomfort should be taken seriously because ligamentous discomfort is sometimes subtle. In academic institutions, it is common for three or four people to repeat each aspect of the exam. It is not uncommon for children who originally tell you that something hurts to tell new examiners that it does not hurt because they quickly learn that when they affirm that they have pain, stimulus will continue to be applied, making the pain worse. One examiner finding tenderness should be enough to consider further evaluation.

Some factors, such as tenderness or pain with palpation, may be underappreciated in a child who is not yet old enough to talk. Similarly, patients with head injury, decreased level of consciousness, or distracting injury or those who are intoxicated may not reliably localize pain in the cervical region, and spinal precautions should be maintained to avoid potential additional injury.

The neurologic examination in a pediatric patient can be difficult, but several factors should be evaluated in a patient with suspected cervical spine injury. Pain in the cervical region should raise suspicion of cervical spine injury. Likewise, paralysis, perceived paresthesias, ptosis, and priapism are neurologic signs highly correlated with SCIs. Complaints of paralysis or parasthesias, even if completely resolved at the time of examination, should be considered an indication of SCI until proven otherwise. Finally, upper extremity position and function can help elucidate the presence and level of an SCI.

Several characteristic SCI syndromes can be diagnosed on initial emergency department evaluation. Spinal cord injuries are generally described as either complete or incomplete depending on the presence or absence of sensory or motor function. Incomplete SCI has a better prognosis for recovery of some motor function after spinal shock resolves. Incomplete lesions have some preservation, even if slight, of sensory or motor function below the area of SCI and at the area of sacral nerve distribution. The determination of complete or incomplete is not a one-time assessment and cannot be reliably made until after spinal shock has resolved. The performance of a rectal exam (or anal wink testing) or bulbocavernosus reflex testing in males can assess for sensation and motor ability in the sacral distribution. Central cord syndrome (seen mostly in extension injuries to the cervical spine) typically consists of arm findings (e.g., decreased tone) greater than leg findings and distal symptoms greater than proximal symptoms (e.g., burning pain in the fingers and hands). Anterior cord syndrome (associated with flexion injuries to the cervical spine) is characterized by complete motor paralysis with loss of pain and temperature sensation; however, position and vibration sensation are preserved in this disorder. Finally, Brown-Séquard syndrome represents hemisection of the spinal cord with ipsilateral loss of motor function and proprioception. There is also contralateral loss of pain and temperature sensation. SCI syndromes are rare in children.

Radiology

Some experts believe that children with neck pain, involvement in an MVC, or any suspicion of cervical injury should receive radiographic evaluation because when used as a screening tool, these factors may be very sensitive in identifying cervical spine injuries in this patient group. Other experts support the use of the NEXUS criteria to determine who needs cervical radiographs. These criteria were derived from a study of 3065 children younger than age 18 years; however, only 4 of 30 cervical spine fractures were in children younger than age 9 years, and none of the 88 children younger than age 2 years had cervical fractures.[47,48] No pediatric cases of SCIWORA were found and the data showed that 45.9% of cervical spine injuries in their cohort were between the levels of C5 and C7. This may reflect the fact that 2160 of the pediatric patients were between 8 and 17 years old. The sensitivity for detection of cervical fractures was reported as 100% (95% confidence interval = 87.8–100%); however, less than 1% of children in the study had an injury, making the 100% negative predictive value less meaningful and the sensitivity (at least in young infants) suspect.[47] The majority of injured patients were older than age 9 years and had characteristics more similar to adults than infants.[48] Because of the limitations of the NEXUS criteria as they pertain to children, a low threshold for imaging must be maintained in children with mechanisms worrisome for cervical injury. A report of discomfort, any significant distracting injury, or even transient neurologic symptoms should be considered an indication for radiologic evaluation.

Radiographic evaluation routinely should consist of three views: a cross-table lateral view, an anteroposterior view, and an open-mouth odontoid view to help visualize the odontoid process of C1. The sensitivity of the three-view cervical spine series is highly variable. The pretest likelihood of fracture must be taken into account when acting on the result or choosing an imaging modality. Interpretation of plain cervical spine radiographs in children may be especially challenging because of the anatomic changes that occur with growth (see Box 35-9). In addition, pseudosubluxation of C2 on C3 is common in children up to adolescence, occurring in approximately 40% of patients.[49] The emergency physician distinguishes between pseudosubluxation and true subluxation by the posterior cervical line and the relationship of the spinolaminar line, also called the line of Swischuk, to the anterior cortical margin of the spinous process at C2. A line is drawn from the anterior cortical margin of the spinous process of C1 down through the anterior cortical margin of C3. If this line at C2 crosses the anterior cortical margin of the spinous process at C2 or is anterior to it by less than 2 mm and no fractures are visualized, the patient likely has pseudosubluxation versus true subluxation at that level (Fig. 35-1).

An important criterion for radiographic clearing of the cervical spine is complete visualization of all seven cervical vertebral bodies down to and including the C7-T1 interface. The predental space should not exceed 4 or 5 mm in children younger than 10 years of age, and the prevertebral soft tissue space should not be greater than normal (variable but generally <1/3 to 1/2 vertebral body width). The four cervical radiographic lines should be evaluated, and the atlanto-occipital alignment should be assessed for dislocation in this region. Other imaging modalities that can be used to delineate cervical fractures include thin-section CT and magnetic resonance imaging. If the dens cannot be adequately assessed by the open-mouth odontoid view, then a transforaminal view or CT scan should be utilized. Patients with high clinical suspicion for fracture but negative plain radiographs should be considered candidates for computed tomographic evaluation and radiologic, orthopedic, or neurosurgical consultation. Eubanks and co-workers provide a discussion on clearing the pediatric cervical spine in their review article.[50]

Classically, young children have been considered at greater risk for upper cervical spine injury. Unfortunately, many occipital cervical junction injuries are immediately fatal. However, survival is possible in some cases.[51] Early detection and immobilization is crucial. Occipital cervical junction injuries should be suspected in any child pedestrian versus vehicle

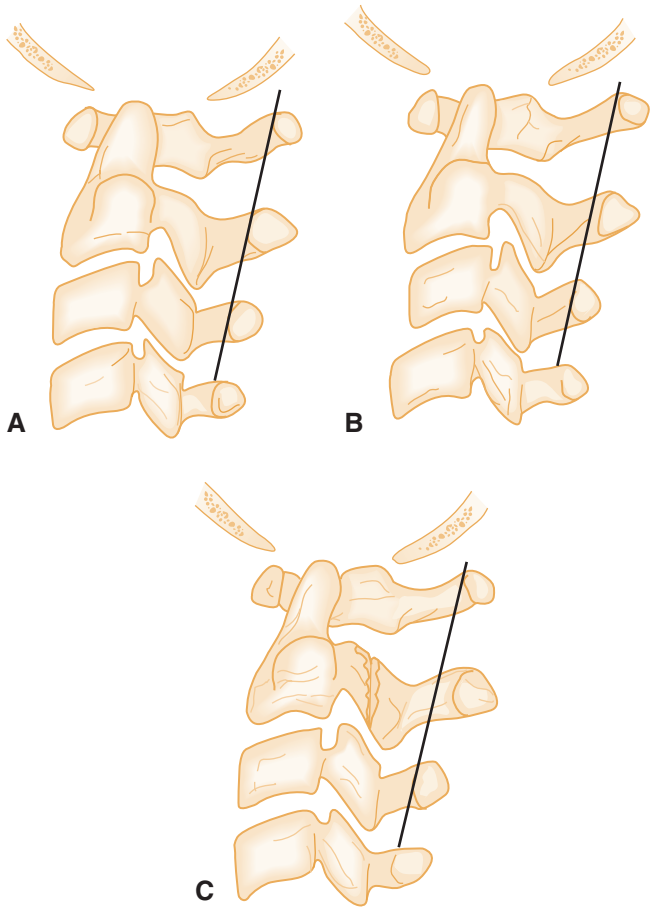


Figure 35-1. Spinolaminar line. Use only to access anterior displacement of C2 on C3. A line is drawn from the cortex of the spinous process of C1 to the cortex of the spinous process of C3, and the relationship of the spinous process of C2 is noted. **A,** Normal line passing through the cortex of C2. **B,** Normal line passing within 1.5 mm of the cortex of C2. **C,** Abnormal line passing greater than 2 mm anterior to the cortex of C2, suggesting underlying fracture of posterior elements of C2. (From American College of Emergency Physicians, American Academy of Pediatrics: APLS: The Pediatric Emergency Medicine Resource, 4th edition, Dallas, Elk Grove Village, Ill, 2004, the College and the Academy.)

accident, especially if a child presents with a laceration under the chin from a forward fall. In many fatal cases, distraction and displacement is obvious. However, in nonfatal cases it can be subtle. A Power's ratio greater than 1 indicates an atlanto-occipital dislocation until proven otherwise (normal, approximately 0.77). Power's ratio is calculated as the ratio of the distance from the basion to the anterior cortex of the posterior arch of the atlas divided by the distance from the opisthion to the posterior cortex of the anterior arch of the atlas. An additional method to suggest this injury is to draw a vertical line from the posterior border of the odontoid and then measure the distance from this line to the basion. If this distance is greater than 12 mm, then atlanto-occipital separation should be suspected. In addition, a traumatic or even sometimes non-traumatic atlantoaxial rotatory subluxation should be suspected in a child with a fixed rotatory cervical abnormality. Classically, this can be differentiated from a muscular torticollis in non-traumatic cases by the history, the time course, and palpation of the sternocleidomastoid muscle on the side contralateral to the direction in which the chin is pointing. When atlantoaxial rotatory subluxation cannot be confidently ruled out clinically, plain radiographs or CT scan should be utilized. In children with upper cervical spine tenderness, it is prudent to consider a fracture of the synchondrosis between the odontoid and C2. This can be difficult to diagnose on plain radiograph, but it is often recognized as a subtle anterior tilt to the odontoid on C2. A CT scan with sagittal reconstructions will clarify this entity.[52]

Management

There are two phases of SCI. Direct injury (initial phase) results in largely irreversible injury to the spinal cord. Indirect injury results from preventable or reversible injury to the spinal cord secondary to ischemia, hypoxemia, and tissue toxicity. Resuscitation of a patient with injury to the cervical spine should focus on prevention or minimization of the indirect causes of injury to the cervical spine. Management of possible spinal cord or column injury should begin in the out-of-hospital phase of emergency care. Most injured children arrive at the emergency department with adequate immobilization. Some more recent evaluations of traditional cervical collars and rigid backboards have shown less than adequate neutral positioning of pediatric patients related to their relatively large cranium in proportion to the rest of their body. Nevertheless, in the absence of modified backboards with cutouts for the occiput of the child, the child should be immobilized with stiff cervical collar, rigid backboard, and external fixation by means of head blocks, cloth tape, or straps to provide adequate precautions. Appropriate padding should be placed under the patient to approximate neutral alignment of the cervical spine and help prevent pressure-related injury. Some emergency medical service agencies' protocols call for small children to be immobilized in their car seats in some circumstances.

Breathing should be assessed to determine the presence of hypoventilation. Patients with SCI may hypoventilate because of diminished diaphragmatic activity or intercostal muscle paralysis. Otherwise normal children held in a supine position have shown reduced ventilatory abilities as measured by the forced vital capacity. Head or chest injury or pulmonary compromise related to contusion, aspiration, or other causes likewise may contribute to ventilatory embarrassment. Supplemental oxygen should be given routinely, and ventilatory assistance by bag-valve-mask ventilation or definitive airway management should be considered in the presence of clinically significant hypoventilation. Finally, circulatory status must be assessed early in the trauma patient and needs to be addressed promptly to prevent end-organ perfusion deficits. Hypotension can result from hypovolemia, neurogenic shock, spinal shock, or a myriad of other less common causes. Spinal shock presents with lower extremity findings of SCI, with flaccid paralysis of skeletal and smooth muscle leading to the appearance of a relative hypovolemia due to diminished systemic vascular resistance. Spinal shock generally resolves in hours to approximately 1 day once some spinal level reflexes return below the site of injury. Neurogenic shock typically occurs after injury to the spinal cord above the level of approximately T6. Patients with neurogenic shock lose their sympathetic tone and present with hypotension in the face of unopposed parasympathetic action such as bradycardia. In each case, fluid administration, parasympathetic receptor blocking agents such as atropine or glycopyrrolate, and vasopressors with chronotropic, vasoactive, and inotropic characteristics (e.g., dopamine) are used. If spinal shock with normal chronotropy and inotropy is found, then fluids and agents with more peripheral vascular vasoconstrictive properties may be preferable, such as phenylephrine or norepinephrine. Spinal shock remains a diagnosis of exclusion, once hemorrhagic shock has been definitively eliminated.

Any patient with definite SCI requires added precautions to ensure appropriate immobilization of the cervical spine. The use of intravenous steroids for blunt injury to the spinal cord continues to be debated in the literature (see Table 35-8). Immediate evaluation by a spinal cord specialist should be sought for all children with SCI. In the absence of such a specialist, the patient should be transported to a center with adequate facilities to care for spinal cord–injured patients.

Even when thoracic or lumbar fractures exist, patients should be expeditiously removed from the backboard to prevent discomfort and morbidity. Sliding boards (smooth movers) can be used to move patients onto scanner tables and back to their trauma beds. Mandatory interhospital transfer rules that require patients to remain on backboards during transport should be discouraged. The initial physician receiving the patient should be able to determine the necessity of the backboard for cervical spine immobilization during transport and, when appropriate, remove the patient from the board before transport.

Cardiothoracic Injury

Perspective

Most serious chest injuries in children (83%) are the result of blunt trauma.[6,53] Most result from MVCs. Isolated chest injury is a relatively infrequent occurrence considering the typical mechanisms of blunt trauma in the pediatric patient. The presence of significant chest injury increases the potential for multisystem trauma mortality by a factor of 10. Sequelae of blunt injury include rib fractures and pulmonary contusion (50%), pneumothorax (20%), and hemothorax (10%).

The overall mortality of pediatric chest trauma is nearly equivalent for blunt versus penetrating trauma. Children subjected to penetrating trauma, in contrast to the injuries associated with blunt trauma, often die from the primary insult. Penetrating trauma accounts for only 15% of thoracic insults in children.[53-55] Nationwide misuse of firearms has resulted in an increasing incidence of penetrating trauma, often with children as victims. The vast majority of these cases are related to the criminal use of handguns; however, improper storage and poor parental supervision lead to devastating consequences in a relatively small, but nevertheless preventable, number of cases each year. Families of children with emotional difficulties or depression should consider removing guns from their homes due to their lethality when used as an instrument of suicide. Specific clinical patterns should alert the clinician to the potential for concurrent abdominal and thoracic injury. Any patient with penetrating trauma at or below the level of the nipples falls into this category. Apparent isolated thoracic trauma does not exclude abdominal injury. All patients with self-inflicted penetrating trauma should also be assessed for ingested toxins.

Principles of Disease

It is important to understand the physiology of pediatric respiration when considering the potential for early decompensation following chest injury. Infants and young children are preferential diaphragm breathers, and any impairment of diaphragmatic mobility compromises ventilation. The presence of gastric distention elevates the diaphragm and severely diminishes the vital capacity of a child. In addition, the particular types of muscle fibers involved in the diaphragm of infants and young children predispose to the sudden development of apnea when these muscles become fatigued. Unlike adults, whose thoracic wall musculature can pull the ribs up anteriorly giving a larger circumference to the chest wall, children's chest wall circumference does not change drastically during respiration because their chest is barrel-like throughout the respiratory cycle. This also decreases the ability of children to increase their vital capacity. For these reasons, children will increase ventilation typically by increasing their respiratory rate. Most important, the presence of adequate oxygenation in a pediatric patient does not always ensure sufficiency of ventilation; confirmatory auscultatory and other physical findings are essential. End-tidal CO_2 capnography can be very useful in this regard in both the intubated and the nonintubated trauma patient.

Infants and children are anatomically protected against blunt thoracic cage trauma because of the compliance of the rib cage. Compressibility of the rib cage dissipates the force of impact, which lessens the likelihood of bony injury. These protective mechanisms also may mask fairly complex pediatric thoracic insults. The compliance of the rib cage allows significant injury to occur with little apparent external signs of trauma. Multiple rib fractures are a marker of serious injury in children, with child abuse being the most likely etiology, especially when fractures are posterior and in various stages of healing. In addition, the pediatric mediastinum is mobile, which favors the development of rapid ventilatory and circulatory collapse in the presence of a tension pneumothorax.

Specific Disorders

Pneumothorax. The development of a traumatic pneumothorax is commonly associated with significant pulmonary injury. In contrast to spontaneous pneumothoraces, these insults do not resolve spontaneously and often are associated with the presence of a hemothorax. Signs and symptoms include external evidence of chest trauma, such as abrasion, contusion, or ecchymoses; tachypnea; respiratory distress; hypoxemia; and chest pain. Decreased breath sounds may not be appreciated in children with pneumothoraces because of the wide transmission of breath sounds in the chest and upper abdomen. It is critical to listen to the chest from the axilla in children. This location helps with lateralization to distinguish decreased breath sounds on one side compared to the other and, after intubation, to assess for proper endotracheal tube position.

Management of a hemopneumothorax noted on chest radiograph includes the placement of a large-caliber chest tube placed far enough posteriorly, near the mid-axillary line, to prevent encroaching on more anterior soft tissue that will later become part of the breast. Chest tube size for hemopneumothorax management can be estimated as four times the size of the endotracheal tube that would be used in the patient (the age plus 12–16) or can be found on a length-based resuscitation tape. A chest tube should be considered for any patient with a pneumothorax who will be undergoing mechanical ventilation. In the most conservative of scenarios, such as small (<20%) simple pneumothoraces that are not under tension in a child who will not be mechanically ventilated, the child may be observed carefully for extended periods with 100% oxygen supplementation for nitrogen washout, and reassessment can be done by repeat chest radiographs at selected intervals or a pigtail catheter can be placed percutaneously using a modified Seldinger technique.

Open Pneumothorax. An open pneumothorax exists when the chest wall is injured sufficiently to allow bidirectional flow of air through the wound. The patient is unable to expand the lung because of equalization of pressures between the atmosphere and the chest cavity. Ventilation and oxygenation are severely impaired.

Management of an open pneumothorax is dictated by the size of the defect and the amount of respiratory compromise. Simple, small puncture wounds in a breathing patient may be treated by covering the chest wall defect with occlusive dressing, such as sterile petroleum gauze. A separate incision should be made for the placement of a thoracostomy tube. As in all cases, defects that are too large to seal adequately or patients who are severely impaired with regard to ventilation are candidates for intubation.

Tension Pneumothorax. Pulmonary air leaks that occur in a one-way valve arrangement favor the development of a tension pneumothorax. Increasing amounts of free air within the pleural cavity cause the mediastinal structures to shift toward the opposite side, compromising cardiac output. The final common pathway involves hypoxia, hypotension, and refractive shock. Most patients with tension pneumothoraces present with severe respiratory distress, decreased breath sounds (often bilaterally), and a shift in the point of maximal cardiac impulse. In the worst scenario, the shifted mediastinum forces contralateral tracheal deviation and distention of the neck veins due to decreased venous return to the thorax. In pediatric patients, signs of tension pneumothorax are often subtle. A short neck and increased soft tissue may make detection of tracheal deviation difficult. Pediatric patients with tension pneumothorax may only have subtle signs or present with only tachycardia, shock, and respiratory distress. The emergency physician should consider the diagnosis of tension pneumothorax and, if detected or strongly suspected, should treat the patient immediately with decompression. Without adequate decompression, respiratory embarrassment, hypotension, and circulatory collapse will occur.

In the out-of-hospital setting, treatment includes needle thoracostomy placed in the second intercostal space in the midclavicular line or possibly in the fourth intercostal space just above the rib and anterior to the mid-axillary line. The needle should be placed above the rib margin to avoid injuring the intercostal vessels. In the emergency department, definitive treatment involves the use of a large-caliber thoracostomy tube that favors drainage of the tension pneumothorax and any accompanying hemothorax.

Hemothorax. Significant bleeding may occur when injury is directed toward the intercostal vessels, internal mammary vessels, or lung parenchyma. Without an upright chest film, it is difficult to quantify the degree of bleeding on plain radiographs. A slightly less radiolucent appearance on the affected side of the chest may be the only sign on a supine radiograph, often associated with a pneumothorax. Development of a massive hemothorax is rare in children and is associated most often with severe impact, such as that seen in high-velocity MVCs, falls from extreme heights, or the use of high-powered firearms. These injuries must be evaluated and treated quickly. Clinically, patients present with decreased breath sounds and dullness to percussion on the affected side. A pneumothorax may coexist with a hemothorax. The pediatric patient may present with early or late signs of hypovolemic shock.

Any alteration in cardiovascular sufficiency should be treated with rapid fluid replacement with isotonic crystalloid solutions. The clinician must also prepare for transfusion with the institution of red blood cell replacement as necessary. Patients who present with profound shock may receive either type-specific or O-negative blood; crossmatched blood may be used for more stable patients. The amount of blood that is salvaged from the chest tube should be quantified to help determine the need for red blood cell replacement. Many centers have the capability to salvage blood from hemothoraces and reinfuse using an autotransfuser. As in all cases of trauma, initial measurement of the hemoglobin is often unreliable and typically underestimates the amount of blood loss due to inadequate time for equilibration.

The treatment of hemothorax includes a tube thoracostomy. The tube needs to be large enough to occupy most of the intercostal space and should be placed laterally and directed posteriorly. In the supine patient with simple pneumothorax, chest tubes are directed superiorly; in hemopneumothorax, they are directed posteriomedially. As in all interventions, repeat chest radiographs should be obtained to confirm tube position and document improvement in lung expansion. The emergency physician is often able to stabilize the patient with red blood cell replacement until surgical intervention is achieved.

Indications for thoracotomy include evacuated blood volumes exceeding 10 to 15 mL/kg of blood immediately after the placement of the chest tube, persistent blood loss (e.g., exceeding 2–4 mL/kg/hr over 3 hours), or continued air leak. Emergency department thoracotomy is reserved for patients with penetrating trauma who deteriorate to cardiopulmonary failure despite maximal resuscitation in the out-of-hospital setting or emergency department. Guidelines for emergency pediatric thoracotomy are often institution specific. Cothren and Moore have suggested an algorithm to guide emergency department thoracotomy in multiply injured trauma patients.[56] Contraindications for emergency department resuscitative thoracotomy after out-of-hospital cardiopulmonary resuscitation (CPR) include (1) blunt trauma with CPR for greater than 5 minutes with asystole and no signs of life on presentation without ultrasound evidence of cardiac tamponade and (2) penetrating trauma with CPR for greater than 15 minutes and asystole with no signs of life on arrival without ultrasound evidence of cardiac tamponade. Patients with penetrating chest trauma and CPR for less than 5 minutes may warrant a left anterior thoracotomy, whereas patients with blunt trauma should have rapid assessment by ultrasound for tamponade. If tamponade is present and CPR has been performed for less than 15 minutes, then a left anterior thoracotomy may be indicated.

Pulmonary Contusion. Penetrating and blunt thoracic trauma may result in the development of a pulmonary contusion. The compliance of the rib cage in children renders them susceptible to the development of pulmonary contusion even in the absence of external signs of chest trauma. Injury to capillary membranes allows the collection of blood within the interstitial spaces, resulting in hypoxia and respiratory distress. If bleeding is severe enough, oxygenation and ventilation are impaired. Initial chest radiographs may not show the classic findings of pulmonary consolidation. In addition, in the early stages of injury, blood gases may be normal.

Treatment of pulmonary contusions includes a careful evaluation for the presence of additional injuries because significant force is necessary to cause the contusions. Most patients may be treated with supplemental oxygen and close monitoring. Most pulmonary contusions resolve without sequelae. Rare cases are associated with the development of acute respiratory distress syndrome.

Traumatic Diaphragmatic Hernia. Children involved in MVCs who are wearing lap belts are predisposed to the development of diaphragmatic herniation.[55,57-59] Mechanisms of injury involve sudden increases in intra-abdominal pressure. Patients initially present in stable condition, with the degree of respiratory distress directly proportional to the amount of abdominal contents that protrude into the pulmonary space. The presence of bruising from lap belt–only compression should alert the clinician to the possibility of diaphragmatic hernia and other intra-abdominal injuries (small bowel injury) and the possibility of associated thoracolumbar spinal insults such as Chance

fractures. Most commonly, the herniation occurs on the left side because the liver is protective against diaphragmatic rupture on the right.

Initial management for these patients involves placement of an NG tube to decompress the stomach. In cases of severe respiratory distress, intubation is indicated. Bag-valve-mask ventilation is avoided whenever possible. Surgery is required for repair of the injury.

Cardiac and Vascular Injuries. Injuries to the heart and large vessels are uncommon in children.[59-61] The most common traumatic cardiovascular injury sustained by children is myocardial contusion. Patients often present with chest wall tenderness or may have a complaint of generalized chest pain. Tachycardia is the most common finding. Elevation of myocardial enzymes may be diagnostic. Patients with myocardial contusions should be monitored closely for the development of dysrhythmias and impaired myocardial function; however, in most cases of myocardial contusion, there are no long-term sequelae. The most life-threatening scenario involving the cardiac structures is the development of cardiac tamponade. Penetrating wounds to the chest are not rare but are potentially survivable if myocardial penetration and tamponade are recognized immediately. Extravasated blood fills the pericardial space and impairs cardiac filling during diastole. Tamponade is most often the result of a penetrating wound. Firearm insult often causes sudden death, and blunt trauma rarely results in the development of cardiac tamponade. Clinically, patients present with tachycardia, distant heart sounds, narrow pulse pressure, jugular venous distention, and pulsus paradoxus. In the scenario of profound hypovolemia, venous distention is absent. The final common pathway involves the development of pulseless electrical activity. Ultrasound can characterize this injury in seconds and guide therapy.

In cardiac and vascular injuries, the electrocardiogram may show anything from tachycardia with low voltage (pericardial tamponade) to findings consistent with acute myocardial injury (ST segment elevation). In the subacute scenario, echocardiography often makes the diagnosis. Bedside transthoracic echocardiography defines the degree of pericardial effusion present and the significance of any diastolic dysfunction present. A simple single subxyphoid view provides the emergency physician with an excellent view of the pericardial sac and heart. Pericardiocentesis may be diagnostic and therapeutic. Definitive treatment involves drainage of the fluid from the pericardial sac. In certain situations, the amount of pericardial blood and clot necessitates the performance of a thoracotomy to evacuate the pericardium adequately.

Commotio Cordis. Commotio cordis is a disorder described in pediatric patients that results from sudden impact to the anterior chest wall (e.g., as seen in baseball injuries), which causes cessation of normal cardiac function.[61-63] The patient may have an immediate dysrhythmia or ventricular fibrillation that is refractory to resuscitation efforts. Significant morbidity and mortality are associated with this disorder, and although most recover completely, some patients require extended treatment with antiarrhythmic agents, cardiac pacemaker placement, inotropic agents, or intra-aortic balloon pump. In patients with prolonged cardiac instability, cardiogenic shock and death are common, despite maximal therapeutic intervention.[62,63]

Abdominal Injury

Perspective

Serious abdominal injury accounts for approximately 8% of admissions to pediatric trauma centers.[2] Abdominal trauma is the third leading cause of traumatic death in children after head and thoracic injuries. Abdominal trauma is the most common cause of unrecognized fatal injury in children. Pediatric abdominal trauma results from blunt causes in the vast majority of cases. Of patients presenting primarily for other associated injuries, 9% die from abdominal trauma associated with these injuries.

Blunt trauma related to MVCs causes more than 50% of abdominal injuries in children and is the most lethal. "Lap belt" injury, including small bowel injury and Chance fractures, may occur in approximately 5 to 10% of restrained children involved in MVCs.[64-66] Another common cause of abdominal injury involves bicycle crashes. Handlebar injuries represent a serious cause of injury and subsequent hospitalization for the pediatric population; patients requiring admission have a mean hospital stay greater than 3 weeks. Often, the effects of bicycle injuries may not be seen on initial presentation, with the mean elapsed time to onset of symptoms being nearly 24 hours after injury. All children with epigastric pain after blunt trauma, especially when concentrated force has been applied in this area, should be considered to have duodenal hematoma until proven otherwise. Pancreatic injury, including transection, should be strongly considered as well.

Sports-related injuries are another common cause of pediatric abdominal trauma. Sports-related injuries are associated most commonly with isolated organ injury as a result of a blow to the abdomen. At particular risk are the spleen, kidney, and intestinal tract in children. Finally, significant abdominal injury occurs in only approximately 5% of child abuse cases, but it is the second most common cause of death in these cases, following deaths resulting from head injury.

Principles of Disease

The anatomy of the child lends special protection from some abdominal injury patterns and predisposes the child to other types of injuries in blunt and penetrating abdominal trauma. Children have proportionally larger solid organs, less subcutaneous fat, and less protective abdominal musculature than adults and relatively more solid-organ injury from blunt and penetrating mechanisms. Children have relatively larger kidneys with fetal lobulations that predispose them to renal injury. Children also have a fairly flexible cartilaginous rib cage that allows for significant excursion of the lower chest wall, permitting compression of the internal organs. The combination of these factors provides the basis for the differences in abdominal injury patterns seen between children and adults.

Clinical Features

Pediatric patients with multiple injuries often present with blunt abdominal injury. In children, history is often limited, traditional signs of decompensation seen in adults are often not as evident, and physical examination can be difficult. Subtle, early abdominal findings may be overlooked, leading to significant morbidity and mortality. The history and examination of young children who have sustained trauma is challenging because it may be difficult to know if the child hurts "all over" or has focal findings. The emergency physician may use distraction with toys, lights, bubbles, or keys to get the child's mind off the examiner and onto the distraction; in this way, areas of tenderness may be located. Child life specialists can assist in distraction techniques, allowing the physician to better concentrate on subtle signs of injury.

Signs and symptoms of abdominal injury in children include tachypnea from impaired diaphragmatic excursion, abdominal

tenderness, ecchymoses, and signs of shock. Lutz and coworkers demonstrated that among restrained children involved in MVCs, those with abdominal bruising were much more likely to have an intra-abdominal injury than those without bruising.[67] One in every nine patients with ecchymosis was found to have an intra-abdominal injury, some requiring surgery. Abdominal distention is a common nonspecific finding that is often the result of air swallowing subsequent to a painful event. Children with hepatic and splenic injuries may have trouble localizing their pain. Kehr's sign (left shoulder pain with spleen injury) may be the only indication of an intra-abdominal injury. Any abdominal tenderness on examination should prompt further evaluation of the abdomen. Vomiting is usually a late sign or one associated with duodenal hematoma or traumatic pancreatic injury. Signs of small bowel injury may be delayed and noted clinically only with serial examinations. Pelvic bone stability and a rectal examination searching for signs of urethral injury (rare) in boys or blood in the stool (girls and boys) and spinal cord injury (girls and boys) may need to be performed in selected cases of trauma. Rectal examination is insensitive and nonspecific when used as a general screening test for all patients after serious trauma. Cases with suspected injury should receive further evaluation even when the rectal exam is unremarkable.

Even minor falls can result in significant splenic injury but with only minimal findings on examination. Repeated examination, prolonged observation, and close attention to vital signs are warranted. Any child with a clinically suspicious abdominal examination should be evaluated further with additional radiologic and laboratory studies and/or admission for serial examination.

Diagnostic Strategies and Management

In patients with suspected abdominal injury or with mechanisms of possible injury, management and resuscitation must be rapid. Because of fear and pain, children can compound the difficulties in the management of serious penetrating or blunt abdominal trauma. Children tend to distend the stomach greatly with ingested air, which can decrease the diaphragmatic excursion. This can compromise respiratory efforts, and early decompression via NG or OG tube insertion should be considered. Children with a stable pelvis and who are not at risk of urethral trauma should have a urinary catheter inserted to decompress the bladder, evaluate for the presence of urinary retention, and examine for the presence of blood in the urine. The bladder should be decompressed before any invasive evaluation of the abdomen, such as DPL, to prevent accidental laceration during the procedure. A rule of thumb for urinary catheter size in children is 5 F in newborn, 6 F in preschool, 8 F in elementary school, 10 F in middle school, and 12 to 14 F in high school.

DPL and diagnostic peritoneal aspiration are occasionally still useful in modern trauma practice. In the unstable multitrauma patient with an equivocal FAST exam, the aspiration of 10 cc of blood, fecal, or vegetable matter from the abdomen typically would indicate intraperitoneal hemorrhage and/or bowel injury and the likely need for laparotomy. The DPL has less use in today's practice but is performed by placing 15 cc/kg of NaCl in the peritoneal space and then removing the fluid by gravity. In blunt trauma, a positive DPL is defined as having greater than 100,000 red blood cells/mL or greater than 500 white blood cells/mL, or gram-negative bacteria or vegetative material (stool) seen on microscopy. DPL does not evaluate for retroperitoneal bleeding. The threshold values must be lowered for penetrating trauma. In general, DPLs are not performed on stable patients because CT scanning can be done quickly and give the clinician far more information, especially about intraparenchymal injury and retroperitoneal injury. CT scanning is not very sensitive for bowel injury and results in significant radiation exposure. This must be kept in mind in decision making and when interpreting test results.

Spleen Injury. Injuries to the spleen are the most common injuries in pediatric abdominal trauma. Children with injuries from MVCs, sudden deceleration injuries, and contact sports–related injuries may sustain splenic trauma. Typical findings include left upper quadrant abdominal pain radiating to the left shoulder. The abdominal examination may show evidence for peritoneal irritation in the left upper quadrant of the abdomen. Patients may be hemodynamically stable or, after significant splenic rupture or laceration, may be persistently hypotensive or in fulminant cardiovascular collapse. Stable patients may undergo CT for radiologic evaluation. Most often, with minor splenic trauma, bleeding is controlled spontaneously without operative intervention; however, all patients with a splenic injury should be evaluated by a surgeon. In cases with a contained splenic subcapsular hematoma, extracapsular bleeding may occur days later. Patients with splenic injury should be admitted to the hospital for close observation and repeated examinations.

Liver Injury. The liver is the second most commonly injured solid organ in the pediatric patient with abdominal trauma. However, it is the most common cause of lethal hemorrhage, with a mortality of 10 to 20% in severe liver injury. Mechanisms of injury causing splenic injury also may cause liver trauma. Tenderness on palpation of the right upper quadrant of the abdomen and the complaint of abdominal pain in this region or in the right shoulder are signs of possible liver injury. Patients managed conservatively often do well; however, patients who are initially treated conservatively but then go on to require delayed laparotomy often have significant morbidity and mortality. Close observation in the hospital, serial abdominal examinations, and serial hemoglobin are recommended.

Renal Injury. The kidney is less susceptible to trauma from forces applied to the anterior abdomen, but it is often injured in the pediatric patient with multiple injuries.[68] Because this organ is retroperitoneal, signs and symptoms of kidney injury are often less obvious and more diffuse than signs and symptoms of other abdominal organ injuries. Often, dull back pain, ecchymosis in the costovertebral region, and hematuria are the only clues to renal injury.[69,70] Renal ultrasound and CT may be used in a stable patient to assess the degree of renal involvement. Other organs, such as the pancreas and gastrointestinal tract, are less frequently injured in pediatric patients.

Penetrating Injury. Penetrating wounds to the abdomen usually require rapid evaluation by a surgeon and, in some cases, operative intervention. The role of DPL in the management of pediatric trauma is controversial. DPL provides the most rapid, objective evaluation of possible intraperitoneal injury. Patients who remain unstable despite fluid resuscitation may be candidates for DPL if they are too unstable for CT and there are multiple potential sites of blood loss. An important role for DPL is in the setting of an underlying small bowel injury. In some patients with small bowel injury, CT findings of free fluid may be ascribed improperly to underlying splenic bleeding. Finally, DPL may be considered in the operating room for patients undergoing emergent craniotomy, when adequate evaluation of the abdomen cannot take place because of the urgency required for intervention for head injury.

Radiology. Because pediatric patients suffer more from injury to the spleen, liver, kidneys, and gastrointestinal tract, CT of the abdomen can provide high sensitivity (except with intestinal injury) and specificity for identification of these

injuries while being relatively noninvasive.[10] Recent studies have clarified that oral contrast does not add to the accuracy of CT; thus, one can avoid delays in evaluation, difficulty with administration, and risk for aspiration.

Another useful procedure in an acutely traumatized pediatric patient is bedside abdominal ultrasound. When used by an experienced clinician, ultrasonography can provide sensitive information about intraperitoneal hemorrhage without invasive measures. Although radiologic evaluation can provide important diagnostic information in a pediatric patient with possible abdominal trauma, any patient with unstable vital signs from an obvious surgically correctable cause should receive immediate operative intervention and not be subjected to delay while obtaining radiographic screening studies. Children with persistent or recurrent hypotension, continued abdominal pain, or persistent abdominal distention should have expedient evaluation by a surgeon.

DISPOSITION

A key decision for the emergency physician is whether to admit a pediatric trauma patient or transfer the patient to a tertiary care facility. The decision for admission in questionable cases should be based on consultation with the surgeon and the patient's primary care physician. Infants and children who are moderately to severely injured have improved outcomes in a pediatric (specific) ICU versus an adult ICU or an adult ICU with a few segregated pediatric beds. The primary role of the emergency physician is to evaluate and stabilize the patient before admission to a pediatric ICU or before transfer to a tertiary care facility. Before transport, it is vital that the child is appropriately stabilized and that the emergency physician communicates directly with the accepting physician at the accepting facility. Extensive radiologic testing should generally not be completed in a facility that cannot potentially manage that which is being looked for unless the emergency physician is confident that it will not delay the transfer to more definitive care and has discussed the plan with the receiving physician. All radiographs, documents, and results of laboratory testing should be sent with the patient. Parents should be informed of the exact location to which the child is being taken and given a map from the transferring facility to the receiving facility. Under no circumstances should the child's likely outcome be downplayed to the patient's parents before transfer because this leads to false expectations and the assumption of poor care if the outcome promised is not achieved.

Indications for admission are many, but the main criterion is to admit patients requiring ongoing monitoring for deterioration or complications of their injuries. In addition, children with suspected physical injury from child abuse may be admitted for their protection and for medical treatment. The threshold for admission should be very low in cases in which the health care team does not believe the child will have the social support or oversight necessary to be appropriately observed or to recover in the home environment. The family should be asked if they have transportation, a phone, and access to emergency medical service if needed.

Cessation of Care

Despite advances in trauma care and system improvement, some injured children will die—some in the emergency department. Cases in which death is certain or has already clearly occurred, such as with decapitation and findings of livor mortis or rigor mortis, do not present treatment dilemmas. Those who do present with signs of life (respirations, blood pressure, pulse, pupil reactivity, or cardiac and electrical activity) should have resuscitative efforts initiated. Cardiac echo can be helpful in some cases to confirm the lack of cardiac activity in patients without a pulse who continue to have electrical activity. Patients who lose their vital signs en route to or in the resuscitation room should receive maximum resuscitative efforts, potentially including emergency thoracotomy.

Organ donation should be considered part of the "Omega survey," which is the final review after death is declared. Signs of maltreatment, congenital abnormality not previously recognized, possible personal identifying marks in unknown cases, and points for future education and study can be gained from one last mental and visual review, as can the potential for some insight related to the cause of death. Organ donation should be offered under local and state guidelines to all families of deceased children. Often, it is viewed as one way parents can make sense of the death of their child. Knowing that their child's death helped many others to live can help parents in their healing.

Parental presence should be considered in all pediatric resuscitation cases. Assigning someone to be with the parent to explain what is happening is essential. Often, the parents' presence can be useful to the resuscitative effort. Information can be obtained immediately when needed from the parents, and they witness the effort that goes into trauma resuscitation. Very rarely, parental presence can present a true hindrance to medical care, in which case the parent can be asked to leave or be escorted out of the room. Parents who witness what the team does for their children during resuscitation seem to better understand the ability and limitations of medicine. In the final analysis, most parents want to be there, and frankly, at the time of death, their presence is more important than the presence of the medical team.

KEY CONCEPTS

- Trauma is the leading cause of death in children in the United States. It accounts for 64% of all deaths in children, totaling 1.5 million injuries and 250,000 hospitalizations annually.
- Proper management of a pediatric trauma patient involves most of the components of standard adult trauma protocols. By paying strict attention to the anatomic and physiologic differences in children, the clinician is assured of the best patient outcomes.
- The leading cause of traumatic shock in children is hypovolemia; management priorities include appropriate ventilation and oxygenation and fluid resuscitation to maintain perfusion.
- The diagnostic test of choice for the evaluation of intra-abdominal injury in a stable patient is CT of the abdomen.
- Controlled hyperventilation should be performed on children with signs of impending brain herniation, and Pco_2 levels should be maintained at 30 to 35 mm Hg to avoid secondary brain injury from excessive hyperventilation and subsequent cerebral vasoconstriction.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 36 Geriatric Trauma

Diane M. Birnbaumer

PERSPECTIVE

Background

At the beginning of the 21st century, nearly 13% of the population in the United States was older than 65 years, and by 2040 one in five people will be within this age range.[1] The financial impact of this aging has been tremendous and will continue to accelerate. The first baby boomer became eligible for Social Security on January 1, 2008, and it is estimated that 365 baby boomers will reach retirement age every hour. More than 35% of total health care dollars spent in the late 1990s was for medical care for patients older than 65 years, and undoubtedly this percentage will continue to rise.[1]

With regard to trauma, elders (patients older than 65 years) account for only 10 to 14% of all victims, but they consume 25 to 33% of trauma-related health care dollars. Injury is the fifth leading cause of death in this age group[2] because of a combination of physiologic changes that alter the older patient's response to trauma and injury mechanisms and patterns that are demographically different from those of younger trauma patients. Even among patients older than 65 years, risk stratification exists. Although the risk of death and significant injury is increased in patients 65 to 80 years of age, traumatized patients older than 80 years are four times more likely to die from their trauma than are younger patients.[3,4] Emergency practitioners must familiarize themselves with these differences among traumatized elder patients as well as understand the differences in resuscitation and stabilization of these patients.

Epidemiology

In younger patients, assault and motor vehicle crashes (MVCs) account for the vast majority of traumatic injuries. In elders, the most common cause of injury is falls,[4,5] followed by MVCs, pedestrians struck by cars, and assaults.[4] In general, elder patients are more likely than younger patients to be injured as a result of activities of daily living.

Falls

Falls are the most common mechanism of injury in elders, accounting for 40% of trauma in patients older than 65 years, and they are the leading cause of injury-related death in this patient population.[4,5] One third of elder patients suffer a significant fall each year, and serious injuries occur in up to one fourth; this rate is increasing rapidly.[5,6] Risk factors for falls include medications (sedatives in particular), cognitive and visual impairment, history of stroke, and arthritis. Most falls occur at home and are same-level falls (i.e., falls from the standing position). Because as many as a one fourth of these falls occur as a result of an underlying medical problem,[7,8] an appropriate medical evaluation is indicated in addition to the trauma assessment and stabilization. Some of the medical causes of falls include strokes, syncope, near-syncope, medications, elder abuse, and hypovolemia (e.g., related to gastrointestinal bleeding, ruptured abdominal aortic aneurysm, sepsis, or dehydration).

The most common injuries sustained in falls are fractures, occurring in 5 to 10% of fall victims.[5,6,9] Up to 10% of patients may sustain a major injury,[9] and head injury is the most concerning of these. Many elder patients are on anticoagulants; this makes them more susceptible to significant head injury as a result of a fall. Some studies have shown the incidence of trauma-related abnormalities on head computed tomography (CT) scans in this group of patients to be as high as 16%, with 1 in 50 requiring neurosurgery.[10] The most common abnormal head CT finding is a cerebral contusion, followed by subdural hematoma; epidural hematomas are rarer in elder patients than in younger patients. The greater the height of the fall, the more likely the patient is to have an abnormal CT scan, but serious head injuries may also be seen in patients who suffer a same-level fall. Overall, the peri-injury mortality rate in elders from falls approaches 12%, and up to 50% die within 1 year of the fall,[9] often related to either recurrent falls or significant medical complications.

Motor Vehicle Crashes

MVCs are the second most common cause of trauma in elders, accounting for 20 to 59% of trauma in this age group.[4,11] Compared with younger patients, older drivers are more likely to be killed or hospitalized because of an MVC even when they are using seat belts.[11] Cognitive impairment, decreased hearing and vision, and slower reaction time are significant risk factors for MVCs in this age group.

Most MVCs involving elders are daytime crashes occurring close to home. These crashes often occur at an intersection and usually involve two cars.[11] An elder is twice as likely as a younger person to be in an MVC when making a left-hand turn, and injuries sustained in these broadside crashes tend to be more severe. A single-vehicle crash should raise suspicion of a medical problem that may have caused the crash and requires a careful history, examination, and workup. MVCs in

elders are less likely to involve alcohol, excessive speeds, or reckless driving than those involving younger patients. The overall fatality rate among elder MVC victims is as high as 21%.[4,11]

Auto versus Pedestrian Incidents

The third most common cause of injury in elders is auto versus pedestrian incidents.[4] As with MVCs, poor eyesight and hearing, as well as decreased mobility and longer reaction times, make pedestrian elders more likely than younger patients to be hit by a motor vehicle. This mechanism accounts for 9 to 25% of trauma in elders and carries the highest fatality rate, reported to be from 30 to 55%.[4]

■ PRINCIPLES OF DISEASE

Physiology and Pathophysiology

Physiologic changes are inevitable with aging. These changes affect the mechanisms of trauma, types of injuries sustained, response to injury, approach to resuscitation, and prognosis for the injured elder patient.

Compared with younger patients, elders have a more severe injury response to any given trauma mechanism and have a decreased ability to respond to the trauma. In addition, preexisting medical problems may be exacerbated by the trauma, and morbidity and mortality may result from underlying diseases such as cardiovascular or cerebrovascular disease rather than the trauma.

Elders are less likely to be involved in reckless trauma than their younger counterparts. Diminished hearing and sight increase the risk of falls, pedestrian injuries, and traffic collisions. Difficulty with gait and coordination because of impaired sensation and proprioception, muscle weakness, degenerative joint disease (DJD), neuromuscular disorders, and dementia lead to increased risk of falls and affect reaction times in pedestrians and MVCs. Finally, medications have a significant impact on the traumatized elder patient. Medications that may alter mental status (sedatives and antidepressants) make the elder patient more susceptible to traffic collisions and falls. Cardiac medications affect the response to hypovolemia and shock as well as resuscitation. Diuretics may lead to volume contraction before the trauma occurs. Profound hypokalemia secondary to diuresis can also cause weakness and an impaired ability to ambulate or effectively operate foot pedals. Anticoagulants clearly affect the risk of bleeding. Many elder patients are taking these medications; studies show that the most commonly prescribed medications in the elderly are diuretics, cardiac agents, psychotropic drugs, and anticoagulants.[12,13]

Cardiovascular System

Cardiovascular reserve decreases with age, and because the aging heart cannot easily increase cardiac output (the maximum achievable heart rate decreases with age), elders tend to respond to hypovolemia with increased systemic vascular resistance. In addition, they are less responsive to the increased circulating catecholamine response to shock, making them at risk for earlier decompensation from hypovolemia. Medications such as antihypertensives may affect their ability to increase systemic vascular resistance, and beta-blockers, calcium channel blockers, and digoxin decrease their ability to develop a tachycardic response to shock. Underlying coronary artery disease increases the risk of myocardial ischemia from hypotension and blood loss. Overall, elders are less able to respond to fluctuations of blood pressure and blood volume that may accompany a traumatic injury than are younger patients, and these changes may exacerbate underlying cerebrovascular and cardiovascular disease.

Pulmonary System

Aging significantly affects the pulmonary system. Reductions in arterial partial pressure of oxygen (Pao_2), forced expiratory volume in 1 second (FEV_1), and vital capacity occur with aging; the lungs become less compliant; and the muscles of respiration weaken. As a result, elders are less tolerant of the volume resuscitation and spinal immobilization that are often needed in resuscitating a trauma victim. In addition, the chest wall is more brittle because of osteoporosis and more rigid because of DJD, making injuries to the chest wall more likely in an elder patient. Combined with the decreased pulmonary reserve in elders, chest wall injuries may quickly lead to respiratory failure in this population of patients. Elders are therefore more likely to require intubation after trauma and are more difficult to wean from respirators after intubation.

Central Nervous System

With aging, the dura mater adheres to the inside of the skull, making epidural hematomas rarer in elders than in younger patients. With age, the brain often atrophies, making it more mobile within the skull during trauma. This atrophy and the resultant stretching of the bridging veins seen in elders make them more susceptible to subdural hematomas than younger patients, even with seemingly minor mechanisms of injury or minimal external evidence of trauma.

Skeletal System

Osteoporosis, a common condition in elders, is a significant risk factor for skeletal injuries such as compression fractures of the thoracic and lumbar spine and other injuries including hip and wrist fractures. These injuries may occur even with relatively minor trauma. Decreased mobility of the joints is also a problem, particularly in the spinal column. This limited mobility increases the risk of spinal injuries, and the locations of these injuries differ in the elder patient. Spinal stenosis, more common in elders than in younger patients, increases the risk of spinal cord damage even in the absence of spinal column injury.

Skin

Skin trauma is common in the elder patient. Aging skin thins and is susceptible to tears and lacerations even with relatively minor trauma. These injuries may be very difficult to repair and often require débridement of devitalized tissue. Prolonged immobilization on a backboard or in a C-collar can result in decubitus ulcers of the back, buttock, or occiput. In addition, elders may be prone to tetanus due to lapses in their active tetanus immunization.

■ SPECIFIC DISORDERS AND INJURIES

Perspective

Multiple trauma in the elder patient is more lethal than in younger patients; a multiply traumatized patient 70 years of age is three times more likely to die than a patient 20 years of age.[4] The combination of comorbid illnesses, increased propensity to trauma, and decreased physiologic reserve often

leads to exacerbation of underlying medical problems and a higher risk of multiple-system organ failure and death in the elder patient.[14]

Spinal Injuries

Physiologic changes with aging predispose the traumatized elder patient to both spinal column and spinal cord injury. DJD leads to decreased spinal mobility and a more brittle spinal column, and osteoporosis makes the bones more likely to fracture. Spinal stenosis often occurs as a result of the aging process; this increases the risk of cord injury even in the absence of a bone injury. Baseline cognitive impairment or acute brain injury may make evaluation of the spine in an elder trauma patient particularly difficult.

The most common mechanism of spinal injury in an older person is a fall. Because of the relative immobility of the cervical spine related to DJD, the most common level of cervical spine injury in elders is C1 to C3,[15-18] a higher level than in younger patients. The most common fracture of the cervical spine in elders is a type 2 odontoid fracture,[15-17] which necessitates adequate visualization of this area of the cervical spine when imaging is performed, often requiring CT scanning with reconstruction. Even if the patient does not suffer a fracture, spinal cord injuries may result from contusion of the cord. Contusion occurs most frequently in hyperextension injuries leading to central cord syndrome (upper extremity greater than lower extremity weakness and sensory loss). Overall mortality from cervical spinal injuries in elders is approximately 14%, triple that of younger patients.[19] Compression fractures of the thoracic and lumbar spine may occur with falls, even those that are seemingly relatively minor, particularly in elder women with osteoporosis. Although spinal cord injuries are relatively rare with these fractures, disability from pain can be significant, and these patients may need admission for adequate pain control. It may also be necessary to differentiate compression fractures from burst fractures, and CT is often helpful in making this distinction.

Head Injuries

Head injuries are the most common cause of mortality directly related to trauma in elder patients. The most common mechanism of significant head injury in elders is falls. Epidural hematomas are rare because of the adherence of the dura mater to the inside of the skull. Cerebral contusions, however, occur in up to one third of head-injured elder patients, and subdural hematomas become more common with age because of the stretching of the fragile bridging veins as the brain atrophies. This atrophied brain is more mobile within the skull, and head trauma may result in shearing of these veins. These patients may present with a broad range of symptoms, from frank coma to a relatively remote history of head trauma and slightly altered mental status.

Mortality from head injury in elders is double that of younger patients, with mortality from subdural hematoma in elders being up to four times higher than in younger patients.[20] When patients have minor head injury, elders may eventually recover full function but often need either in-hospital or home rehabilitation before they can return to their baseline function.[21]

Head CT scanning is the diagnostic test of choice for brain injury, and a contrast study may be necessary if the injury is 7 to 20 days old and an isodense subdural hematoma is suspected. Magnetic resonance imaging (MRI), if available, is an alternative imaging modality in these patients when the injury is subacute and an isodense lesion is suspected.

Chest Injuries

Rigidity of the chest wall related to DJD and osteoporosis makes chest wall injuries more common in elders, even with relatively minor trauma. Because of the frailty of the chest in these patients, lap and shoulder belts in automobiles may actually cause injuries, including multiple rib fractures, flail chest, and sternal fractures. Rib fractures are the most common, and because elders have less pulmonary reserve than younger patients, these fractures may lead to respiratory insufficiency. Elder patients more frequently develop respiratory failure from their trauma and are more likely to require mechanical ventilation. In addition, elders may develop atelectasis, pneumonia, and acute respiratory distress syndrome. With proper care (including pain medication), meticulous attention to pulmonary hygiene, and careful hemodynamic management and monitoring, up to 90% of patients with chest injuries may return to normal life after their injuries.

Abdominal Injuries

Depending on the mechanism of injury, up to 30% of elder trauma patients may suffer a significant intra-abdominal injury, but the abdominal examination may be unreliable in these patients. Because mortality from abdominal injuries in elders is four or five times higher than in younger patients, a diligent search for potential intra-abdominal injuries is crucial. Frequently, this requires some combination of focused abdominal sonography in trauma exam (FAST) and CT scanning of the abdomen, depending on the patient's hemodynamic stability and other system injuries.

Extremity Injuries

Because of the increased bone fragility and predisposition to falls with aging, the musculoskeletal system is the most commonly injured organ system in elder trauma patients. By the age of 75 years, 30 to 70% of patients with osteoporosis sustain a fracture.[22] Although rarely life threatening, these injuries can severely limit the daily activities of elder patients to the degree that these patients may need admission for pain control as well as to arrange adequate home support or rehabilitation.

Upper extremity fractures are common. Distal radial fractures are the most common upper extremity fractures in elders, accounting for up to 50% of fractures, followed by proximal humeral fractures (30%) and elbow injuries (radial head fractures and elbow dislocations; 15%).

Pelvic fractures are common in elder trauma patients, accounting for 25% of these injuries.[23] Pubic rami fractures, the most common pelvic fractures in this age group, may be seen with same-level falls. Although these injuries tend to be stable, pain control and gait training may necessitate hospitalization. High-velocity injury mechanisms (MVCs or auto versus pedestrian incidents) and falls from heights may result in unstable pelvic fractures, which are associated with a mortality of up to 80% if the fracture is open.[23]

Hip fractures are the most frequent lower extremity fractures and the most common cause of admission in elder trauma patients. These injuries are associated with an early mortality rate of 5% and a risk of death of 13 to 30% during the year after the injury (often related to other factors, such as recurrent falls and underlying medical problems).[5] Plain radiographs are often diagnostic, but CT or MRI scanning may be necessary to discover or further delineate subtle fractures in the elder patient with hip pain after a fall.

Tibial plateau fractures may occur with a fall or MVC and most commonly involve the lateral tibial plateau. Patellar frac-

tures may result from a fall directly onto the kneecap, and sunrise views of the patella may be the only way to visualize these injuries. Ankle fractures account for 25% of all lower extremity fractures and most commonly involve the lateral malleolus; treatment often consists of a walking cast.

Soft Tissue Injuries

Elder patients are susceptible to skin injuries related to the thinning of the skin that occurs with aging. Treatment of these injuries often proves to be difficult, and débridement of devitalized tissue and careful local care are often necessary. Elder patients frequently are not up to date with their tetanus immunizations and because of this are at risk for developing this infection. Treatment with both active and passive immunization is often indicated in this group.

Burns

Burns are particularly devastating in the elder patient. More than 90% of burns occur at home, and because elder patients often live alone and have decreased reaction times, deeper and more extensive burns may occur in this age group. Flame burns account for 50% of all burns in this group and 20% of burn-related deaths. Some of these injuries are cooking related; scalds account for 19% and flammable liquid burns for 10%. Despite the fact that the incidence of burns is lower in elders than in younger patients, mortality from this injury is high. Until the mid-1980s, Baux's formula (risk of mortality = age in years + percentage body surface area burned)[24] provided a gross estimate of risk of death from burns. Although advances in burn care during the past two decades have decreased the mortality rate, elders are still at high risk for mortality from burns, with recent data suggesting a mortality rate of approximately 30%. [25] Thinning of the skin and decreased immunocompetence contribute to this higher risk of mortality as well as exacerbation of underlying medical conditions that may be precipitated by the stress of an extensive burn injury and its treatment.

CLINICAL FEATURES

Because elder patients may have significant injuries with subtle findings, a thorough examination supplemented by laboratory testing and radiographic studies is often the most prudent approach to even seemingly minor injuries, depending on the mechanism of injury and the presence of comorbid conditions and particularly certain medications (e.g., anticoagulants).

History

A complete history of the events leading to the injury is needed, and out-of-hospital personnel can be invaluable in providing this information. Falls and MVCs, particularly if they involve a single vehicle, should trigger questioning about possible syncope, hypovolemia, cardiovascular or cerebrovascular events, or a complication of medications. The mechanism of injury should be considered and the different patterns of injury in elder patients evaluated (e.g., higher risk for subdural hematoma, high cervical spine injury, and bone injuries).

Physical Examination

In patients with anything more than the most minor of mechanisms of injury, a thorough head-to-toe examination should be performed. Clothing should be removed in order to allow a complete physical examination. Vital signs may be normal, even in the presence of significant blood loss. Because many elder patients are on antihypertensives, normal blood pressure may in fact signify the presence of hemorrhage. It is important to keep elder trauma patients warm because they are more likely to develop hypothermia when disrobed for examination, and hypothermia increases the risk of mortality related to trauma.

DIAGNOSTIC STRATEGIES

Laboratory

Laboratory evaluation should include serial hemoglobin, hematocrit, or both; prothrombin time and partial prothromboplastin time and an international normalized ratio; serum electrolytes; rapid and formal glucose measurements; and medication levels if indicated. An electrocardiogram is also useful to evaluate the patient for a precipitating event as well as to assess any cardiac ischemia that may be caused by the trauma and resultant injuries.

Radiology

Radiographic studies should be ordered as indicated by the history and physical examination. Plain films of the cervical spine are often difficult to interpret because of baseline DJD; therefore, CT scans of the neck, with particular attention to the more likely injured higher cervical spine, may be necessary to rule out spinal injury. This is particularly true if clinical findings warrant and plain films are inadequate or demonstrate suspicious areas. Plain films of the thoracic and lumbosacral spine should be obtained in patients with posttraumatic pain in these areas. A chest radiograph may be of particular importance both to evaluate the patient for traumatic injuries and to search for signs of congestive heart failure precipitated by the trauma or resuscitation efforts. Plain films of the pelvis are indicated in patients with suggestive mechanisms of injury or pain on examination of the pelvis. Extremity films should include all areas of concern, and CT or MRI scanning may be necessary to diagnose subtle hip fractures. Adequate radiographic imaging to rule out significant intra-abdominal injury may require FAST, CT scanning, or both, depending in the clinical presentation of the patient.

MANAGEMENT

Prehospital Considerations

Because elder patients may have significant injuries even with minor mechanisms of injury, prehospital management is particularly important. Scene assessment is important because prehospital personnel are often the "eyes and ears" for assessing the mechanism of injury, and this information should be solicited from prehospital personnel by emergency department staff. Rapid transport to the hospital is of prime importance. Because elder trauma patients are more likely to suffer significant injuries after even relatively minor events, transportation to a trauma center should be considered for elders who sustain anything more significant than isolated extremity trauma.

Emergency Department

Emergency department assessment of elder patients requires an organized and rapid evaluation for significant injuries and

frequent reassessment to identify deterioration early. Frequent monitoring of vital signs and maintaining a normal core temperature are important in the management of elder trauma patients.

Airway and Breathing

Supplemental oxygen should be administered to all elder trauma patients. Pulmonary insufficiency may develop quickly, and airway management equipment must be readily available. Airway management may be particularly difficult in elders, and potential problems should be anticipated. Cachectic or edentulous patients may be difficult to ventilate with bag, valve, and mask. Decreased mouth opening and limited neck mobility related to DJD may interfere with orotracheal intubation, and preexisting medical problems such as cerebrovascular accidents or renal failure may alter the choice of neuromuscular blocking agents used to facilitate intubation. Dosing of any agent that may affect cardiovascular stability must be carefully considered, and administering lower doses of these drugs is prudent.

Circulation

Fluid and blood resuscitation is particularly challenging in the elder trauma patient. Underlying congestive heart failure may be exacerbated by aggressive circulatory resuscitation, but hypotension and hypovolemia are poorly tolerated, particularly in patients with cardiovascular or cerebrovascular disease. Elder patients who go to the operating room before hemodynamic stabilization have an extremely high mortality rate. The most prudent approach is controlled boluses of warmed isotonic fluids with frequent assessment of physical examination, vital signs, pulse oximetry, and urine output. Hypotension is often an ominous finding and should be corrected, with attention to the potential effects of large fluid volumes on the respiratory system. Normotension in the usually hypertensive patient may be a subtle indication of hemorrhage. Blood transfusion should be strongly considered when the hematocrit drops below 30, and there should be a diligent search for potential sites of blood loss.

Disability

Underlying hearing deficits and residual neurologic deficits from stroke, such as aphasia, motor deficit, or slurred speech, can make assessment of mental status and evaluation for neurologic injury problematic. Information on previous history of deafness or stroke or other neurologic disease should be obtained quickly from the patient or family or both, and an assessment should be made of whether the patient's current condition represents a new or old finding.

DISPOSITION

Typical criteria for admission related to traumatic injuries apply in elders, but other considerations often lower the threshold for hospitalization. If the patient does not have a support system or home situation amenable to careful observation and recovery from even relatively minor injuries, hospital admission may be required. Patients with significant underlying diseases may need admission for monitoring and reassessment until their injuries begin to heal. Often, elder patients may need admission for pain control, particularly those with compression fractures of the spine or pubic rami fractures who may require frequent doses of narcotics for pain control. The use of narcotics can have additional adverse effects for elders that may put them at risk for additional injury, such as postural hypotension or confusion. Chest injuries may be particularly problematic and susceptible to complications, and elder patients with multiple rib fractures (three or more) or one or more displaced rib fractures should be admitted for aggressive pain management and supportive care. In addition, patients with multiple displaced rib fractures may be at risk of delayed death (24–48 hours) from exsanguinations due to severed intercostals vessels. Elders with minor injuries, particularly extremity injuries, may be discharged with appropriate follow-up care and medications.

KEY CONCEPTS

- Elder patients are more susceptible to injuries than younger patients and have a higher mortality rate for any given injury.
- Mechanisms of injury are different in elders than in younger patients. Elder patients are more likely to sustain their injury from a fall, an MVC, or an auto versus pedestrian incident than from an assault.
- Physiologic changes that occur with aging alter the way in which these patients may manifest significant injuries as well as how they tolerate these injuries.
- Emergency physicians must remember that elder trauma patients may have suffered a medical event that precipitated their trauma, or vice versa, and evaluate patients accordingly.
- Resuscitation of elder trauma patients requires oxygen supplementation, a lower threshold for advanced airway control (endotracheal intubation), and aggressive but judicious fluid and blood resuscitation with frequent reevaluation.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 37

Injury Prevention and Control

Stephen W. Hargarten and E. Brooke Lerner

PERSPECTIVE

The science of injury control is based on the concept that trauma is like a disease rather than just the consequence of fate or random occurrences. The principles of disease control are applied to injury as they are successfully applied to infectious diseases. Control of a disease as widespread and multifactorial as injury can occur only through broad interdisciplinary effort, including that of medicine, public health, policy makers, law enforcement, educated citizens, and others (Box 37-1).

Emergency medicine plays a pivotal role in the care of injured patients and in injury control. Approximately one third of all emergency department visits are for the care of injuries, representing 14.4 visits per 100 people.[1] Injury is the leading cause of death for many age groups (Table 37-1). In 2004, 29.6 million people were treated in emergency departments for injuries, of which 93% were not admitted to the hospital.[2] The medical cost of injury-related medical care in the United States is estimated to be $117 billion annually.[2] The emergency care system may be the patient's only interface with the health care system. In addition to providing state-of-the-art acute care, emergency physicians should provide state-of-the-art clinical preventive services for these injured patients,[3-5] as well as work with surgeons, pediatricians, and other specialists to decrease injuries through clinical and policy-relevant research and education.[6]

PRINCIPLES OF THE DISEASE OF INJURY

The major causes of injury include falls, car crashes, gunshots, drownings, and poisonings. Similar to other disease models, injury occurs from the interaction of agent and host through a vector and an environment that is conducive to exposure (Fig. 37-1). *Injury* is a harmful event caused by the acute transfer of energy to a patient that results in tissue and/or organ damage.[7] The energy may be in any form, such as kinetic (e.g., falls and motor vehicle crashes), thermal (e.g., burns and hypothermia), chemical (e.g., poisoning), electrical (e.g., lightning strike), or the absence of energy (e.g., hanging or drowning).[8] Energy is the agent that is delivered to the host (patient) by a vector in an environment with variable risk. Cars and guns are examples of vectors of energy transmission that cause the injury. A car on an icy road is an example of the environment and the vector interacting to increase the likelihood of kinetic energy reaching the host and causing injury.

The goal of injury control, similar to other forms of disease control, is to prevent or decrease the transfer of energy to the host by (1) separating the host from the agent through modification of the environment, (2) equipping the host with protection against the agent, or (3) eliminating or modifying the vector that transmits the energy.[8-13]

The first step in the control of injuries is the recognition that injury is preventable. Common public perception is that injuries are from accidents or random, unexpected events, similar to the way infectious disease was regarded before the discovery of bacteria. Similar to other diseases, characteristics of the host affect prevention strategies, acute care, and rehabilitation outcomes. These include physical characteristics, such as age, gender, size, and motor skills; and mental/behavioral characteristics, such as intelligence, fatigue, alcohol use and abuse, emotional stability, social norms, and lifestyle. Risks for injury and death vary by age (Table 37-1). To decrease the likelihood of an injury, changes in some of these predisposing factors can be made in the host (e.g., through improvement in driving skills or a commitment to wear a seat belt or not to drink and drive) and should be age specific for maximum effect.

Energy is transmitted to the host through a *vector*, such as motorized and nonmotorized vehicles (e.g., car, bicycle, and skateboard), firearms, piercing instruments (e.g., knife and arrow), explosives, and lit cigarettes. Modifying the vector (by elimination or modification of design) and separating the vector from the host are important methods to reduce injury. For example, understanding the biomechanical forces released during an injury event is crucial to understanding vehicle modification.[14-16] This information can assist physicians in educating patients and families to modify or eliminate vectors they encounter during their daily lives—for example, recommending that families properly store and/or use gun locks with household firearms.[17]

When an injury occurs, host–agent interaction and energy transfer take place in an *environment*. This environment can be modified to decrease injury. If the environment does not permit energy transmission, the risk for injury, including intentional injuries to the host (patient), is eliminated.[18] In contrast to altering host risk factors, most environmental modifications require no cooperation or action on the part of the host and are more effective when implemented. Examples are implementing safer road design and lighting to prevent motor vehicle crashes, removing throw rugs to prevent falls, placing fences around pools, and separating bicycle paths and sidewalks from the roadway to protect pedestrians and bicyclists from cars.[12,19]

William Haddon, the first physician administrator for the National Highway Traffic Safety Administration, first described

BOX 37-1 MULTIDISCIPLINARY TEAM APPROACH TO INJURY CONTROL: PREVENTION, ACUTE CARE, AND REHABILITATION

Prevention
Epidemiology
Biomechanics
Education
Public policy
Law enforcement
Engineering
Outcomes research
Emergency preparedness

Acute Care
Trauma system
Emergency medical services
Emergency department care
Hospital care
Clinical guidelines
Clinical prevention services
Outcomes research

Rehabilitation
Physical therapy
Occupational therapy
Mental health providers

using this type of approach in a landmark article on injury control in 1970.[20] He laid out 10 methods for preventing injury (Table 37-2). Haddon later expanded these ideas to incorporate time and developed the Haddon matrix. The matrix recognizes that preventative interventions should be considered for the host, agent, vector, and environment prior to the event, during the event, and after the event. Any type or cluster of injuries can be prevented or reduced in severity using this matrix when the environment, vector, and population most at risk are identified and modified. An example of using this process to reduce car crash injuries is given in Table 37-3. The key to energy transfer reduction or prevention is understanding that (1) injuries are predictable, (2) they follow predictable patterns (e.g., by age or gender), and (3) reliance solely on human factors for prevention has significant limits. A fragile item sent through the mail arrives at its destination intact only if it is properly packaged to reduce the energy we anticipate being placed on the item during transport. Likewise, injuries to people can be prevented by using the cells of the Haddon matrix to mitigate the energy transfer of predictable events.

The History of Injury Control and Emergency Medicine

The avoidance of personal injury is a goal of modern public health, but until the 1940s and 1950s, unintentional injuries were attributed primarily to human error, and prevention was based on educating people to act safely.[10] Unsafe roads were built, and motorized vehicles and other consumer products were manufactured with safety design flaws.[21] This is analogous to supplying untreated tap water to homes and relying on educating people to purify their drinking water to prevent cholera.[11]

In the 1920s, attributing vehicle crashes to poor driver performance led to mandatory licensing of drivers. In the 1930s, when it was realized that vehicle crashes were due not simply to human error but to mechanical factors as well, President

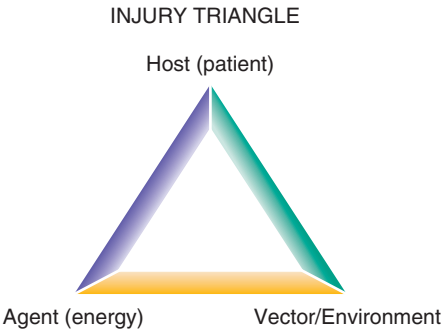


Figure 37-1. The epidemiologic triad can be used as a framework for injury prevention. An injury occurs by the interaction of the host and agent through a vector and an environment that is conducive to injury. Alteration of any of these interactions prevents the injury.[111]

Roosevelt called for automobiles to be made more crashworthy.[8] In 1942, DeHaven, a former World War I pilot turned physiologist, pondering his own survival in an airplane crash when another occupant had been killed, suggested structural provisions be made to vehicles that would distribute the forces of energy over the human body to attenuate the energy transfer and reduce injuries in crashes. He advocated a focus on defining the physical factors that influence survival rather than the human error that caused the crash.[8] Physical factors became a focus of interest as the United States embarked on its space program. Air Force researchers showed that people could withstand splashdown with a sled that decelerates from 30 to 0 mph over a stopping distance of 2 feet.[22] This demonstration was a significant advance in understanding the biomechanics of sudden deceleration.

The recognition that injuries could be addressed similar to diseases occurred in the 1940s, when Gordon, an epidemiologist, suggested that injuries have epidemic patterns, seasonal variation, long-term trends, and demographic distribution and can be examined with methodologies applied to infectious diseases. Gordon also believed that similar to infectious diseases, injury results from the interaction of the agent, host, and environment.[8] In the 1960s, Haddon developed a two-dimensional approach to injury analysis by dividing the factors of agent, host, and environment into three phases: preinjury, injury, and postinjury. This phase-factor matrix has become a mainstay of injury control development. Any injury event can be broken down into the component factors, allowing specific interventions to target specific factors (Table 37-4).[12,23]

In 1985, the publication *Injury in America: A Continuing Public Health Problem* by the National Research Council and the Institute of Medicine called on the public health and health care community to address the injury epidemic.[13] With the establishment of the National Center for Injury Prevention and Control in the Centers for Disease Control and Prevention (CDC), it was acknowledged that the control of injuries belongs in the disease control community and includes health care providers such as emergency physicians.

Soon after its inception, the National Center for Injury Prevention began sponsoring injury control research centers at academic institutions throughout the country. These centers conduct research in all three core phases of injury control (i.e., prevention, acute care, and rehabilitation), and they serve as training centers for injury control specialists and as information centers for the public.[24] In many places, these centers are led by physicians, including emergency physicians. To continue and expand this work, the Society for the Advancement of Violence and Injury Research was created, which is open to

Table 37-1 Ten Leading Causes of Death, United States, 2005, All Races, Both Sexes

	AGE GROUP										
RANK	**<1**	**1–4**	**5–9**	**10–14**	**15–24**	**25–34**	**35–44**	**45–54**	**55–64**	**65+**	**ALL AGES**
1	Congenital anomalies	Unintentional injury	Unintentional injury	Unintentional injury	Unintentional injury	Unintentional injury	Unintentional injury	Malignant neoplasms	Malignant neoplasms	Heart disease	Heart disease
	5552	1664	1072	1343	15,753	13,997	16,919	50,405	99,240	530,926	652,091
2	Short gestation	Congenital anomalies	Malignant neoplasms	Malignant neoplasms	Homicide	Suicide	Malignant neoplasms	Heart disease	Heart disease	Malignant neoplasms	Malignant neoplasms
	4714	522	485	515	5466	4990	14,566	38,103	65,208	388,322	559,312
3	SIDS	Malignant neoplasms	Congenital anomalies	Suicide	Suicide	Homicide	Heart disease	Unintentional injury	Chronic low. respiratory disease	Cerebrovascular	Cerebrovascular
	2230	377	196	270	4212	4752	12,688	18,339	12,747	123,881	143,579
4	Maternal pregnancy comp.	Homicide	Homicide	Homicide	Malignant neoplasms	Malignant neoplasms	Suicide	Liver disease	Diabetes mellitus	Chronic low. respiratory disease	Chronic low. respiratory disease
	1776	375	121	220	1717	3601	6550	7517	11,301	112,716	130,933
5	Placenta cord membranes	Heart disease	Heart disease	Congenital anomalies	Heart disease	Heart disease	HIV	Suicide	Unintentional injury	Alzheimer's disease	Unintentional injury
	1110	151	106	200	1119	3249	4363	6991	10,853	70,858	117,809
6	Unintentional injury	Influenza and pneumonia	Cerebrovascular	Heart disease	Congenital anomalies	HIV	Homicide	Cerebrovascular	Cerebrovascular	Influenza and pneumonia	Diabetes mellitus
	1083	110	52	146	504	1318	3109	6381	10,028	55,453	75,119
7	Respiratory distress	Septicemia	Influenza and pneumonia	Chronic low. respiratory disease	Diabetes mellitus	Diabetes mellitus	Liver disease	Diabetes mellitus	Liver disease	Diabetes mellitus	Alzheimer's disease
	860	85	51	55	202	617	2688	5691	7126	55,222	71,599
8	Bacterial sepsis	Cerebrovascular	Chronic low. respiratory disease	Influenza and pneumonia	Cerebrovascular	Cerebrovascular	Cerebrovascular	HIV	Suicide	Unintentional injury	Influenza and pneumonia
	834	62	49	55	196	546	2260	4516	4210	36,729	63,001
9	Neonatal hemorrhage	Perinatal period	Benign neoplasms	Septicemia	Complicated pregnancy	Congenital anomalies	Diabetes mellitus	Chronic low. respiratory disease	Nephritis	Nephritis	Nephritis
	665	58	40	45	183	436	2045	3977	4141	36,416	43,901
10	Necrotizing enterocolitis	Chronic low. respiratory disease	Septicemia	Cerebrovascular	Influenza and pneumonia	Influenza and pneumonia	Influenza and pneumonia	Viral hepatitis	Septicemia	Septicemia	Septicemia
	546	56	36	43	172	354	934	2314	3912	26,243	34,136

Data from the National Center for Health Statistics, National Vital Statistics System.

Table 37-2 Haddon's Strategies for Preventing the Transfer of Energy to the Host

TECHNIQUE	CAR CRASH	FALLS
1. Prevent the initial marshaling of energy	Manual task/Breathalyzer ignition interlocks Use of alternative transportation	Remove floor obstacles Prevent unnecessary climbing
2. Reduce the amount of energy marshaled	Speed reduction Vehicle mass restrictions	Climbing height restrictions
3. Prevent the release of energy	Breakaway light poles, roadway obstacle removal	Ambulation aids for elderly Worker safety harnesses
4. Modify the rate of spatial distribution of the release of energy from its source	Autobody crumple zones Safety belts, air bags Water barrel barriers	Land with a "roll" Use of safety nets
5. Separate the energy from the host in space or time	Reduce traffic density Homogeneous traffic flow Increase following distance Sidewalks for pedestrians	Safety zones at edge of raised work areas
6. Separate the energy from the host by barrier	Guardrails, concrete median barriers	Guardrails for scaffolds, raised work areas
7. Modify the surface or structure of impact	Collapsible steering columns, padded pillars and bolsters, safety glass	Padded flooring Helmets and hard hats
8. Strengthen the host receiving the energy	Detect and treat premorbid medical conditions	Prevent/treat osteoporosis and strengthen hip flexion in elderly patients
9. Rapidly detect and evaluate damage and counter its continuation and extension	911 and EMS availability Trauma system planning and implementations, and provision of state-of-the-art emergency care	911 and EMS availability Trauma system planning and implementation, and provision of state-of-the-art emergency care
10. Reparative and rehabilitative measures	Provision of state-of-the-art trauma care, rehabilitation, and aftercare	Provision of state-of-the-art trauma care, rehabilitation, and aftercare

Table 37-3 Typical Haddon Matrix (Constructed for Motor Vehicle Injury)

	HOST (DRIVER)	AGENT/VECTOR (CAR)	ENVIRONMENT
Pre-event (before the crash)	Alcohol use Fatigue Experience and judgment Vision	Brake condition Tire quality Center of gravity Load weight	Visibility of hazards Road curvature and gradient Surface coefficient of friction Shoulder height
Event (during the crash)	Medications Motor skills Cognitive function Age	Speed capacity Visual obstructions Speed at impact Vehicle size	Intersections, access control Weather Signalization Speed limits
Postevent (after the crash)	Age Physical condition Medications Social situation	Load containment Deformation zones Fuel system integrity	911 access EMS response Triage and transfer protocols Nearby level 1 trauma center

Adapted from Baker S, et al: *The Injury Fact Book*, 2nd ed. New York, Oxford University Press, 1992.

any group or individual with an interest in advancing research in violence and injury (http://www.savirweb.org).

In 2003, the National Center for Injury Prevention and Control began updating the *CDC Injury Research Agenda* to include acute care research, focusing on research that will improve acute injury care systems.[25] Following this, the National Center for Injury Prevention's Division of Injury and Disability Outcomes and Programs changed its name to the Division of Injury Response, whose mission is "to increase the capacity to prevent injuries and their adverse health effects by working with partners to develop, evaluate, and promote evidence-based surveillance, prevention, and care practices."[26] This center gives a home for acute injury care and acknowledges its importance for prevention. This division has also become a focus point for response to terrorist-related injuries, an important area of injury control.

Methods of Prevention

The history of injury control began with the first injury. Pain from injury is a powerful stimulus for avoidance behaviors. Early prevention technology is seen in the instruments and garb of the earliest armies, shielding people from the harmful kinetic energy of weapons. Such technology included helmets, shields, and suits of armor. As the delivery of kinetic energy became more sophisticated, prevention technology did not keep pace.[15,16] Firearms and automobiles represent new plateaus in harnessing kinetic energy as well as creating a new source of morbidity and mortality.[21,27] The cultural belief was that individuals could avoid vehicular injury by safe driving, and if not, an "accident" occurred. It took more than 50 years to acknowledge that behavior modification alone was insufficient to mitigate high-energy transmission to persons in a haz-

Table 37-4 Ten Leading Causes of Injury Deaths, United States, 2005, All Races, Both Sexes

	AGE GROUP										
RANK	**<1**	**1–4**	**5–9**	**10–14**	**15–24**	**25–34**	**35–44**	**45–54**	**55–64**	**65+**	**ALL AGES**
1	Unintentional Suffocation 748	Unintentional Drowning 493	Unintentional MV traffic 560	Unintentional MV traffic 763	Unintentional MV traffic 10,657	Unintentional MV traffic 7047	Unintentional Poisoning 6729	Unintentional Poisoning 6983	Unintentional MV traffic 4287	Unintentional Fall 15,802	Unintentional MV traffic 43,667
2	Unintentional MV traffic 140	Unintentional MV traffic 489	Unintentional Fire/burn 138	Suicide Suffocation 172	Homicide Firearm 4499	Unintentional Poisoning 4386	Unintentional MV traffic 6491	Unintentional MV traffic 6179	Suicide Firearm 2470	Unintentional MV traffic 7048	Unintentional Poisoning 23,618
3	Homicide Unspecified 129	Unintentional Fire/burn 208	Unintentional Drowning 121	Homicide Firearm 143	Unintentional Poisoning 2484	Homicide Firearm 3780	Suicide Firearm 2855	Suicide Firearm 3472	Unintentional Poisoning 2007	Unintentional Unspecified 5069	Unintentional Fall 19,656
4	Homicide Other, Spec., classifiable 99	Homicide Unspecified 153	Unintentional Other, land transport 47	Unintentional Drowning 132	Suicide Firearm 1962	Suicide Firearm 2269	Homicide Firearm 2010	Suicide Poisoning 1707	Unintentional Fall 1451	Suicide Firearm 3889	Suicide Firearm 17,002
5	Unintentional Drowning 64	Unintentional Pedestrian, Other 129	Homicide Firearm 44	Unintentional Fire/burn 85	Suicide Suffocation 1570	Suicide Suffocation 1524	Suicide Suffocation 1670	Suicide Suffocation 1197	Suicide Poisoning 852	Unintentional Suffocation 3271	Homicide Firearm 12,352
6	Undetermined Suffocation 50	Unintentional Suffocation 126	Unintentional Suffocation 44	Suicide Firearm 84	Unintentional Drowning 649	Suicide Poisoning 757	Suicide Poisoning 1456	Unintentional Fall 1181	Suicide Suffocation 575	Adverse effects 1708	Suicide Suffocation 7248
7	Unintentional Fire/burn 36	Homicide Other, Spec., classifiable 74	Unintentional Pedestrian, Other 25	Unintentional Other, land transport 63	Homicide Cut/pierce 528	Undetermined Poisoning 564	Undetermined Poisoning 944	Homicide Firearm 1097	Unintentional Suffocation 509	Unintentional Fire/burn 1178	Unintentional Unspecified 6551
8	Undetermined Unspecified 30	Unintentional Natural/ environment 38	Unintentional Natural/ environment 17	Unintentional Suffocation 59	Suicide Poisoning 361	Homicide Cut/pierce 474	Unintentional Fall 607	Undetermined Poisoning 1026	Homicide Firearm 405	Unintentional Natural/ environment 1069	Unintentional Suffocation 5900
9	Homicide Suffocation 27	Homicide Firearm 37	Unintentional Poisoning 17	Unintentional Firearm 37	Unintentional Other, land transport 298	Unintentional Drowning 385	Unintentional Drowning 497	Unintentional Fire/burn 506	Unintentional Fire/burn 405	Unintentional Poisoning 931	Suicide Poisoning 5744
10	Unintentional Unspecified 22	Unintentional Fall 34	Three tied* 15	Unintentional Poisoning 34	Undetermined Poisoning 292	Unintentional Fall 295	Homicide Cut/pierce 426	Unintentional Drowning 492	Unintentional Natural/ environment 376	Suicide Poisoning 603	Unintentional Drowning 3582

Data from the National Center for Health Statistics, National Vital Statistics System.
*Unintentional firearm, unintentional struck by or against, and unintentional/unspecified were all tied for 10th place.

ardous environment. Cars were not uniformly equipped with seat belts until the 1960s.[21] It took another two decades before air bags became standard.[15,16,28]

Implementation of effective injury control strategies depends on collaborative efforts with physicians, nurses, out-of-hospital care providers, epidemiologists, biomechanical engineers, public policy makers, law enforcement officers, and lawyers.[19,28,29] A major challenge is the wide diversity of disciplines and interests involved in safety and injury control, many of which are isolated from one another.[10] In the 1990s, important strides were made in community-based injury control programs that rely on coalitions of existing resources with the support of the National Highway Traffic Safety Administration (NHTSA), the CDC, and the State and Territorial Injury Prevention Directors Association. These community coalitions were created to garner existing resources and implement injury countermeasures using "the 3 E's" of public *e*ducation, *e*nforcement of laws, and *e*ngineering modification of hazardous devices and environmental conditions.[19]

INJURY CONTROL IN MEDICAL PRACTICE

Traditionally, physicians have focused on treating the patient after the disease has occurred. As the causes of many diseases have become increasingly understood, education about risk assessment and clinically based prevention has been integrated into medical practice, particularly in areas such as infectious (immunizations) and cardiovascular (smoking cessation) disease. Emergency physicians are incorporating risk assessment, counseling, and referral of patients in high-risk groups for injury, such as with domestic violence patients.[3,5] The Joint Commission for Hospital Accreditation now has emergency department requirements for addressing abused patients.[30]

Emergency care providers are pivotal in the recording and accumulation of data about the injury event, which is useful for surveillance and epidemiologic analysis. Injury control techniques can be incorporated easily into emergency medicine practice as well.[5,31-34] A rational approach to improve injury care in a community (Box 37-2) requires that emergency physicians, surgeons, pediatricians, and physiatrists assume specific roles and activities in promoting injury control. This role for emergency physicians in injury control has been advocated by the American College of Emergency Physicians.[35] Documentation of injury information in the medical record, assessing risk factors in individual patients, counseling and referral, provision of systematized acute trauma care, and public health advocacy are all important.[36-38]

BOX 37-2 INJURY CONTROL IN EMERGENCY MEDICINE PRACTICE

Clinical Preventive Services

Document injury information in the medical record
Ensure that medical records of injury cases contain E codes
Assess behavioral and comorbid risk factors for future injury
Provide risk screening, counseling, and referral
Assess biomechanical risk factors in individual patients
Use biomechanical risk factors for directed evaluation of injured patients
Provide systematized acute trauma care

Population Health, Research, and Policy

Participate in and advocate for inclusive trauma systems
Direct and advocate for rapid, competent emergency medical services response
Lead efforts in policy development, implementation, and evaluation
Lead efforts in educating high-risk groups
Lead efforts to address and modify the environment to reduce risk of injury
Collaborate in multidisciplinary research to reduce injury risk and to improve care

Injury Epidemiology and Documentation

Gathering accurate data is essential to understand the characteristics of a disease—its endemic populations, cyclical variations, geographic characteristics, and effectiveness of interventions. Consistent and comprehensive data must be gathered across the population of injured patients to be used for research,[39,40] hypothesis generation, ongoing monitoring of disease patterns and characteristics,[34,41] and understanding outcomes of prevention and policy interventions. The goal of injury data collection is to discover who is being injured (host), what is injuring them (vector), and the circumstances surrounding the injury (environment).[42,43]

Until recently, good data on the disease of injury have been lacking, and knowledge gaps still exist.[44] Before 1980, the only large civilian databases on injury available for study were mortality data collected by coroners and medical examiners. The Fatal Analysis Reporting System, a comprehensive data set on all car crash deaths in the United States, was established by the NHTSA in 1975[45] for examining the epidemiology of car crashes.[39]

Because death results in only 1 in 1000 people who receive medical care for an injury, conclusions based solely on mortality data are limited.[13,46] The advent of trauma registries in the 1980s increased the sample from patients who die to patients admitted to trauma centers. Because these data are skewed toward the most severe injuries, the conclusions based on these data may have limitations when generalized to the larger population of injured people.[47]

Approximately 93% of injured patients seeking medical care for injury are treated and discharged from the emergency department, many of whom experience significant morbidity resulting in long-term disability and significant cost to society.[13,34,41,46] In recognition of the importance of emergency department data, the CDC developed Data Elements for Emergency Department Systems to define the minimum data set essential for physicians and information systems developers.[48,49] The most crucial data element for the understanding of injury is the *E code*, a system for identifying the cause of injury in a patient's medical record, according to a classification published in the *International Classification of Diseases* (ICD-9-CM).[19] The "E" stands for external cause of injury, such as car crash, fall, or bicycle crash. The cause of injury cannot be extracted from diagnosis codes in medical records. These are "N" codes—the nature of the injury, such as skull fracture, laceration, or contusion. Because injury control depends on identifying the vector that is causing injuries and not just the resultant injuries, the only way to accomplish this systematically is by documenting the appropriate E code for each patient visit. Some states have mandated documentation of E codes for all emergency department discharges.[34,41-43]

The greatest barrier to the collection of E codes in the emergency department is inadequate physician documentation to assign accurate E codes retrospectively from the medical record.[46,50,51] The first step in data gathering should be to completely and legibly document the cause of injury in patient medical records. Because injury problems in a community differ greatly from region to region, community-specific injury control efforts can be generated, implemented, and evaluated.[19,40]

E-coded hospital records can provide the *who*, *what*, and *when* of injury. The question of *where* can be either place of occurrence or place of residence, both of which are important and have implications for planned countermeasures. Hospital records are helpful in determining place of residence of injured patients, which is useful for community education in high-risk neighborhoods. Location-of-injury data are available only from other sources, such as emergency medical services (EMS), police, or other records. These data are more likely to be useful for environmental modification through engineering enhancements, police enforcement, or hazard removal. Linkage of these records to patient visits, either manually for specific research studies or electronically for surveillance, is the next step in gaining a comprehensive understanding of the epidemiology of injury.[52,53] With the increasing availability of desktop computer-based geographic information system programs, this powerful tool can be used to study injury locations with minimal training and resources. The maps generated by these programs can be used to identify areas with injury clusters so that prevention efforts can be focused on areas with the greatest need.[54,55]

Statewide injury data linkages exist in some states and are available for surveillance information[56] and research for unintentional and intentional injuries.[32,40,57] For example, the Crash Outcome Data Evaluation System uses probabilistic linkage to create a database of crash, hospital, EMS, and emergency department information for motor vehicle crashes.[58]

Interest and opportunity to apply injury control principles are growing for medical injuries, also known as medical errors. Medical injuries account for an estimated 50,000 to 98,000 deaths each year in the United States, with hundreds of thousands of nonfatal events occurring in emergency departments, intensive care units, and operating rooms.[44] Emergency physicians can play an important role in using injury control principles and science to reduce medical injuries.[59-62] Application of injury control principles for the identification of injury patterns and for the development and evaluation of injury prevention strategies has great potential.[61,62]

Risk Factor Assessment

Biomechanical Risk Factors

Biomechanical factors responsible for the injury are challenging to understand, occurring in car crashes or gunshots in less than a 10th of a second. Emergency physicians are not trained in engineering principles and have had limited exposure to this "pathophysiology" during training. Ascertaining the forces released on the patient during a blunt (car crash or fall) or penetrating (gunshot or stabbing) injury leads to a directed approach to injury management.[63-66] Extensive research has been done using crash dummies, mathematical models, and computer models to understand the mechanical forces applied in injury and human impact tolerance.[15,16] Although used extensively by the engineering community for design of products, such knowledge is also valuable to the emergency physician in guiding evaluation and treatment based on energy transfer, tissue tolerance, and risk of occult injury.[7] Furthermore, as this information becomes more readily available at the time of crash response through automatic crash notification (e.g., General Motor's On-Star system), it will become more important to understand and correctly interpret what it means in terms of potential injuries.[67]

Injury occurs when energy is delivered to the host in levels that exceed tissue and organ tolerance. This energy can be expressed in G-forces. The G-force that results from a motor vehicle crash, for instance, can be expressed using the following formula:

$$G = \Delta V^2/(\text{stopping distance} \times k)$$

where ΔV is the change in velocity, *stopping distance* is the distance over which the change in velocity occurs, and k is a constant. G-force is inversely related to stopping distance. To minimize energy transfer to the body during a car crash, one must maximize the stopping distance during the event. The formula shows that doubling the stopping distance reduces the G-force by half, but doubling the speed quadruples the force. Less G-force is applied as velocity is reduced over increasing distance, as the vehicle slows during pre-impact braking or deforms during a crash. The same principle underlies engineering features, such as interior padding, collapsible steering columns, water barrel barriers at bridge abutments, and flexible guardrails. All are designed to increase stopping distance, a major principle of automobile and highway safety engineering.[15,16,68]

The addition of the air bag to vehicles in the mid-1980s was a significant improvement in safety engineering because it resulted in increased occupant stopping distance during a crash. The NHTSA estimates that as of 2005, approximately 20,000 lives have been saved by air bags.[69] Initially, these benefits were confined to frontal crashes, but the advent of side curtain air bags and their wide implementation has greatly contributed to the number of lives saved.[70]

As with many new safety countermeasures, there were unintended consequences. First-generation air bags deployed with tremendous force to protect unbelted occupants. These early air bags deployed aggressively at speeds of 140 to 200 mph over 50 msec.[71] Such forces can be lethal to children in the front passenger seat, especially when unrestrained by safety belts, or seated in rear-facing infant seats.[72,73] A new generation of advanced, less aggressive air bags has been used in the vehicle fleet since the late 1990s, which is expected to reduce injuries associated with air bag deployment. For an emergency physician to estimate risk when assessing a patient from a motor vehicle crash, it is essential to understand the differences in risk posed by seating position, restraint type and use, and vehicle type. This information also must be understood to counsel patients properly on safety belt and child restraint use.[39,74]

Understanding mechanisms of injury leads to more effective patient counseling to protect patients and their families against injury. Children less than 55 inches tall should only ride in the rear seats of vehicles. Infant seats should never be positioned in the front seat within range of the air bag. Infants 12 months old or younger and weighing 20 pounds or less should always ride in a rear-facing infant seat, and children older than 12 months and weighing more than 20 pounds should ride forward facing in a toddler seat. A booster seat should be used for children weighing 40 to 80 pounds, allowing for better seat belt positioning and discouraging the child from sitting out of position to see out the windows. If circumstances dictate that a smaller child must ride in the front passenger seat, that seat should be positioned as far to the rear as possible and a seat belt should always be worn.[74] Federal rules allow for air bags to be disabled if there are circumstances necessitating that small children ride in the front seat and for certain medical conditions.[75] Furthermore, increasingly more vehicles are equipped with sensors that turn off the airbag when certain weight thresholds are not met. Physicians caring for short-stature individuals should counsel these patients about the risk of air bag injuries and recommend they sit with at least 10 inches between the sternum and the steering wheel equipped with an air bag. This distance should be measured objectively because people tend not to estimate this distance correctly.[76]

Other safety features have been associated with specific injuries. Automatic "passive" shoulder belts that require manual fastening of the lap portion may result in "submarining" of the torso toward the floorboard when the lap portion is not fastened, while the shoulder belt squeezes the lower rib cage. Such a mechanism explains the association of these devices with liver, spleen, and lung injuries[77] and has led to the discontinuation of these devices. However, since cars can be driven over a number of years, it takes many years to completely remove these dangers from the streets. Since automotive safety improves with each new model year, it is important to learn about these safety features and how they might change an injured patient's presentation.

Knowing the contact surface in falls affects diagnostic and therapeutic interventions because soft surfaces increase stopping distance compared with concrete or packed earth.[15,16] Understanding the biomechanical risks of other injuries, such as tissue forces from the ballistics of bullet wounds, can guide treatment decisions.[14,78]

Behavioral and Comorbid Risk Factors

Recognition of patients at high risk of injury affords opportunity for intervention. Counseling a patient about specific ways to avoid injury in the "teachable moment" after injury is more likely to have an effect than diffuse public education.[79] Family or friends can be recruited to enforce the message to patients or to assist patients in modifying their behavior or environment. Other patient encounters may be used as an opportunity to counsel high-risk patients, such as children at developmental stages that put them at risk for auto versus pedestrian injuries, climbing injuries, or poisoning. It is particularly important to explore the circumstances surrounding injuries to children. A brief review of the injury incident would help physicians and parents identify risks for future injury and opportunities for intervention.[80] Children who come to the emergency department for an injury are likely to be injured again, commonly during falls and motor vehicle crashes.[81] Preschool-age children admitted to the hospital for injury were twice as likely as community controls to have been treated previously in the emergency department for injury and more likely to have been in the emergency department more than once.[82]

Risk factors for intentional injury are complex and involve behavioral, social, and environmental factors, but risk factors for all types of injury include male, low income, illicit drug involvement, previous arrest, and young age.[82-84] In studies using psychosocial inventories, recidivists are more likely to have a low sense of autonomy, to have low levels of spirituality, and to have been a victim of crime in the past.[82] As a practical matter in the emergency department, the most obvious risk factor for future violent injury is prior violent injury. A history of prior significant injury is a strong predictor of injury recidivism, with 10 times the risk of patients with no prior trauma.[84,85] Emergency departments should have protocols in place for the detection and referral of patients likely to be victims of injury in the future, including victims of domestic violence,[3] and for children younger than 18 years injured intentionally, regardless of the age of the perpetrator. In many states, there are mandatory reporting laws for gunshot wounds, stabbing, and other violent acts.[86,87] Interventions provided to injured patients in the health care setting can reduce injury recidivism.[83,88]

In the case of motor vehicle injury, the three behavioral risk factors most likely to result in future injury are speeding, seat belt nonuse, and driving after drinking alcohol. Giving patients the necessary data for them to make an accurate self-assessment about their risks is the essence of patient behavioral intervention.[89] These messages should be part of every injury patient's encounter, when feasible. Particularly important in this context is the screening and referral for alcohol use disorders (AUDs). Alcohol-related crash injury is a national epidemic in the United States, claiming more than 17,000 lives annually and injuring an estimated 870,000 people.[90] Reductions in alcohol-related deaths due to more stringent laws to curb impaired driving, more vigilant public education, and a societal shift toward the condemnation of driving while impaired have not had significant effects on people with AUD. Of patients seen in the emergency department after a motor vehicle crash, 17 to 20% meet criteria for AUD.[91,92] Patients with AUD have higher rates of illness and motor vehicle crash injury than the rest of the population, and patients with AUD are more likely to drive after drinking.[87]

Emergency physicians have a unique role to play in the identification of high-risk patients. In particular, patients with AUD should be detected and referred for formal evaluation and treatment. A structured approach to detect and treat the disease must be brief and effective if it is to be used in a busy emergency department. Screening techniques validated in the emergency department and methods of brief intervention have been thoroughly described.[87]

Successfully treating AUD leads to reduction in alcohol consumption and, consequently, fewer impaired driving episodes, thus leading to a reduction in alcohol-related crash injuries. Evidence suggests that being treated for injury in the emergency department may be an important motivational opportunity to reduce drinking and presents a "teachable moment."[87,92-94] The American College of Surgeons' Committee on Trauma recommends that all trauma centers screen for alcohol and provide interventions as a "part of routine trauma care."[95]

Motor vehicle crashes are the leading cause of death for children older than 24 months in the United States (Table 37-4; see also Table 37-1). The risk of death in a motor vehicle crash can be reduced by half with the use of age-appropriate child restraints. Emergency physicians should understand the various restraint types and recommendations for their use based on age, weight, and height. Every pediatric visit to the emergency department involves transportation to and from the emergency department and is an opportunity to counsel parents on the safe transport of their children.

Acute Care

The acute care component of injury control involves trauma system planning, medical direction of out-of-hospital care, and providing systematized resuscitative care after the injury, whether it occurs close to or far from a trauma center.[96] A crucial part of injury assessment is identification of local resources for management of the injured patient. Algorithms and agreements to transfer the patient to definitive care should be established to avoid secondary injury from delays in transfer or inappropriate care.[97] Likewise, an environment with ready availability of trauma physician specialists should have clear protocols in place for use of those resources.[98] Cost-effective mobilization of injury care resources dictates that in-hospital triage criteria be developed for the care of the injured patient to avoid unneeded overuse of trauma surgery teams.[38,99,100]

Trauma systems can be created that recognize and complement the exigencies of budgetary, geographic, and political constraints that are specific to states or regions. Such flexibility is often impossible when a trauma system is based only on the locations of hospitals that seek trauma center verification or designation.[99]

An *inclusive* trauma care system is one that comprises all acute care and rehabilitation facilities that treat injured patients

and deals with the issues of community access, EMS dispatch and response, triage, transport and transfer protocols, training, communications, availability of definitive care and rehabilitation, and a data collection system. In an inclusive trauma care system, every injured patient (not just patients who live near trauma centers) is cared for by a part of the system. Every hospital has a role in an inclusive trauma system according to the services it is capable of offering, whether it is the expeditious transfer of patients, the treatment of patients without neurotrauma, or the definitive care provided at a trauma center. The system should be designed to monitor patient outcomes and system performance.[101] The finding that level 1 trauma centers improve severe trauma patient outcomes by 25% is further evidence of the importance of an inclusive trauma care system.[102]

Out-of-hospital emergency care is an integral part of injury control.[37] EMS response, triage, and treatment are the first critical steps in injury control after an injury event has occurred. Triage protocols must be well established to avoid unnecessary delays in definitive care.[97] EMS providers have a unique vantage point to help the trauma physician assess a patient's risk factors for immediate injuries and the risk of injury recurrence. EMS providers can observe the environment for information about mechanism of injury. Accurately reporting vehicle damage and other environmental circumstances associated with the injury event elucidates important biomechanical risk factors.[103] EMS providers have also become more involved in primary injury prevention through injury risk identification, documentation of injury data, and safety education programs.[37]

Emergency Medicine Leadership: Advocacy of Public Policy

Passing and enforcing laws are more effective than education in effecting individual behavior change for increasing safety actions such as seat belt and helmet usage.[8,28] Emergency physicians and other trauma physicians are well positioned to provide lawmakers with factual information coupled with the perspective of firsthand experience of the effects of injury. Effective prevention interventions and policies with documented cost savings are more likely to occur when sound, scientific studies are made available to policymakers.[104] Most public health regulations and traffic safety laws are under the jurisdiction of state legislatures and city and county governments. These policymakers are generally much more accessible to physicians and in need of local expertise than are policymakers at the federal level. Emergency physicians need to accept an important advocacy role for reducing injuries and incorporate injury control as a professional activity.[6,105,106]

Community education aimed at people not yet injured may be effective when provided by an emergency physician. Emergency physicians are in a leadership role to deliver the message to school systems, the local housing authority, law enforcement, community service organizations, and policymakers.[32,33] Trauma physicians can be effective spokespersons for injury prevention through the news media, especially after a newsworthy injury event, and can reframe the event from one of personal blame and behavior failure to a broader biosocial issue that requires environmental and policy interventions.[107]

Public policy also determines where resources are used in a community. Environmental modifications and elimination of hazards are effective but often expensive. In contrast to education and law enforcement, environmental modifications are *passive countermeasures* that do not require any action by people. Such modifications might be lengthening a "walk" signal at a busy intersection to reduce auto–pedestrian injuries, especially in the elderly[108]; increasing lighting in areas where personal assaults occur[18]; or changing a playground surface from hard-packed earth to wood mulch.[109] The need for such modifications may be known only if the physician is alert to the circumstances by asking "How did this happen?" and documenting the location and circumstances of injuries seen in daily practice.

KEY CONCEPTS

- Injury is the second most costly disease to society and the most serious disease of young people.[110]
- Through interdisciplinary research, a better understanding of the epidemiology and biomechanics of injury will lead to new control strategies. These strategies would complement advances in acute care and trauma systems, which improve care to the patient after the injury occurs.
- Emergency physicians can incorporate injury control techniques into daily practice through clinical prevention services.
- Increasingly, emergency physicians are leaders in addressing and preventing injuries and complex biosocial problems.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 38 Head Injury

Michelle H. Biros and William G. Heegaard

PERSPECTIVE

Epidemiology

The devastating consequences of head injury have been recorded since ancient times. Early neurosurgical records were primarily observational, with very few suggestions for treatment (Fig. 38-1). Despite centuries of investigation and the development of new and better intensive care, we still have not discovered effective therapies that can be applied after the injury to reverse most pathologic aspects of traumatic brain injury (TBI).

Each year, an estimated 1.5 million people sustain head injury in the United States. Of these, 1.1 million undergo emergency evaluation, including approximately 500,000 children younger than age 14 years.[1] Overall, 80% sustain minor head trauma (Glasgow Coma Scale [GCS] score = 14–15), 10% have moderate head injuries (GCS = 9–13), and 10% have severe head injuries (GCS = ≤8). Almost 20% of all head-injured patients are hospitalized, and approximately 52,000 patients die each year from TBI.

The leading causes of head injury in the civilian population are falls (28%) and motor vehicle collisions. Traumatic brain injury due to blasts has been called the signature injury of the war in Iraq and Afghanistan: TBI of any severity is estimated to affect as many as 10 to 20% of war-time service members.[2] Head injury is the leading cause of traumatic death in patients younger than 25 years and accounts for nearly one third of all trauma deaths.[3] Head injury from child abuse is common and estimated to represent up to two thirds of cases in the 0- to 4-year-old age group.[4] The Centers for Disease Control and Prevention estimates that there are at least 5.3 million Americans currently suffering from some degree of disability due to TBI. As veterans return to the United States, the numbers of patients suffering from the consequences of TBI are projected to increase markedly.

These facts confirm that TBI is a major public health problem. The emergency physician sees patients with head injuries of different clinical severity caused by a variety of mechanisms. External physical signs of head trauma only confirm that injury has occurred; they are not always present in the patient who has sustained serious underlying TBI. The ultimate survival and neurologic outcome of the head trauma patient depend on the extent of TBI occurring at the time of injury, alone or in combination with secondary systemic insults such as hypotension and hypoxia, which worsen the resulting neurochemical and neuroanatomic pathophysiology. Research aimed at reducing or preventing the neurological consequences of head trauma is ongoing, but currently the clinical outcome following TBI depends on the circumstances of injury and early clinical management aimed at reducing the occurrence of secondary brain insults. No effective intervention has been found to reverse the pathologic events initiated by the traumatic event.

PRINCIPLES OF DISEASE

Anatomy and Physiology

Scalp and Cranium

The scalp consists of five tissue layers. The dermis is the outermost layer and is among the thickest layers of skin on the body. The underlying subcutaneous tissue contains the hair follicles and the rich blood supply of the scalp. The large blood vessels of the scalp do not fully constrict if they are lacerated and can be the source of significant blood loss. The middle scalp layer is the galea, which is made of tough fascial tissue. It contains the occipitofrontalis and temporoparietalis muscles, which move the scalp backward and forward, elevate the eyebrows, and wrinkle the forehead. Under the galea is a loose areolar tissue layer. Because the areolar attachments to the rest of the scalp are loose, scalp avulsions frequently occur through this layer. This is also the site for development of subgaleal hematomas, which can become quite large because blood easily dissects through the loose areolar tissue. The deepest layer of the scalp, the pericranium, is firmly adhered to the skull.

The skull comprises the frontal, ethmoid, sphenoid, and occipital bones and two parietal and two temporal bones. The unique layered architecture of the bones of the skull enhances its strength. Each bone consists of solid inner and outer layers, separated by a layer of cancellous bone tissue (the diploe). In adults, the bones of the skull average between 2 and 6 mm in thickness; the bones in the temporal region are usually the thinnest of the skull.[5] The cranial bones form a smooth outer surface of the skull, but within the cranial vault are many bone protrusions and ridges. Contrecoup injuries and contusions far from the site of head impact often occur as the accelerating brain strikes against these uneven bone surfaces.

The inner aspect of the skull is lined with the periosteal dura, which is a thick connective tissue layer that adheres closely to the bone surface. The inner meningeal layer of the dura is the outermost covering of the brain. This dural membrane reflects back on itself to make folds within the cranial

Berengario da Carpi J. *Tractatus Perutilis et Completus de Fractura Cranei*. Venice, J. B. Pederzani, 1535. From the title page of the second edition of the first work devoted to a neurosurgical topic, in this case head injury.

Figure 38-1. Title page of a 16th-century neurosurgical textbook. (From Fringer S: Origins of Science. New York, Oxford University Press, 2001, p 422.)

space. These folds serve to protect and compartmentalize different components of the brain. The midline falx cerebri separates the two cerebral hemispheres from each other. The tentorium cerebelli partitions the cerebellum and brainstem from the cerebral hemispheres. The U-shaped free margin of this dural fold is important in the pathology of the transtentorial herniation syndromes that can complicate severe head injury. Within the margins of the dural reflections, the two dural layers separate to form large dural venous sinuses. Injury to the dural sinuses is associated with significant morbidity and mortality because of the potential for uncontrolled hemorrhage and the difficulty in repairing these structures.

The cranial vault is rigid and nonexpandable, with an average volume in adults of approximately 1900 mL.[6] Cranial contents exit or enter the skull through many foramina. The largest, the foramen magnum, is the site of exit of the brainstem and spinal cord from the cranium.

Brain and Cerebrospinal Fluid

The brain is a semisolid structure, which weighs approximately 1400 g (3 pounds) and occupies approximately 80% of the cranial vault.[6] It is covered by three distinct membranes: the meningeal dura, the arachnoid layer, and the pia. The location of traumatic hematomas relative to these membranes defines the pathologic condition and determines the consequences of the injury.

The major divisions of the brain are the cerebrum, cerebellum, and brainstem. Each lobe of the cerebrum is the source of highly specific neurobehavior, and specific injury to each lobe can disrupt normal behavior patterns. The brain is suspended in the cerebrospinal fluid (CSF), which provides some buffering for the brain during trauma. CSF is produced by the choroid plexus, located primarily in the lateral ventricles of the brain. CSF passes from the ventricular system into the subarachnoid space that surrounds the brain and spinal cord. CSF provides a fluid pathway for delivery of substances to brain cells, elimination of the products of brain metabolism, and transport of peptide hormones and hormone-stimulating proteins from their site of production within the central nervous system (CNS) to their peripheral sites of action.

The normal pressure exerted by the CSF is 65 to 195 mm H_2O or 5 to 15 mm Hg. Blood within the ventricles can obstruct the flow of CSF, causing a traumatic hydrocephalus. Brain injury and its complications can also alter the pH of CSF. Because the pH of CSF influences pulmonary drive and cerebral blood flow (CBF), any alteration can produce detrimental neurophysiologic consequences.[6]

Cerebral Hemodynamics

Blood-Brain Barrier. The blood-brain barrier (BBB) maintains the microenvironment of the brain tissue. Extracellular ion and neurotransmitter concentrations are regulated by movement across this barrier. When the BBB is intact, the ability of neuroactive drugs to penetrate into the brain tissue usually depends on their lipid solubility. Post-traumatic cerebral edema and possibly the biomechanics of the injury itself can cause a prolonged disruption of the BBB for up to several hours after trauma.[7,8] Prolonged disruption of the BBB contributes to the development of post-traumatic vasogenic cerebral edema.

The brain has an extremely high metabolic rate, using approximately 20% of the entire oxygen volume consumed by the body. To provide for its high metabolic demands, the brain requires approximately 15% of the total cardiac output. Optimal regional CBF is maintained by the ability of cerebral vessels to alter their diameter in response to changing physiologic conditions.[8] Hypertension, alkalosis, and hypocarbia promote cerebral vasoconstriction; hypotension, acidosis, and hypercarbia cause cerebral vasodilation. In the normal brain, CBF is maintained at constant levels with a mean arterial pressure (MAP) of 60 to 150 mm Hg. This is referred to as *autoregulation*. Outside this range, the CBF varies linearly with MAP.

Cerebral vasoactivity is very sensitive to changes in systemic carbon dioxide and oxygen partial pressures (P_{CO_2} and P_{O_2}, respectively). The response to changes in P_{CO_2} is nearly linear between P_{CO_2} values of 20 and 60 mm Hg.[9] In this range, lowering P_{CO_2} by as little as 1 mm Hg decreases the diameter of cerebral vessels by 2 or 3%, which corresponds to an overall change in CBF of 1.1 mL per 100 g of tissue per minute. The physiologic response of blood vessels to P_{CO_2} is the rationale for the acute use of brief hyperventilation to control increased intracranial pressure (ICP) after head injury. As P_{CO_2} decreases with hyperventilation, cerebral vasoconstriction occurs. As a result, the volume of blood per unit area of brain tissue decreases. This decrease (even if small) may buffer the effects of increasing edema or an expanding hematoma within the rigid cranial vault. The vasoconstriction produced by extreme changes in P_{CO_2} (20 mm Hg or less) can be so pronounced that some areas of brain experience ischemia; subsequently, tissue hypoxia can occur.[8,10,11] Therefore, hyperventilation must be controlled and monitored, with a goal of maintaining the P_{CO_2} between 30 and 35 mm Hg,[10,11] and reserved for patients who are showing signs of acute herniation. Over 12 to 24 hours, injured vessels may lose their responsiveness to hyperventilation-induced hypocarbia and become vasodilated. Blood may then be shunted to the injured area, resulting in increased brain swelling and mass effect. Prolonged (i.e., beyond the acute resuscitation) or prophylactic hyperventilation is therefore not recommended as a treatment for increased ICP, and hyperventilation is not used for the routine management of head-injured patients with no signs of increased ICP.[9-11] The neurologic effects of hypocapnia are illustrated in Figure 38-2.

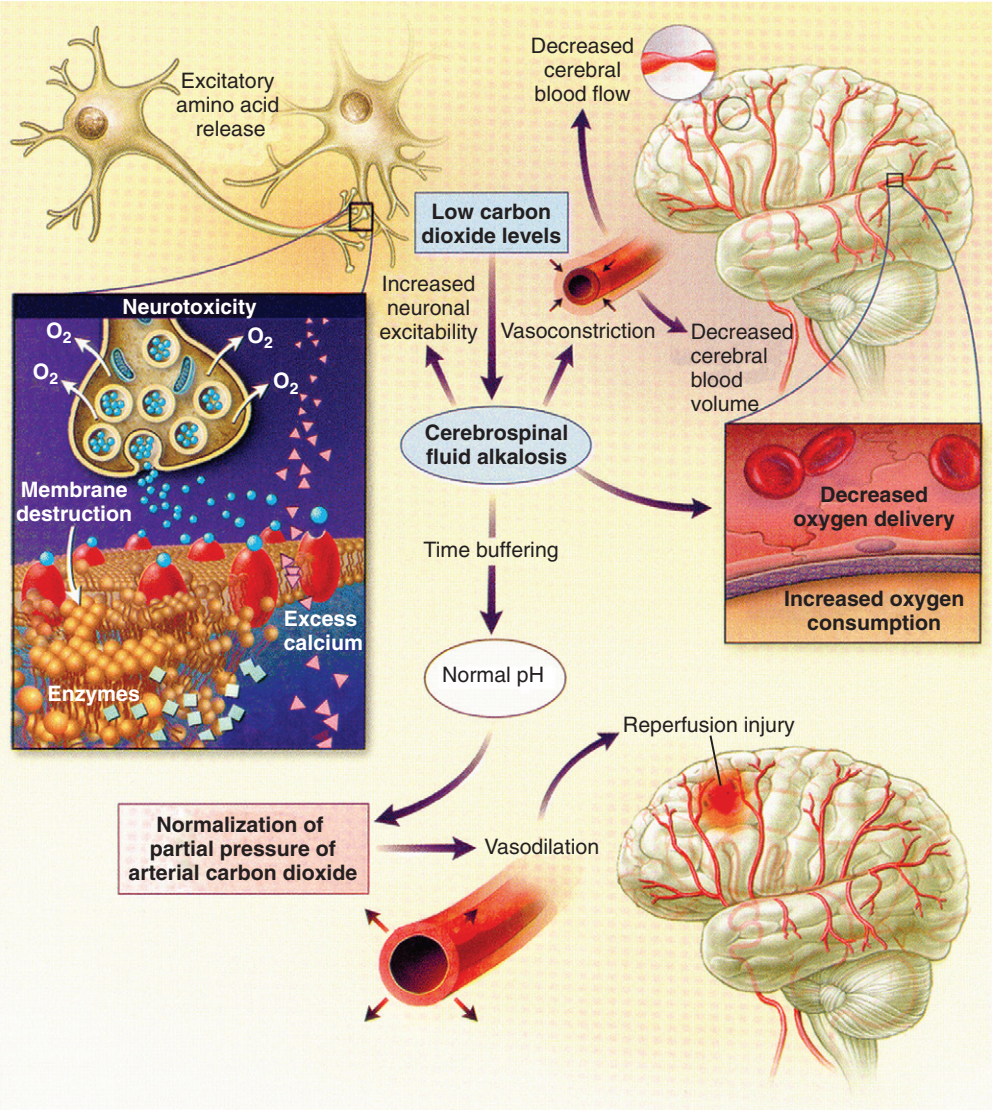


Figure 38-2. Neurologic effects of hypocapnia. Systemic hypocapnia results in cerebrospinal fluid alkalosis, which decreases cerebral blood flow, cerebral oxygen delivery, and, to a lesser extent, cerebral blood volume. The reduction in intracranial pressure may be lifesaving in patients in whom the pressure is severely elevated. However, hypocapnia-induced brain ischemia may occur because of vasoconstriction (impairing cerebral perfusion), reduced oxygen release from hemoglobin, and increased neuronal excitability, with the possible release of excitotoxins such as glutamate. Over time, cerebrospinal fluid pH and, hence, cerebral blood flow gradually return to normal. Subsequent normalization of the partial pressure of arterial carbon dioxide can then result in cerebral hyperemia, causing reperfusion injury to previously ischemic brain regions. (From Laffey JG, Kavanagh BP: Hypocapnia. N Engl J Med 347:43, 2002.)

The cerebral vessels also respond to changes in Po_2. As Po_2 declines, cerebral vessels dilate to ensure adequate oxygen delivery to brain tissue. When brain injury has occurred, increased CBF in the presence of a disrupted BBB can promote the formation of vasogenic edema. Avoiding or reversing hypoxia is therefore an essential goal in the acute management of the head-injured patient.[12] The responses of the cerebral vasculature to changing physiologic conditions protect the brain by increasing the delivery of oxygen to tissue, enhancing the removal of metabolic end products and allowing nearly instantaneous adjustments of regional blood flow to meet the changing metabolic demands.

Cerebral Perfusion Pressure. CBF also depends on cerebral perfusion pressure (CPP), which is the pressure gradient across the brain. The determinants of CPP are MAP and the resistance to CBF produced by mean systemic venous pressure and ICP. Because ICP is higher than mean systemic venous pressure, ICP effects predominate. Therefore, CPP is estimated as MAP minus ICP. CBF remains constant when CPP is 50 to 160 mm Hg. If CPP falls below 40 mm Hg, the autoregulation of CBF is lost, CBF declines, and the resultant tissue ischemia critically affects cerebral metabolism.[8,10] It is essential to avoid or correct hypotension in the patient with multiple trauma who is also head injured so that the CPP can be maintained. Management must also be directed at reducing or preventing increased ICP to ensure adequate CPP to sustain cerebral metabolic needs.

Biomechanics of Head Trauma

Direct Injury. Direct impact head injury occurs when the head is struck by an object or its motion is arrested by another object. The resulting damage depends on the consistency, mass, surface area, and velocity of the object striking the head. Direct injury can also be caused by compression of the head. External signs of trauma are frequently noted at the site of application of the impact or compression force. The skull initially bends inward at the point of contact. If the force is sufficient, a skull fracture can occur. The cranium absorbs some of the applied energy, and some energy is transmitted to the brain by shock waves that travel distant to the site of impact or compression. These shock waves distort and disrupt intracranial contents and temporarily alter regional ICP as they propagate. In general, the more rapidly a force is applied, the greater the damage it causes. The extent of direct injury depends on the vasoelastic properties of the underlying region of brain tissue, the duration of the force applied, the magnitude of the force reaching the brain tissue, and the surface area of the brain that is affected by the application of the force. In cases of penetrating trauma, the mass, shape, direction, and speed of the penetrating object also affect the extent of direct injury.

Direct injury from compression of the head requires significant force because the architecture of the skull provides substantial resistance to deformation. In the clinical setting, compression injury is less common than other types of direct impact. With sufficient and prolonged application of compression force, the ability of the skull to absorb the force is overcome, and multiple linear skull fractures occur. Resulting fractures can be depressed if a high-energy rapid compression force is applied to a small area of the skull. Isolated direct impact injury is rare; direct impact usually sets the head in motion, resulting in simultaneous direct and indirect injury.

Indirect Injury. In indirect brain injury, the cranial contents are set into motion by forces other than the direct contact of the skull with another object. A common example is acceleration–deceleration injury, such as the shaken impact syndrome.[13] No direct mechanical impact is sustained, but the cranial contents are set into vigorous motion. The brain moves within the skull, and bridging subdural vessels are strained. Subdural hematomas may result. Differential acceleration of the cranial contents occurs, depending on the physical characteristics of the brain region. As one brain region slides past another, shear and strain injuries are produced. This movement results in diffuse injuries, such as diffuse axonal injury or concussion. Additional injury occurs as the movement of the intracranial contents is abruptly arrested and the brain strikes the skull or a dural structure. Contrecoup contusions are an example of the injury produced in this manner. In penetrating injury, the traversal of the object produces pressure waves that can strike structures distal to the path of the missile.

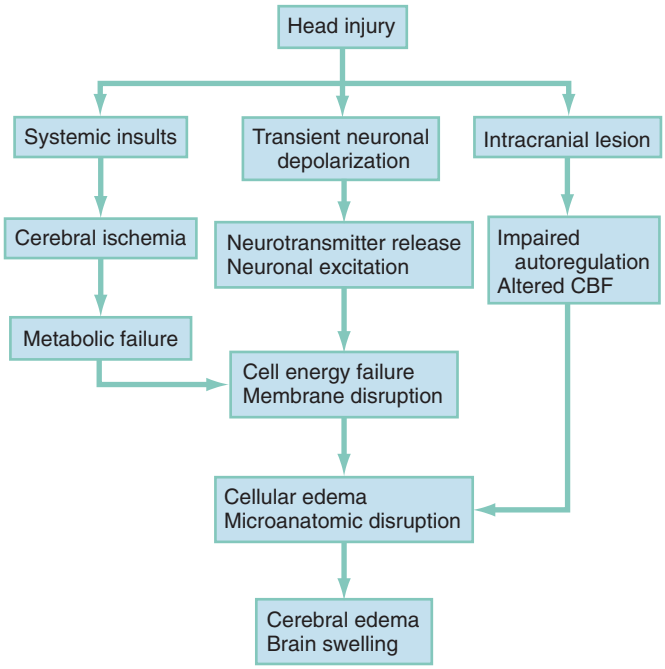


Figure 38-3. Contributing events in the pathophysiology of secondary brain injury. CBF, cerebral blood flow.

Brain Cellular Damage and Death

Primary and Secondary Brain Injuries

The acute clinical picture of the patient with TBI is dynamic and represents the sum of primary and secondary injury. Primary brain injury is mechanical irreversible damage that occurs at the time of head trauma and includes brain lacerations, hemorrhages, contusions, and tissue avulsions. On the microscopic level, primary injury causes permanent mechanical cellular disruption and microvascular injury.[14] No specific intervention exists to repair or reverse primary brain injury; the only way to decrease brain injury is through public health interventions aimed at reducing the occurrence of head trauma.

The circumstances and extent of the primary injury are not the only contributors to the final neurologic outcome after head injury. The traumatic event also produces injury at the functional and anatomic cellular level, which begins soon after the impact and continues for several hours and even days after injury. Secondary brain injury results from intracellular and extracellular derangements that are probably initiated at the time of trauma by a massive depolarization of brain cells and subsequent ionic shifts.[14] Animal studies have revealed a complicated series of neurochemical, neuroanatomic, and neurophysiologic reactions after head injury (Fig. 38-3). The cell has some compensatory mechanisms to protect itself from widespread damage, such as endogenous free radical scavengers and antioxidants. With significant trauma, however, these systems are quickly overwhelmed, and the functional and structural integrity of the cell is threatened. Human studies document similar changes. Studies suggest that abnormal genetic responses may play a role in response to injury, such as prompting apoptotic cell death.[15] The relative importance and contribution of each adverse reaction to the final functional status of the damaged cell are uncertain, as are the rate and duration of each detrimental event. All currently used acute therapies for TBI are directed at reversing or preventing secondary injury. Experimental evidence for many investigational agents aimed at specific steps in the destructive processes suggests that some aspects of secondary brain injury may be reversed or modified. Multiple ongoing head injury trials have been performed with numerous investigational therapeutic interventions; to date, none have proved useful in the clinical setting.[15,16]

Secondary Systemic Insults

The final neurologic outcome after head trauma is influenced by the extent and degree of secondary brain injury. In turn, the amount of secondary brain injury depends on certain premorbid and comorbid conditions, such as the age of the patient and trauma-related systemic events.[17,18] A primary goal in the emergency care of the head-injured patient is prevention or reduction of systemic conditions that are known to worsen outcome after TBI.

Common secondary systemic insults in trauma patients include hypotension, hypoxia, and anemia and hyperpyrexia. *Hypotension*, defined as a systolic blood pressure less than 90 mm Hg, has been found to have negative impact on severe head injury outcome.[19] Systemic hypotension reduces cerebral perfusion, thereby potentiating ischemia and infarction. The presence of hypotension nearly doubles the mortality from head injury and worsens the outcome of the patients who survive.[17,19]

Hyperpyrexia (core body temperature >38.5 °C) is also correlated with worsened outcomes after TBI, and both its magnitude and its duration seem to contribute. The exact mechanism by which it causes damage is yet to be determined but likely involves stimulation of metabolism in injured areas of the brain, thus recruiting blood flow with a resultant increase in ICP.[15]

Hypoxia, defined as a Po_2 less than 60 mm Hg, probably occurs often in the head-injured patient. Causes include (1) transient or prolonged apnea caused by brainstem compression

or injury after the traumatic event; (2) partial airway obstruction caused by blood, vomitus, or other debris in the airway of the traumatized patient; (3) injury to the chest wall that interferes with normal respiratory excursion; (4) pulmonary injury that reduces effective oxygenation; and (5) ineffective airway management, such as the inability to bag-valve-mask or intubate the patient in an effective or timely manner, respectively. The exact incidence of hypoxia in the head-injured patient is difficult to estimate because it is often unnoticed or undocumented in the out-of-hospital setting. When its occurrence is documented, the overall mortality from severe head injury may double or quadruple.[19,20] Increased recognition of the potentially devastating consequences of hypoxia has led to more vigilance in the out-of-hospital and emergency setting.

Anemia caused by blood loss can be detrimental to the head-injured patient by reducing the oxygen-carrying capacity of the blood, thus reducing the amount of necessary substrate delivered to the injured brain tissue. When anemia (hematocrit <30%) occurs in patients with severe head injury, the mortality rate increases.[15] Other potential reversible causes of systemic insult in head injury include hypercarbia, hyperthermia, coagulopathy, and seizures.

Pathophysiology

Increased Intracranial Pressure

ICP represents a balance of the pressures exerted by the contents of the cranial cavity. This relationship is explained by the Monro-Kellie doctrine.[21,22] Because the craniospinal intradural space is almost nonexpandable, the sum of the volume of brain, CSF, and blood within the cranium must remain constant. If the volume of any of these components increases, the volume of another must decrease to maintain a constant ICP. Increased ICP is defined as CSF pressure greater than 15 mm Hg (or 195 mm H_2O) and is a frequent consequence of severe head injury. Initially, as ICP increases as a result of a traumatic mass lesion or edema formation, the CSF is displaced from the cranial vault to the spinal canal, offsetting the increased blood or brain volume. When this compensatory mechanism is overwhelmed, the elastic properties of the brain substance allow tissue compression to provide buffering for the increasing pressure. Depending on the location and the rate of expansion of the traumatic mass lesion and the rate of cerebral edema formation, the intracranial compensatory mechanisms can accommodate an increased volume of 50 to 100 mL. Beyond that, even small additional changes in intracranial volume relationships, such as those caused by vasodilation, CSF obstruction, or small areas of focal edema, cause a dramatic increase in ICP. If ICP increases to the point where CPP is compromised, vasoparalysis occurs and autoregulation is lost. The CBF then depends directly on the systemic MAP. With the loss of autoregulation, massive cerebral vasodilation occurs. Systemic pressure is transmitted to the capillaries, and the outpouring of fluids into the extravascular space can contribute to vasogenic edema and thus further increase ICP. If ICP rises to the level of the systemic arterial pressure, CBF ceases and brain death occurs.

Methods to reduce elevated ICP include hyperventilation, use of osmotic and diuretic agents, and CSF drainage. Uncontrollable increased ICP is defined as an ICP of 20 mm Hg or higher refractory to treatment. If ICP is not controlled, herniation syndromes can occur, resulting in brainstem compression and subsequent cardiorespiratory arrest. In the United States, the use of ICP monitoring and control has become standard in cases of moderate and severe TBI despite the lack of prospective controlled research showing clear efficacy as an individual patient treatment modality.[15]

Brain Swelling and Cerebral Edema

Two primary types of brain swelling occur after head injury. *Congestive brain swelling* results from an increased intracranial blood volume. Hyperemia occurs early after trauma and can persist for the first few days after injury.[23] It is especially common in children. The increased blood volume is most likely caused by vasodilation, which occurs as a compensatory mechanism to maintain optimal CBF in the presence of increased metabolic needs of the damaged brain tissue.

Cerebral edema is an increase in brain volume caused by an absolute increase in cerebral tissue water content. Diffuse cerebral edema may develop soon after head injury; however, its presence and extent do not always correlate with the severity of head injury. On computed tomography (CT) scans, diffuse edema is manifest as bilateral compression of the ventricles, loss of definition of the cortical sulci, or effacement of the basal cisterns (Fig. 38-4). Focal edema adjacent to traumatic mass lesions demonstrates decreased density on CT scans compared with normal tissue. CT can also detect a *mass effect*, caused by edema surrounding a traumatic lesion.

Both vasogenic and cytotoxic cerebral edema occur in the setting of trauma; the incidence and onset of each relative to the other depend on the nature of the injury. *Vasogenic edema* arises from transvascular leakage caused by mechanical failure of the tight endothelial junctions of the BBB.[23,24] Vasogenic edema accumulates preferentially in white matter and can become widespread. It is frequently associated with focal contusions or hematomas. Vasogenic edema eventually resolves as edema fluid is reabsorbed into the vascular space or the ventricular system.

Figure 38-4. Non-contrast-enhanced computed tomography scan showing diffuse cerebral edema. Loss of gray-white differentiation in brain parenchyma is present. Bilateral compression of the ventricles has occurred with loss of cortical sulci.

Cytotoxic edema is an intracellular process that results from membrane pump failure. It is common after head injury and is frequently associated with post-traumatic ischemia and tissue hypoxia. Normal membrane pump activity depends on adequate CBF to ensure adequate substrate and oxygen delivery to brain tissue. If the CBF is reduced to 40% or less of baseline, cytotoxic edema begins to develop. If CBF drops to 25% of baseline, membrane pumps fail and cells begin to die. Congestive brain swelling can contribute to cytotoxic edema if it becomes severe enough to increase ICP and reduce CPP so that cerebral circulation cannot be maintained. Recent work suggests that cytotoxic cerebral edema is the predominant form of edema in patients who have experienced TBI.[25]

Altered Levels of Consciousness

Consciousness is the state of awareness of the self and of the environment, and it requires intact functioning of the cerebral cortices and the reticular activating system (RAS) of the brainstem. An altered level of consciousness is the hallmark of brain insult from any cause and results from an interruption of the RAS or a global event that affects the cortices of both hemispheres.

A patient who has sustained TBI typically has an altered level of consciousness. Head trauma patients may be hypoxic from injury to respiratory centers or from concomitant pulmonary injury. Hypotension from other associated injuries can compromise CBF and affect consciousness. Global suppression may result from an intoxicant consumed before the injury, hypoglycemia, a post-traumatic seizure, or a postictal period following a seizure from any cause. With increasing ICP from brain swelling or an expanding mass lesion, brainstem compression and subsequent RAS compression can occur.

Patients with altered levels of consciousness require careful monitoring and observation. Reversible conditions that can alter mental status, such as hypoxia, hypotension, or hypoglycemia, should be corrected as they are identified.

Cushing's Reflex

Progressive hypertension associated with bradycardia and diminished respiratory effort is a specific response to acute, potentially lethal increases in ICP. This response is called the *Cushing reflex*, or *Cushing's phenomenon*, and its occurrence indicates that the ICP has reached life-threatening levels. The Cushing reflex can occur whenever ICP is increased, regardless of the cause. The full triad of hypertension, bradycardia, and respiratory irregularity is seen in only one third of cases of life-threatening increased ICP.[24]

Cerebral Herniation

Cerebral herniation occurs when increasing cranial volume and ICP overwhelm the natural compensatory capacities of the CNS (Fig. 38-5). Increased ICP may be the result of post-traumatic brain swelling, edema formation, traumatic mass lesion expansion, or any combination of the three. When increasing ICP cannot be controlled, the intracranial contents shift and herniate through the cranial foramen. Herniation can occur within minutes or up to days after TBI. When the signs of herniation syndrome are present, however, mortality approaches 100% without rapid implementation of temporizing emergency measures and definitive neurosurgical therapy.

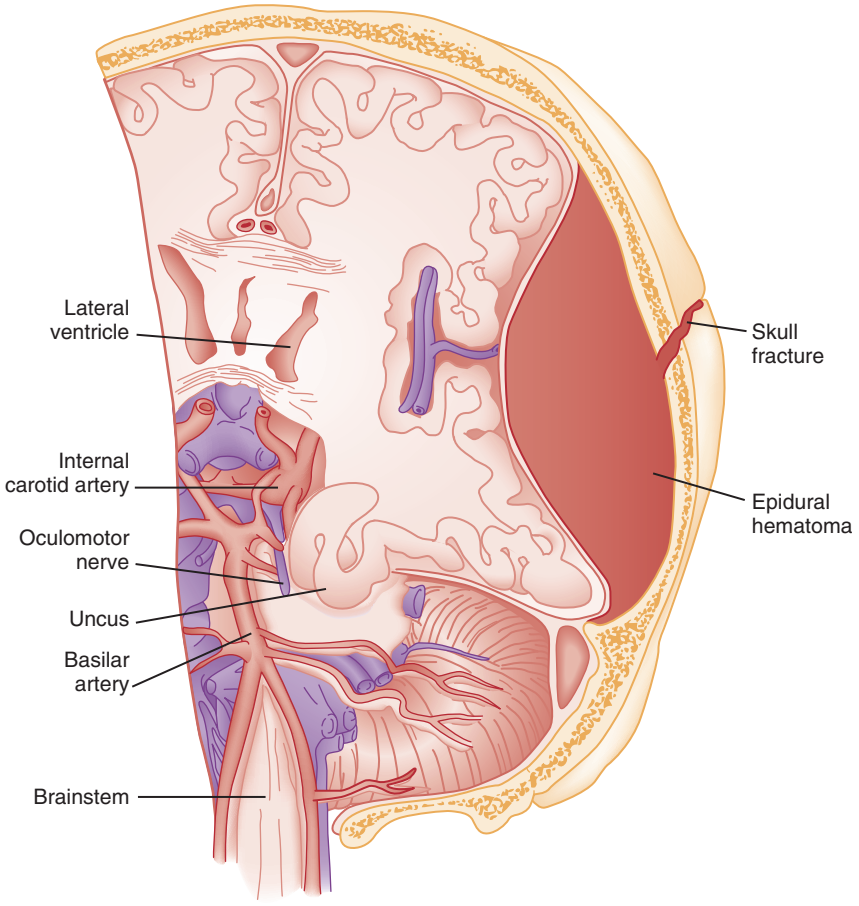


Figure 38-5. Anterior view of transtentorial herniation caused by large epidural hematoma. Skull fracture overlies hematoma. (From Rockswold GL: Head injury. In Tintinalli JE, et al [eds]: Emergency Medicine. New York, McGraw-Hill, 1992, p 915.)

Uncal Herniation. The most common clinically significant traumatic herniation syndrome is uncal herniation, a form of transtentorial herniation. Uncal herniation is often associated with traumatic extra-axial hematomas in the lateral middle fossa or the temporal lobe. The classic signs and symptoms are caused by compression of the ipsilateral uncus of the temporal lobe on the U-shaped edge of the tentorium cerebelli as the brain is forced through the tentorial hiatus. As compression of the uncus begins, the third cranial nerve is compressed; anisocoria, ptosis, impaired extraocular movements, and a sluggish pupillary light reflex develop on the side ipsilateral to the expanding mass lesion. This phase may last for minutes to hours, depending on how rapidly the expanding lesion is changing. As the herniation progresses, compression of the ipsilateral oculomotor nerve eventually causes ipsilateral pupillary dilation and nonreactivity.

Initially in the uncal herniation process, the motor examination can be normal, but contralateral Babinski's responses develop early.[24] Babinski's sign is dorsiflexion of the great toe and fanning of the other toes. Contralateral hemiparesis develops as the ipsilateral peduncle is compressed against the tentorium. With continued progression of the herniation, bilateral decerebrate posturing eventually occurs; decorticate posturing is not always seen with the uncal herniation syndrome. In up to 25% of patients, the contralateral cerebral peduncle is forced against the opposite edge of the tentorial hiatus. Hemiparesis is then detected ipsilateral to the dilated pupil and the mass lesion. This is termed *Kernohan's notch syndrome* and causes false-localizing motor findings.

As uncal herniation progresses, direct brainstem compression causes additional alterations in the level of consciousness, respiratory pattern, and cardiovascular system. Mental status changes may initially be quite subtle, such as agitation, restlessness, or confusion, but soon lethargy occurs with progression to frank coma. The patient's respiratory pattern may initially be normal, followed by sustained hyperventilation. With continued brainstem compression, an ataxic respiratory pattern develops. The patient's hemodynamic status may change, with rapid fluctuations in blood pressure and cardiac conduction. Herniation that is uncontrolled progresses rapidly to brainstem failure, cardiovascular collapse, and death.

Central Transtentorial Herniation. The central transtentorial herniation syndrome is demonstrated by rostrocaudal neurologic deterioration caused by an expanding lesion at the vertex or the frontal or occipital pole of the brain. It is less common than uncal transtentorial herniation. Clinical deterioration occurs as bilateral central pressure is exerted on the brain from above. The initial clinical manifestation may be a subtle change in mental status or decreased level of consciousness, bilateral motor weakness, and pinpoint pupils (<2 mm). Light reflexes are still present but are often difficult to detect. Muscle tone is increased bilaterally, and bilateral Babinski's signs may be present. As central herniation progresses, both pupils become midpoint and lose light responsiveness. Respiratory patterns are affected and sustained hyperventilation may occur. Motor tone increases. Decorticate posturing is elicited by noxious stimuli. This progresses to bilateral decorticate and then spontaneous decerebrate posturing. Respiratory patterns initially include yawns and sighs and progress to sustained tachypnea, followed by shallow slow and irregular breaths immediately before respiratory arrest.

Cerebellotonsillar Herniation. Cerebellotonsillar herniation occurs when the cerebellar tonsils herniate downward through the foramen magnum. This is usually caused by a cerebellar mass or a large central vertex mass causing the rapid displacement of the entire brainstem.[24] Clinically, patients demonstrate sudden respiratory and cardiovascular collapse as the medulla is impinged. Pinpoint pupils are noted. Flaccid quadriplegia is the most common motor presentation because of bilateral compression of the corticospinal tracts. Mortality from cerebellar herniation approaches 70%.[24]

Upward Transtentorial Herniation. Upward transtentorial herniation occasionally occurs as a result of an expanding posterior fossa lesion. Level of consciousness declines rapidly. These patients may have pinpoint pupils from compression of the pons. Downward conjugate gaze is accompanied by the absence of vertical eye movements.[24]

CLINICAL FEATURES AND DIAGNOSTIC STRATEGIES

History

Details regarding the mechanism of injury should be solicited from witnesses or the victim to determine whether the head-injured patient is at high risk for intracranial injury. The patient's condition before trauma may give clues to important, otherwise unsuspected, comorbid factors such as preexisting coagulopathy (i.e., hemophilia). Past medical history, medications (particularly anticoagulants), recent drug or alcohol use, and complaints immediately preceding the traumatic event should be determined.

The patient's current level of consciousness, as well as that immediately before and after the injury and at the arrival of first responders, should be determined. Witnessed posttraumatic seizures or apnea should be reported. If the patient is now awake but was unconscious at some point, it should be determined if the patient has returned to baseline mental status.

Acute Neurologic Examination

General

The goals of the acute neurologic assessment of head-injured patients include detection of life-threatening injuries and identification of neurologic changes in the immediate posttrauma period. An awake, stable patient can undergo a relatively complete neurologic examination. In other patients, an efficient neurologic examination in the emergency setting includes evaluation of mental status, GCS score, pupillary size and responsiveness, and motor strength and symmetry. An accurate neurologic assessment in the immediate posttrauma period serves as a basis for comparison in subsequent examinations. If a formal GCS measure is not possible or is difficult because of comorbid confounders, the patient's mental status should be described in as much detail as possible. Declining mental status after head trauma suggests increasing ICP from an expanding mass lesion or worsening cerebral edema, which may rapidly become life threatening.

Glasgow Coma Scale

The GCS is an objective method of following the patient's neurologic status (Table 38-1). The GCS assesses a patient's best eye, verbal, and motor responsiveness. It was developed for the clinical evaluation of head trauma patients at 6 hours after trauma, and all initial validation studies investigated its application at this time. It was designed for assessment of patients with isolated head trauma who were hemodynamically stable and adequately oxygenated.[26] The GCS is only one aspect of the neurologic examination (i.e., the motor score reflects best limb movement, and it cannot detect subtle changes in mental status). However, because of its interrater

Table 38-1 Glasgow Coma Scale

RESPONSE	SCORE	SIGNIFICANCE
EYE OPENING		
Spontaneously	4	Reticular activating system is intact; patient may not be aware
To verbal command	3	Opens eyes when told to do so
To pain	2	Opens eyes in response to pain
None	1	Does not open eyes to any stimuli
VERBAL STIMULI		
Oriented, converses	5	Relatively intact CNS, aware of self and environment
Disoriented, converses	4	Well articulated, organized, but disoriented
Inappropriate words	3	Random exclamatory words
Incomprehensible	2	Moaning, no recognizable words
No response	1	No response or intubated
MOTOR RESPONSE		
Obeys verbal commands	6	Readily moves limbs when told to
Localizes to painful stimuli	5	Moves limb in an effort to remove painful stimuli
Flexion withdrawal	4	Pulls away from pain in flexion
Abnormal flexion	3	Decorticate rigidity
Extension	2	Decerebrate rigidity
No response	1	Hypotonia, flaccid: suggests loss of medullary function or concomitant spinal cord injury

CNS, central nervous system.

reliability, reliance on objective clinical data, and ease of application, the GCS has become a standard acute measure of neurologic function in patients with altered mental status from any cause, including head trauma.

The acute application (<6 hours) of the GCS in head-injured patients has limitations. Hypoxia, hypotension, and intoxication can falsely lower the initial GCS.[26] Intubation lowers the patient's GCS by automatically assigning a score of 1 for verbal response, regardless of the actual contribution of head injury to the clinical examination. Periorbital edema from direct eye trauma may make assessment of spontaneous eye opening difficult. Extremity fractures or occult spinal cord injuries may interfere with the motor examination. Children and non-English-speaking patients are difficult to assess with the GCS. The GCS may miss subtle mental status changes and does not assess brainstem reflexes or pupillary reflexes. Decisions regarding continued resuscitation of severely head-injured patients should not be based on the initial GCS because of these limitations. Patients must be fully resuscitated, with evacuation of all surgical lesions, must remain hemodynamically stable, and must not be intoxicated before the GCS can be used to predict their prognosis.[26]

Pupillary Examination

An evaluation of the patient's pupil size and responsiveness must be done early in the initial assessment of the head-injured patient. Pupillary asymmetry, the loss of the light reflex, or a dilated pupil suggests herniation syndrome. Traumatic mydriasis, resulting from direct injury to the eye and periorbital structures, may confuse the assessment of the pupillary responsiveness.

Motor Examination: Posturing

The patient's acute motor examination assesses for strength and symmetry. Paralysis obscures involuntary reflexes; attempts should be made to assess the motor exam before paralytic agents are given. Hemiparesis contralateral to a fixed and dilated pupil suggests herniation syndrome. A false-localizing motor examination can be caused by contralateral cerebral parenchymal injury occurring simultaneously with the expanding mass lesion or by Kernohan's notch syndrome (compression of the contralateral cerebral peduncle). False-localizing signs for the motor examination can also be caused by occult extremity trauma, spinal cord, or nerve root injury that makes the examination painful or difficult. If the patient is not cooperative or is comatose, motor movement should be elicited by application of noxious stimuli. Any movement should be recorded. Voluntary purposeful movement must be distinguished from abnormal motor posturing. *Decorticate posturing* is abnormal flexion of the upper extremity and extension of the lower extremity. The arm, wrist, and elbow slowly flex, and the arm is adducted. The leg extends and internally rotates, with plantar flexion of the foot. Decorticate posturing implies injury above the midbrain. *Decerebrate posturing* is the result of a more caudal injury and therefore is associated with a worse prognosis.[19] The arms extend abnormally and become adducted. The wrist and fingers are flexed, and the entire arm is internally rotated at the shoulder. The neck undergoes abnormal extension, and the teeth may become clenched. The leg is internally rotated and extended, and the feet and toes are plantar flexed.

Brainstem Function

In the acute setting, brainstem activity is assessed by the patient's respiratory pattern, pupillary size, and eye movements. The *oculocephalic response* (doll's eyes maneuver) tests the integrity of the pontine gaze centers. This response cannot be tested until cervical spine fractures have been ruled out. The *oculovestibular response* (cold water calorics) also assesses the brainstem. Comatose patients no longer demonstrate nystagmus when cold water is placed in the ear canal; the only response is tonic deviation of the eyes toward the instilled cold water.[24] This response is dampened by cerumen or blood in the patient's ear canal, and the tympanic membrane must be intact to perform this test.

In the severely head-injured patient, the cranial nerve (CN) examination is often limited to the pupillary responses (CN III), gag reflex (CNs IX and X), and corneal reflex (CNs V and VII). Facial symmetry (CN VII) can sometimes be assessed if the patient grimaces with noxious stimuli. In patients who are awake and can cooperate, a formal CN examination should be performed.

Deep Tendon Reflexes and Pathologic Reflexes

Tendon reflexes should be tested for symmetry. An extensor plantar reflex (Babinski's sign) is nonspecific and can be caused by injury anywhere along the corticospinal tract. Rectal sphincter tone and anal reflexes should be determined to assess for spinal cord integrity.

BOX 38-1 Clinical Characteristics of Basilar Skull Fractures

Blood in ear canal
Hemotympanum
Rhinorrhea
Otorrhea
Battle's sign (retroauricular hematoma)
Raccoon sign (periorbital ecchymosis)
Cranial nerve deficits
- Facial paralysis
- Decreased auditory acuity
- Dizziness
- Tinnitus
- Nystagmus

Other Examination Findings

The head and neck should be carefully examined for external signs of trauma that may have also produced underlying TBI. A scalp laceration, contusion, abrasion, or avulsion may overlie a depressed skull fracture. Basilar skull fractures are usually diagnosed by the clinical examination (Box 38-1). Although not always related to severe brain injury, their presence implies that a significant impact force was sustained during head trauma. Carotid artery dissections caused by a hyperflexion-extension neck injury can occasionally be detected by auscultation of a carotid bruit.[24] In these patients, a careful neurologic examination should assess for subtle asymmetry between the carotid arteries. The percentage of concurrent cervical spine injury in patients with severe head trauma may be as high as 10.2%.[27] Often, other spinal regions are also injured.

MANAGEMENT

Severe Traumatic Brain Injury

The neurosurgical literature defines severe head injury as TBI manifested by a postresuscitation GCS of 8 or less within 48 hours. In the emergency setting, however, this definition is not practical because the outcome for the patient beyond the initial resuscitation is not known. Most emergency medicine research defines severe head injury by a GCS score of 8 or less at the acute presentation after injury. The presence of any intracranial contusion, hematoma, or laceration is also considered severe injury (Fig. 38-5).

Approximately 10% of all head-injured patients who reach the emergency department alive have severe head trauma.[1] The clinical prognostic indicators in the acute setting are initial motor activity, pupillary responsiveness, the patient's age and premorbid condition, and the occurrence of secondary systemic insult during the acute period.[25,26] Up to 25% of these patients have lesions requiring neurosurgical evacuation.[15] The prognosis cannot be reliably predicted by the initial GCS or initial CT scan.

The overall mortality in severe head trauma approaches 60%.[1,24] Mortality for children is lower. For nonsurvivors of head injury who reach the hospital alive, the average time to death is 2 days after trauma. Adult survivors of severe head trauma are usually severely disabled; currently, only 7% have moderate disability or a good outcome. Children older than 2 years who survive a severe closed-head injury have a better outcome than adults.

Out-of-Hospital Care

The goals of the out-of-hospital management of the head-injured patient are necessary airway interventions to prevent hypoxia and establishing intravenous (IV) access to treat trauma-related hypotension. An accurate neurologic assessment provides a means to determine the subsequent effectiveness of treatment and should focus on the GCS, pupillary responsiveness and size, level of consciousness, and motor strength and symmetry.

Head trauma can produce profound effects on the cardiovascular system if compression of the brainstem and medulla occurs. Any cardiac dysrhythmia can occur and produce cardiac instability.[28] All head-injured patients should be placed on a cardiac monitor during transport from the accident scene.

The secondary survey of the head-injured patient should include a search for external signs of head trauma. Scalp lacerations may bleed a large volume into a bulky dressing. A less bulky dressing should be used with firm constant manual pressure applied to avoid excessive blood loss. Many severely head-injured patients are initially combative or agitated. Transporting an agitated patient who is fighting against physical restraints may exacerbate physical injury, cause an increase in ICP, and interfere with appropriate stabilization and management. It may be necessary to use out-of-hospital sedation or neuromuscular blockade for control. The use of sedatives or neuromuscular blockade may influence the initial emergency department evaluation of the neurotrauma patient. Therefore, the risks and benefits of this acute intervention must be carefully considered and decisions made on a case-by-case basis. Out-of-hospital protocols allowing the use of sedative agents for selected agitated head-injured patients should be established. Currently used agents include lorazepam (Ativan), diazepam (Valium), midazolam (Versed), and certain butyrophenones (i.e., haloperidol, droperidol, and tripardol).

Severe head injury is the most common reason for helicopter transfers in trauma care. Although the decision to transport by helicopter should be made on a case-by-case basis, considerations for helicopter use from an accident scene include a long extrication time, ground transport of longer than 30 minutes to an appropriate emergency department and trauma care facility, two or more severely injured patients at a scene, and assistance in performing expedient lifesaving procedures, especially airway management.

Controversy exists regarding the benefits of out-of- hospital intubations in patients with severe and moderate head injuries. It is unclear if field intubations truly improve neurologic outcome or survival. Unsuccessful attempts at field intubations may add to out-of-hospital time and increase the risk for aspiration or hypoxia.

In 1997, Winchell and Hoyt[29] showed that patients who had sustained severe head injuries and who were intubated in the out-of-hospital setting had an improved survival compared with those who were not intubated. Since that time, others have challenged this finding. In the San Diego paramedic rapid sequence intubation (RSI) trial, Davis and colleagues[30] found an increase in mortality and morbidity in patients who sustained severe head injuries and underwent out-of-hospital RSI compared to matched historical controls. Potential explanations included frequent hypoxic episodes with associated bradycardia, unintentional hyperventilation, and prolonged scene times for those undergoing out-of-hospital RSI. Wang and colleagues[20] found a fourfold increase in mortality among patients who sustained severe TBI and received ground ambulance intubation compared with emergency department intubation. Flight clinician out-of-hospital intubation was associated

with decreased mortality and improved neurologic outcome, likely due to the higher airway management training requirements of air medical programs. These studies are somewhat limited by lack of generalizability[30-33] (i.e., most emergency medical service systems do not have RSI capabilities) or by the use of nonvalidated outcome measures of neurologic function.[20] Out-of-hospital intubation carries the following risks: frequent hypoxic episodes during intubation attempts with or without concurrent bradycardia; unintentional hyperventilation of intubated patients; prolonged scene times because of the time demands associated with the intubation process; and persistent hypotension, likely from other injuries that go unattended while the airway management occurs. However, hypoxia must be avoided in head-injured patients, and out-of-hospital airway protocols must balance the risks of emergency intubation in an uncontrolled setting with the need to secure an airway at risk.

The key to a successful out-of-hospital RSI program involves well-trained clinicians with specific RSI protocols, involved medical control, frequent continuing education, and consistent quality assurance/improvement. Fakhry and colleagues[34] reported that their helicopter clinicians had a 96.6% RSI success rate with few complications and no esophageal intubations.

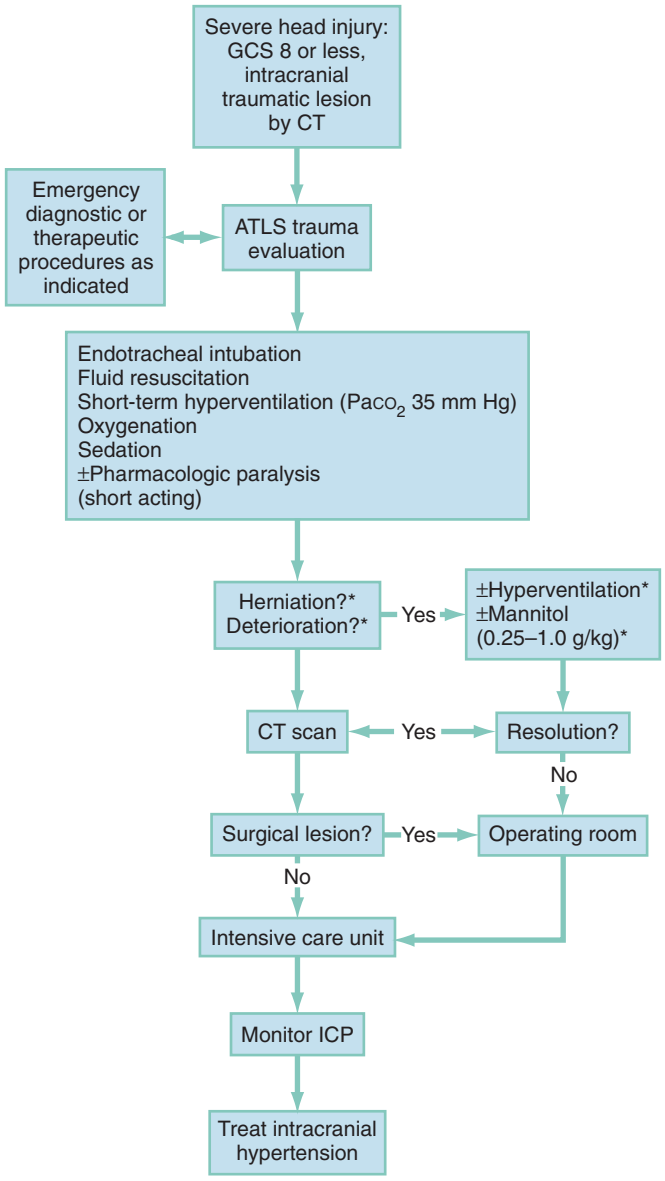
Emergency Department (Fig. 38-6)

Airway. Rapid sequence intubation is an effective and the preferred method for securing the airway in combative or agitated patients. If possible, a brief neurologic examination should be performed before the patient is given any sedative or neuromuscular blocking agents. In general, the agents used for RSI in the head-injured patient are the same as those used for other patients, although attention must be given to the increased ICP that can potentially occur with any physical stimulation of the respiratory tract. Lidocaine (1.5–2 mg/kg IV push) may attenuate the cough reflex, hypertensive response, and increased ICP associated with intubation, although this is vigorously debated.[35,36] If succinylcholine is used, premedication with a subparalytic dose of a nondepolarizing agent can be considered if time permits because fasciculations produced by succinylcholine may increase ICP. The degree of ICP elevation and its clinical significance are unclear, however, and must be balanced against the need for rapidly establishing an airway. Etomidate (0.3 mg/kg IV), a short-acting sedative-hypnotic agent, has beneficial effects on ICP by reducing CBF and metabolism.[37] In addition, etomidate has minimal adverse effects on blood pressure and cardiac output and fewer respiratory depressant effects than other agents.

Hypotension. Hypotension is rarely caused by head injury except as a terminal event. If hypotension is detected at any time in the emergent management of a head-injured patient, a cause other than the head injury should be sought. Some important exceptions occur. Profound blood loss from scalp lacerations can cause hypovolemic hypotension. In small children, hemorrhage into an epidural or subgaleal hematoma can produce profound hypovolemic shock. In the presence of a concomitant high spinal cord injury, neurogenic hypotension may occur. This is rare and usually the cord injury is apparent on physical examination. In less obvious cases, neurogenic hypotension can be differentiated from hypovolemic hypotension by its nonresponsiveness to fluid administration and by the presence of inappropriate bradycardia in the face of hypotension in neurogenic shock.

Systemic hypotension cannot be tolerated in the head-injured patient without profound worsening of neurologic outcome; fluids or blood transfusion should therefore be delivered to maintain a systolic blood pressure of at least 90 mm Hg.[19] The delivery of large amounts of fluid to severely head-injured patients who are hypotensive from other injuries does not produce clinically significant increases in ICP; fluids should never be withheld in the head trauma patient with hypovolemic hypotension for fear of increasing cerebral edema and ICP. Hypotension may interfere with the accurate neurologic assessment of the brain-injured patient. Often, when blood pressure is restored, an improved neurologic status is observed.

Traditionally, normal saline or lactated Ringer's solution has been used for resuscitation of trauma patients with hypovolemic hypotension. Although it is not yet included in practice



*Only in the presence of signs of herniation or progressive neurologic deterioration not attributable to extracranial factors.

Figure 38-6. Initial resuscitation of patient with severe head injury: treatment options. ATLS, advanced trauma life support; CT, computed tomography; GCS, Glasgow Coma Scale; ICP, intracranial pressure; $PaCO_2$, arterial carbon dioxide partial pressure. (From the Brain Trauma Foundation, American Association of Neurological Surgeons, Joint Section on Neurotrauma and Critical Care: Introduction. Guidelines for the management of severe traumatic brain injury. J Neurotrauma 17:465, 2000.)

guidelines on the management of head-injured patients, some researchers suggest that fluid resuscitation with hypertonic saline rather than normal saline may improve neurologic outcome after TBI.[19]

As many as 60% of patients with severe head injury are victims of multiple trauma.[38] The dramatic presentation of the head injury should not distract the clinician from a thorough search for other life threats.

The emergency department neurologic assessment should be compared with the initial out-of-hospital examination, focusing on evidence of neurologic deterioration or signs of increasing ICP. If the patient is deteriorating or has signs of increased ICP, active intervention must be initiated in the emergency department.

Hyperventilation. Acute hyperventilation is a life-saving intervention that can prevent or delay herniation in the patient with severe TBI. The goal is to reduce the P_{CO_2} to the range of 30 to 35 mm Hg. Hyperventilation will reduce ICP by causing cerebral vasoconstriction; the onset of effect is within 30 seconds[24] and probably peaks within 8 minutes after the P_{CO_2} drops to the desired range.[39] In most patients, hyperventilation lowers the ICP by 25%; if the patient does not rapidly respond, the prognosis for survival is generally poor.

Prolonged hyperventilation is not recommended because it may cause profound vasoconstriction and ischemia. This vasoconstriction worsens cerebral blood flow that is already severely compromised during the first 24 hours after TBI.[11] Hyperventilation should be viewed as a short-term lifesaving intervention and should be used only when a patient experiences an acute neurologic decline or demonstrates signs consistent with herniation

Osmotic Agents. Additional therapy for increased ICP includes the use of osmotic diuretics, such as mannitol and hypertonic saline. With deepening coma, pupil inequality, or other deterioration of the neurologic examination, osmotic agents may be lifesaving.

Mannitol is the mainstay for control of elevated ICP acute severe TBI. The Brain Trauma Foundation and the European Brain Injury Consortium recommend mannitol as the osmotic drug of choice.[40,41] However, little comparative data exist on mannitol and other ICP-lowering medications. A Cochrane database review concluded that mannitol may have a small beneficial effect compared to pentobarbital. ICP-directed therapy based on neurologic signs may also be beneficial. However, one study indicates that mannitol may be detrimental compared to hypertonic saline.[42] Further research is needed on optimal osmotic therapy in severe head trauma.

Mannitol (0.25–1 g/kg) can effectively reduce cerebral edema by producing an osmotic gradient that prevents the movement of water from the vascular space into the cells during membrane pump failure and draws tissue water into the vascular space. This reduces brain volume and provides increased space for an expanding hematoma or brain swelling. The osmotic effects of mannitol occur within minutes and peak approximately 60 minutes after bolus administration. The ICP-lowering effects of a single bolus may last for 6 to 8 hours.[40] Mannitol has many other neuroprotective properties. It is an effective volume expander in the presence of hypovolemic hypotension and therefore may maintain systemic blood pressure required for adequate cerebral perfusion. It also promotes CBF by reducing blood viscosity and microcirculatory resistance. It is an effective free radical scavenger, reducing the concentration of oxygen free radicals that may promote cell membrane lipid peroxidation. However, mannitol can produce renal failure or hypotension if given in large doses. It may also induce a paradoxical effect of increased bleeding into a traumatic lesion by decompressing the tamponade effect of a hematoma. Because of these and other potential problems, the use of mannitol should be reserved for head-injured patients with evidence of increasing ICP and neurologic deterioration.[40]

Hypertonic saline (HTS) has been used for severe TBI since 1919.[43] Preclinical studies have demonstrated that HTS can significantly reduce ICP; however, fewer than 300 patients have been enrolled in all clinical trials of HTS. The interpretation of these clinical studies is complicated by variation in protocols, HTS concentration, and administration. Few studies have been prospective, randomized, and controlled. Potential adverse events associated with HTS include renal failure, central pontine myelinoysis, and rebound ICP elevation.[41]

Encouraging clinical data are available on hospitalized pediatric TBI patients treated with a continuous infusion of 3% normal saline for control of intracranial hypertension.[44] The clinical studies using HTS for acute resuscitation of severe TBI are conflicting. Using a post hoc analysis of adult trauma data, Vassar and colleagues[45] and Wade and colleagues[46] showed beneficial effects of HTS on patients with severe TBI. However, Cooper and colleagues[47] found no benefit for out-of-hospital use of HTS in reducing elevated ICP and improving CPP compared to lactated Ringer's in hypotensive patients who had a head injury. Morbidity and mortality outcome data were equal in both groups. In summary, clinical effectiveness data on the use of HTS in head-injured adults for acute treatment of increased ICP are inconclusive, but research on this topic is ongoing.

Barbiturates. Barbiturate therapy is occasionally used in severely head-injured patients to reduce cerebral metabolic demands of the injured brain tissue. Barbiturates also affect vascular tone and inhibit free radical-mediated cell membrane lipid peroxidation. The effects of barbiturates are delayed relative to other acute interventions for reducing ICP; therefore, they are rarely initiated in the emergency department. If other methods of reducing ICP have been unsuccessful, barbiturates may be added in the hemodynamically stable patient. *Pentobarbital* is the barbiturate most often used.[48]

Steroids. Despite their popularity in the past, there is no benefit to giving steroids in head-injured patients. They do not lower ICP, and high-dose methylprednisolone in moderate and severe TBI is associated with increased mortality.[49]

Hypothermia. Although hypothermia remains a significant area of research and promise for severe and moderate TBI patients, the available scientific evidence does not support improved mortality or morbidity with prophylactic hypothermia in adult patients.[50] In a meta-analysis performed by the Brain Trauma Foundation, duration of hypothermic treatment for more than 48 hours was associated with a reduction in mortality. This finding is significantly limited due to small sample sizes.[50]

Cranial Decompression. Patients with signs of herniation who have not responded to other means of ICP reduction and who are rapidly deteriorating in the emergency department should be considered for placement of emergency burr holes. Emergency trephination has been described for centuries (Fig. 38-7). It is a blind invasive procedure, and the chances of localizing the expanding lesions are uncertain. In carefully considered patients, however, emergency cranial decompression may temporarily reverse or arrest the herniation syndrome, providing the time needed to prepare the patient for formal craniotomy.

Most patients who have been unconscious since an accident occurred—with erratic or absent respiratory effort, bilateral fixed and dilated pupils, no spontaneous eye movements, and decerebrate posturing—have sustained diffuse massive brain injury with no focal lesion amenable to emergency decompression. These patients probably do not benefit from emergent

Figure 38-7. Non-contrast-enhanced computed tomography scan of acute epidural hematoma at the level of right midconvexity. There is an associated mass effect and moderate midline shift.

burr holes. Instead, these patients should undergo rapid CT scanning or formal surgical decompression.

Seizure Prophylaxis. Up to 12% of all patients who sustain blunt head trauma and 50% of those with penetrating head injury develop early post-traumatic seizures.[51] Although the occurrence of seizures in the immediate posttrauma period has no predictive value for future epilepsy, early seizures can cause hypoxia, hypercarbia, release of excitatory neurotransmitters, and increased ICP, which can worsen secondary brain injury. Constantly firing neurons are soon depleted of their energy sources, and in the head trauma patient with compromised cerebral metabolism, uncontrolled seizures exacerbate the neurologic deficit.[24]

Box 38-2 lists accepted indications for early anticonvulsant therapy after head trauma. If the patient is actively seizing, benzodiazepines are administered as effective, rapid-acting first-line anticonvulsants. Lorazepam (0.05–0.15 mg/kg IV over 2–5 minutes up to a total of 4 mg) has been found to be most effective at aborting status epilepticus.[51] Diazepam (0.1 mg/kg, up to 5 mg IV, every 10 minutes up to a total of 20 mg) is an alternative. For long-term anticonvulsant activity, phenytoin (18–20 mg/kg IV) or fosphenytoin (15–18 phenytoin equivalents/kg) IV or IM can be given. Fosphenytoin has the advantages of rapid administration, a smaller volume of fluid for the dose delivered, and less hypotension than phenytoin, although its cost is much higher. In a Cochrane review, the use of antiepileptic drugs reduced the risk of early seizures by 66%.[51] Early seizure prophylaxis does not prevent late post-traumatic seizures; the goal is to prevent additional insult to the damaged brain.[52,53]

If the patient has been paralyzed to facilitate management, clinical manifestations of generalized seizures are obscured. Therefore, all paralyzed head-injured patients should have prophylactic anticonvulsant therapy in the acute phase. Continuous electroencephalographic monitoring is necessary for the ongoing assessment of seizure activity in paralyzed patients and, if available, should be initiated in the emergency department or the intensive care unit.

BOX 38-2 INDICATIONS FOR ACUTE SEIZURE PROPHYLAXIS IN SEVERE HEAD TRAUMA

Depressed skull fracture
Paralyzed and intubated patient
Seizure at the time of injury
Seizure at emergency department presentation
Penetrating brain injury
Severe head injury (Glasgow Coma Scale score ≤8)
Acute subdural hematoma
Acute epidural hematoma
Acute intracranial hemorrhage
Prior history of seizures

Antibiotic Prophylaxis. Infection may occur as a complication of penetrating head injury, open skull fractures, and complicated scalp lacerations. Prophylactic antibiotics may be used in these circumstances but are not recommended in patients with otorrhea or rhinorrhea from a basilar skull fracture.[54]

Recombinant factor VIIa (rFVIIa) is a hemostatic agent that was originally developed to treat bleeding in hemophiliacs. Considerable interest has arisen regarding its potential use in intracerebral hemorrhage.[55,56] A single, appropriate dose of rFVIIa for a 70-kg individual can exceed $4500.[56] Experience from the Iraq war has produced conflicting results regarding its benefits in traumatic intracranial hemorrhage. Use of rFVIIa for traumatic head bleeds should be individualized and made in concert with an institution's treatment protocol.

Ancillary Evaluation

Laboratory Tests. The acute management of the severely head-injured patient is directed by physical examination and diagnostic imaging. Ancillary laboratory tests that may provide useful information in the subsequent management of the patient include a urine toxicology screen, blood alcohol level, complete blood count, electrolytes, glucose, and coagulation studies.

Neuroimaging. The advantages and indications for neuroimaging techniques in the acute evaluation of head injury are listed in Table 38-2. In the acute phase, the most useful imaging technique is a non-contrast-enhanced head CT scan. This scan delineates acute intra-axial and extra-axial bleeding, subarachnoid blood, cerebral swelling, ischemic infarction caused by hypoxia after trauma, evidence of increased ICP, and pneumocephalus. Emergency management decisions are strongly influenced by these acute CT scan findings. The bone windows of the CT scan can detect skull fractures (including basilar fractures); plain skull radiographs are not necessary in patients who undergo CT scanning.

Magnetic resonance imaging (MRI) is better than CT in detecting post-traumatic ischemic infarctions, subacute nonhemorrhagic lesions and contusions, axonal shear injury, and lesions in the brainstem or posterior fossa. Monitoring and managing patients in the MRI suite can be very difficult, especially in severe TBI patients who have other life-threatening injuries. MRI is not recommended as the first-line imaging modality for severe or moderate head injury.

Disposition

Consultation. All patients with severe head trauma require an imaging modality to determine the extent and nature of the brain injury and the necessity of neurosurgical intervention.

Table 38-2 Comparison of Head Imaging Modalities

	COMPUTED TOMOGRAPHY SCANS	MAGNETIC RESONANCE IMAGING	ANGIOGRAPHY	SKULL RADIOGRAPHY
Advantages	Fast Patient accessible for monitoring Defines acute hemorrhages, mass effects, bone injuries, hydrocephalus, intraventricular blood, edema	Defines contusions and pericontusion edema, post-traumatic ischemic infarction, brainstem injuries	Helps localize acute traumatic lesions Defines vascular injuries, injuries to venous sinuses Detects mass effects	Readily available May help screen some patients for further imaging studies
Disadvantages	Artifacts arise from patient's movement, foreign bodies Streak artifacts may obscure brainstem or posterior fossa	Slow Patients not easily accessible for monitoring Does not define most acute hemorrhagic lesions Not useful for bone injuries	Does not define nature of acute lesion Does not detect infratentorial masses	Does not indicate presence or absence of intracranial injury
Indications	Acute severe head trauma Acute moderate head trauma Suspected depressed skull fracture High-risk minor head trauma Suspected child abuse in minor head trauma Deteriorating neurologic status	Persistent symptoms with postconcussive syndrome Suspected post-traumatic ischemic infarction Suspected contusions not seen on CT scan	Suspected vascular injury CT scan not available	CT scan may not be done Penetrating head trauma

CT, computed tomography.

Neurosurgical consultation should be obtained as soon as possible to help direct the patient's subsequent management.

Transfer. Severely head-injured patients require admission to an institution capable of intensive neurosurgical care and acute neurosurgical intervention. If this is not available at the receiving hospital, the patient should be transferred to an appropriate institution by the most expedient transport method available.

Priority Management. The hemodynamically unstable patient with multiple trauma that includes head injury presents difficult emergency management decisions. The emergency physician must decide on the sequence that best addresses the most life-threatening pathologic conditions while still preventing morbidity and mortality from other serious injury. If the patient requires immediate surgical intervention for a life-threatening chest or abdominal injury, complete evaluation of the head injury may be curtailed. Moreover, these patients are anesthetized for surgery, and any neurologic deterioration is not detected. Some patients may be too unstable to obtain even an abbreviated head CT scan before emergent surgical intervention for other life threats. In this circumstance, early neurosurgical and general surgical consultation should be coordinated by the emergency physician. Intraoperative ventriculostomies or bilateral trephinations may provide some temporary protection from increasing ICP while the patient undergoes surgical correction of the life-threatening injury. A CT scan can be performed after the primary life threats have been corrected.

Moderate Head Trauma

Approximately 10% of all patients with head injury have sustained moderate TBI, defined as a postresuscitation GCS of 9 to 13.[1] Moderate TBI is often caused by motor vehicle collisions. Most patients with moderate TBI do not die at the scene from their initial head injury and present to the emergency department for stabilization and evaluation.

Moderate TBI produces a number of physiologic abnormalities, including neuronal cell membrane dysfunction and a mild, brief acidosis with no concurrent depletion of adenosine triphosphate. These changes are probably reversible and therefore may be amenable to acute intervention to correct or prevent progression. The neuropathology of moderate brain injury probably represents the front end of the spectrum of pathophysiology seen with severe head trauma. Because of this, patients must be vigilantly monitored to avoid hypoxia and hypotension and other secondary systemic insults that could worsen neurologic outcome.

Clinical Features and Acute Management

A wide variety of clinical presentations occur with moderate head injury. Patients often have experienced a change in consciousness at the time of injury, a progressive headache, post-traumatic seizures, vomiting, and post-traumatic amnesia. On emergency department presentation, patients are often confused or somnolent, but most can still follow commands. Focal neurologic deficits may be present. Many patients with moderate head trauma have concurrent serious facial injuries that may interfere with attempts at securing their airway. Other systemic trauma must also be ruled out.

An important clinical scenario in the spectrum of moderate head injury is that of the "talk and deteriorate" patient. These patients have a GCS score of 13 or greater on presentation but deteriorate to a status of a severe head injury (GCS ≤8) within 48 hours.[57] Although this description can include patients with minor head trauma, most patients who talk and deteriorate present with GCS scores suggesting moderate head trauma. When the syndrome was first described by Reilly more than 30 years ago,[58] the incidence of death in head-injured patients who presented talking was estimated to be as high as 38%.[57-60] However, CT scans were not readily available at that time, and the GCS was not in widespread use. With the current availability of early CT scanning, as well as rapid transport via emergency medical service, injuries are detected earlier, and the incidence of talk and deteriorate is now estimated to be 2.5 to 12%.[57,61] In early descriptions of talk and deteriorate, most patients were found to have sustained subdural or epi-

dural hematomas. More recently, an equal number are found to have contusions with subsequent edema.[57,61] Patients who talk and deteriorate are generally elders with higher injury severity scores.[57,62]In addition, anticoagulation puts patients at increased risk.

Successful management of moderately head-injured patients involves close clinical observation for changing mental status or focal neurologic findings, early CT scanning, and aggressive neurosurgical intervention. When no neurosurgeon is available and the patient develops symptoms consistent with herniation syndrome not reversed by acute hyperventilation and mannitol, emergency department trephination and hematoma evacuation of any amenable lesion should be considered.

Because of the varied presentation of patients with moderate head trauma, the initial examination alone cannot accurately predict who will have surgically correctable intracranial lesions. Approximately 40% of moderately head-injured patients have an abnormal CT scan, and 10% lapse into coma.[63] A CT scan is essential in patients with moderate head trauma to avoid delayed diagnosis of traumatic mass lesions or diffuse injury. This is especially true for elders or patients on anticoagulation therapy.[64,65] Skull radiographs may be useful if the patient has sustained a depressed skull fracture or a penetrating injury but are otherwise rarely helpful.

Disposition

All patients with moderate head injury should be admitted for observation, even with an initial apparently normal CT scan. Ninety percent of patients improve over the first few days after injury.[24,63] Frequent neurologic checks should be initiated, and a repeated CT scan is indicated if the patient's condition deteriorates or fails to improve over the first 48 hours after trauma.

Complications

The overall mortality of patients with isolated moderate TBI is approximately 20%, but the morbidity is substantial. Most moderate TBI patients remain symptomatic for extended periods after head injury. At 3 months after trauma, up to 70% are unable to return to work, 90% have memory difficulties, and more than 90% complain of persistent headaches.[63,66] Almost 50% are left with a long-term disability that interferes with their previous daily activities. In patients with persistent symptoms of headache, confusion, or memory difficulties, delayed MRI may define lesions in the regions related to cognition that cannot be seen on CT. Although not useful in the acute setting, MRI has prognostic value during subsequent care and assists in directing the future rehabilitation of these patients.

Minor Head Trauma

Minor TBI is a temporary and brief interruption of neurologic function after head trauma, which may involve a loss of consciousness. The neuropathology involved in producing signs and symptoms of minor TBI may remain at the neurobiochemical level, without damage to the microstructure.[67] Heightened ionic flux, surges in levels of glutamate transmitters, disruption of enzymatic pathways, and accumulation of lactate and nitric oxide have been reported in brain tissue after experimental minor TBI.[14] Axonal stretching or twisting that may occur with some mechanisms producing minor TBI promote glutamine-induced neurotoxic cascades that may lead to the axonal damage typically described as diffuse axonal injury.[68]

Traditionally, minor TBI was defined as injury producing a GCS score of 13 to 15. However, because many patients with a GCS of 13 have outcomes more consistent with moderate TBI, many authorities now classify minor TBI as that producing a GCS score of 14 or 15.[68] In fact, the GCS is not sensitive enough to be of prognostic usefulness in minor TBI; a perfect score of 15 in the emergency department does not take into account the level of alertness or neurologic status immediately after trauma or the presence or absence of focal neurologic injury.[68]

From a practical standpoint, minor TBI is a clinical diagnosis. The diagnosis requires a credible mechanism of injury. In civilian life, most mechanisms that do not involve direct craniofacial impact cannot produce minor TBI. For example, belted drivers in low-velocity rear-end impact motor vehicle crashes are not subjected to high enough acceleration-deceleration or rotary forces to the head to reach the force threshold needed to produce cerebral injury unless there is also direct impact to the head against a stationary object.[68] It is therefore unlikely that a patient with a whiplash or "jolt" injury would also have minor TBI. Collision sports-related minor TBI can be caused by acceleration-deceleration. It is not known if the forces generated in blast injuries in wounded service personnel are large enough to cause minor TBI without direct head impact.

Clinical and Historical Features

By the time most patients with minor TBI reach the emergency department, their symptoms are resolving or have completely resolved. The most common complaint after minor TBI is headache. Other common problems are nausea and emesis. Patients may also report transient disorientation, confusion, or amnesia. There has been little research to correlate these symptoms with the presence of intracranial lesions in patients with minor TBI.

Clinical signs and symptoms of minor TBI include amnesia for the impact, a period of disordered awareness (with or without loss of consciousness), and a finite period of post-trauma amnesia.[68] Retrograde amnesia is impaired information retrieval and begins with and includes the traumatic event. In minor TBI, it generally lasts up to several minutes and then very rapidly resolves. Post-traumatic amnesia (PTA) is impairment of information encoding and therefore does not resolve. PTA is the period of time from the injury to the return of conscious recall: events during this interval are essentially lost to the patient. PTA is a better predictor of injury severity and eventual outcome than the duration of retrograde amnesia or GCS.[68]

Patients with minor TBI often have balance deficits, impaired verbal memory, delayed language comprehension, and slowed speech.[69] These subtle findings can be overlooked unless a careful and complete neurologic and mental status examination is performed.

Approximately 5% of minor TBI patients presenting to the emergency department with a GCS of 15 have abnormal CT scans.[70] This estimate is probably inflated since at least 25% of minor TBI patients never seek medical care. The incidence of life-threatening lesions that require neurosurgical intervention following minor TBI is less than 1%[68]; the goal of emergency evaluation and management of patients with minor TBI is to identify these high-risk patients. Further diagnostic workup hinges on risk stratification in patients with minor TBI (Box 38-3). The criteria are based on several large studies, but because of inconsistent methodology and reporting, they have limitations. For example, loss of consciousness (LOC) in minor head trauma has historically been considered a risk factor for

BOX 38-3 Risk Stratification in Patients with Minor Head Trauma

High Risk
Focal neurologic findings
Asymmetrical pupils
Skull fracture on clinical examination
Multiple trauma
Serious, painful, distracting injuries
External signs of trauma above the clavicles
Initial Glasgow Coma Scale score of 14 or 15
Loss of consciousness
Post-traumatic confusion/amnesia
Progressively worsening headache
Vomiting
Post-traumatic seizure
History of bleeding disorder/anticoagulation
Recent ingestion of intoxicants
Unreliable/unknown history of injury
Previous neurologic diagnosis
Previous epilepsy
Suspected child abuse
Age >60 yr, <2 yr

Medium Risk
Initial Glasgow Coma Scale score of 15
Brief loss of consciousness
Post-traumatic amnesia
Vomiting
Headache
Intoxication

Low Risk
Currently asymptomatic
No other injuries
No focality on examination
Normal pupils
No change in consciousness
Intact orientation/memory
Initial Glasgow Coma Scale score of 15
Accurate history
Trivial mechanism
Injury >24 hr ago
No or mild headache
No vomiting
No preexisting high-risk factors

significant injury, but the negative predictive value for LOC has not been determined, and many minor TBI patients may have sustained only brief or no LOC. Animal studies and anecdotal reports on humans suggest that the longer the duration of LOC, the more likely that an intracranial lesion exists; however, the actual correlation between the duration of the LOC and the incidence of intracranial lesions or injury severity has not been determined.[69,70] Other high-risk minor head trauma criteria have also been proposed. The key for the emergency physician, however, is to determine the low-risk patient, and these criteria are less controversial.

Imaging Studies

A major and controversial decision regarding the emergency management of minor TBI is whether imaging studies should be performed. Several approaches have been described, but the research behind these suggestions remains confusing primarily because of differences in study populations, definitions, and methods. Because they consult on a selected, more injured set of minor TBI patients, neurosurgeons often advocate liberal CT scanning of most patients with minor TBI with a history of LOC (duration not clearly defined) or with amnesia for the traumatic event.[15] Others advocate only hospital observation because the yield of initial abnormal scans requiring acute neurosurgical intervention is low, but patients who do deteriorate after minor head trauma have substantial morbidity and mortality. If resources allow, prolonged emergency department observation may be practical in some circumstances. For example, intoxicated patients with minor TBI who otherwise fulfill low-risk criteria should undergo meticulous serial evaluations in the emergency department until clinical sobriety is achieved. In these patients, a CT scan may be unnecessary, and observation is beneficial.

The most practical approach regarding imaging in the emergency department patient is probably selective CT scanning or observation based on risk stratification of the minor TBI patient. If the low-risk patient is fully awake and not intoxicated, has no focal neurologic findings, has no clinical evidence of skull fracture, and can be kept under competent observation for 12 to 24 hours, neuroimaging is usually not indicated. Patients with moderate-risk minor head trauma (see Box 38-3) should probably undergo CT scanning or prolonged emergency department observation. Studies have prospectively identified and validated high-risk criteria for adult patients with minor head trauma that correlate with increased likelihood of intracranial lesions. These include the presence of a headache, vomiting, age older than 60 years, drug or alcohol intoxication, short-term memory deficits, external signs of trauma above the clavicles, and post-traumatic seizures.[71, 72] A CT scan should therefore be considered for patients with these high-risk findings as well as the other criteria listed in Box 38-3.

Skull radiography after head trauma in adults has been largely replaced by more sophisticated imaging, when imaging is performed. Facial, scalp, or external signs of head trauma by themselves do not predict TBI and are not indications for screening skull radiographs. The presence of a skull fracture suggests significant impact to the head, and therefore an increased likelihood of TBI, but the absence of a skull fracture does not rule out TBI. Patients with clinical signs of skull fracture have a substantially increased incidence of intracranial lesions associated with their minor head trauma. When the clinical examination shows evidence of skull fractures, CT scanning should be obtained, forgoing plain radiographs.

Although CT scanning is extremely sensitive for acute blood, MRI is more sensitive than CT for detecting diffuse axonal injury, ischemia after TBI, and some hemorrhagic lesions, especially those located at the base of the skull or in the posterior fossa. Functional imaging, such as positron emission tomography (PET), can provide information on the metabolic and neurochemical state of the injured brain. Many studies suggest that significant long-term neuropsychiatric sequelae after minor head trauma can occur despite an initial negative head CT scan, and these may be related to lesions seen initially only by MRI or functional imaging.[14] Functional imaging is not currently within the scope of emergency assessment of minor TBI patients, but it can direct rehabilitation strategies for the small subset of patients who suffer significant morbidity after minor TBI.

Ancillary Studies

No routine laboratory tests are needed for patients with isolated minor head trauma. A urine toxicology screen and blood

alcohol level may be useful in interpreting the patient's mental status. Alcohol can affect the GCS, but this effect is not observed until the blood alcohol concentration is greater than 200 mg/dL; until that level, changes in mental status cannot be explained solely by acute alcohol intoxication.[68]

A number of CNS biomarkers, such as S-100B, neuron-specific enolase, myelin basic protein, cleaved tau, and creatine kinase isoenzyme BB, have been investigated in minor TBI. None of these have been shown to strongly correlate with long-term outcome, and only S-100 B predicts abnormal CT findings in minor TBI. However, S-100B appears to lack CNS specificity and is often elevated in multiple trauma patients with no head injury.[14] To date, serum biomarkers have lacked the precision needed for meaningful application in the emergency setting.

Disposition

Most patients with low-risk minor TBI can be discharged from the emergency department after a normal examination and a reasonable period of observation (i.e., 4–6 hours.).[28] If the emergency physician decides that the patient with moderate- or high-risk minor TBI can be sent home, an appropriate early follow-up should be arranged. Patients should be discharged with instructions describing the signs and symptoms of delayed complications of head injury, should have access to a telephone, and should be monitored in the acute post-trauma period by a responsible, sober adult. If any doubt exists regarding the safety of the discharged patient with minor head injury, a brief inpatient observation period (i.e., 12–24 hours) is advisable.

If a patient with minor head trauma returns to the emergency department because of persistent symptoms, delayed complications of minor head injury should be sought. If a CT scan was not performed, the intensity of symptoms may guide the decision to obtain a CT scan at the second visit. If a negative scan was initially obtained, the decision to rescan is more complex. The literature about repeat scanning in minor TBI is scant; however, in one systematic review of severe and moderate TBI, progression of lesions most commonly correlated with overall injury severity and the patients' use of anticoagulants.[73]

Concussion. A concussion (or complicated minor TBI) is a type of minor TBI usually caused by acceleration-deceleration or rotational injury to a freely mobile head, and it is most commonly associated with collision sports.[74] The injury results in distortion of axons, vasculature, and brain neuroanatomy. As in other types of minor TBI, acute CT or MRI abnormalities are not usually found, but functional imaging (i.e., PET) reveals abnormalities with glucose uptake and blood flow.[14,74,75] Levels of neurotransmitters remain elevated, and a hypermetabolic state may persist in the brain for several days to weeks after the initial injury.

Like patients with minor TBI, concussed patients frequently complain of headaches, dizziness, confusion, and amnesia for the traumatic event and have nonfocal neurologic examinations. Patients with concussion have more severe and persistent symptoms than those with uncomplicated minor TBI. In young children, acute symptoms of concussion differ from those in adults and may include restlessness, lethargy, confusion, or irritability. On presentation, concussed children may be vomiting, tachycardic, or appear pale. These signs and symptoms are usually completely resolved by 6 hours.

Approximately 300,000 yearly sports-related concussions are reported to the Centers for Disease Control and Prevention.[76] A study of concussed football players showed acute symptoms lasting at least 5 days, cognitive impairments lasting 5 to 7 days, and balance deficits lasting 3 to 5 days after concussion; 91% were back to their preinjury baseline by 7 days, but some had deficits on verbal fluency tests as long as 90 days after injury.[76]

The demonstrated period of neurodysfunction and the delayed return to cognitive and physical baseline that follows concussive impact have led to the development of several scoring systems to grade severity of concussions with the goal of determining when it is safe for an athlete to return to play. No single set of guidelines has emerged that has been universally accepted, but all are predicated on the concern about a period of vulnerability following impact. Football players sustaining concussion appear susceptible to an additional concussion, with the majority of reinjury occurring within 10 days after the first injury. This is variably attributed to balance defects, delayed reflexes, delayed speed of information processing, or simply because of continued exposure to collision sports.[75,76]

The *second impact syndrome* (SIS) occurs when an athlete sustains a second concussion before being completely asymptomatic from the first and then experiences a rapid, usually fatal, neurologic decline. It is postulated that persistent neurochemical disruptions and altered autoregulatory mechanisms after a first injury make the brain particularly vulnerable to marked brain swelling and subsequent herniation after a seemingly minor second impact. Although the existence and frequency of the SIS are controversial and debated in the sports medicine literature, its serious implications affect subsequent management decisions regarding head-injured athletes and others with concussion.[67,74,75] All current recommendations for return to play after a sports-related concussion state that players with concussion should not return to play for at least 1 week after they have become asymptomatic. This is usually increased to at least a symptom-free month if an LOC or prolonged post-traumatic amnesia occurred at the time of concussion.

Almost all patients with minor TBI will have rapid and complete resolution of their symptoms,[77] and there is currently no good evidence that uncomplicated minor TBI leads to long-term sequela.[68] However, a subset of patients with concussion report symptoms that persist for long periods after trauma. These persistent symptoms are called the postconcussive syndrome (PCS). The incidence of PCS is reported to be 10 to 25%,[14,68,78] but these estimates are based on inpatient studies and are therefore likely to be high.

The most common delayed or persistent postconcussive complaints are headache, sensory sensitivity, memory or concentration difficulties, irritability, sleep disturbances, and depression. It was long believed that persistent postconcussive symptoms were psychosomatic, litigious, or factitious, and it is likely that the manifestation and expression of PCS depend on factors in addition to injury severity, such as preinjury physical and mental health.[68] However, the presence of abnormalities on functional imaging and with sophisticated neuropsychometric testing suggests a pathophysiologic basis for PCS.[14,79] Studies of concussed athletes (for whom preinjury baseline data are available) show that the cognitive domain most frequently involved in PCS is memory.[14] Dizziness occurring early after trauma is associated with a prolonged PCS.[72]

Management and Disposition

The management decisions faced by the emergency physician are the same as those addressed when evaluating all patients with apparently minor TBI: extent of workup to initiate in the

emergency department and whether the patient can be safely discharged home. Emergency department patients who have a sports-related concussion should probably not be allowed to return to play from the emergency department; current recommendations are for a gradual progressive return to play.[13] Many authorities suggest follow-up at 1 week to determine the duration of symptoms and when the patient can safely return to sports. The possibility of PCS should be considered in all concussed patients, regardless of their initially benign presentation, and it may be prudent to suggest scheduled primary care follow-up for reassessment if symptoms persist.

PEDIATRIC HEAD INJURIES

Epidemiology

Approximately 650,000 children ages 0 to 19 years are emergently evaluated yearly in the United States for head trauma, with approximately 65,000 hospital admissions and 7500 fatalities.[1] TBI accounts for the largest source of childhood mortality and morbidity after trauma. In children, transportation-related injuries or falls account for most head trauma. Child abuse is a common etiology of head injury in young children. Duhaime and colleagues[80] found that nearly 25% of head-injured children younger than 2 years of age had inflicted injuries. In head-injured children younger than 1 year of age, as many as 66% of all injuries and 95% of severe injuries may be nonaccidental.[81]

Pathophysiology

Until the cranial sutures close, children's skulls are more distendable than those of adults. As a result, young children may often sustain less TBI after head trauma than adults with comparable nonfatal mechanisms of injury.[82] However, children appear to have an age-dependent brain vulnerability. Very young children (younger than 1 year) have higher mortality after head trauma than older children with the same severity of injury.[82] Many factors contribute to this. Medical attention is often delayed in children with nonaccidental injuries. Because of limited language and comprehension, an accurate formal neurologic examination in young children is sometimes difficult. Medical personnel tend to underestimate the extent of the injuries in small children and are often reluctant to initiate invasive procedures that may be necessary to aid in the diagnostic workup, such as IV access for sedation in CT scanning.

The types of TBI sustained after head trauma in children differ from those in adults. Children have fewer traumatic mass lesions (with the exception of subdural hematomas in the very young), fewer hemorrhagic contusions, more diffuse brain swelling, and more diffuse axonal injury.[83] Of head-injured patients younger than 20 years of age who talk and deteriorate, 39% have brain swelling only (i.e., no mass lesions), whereas 87% of patients older than 40 who talk and deteriorate have mass lesions.[60]

Clinical Features

As with adults, an accurate description of the mechanism of injury, the appearance of the child immediately before and after the injury, and subsequent events can provide useful information to assist in the evaluation and management of the acutely head-injured child.

In principle, the acute neurologic assessment of head-injured children is the same as that of adults. Pupillary responsiveness and size, corneal reflexes, the presence of a gag or cough reflex, and spontaneous motor movements provide baseline neurologic information that can be followed over time. Additional neurologic assessment can be more challenging. Because of its reliance on developed language skills and the patient's attention and cooperation, the GCS is difficult to apply to children younger than 5 years of age. Modified scales have been developed, but none has been rigorously validated; as yet, no universally accepted coma scale exists for children.[82] Mental status changes, which may be the first symptom of head injury, are difficult to evaluate in children, and often the head-injured toddler has no deficit except irritability.

Children with severe or moderate head injury are clinically similar to adults with these degrees of injury, although children have an increased incidence of post-traumatic seizures after severe head injury. Infants appear to be at especially high risk for post-traumatic seizures.[84] Overall, up to 6% of all head-injured children and 35% of severely head-injured children have early (i.e., within the first week) post-traumatic seizures.[82] Most seizures occur within the first 24 hours and do not predict seizures later in the post-traumatic period. However, early post-traumatic seizures can exacerbate secondary brain injury. Although prophylactic use of anticonvulsants is not recommended to prevent late post-traumatic seizures, acute anticonvulsant prophylaxis is a treatment option in severely head-injured children to prevent early post-traumatic seizures.[44]

Children who sustain minor head trauma often have more pronounced physical signs and symptoms than adults. Despite apparently trivial trauma, children may appear pale, be lethargic, and have frequent emesis and complaints of headaches and dizziness. Concussive injuries in children produce two unique clinical circumstances. Many children experience a brief *impact seizure* at the time of relatively minor head injury. By the time the child is evaluated, he or she is at baseline neurologic function. Impact seizures do not appear to predict subsequent early post-traumatic seizures. However, a post-traumatic impact seizure may confuse the initial assessment of the severity of the head injury and prompt a more aggressive workup than needed. *Postconcussive blindness*, another serious complication of concussive injuries in children, is usually associated with impact to the back of the head. Children experience a temporary loss of vision that can persist from minutes to hours before normal vision returns.

The clinical presentation of post-traumatic *intracranial lesions* in infants can be extremely subtle, especially in those younger than age 6 months. Often, these lesions are associated with scalp injuries and skull fractures but no other symptoms.[82,85] Toddlers are also difficult to assess; the only symptom of an intracranial injury may be irritability. Recent guidelines for the management of head injury in children younger than 2 years of age allow risk stratification and are summarized in Box 38-4.[85,86] Recommendations are also offered regarding the emergency department workup in these very young children.

Inflicted head injury is the most common cause of head injury deaths in infants.[87] Child abuse must be considered in all children with unexplained head injuries or injuries not consistent with the history provided. For example, children who experience low-energy mechanisms of injury (i.e., a short-distance fall) seldom sustain skull fractures; a finding of a fracture should therefore prompt consideration of abuse.[88] The *shaken baby syndrome* involves an acceleration-deceleration brain injury, with the moving brain striking against the interior of the skull. This occurs most often in children younger than age 1 year. Patients present with a broad range of symptoms,

BOX 38-4 MINOR HEAD TRAUMA RISK STRATIFICATION IN CHILDREN YOUNGER THAN AGE 2 YEARS [85,86]

High Risk: CT Recommended for All
Decreased mental status
Focal neurologic findings
Signs of depressed or basilar skull fractures
Acute skull fracture by clinical examination or skull radiographs (if already obtained)
Irritability
Bulging fontanel
Seizure
Vomiting (5 or more times)
Age <3 months
LOC >1 min

Intermediate Risk
CT scan or observation recommended
3 or 4 episodes of vomiting
Transient LOC (<1 min)
History of lethargy or irritability, now resolved
Behavior not at baseline
Nonacute skull fracture (injury more than 24 hr old)

Either CT or SR or observation recommended
High-force mechanism
Fall onto a hard surface
Scalp hematoma
Unwitnessed trauma
Vague history with physical signs of trauma

Low Risk: Observation Recommended
Low-energy mechanism with no signs and symptoms 2 hr after trauma

CT, computed tomography; LOC, loss of consciousness; SR, skull radiograph.

from nonspecific complaints to seizures and coma. Classically described findings include retinal hemorrhages, subdural hematomas, subarachnoid blood, and no signs of external trauma.[88]

Diagnosis and Management

As with adults, pediatric head-injured patients should be assessed for other major trauma and assumed to have cervical spine injury until proved otherwise. Goals of emergency department management are also generally the same: to prevent secondary injury and systemic insults, to prevent increasing ICP, and to detect traumatic mass lesions requiring emergency surgery.

Children with severe TBI who are transported directly to a trauma center have better outcomes than those transported to nontrauma hospitals.[44] It is essential that hypoxia be avoided to decrease the likelihood of secondary brain injury. Hypoxia and hypoventilation are common in pediatric head-injured patients, and they develop more rapidly in children than in adults. In children with GCS less than 8, airway management should be aggressive to prevent hypoxia, aspiration, and hypercarbia and to allow mild hyperventilation if the patient has signs of herniation. There is no evidence to support the advantage of out-of-hospital intubation over bag-valve-mask ventilation of pediatric patients with TBI; scene time should not be prolonged with multiple attempts at endotracheal intubation.[44]

Hypotension should be identified and corrected as soon as possible to ensure adequate cerebral perfusion pressure. There is no evidence to suggest that aggressive fluid resuscitation exacerbates cerebral edema in head-injured children. Occult blood loss from multiple trauma should be considered as a possible cause of hypoperfusion. Spinal injury causing shock should also be considered. In children, unlike adults, hypovolemic hypotension can occur because of head trauma. Hypotension from intracranial bleeding can occur in children younger than 1 year of age with a large linear skull fracture and an underlying large epidural hematoma.[82]The intracranial blood can seep through the fracture and produce a large galeal or subperiosteal hematoma. Hypotension from intracranial bleeding can also occur in a child with hydrocephalus and a functioning shunt. Blood may accumulate without much evidence of increased ICP. Scalp lacerations can also produce significant hemorrhage and subsequent hypotension.

Up to 80% of children with severe head trauma have elevated ICP.[82] In infants, a bulging fontanel suggests elevated ICP. Other signs of elevated ICP include bradycardia, papilledema, declining level of consciousness, and seizures. When increased ICP is indicated by physical examination, methods to reduce ICP should be initiated. As with adults, acute hyperventilation has immediate effects but is never indicated for prophylaxis or for prolonged management of increased ICP.[44] Hyperosmolar therapy is effective at reducing ICP. Although efficacy studies were based on adults, mannitol at doses of 0.25 to 0.5 g/kg has become a mainstay in the treatment of elevated ICP in children with severe TBI. Several studies support the effectiveness of hypertonic saline in lieu of mannitol for elevated ICP in pediatric head-injured patients. Treatment is with a continuous infusion of 3% normal saline at between 0.1 and 1.0 mL/kg body weight, titrated to effect.[18] Severely head-injured children are less likely to have a surgically amenable lesion than adults. Because diffuse brain swelling is the most common finding in severely head-injured children, emergency burr holes are generally ineffective.

When considering minor head injury in children, it is important to differentiate children younger than age 2 years and older children. Children younger than age 2 years with traumatic brain injuries are often difficult to assess and may have subtle clinical findings. In general, the literature supports the conclusion that younger patients are at higher risk for intracranial injury.[89] One clinical sign of potential brain injury in children younger than age 2 years is the presence of a scalp hematoma, especially a large parietal scalp hematoma.[1] In an observational cohort study involving children with low risk for brain injuries, scalp hematomas were present in 93% of children 2 years old or younger who had brain injuries.[90]

The CT scan is the diagnostic imaging modality of choice in the evaluation of moderate or severe pediatric TBI. It should also be strongly considered in pediatric patients with high-risk minor TBI.[85,86,90] However, potential risks are associated with childhood exposure to radiation. Children are more sensitive to radiation than adults because of rapidly dividing cells occurring during growth. The younger the child, the more potential risk. Increased rates of cancer and decreased cognitive performance and academic development have been associated with radiation doses similar to that of a single head CT scan.[85] An additional safety concern is the frequent need to sedate young children in order to obtain an adequate imaging study. In these circumstances, the risks of radiation exposure and sedation should be weighed against the likelihood of an intracranial lesion in the child with minor head trauma.

Many attempts have been made to derive clinical prediction rules for high-risk minor TBI in children. However, unless there is both high sensitivity and high specificity, such rules may actually result in an increased number of CT scans being

performed. Clinical predictors for increased risk of intracranial lesions in children with minor TBI have been described and can help with risk stratification. A meta-analysis including more than 22,000 children suggested that the presence of a skull fracture, focal neurologic signs, documented loss of consciousness, and a presenting GCS score of less than 15 were statistically associated with TBI.[91,92] Many authorities also include a history of protracted vomiting, abnormal mental status or lethargy, obvious scalp hematomas in children 2 years old or younger, and progressively worsening headache.[85]

The use of skull radiographs in the diagnostic workup of head-injured children is controversial but may be appropriate in some circumstances. As with adults, when a CT scan is indicated, skull radiographs are not necessary. Up to 11% of children younger than age 2 years will sustain a skull fracture associated with head trauma, and 15 to 30% of these will have TBI. Therefore, in children younger than age 2 years, a skull fracture is a predictor of TBI.[93] The presence of a skull fracture in children significantly increases the likelihood of intracranial pathology; conversely, a negative radiographic skull screen does not guarantee the absence of TBI. Parietal skull fractures are the most common. Often, fractures occur in infants who sustain relatively minor head injury. Skull films may be useful as a screening tool in determining the need for a CT scan, especially in children 2 years old or younger whose neurologic examination is difficult to obtain and interpret. In alert children younger than age 2 years with minor head injury, a low-risk history, a normal physical examination that includes a normal neurologic and mental status examination appropriate for age, and a scalp hematoma, skull radiographs may be a useful screen.[85] If the skull radiograph is negative for a fracture, a CT scan may be unnecessary. If the skull radiograph shows a fracture, CT imaging is indicated.

In older children, skull radiographs are rarely useful unless a specific lesion is suspected, such as a depressed skull fracture or a penetrating foreign object. Skull fractures are more clinically significant in children than in adults. Fractures, especially complex stellate or multiple injuries, are often seen in abused children, and skull films should be obtained if abuse is suspected. *Ping-pong fractures* occur with concentrated forces that indent the skull. These fractures are unique to infants and appear as multiple indentations in the skull with no significant bone discontinuity. Skull fractures are common in children who have sustained deep scalp lacerations or who have a large scalp hematoma.

Leptomeningeal cysts or *growing skull fractures* are delayed complications of linear skull fractures in infancy. If a tear in the dura accompanies the linear fracture, the meninges may fill with CSF and prolapse through the fracture margins, thus preventing fracture healing.[85] These cysts can grow in size and have the potential to cause a mass effect. If a linear fracture is found by skull radiography, close follow-up is indicated to assess for this delayed complication.

Overall, children who sustain severe head injury have lower mortality and a better neurologic outcome than comparably injured adults. This is probably because of the neuroplasticity of the young brain; however, in children younger than age 2 years, the prognosis after severe head injury is poor.[89] Very young children have immature cerebrovascular autoregulation, which increases the risk of cerebral edema formation. The immature brain has increased susceptibility to permanent injury because of incomplete myelination.

The emergency evaluation of children with minor head injury is especially challenging, given their potentially dramatic presentation and the added difficulty of obtaining an accurate neurologic assessment. Evidence-based consensus guidelines have been proposed for the evaluation and management of minor head injury in children.[85,86] Disposition of pediatric patients with minor head injury is summarized in Box 38-5. Parents should be educated about the warning signs and symptoms of delayed complications of minor head trauma.

BOX 38-5 Recommendations for Management of Minor Closed-Head Trauma in Children

No LOC, Presenting GCS Score of 15
Thorough history and PE
If low-risk traumatic mechanism and classification (see Box 38-3) and normal examination, observation (up to 24 hr) by competent caregiver

Brief LOC (<1 Min), Presenting GCS Score of 15
Thorough history and PE
If low-risk traumatic mechanism and classification (see Box 38-3) and normal examination, observation (up to 24 hr) by competent caregiver
Consider CT scanning if history and/or examination suggest high-risk minor head trauma (see Box 38-3). Skull films should be considered only if CT scanning not available

Presenting GCS Score of 14
Strong consideration for CT scanning

Imaging Recommended
Children <3 months old
- Consider CT scanning unless asymptomatic, low-risk history and PE (see Box 38-3), no scalp hematoma, and trivial traumatic mechanism

Children 3 months to 2 years
- Normal neurologic examination, no symptoms, no scalp hematoma: no imaging
- Normal neurologic examination, no symptoms, scalp hematoma: skull radiographs
- If skull films positive for fracture, follow with CT scanning
- Abnormal neurologic examination, moderate- or high-risk history or PE findings (see Box 38-3): CT scanning

Children >2 years
- Normal neurologic examination, no symptoms, no scalp hematoma: no imaging
- Normal neurologic examination, symptoms, low- or moderate-risk history or PE findings (see Box 38-3): consideration of CT scanning
- Abnormal neurologic examination and/or high-risk history or PE findings (see Box 38-3): CT scanning

CT, computed tomography; GCS, Glasgow Coma Scale; LOC, loss of consciousness; PE, physical examination.

PENETRATING HEAD INJURIES

Epidemiology

Penetrating brain injury (PBI) occurs at a rate of 12 per 100,000 population and can be sustained by missile injuries or impalement.[94] The United States has the highest penetrating head injury rate among developed countries in the world, with the most common cause being gunshot wounds (GSWs). These dramatic injuries are increasing in frequency, and the neuroscientific understanding of the complicated cerebral events that occur with penetrating head injury does not yet equal our understanding of the pathophysiology of blunt injuries.

Civilian GSWs to the head account for approximately 21,000 deaths per year, and up to 66% of all patients who sustain a GSW to the head are dead at the scene.[95] Overall, the mortality caused by a GSW to the head is estimated to be 90%.[96] If the patient is hemodynamically stable, has not sustained secondary systemic insults such as hypoxia or hypotension, has no expanding mass lesions from the missile injury, and has not ingested intoxicants that may interfere with assessment, prognosis after a GSW to the head can be predicted by the presenting GCS and pupillary responsiveness.[97] If the presenting GCS is less than 5, mortality approaches 100%. If the presenting GCS is greater than 8 and the pupils are reactive, survival approaches 75%. Survivors of GSW to the head tend to do well, with up to 60% returning to their former employment.[97]

Pathophysiology

Missile injuries to the head can result in several different patterns of damage. *Tangential wounds* are caused by an impact that occurs at an oblique angle to the skull. If the missile has high velocity but low energy, it can travel around the skull under the scalp without passing through the skull. Intracranial damage, primarily cortical contusions, can occur at the initial site of impact because of pressure waves generated by the impact. In one study, 24% of patients with tangential GSWs also had intracranial hemorrhage, and 16% sustained skull fractures.[98] *Perforating wounds* are usually caused by high-velocity projectiles, which cause through-and-through injuries of the brain with an entrance and an exit wound. This type of injury is largely discussed within the context of military GSWs to the head. In cases of complete traversal (through-and-through) GSW to the head, the entrance wound is usually smaller than the exit wound.

Penetrating missile wounds are produced with moderate- to high-velocity projectiles discharged at close range. The majority of the civilian PBI literature deals with penetrating missile wounds.[96] The penetrating object may travel through the entire skull, bounce off the opposite inner table of the skull and ricochet within the brain, or stop somewhere within the cranial cavity. Bullets that penetrate the skull do not travel in a straight path. The wounding capacity of a firearm is related to the kinetic energy of its missile on impact and how much energy is dissipated in the tissues. Low-velocity missiles tend to be deflected by intracranial structures. The final track is therefore erratic and occasionally bears no relation to the exit or entrance site of the missile. High-velocity missiles can project straight through the tissues and easily fracture bones. Flight stability and the angle at which the bullet strikes its target affect the path through the brain. Within tissue, destabilizing motions include deviation of the longitudinal axis of the bullet from a straight line (yaw), forward rotation of the bullet around its center of mass (tumbling), and oscillatory motion of the bullet axis around its center of mass (rotation). As the bullet passes through the brain, a tissue cavity is created. This cavity can be as much as 10 times the diameter of the missile. A percussion shock wave is also created, lasting 2 msec but causing little tissue destruction.[96]

The morbidity and mortality from missile injuries to the head depend on the intracranial path, speed of entry, and the size and type of the penetrating object. Projectiles that cross the midline or the geographic center of the brain, pass through the ventricles, or come to rest in the posterior fossa are associated with extremely high mortality.[94] High-velocity wounds are associated with greater mortality than low-velocity injuries. Large missiles or missiles that fragment within the cranial vault are usually fatal. The design of the bullet and its fragmentation potential (capacity to deform or fragment) also contribute to final tissue destruction and patients' morbidity and mortality.

Many GSWs to the head are intentionally self-inflicted injuries. The percentage of penetrating head injuries caused by self-inflicted GSWs ranges from 13 to 88%.[97] Characteristics of self-inflicted GSWs include injury on the dominant side, powder burns at the entrance site, and large stellate scalp lacerations caused by dissection of the subgaleal layer by exploding gases released close to the scalp. In suicide attempts, GSWs to the head tend to traverse the midline in the coronal plane and often involve major vascular structures. If the self-inflicted GSW has an entrance through the mouth, injury to the hard palate may occur with potential upper airway compromise. The careful aim and close range of self-inflicted GSWs to the head make these injuries particularly devastating; mortality is higher than with non-self-inflicted penetrating injuries, and odds ratios of death vary between 1.63 and 5.83.[97]

Clinical Features

Physical assessment of the patient with a missile wound to the head focuses on the presenting GCS and pupillary responsiveness. In addition to the physical damage to brain tissue caused by the penetrating injury, other devastating physiologic changes occur immediately after injury. ICP increases, the BBB breaks down, CBF is altered, and cerebral edema develops. Cerebral autoregulation is lost, and CPP may fall.

Management

The emergency department management is directed at reducing the occurrence of the secondary systemic insults of hypoxia and ischemia, with emergent intervention if signs of herniation syndrome develop and the patient is viable. Management should be aggressive until the prognosis can be established by examination and neuroimaging data. When penetration of the cranial vault is established, the patient should be intubated. If the physician waits for coma before intubating the patient, mortality approaches 100%.[99]

Emergency treatment should include IV antibiotics because penetrating missiles are contaminated with skin, bone, and hair. Tissue contamination may be widespread because of the cavitation caused by the missile as it passes through the brain.[100,101] Approximately 90% of all CNS infections associated with penetrating TBI injuries occur within 6 weeks. Most neurosurgeons do not automatically débride bone and missile fragments due to a growing body of literature that shows no evidence that removal of these foreign bodies decreases infection rate.[15]

Between 30 and 50% of patients with PBI develop seizures; 10% of these occur in the first week.[15] Anticonvulsants should be given in the acute setting to prevent early post-traumatic seizures in the patient with PBI, especially if the patient is to be transported to another institution after acute stabilization. Anticonvulsants should not be given beyond the first week after PBI because this has not been shown to prevent the development of late seizures.

Skull radiographs may be useful in determining the number of penetrating fragments and their track. A CT scan defines the precise location of the missile, its intracranial path, the presence of bone or missile fragments, extra-axial or intracerebral blood collections or other traumatic lesions, and pneumocephalus. CT scanning is the radiologic test of choice for PBI.[101] Pneumocephalus is often associated with missile wounds that penetrate the sinuses but can be caused by free air sucked into the penetration cavity behind the projectile.

When a penetrating head injury is caused by *impalement*, the penetrating object should be left in place to be removed at surgery. A skull radiograph shows the size of the object, the angle of impalement, and the depth of penetration. Angiography may be indicated to better discern location referable to key vascular structures.

COMPLICATIONS AFTER HEAD INJURY

Neurologic Complications

Seizures

Post-traumatic seizures are relatively common in the acute or subacute period. Acute post-traumatic seizures are usually brief and are probably caused by transient mechanical and neurochemical changes within the brain. After the acute seizure, the patient often has no additional seizure activity. In the subacute period, 24 to 48 hours after trauma, seizures are caused by worsening cerebral edema, small hemorrhages, or penetrating injuries. Post-traumatic seizures are common in children and can be precipitated by relatively minor head injury.[84] Acute post-traumatic seizure prophylaxis in the emergency department is recommended for some head-injured patients even if they have not had a seizure (see Box 38-2).[53,102] This is especially important in patients who will have neuromuscular blockade to facilitate management or transfer because the clinical manifestations of seizures are lost in these patients. Phenytoin (18–20 mg/kg) is used as a first-line agent for prophylaxis. The decision to maintain the head-injured patient on long-term anticonvulsant therapy during the recovery period depends on the patient's subsequent course. Long-term seizure prophylaxis is not indicated for all patients who have had post-traumatic seizures in the acute or subacute period. The utility of prophylactic anticonvulsants to prevent late post-traumatic seizures has not been proved, and their use is not recommended.[102]

Central Nervous System Infections

Meningitis after Basilar Fractures. Post-traumatic meningitis is caused by a variety of microbes, depending on the portal of bacterial entry. Patients present with typical signs and symptoms of meningitis, including fever, altered mental status, and occasional focal neurologic signs. In patients with a CSF leak after basilar fracture, early meningitis (i.e., within 3 days of injury) is usually caused by pneumococci. Ceftriaxone or cefotaxime is a reasonable antibiotic choice with the addition of vancomycin. Gram-negative organisms often cause meningitis that develops more than 3 days after trauma.[103] A third-generation cephalosporin, with nafcillin or vancomycin added to ensure coverage of *Staphylococcus aureus*, should be started. In children, post-traumatic meningitis may be caused by *Haemophilus influenzae*. Prophylactic antibiotics are not currently recommended in the acute setting in patients with CSF leaks caused by basilar skull fractures.[103]

Brain Abscess. Brain abscesses develop infrequently after penetrating missile injuries to the head. Abscesses can also develop after open depressed skull fractures if bone fragments are not removed or as a postoperative complication. Post-traumatic CSF fistulae and fractures that disrupt air-filled sinuses predispose to the formation of brain abscesses. Clinical manifestations include headaches, nausea, vomiting, declining mental status, signs of increased ICP, or new focal neurologic findings in patients who had been improving after trauma. Occasionally, nuchal rigidity, hemiparesis, or seizures may be present. Systemic signs are often subtle, and CSF leukocytosis may be absent.

Contrast-enhanced CT scanning makes the diagnosis of brain abscess. A ring pattern with a low-density center is characteristic. The enhanced ring represents surrounding altered vascular permeability and therefore is also seen in the cerebritis stage early in abscess formation. Lumbar puncture is often not helpful and should not be performed in the patient with signs of increased ICP (e.g., headache, vomiting, and papilledema).

The treatment of brain abscess is usually operative drainage. The patient with cerebritis may respond to IV antibiotics but requires close monitoring with repeated CT scans. Common organisms isolated from post-traumatic abscesses are *S. aureus* and gram-negative aerobes.[103]

Cranial Osteomyelitis. Cranial osteomyelitis can occur after penetrating injury to the skull. The clinical manifestations include pain, tenderness, swelling, and warmth at the infected site. More than 50% of cases are obvious on plain skull radiographs.[103] Technetium bone scans can help in the diagnosis when the skull radiographs are negative, but false-positive bone scans occur in patients with previous trauma or craniotomy. Adding a gallium scan helps to differentiate infection from other causes of a positive technetium scan. Patients with post-traumatic cranial osteomyelitis require surgical débridement and removal of the infected bone. Antibiotic choice is determined by culture results. If systemic symptoms are present, an underlying subdural or epidural empyema is often present.

Medical Complications

Disseminated Intravascular Coagulation

The injured brain is a source of tissue thromboplastin that activates the extrinsic clotting system. Disseminated intravascular coagulation (DIC) can develop within hours after any injury disrupting brain tissue. It has been detected in nearly all patients with severe TBI.[65] DIC increases morbidity and mortality after severe head trauma as well as the risk of delayed intracranial hemorrhage. If a stable patient with DIC suddenly deteriorates, a repeat CT scan should be obtained to rule out hemorrhage.

The extent of tissue destruction determines the degree of DIC that develops. The diagnosis is based on abnormalities in international normalized ratio, prothrombin and partial thromboplastin time, platelets, plasma fibrinogen levels, and fibrin degradation products. Patients with coagulopathy or abnormal platelet function require interventions to correct these.

Neurogenic Pulmonary Edema

Neurogenic pulmonary edema can develop from minutes to days after head trauma. This noncardiac pulmonary edema probably results from altered hydrostatic forces and microvascular permeability directly caused by brain injury. Lowering the ICP appears to reverse the neurogenic stimulation that causes this edema.[104]

Cardiac Dysfunction

A variety of cardiac rhythm, rate, and conduction abnormalities are detected after head injury. These abnormalities can be life threatening and require aggressive therapy. In addition, adequate cardiac output is essential in head-injured patients to ensure cerebral perfusion. Many head-injured patients with cardiac dysfunction have concurrent myocardial injury from underlying disease or from chest injury. However, brain injury

can cause primary cardiac dysfunction. Cardiac rhythm abnormalities have been reported in up to 70% of all patients with subarachnoid hemorrhage (SAH) and more than 50% of all patients with intracranial hemorrhage.[28] In SAH, the cardiac dysrhythmias may result from autonomic nervous system dysfunction that subsequently affects ventricular polarization. High levels of circulating catecholamines have been measured in head-injured patients, with increased sympathetic nervous system activation.[28]

The most common cardiac dysrhythmia after head injury is *supraventricular tachycardia*, but many other rhythms have been observed. Findings on the electrocardiogram include diffuse large upright or inverted T waves, prolonged QT intervals, ST segment depression or elevation, and U waves. The primary goal in the emergency management of cardiac dysfunction after head trauma is ensuring adequate tissue perfusion and avoiding hypoxia. Dysrhythmias in head-injured patients often resolve as ICP is reduced.[28] Standard advanced cardiac life support protocols should then be used because concurrent cardiac injury may also be present in multiply traumatized patients.

SPECIFIC INJURIES

Scalp Wounds

Scalp lacerations are extremely common after head injury and may be a source of significant bleeding because hemostasis may be difficult to achieve. Methods include direct digital compression of the bleeding vessel against the skull, infiltration of the wound edges with lidocaine with epinephrine, and ligation of identified bleeding vessels. If the galea is lacerated, it can be pulled up with a clamp and its edges folded over the lacerated skin edges to tamponade the bleeding vessels. Raney scalp clips applied to the edges of the wound are also effective. In stable patients, quick closure of the wound, after proper débridement and irrigation, is the most effective way to stop a bleeding scalp laceration and prevent the tissue crush injury that may occur if other compressive methods are used for too long. Obviously, in unstable patients, higher priority interventions take precedence over wound care.

When hemostasis is obtained, the wound should be irrigated to rinse away any debris. The emissary vessels of the subgaleal layer of the scalp drain directly into the diploe veins of the skull. These in turn drain into the venous sinuses. Contaminated or infected scalp wounds therefore have the potential to cause serious intracranial infections. Blood clots and other debris should be removed and the galea and underlying cranium palpated to detect any remaining debris, disruptions, or bone step-offs. Shear injuries to the scalp may deposit contaminants at sites distant from the apparent injury. The complexity of stellate lacerations often interferes with thorough inspection and débridement; stellate lacerations are particularly susceptible to infection. Digital exploration of a scalp wound should be carefully performed; if it is done too vigorously, comminuted or depressed bone pieces may be depressed further, and the examiner's finger is at risk for laceration.

It is easy to confuse a disruption in the galea or a tear in the periosteum with a skull fracture. The base of the laceration should therefore be directly visualized. Clipping away a small area of hair parallel to the edges of the wound may facilitate this. Alternatively, an antibiotic ointment can be applied to the hair immediately surrounding the wound and used to plaster the hair away from the injury site. If the laceration begins on the forehead and extends upward beyond the hairline, surrounding hair should not be removed. Removal obliterates a useful landmark for cosmetic closure and may result in malalignment of the two laceration edges. If hair is accidentally embedded within the repaired laceration, it can delay healing by producing an inflammatory reaction or by serving as a nidus of infection.

Disruption of the galea usually results in a gaping scalp laceration. Large lacerations of the galea must be closed to prevent the edges of the wound from pulling apart as the muscles within the galea contract. The skin, dermis, and galea can usually be repaired in a single layer with interrupted or vertical mattress sutures of 3-0 nylon or polypropylene.[105] In scalp lacerations in which the galea is not involved, staples can be used in the repair.

Because of the rich blood supply of the scalp, even very large scalp avulsions can survive. If the avulsion remains attached to the rest of the scalp by a tissue bridge, it should be reattached to the surrounding tissue. If the avulsion is completely detached from the scalp, it should be treated as any other amputated part and reimplanted as soon as possible.

Scalp abrasions are often contaminated with pieces of dirt or other debris. The wound should be cleaned as thoroughly as possible and inspected for puncture wounds or other areas that penetrate beyond the superficial layers of the skin to ensure the removal of unsuspected foreign bodies. A careful inspection often reveals a small scalp laceration within the abraded area. Antibiotics are usually not needed for carefully managed scalp wounds because rapid healing is facilitated by the rich blood supply of the scalp.

Skull Fractures

Clinical Assessment and Significance

Skull fractures are local injuries caused by direct impact to the skull. The presence of a skull fracture does not always indicate underlying brain injury. However, the force required to fracture the skull is substantial, and all cases of skull fracture must be carefully evaluated to ensure that no additional injury is present. With increasing severity of head injury the likelihood of skull fracture increases, and the presence of a skull fracture after trauma increases the likelihood of having a TBI. It is often difficult to predict the presence of a skull fracture by clinical examination, and if this can be done, it is likely that substantial underlying brain injury is also present. The pattern, extent, and type of skull fracture depend on the force of the impact applied and the ratio of the impact force to the impact area. The fracture usually starts at the point of maximum impact.

Clinically significant skull fractures result in intracranial air and pass through an air-filled space (e.g., sinus), are associated with an overlying scalp laceration (open skull fracture), are depressed below the level of the skull's inner table, or overlie a major dural venous sinus or the middle meningeal artery.[106]

Plain radiographs are most useful in demonstrating a depressed skull fracture, the depth and extent of a penetrating injury, or the presence of an intracranial foreign body. A CT scan with bone windows also demonstrates these findings; therefore, patients undergoing CT do not require skull radiographs.

Linear Fractures

A linear skull fracture is a single fracture that goes through the entire thickness of the skull. Linear skull fractures are clinically important if they cross the middle meningeal groove or

major venous dural sinuses; they can disrupt these vascular structures and cause the formation of epidural hematomas. Most other linear skull fractures are not clinically significant.

It is sometimes difficult to distinguish linear skull fractures demonstrated on radiographs from cranial sutures. In general, fractures are more lucent than vascular grooves and sutures. Sutures are usually less than 2 mm wide in adults; fractures are often 3 mm or greater in overall width and tend to be widest in the midportion and narrow at each end.[106] Linear fractures are most common in the temporoparietal, frontal, and occipital regions of the skull and can usually be visualized on more than one radiographic view. In children, skull fractures heal within 3 to 6 months; in adults, complete healing may take up to 3 years.[106]

Sutural diastasis is the traumatic disruption of a cranial suture. In adults, sutural diastasis often involves the coronal or lambdoid sutures. Sutural diastasis usually occurs when a linear fracture extends into the suture line, and it is rare after sutures have undergone bone fusion.

Comminuted skull fractures are multiple linear fractures that radiate from the impact site. Usually, this injury suggests a more severe blow to the head than that producing a single linear fracture.

A linear *vault* fracture substantially increases the risk of intracranial injury. If any skull fracture is detected, a CT scan should be obtained, and the patient should be carefully observed for delayed complications of head trauma.

Depressed Fractures

Depressed skull fractures are clinically important because they predispose to significant underlying brain injury and to complications of head trauma, such as infection and seizures. When a depressed fracture occurs, traumatic impact drives the bone piece below the plane of the skull. The edges of the depressed portion of skull may become locked underneath the adjacent intact bone and fail to rebound into their previous position. As a result, the depressed piece of bone can penetrate tissue and lacerate the dura. Depressed skull fractures are usually caused by direct impact injury with small blunt objects, such as a hammer or a baseball bat. Most depressed skull fractures occur over the parietal or temporal regions. If the free piece of bone is depressed deeper than the adjacent inner table of the skull, most neurosurgeons consider this injury significant enough to require surgical elevation.

On skull radiographs, depressed fractures may be difficult to visualize. The free piece of bone demonstrates increased or double density because it often overlaps the nonfractured bone or it is viewed relatively rotated from the rest of the adjacent cranium. Tangential views of the skull may increase the ability to visualize the fracture.

Depressed skull fractures can often be felt with palpation of the skull beneath a scalp laceration. This examination should be done cautiously to avoid driving a depressed bone fragment deeper into the cranial tissue. The clinical examination for a depressed skull fracture may be misleading. The mobility of the scalp can result in nonalignment of the fracture with an overlying scalp laceration. As a result, the skull underlying the laceration may be normal, with the depressed area several centimeters away. Scalp swelling may also interfere with physical examination findings and hide any palpable bone defects. The signs and symptoms of a depressed skull fracture depend on the depth of depression of the free bone piece. Approximately 25% of patients sustaining a depressed skull fracture report LOC.[106] Neurologic deficits may be present, depending on the extent of underlying brain tissue injury.

A CT scan is indicated for patients with a history or physical examination that suggests a depressed skull fracture. The CT scan should include bone windows to determine the depth of depression and the presence of concurrent traumatic intracranial lesions. Patients with depressed skull fractures should be admitted for continued observation by a neurosurgeon.

Depressed skull fractures may increase the risk for developing seizures. Emergency department patients suspected of having a depressed skull fracture warrant prophylaxis for post-traumatic seizures, especially if they have an altered level of consciousness or require chemical paralysis. Depressed skull fractures may also increase the risk for meningitis.[106]

Basilar Fractures

Basilar fractures are linear fractures at the base of the skull. The fracture usually occurs through the temporal bone, with bleeding into the middle ear producing hemotympanum. Often, the fracture has caused a dural tear, which produces a communication between the subarachnoid space, the paranasal sinuses, and the middle ear. This offers a route for the introduction of infection into the cranial cavity and is suggested by a CSF leak.[103] As with linear skull fractures, a basilar fracture is not always associated with significant underlying brain injury; these fractures are the result of considerable impact force, however, and TBI must be ruled out.

Basilar fractures can compress and entrap the cranial nerves that pass through the basal foramina, can dislocate the bones of the auricular chain, and can disrupt the otic canal or cavernous sinuses, with subsequent injury to cranial nerves III, IV, and V. Fractures of the sphenoid bone can disrupt the intracavernous internal carotid artery, creating the potential for the formation of pseudoaneurysms or carotid venous fistulae. The diagnosis of a basilar skull fracture is based on associated clinical signs and symptoms (see Box 38-1).

Skull radiographs do not detect basilar fractures well. All patients with clinical evidence suggesting a basilar skull fracture should have a CT scan to define the fracture and to rule out concurrent intracranial pathology, and they should be admitted for observation. Because the basilar skull fracture may afford an entrance for bacteria, antibiotics are often considered. However, most CSF leaks resolve spontaneously with no complications in 1 week, and antibiotics generally are not given prophylactically during the first week of CSF rhinorrhea. If a patient with a previously diagnosed CSF leak returns to the emergency department with fever, the diagnosis of meningitis should be strongly suspected and appropriate workup (i.e., lumbar puncture) and antibiotic treatment initiated immediately. A rare but significant complication of basilar skull fracture is traumatic carotid cavernous fistula (TCCF). In a retrospective review, the overall incidence of TCCF in basilar skull fractures was 3.8%, with middle fossa basilar skull fractures having the highest association.[107]

Open Fractures

A skull fracture is open when a scalp laceration overlies a fracture. If the fracture has disrupted the dura, a communication exists between the external environment and the brain. A fracture that disrupts the paranasal sinuses or the middle ear structures is also considered open. An open skull fracture requires careful irrigation and débridement. Blind probing of the wound should be avoided because it can introduce contaminants into the wound and can further depress comminuted fracture pieces.

Diffuse Axonal Injury

Prolonged traumatic coma not caused by mass lesions, ischemic insult, or nontraumatic causes of coma is thought to result from diffuse axonal injury (DAI). DAI is a pathologic process in which axons are stretched and twisted by the same shear and tensile biomechanical forces that produce concussion. Effected axons are dispersed between areas of undamaged cells. Badly damaged axons become edematous and eventually begin to separate from each other, causing widespread disruption of cortical physiology and microanatomy in the white matter of the brain and brainstem. Complete separation of axons does not always cause cell death; acute uncoupling of cerebral blood flow and metabolism[70] and apoptosis are thought to be the primary factors linked to axonal cell death after DAI. Recovery depends on the reversal or correction of structural and physiologic abnormalities.[14]

DAI is thought to be the cause of persistent traumatic coma that begins immediately at the time of trauma; however, some patients with DAI may recover consciousness briefly before lapsing into prolonged coma. No specific acute focal traumatic lesions are noted on a head CT scan. MRI may be more sensitive in detecting subtle injury in DAI, but it is often not practical to perform MRI on critically injured patients. Occasionally, small petechial hemorrhages in proximity to the third ventricle and within the white matter of the corpus callosum or within the internal capsule of the brainstem are detected. DAI is the most common CT finding after severe head trauma, estimated to occur in 50% of all comatose head-injured patients.[108]

Because clinical diagnostic studies cannot predict the extent of the axonal damage, the severity of the injury is determined by the clinical course. Patients with *mild* DAI are in coma for 6 to 24 hours. Approximately one third of patients with mild DAI demonstrate decorticate or decerebrate posturing, but by 24 hours they are following commands.[108] The mortality in this group is 15% and is associated with infectious complications or concurrent intracranial injuries. Most patients who recover have mild or no permanent disabilities.

Moderate DAI is the most common clinical picture. Patients with moderate DAI are in coma for longer than 24 hours. Often, they are victims of falls or vehicular crashes and have associated basilar skull fractures. Patients may exhibit transient decortication or decerebration but eventually recover purposeful movements. On awakening, patients have prolonged severe post-traumatic amnesia and moderate to severe persistent cognitive deficits. Almost 25% die of complications of prolonged coma.[106]

Severe DAI is almost always caused by vehicular crashes. Patients remain in coma for prolonged periods and demonstrate persistent brainstem dysfunction (posturing) and autonomic dysfunction (e.g., hypertension and hyperpyrexia). Diffuse brain swelling subsequent to injury causes intracranial hypertension. Herniation syndrome can occur if elevated ICP does not respond to medical or surgical intervention. Some patients with severe DAI eventually awaken but are severely disabled. Some patients remain in a persistent vegetative state, but most with severe DAI die from their head injury. All patients with DAI present identically in coma. No early clinical predictor differentiates patients with mild, moderate, or severe DAI.

Contusions

Contusions are bruises on the surface of the brain, usually caused by impact injury. Most often, contusions occur at the poles and the inferior surfaces of the frontal and temporal lobes where the brain comes into contact with bone protuberances in the base of the skull. If the contusion occurs on the same side as the impact injury, it is a *coup injury*; if it occurs on the opposite side, the contusion is a *contrecoup injury*. Contusions also often develop in the brain tissue that underlies a depressed skull fracture. Multiple areas of contused tissue may be produced with a single impact, often in association with other intracranial injuries.

Contusions are produced when parenchymal blood vessels are damaged, resulting in scattered areas of petechial hemorrhage and subsequent edema. Contusions develop in the gray matter on the surface of the brain and taper into the white matter. Often, subarachnoid blood is found overlying the involved gyrus. With time, the associated hemorrhages and edema of a contusion can become widespread and serve as a nidus for hemorrhage or swelling, thus producing a local mass effect. Compression of the underlying tissue can cause local areas of ischemia, and tissue infarction is possible if the compression is significant and unrelieved. Eventually, these ischemic areas become necrotic, and cystic cavities form within them.

The clinical presentation of patients with contusions is frequently delayed. They may have sustained only a brief LOC, but the duration of post-traumatic confusion and obtundation may be prolonged. If contusions occur near the sensorimotor cortex, focal neurologic deficits may be present. Many patients with significant contusions make uneventful recoveries, but contusions may cause significant neurologic problems, including increased ICP, post-traumatic seizures, and focal deficits.

Non-contrast-enhanced CT is the best diagnostic test to discover contusions in the early post-traumatic period. These appear heterogeneous and irregular because of mixed regions of hemorrhage, necrosis, and infarction. Often, the surrounding edematous tissue appears hypodense. By post-trauma days 3 and 4, the blood located within the contusions has begun to degrade, and MRI becomes more useful.

Epidural Hematoma

Epidural hematomas (EDHs) are blood clots that form between the inner table of the skull and the dura. Most EDHs are caused by direct impact injury that causes a forceful deformity of the skull. Often, a fracture occurs across the middle meningeal artery, vein, or a dural sinus. The temporoparietal region is the most likely site for an EDH.[24] The high arterial pressure of the bleeding vessel dissects the dura away from the skull, permitting the formation of the hematoma.

An EDH is usually unilateral, and 20% of patients have other intracranial lesions, usually subdural hematomas or contusions.[24] The deterioration of a patient who has an EDH from arterial bleeding can be rapid and dramatic. Because of their rapid formation, EDHs from arterial bleeding are usually detected within hours after injury and often earlier in children. EDHs that develop from a dural sinus tear develop more slowly, and clinical manifestations may be delayed, with resultant delays in detection.

EDH is primarily a disease of the young and accounts for 0.5 to 1% of all patients who have experienced TBI.[24] EDHs are rare in elders and children younger than 2 years of age because of the close attachment of the dura to the skull in both patient populations. The classic presentation of an EDH is described as head trauma producing a decreased level of consciousness followed by a "lucid" interval. Although the patient's consciousness is less decreased during the lucid interval, a completely normal mental status may not return before a second episode of decreased consciousness occurs. The lucid interval is not pathognomonic for an EDH and occurs in patients who sustain other expanding mass lesions. In fact, only approx-

imately 30% of patients with EDHs present classically.[109] The development of symptoms and signs of EDH is entirely dependent on how quickly the EDH is developing within the cranial vault. Patients with an EDH often complain of a severe headache, sleepiness, dizziness, nausea, and vomiting. A small EDH may remain asymptomatic, but this is rare.[109]

If the patient is not in coma when the diagnosis of EDH is established and if the condition is rapidly treated, the mortality is 5 to 10%. If the patient is in coma, the mortality from EDH is approximately 20%. If the EDH is rapidly detected and evacuated, the functional outcome is excellent.

On CT scan, an EDH appears hyperdense, biconvex, ovoid, and lenticular. The EDH does not usually extend beyond the dural attachments at the suture lines. The margins are sharply defined, and the hematoma usually bulges inward toward the brain (Fig. 38-7). EDHs of mixed density on CT may be actively bleeding.

A posterior fossa EDH is the most common traumatic mass lesion of the posterior fossa and accounts for 5% of EDHs.[24] Direct occipital trauma resulting in a skull fracture that disrupts a venous sinus is the usual cause, and most patients have external evidence of occipital injury. Most patients become symptomatic within 24 hours after injury, with complaints of headache, nausea, vomiting, and nuchal rigidity. Most patients eventually have a decreased level of consciousness. On CT scan, a posterior fossa EDH looks similar to other EDHs, but it may cross the midline and extend above the tentorium to the supratentorial compartment (Fig. 38-8). Mortality approaches 26%.[24]

Recent studies have investigated the indications for immediate operative intervention for EDHs. Epidurals greater than 30 cm^3 in volume should be evacuated surgically, regardless of the patient's GCS score. Furthermore, it is strongly recommended that comatose patients with an acute EDH and anisocoria on pupillary examination undergo surgical evacuation as soon as possible.[110]

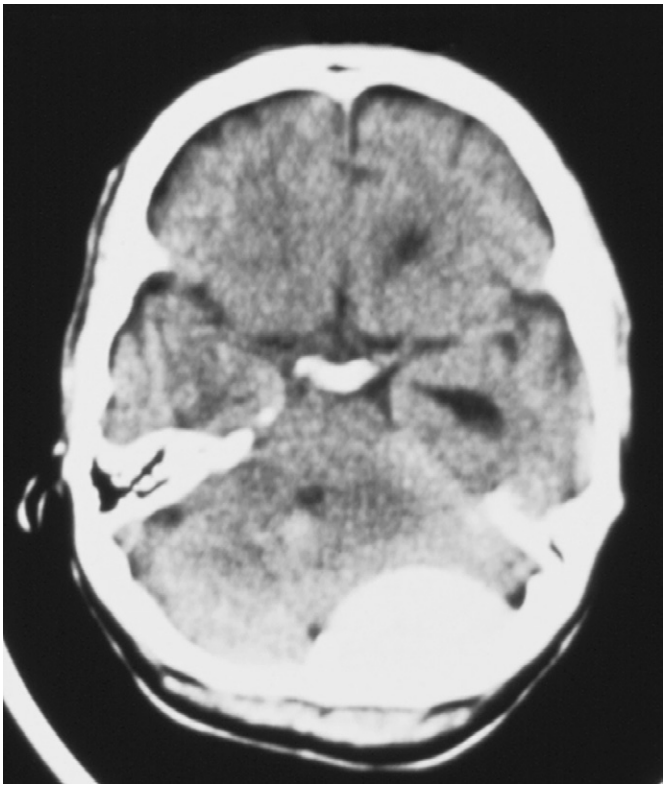


Figure 38-8. Non-contrast-enhanced computed tomography scan of large left posterior fossa, epidural hematoma. The size of the lesion at this high level suggests that it crosses into the supratentorial compartment. This lesion is often associated with occipital bone fracture that disrupts transverse sinus.

Subdural Hematoma

Subdural hematomas (SDHs) are blood clots that form between the dura and the brain. Usually, they are caused by the movement of the brain relative to the skull, as seen in acceleration-deceleration injuries. These hematomas are common in patients with brain atrophy, such as alcoholic or elder patients. In these patients, the superficial bridging vessels traverse greater distances than in patients with no atrophy. As a result, the vessels are more likely to rupture with rapid movement of the head. Once they are ruptured, blood can fill the potential space between the dura and arachnoid.

SDHs are more common than EDHs, occurring in up to 30% of patients with severe head trauma.[111] The slow bleeding of venous structures delays the development of clinical signs and symptoms. As a result, the hematoma compresses the underlying brain tissue for prolonged periods and can cause significant tissue ischemia and damage.

The patient's clinical presentation depends on the amount of brain injury sustained at the time of trauma and the rate of SDH expansion. If the patient with an SDH was rendered unconscious at the time of trauma, the prognosis is poor; these patients often have concurrent DAI. The signs and symptoms after injury that produce an SDH are initially related to the other intracranial injuries that may have been sustained and then to the slow expansion of the SDH.

SDHs are classified by the time to clinical presentation. *Acute* SDHs are symptomatic within 24 hours after trauma. Patients with acute SDHs often have a decreased level of consciousness. Most patients with an SDH present with a GCS score less than 8. Approximately 12 to 38% of patients will have a lucid period at some point in their presentation. The overall mortality of patients who have an SDH and require surgical intervention is between 40 and 60%.[111]

Because of associated brain injury caused by the SDH, the delay in clinical signs and symptoms, and the more advanced mean age of the at-risk population, the mortality associated with SDH is much higher than that associated with EDH. Pupil inequality, motor deficit, and other signs consistent with increased brain swelling may be present on the initial examination. If the patient is deeply comatose at presentation with flaccidity and without signs of brainstem activity, supportive care should be considered in the emergency department. Subsequent management decisions should be discussed with the patient's family and the attending neurosurgeon.

If the SDH is very small (only a few millimeters thick at its widest point on CT scan), some neurosurgeons may choose careful observation for these patients. Even a small SDH may be accompanied by extensive brain tissue damage that can cause an increase in ICP sufficient to precipitate a herniation syndrome. Current consensus guidelines recommend that acute SDHs with a thickness greater than 10 mm or a midline shift of more than 5 mm on CT should be evacuated surgically, regardless of the patient's GCS score.[111] Research indicates that the longer the time between clinical worsening and operative treatment, the worse the patient's clinical outcome.[111] In these cases, surgical evacuation should be performed as soon as possible.

Unlike EDHs, SDHs often extend beyond the suture lines (Fig. 38-9). An SDH may follow the contour of the tentorium and be detected within the interhemispheric fissure (Fig. 38-

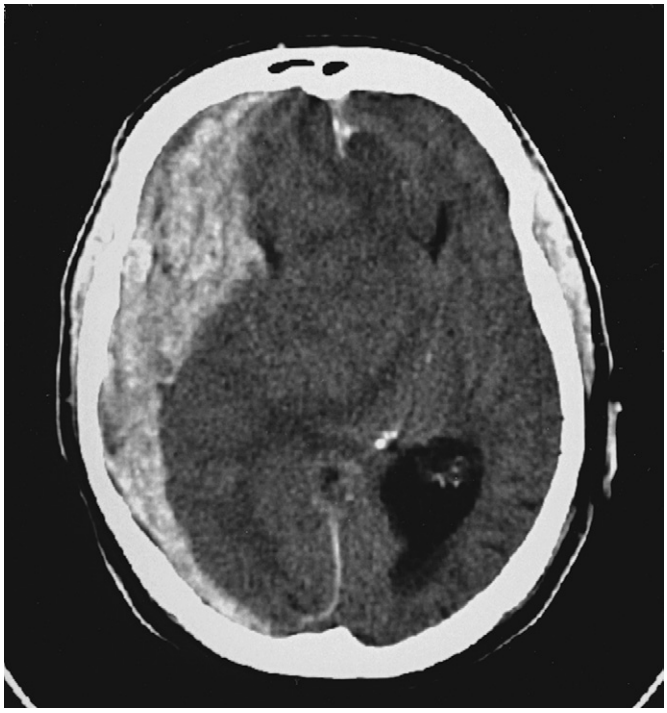


Figure 38-9. Non-contrast-enhanced computed tomography scan of acute right temporal subdural hematoma. There is acute bleeding as well as delayed bleeding, which explains the mixed density. Mass effect is large, with midline shift measuring approximately 2.7 cm right to left. The right lateral ventricle has been obliterated.

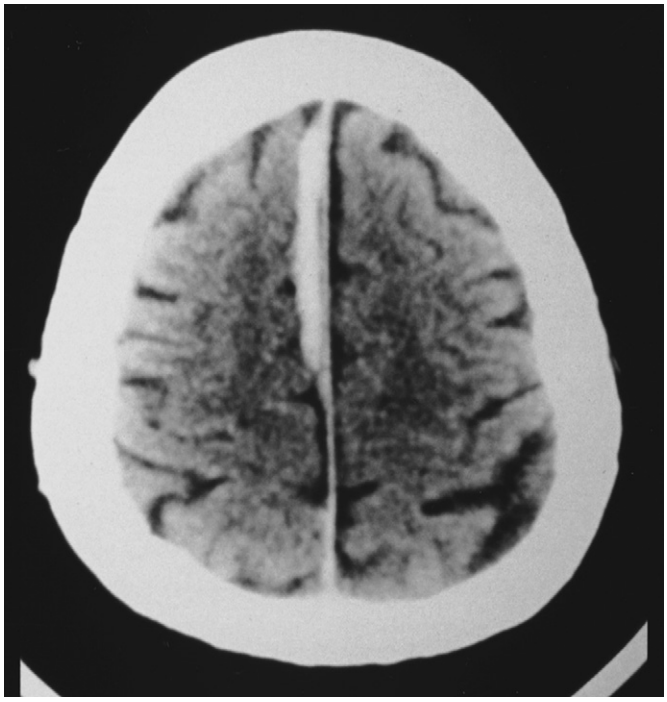


Figure 38-10. Non-contrast-enhanced computed tomography scan of intrahemispheric acute subdural hematoma.

10). Many patients with an acute SDH also show CT evidence of intracerebral lesions contralateral to the SDH.

A *subacute* SDH is symptomatic between 24 hours and 2 weeks after injury. It may appear hypodense or isodense on CT scans. Contrast increases detection of isodense lesions. Patients complain of a headache, altered mental status, muscle weakness, or frank paralysis. Most patients with subacute SDH require surgical evacuation of the lesion.

A *chronic* SDH becomes symptomatic 2 weeks or more after trauma. The signs and symptoms may be very subtle or nonspecific, but many patients demonstrate unilateral weakness or hemiparesis.[24] Most report an altered level of consciousness, but some patients are unable to recall their head injury or describe only a minor injury. In 20% of cases, chronic subdurals are bilateral.[24] A chronic SDH may have initially been a small asymptomatic SDH that eventually expanded due to a combination of recurrent hemorrhage and escape of plasma into the hematoma. At some point, a critical mass is reached, and the chronic SDH becomes symptomatic. On CT scan, a chronic SDH may appear isodense or hypodense to brain parenchyma. In these cases, indirect evidence of the lesion includes a midline shift, effacement of the ipsilateral cortical sulci, and ventricular compression. Contrast may increase the likelihood of identifying a chronic SDH that has become isodense. On CT scan, blood of various ages is seen as a mixed-density lesion. On MRI, a chronic SDH appears hyperdense. The treatment of chronic SDHs is controversial. If they become symptomatic, chronic SDHs require surgical evacuation. Most patients have a good outcome after surgery. Overall, the mortality from surgically drained chronic SDH approaches 4%, with decreased survival in elders.[24]

The prognosis of SDH does not entirely depend on the size of the hematoma but, rather, on the degree of brain injury caused by the pressure of the expanding hematoma on underlying tissue or by other intracranial injury caused by the initial impact. Mortality is highest in older people, patients who have a GCS of 8 or less, and in those with signs of acute herniation syndrome on initial emergency department presentation. Posterior fossa SDHs make up less than 1% of all reported SDHs. They are caused by occipital trauma that tears bridging vessels or venous sinuses. Clinical manifestations of posterior SDH vary but usually include nausea, vomiting, headache, and decreased level of consciousness. Occasionally, cranial nerve palsies may be found, as well as nuchal rigidity, cerebellar signs and symptoms, and papilledema. On a CT scan, a posterior fossa SDH does not cross the midline or extend above the tentorium. The outcome of a posterior SDH is very poor.

In children, the presence of an SDH should prompt consideration of child abuse. Many types of injury can produce SDH in children, but the infant who is repeatedly and forcibly shaken is especially susceptible. Infants may have SDH because of birth trauma. In these cases, the initial clinical manifestation may be a generalized seizure within the first 6 months of life. On examination, the infant may have a bulging fontanel or an enlarged head circumference. A careful history may elicit long-standing constitutional symptoms, such as failure to thrive or lethargy.

Subdural Hygroma

A subdural hygroma (SDHG) is a collection of clear, xanthochromic blood-tinged fluid in the dural space. The pathogenesis of an SDHG is not certain. It may result from a tear in the arachnoid that permits CSF to escape into the dural space or effusions from injured vessels through areas of abnormal permeability in the meninges or in the underlying parenchyma. They may accumulate immediately after trauma or in a delayed manner. Clinically, an SDHG cannot be distinguished from other mass lesions. Often, patients have a decreased level of consciousness or focal motor deficits. They may complain of headaches, nausea, and vomiting. The ICP can increase because of the mass effect, and signs of increased ICP may be present on examination.

On CT scans, SDHGs appear crescent shaped in the extra-axial space. The CT density is the same as that of CSF. Bilateral SDHGs are common. If SDHGs are asymptomatic, observation is reasonable management. Otherwise, they must be surgically evacuated. Mortality varies from 12 to 55 % and appears to depend on the severity of other intracranial injury.

Traumatic Subarachnoid Hemorrhage

Traumatic subarachnoid hemorrhage (TSAH) is defined as blood within the CSF and meningeal intima and probably results from tears of small subarachnoid vessels. TSAH is detected on the first CT scan in up to 33% of patients with severe TBI and has an incidence of 44% in all cases of severe head trauma. It is therefore the most common CT scan abnormality seen after head injury. Data from the National Traumatic Coma Data Bank demonstrate a 60% unfavorable outcome in severely brain-injured patients in the presence of TSAH compared with a 30% unfavorable outcome if no TSAH occurs.[112] An increased incidence of skull fractures and contusions is found in patients with TSAH compared with patients with no TSAH. The amount of blood within the TSAH correlates directly with the outcome and inversely with the presenting GCS.

Patients may complain of headache and photophobia. A non-contrast CT scan makes the diagnosis, with increased density noted within the basilar cisterns. Blood can also be seen within the interhemispheric fissures and sulci.

TSAH with no other brain injury does not generally carry a poor prognosis. The most serious complication of TSAH is worsening of cerebral vasospasm, which may be severe enough to induce cerebral ischemia. Post-traumatic vasospasm is common, occurring approximately 48 hours after injury and persisting for up to 2 weeks. Calcium channel blockers (e.g., nimodipine and nicardipine) have been used in the acute intensive care unit setting to prevent or reduce vasospasm after TSAH. Although a radiographic reduction of vasospasm is not consistently seen, the overall outcome of patients treated with these agents seems to be improved compared with no treatment.[113]

Intracerebral Hematoma

Intracerebral hematomas (ICHs) are formed deep within the brain tissue and are usually caused by shearing or tensile forces that mechanically stretch and tear deep small-caliber arterioles as the brain is propelled against irregular surfaces in the cranial vault. Resulting small petechial hemorrhages subsequently coalesce to form ICHs. Approximately 85% are in the frontal and temporal lobes. They are often found in the presence of extra-axial hematomas, and in many patients multiple ICHs are present.[109] Isolated ICHs may be detected in as many as 12% of all patients with severe head trauma.

The clinical effects of ICH depend on size, location, and whether the bleeding is continuing. ICHs have been reported with all degrees of severity of head trauma. More than 50% of patients with ICH sustain LOC at the time of impact. The patient's subsequent level of consciousness depends on the severity of the impact and coexisting lesions. Combined with contusions, other concurrent lesions, and subsequent perilesion edema, an ICH can produce substantial mass effects and precipitate a herniation syndrome (Fig. 38-11).

An ICH may be detected on the first CT scan immediately after injury but often is not seen for several hours or days. Unlike contusions, ICHs are usually deep in the brain tissue and often become well demarcated over time. On CT scan, an ICH appears as a well-defined hyperdense homogeneous area of hemorrhage (Fig. 38-12).

Figure 38-11. Non-contrast-enhanced computed tomography scan of intracerebral hematoma and contusion in the left occipital region. The scan also shows layering of tentorial subdural hematoma. Mass effect and early uncal herniation are visible as well.

Figure 38-12. Non-contrast-enhanced computed tomography scan of right occipital and temporal intracerebral hematomas, surrounded by mild edema and hemorrhagic contusion. Small intrahemispheric subdural hematoma is visible in posterior interhemispheric fissure. Midline shift is obvious. Ventriculostomy has been placed and is visible as high-density image within ventricles.

Many patients with an ICH require emergent intervention or surgery to control elevated ICP. Mortality is low in patients who are conscious before surgery; in unconscious patients, mortality approaches 45%.[114,115] ICHs that bleed into the ventricles or cerebellum also carry a high mortality rate.

Traumatic Intracerebellar Hematoma

Primary traumatic intracerebellar hematomas are rare but can occur after a direct blow to the occipital area. Often, these patients also have a skull fracture or a posterior fossa SDH. Supratentorial contrecoup hematomas and contusions are also common associated findings.

The clinical presentation of an isolated traumatic cerebellar hematoma is similar to that of other posterior lesions. When other traumatic lesions are present, the picture may be quite confusing. The acute management should first address the most clinically significant lesion. The mortality from isolated traumatic intracerebellar hematoma is very high.

Acknowledgments

The authors thank Emergency Medicine Clinics for allowing us to use certain portions of a recent article in this chapter.[116]

KEY CONCEPTS

Severe and Moderate Head Injuries

- All patients with severe or moderate head injury require serial neurologic examinations while in the emergency department to allow early detection of herniation syndrome related to expanding traumatic mass lesions or increasing cerebral edema. A non-contrast CT scan should be performed on all moderate and severe head-injured patients.
- Acute herniation syndrome manifested by neurologic deterioration should initially be managed with short-term hyperventilation, to a Pco_2 of 30 to 35 mm Hg, with monitoring and then surgical intervention as soon as possible. Long-term hyperventilation is not indicated. Mannitol or hypertonic saline should be used only in patients with increasing ICPs or acute neurologic deterioration.
- Secondary systemic insults such as hypoxia and hypotension worsen neurologic outcome after severe and moderate head trauma and should be corrected as soon as detected in the out-of-hospital or emergency department setting.
- For adult patients, hypotension in the presence of isolated severe head injury is a preterminal event. Hypotension usually results from comorbidity, and its cause should be sought and treated.
- The GCS is a useful clinical tool for following head-injured patients' neurologic status, but because of its limitations, the initial GCS in the emergency department cannot reliably predict prognosis after acute head injury.
- Head-injured patients who have been chemically paralyzed do not have clinical manifestations of seizures; anticonvulsants should be given prophylactically.
- Most "talk and deteriorate" patients who present with moderate head injury have subdural or epidural hematomas. Early detection, CT scan, and expedient surgical intervention are the keys to a good outcome.
- Caution should given to out-of-hospital RSI intubations in severe head injury if the intubations may be prolonged or significantly challenging. Alternative airway management should be considered.

Minor Head Trauma

- Risk stratification of patients with minor head injury into low-risk and high-risk categories can help direct the emergency physician to an appropriate diagnostic workup.
- The decision to perform CT scans on patients with minor head trauma should be individualized but based on consideration of high- and moderate-risk criteria.
- Alcohol can affect the GCS and significantly obscure the neurologic examination. Intoxicated patients should be considered at high risk.
- Most patients with minor head trauma can be discharged from the emergency department after a period of observation but require a competent observer.
- Patients sustaining a concussion are at risk for prolonged and substantial morbidity. Athletes should not be allowed to return immediately to sports activities because of the potential risk of second impact syndrome. All current recommendations for return to play after a sports-related concussion state that players with concussion should not return to play for at least 1 week after they have become asymptomatic. This period is usually increased to at least a symptom-free month if an LOC or prolonged post-traumatic amnesia occurred at the time of concussion.

Pediatric Head Injuries

- Children with severe head trauma have fewer intracranial lesions than adults but more edema. In children, increasing edema alone can cause talk and deteriorate or other significant neurologic decline.
- Skull fractures have more clinical significance in children than in adults.
- In children, unlike adults, hypovolemic hypotension can occur because of head injury, especially in those younger than 1 year of age.
- In very young children, head injury often occurs from nonaccidental causes. Child abuse should be suspected in young children with head trauma, especially those younger than 2 years of age.

Penetrating Head Injuries

- Tangential gunshot wounds are associated with a high frequency of intracranial traumatic lesions; CT scanning should be performed.
- Anticonvulsant prophylaxis and antibiotics should be given to a patient with penetrating head injuries.
- The clinical outcome after gunshot wounds to the head can be predicted by the initial clinical presentation and the missile path through the brain.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 39

Facial Trauma

Mary Pat McKay and Ryanne J. Mayersak

PERSPECTIVE

This chapter discusses the epidemiology, diagnosis, and treatment of injuries to the skin, soft tissue, and bones of the face. A complex structure vital to the function of the person, the face comprises airway openings, entry to the gastrointestinal tract, and special sensory organs, including eyes, ears, and nose. Facial functioning is essential for eating, speaking, and effective nonverbal communication. The appearance and attractiveness of the face have significant implications for social interactions,[1,2] sexual attraction,[3] and self-esteem.[4]

Apart from immediate threat to the patient's airway and special sense organs, injuries to the face can have serious implications for the patient's mental health[5,6] and future functioning. In one study of predominantly unemployed young African American and Hispanic men, 25% had symptoms of posttraumatic stress disorder 1 month after being treated emergently for a midface fracture.[7,8]

Although the emergency physician's main goal must be to address life-threatening problems successfully, the care of facial injuries is aimed at optimizing the patient's long-term appearance.

Four main specialties—ophthalmology, plastic surgery, otolaryngology, and oral and maxillofacial surgery—participate in the care of facial injuries. Among teaching hospitals, the specialties of plastic surgery, otolaryngology, and oral and maxillofacial surgery participate in approximately equal proportions.[9] Among level 1 trauma centers, plastic and oral/maxillofacial surgeons predominate.[10] Early consultation with the appropriate specialist can expedite the care of facial injuries.

Epidemiology

In 2006, there were more than 29 million injury-related visits to U.S. emergency departments.[11] Facial injuries accounted for a significant proportion of these visits and may result from either intentional violence (assaults and attempted suicide) or unintentional trauma (falls, sports, and motor vehicle crashes [MVCs]). Although MVCs used to be the most common cause of facial injuries, windshield improvements, increased use of safety belts, and the prevalence of air bags in vehicles are changing the epidemiology of facial trauma. Dual front-impact air bags have been required in all new vehicles since 1999, and safety belts are required for all passengers in the front row in 49 states (all except New Hampshire).[12] Seat belts and air bags significantly reduce the incidence and severity of facial injury in adults.[13-19] Because they effectively prevent ejection, safety belts specifically avert the extensive scalp and facial degloving injuries associated with being ejected through the windshield.

Alcohol use by vehicle occupants decreases safety belt use and independently increases the risk of facial injury in MVCs.[19] It also increases the risk of interpersonal violence. In one series, alcohol played a role in 49% of all maxillofacial fractures in patients requiring subspecialty care. Among those related to alcohol, 78% were due to interpersonal violence and 13% from MVCs.[20] Interpersonal violence is increasingly cited as the cause of facial injury, particularly in inner-city populations.[21,22] Falls, dog bites, some athletic activities, and flying debris are other common causes of facial injuries.

Because of the lack of external protection, facial injuries are common among riders of other motorized vehicles, particularly those who are not wearing helmets with face guards, including all-terrain vehicles (ATVs) and motorcycles. In one series in Alabama, 32% of injured ATV riders had a facial injury, and the presence of a facial injury was associated with increased overall injury severity.[23]Among the youngest riders, facial injuries predominate: 31.1% of 0- to 5-year-olds injured while riding an ATV required emergency treatment for a facial injury in 2001 through 2003, although multiple safety and medical groups recommend no ATV use by people younger than age 16 years.[24]

In motorcyclists, there is a significant association between facial injury and brain injury.[25] Helmets reduce the risk of brain injury but may not protect against facial trauma unless they include a face guard.[26]

Unfortunately, a separate group of the injured must now be considered: combat veterans. A review of injuries sustained in battle by combatants in Operation Iraqi Freedom and Operation Enduring Freedom and treated by U.S. military medical facilities for at least 72 hours revealed that 19% suffered injuries to the face, ears, or eyes. Nineteen percent of all these injuries were caused by gunshot, 79% by explosive device, and 2% by MVCs.[27]

Among children younger than age 17 years, sports injuries account for 21% of facial and 29% of nasal fractures requiring specialist evaluation.[28] Baseball and football helmets with face guards are successful at preventing childhood facial injuries, and their use should be encouraged by emergency physicians.[29] Children younger than age 6 years seem to be at significant risk for severe facial injuries from bites sustained from the family dog.[30] Interactions between pet dogs and young children require careful supervision.

Facial injuries are a common acute presentation for victims of domestic violence. In one series, 81% of domestic violence victims presented with maxillofacial injuries, 30% of them with facial fractures. The location of the injury was consistent with the predominance of fisted assaults; left-sided injuries predominated.[31] Women presenting to the emergency department with facial injuries should be interviewed privately to allow an opportunity for disclosure and intervention for domestic violence.

Pediatric facial injury accounts for less than 10% of all facial trauma, and the face is the most common area of trauma in children suspected of being victims of abuse.[32] However, the epidemiology of facial trauma among children reflects their physical development and behavioral patterns: toddlers learning to walk have a "falling zone" of trauma to the perioral region, nose, and forehead.[33] Younger children are significantly more likely to have minor soft tissue injuries and to have been the recipient of a dog bite. Severe facial injuries in all pediatric age groups are more likely to be the result of an MVC or assault.[34] Care should be taken by the emergency physician to correlate the child's age and behavioral ability with the history of the injury and the physical findings. In particular, injuries to the lips or frenulum in a nonambulatory infant suggest "bottle jamming," and bruises to the cheeks or neck are less common in falls. Although dental fractures in young children are relatively common,[35] facial fractures before age 5 years are rare.[36] If there is any question, the appropriate local authorities must be contacted.

Even in high-energy MVCs, appropriate use of child safety restraints protects against many facial injuries. The law in all 50 states requires the use of such restraints for children younger than age 4 years, and currently 42 states require booster seats until at least age 6 years and many beyond that age.[37] For children younger than age 15 years who were involved in frontal crashes, those exposed to a deploying frontal impact air bag had a higher incidence of minor facial and chest injuries and severe upper extremity injuries, mostly related to being struck by the bag.[38] As part of preventing facial trauma, parents should be encouraged to ensure that children younger than 12 years ride in the rear seat of the vehicle and all are properly restrained.

PRINCIPLES OF DISEASE

Anatomy

The face is a complex hollow space encapsulated by a bony structure overlaid with muscle and skin. It includes several special sensory organs: the eyes, ears, nose, and mouth.

Bones

The posterior portions of the face form the anterior wall of the calvaria, placing the face and its features in an intimate relationship with the structures of the central nervous system. The anterior facial skeleton is composed of the frontal bone, nasal bones, zygomas, maxillary bones, and mandible (Fig. 39-1). The sphenoid, ethmoid, lacrimal, vomer, and temporal bones lie deep within the facial structure, providing support and important sites for muscular attachments, including the muscles of mastication, speech, and deglutition. This musculature is innervated by cranial nerves IX and X.

Nerve Supply

The most anterior muscle layer includes the muscles of facial expression that are innervated by the seventh cranial nerve, which exists just inferior to the external auditory canal. The trigeminal nerve (cranial nerve V) supplies sensation to the face through three major divisions (I–III). The ophthalmic division (cranial nerve V1) supplies the upper third of the face, including the eye and the nose down to the tip. The maxillary division (cranial nerve V2) provides sensory innervation to the midface and includes the infraorbital nerve. The mandibular division (cranial nerve V3) supplies sensation to the lower third of the face.

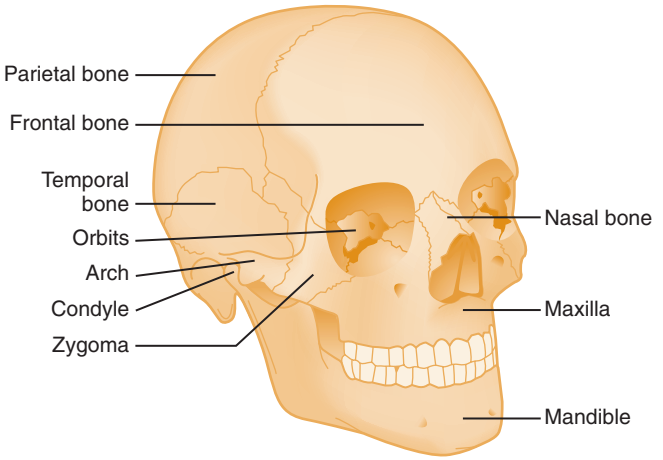


Figure 39-1. Bones of the facial skeleton.

Ears

The ears lie laterally along the sides of the face with the auditory canal exiting through the mastoid process of the temporal bone. The skeleton of the pinna is cartilage covered in closely apposed skin and rolled into a helical shape with a second ridge, the antihelix, defining the inner concha. The external auditory canal, middle ear, cochlea, semicircular canals, and superior origin of the eustachian tube all lie with the temporal bone.

Eyes

The structure of the globe and surrounding ocular musculature is discussed in detail in Chapter 69. The bony orbit is composed superiorly of the frontal bone. The zygoma forms the lateral wall and lateral floor of the orbit. The medial floor and anteromedial wall are formed by the maxilla. The lacrimal and ethmoid bones complete the medial wall, where the orbit is at its most delicate. The medial wall of the orbit forms the lateral walls of the intranasal space.

Nose

The nose serves as a major entryway for air and is composed of cartilage and bone covered by skin with mucosa lining the internal surface. Alar cartilage arches over the entrances to the symmetric, mucosa-lined nares, separated by the anterior cartilage of the septum. Superiorly, the nasal bones create the bridge of the nose. With the head held in a neutral upright position, the floor of the nose is perpendicular to the ground and leads back into the nasopharynx, passing the turbinates laterally and the bony septum medially. The ethmoid bone lies superiorly and crosses midline, behind the nasal bridge, to form the superior portion of the bony nasal septum and the cribiform plate. The vomer comprises the inferior portion of the bony septum, and the palatine process of the maxillary

bone forms the posterior floor of the nose and the hard palate.

Air-containing sinuses are structural features unique to the facial skeleton. They serve to warm and humidify inhaled air and form chambers that create the unique tone of human voices. These sinuses develop over the period of human growth. At birth, only the ethmoid air cells and the mastoid antrum are aerated. The sphenoid sinus and the remainder of the mastoid air cells become aerated at approximately age 3 years. Frontal sinuses form at approximately age 6 years, and maxillary sinuses are not fully developed until age 10 years.

Mouth

The mouth serves as entry to the respiratory and gastrointestinal tracts. In addition, the fine motor movements of the mouth and tongue give humans the ability to communicate through speech. With the mouth in the closed position, the tongue fills the oral cavity. Single rows of teeth lie within the alveolar ridges of the maxilla and the mandible. With the mouth closed, the teeth in normal individuals occlude, with the lower row lying just internal to the upper row. The "usual" occlusion for individuals varies widely; the patient's belief may be the best determinant of whether or not the teeth are meeting as usual. Anterior to the teeth is the vestibule, a fold of mucosa and flexible soft tissue that allows the lips to remain closed while various motor movements occur behind them. The mandible is a U-shaped bone that forms the chin and completes the lower facial skeleton. Containing the lower row of teeth, the body of the mandible meets in midline at the symphysis, which is completely fused by age 2 years. Posterior to the last molar, the bone turns to form the angle of the jaw and continues upward as the ramus of the mandible. At the most superior point of the ramus is the articular surface of the condyle, separated from the superior surface of the temporomandibular joint (TMJ) by an intervening meniscus of fibrocartilage. Anterior to the condyle lies a thin projection, the coronoid process, which provides the insertion point for the temporal muscle.

The skin of the face is among the thinnest of the body, draping over the underlying musculature. Facial skin falls visibly into predictable creases with age, following Langer's lines (Fig. 39-2). At the mouth, nares, and palpebral fissures, the skin is contiguous with the mucosa lining these structures. The skin of the lips is particularly thin and lined with vascular papillae, which give the lips their vermilion hue. Lips are particularly important as part of communication; understanding their movement can allow language without sound (lip reading).

The face is a highly vascular structure; this can have grave implications for the treatment of facial injuries. With the exception of the ophthalmic artery, the superficial blood supply comes from the external carotid artery via the facial, superficial temporal, and maxillary arteries (Fig. 39-3). Soft tissue injuries and fractures that involve these vessels can lead to significant hematomas or exsanguinations. Because the face has extensive anastomotic connections across the midline and between arterial territories, however, ligation of major branches causes minimal ischemia.

Buried within the structure of the face are a series of glandular structures and ducts, which are susceptible to injury. In the eye, the lacrimal glands lie within the orbits, superior and lateral to the globes, and secrete tears through ductules into the folds of the conjunctiva. The liquid flows medially into the puncta of the lacrimal canaliculi and drains into the lacrimal sac and then via the nasolacrimal duct into the nasopharynx.

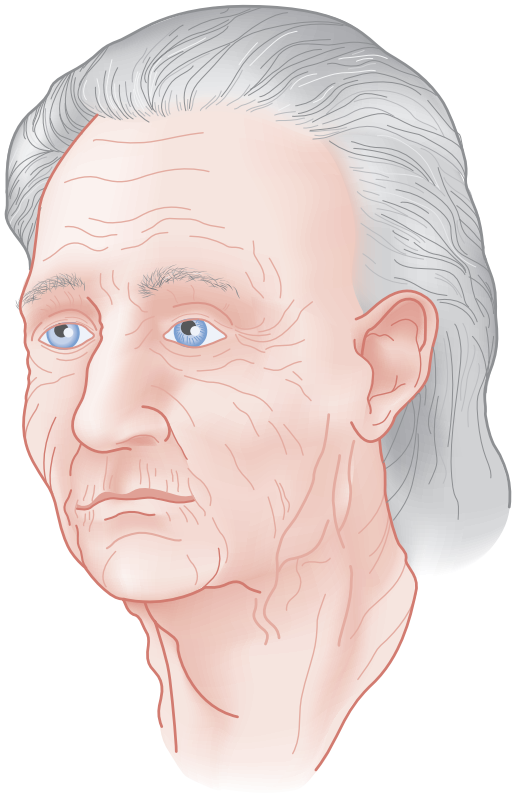


Figure 39-2. Langer's lines: lines of facial expression.

The salivary system consists of the parotid, sublingual, and submandibular glands. The parotid is the largest of these glands, lying just anterior to the ear and wrapping around the mandible. The parotid is superficial to the masseter muscle and drains via Stensen's duct, a 5-cm tube that curves around the anterior edge of the masseter to enter the mouth opposite the second upper molar. In normal subjects, this duct is large enough to be palpated with the masseter clenched (Fig. 39-4). The sublingual glands lie entirely within the floor of the mouth and drain into the mouth via ductules. They surround the ducts draining the submandibular glands (Wharton's ducts). The body of the submandibular gland is folded around the mylohyoid muscle so that a portion lies within the floor of the mouth and a portion lies external to it. The submandibular (Wharton's) ducts run from the external portion of the gland to empty into the mouth on either side of the frenulum of the tongue.

Pathophysiology

The basic mechanism of all injury is the transfer of energy, most often kinetic, to the structures of the body. When the energy overcomes the tolerance of the underlying tissue, injury results. Trauma traditionally has been classified as blunt or penetrating, but in many cases the effect is a combination of the two, such as the forehead injury (contusion and complex laceration) resulting from a child's fall against the sharp corner of a coffee table. The likelihood of injury is related to the amount of energy transferred and the condition of the underlying tissue. Significant injury may result when an 80-year-old falls from standing to a carpeted floor, but it is more likely to result when the face strikes the steering wheel or dashboard in a high-speed MVC.

The mechanism can be broken down into *low-energy* events, such as a fall from standing or walking into the corner of a

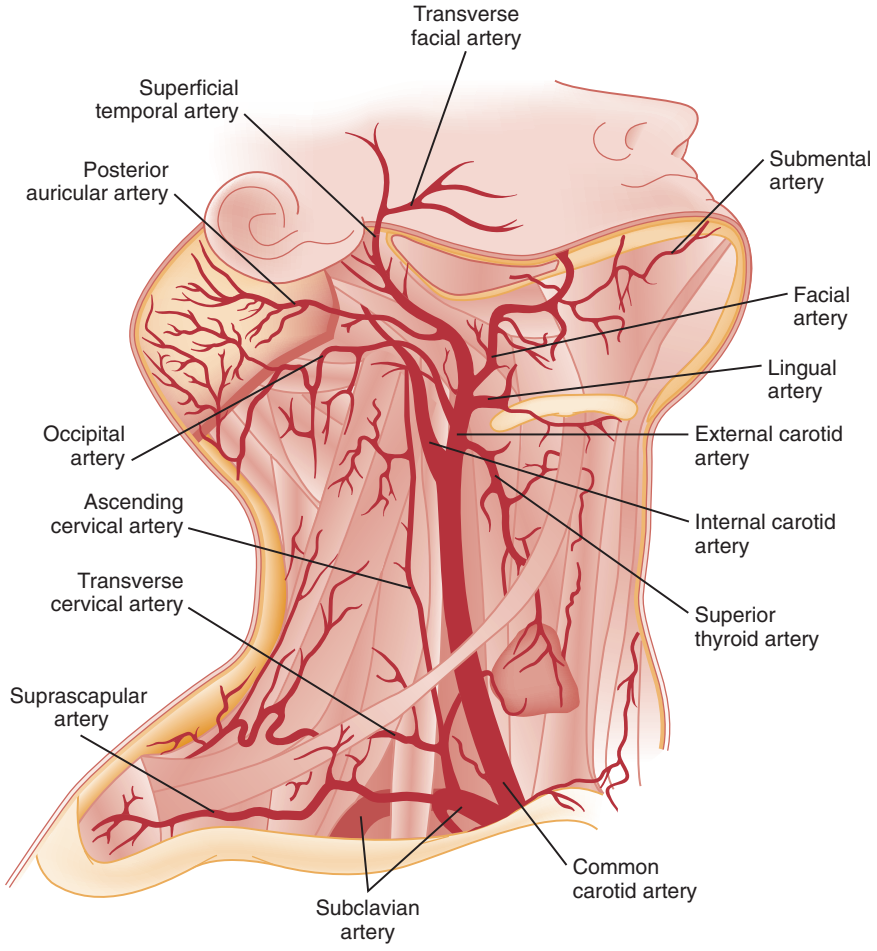


Figure 39-3. Vessels of the face. (Redrawn from *Gray's Anatomy*, 1918.)

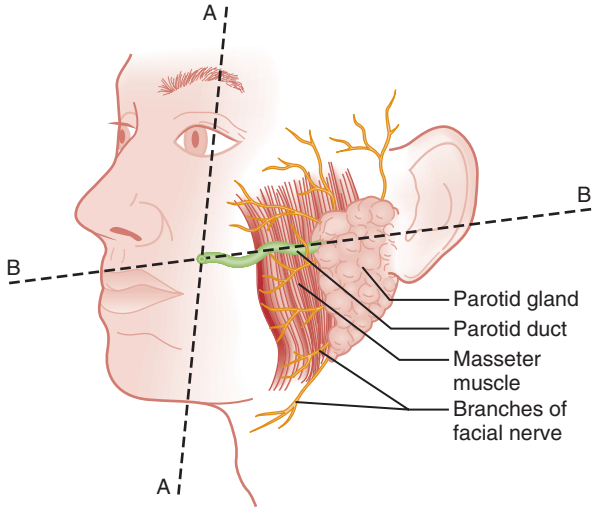


Figure 39-4. Parotid gland and duct (Stensen's) with the surrounding branches of the facial nerve. Line B approximates the course of the duct, which enters the mouth at the junction of lines A and B.

piece of furniture, and *high-energy* events, such as an MVC. Understanding the mechanism of injury can not only help predict the severity of the facial injury but also predict the risk of associated cervical or brain injuries.

Traditional teaching has been that the face protects the brain from injury and that patients with facial trauma are less likely to have a significant brain injury. This does not appear to be correct. Instead, recent work suggests a significant increase in risk for brain injury among blunt trauma patients with facial fractures.[39]

The association between cervical injury and facial injury is unclear. The traditional teaching has been that the presence of a facial injury should increase the suspicion of an injury to the cervical spine. However, most of the studies supporting this idea are assessments of the incidence of cervical spine injury in patients with facial injury.[40,41] When more sophisticated methods are used to assess any association between the two while correcting for the mechanism of injury, patients with facial injury appear to be less likely to have a significant cord injury, and there is no relationship with bony spinal injury.[42] Thus, in a particular patient, cervical and brain injuries should be considered based on the mechanism of injury and presentation of the patient without allowing the presence or absence of a facial injury to change the level of suspicion.

Penetrating trauma to the face from gunshots, stab wounds, blast debris, or impalement is often obvious and dramatic (Fig. 39-5). The astute emergency physician should search avidly for associated intracranial, spinal, or vascular injuries, which are common in these cases.[43] Facial penetration from pellets (BBs) or small blast debris or shrapnel may be less obvious, and the emergency physician must be alert to the possibility based on the history and carefully search for small skin lesions.[44] Unregulated guns created from plastic pipes and aerosol cans that shoot potatoes are used as toys in areas of the United States, mostly among adolescent boys. Significant facial trauma can result from these instruments, which can propel a potato 200 mph.[45]

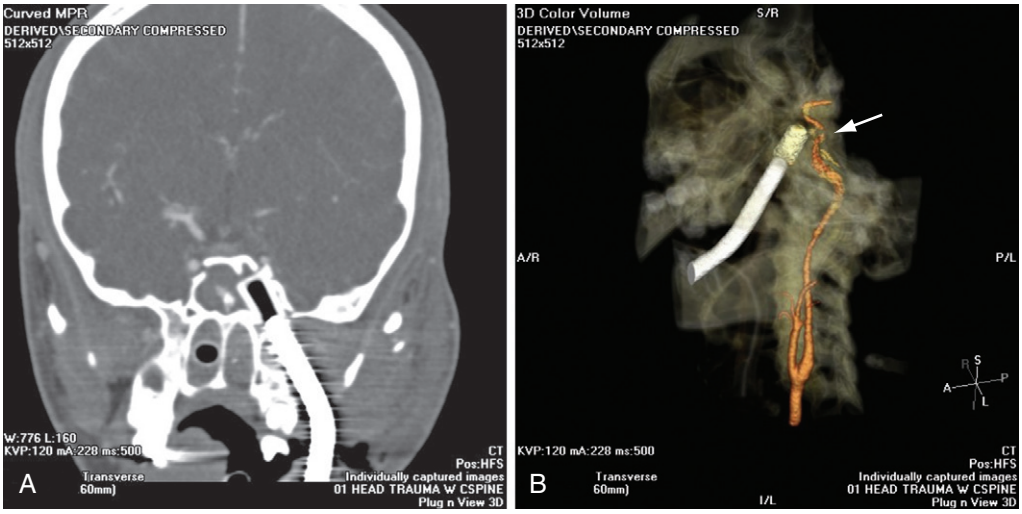


Figure 39-5. Impalement by a turn-signal lever. Computed tomography (**A**) and three-dimensional reconstruction (**B**) from a patient impaled through the face into the cranial cavity by the turn-signal lever from his steering column when his vehicle rolled over in a single-car crash. The color three-dimensional reconstruction reveals a significant injury to the facial artery (*arrow*).

CLINICAL FEATURES

History

The history can provide information about the mechanism of the patient's injury. The emergency physician should be alert to limitations of the history, however, when the patient's consciousness is altered by head injury or intoxication, there is an issue of secondary gain, the police are involved, or abuse is suspected. Patients with a clear sensorium are able to describe the events leading up to the injury and localize pain; deficits in motor or sensory function; and abnormalities of vision, hearing, taste, or smell. Although the association between facial trauma and brain or cervical spine injury is unclear, these possibilities should be considered, and the patient should be questioned regarding headache, peripheral weakness, numbness, or paresthesias.

Physical Examination

Many facial injuries can be identified by simple inspection. During the primary assessment, attention is initially on the patient's airway, and inspection of the oropharynx is an essential first step. Airway compromise is often due to intraoral trauma, and the examiner should note excessive bleeding, drooling, dysphonia, swelling of the tongue or posterior pharynx, and the presence of avulsed teeth. When the patient is stabilized, a secondary survey should include a systematic examination of all facial structures and functions. Bony prominences should be palpated for abnormal motion, bony crepitus, tenderness, or step-off. Tenderness and massive swelling associated with facial trauma may preclude reliable palpation of a fracture. Consequently, areas of significant swelling should be imaged radiographically. Assessment of bony integrity includes testing for possible Le Fort fracture. The upper incisors are grasped and pulled anteriorly. Movement of the upper alveolar ridge (type I), midface (type II), or entire face (type III) indicates a fracture. Wounds may need to be palpated for underlying bony injury or foreign objects; anesthesia may be required for a thorough examination within the wound. Complex lacerations involving the cartilage of the nose or ear, eyelids, lacrimal apparatus, eyebrows, or vermilion border of the lips should be identified because their repair requires special techniques.

Eyes and Orbits

In addition to looking at lacerations and contusions, the face should be evaluated for symmetry. The appearance of the zygomas may be evaluated by looking at the patient from above. This technique also draws attention to the relative position of the eyeballs. Orbital fractures may result in enophthalmos, and a large retrobulbar hematoma may cause exophthalmos. The anterior chamber of the globe should be inspected for hyphema or globe rupture. Hyphema is due to bleeding in the anterior chamber and appears as a layer of blood in the dependent portion of the anterior chamber. A complete examination of the eye requires specific testing. If the patient is able to cooperate, visual acuity should be documented. Contact lenses should be removed. In the event of a significant potential chemical exposure, the pH of the eye may need to be measured. Fluorescein examination of the eye should be performed if there is any concern about corneal abrasion. Victims of MVCs often have particles of glass in the conjunctiva or on the cornea, and these should be sought out and removed. Extraocular motions should be tested. Blow-out fractures of the orbit may result in diplopia on upward gaze secondary to entrapment of the inferior rectus muscle or anesthesia of the midface and upper lip in the distribution of second division of the fifth cranial nerve secondary to neurapraxia resulting from fracture through the infraorbital foramen or compression by a local hematoma.

Oropharynx

The integrity of the mouth and nasal complex may be evaluated by listening to the patient's speech. A muffled or overly nasal voice may indicate occlusion of the nose or nasopharynx, whereas dysarthria may indicate a mandibular fracture, tongue injury, or neurologic problem. Oral injury may result in progressive airway compromise, and dysphonia should alert the clinician to the possible need for active airway management. The intraoral examination includes inspection of the palate, teeth, tongue, and gums and palpation with a gloved finger (the latter only if the patient is able to cooperate). The range of motion of the mandible should be determined. If the maximal incisor opening is less than 5 cm, a mandibular fracture may be present. Trismus is likely to indicate a fracture or significant hematoma within the face. If awake, the patient's

impression about the normalcy of bite occlusion is a more sensitive determinant of a fracture of the mandible than the physician's impression. Being able to perform a tongue blade test (grasping and holding a tongue blade between the teeth while the examiner pulls gently) is associated with greatly reduced probability of mandibular fracture.[46] If the patient is able to crack the tongue blade by biting on both sides of the mouth, the negative predictive value for a mandibular fracture is 95%.[47] Injury to the parotid area should raise suspicion of disruption of Stensen's duct. The opening of the duct opposite the second upper molar should be examined for bleeding while the gland is compressed. If blood is expressed from the duct or the severed ends of the duct are identified within a facial wound, specialized repair over a stent is required to prevent formation of a cutaneous fistula.

Ears

Otoscopy is performed to evaluate the integrity of the external canal, look for hemotympanum, and assess for otorrhea. Clear fluid from the ear after trauma should raise the possibility of a cerebrospinal fluid (CSF) leak. At the bedside, a drop of the fluid may be placed onto filter paper. A rapidly advancing halo of clear fluid around red blood defines a positive test. This is a quick bedside test with good sensitivity (>86%) as long as the mix is approximately 50:50 between blood and other fluid, but it does not differentiate between CSF and saline, saliva, or other clear fluids.[48]

The ear should be inspected for subcutaneous hematomas because these need to be drained.

Nose

The nose is palpated for tenderness, crepitus, or abnormal movement, and then each nare is held closed in turn to ensure the patient is able to breathe through either side. The septum should be examined visually to look for septal hematoma, which appears as a large purple mass extending from the septum. If there is any concern about CSF rhinorrhea, the aforementioned filter test may be performed.

Neurologic Examination

Light touch should be tested for all three branches of the fifth cranial nerve. Motor function (cranial nerve VII) can be examined by having the patient actively wrinkle the forehead, fully open and snug the eyelids shut, smile widely, and bare the teeth. Asymmetry of these movements indicates a potential nerve injury. Peripheral injuries to the seventh cranial nerve should have discernable weakness in the forehead as well as the orbital and oral musculature, whereas central injuries will have preserved forehead function because of crossing fibers distal in the course of the nerve.

The final part of the physical examination is documentation. Facial injuries may be evidence of assault, domestic violence, or child abuse. Careful documentation of findings, including photographs or drawings or both, not only communicates initial findings to other practitioners but also can provide crucial legal evidence because many of these cases have forensic implications or result in litigation.

DIAGNOSTIC STRATEGIES

Imaging

The choice of imaging for facial fractures depends on the patient's stability, the patient's ability to cooperate, and the availability of various options. The two main options are plain x-rays and computed tomography (CT). Fractures are better visualized on CT than magnetic resonance imaging, so magnetic resonance imaging is not an optimal imaging choice. In patients who cannot cooperate for plain x-rays or in whom a fracture or penetrating injury is obvious from the physical examination, CT is the imaging modality of choice.[49] For a complete evaluation, CT scans of the face should include coronal and sagittal reconstructions. Interpreting facial CT scans is an art that requires attention to bones, sinuses, orbital contents, and soft tissue and is best handled by radiologists.

With the increasing use of CT in emergency medicine and the advent of telemedicine, most 24-hour emergency departments have access to CT scanners for facial injuries. CT is now the first choice for all patients in whom a midface fracture is suspected. However, when no scanner is available and in patients with low to moderate pretest probability of a midface or maxillary fracture and who are stable and able to cooperate, the current recommendation is for a single screening view (a Water's or occipitomental view), followed by CT if the film is positive for a fracture or air-fluid level in any sinus.[50-52]

The U shape of the mandible and the presence of nearby bony structures make isolating the mandible on flat film impossible. Simple radiographs of the mandible are less sensitive than panorex radiographs and particularly tend to miss fractures of the condyle (Fig. 39-6). If available, panorex imaging is indicated for isolated mandibular fractures, dental fractures, or fractures of the alveolar ridge. In children, if fracture of the condyle is suspected, coronal CT is more sensitive and specific than panorex studies.[53] Although the traditional teaching has been that the mandible's shape mandates two fractures if it is fractured at all (Fig. 39-7), a case series using CT evaluation found that 42% of mandibular fractures were unifocal.[54]

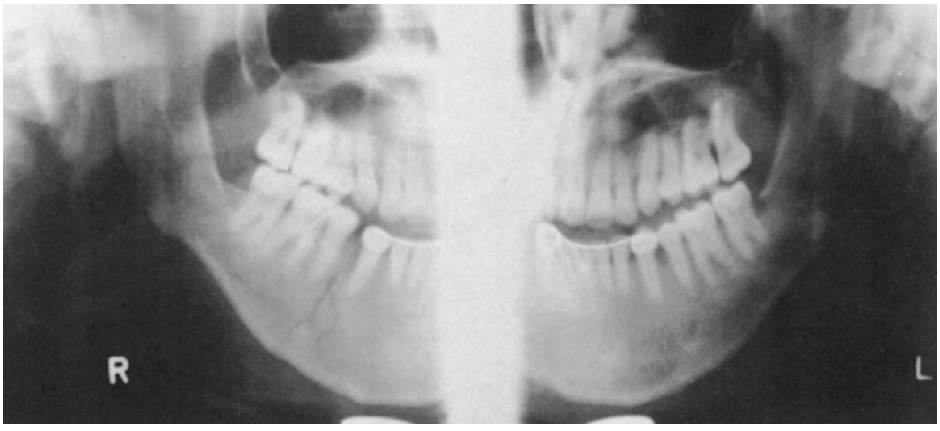


Figure 39-6. Panoramic radiograph of the mandible shows fractures through the left angle and the right body. A dental appliance is in place on the lower incisors.

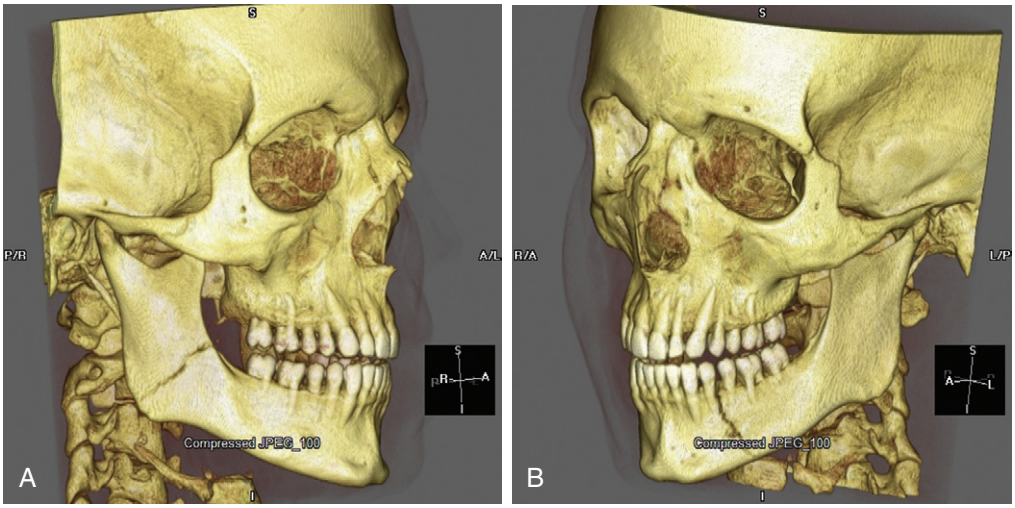


Figure 39-7. Three-dimensional CT reconstructions of minimally displaced mandibular fractures in the same patient as in Figure 39-5.

For patients with complex fractures, new imaging techniques may help improve surgical planning and esthetic outcomes. In displaced orbital fractures, using CT data to measure orbital volumes has shown that after repair, an orbital volume greater than 4% larger than the unfractured side is associated with visible postoperative enophthalmos.[55] This method seems to be useful in predicting which patients might benefit from operative repair.[56] In conjunction with more standard two-dimensional facial CT scans, three-dimensional CT seems to improve the diagnosis and aid preoperative planning for patients with complex fractures of the midface (Fig. 39-8B).[57-60]

Patients with tenderness and swelling isolated to the bony bridge of the nose who do not have a septal hematoma, can breathe through each nare, and have a straight nose do not require nasal bone x-rays in the emergency department because imaging results would not alter treatment. If these criteria are not met, early reduction or referral for surgical intervention may be indicated, and plain films (truly isolated injuries) or CT scanning (if concern for other injuries) is indicated. Plain x-rays may also be performed in the setting of legal concerns. If there is concern for a foreign body in a superficial wound, two standard x-ray views (Water's and Caldwell's or occipitofrontal view) are indicated to triangulate the position of the observed foreign material.

Patients with suspected ocular injuries may benefit from a bedside ultrasound as a noninvasive and economical diagnostic tool, particularly if there is a need for urgent operative management of other injuries and no time for a dedicated facial CT. The different acoustic impedances of the orbit's anatomical structures make the modality operator friendly, and an ultrasound of the eye can readily detect vitreous hemorrhage, retinal detachment, and globe rupture (Fig. 39-9). Prior findings have suggested that high-resolution ultrasound has at least a 94% correlation with axial and coronal CT imaging in the detection of orbital fractures and emphysema.[61]

MANAGEMENT

Management of facial injuries occurs within the overall resuscitation of the patient. Unless the airway is threatened or exsanguination is a concern, treatment of most facial injuries can be deferred until more life-threatening injuries have been stabilized. Care of the patient with penetrating trauma to the

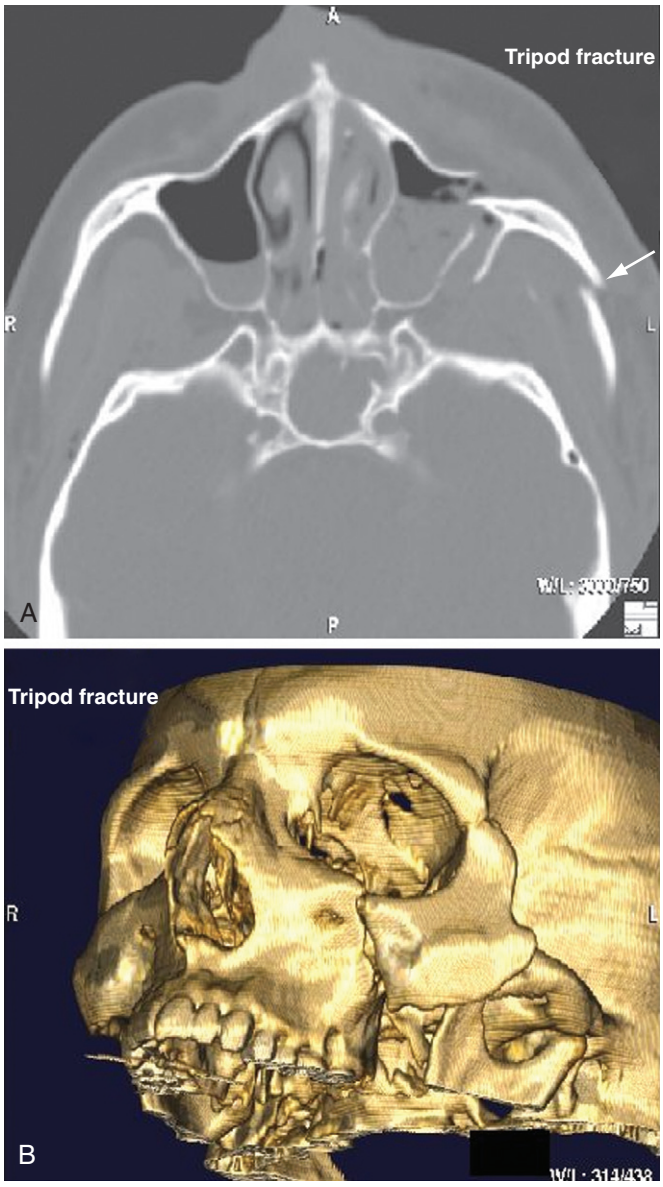


Figure 39-8. Tripod fracture. Computed tomography (**A**) and three-dimensional reconstruction (**B**).

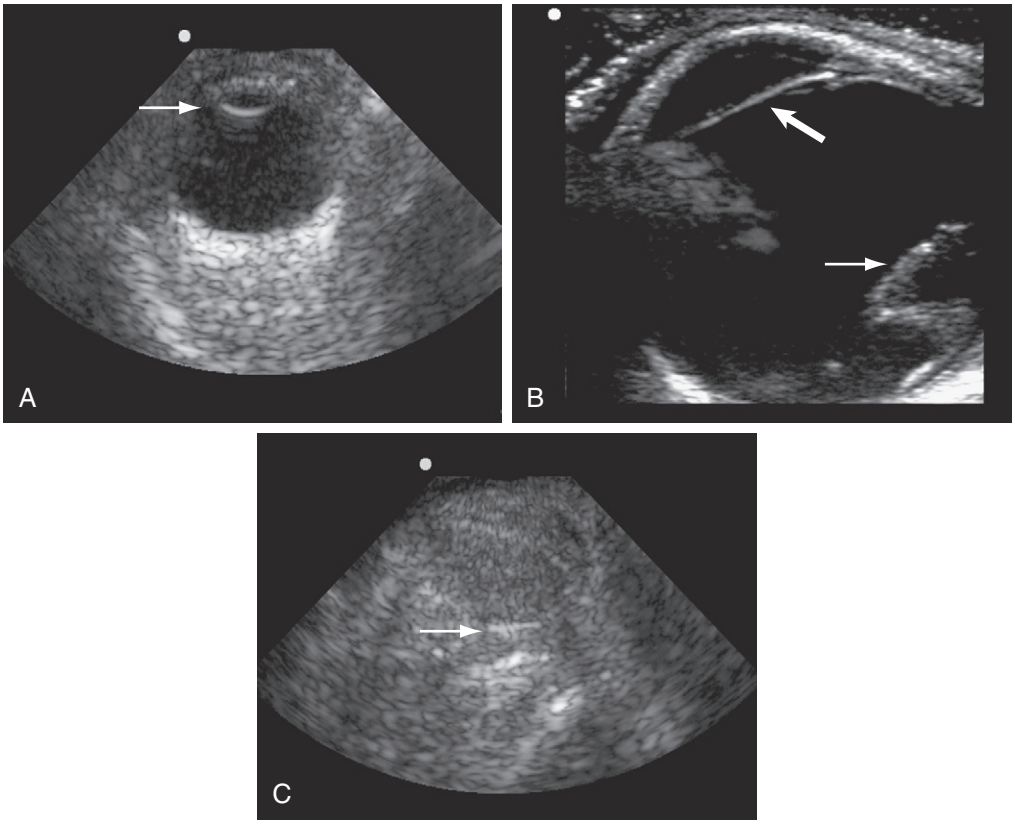


Figure 39-9. Bedside sonogram of the eye. In each image, a small white dot is placed to identify the front of the eye and *thin arrows* identify the lens. Sono A demonstrates a normal eye. Sono B shows a detached retina *(large arrow)*, and Sono C demonstrates a ruptured globe. (Images courtesy of Keith Boniface, MD.)

face should center on standard trauma care, with initial attention focused on maintaining a patent airway, adequate ventilation, and systemic perfusion.

Out-of-Hospital Care

The indications for airway management of a patient with a facial injury are the same as those for other patients: Does the patient have a currently patent airway and, if so, can the patient be expected to maintain it without intervention? If the answer to either question is "no," the patient needs to be intubated. If other injuries preclude the patient from ventilating appropriately, intubation is also required.

Patients with expanding hematomas after facial injury present a special dilemma. Injuries to the facial vasculature may cause significant hematomas that can extend into the neck or down to the supraclavicular area. Such hematomas greatly distort the normal anatomy of the pharynx and neck, making intubation and cricothyroidotomy particularly difficult. If the patient has a patent airway, he or she can speak without difficulty, and the transport time is expected to be short, no intervention should be performed and the receiving institution should be notified so that planning can begin for a difficult airway. If intubation must occur in the field, awake orotracheal intubation should be considered. If certified in its use, emergency medical services personnel should be ready to perform a surgical airway as needed. Gunshot wounds to the lower third of the face are particularly likely to require intubation for airway protection, and a significant proportion of these require a surgical airway.[62]

In the setting of significant facial trauma, active bleeding can obscure the view and make intubation considerably more difficult. Double suctioning may be required, which involves an assistant holding one suction catheter in the posterior oropharynx while the operator uses a second device more anteriorly or inferiorly as needed during the procedure. Conversely, patients with fractures of the mandible may be easier to intubate because increased mobility of the mandible may allow wider opening of the mouth.

Blind nasotracheal intubation is rarely indicated in facial trauma because of concerns about complications.[63] Multiple-injured patients who require intubation may not be breathing actively enough for this method to be of use, and out-of-hospital rapid sequence intubation is associated with a higher success rate and fewer complications.[64] Although reports of intracranial placement of an endotracheal tube in facial trauma are rare, this catastrophic complication is known to occur after blind nasotracheal intubation.[65] Any concern about an injury to the skull base or cribriform plate is a contraindication to using this method of intubation.

Control of local bleeding is the other significant out-of-hospital consideration in facial trauma. In many areas, external compression is sufficient to control bleeding during transport. Epistaxis and significant intraoral bleeding can be more difficult to treat. Even in the setting of significant nasal trauma, the soft portions of the nares can be compressed to stop anterior nasal bleeding. In an awake, alert patient with intraoral bleeding, 4 × 4-inch gauze packing may be placed into the buccal space to provide control. If these maneuvers are insufficient and the patient's injuries require spinal immobilization, intubation may be a necessary first step to control intraoral or nasopharyngeal bleeding. After intubation, large amounts of gauze can be placed via the mouth into the oropharynx and nasopharynx to obtain control via direct pressure.

If out-of-hospital personnel suspect a ruptured globe, special protection against compression of the eye (eye cup or noncontact shielding) should be provided in the field. Avulsed parts, including ears, the tip of the nose, teeth, or completely avulsed

flaps, should be transported with the patient in saline-soaked gauze.

Completely avulsed teeth should be removed and carried with the patient during transport. Neurologically normal, unintoxicated patients may be able to carry avulsed teeth in their mouths, held between gum and buccal mucosa. Patients who are not neurologically normal, who are intoxicated, who require cervical spine immobilization, who are nauseated, or who cannot be transported upright should not be transported with avulsed teeth held in the mouth. In such cases, the risk of aspirating the teeth outweighs any other concerns and the teeth should be transported in a container with sterile saline. Incompletely avulsed teeth should be left in place and not manipulated.

General Measures

The initial evaluation in the emergency department should re-address the question of intubation. In the setting of significant distortion of the mouth, oropharynx, or upper neck by avulsion or hematoma, the awake fiberoptic method may optimize the chances of a successful intubation. When there is significant distortion of the oropharynx or larynx, a laryngeal mask airway may not achieve a sufficiently tight fit to allow ventilation. Emergent cricothyroidotomy is the procedure of choice if endotracheal intubation is impossible.

Unless there is life-threatening hemorrhage from the face, after the airway has been secured, facial injuries can be safely left to the secondary survey. The emergency physician should avoid being distracted by a facial injury and search intensively for head, neck, chest, abdominal, pelvic, and extremity injuries. In-depth ocular examinations and other special testing should not be performed until other serious injuries have been managed emergently.

Significant bleeding can often be controlled by compression. If compression fails, hemostasis can be achieved in the emergency department by ligation of the relevant vessel. Great care should be taken, however, not to clamp or tie structures blindly deep within the face because serious nerve or iatrogenic injury of ductal structures could result. Massive, uncontrollable bleeding from facial fractures occurs rarely and is best treated with arterial embolization, if available.[66,67] Intra-arterial vasopressin has recently been suggested as an option for hemostasis.[68]

In the rare case of a patient acutely exsanguinating from a facial wound, the external carotid artery can be emergently ligated. This ligation is best accomplished with surgical assistance.

Bite wounds, gross contamination, or significant tattooing from foreign bodies should be addressed definitively as soon as possible, given needs of the patient's other injuries. Definitive treatment of simple soft tissue injuries can be left for 24 hours if needed after irrigation and temporary approximation. Ideally, facial fractures are treated early, before significant swelling occurs, or after several days when return of more normal facial contours can aid in the repair. The need for tetanus prophylaxis should be considered for all open wounds. If the injury is an animal bite, the need for rabies prophylaxis should be considered. Because the rabies virus is transmitted to the brain along nerve axons, and symptomatic disease theoretically may occur sooner with wounds of the head, face, and neck, initiating rabies treatment within 5 days of the injury is recommended.

Finally, because lead poisoning has been reported from the ingestion of shotgun pellets in patients with primarily facial injuries, consideration should be given to looking for the presence of pellets in the gastrointestinal tracts of these victims. A plain x-ray of the abdomen suffices. Early endoscopic removal of the pellets should limit future toxicity.[69]

Soft Tissue Injuries

Soft tissue injuries to the face present an acute cosmetic concern for the patient. Areas may be contused, lacerated, abraded, or any combination of the three. When cleaned of any debris, abrasions may be covered in a thin layer of antibiotic ointment and left exposed or covered (as possible given their location). Patients with significant tattooing benefit from topical lidocaine for anesthesia before vigorous scrubbing necessary to remove the embedded material is begun. Careful attention should be placed on removing all of the embedded material as soon as possible because epithelialization requires the creation of a new wound to remove debris later. For contusions, ice and sleeping with the head elevated may limit the degree of swelling anticipated on days 2 and 3. The patient should be cautioned to anticipate the development of periorbital swelling or ecchymosis or both over time as a result of gravity when the primary contusion has been to the brow, forehead, or bridge of the nose.

The most appropriate person to close an open wound may be the emergency physician or a consultant. Decisions about which wounds to close personally and which to ask a consultant to repair are based on the personal judgment of the emergency physician. Factors that may be considered in the decision include resource availability; the size, shape, depth, and location of the wound; and the time commitment that careful, cosmetic wound closure can entail for the emergency physician in a busy emergency department. The patient's priority with facial lacerations is cosmesis, and as such a patient may request specialty services for even minor wounds.[70] Children and patients with behavioral problems may require sedation to allow sufficient control for a cosmetic repair. Repair of facial wounds in uncooperative patients who are acutely intoxicated may be delayed until they become sober enough to cooperate for the procedure.

After anesthesia is obtained, wounds should be explored for depth, foreign bodies, or underlying fractures. Irrigation may not be necessary in simple, clean facial wounds closed within 6 hours.[71] For nongaping wounds less than 3 cm, a single-layer closure may be sufficient.[72] For gaping wounds deeper than the dermis, subcuticular buried sutures using absorbable materials should be placed to close any potential space and relieve any tension on the skin. For skin closure, tissue adhesive is faster and less painful, results in equal cosmetic results in adults and children, and can be used to close the skin over deeper sutures.[73-75] Compared with sutures, tissue adhesive has the additional benefit of not requiring later removal, but care must be taken not to unintentionally glue the eye, nares, or mouth closed.

Antibiotics are not required for simple facial wounds, which rarely become infected. Bite wounds, wounds with any evidence of devascularization, wounds through and through the buccal mucosa, wounds involving the cartilage of the ear or nose, and wounds with extensive contamination (particularly with barnyard or fecal matter) are exceptions to this rule.

The choice of antibiotic therapy will likely be an evolving topic in light of the emergence of community-associated methicillin-resistant *Staphylococcus Aureus* (CA-MRSA). Among spontaneous skin infections requiring an emergency department visit, the prevalence of CA-MRSA is now quite significant for both adults and children.[76,77] In addition, it appears that the incidence of such spontaneous infections requiring emergency department care is also increasing.[78] However, current literature does not suggest choosing antibiotics with

MRSA coverage for wound prophylaxis. If prophylactic antibiotic therapy is needed, the antibiotic should be selected based on the normal bacterial flora associated with the affected site.[79]

SPECIAL CONSIDERATIONS BY SITE

Mouth

Lacerations

Lip lacerations are common and require special consideration to maintain the appearance of the lip edge or vermilion border and the natural architecture of the philtrum. Because infiltration of even a small volume of local anesthetic may distort and blanch the soft tissue, marking the vermilion border (with nonpermanent ink or a scratch of a sterile needle) before anesthesia facilitates a cosmetic repair. To minimize any divots and maximize cosmesis and function, wounds that include the muscular layer should be closed in multiple layers. Skin may be closed with nylon or other nonabsorbable suture; the lip and mucosa should be closed with absorbable suture. Lip lacerations are not amenable to closure with wound adhesives.

Through-and-through lacerations of the mouth should be closed in layers, beginning with the intraoral mucosa and working outward in layers toward the skin. Following closure of the mucosal layer, copious irrigation of the external wound is indicated to remove lingering bacteria that otherwise would be incorporated into the wound. In small case series, prophylactic treatment with penicillin has been shown to decrease the risk of infection after significant through-and-through lacerations.[80] Lacerations that approach the parotid (Stensen's) or submandibular (Wharton's) ducts should be evaluated before intervention for ductal integrity. Saliva milked from the gland should be thin and clear and readily exit the duct. If a duct is involved or there is any doubt, a facial specialist should be consulted for evaluation and repair.

Small lacerations of the tongue or oral mucosa do not require repair. Lacerations that gape (including deep tongue lacerations) collect food and are likely to heal with a significant divot or thick scar that may hinder eating and speaking functions require repair. Deep or gaping lacerations of the tongue or oral mucosa should be closed (in layers if necessary) using absorbable sutures that do not require removal. To facilitate repair, an assistant may be needed to expose the laceration by grasping the tongue between gauze and holding a segment outside of the mouth. Some advocate placing a thick temporary suture through the distal tongue (after appropriate anesthesia) to facilitate this exposure. Discharge instructions for intraoral lacerations (whether or not repaired) should include gentle cleansing (swish and spit) with a mild antiseptic.

Perioral Burns

Young children use their mouths to explore their environment and may lick electrical outlets or bite electrical cords. The wet oral mucosa provides little electrical resistance, and the current penetrates to deeper structures, often causing a full-thickness burn at the commissure of the lip. These children need a systemic evaluation for other electrical injury (see Chapter 140); this discussion is limited to the evaluation and treatment of facial wounds. Perioral burns resulting from electrical injury can result in severe cosmetic problems and microstomia. The initial appearance of the wound may be misleadingly trivial; edema and necrosis progress over several days, and even with healing, the defect may become quite disfiguring. Traditionally, a more acute concern has been bleeding from the labial artery when the maturing burn eschar separates from underlying structures 5 to 21 days postburn, and it was previously recommended that patients be admitted so that such bleeding could be urgently addressed if it occurred. Generally, current practice is discharge with close observation at home and follow-up with otolaryngology and/or plastic surgery to address cosmesis. Large wounds can cause significant early difficulty with eating, however, and patients may require placement of a nasogastric tube for maintenance of nutrition. Initial emergency department treatment of the wound is aimed at treating discomfort and keeping the area clean.

Treatment of these injuries is controversial; options include conservative treatment with early oral splinting, immediate surgery aimed at reconstruction, or delayed excision of the burned area. Later reconstructive repair may be required to preserve mouth opening, eating, and speech clarity.[81] Early involvement of consultants is indicated, even when the burn seems to be trivial. The possibility of abuse or neglect should be considered when a child presents with a perioral burn.

Cheeks

Contusions of the cheek should raise concern for an underlying zygomatic or maxillary fracture. Lacerations of the lateral cheek may involve the parotid gland or Stensen's duct. Failure to identify and repair ductal injury results in retention of salivary fluid and enlargement of the gland or formation of a cutaneous fistula. Lacerations in the area anterior to the tragus may include injury to the facial nerve, and careful neurologic examination should be carried out before closure. Langer's lines change from mostly horizontal in the superior cheek to diagonal at the nasolabial fold, then curve convexly around the mouth; these changes should be taken into consideration when débridement is required as part of a complex repair.

Nose

Because of its anterior position, soft tissue injuries to the nose are common. Almost any trauma can result in epistaxis. Generally, epistaxis is controllable by pinching the cartilaginous anterior nose closed between two fingers and holding compression for approximately 10 minutes. If not, anterior packing is indicated. Intranasal inspection is required in any nasal injury to assess for a septal hematoma, which appears as a dark purple or bluish mass against the septum. Hematomas require drainage because they are associated with necrosis of the septum if left untreated. Simple incision and expression of the clot followed by anterior packing is sufficient. Traditional teaching has been that any patient with nasal packing should receive prophylactic antibiotics to cover *Staphylococcus* and *Streptococcus* species in order to prevent sinusitis and toxic shock syndrome. Toxic shock syndrome is a rare but measurable complication of postoperative nasal packing, occurring in approximately 16/100,000 cases; the incidence with primary packing is unknown.[82]

There is no evidence whether prophylactic antibiotics change the risk of developing toxic shock syndrome or sinusitis in postoperative or primary packing; the few studies that have been done have had sample sizes far too small to show an effect.

Because of its location and structure, fractures of the thin bones of the nasal bridge are common. Patients with contusion or tenderness over the bridge of the nose may be assumed to have fracture of the nasal bones. If the nose is acceptably straight on initial evaluation, there is no septal hematoma, epistaxis is controlled, and the patient is able to breathe out

of each nare, no further evaluation is required emergently for isolated nasal injuries. Although still in use, there is no clinical utility to radiographs of the nasal bones.[83-85]

Swelling over the bridge often precludes determination of the acceptability of the appearance at the time of injury. The patient may be provided with a referral for outpatient specialty follow-up in 3 to 5 days if the appearance at that time (when the swelling has improved) is unacceptable. In a series of surgically repaired simple nasal bone fractures, septal fractures were present in more than 50% of cases. CT did not provide any advantage in diagnosing septal fracture and should be reserved for evaluating patients suspected of having other, more complex fractures.[86]

Children with nasal fractures may have premature closure of sutures and uneven growth, particularly of the vomeroseptal line. In a child, no imaging studies are indicated, but a consultant should evaluate swelling and tenderness over the nose, preferably within 4 days of the injury.[87]

Simple lacerations of the nasal skin may be closed with sutures or tissue adhesive. If needed, anesthesia may be obtained using a nerve block of the infraorbital or supratrochlear nerves. The large pores typically present in the area of the nasal ala increase the likelihood of stitch abscesses after laceration closure in this area. Closure using an absorbable running subcuticular suture may limit the risk of this outcome. If involved, the cartilaginous portions of the ala should be closed in a separate layer. For lacerations through and through the nose, repair should be carried out from the mucosal layer outward, with copious irrigation between layers.

Ears

Blunt trauma to the ear may cause hematoma formation in the subperichondral potential space. Such hematomas are the prelude to the development of a "cauliflower ear" and should be drained by aspiration. Reaccumulation of the hematoma is prevented with a compressive dressing of the ear, but reexamination is crucial, and reaspiration should be performed as necessary.

Ear lacerations often involve the cartilage. The ear may be anesthetized using a field block: 1% lidocaine *without* epinephrine is injected subcutaneously into the skin around the base of the ear. Simple skin wounds may be closed in a single layer. Lacerations to the underlying cartilage should be repaired using absorbable material. If there is significant degloving or loss of overlying tissue, a consultant should be involved; portions of aural cartilage may be saved temporarily in a distant dermal pocket for later reconstruction. Because cartilage is avascular, chondritis, when it occurs, requires extensive débridement and is disfiguring. No randomized trials have been performed, but when the cartilage of the pinna requires repair, antibiotic prophylaxis is recommended. Compressive ear dressings (splints) are indicated after any significant repair. Ear injuries occurring before age 1 year or injuries to both ears in children are rare and should raise the suspicion of abuse.[88]

Eyes

Simple eyelid lacerations may be repaired in a single layer. Wound adhesives should be used with great caution anywhere near the eye; care must be taken not to glue the eyelids open or shut. Lacerations that involve deeper structures, loss of tissue, or the lid margin should be referred to a consultant. The integrity of the lacrimal apparatus can be assessed by instilling fluorescein into the eye and assessing for dye in the wound. A consultant should handle any injury to the sac or lacrimal duct.

Eyebrow lacerations are common because of the overhanging supraorbital ridge. Careful wound exploration should be performed to assess the integrity of the underlying bony structure. No shaving should be performed because the brow hairs may not regrow, and the hairs are necessary for realignment. If débridement is required, it should be done parallel to the hair follicles (skived) rather than perpendicular to the skin. This approach minimizes the bald area of the scar. Closing the deeper muscular layers preserves the normal expressive function of the brow. Injuries to the globe are discussed in Chapter 69.

FRACTURES AND DISLOCATIONS

For the emergency physician, the key to facial fractures is accurate diagnosis and appropriate referral. Many nondisplaced or minimally displaced facial fractures may be handled on an outpatient basis, with definitive repair or fixation delayed several days. Adult fractures develop firm fibrous union within approximately 10 to 14 days; however, definitive repair is performed most easily before day 7. Methods for diagnosing fractures were discussed previously. Fractures to the face of young children are relatively rare and may be incomplete or greenstick fractures. Fibrous union in these cases is rapid; early reduction (within 3 days) is recommended.

Antibiotics are indicated for open fractures and fractures that violate a sinus. Patients with fractures through the nasoethmoid complex that violate the maxillary bones or the floor of the orbit should be cautioned to avoid sneezing and blowing the nose because these activities force air out into the soft tissues of the face.

Surgical repair of simple nasal fractures may be performed closed and the nose splinted internally or packed. Repair of fractures of the floor of the orbit, when necessary, may require the placement of a silicone patch to occlude the opening into the maxillary sinus. Most other fractures of the face that require operative repair are performed using small metal plates (microplates), screws, or wires to stabilize fragments by attaching them to unbroken segments of bone. Efforts are made to return the features to their unfractured locations and to regain facial symmetry, if possible. Complex facial fractures may have to be repaired in a staged fashion, depending on the patient's degree of illness and the amount and quality of the bone remaining. Much of this surgery is best accomplished when the fragments are still freely mobile, but initial swelling has been reduced, on postinjury days 3 to 5.

Specific Considerations by Site

Forehead

Fractures through the superior forehead may occur above the level of the frontal sinus. These are actually skull fractures rather than facial fractures and should be addressed with special attention to risk of injury to the underlying brain. Unlike other skull fractures, frontal skull fractures often require repair for cosmesis alone. More often, fractures in this area involve the anterior portion of the frontal sinus. If even minimally displaced, these fractures require elevation for cosmesis. Fractures through the anterior wall of the frontal sinus are likely to continue through the posterior wall, and a CT scan should be performed to look carefully for this complication; if present, a CSF leak should be assumed until proved otherwise. CSF leaks into the frontal sinus may also present in a delayed manner, days or years after the initial injury.[89] Many frontal sinus fractures require complex repair or obliteration to treat this complication.[90]

The most common simple fracture of the orbit is blow-out fracture of the orbital floor, often caused by a fisted blow or ball striking the globe, increasing intraorbital pressure enough to force orbital contents through the floor. This injury may happen without other significant bony facial injury. When displaced, the bony fragments sag into the underlying maxillary sinus. If the inferior rectus muscle is entrapped in the defect, the patient is unable to elevate the globe on the affected side, resulting in diplopia on upward gaze. Stretch on the infraorbital nerve, which passes through the floor, may cause anesthesia over the anteromedial cheek and upper lip. Because signs of entrapment may result from contusion and edema and be self-limited, immediate repair is not necessary, but careful follow-up is required. Repair typically is performed 1 or 2 weeks after the injury for persistent enophthalmos or diplopia. Because of the acute limitation in the visual field, discharge instructions for patients with acute diplopia should include patching for comfort and a request not to drive until the diplopia is resolved.

Fractures of the medial orbital wall, through the lamina papyracea, are often associated with nasal injury or more general midface fractures, particularly with telescoping of the midfacial skeleton. Herniation of orbital contents into the ethmoids may occur. In one study, patients with orbital fractures with a medial component were more likely to have ocular signs of diplopia or exophthalmos than patients with fractures that did not involve the medial wall.[91] Fractures involving the superior orbit include the base of the frontal sinus, and all of the concerns about the anterior skull mentioned previously apply. Herniation of orbital structures into the frontal sinus is rare but can occur.

Many orbital fractures involve more than one wall of the orbit and may present in a constellation with complex midface fractures (Fig. 39-10). Several classification schemes aimed at improving communication among emergency physicians, radiologists, and maxillofacial surgeons have been proposed,[92-94] but no classification system is generally accepted.

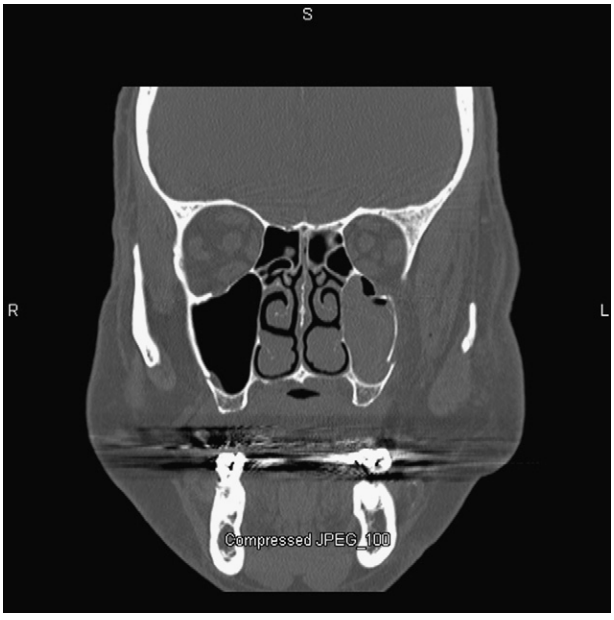


Figure 39-10. Computed tomography shows fractures of the left orbital floor and left lateral maxillary wall. There is streak artifact from dental devices.

Injury to the orbit, particularly fractures, can cause a hematoma to form within the orbit, behind the globe. If significant in size, a retro-orbital hematoma can cause acute exophthalmos. Stretch on the retinal artery limiting flow to the retina or neurapraxia of the retinal nerve may cause decreased visual acuity or blindness. Orbital emphysema associated with fractures of the medial wall or floor rarely results in a space-filling lesion with the same effect. This is a true emergency; drainage of the air or blood via lateral canthotomy with cantholysis is indicated to save the patient's vision. Needle aspiration of entrapped air may also be attempted, but this may be best left to a consultant given the proximity of the globe.

Midface

Tripod (or trimalar) fractures are among the simplest fractures of the midface and include fractures of three bones: the lateral orbit, the zygoma, and the maxilla (Fig. 39-10). Typically caused by a direct blow, these fractures are often displaced and require operative stabilization. If left untreated, the area may "sink" posteriorly and inferiorly, giving an unacceptable appearance of facial asymmetry emphasized by the inferior position of the orbit and malar flattening. On the initial physical examination, there may be a large contusion over the cheekbone, enophthalmos, or malocclusion of the upper teeth. Fractures through the anterior wall of the maxillary sinus may denervate the maxillary teeth because the dentoalveolar nerves run in tunnels in this area.

More complex fractures of the midface are classified using the Le Fort system, although many complex fractures defy classification with this system. A Le Fort I fracture involves a transverse fracture through the maxilla above the roots of the teeth and may be unilateral or bilateral. Patients may complain of malocclusion, and the maxilla may be mobile when the upper teeth are grasped and rocked. A Le Fort II fracture is typically bilateral and pyramidal in shape. It extends superiorly in the midface to include the fracture of the nasal bridge, maxilla, lacrimal bones, orbital floor, and rim. In these cases, the nasal complex moves as a unit with the maxilla when the teeth are grasped and rocked. In the current age of CT scans, in which the full extent of comminution can be appreciated, simple Le Fort III fractures are rare but essentially involve fracturing of the connections between the elements of the skull and the face (craniofacial dysjunction). These fractures start at the bridge of the nose and extend posteriorly along the medial wall of the orbit (ethmoids), along the floor of the orbit (maxilla) and through the lateral orbital wall, and finally break through the zygomatic arch. Intranasally, they extend through all the lesser bones to the base of the sphenoid and frequently are associated with a CSF leak.

Significant force to the bridge of the nose may fracture the deep nasoethmoid complex without creating a formal Le Fort pattern. CT is the initial test of choice in this setting. Fractures to the central portion of the ethmoid bone (cribriform plate) are likely to be associated with a CSF leak and commonly result in anosmia.

If possible, patients with a CSF leak should have the head elevated 40 to 60 degrees. Head elevation minimizes the intracranial pressure, with the idea of decreasing the flow and allowing the leak to seal. Often, these patients are treated with antibiotics; however, this practice is controversial, and most of the studies supporting it involve small, local case series.[95] In one meta-analysis, antibiotics did not decrease the rate of meningitis in the setting of CSF leak.[96] Neurosurgeons should be involved in the care of patients with CSF leaks, although many leaks will spontaneously resolve.[97]

Fractures involving the deeper structures of the midface may be associated with significant bleeding into the nose or oropharynx. Anterior nasal packing may be performed safely in the adult patient with multiple trauma. Even a 10-cm anterior pack should not reach the skull base in a skeletally mature person. Significant or massive bleeding into the posterior nasopharynx presents a complex problem and occurs in less than 1% of patients with midface fractures. It may be treated with nasal packing and immediate fracture reduction.[42,98] Unless the anatomy is well understood and the skull base known to be intact, the use of a long balloon catheter (Foley) should be avoided for control of posterior bleeding. The unintended positioning of these items within the intracranial[99,100] or intraspinal space[101] during blind nasal insertion has been well documented, and when the face is grossly distorted, preinsertion measuring or other methods of preventing this outcome have not been adequately tested. There are no reports of the intracranial placement of commercial catheters designed for posterior epistaxis, but if the midface is significantly distorted or telescoped, they may be long enough to reach the intracranial space. An alternative method for containing posterior nasal bleeding is to provide compression by packing the area with gauze by hand from the oropharynx after intubation.

Zygoma

Isolated fractures of the zygoma are relatively rare, usually the result of a direct blow, and are often displaced. Because the condyle of the mandible may disturb zygomatic fragments while moving, fractures with significant displacement are likely to result in trismus or discomfort with mouth opening. Surgical repair is usually required to return the cheekbone to an acceptable position.

Mandible

Fractures of the mandible can result from any significant force applied to its U shape. Because of its shape, multiple fractures may result from a single blow, and the fracture sites may be distant from the site of impact. Depending on the location of the fractures, the patient may have trismus (fractures of the coronoid process, neck, or rami), dental malocclusion, swelling, and tenderness intraorally or externally. Anesthesia of the lower lip may occur if there is damage to the inferior dental nerve.

Fractures of the symphysis, body, angle, or rami usually require early splinting, typically by the placement of arch bars to accomplish interdental fixation, commonly known as "wiring the jaw shut." Fixation limits fracture motion, decreases the patient's discomfort, and, if the fracture is minimally displaced, may provide complete fracture care. Impacted and nondisplaced fractures occasionally are treated with only a soft diet, and fractures of the coronoid alone usually require no intervention, but these decisions should be made in consultation with an oral surgeon or other specialist. Arch bars may be placed in the emergency department or operating room and typically are placed by a specialist (see Fig. 39-6). Fracture reduction may require the extraction of teeth adjacent to the fracture line. Patients with open fractures require antibiotics and usually hospitalization. When the fractures are closed and adequate stabilization can be obtained, elective operative repair can be performed as an outpatient procedure in 3 to 5 days.

In one study, 17 to 22% of pediatric patients 4 to 11 years old developed facial growth disturbances after a fractured mandible and required later orthognathic surgery for correction. Children younger than 4 or older than 11 years were much less likely to develop this complication.[102] Because of the frequency of this complication, children in this age group with a blow to the chin and any trismus or tenderness over the TMJ should be assessed carefully with panorex imaging for condylar fracture and referred appropriately.

Dental and Alveolar Trauma

Trauma to the teeth may occur with or without other facial injury. In the setting of caries, tooth fractures may occur with eating relatively soft foods. Tooth fractures are classified by the Ellis system. Class I fractures involve only the enamel of the tooth, are not painful, and can await dental evaluation as an outpatient. Class II fractures expose the yellow dentin and may be painful. These also can await dental care, but they may be covered with a dressing of calcium hydroxide and aluminum foil. Class III fractures expose the dental pulp, seen as a red line or dot, and are exquisitely painful. These require early evaluation by dentists or endodontists.

Sufficient energy to the area avulses teeth from their sockets. Multitrauma patients, particularly patients who are intoxicated, required to be supine for cervical spine immobilization, or neurologically impaired, should have avulsed or mostly avulsed teeth removed from the mouth and placed externally in saline as an aspiration precaution. In a critically ill multitrauma patient, avulsed teeth should be among the lowest priorities and replanted only if the care of other injuries would allow it and there is no risk of aspiration if the teeth loosen.

To perform a reimplantation, the physician disturbs the socket as little as possible, gently rinses off the tooth (the root should not be wiped), and places it into the socket where it "clicks" into place. If the tooth is only partially avulsed, extruded, or laterally luxated, it should not be removed; it should be reimplanted or relocated. Intruded teeth should not be manipulated. Reimplantation can be painful and may require local anesthesia with a regional dental block. Alternatively, the area of a single socket may be anesthetized by placing approximately 0.5 mL of 1% lidocaine without epinephrine into the buccal sulcus and gum on the outer side of the alveolar ridge. After reimplantation, the tooth requires stabilization with acrylic splint or wiring to the adjacent teeth.

Replanted teeth may or may not "take" acutely, but it can take weeks to assess the final success of reimplantation. The length of time out of the socket seems to play a critical role in the initial success. Among teeth successfully reimplanted in less than 1 hour, more than 66% were radiographically healed and functionally normal after 5 years. For teeth successfully reimplanted after 3 hours, more than 80% had signs of inflammation and bone resorption after the same period of time.[103]

In children, the front maxillary incisors are most commonly avulsed. After reimplantation, these teeth may ankylose and fail to "grow out" normally, requiring later extraction or orthodontic intervention for cosmesis. This situation is most common among children age 6 to 10 years with avulsed adult teeth.[104]

Avulsed teeth missing after significant trauma should be carefully sought, including obtaining a chest x-ray. In an acute event, the patient may not recall aspirating a tooth; this is more likely if the patient is intoxicated or neurologically impaired. If the tooth is below the diaphragm on the film, it does not require retrieval. Teeth lodged in a bronchus or the esophagus require bronchoscopic or endoscopic retrieval. Aspirated teeth result in pulmonary abscess formation unless removed.

Fractures through the alveolar ridge may result in a group of teeth being dislodged and out of position, often leaning inward. These teeth require stabilization with wire or acrylic splinting after fracture reduction returns the teeth to their

correct location. The involved teeth may or may not survive after such a fracture, and careful follow-up with a dentist or oral surgeon is required.

Temporomandibular Joint

The TMJ is complex, with the condyle of the mandible undergoing rotation and translation anteriorly during normal mouth opening. The function of the joint is preserved by a meniscus, which overlies the condyle. Essentially, the joint between the meniscus and the condyle is a hinged joint, allowing rotation, and the joint between the meniscus and the temporal bone is a sliding joint, allowing translation. A formal, thick joint capsule does not exist at the anteromedial portion of the joint; loose, relatively weak synovial tissue is positioned here to allow translation to occur.

Trauma to the TMJ may tear the meniscus or injure the collateral ligaments holding it in a normal position. This injury can cause the meniscus to fail to translate normally, resulting in clicking or popping as it catches up to the condyle or inability to open the mouth fully because the meniscus completely fails to translate. Patients without fracture but with acute pain and difficulty with mouth opening should be placed on soft foods, asked not to yawn or struggle to open their mouths widely, and referred to an oral surgeon with expertise in TMJ pathology. Pediatric patients with posttraumatic internal derangements of the TMJ are prone to asymmetry of facial growth and retrognathia. In one study, 88% of children injured before their ninth birthday had significant facial abnormalities years later.[105]

Because of the anatomy and function of the joint, anterior dislocation of the TMJ can occur after widely yawning, laughing, kissing, singing, or other activities that involve spontaneous, wide opening of the mouth. When the condyle is out, spasm of the muscles of mastication prevents spontaneous reduction. Significant trauma is more likely to cause a fracture-dislocation. Simple dislocation may be unilateral or bilateral, and the patient complains of being unable to close the mouth. In unilateral dislocation, the jaw is rotated laterally away from the affected joint; bilateral dislocation causes significant protrusion of the jaw. The jaws of these patients are often so widely open that they cannot swallow their secretions and are actively drooling. Speech is often garbled by the patient's inability to touch the tongue to the roof of the mouth or the maxillary teeth. There is a depression in the area of the affected TMJ on inspection of the patient's face.

If the mechanism of injury suggests a fracture, the area should be imaged with plain x-ray or panorex before attempting reduction. To reduce a simple dislocation, the patient should be seated upright. To maximize leverage, the best position may be for the patient to be seated in a regular chair with the operator standing in front of the patient. As in dislocations of other joints, adequate analgesia and sedation are required for success. Using the thumb or index finger placed into the buccal sulcus on either side of the mouth, the angle of the jaw is pressed downward while rotating the symphysis (chin) upward and backward. Care should be taken not to place fingers along the crowns of the teeth; when relocation occurs, spasm of the muscles of mastication snaps the mouth shut with force. If this is the only location possible for the physician's fingers, gauze wrappings should be placed to protect them.

Panorex or x-rays are suggested after the first episode of dislocation. The patient is discharged with pain medicine, a soft diet for 2 weeks, and outpatient follow-up with an oral surgeon. Patients with an episode of dislocation are predisposed to a recurrence. In patients who are frequently dislocating, interdental fixation may be required for 2 or 3 weeks.

DISPOSITION

The decision to discharge or admit patients with facial trauma depends on their associated injuries, general injury severity, and plans for treatment. Patients with isolated facial trauma that has been repaired or stabilized and with no airway issues are usually discharged.

KEY CONCEPTS

- The face is central to the patient's ability to breathe, eat, and communicate. Injuries to the face can have serious psychological and psychosocial consequences.
- Facial injuries may be prevented by the appropriate use of safety belts, child restraints, air bags, helmets, and mouth and face guards.
- The epidemiology of facial injury is changing, with an increasing proportion occurring as a result of interpersonal violence. A careful history is required, and the possibility of abuse should be considered for every patient.
- Shock is rare from facial trauma and results only from obvious external bleeding. Facial injuries should not distract the emergency physician from aggressively searching for other causes of shock.
- Assertive management of the airway is indicated in a patient with significant facial injuries. Surgical management (cricothyroidotomy) may be required, particularly with gunshot wounds.
- Directed facial CT scanning is the best imaging technique in patients with obvious injuries.
- Definitive treatment may be delayed if needed to allow other serious injuries to be addressed.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 40

Spinal Injuries

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PERSPECTIVE

Background

Prehistoric humans undoubtedly suffered little in the way of significant spinal injury. Their semierect posture combined with well-developed posterior cervical muscles protected the cervical spine against day-to-day trauma. Evolution, however, did much to undo this initial protective state. As humans assumed an upright posture, the shoulders dropped away from the newly elevated head and the hypertrophied paraspinous muscles atrophied. This increased the head's range of motion but diminished the spine's protection. Although civilization heightened man's inventiveness, it unfortunately did little to curb his aggressiveness. Automobiles replaced horse-drawn carriages, and fists and clubs gave way to knives and guns, making spinal injuries more common in the modern era.

Epidemiology

Statistics from the National Spinal Cord Injury Database show that motor vehicle collisions (MVCs) account for almost half of all spinal injuries.[1] Speeding, alcohol intoxication, and failure to use restraints are major risk factors. The next most common cause of spinal cord injury (SCI) is falls, followed by acts of violence (primarily gunshot wounds) and sporting activities. There are currently more than 250,000 spinal injury victims living in the United States, and 11,000 new cases occur each year. Approximately 80% of victims are male, and the average age at injury is 38 years. The lifetime cost to care for SCI victims ranges from $500,000 for people older than 50 years with incomplete motor function to $3 million for people younger than 25 years with complete paraplegia. The total cost to society from life-long medical expenses and lost productivity is estimated to be more than $5 billion.[2] The devastating emotional and psychological impact on the victims and their families is incalculable.

PRINCIPLES OF DISEASE

Anatomy and Physiology

The human spine consists of 33 bony vertebrae: 7 cervical, 12 thoracic, 5 lumbar, 5 sacral (fused into one), and 4 coccygeal (usually fused into one) (Fig. 40-1).[3] These 26 individual units are separated from one another by flexible intervertebral disks and connected to form a single functioning unit by a complex network of ligaments. In addition to providing basic structural support, the vertebral column protects the spinal cord, which extends from the midbrain to the level of the second lumbar vertebra. Nerves that receive and transmit sensory, motor, and autonomic impulses pass to and from the spinal cord through intervertebral foramina.

To assess the stability of spinal injuries below C2, it is helpful to view the spine as consisting of two columns. The anterior column is formed by alternating vertebral bodies and intervertebral disks held in alignment by the anterior and posterior longitudinal ligaments (Fig. 40-2A). The posterior column, which contains the spinal canal, is formed by the pedicles, transverse processes, articulating facets, laminae, and spinous processes. It is held in alignment by the nuchal ligament complex (supraspinous, interspinous, and infraspinous ligaments), the capsular ligaments, and the ligamentum flavum (see Fig. 40-2B). If both columns are disrupted, the spine will move as two separate pieces, and there is a high likelihood of that movement causing or worsening an SCI. In contrast, if only one column is disrupted, the other column resists further movement, and the likelihood of an SCI occurring is much less and depends on the strength of the intact ligaments.

Pathophysiology

Classification of Spinal Column Injuries

Acute spinal injuries are classified according to the mechanism of trauma: flexion, flexion-rotation, extension, and vertical compression (Table 40-1).[4,5]

Flexion. Pure flexion injuries involving the C1-C2 complex can cause unstable *atlanto-occipital* or *atlantoaxial joint dislocation*, with or without an associated fracture of the odontoid (Fig. 40-3). These injuries are considered unstable due to their location and the relative lack of muscle and ligamentous support.

In pure flexion injuries below C2, a longitudinal pull is exerted on the strong nuchal ligament complex, which usually remains intact. Most of the force is expended on the vertebral body anteriorly, causing a *simple wedge fracture.* Radiographically, there is a diminished height and increased concavity of the anterior border of the vertebral body, an increased density of the vertebral body resulting from bony impaction, and prevertebral soft tissue swelling (Fig. 40-4). Because the posterior column remains intact, this injury is usually stable and rarely accompanied by nervous system damage. However, spinal instability may occur with severe wedge fractures (loss of more

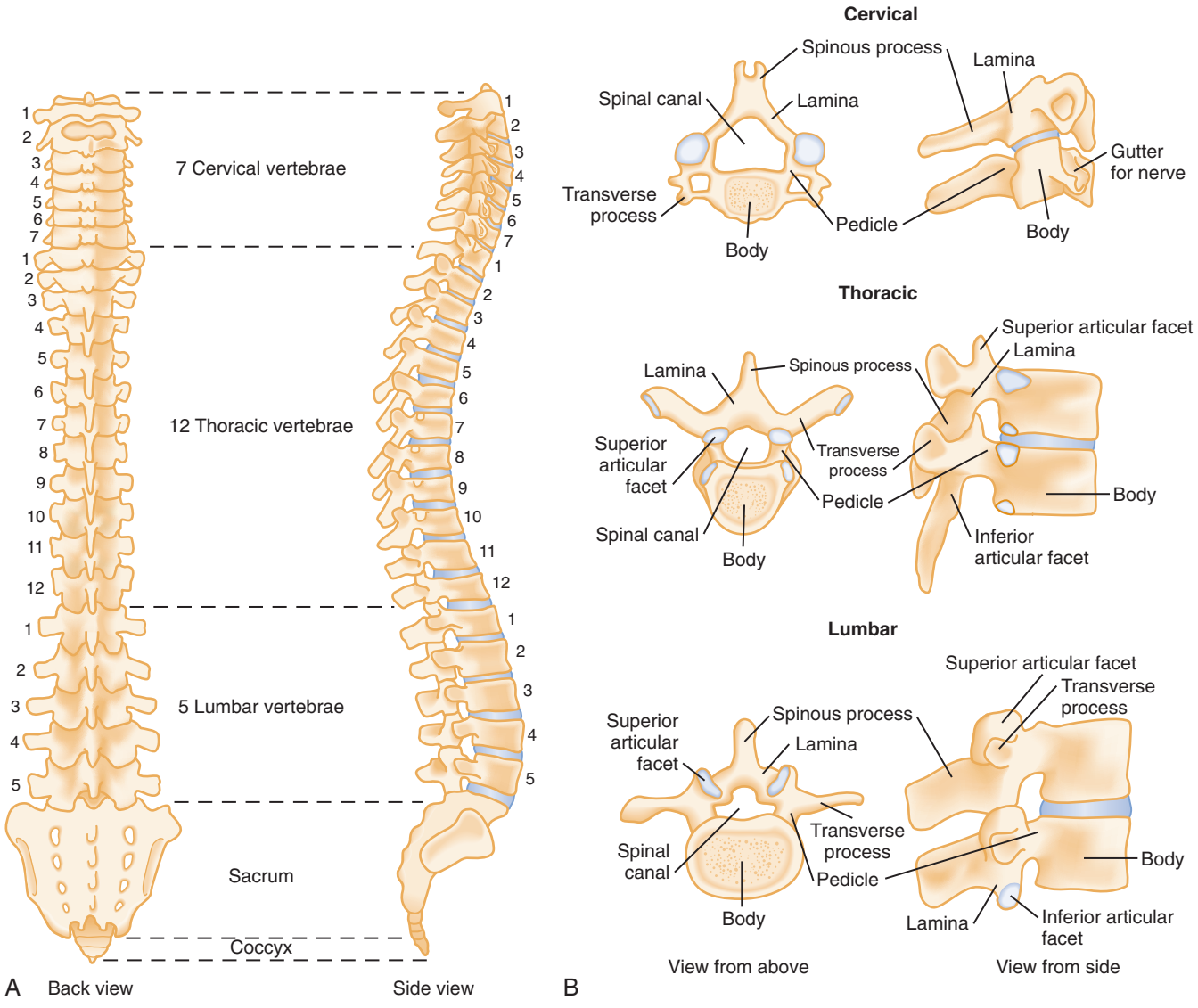

Figure 40-1. **A**, Vertebral column. **B**, Typical vertebrae.

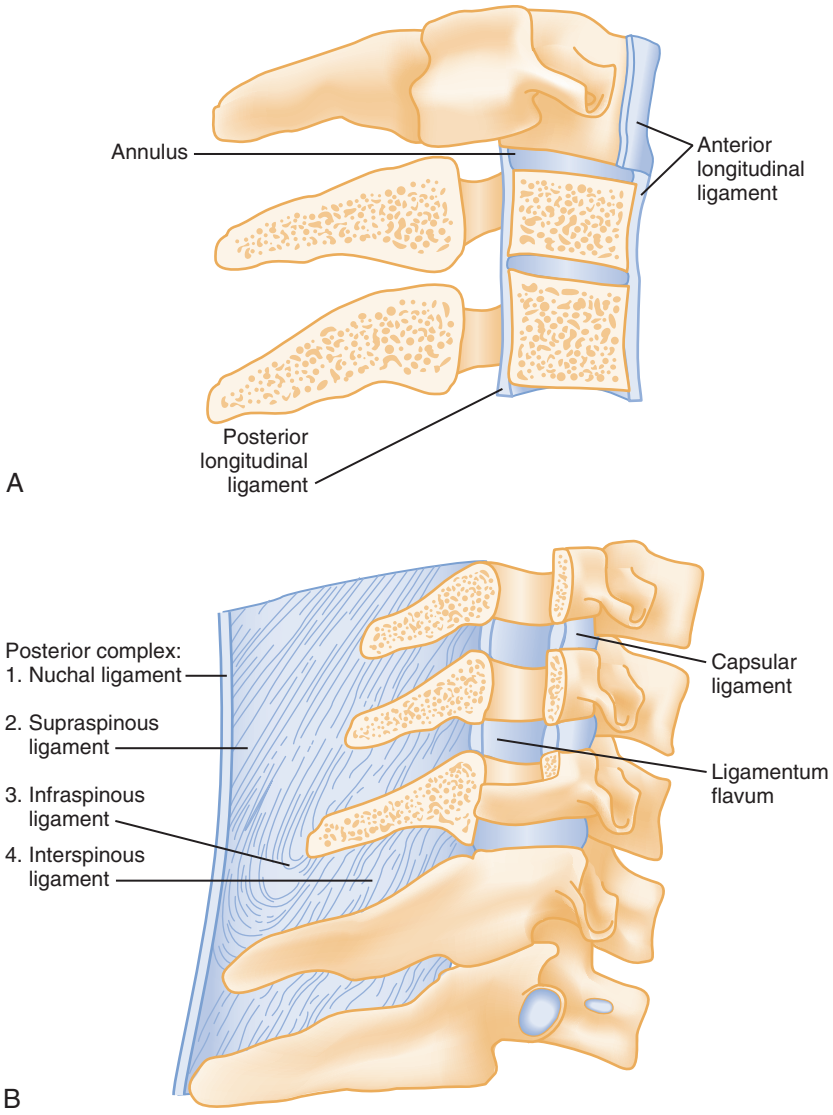

Figure 40-2. **A**, Ligaments of the anterior column. **B**, Ligaments of the posterior column.

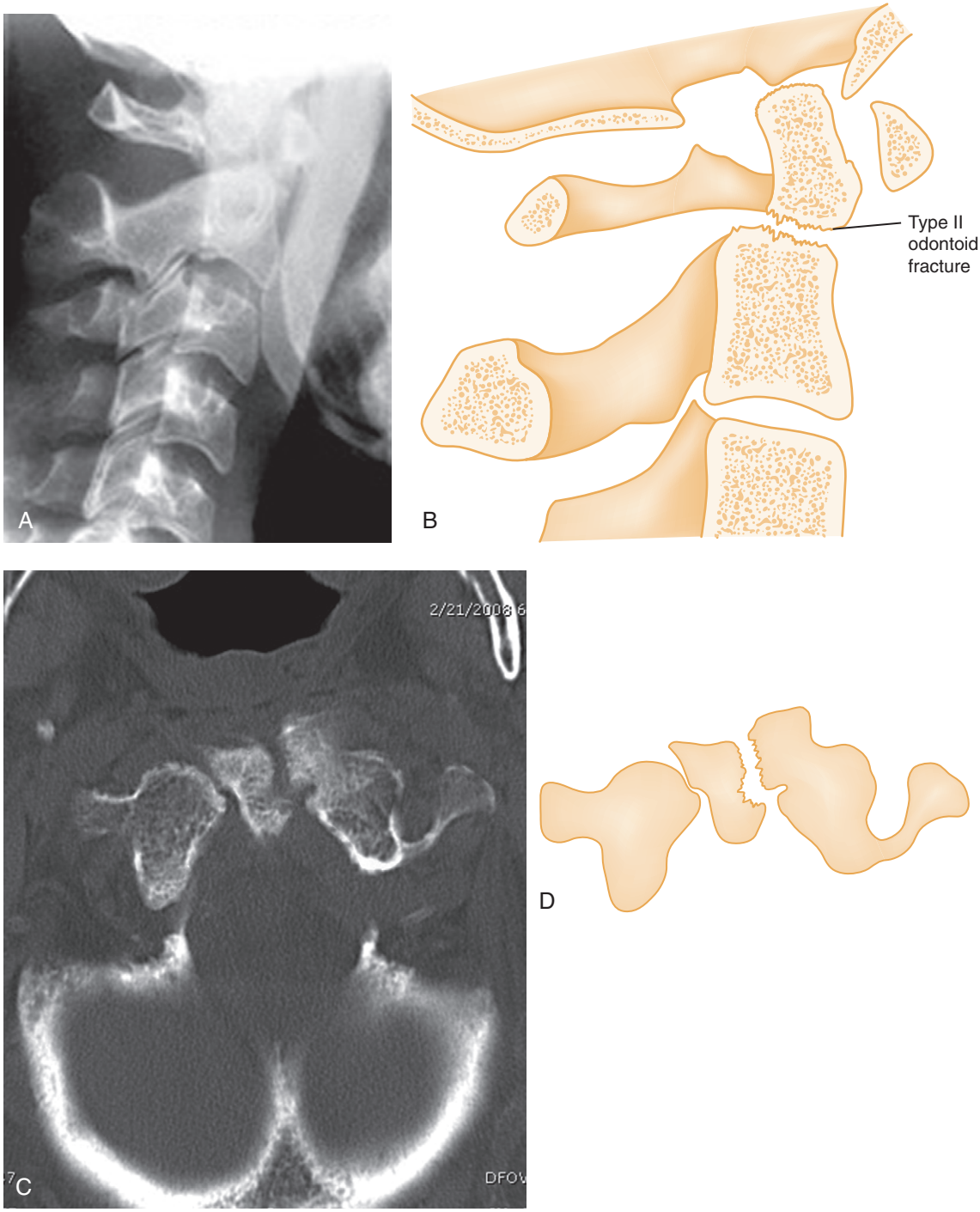

Figure 40-3. **A** and **B,** Odontoid fracture with anterior dislocation. Mechanism: flexion with shearing. Stability: unstable. **C** and **D**, A fracture through the odontoid process is demonstrated along with retropharyngeal swelling.

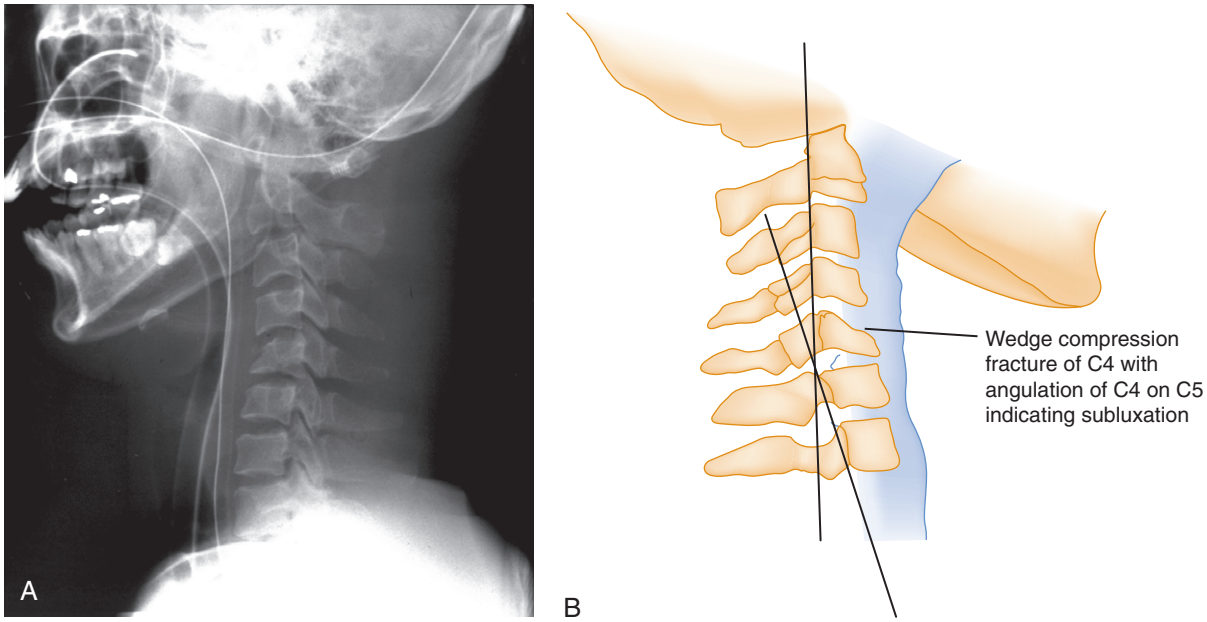

Figure 40-4. **A,** Lateral view of a wedge fracture of C4 with angulation. Mechanism: flexion. Stability: mechanically stable. **B,** Note the anterior wedging of the C4 vertebral body and angulation of C4 on C5.

Table 40-1 Classification of Spinal Injuries

MECHANISM OF SPINAL INJURY	STABILITY
Flexion	
Wedge fraction	Stable
Flexion teardrop fracture	Extremely unstable
Clay shoveler's fracture	Stable
Subluxation	Potentially unstable
Bilateral facet dislocation	Always unstable
Atlanto-occipital dislocation	Unstable
Anterior atlantoaxial dislocation with or without fracture	Unstable
Odontoid fracture with lateral displacement fracture	Unstable
Fracture of transverse process	Stable
Flexion-Rotation	
Unilateral facet dislocation	Stable
Rotary atlantoaxial dislocation	Unstable
Extension	
Posterior neural arch fracture (C1)	Unstable
Hangman's fracture (C2)	Unstable
Extension teardrop fracture	Usually stable in flexion; unstable in extension
Posterior atlantoaxial dislocation with or without fracture	Unstable
Vertical Compression	
Bursting fracture of vertebral body	Stable
Jefferson fracture (C1)	Extremely unstable
Isolated fractures of articular pillar and vertebral body	Stable

than half the vertebral height) or multiple adjacent wedge fractures, and such injuries are best treated as being potentially unstable.

A *flexion teardrop fracture* results when severe flexion forces cause anterior displacement of a wedge-shaped fragment (resembling a teardrop) of the anteroinferior portion of the involved vertebral body (Fig. 40-5). Since this injury commonly involves ligamentous disruption, it is often associated with neurologic injury.

The *clay shoveler's fracture* is an oblique fracture of the base of the spinous process of one of the lower cervical segments (Fig. 40-6). The injury derives its name from its common occurrence in clay miners in Australia during the 1930s. When a miner lifted a heavy shovelful of clay, abrupt head flexion against the supraspinous ligament resulted in an avulsion fracture of the spinous process. Today, this fracture is more commonly seen following direct trauma to the spinous process and after sudden deceleration MVCs that result in forced neck flexion. Since this injury involves only the spinous process, it is stable and not associated with neurologic involvement.

Pure *spinal subluxation* occurs when the ligamentous complexes rupture without an associated bony injury. This injury begins posteriorly in the nuchal ligament and proceeds anteriorly to involve other ligaments. The lateral radiograph with the neck in the neutral position may show a widening of both interspinous and intervertebral spaces posteriorly at the level of injury, and oblique views may demonstrate a widening or abnormal alignment of the facets (Fig. 40-7). These findings are often subtle and may be missed if flexion and extension views are not obtained. Although rarely associated with neurologic damage, this injury is potentially unstable.

Bilateral facet dislocations occur when a greater force of flexion causes soft tissue disruption to continue anteriorly to the annulus fibrosis of the intervertebral disk and the anterior longitudinal ligament, resulting in an extremely unstable condition. The forward movement of the spine causes the inferior articulating facets of the upper vertebra to pass upward and over the superior facets of the lower vertebra, resulting in anterior displacement of the spine above the level of injury.

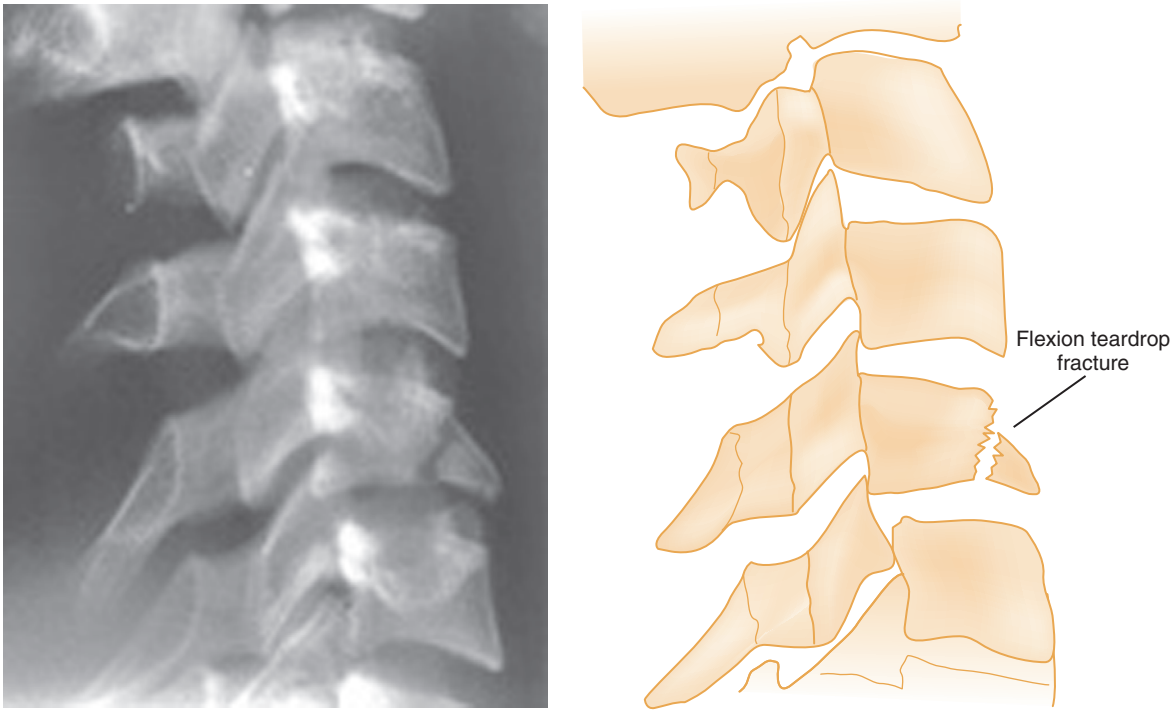

Figure 40-5. Lateral view of a teardrop fracture. Mechanism: flexion. Stability: unstable. The fractured fragment off the C5 body resembles a teardrop.

Radiographically, the anterior displacement will appear to be greater than one half of the anteroposterior (AP) diameter of the lower vertebral body with the superior facets anterior to the inferior facets (Fig. 40-8).

Shear Injury. Trauma to the head directed in an AP direction may result in fracture of the odontoid process above the transverse ligaments (type I) or, more commonly, at the base of the odontoid process where it attaches to C2 (type II) (Fig. 40-9). Slight angulation of the force may result in extension of the fracture into the body of C2 (type III). Type II odontoid fractures are unstable and often complicated by nonunion. Spinal cord injury is uncommon but can occur.

Flexion-Rotation. *Rotary atlantoaxial dislocation* is an unstable injury visualized best on open-mouth odontoid radiographs (Fig. 40-10). If the skull is shown obliquely, there may be a false-positive asymmetry between the odontoid process and the lateral masses of C1. However, when the x-ray reveals symmetrical basilar skull structures, a unilaterally magnified lateral mass confirms a C1-C2 dislocation.

A *unilateral facet dislocation* involves both flexion and rotation. The rotational component of this injury occurs around one of the facet joints, which acts as a fulcrum. Simultaneous flexion and rotation cause the contralateral facet joint to dislocate, with the superior facet riding forward and over the tip of the inferior facet and coming to rest within the intervertebral foramen. In this position, the dislocated articular mass is mechanically locked in place, making this a stable injury, although the posterior ligament complex is disrupted. The frontal radiograph shows the spinous processes above the level of dislocation displaced from the midline in the direction of the rotation (Fig. 40-11A and B). The lateral radiograph shows a forward displacement of the dislocated segment on the vertebra below (less than one half the AP diameter of this vertebral body) and a rotation of the dislocated vertebra and those above it (see Fig. 40-11C and D). Cervical fractures and dislocations may cause torticollis, but torticollis may also be due to a benign process such as a muscle spasm. It may be difficult to differentiate torticollis due to cervical fracture or dislocation from torticollis caused by severe muscle spasm, however, and oblique projections may be necessary to demonstrate the dislocated facet joint (see Fig. 40-11E and F).

Due to the varying shapes of the articular processes, particularly between the cervical and lumbar regions, different types of flexion-rotation injuries result. In the cervical region, where articular processes are small, flat, and almost horizontal, unilateral facet dislocations occur as described previously. In the lumbar region, however, where articular processes are large, curved, and nearly vertical, unilateral facet dislocation is rare. Instead, one or both articular processes fracture, and the upper vertebra swings forward. Commonly seen in the thoracolumbar and lumbar region, this rotation fracture-dislocation is unstable (Fig. 40-12).

Extension. The *posterior neural arch fracture* of the atlas (C1) results from the compression of the posterior elements between the occiput and the spinous process of the axis (C2) during forced neck extension (Fig. 40-13). Although the anterior arch and the transverse ligament remain intact, this fracture is potentially unstable because of its location.

The *hangman's fracture*, or traumatic spondylolysis of C2, occurs when the cervicocranium (the skull, atlas, and axis functioning as a unit) is thrown into extreme hyperextension as a result of abrupt deceleration. Bilateral fractures of the pedicles of the axis occur with or without dislocation (Fig. 40-14). Although this lesion is unstable, cord damage is often minimal because the AP diameter of the neural canal is greatest at the C2 level, and the bilateral pedicular fractures permit the spinal canal to decompress itself. Originally described in victims of hanging injury, today it is most often the result of head-on MVCs.

The *extension teardrop fracture* occurs when abrupt extension of the neck causes the anterior longitudinal ligament to pull

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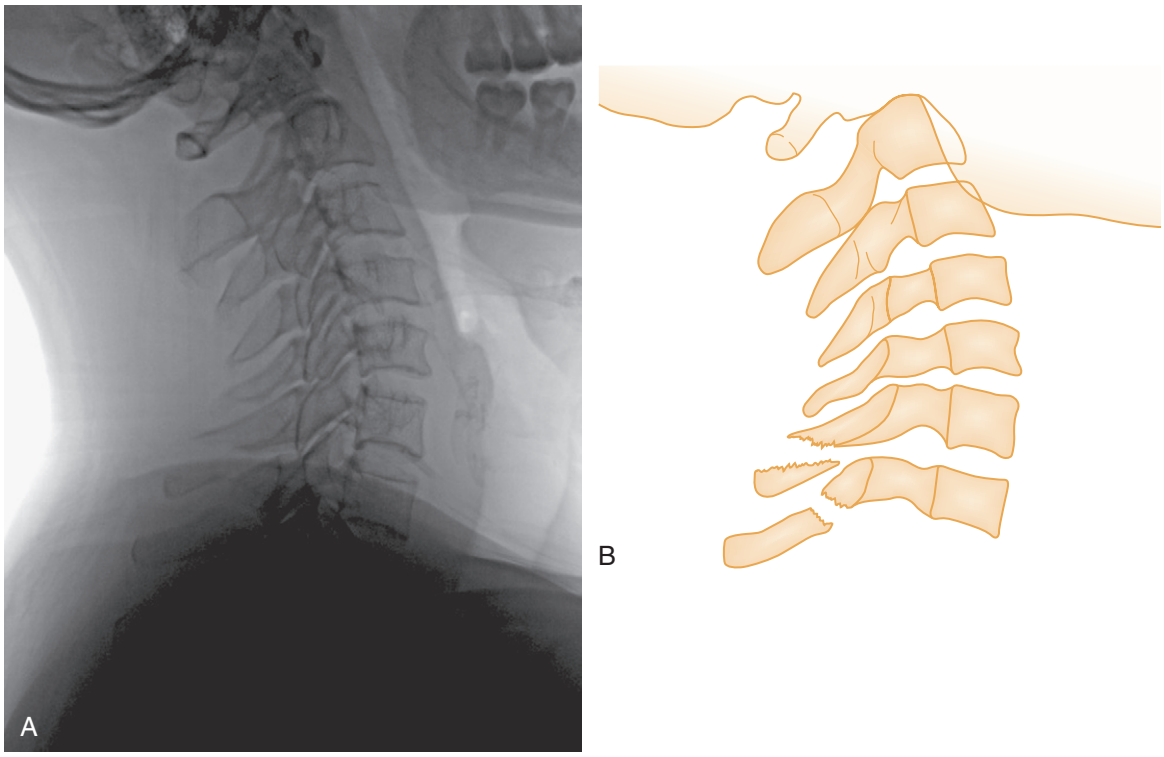


Figure 40-6. Clay shoveler's fracture. Mechanism: flexion. Stability: mechanically stable. **A** and **B**, Note the avulsed fragment off the tip of the C7 spinous process in an underpenetrated lateral view.

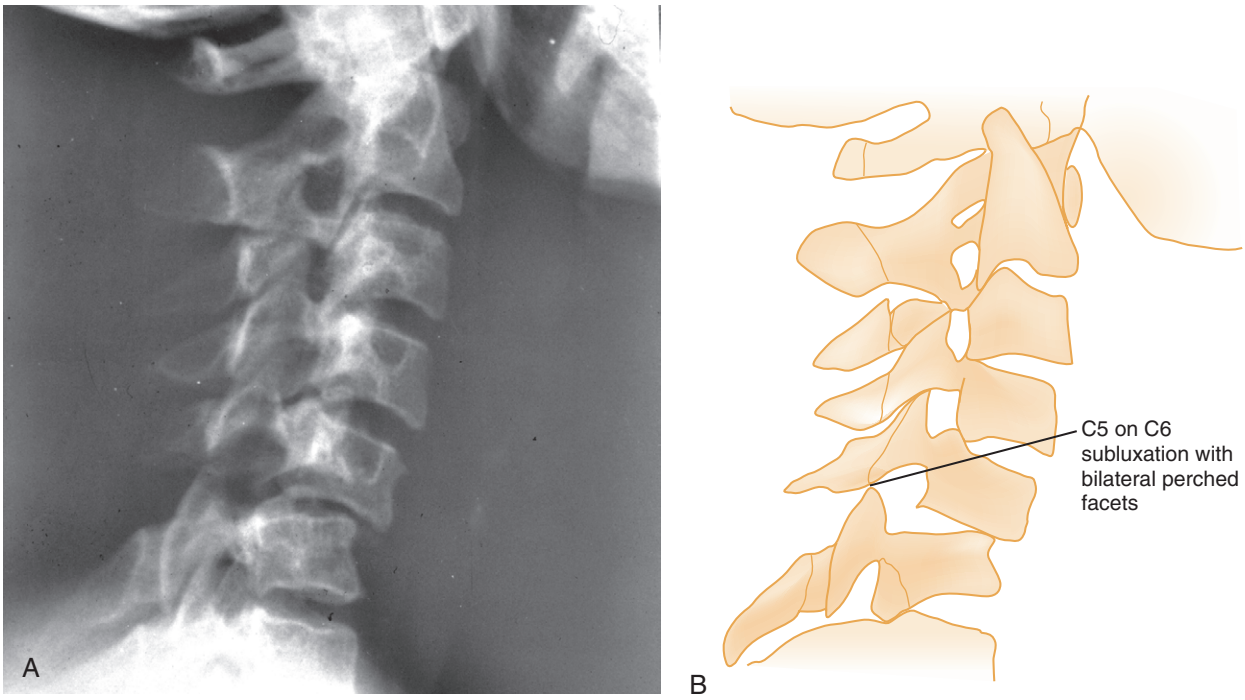


Figure 40-7. Subluxation with bilateral "perched" facets at C5 and C6. Mechanism: flexion. Stability: unstable. **A** and **B**, Lateral view shows severe subluxation of C5 on C6.

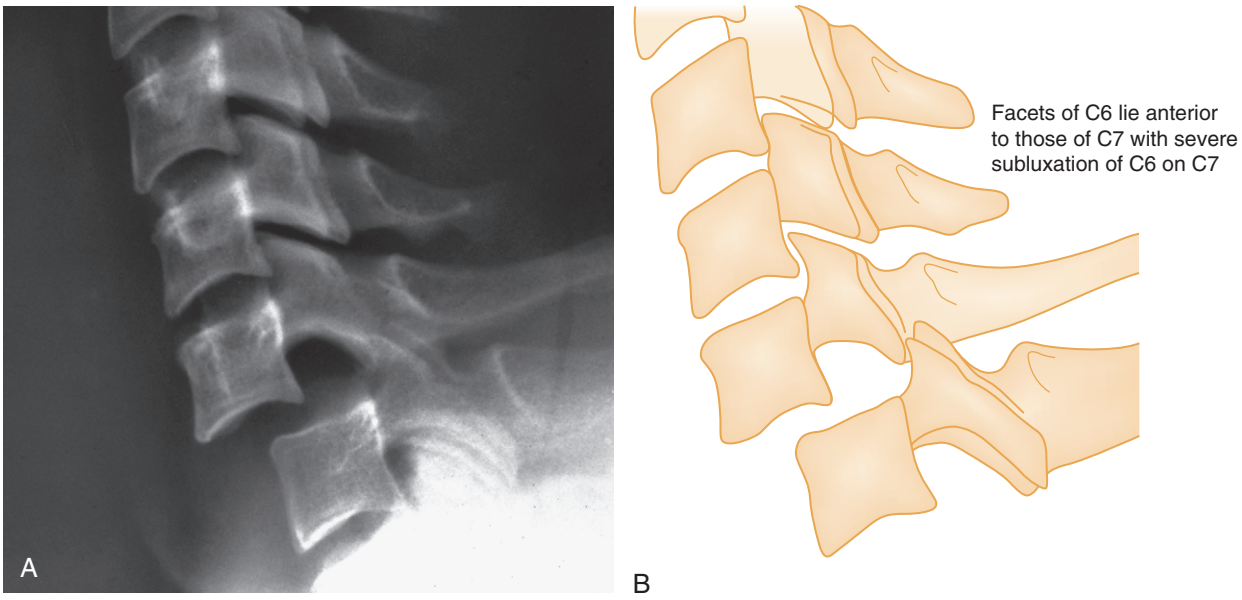
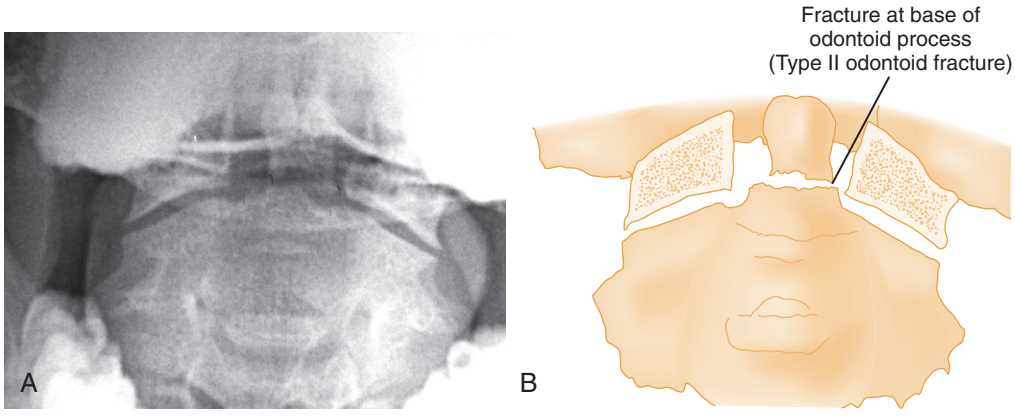


Figure 40-8. Facets of C6 lie anterior to those of C7 with severe subluxation of C6 on C7.



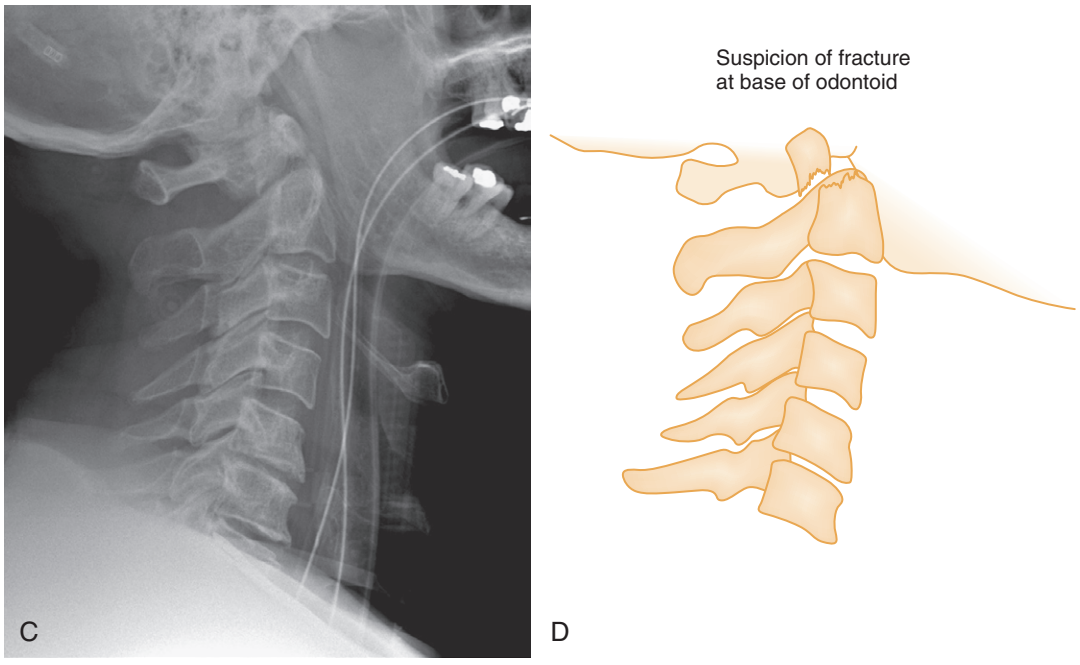
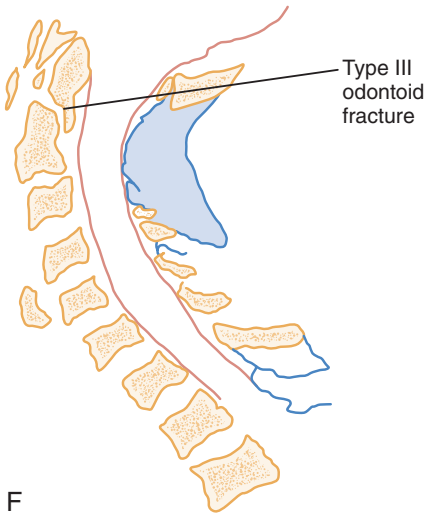
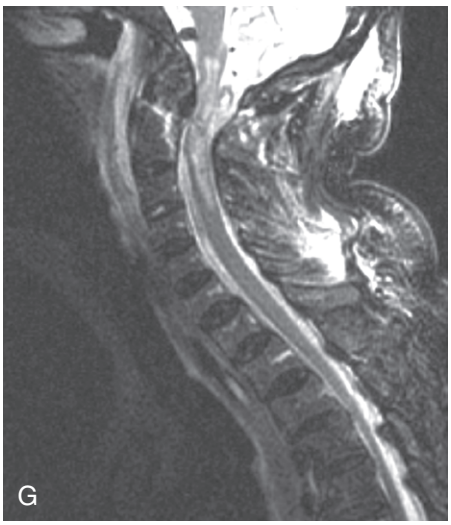


Figure 40-9. **A** and **B**, Odontoid fracture with lateral displacement. Mechanism: flexion. Stability: unstable. The tip of the odontoid process is laterally displaced in this lateral flexion injury. **C** and **D**, Lateral radiograph with suspicion of an odontoid fracture.





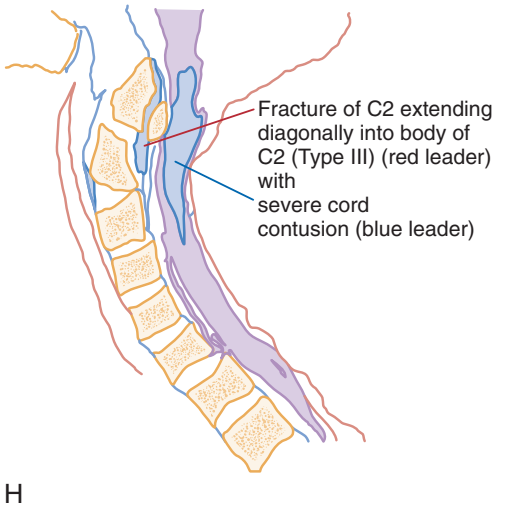


Figure 40-9, cont'd **E** and **F**, T_1-weighted magnetic resonance imaging (MRI) clearly shows a type III odontoid fracture. **G** and **H**, T_2-weighted MRI shows severe spinal cord contusion associated with this fracture.

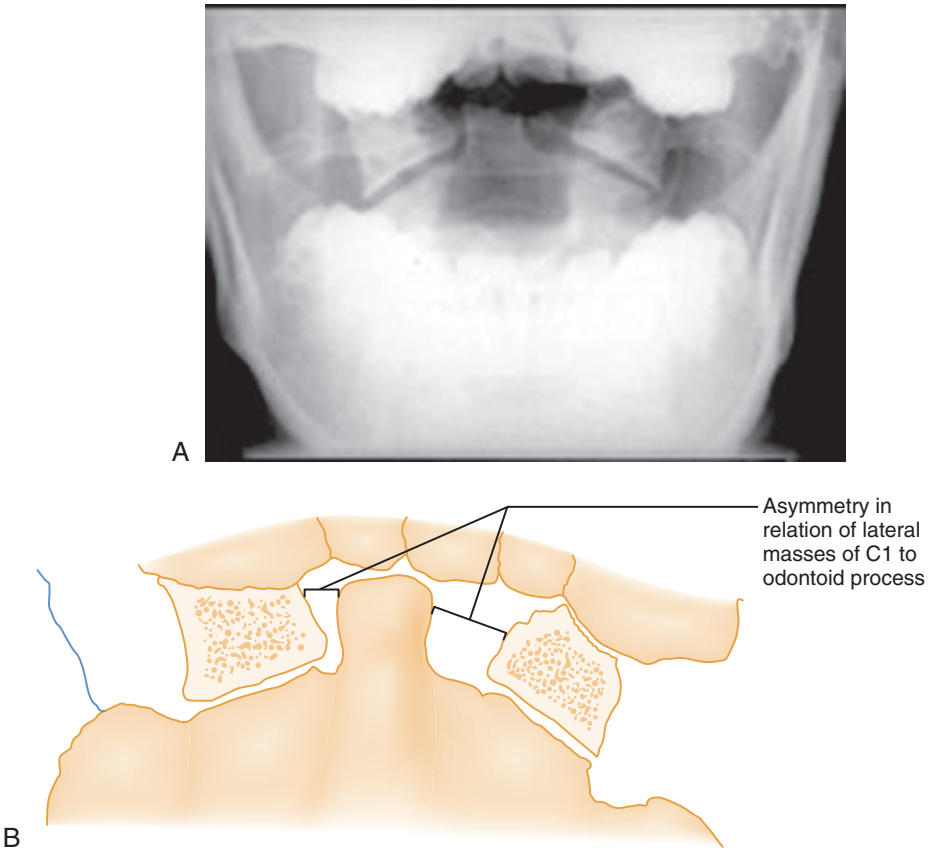


Figure 40-10. Rotatory subluxation of C1 on C2. Mechanism: rotation. Stability: unstable. **A** and **B**, There is marked asymmetry in the relationship of the lateral masses of C1 to the odontoid process. Rotation causes the right lateral mass to appear slightly larger (farther from the x-ray film) than the left (closer to the x-ray film).

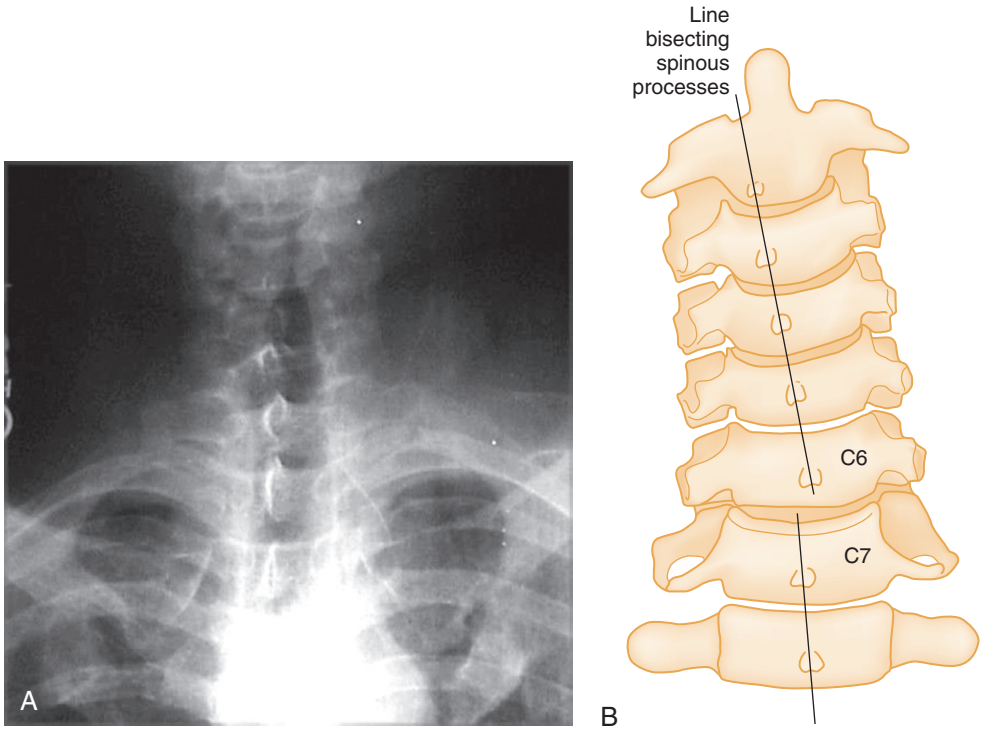
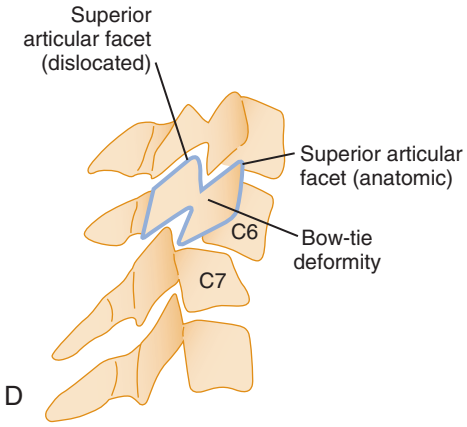
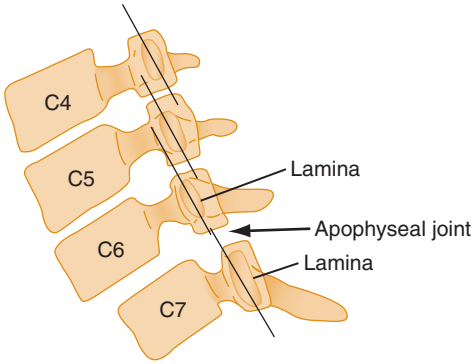
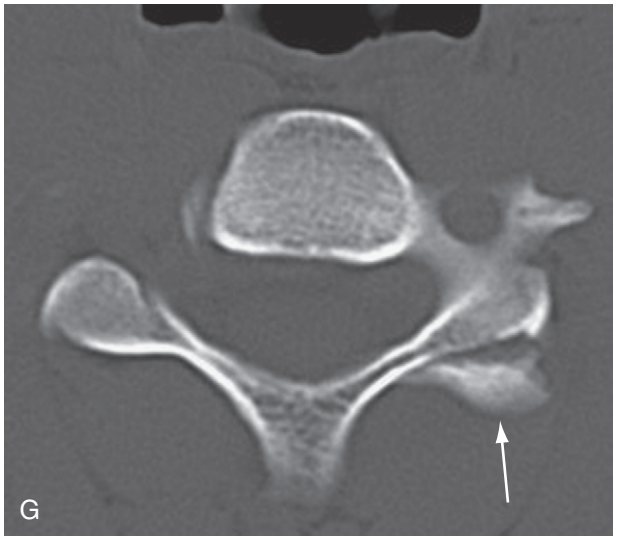


Figure 40-11. Unilateral facet dislocation. Mechanism: flexion and rotation. Stability: stable. **A** and **B**, Anterior view showing the spinous processes of the cervical vertebrae offset in relation to the thoracic vertebrae.







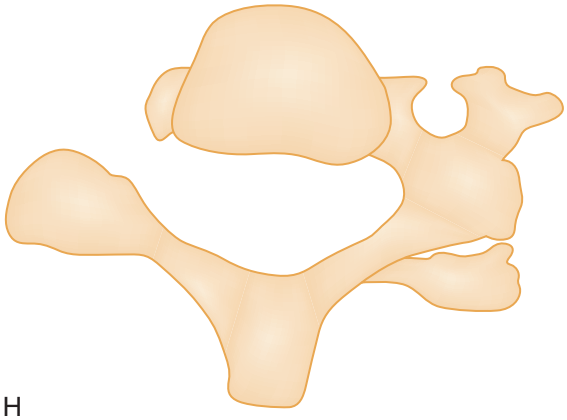


Figure 40-11, cont'd **C** and **D**, Lateral view showing one dislocated articular facet of C5 lying anterior to the corresponding facet of C6 and creating a "bow-tie" deformity. The C5 vertebral body is subluxed anteriorly on C6. **E** and **F**, Oblique view of unilateral facet dislocation with the lamina of C6 projecting into the neural foramen. **G** and **H**, CT scan showing facet dislocation. Inferior facet *(arrow)* lies superior to superior facet.

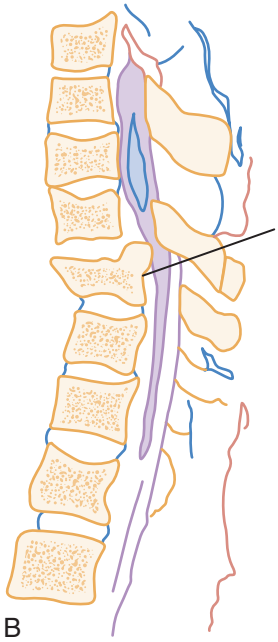


Figure 40-12. **A** and **B**, Magnetic resonance image showing fracture-dislocation of the thoracic spine.

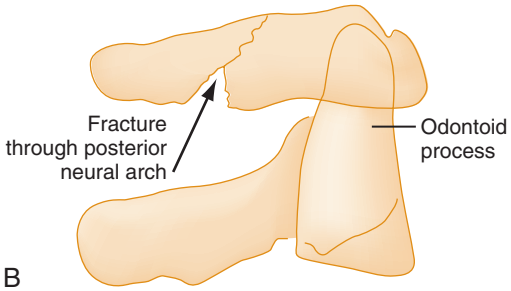


Figure 40-13. Posterior neural arch fracture of C1. Mechanism: extension. Stability: unstable. **A** and **B**, The fracture line is well visualized.

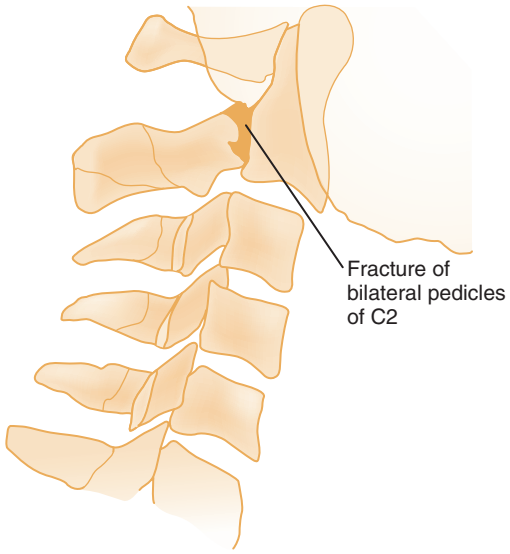


Figure 40-14. Hangman's fracture. Mechanism: extension. Stability: unstable. Fracture lines extending through the pedicles of C2 are well visualized. Retropharyngeal soft tissue swelling is apparent.

the anteroinferior corner of a vertebral body away from the remainder of the vertebra, producing a triangular-shaped fracture that is radiographically similar to the flexion teardrop fracture (Fig. 40-15). Often occurring in lower cervical vertebrae (C5-C7) from diving accidents, this unstable injury may be associated with a central cord syndrome caused by the ligamentum flavum buckling into the spinal cord.[6]

Vertical Compression. Vertical compression injuries occur in the cervical and lumbar regions, which are capable of straightening at the time of impact. When forces are applied from either above (skull) or below (pelvis or feet), one or more vertebral body endplates may fracture. The nucleus pulposus of the intervertebral disk is forced into the vertebral body, which is shattered outward, resulting in a *burst fracture*. The lateral radiograph shows a comminuted vertebral body. The frontal radiograph demonstrates a characteristic vertical fracture of the vertebral body, which helps differentiate it from the simple wedge fracture and the flexion teardrop fracture. This is a stable fracture since all the ligaments remain intact. However, fracture fragments may impinge on or penetrate the ventral surface of the spinal cord and cause an anterior cord syndrome (see Fig. 40-15).

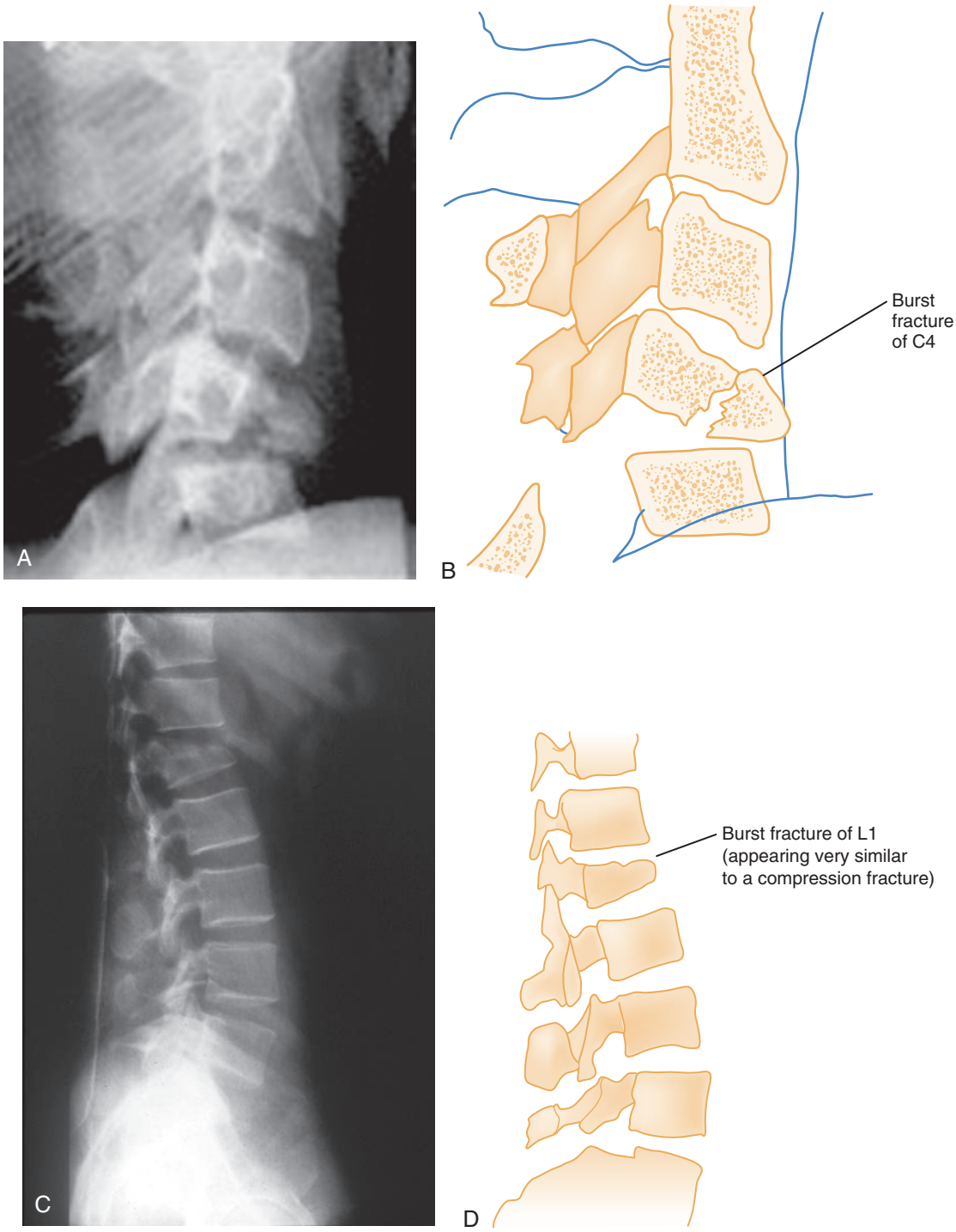
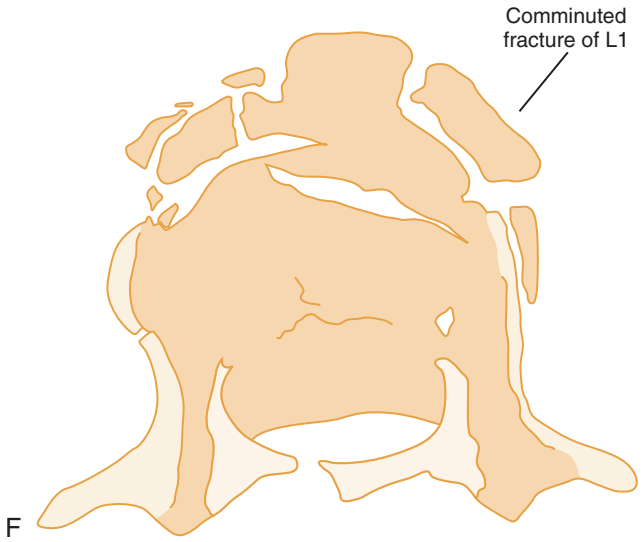


Figure 40-15. Burst fracture of a vertebral body. Mechanism: vertical compression/flexion. Stability: unstable. **A** and **B**, There is a compression fracture of the C4 vertebral body. During the bursting process, the anterior segment of the fracture protrudes anteriorly and its posterior aspect protrudes posteriorly into the spinal canal. Such protrusion is often associated with anterior cord syndrome. The cervical spine is abnormally angulated. **C** and **D**, Lateral radiograph showing a burst fracture of L1, appearing very similar to a compression fracture. Mechanism: flexion. Stability: usually stable.



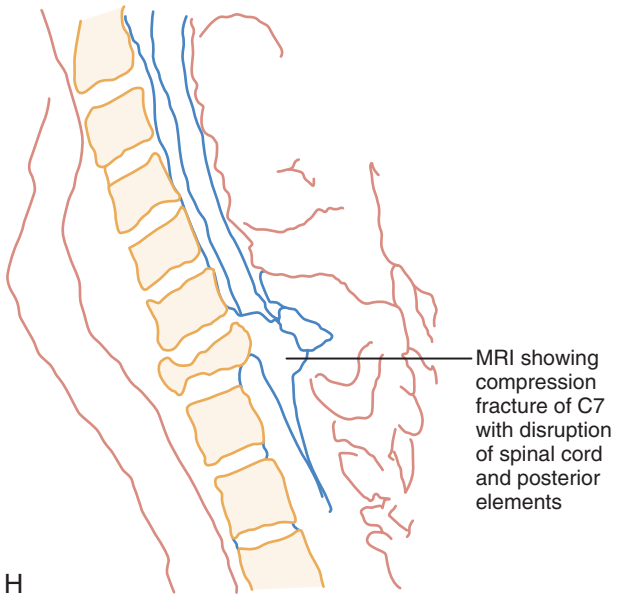


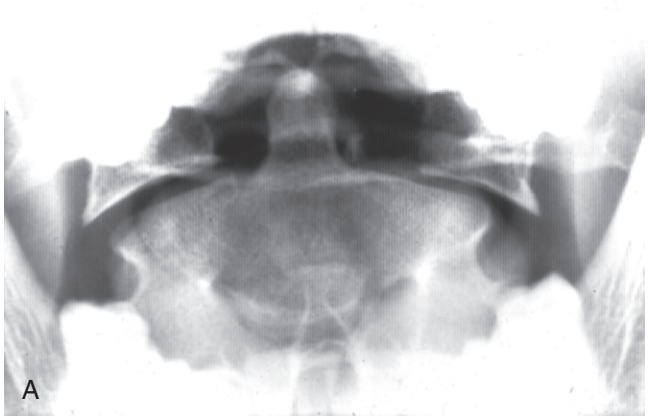
Figure 40-15, cont'd **E** and **F**, Computed tomographic scan of L1 in the same patient showing comminution of the fracture and retropulsion of fragments into the spinal canal. **G** and **H**, Magnetic resonance image (MRI) showing a burst fracture of C7 with complete spinal cord disruption.

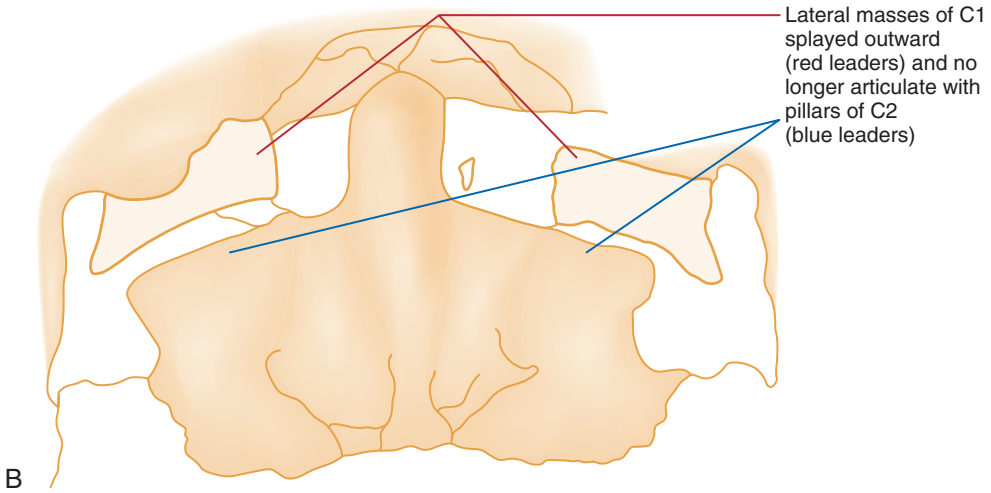
The *Jefferson fracture* of C1 is an extremely unstable injury that occurs when a vertical compression force is transmitted through the occipital condyles to the superior articular surfaces of the lateral masses of the atlas. This force drives the lateral masses outward, resulting in fractures of the anterior and posterior arches of the atlas and a disruption of the transverse ligament. Since this injury is often associated with prevertebral hemorrhage and retropharyngeal swelling, the lateral film may demonstrate a widening of the predental space between the anterior arch of C1 and the odontoid, or dens. The open-mouth view will demonstrate a bilateral offset of both right and left lateral masses of C1 relative to the lateral masses of C2. A fracture should be diagnosed when the sum of the offset distances from the right and left sides exceeds 7 mm (Fig. 40-16). However, when the fragments are minimally displaced, the Jefferson fracture is difficult to recognize, and computed tomography (CT) may be necessary.

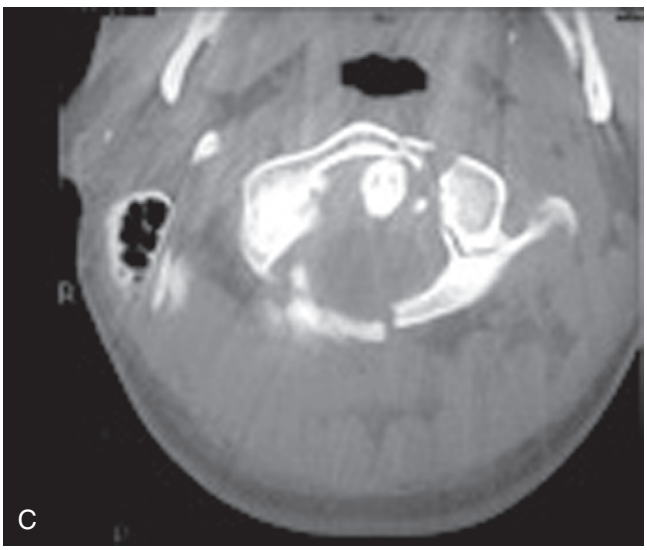
Vertical compression fractures may rarely result in isolated fractures of the articular pillar or the vertebral body, exhibiting vertical and oblique lines of fracture.

Classification of Spinal Cord Injuries

Primary Spinal Cord Injury. The spinal cord may be injured in a number of ways.[6] First, penetrating trauma or massive blunt trauma with disruption of the vertebral column may cause the







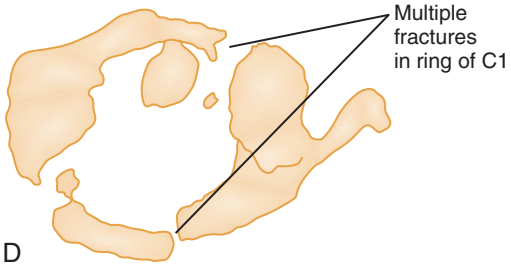


Figure 40-16. Jefferson fracture. Mechanism: vertical compression. Stability: unstable. **A** and **B**, Bilateral lateral displacement of the lateral masses of C1 with respect to the articular pillars of C2 confirms a Jefferson fracture and differentiates it from fracture of the posterior neural arch of C1 on an anteroposterior view. **C** and **D**, Computed tomographic scan of C1 showing two fracture sites in the ring of C1 with lateral displacement of the lateral mass on the right.

transection of neural elements. Since neurons within the central nervous system do not regenerate, such injuries are irreversible. Less severe blunt trauma may have similar effects resulting from a displaced bony fragment or a herniated disk.

Second, when elderly patients with cervical osteoarthritis and spondylosis are subjected to forcible cervical spine extension, the spinal cord may be compressed between an arthritically enlarged anterior vertebral ridge and a posteriorly located hypertrophic ligamentum flavum (Fig. 40-17). This injury frequently results in a central cord syndrome.

Primary vascular damage to the spinal cord, a third mechanism of injury, may occur in several ways. The spinal cord may

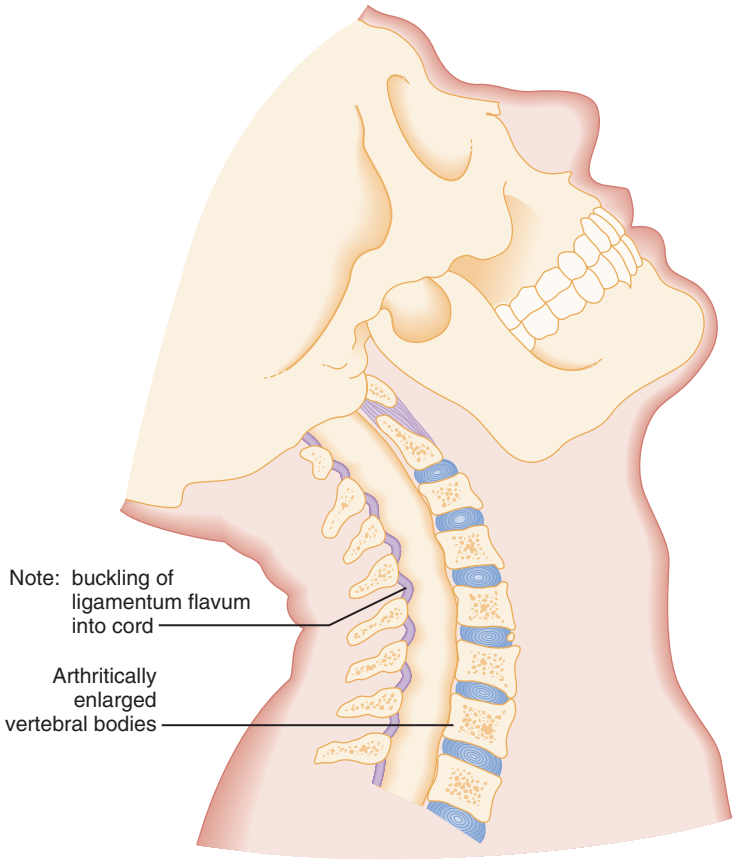


Figure 40-17. Elderly patients subjected to extension forces can sustain cervical spinal cord injury as a result of compression of the spinal cord between the posterior hypertrophic ligamentum flavum and the arthritically enlarged anterior vertebral bodies.

be compressed by an extradural hematoma, particularly in patients who are on anticoagulants or have bleeding disorders. Vascular injuries should also be suspected when there is a discrepancy between the clinically apparent neurologic deficit and the known level of spinal injury. For example, a lower cervical dislocation may compress the vertebral arteries as they travel within the spinal foramina of the vertebrae. This compression may result in thrombosis and decreased blood flow through the anterior spinal artery that originates from both vertebral arteries at the level of C1 (Fig. 40-18). On physical examination, such an injury may erroneously appear to be localized to the level of C1 or C2. Also, the great radicular artery of Adamkiewicz, originating from the aorta and entering the spinal canal at the level of L1, sends branches as cephalad as T4. Therefore, a lumbar fracture or dislocation can produce a neurologic deficit as high as T4.

Secondary Spinal Cord Injury. The maximum neurologic deficit following blunt spinal cord trauma is often not seen immediately and may instead progress over many hours. The histopathology of the so-called secondary spinal cord injury has been studied extensively in experimental animal models.[7-9] It is now thought that primary SCI initiates a complex cascade of events, involving free radical-induced lipid peroxidation reactions, which results in progressive ischemia of gray and white matter during the postinjury period (Fig. 40-19). Other factors, such as hypoxia, hypotension, hyperthermia, hypoglycemia, and mishandling by medical personnel, also affect the ultimate extent of SCI.

CLINICAL FEATURES

Neurologic Evaluation

The initial neurologic evaluation of a patient with a suspected spinal injury should begin with simple observation. Careful inspection of the patient's entire body, beginning with the head and proceeding downward, may reveal telltale signs of possible spinal involvement. Significant head and facial trauma have a 5 to 10% incidence of associated cervical spine injuries.[10,11] Scapular contusions suggest a rotation or flexion-

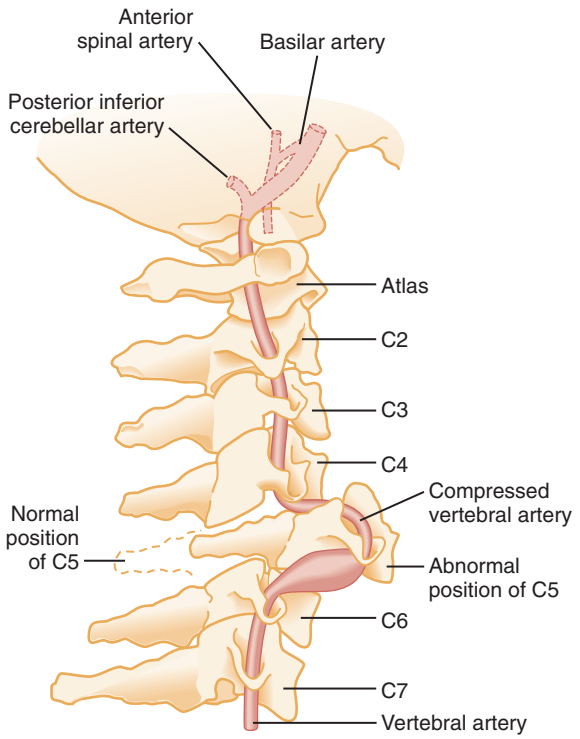


Figure 40-18. Mechanism of vascular injury of the spinal cord resulting from cervical vertebral injury.

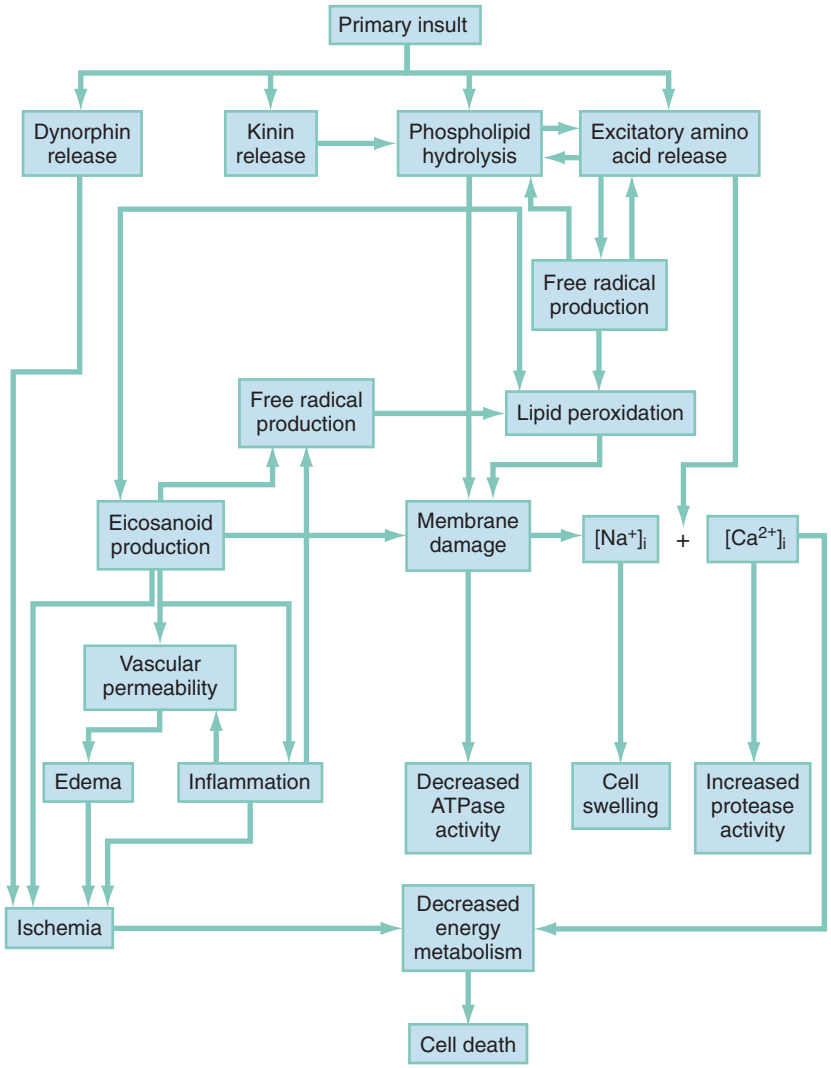


Figure 40-19. Speculative paradigm of secondary pathophysiologic events after primary traumatic injury to the spinal cord. (From Anderson D, Hall E: Pathophysiology of spinal cord trauma. Ann Emerg Med 22:989, 1993.)

rotation injury of the thoracic spine. Chest and neck abrasions from automobile shoulder belts and lower abdominal markings from lap belts indicate possible blunt carotid and vertebral injuries, as well as spinal, intrathoracic, and intra-abdominal injuries. As occurs with falls from considerable heights, injuries to the gluteal region, calcaneal fractures, and severe ankle fractures suggest a compression type of spinal injury.

The patient should be observed for the presence and symmetry of both voluntary and involuntary movements. An abnormal breathing pattern may provide an important clue to a cervical injury. The diaphragm is innervated by the phrenic nerve, which originates at the C3-C4 level. The intercostal muscles of the rib cage are supplied by nerves that originate in the thoracic spine; thus, an abdominal breathing pattern indicates an injury below the C4 level. The presence of Horner's syndrome, characterized by unilateral ptosis, miosis, and anhidrosis, may result from a disruption of the cervical sympathetic chain, usually at the level of C7-T2.[5] Priapism may occur with severe SCI.

The physician should speak with the patient during the inspection process. This important part of the patient's assessment should not be overlooked in trauma cases because it provides the patient with reassurance and the physician with valuable information. Patients may experience pain in the sensory dermatome corresponding to the level of the spinal injury. For example, a C2 lesion may cause occipital pain, whereas discomfort in the area of the trapezius muscle, particularly in the absence of signs of local trauma, suggests a C5 injury. The past medical history is important because certain conditions predispose patients to cervical injury. For example, patients with Down syndrome are predisposed to atlanto-occipital dislocation, whereas those with rheumatoid arthritis are prone to rupture of the transverse ligament of C2 with even minor trauma.

Palpation of the entire spine and paraspinal musculature may reveal areas of tenderness, deformity, or muscle spasm. A "gibbus" deformity or step-off may be appreciated with severe subluxation. Widening of an interspinous space indicates a tear in the posterior ligament complex and a potentially unstable spinal injury.

The motor activity of the body is complex. Since a single motion is often governed by muscles innervated by multiple spinal segments, localizing a spinal lesion based solely on an assessment of motor function is extremely difficult. Testing the presence and strength of those motions outlined in Table 40-2, however, provides a rapid baseline assessment. When a deficit is noted, the motor examination and the remainder of the neurologic examination should be repeated at frequent intervals because progression of dysfunction may occur. If there is apparent total loss of function, every effort should be made to elicit the most minimal of motor responses since any response markedly alters the prognosis for recovery. A slight toe flicker in an otherwise paralyzed individual indicates that the patient may again eventually walk unassisted.

Table 40-2 Spinal Motor Examination

LEVEL OF LESION	RESULTING LOSS OF FUNCTION
C4	Spontaneous breathing
C5	Shrugging of shoulders
C6	Flexion at elbow
C7	Extension at elbow
C8-T1	Flexion of fingers
T1-T12	Intercostal and abdominal muscles*
L1-L2	Flexion at hip
L3	Adduction at hip
L4	Abduction at hip
L5	Dorsiflexion of foot
S1-S2	Plantar flexion of foot
S2-S4	Rectal sphincter tone

*Localization of lesions in this area is best accomplished with the sensory examination.

Table 40-3 Spinal Reflex Examination

LEVEL OF LESION (AT OR ABOVE)	RESULTING LOSS OF REFLEX
C6	Biceps
C7	Triceps
L4	Patellar
S1	Achilles

The presence of cord-mediated *deep tendon reflexes* can be helpful as a localizing, diagnostic aid (Table 40-3). Classically, muscle paralysis associated with intact deep tendon reflexes indicates an upper motor neuron (spinal cord) lesion, whereas paralysis associated with absent deep tendon reflexes indicates a lower motor neuron (nerve root or cauda equina) lesion. This differentiation is important because the latter condition is often caused by a surgically correctable lesion. After the initial period of areflexia, reflexes gradually return after 1 to 3 days, and after 1 to 4 weeks, patients with SCI will manifest characteristic hyperreflexia and spasticity.[12] However, since reflexes are typically absent during the initial phase of spinal shock, the examination of reflexes is less useful in the emergency department.

Sensory function can be quickly evaluated using a structured approach (Table 40-4) or by referring to a graphic sensory dermatome chart (Fig. 40-20). After locating an area of hypesthesia, one should carefully delineate the area by slowly moving the stimulus from areas of decreased sensation outward, rather than the reverse, because patients are much more sensitive to the appearance of sensation than to its disappearance. This test should be performed first with a cotton wisp to assess sensitivity to light touch, a posterior column function. A pin should then be used to assess pain sensation, which is an anterior spinothalamic tract function. The presence of islands of sparing of sensation within an affected dermatome or below the level of apparent total dysfunction, even in the presence of complete motor paralysis, indicates that the patient has a very good chance of functional motor recovery.[13] An accurate baseline sensory examination is imperative because a cephalad progression of hypesthesia is the most sensitive indicator of deterioration. When this is observed in the cervical region, one should anticipate impending respiratory failure and take steps to ensure airway stabilization.

Table 40-4 Spinal Sensory Examination

LEVEL OF LESION	RESULTING LEVEL OF LOSS OF SENSATION
C2	Occiput
C3	Thyroid cartilage
C4	Suprasternal notch
C5	Below clavicle
C6	Thumb
C7	Index finger
C8	Small finger
T4	Nipple line
T10	Umbilicus
L1	Femoral pulse
L2-L3	Medial aspect of thigh
L4	Knee
L5	Lateral aspect of calf
S1	Lateral aspect of foot
S2-S4	Perianal region

Complete Spinal Cord Lesions

A complete spinal cord lesion is defined as total loss of motor power and sensation distal to the site of an SCI. Functional motor recovery is rare in patients with a total cord syndrome that persists for longer than 24 hours after the injury.[5] Before diagnosing a total cord syndrome, however, two points should be considered. First, any evidence of minimal cord function, such as sacral sparing, excludes the patient from this group. Signs of sacral sparing include perianal sensation, normal rectal sphincter tone, or flexor toe movement. The presence of any of these signs indicates a partial lesion, usually a central cord syndrome, and the patient may have marked functional recovery, including bowel and bladder control and eventual ambulation.

Second, it is important to note that a complete spinal cord lesion may be mimicked by a condition known as *spinal shock*. Spinal shock results from a concussive injury to the spinal cord that causes total neurologic dysfunction distal to the site of injury.[14] Spinal shock may persist for a few days or a few weeks. The end of spinal shock is heralded by the return of the bulbocavernosus reflex, which is a normal cord-mediated reflex elicited by placing a gloved finger in the patient's rectum and then squeezing the glans penis or clitoris or by tugging gently on the Foley catheter. An intact reflex results in rectal sphincter contraction. Absence of this reflex indicates the presence of spinal shock, during which time the patient's prognosis cannot be accurately assessed. A complete spinal cord lesion will remain unchanged following the cessation of spinal shock.

Incomplete Spinal Cord Lesions

Approximately 90% of incomplete spinal injuries can be classified as one of three clinical syndromes: the central cord syndrome, the Brown-Séquard syndrome, and the anterior cord syndrome (Fig. 40-21).[5] The most common is the *central cord syndrome*, which is often seen in patients with degenerative arthritis of the cervical vertebrae when their necks are hyperextended. The ligamentum flavum buckles into the cord, resulting in a concussion or contusion of the central portion of the cord, which affects the central gray matter in the most central portions of the pyramidal and spinothalamic tracts. Since fibers that innervate distal structures are located in the

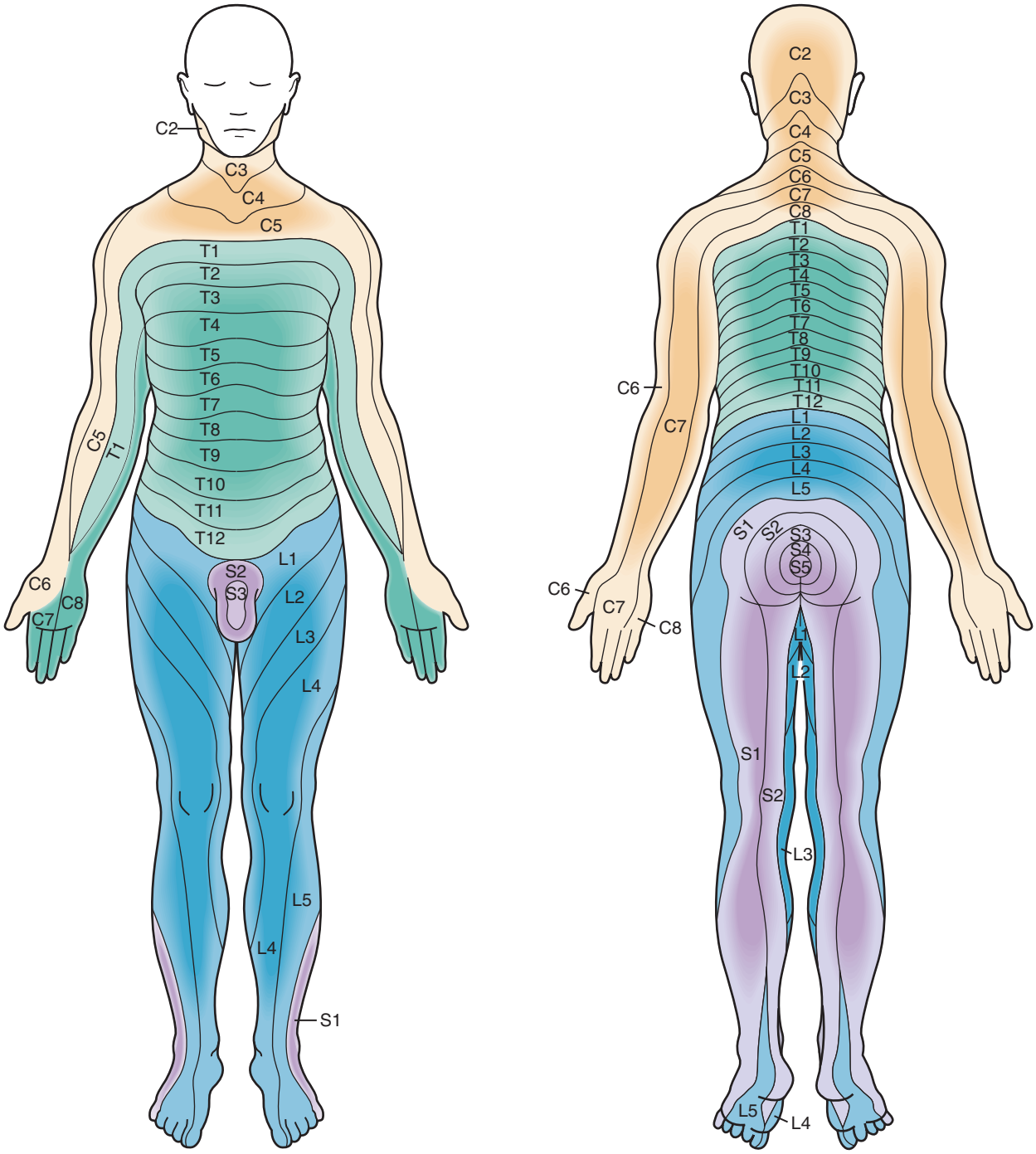


Figure 40-20. Sensory dermatomes.

periphery of the spinal cord, these patients have a greater neurologic deficit in the upper extremities than in the lower extremities. With more severe injuries, patients may appear to be almost completely quadriplegic and have only minimal evidence of sacral sparing. The prognosis for patients with this syndrome is variable. More than 50% of patients with a severe central cord syndrome become ambulatory and regain bowel and bladder control, as well as some hand function.[13]

The *Brown-Séquard syndrome*, or hemisection of the spinal cord, usually results from penetrating trauma but may also be seen following lateral mass fractures of the cervical spine. Patients with this lesion have ipsilateral motor paralysis and contralateral sensory hypesthesia distal to the level of injury; however, either finding may predominate depending on the exact location and extent of injury. Moreover, since the fibers of the lateral spinal thalamic tract cross at a different level to the contralateral side, the pain and temperature loss may be found variably one or two segments above the lesion. Virtually all patients maintain bowel and bladder function and unilateral motor strength, and most become ambulatory.[5]

The *anterior cord syndrome* usually results from hyperflexion injuries causing cord contusion, by the protrusion of a bony fragment or herniated disk into the spinal canal, or by laceration or thrombosis of the anterior spinal artery. This syndrome is characterized by paralysis and hypalgesia below the level of injury with preservation of posterior column functions, including position, touch, and vibratory sensations. Suspicion for an acute anterior cord syndrome warrants immediate neurosurgi-

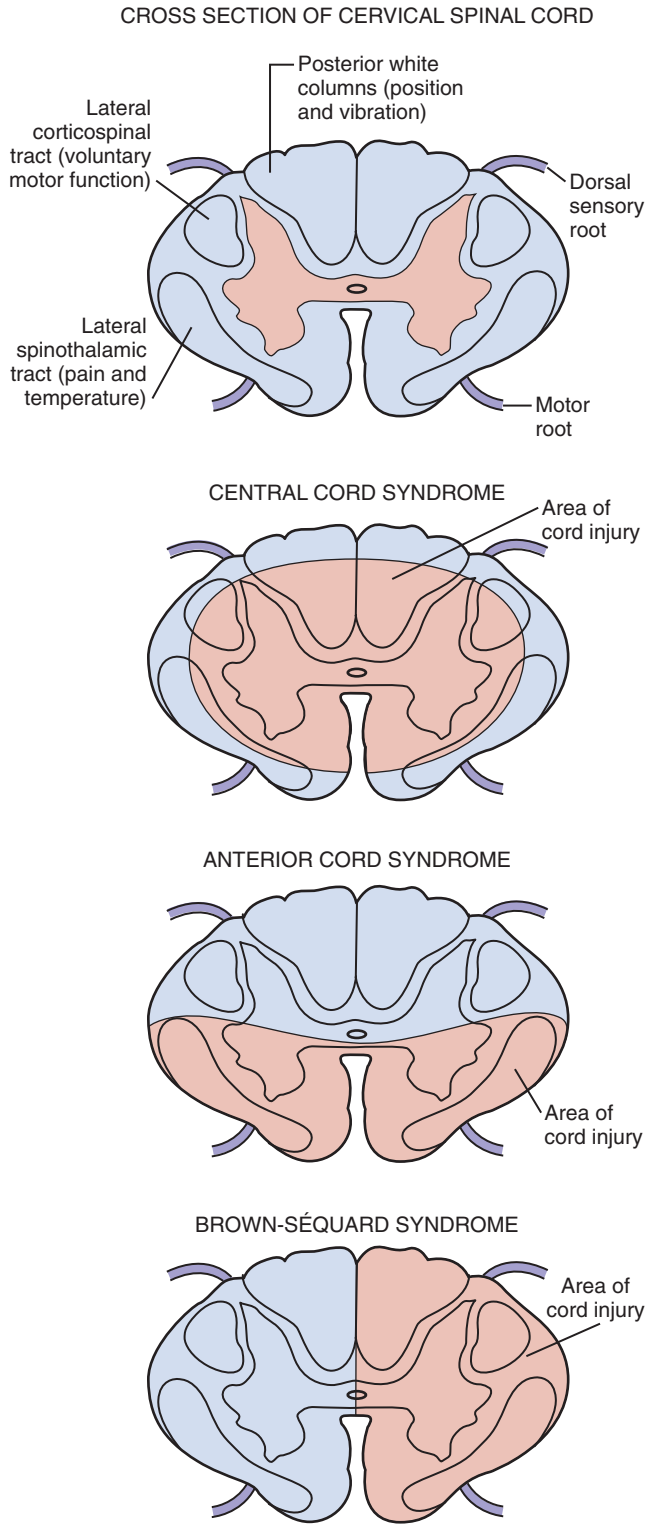


Figure 40-21. Incomplete spinal cord syndromes.

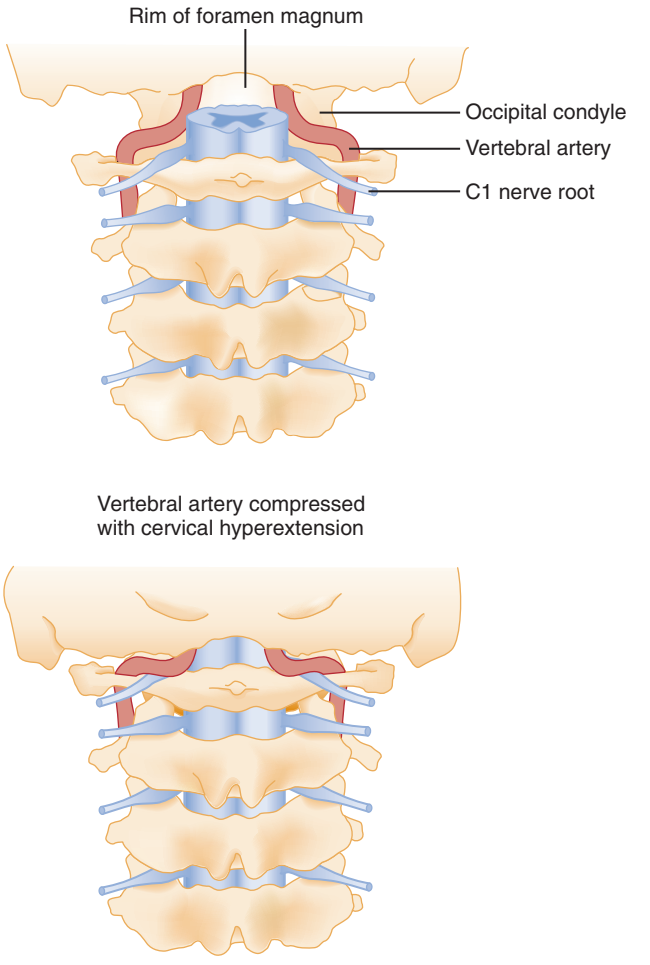


Figure 40-22. Mechanism of vertebral artery injury in extension injuries of the cervical spine.

cal consultation since it may be due to a surgically correctable lesion. Following surgical intervention, patients have variable degrees of recovery during the first 24 hours but little improvement thereafter.[5]

There are several less common spinal cord syndromes that may result from a direct injury to the cervicomedullary junction and upper cervical segments or from vertebral artery occlusion due to severe hyperextension (Fig. 40-22).[5] The *posteroinferior cerebellar artery syndrome* may produce dysphagia, dysphonia, hiccups, nausea, vomiting, dizziness or vertigo, and cerebellar ataxia. The *Dejeune onion skin pattern* of analgesia of the face is caused by damage to the spinal trigeminal tract. *Horner's syndrome* results from damage to the cervical sympathetic chain and is characterized by ipsilateral ptosis, miosis, and anhidrosis. Injuries below the L2 level can result in an *acute cauda equina syndrome*, characterized by perineal or bilateral leg pain, bowel or bladder dysfunction, perianal anesthesia, diminished rectal sphincter tone, and lower extremity weakness.

The syndrome of spinal cord injury without radiographic abnormality (SCIWORA) is seen primarily in younger children but may occur in any age group.[15-17] The mechanism is unclear but has been ascribed to the increased ligamentous elasticity seen in the young, leading to transient spinal column subluxation, stretching of the spinal cord, and vascular compromise. Patients often experience a brief episode of upper extremity weakness or paresthesias followed by neurologic deficits that appear hours to days later. The prognosis for patients with SCIWORA is variable, depending on the degree of neurologic impairment and the rate of resolution.

DIAGNOSTIC STRATEGIES

Radiographic Evaluation

Indications

Clinicians have historically taken a liberal approach to ordering cervical spine radiographs in the setting of trauma since failure

to recognize an SCI may result in devastating neurologic consequences. According to the National Hospital Ambulatory Care Survey, only 4% of all cervical spine radiographs demonstrate a fracture.[18] There is also great practice variation among emergency physicians, with a sixfold range in radiography ordering rates.[19]

In an effort to standardize clinical practice and guide physicians to be more selective in their use of radiography without jeopardizing patient care, two clinical decision rules have been developed. The first rule to be developed, the National Emergency X-Radiography Utilization Study (NEXUS) Low-Risk Criteria (NLC), was based on a multicenter prospective observational study involving 34,069 trauma patients seen at 21 U.S. emergency departments. The decision instrument required patients to meet five criteria in order to be classified as having a low probability of injury: (1) no midline cervical tenderness; (2) no focal neurologic deficit; (3) normal alertness; (4) no intoxication; and (5) no painful, distracting injury. The decision rule identified all but 8 of the 818 patients who had spinal injuries. Only 2 of these patients had a clinically significant injury, whereas only 1 required surgical stabilization, and neither sustained a permanent neurologic injury.[20] Sensitivity, specificity, and negative predictive value of the NLC were calculated and were respectively found to be 99.6, 12.9, and 99.8%.[20]

Due to concerns about the low specificity of the NLC, Stiell and colleagues developed the Canadian C-spine rule (CCR) based on 25 selected clinical predictor variables associated with spine injury. In 2003, the CCR was prospectively studied and compared to the NLC in the nine Canadian tertiary care hospitals. Of 8283 patients, 162 were found to have "clinically significant" injuries, and the sensitivity, specificity, and negative predictive values of the CCR were respectively 99.4, 45.1, and 100%.[21] The CCR is composed of the following three questions:

1. Are there any high-risk factors that mandate radiography?
2. Are there any low-risk factors that allow safe assessment of range of motion?
3. Is the patient able to actively rotate his or her neck 45 degrees to the left and right?

High-risk factors include age older than 65 years, a "dangerous mechanism of injury" (a fall from a height >1 m, an axial loading injury, high-speed motor vehicle crash [>100 km/hr], rollover, ejection, motorized recreational vehicle, or bicycle collision), or the presence of paresthesias. Low-risk factors include simple rear-end vehicle crashes, sitting position in the emergency department, ambulatory at any time, delayed onset of neck pain, and the absence of midline neck tenderness. Although the NEXUS criteria are more widely utilized in the United States, both studies support the recommendation that cervical spine radiographs be obtained only for patients in whom spinal injury is suspected based on clinical assessment.

There is some controversy as to which of the two rules to implement. There are methodologic differences in the respective study designs, such as different inclusion and exclusion criteria.[21] Prior to the widespread application of any prediction rule, external validation is necessary to assess its generalizability. Nevertheless, the use of either rule has been shown to significantly limit the number of unnecessary radiographs while missing only rare patients with clinically significant injuries.

Cervical Plain Radiographs

Normal cervical spine radiographs in AP, lateral, swimmer's, oblique, and odontoid views are presented in Figures 40-23 and 40-24. All vertebrae suspected of being injured must be visualized. The C7-T1 vertebra may be obscured in muscular or obese patients, as well as in patients with spinal lesions that result in paralysis of the muscles that act to depress the shoulders. The paralysis leaves the trapezius muscles, which elevate the shoulders, unopposed. Such lesions are located in the lower cervical region. The shoulders can usually be depressed by pulling the patient's hands toward the feet, using slow, steady traction. Movement should occur only at the shoulder girdle while the head and neck remain immobilized. Note that the head and neck should not be pulled in opposition to the person pulling down the shoulders because this may induce a distraction injury. If this maneuver is unsuccessful or difficult to perform because of upper extremity injuries, a transaxillary or swimmer's view of the lower cervical vertebrae may be helpful. The upper three or four thoracic vertebrae are also difficult to visualize on routine lateral views of either the cervical or thoracic spine, and a swimmer's view, an oblique radiograph, or CT is often needed for adequate evaluation of the thoracic spine.

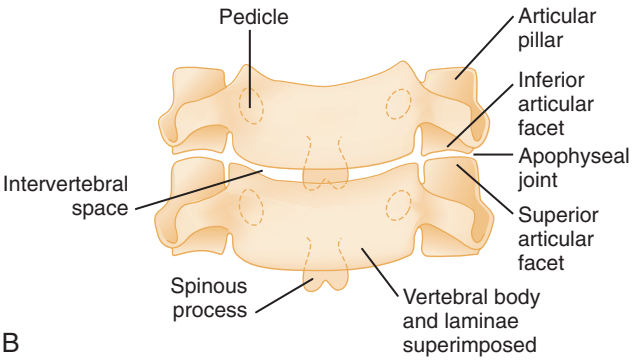
Although the cross-table lateral view of the cervical spine is the most helpful x-ray in diagnosing spinal injures, its inadequacy as the sole view is well documented.[22] Since the diagnostic yield is significantly increased when the AP and odontoid views are included, all three views of the cervical spine should be evaluated prior to discontinuation of cervical spine immobilization.[23] The NLC shows that a technically adequate three-view trauma series will fail to diagnose spinal injury in only .07% of patients with injuries and in only .008% of patients with unstable injures.[24]

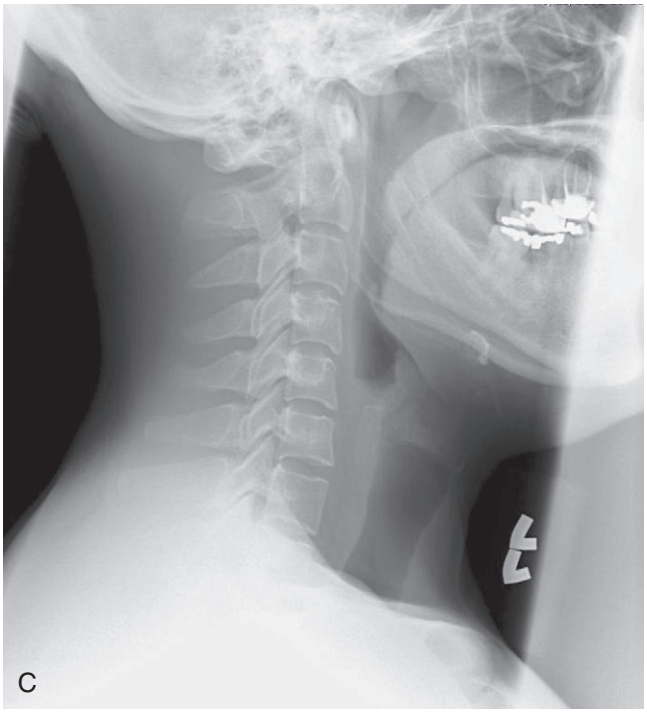
Cross-Table Lateral View. The inspection of the lateral cervical spine film should be methodical and complete. To do this, it is helpful to remember the "ABCs" of interpreting the lateral film, where *A* stands for alignment, *B* for bony abnormalities, *C* for cartilage-space assessment, and *s* for soft tissues.

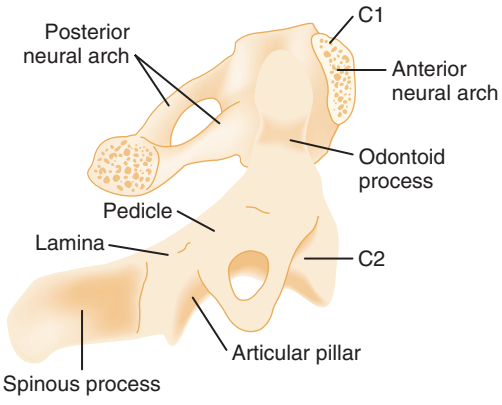
To check the alignment, two imaginary lines are drawn that separately connect the anterior and posterior margins of the vertebral bodies, the anterior and posterior contour lines. A third line, the spinolaminal line, connects the bases of the spinous processes extending to the posterior aspect of the foramen magnum (Fig. 40-25). All three lines should form a smooth, continuous lordotic curve, and any disruption of these lines suggests a bony or ligamentous injury. An exception to this rule is the pseudosubluxation of C2 and C3, which is commonly seen in infants and children. This phenomenon is attributed to their immature muscular development and a hypermobile spine. Thus, if a high cervical injury is suspected in a child, the posterior cervical line, which connects the points bisecting the bases of the spinous processes of C1 and C3, should be used (Fig. 40-26). If the base of C2 lies more than 2 mm anterior or posterior to the posterior cervical line, an injury at that level should be suspected.[25] On the lateral view, the predental space, which is the distance between the anterior aspect of the odontoid process and the posterior aspect of the anterior ring of C1, should not exceed 3 mm in an adult or 5 mm in a child (see Fig. 40-26). A widening of this space may indicate a Jefferson fracture of C1.

Next, bony abnormalities should be assessed. Subtle changes in bony density should be noted. Areas of decreased density, seen in patients with rheumatoid arthritis, osteoporosis, or metastatic osteolytic lesions, are more apt to succumb under stress. Acute compression fractures of the vertebral bodies and metastatic osteoblastic lesions result in areas of increased bone density.

The emergency physician may diagnose subluxations and dislocations through cartilage-space assessment. A slight anterior or posterior widening of the intervertebral space or







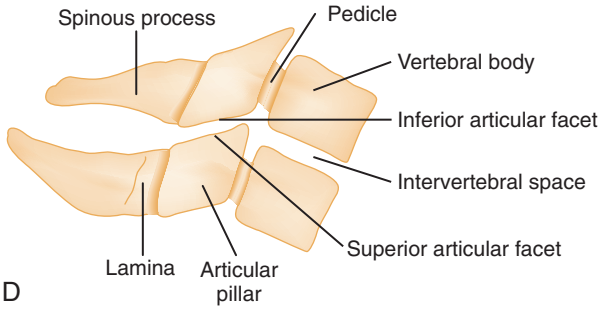
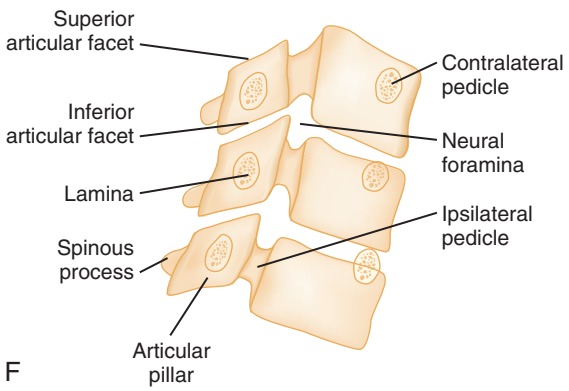


Figure 40-23. Views of the cervical spine. **A** and **B**, Anteroposterior view. **C** and **D**, lateral view.



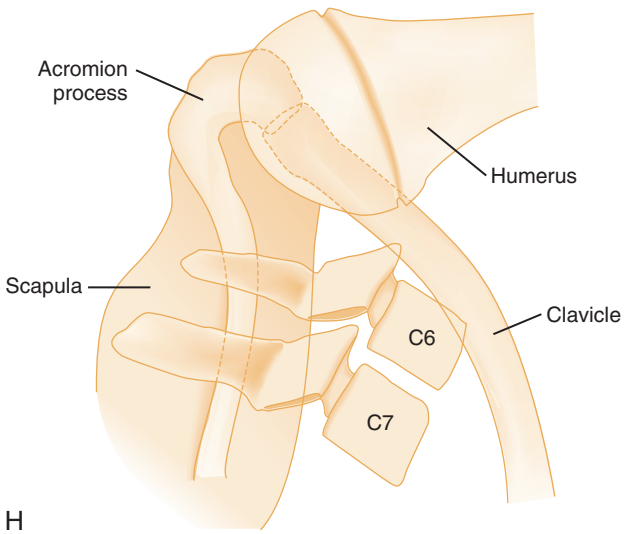


Figure 40-23, cont'd **E** and **F**, Oblique view. **G** and **H**, Swimmer's view.

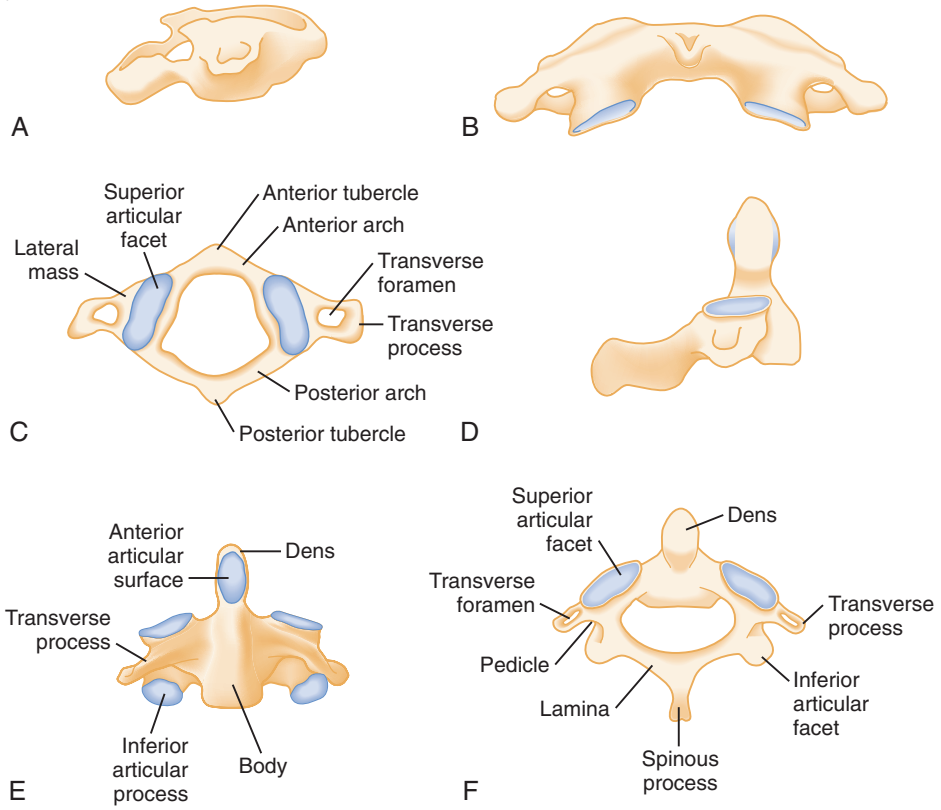
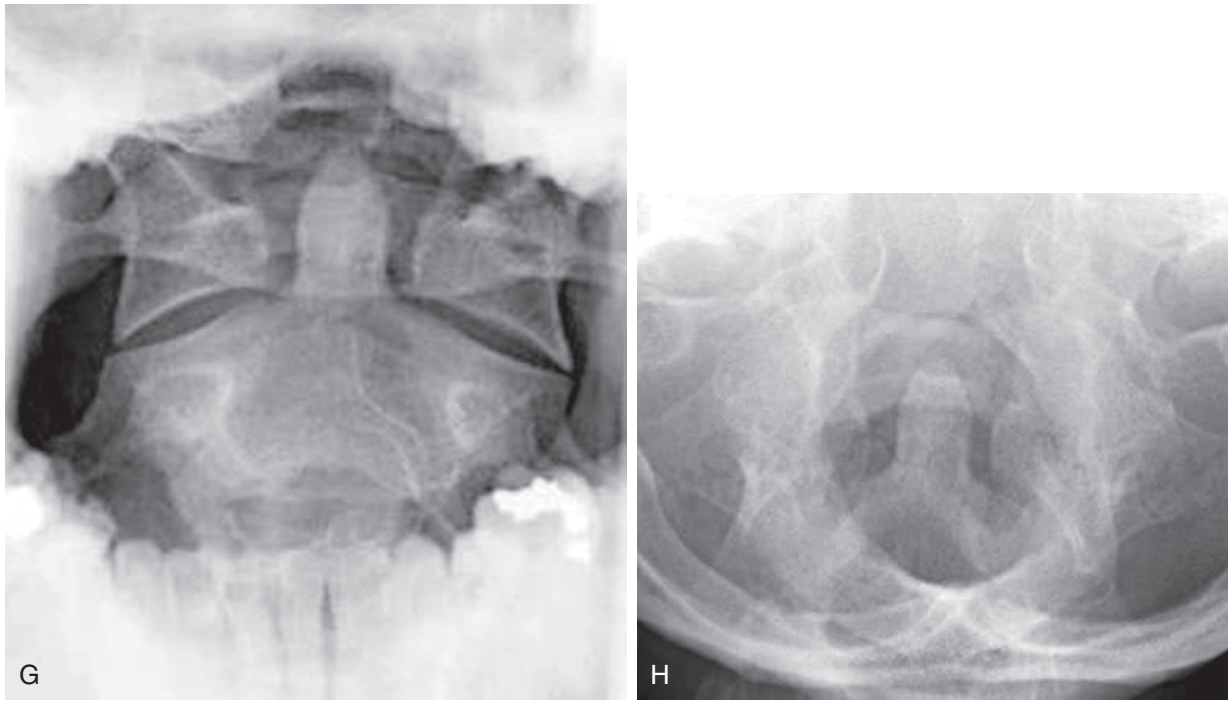
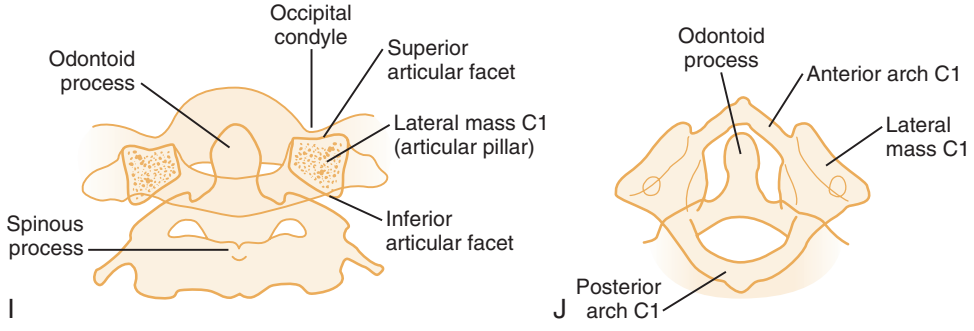


Figure 40-24. Views of C1 and C2. **A**, Atlas in a lateral view. **B**, Atlas in a frontal view. **C**, Atlas in an above view. **D**, Axis in a lateral view. **E**, Axis in a frontal view. **F**, Axis in an above view. **G** and **H**, Open-mouth view. **I** and **J**, Closed-mouth view.





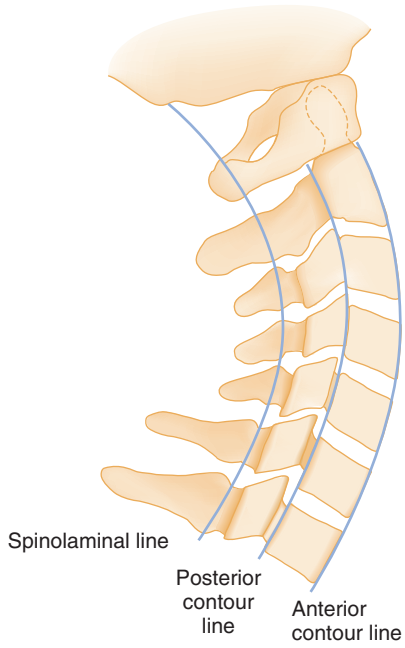


Figure 40-25. Normal structural relationships of the lateral cervical spine.

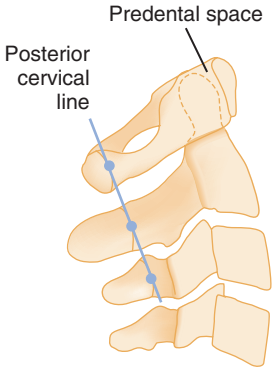


Figure 40-26. Posterior cervical line of a normal lateral spine.

the interspinous space may be the only clue to an unstable dislocation.

Finally, the soft tissues of the retropharyngeal space should be assessed for the presence of prevertebral swelling and hemorrhage, often the only radiographic sign of spinal injury. The retropharyngeal space, measured from the anterior border of the body of C2 to the posterior wall of the pharynx, should not exceed 7 mm in children or adults (Fig. 40-27A and C). At the level of C3 and C4, this measurement should not exceed 5 mm or should be less than one half the width of the vertebral body at that level. Below the level of C4, the prevertebral soft tissue space is widened by the esophagus and the cricopharyngeal muscle. Here, the retrotracheal space, measured from the anterior border of the body of C6 to the posterior wall of the trachea, should not exceed 22 mm in adults or 14 mm in children younger than age 15 years. In children younger than age 2 years, the retropharyngeal space may normally appear widened during expiration; thus, inspiratory films should be obtained.[26] Air in the prevertebral space may indicate rupture of the esophagus or some portion of the respiratory tree, and anterior bulging of the prevertebral fat stripe is an excellent sign of an underlying bony or soft tissue injury.

Odontoid View. The second film obtained in the emergency department is the open-mouth or closed-mouth view of the atlas and axis (see Fig. 40-24G-J). Nonfusion of the odontoid in children and congenital anomalies of the odontoid in adults may mimic fractures.

AP View. The AP spinal film completes the spinal series. The spinous processes should form a straight line, and the laryngeal and tracheal air shadows should be midline (see Figs. 40-23B and 40-27D). The regular outline of the lateral masses should be verified, and the pedicles viewed end on can be checked for fracture. Widening of the interpedicular distance compared to adjacent vertebrae suggests a burst fracture (Fig. 40-28).

In addition to searching for fractures of vertebral bodies and transverse processes, bulging of the mediastinal stripe may be the only evidence of a thoracic vertebral body fracture. Fractures of the upper thoracic vertebrae may cause a posterior mediastinal hemorrhage that produces mediastinal widening on the chest x-ray similar to that seen with aortic rupture.

Oblique Views

Oblique views of the cervical spine may be helpful to confirm a suspected posterior laminar fracture, a unilateral facet dislocation, or a real subluxation.[27] However, with the advent of high-resolution computed tomography, suspicion of these injuries on plain films ordinarily leads to CT rather than the obtaining of oblique views. The normal lamina appears as an intact ellipse (see Fig. 40-23E and F), and a posterior laminar fracture disrupts the appearance of this ellipse (Fig. 40-29). Normal overlapping laminae have the appearance of shingles on a roof (see Fig. 40-27A and B). Integrity of these shingles excludes the presence of a unilateral facet dislocation, whereas disruption confirms it (see Fig. 40-11E and F). The normal interlaminar distance, measured from the center points of successive laminar ellipses on an oblique view, should be equidistant. An increased interlaminar distance, due to lack of capsular ligamentous integrity, indicates true subluxation (Fig. 40-30).

Flexion and Extension Views

Flexion and extension (F/E) views are often obtained when there is concern for ligamentous injury, despite negative standard radiographs. Instability of the cervical spine is suggested by any of the following: more than 3.5 mm of horizontal displacement between the disks, displaced apophyseal joints, widened disk spaces, loss of greater than 30% of the disk height, or the presence of a prevertebral hematoma.[28] The exact role and timing of the use of F/E views are controversial, however. The NEXUS investigators demonstrated that 86 of the 818 (10.5%) patients ultimately found to have cervical injury underwent F/E testing.[29] Although 2 patients had bony injuries and 4 patients had subluxations demonstrated only on F/E views, all 6 patients had other injuries apparent on routine radiographs. In the acute setting, F/E radiographs have been reported to have unacceptably high false-positive and false-negative rates since minor subluxations may be masked by concomitant muscle spasm.[30,31] Thus, delayed F/E views obtained a week or two following injury may be more helpful. Moreover, other studies, such as CT and magnetic resonance imaging (MRI), appear to be superior imaging modalities in patients with severe, localized symptoms who have normal radiographs.[32]

CT Scan

Conventional radiography is limited as a result of the nature of equipment, difficulties in positioning, lack of patient coop-

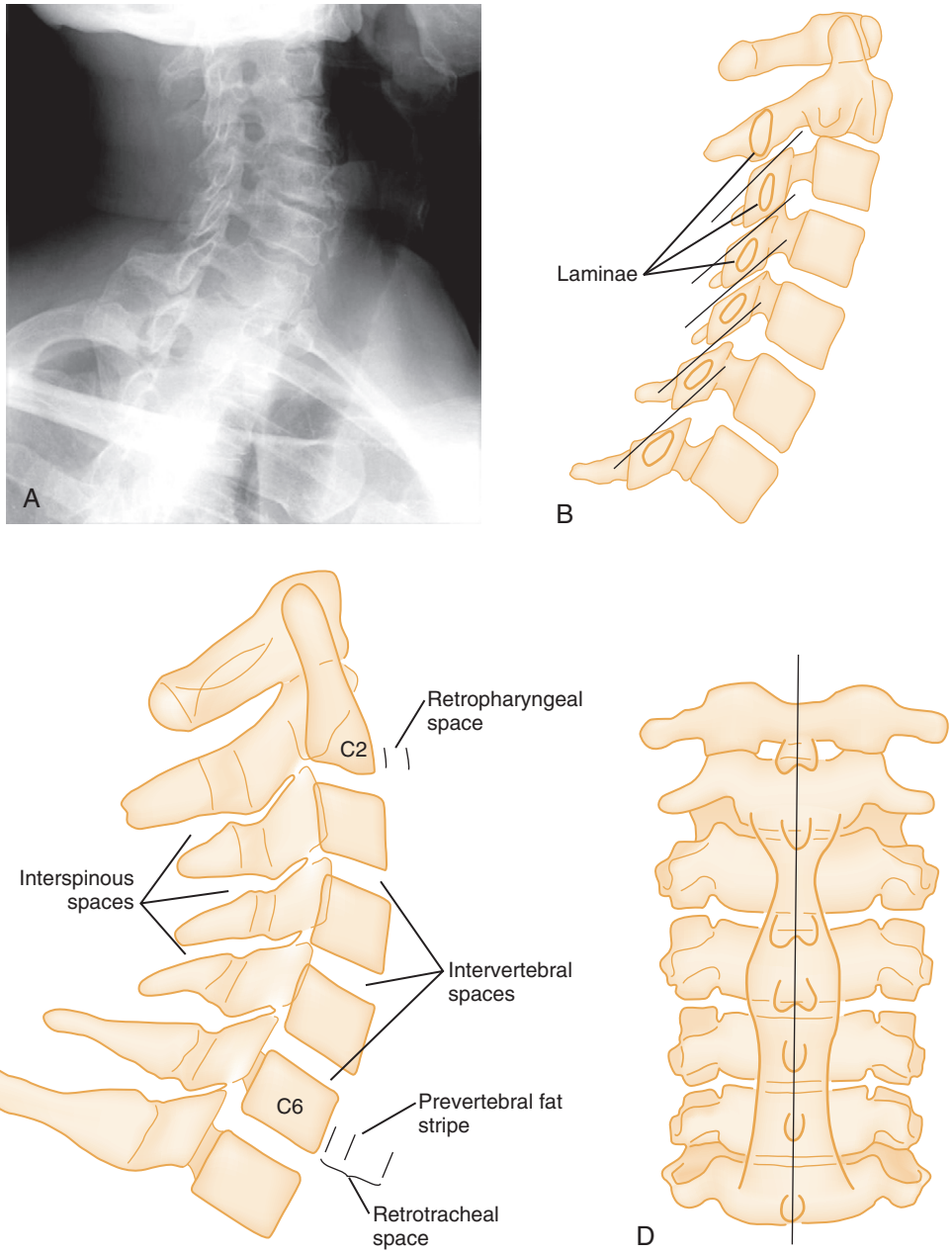


Figure 40-27. **A** and **B**, Normal structural relationships of the cervical spine laminae in an oblique view form a "shingles on a roof" appearance. **C** and **D**, Normal relationship between soft tissues and bony structures of the cervical spine in the lateral and anteroposterior (AP) views. **C**, In the lateral view, the intervertebral spaces and interspinous spaces should be compared with the spaces above and below for asymmetry and important clues in flexion and extension injuries. The retropharyngeal and retrotracheal soft tissues are measured at the C2 and C6 levels for swelling. **D**, In the AP view, the tracheal and laryngeal air shadows should be within the midline. A straight line should connect points bisecting the spinous processes. If such is not the case, rotatory injuries must be suspected.

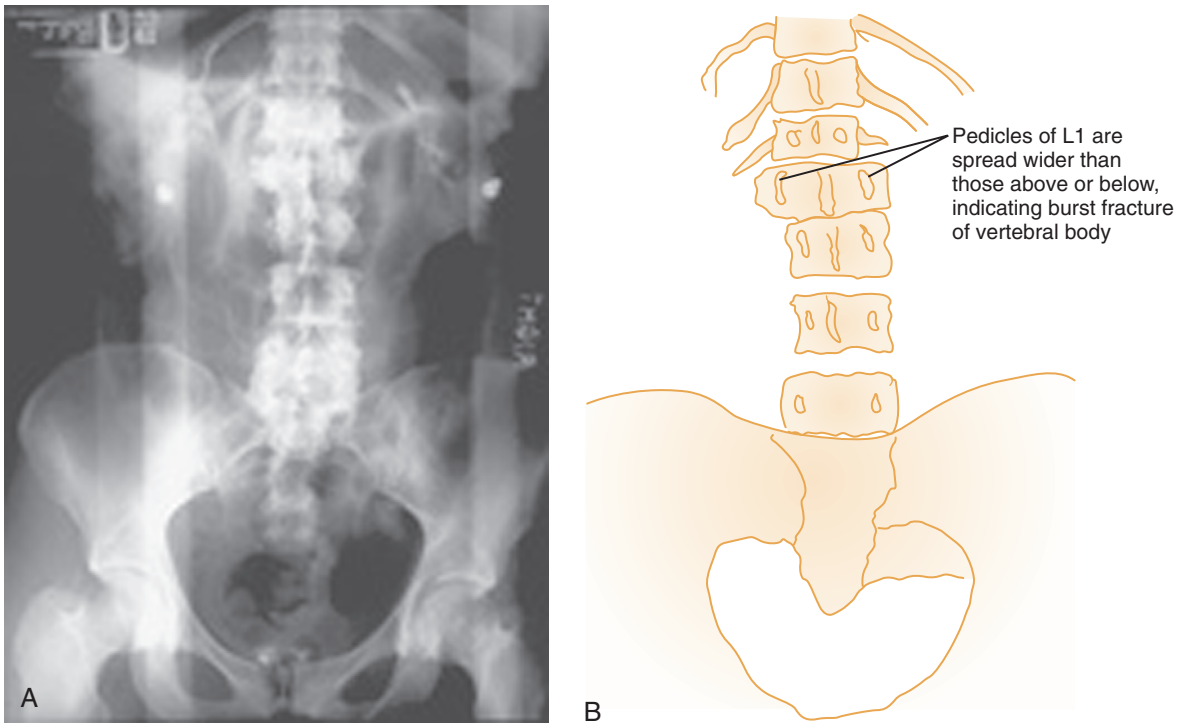


Figure 40-28. **A** and **B**, Burst fracture of L1. An anteroposterior radiograph shows increased distance between the pedicles of L1 in comparison to adjacent vertebrae. An intravenous pyelogram showed renal injury on the left.

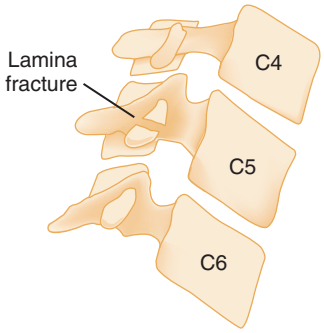


Figure 40-29. Oblique view of a laminar fracture. A fracture line extending through the lamina of C5 is well demonstrated on an oblique view.

eration, and the often critical status of trauma patients. The incidence of an inadequate lateral cervical view, specifically visualization of C7 to T1, is as high as 25%.[29] The CT scan effectively deals with these limitations and in many cases is the technique of choice for the definitive evaluation of acute cervical spine trauma.[33-37] CT also permits examination without moving the patient from the supine position and is thus preferable in terms of fracture stabilization, airway control, and other life-support measures.

The superiority of CT in fracture detection is a critical advantage (Figs. 40-31, 40-32, and 40-33); thus, unclear fractures or displacements on standard radiographs should be further evaluated by a CT scan. Since fractures in contiguous and noncontiguous vertebrae are fairly common, CT scan should be obtained to visualize the entire cervical spine. CT can also identify bony fragments, acute disk herniation, a foreign body, paraspinal hematoma, or an extramedullary hematoma.

A study comparing CT to plain radiography demonstrated the sensitivity in the detection of spine fractures to be 70% for plain radiography compared with 100% for CT, and there was a significant reduction in mean time in the radiology department with CT (1.0 vs. 1.9 hours, $P < .001$).[38] In another study, CT identified 99.3% of all fractures of the cervical, thoracic, and lumbar spine after high-energy trauma, and those missed by CT required minimal or no treatment.[39,40]

Due to the advantages of CT, some authorities argue that routine plain radiographs of the spine are unnecessary when CT is readily available. Investigators have assessed whether data collected from CT scans of the abdomen and pelvis obtained for the evaluation of chest and abdominal injuries provide sufficient data to screen for spinal fractures, thereby decreasing the time and cost of spine injury evaluation. In a retrospective review of 3537 blunt trauma patients, of whom 236 (7%) sustained a cervical, thoracic, or lumbar fracture, Brown and colleagues reported that CT identified 99.3% of all fractures. The one cervical and one thoracic fracture missed by CT respectively required minimal treatment with a rigid cervical collar or no treatment.[39] CT is also thought to be adequate to clear cervical spines even in the obtunded blunt trauma patient.[41] In fact, the Eastern Association for the Surgery of Trauma practice management guidelines recommend clearance of the cervical spine after performance of a CT of C1-C2 and three views of the cervical spine in the unreliable, obtunded patient.[42] However, there remains controversy regarding clearance of the cervical spine in the obtunded patient.

The spiral (helical) CT scan provides continuous acquisition of data (volume scan) via a rotating x-ray tube and simultaneous patient movement through the CT gantry (Fig. 40-34). The ability to reconstruct axial CT data in two-dimensional and three-dimensional formats is helpful to nonradiologists, who are less accustomed to performing the mental integration

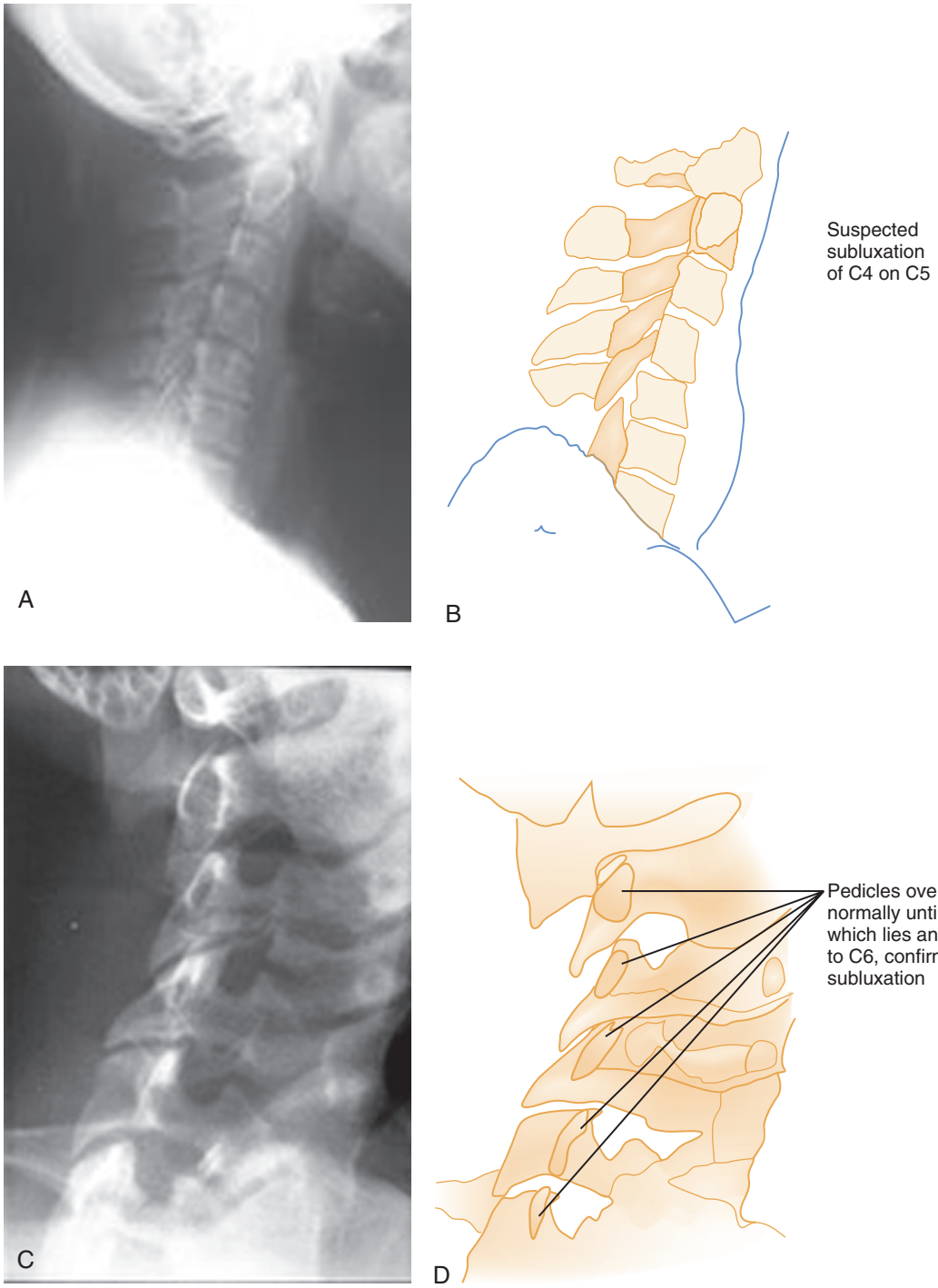


Figure 40-30. **A** and **B**, True subluxation, lateral view. Anterior subluxation of C5 on C6 is questionable. **C** and **D**, True subluxation, oblique view. The pedicle of C5 lies slightly anterior to that of C6, thus confirming subluxation.

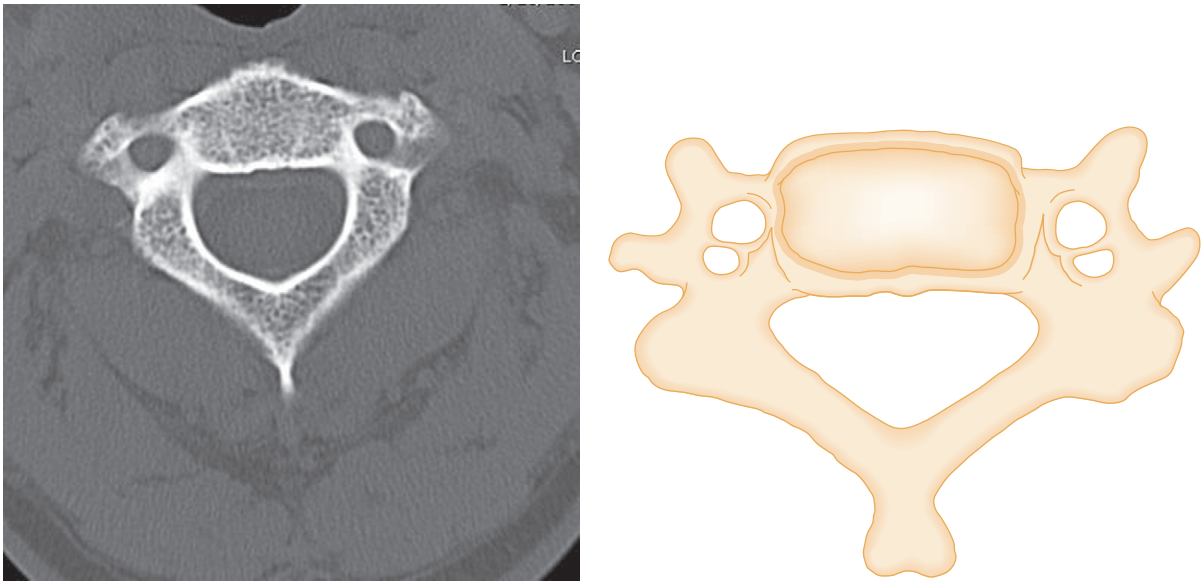


Figure 40-31. Normal axial computed tomographic section of the cervical vertebra.

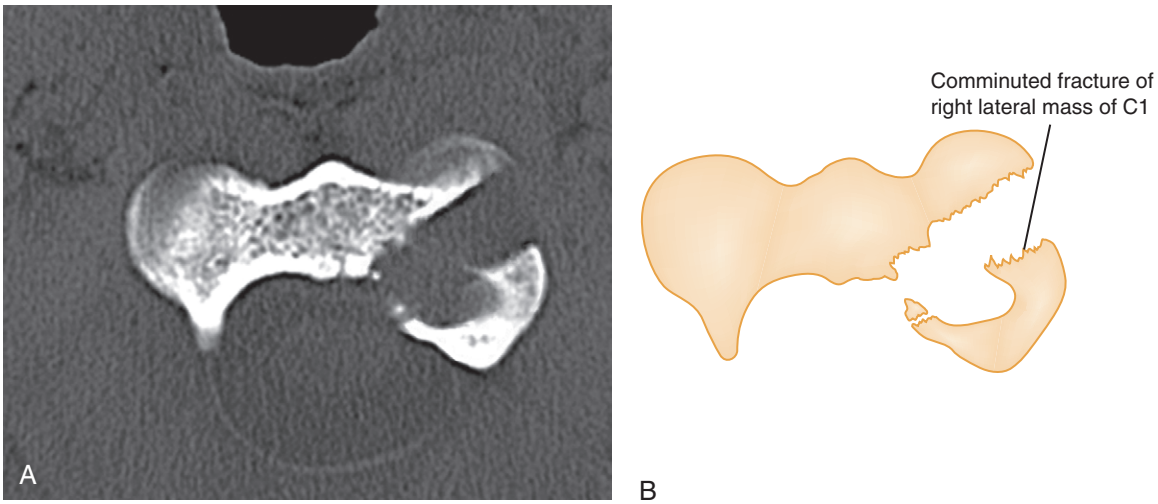


Figure 40-32. C1 fracture through the left lateral mass.

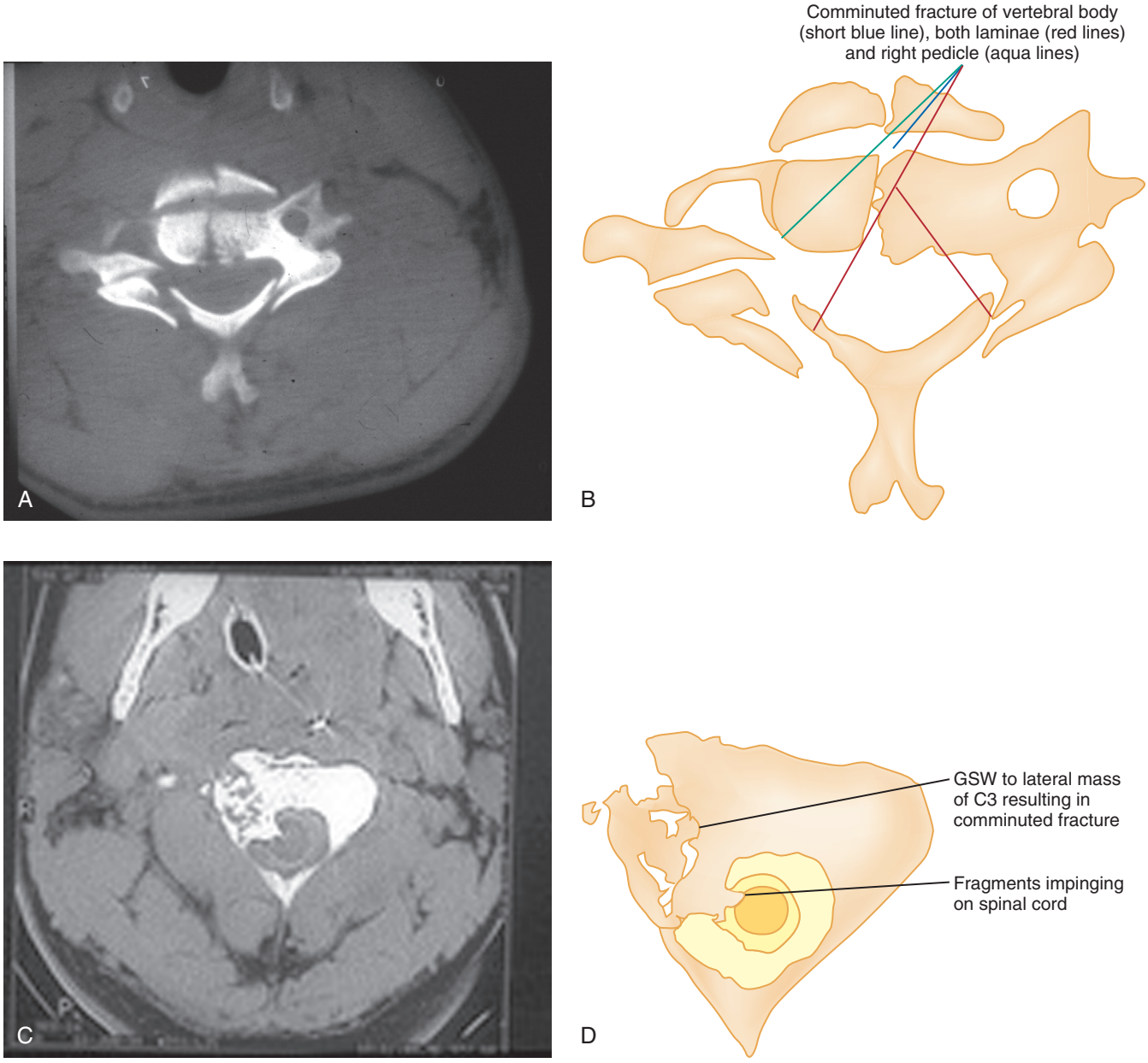


Figure 40-33. **A** and **B**, Axial computed tomography of C5 showing a comminuted vertebral body fracture and bilateral lamina fractures with narrowing of the spinal canal. **C** and **D**, Gunshot wound (GSW) of the lateral mass with fragments impinging on the spinal cord.

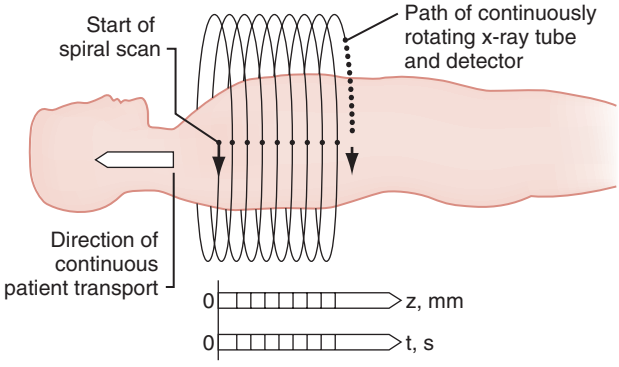


Figure 40-34. Technique for performing a spiral computed tomographic scan.

of multiplanar images (Fig. 40-35). The spiral CT scan can demonstrate cervical spine injuries not apparent on plain film or axial CT images (Fig. 40-36).

Potential disadvantages of CT include cost and radiation exposure. However, in one study, although CT was associated with higher mean overall spinal imaging charges than plain radiography ($4386 vs. $513, $P < .001$), there was no statistically significant difference when comparing spinal imaging cost per patient ($172 vs. $164, $p > .05$).[43] In the same study, radiation exposure for CT was higher than for plain radiography for cervical spine imaging (26 vs. 4 mSv), but CT had lower levels of radiation exposure for thoracolumbar imaging (13 vs. 26 mSv).[43]

MRI Scan

MRI, with its superior resolution and lack of ionizing radiation, also has the primary advantage of the ability to directly image

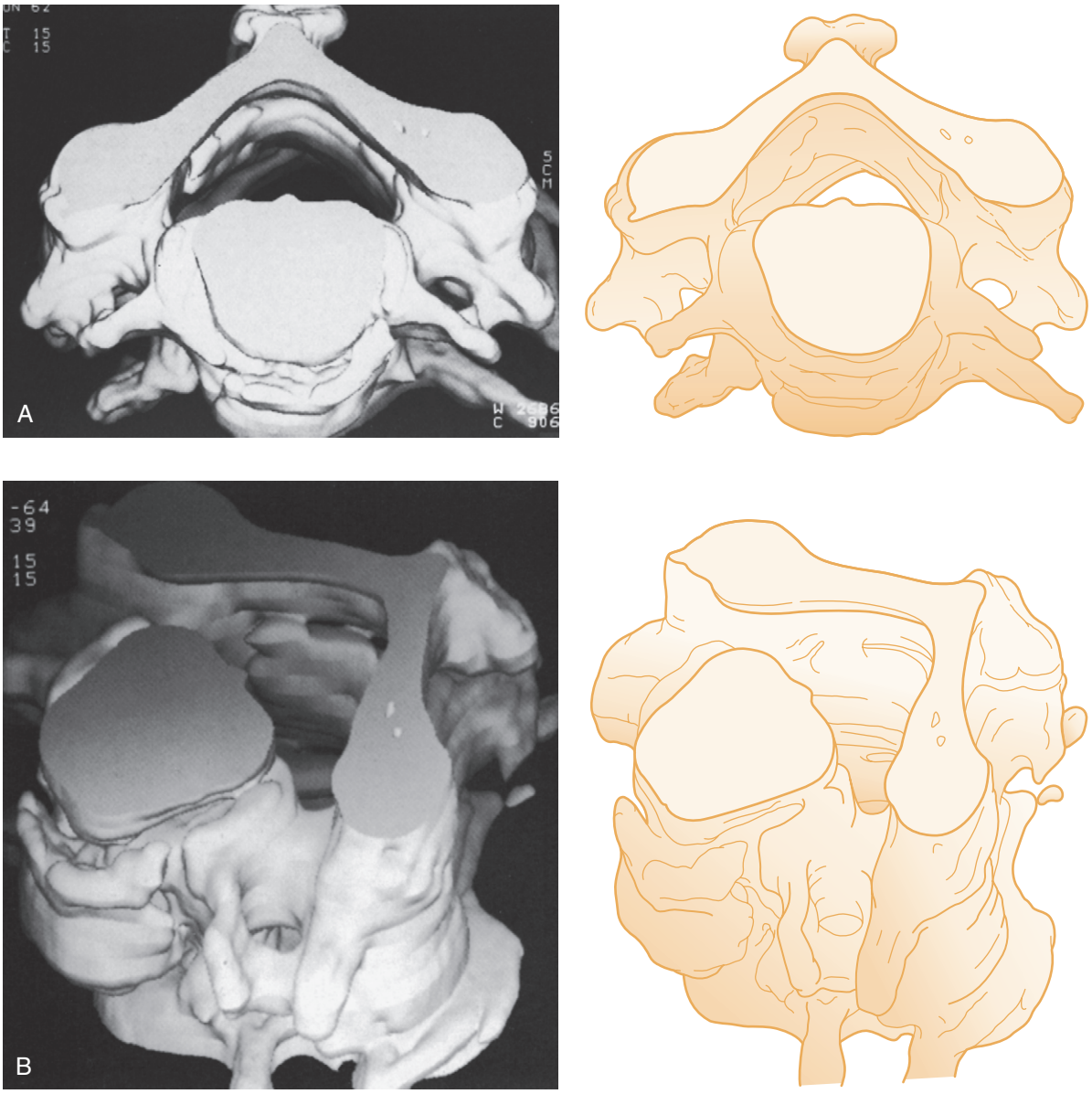


Figure 40-35. Three-dimensional computed tomography images of the cervical vertebrae. **A**, Superior view. **B**, Oblique view.

nonosseous structures, including intramedullary and extramedullary spinal abnormalities that potentially cause neurologic deficit (Fig. 40-37). Its major impact has therefore been in demonstrating potentially surgical correctable lesions, including acute disk herniation, ligamentous injury, bony compression, epidural and subdural hemorrhage, and vertebral artery occlusion (Fig. 40-38). MRI can identify three separate patterns of SCI, including acute cord hemorrhage, cord edema or contusion, and mixed cord injury. Patients with cord edema or contusion show significant neurologic improvement, whereas those with cord hemorrhage (Fig. 40-39) fare far worse. MRI therefore has diagnostic and prognostic capabilities in the evaluation of cervical spine injury. MRI is also viewed as the best diagnostic imaging modality for SCIWORA, in which MRI may demonstrate central disc herniation, spinal stenosis, cord edema, and contusion.[44]

Contraindications to MRI include the presence of a pacemaker, cerebral aneurysm clips (MRI-compatible clips are now available), and metallic (ferromagnetic) foreign bodies. In addition, MRI cannot be used when MRI-incompatible life-support, monitoring systems, and cervical traction devices are employed (although MRI-compatible support systems exist). Plain films and CT are still superior to MRI in evaluating osseous anatomy and fractures, particularly posterior-element fractures.

The role of MRI in the evaluation of acute cervical spine trauma continues to evolve, and some advocate an immediate MRI in patients with clinical signs or plain film evidence suggesting ligamentous injury, particularly when prevertebral swelling is noted (Fig. 40-40).[45] Most recommend MRI for patients with a strong clinical suggestion of an occult spine injury who have normal plain radiographs, including those with persistent neck pain or neurologic deficit. However, when CT findings are normal, some studies have demonstrated that MRI may not be necessary to exclude unstable injuries, even in the obtunded or "unreliable" patient.[46,47] MRI is useful in the evaluation of the previously traumatized spinal cord.[48] Progressive neurologic dysfunction in a previously stable cord-injury patient may indicate undiagnosed disk or bone impingement on the spinal cord, myelomalacia, a developing

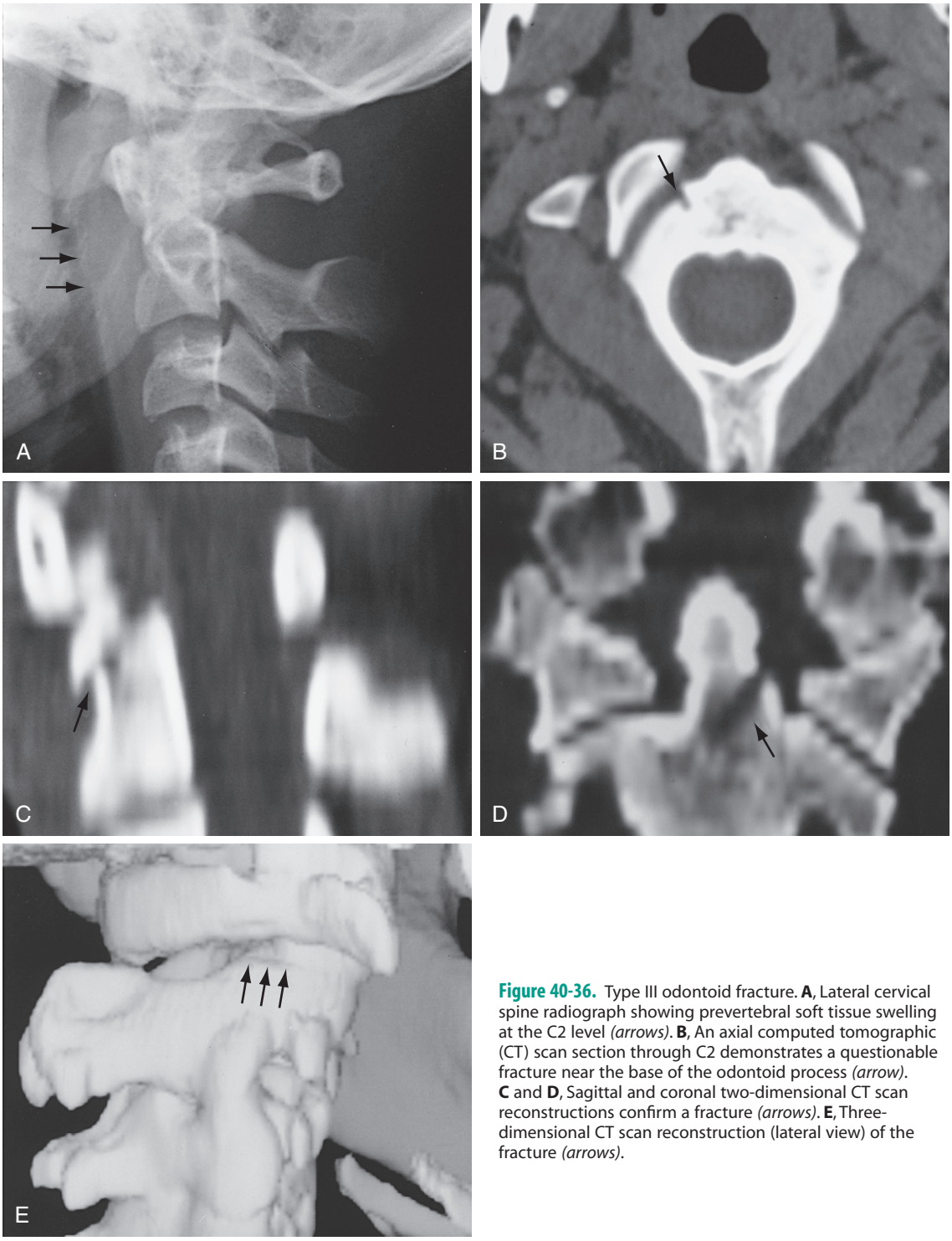


Figure 40-36. Type III odontoid fracture. **A**, Lateral cervical spine radiograph showing prevertebral soft tissue swelling at the C2 level *(arrows)*. **B**, An axial computed tomographic (CT) scan section through C2 demonstrates a questionable fracture near the base of the odontoid process *(arrow)*. **C** and **D**, Sagittal and coronal two-dimensional CT scan reconstructions confirm a fracture *(arrows)*. **E**, Three-dimensional CT scan reconstruction (lateral view) of the fracture *(arrows)*.

intramedullary (post-traumatic) syrinx, or subarachnoid cystic changes (Fig. 40-41), which can all be diagnosed by MRI.

■ MANAGEMENT

A spinal injury should be suspected in all trauma victims with an unknown or suggestive mechanism of injury associated with complaints of neck or back pain, evidence of significant head or facial trauma, spinal tenderness, signs of focal neurologic deficit, impaired consciousness, potentially distracting injuries, or unexplained hypotension. All patients suspected of having a significant spinal injury should be approached in a manner similar to that outlined in Figure 40-42.

Spinal Column Stabilization

Out-of-Hospital Care

Paramedical personnel should suspect a spinal injury in any victim of trauma, especially craniofacial injuries caused by motor vehicle accidents, assaults, falls, and sports. Trauma victims may have an altered state of consciousness resulting

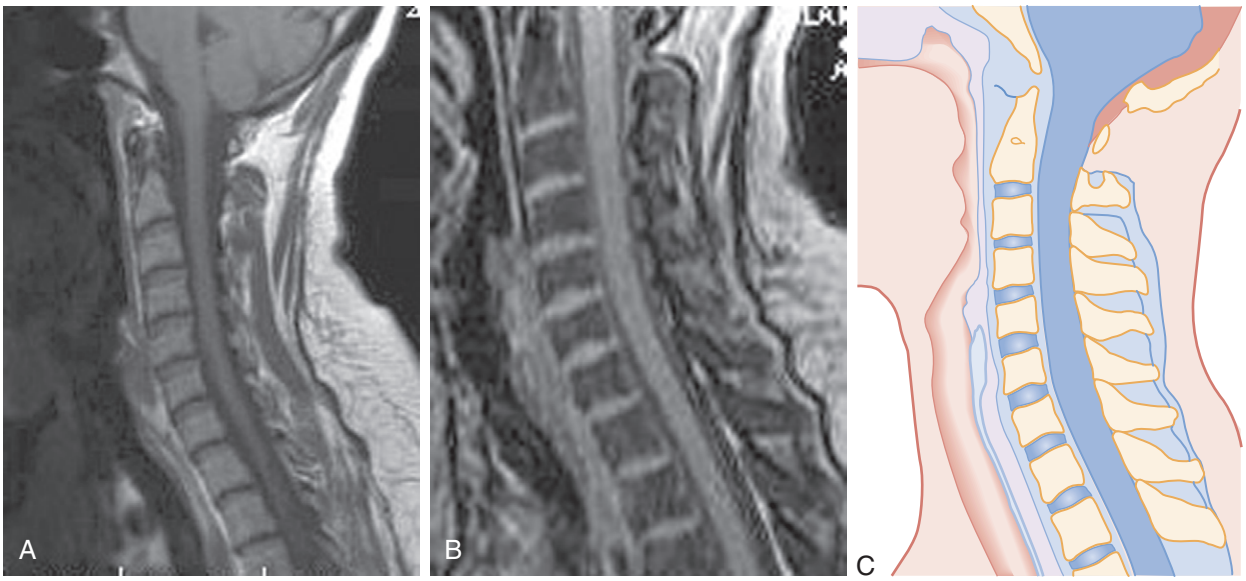


Figure 40-37. Normal sagittal magnetic resonance images of the cervical spine: T_1-weighted (**A**) and flip-angle (**B**) scans. **C**, Illustration of the cervical spine.

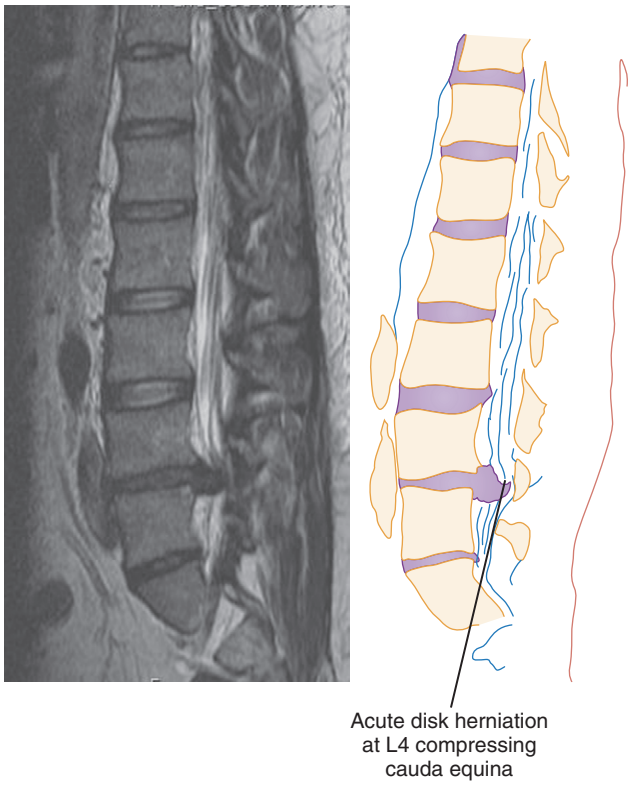


Figure 40-38. Magnetic resonance image showing acute L4 disk herniation with compression of the cauda equina.

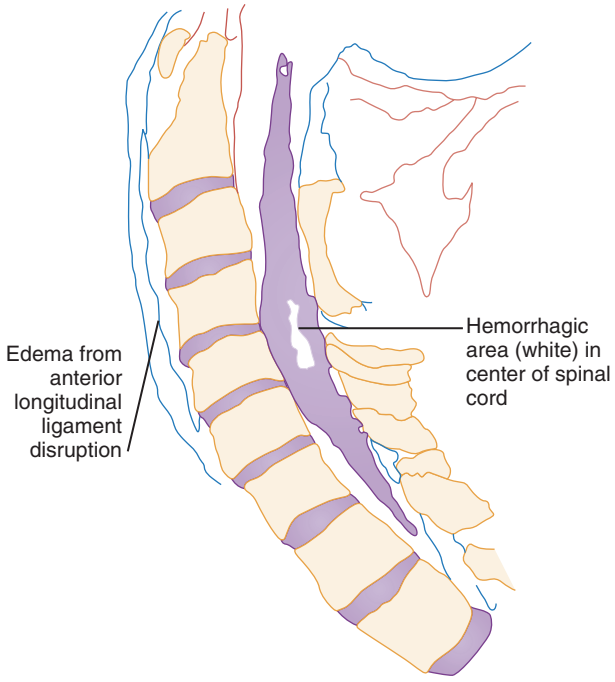


Figure 40-39. Magnetic resonance image showing a small area of central cord hemorrhage and both anterior and posterior ligamentous disruption.

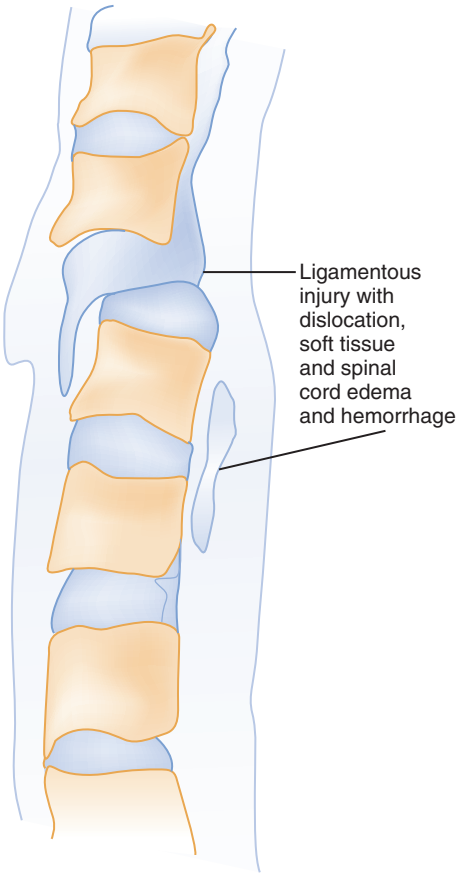


Figure 40-40. Anteroposterior longitudinal ligament disruption. A sagittal magnetic resonance image demonstrates ligamentous disruption between C4 and C5 with blood tracking in the anterior spinal canal.

Figure 40-41. Magnetic resonance image showing post-traumatic syrinx of the spinal cord.

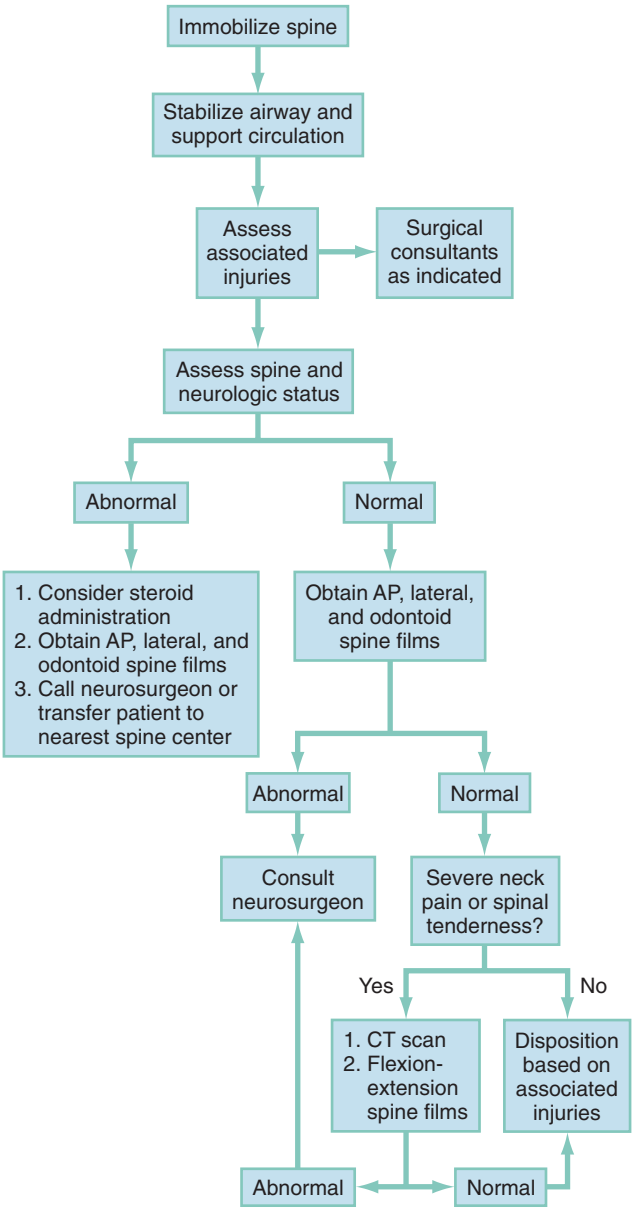


Figure 40-42. Approach to a patient with suspected cervical spine injury.

from drug or alcohol intoxication, head trauma, or shock that makes cooperation difficult and spinal movement likely, unless steps are taken to immobilize the potentially traumatized spine.

Spinal immobilization should be initiated at the scene and maintained until a spinal injury is excluded in the emergency department. A variety of effective spinal immobilization orthoses are commercially available. The most widely used, and perhaps most effective, approach uses the combination of a spinal backboard, a rigid cervical collar, and supportive blocks placed on either side of the head held in place by straps or tape stretched across the patient's forehead.[49-53] The heads of children younger than age 8 years are somewhat large in proportion to their bodies, resulting in mild neck flexion when they are placed on a flat backboard. This can be avoided by using a special backboard with an occipital recess or by placing a rolled sheet under the child's upper back to mildly elevate the thorax.[52] Further out-of-hospital care should be directed at evaluation and stabilization of associated injuries or problems requiring immediate intervention.

Emergency Department

Trauma victims who arrive at the emergency department with spinal immobilization should be quickly assessed by a physician. If the probability of spinal injury is moderate to high, it is advisable to remove the patient's clothes, evaluate any associated injuries, and perform resuscitative maneuvers without removing the immobilization apparatus. When the probability of injury is low, the immobilization device may be removed and the patient carefully assessed before further tests are ordered.

Patients with probable spinal injury who are conscious and cooperative should be cautioned against attempted movement until radiographic studies have been performed. Patients who are uncooperative because of head injury, drug or alcohol intoxication, hypotension, or the presence of multiple painful injuries require a more aggressive approach, including consideration of the use of chemical sedation and mechanical restraints. Suspected thoracic and lumbar spinal injuries are best managed by simply keeping the patient supine and immobile. The goal of stabilization in cases of cervical spine trauma is the immobilization of both the neck and the body because any movement may extend the initial injury. If the patient is not already immobilized on a backboard, the torso should be firmly anchored to the examining table by straps or rolled sheets. Supportive blocks or sandbags can be placed on either side of the head and a piece of 3-inch tape then placed across the forehead and blocks to immobilize the head and neck. A combative patient may require an individual assigned to hold the patient's head in alignment with the longitudinal axis of the body. Sedation, drug-induced paralysis, and intubation may be required for patients who pose a danger to themselves because of excessive movement. Spinal precautions should be maintained in patients with an altered sensorium until the presence of an injury can be excluded clinically or radiographically. Suctioning should be immediately available to prevent aspiration, and emergency department personnel must be aware of this ever-present possibility. When vomiting occurs, patients should immediately be placed on their side, while spinal alignment is maintained, and suctioning performed.

Airway Management

The emergency physician should anticipate airway management problems in patients with cervical spinal injuries. Lesions above the level of C3 may cause immediate respiratory paralysis, and lower lesions that are ascending from the spread of edema may cause delayed phrenic nerve paralysis, as well as ascension of the neurologic injury above the level of C3. Cervical injuries may also be associated with airway obstruction from retropharyngeal hemorrhage or edema or maxillofacial trauma. In addition to head or chest injuries requiring airway control or respiratory support, acute pulmonary edema has also occurred after cervical spine injuries unassociated with significant head injury.

According to the American College of Surgeons' (ACS) advanced trauma life support guidelines, the preferred method of airway management for patients with traumatic cardiopulmonary arrest, even with evidence of spinal injury, is rapid sequence intubation (RSI) with orotracheal intubation in the presence of in-line spinal stabilization.[54] This is also the recommended approach for patients who are breathing but unconscious and in need of airway control or ventilatory support.[55-65] The value of in-line spinal stabilization has been questioned in a review of the topic that notes that the data supporting the use of in-line stabilization come from cadaver

studies, observations on uninjured volunteers, and several case series; that there is little evidence to support the contention that orotracheal intubation without in-line stabilization, which causes less spinal motion than the chin thrust maneuver, is unsafe in spinal injured patients; that the incidence of spinal injury in trauma patients requiring intubation, who often have intracranial injuries, is quite low; and that there is evidence that in-line stabilization diminishes the laryngoscopic view, possibly leading to failed intubation and severe hypoxemia, which has been shown to predict poor outcomes in central nervous system injury.[66] The authors note that despite this information, clinicians will be hesitant to forgo in-line stabilization because it is recommended by the ACS and suggest that further studies in trauma airway management be performed using intubating supraglottic airways, optical stylets, and video laryngoscopes. Cricothyrotomy should be considered for patients with severe maxillofacial injuries and when RSI is contraindicated or if attempts at orotracheal intubation fail (see Chapter 1).

Spinal Shock

Spinal shock is a clinical syndrome characterized by the temporary loss of neurologic function and autonomic tone below the level of an acute spinal cord lesion.[14] Patients usually exhibit flaccid paralysis with loss of sensation, deep tendon reflexes, and urinary bladder continence, along with bradycardia, hypotension, hypothermia, and intestinal ileus. Spinal shock may last from less than 24 hours to more than 2 weeks.[67] Its cessation is heralded by the return of the bulbocavernosus reflex.

Neurogenic hypotension secondary to spinal shock, which is caused by loss of vasomotor tone and lack of reflex tachycardia from disruption of autonomic ganglia, should always be a diagnosis of exclusion in the trauma victim. It should not be considered the cause of hypotension unless the patient is flaccid and areflexic; reflex tachycardia and peripheral vasoconstriction are absent; and, most important, the possibilities of coexisting hemorrhagic shock, cardiac tamponade, or tension pneumothorax have been eliminated. The absence of vasomotor activity in patients experiencing neurogenic hypotension can mask the usual presentation of these life-threatening injuries.

Although there is no consensus in the literature regarding the most appropriate treatment of neurogenic hypotension, it is prudent to begin the resuscitation of all newly arrived, hypotensive trauma victims with crystalloid fluid infusion.[68] Most cases of pure neurogenic hypotension are mild (e.g., systolic blood pressure >90) and will initially respond to this approach. Severe (e.g., systolic blood pressure <70) neurogenic hypotension, seen in 20 to 30% of all spinal injuries, occurs most commonly with severe high cervical injuries associated with total or near-total loss of neurologic function.[14] Fluid resuscitation is often ineffective in such patients and may result in fluid overload if aggressively pursued. As a result, symptomatic neurogenic hypotension should be managed with fluids, Trendelenburg positioning (unless contraindicated because of concomitant head injury), vasopressors, or cardiac pacing—based on hemodynamic monitoring—once the diagnosis is established and the coexistence of other causes of traumatic shock is excluded.

Pharmacologics for Incomplete Cord Injury

Experimental animal models of SCI support the concept that delayed biochemical damage, occurring hours to days following an initial traumatic insult, contributes to ongoing tissue loss and worsening neurologic function. As a result, numerous neuroprotective treatment strategies have been investigated in both laboratory animal studies and human clinical trials, and the search for an effective treatment is under way (Box 40-1).[69-86] Methylprednisolone is currently the only agent routinely used for human victims of SCI, and its use is highly controversial.

The National Acute Spinal Cord Injury Study (NASCIS) investigators published several studies showing that early administration of high-dose methylprednisolone improves the neurologic outcome of SCI victims.[74-77] Methylprednisolone is administered as an initial 30 mg/kg IV bolus followed by an infusion of 5.4 mg/kg/hr. The infusion is maintained for 24 hours in patients who are treated within 3 hours of injury, and it is maintained for 48 hours in patients who are treated within 3 to 8 hours following injury. The administration of steroids resulted in a worse outcome when started after 8 hours.

The NASCIS studies have been criticized for having methodologic flaws and for failing to assess whether the mild neurologic improvement seen in patients treated with

BOX 40-1 Treatment Strategies for Acute Spinal Cord Injury Currently under Investigation

A. Reduce the effects of the damage
   1. Maintain circulation
   2. Maintain oxygenation
   3. Reduce neurotoxins and free radicals (methylprednisolone, glutamate receptor antagonists)
   4. Reduce inflammation (cytokine, Rho, interleukin-10, tumor necrosis factor blockers)
   5. Reduce apoptosis (nitric oxide inhibitors, calpains)
B. Encourage correct neuron function/connections
   1. With cells
      a. Schwann cells
      b. Olfactory ensheathing glial cells
      c. Astrocytes
      d. Reengineered fibroblasts
      e. Macrophages
      f. Oligodendrocyte precursors
   2. With matrix modifiers
      a. Netrins
      b. Neural glues (PEG/synthetic hydrogels)
   3. With nerve grafts
      a. Peripheral nerve implants
C. Enhance regeneration/axon growth
   1. Inhibitor neutralizing antibody
      a. Anti-NOGO
   2. Neutrophin-3
   3. Acidic fibroblast growth factor
   4. Brain-derived neurotropic factor
   5. Rho antagonists
D. Replace lost nerve cells
   1. Fetal tissue
   2. Stem cells
E. Inhibit scar/gliosis formation
   1. Decorin
   2. Chondroitinases
F. Reduce neurocircuit deficits
   1. Potassium channel blockers
   2. Sodium channel blockers
   3. Glutamate receptor blockers

Adapted from Donovan WH: Spinal cord injury—Past, present and future. J Spinal Cord Med 30:85, 2007.

methylprednisolone actually results in an improvement in day-to-day functioning.[87,88] Moreover, other studies have reported that patients treated with methylprednisolone have a higher rate of respiratory and gastrointestinal complications compared with placebo-treated patients.[89] The most recent guidelines published by the Consortium for Spinal Cord Medicine (which includes the American Association of Neurological Surgeons, the American College of Emergency Physicians, the Congress of Neurological Surgeons, the American Association of Orthopaedic Surgeons, and the International Spinal Cord Society) in 2008 state that "no clinical evidence exists to definitively recommend the use of any neuroprotective pharmacologic agent, including steroids, in the treatment of acute spinal cord injury to improve functional recovery."[90] Despite this, the *Cochrane Database Systematic Review* maintains that "high-dose methylprednisolone steroid therapy is the only pharmacologic therapy shown to have efficacy in a Phase Three randomized trial when it can be administered within 8 hours of injury … and that there may be additional benefit by extending the maintenance dose from 24 to 48 hours if treatment is not started until between 3 and 8 hours after injury."[91] Although a recent survey of U.S. spine surgeons found that 86% routinely administer steroids to spine-injured patients, only 21% believed that it improved patient recovery and the most common justification given for administering steroids was "medicolegal concerns."[92] A similar survey of emergency departments and neurosurgical units in the United Kingdom found wide variations in practice.[93] At this time, however, there is no substantive evidence to support the utilization of prednisolone for acute blunt partial SCI, and because of the possibility of severe side effects, its use can only be considered, at best, an option.

Associated Injuries

Cardiopulmonary

Although deterioration in a trauma victim's cardiopulmonary status is usually the result of hemorrhagic shock or direct injury to the heart or lungs, it may reflect the development of pulmonary edema that occasionally occurs in response to brain and spinal cord injury.[94] Spinal cord trauma may stimulate an intense sympathetic discharge with two subsequent effects. First, pulmonary capillary endothelial cells are disrupted, leading to the pulmonary capillary leak syndrome, in which pulmonary edema occurs in the presence of normal pulmonary artery pressures (<18 mm Hg). Second, marked increases in afterload may cause left ventricular dysfunction, leading to pulmonary edema associated with a high pulmonary artery pressure (>18 mm Hg). Volume overload from aggressive fluid resuscitation can also contribute to the development of pulmonary edema. As a result, the management of such patients is often complex and may require the careful balancing of fluid requirements, afterload reducing agents, and artificial ventilation with positive end-expiratory pressure.[94]

Gastrointestinal and Genitourinary

If SCI renders the abdominal examination unreliable, an abdominal CT scan, ultrasound, diagnostic peritoneal lavage, or some combination is often necessary.[95] During the acute stages of SCI, both the gastrointestinal tract and the bladder become atonic. Thus, once a patient has been stabilized, a nasogastric tube should be placed to prevent gastric distention, and a Foley catheter should be placed to prevent bladder distention and to monitor fluid output. Gastrointestinal bleeding from stress ulcers occurs in 2 to 20% of spinal trauma patients.[96] Thus, either ulcer prophylaxis with histamine H_2 receptor antagonists or proton pump inhibitors should be initiated.[90]

Skin

Denervated skin is extremely susceptible to pressure necrosis. Pressure sores can develop in less than 1 hour in such patients, particularly if they are managed on unpadded spinal carts. Padding pressure areas with sheepskin or foam padding early in the course of therapy can help minimize decubitus ulcers.

Definitive Treatment and Prognosis

The role of immediate surgical intervention in the management of spinal injuries is currently limited to relieving impingement on the spinal cord caused by foreign bodies, herniated disks, bony fracture fragments, or an epidural hematoma.[97,98] Surgery may be necessary later to stabilize severe bony injuries or to reduce spinal dislocations. The timing of surgical intervention is controversial, and there are no well-designed studies that have determined whether early (<12 hours) versus late decompression is beneficial.[90]

Major spinal injuries were once almost uniformly fatal. Most patients died of pulmonary complications or sepsis resulting from skin necrosis or urinary infection. The advent of antibiotic therapy made long-term survival not only possible but also expected. Today, patients with SCIs are best managed by early referral to a regional spine injury center, where a team of neurosurgeons, orthopedic surgeons, psychologists, and physical therapists can initiate rehabilitation. Specialized SCI treatment centers offer patients a chance to return to a productive life within the limits of their disability. Experience has shown that with the exception of those patients with high cervical lesions (above C5), most patients attain sufficient independence to live outside of a high-level care environment.[99]

■ DISPOSITION

Cervical Sprain

Musculoskeletal injuries of the spine involving only mild to moderate discomfort and no neurologic impairment, no abnormal radiographic findings, and no other injuries requiring hospitalization are best managed on an outpatient basis. Treatment should include analgesics and referral for follow-up evaluation. Up to 27% of patients experiencing neck pain in the emergency department following trauma will continue to have symptoms at 1 year.[100,101]

Minor Fractures

Most patients with spinal fractures require hospitalization. Patients with isolated cervical vertebral body compression fractures or spinous process fractures may be managed on an outpatient basis if the mechanism of injury is not significant, there is no evidence of neurologic impairment or associated ligamentous instability, and the degree of patient distress is not severe. Appropriate follow-up care should be arranged in all instances because even minor spinal injuries may be associated with prolonged disability resulting from chronic pain.[100-103]

For patients with minor wedge fractures (<10% wedge fractures) who do not have an associated ileus or neurologic deficit, outpatient management may be possible. However, most wedge fractures of the thoracic and lumbar spine are usually best managed in the hospital for several reasons.[104,105] First, patients with these injuries usually have marked discomfort,

often requiring parenteral narcotics. Second, significant force is generally required to fracture thoracic or lumbar vertebrae, and associated intrathoracic or abdominal injuries should be considered. Finally, lower thoracic and lumbar fractures are often associated with prolonged and occasionally delayed gastrointestinal ileus, requiring continuous nasogastric suction.

KEY CONCEPTS

- Victims of motor vehicle crashes, falls from heights, and sports-related injuries should have their entire spines examined for evidence of injury. Spinal radiographs should be obtained in the presence of suggestive symptoms or signs, or when an abnormal mental status or distracting injuries hamper clinical assessment.
- In order to prevent inadvertent movement of the spinal column, spinal precautions should be maintained in patients with altered mentation until the presence of a spinal injury can be excluded either clinically or radiographically.
- Evidence that high-dose methylprednisolone is a clinically efficacious intervention in the management of acute blunt partial SCI is lacking, and because of the possibility of severe side effects, its use can only be considered, at best, an option.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 41

Neck

Kim Newton

PERSPECTIVE

Neck trauma can result in a spectrum of injuries and complications ranging from incidental to life-threatening, including hemorrhagic shock, acute neurologic injury, and airway obstruction. Vascular and laryngeal injuries can rapidly compromise the airway, challenging the most experienced physician. Stable-appearing patients can harbor insidious injuries associated with high morbidity and mortality if not recognized and treated in a timely manner. Practicing emergency physicians not only must be familiar with the spectrum of injuries and subtle presentations associated with neck trauma but also should be well versed in neck anatomy, diagnostic evaluation, management controversies, and airway salvage techniques.

Neck trauma is divided into three major mechanisms: blunt, penetrating, and strangulation or near hanging. The injuries caused by these mechanisms can be further categorized into injuries of the airway (laryngotracheal), digestive tract (pharyngoesophageal), vascular system, and neurologic system. Each of these injuries has unique features and is discussed separately.

PRINCIPLES OF DISEASE

Pathophysiology

Penetrating Trauma

The incidence of penetrating neck trauma is reported to be 0.4 to 5% of all traumatic injuries and typically results from one of three major mechanisms: gunshot wounds (GSWs), stab wounds, and miscellaneous injuries that include impalement and shrapnel wounds.[1,2] GSWs are further divided into high-velocity and low-velocity injuries. High-velocity missiles include military-style weapons and hunting rifles that can achieve bullet velocities of 2200 to 3200 feet/second or greater. These missiles can easily penetrate soft tissue or bone; their pathway is generally direct and predictable unless deflected, although they can also cause remote injuries through a blast effect. Bone penetration requires a minimum velocity of 350 feet/second. Low-velocity injuries (small-caliber handguns and air guns) are caused by missiles that travel at significantly slower velocities (e.g., 300 feet/second for .22-caliber pistols). Slower moving missiles tend to produce erratic pathways, often demonstrating no direct relationship to the entrance or exit wounds.[3] Blast or cavitation effect pertains mainly to higher velocity missiles (>1000 feet/second). Cavitation refers to the immediate release of kinetic energy as the bullet enters the tissue. This energy release causes temporary displacement of the surrounding tissue with cavity formation along the bullet's pathway. Cavitation can cause extensive soft tissue damage beyond that caused directly by the bullet.

The neck zone and mechanism of injury should be noted because lower energy injuries (knife, handgun, or long-range birdshot or buckshot) cause a 50% lower incidence of clinically significant lesions (Fig. 41-1).[4] Zone I and III injuries pose a greater surgical challenge, and clinicians are more likely to order preoperative diagnostic tests to determine the best surgical approach (Table 41-1).[4]

Stab wounds, being of very low velocity compared with missiles and most often limited to one side of the neck, are more amenable to nonsurgical management. Miscellaneous penetrating neck wounds can occur from any object capable of impalement, puncture, or laceration but most often result from glass fragments after motor vehicle crashes or from dog bites. The overall mortality rate for penetrating neck injuries is 2 to 6%, and the leading cause of immediate death is exsanguination.[1,5]

Blunt Trauma

Blunt neck trauma most frequently results from motor vehicle crashes but can occur after assaults, "clothesline" injuries, strangulation, and sports injuries.[6] Blunt vascular injuries are rare[7] but represent some of the most underdiagnosed injuries seen by emergency physicians and trauma surgeons.[4] Blunt injuries to the aerodigestive and vascular tracts are uncommon compared with penetrating injuries but can cause acute airway compromise and delayed complications.

Anatomy

The neck is a complex, closed anatomic area dense with vital structures and invested with fascia creating several compartments. Because of this close anatomic relationship, vascular injury with hemorrhage either can be tamponaded by fascial planes and neighboring structures or can cause marked anatomic distortion, making evaluation and airway management extremely difficult. Two methods are used to describe the external neck: zones and triangles.[8] Anatomically, the neck has been divided into triangles (anterior and posterior). The *anterior triangle* is laden with vital structures (neurovascular

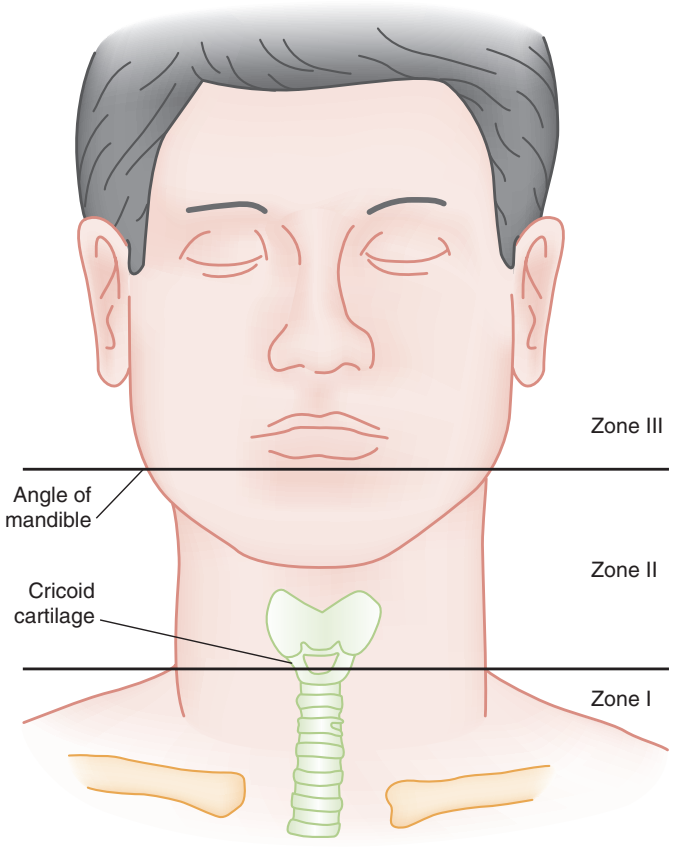


Figure 41-1. Zones of the neck.

Table 41-1 **Incidence of Injuries in Penetrating Neck Trauma**

LOCATION	NUMBER (1275 TOTAL)	PERCENTAGE*
Arterial	320	12.8
Venous	281	11.3
Tracheolaryngeal	253	10.1
Pharyngoesophageal	240	9.6
Spinal cord	76	3
Neurologic, other	85	3.4
Thoracic duct	20	0

*Incidence based on other reported series.
From McConnell DB, Trunkey D: Management of penetrating trauma to the neck. Adv Surg 27:97, 1994.

and aerodigestive tracts) and is bordered anteriorly by the midline, posteriorly by the sternocleidomastoid muscle, and superiorly by the lower edge of the mandible. The *posterior triangle* is located within the boundaries of the sternocleidomastoid muscle anteriorly, the clavicle inferiorly, and the anterior border of the trapezius muscle posteriorly. Excluding spinal trauma, injury to this region often has a more favorable prognosis because of the relative paucity of vital structures.

Current practice favors division of the neck into zones I, II, and III. This division has both anatomic and management implications for penetrating neck trauma. *Zone I* (base of neck) extends superiorly from the sternal notch and clavicles to the cricoid cartilage. It comprises the thoracic outlet below the cricoid cartilage. Injury to this region can affect both neck and mediastinal structures. *Zone II* (midneck) is the area between the cricoid cartilage and the angle of the mandible. Zone II injuries are therapeutically distinct because they lie in the most exposed region of the neck, making these injuries accessible to direct surgical visualization with easier proximal and distal vascular control. *Zone III* (upper neck) extends from the angle of the mandible to the base of the skull. As with zone I injuries, proximal and distal vascular control in this region is difficult to achieve (Box 41-1).

Two fascial layers, the superficial fascia and the deep cervical fascia, cover neck structures. The superficial fascia covers the platysma muscle and is located just below the skin. The deep cervical fascia is divided into three parts: The *investing layer* surrounds the neck and splits to encase the sternocleidomastoid and trapezius muscles; the *pretracheal layer* adheres to the cricoid and thyroid cartilages and travels caudally behind the sternum to insert on the anterior pericardium; and the *prevertebral layer* envelops the cervical prevertebral muscles and extends to form the axillary sheath, which covers the subclavian artery. The pretracheal layer is clinically important because of its connection from the neck to the anterior mediastinum. Missed aerodigestive injuries can result in mediastinitis because of this anatomic continuity. The carotid sheath is made of portions from all three divisions of the deep cervical fascia. The *platysma muscle*, sandwiched between the superficial and deep cervical fascia, covers the anterolateral neck. It has clinical significance because of its superficial location and proximity to vital structures. If the platysma muscle is violated, injury to these structures should be suspected. Examination of any penetrating neck wound should document the zone or

BOX 41-1 **VASCULAR AND OTHER CONTENTS IN NECK ZONES**

Zone I
Proximal common carotid artery
Vertebral artery
Subclavian artery
Major vessels of upper mediastinum
Apices of lungs
Esophagus
Trachea
Thyroid
Thoracic duct
Spinal cord

Zone II
Carotid artery
Vertebral artery
Larynx
Trachea
Esophagus
Pharynx
Jugular vein
Vagus nerve
Recurrent laryngeal nerve
Spinal cord

Zone III
Distal carotid artery
Vertebral artery
Distal jugular vein
Salivary and parotid glands
Cranial nerves IX–XII
Spinal cord

zones of injury and presence of platysma violation without Blind probing is discouraged as it may dislodge a clot and induce major hemorrhage.[9]

CLINICAL FEATURES

Patients with neck injury can manifest numerous signs and symptoms, but most are nonspecific. This makes diagnostic strategies difficult, especially in the stable patient. Much debate in the current literature centers on the safest and most cost-effective approach to evaluating patients with possible neck injury. Serial examinations are crucial, searching for evidence of progressive airway or vascular compromise. Features that suggest decompensation in a previously stable patient can include dyspnea, dysphonia, stridor, drooling, expanding hematoma, bruit, cerebral ischemia, or shock.

DIAGNOSTIC STRATEGIES

The reliability of physical examination, coupled with ancillary studies, in detecting serious neck injury in a stable patient is becoming less controversial. Researchers historically remained divided between those who did and those who did not believe that physical examination alone was adequate in determining which patients needed ancillary studies.[9-13] A prospective study of 393 patients with penetrating neck injuries determined that 30% of patients with no physical findings subsequently had positive neck explorations.[9] In contrast, a prospective series of 223 patients with penetrating neck wounds found that physical examination was reliable in determining which patients needed vascular or esophageal diagnostic studies.[10] Stable patients should be evaluated for the presence of "soft" and "hard" signs of aerodigestive or neurovascular injury (Box 41-2). Most patients with hard signs benefit from surgical intervention. Controversy surfaced over the stable patient with soft or no signs of injury. Historically, management of penetrating neck trauma has undergone a similar evolution to trauma in other regions in that management has progressed from a policy of mandatory exploration to one of selective management based on ancillary studies and serial physical examination.[14,15]

BOX 41-2 "SOFT" AND "HARD" SIGNS OF PENETRATING NECK TRAUMA

Soft Signs
Hemoptysis/hematemesis
Oropharyngeal blood
Dyspnea
Dysphonia/dysphagia
Subcutaneous or mediastinal air
Chest tube air leak
Nonexpanding hematoma
Focal neurologic deficits

Hard Signs
Expanding hematoma
Severe active bleeding
Shock not responding to fluids
Decreased/absent radial pulse
Vascular bruit/thrill
Cerebral ischemia
Airway obstruction

MANAGEMENT

Stable Patients

Ideally, stable patients with neck injury should be transported to a trauma center. Despite a stable initial appearance, airway compromise can ensue rapidly and intervention is essential at the first sign of airway distress. Necessary interventions should be initiated during transport to the emergency department rather than at the scene to avoid delays in definitive care. Open wounds should be covered and sufficient compression applied to control bleeding and prevent air embolus without occluding the airway or blood flow to the brain. Consideration of cervical spine damage, especially in the face of blunt trauma, or in the presence of neurologic deficits should prompt the application of a cervical collar.

Unstable Patients

Airway management must be the highest initial priority in the unstable patient. Cervical spine immobilization is typically unnecessary in penetrating neck trauma unless the patient has coexistent blunt trauma or evidence of a spinal cord injury. Oral intubation using rapid sequence intubation (RSI) is considered safe in most patients with neck trauma.[16,17] When the airway has been stabilized, breathing assessment is standard, with consideration of the associated risk of hemothorax or pneumothorax, seen primarily with penetrating zone I injuries. Caution is required when bag-valve-mask ventilation is necessary because air can be forced into injured tissue planes, resulting in massive subcutaneous emphysema and subsequent airway distortion or, rarely, air embolus. Active bleeding sites or wounds with blood clots should not be probed because massive hemorrhage can ensue. Ideally, bleeding is controlled by direct pressure. Blind clamping of active bleeding sites should be avoided because of the high concentration of neurovascular structures in the neck. If a vascular injury is suspected, mild Trendelenburg's position is recommended to reduce the risk of air embolism. Intravenous access is best placed on the noninjured side, avoiding the ipsilateral neck or upper extremity until vascular injury has been excluded. Cervical collars might obscure neck pathology and preclude adequate examination. Partial removal of the collar while maintaining in-line stabilization may be necessary to perform adequate serial examinations.

The presence of profound shock or cardiopulmonary arrest unresponsive to fluids or emergency department thoracotomy should prompt the physician to consider venous air embolism (VAE). If this condition is suspected, the patient should be placed in a head-down, left lateral decubitus position to cause intracardiac air to accumulate in the apex of the right ventricle. If this maneuver alone does not improve cardiac output, aspiration of air from the apex of the right ventricle either through an ultrasound-guided pericardiocentesis needle or under direct vision after emergency department thoracotomy may be lifesaving. Evidence of cerebral ischemia, as manifested by profound alteration in consciousness, or stroke-like symptoms suggest injury to the cervical vessels or cerebral arterial air embolism.

Caution is advised in any patient with suspected vascular injury who requires a nasogastric tube (NGT). The retching typically seen with placement can dislodge a hematoma, resulting in immediate hemorrhage. If indicated, an NGT should ideally be placed after the patient is intubated. Conversely, an NGT can be therapeutic by removing gastric contents to prevent aspiration, and it can be diagnostic because a bloody aspiration implies visceral injury.

Airway Management

Orotracheal Rapid Sequence Intubation

Although the ideal airway technique for neck trauma patients has been debated during the past decade, orotracheal intubation using RSI has been shown to be safe and effective and it should be considered the first-line airway technique unless contraindications exist.[16,17] Orotracheal RSI is often successful even after neck trauma with airway distortion.[18] RSI has also been shown to be superior to intubation without neuromuscular blocking agents.[19] However, RSI medications should be used only by an experienced intubator. Concern that complete muscle relaxation would lead to airway obstruction or that excessive movement would cause worsening of unstable cervical spine fractures has not been borne out.[16,20] There are numerous alternatives for achieving intubation, but the emergency physician must be familiar with their limitations in the setting of neck trauma.[21] Less commonly used airway salvage techniques, however, may diminish the emergency physician's comfort level and prolong the airway stabilization procedure.

If the cervical spine must remain immobilized, an assistant should maintain in-line stabilization of the head and neck.[22] Relative contraindications to RSI include massive facial trauma or suspected laryngeal injury. When time allows, an initial inspection of the airway can be made using a laryngoscope in the awake patient. In cases in which orotracheal intubation is expected to be difficult, an attempt to intubate over a nasopharyngoscope may be prudent in patients who do not have massive bleeding into the oropharynx. All emergency physicians must have a thorough knowledge of alternative techniques for intubation in the event that orotracheal RSI fails.[21,23,24] If the emergency physician does not have the ability to utilize a nasopharyngoscope, it may be valuable to consult an anesthesiologist or ear, nose, and throat physician in the emergency/urgent situation.

Nasotracheal Intubation

Historically, nasotracheal intubation was recommended for the majority of trauma patients, especially if cervical spine injury was suspected (see Chapter 1). Early versions of the Advanced Trauma Life Support courses also taught that blind nasotracheal intubation (BNTI) was the procedure of choice in patients with neck trauma.[25] BNTI may have serious complications, including bleeding, vomiting, aspiration, increased intracranial pressure, turbinate damage, and sinusitis. In addition, if cervical spine injury has not been excluded, cervical protection can be difficult to maintain because of the retching and neck movement due to procedural discomfort often seen during BNTI in awake patients. Older studies have shown that success rates for BNTI range from 66 to 93%.[26] Although a more recent study demonstrated a 90% success rate with BNTI for trauma patients, it should be considered only if the other techniques described have been unsuccessful.[27] Nasotracheal intubation is contraindicated in those with suspected midface or basilar skull fractures or laryngeal injury, yet barring contraindications may be possible in an apneic patient using Magill forceps.

Surgical-Invasive Airways

Cricothyrotomy remains a common airway salvage technique used by many emergency physicians when endotracheal intubation is not possible.[21] Despite clear descriptions of this technique in the literature,[28] it is not always simple to perform. Anterior neck hematoma or potential laryngeal injury should make the intubator consider a different means of securing the airway because release of a tamponaded cervical hematoma may prove devastating. Although it appears efficacious, controversy surrounds the safety of out-of-hospital cricothyrotomy when performed by emergency medical services personnel.[29] Percutaneous transtracheal jet insufflation, an effective method of providing a temporizing airway in selected adult or pediatric trauma patients, is fraught with potential complications. These include inadvertent catheter dislodgment resulting in massive subcutaneous emphysema, catheter kinking, perforation of the posterior wall of the trachea and esophagus, pneumothorax, and hypercarbia. Complete upper airway obstruction is considered a contraindication because barotraumas can result from inadequate exhalation.[21,30]

Miscellaneous Techniques

Other airway techniques include fiberoptic laryngoscopy and bronchoscopy, which have been used successfully for difficult airways, although excessive bleeding can render visualization difficult. Lack of experience and time constraints are cited as reasons why these techniques are not preferred in the emergency department.[1,16] Emergency tracheostomy is not a common emergency department procedure because it is technically difficult and time-consuming to perform. It should be attempted only in select cases in which other techniques are contraindicated or not available. Although reported in the literature, esophageal obturator airway, retrograde intubation, laryngeal mask airway, and awake endotracheal intubation are generally not used as primary procedures or airway salvage techniques in trauma patients.[31,32]

Pediatric Considerations

Airway management in the pediatric trauma patient tends to be more anxiety-provoking, in part because of the different anatomic considerations. Ideally, the approach to the pediatric airway is similar to that to the adult airway, using orotracheal RSI. The incidence of unstable cervical fractures in children is lower than in adults.[33] As in adults, airway salvage techniques may be necessary, but fewer options are available in young children. The airway of the young child and infant is higher and more anterior, with the narrowest region of the airway at the cricoid cartilage.[34] The small cricothyroid membrane and the soft, poorly mineralized pediatric larynx make cricothyrotomy contraindicated in children younger than 10 years. Emergency tracheostomy, which is a difficult procedure in young children, or transtracheal jet insufflation can serve as a salvage technique.[35] BNTI in the infant and very young child is also not recommended, in part because the smaller endotracheal tubes are too pliable to be consistently passed.

Cervical Spine

Numerous papers have been written on the safety of orotracheal intubation in patients with known or suspected cervical spine injury.[18,36,37] Historically, cadaver studies generated fear of head movement during intubation, thus causing some to abandon the orotracheal route of intubation. However, RSI with in-line stabilization has not been shown to produce neurologic sequelae in humans and is believed to be a safe means of securing the airway in patients with both penetrating and blunt cervical trauma.[16,31] Fear of delayed neurologic sequelae from cervical spine injury following intubation should not preclude using RSI with in-line stabilization. Neurologically intact patients with unstable cervical fractures secondary to penetrating trauma rarely manifest delayed neurologic

sequelae.[5,38] There is greater concern for occult or overt cervical spine injury in the patient with blunt neck or multisystem trauma, although cervical spine injuries in this population are not as common as once thought. Armed with this knowledge and barring contraindications, emergency physicians should use the airway technique with which they are most comfortable. Delays in securing an airway because of indecision regarding which technique to use can lead to hypoxic brain injury.

Mandatory versus Selective Exploration

The debate is ongoing in the trauma literature concerning the best way to manage penetrating neck injuries. Before World War II, patients with penetrating neck trauma were treated expectantly rather than aggressively despite unacceptably high mortality rates (18–35%).[1] In an attempt to reduce the mortality associated with penetrating neck injuries, the concept of mandatory surgical exploration of all penetrating neck wounds was developed.[39] Mandatory surgery drastically reduced mortality rates to 6%.[4] Wartime experience justified the ongoing utilization of mandatory surgery in victims with penetrating neck injury, and this was widely accepted for decades.[40]

Despite low mortality rates achieved with mandatory surgery, negative neck explorations concurrently increased 40 to 63% during the mid- to late 1900s as many institutions adopted a mandatory surgical approach.[2] As with other traumatic injuries, an effort to reduce the negative exploration rate while maintaining low morbidity and mortality rates led to the concept of *selective surgical management*, which remains institution specific. Selective management offers a spectrum of approaches, ranging from serial physical examinations to an array of diagnostic tests in the stable patient. A selective approach is justified because (1) military injuries were often secondary to high-velocity missiles, as opposed to currently used weapons (e.g., knives and handguns) and animal bites; and (2) improved technology currently allows much greater accuracy in the detection of injuries. A review of zone II penetrating neck trauma cites similar overall mortality rates of 5.85% in the mandatory group and 3.74% in the selective group.[41] Current literature favors a selective approach, with the trend in the past decade being to minimize invasive procedures.[42,43]

Transcervical Gunshot Wounds

Transcervical gunshot wounds (TC-GSWs) represent a subset of penetrating neck trauma and are included in the debate between mandatory and selective management schools. TC-GSWs are associated with a twofold increased incidence of injuries compared with GSWs that do not cross the midline (79 vs. 31%). The most common injury seen is vascular (48%), followed by spinal cord (24%).[44] Although some centers still practice mandatory exploration for these injuries, prospective studies suggest that stable patients with TC-GSWs can be safely evaluated using a selective surgical approach with the appropriate diagnostic studies and frequent serial examinations.[44] GSWs in the anterior midline also involve an increased incidence of vascular and visceral injuries, and a more aggressive diagnostic approach should be considered in these patients.

DISPOSITION

Many patients who present to the emergency department with penetrating or blunt neck trauma have predetermined disposition, especially when their condition warrants further diagnostic studies, surgery, or intensive care. Most stable patients should be admitted for observation. All patients with platysma muscle violation should be admitted to the surgical service for ongoing observation, regardless of their stability. Careful observation should be maintained for patients with blunt neck injury because they can manifest delayed signs and symptoms of viscerovascular injury with serious consequences.

Because smaller hospitals may have neither the ancillary support nor the personnel to perform serial bedside examinations, mandatory exploration might be in the patient's best interest in these facilities. Level I trauma centers generally have sufficient ancillary support and diagnostic tools and are more suited to avoid surgery safely in stable patients. Studies suggest that surgeons with trauma experience tend to perform fewer neck explorations.[36]

SPECIFIC INJURIES

Pharyngoesophageal Trauma

Epidemiology

Esophageal injuries are infrequently reported after penetrating neck trauma, representing only 0.11% of all trauma admissions.[37] Blunt esophageal perforation is even less common, with only 10 case reports in the literature before 1990. The low incidence of injury most likely results from the relatively protected position of the esophagus. The cervical esophagus is injured more often than the distal segment. Mortality from esophageal injuries has remained relatively high during the past two decades, with an overall rate of 19–22%.[37,45]

Pathophysiology

Early diagnosis of esophageal injury is crucial because spillage of orogastric contents with bacterial contamination leads to florid inflammation, infection (abscess and mediastinitis), and death. Esophageal injuries represent the most frequently missed injuries in the neck[39] and may be the leading cause of delayed death resulting from neck trauma.

Clinical Features

Although there are no pathognomonic signs of esophageal injury, soft signs of injury include hematemesis, odynophagia, subcutaneous emphysema, and blood in the saliva or NGT; the presence of these should increase concern for esophageal injury. Other associated findings include dyspnea, hoarseness, stridor, cough, pain and tenderness in the neck, and resistance to passive neck movement.

Physical examination has been shown to be unreliable in diagnosing esophageal injury, with an accuracy of only 72%.[46] Because timely diagnosis is very important, most believe that sole reliance on physical examination is not warranted in stable patients with soft signs of esophageal injury.[45,47]

Diagnostic Strategies

Unfortunately, esophageal injuries are difficult to diagnose. To compound this, delays in diagnosis and thus treatment are strongly associated with adverse outcomes.[4,10,45] Inherent delays in diagnosis and operative repair are believed to contribute to the increased morbidity and mortality seen with these injuries; however, it is not known what constitutes a safe delay. Because of diagnostic difficulty seen with digestive tract injuries, proximity wounds should prompt an aggressive search

for an esophageal injury. Timely diagnosis is believed to be associated with decreases in morbidity and mortality, but this time frame has yet to be defined.[37,45]

Diagnosing esophageal injury often depends on more than a high clinical suspicion. Contrast esophagography is considered relatively unreliable for diagnosing esophageal injuries, with a sensitivity of 80 to 89%.[41,46] This study requires adequate views for accurate interpretation and thus requires the patient's cooperation. Flexible endoscopy has been reported as insensitive, primarily missing proximal esophageal injuries because the scope is unable to efface the mucosa in this region as can a rigid endoscope.[4] The combination of rigid esophagoscopy and contrast esophagography is much more sensitive, but the former requires general anesthesia. Currently, the combination of contrast swallow and flexible endoscopy appears to be accurate in diagnosing esophageal injuries, yielding a sensitivity of 100%.[46] Despite the selective management options mentioned, a prospective study suggested that only obtunded or symptomatic patients (hematemesis, painful swallowing, or subcutaneous emphysema) need studies to exclude esophageal injuries.[10] Plain films of the neck and chest radiographs suggest esophageal perforation if pneumomediastinum or retropharyngeal air is present.[48,49] Many agree that only select populations should undergo a watch-and-wait approach and that the vast majority of patients with suspected esophageal injury need definitive diagnosis and treatment.[49]

With the advent of the higher resolution computed tomography (CT) scan, there has been a controversial suggestion that high-speed, thin-cut CT scanning may increase the sensitivity for penetrating zone II esophageal injuries and either supplement the physical examination in selectively managed patients or negate the need for other diagnostic studies.[50] However, sole reliance on this diagnostic modality is currently not supported by the literature when searching for esophageal injuries. CT scan can be useful to look at the wound track or trajectory of a bullet in the instance of penetrating trauma, thus helping to determine if a proximity wound is likely, but it has not been shown to be sensitive as a stand-alone diagnostic modality.[51,52]

Management

When esophageal injury is suspected, broad-spectrum antibiotics with anaerobic coverage should be administered, and the patient should receive nothing by mouth pending surgical exploration. Preoperative placement of an NGT with suction may reduce the spillage of gastric contents into the wound.

Laryngotracheal Trauma

Mechanisms of Disease

Laryngotracheal (LT) injuries account for less than 1% of all trauma injuries, with most confined to the cervical trachea. Most LT injuries result from direct blunt force sustained in motor vehicle crashes, in which the extended neck strikes the steering wheel or dashboard and the larynx is compressed between the fixed object and the cervical spine. Other mechanisms leading to LT injuries include clothesline injuries, improperly fitting shoulder harnesses, near hanging, assaults, athletic events, attempted strangulation, and iatrogenic wounds. Penetrating LT injuries comprise 10% of all penetrating neck trauma.[4] Associated cervical spine injuries should always be considered simultaneously, especially when evaluating a patient with blunt neck trauma.

The cricoid cartilage is the only complete solid ring in the larynx. Fractures of the cricoid cartilage can lead to death through acute airway obstruction and are the most serious laryngeal injuries. Calcification of the laryngeal cartilages begins during the teenage years, and fractures before this age are much less likely to appear on plain neck films. The degree of airway obstruction after blunt trauma to the larynx is inversely related to the degree of cartilage calcification, putting children at highest risk.

Clinical Features

There is no consensus on whether all surgically significant LT injuries will present clinically at the time of initial evaluation in the emergency department.[20,53] Bubbling or air leakage from a neck wound should signal injury to the respiratory tract and is considered a hard sign of LT injury. Massive subcutaneous air and bony crepitus over the larynx suggest LT injury, as does a clothesline mechanism.[54] Other clinical features of LT injury include dysphonia, aphonia, dyspnea, stridor, hemoptysis, subcutaneous emphysema, laryngeal crepitus, neck tenderness or pain over the larynx, a visible neck wound, or loss of anatomic landmarks secondary to hematoma. Pain with tongue movement implies injury to the epiglottis, hyoid bone, or laryngeal cartilage.[1] In one study, dyspnea and stridor were the most common signs of injury in children with LT trauma.[55] Others cite subcutaneous air found by examination or on radiographs and tenderness over the larynx or trachea as the most common findings.[56]

Diagnostic Strategies

Diagnostic evaluation options exist for the stable patient. Missed injuries can lead to long-term sequelae, including voice change, dysphagia, laryngeal stenosis, and chronic pain. Patients with penetrating trauma are managed by a mandatory or selective protocol. Plain radiographs should be evaluated for extraluminal air, edema, foreign bodies, and fracture of the cartilaginous laryngeal structures. Laryngoscopy or flexible nasopharyngoscopy allows direct evaluation of laryngeal integrity. With appropriate local anesthesia, laryngoscopy is well tolerated by most patients who remain in cervical spine immobilization, and it can detect hypopharyngeal tears. Rigid endoscopy is useful to evaluate injury distal to the larynx but requires general anesthesia.[57]

Spiral CT scanning is a valuable adjunct, quickly providing detailed information about laryngeal integrity and the surrounding region.[51] CT is useful for detecting fractures of the hyoid bone, disrupted laryngeal or tracheal cartilages, significant exolaryngeal or endolaryngeal hematoma, and dislocations of the cricothyroid or cricoarytenoid joints and also for assessing vocal cord integrity and airway lumen diameter. Despite these advantages, CT has limitations and should not be relied on to detect mucosal perforations, degloving injuries of the cartilage with denuded mucosa, and certain types of LT separation. CT is not exclusively utilized in penetrating neck trauma and may be less helpful when evaluating poorly calcified pediatric cartilaginous structures because these fractures can be more difficult to visualize.

Widespread access to ultrasound has led to an increase in its use for trauma patients. Some advocate ultrasound to detect blunt laryngotracheal injuries such as laryngotracheal separation; however, larger studies are needed to confirm the utility of this modality.[58] CT is a good primary tool to assess for LT injury. Direct visualization via endoscopy can provide additional information in select cases where mucosal injury is likely and surgical exploration is not immediately indicated.

Management

Airway compromise in patients with LT trauma can be immediate or delayed. Clinical judgment must be exercised in

patients who initially appear to have stable, patent airways if they are to be sent to other departments for further diagnostic testing. Delayed airway occlusion can be rapid and life-threatening, and these patients require close monitoring. Airway management controversies persist, and the question regarding the safest technique for intubation (orotracheal, cricothyrotomy, tracheostomy, fiberoptic scope, or adjuncts) is unresolved. Orotracheal intubation can complete a partial LT separation or create a false passage. Likewise, cricothyroidotomy can further damage an injured larynx. If complete LT separation is present with distal retraction of the trachea, orotracheal intubation is likely to be unsuccessful, and tracheostomy might unknowingly be performed proximal to the tracheal segment. Tracheostomy in these cases is best done at the fourth or fifth tracheal ring to avoid the larynx. Because blunt LT injuries are often seen in association with multisystem trauma, they can be easily overlooked when other overt injuries are present, but these injuries in association with the need for emergent airway stabilization portend a higher mortality.[59]

Vascular Trauma

The great vessels of concern in the neck include the carotid, subclavian, and vertebral arteries and the internal and external jugular veins. Injury to these vessels can produce morbidity and mortality through exsanguination, hematoma expansion with subsequent airway distortion and compromise, direct vessel injury leading to vascular occlusion, or embolization of a foreign body (e.g., shotgun pellet to brain or heart). Carotid artery dissection may follow even trivial neck trauma and can result in stroke in young, otherwise healthy patients. The presence of delayed-onset, evolving central neurologic deficits in a patient with neck trauma should prompt assessment of the carotid arteries for dissection. Combined data from 16 studies of penetrating neck trauma during a 25-year period found that the carotid artery was the most commonly injured artery with an incidence of 6.7%. This was followed by subclavian artery injuries (2.2% incidence) and vertebral artery injuries (1.3%).[4]

Epidemiology

Penetrating Injury Vascular injuries represent 25% of all penetrating neck wounds, and mortality rates range from 10 to 50%.[5,41] GSWs are more likely to be associated with hard signs of vascular injury than are stab wounds.[39] Hard signs of vascular injury include pulsatile bleeding, rapidly expanding hematoma, bruit, or focal neurologic deficits consistent with carotid or vertebrobasilar arterial occlusion. Exsanguination from vascular injuries is the most common cause of immediate death after penetrating neck trauma. The jugular vein is the most frequently injured vessel in the neck,[41] although the common carotid artery is the most frequently injured artery (22% of all cervical vascular injuries).[46] The vertebral artery is injured in only 1.3% of all cases.[4] Vertebrobasilar arterial injuries may follow relatively minor trauma, such as chiropractic neck manipulation, but most commonly occur in association with fractures of the spinal column. They typically arise after a delay of hours to months with signs of posterior circulation embolus or infarction, and they portend a poor prognosis.

Blunt Injury Three to 10% of all carotid injuries result from some form of blunt trauma, but blunt carotid injuries affect only 0.08 to 0.33% of all blunt trauma victims.[60,61] Mortality rates for blunt cervical vascular injuries range from 20 to 40%. Blunt cervical vascular injuries are rare, and until the mid-1990s, only 480 cases had been reported in the literature.[61] Because the internal carotid artery is the most frequently injured artery, many studies use blunt vascular and carotid artery injuries synonymously, although the vertebral artery is injured in up to 20% of cases.[62] The actual incidence of blunt vascular injuries may be higher because of asymptomatic cases and difficulties in making the diagnosis. Blunt vascular injury should be suspected in patients with flexion-extension mechanisms, neck seat belt sign, diffuse axonal brain injury, and midface, mandibular, or basilar skull fractures.[7]

Pathophysiology

Penetrating Injury Most cases of penetrating trauma in adults are caused by knife or bullet wounds.[10] Vessel damage most often results from direct injury, although the blast effect can cause intimal injury without directly striking the vessel, making the vascular insult similar to that seen with blunt trauma. Some centers routinely obtain angiographic studies of all significant neck wounds; others restrict angiography to zone I and zone III injuries. In the past decade, reliance on CT angiography (CTA) has become increasingly common.[63] Zone I injuries in particular can harbor clinically occult arterial injuries, and routine preoperative arteriography has been historically advocated to detect injury and facilitate a judicious surgical approach when positive. Likewise, zone III vascular injuries can be exceedingly difficult to approach surgically, and thus some surgeons still prefer preoperative CT-A followed by exploration for any positive or equivocal findings. Many surgeons believe that preexploratory vascular studies are noncontributory in zone II injuries and may lead to delays in definitive care because these lesions are easily approached surgically.

Blunt Injury Blunt trauma to the cervical vessels can result in a spectrum of arterial injuries, including intimal tears, thrombosis, dissection, and pseudoaneurysm.[6,62,64] Embolization can occur from a thrombus that develops at the injury site. The most common mechanism for blunt internal carotid artery injury is sudden, forceful hyperextension and lateral rotation of the neck. This mechanism can cause stretching of the carotid artery over the transverse processes of the upper cervical vertebrae, resulting in intimal injury.[62] Other mechanisms responsible for this type of injury include direct blunt force to the side of the neck, intraoral trauma (e.g., children falling on lollipops), and basilar skull fractures, which have rarely been associated with injury to the intracranial portion of the carotid artery. Blunt carotid artery injuries most often result from motor vehicle accidents but have also been reported after fights, athletic events, seat belt injuries, clothesline injuries, and near hangings.[62,64] Seat belt signs on the neck may suggest insidious vascular injury, but a review of 131 patients with a seat belt sign at the neck found that only 0.76% had a significant vascular injury.[65]

Clinical Features

The debate regarding whether the physical examination is sensitive enough to detect vascular injuries in stable patients with minimal signs and symptoms is unresolved. Angiographically documented arterial injuries have not been reliably detected by physical examination in some series.[66] Others argue that although discrepancies may exist, they are not clinically relevant in the asymptomatic patient and rarely change management, and thus they conclude that serial examinations are adequate. Signs and symptoms of vascular injury include pulsatile hematoma, bruits, pulse deficit, hemothorax, airway compromise (from hematoma expansion), shock, and neurologic deficits.

Delayed presentation of a vascular injury is most often neurologic in nature, with symptoms ranging from transient

ischemic attack (TIA) to global cerebral ischemia. Horner's syndrome has been associated with vascular injury, particularly carotid artery dissection.[67] Delays in the onset of neurologic sequelae of weeks to years have been reported. TIAs usually result from release of small emboli from the injured vessel, which can herald the onset of a profound deficit. Thus, any focal neurologic abnormality should prompt the emergency physician to include vascular injuries in the differential diagnosis, especially after a normal head CT scan.

Because they are rare or delayed in their presentation, blunt vascular lesions are often not considered initially. Other injuries can divert the emergency physician's attention to more immediately life-threatening wounds. Diagnosis is also often delayed because 17 to 35% of patients do not develop neurologic symptoms for more than 24 hours.[68] Drugs, alcohol, or head trauma can further obscure or contribute to delays in the diagnosis of blunt vascular injury. Because of the low incidence of blunt vascular injuries, no large prospective study has fully defined the "at-risk" patient.

Diagnostic Strategies

There is also controversy regarding how aggressive the search should be for vascular injuries using surgical exploration or other diagnostic modalities in the patient with minimal symptoms. Blunt cervical vascular injuries represent some of the most underreported injuries because of their insidious presentation but ultimate association with a catastrophic neurologic outcome.

Conventional arteriography has been used extensively to detect vascular injury in patients with both blunt and penetrating injuries. A four-vessel arteriogram is time-consuming and expensive but historically felt to be helpful in planning the best surgical approach. The majority of patients require four-vessel studies, although occasionally a two-vessel (ipsilateral carotid and vertebral) arteriogram may be warranted if the injury is isolated to one side of the neck.[1] If ordered, these contrast studies should include the intracranial portion of the carotid artery with zone III injuries or suspected blunt cervical trauma. Zone I injuries should include the aortic arch with its branches. Although controversial, some still consider angiography as the "gold standard" for diagnosing vascular injuries[69]; if the study is negative, many recommend nonsurgical management when aerodigestive injuries have been excluded. Despite a sensitivity and specificity of nearly 100% and a complication rate of less than 2% for arteriography, other, less invasive diagnostic tests have been evaluated for accuracy, speed, cost, and efficacy.[70]

Duplex ultrasonography has been used in combination with or instead of arteriography to exclude cervical vascular injury in patients with both penetrating and blunt trauma.[71] Despite clinical success, limitations of ultrasonography include the risk of missing zone I and zone III injuries and the lack of 24-hour availability at many centers. Whether duplex scanning can reliably detect pseudoaneurysms or intrathoracic, distal internal carotid, and vertebral artery injuries remains unproved. Also, some patients must remain in cervical spine protection, limiting neck manipulation necessary for optimal views. Many surgeons are not comfortable with serial duplex examinations as a means of detecting traumatic vascular lesions and continue to use arteriography as the mainstay of diagnosis.

With the advent of newer generation machines, CTA (CT angiogram with 64-slice or more) has largely replaced conventional angiography. Part of the attraction is that they are rapid, readily available, and accurate.[72-74] CTA allows for the detection of many types of vascular injuries, and it characterizes cervical soft tissues, cervical vertebrae, and spinal cord as well as aerodigestive structures. Increasingly, more centers rely on CTA when no clear surgical indications are apparent, although CTA can potentially miss lethal lesions, such as pseudoaneurysms. Centers that prefer a selective approach are increasingly reporting success with this modality in the face of platysma violation.[75] Magnetic resonance angiography (MRA) has also been reported to be helpful despite high cost and lack of 24-hour availability.[76] MRA has additional distinct disadvantages that include remote location in many centers, contraindication if metallic foreign body (bullet fragments), and inability to directly visualize the neck during the procedure for expanding hematoma. Because neither CTA nor MRA has consistently proven to have the arteriogram's high degree of accuracy for detecting blunt or penetrating vascular injuries, they should not be relied on solely at the exclusion of proven diagnostic modalities.

Head CT scans are often ordered in response to ischemic neurologic deficits because many suspect closed-head injury initially. When these symptoms result from traumatic occlusion or dissection of the carotid artery, the head CT scan is frequently normal because the ischemic changes are often not obvious for more than 24 hours. Any unexplained focal or hemispheric neurologic deficits should prompt the emergency physician to consider vascular injuries.

Although not indicated in most cases of suspected vascular injury, plain films can occasionally be useful. Anteroposterior and lateral neck films can help determine a bullet trajectory by comparing the entrance wound with the location of the foreign body, if present. Chest radiographs allow evaluation of the mediastinum and identification of hemothorax or pneumothorax.

Management

Blunt Injury Treatment options for blunt artery injuries depend in part on the mechanism and type of injury and location of the lesion. Treatment modalities include surgery, anticoagulation, and observation. Anticoagulation, antithrombotic therapy, and endovascular stenting have all been successful treatments in the long-term treatment of blunt vascular injuries, although heparin is the preferred treatment in the acute phase for carotid artery dissection absent any major contraindications.[77] Others have not found heparin to be beneficial.[62] Antiplatelet therapy has been suggested for carotid artery dissection to prevent clot propagation.[60] Because of possible complications, none of these treatment modalities should be initiated without appropriate consultation. Surgical treatment includes ligation, resection, thrombectomy, and stent placement.[1,62]

Penetrating Injury The ideal management strategy for injuries of the vascular system resulting from penetrating trauma has not been determined. Because many of these patients are young with anticipated "clean" carotid arteries, some surgeons routinely attempt surgical repair. Because of concern that reperfusion might convert an ischemic infarction to a hemorrhagic infarction in patients with profound neurologic deficit, others prefer ligation over repair in a select population of patients.

Venous Air Embolism VAE is a subset of vascular injuries that can lead to life-threatening complications if not detected. VAE has been reported after blunt, penetrating, and iatrogenic mechanisms. VAE occurs when air enters the injured vessel, usually during inspiration, resulting in distal vascular occlusion and infarction. In any patient with a suspected major venous injury, direct pressure should be maintained over the wound while the patient is kept in the Trendelenburg position. Autopsy reports on trauma victims reveal air in both the right

side of the heart and the pulmonary artery. When standard treatment fails in a pulseless trauma patient, VAE should be immediately suspected and the right ventricle aspirated for air after the aorta is cross-clamped. Rarely, air embolism has been reported with arterial injuries as well.[1]

Nervous System

When evaluating any patient with neck trauma, the examiner must remember that the brachial plexus, peripheral nerve roots, cervical sympathetic chain, and cranial nerves VII, IX, X, XI, and XII are vulnerable, as well as the spinal cord. Neurologic deficit can also result from vascular injury with subsequent cerebral ischemia. Complete cord injury can result in spinal (neurogenic) shock with paraplegia, bradycardia, and hypotension. Brown-Séquard syndrome (hemisection of the spinal cord) arises with ipsilateral hemiplegia and contralateral sensory deficit. Brachial plexus, spinal root, and peripheral nerve injuries have been reported after neck trauma and can result in both sensory and motor deficits. Phrenic nerve injury may compromise spontaneous respiration by causing ipsilateral diaphragmatic paralysis. Hoarseness can result from direct laryngeal trauma, but injury to the recurrent laryngeal nerve, which branches off the vagus nerve (cranial nerve X), should also be suspected, with vocal cord paralysis on the affected side.

Thoracic Duct, Glandular, and Retropharyngeal Injuries

Other, less common injuries have been reported in association with neck trauma with variable signs and symptoms. Thoracic duct injuries are less likely to be apparent initially and are frequently diagnosed intraoperatively or after development of a chylothorax. Glandular wounds, including those of the thyroid, parathyroid, and salivary glands, are reported rarely. Retropharyngeal hematomas are also extremely rare but can result in life-threatening airway compromise.[1,78]

Near Hanging and Strangulation

Epidemiology

Hanging and strangulation represent the second most common form of suicide in the United States after firearm use.[79] The number of deaths from suicidal hanging is increasing.[80] Approximately 5330 strangulation deaths occur annually in the United States.[81]

The terms *hanging* and *strangulation* are often used interchangeably, with hanging being a subset of strangulation. Hanging is categorized as judicial (complete hanging) or nonjudicial (incomplete hanging). *Complete hanging* refers to the presence of a ligature around the victim's neck and a subsequent drop resulting in the victim being freely suspended. In contrast, *incomplete hanging* refers to the partial suspension of the victim's body with some part still in contact with the ground. Judicial hanging victims classically fall at least the height of their body, whereas incomplete hanging is more likely to be seen in confined spaces (e.g., homes and jail cells), where a fall from height resulting in full body suspension is less possible. On the basis of the location of the ligature knot, hanging is further divided into atypical and typical categories. *Typical hanging* refers to the knot being midline directly under the occiput, which leads to a higher likelihood of complete arterial occlusion. *Atypical hanging* refers to all other knot placements.[82]

Manual strangulation and *ligature strangulation* refer to external compression of the neck, usually by hands or ligature, but independent of the weight of the victim. *Postural strangulation*, generally seen in the younger pediatric population, refers to death sustained by the victim's body weight compressing the anterior neck against a firm object.[83]

Pathophysiology

Judicial hanging with adequate fall distance results in forceful distraction of the head from the neck and body. This classically leads to high cervical fractures, complete cord transection, and death. Attempted-suicide hangings frequently occur at inadequate height and therefore tend to mimic nonjudicial strangulation. Cervical fractures in the latter group are rare, and no fractures have been reported in near-hanging victims.[83] In essentially all types of nonjudicial strangulation, the ligature or external force initially applied causes venous congestion with stasis of cerebral blood flow leading to unconsciousness. Once the person is limp, the ligature or external force can tighten further, leading to complete arterial occlusion and ultimately to brain injury or death. Vagal reflexes resulting from pressure on the carotid body may contribute to fatal dysrhythmias, as may increased sympathetic tone from pericarotid sinus pressure. Compression of the airway does not play as significant a role in incomplete hanging as vascular occlusion.[82]

Pulmonary sequelae are frequently seen in near-hanging victims and include pulmonary edema, bronchopneumonia, and adult respiratory distress syndrome (ARDS).[82] These complications are responsible for most in-hospital deaths after near hanging. Pulmonary edema occurs from one of two mechanisms. *Neurogenic* pulmonary edema results from centrally mediated, massive sympathetic discharge. Because it is more often seen in association with serious brain injury, neurogenic pulmonary edema has poor prognostic implications. *Postobstructive* pulmonary edema is generally associated with a better neurologic outcome. It is initiated by marked negative intrapleural pressure, which is generated by forceful inspiratory effort against an extrathoracic obstruction. When the obstruction is removed, the onset of pulmonary edema can be rapid and lead to ARDS.[82]

Clinical Features

External trauma may or may not be evident, depending on the mechanism of injury. If present, ligature marks appear as indentations around the neck, ranging from mild erythema to leather-like grooves following the course of the ligature. Fingernail scratches, abrasions, and contusions are variably present on the external neck as well. *Tardieu*'s *spots* are highly correlated with asphyxial deaths; these petechial hemorrhages are seen in the conjunctiva, mucous membranes, and skin cephalad to the ligature marks. They occur when the venous pressure rises in response to ligature tightening. Laryngeal injuries are reported in near-hanging victims. Thyroid cartilage fractures are seen in approximately 50% of all nonjudicial hanging deaths, and hyoid bone fractures occur in 20%. Cricoid cartilage fractures are rarely reported. Manual strangulation is responsible for the majority of fractures.[82] Resulting laryngeal fractures are rarely clinically significant in survivors, and standard airway techniques are recommended.

Vascular injury leading to delayed neurologic sequelae after near hanging is rare but reported. It most often results from carotid intimal dissection or thrombus formation, resulting in partial or complete vascular occlusion or embolism.[83] Carotid vascular studies should be considered in patients with unexplained focal or global neurologic deficits.[84]

Management

Frequently, ventilatory support is indicated to maintain adequate oxygenation and ventilation in the comatose patient. The addition of positive end-expiratory pressure is often necessary, especially when pulmonary edema or ARDS develops.[82] Aggressive resuscitation is warranted in the unconscious patient; the initial Glasgow Coma Scale score is generally not predictive of outcome.[85,86] The altered or comatose patient should be assumed to have cerebral edema with elevated intracranial pressure, and cerebral resuscitation measures need to be actively initiated using standard technique.

Definitive studies providing guidelines on the management of hypoxic brain injury specifically related to near-hanging or strangulation injuries are lacking. Therefore, prudent cerebral protection measures may be interpreted from other data on this topic (and are discussed in detail in Chapter 6).

KEY CONCEPTS

- Neck trauma results from one of three major mechanisms: blunt injury, penetrating injury, or near hanging/strangulation.
- The leading cause of immediate death after neck trauma is exsanguination secondary to vascular injury.
- The leading cause of delayed death after neck trauma is esophageal injury. These wounds are rare, frequently insidious, and associated with high mortality rates if missed.
- Neck wounds should never be probed through the platysma muscle because massive hemorrhage or air embolus can ensue.
- Cervical collars can obscure impending airway disasters (e.g., expanding hematomas) and other signs suggestive of injury if not removed periodically to allow serial examinations.
- Unless a contraindication exists, orotracheal rapid sequence intubation is safe and effective in the hands of an experienced intubator.
- Vascular injuries resulting from blunt trauma represent some of the most underreported injuries because of their propensity for delayed neurologic sequelae.
- There is ongoing debate regarding whether physical examination is sensitive at detecting visceral or vascular injury, and the role of angiography versus serial examination is unresolved.
- Suspicion of venous air embolism should prompt direct wound pressure, occlusive dressings, Trendelenburg's position, and, if the patient is in cardiopulmonary arrest, aspiration of air from the right side of the heart.
- Transcervical gunshot wounds are a subset of injuries with a twofold increased incidence of visceral-vascular injuries compared with injuries that do not cross the midline.
- All near-hanging or strangulation patients who are comatose or have altered consciousness may have elevated intracranial pressure, and appropriate cerebral resuscitation measures should be initiated.
- The leading cause of in-hospital death in this population is pulmonary complications (pneumonia, pulmonary edema, and ARDS).

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 42

Thoracic Trauma

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EPIDEMIOLOGY

Thoracic injury directly accounts for 20 to 25% of deaths resulting from trauma, accounting for more than 16,000 deaths annually in the United States. The most common cause of injuries leading to accidental deaths in the United States is motor vehicle collisions, in which immediate deaths are often due to a rupture of the myocardial wall or the thoracic aorta. Early deaths (within the first 30 minutes to 3 hours) resulting from thoracic trauma are often preventable. Causes for these include tension pneumothorax, cardiac tamponade, airway obstruction, and uncontrolled hemorrhage. Because these problems are often reversible or may be temporized nonoperatively, it is vital that emergency physicians be thoroughly familiar with their pathophysiology, clinical presentation, diagnosis, and treatment.[1]

Approximately 75% of patients with thoracic trauma can usually be managed expectantly with simple tube thoracostomy and volume resuscitation. As such, initial care and disposition of these patients is usually performed by emergency physicians. Definitive care of these patients is often multidisciplinary in nature, involving trauma surgeons, cardiothoracic surgeons, and intensivists. Improvement in the understanding of the underlying physiologic mechanisms involved and the advancement of newer imaging modalities, minimally invasive approaches, and pharmacologic therapy contribute to decreasing the morbidity and mortality of these injured patients. The role of multidetector helical computed tomography (CT) scanning in the evaluation of trauma patients continues to expand. Although CT scans provide much greater diagnostic sensitivity than plain radiography, the precise indications for CT scanning for trauma patients remains unclear. Concerns regarding cost, contrast-induced nephrotoxicity, and cumulative radiation exposure to the thorax have been mounting.[2]

Injuries to the lung parenchyma are common in severely injured patients and include contusion, laceration, or hematoma.[1] Hemothorax and pneumothorax are also common injuries in patients with thoracic trauma. Treatment of these injuries has changed during the past decade primarily because of advances in diagnostic imaging techniques and an increased understanding of the pathophysiology.

CHEST WALL INJURY

Epidemiology

Among victims sustaining thoracic trauma, approximately 50% will have chest wall injury: 10% minor, 35% major, and 5% flail chest injuries.[1] Chest wall injuries are not always obvious and can easily be overlooked during the initial evaluation.

Anatomy/Pathophysiology

An intact chest wall is necessary for normal ventilation. Outward expansion of the thorax by the respiratory muscles with descent of the diaphragm creates negative intrathoracic pressure. This causes passive air entry into the lungs during inspiration. Chest trauma, particularly blunt trauma, can severely disturb the physiology of respiration. Fortunately, most individuals have substantial respiratory reserve and can tolerate significant chest wall injury with adequate support.

Clinical Features

Elderly patients or those with preexisting pulmonary disease are sometimes unable to compensate for even minor chest wall trauma and therefore require closer attention. It is important to completely disrobe the patient and observe the respiratory rate, adequacy of tidal volume, and respiratory effort. Many chest wall injuries may be detected only by careful palpation of the chest wall, noting any areas of deformity, tenderness, or crepitus.

RIB FRACTURE

Epidemiology

Simple rib fractures are the most common form of significant chest injury, accounting for more than half the cases of blunt trauma.[1] The susceptibility to rib fracture increases with age. The importance of this injury is not the fracture itself but, rather, the associated potential complications, particularly pneumothorax, hemothorax, pulmonary contusions, and posttraumatic pneumonia. Rib fractures in children signify serious trauma to the thorax and have a high incidence of underlying injury.

Anatomy/Pathophysiology

Ribs usually break at the point of impact or at the posterior angle, which is structurally the weakest area. The fourth through ninth ribs are most commonly involved. Ribs 1 to 3 are relatively protected, and ribs 9 to 12 are more mobile at the anterior end. This confers the "high" and "low" ribs relative resistance to fracture. Fractures occur more commonly in

adults than in children, and this is attributed to the relative inelasticity of the older chest wall compared to the more compliant nature of the chest wall in children.

The true danger of rib fracture involves not the rib itself but the potential for penetrating injury to the pleura, lung, liver, or spleen. Fractures of ribs 9 to 11 are associated with intra-abdominal injury. Patients with right-sided rib fractures are almost three times more likely to have a hepatic injury, and patients with left-sided rib fractures are almost four times more likely to have a splenic injury.[3] Fractures of ribs 1 to 3 may indicate severe intrathoracic injury. The presence of two or more rib fractures at any level is associated with a higher incidence of internal injuries. Elderly patients with multiple rib fractures have a greater incidence of pneumonia and a higher mortality compared to patients younger than age 65 years.[4-6] To prevent a minor injury from developing into a serious complication, these fractures should be diagnosed rapidly and treated expectantly.

Clinical Features

The diagnosis can be suspected clinically, with tenderness, bony crepitus, ecchymosis, and muscle spasm over the rib being the most common findings. Also, bimanual compression of the thoracic cage remote from the site of injury (barrel compression test) usually produces pain at the site of fracture.

Diagnostic Strategies

Although clinical impression and physical findings are sensitive, they are not specific and are therefore unreliable for making an accurate diagnosis. Chest x-ray (CXR) films often do not demonstrate the presence of rib fractures but are of greatest value in suggesting significant intrathoracic and mediastinal injuries. Although the upright posteroanterior chest radiograph has a higher yield in detecting rib fractures or their complications compared to other views, CT scans are significantly more effective than CXR in detecting rib fractures (Fig. 42-1).[7] Rib series, expiratory, oblique, and coned-down views should not be used routinely. However, if simple rib fractures are strongly suspected or recognized on a clinical basis, there is no need to routinely obtain a CT unless other intrathoracic pathology needs to be studied.

Nonetheless, x-ray studies are often ordered, even though 50% of single-rib fractures are not seen on the initial x-ray study. A CT scan should be considered based on the mechanism of injury, physical examination, hemodynamic and respiratory parameters, abnormal findings on CXR (especially widened mediastinum), or clinical evidence of multiple rib fractures, especially of the lower ribs (which may herald a splenic or hepatic injury).

Figure 42-1. Multiple rib fractures seen on chest CT scan. (Also note presence of bilateral hemothoraces.)

Management

Treatment of patients with acute rib fractures is based on adequate pain relief and the maintenance of pulmonary function. Oral pain medications are usually sufficient for young and healthy patients. Continuing daily activities and deep breathing should be stressed to ensure ventilation and prevent atelectasis. It is helpful to advise patients to take their pain medications and wait 30 to 45 minutes before performing deep breathing exercises, perhaps with an incentive spirometer. Pain relief must be effective or patients will not maintain activity. Binders, belts, and other restrictive devices should not be used because although they can decrease pain, they also promote hypoventilation with subsequent atelectasis and pneumonia.

The greater the number of fractured ribs, the higher the mortality and morbidity rates. Patients with three or more fractured ribs, despite the lack of other traumatic injuries, should likely be hospitalized to receive aggressive pulmonary therapy and appropriate effective analgesia. Elderly patients with six or more fractured ribs should be treated in intensive care units due to high morbidity and mortality. Older patients will probably require narcotic preparations, but care should be taken to avoid oversedation.[8]

Multiple rib fractures in trauma patients are associated with significant morbidity and mortality. Intercostal nerve blocks with a long-acting anesthetic such as bupivacaine with epinephrine may relieve symptoms up to 12 hours with excellent results. This consists of administering 1 or 2% lidocaine or 0.25% bupivacaine along the inferior rib margin several centimeters posterior to the site of the fracture. One rib above and one rib below the fractured rib must also be blocked to obtain optimal analgesia. Other alternatives for hospitalized patients include patient-controlled analgesia, nebulized morphine, and thoracic epidural analgesia.[9]

Clinical Course

Most rib fractures heal uneventfully within 3 to 6 weeks, and patients should expect a gradual decrease in their discomfort during this period. Analgesics are usually necessary during the first 1 or 2 weeks. However, in addition to the complications of hemopneumothorax, atelectasis, and pneumonia, rib fractures can result in post-traumatic neuroma or costochondral separation. These unusual complications are painful and heal slowly. Special attention should be paid to patients with displaced rib fractures, who may sustain delayed hemorrhage and death. These are typically intercostal artery tears that clot off and then rebleed.[10]

■ STERNAL FRACTURE

Epidemiology

Sternal fractures and dislocations are caused primarily by anterior blunt chest trauma, usually from automobile collisions when the chest strikes the steering wheel. Risk factors for sternal fracture from blunt trauma include types of vehicular passenger restraint systems and patient age. Restrained passengers are more likely than unrestrained passengers to suffer sternal fracture. In fact, the rate of occurrence of sternal frac-

tures has increased threefold since the use of across-the-shoulder seat belts became widespread.

Anatomy/Pathophysiology

Sternal fracture usually results from the diagonal strap of a seat belt restraining the upper part of the sternum. During rapid deceleration from a frontal impact, the forward thrust of the body against the fixed seat belt across the sternum results in a fracture at that location. The location of the sternal fracture varies depending on the position of the belt, patient size, the magnitude of the impact, and the vector of the forces.

Similarly, depending on patient age, the likelihood of sternal fracture is variable. In general, sternal fractures are more common in older patients than in younger patients, and they are slightly more common in women than in men. It is believed that the more elastic and pliable chest wall of younger people allows more efficient transmission of kinetic energy to the underlying mediastinum. Although skeletal injury is less likely to occur in younger patients, damage to soft tissue structures underneath is greater. In older patients, the energy of impact is dissipated in the sternum, resulting in fewer intrathoracic injuries but a higher frequency of sternal fractures. Severe multiple rib fractures and lung contusion are concomitant injuries in more than 10% of diagnosed sternal fractures.

The natural history of a nondisplaced sternal fracture is contrary to intuition. It had been thought that the magnitude of the forces required to fracture the sternum must be associated with significant trauma to the mediastinal structures. However, isolated sternal fractures are relatively benign, with low mortality (<1%) and low intrathoracic morbidity.[11]

Cardiac complications, such as myocardial contusion, occur in 1.5 to 6% of cases. There is no association between sternal fracture and aortic rupture. Spinal fractures are seen in less than 10% of cases and rib fractures in 21%.[12] Although sternal fractures may occur in the context of major blunt chest trauma, the presence of a sternal fracture does not imply other major life-threatening conditions. However, associated mediastinal injuries should be considered.

Mediastinal hematomas, whether or not they are related to aortic injuries, can be life-threatening. The dual problem of acute blood loss and sudden alterations in cardiopulmonary physiology can result in hemodynamic deterioration. In addition to circulatory collapse from exsanguination, mediastinal hematomas can cause death from compression of adjacent structures.

Clinical Features

Sternal fractures typically present with anterior chest pain, point tenderness over the sternum, ecchymosis, soft tissue swelling, or palpable deformity. These findings together with the history can often lead to the diagnosis.

Diagnostic Strategies

Most sternal fractures are transverse, and a lateral radiographic view is often diagnostic. These fractures can be missed radiographically because a lateral plain CXR film is not usually obtained during the initial trauma evaluation. Furthermore, plain films are sometimes inconclusive. Even if the sternal fracture is diagnosed by plain radiographs, the extent of the injury is often underappreciated. The advent of helical CT, especially with three-dimensional images of the skeletal system, has resulted in markedly improved diagnosis of sternal fractures. Although most nondisplaced sternal fractures are not associated with significant intrathoracic injuries, a conservative approach is to obtain a chest CT to rule out any other pathology. This may be clinically important in determining the best management of the sternal fracture in terms of conservative management versus surgical fixation.[13] Chest CT also helps to rule out any associated mediastinal injuries.

Management

Treatment consists of providing adequate analgesia. In the absence of associated injuries, patients with isolated sternal fractures who can achieve adequate pain control with oral medications can be safely discharged home. However, a small subset of patients have sternal fractures that are displaced or produce overlying bone fragments that may cause severe pain, respiratory compromise, and, if untreated mechanically, result in nonunion. These patients are best referred for operative fixation.[14]

COSTOCHONDRAL SEPARATION

Costochondral separation may also be caused by blunt anterior chest trauma. The signs and symptoms are similar to those of rib fracture, but because of the poor vascularity of healing cartilage, pain may persist for many weeks. The CXR film is usually normal, but there is a snapping sensation with deep respiration. Outpatient management of these patients is similar to that of patients with rib fractures. Flail chest can also occur from massive costochondral separation, but this is uncommon.

FLAIL CHEST

Epidemiology

Flail chest is a fairly uncommon injury and was found in almost one third of major trauma patients with chest injuries in a large series. Its exact incidence is unknown.

Anatomy/Pathophysiology

Flail chest results when three or more adjacent ribs are fractured at two points, allowing a freely moving segment of the chest wall to move in paradoxical motion (Fig. 42-2). Because of its common association with pulmonary contusion, it is one of the most serious chest wall injuries (Fig. 42-3).

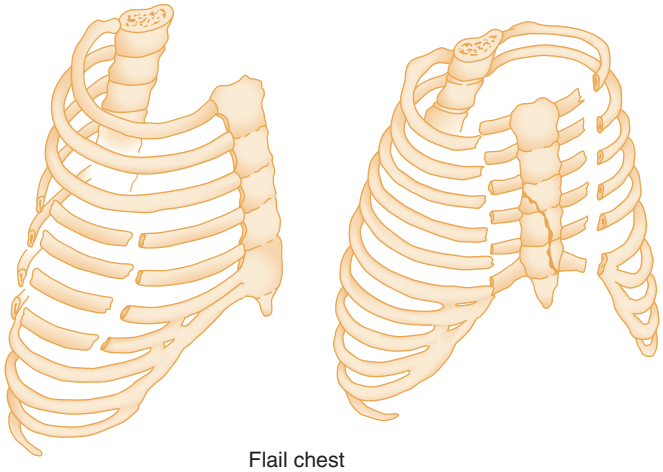

Figure 42-2. Flail chest. Fracture of several adjacent ribs in two places with lateral flail or central flail segments.

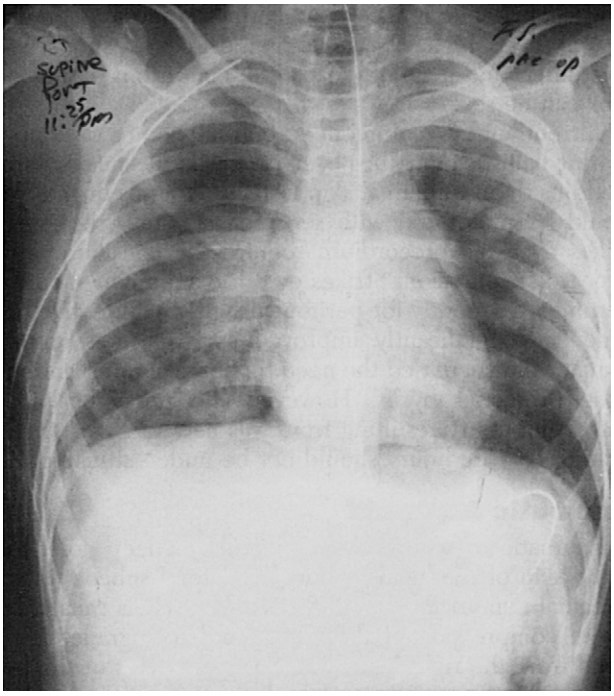

Figure 42-3. Bilateral alveolar infiltrates suggesting pulmonary contusion. Pneumopericardium and pneumomediastinum are also present.

The physiology of respiration is adversely affected by flail chest in a number of ways. The paradoxical motion of the chest wall is the hallmark of this condition, with the flail segment moving inward with inspiration and outward with expiration. Underlying pulmonary contusion is considered to be the major cause of respiratory insufficiency with flail chest. In addition, the pain of the injury causes muscular splinting with resultant atelectasis, hypoxemia, and decreased cardiac output.

Clinical Features

Flail chest is usually diagnosed by physical examination. This requires exposure of the patient's thorax and examination of the chest wall for paradoxical motion. Pain, tenderness, and crepitus can direct the examiner. In addition, the flail segment can sometimes be visualized to move separately and in an opposite direction from the rest of the thoracic cage during the respiratory cycle. Endotracheal intubation and positive pressure ventilation will internally splint the chest wall, making the flail segment difficult to detect on physical examination.

Diagnostic Strategies

Multiple rib fractures can usually be identified on CXR films. CT scan is much more accurate than plain films in detecting the presence and extent of underlying injury and contusion to the lung parenchyma. It is utilized routinely in some centers for all patients with major chest trauma.

Management

Out-of-hospital or emergency department (ED) stabilization of the flail segment by positioning the person with the injured side down or placing a sandbag on the affected segments has been abandoned. These interventions actually inhibit expansion of the chest and increase atelectasis of the injured lung. Oxygen should be administered, cardiac and oximetry monitors applied if available, and the patient observed for signs of an associated injury such as tension pneumothorax.

The outcome of flail chest injury is a function of associated injuries. Because many different physiologic mechanisms have been implicated in flail chest, there is no consensus about hospital treatment. The cornerstones of therapy include aggressive pulmonary physiotherapy, effective analgesia, selective use of endotracheal intubation and mechanical ventilation, and close observation for respiratory compromise.

Respiratory decompensation is the primary indication for endotracheal intubation and mechanical ventilation for patients with flail chest. Obvious problems, such as hemopneumothorax or severe pain, should be corrected before intubation and ventilation are presumed necessary. In fact, in the awake and cooperative patient, noninvasive continuous positive airway pressure (CPAP) by mask may obviate the need for intubation.[15] In general, the most conservative methods for maintaining adequate oxygenation and preventing complications should be used. Adequate analgesia is of paramount importance in patient recovery and may contribute to the return of normal respiratory mechanics.

Patients without respiratory compromise generally do well without ventilatory assistance. Several studies have found that patients treated with intercostal nerve blocks or high segmental epidural analgesia, oxygen, intensive chest physiotherapy, careful fluid management, and CPAP, with intubation reserved for those patients who fail this therapy, have shorter hospital courses, fewer complications, and lower mortality rates.[16] Avoidance of endotracheal intubation, particularly prolonged intubation, is important in preventing pulmonary morbidity because intubation increases the risk of pneumonia.

There is also evidence that early operative internal fixation of the flail segment results in a speedier recovery, decreased complications, and better cosmetic and functional results, and that it is cost-effective. Indications for open fixation for flail chest include patients who are unable to be weaned from the ventilator secondary to the mechanics of flail chest, persistent pain, severe chest wall instability, and a progressive decline in pulmonary functions.[14]

The patient with flail chest should be treated in the ED as if pulmonary contusion exists regardless of whether mechanical ventilation is used. The mortality rate associated with flail chest is between 8 and 35% and is directly related to the underlying and associated injuries. However, unilateral flail chest was reported to be infrequently associated with death in one large series.[17] Those who recover from flail chest may develop long-term disability with dyspnea, chronic thoracic pain, and exercise intolerance.

■ NONPENETRATING BALLISTIC INJURY

Epidemiology

Many law enforcement officers, emergency medical services personnel, and private security guards wear lightweight synthetic body armor for protection against gunshot injury. In addition, there have been a number of reports of armed robbers wearing such vests in anticipation of exchanging gunfire with police or security personnel.[18] These vests are "bullet resistant" rather than "bulletproof," depending on the weapon being used against them. They are composed of many different combinations of synthetic fibers such as Kevlar.

Another type of nonpenetrating ballistic injury is caused by rubber bullets and beanbag shotgun shells. Rubber bullets have been used for many years by police agencies throughout

the world for crowd dispersal and for nonlethal use of force. Beanbag shotgun shells are nylon bags filled with pellets, which are fired from a standard shotgun. Both of these projectiles have the potential to cause serious injury despite their classification of "nonmetal" or "less than lethal" use of force.[19]

Anatomy/Pathophysiology

Although bullet penetration is usually prevented, the heart, liver, spleen, lung, and spinal cord are vulnerable to nonpenetrating ballistic injury that may occur despite innocent-appearing skin lesions.

Bullet-resistant vests are usually capable of stopping penetration by the low-velocity missiles of most handguns, but the kinetic energy of the missile can be transmitted through the layers of protective cloth or armor and produce significant injury without penetration.

Clinical Features

Patients who have been shot with "less-than lethal projectiles" or with standard bullets while wearing bullet-resistant vests usually present with erythema, ecchymosis, and marked tenderness to palpation over the impacted area. There may be a projectile, such as a beanbag, still located in the wound. The area of tenderness and surrounding structures should be carefully palpated to identify any subcutaneous emphysema, crepitus, or bony step-offs.

Diagnostic Strategies

Plain film radiography should be used to identify any retained foreign bodies and any fractures or cortical violation. Strong consideration should be given for CT scanning based on the type of projectile, the clinical examination, and the degree of tenderness and location of the wounds.

Management

It is recommended that all victims of nonpenetrating ballistic injury be observed closely, with consideration for overnight observation. This is particularly true for injuries over the abdomen, where serial examinations in coordination with CT scanning will help to detect internal injuries that may present in a delayed manner. Use of protective body armor has resulted in significantly improved survival rates and has dramatically decreased the need for surgical intervention in those protected by it. In addition, "less than lethal" projectiles, such as rubber bullets and beanbag shotgun shells, offer law enforcement an alternative to conventional weapons that are considered "use of deadly force." However, the possibility of an underlying injury resulting from this form of nonpenetrating ballistic injury should not be underestimated.

TRAUMATIC ASPHYXIA

Anatomy/Pathophysiology

Traumatic asphyxia is a rare syndrome caused by a severe compression of the thorax by a very heavy object causing a marked increase in thoracic and superior vena caval pressure, resulting in retrograde flow of blood from the right heart into the great veins of the head and neck. The vena cava and the large veins of the head and neck do not have valves and allow the transmission of pressure to the capillaries of the head and neck, which become engorged with blood.

Clinical Features

Traumatic asphyxia is characterized by a deep violet color of the skin of the head and neck, bilateral subconjunctival hemorrhages, petechiae, and facial edema. Stagnation develops from capillary atony and dilation, and as the blood desaturates, purplish discoloration of the skin occurs.[20] Although the appearance of these patients can be quite dramatic, the condition is usually benign and self-limited.[20]

Diagnostic Strategies

The clinical significance lies with the possibility of intrathoracic injury from the violent force necessary to produce traumatic asphyxia. Chest wall and pulmonary injuries are most common. If the patient's examination and CXR show worrisome features, CT scanning of the chest should be performed.

Disturbance of vision has been attributed both to retinal hemorrhage, which is generally a permanent injury, and to retinal edema, which may cause transient changes in vision. One third of these patients lose consciousness, usually at the time of injury. Intracranial hemorrhages are rare, probably because of the shock-absorbing ability of the venous sinuses, but CT scan of the head should be done in patients with neurologic complaints. Neurologic manifestations typically clear within 24 to 48 hours, and long-term sequelae are uncommon.[21]

PULMONARY INJURIES

Subcutaneous Emphysema

Anatomy/Pathophysiology

Subcutaneous emphysema in the presence of chest wall trauma usually indicates a more serious thoracic injury. Although the presence of air in the tissues is a benign condition, in cases of chest trauma it usually represents serious injury to any air-containing structure within the thorax. Air enters the tissues either extrapleurally or intrapleurally. Extrapleural tears in the tracheobronchial tree allow air to leak into the mediastinum and soft tissues of the anterior neck, producing a pneumomediastinum, which may progress to a tension pneumomediastinum. Intrapleural lesions, however, usually produce a pneumothorax by allowing air to escape the lung through the visceral pleura into the pleural space and then through the parietal pleura into the thoracic wall.

An esophageal tear resulting from Boerhaave's syndrome or penetrating injury may also produce a pneumomediastinum manifested by subcutaneous emphysema over the supraclavicular area and anterior neck. An additional cause of subcutaneous emphysema, which may or may not be indicative of intrathoracic injury, is found immediately adjacent to a penetrating wound of the thorax. A small amount of air may be introduced into the adjacent subcutaneous tissues from the outside at the time of penetration. However, it must be assumed that this is secondary to a pneumothorax or pneumomediastinum, and appropriate diagnostic and therapeutic maneuvers to rule out or treat the intrathoracic injury should be carried out.

The presence of localized subcutaneous emphysema over the chest wall in the presence of blunt trauma is usually indicative of the presence of a traumatic pneumothorax, whereas the presence of subcutaneous emphysema over the supraclavicular area and anterior neck usually indicates a pneumomediastinum.

Rarely, a pneumomediastinum may progress to a tension pneumomediastinum, which may be life-threatening secondary to the presence of a tension pneumopericardium. This most often occurs in patients who are undergoing positive pressure ventilation and have a pneumopericardium visible on CXR examination. They may also have a Hamman's crunch, which is a crunching sound with each heartbeat heard on cardiac auscultation.

Management

Tension pneumothorax must be considered and treated appropriately. If a tension pneumopericardium is suspected, then an immediate pericardiocentesis with aspiration of air from the pericardial space may be lifesaving.

Although subcutaneous emphysema is a benign condition, massive accumulations can be uncomfortable to the patient. The underlying cause, such as pneumothorax, ruptured bronchus, or ruptured esophagus, must be treated appropriately. Benign pneumomediastinum secondary to a Valsalva maneuver is treated with observation and high-flow oxygen to facilitate the reabsorption of nitrogen from tissues since the volume of nitrogen causes the discomfort.

Pulmonary Contusion

Epidemiology

Pulmonary contusion is reported to be present in 30 to 75% of patients with significant blunt chest trauma, most often from automobile collisions with rapid deceleration.[1] Pulmonary contusion can also be caused by high-velocity missile wounds and the high-energy shock waves of an explosion in air or water. Pulmonary contusion is the most common significant chest injury in children, and it is most commonly caused by an automobile or pedestrian accident.[21]

Anatomy/Pathophysiology

Pulmonary contusion is a direct bruise of the lung parenchyma followed by alveolar edema and hemorrhage but without an accompanying pulmonary laceration, as first described by Morgagni in 1761.[22]

The early diagnosis of pulmonary contusion is important if treatment is to be successful. The onset may be insidious, and therefore it must be suspected from the history of the mechanism of injury rather than the initial CXR. Great force is required to produce pulmonary contusion, such as from a fall from height, motor vehicle crashes, and other forms of significant trauma.

Clinical Features

The clinical manifestations include dyspnea, tachypnea, cyanosis, tachycardia, hypotension, and chest wall bruising. There are no specific signs for pulmonary contusion, but hemoptysis may be seen sometime during the patient's course, and moist rales or absent breath sounds may be heard on auscultation. Palpation of the chest wall commonly reveals fractured ribs. If flail chest is discovered, pulmonary contusion is commonly present.

Surprisingly, many of the worst contusions occur in patients without rib fractures. It has been theorized that the more elastic chest wall, as in younger individuals, transmits increased force to the thoracic contents. Although isolated pulmonary contusions can exist, they are associated with extrathoracic injuries in the majority of patients.[23]

Figure 42-4. Chest CT scan showing bilateral alveolar infiltrates suggesting pulmonary contusion. There are also multiple rib fractures and subcutaneous emphysema.

Diagnostic Strategies

Care must be taken not to focus on more dramatic injuries at the expense of failing to recognize the evolving pulmonary contusion. This is particularly true with the initial x-ray studies when overlying rib fracture, pneumothorax, aspiration pneumonitis, or poor radiograph quality may mask the contusion.

Typical radiographic findings begin to appear within minutes of injury and range from patchy, irregular, alveolar infiltrate to frank consolidation (Fig. 42-4). Usually, these changes are present on the initial examination, and they are always present within 6 hours. The rapidity of changes on CXR visualization usually correlates with the severity of the contusion.

The increased frequency of CT scans for blunt trauma patients has resulted in a corresponding increase in the diagnosis of pulmonary contusions. CT scans have been shown to detect twice as many pulmonary contusions as plain radiographs.[7] Some authors suggest that pulmonary contusions only visible on CT scan and not on plain radiographs may not be clinically significant.[24]

Chest CT scan is particularly valuable to identify a pulmonary contusion in the acute phase after injury since plain CXRs have a low sensitivity.[7] Although CT scan may not be necessary to make the diagnosis of a pulmonary contusion that is evident on plain chest radiography, it may be helpful to further define the extent of the contusion and to identify other thoracic injuries. Infectious complications, sternoclavicular joint dislocation, pneumothorax, misplaced endotracheal tube, intraperitoneal air, and vertebral fracture have all been identified by CT scan in the trauma patient.

Pulmonary contusion should be differentiated from the adult respiratory distress syndrome (ARDS) with which it is often confused because the radiographic appearance of the two conditions may be similar. The contusion usually manifests within minutes of the initial injury, is usually localized to a segment or a lobe, is often apparent on the initial chest study, and tends to last 48 to 72 hours. ARDS is diffuse, and its development is usually delayed, with onset typically between 24 and 72 hours after injury.[25]

Arterial blood gases may be helpful in making the diagnosis of pulmonary contusion because most patients are hypoxemic at the time of admission. A low Po_2 alone may be reason to suspect pulmonary contusion. A widening alveolar-arterial oxygen difference indicates a decreasing pulmonary diffusion capacity of the patient's contused lung, and it is one of the earliest and most accurate means of assessing the current status, progress, and prognosis.

Management

Treatment for pulmonary contusion is essentially the same as that for flail chest. When only one lung has been severely contused and has caused significant hypoxemia, consideration should be given to intubating and ventilating each lung separately using a dual-lumen endotracheal tube and two ventilators. This allows for the difference in compliance between the injured and the normal lung and prevents hyperexpansion of one lung and gradual collapse of the other.[26] As with flail chest, however, intubation and mechanical ventilation should be avoided if possible because they are associated with an increase in morbidity, including pneumonia, sepsis, pneumothorax, hypercoagulability, and longer hospitalization.

Certain patients may benefit from a trial of noninvasive positive pressure ventilation with CPAP in order to avoid intubation and mechanical ventilation. In those patients most severely injured with extensive pulmonary contusions and the development of ARDS with severe hypoxia refractory to conventional therapy, some small studies suggest a possible role for extracorporeal membrane oxygenation.[27]

Certain procedures may ameliorate the pulmonary contusion, including the restriction of intravenous fluids to maintain intravascular volume within strict limits and aggressive supportive care consisting of vigorous tracheobronchial toilet, suctioning, and pain relief. These maneuvers may preclude the need for ventilator support and allow a more selective approach to flail chest and pulmonary contusion.

Another area of controversy in the management of pulmonary contusions is the appropriate use of crystalloid versus colloid solutions in resuscitation of the multiply injured patient with suspected contusion. Because of the potential for colloid sequestration within the pulmonary alveoli due to capillary leak, colloids are not recommended for use in treating these patients.

Pneumonia is the most common complication of pulmonary contusions, and it significantly worsens the prognosis. It develops insidiously, especially in patients treated with prophylactic antibiotics. The use of antibiotics should be reserved for specific organisms rather than given prophylactically.

Pulmonary Laceration

The lungs are most often lacerated from penetrating injury, but they may also be injured by the inward projection of a fractured rib or avulsion of a pleural adhesion. These injuries are usually minor and rarely life-threatening, and they can usually be treated with observation or tube thoracostomy. Severe lacerations are present in only 3% of patients with thoracic trauma, and they are usually associated with hemopneumothorax, multiple displaced rib fractures, and hemoptysis. Often, these life-threatening lacerations require thoracotomy with resection to control bleeding.

Pneumothorax

Epidemiology

Pneumothorax, which is the accumulation of air in the pleural space, is a common complication of chest trauma. It is reported to be present in 15 to 50% of patients, and it is invariably present in those with transpleural penetrating injuries.[1]

Anatomy/Pathophysiology

Pneumothorax can be divided into three classifications depending on whether air has direct access to the pleural cavity: simple, communicating, and tension. A pneumothorax is considered simple (Fig. 42-5) when there is no communication with the atmosphere or any shift of the mediastinum or hemidiaphragm resulting from the accumulation of air. It can be graded according to the degree of collapse as visualized on the chest radiograph. A small pneumothorax occupies 15% or less of the pleural cavity, a moderate one 15 to 60%, and a large pneumothorax more than 60%. Traumatic pneumothorax is most often caused by a fractured rib that is driven inward, lacerating the pleura. It may also occur without a fracture when the impact is delivered at full inspiration with the glottis closed, leading to a tremendous increase in intra-alveolar pressure and the subsequent rupture of the alveoli. A penetrating injury such as a gunshot or stab wound may also produce a simple pneumothorax if there is no free communication with the atmosphere.

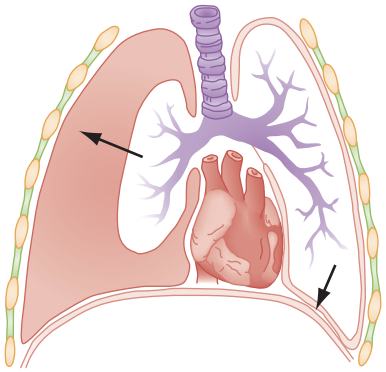

Figure 42-5. Closed pneumothorax. Simple pneumothorax is present in the right lung with air in the pleural cavity and collapse of the right lung.

Communicating Pneumothorax. A communicating pneumothorax (Fig. 42-6) is associated with a defect in the chest wall and most commonly occurs in combat injuries. In the civilian sector, this injury is most commonly secondary to shotgun wounds. Air can sometimes be heard flowing sonorously in and out of the defect, prompting the term "sucking chest wound." The loss of chest wall integrity causes the involved lung to paradoxically collapse on inspiration and expand slightly on expiration, forcing air in and out of the wound. This results in a large functional dead space for the normal lung and, together with the loss of ventilation of the involved lung, produces a severe ventilatory disturbance.

Tension Pneumothorax. The progressive accumulation of air under pressure within the pleural cavity, with shift of the mediastinum to the opposite hemithorax and compression of the contralateral lung and great vessels, is the constellations of findings in tension pneumothorax (Figs. 42-7 and 42-8). It occurs when the injury acts like a one-way valve, prevents free bilateral communication with the atmosphere, and leads to a progressive increase of intrapleural pressure. Air enters on inspiration but cannot exit with expiration. The resulting shift of mediastinal contents compresses the vena cava and distorts the cavoatrial junction, leading to decreased diastolic filling of the heart and subsequent decreased cardiac output. These changes result in the rapid onset of hypoxia, acidosis, and shock.

Clinical Features

Shortness of breath and chest pain are the most common presenting complaints of pneumothorax. The patient's appearance is highly variable, ranging from acutely ill with cyanosis and tachypnea to misleadingly healthy. The signs and symp-

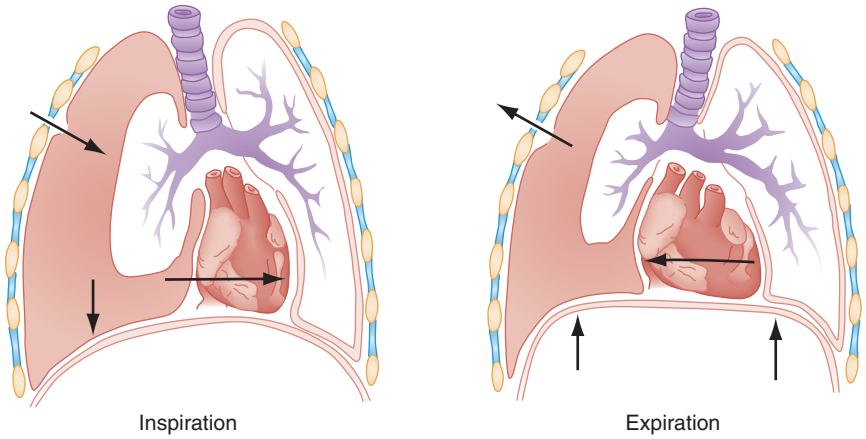

Figure 42-6. Communicating pneumothorax. Collapse of the right lung and air in the pleural cavity are seen, with communication to outside through a defect in the chest wall. In a sucking chest wound, lung volume is greater with expiration.

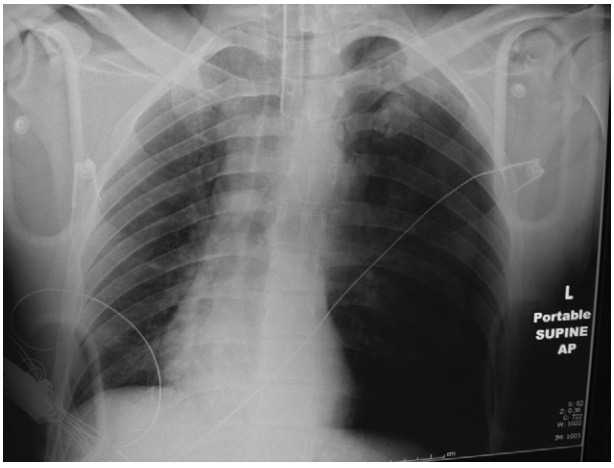

Figure 42-7. Tension pneumothorax seen in intubated patient.

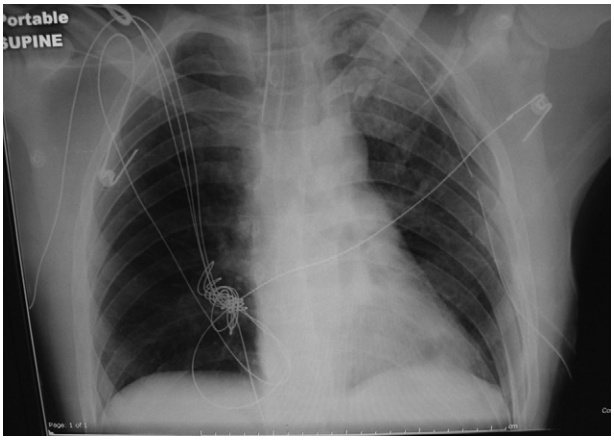

Figure 42-8. Resolution of the tension pneumothorax seen in Figure 42-7 with placement of a left-sided tube thoracostomy.

toms are not always correlated with the degree of pneumothorax. The physical examination may show decreased or absent breath sounds and hyperresonance over the involved side as well as subcutaneous emphysema, but small pneumothoraces may not be detectable on physical examination.

Patients with tension pneumothorax become acutely ill within minutes and develop severe cardiovascular and respiratory distress. They are dyspneic, agitated, restless, cyanotic, tachycardic, and hypotensive and display decreasing mental activity. The cardinal signs of tension pneumothorax are tachycardia, jugular venous distention (JVD), and absent breath sounds on the ipsilateral side. However, JVD may not reliably be present with massive blood loss. Hypotension will not occur as early as hypoxia and may represent a preterminal event.

Diagnostic Strategies

Because intrapleural air tends to collect at the apex of the lung, the initial chest radiograph should be an upright full inspiratory film if the patient's condition permits. An upright film will often reveal small pleural effusions that are not visible on supine films, and it also allows better visualization of the mediastinum. Although the chest radiograph has traditionally been the preferred initial study for diagnosing a simple pneumothorax, emerging literature suggests that a simple pneumothorax can be identified during the initial ultrasound examination of the trauma patient as part of the focused assessment with sonography for trauma (FAST) examination. Because FAST is becoming part of the routine initial evaluation of trauma patients, evaluation for the presence of a pneumothorax should be included in this rapid, bedside exam, especially since this is performed prior to chest radiograph. In fact, several studies have found that the ultrasound has greater sensitivity for a pneumothorax than chest radiography.[28,29]

If a pneumothorax is suspected but not visualized on the initial inspiratory film, an expiratory film should be obtained because it makes the pneumothorax more apparent by reducing the lung volume. Notably, as many as one third of initial CXR films will not detect a pneumothorax in trauma patients.[7] Although it is not recommended as a primary method of diagnosing pneumothorax, the CT scan is very sensitive in finding a small pneumothorax even in the supine patient. When CT scans are obtained to evaluate the abdomen, it may be helpful to take a few low cuts into the chest to exclude the presence of a small pneumothorax.

Occult Pneumothorax

A pneumothorax that is absent on initial CXR but is identified on subsequent chest or abdominal CT scan is called an occult PTX. Studies have found high rates of occult PTX diagnosed on abdominal CT that were absent on initial CXR (Fig. 42-9).[7,30] One such study noted that two thirds of patients with occult PTX subsequently required tube thoracostomy.[31]

The diagnosis and treatment of tension pneumothorax should not be delayed just because the patient is normotensive. Although tension pneumothorax usually occurs dramati-

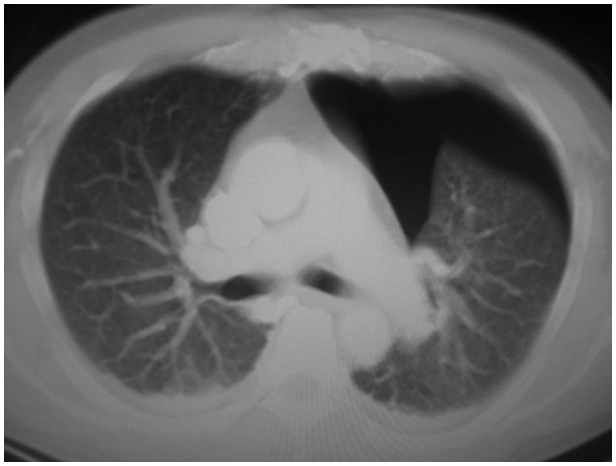

Figure 42-9. Occult pneumothorax. Large left-sided pneumothorax seen on chest CT scan, which was not visible on chest x-ray.

BOX 42-1 INDICATIONS FOR TUBE THORACOSTOMY

- Traumatic cause of pneumothorax (except asymptomtic, apical pneumothroax)
- Moderate to large pneumothorax
- Respiratory symptoms regardless of size of pneumothorax
- Increasing size of pneumothorax after initial conservative therapy
- Recurrence of pneumothorax after removal of the initial chest tube
- Patient requires ventilator support
- Patient requires general anesthesia
- Associated hemothorax
- Bilateral pneumothorax regardless of size
- Tension pneumothorax

From Dougall AM, et al: Chest trauma—Current morbidity and mortality. *J Trauma* 17:547, 1977.

cally, the clinical diagnosis is sometimes obscure, and CXR examination may be required to suggest the diagnosis. This film will show complete lung collapse and shift of the mediastinum to the opposite side. Ideally, the diagnosis and treatment should be completed without a CXR examination because the delay in obtaining this radiograph may adversely affect patient outcome.

Management

In the setting of penetrating trauma where the patient is asymptomatic and the initial CXR study is negative, the patient can be safely observed and the x-ray repeated. Previously, it was thought that if the patient was still asymptomatic and the radiograph negative after 6 hours, the patient could be discharged. Recent experience indicates that 3 hours is probably effective and safe for observation with repeat x-ray film before discharge for patients with penetrating trauma.[32] Patients with blunt trauma with a high clinical suspicion for pneumothorax should still await a 6-hour delayed CXR prior to discharge. However, if the stable patient receives an initial screening chest CT that is negative for pneumo- or hemothorax, the literature suggests that obtaining a delayed CXR is unnecessary, and these patients may be discharged from the ED.[33]

Simple Pneumothorax. Treatment of a simple pneumothorax depends on its cause and size. Most advocate treating a traumatic pneumothorax with a chest tube to correct any respiratory compromise; treatment with a chest tube is generally thought to be safer than observation in these patients. Small pneumothoraces, whether spontaneous or traumatic, have been treated with hospitalization and careful observation if the patient is otherwise healthy, symptom free, does not need anesthesia or positive pressure ventilation, and the pneumothorax is not increasing in size.

Isolated apical pneumothoraces of less than 25% may be observed in patients with stab wounds. This conservative method seldom has application in multisystem trauma, and a chest tube should be inserted immediately for any signs of deterioration. Some suggest that because it is small and lacks symptoms, occult traumatic pneumothorax found only on CT scan can be observed and does not need treatment. Studies indicate that these injuries can be handled like small but initially detectable pneumothoraces with observation in hemodynamically stable patients without symptoms. However, one third of those who require positive-pressure ventilation will have progression of the pneumothorax and will require tube thoracostomy, perhaps under exigent circumstances.[34,35]

Any moderate to large pneumothorax should be treated with a chest tube. The indications for tube thoracostomy are listed in Box 42-1. The preferred site for insertion is the fourth or fifth intercostal space at the anterior or midaxillary line. If the tube is positioned posteriorly and directed toward the apex, it can effectively remove both air and fluid. This lateral placement of the tube is preferred not only because it is more efficient but also because it does not produce an easily visible cosmetic defect, as does the anterior site at the second interspace at the midclavicular line. With multisystem trauma, an adequate size chest tube (36–40 F in adults and 16–32 F in children) should always be used, particularly in cases of major trauma, when hemothorax is likely to occur.

Care must be taken to be certain the vent holes along the side of the tube are all inside the chest cavity. A radiopaque line along the side of the tube with interruptions at these drainage holes helps greatly when radiographically interpreting tube position. The tube should be attached to a water seal drainage system that allows reexpansion of the pneumothorax. If there is significant air leak or a large hemothorax, the tube may be connected to a source of constant vacuum at 20 to 30 cm H_2O for more rapid reexpansion. Tube thoracostomy does have some potentially serious complications, including the formation of a hemothorax, pulmonary edema, bronchopleural fistula, pleural leaks, empyema, subcutaneous emphysema, infection, and contralateral pneumothorax. To reduce the incidence of empyema and pneumonitis, current recommendations include the administration of empirical antibiotics with all tube thoracostomy placements.[36] Pneumothoraces that have been present for more than 3 days should be reexpanded gradually without suction to avoid inducing reexpansion pulmonary edema.

Communicating Pneumothorax. For a patient with a communicating pneumothorax in the out-of-hospital setting, the defect should be covered immediately, which helps convert the condition to a closed pneumothorax and eliminates the major physiologic abnormality. An occlusive dressing of petrolatum gauze can be applied, but care should be taken because this can convert the injury to a tension pneumothorax, especially in patients who are intubated and undergoing positive-pressure ventilation. The wound should never be packed because the negative pressure during inspiration can suck the dressing into the chest cavity. These considerations are not as important once the patient is in the ED, where endotracheal intubation and tube thoracostomy can be performed. Positive-pressure ventilation can then be started without the fear of

producing a tension pneumothorax, and the patient can be prepared for definitive surgical repair.

Tension Pneumothorax. When the diagnosis of tension pneumothorax is suspected clinically, the pressure should be relieved immediately with needle thoracostomy, which is performed by inserting a large-bore (14-gauge or larger) catheter, at least 5 cm in length, through the second or third interspace anteriorly or the fourth or fifth interspace laterally on the involved side. This method can be easily performed in the field or ED, allowing vital signs to improve during transport or preparation for a tube thoracostomy.[37]

The intubated patient in the ED who is receiving positive-pressure ventilation and external cardiac compressions is at particular risk for developing tension pneumothorax. Fractured ribs from cardiopulmonary resuscitation (CPR) can penetrate lung parenchyma and cause pneumothorax. Positive-pressure ventilation then increases intrapleural pressure and produces a tension pneumothorax. The earliest sign of this complication is an increase in resistance to ventilation. If the patient has vital signs, the blood pressure will fall and the central venous pressure (CVP) will rise. Misplacement of an endotracheal tube does not result in tension pneumothorax but, rather, asymmetry of breath sounds. If tension pneumothorax is suggested, the clinician should proceed with therapy.

Hemothorax

Epidemiology

Hemothorax, which is the accumulation of blood in the pleural space after blunt or penetrating chest trauma, is a common complication that may produce hypovolemic shock and dangerously reduce vital capacity. It is commonly associated with pneumothorax (25% of cases) as well as extrathoracic injuries (73% of cases).[38]

Anatomy/Pathophysiology

Hemorrhage from injured lung parenchyma is the most common cause of hemothorax, but this tends to be self-limited unless there is a major laceration. Specific vessels are less often the source of hemorrhage, with intercostal and internal mammary arteries causing hemothorax more often than hilar or great vessels. Bleeding from the intercostal arteries may be brisk, however, because they branch directly from the aorta.

Management

Close monitoring of the initial and ongoing rate of blood loss must be performed. Immediate drainage of more than 1500 mL of blood from the pleural cavity is usually considered an indication for urgent thoracotomy. Perhaps even more predictive of the need for thoracotomy is a continued output of at least 200 mL/hr for 3 hours. General considerations for urgent thoracotomy are outlined in Box 42-2.[39]

Clinical Features

Depending on the rate and quantity of hemorrhage, varying degrees of hypovolemic shock will be manifested. Tactile fremitus is decreased, and breath sounds are diminished or absent.

Diagnostic Strategies

Blunting of the costophrenic angles on upright chest radiograph requires at least 200 to 300 mL of fluid. The supine view chest film is less accurate, and it may be more difficult to make the diagnosis with the patient in this position. Unfortunately, this is often the only film available because of the patient's unstable condition. In the supine patient, blood layers posteriorly, creating a diffuse haziness that can be rather subtle, depending on the volume of the hemothorax (Fig. 42-10).

As is the case with pneumothoraces, CT scan has much greater sensitivity than chest radiography in the detection of hemothorax, with some studies reporting up to a 25% incidence of hemothoraces diagnosed by CT that were not detected on chest radiography.[7] Perhaps more important, almost half of these occult hemothoraces underwent drainage with tube thoracostomy (Fig. 42-11).[40] Delayed hemothorax may be associated with significant morbidity because the residual blood may serve as a nidus for the development of empyema or fibrothorax.

BOX 42-2 INDICATIONS FOR THORACOTOMY

- Initial thoracostomy tube drainage is >20 mL/kg of blood
- Persistent bleeding at a rate >7 mL/kg/hr
- Increasing hemothorax seen on chest x-rays
- Patient remains hypotensive despite adequate blood replacement, and other sites of blood loss have been ruled out
- Patient decompensates after initial response to resuscitation

Management

Treatment of hemothorax consists of restoring the circulating blood volume, controlling the airway as necessary, and evacuating the accumulated blood. Tube thoracostomy allows constant monitoring of the blood loss as well as reexpansion of the lung. A large-bore tube (36–40 F) should be inserted in the fifth interspace at the anterior axillary line and connected to underwater seal drainage and suction (20–30 mL H_2O).

Although small hemothoraces may be observed in stable patients, a moderate hemothorax or any hemothorax in an unstable or symptomatic patient requires tube thoracostomy. Severe or persistent hemorrhage requires thoracotomy. Studies are required to better delineate the size of a hemothorax detected on CT scan that requires tube thoracostomy drainage.

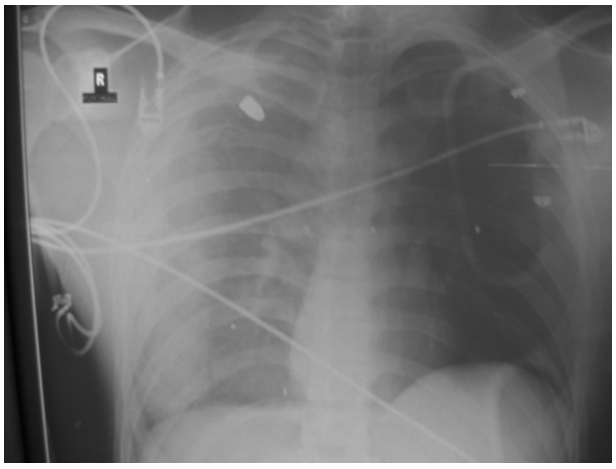

Figure 42-10. Hemothorax secondary to gunshot wound. Note haziness over right hemithorax with bullet seen in right upper lobe.

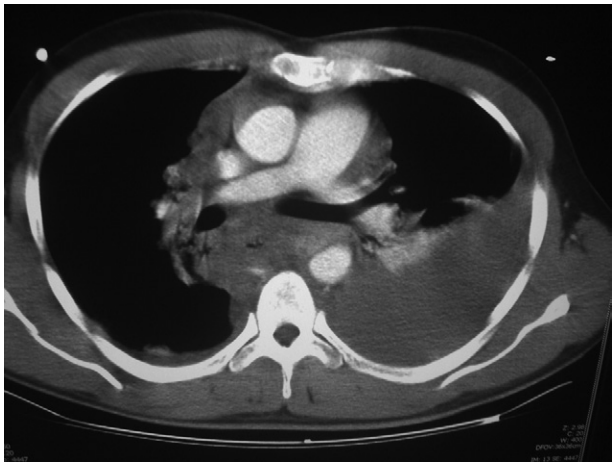

Figure 42-11. Multiple rib fractues with extensive subcutaneous emphysema, with no pneumothorax seen.

Autotransfusion has been successfully used in tube thoracostomy. Recent simplification and commercial availability of the equipment have made autotransfusion feasible in most EDs. Autotransfusion also eliminates the risk of incompatibility reactions and transmission of certain diseases such as hepatitis C. Because the majority of blood loss occurs immediately after tube thoracostomy placement, autotransfusion apparatus must be immediately available in the ED.

As a result of the increasing frequency of chest CT scans, it has been found that there may be a greater frequency of misplaced thoracostomy tubes than is evident on conventional chest radiographs. Almost 25% of patients in one series subsequently required operative intervention as a result of complications from penetration of the lung parenchyma from tube thoracostomies.[41] (Fig. 42-12)

Although beyond the scope of emergency medicine, mention is made of the role of thoracoscopy. Video-assisted thoracic surgery (VATS) is particularly useful for evaluation and evacuation of retained hemothorax, control of bleeding from intercostal vessels, and diagnosis and repair of diaphragmatic injuries.[42] As surgeons gain more experience with the technique, VATS will likely become more widely used for other indications as well, given the decreased morbidity and length of hospital stay compared to open thoracotomy.[43]

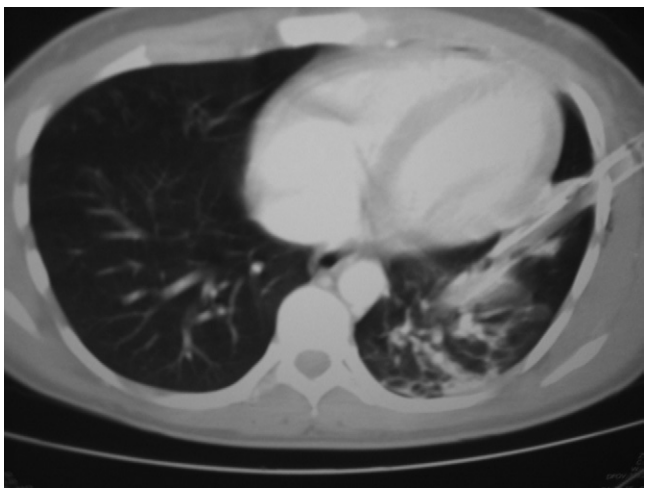

Figure 42-12. Penetration of lung parenchyma by tube thoracostomy, with large residual pneumothorax, seen on CT scan.

TRACHEOBRONCHIAL INJURY

Epidemiology

Tracheobronchial injuries may occur with either blunt or penetrating injuries of the neck or chest. Penetrating injuries tend to be more obvious because of their nature, alerting both the patient and the physician, whereas blunt injuries can be occult. Motor vehicle collisions are the most frequent mechanism causing tracheobronchial injury, accounting for more than half of all cases.[44]

Although there has been an increase in the occurrence of tracheobronchial disruption, it is still a relatively rare injury, occurring in fewer than 3% of patients with significant chest injury. Its associated mortality rate is reported to be approximately 10%, although mortality rates are significantly affected by associated injuries and the timing of diagnosis and surgical repair.[45,46]

Anatomy/Pathophysiology

Tracheobronchial injuries caused by knife wounds develop almost exclusively from wounds in the cervical trachea, whereas gunshot wounds may damage the tracheobronchial tree at any point. Intrathoracic injury to the tracheobronchial tree occurs most commonly from blunt trauma. These injuries may result from direct blows, shearing stresses, or burst injury. A direct blow to the neck may crush the cervical tracheal against the vertebral bodies and transect the tracheal rings or cricoid cartilage. Shear forces on the trachea will produce injury at the carina and the cricoid cartilage, which are its relatively fixed points.

Sudden deceleration of the thoracic cage, as occurs in a decelerating auto accident, pulls the lungs away from the mediastinum, producing traction on the trachea at the carina. When the elasticity of the tracheobronchial tree is exceeded, it ruptures. It has also been suggested that if the glottis is closed at the time of impact, the sudden increase in intrabronchial pressure will rupture the tracheobronchial tree. Regardless of the mechanism, more than 80% of these injuries occur within 2 cm of the carina.

Clinical Features

Massive air leak, hemoptysis, and subcutaneous emphysema should suggest the diagnosis of major airway damage. Subcutaneous emphysema is typically the most common physical finding.[46] Auscultation of the heart may reveal a Hamman's crunch. Patients with tracheobronchial disruption have one of two distinct clinical pictures. In the first group of patients, the wound opens into the pleural space, producing a large pneumothorax. A chest tube fails to evacuate the space and reexpand the lung, and there is continuous bubbling of air in the underwater seal device.

In the second group of patients, there is complete transection of the tracheobronchial tree but little or no communication with the pleural space. A pneumothorax is not usually present. The peribronchial tissues support the airway enough to maintain respiration, but within 3 weeks granulation tissue will obstruct the lumen and produce atelectasis. These patients are relatively free of symptoms at the time of injury but weeks later have unexplained atelectasis or pneumonia. Radiographic signs in either group of patients are pneumomediastinum, extensive subcutaneous emphysema (Fig. 42-13), pneumothorax, fracture of the upper ribs (first through fifth), air surrounding the bronchus, and obstruction in the course of an air-filled bronchus.

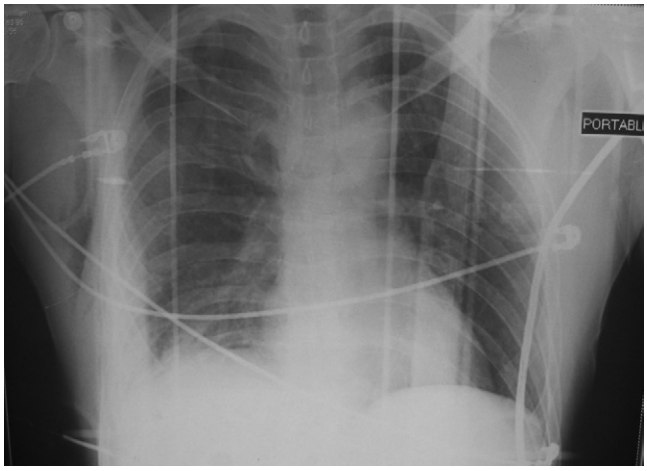

Figure 42-13. Left-sided hemothorax seen on chest CT.

Diagnostic Strategies

When tracheobronchial injury is suspected, bronchoscopy should be performed. Fiberoptic bronchoscopy is the most reliable means of establishing the diagnosis and determining the site and extent of the injury. However, CT scan has been shown to have high sensitivity in detecting tracheobronchial injury.[47] Bronchopleural fistula (a communication between a bronchus and the lung parenchyma) can occur as a complication of tracheobronchial disruption and in some cases has been treated successfully via the fiberoptic bronchoscope. A mediastinal fluid collection and/or evidence of mediastinitis may be noted on chest CT.

Management

If possible, endotracheal intubation over a bronchoscope should be performed since it allows visualization of the tube as it passes beyond the site of injury. When attempting blind intubation, care must be taken to not place the endotracheal tube through a transected airway into the soft tissue or a false passage or to convert a partial tracheal tear into a complete one.

The standard treatment for tracheobronchial injury has been surgery. However, conservative medical treatment of such injuries has been reported for tracheobronchial injury patients who meet strict selection criteria. These include patients without any major symptoms, including esophageal-associated injuries, progressive subcutaneous or mediastinal emphysema, severe dyspnea requiring intubation, difficulty with mechanical ventilation, pneumothorax with an air leak through the chest drains, open tracheal injuries, or mediastinitis.[46] In most cases, thoracotomy with intraoperative tracheostomy and surgical repair of the disrupted airway should be performed as soon as possible.

■ DIAPHRAGMATIC INJURY

Epidemiology

Diaphragmatic rupture is present in 1 to 6% of major thoracic injuries.[48,49] Diaphragmatic rupture occurs most commonly after blunt thoracoabdominal trauma, such as occurs in motor vehicle accidents or falls from heights.

Anatomy/Pathophysiology

Diaphragmatic hernia is a herniation of abdominal structures within the thoracic cavity through a defect on the diaphragm. Because of pressure gradients across the diaphragm, these injuries are associated with herniation and a potential risk of strangulation of abdominal viscera. Signs and symptoms may not occur during trauma center admission and may be delayed for as long as months to years.[49] In one study, delayed recognition of incarcerated diaphragmatic hernia after stab wounds to the lower chest and upper abdomen was associated with a mortality rate of 36%.[50]

When diaphragmatic rupture secondary to blunt trauma occurs, the right hemidiaphragm is ruptured in 15 to 24% of cases and the left in 70 to 80%. Five to 8% of cases are bilateral. It is generally accepted that this is due to the protective effect of the liver on the right hemidiaphragm. In penetrating injuries of the upper abdomen and lower thorax, such as from gunshot wounds and stab wounds, possible diaphragmatic injury should be considered.

In cases of blunt injury, the raised pressure within the abdominal cavity causes the tear of the diaphragm, and the pressure difference forces the abdominal organs through the diaphragmatic defect. Because blunt trauma can cause multiple organ injuries, these coexisting injuries can mask the more silent diaphragmatic injuries and diaphragmatic rupture may be initially overlooked. Negative intrathoracic pressure generated by inspiration tends to draw abdominal contents into the thorax. This effect is lost with the use of intubation and positive-pressure ventilation. Because there is also a plugging effect of the viscera over the defect, migration of the abdominal organs within the thorax is usually delayed, so these injuries are diagnosed in only 10% of cases in the acute phase.[51] An overlooked diaphragmatic injury in the acute phase sometimes presents as a hernia with obstruction, incarceration, or perforation of bowel many years later.

Diagnostic Strategies

The diagnosis and management of diaphragmatic injuries are problematic because these injuries present with variable clinical and radiological signs. Accurate diagnosis of traumatic diaphragmatic hernia is essential because prompt surgical repair is the treatment of choice.

Chest radiography is the first imaging study to determine the presence of diaphragmatic rupture, but a plain chest radiograph immediately after the accident presents suspicion about the diagnosis of a ruptured diaphragm in only 20 to 34% of cases. CT examination of the abdomen and chest is a very useful and reliable tool in the evaluation of blunt diaphragmatic injury, but the injury site and type affect its sensitivity.[52] CT can demonstrate findings consistent with diaphragmatic injury, such as diaphragmatic discontinuity, intrathoracic herniation of abdominal contents, and waistlike constriction of abdominal viscera (the "collar sign"). An isolated omental herniation is clearly detected on nonenhanced CT due to its fatty nature and crescent shape, and a CT with intravenous contrast will more clearly reveal the contrast-enhancing omental vessels. If the stomach or intestine is herniated, distended intestinal segments containing air-fluid levels are visualized on the supine position images. It is reported that helical CT can be used to detect 78% of left-sided and 50% of right-sided injuries.[53] Efflux of peritoneal lavage fluid through a thoracostomy tube is also diagnostic of a diaphragmatic hernia.

Although magnetic resonance imaging is not useful in most traumatic diaphragmatic hernia cases due to its relatively long duration and sensitivity for motion artifact, it is preferred in

selected patients, especially in delayed traumatic diaphragmatic herniation cases from small penetrating injuries. Laparoscopy for diagnosis and repair of small left-sided diaphragmatic injury due to penetrating trauma is the preferred modality.[54] Patients with right-sided small penetrating lesions typically do not experience herniation because of the protective effect of the dome of the liver on the right side.

Management

Because diaphragmatic injuries have been taken as a predictor of serious associated injuries in trauma and a marker of severity,[4] prompt treatment of diaphragmatic rupture is important in the trauma patient. The treatment of choice is surgery. CT scan should identify the site and extent of herniation, herniated organs, complications, and damage to associated organs. Although they are not without complications, laparoscopy and thoracoscopy may be used for diaphragmatic hernia repair.

The incidence of diaphragmatic involvement after penetrating thoracoabdominal injury is high, making nonoperative, expectant management of these patients potentially unsafe. Mandatory evaluation of the diaphragm with laparoscopy to exclude injury in all asymptomatic, hemodynamically normal patients is recommended.[55] In the absence of significant hemoperitoneum or other factors preventing adequate visualization of the diaphragm, laparoscopy is a sensitive means of excluding occult diaphragmatic injury in these patients. When significant hemoperitoneum is encountered on laparoscopy or other factors are present that prohibit adequate evaluation of the diaphragm, conversion to an open exploration should be considered to fully visualize the diaphragm at risk and exclude additional injuries.

CARDIOVASCULAR TRAUMA

Blunt Cardiac Trauma

Epidemiology

Blunt cardiac injury usually results from high-speed motor vehicle collisions, in which the chest wall strikes against the steering wheel. Other causes, such as falls from heights, crushing injuries, blast injuries, and direct blows, are less common. The significance of blunt injuries as a cause of myocardial or cardiac contusion was described more than 50 years ago by Bright and Beck.[56] Nevertheless, the diagnosis of a blunt injury to the heart remains elusive because of the usual concomitant serious injuries to other body organs and, more important, because there is no gold standard for making the diagnosis.

The importance of detecting blunt myocardial injury lies in the recognition of associated potentially fatal complications. Life-threatening dysrhythmias, conduction abnormalities, congestive heart failure, cardiogenic shock, hemopericardium with tamponade, cardiac rupture, valvular rupture, intraventricular thrombi, thromboembolic phenomena, coronary artery occlusion, ventricular aneurysms, and constrictive pericarditis have all been reported as complications.

Anatomy/Pathophysiology

Blunt cardiac trauma may be viewed as part of a continuous spectrum (i.e., myocardial concussion, contusion, infarction, and rupture).[57] Myocardial concussion occurs when a blunt injury to the interior chest produces a "stun" response in the myocardium. No permanent cellular injury occurs, but transient clinical effects may result. Myocardial contusion is the least severe form of injury that can be demonstrated pathologically. Cellular injury occurs with extravasation of red blood cells into the muscle wall, along with localized myocardial cellular necrosis. Permanent myocardial damage is rare. Traumatic myocardial infarction (MI) results from either direct trauma to the coronary arteries or a severe contusion of the myocardium, leading to irreversible cellular injury and ultimately cell death. Direct injury to the coronary arteries via laceration, thrombosis, or spasm is thought to be the most common mechanism for traumatic MI. Cardiac rupture is obviously the most severe form of blunt cardiac injury.

Myocardial Concussion

The term *myocardial concussion* or *commotio cordis* is used to describe an acute form of blunt cardiac trauma that is usually produced by a sharp, direct blow to the midanterior chest that stuns the myocardium and results in brief dysrhythmia, hypotension, and loss of consciousness. If the patient survives the initial dysrhythmia, there are no lasting histopathologic changes, and it is difficult to make the definitive diagnosis of myocardial concussion. This presumptively explains those cases of sudden death after a blow to the chest in which no histopathologic changes in the myocardium are demonstrated at autopsy.[58]

If prolonged cellular dysfunction occurs, it may result in a nonperfusing rhythm, such as asystole or ventricular fibrillation, and irreversible cardiac arrest. There are a number of documented cases of successful resuscitation with rapid provision of CPR and the use of an automated external defibrillator.[59]

Myocardial Contusion

Epidemiology

Myocardial contusion has been a diagnosis describing a very poorly understood and nebulous condition. Decades of research and widely varied clinical practice have failed to produce a consensus regarding its diagnosis, complication rate, and proper disposition. The incidence of myocardial contusion varies from 3 to 55% in reported series of severe closed-chest trauma, depending on the criteria used for establishing the diagnosis.[60,61]

Anatomy/Pathophysiology

Several mechanisms have been postulated by which the heart may be injured in cases of nonpenetrating trauma. A direct blow to the chest transmits energy through the ribs to the spine. When a large force is applied to the chest wall over an extended period, the sternum is displaced posteriorly, and the heart is compressed between the sternum and vertebrae or an elevated diaphragm. Either can result in cardiac injury. Increased intrathoracic pressure from a direct blow to the chest may contribute to the injury. In addition, compression of the abdomen and pelvis may displace abdominal viscera upward and result in cardiac injury.

A myocardial contusion is histologically characterized by intramyocardial hemorrhage, edema, and necrosis of myocardial muscle cells. These histologic findings are similar to those seen in acute MI. An accumulation of edema and cellular infiltrate in the wall of the heart may result in a decrease in ventricular compliance, resulting in cardiac dysfunction.

Most myocardial contusions heal spontaneously, with resolution of cellular infiltrate and hemorrhage leading to scar for-

mation. Small pericardial effusions occur in more than 50% of cases of contusion, usually during the second week. These are probably caused by pericardial irritation, and they neither imply significant cardiac injury nor increase the risk of tamponade. A fibrinous reaction at the contusion site may also occur, resulting in pain, a friction rub, and adhesion to the pericardium. In a few cases, the reabsorption of the hematoma is accompanied by necrosis of the ventricular wall, which may result in a delayed rupture of the myocardium or a scarred and weakened area with subsequent development of a ventricular aneurysm. If necrosis occurs, it will usually be manifested in the second week after injury and is one of the causes of delayed sudden death after blunt trauma to the chest.

Clinical Features

Myocardial contusion presents clinically as a spectrum of injuries of varying severity. Although the majority of patients with myocardial contusion have external signs of thoracic trauma (e.g., contusions, abrasions, palpable crepitus, rib fractures, or visible flail segments), the absence of thoracic lesions decreases the suspicion but never excludes cardiac injury. Other associated injuries may include pulmonary contusion, pneumothorax, hemothorax, external fracture, and great vessel injury. The most sensitive but least specific sign of myocardial contusion is sinus tachycardia, which is present in approximately 70% of patients with documented myocardial contusions. A reduction in cardiac output, which can be clinically insignificant or manifest as pronounced cardiogenic shock, may occur in patients with significant cardiac contusion.

Diagnostic Strategies

Significant controversy exists regarding the importance of establishing the diagnosis of myocardial contusion in otherwise hemodynamically stable patients.[62]

Even when the diagnosis of a myocardial contusion is considered, confirming the diagnosis without a true gold standard is problematic. Clinical evidence is often nonspecific, especially in the setting of multiple trauma. Patients may have dysrhythmias or ST wave changes caused by significant hypoxia as a result of pulmonary injuries or blood loss, which are reversed once the hypoxemia or blood loss is corrected. Likewise, severe intracranial injury, electrolyte abnormalities, and excessive vagal or sympathetic tone may give rise to dysrhythmias or an abnormal electrocardiogram (ECG). Under these conditions, ECG abnormalities may not represent true myocardial damage. On the contrary, they may cause one to overlook the potential for traumatic cardiac injury. One large series of blunt trauma patients found that blunt cardiac injury was a significant risk factor for cardiac dysrhythmia.[63]

Because myocardial contusion cannot be positively identified short of biopsy or autopsy, there is much confusion regarding the role of the various laboratory and imaging studies used to diagnose myocardial injury. Multiple studies utilizing cardiac biomarkers have been unhelpful in establishing or excluding the diagnosis. Furthermore, the vast majority of myocardial contusions probably do not cause clinically significant complications. Based on mechanism alone, the relative risk of a life-threatening dysrhythmia is far too low to warrant routine admission to rule out myocardial contusion in all patients with blunt chest trauma. Several studies suggest that very few patients diagnosed with myocardial contusion develop cardiac complications requiring therapeutic intervention or a change in management. Therefore, a routine cardiac workup is not indicated in most blunt thoracic trauma victims.[62] The usefulness of diagnostic studies is to identify patients at low risk who can be safely discharged from the ED and not to diagnose the presence of a myocardial contusion.

Diagnostic strategies that have been used to "diagnose" myocardial contusion and assess the risk of complications and the need for admission include ECG, biochemical cardiac markers (serum creatinine kinase [CK-MB] isoenzyme levels or troponin I or T levels), two-dimensional echocardiography, and CT scan.

Electrocardiogram. The ECG after blunt chest trauma may be normal or may show nonspecific abnormalities. Because of its anterior position in the thorax and proximity to the sternum, the right ventricle is far more likely to be injured than the left ventricle. The standard 12-lead ECG is relatively insensitive to right ventricular damage, as demonstrated by pathologic evidence of cellular damage in patients with normal ECGs. A cardiac contusion usually results in moderate right ventricular damage with only minor electrical changes, which can easily be missed on ECG. Right-sided ECGs (the addition of V4R) have not been found to be of any benefit.[64]

Little is known about the relative risk of dysrhythmia as a function of the ECG abnormality, and any new ECG finding warrants consideration of further diagnostic studies or admission for further monitoring. A severely injured right ventricle may cause a right bundle branch block, usually transient. Less commonly, various degrees of atrioventricular block have been documented after blunt chest trauma. Sinus tachycardia and ventricular and atrial extrasystoles are the most frequently reported rhythm disorders. More serious arrhythmias, such as atrial fibrillation, ventricular tachycardia, and ventricular fibrillation, occur less often but may acutely compromise the hemodynamic state or even result in sudden death.[63]

A few cases of delayed life-threatening dysrhythmia have been reported up to 12 hours after injury, and patients may develop less lethal dysrhythmias up to 72 hours after injury. The onset of ECG changes may be delayed up to 48 hours after injury, and all ECG changes usually resolve in 4 to 60 days.[63] The presence of ECG abnormalities is neither specific enough to confirm the diagnosis of myocardial contusion nor reliable enough to predict subsequent complications.

Cardiac Enzymes. Since myocardial contusion is histologically characterized by intramyocardial hemorrhage and necrosis of myocardial muscle cells, similar to those seen in acute myocardial infarction, cardiac enzymes were the first screening tool used to detect myocardial injury. Creatine kinase is nonspecifically increased in trauma patients due to associated skeletal muscle injury, and CK-MB levels have also been found to be falsely elevated and thus be very nonspecific in multitrauma patients. Thus, the use of CK-MB levels is of very limited utility to screen for myocardial contusion and is no longer recommended.[65-67]

Although serum cardiac troponin is highly specific for myocardial injury in the setting of acute myocardial infarction, elevated troponin levels have been found to have much lower sensitivity for myocardial contusion, and they may occur in the absence of a significant direct myocardial contusion.[67] However, such studies are limited because no true gold standard exists to confirm the diagnosis. Several studies have suggested that the combination of a normal troponin and a normal 12-lead ECG has a negative predictive value to "rule out" myocardial contusion of 100%, suggesting that these patients do not need any other workup or monitoring specific to possible myocardial contusion.[68] If there is concern due to nonspecific ECG abnormalities or an elevated troponin level on initial evaluation in the ED, a secondary measurement after 4 to 6 hours should be performed to reliably exclude myocardial injury.[61,66]

Echocardiography. Echocardiography provides a means for direct visualization of cardiac structures and chambers. Since

contused myocardium resembles infarcted myocardial tissue both histologically and functionally, two-dimensional echocardiography is useful in diagnosing myocardial contusion by evaluating wall motion abnormalities. It is also useful in identifying associated lesions such as thrombi, pericardial effusion, and valvular disruption. Furthermore, echocardiography offers the practical advantages of being portable, noninvasive, and easy to use at the bedside. If patients have painful chest wall injuries, transthoracic echocardiography may be limited. In these cases, transesophageal echocardiography (TEE) is an alternative.[61,62]

Management

Appropriate workup and treatment of the patient with suspected myocardial contusion begins with accurate out-of-hospital evaluation. Paramedics should observe and relay information to the ED concerning mechanism of injury, status of the motor vehicle, steering wheel and dashboard damage, use of seat belts and air bags, speed of the vehicle before the accident, and position of the patient when found. Pertinent clinical data to be recorded include vital signs, level of consciousness, cardiac rhythm, and the presence of chest wall trauma.

The value of admitting and carefully monitoring patients with suspected mild cardiac contusions is not supported. The latest studies do suggest that troponin levels are very helpful in risk stratification of patients suspected of having myocardial contusion.[67,68] One such strategy is to obtain an emergent echocardiography for all severely injured patients who present with hemodynamic instability and are suspected to have structural damage to the heart and/or great vessels. A similar recommendation exists for severely injured patients with a sternal fracture, although the presence of an isolated sternal fracture is not necessarily a sign of cardiac injury. Increased levels of troponin I or troponin T or ECG abnormalities indicate a higher risk of developing cardiac complications. Further investigation, including echocardiography, serial ECGs, and serial troponin levels, is recommended.[61,67,68]

In patients who have minor injuries and are otherwise asymptomatic, elevated levels of troponin I or T and minor ECG abnormalities do not necessarily indicate a clinically significant myocardial contusion. Very few of these patients will develop complications. However, normal troponin I or T levels (4–6 hours after injury) along with normal (or unchanged) ECGs correlate with minimal risk of cardiac complications. Therefore, in-hospital monitoring may be limited to those patients with significant, acute ECG abnormalities and/or elevated troponin concentrations. Serial ECGs and troponins should be obtained until the results return to normal.

Echocardiography is rarely required in this low-risk subset of patients who have minor injuries and are otherwise asymptomatic. If the patient's clinical status deteriorates, or there is inconsistency between the troponins and ECG changes, echocardiography can be very useful to rule out structurally significant myocardial injuries.

On admission, treatment of a suspected myocardial contusion should be similar to that of an MI: intravenous line, cardiac monitoring, and administration of oxygen and analgesic agents. Dysrhythmias should be treated with appropriate medications as per current advanced cardiac life support guidelines.[69] No data exist to support prophylactic pharmacologic agents for dysrhythmia suppression. Measures should be taken to treat and prevent any conditions that increase myocardial irritability (e.g., metabolic acidosis).[61] Thrombolytic agents and aspirin are contraindicated in the setting of acute trauma. In rare instances of acute MI associated with trauma, angioplasty may be a treatment option.

In the setting of depressed cardiac output caused by myocardial contusion, judicious fluid administration is required. Dobutamine may be useful after optimal preload is ensured. Intra-aortic balloon counterpulsation has been used successfully in refractory cardiogenic shock. The priority is to be certain that the decreased cardiac output is not the result of other undiagnosed injuries, particularly aortic rupture.

Prognosis

The prognosis of a patient with myocardial contusion depends on the character and magnitude of the initial trauma, the size and location of the contusion, the preexisting condition of the coronary arteries, and, most important, any other organ trauma and its complications. Major morbidity and mortality correlate most closely with the number of associated serious injuries. Recovery without complications is the usual course.

Myocardial Rupture

Myocardial rupture refers to an acute traumatic perforation of the ventricles or atria, but it may also include a pericardial rupture or laceration or rupture of the interventricular septum, interatrial septum, chordae, papillary muscles, or valves. A delayed rupture of the heart may also occur weeks after nonpenetrating trauma, probably as a result of necrosis of a contused or infarcted area of myocardium.

Epidemiology

High-speed motor vehicle crashes are responsible for most cases of traumatic myocardial rupture. Myocardial rupture is almost always immediately fatal and accounts for 15% of fatal thoracic injuries. It has been estimated that blunt cardiac rupture accounts for 5% of the 50,000 annual highway deaths in the United States.[1] In various series, the incidence of cardiac rupture in cases of blunt chest trauma ranges from 0.5 to 2%.[71] The most common cause of death in cases of nonpenetrating cardiac injuries is myocardial rupture. Approximately one third of these patients have multiple chamber rupture and one fourth have an associated ascending aortic rupture. Bright and Beck reviewed 152 autopsy cases of traumatic cardiac ruptures and found that 20% of patients survived 30 minutes or more, which would have allowed them to reach the operating room had the problem been recognized.[56] The first report of successful repair of blunt cardiac rupture was published in 1955 and involved a patient with right atrial rupture.[70]

Anatomy/Pathophysiology

The chambers most commonly involved in cardiac rupture are the ventricles; ruptures occur almost equally on each side. Ruptures of the atria are less common, with right atrium rupture being more common than left. Multiple chamber involvement occurs in 20% of patients.[70] Twenty percent of nonsurvivors have concomitant aortic rupture.

A rupture occurs during closure of the outflow track when there is ventricular compression of blood-filled chambers by a pressure sufficient to rupture the chamber wall, septum, or valve. This is the most likely mechanism for ventricular rupture when injury occurs in diastole or early systole concomitant with maximal ventricular distension. The atria are most susceptible to rupture by sudden compression in late systole when these chambers are maximally distended with venous blood and the atrial ventricular valves are closed. Other

proposed mechanisms of rupture include (1) deceleration shearing stresses acting on the "fixed" attachment of the inferior and superior vena cava at the right atrium; (2) upward displacement of blood and abdominal viscera from blunt abdominal injury that causes a sudden increase in intracardiac pressure; (3) direct compression of the heart between the sternum and vertebral bodies; (4) laceration from a fractured rib or sternum; and (5) complications of a myocardial contusion, necrosis, and subsequent cardiac rupture.

Because of the nature of the mechanisms involved in cardiac rupture, associated multisystem injuries are common. More than 70% of reported survivors of myocardial rupture have other major associated injuries, including pulmonary contusions, liver and spleen lacerations, closed-head injuries, and major fractures. Twenty percent of nonsurvivors have concomitant aortic ruptures.[72]

The immediate ability of the patient to survive cardiac rupture depends on the integrity of the pericardium. Two thirds of patients with cardiac rupture have an intact pericardium and are protected from immediate exsanguination. These patients may survive for variable periods but eventually develop significant hemopericardium and pericardial tamponade. One third of patients with cardiac rupture have associated pericardial tears and succumb promptly to exsanguination.

Occasionally, patients survive if the pericardial tear is small or the rupture is small enough to seal itself. A small pericardial laceration may allow partial and intermittent release of tamponade while still controlling bleeding. In one series of patients with confirmed myocardial rupture, 40% of patients had isolated rupture of the right atrium. The overall mortality rate was 81%, with none of the patients with two chamber rupture, ventricular rupture, or absence of vital signs upon arrival at the ED surviving.[70,72]

Clinical Features

The clinical presentation of a patient who has sustained a myocardial rupture is usually that of cardiac tamponade or severe hemorrhage. Rarely, a patient is seen with a large hemothorax, hypotension, and hypovolemia, suggesting rupture with associated pericardial tear. A patient with an intact pericardial sac and developing tamponade displays physical findings of tamponade usually with subsequent clinical deterioration. Initial inspection of the torso may reveal little more than a bruised area over the sternum or no external physical evidence. More often, however, signs of significant chest trauma or other associated injuries will be present indicating a mechanism of injury that could result in myocardial rupture. Auscultation may reveal a harsh murmur, known as a "bruit de moulin," which sounds like a splashing mill wheel.

In a review of survivors of myocardial rupture, common symptoms and signs included hypotension (100%); elevated CVP (95%); tachycardia (89%); distended neck veins (80%); cyanosis of the head, neck, arms, and upper chest (76%); unresponsiveness (74%); distant heart sounds (61%); and associated chest injuries (50%).[70,72,73]

The following findings are suggestive of pericardial rupture:

1. Hypotension disproportionate to the suspected injury
2. Hypotension unresponsive to rapid fluid resuscitation
3. Massive hemothorax unresponsive to thoracostomy and fluid resuscitation
4. Persistent metabolic acidosis
5. The presence of pericardial effusion on echocardiography or elevation of CVP and neck veins with continuing hypotension despite fluid resuscitation

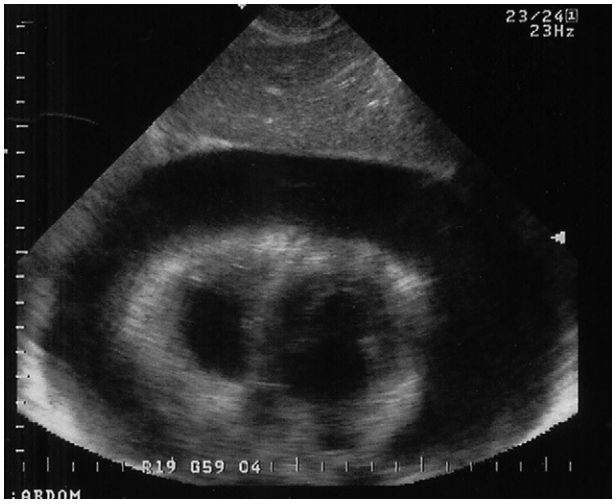

Figure 42-14. Echocardiogram demonstrating pericardial fluid with cardiac tamponade.

Diagnostic Strategies

Early use of ED ultrasound may facilitate the early diagnosis of cardiac rupture and pericardial tamponade.[74] The combination of shock and jugular venous distension (or an elevated CVP) in a patient with blunt chest trauma should immediately suggest pericardial tamponade. However, in patients with coexistent hemorrhage from other injuries, JVD may be absent. Other considerations include tension pneumothorax, right ventricular myocardial contusion, superior vena cava obstruction, ruptured tricuspid valve, or preexisting pulmonary disease. Sonographic visualization of pericardial fluid in this setting mandates emergent thoracotomy (Fig. 42-14).

A chest radiograph should be obtained immediately in all cases of acute, blunt chest injuries. Although this study usually does not help diagnose cases of myocardial rupture, it notes the presence of other intrathoracic injuries (e.g., hemothorax, pneumothorax, and signs of possible aortic dissection). An increase in the size of the cardiac silhouette more commonly reflects preexisting disease or valvular incompetence with chamber enlargement caused by increased filling pressures. ECG changes may occur with myocardial injury, but these are often nonspecific for myocardial rupture. Early use of bedside echocardiography in the ED should be performed in any case of suspected cardiac rupture, pericardial tamponade, a previously undiagnosed murmur, or shock unexplained by other etiologies (e.g., exsanguination).

Management

When nonhospital medical personnel evaluate a patient who has sustained blunt chest trauma, they should concentrate on rapid transport and pay attention for any signs of pericardial tamponade. En route to the hospital, the possibility of a tension pneumothorax should be considered as well.

In the ED, treatment of patients with a myocardial rupture is directed toward immediate decompression of cardiac tamponade and control of hemorrhage. Pericardiocentesis may be effective in cases of a small rupture, but it is usually performed as a diagnostic or temporizing therapeutic procedure until surgical correction can be undertaken. Emergency thoracotomy and pericardiotomy may be required in the ED if the patient has rapidly deteriorating vital signs or a cardiac arrest. After emergency thoracotomy and pericardiotomy, the myocardial rupture should be controlled until the patient can be trans-

ported to the operating room for definitive repair. Hemorrhage from a ruptured atrium can often be controlled by finger occlusion or application of a vascular clamp. Insertion of a Foley catheter through the defect, followed by inflation of the balloon and traction on the catheter, may also control the bleeding. Ventricular rupture can usually be controlled by direct digital pressure or by suturing with nonabsorbable vascular sutures.

Cardiopulmonary bypass is required in only 10% of successful repairs of myocardial rupture.[75] Therefore, for patients with suspected myocardial rupture, it is appropriate to undertake emergency thoracotomy in institutions that have qualified surgeons but no immediate access to cardiopulmonary bypass.

Prognosis

Reported survival rates for patients with myocardial rupture and an intact pericardium vary widely. Although only a small number of survivors of ventricular rupture have been previously reported,[73-75] a small case series reported that four out of a total of five patients with blunt cardiac rupture who arrived at the ED with vital signs ultimately survived.[75] Most survivors of cardiac rupture are patients with atrial rupture, including one patient with multiple atrial tears. Most undergo surgical repair within 3 or 4 hours of injury.[73] Approximately 60% of successful repairs have been performed more than 60 minutes after injury.

Miscellaneous Cardiac Injuries

The occurrence of intracardiac injuries that result from blunt chest trauma (e.g., septal defects or valvular injuries) is less common. Valve rupture may involve the chordae tendinae, leaflets, or papillary muscles. Involvement of the aortic valve is more common than involvement of the mitral or tricuspid valves. Mitral and tricuspid valve injuries associated with a pericardial laceration have been reported in a survivor of blunt chest trauma. The exact incidence of cardiac valvular injuries and septal defects is unknown. Serial echocardiography and monitoring of ECG changes as well as frequent auscultation may aid in earlier diagnosis of these lesions.

Clinical Features

The clinical presentation of these patients depends on which valve or septum is involved and whether coincident cardiac injuries are present. A complete rupture of the mitral valve usually results in immediate death. The clinical presentation of an incomplete rupture depends on the hemodynamic state of the patient. Cardiogenic shock is common. Findings of acute mitral insufficiency and rapidly developing pulmonary edema are usually predominant. A loud, harsh diastolic murmur with frank left heart failure suggests acute aortic insufficiency. If the patient is in a low output state, the associated thrills and murmurs of aortic or mitral insufficiency may not be appreciated. The signs and symptoms of tricuspid insufficiency that follow a rupture of that valve may be less dramatic or even minimal. Examination may reveal only a diastolic murmur and prominent V waves of the jugular venous pulsations.

Patients with isolated septal defects may have minimal symptoms of exertional dyspnea or severe progressive shock and pulmonary edema, depending on the size and location of the defect. Dysrhythmias and conduction defects are rare because the lower muscular septum is principally involved. The typical holosystolic murmur along the left sternal border is an important clue in diagnosing a ventricular septal defect, but it may not appear for days or months after the injury. Serial echocardiography and ultimately cardiac catheterization for both valvular and septal defects are necessary for a definitive diagnosis.

Management

The therapy selected depends primarily on how well the patient tolerates the insult. Many years may elapse before operative treatment is required. In cases of ventricular septal defects, a period of observation is valuable because there have been reports of the spontaneous closure of traumatic ventricular septal defects months after the injury when the defects and resultant shunt are small. Medical therapy commonly relieves the symptoms of congestive failure, but intractable or progressive heart failure or the development of pulmonary hypertension usually indicates the need for surgery.

Penetrating Cardiac Injury

Penetrating cardiac injuries are one of the leading causes of death in the setting of urban violence. Improvements in emergency medical services systems during the past few years along with an emphasis on rapid transport are responsible for an increasing number of cardiac injury patients arriving in impending or full cardiopulmonary arrest at busy urban trauma centers. The proportion of gunshot wounds versus stab wounds varies widely in reported case series, depending on the location of the trauma center.

The right ventricle is affected more often (43%) than the left ventricle (34%) due to its anterior anatomic location. The left or right atrium is affected in 20% of cases.[75,76] One third of penetrating cardiac wounds affect multiple chambers, and survival is much worse in these cases. In 5% of cases, a coronary artery is lacerated, although these injuries usually involve a distal segment of the artery and rarely produce significant acute MI when they are ligated. More proximal coronary artery lacerations require coronary bypass.[76] Rarely, the interventricular septum, a valve, papillary muscle, or chordae tendinae is lacerated, producing an acute shunt or valvular insufficiency. These lesions are poorly tolerated and can quickly produce massive pulmonary edema and cardiogenic shock.

Two conditions may occur after penetrating heart injury: (1) exsanguinating hemorrhage if the cardiac lesion communicates freely with the pleural cavity or (2) cardiac tamponade if the hemorrhage is contained within the pericardium. Patients with exsanguinating wounds frequently die before they reach medical attention, or they present with rapidly progressive hemorrhagic shock culminating in cardiac arrest. This presentation is most typically seen in patients sustaining gunshot wounds to the heart. These patients often require immediate resuscitation by ED thoracotomy if they meet the criteria listed in Box 42-3. Cardiac tamponade is a life-threatening condition but appears to offer some degree of protection and increased survival in patients with penetrating cardiac wounds.

Acute Pericardial Tamponade

Epidemiology

The reported incidence of acute pericardial tamponade is approximately 2% in patients with penetrating trauma to the chest and upper abdomen; it is rarely seen after blunt chest trauma. It occurs more commonly with stab wounds than with gunshot wounds, and 60 to 80% of patients with stab wounds involving the heart develop tamponade.[76] Patients with acute pericardial tamponade can deteriorate in minutes, but many can be saved if proper steps are taken.

BOX 42-3 INDICATIONS FOR EMERGENCY DEPARTMENT THORACOTOMY

Penetrating Traumatic Cardiac Arrest
Cardiac arrest at any point with initial signs of life in the field
Blood pressure <50 mm Hg systolic after fluid resuscitation
Severe shock with clinical signs of cardiac tamponade

Blunt Trauma
Cardiac arrest in the emergency department

Miscellaneous
Suspected air embolus

Anatomy/Pathophysiology

The primary feature of a pericardial tamponade is an increase in intrapericardial pressure and volume. As the volume of the pericardial fluid encroaches on the capacity of the atria and ventricles to fill adequately, ventricular filling is mechanically limited and thus the stroke volume is reduced. This results in decreased cardiac output and ultimately diminished arterial systolic blood pressure and decreased pulse pressure. As little as 60 to 100 mL of blood and clots in the pericardium may produce the clinical picture of tamponade. Concomitantly, CVP rises because of the mechanical backup of blood into the vena cava.

Several compensatory mechanisms then occur. The heart rate and total peripheral resistance rise in an attempt to maintain adequate cardiac output and blood pressure. A less effective compensatory response, resulting in a greater rise of CVP, is an increase in venomotor tone caused by contractions of the smooth muscles within the wall of the vena cava.

The diagnosis of pericardial tamponade should be suspected in any patient who has sustained a penetrating wound or blunt trauma to the thorax or upper abdomen. One is never certain of the trajectory of the bullet or the length, force, and direction of a knife thrust upon initial evaluation. Obviously, wounds directly over the precordium and epigastrium are more likely to produce a cardiac injury resulting in tamponade than those in the posterior or lateral thorax. Nevertheless, it must be assumed that a penetrating wound, particularly a gunshot wound, anywhere in the thorax or upper abdomen may have injured the heart. Rapid bedside echocardiography, performed as part of the standard FAST exam, easily detects a pericardial effusion causing cardiac tamponade.[77,78]

Clinical Features

Patients with cardiac tamponade may initially appear deceptively stable if the rate of bleeding into the pericardial space is slow or if the pericardial wound allows intermittent decompression. Other patients may complain primarily of difficulty breathing, which suggests pulmonary rather than cardiac pathology.

The physical findings of pericardial tamponade are hypotension, distended neck veins, and, rarely, distant or muffled heart tones. This so-called Beck's triad is sometimes difficult to demonstrate clinically, especially in the midst of a major resuscitation with concomitant hypovolemia.[79] Although the most reliable signs of pericardial tamponade are an elevated CVP (>15 cm H_2O) in association with hypotension and tachycardia, bedside echocardiography performed as part of the FAST exam rapidly identifies pericardial tamponade and has largely replaced the use of CVP measurements to make the diagnosis. Echocardiography also distinguishes pericardial tamponade versus tension pneumothorax when the triad of elevated CVP, hypotension, and tachycardia is present.

Acute pericardial tamponade may be seen with three distinct clinical pictures. If the hemorrhage is confined to the pericardial space, the patient is initially normotensive but will have a tachycardia and elevated CVP. If untreated, most of these patients go on to develop hypotension. If significant hemorrhage has occurred outside the pericardial sac, either through a tear in the pericardium or from associated trauma, the clinical picture is that of hypovolemic shock with hypotension, tachycardia, and a low CVP. If the CVP rises to a level of 15 to 20 cm H_2O with volume replacement and hypotension and tachycardia persist, the presence of a pericardial tamponade must be considered. One must also consider other causes, such as a tension pneumothorax, Valsalva maneuver, or pulmonary edema secondary to fluid overload.

The third clinical picture is that of an intermittently decompressing tamponade. In this case, intermittent hemorrhage from the intrapericardial space occurs, decompressing and partially relieving the tamponade. The clinical picture may wax and wane depending on the intrapericardial pressure and volume and total blood loss. In general, this condition is compatible with a longer survival than are the first two clinical presentations.

Pulsus paradoxus is defined as an excessive drop in systolic blood pressure during the inspiratory phase of the normal respiratory cycle. This sign may be an additional clue to the presence of pericardial tamponade, but it is often difficult to measure during an intensive resuscitation or in the presence of shock.

Diagnostic Strategies

Ultrasound. Ultrasound (US), which is now widely available in EDs throughout the world, enables rapid, accurate, and noninvasive diagnosis of pericardial tamponade.[80] This study can be performed at the bedside in the ED during the initial resuscitation of the patient as part of the FAST exam. Although the sonographic definition of tamponade is the simultaneous presence of pericardial fluid and diastolic collapse of the right ventricle or atrium, the presence of pericardial fluid in a patient with chest trauma is highly suggestive of pericardial hemorrhage (see Fig. 42-14). An indirect sonographic sign of tamponade is the demonstration of a dilated inferior vena cava in a hypotensive patient. EDs performing cardiac ultrasonography using subcostal and long parasternal views have reported a sensitivity of 98.1% and a specificity of 99.9% for the detection of pericardial effusion.[79] Because US is noninvasive and extremely accurate, its immediate availability in the initial phase of a major trauma resuscitation can be very helpful in detecting pericardial fluid before the patient deteriorates hemodynamically.

Electrocardiography. Many ECG changes of pericardial tamponade have been described in the literature, but few are diagnostic, and each is more likely to be seen with chronic rather than acute tamponade. Electrical alternans has been reported to be a highly specific marker of pericardial tamponade. Electrical alternans is an ECG change in which the morphology and amplitude of the P, QRS, and ST-T wave in any single lead alternate in every other beat (Fig. 42-15). The postulated cause is the mechanical oscillation of the heart in the pericardial fluid, which is called the swinging heart phenomenon. In uncomplicated pericardial effusion, the heart swings back and forth but returns to approximately the same position before the next systole. Electrical alternans does not occur in this situation.

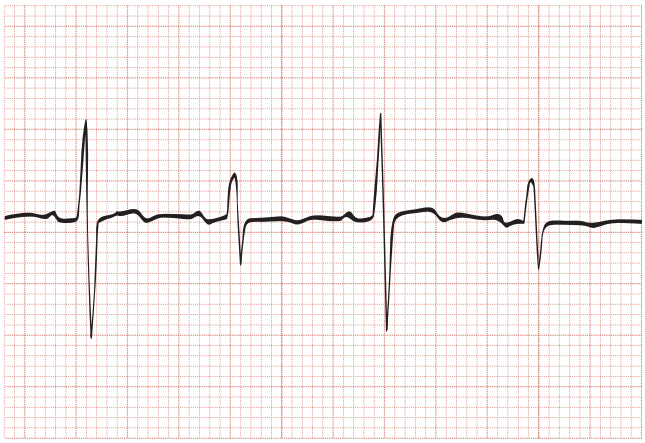

Figure 42-15. Lewis lead ECG revealing total electrical alternans of the QRS complexes. (From Sotolongo RP, Horton JD: Total electrical alternans in pericardial tamponade. Am Heart J 101:853, 1981.)

Echocardiographic studies have revealed that when fluid accumulates to a critical extent and cardiac tamponade ensues, the frequency of cardiac oscillation may abruptly decrease to half the heart rate. The cardiac position will alternate, with the heart returning to its original position with every other beat, and electrical alternans may be seen. Electrical alternans, when present, is pathognomonic for tamponade. However, it is much more common in chronic pericardial effusions that evolve into a tamponade, and it is rarely seen in acute pericardial tamponade.

Radiography. The radiographic evaluation of the cardiac silhouette in acute pericardial tamponade generally is not helpful, unless a traumatic pneumopericardium is present. Because small volumes of hemopericardium lead to tamponade in the acute setting, the heart will typically appear normal. This is in contrast to the "water-bottle" appearance of the heart with chronic pericardial effusion. This latter condition is tolerated for a long period.

Management

Out-of-Hospital Care. Field treatment for cases of pericardial tamponade is essentially the same as that outlined for any victim of major trauma. The diagnosis of tamponade should be suspected by the location of penetrating wounds or by the patient's poor response to vigorous volume resuscitation. Tension pneumothorax, which is much more common, may mimic acute pericardial tamponade. If the patient presents in extremis or the clinical condition rapidly deteriorates, consideration should be given to performing a needle thoracostomy, which, if not therapeutic, suggests pericardial tamponade under the appropriate clinical presentation by virtue of "diagnosis of exclusion." Expedient transport to the nearest trauma center should be of paramount concern.

Emergency Department. When the patient arrives in the ED, volume expansion with crystalloid solution via two or three large-bore (14- or 16-gauge) catheters should be established immediately. The presence of a pneumothorax or hemothorax, which is often associated with penetrating cardiac trauma, must be treated expeditiously with tube thoracostomy. Bedside echocardiography should be performed as quickly as possible to establish the diagnosis of pericardial tamponade, which then mandates urgent surgical repair.

There is increasing controversy regarding the role of pericardiocentesis. In the past, it was recommended that pericardiocentesis should be performed for both diagnostic and therapeutic reasons. Aspiration of as little as 5 to 10 mL of blood may result in dramatic clinical improvement. However, it should be emphasized that pericardiocentesis is not a benign or invariably successful procedure. Blood in the pericardial space tends to be clotted and aspiration may not be possible. Possible complications include the production of pericardial tamponade, the laceration of coronary artery or lung, and induction of cardiac dysrhythmias. Whenever possible, pericardiocentesis should be performed under sonographic guidance because this approach will increase the success rate and decrease the incidence of complications. A pigtail catheter may be introduced into the pericardial space for repeated aspirations while preparations are under way to quickly transport the patient to the operating room for definitive therapy. If pericardiocentesis is unsuccessful or the clinical status deteriorates, and if acute pericardial tamponade remains important in the differential diagnosis, thoracotomy should be performed as quickly as possible.[81] Patients with penetrating cardiac injury invariably require surgical repair. The location (operating room vs. ED) and timing (immediate vs. urgent) depend on the patient's clinical status.

Emergency Department Thoracotomy. Emergency department thoracotomy (EDT) is a drastic, dramatic, and potentially lifesaving procedure in which emergency physicians should be proficient. Although the procedure is not described in detail here, a few technical points merit discussion. A left lateral incision is preferred because it is rapidly accomplished; allows the best exposure of the heart, aorta, and left hilum; and facilitates open cardiac massage and internal defibrillation.[81] With right-sided or multiple injuries, it may be necessary to extend the incision across the sternum and right chest wall, creating a "clamshell" incision. The internal mammary arteries need to be ligated if this maneuver restores effective perfusion. After the heart is sufficiently exposed, the pericardium is incised anterior to the phrenic nerve. Release of a tamponade may rapidly restore cardiac output. The heart is then delivered through the pericardium and penetrating wounds are identified.

There are several alternatives for repairing cardiac wounds. Small wounds can be compressed by digital pressure to control bleeding in route to the operating room. If the injury is quite large, balloon tamponade can be achieved by applying gentle traction on a Foley catheter inserted into the wound with the balloon inflated with saline. This can temporarily stop the hemorrhage to allow suture repair of the injury (cardiorrhaphy) or to gain time while the patient is transferred to the operating room for a more definitive surgical procedure. Lacerations of the atria can be temporarily controlled with a vascular clamp.

Suture of cardiac wounds over pledgets is the time-honored and effective technique but is technically more difficult and more time-consuming. The use of a monofilament suture, such as 2-0 prolene, is recommended. Some trauma surgeons recommend stapling cardiac wounds with standard skin staplers since this technique has been shown to be much quicker and equally effective in closing these wounds, and there is also a report on the use of a collagen mesh attached with fibrin glue mesh to rapidly repair a ventricular laceration.[82,83]

Care must be taken to avoid ligating coronary arteries during the repair. Direct insertion of a large-bore catheter (e.g., a 5-F catheter) into the left atrial appendage provides a route for rapid infusion of fluids. If the heart is empty or the patient fails to respond to rapid fluid administration, the aorta is cross-clamped to divert cardiac output to the brain and heart. Prolonged ischemia and severe acidosis often result in postresuscitation myocardial depression with ineffective contraction and diminished cardiac output.

Indications for Emergency Department Thoracotomy. Although it is often tempting to perform EDT on all traumatic arrest victims pre-

senting to the ED, there are clearly cases in which it has virtually no chance of salvaging the patient. In addition, EDT is costly; requires the undivided attention of all personnel in the ED, diverting care from other more salvageable critical patients; and poses a risk to ED personnel for injury from needle sticks and other blood-contaminated exposures.[84] Consequently, guidelines have been established for performing EDT to restrict the procedure to patients with some chance of achieving a neurologically functional outcome (see Box 42-3).[85]

Patients with penetrating trauma with signs of life in the field, even if only electrical activity on cardiac monitor or agonal respirations, are candidates for EDT if transport times are less than 10 minutes.[84-88]

Prognosis

After penetrating wounds to the heart, several factors adversely affect survival, including gunshot wound mechanisms and wounds that involve the left ventricle, multiple cardiac chambers, intrapericardial great vessels, or one or more coronary arteries. The factors favorable to survival include stab wound mechanisms with minor perforations, isolated right ventricular wounds, a systolic blood pressure greater than 50 mm Hg on arrival at the ED, and the presence of cardiac tamponade.

Survival rates after EDT have been correlated with the mechanism and location of injury, field and transport times, the duration of arrest, and the physiologic status of the patient in the out-of-hospital and hospital settings. Although reported survival rates from EDT vary widely, they are consistently higher in victims with isolated cardiac injuries secondary to stab wounds versus gunshot wounds.[86-88]

A meta-analysis of the literature found that EDT had an overall survival rate of 7.4%, with normal neurologic outcomes noted in 92.4% of surviving patients. Survival rates for mechanism of injury were 9% for penetrating injuries and 1% for blunt injuries. When penetrating injuries were further separated, the survival rates were 17% for stab wounds and 4% for gunshot wounds. The presence of pericardial tamponade is a favorable prognostic finding.[87]

Blunt Aortic Injury

Epidemiology

Blunt aortic injury is a life-threatening injury, usually resulting from either unrestrained frontal collisions or violent lateral blunt impact to the chest.[89] Blunt aortic injury includes a spectrum of lesions, ranging from a small intimal tear to frank rupture, which usually cause rapid lethal hemorrhage. The most common sites of injury are the aortic isthmus and the ascending aorta just proximal to the origin of the brachiocephalic vessels.[84] Sixty to 90% of patients with blunt aortic injury die at the site of accident or within hours of hospital admission.[99,90] However, an increasing number of patients arrive at a treatment facility because of improvement in out-of-hospital care, more aggressive resuscitation in the field, and rapid transportation to a trauma center. The early survival rate of such patients depends on the initial resuscitation and/or the timeliness and correct choice of the diagnostic procedures. A rapid and accurate diagnosis is thus mandatory to optimize treatment and maximize patient survival.

Anatomy/Pathophysiology

Blunt aortic injury encompasses various histologic lesions. Minor blunt aortic injuries (grade 1, intramural hematoma or limited intimal flap) and major blunt aortic injuries (grade 2, subadventitial rupture or modification of the geometric shape of the aorta; and grade 3, aortic transection with active bleeding or aortic obstruction with ischemia) can be differentiated by TEE. Whereas minor blunt aortic injuries appear to have a good prognosis, major blunt aortic injuries involve the entire depth of both the intimal and the medial layers and may lead to adventitial rupture, resulting in sudden death at the scene of the accident or during the first hours of hospitalization.[89,90]

Several theories about the mechanism of aortic rupture have predominated in the literature. The descending thoracic aorta is relatively fixed and immobile because of its tethering by intercostal arteries and the ligamentum arteriosum. With sudden deceleration, the more mobile aortic arch swings forward, producing a shearing force or "whiplash effect" on the aorta at the isthmus. A bending stress at the isthmus, created by sudden lateral oblique chest compression, may also result in rupture by causing flexion of the aortic arch on the left mainstem bronchus and the pulmonary artery. It has been suggested that the forces created by the whiplash effect or lateral oblique compression may not be sufficient to provoke aortic tears. It is now postulated that those injuries may be caused by inferior and posterior rotation of anterior thoracic osseous structures (manubrium, first rib, and medial clavicles), pinching and shearing the interposed aorta as they strike the vertebral column.

Rupture of the ascending aorta just distal to the aortic valve likely occurs through a different mechanism. At the time of rapid deceleration and chest compression, the heart is displaced into the left posterior chest, which causes a shearing stress just above the aortic valve. A sudden increase in intra-aortic pressure, "the waterhammer effect," may also cause an explosive rupture of the aorta at this location. Involvement of the coronary ostia with coronary artery occlusion may occur in association with tears to the ascending arch. The intraluminal pressure tolerance of the aorta may be exceeded in a high-speed motor vehicle crash. It is likely that a combination of the preceding mechanisms accounts for the multiple aortic ruptures that have been found in 20% of traffic accident victims examined at autopsy.[90]

A total of 80 to 90% of aortic tears occur in the descending aorta at the isthmus, just distal to the left subclavian artery (Figs. 42-16 and 42-17).[91,92] Other less common sites of involvement are the ascending aorta, the distal descending aorta at the level of the diaphragm, the midthoracic descending aorta, and the origin of the left subclavian artery. Although ruptures of the ascending aorta are much less common than those of the descending aorta, they have a 70 to 80% incidence of associated lethal cardiac injuries. This is in contrast to ruptures at the isthmus, which have a 25% incidence of associated cardiac injuries. Lethal cardiac injuries commonly include pericardial tamponade, aortic valve tears, myocardial contusion, or coronary artery injuries. Passenger ejection, pedestrian impact, severe falls, and crush injuries commonly result in ascending thoracic aortic ruptures. Survival long enough to be evaluated in the ED is rare among patients who sustain an ascending aortic rupture.[91]

Aortic rupture may occur from causes other than high-speed motor vehicle crash deceleration. Rupture has been documented as a complication of external cardiac massage and has been known to occur after fracture-dislocations of the thoracic spine, presumably as the result of direct shearing force. Vertical deceleration injuries resulting from falls can cause a rupture of the ascending aorta by producing an acute lengthening of the ascending aorta. This is the likely mechanism responsible for aortic rupture in the setting of airplane and elevator accidents. Direct kicks by animals, crush injuries, sudden burial by landslide, and air bag deployment have also been reported

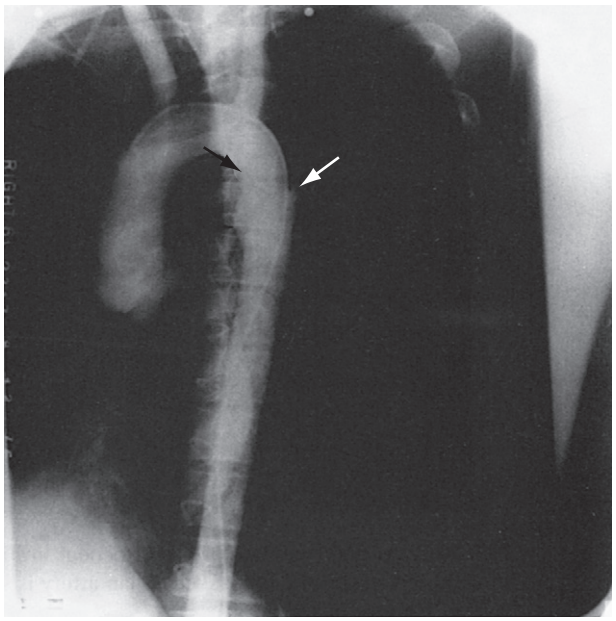

Figure 42-16. Aortogram shows tear in aorta *(arrows)* at the most common location, at or just distal to takeoff point of left subclavian artery, which is not visualized.

as causes of aortic rupture. Direct compression of the compliant thorax has been postulated to contribute to aortic rupture in children. Displaced fractures of the sternum, ribs, and clavicle have also been shown to directly lacerate the aorta.

Clinical Features

The possibility of aortic disruption must be considered in every patient who sustains a severe deceleration injury. This is especially true if the automobile was moving in excess of 45 mph or if there is evidence of severe blunt forces to the chest (e.g., from a damaged steering wheel).[93] In the case of any moderate- or high-speed motor vehicle accident, it is imperative that paramedics carefully evaluate the extent of damage to the vehicle, the complaints of the victims, and the physical manifestations of blunt chest trauma. This information should be promptly relayed to the emergency physician.

Despite the severe nature of the injury, the clinical manifestations of an aortic rupture are often deceptively meager. Associated pulmonary, neurologic, orthopedic, facial, and abdominal injuries are commonly present. Coexisting injuries can mask the signs and symptoms of an aortic injury or divert the physician's attention away from the more lethal aortic rupture. The absence of any external evidence of a chest injury does not eliminate the possibility of an aortic tear. One third to one half of patients reported in the literature have no external signs of chest trauma.[89]

The most common symptom is interscapular or retrosternal pain. It is often found in nontraumatic aortic dissection but is present in only 25% of patients with a traumatic aortic disruption. Other symptoms described in the literature but uncommonly present include dyspnea resulting from tracheal compression and deviation, stridor or hoarseness caused by compression of the laryngeal nerve, dysphagia caused by esophageal compression, and extremity pain caused by ischemia from decreased arterial flow.

Clinical signs are uncommon and nonspecific. Generalized hypertension, when present, may be an important clinical sign. Sympathetic afferent nerve fibers, located in the area of the aortic isthmus, are capable of causing reflex hypertension as a response to a stretching stimulus. A less common clinical finding is the acute onset of upper extremity hypertension, along with absent or diminished femoral pulses. This pseudocoarctation syndrome has been reported to occur in up to one third of these patients and is attributed to compression of the aortic lumen by a periaortic hematoma.

The presence of a harsh systolic murmur over the precordium or posterior interscapular area may be heard in up to one third of patients. The murmur is thought to result from the turbulent flow across the area of transection. A less commonly encountered physical finding is a swelling at the base of the neck caused by the extravasation of blood from the mediastinum, which results in an increased neck circumference or a pulsatile neck mass. Other clinical signs suggestive of aortic rupture include lower extremity pulse deficit and lower extremity paralysis. Initial chest tube placement output in excess of 750 mL is also suggestive of aortic rupture, especially if the hemothorax is left sided. However, the physical examination is neither sensitive nor specific for aortic injury, preventing accurate diagnosis without ancillary studies.

Diagnostic Strategies

Chest Radiography. Radiography of the chest is a valuable tool when aortic rupture is suspected. Many patients have died because the presence and significance of radiographic findings were not appreciated. An increase in the width of the superior mediastinum is the most sensitive sign and is found in 50 to

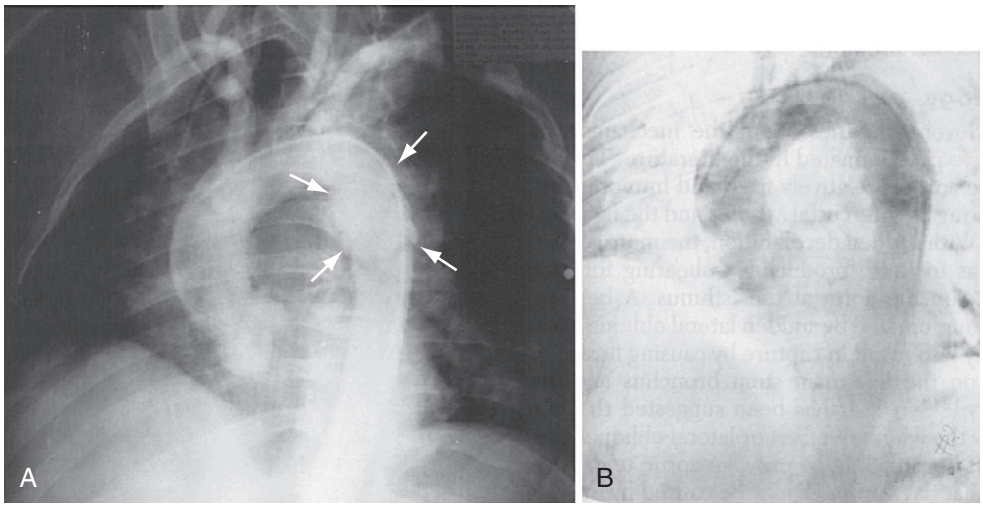

Figure 42-17. **A,** Follow-up aortogram of patient in Figure 42-16. Arch study with catheter in ascending aorta. Tear in aorta *(arrows)* distal to the left subclavian artery is seen with dissection and extravasation of contrast material. **B,** Reverse image.

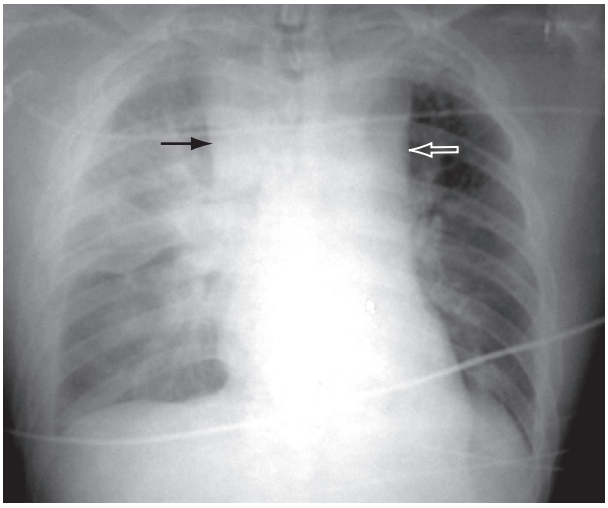

Figure 42-18. Anteroposterior radiograph of the chest showing wide mediastinum *(arrows)*.

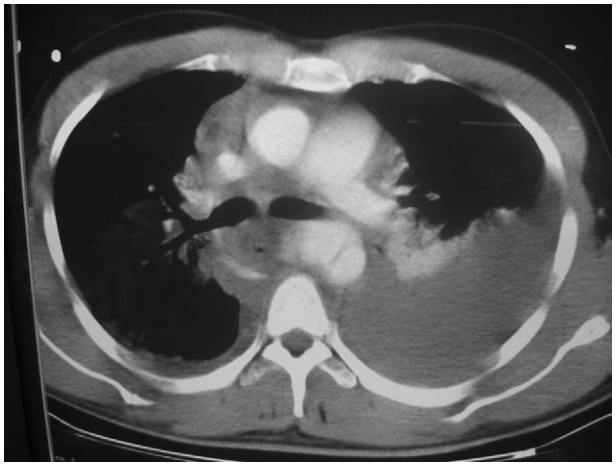

Figure 42-19. Chest CT demonstrating periaortic hemorrhage and an intimal flap.

92% of aortic ruptures (Fig. 42-18).[94,95] However, specificity of this radiologic sign is as low as 10%.

Mediastinal widening may be caused by venous bleeding from a clavicle, thoracic spine, or sternal fracture; pulmonary contusions; a previous mediastinal mass; a misplaced CVP catheter; or magnification caused by the anteroposterior and supine position of a portable chest radiograph. Hence, the sign is not pathognomonic for aortic rupture.

Commonly cited guidelines for abnormal mediastinal widening include a mediastinal width greater than 6 cm in the erect posteroanterior film, greater than 8 cm in the supine anteroposterior chest film, or greater than 7.5 cm at the aortic knob or a ratio of mediastinal width to chest width greater than 0.25 at the aortic knob. There is disagreement regarding the reliability of these parameters in confirming or excluding aortic rupture. A subjective interpretation of mediastinal widening is more reliable than direct measurement of mediastinal width.[95] Positioning of the patient and the degree of inspiration are important factors in assessing the mediastinum. Every effort should be made to obtain a standard upright inspiratory posteroanterior film, if clinically feasible, before a mediastinum is declared abnormal to avoid false-positive interpretations.

Current literature is replete with various diagnostic radiologic criteria thought to be sensitive indicators of aortic rupture.[96,97] Several authors have shown that an interpretation of widened mediastinum and an obscured aortic knob are the most reliable signs of aortic rupture. The opacification of the clear space between the aorta and the pulmonary artery, displaced nasogastric tube, widened paratracheal stripe, or widened right paraspinal interface is thought to provide the most specific evidence for aortic rupture.[94,96,97] Others believe that deviation of the nasogastric tube to the right in combination with depression of the left main stem bronchus below 40 degrees from the horizontal is the most reliable sign positively associated with the diagnosis.

Other reported radiologic signs of a ruptured aorta include left hemithorax, obliteration of the medial aspect of the left upper lobe apex (left apical pleural cap), deviation of the trachea to the right, and multiple rib fractures. Fractures of the first and second ribs, once classically described as highly suggestive of aortic injury, do not appear to be associated with increased risk compared with that of patients without these fractures.

Although previous reports suggested that a negative chest radiograph is highly predictive of a normal aortogram, several studies have challenged this widely held belief.[94,96,97] The sensitivity of a negative chest radiograph (i.e., normal mediastinum) is limited. Several authors recommend liberal use of helical chest CT scanning in patients with high-speed deceleration mechanisms of injury. Reported rates of false-negative CXRs with no mediastinal widening in patients with proven aortic injury vary from 0 to 45%.[94,96,97]

Chest CT Scan. Chest CT scans have largely replaced the need for aortography to detect aortic rupture.[98-104] The development of the new multidetector helical CT scans in the early 1990s revolutionized trauma radiology with its speed and superior definition, thereby largely negating the negative results obtained with conventional scans. New helical CT scans have almost 100% sensitivity and specificity for rapidly detecting aortic injury while requiring only intravenous contrast administration (Fig. 42-19). A normal aortic contour on CT, even in the presence of a mediastinal hematoma, has been shown to be highly accurate in excluding thoracic aortic disruption.[98-104]

A chest CT scan with intravascular contrast offers a number of advantages over aortography. It is noninvasive, provides significantly more information on other thoracic injuries than chest radiography, and can be performed more rapidly than angiography. At most centers, an immediate chest CT scan is readily available. In addition, in the group of patients with a widened mediastinum, CT evaluation may be useful in evaluating not only the aorta but also the spine because spinal fractures may be the cause of a widened mediastinum. It is now recommended that all patients with a mechanism of injury suggestive of potential aortic injury should undergo CT evaluation of the mediastinum, irrespective of chest radiographic findings.[99]

Transesophageal Echocardiography. TEE is an alternative method to CT scanning or aortography for establishing the diagnosis of aortic rupture.[105-107] It offers a number of advantages over other diagnostic studies: It is fast, does not require intravenous contrast or radiation exposure, provides concomitant evaluation of cardiac function, and can be performed in the ED. Sedation is necessary to avoid hypertension while inserting the probe. TEE is contraindicated in patients with esophageal injury.

TEE allows identification of an intimal flap, as well as a periaortic hematoma (Fig. 42-20). When only a monoplane TEE is used, the upper portion of the ascending aorta represents a blind zone because of the interposition of the air-filled

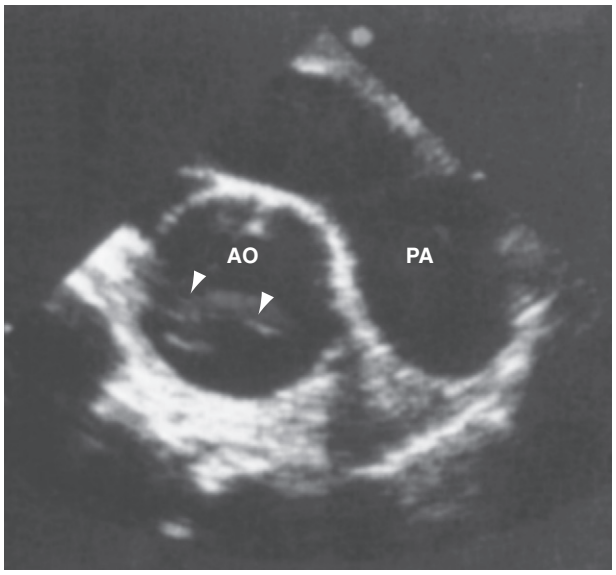

Figure 42-20. Transesophageal echocardiogram shows periaortic hemorrhage and aortic dissection *(arrows)*. AO, aorta; PA, periaortic.

trachea. However, because the vast majority of injuries are located at the isthmus, TEE is highly accurate, with a reported sensitivity of 87 to 100% and a specificity of 98 to 100%.[108-110] When available, TEE offers an alternative to a chest CT scan as a diagnostic screening test for aortic injury.

In patients with severe blunt chest trauma, TEE and CT have been found to have similar diagnostic accuracy for the identification of surgical acute traumatic aortic injury. In addition, TEE also allows the diagnosis of associated cardiac injuries and is more sensitive than CT for the identification of intimal or medial lesions of the thoracic aorta.[108]

Aortic repair may be feasible based on TEE alone, but aortography is still needed when TEE results are equivocal, when TEE is not tolerated or contraindicated, or when other suspected vascular injuries require evaluation by arteriography.[109]

Intravascular Ultrasound. Intravascular US has been described in the detection of subtle injuries to the aorta. This modality involves a small ultrasound probe that is inserted through the femoral artery and guided up the aorta. Currently, availability is limited to a few trauma centers because the technique requires sophisticated equipment and is performed in the operating room or angiography suite. Preliminary data suggest that intravascular US is extremely sensitive and specific in detecting blunt aortic injury.[110]

Aortography. Aortography, long considered the gold standard for establishing the diagnosis of aortic disruption, has been replaced almost completely by high-resolution helical CT scanners.[106] The major objective for patients with a ruptured aorta is the early recognition of the lesion before adventitial disruption and exsanguination. Multiple aortic tears occur in 15 to 20% of cases, necessitating precise anatomic localization of these injuries. Before the widespread availability of helical CT scanners, aortography was recommended not only for patients with a widened mediastinum but also for those who had sustained significant blunt chest trauma and who had any of the radiologic signs previously mentioned. An aggressive approach is particularly warranted in elderly patients.

Aortography should be delayed in patients with more immediate life-threatening injuries to the abdomen, pelvis, and head. In circumstances in which aortography must be delayed, it is important to provide medical management and maintain the systolic blood pressure below 120 mm Hg with antihypertensive agents.[111]

High-quality aortography can be performed with the aid of a rapid film changer by directly injecting the contrast medium into the root of the aorta through a catheter. The procedure involves a risk of further damage to the aorta or other ruptured vessel if the catheter crosses the site of the injury; however, this risk can be reduced by using meticulous technique, a soft-tipped C-curve guidewire, and fluoroscopy. Simultaneous coronary angiography is often indicated, particularly in patients with an aortogram that shows a tear in the ascending aorta, because involvement of the coronary ostia by the dissection or the presence of significant arteriosclerotic disease may warrant coronary artery bypass grafting together with surgical repair of the aorta.

As surgeons have gained more experience with the diagnostic capabilities of helical CT scanning, the need for preoperative angiography has declined. Aortography should now be reserved for high-risk patients with indeterminate helical chest CT scans.[99,111]

Management

Out-of-Hospital. In the out-of-hospital care of any patient who has sustained blunt chest trauma, evaluation for possible aortic rupture should concentrate on identifying a mechanism of injury compatible with aortic rupture and treating hypotension, tension pneumothorax, and pericardial tamponade. Immediate communication of the patient's condition and expeditious transport to a trauma center will increase the patient's chance for survival.

Emergency Department. Because of the ever-present risk of sudden free rupture and exsanguination, repair of the lesion should be performed as soon as the diagnosis is made. Management of the patient with multiple injuries who has documented rupture of the thoracic aorta depends on the nature of associated injuries. Surgical repair of the aortic rupture should be delayed in the presence of life-threatening intracranial or intra-abdominal injury or profuse retroperitoneal hemorrhage.[99] Consideration for delay of the procedure should be made for patients at high risk for infection (e.g., those who have extensive body surface burns, contaminated large open wounds, established sepsis, or severe respiratory insufficiency caused by thoracic trauma).

Careful regulation of blood pressure is mandatory until definitive surgical repair can be performed. If operative repair is delayed, the systolic blood pressure should be maintained between 100 and 120 mm Hg. The objective of lowering the blood pressure is to decrease the shearing jet effect of an elevated pulse pressure, thus decreasing the possibility of continued adventitial dissection and subsequent free rupture.[111]

Esmolol, a short-acting titratable beta-blocker, may be ideally suited for this purpose because, unlike nitroprusside sodium, it decreases the pulse pressure and minimizes the shearing effect on the intact adventitia of the aorta. If blood pressure is not adequately controlled, nitroprusside sodium can be added as a second agent after the pulse pressure has been decreased with a short-acting beta-blocker.

Surgical Techniques

Many surgical techniques have been described since the first successful repair by Passaro and Pace in 1959.[112] In those patients who survive operative repair, paraplegia due to spinal cord ischemia has been a significant complication,

traditionally affecting as many as 10 to 20% of such patients.[113,114] The major variable thought to be related to spinal cord ischemia and subsequent development of paraplegia has been aortic cross-clamp times.[115] Blunt aortic injury ranges from a simple tear (usually distal to the origin of the subclavian artery) to complex injuries involving the proximal aorta and branch vessels.

Many surgeons have reported the use of cardiopulmonary bypass techniques in surgical repair to allow for distal spinal cord perfusion with significantly reduced incidence of paraplegia.[113-117] This is especially true for patients with complex aortic injuries, for which the aortic cross-clamp times are typically prolonged.[113]

The pathologic condition found dictates the type of repair. A synthetic graft is often required because of extensive tension on the vessel walls or jagged torn ends of the vessel. Data on successful primary repair of aortic disruption are encouraging. The procedure requires less operative time and has a lower potential infection risk, blood loss through a prosthesis is avoided, the possibility of pseudoaneurysm formation is eliminated, and secondary embolism arising from mural thrombosis is avoided. Multiple tears of the descending thoracic aorta have been successfully repaired using the primary suture technique. Direct end-to-end anastomosis appears to be most feasible in the younger population.

For patients who arrive at the hospital alive but who have descending thoracic aortic injuries, the incidence of mortality during surgery ranges from 20 to 30%, and the paraplegia rate is 5 to 7%.[113,118-120] Younger patients have the highest survival rate. Mortality is related to the presence or absence of extensive dissection and to the preoperative condition of the patient.

There is a growing body of evidence demonstrating the safety and efficacy of endovascular repair of traumatic aortic tears. This involves the use of a stent placed through a femoral or iliac artery approach. Preliminary data indicate that success rates and complication rates are comparable if not better than those of traditional open surgical repairs and that the risk of major surgery and subsequent paraplegia from prolonged aortic clamping is significantly reduced with endovascular repair. Emerging literature suggests that endovascular repair with stenting is replacing open repair as the treatment of choice for blunt aortic injury.[119-125]

ESOPHAGEAL PERFORATION

Epidemiology

Perforation of the esophagus has been called the most rapidly fatal perforation of the gastrointestinal tract because death is almost ensured if the diagnosis is delayed more than 24 hours.[126] The classic description of esophageal perforation resulting from forceful vomiting was published in 1724 by Boerhaave, and between 1724 and 1941, the occurrence of Boerhaave's syndrome was almost uniformly fatal.[127] In 1941, the first successful surgical treatment, a drainage procedure, was reported, and in 1947 the first successful closure of a ruptured esophagus was described. Since then, improved surgical techniques, a greater physician awareness leading to a more prompt diagnosis, the availability of more effective antibiotics, and better general supportive measures have reduced the mortality to approximately 20%.[126] Mortality data cited for perforation are affected by several variables, such as location (with perforations of the thoracic segment having the highest mortality rate), mechanism of injury, time elapsed between injury and diagnosis, the presence of preexisting esophageal disease, and general health of the patient.

Anatomy/Pathophysiology

The anatomic feature responsible for the prolonged morbidity and high mortality associated with esophageal perforation is the lack of an esophageal serosal covering that allows perforation at any level direct access to the mediastinum. Perforations in the upper or cervical esophagus enter the retropharyngeal space, where fascial planes extend from the base of the skull to the bifurcation of the trachea. Perforations in the midesophagus and lower esophagus enter directly into the mediastinum. Only the thin mediastinal pleura prevents free access to the entire pleural cavity, and this barrier is commonly overcome by continued drainage and the massive exudative inflammatory reaction induced by chemical and bacterial mediastinitis. When the mediastinal pleura is penetrated, the negative pressure generated by respiratory efforts tends to increase the soilage by promoting drainage from the gastrointestinal tract into the mediastinum and pleural space.

When esophageal rupture results from emetic pressure, as in cases of Boerhaave's syndrome, the intrinsic weakness of the left posterior distal esophagus is important. Other areas (including cervical, midthoracic, and infradiaphragmatic sites) have been reported only rarely to rupture secondary to emesis. In addition, the esophagus has three areas of anatomic narrowing[128]: the cricopharyngeal muscle near the esophageal introitus, the level at which the esophagus crosses the left main stem bronchus and the aortic arch, and the gastroesophageal junction. In the absence of a preexisting esophageal disease such as carcinoma, it is unusual for a perforation caused by a foreign body to occur anywhere other than at these three sites. Foreign bodies may cause perforation by direct penetration, pressure, or chemical necrosis.

Etiology

The most common causes of an esophageal perforation are shown in Box 42-4.

Iatrogenic

Most esophageal perforations are iatrogenic, most commonly as a complication of instrumentation (59% of all patients).[126] The rigid endoscope is the most common offender, particularly when general anesthesia is used. Although use of the flexible endoscope has made this complication less likely, the total number of perforations has increased as more procedures are performed. Injuries tend to occur near either the cricopharynx or the cervical esophagus as the endoscope is inserted.[129] Endoscopic procedures that are too vigorous in the presence of a corrosive burn or carcinoma are also a common cause of iatrogenic esophageal injury.

Esophageal dilation performed for benign or malignant strictures of the esophagus is the second most common iatrogenic cause of esophageal perforations.[129] Increasing the dilator size too rapidly during these procedures may lead to perforation. The preexisting fibrotic process that resulted in the stricture

BOX 42-4 MOST COMMON CAUSES OF ESOPHAGEAL PERFORATION

1. Iatrogenic
2. Foreign bodies
3. Caustic burns
4. Blunt or penetrating trauma
5. Spontaneous rupture (Boerhaave's syndrome)
6. Postoperative breakdown of anastomosis

tends to scar the surrounding mediastinal tissues, however, limiting free access to the mediastinum provided by many other perforations. In the ED, nasotracheal or nasogastric intubations are the most common causes of iatrogenic perforation, with the perforation usually occurring in the pyriform sinus. In a closed claims analysis published in 1999, esophageal injuries by anesthesiologists were overwhelmingly associated with difficult intubations.[130] Risk factors for a difficult airway include obesity, cervical arthritis, haste, and improper muscle relaxation. Claims involving airways that were classified as "nondifficult" involved other esophageal instrumentation, such as a nasogastric tube, esophageal dilator, or esophageal stethoscope. In all cases, esophageal injuries were more severe than any other type of airway injury sustained during airway maneuvers.

The use of an esophageal obturator airway was also associated with occasional esophageal trauma, specifically mid-esophageal perforation. Use of the esophageal obturator airway's most recent successor, the laryngotracheal Combitube, does not seem to be associated with trauma more severe than occasional esophageal abrasions or contusions.

Several cases of esophageal rupture secondary to compressed air have been reported, including two cases of pharyngoesophageal perforation secondary to gas in carbonated beverages and in tartaric acid-sodium bicarbonate mixtures administered to treat esophageal food impactions. Esophageal perforation has also been caused by placement of a cervical fixation device and secondary to the Heimlich maneuver.

Foreign Bodies

Foreign bodies can cause an esophageal injury by direct laceration, by pressure necrosis, or during endoscopic removal.[131] Small perforations tend to seal without sequelae, but pressure necrosis or lacerating injuries provide ample access to the mediastinum.[128] Foreign bodies usually lodge in the cervical esophagus, but if a distal stricture is present, this too is a common site. In children younger than 4 years, the cricopharyngeal narrowing is the usual point of foreign body impaction. After age 4 years, most objects pass this region and traverse the remaining normal esophagus. In adults, a foreign body impaction, especially in cases of repeated episodes, raises the possibility of a stricture and mandates further investigation.

In elderly patients, foreign bodies commonly enter the esophagus because of a loss of oral tactile sensation resulting from intoxication or a poorly fitting set of dentures.[132] Inadequate dentures may also lead to the swallowing of large pieces of poorly chewed food. Other esophageal foreign bodies include sharp fish or chicken bones and corn chips that may impale the esophageal wall leading to eventual leakage.

Caustic Burns

Caustic burns of the esophagus occur from intentional or accidental ingestion of acid or alkali. There are two peaks of incidence: 1 to 5 years of age, when ingestion is usually of a small amount of material and accidental, and in the teens and 20s, when larger quantities are ingested during suicide attempts. Symptoms include hematemesis, respiratory distress, vomiting, drooling, or the presence of oropharyngeal lesions on physical examination.[129] Perforation usually occurs during the latent granulation stage of the disease, approximately 4 to 14 days after ingestion.

The liquefaction necrosis classically resulting from strong alkali burns (pH > 12) is more likely to cause esophageal perforation than the coagulation necrosis resulting from strong acid burns (pH < 2). Individuals ingesting alkali substances with a pH less than 11.5 rarely sustain injuries more serious than superficial mucosal burns. Acid ingestions cause damage more frequently in the stomach than in the esophagus.[129]

In treating a patient who has ingested a caustic substance, decontamination should involve only the rinsing of the mouth. Dilution of the substance with milk or water has been suggested; however, further liquid ingestion should be avoided if there is suspicion of perforation. Emesis, gastric lavage, and charcoal should be avoided.

Endoscopy within the first 6 to 18 hours may be used to determine the extent of the injury and to guide therapy. Antibiotics are reserved for patients with evidence of perforation, and steroids are suggested by some authors if the burns are circumferential or transmural. Other authors have shown that in the setting of large alkali ingestions, corticosteroids not only did not prevent the formation of esophageal stenosis but also increased the risk of other complications.[133]

Although admission after significant ingestion is the rule, some authors suggest that in the setting of accidental ingestion in children and in the absence of symptoms, endoscopy and admission may not be indicated.[134] Esophagoscopy is commonly undertaken to ascertain the presence or absence of esophageal injury. Advancing the esophagoscope beyond the first burn in the esophagus increases the risk of perforation and is a common iatrogenic cause of esophageal perforation.

Penetrating and Blunt Trauma

Because of its well-protected position posteriorly, esophageal trauma occurs in approximately 5% of patients with injuries to the neck, but only 1% of blunt trauma victims, and it is usually not an isolated injury.[135] Cervical esophageal injuries are the most common because of a lack of protection by the bony thorax, and the trachea is the most common associated site of injury.[136] In some cases, the esophageal injury may be overlooked initially because of the dramatic presentation of a patient with a tracheal injury.

Typical symptoms seen in cervical esophageal injuries include neck pain, dysphagia, cough, voice changes, and hematemesis. Physical findings may include neck tenderness, resistance to flexion, crepitus, or stridor.[136] In one large series, the most common life-threatening problem in the ED was compromise of the airway. Most of these cases were handled using rapid sequence intubation, but a significant number (12%) of patients required cricothyroidotomy.[135]

If the patient's condition is stable, a preoperative esophagogram with a liquid-soluble agent should precede any endoscopy. Although chest and neck radiograph and CT also may be used to diagnose this injury, emergent bedside flexible endoscopy seems to be the test of choice to confirm negative findings on esophagography (especially in the setting of penetrating trauma).[135-137] Operative repair is indicated in most of these injuries (>90%) and should be done as quickly as possible to avoid the development of fistulae, mediastinitis, or abscess formation.

Blunt traumatic injuries to the esophagus occur much less often than penetrating injuries. The pathophysiology and prognosis of blunt injuries to the esophagus are similar to those of spontaneous rupture or emesis. In some cases, rupture of the cervical esophagus has been reported in association with cervical spine fracture.

Spontaneous Rupture

Spontaneous esophageal ruptures, postemetic ruptures, and Boerhaave's syndrome are synonymous terms. This esophageal injury is associated with a poor prognosis because the forces required to rupture the esophagus result in almost

instantaneous and massive mediastinal contamination. The distal esophagus is the usual site of injury, with a longitudinal tear occurring in the left posterolateral aspect. More than 80% of these injuries occur in middle-aged men who have ingested alcohol and large meals.

In vitro, a tear similar to that seen in cases of Boerhaave's syndrome requires a force of 3 to 6 psi, which may be generated in vivo by gastric pressure caused by the reverse peristalsis (seen with emesis) pushing against a closed cricopharyngeal muscle.[138] The role of preexisting gastrointestinal disease in spontaneous rupture of the esophagus is unclear. Some authors emphasize its importance, whereas others report that 80% of esophageal ruptures occur in a previously normal esophagus.[138] Less pressure is required to perforate a diseased esophagus. Approximately 25% of patients with Boerhaave's syndrome have no history of emesis.[138] Increases in intra-abdominal pressure resulting from blunt trauma, seizures, childbirth, laughing, straining at stool, and heavy lifting have all been reported to cause this injury.

Diagnostic Findings

The diagnosis of esophageal perforation is aided by consideration of clinical circumstances. In patients with classic Boerhaave's syndrome, emesis is followed by severe chest pain, subcutaneous emphysema, and cardiopulmonary collapse. Development of these signs and symptoms after instrumentation of the esophagus or removal of an esophageal foreign body is relatively straightforward. One third of cases of perforated esophagus are atypical, however.[134] Only a careful history and physical examination supplemented with appropriate laboratory and diagnostic studies enable the clinician to diagnose a subtle case at an early stage. When considering any of the diagnoses listed in Box 42-5, a perforated esophagus should also be considered.

BOX 42-5 CLINICAL CONDITIONS THAT MAY MIMIC ESOPHAGEAL PERFORATION

1. Spontaneous pneumomediastinum
2. Aortic aneurysm (thoracic)
3. Pulmonary embolus
4. Perforated peptic ulcer
5. Myocardial infarction
6. Pancreatitis
7. Mesenteric thrombosis
8. Cholecystitis
9. Pneumonia

Clinical Features

The most reliable symptom of an esophageal injury is pleuritic pain localized along the course of the esophagus that is exacerbated by swallowing or neck flexion (Fig. 42-21). Pain may be located in the epigastrium, substernal area, or back; usually worsens over time; and may migrate from the upper abdomen to the chest. As the infectious process worsens, dyspnea usually ensues.

The early physical signs of an esophageal perforation are sparse. As air and caustic contaminated material move through the esophageal tear into the mediastinum and pleural space, and before any subcutaneous air is palpable at the root of the neck, the mediastinal air may impart a nasal quality to the voice.[139] Mediastinal air may surround the heart and produce a systolic crunching sound (Hamman's crunch). As air and fluid move into the pleural space, signs of a hydropneumothorax or an empyema may develop. Eventually, the air travels into the subcutaneous tissues, dissecting into the neck, where subcutaneous emphysema may first become evident. This classic sign is present in only approximately 60% of patients, however, and in the absence of a tracheal injury, it may occur in only 30%.[139] As the infectious and inflammatory process advances, the patient's general appearance and vital signs begin to manifest the signs of cardiopulmonary collapse and sepsis with fever, cyanosis, hypotension, anuria, and eventually death.

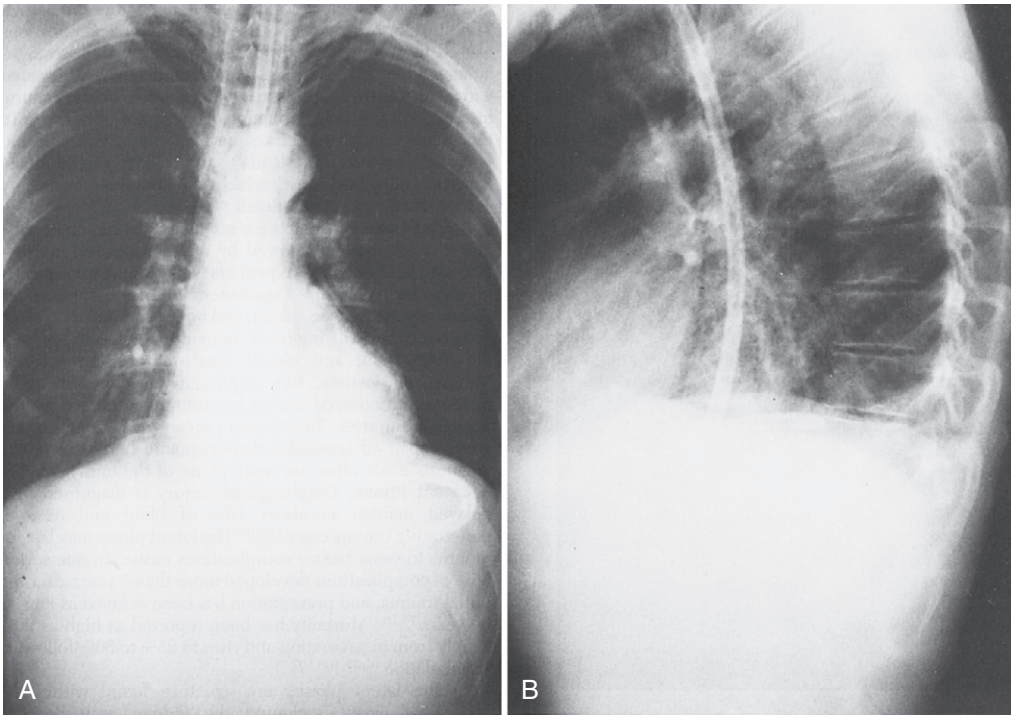

Figure 42-21. **A,** Chest radiograph of a 36-year-old man with acute onset of pleuritic chest pain after forceful vomiting. **B,** Chest radiograph shows mediastinal and subcutaneous air typical of ruptured esophagus. Mediastinum is not yet widened, and there is no soilage of the pleural cavity.

Diagnostic Strategies

Laboratory studies provide largely nonspecific findings. If tested, the pleural effusion of esophageal perforation may show a high salivary amylase level and a low pH. The radiographic examination usually suggests the diagnosis of an esophageal perforation. The classic chest radiograph findings are as follows:

1. Mediastinal air with or without subcutaneous emphysema
2. Left-sided pleural effusion
3. Pneumothorax
4. Widened mediastinum

Lateral views of the cervical spine may reveal air or fluid in the retropharyngeal area that is characteristic of a cervical esophageal perforation but also is found when perforations in the lower parts of the esophagus release air or fluid that dissects superiorly (Fig. 42-22). Most patients exhibit one or more of these abnormalities at some point in the course of the illness, but radiographic evidence of the perforation may be absent early on.

The literature is not conclusive on whether insoluble barium contrast medium or water-soluble diatrizoate meglumine (Gastrografin) is the preferred initial study. Gastrografin does not obscure visualization with subsequent endoscopy, and it produces less mediastinal soiling than does barium. It is generally recommended that the initial study use this water-soluble agent; then, if no leak is shown, a barium study may be undertaken to better define the mucosal detail.

Endoscopy, similar to contrast studies, is not an infallible aid in establishing the presence or absence of an esophageal perforation. The size and location of the perforation and the skill of the endoscopist are important factors in the low incidence of false-negative studies. If the accuracy of the endoscopy is in doubt, an esophagogram should be performed.

Helical CT using dilute oral contrast has been reported as a safer, faster, and less manpower-intensive diagnostic exam.[139]

Figure 42-22. Lateral view of the cervical spine revealing air in the retropharyngeal area.

Management

Early diagnosis can best be accomplished if one is aware of the pathophysiology and clinical settings in which esophageal perforations occur. Time is crucial in minimizing the mortality and morbidity of this condition. If the diagnosis is strongly suggested or confirmed, management should include broad-spectrum antibiotics (covering oral flora), volume replacement, and airway maintenance.[133] An emergency surgical consultation should be obtained because prognosis worsens as time passes, with mortality almost doubling in the first 12 hours.[139]

Although operative therapy is standard, nonoperative therapy is an option for patients with well-contained perforations, minimal mediastinal involvement, and without evidence of sepsis.[131] In such cases, the patient is placed NPO for at least 72 hours, broad-spectrum antibiotics are initiated, and usually total parenteral nutrition treatment is begun. The use of nasogastric tubes should be discouraged because they may increase gastroesophageal reflux and worsen the contamination of the mediastinum.[129,139]

KEY CONCEPTS

- Even relatively minor chest wall injuries, such as rib fractures, may result in serious complications in elderly patients and patients with preexisting pulmonary disease.
- Children are more susceptible to pulmonary contusion because of greater compliance of the chest wall.
- Unless there are abnormalities on the initial ECG, there is no need to pursue the diagnosis of myocardial contusion with more sophisticated tests.
- Many patients with myocardial rupture or traumatic aortic rupture survive to reach the hospital and can be salvaged with rapid diagnosis and intervention.
- Pericardial tamponade can be diagnosed accurately before hemodynamic decompensation occurs by standard cardiac ultrasound performed by emergency physicians.
- Chest CT should be considered for patients with mechanisms of injury concerning for blunt aortic injury even in the presence of normal chest radiographs.
- Injury of the esophagus is relatively common with penetrating trauma of the chest or neck. Because the presentation is initially subtle and the potential complications are severe, the diagnosis of esophageal perforation must be actively pursued in cases in which the trajectory of the penetrating wound potentially involves the esophagus.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 43

Abdominal Trauma

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PERSPECTIVE

Background

The management of abdominal trauma should be approached in an organized, vigilant, and knowledgeable manner. Reliance on key clinical features and the timely use of diagnostic procedures significantly improves morbidity and mortality rates. Missed or delayed diagnoses remain the most serious pitfalls in the management of abdominal injuries.[1]

Penetrating Abdominal Trauma

Whether by accident or intention, penetrating trauma can result from a wide variety of weapons or instruments, and certain elements of therapy vary accordingly. The management of penetrating trauma has changed dramatically since 1960, when Shaftan introduced the concept of selective laparotomy and serial observations.[2] Before that time, surgery was mandatory. The careful integration of physical examination and certain diagnostic procedures, notably local wound exploration (LWE), diagnostic peritoneal lavage (DPL), ultrasonography (US), computed tomography (CT), and laparoscopy, now provides the emergency physician and trauma surgeon with an accurate means of determining whether laparotomy should be undertaken. The approach varies according to the clinical status of the patient, the instrument responsible for injury, and the site of penetration. Nonoperative management has gained favor for both stab wounds and gunshot wounds (GSWs) with the intent of reducing the incidence of and morbidity from nontherapeutic laparotomies.[3,4]

Blunt Abdominal Trauma

Blunt trauma to the abdomen (BAT) is a supreme challenge to the emergency specialist's clinical acumen. Historical data may be incomplete, absent, or presumptive. The symptoms and signs can be unreliable and obfuscated by head injury, alcohol, or other toxins. The likelihood of trauma to systems other than the abdomen adds further complexity, underscoring the need for a carefully organized approach.

Epidemiology

Blunt injuries carry a greater risk of mortality than penetrating injuries because they are more difficult to diagnose and are commonly associated with severe trauma to multiple intraperitoneal organs and extra-abdominal systems.

Penetrating Abdominal Trauma

Wounds from stabbing implements occur nearly three times more often than wounds from firearms, but the latter have a significantly greater associated mortality rate and are responsible for 90% of the deaths from penetrating trauma.[5] The small intestine, colon, and liver are, successively, the most likely organs to sustain injury after penetrating trauma.[5] The highest risk of death from penetrating injury occurs among African Americans in the 15- to 34-year-old age range, followed by Hispanic persons in that same age group. The rate for non-Hispanic whites is greatest at 75 years of age and older. The predominant intent is homicide among African Americans and suicide among non-Hispanic whites.[6,7]

The use of firearms in the United States contributes heavily to the morbidity and mortality associated with trauma. The current U.S. civilian population is the most heavily armed in history. Over 42 million U.S. households have firearms, and there are more than 57 million gun owners.[8] The number of homicides committed with firearms exceeds the number of homicides resulting from all other forms of violence combined. More than 850,000 American civilians have been killed by bullets in this century alone, and GSWs continue to occur with an increasing incidence in major U.S. cities.[9]

Blunt Abdominal Trauma

The spleen is the organ most often injured, and in nearly two thirds of these cases, it is the only damaged intraperitoneal structure. The liver is the second most commonly injured intra-abdominal organ, and the intestine is the most likely hollow viscus to be damaged.

The automobile is the major cause of BAT. Motor vehicle crashes and auto-pedestrian crashes have been cited as causes in 50 to 75% of cases, blows to the abdomen in approximately 15% of cases, and falls in 6 to 9%.[10-12]

Pediatrics

Each year in this country, trauma results in approximately 22,000 deaths and accounts for $160 billion of health care expenditures for children to the age of 16 years. Nearly 10% of children admitted to pediatric trauma centers are proven to have abdominal injury, and this category follows only head and thoracic trauma as the cause of injury-related death.[13] Blunt mechanism causes approximately 85% of pediatric injury, although penetrating violence is becoming a greater concern.

As is true with adults, motor vehicle crashes are responsible for most of the morbidity and mortality in cases of trauma in children.[9] Auto-pedestrian accidents and falls out of cars cause a significant percentage of these.

Child abuse continues to gain attention, and deservedly so. It is both common and extremely harmful. Soft tissue, skeletal, and intracranial injuries are most likely, but abdominal injuries occur occasionally and are second only to head injuries as the cause of death. Children in the preverbal stage, generally those younger than 2 years of age, are at greatest risk. The history of trauma is extremely difficult to obtain because of the inability or fear of the child to communicate and the reluctance of parents to divulge information. Injuries inconsistent with the history provided or not in keeping with the child's level of physical maturity should alert the physician to the possibility of child abuse.

PRINCIPLES OF DISEASE

Anatomy and Physiology

The abdominal cavity and its contents can be reached not only through the anterior abdominal wall and lower chest but also through the flank, back, and buttocks. Missiles can also lodge intraperitoneally after traversing proximal extremities. The *anterior abdomen* is defined as that region between the anterior axillary lines from the anterior costal margins to the groin creases. The *low chest* begins at the nipple line or fourth intercostal space anteriorly and the inferior scapular tip or seventh intercostal space posteriorly and then extends down to the inferior costal margins. The *flank* is between the anterior and posterior axillary lines bilaterally from the inferior scapular tip to the iliac crest. The *back* is between the posterior axillary lines, beginning at the inferior scapular tip and extending down to the iliac crest. The intraperitoneal cavity is vulnerable when penetration occurs as high as the fourth intercostal space anteriorly and the sixth or seventh laterally and posteriorly because the diaphragm can ascend to this level during expiration. Likewise, simultaneous thoracic abdominal penetration has been found in 20 to 40% of cases of abdominal thoracic trauma.[14] Scrutiny of entrance and exit sites, as well as wound tracts, is imperative.

Pathophysiology

Penetrating Abdominal Trauma

The instruments responsible for penetrating injuries of the abdomen are varied. Knives, handguns, rifles, and shotguns are at the fore, but flying glass, scissors, arrows, picket fences, horned animals, and the like, although less common, can cause pronounced morbidity as well. Certain impalement injuries caused by fences, stakes, or similar objects can be treated as stab wounds. Likewise, various propelled missiles from lawn mowers, chain saws, and other machinery or resulting from violent weather should be managed as GSWs.

Fragmentation injuries produced by grenades and bombs are rare in this country, but industrial explosions can produce similar injuries, which are best categorized as shotgun-type wounds. BAT from blast effect can coexist in this setting. More widespread acts of terrorism would increase the number of these injuries.

The liver, followed by the small bowel, is the organ most often damaged by stab wounds, in keeping with the surface area each of these structures presents.[15] The frequency of organ injury caused by GSW is greatest for the small bowel, followed by the colon and then the liver.[5] Typically, multiple organ injuries are sustained, notably perforations to bowel. This same pattern is seen in the pediatric patient.

Stab Wounds. Knives are not the sole implements used in stabbings. Ice picks, pens, coat hangers, screwdrivers, and broken bottles, to name a few, have been used by assailants. Stab wounds to the abdomen occur most commonly in the upper quadrants, the left more commonly than the right. They are multiple in 20% of cases and involve the chest in up to 10% of cases. Most stab wounds do not cause an intraperitoneal injury, and the incidence varies with the direction of entry into the peritoneal cavity. Anterior stab wounds penetrate the peritoneum in approximately 70% of cases but inflict a visceral injury in only half of these.[15] Lower chest wounds are associated with a 15% incidence of coincident intraperitoneal damage in addition to the expected high rate of diaphragmatic injuries.[16] Abdominal entries from the flank and back have reported incidences of up to 44 and 15%, respectively.[17,18] The organ injured cannot be well predicted by the site of entry in the abdominal wall. The liver and spleen are the viscera most commonly damaged.

Gunshot Wounds. The science of ballistics is complex, but a few basic principles are helpful in understanding the pathophysiologic processes of these injuries. The magnitude of the injury is proportional to the amount of kinetic energy imparted by the bullet to the victim, according to the following equation:

$$E = \frac{7000\,mv^2}{2\,g}$$

E is the kinetic energy (in foot-pounds), m is the mass of the bullet, v is the velocity of the bullet (in feet per second), and g is gravitational acceleration (in feet per second). In other words, the degree of injury depends on the mass of the bullet and the square of its velocity.[19] Additional factors that affect injury created by a missile include the resistance and viscoelastic properties of the tissue through which it passes, as well as the stability of the missile in this medium. Missile velocities are categorized as low (slower than 1100 ft/sec), medium (1100–2000 ft/sec), and high (faster than 2000–2500 ft/sec); the impact velocity is the most important determinant of wounding capability. The impact velocity depends on the distance between the firearm and the victim, the muzzle velocity, and various characteristics of the missile. At medium and high velocities, the missile has an explosive effect and creates a temporary passage in the tissue along its course. The size of this passage is directly proportional to the specific gravity of the penetrated tissue. This sudden formation of a tract displaces nearby organs and vascular structures, and bone and viscera may be fractured or torn without being directly struck by the missile. Several cases have been reported of an intraperitoneal injury caused by a bullet that remained extraperitoneal throughout its entire course.[20] Solid viscera such as the liver and spleen are more vulnerable to this effect.

High-Velocity Missiles. Wounds from high-velocity missiles involve additional problems. First, external contaminants tend to be dragged into the wound. Second, the closure of the tract immediately after the bullet's passage may lead to an underestimation of tissue damage. Finally, high-velocity bullets can fragment internally. In fact, a missile at any velocity can fragment after contact with bone and cause additional multiple trajectories and injuries. Civilian wounds have usually resulted from low-velocity handguns, but unfortunately a trend toward more destructive weapons such as the .38 and .357 may be occurring.

Shotgun Wounds. The shotgun was designed to strike a small, fast-moving target at close range. Because of the ballistic shape

of the individual pellets, a rapid falloff in velocity occurs, making this weapon ineffective in producing severe wounds at long distances. An initial muzzle velocity of 1300 feet per second drops to 950 feet per second within 20 yards, a decrease of 25%. At close range (<15 yards), however, the shotgun is extremely lethal.

The kinetic energy imparted to the victim depends on the pellet's size, the number of striking pellets, the type and amount of powder, and the barrel choke (constriction). The most important variable is the distance between the shotgun and the victim. At a distance of 10 yards, 19% of the pellets cluster in a 9-inch diameter circle if fired from a full choke (maximum constriction) barrel. At a distance of 20 yards, the circle is approximately double that diameter. Because the kinetic energy is proportional to the square of the velocity, a 25% loss of velocity at 20 yards results in a significant decrease in the damage produced by the blast.

Shotgun wounds were previously classified in three groups according to the range and pattern of distribution. More recently, classification has been according to the pattern of injury on the victim. Based on distance from the weapon to the victim, type I wounds involve a long range (>7 yards) and a penetration of subcutaneous tissue and deep fascia only. Type II wounds occur at a distance of 3 to 7 yards and may create a large number of perforated structures. Type III wounds occur at point-blank range (<3 yards) and involve a massive destruction of tissue. When categorized by pattern, type I wounds produce a spread greater than 25 cm; type II, 10 to 25 cm; and type III, less than 10 cm, respectively, in diameter.[21] The tissue damage is proportional to the specific gravity and inversely proportional to the elastic properties of the affected organ. Thus, the liver is more vulnerable than the lungs to this injury. Close-range shotgun wounds, in addition to the shot, force external contaminants (e.g., clothing and parts of the shell wadding) into the wounds. Type III wounds carry a substantial mortality risk.

Blunt Abdominal Trauma

Several pathophysiologic mechanisms have been described to occur in patients with BAT. First, sudden and pronounced rises in intra-abdominal pressures created by outward forces can cause rupture or burst injury of a hollow organ. Lap-belt restraints produce such a mechanism. Second, the compression of abdominal viscera between the applied force to the anterior wall and the posterior thoracic cage or vertebral column produces a crushing effect. Solid viscera are especially vulnerable to this injury, helping account for the high incidence of liver and spleen injuries in cases of BAT. Crush injuries are more likely to occur with the lax abdominal wall characteristic of elderly and alcoholic patients. Finally, acceleration and deceleration forces affecting both hollow and solid viscera cause organs and vascular pedicles to shear, especially at relatively fixed points of attachment.

Seat Belt Injuries. Unrestrained front and rear seat passengers are at unequivocally greater risk of intra-abdominal injury than their restrained counterparts.[22] The three-point shoulder-lap belt is the most effective restraining system and is associated with the lowest incidence of abdominal injuries, compared with older systems. However, abdominal injuries are still ascribed to shoulder-lap and lap-belt systems. The shoulder belt component can lead to right-sided and left-sided rib fractures for the driver and front seat passenger, respectively, with potential for injury to underlying abdominal viscera. Improper underarm usage of the shoulder belt increases compressive forces to the upper abdomen, particularly in the event of a front-end crash.

Injuries resulting from solitary lap belts are most often to the abdomen. This is true of nearly half the injuries caused by lap belts. The pathogenesis is usually the compression of bowel between the belt and the vertebral column. Occasionally, an acute short closed-loop obstruction occurs along with perforation secondary to the sudden generation of high intraluminal pressures. The resultant injury is primarily a contusion or perforation of the intestines or a tear of the mesentery.

Clinically, two symptom patterns emerge. Approximately one fourth of these patients develop evidence of a hemoperitoneum secondary to mesenteric lacerations. In the remainder, the intestinal injury most commonly involves the jejunum, and the initial signs and symptoms are often absent or considered insignificant. Subsequent delays in diagnosis of up to 8 weeks have been reported. The "seat belt sign," contusion or abrasion across the lower abdomen, is found in less than one third of patients with abdominal injuries caused by lap belts. Its presence, however, is highly correlated with intraperitoneal pathologic lesions.[23] Rupture of the diaphragm, an elusive diagnostic problem, can also occur. Rare cases of acute abdominal aortic dissection with incomplete or complete occlusion have also been described, and injuries to the lumbar spine are not uncommon.[24]

Iatrogenic Injuries. Although well intentioned, diagnostic and therapeutic efforts in patient care are not risk-free. Abdominal injuries may be sequelae of various medical procedures and in certain instances not only are extremely difficult to recognize but may contribute to or cause pronounced morbidity or death. Numerous procedures may cause an iatrogenic injury.

Artificial ventilation can lead to gastric distention, particularly in children. Besides compromising ventilation and increasing the risk of vomiting and aspiration, a significant distention may lead to an esophageal or gastric laceration and perforation. These may occur with bag-mask ventilations, an inadvertent esophageal intubation with a nasotracheal or endotracheal tube, or the mistaken connection of the nasogastric tube to oxygen rather than suction. The esophageal obturator airway and similar devices placed in the trachea cause an airway obstruction and the unintended ventilation of the esophagus and stomach. Esophageal, gastroesophageal junction, and gastric lacerations are evidenced by bloody emesis or nasogastric return. If a gastric perforation occurs and positive-pressure breathing is maintained, a tension pneumoperitoneum with inferior vena cava compression and decreased cardiac output may ensue. External cardiac compressions have produced splenic, hepatic, and gastric injuries. Manual thrusts to clear an airway obstruction, as taught in basic life support courses, and the Heimlich maneuver have caused rib fractures with lacerations and the rupture of abdominal viscera. In cases of a cardiac arrest, these injuries may be occult but life-threatening. If hypotension occurs after cardiopulmonary resuscitation, an abdominal injury and hemorrhage must be considered along with cardiogenic shock.[25]

Tube thoracostomy has resulted in injury to the liver and spleen. These injuries may result from an unknown elevation of the diaphragm on the side of the thoracostomy or the placement of the tube too low in the chest with resulting intra-abdominal penetration. Peritoneal lavage, paracentesis, and peritoneal dialysis have caused a series of complications, especially vascular penetration and bowel perforation. Signs of blood loss from a hemoperitoneum in the former case and peritonitis in the latter will evolve.

A liver biopsy can lead to a hemoperitoneum or hemobilia. Endoscopic procedures of the bowel may cause a hollow viscus perforation and peritonitis, particularly when a biopsy is performed.[26] Peritoneoscopy has been reported to cause small-bowel perforations and iliac vessel lacerations. Barium

enemas have an extremely low incidence of perforation but can be another cause of unexplained peritonitis and pneumoperitoneum.

Pediatrics. Congenital anomalies and intra-abdominal neoplasms may be first discovered after a history of blunt trauma. Coagulopathies (e.g., hemophilia) can contribute to the pathologic condition and complicate therapy after apparent minor trauma to the abdomen.

A child's abdomen has poorly developed musculature and a relatively smaller anteroposterior diameter. These factors increase the vulnerability of a child's abdominal contents to compression between a blunt anterior force and the solid posterior vertebrae. The rib cage is extremely compliant in children and less prone to fractures but nonetheless provides only partial protection against splenic and hepatic injuries.

The liver, spleen, and kidney are the organs most commonly damaged by blunt mechanism of all varieties, and the incidence of injury for each of these three solid viscera is roughly the same. Gastrointestinal tract perforation is not uncommon with blunt trauma, and these injuries may be isolated. In cases of nonaccidental trauma, those injuries seen most commonly are duodenal and small-bowel hematomas and perforations, pancreatic contusions, lacerations and pseudocysts, lacerations and rupture of the liver and spleen, and lacerations of mesenteric vessels.

CLINICAL FEATURES

History

The patient's history may be unobtainable, elusive, or temporarily deferred while resuscitative measures are carried out. When the situation permits and a reliable source is available, obtaining certain information is valuable.

The patient's ability to relate the course of events may be compromised by head or spinal cord injury, alcohol intoxication, mental retardation, hysteria, and exposure to any number of toxins. At times, the trauma may have preceded the onset of symptoms by days or weeks and may have been forgotten or considered trivial by the patient. Witnesses at the scene, particularly paramedical personnel, often provide the most reliable data.

Knowledge of substance exposure or events that could interfere with the clinical evaluation of the patient is helpful. Alcohol or drug use, a head or spinal cord injury, and psychiatric problems are the most common among these factors. Appreciation of comorbid medical conditions, particularly cardiovascular disease and coagulopathies, optimizes fluid and blood component therapy. Finally, when a first responder care team or transferring hospital is involved, the patient's vital signs, physical assessment, preadmittance course, and response to therapy should be obtained. Clinical records and laboratory and radiologic studies obtained at an outlying hospital should be carefully reviewed. The symptomatology in cases of abdominal trauma is twofold. Volume loss may produce orthostatic or frank dizziness, light-headedness, and confusion. A hematic, infectious, acidic, or enzymatic irritation of the peritoneum produces pain. The pain may be clearly present at the outset or delayed for hours to days.

The patient's communication may be dulled or ineffectual, or the subjective sensation of pain may be impaired by a spinal cord injury or an underlying medical problem such as diabetes. Occasionally, intense competing pain at another body site dominates and distracts both the patient and physician away from the abdomen. Abdominal pain can be localized, as it sometimes is in the left upper quadrant with a splenic injury, or diffuse, as in septic peritonitis subsequent to bowel perforation. Referred pain to the right and left shoulder tips or neck can occur with hemoperitoneum, particularly when the patient has been in the Trendelenburg position, allowing the blood to irritate the diaphragm; this most often occurs with hepatic and splenic injuries. Pain referred to the testicle is compatible with a retroperitoneal injury and is seen most commonly with urogenital and duodenal trauma.

Nausea and vomiting can accompany peritoneal irritation or hypovolemia. These can also be caused by an obstruction, as can occur with a duodenal hematoma. Dyspnea sometimes occurs with gastric distention or diaphragmatic irritation or when abdominal contents herniate into the chest, impairing respiratory dynamics.

Penetrating Abdominal Trauma

Stab Wounds. It is helpful to obtain information regarding the mode of injury from the patient, paramedic, or witnesses. The number of stabs inflicted, type and size of the instrument, posture of the victim relative to the direction of assault, estimated blood loss at the scene, time of injury, and response to fluids should be sought. A significant proportion of victims of stab wounds are found under the influence of alcohol or another drug. This state can make obtaining an accurate history a futile effort and further compromise the validity of symptoms and signs.

Gunshot Wounds. As initial stabilization measures are instituted in the emergency department (ED), the emergency physician can elicit certain facts that can contribute greatly to the evaluation of the patient. These include the weapon used, its distance from the victim when shot, the position of the victim in relationship to the weapon when fired, the suspected number of shots, the blood loss at the scene, the amount and type of field fluids administered, and the vital signs during the course of treatment by first responders.

Blunt Abdominal Trauma

With blunt-force injuries, specifically those resulting from vehicular trauma, inquiries should be made regarding the extent of damage to the car; the patient's location within the car; whether the patient struck the steering wheel; whether seat belts were used, and if so, what type; and whether front or side air bags were deployed. The magnitude of injury to pedestrians varies with the speed and size of the striking vehicle. A triad of injuries to the torso, cranium, and lower aspect of the lower extremity has been well described, and pathologic lesions discovered in two of these sites should prompt careful attention to the third. Motorcycle crashes can be placed in one of four categories: frontal, lateral or angular, ejection, or "laying the bike down." Different pathologic lesions can be projected based on the offending mechanism.

Pediatrics

Assessment and management of abdominal injuries in children are based on the same principles as those used in adults. The symptoms and signs are similar and in alert, cooperative patients are valuable. Age-related difficulties in communication, fear-induced uncooperative behavior, or a concomitant head injury, however, make the clinical examination less reliable. In cases of unexplained abdominal tenderness or peritonitis, it is important to inquire about vaginal bleeding or discharge and rectal bleeding and to examine the rectum and vagina for foreign bodies. Such objects may be inserted by inquisitive children or by adults during acts of child molestation.

Physical Examination

Abdominal trauma provokes a wide spectrum of presentations that range from seemingly insignificant symptoms and signs to severe shock and coma. Evidence of abdominal tenderness, peritoneal irritation, gastrointestinal hemorrhage, and hypovolemia not attributable to extra-abdominal causes represents most of the signs suggestive of an intraperitoneal injury. These signs may be initially absent or obscure, and careful attention to the abdomen with serial examinations can aid in making an early, accurate diagnosis.

The physical examination of a hemodynamically unstable patient is performed coincident with therapy, but care and thoroughness are not precluded by these circumstances. When an obvious intracranial, thoracic, or orthopedic injury is present, abdominal symptoms or findings may be obscured, and abdominal injury must always be considered. Chest trauma itself is a risk factor for coincident intraperitoneal pathology. This is particularly true in cases of possible multiple blunt trauma accompanied by a head injury, coma, or obtunded mental status resulting from drug or alcohol ingestion.

The abdomen, then, should neither be ignored nor be the sole focus of the emergency physician. All of the patient's clothing must be removed, and a careful inspection of the patient's body should be conducted, to include the scalp, perineum, skin folds, and beneath the hair. Wounds from penetrating trauma can be exceptionally small, difficult to find, but yet lethal.

Hypotension in the acute stage results from hemorrhage that is most often from a solid visceral or vascular injury. Traumatic pancreatitis may produce significant third-space fluid loss, but hours to days are usually required for this to appear, and shock is an uncommon presentation.[27] When hypotension accompanies significant multiple blunt trauma and is unexplained, one should assume the presence of intraperitoneal hemorrhage until it is excluded. However, a known extra-abdominal source of hemorrhage does not mitigate the need to evaluate the peritoneal cavity. A head injury alone does not explain shock except in cases of profound head injury or in the very small infant for whom traumatic intracranial or extracranial (e.g., cephalohematoma) blood loss may be proportionally substantial.[28]

In cases of penetrating trauma, inspecting the abdomen for entrance and exit wounds may help determine the path of injury. Distention can occur as a result of pneumoperitoneum, gastric dilation, or ileus produced by peritoneal irritation. An ecchymotic discoloration of the flanks (Gray-Turner sign) or umbilicus (Cullen's sign) indicates retroperitoneal hemorrhage, but these signs are usually delayed for 12 hours to several days. Abdominal contusions can result from various implements, and when caused by lap belts, they herald abdominal injuries in one third of cases.

Markedly decreased or absent bowel sounds have traditionally been considered one of the more reliable clinical parameters of intraperitoneal injuries. However, the presence of audible peristalsis, although uncommon, does not rule out ileus or serious injury, and the absence of bowel sounds occurs in up to 20% of patients with a suspected injury from abdominal trauma who prove to have no such injury at laparotomy. In such instances, coexisting electrolyte disturbances or thoracolumbar vertebral body or transverse process fractures may be responsible for the ileus. Auscultation of bowel sounds in the thorax should alert the emergency physician to the presence of a diaphragmatic injury.

Local or generalized tenderness is palpated in approximately 90% of alert patients with an intra-abdominal visceral injury. Local and generalized rebound tenderness and rigidity can be signs of peritoneal irritation and occur less commonly. These signs lack specificity, however, and can be found with lower rib fractures and contusions of the thoracoabdominal wall. These findings or, more important, their absence, are more reliable in alert patients. However, false-positive and false-negative abdominal manifestations have been well demonstrated even in conscious, responsive patients.[29,30]

Rarely, encapsulated bleeding into regions walled off by blood clots or adhesions can form palpable intra-abdominal masses; these usually appear at least several hours later. Severe contusions of the abdominal wall can cause tenderness and voluntary guarding that is localized and usually exacerbated by use of the affected muscle. A palpated mass can represent a rectus hematoma or ventral hernia. Shifting dullness results from a massive hemoperitoneum and is accompanied by signs of shock. A loss of gastric tympany in the left upper quadrant can be found with enlarging splenic injuries. Dullness to percussion over the flank that is not affected by position suggests a retroperitoneal hematoma, but it is an uncommon finding.

A rectal examination rarely reveals blood or subcutaneous emphysema, but the presence of either is highly correlated with abdominal injuries. The evaluation of rectal tone is an important part of determining the patient's spinal cord integrity, and palpation of a high-riding prostate suggests urethral injury.

A nasogastric tube should routinely be placed in the absence of severe maxillofacial trauma to decompress the abdomen, decrease the likelihood of aspiration, and determine whether blood is present. Orogastric placement should be used when a cribriform plate fracture or unstable midface fractures are suggested to prevent intracranial insertion. Foley catheters are useful in unstable patients for following renal output and rapidly obtaining urine samples to search for blood, myoglobin, and toxins.

Thus, a number of signs are valuable in assessing the patient with abdominal trauma. Although the presence of physical findings makes intraperitoneal injury more likely, their absence does not preclude serious pathology, and none is exclusively diagnostic of a specific injury. Extensive observation and the use of certain laboratory procedures greatly help prevent erroneous or missed diagnoses.

Penetrating Abdominal Trauma

Stab Wounds. Serial physical examinations performed by the same observer are gaining acceptance in centers where these have been found useful, particularly with patients who are alert, communicative, and neurologically intact. The presence of intoxicants does not necessarily preclude reliance on examination but may undermine its value.[31] In other series, patients with impressive physical findings after penetrating trauma to the abdomen have undergone exploratory laparotomy, with negative results in 14 to 28% of cases.[32] Moreover, up to one third of patients with significant intra-abdominal injuries have no suggestive physical signs, particularly when a retroperitoneal injury has occurred.[33]

Gunshot Wounds. As with blunt or other modes of penetrating trauma, there is dispute regarding the value of the physical examination of patients with abdominal GSWs. In various series, 20% of patients with a documented intraperitoneal injury had no peritoneal signs before exploration.[33] Moreover, objective physical findings suggestive of intra-abdominal damage have been misleading and falsely positive in 15% of patients in whom laparotomy revealed no injury. Other authors contend that selective management can be undertaken safely when physical examination is the fundamental evaluative measure.[4,31]

Blunt Abdominal Trauma

Overall, the accuracy of the physical examination in patients with BAT is 55 to 65%.[29] The initial presentation may be exceptionally benign in cases of blunt intra-abdominal injury. The most reliable symptoms and signs in alert patients are pain, tenderness, and peritoneal findings, particularly when risk factors for abdominal injury are present. When altered sensorium intercedes, the physical signs become less reliable. Frequent evaluations by the same examiner are indicated even in alert patients but especially in sensorium-altered patients, particularly as they become more lucid.

DIAGNOSTIC STRATEGIES

Laboratory

Hematologic and chemical values are of limited use in the treatment of the acutely traumatized patient.[34] These laboratory tests should be considered adjuncts to diagnosis and not substitutes for clinical assessment.

Hematology

Hematocrit. The hematocrit reflects baseline value, extent of and time from hemorrhage, exogenous fluid administration, and endogenous plasma refill. The last of these is a physiologic compensatory shift of extracellular fluid into the intravascular space, the intent of which is to restore the original blood volume. Based on a study of volunteers sustaining a 10 to 20% blood loss, this restoration proceeds at a rate of only 40 to 90 mL/hr for the first 10 hours and requires 30 to 40 hours for completion.[35] However, patients evidencing hemorrhagic shock with a blood loss of at least 40% demonstrate much faster plasma refill rates, estimated as high as 1500 mL in the first 90 minutes after injury, with significant decreases in hematocrit within this period. Although the hematocrit is an easily acquired measure, it is often a conundrum when viewed in isolation, and serial determinations are more helpful.

White Blood Cell Count. The white blood cell (WBC) count has little discriminatory value in cases of abdominal trauma, particularly its acute phase.[34] The WBC count may be normal or may show a modest leukocytosis (12,000–20,000/mm^3 with or without left shift), which can occur in the setting of multisystem trauma as a result of stress-induced demargination in the absence of any intra-abdominal process or may result from tissue injury, acute hemorrhage, or peritoneal irritation.

Chemical

Pancreatic Enzymes. Neither serum amylase nor lipase is useful in the evaluation of acute abdominal trauma. Normal levels do not exclude a major pancreatic injury, and elevated values may be caused by any of an assortment of reasons in addition to an injured pancreas. The use of serum amylase isoenzyme measurements has not appreciably improved accuracy. Nontraumatic causes of hyperamylasemia include several diseases and the use of alcohol, narcotics, and various other drugs. Amylase or lipase may also be elevated with pancreatic ischemia produced by the systemic hypotension that often accompanies trauma. Clearly, these enzymes are neither highly specific nor sensitive for pancreatic injuries. Elevated or rising levels may indicate damage but in themselves are not conclusive.[36] In these cases, clinical correlation and further investigation are indicated.

Base Deficit. Metabolic acidosis in the setting of trauma can suggest the presence of hemorrhagic shock. This can be witnessed chemically as a decreased serum bicarbonate level, increased base deficit, or elevated serum lactate level. Although normal values do not exclude abdominal injury, substantive abnormalities, such as a base deficit greater than or equal to 6, may be predictive. These findings should be considered in clinical context, because the resolution of the laboratory findings will lag behind the clinical improvement of the patient.

Liver Function Tests. Elevated serum transaminases can result from hepatic trauma but do not distinguish minor contusions from severe injury.[37] Alternatively, these may be symptomatic of alcohol-induced liver damage. Elevated liver transaminase levels may be useful for screening pediatric patients for intentional trauma (see Chapter 63).

Toxicology Analysis. Screens for ethanol and drug use are often used in trauma centers. Their utility in the management of abdominal trauma per se has not been established, particularly in patients with normal mental status.[38] Positive study findings may prompt the emergency physician to interdict and the patient to decrease the recidivistic use of ethanol or drugs.

Radiology

Resuscitation and initial stabilization measures must always precede abdominal radiographic studies. Basic plain radiography in the trauma bay is of limited value, although a chest film to screen for significant hemo- or pneumothorax before the patient is transferred to the CT scanner facilitates early stabilization of these injuries. Any potential cervical or lower spinal injury must be presumed present based on the mechanism of the trauma, the patient's symptoms, and physical examination findings. A portable cross-table radiograph in the trauma bay is insufficient to exclude any such injury. In the hemodynamically stable patient, depending on physical findings and whether the patient is able to communicate about pain, pelvis radiographs may be deferred to the radiology suite or omitted entirely (see following section). In patients whose symptoms and signs demonstrate a likely need for exploratory laparotomy, delay to operation because of radiologic diagnostics is permissible only when the patient has been stabilized and only if studies might aid in determining management. Adequate radiographic detail cannot be achieved in an uncooperative patient. Trained personnel must accompany any patient whose condition might deteriorate precipitously. Moving the patient from the relative security of the trauma resuscitation room to the radiology suite creates increased risk for the patient because of the relative decrement in monitoring and personnel in attendance.

Plain Films

The chest radiograph and anteroposterior pelvic films can be invaluable in some cases of penetrating and blunt trauma, depending on the presentation and results of initial evaluation. Plain abdominal films can demonstrate the location or track of the missile(s) in gunshot and shotgun injury but are of little value in blunt trauma or nonprojectile penetrating trauma, particularly if CT of the abdomen is anticipated. If plain radiography of the abdomen is done, the finding of rib, pelvic, vertebral body, or transverse spinous process fractures in the blunt trauma patient warrants special consideration for nearby visceral damage.

Very small quantities of readily detectable free intraperitoneal air are present in most patients with gastric, duodenal bulb, and colonic perforations but in fewer than one fourth of those with jejunal and ileal perforation. These are seen more readily on CT than plain films. Free intraperitoneal air uncommonly can be generated by mediastinal or pulmonary injury,

as well as by barotrauma, and thus its presence is not pathognomonic of hollow viscus perforation. Intraperitoneal air is mobile, and to maximize visualization the patient should be kept in the appropriate upright or decubitus position for 10 to 15 minutes, if this is tolerable, before upright chest or decubitus abdominal radiographs are obtained. In upright films, air is located under the diaphragm or the central tendon of the diaphragm anteriorly. In supine films, air tracks under peritoneal attachments, such as the falciform ligament and urachus, up to the anterior abdominal wall. On films in which the patient is in a lateral decubitus position, air is located in the superior flank and outlines the lateral liver edge (Fig. 43-1). In cases of gastric perforations, air may be limited to the lesser sac. A rupture of a retroperitoneal hollow viscus can be detected by a stippling pattern outlining the duodenum, kidney, or psoas muscle (Fig. 43-2). Extraperitoneal colonic perforations may extravasate air, which outlines the psoas muscle and perinephric region. All of these injuries are much more readily identified and localized using abdominal CT.

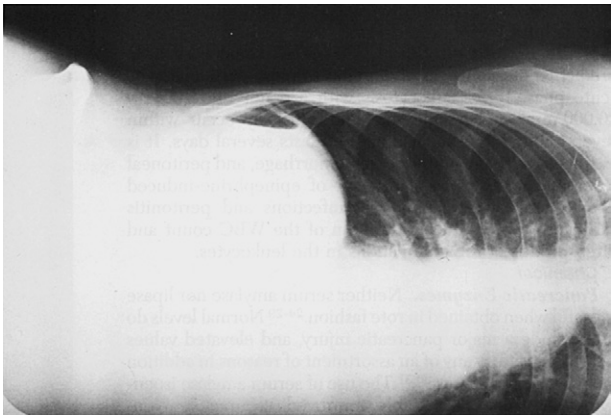


Figure 43-1. Demonstration of free intraperitoneal air on left lateral decubitus film. This is the preferred decubitus position because it avoids confusion with the gastric bubble and splenic flexure.

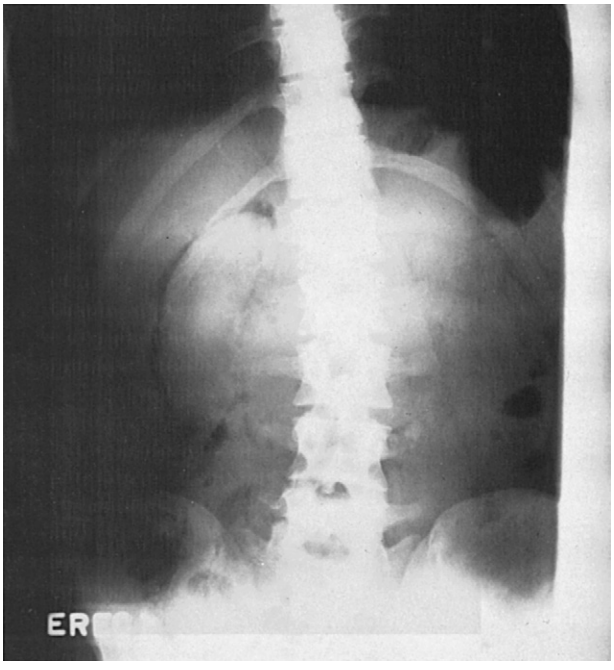


Figure 43-2. Erect film demonstrates the soap bubble appearance of retroperitoneal air outlining the right kidney. Duodenal perforation is the responsible pathologic condition.

Foreign bodies and missiles are easily identified on abdominal films. Therefore, their absence without a known exit wound warrants further search of other body cavities (e.g., the chest, upper thighs, buttocks). A ricochet off the spine or pelvis into the chest or proximal extremities can occur. An entry into the vascular system may carry the object toward and into the right side of the heart or peripherally into the arterial tree. It may also find its way into the gastrointestinal tract and either produce obstruction or pass through unnoticed.

Computed Tomography

Over the last 30 years, CT has continued to advance its place among diagnostics for trauma. Evolution to 16- and 64-slice helical and spiral scanners has improved resolution and greatly decreased the time required for the scan itself.[39]

Advantages. In most situations, CT has supplanted DPL, because of its higher predictive ability for operative lesions and the fact it is noninvasive. CT can define the injured organ and the extent of the injury. It is most accurate for solid visceral lesions and accurately discerns the presence, source, and approximate quantity of intraperitoneal hemorrhage (Fig. 43-3). It can demonstrate active bleeding from the liver or spleen and can be used to determine whether therapeutic angiographic embolization is indicated.[40] CT also evaluates the retroperitoneum (Fig. 43-4), an area not sampled by DPL, as well as the vertebral column and can be readily extended above or below the abdomen to visualize the thorax or pelvis.[41] CT also provides definitive evaluation for most possible injuries to the urinary tract, including renal artery injury.[42] It can also detect other vascular hemorrhage and obviate the need for angiography in some patients.[43] CT is particularly helpful in guiding nonoperative management of solid organ damage.[44-46] This includes as-needed follow-up studies of convalescing patients with these injuries. It has also proven effective when incorporated in delayed fashion for patients with decreasing hematocrit, increasing base deficit, or subtle examination changes. By minimizing the incidence of nontherapeutic laparotomies for self-limited injury to the liver or spleen, it decreases morbidity and cost attendant to this operation.[47] Increasingly, trauma centers are using CT with intravenous (IV) contrast only, as it has been shown that little additional

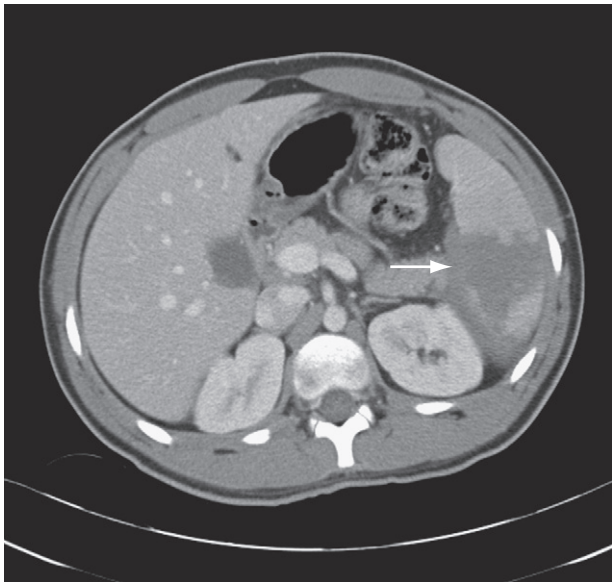


Figure 43-3. Grade 4 splenic laceration (*arrow*).

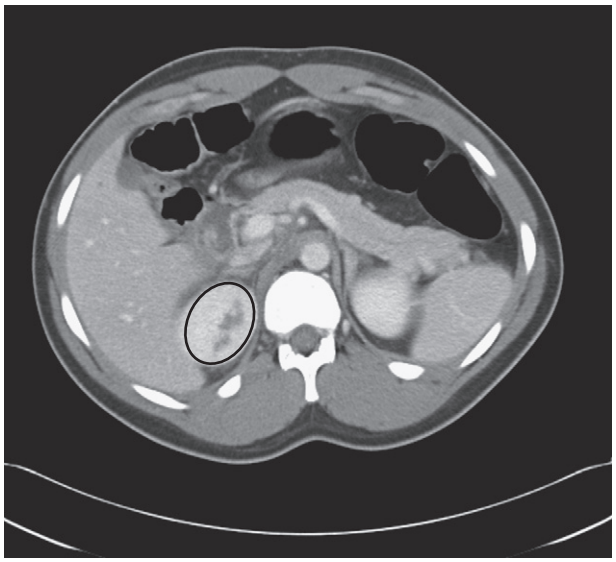
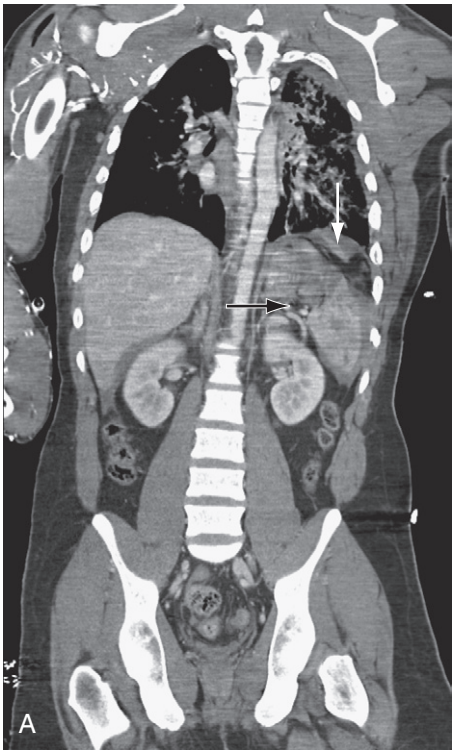


Figure 43-4. Grade 3 right renal laceration (*encircled*).



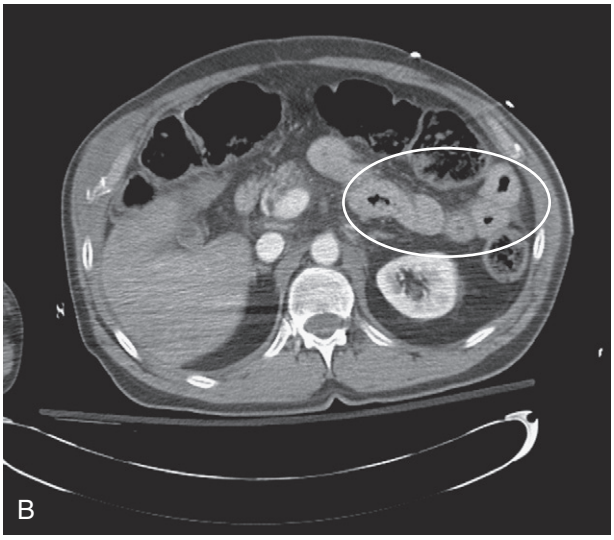


Figure 43-5. **A.** Grade 4 splenic laceration (*black arrow*) with diaphragmatic rupture (*white arrow*) **B.** Small-bowel edema concerning for hollow viscus injury (*encircled*).

information is provided by the addition of oral contrast, which delays scanning and may pose an aspiration risk for the patient.[48,49]

Disadvantages. Disadvantages of CT include its insensitivity for injury of the pancreas, diaphragm, small bowel, and mesentery, although detection of these injuries is improving[48,49] (Fig. 43-5A and B). These latter two are particularly worrisome because isolated coincidental hollow viscus injury in patients with blunt trauma, although uncommon, is not rare, and increased morbidity and death can ensue if diagnosis is missed or goes undetected for a prolonged period. Findings on CT scans, including the possible quantity of hemoperitoneum or the presence of isolated free fluid, are not able to forecast well the need for operative intervention.[50] Complications can result from IV contrast administration or uncommonly from contrast material administered orally.[51] Moreover, oral contrast delivery to opacify the bowel is infrequently useful and often omitted.[48,52-54] Oral contrast is not necessary in the follow-up evaluations of stable splenic injuries.[45,46]

Technique. The technique for CT is reasonably standardized, but certain conventions are debated. The studies should begin in the low chest and be taken through the pelvis. If chest scanning is also required, a single continuous scan is obtained from the root of the neck to the floor of the pelvis. "Quick look" but less thorough studies are not effective and should be avoided, and preliminary reads from the CT control room do not have the added accuracy of reconstituted scans and may, therefore, miss subtle injuries such as intimal tears of the thoracic aorta. Most centers perform enhanced (IV contrast) and nonenhanced scans because the latter alone may not demonstrate intraparenchymal hematomas well. Other practitioners believe that the noncontrast portion contributes little other than time to the procedure.

Contrast Studies

Contrast studies with a water-soluble medium (e.g., Gastrografin) can be helpful in cases of suggested gastric, duodenal, and rectal perforations (Fig. 43-6). Barium mixtures should be used to visualize intramural duodenal hematomas.[55] CT may be able to discern duodenal hematomas and can distinguish these from perforations.[56]

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is usually impractical and sometimes impossible to perform in the acute phase of multiple blunt trauma. Currently, in acutely injured trauma patients, MRI should be reserved for the evaluation of spinal fractures and elusive diaphragmatic defects.

Angiography

Angiography, a time-consuming procedure, is usually reserved for the unstable patient with blunt trauma and pelvic fracture in whom it can be used to embolize bleeding vessels (Fig. 43-7). It can be a means of staunching solid visceral hemorrhage from blunt trauma, notably of the spleen,[39] and has been used

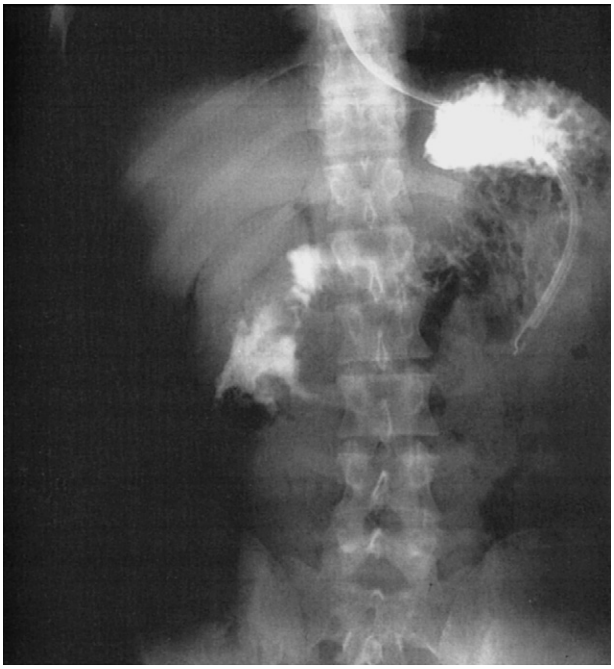


Figure 43-6. Gastrografin study demonstrating rupture of the second portion of the duodenum with extravasation of contrast material.

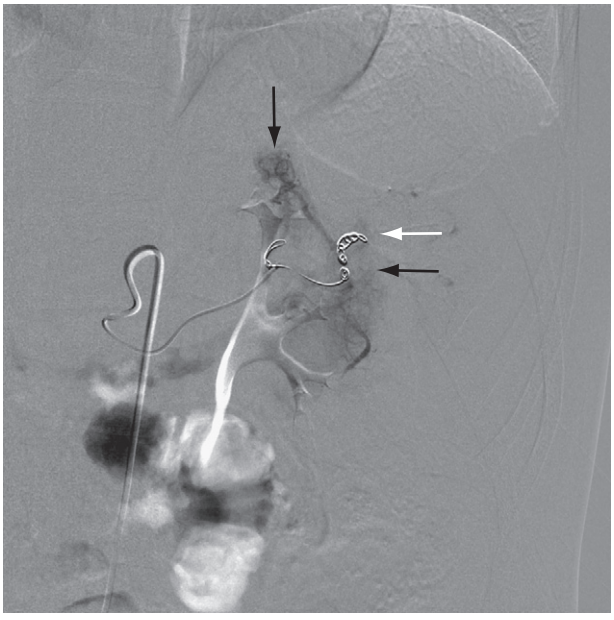


Figure 43-7. Angioembolization of splenic laceration. Note coil in the splenic artery (*white arrow*) and blush representing active hemorrhage stemming from two branches (*black arrows*).

rarely for diagnosing intraperitoneal and retroperitoneal hemorrhage after trauma by a penetrating mechanism.[23] Angiography can also be used in the further workup of a patient in whom vascular pedicle injury is possible, particularly of the kidney.

Bedside Procedures

Ultrasonography

Ultrasonography's primary role is detecting free intraperitoneal blood after blunt trauma. This is accomplished by a focused assessment with sonography for trauma (FAST) US examination of Morrison's pouch, the splenorenal recess, and the pouch of Douglas, which depend on portions of the intraperitoneal cavity where blood is likely to accumulate (Fig. 43-8A–E). Anechoic areas caused by the presence of blood are best visualized when contrasted against solid organs (e.g., liver, spleen, and kidneys). With penetrating mechanisms, an extended FAST (E-FAST) US adding visualization of the pleura can help in the evaluation of the pericardial space and intraperitoneal spaces and detect pneumothorax.[57] US has also been used to inspect thoracoabdominal wound tracts with some success.[58]

Advantages. Ultrasonography carries a host of advantages. It is a portable instrument that can be brought to the bedside in the trauma resuscitation area. Studies of the pericardial, intraperitoneal, and thoracic spaces can be accomplished in less than 5 minutes. FAST US has a sensitivity in detecting as little as 100 mL and, more typically, 500 mL of intraperitoneal fluid that ranges from 60 to 95% in most recent studies, and the specificity for establishing hemoperitoneum is excellent.[59] Therefore, when time is precious in the critical patient, the FAST can provide rapid answers to the key question in the decision matrix, which is whether hemoperitoneum is present. Unlike DPL, the FAST can evaluate intrathoracic structures, is noninvasive, and can be performed serially and by multiple technicians. Unlike CT, it is not a potential radiation hazard and does not require administration of contrast agents. Accuracy correlates with length of training and experience, but expertise can be readily achieved in emergency medicine and surgical training programs.[60] Serially performed FAST increases its diagnostic accuracy for organ injury in patients with BAT.[61,62] Furthermore, E-FAST adds thoracic windows to detect the presence of pneumothorax in patients presenting after either penetrating or blunt abdominal trauma. These additional views detect pneumothorax with a sensitivity of almost 59% and a specificity of up to 99% compared with CT, but more importantly it is three times more sensitive than a portable supine chest radiograph done in the trauma bay, which has a sensitivity of only 20%.[63] Newer studies advocate adding sonographic contrast to further delineate solid organ injuries with minimal hemoperitoneum, especially those of the spleen and liver, which might be amenable to nonoperative management.[64-66] Overall, US can serve as an accurate, rapid, and less expensive diagnostic screening tool than DPL or CT.[67-70]

Disadvantages. The FAST study does not image solid parenchymal damage, the retroperitoneum, or diaphragmatic defects well. It is technically compromised by the uncooperative, agitated patient, as well as by obesity, substantial bowel gas, and subcutaneous air. Indeterminate studies require follow-up attempts or alternative diagnostic tests.[62] It is less sensitive and more operator-dependent than DPL in revealing hemoperitoneum and cannot distinguish blood from ascites. For unclear reasons, US has a high (31%) false-negative rate in detecting hemoperitoneum in the presence of pelvic fracture.[71] The FAST study, as well as DPL, does not detect the presence of solid parenchymal damage if free intraperitoneal blood is absent, as in subcapsular splenic injury.[71,72] Finally, US is poor at recognizing bowel injury in which hemorrhage tends to be inconsequential, and failure to diagnose hollow viscus perforation in a timely manner can have catastrophic results.[73]

Diagnostic Peritoneal Lavage

Although largely supplanted by the FAST examination and CT, DPL still has a role in certain cases.

DPL comprises two interrelated steps. The first is the attempted aspiration of free peritoneal blood. The recovery of

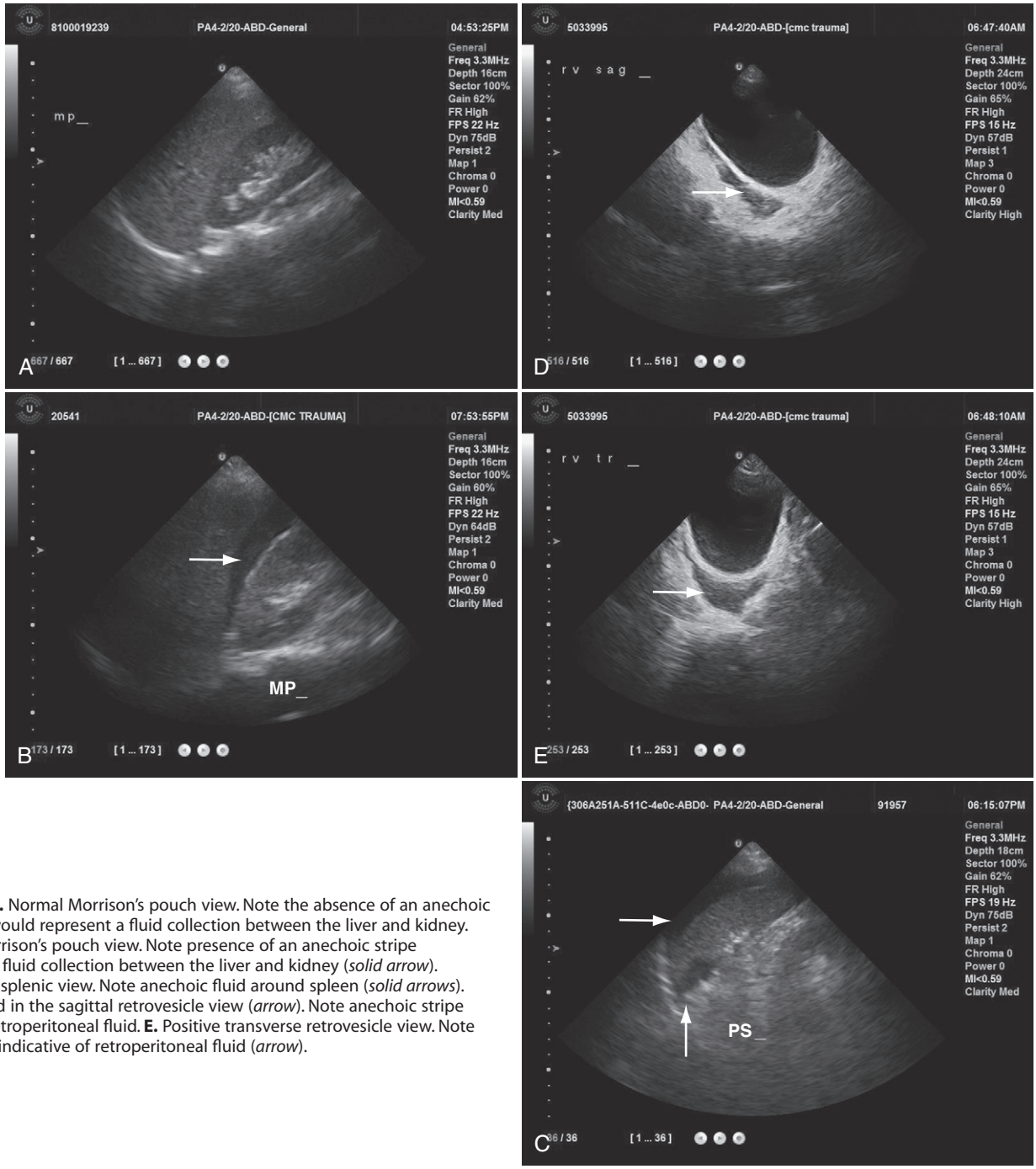


Figure 43-8. **A.** Normal Morrison's pouch view. Note the absence of an anechoic stripe, which would represent a fluid collection between the liver and kidney. **B.** Positive Morrison's pouch view. Note presence of an anechoic stripe representing a fluid collection between the liver and kidney (*solid arrow*). **C.** Positive perisplenic view. Note anechoic fluid around spleen (*solid arrows*). **D.** Positive fluid in the sagittal retrovesicle view (*arrow*). Note anechoic stripe indicative of retroperitoneal fluid. **E.** Positive transverse retrovesicle view. Note anechoic area indicative of retroperitoneal fluid (*arrow*).

10 or more milliliters of frank blood from the peritoneum is a strong predictor of intraperitoneal injury, and the procedure is then terminated. If aspiration findings are negative, lavage is conducted in which the peritoneal cavity is washed with saline. This fluid is introduced by catheter, recovered by gravity drainage, and analyzed. The sole absolute contraindication to DPL is the established need for laparotomy. Relative contraindications include prior abdominal surgery or infections, coagulopathy, obesity, and second- or third-trimester pregnancy.

The lavage catheter may be introduced into the peritoneal space by a closed method in which the catheter is inserted in a blind percutaneous fashion by the Seldinger technique; a semiopen technique in which sharp and blunt dissection to the rectus fascia is followed by Seldinger-based delivery of the catheter; and an open technique, which extends the semiopen method through the rectus fascia with direct visualization of the peritoneum (Table 43-1).[74]

Advantages. In cases of blunt trauma, DPL's primary remaining use is the triage of the patient who is hemodynamically unstable and has multiple injuries with an equivocal FAST examination. In this complex scenario, DPL can promptly reveal or exclude the presence of intraperitoneal hemorrhage and can serve as an indication for laparotomy. Rarely, DPL is used to discern potentially serious bowel perforations in patients who are poor candidates for serial clinical observations (e.g., those with coma) and for whom other diagnostic methods can be unreliable.[75]

After a stab wound to the abdomen, low chest, flank, or back, DPL can meet three needs: (1) immediate disclosure

Table 43-1 Preferred Site of Diagnostic Peritoneal Lavage

CLINICAL CIRCUMSTANCE	SITE	METHOD
Standard adult	Infraumbilical midline	C or SO
Standard pediatric	Infraumbilical midline	C or SO
Second- and third-trimester pregnancy	Suprauterine	FO
Midline scarring	Left lower quadrant	FO
Pelvic fracture	Supraumbilical	FO
Penetrating trauma	Infraumbilical midline*	C or SO

*The stab wound or gunshot wound site should be avoided.
C, closed (percutaneous Seldinger technique); FO, fully open; SO, semiopen.
From Marx JA: Peritoneal procedures. In Roberts JR, Hedges JR (eds): Clinical Procedures in Emergency Medicine, 4th ed. Philadelphia, Saunders, 2004, p 850.

Table 43-2 Diagnostic Peritoneal Lavage Red Blood Cell Criteria (per mm³)

	POSITIVE	INDETERMINATE
Blunt trauma	100,000*	20,000–100,000
Stab wound		
Anterior abdomen	100,000	20,000–100,000
Flank	100,000	20,000–100,000
Back	100,000	20,000–100,000
Low chest	5000–10,000	1000–5000
Gunshot wound	5000–10,000	1000–5000

*In a hemodynamically stable patient with pelvic fracture and positive or equivocal red blood cell count, computed tomography should be obtained to corroborate or refute intraperitoneal injury.

of hemoperitoneum, particularly in a patient who may have mediastinal or pulmonary causes of or contributors to hypotension, (2) determination of intraperitoneal organ injury, and (3) detection of isolated diaphragmatic violation. Laparotomy is undertaken more commonly on clinical grounds for GSWs. In these situations, DPL can serve these same tasks, but it is used far less often.[76]

Disadvantages. The morbidity associated with DPL occurs at a low rate and can be categorized as local or systemic infection, intraperitoneal injury, and technical failure. Wound complications, including hematoma and infection, occurred in 0.3% of cases in two large reviews.[77]

Technical failure can result in an inaccurate study and difficulty with fluid collection. A faulty technique with inadequate hemostasis or the insertion of the catheter through an abdominal wall hematoma can create a hemoperitoneum of sufficient magnitude to produce positive results. In addition, DPL is exquisitely sensitive for hemoperitoneum and in a hemodynamically stable patient can lead to unnecessary laparotomy. False-negative interpretations can result from the failure to recover lavage fluid. This can occur in the following circumstances[74]: (1) inadvertent placement of the catheter into the preperitoneal space, (2) compartmentalization of fluid by adhesions, (3) impedance of fluid egress by obstructing omentum, and (4) large diaphragmatic tears typical of blunt mechanism that permit lavage fluid to move from the intraperitoneal to the intrathoracic cavity.

Results. A battery of hematologic, chemical, enzymatic, and microscopic tests has been applied to peritoneal aspirate and lavage effluent. Gross inspection of the effluent alone is considered neither adequate nor reliable. There is little correlation between fluid color and cell count.

In cases of blunt trauma, the aspiration of 10 mL or more of blood has a positive predictive value of greater than 90% for intraperitoneal injury, predictably solid visceral or vascular, and is responsible for approximately 80% of true positive DPL findings in blunt trauma.[77] The red blood cell (RBC) count of the lavage fluid is the next most widely used and accurate parameter (Table 43-2).

In cases of blunt trauma, an RBC count exceeding 100,000/mm³ is considered positive and generally specific for injury. However, while sensitive to the presence of injury, it may detect self-limited pathology for which laparotomy is unnecessary.

In patients with pelvic fractures, there is a well-known association between false-positive peritoneal lavage in the presence of retroperitoneal hematoma and pelvic fracture.[78] This is ascribed to tears in the posterior peritoneum, diapedesis of RBCs across the peritoneum into the peritoneal cavity, or dissection of a retroperitoneal hematoma out of the pelvis to the anterior abdominal wall. However, the key aspect in the setting of pelvic fracture is a positive aspiration finding because this presages active intraperitoneal hemorrhage in more than 85% of cases.[79] CT, often preceded by the FAST examination, is the standard method by which pelvic fracture with possible intraperitoneal or retroperitoneal hemorrhage is evaluated.[80]

With anterior abdominal stab wounds, aspiration of 10 mL of gross blood or the return of lavage fluid with an RBC count greater than 100,000/mm³ carries a sensitivity exceeding 90% (see Table 43-2).[81] The incidence of visceral injury with counts less than 100,000/mm³ ranges from 1 to 29%. It is recommended that patients with equivocal RBC counts be carefully observed for 12 to 24 hours.[82] Most injuries associated with RBC counts less than 100,000/mm³ are to hollow viscera, and clinical manifestations of these should develop within this observation period. Some advocate lowering the threshold to 10,000 RBC/mm³ to decrease missed hollow viscus injury.[83] However, others cite an increased negative laparotomy rate with the lowered threshold and instead advocate adding a WBC count above 500/mm³ or the presence of bile or amylase to the 100,000/mm³ cutoff to better diagnose these injuries.[81]

With lower chest stab wounds, a positive RBC count of 5000 to 10,000/mm³ should be considered as evidence of diaphragmatic injury. Because of the more serious nature and greater likelihood of an injury with abdominal gunshot wounds, RBC counts of 5000/mm³ are advocated as the cutoff, because these signal peritoneal penetration, if not injury.[77] Increasingly, laparoscopy has supplanted DPL for the purpose of identifying or excluding diaphragmatic injury in lower chest penetrating trauma.

WBCs enter the peritoneal cavity as part of shed blood or in response to an inflammatory stimulus. However, this finding lags after injury by 3 to 6 hours. Initial elevated counts greater than 500/mm³ are nonspecific and unhelpful.[84] At no time after injury can an isolated elevated WBC count be considered to accurately indicate significant intra-abdominal injury, and its use, therefore, is not recommended.

Although used in the past, elevations in lavage amylase and the presence of bile are nonspecific.

Other parameters, such as Gram's stain of lavage fluid, are not of diagnostic value.

Local Wound Exploration

Because stab wounds do not reach the peritoneum in a significant number of cases, local wound exploration (LWE) is useful in determining the depth of penetration. The wound should

be infiltrated with a local anesthetic containing epinephrine and thoroughly prepared for exploration. The stab wound may be extended if required and then carefully visualized through each successive layer of tissue. Blind probing with digits, instruments, or cotton-tipped swabs is inaccurate, unless the peritoneal cavity is obviously freely entered. Blind probing of chest injuries adds no potential additional information and may be hazardous. If LWE indicates that the peritoneum is violated, further diagnostics are indicated. Likewise, when the end of the wound tract cannot be determined clearly, peritoneal entry must be presumed. When the stab wound is documented to be superficial to the abdominal cavity, the patient can be safely discharged home after appropriate wound care.[85]

LWE is generally advocated in cases of anterior abdominal stab wounds, but in other areas the decision is less clear. Abdominal, flank, and back wounds have been evaluated with this method, particularly when the entry is more superficial.[17,18] The flesh of obese or heavily muscled patients in particular can present technical problems and decrease the reliability of exploration while increasing its risk. Wound explorations in patients with multiple entrances are not economically justifiable, and peritoneal penetration should be assumed. Deep exploration over the thoracic cage is precluded by attendant complications to neurovascular structures and pleura. However, careful inspection of superficial chest wounds (e.g., slash wound) is safe and can provide valuable data. CT, laparoscopy, or thoracoscopy is occasionally used in lieu of LWE.

Special Procedures

Laparoscopy

Laparoscopy is increasingly finding a role in some trauma centers. General anesthesia in an operating suite is required. Laparoscopy has been most useful in assessing penetrating trauma, especially for injury to the diaphragm and intrathoracic abdominal organs.[86] It has a reported sensitivity of 87.5% and specificity of 100% for detection of diaphragmatic injury after PAT, with a positive predictive value of 100% and negative predictive value of almost 97%.[87] Organs repaired via the laparoscope include the diaphragm, solid intraperitoneal viscera, stomach, and small bowel. Wound tracts have been assessed as accurately as by LWE. Very little experience in blunt trauma has been documented thus far.

Drawbacks of laparoscopy include poor sensitivity for hollow visceral injury, notably to the small bowel, and difficulty in assessing the retroperitoneum and extent of damage to the liver and spleen.[88] Complications can result from trocar misplacement. If the diaphragm has been violated by the original trauma, pneumothorax or tension pneumothorax can occur during the insufflation phase. At this time, the greatest value of laparoscopy is in the evaluation and management of equivocal penetrating wounds to the thoracoabdominal region in stable patients. This approach can realize a reduced incidence of nontherapeutic laparotomy.[88,89]

DIFFERENTIAL CONSIDERATIONS

Trauma versus Medical Condition

Medical and traumatic pathologic conditions can be coincident or lead one to the other. For instance, hypoglycemia or a generalized convulsive seizure may precipitate a motor vehicle crash, and the patient's altered mental status may incorrectly be ascribed to closed-head injury, delaying diagnosis of the medical condition. Patients with infectious mononucleosis can experience splenic rupture after relatively trivial trauma, and presentation may be delayed. Finally, patients who have premorbid coagulopathy or who are on therapeutic anticoagulation may sustain serious intracranial hemorrhage from otherwise unconcerning head trauma.

Single versus Multisystem Trauma

Emergency physicians must be wary and not miss the proverbial forest for the trees. For instance, the pedestrian struck by a car who has an alleged isolated tibiofibular fracture may well harbor significant intra-abdominal pathology as well, irrespective of a nontender abdomen.

Single versus Multiple Intraperitoneal Organ Injury

There has been an increasing trend toward nonoperative management of known intraperitoneal solid organ injury, specifically of the spleen and liver. It must be remembered, however, that coincident hollow viscus pathologic lesions may exist but not be discernible initially to clinical examination or certain diagnostic studies.

Intraperitoneal Injury versus Necessary Laparotomy

Formerly, suspicion or knowledge of any intraperitoneal injury mandated laparotomy. Now, diagnostic effort is appropriately aimed at determining whether surgery is necessary or whether the injury is self-limited and does not require repair measures.

MANAGEMENT

General Measures

Field Treatment

The field approach to multiple or serious trauma focuses on rapid transportation to a capable receiving ED. The initial measures taken vary with the need for active airway management, the presence of concomitant injuries, and the skills of the first responder personnel. Hemorrhage is the major life threat in cases of PAT or BAT, and two large-bore IV lines should be inserted in transit when possible. Penetrating wounds and eviscerations in particular should be covered with sterile dressings. Contact should be made with the base-station physician to communicate pertinent matters of the history, vital signs, treatment measures and their effects, and the estimated time of arrival.

Emergency Department

The general principles of trauma care apply (see Chapter 33). The use of diagnostic aids for abdominal trauma should be carefully restricted according to the patient's stability and the usefulness of the information sought in guiding management. Those patients who do not require immediate laparotomy will likely undergo one or more diagnostic procedures to determine whether abdominal injury exists and, if so, whether operative intervention is necessary.

Thoracotomy. Thoracotomy and subsequent cross-clamping of the descending aorta have been used to stabilize patients with thoracoabdominal injuries and profound hypovolemic shock. However, it is rarely lifesaving in the ED (see Chapter 33).

In a patient with massive abdominal injuries and hypotension secondary to a hemoperitoneum, the primary purpose of

aortic cross-clamping is to shunt available blood into the coronary and cerebral circulation during resuscitation. Second, it is helpful in providing proximal bleeding control of certain vascular and parenchymal injuries, although continued bleeding can occur via collateral flow, until direct clamping, packing, or repair is achieved. Third, it can allow direct atrial access for rapid fluid administration. Finally, it has been advocated as a prophylactic measure in the operating room before laparotomy is performed for a massive hemoperitoneum. In certain instances, abdominal decompression, particularly in the face of a vascular injury, may result in worsening shock and death.

Antibiotics. An intestinal perforation and spillage can occur after blunt or, more commonly, penetrating trauma to the abdomen. Anaerobes and coliforms are the predominant organisms found. Antibiotics given prophylactically have been demonstrated to be effective in decreasing the incidence of intra-abdominal sepsis and should be given as soon as such an injury is suggested. A single preoperative dose of a broad-spectrum antibiotic or combination of antibiotics that covers both aerobic and anaerobic organisms, such as piperacillin-tazobactam (3.375 mg IV), is recommended.[90,91]

Penetrating Abdominal Trauma: Stab Wounds

Diagnostic Studies

The purpose of diagnostic studies is to determine whether the peritoneal cavity has been violated or whether there is intraperitoneal injury requiring operative repair. Tests used for the former purpose include plain films, LWE, US, and laparoscopy. Those most commonly used with the latter intent are DPL, serial physical examinations, laparoscopy, US, and CT. These modalities are undertaken only if clinical determinants that would mandate laparotomy do not exist.

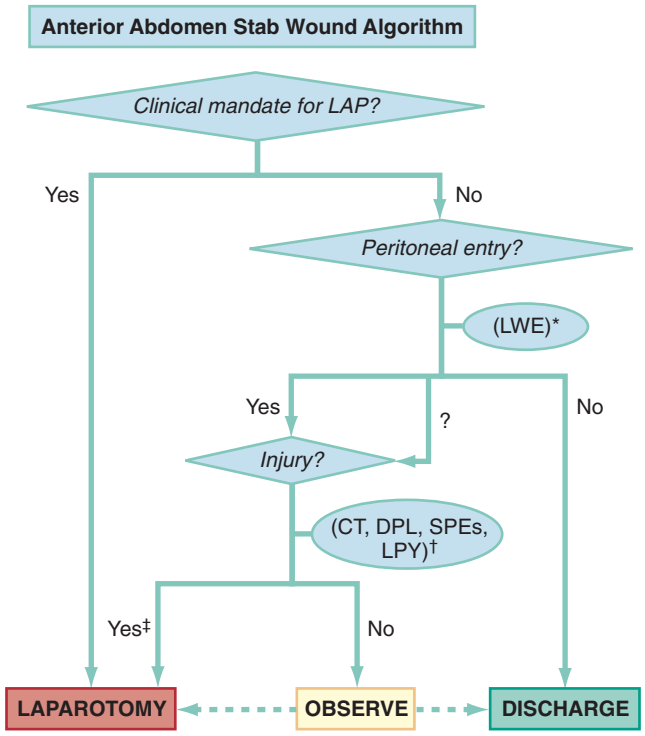


Figure 43-9. Anterior abdomen stab wound algorithm. *Plain films, focused assessment with sonography for trauma (FAST), laparoscopy (LPY), and computed tomography (CT) can also assess peritoneal entry. †CT, diagnostic peritoneal lavage (DPL), serial physical examinations (SPEs), or LPY can be used in singular or complementary fashion depending on the clinical scenario. ‡Expectant management of injuries is infrequently attempted. FAST, focused assessment with sonography for trauma; LAP, laparotomy; LWE, local wound exploration.

Management

Selective management of abdominal stab wounds is now well accepted because of the relatively low incidence of intraperitoneal injuries coupled with the success of various diagnostic strategies.[92] The appropriateness of these strategies is predicated on the basis of penetration site, clinical status of the patient, and the experience and preference of an institution and its personnel. Formerly, the goal of mandatory exploration of all stab wounds was to eliminate missed injuries. Currently, selective management has resulted in a tremendous reduction in unnecessary laparotomies and their associated morbidity, with minimal and acceptable loss in sensitivity for significant intraperitoneal injury. Although certain authors promote the relative safety of nontherapeutic operations, others cite considerable immediate and delayed hazards, as well as increased cost.[4] It is generally preferred that the nondiagnostic laparotomy rate be less than 15%.

Anterior Abdomen. In approaching the management of stab wounds to the anterior abdomen, the clinician is faced with three fundamental tasks. The first and most important is to determine whether clinical indications point to the need for laparotomy. The presence of one or more of these indications, particularly in the context of an unstable patient, sets the course to exigent operation. If none is found, however, the clinician may address the second issue of whether the peritoneal cavity has been violated. If it can be definitively demonstrated that it has not, no further diagnostics are required, and the patient can be discharged. If the cavity has been violated, or if it cannot be determined that the cavity has not been violated, the third question must be answered: Is there an injury and, if so, is laparotomy required? Figure 43-9 is an algorithm based on the answers to these three questions and follows clinical indicators of injury, LWE, DPL, CT, and other radiologic modalities. Other strategies rely more heavily on other techniques, such as serial abdominal examinations or laparoscopy.[85,92-96]

Step I: Clinical Indications for Laparotomy. Seven clinical determinants are used to predict the need for laparotomy after stab wounds to the abdomen (Table 43-3). Although there is consensus regarding the reliability of some of these, each has suboptimal predictive value.

1. *Hemodynamic compromise.* This is the preeminent indication of the need for laparotomy and is the most frequent reason that a patient is taken urgently to the operating room without preliminary diagnostic studies. This is typically an appropriate approach after middle and lower abdominal penetration.[15,95,97,98] However, stab wounds to the upper abdomen and lower chest may produce hemodynamic instability because of intrathoracic hemorrhage, pneumothorax, or pericardial tamponade.
2. *Peritoneal signs.* There is considerable debate over the reliability of peritoneal signs, particularly in the early postinjury period. Among physical examination findings, unequivocal peritoneal signs have the highest positive predictive value, whereas an entirely normal examination even in the presence of mild to moderate intoxication has the greatest negative predictive value for therapeutic laparotomy.[15,95,97]

Table 43-3 Clinical Indications for Laparotomy Following Penetrating Trauma

MANIFESTATION	PREMISE	PITFALL
Hemodynamic instability	Major solid visceral or vascular injury	Thorax or mediastinum, causal or contributory
Peritoneal signs	Intraperitoneal injury	Unreliable, especially immediately postinjury
Evisceration	Additional bowel, other injury	No injury in one fourth to one third of stab wound cases
Diaphragmatic injury	Diaphragm	Rare clinical, radiographic findings
Gastrointestinal hemorrhage	Proximal gut	Uncommon, unknown accuracy
Implement in situ	Vascular impalement	Comorbid disease or pregnancy creates high operative risk
Intraperitoneal air	Hollow viscus perforation	Insensitive; may be caused by intraperitoneal entry only or be due to cardiopulmonary source

Modified from Marx JA: Diagnostic peritoneal lavage. In Ivatury RR, Cayten CG (eds): The Textbook of Penetrating Trauma. Baltimore, Williams & Wilkins, 1996, p 337.

3. *Evisceration*. With isolated omental evisceration, both a selective and a mandatory operating approach have been espoused. Omentum has been successfully ligated, excised, and restored to the peritoneal cavity.[98] However, patients with viscus or omental evisceration sustain up to an 80% incidence of major intraperitoneal injury, rendering laparotomy a reasonable next step in management.[15,97]
4. *Left-sided diaphragmatic injury*. In contradistinction to blunt mechanism, penetrating trauma to the diaphragm produces small tears and evanescent clinical clues to their presence. Thus, clinical examination and plain chest films are rarely diagnostic of injury. Other diagnostic measures, such as DPL or laparoscopy, or a mandatory laparotomy approach is necessary to discern this pathologic condition.[99]
5. *Gastrointestinal hemorrhage*. Recovery of blood via a nasogastric tube or emesis may reflect a violation of the stomach or duodenum but is an unusual occurrence.[15,92,98] Likewise, examination of the rectum or vagina may reveal hemorrhage that is the result of intraperitoneal or retroperitoneal trauma.
6. *Implements in situ*. The conservative and widely held maxim is to remove implements in situ of the torso in the operating room. This is to ensure expeditious control of hemorrhage should the implement reside within a vascular space or highly vascularized organ. Although implements in situ are most safely removed in the operating room, exceptions to this practice exist. These include situations in which ED resuscitation is impeded by the presence of the implement or the patient is at high risk for significant morbidity from nontherapeutic laparotomy because of severe comorbid conditions or pregnancy, for example.
7. *Intraperitoneal air*. The presence of free intraperitoneal air is often not sought because of the insensitivity and nonspecificity of this finding. Free intraperitoneal air can impute communication of the weapon with the intraperitoneal space or the presence of pulmonary or mediastinal injury. Thus, it does not necessarily indicate hollow visceral perforation and should not be used in isolation as an indicator for operation.

Step II: Peritoneal Violation. If clinical indications for laparotomy are absent, a logical next step is assessing the wound tract itself. The presence of peritoneal violation can be determined by a variety of means. There is great value in establishing that a wound tract is superficial to the peritoneal, retroperitoneal, intrathoracic, and pericardial cavities. In this event, the patient can be discharged from the ED after receiving appropriate wound care.[85,93] If a study is inconclusive, it should be assumed that one or more of these cavities have been violated and that other means of assessment are required. The five methods of assessing the intactness of the peritoneum are as follows:

1. *Evisceration*. Evisceration of bowel or omentum is clear evidence of peritoneal entry. These situations are usually handled by mandatory laparotomy. In certain centers, however, these eviscerations are reduced in the ED and further diagnostics pursued.[97,98]
2. *Intraperitoneal air*. A finding of intraperitoneal free air on an upright chest or a lateral decubitus abdominal radiograph generally establishes that the weapon has entered the peritoneal cavity and drawn air in with it, has disrupted a hollow viscus, or both. Rarely, a false-positive determination of peritoneal entry can be made when the actual source of intraperitoneal free air is the pulmonary tract.
3. *Local wound exploration*. This has been demonstrated to be an effective tool in determining the depth of the stab wound tract.
4. *Ultrasonography*. US demonstrating hemoperitoneum, pneumoperitoneum, or pericardial effusion identifies peritoneal penetration.[57] However, its reliability as a sole indicator for injury is not as dependable as that in BAT and carries a 15% negative laparotomy rate when used as such. In addition, a negative FAST does not rule out peritoneal violation.[99] US may also be used as an adjuvant to LWE to determine intactness of fascia. Although a small study demonstrated it can positively rule in fascial penetration, it is unreliable to rule this out.[58] Experience with US for this purpose has been successful but very limited.
5. *Laparoscopy*. This has compared favorably with LWE in assessing the wound tract but requires far more expertise and carries a far greater risk of complications. It is the most invasive and costly means of evaluating the integrity of the peritoneum. However, laparoscopy may also discover and serve as the mode of repair of certain diaphragmatic or organ injuries, or both.[86,88,89,100] And some postulate that its use in experienced centers actually decreases length of stay and therefore cost.[88,89]

Step III: Injury Requiring Laparotomy. In this algorithm, patients requiring an operation on clinical grounds have proceeded to laparotomy, and those in whom peritoneal, retroperitoneal, intrathoracic, and pericardial cavity violations have been excluded are discharged home. The patients remaining have presumed or known peritoneal violation. The next consideration is whether injury exists that dictates operative repair, as organ injury is present in just over 60% of patients with peritoneal violation.[15] In any case, patients who reach this stage of evaluation should be observed for at least 12 to 24 hours.[94,95]

For the past 25 years, the diagnostic standard for addressing the issue of intraperitoneal injury has been DPL. It is especially valuable as a rapid means of determining hemoperitoneum in the critical patient and for the discovery of occult hollow viscus perforation and isolated diaphragmatic injury.[77,83]

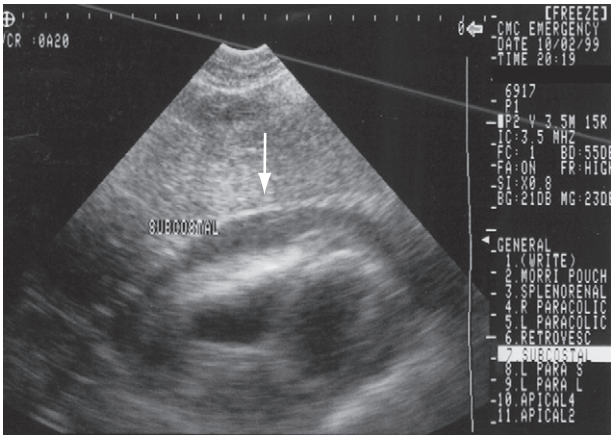


Figure 43-10. Pericardial effusion seen on subcostal view (*arrow*). The white line is the pericardium, and the anechoic space below represents a fluid collection in the pericardial space.

However, it is invasive, and thus many centers advocate other less invasive adjuvant testing methods coupled with serial physical examinations as the next step in management, reserving DPL use for those with unreliable exams or wounds in the thoracoabdominal area where diaphragmatic injury must be ruled out.[92,95]

US may be somewhat less accurate than DPL in establishing the presence or absence of hemoperitoneum, but it can simultaneously ascertain hemopericardium (Fig. 43-10), and in most centers US can be accomplished as quickly as or more quickly than peritoneal aspiration. Emphasis on serial examinations with selective use of other studies on an as-needed basis can be successful when an adequate number of experienced clinicians are available.[57,99,101]

CT has been particularly useful for potential colorectal trauma or further assessment of patients submitted to serial examination alone. However, some centers routinely perform CT in these cases and not simply for possible colorectal trauma.[102,103] Most utilize triple contrast (oral, rectal, and IV), although some newer studies cite equal accuracy with IV contrast only.[104] Hollow viscus and occult diaphragmatic injuries remain the most missed injuries on CT (even with use of triple contrast), although with the advent of mulitdetector CT scanners this is decreasing.[105]

Laparoscopy works best in experienced hands for restricted indications. However, its routine use is gaining favor in some institutions experienced with its use. Benefits include the ability to detect organ injury (including diaphragmatic injury) and simultaneously repair some injuries, thus decreasing negative and nontherapeutic laparotomy rates.[14,88,89,100]

Thoracoabdominal. Even a single stab wound to the low chest can violate the mediastinum, thoracic cavity, diaphragm, peritoneal cavity, and retroperitoneum. The risk of diaphragmatic penetration from a left thoracoabdominal stab wound has been measured at 17%.[86] When all thoracoabdominal wounds are considered, the risk of occult injury is 7%.[100] US can be extremely useful in quickly assessing for hemopericardium and hemoperitoneum in the marginally stable patient when thoracotomy or laparotomy is not already clinically indicated.[106] LWE of slash-type wounds may obviate the need for further evaluation. However, the depth of investigation cannot be taken beyond the anterior rib margin to maximize safety and accuracy. Further assessment for intraperitoneal and diaphragmatic injury can be made by DPL. The RBC criterion is lowered to 5000 to 10,000/mm^3 to optimize sensitivity for isolated diaphragmatic injury.[77] Laparoscopy or thoracoscopy can visualize and potentially repair the diaphragm and other organs. Newer multidetector CT and MRI show promise in excluding diaphragmatic injury. CT has a sensitivity of 94% and specificity of almost 96% for detecting diaphragmatic injury. However, equivocal scans must be followed up with more definitive management, including DPL or exploratory laparotomy.[105] A very conservative approach to the left lower chest stab wound, in particular, is mandatory exploration. This approach avoids any opportunity for missed diaphragmatic rents and their delayed consequences but results in an exceptionally high incidence of nontherapeutic operation. Rapid-slice helical CT or MRI may provide a solution to this vexing concern, but data are limited to date.

Flank and Back. The incidence of retroperitoneal injuries after stab wounds to the flank and back is greater than with injury to the anterior wall. However, risk of intraperitoneal organ injury is significant, ranging from 15 to 40%.[16] Again, LWE can be a useful diagnostic first step. However, the paraspinal muscles are quite thick, rendering the procedure more difficult. DPL is useful for diaphragmatic and intraperitoneal evaluation and, if it yields negative findings, can be followed by CT.[18] Triple-contrast CT is becoming the preferred method of evaluation in hemodynamically stable patients, and coupled with observation it may safely allow nonoperative treatment in these patients.[89,92]

Implement in Situ. It is routinely advised that foreign bodies in situ of the torso be removed under operating conditions. This is considered safest in the event that the implement is intravascular or in a highly vascularized organ. Plain films are generally all that is required. CT may be indicated in stable patients if plain films suggest impalement of major vascular structures. Angiography may also be necessary. For pregnant patients or those with severe comorbid illness in whom unnecessary laparotomy should be strictly avoided, CT may be able to discern the depth of entry and extent of injury. In these cases, the foreign body may be removed safely outside of the operating room.

Penetrating Abdominal Trauma: Gunshot Wounds

Diagnostic Studies

Diagnostic studies are used in a fashion similar to that for stab wounds. Moreover, the same diagnostic agents are applied, although in more restricted circumstances. The principal uses of diagnostic studies are to determine whether the missile has entered the peritoneal cavity or if injury requiring operative intervention has occurred.

Management

Like stab wounds, GSWs typically produce multiple organ injuries and a high incidence of hollow visceral injury. However, the risk of mortality is significantly greater, especially if vascular structures are involved. Missiles striking the low chest commonly penetrate both intrathoracic and abdominal structures, including the diaphragm.

Abdominal GSWs enter the peritoneal cavity in approximately 80% of cases, and in more than 90% of those involving penetration there is intraperitoneal damage.[33] These statistics significantly exceed the figures for stab wounds, and most trauma surgeons adjust their management to a conservative bent accordingly. We promote the principle that although selective management is widely accepted for stab wounds, its application in the management of GSWs is more limited, and therefore conservative clinical criteria for mandatory laparot-

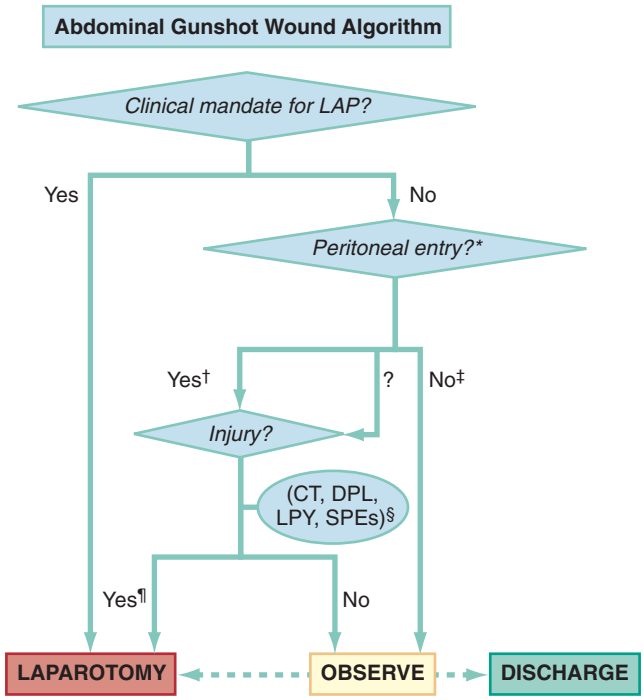


Figure 43-11. Abdominal gunshot wound algorithm. *Can be assessed by missile path, plain films, local wound exploration, ultrasonography (US), and laparoscopy (LAP). †Most centers proceed to LAP if peritoneal entry is suspected. ‡Patients with documented superficial and low-velocity injuries can be discharged; unknown-depth or high-velocity injuries require further tests or observation. §Computed tomography (CT), diagnostic peritoneal lavage (DPL), laparoscopy (LPY), or serial physical examinations (SPEs) can be used in singular or complementary fashion depending on the clinical scenario. ¶Expectant management of injuries caused by gunshot wounds is rarely attempted.

omy should be applied. Other authors argue, however, that although peritoneal penetration and intraperitoneal injury are far more likely to result from GSWs, damage requiring operative repair should be the instrumental concern, and this may be less common than previously stated. More recent series report intra-abdominal injury in only 70 to 80% of cases, supporting the contention that nonoperative management could be appropriate for a substantial percentage of patients.[3,31,104]

A prudent approach to GSWs to the abdomen can follow the same sequential three-step algorithm as for stab wounds (Fig. 43-11). First and foremost, are there clinical grounds for operation? Second, if none exists, has peritoneal violation occurred? Third, is there injury requiring laparotomy? In those centers that adhere to the tenet that known or suggested peritoneal violation imputes a high likelihood of intraperitoneal injury, clinicians proceed to laparotomy if the second question is answered affirmatively. Those who believe that there is a lower incidence of significant organ damage use other diagnostic agents, including serial physical examination, irrespective of whether the peritoneal cavity has been violated.

Step I: Clinical Indications for Laparotomy. These clinical demands are similar to those proposed for stab wounds (see Table 43-3).

Step II: Peritoneal Violation. Six methods are used to determine whether the missile has entered or traversed the peritoneal cavity. This question is most germane for those centers that perform laparotomy based on peritoneal violation alone.

1. *Missile path.* Clear entrance and exit wounds allow for a reasonably reliable estimate of the missile path. However, multiple GSWs ricochet, and the tendency of low-velocity missiles to follow fascial planes of lower resistance can render this approach misleading.
2. *Plain films.* An anteroposterior and lateral projection of the abdomen can assist in placing the missile in the peritoneal cavity, but such estimations are imprecise and are largely unhelpful in patients with through-and-through or multiple GSWs.
3. *Local wound exploration.* Because GSWs produce considerably more tissue damage than stab wounds, LWE is a less useful tool for GSWs of the abdomen, flank, and back. Its role should likely be restricted to low-velocity projectiles with suggested superficial entry. Because of the much greater technical difficulty and hazard in visualizing these extensive missile tracts, there is a tendency to underestimate the degree of damage.[31]
4. *Ultrasonography.* The experience with US in coincidentally assessing wound tracts and the mediastinum for low chest and upper abdominal penetration has been successful but very limited.
5. *Laparoscopy.* Laparoscopy is the most invasive and costly means of evaluating the integrity of the peritoneum. However, it may also discover and serve as the mode for repair of certain diaphragmatic or organ injuries, or both.[31,87,89]
6. *CT.* CT has been helpful when bullet trajectory is indeterminate and has shown a sensitivity and specificity of 90.5 and 96%, respectively, for identifying intra-abdominal injury.[103,104]

Step III: Injury Requiring Laparotomy. In most institutions, the algorithm terminates after the second step, in which determination or strong suspicion of peritoneal violation presupposes the need for laparotomy. At more liberal centers, these facts are deemed insufficient and additional diagnostics are undertaken.

1. *Serial examinations.* Patients with normal examination findings or localized wound tenderness can be observed only if clinical circumstances and institutional policy allow. Physical examination may be more reliable than previously thought in the presence of alcohol or illicit drug intoxication.[31]
2. *Diagnostic peritoneal lavage.* Peritoneal lavage has been highly successful in determining or excluding intraperitoneal injury. When DPL is used, all criteria for positivity remain the same with the exception of the RBC count, which is lowered to 5000 to 10,000 RBCs/mm^3 to maximize sensitivity.[77,97]
3. *CT.* Higher resolution scanners may augment the ability of CT to identify hollow visceral damage in addition to solid organ and vascular pathologic lesions.[31,104]
4. *Laparoscopy.* The greatest use for laparoscopy is in the evaluation of the diaphragm in patients with left thoracoabdominal GSWs who do not have indications for standard operative intervention.[31]

Thoracoabdominal. Patients with GSWs to the low chest have intraperitoneal injuries reported in 45% of cases. Clinical indications for laparotomy are unchanged. Diagnostic peritoneal lavage is particularly helpful in these cases to discern diaphragm injury, and the RBC threshold of 5000 to 10,000/mm^3 produces excellent sensitivity, but a combination of CT and serial examinations is more commonly used.

Flank and Back. In the past, operative exploration was generally recommended because of the increased likelihood of a serious injury and the greater fallibility of both the physical examination and DPL in cases of retroperitoneal injuries. However, as

multidetector CT scanners have evolved, contrast CT to delineate retroperitoneal pathologic lesions is typically the initial diagnostic test of choice in a stable patient.[4,97] As with stab wounds, laparoscopy or observation alone can be attempted in selected circumstances.[103]

Shotgun Wounds. Type I injuries can be effectively managed by reserving laparotomy for patients with clear peritoneal signs or progressive abdominal tenderness. Certain authors advocate an expectant approach to type II injuries, stating that small punctures of the bowel cause no wound eversion and no peritoneal leakage and will spontaneously close.[76] A more prudent approach is to perform laparotomy in cases of these penetrating wounds, especially if there are signs of peritonitis. Reconstruction of abdominal wall defects may be required. Type III injuries are commonly associated with multiple organ injuries, shock, and pronounced tissue destruction, requiring hemostasis and extensive débridement.

Blunt Abdominal Trauma

Diagnostic Studies

Most centers assimilate physical examination, bedside ultrasonography, CT, and, less commonly, DPL into a clinical algorithm.[107] Other tests, such as angiography, may be indicated. To reiterate, a clinical assessment of an alert patient that depends on abdominal findings alone is reasonably accurate but is accompanied by both false-positive and false-negative errors.[29,108-109] Such an assessment is more hazardous for a patient who is under the influence of a variety of toxins or whose examination is compromised by a head injury, spinal injury, or difficulty in communication resulting from retardation, a language barrier, or age.

The purpose of diagnostic studies in patients with BAT is twofold (Table 43-4): to discern or eliminate the presence of hemoperitoneum in the patient whose condition is critical and unstable to properly sequence management, and in less urgent circumstances, to demonstrate organ injury that requires operative repair.

Determining Hemoperitoneum

FAST Ultrasonography. FAST US has a safety advantage in that it can be performed rapidly and conducted in the resuscitation suite in the ED. In contradistinction to DPL, the FAST US is hazard-free, and serial examinations can be undertaken with ease in any patient. In hypotensive patients, the FAST US has excellent sensitivity for hemoperitoneum requiring surgical intervention, and most centers proceed to exploratory laparotomy in these patients.[67,107,111] However, in those with a negative FAST, intra-abdominal injury requiring operative repair cannot be excluded.[107,112]

Diagnostic Peritoneal Lavage. DPL is exceptionally sensitive in discovering hemoperitoneum, with a false-negative rate of less than 2%. This procedure can be performed in virtually any patient by varying the site and technical method. Aspiration of the peritoneum generally requires less than 5 minutes.[74]

Computed Tomography. Although CT can both visualize and estimate the quantity of hemoperitoneum, the time required to accomplish the procedure, including transport of the patient and setup, can be problematic, depending in part on the location of the scanner. Moreover, the ability to carry out CT in a safe manner depends on the availability and expertise of personnel to monitor the patient while he or she is in the CT scanner.

Demonstrating Organ Injury That Requires Laparotomy.

Indications for the respective studies vary with clinical need and with the experience, resources, and attitudes of individual institutions.

Ultrasonography and Diagnostic Peritoneal Lavage. Prompt FAST US (or, less commonly DPL) is clearly warranted in the acutely injured and unstable patient with multiple trauma.

The primary value of the FAST US is in the search for hemoperitoneum. It is far less reliable in specifying organ pathology, with the exception of traumatic pancreatic pseudocysts.

Computed Tomography. CT alone is sufficient and appropriate in the patient who is hemodynamically stable and has no obfuscating clinical factors. The great advantage of CT is its ability to identify specific organ injuries and simultaneously evaluate the retroperitoneum.[112] It is the most capable instrument in diagnosing liver and spleen pathologic lesions, and it allows visualization and semiquantitation of hemoperitoneum.

Laparoscopy. At this time, the role of laparoscopy in trauma cases is relegated mostly to a penetrating mechanism.

Table 43-4 Diagnostic Studies in Blunt Abdominal Trauma

SCENARIO	STUDY PURPOSE	PRIMARY STUDY	ALTERNATIVE/COMPENSATORY
Hemodynamically Unstable			
General	IPH	FAST, DPA	—
Pelvic fracture	IPH	FAST, DPA*	—
Hemodynamically Stable			
General	OI[†‡]	FAST, CT	DPL, SPEs
Nonoperative management[§]	OI	FAST, CT[¶]	DPL**, SPEs
CHI	OI, HVI	FAST, CT[¶]	SPEs[††]
BAI	IPH	FAST, DPA	CT[‡‡]

*Positive peritoneal aspirate mandates laparotomy, positive red blood cell count only, warrants attention to pelvic fracture.
[†]To discover fluid/blood suggesting injury.
[‡]FAST for OI much less reliable than for IPH.
[§]Institutional capability should be carefully considered.
[¶]CT less reliable for HVI than for solid visceral injury.
**Complementary to CT if HVI suspected.
[††]SPEs are unreliable in the patient with CHI.
[‡‡]May be more appropriate if helical CT is primary study for BAD or can be rapidly acquired.
BAI, blunt aortic injury; CHI, closed head injury; CT, computed tomography; DPA, diagnostic peritoneal aspiration; DPL, diagnostic peritoneal lavage; FAST, Focused Assessment with Sonography for Trauma; HVI, hollow viscus injury; IPH, intraperitoneal hemorrhage; OI, organ injury; SPEs, serial physical examinations.

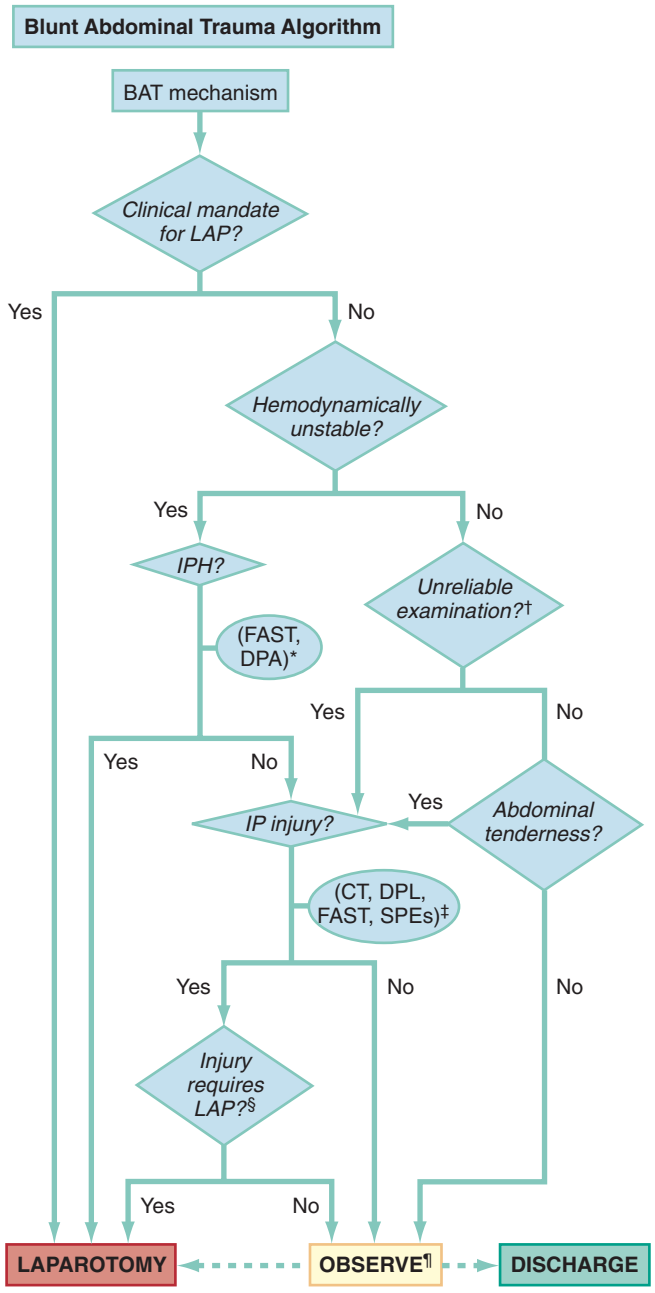


Figure 43-12. Blunt abdominal trauma (BAT) algorithm. *Determined by unequivocal free intraperitoneal fluid on FAST ultrasound or positive peritoneal aspiration on diagnostic peritoneal aspiration (DPA). †Can be unreliable because of closed head injury, intoxicants, distracting injury, or spinal cord injury. ‡One or more studies may be indicated. §Need for laparotomy is based on clinical scenario, diagnostic studies, and institutional resources. ¶Duration of observation should be 6 to 24 hours depending on whether diagnostic tests have been performed, the results of the tests, and clinical circumstances including the absence of factors rendering the examination unreliable. CT, computed tomography; DPL, diagnostic peritoneal lavage; FAST, focused assessment with sonography for trauma; IP, intraperitoneal; IPH, intraperitoneal hemorrhage; LAP, laparotomy; SPEs, serial physical examinations.

Management

In cases of blunt trauma, it is the exception when a patient undergoes laparotomy based on clinical grounds alone. Far more typically, one or a complementary battery of diagnostic tests are performed. The choice of these tests is influenced by the patient's hemodynamic status, the clinical scenario, and the institution's resources and preferences (Fig. 43-12).

Table 43-5 Clinical Indications for Laparotomy after Blunt Trauma

MANIFESTATION	PITFALL
Unstable vital signs with strongly indicated abdominal injury	Alternative sources, shock
Unequivocal peritoneal irritation	Unreliable
Pneumoperitoneum	Insensitive; may be due to cardiopulmonary source or invasive procedures (diagnostic peritoneal lavage, laparoscopy)
Evidence of diaphragmatic injury	Nonspecific
Significant gastrointestinal bleeding	Uncommon, unknown accuracy

Clinical Indications for Laparotomy. Immediate laparotomy after injury from a blunt mechanism is rarely determined solely by clinical parameters. Potential indications are any of the following (Table 43-5):

1. Unexplained signs of blood loss or hypotension in a patient who cannot be stabilized and in whom intra-abdominal injury is very strongly suggested
2. Clear and persistent signs of peritoneal irritation
3. Radiologic evidence of pneumoperitoneum consistent with a viscus rupture
4. Evidence of a diaphragmatic rupture
5. Persistent, significant gastrointestinal bleeding seen in the nasogastric return or in vomitus

Establishing the need for urgent celiotomy on clinical grounds is particularly problematic in the patient with multiple blunt injuries. Numerous extra-abdominal potential sources of hypotension exist. In addition, there is often coincident head injury or intoxication to further impair the reliability of examination. A nontherapeutic laparotomy may imperil the patient, not so much because of the potential morbidity of the procedure but rather because more vital diagnostic and therapeutic steps are delayed. Where confusion exists, corroborative diagnostic tests are strongly preferred.

Hemodynamically Unstable Patients. In the patient with multiple blunt injuries who is threatened by shock, three cavities are immediately targeted. Chest and pelvic radiographs are performed to identify the source of blood loss in the thoracic and retroperitoneal spaces, respectively. FAST US or peritoneal aspiration is undertaken to reveal or exclude the presence of blood in the peritoneal cavity. Hemoperitoneum in a clinically unstable patient is a mandate for laparotomy.

Hemodynamically Stable Patients. In patients who are hemodynamically stable, CT is the widely preferred diagnostic modality because of its ability to specify organ pathology, semiquantitate hemoperitoneum, and study nonabdominal body regions. Its potential drawbacks in certain clinical circumstances must be understood, however. US, DPL, and, very uncommonly, laparoscopy can be used in a complementary or primary mode.

Operative versus Nonoperative Management. Patients with certain intraperitoneal injuries can be watched expectantly and need not be subjected to laparotomy. Specifically, this has been successful with even moderate- to high-grade liver or spleen trauma.

Failures, including deaths, have occurred with this approach, however. Thus, although it is preferable to avoid unnecessary laparotomy, it is imperative to prevent significant morbidity or mortality by waiting too long. The patient with normal sensorium and minor to intermediate severity of mechanism is a superior candidate for expectant management. It is critical that an institution appraise its ability to treat such patients. This includes having experienced nursing staff, trauma surgeons, and radiologists and the ability to take a patient to undergo laparotomy urgently if the need arises.

Several pitfalls in the expectant approach are noteworthy. First, multiple injuries of intraperitoneal organs, including hollow viscera, are common.[114] Operative management of hollow visceral injury is necessary, and delay can have severe consequences.[73] The ability of CT to detect coincident injury to these structures was discussed earlier. The patient with multisystem injury and, specifically, closed head trauma is most vulnerable to having delayed diagnosis of perforated intestinal injury.[115] Second, expectant management may lead to increased use of blood products. Finally, this management approach fails in those patients whose hemorrhage is not amenable to therapeutic angiography and embolization and does not abate from apparent or misperceived minor injury of solid organs. In such cases, the lag time from injury to operation may increase morbidity and mortality.[73,75]

Pelvic Fracture. In the setting of pelvic fracture, the clinical triage determinant is the presence or absence of hemoperitoneum (Fig. 43-13). Although the sensitivity of FAST US in patients with pelvic fractures is decreased, it still serves as a tool to triage the patient to the next intervention.[116] In an unstable patient, a positive FAST US is followed by a supraumbilical peritoneal aspirate. If this reveals 10 mL or greater of blood, then the patient should expeditiously move to laparotomy. If instead urine or other fluid is aspirated, then the patient should undergo pelvic angiography prior to laparotomy. If the FAST US is negative, then the patient should proceed to angiography with the presumed diagnosis of a life-threatening retroperitoneal bleed. In stable patients, early mechanical pelvic stabilization is advised (see Chapter 52) and CT, followed by pelvic angiography and embolization, are undertaken as early as possible in the context of the multiple injuries.

Multiple System Injury. Treatment of the abdominal trauma patient with more than one life-threatening injury cannot be dogmatic. It is not unusual to confront intraperitoneal hemorrhage in a patient with apparent closed head injury or suspected blunt aortic disruption or both. Repair of the abdomen is said to take precedence over that of the head and chest. However, these situations are highly complex, and decision making is influenced by numerous and dynamic variables. The key tenet is that a patient with known hemoperitoneum whose vital signs cannot be stabilized must undergo laparotomy or face imminent exsanguination.

Closed Head Injury. In general, patients with coincident severe closed head injury but without frank coma or lateralizing signs do not have intracranial lesions that require craniotomy.[117] When lateralizing features do exist, the clinician must choose between rapid prelaparotomy CT of the head or preemptive burr holes at laparotomy. This judgment rests mostly on the clinical state of the patient with particular regard to his or her response to resuscitative measures and the timely availability of CT.[118] An approach to this scenario is presented in Figure 43-14.

Blunt Aortic Injury. Clinical or radiographic features that portend great vessel injury, notably a widened mediastinum on a supine anteroposterior chest radiograph, have variable sensitivity and specificity. In addition, although the course of any

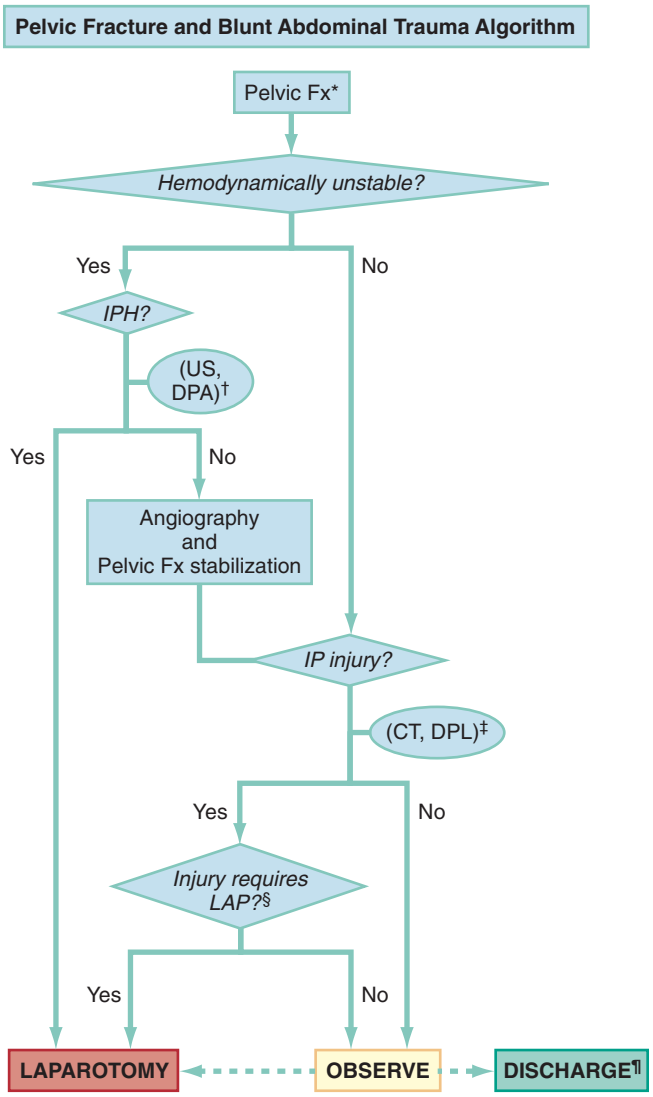


Figure 43-13. Pelvic fracture (Fx) and blunt abdominal trauma algorithm. *Certain pelvic fractures are more likely to cause pelvic vascular disruption and subsequent retroperitoneal hemorrhage. †Determined by unequivocal free intraperitoneal fluid on focused assessment with sonography for trauma (FAST) or positive peritoneal aspiration on diagnostic peritoneal aspiration (DPA). ‡One or more studies may be indicated. Serial physical examinations are generally considered unreliable owing to the presence of pelvic fracture. §Need for laparotomy is based on clinical scenario, diagnostic studies, and institutional resources. ¶Discharge from the perspective of need for further consideration for laparotomy. CT, computed tomography; DPL, diagnostic peritoneal lavage; IP, intraperitoneal; IPH, intraperitoneal hemorrhage; LAP, laparotomy.

single aortic lesion is unpredictable, there is more likely than not a lag of at least several hours before rupture. Therefore, exigent laparotomy should precede great vessel diagnostics. Should the patient's condition precipitously deteriorate, left lateral thoracotomy allows for aortic cross-clamping with its circulatory benefits and generally affords access to the injured portion of the vessel (Fig. 43-15).

Pediatrics. Children are prone to aerophagia, and decompressive nasogastric tubes are particularly important to help prevent compromised lung function and aid in the abdominal examination. Care must be taken in fluid resuscitation and drug administration, with attention being paid to the patient's size, using surface area or body weight as a guide. Because of their size and relatively larger surface area, children are more susceptible to hypothermia resulting from the administration of unwarmed

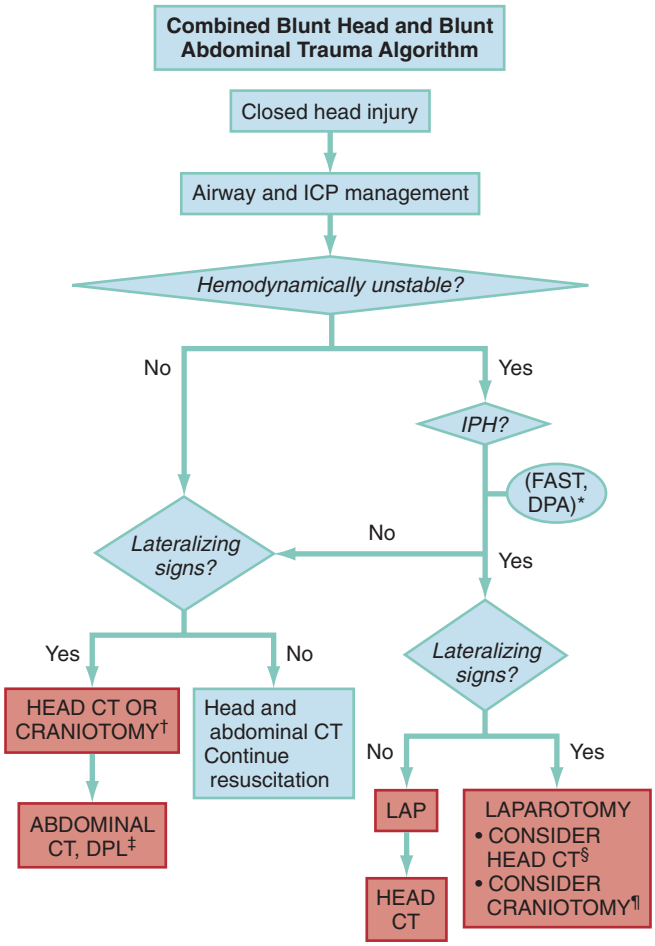


Figure 43-14. Combined blunt head and blunt abdominal trauma algorithm. *Determined by unequivocal free intraperitoneal fluid on focused assessment with sonography for trauma (FAST) or positive peritoneal aspiration on diagnostic peritoneal aspiration (DPA). †Craniotomy or burr holes based on clinical picture and unavailability of computed tomography (CT). ‡Diagnostic peritoneal lavage (DPL) can be complementary to CT in determining hollow viscus injury. §Consider prelaparotomy (LAP) head CT based on clinical picture and availability of CT. ¶Consider craniotomy or burr holes simultaneous with laparotomy. ICP, intracranial pressure; IPH, intraperitoneal hemorrhage.

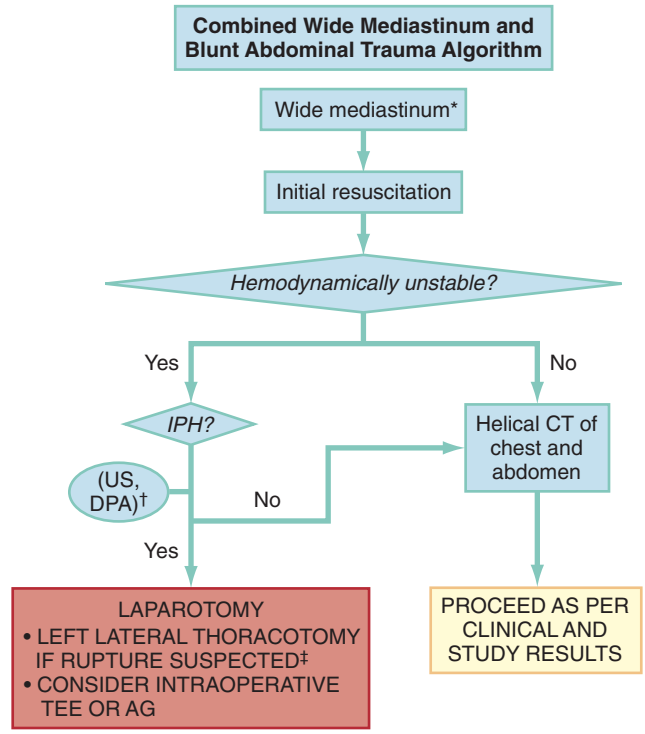


Figure 43-15. Combined wide mediastinum and blunt abdominal trauma algorithm. *Preferably based on upright posteroanterior film and mechanism of injury; other radiographic signs or mechanism alone may signal need for evaluation. †Determined by unequivocal free intraperitoneal fluid on focused assessment with sonography for trauma (FAST) or positive finding on diagnostic peritoneal aspiration (DPA). ‡Allows surgical access to majority of aortic disruption sites. AG, aortogram; CT, computed tomography; IPH, intraperitoneal hemorrhage; TEE, transesophageal echocardiogram.

fluids and blood products. The use of overhead heat lamps, blood warmers, and prewarmed IV fluids helps prevent this condition.

Children with major injuries may cause fear and anxiety even in the most experienced emergency physician or surgeon. It is imperative to maintain careful vigilance and overcome any tendency to avoid indicated procedures.

For physiologic reasons, the expectant management of blunt hepatic or splenic injury has better success in the child than in the adult patient.[119-121] If stability exists, nonoperative management can ensue if capable personnel and resources are present.[122] CT is the primary diagnostic method in both the initial and convalescent periods for defining and grading solid organ injury. As for adults, this modality is insensitive to the discovery of hollow viscus and, to a lesser degree, pancreatic pathologic conditions.[123]

FAST has been found to be useful for the detection of free fluid and can be used in triage to send the unstable child with visualized hemoperitoneum for laparotomy.[72] However, the FAST appears to have less sensitivity in children than in the adult experience. Therefore, DPL, specifically peritoneal aspiration, can also uncover hemoperitoneum in the initial treatment of the critical, multiply injured child. Reliance on cell count alone has prompted significant nontherapeutic laparotomy rates.

In the course of expectant treatment, the child should undergo laparotomy if instability develops, transfusion requirements are excessive, peritoneal signs are unequivocal, or observation is not feasible because of associated injuries or lack of institutional resources. Closed head injury need not preclude nonoperative management of known solid parenchymal injury, but the risk associated with undiscovered and coincident hollow viscus perforation is greatly increased. The diagnostic approach to penetrating trauma in children is the same as that in adults.

Transfer. Trauma patients in rural settings may require a stabilizing damage control laparotomy by a general surgeon prior to being transferred to a trauma center for definitive care.[124]

KEY CONCEPTS

- The accuracy of physical examination is limited in cases of blunt and penetrating trauma. It is rendered less reliable by distracting injury, altered sensorium (e.g., head trauma, alcohol or drug intoxication, mental retardation), and spinal cord injury.
- Implements and missiles frequently violate the lung parenchyma, diaphragm, mediastinum, intraperitoneal cavity, and retroperitoneum in some combination.
- The choice of diagnostic studies for abdominal trauma is based on clinical need first and foremost, as well as study availability and the accuracy of that study in a respective center.
- FAST US and peritoneal aspiration are rapid methods of determining or excluding the presence of hemoperitoneum in the critically ill blunt or penetrating trauma patient. DPL is more sensitive but invasive. FAST is noninvasive and is equally accurate, and it can simultaneously evaluate for hemopericardium and pneumothorax.
- Clinical indications for laparotomy are more dependable in and more frequently applicable to cases of penetrating trauma than cases of blunt trauma.
- The critical determinant in hemodynamically unstable patients with pelvic fracture is the existence of active intraperitoneal hemorrhage. Discovery of this by FAST US, CT, or peritoneal aspiration advises laparotomy, whereas its absence prompts diagnostic and potentially therapeutic angiography.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 44 Genitourinary System

Michael S. Runyon

PERSPECTIVE

Despite considerable advances in the initial evaluation and management of severe injuries, confusion remains regarding the recognition and subsequent management of genitourinary trauma. Only major renovascular injuries or a severely shattered kidney, both of which are rare, portend a rapid death. Thus, most genitourinary injuries pale in comparison with the immediate life threats posed by concomitant injuries to the head, chest, and abdomen. Hence, the urinary tract as an anatomically injured system is by necessity relegated to a position of secondary importance. Nevertheless, to maintain excellence and expertise in the overall treatment of all injured patients, it is mandatory for the emergency physician to have a thorough understanding of the global spectrum of genitourinary injury and how it can affect patient outcomes.

Genitourinary trauma is frequently a covert entity and is associated with a wide array of injury. Approximately 10% of all multiply injured patients have some manifestation of genitourinary involvement.[1] Because of its relatively infrequent occurrence and often subtle presentation, it may be overlooked in the initial evaluation of the multiply injured patient. Prompt identification and appropriate management of genitourinary injuries can minimize potential long-term complications, including renal insufficiency, chronic hypertension, incontinence, and sexual dysfunction. The astute emergency physician can accomplish this goal by a stepwise evaluation that considers the mechanism of injury, pertinent physical exam findings, urinalysis, and adjunctive diagnostic imaging.

For the stable patient, the urinary tract is unique in that diagnostic evaluation is always done in a retrograde fashion; that is, clinical suggestion and elimination of urethral injury before bladder injury before ureteral or renal injury. Adherence to this axiom enables the discovery of virtually any important urinary tract injury. Deviations from this practice may be necessary when life-threatening renal injuries are discovered.

Definitions

For purposes of investigation and staging of urologic injuries, genitourinary trauma is divided into lower tract (bladder or urethral injury), upper tract (renal or ureteral injury), and external genitalia (penile, scrotal, testicular, and vulvar injury). Each category is further subdivided on the basis of a blunt or penetrating mechanism of injury.

Historical Perspective

The basic tenets of lower urinary tract injury have not changed appreciably in the last 25 years. A thoroughly performed physical examination and the recognition of blood at the urethral meatus or gross hematuria identify all significant lower urinary tract injuries. Major advances in the identification of significant upper tract genitourinary injuries, their clinical markers, and ultimate staging procedures have come to the forefront over the last few decades. Before 1985, any trauma patient with any amount of microhematuria was labeled "at risk" for genitourinary injury and received an intravenous pyelogram (IVP). This was neither diagnostically definitive nor cost-effective and simply perpetuated the existing confusion and controversy. In 1985, Nicolaisen and colleagues published the first of a series of articles that established guidelines for identifying significant upper tract genitourinary injuries, their markers, and the diagnostic studies that define the exact extent of these injuries and aid in subsequent patient management.[2] In addition, the advent of ultrasonography has greatly simplified the diagnosis and management of external genitalia trauma.

CLINICAL FEATURES

The signs, symptoms, and examination findings of genitourinary trauma are varied and nonspecific. Acutely, these may include flank, abdominal, rib, back, or scrotal pain; urinary retention; penile or scrotal ecchymosis or hematoma; blood at the urethral meatus; and an abnormally positioned prostate on digital rectal exam. Renovascular hypertension may be the only finding weeks to months after injury.

Physical Examination

Examination of the torso and pelvis during the secondary survey is the first step in the evaluation for urologic injury. Any evidence of abdominal tenderness should alert the examining physician to the possibility of a bladder rupture in addition to other intra-abdominal injuries. This likelihood increases significantly in the presence of a pelvic fracture. Tenderness elicited by pelvic compression or palpation of the pelvic girdle or pubic symphysis supports the diagnosis of a potential pelvic fracture with possible lower urinary tract injury.

Examination of the genitalia can be informative. The emergency physician should examine for evidence of hematoma or

ecchymosis of the penile shaft, scrotal skin, or perineum. Gross blood at the urethral meatus is suggestive of a urethral injury and dictates the need for retrograde urethrography. In circumstances in which emergency surgical exploration for life-threatening injuries is needed, the retrograde urethrogram can be performed in the operating room or after the operative procedure. In the male patient, classic teaching dictates that a Foley catheter should never be introduced when urethral injury is possible without first evaluating urethral integrity by retrograde urethrography. The concern is that trauma from the catheter placement may convert a partial urethral tear into a complete disruption. Although the literature on this topic is sorely lacking, one small retrospective review of 13 cases of urethral injury demonstrated no evidence that a blind attempt to insert a urinary catheter worsened the initial injury.[3]

Careful inspection for blood at the vaginal introitus is particularly important in the female patient known to have a pelvic fracture. A vaginal examination can discern vaginal lacerations or urethral disruption caused by displaced bony pelvic fracture fragments. This examination should be conducted carefully so as to protect the hands of the examiner from injury as well as to prevent worsening of the injuries themselves. Unlike with male urethral injuries, urethrography is technically difficult and not routinely recommended in females thought to have urethral injuries because of the urethra's short length. The inability to pass a Foley catheter in a premenopausal female patient with a pelvic fracture signifies the potential for urethral injury and possible need for suprapubic urinary drainage. Successful passage of a Foley catheter in a patient with blood at the vaginal introitus does not exclude urethral injury, however, and these worrisome physical examination findings must be conveyed to the urologist, who can plan subsequent endoscopic or radiographic urethral evaluation accordingly.[4-6] In an older postmenopausal female trauma patient, urethral injury must be distinguished from a superiorly retracted urethral meatus and accompanying meatal stenosis. These preexisting conditions are common in an atrophic vaginal setting, and a 12- or 14-Fr coudé or Foley catheter usually is required to achieve successful bladder access.

The digital rectal examination evaluates sphincter tone, bowel wall integrity, the presence or absence of gross blood, and the position of the prostate. Normally, the posterior lobe of the prostate is palpable and well defined (Fig. 44-1). A pelvic fracture may disrupt the puboprostatic ligaments and the prostatomembranous urethra, resulting in significant retropubic venous bleeding. This may produce a large pelvic hematoma that can displace the prostate superiorly, resulting in a boggy, ill-defined mass on rectal examination (Fig. 44-2). Although it has long been recommended as part of the routine evaluation of all trauma patients, multiple studies have questioned the utility of the rectal examination in this setting and have specifically demonstrated that a palpably abnormal prostate is an insensitive indicator of urethral injury.[7-9] Thus the decision to evaluate for urethral injury should consider additional clinical features and not rely solely on the findings of the rectal examination.

Foley Catheter

In any trauma patient presenting with a major mechanism of injury and the absence of any findings suggestive of urethral injury, a Foley catheter should be passed into the bladder. The initial bladder effluent must be observed by the physician. Because of its importance in dictating subsequent patient evaluation, gross hematuria is conservatively defined as any color to the urine other than clear or yellow. The presence of gross hematuria indicates urologic injury. Rarely, severe rhabdomyolysis produces large quantities of urine myoglobin, the gross appearance of which can be confused with gross hematuria. In these cases, urinalysis documents the absence of red blood cells (RBCs) consistent with myoglobinuria. Most significant lower urinary tract injuries are accompanied by either the presence of a pelvic fracture with blood at the urethral meatus or gross hematuria on Foley catheter placement. Upper tract trauma, however, tends to be more subtle. It is often coincident with nonurologic organ disruption, the bleeding from which can be life-threatening. These events may dictate rapid volume resuscitation that can clear gross hematuria

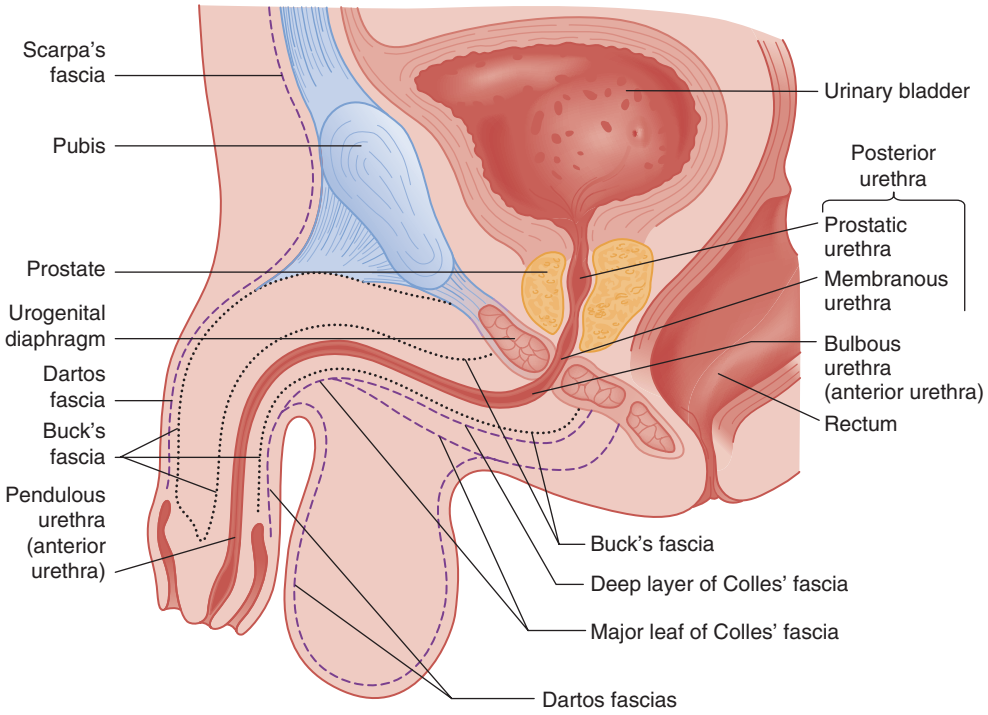


Figure 44-1. Anatomy of male genitalia.

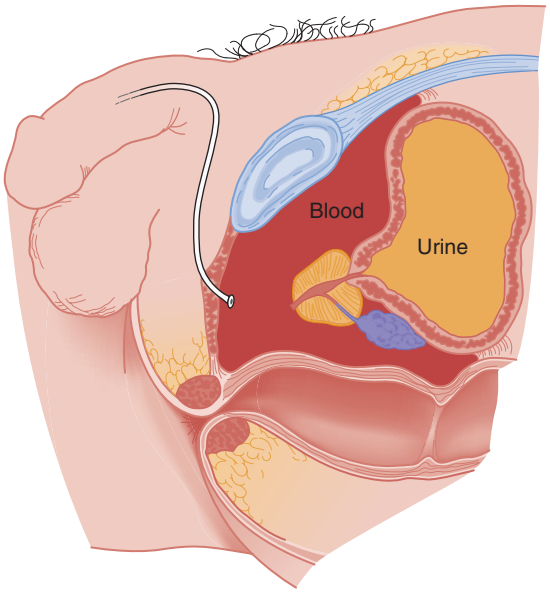


Figure 44-2. Injury to the posterior (membranous) urethra. The prostate has been avulsed from the membranous urethra secondary to fracture of the pelvis. Extravasation occurs above the triangular ligament and is periprostatic and perivesical. (From McAninch JW: In Tanagho EA, McAninch JW [eds]: Smith's General Urology, 14th ed. Norwalk, Conn, Appleton & Lange, 1995.)

quickly. Moreover, blunt injury to the renovascular pedicle or penetrating ureteral injury may not produce gross or even microscopic hematuria.

LOWER URINARY TRACT

URETHRAL TRAUMA

Anatomy

The urogenital diaphragm divides the anterior (bulbous and pendulous) urethra from the posterior (membranous and prostatic) urethra. Contrary to early descriptions, the urogenital diaphragm does not completely encircle the membranous urethra, but rather forms an incomplete sling that offers posterior and lateral support.[5] The prostatic urethra is attached to the posterior symphysis pubis by the puboprostatic ligaments. A fracture of the pelvis with displacement of the symphysis may result in a laceration or avulsion of the prostatic urethra because of the shearing force on the fixed prostatic and membranous urethra. Injuries to the anterior and posterior urethra are caused by different mechanisms, involve different symptoms, and are treated differently.

Pathophysiology

Urethral disruption is the most significant injury that must be identified. Failure to do so may lead to significant morbidity. Urethral manipulation can convert a partial urethral tear into a complete tear, thus precluding accurate assessment of urinary output and subsequently potentiating the long-term complications of urethral trauma (e.g., urethral stricture formation and urinary incontinence). Anterior urethral injuries are most often caused by straddle injuries, falls, gunshot wounds, and self-instrumentation (Fig. 44-3).

Pelvic fractures account for most posterior urethral injuries (see Fig. 44-2). The risk of urethral injury varies with the specific type of pelvic fracture. High risk fractures include the straddle fracture, in which all four pubic rami are involved, and the Malgaigne fracture, which involves fracture and displacement of both ischiopubic rami anteriorly and the ipsilateral sacrum, sacroiliac joint, or ilium posteriorly. Urethral injuries are rarely associated with fractures that do not involve the ischiopubic rami.[5,10] In a prospective, single-center study of 203 consecutive male patients with pelvic fractures, 51 sustained urethral injuries. Malgaigne and straddle fractures were significantly associated with urethral injuries, with odds ratios of 3.4 and 3.85, respectively. In the same series, the highest risk for urethral injury was seen in patients suffering a straddle fracture with concurrent sacroiliac diastasis (odds ratio 24). Among those sustaining fractures not involving the anterior pelvic arch, none had urinary tract injury.[10]

Clinical Features

During the secondary survey, examination of the lower abdomen, pelvis, genitalia, and rectum provides both direct and indirect evidence to support or refute urethral injury. Urethral integrity is supported by lack of pelvic and suprapubic tenderness; absence of penile, scrotal, or perineal hematoma; lack of blood at the urethral meatus; and normal findings on digital rectal examination. These physical findings permit the

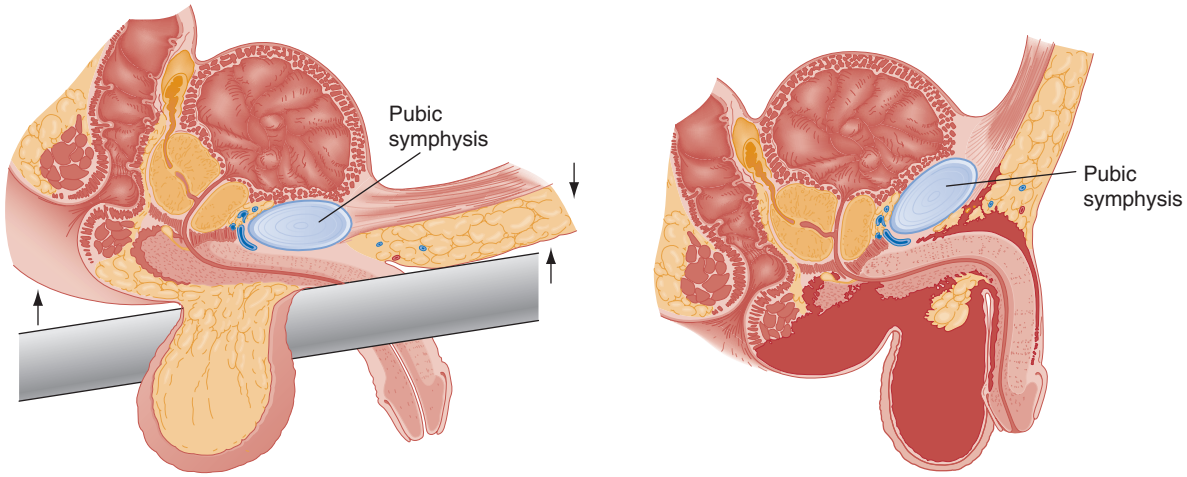


Figure 44-3. Injury to the bulbous urethra. *Left:* Mechanism: Usually a perineal blow or fall astride an object, crushing the urethra against inferior edge of pubic symphysis. *Right:* Extravasation of blood and urine enclosed within Colles' fascia. (From McAninch JW: In Tanagho EA, McAninch JW [eds]: Smith's General Urology, 14th ed. Norwalk, Conn, Appleton & Lange, 1995.)

safe passage of a 14- or 16-Fr Foley catheter into the bladder if the patient is unable to void and provide a suitable specimen for evaluation.

Diagnostic Strategies

Catheter Placement

The following technique for catheter placement assumes a normal urethra and includes the use of sterile technique, proper control of the foreskin, the use of copious amounts of lubricating jelly, and the gentle passage of a 14- or 16-Fr Foley or coudé catheter into the bladder. In all uncircumcised patients, continuous foreskin retraction with a folded 4 × 4 inch gauze pad is necessary to control the foreskin during catheter placement (Fig. 44-4). Without this maneuver, the foreskin tends to repeatedly reduce itself over the glans penis, which contaminates the field and complicates the catheterization attempt. Slight resistance to the advancing catheter should be expected secondary to voluntary contraction of the external sphincter. This is more apt to occur in a combative, anxious trauma patient than in a cooperative or unconscious patient. When this occurs, the patient should be reassured and asked to relax the perineum and rectal area while gentle advancing pressure is applied to the catheter. This combined approach allows the catheter to navigate the external sphincter successfully and pass easily into the bladder. If reassurance and relaxation do not allow easy passage of the catheter in a male patient with clinical features suggestive of urethral injury, it should be removed and a retrograde urethrogram performed. In all cases, the catheter must be passed to its fullest extent before the balloon can be inflated safely, withdrawn to the point of catheter balloon approximation with the bladder neck, and left to drain. Inflation of the catheter balloon under any other circumstances may result in iatrogenic urethral trauma.

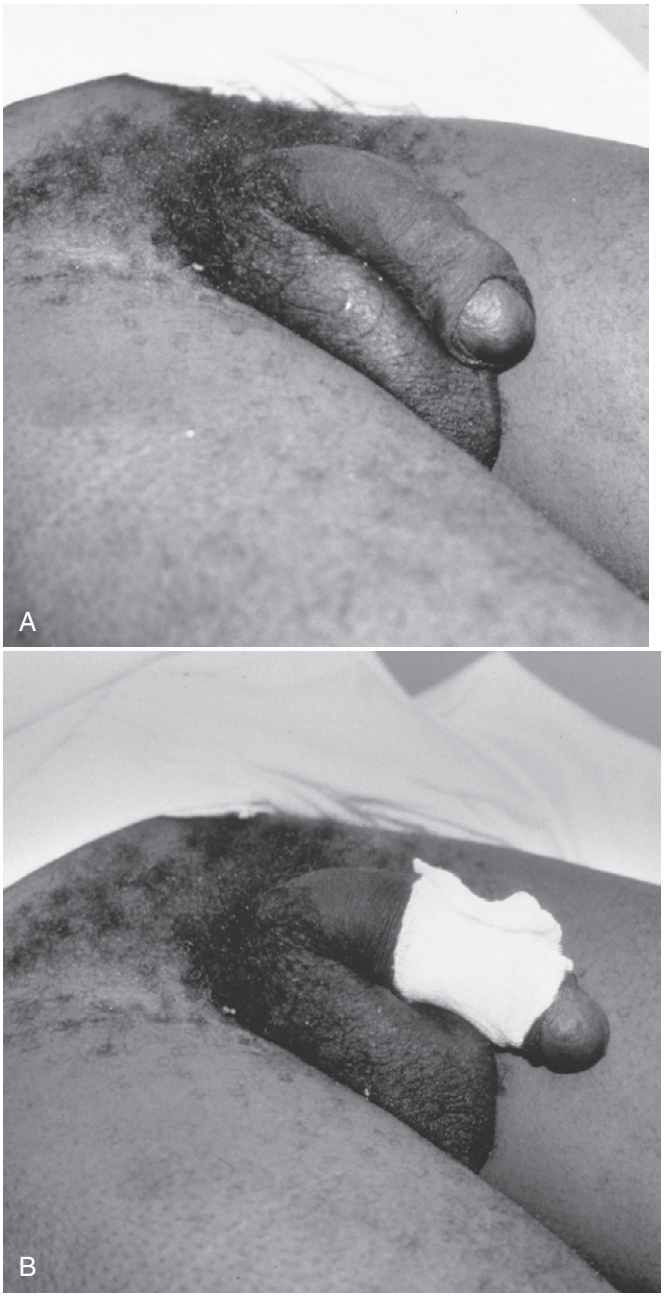


Figure 44-4. **A,** A normal uncircumcised man. **B,** Foreskin has been retracted and a folded 4 × 4 inch gauge sponge wrapped around it to prevent foreskin reduction during instrumentation.

Successful passage of a Foley catheter precludes a complete urethral disruption. Nonetheless, the possibility of a partial urethral injury not manifested by history, mechanism of injury, or physical examination does exist. If this injury is suggested initially, a retrograde urethrogram should be obtained. The presence of urethral extravasation together with contrast material filling the bladder is diagnostic of a partial urethral injury (Fig. 44-5). Identification of a partial urethral injury enables one careful attempt at urethral placement of a 12- or 14-Fr Foley or coudé catheter, depending on the size of the patient.[6] If any difficulty is encountered, the catheter should be removed and a urologist consulted. If a partial urethral tear is suggested subsequent to successful passage of a Foley catheter, a small feeding tube can be placed alongside the urethral catheter and a modified retrograde urethrogram performed. In this circumstance, the urethrogram is for documentation and subsequent management purposes only because appropriate therapy (Foley catheter drainage) has already been instituted.

Radiology

In male patients with possible urethral injury, a retrograde urethrogram is the diagnostic procedure of choice. Retrograde urethrography is not an emergency and should always follow more critical resuscitative measures.

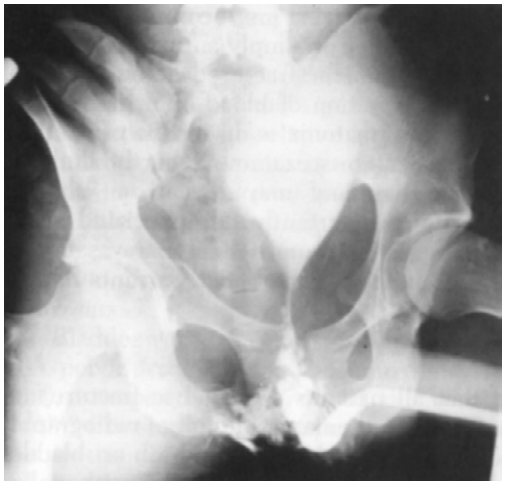


Figure 44-5. Retrograde urethrogram demonstrates a partial urethral disruption. Note the elongation of the posterior urethra with filling of the bladder. (From Spirnak JP: Pelvic fracture and injury to the lower urinary tract. Surg Clin North Am 68:1057, 1988.)

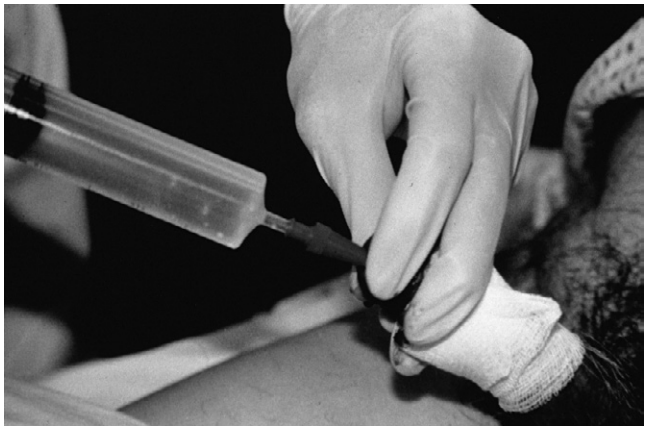


Figure 44-6. Christmas tree adapter on the end of a 60-mL syringe has been gently placed inside the fossa navicularis in preparation for retrograde urethrography.

In a patient with a pelvic fracture, the entire retrograde urethrogram should be conducted with the patient in a supine rather than oblique position. Certain authors recommend oblique films for portions of the retrograde urethrogram to enhance urethral definition. These views add little information to a good supine study. More important, pelvic fractures are often associated with significant venous bleeding and hematoma formation. Maintenance of this stable hematoma can be crucial in the initial hemodynamic resuscitation of the patient. Any patient movement from the supine to the oblique position has the potential to disrupt the organized hematoma with resultant significant and potentially lethal rebleeding. The entire urethral integrity can be defined with the patient in the supine position throughout the examination, aided by oblique stretching of the penis over the left or right thigh to promote necessary urethral unfolding.

A preinjection kidney, ureter, and bladder (KUB) film is first obtained. In uncircumcised patients, the penile foreskin is retracted and secured with a folded 4 × 4 inch gauze pad (see Fig. 44-4). The penis should be held between the long and ring fingers of the nondominant hand. A simple Christmas tree adapter, a Cooke adapter placed on the end of a 60-mL Toomey syringe, or a Toomey syringe alone is gently passed into the urethral meatus until a snug fit inside the meatus is confirmed. The distal end of the syringe is secured with the thumb and index fingers of the nondominant hand (Fig. 44-6). Some authors have recommended inflation of a Foley catheter balloon just proximal to the fossa navicularis or the use of other cumbersome adjuncts to facilitate injection of contrast media. These techniques should be avoided, however, because they promote leakage of contrast material around the penis, which can simulate extravasation on the urethrogram and promote a spurious examination. Next, 60 mL (or 0.6 mL/kg in children) of full-strength or half-strength water-soluble contrast medium is injected slowly over 30 to 60 seconds. Overly forceful injection may result in intravasation of contrast material into the urethral venous plexus. A radiograph is taken during the injection of the last 10 mL of contrast material. Retrograde flow through the urethra and into the bladder without extravasation ensures continuity of the urethra and absence of urethral injury (Fig. 44-7). Extravasation of contrast material outside the urethra with concomitant evidence of bladder filling distinguishes a partial urethral injury (see Fig. 44-5) from a complete urethral disruption, in which contrast material will be absent from inside the bladder (Fig. 44-8). The latter situation requires urologic consultation for appropriate management, the timing and specifics of which remain controversial and depend on the location and mechanism of injury.[6,11,12] In the interim, if measurement of urinary output is essential, the bladder should be accessed by the suprapubic placement of a peel-away sheath and Foley catheter using the Seldinger technique (Fig. 44-9). When venous intravasation of contrast is suggested, a postvoid film demonstrates clearing of any intravasated material while extravasated contrast from a urethral injury remains.

Management

If the clinical features of urethral injury are absent or the urethrogram is normal, the urethra is intact and a Foley catheter can be passed into the bladder. If a partial urethral disruption is identified, one careful attempt to pass a 12- or 14-Fr Foley

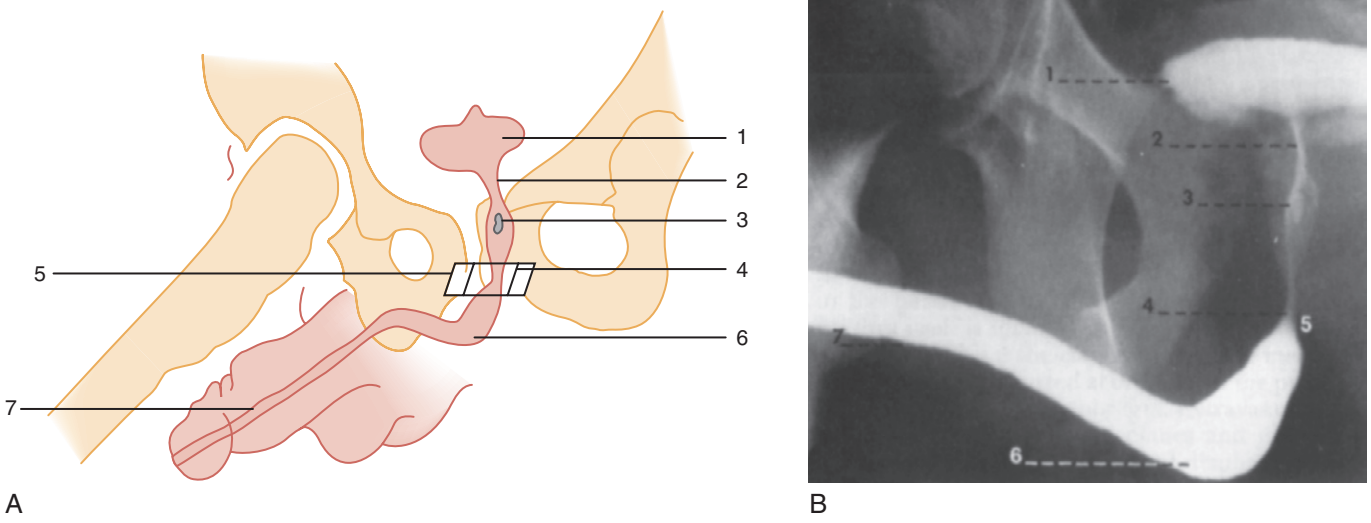


Figure 44-7. Normal anatomy is demonstrated by a line drawing (**A**) and by dynamic retrograde urethrography (**B**). (1) Bladder, (2) prostatic urethra, (3) verumontanum, (4) membranous urethra, (5) position of the urogenital diaphragm, (6) bulbous urethra, and (7) penile urethra. The penile and bulbous urethra together are considered the anterior urethra; the prostatic and membranous urethra constitute the posterior urethra. (Adapted from McCallum RW, Colapinto V: Urological Radiology of the Adult Male Lower Urinary Tract. Springfield, Ill, Charles C Thomas, 1976.)

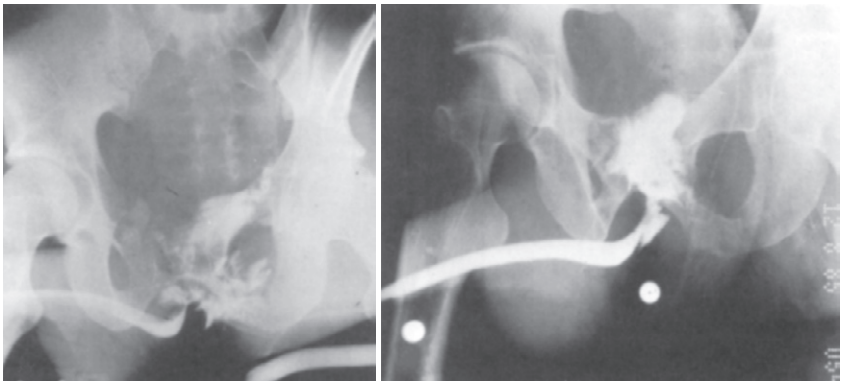


Figure 44-8. Retrograde urethrograms from two patients, each demonstrating complete urethral disruption. Note the absence of bladder filling, a finding diagnostic of complete disruption. (From Spirnak JP: Pelvic fracture and injury to the lower urinary tract. Surg Clin North Am 68:1057, 1988.)

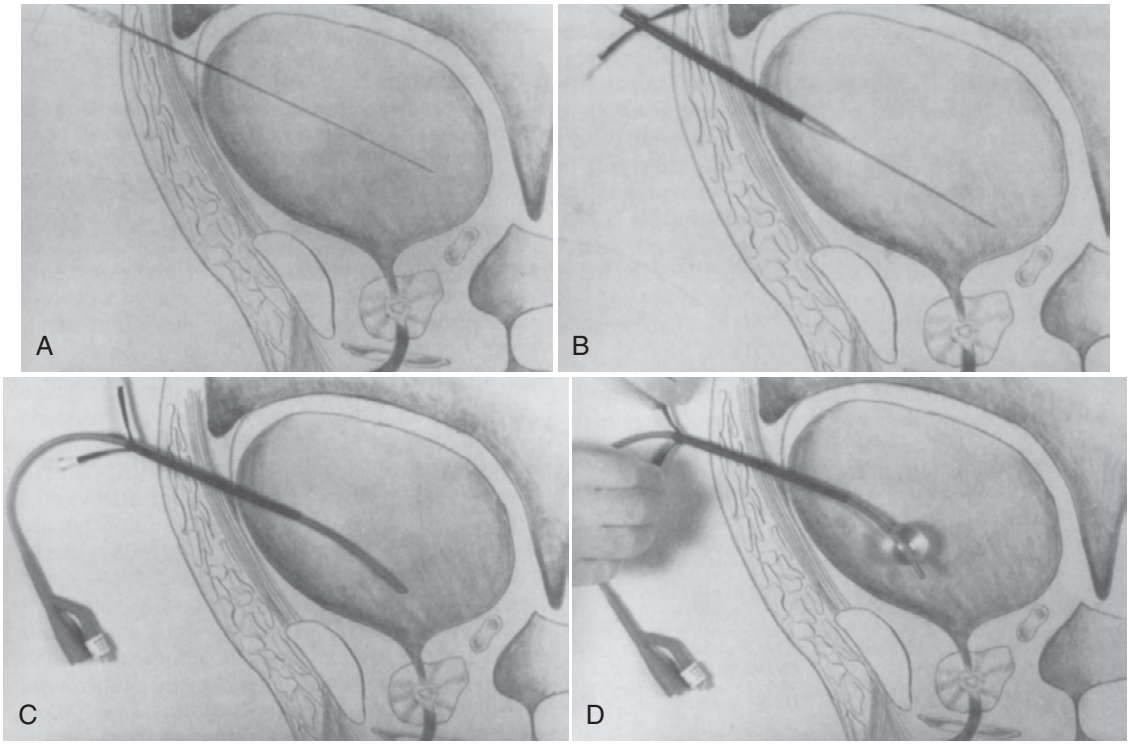


Figure 44-9. Percutaneous placement of a suprapubic tube with peel-away sheath introducer. **A,** An 18-gauge needle is in the bladder. A guidewire is advanced through the needle. **B,** A dilator and peel-away sheath are advanced over the guidewire. **C,** The dilator and guidewire are removed. Through the peel-away sheath, an appropriately sized catheter can be introduced into the bladder. **D,** The balloon is inflated, and the sheath is pulled back and peeled away. (From O'Brien WM: Percutaneous placement of suprapubic with peel away sheath introducer. J Urol 145:1015, 1991.)

or coudé catheter can be undertaken. If this is unsuccessful or if a complete urethral tear of the urethra is detected, placement of a suprapubic catheter is often needed especially if the patient is in shock or requires osmotic therapy for a severe head injury.

The optimal definitive management of urethral injuries remains a subject of controversy in the urologic literature.[6,11,12] Pertinent variables include the location of the injury (anterior vs. posterior), extent of the disruption (partial vs. complete), mechanism of injury, hemodynamic stability of the patient, and the presence of associated injuries. Treatment options vary from allowing a partial disruption to heal over a stenting urethral catheter to early or delayed, open or endoscopic repair. Adjunctive suprapubic urinary drainage is frequently indicated. Regardless of the specific management plan, the ultimate goals are the preservation of urinary continence and sexual function and avoiding the disruption of any pelvic hematoma.

In female patients, proximal urethral injuries are managed by immediate surgical exploration and repair as conservative management with proximal urinary diversion alone is associated with an increased risk of urethrovaginal fistulas or obliterative urethral strictures. Distal injuries may be managed by urethral catheterization. Regardless of the location of the urethral injury, associated vaginal lacerations require transvaginal repair to reduce the incidence of fistula formation.[6]

BLADDER TRAUMA

Anatomy

When empty, the bladder lies almost entirely within the bony pelvis. It rests on the pubis and adjacent pelvic floor parts. When full, the bladder can extend up to the level of the umbilicus, where it is most vulnerable to blunt and penetrating trauma. The bladder consists of an inner longitudinal, a middle

circular, and an outer longitudinal muscle layer. These three layers constitute the detrusor muscle, which contracts to propel urine out the urethra. Blood is supplied to the bladder by the internal iliac artery and vein. The nerve supply comes from the lumbar and sacral segments of the spinal cord. It includes parasympathetic motor fibers to the detrusor muscle and sensory fibers to the detrusor that give rise to the sensation of fullness and urgency when the detrusor is stretched. Sympathetic fibers innervate the blood vessels of the bladder and the bladder neck musculature.

Pathophysiology

Greater than two thirds of bladder injuries result from blunt trauma. Approximately 90% result from motor vehicle collisions as a result of trauma sustained due to ejection from the vehicle or the compressive force of the seat belt on a distended bladder. Approximately 80% of blunt bladder injuries are associated with fractures of the bony pelvis.[13] Additional life-threatening, nonurologic injuries are common and confer a significant mortality risk.[13,14] Penetrating injuries may be inflicted by gunshot wounds, stab wounds, or impalement injuries. The diagnostic evaluation of the bladder, like the urethra, can be accomplished quickly without elaborate radiographic equipment or can be part of the computed tomographic (CT) evaluation performed for the evaluation of nonurologic injuries.

Bladder injuries are classified as contusions, intraperitoneal ruptures, extraperitoneal ruptures, or a combination of intraperitoneal and extraperitoneal ruptures. Proper classification is important because treatment options differ with injury type. Intraperitoneal bladder rupture results from blunt lower abdominal trauma in a patient with a distended bladder. These blunt forces are directed to the dome of the bladder where the urachus originates during embryonic life. Because of this developmental hiatus, the dome is attenuated and represents the anatomic area most susceptible to rupture from the sudden rise in intravesical pressure associated with blunt trauma. The dome also is unique in its isolated peritoneal reflection so that rupture in this area most likely results in intraperitoneal urinary contamination.

Extraperitoneal rupture occurs almost exclusively with pelvic fractures when the associated shearing forces result in tearing of the anterolateral bladder wall at its fascial attachments. Occasionally, extraperitoneal rupture results from bladder laceration by a bone spicule from the fractured pelvis.[13] Extravasated urine may be confined to the perivesical space or may dissect along tissue planes and extend to the penis, scrotum, thigh, anterior abdominal wall, obturator foramen, or retroperitoneum.[13,15,16]

Clinical Features

Lower abdominal or suprapubic pain, the inability to urinate, or the presence of blood at the urethral meatus may alert the physician to the possibility of lower urinary tract trauma.

Diagnostic Strategies

Laboratory

Gross hematuria is the cardinal sign of bladder injury and is present in greater than 95% of cases.[13,17,18] In the setting of pelvic fracture, gross hematuria indicates the need to investigate for bladder injury. Relative indications for bladder imaging include gross hematuria without pelvic fracture and microhematuria in the setting of pelvic fracture.[13] Grossly clear urine in a blunt trauma patient without a pelvic fracture virtually eliminates the possibility of bladder rupture.

Radiology

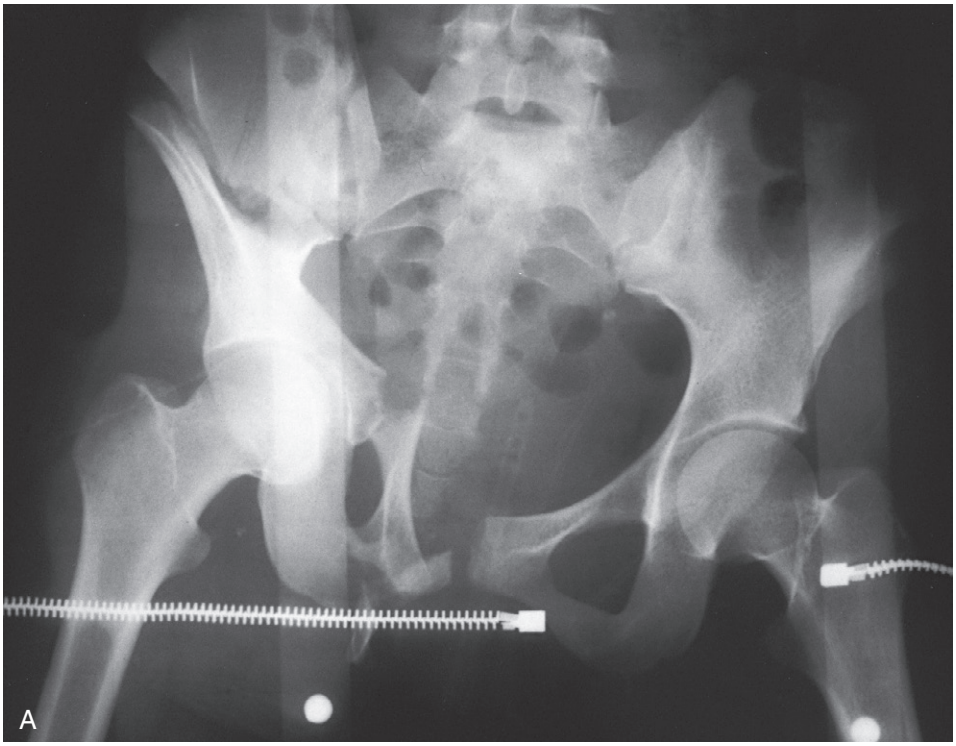
Conventional retrograde cystography and retrograde CT cystography are the diagnostic procedures of choice for suggested bladder injury.[19-21] It is key that these studies *not* be done in an antegrade fashion, as such studies (e.g., injecting intravenous [IV] contrast material, clamping the Foley catheter, and allowing the examination to depend on antegrade filling of the bladder from renal excretion of progressively dilute contrast material) may produce incomplete and spurious findings due to inadequate distention of the bladder.

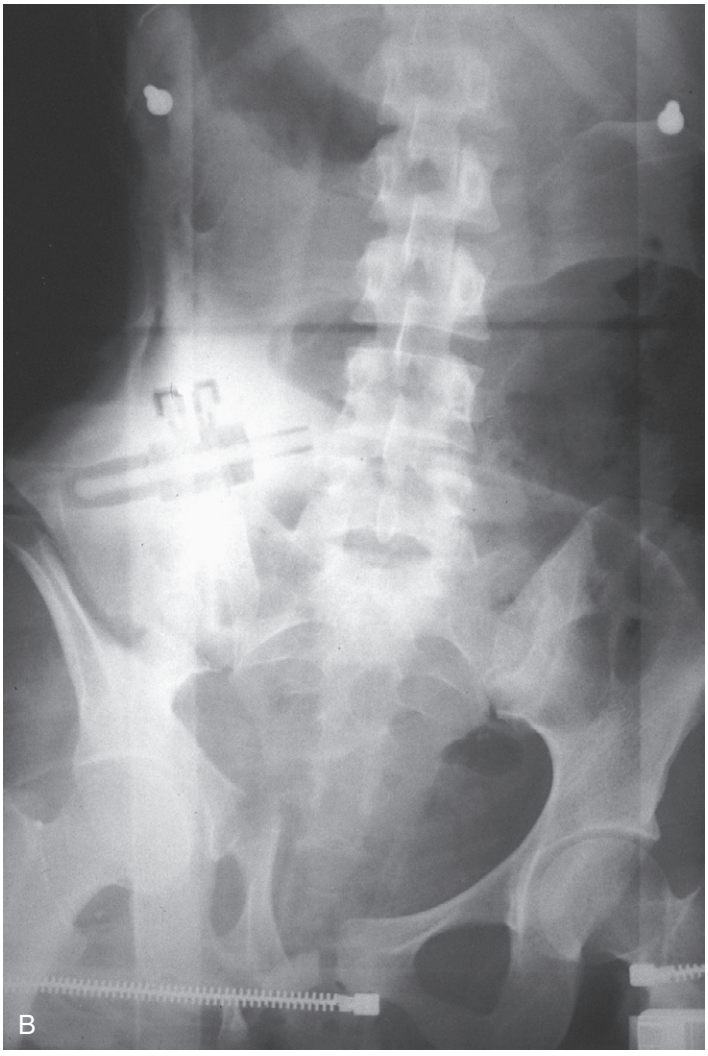
Conventional Retrograde Cystogram. Performance of either conventional plain film retrograde cystography or CT retrograde cystography assumes or follows exclusion of urethral trauma and the presence of an indwelling Foley catheter in the bladder. A Toomey syringe alone without its central piston is used for gravity instillation of contrast material (Fig. 44-10). Allowing the contrast material to freely infuse from a hanging bottle connected to an indwelling Foley catheter runs the risk of the tubing becoming disconnected, with contrast material subsequently leaking onto the examination table (Fig. 44-11A and B). This promotes an inaccurate examination that may result in an unnecessary operative procedure (Fig. 44-11C). In the setting of pelvic fracture, it is imperative that the patient remain supine throughout the examination rather than be repositioned obliquely for selected radiographs. This lessens the potential for rebleeding from an organized retropubic hematoma.

A preliminary KUB or scout film is obtained to provide a baseline evaluation of the pelvis, abdomen, and surrounding bony structures. It will become the film of reference for the postevacuation radiograph obtained after completion of the cystogram. Potential areas of extravasation on the postevacuation film will be confirmed when compared with the preliminary KUB film (Fig. 44-12). Contrast material should not be instilled into the bladder until the quality and anatomic information on the preliminary KUB film are confirmed.

Full-strength water-soluble contrast medium is instilled under gravity filling to one of three endpoints: (1) 100 mL with immediate fluoroscopic evidence of gross extravasation; (2) a total instillation of 300 to 400 mL in any patient 11 years of age or older; in patients younger than 11 years, the correct amount of contrast medium is determined by the formula

Figure 44-10. Retrograde cystogram. A Toomey syringe without its central piston is connected to the catheter and held by the examiner while gravity-instilled contrast material fills the bladder.





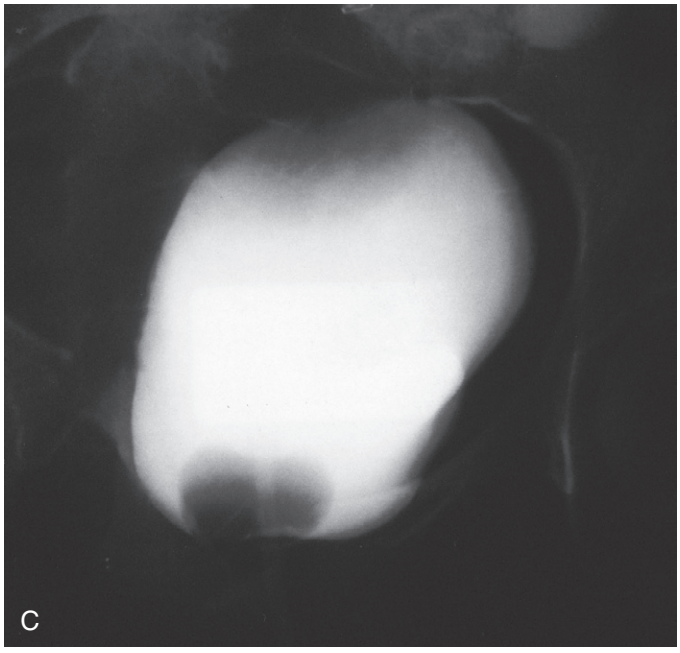


Figure 44-11. Spurious retrograde cystogram. This examination resulted when the tubing from the contrast bottle became disconnected from the Foley catheter after both were placed on the examination table, and bladder filling was completed without direct supervision. **A,** Kidney, bladder, ureter (KUB) film. **B,** Postinfusion KUB film interpreted as intraperitoneal bladder perforation. **C,** Intraoperative retrograde cystogram showing no evidence of extravasation.

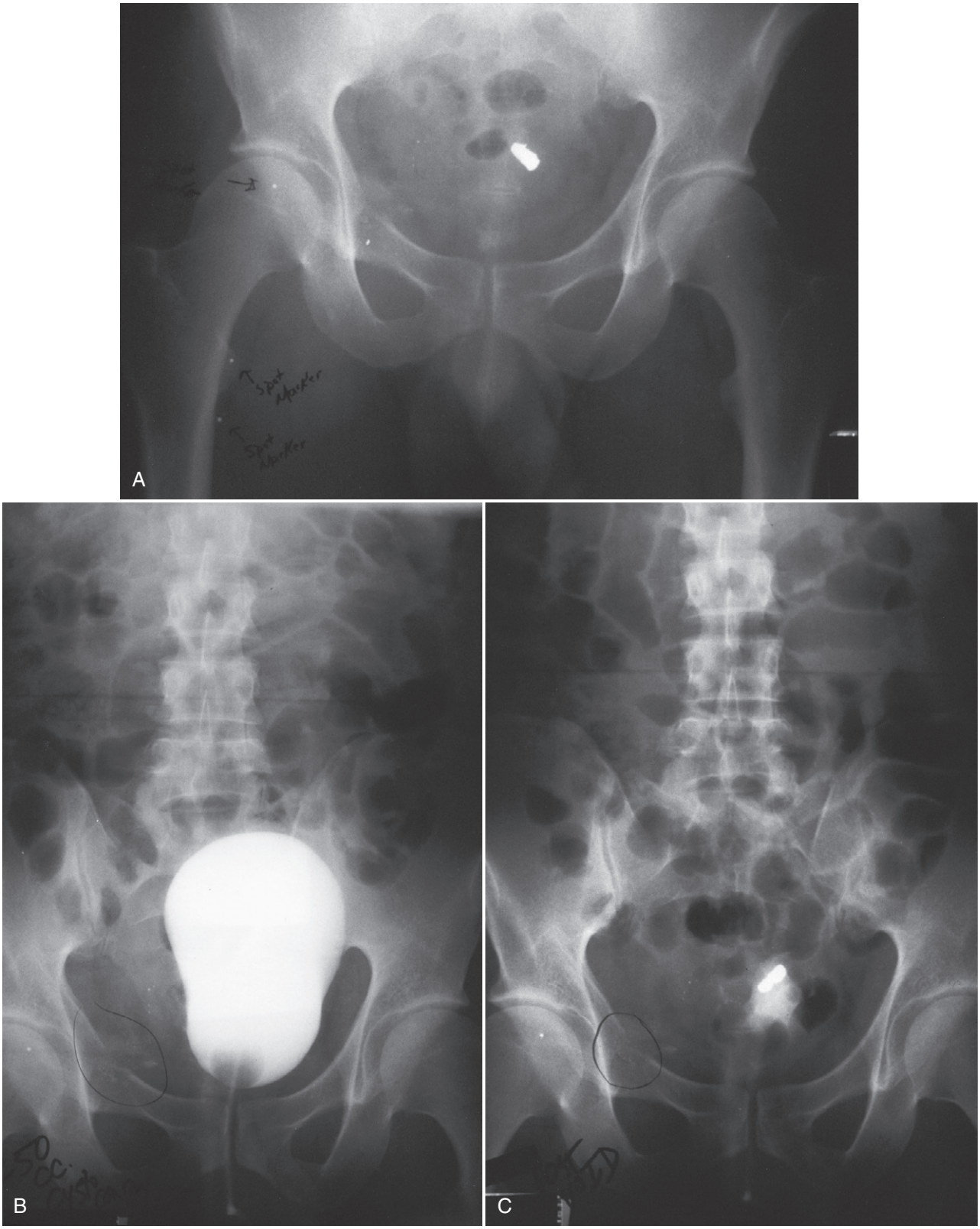


Figure 44-12. Retrograde cystogram. **A,** Preliminary kidney, bladder, ureter (KUB) film. **B,** Film of filled bladder. **C,** Postevacuation film comparing posterior extravasation with the preliminary KUB film.

(age in years + 2) × 30; or (3) the instillation of a lesser amount than 100 mL, which initiates a bladder contraction. This becomes evident by the retrograde filling of the Toomey syringe with bladder contents. After a few minutes, the original contrast material can again be instilled to the point of stimulating a bladder contraction, at which time an additional 50 mL of full-strength contrast material should be injected slowly but forcefully into the bladder. The Foley catheter is clamped, and an anteroposterior radiograph is taken of the filled bladder (Fig. 44-13A and B). A lateral film may help clarify any areas in

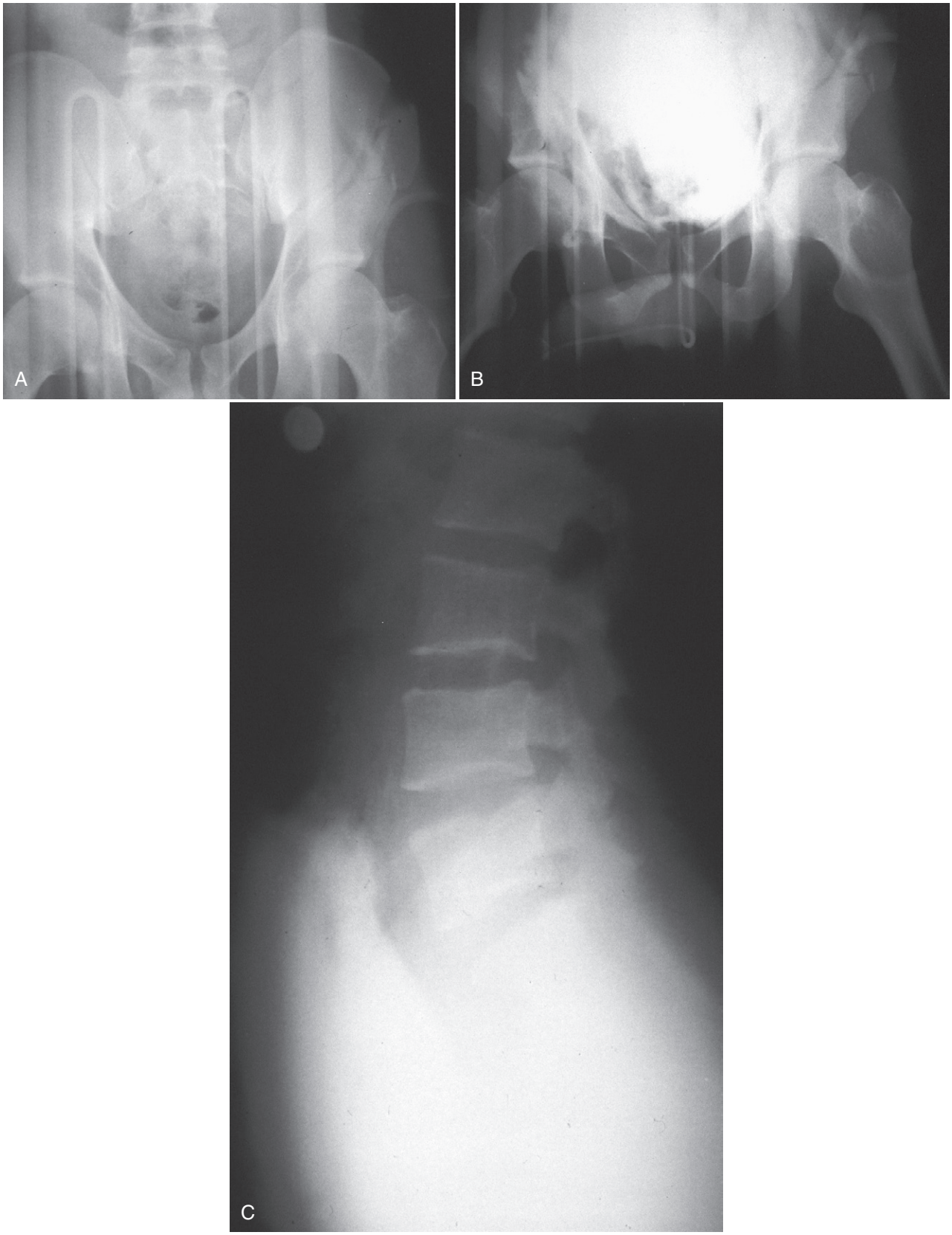


Figure 44-13. Retrograde cystogram. **A,** Preliminary kidney, bladder, ureter (KUB) film. **B,** Film of filled bladder showing extravasation that could be intraperitoneal, as well as extraperitoneal. **C,** Film of patient in a lateral position shows no evidence of intraperitoneal extravasation.

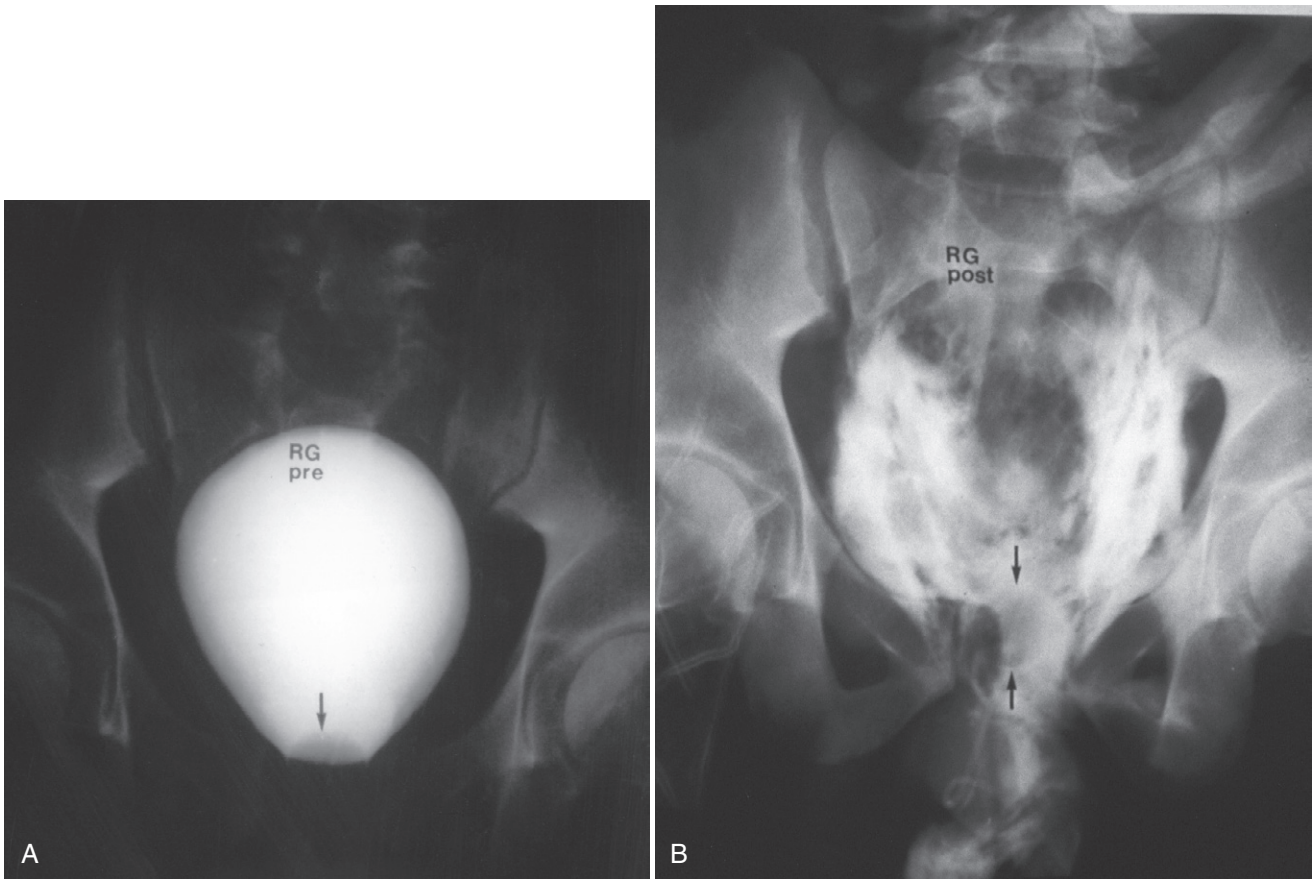


Figure 44-14. Retrograde cystogram. **A,** Film of filled bladder. **B,** Postevacuation film showing extensive extraperitoneal extravasation. *Arrows* point to the Foley catheter balloon.

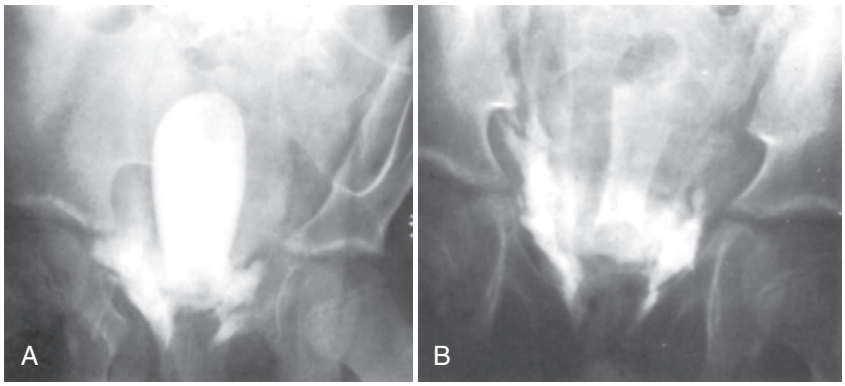


Figure 44-15. Cystographic appearance of extraperitoneal bladder perforation. **A** and **B,** Note the teardrop deformity caused by extrinsic compression by the pelvic hematoma and the flamelike wisps of extravasation confined by the pelvis. The bladder itself is elongated by a collection of perivesicular fluid. (From Spirnak JP: Pelvic fracture and injury to the lower urinary tract. Surg Clin North Am 68:1057, 1988.)

question (Fig. 44-13C). After the film of the filled bladder meets standards for quality and detail, the bladder should be completely evacuated into a large basin or, preferably, into an available bedside drainage bag. Any spillage of contrast material onto the pelvic genitalia or examination table may lead to false-positive findings on the postevacuation radiograph. The postevacuation film may disclose evidence of posterior bladder wall or extraperitoneal extravasation not seen on the anteroposterior radiograph of the filled bladder (Figs. 44-12 and 44-14).

In cases of extraperitoneal bladder perforation, contrast material is evident in the area of the pubic symphysis and pelvic outlet (Fig. 44-15). With intraperitoneal perforation, contrast material outlines intraperitoneal structures (e.g., loops of bowel, the liver, and spleen) (Fig. 44-16).

Several studies have documented that false-negative results are associated with the use of less than 300 to 400 mL or an age-appropriate amount of contrast material for cystography.[15] This has been seen primarily in penetrating bladder injuries in which the perforation from a small-caliber gunshot wound or a thin blade stab wound can be missed. The anatomically interlacing bladder wall muscle fibers are arranged such that these wounds lend themselves to immediate muscle fiber reapproximation and tenuous sealing of the wound by covering peritoneum and intra-abdominal mesentery. Unless an adequate amount of full-strength contrast material is used to fully distend or even overdistend the bladder, extravasation will not be evident, the injury will be missed, and there will be potential for significant morbidity.

Computed Tomography Retrograde Cystogram. The same anatomic information regarding bladder injury may be obtained using retrograde CT cystography rather than routine plain film radiography.[19-21] CT cystography is best obtained in trauma

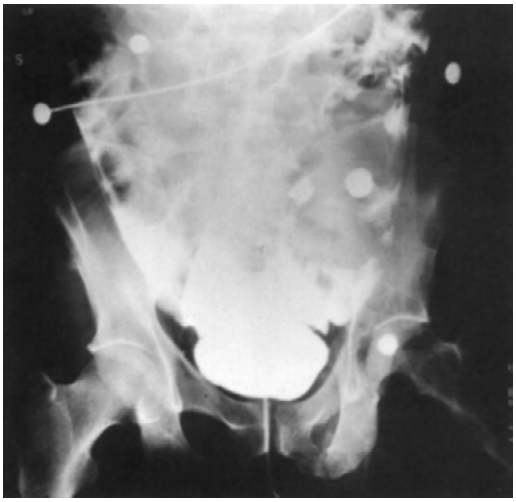


Figure 44-16. Cystographic appearance of intraperitoneal bladder perforation. Cystogram reveals massive intraperitoneal perforation and extravasation. (From Spirnak JP: Pelvic fracture and injury to the lower urinary tract. Surg Clin North Am 68:1057, 1988.)

patients who are undergoing CT evaluation for other possible injuries.

In either study, undiluted water-soluble contrast medium must first be instilled in a retrograde fashion. Intraperitoneal perforation is disclosed on helical CT scan by the presence of extravasated contrast material throughout the abdominal cavity (i.e., contrast ascites). Extraperitoneal extravasation is more difficult to visualize but can be appreciated on images taken through the pelvic area (Fig. 44-17A and B).

Management

In cases of bladder contusions, there is no evidence of extravasation on retrograde cystography. For these injuries, expectant management with or without Foley catheter drainage is the standard of care.[13,22] Most uncomplicated extraperitoneal bladder ruptures heal spontaneously with urinary catheter drainage alone. Indications for operative repair of extraperitoneal ruptures include the presence of concomitant injury to the rectum or vagina, injury involving the bladder neck, or when laparotomy is required for other injuries. Intraperitoneal bladder rupture requires surgical repair. Without operative intervention, lower urinary tract contamination will infect initially sterile urine and promote the development of subsequent bacterial peritonitis. Bladder repairs are never emergencies and normally follow operative repair of life-threatening injuries.

UPPER TRACT

Renal Trauma

Perspective

Renal trauma rarely occurs in isolation. Concomitant nonurologic injuries may result in hemodynamic instability, necessitating prompt intervention and relegating the search for renal injury to a position of secondary importance. Significant renal injuries define a small subset of the trauma population at large, and mortality from renal trauma accounts for less than 0.1% of trauma deaths.[23] This fact may lead to complacency and causes some of these injuries to be overlooked initially. Renal injuries are graded 1 through 5 according to the American Association

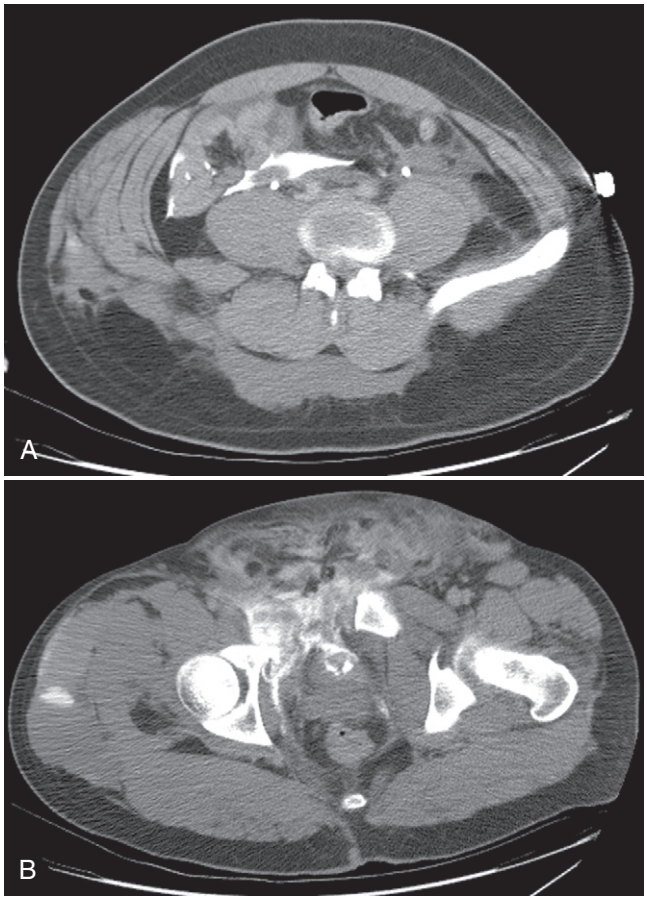


Figure 44-17. Bladder rupture. **A,** Intraperitoneal rupture shows contrast material extravasated from the bladder outlining loops of bowel in the lower abdomen. **B,** Extraperitoneal rupture shows contrast material extravasating into the disrupted soft tissue plains of the anterior and left pelvic side wall. (Courtesy of Charlotte Radiology, Emergency Radiology Section, Charlotte, North Carolina.)

for the Surgery of Trauma Organ Injury Scaling Committee Guidelines, which identifies most injuries requiring operative intervention.[24,25]

Complications

Urinary extravasation is the most common complication of renal trauma, occurring in 10 to 30% of penetrating trauma and 2 to 18% of blunt injuries.[23] There is considerable controversy in the urologic literature regarding the incidence of hypertension after renal trauma with reported rates varying greatly from as little as 0.2% to as much as 55%.[23,26] Many experts currently believe the overall risk of hypertension after most renal injuries to be quite low.[23,26,27] Factors affecting the risk of hypertension following renal trauma include the specific injury type and severity, with renal artery occlusion, although rare, imparting a risk of up to 50%.[23,27]

Anatomy and Physiology

The kidneys are located in the retroperitoneal space, are surrounded by adipose tissue and loose areolar connective tissue, and lie along the lower two thoracic vertebrae and the first four lumbar vertebrae (Fig. 44-18). The kidneys are not fixed. They move with the diaphragm and are supported by their renal arteries, veins, and adipose tissue, which is connected to a layer of fibrous tissue called the renal fascia, or Gerota's fascia.

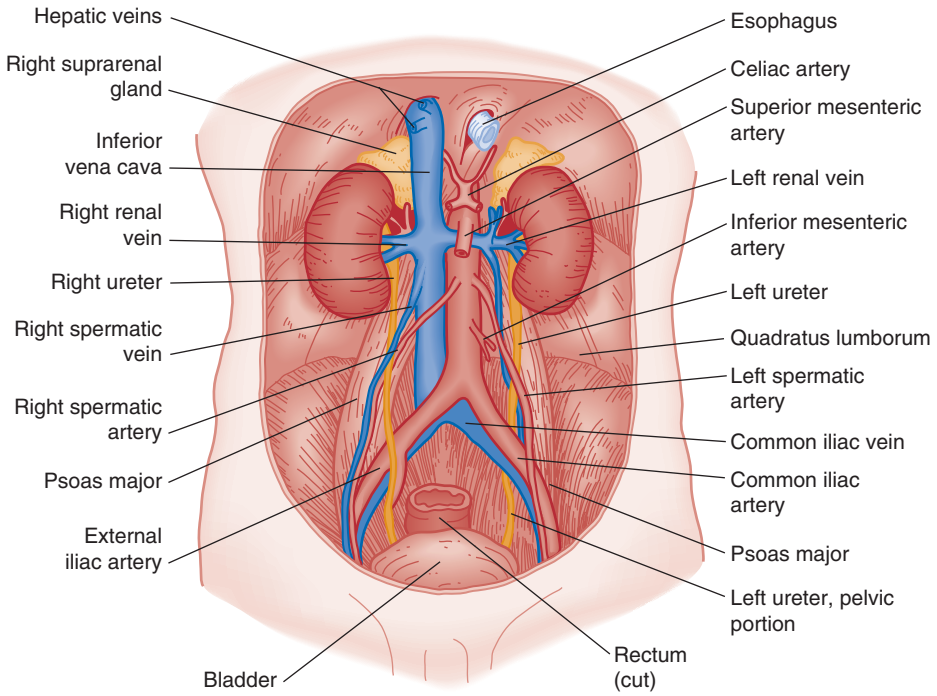


Figure 44-18. Dissection of abdomen showing kidneys and ureters and their relationship to other anatomic features in the retroperitoneal space.

The indented medial border of the kidney is called the *hilum*. The major renal vessels and ureter make up the renal pedicle and enter and exit at the hilum. The longitudinal section of the kidney (Fig. 44-19) shows an outer renal cortex and an inner renal medulla with its columns of Bertin. Each column of Bertin forms a papilla that empties into the renal pelvis. The renal pelvis is a funnel-shaped sac with cup-shaped extensions called *calyces*, which receive urine from each papilla and are the important decompression areas for rises in intrapelvic pressure.

The kidneys are perfused by 1200 mL of blood per minute, or 20 to 25% of cardiac output. Of this, 90% goes to the cortex and 10% to the medulla. Reduced blood flow to the kidney, whether from blunt or penetrating injury, causes renin to be released from the juxtaglomerular cells. Renin enters the bloodstream and combines with a plasma protein to form angiotensin. Angiotensin raises blood pressure by causing arteriolar vasoconstriction and acting on the adrenal cortex to augment aldosterone secretion. Aldosterone acts on the renal tubules to promote sodium reabsorption. Water follows passively with subsequent increase in blood volume. These changes increase blood flow to the kidney and other organs. The body requires only one third of normal renal function to sustain life. It is unusual in cases of genitourinary trauma to lose total renal function unless the patient has only one kidney, which carries a 1 in 1000 to 1 in 5000 incidence.[28]

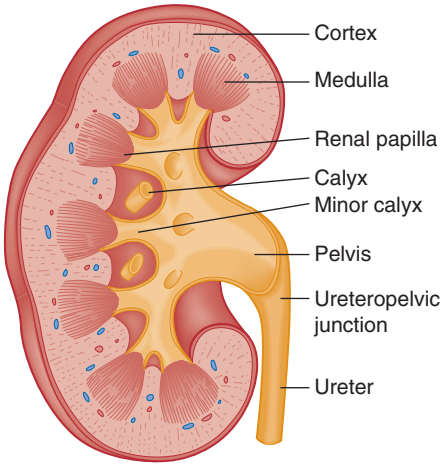


Figure 44-19. Longitudinal section of kidney.

Epidemiology

Renal injury occurs in 1 to 5% of hospitalized trauma patients and represents the most common of all genitourinary injuries.[12,27] Associated organ injuries occur in 61 to 100% of penetrating trauma and 35 to 55% of blunt injuries.[23] Blunt trauma accounts for approximately 90% of injuries and occurs most often after motor vehicle collisions, falls from heights, or direct blows to the flank. The pathophysiologic mechanisms include rapid deceleration, displacement, and, rarely, an explosion-type injury of the ureteropelvic junction. Penetrating injuries tend to be more severe and are associated with a higher nephrectomy rate.[12]

Renal vein injuries are more common than renal artery avulsions or intimal tears. Both injuries are often associated with rapid deceleration events. Most venous injuries tend to be partial rather than complete tears. As expected, a venous injury can potentially contribute more to a patient's unstable hemodynamic status than an arterial injury as the protective secondary vasospasm that occurs following arterial transection does not occur with venous injuries. IV contrast-enhanced helical CT identifies most renal artery disruptions, whereas renal vein injuries must be indirectly diagnosed by the presence of a normal-appearing kidney in association with a large hematoma disproportionate to the rest of the radiographic study.

Diagnostic Strategies

Laboratory

Hematuria. The presence, absence, or degree of hematuria correlates poorly with the severity of renal injury. This is especially true in the setting of penetrating trauma. In select cases of blunt trauma, the distinction between gross and microscopic hematuria can be used to guide clinical decision-making when considered along with the patient's hemodynamic status and the mechanism and severity of injury.[12,27,29,30] Formerly, a trauma patient who exhibited gross or microscopic hematuria was labeled "at risk" for urologic injury and underwent IVP. Experience has shown that most of the identifiable injuries were renal contusions that could be managed expectantly. Moreover, in a significant number of severely traumatized patients, vigorous initial fluid resuscitation precluded satisfactory contrast concentration in the kidney, yielding an incomplete, nondiagnostic initial radiographic examination.

In 1989, Mee and associates published the hallmark article that established guidelines for the evaluation and treatment of renal trauma. Their 10-year prospective study of 1146 consecutive patients with blunt (88%) and penetrating renal trauma established that clinically significant blunt renal injuries are associated with gross hematuria, microscopic hematuria with shock (any systolic blood pressure less than 90 mm Hg), or, rarely but importantly, a history of sudden deceleration injury without hematuria or shock. In the same series, there was no correlation between the presence or absence of hematuria and the extent of renal injury among 139 cases of penetrating trauma.[30]

Pediatrics. In children, the kidney is the most commonly injured genitourinary organ.[31] Controversy exists in the urologic literature as to whether the adult criteria for renal imaging following blunt trauma can be safely applied to the pediatric population.[27,32,33] Owing to significant differences in physiology, hypotension is a late and unreliable indicator of shock in children.[12,27] Additionally, unlike in adults, major blunt renal injuries can occur in the presence of microhematuria. The literature has defined 50 RBCs/hpf as the threshold below which imaging could be confidently dispensed with without missing significant injuries in children.[33,34] Current guidelines support imaging for pediatric (16 years old or younger) patients with blunt renal trauma in the presence of gross hematuria, with microhematuria greater than 50 RBCs/hpf, or with significant deceleration injuries.[27,35] As with adults, IV contrast-enhanced helical CT scanning is the diagnostic imaging technique of choice.

Radiology

Computed Tomography. IV contrast-enhanced helical CT is the diagnostic radiographic procedure of choice in evaluating significant upper tract renal trauma.[12,27,29,36] CT detects renal contusions, lacerations, renal pedicle injuries, devitalized segments, and urinary extravasation (Fig. 44-20A-E). It allows for grading of renal injuries and provides important information about concomitant nonurologic injuries to abdominal and pelvic structures. Additional images obtained 10 minutes after contrast injection enable the detection of delayed extravasation and increases diagnostic accuracy.

Angiography. Angiography may be a useful adjunct to CT imaging in the stable trauma patient with suggested renovascular injury, such as renal artery thrombosis, laceration, or pseudoaneurysm, and may be therapeutic in cases where stenting or embolization are indicated.[19,29,36]

Intravenous Pyelography. Formerly, IVP was the most common imaging modality employed in the evaluation of renal trauma. It has been shown to be less accurate than CT, is time-consuming and labor-intensive, and images only the urinary tract.[29] Despite these significant limitations, it may play a limited role in the initial evaluation of suggested renal trauma when CT is not readily available. In patients requiring immediate surgical intervention for other indications, a "one-shot IVP" performed in the emergency department or, more commonly, on the operating table may provide limited information to help the surgeon to stage upper tract injuries and confirm bilateral renal function. This test is performed by obtaining a single KUB film 10 minutes after the injection of 2 mL/kg of IV contrast (maximum 150 mL).[28]

Ultrasound. Ultrasound is not sufficiently sensitive to rule out possible renal trauma as it has been shown to miss up to 78% of known renal injuries.[29,36] In the multiply injured trauma patient, ultrasound is useful in the evaluation for free fluid in the abdomen and pelvis, which may herald other significant nonrenal injuries; however, this modality cannot reliably distinguish blood from other types of fluid such as ascites or extravasated urine. Moreover, free intraperitoneal fluid may be absent in up to 65% of isolated renal injuries.[19,36]

Management

Blunt Injury

In the absence of a significant deceleration mechanism, adult blunt trauma patients without gross hematuria or shock (any systolic blood pressure < 90 mm Hg) and pediatric blunt trauma patients with microhematuria of 50 RBCs/hpf or fewer can be confidently discharged from the emergency department if hospital admission is not otherwise indicated. Outpatient urology follow-up until microhematuria has cleared is advisable to be certain it does not represent another more serious underlying condition.

The optimal management of blunt renal trauma depends on the type and severity of injury (Figs. 44-21 and 44-22), the patient's hemodynamic status, and the management plan for any associated nonurologic injuries. The American Association for the Surgery of Trauma Organ Injury Severity Scale for the Kidney stratifies injuries and has been shown to correlate with the need for surgical intervention and the rate of nephrectomy.[24] Grade I injuries include simple contusions and subcapsular, nonexpanding hematomas without parenchymal laceration. Grade II injuries are parenchymal lacerations less than 0.1 cm in depth without urinary extravasation and a stable, nonexpanding hematoma. Grade III injuries are parenchymal lacerations greater than 0.1 cm in depth without urinary extravasation. Grade IV injuries involve lacerations extending through the cortex, medulla, and collecting system or main renal artery or vein injuries with contained hemorrhage. Grade V injuries involve completely shattered kidneys or avulsion of the renal hilum and devascularization of the kidney.[24] In one large retrospective review of 2467 patients with renal injury, the need for surgery increased from 0% of grade I injuries to 93% of grade V injuries. Likewise, the nephrectomy rate increased from 0% of grade I and II injuries to 86% of grade V injuries. Given that 80 to 90% are grade I or II, most blunt renal injuries can be managed nonoperatively with bedrest until any gross hematuria clears and periodic follow-up imaging to assess for injury resolution and to document renal function.

Immediate operative intervention is indicated for persistent life-threatening hemorrhage of possible renal origin. Restoration of normal renal function is unlikely after main renal artery injury, and nephrectomy may be required, especially in the presence of greater than 2 to 3 hours of complete or 6 hours of partial renal ischemia.[27,37] In select patients, arteriography

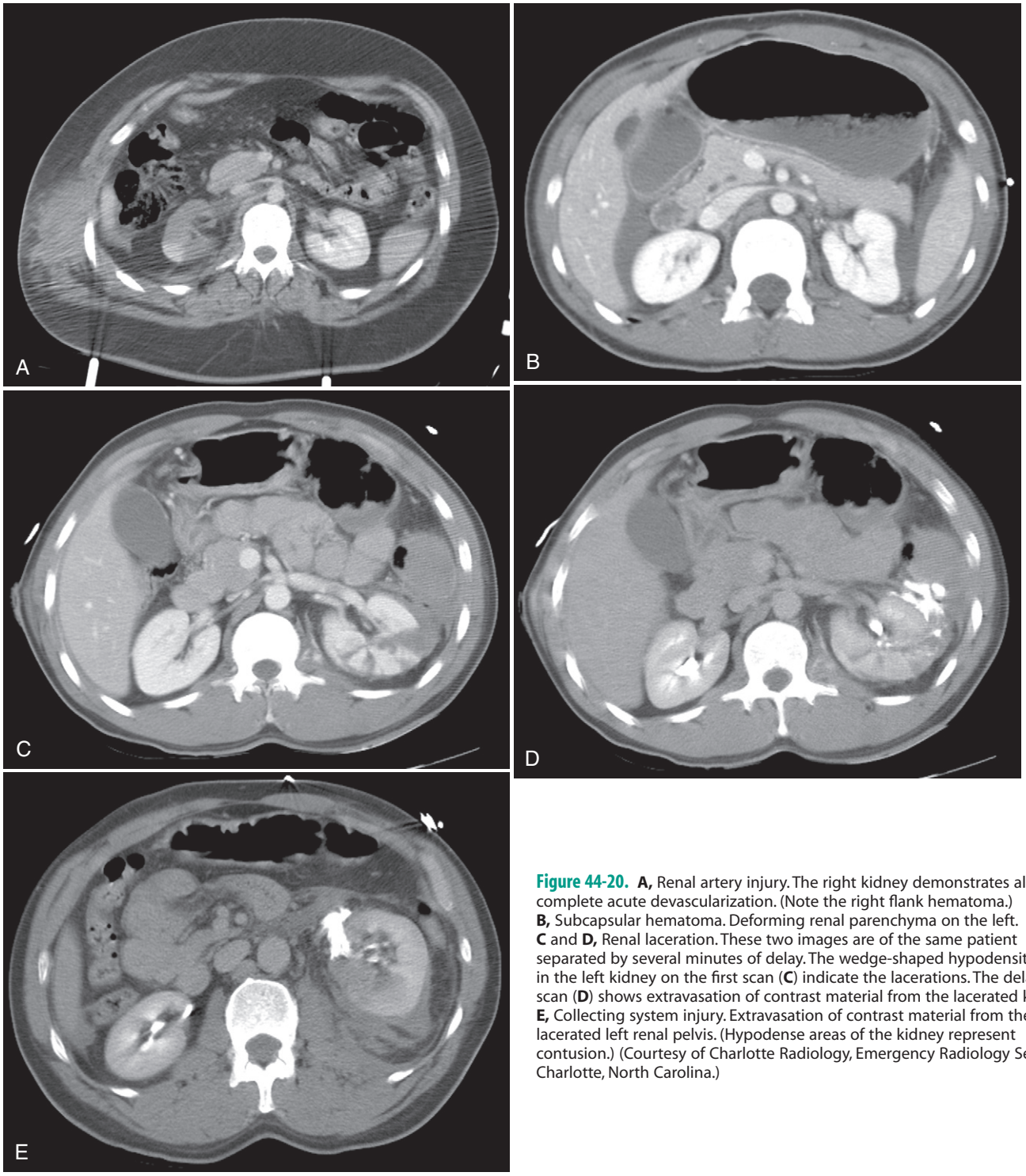


Figure 44-20. **A,** Renal artery injury. The right kidney demonstrates almost complete acute devascularization. (Note the right flank hematoma.) **B,** Subcapsular hematoma. Deforming renal parenchyma on the left. **C** and **D,** Renal laceration. These two images are of the same patient separated by several minutes of delay. The wedge-shaped hypodensities in the left kidney on the first scan (**C**) indicate the lacerations. The delayed scan (**D**) shows extravasation of contrast material from the lacerated kidney. **E,** Collecting system injury. Extravasation of contrast material from the lacerated left renal pelvis. (Hypodense areas of the kidney represent contusion.) (Courtesy of Charlotte Radiology, Emergency Radiology Section, Charlotte, North Carolina.)

with hemorrhage control by embolization is a reasonable alternative to laparotomy.[12] When laparotomy is required for other injuries prior to adequate radiographic evaluation, blunt renal trauma may be surgically staged. In this setting renal exploration is indicated in the presence of an expanding, pulsatile, or uncontained retroperitoneal hematoma that is thought to indicate renal pedicle avulsion or when the injured kidney is not visualized on the one-shot IVP.[29]

Penetrating Injury

In cases of penetrating renal trauma, the presence or absence of hematuria is of no consequence in predicting upper urinary tract injury. The location of the penetrating injury in relation to the urinary tract is the most important determining factor in deciding the need for radiographic investigation. Therefore, the absence of hematuria in a patient with a gunshot or stab wound in proximity to the urinary tract does not eliminate the need for IV contrast-enhanced CT as the initial diagnostic examination. Additional images obtained at 10 minutes after contrast injection are indicated to evaluate for delayed contrast extravasation and maximize the sensitivity of the study. Significant injuries to the kidney and ureter may occur in penetrating trauma *without* hematuria.[12,27,30] The majority of penetrating renal injuries require surgical intervention.

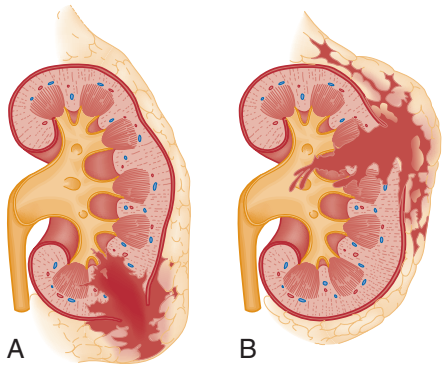


Figure 44-21. Major renal lacerations. **A,** Deep medullary laceration. **B,** Laceration into collecting system. (From Nicolaisen GS, et al: Renal trauma: Re-evaluation of the indications for radiographic assessment. J Urol 133:183, 1985.)

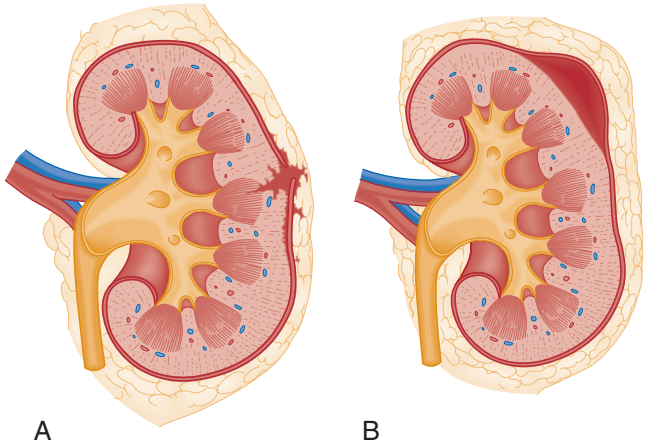


Figure 44-22. Minor renal injuries. **A,** Minor renal laceration. **B,** Renal contusion. (From Nicolaisen GS, et al: Renal trauma: Re-evaluation of the indications for radiographic assessment. J Urol 133:183, 1985.)

■ URETERAL TRAUMA

Pathophysiology

Approximately 80% of ureteral injuries are iatrogenic, resulting from complications of abdominal or pelvic surgery, with the remainder due to external trauma. The ureters are relatively protected from injury by the bony pelvis, vertebral column, and psoas muscle. Thus, ureteral trauma is rare, representing only 1% of all genitourinary injuries. Gunshot wounds are the most frequently reported mechanism, with ureteral injuries complicating 2 to 3% of abdominal gunshot wounds.[38,39]

Blunt force trauma causes ureteral injury when a significant decelerating force results in avulsion of the ureter from its fixed points at the ureteropelvic junction or, less commonly, the ureterovesicular junction. Due to the significant force required for ureteral injury, concomitant major organ injury occurs in approximately 90% of cases, and hypotension is present in greater than 50%.[40]

Clinical Features

There are no reliable signs and symptoms of ureteral injury in the acutely injured patient. Hematuria (gross or microscopic) is frequently present but may be absent in greater than 25% of patients, and thus its absence alone cannot be relied on to exclude the diagnosis.[40] After blunt trauma, ureteral injury should be considered in patients with a significant decelerating mechanism, gross hematuria, or microscopic hematuria with hypotension. With penetrating mechanisms, ureteral injury should be considered when the injuring force occurs in proximity to the anatomic course of the ureter. Missed ureteral injury may manifest in a delayed fashion with a variety of signs and symptoms, including fever, nausea and vomiting, hematuria, flank pain, and a palpable flank mass.

Diagnostic Strategies

IV contrast-enhanced CT of the abdomen and pelvis is highly sensitive for visualization of upper tract injuries and is often indicated for the investigation of associated nonurologic injuries. Additional images obtained 10 minutes after contrast injection enable the detection of delayed extravasation and increase diagnostic accuracy.[19]

Retrograde pyelography (Fig. 44-23) is slightly more sensitive than IV contrast-enhanced CT for the evaluation of ureteral injury, but its performance is frequently impractical in the multiply injured patient and it is rarely undertaken in lieu of CT. Likewise, a formal IVP, although sensitive, is of limited utility due to the significant time required for study completion.[40] In patients requiring immediate surgical intervention for other indications, a "one-shot IVP" performed in the emergency department or, more commonly, on the operating table may provide limited information to help the surgeon to stage upper tract injuries and confirm bilateral renal function. This test is performed by obtaining a single KUB film 10 minutes after the injection of 2 mL/kg of IV contrast (maximum 150 mL). The presence or absence of ureteral injury is subsequently confirmed during operative exploration.

Management

Operative repair is indicated for all ureteral injuries. With early diagnosis and appropriate treatment, the kidney and ureter can be saved in most cases. The complications of missed ureteral injuries are significant and include extended hospital stays, persistent urinoma, sepsis, loss of renal function, and death.[41,42]

EXTERNAL GENITALIA

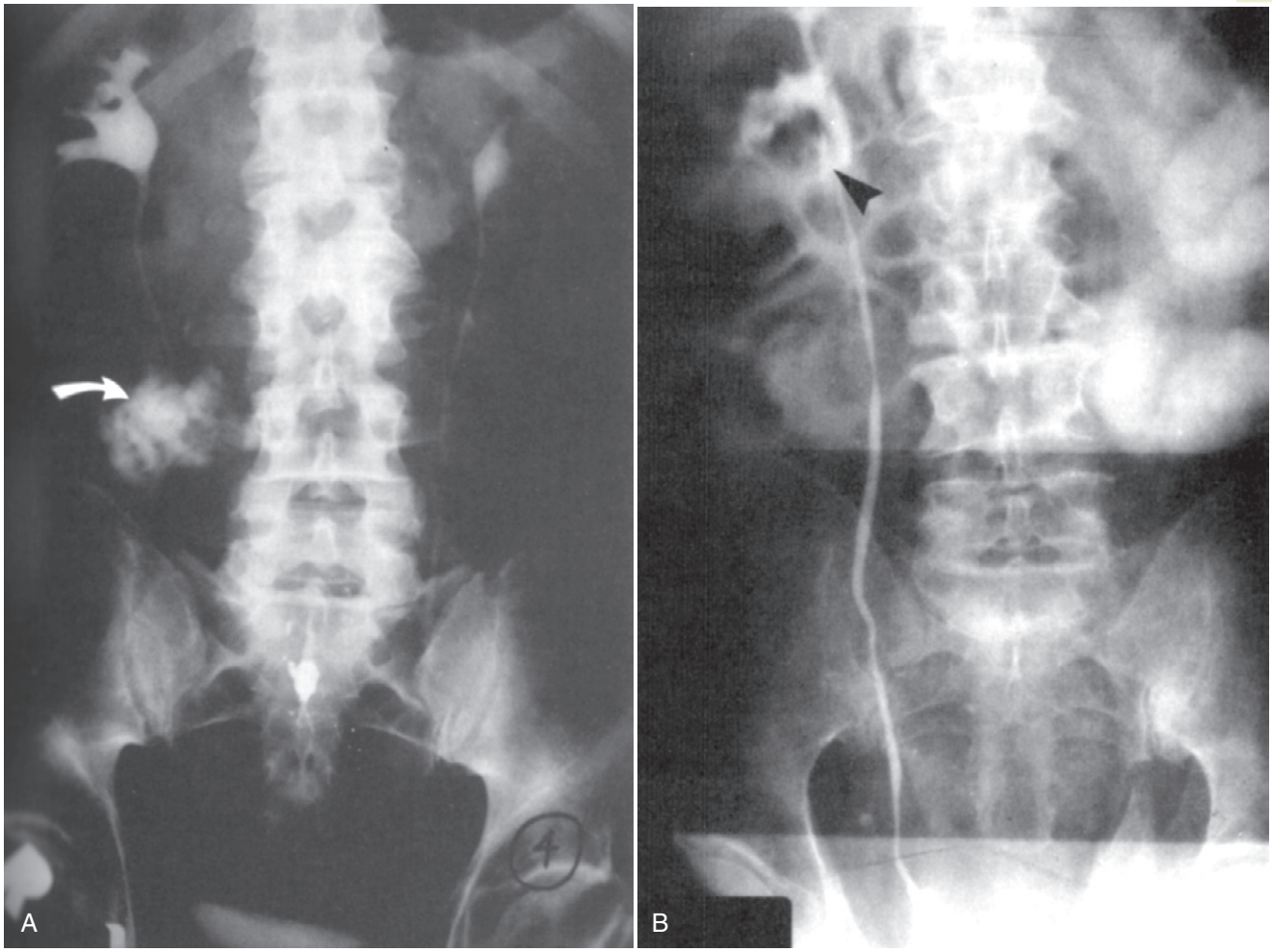
■ PENILE TRAUMA

Anatomy

The penis contains three masses of erectile tissue (Fig. 44-24). The two corpora cavernosa constitute the main bulk and lie in the center of the penis. The smaller corpus spongiosum lies on the ventral surface of the penis, encases the urethra, and expands at the penile tip to form the glans penis. Blood is supplied by arteries lying in each of the three erectile masses and by the two dorsal penile arteries. A single dorsal vein drains most of the penis. The tunica albuginea is a dense fibrous envelope that surrounds the corpus spongiosum and each corpus cavernosum. Buck's fascia overlies the tunica albuginea enclosing all three of the erectile masses, the dorsal arteries, dorsal nerve, and deep dorsal vein within a common compartment.

Clinical Features

Important historical factors to ascertain include the mechanism of injury and the state of the penis, flaccid or erect, at the time the injuring force was inflicted, as well as tetanus



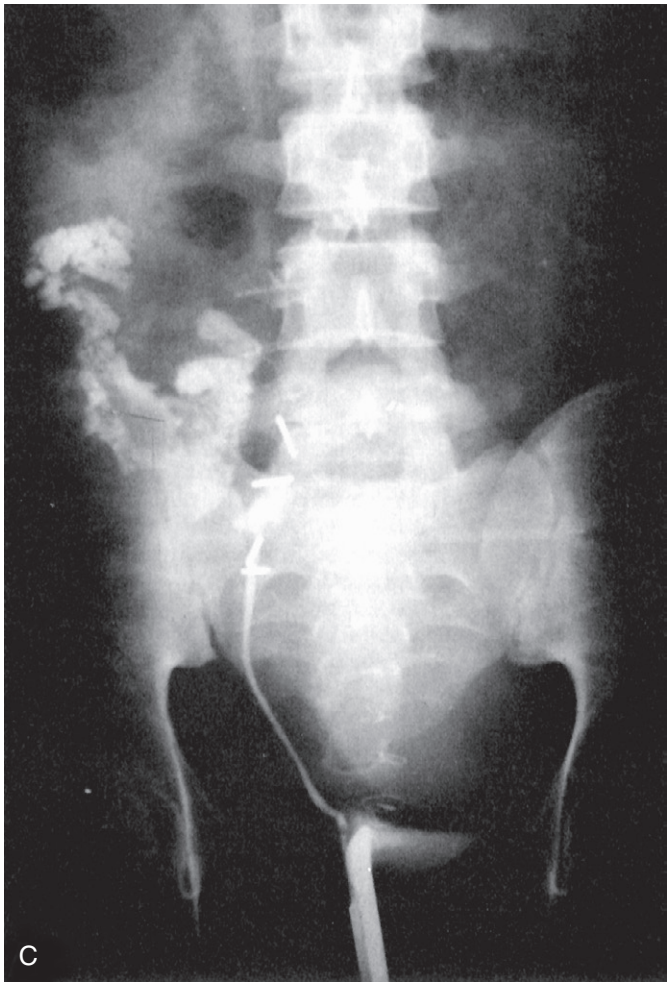


Figure 44-23. Ureteral injuries. **A,** Intravenous pyelography (IVP) of patient with upper ureteral injury demonstrating extravasation *(white arrow)*. **B,** Retrograde pyelogram demonstrating extravasation at the ureteropelvic junction *(black arrowhead)*. **C,** Retrograde pyelogram demonstrating extravasation into a urinoma in a patient with delayed diagnosis. (From Presti JC Jr, Carroll PR, McAninch JW: Ureteral and renal pelvic injuries from external trauma: Diagnosis and management. J Trauma 29:370, 1989.)

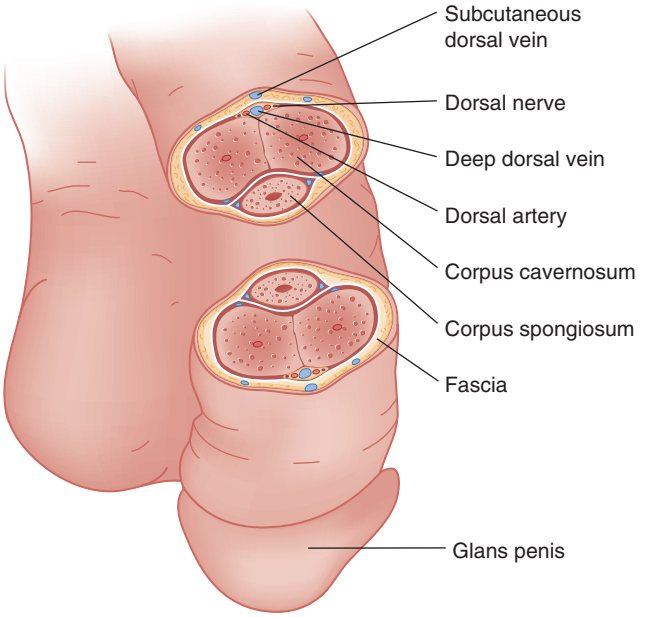


Figure 44-24. Cross-sectional view of the penis.

immunization status. Penile injuries range from small lacerations or contusions to skin degloving or amputation. Strangulation injuries of the penile shaft inflicted by an encircling piece of string or hair may be seen in children (Fig. 44-25). Adolescents and adults may present with various objects of penile incarceration such as bottles, washers, and metal rings (Fig. 44-26). These objects are often used to facilitate masturbation, prevent detumescence, and heighten sexual pleasure. Prolonged application of these devices may result in loss of superficial skin, deep urethral necrosis, or eventual need for penile amputation.[43]

The pendulous nature of the flaccid penis provides a measure of protection from blunt injury. By contrast, forceful bending of the erect penis may result in traumatic rupture of the corporus cavernosum, or penile fracture, due to tearing of the tunica albuginea. This injury may occur during vigorous sexual intercourse or masturbation. The patient often reports hearing a snapping sound followed by immediate pain, detumescence, and a slowly progressive penile hematoma (Fig. 44-27). In the majority of cases, the swelling and ecchymosis are localized to the penile shaft and contained by Buck's fascia. The resultant appearance has been described as an "eggplant deformity." If Buck's fascia is torn, blood may track along fascial planes to the scrotum, perineum, and pubis. The corporal defect may be palpable on physical examination. Urethral injury occurs in 10 to 38% of penile fractures.[43] The diagnosis is suggested by the presence of gross hematuria, blood at the urethral meatus, or the inability to void, but may occur even in the absence of these clinical findings. Urethral injury is present in up to 50% of all penetrating penile injuries.[19]

Penetrating trauma to the external genitalia may be inflicted by stab wounds or gunshot wounds. These injuries are frequently associated with concomitant injuries to the bladder, urethra, rectum, testis, and the iliac and femoral vasculature.[43] Penile amputation may result from interpersonal violence or as a manifestation of severe psychiatric disease.

The testicles are vulnerable to injury due to their location, but are relatively protected by the mobility of the scrotum, the tough tunica albuginea that surrounds the testes, and the cremasteric reflex. Eighty-five percent of testicular injuries are inflicted by blunt trauma, most commonly during sporting endeavors.[44] Mechanisms include falls, kicks, and direct strikes by thrown objects. Testicular rupture occurs in greater than 40% of blunt scrotal trauma in patients who present to the hospital.[12,45] Additional injuries include scrotal hematoma, hematocele, intratesticular hematoma, traumatic testicular torsion, testicular avulsion, testicular displacement, and epididymal injury. Symptoms include severe pain, faintness, nausea, vomiting, and occasionally urinary retention secondary to pain. Physical examination is often inadequate due to significant pain and swelling.[45]

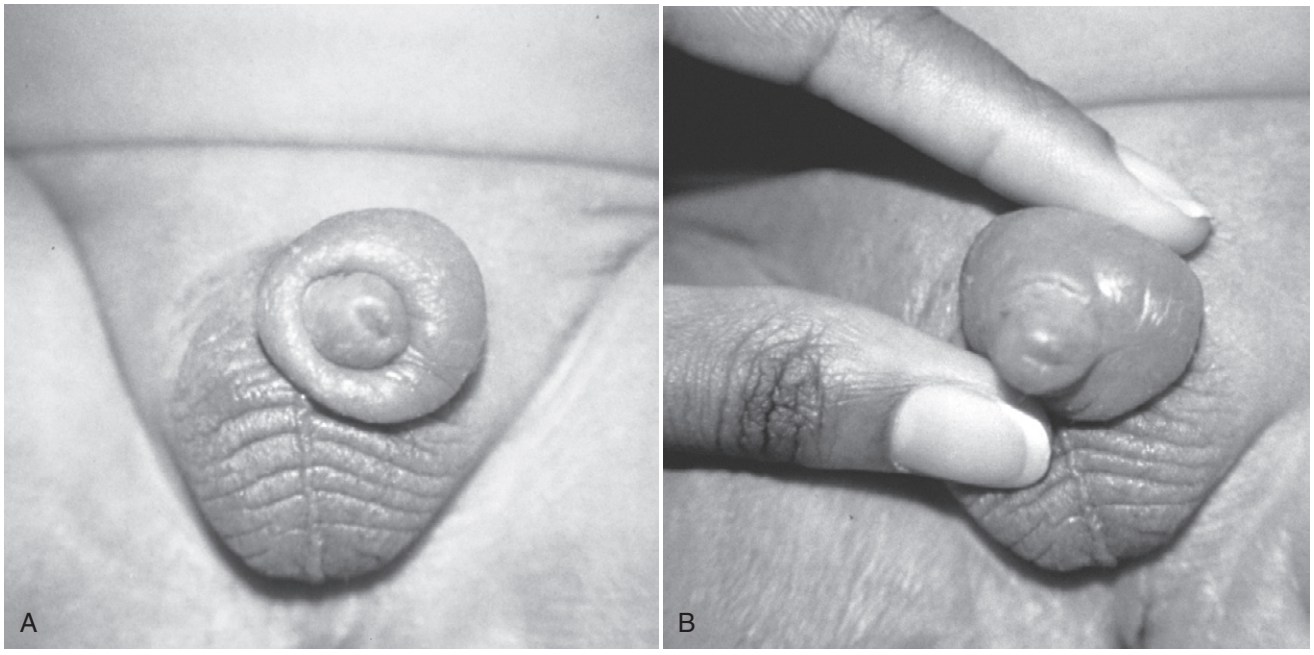


Figure 44-25. Idiopathic foreskin edema. **A,** This is the same picture that can be seen with penile strangulation injuries in children. **B,** The edematous foreskin must be retracted proximally and distally and encircling hair, string, or other objects looked for that may lead to vascular compromise.

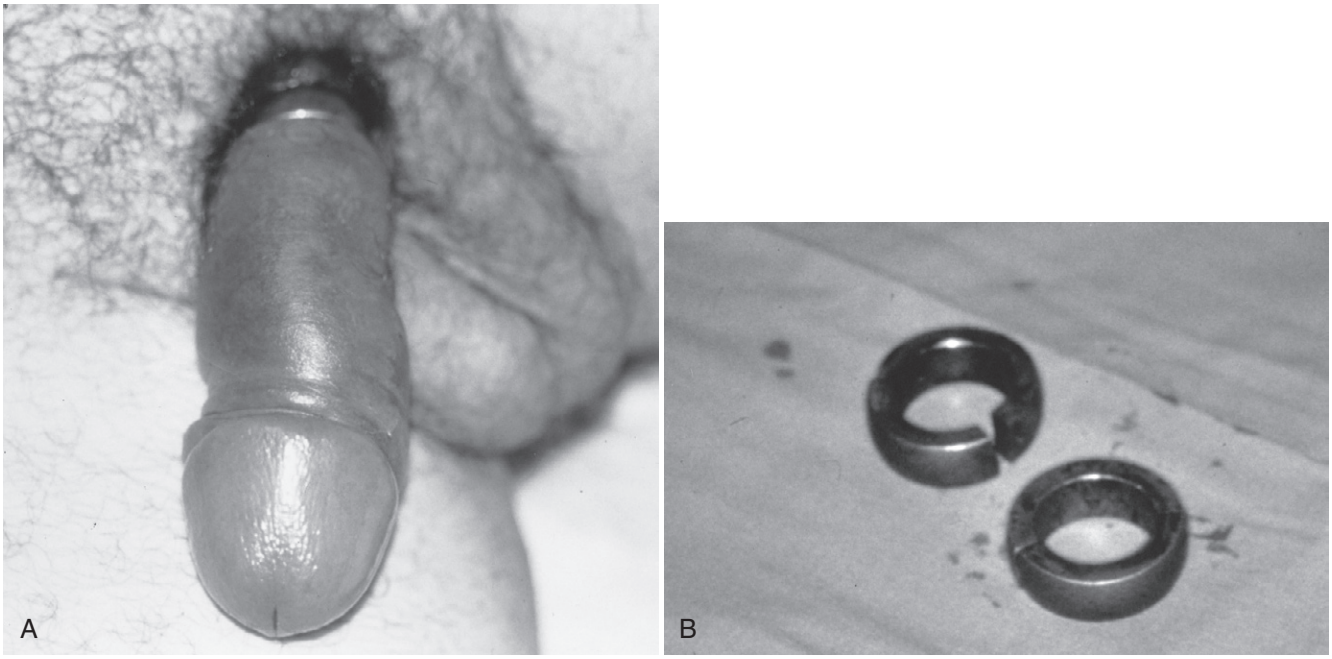


Figure 44-26. **A,** Self-induced priapism. This patient placed two steel washers (**B**) around the base of his penis to prolong his erection. Subsequent priapism developed, and the incarceration necessitated emergency intraoperative removal with a pneumatic orthopedic drill.

Figure 44-27. Fracture of the penis. Traumatic rupture of the corpus cavernosum, usually associated with sexual activity, results in a profound penile hematoma, most often requiring operative repair.

Genital bite wounds may be inflicted by humans during sexual activity or by animals. The predominant human oral bacterial organism in genital bite wounds is *Eikenella corrodens*; however, transmission of viral infections, including hepatitis and HIV is possible.[43] Dog and cat bites may lead to pathogenic infections with *Pasturella multocida* and anaerobic organisms. With animal bites, the possibility of rabies transmission must be considered.

Injuries to the female external genitalia may result from pelvic fractures, sexual assault, or straddle-type mechanisms. Hematomas and lacerations are the most common injuries. Physical examination includes evaluation for associated injuries of the vagina, urethra, bladder, and rectum. Screening for interpersonal violence should be considered in all women presenting with injuries to the external genitalia.

In children, blunt or penetrating injury to the external genitalia may be inflicted by straddle-type injuries or falls onto sharp objects. Child abuse should be considered and investigated when the explanation given for the event does not match the type of injury and objective physical findings. Examples include bruises that look like pinches, cigarette burns, or a penile injury reportedly caused by a falling toilet seat in a child who is too small to stand unsupported.

Diagnostic Strategies

A careful physical examination is usually sufficient to diagnose most blunt penile injuries. Retrograde urethrography is indicated in cases of suggested urethral injury, which should be considered in the presence of concomitant penile or scrotal hematoma, hematuria, or blood at the urethral meatus. Rarely, atypical presentations of penile fracture may require adjunctive imaging. Corpus cavernosography, ultrasound, and magnetic resonance imaging have all been advocated for this indication.[43,46,47] The acquisition of penile imaging should occur in consultation with the treating urologist.

Unlike penile injuries, physical examination is frequently inadequate for the assessment of blunt scrotal trauma. Ultrasound is the test of choice owing to its greater than 95% sensitivity for testicular rupture when the diagnosis is based on the finding of a heterogeneous echo pattern of the testicular parenchyma with a loss of contour definition (Fig. 44-28).[45,48] Scrotal imaging is rarely indicated after penetrating trauma because surgical exploration is usually warranted.

Management

Constricting devices must be promptly identified and removed, a procedure that can test the ingenuity of even the most experienced emergency physician (see Fig. 44-26). Various creative

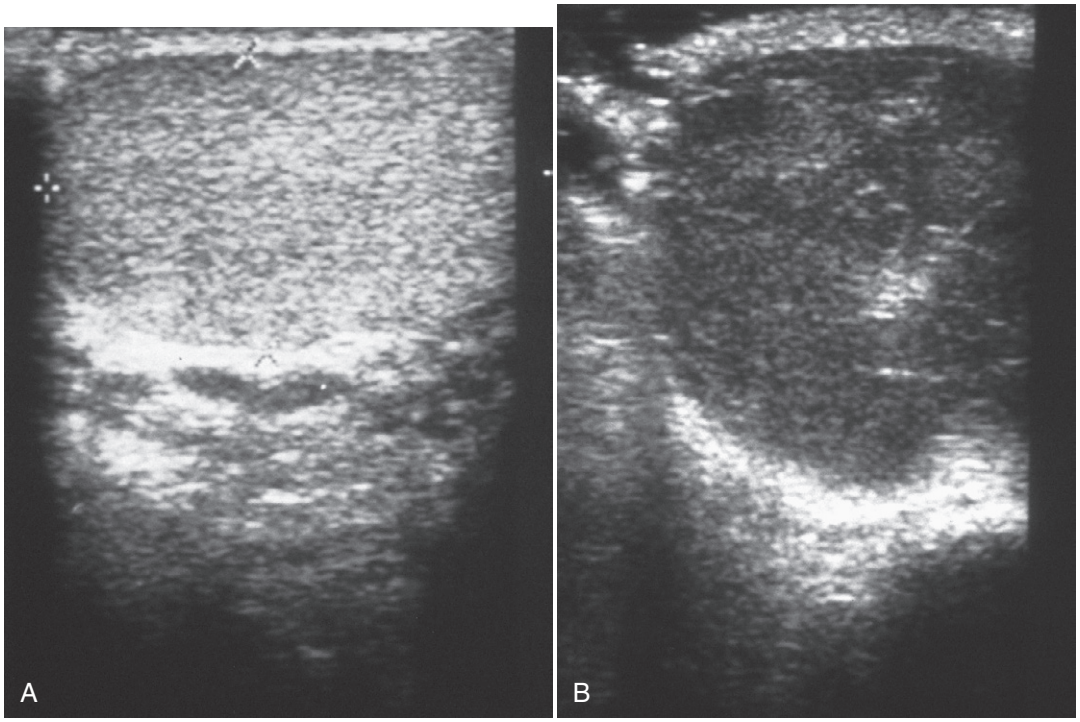


Figure 44-28. Testicular rupture. **A,** Testicular ultrasonogram demonstrates the normal homogeneous testicular pattern. **B,** The heterogeneous pattern of injury, tumor, or disruption.

techniques, using saws, metal cutters, or emery wheels, may be necessary to remove some metal objects. Reconstructive surgery of the penis may eventually be needed but is usually delayed until penile tissue viability has been determined. Fortunately, each corpora body has a separate blood supply and may be preserved even though the penile skin may slough and require skin grafting.

Superficial penile hematomas without rupture of the tunica albuginea and no immediate detumescence of the erect penis may be treated conservatively with the local application of ice and administration of nonsteroidal anti-inflammatory drugs (NSAIDs).[12] Superficial lacerations of the penile and scrotal skin may be primarily approximated with 4-0 chromic or Vicryl absorbable suture. Patients with degloving penile injuries and scrotal skin loss should be treated by a urologist and plastic surgeon in the operating room with cleansing, débridement, and skin flaps or skin grafts.

With penile fracture, immediate surgical repair of the tunica albuginea defect (within 24–36 hours after injury) is indicated to maximize functional outcomes.[12,44,46] Early surgical exploration and repair are recommended for most penetrating injuries to the penis.[49] Penile amputation may be managed by reimplantation or local reshaping. Successful reimplantation may be achieved even up to 24 hours after amputation.[43,44] The recovered amputated penis should be carefully wrapped in sterile, saline-moistened gauze and placed in a plastic bag. That bag is then placed in a second plastic bag containing ice. Hemostasis of a bleeding penile stump can usually be achieved with direct pressure.

After blunt scrotal trauma, surgical exploration is indicated for treatment of testicular rupture, large hematocele, traumatic torsion, and testicular dislocation. Testicular salvage rates are 80 to 90% when surgical exploration occurs within 72 hours and less than 50% when exploration is delayed beyond 72 hours.[44] In patients with a sonographically normal, homogenous-appearing testicle, exploration is not necessary.[45] Testicular contusions are treated with bedrest, ice packs, NSAIDs, and urology follow-up. Surgical exploration is indicated in nearly all cases of penetrating scrotal trauma.[45,49]

Patients presenting with simple bite wounds within 6 to 12 hours after injury without gross contamination can be treated with irrigation and primary closure.[43,44] Broad-spectrum antibiotic coverage with an agent such as amoxicillin-clavulanate is indicated. Grossly contaminated or infected wounds should be irrigated, covered with a sterile dressing, and managed in conjunction with the consulting urologist.

Human bite wounds represent a potentially serious polymicrobial infection. When cellulitis is present, immunocompromised patients should be admitted to the hospital for broad-spectrum IV antibiotic coverage for both aerobic and anaerobic organisms with an agent such as piperacillin-tazobactam. Immunocompetent hosts may be treated in the outpatient setting with broad-spectrum oral antibiotics, NSAIDs, and reevaluation in 48 hours.

KEY CONCEPTS

- Diagnostic evaluation of the urinary tract is generally undertaken in retrograde fashion, that is, suggestion and elimination of urethral injury before bladder injury before ureteral or renal injury.
- Urethral injury is suggested by the presence of a pelvic fracture, blood at the urethral meatus, an abnormally positioned prostate on rectal examination, or evidence of a perineal, scrotal, or penile hematoma.
- Gross hematuria alone or in conjunction with a pelvic fracture is the absolute marker for significant bladder injury. Grossly clear urine in a trauma patient without a pelvic fracture virtually eliminates the possibility of bladder rupture.
- Bladder injury should be ruled out by retrograde cystography, which is more accurate than methods using anterograde contrast administration.
- Adults at risk for significant blunt renal injury have gross hematuria, microhematuria with shock, or a history of sudden deceleration. Children at risk for significant blunt renal injury have hematuria with greater than 50 RBCs/hpf or a history of significant deceleration.
- IV contrast-enhanced helical CT with delayed images at 10 minutes after contrast injection is the imaging modality of choice for suggested upper tract injury.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 45 Peripheral Vascular Injury

Edward J. Newton and Sanjay Arora

PERSPECTIVE

Injury to major arteries or veins is often life-threatening but invariably poses a threat to the viability of the affected limb. Historically, because of rapid blood loss, injury to major vessels was often quickly fatal in the field. Most patients who survived to reach a hospital had relatively minor vascular injuries. However, with the advent of modern emergency medical services systems with advanced extrication methods and rapid transport, more patients with major vascular injury reach the hospital alive.[1] In addition, the incidence of penetrating civilian injuries from interpersonal violence and blunt injuries from motor vehicle–related trauma in the United States has increased dramatically during the past 50 years. Consequently, emergency physicians are frequently confronted with critically ill patients harboring overt or occult vascular injuries. Management of vascular injuries has evolved with advances in diagnostic methods and surgical techniques. Treatment of vascular injuries before and during World War II was simple ligation of the peripheral artery or vein involved. This approach resulted in limb amputation rates ranging from 40% for axillary artery injuries to 72% for popliteal artery injuries. During the Korean War, routine attempts to repair injured arteries decreased the amputation rate for popliteal injuries to 32%.[2] During the Vietnam War, repair of penetrating axillary and popliteal artery injuries with routine angiography and improved surgical techniques resulted in decreases in the amputation rate to as low as 5 and 15%, respectively, which approach the current rate of amputation for civilian injuries.[2,3] However, extrapolation of high-velocity military wound data to low-velocity civilian gunshot wounds may not be valid, and even lower rates might be expected with civilian wounds.

Tremendous progress has been achieved in diagnostic and therapeutic techniques for dealing with peripheral vascular injuries, and several noninvasive diagnostic modalities have emerged as accurate alternatives to surgical exploration or angiography. These techniques are easily used in the emergency department, and the goal of timely detection and repair of serious vascular injuries is achievable in the vast majority of cases.

Epidemiology

Throughout the world, the etiology of peripheral vascular injuries is divided almost equally between blunt and penetrating mechanisms. In the United States, 70 to 90% of these injuries are due to penetrating wounds mainly due to the high rate of penetrating trauma in inner-city urban areas.[4-6] Although the incidence of low-velocity gunshot wounds has decreased during the past several years, gunshot wounds remain the second leading cause of death in the 15- to 34-year-old age group in the United States.[7] Because of the increased use of percutaneous endovascular diagnostic and therapeutic procedures, the incidence of iatrogenic vascular injuries has increased and accounts for up to one third of all cases in some series.[8,9] Major venous injuries are present in 13 to 51% of cases, but more than 80% are associated with arterial injury as well.[10] Approximately 90% of patients with vascular injury are male, and most are younger than age 40 years.[5]

PRINCIPLES OF DISEASE

Pathophysiology

Blunt and penetrating types of trauma result in a similar spectrum of vascular injuries, although the mechanisms of injury differ. Although blunt vascular injuries are less common than penetrating injuries, they are often more severe and more commonly require amputation because of associated injuries to nerves, bone, and soft tissue. Certain mechanisms of injury, such as animal bites that crush and lacerate vessels, combine penetrating and blunt mechanisms.

Penetrating Trauma

Penetrating trauma from gunshot wounds results in the formation of a temporary cavity within distensible soft tissues with almost immediate recoil of these tissues. The size of the cavity and hence the degree of soft tissue injury depend directly on the velocity of the missile, as well as the tumble and yaw of the bullet. Consequently, gunshot wounds can cause direct arterial laceration or transection in addition to vascular injury at some distance from the track of the bullet. The latter injuries tend to be tears in the intima of an artery with subsequent thrombosis that may not become apparent for hours to months after the injury.

Stab wounds can cause vascular injury by complete or partial transection of vessels. Partial laceration of an artery may produce few symptoms of arterial insufficiency on initial evaluation but commonly results in delayed complications. The vascular structures at risk can be predicted more reliably with stab wounds than with gunshot wounds by taking into consid-

eration the anatomic location, the depth and direction of the wound, and the implement involved.

Shotgun wounds are less common than gunshot or stab wounds and cause injuries varying from minor soft tissue wounds to massive destruction of soft tissue and bone, depending primarily on the range from which the shotgun was fired. The presence of multiple missiles ranging from 9 or 10 (buckshot) to dozens (birdshot) also complicates the evaluation of these injuries because of the many potential sites for vascular injury to occur. In addition, close-range shotgun wounds can cause significant blunt trauma to blood vessels, as well as a higher rate of bone and nerve injury than occurs with gunshot wounds. Migration of pellets proximally through the venous system to the heart or migration through an artery with subsequent distal occlusion has been reported frequently as a delayed complication.

Blunt Trauma

Blunt injury involves avulsion forces that can stretch vessels beyond their capacity or direct crushing injury that disrupts the vessel wall. Fracture fragments resulting from blunt extremity trauma can lacerate or entrap vessels. Vascular injury can range from small intimal tears to complete avulsion of arteries and nerves. Open avulsion injury of a limb is particularly severe because the skin is the final structure to tear, and once such tearing occurs, it is inevitable that vessels and nerves will be torn as well.[11] Vascular injury must also be suspected in patients with massive soft tissue avulsion or crush injury, displaced long bone fractures, electrical or lightning injuries, and severe burns, as well as in those with compartment syndrome from trauma or prolonged immobilization as a result of stroke, coma, drug overdose, or other causes.[12-15] Dog bites that are inflicted by large animals, such as those used by law enforcement, are particularly prone to arterial injury and wound complications.[12,13] Collateral circulation may continue to perfuse the limb adequately, but injuries that occur proximal to the collateral branch point or that involve both the main trunk and collateral branches will preclude adequate flow.

Distal ischemia results from the inability of tissues to continue aerobic metabolism. Eventually, anaerobic metabolism consumes all substrate, thereby resulting in the accumulation of lactic acid. As ischemia progresses, cellular integrity is lost and irreversible cell death occurs. A vicious cycle of tissue edema and further impairment of the blood supply occurs.

When no specific measures are taken to cool the limb, it is said that the limb is undergoing "warm ischemia" at room temperature. Although individuals may vary, 6 hours of complete warm ischemia is generally considered the point at which irreversible nerve and muscle damage begins to occur. After 6 hours of warm ischemia, 10% of patients will have irreversible damage; by 12 hours, 90% will have irreversible damage. Artificially cooling the limb to just higher than freezing temperature will reduce the metabolic demands of unperfused tissues and greatly prolong the tissue's tolerance of ischemia to 24 hours or more.

Two main types of vascular injury can result from trauma: *occlusive injury* (transection, thrombosis, and reversible spasm), in which all effective perfusion distal to the occlusion is lost, and *nonocclusive injury* (intimal flap, dissection, arteriovenous fistula [AVF], and pseudoaneurysm), in which some arterial flow continues past the injury.

Complete Occlusive Injury

Transection. The most common vascular injury is complete transection in which distal flow is effectively eliminated. Cleanly transected arteries will often retract and undergo spasm so that blood loss is minimized. With longitudinal arterial lacerations and venous injuries, blood loss cannot be limited by this means, and such injuries tend to result in greater blood loss. Pulsatile bleeding may lead to exsanguinating hemorrhage and shock.

Figure 45-1. Complete thrombosis of the distal brachial artery after reduction of a posterior elbow dislocation. (Courtesy of D. Demetreades, MD.)

Thrombosis. Intraluminal thrombosis (Fig. 45-1) may occur in an injured artery acutely (within 24 hours) or may be delayed for many months. Acute thrombosis is initiated by stasis resulting from compression of the artery or from a disruption in the intima of an artery that becomes a nidus for thrombus formation. As the thrombus propagates, complete occlusion of the vessel can occur. Delayed thrombosis can occur months to years after injury if the injured vessel heals with stricture formation and decreased blood flow distally, followed by stasis and clot formation.

Reversible Arterial Spasm. The precise cause and incidence of significant reversible arterial spasm after trauma are unknown. In many cases, the spasm occurs at some distance from the site of traumatic injury. In response to a traumatic stimulus, segmental narrowing of an artery may occlude the artery and produce distal ischemia. The spasm usually reverses with conservative treatment (topical warm saline or topical nitroglycerin paste), but prolonged spasm may require infusion of vasodilators such as nitroglycerin, calcium channel blockers, alpha blockers, nitroprusside, specific prostaglandin inhibitors, or warm saline.[16] In many series, segmental arterial spasm is the most common arteriographic finding. However, it should never be assumed on clinical grounds that symptoms of ischemia are due to arterial spasm; that diagnosis is based on arteriographic results only.

Nonocclusive Injuries

Intimal Flap. An intimal flap occurs when there is a break in the intima of a vessel, generally from excessive stretch or concussive forces. Although flow is not altered by small flaps and the associated soft tissue wounds often appear benign initially, these intimal flaps may become a nidus for thrombosis that can

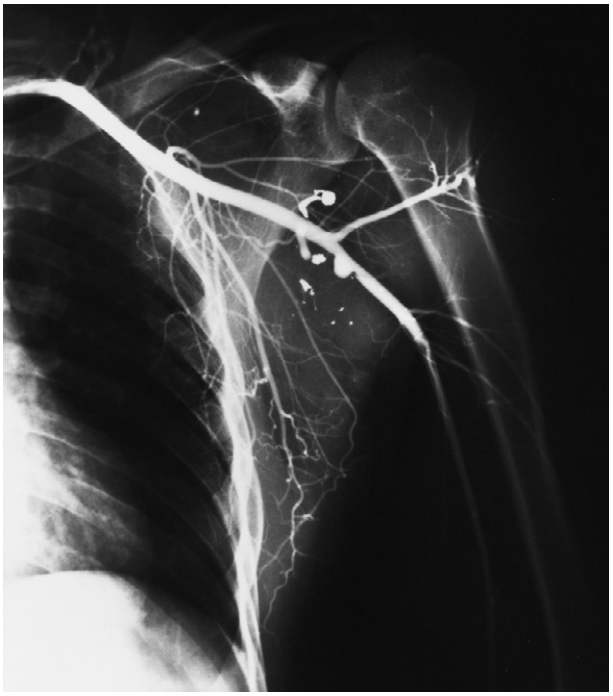


Figure 45-2. Multiple small pseudoaneurysms of the axillary artery after penetrating injury. (Courtesy of D. Demetreades, MD.)

occur hours to months after the initial injury. However, most intimal flaps heal spontaneously, and asymptomatic injuries that do not disrupt perfusion of the limb can be treated conservatively.

Pseudoaneurysm. A true aneurysm contains all three layers of the vessel wall (intima, media, and adventitia) and rarely is caused by trauma. A pseudoaneurysm is formed following a tear in a vessel wherein the hemorrhage is contained by surrounding fascia and the resulting hematoma is gradually encased by a capsule of fibrous tissue, analogous in consistency to the adventitia of a normal vessel (Fig. 45-2). Because it is relatively thin walled, rupture of a pseudoaneurysm is a distinct possibility. In addition, because its diameter inevitably expands under arterial pressure over days to months, compression of adjacent tissue may result in neuropathy, venous obstruction with resultant peripheral edema and venous thrombosis, and even erosion into adjacent bone.[17] The cavity of a pseudoaneurysm is in direct communication with the lumen of the vessel, so embolization of mural clots may produce distal arterial occlusion. Patients with pseudoaneurysm are commonly seen months to years later with symptoms of compression neuropathy or peripheral arterial embolism or for investigation of a soft tissue "tumor" that represents the growing aneurysm.

Arteriovenous Fistula. An AVF is formed when both the artery and an adjacent vein are injured. Higher pressure arterial flow is directed into the lower pressure vein, thereby diverting the blood supply to distal tissues and engorging the distal veins. Because the aperture of the fistula is often relatively narrow and thus results in turbulent flow, a bruit and palpable thrill are common diagnostic findings. Symptoms are primarily those of distal ischemia, but rarely high-output congestive heart failure may occur when large central vessels are involved. Symptoms are often delayed for months because it takes time for the fistula to mature.

Compartment Syndrome. Compartment syndrome is most common after crush injury or a long bone fracture but may also be seen after reperfusion of an ischemic limb. Initially, blood flow is diminished and the injury can be considered nonocclusive. Progressive edema elevates tissue pressure above capillary pressure, thus ending arterial perfusion and initiating a cascade of events that results in compartment syndrome. The risk for this complication is increased when ischemia time is prolonged; in the presence of combined arterial and venous injury; after ligation or repair of a major artery or vein; or in the presence of significant soft tissue injury, frequently concomitant with a long bone fracture.[5] Smaller caliber vessels are compressed first, whereas larger vessels remain relatively patent and compartment pressure rarely exceeds arterial pressure, so pulses may be palpable until late in the course. If allowed to progress, however, all blood flow may end and the injury is then an occlusive one. After restoration of arterial flow to a previously ischemic limb, a cascade of reperfusion injury has been identified that results from release of oxygen free radicals, lipid peroxidation, and influx of intracellular calcium. These mediators give rise to progressive cellular damage, edema, and necrosis, thereby propagating the vicious cycle that increases compartment pressure.[18] Consequently, frequent reexamination of the limb is indicated to assess compartment pressure after arterial repair.

CLINICAL FEATURES

Detection and treatment of vascular injuries must take place within the context of the overall resuscitation of the patient according to established principles of trauma care.[19] If the source of bleeding is readily identifiable, it is compressed with digital pressure. While control of active bleeding is being achieved in this manner, detection and treatment of other life-threatening injuries proceed concurrently. Peripheral vascular injury can occur coincident with other life-threatening trauma, which may take higher priority in resuscitating the patient. In other cases, peripheral vascular injury may be the most serious or only injury, and evaluation and management of this type of injury can proceed directly. Despite rapid transport to a hospital through a modern emergency medical service, injury to large central arteries and veins is still often fatal, and many of these deaths occur before medical contact. Patients who survive to reach the hospital may have obvious exsanguinating hemorrhage or only very subtle signs of vascular injury. Many patients have no evidence of injury but are considered at risk for vascular injury because of penetrating wounds in close proximity to major neurovascular bundles or because they have sustained high-risk injuries such as posterior knee dislocation. Patients who remain hypotensive after an initial fluid challenge may harbor an occult vascular injury if no other cause is found. In addition, patients with symptoms of intermittent claudication or with unexplained peripheral embolization and a history of previous trauma to the limb should be suspected of having occult arterial injury.

Peripheral vascular injury can be divided into three categories by physical examination: hard findings, soft findings, and asymptomatic high-risk wounds based on the mechanism of injury.

Hard Findings of Vascular Injury

Many patients have the classic "hard" findings of arterial injury, including pulsatile bleeding, loss of distal pulses, an audible bruit or palpable thrill indicative of an AVF, or an expanding or pulsatile hematoma.[20] In addition, pallor or cyanosis and decreased temperature are common in a poorly

perfused extremity, and massive distention of distal superficial veins may indicate an AVF as arterial flow is directed into distensible veins. The incidence of arterial injury in patients with any hard finding is consistently greater than 90%,[21,22] and the presence of these findings requires further investigation by emergency angiography or immediate surgical intervention, depending on the duration of warm ischemia and the overall status of the patient.

Soft Findings of Vascular Injury

An additional group of patients have "soft findings" of vascular injury, including a palpable but diminished pulse in comparison to the uninjured extremity, isolated peripheral nerve injury, history of severe hemorrhage in the field, unexplained hypotension, or a large nonpulsatile hematoma.[20-22] The significance of prolonged capillary refill is controversial; some experts find it to be a reliable sign of vascular injury (when combined with a pulse deficit) and consider delayed capillary refill to be a valid soft sign of vascular injury. Others have found this sign to be a nonspecific and unreliable predictor of arterial injury.[2,5] Delayed capillary refill by itself is insufficient to diagnose arterial injury, but in combination with other physical signs, it supports the diagnosis.

Isolated penetrating injury to a peripheral nerve is commonly associated with vascular injury because of the close proximity of these structures within the neurovascular bundles. Vascular injury occurs in 8 to 45% of cases of penetrating peripheral nerve injury.[23,24] Conversely, vascular injuries have associated peripheral nerve injury in almost half of cases. It is sometimes difficult to distinguish whether the pain, paresthesias, or paralysis is due to a primary nerve injury, an associated vascular injury causing compression of the nerve, or compartment syndrome. In general, primary nerve injury occurs immediately at the time of injury, whereas vascular neuropathy occurs over minutes to hours after the injury. Up to 35% of patients with "soft" findings of vascular injury have positive angiographic studies, although only a small proportion of these injuries require emergency repair.[20,24,25]

High-Risk Injuries

The proximity of a penetrating wound to a neurovascular bundle is defined imprecisely. Various definitions include 1 cm, 1 inch, or 5 cm as constituting "proximity." Certainly, penetrating wounds that occur within 1 cm of a major neurovascular bundle or whose presumed trajectory has crossed such a bundle ("proximity wounds") are more likely to produce an occult vascular injury. Major neurovascular bundles include large limb arteries proximal to critical branch points, such as the axillary, brachial, common femoral, and popliteal arteries (Figs. 45-3 and 45-4).[26] In addition, a small minority of patients with high-risk injuries, such as bites from large dogs or other animals, severely displaced fractures, crush injuries, or major joint dislocations (especially knee dislocation), will initially have occult vascular injury that may not be detected by physical examination. The risk of missing such injuries is that the traditional 6-hour window of warm ischemia time will be exceeded or the patient will experience delayed complications resulting in loss of the limb. For example, patients with intimal flaps may be completely asymptomatic initially but can subsequently be subject to arterial thrombosis. Similarly, pseudoaneurysms progressively enlarge to produce compression of adjacent structures but may be very small and undetectable on initial physical examination. Consequently, many centers routinely perform some ancillary confirmation of arterial patency in these cases.

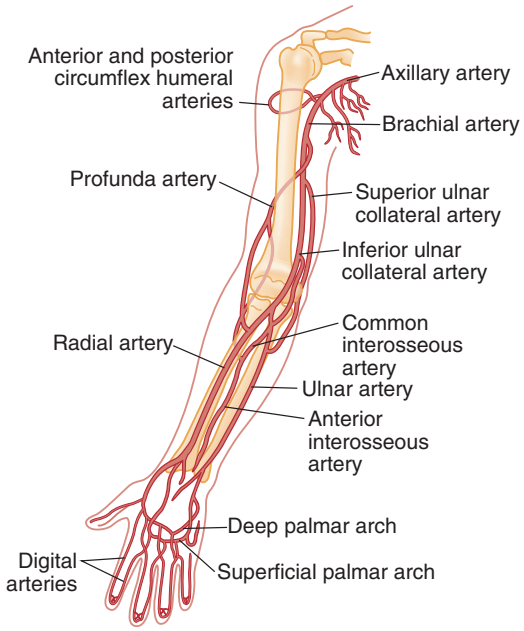


Figure 45-3. Major arteries of the upper limb. (From Snell R, Smith M [eds]: Clinical Anatomy for Emergency Medicine. St. Louis, Mosby, 1993.)

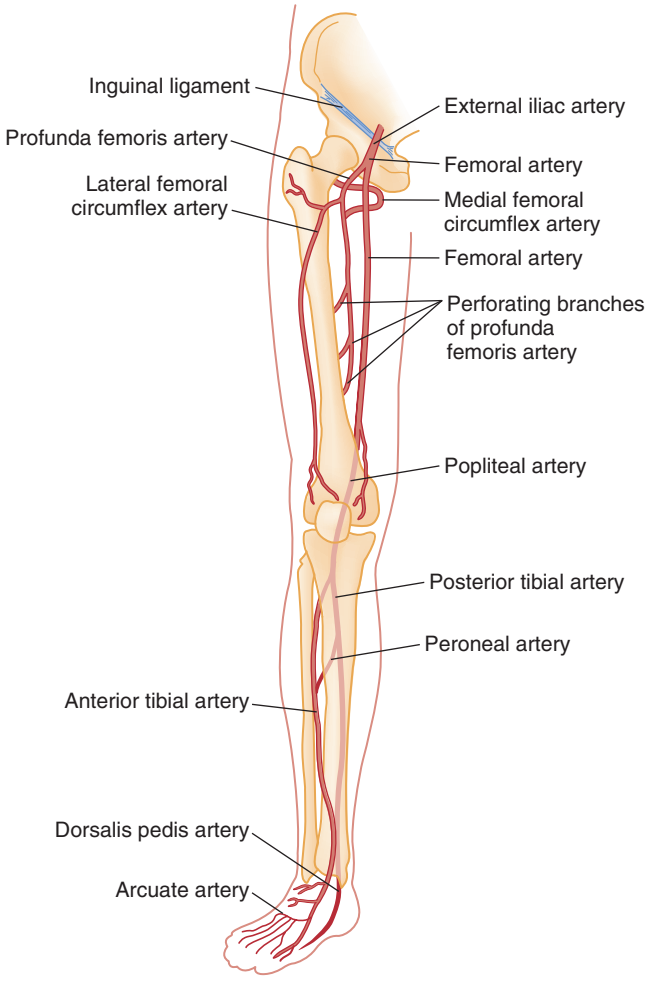


Figure 45-4. Major arteries of the lower limb. (From Snell R, Smith M [eds]: Clinical Anatomy for Emergency Medicine. St. Louis, Mosby, 1993.)

History

In patients who achieve and maintain hemodynamic stability, a more comprehensive history can be obtained. Important historical points to note include the exact time and mechanism of the injury. The time of injury is important because of the significant morbidity that results from prolonged warm ischemia time. The mechanism is of clinical and often forensic importance in that the injury is frequently inflicted during an assault or other violent crime, in the context of domestic violence or physical abuse, or in association with work. Various mechanisms of injury may mandate special reporting and may alter the patient's ultimate disposition. Certain types of injuries, such as crush or bite wounds, are particularly prone to complications. The occupation, avocation, and hand dominance of the patient are pertinent because a more aggressive strategy may be indicated in certain cases. Medical conditions that pose a risk of complications are important to note. Patients who are immunocompromised because of diabetes, acquired immunodeficiency syndrome, asplenia, cancer, or steroid use are at increased risk for infection and impaired wound healing. Patients with previous vascular insufficiency have more tenuous perfusion, are more susceptible to ischemia from elevated compartment pressure, and have a higher incidence of complications. As with most aspects of trauma care, patients whose sensorium is altered by head injury or intoxication, patients with spinal cord injury who cannot perceive pain, and those with significant painful distracting injuries will not reliably be able to report pain or paresthesias suggesting vascular insufficiency, so extra caution must be exercised in these cases.

Physical Examination

Surprisingly, in this era of increased reliance on technology, meticulous physical examination in combination with comparison of blood pressures in the affected and unaffected limbs has reemerged as the mainstay of diagnosis of vascular injury.[21] Physical examination is directed at discovering evidence of local wound complications and distal ischemia suggestive of vascular injury. Palpation of pulses in the affected extremities is the initial step. A comparison of the strength and quality of the pulses between the injured limb and its uninjured counterpart is then made. Isolated detection of a pulse deficit distal to the site of injury is a finding that merits further investigation rather than immediate surgery because palpation of pulses is a relatively inaccurate means of predicting arterial injury. False-positive findings of a pulse deficit may occur because of shock, in which all pulses are diminished; congenital absence of a pulse in one extremity; preexisting vascular disease; or arterial spasm or compression. A false-positive finding of a pulse deficit occurs in 10 to 27% of cases.[5,21] False-negative findings can occur with transmission of the pulse through a "soft clot," past an intimal flap, or through collateral circulation. Distal pulses can persist in 6 to 42% of patients despite significant arterial injury.[27] Compression of an artery by casts, splints, or dressings may produce a pulseless extremity, and these should be removed if evidence of ischemia occurs. Finally, although the pulse may be absent, the limb may be well perfused by collateral arterial supply, thus making repair of the arterial injury less compelling. Simultaneous palpation of the injured and unaffected limbs can detect relatively small differences in skin temperature that may suggest hypoperfusion. Testing two-point discrimination on the injured and unaffected limbs is similarly an effective means of detecting sensory deficits. Auscultation over the site of injury is an often-ignored examination that may reveal a bruit suggestive of an AVF. A bruit is audible in more than half of patients with an AVF.[28] Repeated examination of the hematoma adjacent to the wound is indicated to determine whether it is expanding or pulsatile.

Despite the limitations just noted, reliance on the history and physical examination to triage patients into immediate surgery, angiography, and observation groups has been found to be relatively dependable, with a sensitivity of 92% and a specificity of 95%.[21]

DIAGNOSTIC STRATEGIES

The diagnostic strategy for detection of peripheral vascular injury must be tailored to the clinical situation. Patients with clearly evident major arterial injury (e.g., pulsatile hemorrhage from a penetrating wound with a cold, pulseless distal end of the extremity) may require emergency operative intervention without the potential benefit of any ancillary confirmation of their injury. Occasionally, the use of an intraoperative angiogram may be helpful in delineating the exact location and nature of the injury in patients taken directly to the operating room. However, delaying definitive treatment of an obvious arterial injury that is approaching the 6-hour limit of warm ischemia time to obtain an angiogram is ill advised.

Plain Radiography

Plain radiographs of the affected extremity are indicated to detect fractures, joint penetration, and foreign bodies. With gunshot wounds, the sum of the number of intact bullets seen on x-rays and the number of wounds in the body must be an even number. Failure to locate a bullet can result in unexpected complications. Rarely, bullets or shotgun pellets can migrate distally and produce vascular occlusion or migrate proximally through the venous system to the heart. These emboli are readily detected on plain radiographs if the search is vigilant.[29,30] Lead bullets retained within a synovial joint can result in systemic absorption and elevated lead levels and should be removed electively.[31-37]

Pulse Oximetry

Several relatively simple noninvasive maneuvers can be performed at the bedside to elicit evidence of arterial injury. The use of pulse oximetry has been suggested as a means of identifying limb ischemia after trauma, but it has been found to be relatively insensitive for this purpose. Clearly, in the absence of a pulse, no reading can be obtained. As the technology of transcutaneous measurement of physiologic indices advances, measurement of tissue oxygenation by near-infrared spectroscopy to quantify muscle oxyhemoglobin may prove more useful in detecting vascular injury because these devices are portable, noninvasive and simple to use and appear to provide more accurate information than pulse oximetry.[38-43]

Hand-held Doppler

An inability to palpate pulses in an injured extremity should be verified by auscultation with a hand-held Doppler unit. Apart from the absence of any signal, arterial injury may be suggested by a change in the usual triphasic quality of the Doppler pulse to a biphasic or monophasic waveform as the pulse is "damped" by partial occlusion. Although more sensitive, auscultation of the pulse by Doppler is subject to the same types of limitations as is palpation of the pulse.

Ankle-Brachial Index and Arterial Pressure Index

Determination of the ankle-brachial index (ABI) or the arterial pressure index (API) has been well studied and provides more accurate information than physical examination alone. Systolic pressure is measured by inflating a standard blood pressure cuff proximal to the injury and recording handheld Doppler systolic pressure distal to the injury. The process is repeated on the uninjured limb, and a ratio of injured to uninjured systolic pressure is calculated (API). Generally, a ratio less than 0.90 is considered abnormal and is an indication for further investigation. In several studies, an API less than 0.90 yielded a sensitivity of 95%, specificity of 97%, positive predictive value of 100%, and negative predictive value of 95%.[2,5,20,44-47] However, a few studies have found API to be less accurate, including one in which a cutoff of 0.90 resulted in a false-negative rate of nearly 40%; nevertheless, the use of an API ratio less than 0.90 can eliminate a large number of unnecessary angiograms for proximity wounds and increase the diagnostic efficiency of angiography or computed tomographic angiography (CTA) by limiting its use to high-yield cases.

Patients with an API of 0.90 to 0.99 merit observation for 12 to 24 hours for repeated physical examination and API measurements to detect evolving injury. Patients with a normal physical examination and normal ABI can be safely discharged from the emergency department provided there are no other injuries requiring admission.[47]

Exclusive reliance on API to screen for arterial injury has significant limitations. Comparisons cannot be made when both limbs are injured or when severe soft tissue mangling precludes placing a blood pressure tourniquet or locating the artery to be measured with the Doppler unit.[20] As with physical examination, the sensitivity of API is limited when an intimal flap allows near-normal flow or when collateral circulation is sufficient to produce near-normal systolic pressure, as in proximal injuries to the subclavian or iliac vessels. Certain arteries (e.g., the profunda femoris, profunda brachii, and peroneal arteries) normally do not produce palpable pulses, and API is of limited utility in these injuries. Shotgun wounds often have normal APIs despite multiple small arterial wounds; angiography is the preferred diagnostic modality in this group. As with angiography, API cannot detect venous injuries.

Despite the limitations previously noted, API has proved effective in screening patients with proximity wounds. The vast majority of injuries missed by API heal spontaneously. Those that do not heal are generally seen within 3 months with signs of arterial injury and can be repaired electively.

Ultrasound

The development of relatively small portable ultrasound (US) units has made possible direct visualization of both arterial and venous flow in major vessels. There are several different types of US that can detect vascular injury, and newer, more accurate techniques are being developed rapidly. B-mode (real-time) ultrasound is the most readily available form of US in portable units. It can easily visualize arterial pulsation in major vessels. Loss of pulsation distal to an obstruction or thrombosis is readily apparent. However, B-mode US cannot visualize certain anatomic areas accurately (subclavian and iliac vessels) because of overlying gas and is unreliable in detecting a fresh, relatively nonechogenic thrombosis or hematoma. As blood liquefies within a hematoma, it becomes echolucent and more readily distinguishable from surrounding tissues.

Doppler US interprets sound moving toward or away from the transducer as flow. Venous flow is heard as a low-pitched hum, whereas arterial flow has a higher pitched triphasic quality. The combination of B-mode and Doppler US is called duplex US and has enhanced accuracy in examining blood vessels. Duplex scans showing a focal increase in peak systolic velocity suggest partial obstruction of the vessel. However, duplex scanning is slightly less accurate in detecting injuries that do not decrease flow, such as small pseudoaneurysms, AVF, and intimal flaps.[48] Also, it is technically limited in examining certain anatomic areas, such as the profunda femoris and profunda brachii arteries and the iliac and subclavian vessels. Duplex US findings may be subtle, and as with other applications of US, its accuracy is highly operator dependent. Despite these limitations, the sensitivity of duplex US in comparison to standard angiography ranges from 83 to 100%, with a specificity of 99 to 100% and an accuracy of 96 to 100%.[20,48-50]

Color flow Doppler converts Doppler echoes into quantitated visual signals. Flow toward the transducer is seen as red, and flow away from the transducer is seen as blue. The intensity of the color (the number of pixels on the screen) is proportional to flow through the vessel. Small prospective studies have indicated a high rate of accuracy in detecting arterial injury.[48-50] Absence of flow is readily apparent, but more subtle injuries, such as intimal flaps and small pseudoaneurysms, are more difficult to identify. In addition, color flow Doppler is more accurate than standard venography in detecting major venous injuries.[49] The overall sensitivity of color flow Doppler in detecting arterial injury is 50 to 90%, with a specificity of 95 to 99%. The sensitivity for detecting injuries requiring surgical repair is greater than 90%.

The use of intravascular US for examination of abdominal aortic aneurysms has been well documented. Although not yet applicable to smaller peripheral vessels, with further reduction in size of the transducers, this technique may eventually be applicable for peripheral vascular injury as well.

Computed Tomography and Magnetic Resonance Imaging

With a few important exceptions, computed tomography (CT) with contrast enhancement (CTA) has largely replaced catheter-based angiography for the detection of peripheral vascular injury in most trauma centers. Multidetector helical CT (MDCT) scanners have proven very accurate for diagnosis of peripheral vascular injury in multiple series with a sensitivity of 93 to 100% and specificity of 87 to 100% compared to catheter-based angiography.[51-63] The advantages of CTA over catheter-based angiography are that it is noninvasive, readily available, less costly, and provides information on other injuries in the region being studied. However, there are several pitfalls in the use of MDCT angiography. Metallic artifact from bullets, orthopedic hardware, or other penetrating objects may obscure visualization of parts of a vessel.[58] Venous injuries may be missed depending on the phase of the contrast.[58] Due to the enhanced detail, accuracy, and speed of image acquisition with 64-256-slice CT scanners and the ability to perform three-dimensional reconstructions, reliance on this modality will likely increase in the future. Magnetic resonance imaging angiography has been described and accurately detects vascular injuries but has yet to prove clinically useful.[64,65]

Arteriography

The policy of routinely exploring proximity wounds greatly improved the preservation of injured limbs in World War II. With the advent of arteriography, it became apparent that

many negative wound explorations could be avoided with routine arteriography. In a study using routine arteriography, the negative surgical exploration rate in patients with "soft signs" of arterial injury or with proximity wounds decreased from 84 to 2%.[66] As a result, until recently, catheter-based contrast angiography has been the gold standard for diagnosing peripheral arterial injury, with a sensitivity of 99% and specificity of 97%.[20]

Beginning in the 1980s, the number of civilian penetrating wounds increased dramatically. Because of high cost, limited availability at all hours, and poor reimbursement rates, the policy of routine arteriography for proximity wounds has been questioned. From a practical perspective, the time required to mobilize the angiography team and perform the study may be several hours, thus making this option less desirable when dealing with the time limitations posed by arterial injury. In addition, arteriography has a small but measurable complication rate, including allergic reactions to contrast media, renal complications, hematoma formation, and false aneurysm formation at the site of cannulation. Finally, the clinical utility of the information provided by arteriography has become increasingly suspect in recent years as more of these injuries have been managed expectantly. Routine "exclusion" arteriography for proximity wounds detects unsuspected arterial injury in 0 to 21% of cases.[25,66,67] However, relatively few of these patients require emergency surgery. In a series of 284 patients who underwent routine angiography for proximity wounds, 17% had unsuspected arterial injury detected, but only 1.8% (5 patients) required emergency surgical repair.[68] In other series reporting on a total of 483 patients who underwent angiography for proximity wounds, only one arterial injury that required emergency repair was discovered.[66-70] In the presence of "soft signs" of injury, the yield for angiograms increases to 29 to 35%, but many of these injuries do not require emergency repair and can be detected by noninvasive means.[68] In addition, angiography results in an approximately 5% false-positive and false-negative rate compared with surgical exploration. Many of the injuries detected on angiography are due to reversible vasospasm or very small intimal defects that generally heal spontaneously. Consequently, angiography for proximity wounds can detect injury in up to 21% of cases but results in acute surgical intervention in only 0 to 4.4% of cases.[66] Many centers now successfully manage proximity wounds by repeated physical examination over a 24-hour period and reserve CTA for those with abnormal physical findings or an ABI less than 0.9.[45,71-73] Angiography is also limited in that it cannot detect major venous injuries, which are increasingly being repaired surgically. The use of angiography is difficult in children because of the small caliber of their vessels and a propensity for vasospasm induced by angiography. Consequently, physical examination and noninvasive methods are preferred for detection of vascular injury in young children.[69]

Digital subtraction angiography (DSA) has been used for detecting vascular injuries as well. DSA has been found to be more accurate than standard angiography for detection of extravasation and has the advantage of requiring the administration of a smaller load of contrast material. However, the field of view is much smaller with DSA than with standard angiography, thus making it technically difficult to study the entire course of a limb artery with DSA. Standard angiography is also more accurate than DSA in detecting intimal flaps and dissection.

Both traditional angiography and CTA have the advantage over other diagnostic techniques in that they can also be used to treat many lesions. Embolization of pseudoaneurysms, endovascular stent insertion to bypass a dissection or AVF, and injection of thrombolytic agents to dissolve thrombus are routinely performed via intra-arterial catheter. Because of increased reliance on endovascular treatment, many of the lesions detected by other means ultimately still require angiography.

TREATMENT

Initial treatment is directed at ensuring a patent airway and adequate air exchange before assessing the circulation. Once this is accomplished, active hemorrhage is controlled by direct digital pressure. Blind clamping of a bleeding vessel is not recommended because of the risk of crushing adjacent nerves; however, clamping a clearly visible vessel can be effective. The use of tourniquets is similarly discouraged because occlusion of veins results in increased compartment pressure and an increased risk for venous thrombosis.[5] However, recent reports in the military literature have found the use of tourniquets for up to 6 hours to be safe and effective.[74] In cases in which proximal and distal control of large vessel injuries cannot be readily achieved in the emergency department, insertion of a Foley catheter into the wound and inflation of the balloon with sterile water can temporarily tamponade the bleeding. Intravenous lines should not be started in the injured extremity because they may be ineffective in delivering resuscitation fluid and because extravasation from an injured vein may increase compartment pressure. Serial hemoglobin determinations may indicate unexpected blood loss from occult vascular injury. Patients with significant blood loss should have blood typed and crossmatched and may require immediate transfusion for stabilization. Patients with significant vascular injury often remain hypotensive despite such infusion and require further volume infusion or blood transfusion. Moribund patients with multiple severe injuries may require urgent amputation as part of their overall stabilization or extrication from wrecked automobiles. Between 50 and 70% of patients with severely mangled limbs require urgent amputation, especially if they have multisystem trauma.[75]

The issue of "hypotensive resuscitation" is controversial with regard to major vascular injuries. A tenuous clot can form in injured arteries and prevent further blood loss as long as the patient remains hypotensive. Once arterial pressure reaches a critical but variable point, the clot may be expelled and massive blood loss can ensue. Therefore, when the arterial injury is inaccessible for occlusion by direct pressure, the target blood pressure for resuscitation should be lowered to a systolic pressure of approximately 90 mm Hg. Overly aggressive and rapid fluid administration in the field or in the emergency department can produce transient intravascular hypervolemia and may ultimately increase the rate of blood loss. Close monitoring of vital signs and the total volume of fluid infused is indicated in these situations.

Once a vascular injury is identified, a specific diagnostic and therapeutic strategy can be developed that is consistent with the severity of the injury, the presence of other injuries, and the resources available. In hospitals without the ability to perform vascular repair, transfer to a trauma center should be initiated early. In cases in which the transfer will involve a delay of several hours, cooling the ischemic limb by packing it with ice will avoid exceeding the critical six-hour cutoff for warm ischemia.

Major Vascular Injuries

Major vascular injuries that compromise the viability of a limb must be repaired within 6 hours to avoid irreversible ischemic neuropathy and myonecrosis.[5] Treatment of vascular injury

has changed dramatically in the past 10 years. Endovascular treatment with self-expanding stents is currently the preferred technique for repair of these injuries in stable patients, and the majority of arterial repairs in the United States are now done with this technique.[76-78] In hemodynamically unstable patients, open surgical repair is still preferred. If other life-threatening injuries must be repaired first, a temporary polytetrafluoroethylene (PTFE) vascular shunt can be placed in the operating room to restore perfusion to a limb.[79] These temporary PTFE shunts can be left in place for up to 24 hours before thrombosis begins to occur within the shunt. Major arterial transection or thrombosis is ideally repaired by end-to-end reanastomosis if possible without placing undue tension on the suture line. If a larger segment of the artery is destroyed, interposition of a reverse saphenous vein graft is the preferred technique. PTFE grafts are suitable for grafting larger arteries if necessary, but they tend to occlude when used in smaller arteries (e.g., distal to the femoral or brachial arteries). Before completing the reanastomosis, a Fogarty catheter is passed through both ends of the repair to extract any thrombi that may have formed. The distal circulation is flushed with a dilute 1:10 solution of heparin or enoxaparin to prevent early clot formation. Systemic administration of heparin is usually contraindicated in major trauma patients. Assessment of distal perfusion and, in particular, compartment pressures is indicated frequently after repair and reperfusion of the limb. The use of broad-spectrum antibiotics is recommended before commencing a vascular repair.

Apart from excision of the affected arterial segment and repair of the vessel, less invasive techniques have been developed to manage pseudoaneurysms. Percutaneous embolization with Silastic beads, gel clot emboli, or thrombogenic coils is often successful.[80] Placement of an endovascular stent can exclude the aneurysm and is also a successful alternative to open repair.[81] Similarly, repair of an AVF can be undertaken through open surgical ligation of the fistulous connection, by endovascular placement of a stent to exclude the fistula, or by percutaneous embolization of the fistulous tract.[80]

Late Complications

Despite timely optimal repair of arterial injuries, approximately 21% of patients experience delayed complications requiring further surgical intervention, including delayed amputation. The most common of such complications is delayed thrombosis, which often occurs after many months as stenosis at the repair site progresses. Other complications include intermittent claudication, chronic pain or edema of the limb, and aneurysm formation in the graft.[82]

Venous Injuries

Venous injuries may be primarily ligated if the condition of the patient cannot tolerate prolongation of surgery. However, the current trend is to repair major venous injuries if possible, particularly in the lower extremity, because wound healing is improved and the incidence of compartment syndrome, venous thrombosis, pulmonary embolism, and chronic edema is decreased.[83-85] Extensive venous collaterals in the upper extremity make surgical repair less compelling.

The timing of repair of a vascular injury when associated with complex fractures requiring fixation is controversial. Historically, the fracture was repaired first to give a more accurate measurement of limb length and the length of graft required for vascular repair and because of fear that manipulation of long bones during reduction might damage the vascular repair. However, the need for postoperative fasciotomy is higher in these patients than in those who undergo vascular repair first (80 vs. 36%), and vascular repair is limited by warm ischemic time.[86] Currently, in most centers, vascular repair is prioritized over orthopedic repair, although temporizing PTFE shunts may be used to restore perfusion during fracture repair.

Minor Vascular Injuries

Increasingly, minor nonocclusive vascular injuries are being treated expectantly. Criteria for observation of vascular injuries include low-velocity missile wounds, intact distal circulation, absence of active hemorrhage, and minimal arterial wall disruption on angiography if performed. Angiographic or CTA findings meeting these criteria include intimal flaps extending less than 5 mm and pseudoaneurysms smaller than 5 mm in diameter.[5] Follow-up of these injuries with repeat angiography or US reveals that approximately 85% resolve spontaneously.[68] Patients meeting these criteria can be monitored as outpatients for 3 months, with repeat physical examination and US to detect delayed complications.[25,68,87] However, almost all pseudoaneurysms ultimately require repair and, once discovered, should be repaired electively rather than undergoing continued observation. Failure to detect and repair occult arterial injuries in children often results in severe differential limb growth, and thus a more aggressive policy of repairing any arterial injury that causes even a relatively minor decrease in blood flow to a child's growing limb may be justified.

SPECIFIC INJURIES

Upper Extremity

Subclavian Artery and Vein

Subclavian artery injuries are uncommon and represent 1 or 2% of all vascular trauma.[88] Isolated injury to the subclavian vein is more common than isolated arterial injury, but in almost half the cases both the vein and the artery are injured.[89] The vast majority (95–99%) are penetrating wounds, and because of massive hemorrhage, these injuries are often lethal before arrival at a hospital. Mortality in those who reach the hospital alive averages 15%, but overall mortality as high as 75% has been reported.[90,91] Interestingly, morbidity is higher with a blunt mechanism, whereas mortality is higher with penetrating wounds.[92] The right subclavian artery arises from the brachiocephalic artery, and the left arises from the arch of the aorta. From their origin, they course posterior and inferior to the clavicles to the outer margins of the first ribs, where they become the axillary artery and vein. The left subclavian rises higher than the right and extends into the root of the neck.[26]

The clinical manifestation is that of hemorrhagic shock in 77% of cases. Occasionally, unsuspected subclavian vascular injury is discovered at thoracotomy performed for excessive blood loss from a chest tube.[89] Approximately 60% have an associated pneumothorax or hemothorax, and additional injury to mediastinal and spinal structures is relatively common.[88] Symptoms of limb ischemia may be apparent with absent radial and brachial pulses. However, pulses are completely absent in only 33% of cases because collateral flow from the thyrocervical trunk may provide sufficient perfusion to avoid the symptoms and signs of ischemia.[89] Neurologic deficits in the upper extremity occur in more than half of patients. The most severe of these injuries is disruption of the brachial plexus, which occurs in almost 50% of patients with blunt injury.[89]

In a series of 100 cases of subclavian artery injury, the combination of physical examination and chest x-ray findings

suggestive of subclavian injury (hemothorax, pneumothorax, apical pleural cap, or wide mediastinum) was 100% sensitive and could have eliminated the need for 69% of the arteriograms obtained.[90] If the patient's clinical condition permits, angiography can provide an accurate diagnosis and can locate the injury precisely. APIs are relatively inaccurate with proximal thoracic outlet injuries because of collateral arterial flow. US techniques are also relatively inaccurate in detecting subclavian injuries because of interference by overlying gas-filled lung tissue. Therefore, in cases in which the clinical diagnosis is equivocal ("soft signs" of injury or proximity wounds), arteriography (CTA or catheter based) is required to detect the injury. Immediate proximal and distal control of the subclavian artery is very difficult. An incision along the course of the clavicle is recommended but often needs to be extended to a sternotomy.[59] If primary reanastomosis is not possible, synthetic grafts are usually successful but have a tendency to fracture over time due to the wide range of motion at the shoulder and resultant compression of the graft by the first rib and clavicle.[93]

Blunt subclavian injuries are often associated with clavicular fracture or dislocation. Isolated first rib fracture is rarely combined with vascular injury unless posterior displacement occurs. However, first rib fracture in association with other major injuries, such as a wide mediastinum on chest x-ray, an expanding hematoma, an upper extremity pulse deficit, or a brachial plexus injury, is accompanied by arterial injury in 24% of cases and merits investigation by angiography or CTA.[94] Several cases of shear injury of the subclavian artery have been reported to result from a loose shoulder restraint of a seat belt during a motor vehicle accident. Overall, blunt subclavian artery injuries have a higher morbidity than penetrating injuries because of higher rates of limb amputation and associated brachial plexus injury.[88]

Subclavian vein injuries are even more lethal than those to the artery. In addition to massive blood loss, there is a relatively high risk of massive air embolism, which is frequently fatal in association with penetrating subclavian vein injuries.

Axillary Artery and Vein

Injury to the axillary vessels constitutes 3 to 9% of all vascular injuries and is divided nearly equally between penetrating and blunt mechanisms.[3] Forceful reduction of a chronically dislocated shoulder is a common iatrogenic cause of axillary artery injury. The axillary artery courses from the lateral border of the first rib to the inferior border of the teres major muscle, where it becomes the brachial artery. The axillary vein runs medial to the artery. The extensive anastomotic arterial connections around the shoulder joint usually permit good collateral flow,[26,89] and up to half of these patients will have palpable pulses as a result of collateral circulation.[95] Because of the close proximity of the brachial plexus and the axillary vessels, significant denervation of the upper extremity can occur. Near-avulsion injuries resulting in scapulothoracic dissociation invariably produce severe disruption of the brachial plexus and often ultimately result in amputation despite successful vascular repair. There is a high rate of amputation for the combination of axillary vascular and brachial plexus injury, mainly because the presence of a flail limb results in amputation for placement of a prosthesis. In addition, patients with a flail limb have a 40-fold increased rate of suicide.[11]

Brachial Artery

The brachial artery continues from the lower border of the teres major muscle and divides into the radial and ulnar arteries at the level of the proximal aspect of the radial head. The median and ulnar nerves and the basilic vein are in close proximity to the brachial artery. The profunda brachii artery is a major branch that arises slightly after the origin of the brachial artery and often contributes good collateral flow if the brachial artery is injured distal to this branch point.[26,89] Brachial artery injuries occur as a result of penetrating trauma, humeral shaft fracture, elbow dislocation, or animal bites. They are the most common major vascular injuries in the upper extremity. In 75% of cases, the radial pulse is absent.[27] Studies have shown that limb salvage rates have improved to nearly 100% due to efficient out-of-hospital transport, improved surgical techniques, and shorter time to first antibiotic dose.[96] Repair is indicated in all cases because the amputation rate is high with ligation.

Forearm Arteries

The radial artery begins in the cubital fossa and runs superficially to the distal end of the radius, where it ultimately joins the deep branch of the ulnar artery to form the deep palmar arch of the hand. The ulnar artery begins in the cubital fossa and runs with the ulnar nerve anterior to the flexor retinaculum, at which point it joins the radial artery to form the superficial palmar arch of the hand.

Injuries detected by arteriography or US that are below the bifurcation of the arterial supply in the upper extremity do not need to be repaired unless there are signs of ischemia in the hand; hard signs of arterial injury such as an expanding hematoma, pseudoaneurysm, or AVF; or injury to both radial and ulnar arteries. However, some authors recommend repairing all these injuries because of the risk of intermittent claudication or cold intolerance in patients who have one artery ligated. Certain patients are almost exclusively dependent on the ulnar arterial supply to the hand because of an underdeveloped deep palmar arch. Clearly, ulnar artery injuries must be repaired in these patients. Compartment syndrome in the forearm is common after repair of proximal arteries and veins and may require fasciotomy.

Lower Extremity

Iliac Artery and Vein

Given the intra-abdominal course of the iliac vessels, virtually all these injuries have associated trauma to the small or large intestine, bladder, solid viscera, or bony pelvis. The common and external iliac arteries are injured with equal frequency and more often than the internal iliac vessels.[97] In moribund patients, an initial "damage control" laparotomy with temporary vascular shunting of the iliac vessels is often necessary as resuscitation continues. After the patient has overcome lactic acidosis, hypothermia, and coagulopathy, a second definitive repair can be undertaken. Surprisingly, the incidence of infection of synthetic or autologous grafts is rather low despite the high degree of bacterial contamination associated with perforation of a hollow viscus. Distal ischemic complications occur in approximately one third of repaired iliac arteries, and subsequent amputations are required in up to 18%.[97]

Femoral Artery and Vein

The external iliac vessels become the common femoral vessels at the inguinal ligament. After giving off the profunda femoris artery in the femoral triangle, the femoral artery continues as the superficial femoral artery almost vertically to the adductor tubercle of the femur and enters the popliteal fossa as the

popliteal artery. There are extensive proximal collaterals around the hip joint, including the gluteal, obturator, and pudendal branches of the iliac artery.[26]

Femoral artery and vein injuries are the most common vascular injuries seen in major trauma centers. Common femoral artery injury occurs as a result of intertrochanteric hip fracture, hip dislocation, and iatrogenic injury from the placement of arterial catheters or from hip replacement surgery, although 86% of femoral artery injuries are due to penetrating wounds.[98] Ligation of the common femoral artery culminates in amputation of the lower extremity in 80% of cases, so repair should be attempted in all cases. Experimental data indicate that the use of *N*-acetylcysteine may reduce the degree of ischemia after femoral artery injury and help reduce the high rate of amputation.[99] Penetrating wounds of the thigh result in femoral artery injury in 6.2% of cases, and up to 40% of these injuries are clinically occult. A medial or anteromedial wound track is present in virtually all these cases, and some centers routinely perform angiography on these medial wounds.

Popliteal Artery and Vein

The popliteal artery gives off the genicular branches in the popliteal fossa and then divides into the anterior and posterior tibial arteries at the lower border of the popliteus muscle. The peroneal artery arises from the posterior tibial artery slightly after its origin. The anterior and posterior tibial arteries and the peroneal artery form the trifurcation of the popliteal artery, and each runs with a corresponding vein and nerve in different compartments of the leg.[26]

The most common cause of popliteal artery injury is posterior knee dislocation in which bony elements directly lacerate or cause thrombosis of the artery. Displaced fractures of the knee, particularly tibial plateau fractures, may also result in popliteal artery injury. Anterior knee dislocations may cause excessive stretch on the popliteal vessels that can culminate in arterial thrombosis, but this injury is relatively rare. Overall, knee dislocation results in popliteal artery injury in 25 to 33% of cases.[100] Up to 40% of these injuries may be clinically occult, and diagnosis is delayed in up to 40% of cases,[2] although other series note that more than two hard signs of ischemia occur immediately in 71 to 94%.[4,5] Twenty-five percent of cases have an associated injury to the peroneal and posterior tibial nerves. In half the cases, the knee dislocation may reduce spontaneously, leaving little evidence of the original trauma, particularly in obtunded patients.[101] Patients showing complete ligamentous disruption of the knee on physical examination should be suspected of having a spontaneously reduced knee dislocation. Hemarthrosis may also be absent if the joint capsule is torn because blood can track into the fascial planes of the leg.

No consensus has been reached on the diagnostic approach to detect popliteal artery injury resulting from documented or suspected knee dislocation. There are three possible strategies, and each has proponents and detractors. The first option is to perform routine arteriography on every case of knee dislocation.[102,103] The second is to perform arteriography on selected cases in which vascular injury is not certain despite the combination of physical signs, abnormal ABI measurement, or findings on noninvasive tests such as color flow Doppler, duplex scan, or CTA.[104] The third option is to rely completely on these physical findings and ABI. If both these findings are normal, advocates of this approach claim 100% negative predictive value for vascular injury that requires surgery.[46,71,73,105,106] The choice of these options is institution specific, but most centers continue to use angiography in selected cases. Abnormal ABI and US (duplex and color flow Doppler) have been found to be very accurate in detecting popliteal injuries, and many centers reserve angiography or CTA for cases in which noninvasive tests result in equivocal findings. As a general rule, high-energy mechanisms of trauma (e.g., auto vs. pedestrian and motor vehicle collision) and posterior knee dislocations are more likely to produce popliteal artery injury than are low-energy mechanisms (e.g., sports injuries), and a more aggressive diagnostic approach (i.e., angiography or CTA) may be warranted in such cases. However, patients with *penetrating* trauma and more than one hard sign of popliteal artery injury can be taken directly to the operating room for repair because delaying these cases to obtain an angiogram is "superfluous, unnecessary, costly, and potentially dangerous."[106] Patients with *blunt* trauma can have false-positive hard findings generated by soft tissue swelling and external arterial compression, and these patients should undergo diagnostic testing first to confirm arterial injury. The amputation rate for popliteal injuries was as high as 40% in the past, but current rates are lower. In one large series, the amputation rate was 20%, but a high rate of permanent disability was found at 2-year follow-up.[107] Another series reported no amputations with modern diagnostic and repair techniques.[5,106] Factors that place patients at higher risk of amputation include severe mangling of the extremity or delay in repair exceeding 8 hours of warm ischemia time.[101] Because of the high incidence of compartment syndrome with lower leg injuries, fasciotomy is required in 36 to 62% of cases, and some centers routinely perform fasciotomy in all such cases.[108] Approximately two thirds of patients with popliteal artery injury will have persistent deficits caused by peripheral nerve injury, chronic ischemia, or amputation.

Lower Leg Arteries

The popliteal artery divides into three branches—the anterior and posterior tibial and the peroneal arteries at the inferior margin of the popliteal fossa. Injuries below the trifurcation at the knee may need repair if hard signs of arterial injury are apparent in the foot or if two of the three arteries are occluded on angiography.[25] However, vascular injuries in the lower part of the leg are notorious for causing compartment syndrome and need to be monitored closely. Amputation is usually due to a combination of soft tissue, nerve, and bone injuries. If significant injury to all three of these tissues is present, the amputation rate may reach 54%.[25,109] The combination of orthopedic and vascular injury, particularly as a result of crush injury, and shock on initial evaluation culminates in amputation in 35% of cases and should be considered a poor prognostic sign for limb viability.[110]

DISPOSITION

Patients with confirmed injury to major vessels, equivocal findings on diagnostic tests, or symptoms of limb ischemia must be admitted to the hospital for further investigation or observation. Consultation with a vascular surgeon is indicated as soon as vascular injury is strongly suspected or the need for emergency operative repair established. Patients who are unstable because of vascular or other injuries may undergo further investigation or exploration in the operating room. If the treating hospital is incapable of performing vascular surgery or appropriate investigations, transfer to a trauma center should be initiated. Delaying transfer for angiograms of proximity wounds in centers that are incapable of acting on positive results is unwise because it often delays definitive care beyond the safe limits of warm ischemia time.

KEY CONCEPTS

- The overall condition of the patient determines the extent of diagnostic study and stabilization in the emergency department. Critical patients may require immediate surgery, which should not be delayed for confirmatory study of obvious vascular injury.
- Arterial injury may be readily apparent or clinically occult. Up to 21% of proximity wounds show arterial injury on angiography. Similarly, various US modalities and abnormal APIs frequently detect clinically unapparent vascular injuries.
- Symptoms of arterial injury may be delayed by hours to months after the initial injury. Late onset of symptoms suggests delayed thrombosis, pseudoaneurysm or AVF formation, compartment syndrome, or intermittent claudication resulting from stenosis or reliance on small-caliber collateral vessels for arterial perfusion.
- Reperfusion injury can occur after restoration of arterial flow and result in compartment syndrome. Frequent reexamination of the reperfused limb is indicated in the postoperative period.
- Compartment syndrome frequently develops in limbs with arterial injury, and fasciotomy is often required.
- CT angiography is playing an increasing role in the diagnosis of vascular injury and is increasingly replacing catheter-based angiography for this purpose.
- Many vascular injuries are amenable to endovascular treatment with self-expanding stents. This results in fewer complications, lower cost, and earlier discharge from hospital.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 46

General Principles of Orthopedic Injuries

Joel M. Geiderman and Dan Katz

MANAGEMENT PRINCIPLES

Patients with orthopedic injuries and nontraumatic musculoskeletal disorders compose a large portion of the more than 100 million patients who present annually to U.S. emergency departments (EDs). Although only rarely life-threatening, orthopedic injuries may threaten a limb or its function, and accurate early diagnosis and treatment can avert long-term complications. Many of these injuries can and should be treated definitively by the emergency physician. Consultation with an orthopedist should be sought for the treatment of most long bone fractures, open fractures, and injuries with neurovascular compromise and for follow-up of certain patients initially treated in the ED.

Orthopedic injuries often occur as a result of accidents (industrial or otherwise) and frequently involve young, otherwise healthy, working individuals. Accurate initial diagnosis, treatment, and documentation assume great importance medically and economically. Many problems can be avoided if the following 10 general principles are kept in mind:

1. Most orthopedic injuries can be predicted by knowing the chief complaint, the age of the patient, the mechanism of injury, and an estimate of the amount of energy delivered.
2. A careful history and physical examination predict radiographic findings with a high degree of accuracy. A presumptive diagnosis prior to a radiographic study may prompt the physician to order special views required to correctly diagnose an injury. Many fractures were accurately described before the advent of roentgenology (Table 46-1).
3. If a fracture is suggested clinically, but radiographic films appear negative, the patient should initially be treated with immobilization as though a fracture were present.
4. Criteria for adequate radiographic studies exist; inadequate studies should not be accepted.
5. Radiographic studies should be performed before attempting most reductions except when a delay could be potentially harmful to the patient or in some field situations.
6. Neurovascular competence should be checked and recorded before and after all reductions and following application of immobilization.
7. Patients must be checked for the ability to ambulate safely before discharge from the ED and should not be discharged unless this can be established.
8. Patients should receive explicit aftercare instructions before leaving the ED, covering such areas as monitoring for signs of neurovascular compromise or increasing compartment pressure, cast care, weight bearing, crutch use, and an explicit plan and timing for follow-up.
9. In a patient with multiple trauma, noncritical orthopedic injuries should be diagnosed and treated only after other more threatening injuries have been addressed.
10. All orthopedic injuries should be described precisely and according to established conventions. When communicating with an orthopedic consultant, this may affect decisions regarding disposition of a patient and operative versus nonoperative management.

Physical Examination

FRACTURES

Fracture Nomenclature

Describing orthopedic injuries using precise language according to established convention enables accurate, clear communication with other parties. Terms commonly used to describe a fracture are listed in Box 46-1. A fracture is a break in the continuity of bone or cartilage. Clinically a history of loss of function, pain, tenderness, swelling, abnormal motion, and deformity suggests a fracture. Radiographic studies are the mainstay of diagnosis and are usually, although not always, confirmatory. At times, special views, radionucleotide bone scans, computed tomography (CT), or magnetic resonance imaging (MRI) are necessary to confirm a clinical impression. These studies should be considered when the clinical evidence is at odds with the findings of routine radiography.

General Descriptors

Description of a fracture should begin by stating whether the fracture is *closed* or *open* (less desirable terms are *simple* or *compound*). In a closed fracture, the skin and soft tissue overlying the fracture site are intact. The fracture is open if it is exposed to the outside environment in any manner. This exposure may be as obscure as a puncture wound or as gross as splintered bone protruding through the skin. It is sometimes difficult to determine whether a small wound in proximity to a fracture actually communicates with that fracture. Some physicians advocate probing such a wound with a blunt sterile swab to

Table 46-1 Common Fracture Names and Their Origins

FRACTURE EPONYM	DESCRIPTION	COMMENT
Aviator's	Vertical fracture of the neck of the talus with subtalar dislocation and backward displacement of the body	First described in flyers during World War I. Arises from forced dorsiflexion of the foot in flying accidents and in traffic accidents after a head-on collision
Barton's	Intra-articular fracture-dislocation of the wrist	Considered complicated and unstable. Requires surgical reduction in most cases. Described by Barton in 1838 before the advent of radiography
Dorsal Barton's	Oblique intra-articular fracture of the dorsal rim of the distal radius with displacement of the carpus along with the fracture fragment	Results from high-velocity impact across the articular surface of the radiocarpal joint, with the wrist in dorsiflexion at the moment of impact
Volar Barton's	Wedge-shaped articular fragment sheared off the volar surface of the radius (volar rim fracture), displaced volarly along with the carpus	Similar mechanism as dorsal Barton's but with wrist in volar flexion at time of injury. Also referred to as a reverse Barton's. Much rarer than dorsal Barton's
Bennett's	Oblique fracture through base of the first metacarpal with dislocation of the radial portion of the articular surface	Usually produced by direct force applied to the end of the metacarpal. Dorsal capsular structures disrupted by the dislocation. Marked tenderness along medial base of thumb
Bosworth	Fracture-dislocation of the ankle resulting in the fibula being entrapped behind the tibia	Rare injury, produced by a severe external rotation force applied to the foot. Physical examination reveals foot severely externally rotated in relation to the tibia
Boxer's	Fracture of the neck of the fourth or fifth metacarpal	Results from striking a clenched fist into an unyielding object, usually during an altercation, or against a wall, out of frustration or anger
Chance's	Vertebral fracture, usually lumbar, involving the posterior spinous process, pedicles, and vertebral body	Caused by simultaneous flexion and distraction forces on the spinal column, usually associated with use of lap seat belts. Anterior column fails in tension along with the middle and posterior columns. May be misdiagnosed as a compression fracture
Chauffeur's	Solitary fracture of radial styloid	Occurs from tension forces sustained during ulnar deviation and supination of the wrist. Name derives from occurrence in chauffeurs who suffered violent, direct blows to the radius incurred while turning the crank on a car, only to have it snap back, during previous eras
Clay shoveler's	Fracture of the tip of the spinous process of the sixth or seventh cervical vertebra	First described in Australian clay shovelers who sustained a fracture of the spinous process by traction as they lifted heavy loads of clay
Colles'	Fracture of the distal radius with dorsal displacement and volar angulation, with or without an ulnar styloid fracture	Most common wrist fracture in adults, especially in the elderly. Results from fall on an outstretched hand. Also known as silver fork deformity, which accurately describes the gross appearance in the lateral view. First described by Colles in 1814, before the advent of radiography
Cotton's	Trimalleolar fracture	Fracture of the lateral malleolus, the posterior malleolus, and either a fracture of the medial malleolus or a disruption of the deltoid ligament with visible widening of the mortise on ankle radiograph
Dashboard fracture	Fracture of the posterior rim of the acetabulum	Named for mechanism of injury: a seated passenger striking the knee on a dashboard, driving the head of the femur into the acetabulum
Dupuytren's	Fracture-dislocation of the ankle	Results from a similar mechanism as the better known Maisonneuve fracture (i.e., external rotation of the ankle), resulting in either deltoid ligament rupture or medial malleolus fracture, diastasis of the inferior tibiofibular joint, and indirect fracture of the fibular shaft. Maisonneuve was the student of Dupuytren
Essex-Lopresti	Fracture of radial head with dislocation of distal radioulnar joint	Results from longitudinal (axial) compression of the forearm
Galeazzi's	Fracture of the shaft of the radius with dislocation of the distal radioulnar joint. Ligaments of inferior radioulnar joint are ruptured and head of ulna displaced from ulnar notch of the radius	Results from fall on outstretched hand, with the wrist in extension and the forearm forcibly pronated. Inherently unstable with tendency to redisplace after reduction
Hangman's	Fracture-dislocation of atlas and axis, specifically of pars interarticularis of C2 and disruption of C2-3 junction. Separation occurs between second and third vertebral bodies from anterior to posterior side	Results from extreme hyperextension during abrupt deceleration. Most common cause is the forehead striking the windshield of a car during a collision. A bit of a misnomer in that hanging usually produces death by strangulation rather than cord damage

Table 46-1 Common Fracture Names and Their Origins—cont'd

FRACTURE EPONYM	DESCRIPTION	COMMENT
Hume	Fracture of the proximal ulna associated with forward dislocation of the head of the radius	Essentially a high Monteggia injury
Jefferson	Burst fracture of ring of C1, or atlas	Axial loading results in a shattering of the ring of the atlas. Decompressive type of injury. Associated with disruption of transverse ligament; an unstable injury
Jones'	Transverse fracture of the metatarsal base, occurring at least 15 mm distal to the proximal end of the bone, distal to the insertion of the peroneus brevis	Should not be confused with the more common avulsion fracture of fifth metatarsal styloid, produced by avulsion at the insertion of the peroneus brevis. Jones described the fracture that bears his name in 1902, after suffering the injury himself while dancing
Le Fort	Maxillary fracture	Types I, II, and III (see Chapter 39)
Le Fort-Wagstaffe	Avulsion fracture of the anterior cortex of the lateral malleolus	Rare pull-off injury of the fibular attachment of the anterior tibiofibular ligament
Lisfranc's	Fracture located around the tarsometatarsal (Lisfranc's) joint, usually associated with dislocation of this joint	Lisfranc, a field surgeon in Napoleon's army, described an amputation performed through the tarsometatarsal joint in a soldier who caught his foot in a stirrup when he fell off his horse. Since then, the joint has borne his name
Maisonneuve	Fracture of proximal third of fibula associated with rupture of the deltoid ligament or fracture of the medial malleolus and disruption of the syndesmosis	Results from external rotation of the ankle with transmission of forces through syndesmosis; proximally the force is relieved by fracture of the fibula. Described experimentally in 1840, before radiography
Malgaigne	Fracture of the ilium near the sacroiliac joint with displacement of the symphysis, or a dislocation of the sacroiliac joint with fracture of both ipsilateral pubic rami	Resultant pelvic injury is unstable. Described by Malgaigne, based on clinical findings, in 1847
March	Fatigue, or stress, fracture of the metatarsal	Arises from long marches or other repetitive use trauma (e.g., marathon running) or less commonly from single stumbling movements
Monteggia's	Fracture of the junction of the proximal and middle thirds of the ulna associated with anterior dislocation of the radial head	Usually caused by fall on outstretched hand along with forced pronation of forearm or by a direct blow on the posterior aspect of the ulna. Reported by Monteggia in 1814
Nightstick	Fracture of either ulna or radius, or both	Name derived from a citizen's attempt to protect himself from a police officer's baton or "nightstick" by offering the forearm
Piedmont	Closed fracture of the radius at the middle third/distal third junction, without associated ulnar fracture	Named for a series of cases presented at the Piedmont Orthopaedic Society of Durham, North Carolina
Pott's	Definitions vary (see comment); most commonly a bimalleolar fracture or a fracture of the distal fibula, 4–7 cm above the lateral malleolus	The exact fracture Pott described in 1769 is uncertain; clearly it referred to a fracture of the lower fibula, usually associated with other fractures or dislocations about the ankle
Rolando's	Intra-articular fracture at base of metacarpal. Frequently Y- or T-shaped, or may be severely comminuted	Produced by an axial load with the metacarpal in partial flexion. Worse prognosis than a Bennett's fracture and, fortunately, rarer
Salter-Harris	An epiphyseal fracture occurring in children or adolescents	Graded I–V, depending on degree of involvement and/or displacement of epiphysis and metaphysis (see text dealing with Salter-Harris fractures and also Figure 46-1)
Smith's	Extra-articular fracture of the distal radius with volar displacement of distal fragment	Reverse of the Colles' fracture but much more uncommon. Sometimes referred to as a "garden spade" deformity. Usually results from fall with force to back of hand. First described by Smith in 1847
Stener	Avulsion of the ulnar corner of the base of the proximal phalanx of the thumb	Bony equivalent of rupture of the ulnar collateral ligament, or "gamekeeper's thumb"
Teardrop	Wedge-shaped fracture of the anteroinferior portion of the vertebral body, displaced anteriorly	Commonly involves a ligamentous injury and may produce neurologic injury
Thurston Holland's fragment	Triangular metaphyseal fragment that accompanies the epiphysis in Salter-Harris type II fractures	Described by Thurston Holland in 1929. The name is commonly hyphenated, although technically it should not be
Tillaux	Isolated avulsion fracture of the anterolateral aspect of the distal tibial epiphysis	Occurs in older adolescents (12–15 years old) after the medial parts of the epiphyseal plates close, but before the lateral part closes. External rotation force places stress on anterior talofibular ligament. Described by Tillaux in 1872

establish a relationship; no study has established the safety, benefit, or accuracy of this maneuver. If doubt exists, an open fracture should be assumed to be present.

The next item that should be noted in the description of a fracture is the exact anatomic location, including the name of the bone, left or right, and standard reference points along the bone, for example, the *humeral neck* or *posterior tibial tubercle*.

Box 46-1 FRACTURE DESCRIPTION

Identification
Open versus closed
Exact anatomic location
Direction of fracture line
Simple/comminuted
Position (displacement, alignment)

Additional Modifiers
Complete versus incomplete
Involvement of articular surface (%)
Avulsion
Impaction
  Depression
  Compression

Special Situations
Pathologic
Stress

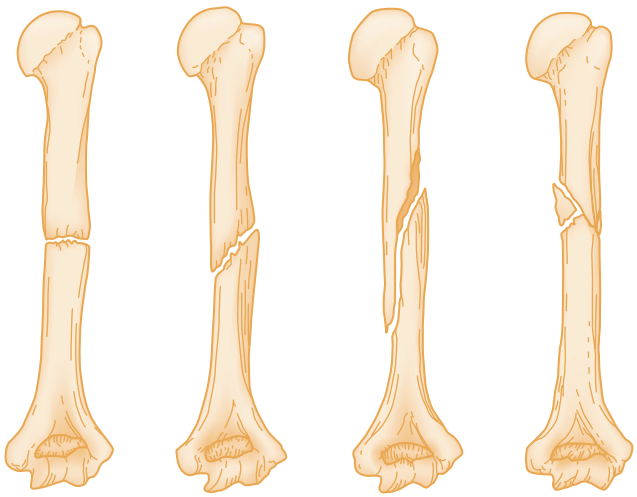


Figure 46-1. Types of fractures. **A,** Transverse. **B,** Oblique. **C,** Spiral. **D,** Comminuted.

Long bones can be divided into thirds—proximal, middle, or distal—and these thirds or the junction of any two of them (e.g., the junction of the middle and distal third of the tibia) are used to describe fractures. The most descriptive language possible should be used. It is better to say "closed fracture of the right ulnar styloid" than "closed fracture of the right distal ulna" because the former conveys more precise anatomic information.

An additional modifier describes the direction of the fracture line in relation to the long axis of the bone in question. A *transverse* fracture occurs at a right angle to the long axis of the bone (Fig. 46-1A), whereas an *oblique* fracture runs oblique to the long axis of the bone (Fig. 46-1B). A *spiral* fracture results from a rotational force and encircles the shaft of a long bone in a spiral fashion (Fig. 46-1C). A fracture with more than two fragments is termed *comminuted* (Fig. 46-1D).

The position and alignment of the fracture fragments (i.e., their relationship to one another) should be described. Fragments are described relative to their normal position, and any deviation from normal is termed *displacement*. By convention, the position of the distal fragment is described relative to the proximal one. Displacement may be described as a quantitative measurement (i.e., in millimeters) or as a percentage of the bone width. Figure 46-2 shows a dorsal displacement of the fractured radius, and Figure 46-3 shows lateral, or valgus, displacement of the distal tibia and fibula.

The terms *valgus* and *varus* are sometimes confusing. *Valgus* denotes a deformity in which the described part is angled away from the midline of the body. Conversely, *varus* denotes a deformity in which the angulation of the part is toward the midline. *Alignment* refers to the relationship of the longitudinal axis of one fragment to another; deviation from the normal alignment is termed *angulation*. The direction of angulation is determined by the direction of the apex of an angle formed by the two fracture fragments (Fig. 46-4). This angle is opposite to the direction of displacement of the distal fragment. The relative position or angulation of the distal fragment of a fracture may also be described with terms such as radial or ulnar, dorsal or volar, anterior or posterior, and lateral or medial. One should also be aware of rotational deformity, present when the distal fragment of a fracture is rotated to some degree along the axis of the bone itself. Especially in the hand, radial or ulnar deviation of a flexed finger can occur, and radiographs often underestimate the degree of clinical deformity and rotation present.

Descriptive Modifiers

A fracture is termed *complete* if it interrupts both cortices of the bone and *incomplete* if it involves only one. It should be noted whether a fracture extends into and involves an *articular surface*. Frequently the percentage of articular surface involved can only be estimated; in some cases, the percentage that is

Figure 46-2. Dorsal displacement of distal radius.

Figure 46-3. Valgus displacement of the distal tibia and fibula. The distal segment is angled away from the midline of the body.

actually involved dictates the need to perform a surgical reduction. In general, it is important that the articular surface be restored to anatomic integrity to prevent consequent traumatic arthropathy.

Avulsion fracture refers to a bone fragment that is pulled away from its normal position by either the forceful contraction of a muscle (Fig. 46-5A) or the resistance of a ligament to a force in the opposite direction (Fig. 46-5B). *Impaction* refers to the forceful collapse of one fragment of bone into or onto another. In the proximal humerus, this collapse typically occurs in a telescoping manner, particularly in elderly patients, whose bones are soft and brittle. In the tibial plateau, impaction occurs frequently in the form of a depression (Fig. 46-6A and B), and in the vertebral bodies, impaction frequently occurs in the form of compression (Fig. 46-6C).

A fracture that occurs through abnormal bone is termed *pathologic*. A pathologic fracture is suggested whenever a fracture occurs from seemingly trivial trauma. Diseases that cause structural weakness predisposing to injury include primary or metastatic malignancies, cysts, enchondromata, and giant-cell tumors. In addition, osteomalacia, osteogenesis imperfecta, scurvy, rickets, and Paget's disease all weaken bones, making them susceptible to fracture. The term *pathologic* also is applied to fractures through osteoporotic bone when the demineralization is a result of disease, as in polio. Fractures through osteoporotic bone of the elderly usually are not described as pathologic. When fractures occur in normal bones and a history of "trivial trauma" is elicited, violence or battering should be suspected. Repeated low-intensity forces may lead to resorp-

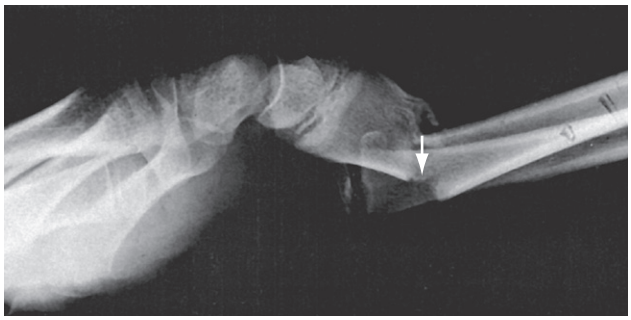
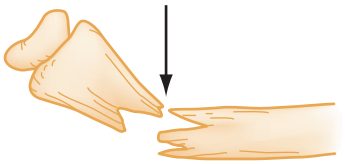
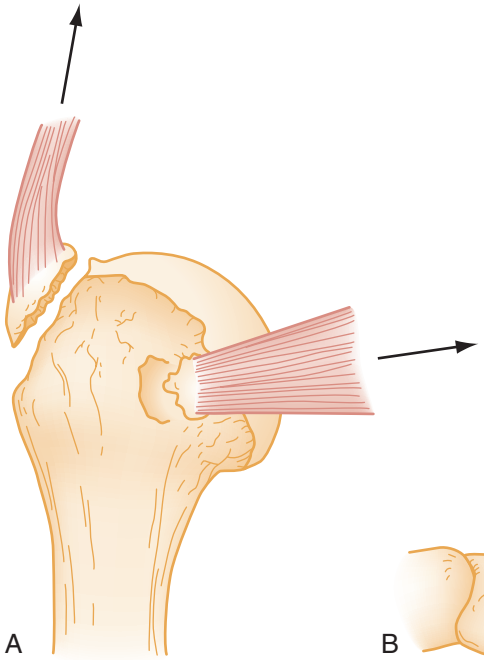


Figure 46-4. Volar angulation of a fractured radius.





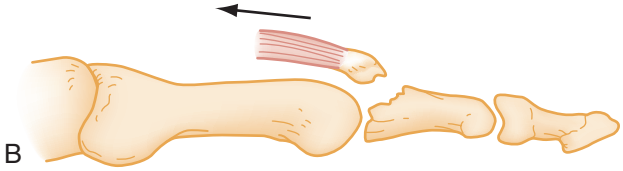


Figure 46-5. Avulsion fractures. **A,** Musculotendinous avulsions of small bone fragments from the head of the humerus. **B,** Extensor tendon avulsion of bone from the base of the middle phalanx.

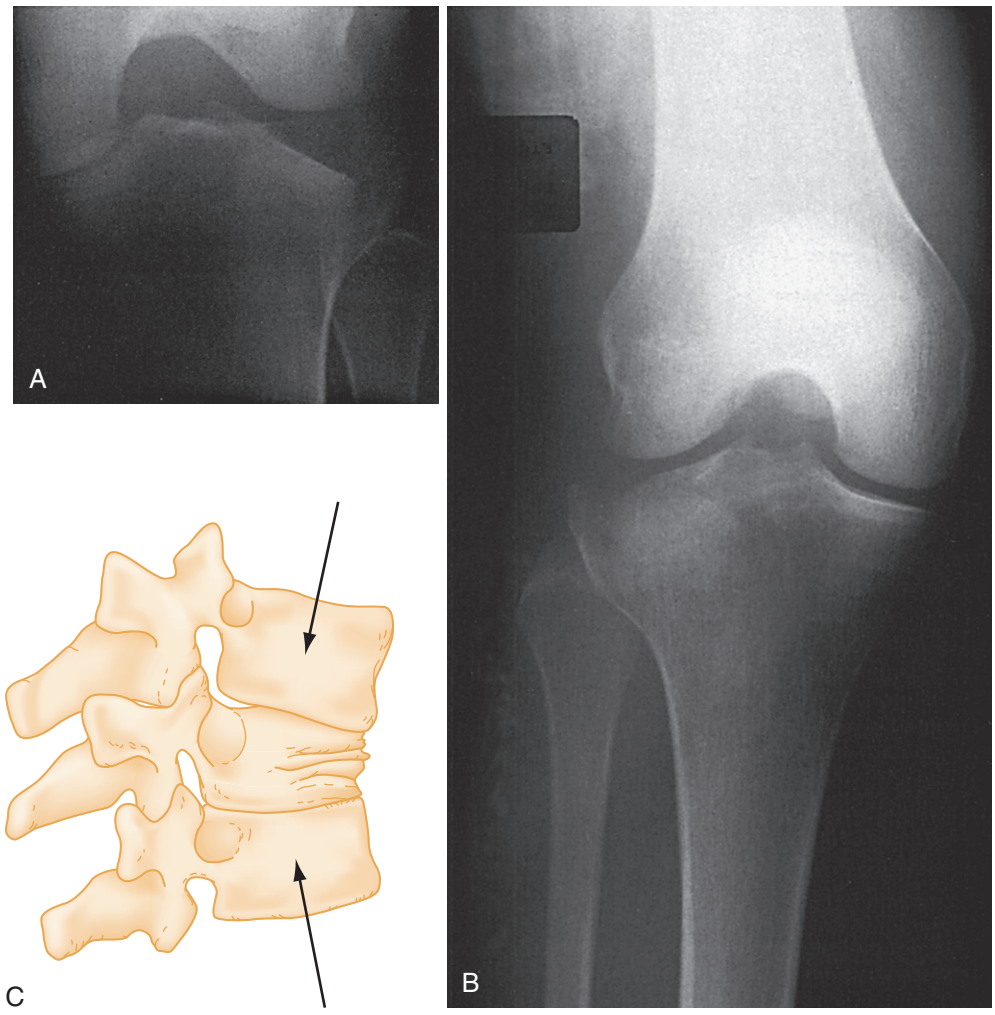


Figure 46-6. **A** and **B,** Tibial plateau fracture. **C,** Vertebral body compression fracture.

tion of normal bone, resulting in a stress fracture. Other names for this condition are *fatigue fracture* and *march fracture* (see Table 46-1). Most stress fractures occur in the lower extremities and commonly affect individuals involved in activities such as running, basketball, aerobics, and dancing. Extrinsic factors such as training regimens, type of equipment used, and nutrition habits, as well as intrinsic factors such as anatomic variation, muscle endurance, and hormonal factors have all been associated with stress fractures. These injuries may not be recognizable on initial plain films; therefore, management should be based on clinical diagnosis.[1] The tibia, fibula, metatarsals, navicular, cuneiform, calcaneus, femoral neck, or femoral shaft may be involved.[2,3]

Fracture Eponyms

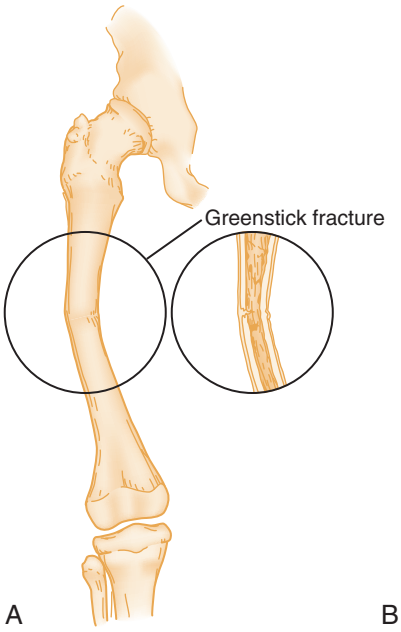
Many fractures were described before the advent of radiography and are described by an eponym rather than the exact bony injury. These eponyms reflect the rich history of orthopedic care and, despite the objections of some, are still commonly used to describe orthopedic injuries (see Table 46-1).

Fracture Healing

Specific fractures are discussed in subsequent chapters. In general, the goal is to realign bony fragments so that healing or union can take place and normal function is restored. The process from fracture to union begins with a hematoma, caused by rupture of vessels crossing the fracture line. The hematoma bridges the fragments and is followed by an inflammatory phase when granulation tissue forms on the fracture surfaces. Resorption of the hematoma provides the first continuity between the fragments; however, this procallus provides no structural rigidity for bearing stress. With remodeling, callus subsequently is formed on the periosteal and endosteal surfaces of the bone, acting as a biologic splint. This area first becomes mineralized by deposition of calcium phosphate and then undergoes osseous metaplasia. Callus is resorbed as the original fracture surfaces develop firm bony union. In some bones, such as the skull and the neck of the femur, where periosteum is deficient, there may be virtually no callus formation.

Radiographic studies conducted 10 to 14 days after injury show the bone surrounding the fracture line becoming less dense because of localized bone resorption and hyperemia associated with the formation of granulation tissue. As a result, the fracture becomes considerably easier to visualize radiographically about 10 days after injury. After 2 to 3 weeks, soft tissue swelling has regressed, and callus first becomes visible, initially in a mottled pattern and then taking on a dense appearance. The callus undergoes organization, with peripheral margins becoming smooth as physically unstressed portions are resorbed.

For a healthy adult, the whole process from injury to consolidation takes about 2 months for the humerus and about 4 months for a large bone such as the femur. Oblique fractures



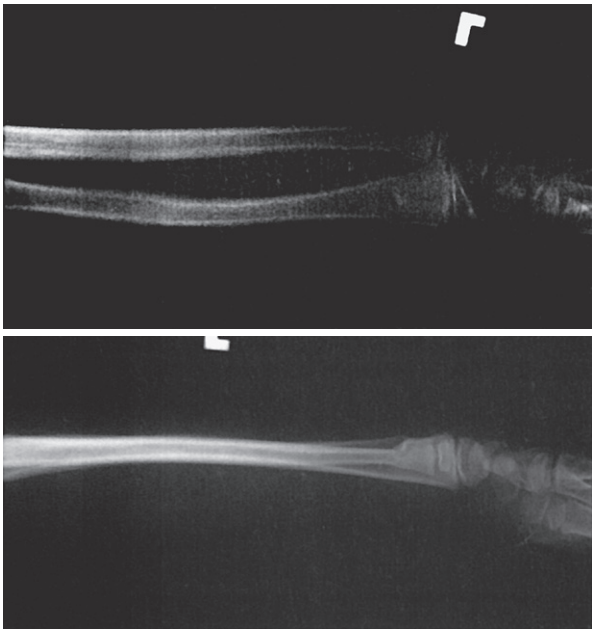


Figure 46-7. **A,** Greenstick fracture of midshaft of femur. **B,** Torus fracture of distal third of radius.

tend to heal more quickly than transverse fractures. Healing is quicker in children and slower in the elderly. The rate of fracture healing is affected by many factors, including the type of bone (cancellous bone heals faster than cortical bone); degree of fracture and opposition; and systemic states, such as hyperthyroidism or excess corticosteroidism. Exercise speeds healing, whereas chronic hypoxia has been known to slow repair.

The presence of abundant callus seen on radiograph that is beginning to organize is usually associated with clinical union. If any suggestion of movement at the fracture site is noted on clinical examination, union must be regarded as inadequate. Several terms are used to denote abnormal union. *Delayed union* is union that takes longer than usual for a particular fracture location. *Malunion* occurs when a residual deformity exists. *Nonunion* is the failure of a fracture to unite. When nonunion results in a false joint, it is termed a *pseudarthrosis*.

If the ends of the bone have remained constant on serial films and an adequate surrounding sheath of organizing callus can be seen, it is permissible for the patient to return to limited active use, even if the original fracture remains visible. The final process of consolidation develops later.

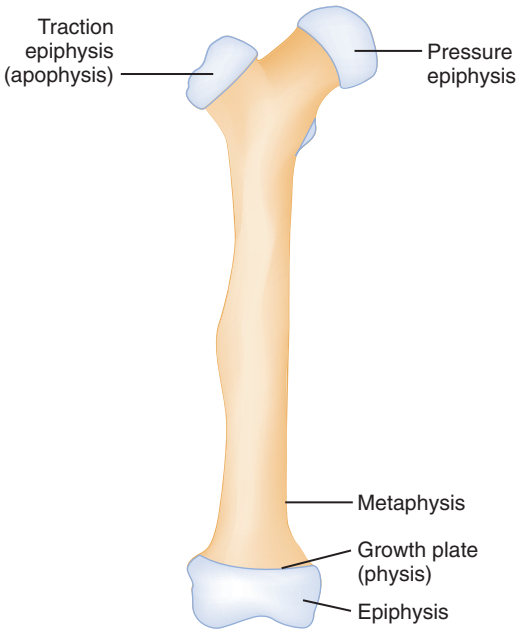


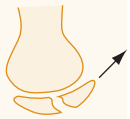
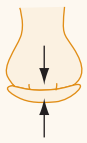
Figure 46-8. Anatomy of growing bone.

Fractures in Children

Certain features of children's bones distinguish pediatric fractures from adult fractures. Bones of children are necessarily soft and resilient and sustain numerous incomplete fractures. *Greenstick* fractures are incomplete angulated fractures of long bones. The resultant bowing of the bone causes an appearance resembling a moist, immature branch that breaks in a similar fashion when bent (Fig. 46-7A). A *torus* fracture is another form of incomplete fracture, characterized by a wrinkling or buckling of the cortex. In Greek architecture, a torus is a bump at the base of a column, and these fractures, occurring at the end of long bones, take on such an appearance. These fractures may be extremely subtle on radiographs (Fig. 46-7B).

Another feature of growing long bones that is a frequent source of trouble and confusion is the presence of epiphyses, cartilaginous centers at or near the ends of bone that give rise to growth of the bone. Figure 46-8 is a schematic review of the anatomy of a growing bone. Because cartilage is radiolucent, the cartilaginous portion of an epiphysis is not visualized on radiographs. A tendency exists to consider only the ossified nucleus and to ignore the cartilaginous structure that bridges to the metaphysis. Cartilage is present even before an ossified nucleus is seen. Because the epiphyseal growth plate is represented by a radiolucent line, confusion may exist as to whether a fracture line is present. These complexities in interpreting radiographs in children sometimes, but not always, require comparison radiographic views of the noninjured side. Injuries to the epiphyses may result from either compressive or shearing forces. These injuries are relatively common during childhood as opposed to sprains or shaft fractures and must be considered in children with a "sprained ankle" because of the relative weakness of the cartilaginous growth zone, which

Table 46-2 Salter-Harris Classification

	DESCRIPTION	DIAGRAM
Type I	Fracture extends through the epiphyseal plate, resulting in displacement of the epiphysis (this may appear merely as widening of the radiolucent area representing the growth plate)	
Type II	As above; in addition, a triangular segment of metaphysis is fractured	
Type III	Fracture line runs from the joint surface through epiphyseal plate and epiphysis	
Type IV	Fracture line occurs as in type III but also passes through adjacent metaphysis	
Type V	This is a crush injury of the epiphysis; it may be difficult to determine by radiographic examination	

separates before stronger ligaments and bones are torn or broken. Epiphyseal injuries should be described according to the Salter-Harris classification (Table 46-2).

Type I injuries involve only a slip of the zone of provisional calcification. Comparison radiographs are usually necessary to detect small slips. Swelling and tenderness over an epiphysis (e.g., of the lateral ankle) and a negative radiograph suggest an epiphyseal injury, rather than a sprain, because the epiphysis is weaker than the overlying ligaments.

Type II injuries are similar to type I injuries, with a fracture extending into the metaphysis. The triangular metaphyseal fragment sometimes is referred to as the *Thurston Holland sign* (see Table 46-1). Type II injuries account for approximately three fourths of all epiphyseal fractures. Because the germinal layer is not involved, growth disturbance usually does not occur with type I and II injuries.

Type III injuries are composed of a slip of the growth plate plus a fracture through the epiphysis, involving the articular surface. Because this fracture involves the germinal layer, growth may be disrupted. Anatomic reduction does not eliminate the possibility of growth disturbance. Type IV fractures are similar to type III fractures, with the additional involvement of a metaphyseal fracture. Anatomic reduction is essential and usually requires surgery. Growth disturbance occurs in a high proportion of patients.

Type V fractures are crush injuries of the epiphyseal plate, usually produced by a compressive force.[3] This type of injury usually occurs in joints that move in one plane, most commonly the knee and ankle. Because this injury occurs in a radiolucent area, the injury may be difficult to diagnose on radiograph, but it is suggested by mechanism of injury and pain over the epiphysis. The diagnosis can be established by MRI if hemorrhage or a hematoma is identified within the growth plate immediately after injury.[5] Also reported is loss of MRI signal from the cartilage.[6] Growth arrest, manifest by shortening or angulation, is the rule in this injury. Type V injuries are extremely rare.

In a study of 410 fractures in children, 16.3% were torus fractures, and 13.9% were epiphyseal injuries.[7] Dislocations and subluxations were rare (3%), and most involved the radial head or the patella. There were no shoulder dislocations. The most common sites were the bones of the distal forearm and the hands (usually the phalanges), each group accounting for 20% of the total. The clavicle was involved 13% of the time; the elbow, 8%; the ankle, foot, and femur, 7% each; and the midforearm, lower leg, and humerus, 4 to 6% each.

Another study found an incidence of epiphyseal injury of 18% in 2000 bony injuries in children.[8] The peak age at the time of injury was 12 years in boys and 11 years in girls. In this series, the incidence of injury by category was type I, 8.5%; type II, 73%; type III, 6.5%; type IV, 12%; and type V, 0.5%. The sole Salter-Harris type V injury in this series occurred in the proximal tibia. The most frequent sites of Salter-Harris type III fractures are the phalanges and distal tibia, and most type IV fractures occur in the distal humerus and distal tibia. The overall frequency of growth arrest in all injuries is 1.4%, whereas the frequency of serious complications is less than 0.6%. The prognosis depends more on the location of the fracture than the Salter-Harris classification. The proximal tibia is the most common site for growth disturbance. Because the epiphysis is closer to fusing, the chances of growth disturbance are less; this influences decision making in terms of surgical versus conservative management.

Diagnostic Modalities for Fracture Diagnosis

Plain Radiography

Plain radiography is the mainstay in diagnosing fractures. In addition to confirming or excluding fractures, other pathologic conditions can be identified. With penetrating trauma, foreign bodies, air, and gas also may be detected. With minor trauma, and when good follow-up monitoring is ensured, it is acceptable to delay radiography. Delay cannot be permitted, however, when the suggested injury is one that might be made worse by delayed diagnosis, such as a nondisplaced hip fracture.

At least two views perpendicular to each other are mandatory in examining long bones, and an oblique view also is usually obtained. In certain locations, such as the phalanges, oblique views are necessary. If doubt still exists, the clinician should ask for more views in various degrees of obliquity to the other films. A fracture line is most visible when it is parallel to the x-ray beam and is invisible when it is exactly 90° to the beam. *The clinician should never accept a study that examines the bone in only one plane.* When a long bone is found to be fractured, it is imperative that the bone be viewed radiographically in its entire length.

Each film must be examined to ensure that proper technique is used and that no important area is omitted from the film. Overexposed films may fail to reveal an abnormality. Although some fine detail is lost on portable films, these are acceptable in unstable patients, in whom the risk of moving the patient does not outweigh the benefit of the more detailed study. Computed (digital) radiography is now in widespread use. An advantage of this technique is the ability to alter the image-processing parameters based on a specific clinical problem after an exposure has been made.[9] Disadvantages are that the spatial resolution of computed radiographs, and especially of computer monitor formats, is less than that of standard screen-film combinations and that minimization is often necessary when larger body parts, such as the thoracic spine, lumbar spine, and pelvis, are being examined. Despite these considerations, computed radiography seems to be acceptable and does not seem to diminish reader performance significantly.[9]

Even with good technique, some fractures are not visible initially and do not appear until the margins of the fracture absorb. Absorption widens the radiolucent line, and a defect appears in 7 to 10 days. At that time, new bone produced beneath the periosteum at the margins of the fracture accentuates the fracture. Accordingly, if a fracture is suggested but not visible at the initial visit, the injury should be treated as a fracture and reexamined clinically and radiographically in 7 to 10 days, and the patient should be informed of the rationale for this regimen.

Stress views of joints are used in some instances to evaluate the degree of ligamentous injury. Some authors argue against the use of stress views, citing a risk of further injuring an already traumatized structure, additional radiation exposure to the patient and the technologist, and the possibility that pain may not allow sufficient stress to be applied. For these reasons, stress views should be used judiciously in circumstances when other methods of evaluating ligamentous injuries are not available. *Comparison views* are useful in selected situations but should not routinely be performed in all pediatric examinations.[10] If a fracture is definitely present on the affected side, the comparison view exposes the child to radiation and adds expense with no benefit. Similarly, an experienced physician generally is able to read a normal film with reasonable certainty. It is reasonable to use comparison views in instances when radiographs are inconclusive and when the confusion arises specifically out of the need to distinguish between a possible fracture and normal developmental anatomy. Obtaining a wide field of the affected extremity is more useful than routine comparison views for a young child because the child often does not localize the pain well; this is especially true with regard to complaints of knee pain in cases of hip injury or wrist complaints in forearm and elbow injury. Comparison views sometimes are helpful in adults when a question of accessory ossicles or nonfused bones (e.g., bipartite patella) exists because these anomalies are usually bilateral. The bleeding that inevitably accompanies fractures may produce soft tissue swelling, which may impinge on or obliterate overlying muscle planes. Fat pads, such as in the elbow, may be displaced. Another useful sign is the fat-fluid level, which may accompany fractures extending into the knee joint. The fat-fluid level is visible, however, only if the cross-table technique is used.

The bones themselves should be examined systematically. Normal adult bones possess a smooth unbroken contour. A distinct angle is highly suggestive of a fracture. In an adult, the typical fracture is represented by a lucent line that interrupts the smooth contour and usually extends to the opposite side. Nutrient arteries may be confused with fractures, but have different radiographic characteristics: They are fine, sharply marginated, extend obliquely through the cortex, and are less radiolucent than fractures. *Pseudofractures* can be created by soft tissue folds, bandages or other overlying material, or a radiographic artifact called the *Mach effect*. If lucencies extend beyond the bones, the line is highly unlikely to represent a fracture. Anomalous bones and calcified soft tissue likewise may be mistaken for fractures. Avulsions and small fracture fragments have an irregular, uncorticated surface, and a defect in the adjacent bone is present, whereas anomalous ossification centers (accessory ossicles) and sesamoids are characterized by smooth cortical margins. Reference texts are useful in identifying and confirming these anomalies because they tend to occur in predictable locations.[11] Compression fractures are represented by increased density rather than a lucency. Finally, the most commonly missed fracture is the second fracture. One must be diligent in searching for additional fractures after discovering the first fracture on a study. In particular, certain paired fractures, such as the distal tibia and proximal fibula, should be sought out.

Special Imaging Techniques

Radionucleotide Bone Scanning. In the past, radionucleotide bone scanning was used to detect skeletal abnormalities not radiographically evident in children and adults.[12] Occult lesions, especially stress fractures, acute osteomyelitis, and tumors, can be detected on these scans, although there are problems with specificity and sensitivity. This modality has been largely supplanted by CT and MRI and now is seldom used.

Computed Tomography. CT is used to confirm possible fractures or to define better displacement, alignment, or fragmentation of fractures. It also is useful in trauma to rule out cervical spine fracture when plain films are equivocal and in noncompressive vertebral fractures to assess the number of fragments and their spatial relationship to the spinal canal. CT is used frequently to define the integrity of articular surfaces in the acetabulum, knee, wrist, or ankle and in Salter-Harris type IV fractures.[4]

Magnetic Resonance Imaging. MRI constitutes the most advanced noninvasive examination of orthopedic structures, delineating lesions of bone, cartilage, ligaments, and other structures, such as menisci, disks, and epiphyseal structures. MRI is expensive and time-consuming and should be reserved for instances when the diagnosis is in doubt and specific findings would alter the treatment.

Complications of Fractures

Infection (Osteomyelitis)

Any fracture communicating with the surface of the skin is termed an open fracture. Open fractures are treated as true orthopedic emergencies because of the risk of infection; the dreadful nature of the complication of osteomyelitis dictates that no time should be wasted in initiating therapy (Box 46-2). Wounds should be covered with sterile dressings, and paren-

Box 46-2 Classification and Emergency Management of Open Fractures

Grades

Grade I: Wound < 1 cm long, punctured from below
Grade II: Laceration 5 cm long; no contamination or crush; no excessive soft tissue loss, flaps, or avulsion
Grade III: Large laceration, associated contamination or crush; frequently includes a segmental fracture
IIIA: Involves extensive soft tissue stripping of bone
IIIB: Periosteal stripping has occurred
IIC: Major vascular injury present

Management

1. Control hemorrhage in field with sterile pressure dressing after carefully removing gross debris (e.g., wood, clothing, leaves).
2. Splint without reduction, unless vascular compromise is present.
3. Irrigate with saline and cover with saline-soaked sponges after arrival in the emergency department.
4. Begin intravenous antibiotic prophylaxis, usually a first-generation cephalosporin for grade I, with the addition of an aminoglycoside for grades II and III.
5. Administer tetanus prophylaxis, including tetanus immune globulin, for large crush wounds.

teral antibiotics should be instituted as early as possible. Currently, suggested therapy includes a first-generation cephalosporin, such as cefazolin, for all open fractures, with the addition of an aminoglycoside for grade II or III fractures.[13,14] Although the traditional recommendation has been to obtain culture and sensitivity before starting antibiotics, the usefulness of this approach has not been supported by a controlled study.[15] A retrospective analysis of perioperative cultures in open fractures in children failed to show any value in predicting the identity of subsequent infecting pathogens.[16] It is prudent to omit such cultures.

Certain open fractures of the finger present a notable exception to the previous recommendation. Such injuries, especially an open distal tuft fracture, are common when the phalanx of a finger is subject to crush injury (e.g., by a door), and there exists a skin defect overlying a fractured bone. In a prospective randomized, placebo-controlled study of 193 patients with open fracture of the finger, flucloxacillin or placebo was administered to randomized patients with open phalangeal fractures, and both groups were treated with aggressive surgical irrigation and débridement. No significant difference was found in the infection rate between the groups, and no patient developed osteomyelitis. The data suggest that vigorous irrigation and débridement are adequate primary treatment for open phalangeal fractures in fingers with intact digital arteries.[17] Such injuries might be repaired by the emergency physician without consultation.

Hemorrhage

Because of the rich blood supply to the skeleton, fractures can result in large amounts of blood loss, shock, and death from exsanguination. In particular, certain pelvic fractures can cause great blood loss because adequate tamponade is not possible. In adults, blood loss can range from 100 mL from a forearm fracture to 3 L from a pelvis fracture (Table 46-3).

Vascular Injuries

Vascular injuries characteristically are associated with certain fractures. Fractures and dislocations about the knee result from tremendous force that often injures the popliteal artery. In the extremities, assessment of vascular injuries may be difficult. The initial survey should note the presence or absence of pulses and the state of capillary filling. If an end artery is completely disrupted, the tissue distal to the injury may exhibit the classic five *P's*: pain, pallor, pulselessness, paresthesias, and paralysis. Incomplete and subclinical injuries occasionally occur, however, that initially may be asymptomatic and nondetectable. Likewise, in an unconscious, multiply injured patient, major vascular injuries may not be obvious. The mechanism of injury and anatomy dictate the need to assess the possibility of an injured vessel. If pulses cannot be palpated, a Doppler stethoscope should be used to listen for blood flow. Even palpable pulses may be misleading, however, because it has been shown that in 10 to 20% of significant arterial injuries, distal pulses may initially be normal. When pulses are present, but the mechanism of injury suggests the possibility of vascular injury, additional diagnostic studies or surgical exploration may be necessary. Late complications of undiagnosed vascular injuries include thrombosis, arteriovenous fistulae, aneurysm, false aneurysm, and tissue ischemia with limb dysfunction.

Traditionally, conventional arteriography has been the diagnostic modality of choice in evaluating vascular injuries; however, it is invasive and costly. Alternative methods of vascular assessment include arterial pressure indices and serial physical examinations. Recent advances in computed tomographic angiography have proven it an effective alternative to conventional arteriography, and its advantages include immediate availability and noninvasiveness.[18]

Table 46-3 Blood Loss Associated with Fracture in Adults

FRACTURE SITE	AMOUNT OF BLOOD LOSS (ML)
Radius and ulna	150–250
Humerus	250
Tibia and fibula	500
Femur	1000
Pelvis	1500–3000

Nerve Injuries

Nerves can be injured by either blunt or penetrating trauma. *Neurapraxia* is the contusion of a nerve, with disruption of the ability to transmit impulses. Paralysis, if present, is transient, and sensory loss is slight. Normal function usually returns to a neurapraxic nerve in weeks to months. *Axonotmesis* is a more severe crush injury to a nerve. The injury to nerve fibers occurs within their sheaths. Because the Schwann tubes remain in continuity, spontaneous healing is possible but slow. *Neurotmesis* is the severing of a nerve, usually requiring surgical repair. Age, site, injured nerve, and delay between injury and repair have all been shown to influence prognosis after microsurgical repair.[19] Because of proximity, specific nerve injuries characteristically accompany certain fractures (Table 46-4).

When the nerve is completely severed, all functions are absent, including superficial sensation to touch, pain, and temperature; deep sensation to muscle and joint movements, position, deep pressure, and vibration; motor supply and deep tendon reflexes (to distally innervated muscle groups); and response to electrical stimulation. For less severe injuries, any subjective change in sensation should be noted. Light touch is a good screening test. Two-point discrimination is a more sensitive examination and should be used routinely in evaluating digital nerves. Separating the ends of a paper clip and asking the patient to discriminate between one or two points may easily accomplish this. Two-point discrimination may be of limited value in children in whom a subjective response may be misleading; this is also true in patients with calloused fingertips and in patients who are uncooperative, comatose, in severe pain, or intoxicated. Testing for sympathetic nerve function using the O'Riain wrinkle test may be helpful.[20] Soaking the normally innervated digits in warm saline for 20

Table 46-4 Nerve Injuries Accompanying Orthopedic Injuries

ORTHOPEDIC INJURY	NERVE INJURY
Elbow injury	Median or ulnar
Shoulder dislocation	Axillary
Sacral fracture	Cauda equina
Acetabulum fracture	Sciatic
Hip dislocation	Femoral nerve
Femoral shaft fracture	Peroneal
Knee dislocation	Tibial or peroneal
Lateral tibial plateau fracture	Peroneal

Table 46-5 Life-Threatening or Limb-Threatening Emergencies

CONDITION	POSSIBLE ADVERSE OUTCOME
Open fracture	Osteomyelitis
Fracture or dislocation with major vascular disruption (especially popliteal)	Amputation
Major pelvic fracture	Exsanguination
Hip dislocation	Avascular necrosis of femoral head
Compartment syndrome	Ischemic contracture; myoglobinuria, renal failure

minutes causes the digital pulps to wrinkle through a mechanism that is not understood. The presence of wrinkling probably indicates the nerve is intact, whereas absence of wrinkling may be more difficult to interpret. The ninhydrin test, another sudomotor test used to assess peripheral nerve integrity, is reportedly more reliable than the O'Riain test, but is not practical to perform in the ED.

Compartment Syndrome

Compartment syndrome is a serious acute emergency complication that should be considered whenever pain and paresthesias occur in an extremity after a fracture within an enclosed osseofascial space (Table 46-5). The immediate threat is to the viability of nerve and muscle tissue within the involved compartment, but infection, gangrene, myoglobinuria, and renal failure also may ensue. Compartment syndrome is associated most commonly with a closed long bone fracture of the tibia, but it also is well described in the thigh, forearm, arm, hand, and foot.[21-25] In addition, compartment syndrome can occur with soft tissue trauma alone and even with open fractures. It also has been described in a host of unusual situations, including prolonged procedures in the lithotomy position, the tuck position (knees tucked to the chest for lumbar surgery), coma, spontaneous hemorrhage, intravenous injections, and the application of excessive traction in treatment of a fracture.[26-28]

Pathophysiology. Increased pressure in a closed nonexpandable compartment essentially represents a mismatch between the volume of that space and its contents. As such, it may arise from one of three circumstances: (1) increased compartment contents, (2) decreased compartment volume, or (3) external pressure (Box 46-3). As tissue pressure increases, so does venous pressure, resulting in compromise of the local circulation and tissue hypoxia; this is believed to occur at pressures that are above normal diastolic pressure but below systemic arterial pressure because of a reduced arteriovenous gradient at the tissue level. The body responds by releasing histamine in an attempt to dilate capillaries and increase blood flow to the affected area. Histamine also increases capillary membrane permeability, resulting in a leak of proteins and fluid into the surrounding tissue, further increasing compartment pressure.

As tissue pressure continues to increase, venous blood flow is impaired as capillary perfusion pressure is exceeded. Finally, arterial capillary blood flow falls to a point where the basic metabolic needs are no longer met, leading to ischemic necrosis of muscles and nerves within the compartment. An important concept in the management of compartment syndrome is that because local venous pressure cannot be significantly below local tissue pressure, and because elevation of a dependent limb decreases local arterial pressure by 0.8 mm Hg for each 1 cm of limb elevation, elevation of a limb with resultant reduction in the local arteriovenous gradient may be counterproductive and may exacerbate compartment syndrome. Vascular spasm seems to play an insignificant or minimal role in the development of compartment syndrome, as evidenced angiographically, where spasm has never been shown, and clinically, where it is observed that distal pulses usually are maintained until late in the course.

Normal compartment pressure is 0 mm Hg. Microcirculation generally is impaired when tissue pressures reach 30 mm Hg or more; however, some patients can tolerate much higher

Box 46-3 Causes of Compartment Syndrome

Increased Compartment Content
- Bleeding
  - Major vascular injury
  - Coagulation disorder
  - Anticoagulant therapy
- Increased capillary filtration
  - Reperfusion after ischemia
    - Arterial bypass grafting
    - Embolectomy
    - Ergotamine ingestion
    - Cardiac catheterization
    - Lying on limb
  - Trauma
    - Fracture
    - Convulsion
  - Intensive use of muscle
    - Exercise
    - Seizures
    - Eclampsia
    - Tetany
  - Burns
    - Thermal
    - Electrical
  - Intra-arterial drug injection
  - Orthopedic surgery
    - Tibial osteotomy
    - Hauser's procedure
    - Reduction and internal fixation of fractures
  - Snakebite
- Increased capillary pressure
  - Intensive use of muscles
  - Venous obstruction
    - Phlegmasia cerulea dolens (i.e., acute inflammation and edema of the legs)
    - Ill-fitting leg brace
    - Venous ligation
  - Diminished serum osmolarity (i.e., nephrotic syndrome)

Decreased Compartment Volume
- Closure of fascial defects
- Excessive traction on fractured limbs

Miscellaneous
- Infiltrated infusion
- Pressure transfusion
- Leaky dialysis cannula
- Muscle hypertrophy
- Popliteal cyst

External Pressure
- Tight casts, dressings, or air splints
- Lying on limb

From Matsen FA III: Compartmental Syndromes. New York, Grune & Stratton, 1980.

Box 46-4 REPORTED ANATOMIC LOCATIONS OF COMPARTMENT SYNDROMES

Lower Extremity
Leg
- Anterior compartment
- Lateral compartment
- Deep posterior compartment
- Superficial posterior compartment

Thigh
- Quadriceps compartment

Buttock
- Gluteal compartment

Upper Extremity
Hand
- Interosseous compartment

Forearm
- Dorsal compartment
- Volar compartment

Arm
- Deltoid compartment
- Biceps compartment

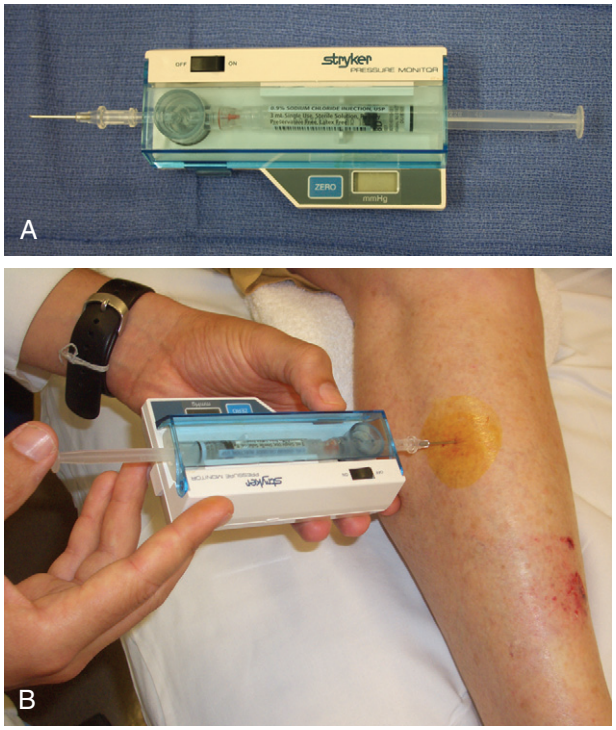


Figure 46-9. **A,** Hand-held device for measuring compartment pressure. **B,** Insert device perpendicular to skin.

compartment pressures without compartment syndrome developing. Controversy exists over attempts to define compartment syndromes on the basis of specific tissue pressure. The tolerance to tissue ischemia varies among individuals because of shock, compensatory hypertension, altered tone in resistance vessels, and other unknown factors. Inadequate perfusion and relative ischemia begin when tissue pressure within a closed compartment increases to within 20 mm Hg of a patient's diastolic pressure or, more accurately, within 30 mm Hg of the mean arterial pressure.[29] When tissue pressure equals or exceeds the patient's diastolic pressure, tissue perfusion effectively ceases. The development of muscle ischemia depends not only on the magnitude but also on the duration of elevated pressure. Intracompartmental pressures do not measure muscle and nerve ischemia but rather suggest the existence of the proper setting for compartment syndrome.

Anatomic Considerations and Risk Factors. Compartment syndrome theoretically can develop in any location where neuromuscular tissue is contained in a limiting envelope. The condition has been reported in the leg, thigh, buttock, arm, forearm, and hand (Box 46-4). By virtue of its location and higher likelihood of sustaining high-energy trauma, the leg, particularly the anterior compartment, is most commonly involved.

In a study of 164 patients treated over an 8-year period in the United Kingdom, a fracture was present in 69%, and half of these involved the tibial shaft.[30] Perhaps more significant is that 31% of patients had only soft tissue injury *without* fracture. Most patients were men younger than age 35. Ten percent of patients either had a bleeding disorder or were taking anticoagulants. Traffic accidents and sports activities were the most common mechanisms of injury.

Clinical Presentation. In a conscious and fully oriented patient, pain that is disproportionate to the injury or physical findings is a hallmark finding in compartment syndrome. Pain often is characterized as deep, burning, and unrelenting and is difficult to localize. The need for increasing amounts of analgesics should not lead the clinician automatically to the conclusion that the patient is drug-seeking; rather, it should serve as a prompt to the possibility that a compartment syndrome is developing or is present.

Pain on passive stretching of the muscle groups in the suggestive compartment is an important finding. In addition, active flexion of involved muscles may produce pain. Other reliable suggestive signs and symptoms are hypoesthesias and paresthesias in the distribution of nerves crossing the compartment or tenderness, tenseness, or the sensation of tightness of the compartment.

Skin color, temperature, capillary refill, and distal pulses all are unreliable monitors for compartment syndrome because the pressure necessary to produce compartment syndrome is well below arterial pressure. Pallor and loss of pulses are late and ominous signs. Diminished pulses should suggest concomitant pathologic conditions responsible for reduced arterial flow. Although it is still frequently taught that the five *P's* (pain, pallor, pulselessness, paresthesias, and paralysis) are signs and symptoms of compartment syndrome, this is generally not true. Rather they are the signs of acute disruption of arterial flow. Subjective complaints are an important indicator of compartment syndrome. Patients who are not fully alert or cooperative must be assessed with particular care.

Diagnostic Tests. If the history and examination suggest compartment syndrome, compartment pressures should be measured using any of the commercially available monitors (Fig. 46-9). The two most common methods of determining compartment pressures are the slit-catheter techniques and the side-port needle. The Stryker device is a hand-held digital display that is easy to use with minimal training. Care must be taken to zero the monitor in on the plane in which it will be inserted to account for the effects of gravity. It is also paramount that the appropriate compartment is measured. Pressures of less than 30 mm Hg generally do not produce compartment syndrome. Pressures exceeding 30 mm Hg or within 30 mm Hg of the patient's mean arterial pressure are an indication for fasciotomy. Serial or continuous pressure measurements should be performed in cases that are not clear-cut. Compartment syndrome can occur at pressures significantly below systemic pressure. Doppler ultrasound is not useful in evaluating these patients because excellent arterial blood flow may be documented even in the presence

of a significant compartment syndrome. Newer devices based on near-infrared spectroscopy (NIRS) measurement of tissue oxygenation have proven effective experimentally in detecting compartment syndrome but will require validation in the clinical setting before widespread application.[31]

Treatment, Complications, and Disposition. Complete fasciotomy is the only treatment that can reliably normalize elevated compartment pressure. Preparation for surgery must be done as quickly as possible. Delaying fasciotomy for more than 12 hours often results in irreversible muscle and nerve damage. While the patient is awaiting definitive treatment, the affected part should *not* be elevated above the level of the heart because this maneuver does not improve venous outflow and reduces arterial inflow. Slight dependency has been suggested to maximize the pressure head in the extremity.

Rhabdomyolysis, hyperkalemia, and myoglobinuria may occur and should be managed aggressively to avoid renal failure. Lactic acid also is released from necrotic muscle tissue. Other complications include infection and tissue loss. Delayed treatment results in loss of nerve and muscle function and eventual contracture formation. The magnitude of these disasters may be measured by the fact that in 2004, the average indemnity award in cases of missed compartment syndrome was nearly $426,000. Awards were proportional to the delay beyond 8 hours in performing fasciotomy and the number of the "five P's" indicating ischemia that were present during the initial missed diagnosis.[32] For these reasons, when the diagnosis of compartment syndrome is confirmed, fasciotomy should be done without delay.

Avascular Necrosis

Because of their blood supply, certain bones may undergo avascular necrosis after fracture, especially if fractures are comminuted and go untreated for any length of time. The femoral head, talus, scaphoid, lunate, and capitate are particularly prone to this complication.[33-36]

Complex Regional Pain Syndromes (Reflex Sympathetic Dystrophy and Causalgia)

Definitions. The terms *reflex sympathetic dystrophy* (RSD) and *causalgia* have been used to describe pain syndromes that sometimes follow fractures, orthopedic surgery, soft tissue injuries, and other unrecognized trauma to the limbs and their appendages. Other names previously used for this spectrum of posttraumatic injuries include *Sudeck's atrophy, shoulder-hand syndrome,* and *postinfarction sclerodactyly*. In an attempt to reduce misunderstanding about their etiology and treatment, the International Association for the Study of Pain issued a consensus statement renaming the syndromes formerly called RSD and causalgia.[37,38] *Complex regional pain syndrome type I* (CRPS-I), replacing the term RSD, is a pain syndrome that develops after an initiating noxious event, extends beyond the distribution of a single peripheral nerve, and is usually disproportionate to the inciting event. The site is most often the distal end of the affected extremity, with a distal-to-proximal gradient. It is associated with edema, changes in blood flow to the skin, abnormal sudomotor activity in the region of the pain, allodynia (pain resulting from non-noxious stimulation to the skin), hyperpathia (pain persisting or increasing after mild or light pressure), or hyperalgesia. The presence of a condition that otherwise would explain the degree of pain and dysfunction excludes the diagnosis of CRPS-I. Because so much of the literature still refers to RSD, this chapter still uses the terms RSD and CRPS-I interchangeably. The definition of *CRPS-II* is the same as for CRPS-I except that there is demonstrable peripheral nerve injury. This term replaces *causalgia* under the International Association for the Study of Pain taxonomy.

Pathogenesis and Etiology. The pathogenesis of CRPS-I has not been elucidated. The sympathetic nervous system seems to play a role in the maintenance of the symptoms in some, but not all, patients. Cases of CRPS-I have been reported after fractures and as iatrogenic complications of surgery or after minor procedures, including subcutaneous excision and intravenous injection. Forceful manipulations and tight casts also are alleged to have produced the syndrome. In 10 to 26% of patients, no inciting event is identified.[39,40]

Although malingering and secondary gain are suspected in some patients, they are not the causes in most patients, as evidenced by pathologic tissue changes in patients who actually have CRPS-I.[41] CRPS-I occurs in children and adolescents.[42] Girls are affected three times as often as boys, and the median age is 12 years. The lower limb is affected twice as often as the upper, and history of inciting trauma can be identified in only half the children with the disorder.

Diagnosis. No correlation exists between the severity of the original trauma and the incidence, severity, and cause of the symptoms, making early diagnosis a challenge, especially after trivial injury. Early diagnosis is crucial because the earlier treatment is initiated, the better the response. The diagnosis is not always easy to make, however.

An RSD score consisting of nine criteria has been proposed to aid in the diagnosis of RSD and to enhance comparisons of outcome studies.[43] The criteria are as follows:

1. Allodynia (pain resulting from non-noxious stimulation to the skin) or hyperpathia (pain persisting or increasing after mild or light pressure)
2. Burning pain
3. Edema
4. Color or hair growth changes
5. Sweating changes
6. Temperature changes
7. Radiographic changes (i.e., demineralization)
8. Quantitative measurement of vasomotor/sudomotor disturbance
9. Triple-phase bone scan consistent with RSD

One point is given for each positive criterion, none if absent, and half a point if equivocal. Patients with more than five points are probable RSD patients. Pain that is abolished with temporary selective sympathetic blockade is another test that is highly suggestive of RSD.

Treatment. Treatment of CRPS is controversial. Debate arises because randomized, placebo-controlled studies are lacking; individual response to treatment varies; and experts disagree regarding the pathogenesis of the disease. A multidisciplinary approach, including physical therapy and psychological counseling, is often necessary to treat CRPS.[44] For some patients, definitive treatment involves sympathetic blockade, usually with regional anesthesia and occasionally by surgical sympathectomy.[45] Oral medications, including biphosphonates, calcitonin, indomethacin, corticosteroids, tricyclic antidepressants, gabapentin, acupuncture, spinal cord stimulation, regional nerve blocks, and others, have been used to treat RSD with variable success.[39,46] In one study, vitamin C was shown to reduce the incidence of RSD after wrist fracture.[47]

Fat Embolism Syndrome

Fat embolism refers to the presence of fat globules in the lung parenchyma and peripheral circulation after a long bone frac-

ture or major trauma.[48] The phenomenon of fat embolization is probably common as a subclinical event after long bone fracture. Intravascular fat droplets appear in nearly one of five patients admitted with major trauma, although not all patients are symptomatic or require treatment.

Fat embolism syndrome is a serious manifestation of fat embolism, occurring most commonly after long bone fractures (usually tibia and fibula) in young adults and after hip fractures in elderly patients. Symptoms usually appear 1 to 2 days after an acute injury or after intramedullary nailing. Respiratory distress and hypoxemia are the earliest, most common manifestations. Acute respiratory distress syndrome (ARDS) may occur and is the usual cause of death. Neurologic involvement, manifesting as restlessness, confusion, or deteriorating mental status, also is an early sign, as are thrombocytopenia and a petechial rash. Fever, tachycardia, jaundice, retinal changes, and renal involvement may occur. Fat is seen in the urine in 50% of patients within 3 days of the injury. The incidence of full-blown fat embolism syndrome varies from 0.5 to 2% in patients with isolated long bone fractures to 5 to 10% in patients with multiple fractures. Management of fat embolism syndrome is primarily supportive, usually in an intensive care unit. The mortality rate is 20%, but most patients recover without severe sequelae.[49] No specific therapy has shown benefit.

Fracture Blisters

Fracture blisters are tense blisters or bullae that accompany high-energy injuries in areas of relatively little skin coverage over a fracture site. The ankle, elbow, foot, and knee (in that order) are the most common sites; all of these contain fewer hair follicles and sweat glands to anchor together the epidermal-dermal junction than do other limb locations.[50] Fracture blisters are believed, in many cases, to occur in the setting of increased underlying tissue pressure and may be a harbinger of compartment syndrome.

Early surgical intervention reduces the incidence of fracture blister formation.[50] In addition, the presence of a fracture blister requires an alteration of the surgical approach or a delay in surgery. Most experts discourage incisions through a fracture blister because such incisions seem to increase infection and skin breakdown. Measures to perform early surgery after high-energy injuries and to minimize increases in tissue pressures might reduce the incidence of this complication. Intact blisters should be covered with povidone-iodine solution and a sterile dressing. Unroofing the blister and applying coverage with silver sulfadiazine paste has been reported to decrease the incidence of complications.[50]

Complications of Immobilization

Fractures frequently result in long periods of immobilization. Immobility may lead to multiple medical problems, especially in elderly patients, including pneumonia, deep venous thrombophlebitis, pulmonary embolism, urinary tract infection, wound infection, decubitus ulcers, muscle atrophy, stress ulcers, gastrointestinal hemorrhage, and psychiatric disorders (Box 46-5). Early ambulation is a major goal of optimal orthopedic care.

Box 46-5 COMPLICATIONS OF FRACTURES AND IMMOBILITY

Fractures
Hemorrhage
Vascular injuries
Nerve injuries
Compartment syndrome
Volkmann's ischemic contracture
Avascular necrosis
Reflex dystrophy
Fat embolism syndrome

Immobility
Pneumonia
Deep venous thrombosis
Pulmonary embolism
Urinary tract infection
Wound infection
Decubitus ulcers
Muscle atrophy
Stress ulcers

SUBLUXATION AND DISLOCATIONS

Nomenclature

Abnormal forces applied to joints may result in the loss of continuity between two articulating surfaces. Partial loss of continuity is termed *subluxation*, and complete loss is termed *dislocation*. In general, dislocations are named for the major joint involved, as in a dislocated shoulder or hip. In three-bone joints, the injury is named for the joint involved if the disturbance involves the two major bones, or, if the lesser bone is involved, the disturbance is named for that bone. Separation of the femur from the tibia is termed *dislocation of the knee*, whereas displacement of the patella from its normal articulation is termed *dislocation of the patella* (Fig. 46-10). At the elbow, separation of the olecranon from the humerus is a *dislocation of the elbow*, whereas separation of the radius from the humerus is termed *radial head dislocation*.

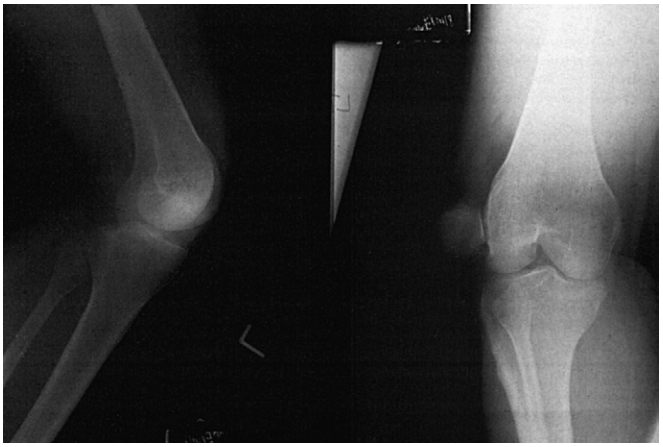


Figure 46-10. Dislocation of the patella.

Dislocations and subluxations should be described according to the direction of the distal segment relative to the proximal segment or of the displaced bone relative to the normal structures. The injury shown in Figure 46-11 is termed *dorsal dislocation of the interphalangeal joint of the thumb*. Disruption of articulation also may occur in combination with a fracture. The term *fracture-dislocation* is used to describe this combination. If the overlying skin is broken in any way, dislocations, subluxations, or fracture-dislocations are described as open and constitute the same emergency as does an open fracture alone.

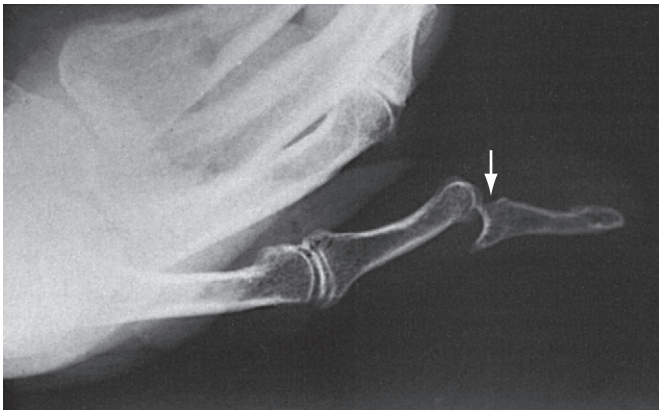


Figure 46-11. Dorsal dislocation of the distal phalanx of the thumb.

Assessment

In most cases of dislocation, severe to excruciating pain exists because the joint capsule is stretched or torn. Movement of the joint exacerbates the pain. This useful sign is lost in an obtunded, intoxicated, or unconscious patient and may result in a missed diagnosis if a careful survey is not performed. Some dislocations, such as anterior shoulder dislocation, have an obvious deformity, whereas others, such as posterior shoulder dislocation, may be subtle. Swelling of soft tissues also may obscure the diagnosis, such as in the tarsal-metatarsal region. Gentle passive testing of range of motion should be performed but never forced. Assessment for neurovascular function is similar to that for fracture. Certain dislocations (e.g., knee) are so commonly associated with vascular injuries that a careful assessment of blood flow is important in evaluating these injuries.

Plain radiographic studies detect most dislocations, provided that the correct views are ordered. Radiographs should be performed before and after attempts at reduction of first-time or complicated dislocations, unless there is neurovascular compromise. This confirms the diagnosis and ensures that associated fractures are documented before treatment is undertaken.

Treatment

Methods of relocating specific joints are reviewed in subsequent chapters, but a few general principles apply. In general, the sooner a joint is relocated, the better. Later, swelling and muscle spasm make reduction more difficult. Also, pain is not adequately relieved until the dislocation is reduced. In the hip, early reduction is mandatory to restore vascular supply and to avert the complication of avascular necrosis. Before attempting relocation, adequate analgesia or conscious sedation should be used. Nerve blocks are especially useful on the digits. The general principle of reducing a dislocation is to re-create and reverse the mechanism of injury, pulling the proximal end of the dislocated bone out and away from whatever is trapping it in its final resting place. As this maneuver is accomplished, the disarticulated surface is manipulated back or may snap back spontaneously toward its normal anatomic position. If the reduction is difficult, it should not be forced. A single good attempt is better than repeated attempts in an inadequately relaxed patient. Some joints cannot be reduced in the ED because (1) the opposing muscles are contracting too forcefully and general anesthesia is necessary to overcome these forces or (2) mechanical obstruction by a bony fragment or a torn piece of cartilage, tendon, joint capsule, or skin requires surgical removal for reduction to occur.[51]

SOFT TISSUE INJURIES

Sprains

Nomenclature

Ligamentous injuries resulting from an abnormal motion of a joint are termed *sprains*. A sprain is defined as injury to the fibers of a supporting ligament of a joint. Sprains may be graded according to the severity of pathologic findings; clinically, however, the grades are often indistinct. *First-degree* sprains are characterized by minor tearing of ligamentous fibers with resultant mild hemorrhage and swelling. Minimal point tenderness can be elicited. Stressing the ligament produces some pain, but there is no opening or abnormal joint motion.

A *second-degree* sprain is a partial tear of a ligament, meaning more fibers are torn than in the first-degree injury. Clinical findings include moderate hemorrhage and swelling, tenderness, painful motion, abnormal motion, and loss of function. There may be a tendency toward persistent instability and recurrence, and prevention of these complications is a major goal of treatment.

A *third-degree* sprain describes the complete tearing of a ligament. Signs include a further exaggeration of the signs mentioned for second-degree sprain. In addition, stressing the joint reveals grossly abnormal joint motion, provided that this is not limited by pain or swelling. Analgesia and the evacuation of a hemarthrosis may be used to allow a more complete diagnosis of these injuries. Chronic joint instability is the rule if severe ligamentous injuries do not heal properly.

Assessment

The clinical presentation of a sprain of the extremity may be indistinguishable from that of a fracture. The injury frequently occurs during vigorous athletic activity when forces applied in opposite directions result in a joint being stressed in an abnormal or exaggerated direction. The patient may complain of hearing a "snap" or a "pop" at the moment of injury and conclude that a fracture must be present. Other patients report "seeing stars" or "almost passing out" at the moment the injury occurred and may still be in extreme pain, appearing pale and diaphoretic if seen shortly after the injury. Analgesia should be provided to these patients. Evaluation should include a careful history of the exact sequence of events at the time of the injury and ascertaining the position of the extremity and the forces applied to it at that moment. A history of any sounds that accompanied the injury should be elicited. Examination of the joint should include stressing it to show abnormal motion. If radiographs are planned to rule out a fracture anyway or if exquisite pain is produced by mild attempts to apply stress, it is probably better to delay stressing until films have verified the absence of a significant fracture. Plain radiography is indicated in some, but not all, cases to rule out a fracture. It has been well demonstrated that clinical decision rules can reduce the number of radiographic studies without missing significant fractures.[52-55]

Avulsion fractures may occur concomitantly with sprains. In children, epiphyseal fractures occur more commonly than ligamentous disruption because of the relative ligamentous strength compared with the ease of disrupting the epiphyses. Arthroscopy or MRI is indicated in the follow-up evaluation of some of these injuries (e.g., for suspected cruciate tears) when significant pain or disability is present.[56-58]

Treatment and Disposition

Specific management of sprains varies depending on the location and severity of the injury. In general, initial measures should include the traditional recommendations of ice, elevation, and analgesia. Nonsteroidal anti-inflammatory drugs (NSAIDs) are effective analgesics in many patients. Several studies have found more rapid decrease in swelling, increased exercise endurance, and earlier return to work with use of NSAIDs.[59]

Immobilization is used to provide protection and comfort in the initial management of most injuries, using one of the following methods. Because the severity of injury is sometimes difficult to establish at the first visit, it is reasonable to immobilize the affected joint for the first 48 to 72 hours, after which the extent of injury can be better determined. At that time, early mobilization is often desirable, particularly in lateral ankle injuries because this leads to earlier return to work and athletic activities and better preservation of proprioceptive neuromuscular function.[60] Use of an inflatable "air cast" alone or in conjunction with an elastic ankle wrap has been shown to be effective in decreasing the symptomatic period.[61] For lower extremity injuries, protected weightbearing with crutches provides patients with comfort and avoids motion of the impaired part. In elderly patients, safe ambulation sometimes cannot be accomplished, and a short hospitalization or admission to a skilled nursing facility may be necessary.

For complete or nearly complete ligamentous disruption, urgent orthopedic consultation is usually mandatory. Less severe injuries can be followed up 3 to 7 days postinjury when acute swelling has subsided. Copies of plain films ordered in the ED should be sent with the patient if possible. Physical therapy and rehabilitative exercises sometimes are begun at these visits and carried on for several weeks. Because ligaments are relatively avascular, healing is slow, and patients with significant sprains should be informed of this. Sprains should be diagnosed as precisely as possible and should not be trivialized. Too often, after radiographs have ruled out fracture of an affected extremity, the term *sprain* is applied indiscriminately, or the patient is told that the injury is *only* a sprain, a misleading expression that should be avoided. Aside from creating false expectations regarding recovery, thoughtless mislabeling of injuries not in evidence may lead to missed occult fractures in adults or epiphyseal injuries in children.

Strains

Nomenclature

A *strain* is an injury to a musculotendinous unit resulting from violent contraction or excessive forcible stretch. The term *pulled muscle* sometimes is used interchangeably with muscle strain. These injuries are graded in a manner similar to sprains.

A *first-degree* strain is a minor tearing of the musculotendinous unit, characterized by swelling, local tenderness, and minor loss of function. Findings increase along a continuum such that in a *second-degree* strain, more fibers are torn, but without complete disruption; swelling, ecchymosis, and loss of strength are more marked. In a *third-degree* strain, the muscle or tendon is completely disrupted, with resultant separation of muscle from muscle, muscle from tendon, or tendon from bone. An accompanying avulsion fracture may be present on radiographs in either second- or third-degree injuries.

Assessment

Signs and symptoms include pain, ecchymosis, swelling, and loss of function. A force applied to the muscle, either passive stress or active contraction, produces sharp pain at the site of injury even as the injured muscle may be relatively comfortable at rest. A palpable defect sometimes is present at the site of a complete rupture, which usually involves the region of the muscle tendon junction, or a bunching up of the muscle may be appreciated. Ultrasound is increasingly being used to diagnose an assortment of soft tissue injuries including rotator cuff tears, tendon ruptures, and muscle tears.[62,63] Among nonathletes, strains commonly are seen in patients who have either overstressed a muscle group or tried to generate excessive force in a unconditioned muscle. Examples are the weekend gardener or mover who presents on Monday morning with lower back strain, the aerobics student who strains the rectus muscles, and the weightlifter who presents with chest wall pain resulting from pectoralis major strain. These are usually first-degree injuries, and the onset is slow. Rapid acceleration (e.g., in a tennis player) may result in a third-degree gastrocnemius or plantaris tear, whereas pushing off to jump is a common cause of ruptures of the Achilles tendon in a basketball player. A sudden violent attempt at lifting in an older individual can result in a complete biceps brachii disruption. Sudden generation of forces of which the thighs are capable results in second-degree strain of the hamstrings, quadriceps, or thigh abductor muscles.

In athletes, generation of tremendous contraction forces coupled with excessive forcible stretching (while the body may be either accelerating or "planting") results in severe strains. Involvement of almost any muscle group is possible, and the onset of such injuries is usually acute. Immediate removal from activity, application of ice, and rest of the affected limb for 48 to 72 hours usually are advised to prevent further injury. A competitive athlete usually is unable to continue anyway because of the accompanying loss of function. After a brief rest period, however, early mobilization and rehabilitation should be encouraged.

Treatment and Disposition

Treatment depends on the degree of disruption, location, and functional loss. Most first-degree injuries respond in a few days to rest, application of ice, and, for some patients, analgesics. NSAIDs commonly are recommended and prescribed, although their efficacy for other than analgesic purposes is unproven. Second-degree strains are treated similarly, with protection against aggravating activity required for longer periods. Third-degree strains receive similar initial treatment in the ED plus early orthopedic consultation. Some of these injuries are amenable to surgical repair, whereas others may be treated with immobilization. The muscle affected and the age, occupation, and activity level of the patient all are factors in deciding whether surgical intervention is appropriate. Many athletes and their trainers believe and it is universally espoused that many strains can be prevented by proper training, warm-up, stretching exercises, and avoidance of overexertion, although limited scientific data exist to support these recommendations.[64,65]

Tendinitis and Tendinosis

Tendinitis is classically described as an inflammatory condition characterized by pain at tendinous insertions into bone, occurring in the setting of overuse.[66,67] It is now believed that the pathophysiology of this condition is more complex than

mere overuse, with the roles of load and use affecting cell-matrix interaction.[68] Etiologic factors are believed to include aging, with decreased blood supply and decreased tensile strength; muscle weakness and imbalance; insufficient flexibility; male gender; obesity (in weight-bearing joints); smoking; malalignments; training errors; and improper equipment.[69,70] Additionally, certain systemic diseases, including diabetes mellitus, chronic renal failure, rheumatoid arthritis, and systemic lupus erythematosus; steroid use; and occasionally fluoroquinolone use are associated with the development of tendinopathy.[71]

With chronicity, involved tissues are characterized morphologically by signs of chronic rather than acute inflammation (infiltration by macrophages, plasma cells, and lymphocytes rather than leukocytes) and degeneration (cell atrophy). It also has been shown that prostaglandin E_2 levels are normal.[72] This evolving understanding of tendinitis in the future should allow for more logical treatment of these injuries aimed at the underlying pathophysiology. It also has led some authors to propose that chronic painful conditions of the tendon should be referred to as *tendinosis* rather than *tendinitis* or other terms previously used to describe this condition, including *tendonitis*, *degenerative changes*, *chronic tendinopathy*, or *partial rupture*.[69,73] In this chapter, *tendinitis* and *tendinosis* are used interchangeably.

Common sites for tendinitis are the rotator cuff of the shoulder, the Achilles tendon, the radial aspect of the wrist (de Quervain's tenosynovitis), and the insertion of the hand extensors on the lateral humeral epicondyle (tennis elbow). Also commonly involved in athletes are the patellar tendon, particularly in athletes engaged in jumping sports; the biceps femoris, semitendinosus, and semimembranosus (hamstring syndrome); posterior tibial tendon (shin splint syndrome); the iliotibial band; and the common wrist flexors (medial epicondylitis) seen in little league pitchers and golfers.[68] In some locations, most commonly the shoulder, calcium deposition occurs along the course of the tendon, resulting in a painful condition termed *calcific tendinitis*. This condition also may occur in the wrist, hand, neck, hip, knee, ankle, or foot.[74]

Physical examination reveals pain with motion and limitation of function and may include point tenderness and palpable crepitus over the involved tendon with motion. In general, a clinical test can be performed by forcible flexion of the involved muscle while keeping the point of insertion fixed or by operating the involved muscle against resistance. Either test should intensify the discomfort. Radiographs are usually negative. A small fleck of bone may suggest an avulsion, or the surface of the bone at the attachment may be roughened, indicating periostitis. As mentioned, there also may be calcium deposits along the course of the tendon, which should not be confused with an avulsion fracture. Ultrasound is sometimes useful in confirming the diagnosis of tendinitis. Although a normal tendon is characterized by a relatively homogeneous pattern, tendinitis is characterized by one or more of the following features: loss of the fibrillar echotexture, focal tendon thickening, diffuse thickening, focal hypoechoic area, irregular or ill-defined borders, or microruptures.[75]

There is little evidence to support any specific treatment for tendinosis. The classic approach consists of rest, ice, and NSAIDs initially, followed by rehabilitation and training and control of force loads to prevent recurrences. Although NSAIDs may be useful for a brief period at the onset of symptoms for their analgesic effects, no evidence exists that they significantly alter the pathophysiology of this condition, and no rationale exists for ordering them in patients at any risk for complications from this class of drugs.[76] Peritendinous local infiltrations of anesthetics and corticosteroids may be useful but should not be repeated too often because tendon rupture may occur. Injection therapy is especially useful in calcific tendinitis around the shoulder. Injection of steroids directly into the Achilles tendon should be avoided because of reports of partial or complete rupture after even a single injection. Some cases of calcific tendinitis that do not respond to conservative therapy may require either arthroscopic or open surgery.[77,78]

Bursitis

Bursitis is a painful inflammation of the bursa that may be traumatic, infectious, or related to systemic illness. Commonly involved sites include the olecranon, the greater trochanter of the femur, and the prepatellar and anserine bursae around the knee. Physical findings are tenderness and swelling over the involved bursa, whereas warmth and overlying erythema may signal infection. If infection is suggested, aspiration of the bursal fluid and Gram's staining and culture are recommended. Otherwise, treatment may be conservative and is similar to treatment for tendonitis, with ice, NSAIDs, or steroid injections. Most patients can be treated as outpatients.[79]

TREATMENT MODALITIES

Splinting and Bandaging

Suggested or confirmed fractures or dislocations should be splinted to avoid damage to muscles, nerves, vessels, and the skin. Splinting also may restore blood flow to ischemic tissue by removing pressure caused by a bone fragment resting against a blood vessel. Finally, splinting relieves pain; conversely, movement of fracture fragments results in severe pain.

Field Care

Splinting should begin in the field because it reduces the risk of further neurovascular compromise, prevents a closed injury from potentially being converted to an open one during transport, reduces the patient's pain, and facilitates subsequent ED assessment and imaging. Numerous commercial devices are available, and most ambulances carry an assortment of immobilization devices (Fig. 46-12). Minimal equipment includes long and short backboards, cervical collars, sandbags, and extremity splints. A half-ring traction splint also is essential. Inflatable air splints are favored by some authors because they are convenient, easy to apply, transparent, and radiolucent and because they tamponade low-pressure bleeding. Other authors prefer to avoid these devices because theoretically they could contribute to the development of a compartment syndrome. If used, inflatable splints should be inflated only by mouth and to the point that still permits indentation by gentle finger pressure.

Field personnel should splint possible fractures before the patient is moved. Severely angulated long bone fractures should be straightened in the field before they are splinted. Splints should be applied in such a way as to immobilize the joints above and below the fracture site to avoid motion of the involved bone. The skin should be padded to avoid local necrosis, and the splint should be secured by a circumferential wrapping material. This material should allow for some expansion and should not be applied in a constricting manner.

Emergency Department Care

In the ED, the indications for splinting are the same as in the field. All splints should be checked and, if properly applied,

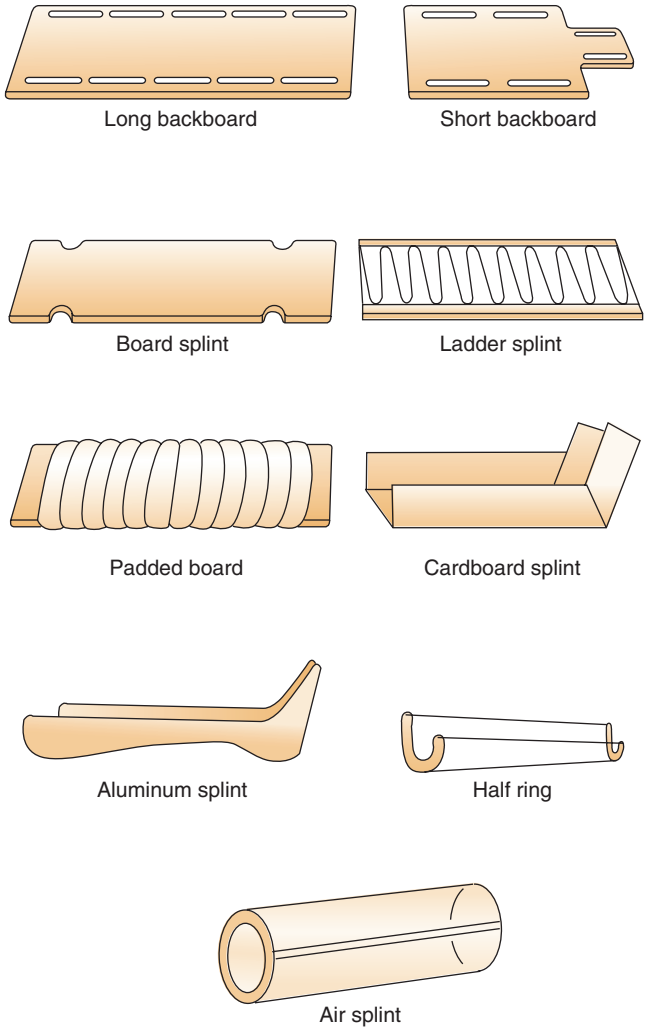


Figure 46-12. Commercial splints.

need not be changed. Splinting or other immobilization is also used after diagnosis and treatment of injuries. In some cases, a splint is all that is needed for definitive treatment. Injuries other than sprains and fractures (e.g., inflammatory and infectious processes, bites, burns, and repaired injuries of muscle bellies or tendons) also benefit from immobilization. Splints also can be used to improve function, such as with wrist drop that accompanies radial nerve palsy. When the injury is immobilized, it is important to stress elevation of the affected part to avoid edema formation. Many different devices and materials are available. Some devices that are commonly used are described next.

Upper Extremity

Sling-and-Swathe and Velpeau Bandages. Sling-and-swathe and Velpeau bandages are useful in immobilizing the shoulder, humerus, and elbow. They are commonly used after reduction of dislocated shoulders and to treat impacted fractures of the humeral neck. The axillae should be padded and powdered to avoid skin maceration. A commercial shoulder immobilizer also is available and is useful after reduction of a shoulder dislocation. Its advantages are ease of application and ease of removal and reapplication by the patient for bathing.

Clavicle Splint. Historically, middle third fractures of the clavicle routinely were initially treated with a figure-of-eight clavicle strap with or without the addition of a sling. This device is commercially available or can be fashioned from tubular stockinette. If used, a clavicle splint should be applied snugly enough to keep the shoulders back in the "at-attention" position, but not so tight as to compress the axillary artery or brachial plexus. Chafing of the skin can be avoided by padding and powdering the axillae. Superiority of the figure-of-eight clavicle strap over a simple sling has not been shown.

Figure 46-13. Wrist splints.

Plaster and Fiberglass Splints. Well-fitting, customized plaster splints can be fashioned easily to immobilize the elbow, forearm, wrist, and hand. The advantage of these splints is the ability to mold them to an exact size and shape (e.g., along the ulnar side of the forearm and hand to immobilize a midshaft fourth or fifth metacarpal fracture, the so-called gutter splint). Several commercially available products consist of multiple layers of plaster or fiberglass strips, inside a covering of foam and flannel, on a continuous roll that can be applied to any length. While the splint is still wet, a bandage is wrapped over it, and the splint is molded and held in the desired position as the plaster or fiberglass resin hardens.

Forearm and Wrist Splints. Numerous preformed splints are available for splinting fractures of the distal forearm and wrist. They are lightweight, neat, and easy to apply and are easily removed and replaced by the patient (Fig. 46-13).

Lower Extremity

Femur and Hip. Fractures of the femoral shaft can be immobilized by using a traction device, such as the Hare traction splint or a similar appliance (Fig. 46-14). These devices should be applied in the field if possible; most ambulances carry them. The principle is that a proximal ring engages the ischial tuberosity for countertraction while the longitudinal traction is applied through the ankle by means of an ankle hitch. A commercial ankle hitch is recommended, but if one is not available, an improvised hitch can be fashioned with a triangular

Figure 46-14. **A,** Hare traction splint. **B,** The commercial hitch is designed to protect the ankle and heel during traction.

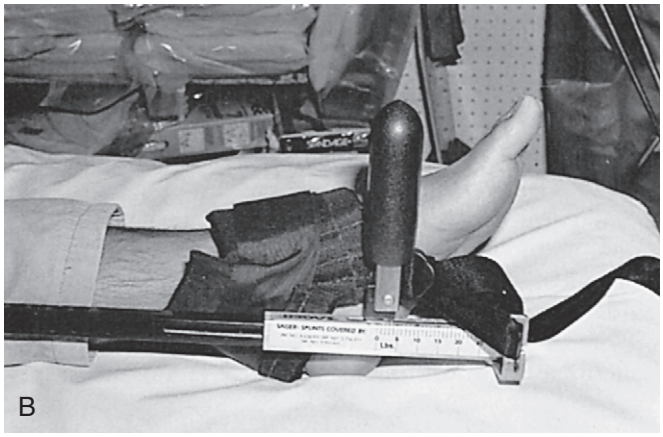


Figure 46-15. **A,** Sager splint. **B,** Detail of distal splint end.

bandage or a wide piece of cloth tied in a Collins hitch. The patient's ankle bones, Achilles tendon, and arch of the foot should be padded, and the circulation should be checked to ensure it is intact. A properly applied splinting device relieves pain from a fracture rather than exacerbating it.

The Sager splint might offer advantages over other appliances in that it is applied to the medial and lateral aspect of the thigh rather than having a half-ring posteriorly (Fig. 46-15). The Sager splint is more acceptable for use in the presence of pelvic fractures and avoids compression of the sciatic nerve. Because the half-ring devices may produce angulation at the fracture site, the Sager device is purported to result in better alignment, although this has never been measured. The Sager splint is shorter and more compact than the Hare traction splint, rendering it more acceptable for certain transport helicopters and body scanners. Also, the amount of traction is metered at the ankle, and overtraction can be avoided.

Knee. Commercially available knee immobilizers can be used after acute injuries to provide firm but not rigid stabilization of the knee. The device is essentially a foam cylinder with medial and lateral aluminum stays, attached by Velcro straps, and spanning the upper thigh to upper ankle. This device is commonly used after trauma to let the knee "cool off" until a better physical examination or diagnostic study can be performed in a few days.

Another dressing that may be applied at the knee is the Jones "compression" dressing. Some authors believe the word *compression* should not be used here to discourage application that is too tight. The Jones dressing is a bulky dressing that is used by some clinicians in situations when swelling is expected, including internal fixation procedures. The ability to flex and extend at the knee is maintained. The dressing consists of a thick layer of absorbent cotton bandage (Webril) wrapped with an elastic bandage, followed by another layer of cotton bandage, followed by an additional elastic wrap. If more stability is required, slabs of plaster can be placed on the medial and lateral side of the limb, just under the last bandage. Caution must be exercised because burns have been reported with this type of dressing when too many layers of plaster are used. A similar type of bulky dressing may be used for some injuries of the ankle and fractures of the calcaneus. In general, commercial knee immobilizers have replaced the Jones dressing in the treatment of acute knee injuries.

Ankle. Immobilization of the ankle can be accomplished by numerous means. Plaster splints can be used temporarily for the treatment of nondisplaced ankle fractures or for the treatment of severe sprains. These can be fashioned in the same manner as described for the upper extremity. An alternative method is to apply a full circular cast, bivalve it on either side, discard the anterior piece, and affix the posterior mold with an elastic bandage or bias-cut stockinette. Most ankle injuries should be splinted with the patient's ankle in neutral position.

Injuries to the Achilles tendon, plantaris muscle, or gastrocnemius muscle initially should be treated with the foot held in slight equinus (plantar flexion) for comfort. The toes should be free to move distal to the metatarsophalangeal joints, and the proximal border should end below the tibial tubercle to avoid pressure on the peroneal nerve.

Adhesive strapping is an alternative method of ankle immobilization that provides good support and limitation of motion. Taping reportedly loses its "protective properties" with cyclic loading and sweating; although this is cited as a disadvantage, it may actually be helpful in encouraging and allowing early mobilization. This method is lightweight and not bulky, and a shoe can be worn over it. Tape is applied in a noncontinuous manner, which allows for swelling and avoids constriction. First, the hair is shaved. Next, strips of tape are measured and torn off; 1½-inch or 2-inch cloth-backed adhesive tape or Elastoplast is used. Elastoplast is an elastic-backed tape, constructed to stretch only in the longitudinal direction; this serves to spring the foot back automatically to a neutral position if the foot is plantar-flexed for any reason. The tape should be applied directly to the skin after a skin adherent, such as tincture of benzoin, is applied. The tape should lie flat because wrinkles may damage the skin (Fig. 46-16).

A dome-paste bandage, or Unna's boot, is a bandage impregnated with zinc oxide, calamine lotion, glycerin, and gelatin that also is well suited to immobilizing an ankle sprain.[80] This combination is gentle to the skin, which is especially important if atrophy or venous incompetence is present. In addition, hair need not be shaved, the bandage is easy to apply, and a shoe can be worn over it. Some patients complain about the sticky sensation against the skin, especially in warm weather. Another disadvantage is that it is applied concentrically, and problems can arise if the bandage is wrapped too tightly. The bandage should be applied directly to the skin, starting at the foot and working upward; it should overlap at each turn approximately half the width of the previous turn and continue up to just below the tibial tubercle. Then the bandage should be covered with either bias-cut stockinette or an elastic bandage. The dome-paste bandage hardens to about the consistency of sturdy cardboard and provides firm support. Removal is best accomplished with bandage scissors.

An increasingly preferred device for moderate to severe lateral ankle sprains is a commercial support composed of molded plastic with Velcro straps (e.g., Air Cast, AirStirrup) (Fig. 46-17).[60,81] This product may be worn in the patient's shoe and permits early weightbearing and return to activity. It is designed to permit dorsiflexion and plantar flexion but to limit inversion and eversion, a concept referred to as *functional bracing*. Some authors also find this device useful during athletic activities instead of adhesive taping to prevent recurrences.[61,82,83] Although these orthoses are relatively expensive, the cost might be more than offset by their ease of application, their reusability, and the benefit derived from earlier return to work.[81]

Severe ankle sprains also may benefit from immobilization in a CAM Walker, which is a commercial appliance consisting of a layer of padding extending from the tibial tubercle to the metatarsal heads, supported by metal plates along the length of the lower leg. These plates articulate with a molded hard plastic boot at the ankle. The position of the foot can be adjusted as desired, and when set, the ankle is kept firmly immobile. The rounded undersurface of the boot allows for ambulation without movement of the ankle joint.

Casts

Plaster casts perform a function similar to splints in that they provide stability and pain relief. Casts sometimes are used in

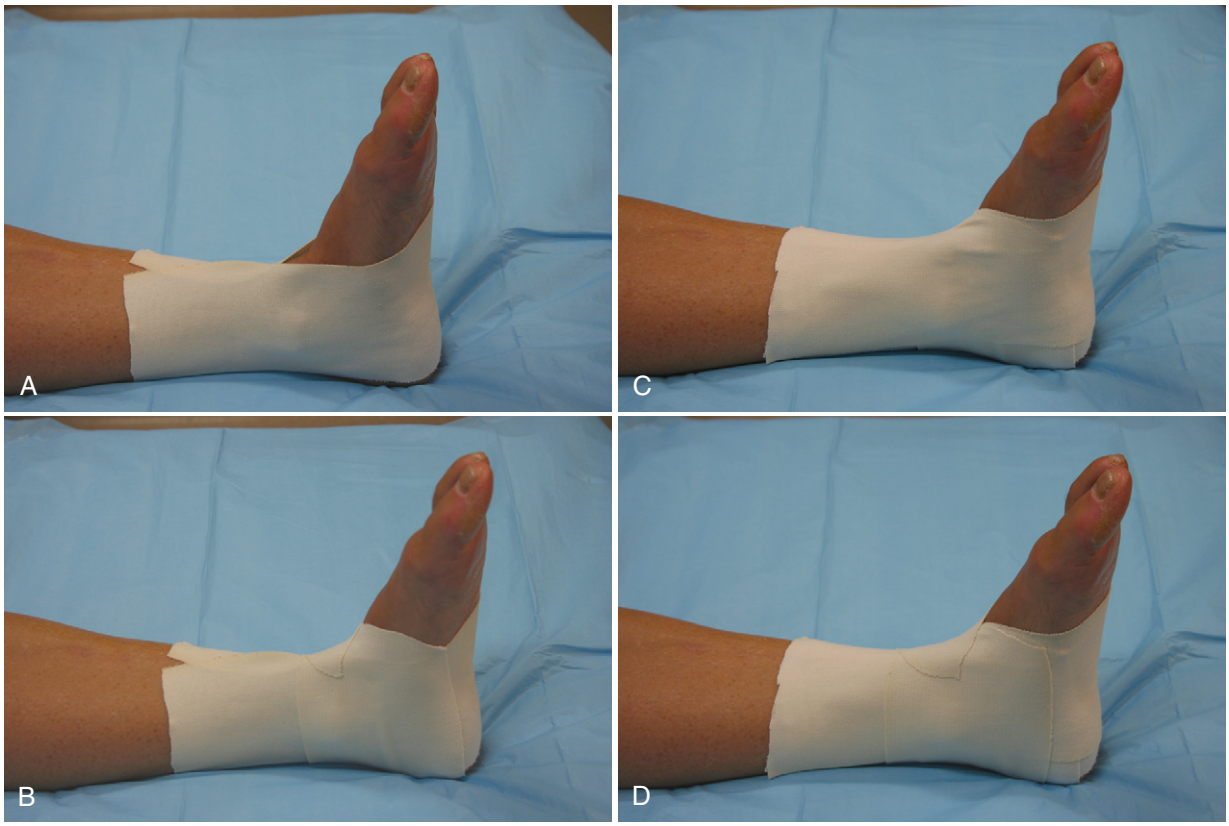


Figure 46-16. **A-D,** Application of adhesive strips to immobilize the ankle.

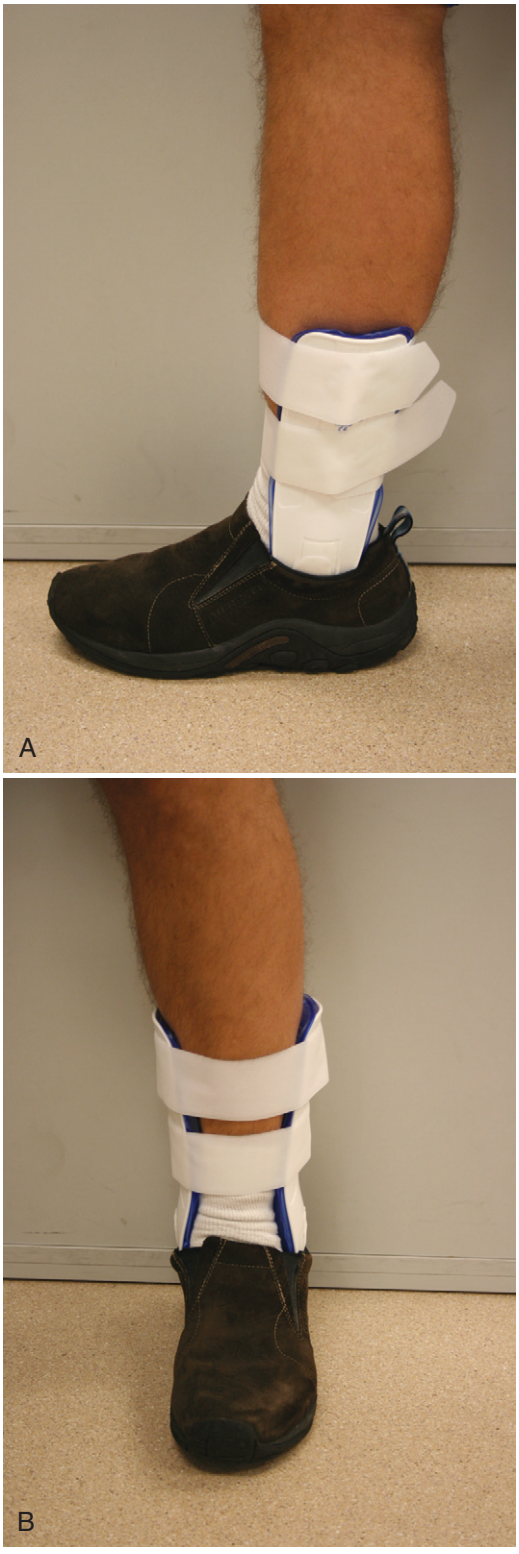


Figure 46-17. Air Cast. **A,** Lateral view. **B,** Anterior view.

conjunction with internal stabilizing devices, such as Kirschner wires or Steinmann pins. Casts are not mandatory for all fractures, and in situations in which they are, application is usually not an immediate necessity. Swelling and subsequent pressure under the cast are highest during the first 24 hours after injury.[84] Plaster is applied as strips or rolls of cloth that are impregnated with a hemihydrate of calcium sulfate. When this cloth is dipped in lukewarm water, a creamy paste is formed that can be molded into a cast. An exothermic reaction takes place that causes the plaster to harden and can burn the skin.[85] Factors that have been shown experimentally to increase skin temperatures during plaster application are dip-water temperatures greater than 24° C, cast thickness greater than eight plies, and inadequate ventilation of the newly applied cast.

Immersing the plaster in water for too short a time or squeezing too much water out also may lead to generation of excess heat. To avoid pressure on the skin and over bony prominences, stockinette and layers of cotton sheet wadding (Webril) are snugly applied first. Padding that migrates under a formed cast can be uncomfortable and result in pressure sores. Padding alone does not prevent burns.[86]

Variations of the basic cast exist. A window may be placed in the cast, and the cutout area may be used as access to skin wounds that require care during immobilization. Walking heels may be worked onto a lower extremity cast and should be placed in the center of the foot. Synthetic casts (fiberglass and other materials) are lightweight, durable, and water-resistant. In addition, their setting temperatures are significantly lower, and they are less likely to produce burns.[87] However, they are more expensive and more difficult to apply.

Patients with casts may present to the ED for complaints related to their casts; these usually are pain, local irritation, swelling, or numbness of the distal part. A cast that is too tight results in swelling, pain, coolness, and change in skin color of the distal parts. Pain also may be caused by the initial injury or by local pressure, or it may be a result of a developing compartment syndrome or wound infection. The safest thing to do if a patient complains of pain is to bivalve the cast and inspect the extremity. This is done by cutting the plaster and the padding on each side and removing half the cast at a time, using the other half as a mold to keep the extremity immobile. Afterward, the bivalved cast can be held together with bias-cut stockinette or elastic wrap until a new cast is applied. If relieving external pressure does not alleviate symptoms, the diagnosis of compartment syndrome should be seriously considered. Casts may obscure wound infections, sources of sepsis, and even the source of tetanus. The clinician should not hesitate to bivalve the cast and inspect the extremity.

The need for mandatory routine cast checks 1 day after initial application has been questioned.[88] In a retrospective study of 250 patients, none experienced problems from neurovascular compression, although 24% required some alteration of the cast. In the study, it may be simply that the casts were applied incorrectly in the first place. It is probably advisable to continue routine cast checks if casts are applied in the ED.

Thermal Therapy

Some confusion exists as to the role of cryotherapy versus heat therapy in the treatment of acute orthopedic injuries. Part of this confusion arises because heat may be more soothing to the patient. Cold causes vasoconstriction, limiting blood flow and hemorrhage into the traumatized area. Metabolic requirements are reduced in cooled tissues, as is histamine, and less capillary breakdown occurs as a result. Reduced blood flow also limits edema formation. Lower extravascular fluid pressure allows for better lymphatic drainage of injured areas. Cryotherapy produces three, and perhaps four, stages of sensation of which the physician and the patient should be aware. In the first stage, a cold sensation is noted for 1 to 3 minutes. The second stage consists of a burning or aching sensation for 2 to 7 minutes after the application of cold. This stage is uncomfortable, but must be endured to receive the benefits of the next two stages. Heat therapy, by contrast, is soothing,

and patients are likely to prefer this to the second stage of cryotherapy. The third stage begins 5 to 12 minutes after the application of ice and produces local numbness or anesthesia. The pain-spasm cycle is interrupted. While under this anesthetic effect, passive exercise may be desirable. This exercise helps to prevent atrophy, mobilize edema, clear injury debris, and reduce adhesions. However, several reviews of cryotherapy for soft tissue injury all reflect the lack of adequate science in establishing recommendations for cryotherapy. Application of ice appears to be effective in reducing pain, but there is no credible evidence that it accelerates healing.[89-91]

A fourth stage sometimes occurs 12 to 15 minutes after intense cryotherapy is begun, consisting of reflex deep tissue vasodilation without a corresponding increase in metabolism (reminiscent of the situation in rewarming shock). Because of this, a maximum of 15 minutes of cold application per treatment usually is advised.[92,93] An experimental study using triple-contrast bone scans compared the effect of icing times from 5 to 25 minutes on blood flow to the knee. Five minutes produced a measurable decrease in all tissues of the knee, whereas 25 minutes increased this effect fourfold and produced the overall maximal effects. A paradoxical increase in blood flow, perhaps reflecting reflex vasodilation, occurred at 10 minutes but then reversed.[94] These results suggest that longer icing times than previously recommended may be beneficial. Absolute contraindications to cryotherapy include severe cold allergy (with hives and joint pain) and Raynaud's phenomenon and disease. Relative contraindications include some rheumatoid conditions and paroxysmal cold hemoglobinuria with renal dysfunction and secondary hypertension. Anesthetic skin in a paralyzed or comatose patient is at risk with ice therapy. One case of gangrene has been reported, but in this instance cold was applied for 16 hours a day for 2 months.[95] These contraindications to cryotherapy are rare, especially in the athletic population most at risk for serious injuries. Heat increases blood flow and the inflammatory response and edema. Warm tissues and cells have a higher metabolic rate and increased requirements of nutrients and oxygen. Ice, rather than heat, is the method of choice of most authorities in the acute treatment and rehabilitation of acute orthopedic injuries and should be initiated as soon as possible for maximum benefit.

KEY CONCEPTS

- Compartment syndrome is associated most commonly with a closed long bone fracture of the tibia but also is well described in the thigh, forearm, arm, hand, and foot and can occur with soft tissue trauma alone. Elevation of a limb with resultant reduction in the local arteriovenous gradient may be counterproductive and may exacerbate compartment syndrome.
- Because of their blood supply, certain bones may undergo avascular necrosis after fracture, especially if fractures are comminuted and go untreated for any length of time. The femoral head, talus, scaphoid, and capitate are particularly prone to this complication.
- Fat embolism syndrome is a serious manifestation of fat embolism, occurring most commonly after long bone fractures in young adults (usually tibia and fibula) and after hip fractures in elderly patients. Respiratory distress syndrome is the earliest, most common, and serious manifestation. Neurologic involvement, manifesting as restlessness, confusion, or deteriorating mental status, is also an early sign, as are thrombocytopenia and a petechial rash.
- In children, epiphyseal fractures occur more commonly than ligamentous disruption because of the relative ligamentous strength compared with the ease of disrupting the epiphyses.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 47 Hand

Everett T. Lyn and Thomas Mailhot

PERSPECTIVE

The hand is intricate, dynamic, and unique in function. It combines extreme mobility, precision, power, and sensation and is used to express and execute. Because the hands are used more to manipulate the environment than the rest of the body, they are commonly injured. Function depends on intact relationships among intrinsic structural components, musculotendinous units originating from more proximal areas, and motor and sensory connections with the central nervous system. Restoration of function rather than appearance is the primary goal in management of hand injuries and infections. Early recognition and timely initiation of therapy for limb-threatening conditions are essential to an optimal outcome. The fate of the injured hand depends largely on the physician who provides initial care. Mismanagement may result in unnecessary functional loss that may not be recoverable, even with the best convalescent care. An understanding of the functional anatomy of the hand is necessary for the appropriate evaluation and management of these disorders.

Epidemiology

Overall, hand injuries are reported to represent 5 to 10% of visits to an emergency department (ED), and approximately 6% of the patients have deep, significant injuries.[1] Injuries have environmental, occupational, and recreational causes and are seen in all age groups. The spectrum of injury includes infections, lacerations, fractures, crush wounds, amputations, and burns. It is estimated that 10% of all patients with hand injuries require referral to a hand specialist, and most patients referred from EDs have fractures.[2] The disability potential of hand injuries generally is high; such disability may involve loss of strength, flexibility, or sensation. According to available data, hand injuries account for 19% of lost-time injuries and for 9% of worker compensation cases.[3] Approximately 3 to 4 million working days are lost each year as a result of hand injuries.[4] Overall, hand and fingers are the most frequent body parts injured in the workplace and cared for in EDs.[5]

PRINCIPLES OF DISEASE, FUNCTIONAL ANATOMY, PHYSIOLOGY, AND EXAMINATION OF THE HAND

Terminology

To avoid confusion, it is important that standard terminology for the surface anatomy of the hand be used (Fig. 47-1). The back of the hand and fingers is called the *dorsal surface*, and the palm side is called either the *palmar* or the *volar surface*. The borders of the hand are *radial* and *ulnar*. The five digits often are designated by numerals, but common names are preferable: I (thumb), II (index finger), III (long or middle finger), IV (ring finger), and V (little finger). Each finger has three joints: the metacarpophalangeal (MCP), the proximal interphalangeal (PIP), and the distal interphalangeal (DIP) joints. The thumb has an MCP joint and only one interphalangeal (IP) joint. There are proximal, middle, and distal phalanges in the fingers and only a proximal and a distal phalanx in the thumb. The *thenar mass* or *eminence* refers to the muscular area on the palmar surface overlying the thumb metacarpal. The *hypothenar eminence* is the muscle mass on the palmar surface overlying the little finger metacarpal.

Hand and digit motion has been standardized and is illustrated in Figures 47-2 through 47-6. The carpometacarpal (CMC) joint is more mobile in the thumb than in the other fingers and is the key to the grasp and dexterity that characterize the human hand. Motions of this joint include *palmar abduction* (also called *flexion*), *radial abduction*, *retroposition* (*extension*), *adduction*, and *opposition* (see Fig. 47-6). The IP joints are essentially hinge joints and are capable of only two motions: flexion and extension.

Structural Framework

Skin Cover

The hand has two skin surfaces, each with different functions. The skin of the palm is thick compared with the dorsal skin and is stabilized by fibrous connections on its deep surface. The skin creases in the palmar aspect of the hand are largely transverse and represent adherence between skin and underlying fascia, without intervening adipose tissue. These features facilitate flexion and limit the development of inflammatory edema in the palm.[6] The other noteworthy characteristic of the palmar skin is the unique arrangement of epithelial ridges of the dermis that form cutaneous striations. These ridges have forensic importance in the pulp as "fingerprints" and play an important role in increasing friction for grasping objects.[7]

The dorsal skin is relatively thin and mobile, permitting motion of the various joints. As a path of least resistance, the dorsum of the hand also swells easily after inflammation or trauma, which may limit flexion of the MCP joints.[7] In addition, infection in the palmar aspect of the hand may cause

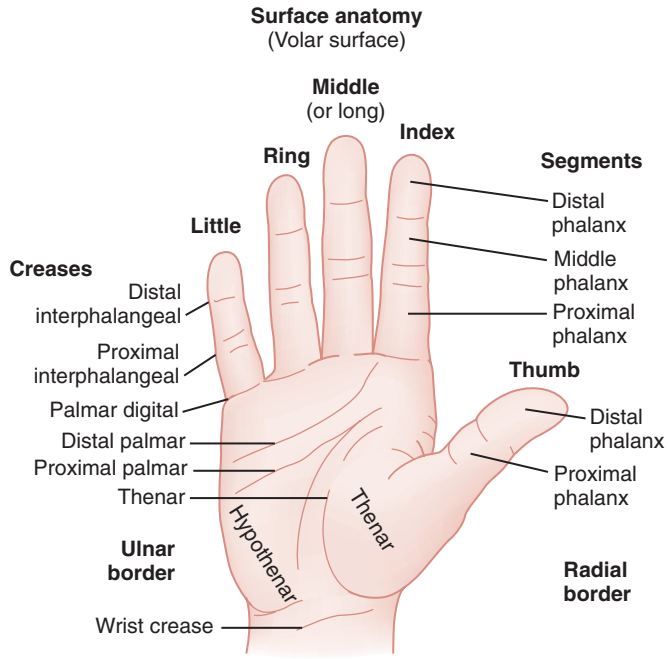


Figure 47-1. Surface anatomy of the hand. (From Burton RI, et al: The Hand: Examination and Diagnosis, 3rd ed. New York, Churchill Livingstone, 1990, p 6.)

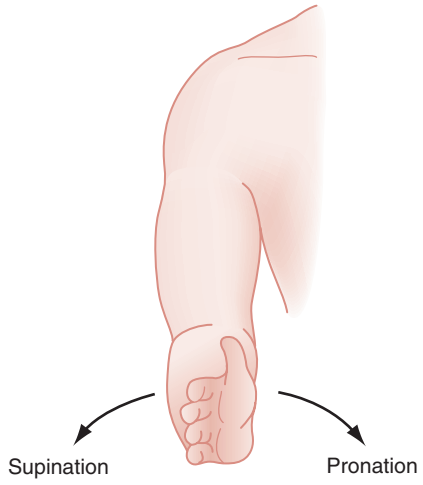


Figure 47-2. Supination and pronation of the hand.

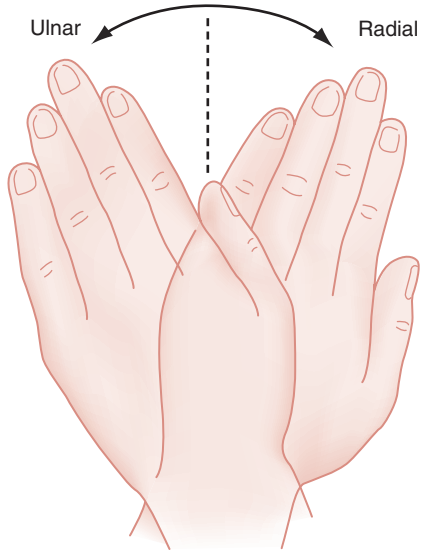


Figure 47-3. Ulnar and radial deviation of the hand.

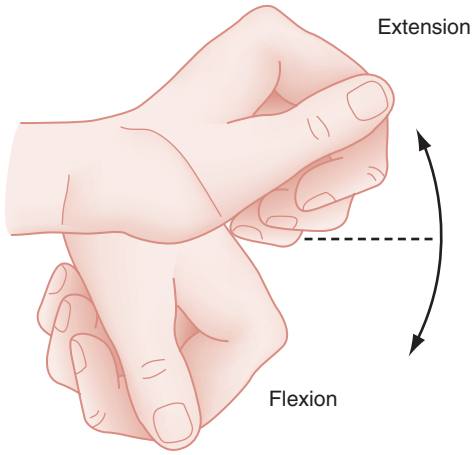


Figure 47-4. Wrist extension and flexion.

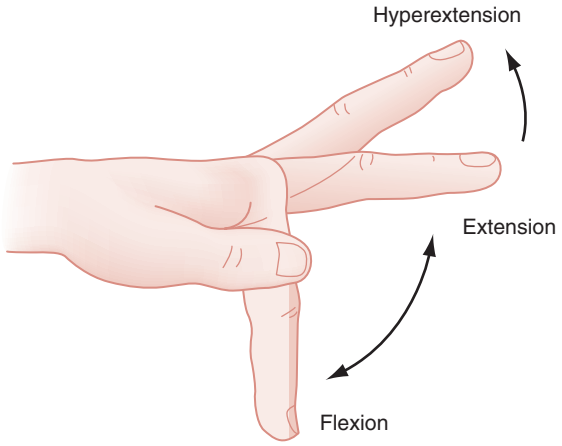


Figure 47-5. Finger flexion is volar and occurs at the metacarpophalangeal joint; extension and hyperextension are as shown.

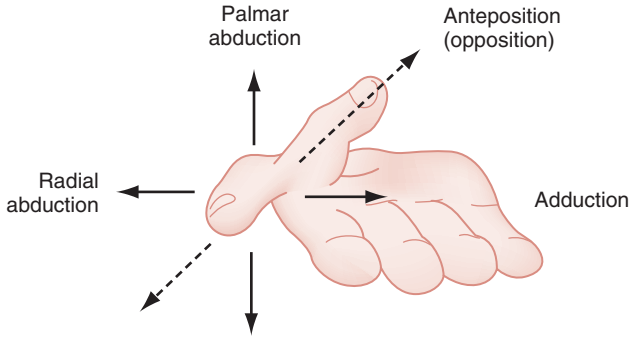


Figure 47-6. Perpendicular view of thumb mobility.

dorsal swelling; this finding can be misleading without a careful physical examination.

Skeleton

The hand and wrist contain 27 bones: 14 phalangeal bones, 5 metacarpal bones, and 8 carpal bones (Fig. 47-7). The eight small carpal bones in the region of the wrist are strongly united to one another by ligaments. These bones form synovial joints and are arranged in two rows, proximal and distal, with four bones in each row. Together the bones of the carpus present a concavity on their volar surface, which is bridged by a strong

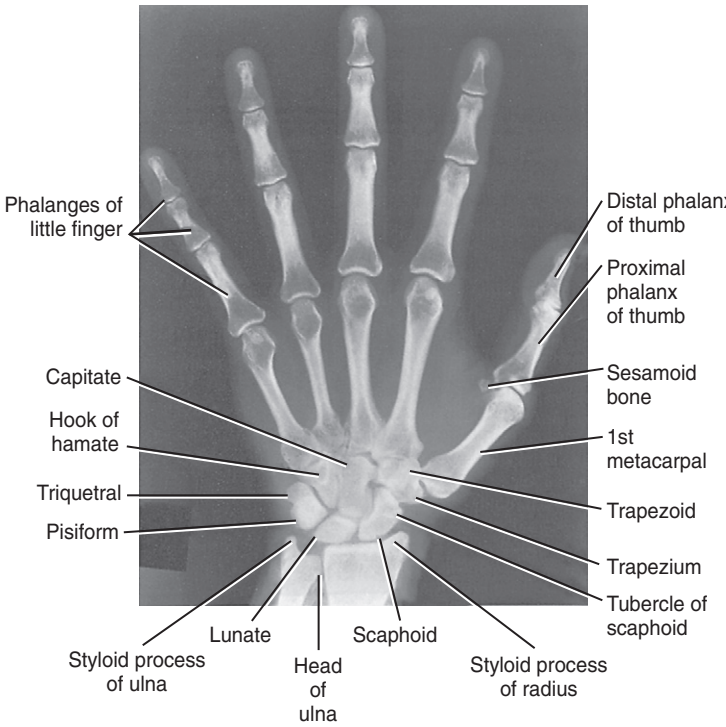


Figure 47-7. Posteroanterior radiograph of the wrist and hand with the forearm pronated. (From Snell RS, Smith MS: Clinical Anatomy for Emergency Medicine. St. Louis, Mosby, 1993, p 650.)

membranous band, the flexor retinaculum. In this way, the bridge and the bones form a tunnel, known as the *carpal tunnel*, through which pass the median nerve and the long flexor tendons of the fingers. The IP joints are inherently more stable than the MCP joint, by virtue of their bicondylar configuration, which gives a modified tongue-in-groove appearance (Fig. 47-8).

The soft tissue supporting these joints includes the capsular ligamentous structures, which afford stability, and the tendinous structures, which generate mobility. The metacarpal and IP joints are stabilized on both sides by collateral ligaments and anteriorly by a palmar fibrocartilaginous "volar plate." Because of anatomic differences between the metacarpals and phalanges, the IP collaterals are tight throughout the entire range of motion, whereas the collaterals of the MCP joint are tightest in flexion (Fig. 47-9). The IP joints are hinges, but the MCP joint has additional side-to-side mobility and rotational movement to facilitate efficient grasp.[7] The clinical importance of these differences is that to minimize the development of contractures after joint injuries, the preferred position of immobilization of the PIP joints is extension, whereas the MCP joints are more properly placed in flexion.

The structure and arrangement of the metacarpals are noteworthy. The metacarpals participate in three arches: the proximal (carpal) and distal (metacarpal) transverse arches and the longitudinal arch[8] (Fig. 47-10). The index and long finger metacarpals form a fairly immobile segment because of their ridged articulation with the carpals. The adjacent metacarpals are more mobile. This unique anatomy gives the human palm a longitudinal and transverse concavity when the thumb is

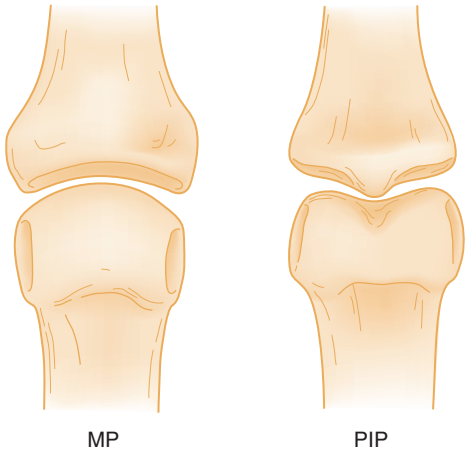


Figure 47-8. The metacarpophalangeal (MP) and proximal interphalangeal (PIP) joints are quite different structurally. The PIP joint has a bicondylar configuration, making it inherently more stable than the globular MP joint. (From DeLee JC, Drez D Jr: Orthopedic Sports Medicine: Principles and Practice, 2nd ed. Philadelphia, Saunders, 2003.)

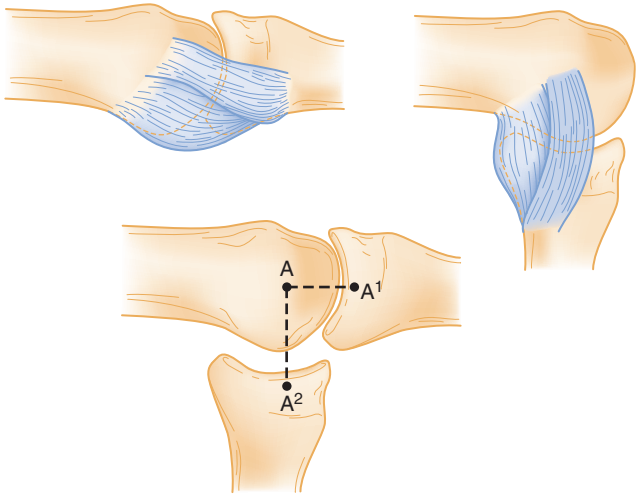


Figure 47-9. The shape of the metacarpal head is eccentric, resulting in a cam effect that makes the collateral ligaments more taut in flexion than in extension. Distance A-A^1 is less than A-A^2. The cam effect is not present in the proximal interphalangeal joint. (From DeLee JC, Drez D Jr: Orthopedic Sports Medicine: Principles and Practice, 2nd ed. Philadelphia, Saunders, 2003.)

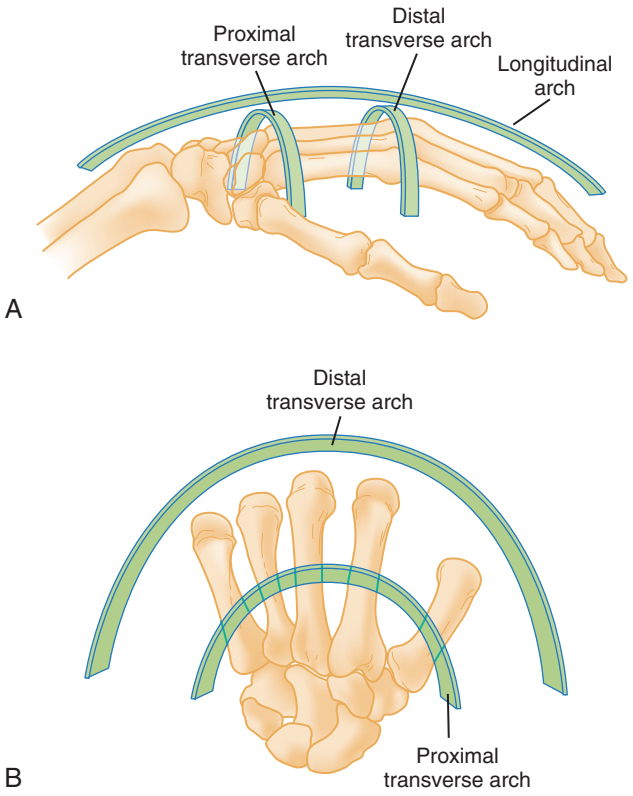


Figure 47-10. The three arches of the metacarpals. **A,** Sagittal view. **B,** Transverse view. (From American Society for Surgery of the Hand: Regional Review Course in Hand Surgery Syllabus, 10th ed. Aurora, Colo, ASSH, 1990.)

Figure 47-11. Normal location of the epiphysis of the hand. All of the phalangeal epiphyses are located at the proximal end. The metacarpophalangeal epiphyses all are distally situated, however, except for that of the wrist, which is proximal. (From Harris WH, Harris CC: The Radiology of Emergency Medicine. Baltimore, Williams & Wilkins, 1993, p 440.)

alongside the index finger; however, this changes to an oblique gutter when the thumb is extended.

The small bones of the child's hand differ significantly from the bones of the adult and from other long bones because of the presence of an epiphysis or growth plate at one end of the bone. The phalangeal epiphyses and the thumb metacarpal epiphysis are located at the proximal end, and the finger metacarpal epiphyses are located at the distal end of the bone (Fig. 47-11). In boys, the proximal phalangeal epiphysis appears at 15 to 24 months and fuses at 16 years. In girls, it appears at 10 to 15 months and fuses at 14 years.[9] The time of appearance and fusion is related to skeletal maturity and can be judged accurately until puberty from hand and wrist radiographs, because the sequence of development is age-specific.[10]

Muscle and Tendon Function

The muscles that power the hand may be divided into extrinsic and intrinsic muscles. The intrinsic muscles have their origins and insertions within the hand. The extrinsic muscles have origins in muscle bellies in the forearm and tendinous insertions on bones in the hand. They are divided further into extrinsic flexor and extensor muscles. The flexors of the digits in the hand lie on the volar surface of the forearm; the extensors are on the dorsal surface.

Intrinsic Musculature

The intrinsic muscles of the hand include the muscles of the thenar and hypothenar eminences, the adductor pollicis, the interossei, and the lumbricals (Fig. 47-12). The thenar muscles cover the thumb metacarpal. This group includes the abductor pollicis brevis, opponens pollicis, and flexor pollicis brevis. These muscles originate in the flexor retinaculum and on the carpal bones and insert at the base of the first metacarpal and first proximal phalanx. They act in concert with the long flexors and extensors to carry the thumb through its intricate range of motion. The muscles are evaluated by palpating the thenar eminence for contraction as the patient brings together the tips of the thumb and little finger. They also can be tested by asking the patient to place the dorsum of the hand on a flat surface and to raise the thumb up straight to form a 90-degree angle with the palm. The thenar muscles usually are innervated by the motor branch of the median nerve. In some cases, they may be partially innervated by the ulnar nerve.

The adductor pollicis arises from the second and third metacarpals and inserts on the first proximal phalanx. This muscle is innervated by the ulnar nerve. Thumb adduction is tested separately by having the patient forcibly hold a piece of paper between the thumb and radial side of the index proximal phalanx. If the adductor pollicis is weak or nonfunctioning, the thumb IP joint flexes with this maneuver (Froment's paper sign).[11] In this evaluation, the two hands should be compared.

The lumbrical muscles arise from the sides of the flexor digitorum profundus (FDP) tendons; the interossei muscles lie between the metacarpal bones and originate from them. Both of these muscle groups insert in the extensor expansions of digits II to V and act on the fingers to flex the MCP joints and extend the IP joints. The radial two lumbricals are innervated by the median nerve, and the ulnar two are innervated by the ulnar nerve. The seven interossei (three palmar and four dorsal) can be considered together. They lie on either side of the finger metacarpals and are innervated by the ulnar

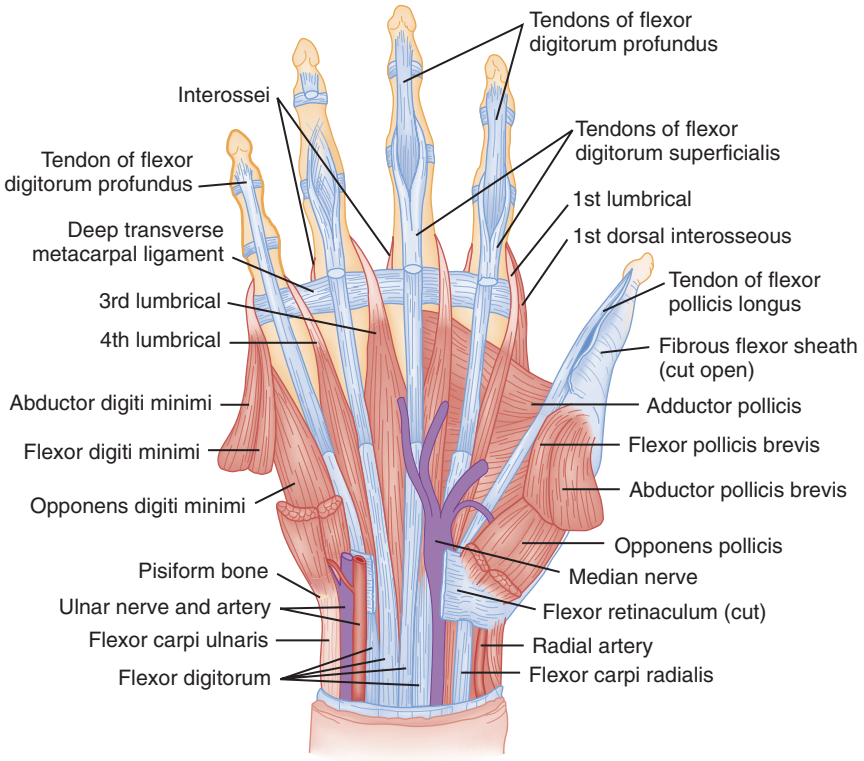


Figure 47-12. Anterior view of the palm of the hand. The palmar aponeurosis and the greater part of the flexor retinaculum have been removed to display the median nerve, the long flexor tendons, and the lumbrical muscles. Segments of the tendons of the flexor digitorum superficialis muscle have been removed to show underlying tendons of the flexor digitorum profundus muscles. (From Snell RS, Smith MS: Clinical Anatomy for Emergency Medicine. St. Louis, Mosby, 1993, p 641.)

nerve. The dorsal interossei abduct the fingers away from the midline; the volar muscles adduct the fingers. For an accurate test that isolates their function from the extrinsic muscles, the patient should place the palm flat on a table, extend the digit, and move it from side to side.

The hypothenar group of intrinsic muscles includes the opponens digiti minimi, the flexor digiti minimi, and the abductor digiti minimi. These muscles arise from the carpal bones and in the flexor retinaculum and insert on the proximal phalanx and metacarpal of the little finger. The flexor and abductor flex the proximal phalanx and abduct the little finger. The three muscles are evaluated as a group by having the patient place the wrist in a neutral position and abduct the little finger (move it away from the other fingers) against resistance. This muscle mass is palpated at that time, and a dimpling of the hypothenar skin is noted. All of the intrinsic muscles of the little finger are innervated by the ulnar nerve.

Extensor Tendons

The extensor tendons are on the dorsal side of the forearm, wrist, and hand. The nine extensor tendons cross the wrist joint dorsal to its axis of rotation, pass under the extensor retinaculum, and are separated on the dorsum of the hand by a series of six fibro-osseous canals or compartments. Fig. 47-13 outlines the compartments and their contents. The fibrous roof of these compartments prevents the tendons from bowstringing dorsally during active finger extension, particularly when the wrist also is extended.

The first dorsal wrist compartment contains the tendons of the abductor pollicis longus, which inserts at the dorsal base of the thumb metacarpal, and the extensor pollicis brevis, which inserts on the proximal phalanx of the thumb. The abductor pollicis longus serves to abduct the first ray radially, and the extensor pollicis brevis acts primarily to extend the ray at the MCP joint. These tendons are evaluated by having the patient abduct and extend the thumb with resistance applied to the thumb; they can be palpated on the radial side of the wrist during this maneuver.

Two tendons lie in the second compartment: the extensor carpi radialis longus and brevis. These tendons insert at the dorsal base of the index and middle metacarpals. They act primarily to extend and deviate the wrist radially. These tendons can be palpated by having the patient extend the wrist against resistance while making a fist.

In the third compartment, a single tendon, the extensor pollicis longus, arises from the deep muscles of the midforearm, passes around a bony prominence on the dorsum of the wrist termed *Lister's tubercle*, and inserts on the base of the distal phalanx of the thumb. This tubercle can be palpated just proximal to the wrist joint. The extensor pollicis longus forms the dorsal border of the anatomic snuffbox, and the abductor pollicis longus forms the volar border (Fig. 47-14). The floor of this area contains the radial artery and two carpal bones, the scaphoid and trapezium. The extensor pollicis longus functions to extend and adduct the entire first ray and extend and hyperextend the IP joint of the thumb. This muscle is evaluated by placing the hand flat on a table and having the patient lift only the thumb off the surface. Because the abductor pollicis brevis and the adductor pollicis add terminal extension, complete laceration of the extensor pollicis longus tendon may not eliminate the patient's ability to extend the thumb.[12]

The tendons that extend the fingers—the extensor indicis proprius and the extensor digitorum communis—are in the fourth compartment. The extensor digitorum muscle divides into four tendons proximal to the wrist. In the dorsum of the hand, these tendons are connected by juncturae, which help stabilize them to their insertions in the extensor expansions of digits II to V. The tendon to the index finger is joined on its radial side by the tendon of the extensor indicis proprius. The tendon to the little finger is joined on its ulnar side by two slips from the extensor digiti minimi. The extensor digiti minimi is contained in the fifth dorsal compartment and lies

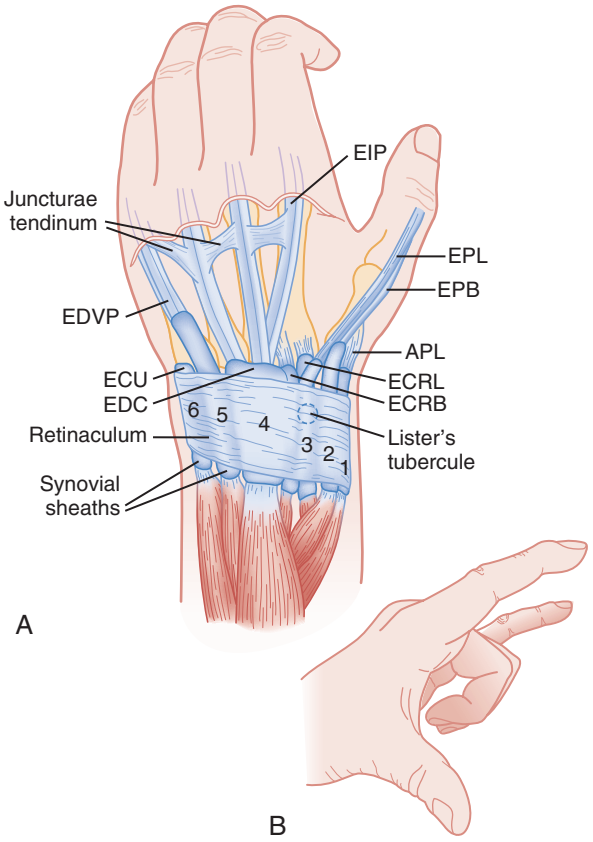


Figure 47-13. **A,** The extensor tendons gain entrance to the hand from the forearm through a series of six canals, five fibro-osseous and one fibrous (the sixth dorsal compartment, which contains the extensor digiti quinti proprius [EDQP]). The first compartment contains the abductor pollicis longus (APL) and extensor pollicis brevis (EPB); the second, the radial wrist extensors; the third, the extensor pollicis longus (EPL), which angles around Lister's tubercle; the fourth, the extensor digitorum communis (EDC) to the fingers and the extensor indicis proprius (EIP); the fifth, the EDQP; and the sixth, the extensor carpi ulnaris (ECU). The communis tendons are joined distally near the metacarpophalangeal joints by fibrous connections called *juncturae tendinum*. Beneath the retinaculum, the extensor tendons are covered with a synovial sheath. **B,** The proprius tendons to the index and little fingers are capable of independent extension, and their function may be evaluated as depicted. With the middle and ring fingers flexed into the palm, the proprius tendons can extend the ring and little fingers. ECRB, extensor carpi radialis brevis; ECRL, extensor carpi radialis longus. (From Doyle JR: Extensor tendons—acute injuries. In Green DP [ed]: Operative Hand Surgery. New York, Churchill Livingstone, 1993, p 1927.)

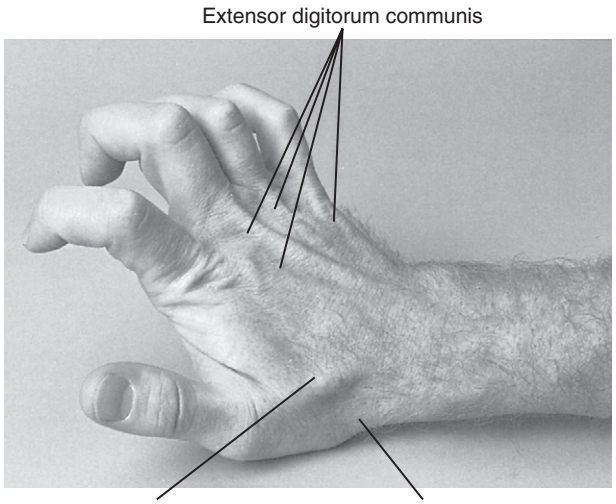


Figure 47-14. Surface anatomy of the wrist and hand. The tendons that are palpated with the thumb abducted and extended form an anatomic snuffbox.

ulnar to the small finger extensor. The extensor indicis lies ulnar and deep to the index extensor. The dual extensor system for the index and small fingers gives these two digits extension independent of the other digits. The middle finger and especially the ring finger have considerably limited independent extension. The restrictive motion is due to the juncture, which also prevents retraction of the proximal tendon end after distal division of an extensor. Complete division of an extensor proximal to the juncture can be associated with normal MCP joint extension.[7] This extension occurs through the juncture connection. The extensor digitorum communis tendons can be evaluated by asking the patient to straighten out all of the fingers. The function of the extensor indicis proprius can be isolated from the common extensors by asking the patient to make a fist and then to point the second digit. The extensor digiti minimi is examined by having the patient straighten the little finger while the hand is closed into a fist.

The extensor mechanism of each digit is a complex interrelationship of muscle tendon units of the long extrinsic extensor tendons and the intrinsic system (Fig. 47-15). The extensor expansion divides into a central slip that attaches to the middle phalanx and two lateral bands that join with the tendons of the lumbrical and interosseous muscles and attach to the base of each distal phalanx. The interossei and lumbrical muscles insert in the lateral aspects of the dorsal hood. Most of the power of the common extensors serves to extend the MCP joint. Distal digit extension is provided by continuation of the lateral band mechanism and the oblique retinacular ligament. Because of this complex anatomy, injuries involving the extensor mechanism require meticulous repair.

The sixth compartment contains the extensor carpi ulnaris. This tendon passes distal to the head of the ulna on the ulnar aspect of the wrist and inserts on the base of the little finger metacarpal. The extensor carpi ulnaris functions to extend and deviate the wrist ulnarly. This tendon is evaluated by having the patient extend and push the hand to the ulnar side against resistance; the tendon can be palpated distal to the ulnar styloid process.

Flexor Tendons

The flexor tendons reside on the volar side of the forearm and cross the wrist joint volar to its axis. Generally, 12 tendons function to flex the wrist and digits; 3 of them—the flexor carpi radialis, flexor carpi ulnaris, and palmaris longus—primarily flex the wrist and deviate the wrist radially or ulnarly (Fig. 47-16). The remaining tendons pass into the digits through the carpal tunnel. A single tendon, the flexor pollicis longus, inserts on the distal phalanx of the thumb, and two flexor tendons go to each remaining finger. The flexor digitorum superficialis (FDS) tendons bifurcate near the base of the proximal phalanges and surround the tendons of the FDP before inserting on the middle phalanges of digits II to V (Fig. 47-17). The FDS flexes all of the joints it crosses, including the wrist, PIP joints, and MCP joints. The profundus tendons lie deep to the superficialis tendons over most of their course in the forearm. At the level of the MCP joint, they perforate the superficialis tendon to emerge to a superficial position. They insert at the base of the distal phalanx and act primarily to flex the DIP joint and all joints flexed by the FDS. From the level of the MCP joint

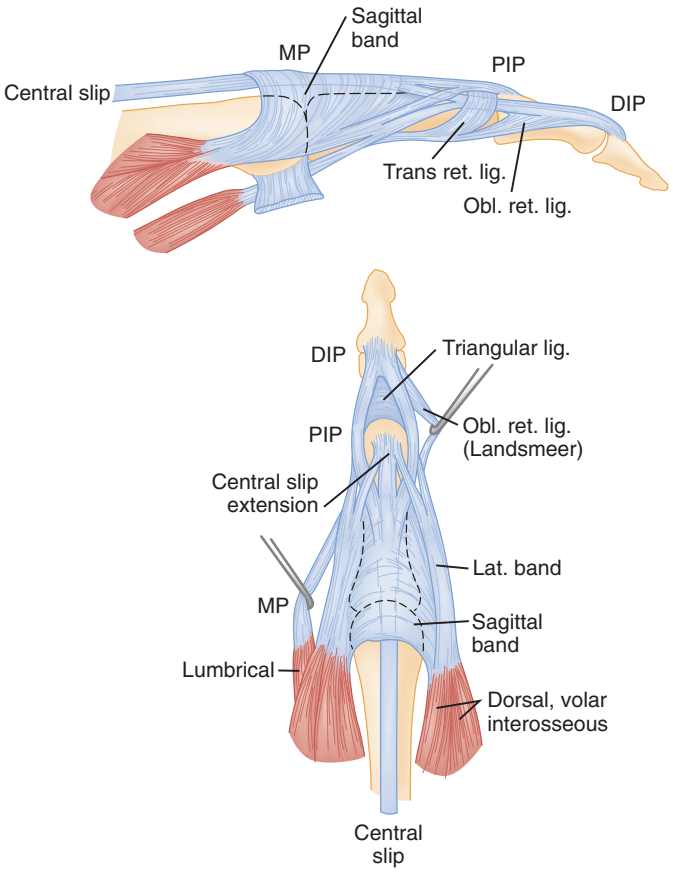


Figure 47-15. The extensor tendon at the metacarpophalangeal (MP) joint level is held in place by the transverse lamina or sagittal band, which tethers and centers the extensor tendons over the joint. This sagittal band arises from the volar plate and the intermetacarpal ligaments at the neck of the metacarpals. Any injury to the extensor hood or expansion may result in subluxation or dislocation of the extensor tendon. The intrinsic tendons from the lumbrical and interosseous muscles join the extensor mechanism at approximately the level of the proximal and midportion of the proximal phalanx and continue distally to the distal interphalangeal (DIP) joint of the finger. The extensor mechanism at the proximal interphalangeal (PIP) joint is best described as a trifurcation of the extensor tendon into the central slip, which attaches to the dorsal base of the middle phalanx and the two lateral bands. These lateral bands continue distally to insert at the dorsal base of the distal phalanx. The extensor mechanism is maintained in place over the PIP joint by the transverse retinacular ligaments. (From Doyle JR: Extensor tendons—acute injuries. In Green DP [ed]: Operative Hand Surgery. New York, Churchill Livingstone, 1993, p 1928.)

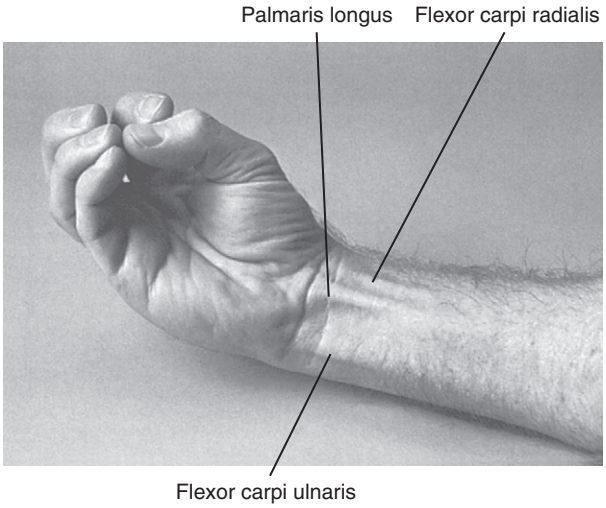


Figure 47-16. Palmaris longus accentuation.

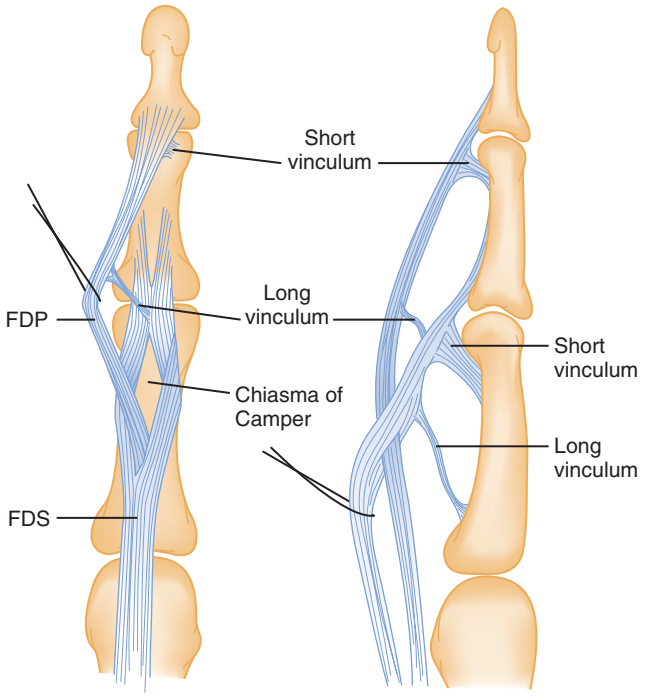


Figure 47-17. Anatomy of flexor digitorum superficialis (FDS) and profundus (FDP) in the finger. (From Schneider LH: Flexor Tendon Injuries. Boston, Little, Brown, 1985.)

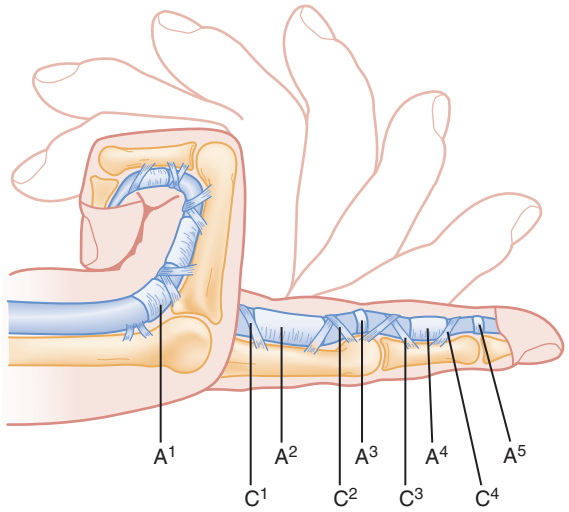


Figure 47-18. The flexor pulley system. The pulleys are thickenings in the fibrous flexor sheath. There are five annular pulleys (transversely oriented fibers) (A^1 to A^5). There are four cruciate pulleys (oblique with some crisscrossing fibers) (C^1 to C^4). (Courtesy of Kleinert, Kutz and Associates Hand Care Center.)

distally, the two flexor tendons become enclosed in a fibrous flexor sheath lined by synovium. Regions of thickening in this sheath form pulleys that help prevent bowstringing of the flexor tendons across the joint and assist smooth, effective flexion (Fig. 47-18).

After observation, each muscle-tendon unit is tested with a functional examination. The flexor carpi radialis, palmaris longus, and flexor carpi ulnaris are tested together by having the patient flex the wrist against resistance while the examiner palpates the individual tendons. The tendon of the flexor pollicis longus attaches to the base of the distal phalanx of the thumb and flexes the thumb MCP and IP joints. This tendon is tested by having the patient bend the tip of the thumb

Figure 47-19. To test for an intact profundus tendon, the examiner maintains the digit in extension while the patient attempts to flex the terminal phalanx.

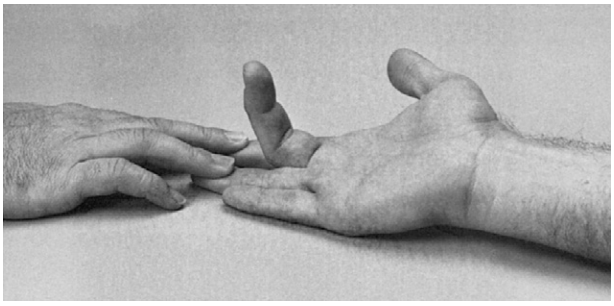


Figure 47-20. Examination to assess function of the flexor digitorum superficialis.

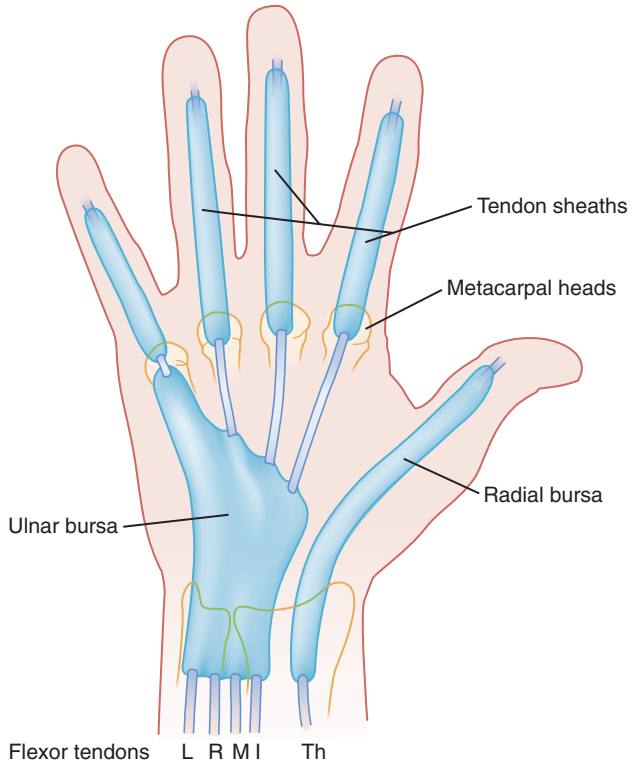


Figure 47-21. Radial and ulnar bursae and their relation to flexor tendons and to each other. I, index finger; L, little finger; M, middle finger; R, ring finger; Th, thumb. (From Siegel DB, Gelberman RH: Infections of the hand. Orthop Clin North Am 19:779, 1988.)

against resistance. FDP function can be tested by having the patient flex the distal phalanx of each finger while the PIP is stabilized in extension by the examiner (Fig. 47-19). The FDS is tested individually by asking the patient to flex the PIP joint while the other fingers are held in extension to block the flexion produced by the profundus tendons (Fig. 47-20). This is a subtle but important distinction, because lacerations of the digital creases can easily damage one or more of the tendons or adjacent neurovascular bundles. The FDP is more commonly lacerated in the finger because of its paradoxically superficial position.

If movement against resistance is intact but accompanied by pain or diminished strength, the involved tendon may be partially disrupted. Pathologic nodular swelling of one of the long flexor tendons may result in intermittent catching, or "triggering," on a thickened flexor sheath anterior to the MCP joint. In this condition, known as *trigger finger*, a palpable and sometimes audible snapping can be appreciated when the patient is asked to flex and extend the fingers. Steroid injections have been suggested as first-line treatment for trigger finger in nondiabetic patients.[13]

Synovial Spaces

Bursae are synovial sheaths that cover tendons as they pass through osseofibrous tunnels. They contain synovial fluid and serve two essential functions: They decrease friction during tendon movement, and they help supply nutrients to the relatively avascular tendons (Fig. 47-21). These sheaths also can provide pathways for spread of infection. Extensor tendons do not lie within definite sheaths and are afforded a greater resistance to infections. The synovial sheaths of the flexors in the index, middle, and ring fingers are enclosed from their insertion to approximately the level of the distal palmar crease. The sheath of the flexor pollicis longus extends from the tip of the thumb to the proximal volar wrist crease, where it communicates with the radial bursa in the palm and carpal tunnel. Similarly, the synovial sheath of the little finger communicates with the ulnar bursa. Clinical features of flexor tenosynovitis are caused by inflammation and distention of these synovial sheaths. Kanavel[14] described the classic signs: a flexed posture of the digits, pain on passive extension of the digits, incomplete flexion, and tenderness of the synovial sheath.

Blood Supply

Arterial System

The hands and the digits have a dual blood supply (Fig. 47-22). The major blood supply to the hand is from the radial and ulnar arteries. The radial artery lies on the anterior aspect of the radius in the distal part of the forearm. It continues around the lateral side of the wrist onto the dorsum of the hand by passing deep to the tendons of the abductor pollicis longus and the extensor pollicis brevis. On entering the palm, the radial artery terminates as the deep palmar arch. The ulnar artery enters the hand anterior to the flexor retinaculum on the radial side of the ulnar nerve and pisiform bone. The artery gives off a deep branch and then continues into the palm as the superficial palmar arch. This complex arterial arch system anastomoses and sends branches to the individual digits and the deep palmar spaces. Because of extensive collateralization, the hand usually survives even if both vessels are transected at the wrist.[15] The circulation of the hand is evaluated by palpating the radial and ulnar arteries on the volar aspect of the wrist, by assessing the color and warmth of the skin, and by testing capillary refill. Because "normal" findings vary among patients, the injured hand should be compared with the unaffected side.

Figure 47-22. Arteriogram of the hand. The ulnar artery is the principal contributor to the superficial palmar arch. (Courtesy of Dr. D. Armstrong, Associate Professor of Radiology, University of Toronto, Ontario, Canada.)

Although *Allen's test* is an imperfect predictor of vascular compromise, it is commonly used to determine the patency of the arteries supplying the hand and the contributions to the circulation of the hand derived from each of the major vessels. The radial and ulnar arteries are compressed by the examiner at the wrist (Fig. 47-23). The patient opens and closes the hand repeatedly to exsanguinate it and then maintains a relaxed position. The radial artery is released. If the palm and fingers fill immediately with blood, the radial artery is patent, with good collateral flow into the ulnar artery system. To evaluate the ulnar artery, the same steps are repeated, but the ulnar artery is released. This method also can be used on a single digit to help evaluate the patency of each digital vessel to that finger. Similar to the hand, the digit usually survives even if both digital vessels are transected at the base of the finger; however, healing of associated injuries may be delayed or may be compromised by excessive scar formation because of associated, although relative, ischemia.[15]

Venous and Lymphatic Systems

The veins generally follow the arterial pattern in the deep system. The abundant dorsal, superficial veins are more extensive than the deep system and drain most of the blood from this region. The lymphatic vessels essentially follow the veins, with most lymph flowing into channels in the dorsal subcutaneous space. This vascular anatomy and the laxity of the dorsal skin account for palmar infections causing swelling on the dorsum rather than on the palmar surface of the hand.

Nerve Supply

The nerve supply to the hand comes from the radial, ulnar, and median nerves. All three nerves control movement of the wrist, fingers, and thumb. In the hand, the ulnar and median nerves are mixed motor and sensory nerves, whereas the radial nerve is purely sensory. Each of the three major nerves passes

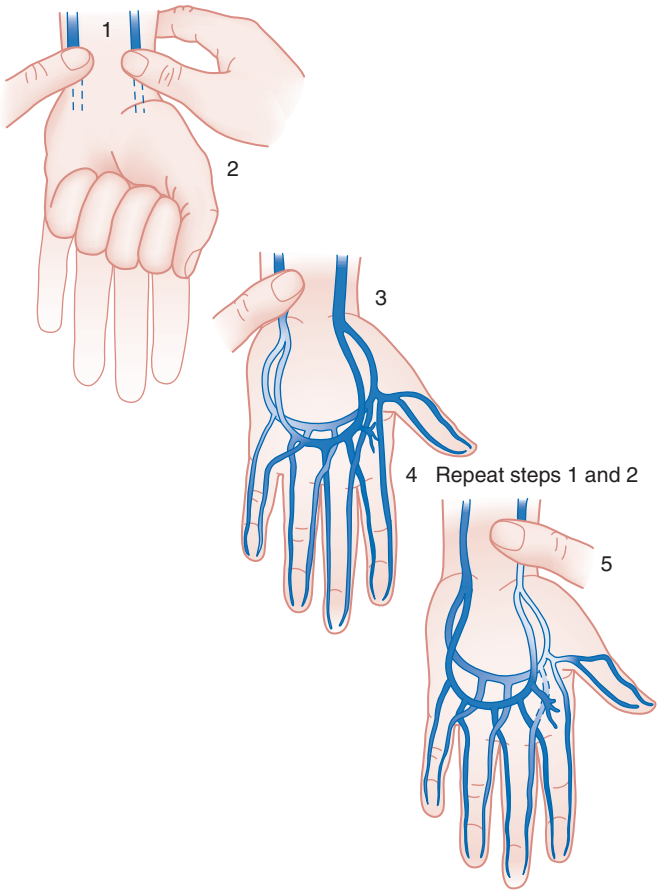


Figure 47-23. Allen's test. (From American Society for Surgery of the Hand: The Hand: Examination and Diagnosis, 3rd ed. New York, Churchill Livingstone, 1990, p 46.)

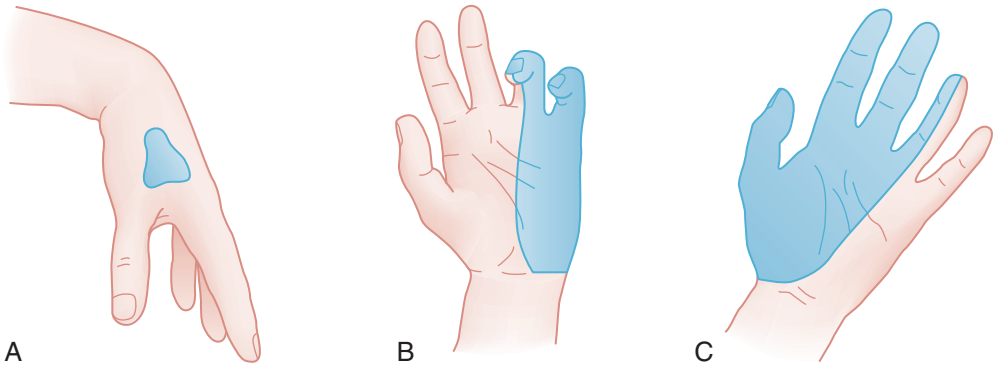


Figure 47-24. Deformities of the hand. **A,** Radial palsy—wristdrop. **B,** Ulnar nerve palsy—*main en griffe* (clawhand). **C,** Median nerve palsy—*main en singe* ("monkey hand"). The *shaded areas* represent the usual distribution of anesthesia. (From Ellis H: Clinical Anatomy: A Revision and Applied Anatomy for Clinical Students, 7th ed. Oxford, UK, Blackwell Scientific, 1983.)

through a muscle in the forearm, and each passes points of potential entrapment en route to the hand.

Motor Innervation

The radial nerve (formed from nerve roots C6 through C8) passes through the supinator muscle and enters the dorsal aspect of the wrist between the radial styloid and Lister's tubercle. At this level, the nerve has a purely sensory function. Its important motor function is to innervate the dorsal extrinsic muscles in the forearm, which extend the wrist and MCP joints and abduct and extend the thumb. No intrinsic muscles in the hand are innervated by the radial nerve. Motor function in this nerve is tested by having the patient extend the wrist against resistance. Proximal injury to the radial nerve causes a condition known as *wristdrop*: The fingers are held in flexion at the MCP joints, and the thumb is adducted (Fig. 47-24A).

The ulnar nerve (C7, C8, and T1) passes through the flexor carpi ulnaris muscle in the forearm and lies ulnar to the artery and superficial to the flexor retinaculum. It enters the hand at the wrist through the *ulnar tunnel*, or *Guyon's canal*. The ulnar nerve innervates the hypothenar muscles, the seven interosseous muscles, the lumbrical muscles to the ring and little fingers, and the adductor pollicis. Innervation of the flexor pollicis brevis is variable. In the forearm, the flexor carpi ulnaris and the ulnar half of the FDP also are innervated by the ulnar nerve. Loss of motor function of the ulnar nerve results in inability to pinch a piece of paper tightly between the thumb and the index finger. A late characteristic of distal ulnar damage is Duchenne's sign, manifested by clawing of the ring and little fingers (see Fig. 47-24B). The ring and little fingers are hyperextended at the MCP joints by the extensor digitorum communis (radial nerve) and flexed at the IP joints by the FDP (intact proximal ulnar nerve). In addition, the interosseous and hypothenar muscles are atrophied.

The median nerve enters the forearm through the pronator teres muscle. At that level, it innervates that muscle, the flexor carpi radialis, the FDS, the radial part of the FDP, the flexor pollicis longus, and the pronator quadratus. The branch of the median nerve that innervates the last three muscles is called the *anterior interosseous nerve*. The median nerve enters the hand through the carpal tunnel accompanied by the nine extrinsic flexor tendons of the digits. The thenar motor branch (recurrent median nerve) innervates the abductor pollicis brevis, the opponens pollicis variably, and the flexor pollicis brevis. Common digital branches innervate the lumbrical muscles to the index and long fingers. Injury to this nerve occurs most commonly at the level of the wrist, by laceration or by compression in the carpal tunnel. Motor function is tested by having the patient appose the thumb to the index digit. Injury to the median nerve in the upper forearm or at the elbow usually results in weakness or absence of flexion of the index finger distal phalanx, the middle phalanx, and the thumb and weakness of thumb abduction and opposition.[16] With passage of time, the muscles of the thenar eminence atrophy, leaving the hand with a flattened and "apelike" appearance (see Fig. 47-24C).

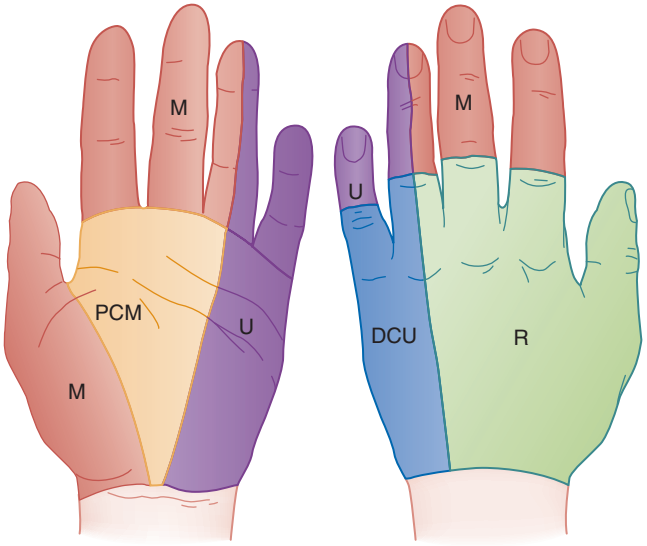


Figure 47-25. The cutaneous nerve supply in the hand. *Left*, Palmar aspect; *right*, dorsal aspect. DCU, dorsal cutaneous branch of ulnar nerve; M, median; PCM, palmar cutaneous branch of median nerve; R, radial; U, ulnar. (Courtesy of Kleinert, Kutz and Associates Hand Care Center.)

Sensory Innervation

The typical distribution of the sensory nerves to the hand is shown in Figure 47-25. Because some overlap occurs between various sensory nerves, it is preferable to test sensation in the areas least likely to have dual innervation. The anatomic area of least ulnar variation and overlap is the volar tip of the little finger. The median nerve exclusively innervates the volar tip of the index finger. The dorsal first web space is entirely within the radial nerve distribution.

Several methods exist to assess sensation. The preferred method, which is most accurate and objective, is comparative two-point discrimination. An uninjured hand is able to distinguish two points that are 2 to 5 mm apart at the fingertips and 7 to 10 mm apart at the base of the palm. The dorsum of the hand is the least sensitive region, with a normal threshold at 7 to 12 mm. Two-point threshold distances wider than these ranges indicate impaired sensory function.[16] The threshold and two-point discrimination tests may be of limited value in

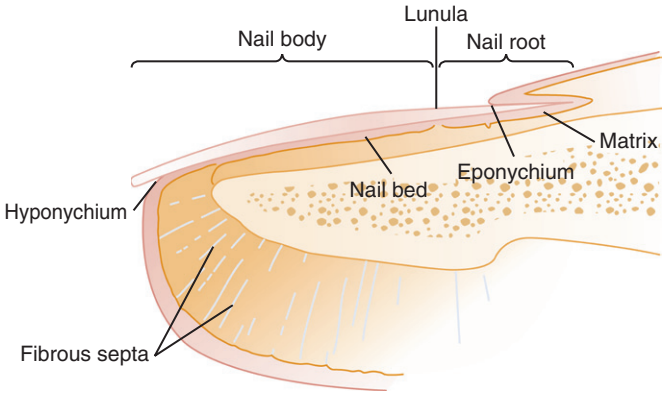


Figure 47-26. Sagittal section of the distal finger, showing structures of the fingertip. (From Siegel DB, Gelberman RH: Infections of the hand. Orthop Clin North Am 19:779, 1988.)

children, patients with heavily calloused fingertips, uncooperative patients, comatose patients, patients in severe pain, or suspected malingerers.

Fingertip

The fingertip generally is defined as the area distal to the insertion of the flexor profundus and extensor tendons (Fig. 47-26). The pulp is the tissue of the fingertip between the volar skin and the distal phalangeal bone. The fingertip is well padded by adipose tissue and is covered by highly innervated skin that is tethered to the distal phalanx by a series of fibrosepta. The dorsal skin is thinner and less vascularized than the volar skin. Sensation is supplied by nerves that travel with arteries bilaterally along the radial and ulnar aspects of the fingers. The arteries branch to form volar anastomoses or arches similar to those in the palm. Dorsal branches supply the nail bed and matrix.

Nail

The nail (or nail plate) consists of compacted scales that originate from cornified epithelial cells. The proximal part of the nail is called the *root*; it emerges from a groove in the skin to form the body of the nail, which is exposed. The root of the nail is covered by a fold in the skin called the *proximal nail fold*. A small portion of the epidermis of the nail fold extends out over the proximal body of the nail to form the cuticle, or *eponychium*. The floor of the nail plate or nail bed is composed of tissue known as the *nail matrix*. The distal skin of the nail bed complex is called the *hyponychium*. The skin overlying the nail laterally is called the *perionychium*. The semicircular white crescent region near the nail fold is called the *lunula*.

The nail bed complex on the dorsum of the fingertips is important in providing additional stabilization of the palmar soft tissues against compression and shear forces. The nail grows from the nail matrix along the nail bed and is firmly adherent to the bed. It is now believed that the entire nail bed is active in the generation and migration of the nail. As new nail forms, it glides forward over the nail bed at a rate of approximately 0.5 to 1.2 mm per week (toenails grow much more slowly). The nail itself is a hard, firm, and relatively translucent structure; the underlying vascular tissue showing through gives the nail its pink appearance. A smooth nail bed is essential to normal function. If the nail bed sustains injury that is not repaired accurately, granulation tissue forms scar that impedes normal nail production and growth. The result may be a split or absent nail that is cosmetically unappealing and sometimes functionally debilitating.[17]

CLINICAL FEATURES: SIGNS AND SYMPTOMS

The initial evaluation of an acutely injured hand is crucial because it affords the best opportunity for accurate assessment of the extent of damage and for restoration of altered anatomy.[18] Evaluation of any hand injury should begin by obtaining the historical facts of the patient's age, occupation, hand dominance, and previous hand impairment or injury. In traumatic injuries, elapsed time since the injury, mechanism of injury, posture of the hand at the time of injury, and treatment before arrival in the ED all are useful data. In nontraumatic problems, pain, swelling, sensory change or contracture, timing of symptoms, presence of similar symptoms in other extremities, aggravating or alleviating factors, and functional impairment are useful historical points. A review of the medical history and a review of systems complete the evaluation.

After a detailed history is taken, the entire extremity should be exposed and evaluated when the hand is examined. A system of priorities, based primarily on threat to ultimate function, should direct the sequence of the examination. In order of priority, the examination includes evaluation of vascular and neurologic integrity, skin cover, skeletal stability, and joint and tendon function (Box 47-1). The general appearance of the

BOX 47-1 GENERAL PHYSICAL EXAMINATION OF THE HAND

I. General appearance
   A. Active hemorrhage
   B. Amputations or avulsions
   C. Position at rest
II. Skin
   A. Integrity
   B. Moisture
   C. Swelling or edema
   D. Discoloration
   E. Inflammation
   F. Scars
III. Vascular
   A. Color and warmth
   B. Pulses
   C. Capillary refill
   D. Allen's test
IV. Neurologic
   A. Motor function
      1. Ulnar nerve—finger abduction and adduction
      2. Radial nerve—wrist extension
      3. Median nerve—flexion of digits I, II, and III; thumb opposition
   B. Sensory function
      1. Ulnar nerve—tip of digit V
      2. Median nerve—tip of digit II
      3. Radial nerve—dorsal first web space
V. Bone and joint
   A. Deformity
   B. Local tenderness
   C. Pain with axial compression
   D. Joint range of motion
   E. Ligamentous stability: distal interphalangeal, proximal interphalangeal, and metacarpophalangeal joints
VI. Musculotendinous
   A. Function of each muscle-tendon group
   B. Strength against resistance
   C. Pain with motion

hand should be noted, with focus on its color, presence of swelling or edema, and any abnormal posture or position. In traumatic injuries, the precise area of maximal tenderness should be localized. Rotational, angular, and shortening deformities should be noted with regard to direction and extent. Angular deformity may be seen best with the fingers in full extension. Rotational deformity is best observed during digital flexion. Digital or wrist block anesthesia may be helpful in some cases to accurately assess fracture deformity and stability during digital motion and, if necessary, stress testing. Open wounds should be assessed with regard to location, relationship to skin creases, direction and viability of skin flaps, extent of skin loss, degree of contamination of the wound, and extent of soft tissue injury. The examiner must have a sterile field, good light, adequate exposure, and a nearly bloodless field for a thorough evaluation. The complete examination also may require an evaluation of active shoulder motion, elbow motion, and pronation and supination of the forearm and assessment of the contralateral hand.

DIAGNOSTIC STRATEGIES: RADIOLOGY

Despite the development of numerous new and sophisticated imaging techniques, plain radiography remains the most important imaging modality for the hand and wrist. The standard radiographic series of the hand should include a posteroanterior, a true lateral, and an oblique projection (Fig. 47-27). With correct positioning, the bones do not overlap on the film, allowing complete evaluation of each area for visualization of fractures, subluxation, dislocation, deformities, and retained radiopaque foreign bodies.[19] On a hand series, the wrist is not properly positioned for radiographic examination, and vice versa; if the patient has injuries to the hand and wrist, a separate radiographic series should be obtained.

Figure 47-27. Normal hand radiographs. **A,** Anteroposterior view. **B,** Lateral view. **C,** Oblique view. The hand is routinely examined in three different planes to identify fractures that may escape detection on the usual anteroposterior and lateral views because of overlapping bony structures. (From Rosen P, et al: Diagnostic Radiology in Emergency Medicine. St. Louis, Mosby, 1992, p 179.)

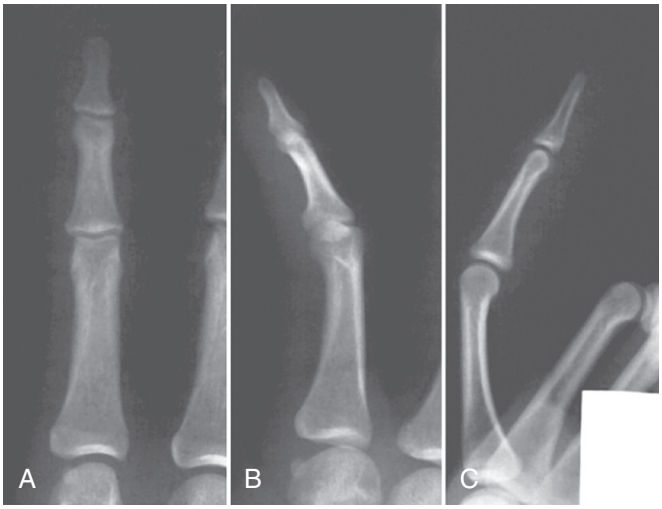


Figure 47-28. **A** to **C,** Normal radiographic appearance of fingers of three different patients.

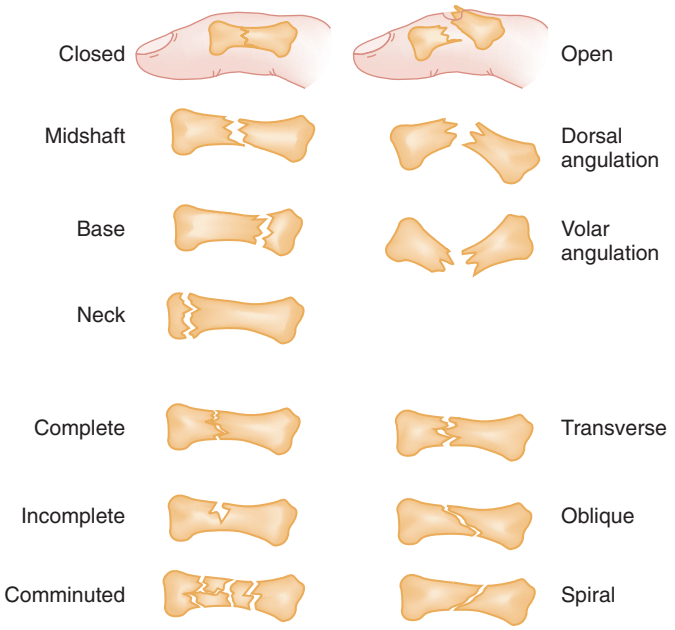


Figure 47-29. Fracture terminology. (From Idler RS, et al [eds]: The Hand: Examination and Diagnosis, 3rd ed. New York, American Society for Surgery of the Hand, 1990, p 64.)

For an adequate posteroanterior view, the forearm and hand should be fully pronated so that the palm rests flat on the film. This view forms the basis for all assessments but is poor at showing fractures of the articular surface of the metacarpal head. The lateral view normally is a radioulnar projection and is made by positioning the palm and forearm at 90 degrees to the film with the fingers splayed. This view is essential to show displacement of fracture fragments and joint dislocations. If the projection is not a true lateral view, joint dislocation, avulsion fractures, or fractures through the articular surface of the base of the phalanx may be overlooked. The oblique view is obtained with the hand and forearm pronated at 45 degrees to the film. It is particularly useful for assessing dislocation of the MCP and CMC joints and fractures at the base of the metacarpal bones. When injury is confined to the distal end of a single digit, radiologic evaluation should be limited to that digit, but the same projections are used (Fig. 47-28).

Special views are used to diagnose specific injuries. The standard views of the hand do not give true posteroanterior and lateral projections of the thumb because the plane of the thumb is at 90 degrees to that of the fingers. Separate posteroanterior and lateral views of the thumb should be requested. The posteroanterior projection of the thumb is obtained with the hand and forearm hyperpronated so that the dorsal surface of the thumb and first metacarpal rests flat on the film. The lateral view is obtained by pronating the hand and forearm to allow the lateral surface of the thumb to lie on the film. Stress views are used most often to rule out ligamentous injury to the first MCP joint. Localized widening of the joint space or subluxation may indicate a significant collateral ligament injury. Plain radiographs taken in multiple projections can help detect and localize soft tissue foreign bodies. Whether an object can be visualized will depend on its composition, configuration, size, and orientation. Many foreign bodies encountered in the ED, including almost all glass, are more dense than soft tissue and can be readily seen on plain radiographs.[20]

MECHANISMS OF INJURY AND MANAGEMENT

Trauma

The bones of the hand are the most commonly fractured bones in the body. Radiologic evaluation of significant hand injuries is mandatory. Any hand injury that causes swelling should be evaluated radiographically with a minimum of three views. Although the classification of hand fractures is difficult and at times confusing, it generally is done according to the nature and site of the fracture line and whether the fracture is open or closed (Fig. 47-29).

A fracture is unstable if it cannot be reduced or maintained in an anatomic or near-anatomic position without fixation when the hand is placed in the "safe" or functional position. The four principal determinants of fracture stability or instability are (1) fracture configuration, (2) integrity of the periosteal sleeve and surrounding soft tissues, (3) muscle balance or imbalance, and (4) external forces.

In general, transverse fractures have a stable configuration. Spiral, oblique, and comminuted fractures are unstable. The degree of displacement also is an indicator of potential fracture instability. Fractures of inherently unstable configuration may be stable if they are nondisplaced or only minimally displaced because the periosteum is undamaged or minimally disrupted. Displacement is defined by the deformity it creates and can result in rotation, angulation, shortening, or a combination of these fractures. Although shortening has an adverse effect on muscle tension, the hand accommodates more easily to this component of deformity than to others.[21]

Definitive management of many hand fractures is controversial and beyond the scope of this discusion. The emphasis here is on appropriate initial interventions, including proper splinting techniques to minimize morbidity and recognizing which fractures may require operative fixation and their potential complications. Most closed injuries may be treated initially in the ED. Most open, intra-articular, periarticular, and unstable fractures require operative management by a hand surgeon.[21]

Distal Phalanx Fractures

Pathophysiology and Clinical Features. Fractures of the distal phalanx are the most common fractures of the hand. They occur most often as a result of crush or shearing forces, usually as a sports-related injury in children and adolescents, industrial accidents

Figure 47-30. Tuft fracture of the distal phalanx of the thumb, anteroposterior view. This radiograph reveals the comminuted displaced fracture fragments and some radiopaque foreign material on the substance of the nail. (From Rosen P, et al: Diagnostic Radiology in Emergency Medicine. St. Louis, Mosby, 1992, p 180.)

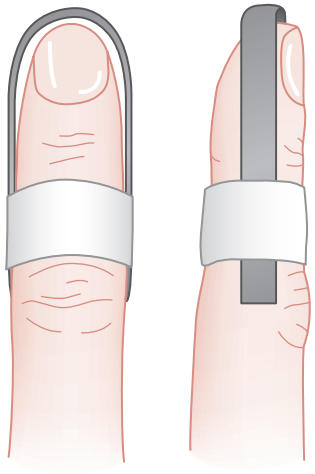


Figure 47-31. The hairpin splint used for distal phalangeal fractures. (From Simon RR, Koenigsknecht SJ: The hand. In Simon RR [ed]: Emergency Orthopedics: The Extremities, 2nd ed. Norwalk, Conn, Appleton & Lange, 1995, p 59.)

in adults, or accidental falls in elderly persons.[22] Distal phalangeal fractures are classified as extra-articular fractures (longitudinal, transverse, and comminuted) or intra-articular fractures. The most common location for these fractures is the distal tuft (Fig. 47-30). Because the mechanism of injury is usually direct trauma, tuft fractures often are comminuted and usually are associated with soft tissue injury to the nail, nail bed, and nail matrix.[23] Supporting fibrous septa that radiate from the bone to the skin prevent displacement of fracture fragments and act to contain soft tissue swelling, contributing to the severe pain that can accompany these fractures. Examination typically reveals tenderness and swelling over the distal phalanx, including the pulp.

Fractures at the base of the distal phalanx may be associated with tendon avulsion. As previously mentioned, the flexor profundus tendon attaches to the volar aspect of digits II through V, and the terminal slip of the extensor tendon attaches on the dorsal surface of the distal phalanx. In the distal phalanx of the thumb, the flexor pollicis longus inserts on the volar base, and the extensor pollicis longus inserts on the dorsal base. These tendons can avulse when subjected to excessive stress. Clinically, loss of function is evident, and small avulsion fractures along the dorsal or volar surface may be seen on radiographs. These fractures are considered intra-articular, and their management is as for other tendon injuries.

Management. Treatment of most fractures of the distal phalanges is directed toward the accompanying soft tissue injury. Closed tuft fractures need only symptomatic treatment with elevation (to reduce swelling) and analgesics. Fracture immobilization is rarely necessary; however, a short volar splint or hairpin splint (Fig. 47-31) is recommended for 2 to 3 days to protect the tip of the finger from further trauma and allow swelling without constriction. Immobilization should not include the PIP joint. Transverse shaft fractures with angulation or displacement may be irreducible because of interposition of soft tissue. Closed reduction may be attempted with dorsal traction on the distal fragment followed by immobilization with a volar splint and repeat radiographs for documentation of position. If this approach is unsuccessful, referral to a hand surgeon is indicated for Kirschner wire fixation.[23]

Distal phalangeal fractures associated with nail bed laceration are considered open fractures. This may be obvious if the nail has been avulsed or torn, but recognition of nail bed laceration is more difficult in closed tuft fractures with an intact nail despite presence of a subungual hematoma. Subungual hematomas often are associated with occult lacerations of the nail bed, and in such cases, removal of the nail for accurate assessment and laceration repair uncommonly may be required.

Complications. Distal phalanx fractures generally are uncomplicated; however, distal phalanx fractures that appear apparently innocuous can result in prolonged morbidity, especially if associated with soft tissue crush injury. In a long-term follow-up series, DaCruz and associates[24] showed that at 6 months 31% of tuft fractures had not healed radiographically and 70% of all patients had bothersome symptoms, including numbness, hyperesthesia, and cold sensitivity. Trauma to the nail bed may result in abnormal nail growth despite exact tissue approximation. Failure to recognize and extricate an entrapped nail bed in the fracture site may result in nonunion of the fracture. Osteomyelitis from open fractures is a rare but potentially serious complication.

Proximal and Middle Phalangeal Fractures

Pathophysiology and Clinical Features. Because the anatomy, mechanism of injury, and treatment for proximal and middle phalangeal fractures are similar, these fractures are discussed together. The proximal phalanx has no tendinous attachments. Fractures in this region have a typical volar angulation resulting from forces exerted from the extensors and the interosseous muscles. The middle phalanx has two important insertions. The tendon of the FDS divides and inserts along nearly the entire volar surface of the phalanx, and the extensor tendon inserts on the proximal dorsal base of the middle phalanx. Because of this alignment, fractures at the base of the middle

phalanx usually result in dorsal angulation, and fractures at the neck of the middle phalanx usually result in volar angulation.[25] The mechanism of injury often determines the nature of the fracture; a direct blow is more likely to cause a transverse or comminuted fracture, whereas a twisting injury more often results in an oblique or spiral fracture. Associated injuries may include contusion or transection of digital nerves, vascular disruption, and tendon rupture.

Intra-articular fractures include condylar fractures; comminuted fractures; dorsal, volar, or lateral base fractures; fracture-dislocations; and shaft fractures involving the joint. Extra-articular fractures involve the neck, shaft, or base of the phalanx. Although most phalangeal fractures may be easily seen, condylar fractures and displaced neck fractures are not always apparent on anteroposterior radiographs; oblique views may be needed to identify them.[26] Rotational deformities are difficult to determine by radiologic study but may appear on the lateral view as discrepancies in the diameter of the shaft at the fracture site.

Skeletal alignment can be assessed radiographically, but rotational alignment must be judged clinically by the relationship of the finger to adjacent normal fingers (Fig. 47-32). Symmetrical flexion of adjacent injured and normal fingers at their MCP and PIP joints is the best possible guide to accurate rotational alignment of the injured segment.[25] Normally, all of the fingers of the closed fist except the thumb should point to the scaphoid. Alternatively, when the fingers are loosely flexed, the nails of opposing digits should lie in the same parallel plane (Fig. 47-33). The noninjured hand should be used for comparison.

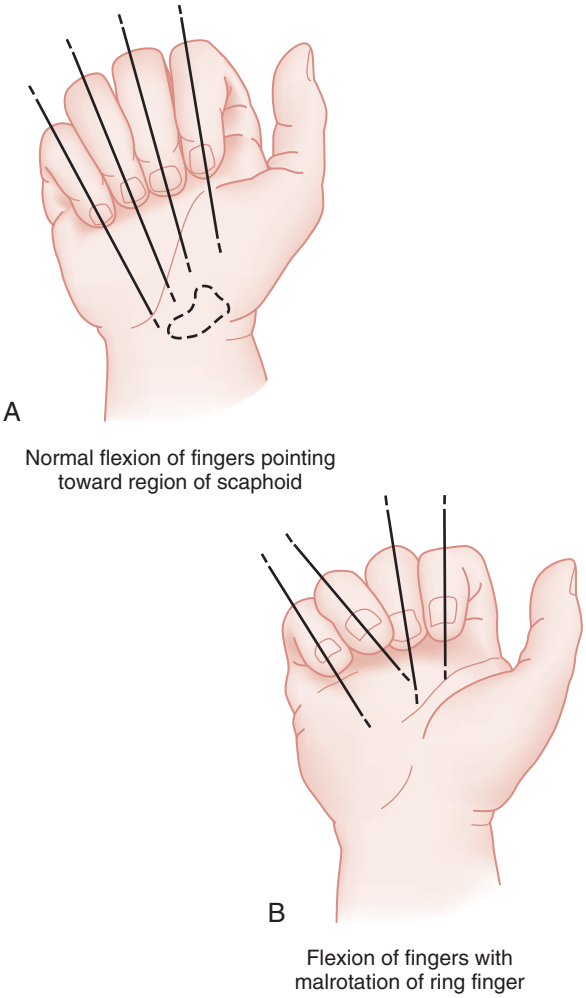


Figure 47-32. Any malrotation of a metacarpal or phalangeal fracture must be corrected. **A,** Normally all fingers point toward the region of the scaphoid when a fist is made. **B,** Malrotation at fracture causes the affected finger to deviate. (From Jobe MT, Calandruccio JH: Fractures, dislocations and ligamentous injuries. In Canale ST [ed]: Campbell's Operative Orthopedics, 10th ed. St. Louis, Mosby, 2003, p 3484.)

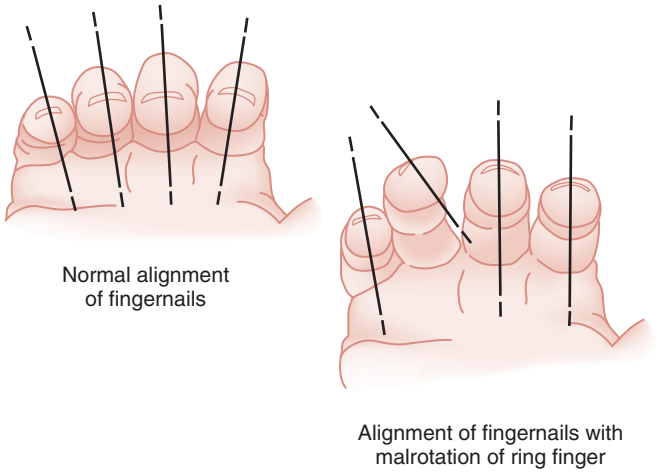


Figure 47-33. Observing the plane of the fingernails helps detect any malrotation at the fracture. (From Jobe MT, Calandruccio JH: Fractures, dislocations and ligamentous injuries. In Canale ST [ed]: Campbell's Operative Orthopedics, 10th ed. St. Louis, Mosby, 2003, p 3484.)

Management. Similar to metacarpal fractures, phalangeal fractures require precise anatomic alignment to ensure a good result because of the intimate relationship of the flexor and extensor tendons to the phalanx.[25] Appropriate treatment selection depends on accurate assessment of fracture stability. The angle of the fracture is an important factor in determining this stability. Transverse fractures usually are stable, whereas oblique fractures are inherently unstable. It also is important to ascertain whether the fracture has been impacted or displaced and what deforming forces are acting on it. If there is any question of the fracture's stability, the digit should be anesthetized, and stress should be applied. Reduction of phalangeal fractures usually is not necessary because approximately 75% are stable and nondisplaced.[27] Patients with such fractures should be started on early protected motion as soon as pain subsides (within the first 3 to 5 days). Protection is provided by taping the injured digit to an adjacent normal finger, a form of *dynamic splinting*. This technique, known as "buddy-taping," encourages the patient to move the finger and use the hand as normally as possible while the fracture heals (Fig. 47-34).

If the fracture is displaced or unstable, it is not suitable for dynamic splinting. In general, treatment depends on the type of trauma and the ability to achieve a stable reduction. Phalangeal fractures that are satisfactorily managed by closed reduction can be immobilized by several methods. In such cases, it is advisable to immobilize the wrist and the injured finger. Specific types of immobilization include circular cast, the *Böhler method* of incorporating a cast with an outrigger, gutter splints, and anterior and posterior splints (Fig. 47-35). The period of immobilization of phalangeal fractures should not exceed 3 weeks, to prevent stiffness and to minimize disability. In addition to temporary immobilization, ED management includes ice for comfort, elevation, analgesics, and referral for follow-up care. Repeat radiographs in 7 to 10 days are recommended to ensure that no delayed displacement has occurred.

Figure 47-34. The injured finger is splinted to the adjacent normal finger. This splint provides support for the injured digit while permitting motion of the metacarpophalangeal joint and some motion at the interphalangeal joint. A piece of felt cut to the proper size is inserted between the fingers, and the two digits are taped together as shown. (From Simon RR, Koenigsknecht SJ: The hand. In Simon RR [ed]: Emergency Orthopedics: The Extremities, 3rd ed. Norwalk, Conn, Appleton & Lange, 1995, p 518.)

Unstable fractures that cannot be reduced by closed manipulation and maintained with external splinting require internal fixation. Midshaft transverse fractures tend not to be amenable to closed reduction; similarly, spiral oblique fractures and intra-articular fractures are inherently unstable and require surgical fixation if a significant portion of the articular surface is involved.[28] Intra-articular fractures of the proximal metaphysis of the middle phalanx that have extreme comminution may require treatment in static or dynamic traction or external fixation with or without ancillary Kirschner wire fixation.[28]

Complications. Malunion is the most common bony complication of phalangeal fractures and may result from malrotation, volar or lateral angulation, or shortening. Malrotation usually is seen after oblique or spiral fractures of the proximal and middle phalanges and may require osteotomy through the phalanx or metacarpal for correction. Volar angulation of proximal phalangeal fractures greater than 25 to 30 degrees results in pseudoclawing. This deformity makes use of the hand awkward and is esthetically unacceptable. Other potential complications include diminished motion resulting from tendon adhesions and stiffness of the PIP joint after intra-articular fractures with incongruity.[25]

Metacarpal Fractures

Metacarpal fractures generally are divided into two groups: fractures involving the first metacarpal and fractures involving metacarpals II through V. This distinction is based on the fact that the base of the thumb metacarpal is biomechanically distinct from the remaining metacarpals because of its high degree of mobility. For this reason, these two groups are discussed separately.

Metacarpal Fractures of Digits II Through V

The hand can adjust functionally to dorsal angulation in the metacarpal equal to its motion at the CMC joint, plus 10 to 15 degrees in some patients. Because the index and middle fingers are immobile at their CMC joints, they may accommodate only 10 to 15 degrees of dorsal angulation. The ring finger usually has 20 to 30 degrees of mobility at its CMC joint and may accommodate 40 to 45 degrees of dorsal angulation. The small finger generally has 30 to 50 degrees of motion at its base and may accommodate 50 to 70 degrees of dorsal angulation. Finger metacarpals may tolerate 10 to 15 degrees of lateral angulation and 3 to 4 mm of shortening. Rotational deformity, most commonly seen in spiral and oblique fractures, is poorly tolerated. A small amount of rotational deformity can translate into a substantial digital overlap when the fingers are closed to form a fist. More than 5 degrees of malrotation may cause overlapping (scissoring) of the fingers during flexion.[21] Surgical intervention is indicated with 2 to 3 mm of shortening, 1 mm of articular surface step-off, or greater than 25% articular involvement.[25]

Metacarpal Head Fractures

Pathophysiology. Fractures of the metacarpal head are rare. They usually occur as a result of direct trauma or crush injury and typically are comminuted.[23] These fractures occur distal to the attachment of the collateral ligaments. Physical examination reveals tenderness and swelling over the involved MCP joint. Pain is increased if axial compression is applied along the extended digit. The presence of lacerations over the metacarpal heads is significant and suggests the possibility of an open fracture or human bite injury.

Diagnostic Strategies: Radiology. Although routine radiographic imaging of the injured hand reveals most fractures, the metacarpal heads can be difficult to assess because of overlap on the lateral view. In such cases in which clinical suspicion of a fracture exists and the initial radiographic appearance is normal, the Brewerton "ball-catcher's" view may be helpful.[29] This view is obtained with the digits in 65 degrees of flexion at the MCP joints and the x-ray beam angled 15 degrees radially, projecting the metacarpal heads in profile. Occasionally, com-

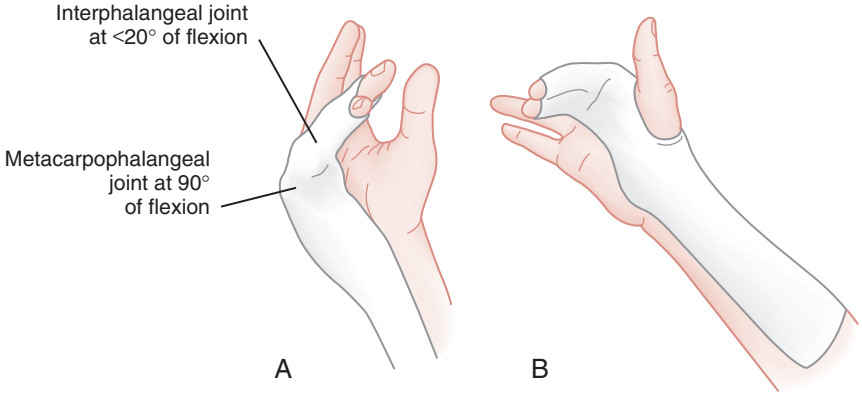


Figure 47-35. Gutter splints are used for the treatment of phalangeal and metacarpal fractures. **A,** Fractures of the ring and little fingers are immobilized in an ulnar gutter splint. **B,** Fractures involving the index finger and the long finger are immobilized in a radial splint. The splint is made by using plaster sheets cut to the proper size. The measurement should be from the tip of the finger to a point two thirds of the way up the forearm. (From Simon RR, Koenigsknecht SJ: The hand. In Simon RR [ed]: Emergency Orthopedics: The Extremities, 3rd ed. Norwalk, Conn, Appleton & Lange, 1995, p 519.)

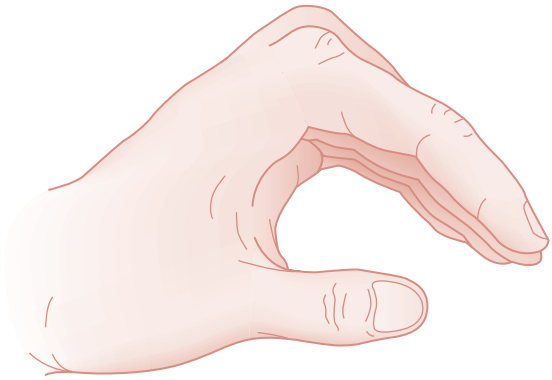


Figure 47-36. The "safe" position described by James. (Modified from Stern PJ: Fractures of the metacarpals and phalanges. In Green DP [ed]: Green's Operative Hand Surgery, 4th ed. New York, Churchill Livingstone, 1999.)

puted tomography also may be required to evaluate accurately the degree of displacement of intra-articular fractures at the MCP level.

Management. Emergency management of closed metacarpal head fractures consists of elevation, ice for comfort, analgesics, and immobilization of the hand in the "safe" or functional position, which balances the forces of the intrinsic muscles. In this position, shown in Figure 47-36, the wrist is extended 20 degrees, the MCP joints are flexed to 90 degrees, and the PIP and the DIP joints are extended. Referral to a hand surgeon for management and follow-up evaluation is required in all cases. Because these are intra-articular fractures, displacement by more than 1 to 2 mm predisposes the patient to a poor result; however, little consensus has been reached regarding optimal definitive treatment.[30]

Lacerations or puncture wounds over the dorsum of the MCP joint associated with a metacarpal head fracture should be considered open until proven otherwise. Such injuries often are caused by a clenched-fist injury and are highly contaminated wounds. Emergent consultation with a hand surgeon for operative débridement and irrigation is recommended. Prophylactic coverage with a cephalosporin is routinely recommended, although patients with highly contaminated wounds also should receive penicillin with a β-lactamase inhibitor and an aminoglycoside.[31] Several studies have found preoperative wound cultures to be of no value in predicting the risk of infection or identifying the likely pathogen, and some clinicians have abandoned their use.[32,33]

Complications. Metacarpal head fractures may be associated with debilitating hand complications, including avascular necrosis, rotational malalignment, interosseous muscle fibrosis, extensor tendon injury or fibrosis, and chronic stiffness of the MCP joint. Many of these fractures also may require late arthroplasty.[23]

Metacarpal Neck Fractures

Pathophysiology. Fractures of the metacarpal neck are among the most common fractures in the hand. The mechanism of injury is a direct impaction force (e.g., a punch with a closed fist). A *boxer's fracture* is a fracture of the neck of the fifth metacarpal (Fig. 47-37). Most metacarpal neck fractures have a typical apex dorsal angulation (palmar angulation of the distal fragment). They are inherently unstable because of the deforming muscle forces and frequent comminution of the volar cortex. Management generally is difficult because of this instability and the difficulty in maintaining reduction.

Management. For treatment purposes, metacarpal neck fractures are divided into two groups: fractures involving the ring and little finger metacarpals and fractures involving the index and long finger metacarpals. There is considerably more mobility of the metacarpals of the ring and little fingers compared with the index and long fingers. This greater mobility makes them more prone to fracture, and the relative immobility of the index and long finger metacarpals increases the need for accurate alignment after reduction. Generally, less than 15 degrees is allowed in the index and long finger metacarpals; in the ring and little finger metacarpals, 35 degrees and 45 degrees of angulation, respectively, are allowed. Any rotational malalignment must be completely corrected.

Figure 47-37. Boxer's fracture *(arrow)*. (From Harris JH Jr, et al: The Radiology of Emergency Medicine. Baltimore, Williams & Wilkins, 1993, p 444.)

Nondisplaced ring and little finger metacarpal fractures without angulation deformity can be treated initially with ice, limb elevation, analgesia, and immobilization in a gutter splint. Nondisplaced, nonangulated metacarpal fractures of the index and long finger metacarpals are treated similarly. The splint should be in standard position of function and extend from below the elbow up to, but not including, the PIP joint. Generally, it is recommended to begin PIP and DIP motion without delay. Protected MCP motion can begin in 3 to 4 weeks.[23] For isolated fractures of the little finger metacarpal neck, some clinicians advocate immediate mobilization of fractures regardless of the degree of angulation. Results with this approach include excellent function, with only minor cosmetic deformity, and early return to work. Early follow-up evaluation is advised to exclude residual angulation, rotational deformity, and delayed displacement.[34]

Reduction of ring and little finger metacarpal neck fractures with significant angulation or deformity may be attempted in the ED. After appropriate anesthesia is obtained, usually with a hematoma block, traction is applied on the metacarpal to disimpact the fracture. The MCP joints and IP joints are flexed at 90 degrees, and simultaneous pressure is applied in a volar direction over the metacarpal shaft and in a dorsal direc-

Figure 47-38. The 90-90 method for metacarpal neck fracture reduction.

tion over the flexed PIP joint (Fig. 47-38). This maneuver is termed the *90-90 method* and should complete reduction. A gutter splint in position of function should be applied. Postreduction radiographs should be obtained immediately and after 1 week to ensure that reduction has not been lost. If closed reduction cannot be achieved or maintained, pin fixation by a hand surgeon is necessary, and early referral is indicated.

Displaced or angulated index or long finger metacarpal neck fractures commonly require anatomic reduction and surgical fixation. ED management consists of ice, limb elevation, and the application of a volar splint. Prompt referral to a hand surgeon is mandatory.

Complications. Metacarpal neck fractures may have an associated rotational component that can impair function and result in overlapping of the affected finger over an adjacent finger. If excessive angulation is not corrected, the patient may experience forced hyperextension of the MCP joint and flexion of the PIP joint when extending the finger and pain when tightly grasping objects. Other complications include extensor tendon injury and collateral ligament damage. Nonunion is rare after closed metacarpal fractures.

Metacarpal Shaft Fractures

Pathophysiology. There are three types of metacarpal shaft fractures: transverse, oblique or spiral, and comminuted. Transverse and comminuted fractures usually result from a direct blow and commonly exhibit dorsal angulation (Fig. 47-39). Indirect trauma or rotational torque applied to the finger may result in a spiral shaft fracture. These fracture fragments tend to shorten and rotate rather than angulate.

Management. Metacarpal shaft fractures are treated differently from fractures involving the neck because rotational deformity and shortening are more likely, and less angular deformity is acceptable. In general, any rotational deformity must be corrected. Angulation deformities are unacceptable in the index and long finger metacarpals, whereas a small amount of angulation may be compensated for in the ring and little finger metacarpals. Acceptable reduction is less than 10 degrees of angulation in the former and less than 20 degrees in the latter, with less than 3 mm of shortening and normal rotational alignment.[21]

Most metacarpal shaft fractures can be managed initially with ice, limb elevation, analgesia, and immobilization in a gutter splint. The splint should include the wrist and the entire metacarpal shaft, but not the MCP joint if the fracture is proximal to the neck. Repeat radiographic examination and referral to a hand surgeon are recommended. If manipulative

Figure 47-39. This radiograph shows the typical dorsal angulation of fractures of the metacarpal shafts. These fractures usually are the result of a direct blow and generally angulate dorsally because of the volar force exerted by the interosseous muscles. (From Green DP, Rowland SA: Fractures and dislocations in the hand. In Rockwood CA Jr, Green DP [eds]: Fractures in Adults. Philadelphia, JB Lippincott, 1991, p 490.)

reduction is necessary, operative fixation usually is indicated. Multiple displaced metacarpal shaft fractures, oblique or spiral fractures with rotational deformity, irreducible transverse fractures, and displaced open fractures will require internal fixation.[34]

Complications. Complications seen in metacarpal shaft fractures are similar to the complications described for other metacarpal fractures. In addition to malrotation, which can cause a chronic painful grip, limitation of extensor function and interosseous muscle fibrosis may develop.

Metacarpal Base Fractures

Clinical Features. Fractures of the metacarpal base generally are stable and occur infrequently. They may result from either a direct blow over the base of the metacarpal or an axial force or torque applied along the digit. Examination reveals tenderness and swelling at the base of the involved metacarpal, and a significant degree of rotational deformity may be evident. Fractures at the base of the ring or little finger metacarpals may cause injury to the motor branch of the ulnar nerve, resulting in paralysis of the intrinsic hand muscles. In addition, they may be associated with a carpal bone fracture.

Management. Initial management in the ED consists of ice, limb elevation, analgesia, and immobilization in a bulky compressive dressing or volar splint with referral to a hand surgeon for definitive management.

Complications. Metacarpal base fractures may be associated with extensor or flexor tendon damage and significant rotational malalignment. Chronic CMC joint stiffness often is associated with intra-articular fractures and may necessitate arthrodesis or arthroplasty.

Thumb Metacarpal Fractures

Fractures of the thumb metacarpal are relatively uncommon because of its high degree of mobility. Although the shaft occasionally may be involved, most fractures involve the base of the metacarpal. These fractures are classified into two groups: extra-articular and intra-articular. The two common types of intra-articular fractures of the thumb are Bennett's and Rolando's fractures.

Extra-articular Fractures

Extra-articular fractures are seen more commonly than intra-articular fractures and usually result from direct trauma or impaction. The three types of extra-articular fractures are transverse, oblique, and epiphyseal in children. Examination reveals localized pain and swelling over the fracture site.

Mobility of the thumb metacarpal allows 20 to 30 degrees of angular deformity without functional impairment. Patients with extra-articular fractures with a greater degree of angulation should undergo closed reduction, postreduction radiographic evaluation, and immobilization of the thumb in abduction with its IP joint extended using a thumb spica cast for 4 weeks. Transverse fractures usually are stable and can be managed with closed reduction and immobilization. If the fracture is oblique, it may require Kirschner wire fixation because of instability and a propensity for rotational deformity.[21]

Intra-articular Fractures

Bennett's Fracture. *Bennett's fracture* is an intra-articular fracture at the base of the thumb metacarpal combined with a dislocation or subluxation of the CMC joint. The ulnar portion of the metacarpal remains in place, and the larger fragment subluxates dorsally because of the pulling force of the abductor pollicis longus and adductor pollicis muscles (Fig. 47-40). There is complete disruption of the ligaments around the CMC joint. Because stability is conferred mostly by the dorsal ligament (posterior oblique CMC ligament), dislocation ensues. The mechanism of injury usually involves an axial force acting on a partially flexed metacarpal (e.g., striking a rigid object with a closed fist). This is the most common fracture of the thumb base.[35]

Figure 47-40. Bennett's fracture, anteroposterior view. Avulsion fracture of the articular surface of the first metacarpal with subluxation at the carpometacarpal joint *(arrow)*. This fracture must be differentiated from Rolando's fracture and the more common extra-articular varieties. (From Rosen P, et al: Diagnostic Radiology in Emergency Medicine. St. Louis, Mosby, 1992, p 181.)

Bennett's fracture requires an anatomic reduction. Treatment goals are to achieve stability of the CMC joint by rejoining the volar lip fragment to the first metacarpal and to restore articular congruity. Initial management consists of immobilization in a thumb spica splint, ice, limb elevation, and analgesia. Early referral to a hand surgeon is warranted because although closed reduction can be achieved, the fragments are difficult to hold in position as a result of the pulling forces of the abductor pollicis longus and adductor pollicis muscles. Definitive treatment consists of conservative management, closed reduction with percutaneous pinning, or, if anatomic reduction fails or the fracture fragment represents greater than 20% of the articular surface, open reduction and internal fixation.[25]

Rolando's Fracture. *Rolando's fracture* is a comminuted fracture of the base of the thumb metacarpal. Various degrees of comminution occur, but the typical configuration is in a Y- or T-shaped pattern. The severity of comminution often is underrepresented on radiographic studies. The mechanism of injury is the same as in Bennett's fracture, but Rolando's fracture occurs much less commonly and generally carries a much worse prognosis.

ED management of Rolando's fracture consists of immobilization in a thumb spica splint, ice, limb elevation, analgesia, and early referral to a hand surgeon for surgical reduction. Definitive treatment is controversial and depends on the severity of comminution at the base of the thumb and the degree of displacement. If open reduction is indicated, a plate often is placed dorsally to maintain the reconstruction; with severe comminution, Kirschner wire fixation, bone graft placement, and external fixation may be used for continued distraction until healing occurs.[36]

Complications. Complications include joint stiffness, degenerative arthritis, and malunion. Malunion is the most common late complication but usually is well tolerated at the thumb CMC joint.[37] Posttraumatic arthritis is more common after Rolando's fracture and may require arthrodesis or resection hemiarthroplasty. Nonunion is rare.

Pediatric Fractures of the Hand

Pathophysiology and Assessment. The hand is the most commonly injured body part in children.[38] In young children, the most common hand fracture involves a crush injury of the fingertip with an open fracture of the distal tuft.[39] The most distinctive feature of the immature skeleton is the presence of epiphyseal growth centers. Although the cartilaginous epiphysis is believed to be a weak link in the immature skeleton, injuries involving this region reportedly account for only 18% of pediatric fractures.[40]

The Salter-Harris classification of epiphyseal fractures is used to direct treatment and predict outcome. The injuries are classified numerically I through V, with higher numbers corresponding to an increased risk for growth disturbance.[41] The proximal phalanx is the most frequently fractured bone among the phalanges.[42] The most common epiphyseal fracture in the hand is a Salter-Harris type II fracture of the proximal phalanx.[38] It usually results from a twisting or hyperextension mechanism and most often involves the ring and little fingers and the thumb. Although lack of cooperation in this age group may make examination difficult, the clinician should look for swell-

ing, ecchymosis, and deformity. In addition, the examiner should palpate for bony tenderness and for tenderness over the collateral ligaments. Persistent limitation of motion in a young child usually implies a significant injury of the bones or joints of the digit.

Radiologic studies should be obtained and should include the same views that are obtained in an adult. In addition, comparison views may be helpful, particularly in subtle fractures. Epiphyseal fractures may be particularly difficult because they appear differently at different ages, and their varied radiographic appearance may be mistaken for a fracture.

Management. Most pediatric hand fractures can be readily treated with either simple splinting or closed reduction, followed by brief immobilization, usually for no longer than 3 weeks. A plaster or fiberglass gutter splint incorporating the adjacent uninjured finger and including the wrist is the best means of immobilizing a child's finger fracture. The previously mentioned safe position still should be used whenever possible. Some clinicians advocate that in children, even stable injuries that ordinarily would be treated by buddy-splinting in an adult should be protected with full splinting for several weeks to prevent further injury. Open reduction and surgical fixation may be necessary for displaced intra-articular fractures, displaced Salter-Harris type III or IV fractures, and unstable fractures that cannot be maintained by closed methods.[43]

Complications. Pediatric hand fractures heal more quickly compared with similar injuries in adults. In addition, remodeling allows correction of some step-offs or angular deformities in younger children but does not correct rotational deformities. The ability of bone to correct angular deformities by remodeling is diminished with age and cannot be relied on for adequate correction in adolescents and adults. Residual deformity is the most commonly reported complication. Other complications, including joint stiffness, tendon adherence, and nonunion, are rarely seen.

Soft Tissue Injuries

Soft tissue injuries of the hand are extremely common, accounting for 82% of hand injuries seen in the ED.[44] Trauma accounts for most of these injuries to the tendons, ligaments, and cartilage. Although such injuries are not life-threatening, they may result in potentially disabling complications, including joint laxity, loss of motion, chronic pain, swelling, and deformity.

Dislocations and Ligamentous Injuries

Ligamentous injuries to the hand are common and often missed. Injury may range from mild sprain to complete rupture and may produce various degrees of joint instability. Purely ligamentous injuries may be "tears in continuity" (grade I), partial tears (grade II), or complete tears (grade III). The disruption of joints may be complete, with the articular surfaces completely separated (a dislocation), or incomplete, leaving the articular surfaces in partial communication (a subluxation).

Because the goal of treatment is to restore functional stability, it is essential to perform a systematic evaluation of joint stability. Functionally, stability may be determined by using a *two-phase test* of the IP and MCP joints of the hand. Because range of motion is heavily influenced by pain, accurate assessment generally requires digital or wrist block anesthesia in even the most cooperative patients. Active stability is tested by allowing the patient to move the digit through the normal range of motion. Completion of a full range without displacement indicates that adequate joint stability remains. Passive stability is assessed by applying gentle radial and ulnar stress to each collateral ligament and posteroanterior stress to assess volar plate integrity. Stress testing should be done in extended and moderately flexed positions to avoid the stabilizing effect of the volar plate. Comparisons with the same joint of the uninvolved hand may assist in the diagnosis. Supplemental stress radiographs also may be helpful in evaluating difficult cases.[45]

The diagnosis of incomplete or partial ligamentous injuries is made when the joint is stable to active and passive stress but is significantly swollen, with pain elicited on stress and palpation of the involved ligament systems. The examiner should attempt to ascertain whether the most tender area is over the central slip (dorsal), collateral ligaments (radial and ulnar), or volar plate (volar). Grade I and II injuries exhibit stability with pain on stress testing. Grade III injuries show instability on stress testing. Stability of the joint provides strong evidence that optimal functional recovery would result from short-term immobilization rather than surgical intervention. Because of the three-dimensional boxlike configuration that the collateral ligaments and volar plate form around the joint, wide displacement indicates that at least two components of the ligament box complex are disrupted[23,44] (Fig. 47-41). Joints with demonstrable instability should be immobilized in a gutter splint and the patient referred to a hand surgeon to determine whether surgical repair is necessary. Immobilization should be done with the IP joints splinted at 30 degrees of flexion and the MCP joints splinted at 45 to 50 degrees of flexion; when the thumb MCP is involved, it should be splinted in 30 degrees of flexion. Because the long-term effects of joint injuries are almost always joint stiffness and loss of flexion rather than persistent instability, the immobilization period usually is brief (2 to 3 weeks) and should be followed by a gradual procession of active range-of-motion exercises.[23]

Interphalangeal Joint Injuries

Distal Interphalangeal Joint. The DIP joint structure is analogous to that of the PIP joint. Additional stability is provided by the adjacent insertions of the flexor and extensor tendons, and dislocations are uncommon. Most dislocations are dorsal and usually are associated with an open wound (Fig. 47-42). Routine radiographs are used more often to rule out associated fractures than to confirm a suspected diagnosis. Treatment consists of closed reduction performed under digital or wrist block anesthesia, followed by active and passive stability testing. Reduction usually is accomplished easily by longitudinal traction and hyperextension to distract the bayonet-opposed distal phalanx followed by direct application of dorsal pressure to the base of the distal phalanx. Irreducible fractures require surgery for open reduction. The irreducibility may be due to interposition of an avulsed fracture fragment in the joint, entrapment of the profundus tendon, or buttonhole tear through the volar plate.[46]

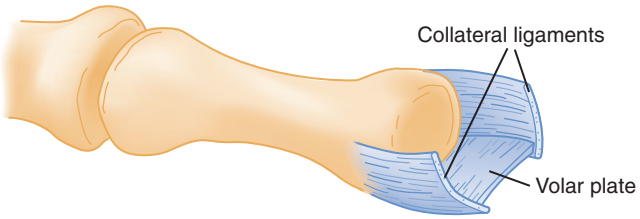


Figure 47-41. The collateral ligaments on either side of the joint and the volar plate form a boxlike support around the joint. (From Simon RR, Koenigsknecht SJ: The hand. In Simon RR [ed]: Emergency Orthopedics: The Extremities, 3rd ed. Norwalk, Conn, Appleton & Lange, 1995.)

Figure 47-42. Dorsal dislocation of the distal interphalangeal joint without associated fracture. (From Harris JH Jr, et al: The Radiology of Emergency Medicine. Baltimore, Williams & Wilkins, 1993, p 446.)

If the dislocation is open, the joint is contaminated, and treatment should include débridement and copious wound irrigation. The skin should be sutured and the joint splinted in slight flexion with a dorsal splint for 3 weeks. Most authorities recommend prophylactic antibiotics.[46]

Proximal Interphalangeal Joint. Dislocations of the PIP joint are the most common ligament injuries in the hand. Stability is derived from the strong conjoined attachments of the paired collateral ligaments and the volar plate. Three types of displacement of the PIP joint may occur: dorsal, lateral, and volar. The mechanism of injury usually is sports-related, with a high-velocity blow to the end of the finger, which causes an axial load and hyperextension. Simple dorsal dislocations result when the volar plate ruptures and the middle phalanx assumes the position of bayonet opposition. Alternatively, a lateral dislocation may result from a radially or ulnarly directed force on the joint that leads to rupture of one collateral ligament and at least partial avulsion of the volar plate from the middle phalanx. In lateral dislocations, the ratio of radial-to-ulnar collateral ligament (UCL) rupture is 6:1, and the digit usually is ulnarly deviated. Volar dislocation of the PIP joint is rare. The most common mechanism of injury is a rotary longitudinal compression force on a semiflexed middle phalanx that results in unilateral disruption of a collateral ligament and partial avulsion of the volar plate. Physical examination reveals swelling and tenderness over the PIP joint and inability to extend the joint. Routine radiographs of the injured digit reveal the type of dislocation and any associated avulsion fractures.

Management. Small bone fragments at attachment sites seen on radiographs are associated with avulsions of minor ligamentous attachment points and do not indicate the need for open repair. Avulsion fractures involving 33% or more of the articular surface usually are unstable and require surgery.[47]

Most closed dorsal and lateral PIP dislocations are treated nonoperatively.[48] Reduction is facilitated by digital nerve block and usually can be accomplished by longitudinal traction and mild hyperextension followed by firm dorsal pressure on the proximal aspect of the middle phalanx. When reduction has been achieved, active motion is tested. Reduction is stable if no displacement occurs during active range of motion and passive stressing of the joint. More than 20 degrees of deformity and instability with lateral testing indicate a complete ligamentous injury.[49] If stability is maintained during active range of motion, treatment consists of 3 weeks of immobilization in 20 to 30 degrees of flexion, followed by active exercises. Although stiffness, pain, and swelling are likely to persist for months, the long-term prognosis is good, and subluxation usually does not recur unless the finger is hyperextended again.[21] If the dislocation is irreducible or there is evidence of complete ligamentous disruption with dislocation on active range of motion, operative repair is required.

The management of volar dislocations of the PIP joint is controversial. The dislocation has been described as irreducible and requiring open reduction; however, some authorities state that most volar dislocations can be reduced by a closed technique of applying gentle traction with MCP and PIP joints flexed.[46] A stable reduction with repair of the soft tissue structures and transarticular pinning in the fully extended position also has been recommended.[46]

Injury to the Metacarpophalangeal Joints of the Fingers

Pathophysiology. MCP dislocations are considerably less common than dislocations of the PIP joint. The MCP joints of the fingers are resistant to ligamentous injury and dislocation because of their inherent ligamentous structure, their surrounding supporting structures, and their protected position at the base of the fingers. Like the DIP and PIP joints, each MCP joint has two collateral ligaments and a volar fibrocartilaginous plate; however, the MCP joints are condyloid joints and permit, in addition to flexion and extension, 30 degrees of lateral motion while the joint is extended. Because of the shape of this articulation, the joint is more stable in flexion when the collateral ligaments are stretched than when they are in extension. They are most vulnerable to injury from forces directed ulnarly and dorsally.

Isolated injury to the collateral ligaments and volar plate of the MCP joint is rare. These injuries usually occur with hyperextension stress applied to the MCP joint with the finger extended. The patient has ecchymosis and swelling of the joint. Examination reveals tenderness along the joint and varying degrees of instability. The radiographic appearance usually is normal on routine views, but some clinicians recommend a Brewerton view to show any evidence of avulsed bone fragments.[50] Treatment for most of these injuries consists of application of a gentle compression dressing with light plaster reinforcement and early orthopedic referral.

Dislocations of the MCP joints of the fingers are relatively rare injuries and usually are dorsal. The most common digit involved is the index finger, followed by the little finger. These dislocations result from hyperextension forces that rupture the proximal volar plate and are divided into simple and complex types. In the simple dislocation (subluxation), the joint appears to be hyperextended to 60 to 90 degrees, and the articular surfaces are in contact without interposed soft tissue. With complex (complete) dislocations, the MCP joint is in moderate hyperextension and angulated, the metacarpal head is prominent in the palm, and the distended palmar skin is dimpled. Complex dislocations have a less striking presentation but represent a more severe injury; the volar plate is interposed in the MCP joint space, and closed reduction is not possible (Fig. 47-43). Radiographic examination shows an obvious dislocation on the lateral view. Posteroanterior views reveal widening of the joint space in complex dislocations. In addition, sesamoids may be seen in the joint; this finding is pathognomonic for this injury (Fig. 47-44).

Management. After appropriate anesthesia is obtained, simple dorsal dislocations should be reduced in a way that prevents entrapment of the volar plate in the joint. Reduction is accomplished by flexing the wrist to relax the flexor tendons and applying firm pressure over the dorsum of the proximal phalanx

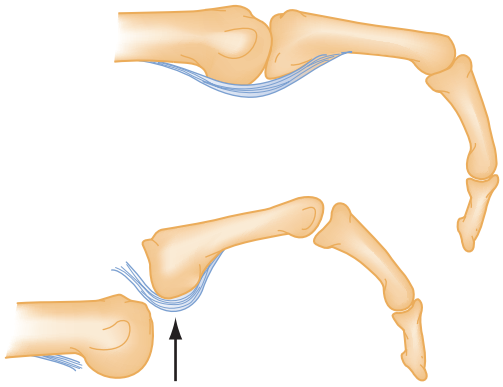


Figure 47-43. The most important element preventing reduction in a complex metacarpophalangeal dislocation is interposition of the volar plate within the joint space *(arrow)*. It must be extricated surgically. (From Green DP, Rowland SA: Fractures and dislocations in the hand. In Rockwood CA Jr, Green DP [eds]: Fractures in Adults. Philadelphia, JB Lippincott, 1991, p 521.)

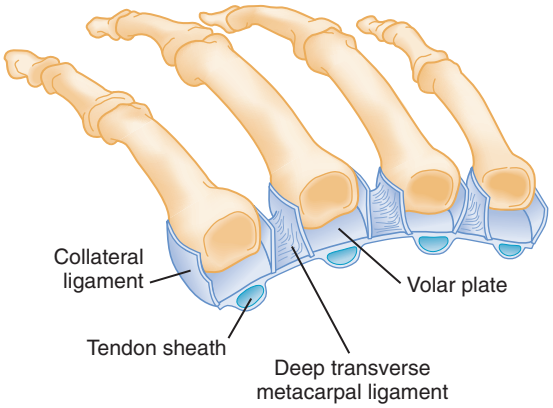


Figure 47-45. The volar plates of four palmar metacarpals are held together firmly by the deep transverse metacarpal ligament, which is continuous with the volar plate. Eaton calls this the "intervolar plate ligament." (From Green DP, Rowland SA: Fractures and dislocations in the hand. In Rockwood CA Jr, Green DP [eds]: Fractures in Adults. Philadelphia, JB Lippincott, 1991, p 518.)

Figure 47-44. A pathognomonic radiographic sign of complex metacarpophalangeal dislocation is the presence of a sesamoid bone in the widened joint space, indicative of interposition of the entrapped volar plate. (From DeLee JC, Drez D Jr, Miller MD: Orthopedic Sports Medicine: Principles and Practice, vol 2, 2nd ed. Philadelphia, Saunders, 2003, p 1387.)

in a distal and volar direction. Excessive hyperextension or longitudinal traction should be avoided. The MCP joints should be splinted in flexion, and referral to a hand surgeon is necessary. Complex dorsal dislocations do not reduce with closed methods and require operative reduction. Volar dislocations are rare and generally require operative reduction.

Injury to the Carpometacarpal Joints of the Fingers

Pathophysiology. The CMC joints of the digit form the base of the transverse metacarpal arch of the hand. The metacarpal bases articulate with each other and with the distal carpal row in a complex interlocking structural arrangement. The joints are supported by strong dorsal, volar, and interosseous ligaments and are reinforced by the broad insertions of the wrist flexors and extensors (Fig. 47-45). Dislocations of the CMC joints are uncommon and often are missed.[51] Overall, the most commonly injured CMC joint is the little finger, and most of these injuries are dorsal fracture-dislocations.[52] The injury occurs as a result of motor vehicle collisions, falls, crushes, and closed-fist trauma.

Clinical Features and Diagnostic Strategies. Clinically the patient has swelling on the dorsum of the hand and tenderness over the involved CMC joints. Routine radiographs must be viewed carefully because fracture lines may be subtle, and the metacarpals may be obscured by superimposition. Other radiographic views that may be helpful include multiple oblique, forearm in 30-degree pronation, and Brewerton views.[52]

Management. Initial treatment consists of ice for comfort, limb elevation, and analgesia. Closed reduction of the dorsal fracture-dislocation may be attempted after adequate regional anesthesia has been obtained. Traction and flexion with simultaneous longitudinal pressure on the metacarpal base, followed by extension of the metacarpal head when length has been restored, generally result in reduction. Even in cases in which reduction is achieved by closed means, early referral to a hand surgeon is needed because Kirschner wire fixation is advisable to ensure adequate stability. The late sequelae of fracture-dislocations include pain and weakness from traumatic arthritis secondary to imprecise alignment or chronic dislocation of the CMC joints.

Injury to the Interphalangeal Joint of the Thumb

The IP joint of the thumb is similar to a finger DIP joint except that the phalanges of the thumb typically are larger and stronger than the phalanges of the fingers. Even with the thumb's vulnerable position, IP dislocation is uncommon. Most dislocations are dorsal, and they often are associated with open injuries. Reduction usually is simple after a median nerve block. The joint usually remains stable because the volar plate remains attached to the distal phalanx, and immobilization in mild flexion for 3 weeks usually suffices for successful management.

Injury to the Metacarpophalangeal Joint of the Thumb

The MCP joint of the thumb is a condyloid joint that allows mainly flexion and extension; however, it also permits some degree of abduction, adduction, and rotation. Its volar plate

and collateral ligaments are stronger than in other MCP joints, but its vulnerable position leads to frequent traumatic injury. Overall, injury to the MCP joint of the thumb accounts for five times the number of injuries of all other MCP joints combined.

Most dislocations of thumb MCP joints are dorsal and result from a hyperextension force that ruptures the volar plate, joint capsule, and at least part of the collateral ligament. As with other dorsal MCP dislocations, displacement ranges in extent from subluxation of the phalanx to a complex dislocation with the proximal phalanx resting over the metacarpal head. The complex dislocation is not easily reduced because of volar plate entrapment in the joint. Clinically the complex dislocation may show a dimple over the thenar eminence. Radiographic studies confirm the dorsal dislocation and reveal the sesamoids in close proximity to the proximal phalanx.

Management. Closed reduction may be attempted after radial and median nerve wrist block anesthesia has been obtained. Pressure is directed distally on the base of the proximal phalanx, with the metacarpal flexed and adducted. If reduction is difficult, the IP joint and wrist can be flexed to relax the entrapped flexor pollicis longus tendon. When restoration of anatomic position has been accomplished, the collateral ligaments should be tested, and reduction should be confirmed by radiographic assessment. Stability to active range of motion and stress testing suggests that immobilization in a thumb spica splint with the MCP joint in 20 degrees of flexion for 4 weeks constitutes adequate treatment. Nonreducible (complex) dislocations or dislocations with significant lateral instability require open reduction and operative repair. Hyperextension, instability, and chronic pain on pinching may occur after these injuries.

Ulnar Collateral Ligament Injuries (Gamekeeper's Thumb, Skier's Thumb)

Pathophysiology. Injury to the UCL was first described as an occupational hazard of Scottish gamekeepers, who damaged their thumbs by a repeated maneuver involving twisting the necks of hares.[53] Skiing is now the most common cause of acute and chronic injury to the UCL.[54] *Skier's thumb* is the most common upper extremity injury in skiing and results from interference with release of the pole at the moment of impact during a fall. UCL rupture occurs 10 times more often than radial collateral ligament injury.[55] The mechanism of injury is forced radial deviation (abduction), and the subsequent tear usually occurs at the insertion into the proximal phalanx. Stener[56] showed that in nearly two thirds of cases of complete UCL rupture, the adductor pollicis becomes interposed between the superficial proximal portion and the deep distal portion of the ligament (see Fig. 47-45). Besides the collateral ligament injury, associated injuries of the dorsal capsule and volar plate are common.

Clinical Features. Physical examination reveals swelling and localized tenderness over the ulnar border of the joint and weakness of pinch. Complete and partial ruptures usually can be differentiated by clinical examination. Valgus stress testing of the UCLs is required and should be performed with the joint in full extension and in 30 degrees of flexion to avoid the stabilizing effect of the volar plate. If the examination elicits pain and guarding, the test should be done after median and radial nerve block at the wrist or with use of local infiltration anesthesia. More than 35 degrees of joint laxity or 15 degrees of laxity beyond that present in the uninjured thumb is consistent with complete UCL rupture.[38] Routine radiographs should be obtained before the joint is stressed and may reveal a bony avulsion from the insertion of the UCL into the proximal phalanx or an associated condylar fracture. Radiographic findings of proximal phalanx volar subluxation and radial deviation may indicate complete UCL rupture.[38] Because of the difficulty in diagnosing complete rupture, it is commonly misdiagnosed as a simple sprain in the ED, potentially resulting in chronic disability.[57]

Management. Acute partial ruptures of the UCL can be treated effectively with a 4-week period of immobilization in a thumb spica cast; full recovery is the rule. Complete ligament tears require surgical repair because a high percentage are associated with soft tissue interposition from the adductor aponeurosis (Stener's lesion), with limited predicted healing potential. Anatomic repair within 3 weeks of injury achieves good or excellent results in 90% of affected patients.[38] Long-term complications include chronic pain and instability with the loss of pinch strength, which may necessitate arthrodesis.

Radial Collateral Ligament Injuries

Radial collateral ligament injuries of the MCP joint of the thumb are less common but equally debilitating.[55] The usual mechanism is forced adduction with or without hyperextension. Diagnosis and treatment generally are similar to those for UCL injuries; however, anatomic differences between the two sides of the MCP joint do not permit a Stener-like lesion on the radial side, and the role of surgical repair is not well defined.[38]

Injuries to the Carpometacarpal Joint of the Thumb

Injuries of the volar ligament of the thumb CMC joint, similar to those of other joints of the hand, may be complete or partial. Complete rupture permits the entire thumb metacarpal to dislocate dorsally. Controversy exists regarding the ligament most responsible for stability of the thumb CMC joint, although most recent evidence implicates the dorsoradial ligament in dislocations at this joint.[58] These dislocations are reduced easily but are unstable after reduction. Initial management consists of ice, analgesia, limb elevation, and application of a thumb spica splint. The patient should be promptly referred to a hand surgeon for possible operative repair of the ligament. If the capsule is allowed to heal with imperfect metacarpal reduction, joint instability may result, with progressive degenerative changes leading to chronic pain.

Tendon Injuries

Tendon injuries may involve one or more of the extensor or flexor tendons in the hand and encompass a spectrum of abnormalities, ranging from simple stretching of the fibers to complete tendon rupture with or without an associated avulsion fracture. The most common mechanisms of injury of tendons are lacerations, avulsions, and crush injuries. In a normal resting position, the fingers are flexed, with the little finger having the greatest degree of flexion and the index finger having the least. In the resting hand, a finger with a greater or lesser degree of flexion than that of the opposite hand often indicates a tendon injury. This observation may be especially useful in an uncooperative or pediatric patient. If the patient can move a joint, but active flexion or extension is limited or painful, a partial tendon laceration may be present. To assess the tendons adequately, motion should be tested against resistance. This testing may cause a partially ruptured tendon to rupture but identifies a lesion that needs surgical repair. The tendon should be placed in maximal stretch before testing to provide for the greatest strength during contraction. As a general rule, extensor injury causes greater impairment of motion than that due to a similar flexor injury. Vessels and nerves travel closely with flexor tendons, particularly in the fingers. Damage to one of these structures is likely to be associated with damage to the other two.

The position the hand was in when the injury occurred is important. When trauma occurs while the hand is held in flexion, the flexor tendons may be transected, and the distal stump would lie distal to the wound. If the hand is in the extended position, however, the tendon stumps would lie at the wound edges. When the tendons are injured by a direct blow to the hand or the fingers, the closed injury may hide significant tissue damage. Partial tendon lacerations may be associated with small surface wounds. To help exclude injury, wounds and visible tendons should be inspected while the joints are taken through a full range of motion.

Extensor Tendon Injuries

The most common site of tendon injury is the extensors over the dorsum of the hand. The extensors are predisposed to laceration because of their superficial location on the dorsum of the hand and the minimal amount of subcutaneous tissue between the tendon and overlying skin. This anatomic arrangement also predisposes the extensor mechanism to more complex tendon injuries, including abrasion, crush, and avulsion. Because the extensor tendons are not constrained in tight fibro-osseous canals except in the wrist, they also are easily located and repaired.

Injuries to the extensor tendons have been grouped into anatomic zones for easy understanding and classification. Different systems for assigning zones have been described, but the most widely accepted is that of Verdan[12] (Fig. 47-46). This system defines eight zones, from zone I at the DIP joint level to zone VIII at the distal forearm level. The use of zones is convenient for assessing injury patterns, repair techniques, and rehabilitation.

Zone I Injuries

Pathophysiology. Zone I is the area over the distal phalanx and DIP joint. In this region, the conjoint extensor tendon is well defined and dorsally positioned. Injuries that occur here disrupt the terminal extensor tendon; they may be open or closed and may occur with or without a fracture. Complete laceration of the conjoint tendon results in a flexed posture of approximately 40 degrees at the DIP joint. Partial transection results in a lesser extension lag and a decrease in the strength of extension against resistance from a flexed position. The extension lag may increase if the partial injury is not treated appropriately. For this reason, exploration of dorsal lacerations near the DIP joint is important.

Mallet finger is the most common injury in zone I and refers to a closed disruption of the distal extensor apparatus.[23] As a result of loss of extensor tendon continuity to the distal phalanx, there is a flexion deformity of the DIP joint. The injury can be seen in any finger but is most common in the long, ring, and little fingers. Overall, mallet finger represents the most common tendon injury in the hand seen in athletes.[59] The mechanism of injury often is sudden forceful flexion of an extended finger when an object, such as a ball, strikes the tip of the finger. This mechanism is commonly encountered in athletes and often is described as "jamming" the finger. Other mechanisms include hyperextension with axial compression and direct crush injury at the DIP joint. Three types of injury patterns are recognized: type 1 tendon rupture (no fracture), type 2 tendon avulsion with a small bone fragment, and type 3 tendon avulsion with a large bone avulsion (25 to 33% of the articular surface)[60] (Fig. 47-47). Fracture fragments of variable size are seen in one fourth to one third of cases (Fig. 47-48). Small avulsion fractures usually are the result of hyperflexion injuries, whereas large fracture fragments usually result from a hyperextension mechanism.[60]

Clinical Features. In the acute injury, clinical findings include swelling, pain, and tenderness over the DIP joint. The distal phalanx is flexed because of the unopposed action of the FDP. There is usually complete passive but incomplete active extension at the DIP joint. Although the diagnosis is easily made, the patient often seeks treatment late because the functional disability is not great.

Management. Although various treatment protocols have been proposed, splinting of the interphalangeal joint for 6 to 8 weeks has yielded good results while minimizing morbidity in a majority of patients.[61] The primary goal of treatment is the maintenance of continuous DIP joint extension until tendon healing occurs. Treatment of type 1 and 2 injuries is nonoperative. Immobilization can be accomplished with either a volar or a dorsal splint made from a variety of materials, including aluminum and plastic (Fig. 47-49). The DIP joint is immobi-

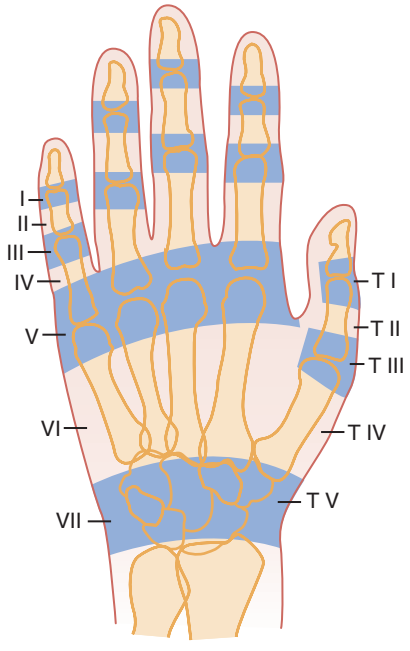


Figure 47-46. Zone classification for extensor tendon injuries. (From Kleinert HE, et al: Flexor tendon injuries. Surg Clin North Am 61:267, 1981.)

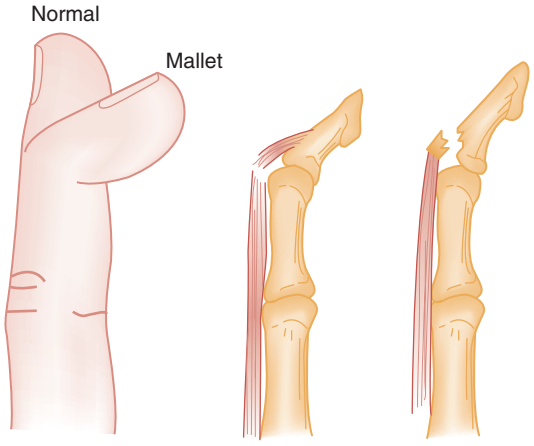


Figure 47-47. Mallet finger occurs with loss of extensor function to the distal phalanx. This may be caused by a tear of the tendon itself or an avulsion fracture of the dorsal base of the distal phalanx.

Figure 47-48. Mallet finger fracture, lateral view. This is an intra-articular avulsion of the dorsal surface of the distal phalanx *(arrow)*. (From Rosen P, et al: Diagnostic Radiology in Emergency Medicine. St. Louis, Mosby, 1992, p 181.)

lized in slight hyperextension for 6 to 8 weeks, but the PIP and MCP joints are allowed to move freely.[23,62] Definitive treatment of a type 3 injury is controversial. Some authorities recommend operative repair; others recommend conservative management with uninterrupted splinting of the digit.[12]

Open zone I injuries that divide the extensor tendon are treated by suturing the cut ends (Fig. 47-50). Partial and compete lacerations are repaired with either a roll suture or figure-of-eight stitch using 5–0 nonabsorbable sutures. This repair should be followed by continuous splinting of the DIP joint in full extension for a minimum of 6 weeks.

Prognosis. More than 80% of patients who receive conservative treatment for mallet finger report successful outcomes; however, most patients do not regain full mobility at the DIP joint.[63] Possible delayed complications include dorsal deformity, cold intolerance, pain, and the so-called swan neck deformity (Fig. 47-51). This abnormality develops when the lateral bands displace proximally and dorsally, resulting in increased extension forces on the PIP joint. Secondarily, the extensor lag at the DIP joint increases because the force of the FDP tendon is unopposed. The swan neck deformity is not seen acutely, unless the injured finger has a normally hyperextended PIP joint. Classically, this deformity occurs as a complication of a chronic untreated mallet finger.[12]

Zone II Injuries

Zone II is the area over the middle phalanx. As the lateral bands blend dorsally to form the conjoint tendon, they are thin and oriented around the dorsal half of the middle phalanx. Injuries here usually are the result of a simple laceration, which seldom transects all of the dorsal apparatus. Examination reveals a typical mallet deformity. The treatment is identical to that for open zone I injuries.

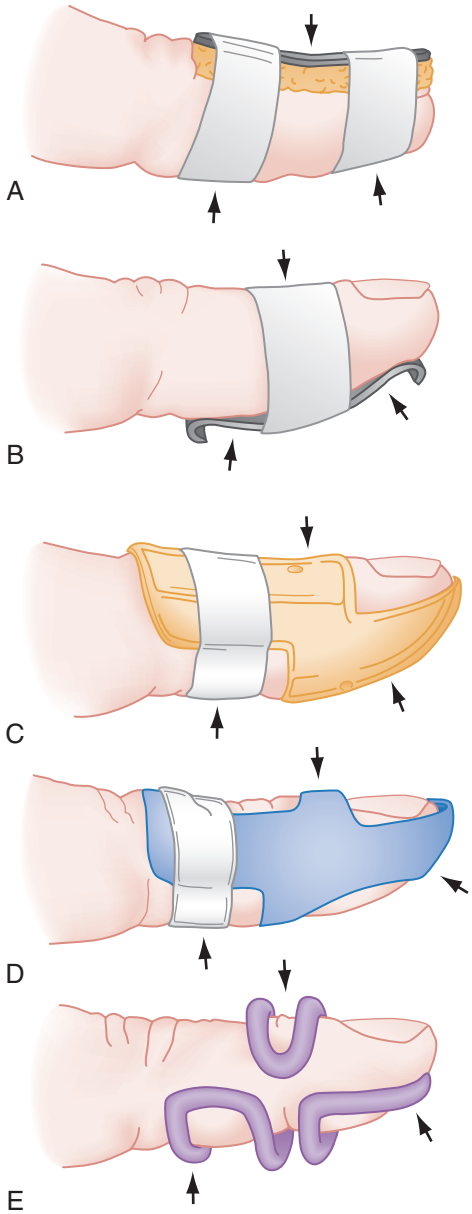


Figure 47-49. Only the distal interphalangeal joint is immobilized in treating mallet fingers. This may be done with a dorsal padded aluminum splint (**A**), a volar unpadded aluminum splint (**B**), a Stack splint (**C**), a modified Stack splint (**D**), or an Abouna splint (**E**). Each of these splints uses a three-point *(arrows)* fixation principle. (From Green DP, Rowland SA: Fractures and dislocations in the hand. In Rockwood CA Jr, Green DP [eds]: Fractures in Adults. Philadelphia, JB Lippincott, 1991, p 450.)

Zone III Injuries

Pathophysiology. Zone III is the area over the PIP joint. The central tendon is the most commonly injured structure in this zone; such injuries are the second most common closed tendon injury in athletes.[59] The mechanisms for closed rupture include forced flexion of an actively extended finger, a direct blow to the dorsum of the PIP joint, and hyperextension with volar dislocation of the PIP joint. It often results from a "jamming" injury. Lacerations that occur just distal to the PIP joint also may divide the central tendon and readily extend into the joint. Wounds must be carefully explored to define the status of the PIP joint capsule.

Disruption of the central tendon causes an imbalance in the extensor mechanism. The FDS is now unopposed and flexes the PIP joint. The lateral bands displace volarly to the axis

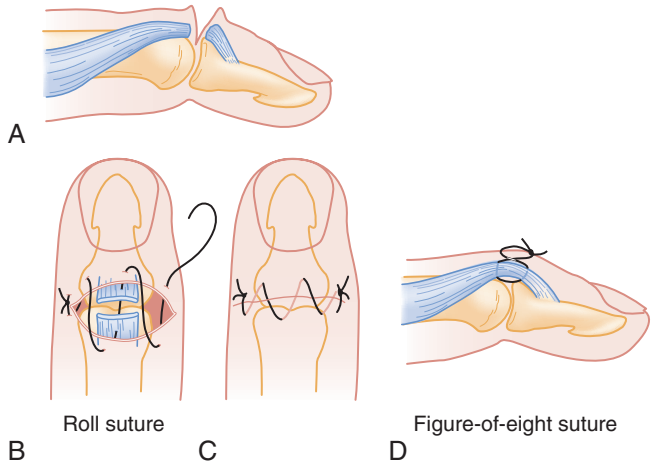


Figure 47-50. Lacerations of the extensor mechanism over the distal joint with mallet finger deformity (**A**) can be repaired by a roll-type suture, which simultaneously approximates skin and tendon (**B** and **C**). A small dressing is applied with a splint to maintain the joint in full extension. Sutures are removed at 10 to 12 days. A figure-of-eight vertical suture (**D**) also may be used, which simultaneously closes the defect in tendon and skin. Splinting is mandatory for 6 weeks. (From Doyle JR: Extensor tendons—acute injuries. In Green DP [ed]: Operative Hand Surgery. New York, Churchill Livingstone, 1993, p 1939.)

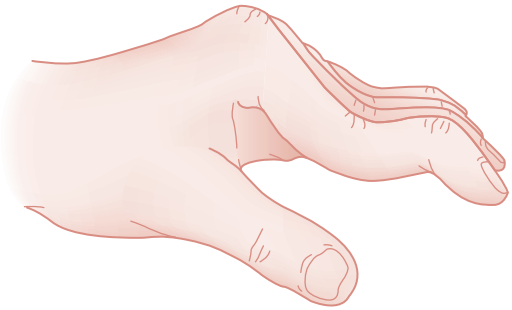


Figure 47-51. Swan neck deformity of the fingers.

of the PIP joint and become flexors of the joint. In addition, the extensor hood retracts proximally, causing extension of the MCP and DIP joints. The resulting tendon imbalance leads to the so-called *boutonnière* (buttonhole) deformity, with flexion of the PIP joint and hyperextension of the DIP and MP joints (Fig. 47-52). Although open injuries of the central tendon may cause an acute boutonnière deformity, this usually is delayed several weeks after a closed athletic injury.

Clinical Features. Early diagnosis of a closed central tendon rupture or avulsion is difficult before the boutonnière deformity has developed. The patient typically has a history of trauma to the involved digit and a painful, swollen PIP joint. The finger is held in slight flexion at the PIP joint and slight extension at the DIP joint. Rupture of the central tendon may be differentiated from the more common injury to the collateral ligament by the location of the maximal area of tenderness on the dorsum rather than on the sides of the joint, and by the patient's inability to extend the PIP joint actively. PIP joint extension can be tested by having the patient attempt to extend the fingers against slight resistance with the hand flat on the table and the PIP joint flexed 90 degrees over an edge of a table (the *tabletop test*). The radiographic appearance typically is normal but may be diagnostic if an avulsion fracture of the volar base of the middle phalanx is visualized on the lateral view.

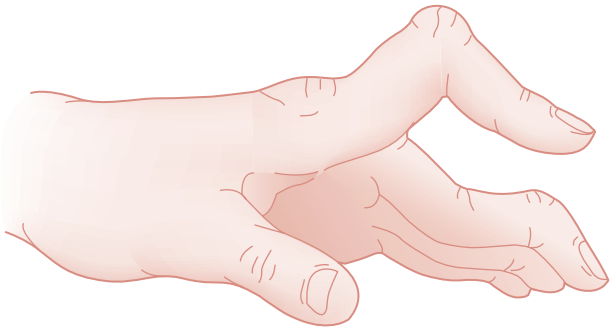


Figure 47-52. Buttonhole (boutonnière) deformity of the index finger, with swan neck deformity of the other fingers.

Management. Patients with suspected closed central tendon injuries should be managed with splinting of the PIP joint in full extension for 5 to 6 weeks. Only the PIP joint should be immobilized, and passive and active DIP joint flexion is encouraged from the outset. Operative repair may be required for an acute closed boutonnière injury associated with a displaced avulsion fracture and injury with volar PIP joint dislocation. Early referral to a hand surgeon is advised.

When an acute boutonnière deformity is caused by an open injury, exploration of the central slip is mandatory, and a hand surgeon should be consulted. Primary repair of the tendon and Kirschner wire fixation of the PIP joint often are performed. If the joint capsule has been violated, the joint should be thoroughly débrided and irrigated, and the use of prophylactic antibiotics is recommended.

Zone IV Injuries

Zone IV includes the area over the proximal phalanx. The clinical findings are similar to those with zone III injury but are less severe because the PIP joint and lateral bands are intact. The resulting injury usually is partial, and the tendon ends usually do not retract appreciably. These injuries are treated with primary or delayed primary repair and appropriate splinting for 3 to 6 weeks. Simple injuries in this zone can be well approximated with 5–0 nonabsorbable sutures with buried knots. Immobilization should be done with maintenance of the wrist in extension and the MCP joints in approximately 15 degrees of flexion. Tendon adhesions are common in this zone because of associated damage to the periosteum.

Zone V Injuries

Zone V injuries involve the areas over the MCP joint and should be presumed to be due to a human bite until proven otherwise. These injuries occur most commonly over the MCP joints of the long and ring fingers. Radiographs are mandatory and may include Brewerton views to assess the metacarpal head closely for injury. The clinical findings with injuries to the extensor tendon at this level are flexion of the MCP joint and inability to extend the joint fully.

In an open joint injury caused by a human bite, the potential for mixed aerobic and anaerobic infections is high. Operative exploration, débridement, and irrigation are necessary. A combination of a β-lactam and a β-lactamase inhibitor drug is recommended empirically for infections related to human bites.[31] In penicillin-allergic patients, clindamycin in combination with a fluoroquinolone may be given.[31] The wound is left open and may be closed at 4 to 5 days if free from infection. The

resultant tendon injury usually is only a partial laceration, which may be managed with primary or delayed primary repair.

For simple lacerations at this level caused by a sharp, clean object, primary repair is indicated. The involved tendon ends do not retract and can be approximated with 4–0 nonabsorbable sutures. Sagittal bands also must be repaired if injured to prevent loss of extension or subluxation. The wrist and MCP joints should be immobilized. Early referral to a hand surgeon is advised.

Zone VI Injuries

Zone VI includes the area of the dorsum of the hand. Although these injuries may be similar in clinical appearance to zone V injuries, the joint is not involved, and these injuries generally are not as severe. Because the extensor tendons are superficial at this level, a relatively trivial-appearing skin laceration may be associated with one or more tendon lacerations. If the injury is proximal to the junctura tendineae, the patient may be able to extend the involved MCP joint because weak extensor forces are transmitted to the junctura from adjacent extensor tendons.

The tendons in this area are round or oval and easily exposed. Primary repair using a modified Kessler stitch with a 4–0 nonabsorbable material or a figure-of-eight stitch with a buried knot on the deep, palmar surface of the tendon suffices. This repair is followed by immobilization of the wrist at 30 degrees of extension and the MCP joint in neutral position. Referral to a hand surgeon for delayed primary repair also is appropriate.

Zone VII and VIII Injuries

Zone VII and VIII injuries involve the wrist and forearm. Management follows basic principles for tendon injuries.

Flexor Tendon Injuries

Pathophysiology. Flexor tendon injuries are not as common as injuries to the extensor complex and often have a subtle clinical presentation. The most common mechanism of injury is laceration, but closed traumatic disruption also may occur. FDP avulsion is the third most common tendon rupture in the hand in athletes.[59] This injury usually is sports-related and involves a hyperextension force applied to an actively flexing digit; the classic example is that of an injured digit in a football player who grabs the clothing of an opponent who is breaking free from a tackle. Although the reason is not clearly understood, more than 75% of these injuries involve the ring finger.[62] Because of the closed nature of these injuries, the patient may not seek immediate care, or the condition initially may be misdiagnosed.

Clinical Features. Careful assessment is necessary to diagnose flexor tendon disruption and associated neurovascular injury. With the normal hand at rest, there is a cascade of flexion of the digits, beginning with less flexion at the index finger and progressing to more flexion toward the little finger. An injury to a flexor tendon may be evident if the involved finger does not assume a naturally flexed position. Complete disruption of the profundus tendon results in an extended position of the DIP joint as a result of unopposed extensor forces. If the FDS is completely severed, or a partial tendon injury has occurred, the digit rests in less flexion than normal. An abnormal posture of the injured digit may suggest a flexor tendon injury; this usually is confirmed by a functional examination. The FDP and the FDS should be tested separately as previously described. This examination requires careful observation: The patient may flex the distal tip with an intact profundus, but an injury to the FDS precludes flexion at the PIP joint. Disruption of the FDP tendon leads to loss of flexion at the DIP joint, instability in pinch, and loss of grip strength. Partial flexor tendon lacerations may be clinically occult. Because the tissue is torn and not lacerated, the degree of soft tissue injury and hemorrhage is greater than that seen with a laceration in the same zone. As a result, subsequent scarring within the sheath often is significant, and the adjacent superficialis tendon may become secondarily involved.[62] Such injuries may be present if the patient complains of subjective weakness or if an abnormal position of the hand is observed at rest. Clinically, injuries are associated with pain and weakness with flexion against resistance. Despite these findings, it may not be possible to arrive at a complete and accurate diagnosis until the wound is surgically explored. The palmaris longus, which is not present in approximately 15% of people, is not a functionally significant wrist flexor. Palmaris longus lacerations have tremendous diagnostic significance, however, because most of these injuries (80 to 90%) are associated with concomitant partial or complete median nerve lacerations. For this reason, all patients with palmaris longus lacerations should be assumed to have median nerve laceration until such injury has been ruled out.[63]

Management. Flexor tendon repairs require the expertise of a hand surgeon. Immediate or delayed primary repair is now advocated for most acute flexor tendon injuries, including avulsions of the FDP and injuries involving the so-called *no man's land*, which extends from the distal palmar crease to the midportion of the middle phalanx. The advantages of primary repair with surgical reapproximation over secondary grafting for treatment of acute injuries have been well described in the literature.[64] Relative contraindications to immediate primary flexor repair are few and include crush wounds with poor skin coverage or tendon loss greater than 1 cm, possibly contaminated injuries over 12 hours old that cannot be converted to clean wounds (human bites are not repaired initially), the presence of inadequate pulleys, inability of the patient to cooperate, and lack of surgical experience in the necessary techniques.[65] In such cases, a delayed primary repair can be performed 10 days after injury. Secondary repair of flexor tendons may be performed 4 weeks after injury, but repair is considered late after that. Generally, the results of primary, delayed primary, and early secondary repair are approximately equal. Treatment of partial flexor tendon lacerations is controversial, but referral to a hand surgeon for further exploration and possible repair is prudent.

If a hand surgeon is not immediately available, open wounds should be copiously irrigated and closed with 5–0 nylon and the hand splinted with the wrist in 30 degrees of flexion—the MCP joints flexed approximately 70 degrees and the IP joint flexed 10 to 15 degrees. This flexion ensures that no further damage occurs to the tendon and that the tendon will not contract further on movement. The patient also should receive tetanus immunization as indicated, and most authorities recommend empirical use of broad-spectrum antibiotics. Most closed tendon injuries require referral to a hand surgeon because of the risk of long-term disability.

Complications. With optimal management, most patients with flexor tendon injuries have good to excellent outcomes.[66] With injuries involving the no man's land, results may be poor, and tendon grafting occasionally is required. Overall, adhesions remain the most significant problem after operative repair. Other complications include triggering, bowstringing, and intratendinous epidermoid cyst formation.[67]

Mutilating Injuries

Mutilating injuries to the hand are encountered frequently in the ED. These are severe multistructural injuries that destroy

the anatomy and functional integrity of the hand. Initial evaluation should focus on preservation of vital structures, analgesics, early consultation, wound care with débridement of devitalized tissue, and antibiotics. Evolving over recent years is a more aggressive push with respect to procedure timing, whether a single-stage or multistage strategy is used.[68] Successful long-term clinical and socioeconomic outcomes have brought focused attention on procedure timing. The concept of early primary reconstruction with fast rehabilitation should be pursued based on case profile.[68] One such type is snowblower-associated or lawnmower-associated hand injuries, which can result in substantial deformity and disability. Snowblower injuries typically occur in clusters and are responsible for approximately 1000 amputations and 5000 ED visits annually.[69] The dominant hand is involved approximately 86% of the time, with middle and ring fingers most commonly injured. Phalangeal fractures are the most common type of injury.[70] Snowblower injuries often are managed as open fractures with intravenous antibiotics, irrigation, and débridement, with repair of bone, soft tissue, and nail bed structures.[70] Irreparable devascularization currently is considered the only absolute indication for immediate or early digital amputation after injury.[71] The concept and techniques for reimplantation and revascularization in mutilating injuries in children are similar to those in adults.[72]

Fingertip Injuries

Fingertip injuries may involve any structures distal to the DIP joint, including the skin, volar pulp tissue, distal phalanx, nail, nail bed, and related structures. These are among the most common injuries of the upper extremity and, although usually minor, may have significant long-term consequences. The goals of management are to maintain finger length and to achieve good tissue coverage, near-normal sensibility, and early functional recovery.

Fingertip Amputations

Classification. Fingertip amputations are the most common type of amputation of the upper extremity. In zone I injuries (Fig. 47-53), the proximal two thirds of the nail bed is preserved. In zone II injuries, bone is exposed, and in zone III injuries, the entire nail bed is lost. Radiographic studies are indicated if bony avulsion injury or fracture cannot be excluded. Most of these fingertip injuries can be managed on an outpatient basis.

Management. Treatment of distal fingertip injuries is controversial; consequently, management must be individualized, and few guidelines are available. Generally, most hand surgeons try to maintain length of the thumb by whatever means possible.[73] The index finger is considered next before the other fingers. An intact pulp-to-pulp pinch mechanism is the principal goal. Other factors to consider include the patient's age, health, occupation, and handedness.

In most fingertip amputations distal to the DIP joint, adequate care can be provided with conservative wound management. The simplest and often best method for managing a fingertip amputation is allowing the wound to heal by secondary intention. This method generally is effective and produces good results if the wound is less than 1 cm. Large dorsal wounds also heal well by this method. It is the treatment of choice in childhood fingertip amputations, particularly when no bone is exposed. In cases in which a small protuberance of phalangeal bone (extending no more than 0.5 cm) is exposed, it may be trimmed back with a rongeur to just below skin level and the wound allowed to heal by secondary intention; if the bone is left exposed without soft tissue coverage, the patient will need an operative procedure. In most cases, the wound heals through a process of granulation, wound contracture, and reepithelialization within a few weeks. Initial management should include careful and meticulous wound cleansing, a nonadherent dressing, appropriate tetanus prophylaxis, and splinting to protect the tip. Amputations that involve the distal phalanx usually are treated as contaminated open fractures with an initial intravenous dose of a cephalosporin followed by an oral course. Patients should have appropriate follow-up care to ensure adequate healing and recovery.

Management of fingertip injuries involving significant soft tissue (especially volar) or bone loss usually requires the expertise of a hand surgeon. Surgical management may include primary closure, full-thickness or partial-thickness skin grafts, composite grafts, adjacent flaps, regional flaps from the hand, distant flaps, and reimplantation. With most of these operative techniques, repair is best performed as a primary procedure under ideal circumstances or as a delayed procedure when necessary. A flap may be used to cover exposed bone or soft tissue avulsion and to add bulk to the tip. The nail bed tissues should be preserved because the presence of a nail affects the cosmetic result. At least 5 mm of healthy nail bed distal to the lunula is needed for nail adherence. Skin grafting is a common method for treating fingertip amputations with significant avulsed tissue and can provide a functional and an esthetic reconstruction.

Complications. These injuries commonly leave the patient with a painful, cold-intolerant fingertip; this complication has been described after primary closure, coverage with grafts or flaps, and healing by secondary intention. Skin grafting may result in induration, fissuring, and diminished sensibility. Nail deformity is common, particularly with considerable volar loss of tissue.[74]

Acute Nail Bed Injuries

Injuries of the nail bed most commonly result from localized trauma to the nail with subsequent compression of the nail bed. The most common type of injury is the simple laceration followed by stellate laceration, crush, and avulsion.[75] The middle and distal thirds of the nail bed are the most common sites of injury, and 50% of these injuries involve fractures of the distal phalanx or tuft.[76] Radiographs are required in most cases to show occult fractures and foreign bodies.

Subungual Hematoma

Subungual hematomas result from crush injury or blunt trauma to the nail bed with bleeding from the rich vascular bed. The nail bed is predisposed to injury because it is interposed between the firm nail and the distal phalanx. The injury is manifested by pain and dark red to black discoloration of the nail bed and is classified by the percentage of area beneath the

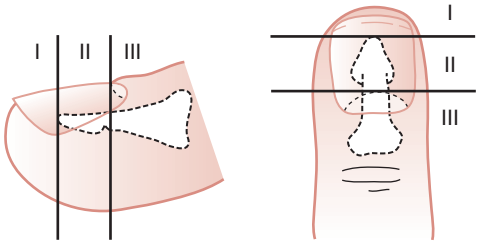


Figure 47-53. Classification of nail bed and fingernail injuries: zone I, distal to the bony phalanx; zone II, distal to lunula (between distal end of lunula and end of phalanx); zone III, proximal to distal end of lunula. (From Rosenthal EA: Treatment of fingertip and nail bed injuries. Orthop Clin North Am 14:675, 1983.)

nail that is involved. When the fingertip is unstable or the mechanism of injury suggests a significant distal phalanx fracture, a radiograph should be obtained to identify associated fracture.

Management. Small subungual hematomas do not require drainage; the blood is incorporated into the nail and eventually removed with the free edge. Large hematomas cause significant discomfort and should be removed by nail trephination with a heated paper clip or a hot microcautery unit. Some clinicians recommend a surgical scrub of the finger before perforation of the nail to prevent contamination of the subungual area and the subsequent risk of infection and potential osteomyelitis, but this generally is unnecessary. Anesthesia is not necessary, and pain relief is immediate with decompression. If a significant fracture is present, the digit should be splinted. Although a distal phalangeal fracture with a subungual hematoma is technically an open fracture, such injuries usually heal without problems. Ungual tuft fractures are not associated with osteomyelitis. The risk of infection with an open fracture of the phalanx proper must be considered, and a broad-spectrum antibiotic and close follow-up monitoring are recommended. Patients with significant hematomas should be informed that they may lose the nail.

Some authorities recommend nail removal and nail bed repair if the size of the subungual hematoma is greater than 50% of the nail area. Simon and Wolgin[77] attempted to correlate the association between subungual hematoma size, digital phalanx fractures, and occult nail bed lacerations. In their series, patients with a subungual hematoma greater than half the size of the nail had a 60% incidence of nail bed laceration requiring repair, and if an associated fracture of the distal phalanx was present, the incidence was 95%. If more than 25% to 50% of the visible portion of the nail is undermined by hematoma, many clinicians recommend removal of the nail, inspection of the nail bed, and repair of injuries.[78] However, several studies have found no notable differences in outcome between nail trephination alone and formal nail bed repair regardless of hematoma size in cases with an intact nail and nail margins.[78-80] As a result, many authorities now recommend nail removal and repair of the nail bed only if the nail is broken or the nail edges are disrupted.[75]

Nail Bed Lacerations

Lacerations of the nail bed should be repaired to minimize esthetic deformity and the duration of functional impairment. These injuries generally do well after primary repair, but late reconstruction of the nail bed is unpredictable, and usually little improvement is obtained.

Simple and crushing lacerations should be repaired accurately with 5–0 or 6–0 absorbable suture, ideally under loupe magnification. The results with both injuries should be satisfactory in more than 90% of cases.[80] After the nail bed is accurately approximated, a hole is burned through the nail to allow drainage of blood from the subungual area after the nail is reinserted into the nail fold. The avulsed nail may be sutured in place or secured with tape. A single thickness of nail-shaped Adaptic or other nonadherent gauze may be placed in the nail fold if the nail is unavailable. The replaced nail or gauze is used as a temporary splint to help protect the integrity of the underlying nail bed and maintain the fold for new nail growth and to help prevent synechiae and subsequent nail deformity. Complete nail growth takes 70 to 160 days, but after the injury the growth pattern often is changed.

Nail bed avulsion commonly leaves fragments of nail bed attached to the undersurface of the avulsed nail.[81] In these cases, it is advisable to replace the nail as accurately as possible onto the avulsion site. Repair should be done using mattress sutures without attempting to separate the nail from the nail bed. If the tissue is not available and the defect is small, effective healing occurs by secondary intention.

Clenched-Fist Injuries

All human bites should be considered serious in nature and at risk for significant complications. Clenched-fist injuries, also called "fight bites," are notorious for being the worst human bites. Inadequate initial management leads to significant morbidity. Misleading history, innocuous wound appearance, intoxication and lack of cooperation of the patient leading to inadequate examination, patient reluctance to admit the nature of the injury, delayed presentation, and inadequate exploration all may lead to mismanagement. Clenched-fist injuries are associated with the highest incidence of complications of any closed-fist injury and of any type of bite wound.[82]

Clinical Features. The classic injury is a bite wound over the third MCP joint, but injury can occur over any joint. Soft tissue injury is apparent with possible extensor tendon injury and violation of the joint capsule. When the fist is subsequently opened, the bacterial inoculum is dragged with the extensor tendon and soft tissue proximally into the dorsum of the hand.[82] Presentation may be acute or delayed. Swelling, limited range of motion, erythema, and pain out of proportion to the apparent severity of injury are typical findings. Pain is more severe with range of motion.

Management. Aggressive management is indicated with these injuries. Radiographs should be considered in all cases. Immediate consultation with a hand surgeon is advised. Analgesics, tetanus, cultures, intravenous antibiotics, appropriate wound care, elevation of the affected limb, and hospital admission should be considered for all patients. Foreign bodies must be excluded with radiologic studies and possibly exploration. Tendon injuries must be ruled out with careful exploration. The hand should be splinted in the position of function. Pathogens usually are polymicrobial, with *Staphylococcus aureus*, streptococci, and anaerobes the predominant species. Multiple-drug regimens are recommended; amoxicillin–clavulanic acid or penicillin with a first-generation cephalosporin is commonly used.

High-Pressure Injection Injuries

Epidemiology. High-pressure injection injuries to the hand are uncommon, and most are occupation-related. The usual cause is an accident involving industrial equipment, with machinery such as grease guns, spray guns, and diesel engine injectors accounting for most of these injuries.[83] A wide variety of materials, including paint, paint thinner, grease, oil, hydraulic fluid, plastic, wax, water, and semifluid cement, have been reported to be injected. Generally, substances that are highly viscous (e.g., grease) require higher forces to produce injury than those from paint, oil, and solvents. The high pressures involved are sufficient to penetrate skin from a distance, and contact of the device with the hand is not a prerequisite for injury to occur. High-pressure injection injuries have been associated with amputation rates as high as 60 to 80%.[84] Recent data suggest amputation rates of 30%, which may be due to higher vigilance and recognition of early tissue injury.[85] Early recognition and intervention are essential. Even with early intervention, the injury leads to significant impairment. Amputation is more likely if débridement is delayed more than 6 hours.[84]

Pathophysiology. Patient characteristics and injury circumstances often are similar in high-pressure injection injuries. The patient generally has a history of coming into close

proximity to the jet stream during cleaning of the nozzle or testing or operation of the equipment. The patient usually is an inexperienced worker, and the nondominant hand most commonly is involved, with the index finger the most common site.

Tissue injury from high-pressure injection generally depends on physical, chemical, and biologic factors. Of particular importance are the type, amount, and velocity of injected material and the anatomic location of the injury. The most important factor is the type of material injected, which determines the likely tissue inflammatory response and the resulting fibrosis that develops during healing. Paint and paint thinner produce a large, early inflammatory response, resulting in a high percentage of amputations.[86] By contrast, grease injuries cause a small inflammatory response and carry a lower amputation rate but are associated with oleogranuloma and fistula formation, scarring, and loss of digit function.[86] The amount of material injected into the confined space of the digits or palm determines the degree of mechanical distention and the potential for vascular compromise. The velocity of the injected material and the site of tissue penetration determine dispersion, which may include the digit, hand, and forearm. Injection injuries to the palm and thumb produce less tissue loss than that from injections of the fingers.[87]

Clinical Features. The patient who seeks treatment early after injury may have minimal symptoms with either an innocuous entrance wound or no visible break in the skin. Fusiform swelling resulting from mechanical distention of the tissue by the injectant usually is apparent. Several hours later, the involved digit or palm becomes extremely painful, swollen, and pale because of vascular compromise and tissue necrosis. Careful examination is necessary to document the extent of injury and associated neurovascular function. Radiographs of the involved hand can help determine the spread of material and the amount of débridement necessary, because certain injected materials are radiopaque. In addition, they may reveal subcutaneous emphysema.

Management. Initial ED management includes splinting, elevation of the affected limb, tetanus prophylaxis, analgesia, and broad-spectrum antibiotics. Digital blocks are contraindicated because of the potential for increased tissue pressure, which may aggravate vascular compromise. Urgent hand surgery consultation is warranted because most cases require early extensive surgical decompression and débridement. The keystone in treatment of these injuries is prompt recognition of the severe nature of the injury and aggressive early débridement. Current treatment methods using irrigation and wide débridement have significantly reduced the amputation rate.[88]

Complications. Early recognition and treatment, including operative decompression and débridement, greatly influence outcome. Early surgical amputation should be considered in cases in which the affected digit is initially cool or poorly perfused.[89] In most other cases, joint stiffness is a late sequela.

Amputations and Ring Avulsion Injuries

Few epidemiologic studies have been done on amputation injuries. Traumatic amputations have been reported to constitute 0.1 to 1% of all hand injuries.[2] Amputation may be complete or partial. Injuries with interconnecting tissue between the distal and the proximal portions are considered incomplete, or partial, amputations. Complete amputations will necessitate replantation, whereas with partial amputations, revascularization is attempted. Traumatic amputations most commonly result from local crush injuries and occur infrequently from a sharp guillotine mechanism. Partial and complete amputations reportedly occur with equal frequency. The former are often related to the use of power saws and lawnmowers.

Ring avulsions include a spectrum of injuries from partial degloving of the skin of a finger to loss of the entire digit and entire length of a flexor tendon. These injuries usually occur when a ring on a finger catches on an object during a fall. In addition to neurologic and arterial injuries, there may be complete disruption of the venous return of the finger. Generally, these injuries represent complex management problems, and treatment may range from primary amputation to microvascular repair with reimplantation and free tissue transfer in addition to local flap, pedicle flap, or graft coverage.[90]

The initial care and treatment for the patient who has had a body part amputated are the same as for any trauma patient. After the initial primary assessment and stabilization of the patient, the injured extremity should be examined carefully with documentation of neurologic, vascular, and musculotendinous function. Subsequent care should be directed toward preservation of the limb and its components. General management goals include the following: (1) provide supportive care, such as control of hemorrhage with direct pressure and elevation; (2) prolong the time that the amputated tissues remain viable; (3) protect wounds from further injury; and (4) arrange expeditious consultation by a surgical subspecialist. With few exceptions, all completely amputated parts should be considered for reimplantation, and all partially amputated parts should be considered for revascularization.

In complete amputations, the proximal stump and the amputated part should be examined for degree of tissue injury, contamination, and associated injuries. Gross contaminants can be removed by irrigation with normal saline. Local antiseptics, especially hydrogen peroxide or alcohol, should not be used because they may damage viable tissues. The wound should not be manipulated, clamped, tagged, or traumatized further in any way. The stump should be covered with a saline-moistened sterile dressing to prevent further contamination and desiccation and the limb elevated to help reduce edema and control bleeding. The amputated part requires minimal handling and should be cooled as soon as possible. After being wrapped in saline-moistened gauze, the part is sealed in a dry plastic bag, which is placed in ice water. Ice should not come in direct contact with the tissue because this can cause local damage. Amputated parts should not be discarded or sent to the pathology department because even if they cannot be replanted, they may serve as a donor source for skin, bone, or vessel grafts. Radiographs of the amputated part and proximal stump should be obtained. The use of analgesic medications may be necessary, and appropriate tetanus prophylaxis can be administered. The use of prophylactic antibiotics is indicated in amputation injuries because significant devitalized tissue often is present. Most authorities recommend empirical coverage for *S. aureus* with a combination of penicillin G and an antistaphylococcal antibiotic or first-generation cephalosporin.

Treatment for partial amputations with vascular compromise is the same as that just described. The wound should be cleaned with normal saline irrigation, and the injured part wrapped in a sterile moist dressing and splinted to protect it from further injury. Cold packs are applied to the dressings to prevent warm ischemia.

The time for which an amputated part can survive before reimplantation has not been determined. As a general rule, the more proximal the amputation, the less ischemia time the amputated part can tolerate. Attempts to extend viability during ischemia have shown that the most important controllable factor is the temperature of the amputated part. Warm

BOX 47-2 CLASSIC INDICATIONS FOR AND CONTRAINDICATIONS TO REPLANTATION

Indications
- Multiple digits
- Thumb
- Wrist and forearm
- Sharp amputations with minimal to moderate avulsion proximal to the elbow
- Single digits amputated between proximal interphalangeal joint and distal interphalangeal joint (distal to flexor digitorum superficialis insertion)
- All pediatric amputations

Contraindications
- Amputations in unstable patients secondary to other life-threatening injuries
- Multiple-level amputations
- Self-inflicted amputations
- Single-digit amputations proximal to the flexor digitorum superficialis insertion
- Serious underlying disease, such as vascular disease, complicated diabetes mellitus, or congestive heart failure
- Extremes of age

ischemia may be tolerated for 6 to 8 hours; cooling the part to 4° C extends this time to approximately 12 to 24 hours with distal amputations. Successful reimplantation of digits after 40 hours of warm ischemia has been reported.[91]

The decision of whether to attempt reimplantation should be made by the surgeon who is responsible for performing the procedure. On occasion, final judgment regarding replantation may be delayed until after microscopic inspection of vessels and nerves has been completed.[92] Patient selection generally is based on the nature and level of the injury and patient age and health-related factors. The classic indications for and contraindications to reimplantation are listed in Box 47-2. The thumb is needed to preserve the function of opposition, and all such traumatic amputations should be considered for microvascular salvage regardless of the level of amputation or mechanism of injury. Loss of the thumb is equivalent to a 40% loss of function of the hand.[93] Similarly, all amputations in children should be considered for reimplantation. In reimplantation of digits amputated distal to the insertion of the FDS between the PIP joint and the DIP joint, good motor and sensory function often is achieved. If the amputated part is crushed, mangled, or amputated at multiple levels, however, reimplantation usually is contraindicated. With digits that cannot be replanted, skin coverage by flaps or ray resection will be required.

Complications. Replanted fingers and hands never regain premorbid function. Replanted and revascularized parts may develop cold intolerance, stiffness, loss of sensation, pain, malunions, and nonunions. Even successful reimplantations may require repeated operative procedures and involve prolonged disability. Necrosis is an obvious sign of failure.

Vascular Injuries

Significant vascular disorders of the hand are uncommon compared with other problems of the hand. The vascular supply to the hand and digits is duplicated so that isolated arterial injuries to either side seldom result in ischemia. Lacerations of the arteries of the hand may stop bleeding by the time the patient is evaluated; in these situations, a history of pulsatile bleeding is highly suggestive of an arterial injury. Although most arterial injuries are the result of penetrating trauma, blunt trauma to the hand occasionally can result in arterial thrombosis or a false aneurysm.[94] In addition, associated injuries should not be overlooked. Because digital nerves invariably cross with and are superficial to the digital artery, an arterial lesion should raise the possibility of an accompanying nerve injury.

Circulatory status is assessed as previously described by observation for cyanosis or pallor, palpation of radial or ulnar pulses at the wrist, assessment of capillary refill, and the use of Allen's test. Ischemic pain is the most common initial complaint of patients with vascular insufficiency, along with physical manifestations of pallor and gangrene. The presence of a mass, with or without pain and tenderness, is the second most common initial complaint.

Management. Lacerations or amputations of the upper limb rarely cause life-threatening hemorrhage. Even a major vessel that is completely transected usually retracts, constricts, and clots. Major vessels often continue to bleed briskly, however, from partial transections with life-threatening hemorrhage. Usually, hemorrhage can be adequately controlled with direct pressure and limb elevation. If necessary, a proximally placed blood pressure cuff inflated to 30 mm Hg above systolic pressure can be used for short periods (less than 30 minutes) to control severe bleeding. Vascular clamps and hemostats should not be used in the ED to control bleeding in the hand because of the danger of inadvertently crushing nerves and tendons. Lacerated arteries should be repaired if symptoms of ischemia or an associated nerve injury are present. Arterial repair is not mandatory in isolated arterial injuries with good distal vascularity because there is a high rate of thrombosis after reanastomosis. If the decision is made not to repair a lacerated artery, both stumps should be ligated to prevent further bleeding. Palmar arch lacerations may be difficult to visualize in the ED and usually require surgical exploration to control bleeding.

Compartment Syndrome in the Hand

A *compartment syndrome* develops when elevated pressure within a closed fascial space reduces perfusion to the point of muscle and nerve dysfunction. In the hand, 10 compartments are evident on cross section through the palm (Fig. 47-54). In

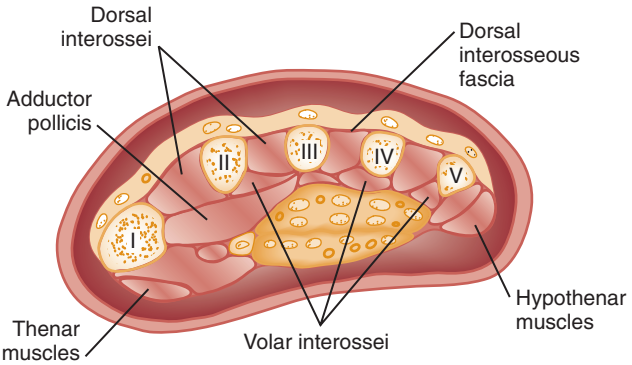


Figure 47-54. Cross section through the palm showing structures involved in forming the compartments of the hand. (From Rowland SA: Fasciotomy: The treatment of compartment syndrome. In Green DP [ed]: Operative Hand Surgery, 3rd ed. New York, Churchill Livingstone, 1993, p 670.)

addition, the fingers are compartmentalized by fascia and skin at flexor creases. Because these compartments are not interconnected, each additional compartment must be surgically decompressed if muscle ischemia is suspected.[95,96]

Nerve Injuries

Nerve injuries may result from a direct blow, puncture or laceration, crush injury, injection injury, or amputation. These injuries are divided into three main groups: neurapraxia, axonotmesis, and neurotmesis. In *neurapraxia*, there is loss of function of the nerve, but the axon, Schwann's sheath, and endoneurium remain intact. Recovery in these cases is usually complete within days. In *axonotmesis*, the axon is severed within an intact endoneurial tube. The distal axon degenerates and is absorbed after disruption. The proximal portion of the severed axonal stump can regenerate along the intact endoneurial tube at a rate of approximately 1 to 3 mm/day. *Neurotmesis* refers to complete disruption of all nerve elements. Regrowth of the proximal axonal endings does not occur along the endoneurial tubes, unless the severed nerve endings are reapproximated.[97]

Peripheral nerve injuries are diagnosed by physical examination showing loss of motor or sensory function. Specific nerves at risk should be examined as previously outlined. Injury most commonly involves one of the digital nerves but also may be localized to the median, radial, or ulnar nerve.[38]

Management. Identification of the injury and appropriate referral are important aspects in the initial management of patients with nerve injuries in the hand. Patients with closed nerve injuries not associated with compartment syndromes should be referred to a hand specialist for serial examinations. All digits that have lost function as a result of a nerve injury should be splinted to prevent further inadvertent injury. If function does not return within 3 weeks, electromyograms and nerve conduction studies can help differentiate neurotmesis from axonotmesis and determine the need for surgical exploration.[97,98]

Lacerated nerves require reapproximation by hand surgeons. In general, all motor branches of the ulnar and median nerves should be repaired. Additionally, digital nerve injuries proximal to the DIP crease on the radial aspect of the index finger, the ulnar aspect of the little finger, and both sides of the thumb should be considered for repair.[54] Clean, single-nerve lacerations should be repaired primarily when feasible. Complex nerve injuries may involve wound contamination or extensive tissue damage and usually are managed by delayed repair to allow for improved soft tissue conditions. Although the functional recovery is never complete, a good outcome can result from primary and delayed repair. In general, sensory recovery returns more often than does motor function.

Complications. Complications of nerve injuries include motor and sensory loss, atrophy from denervation, chronic paresthesias, regrowth of painful neuromas, and sympathetic dystrophy.

Infections of the Hand

The unique anatomic structures of the hand affect the nature of infections in this region of the body. In general, hand infections can be divided into infections involving the skin, subcutaneous tissues, fascial spaces, tendon, joint, and bone. Fibrous compartments of the distal fingertips contain the spread of infection, whereas flexor tendon sheaths allow infection to travel considerable distances along the lengths of the tendons from the original site. Infections in the deep spaces of the palm usually manifest on the dorsal surface of the hand.

Paronychia

Pathophysiology. A *paronychia* is a localized superficial infection or abscess involving the lateral nail fold. It is the most common infection in the hand and is thought to be caused by frequent trauma to the delicate skin around the fingernail and cuticle. Clinically, swelling and tenderness of the soft tissue along one or both sides of the lateral nail fold are evident. A paronychia begins as a cellulitis, but a frank abscess may form, and occasional extension to the overlying proximal nail (termed an *eponychia*) may be seen. *S. aureus* is the most common isolate, followed by streptococci.[97] Paronychias in children often are caused by anaerobes, presumably because of finger sucking and nail biting common in this age group.[98] Atypical mycobacteria and *Candida albicans* should be considered as etiologic agents in chronic cases.[99]

Management. In the early cellulitis phase, management consists of frequent warm soaks, elevation of the affected limb, and administration of an oral antistaphylococcal antibiotic, such as dicloxacillin or cephalexin. When the area becomes fluctuant, drainage is necessary and usually is curative. Adequate drainage often can be obtained by lifting the skin edge off the nail to allow the pus to drain (Fig. 47-55). This can be accomplished without anesthesia in selected patients, but drainage for more extensive lesions is best carried out under digital block anesthesia. After the eponychium has been softened by soaking, a No. 11 blade scalpel or an 18-gauge needle may be advanced parallel to the nail and under the eponychium at the site of maximal swelling.[100] If the infection is more extensive, the lateral one fourth of the nail may be bluntly dissected from the underlying nail bed and germinal matrix, and the lateral nail plate excised. After the cavity is irrigated, a small piece of packing gauze may be slipped under the eponychium for 24 hours to provide continual drainage. Cultures are not indicated. Antibiotics are commonly prescribed, although this is not essential if drainage is complete or if the surrounding area of cellulitis is minimal. Most paronychias resolve in 5 to 10 days, and patients are advised to obtain primary care follow-up evaluation. A well-known complication of even a properly drained paronychia is osteomyelitis of the distal phalanx. Patients with a chronic, indolent infection of the perionychium seldom respond to ED intervention. These patients should be referred to a dermatologist or hand surgeon because of the prolonged treatment required.

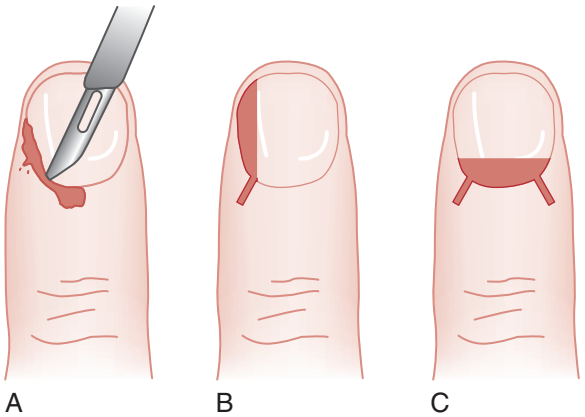


Figure 47-55. Drainage of paronychia. **A,** Eponychial fold is elevated from the nail for a simple paronychium. **B,** Lateral nail is removed if pus tracks under it. A small eponychial incision may be necessary. **C,** Proximal nail is removed if pus tracks under it. Two incisions are needed to remove the proximal nail. (From Moran GJ, Talan DA: Hand infections. Emerg Med Clin North Am 11:601, 1993.)

Felon

Pathophysiology. A *felon* is an infection of the pulp of the distal finger or thumb. It differs from other types of subcutaneous abscesses because of the presence of multiple vertical septa that divide the pulp into small fascial compartments. The usual cause is penetrating trauma with secondary bacterial invasion. The most common pathogen is *S. aureus*, although gram-negative organisms and polymicrobial infections also have been described.[100] Although the septa may facilitate an infection in the pulp and inhibit drainage after incomplete surgical decompression, they provide a barrier that protects the joint space and the tendon sheath by limiting the proximal spread of infection. Clinically a felon begins as an area of cellulitis and inflammation that progresses rapidly to severe throbbing, pain, swelling, and increased pressure in the distal pulp space.

Management. Traditional management of felons emphasizes the need for early and complete incision through the septa to provide adequate drainage and to relieve pressure in septal compartments. Most felons can be drained by a single lateral incision.[100] The incision should be made along the ulnar aspect of digits II to IV and the radial aspects of digits I and V, avoiding pincher surfaces. The incision is begun approximately 0.5 cm distal to the DIP joint crease and dorsal to the neurovascular bundle of the fingertip. The incision is extended to the free edge of the nail (Fig. 47-56). The wound should be irrigated and loosely packed with gauze, and the affected finger splinted. The packing is removed in 48 to 72 hours, and the wound is left to close secondarily. Most felons are treated empirically with an antistaphylococcal oral antibiotic for at least 5 days pending culture results. Some authorities recommend draining this abscess where it "points," using a volar midline incision that does not cross the distal flexion crease.[101]

Complications. If untreated, the expanding abscess can extend toward the phalanx, producing an osteitis or osteomyelitis, or toward the skin, resulting in necrosis and formation of a sinus tract on the palmar surface of the digital pulp. Other complications include soft tissue and bony tuft necrosis, osteomyelitis, septic arthritis of the DIP joint, and flexor tenosynovitis from proximal extension. The lateral incision used to drain felons commonly leaves unstable finger pads or may result in painful neuromas or anesthetic fingertips. "Fishmouth" incisions may destroy the blood supply to the fingertip.[101] Longitudinal midline incisions on the volar surface may leave scars over an important area for sensation but do not have the other disadvantages of lateral incisions. Any incision that is made too deeply and proximally can injure the flexor tendon sheath, initiating a tenosynovitis.

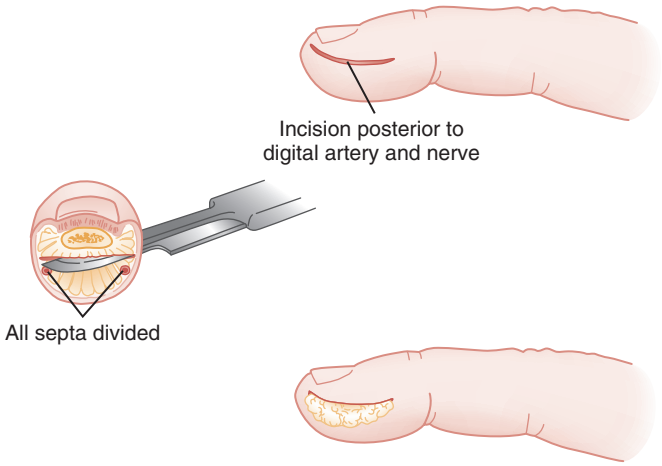


Figure 47-56. Incision and drainage of felon using the unilateral longitudinal approach. Most felons should be drained using this incision. (From Milford L: In Crenshaw AH [ed]: Campbell's Operative Orthopedics, 8th ed. St. Louis, Mosby, 1992.)

Herpetic Whitlow

Epidemiology and Pathophysiology. Herpetic whitlow is a self-limited herpes simplex viral infection of the distal finger. It is the most common viral infection of the hand. Infection by human herpes simplex virus type 1 or 2 is clinically indistinguishable.[102] Direct inoculation of the virus into an open wound or broken skin is the usual mechanism of primary infection. Herpetic whitlow commonly is reported in adult women with genital herpes and children with coexistent herpetic gingivostomatitis. Health care workers are at increased risk for development of this infection as an occupational hazard secondary to exposure to orotracheal secretions; however, a review of herpes infection in the hand found that only 14% of adult cases occur in health care workers.[103] The overall incidence has decreased, probably as a result of heightened awareness of the condition and strict infection control precautions.

Clinical Features. The infection usually involves a single finger and begins with localized pain, pruritus, and swelling, followed by the appearance of clear vesicles. Systemic symptoms usually are absent; however, secondary infection of the vesicles can occur.[102] More typically, the vesicles coalesce over 2 weeks to form an ulcer, which may develop a hemorrhagic base. At this stage, it may be difficult to distinguish herpes simplex infection of the hand from more common bacterial infections, such as felon or paronychia. The distinction is important because drainage of the herpetic lesions is contraindicated and may lead to viral dissemination and secondary bacterial infection. A careful history is important to determine risk of a possible herpetic etiology. On examination, tenderness is present but is noticeably less than that typical for bacterial infections. In addition, the pulp space remains soft and does not become tense, as it does in a bacterial felon.[104]

Diagnostic Strategies. The diagnosis usually is made clinically on the basis of the appearance of the lesion and the history of recurrence or potential sources of inoculation. The diagnosis may be confirmed by viral culture or a Tzanck smear showing multinucleated giant cells in a scraping taken from the base of an unroofed vesicle.[104]

Management. Herpetic whitlow usually resolves spontaneously in 3 to 4 weeks, although recurrence is common, occurring in up to 20% of cases. The main goals of treatment are to prevent oral inoculation or transmission of the infection and to provide symptomatic relief. The involved digit should be kept covered with a dry dressing. Oral acyclovir has a role in treatment for immunocompromised patients and patients with frequently recurring infections, but its role in nonimmunocompromised patients is less clear.[104] Topical acyclovir has not been shown to be effective in either the treatment or the prophylaxis of this disorder.

Tenosynovitis

Pathophysiology. Acute synovial space infections in the hand usually involve the flexor tendon sheaths and the radial and ulnar bursae. The tendon sheaths are double-walled, with a visceral layer adherent to the tendon and a parietal layer extending from the midpalmar crease to just proximal to the DIP joint. The flexor tendon sheath of the thumb is continuous with the radial bursa of the palm, and the small finger

sheath is continuous with the ulnar palmar bursae. The ulnar bursa surrounds the superficial and deep flexor tendons, and the radial bursa surrounds the flexor pollicis longus. These two bursae communicate in 80% of persons; in most instances, however, the tenosynovial coverings of digits II, III, and IV do not communicate. Infections in the synovial spaces in the hand tend to spread along the course of the flexor tendon sheaths and may spread to the midpalmar, thenar, and lumbrical compartments. Infections usually are caused by penetrating trauma to the sheath, but they occasionally result from hematogenous spread. The most commonly isolated organisms are *S. aureus* and streptococci, followed by gram-negative organisms and enterococci.[106]

Clinical Features. Four cardinal signs of acute flexor tenosynovitis usually are present and help differentiate tenosynovitis from other soft tissue infections in the hand: (1) tenderness along the course of the flexor tendon, (2) symmetrical swelling of the finger, (3) pain on passive extension, and (4) a flexed posture of the finger.[14] All four signs may not be present early in the course of infection. The third sign may be the most important. Early recognition and treatment are essential because elevated pressure within the enclosure of the flexor tendon sheath can occlude the already tenuous circulation to the tendon, resulting in necrosis and proximal spread.

Management. All patients with flexor tenosynovitis require hospital admission and prompt consultation with a hand surgeon to determine whether open drainage or closed tendon sheath irrigation is indicated. In early cases or uncertain diagnoses, the hand should be splinted in a bulky dressing and elevated, and intravenous antibiotics should be initiated. Infections secondary to penetrating trauma should be treated with a penicillinase-resistant antistaphylococcal penicillin or first-generation cephalosporin. Disseminated gonorrhea must be considered in all sexually active persons, especially if a traumatic cause for the infection is not apparent. In such cases, some authorities recommend empirical treatment with ceftriaxone until results of final cultures (including mucosal sites) are available.[107,108] Surgical treatment is indicated for established cases or when improvement is not evident within 24 hours.

Deep Space Infections

Anatomy and Pathophysiology. The deep fascial or palmar spaces of the hand include the midpalmar space, the hypothenar space, and the thenar space. Three additional, more superficial spaces of the hand are the dorsal subcutaneous space, the dorsal subaponeurotic space, and the interdigital web space[109] (Fig. 47-57). Although anatomically distinct from the deep spaces owing to their lack of well-defined anatomic borders, superficial spaces can harbor infections that present similarly to deep space infections.[109] The fascial spaces are potential rather than actual spaces in a normal hand.[110] These closed compartments are susceptible to infection from direct penetrating trauma, infection in contiguous compartments, or hematogenous seeding. The most commonly isolated pathogens are *S. aureus*, streptococci, and coliforms.

Clinical Features. The unique anatomic features of the deep fascial spaces lead to characteristic clinical findings when these regions are involved with pyogenic infection. The dorsal subaponeurotic abscess causes swelling and erythema on the dorsum of the hand. Pain with passive movement of the extensor tendons often is present, but it may be difficult to distinguish clinically from simple cellulitis on the dorsum of the hand. Subfascial web space infections commonly result when palmar blisters become secondarily infected. The infection tends to spread dorsally into the interdigital space and produce

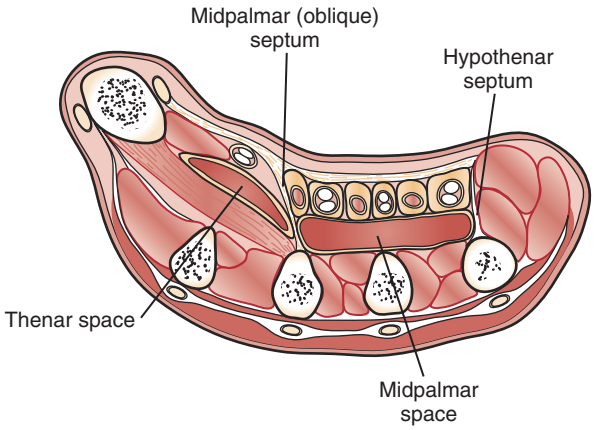


Figure 47-57. Potential midpalmar spaces. (From Neviasser RJ: In Green DP [ed]: Operative Hand Surgery, 3rd ed. New York, Churchill Livingstone, 1993, p 1028.)

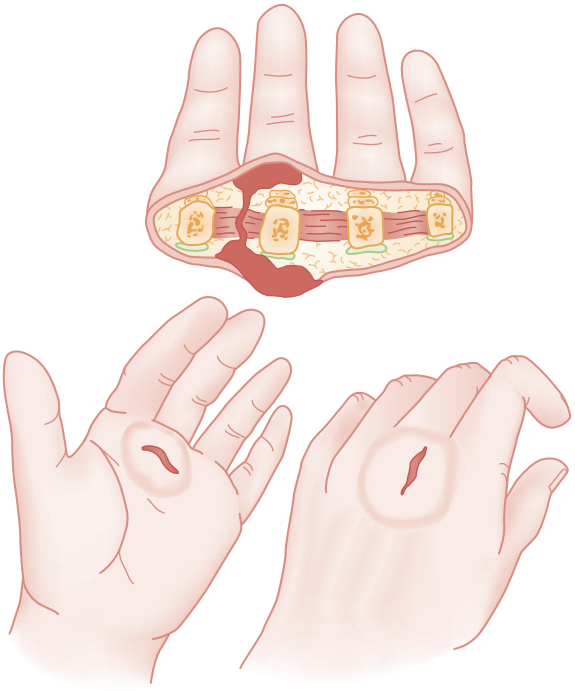


Figure 47-58. Collar-button abscess. The palmar space infection has spread to the dorsum of the hand. (From Lewis RC Jr: Infections of the hand. Emerg Med Clin North Am 3:263, 1985.)

a characteristic hourglass configuration, or the so-called collar-button abscess (Fig. 47-58). Thenar space infections are characterized by pain and swelling of the thenar eminence and the first web space; the thumb is held in abducted and flexed position.[110] In midpalmar infections, clinical features include loss of the normal hand concavity and tenderness of the central palm; movement of digits III and IV is painful. Suppurative tenosynovitis of the second digit can rupture proximally into the thenar space, with subsequent abscess formation. Tenosynovitis of digits III, IV, and V may be responsible for a midpalmar space infection.

Management. Treatment of all deep fascial space infections involves intravenous antibiotics and operative exploration and drainage by experienced surgeons. The most common practice is to use broad-spectrum empirical coverage with a β-lactamase–resistant penicillin or a first-generation cephalosporin.

Septic Arthritis

Pathophysiology. Septic arthritis in the hand may involve the IP, MCP, CMC, or radiocarpal joints. These joints usually are infected by direct inoculation of bacteria from penetrating trauma or by spread from contiguous infective process, such as a felon or tenosynovitis. Hematogenous spread may occur but is less common than in other joints of the body. *S. aureus* is the most common cause; streptococci, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, and coliforms are involved much less commonly.[110] A survey at a large county hospital found that the most common isolated organisms were staphylococci and streptococci in nearly equal numbers, with enterococcus, corynebacterium, and anaerobes encountered rarely.[110-112] Monarticular nontraumatic septic arthritis also may be caused by *Neisseria gonorrhoeae*.

Clinical Features. Clinically the involved joint appears red and swollen and is extremely tender; an overlying puncture wound may be visible. The joint is held in a position that maximizes its volume, and passive motion of the joint, however slight, is painful. In contrast with flexor tenosynovitis, tenderness is localized to the involved joint.[113] Pain also may be elicited by axial compression of the joint. The diagnosis is made by arthrocentesis.

Management. Treatment includes parenteral antibiotics with a semisynthetic antistaphylococcal penicillin and emergent drainage of the joint. Most infected joints require open drainage, but some hand surgeons may choose to manage certain cases with closed joint catheter irrigation and repeated aspiration.

Osteomyelitis

Osteomyelitis in the hand occurs most commonly with open fractures or with secondary involvement of bone from soft tissue infections. The incidence of infection in open fractures of the hand is much lower than in open long bone fractures and is reported to be 1 to 11%. McLain and colleagues[114] found that injuries with severe skeletal trauma, gross contamination, and significant soft tissue injury have the highest risks for infection. The presentation of osteomyelitis is seldom rapid and fulminant, unless associated with septic arthritis or other deep space infection of the hand. Physical signs may include fever, localized redness, swelling, warmth, and tenderness. Children with osteomyelitis may present with pseudoparalysis, manifested as refusal to use the affected limb.[115] Radiographs may show bone destruction or periosteal elevation. Treatment includes débridement of infected bone and sequestra and parenteral antibiotics.

Nontraumatic Disorders of the Hand

Stenosing Tenosynovitis

The most common type of stenosing tenosynovitis in the hand involves the flexor tendons at the level of the MCP joint where the tendon passes through the pulley systems. Repetitive strain can result in tendon and pulley hypertrophy with localized tenderness. When painful blocking of flexion and extension is noted at the involved joint, the condition is called trigger finger, as noted earlier. The ring and long fingers are the most commonly involved digits. Injection therapy is recommended and works well in most patients. A mixture of 0.25 mL of 1% lidocaine and 0.75 mL of steroid suspension is given through the web space and over the nodule.[116] After the injection, extension of the finger usually is possible. The finger should be splinted in extension, and referral to a hand surgeon is advised because multiple injections or surgical release may be required.

Ganglion

A ganglion is the most common soft tissue tumor of the hand and consists of a synovial cyst from either a joint or the synovial lining of a tendon that has herniated. Ganglia contain a jelly-like fluid that is secreted by the synovial tissue. They are common in the wrist and the flexor tendon sheaths of the fingers and usually have an insidious onset. Patients rarely recall a specific inciting traumatic event.[117] Patients commonly complain of a dull ache or mild pain over the ganglion. Reassurance is important, and the patient should be informed of the benign nature of the lesion. A large or troublesome ganglion can be aspirated. Because of the high rate of recurrence, definitive treatment is operative excision, which is done on an elective basis.[115]

Foreign Bodies in the Hand

Penetrating trauma to the hand may result in a foreign body becoming lodged in the soft tissues. The presence of a foreign body should be considered in any wound regardless of its size. A detailed and accurate history of the injury should be obtained because the mechanism often gives clues to the possibility of a foreign body. The most common foreign bodies are pieces of wood, glass, or metal. Useful signs of occult foreign bodies include sharp pain with deep palpation over a puncture wound, pain associated with a mass, and failure of a wound to heal or persistence of pain with movement.[118]

Initial examination of hand wounds should include local exploration using sterile technique in a bloodless field. After exploration and removal of easily accessible foreign bodies, radiographs should be taken, using soft tissue technique with multiple views. Radiographs are the best method for detecting radiopaque foreign bodies and detect metals, most glass, many plastics, gravel, and sand.[118] Wooden foreign bodies are difficult to visualize radiographically.[117] Whether an object shows on plain radiographs depends on its composition, configuration, size, and orientation. When a foreign body is clinically suspected and the initial radiographic appearance is normal, other imaging methods should be considered. The identification of nonmetallic objects such as splinters may be improved by the use of modalities including computed tomography, magnetic resonance imaging, and ultrasound studies.[118-121]

Management. Removal of embedded foreign bodies can be difficult and time-consuming, and potential damage to tissues caused by the procedure must be weighed against the risk posed by the specific foreign body. Generally, if a foreign body contaminating a wound is clearly visible and likely to be easily extractable during local exploration, it should be removed in the ED. In some cases, the entrance wound may need to be enlarged with a small skin incision. In general, foreign bodies should be removed only under direct vision. When the object is buried within the intricate anatomy of the hand, this procedure should be deferred to a hand specialist.

Decisions regarding the necessity and timeliness of removal of a foreign body are based on the size and the reactivity of the foreign body, proximity to vital structures, degree of wound contamination, and presence or absence of symptoms.[116] Foreign bodies that cause continued pain, interfere with hand function because of their size or their position, or cause local or systemic toxicity (e.g., paints or mercury) should be removed. With foreign bodies associated with fractures, prompt surgical débridement is necessary to prevent osteomyelitis.[119] Wounds that are grossly contaminated with soil or organic material

require immediate irrigation, débridement, and removal of the foreign body. Foreign bodies near tendons, nerves, and vessels and foreign bodies causing ischemia or hemorrhage require cautious removal under optimal conditions.

Patients who do not require immediate removal of the foreign body may be referred to a hand surgeon for delayed surgical exploration. If the hand specialist plans to remove the object within 3 to 4 days after injury, and if bacterial contamination is minimal, the wound may be closed primarily. Initial treatment also should include tetanus prophylaxis and an appropriate wound dressing. The patient should be informed about the presence of the foreign body and the reason for delayed removal. If no removal is planned, the physician should explain to the patient that the dangers of removal outweigh the benefits.

Complications. Foreign bodies can damage soft tissues, provoke excessive inflammation with granuloma formation, predispose the patient to infection, and cause systemic toxicity. Iatrogenic damage to tissue can result from blind probing or excessively aggressive searches for foreign bodies; such maneuvers should be avoided, particularly in the hand.

KEY CONCEPTS

- Injuries and infections of the hand are among the most commonly encountered problems in the ED.
- An accurate history and carefully performed physical examination of the hand have a central role in evaluation and treatment. Hand radiographs should be obtained if suggestive signs are present. High-technology diagnostic modalities are rarely indicated.
- The best functional outcomes of hand injuries usually are achieved by accurate initial evaluation and treatment.
- A key factor in the evaluation of hand injuries is determining which entities require specialty referral or urgent consultation.
- Management of the injured hand should focus on restoring function and minimizing long-term disability.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 48 Wrist and Forearm

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WRIST

PERSPECTIVE

The wrist is anatomically and biomechanically complex. This complexity allows for its diverse functional capabilities, but also puts it at risk for injury. Bony and ligamentous injuries are common, and a detailed knowledge of relevant anatomy and appropriate clinical evaluation and an understanding of mechanism of injury are essential for proper diagnosis and treatment. Although certain wrist injuries may provide a diagnostic challenge, most are evident on routine radiographic views and can be diagnosed and treated by an emergency physician.

Anatomy

By definition, the wrist includes the distal radioulnar joint (DRUJ), the radiocarpal joint, and the midcarpal joints. With these complex articulations, the wrist is capable of flexion, extension, and radial and ulnar deviation. Pronation and supination of the hand occur at the proximal radioulnar joint and the DRUJ.

The bones of the wrist joint include the distal articular surfaces of the radius and ulna and the bones of the carpus (Fig. 48-1). The distal radius articulates directly with the proximal carpal row, and the articular surface of the ulna is separated from direct contact with the carpus by the triangular fibrocartilage. The carpal bones are divided into two rows: a proximal row consisting of the scaphoid, lunate, triquetrum, and pisiform and a distal row consisting of the trapezium, trapezoid, capitate, and hamate.

The stabilizing ligaments of the wrist joint are divided into two major groups: the extrinsic ligaments and the intrinsic ligaments. The *extrinsic* ligaments link the carpal bones to the distal radius and ulna and the metacarpals, and the *intrinsic* ligaments interconnect the individual carpal bones. The extrinsic ligaments are divided further into a volar and a dorsal group. The volar extrinsic ligaments are divided into two V-shaped ligamentous bands called the *proximal* and *distal arcades*, which generally are thicker and stronger than the dorsal extrinsic ligaments and are the most important in providing ligamentous stability to the wrist. Between these volar arcades is an area relatively devoid of ligamentous support called the *space of Poirier*. This space enlarges when the wrist is dorsiflexed, and an injury to the joint capsule in this region can result in significant carpal instability (Fig. 48-2). The intrinsic ligaments interconnect adjacent carpal bones within each carpal row. The most important of these ligaments for maintaining carpal stability are the scapholunate and lunotriquetral ligaments.

Most structures that cross the wrist joint are contained within individual compartments formed by the deep fascia of the wrist. On the dorsal surface of the wrist, the extensor tendons are divided by the extensor retinaculum into six compartments, each having a separate synovial sheath that extends proximal and distal to the retinaculum. On the volar surface of the wrist, the flexors of the digits and the median nerve are contained within the carpal tunnel, which is formed by the flexor retinaculum and its attachments to the carpal bones. Radial to the carpal tunnel, the flexor carpi radialis tendon crosses the wrist joint in its own compartment.

The vascular supply to the wrist is provided by the radial and ulnar arteries, which join in a series of dorsal and palmar arches to supply the bones of the carpus. The intrinsic blood supply to most carpal bones enters the distal portion of the bone, leaving the proximal portion at risk for devascularization and avascular necrosis when fractured. This is particularly true for the scaphoid, capitate, and lunate because they each receive their blood supply from a single vessel (Fig. 48-3).

The innervation of the wrist and hand is by the radial, median, and ulnar nerves. The radial nerve and the dorsal sensory branch of the ulnar nerve cross the dorsum of the wrist near the radial and ulnar styloids. The median nerve crosses the volar radial aspect of the wrist within the carpal tunnel, just lateral to the palmaris longus tendon, and the ulnar nerve is within Guyon's canal between the pisiform and the hook of the hamate (see Fig. 48-3).

CLINICAL FEATURES

The clinical examination of the patient with a wrist injury begins with a complete history, including the mechanism of injury and the site of maximal pain or tenderness. Most wrist injuries are caused by a fall on the outstretched hand. The physical examination begins with inspection of the wrist, using the opposite noninjured wrist as the "normal" reference, and includes an assessment of the presence of swelling, discoloration or obvious deformity, and the ability of the patient to move the joint through a normal range of motion.

On palpation, several bony prominences in the wrist serve as useful landmarks, and the locations of these are best described in relation to the major reference points in the

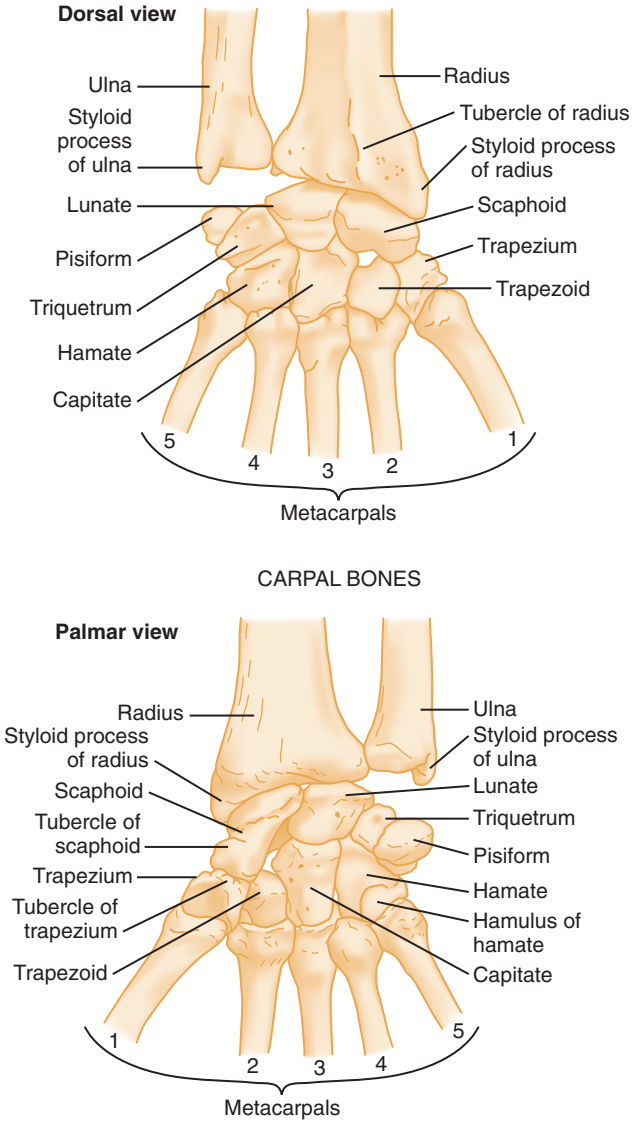


Figure 48-1. Bones of the wrist. The wrist joint includes the distal articular surfaces of the radius and ulna and the proximal and distal carpal rows. (Redrawn from Netter FH: Atlas of Human Anatomy, 3rd ed. Teterboro, NJ, Icon, 2003.)

wrist—the radial and ulnar styloids. Lister's tubercle can be palpated on the dorsum of the wrist just ulnar to the radial styloid. This is an important landmark because just distal to the tubercle lies the scapholunate joint, an important site of ligamentous injury in the wrist. Just distal to the radial styloid is the anatomic snuffbox, bordered radially by the abductor pollicis longus and extensor pollicis brevis tendons and ulnarly by the extensor pollicis longus tendon. The body of the scaphoid is palpable within the snuffbox and is more prominent with the wrist in ulnar deviation.[1] The triquetrum is palpable just distal to the ulnar styloid in the proximal carpal row and can be made more prominent with radial deviation of the wrist. With the wrist in neutral position, the capitate is palpable in a small depression found midway between the base of the third metacarpal and Lister's tubercle. Bringing the wrist into flexion can bring the lunate forward into a palpable position at this same site. On the volar aspect of the wrist, the scaphoid tubercle is palpable just distal and palmar to the radial styloid. It is felt as a rounded prominence at the base of the thenar muscles and is especially prominent when the wrist is extended. On the ulnar border of the wrist, the pisiform is palpable at the base of the hypothenar muscles, just distal to the distal wrist crease. In addition, approximately 1 cm distal and radial to this point, one can palpate the prominence formed by the hook of the hamate.

The clinical examination also includes an assessment of the neurovascular status. Radial and ulnar pulses are easily palpable on the volar surface of the wrist, and the presence of pulses should be documented in all injuries to the wrist.

DIAGNOSTIC STRATEGIES: RADIOLOGY

Plain radiographs remain the cornerstone of diagnosis of fractures and dislocations of the wrist. Routine radiographic views include the posteroanterior, lateral, and oblique projections, each obtained with the wrist in neutral position. Accurate interpretation of these views requires knowledge of the normal appearance and anatomic relationships of the distal radius, ulna, and carpal bones.

On the posteroanterior view of the wrist, the radial styloid process extends beyond the end of the articular surface of the ulna by a normal distance of 9 to 12 mm. This normal difference in length is called the *radial length measurement*. The ulnar slant of the articular surface of the radius, referred to as *radial inclination*, is visible on the posteroanterior view and normally measures 15 to 25 degrees. Both of these measurements are important in assessing the degree of radial shortening seen in association with some fractures of the distal radius (Fig. 48-4).[2] The normal appearance of the carpus on the posteroanterior view shows an approximately equal distance (usually 1 to 2 mm) between each of the carpal bones, and opposing articular surfaces are parallel to one another (an arrangement known as *parallelism*). On radiographs, three smooth curves normally can be drawn along the carpal articular surfaces (Fig. 48-5). Disruption of these curves or widening of the carpal spaces is an indication of carpal ligament disruption and carpal instability.[3]

On the lateral view of the wrist, the normal volar tilt of the distal radial articular surface is visible and normally measures between 10 and 25 degrees (Fig. 48-6). The normal alignment of the distal radius with the lunate and capitate also is seen on the lateral view, which will show two concentric cups, the cup of the distal radius containing the lunate and the cup of the distal lunate containing the capitate. Ideally the long axis of the radius, lunate, capitate, and third metacarpal should appear as a straight line on the lateral view, although the "normal" alignment usually is within 10 degrees of this ideal line (Fig. 48-7). The carpal alignment on the lateral view is defined further by the scapholunate angle, which normally measures 30 to 60 degrees, and the capitolunate angle, which inormally is 0 to 30 degrees (Fig. 48-8). Abnormalities in these angles are seen in patients with carpal ligament injuries and carpal instability.

The soft tissues of the wrist also offer valuable clues to the presence of underlying bony injuries. On the lateral view of the wrist, the pronator quadratus line is visible as a linear fat collection in the volar soft tissues just anterior to the distal radius and ulna (Fig. 48-9). Fractures of the distal radius or ulna result in volar displacement or complete obliteration of this line.

Additional radiographic views of the wrist include posteroanterior views in ulnar and radial deviation, lateral views in maximal flexion and extension, and the clenched-fist anteroposterior view. These views are useful to delineate further abnormal motion of the carpus resulting from carpal ligament injuries. Specific scaphoid views, obtained with the wrist

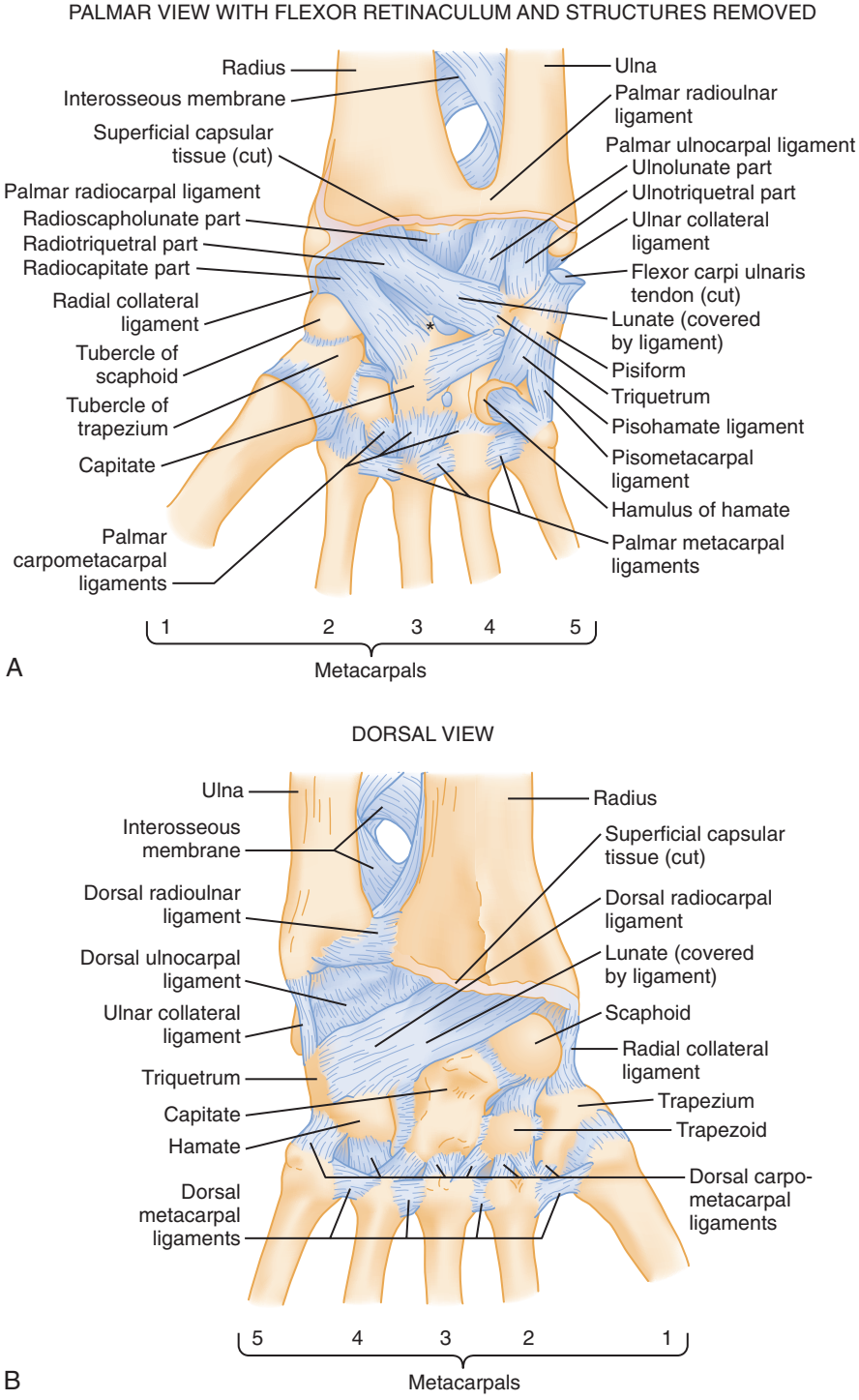


Figure 48-2. Ligaments of the wrist. **A,** The volar extrinsic ligaments are the most important ligaments in providing stability to the wrist and include the radial collateral ligament, radiocapitate ligament, radioscaphoid ligament, radiotriquetral ligament, ulnotriquetral ligament, capitotriquetral ligament, and ulnar collateral ligament. The space of Poirier (*) is a gap in the volar ligaments and the site of potential weakness. **B,** The intrinsic (intercarpal) ligaments interconnect the individual carpal bones. The most important of these are the scapholunate ligament and the lunotriquetral ligament. (Redrawn from Netter FH: Atlas of Human Anatomy, 3rd ed. Teterboro, NJ, Icon, 2003.)

pronated and in ulnar deviation, allow for better visualization of the scaphoid along its long axis. The carpal tunnel view is performed with the wrist hyperextended and provides an axial view of the bony margins of the carpal tunnel. This view and the reverse (supinated) oblique view help identify fractures involving the hamate, especially the hook of the hamate, and the pisiform[4] (Table 48-1).

CARPAL INJURIES

Scaphoid Fractures

The scaphoid is the most commonly fractured of the carpal bones and accounts for more than 62 to 87% of all carpal fractures.[5] This fracture typically is seen in young adults 15 to 30 years of age and occurs after a fall on the outstretched hand.

PALMAR VIEW WITH STRUCTURES PASSING THROUGH AND OVER CARPAL TUNNEL

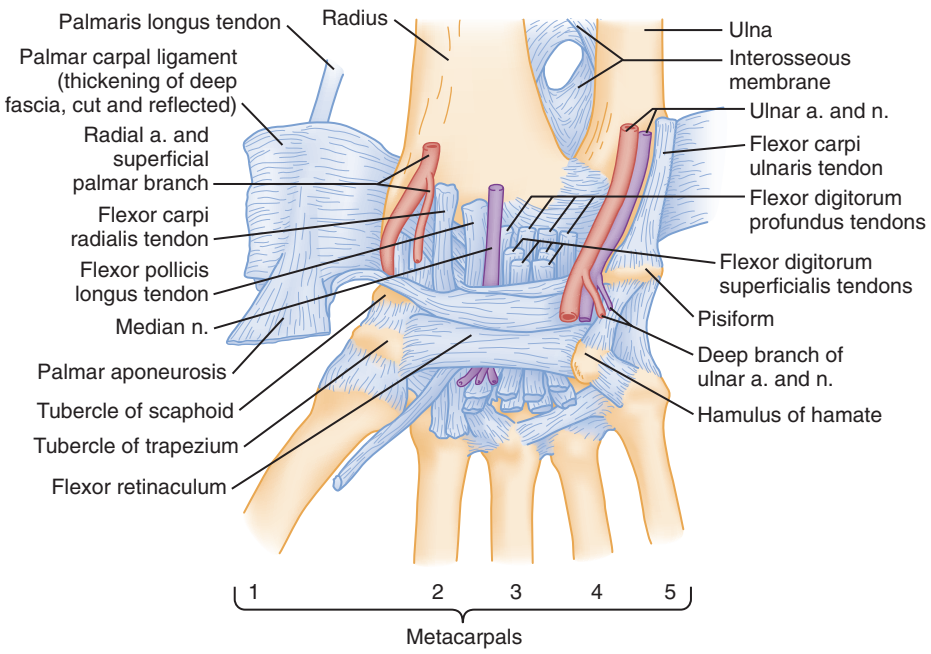


Figure 48-3. Vascular supply to the wrist. Note the relationship of the wrist ligaments to the neurovascular supply to the wrist. (Redrawn from Netter FH: Atlas of Human Anatomy, 3rd ed. Teterboro, NJ, Icon, 2003.)

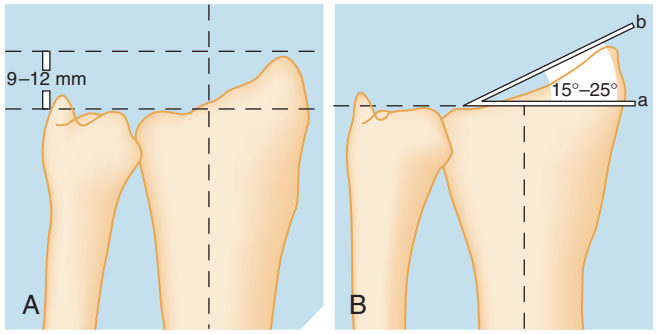


Figure 48-4. Normal radiographic appearance of the wrist on a posteroanterior view. **A,** Radial length measurement. The radial styloid extends 9 to 12 mm beyond the articular surface of the distal ulna. **B,** The ulnar slant of the distal radius normally measures 15 to 25 degrees. (From Greenspan A: Orthopedic Radiology: A Practical Approach, 2nd ed. New York, Gower Medical Publishing, 1992.)

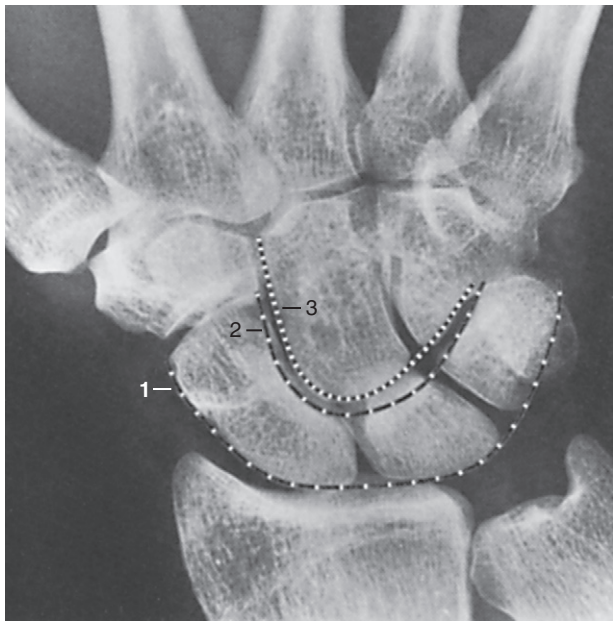


Figure 48-5. Wrist arcs. On a posteroanterior radiographic view of a normal carpus, three arcuate lines (labeled 1 to 3) can be drawn along the carpal articular surfaces. (From Weissman BN, Sledge CB: Orthopedic Radiology. Philadelphia, Saunders, 1986.)

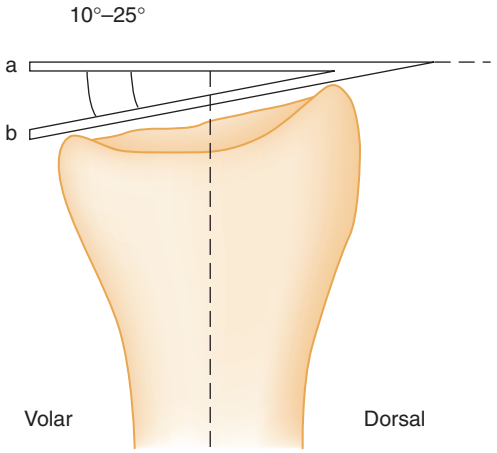


Figure 48-6. Normal radiographic appearance of the wrist on a lateral view. The distal radius has a normal volar tilt of 10 to 25 degrees. (From Greenspan A: Orthopedic Radiology: A Practical Approach, 2nd ed. New York, Gower Medical Publishing, 1992.)

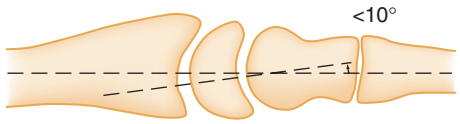


Figure 48-7. Normal relationship of carpal bones on a lateral radiographic view. Concavity of radius and lunate and convexity of capitate form three C-shaped areas *(stippled)* along a straight line that runs through the central axis of these bones.

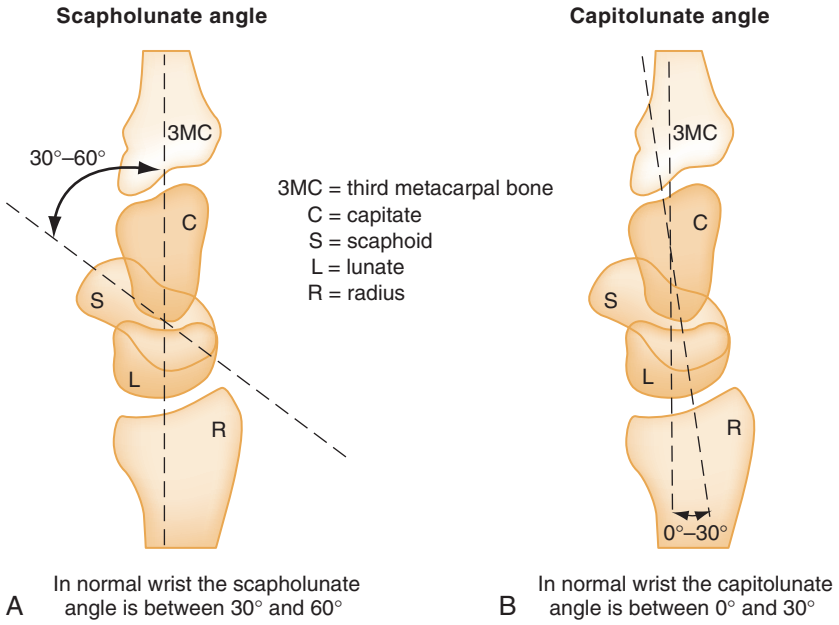


Figure 48-8. **A,** The normal scapholunate angle is formed by the intersection of the longitudinal axes of the scaphoid and lunate and normally measures 30 to 60 degrees. **B,** The normal capitolunate angle is formed by the intersection of the capitate and lunate central long axes and normally measures 0 to 30 degrees. (From Greenspan A: Orthopedic Radiology: A Practical Approach, 2nd ed. New York, Gower Medical Publishing, 1992.)

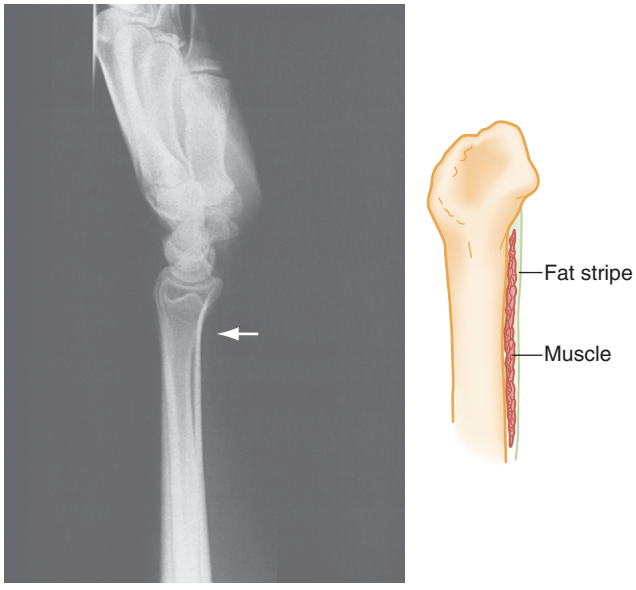


Figure 48-9. The pronator quadratus is a narrow fat stripe *(arrow)* located 1 cm from the volar surface of the radius on the normal lateral wrist view. (From Propp DA, Chin H: Forearm and wrist radiology—Part I. J Emerg Med 7:393, 1989.)

Table 48-1 Additional Radiographic Wrist Views

RADIOGRAPHIC VIEW	BENEFIT
Clenched fist view	Exposes scapholunate ligament injury; pushes capitate into proximal carpal row
Scaphoid view	Elongates scaphoid; exposes wrist fractures
Carpal tunnel view	Identifies fractures involving hamate and pisiform; identifies bony encroachment onto carpal tunnel

Scaphoid fractures are rare in skeletally immature patients because the carpus is composed entirely of cartilage at birth and remains predominantly cartilaginous until the late childhood and adolescent years.[6] Fractures of the scaphoid are classified by the anatomic location of the fracture line and may be divided into three groups: fractures of the tuberosity and distal pole, fractures of the wrist, and fractures of the proximal pole. Fractures through the wrist of the scaphoid are the most common of these three patterns and account for approximately 70 to 80% of all scaphoid fractures.[7]

Clinically, patients complain of dorsal radial wrist pain just distal to the radial styloid, with limited range of motion of the wrist and thumb. Classically, physical examination reveals tenderness on palpation of the scaphoid and swelling within the anatomic snuffbox. Pain also may be elicited with palpation of the scaphoid tubercle volarly, with axial compression of the thumb metacarpal, with resisted supination, and with limited thumb range of motion and pain at the end of arc of motion, especially with flexion and radial deviation.[8] Overall, clinical examination has excellent sensitivity for identification of fracture, but low specificity (74 to 80%).[9,10]

Radiographic diagnosis of scaphoid fractures often is difficult, and special scaphoid views should be requested when a fracture is suspected on the basis of the clinical findings. A visible fracture lucency may be occult, and a more subtle change such as obliteration or displacement of the scaphoid fat pad may be the only clue to the presence of a fracture, although these signs are not reliably present.[11] Plain radiographs taken soon after injury fail to detect 14% of scaphoid fractures.[12] For this reason, and because of the associated risk of nonunion when diagnosis and immobilization are delayed, patients clinically suspected of having a scaphoid fracture were often treated with cast immobilization. Recent evidence, however, has called into question the practice of immobilizing the wrist in all patients with suspected scaphoid injuries and has suggested that the use of more advanced imaging modalities is both accurate and cost-effective and that such studies should be performed earlier rather than later. Cost of time off from work and serial casting and office visits easily exceed the cost of a magnetic resonance imaging (MRI) study or computed tomography (CT) scan for definitive diagnosis.[13,14]

Historically, bone scans were used 72 to 96 hours after injury to detect scaphoid fracture.[15,16] Currently, MRI is used to detect these radiographically occult fractures, with sensitivity rates of 100%. A strong correlation has been shown between bone scan and MRI of the scaphoid.[16,17]

Treatment of uncomplicated, undisplaced scaphoid fractures involves immobilization in a short arm thumb spica cast (Fig. 48-10), although some specialists prefer to use a long arm cast for the first 2 weeks of immobilization, replacing this with a short arm cast for the remainder of the immobilization period.

Figure 48-10. Thumb spica cast.

The duration of immobilization varies relative to the location of the fracture but averages 12 weeks, with the more proximal fractures requiring longer immobilization to ensure adequate healing. This variability in healing time is related directly to the pattern of blood supply to the scaphoid, which flows from the distal to the proximal portion of the bone through the scaphoid tuberosity. This pattern of blood flow also accounts for the higher incidence of avascular necrosis (AVN) and fracture nonunion in the more proximal fractures. Overall, AVN is seen in approximately 13 to 40% and nonunion in 5 to 12% of scaphoid fractures, with the risk of complications being greatest in fractures of the proximal pole.[18-20] Because of the increased risk of AVN or nonunion, any scaphoid fracture that is displaced more than 1 mm or is associated with an increase in the normal scapholunate or capitolunate angles requires prompt orthopedic referral for consideration of operative treatment.

Lunate Fractures

Fractures of the lunate are relatively uncommon, representing fewer than 1.4% of all carpal fractures.[21] This injury occurs more commonly in persons with a congenitally short ulna, owing to compromise of the normal triangular fibrocartilage support. The usual mechanism of injury involves a fall on the outstretched hand, causing extreme dorsiflexion, with transmittal of the resultant force from the capitate to the lunate. Patients have pain over the dorsum of the wrist, which is exacerbated by axial loading of the long finger metacarpal. On examination, tenderness may be elicited by palpation over the dorsum of the wrist in the depression felt just distal to Lister's tubercle.

Fractures of the lunate may be difficult to see on plain radiographs because of overlap of the distal radius, ulna, and other carpal bones. For this reason, and because of the risk of avascular necrosis in missed injuries, suspected lunate fractures should be immobilized in a short arm cast until a fracture can be confirmed or excluded by CT or MRI.

Lunate fractures are treated with immobilization in a short arm cast, with orthopedic follow-up evaluation in 1 to 2 weeks. Complications include progression to carpal instability, nonunion, and AVN. Posttraumatic AVN is a sequela in 20% of fractures and is called *Kienbock's disease.* In well-established

cases of Kienbock's disease, the lunate appears sclerotic and fragmented on radiographic examination, and ultimately the bone collapses with resultant proximal migration of the capitate. These changes cause secondary osteoarthritis of the radiocarpal joint and chronic wrist pain. Treatment involves operative intervention, with correction of the articular abnormalities either by lengthening the ulna or by shortening the radius. In more advanced cases, excision and prosthetic replacement of the lunate or arthrodesis may be necessary.[22]

Triquetral Fractures

Fracture of the triquetrum, the second most common fracture of the carpals, usually results either from a direct blow to the bone, causing a fracture of the body, or from a fall on the outstretched hand. In the latter scenario, the mechanism of fracture is believed to be impact of the ulnar styloid or proximal hamate against the triquetrum, which results in a dorsal chip fracture.[23] Patients have localized tenderness over the dorsum of the wrist just distal to the ulnar styloid. On physical examination, swelling may be noted in this same area, and wrist motion is limited because of pain. The fracture is best seen on the standard lateral view of the wrist as a small dorsal chip fragment, although a more oblique pronated lateral view may be necessary (Fig. 48-11). Treatment with immobilization in a short arm cast or splint usually results in an uncomplicated course, with prompt fracture healing over 4 to 6 weeks.

Pisiform Fractures

The pisiform is a unique carpal bone because it is a sesamoid bone that lies within the flexor carpi ulnaris tendon and articulates on its dorsal surface with the triquetrum. Fractures of the pisiform usually occur from a fall on the outstretched hand but also may be seen with direct blows to the hypothenar eminence. On clinical examination, there is tenderness over the ulnar aspect of the volar wrist crease, which may be exacerbated with wrist flexion and ulnar deviation.[24] Fractures of the pisiform can impinge on Guyon's canal, resulting in ulnar nerve injury. Paresthesias in the distribution of the ulnar nerve and hand clumsiness from intrinsic muscle dysfunction can occur. Pisiform fractures are poorly seen on routine wrist radiographs, so special views must be requested. A reverse (supinated) oblique view and the carpal tunnel view allow for better visualization of these fractures.[4]

Fractures of the pisiform generally carry an excellent prognosis and are treated with immobilization in a short arm cast or splint for 3 to 4 weeks. In injuries with evidence of nerve compromise, orthopedic consultation for possible urgent surgical decompression is indicated to restore nerve function. Fractures that are complicated by nonunion may require excision of the pisiform to prevent chronic pain.

Figure 48-11. Triquetral dorsal chip fracture: Lateral wrist view.

Hamate Fractures

Hamate fractures are rare and account for approximately 2% of all carpal bone fractures. The hook or hamulus is the most common site of fracture, although fractures through the articular surfaces and body also are seen. Fracture of the hook usually occurs from a fall on the outstretched hand or from a direct blow to the palm of the hand. Commonly, the use of hammers and vibration from equipment also can cause fractures. Patients present with pain over the hypothenar eminence with associated decreased grip strength. Pain may be localized on palpation of the hamate, 1 cm distal and radial to the pisiform. Fractures of the hamate body and articular surface usually are seen on posteroanterior views of the wrist, but fractures of the hook are seen best on the reverse oblique and carpal tunnel views.[4] When findings on these views are inconclusive, a CT scan may allow confirmation of fracture.[5,25] Plain radiographs can detect 71% of hamate fractures, whereas CT scan is 100% sensitive.[5]

Initial treatment is by immobilization in a short arm cast with orthopedic follow-up evaluation in 1 to 2 weeks. Fractures of the hook of the hamate often are complicated by associated ulnar nerve injury or progression to nonunion. In both instances, operative intervention with excision of the hook at the fracture site is necessary.[5]

Trapezium Fractures

Fractures of the trapezium are uncommon and represent only 1 to 5% of all carpal injuries. There are two main types of fractures: fractures involving the body and fractures involving the trapezial ridge. A direct blow to the adducted thumb causes fracture through the body of the trapezium, with transmittal of the force by the base of the thumb metacarpal. Avulsion fractures of the trapezial ridge occur with forceful radial deviation or rotation of the wrist. On examination, patients complain of pain with movement of the thumb and on direct palpation of the trapezium just distal to the scaphoid in the anatomic snuffbox. Fractures are seen best on slightly pronated oblique views of the wrist, although a true anteroposterior view of the trapezium (Roberts' view) or CT scan may be necessary.[26] These injuries are treated with immobilization in a thumb spica cast for 6 weeks, unless the fracture is displaced or involves the carpometacarpal joint, in which case referral for open reduction and fixation is indicated.

Capitate Fractures

The capitate lies in a central position in the distal carpal row, and because of this protected location, it is rarely fractured. When fracture does occur, the mechanism generally is a direct blow to the dorsum of the wrist. Fracture also may be seen in association with a perilunate dislocation after a fall on the outstretched dorsiflexed hand. Clinical examination reveals dorsal wrist pain and swelling, with localized tenderness on palpation of the capitate. Fractures usually are visible on the standard posteroanterior view of the wrist, although the lateral view may be helpful in determining the presence of rotation or displacement of the fracture fragment.

Undisplaced isolated fractures of the capitate may be managed with immobilization in a short arm cast for 6 weeks. Any fracture with displacement or associated carpal dislocation requires prompt orthopedic referral for open reduction and fixation. Complications of nonunion and avascular necrosis of the proximal fragment are rare, but do occur, because the capitate receives its blood supply through its distal half.[24]

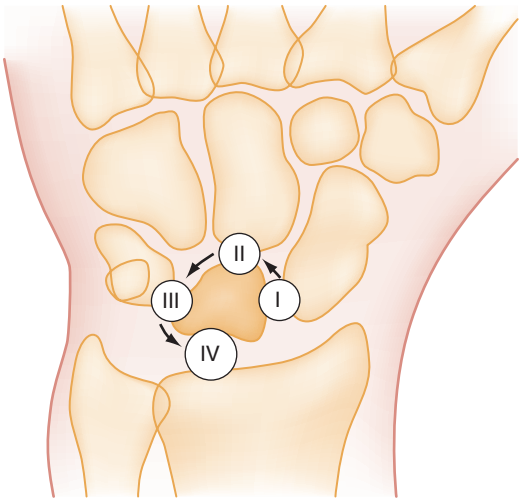


Figure 48-12. Sequential stages of carpal dislocation. Each of four stages represents a sequential intercarpal ligament injury proceeding around the lunate. (From Greenspan A: Orthopedic Radiology: A Practical Approach, 2nd ed. New York, Gower Medical Publishing, 1992.)

Trapezoid Fractures

The trapezoid rarely is fractured; such fractures account for less than 1.3% of all carpal bone fractures.[5] Trapezoid fractures most commonly are seen in association with other carpal fractures. The typical mechanism of injury is a direct blow down the long axis of the index metacarpal, which may result in isolated fracture to the trapezoid or may cause a dorsal fracture-dislocation. On clinical examination, pain and tenderness are localized over the dorsum of the wrist at the base of the second metacarpal. The fracture may be visible on routine posteroanterior views of the wrist; however, oblique views or CT may be necessary to visualize this injury. Undisplaced fractures are treated with immobilization in a short arm cast for 6 weeks, and fracture-dislocations warrant prompt orthopedic referral for reduction and fixation.[24]

Carpal Instability

Mayfield and associates[27] described a progressive pattern of carpal ligamentous injury caused by wrist hyperextension, ulnar deviation, and intercarpal supination. Their studies of the pathomechanics of these injuries led to the classification of carpal instability into four distinct stages. Each stage represents a sequential intercarpal injury beginning with scapholunate joint disruption and proceeding around the lunate, creating progressive carpal instability (Fig. 48-12). Each stage also may be associated with specific bony fractures, which if present should alert the physician to the possibility of an occult perilunate ligamentous injury. These associated fractures include fractures of the radial styloid, scaphoid, capitate, and triquetrum.

A *stage I injury*, or scapholunate dissociation, results in a characteristic widening of the scapholunate joint on the posteroanterior view, which has been called the "Terry Thomas sign," after the British comedian with a gap between his front teeth.[28] If associated with rotary subluxation of the scaphoid, the scaphoid is seen end on with the cortex of the distal pole appearing as a ring shadow over the scaphoid; this is called the *signet ring sign* (Fig. 48-13). The radiographic appearance may be normal on routine views, so when a scapholunate ligament injury is suspected clinically, additional stress views should be obtained. Views taken with a clenched fist and with ulnar deviation (the clenched-fist anteroposterior view) accentuate widening of the scapholunate joint.

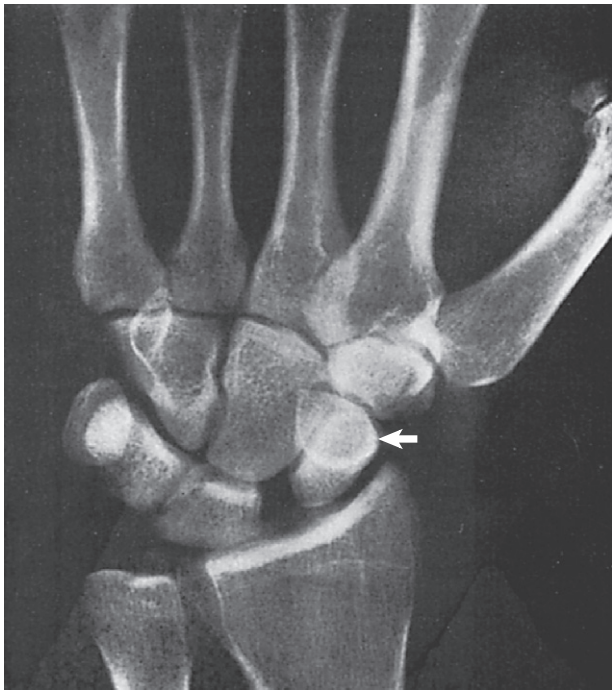


Figure 48-13. Scapholunate dissociation with scaphoid subluxation. Posteroanterior wrist view shows characteristic widening of the scapholunate joint and a ring shadow over the scaphoid *(arrow)*. (From Sonnenberg J: Carpal injuries. Trauma Q 1:71, 1985.)

A stage *II injury*, or perilunate dislocation, is seen best on the lateral view of the wrist. Although the lunate remains in position relative to the distal radius, the capitate is dorsally dislocated. The posteroanterior view shows overlap of the distal and proximal carpal rows and also may show an associated scaphoid fracture or subluxation[29] (Fig. 48-14).

A *stage III injury* appears identical to a stage II injury but includes a dislocation of the triquetrum that is seen best on the posteroanterior view, with overlap of the triquetrum on the lunate or hamate. This injury may be associated with a volar triquetral fracture.

Figure 48-14. Perilunate dislocation. The lateral radiographic view shows the lunate in normal position and the capitate dorsally dislocated. (From Propp DA, Chin H: Forearm and wrist radiology—Part I. J Emerg Med 7:393, 1989.)

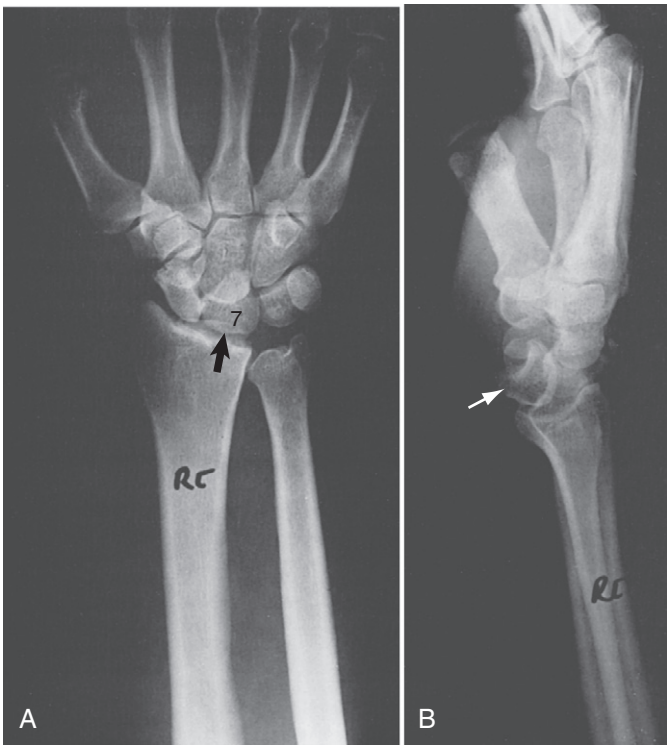


Figure 48-15. Lunate dislocation. **A,** This posteroanterior view shows the characteristic triangular shape of the lunate bone *(7, arrow)*. **B,** Volar displacement of the lunate resembles a spilled teacup on the lateral view *(arrow)*, with dorsal displacement of the capitate. (From Propp DA, Chin H: Forearm and wrist radiology—Part I. J Emerg Med 7:393, 1989.)

A *stage IV injury*, or lunate dislocation, results in a characteristic triangular appearance of the lunate on the posteroanterior view that is due to the rotation of the lunate in a volar direction. This triangular appearance is known as the "piece of pie sign." This rotation also is visible on the lateral view of the wrist, in which the lunate looks like a cup tipped forward and spilling its contents into the palm. This latter appearance is called the "spilled teacup sign." On the lateral view, the capitate is seen to lie posterior to the lunate and often has migrated proximally to contact the distal radius (Fig. 48-15).

Patients with these carpal dislocation injuries typically have a history of a fall on the outstretched hand. They complain of pain and swelling over the dorsum of the wrist, with limited range of motion. On physical examination, tenderness to palpation is noted over the dorsum of the wrist, particularly in the region of the scapholunate ligament. With perilunate and lunate dislocations, visible deformity of the wrist also is apparent, and two-point sensation in the median nerve distribution often is diminished. A provocative maneuver such as *Watson's scaphoid shift test* often will increase pain and produce a clunk or snap.[30] Complications of carpal dislocation injuries include median nerve injury and chronic carpal instability with resultant degenerative arthritis.

Bone scintigraphy is a nonspecific test for scapholunate instability. It may be somewhat useful when findings are negative; however, positive findings simply localize the site of injury. MRI has been shown to have relatively low sensitivity (63%) and specificity (86%) for the diagnosis of scapholunate injury.[31,32] Arthroscopy has become the "gold standard" modality for identifying and grading scapholunate injuries. It allows superior detection of internal derangement of wrist ligaments and a more accurate visualization of the articular surfaces.[33]

Carpal dislocation injuries require orthopedic consultation in the emergency department for reduction and stabilization. Either arthroscopically guided reduction and pinning or open reduction with ligament repair is now recommended for the optimal management of these acute injuries.

Intercalated Segment Instability

Not all patterns of carpal instability follow the pattern described by Mayfield and associates.[29] Two other common types of carpal instability—*dorsal intercalated segment instability* (DISI) and *volar intercalated segment instability* (VISI)—are better understood as a pattern of midcarpal joint collapse[34] (Fig. 48-16). These patterns of carpal instability are recognized radiographically by specific deformities on the lateral view of the wrist (Fig. 48-17).

With the DISI pattern of instability, there is dorsiflexion of the lunate relative to the capitate, which results in an increase in the scapholunate and capitolunate angles. With the VISI pattern of instability, there is volar flexion of the lunate relative to the capitate, with a decrease in the scapholunate angle and an increase in the capitolunate angle. These angles are best visualized on the lateral view radiograph, on which the articular surface of the lunate appears to be tilting dorsally (in DISI) or volarly (in VISI). DISI is the most common pattern of carpal instability and may occur after scapholunate dissociation or with scaphoid fractures with or without associated perilunate dislocation. VISI occurs after lunotriquetral or triquetrohamate joint disruption. Either pattern may be seen in association with radiocarpal joint malalignment, as is seen in lunate collapse with Kienbock's disease, rheumatoid arthritis, or congenital carpal ligamentous laxity.[34,35]

Clinically, patients have chronic pain, weakness, and limited range of motion of the wrist and may complain of the wrist clicking with ulnar deviation. On physical examination, point tenderness can be elicited over the area of primary injury, usually the scapholunate or lunotriquetral joints. Gross deformity of the wrist, resulting from subluxation, also may be apparent on comparison with the unaffected "normal" wrist. Patients should be referred to an orthopedic surgeon for definitive treatment of these injuries. Operative treatment involves reduction and stabilization, with ligamentous reconstruction or repair.

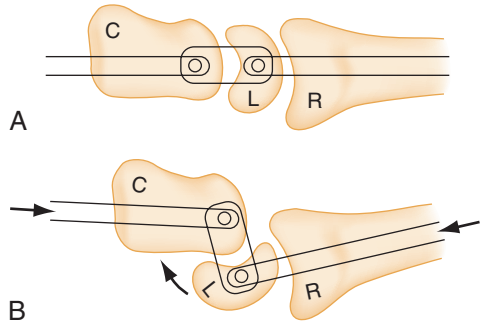


Figure 48-16. The wrist as a link mechanism. **A,** The distal radius (R), proximal carpal row (represented by the lunate [L]), and distal carpal row (represented by the capitate [C]) compose the individual links of this mechanism. **B,** With axial compression *(arrows)*, carpal collapse occurs in a zigzag pattern if there is loss of the carpal longitudinal supports (the scaphoid and ligamentous attachments). (From Green DP: Operative Hand Surgery, vol 1, 3rd ed. New York, Churchill Livingstone, 1993.)

DISTAL RADIUS AND ULNA INJURIES

Colles' Fracture

Colles' fracture, first described in 1814, is the most common wrist fracture seen in adults.[36] It is a transverse fracture of the distal radial metaphysis, which is dorsally displaced and angulated. The fracture usually is located within 2 cm of the radial articular surface and may be associated with intra-articular extension into the radiocarpal or radioulnar joints. There is commonly an associated fracture of the ulnar styloid.

Clinically, patients have a history of a fall on the outstretched hand and complain of immediate pain and swelling over the dorsum of the wrist. On examination, there is an obvious "dinner fork" deformity of the wrist caused by the dorsal displacement and angulation of the fracture. A neurovascular examination should be performed to exclude an associated median nerve injury or vascular compromise caused by this deformity or by fracture fragments.

The posteroanterior and lateral views of the wrist show the fracture through the radial metaphysis. The posteroanterior view may show extension of the fracture into the radioulnar or radiocarpal joints and shows the amount of radial shortening present. The degree of dorsal displacement and angulation is best seen on the lateral view, with loss of the normal volar tilt of the distal radial articular surface (Fig. 48-18).

Colles' fracture requires early anatomic reduction with full restoration of radial length and correction of the dorsal angulation either to a neutral position or ideally to the normal volar tilt position. Closed reduction, using local or regional anesthesia, with cast immobilization is successful in most cases (Fig. 48-19). An effective method of anesthesia is placing a 22-gauge needle in the dorsum of the distal radius, withdrawing until a hematoma is encountered, then instilling 5 to 10 mL of 2% lidocaine (Xylocaine) (Fig. 48-20). Use of finger traps also is an effective means of obtaining the reduction to allow positioning for casting (Fig. 48-21). The more comminuted and

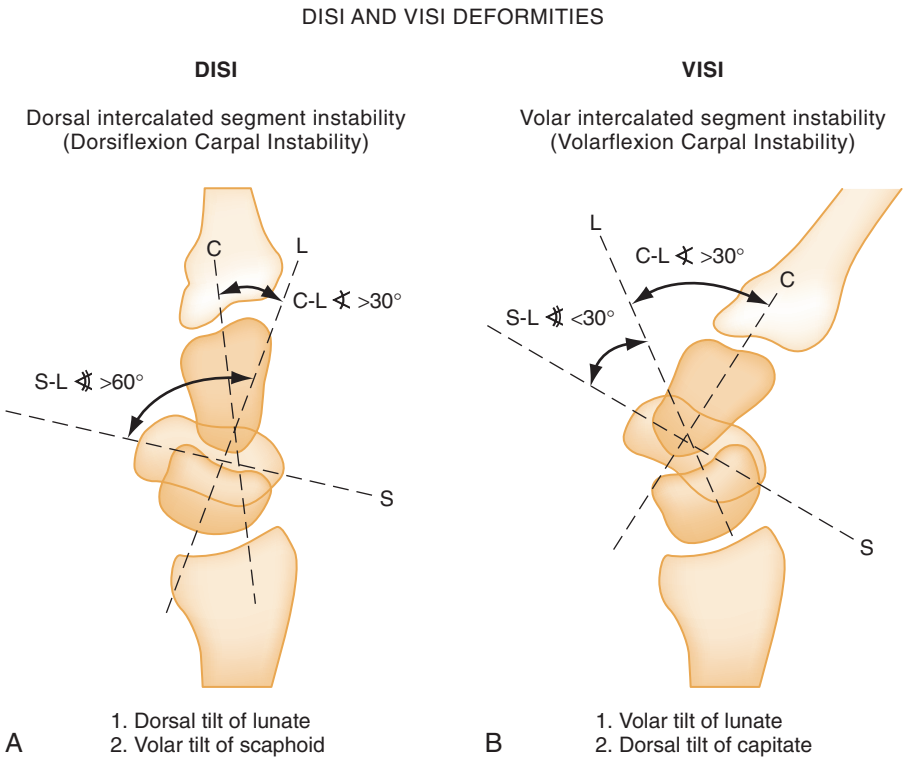


Figure 48-17. **A,** Dorsal intercalated segment instability (DISI). In this pattern of carpal instability, the scapholunate angle measures more than 60 degrees, and the capitolunate angle measures more than 30 degrees. **B,** Volar intercalated segment instability (VISI). In this pattern of carpal instability, the scapholunate angle measures less than 30 degrees, and the capitolunate angle measures more than 30 degrees. (From Propp DA, Chin H: Forearm and wrist radiology—Part I. J Emerg Med 7:393, 1989.)

Figure 48-18. Colles' fracture. **A,** Posteroanterior view shows fracture and shortening of the radius. **B,** Lateral view shows typical dorsal displacement and angulation of the radial fracture. (From Propp DA, Chin H: Forearm and wrist radiology—Part I. J Emerg Med 7:393, 1989.)

Figure 48-19. Short arm cast.

Figure 48-20. Hematoma block.

Figure 48-21. Finger traps.

Table 48-2 Criteria for Reduction of Colles-Type Distal Radius Fractures

- Intra-articular step-off >1 mm
- Radial inclination <15 degrees
- Volar tilt less than neutral (0 degrees)
- Shortening or loss of radial length greater than 2 mm as compared with the opposite side

displaced the fracture, the more likely it is that operative reduction will be necessary. Complicated fractures with significant displacement (more than 20 degrees of dorsal angulation), marked dorsal comminution, or intra-articular extension merit close follow-up by an orthopedic specialist, because loss of reduction is frequent with these injuries, mandating early operative reduction with internal or external fixation. Immediate referral to an orthopedic surgeon should be considered if initial attempts at closed reduction are unsuccessful, if there is associated neurovascular compromise, or if the fracture is open. (Table 48-2).

Complications of Colles' fracture are seen most often in elderly patients and in patients with inadequate fracture reduction.[37,38] Median nerve injury may occur acutely either from traction from the original fracture displacement or with direct injury to the nerve by fracture fragments. Injury to the median nerve also has been described after closed reduction because of traction on the nerve, direct pressure from the cast or related to position of immobilization, or swelling causing compression in the carpal tunnel. Treatment entails repositioning, decreasing the splint pressure, or occasionally carpal tunnel release. For this reason, it is important to document neurologic function before and after fracture reduction. A more common complication is malunion of the fracture, resulting in chronic wrist pain and limited range of motion. This

complication is more likely to arise in cases of fracture involving the radiocarpal joint.

Smith's Fracture

Smith's fracture is a transverse fracture of the metaphysis of the distal radius, with associated volar displacement and volar angulation. In some cases, the fracture may extend into the radiocarpal joint. Because the resultant deformity is opposite to that seen in Colles' fracture, Smith's fracture often is called a *reverse Colles' fracture*. The typical mechanism of injury involves a direct blow to the dorsum of the wrist or a fall onto the dorsum of the hand resulting in extreme palmar flexion. The fracture also may be seen after a fall backward on an outstretched hand with the forearm in supination. The patient has a swollen, painful wrist, which is deformed, with fullness visible on the volar aspect. The fracture is visible on posteroanterior and lateral radiographs of the wrist, but the lateral view best shows the degree of volar displacement and angulation (Fig. 48-22).

Treatment of this fracture involves closed reduction with cast immobilization for 6 to 8 weeks; however, molding of the cast to maintain the reduction can lead to median nerve compression. Orthopedic consultation is recommended because open reduction and internal fixation may be required. Complications include median nerve injury, malunion, and posttraumatic arthritis, especially in fractures with significant displacement or intra-articular extension. As with Colles' fracture, prognosis is most favorable in patients with successful reduction, with restoration of the normal radial length and volar tilt.[39]

Figure 48-22. Smith's fracture. **A,** Posteroanterior view shows a metaphyseal fracture of the radius with shortening. **B,** Lateral view shows volar displacement of the distal fracture fragment along with the carpus. (From Propp DA, Chin H: Forearm and wrist radiology—Part I. J Emerg Med 7:393, 1989.)

Barton's Fracture

Barton's fracture is an oblique intra-articular fracture of the rim of the distal radius, with displacement of the carpus along with the fracture fragment. The fracture may involve the dorsal rim of the radius with dorsal carpal subluxation (classic Barton's fracture), or it may involve the volar rim with volar carpal subluxation (volar Barton's fracture). These fractures are rare and account for only 0.5 to 1.6% of all distal radius fractures.[42] The volar–anterior margin fracture is seen more often than the dorsal–posterior margin fracture.

The mechanism of injury for these fractures is a high-velocity impact across the articular surface of the radiocarpal joint, with the wrist in either volar flexion (causing a volar rim fracture) or dorsiflexion (causing a dorsal rim fracture). Volar and dorsal rim fractures are easily visible on posteroanterior and lateral wrist radiographs; however, the lateral view best shows the degree of articular surface involvement and the amount of associated fracture displacement (Fig. 48-23).

Treatment of these fractures requires orthopedic consultation for reduction and stabilization. Closed reduction occasionally may be successful. Most authorities now advocate early operative management, however, with either closed reduction performed under fluoroscopy followed by percutaneous pinning or open reduction and internal fixation to restore accurately the articular surface of the radius and stabilize the carpus.[40] Complications include posttraumatic arthritis of the radiocarpal joint and delayed carpal instability. Both complications are seen more commonly when reduction fails to achieve or maintain anatomic realignment of the radiocarpal joint surface.

Hutchinson's Fracture

Hutchinson's fracture, or chauffeur's fracture, is an intra-articular fracture of the radial styloid. The mechanism of injury is usually a direct blow or fall resulting in trauma to the radial side of the wrist. The term chauffeur's fracture originated in the era of hand-cranked automobiles, when this injury occurred because of direct trauma to the radial side of the wrist from the recoil of the crank. The fracture is seen best on the posteroanterior view of the wrist, as a transverse fracture of the radial metaphysis with extension through the radial styloid into the radiocarpal joint (Fig. 48-24).

Nondisplaced fractures may be immobilized in a short arm cast for 4 to 6 weeks; however, displaced fractures require open or closed reduction and fixation. Because the radial styloid is the primary site of attachment for many of the ligaments of the wrist, accurate fracture reduction and union are crucial.[41] Complications of radial styloid fracture include associated scapholunate ligament disruption and posttraumatic arthritis, both of which are more likely when there is fracture displacement.

Radioulnar Joint Disruption

Dislocation of the DRUJ may be seen in association with distal radial fractures and Galeazzi's fractures. It also may be seen as an isolated injury without fracture. Diagnosis often is difficult because plain radiographs commonly are reported as normal in appearance, so certain characteristic findings on careful clinical examination may constitute the only clue to the presence of this injury.

The typical mechanism of injury is a fall on the outstretched hand with either hyperpronation, resulting in dorsal dislocation, or hypersupination, causing volar dislocation of the ulna. Another mechanism known to cause DRUJ dislocation is that

Figure 48-23. Volar Barton's fracture. Lateral radiographic view shows typical oblique intra-articular fracture of the volar rim of the radius with associated volar displacement of the distal radial fragment along with the carpus. (From Harris JH, et al: The Radiology of Emergency Medicine, 3rd ed. Baltimore, Williams & Wilkins, 1993.)

Figure 48-24. Hutchinson's fracture. Posteroanterior radiographic view shows intra-articular fracture of the radial styloid. (From Greenspan A: Orthopedic Radiology: A Practical Approach, 2nd ed. New York, Gower Medical Publishing, 1992.)

obtained when the hand is caught in rotating machinery, resulting in the same forcible hyperpronation or supination. This forcible rotation of the wrist causes disruption of the triangular fibrocartilage complex, the major stabilizer of the DRUJ, and may result in an associated avulsion fracture of the ulnar styloid.

Patients with this injury have a history of sudden onset of pain with a "snapping" sensation in the wrist, swelling, and limited range of motion. On examination, tenderness is present over the ulnar aspect of the wrist, with palpable crepitus on supination and pronation. With a dorsal dislocation of the ulna, the ulnar styloid appears more prominent than on the unaffected side, and significant pain and limitation of movement are noted on supination of the wrist. With a volar dislocation of the ulna, there is loss of the normal ulnar styloid prominence, with pain and limitation of movement on pronation. These characteristic clinical findings should alert the physician to the possibility of DRUJ disruption and prompt the appropriate investigations to confirm the presence or absence of this injury.

Plain radiographs of the wrist may show the presence of DRUJ dislocation, but pain and inability of the patient to rotate the wrist fully may cause a false-negative result because a true lateral view cannot be obtained. It also is important to assess for radial head fractures because these fractures commonly are associated with DRUJ disruption. If there is significant clinical suspicion of injury and the radiographic appearance is normal, a CT scan of the DRUJ is recommended.[42,43]

Treatment of these acute injuries requires orthopedic consultation for reduction and stabilization. Closed reduction with the forearm in supination followed by application of a long arm cast often is successful. Alternatively, open reduction frequently is necessary with volar dislocations because the ulnar head often is locked on the volar distal radius. Operative reduction also is necessary in dorsal dislocations to repair the associated injury to the triangular fibrocartilage complex. Immobilization in a long arm cast usually is maintained for 6 weeks.

Pediatric Fractures of the Distal Radius

Fractures of the distal radius in children may be divided into two types: fractures involving the distal radial metaphysis and fractures involving the growth plate. They usually occur as a result of a fall on an outstretched hand with the wrist forcibly dorsiflexed. Fractures of the radial metaphysis are of three types: torus fractures, greenstick fractures, and complete fractures.

The torus fracture is the most common of these fractures and results in a buckling of the radial cortex, which, because of the strong periosteum, occurs without significant displacement (Fig. 48-25). These fractures are treated with immobilization in a short arm cast with orthopedic follow-up evaluation. Healing usually occurs over 2 to 3 weeks, and complications are rarely seen.[44]

Greenstick fractures also are incomplete metaphyseal fractures, with disruption of the cortex on one side and angulation or bowing on the opposite side. By definition, these fractures are displaced and require reduction achieved with use of regional or general anesthesia if angulated more than 10 degrees. Angulations of less than 10 degrees usually remodel.

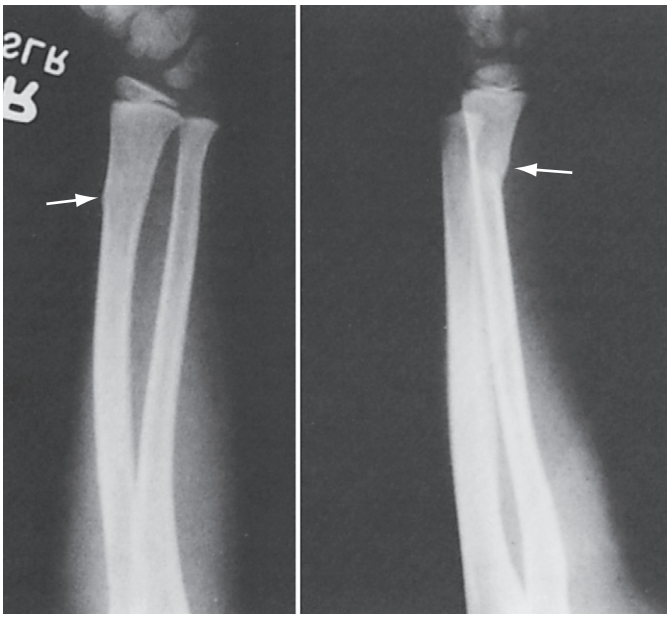


Figure 48-25. Torus fracture of the distal radius. Anteroposterior *(left)* and lateral *(right)* radiographic views of the wrist show a radial torus fracture with buckling of the radial cortex. (From Dvorkin ML: Office Orthopaedics. Norwalk, Conn, Appleton & Lange, 1993.)

Short arm well-molded cast immobilization is recommended, with close orthopedic follow-up to ensure maintenance of reduction.

Complete fractures of the radial metaphysis involve complete disruption of both cortices of bone and usually result in significant displacement and angulation. These fractures also may be associated with a fracture of the distal ulna. Closed reduction by an orthopedic surgeon with use of regional or general anesthesia may be successful, but if alignment is unsatisfactory or if the fracture is unstable, open reduction with internal fixation may be necessary.[45]

In 1963, Salter and Harris classified growth plate injuries in children (Table 48-3). Growth plate or physeal fractures of the distal radius are usually Salter-Harris type I or type II. Although these injuries result in disruption of the growth plate, they rarely result in growth disturbance.[46] Type I injuries cause pain and palpable tenderness over the distal radial physis, with the only radiographic abnormality being volar displacement of the pronator quadratus fat pad. These injuries may be treated with a short arm cast or splint immobilization for 3 to 4 weeks; orthopedic follow-up evaluation within 1 week of the injury is advised. Type II injuries involve a fracture through the radial metaphysis and the physis and are visible on routine wrist radiographs as a triangular metaphyseal fragment on the dorsal surface of the radius (Fig. 48-26). These fractures may be complicated by displacement of the radial epiphysis or by an associated fracture of the distal ulna. If displacement is present, these injuries require orthopedic referral for closed reduction with the patient under general anesthesia and immobilization in a short arm cast for 6 weeks. Operative fixation may be necessary if adequate alignment cannot be achieved or maintained with closed reduction and casting.

Table 48-3 Salter-Harris Classification of Growth Plate Injuries in Children

SALTER-HARRIS TYPE	RADIOGRAPHIC FINDING(S)	COMPLICATION(S)
I	Epiphyseal and metaphyseal separation No fracture visible on radiograph	None
II	Fracture through metaphysis and physis (Thurston Holland sign)	Usually none
III	Fracture through epiphysis to physis	Concern with anatomic alignment High rate of displacement during cast wear
IV	Fracture from epiphysis through physis to metaphysis	Early partial growth arrest Surgical management recommended
V	Severe crush force through epiphysis to an area of the physis Normal appearance on *initial* radiographs	Severe growth arrest with progressive shortening or angular deformity Premature or uneven physeal fusion
VI (Modification of Salter-Harris classification by Mercer Rang)	Peripheral bruise or injury to the perichondrial ring or periosteum at the edge of the physis	Severe growth arrest, angular deformity, or osseous bridge formation between physis and metaphysis Osteochondroma formation

■ SOFT TISSUE INJURIES OF THE WRIST

Carpal Tunnel Syndrome

Carpal tunnel syndrome (CTS) is a neuropathy of the median nerve at the wrist that occurs as a result of compression of the median nerve within the carpal tunnel. CTS is one of the most common nerve entrapment syndromes, with a lifetime incidence of 5.8% in women and 0.6% in men.[47] The transverse carpal ligament and the volar surfaces of the carpal bones form the carpal tunnel. It is a rigid compartment that contains nine flexor tendons (the flexor pollicis longus tendon, four flexor digitorum superficialis tendons, and four flexor digitorum profundus tendons) and the median nerve. Any process, local or systemic, that results in an increase in pressure within this compartment may produce carpal tunnel syndrome.

The most common causes of carpal tunnel syndrome are distal radius fractures and repetitive strain. Carpal tunnel syndrome also can be associated with numerous systemic conditions such as rheumatoid arthritis, hypothyroidism, diabetes mellitus, renal failure, congestive heart failure, acromegaly, and collagen vascular diseases. Each of these systemic diseases is thought to produce an increase in pressure within the carpal tunnel from thickening of the flexor synovia or transverse carpal ligament. Hormonal changes associated with pregnancy and menopause also are known to cause carpal tunnel syndrome, probably from retention of fluid in the soft tissues about the wrist.[48]

The classic symptoms include a gradual onset of numbness, paresthesia, and pain in the thumb, index finger, and long finger. These symptoms often are bilateral and are worse during the night and after strenuous activities. Typically,

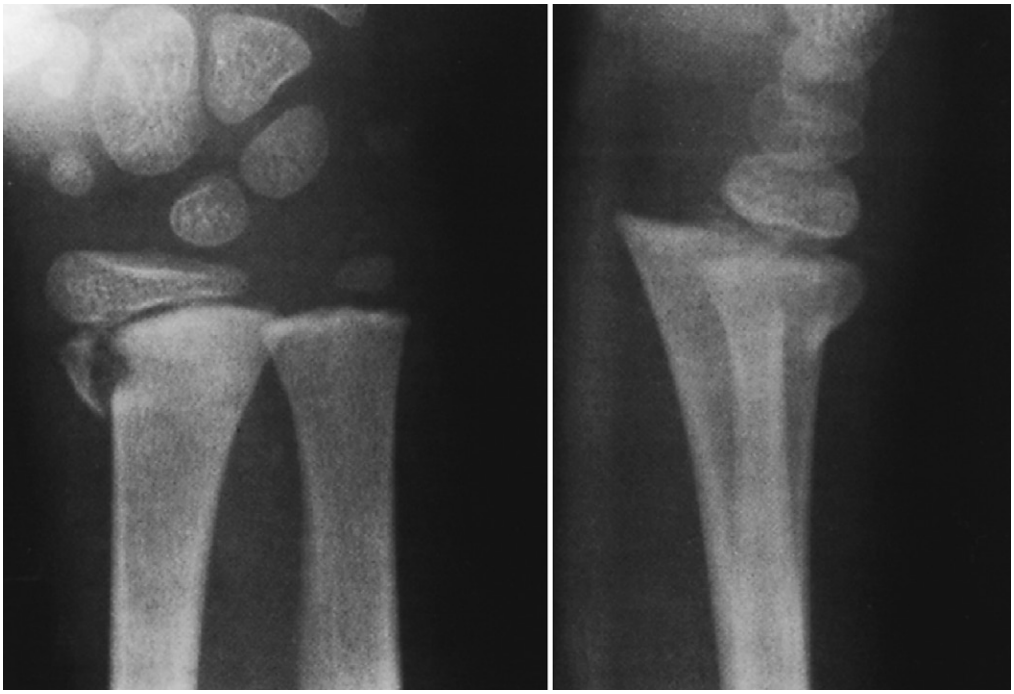


Figure 48-26. Salter-Harris type II distal radial fracture. Anteroposterior *(left)* and lateral *(right)* radiographic views of the wrist show the typical triangular metaphyseal fracture fragment, with associated epiphyseal fracture displacement. (From Harris JH, et al: The Radiology of Emergency Medicine, 3rd ed. Baltimore, Williams & Wilkins, 1993.)

patients report numbness and paresthesias on awakening that lessen when the hands are shaken or held in a dependent position.

Examination of the neck and chest is important to detect cervical radiculopathy or thoracic outlet syndrome, which can mimic carpal tunnel syndrome. The most sensitive provocative test is the wrist flexion test, or Phalen's test (sensitivity of 76% and specificity of 80%)[49] (Fig. 48-27). This test is performed by asking the patient to flex the wrists fully for 60 seconds while holding the forearms in a vertical position. The test result is positive if paresthesias or numbness develops in the median nerve distribution.

Another test is that for Tinel's sign, which is pain or paresthesias in the median nerve distribution elicited by light tapping or percussion over the median nerve at the wrist. Analysis of the literature suggests, however, that Tinel's sign (sensitivity of 42 to 85%; specificity of 54 to 98%) is not as powerful as Phalen's test in detecting median nerve compression, although neither is 100% sensitive.[50] An additional test, Durkan's compression test, which consists of application of pressure directly over the median nerve at the carpal tunnel, has a sensitivity of 87% and specificity of 90%.[51]

Because none of these physical tests is completely reliable in making the diagnosis of carpal tunnel syndrome, nerve conduction studies have been used to confirm the diagnosis, with reports of 85 to 90% sensitivity.[50] MRI and high-resolution ultrasound studies occasionally are used for confirmation, but the diagnosis of carpal tunnel syndrome is primarily clinical.[51]

Conservative (nonoperative) treatment for carpal tunnel syndrome yields variable results. Specific measures include splinting the wrist in a neutral position and cortisone injections in the carpal tunnel. Splinting initially may be prescribed full time for 3 or 4 weeks and then reduced to splinting at night only. Kaplan identified five important factors in determining the success of nonoperative treatment: (1) age older than 50 years; (2) duration longer than 10 months; (3) constant paresthesias; (4) stenosing flexor tenosynovitis; and (5) positive Phalen's test result at less than 30 seconds. Two thirds of patients in his series were cured by medical treatment when none of these factors were present. However, 59.6% with one factor, 83.3% with two factors, and 93.2% with three factors did not improve. No patient with four or five factors was cured by medical management.[52] Nonsteroidal anti-inflammatory drugs have proved to be of little benefit. Surgical release of the flexor retinaculum to unroof the carpal tunnel is indicated when nonoperative management fails.[53,54]

Figure 48-27. Phalen's test.

FOREARM

PERSPECTIVE

Accurate evaluation of forearm injuries requires a thorough knowledge of the complex anatomic relationships between the radius and the ulna. The ulna may be thought of as a stable structure around which the radius rotates, allowing supination and pronation to occur. With any injury to the forearm, the clinician should suspect an associated injury involving the elbow or wrist joints. The clinical and radiologic evaluation of

forearm injuries should include the wrist and elbow. The biomechanical interdependence of the radius and the ulna means that accurate reduction and fixation of forearm fractures will be essential to maintain full pronation and supination.[54] Longitudinal rupture of the interosseous membrane that joins the diaphyseal shafts of the radius and ulna is known as the *Essex-Lopresti lesion*. This condition renders the forearm unstable, painful, and weak, It is difficult to diagnose because the plain radiographic appearance is essentially normal, and MRI is the diagnostic modality of choice.[55]

Anatomy

The bones of the forearm consist of the radius and the ulna, which articulate at each end at the proximal radioulnar joint and the DRUJ. The capsule of the elbow joint and the annular ligament provide soft tissue support at the proximal articulation. Distally, the anterior and posterior radioulnar ligaments and the triangular fibrocartilage complex support the radioulnar joint. Of all of these soft tissue supports, the triangular fibrocartilage complex acts as the major stabilizer of the DRUJ. The interosseous membrane and the supinator, pronator teres, and pronator quadratus muscles join the shafts of the radius and ulna. These muscles act as important supports to the radial and ulnar shafts and are responsible for the significant bone displacement seen with some forearm fractures.

The forearm is divided into two compartments, one volar to the forearm bones and interosseous membrane and one dorsal, and the antebrachial fascia encloses each compartment. The volar compartment contains the flexors and pronators of the wrist and hand, and the dorsal compartment contains the extensor muscles of the wrist and hand. The muscles of each compartment are divided further into a superficial and a deep layer. The nerves and vessels of each compartment lie between the superficial and the deep muscle layers (Table 48-4).

CLINICAL FEATURES

The clinical assessment of patients with forearm injuries begins with a detailed history of the mechanism of injury. The physical examination includes inspection of the injured forearm, taking note of any deformity or discoloration or lacerations of the overlying skin. Observation of the patient's attempts at range of motion at the wrist and elbow joints is important, and results can be compared with range of motion of the "normal" uninjured side. The site of maximal tenderness should be determined by palpation along the entire length of the radius and ulna and by palpation of the soft tissues over the dorsal and volar surfaces of the forearm. The neurovascular examination of the forearm should include evaluation of the brachial artery pulse proximally and the radial and ulnar pulses distally and an assessment of distal radial, median, and ulnar nerve function.

DIAGNOSTIC STRATEGIES: RADIOLOGY

The routine radiographic views of the forearm are anteroposterior and lateral views and should include the wrist and elbow joints. The inclusion of the joint above and below the forearm is crucial because a fracture or dislocation at one end may be associated with a similar abnormality at the opposite end. The normal anatomic relationships between the distal radius and ulna, including the radial length measurement, the normal volar tilt of the radius, and the ulnar slant of the distal radial articular surface, are described in the section on radiology of the wrist (see Fig. 48-4). These same relationships are visible on the anteroposterior view of the forearm. The normal proximal radial alignment is seen best on the lateral view of the forearm, on which a line drawn through the proximal radial shaft and radial head should intersect the capitellum (Fig. 48-28). This *radial line* alignment is particularly important to assess in looking for the presence of a radial head dislocation.

Observing the orientation of several bony projections of the radius and ulna assesses normal alignment of the radial and ulnar shafts. On the normal anteroposterior view, the radial styloid should point in a radial direction, and the biceps tuberosity of the proximal radius should point in an ulnar direction. On the normal lateral view, the ulnar styloid should point dorsally, and the coronoid process of the proximal ulna should

Table 48-4 Structures of Compartments of the Forearm

COMPARTMENT	MUSCLES	NERVES	VESSELS
Volar			
Superficial layer	Pronator teres Flexor carpi radialis Palmaris longus Flexor carpi ulnaris	Median nerve (except for flexor carpi ulnaris: supplied by ulnar nerve)	Ulnar and radial arteries
Deep layer	Flexor digitorum superficialis Flexor pollicis longus Pronator quadratus Flexor digitorum profundus	Median nerve (except for medial half of flexor digitorum profundus: supplied by ulnar nerve)	Ulnar and radial arteries
Dorsal			
Superficial layer	Brachioradialis Extensor carpi radialis longus Extensor carpi radialis brevis Extensor digitorum Extensor digiti minimi Extensor carpi ulnaris	Radial nerve	Ulnar artery
Deep layer	Supinator Abductor pollicis longus Extensor pollicis brevis Extensor pollicis longus Extensor indicis proprius	Radial nerve	Ulnar artery

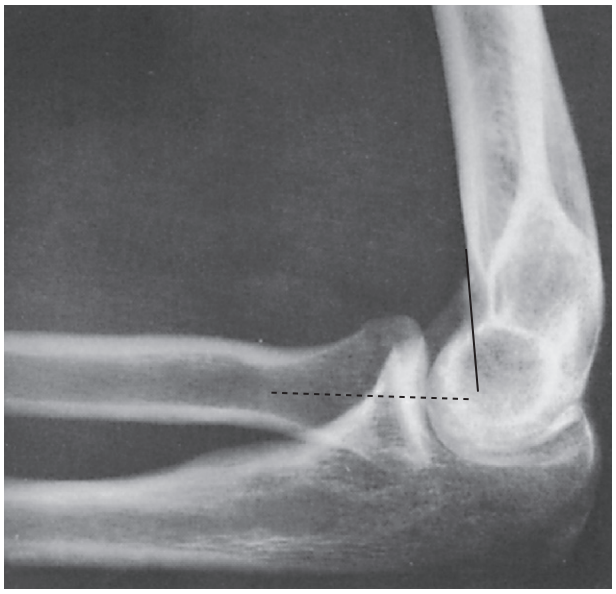


Figure 48-28. Lateral radiographic view of a normal elbow. A line *(dashed)* bisecting the proximal radial shaft also bisects the capitellum. (From Weissman BN, Sledge CB: Orthopedic Radiology. Philadelphia, Saunders, 1986.)

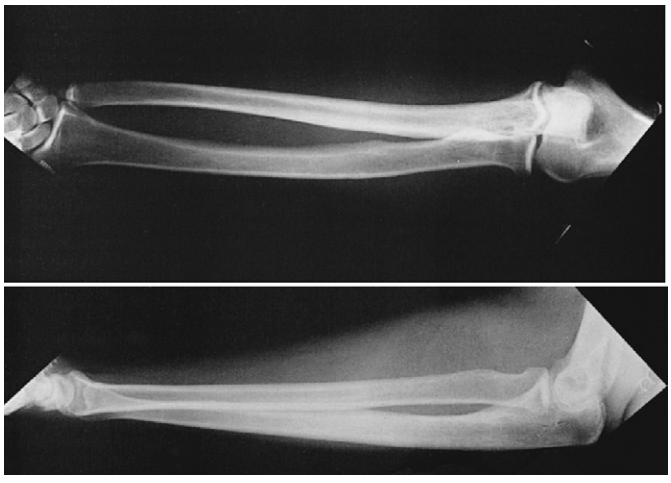


Figure 48-29. Normal anteroposterior *(top)* and lateral *(bottom)* radiographic views of the forearm. Both bones should be visible for their entire length, and the radiograph should include the wrist and elbow joints. (From Propp DA, Chin H: Forearm and wrist radiology—Part I. J Emerg Med 7:393, 1989.)

point volarly. Any alteration in these normal relationships implies an abnormal rotational or axial deformity (Fig. 48-29).

FOREARM FRACTURES

Shaft Fractures of Radius and Ulna

Forearm fractures are among the most common and constitute 20% of all fractures treated in the emergency department.[56] Fracture of the radial and ulnar shafts usually occurs as a result of a direct blow to the forearm but may be seen after a fall on the outstretched hand. In either case, the degree of force required to fracture both bones usually results in fracture displacement. Clinically, patients have obvious deformity of the forearm, with pain and swelling at the fracture site. All movements of the forearm and hand are resisted because of pain. A neurovascular examination is indicated to rule out associated neurologic impairment or early compartment syndrome. Anteroposterior and lateral radiographs of the forearm must include elbow and wrist joints to exclude an associated dislocation or articular fracture. Although these fractures usually are obvious on clinical examination, plain radiography constitutes an accurate means of determining the amount of fracture displacement and comminution.

Undisplaced fractures are rare in adults, but when they do occur, they are treated conservatively with immobilization in a long arm cast for a minimum of 8 weeks. Prompt orthopedic follow-up evaluation and repeat radiographs should be arranged within 1 week of injury to ensure that displacement did not occur after casting.[57] Displaced fractures of the radial and ulnar shafts are treated surgically, with application of an appropriate splint, and an orthopedic referral should be obtained for open reduction and internal fixation. Fracture healing usually is complete in 6 months. Nonunion and malunion may occur in 3 to 5% of cases.[58] The most significant complication of this fracture is a compartment syndrome, which may result from the initial trauma or develop after surgery.

Ulnar Shaft Fractures

Isolated ulnar shaft fractures, or "nightstick fractures," are relatively common and usually are caused by a direct blow to the forearm. Patients have localized pain and swelling over the site of the fracture. Radiographs of the forearm show this fracture and depict the degree of fracture displacement if present.

Undisplaced fractures of the distal third of the ulna may be treated with immobilization in a short arm cast for 6 to 8 weeks. Fractures of the middle or proximal third of the ulna require long arm cast immobilization. Weekly follow-up monitoring is recommended to confirm continued lack of displacement during the period of fracture healing. If loss of fracture position occurs, open reduction and internal fixation are necessary.

Displaced fractures of the ulna are defined as fractures with more than 10 degrees of angulation or fractures with displacement greater than 50% of the diameter of the ulna.[59,60] Whenever significant displacement is present, radiographs should be examined carefully to rule out an associated dislocation of the radial head (Monteggia's fracture). Patients with isolated displaced ulnar shaft fractures should be referred to an orthopedic surgeon for open reduction and internal fixation. Most fractures heal uneventfully, with excellent results. Fractures of the middle third of the shaft may be complicated by nonunion if adequate reduction is not achieved or maintained.[60,61]

Monteggia's Fracture

In 1814, Monteggia described a fracture at the junction of the proximal and middle thirds of the ulna associated with anterior dislocation of the proximal radial head. This original description accounts for only 60 to 65% of proximal ulnar fractures with associated radial head dislocation. The entire spectrum of fracture-dislocations has since been classified by Bado[62] into four types of *Monteggia lesions*, depending on the site of the proximal ulnar fracture and the direction of fracture angulation and associated radial head dislocation. Overall, this injury is rare and accounts for only 1 to 2% of all fractures of the radius and ulna.[63]

The mechanism of injury of Monteggia's fracture is forced pronation of the forearm during a fall on the outstretched hand

or a direct blow to the posterior aspect of the ulna. On clinical examination, pain and tenderness are present at the fracture site, and range of motion is limited at the elbow joint. The forearm may appear shortened compared with the unaffected side, and the radial head dislocation may be palpable in the antecubital fossa. A complete neurovascular examination is essential to rule out an associated radial nerve injury, which may be present in 3 to 70% of cases, although almost all of these neuropraxias heal spontaneously.[63]

The proximal ulnar fracture is readily seen on anteroposterior and lateral radiographs of the forearm, but the elbow joint must be examined carefully to avoid missing the associated radial head dislocation (Fig. 48-30). This dislocation is commonly missed, and delayed diagnosis has been reported in 24% of cases.[64] To avoid overlooking the associated radial head dislocation, the alignment should be confirmed on anteroposterior and lateral radiographs. A line drawn through the radial shaft and head on these views normally should intersect the capitellum on all views.

Treatment of Monteggia's fracture is surgical, and immediate orthopedic referral should be arranged for definitive open reduction and internal fixation. An exception may be made in a pediatric patient, in whom closed reduction followed by a long arm cast may be effective. Casts should be in a flexed and supinated position to maintain fracture position. Flexion should be as close to 90 degrees as possible while ensuring the maintenance of a good radial pulse. Common complications include malunion or nonunion of the ulna fracture with redislocation or subluxation of the radial head. These complications are more likely to occur when the diagnosis has been delayed or when fracture fixation has been inadequate.[64]

Figure 48-30. Monteggia's fracture-dislocation. Fractures of the ulna diaphysis, with anterior angulation and associated anterior dislocation of the radial head, can be seen on this lateral radiographic view. (From Propp DA, Chin H: Forearm and wrist radiology—Part I. J Emerg Med 7:393, 1989.)

Galeazzi's Fracture

Galeazzi's fracture involves the junction of the middle and distal thirds of the radius, with an associated dislocation or subluxation of the DRUJ. This rare injury accounts for only 3 to 7% of all fractures of the forearm. Galeazzi's fracture typically results from a fall on the outstretched hand, with the wrist in extension and the forearm forcibly pronated. Another less common but well-described mechanism of injury is a direct blow to the dorsoradial aspect of the wrist. Clinical examination often is the key to diagnosis, because disruption of the DRUJ may not be apparent otherwise. The radial fracture causes obvious swelling and deformity on the radial side of the forearm, and pain is localized over the fracture site. In addition, the DRUJ is swollen and painful on palpation, and the ulnar head appears prominent compared with the unaffected wrist.

On the anteroposterior radiograph, a transverse or short oblique fracture of the radius is visible at the junction of the middle and distal thirds of the radius. The radius appears shortened, and an increase in joint space may be visible between the distal radius and ulna. The lateral view shows dorsal angulation of the radial fracture, and the head of the ulna is displaced dorsally (Fig. 48-31). An associated ulnar styloid fracture is seen in approximately 60% of cases and should alert the physician to the presence of disruption of the DRUJ.[65]

Galeazzi's fractures are inherently unstable. Occasionally, if the radial fracture is distal, a closed reduction of the radius and reduction of the DRUJ in supination with a long arm cast can be successful. However, less than 10% of patients have a good outcome with closed treatment—accordingly, the term "fracture of necessity" has been used to describe Galeazzi fractures, implying that operative repair is mandatory.[66] The instability is the result of several factors, including the distracting pull of the brachioradialis and pronator quadratus muscles and the associated disruption of the DRUJ.

Figure 48-31. Galeazzi's fracture-dislocation. The radiographs (*left*, anteroposterior view; *right*, lateral view) show an obvious fracture of the distal third of the radius with severe displacement and an associated dislocation of the distal radioulnar joint *(arrow)*. (From Harris JH, et al: The Radiology of Emergency Medicine, 3rd ed. Baltimore, Williams & Wilkins, 1993.)

Operative treatment involves open reduction and internal fixation of the radial shaft fracture, with immobilization of the forearm in supination to maintain reduction of the DRUJ. Reports have suggested that failure of closed reduction of the DRUJ in some patients is due to soft tissue interposition, and in these cases open reduction and fixation of the DRUJ is recommended.[67]

Complications of Galeazzi's fracture include malunion and nonunion of the radial fracture and recurrent subluxation or dislocation of the DRUJ. These complications result in chronic pain, with significant limitation of pronation and supination, and are thought to be largely avoidable with appropriate open anatomic reduction and rigid internal fixation of the fracture.[68,69]

Pediatric Forearm Fractures

Shaft Fractures of Radius and Ulna

In children, fractures to both bones of the forearm usually occur as a result of a fall on the outstretched hand. Fractures generally are classified into three types: buckle, or torus, fractures; incomplete, or greenstick, fractures; and complete fractures. The forearm fracture usually is obvious clinically, with significant pain, swelling, and visible deformity at the fracture site. Anteroposterior and lateral radiographs of the forearm distinguish whether fractures are complete or incomplete and show the degree of angulation and rotational deformity (Fig. 48-32).

The objective of successful treatment of forearm fractures in children does not differ significantly from treatment in adults; the goal is successful reduction of fracture deformity. Nevertheless, in children, an important consideration is the potential for spontaneous correction of residual fracture angulation with bone remodeling. The younger the child (especially younger than 10 years of age), and the closer the fracture is to the growth plate, the greater the potential for remodeling. These principles govern the acceptability of fracture reduction, and generally, angulation of less than 10 degrees is considered acceptable.[70]

Greenstick and complete forearm fractures require orthopedic referral for closed reduction with the patient under deep procedural sedation or general anesthesia. Results usually are excellent if correction of angular and rotational deformity is achieved and maintained. Immobilization in a long arm cast usually is necessary for 7 to 8 weeks. Open reduction and internal fixation occasionally are necessary if closed reduction is unsuccessful or if correction cannot be maintained with casting. Complications of malunion and nonunion are rarely seen because of rapid healing and a tremendous capacity for remodeling in this population.[45]

Plastic Deformation

The occurrence of plastic deformation of bone is unique to children and refers to a bending of the bone without overt fracture. Plastic deformation may be seen as an isolated injury to the radius or ulna, or it may be seen in one bone in combination with a fracture of the other bone. Clinically, this injury produces localized pain and deformity of the forearm, and radiographically, it appears as a fixed curvature of the bone shaft (Fig. 48-33). If significant curvature is present, the deformity is obvious, and pronation and supination are significantly restricted. Treatment requires orthopedic referral for closed reduction with the patient under general anesthesia and immobilization in a long arm cast for 6 to 8 weeks.[71]

Figure 48-32. Pediatric forearm fracture. Anteroposterior *(left)* and lateral *(right)* radiographic views show radial and ulnar shaft fractures with dorsal angulation. (From Dvorkin ML: Office Orthopaedics. Norwalk, Conn, Appleton & Lange, 1993.)

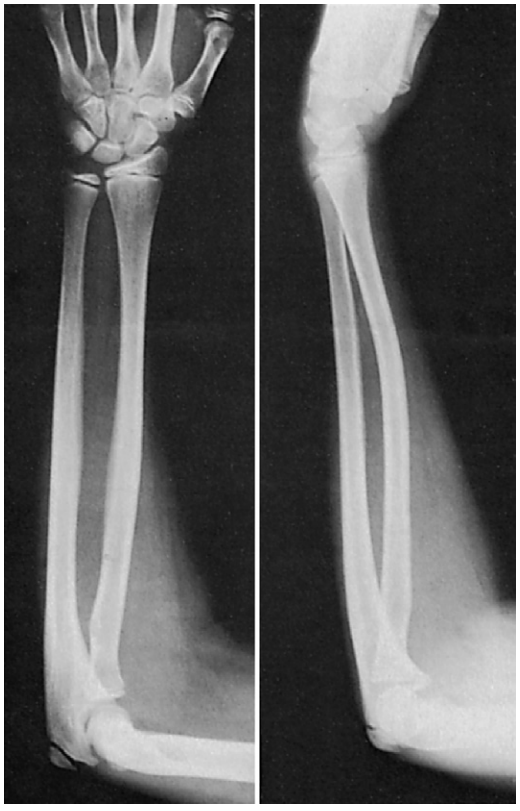


Figure 48-33. Acute plastic bowing fracture of the forearm. Anteroposterior *(left)* and lateral *(right)* radiographic views show broad volar bowing of the radial shaft with no visible fracture lucency. (From Komara JS, et al: Acute plastic bowing fractures in children. Ann Emerg Med 15:585, 1986.)

KEY CONCEPTS

- Plain radiographs fail to detect 15% of scaphoid fractures. For this reason, and because of the associated risk of nonunion when diagnosis and immobilization are delayed, patients clinically suspected of having a scaphoid fracture should undergo CT scan or MRI for diagnosis of occult fracture.
- Triquetral fracture is best seen on the standard lateral view of the wrist as a small dorsal chip fragment, although a more oblique pronated lateral view may be necessary.
- Lunate dislocation results in a characteristic triangular appearance of the lunate on the posteroanterior view (piece of pie sign) due to the rotation of the lunate in a volar direction. This rotation also is visible on the lateral view of the wrist, on which the lunate looks like a cup tipped forward and spilling its contents into the palm (spilled teacup sign).
- In carpal dislocations, the articular surfaces on the posteroanterior view form three parallel arcs. The articular surfaces between carpal bones are parallel and 1 to 2 mm apart (parallelism).
- Colles' fracture requires prompt anatomic reduction in the emergency department, with full restoration of radial length and correction of the dorsal angulation either to a neutral position or, ideally, to the normal volar tilt position. Closed reduction, using local or regional anesthesia, with cast immobilization is successful in most cases.
- Anteroposterior and lateral views of the forearm must include the wrist and elbow joints because radial and ulnar forearm fractures may be associated with proximal, radial, or DRUJ dislocations.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 49 Humerus and Elbow

Joel M. Geiderman and Sam S. Torbati

PERSPECTIVE

Injuries in the region of the elbow have a high potential for complications and residual disability. Early recognition of neurovascular and soft tissue complications improves the outcome in many of these injuries.

Anatomy

The humerus is a long bone that articulates proximally, at the shoulder, with the glenoid of the scapula to form the glenohumeral joint and distally with the radius and ulna to form the three-way elbow joint. The upper end of the humerus, the humeral head, is shaped like a near-hemisphere. Adjacent to the humeral head are two bony prominences, the greater and lesser tuberosities. Between these, on the anterolateral aspect of the humerus, runs the bicipital groove. The shaft of the humerus extends from the upper border of the insertion of the pectoralis major muscle superiorly to the supracondylar ridges inferiorly. The shaft is cylindrical on cross section in the upper half and tends to become flat in the distal portion in an anteroposterior direction. Three surfaces are described. The anterolateral surface presents the deltoid tuberosity for the insertion of the deltoid muscle, and below this is the radial soleus, which transmits the radial nerve and profunda artery. The anteromedial surface forms the floor of the intertubercular groove, but it normally has no outstanding surface markings. An exception is when the supracondylar process is present. The posterior surface is the origin for the triceps and contains the spiral groove.

The bony anatomy of the distal humerus and elbow is diagrammed in Figure 49-1. The distal end of the humerus tapers into two columns of bone, the medial and lateral condyles. Between the condyles, the bone thins, and the recess created is the coronoid fossa. The more proximal nonarticular portions of the condyles are the epicondyles. Just proximal to the epicondyles, the supracondylar ridges run up each side of the humerus. Collectively, these areas serve as points of origin for the muscles of the forearm. The wrist flexors originate from the medial epicondyle, and the wrist extensors originate from the lateral epicondyle. Fractures of the distal humerus often result in fragment displacement because of the pull of these strong forearm muscles on attachment sites.

The bony anatomy of the elbow allows for two complex motions: flexion-extension and pronation-supination. The elbow is composed of three articulations within a common joint cavity. The trochlea is the articular surface of the medial condyle and articulates with the deep trochlear notch of the ulna formed by the olecranon inferiorly and posteriorly and by the coronoid process anteriorly. This articulation permits hinged flexion and extension at the elbow. The articular surface of the lateral condyle is the capitellum, which permits the radius to hinge on the elbow. The proximal radius consists of a disklike head supported by the smooth narrow radial neck. The radial head articulates with the capitellum of the humerus and with the radial notch of the ulna.

Four ligamentous structures are important in evaluating elbow injuries (Fig. 49-2). The radial head is held in place by the annular ligament and the radial collateral ligament. Rotation of the radial head within the annular ligament permits pronation and supination. In addition, the ulnar collateral ligament and anterior capsule add stability to the joint. These structures may be severely damaged from fracture or dislocation of the joint.

The soft tissues of the upper arm are divided into two compartments: anterior and posterior. The anterior compartment contains three muscles—the biceps brachii, the brachialis, and the coracobrachialis—and the brachial artery, median nerve, musculocutaneous nerve, and ulnar nerve. The only two structures contained in the posterior compartment are the triceps brachii muscle and the radial nerve.

The neurovascular structures of this area are diagrammed in Figure 49-3. The brachial artery, the continuation of the axillary artery, travels with the median nerve in the anterior compartment of the upper arm. It enters the antecubital fossa as diagrammed and bifurcates into the radial and ulnar arteries.

The median nerve runs with the brachial artery as shown. One important anatomic variation is the presence of a supracondylar process (in approximately 2.5% of cases) just proximal to the medial epicondyle (Fig. 49-4). When the supracondylar process is present, the median nerve and brachial artery must traverse behind this process, then forward between a fibrous band connecting the process to the epicondyle. Median nerve symptoms may develop if this process is fractured or if an injury causes swelling in the vicinity of the supracondylar process.

The radial nerve leaves the axilla and spirals posteriorly around the humerus between the heads of the triceps in the radial groove. It reenters the anterior compartment of the arm laterally, crossing the elbow anterior to the lateral epicondyle to innervate the extensors of the wrist and fingers. Because of its close relationship to the shaft of the humerus, the radial nerve is particularly susceptible to injury with fractures of the midshaft of the humerus. Fixed in position by the intermuscular septum, the nerve may become trapped between fracture fragments, particularly when reduction is attempted.

The ulnar nerve runs parallel to the median nerve. Halfway down the arm, it penetrates the intermuscular septum to run

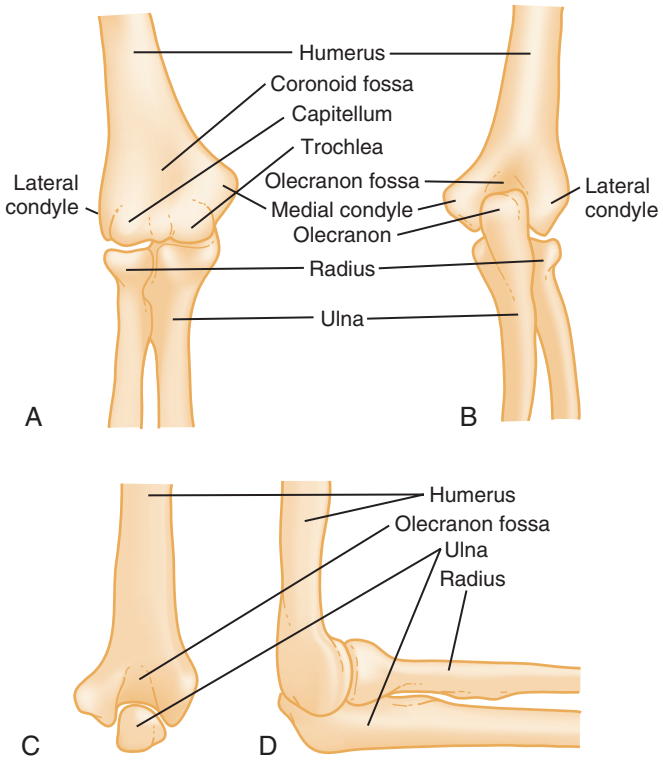


Figure 49-1. Bony anatomy of distal humerus and elbow region. **A,** Anterior view. **B,** Posterior view. **C,** Posterior view, 90 degrees flexion. **D,** Lateral view. Right elbow is shown. (Modified from Connolly JF: DePalma's Management of Fractures and Dislocations. Philadelphia, WB Saunders, 1981.)

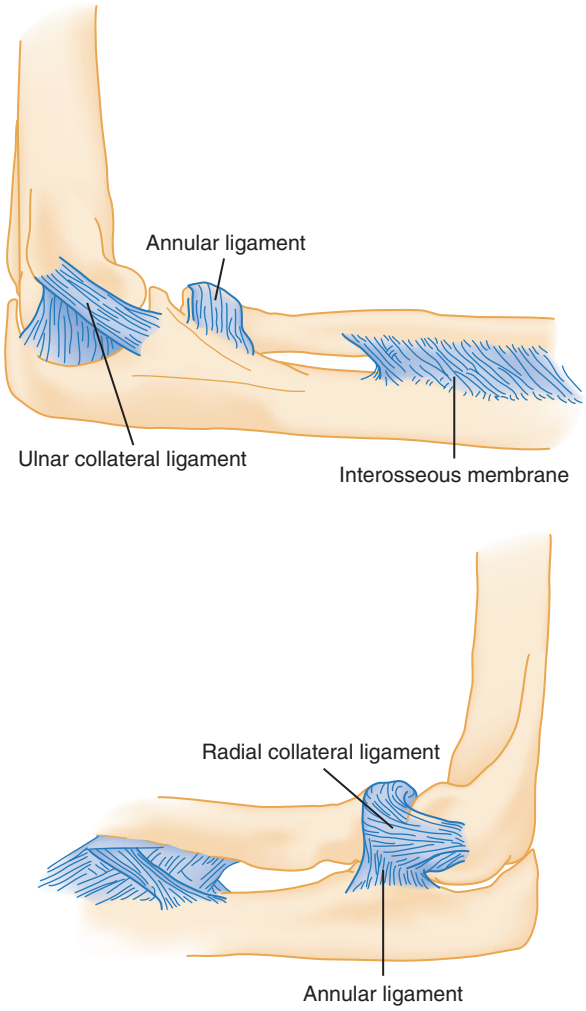


Figure 49-2. Ligamentous structures of elbow. (From Simon R, Koenigsknecht S: Emergency Orthopaedics: The Extremities, 2nd ed. Norwalk, Conn, Appleton & Lange, 1987.)

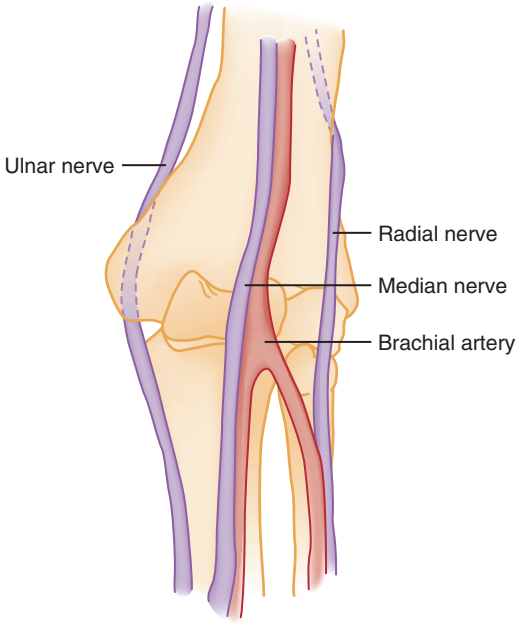


Figure 49-3. Neurovascular structures of elbow region. Volar surface of left elbow is shown.

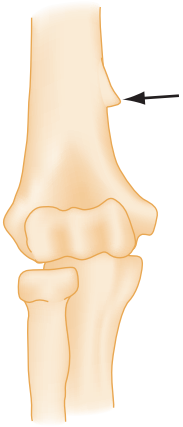


Figure 49-4. Supracondylar process of the humerus (*arrow*). Volar surface of right elbow is shown.

along the medial aspect of the triceps muscle in the posterior compartment. It enters the forearm by passing behind the medial condyle. Fractures in the vicinity of the medial condyle place this nerve at considerable risk for injury.

Three elbow bursae are clinically important. The olecranon bursa is located between the olecranon and the skin posterior to the joint. This bursa provides protective padding and allows smooth movement of the skin over the olecranon. Because of its position, it is often a site of traumatic or infectious bursitis. The radiohumeral bursa provides for smooth movement over the radial head with supination and pronation. A third bursa cushions the biceps tendon from the radius during flexion of the elbow. As evident by the descriptions of these structures, all are vulnerable when significant skeletal injury occurs in this region.

CLINICAL FEATURES

History

A history detailing musculoskeletal complaints includes a description of any pain in terms of quality, duration, location, palliative and provocative activities, severity, and radiation. Past medical history and occupational factors are important in chronic problems. For traumatic injuries, a complete account of the incident is important because it provides information about the mechanism of injury and some estimate of the energy delivered. Subjective complaints of numbness or weakness distal to the injury are important clues to possible neurovascular injury. In dealing with injuries in children, the possibility of child abuse must be considered.

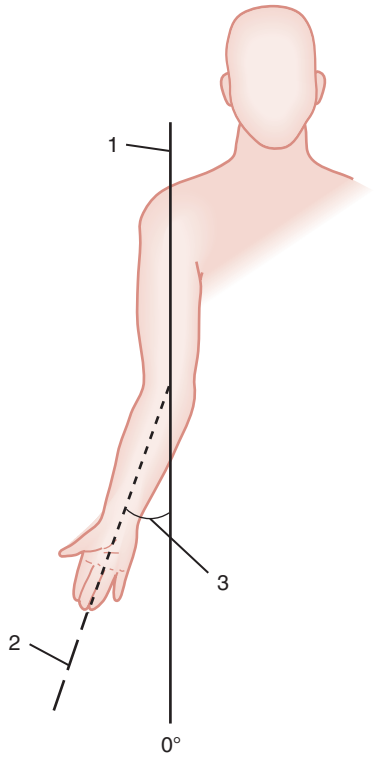


Figure 49-5. Carrying angle (*3*) is formed by intersection of lines drawn parallel to long axis of humerus (*1*) and ulna (*2*). (Modified from Ruiz E, Cicero J: Emergency Management of Skeletal Injuries. St Louis, Mosby, 1995.)

Physical Examination

Inspection of the upper extremity is important, but manipulation of the painful extremity should be minimized and postponed to the end of the examination when possible. This is especially important with children. A great deal of useful information can be gathered by simple inspection and comparison with the contralateral limb. The position in which the extremity is held should be noted. Children with extension-type supracondylar fractures present with the arm held at the side with a characteristic S-shaped configuration, whereas with flexion-type supracondylar fractures, the forearm is supported with the opposite hand with the elbow flexed to 90 degrees. Patients with radial head subluxation have the elbow only slightly flexed and hold the forearm in pronation.

Deformity is evidence not only of significant injury, but also of the type of injury. Increased prominence of the olecranon suggests a posterior dislocation of the elbow or extension supracondylar fracture, whereas loss of the normal olecranon prominence indicates anterior dislocation or flexion supracondylar fracture. The extremity also should be inspected for wounds that may indicate an open fracture, evidence of swelling, and change in color of the distal extremity.

One special aspect of the elbow examination is the determination of the carrying angle, the normal outward angulation of the extended forearm at the elbow. This angle allows the long axes of the humerus and forearm to become superimposed when the elbow is flexed (Fig. 49-5). This angle varies from 5 to 20 degrees in adults, with men having less angulation than women. Measurement of the carrying angle is helpful in assessing subtle supracondylar fractures in children. As shown in Figure 49-6, lines drawn parallel to the shafts of the humerus and ulna intersect to form an angle with a mean measurement in children of 13 degrees, although this angle varies widely.[1] A difference in carrying angles of greater than 12 degrees (from one side to the other for a particular individual) is associated with fractures.

The vascular status of the extremity is of highest priority. Brachial, radial, and ulnar pulses should be palpated and documented. The ulnar pulse is not palpable in some normal people. Although brisk capillary refill suggests adequate tissue perfusion, a hand-held Doppler device often is required to evaluate major vessel flow if significant swelling is present or if the pulses are not palpable. Any suggestion of arterial injury requires immediate investigation. Poor perfusion may result from direct arterial injury, compression or kinking in the instance of significant displacement from a fracture or dislocation, or a compartment syndrome. Passive extension of the fingers produces severe pain in the forearm in the presence of flexor (volar) compartment ischemia. Of the five *P's* associated with arterial occlusion (pain, paresthesia, pallor, pulselessness, and paralysis), pain is the only dependable early sign of compartment syndrome. Orthopedic consultation and measurement of compartment pressures should be considered for patients who have pain disproportionate to their injury. Other modalities used to evaluate vascular status before calling in the orthopedist include measurement of the ankle-brachial index and color flow Doppler (see Chapter 45 for further details).

Neurologic evaluation includes assessment of the radial, median, and ulnar nerves. After evaluation of neurovascular function, all bony prominences are palpated, and areas of tenderness are noted carefully and documented. Crepitus and bony deformities are highly suggestive of fracture or dislocation. The radial head specifically should be palpated for tenderness, and any noticeable effusion should be noted.

The range of motion of the elbow in all planes (i.e., flexion-extension and pronation-supination) should be determined and documented. With the forearm supinated, the normal range of motion is 0 degrees in full extension to 150 degrees in full flexion. A mild degree of hyperextension is normal in

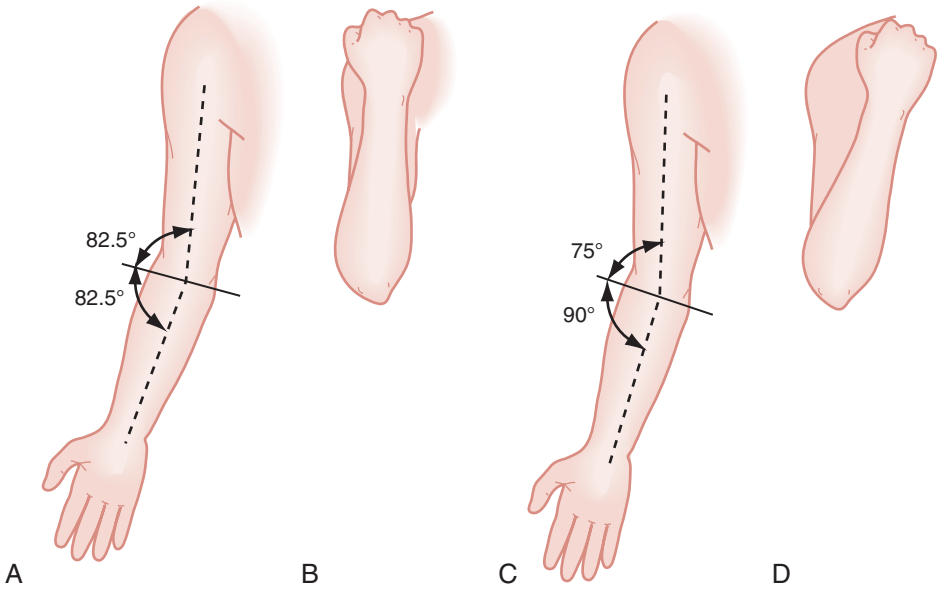


Figure 49-6. **A,** The axis of the elbow joint bisects the angle formed by the long axes of the humerus and forearm. **B,** This allows these axes to become superimposed when the elbow is flexed. **C,** If the axis of the elbow joint was perpendicular to the long axis of the forearm, the respective axes would diverge when the elbow was flexed, as shown in **D**.

some individuals and should be symmetrical. With the elbow flexed at 90 degrees and the thumb facing up, the forearm normally supinates and pronates 90 degrees. Range-of-motion testing may be impossible with severe injuries and can be postponed until after radiographic evaluation, avoiding manipulating fractures and dislocations. Any manipulation of the extremity must be followed by reexamination because neurovascular injury has been reported with nearly every therapeutic procedure.

Radiographic Findings

It is not necessary to obtain radiographs in all cases. Although clinical decision rules for the elbow have not been validated, it is reasonable to perform radiography when there is significant limitation in range of motion, obvious deformity, joint effusion, or significant tenderness over any of the bony prominences or the radial head. In the absence of these, it seems appropriate to omit radiography. The threshold for radiography should be much lower in pediatric populations due to the presence of open growth plates and limitation in the physical exam.

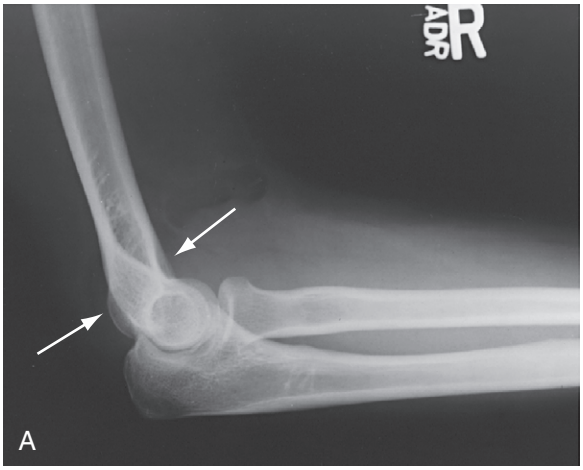
Routine views of the elbow include at least the anteroposterior and lateral views, with consideration given to obtaining oblique views for certain injuries. Anteroposterior and oblique views are taken with the elbow extended. The lateral view is taken with the elbow in 90 degrees of flexion and the thumb pointing upward. Positioning of the elbow is important because anything but a true lateral view makes accurate interpretation of soft tissue findings and alignment difficult. Corresponding views of the opposite extremity may be helpful, especially for children, but should not be ordered routinely.

Many fractures in the elbow region are obvious on plain film, with cortical disruption, angulation, or displacement of fragments. Minor fractures can be subtle and may be missed. Special attention to the contour of the radial head and the fat pads reduces the risk of missing fractures. The normal cortex of the radius is smooth and has a gentle continuous concave sweep. If consistent with history and physical findings, any disruption of this smooth arc is considered evidence of fracture. Abnormalities within the soft tissues on elbow films are particularly important and may be the only radiographic sign of a fracture. Normally, fat surrounding the proximal elbow joint is hidden in the concavity of the olecranon and coronoid fossae. The radiographically normal elbow has only a narrow strip of lucency anteriorly (the anterior fat pad), and a posterior fat pad is not visible. Injuries that produce intra-articular hemorrhage cause distention of the synovium and displace the fat out of the fossa, making the posterior fat pad visible on lateral radiographic views. The anterior fat pad also is altered by this swelling, becoming more prominent and taking the shape of a spinnaker sail from a boat: "sail sign" (Fig. 49-7). In the setting of trauma, more than 90% of patients with the "posterior fat pad" sign have intra-articular skeletal injury. These soft tissue findings occur even with subtle fractures, and when present in the setting of trauma, an occult fracture is considered to be present even when not visible on radiograph. In adults, a radial head fracture is implied, whereas in children, a supracondylar fracture is the probable underlying injury. In the absence of trauma, the presence of a fat pad suggests other causes of effusion (e.g., gout, infection, bursitis). The fat pad sign may be absent with a fracture if the injury is severe enough to have ruptured the capsule.

The anterior humeral line is a line drawn on a lateral radiograph along the anterior surface of the humerus through the elbow. Normally this line transects the middle third of the capitellum (Fig. 49-8). With an extension supracondylar fracture, this line either transects the anterior third of the capitellum or passes entirely anterior to it. The abnormal relationship between the anterior-humeral line and capitellum may be the only evidence of a minimally displaced supracondylar fracture.

Another diagnostic aid in evaluating radiographs of possible supracondylar fractures in children is the determination of Baumann's angle. As shown in Figure 49-9, the intersection of a line drawn on the anteroposterior film through the midshaft of the humerus and the growth plate of the capitellum defines an angle of approximately 75 degrees. In normal children, Baumann's angle is the same in both elbows, and it has been suggested that a comparison between the injured and uninjured sides be used to assess the accuracy of reduction. An increase in Baumann's angle indicates medial tilting of the distal fragment. Alteration in Baumann's angle is thought to predict the final carrying angle when the fracture heals, although there is controversy regarding its reliability.[2]

Radiographic evaluation of the elbow in children is difficult because of the presence of multiple ossification centers (Fig. 49-10). Table 49-1 lists the typical age of first appearance



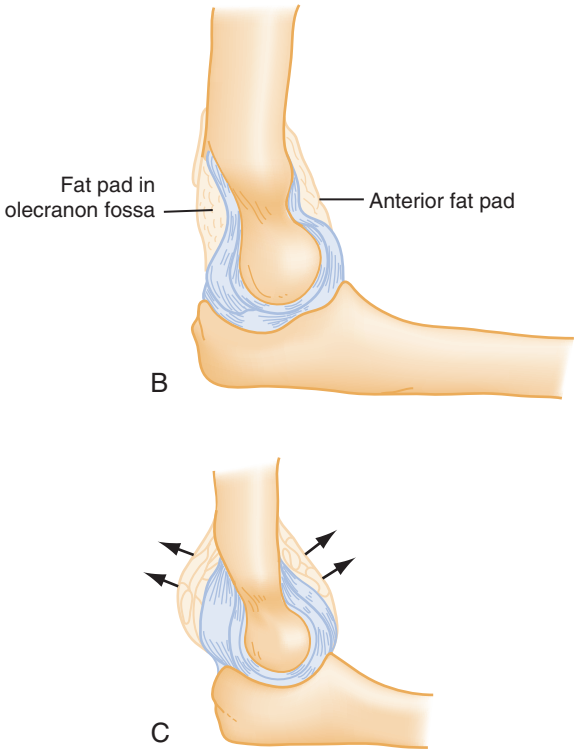


Figure 49-7. **A,** Anterior and posterior fat pads seen on lateral study (*arrow*). **B,** The anterior fat pad is normally a thin radiolucent stripe; the posterior fat pad is now seen. **C,** An effusion displaces both fat pads. This posterior fat pad is now visible.

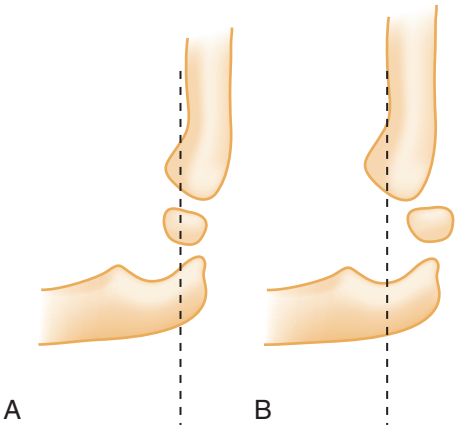


Figure 49-8. **A,** A line drawn down the anterior surface of the humerus on a lateral film should transect the middle of the capitellum. **B,** With an extension supracondylar fracture, the line passes more anteriorly. (From Simon R, Koenigsknecht S: Emergency Orthopaedics: The Extremities, 2nd ed. Norwalk, Conn, Appleton & Lange, 1987.)

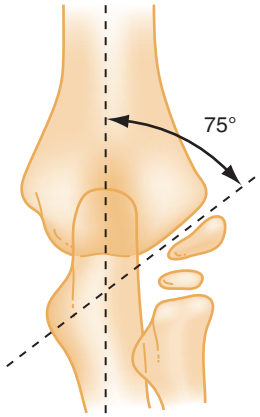


Figure 49-9. Worlock P: Baumann's angle as measured on anteroposterior film. (From Supracondylar fractures of the humerus. J Bone Joint Surg [Br] 68:755, 1986.)

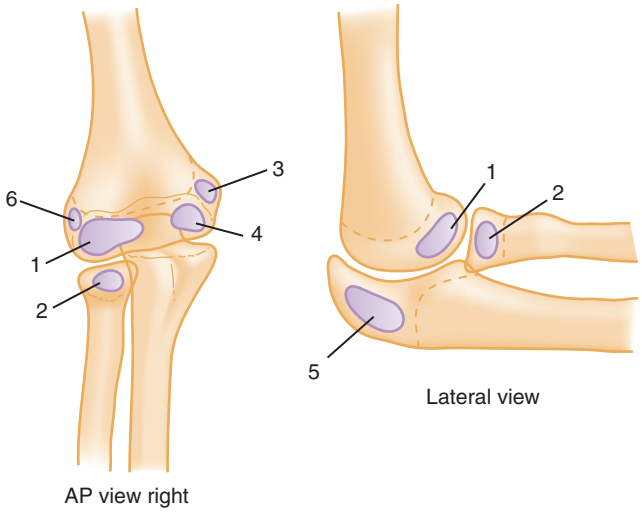


Figure 49-10. Secondary growth centers of the elbow. (*1*) Capitellum; (*2*) radial head; (*3*) medial epicondyle; (*4*) trochlea; (*5*) olecranon; (*6*) lateral epicondyle. (From Townsend DJ, Bassett GS: Common elbow fractures in children. Am Fam Physician 53:2031, 1996.)

Table 49-1 Ossification Centers of the Elbow: CRITOE

OSSIFICATION CENTERS	AGE OF APPEARANCE
Capitellum	1–2
Radial head	4–5
Internal (medial) epicondyle	4–5
Trochlea	8–10
Olecranon	8–9
External (lateral) epicondyle	10–11

and fusion of ossification centers. Comparison views of the uninjured elbow are often helpful in distinguishing fractures from the normal epiphyses and ossification centers.

Management

General management principles for humerus and elbow injuries are similar to those for other orthopedic injuries. Limb-threatening conditions, such as vascular injury, must be addressed immediately by reduction of fractures or surgical exploration. The limb should be splinted in a position of comfort, and appropriate analgesia should be provided. Antibiotics are administered for suggested open fractures. Prolonged immobilization of the elbow frequently results in stiffness of the joint that requires extensive physiotherapy to restore normal function. For this reason, range-of-motion exercises are begun early in the convalescent period, often before a fracture has healed completely.

■ FRACTURES

Injuries in the region of the shaft of the humerus and about the elbow fall into several categories (Box 49-1). Emergency department (ED) management varies with location and type of fracture or dislocation.

Fractures of the Shaft of the Humerus

Pathophysiology

Fractures of the humeral shaft commonly result from a direct blow to the arm, such as occurs during a fall or motor vehicle crash. Severe twisting of the arm or a fall on an outstretched hand can also produce this type of fracture. Fractures produced by violent muscle contraction, such as occur when throwing a javelin or baseball, also are reported.[3] Motion of the humerus is controlled by several muscle groups, which also influence the fracture pattern of the humeral shaft. If the fracture is located proximal to the attachment of the pectoralis major, the proximal fragment of the humerus abducts and rotates internally owing to the action of the rotator cuff, whereas the distal fragment is displaced medially by the pectoralis major (Fig. 49-11A). If the fracture occurs below the pectoralis major insertion but above the deltoid insertion, the distal fragment is displaced laterally by the deltoid muscle, and the proximal fragment is displaced medially by the pull of the pectoralis major, latissimus dorsi, and teres major muscles (Fig. 49-11B). In fractures occurring distal to the deltoid insertion, the proximal fragment is abducted by the deltoid, and the distal fragment is proximally displaced (Fig. 49-11C). The shaft of the humerus most commonly fractures in the middle third in a transverse fashion (Fig. 49-12).

BOX 49-1 CLASSIFICATION OF FRACTURES

I. Humerus fractures
  A. Shaft of the humerus fractures
  B. Distal humerus fractures
    1. Supracondylar
      a. Extension
      b. Flexion
    2. Transcondylar
      a. Extension
      b. Flexion
    3. Intercondylar
      a. Nondisplaced
      b. Separated
      c. Separated and rotated
      d. Combination with articular surfaces
    4. Condylar
      a. Medial
      b. Lateral
    5. Articular surface
      a. Capitellum
      b. Trochlea
    6. Epicondylar
      a. Medial
      b. Lateral
II. Radial head fracture
  A. Nondisplaced
  B. Displaced
  C. Comminuted
III. Ulnar fracture
  A. Olecranon fracture
  B. Cornoid fracture

Clinical Features

The patient complains of localized pain. The arm is visibly swollen and cannot be used. When a fracture is complete, bony crepitus is felt in the shaft of the humerus with any manipulation of the arm. The arm may be shortened or rotated, depending on the displacement of the fracture fragments. When the fracture is incomplete, the skeleton is tender to palpation and swollen, but not otherwise deformed. A complete neurovascular examination is indicated. Attention should be directed to radial nerve function because injury to this nerve is the most common complication associated with humeral shaft fractures.

Radiographic findings are confirmatory. Studies routinely should include the shoulder and elbow joints. The humerus is a common site for benign tumors, unicameral cysts, and primary bone malignancies. The humeral shaft also is a common site for metastatic disease. Thinning of the cortex and abnormal osteoblastic or osteoclastic activity are evidence of a pathologic fracture (see Fig. 49-12). These fractures do not heal without concomitant treatment of the underlying pathologic condition.

Management

Closed fractures that are isolated injuries are treated conservatively with a high degree of success. Elaborate attempts at fracture reduction and external immobilization are unnecessary and sometimes detrimental to healing. Humeral shaft fractures remain surrounded by a richly vascularized envelope of muscle so that fracture reduction is accomplished most easily with the aid of gravity and muscle balance. Fractures that are nondisplaced or minimally displaced are immobilized by adding a coaptation, or "sugar-tong," splint, to the sling and swathe (Fig. 49-13). This is accomplished by first padding the extremity, then carrying a long plaster splint from the lateral side of the shoulder, down the lateral aspect of the upper arm, around the elbow with the elbow flexed, and then up the inner aspect of the arm to the axilla. The sugar tong is wrapped in an elastic bandage, and a sling is used to support the arm in 90 degrees or less of flexion. The weight of the splint aided by gravity applies traction at the same time it immobilizes the fracture. Some authorities use the coaptation splint for only the first 10 to 14 days of treatment followed by a functional brace.

If the fracture is grossly displaced or comminuted, the hanging cast technique sometimes is used. This technique is especially effective with spiral fractures. The cast is light-

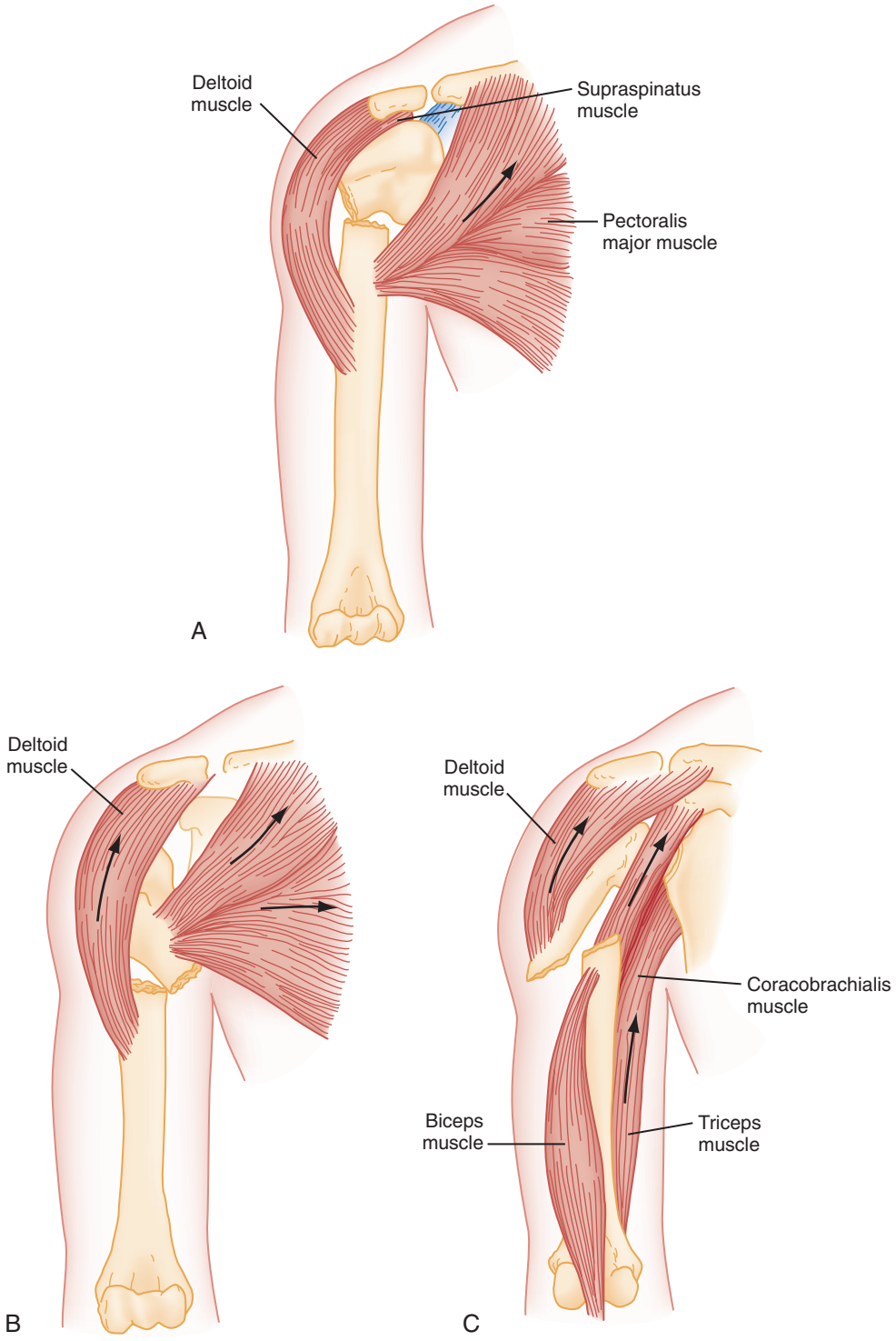


Figure 49-11. Influence of muscles on displacement of humeral shaft fractures based on fracture location. **A,** Fracture is proximal to the attachment of the pectoralis major muscle. **B,** Fracture is between insertion of the pectoralis major and deltoid muscles. **C,** Fracture is distal to the deltoid insertion.

weight, applied at least 1 inch proximal to the fracture site, and extends to the distal palmar crease of the hand. The elbow is flexed 90 degrees, and the wrist is placed in the neutral position. The sling is attached through a loop at the wrist. Angulation is corrected by placing the plaster loop on the dorsal aspect of the cast (to reduce lateral angulation) or on the volar side of the cast (to reduce medial angulation). Anterior or posterior angulation is corrected by altering the length of the sling apparatus (Fig. 49-14). Care must be taken not to make the cast too heavy because this would distract fracture fragments. The hanging cast has the disadvantage of requiring gravity for traction and requires that the patient remain upright at all times, including during sleep, a situation that many patients find intolerable. Neurovascular examination is repeated after the application of any splint or cast. Loss of nerve function from entrapment of the nerve between fragments can occur after these interventions.

Open reduction and internal fixation (Fig. 49-15) is necessary in certain circumstances, including open fractures, presence of multiple injuries that preclude mobilization, bilateral fractures, poor reduction, poor patient compliance, failure of closed treatment, and fractures through pathologic bone.[4,5] Isolated radial nerve palsy usually is assumed to be a neurapraxia and is managed nonoperatively. Exploration and

Figure 49-12. Pathologic fracture of proximal humerus.

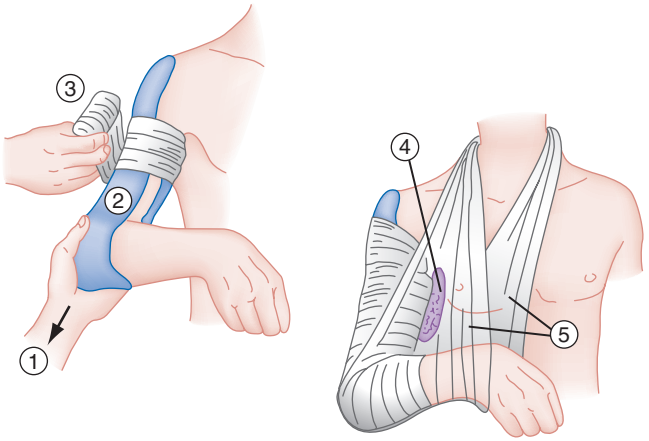


Figure 49-13. Sugar-tong splint for humeral shaft fractures. Gentle traction is applied (*1*) as the splint is placed (*2*) from over the deltoid laterally, under the elbow, and up into the axilla. An elastic wrap holds the splint in place (*3*). The axilla must be padded (*4*), and a sling is used (*5*). (Modified from Connolly JF: DePalma's Management of Fractures and Dislocations. Philadelphia, WB Saunders, 1981.)

internal fixation are indicated, however, if the radial nerve palsy develops after manipulation because this is highly suggestive of nerve entrapment.[4]

All patients with humeral shaft fractures should be referred to an orthopedic surgeon for close follow-up monitoring. When dependency casting is used, follow-up evaluation within 24 to 48 hours is recommended to be certain that the alignment has been maintained. Emergent referral to an orthopedist is recommended for patients with evidence of radial nerve injury, severely displaced or comminuted fractures, open fractures, or fractures associated with forearm fractures in the same extremity.

Complications

The most common complication, radial nerve injury, occurs in 20% of humerus fractures. This nerve injury is most often a benign neurapraxia that resolves spontaneously in most patients, although recovery may take several months. Radial nerve injuries associated with penetrating trauma or open fractures are likely to be permanent and usually warrant operative exploration. Median and ulnar nerve injuries are rarely seen, usually in the presence of penetrating trauma. Injuries to the brachial artery occur rarely and, if clinically suggested, angiography or other vascular studies should be considered.

Fractures of the Distal Humerus

Supracondylar Fractures

Distal humerus fractures that occur proximal to the epicondyles are called *supracondylar fractures*. This fracture is almost exclusively an injury of the immature skeleton. The peak incidence is in children 5 to 10 years old; the average age in a large combined series was 6.7 years.[6] This injury rarely occurs after age 15 and accounts for approximately one half of all

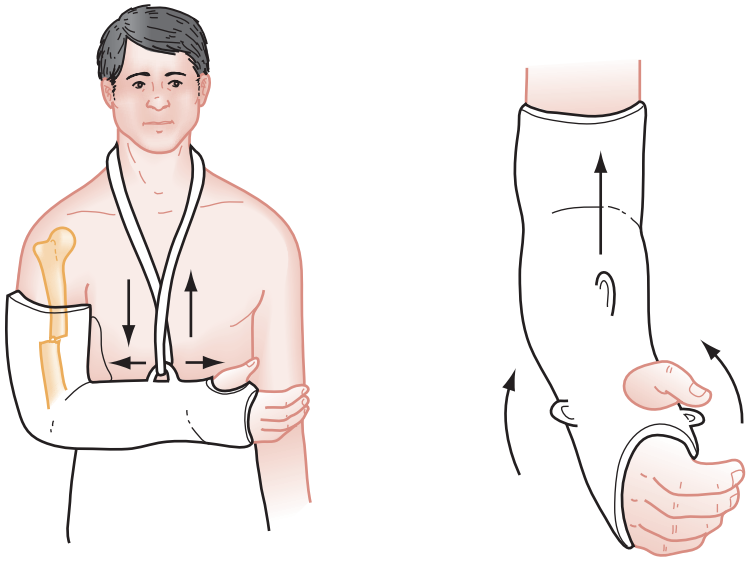


Figure 49-14. Hanging cast technique.

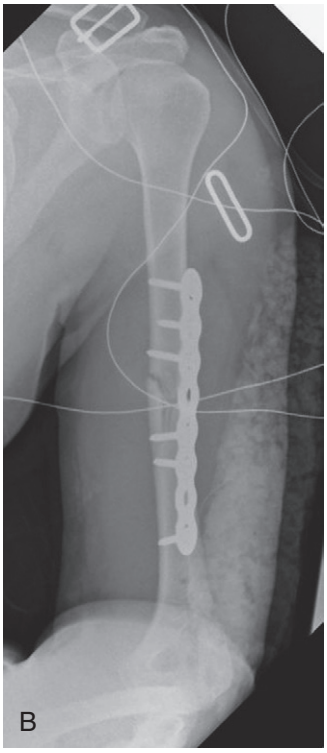


Figure 49-15. Midshaft humerus fracture: (**A**) before and (**B**) after open reduction and internal fixation.

elbow fractures and one third of pediatric limb fractures. In children, the tensile strength of the collateral ligaments and joint capsule of the elbow is greater than that of bone. In adults, the reverse is true, and a posterior elbow dislocation is sustained instead. Supracondylar fractures are classified as either extension or flexion fractures, depending on the mechanism of injury and the displacement of the distal fragment. Of these injuries, 98% are of the extension type.

Extension Supracondylar Fractures

Pathophysiology. Extension supracondylar fractures occur as a consequence of a fall on the outstretched arm, when the elbow is either fully extended or hyperextended (e.g., a fall off the "monkey bars"). The elbow is likely to be in the latter position at the time of the fall because ligamentous laxity, with hyperextension of the joints, is a normal phenomenon in younger children. With the forearm acting as a lever,[7] the ground reaction produces a moment of force at the elbow (Fig. 49-16). Ultimately the distal humerus fails anteriorly in the supracondylar area. The strong action of the triceps tends to pull and displace the distal fragment in a posterior and proximal direction. There may be anterior angulation of the sharp distal end of the proximal fragment into the antecubital fossa, endangering the brachial artery and median nerve (Fig. 49-17). In most cases, however, the brachialis muscle protects the anterior neurovascular structures from injury.

Clinical Features. A child with a complete fracture comes to the ED holding the upper extremity immobile in extension to the side, with a typical S-shaped configuration and tenderness and swelling in the region of the elbow. Prominence of the olecranon attached to the posteriorly displaced distal fragment is similar to that seen with posterior dislocation of the elbow. When an incomplete supracondylar fracture exists, the diagnosis may be less obvious, with an elbow effusion as the only clinical sign. A careful neurovascular examination is essential. Although palpation is useful in determining the site of injury, the examining physician should avoid manipulation of the injury to elicit crepitus because movement can cause further neurovascular damage. Alleviating pain often facilitates the examination.

Diagnostic Strategies. On radiographic examination, the distal fragment is often displaced on the lateral view. This displacement is most likely to occur with a complete fracture wherein the muscle activity results in proximal migration of the distal fragment. Because this fracture occurs in children, 25% of supracondylar fractures are of the greenstick variety with the posterior cortex remaining intact. Subtle changes (e.g., the presence of a posterior fat pad or an abnormal anterior humeral line) may be the only radiographic clues to the presence of a fracture (Fig. 49-18). In displaced fractures on the anteroposterior view, the distal fragments may be displaced either medially or laterally in relationship to the humerus. Often, with minimally displaced fractures, the fracture line is transverse and not visible on the anteroposterior view. Based on radiographic findings, extension supracondylar fractures are classified into three types: type I, minimal or no displacement; type II, displaced fracture, posterior cortex intact; and type III, totally displaced fracture, anterior and posterior cortex disrupted.

Management. Nondisplaced fractures (type I) are immobilized primarily for comfort and protection because they are inherently stable. They are treated in a splint or cast flexed to 90 degrees with the forearm in neutral rotation. Protected active range of motion is begun in approximately 3 weeks. Even without definite radiographic findings, a child with localized tenderness consistent with a supracondylar fracture should be splinted and referred for follow-up examination. A radiographic study performed a few weeks after the injury may reveal periosteal new bone formation in the supracondylar region.

Minimally displaced (type II) fractures that are stable after reduction can be treated with splinting or casting with the elbow flexed. Some authors recommend flexion to 110 to 120 degrees for this injury.[6,8,9] This position uses the intact posterior periosteum as a tension band to hold the reduction; however, if swelling or circulatory obstruction prevents this much flexion, it cannot and should not be used.

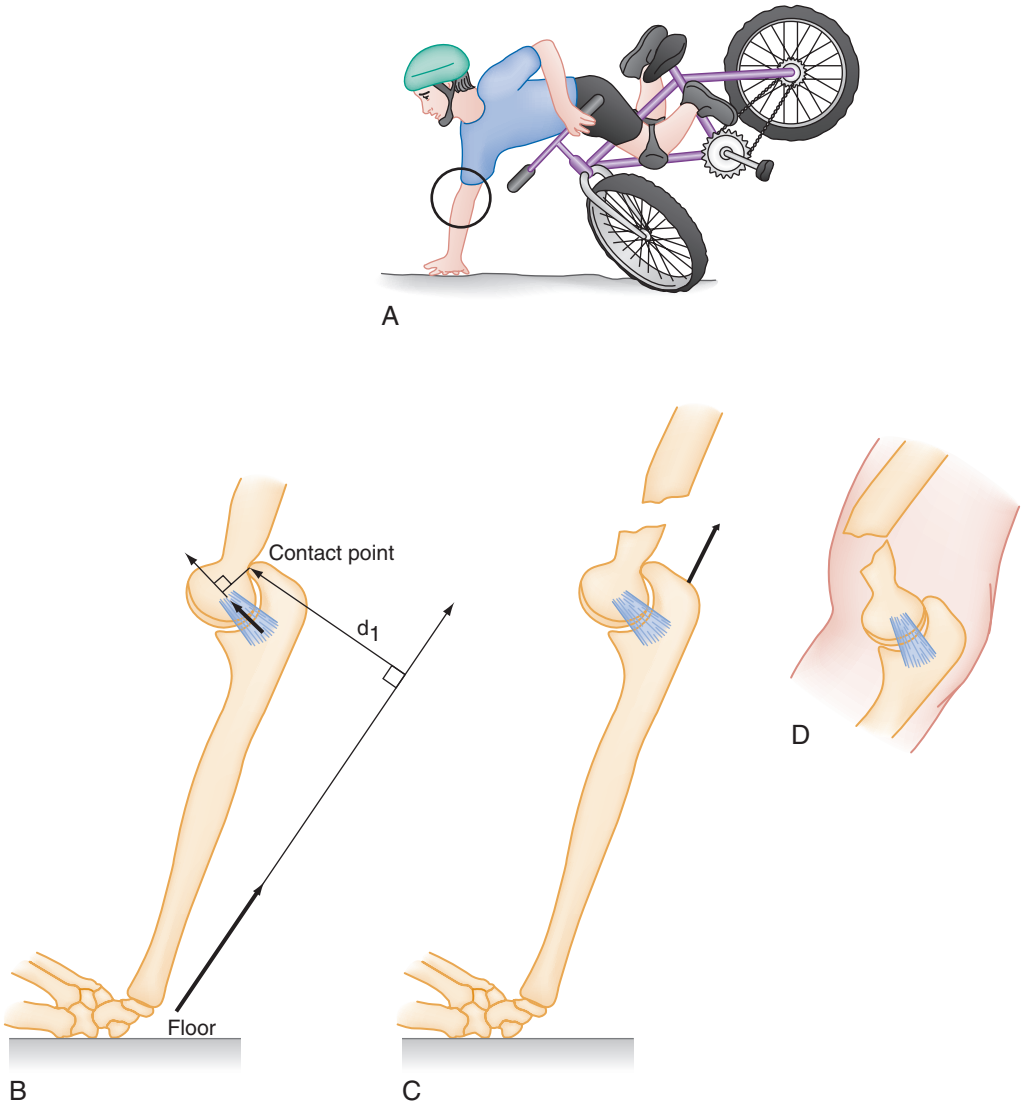


Figure 49-16. Mechanism of injury, extension supracondylar fractures. **A,** Fall on outstretched arm produces hyperextension of elbow. **B,** Ulna levers against distal humerus. **C,** Humerus fails, triceps exerts unopposed force. **D,** Distal fragment displaces.

The greater the flexion at the elbow, the greater is the chance of vascular impairment. When swelling peaks at 24 to 48 hours, the risk of vascular obstruction and compartment syndrome is the greatest. Occasionally, these injuries must be pinned percutaneously to maintain stability, especially if a significant rotational component is present. Percutaneous pinning of a fracture after reduction has grown in popularity in recent years.[10]

Type III totally displaced fractures generally are the result of more severe injuries that produce more swelling than type I or type II injuries. Displacement necessitates the reestablishment of length, increases the chance of varus deformity, and increases the chances of interposed soft tissues and neurovascular injury. For all these reasons, patients with type III fractures require immediate orthopedic consultation in the ED and should be admitted to the hospital for frequent neurovascular checks and closed versus open fixation and percutaneous pinning.

These general principles should be adhered to in treating these injuries: (1) achieving adequate reduction, (2) properly assessing reduction, and (3) maintaining the reduction. Closed reduction is attempted with the patient under anesthesia. If closed reduction is not possible or if the brachial artery seems to be trapped in the fracture site, open reduction may be necessary. When adequate reduction has been achieved, most authorities recommend percutaneous pin fixation to maintain the reduction.[7,11-13]

Reduction in the ED is indicated only when the displaced fracture is associated with vascular compromise that threatens the viability of the extremity. Under these conditions, closed reduction should be attempted. After appropriate procedural sedation, an assistant fixes the arm of the patient. The physician grasps the patient's wrist and applies steady, firm traction in line with the long axis of the limb (Fig. 49-19A). The forearm is kept in the neutral, thumb-up position. While traction is maintained, correction of any medial or lateral displacement is accomplished with the other hand at the elbow (Fig. 49-19B). If the distal fragment is displaced laterally, it is pushed inward; if it is displaced medially, it is pushed outward.

After length is restored and the angular deformity is corrected, the thumb of the free hand is placed over the anterior surface of the proximal fragment with the fingers behind the olecranon. While traction is maintained, the elbow is gently flexed to just beyond 90 degrees (Fig. 49-19C). Angulation is corrected to a normal carrying angle.

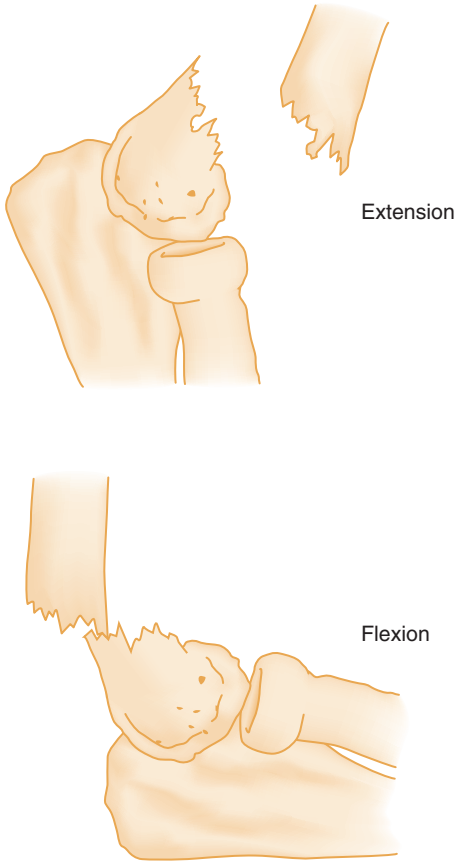


Figure 49-17. Supracondylar fractures, extension and flexion. (Adapted from Simon R, Koenigsknecht S: Emergency Orthopaedics: The Extremities, 2nd ed. Norwalk, Conn, Appleton & Lange, 1987.)

Figure 49-18. Supracondylar fracture (*arrow*) with anterior and posterior fat pads visible.

Medially displaced supracondylar fractures are most prone to tilt into cubitus varus and are immobilized with the forearm pronated to tighten the brachioradialis and common extensor muscles. This procedure closes the fracture laterally. The less common laterally displaced fracture is immobilized in supination to close the fracture medially.

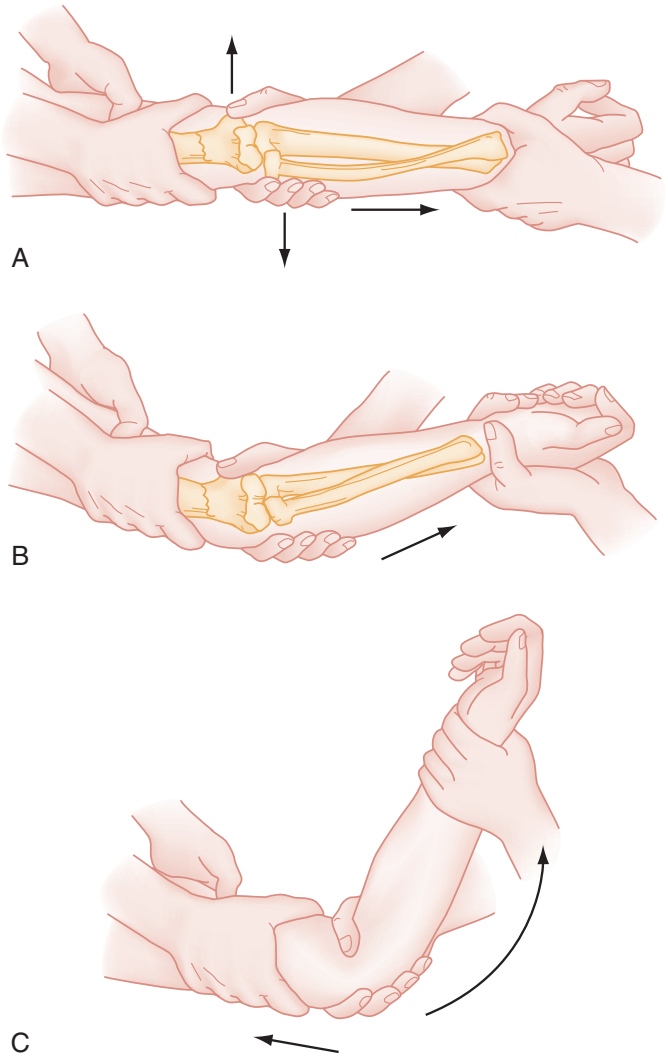


Figure 49-19. **A-C,** Steps in reduction of displaced supracondylar fracture (see text).

Only one attempt should be made at manipulation. Multiple attempts increase the likelihood of neurovascular injury and swelling. If reduction is unsuccessful, simple traction on the extended elbow may restore vascular supply. When reduction is performed, follow-up radiographs are obtained to ensure adequate reduction. Neurovascular function is checked at frequent intervals. Cylinder casts are not applied initially because they increase the risk of forearm ischemia; a posterior plaster splint provides safe and adequate immobilization.

Patients with type I fractures can be discharged safely from the ED with instructions to elevate the extremity and apply ice and have a follow-up evaluation in 1 to 2 days. Fractures that require manipulation usually warrant admission to the hospital to ensure compliance and for neurovascular monitoring.

Complications. Ten percent of children lose the radial pulse temporarily, most often as a result of swelling and not direct brachial artery injury. Reducing the fracture, avoiding flexing the elbow more than 90 degrees, and elevating the arm help prevent secondary obstruction to arterial flow. Compartment syndrome, or Volkmann's ischemic contracture as a result of prolonged ischemia of the forearm, is a dreaded complication but is rare in this era (reported incidence < 0.5%).[10]

The most common complication is the loss of the carrying angle, resulting in a cubitus varus, or "gunstock," deformity.

Measurement of Baumann's angle after reduction is predictive of the final carrying angle. Cubitus varus has been reported previously in 25 to 60% of patients, depending on the treatment method used.[2,14] This incidence has decreased significantly (<10%), with the use of percutaneous pinning. The distal humerus has little capacity to remodel because only 20% of the growth of the bone derives from the distal physis. A small amount of extension or flexion deformity produces little disability, has the greatest chance of remodeling, and is not a major cosmetic concern. Valgus or varus deformities, being in the coronal plane, have little or no chance of remodeling. Although cubitus varus is not a significant functional disability, it presents a significant cosmetic problem. In most cases, this complication can be corrected at a later time by an osteotomy.[15]

Nerve injuries occurred in 7% of 4520 fractures compiled from 31 major reported series. The incidence increases to a range of 19 to 49% with increasing severity of fracture displacement.[16] The radial, median, and ulnar nerves all are commonly involved. Most deficits seen at the time of injury are neurapraxias that resolve with conservative management. Motor function returns within 7 to 12 weeks, whereas recovery of sensation may take more than 6 months.[17]

Flexion Supracondylar Fractures

Pathophysiology. Flexion-type injuries are much less common, with a reported frequency of 1 to 10%; they account for 2% of all supracondylar fractures in a large pooled series of 7212 patients. The mechanism of injury is a direct blow to the flexed elbow. Energy is transferred from the posterior aspect of the proximal ulna to the distal humerus, resulting in a supracondylar fracture with anterior displacement of the distal fragment. As the fragment displaces, the periosteum is torn posteriorly.

Clinical and Radiographic Features. The elbow is usually held in flexion rather than the extremity presenting in the S-shaped configuration seen in extension-type injuries. In displaced fractures, the normal olecranon process is not palpable, in contrast to the increased prominence of the olecranon seen with extension injuries.

Radiographically, these injuries can be classified into three types, similar to extension injuries:

- Type I fracture—undisplaced or minimally displaced
- Type II fracture—incomplete fracture; anterior cortex intact
- Type III fracture—completely displaced; distal fragment migrates proximally and anteriorly

Plain films may reveal a simple increase in the anterior angulation of the distal supracondylar fragment or gross displacement of the distal fragment proximal and anterior to the distal end of the proximal fragment. In the latter case, the distal end of the proximal fragment protrudes posteriorly. A line down the anterior humeral shaft intersects the capitellum either normally or posteriorly in these fractures, depending on whether there is anterior displacement.

Management. When the posterior periosteum is torn, the anterior periosteum functions as a tension band with the arm in extension. In type I fracture, the periosteum is minimally displaced. These injuries do not need to be immobilized in extension. The elbow can be comfortably flexed and should be immobilized in a splint as with extension injuries. Type II and III injuries should be referred to an orthopedist emergently. Type II injuries are manipulated into extension, then held either in a long arm cast or with percutaneous pins. Type III injuries often require open reduction (Fig. 49-20).

Complications. The most common complication is injury to the ulnar nerve by the proximal fragment. The radial and median nerves are rarely injured. Stiffness of the elbow also may occur, especially after open reduction. Cubitus valgus may occur, but is not as cosmetically problematic as cubitus varus.

Figure 49-20. Type III supracondylar fracture with significant displacement of distal fragment.

Transcondylar Fractures

Transcondylar (or dicondylar) fractures have a fracture line, either transverse or crescent-shaped, that passes through both condyles within the joint capsule just proximal to the articular surface (Fig. 49-21). As with supracondylar fractures, two types have been described—extension and flexion—based on the position of the elbow when fractured. Extension types are the most common. The mechanism of injury is similar to that for supracondylar injuries. In contrast to supracondylar fractures, however, the injury is more common in elderly individuals with fragile, osteoporotic bone. These fractures generally are difficult to treat because the small distal fragment possesses little extra-articular bone, and only a small amount of bone contact is available for union.[18] During healing, excessive callus may form in the olecranon or coronoid fossae with residual loss of motion. Orthopedic consultation should be immediately obtained for these injuries.

Intercondylar Fractures

Intercondylar fractures are usually T-shaped or Y-shaped fractures with variable degrees of separation of the condyles from each other and from the proximal humerus fragment (Fig. 49-22). The distal portion of the fracture extends to the articular surface of the distal humerus. These injuries are rare and generally are seen in adults in their 50s and 60s.[19] The usual mechanism of injury is direct trauma to the elbow that drives the olecranon against the humeral articular surface and splits the distal end.

Clinical and Radiographic Features. Patients with intercondylar fractures complain of pain at the elbow, which on examination is

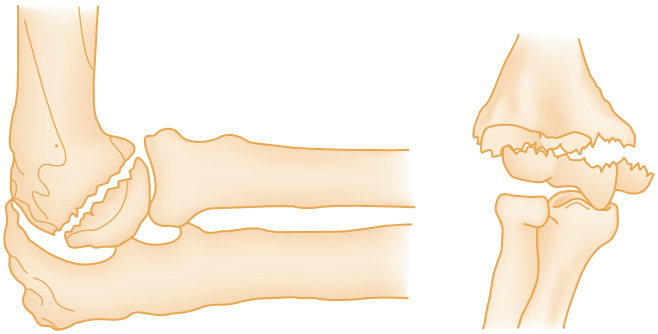


Figure 49-21. Transcondylar fracture of distal humerus. (*Left* from Ruiz E, Cicero J: Emergency Management of Skeletal Injuries. St Louis, Mosby, 1995. *Right* modified from Simon R., Koenigsknecht S: Emergency Orthopaedics: The Extremities, 2nd ed. Norwalk, Conn, Appleton & Lange, 1987.)

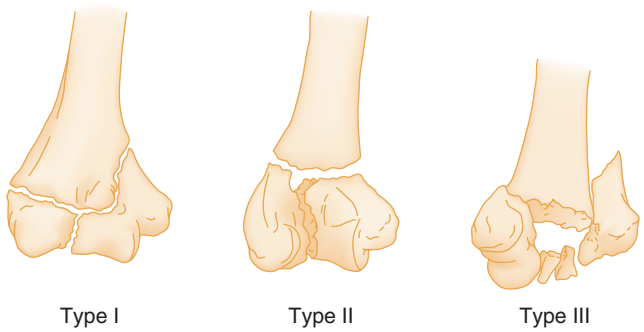


Figure 49-22. Intercondylar T fractures, types I, II, and III. (From Connolly JF: DePalma's Management of Fractures and Dislocations. Philadelphia, WB Saunders, 1981.)

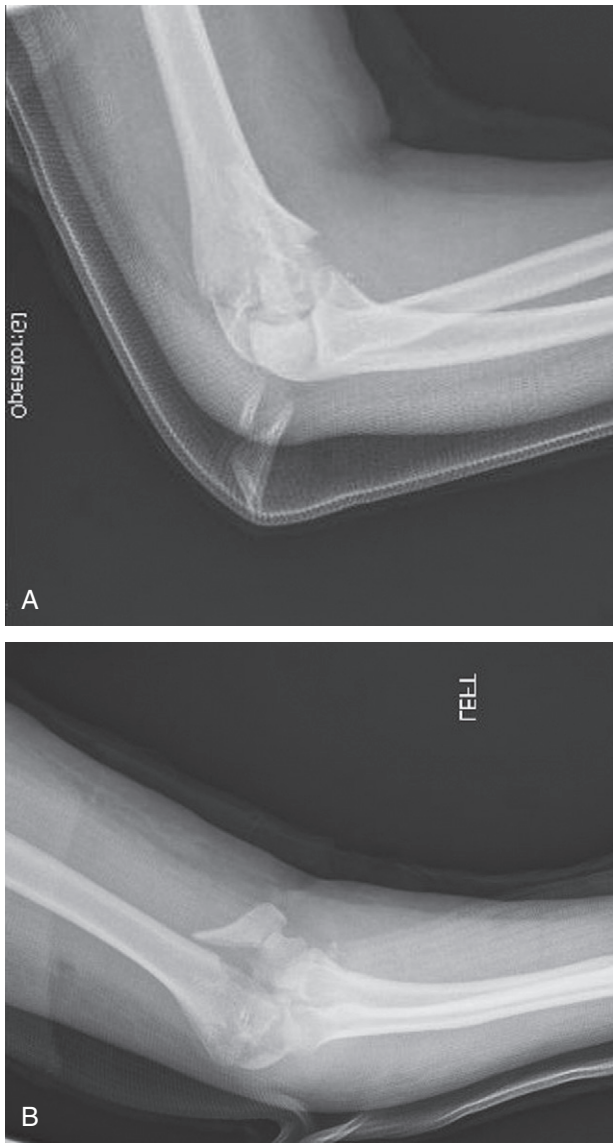


Figure 49-23. Intercondylar fracture, type III. **A,** Lateral and **B,** Anteroposterior views.

tender to palpation. Good-quality anteroposterior and lateral radiographic views are essential in evaluating fracture displacement and comminution (Fig. 49-23). Computed tomography may be used to delineate fracture patterns further. Neurovascular complications are not common with these injuries.

Management. Intercondylar fractures are notoriously difficult and complicated to treat.[20,21] The goal of treatment is to reestablish articular congruity and alignment and to begin active motion as soon as possible. Open reduction with rigid internal fixation is usually preferred. Closed treatment has been recommended for elderly patients, for patients with medical conditions that prohibit surgery, and historically for patients with nondisplaced fractures. These injuries all should be referred to an orthopedic surgeon emergently. Similar to supracondylar fractures, manipulation should be avoided, unless limb-threatening ischemia is present. Traction across the elbow with the arm extended is helpful in restoring blood flow to an ischemic forearm.

Complications. Historically, loss of elbow joint function is the most common complication reported, although this now can be largely avoided with optimal surgical technique.[22] Any method of treatment that requires prolonged immobilization is likely to result in fibrosis or ankylosis of the joint. Neurovascular complications are rare.

Lateral Condyle Fractures in Children

Lateral condyle fractures are the second most common fractures involving the elbow in children, after supracondylar fractures.[23] The fracture has a similar age distribution to a supracondylar fracture and occurs after a fall on the outstretched hand, with a varus stress applied to the extended arm.

Clinical and Radiographic Features. Tenderness and swelling are noted over the lateral aspect of the elbow. Generally, children exhibit less swelling than with supracondylar fractures, and neurovascular compromise is uncommon. Diagnosis is usually made on standard anteroposterior and lateral views, although an oblique view also may be helpful. These fractures are notoriously difficult to diagnose because fractures with minimal displacement are difficult to see radiographically and are often misdiagnosed as supracondylar humerus fractures.

Management. Nondisplaced fractures are treated nonoperatively with a cast, whereas fractures with any displacement require closed or open reduction with percutaneous pin fixation for 3 to 4 weeks.[23,24]

Complications. The risk for neurovascular compromise is much lower than that of supracondylar humerus fractures. Fractures diagnosed and treated in a timely manner should have few complications, although historically, nonunion, cubitus varus or valgus, and fishtail deformity (avascular necrosis) have been reported.[25]

Medial Condyle Fractures in Children

Medial condyle fractures are rare, constituting 1 to 2% of pediatric elbow fractures.[26] These fractures are type IV Salter-Harris injuries with physeal injury a possible outcome. The mechanism of injury is believed to be a valgus force on the extended elbow.

Clinical and Radiographic Features. The patient presents with tenderness and swelling over the medial aspect of the elbow. Anteroposterior, lateral, and oblique films may show the fracture in older children, but because the trochlea does not ossify until about age 9, plain films in younger children do not show the fracture. Magnetic resonance imaging (MRI) may be necessary to confirm the diagnosis in these patients.

Management. Operative treatment is indicated if displacement is greater than 2 mm; otherwise, conservative treatment is sufficient.

Complications. A study of 21 patients with medial condyle fractures revealed a 33% complication rate.[26] Complications included loss of reduction requiring reoperation, avascular necrosis, nonunion, and cubitus varus. Most minimally displaced fractures healed uneventfully.

Condylar Fractures in Adults

Condylar fractures are rare in adults and typically involve the articular surface and the nonarticular portion of the distal humerus, including the epicondyle (Fig. 49-24). The status of the lateral trochlear ridge is the key to analyzing humeral condyle fractures. It may be involved with either medial or lateral condylar fractures and, when incorporated into the distal fragment, is far more likely to result in instability.

Pathophysiology. Lateral condylar fractures are uncommon, although more common than those of the medial condyle. The mechanism of injury is either a direct blow to the lateral aspect of the flexed elbow or a force that results in adduction and hyperextension with avulsion of the lateral condyle. Medial condylar fractures are rare and result from either a direct blow to the apex of the flexed elbow or a fall on the outstretched arm with the elbow forced into varus.

Clinical and Radiographic Features. The presentation of condylar fractures is similar to that of other distal humerus fractures, with swelling, tenderness, and crepitus localized over either the medial or the lateral elbow. On palpation, independent motion of the involved condyle may be appreciated. In lateral condylar fractures, findings may be accentuated with movement of the radius. On radiographic examination, lateral condylar fractures show a widening of the intercondylar distance. The distal fragment is often displaced, most commonly posteriorly and inferiorly. Because of the location of the ulnar nerve, it is imperative to test its function when this fracture is present. Medial condylar fractures are associated with tenderness over the medial condyle and pain with flexion of the wrist against resistance. On radiographic examination, displaced distal fragments tend to be anterior and inferior because of the pull of the forearm flexors.

Management. Immediate treatment depends on radiographic findings. For undisplaced or minimally displaced condylar fractures, immobilization of the flexed elbow in a long arm posterior plaster splint is sufficient. For lateral condylar fractures, the forearm should be supinated and the wrist extended to relieve the tension on the extensor muscle attachments. For medial condylar fractures, the reverse is true (i.e., the forearm should be pronated and the wrist flexed). For fractures displaced greater than 3 mm, surgical fixation is required.

Complications. Complications include nonunion, restricted range of motion, joint instability, cubitus valgus or varus deformity, arthritis, and ulnar neuropathy. Because of the high rate of complications, all condylar fractures should have orthopedic consultation.

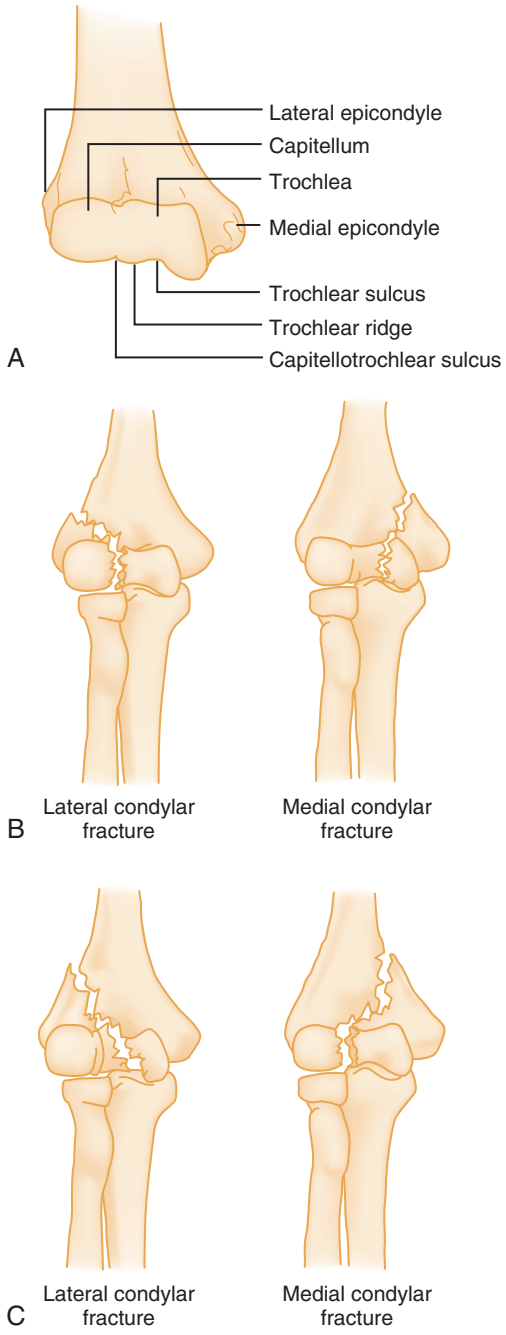


Figure 49-24. Condylar fractures. **A,** Normal anatomy. **B,** Lateral trochlear ridge not in fracture fragment (stable). **C,** Lateral trochlear ridge included with fracture fragment (unstable). (Modified from Simon R, Koenigsknecht S: Emergency Orthopaedics: The Extremities, 2nd ed. Norwalk, Conn, Appleton & Lange, 1987.)

Articular Surface Fractures

Capitellum Fractures

Pathophysiology. Although fractures of the capitellum and trochlea do occur as isolated injuries, more often they occur as a result of posterior dislocation of the elbow. Injury to the capitellum occurs when the patient falls on an outstretched hand, jamming the radial head upward, similar to a piston, shearing

Figure 49-25. Fracture of the capitellum.

off the capitellum into the radial fossa. Because the capitellum has no muscular attachments, the fragment may remain nondisplaced. More often, the fragment is displaced (usually anteriorly, but occasionally posteriorly). Because of this mechanism, a radial head fracture also may be present.

Clinical and Radiographic Features. The development of significant signs and symptoms may be delayed with capitellum fractures. Eventually, swelling within the capsule results in severe pain that manifests as well-localized tenderness on examination. Flexion of the elbow increases pain. A true lateral plain film usually shows the fragment lying anterior and proximal to the main portion of the capitellum (Fig. 49-25).

Management. Treatment begins in the ED with a posterior splint, ice packs, elevation, compression, and analgesia. Accurate anatomic alignment, rigid internal fixation, and early mobilization are prerequisites for a good functional result.[27] Fractures of the articular surfaces can be treated nonsurgically only if radiographs show perfect anatomic alignment.

Complications. Complications include post-traumatic arthritis, avascular necrosis of the fracture fragment, and restricted range of motion.

Trochlea Fractures

Pathophysiology. Isolated fractures of the trochlea are exceedingly rare because of the structure's protected position deep within the elbow joint. The shearing force of the ulna against the trochlea is associated more commonly with posterior elbow dislocation.

Clinical Features. The elbow is painful, with an effusion and limited range of motion because this is an intra-articular injury. On the radiograph, a fragment is seen lying on the medial side of the joint, just distal to the medial epicondyle, and signs of joint effusion are visible. The fracture may extend into the distal portion of the medial epicondyle.

Management. Nondisplaced fractures may be treated with a posterior splint for 3 weeks followed by early range-of-motion exercises. Displaced fractures should be treated operatively; fragments that can be internally fixed are repaired, whereas small fragments are excised. Immobilization should be minimized to 10 to 14 days.[28,29]

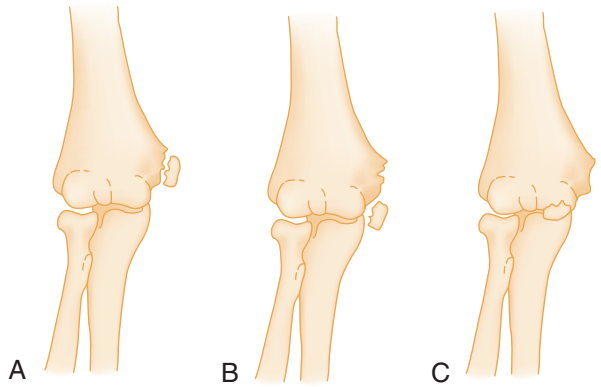


Figure 49-26. Fractures of medial epicondyle. **A,** Minimal displacement. **B,** Marked displacement. **C,** Displacement into joint. (From Connolly JF: DePalma's Management of Fractures and Dislocations. Philadelphia, WB Saunders, 1981.)

Epicondyle Fractures

Most epicondylar fractures involve the medial epicondyle. Medial epicondyle fractures are most common in children and adolescents and often involve the apophysis, which is the last ossification center to fuse in the distal humerus, usually after age 15. Fractures through this ossification center usually occur in adolescence and constitute 11% of pediatric elbow fractures.[30] These are not Salter-Harris injuries because the apophysis is involved rather than the physis. Because the lateral epicondyle is almost level with the flattened outer surface of the lateral condyle, it has only minimal exposure to a direct blow, and fracture is extremely rare.

Pathophysiology. Medial epicondyle injuries occur from a variety of mechanisms. First, avulsion fractures are associated with posterior elbow dislocations in patients younger than 20 years.[31] Second, repetitive valgus stress (as with throwing a ball) results in eventual avulsion fracture of the epicondyle (Little League elbow). Another reported cause of fracture separation of the medial epicondyle, usually in adolescent boys, is from arm wrestling.[32] Violent muscular forces associated with a shifting center of gravity during this activity seem to produce an avulsion just before closure of the epiphyseal plate. Finally, a direct blow to the medial epicondyle can cause this injury.

Clinical and Radiographic Features. The elbow is held in flexion, and any movement is resisted. Isolated fractures are associated with focal tenderness over the medial epicondyle. Use of the forearm flexors increases pain because their attachment is along the medial epicondyle. Ulnar nerve function should be evaluated. When associated with a posterior dislocation, the examination reveals a prominent olecranon.

Simple fractures of the medial epicondyle are extra-articular injuries with limited soft tissue injury.[23] They generally do not produce a fat pad sign on the lateral radiographic view of the elbow. A posterior fat pad or significant swelling of the joint should suggest concurrent injuries, such as elbow dislocation. Careful radiographic evaluation is especially important because fracture fragments may migrate into the joint space. If the fragment is overlying the joint line on radiographic examination, it should be considered intra-articular (Fig. 49-26). Radiographic detection of the intra-articular fragment is often difficult.[31] Associated ulnar nerve palsy may be present with an entrapped fragment. Fragments may be difficult to see on radiographs, and a true anteroposterior view is difficult to obtain because of severe pain on extension. In an adolescent patient, there is a tendency to confuse the normal radiolucent epiphyseal growth plate with a fracture. Additionally, mini-

mally displaced fractures may be difficult to appreciate with radiographs. Comparison films of the uninjured elbow may be necessary. If dislocation is present, repeat radiographs taken after reduction should be evaluated for fragment location.

Management. If the fracture fragment is minimally displaced (<5 mm), treatment with a posterior splint is appropriate.[33] To minimize distraction of the fragment by the forearm flexors, the elbow and wrist are flexed with the forearm pronated.

Treatment of displaced fractures is controversial. In the past, the amount of displacement often dictated the need for surgery. Results of operative and nonoperative treatment seem to be good, however, regardless of the degree of displacement.[34] Some experts advocate surgery for patients who participate in high-performance athletic activities that involve the injured extremity, but controlled studies are lacking.[24] Intra-articular fragments that cannot be removed from the joint by manipulation are an indication for surgery.[34] Immediate orthopedic consultation should be sought for these injuries. Treatment of the rare lateral epicondylar fracture in an adult involves simple immobilization until pain resolves.[35]

Little Leaguer's Elbow

Little Leaguer's elbow warrants special mention. An adolescent pitcher traumatizes immature epiphyses by repetitive throwing. Throwing the curve ball or breaking ball has been implicated as a particular culprit, although the most important factor appears to be the total number of pitches per game.[36] It has been shown in a group of highly competitive young baseball players that this injury is also common in catchers and fielders.[37] The adolescent bone structure cannot withstand the extreme loading produced by repetitive hard throwing. Avulsion of the medial epicondyle or compression fracture of the subchondral bone of the lateral condyle or radial head may result (Fig. 49-27). This diagnosis should be sought in an athletic adolescent with medial epicondyle or radial head pain in the absence of acute injury by history. Adolescents with this condition should be forced to rest the elbow if throwing causes pain. After healing occurs, the amount of throwing and technique should be monitored carefully. The Committee on Sports Medicine and Fitness of the American Academy of Pediatrics and Little League Baseball recommend preventive measures to avoid these injuries, especially in pitchers. The latest updates on new rules set forth by Little League Baseball can be found at www.littleleague.org.

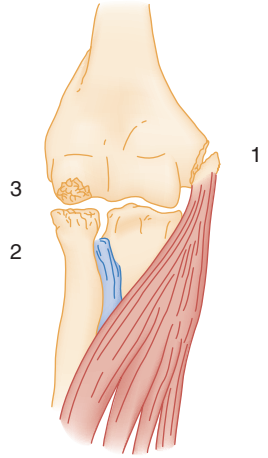


Figure 49-27. Little leaguer's elbow. Avulsion fracture of medial epicondyle (*1*). Compression fractures of the radial head (*2*) and capitellum (*3*). (From Connolly JF: DePalma's Management of Fractures and Dislocations. Philadelphia, WB Saunders, 1981.)

Olecranon Fractures

Pathophysiology. Fractures of the olecranon may result from one of several mechanisms. Most commonly, a direct blow as a result of a fall, a motor vehicle or motorcycle crash, or an assault produces this injury. Such injuries are frequently comminuted. Less commonly, indirect force applied by forceful contraction of the triceps while the elbow is flexed during a fall can cause a transverse or oblique fracture through the olecranon. A combination of direct and indirect forces is believed also to cause some of these fractures. Olecranon fractures occur in adults and less commonly in children.[38] The anatomic integrity of the olecranon is essential for triceps strength and normal function of the elbow, similar to the way intact patellar function is necessary for extension of the knee.

Clinical Features. Physical findings may include tenderness and pain over the olecranon, a palpable separation at the fracture site, or the inability to extend the elbow against force. This last finding indicates complete discontinuity of the pulling mechanism and the consequent failure of triceps function. The neurovascular status should be examined, with special attention given to the ulnar nerve distribution because this structure is most vulnerable to injury in this location. Loss of sensation over the palmar aspect of the fifth digit and hypothenar eminence or motor weakness in the interossei muscles of the hand suggests ulnar nerve injury.

Diagnostic Strategies. Lateral radiographic views are most helpful. In addition to noting the fracture, the degree of comminution, the extent of articular surface disruption, and the amount of displacement in the 90-degree flexion position should be noted. Nondisplacement in this position indicates that the triceps aponeurosis is intact, and prolonged immobilization is unnecessary. Displacement of more than 2 mm is considered an indication for surgery (Fig. 49-28A). A fracture line that increases in separation with flexion of the elbow also is considered a displaced fracture. When this fracture is associated with elbow dislocation, the plane of instability is located through the fracture site and the radiohumeral joint, resulting in posterior displacement of the proximal fragment of the ulna and anterior dislocation of the radius and ulna as a unit (Fig. 49-28B).

Management. Undisplaced fractures can be treated conservatively on an outpatient basis with ice, compression, immobilization in 45 to 90 degrees of flexion, and analgesia. Follow-up films should be done at frequent intervals to ensure that subsequent displacement does not occur. Range-of-motion exercises can be started within 3 weeks in many cases.

Displaced fractures or fracture-dislocations require open reduction and internal fixation and should be referred immediately to an orthopedic consultant. Displaced fractures in elderly patients sometimes are treated conservatively, but this should be left to the discretion of the consultant. Orthopedic referral also is necessary when ulnar nerve symptoms are present. These symptoms occur in 10% of patients, and in most cases the injury is an ulnar contusion that resolves spontaneously. The long-term outcome of treated olecranon fractures in adults is usually favorable with a low incidence of subsequent arthritis.[39]

Radial Head and Neck Fractures

Pathophysiology. Radial head and neck fractures generally are produced by an indirect mechanism, typically a fall on an outstretched hand. The radius transmits the force upward, drives the radial head against the capitellum, and results in fracture of the weaker radial head or neck. Although the fracture of the radial head may be the only radiographic finding, damage to the articular surface of the capitellum and injury to the collat-

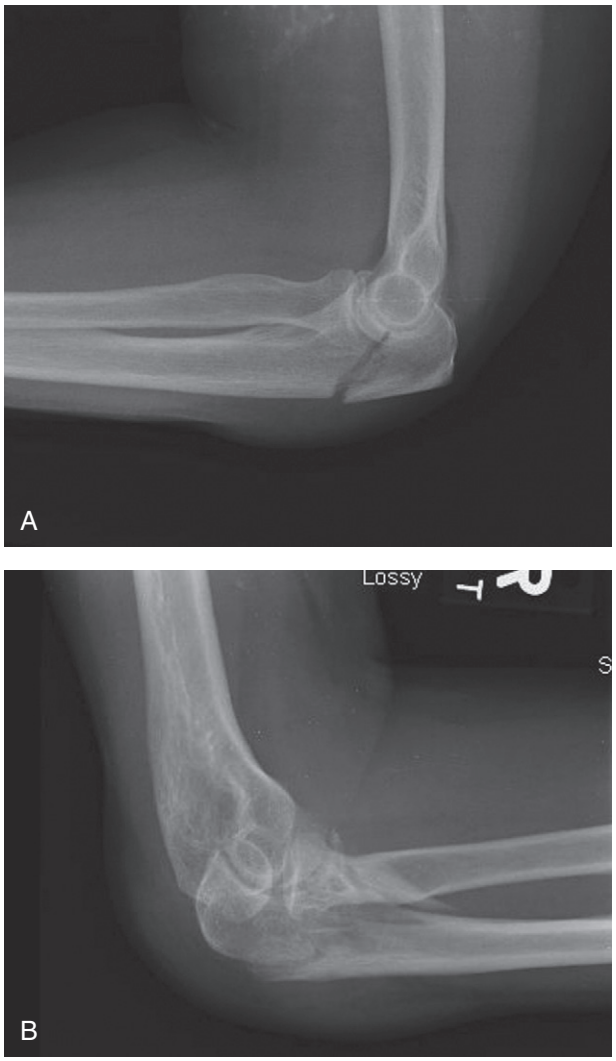


Figure 49-28. **A,** Olecranon fracture with displacement, **B,** Fracture accompanied by radial head dislocation.

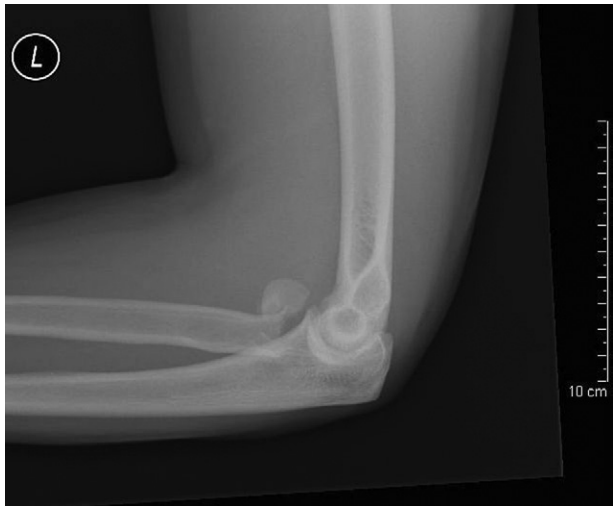


Figure 49-29. Radial head fracture with displacement.

Figure 49-30. Elbow dislocation, posterior and anterior. (Modified from Simon R, Koenigsknecht S: Emergency Orthopaedics: The Extremities, 2nd ed. Norwalk, Conn, Appleton & Lange, 1987.)

eral ligament commonly occur. Displacement of the radial head fragment suggests considerable force and significant soft tissue injury. This injury is characterized by localized tenderness over the radial head or pain with passive rotation of the forearm.

Diagnostic Strategies. Radiographic findings range from a subtle disruption of the usual gradual sweep of the radial neck and head surface to an obvious displaced or comminuted fracture (Fig. 49-29). Undisplaced fractures are notoriously difficult to see on radiographs. Tenderness coupled with a positive fat pad sign on radiograph should be treated as a radial head fracture even in the absence of a visible fracture. Radial head fractures are classified into four types:

- Type I—undisplaced fractures
- Type II—marginal fractures (involving <30% of the articular surface) with displacement, including impaction or angulation
- Type III—comminuted fractures of the entire radial head
- Type IV—any of the above with elbow dislocation

Management. Type I nondisplaced fractures are treated symptomatically by a brief period of sling support and early range-of-motion exercises (within 24–48 hours). Aspiration of the hemarthrosis and injection of 0.5% bupivacaine into the joint space may give dramatic relief of pain and improve the range of motion.[40] Most patients with this injury recover well in 2 to 3 months. A few do poorly, however, with long-term pain, contracture, or inflammation.

Type II injuries usually are treated similarly, with aspiration, instillation of bupivacaine, and immobilization in the ED, followed by a trial period of range-of-motion exercises. In these cases, aspiration of the joint and instillation of bupivacaine not only relieve pain, but also allow testing of the range of motion to identify entrapped fragments. Radial head excision sometimes is performed later if the patient fails to improve. Early excision is advised for type II fractures when a mechanical block is present and for most type III fractures. Long-term functional results after radial head excision are acceptable in most patients, although a few have some functional disability after this procedure.[41,42] Type IV injuries are treated for the elbow dislocation as described next and for the specific radial head lesion.

DISLOCATION AND SUBLUXATION

Elbow Dislocation

Because of its anatomic structure, the elbow is inherently subject to mechanical instability, and dislocations are common. The elbow is second only to the shoulder as the most commonly dislocated large joint. *Elbow dislocation* is a term usually used to describe a disruption of the relationship between the humerus and the olecranon. Generally the radius and ulna, bound together firmly by the annular ligament and interosse-

ous membrane, displace as a unit. Most classifications refer to the abnormal position of the ulna relative to the humerus. The elbow most often dislocates posteriorly, although it may dislocate anteriorly, medially, or laterally (Fig. 49-30). A dislocation also may occur between the radius and ulna, and such dislocations rarely occur concurrently with the ulnohumeral type. The latter are termed *divergent* dislocations.

Dislocation of the elbow requires considerable energy, and it is not surprising that a significant number of dislocations are associated with fractures of adjacent bony structures. A fracture-dislocation injury is referred to as a complex elbow dislocation. Immediate reduction of these dislocations is imperative to relieve pain and to prevent circulatory embarrassment or cartilaginous damage.

Posterior Elbow Dislocation

Pathophysiology. The mechanism of injury is a fall on the outstretched hand or wrist, the elbow being either extended or hyperextended at the time of impact. A valgus stress usually also occurs. The resultant forces lever the ulna from the trochlea and produce the dislocation.

Clinical and Radiographic Features. Patients hold the elbow in flexion at approximately 45 degrees and have marked prominence of the olecranon. Some elbow dislocations reduce before examination in the ED, presenting a confusing picture. In any case, significant diffuse tenderness and swelling are present. Neurovascular status must be checked because brachial artery and median nerve injuries have been described. Neurovascular injury may occur from numerous mechanisms, including the initial traction, local swelling, and entrapment during reduction.[43] Repeat examinations are mandatory.

A radiographic example of elbow dislocation before reduction is provided in Figure 49-31. Radiographic evaluation is crucial before manipulation to rule out fractures that can mimic dislocation on examination. Also, several fractures commonly occur in conjunction with dislocation, and these need to be identified and treated when present. These include fractures of the distal humerus, radial head, and coronoid process.

Management. Orthopedic consultation is usually not necessary to proceed. Reduction should be attempted immediately especially if there is neurovascular compromise. Intra-articular injection of local anesthetic may provide adequate analgesia to allow for closed reduction. Procedural sedation is very helpful and often required to facilitate reduction. Rarely is a regional block or general anesthesia needed. Posterior dislocations are reduced with an assistant immobilizing the humerus and applying countertraction while traction is applied to the distal forearm. The ideal position is for the elbow to be flexed at 30 degrees with the forearm supinated while distal traction is applied. When the capitellum slides over the coronoid process, a coupling sound occurs as the articular surfaces mesh. If reduction is unsuccessful with this technique, the physician should apply downward pressure at the proximal forearm and apply pressure behind the olecranon while maintaining in-line traction. This downward force may help "unlock" the coronoid process, which may be trapped in the olecranon fossa. The joint is gently moved through its normal range of motion to check stability. If stable, the elbow is flexed to approximately 90 degrees and immobilized with a posterior plaster mold. The neurovascular status should be rechecked. Postreduction radiographs are important to avoid missing concomitant fractures of the coronoid process or radial head or, in children, separation of the medial epicondylar apophysis.

Postreduction management includes immobilization in a posterior splint with the elbow in as much flexion as circulation allows. The arm is suspended in a sling. Circular casting should be avoided initially. Patients can be discharged with instructions to apply ice, elevate, and watch for signs of vascular impairment. Patients should not be discharged until and unless they can follow such instructions. If the elbow is stable after reduction, gentle range-of-motion exercises may be initiated in 3 to 5 days. Unstable joints may require either prolonged immobilization in the presence of ligamentous instability or internal fixation for instability associated with fracture.[44]

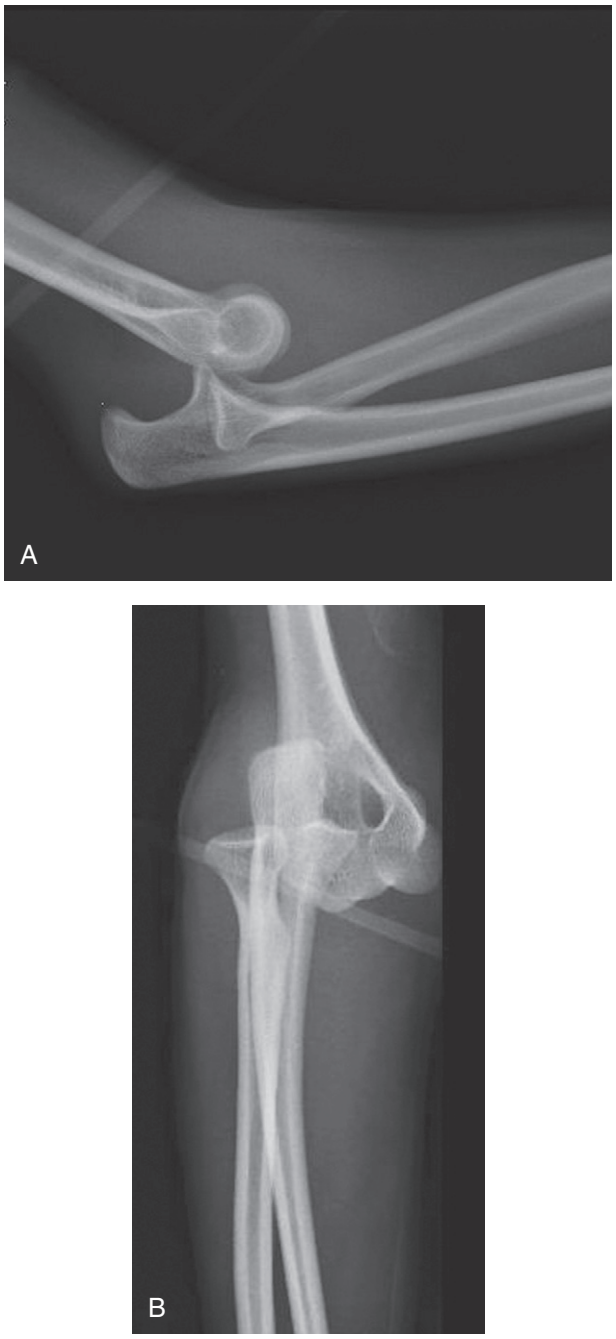


Figure 49-31. Characteristic posterior dislocation of elbow, lateral (**A**) and anteroposterior (**B**) views.

Complications. The most serious complication of elbow dislocation is vascular compromise. Severe disruption results in injury to the brachial artery in 8% of cases.[45] Vascular injury should be sought when a wide opening between the tip of the olecranon and the distal humerus is palpated or seen on a radiograph. The presence of distal pulses is not proof of an intact artery, and if a question of vascular compromise

exists, emergent vascular studies or consultation is indicated. Median nerve traction injuries and entrapment also have been reported. Loss of median nerve function after reduction should prompt immediate orthopedic consultation. Recurrent dislocation of the elbow is rare.

Medial and Lateral Dislocations

Medial and lateral elbow dislocations are produced by a similar mechanism as in posterior dislocations with a vector of force displacing the ulna and radius as a unit either medially or laterally. The anteroposterior view is the key to determining these dislocations. Reduction is carried out with the arm in slight extension, but otherwise is similar to that for posterior dislocation. Care must be taken not to convert these to posterior dislocations during reduction. Complications and aftercare are the same as for posterior dislocations.

Anterior Elbow Dislocation

Pathophysiology. Anterior dislocations are rare and occur as a result of a blow from behind to the olecranon while the elbow is in the flexed position. Severe associated soft tissue trauma is present, including avulsion of the triceps mechanism or vascular disruption. These dislocations are frequently open.

Clinical Features. The upper arm appears shortened and the forearm elongated. The elbow is fully extended, and the forearm is supinated. The olecranon fossa is palpable posteriorly.

Management. Reduction of closed injuries is performed with distal traction of the wrist and a backward pressure on the forearm, while grasping the distal humerus. A click usually indicates that reduction has been achieved. These injuries have a higher incidence of vascular impairment than the more common posterior dislocation, but ulnar nerve injuries are unusual.[46] Emergent orthopedic referral is advised and is mandatory for open injuries or when vascular disruption is suggested.

Radial Head Subluxation

Pathophysiology

Subluxation of the radial head is a common injury, representing more than 20% of upper extremity injuries in children. Children aged 1 to 4 years are most often affected, although cases have been reported in children 6 months to 15 years of age. Girls are affected more commonly than boys and the left arm is more commonly affected than the right.[47] This injury is called *nursemaid's elbow* or *pulled elbow* because it results from a sudden longitudinal pull on the forearm while the child's arm is in pronation. Stretching of the annular ligament allows fibers to slip between the capitellum and the head of the radius, resulting in an inability of the child to supinate the arm. By the age of 5, the annular ligament becomes thick and strong and thus is far less likely to tear or be displaced. There is a recurrence rate of about 20% for this injury.[48]

Clinical and Radiographic Features

The classic history, present approximately half of the time,[47] is that of the forearm being pulled while in pronation with the elbow extended. Other mechanisms include direct trauma to the elbow or a twisting motion of the arm. Among children younger than 6 months, the mechanism of subluxation involves rolling over in bed, which may trap the involved forearm under the body with resulting longitudinal traction on the joint.[49] Clinically the arm is held in passive pronation, with slight flexion at the elbow. The child is unable or unwilling to move the arm. Resistance to supination and tenderness on direct palpation over the head of the radius are present. Swelling, ecchymosis, and deformity are absent. Examination should include inspection and palpation of the entire extremity, including the clavicle.

Radiographs appear normal and are not required when the history suggests this injury. If there is swelling or deformity, if there is an uncharacteristic history, if the child does not resume use of the arm after reduction, or if there is a possibility of child abuse, appropriate radiographic studies are recommended. If palpation of the forearm, wrist, or humerus away from the elbow elicits reproducible tenderness, radiographs should be taken to exclude other diagnoses.

Management

Reduction may be attempted on children with typical presentations and is safe even when the classic history is absent.[50] Supination-flexion method is the method most commonly used. Reduction is achieved by supination of the forearm while slight pressure on the radial head is applied with the examiner's thumb. In one continuous motion, the elbow is supinated and flexed with gentle traction applied. A click often, but not always, is felt as the radial head reduces

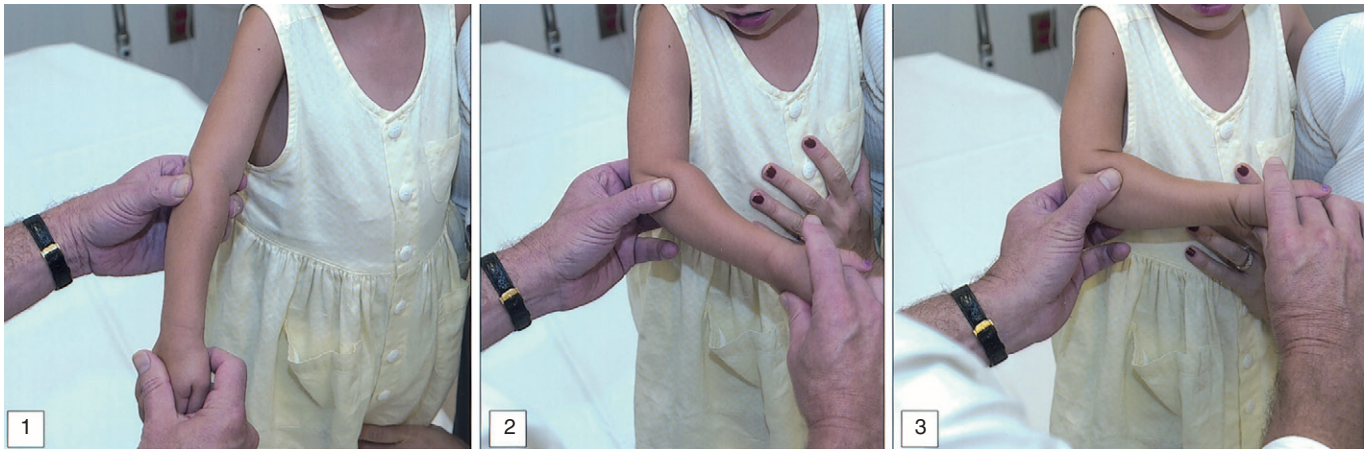


Figure 49-32. Subluxation of the radial head. Method of reduction: (*1*) Apply pressure to radial head, (*2*) supinate the forearm, and (*3*) flex elbow, in one continuous motion.

(Fig. 49-32). A second technique of reduction, hyperpronation, has a higher reported success rate of reduction on the first attempt.[51] With the hyperpronation method, the child's elbow is supported with moderate pressure applied to the radial head. The examiner then grips the child's distal forearm and hyperpronates the forearm, resulting in a click felt over the radial head (Fig. 49-33).

Many patients are asymptomatic within 5 to 10 minutes; 90% of patients regain use of the arm within 30 minutes. Hearing or palpating a click is associated with success. It is a good idea for the physician to leave the room and for parents to distract the child to show return of normal function. A fearful child often does not use even the successfully reduced limb. If function does not return within 24 hours, the patient should be reevaluated. After successful reduction, no additional treatment, immobilization, or activity reduction is necessary. Parents and caregivers should be instructed to avoid excessive traction on the child's forearm to prevent recurrent radial head subluxation. Recurrent radial head subluxation rates range from 27 to 39%.[52,53] Most of these injuries are unintentional on the part of the caregiver, but inflicted injury should be considered in suggestive cases.

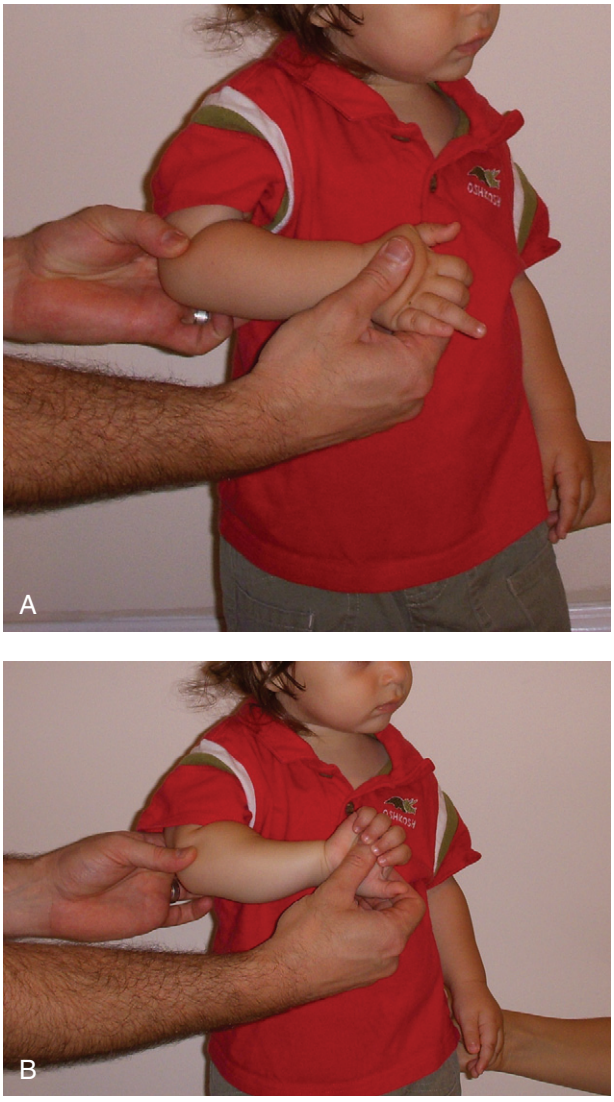


Figure 49-33. Hyperpronation method of radial head subluxation reduction: (*1*) Support elbow with pressure to radial head, (*2*) then hyperpronate the arm distally.

SOFT TISSUE DISORDERS

Epicondylitis (Tennis Elbow)

Pathophysiology

Tennis elbow is a term first introduced in the 1880s to describe an inflammatory process that involves the radiohumeral joint or lateral epicondyle of the humerus. It is a common exercise-related syndrome, and the mechanism is thought to be repetitive pronation and supination of the forearm. The actual pathologic nature of this syndrome is unclear. Radiohumeral bursitis or synovitis, tendinitis of the common extensor tendon, periostitis of the lateral epicondyle, and entrapment by scar tissue of the radial nerve all have been suggested as culprits in this syndrome. Histologically the abnormality has been described as *angiofibroblastic hyperplasia*, a term subsequently modified to *angiofibroblastic tendinosis*. The cause has been theorized to be a degenerative process because of the paucity of acute inflammatory cells seen histologically.[54] Medial tennis elbow and posterior tennis elbow have been reported, the former involving the pronator teres and flexor carpi radialis insertions and the latter involving the triceps tendon. The following discussion pertains to lateral tennis elbow.

Clinical and Radiographic Features

Whatever the cause, the onset is usually gradual. Patients have complaints of dull pain over the lateral aspect of the elbow, increased by grasping or twisting motions. Tenderness is located over the lateral epicondyle or radiohumeral joint. Supination and pronation against resistance may be painful. Pain can be shown by stretching the wrist extensors. To test this, the elbow is extended, the forearm pronated, and the wrist fully dorsiflexed.

Radiographic findings may be normal, although with chronicity, calcifications may be present over the lateral epicondyle. Characteristic MRI findings also have been described, although MRI is not indicated and generally not available in the ED.[55]

Management

Traditional treatment includes protection, rest, ice, compression, elevation, and medication. Initial therapy includes avoidance of the inciting activity and immobilization with a sling. Nonsteroidal anti-inflammatory drugs are often used, but their efficacy probably is limited to their analgesic rather than their anti-inflammatory properties.[56] Injection of a corticosteroid at the point of tenderness provides some pain relief in most patients.[57-59] Because corticosteroids weaken collagen, premature resumption of heavy loading of the tendon at the lesion should be avoided, as should injection directly into the tendon.[60] Patients with pain that persists despite treatment and a rehabilitation program should be referred for possible surgery.[61] Modification of athletic technique is recommended after the symptoms subside.

Olecranon Bursitis

Pathophysiology

Although several bursae are located in the elbow region, the olecranon bursa is the one most often involved in an isolated pathologic process. Olecranon bursitis commonly is caused by repetitive minor trauma, such as leaning on the elbow during work activities. It also may result from an inflammatory process,

such as gout or an infectious process within the bursa (septic bursitis). Septic olecranon bursitis occurs most commonly in patients engaged in work that predisposes to repetitive trauma to the elbow, such as gardening or plumbing.

Clinical Features

Patients usually have progressive pain, tenderness, and swelling over the olecranon. Some patients with septic bursitis have an abrupt onset instead, with a rapid increase in pain over a few hours. On examination, the septic bursa is typically swollen, hot, erythematous, and tender. Flexion often is limited by pain brought on by tightening of the skin over the inflamed bursa. Minor breaks in the skin, frank abrasions, or healing lacerations over the bursa may be present. In one small series, 7 of 20 patients with septic olecranon bursitis were febrile (38.5–40.3° C), 75% had cellulitis, and 25% had regional adenopathy. Noninfectious bursitis usually presents with less warmth and erythema. The skin is intact, and swelling may be the only finding. The most important aspect of evaluation is the differentiation of a septic process from a benign inflammatory one. This differentiation may be difficult on clinical grounds because considerable overlap exists in the histories and physical findings.

Diagnostic Strategies

If doubt exists, aspiration of the bursa should be performed and the aspirate sent for crystals, white blood cell count, Gram's stain, and cultures. Unless it is frankly bloody, traumatic nonseptic olecranon bursitis usually has a leukocyte count of less than 1000 cells/mm^3, whereas septic bursal fluid usually has greater than 10,000 white blood cells/mm^3.

Management

Aspiration is diagnostic and therapeutic because relief of pressure relieves some of the pain. In cases of purulent bursitis, the bursa should be drained, and appropriate antibiotics should be begun in the ED. Pending culture results, empiric antibiotics should include coverage for routine skin organisms as well as methicillin-resistant *Staphylococcus aureus* (MRSA). Bursitis refractory to aspiration and appropriate antibiotics may require incision and drainage. Noninfectious bursitis can be managed with a compression dressing, ice, nonsteroidal anti-inflammatory medications, and avoidance of the inciting activity. Patients who have had their bursa aspirated should be rechecked within 24 to 48 hours to verify culture results and monitor their response to treatment.

Biceps Tendon Rupture

Pathophysiology

Biceps tendon rupture occurs most commonly in the proximal portion of the long head of the biceps. It is most common in middle-aged athletes or physical laborers who sustain repetitive microtrauma to the tendon. Patients experience a snapping sound and pain in the anterior shoulder during strenuous activities that produce rapid loading of the muscle. Rupture also occurs distally, usually as an avulsion from the insertion on the radial tuberosity, although ruptures at the musculotendinous junction occasionally occur. Rupture of the distal biceps tendon occurs almost exclusively in men, most commonly between the ages of 40 and 60, and most often involves the dominant arm.[62] The inciting event is usually an unexpected extension force applied to the arm flexed at 90 degrees. The pathophysiology of tendon rupture is poorly understood, although tendon rupture generally occurs in the setting of underlying tendinosis. Diabetes, chronic renal failure, systemic lupus erythematosus, rheumatoid arthritis, and steroid or fluoroquinolone therapy all may result in tendinosis. Smoking has been shown to be strongly associated with distal biceps tendon rupture.[63]

Clinical Features

The diagnosis is usually obvious. In proximal tendon rupture, the patient usually has a visible defect at the top of the bicipital groove with bunching of the muscle distally. Flexing of the elbow produces pain at the proximal insertion. Flexion remains intact, however, because the short head of the biceps usually maintains its integrity. With distal ruptures, the patient complains of pain and tearing in the antecubital region. There is a visible deformity and palpable defect of the biceps muscle belly with weakness of elbow flexion and supination. If the tendon is completely ruptured, there is a bunching up of the muscle, and this effect is accentuated when the patient attempts flexion. Radiographs are not revealing and usually not necessary. MRI may be useful when a partial rupture is suggested.

Management

All patients require urgent referral to an orthopedist. Early anatomic repair of complete ruptures usually is recommended. Partial ruptures occasionally respond to conservative treatment, but also may require surgical repair. The arm should be splinted and the patient advised to apply ice and be given analgesics while awaiting orthopedic consultation.

KEY CONCEPTS

- Clinical decision rules for the elbow joint have not been validated. It is reasonable to obtain radiographs when there is significant limitation in range of motion, obvious deformity, joint effusion, or significant tenderness over any of the bony prominences or the radial head. In the absence of these, it would seem appropriate to omit radiographs in adults. The threshold for imaging should be lower in pediatric patients due to the presence of open growth plates and limitation in the physical exam.
- In children with wrist pain and traumatic mechanism of injury, the absence of a clear-cut explanation for the pain (e.g., no abnormal radiographic findings) should prompt consideration of an elbow injury causing referred pain to the wrist.
- In the setting of trauma, more than 90% of patients with the posterior fat pad sign of the elbow have intra-articular skeletal injury. In adults, a radial head fracture is implied, whereas in children, a supracondylar fracture is the probable underlying injury. In the absence of trauma, other causes of effusion (e.g., gout, infection, or bursitis) should be considered.
- The most common complication, radial nerve injury, occurs in 20% of humerus fractures. This is most often a benign neurapraxia that resolves spontaneously in most

patients, although recovery may take several months. Radial nerve injuries associated with penetrating trauma or open fractures are likely to be permanent and usually warrant operative exploration.

- Generally the radius and ulna, bound together firmly by the annular ligament and interosseous membrane, displace as a unit and typically dislocate posteriorly, although anterior, medial, or lateral dislocations may occur.
- Radiographic studies are not required when the history suggests radial head dislocation (nursemaid's elbow). If there is swelling or deformity, if there is an uncharacteristic history, if the child does not resume use of the arm after reduction, or if there is a suggestion of child abuse, appropriate radiographic studies should be obtained.
- Biceps tendon rupture occurs almost exclusively in men, most commonly between ages 40 to 60, most often involving the dominant arm, and usually subsequent to an unexpected extension force applied to the arm flexed at 90 degrees. Smoking, diabetes, chronic renal failure, systemic lupus erythematosus, rheumatoid arthritis, and steroid or fluoroquinolone therapy may predispose to this injury.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 50 Shoulder

Mohamud Daya and Yoko Nakamura

PERSPECTIVE

The shoulder joint is a unique and complex articulation unit. It has the largest range of motion of any appendicular joint in the body and can be moved through a space that exceeds a hemisphere in extent. The nature of such injuries has been long recognized: Wall paintings in Egyptian tombs from 3000 BCE show accurate drawings of manipulations (similar to the Kocher technique) used to reduce shoulder dislocations.[1] Hippocrates may have been the first to outline extensively the diagnosis and treatment of shoulder dislocations.[2]

Shoulder injuries are commonly encountered in emergency medicine. Statistical studies show that 8 to 13% of all athletic injuries involve the shoulder and that shoulder dislocations account for more than 50% of all major joint dislocations seen in the emergency department (ED). Almost every major sport or athletic activity involves use of the shoulder joint in one way or another. The shoulder can be injured by trauma (indirect or direct) or by overuse. Traumatic injuries tend to occur in football and ice hockey, whereas overuse injuries (impingement syndromes) are more common in swimming and baseball. Shoulder injuries also are common in wrestling, tennis, volleyball, and javelin throwing.[3]

In general, children are vulnerable to the same injuries as those incurred by adults; however, the presence of the epiphysis and its growth plate changes the pattern of injuries.[4] The strength of the joint capsule and its ligaments is two to five times greater than that of the epiphyseal plate. An injury that produces a sprain or dislocation in an adult often causes a fracture through the hypertrophic zone of the growth plate in a child. The shoulder girdle has epiphyseal plates at the acromion process, proximal humeral head, coracoid process, glenoid cavity, and medial end of the clavicle. Complete or greenstick fractures of the clavicle and fractures of the proximal humeral epiphysis are encountered more commonly in the pediatric population. Most shoulder injuries in children can be treated conservatively, with a good prognosis for full return of function.[4]

PRINCIPLES OF DISEASE

Anatomy

The shoulder girdle connects the upper extremity to the axial skeleton (Fig. 50-1). It consists of three bones, the *clavicle*, *humerus*, and *scapula*; three joints, the *acromioclavicular*, *glenohumeral*, and *sternoclavicular* joints; and one pseudoarticulation, the *scapulothoracic*.

The sternoclavicular joint (SCJ) represents the only true articulation between the upper extremity and the axial skeleton (Fig. 50-2). Stabilizers of this diarthrodial joint include the anterior and posterior sternoclavicular ligaments, the interclavicular ligament, and the costoclavicular ligament. The costoclavicular ligament opposes the pull of the sternocleidomastoid and is the most important stabilizing ligament.[5] The SCJ participates in all movements of the upper extremity and is the most moved joint in the body.[6] The superior mediastinum with its great vessels, trachea, esophagus, thoracic duct, lung apices, and other important structures is immediately posterior to the joint.

The clavicle is an S-shaped bone that acts as a strut to support the upper extremity and keep it away from the chest wall. It articulates medially with the sternum and laterally with the acromion process. The clavicle provides the neck with an acceptable cosmetic appearance and protects the subclavian vessels and brachial plexus. Its middle third, which is thin and untethered, is the most commonly fractured segment.[7]

The acromioclavicular joint (ACJ) connects the lateral end of the clavicle with the medial aspect of the acromion process (Fig. 50-3). The diarthroidal acromioclavicular joint has little or no bony stability and is dependent on the associated ligaments and muscles for support.[8] The weak acromioclavicular ligaments provide posterior support while the clavicular and acromial attachments of the deltoid and trapezius muscles provide static and dynamic support for the superior aspect of the joint. The most important stabilizers are the coracoclavicular ligaments (conoid and trapezoid), which provide vertical and anterior support.

The scapula is a flat triangular bone that forms the posterior aspect of the shoulder girdle. The thin body of the scapula lies flat against the posterior thorax and widens laterally to form the glenoid fossa. Its thickened borders are the attachment sites for 18 muscle origins and insertions.[9] Its thick muscle coat and ability to recoil along the posterior chest wall protect the scapula from both direct and indirect trauma.

A synovial membrane extends from the glenoid fossa to the humeral head. The membrane is large and redundant inferiorly to accommodate the extensive range of movement. Overlying the synovial membrane is a loose and redundant fibrous capsule. Anteriorly, the capsule is thickened to form the superior, middle, and inferior glenohumeral ligaments. The ante-

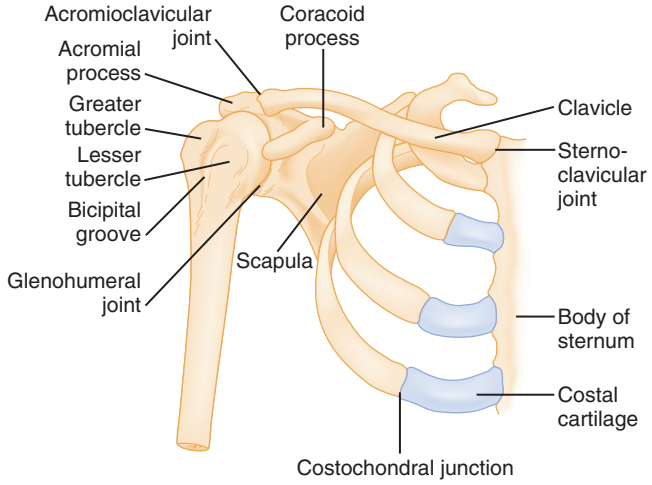


Figure 50-1. Anatomy of the shoulder girdle. (From Roy S, Irwin R: Sports Medicine: Prevention, Evaluation, Management and Rehabilitation. Englewood Cliffs, NJ, Prentice Hall, 1983.)

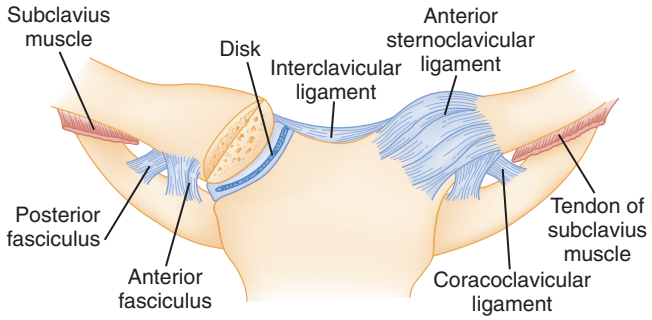


Figure 50-2. Ligaments and the interarticular disk of the sternoclavicular joint. (Redrawn from DePalma AF: Surgery of the Shoulder, 3rd ed. Philadelphia, JB Lippincott, 1983.)

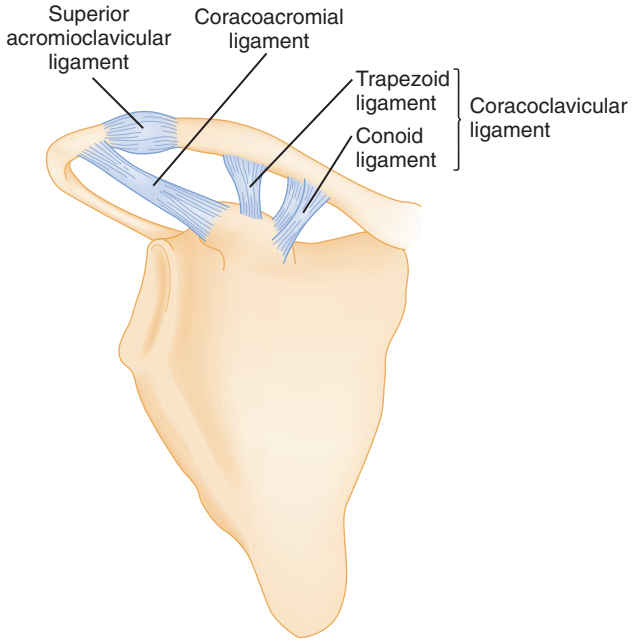


Figure 50-3. Ligaments of the acromioclavicular joint. (Redrawn from DePalma AF: Surgery of the Shoulder, 3rd ed. Philadelphia, JB Lippincott, 1983.)

rior band of the inferior glenohumeral ligament is the most important restraint to anterior glenohumeral dislocations.[10]

The glenohumeral articulation is a ball-and-socket–type joint that depends largely on associated capsule, muscles, and ligaments for stability (Fig. 50-4). A negative intracapsular pressure completes the stabilization mechanism.[10,11] The absence of bony stability permits a range of motion, however, that is greater than that of any other joint in the body.

The proximal humerus articulates with the glenoid fossa and provides for the attachment of many important muscles. The supraspinatus, infraspinatus, and teres minor insert onto facets of the greater tuberosity, whereas the subscapularis inserts onto the lesser tuberosity. Together, this group of muscles forms the rotator cuff, which helps stabilize the humeral head within the glenohumeral joint (Fig. 50-5). The long head of the biceps tendon originates from the supraglenoid tubercle and ascends over the humeral head to enter the arm via the bicipital groove. The long head acts as an additional stabilizer for the superior and anterior aspects of the glenohumeral joint (see Fig. 50-5). Long muscles that cross the articulation are involved primarily in movements of the glenohumeral joint. The pectoralis major, latissimus dorsi, and teres major muscles all insert into the humeral intertubercular groove. Displacements encountered with fractures of the humerus usually reflect the pull of these attached muscle groups. The proximal humerus is composed primarily of trabecular bone with a thin cortical shell. Changes in bone density with age (osteoporosis) greatly increase the risk of fractures in this area.[7]

The brachial plexus and subclavian vessels enter the shoulder girdle complex superiorly between the clavicle and the first rib, traverse under the coracoid process, and exit anterior to the inferior aspect of the glenohumeral joint as the median, ulnar, and radial nerves and axillary vessels. These nerves represent the final branches of the upper bracial plexus (nerve roots C5 to C8), and injuries to the brachial plexus invariably result in significant shoulder dysfunction.

CLINICAL FEATURES

History

Most complaints usually involve some combination of pain, stiffness, instability, and weakness. Pain can result from many different conditions extrinsic and intrinsic to the shoulder. Extrinsic sources of shoulder pain include disorders of the cervical spine, thoracic outlet syndromes, and Pancoast tumors. In addition, pain can be referred to the shoulder from myocardial processes, diaphragmatic irritation (e.g., subphrenic abscess, lower lobe pneumonia, splenic hematoma, ruptured ectopic pregnancy, gallbladder disease), and gastric or pancreatic diseases.

Acute intrinsic pain usually is associated with a traumatic event. The most important factors to determine are the time and mechanism of injury, its precise location, and the intensity of the pain. Occasionally the patient may have acute pain in the absence of associated trauma (e.g., calcific tendinitis). Shoulder pain also can manifest in an insidious manner, unrelated to any precipitating factor. In these instances, the duration, location, character, and aggravating and alleviating factors of the pain should be noted. Intrinsic shoulder pain in general does not radiate past the elbow.

Stiffness usually signifies a restricted range of motion resulting from an underlying painful condition of the shoulder. Instability can be seen in the form of an obvious subluxation or dislocation. Alternatively, the patient may describe the sensation of the shoulder's almost "going out." A rotator cuff tear

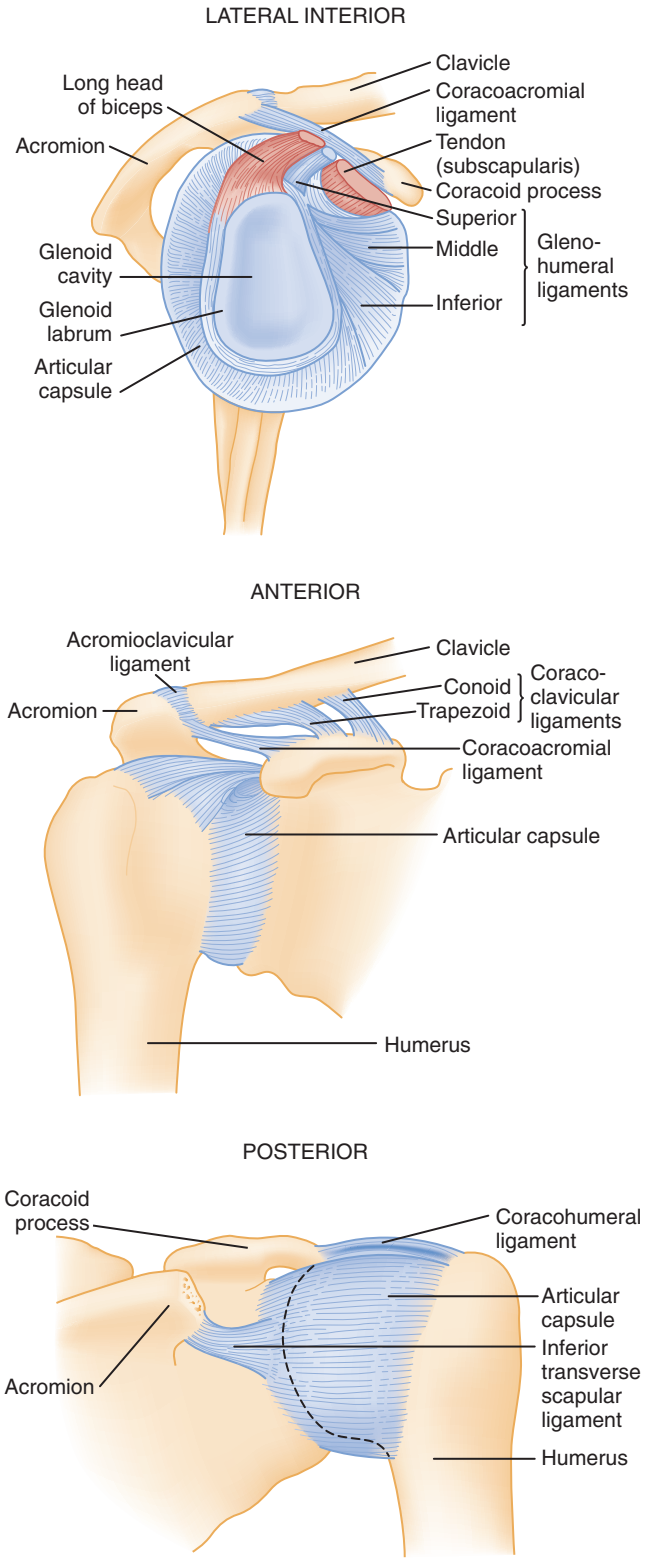


Figure 50-4. Anatomy of the glenohumeral joint.

or an underlying nerve lesion usually causes significant shoulder weakness.

Physical Examination

The shoulder should be inspected from the anterior, posterior, and lateral positions. Any obvious deformity, ecchymosis, laceration, swelling, or hematoma should be noted. The masses of the trapezius, deltoid, infraspinatus, and supraspinatus muscles should be compared with the unaffected side to detect any atrophy.

Palpation of the shoulder should be performed systematically, beginning at the SCJ and moving laterally along the clavicle to the ACJ. Next the scapula, glenohumeral joint, and humerus are palpated. Any point tenderness, crepitus, swelling, or deformity should be noted.

Active and passive ranges of motion should be tested. Active range of motion is best determined with the patient in the sitting position, which eliminates the contributions of the lumbar spine and lower extremity joints. Passive range of motion is best evaluated with the patient in the supine position. The degrees of abduction, forward flexion, extension, and internal and external rotation should be recorded and compared with those for the unaffected extremity. In addition, the motion of the scapulothoracic articulation should be observed carefully in all cases. After 45 degrees of abduction, the scapula moves approximately 1 degree for every 2 degrees of glenohumeral motion.

A thorough neurovascular examination should be performed and findings recorded in all cases before and after all manipulations. The vascular status is checked by assessing the brachial, radial, and ulnar pulses with the arms in various positions. The presence of pallor, paresthesias, or an expanding hematoma should raise suspicion for a vascular injury. A complete sensory (light touch and pinprick) and full motor examination also should be performed. The brachial plexus can be tested by evaluating the myotomes and dermatomes pertinent to each nerve root (Table 50-1).

Table 50-1 Sensory and Motor Components of the Brachial Plexus

SPINAL LEVEL	SENSORY AREA	MUSCLE
C2–4	—	Trapezius
C5	Lateral arm	Deltoid
C6	Lateral forearm and thumb	Biceps
C7	Tip of long finger	Thumb extensors
C8	Tip of little finger and medial forearm	Finger flexors
T1	Medial arm	Hand interossei

DIAGNOSTIC STRATEGIES

Radiology

The initial assessment of traumatic injuries includes a three-view series of radiographs consisting of true anteroposterior (45-degree lateral), transscapular lateral, and axillary lateral views (Figs. 50-6 and 50-7). The true anteroposterior view (see Fig. 50-7B) is preferred over standard anteroposterior views because it shows the glenohumeral joint without any bony overlap. Standard anteroposterior views taken with the joint in internal and external rotation profile the lesser and greater tuberosity and are more useful in the evaluation of soft tissue conditions.

Acceptable orthogonal views include the axillary lateral, transscapular lateral, and apical oblique.[12] The preferred view is the *axillary lateral* (see Fig. 50-7A), which projects the glenohumeral joint in a cephalocaudal plane. This view is particularly useful for defining the relationship of the humeral head with the glenoid fossa and in identifying lesions of the coracoid

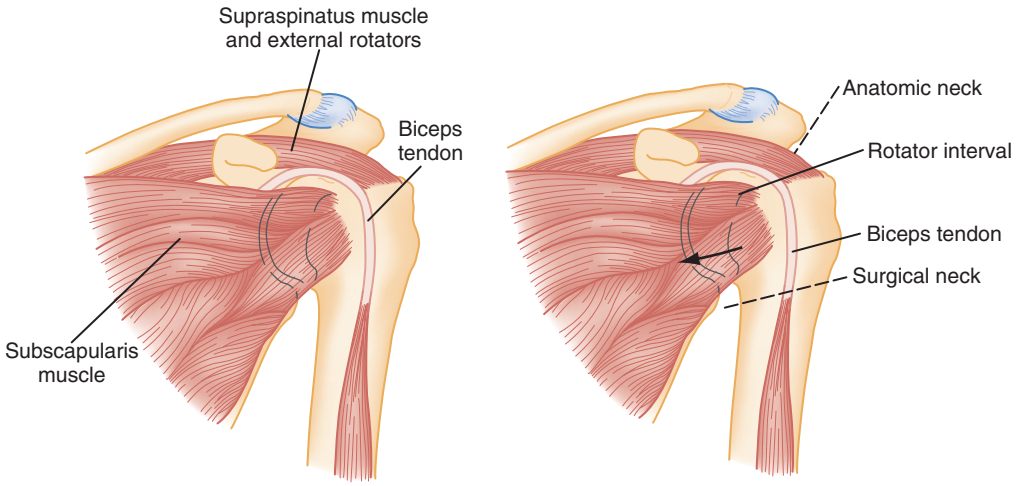


Figure 50-5. The rotator cuff.

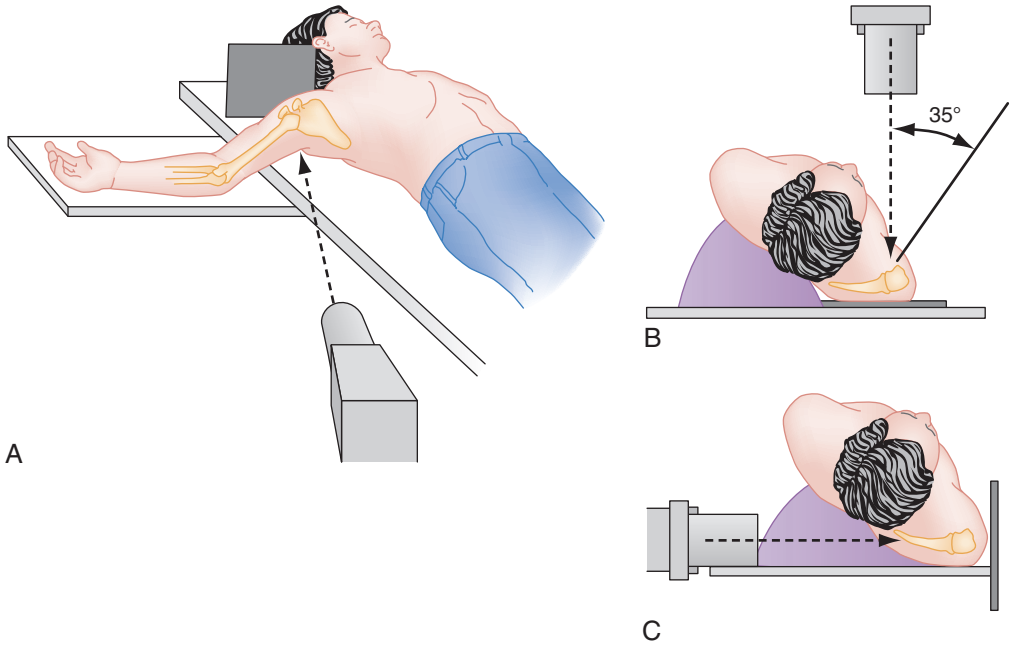


Figure 50-6. Positions for the trauma series of shoulder radiographs. **A,** Axillary view. **B,** True anteroposterior (35-degree oblique) view. **C,** Transscapular lateral view.

process, humeral head, and glenoid rim. Some degree of abduction is required to obtain the axillary view. The difficulty in obtaining this view has led to the popularity of the *transscapular* view (see Fig. 50-7B). Advantages of this projection include its simplicity and reproducibility and a clear delineation of anatomic structures. In this view, the scapula is projected as a Y, with the body forming the lower limb and the coracoid and acromion processes forming the upper limbs. The humeral head normally is superimposed over the glenoid, which is located at the junction of the three limbs. This view is particularly useful in identifying anterior and posterior glenohumeral dislocations. The *apical oblique* view (obtained by placing the injured shoulder in a 45-degree oblique position and angling the central ray 45 degrees caudally) shows the glenohumeral joint in a unique coronal projection. This view can be obtained easily and painlessly and has been found to be more sensitive than the transscapular view for detecting bone and joint abnormalities in the injured shoulder.

Plain radiographs are the mainstay of the radiologic examination in the ED, but in selected circumstances, additional bone and soft tissue details may be obtained using computed tomography (CT) or magnetic resonance imaging (MRI).[13]

SPECIFIC INJURIES

Fractures

Clavicle

Pathophysiology. The clavicle accounts for 5% of all fractures and is the most commonly fractured bone in children. Epidemiologic studies in adults have documented an annual incidence rate of 30 to 50 per 100,000 population, with a 2:1 male-to-female ratio.[14,15] Clavicular fractures are classified anatomically and mechanistically into three groups. Fractures of the medial third are uncommon (5%) and occur as a result of a direct blow to the anterior chest. Fractures of the middle third are the most frequent (Fig. 50-8), accounting for 80% of all injuries. The usual mechanism of injury involves a direct force applied to the lateral aspect of the shoulder as a result of a fall, sporting

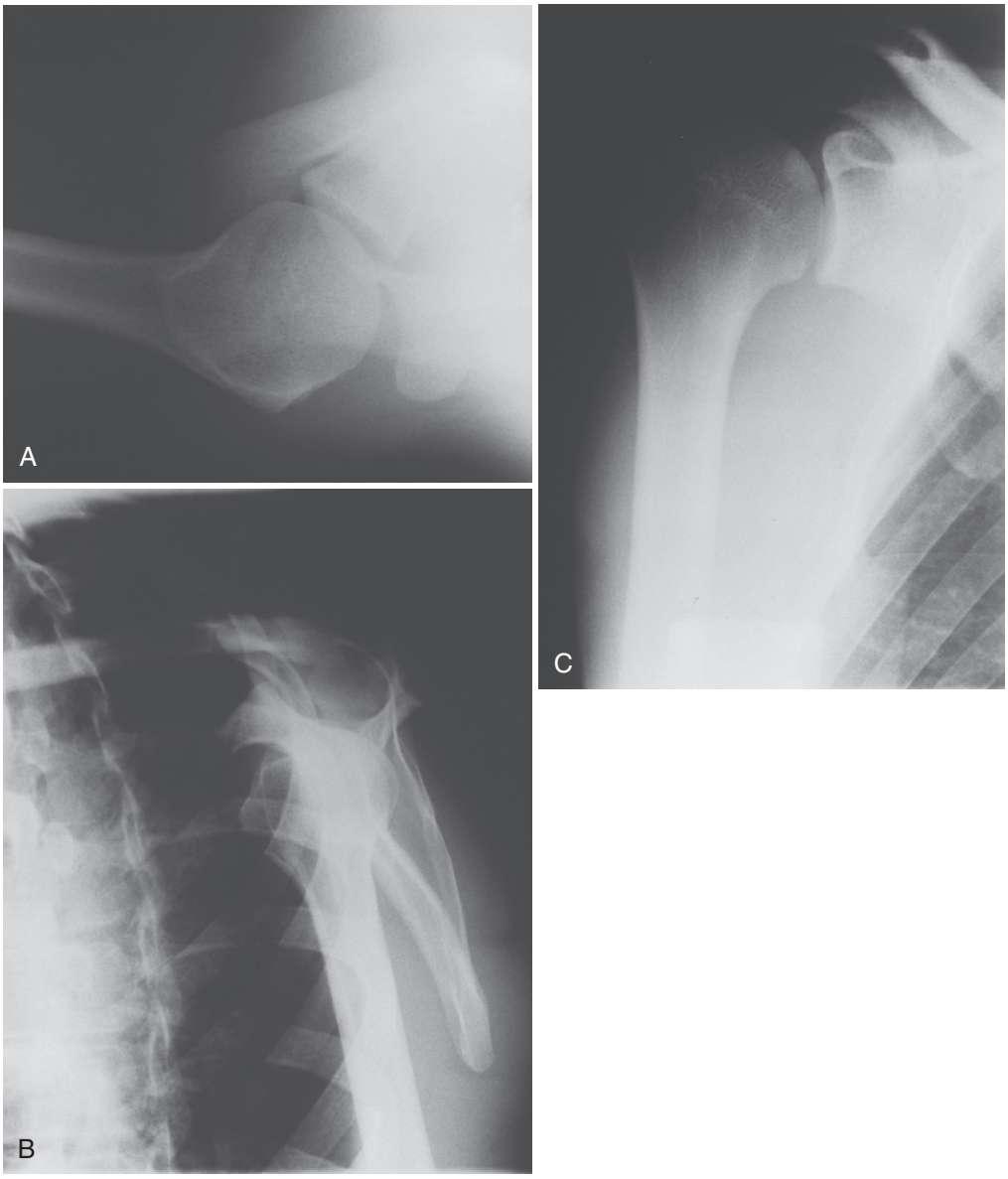


Figure 50-7. Normal axillary (**A**), true anteroposterior (**B**), and transscapular lateral (**C**) radiographic views (i.e., trauma series) of the shoulder.

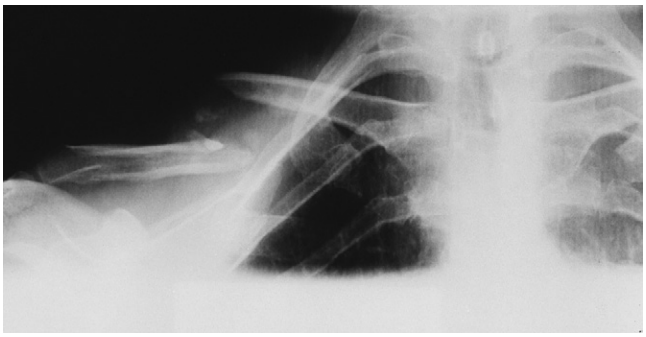


Figure 50-8. Displaced midclavicular fracture.

injury, or motor vehicle accident. Fractures of the lateral third (15%) result from a direct blow to the top of the shoulder and are classified further into three subtypes.[16] Type I fractures are stable and minimally displaced because the coracoclavicular ligament remains intact. Type II fractures are associated with a torn coracoclavicular ligament and have a tendency to displace because the proximal fragment lacks any stabilizing forces. Type III injuries involve the articular surface (Fig. 50-9).

Clinical Features. The patient has pain over the fracture site, and the affected extremity is held close to the body. With fractures of the middle third, the shoulder typically is slumped downward, forward, and inward. This positioning is a result of the effect of gravity and the pull of the pectoralis major and latissimus dorsi on the distal fragment. The proximal fragment often is displaced upward by the action of the sternocleidomastoid. The head is often tilted toward the injured side in an attempt to relax the effects of these displacing muscular forces. Ecchymosis, crepitus, and a palpable or visible deformity may be noted over the fracture site. Although associated neurovascular injury is rare, the close proximity of the subclavian vessels and brachial plexus demands a thorough assessment. Associated pneumothorax and pulmonary injuries are also rare unless an open fracture is present.[17] The newborn clavicle fracture suffered during childbirth classically manifests as an uneventful "lump," representing the area of subsequent callus formation, in a child brought in by a concerned parent.

Management. Principles of initial management include pain control, immobilization, and proper follow-up care. Fractures

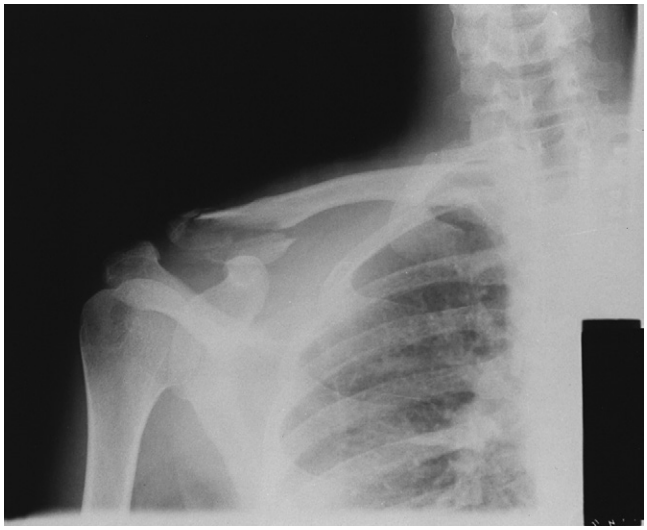


Figure 50-9. Type III lateral clavicular fracture (intra-articular). (Courtesy of David Nelson, MD.)

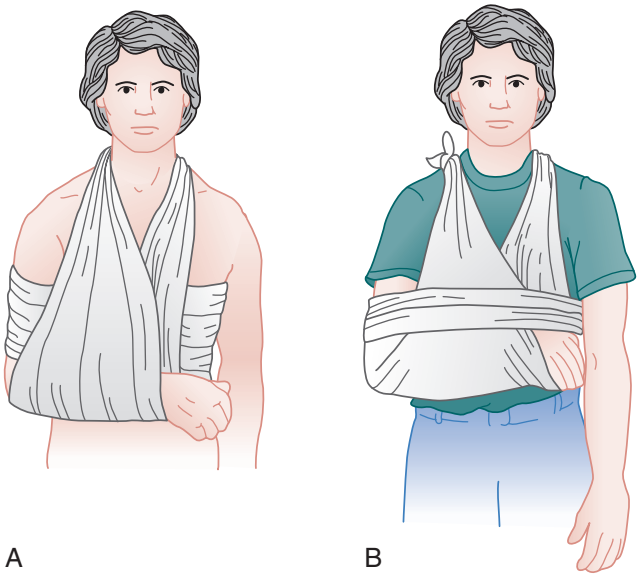


Figure 50-10. Shoulder immobilization. **A,** Sling over swathe. **B,** Velpeau sling immobilization.

of the clavicle can be immobilized with supportive devices, such as a simple sling or sling and swathe (Fig. 50-10). Another immobilization technique for midclavicular fractures still recommended in the orthopedic literature, although its efficacy is not supported by evidence, is the clavicular (figure-of-eight) splint (Fig. 50-11). This splint is applied after closed reduction of the fracture, which is accomplished by pulling the shoulders up and back. Such reductions are difficult to maintain and may be associated with increased discomfort at the fracture site. Use of clavicular splints also can lead to skin irritation and compression of the neurovascular bundle in the axilla. Because some degrees of malunion and shortening are associated with an acceptable functional and cosmetic outcome, treatment with a simple sling is a valid and appropriate alternative to the clavicular splint in the ED.[18]

Disposition. Immediate orthopedic consultation should be sought for open fractures or fractures associated with neurovascular injuries or skin tenting. More urgent orthopedic consultation (before 72 hours) is recommended for type II lateral

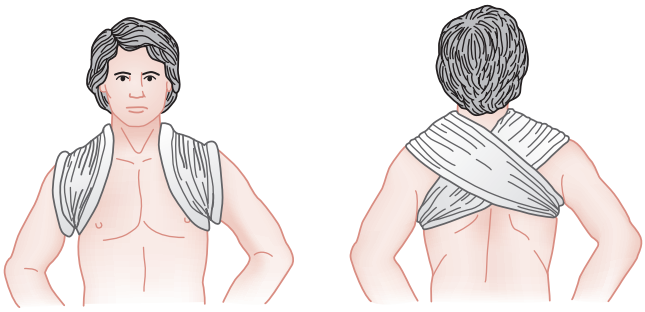


Figure 50-11. Clavicular or figure-of-eight splint.

Figure 50-12. Greenstick fracture of the clavicle *(arrow)*.

clavicle fractures because these fractures have a 30% incidence of nonunion and may require surgical repair.[16] Severely comminuted or displaced fractures of the middle third (defined as more than 20 mm of initial shortening) may also benefit from early orthopedic referral because these injuries have been associated with a higher incidence of nonunion.[19,20] Greenstick fractures of the midclavicle are common in children (Fig. 50-12). Most of these fractures are nondisplaced and heal uneventfully. Initial radiographs may appear normal despite suggestive clinical findings. In these instances, the arm should be immobilized in a simple sling and the radiographic evaluation repeated in 7 to 10 days if symptoms persist.

Most fractures of the clavicle heal uneventfully, and follow-up can be provided by a primary care physician. A sling should be worn until repeat radiographs show callus formation and healing across the fracture site. Passive shoulder range-of-motion exercises (Fig. 50-13) are encouraged to reduce the risk of adhesive capsulitis. Younger children generally require shorter periods of immobilization (2 to 4 weeks) than adolescents and adults (4 to 8 weeks). Vigorous competitive play should be avoided until the bone healing is solid. A full motion of the shoulder and an absence of pain are two good clinical signs that the fracture has healed.

Complications. Complications are unusual, with the most common ones being delayed union or nonunion.[14-16] Complications after fractures of the medial third resemble those associated with posterior sternoclavicular dislocations. Fractures of the middle third have been associated with injuries to the neurovascular bundle and the pleural dome. Articular surface injuries (type III lateral clavicle fractures) can lead to subsequent osteoarthritis of the ACJ.

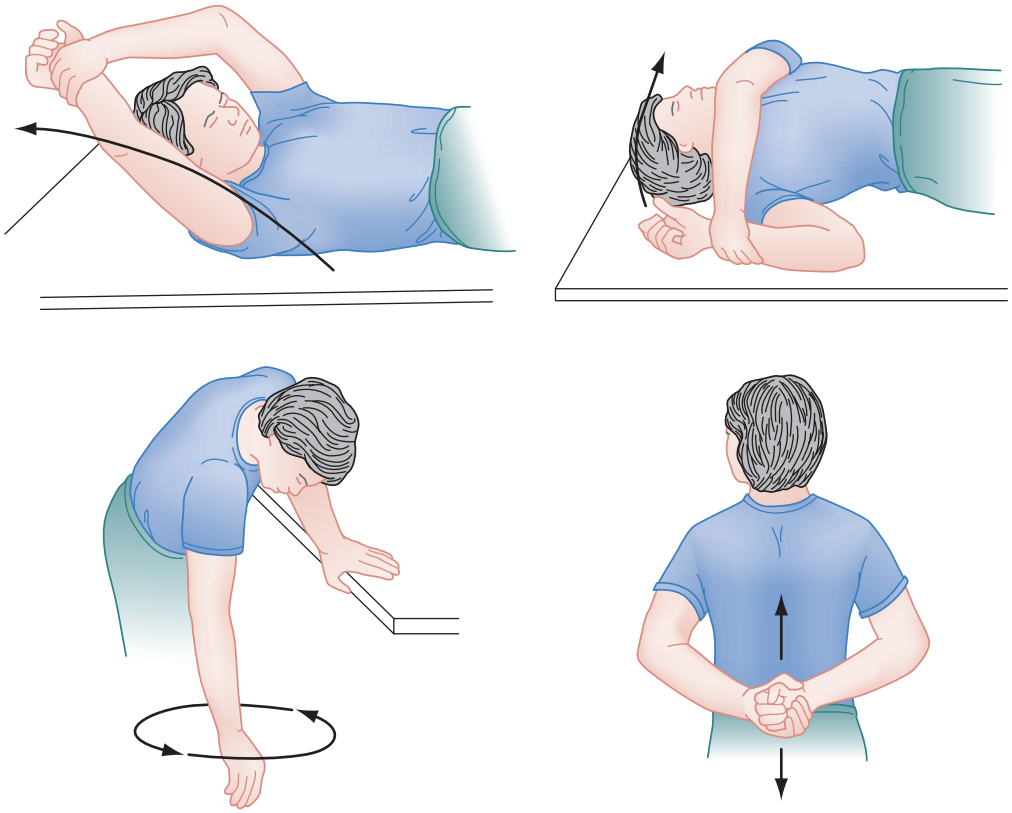


Figure 50-13. Types of active and passive shoulder exercises. *Top left*, active flexion; *top right*, active external rotation; *bottom left*, pendular; and, *bottom right*, active internal rotation.

An uncommon but important association is that between clavicle fractures and atlantoaxial rotatory displacement (AARD).[19] Most cases occur in girls younger than 10 years of age. The pathophysiology may involve a lax or disrupted alar ligament along with sternocleidomastoid spasm.[19,21] Early diagnosis is important because delayed diagnosis can lead to a chronic deformity requiring surgery. AARD should be suspected if the child has a clavicle fracture and demonstrates a "cocked-robin" position with the head bent toward the fractured side but rotated in the opposite direction. The injury is best demonstrated by CT and, if recognized early, can be treated with a soft cervical collar or halo traction.[19]

Scapula

Pathophysiology. Fractures of the scapula are rare injuries, with an annual incidence of 10 to 12 per 100,000 population.[22] They account for 1% of all fractures and occur primarily in men 30 to 40 years old.[9] In general, considerable force and energy are required to fracture the scapula. Most fractures result from high-speed motor vehicle collisions (MVCs), falls from heights, or crush injuries.[9,23,24] Coracoid process fractures usually are avulsive, and glenoid rim fractures are commonly associated with anterior glenohumeral dislocations. An acromial process fracture usually results from a direct blow to the top of the shoulder.

The most important aspect of scapular fractures is the high incidence (75% to 98%) of associated injuries to the ipsilateral lung, chest wall, and shoulder girdle complex.[9,23,24] The most common associated orthopedic injuries are fractures of the ribs, proximal humerus, and clavicle. Associated lung injuries include pneumothorax, hemothorax, and pulmonary contusion; these may manifest in delayed fashion, 2 to 3 days after the initial injury. Associated injuries of the head, spinal cord, brachial plexus, and subclavian or axillary vessels are more significant but less common.[9,23,24] Of note, blunt aortic injury is not more common in patients with a fractured scapula.[24]

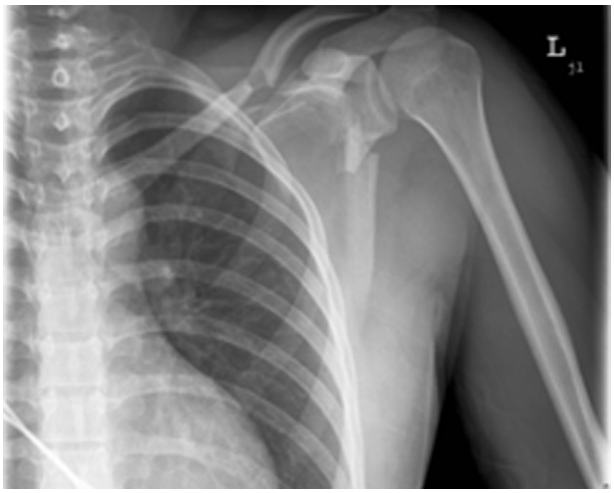


Figure 50-14. Type II scapular fracture involving the neck of the scapula. Note the associated midclavicular fracture.

Fractures of the scapula can be classified according to their anatomic location. In the system proposed by Ada and Miller,[23] type I fractures involve the acromion process, scapular spine, or coracoid process. Type II fractures involve the scapular neck (Fig. 50-14), and type III injuries are intra-articular fractures of the glenoid fossa. The most common are type IV fractures, which involve the body of the scapula.[23]

Clinical Features. In a conscious patient, the shoulder is adducted, and the arm is held close to the body. Any attempts at movement result in significant pain. Associated tenderness, crepitus, or hematoma may be noted over the fracture site. The clinical findings occasionally mimic those with a rotator cuff tear. Hemorrhage into the rotator cuff associated with the

scapula fracture can result in spasm and a temporary reflex inhibition of function (pseudorupture).[23] The presence of a scapula fracture mandates a thorough search for associated thoracic, intracranial, orthopedic, and neurovascular injuries.

Diagnostic Strategies: Radiology. The trauma series of shoulder radiographs will reveal most fractures, as will careful examination of the scapula on the trauma chest radiograph. The axillary lateral view is especially useful in evaluating fractures of the glenoid fossa and the acromion or coracoid process.[9] An os acromiale (unfused acromial process epiphysis) is present in 3% of the population and should not be confused with a fracture of the acromion.[7] A comparison film can be useful because the abnormality is present bilaterally in 60% of cases. In many patients, fractures of the scapula initially are overlooked despite being readily apparent on the initial supine trauma chest radiograph because of the life-threatening nature of the associated injuries.[9]

Management. Most fractures, including fractures with severe comminution and displacement, heal rapidly with conservative therapy.[9,23] Initial therapy consists of analgesia and immobilization in a sling to support the ipsilateral upper extremity. Passive shoulder exercises (see Figure 50-13) are initiated as soon as discomfort subsides, to reduce the risk of adhesive capsulitis. In general, patients require a sling for 2 to 4 weeks.

Fractures of the body and spine usually require no further therapy. Nondisplaced fractures of the acromion process also respond well to conservative therapy. Displaced acromial fractures that impinge on the glenohumeral joint require surgical management. Rarely, the acromion is fractured as part of a superior dislocation of the humeral head. In these instances, an accompanying tear of the rotator cuff is invariably present and requires surgical repair. If the coracoclavicular ligaments remain intact, fractures of the coracoid process respond well to conservative therapy. Severely displaced coracoid fractures with ruptured coracoclavicular ligaments usually require open reduction and internal fixation.[6] Scapular neck and glenoid fossa fractures present the most difficult management issues. Although most of these injuries do well with conservative therapy, open reduction and internal fixation are recommended for severely displaced or angulated fractures.[23]

In a review of 520 scapula fractures from 22 case series, Zlowodzki and coworkers reported that 80% of all fractures with glenoid involvement were treated operatively, whereas 83% of all neck injuries and 99% of all isolated scapula body fractures were treated nonoperatively.[22]

Complications. Associated injuries of the ipsilateral lung, chest wall, and shoulder girdle account for most complications after fractures of the scapula. A shear-type brachial plexus injury has been associated with fractures of the acromion process. Neurovascular (brachial plexus, axillary artery) injuries also have been reported with fractures of the coracoid process.[6] Scapular neck, body, or spine fractures that extend into the suprascapular notch can injure the suprascapular nerve.[6] Delayed complications include adhesive capsulitis and rotator cuff dysfunction.

Proximal Humerus

Pathophysiology. Fractures of the proximal humerus are common and account for 4 to 5% of all fractures.[25] A prospective Swedish study reported an incidence of 114 per 100,000 population, with a mean age at occurrence of 67 years and a female-to-male ratio of 3:1.[26] These fractures occur primarily in the older population, in whom structural changes associated with aging (osteoporosis) weaken the proximal humerus, predisposing it to injury. Although most of these injuries involve minimal displacement and are adequately managed with conservative therapy, significantly displaced fractures may require operative intervention. Displacements encountered with fractures of the humerus usually reflect the pull of the attached muscle group.

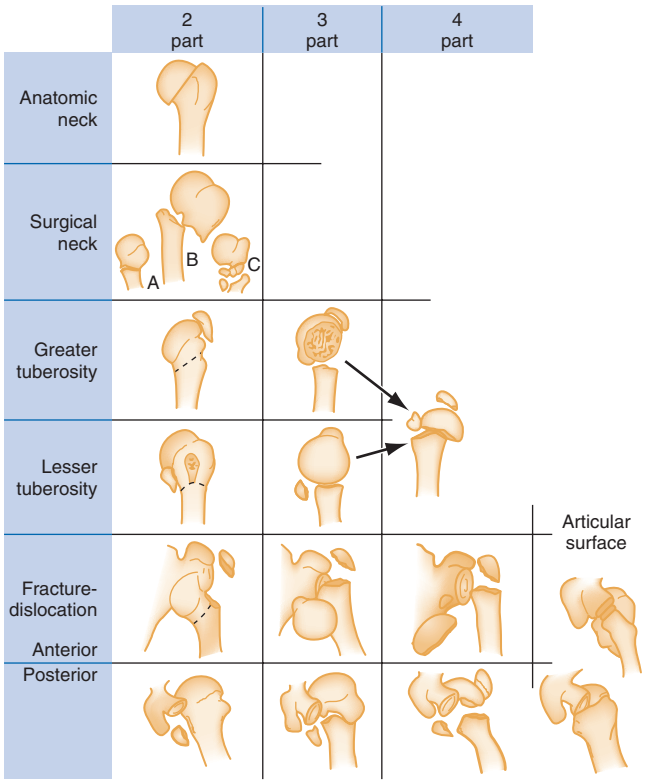


Figure 50-15. Neer's classification of proximal humeral fractures. (From Neer CS: Displaced proximal humeral fractures: Part 1. Classification and evaluation. J Bone Joint Surg Am 52:1077, 1979.)

Fractures of the proximal humerus separate along old epiphyseal lines, producing four distinct segments consisting of the articular surface (anatomic neck), greater tuberosity, lesser tuberosity, and humeral shaft (surgical neck). The Neer classification system (Fig. 50-15) is based on the relationship of these fracture fragments.[27,28] In this system, a segment is considered displaced if it is angled greater than 45 degrees or separated more than 1 cm from the neighboring segment. Because this classification system considers only displacement, the number of fracture lines is irrelevant. There are four major categories of fracture: minimal displacement (Fig. 50-16), two-part displacement (Fig. 50-17), three-part displacement, and four-part displacement. When present, anterior and posterior dislocations are included as part of the classification. Impaction and head-splitting fractures are classified separately.

The classic mechanism of injury involves a fall on an outstretched abducted arm. Concurrent pronation limits further abduction and levers the humerus against the acromial process; this produces a fracture or dislocation, depending on the tensile strengths of the bone and surrounding ligaments. Older patients are prone to fracture, whereas younger persons are apt to have dislocations. The combined injury (fracture and dislocation) may be seen in middle-aged patients. Proximal humerus fractures also may result from a direct blow to the lateral side of the arm or from an axial load transmitted through the elbow. High-energy mechanisms and polytrauma are more common in younger persons.

Clinical Features. The affected arm is held close to the body, and movement is restricted by pain. Tenderness, hematoma,

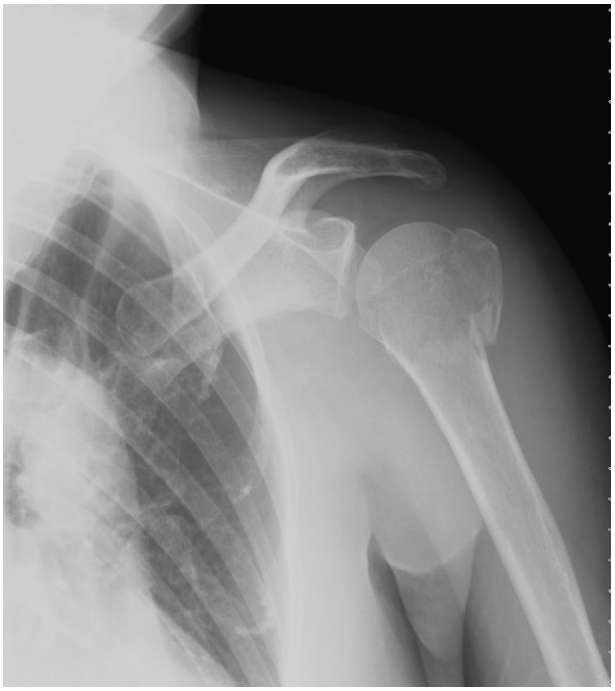


Figure 50-16. Three-part minimally displaced fracture of the proximal humerus involving the greater and lesser tuberosities.

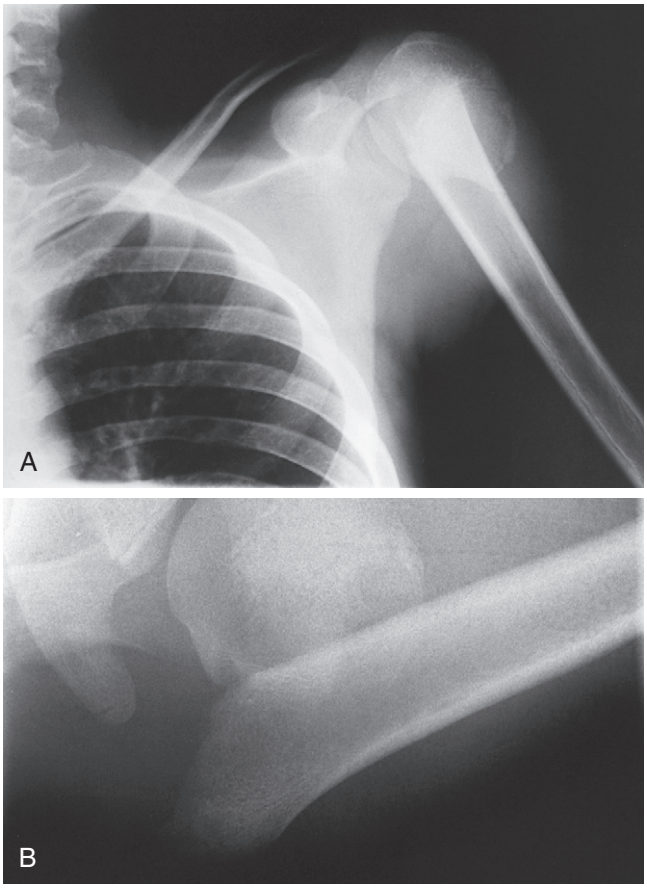


Figure 50-17. Anteroposterior (**A**) and axillary (**B**) radiographic views of a two-part displaced fracture of the proximal humerus. The degree of displacement often is better visualized on the axillary view. (Courtesy of David Nelson, MD.)

ecchymosis, deformity, or crepitus may be noted over the fracture site. A thorough neurovascular examination is essential to identify associated injuries of the axillary nerve, brachial plexus, or axillary artery. The three-view trauma series of shoulder radiographs will allow for assessment of the number of fracture fragments and degree of displacement or angulation.

Management. Minimally displaced fractures (see Fig. 50-16) constitute 80 to 85% of all cases. No displacement or angulation is present, and the fracture segments are held together by the capsule, periosteum, and surrounding muscles. Initial treatment consists of adequate analgesia and immobilization with a sling or sling and swathe device. The former is more comfortable, and a Cochrane review of 12 randomized trials found only limited evidence that use of special bandage immobilization affected time to fracture union or functional outcome.[29] Traditionally, it has been recommended that immobilization be continued until clinical union is achieved (head and shaft are seen to move together). The Cochrane review also noted that immediate or earlier commencement of physiotherapy (within 1 week) resulted in less pain and faster recovery than with prolonged immobilization.[29] Initial passive exercises (see Fig. 50-13) are gradually replaced by more active and resistive exercises. Most nondisplaced fractures heal over 4 to 6 weeks.

The treatment of two-part, three-part, and four-part displaced fractures is beyond the scope of this discussion. An orthopedic surgeon should be consulted, because many of these injuries require operative repair.[28] Prospective and retrospective observational studies, however, have failed to show a significant functional difference between operative and nonoperative treatment of displaced two-part and three-part fractures in elderly patients. Current literature continues to support operative treatment of four-part fractures in the elderly when the procedure of choice is hemiarthroplasty.[30]

Fracture-dislocation injuries also may require treatment by an orthopedic surgeon. Of note, reductions of these injuries in the ED often are unsuccessful, and these manipulations can cause separation of previously undisplaced segments. Closed reduction under radiologic control and general anesthesia may be preferable.[29]

Posterior glenohumeral dislocations usually are associated with anteromedial impression fractures of the articular surface. A similar fracture of the posterolateral aspect of the humeral head is present with anterior dislocations (Hill-Sachs deformity). Impression fractures involving less than 20% of the articular surface usually are stable. With more than 20% involvement, the reduction usually is unstable and requires surgical repair.

Complications. The most common complication of proximal humeral fractures is adhesive capsulitis (so-called frozen or stiff shoulder). This complication can be prevented by the early initiation of pendular shoulder exercise, along with a thorough rehabilitation program. One of the most devastating complications is that of avascular necrosis (AVN) of the humeral head. The highest rate of AVN (up to 90%) has been documented for four-part fractures.[30] Repeated forceful attempts at reduction of fracture-dislocations may be associated with subsequent heterotopic bone formation (myositis ossificans). Neurovascular injuries (axillary nerve, brachial plexus, and axillary artery) may be encountered with displaced surgical neck fractures and fracture-dislocations.

Proximal Humeral Epiphysis

Pathophysiology. Fractures of the proximal humeral epiphysis are uncommon and account for 10% of all shoulder fractures in

children.[31] The injury can occur at any age while the epiphysis remains open but is most common in boys 11 to 17 years of age. The most common mechanism of injury involves a fall onto the outstretched hand, and the fracture typically occurs through the zone of hypertrophy in the epiphyseal plate. Injuries can be classified according to their location (Salter system), stability, and degree of displacement.[6]

Clinical Features. The patient holds the injured arm tightly against the body by the opposite hand. The area over the proximal humerus is swollen and extremely tender to palpation. Radiographs obtained at 90 degrees to each other confirm the diagnosis. Comparison views may be helpful with minimally displaced fractures.

Management. Fractures of the proximal humeral epiphysis should not be taken lightly, because the potential for growth disturbance exists even under the most ideal conditions. The active healing process at the site of an epiphyseal injury makes delayed reduction extremely difficult. Early orthopedic consultation should be obtained for all such injuries. Children younger than 6 years of age usually have Salter I epiphyseal injuries (Fig. 50-18), which can be treated conservatively with sling and swathe immobilization and analgesic agents. Children older than 6 years usually have a Salter II epiphyseal injury. Salter II injuries with more than 20 degrees of angulation should be reduced.[32] Closed reduction is accomplished by reversing the mechanism of injury. Imperfect reductions often are acceptable because growth and remodeling correct the deformity with time. After reduction, unstable injuries should be immobilized in a shoulder spica cast, whereas stable lesions can be immobilized with a sling and swathe. Fractures of the proximal humeral epiphyses generally heal in 3 to 5 weeks.[32]

Complications. Complications are rare and include malunion, growth plate disturbances, and injuries to the neurovascular bundle. Markedly displaced or angulated fractures are more likely to result in a residual loss of mobility.[31]

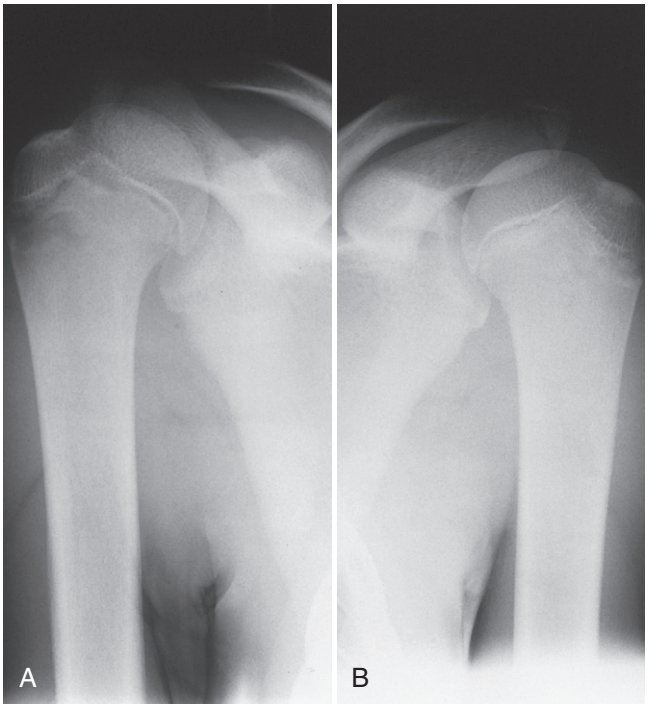


Figure 50-18. **A,** Salter I injury of the right proximal humeral epiphysis. **B,** Normal left side is included for comparison.

Dislocations

Sternoclavicular

Pathophysiology. Sternoclavicular joint (SCJ) dislocations are infrequent and account for less than 1% of all dislocations.[33] Significant forces are required to disrupt the strong ligamentous stabilizers of this joint. The most common causes are MVCs and injuries sustained in contact sports, such as rugby or football. The SCJ can dislocate in an anterior or a posterior direction. Anterior dislocations, which result from indirect forces, are more common (9:1 ratio).[5] The usual mechanism of injury (Fig. 50-19) involves an anterolateral force to the shoulder, followed by backward rolling, which levers the medial clavicle out of its articulation. Posterior dislocations (Fig. 50-20) can result from a direct blow to the medial clavicle (30%) or from delivery of a posterolateral force to the shoulder, followed by inward rolling (70%). Posterior dislocations can be associated with life-threatening injuries within the superior mediastinum.

Injuries to the SCJ can be graded into three types.[5] A grade I injury is a mild sprain secondary to stretching of the sternoclavicular and costoclavicular ligaments. A grade II injury is associated with subluxation of the joint (anterior or posterior) secondary to rupture of the sternoclavicular ligament. The costoclavicular ligament remains intact. Complete rupture of the sternoclavicular and costoclavicular ligaments results in a grade III injury (dislocation). In patients younger than 25 years of age, these actually represent Salter type I injuries, because the medial epiphysis of the clavicle has not yet fused.[34]

Clinical Features. Clinical suspicion is the most important factor in diagnosing these injuries, and prompt diagnosis is vital because it is associated with a better prognosis. Patients will present with the injured extremity flexed at the elbow and supported across the trunk by the opposite arm.[35] Pain results from any movement of the upper extremity or lateral compression of the shoulders. The SCJ may be mildly swollen and tender to palpation. With an anterior dislocation, the displaced medial end of the clavicle may be palpable. Posterior dislocations are associated with more severe pain, and the neck is often flexed toward the injured side.[5] The clavicular notch of the sternum may be palpable, and complaints of hoarseness, dysphagia, dyspnea, and weakness or paresthesias in the upper extremities have been documented. Rarely, airway complications can occur. These patients should be examined thoroughly to identify any injuries to superior

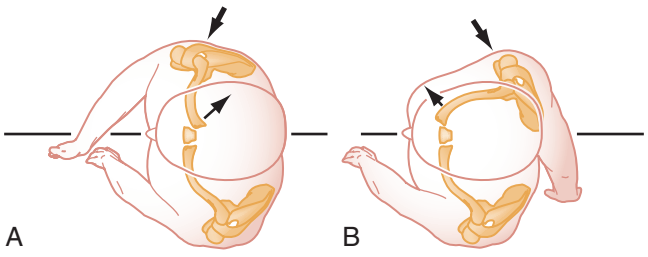


Figure 50-19. Mechanisms that produce anterior and posterior displacements of the sternoclavicular joint. **A,** When the patient is lying on the ground and a compression force *(upper arrow)* is applied to the posterolateral aspect of the shoulder, the medial end of the clavicle is displaced posteriorly *(lower arrow)*. **B,** When the lateral compression force *(upper arrow)* is directed from the anterior position, the medial end of the clavicle is dislocated anteriorly *(lower arrow)*. The same mechanism could apply with any type of lateral compression injury of the shoulder. (From Neer CS, Rockwood CA: Fractures and dislocations of the shoulder. In Rockwood CA, Green DP [eds]: Fractures in Adults, 4th ed. Philadelphia, JB Lippincott, 1984.)

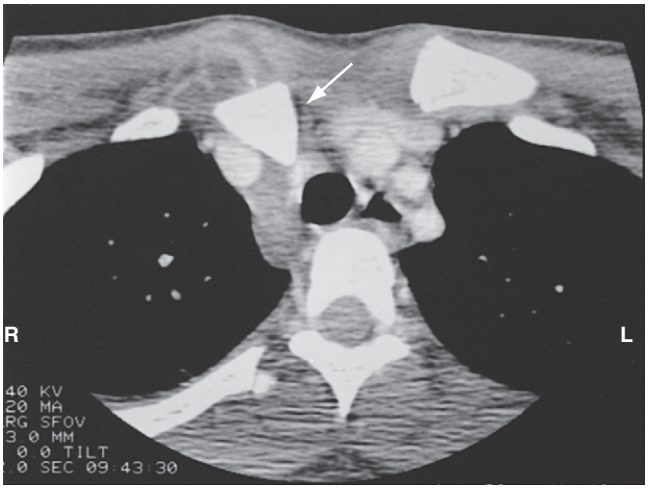


Figure 50-20. This computed tomography scan shows posterior dislocation of the right sternoclavicular joint *(arrow)* with compression of the superior mediastinum. (Courtesy of Donald Sauser, MD.)

mediastinal or intrathoracic structures. The presence of cyanosis and venous congestion of the neck and arm is typical of an innominate vein injury.[35] When necessary, appropriate consultation should be obtained immediately.

Diagnostic Strategies: Radiology. Although the diagnosis of sternoclavicular dislocation can be made clinically, it should be confirmed radiologically. Findings on standard anteroposterior, oblique, and specialized (40-degree cephalic tilt) views often are difficult to interpret because of overlapping rib, sternum, and vertebral shadows. These dislocations and associated injuries are best visualized by CT (see Fig. 50-20).[13] Ultrasound imaging also may be a useful adjunct in some circumstances.[5]

Management. Treatment of grade I injuries includes immobilization (simple sling), adequate analgesia, and primary care follow-up. Immobilization generally is maintained (1 to 2 weeks) until full painless motion is restored. Grade II injuries should be immobilized with a sling or soft clavicular (figure-of-eight) splint and referred for orthopedic follow-up care. The figure-of-eight splint is preferred because it maintains the clavicle in a more anatomic position. Grade II injuries require a longer course of immobilization (3 to 6 weeks) and are more likely to be associated with persistent pain.[5,6] All grade III injuries should be managed by closed reduction.

Anterior dislocations may be reduced in the ED after orthopedic consultation and intravenous analgesia (Fig. 50-21). A rolled sheet is placed posteriorly between the shoulder blades to elevate both shoulders approximately 5 cm above the table. Traction is applied to the arm in an extended (10- to 15-degree) and abducted (90-degree) position. If reduction does not occur, an assistant can add inward pressure on the medial end of the clavicle. Stable reductions should be maintained in a clavicular splint and referred for orthopedic follow-up care.[5,6] Most reductions are unstable. Because the deformity is primarily cosmetic and not functional, the current treatment of choice for recurrent anterior dislocations is benign neglect.

Posterior dislocations constitute true orthopedic emergencies and should be reduced expeditiously.[5] Ideally, reduction of posterior dislocations should be attempted in the operating room with the patient under general anesthesia, although it can be attempted in the ED with use of conscious sedation. Emergency reduction may be required for patients with airway obstruction or vascular compromise. The patient is positioned as described previously, and traction is applied in an extended and abducted position. If traction alone does not reduce the

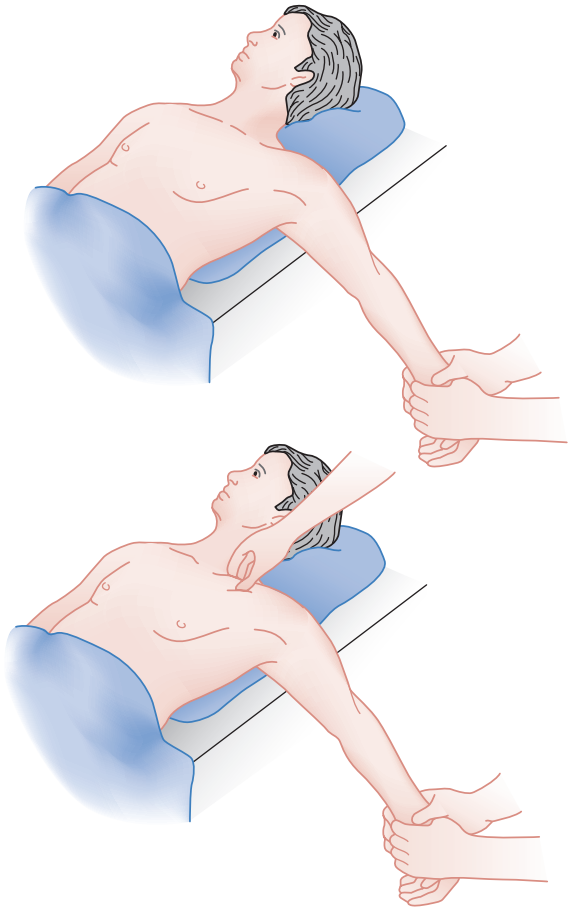


Figure 50-21. Reduction of dislocated sternoclavicular joints. (From Simon RR, Koenigsknecht SJ: Emergency Orthopedics: The Extremities, 2nd ed. Norwalk, Conn, Appleton & Lange, 1987.)

dislocation, concurrent clavicular manipulation may be helpful. After sterile preparation of the skin, the clavicle shaft is grasped with a sterile towel clip and pulled out anterolaterally. When reduced, these injuries generally are stable and can be immobilized with a clavicular splint. Buckerfield and Castle[36] described an alternate method of reduction for posterior dislocations. In this technique, traction is applied to the adducted arm while both shoulders simultaneously are forced posteriorly using direct pressure. This technique levers the clavicle into place and requires much less force than the traditional abduction-extension method.

Complications. Complications of anterior injuries are primarily cosmetic. By contrast, 25% of posterior dislocations may be complicated by life-threatening injuries to intrathoracic and superior mediastinal structures. Ono and colleagues reviewed data for 102 cases reported in the literature as of 1998 and documented complications in 31 patients (30%), with three deaths.[35] These include compression or laceration of the great vessels, tracheoesophageal fistula, tracheal compression, pneumothorax, thoracic outlet syndrome, and brachial plexus injuries. A potential long-term complication of both anterior and posterior injuries is degenerative osteoarthritis.

Acromioclavicular Joint

Pathophysiology. Injuries of the ACJ occur primarily in young men and account for 25% of all dislocations about the shoulder girdle.[26] The annual incidence is 15 per 100,000 population, and most injuries result from participation in contact sports,

such as football, rugby, ice hockey, and wrestling.[26] A small percentage of injuries are caused by MVCs and falls.

The most common mechanism of injury involves a fall or direct blow to the point of the shoulder with the arm adducted. The resultant force drives the scapula downward and medially to produce the injury. The weak acromioclavicular ligaments rupture first. With increasing force, the coracoclavicular ligament ruptures, and the attachments of the deltoid and trapezius muscles are torn from the distal clavicle. The ACJ also can be injured after a fall onto the outstretched hand. In this instance, the force is transmitted to the acromioclavicular ligaments only, and the coracoclavicular ligament, which is relaxed, remains uninjured.[37]

Classification is based on the degree of damage sustained by the acromioclavicular and coracoclavicular ligaments[8] (Fig. 50-22). The most commonly used system is that modified by Rockwood.[34] Type I injuries are sprains of the acromioclavicular ligaments with no separation of the acromion and clavicle. Type II injuries are associated with disruption of the acromioclavicular ligaments. The joint space is widened, and the clavicle is displaced slightly upward. There are minor tears in the attachments of the deltoid and trapezius muscles, but the coracoclavicular ligament remains intact, and the coracoclavicular distance is maintained. A type III injury is characterized by complete disruption of the acromioclavicular ligaments, coracoclavicular ligament, and muscle attachments. The joint space is widened, and the coracoclavicular distance is increased by 25 to 100%. The clavicle is displaced upward by the pull of the trapezius, and the shoulder is displaced downward by the effect of gravity. In type IV and V injuries, the ligamentous and muscle disruptions are similar to the disruptions encountered in type III injuries, but the clavicle is displaced either posteriorly into the trapezius (type IV) or superiorly in an exaggerated (coracoclavicular distance increased 100 to 300%) fashion (type V). In the rare type VI injury, the clavicle is displaced inferiorly.

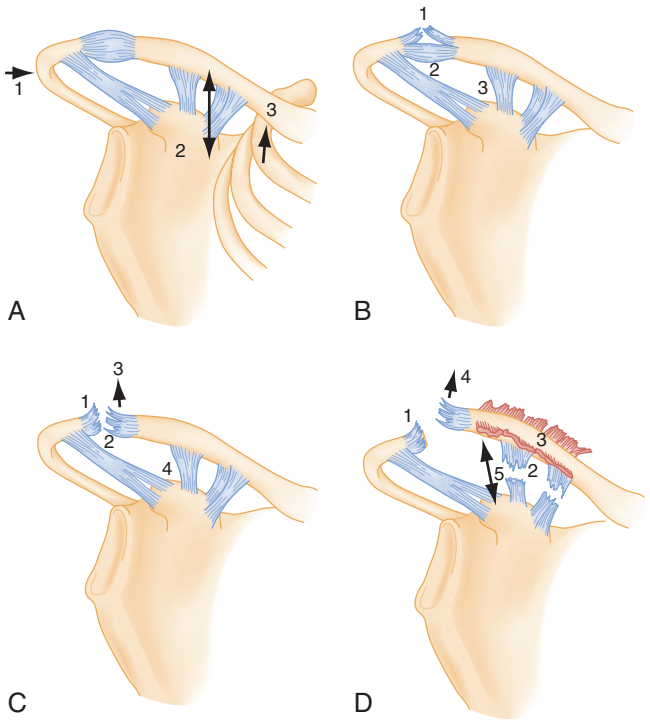


Figure 50-22. Mechanism of injury and classification of acromioclavicular joint injuries. *Arrows* indicate direction of applied force and relevant movement. **A,** The direct force is applied to the point of the shoulder (1); the scapula and attached clavicle are forced downward and medially; the clavicle approaches the first rib (2). If the force continues, the first rib abuts the clavicle, producing a counterforce (3). Depending on the magnitude of the force, a grade I, II, or III sprain may occur. **B,** Grade I sprain. A few fibers of the acromioclavicular ligament stretch, and a few tear (1); the acromioclavicular joint is stable (2); the coracoclavicular ligament is intact (3). **C,** Grade II sprain (subluxation). The capsule and the acromioclavicular ligament rupture (1); the joint is lax and unstable (2); the end of the clavicle rides upward, with displacement usually less than half of the width of the end of the clavicle (3); the coracoclavicular ligament remains intact (4); the attachments to the trapezius and deltoid remain intact. **D,** Grade III sprain (dislocation). The capsule and acromioclavicular ligaments rupture (1); the coracoclavicular ligament ruptures (2); the insertions of the trapezius and deltoid tear away (3); the clavicle rides upward (4); the interval between the clavicle and the coracoid process is greatly increased (5). (From DePalma AF: Surgery of the Shoulder, 3rd ed. Philadelphia, JB Lippincott, 1983.)

Clinical Features. Patients should be examined while they are in the sitting or standing position because the supine position can mask ACJ instability. It is helpful to visualize both shoulders simultaneously to assess for symmetry. Type I and type II injuries are associated with mild tenderness and swelling over the ACJ margin, with minimal deformity. A full range of motion often is possible, although painful. Patients with type III, IV, V, and VI injuries usually have severe pain and hold the arm tightly adducted to reduce traction stress across the joint. In type III injuries, the shoulder hangs downward and the clavicle rides high, producing a characteristic clinical deformity. In type IV injuries, the clavicle may be palpable posteriorly, and in type V injuries, the clavicle may be palpable subcutaneously above the acromion. In type VI injuries, the shoulder assumes a flattened clinical appearance as seen from the side.

Diagnostic Strategies: Radiology. The energy settings used for the three-view shoulder trauma series usually overpenetrate the ACJ. Specific ACJ views that use one-third to two-thirds less intensity should be ordered. The recommended projections include an anteroposterior view of both joints on a single wide film, an axillary lateral view, and a 15-degree cephalic tilt view.[8,34] The axillary lateral view is useful for identifying associated fractures and posterior dislocation of the clavicle. The normal coracoclavicular distance ranges between 11 and 13 mm. A difference of more than 5 mm between the injured and uninjured sides is diagnostic of a complete coracoclavicular disruption. With type I injuries, the radiographic appearance is essentially normal. With type II injuries, radiographs show widening of the joint and a slight upward or posterior displacement of the clavicle but a normal coracoclavicular distance. With type III, IV, and V injuries, radiographic features include a widened joint, an increased coracoclavicular distance, and either superior or posterior displacement of the clavicle (Fig. 50-23). Historically, stress views of the ACJ have been recommended to differentiate between type II and type III injuries.[38] Such views lack efficacy for this purpose, and their routine use is unnecessary.[39]

Management. Type I and II injuries should be immobilized in a sling for comfort and to protect against further injury. Patients with these injuries should be referred for follow-up with their primary care physician. When pain has subsided (1 to 3 weeks), range-of-motion and strengthening exercises can begin, with a return to sports when pain-free function has been achieved.[8]

Type IV, V, and VI injuries require early surgical treatment. The management of type III injuries has changed dramatically since the 1980s. Most studies have concluded that conservative treatment provides functional results equivalent to or, in some cases, better than those obtained with surgical intervention. In addition, surgical patients have longer recovery times and higher complication rates.[8] The main complications of conservative therapy are the persistence of nuisance symp-

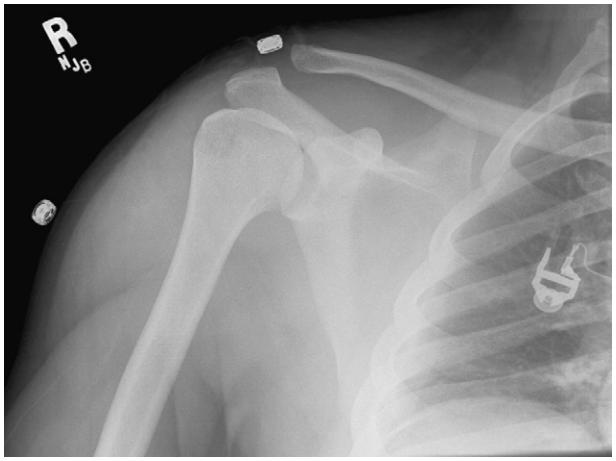


Figure 50-23. Third-degree sprain of the acromioclavicular joint. The coracoclavicular distance is increased.

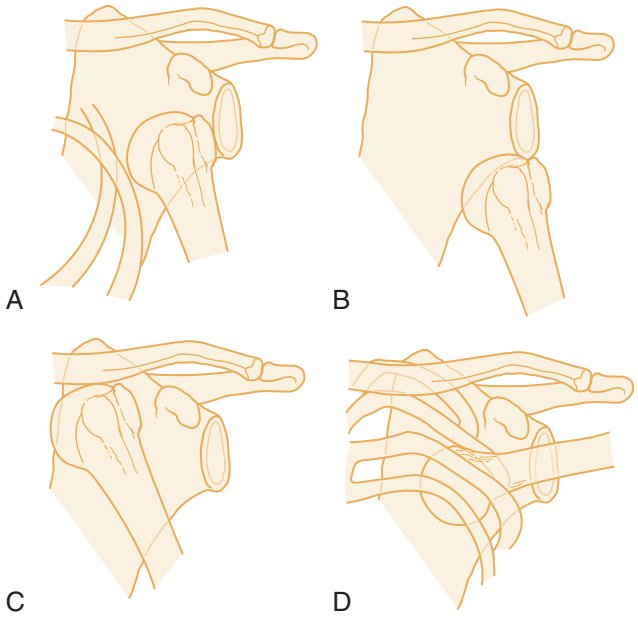


Figure 50-24. Types of anterior dislocation. **A,** Subcoracoid. **B,** Subglenoid. **C,** Subclavicular. **D,** Intrathoracic. (From DePalma AF: Surgery of the Shoulder, 3rd ed. Philadelphia, JB Lippincott, 1983.)

toms (clicking or minor pain) and a cosmetic deformity. Selected patients who are young, have severe displacement (more than 2 cm), and perform repetitive overhead activities may be candidates for surgical intervention.[8] Treatment of type III injuries in the ED should consist of sling immobilization and early orthopedic referral (within 72 hours) if the patient is deemed to be a potential surgical candidate. The initial therapy in all cases should include adequate analgesia.

Complications. The most common concurrent injuries are associated fractures of the clavicle and coracoid process. The most common complications of ACJ injuries are residual symptomatic instability and tenderness over the joint due to secondary degenerative changes.[8] Acromioclavicular arthritis typically manifests as an impingement syndrome with shoulder pain between 120 and 180 degrees of abduction.

Glenohumeral Dislocations

Perspective. The glenohumeral joint is the most commonly dislocated major joint in the body. The lack of intrinsic bone stability in conjunction with its wide range of motion predisposes the joint to dislocations. The annual incidence is 17 per 100,000, and two distinct age peaks are recognized, the first in men 20 to 30 years of age and the second in older women.[40] The glenohumeral joint can dislocate anteriorly, posteriorly, inferiorly, or superiorly. Anterior dislocations account for 95 to 97% of all glenohumeral dislocations. Posterior dislocations account for most of the remainder, whereas inferior and superior dislocations are rare.

Anterior Dislocations

Pathophysiology. Anterior dislocations can result from indirect or direct forces. The most common mechanism of injury consists of an indirect force transferred to the anterior capsule from a combination of abduction, extension, and external rotation. In younger persons, the injury usually is sustained during athletic activities involving rapid movements, and a characteristic pathologic feature is avulsion of the anteroinferior glenohumeral ligament with capsulolabral detachment (Bankart lesion).[40] In older patients, a fall onto the outstretched arm is the more common mechanism of injury, and an accompanying rotator cuff tear is common.[40] Rarely, a direct force applied to the posterolateral aspect of the shoulder can force the humeral head out of the glenoid fossa anteriorly.

Anterior dislocations can be classified according to their etiology (traumatic or nontraumatic), frequency (primary or recurrent), and the anatomic position of the dislocated humeral head. After dislocation, the humeral head can assume a subcoracoid, subglenoid, subclavicular, or intrathoracic position (Fig. 50-24). The *subcoracoid* is the most common type of anterior dislocation. The head is displaced anteriorly and rests on the scapular neck inferior to the coracoid process. The next most common type is the *subglenoid* dislocation, in which the head is anterior and inferior to the glenoid fossa. Together, the subcoracoid and subglenoid types account for 99% of all anterior dislocations. *Subclavicular* and *intrathoracic* dislocations are extremely rare and involve the addition of strong lateral to medial forces that push the humeral head medially.

Clinical Features. The patient is in severe pain, with the dislocated arm held in slight abduction and external rotation by the opposite extremity. The lateral edge of the acromion process is prominent, and the normally rounded shoulder assumes a "squared-off" appearance. The coracoid process is indistinct, and the anterior shoulder appears full. The patient leans away from the injured side and cannot adduct or internally rotate the shoulder even slightly without severe pain. A neurovascular examination is performed to identify associated injuries of the brachial plexus, axillary nerve, radial nerve, or axillary artery. The reported incidence of axillary nerve injuries after anterior glenohumeral dislocation ranges from 5 to 54%, and they are more frequent in patients older than 50 years of age.[41,42] Axillary nerve function can be assessed by testing for sensation over the lateral aspect of the shoulder and by testing motor function of the teres minor and deltoid muscles. Deltoid function is tested by having the patient attempt shoulder abduction while the examiner feels for muscle contraction. Motor testing is more accurate because sensory testing can be misleading owing to the presence of overlapping cutaneous nerve root dermatomes.

Diagnostic Strategies: Radiology. The trauma series of radiographs will confirm the clinical diagnosis and identify the position of the humeral head (Fig. 50-25). Associated fractures may be present in 50% of cases. The most common of these is a compression fracture of the posterolateral aspect of the humeral head caused by forceful impingement against the anterior rim

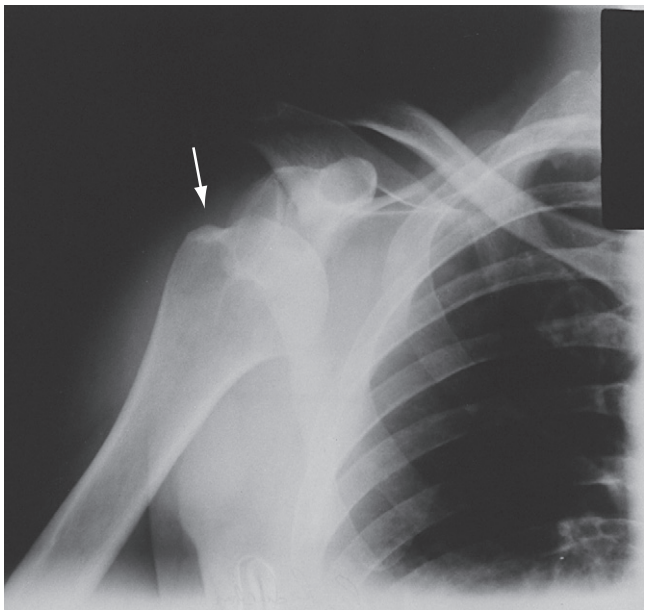


Figure 50-25. Recurrent anterior subcoracoid dislocation with Hill-Sachs deformity of the humeral head *(arrow)*.

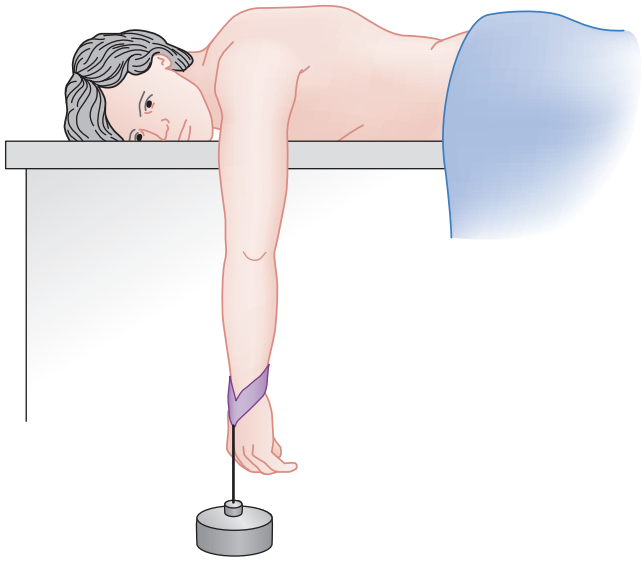


Figure 50-26. Stimson or hanging weight method of reduction for anterior shoulder dislocations.

of the glenoid fossa. This defect in the humeral head, or Hill-Sachs deformity (see Fig. 50-25), is reported to be present in 11 to 50% of all anterior dislocations. The actual incidence is probably much higher, because minor compression fractures are difficult to visualize on plain radiographs. The defect is best visualized on an internal rotation anteroposterior view of the glenohumeral joint. A corresponding fracture of the anterior glenoid rim (Bankart's fracture) is present in approximately 5% of cases.[10] Avulsion fractures of the greater tuberosity are present in 10 to 15% of cases.[10,41]

Management. Reduction of the dislocation should be accomplished expeditiously, because the incidence of neurovascular complications increases with time.[42] Radiographic documentation of the type of dislocation and any associated fractures should be obtained *before* attempting reduction. Reduction can be accomplished using various techniques, most of which involve traction, leverage, or scapular manipulation principles.[43] No good comparative studies of one reduction technique over another have been conducted. The ideal method should be simple, quick, and effective; require little assistance; and cause no additional injury to the shoulder. It is wise to be familiar with several techniques of reduction, because none is uniformly successful.

Good muscle relaxation often is the key to a successful reduction. Occasionally, reductions can be accomplished without the use of any analgesia, especially if the time from injury to reduction is short or if the dislocation is a recurrent one. Muscle relaxation and analgesia also can be provided through intra-articular injection of a local anesthetic agent. This technique is especially useful when procedural sedation is contraindicated. Under sterile technique, the joint is entered 2 cm inferior to the lateral edge of the acromion using an 18-gauge or 20-gauge needle. Any associated hemarthrosis is aspirated; then 20 mL of 1% lidocaine is injected over 30 seconds. The patient is allowed to relax for 15 minutes before reduction is attempted. The published studies to date all have used lidocaine, although it would be reasonable to expect similar results with other local anesthetic agents such as bupivicaine.

Kuhn recently reviewed six randomized controlled trials comparing intravenous sedation and intra-articular lidocaine.[44] Outcomes in these studies included success rates, complications, and time spent in the ED. Although the reduction techniques were not controlled in these studies, none showed a statistical difference in the reduction success rates, which averaged 92% for both the intra-articular lidocaine and intravenous sedation groups.[44] Complication rates were quite different, however, averaging 0.9% in the intra-articular lidocaine group and 16.4% in the intravenous sedation group. In two studies, time spent in the ED was significantly less for the intra-articular lidocaine group.[45]

Gentle traction in various directions (forward flexion, abduction, overhead, lateral) is used to overcome the muscle spasm that holds the humeral head in its dislocated position.[43] In the *Stimson* or *hanging weight technique* (Fig. 50-26), the patient is placed prone, with the dislocated arm hanging over the edge of the examining table. A 10- or 15-pound weight attached to the wrist or lower forearm provides traction in forward flexion. Reduction usually occurs over 20 to 30 minutes. In the *traction-countertraction method* (Fig. 50-27), traction is applied along the abducted arm while an assistant using a folded sheet wrapped across the chest applies countertraction. The *forward elevation maneuver* of Cooper and Milch also is simple and safe. The arm initially is elevated 10 to 20 degrees in forward flexion and slight abduction. Forward flexion is continued until the arm is directly overhead. Abduction is increased, and outward traction is applied to complete the reduction. Another simple and effective traction technique is the *Snowbird technique*, which has a reported success rate of 97%.[46] In this method, the patient is seated in a chair, and the affected arm is supported by the patient's unaffected extremity. A 3-foot loop of 4-inch cast stockinette is placed along the proximal forearm of the involved extremity with the elbow at 90 degrees. The patient is assisted or instructed to sit up, and the physician's foot is placed in the stockinette loop to provide firm downward traction. The physician's hands remain free to apply any gentle external pressure or rotation as needed until reduction is accomplished.

The most commonly recommended leverage technique is the *external rotation method of Liedelmeyer*.[47] With the patient in the supine position, the involved arm is slowly and gently adducted to the side. The elbow is flexed to 90 degrees, and slow, gentle external rotation is applied to achieve reduction

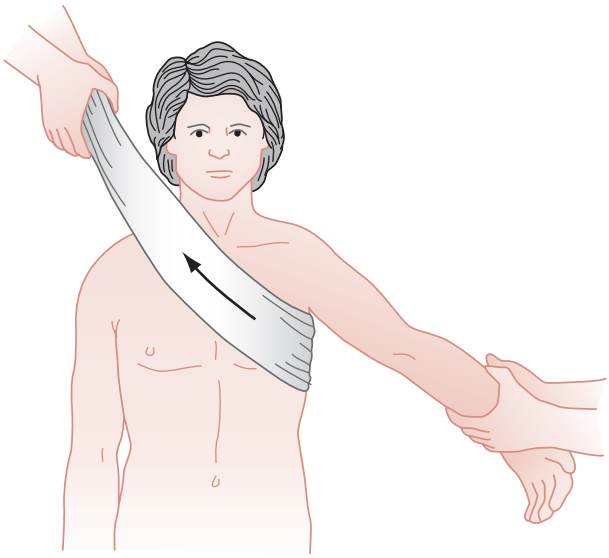


Figure 50-27. Traction-countertraction method for reducing anterior shoulder dislocations.

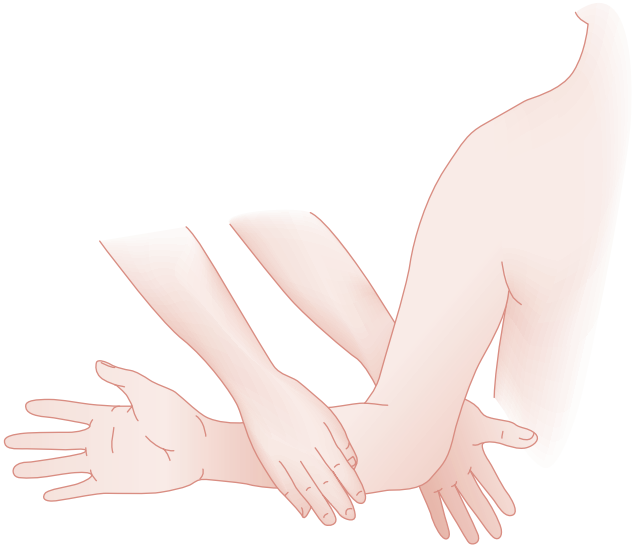


Figure 50-28. External rotation technique for reducing anterior shoulder dislocations. The involved arm is slowly adducted to the patient's side, and the elbow is flexed 90 degrees. Gentle external rotation is applied to the forearm to achieve reduction. (From Simon RR, Koenigsknecht SJ: Emergency Orthopedics: The Extremities, 2nd ed. Norwalk, Conn, Appleton & Lange, 1987.)

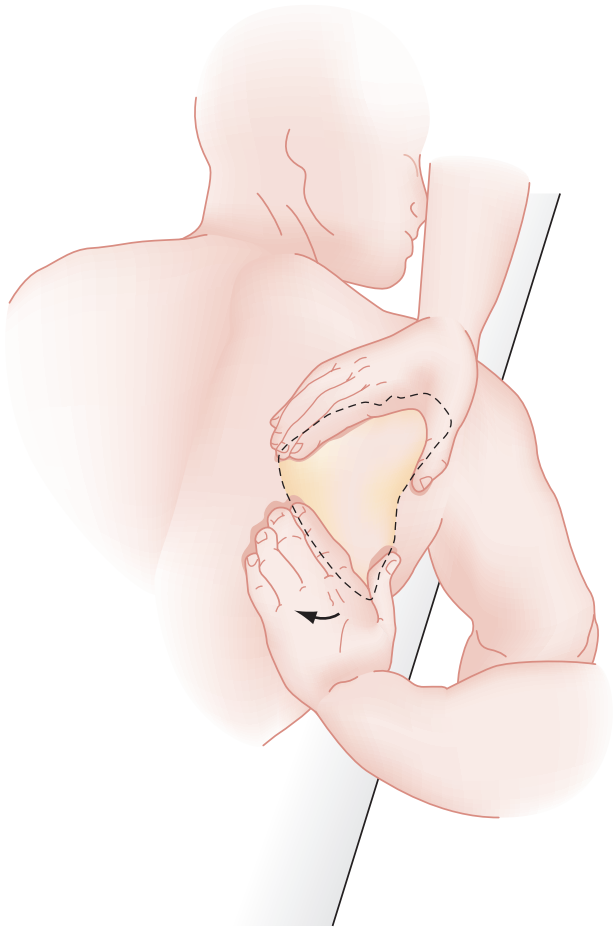


Figure 50-29. Proper hand position and direction of rotation during shoulder relocation using the scapular manipulation technique. *Arrow* indicates direction of applied force. (From Kothari RU, Dronen SC: The scapular manipulation technique for the reduction of acute anterior shoulder dislocations. J Emerg Med 8:625, 1990.)

(Fig. 50-28). Success rates with this method range from 78 to 90%.[44]

Scapular manipulation accomplishes reduction by repositioning the glenoid fossa rather than the humeral head and can be successful with minimal analgesia or muscle relaxation. The patient is placed in the prone position with the affected arm hanging off the table as for the Stimson technique. After the application of downward traction (manual or hanging weights), the scapula is manipulated by rotating the inferior tip medially (Fig. 50-29) while stabilizing the superior and medial edges with the opposite hand.[48] McNamara[49] also described a seated modification of the scapular method in which traction is applied in the forward horizontal position while an assistant manipulates the scapula. Scapular manipulation can be difficult in heavyset patients, in whom it is difficult to palpate and grasp the inferior tip of the scapula. More traditional techniques, such as the Hippocratic method (traction with the foot in the axilla) and the Kocher maneuver (leverage, adduction, and internal rotation), are no longer recommended because of a high incidence of associated complications (axillary nerve injury, humeral shaft and neck fractures, capsular damage).

The neurovascular examination must be repeated and findings recorded after any attempt at reduction. It also is generally recommended that radiographic studies be repeated to confirm reduction and to identify any associated fractures not apparent on prereduction films. Some studies have questioned the need for and cost-effectiveness of routine postreduction radiographs.[50-52] The study investigators did not find any new clinically significant fractures on postreduction radiographs and argued that in most instances, a successful reduction can be determined clinically by the presence of a palpable clunk, decrease in pain, and improvement in the range of motion. Reduction in the number of postreduction radiographs also decreases costs and shortens the ED throughput times.[52] The findings on most of these studies are very subjective, however, and one cannot assume that all practitioners will have the same clinical acumen. Other studies show that as many as 7.5% of fractures initially were detected only on postreduction films.[53] Plain radiography of the shoulder is readily available and presents little or no risk to the patient. Unfortunately, failure to confirm reduction with radiographs and failure to diagnose all associated fractures could lead to malpractice claims. For these reasons, imaging of suspected shoulder dislocations remains

advisable in most cases, with the possible exception of some patients presenting with a history of recurrent dislocations in the absence of trauma. Even in these cases, a postreduction film may be advisable, whereas prereduction films may not be necessary.

After reduction, the affected extremity is immobilized using a sling and swathe bandage or a Velpeau sling (see Fig. 50-10). Patients should be discharged with adequate analgesia and appropriate follow-up referral. Primary dislocations and complicated cases (associated fracture, rotator cuff tear, axillary nerve injury) should receive orthopedic follow-up care. In uncomplicated cases, the shoulder is immobilized for 3 to 6 weeks in younger patients and for 1 to 2 weeks in those who are older than 40 years.[10]

The traditional position of immobilization is with the shoulder in internal rotation. Studies suggest that this positioning may delay healing and is associated with a higher recurrence rate.[54] In a randomized clinical trial, Itoi and coworkers[55] found that 3 weeks of immobilization in 10 degrees of external rotation was associated with a zero recurrence rate at 13 to 15 months, compared with a 30% recurrence rate with sling immobilization in internal rotation. If these preliminary findings are confirmed by additional trials, sling immobilization may be replaced by external rotation splints. Regardless of the immobilization technique, early initiation of shoulder exercises (see Fig. 50-13) helps reduce the risk of adhesive capsulitis. A meticulous rehabilitation program aimed at restoring the static and dynamic stabilizers of the glenohumeral joint follows the period of immobilization.[10]

Complications. Complications include the aforementioned fractures and neurovascular injuries. Most axillary nerve injuries are neurapraxic, and the prognosis for recovery of function is good.[42] Rotator cuff tears may be present in 10 to 15% of cases.[56] Rotator cuff tears are especially common in primary dislocations in patients older than 40 years of age. In this setting, failure to abduct the arm often is misdiagnosed initially as an axillary nerve injury. Most of these patients require tendon and capsular repair to restore shoulder stability.[56] Recurrence also is a common complication after anterior dislocation, and patients younger than 30 years have a reported recurrence rate of 79 to 100%. A Hill-Sachs deformity or glenoid rim fracture is associated with increased risk of recurrence.[10] Recent studies suggest that the traditional method of treatment (immobilization followed by physical therapy) is ineffective in preventing redislocation in young, highly athletic persons. Arthroscopic studies of primary anterior dislocations in such patients have detected a high incidence of anterior-inferior capsulolabral avulsions (Perthes-Bankart lesion) from the glenoid rim. This avulsion is believed to be the primary predisposing factor for recurrence, and affected patients seem to benefit from early arthroscopic repair of the lesion.[57] Recurrence rates decline with increasing age and in the presence of a greater tuberosity fracture.[10]

Anterior Subluxation

Transient anterior subluxation of the shoulder is encountered often in young athletic adults. The patient complains of sudden sharp shoulder pain and weakness ("dead arm syndrome") while performing an abduction and external rotation maneuver. The patient also may relate a sensation of the shoulder's slipping in and out. The radiographic appearance usually is normal, and presence of an apprehension sign confirms the diagnosis. To elicit this sign, the injury motion (abduction and external rotation of the arm) is gently reproduced while applying an anterior force to the posterior shoulder (Fig. 50-30). This maneuver increases the pain and may cause anterior displacement of the humeral head. In a positive test, the patient will actively resist further external rotation and/or appear apprehensive. A lax or redundant anterior capsule is thought to be responsible for this syndrome, and recurrent episodes are common. These patients should be referred for orthopedic follow-up care because definitive therapy (capsulorrhaphy) is surgical.

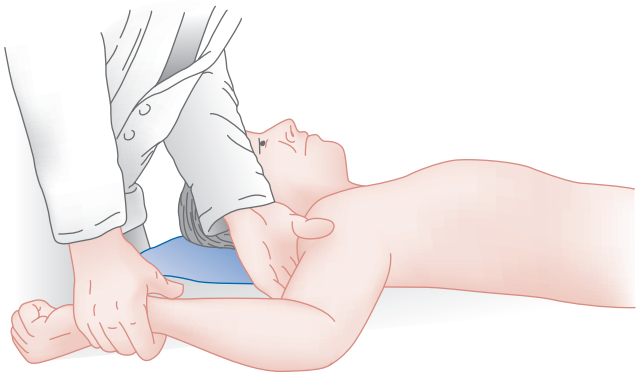


Figure 50-30. Technique for performing the shoulder apprehension test. (From Simon RR, Koenigsknecht SJ: Emergency Orthopedics: The Extremities, 2nd ed. Norwalk, Conn, Appleton & Lange, 1987.)

Posterior Dislocation

Pathophysiology. Posterior dislocations are rare and account for 2% of all glenohumeral dislocations.[58] This rarity is explained partly by the anatomy of the shoulder girdle. The 45-degree angulation of the scapula on the thoracic cage positions the glenoid fossa posterior to the humeral head, which serves as a partial buttress against posterior dislocation. More than 50% of posterior dislocations are missed on initial evaluation, and many remain unrecognized ("locked posterior dislocations") for weeks or months.[59,60]

A posterior dislocation can result from several distinct mechanisms of injury. Convulsive seizures (epileptic or after electrical shock) have been associated with unilateral or bilateral posterior dislocations. In this instance, the larger and stronger internal rotator muscles (latissimus dorsi, pectoralis major, teres major, subscapularis) overpower the weaker external rotators (teres minor, infraspinatus) to produce the injury.[59] A posterior dislocation also can occur after a fall onto the outstretched hand with the arm held in flexion, adduction, and internal rotation or after a direct blow to the anterior aspect of the shoulder. Acute posterior dislocations are classified into three types—subacromial, subglenoid, and subspinous—based on the final resting position of the humeral head. The subacromial variety accounts for 98% of all posterior dislocations.[58]

Clinical Features. Early diagnosis is essential to prevent long-term functional complications. As mentioned, the initial examining physician misses the diagnosis with some regularity, in part because of an overreliance on radiologic findings and an underreliance on the clinical examination. The most common misdiagnosis is adhesive capsulitis.[58,60] The patient holds the affected arm across the chest in adduction and internal rotation. Although usually painful, the injury can be relatively painless.[59] The normal shoulder contour is replaced by a flat, squared-off appearance, and the coracoid process is prominent and easily palpated. The humeral head may be palpable posteriorly beneath the acromion process. Abduction is severely limited, and external rotation is completely blocked.

Diagnostic Strategies: Radiology. Standard anteroposterior radiographs can appear deceptively normal with posterior dislocations. The common difficulty with identifying posterior dislocation in the frontal plane has led to the description of several characteristic radiographic features. Standard antero-

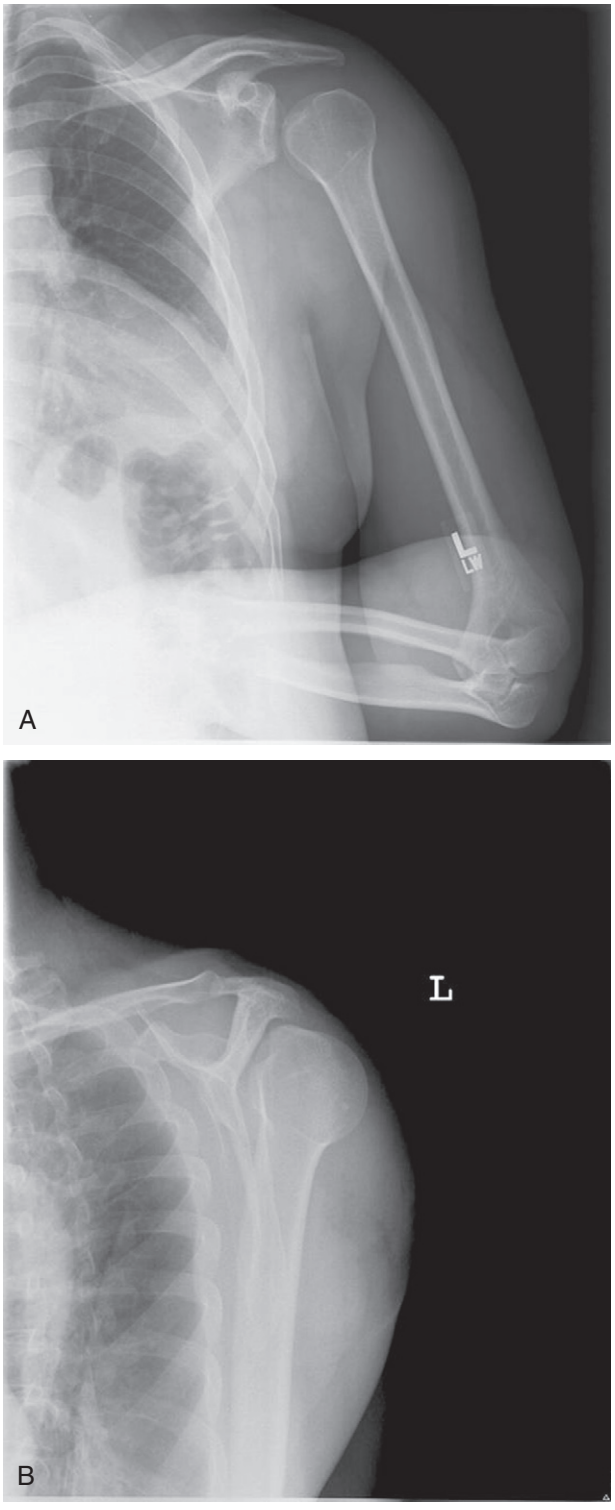


Figure 50-31. Anteroposterior (**A**) and transscapular (**B**) radiographic views of a posterior glenohumeral dislocation. Note the "lightbulb" or "drumstick" appearance of the humeral head.

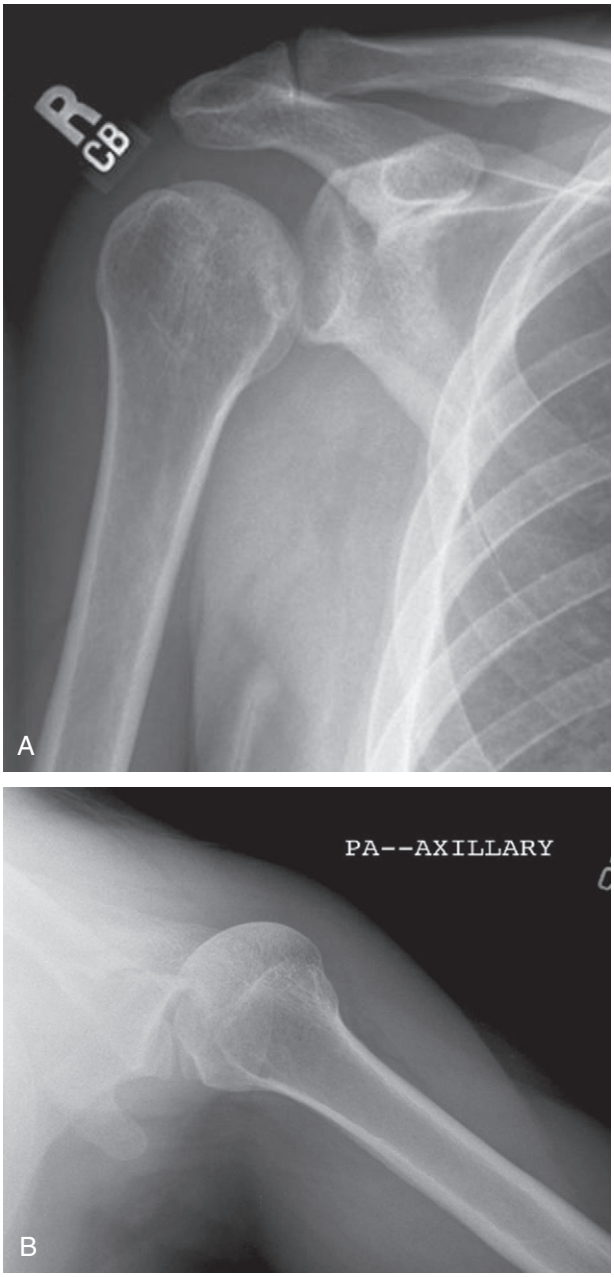


Figure 50-32. True anteroposterior (**A**) and axillary (**B**) radiographic views of a posterior glenohumeral dislocation. Note the abnormal overlap of the glenoid rim and humeral head and the impaction fracture of the anteromedial humeral head (reverse Hill-Sachs deformity).

posterior films show loss of the half-moon elliptical overlap of the humeral head and glenoid fossa. In addition, the distance between the anterior glenoid rim and the articular surface of the humeral head is increased (the rim sign). The humeral head is profiled in internal rotation and takes on a "lightbulb" or "drumstick" appearance (Fig. 50-31). A true anteroposterior film shows abnormal overlap of the glenoid fossa with the humeral head (Fig. 50-32). Finally, an impaction fracture of the anteromedial humeral head (reverse Hill-Sachs deformity) is invariably present (see Fig. 50-32). This fracture may produce a curvilinear density on the frontal projection parallel to the articular cortex of the humeral head (the trough sign). An orthogonal view, such as an axillary lateral, transscapular (see Fig. 50-31), or apical oblique, confirms the diagnosis. The axillary lateral view or apical oblique view also identifies associated fractures of the humeral head and posterior glenoid rim. CT may be helpful in some instances.[61]

Management. Orthopedic consultation should be obtained for all posterior dislocations. Closed reduction may be attempted in the ED with the patient under conscious sedation. The technique of reduction incorporates axial traction in line with the humerus, gentle pressure on the posteriorly displaced head, and slow external rotation. If this technique fails, reduction with the patient under general anesthesia is indicated.

After reduction, the shoulder should be immobilized in external rotation with slight abduction.[60] Patients whose injury was missed initially and present with a chronic or locked posterior dislocation should be discussed with the on-call orthopedist. Locked posterior dislocations usually require open reduction and internal fixation or arthroplasty.[60,61]

Complications. Fractures of the glenoid rim, greater tuberosity, lesser tuberosity, and humeral head account for most associated injuries. The subscapularis muscle rarely may be avulsed from its insertion site on the lesser tuberosity. Neurovascular injuries are uncommon because the anterior location of the neurovascular bundle protects it from injury. Recurrent posterior dislocations occur in 30% of patients and predispose the joint to degenerative changes.

Inferior Glenohumeral Dislocation (Luxatio Erecta)

Pathophysiology. Luxatio erecta is a rare type of glenohumeral dislocation in which the superior aspect of the humeral head is forced below the inferior rim of the glenoid fossa. Less than 1% of all shoulder dislocations are of this variety, and the mechanism of injury involves either indirect or direct forces.[62] Most inferior dislocations result from indirect forces that hyperabduct the affected extremity. This causes impingement of the humeral head against the acromion process. Further levering of the humeral shaft against the acromion ruptures the capsule and dislocates the head inferiorly (Fig. 50-33). Application of a direct axial load to an abducted shoulder also can disrupt the weak inferior glenohumeral ligament and drive the humeral head downward.

Clinical Features. Clinically the patient has the arm locked overhead in 110 to 160 degrees of abduction. The elbow usually is flexed, and the forearm typically rests on top of the head. The shoulder is fixed in this position, and any attempts at movement result in significant pain. The inferiorly displaced humeral head may be palpable along the lateral chest wall. A thorough neurovascular examination is essential to evaluate for associated injuries

Diagnostic Strategies: Radiology. Many cases of luxatio erecta are mistakenly diagnosed and treated as subglenoid anterior dislocations because the radiographic features of these two clinical entities are remarkably similar. Standard anteroposterior radiographs show the superior articular surface inferior to the glenoid fossa (Fig. 50-34). In addition, the humeral shaft characteristically lies parallel to the spine of the scapula on the anteroposterior view. This radiographic feature is useful in distinguishing luxatio erecta from a subglenoid anterior dislocation: In the latter, the humeral shaft lies parallel to the chest wall. Associated fractures of the acromion, coracoid, clavicle, greater tuberosity, humeral head, and glenoid rim are common.

Management. If possible, orthopedic consultation should be obtained before closed reduction using procedural sedation is attempted in the ED. Reduction usually can be accomplished by traction-countertraction maneuvers. The operator applies traction in line with the humeral shaft, while an assistant applies countertraction across the shoulder (Fig. 50-35). Gentle abduction usually reduces the dislocation, and the arm is brought down into an adducted position. Multiple attempts may be necessary; occasionally, "buttonholing" of the capsule

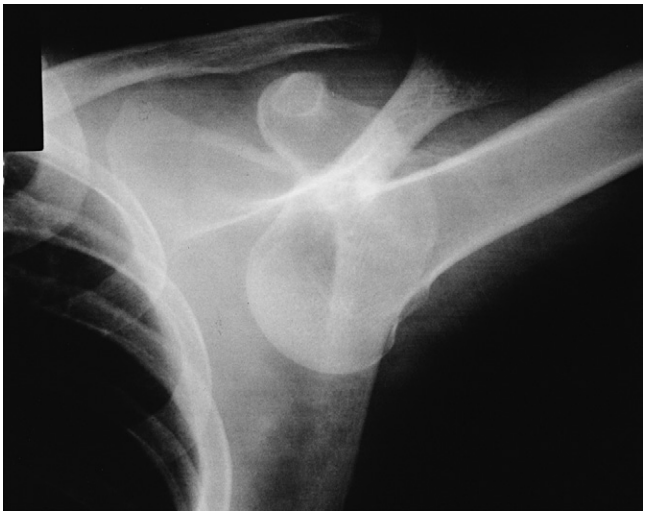


Figure 50-34. Anteroposterior radiographic view of an inferior glenohumeral dislocation. The humeral shaft lies parallel to the spine of the scapula.

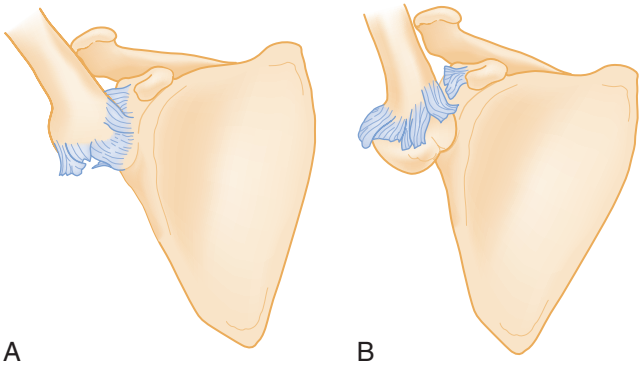


Figure 50-33. Luxatio erecta. **A,** The mechanism by which this injury occurs in hyperabduction. **B,** This is always accompanied by disruption of the rotator cuff and tear through the inferior capsule. (From Simon RR, Koenigsknecht SJ: Emergency Orthopedics: The Extremities, 2nd ed. Norwalk, Conn, Appleton & Lange, 1987.)

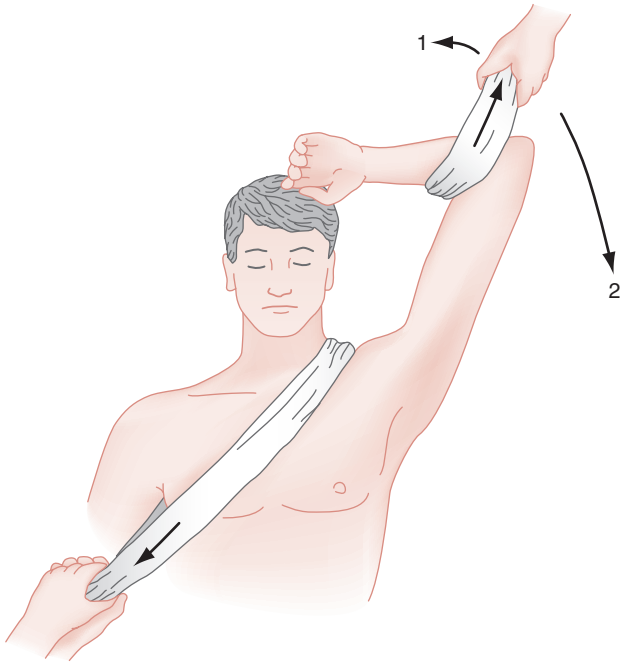


Figure 50-35. Traction-countertraction method for reduction of luxatio erecta humeri. *Arrows* indicate direction of applied force and relevant movement. The initial maneuver (1) includes steady axial traction in line with the humeral shaft position, followed by gentle abduction. This reduces the glenohumeral dislocation. At this point (2), the arm is brought down to a position of adduction and internal rotation. (From Davids JR, Talbott RD: Luxatio erecta humeri. Clin Orthop 252:144, 1990.)

will prevent closed reduction, necessitating open reduction. An alternative approach is the two-step closed reduction maneuver, in which the inferior dislocation is first converted into an anterior dislocation before being reduced.[63] Initially, one hand is placed on the shaft of the dislocated humerus and the other hand on its medial condyle. The hand on the shaft initiates an anteriorly directed force rotating the humeral head from an inferior to an anterior position. The adducted humerus can then be externally rotated to reduce the head into the glenoid fossa. The reported advantages of the two-step maneuver are that it requires a single operator, fewer attempts, minimal force, and only local analgesia or minimal procedural sedation.[63]

Complications. Neurapraxic lesions of the brachial plexus are common, and thrombosis of the axillary artery has also been associated with luxatio erecta.[62] Other associated injuries include tears of the rotator cuff and avulsion fractures of the greater tuberosity. Adhesive capsulitis is a common long-term complication of luxatio erecta.

Scapulothoracic Dislocation

Scapulothoracic dissociation is a rare and severe injury characterized by complete disruption of the scapulothoracic articulation and may be thought of as a partial or complete internal forequarter amputation.[64] The mechanism of injury involves a massive blunt force directed over the shoulder or severe traction force applied to the upper extremity. Approximately 50% of the reported cases involve motorcycle accidents, with the injury occurring when the motorcyclist hangs onto the handlebars while the body is forced away.[65] The diagnosis is based on history, clinical findings, and radiologic studies. The injury often is overlooked at first, because most patients have multiple injuries that distract the treating physician.[65] Massive local soft tissue swelling of the shoulder along with greater than 1 cm of lateral displacement of the scapula on the anteroposterior chest radiograph is pathognomic for scapulothoracic dissociation. Associated osseous injuries include acromioclavicular separation, displaced fractures of the clavicle, and dislocations of the sternoclavicular joint. Vascular lesions have been reported in 88% of patients and severe neurologic injuries in 94%, so a thorough assessment for these injuries is essential.[64] Outcomes generally are poor, with death in 10% of cases and a flail anesthetic upper extremity in complete brachial plexus injuries. Many of these latter cases eventuate in upper extremity amputation.[64]

Soft Tissue Conditions

Impingement Syndromes: Rotator Cuff Tendinitis, Subacromial Bursitis

Pathophysiology. *Rotator cuff tendinitis* and *subacromial bursitis* can be considered part of a pathophysiologic continuum whose endpoint is represented by complete rupture of the rotator cuff. These two conditions are common causes of shoulder pain and have similar clinical presentations.[66] A key clinical feature is the presence of a painful arc sign (Fig. 50-36).

The subacromial space is the area between the coracoacromial arch and the greater tuberosity of the humerus. This space, which is only a few millimeters wide, contains the long head of the biceps, the rotator cuff, and the subacromial bursa. The bursa provides the gliding mechanism between the musculotendinous cuff and the coracoacromial arch. The functional arc of shoulder elevation is forward, which normally leads to impingement of the cuff and bursa under the anterior third of the coracoacromial arch. Similar impingement also occurs between 60 and 120 degrees of abduction and with the extremes of adduction. The critical wear from impingement is centered on the supraspinatus tendon, near its insertion on the greater tuberosity.[67] Micro-opaque injection studies also have shown a relative avascularity within this "critical" area. The hypovascularity, in conjunction with repeated wear and age-related degenerative changes, ultimately results in rotator cuff tendinitis. Narrowing of the subacromial space (anatomic variants of anterior acromion) and occupations that require excessive overhead activity accelerate the entire process. With time, the inflammatory reaction spreads to involve the adjacent bursa. This inflammation leads to edema, thickening, and fibrosis, further narrowing the subacromial space (secondary impingement); this is eventually followed by attritional changes within the rotator cuff. Because the rotator cuff is a primary humeral head depressor, loss of function adds to the secondary impingement process.[66]

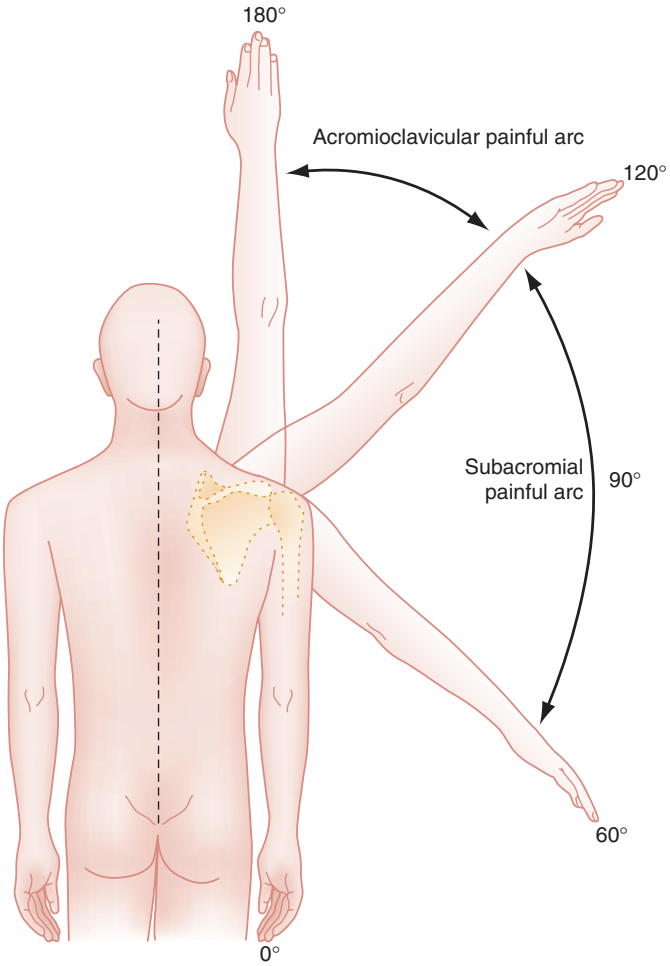


Figure 50-36. Arcs of painful abduction: subacromial painful arc, 60 to 120 degrees; acromioclavicular painful arc, 120 to 180 degrees. (From DePalma AF: Surgery of the Shoulder, 3rd ed. Philadelphia, JB Lippincott, 1983.)

The impingement process also may involve the long head of the biceps. In such cases, bicipital tendinitis, degeneration, or rupture may be present. If osteoarthritis of the ACJ has narrowed the subacromial space, the pathologic process can be accelerated. Impingement in this context occurs between 120 and 180 degrees of abduction (see Fig. 50-36).

Clinical Features. Neer[67] classified the progressive pathologic processes into three stages (Table 50-2). Patients in *stage 1* complain of a dull ache around the deltoid area after strenuous activity. On examination, tenderness can be elicited over the

Table 50-2 Three Progressive Stages of Impingement Lesions

STAGE	PATHOLOGIC FINDINGS	AGE (YR)	COURSE	TREATMENT
1	Edema, hemorrhage	<25	Reversible	Conservative
2	Fibrosis, tendinitis	25–40	Recurrent pain with activity	Conservative, surgical
3	Bone spurs, tendon rupture	>40	Progressive disability	Surgical

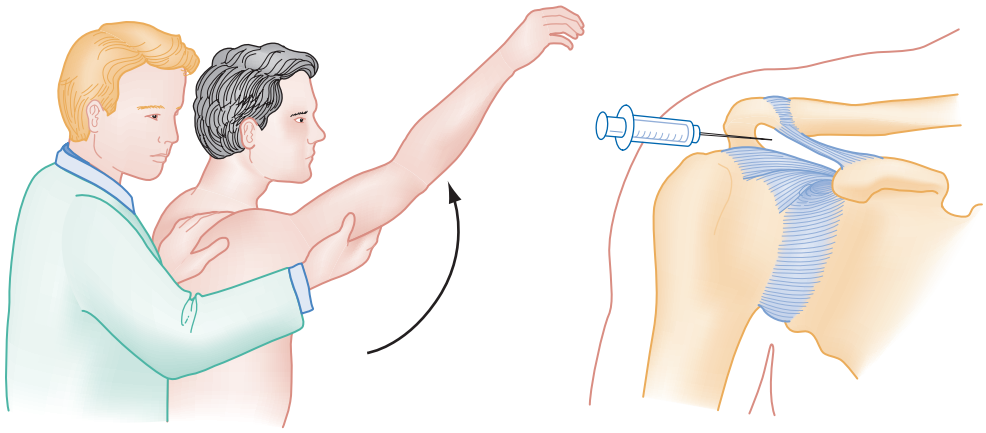


Figure 50-37. Impingement injection test. The impingement sign is elicited with the patient seated or standing and the examiner standing. Scapular rotation is prevented with one hand while the other hand raises the arm in forced forward elevation *(arrow)*, causing the greater tuberosity to impinge against the acromion. This maneuver produces pain in patients with impingement lesions of all stages. It also causes pain in many other shoulder conditions. In the case of impingement lesions, the pain caused by this maneuver is relieved by the injection of 10 mL of 1% lidocaine beneath the anterior acromion. This test is useful in separating impingement lesions of all stages from other causes of shoulder pain. (Redrawn from Neer CS: Impingement lesions. Clin Orthop 173:70, 1983.)

supraspinatus and anterior acromion. A painful arc of abduction between 60 and 120 degrees is characteristic. The Neer impingement sign (Fig. 50-37) has a sensitivity of 68% for all three stages. Several other tests have been described for the diagnosis of impingement syndrome. The combination of the Hawkins-Kennedy impingement sign (arm placed into 90 degrees of flexion followed by internal rotation), the painful arc sign, and the infraspinatus muscle test (resistance to internal rotation with arm adducted and elbow flexed to 90 degrees) provided the best post-test probability (95%) in one large clinical study.[68]

Stage 2 is characterized by more persistent pain that is particularly severe at night. The inflammatory process within the bursa and tendons leads to the formation of minor adhesions. Disruption of these adhesions is thought to account for the nighttime pain. Physical findings are similar to those in stage 1. In addition, bursal thickening leads to increased soft tissue crepitus within the glenohumeral joint.

The hallmark of *stage 3* is significant tendon degeneration after a prolonged history of tendinitis and bursitis. Findings in this stage are discussed in the subsequent section on tears of the rotator cuff. The radiographic appearance usually is normal in stages 1 and 2. Findings in stage 3 are similar to those with complete tears of the rotator cuff.

The differential diagnosis of impingement syndrome is extensive and includes intrinsic and extrinsic causes of shoulder pain. Extrinsic sources include the cervical spine, lung, heart, and diaphragm. Intrinsic conditions include acromioclavicular arthritis, adhesive capsulitis, calcific tendinitis, and traumatic anterior subluxation. A Neer impingement sign may be present in many of these other conditions. Relief of pain after the subacromial injection of 10 mL of 1% lidocaine (impingement test—see Fig. 50-37) helps localize the condition to the subacromial space.

Management. Initial treatment in stage 1 impingement syndrome is conservative and consists of rest, nonsteroidal antiinflammatory drugs (NSAIDs), and modification of activities that produce impingement. In stage 2, emphasis is on maintaining flexibility and range of motion through physiotherapy and rotator cuff strengthening exercises. Patients with stage 1 and 2 disease who present to the ED reporting treatment failure with NSAIDs may benefit from a subacromial injection of corticosteroids (Table 50-3). Corticosteroid injections take 3 to 4 days for their full effect and must be injected accurately into the subacromial bursa.[69] Patients with treatment-refractory stage 2 and stage 3 disease may require decompression surgery to control pain. Patients with stage 2 and 3 disease may benefit from referral to an orthopedist for more detailed evaluation and treatment.

Rotator Cuff Tears

Pathophysiology. The rotator cuff acts as a dynamic stabilizer of the glenohumeral joint. Its primary function is to hold the humeral head in place throughout the full range of motion (see Fig. 50-5). In addition, it contributes power in all directions and is responsible for specific movements. The infraspinatus and teres minor act as external rotators, whereas the subscapularis is an internal rotator. The supraspinatus is essential for the first 30 degrees of shoulder abduction.

The tenuous blood supply of the rotator cuff, abusive tensile overload, and chronic wear under the coracoacromial arch predispose it to age-related degenerative changes. The advanced stage of this process is characterized by complete rupture of the rotator cuff.

The role of impingement in the development of rotator cuff tears is controversial. Primary impingement (e.g., acromial variance) is uncommon but when present accelerates the

Table 50-3 Potency, Duration of Action, and Recommended Dose of Commonly Used Corticosteroid Preparations

PREPARATION (TRADE NAME)	RELATIVE POTENCY	DURATION OF ACTION	SUBACROMIAL DOSE (MG)
Hydrocortisone acetate (Hydrocortone)	1	Short	25–37.5
Betamethasone sodium phosphate and acetate (Celestone Soluspan)	25	Short/long	6
Methylprednisolone acetate (Depo-Medrol)	5	Long	40–80
Triamcinolone acetonide (Kenalog-10)	5	Long	10–20
Triamcinolone hexacetonide (Aristospan)	5	Long	20
Triamcinolone diacetate (Aristocort)	5	Long	25
Dexamethasone acetate (Decadron-LA)	25	Long	4–16

degenerative process. More often, weakening or rupture of the cuff with age allows for superior migration of the humeral head, which results in secondary impingement. This impingement produces secondary changes within the subacromial space and symptoms characteristic of the impingement syndrome.

Rotator cuff tears typically involve the dominant arm and occur in men older than 40 years of age. The occupational history is significant for strenuous work requiring overhead activity. Most tears occur near the attachment of the supraspinatus and can extend anteriorly into the subscapularis or posteriorly into the infraspinatus. Tears can be classified according to their size, completeness, pattern location, or duration. A clinically useful system is to divide tears into acute or chronic types. *Acute tears* (10%) usually are associated with a specific traumatic event. Often no history of previous shoulder problems can be identified. The most common mechanism of injury is forced abduction associated with significant resistance; this usually occurs when the patient attempts to break a fall with an outstretched hand. Alternatively, the tendon rupture may occur with attempts to lift a heavy object or with a fall directly onto an immovable object.[70]

Clinical Features. With *acute tears*, patients typically complain of a sudden tearing sensation in the shoulder followed by severe pain that radiates into the arm. Pain and secondary muscle spasm limit shoulder motion. Physical findings depend on the completeness, size, and location of the tear. Point tenderness is usually present over the site of rupture (greater tuberosity). A palpable defect also may be present. Subacromial injection of 10 mL of 1% lidocaine eliminates pain and allows for proper evaluation of motor function. The patient with a large tear cannot initiate shoulder abduction. A discrepancy between active and passive range of motion is highly suggestive of a rotator cuff tear.[70] The drop-arm test, performed by passively abducting the arm to 90 degrees and asking the patient to hold the arm in this position, is positive with significant tears. Slight pressure on the distal forearm or wrist causes the patient to drop the arm suddenly. The acute pain resulting from hemorrhage and spasm subsides over a few days. Repeat examination at this point confirms the loss of function in significant tears.

Chronic tears account for approximately 90% of all lesions. Chronic tears are attritional and more insidious in their presentation. Early findings include the painful arc sign as a result of secondary impingement. The pain is worse at night and interferes with sleep. Worsening pain is followed by the gradual onset of weakness in the arm. Flexion and abduction are affected first. The patient attempts to initiate abduction using scapulothoracic movement. Internal rotation is weakened by anterior extension of the tear. Posterior extension compromises external rotation. The drop-arm test result is positive with large tears, and atrophy of the supraspinatus and infraspinatus muscles may be seen. In a large clinical study, the combination of the painful arc sign, drop-arm test, and positive infraspinatus muscle test results produced the best post-test probability (91%) for full-thickness rotator cuff tears.[68]

Diagnostic Strategies: Radiology. Radiographs may be normal in acute and chronic tears, but more often they show evidence of nonspecific degenerative changes within the glenohumeral joint and subacromial space. The greater tuberosity can have a sclerotic or cystic appearance. Osteophytic spurs and sclerosis of the undersurface of the acromion may narrow the subacromial space. The hallmark of a complete tear is superior displacement of the humeral head. This displacement is best seen on an external rotation view. The normal distance from the superior aspect of the humerus to the undersurface of the acromion ranges from 7 to 14 mm. A distance of less than 6 mm is highly suggestive of a complete tear. Outpatient ultrasound examination, MRI, or an arthrogram can confirm the diagnosis. In a recent study, the overall accuracy of ultrasonography in the detection of partial- and full-thickness rotator cuff tears was 87%, using arthroscopy as the "gold standard" diagnostic modality.[71]

Management. Acute tears should be immobilized in a sling and the patient referred promptly for orthopedic follow-up care. Early surgical repair (before 3 weeks) is preferred in these instances, especially for a young or active person. The management of chronic tears includes pain control and a shoulder rehabilitation program. Painful arc symptoms may respond to subacromial injection of a corticosteroid (see Table 50-3). Orthopedic follow-up care is essential because patients with persistent pain and weakness may require surgical repair.

Lesions of the Biceps Muscle

The biceps is composed of two heads. The long head originates from the supraglenoid tubercle and glenoid labrum and ascends over the humeral head to enter the arm by way of the bicipital groove. The long head is covered by a synovial sheath and is held in place within the groove by the coracohumeral and transverse humeral ligaments. The short head of the biceps originates from the coracoid process and inserts with the long head onto the tuberosity of the radius. The biceps is responsible for flexion as well as supination at the elbow and serves as a stabilizer for the glenohumeral joint.

Bicipital Tendinitis

Pathophysiology. Anatomically the long head of the biceps is subject to the same stresses as those incurred by the rotator cuff within the subacromial space. Irritation and microtrauma as a result of repetitive elevation or abduction of the shoulder produce an inflammatory reaction within the synovial sheath.

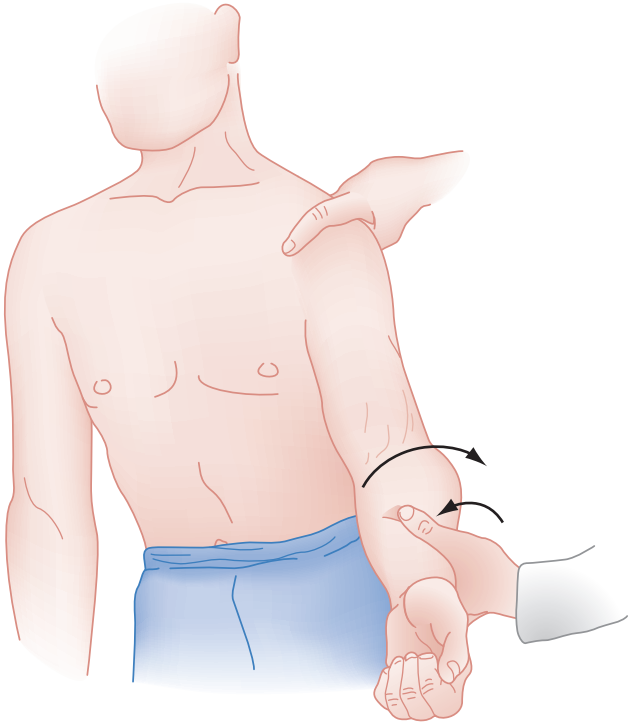


Figure 50-38. Yergason's test. With the elbow flexed, supination of the forearm *(arrows)* against resistance causes pain in the anterior and inner aspect of the shoulder. (From DePalma AF: Surgery of the Shoulder, 3rd ed. Philadelphia, JB Lippincott, 1983.)

Bicipital tendiniits usually is associated with other acromial arch impingement conditions (e.g., subacromial bursitis, rotator cuff tendinitis).[72]

The typical patient is middle-aged and involved in an occupation or recreational activity that requires overhead movement. The presenting complaint is pain in the anterior part of the shoulder that radiates into the upper arm. The pain usually is initiated by some minor traumatic event involving forceful contraction of the biceps. Pain increases with activity and decreases with rest. Abduction and external rotation in particular are painful. Pain is worse at night and may interfere with sleep.

Primary bicipital tendinitis is uncommon (5% of cases) and affects much younger persons.[72]

Clinical Features. On examination, point tenderness can be elicited over the biceps tendon as it passes through the bicipital groove. This is best shown with the arm in 10 degrees of internal rotation. Active range of motion is limited by pain, but the passive range remains intact. Supination against resistance—the *Yergason test*—with the arm adducted and the elbow flexed to 90 degrees reproduces the pain in 50% of cases[72] (Fig. 50-38). Another proactive test is the *biceps resistance test* (Speed test), in which forward flexion of the shoulder (elbow extended and forearm supinated) carried out against resistance produces pain in the bicipital groove.

Diagnostic Strategies: Radiology. Radiographs may show evidence of subacromial space impingement by associated acromioclavicular arthritis and osteophytic spurs. The preferred imaging modalities are ultrasonography and MRI.[72]

Management. Emergency treatment consists of rest (immobilization in a sling), application of ice, and an NSAID regimen. Gentle stretching exercises are encouraged as symptoms subside. Refractory or progressive cases should be referred to an orthopedic surgeon. Although the bicipital sheath can be injected with a corticosteroid preparation, the procedure is technically difficult, and inadvertant direct tendon injection can lead to tendon rupture. Subacromial decompressive surgery may be necessary in patients who fail to respond to conservative therapy.[72]

Ruptures of the Biceps Tendon

Pathophysiology. Ruptures of the biceps tendon can be classified into proximal and distal types. Distal ruptures are rare and are not discussed here. Proximally, microtears and other age-related attritional changes within the long head predispose it to rupture.[70] The rupture can be spontaneous or may follow a traumatic event involving either forced extension or resisted supination and flexion.

Clinical Features. The classic history of an acute rupture is that of a sudden snap or pop, followed by pain and ecchymosis along the arm. The tendon usually ruptures at its weakest point, which is just distal to the exit from the glenohumeral joint cavity. With a complete rupture, distal retraction of the muscle results in a "Popeye" appearance of the arm. A difference in muscle contour (Ludington sign) also may be seen when both arms are placed behind the head and the biceps muscles are contracted.[73] Functionally, forearm supination is weakened, but elbow flexion stays strong because the coracobrachialis and short head of the biceps remain intact. Most bicep tendon ruptures are associated with the impingement syndrome and a rotator cuff tear.

Diagnostic Strategies: Radiology. Radiographic findings usually are unremarkable, and the confirmatory test of choice is an MRI study.

Management. The injured arm should be immobilized in a sling with the elbow in 90 degrees of flexion. The local application of ice may provide temporary relief. Analgesia should be provided, and the patient should be referred to an orthopedic surgeon within 72 hours for further evaluation and treatment. Surgical repair is a consideration in young, active persons. In older patients, conservative therapy (range-of-motion and strengthening exercise) is preferred because the cosmetic deformity is minimal and the mild functional loss usually is acceptable.

Subluxations and Dislocations of the Biceps Tendon

Subluxations and dislocations of the biceps tendon usually are associated with a congenitally shallow bicipital groove or atraumatic (attritional) tears of the coracohumeral and transverse humeral ligaments. The patient complains of a snapping sensation in the upper arm with abduction and external rotation. External and internal rotation of the abducted shoulder shows dislocation and relocation of the tendon. With complete dislocation, the arm may reflexively drop to relocate the tendon. These conditions may require operative repair and should be referred to an orthopedist.

Calcific Tendinitis

Pathophysiology. Rotator cuff calcific tendinitis affects up to 10% of the population and frequently is encountered in the ED. The condition affects people in their 40s and 50s and is rare in persons younger than age 30 or older than age 60. Calcific deposits occur primarily in the supraspinatus tendon near its attachment to the greater tuberosity. Deposits also may involve the infraspinatus, teres minor, or subscapularis tendons. Women are more often affected than men, and 10% of the patients have bilateral deposits. In the precalcific stage, the tendon undergoes fibrocartilaginous transformation. The precipitating factors for this change are unclear and may involve hypoxia- or stress-related degenerative changes within the tendon.[74] Calcium crystals are deposited and coalesce within

the matrix of the tendon. Subsequent invasion of vascular channels into the deposit allows for the influx of neutrophils and macrophages (inflammatory response), which remove the calcification through phagocytosis. Finally, fibroblasts form collagen to create a postcalcification scar.[74]

Clinical Features. The clinical presentation can be divided into silent, subacute, and acute phases based on the physical characteristics of the calcific deposits and the nature of the inflammatory response within the tendon and subacromial bursa. The *silent* phase consists of a dry, powdery deposit with no surrounding inflammatory reaction. It usually is an incidental diagnosis when shoulder radiographs are obtained for other purposes. The deposits may remain painless and eventually reabsorb.

The painful arc syndrome is a hallmark of the *subacute* phase of calcific tendinitis. Enlargement and softening of the deposit lead to narrowing of the subacromial space, resulting in impingement under the acromial arch. Pain experienced between 60 and 120 degrees of abduction (see Fig. 50-36) is characteristic.

A severe inflammatory reaction within and around the deposit produces the *acute* phase of calcific tendinitis. The deposit becomes milky and has the appearance of an acute abscess. The patient is in severe pain and holds the arm close to the chest. Active and passive range of motion is severely limited. The shoulder is warm and extremely tender to the touch. Severe pain is related to increased intratendinous pressure, and spontaneous rupture of the deposit into the subacromial bursa can be associated with dramatic relief of symptoms.

Diagnostic Strategies: Radiology. Radiographs show calcific deposits in the involved tendon (Fig. 50-39). For the supraspinatus, calcific deposits are best seen on the internal and external rotation anteroposterior views. The axillary view is useful for showing calcification within the other tendons of the rotator cuff.

Management. Subacute symptoms usually respond to NSAIDs and measures to limit any offending activity. The acute phase should be treated with sling immobilization, NSAIDs, and analgesia. Subacromial injection of a local anesthetic may provide dramatic temporary relief in the ED. Needle lavage (puncturing of the calcific deposits to decrease intratendinous pressure in the operating room or under fluoroscopy) also has been described as an effective treatment during the acute phase.[74] The subacromial injection of corticosteroids for impingement symptoms is controversial because these agents may delay the process of calcium resorption, thereby interfering with the natural course of the condition. Patients with chronic symptoms may benefit from extracorporeal shock wave therapy or surgical removal of the calcific deposit.[75] Early shoulder range-of-motion exercises should be encouraged in all patients to minimize the risk of adhesive capsulitis. All symptomatic patients should be referred for orthopedic follow-up care.

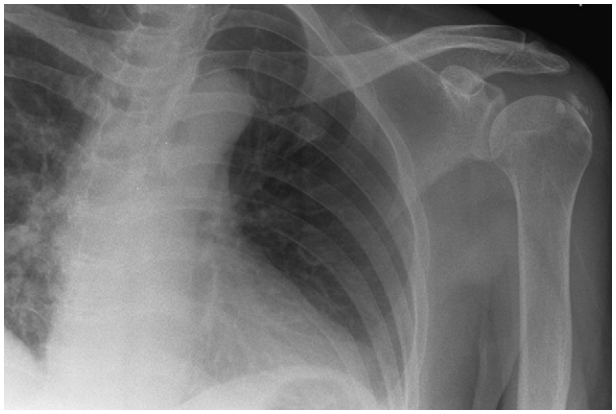


Figure 50-39. Rotator cuff calcific tendinitis.

Adhesive Capsulitis

Pathophysiology. Adhesive capsulitis ("frozen shoulder") is a specific diagnostic entity characterized by an inflammatory reaction within the capsule and synovium of the glenohumeral joint. The inflammatory reaction results in the formation of adhesions within the capsule and inferior axillary fold, leading to restricted active and passive range of motion. The prevalence rate is 2%, with a female-to-male ratio of 58:42.[76] The condition also is more common in diabetic patients. Adhesive capsulitis must be differentiated from other, more common causes of the painful stiff shoulder; this distinction is important because any painful condition of the shoulder (e.g., calcific tendinitis, rotator cuff tear, osteoarthritis, or trauma) may be associated with decreased range of motion.[76] Although the cause of adhesive capsulitis is unknown, any condition associated with prolonged dependency of the arm can result in capsular contraction, including voluntary immobilization after calcific tendinitis, rotator cuff injury, mastectomy, or a distal upper extremity injury (Colles' fracture).

Clinical Features. The typical patient is a diabetic woman between 40 and 60 years of age. The nondominant arm usually is affected, and the patient has trouble with the activities of daily living. The pain often is severe at night and localized over the deltoid area. There is uniform limitation of all glenohumeral movement, including flexion, abduction, and rotation. On passive testing, a sense of mechanical restriction of joint motion can be appreciated by the examiner. Shoulder radiographs usually are normal in appearance if no associated pathologic condition is present.

Management. The best form of therapy is preventive in nature. Prolonged immobilization must be avoided, and early motion of the shoulder should be encouraged in all instances (see Fig. 50-13). Treatment of adhesive capsulitis in the ED consists of NSAIDs and referral to an orthopedic surgeon. Initial therapy usually is conservative and consists of a gentle assisted exercise program along with intra-articular steroid injection. Surgical treatment, including manipulation under anesthesia and arthroscopic capsular release, is reserved for patients in whom at least 6 months of nonoperative treatment has failed to produce improvement.[76]

Injection Therapy. The local injection of corticosteroid preparations can be useful in many painful conditions that affect the shoulder, including rotator cuff tendinitis and subacromial bursitis. Evidence-based research that supports or refutes the use of injection corticosteroid therapy is limited and conflicting.[77] Potential explanations for discordant results of randomized controlled studies include differing outcome definitions and the observation that subacromial injections are difficult to give.[78] The accuracy of needle placement for subacromial injections has been reported to be 70%.[69] Although useful for relieving the inflammatory reaction, corticosteroid injections in general do not alter the underlying disease process. Corticosteroids inhibit all phases of the inflammatory response, including leukocyte migration, edema formation, mediator release, vascular permeability, collagen deposition, and fibroblast proliferation. Systemic complications are rare after local injection therapy. Site-specific complications include articular cartilage damage, tendon weakening or rupture, and subcutaneous atrophy. The incidence of local complications correlates

with the injection technique, dose used, and frequency of administration. Direct tendon injection must be avoided at all times, and the number of steroid injections should be limited to two per shoulder since a high failure rate for rotator cuff repairs has been reported in patients who have received more than three preoperative subacromial injections.[69]

Numerous corticosteroid preparations are available (see Table 50-3). Injection of a long-acting agent or a combination of a short-acting and a long-acting agent is preferred. The dose used depends on the size of the joint or bursa and the response of the individual patient. With concurrent use of a local anesthetic agent for acute pain relief, better diffusion of the steroid preparation may be obtained.

After injection, the shoulder should be immobilized, and activity should be limited for several days to protect against further injury. Improvement usually begins within 1 to 7 days and can last weeks to months, depending on the preparation and underlying condition. Local anesthetic injection may result in dramatic temporary relief of symptoms in the ED.

KEY CONCEPTS

- A thorough neurovascular exam is essential and must be repeated after any manipulation.
- Axillary nerve function is best evaluated by testing the motor function of the deltoid muscle.
- The three-view trauma series leads to an accurate radiographic diagnosis of most fractures and dislocations, although specialized views are necessary in some instances. The presence of unfused epiphyses in adolescents and young adults is an important consideration, and comparison films may be indicated on a selective basis.
- Most fractures can be treated conservatively with good functional outcomes.
- The most important aspect of scapular fractures is the high incidence of associated injuries to the ipsilateral lung, chest wall, and shoulder girdle complex.
- Posterior SCJ dislocations can be associated with life-threatening injuries within the superior mediastinum, and the preferred imaging technique is a CT scan.
- If the coracoclavicular distance exceeds 10 to 13 mm, or if a difference of more than 5 mm in this distance is observed between the injured and the uninjured sides, a grade III ACJ dislocation should be suspected.
- Most studies have concluded that conservative treatment of type III ACJ dislocations provides functional results equal to or, in some cases, better than those with surgical intervention.
- A compression fracture of the posterolateral aspect of the humeral head (Hill-Sachs deformity) is present in a large percentage of anterior glenohumeral dislocations.
- Recurrence is a common complication after anterior dislocation, especially in patients younger than 30 years of age, and such patients may benefit from arthroscopic repair.
- Posterior dislocation should be included in the differential diagnosis of any shoulder injury. A posterior dislocation should be suspected in any patient who complains of shoulder pain or discomfort after a convulsive episode and in the presence of a lesser tuberosity fracture.
- It is important to evaluate the relationship between the spine of the scapula and the longitudinal axis of the humerus to avoid missing an inferior glenohumeral dislocation.
- Early initiation of passive shoulder range-of-motion exercises helps reduce the risk of adhesive capsulitis when the shoulder is immobilized for any reason.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 51

Musculoskeletal Back Pain

Michelle Lin

LOW BACK PAIN

PERSPECTIVE

Background

Approximately 70 to 90% of adults during their lifetime experience *acute low back pain*, defined as pain lasting less than 6 weeks in duration.[1,2] The etiology for the back pain remains unknown in 85% of affected persons after appropriate initial investigation—a situation frustrating for both physician and patient.[3] Frequent diagnoses in such cases include "acute lumbosacral strain," "lumbago," and "mechanical back pain." These nonspecific, catch-all terms reflect the diagnostic challenge and lack of pathognomonic tests for low back pain. More accurately, these patients should be diagnosed with *idiopathic low back pain*. Regardless, most cases resolve spontaneously within 6 weeks. In recent studies on the management of acute low back pain, the most significant discovery—contradictory to traditional teaching from the 1980s—is the need to avoid bedrest for these patients, including those with sciatica symptoms.[4,5] Management recommendations for chronic back pain remain controversial, however, and the condition accounts for a significant proportion of costs to the health care system.

Epidemiology

In the ambulatory care setting, the medical complaint of back pain is the fifth most common reason for a visit to a physician's office, with 15 million annual visits in the United States.[6] Low back pain primarily affects adults 30 to 60 years of age and has a tremendous impact on worker productivity, with significant economic consequences. In people younger than 45 years of age, persistent chronic back pain ranks as the leading cause of disability among chronic ailments. Among people 45 to 64 years of age, it ranks third, behind coronary disease and arthritis.[7] It also is the second leading cause of pain resulting in lost productive time from work, following headache.[8] Overall, patients with back pain account for billions of dollars in total direct and indirect costs in the United States.[1,2,9]

The natural history of most cases of low back pain follows a benign and self-limited course. In a large pooled analysis, back pain decreases by 58% within 1 month. If the pain does not resolve within 3 months, however, it is unlikely to resolve after 12 months. The recurrence rate for pain is 66 to 84% within the first 12 months.[10]

Risk factors for low back pain are continually being investigated. Data obtained so far have been inconclusive and often contradictory.[11,12] It seems that the most consistent risk factor for future back problems is a history of previous back problems. Heavy lifting, pushing and pulling, or vibration at work; poor job satisfaction; smoking; and family history all seem to predispose to future back problems, whether causal or merely linked.[1,9,13-15] Early evidence also points to a genetic predisposition to lumbar disk disease.[16] Multiple other factors have been investigated, including body habitus, various occupations, and psychological profile, with conflicting results.[11,17,18]

PRINCIPLES OF DISEASE

Anatomy and Physiology

The lumbosacral spine consists of five lumbar vertebrae and the sacrum. Moving from anterior to posterior, each vertebra can be divided into the cylindrical vertebral body, two pedicles, two transverse processes, two overarching laminae, and a spinous process. These structures surround the neural canal, which houses the spinal cord and nerve roots and has a midsagittal anteroposterior diameter of 15 to 23 mm. The paired superior and inferior articulating processes join the articulating processes one vertebral level above and below. Each articulation site is called a *facet joint*. An intervertebral disk interposes between each vertebral body, providing elasticity and stability to the vertebral column. Each disk consists of an inner colloidal gelatinous substance, the *nucleus pulposus*, and an outer capsule, the *annulus fibrosus*, which is thinner posteriorly than anteriorly (Fig. 51-1).

Various ligaments and muscles also provide stability to the lumbosacral spine. The anterior and posterior longitudinal ligaments course along the anterior and posterior surfaces of the vertebral bodies. The posterior longitudinal ligament forms a border between the intervertebral disks and the neural canal. As expected, because this ligament thins as it runs inferiorly from L1 to S1, 95% of lumbar disk herniations occur at the L4–5 and L5–S1 levels, causing pain and neurologic deficit in the L5 to S1 distribution. Most herniations extrude posterolaterally to impinge a nerve root asymmetrically.[19] The ligamentum flavum courses just anterior to the laminae within the neural canal. With age, this ligament can thicken, potentially causing spinal stenosis.

The spinal cord ends at the L1–2 interspace, and the lower cauda equina nerve roots extend inferiorly, exiting the sacral

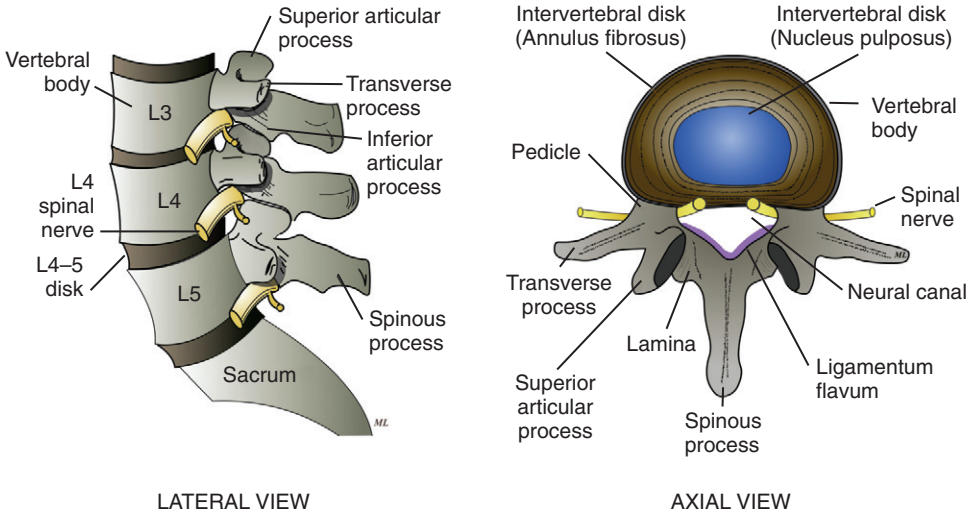


Figure 51-1. Lateral and axial views of lumbar vertebral anatomy.

foramina as peripheral nerves to the lower extremity. Pain fibers supplying structures in the lumbosacral region primarily arise from the posterior rami and sinuvertebral nerves at each lumbar vertebral level. The nucleus pulposus and inner annular fibers of the intervertebral disk are unique in their lack of any pain fibers.[20] This anatomic feature correlates consistently with magnetic resonance imaging (MRI) evidence of disk pathology in 28 to 33% of asymptomatic patients. The significance of these findings is unclear.[9,20,21]

Pathophysiology

Most conditions of low back pain have no proven cause. It is estimated that 85% of patients have no definitive diagnosis and are presumed to have pain originating from the soft tissue, including the muscles and ligaments.[9,19] In the other 15% of patients with a known etiology, the pain may originate in the (1) nerve root, (2) articular facets, or (3) bone itself.

In low back pain of *nerve root origin*, a spinal nerve root can become inflamed and painful with external impingement. Disk herniation, usually at the L4–5 and L5–S1 levels, is the most common cause of *sciatica* (i.e., pain radiating down the posterior leg from sciatic nerve root irritation). As the disk starts to desiccate and degenerate, starting in their 30s, patients are at increased risk for outward herniation of the nucleus pulposus with consequent nerve root impingement. With further aging, these disks progressively shrink in size. In keeping with these findings, disk herniations typically are found in patients 30 to 50 years of age. Local nerve ischemia from physical compression also may contribute to the inflammation and pain. Studies also show that exposure of the nucleus pulposus during disk herniation may result in local neural inflammation, leading to pain.[22] Nerve root impingement also can occur with spinal stenosis, a narrowing of the neural canal from congenital narrowing or, more often, from degenerative or hypertrophic changes of the disks, vertebrae, facet joints, and ligamentum flavum.[23]

The two most critical conditions causing nerve irritation are cauda equina syndrome and a spinal epidural abscess. *Cauda equina syndrome* is most commonly due to a massive central disk herniation usually compressing multiple, bilateral nerve roots, causing back pain radiating to both legs, saddle anesthesia, and impaired bowel and bladder function. Emergent surgical decompression is indicated to preserve neurologic function. An *epidural abscess* similarly results in nerve root impingement, causing significant back pain. These rare infections develop most commonly from the hematogenous spread of *Staphylococcus aureus*.[19]

Congenital and developmental spinal abnormalities also may cause back pain by nerve root inflammation in some cases, but much less frequently than was thought previously. Conditions such as kyphosis and scoliosis usually do not cause pain unless the degree of vertebral column misalignment is pronounced.[24] Similarly, spondylolisthesis (slippage of one vertebral body on another) does not usually cause pain if the slippage is less than 25% of the vertebral body depth. Even in patients with higher grades of anterior slippage (anterolisthesis), the development of severe back pain is rare. Although it is one third as common as anterolisthesis, backward slippage (retrolisthesis) is almost always associated with back pain. Spondylolisthesis occurs most often at the L5–S1 level (82.1%), followed by the L4–5 level (11.3%) and the L3–4 level (0.5%).[25] Multifactorial causes of spondylolisthesis include degenerative changes and trauma. Spondylolisthesis often is associated with bilateral pars interarticularis defects in the affected vertebra (spondylolysis).

In low back pain of *articular facet origin*, as with any other joint in the body, degenerative changes in the synovial articular facets in the lumbosacral spine occur with age. Although the exact role and significance of articular facet joints in back pain are unclear, facet pathology for it has been suggested to contribute to 15 to 45% of chronic back pain cases.[26]

In low back pain of *bone origin*, direct irritation of the vertebral bone and its periosteum can cause back pain. The causes for spondylitis (osteomyelitis of the axial skeleton) can range from a slowly progressing tuberculosis infection (Pott's disease) to a more acute bacterial infection. Typically, bacteria seed the bone from a hematogenous source, such as from a skin wound or urinary tract infection, or directly from intravenous drug use. The most common bacterial culprit is *S. aureus*. Primary and metastatic bone neoplasms can cause back pain from tumor infiltration into the bone. Primary bone tumors, such as multiple myeloma, chordoma, Ewing's sarcoma, and osteosarcoma, are 25 times less frequent than metastatic disease.[27] Of the neoplasms, breast, lung, prostate, thyroid, and kidney cancers and lymphoma are the most likely to metastasize to bone. Inflammatory conditions, such as ankylosing spondylitis and other arthropathies, and osteoporosis also can cause back pain. In osteoporosis, the generalized decrease in bone mineralization can cause pain from microfractures of the vertebral column.

Referred pain, most commonly from intraperitoneal and retroperitoneal abdominal pathology, also must be considered in patients with back pain. Functional processes play a substantial role in back pain, especially for prolonged symptoms lasting more than 4 to 6 weeks. Functional causes range from fear, depression, and personality disorders to financial motivation. In such cases, no anatomic or pathophysiologic correlation with the reported pain can be found.

Chronic back pain is complex and multifactorial. Not only are the structural causes unclear, but the nonphysical factors are variable and difficult to determine. It is likely that many of these patients do have some kind of chronic pain. What is unknown is why chronic pain triggers depression, drug dependence, and malingering in some people but not in others. One difference may be the degree of disruption that the condition causes in the patient's lifestyle. A normally active and athletic person who is incapacitated is more profoundly affected than someone who is habitually sedentary. Psychological factors and potential compensation play a large role in the behavior of many patients with chronic back pain.[28,29]

Pediatric back pain results in a diagnosis more often than adult pain.[30,31] Children complaining of back pain require appropriate investigation. They may turn out to have spondylolysis with a variable degree of spondylolisthesis, Scheuermann's disease (kyphosis and osteochondritis of the vertebral endplates), an infectious disease, or a neoplastic process. Disk herniation in children is comparatively rare, but when it does occur, the presentation is similar to that in adults.[30]

CLINICAL FEATURES

Signs and Symptoms

A thorough history and physical examination are crucial in evaluating all patients with acute low back pain. The classic historical (Table 51-1) and physical findings with various entities associated with low back pain are reviewed in this section. Although most of these etiologic disorders are benign, four such disorders have been identified by the Agency for Health Care Policy and Research as "cannot miss" or "red flag" diagnoses: spinal fracture, cauda equina syndrome, spinal infection, and malignancy.[32] A methodical and focused approach to the history and physical examination can help assess the patient's pretest probability for each of these disease entities and determine whether further tests should be ordered.

Table 51-1 Historical Clues for the Etiology of Low Back Pain

QUESTIONS FOR PATIENT	POTENTIAL DIAGNOSIS
Does the back pain radiate down past the knees?	Radiculopathy and likely a herniated disk
Is the pain worse with walking and better with bending forward and sitting?	Spinal stenosis
Do you have morning back stiffness that improves with exercise?	Ankylosing spondylitis
Are you older than 50 years of age?	Osteoporotic fracture, spinal malignancy
Has there been any recent history of blunt trauma?	Fracture
Do you take long-term corticosteroids?	Fracture, spinal infection
Do you have a history of cancer?	Spinal metastatic malignancy
Does your pain persist at rest?	Spinal malignancy, spinal infection
Has there been persistent pain for longer than 6 weeks?	Spinal malignancy
Has there been unexplained weight loss?	Spinal malignancy
Is the pain worse at night?	Spinal malignancy, spinal infection
Are you immunocompromised (e.g., HIV infection, alcoholism, diabetes)?	Spinal infection
Have you had fevers or chills?	Spinal infection
Do you have pain, weakness, or numbness in both legs?	Cauda equina syndrome
Do you have bladder or bowel control problems?	Cauda equina syndrome

HIV, human immunodeficiency virus.

Uncomplicated Musculoskeletal Back Pain

Most patients with back pain can be classified in the category of those with uncomplicated musculoskeletal back pain, after exclusion of worrisome disease processes. Often, patients are unable to recall an inciting incident. The pain usually is characterized as an "ache" or "spasm" and is localized asymmetrically in the lumbar paraspinous muscle, with radiation to the buttock or posterior thigh proximal to the knee. Movement exacerbates the pain, and rest relieves it. No associated deficit in sensation, strength, or bowel or bladder sphincter tone is identified in the history or on the clinical examination. The sole physical findings may be regional lumbosacral tenderness and a limited range of motion of the lower back. This diagnosis of exclusion is made only after ruling out the more worrisome causes of back pain.

Radiculopathy

Approximately 1% of all patients with low back pain exhibit signs of lumbar radiculopathy (i.e., nerve root irritation).[33] The most common etiologic process is herniation of a lumbar disk; other causes include spinal stenosis, malignancy, and infection. The most common type of lumbar radiculopathy is sciatica—an L5 or S1 radiculopathy. Patients with sciatica describe their pain as radiating from the low back to the legs, distal to the knee. Such pain is characterized as "shooting," "lancing," "sharp," or "burning." Associated symptoms include focal numbness or weakness in one of the lower extremities. Exacerbating triggers include sitting, bending, coughing, and straining; relieving factors include lying supine and still.

On physical examination, the patient frequently exhibits tenderness to palpation in the sciatic notch. The *straight leg raise* (SLR) *test* is a fairly sensitive assessment tool to determine if the patient has sciatica. The SLR test is done with the patient supine and the legs extended. The symptomatic leg is passively raised while keeping the knee straight. The presence of back pain, which radiates past the knee when the leg is elevated 30 to 70 degrees, suggests an L5 or S1 radiculopathy. If the SLR test results in isolated low back pain without radiation symptoms to the legs, however, it is considered to be a *negative* finding. Through pooled analysis, the SLR test has a sensitivity of 91% but a low specificity of 26%, meaning that a negative result is fairly accurate in ruling out sciatica.[34] Corroborative tests for sciatica include the "bowstring sign" (reproduction of pain with deep palpation of the taut "bowstring" posterior tibial nerve in the midline popliteal fossa) and

reproduction of pain with foot dorsiflexion when the leg is elevated just short of the pain threshold during the SLR test. As an alternative to the SLR test, with the patient in a seated position, the knee can be extended ("flip test"), which also should stretch the sciatic nerve. Reproduction of the pain often causes the patient to lean backward reflexively from the pain, almost "flipping" back into a supine position.

A *crossed SLR test* is done by passively raising the patient's asymptomatic leg while keeping the knee straight. The presence of pain radiating from the back to the opposite affected leg has a sensitivity of only 29% but a high specificity of 88% for sciatica, meaning that a positive result on crossed SLR testing is almost pathognomonic for sciatica, whereas a negative result is nondiagnostic.[34]

A *reverse SLR test* is performed to detect L3 or L4 radiculopathy. With the patient prone, each hip is passively extended. If there is irritation of the L3 or L4 nerve root, pain is elicited.

In addition to stressing lumbar nerve roots, a thorough examination of the lower extremities detects subtle abnormalities associated with radiculopathies. This examination includes mapping the distribution of pain and assessing individual nerve root function, specifically strength, sensation, and reflexes. For the sensory examination, the earliest deficit can be detected by examining the most distal aspect of the dermatome. Specifically, light touch and pinprick sensation should be tested on the medial foot (L4), in the area between the great and second toes (L5), and on the lateral foot (S1) (Fig. 51-2).

Herniated Disk

Patients with herniated lumbar disks usually are 30 to 50 years of age and often have a long history of recurrent nonradicular low back pain, theoretically from irritation of the outer annular fibers of the disk. When the nucleus pulposus of the disk prolapses through the annulus fibrosus, local nerve root inflammation and radiculopathy result. Coughing, sitting, and any movement in general exacerbate the patient's pain and radiculopathy symptoms. The severity of leg pain from radiculopathy often overshadows the back pain. Sciatica findings have a sensitivity of 95% for lumbar disk herniation, meaning that herniation is extremely unlikely in the absence of sciatica.

The physical examination should focus on lower extremity neurologic function and signs of radiculopathy. Weakness of ankle dorsiflexion, great toe extension, ankle plantar flexion, and knee extension is associated with respective specificities of 70%, 70%, 95%, and 99% for lumbar disk herniation.[19]

Spinal Stenosis

Patients with spinal stenosis are typically older (mean age of 55 years) and constitute only 3% of all patients with low back pain.[3,35] The classic history, identified in 60 to 75% of patients with spinal stenosis, is one of subacute or chronic pain and lower extremity radiculopathy that occurs with walking and is relieved with rest and, uniquely, bending forward at the waist.[36] Because these symptoms mimic peripheral vascular claudication symptoms, pain from spinal stenosis is termed *pseudoclaudication*. Typically, vascular claudication lasts 5 minutes after resting, whereas pseudoclaudication lasts 10 to 15 minutes. Patients with spinal stenosis obtain symptom relief with spine flexion and bending forward because these maneuvers increase spinal canal diameter and reduce spinal cord tension. Similarly, sitting also helps to relieve the symptoms in these patients, in contrast with patients with herniated disks. A typical history describes walking uphill without pain but experiencing pain on walking downhill, when the back is extended.

On physical examination, most patients are found to have a lumbar radiculopathy at one or multiple levels and increased back pain with extension.[36] Classically, patients with spinal stenosis walk with a slightly bent-forward position. To help differentiate spinal stenosis from vascular claudication, peripheral pedal pulses and ankle-brachial indices should be checked.

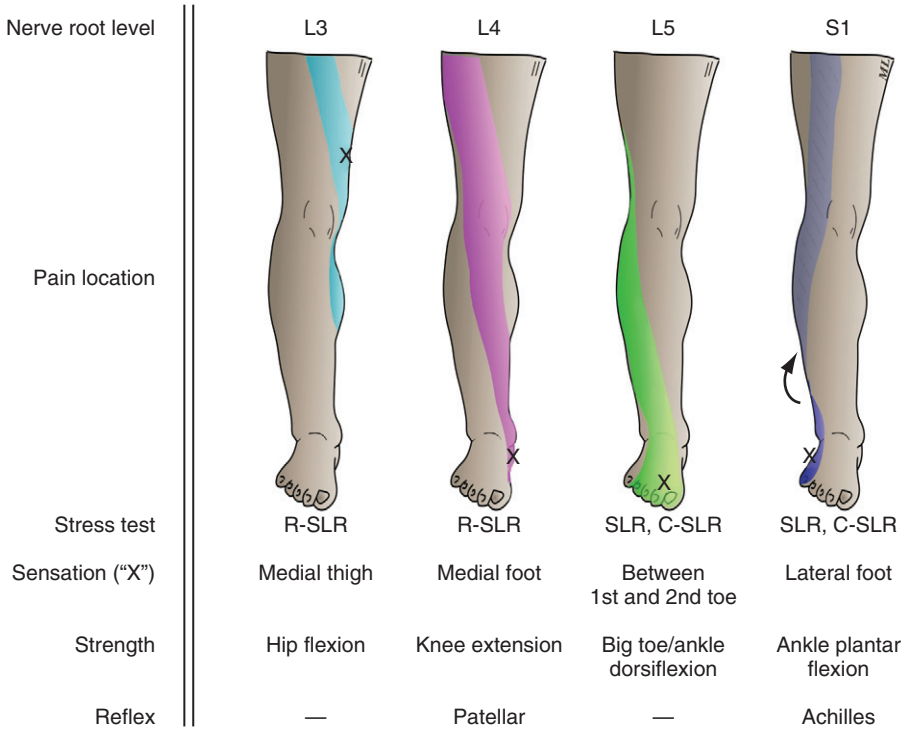


Figure 51-2. Physical examination findings for L3–S1 radiculopathy. The X marks the ideal location to test for sensation for each nerve root. C-SLR, crossed straight leg raise; R-SLR, reverse straight leg raise; SLR, straight leg raise.

Degenerative Spondylolisthesis

Most cases of spondylolisthesis, forward displacement of one vertebral body over another, are caused by degenerative changes. This condition is most prevalent in adults older than age 50 and occurs most commonly at the L4–5 and L5–S1 junctions. Two thirds of older patients with radiographically documented degenerative spondylolisthesis are asymptomatic.[37] For patients with pain, bending, twisting, and lifting activities aggravate the symptoms. Radiculopathies, spinal stenosis symptoms, or both may coexist. On physical examination, clinical findings may include a loss of lumbar lordosis, a step-off along the midline spine if the spondylolisthesis is severe, tight hamstrings, or a radiculopathy.

Arthropathies

Inflammatory arthropathies, such as ankylosing spondylitis, rheumatoid arthritis, and psoriatic arthritis, all are associated with subacute and chronic low back pain. Patients with these conditions exhibit a decreased range of spinal flexibility. Commonly with ankylosing spondylitis, patients complain of morning back stiffness and pain relief with exercise. On physical examination, patients with inflammatory arthropathy (not just AS) may have nonspecific manifestations, such as decreased spinal mobility, sacroiliac joint tenderness, and decreased chest expansion.

Red Flag Diagnosis: Fracture

In all patients who have experienced significant blunt trauma to the back or only minimal trauma in the setting of osteoporosis, fractures of the spinal column must be considered. Among patients taking long-term corticosteroids, who are predisposed to the development of early osteoporosis, back pain had a specificity of 99.5% for a spinal fracture in one series.[19] This subpopulation of patients must be assessed for a fracture despite the absence of trauma. On examination, tenderness along the midline spine and paraspinous muscles from concurrent muscle spasm usually can be elicited.

Red Flag Diagnosis: Cauda Equina Syndrome

Cauda equina syndrome results from a sudden compression of multiple lumbar and sacral nerve roots. Although it is an extremely rare presentation of back pain, it constitutes a neurosurgical emergency. The usual cause is a massive central disk herniation, but other potential etiologic disorders include spinal epidural abscess, hematoma, trauma, and malignancy. Patients with cauda equina syndrome present with back pain and multiple-level radiculopathies, often involving both legs. Difficulty with bladder or bowel function also may be a feature. Diagnostic dilemmas arise because patients can present atypically with equivocal neurologic compromise and only mild to moderate pain.

The most consistent examination finding in cauda equina syndrome is urinary retention. With a high sensitivity for this finding of 90%, this disease process is unlikely if the patient's postvoid residual urine volume is less than 100 to 200 mL. *Saddle anesthesia*, sensory deficit over the buttocks, upper posterior thighs, and perineal area, frequently is an associated finding, with a sensitivity of 75%. In 60 to 80% of cases, the rectal examination reveals decreased sphincter tone.[19]

Red Flag Diagnosis: Spinal Infection

Epidural abscess and spondylitis (osteomyelitis of the vertebral bone) are two types of dangerous spinal infections. Patients at higher risk include injection drug users, alcoholics, immunocompromised patients (e.g., patients with human immunodeficiency virus, diabetes mellitus, chronic renal failure, or long-term corticosteroid use), the elderly, patients who have sustained blunt trauma to the back, patients with an indwelling catheter, and patients with a recent bacterial infection. With epidural abscess, approximately 20% of patients have no comorbid illnesses or risk factors. The most common bacterial culprit is *S. aureus*, spreading hematogenously from a remote site or from direct extension of a local infection, such as spondylitis or disk space infection. Less common culprits are streptococcal strains and enteric gram-negative bacilli. Patient history reveals back pain even at rest and subjective fevers. On physical examination, there is often tenderness to percussion over the spinous process near the abscess location. Spinal epidural abscess remains a diagnostic challenge because approximately 50% of the patients have no neurologic deficits, and 50% may be afebrile on initial presentation.[38] With this subtle and often chronic presentation, many cases are misdiagnosed on initial presentation. Accordingly, an awareness of this entity as a possible cause of low back pain is important for prompt diagnosis of this neurosurgical emergency, which carries a mortality rate as high as 23%.[38,39]

With spondylitis, infection often begins as a subtle hematogenous seeding of the disk space, causing diskitis. Subsequent contiguous spread of the disk space infection causes vertebral endplate erosion, leading to spondylitis. As with epidural abscess, the most common bacterial culprit is *S. aureus*. Less commonly, enteric gram-negative bacilli and *Mycobacterium tuberculosis* (in Pott's disease) are the infecting organisms. Injection drug users also are at risk for *Pseudomonas* spondylitis. The history typically reveals a more indolent course of back pain, with subjective fevers. The physical examination findings can range from nonspecific tenderness of the spine to radiculopathy and cauda equina syndrome. Similarly nondiagnostic, the presence of fever has a sensitivity of only 27 to 50% for spondylitis.[19]

Red Flag Diagnosis: Malignancy

Vertebral infiltration with a tumor can be caused by either a primary or, more commonly, a metastatic malignancy. Affected patients generally are older than 50 years of age and often complain of subacute or chronic back pain that is worse at night. Risk factors include a history of known cancer (98% specificity), unexplained weight loss (94% specificity), persistent pain despite bedrest (90% specificity), and pain lasting more than 1 month (81% specificity).[40] On examination, these patients typically have mild to moderate spinal tenderness. Examination of the organs in which tumors are most likely to metastasize to bone, including breast, prostate, and lung, is indicated.

Referred Back Pain

Referred pain often is difficult to differentiate from pain originating from the lumbosacral structures. It is vital, however, to make the distinction. A sudden onset of severe, "tearing" back pain is classically an aortic dissection. Abdominal pain radiating to the back may be due to a ruptured abdominal aortic aneurysm in an elderly patient with atherosclerotic disease. Alternatively, abdominal pain radiating to the back could be from pancreatitis in a chronic alcoholic. Unilateral paraspinal pain associated with fever and nausea in a young woman could indicate pyelonephritis. In all such cases, a thorough examination of the abdomen, genitourinary system, and cardiovascular system is essential. Pinpointing the primary cause of the pain may radically alter the therapy for the patient.

Functional Back Pain

Distinguishing functional pain from "real" pain often is difficult, but several clues can be elicited from the history. A prolonged history of nonanatomic pain complaints, vague pain descriptions without localization, multiple lawsuits over similar problems, and lack of coordinated care for a problem that otherwise seems to dominate the patient's life all suggest that a search for a physical cause would be fruitless. In such cases, secondary gain for the patient's complaints often is likely.

On physical examination, maneuvers can be performed to try to detect functional back pain, if a psychological overlay is suspected. The first recommended maneuver is performing the SLR test from the sitting instead of the supine position. Seemingly focused on the knee examination, the physician extends the patient's knee; this physiologically reproduces the SLR by stretching the L5 and S1 nerve roots. A positive response includes reproduction of the patient's pain and extension of the back while seated to decrease traction on the sciatic nerve. A positive result on SLR testing in the supine position but a negative result in the seated position, and vice versa, suggests a nonphysiologic cause for the pain.

A second sign is apparent superficial tenderness. Some patients, to impress the physician with their degree of pain, respond dramatically to superficial palpation. This response is atypical for patients with genuine back pain. Nondermatomal sensory loss and widespread nondermatomal pain complaints also are unlikely to be caused by physiologic processes.

Third, back pain should not be elicited by pushing down on the patient's scalp against the cervical spine. This maneuver axially loads only the cervical and not the lumbar spine.

Fourth, a patient who generally overreacts during the examination probably is not giving a true reflection of the actual discomfort. All of these signs are believed to correlate well with psychopathology but have poor prognostic value. They are suggestive of malingering and functional complaints but are neither sensitive nor specific enough to rule out organic pathology.[41,42]

Back Pain in the Elderly

In elderly persons with back pain, musculoskeletal processes and disk herniation are less likely etiologic disorders. Instead, spinal stenosis and degenerative spondylolisthesis should be considered. Also, the incidence of more worrisome diagnoses, such as an osteoporotic fracture, spinal infection, and malignancy, is much greater in this patient population. Consequently, in these cases, the threshold for further investigation should be much lower.

Back Pain in Children

The likelihood of a congenital cause for back pain, such as leg-length discrepancy and spondylolisthesis, is greater for children than for adults. Spondylolisthesis is diagnosed most often in patients older than 10 years of age who are involved heavily in sports and complain of low back pain worsened with activity. In a retrospective study in an urban pediatric emergency department (ED) over a 1-year period, the most common causative disorders in patients with back pain complaints included direct trauma (25%), muscular strain (24%), sickle cell crisis (13%), idiopathic (13%), urinary tract infection (5%), and viral syndrome (4%).[30] A history suggesting infection or malignancy in children is similar to that in adults. Radicular symptoms are relatively rare in children. Functional processes are suggested when the pain is present only with certain undesired activities, such as housework or chores.

■ DIAGNOSTIC STRATEGIES

Laboratory Evaluation

In the absence of historical and physical findings suggesting "red flag" diagnoses for low back pain, laboratory evaluation is unnecessary. When a patient presents with back pain suggestive of a spinal infection or malignancy, however, laboratory studies may help with risk stratification. Specifically, a complete blood cell count, erythrocyte sedimentation rate (ESR), and urinalysis should be performed. Additional laboratory studies should be tailored to the patient's history and physical examination. Liver function testing and determination of amylase or lipase level may be indicated to investigate abdominal complaints.

For a spinal infection, the ESR usually is elevated (above 20 mm/hour), whereas the serum white blood cell (WBC) count may or may not be elevated.[43] In one study, 13 of 40 (32%) patients with a spinal epidural abscess had a falsely reassuring WBC count less than 11,000/μL.[39] When patients are diagnosed with a spinal infection, blood should be drawn for cultures because a single strain, most commonly *S. aureus*, can be isolated in 50 to 90% of the cases.[39,44] Performing a lumbar puncture to evaluate the cerebrospinal fluid is unnecessary and is relatively contraindicated because of the risk of seeding the fluid with bacteria.

For a bony malignancy, the ESR also usually is elevated, whereas the WBC may be equivocal. The hematocrit may be low secondary to anemia of chronic disease. Other additional helpful laboratory tests include measurement of alkaline phosphatase, prostate-specific antigen assay, and serum immunoelectrophoresis and urine testing for light chains (for multiple myeloma).

Radiology

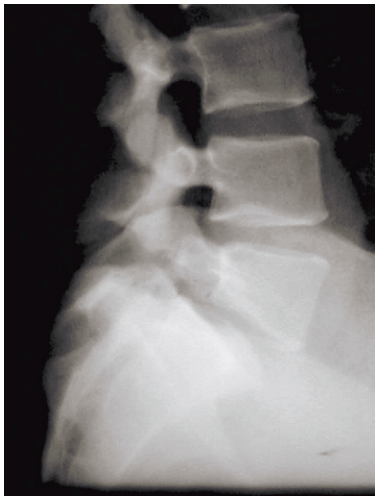
Plain Radiography

The utility of "screening" lumbosacral plain radiographs for all patients with acute low back pain is extremely low. Plain radiographs contribute little to patient management in the absence of concerning "red flag" findings and needlessly expose the patient to radiation.[45] Most patients with back pain do not need radiographs. In those cases in which radiographs have been obtained, normal findings are usual, but incidental findings, which may or may not be the true cause of the patient's pain, also are relatively common and may include spondylolisthesis, abnormal spinal curvature, disk space wedging, or degenerative changes.[9] Currently accepted indications for radiographs in patients with back pain are listed in Box 51-1.

Patients with radicular symptoms suggesting a herniated disk do not require radiographs. In addition to being undetect-

BOX 51-1 INDICATIONS FOR PLAIN LUMBOSACRAL RADIOGRAPHS IN PATIENTS WITH LOW BACK PAIN

- Age younger than 18 or older than 50 years
- Any history of malignancy or unexplained weight loss
- Any history of fever, immunocompromise, or injection drug use
- Recent trauma, other than simple lifting
- Progressive neurologic deficits or other findings consistent with cauda equina syndrome
- Prolonged duration of symptoms beyond 4 to 6 weeks



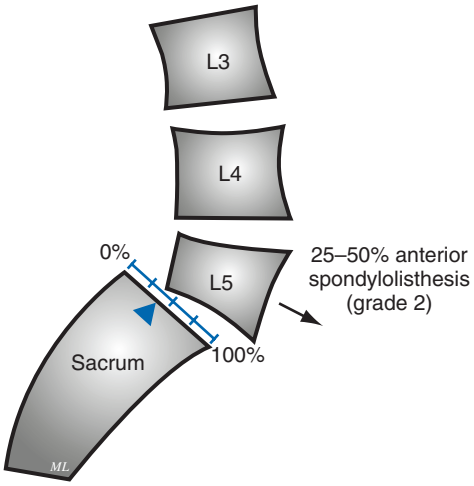


Figure 51-3. Lateral plain radiograph and schematic diagram of grade 2 anterior spondylolisthesis of L5 on S1. Grading is based on the percentage of slippage, with 0 to 25%, 25 to 50%, 50 to 75%, and greater than 75% corresponding to grades 1 to 4, respectively.

able on plain radiographs, disk herniations resolve with conservative management in most cases.

If radiographs are obtained, anteroposterior and lateral views usually are sufficient in the ED, although many centers also prefer to obtain a coned-down lateral sacral view. Oblique views are not necessary except in children, in whom spondylolysis and spondylolisthesis may be more prevalent.[46]

On plain radiographs, spondylolisthesis, vertebral osteomyelitis, and vertebral metastatic disease have classic appearances. Spondylolisthesis (Fig. 51-3) is classified into grade 1 through grade 4 based on the severity of the anterior slippage of one vertebral body over another. Grade 1, which is often asymptomatic, involves less than 25% slippage. Grade 2 through grade 4 involves 25 to 50%, 50 to 75%, and at least 75% slippage, respectively.

Spondylitis (Fig. 51-4) is characterized by erosion of contiguous vertebral endplates and a shortened disk space height, best seen on the lateral view. Because the anterior subchondral vertebral bone and disk space are highly vascular, it follows that spondylitis has a predilection for these areas because of the hematogenous spread of infection. With more advanced disease, vertebral bone erosion and collapse may occur.

Vertebral metastatic disease (Fig. 51-5) can manifest as either a blastic (hyperdense) or a lytic (hypodense) lesion and has a predilection for the vertebral body and pedicles. In contrast with osteomyelitis, the intervertebral disk space is spared.

If a red flag diagnosis is of concern, a plain radiograph may rule out a fracture but may not be adequate to rule out other pathologic processes, such as cauda equina syndrome, spinal infection, and malignancy. For cauda equina syndrome, patients more often have normal or nonspecific plain film findings because the most common etiology is a central disk herniation. For spinal infection and vertebral malignancy, the sensitivity of a plain radiograph is only fair at 82% and 60%, respectively.[45] In these cases, the patient subsequently should undergo MRI if the there is a high clinical suspicion.

Computed Tomography and Magnetic Resonance Imaging

For assessment of fractures of the vertebral column, computed tomography (CT) is superior to MRI. In the case of a fracture, CT helps to elucidate the integrity of the spinal canal and the risk for spinal cord impingement. For all other red flag diagnoses—cauda equina, spinal infection, and malignancy—MRI is the definitive investigative modality. Its superior tissue resolution, especially of the spinal cord and intervertebral disks, and its capability of generating more accurate sagittal reconstructions make MRI the ideal imaging modality. MRI is able to differentiate subtle soft tissue pathology, such as a spinal epidural abscess (Fig. 51-6). No radiation exposure is incurred with MRI, whereas one CT scan of the spine exposes the patient to approximately 4 years' worth of natural background radiation.[47]

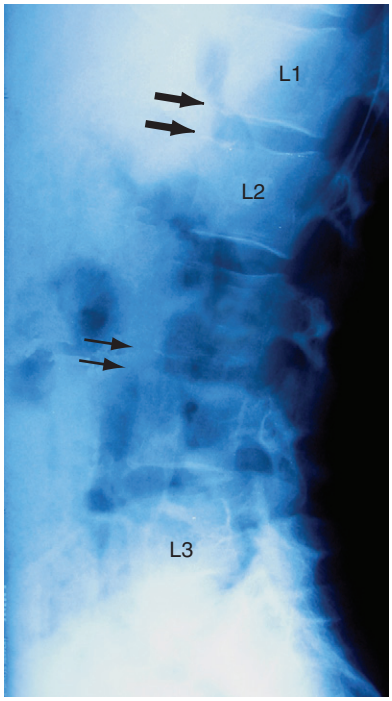


Figure 51-4. Lateral plain radiograph shows *Staphylococcus aureus* spondylitis of L3 and L4. There is narrowing of the L3–4 disk space and erosion of the vertebral endplates of L3 and L4 *(small arrows)*. Notice the distinct vertebral endplate margins in unaffected areas *(large arrows)*.

Although disk herniation is easily visualized on MRI, patients with findings consistent with an uncomplicated disk herniation (i.e., without objective findings of motor or sensory deficit on examination) should not routinely undergo MRI imaging because of the self-limited nature of the disease in most cases. Overimaging in patients with lumbar radiculopathy may lead to an overdiagnosis of disk herniations because

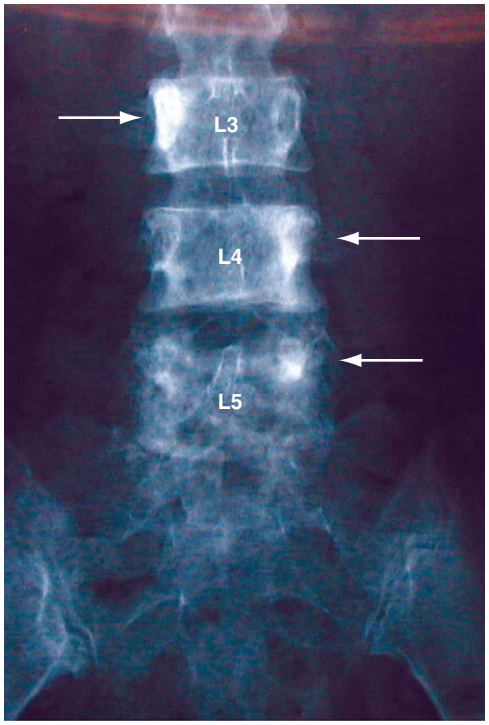


Figure 51-5. Anteroposterior plain radiograph shows blastic infiltration of metastatic breast cancer to the pedicles of L3 to L5 *(arrows)*.

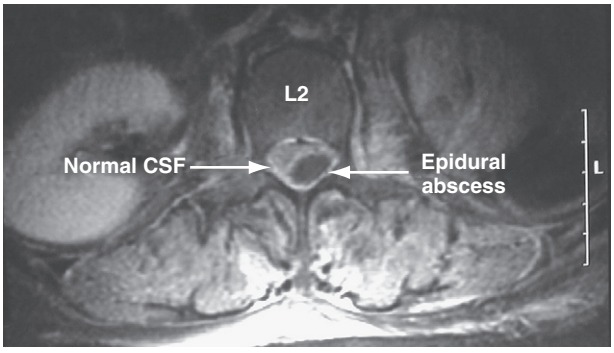


Figure 51-6. Axial T_2-weighted magnetic resonance imaging of *Staphylococcus aureus* L2 epidural abscess impinging the dorsolateral aspect of the spinal canal. CSF, cerebrospinal fluid. (Image contributed by Dr. Stephen Bretz.)

incidental MRI-documented herniations have been shown to occur in 28 to 33% of asymptomatic patients. The result may be unnecessary surgical intervention.[9,48,21]

Special Investigations

Unless a process other than uncomplicated back pain or disk herniation is suspected, other investigations are not required. MRI is the definitive test for most conditions. Radionuclide scans have been used for locating suspected malignancy, infectious foci, and occult fractures as in spondylolysis. Nuclear medicine scans are regarded as sensitive but nonspecific.

DIFFERENTIAL CONSIDERATIONS

Nonspecific low back pain is in many ways a diagnosis of exclusion. In a typical patient, within the 18- to 50-year age range with acute low back pain and with no radiculopathy, previous malignancy, weight loss, or fever, the diagnosis is almost certainly uncomplicated musculoskeletal back pain. When the patient falls outside of the aforementioned parameters, a wide variety of diagnostic possibilities must be entertained.

Almost anything can cause low back pain. Box 51-2 presents an extensive list of diagnostic considerations, but it is useful to look at the most common and most serious causes of low back pain other than musculoskeletal lumbosacral pain. One of the most life-threatening causes of referred back pain is a leaking or ruptured abdominal aortic aneurysm. The reader is referred to appropriate chapters for further discussion of specific problems.

MANAGEMENT

Because most patients with acute low back pain without objective sensory or motor loss on examination experience symptomatic resolution within 4 to 6 weeks, only conservative management is needed. In general, MRI and surgery are reserved for the few patients who have worrisome systemic signs and patients with refractory, debilitating back pain. Over the past few decades, the accepted practice has shifted 180 degrees, from an overaggressive recommendation for invasive surgical intervention to the minimalistic recommendation of symptomatic pain control and early return to activity. The recommended role of the physician in back pain management is to obtain a correct diagnosis, rule out significant pathology, avoid excessive investigation, provide analgesia, and educate the patient.[49] The management for various etiologic categories of disorders that may cause low back pain is summarized in Figure 51-7. For management of fractures and referred pain, the reader is referred to the appropriate chapters.

Uncomplicated Musculoskeletal Back Pain

Besides a thorough history and physical examination, no further investigations are required for uncomplicated low back pain. Only pain control and patient education are indicated. Aside from an initial parenteral opioid or nonsteroidal anti-inflammatory drug, most patients can be managed with oral nonsteroidal medications. Ibuprofen is an ideal choice because it is inexpensive, but various nonsteroidal anti-inflammatory drugs have been shown to have the same efficacy. It is unclear whether ibuprofen is superior to acetaminophen.[50] Short-term opioids also occasionally are needed for breakthrough pain in the acute setting. Various other medications have been advocated, including benzodiazepines and other muscle relaxants. Based on the current conflicting literature, these medications probably do not provide a significant added benefit, but they do increase the incidence of side effects such as drowsiness and drug dependence.[51] Corticosteroids have no role in the treatment of uncomplicated low back pain.

In terms of patient education, one of the outdated practices of back pain management was that physicians convinced patients that they were sick. This was done by overinvestigating, overtreating, putting patients to bed, and taking them off work. It now has been shown convincingly and repeatedly that all of those interventions are excessive. Instead, patients should be educated about why they are not undergoing radiographic studies of their lumbosacral spine or laboratory tests and should be reassured of the likely benign course of the pain. Most patients can be convinced by education and an explanation of radiation dosing. A typical lumbosacral spine series involves as much gonadal irradiation as that incurred with a daily chest radiograph for 5 or 6 years.[52] Patients also are discouraged from the outdated recommendation of strict bedrest. Compared with patients who are prescribed strict

BOX 51-2 Differential Diagnosis for Low Back Pain

Localized/Common
Uncomplicated musculoskeletal back pain
Intervertebral disk herniation
Spinal stenosis
Spondylolisthesis
Osteoarthritis
Fracture

Localized/Uncommon
Infection
Spondylitis
Epidural abscess
Diskitis
Herpes zoster

Malignancy
Metastatic
- Breast
- Lung
- Prostate
- Kidney, thyroid, colon (less common)

Primary
- Multiple myeloma
- Lymphoma
- Leukemia
- Primary cord/extradural tumors
- Osteoid osteoma
- Other primary bone tumors

Pediatric
Spondylolisthesis/spondylolysis
Severe scoliosis
Scheuermann's disease

Rheumatologic
Ankylosing spondylitis
Psoriatic arthritis
Polymyalgia rheumatica
Reiter's syndrome

Vascular
Arteriovenous malformation of spinal cord
Epidural hematoma

Life-Threatening Referred Pain
Abdominal aortic aneurysm

Gastrointestinal System
Biliary pathology
Pancreatitis
Peptic ulcer disease
Diverticulitis

Genitourinary System
Renal colic
Pyelonephritis
Prostatitis
Cystitis

Gynecologic System
Menstrual cramps
Spontaneous abortion
Labor
Ectopic pregnancy
Pelvic inflammatory disease
Endometriosis
Ovarian cyst
Ovarian torsion

Hematologic System
Sickle cell crisis

Functional
Somatization disorder
Depression
Fibrositis
Malingering

bedrest, patients who remain active experience earlier resolution of pain and return to work sooner.[4] Patients should be made aware, however, that the back pain has a 66 to 84% likelihood of recurring within 12 months.[10]

Other supplemental treatment modalities have been shown to be of debatable efficacy in the management of acute and chronic low back pain. These include acupuncture, physiotherapy, chiropractic manipulation, massage, ultrasound, traction, and transcutaneous nerve stimulation.[9,53-56]

Lumbar Disk Herniation

Like patients with uncomplicated low back pain, patients with disk herniations and radiculopathy do not benefit from strict bedrest.[5,49] In the acute setting, these patients should receive analgesics, but further investigation with laboratory tests and radiographs is not necessary. Most of these patients experience symptomatic resolution within 6 weeks with conservative, nonsurgical management.[57,58]

Corticosteroid injections into the epidural space have been advocated for sciatica in the belief that this treatment helps to relieve some of the inflammation associated with disk herniation. Although some reduction of symptoms may be obtained initially, no long-term benefit or reduction in the need for later surgery has been documented.[59] The use of systemic steroids in back pain and disk herniation remains controversial. Although there is no proven benefit, the anti-inflammatory effects make empirical sense in the context of radiculopathy. A large retrospective review showed no definite benefit of systemic steroids in either setting, but the definitive trial is yet to be done.[51]

When the pain from disk herniation persists for longer than 4 to 6 weeks, outpatient MRI is indicated. With a documented herniation, these patients may benefit from surgical diskectomy although this remains controversial compared to conservative management.[60] Other indications for surgery include intractable pain and worsening motor or sensory deficit. Although surgical patients tend to have earlier relief of pain compared with nonsurgical patients, the 4- and 10-year results are the same. Microsurgery techniques and laser therapy have not been shown to confer any advantage over conventional techniques.[61]

Spinal Stenosis

Patients with spinal stenosis should be managed conservatively with pain medications. In the absence of alarming red flag findings, these patients do not require laboratory or radiographic studies in the ED. These patients may be candidates for surgery if they show any of the following conditions: pro-

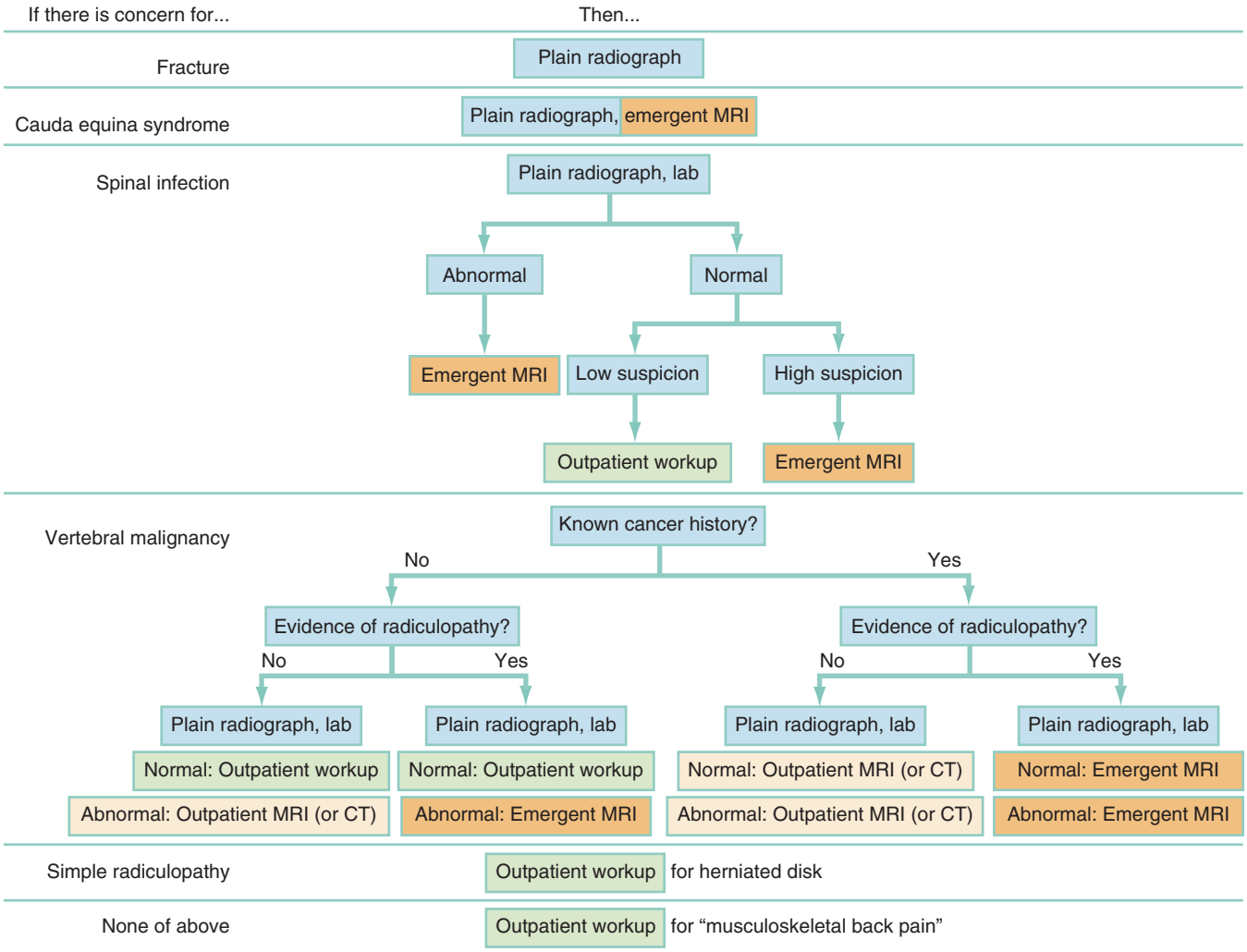


Figure 51-7. Algorithm for management of low back pain. The patient's history may be concerning for more than one red flag diagnosis.

gressive neurologic deficit, progressive reduction in ability to walk secondary to pseudoclaudication, evidence of cauda equina syndrome, or intractable pain. Elective surgical decompression is more controversial. A 10-year longitudinal study showed that no findings predicted which patients would benefit more from surgery than from conservative management.[62] The benefits of surgery also must be weighed against the risks of surgery itself, because these patients usually are elderly.

Degenerative Spondylolisthesis

Patients with symptomatic degenerative spondylolisthesis are managed conservatively with analgesia and lifestyle changes, which include the avoidance of repetitive bending, heavy lifting, and twisting at the waist. For patients with refractory or severe back pain, outpatient MRI and neurosurgical referral for possible operative decompression are recommended.

Red Flag Diagnosis: Fracture

See Chapter 40, Spinal Injuries.

Red Flag Diagnosis: Cauda Equina Syndrome

Cauda equina syndrome is a neurosurgical emergency that requires urgent operative decompression to help preserve distal neurologic function. All patients with concerning findings, such as saddle anesthesia or a large postvoid residual volume, require emergent MRI. On average, outcome is improved if decompression takes place within 48 hours of symptom onset.[63] Early evidence, however, indicates that delayed operative decompression under a more controlled setting may be performed without any adverse effects, particularly in patients who have overflow urinary incontinence.[64]

Red Flag Diagnosis: Spinal Infection

If findings on the history or physical examination are worrisome for a spinal infection, further investigation is of paramount importance. With a low index of suspicion, normal results on serum WBC count, ESR, and lumbosacral plain radiograph can safely rule out infection. The patient's history and examination are worrisome for spinal infection and further investigation is paramount. In patients with moderate to high pretest probability for a spinal infection, the next step is to obtain an emergent MRI.

Pyogenic spinal infections should be treated with neurosurgical drainage and decompression, in addition to broad-spectrum intravenous antibiotics that cover at least for *S. aureus* and gram-negative bacilli until blood culture results return. Vancomycin should be included in the antibiotic regimen, given the increased prevalence of methicillin-resistant *S. aureus*. For injection drug users, antibiotic coverage for

Pseudomonas is necessary. The recent literature suggests that a nonsurgical management approach may be acceptable for patients at lower risk, such as those who are hemodynamically stable and neurologically intact.[65]

Red Flag Diagnosis: Malignancy

An algorithmic guideline to the management of back pain that is worrisome for malignancy involves subdividing patients into two categories: patients with and patients without a history of previous cancer. Development of spinal metastasis has been reported in 20 to 85% of patients with cancer.[66,67] These patients are subdivided further into those with and those without evidence of a radiculopathy.

Most patients fall into the classification of *back pain without a history of cancer and without a radiculopathy*. They have a history that is only suggestive of a malignancy, such as unexplained weight loss or back pain that is worse at night. These patients require further risk stratification with plain radiographs and laboratory tests, including a complete blood cell count and ESR. With normal results, these patients can be referred to their primary care physician for further workup. The physician should not feel completely reassured that malignancy has been ruled out, however, because plain films have a false-negative rate of 10 to 17% for vertebral bone metastasis. This false-negative rate is likely to be due to the fact that a cancer needs to erode at least 50% of the bone before becoming radiographically apparent.[68] With abnormal results, such as a bone lesion or extremely elevated ESR level (above 100 mm/hour), an urgent CT scan or MRI should be performed on an outpatient basis within the next 3 to 7 days.

For patients *without a history of cancer but with signs of radiculopathy*, the workup also includes a plain radiograph, complete blood cell count, and ESR. If the test results are normal, the patient should be referred to his or her primary care physician for further evaluation for malignancy and other potential causes of radiculopathy, including spinal stenosis and disk herniation. If the workup shows a bone lesion on plain radiographs or an extremely elevated ESR level (greater than 100 mm/hour), the patients should undergo emergent MRI because (1) the presence of radiculopathy may be an early harbinger of impending spinal cord compression from a mass effect and (2) it often is difficult on plain radiography to distinguish between a neoplasm from early spondylitis (especially tuberculous osteomyelitis) and an osteoporotic fracture causing a vertebral collapse.[69] If MRI is unavailable, multidetector CT imaging can be performed initially to screen for the presence of malignant bone infiltration, although definitive spinal cord and nerve root imaging will require MRI. The presence of a vertebral mass lesion on CT images suggests spinal cord compression by the mass as a cause for the pain and other symptoms.

For patients *with a history of previous cancer and low back pain*, advanced imaging is indicated, either emergently or urgently within 3 to 7 days. In the absence of clinical manifestations of radiculopathy, these patients should undergo outpatient MRI (or CT) regardless of plain radiography findings and laboratory results. Plain radiography is too insensitive to rule out a vertebral neoplastic process definitively. If radiculopathy is present, however, these patients require emergent MRI regardless of plain radiography findings because of the concern for spinal cord compression. In a study of patients with a confirmed diagnosis of cancer who had back pain and radiculopathy, the risk of epidural spinal cord compression was 25% despite normal radiographic findings, and 88% with radiographic evidence of vertebral metastasis.[70]

In all patients undergoing emergent MRI to evaluate for vertebral malignancy and cauda equina syndrome, dexamethasone should be administered as soon as these conditions are suspected to reduce the potential mass effect. In addition to high-dose corticosteroids, patients with a vertebral neoplasm also may benefit from radiation therapy.

Pediatric Back Pain

Management of back pain in children is similar to management for adults and depends on the underlying causative disorder. Spondylolisthesis is managed by observation, with only 4 to 5% of cases worsening. Progression usually stops as skeletal maturity is achieved in the late teens. Current recommendations are for limited contact sports in children with less than 30 to 50% slippage and surgical stabilization for children with slippage greater than 30 to 50%. Treatment becomes more aggressive if the child is symptomatic.[71]

Chronic Back Pain

Patients with chronic back pain often are regarded as the most challenging of all patients with back pain. The cause of chronic back pain is complex and multifactorial and usually requires a multidisciplinary approach for the greatest chance for success. Psychosocial factors, including depression, drug dependence, and financial gain, undoubtedly play a significant role in the behavior of many of these patients, making proper assessment and treatment impossible in the ED.

After appropriate evaluation has ruled out a red flag cause for the back pain, ED management involves analgesia and referral for follow-up care. The main decision usually centers on the use of narcotics, which should be individualized in accordance with the physician's assessment of the clinical scenario. Patients exhibiting drug-seeking behavior classically are from out of town, have a primary care physician who cannot be contacted, or are reportedly allergic to all nonopioid medications.

DISPOSITION

Almost all patients with uncomplicated back pain can be discharged from the ED with follow-up with their primary care physician. In rare circumstances, severe pain or inadequate support for convalescence at home may preclude discharge. For patients who have a red flag diagnosis of cauda equina syndrome or epidural abscess, immediate neurosurgical consultation is required for emergent surgical decompression. For patients with spondylitis, hospitalization will be necessary for administration of intravenous antibiotics. With intractable pain from vertebral malignancy, the decision to hospitalize the patient for pain control, administration of high-dose corticosteroids, and radiation therapy should be made in conjunction with a neurosurgeon, an oncologist, and a radiation therapist.

One of the most important aspects of management of low back pain is the discharge instructions for the patient. Not only are clear and simple instructions useful to the patient, but they also constitute a medicolegal necessity for the physician. Physicians are advised to avoid using purely medical terms. The discharge instructions should include the following:

1. *Diagnosis*: Distinguish between uncomplicated (musculoskeletal) back pain and diskogenic radiculopathy.
2. *Activity*: Recommend maintaining active mobility as limited only by pain, avoiding heavy lifting until symptoms resolve, and getting back to full activity as soon as possible.

3. *Reassurance*: Educate patients about the likely benign nature of the etiologic condition responsible for the pain.
4. *Warnings:* Instruct patients to return to the ED immediately if they experience any of the following: fever; loss of bladder or bowel control; numbness or tingling around the anus, vagina, or penis; or new pain or weakness down one or both legs.

Pediatric patients with back pain require the same discharge instructions as for adults. In patients with pain secondary to spondylolisthesis, activity restrictions should be made in conjunction with an orthopedic surgeon. ED disposition for a patient with chronic back pain is relatively simple: pain management with nonopioids, when possible, and referral to a primary care physician for follow-up care. The prognosis is guarded because patients who are off work for 6 months usually are still off work after 2 years.[28]

UPPER BACK PAIN

PERSPECTIVE

Background

Thoracic pain is far less common than low back pain. Thoracic pain usually has a musculoskeletal origin, but other, more emergent causes must be considered first, including thoracic aortic dissection, pulmonary embolism, and esophageal disease. Compared with lumbar disk herniation, which is fairly common, thoracic disk disease is extremely rare, difficult to diagnose, and difficult to treat.

Epidemiology

The actual incidence of thoracic pain is unknown. The incidence of symptomatic thoracic disk disease is low, with estimates at 1 in 1 million.[72] The average age is in the 40s with equal gender distribution. Surgery for thoracic disks accounts for less than 4% of all disk operations.[73] Metastases are more common in the thoracic spine than in the lumbar spine, with 60 to 70% of spinal metastases localizing there.[9,74]

PRINCIPLES OF DISEASE

Anatomy and Physiology

The thoracic vertebral column can be regarded as an extension of the cervical column with the addition of ribs. There are 12 thoracic vertebrae, connected by the anterior and posterior longitudinal ligaments and the ligamentum flavum, similar to the lumbar vertebrae. Also similarly, intervertebral disks provide elasticity and stability to the thoracic column. The spinal canal diameter remains unchanged through the thoracic and lumbar levels, but at the thoracic level, the space around the spinal cord is smaller than at the lumbar level. Because lumbar nerve fibers have not yet branched off from the spinal cord, the thoracic cord is thicker than the lumbar cord. Significant neurologic abnormalities may result from minimal spinal canal impingement at the thoracic level.

Pathophysiology

Common thoracic soft tissue pain is likely to be a combination of sprain and muscle inflammation. As in the lower back, innervation of the paravertebral area is provided by the sinuvertebral nerve, and any anatomic disruption of surrounding structures results in nonspecific pain. Thoracic disk herniations, which most commonly occur in the midthoracic to lower thoracic spine, cause pain and neurologic symptoms in much the same way as for lumbar disks. It is not clear why the clinical presentation is so varied, although a possible cause is a higher number of centrally herniated disks, resulting in much more frequent myelopathic symptoms.[73]

CLINICAL FEATURES

Symptoms and Signs

History

Nondiskogenic thoracic back pain usually manifests as paraspinal discomfort. A history of trauma or recent unusual activity may or may not precede the onset of pain. Complaints with thoracic disk herniations are variable but usually are associated with long-standing pain or neurologic symptoms, or both. Pain may be localized to one part of the thoracic vertebrae, it may radiate down to the sacrum, or it may have a radicular component along the ribs. Central disk herniation can manifest as diffuse abdominal and back pain or burning sensation in the lower extremities. Associated findings may include mild weakness, spasticity, gait disturbance, bowel or bladder dysfunction, and paraplegia. These usually progress until the condition is diagnosed. Because of the variable and often subtle signs and symptoms, thoracic disk disease typically is not diagnosed until 20 months after the first clinical presentation. Pain from other causes should be sought in the initial assessment. A history of trauma, fever, previous malignancy, cardiovascular disease, or gastrointestinal problems may indicate problems originating outside the thoracic spine and may warrant further investigation.

Physical Examination

In patients with benign musculoskeletal pain, the physical examination fails to disclose evidence of a pathologic process. These patients may experience mild to moderate paraspinal tenderness to palpation, pain with motion, and even discomfort from chest wall expansion with respirations, but objective findings are minimal.

Physical findings in patients with thoracic disk herniation will vary with the location and degree of herniation. Objective findings may range from a normal-looking spine to loss of posterior column function (position, touch, vibration) or unilateral or bilateral weakness. Gait and sensory abnormalities are common. Hypotonic abdominal reflexes may be present with distal hyperreflexia. A Babinski response may be present. Myelopathy may result in urinary retention. Muscle wasting may be present with chronic symptoms. The possibility of other pathologic conditions should be kept in mind during the physical examination, with appropriate assessment tailored to the presentation and level of clinical suspicion.

DIAGNOSTIC STRATEGIES

Laboratory Evaluation

In the face of an unremarkable history and physical examination, the likelihood that laboratory evaluation will yield useful results is extremely small. In appropriate clinical circumstances, assessment for malignancy, infection, and inflammation should be undertaken.

Radiology

The usefulness of radiologic assessment is dubious in a patient with atraumatic acute thoracic back pain in whom preexisting illness or neurologic abnormalities are absent. As a general

BOX 51-3 DIFFERENTIAL DIAGNOSIS FOR THORACIC BACK PAIN

- Uncomplicated musculoskeletal back pain
- Spinal cord and nerve root pathology (e.g., disk herniation, tumor, hematoma)
- Vertebral column disease (e.g., primary or metastatic malignancy, osteomyelitis)
- Disk infection
- Primary neurologic disease
- Degenerative and autoimmune arthropathies
- Herpes zoster
- Vascular disease (e.g., thoracic aortic dissection, acute coronary syndrome, pulmonary embolism)
- Thoracic cavity pathology (e.g., pleuritis, pericarditis, pneumonia, esophageal pathology)
- Intraperitoneal and retroperitoneal abdominal pathology (e.g., peptic ulcer disease, pancreatitis, hepatobiliary disease)

guide, however, the following factors should prompt basic radiologic studies and appropriate further investigations: clinical suspicion for presence of other conditions; unexplainable symptoms; extremes of age; concern for trauma, tumor, infection, gastrointestinal pathology, or vascular pathology; and prolonged symptoms. Like patients with lower back pain, patients with a history of cancer and upper back pain should undergo plain radiography and possibly CT or MRI to assess for vertebral metastatic disease, especially because metastases have a predilection for the thoracic spine.

MRI has become the modality of choice for evaluating a herniated thoracic disk. The incidence of asymptomatic disk herniations seen on MR images is 37%. Most herniated thoracic disks, whether symptomatic or not, have been reported to recede spontaneously.[72]

DIFFERENTIAL CONSIDERATIONS

Although muscular back pain is extremely common, Box 51-3 summarizes the important considerations in the expansive differential diagnosis for thoracic back pain.

MANAGEMENT

Commonly, thoracic musculoskeletal pain is managed with analgesia. No studies have shown the need for any difference in management from that for musculoskeletal low back pain.

Thoracic disk disease is difficult to diagnose and manage. Symptomatic pain management and outpatient follow-up care are recommended. In view of the limited space in the spinal canal at the thoracic level compared with the lumbar level, spinal cord compression from a herniated disk is more likely at the thoracic level. Any disk herniation that precipitates an acute neurologic deficit warrants MRI and early neurosurgical evaluation.

DISPOSITION

Patients with benign back pain in any part of the thoracic vertebral column can be discharged with referral for follow-up care by the primary care physician. Patients with a suspected thoracic disk herniation require close outpatient follow-up. Most cases of subjective discomfort resulting from thoracic disk disease without objective neurologic findings resolve spontaneously, with one study showing a 77% improvement rate.[72] Although clear guidelines are lacking for when emergent neurosurgical consultation is required for thoracic disk herniation, patients with significant pain or neurologic compromise should be assessed rapidly.

KEY CONCEPTS

- The key to differentiating between benign and serious pathology in low back pain is a focused and thorough history and physical examination.
- The absence of sciatica findings practically rules out a lumbar disk herniation.
- Screening laboratory tests and plain radiographs are not indicated for patients with uncomplicated low back pain or a simple disk herniation.
- The best treatment for uncomplicated back pain and disk herniation is analgesia and resumption of normal activities—not bedrest.
- Age younger than 18 or older than 50 years, fever, injection drug use, immunocompromised status, symptoms lasting more than 4 to 6 weeks, night pain, and previous malignancy all are red flag warnings of potentially serious causes of back pain and should be heeded and evaluated accordingly.
- Although thoracic disk herniation can result in significant upper back pain, other, more dangerous etiologic disorders, such as aortic dissection, pulmonary embolism, and acute coronary syndrome, must be considered first.
- The associated findings on the neurologic examination with thoracic disk herniations can be extremely variable, ranging from nonspecific paresthesias to significant upper motor neuron weakness.
- The incidence of vertebral metastatic malignancy is higher in the thoracic spine than in the lumbar spine.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 52 Pelvic Trauma

Stephen B. Choi and A. Adam Cwinn

PERSPECTIVE

Background

Patients with traumatic pelvic ring injury may represent an immense challenge for the emergency physician. First, patients with pelvic ring fractures are at risk for exsanguinating pelvic hemorrhage. Furthermore, the profound magnitude of force required to disrupt the pelvic ring frequently causes severe injuries to other organ systems. The resuscitation from hemorrhagic shock, rapid identification of other major injuries and sites of blood loss, and the coordination of definitive angiographic and surgical treatments are paramount to achieving good clinical outcomes.

Epidemiology

The majority of high-energy pelvic ring injuries are caused by motor vehicle collisions (MVCs), motorcycle crashes, and pedestrians being struck by motor vehicles. Together, these account for 80 to 84% of pelvic fractures. Falls from height account for 5 to 12%[1-5] of pelvic fractures. The mortality rates reported in the literature associated with pelvic fracture range from 9 to 22%[1-5]; however, those patients who present with shock on arrival to the hospital have mortality rates between 33 and 57%.[3,4] Increased age, shock on arrival at the hospital, high injury severity and revised trauma scores, and the need for transfusion have all been shown to increase the risk of death.[3-6] The mortality rate among pedestrians struck by motor vehicles who sustain pelvic injury has been shown to be 23%.[7]

Despite advances in motor vehicle safety designs, the incidence of pelvic fracture secondary to MVCs has not decreased and in fact may be increasing.[8] Rates of pelvic fracture secondary to MVC range from 10 to 28%.[6,9,10] Lateral impact remains the most prevalent mechanism for pelvic trauma in collisions, for which the widespread advent of front airbags has little effect. Some have speculated that the increased popularity of sport-utility vehicles in past decades is contributing to the severity of side-impact injuries, specifically as a result of the higher bumper in these vehicles impacting the side of lower cars.[6,8,9]

PRINCIPLES OF DISEASE

Anatomy

Detailed descriptions of pelvic anatomy may be found in standard anatomy texts. This section focuses on the relevant anatomy essential to understanding pelvic injuries.

Bony and Ligamentous

The pelvic ring is made up of right and left innominate bones and the sacrum. The innominate bones consist of the pubis, ischium, and ilium (Fig. 52-1). The bony pelvis provides protection for its visceral contents, serves as attachment points for muscles, and transmits weight from the trunk to the lower limbs. The main weight-bearing forces are transmitted through the posterior wall of the pelvis, called the *posterior arch*, which is composed of thick bone and ligaments. The rich network of major arteries, veins, and nerves that course adjacent to the anterior wall of the posterior arch may be injured concomitantly with forces causing bony injuries of this arch.

Knowledge of the ligamentous attachments of the pelvic ring is crucial to understanding how stability is maintained or disrupted in pelvic injury. The stability of the pelvis is maintained by ligaments, as well as the muscles and fascia that make up the pelvic floor. Anteriorly, the symphysis pubis provides the major mechanical stability. Posteriorly, a complex of strong ligaments—the sacrospinous, sacrotuberous, iliolumbar, and anterior and posterior sacroiliac (SI) ligaments—maintains the integrity of the posterior arch (Fig. 52-2). It is important to appreciate that mechanically unstable pelvic fractures are unstable primarily because of the disruption of these posterior ligaments.

Vascular

Most of the blood supply to the pelvis comes from the left and right internal iliac arteries. The internal iliac arteries course at the level of the SI joints. The various arteries that derive from the internal iliac arteries initially run in close proximity to the posterior pelvic arch and eventually anastamose extensively with one another, forming a rich collateral network (Fig. 52-3). The superior gluteal artery is the largest branch and is commonly injured in fractures of the posterior pelvic arch. The obturator and internal pudendal branches are often injured in fractures involving the pubic rami.

The venous system also has many collateral branches and is without valves, allowing bidirectional flow. The veins are arranged in a plexus that adheres closely to the pelvic walls. Because these veins are thin-walled, they do not have the ability to constrict in response to damage. This anatomic arrangement of the arteries and veins accounts for the hemorrhage often seen with pelvic fractures. It is important to note that an intact peritoneum helps to tamponade and limit bleeding to the retroperitoneal space.

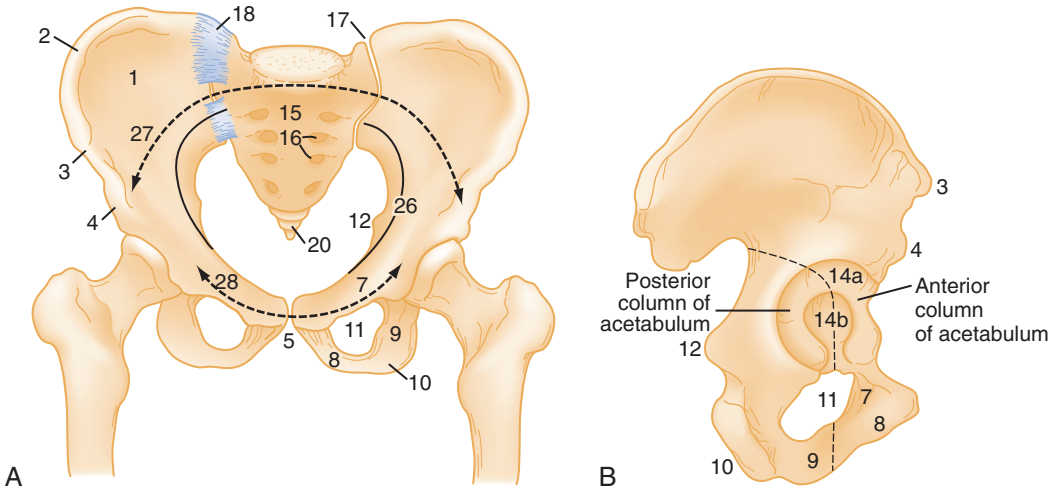


Figure 52-1. Bony pelvic anatomy. **A,** Anterior view of pelvis. **B,** Lateral view of right innominate bone. (*1*) Iliac fossa, (*2*) iliac crest, (*3*) anterior superior iliac spine, (*4*) anterior inferior iliac spine, (*5*) symphysis pubis, (*7*) superior ramus of pubis, (*8*) inferior ramus of pubis, (*9*) ramus of ischium, (*10*) ischial tuberosity, (*11*) obturator foramen, (*12*) ischial spine, (*14*) acetabulum ([*14a*] articular surface, [*14b*] fossa), (*15*) sacrum, (*16*) anterior sacral foramina, (*17*) sacroiliac joint, (*18*) anterior sacroiliac ligament, (*20*) coccyx, (*26*) arcuate line, (*27*) posterior or femorosacral arch, through which main weight-bearing forces are transmitted, (*28*) anterior arch.

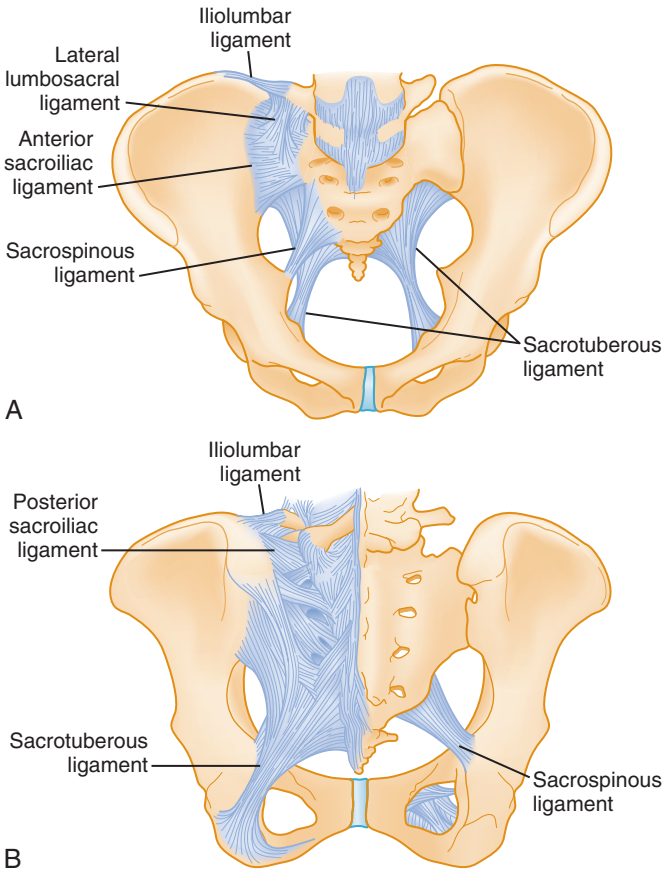


Figure 52-2. **A,** Anteroposterior view of the pelvis indicates that the sacrospinous ligament is a triangular strong ligament lying anterior to the sacrotuberous ligament, which is a strong broad band extending from the lateral portion of the dorsum of the sacrum to the ischial tuberosity. **B,** The major posterior stabilizing structures of the pelvic ring, that is, the posterior tension band of the pelvis, include the iliolumbar ligament, posterior sacroiliac ligaments, sacrospinous ligaments, and sacrotuberous ligaments.

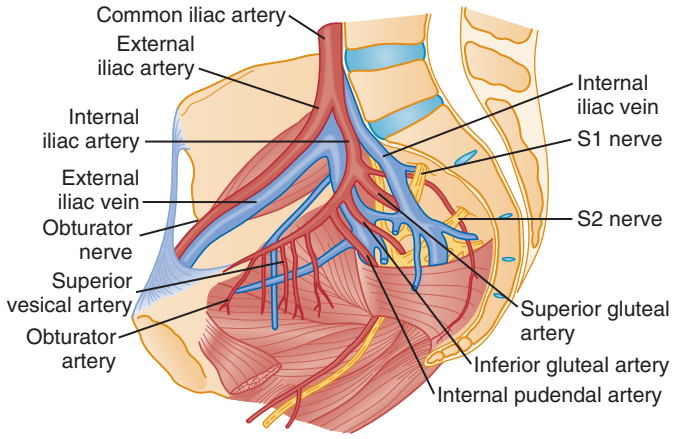


Figure 52-3. The internal iliac plexus of arteries and veins. (From Tile M: Fractures of the Pelvis and Acetabulum, 3rd ed. Philadelphia, Lippincott Williams & Wilkins, 2003.)

Neurologic

The cauda equina courses through the sacral spinal canal and exits through the sacral neural foramina to form the lumbar and sacral plexus. Injury to the posterior bony pelvis and sacrum may result in neurologic deficits in the lower extremities and autonomic dysfunction involving the bowel, bladder, and genitalia.

Pathophysiology and Key Patterns of Pelvic Fracture

Numerous classification schemes exist for pelvic fractures. Two widely used schemes for pelvic injury are presented here. The classification by Tile stresses the biomechanical stability of the pelvic ring[11] (Box 52-1). The Young-Burgess classification emphasizes the mechanisms of injury[12] (Box 52-2). From a practical viewpoint, it is highly useful to consider both of these elements in the assessment of a pelvic ring fracture. For the emergency physician, a good understanding of both the underlying principles of pelvic stability and mechanisms of injury is far more important than a detailed knowledge of the

BOX 52-1 TILE'S CLASSIFICATION OF PELVIC FRACTURES

Type A—Stable, posterior arch intact
Includes avulsion fractures, isolated iliac wing fracture, pubic rami fractures, minimally displaced ring fracture, transverse fractures of the sacrum or coccyx.
Type B—Partially stable, incomplete disruption of the posterior arch
Includes anteroposterior injuries (open book) and lateral compression injuries. May be unilateral or bilateral. These injuries are rotationally unstable but vertically stable.
Type C—Unstable, complete disruption of the posterior arch
Includes iliac, sacroiliac, and vertical sacral injuries that result from vertical shearing forces. May be unilateral or bilateral. These injuries are both rotationally and vertically unstable.

From Tile M: Fractures of the Pelvis and Acetabulum, 3rd ed. Philadelphia, Lippincott Williams & Wilkins, 2003.

BOX 52-2 YOUNG-BURGESS CLASSIFICATION OF PELVIC FRACTURES

Anteroposterior Compression
I. Symphysis diastasis < 2.5 cm
II. Symphysis diastasis > 2.5 cm, sacrospinous and anterior sacroiliac ligament disruption, results in rotational instability
III. Symphysis diastasis > 2.5 cm, with complete disruption of the anterior and posterior SI ligament, results in complete rotational and vertical instability

Lateral Compression
I. Sacral crush injury on ipsilateral side
II. Sacral crush injury with disruption of posterior SI ligaments, iliac wing fracture may be present (crescent fracture), rotationally unstable
III. Severe internal rotation of ipsilateral hemipelvis with external rotation of contralateral side ("windswept" pelvis), rotationally unstable

Vertical Shear
Vertical displacement of symphysis and sacroiliac joints resulting in complete rotational and vertical instability

Combined Mechanisms
Any combination of the above mechanisms

SI, sacroiliac.
From Burgess AR, Eastridge BJ, Young JW, et al: Pelvic ring disruptions: Effective classification system and treatment protocols. J Trauma 30:848, 1990.

numerous subtypes of injury that exist within the classification schemes.

Stable Injuries (Tile Type A)

Fractures of individual bones without involvement of the pelvic ring represent one third of all pelvic fractures. In general, most stable pelvic fractures heal well with rest and analgesic drugs for pain control (Fig. 52-4).[11]

Undisplaced or Minimally Displaced Fractures of the Pelvic Ring. The normal pelvis is not totally rigid because of the slight mobility

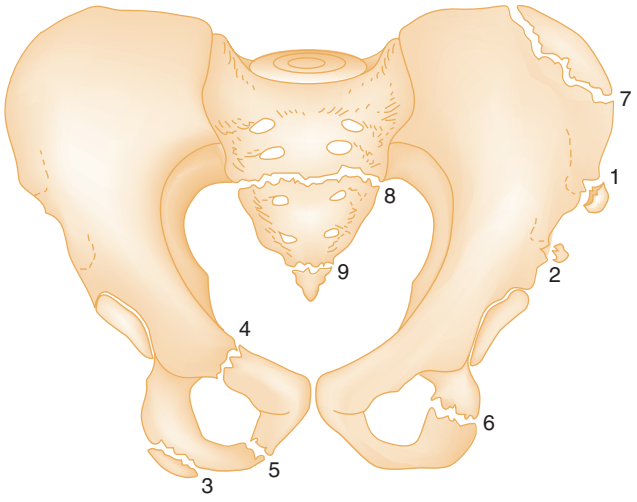


Figure 52-4. Fractures of individual pelvic bones. (*1*) Avulsion of anterosuperior iliac spine, (*2*) avulsion of anteroinferior iliac spine, (*3*) avulsion of ischial tuberosity, (*4*) fracture of superior pubic ramus, (*5*) fracture of inferior pubic ramus, (*6*) fracture of ischial ramus, (*7*) fracture of iliac wing, (*8*) transverse fracture of sacrum, (*9*) fracture of coccyx. (From Tile M: Fractures of the Pelvis and Acetabulum, 3rd ed. Philadelphia, Lippincott Williams & Wilkins, 2003.)

at the SI joints and symphysis pubis and the inherent elasticity of bone. A single break in the ring is possible. Nevertheless, the pelvis is not totally forgiving, and identification of a single break in the ring should prompt a search for a second disruption.

An isolated fracture of the superior or inferior pubic ramus is the most common pelvic fracture. These fractures are stable. They are common fractures in elderly people after a fall and must be considered in the evaluation of an acutely painful hip. Fracture of the body of the ischium is a rare injury that may result from a fall in the sitting position. These fractures around the obturator foramen are treated conservatively with bedrest, analgesia, and early mobilization.

Fracture of the superior and inferior pubic rami on the same side is a commonly encountered injury after a fall or MVC. These are generally stable fractures and are treated conservatively. However, the presence of significant displacement at the fracture site always indicates a second disruption elsewhere in the pelvic ring that must be diagnosed. Alternatively, fractures of both rami on the same side may be associated with an unrecognized impaction fracture of the posterior pelvis.

If the patient with a ramus fracture complains of posterior pelvic pain and plain radiographs do not reveal posterior injury, further investigations may reveal occult posterior fractures. A study performed more than 30 years ago found that patients who sustained apparently isolated pubic ramus fractures showed increased uptake of radionuclides on bone scans in the acetabulum and SI joint, suggesting that occult bony or ligamentous injury accounted for the complaints of pain.[13] More recently, a study that prospectively evaluated elderly patients who were diagnosed with isolated ramus fractures on plain films found that 95% had sacral fracture detected by magnetic resonance imaging.[14]

Also termed a *straddle fracture*, four-pillar injuries refer to fractures of both pubic rami on both sides of the symphysis pubis, causing the so-called butterfly segment (Fig. 52-5). The injury is produced by a direct blow with a straddle mechanism. Although these fractures may occur without posterior arch disruption, four-pillar injuries are also commonly associated with lateral compression or vertical shear forces that may cause concomitant injuries to the posterior pelvic arch. CT of the pelvis is required in cases of four-pillar injuries to detect and

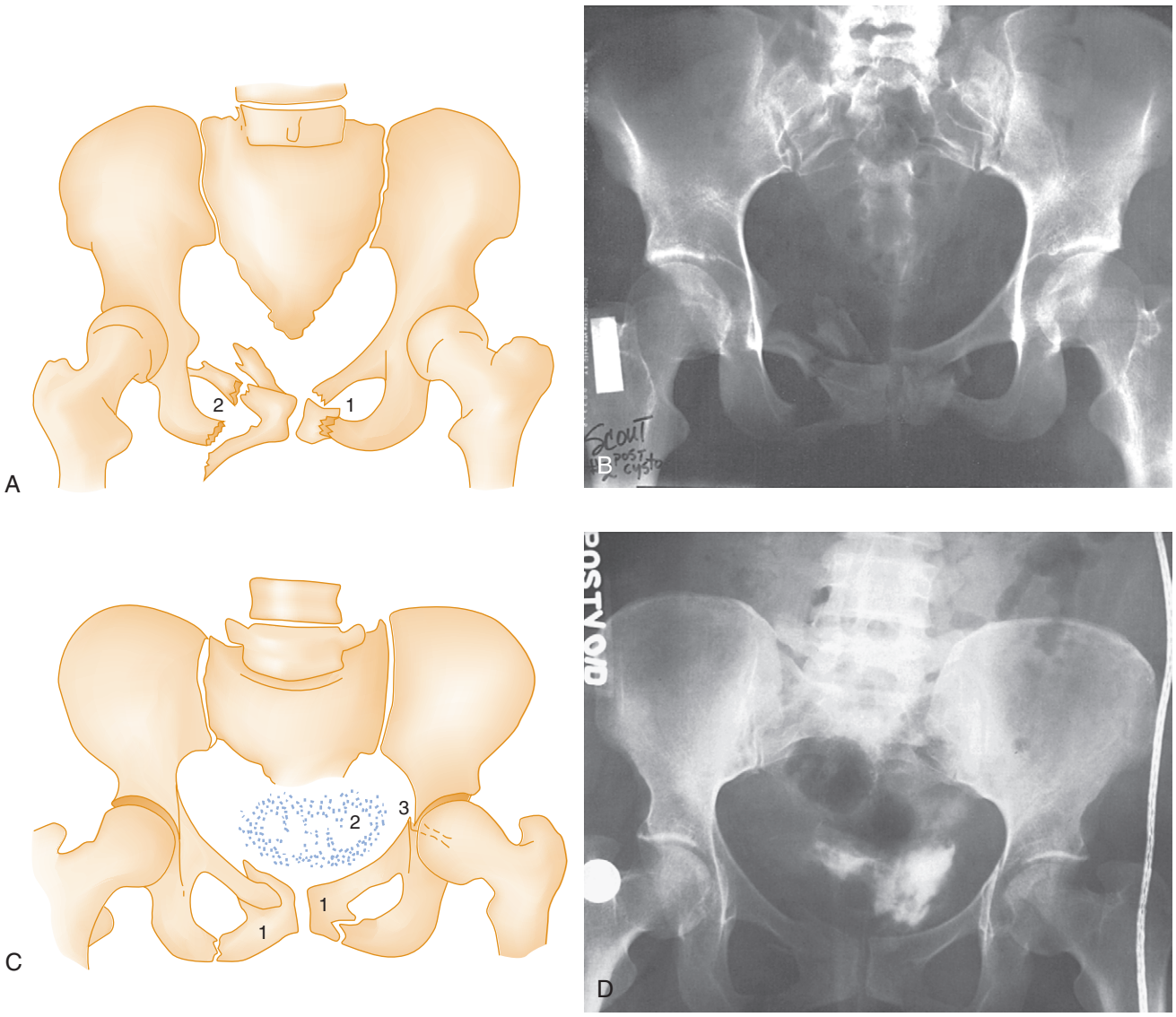


Figure 52-5. Four-pillar (straddle) fracture. **A** and **B,** Partial inlet view of pelvis shows straddle fracture. (*1*) and (*2*) Marked comminution of left pubic bone and comminuted right superior and inferior rami. This partial inlet projection shows displacement of fragments into the pelvis, which is not evident on the anteroposterior view of the same patient in **C** and **D**. A true inlet projection and computed tomography scan (not available) would provide further information about the posterior arch, which is injured frequently in straddle fractures and always should be imaged (see text). **C** and **D,** Postvoid cystogram of the same patient with anteroposterior pelvis. (*1*) Fractures of pubic rami are seen again but do not appear to be as displaced compared with **A** and **B** because this projection is an anteroposterior view: even minor degrees of angulation of the x-ray beam can change the appearance of pelvic fracture displacement, (*2*) extravascular contrast indicates bladder rupture, (*3*) left acetabular fracture is seen in this projection but not in **B** because of the difference in projection. The acetabular fracture disrupts the ilioischial line (see also Fig. 52-13) and is a posterior column fracture.

classify precisely the posterior arch injury and plan orthopedic treatment.[11] The genitourinary tract frequently is injured concomitantly with this type of pelvic fracture and must be evaluated carefully (see Fig. 52-5).

Isolated fracture of the iliac wing was described by Duverney in 1751 and now bears his name. It is caused by direct trauma to the iliac crest, usually by lateral compression forces. Although displacement is usually minimal because of the arrangement of the muscle attachments of the abdominal wall, orthopedic consultation is recommended. The fracture may extend into the acetabulum, altering the treatment and prognosis. Severely displaced fractures of the iliac wing require open reduction and internal fixation.[11]

Transverse Fractures of the Sacrum. These injuries do not compromise the pelvic ring. Transverse fractures at or below S4 are unlikely to be accompanied by neurologic injury.[15] An upper sacral transverse fracture is the result of a flexion injury, such as being struck on the lower back by a heavy load while bending over, or by direct forces to the sacrum, as in a fall from a great height.[15] The patient complains of pain in the buttocks, perirectal area, and posterior thighs. There may be local pain, swelling, and bruising overlying the sacrum, and on gentle bimanual rectal examination, severe pain, abnormal motion, and palpable hematoma may be elicited. Radiographically the fracture may be difficult to visualize on anteroposterior (AP) and lateral projections, in which case an outlet view may be helpful. Simple transverse fractures at or below S4 are treated conservatively. Above S4, neurologic injuries are common, necessitating careful clinical evaluation and surgery when neurologic compromise is present.

Avulsion Fractures. These usually occur during athletic activities and are the result of a sudden, forceful muscular contraction or excessive muscle stretch. They are seen more commonly in older children and teenagers before closure of the corre-

sponding physis occurs; adults may have the same symptoms from ligamentous injury at these sites without radiographic abnormality.

The ischial tuberosity may be avulsed during strenuous contraction of the hamstrings. There is pain on palpation of the involved tuberosity, and this pain is increased by flexion of the hip with the knee in extension (hamstrings stretched), but not with the knee flexed (hamstrings relaxed). Ischial tuberosity avulsion also may cause chronic discomfort with no history of acute injury.

A portion of the iliac crest epiphysis may be avulsed by contraction of the abdominal muscles. Similarly, the anterior superior iliac spine may be avulsed by forcible contraction of the sartorius muscle. Forceful contraction of the rectus femoris (as in kicking a ball) can result in the less common injury of anterior inferior iliac spine avulsion; however, this radiographic finding must be distinguished from a normal variant, the os acetabuli, which is a secondary center of ossification at the superolateral margin of the acetabulum.[16] Clinical examination is similar in these injuries and reveals local pain, swelling, and limitation of motion.

Conservative treatment, including analgesia and bedrest in a position that avoids tension on the affected muscles, is generally all that is required for avulsion injuries; surgical treatment is rarely necessary. Orthopedic consultation is advised for follow-up care.

Stress Fractures. These injuries occur with vigorous athletic or military training and in the last trimester of pregnancy.[17] Diagnosis of stress fractures is based on the clinical evaluation and can be confirmed by radionuclide bone scan, although magnetic resonance imaging has been shown to be a superior method for detecting these injuries.[18]

Pathologic and Insufficiency Fractures. Pathologic fracture related to neoplasm, Paget's disease, or dietary osteomalacia is included in the differential diagnosis. Radiation therapy has also been shown to increase the risk of pelvic fracture.

Partially Stable and Unstable Injuries (Tile Types B and C)

These injuries are caused by high-energy impacts. The forces applied to the pelvis determine the types of injuries that occur. Broadly, forces may be applied to the pelvic ring in AP, lateral, or vertical directions that result in characteristic injury patterns; combinations of forces result in more complex injuries. The terms *unstable fracture* (referring to mechanical stability) and *unstable patient* (referring to hemodynamic status) should not be confused, although a cause-and-effect relationship often exists.

Anteroposterior Compression. Severe AP compression forces result in disruption at or near the symphysis pubis. Symphysis widening of less than 2.5 cm is considered a stable injury; however, with continued force in the AP direction, the hemipelvis externally rotates, tearing the sacrospinous, sacrotuberous, and anterior SI ligaments. The SI joint opens and hinges on the intact posterior SI ligaments. The resulting injury is aptly described as an "open-book" fracture. The pelvis is rotationally unstable in the horizontal plane, but the intact posterior SI ligaments maintain vertical stability.[11,12]

When diastasis of the pubic symphysis is greater than 2.5 cm on the AP radiograph, the posterior injury is usually seen as widening of the SI joint and occasionally as a sacral or iliac fracture (Fig. 52-6).[11] If the injurious forces continue, they may separate the hemipelvis, and the SI joint is seen as widely separated on the plain AP radiograph (Fig. 52-7) and the CT scan.[11] The AP radiograph may be misleading in suggesting a pure open-book fracture in cases with symphysis disruptions greater than 2.5 cm. These cases commonly are associated with vertical shear fractures, and careful clinical and CT assessment for vertical instability is essential to classify the fracture properly and plan treatment.[11]

These same forces also may injure the neurologic and vascular structures at the posterior arch; the overall volume of the pelvis is increased in the open-book injury, facilitating the expansion of a retroperitoneal hematoma. In several studies of patients with major pelvic ring disruptions, patients with severe grades of AP compression injuries have the highest crystalloid and blood requirements.[12,19]

Lateral Compression. Lateral compression of the pelvic ring results in varying degrees of internal rotation of the affected hemipelvis. Initially, this causes buckling of the sacrum and horizontal pubic rami fractures. Rami fractures may occur on the ipsilateral or contralateral side, the latter being referred to as the "bucket-handle" fracture (Fig. 52-8).

As the magnitude of force increases, the symphysis may disrupt, causing overlapping of the pubic bones. Note that on plain radiographs, evidence of injury to the sacrum may be subtle; overlapping pubic bones with any significant displacement should prompt a search for a posterior injury.

Similar to the AP injury, with increasing disruption of the posterior ligaments comes increasing rotational instability. In the most severe lateral compression trauma, the ipsilateral pelvis internally rotates to such a degree that the contralateral pelvis may externally rotate. This is referred to as the "windswept" pelvis. Although lateral compressive injuries may result in varying degrees of rotational instability, the vertical stability of the pelvis is maintained (see Fig. 52-6).

As internal rotation causes the pelvic volume to decrease, lateral compressive injuries are generally associated with lesser degrees of blood loss than are AP injuries.

Vertical Shear. Vertical shear injuries represent the most unstable injuries to the pelvic ring and are associated with violent axial loading of the hemipelvis (e.g., fall from height, "submarining" underneath a dashboard). Fractures occur in vertical planes. Anteriorly, the symphysis and rami may be disrupted. Posteriorly, gross displacement and instability in the rotational and vertical planes may be present through the sacrum, the SI joint, or the ilium such that the hemipelvis may displace posteriorly and/or cephalad[11,12] (see Fig. 52-6).

Avulsion of the ischial spine, the lower lateral lip of the sacrum, and the transverse process of the fifth lumbar vertebra (sites of insertion of ligaments) (Fig. 52-9 and Box 52-3) are important clues to the presence of vertical shear fractures.[11] The vertical shearing forces that act on the bone also act on the rich vascular network and nerve plexus that are directly adjacent to the bone. This activity accounts for the major hemorrhage and neurologic injuries associated with vertical shear fractures.

Vertical Sacral Fractures. A crucial distinction in considering sacral fractures is that transverse fractures do not involve the pelvic ring, but vertical fractures do. Vertical sacral fractures are caused by high-energy injuries and are classified into three groups according to whether the fracture line extends (1) laterally to the sacral foramina, (2) through the foramina, or (3) medially to the foramina involving the central spinal canal.[20] The diagnosis of this fracture on radiographs hinges on careful examination of the symmetrical cortical lines that are normally present at the superior margins of the sacral foramina on the AP view. Disruption, distortion, or asymmetry of these lines is an important marker of sacral fractures.[16]

There is a high risk of neurologic complications associated with these injuries: 6% when lateral to the foramina, 28% when through the foramina, and 58% when medial to the foramina.[20] Surgery is commonly necessary for fractures associated with neurologic dysfunction.

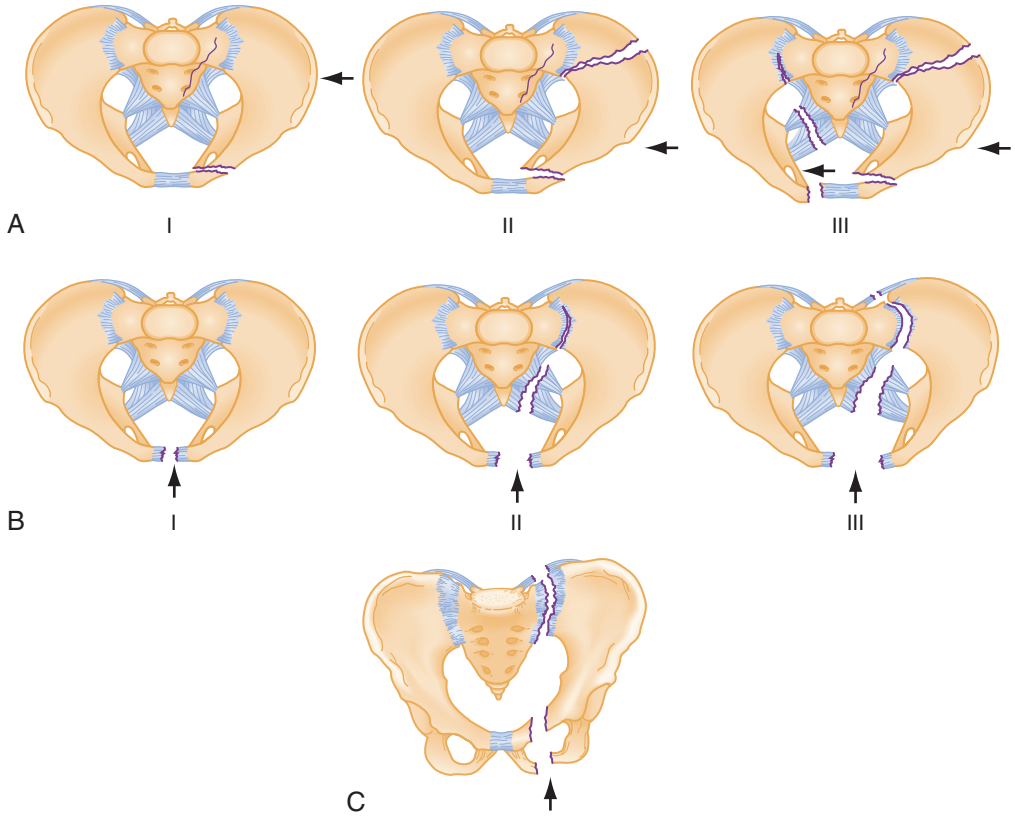


Figure 52-6. Young-Burgess classification. **A,** Lateral compression. Type I: A posteriorly directed force causing a sacral crushing injury and horizontal pubic ramus fractures ipsilaterally. Type II: A more anteriorly directed force causing horizontal pubic ramus fractures with an anterior sacral crushing injury and either disruption of the posterior sacroiliac joints or fractures through the iliac wing. Type III: An anteriorly directed force that is continued, causing external rotation of the contralateral side; the sacroiliac joint is opened posteriorly, and the sacrotuberous and spinous ligaments are disrupted. **B,** Anteroposterior (AP) compression. Type I: Symphysis disrupted but with intact posterior ligamentous structures. Type II: Continuation of a type I fracture with disruption of the sacrospinous and potentially the sacrotuberous ligaments and an anterior sacroiliac joint opening. Type III: Continuation force disrupts the sacroiliac ligaments. **C,** Vertical shear. Vertical fractures in the rami and disruption of all posterior ligaments. This injury is equivalent to an AP type III or a completely unstable and rotationally unstable fracture. Arrow indicates the direction of force. (Redrawn from Young JWR, Burgess AR: Radiologic Management of Pelvic Ring Fractures. Baltimore, Munich, Urban & Schwarzenberg, 1987. Browner: Skeletal Trauma: Basic Science, Management, and Reconstruction, 3rd ed. Copyright © 2003 Saunders, an Imprint of Elsevier.)

Open Pelvic Fractures

An open pelvic fracture is present when there is direct communication between the fracture site and a skin, rectal, or vaginal wound. These are potentially lethal injuries, especially if the open nature is not recognized: hemorrhage accounts for early mortality, but sepsis is the major cause of delayed death.[21] The majority of case series prior to 1991 reported mortality rates greater than 50%; reported rates between 1991 and 1999 ranged between 5 and 30%,[21] although a recent series reported a 45% mortality rate.[22]

The skin over the posterior pelvis and gluteal area and perineum must be inspected carefully for wounds. Some fractures are open only by virtue of a bone spicule penetrating the vagina or rectum, but these must be identified by careful digital rectal and vaginal examinations. Hemorrhage from a large open laceration should be treated by direct manual pressure or pressure dressing. Pelvic fractures communicating with the rectum have traditionally mandated a diverting colostomy; however, a systematic review of the literature on this topic found no difference in infection rates between patients treated with colostomy and those treated without.[23]

Penetrating Pelvic Trauma

Because of the complex anatomy of the viscera, blood vessels, and nerves within the pelvis, penetrating trauma to this area presents a major challenge to the physician. Overall mortality in this group of patients has been reported to be 6 to 12%, but the mortality rate of patients in shock is 50%.[24,25] At surgery, vascular injuries singly and in combination were found to involve the aorta; common iliac artery; and external, internal, and common iliac veins. Injuries to genitourinary structures and hollow viscera were common, and a particular concern was fecal contamination from colorectal injury. When present, the finding of blood on digital rectal examination is an important clue that rectal injury has occurred. Emergent surgical consultation is required in all cases of penetrating pelvic trauma.

CLINICAL FEATURES

History

Understanding the mechanism of injury is an important means of determining a patient's risk of having a pelvic fracture and the severity of the fracture when present. Low-energy injuries (e.g., fall on level ground) typically cause stable injuries to the pelvis; patients who have sustained high-energy injuries (e.g., MVCs, falls from heights) are at risk for unstable fracture patterns of the pelvis as well as associated injuries to other organ systems.

Determining the direction of forces applied to the pelvis can also give important clues to the types of injury sustained.

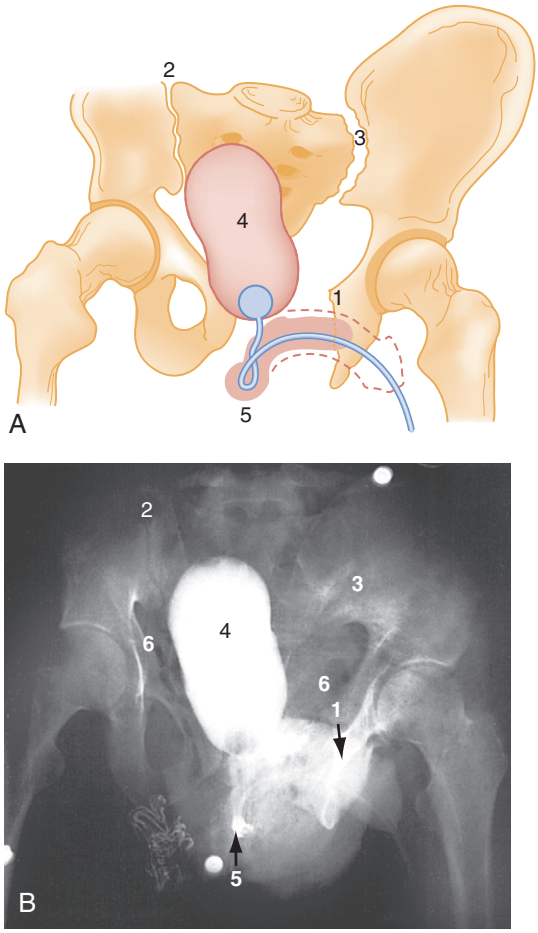


Figure 52-7. Interpretive drawing (**A**) and radiograph (**B**). Severe unilateral open-book fracture from anteroposterior compression forces that is also open (compound). (*1*) Separated pubic symphysis with asymmetry of hemipelvis, (*2*) normal sacroiliac joint, (*3*) separated sacroiliac joint, (*4*) cystogram with displacement and abnormally elongated shape of bladder caused by retroperitoneal hematoma associated with separated left sacroiliac joint, which has pushed the bladder to the right, (*5*) extravasated contrast into perineum from urethral rupture, (*6*) soft tissue air indicating an open fracture.

Anterior-posterior forces (e.g., head on MVCs) may cause open-book injuries to the pelvis. Lateral forces to the pelvis (e.g., side impact collisions) may disrupt the posterior ligaments; however, the pelvic floor generally remains intact. Vertical shear injuries (e.g., falls from height) may disrupt the posterior ligaments and pelvic floor causing gross instability of pelvis.

Age is an important consideration in patients with pelvic fracture. Studies consistently demonstrate higher morbidity and mortality among older patients with pelvic fracture.[26] Osteopenic bone may be disrupted by lesser forces. Decreased physiologic reserves in older patients may limit success in the acute resuscitation and definitive treatment of injuries.

Injuries to other organ systems are extremely common in patients with pelvic fracture.[2,4,5] It is important to identify all major injuries to other organ systems in order to prioritize definitive surgical treatment for the multiply traumatized patient. In women, it is important to consider the possibility of pregnancy and to test for pregnancy whenever appropriate.

Physical Examination

On inspection, rotation of the iliac crests indicates a serious pelvic fracture. Leg length discrepancy may suggest a hip injury or cephalad migration of an unstable hemipelvis. Careful inspection of the skin and skin folds is necessary to identify open fractures. Perineal ecchymosis or hematoma may be observed, and in cases when many hours have elapsed since the injury, ecchymosis in the periumbilical area (Cullen's sign) or flanks (Grey Turner's sign) from retroperitoneal hemorrhage may be present. The presence of point tenderness on palpation anywhere on the pelvic ring from the symphysis anteriorly to the sacrum and SI joints posteriorly is an indicator of pelvic ring injury in alert patients without distracting injury.[27]

Manipulation of the pelvis must be kept to a minimum. "Spring boarding" of the pelvis to assess stability of the pelvic ring should be strictly avoided as this maneuver has the potential to disrupt any tenuous blood clotting that may have occurred around a fracture site and may therefore worsen hemorrhage.

The penis should be milked to examine for blood at the meatus. The digital rectal examination should evaluate sensation, sphincter tone, position and consistency of the prostate, presence of a presacral hematoma, bony contour of the sacrum and coccyx, mucosal penetration of bony spicules, and presence of frank or occult blood. In the setting of a pelvic fracture, female patients should undergo a vaginal examination to diagnose an open fracture. Because it is possible to create an open fracture iatrogenically through the vaginal or rectal wall, digital rectal and vaginal examinations should be performed carefully, especially in an unconscious patient who cannot localize pain. The examiner should be mindful when performing these examinations that bony spicules can cause him- or herself injury. Extravasated urine may be detected in the scrotum or the subcutaneous tissues of the penis, vulva, or abdominal wall. The presence and quality of pulses in the lower limb should be assessed, as should sensation, strength, and deep tendon reflexes.

Associated Pelvic Injuries

Urologic

The overall incidence of bladder or urethral disruption associated with any pelvic fracture is approximately 6%[2] with increased risk among those with severe pelvic injuries.[2] Urethral rupture in women with pelvic fractures has been reported[28] but is exceedingly rare.[29]

A review of 721 patients with pelvic fracture revealed an incidence of bladder rupture in 5% of patients. Those with fractures of the anterior arch of the pelvis are at greatest risk for bladder injury: diastasis of the symphysis more than 1 cm and fracture around the obturator ring with displacement greater than 1 cm were associated with a 10- and 3-fold increased risk of bladder rupture, respectively.[30]

The presence of gross hematuria mandates evaluation of the lower urinary tract. Blood at the urethral meatus necessitates a retrograde urethrogram followed by a cystogram. Gross hematuria is investigated by a combination of urethrography, intravenous pyelography, cystography, and CT. The sequence and types of examinations are individualized for each patient.

Sexual dysfunction in both men and women is a recognized complication of pelvic trauma. The incidence of impotence associated with urethral rupture is significant. In the absence of urethral injury, impotence still may occur secondary to neurovascular disruption associated with the pelvic fracture.[31]

Neurologic

Neurologic injury occurs commonly in patients with vertical sacral fractures or transverse fractures above the S4 level.

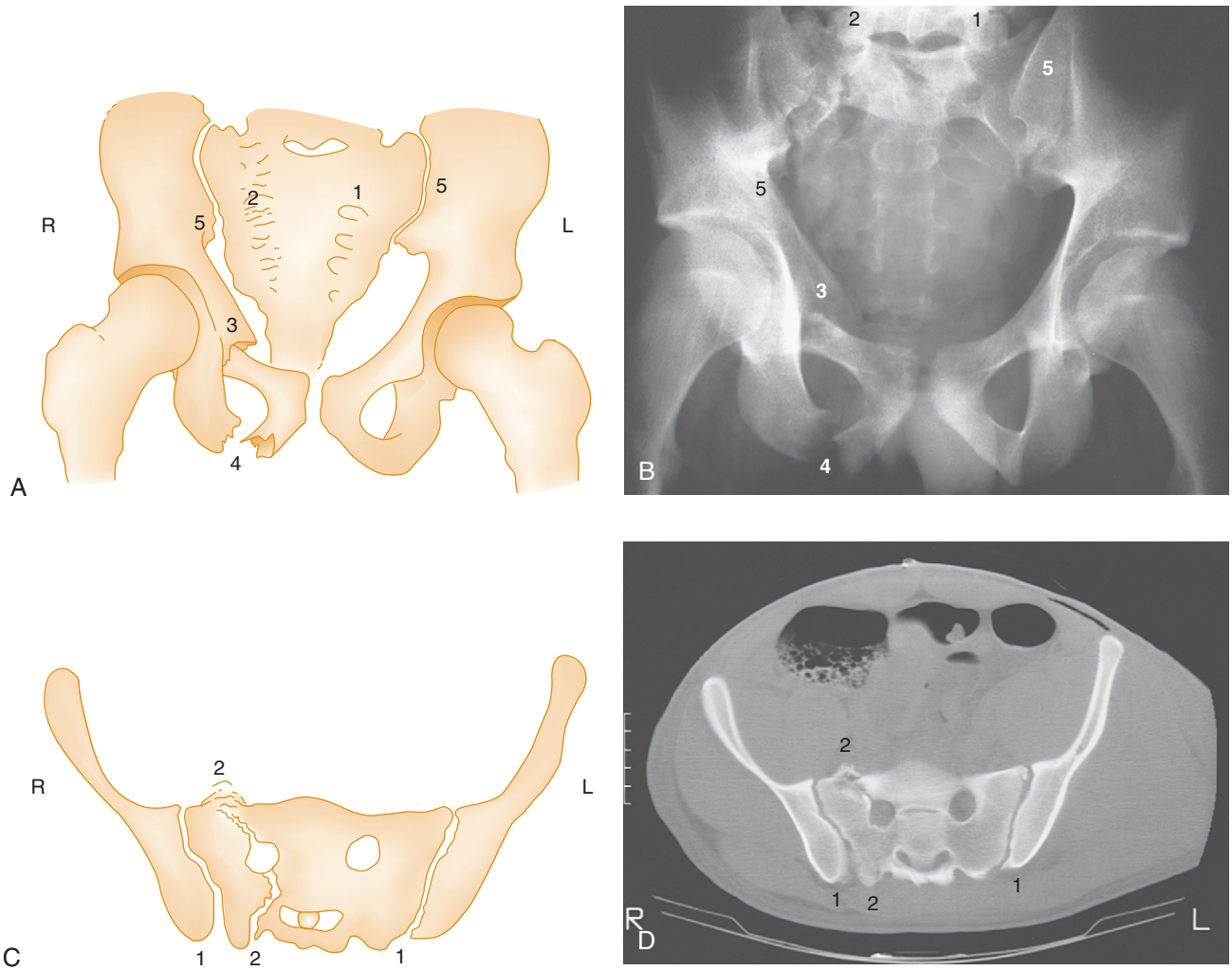


Figure 52-8. Lateral compression fracture. **A** and **B,** Anteroposterior view of the pelvis. (*1*) Normal sacral foraminal lines on the left, (*2*) sacral foraminal lines on the right are indistinct and do not mirror the normal side, indicating the subtle second break in the pelvic ring, (*3*) and (*4*) fractures of the superior and inferior pubic rami are overriding and displaced, indicating the lateral compression forces (there must be a second break in the pelvic ring), (*4*) is the "bucket-handle" fracture, (*5*) normal sacroiliac joints. **C** and **D,** Computed tomography scan of same pelvis. (*1*) Normal sacroiliac joints, (*2*) compression fracture of the sacrum through the foramen corresponding to the loss of definition of the foraminal lines in **A** and **B.**

Among patients with vertical fractures that involve the foramina, 28% have associated neurologic deficits. In patients with fractures medial to the foramina involving the spinal canal, 56% have neurologic deficits.[20]

Cauda equina syndrome and various plexopathies and radiculopathies may occur as follows. Injury to the L5 root may cause weakness of muscles in the anterior tibial compartment and sensory deficits in the dorsum of the foot and lateral calf. Injury to S1 and S2 roots may cause weakness of hip extension, knee flexion, and plantar flexion and sensory deficits on the posterior aspect of the leg, sole and lateral foot, and genitalia. Injury to S2-S5 roots and distal afferent, efferent, and autonomic fibers causes sensory deficits in the perineum, sexual dysfunction, and bowel and bladder dysfunction. Cauda equina syndrome may be fully or partially present with sacral fractures: Hyperesthesia and later anesthesia occur in a saddle-shaped distribution in the groin; in addition, weakness of ankle plantar flexion, hamstrings, and gluteus muscles and decreased or absent ankle jerk are present. With involvement of the lower sacral roots, a neurogenic bladder with overflow incontinence, motor and sensory deficits in the lower extremities, anal sphincter dysfunction, and sexual dysfunction may occur. All patients with neurologic deficits from sacral fractures require orthopedic or neurosurgical consultation.

Gynecologic

Blood at the introitus may indicate a urethral injury, open pelvic fracture, or local laceration without communication with the bony pelvis. Delayed urologic and sexual dysfunction and complications with pregnancy are common following pelvic injury.[32] Gynecologic consultation is indicated when there is injury to the female reproductive tract in association with a pelvic fracture.

Associated Nonpelvic Injuries

The magnitude of force required to disrupt the pelvis commonly results in severe injuries to other organ systems. Among those patients who die with pelvic fracture, it is rare that the pelvic fracture is an isolated injury.[1,2,19,33,34]

Some authors have described patterns of associated nonpelvic injuries with certain patterns of pelvic fracture[19]; however, this has not been consistently reproduced in the literature.[35] Severe injuries to head, spine, thorax, and abdomen may occur with both stable and unstable pelvic fractures; they may all occur with all major mechanisms of pelvic injury. One associated injury that reflects the dispersion of enormous forces throughout the body is the rupture of the thoracic aorta: albeit

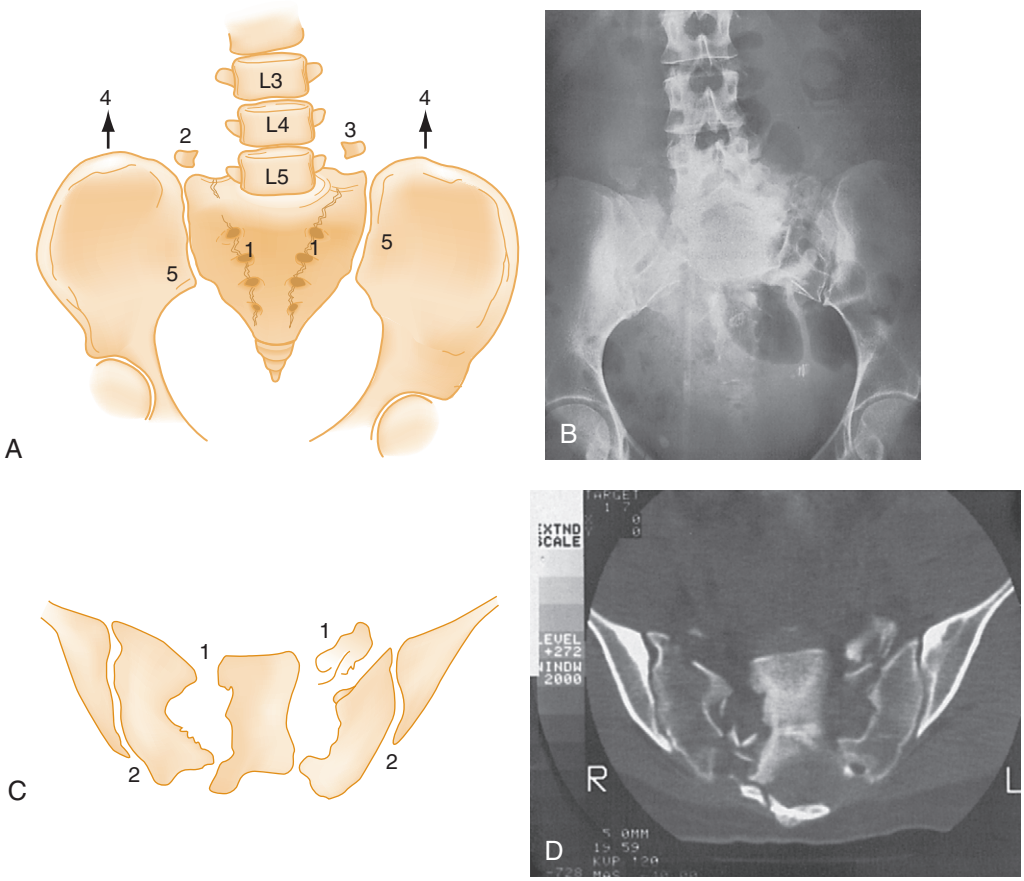


Figure 52-9. **A** and **B,** Vertical shear fractures bilaterally. At first glance, the pelvis appears normal because of the smooth, uninterrupted arcuate line, but careful interpretation reveals the extremely critical nature of the injuries: (*1*) Fractures through the sacrum—note loss of definition and symmetry of sacral foramina, indicating vertical fractures through both sides of the sacrum (see computed tomography scan in **D**). (*2*) Transverse process fragment from right L5 (iliolumbar ligament attachment) is pathognomonic for a vertical shear fracture through the right sacrum. (*3*) Transverse process fragment from left L5, pathognomonic for a vertical shear fracture through the left sacrum. (*4*) Both hemipelves are dislocated cephalad because of the double-ring fractures through each side of the sacrum. This dislocation explains why the L5 transverse processes appear so close to the iliac crests (the body of L5 is obscured because of rotational dislocation of the central free sacral fragment posteriorly and because of technique). (*5*) Normal sacroiliac joints. **C** and **D,** Computed tomography scan of same pelvis. (*1*) Bilateral comminuted fractures of sacrum with lateral displacement of both hemipelves, (*2*) normal sacroiliac joints.

uncommon in blunt trauma, it is five to eight times more likely in patients with pelvic fracture.[2,36]

■ DIAGNOSTIC STRATEGY

Radiology

Plain Radiography

Routine radiographs of the pelvis are not necessary in cases of blunt trauma if the patient is asymptomatic, awake, and alert and has a normal physical examination of the pelvis.[37-39] However, routine AP plain radiograph of the pelvis (PXR) is advised by the Advanced Trauma Life Support (ATLS) guidelines for patients with severe mechanisms of injury who are symptomatic or whose examination is compromised by either decreased level of consciousness or distracting injuries.

On the AP radiograph, the symphysis pubis is normally no more than 5 mm wide, and a small (1- or 2-mm) vertical offset of the left and right pubic rami is normal.[16] Overlapping at the symphysis pubis is abnormal and is the result of a severe crushing injury. Normally the SI joint is approximately 2 to 4 mm wide.[16]

On the AP view, the physician may judge the degree of pelvic rotation caused by technique and positioning by the presence of asymmetry in the size and shape of the left and right obturator foramina and iliac wings. Diastasis of the SI joint also causes an asymmetrical appearance of the obturator foramina and the iliac wings: If there is displacement into external rotation, the affected iliac wing appears broader, and the anterior iliac spine appears more prominent.[16] Avulsion fracture of the fifth lumbar transverse process by the iliolumbar ligament often accompanies an SI joint disruption or a vertical sacral fracture and is a valuable clue to posterior arch injuries[16] (see Fig. 52-9; Box 52-3).[8]

Recently, the reliability of the single AP PXR to detect pelvic fractures has been questioned. Two case series have

BOX 52-3 RADIOGRAPHIC CLUES TO POSTERIOR ARCH FRACTURES

- Avulsion of L5 transverse process*
- Avulsion of ischial spine*
- Avulsion of lower lateral lip of the sacrum (sacrotuberous ligament)*
- Displacement at the site of a pubic ramus fracture
- Asymmetry or lack of definition of bone cortex at superior aspect of the sacral foramina

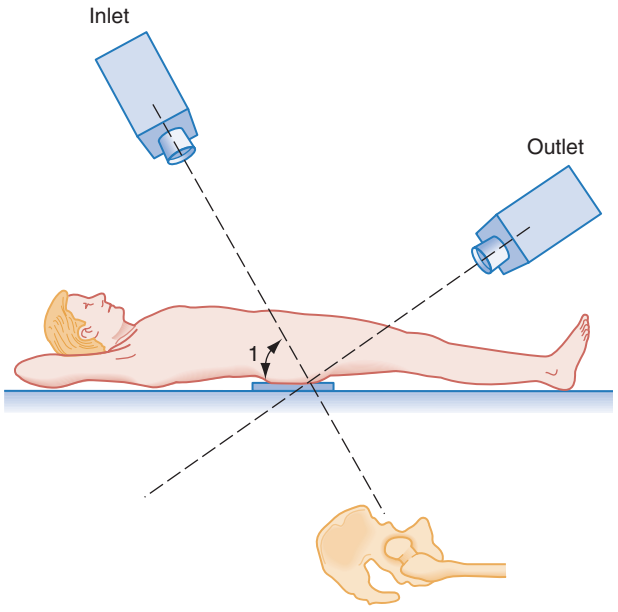
*Always indicates mechanical instability.

reported sensitivities of only 64 and 68% with specificities of 90 and 98%, respectively,[40,41] thus prompting a question of the utility for PXR when patients are to undergo immediate abdominopelvic CT evaluation. In particular, sacral fractures and SI joint disruptions may not be well visualized on the AP view. However, the addition of inlet and outlet views of the pelvis has been shown to increase the sensitivity and specificity of plain radiographs in detecting significant pelvic fracture (Fig. 52-10)[42] and SI joint disruption and should be considered in all patients with presumed stable anterior pelvic ring injuries with any complaints of posterior pelvic pain.

When patients are too unstable to undergo CT investigation, the AP PXR is useful in screening for pelvic injuries that are most associated with major blood loss. Findings on AP PXR that have been reported to predict the need for transfusion include open-book fracture or displacement of 0.5 cm or more at any fracture site in the pelvic ring[43] and displaced symphysis pubis or displaced obturator ring fracture.[44] It is important to note that all of these signs may be associated with posterior pelvic injury. As such, the PXR is a vital test in the absence of CT and should be used to alert both surgeons and angiographers to the potential need for definitive management of pelvic hemorrhage.[45]

Computed Tomography

CT has become the imaging test of choice for evaluating the injured pelvis. CT provides detailed information about the posterior arch and rotational deformities that indicate the relative stability of the pelvic ring; furthermore, the acetabulum, which may be difficult to assess with plain radiographs, can be well visualized using CT. CT has demonstrated a much higher sensitivity and specificity over plain radiography in detecting pelvic fracture.[40,41] Furthermore, abdominopelvic CT provides detailed information about concomitant injury to abdominal organs that aids in the planning of laparotomy, external fixa-



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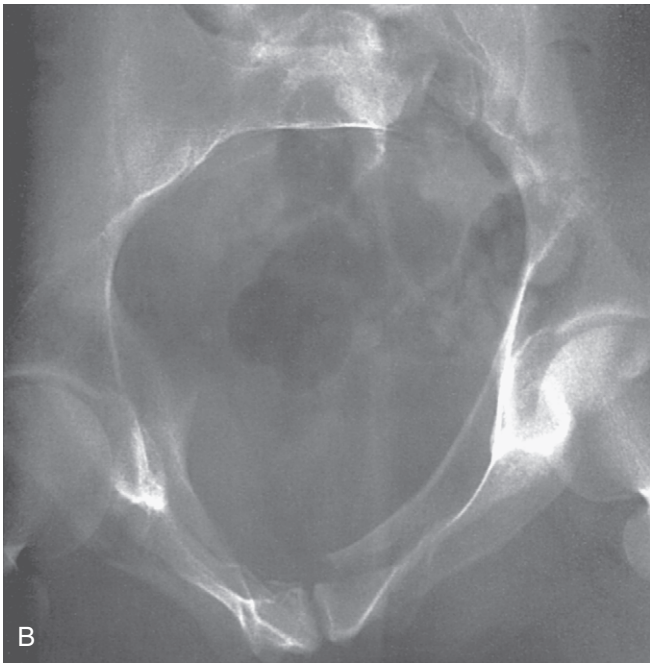

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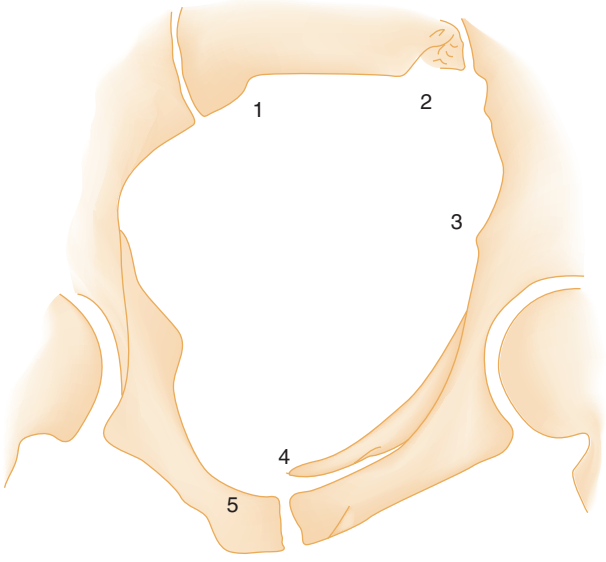


C

Figure 52-10. **A,** The inlet and outlet views. The inlet view is angled 60 degrees to the plate from head to feet; the outlet view is angled 30 degrees in the opposite direction. Both views can be obtained with a portable machine if necessary. Injuries to the sacrum and sacroiliac joint are commonly difficult to visualize with the anteroposterior view only. The combination of all three views allows the identification of virtually all significant injuries to the bony pelvis. **B,** Inlet of pelvis is well demonstrated in this radiograph of a unilateral vertical shear fracture with cephalad and posterior displacement of the left hemipelvis. **C,** Schematic of unilateral vertical shear fracture. (*1*) Normal sacral ala on the right side, (*2*) left sacral ala is indistinct because of a vertical fracture, and the cephalad and posterior displacement of this hemipelvis is shown by this inlet projection, (*3*) ischial spine on the left is partially obscured by bowel gas, but it is located more cephalad compared with the right spine because of cephalad displacement of the left hemipelvis, (*4*) fractured left superior pubic ramus with displacement cephalad, (*5*) the inlet view is taken looking through the superior and inferior pubic rami, which are superimposed so that the obturator foramina are not seen.

tion of the pelvis, angiography, and definitive orthopedic management of the pelvic injury. Given the speed with which current CT scanners are able to obtain images, it is recommended that all but the most hemodynamically unstable patients undergo CT investigation.

Evaluation of Hemorrhage

Hemorrhage is the most devastating direct complication of pelvic fracture. In the original series of high-energy pelvic injuries used to formulate their classification system, Burgess and colleagues' analysis of blood transfusions required an average of 14.8 U in the AP compression group, 9.2 U in the vertical shear group, and 3.6 U in the lateral compression group.[12] The finding has been confirmed in more recent studies that demonstrate that unstable fracture patterns increase the need for transfusion and risk of mortality,[45] with one series reporting median of 10 U of blood required (range 1–70 U).[3]

Bleeding results from lacerations of the rich vascular network supplying the pelvis and collects in the retroperitoneal space, but bleeding also may occur from the marrow at the fracture sites.[46] Coagulopathy is another cause of persistent retroperitoneal bleeding and should be considered when the patient does not respond to fluid and blood replacement.

Pelvic hemorrhage is commonly venous in origin and may be contained and tamponaded retroperitoneally by an intact peritoneum. However, it is possible for bleeding to extend beyond the retroperitoneum and dissect into the anterior abdominal wall (to the chagrin of the unwary clinician who introduces a scalpel or peritoneal dialysis catheter) or through the peritoneum into the abdominal cavity.

The combination of both pelvic and intra-abdominal bleeding is associated with devastating outcomes.[45] In one large series, major pelvic injury was associated with intra-abdominal injuries in 31%; the liver and spleen were injured in 10 and 6% of these cases, respectively.[2] In the patient with pelvic fracture who presents in shock, it is important to establish early on whether there is hemorrhage within the abdominal cavity necessitating laparotomy. Diagnostic strategies for evaluation of pelvic fracture-associated hemorrhage include diagnostic peritoneal lavage (DPL), ultrasound, and CT. Regardless of the modality of evaluation, it is crucial to avoid unnecessary laparotomy because of the higher mortality rate for hemodynamically unstable patients with pelvic fractures who undergo a negative abdominal exploration.

Diagnostic Peritoneal Lavage

DPL is a widely accepted, rapid, and accurate means of establishing the presence of intra-abdominal hemorrhage. Although it has been largely supplanted in many centers by ultrasound and CT, DPL nevertheless remains an effective tool to assist with difficult triage decisions in the trauma patient. A pelvic fracture presents a special situation for DPL because of the possibility that a retroperitoneal hematoma may dissect into the anterior abdominal wall. However, when a fully open technique is used (i.e., the peritoneum is entered under direct visual control), the false-positive and false-negative rates are each 0.7%.[47]

The DPL may be performed in the infraumbilical location in most patients; however, the supraumbilical location should be employed if any of the following conditions are present: prior abdominal scars, time delay since the injury of more than 1 hour, or a hematoma encountered during the procedure.[47]

A negative peritoneal aspirate indicates that the peritoneal cavity is not a major source of bleeding or a significant contributor to hemorrhagic shock. Assuming that external and thoracic sources of blood loss have been eliminated as causes of hemodynamic instability, a negative peritoneal aspirate in a patient with a major pelvic fracture indicates pelvic hemorrhage. Angiography with rapid therapeutic embolization and mechanical fracture stabilization should be pursued.

Gross aspiration of blood indicates possible major intra-abdominal hemorrhage and laparotomy is recommended at the earliest opportunity for hemodynamically unstable patients.[47] The lavage that is positive by cell count criteria alone is a special situation. If these patients are hemodynamically unstable, it is advisable to perform angiography with therapeutic embolization and external pelvis fixation before laparotomy.[46,47]

Ultrasound

Focused assessment with sonography for trauma (FAST) is widely used to identify free intraperitoneal fluid in the trauma patient. An important caveat to note is that FAST is not helpful for evaluating the retroperitoneal space where pelvic hemorrhage occurs. Although a positive FAST study that shows free fluid is widely used as a triage point to decide on laparotomy in a hemodynamically unstable patient, its reliability in patients with major pelvic injury has been questioned. Sensitivities ranging from 24 to 81% and specificities ranging from 87 to 96% for the detection of hemoperitoneum have been reported[48,49] in patients with pelvic fracture.

Although these reports come from retrospective case series—and therefore do not necessarily represent the highest levels of evidence—the high incidence of false-negative FAST exams reported in the literature among patients with pelvic injury is nonetheless cause for concern. This is because pelvic and intra-abdominal hemorrhages are highly associated and, in combination, result in major blood loss.[45]

Computed Tomography

CT is unquestionably the diagnostic test of choice for detecting pelvic and intra-abdominal injuries. It reveals bleeding in both the peritoneal and retroperitoneal spaces. CT with intravenous contrast often can distinguish a stable hematoma from ongoing bleeding from pelvic arteries. The presence or absence of extravasated intravenous contrast material on CT scan of the pelvis is useful in predicting which patients will require therapeutic angiography[50]; however, its absence does not rule out ongoing pelvic bleeding: One series found the sensitivity for the detection of arterial bleeding by CT to be only 66% in patients who also had angiography.[51]

■ MANAGEMENT

Resuscitation

The mortality rate in patients with blunt trauma who have the combination of pelvic ring fractures and hemorrhagic shock is approximately 50%.[1,2] ATLS guidelines advocate the initial use of crystalloid solutions to stabilize vital signs in the trauma patient. However, when severe hypotension is present in patients with severe pelvic fracture, transfusion of blood products (including packed red blood cells, plasma, platelets, and occasionally cryoprecipitate) is crucial early in the resuscitation. Some patients appear to achieve hemodynamic stability after minimal volume infusion only to decompensate precipitously. It is important to note that case series commonly report patients with severe pelvic injury requiring transfusion of packed red blood cells in the order of 10 to 20 U within the first 24 to 48 hours.

The endpoint for fluid resuscitation should be evidence of end-organ perfusion. A large body of evidence from animal studies suggests that standard volumes of crystalloid fluids typically used in traumatic hemorrhagic shock to restore normal heart rate and blood pressure lead to greater volumes of blood loss compared with low-volume resuscitation strategies that accept lower systemic blood pressures.[52,53] For patients with severe pelvic fracture, attempts to achieve normocardia and normotension with fluid resuscitation in the ED should not delay more definitive treatments to halt the hemorrhagic process.

Lower limb intravenous sites should be avoided in patients with severe pelvic fractures because the infused products may be delivered to the retroperitoneal space.[54]

Box 52-4 details the methods for controlling hemorrhage in the ED phase of the care of patients with pelvic fractures.

Control of Hemorrhage

In addition to blood transfusion, two important therapeutic modalities for control of hemorrhage are mechanical stabilization of the pelvis and angiographic embolization. There has been some debate as to which of these modalities should take precedence, and this has been predicated on institutional availability. As a general rule, angiography with therapeutic embolization of bleeding arteries is more effective than and takes precedence over external fixation.[55,56]

Stabilizing the Pelvis

Noninvasive Techniques. The most readily available means to quickly stabilize the pelvis in the ED may be realized with a simple sheet and towel clamps. Wrapping the pelvis tightly with a sheet and securing this with towel clamps has been shown to be effective in reducing an open-book pelvic injury (Fig. 52-11),[57,58] thereby reducing the potential volume in the pelvis for blood loss.

Other devices have been developed to facilitate noninvasive splinting of the pelvis. One retrospective comparison of patients with exsanguinating pelvic hemorrhage found that patients treated with a noninvasive splinting device had substantially lower transfusion requirements than those who had formal external fixation of their pelvis performed emergently (4.9 U vs. 17.1 U in the first 24 hours, $p = 0.008$). However, there was no statistically significant change in mortality between the two groups (26% vs. 37%, $p = 0.11$).[59]

Patients who have sustained AP open-book injuries are likely to derive the most benefit from tight wrapping of the pelvis. This maneuver may not be desirable when lateral compression forces have already internally rotated the hemipelvis because indiscriminately forceful wrapping may, in fact,

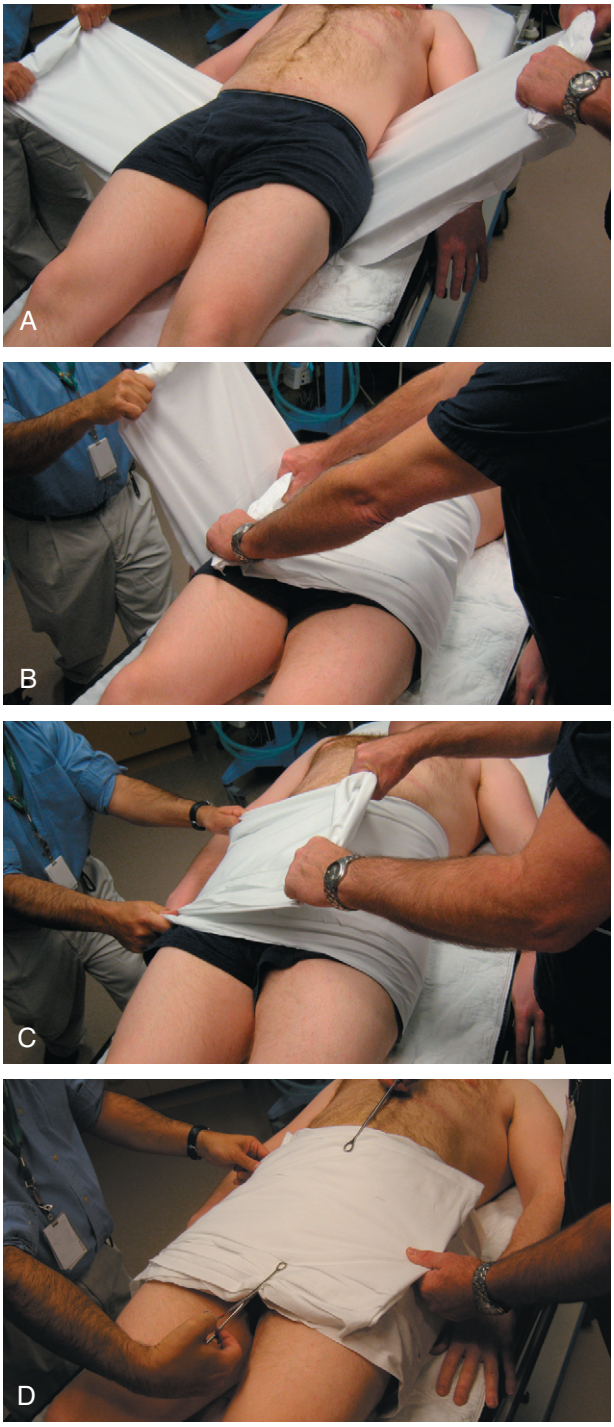


Figure 52-11. **A,** Circumferential pelvic antishock sheeting is applied in this example patient. The patient's clothing should be removed before application. The sheet is positioned beneath the patient's pelvis smoothly. The ends of the sheet are crossed in an overlapping manner anteriorly **(B)** and are pulled taut **(C)**. Clamps secure the smooth and snug sheet **(D)**.

BOX 52-4 PELVIC FRACTURE–RELATED HEMORRHAGE: GOALS IN THE EMERGENCY DEPARTMENT

1. **Resuscitation:** Recognize the patient who is in hemorrhagic shock, and initiate blood transfusion early in the resuscitation.
2. **Recognition:** Realize that patients with posterior arch injuries are at higher risk for pelvic hemorrhage.
3. **Evaluation:** Identify associated nonpelvic injuries (especially head, chest, and intra-abdominal) that contribute immensely to increase in mortality in patients with pelvic fracture.
4. **Stabilization:** Wrapping the pelvis in a sheet and towel clamps is the easiest way to immobilize the pelvis in the emergency department. Stabilization by external fixation or pelvic C-clamp should be performed by orthopedic surgeons.
5. **Control of pelvic bleeding:** Angiography is highly effective in treating pelvic arterial hemorrhage. Pelvic packing during laparotomy is another way of controlling bleeding. Institutional practices determine if one or both techniques are used.

worsen the degree of displacement. Here, some judgment is required to discern whether one is wrapping the pelvis to reduce the volume of an externally rotated pelvis versus splinting a pelvis that is internally rotated due to lateral compression in order to minimize pelvic movement that may occur, especially when transferring the patient.

Invasive Fixation. External fixation of the pelvis is always performed by orthopedic surgeons. The goal of fixation is to prevent movement at pelvic fracture sites and attendant bleeding.[11] Although the acute application of an external fixator has not been proved to decrease morbidity or mortality in a prospective study, there is evidence that this technique improves clinical outcome by limiting hemorrhage and restoring mechanical integrity.[46] Application of the fixator is time-consuming; therefore, it should not delay more definitive treatment of pelvic bleeding by angiography or the treatment of other sources of severe blood loss. The timing of the application of the external fixator requires coordination between the trauma surgeon and orthopedic surgeon. Early surgical consultation is vital to efficient planning and prioritization of surgical management.

Many stable AP and lateral compression fractures can be treated definitively by the external fixator.[11] When the pelvis is vertically displaced, traction combined with external fixation is necessary to reduce the pelvis while waiting for definitive open surgical repair.[11] Most fixators can be constructed to allow convenient surgical access to the abdomen and groin.

The pelvic C-clamp can theoretically be applied rapidly by the orthopedic surgeon in the ED to externally stabilize the posterior pelvic arch on an emergency basis.[60,61] It is likely more effective in reducing AP than vertical injuries.[62] Institutional practices may influence the use of C-clamp over standard external fixation. Although the C-clamp may aid in stabilizing blood loss, its application does not obviate the need for angiography.[63] It is unclear whether the C-clamp offers any additional advantage over wrapping the pelvis with a sheet during initial resuscitation efforts.

Angiography and Embolization

Arteriography and venography have been investigated for managing hemorrhage associated with pelvic fractures. Although pelvic bleeding is commonly venous in origin, venography is not useful in managing these cases: the extensive anastamoses and valveless collateral flow make embolization ineffective. In contrast, arteriography is excellent at both diagnosing and managing arterial bleeding.

The arteriogram is performed with the contrast material injected through the femoral artery on the least-injured side or via the upper extremity. The examination starts above the level of the aortic bifurcation and proceeds to selective branches of the internal iliac (hypogastric) artery.[64] Transcatheter embolization using thrombogenic coils, foam, or spherules is employed to stop the hemorrhage from the branches of the internal iliac artery.

Embolization is highly effective for controlling arterial bleeding. One case series of 556 patients undergoing pelvic angiography reported that repeat angiography was necessary in only 7.5% of patients due to ongoing bleeding. These authors found that hypotension, a need for more than 2 U of packed red cells, symphysis widening, and more than two arteries embolized at the first angiogram predicted the need for repeat angiography.[65]

Angiography is indicated when hypovolemia persists in a patient with a major pelvic fracture, despite control of hemorrhage from other sources. Although it is impossible to determine whether bleeding is venous or arterial in origin until angiography is performed, one study found that inadequate response to initial resuscitation (defined as failure to maintain a systolic blood pressure above 90 mm Hg after the administration of 2 U of packed red cells, or less) and the presence of contrast extravasation on admission CT were both indicative of active arterial bleeding.[55] Although the presence of contrast extravasation on CT is an indication for angiography, the absence of contrast blush on CT is not sufficient to rule out serious pelvic bleeding.[55,66]

The timing of angiography is individualized for each patient depending on priorities for treatment of concomitant injuries. Posterior arch disruptions are associated with the most severe hemorrhage; angiography should be considered at an early stage for these patients. Whether patients undergo angiography immediately from the ED or angiography immediately precedes laparotomy, it is important to be mindful of the logistical delay that often occurs in mobilizing the angiography team, so this intervention should be anticipated as early as possible. The transfer of the patient to the angiography suite also requires orchestrating the necessary personnel and equipment to care for the critically injured patient there.

Hemodynamically Unstable Patients with Pelvic and Intra-abdominal Hemorrhage

Patients who hemorrhage from both the pelvis and abdomen have mortality rates above 40% and deserve special consideration. These patients may be too unstable to undergo CT imaging. Prioritizing the need for laparotomy versus angiography in these patients may be challenging when the need for laparotomy is based on the detection of intra-abdominal fluid by FAST or DPL. In these cases, it is crucial that the efforts of the general surgeon, orthopedic surgeon, and interventional radiologist be coordinated to optimize the timing of necessary procedures.

Gross aspirates of blood on DPL are strong indicators for prompt laparotomy. Given the high rates of false-negative FAST exams in pelvic trauma, caution must be used when making difficult triage decisions regarding laparotomy versus angiography on the basis of FAST findings in this setting. However, when the FAST exam does reveal hemoperitoneum, it is generally accepted that laparotomy be pursued first.[67] When concurrent pelvic bleeding is highly suggested (e.g., severe open-book pelvis), it is advisable that angiography promptly follow laparotomy.

It may be appropriate for the orthopedic surgeon to place either an external fixator or pelvic C-clamp at the time of laparotomy. Packing of the pelvis at the time of laparotomy has been reported as a means to obtain hemostasis in pelvic hemorrhage.[68,69] Although there is limited evidence from clinical studies to support packing, it is regularly used at some centers, especially in Europe. Part of the rationale for employing packing rather than angiography is the fact that pelvic bleeding is commonly venous in origin, for which arteriography is useless. In contrast, packing may aid in tamponading bleeding from the posterior venous plexus. It is recommended that the pelvis be stabilized prior to packing to provide solid structural support against which packing may be performed.[69]

When FAST or DPL do not reveal hemoperitoneum in the presence of severe pelvic fracture, emergent angiography should be arranged. If pelvic bleeding continues despite angiography (i.e., secondary to venous bleeding), open stabilization and packing should be considered as the next step.

For any trauma center, planning for challenging clinical situations among trauma surgeons and angiographers and the creation of protocols for care may be useful in optimizing a timely and coordinated response.[56]

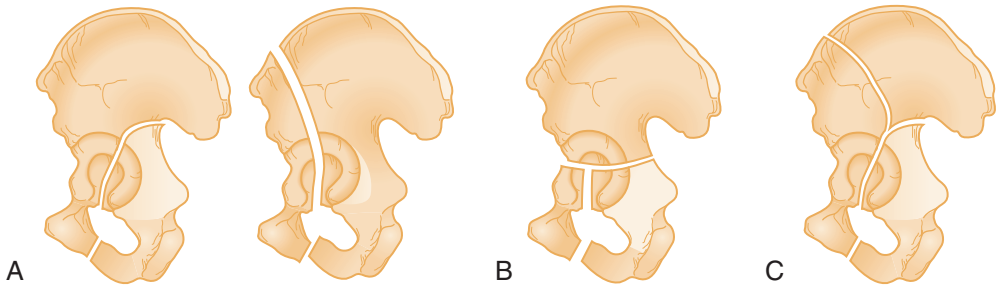


Figure 52-12. Universal classification of acetabular fractures. **A,** Type A: Fractures of one column or one wall, for example, posterior column (**left**) and anterior (**right**) column. **B,** Transverse or T-type fractures involving both columns but by definition always leaving a fragment of articular cartilage attached to the proximal ilium and, thus, to the axial skeleton. **C,** Type C: Two-column fracture of the acetabulum. By definition, no portion of the articular surface remains attached to the axial skeleton because fracture of both columns of the ilium is proximal to the joint. (From Tile M: Fractures of the Pelvis and Acetabulum, 3rd ed. Philadelphia, Lippincott Williams & Wilkins, 2003.)

Acetabular Fractures

Many pelvic fractures in adults involve the acetabulum. Pain and inability to bear weight are the hallmark complaints associated with acetabular fractures. On clinical exam, pain on percussion of the sole of the foot or the greater trochanter may reproduce pain. It is important to note the presence of neurologic deficit as the sciatic nerve is commonly injured. Fracture or dislocation of the patella (or both) are also common. Acetabular fractures are broadly classified into three types[11] (Fig. 52-12, Box 52-5).

Type A fractures may be subdivided into anterior and posterior column injuries. Posterior wall fractures are the most common acetabular injuries and are generally caused by a forceful impact to a flexed knee (e.g., dashboard injury)—the force is transmitted up through the femur through the posterior acetabulum. An associated posterior dislocation of the hip is frequently associated with posterior rim fracture of the acetabulum and may result in an unstable hip joint and recurrent dislocation. Posterior hip dislocation is commonly associated with secondary sciatic nerve injury. The anterior column of the acetabulum is commonly injured when a superior ramus fracture extends into the low anterior column.

Type B fractures involve both anterior and posterior columns, but a portion of the acetabulum remains attached to the ilium. When the columns are split, this is referred to as a T fracture. The T fracture is associated with the worst prognosis, owing to the difficulty in obtaining open anatomic reduction.

Type C fractures are readily apparent on plain radiographs as a result of disruption of the ilium.

Assessment of the AP pelvic radiograph should focus on the disruption of the ilioischial and iliopectineal lines as well as the anterior and posterior lips of the acetabulum (Fig. 52-13). Ramus fractures should be evaluated for possible extension into the acetabulum. Oblique views of the acetabulum (Judet's views) can aid in visualizing the anterior and posterior columns. CT is, without question, the imaging test of choice for visualizing acetabular fractures and planning for possible surgical repair. All patients with acetabular fracture require orthopedic referral in the emergency department.

BOX 52-5 CLASSIFICATION OF ACETABULAR FRACTURES

Type A
Fractures of one column of the acetabulum (anterior or posterior column)

Type B
Transverse (T-type) fractures through both anterior and posterior columns; portion of acetabulum remains attached to proximal ilium

Type C
Transverse (T-type) fractures through both anterior and posterior columns; no portion of acetabulum remains attached to axial skeleton

From Tile M: Fractures of the Pelvis and Acetabulum, 3rd ed. Philadelphia, Lippincott Williams & Wilkins, 2003.

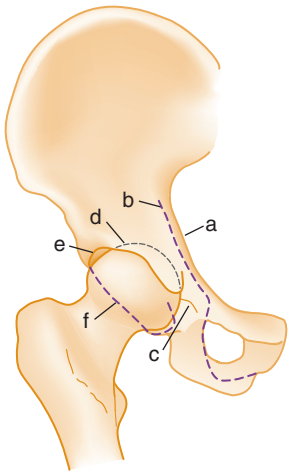


Figure 52-13. Schematic drawing of radiographic anatomy of acetabulum in anteroposterior pelvis projection. (*a*) Arcuate (iliopubic) line. (*b*) Ilioischial line. (*c*) Radiographic U, or teardrop, caused by superimposition of parasagittal surface of ilium onto anteroinferior portion of acetabulum. (*d*) Acetabular roof. (*e*) Anterior lip of acetabulum. (*f*) Posterior lip of acetabulum. (Redrawn from Rogers LF, Novy SB, Harris NF: Occult central fractures of the acetabulum. AJR Am J Roentgenol 124:98, 1975.)

Coccyx Fractures

Fractures of the coccyx occur frequently after a fall in the sitting position or a kick. Fracture and injury also may occur during parturition. Physical examination reveals local tenderness to palpation in the gluteal crease, with pain and, sometimes, abnormal motion of the coccyx during palpation on digital rectal examination. Normally the tip of the coccyx moves 30 degrees anteriorly and 1 cm laterally.[70] Displacement also is diagnosed on rectal examination, but attempts at reduction are not recommended.

Radiographic confirmation of a coccygeal fracture is not always necessary. Displaced fractures often are seen on the lateral view, but the diagnosis is evident on rectal examination.

Undisplaced fractures may be difficult to show radiographically. The physician must decide whether the knowledge gleaned from radiographic studies would alter the therapy to a degree that warrants radiation exposure to the pelvis, especially considering that most of these fractures occur in women.

Treatment of coccygeal fracture consists of bedrest, stool softeners, analgesia, and sitz baths to relieve muscle spasm. As activity is increased, maneuvers that may minimize discomfort include using an inflatable rubber donut cushion, alternate sitting on the side of each buttock, slouching to displace body weight more proximally, and sitting on a hard chair rather than a soft one (sinking into a soft chair may distribute weight onto the coccyx).[70] Because of muscle action on the fragment, healing is slow and patients must be cautioned that discomfort may be prolonged. In the case of persistent severe disability, an orthopedic consultation is indicated for considerations of local steroid injection or possible coccygectomy.[71] Other causes of coccydynia (besides fracture) include trauma during parturition; faulty posture; midline disk herniations (caused by nonsegmental referral of pain from irritation of the dura); lumbar facet arthropathy; compression of the first, fourth, and fifth sacral roots; neuralgia from sacral plexopathy or sacrococcygeal neuropathy; infections; and local tumors.[70]

KEY CONCEPTS

- The most serious pelvic ring injuries caused by high-energy impact include (1) AP compression fractures (open book), (2) vertical shear fractures, and (3) any fractures that involve significant displacement. These are associated with major blood loss and transfusion requirements.
- Pelvic injury is a marker for serious injury to other organ systems. The vast majority of patients who die with pelvic fracture are those who have sustained multiple trauma.
- Careful examination of the skin in the perineum and buttocks and digital rectal and vaginal examinations are necessary to diagnose open fractures because these are associated with the highest mortality rates.
- CT is the imaging test of choice to diagnose pelvic fracture and concurrent intra-abdominal injuries for patients stable enough to undergo CT. CT aids in establishing surgical priorities and planning of definitive orthopedic care.
- In the hemodynamically unstable patient who cannot undergo CT imaging, the AP radiograph usually reveals those pelvic fractures most closely associated with major pelvic bleeding. Inlet and outlet radiographs improve the sensitivity and specificity of pelvic plain radiography.
- Trauma hospitals should have institutional guidelines and mechanisms to access angiography and external fixation.
- The combination of posterior arch fracture plus hypotension is associated with a mortality rate of approximately 50%. Early resuscitation with blood products is recommended. Decisions regarding the need for angiographic transcatheter embolization and external pelvic fixation must be made early in the course of care.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 53

Femur and Hip

James F. Fiechtl and Robert W. Fitch

PERSPECTIVE

Background

Ancient Egyptian and Greek drawings depict a lame person afflicted with hip deformities ambulating with a cane. The first available written description of a hip fracture was by the 16th-century French surgeon Ambroise Paré.[1] In 1850, Von Langenbeck was the first to attempt repair of a hip fracture with a nail for internal fixation. Later, Davis used ordinary wood screws in an attempt to aid the healing of femoral neck fractures.[2] With the advent of radiography in the 19th century, the types of fractures and dislocations became easily identifiable, thus allowing discussion and investigation of management strategies, classification systems, and prognosis.

Epidemiology

Both age and gender are important predisposing factors for specific injury patterns seen in and pathologic conditions affecting the hip, femur, and thigh.

As a whole, the elderly segment of society almost universally suffers from some type of hip pathology. Osteoarthritis of the hip can severely limit the affected person's ability to perform activities of daily living. Approximately 6 million women in the United States suffer from osteoporosis, and an additional 17 million have osteopenia, both of which predispose to hip fracture.[3] During the late 1990s, approximately 250,000 patients a year sought treatment in emergency departments (EDs) after sustaining a hip fracture.[4] As baby boomers mature, the number of hip fractures is expected to reach half a million a year by 2050.[5] Eighty percent of femoral neck fractures occur in men. The average age of patients who sustain femoral neck fractures is 72 years for men and 77 years for women.[6] On average, intertrochanteric fractures occur 10 to 12 years later than those of the femoral neck, and women are afflicted eight times more often than men.[7] Overall, three quarters of all hip fractures occur in postmenopausal women older than 50 years.[3]

Perthes' disease—avascular necrosis (AVN) of the femoral head—is four times more common in boys than in girls and occurs between 3 and 12 years of age. Slipped capital femoral epiphysis (SCFE) is twice as common in boys and peaks at 13 years of age among boys and 11 years among girls, in association with the onset of puberty.

PRINCIPLES OF DISEASE

Anatomy of the Hip and Femur

Skeletal Anatomy

The femoral head is firmly seated in the acetabulum, which is reinforced by labral cartilage. The well-developed capsule, overlying ligaments, and proximal musculature of the lower extremity add strength to the joint (Fig. 53-1). The nearly spherical femoral head articulates with the acetabular cup in a variation of the ball-and-socket joint.

The femur is the longest and strongest bone in the human body and is routinely subjected to substantial forces produced during powerful muscle contraction and weight transmission. In an anatomic position, the two femurs extend obliquely from the pelvis medially to the knee and bring the legs closer to the midline, where they can best support the body. Structurally, the femoral neck serves as an oblique strut between the pelvis (the horizontal beam) and the shaft of the femur (the vertical beam) (Fig. 53-2). The length, angle, and narrow circumference of the femoral neck permit substantial range of motion at the hip, but these same characteristics subject the neck to incredible shearing forces. A fracture results when these forces exceed the strength of the bone. As drawn on an anteroposterior radiograph, the *intertrochanteric line*, an oblique line connecting the greater and lesser trochanters, marks the junction of the femoral neck and its shaft.

The bone in the femoral head, neck, and intertrochanteric region is predominantly cancellous, which is less resistant to torsional forces. Distal to the intertrochanteric region, including both the subtrochanteric region and femoral shaft, the bone is cortical, requiring great forces to break. At the distal metaphysis, the femur widens and the cortical bone thins, lessening its resistance to stress.

Musculature

The musculature of the hip and thigh is the largest and most powerful in the human body. The muscles in this region of the body are located within three different compartments, each containing associated nerves and vessels (Table 53-1). The muscles also are grouped according to their primary action at the hip. Knowledge of the major muscle actions offers

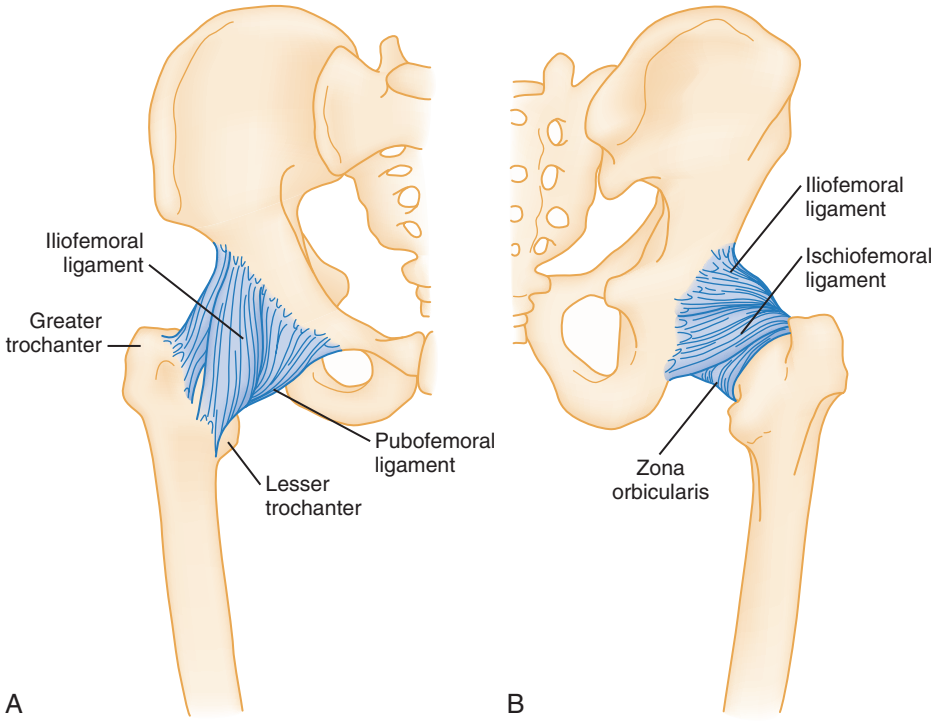


Figure 53-1. The ligaments of the hip combine to form a tough joint capsule, as seen on both anterior (**A**) and posterior (**B**) radiographic views.

insight into the injury patterns and deformities commonly seen (Fig. 53-3).

Vascular Anatomy

Arterial Supply

The arterial supply to the femoral head arises from three sources (Fig. 53-4). The major source is the ascending cervical arteries as they branch off the extracapsular ring and run along the femoral neck beneath the synovium. Some blood is supplied to the femoral head from the second source, within the marrow spaces—the intraosseous cervical vessels. A third and dubious source is the foveal artery as it lies within the ligamentum teres.

As the external iliac artery passes beneath the inguinal ligament, it becomes the common femoral artery.[8] At this point the artery is located midway between the anterior superior iliac spine and the symphysis pubis. Approximately 3 to 4 cm distal to the inguinal ligament, the common femoral artery branches to form the superficial and deep femoral arteries. The larger superficial femoral artery passes along the anteromedial aspect of the thigh and terminates at the junction of the middle and lower thirds of the thigh. Here, the superficial femoral artery passes through the adductor hiatus and becomes the popliteal artery. The deep femoral artery runs posterolateral to the superficial femoral artery, supplies the hamstrings, and terminates in the distal third of the thigh as small branches piercing the belly of the adductor magnus. These perforating branches constitute an additional site of potential injury. The abundant blood supply of the thigh aids in healing fractures of the femoral shaft.

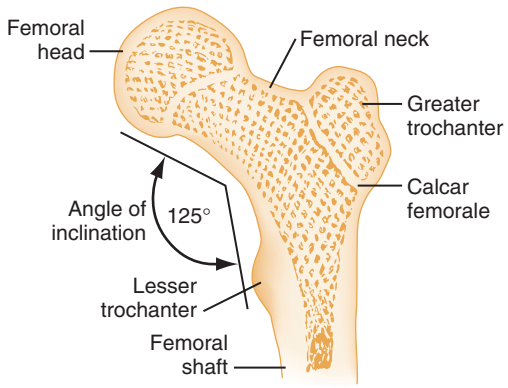


Figure 53-2. Bony architecture of proximal end of the femur.

Venous System

In the proximal two thirds of the thigh, the common and superficial femoral veins lie adjacent to the common and

Table 53-1 Structures within Compartments of the Thigh

COMPARTMENT	MUSCLES	NERVES	VESSELS
Anterior	Quadriceps femoris, sartorius, iliacus, psoas, pectineus	Lateral femoral cutaneous	Femoral artery and vein
Medial	Gracilis, adductor longus and magnus, obturator externus	Obturator	Profundus femoris artery, obturator artery and vein
Posterior	Biceps femoris, semitendinosus, semimembranosus, adductor magnus	Sciatic, posterior femoral cutaneous	Profundus femoris artery branches

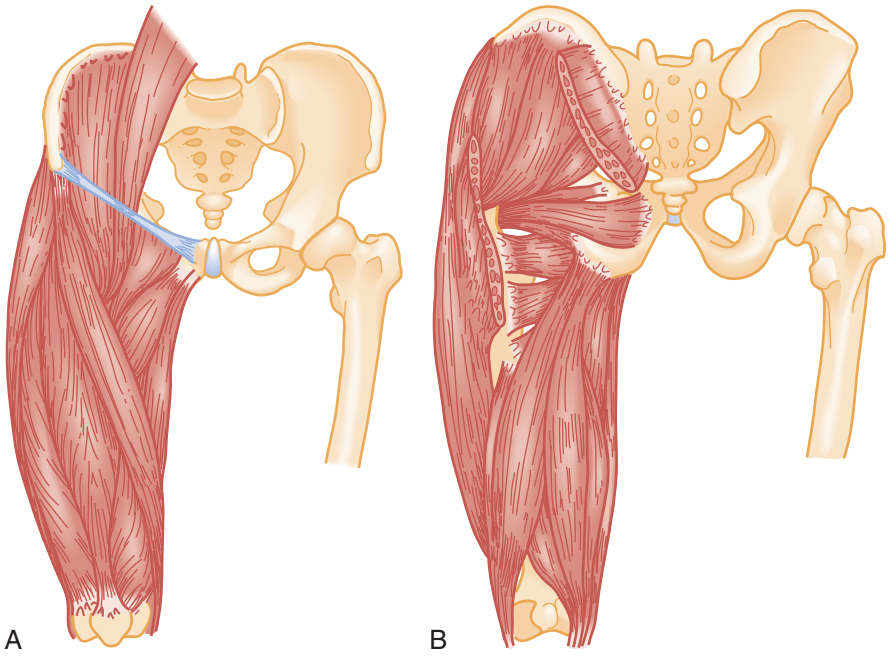


Figure 53-3. **A** and **B,** Anatomic illustration of the major muscles acting about the hip and thigh.

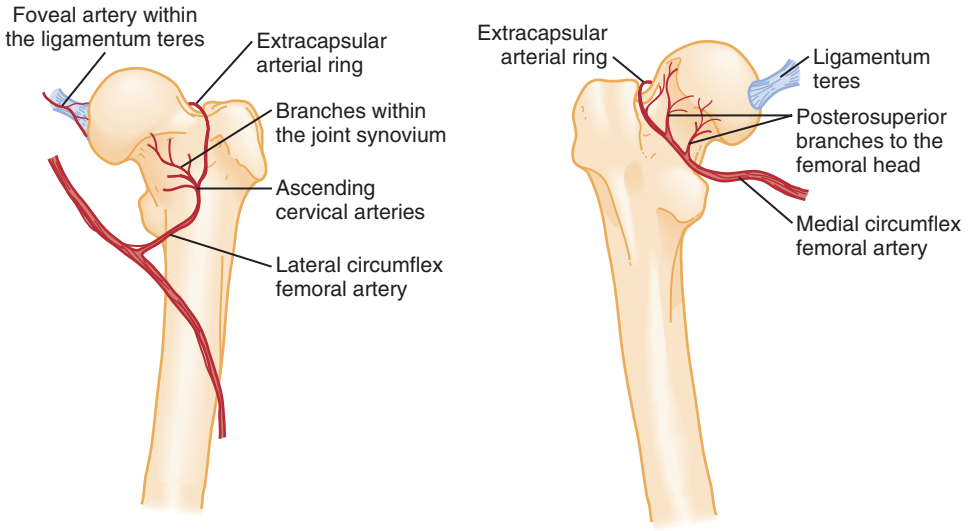


Figure 53-4. The arterial blood supply of the femoral neck and head is provided to varying degrees by three sources: the ascending cervical arteries, the arterial branches within the marrow *(not illustrated),* and the dubious foveal artery within the ligamentum teres.

superficial femoral arteries. At the inguinal ligament, the common femoral vein is posterior and medial to the common femoral artery and moves to the lateral position as it passes distally. The deep femoral vein and the greater saphenous vein are the two main tributaries to the common and superficial femoral veins. The deep femoral vein and artery run parallel as the vein joins the superficial femoral vein just distal to the inguinal ligament. The greater saphenous vein arises in the dorsum of the foot and ascends anterior to the medial malleolus. This vein is relatively superficial as it passes up the medial aspect of the leg to join the common femoral vein distal to the inguinal ligament.[8]

Nerves

The femoral and sciatic nerves are the major nerves within the thigh. The femoral nerve is the largest branch of the lumbar plexus; it passes under the inguinal ligament lateral to the femoral artery and divides into anterior and posterior branches soon after entering the thigh. The sensory divisions of the anterior branch, the intermediate and medial cutaneous nerves, supply sensation to the anteromedial aspect of the thigh. The motor division of the anterior branch innervates the pectineus and sartorius muscles. The posterior femoral branch gives off the saphenous nerve, which supplies sensation to the skin along the medial aspect of the lower part of the leg. The posterior branch also supplies motor function to the muscles of the quadriceps femoris group.[8]

The sciatic nerve is the largest peripheral nerve in the body. It arises from the sacral plexus. The sciatic nerve exits the pelvis through the greater sciatic foramen and travels through the posterior of the thigh; it extends from the inferior border of the piriformis to the distal third of the thigh. The sciatic nerve gives off articular branches that supply the hip joint. In the thigh, muscular branches innervate the adductor magnus and hamstring muscles. Just proximal to the popliteal fossa, the sciatic nerve divides to form the tibial and common peroneal nerves.[8]

Pathophysiology

Fractures of the Femur and Hip

The pathophysiology of femur and hip fractures is discussed in the description of individual fractures. The vast majority of hip fractures occur in elderly patients with preexisting bone disease and result from relatively low-energy trauma, usually a ground-level fall. Major trauma such as motor vehicle collisions or falls from significant heights is responsible for a majority of fractures in young, otherwise healthy individuals.

Osteoarthritis of the Hip

As the population ages, a greater percentage of the population will suffer with the chronic pain associated with degenerative osteoarthritis of the hip. Overall, osteoarthritis ranks fourth in health impact in women and eighth in men in the western world.[9] Disability often results from persistent pain and limited physical mobility. The progression of osteoarthritis can be demonstrated with serial radiographs of the affected hip (Fig. 53-5); however, radiographic findings do not necessarily correlate with symptoms.[10]

Osteoporosis of the Femur

Osteoporosis is the leading cause of hip fracture. Osteoporosis currently affects more than 10 million people in the United States, and osteoporosis is projected to affect approximately 14 million adults older than 50 years by the year 2020. The number of hip fractures attributable to osteoporosis is expected to be 6.3 million by the year 2050, although the incidence in women is decreasing in recent years, probably because of an increased awareness and more aggressive treatment of osteoporosis.[11,12] Hip fractures can have a devastating impact: One in five patients die during the first year after a hip fracture, mostly from causes other than the fracture itself; one third require nursing home placement after hospital discharge; and less than one third regain their pre-fracture level of physical function.[11] The economic impact of these fractures is enormous.

The pathophysiology of osteoporosis is not completely understood, but strong associations with hormonal changes related to aging, genetic predisposition, vitamin D deficiency, lack of physical activity, and smoking have been recognized.[13] Severe osteoporosis and hip fractures are most common in elderly white women; however, a decrease in bone density after age 30 is seen across all demographic groups. Radiography of the head of the femur can quantify the degree of osteoporosis, even in the nonfractured hip. The trabeculae of the femoral head and neck strengthen the bone and support the large mechanical forces produced across the hip joint. As osteoporosis begins and then progresses, these trabeculae disappear. This loss of trabeculae weakens the bone and increases the risk of fracture.

Avascular Necrosis

When a patient has an increasingly painful hip, buttock, thigh, or knee and no history of recent trauma, AVN of the femoral head should be considered. AVN has been referred to as aseptic necrosis, ischemic necrosis, and osteonecrosis. It is the result of ischemic bone death of the femoral head after compromise of its blood supply. AVN is bilateral in 52% of patients. It is common in relatively young patients, the mean age at diagnosis being 37 years.[14] Although a specific etiologic disorder is not identified in 20% of the cases, known atraumatic causes include chronic corticosteroid therapy, chronic alcoholism, hemoglobinopathy (e.g., sickle cell anemia), dysbarism, and chronic pancreatitis.[14] AVN necrosis also is an emerging complication associated with protease inhibitor therapy in patients infected with HIV[15] (Fig. 53-6).

Traumatic AVN is a subacute manifestation after hip dislocation or femoral neck fracture. It is more common in males and African Americans. The incidence of AVN as a subacute complication of hip dislocation can reach 40%. Its development is clearly related to both the initial degree of trauma and the amount of time that the femoral head remains out of joint. Reduction of the hip within 6 to 12 hours after dislocation significantly decreases the incidence of AVN.[16] For this reason, hip dislocation should be considered one of the few orthopedic emergencies. The emergency physician should perform reduction of the hip if there is any delay in orthopedic consultation.

Even with optimal treatment, femoral neck fractures are complicated by AVN in 11 to 19% of cases. For all practical purposes, femoral neck fractures are effectively intra-articular fractures. Acutely, bleeding from the fracture site may cause high intracapsular pressure and a tamponade effect on the femoral head, thereby further impairing the blood supply.[17] In addition, if the bone fragments are not impacted, synovial fluid

Figure 53-5. Radiographic evidence for the development of osteoporosis or degenerative joint disease of the hip is demonstrated with serial radiographs in the same patient over several years. **A,** The symptoms initially are more dramatic than would be expected with the radiographic findings of increased sclerosis along the weight-bearing surface of the superior acetabulum. **B,** The joint space is lost. **C,** Erosion of the head and acetabular surfaces and reactive bony cystic changes are now evident.

Figure 53-6. Avascular necrosis of the left femoral head. Note the asymmetry of the joint and the collapse of the femoral head.

will lyse the blood clot. Such lysis prevents the development of capillary buds and the scaffolding needed for osseous repair. These factors all contribute to make AVN of the femoral head a common complication. Conversely, intertrochanteric and subtrochanteric fractures are located in an area of rich blood supply provided by an extracapsular arterial supply. AVN rarely complicates these fractures.

Treatment of AVN should be directed at reversing the underlying cause. Supportive treatment is the mainstay, with total hip replacement reserved for severe cases.

Calcifying Lesions of the Femur and Hip

Myositis Ossificans

Myositis ossificans (heterotrophic ossification) is pathologic bone formation at a site where bone is not normally found. Traumatic myositis ossificans results most commonly from a direct blow to muscle. The incidence of myositis after a direct blow has been reported as 9 to 17% and is thought to be related to the severity of the injury.[18] The thigh and hip muscles are most commonly involved. Increased susceptibility to myositis ossificans has been described in persons with hemophilia or other bleeding disorders in conjunction with soft tissue injury.[19] The incidence of myositis ossificans after hip surgery is approximately 2%, but these lesions are clinically significant in only 10 to 20% of cases.[19]

Bleeding into the muscle after trauma produces a local hematoma with subsequent new bone formation within the hematoma. This inappropriate response also may result from repeated minor trauma, for unknown reasons. Myositis ossificans should be suspected when symptoms persist past 10 to 14 days or if symptoms intensify several weeks after the trauma.[18] The ossific mass often is palpable and may limit motion, depending on its location.

Radiographically, myositis ossificans appears as irregularly shaped masses of heterogeneous bone in the soft tissues around the joint or along fascial planes. It may be seen as early as 18 to 21 days after injury, but typically radiographic evidence lags behind onset of symptoms by weeks. Its appearance may simulate primary bone neoplasm, especially when the periosteum is involved. Osteosarcoma and periosteal osteogenic sarcoma should be considered in the differential diagnosis.

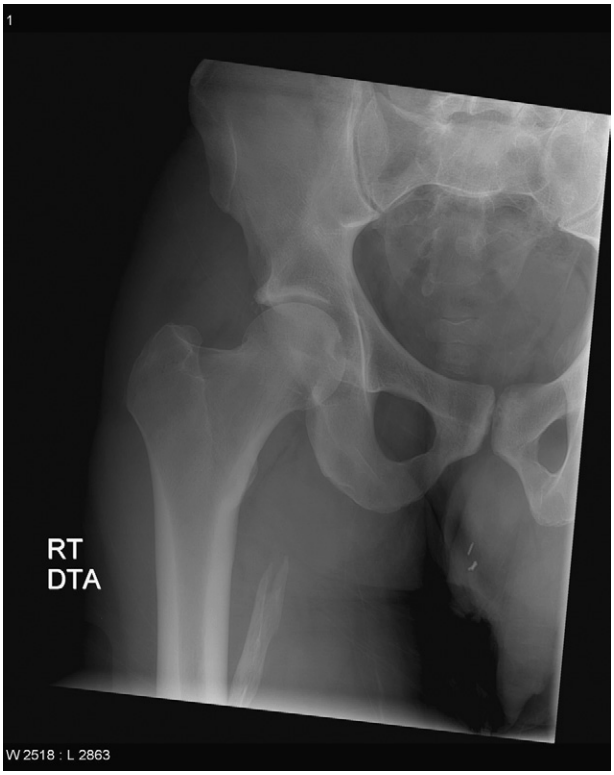


Figure 53-7. Myositis ossificans of the proximal end of the femur. Lesions may be immature or mature such as this one, with well-organized calcifications.

Treatment of myositis ossificans is based on the RICE principle of rest, ice, compression, and elevation. Immobilization of the extremity may prevent retraction of ruptured muscle and increasing size of hematoma formation but should be limited to less than 48 hours. Once a stable scar has formed, range of motion within limits of pain should be initiated. Although indomethacin commonly is used to prevent heterotopic ossification after surgery, it has not been validated for the prevention as well as the treatment of myositis ossificans.[18,19] Its use based on the principle of inhibiting bone formation does not seem to be contraindicated.[18] Operative removal of a mature lesion may be indicated if the lesion is near a joint or is causing permanent impairment or pain (Fig. 53-7).

Calcific Bursitis and Calcifying Peritendinitis

Calcification surrounding tendons and bursae or occurring in the joint capsule is referred to as calcific bursitis or calcifying peritendinitis. The cause of these lesions is unknown but may be similar to that of myositis ossificans. No relationship has been documented between the radiographic findings and acute symptoms. Calcific bursitis is uncommon, but when it does occur, it most frequently affects the trochanteric bursa of the hip (Fig. 53-8). Other possible affected areas include gluteal muscles and the hip flexors and adductors. The bursal calcification is seen on radiographs as an amorphous, poorly marginated line that is clearly separate from the cortex of the femur. Treatment should focus on stretching and strengthening of the hip.

Neoplastic Disease in the Hip

The most common neoplastic disease of bone is metastatic, generally from breast, kidney, lung, thyroid, and prostate tumors. Primary bone lesions also occur, with the most common

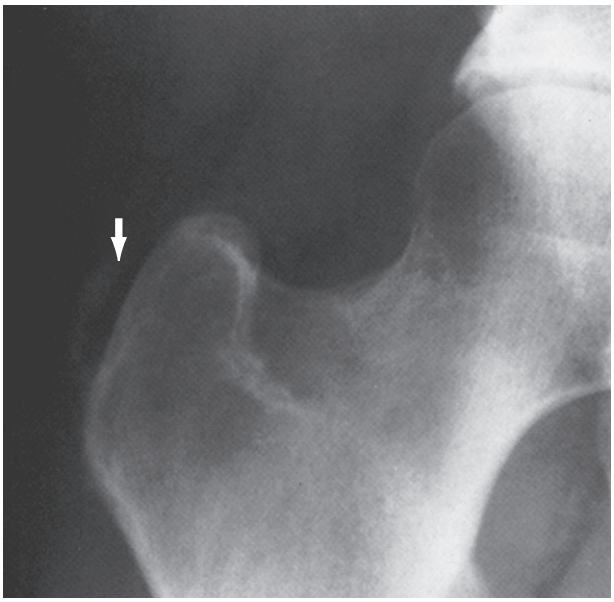


Figure 53-8. Calcific trochanteric bursitis. Faint calcification *(arrow)* in the region of the trochanteric bursa is noted along the lateral cortex of the greater trochanter. (From Harris JH, Harris WH, Novelline RA: The Radiology of Emergency Medicine, 3rd ed. Baltimore, Williams & Wilkins, 1993.)

being osteoid osteoma (Fig. 53-9). Bone lesions may be osteoblastic or osteolytic. Patients may present to the ED with significant bone pain or a large bothersome mass, such as a solitary osteochondroma (Fig. 53-10). Neoplasms place the patient at higher risk for pathologic fracture, especially if the lesions are large or lytic or have eroded the cortex.

■ CLINICAL FEATURES

History

Age and gender are predisposing factors for certain injuries. A detailed description of any antecedent trauma or other precipitating events often is helpful. With trauma, details of the mechanism of injury may aid in predicting injury patterns. With stress fractures, an alteration in physical activity or exercise routine provides a clue to the diagnosis. Systemic illnesses or known metabolic disorders should be noted. Any past steroid use is important to identify because it predisposes patients to AVN in the femoral head. A linear relationship has been recognized between the cumulative steroid dose and the incidence and severity of osteoporosis and hip fracture.[21] Previous cancer, irradiation, and chemotherapy are clues to pathologic fractures.

True hip joint pain is groin pain, so a review of systems should include information that may help in ascertaining the etiology of both typical and atypical groin pain. Atypical pain here may be the result of nephrolithiasis, pelvic inflammation, infection or tumor, inguinal and femoral hernia, or adenopathy from genital or cutaneous infection. A history of low back pain may suggest radiculopathy as the cause of the patient's pain. Elderly patients with a hip fracture sustained in a fall at home may be unable to summon help for hours to days. They often have severe dehydration, electrolyte abnormalities, rhabdomyolysis, and renal insufficiency and require a thorough evaluation of these metabolic parameters before surgery is considered.[22] In addition, the reason for the fall should be determined if possible because it may reveal other comorbid conditions (e.g., syncope, cardiac dysrhythmias, polypharmacy, alcoholism). Sedative or antihypertensive medications predispose elderly patients to falling and should be prescribed carefully. Elderly patients may have sustained additional painful injuries in a fall, most commonly fracture of a vertebral body or wrist. A high index of suspicion for cervical spine and intracranial injuries also must be maintained. Young patients with a hip fracture resulting from high-energy mechanisms have concomitant injuries in 40 to 75% of cases.[16] Pediatric patients with hip pathology will present with knee pain as the sole complaint.

Physical Examination

Management principles for injuries of the hip and femur are the same as those for traumatic injuries elsewhere in the body.

Hypotension is a problem commonly encountered during the initial resuscitation of a multitrauma patient; however, hemorrhagic shock from an isolated femoral fracture should be a diagnosis of exclusion. Although up to 3 units of blood may be lost into the thigh with a femoral shaft fracture, with subsequent hypotension, cardiac, pulmonary, intra-abdominal,

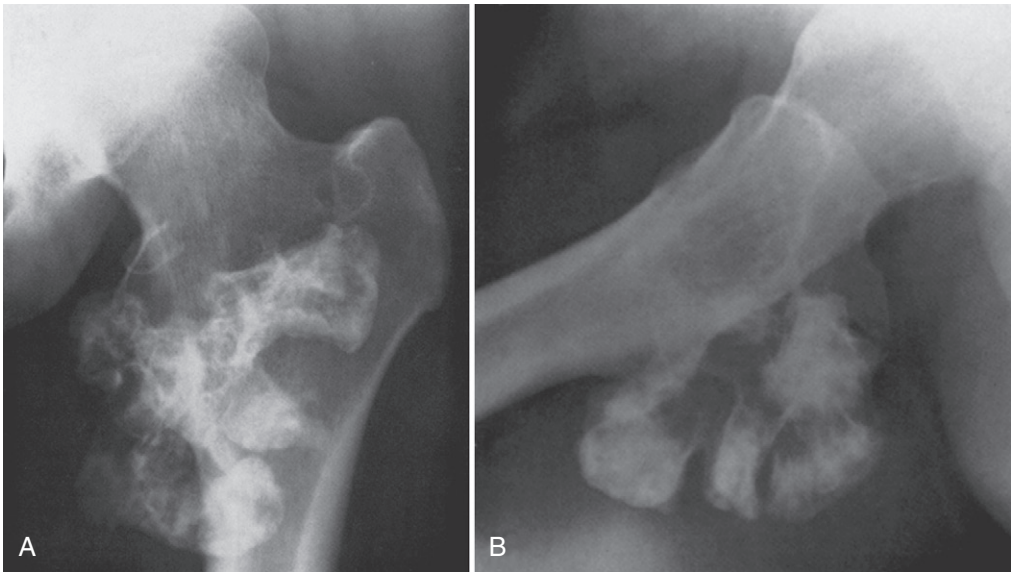


Figure 53-9. Classic radiographic appearance of a solitary osteochondroma of the femur as seen in the anteroposterior (**A**) and frogleg lateral (**B**) views. This lesion is a cartilage-capped bony excrescence, typically arising from the cortex of long tubular bones. (From Harris JH, Harris WH, Novelline RA: The Radiology of Emergency Medicine, 3rd ed. Baltimore, Williams & Wilkins, 1993.)

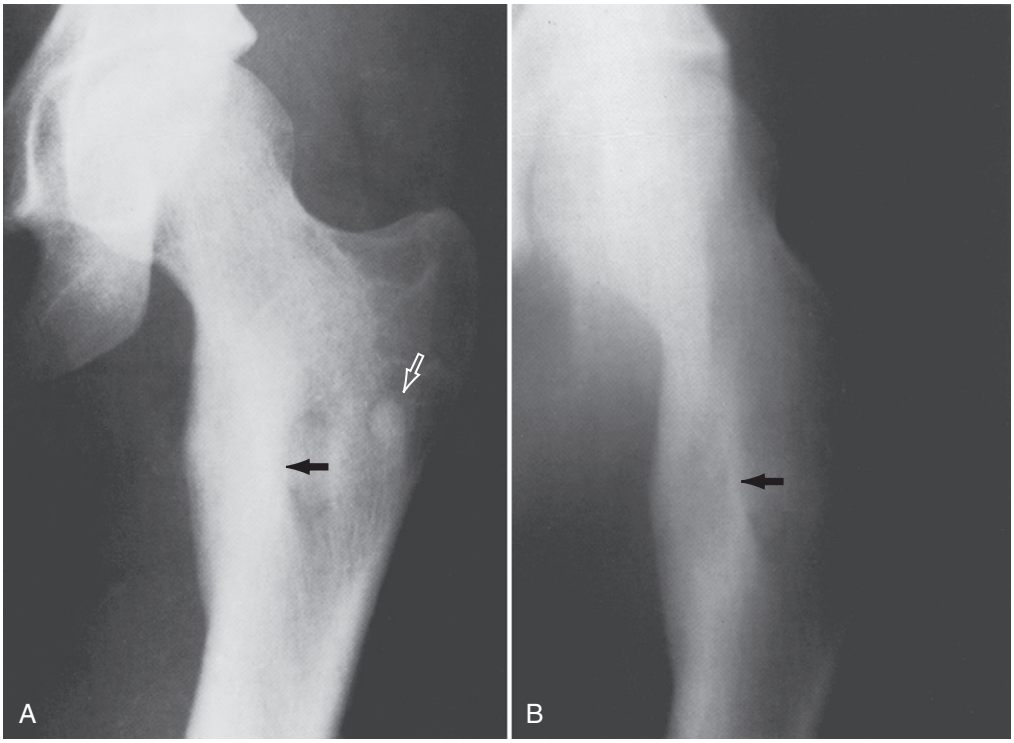


Figure 53-10. Osteoid osteoma of the femur *(solid black arrow)*. **A,** A large focal area of greater density than that of the surrounding femur represents both cortical and endosteal proliferation. The new cortical bone is smooth and sharply delineated, indicative of a nonaggressive process. The *open arrow* represents a bone island. **B,** A frontal-view tomogram demonstrates an oval central radiolucent nidus *(solid black arrow)*. (From Harris JH, Harris WH, Novelline RA: The Radiology of Emergency Medicine, 3rd ed. Baltimore, Williams & Wilkins, 1993.)

and pelvic trauma must first be considered and excluded. Hypotension, neurovascular compromise, or suspicion for multiple injuries will necessitate transfer to a trauma center while initial stabilizing measures are being undertaken in the ED.

After other life-threatening conditions have been addressed, the injured extremity should be carefully evaluated. Visual inspection will reveal any pallor, ecchymosis, asymmetry, or deformity. Abrasions, lacerations, or open wounds are critical because their presence alters the management of concomitant fractures. The position that the leg assumes offers a clue to what may be found radiographically. In the presence of a displaced femoral neck fracture, the leg classically assumes the position of external rotation, abduction, and slight shortening. In intertrochanteric fractures, the leg is found in internal rotation with mild shortening. Shortening or a limb length discrepancy is found with fractures, dislocations, and osteoarthritis. Nondisplaced fractures, including stress fractures, will not produce limb shortening or rotation but will be painful on passive range of motion, particularly internal and external rotation. These fractures also will prevent the patient from being able to perform a straight leg raise. In patients with obvious deformities, range of motion should be deferred until after radiographs have been obtained.

Systematic examination will reveal any tenderness or warmth. Active and passive range of motion and muscle strength, though offering important information, frequently are limited by pain. Detailed neurovascular assessment is vital. Femoral nerve and arterial injury often occurs with subtrochanteric and femoral shaft fractures or anterior hip dislocation. The sciatic nerve can be injured with a hip fracture or posterior hip dislocation. Neurologic examination includes evaluation of light touch and pinprick sensation. Femoral, popliteal, dorsalis pedis, and posterior tibial pulses are assessed. Comparative blood pressures obtained by Doppler examination in the injured and uninjured extremities may be useful in diagnosing occult femoral arterial injuries. If the systolic pressure in the affected extremity is 90% or less (ratio less than 0.9) than that in the unaffected extremity, additional diagnostic studies should be undertaken. Additional diagnostic studies include Doppler flow ultrasound imaging, CT angiography, or angiography alone. The ankle-brachial index also can be similarly determined by comparing the systolic pressures of the affected extremity and of the ipsilateral arm. An index less than 0.9 necessitates further diagnostic studies.[23]

DIAGNOSTIC STRATEGIES

Radiographic Anatomy and Evaluation

Normal radiographic and skeletal anatomy is familiar to emergency physicians (Fig. 53-11). One common inaccuracy merits clarification: The soft tissue linear radiolucencies superolateral and inferomedial to the femoral head and neck do not represent the hip capsule, as is commonly believed. Instead, they represent the fat within the fascial plane covering the gluteus minimus superiorly and the tendon of the iliopsoas muscle inferiorly.[24] Comparison of these lines on the symptomatic side with those on the unaffected side should not be used to determine whether an effusion of the hip is present.

True anteroposterior and lateral radiographs of the femur usually are adequate for the evaluation of potential fractures. The femur should be in as much internal rotation as possible. The fracture line may be very subtle, particularly with femoral neck fractures. Experts have found three methods useful in identifying inconspicuous fractures. The use of Shenton's line is described in a subsequent section on hip dislocations (see Fig. 53-24). (Lowell[25] described a second method, which is illustrated in Fig. 53-15.) In searching for a fracture of the femoral neck, both the medial and lateral cortical margins of the femoral head and neck must be carefully examined for the normal S and reverse S curves seen on radiographs of nonfractured hips. The convex outline of a normal femoral head smoothly joins the concave outline of the femoral neck when in anatomic position. This produces an S curve and a reverse S curve regardless of the orientation of the radiographic projection. A fracture produces a tangential or sharp angle, indicative

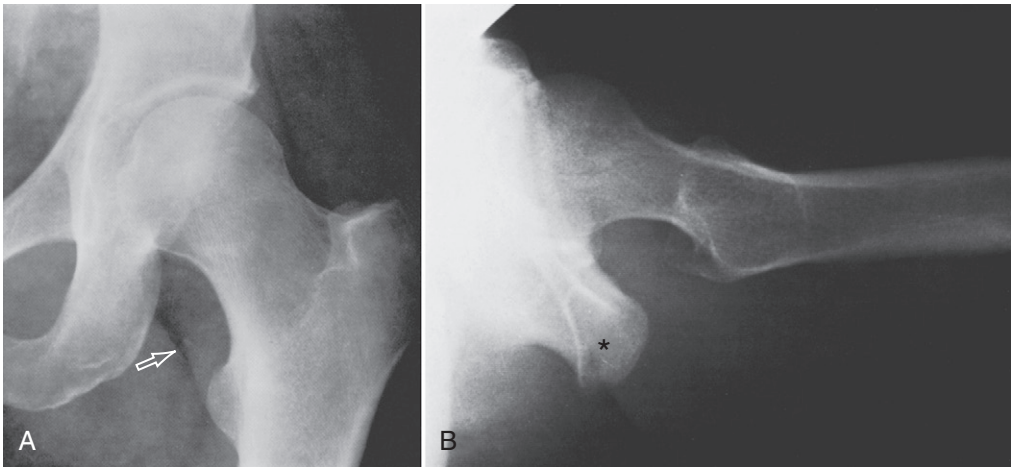


Figure 53-11. Normal radiographic anatomy of the hip. **A,** Anteroposterior view of the normal adult hip. The *open arrow* indicates the edge of the iliopsoas muscle shadow. This muscle lies immediately on the capsule of the hip joint. The small concavity in the center of the femoral head is for the attachment of the ligamentum teres. **B,** Cross-table lateral view of the hip demonstrating the normal relationship of the femoral head to the neck. The *asterisk* indicates the ischial tuberosity. (From Harris JH, Harris WH, Novelline RA: The Radiology of Emergency Medicine, 3rd ed. Baltimore, Williams & Wilkins, 1993.)

of disruption of the normal anatomic relationship. A third method, useful in the evaluation of seemingly unremarkable hip radiographs, is to trace the trabecular lines as they pass from the femoral shaft to the femoral head. These lines will be disrupted as they pass through the fracture site, and such disruption often provides the only if subtle clue. If a fracture is found, radiographs of the knee should be obtained as well. It is a basic orthopedic principle to image the joint above and below any fracture.[23]

Occult Hip Fracture

If radiographs do not show a fracture, the patient must be observed while ambulating. Inability to ambulate or difficulty in ambulation heightens the suspicion of occult fracture. Approximately 2 to 10% of all hip fractures are radiographically "occult" on plain films.[26] Failure to detect these injuries results in increased mortality, risk of subsequent displacement of the fracture, and a higher incidence of AVN.[27] When a painful hip prevents ambulation and plain radiographs do not reveal a fracture, magnetic resonance imaging (MRI) should be performed.[26] In addition, elderly patients with unexplained chronic hip pain for more than 3 weeks may harbor an occult fracture even if they continue to ambulate. T_1-weighted MRI will reveal fracture that was imperceptible at the time of injury with 100% accuracy and has been found to be cost-effective when compared with other strategies.[27] A small study comparing CT scans against MRI in the diagnosis of occult hip fractures revealed a 66% misdiagnosis rate for CT scans.[26] MRI remains the "gold standard" modality for diagnosing occult hip fractures and helps determine the treatment of these fractures (Fig. 53-12).

Bone scans have been useful in these patients, yet such scans lack adequate sensitivity. To identify most occult fractures, the scan must be delayed 72 hours after the injury. The intervening 3 days of bedrest and hospitalization until a bone scan can be performed are costly and not without risk. Various measures should be implemented to diminish the likelihood of deep vein thrombosis.

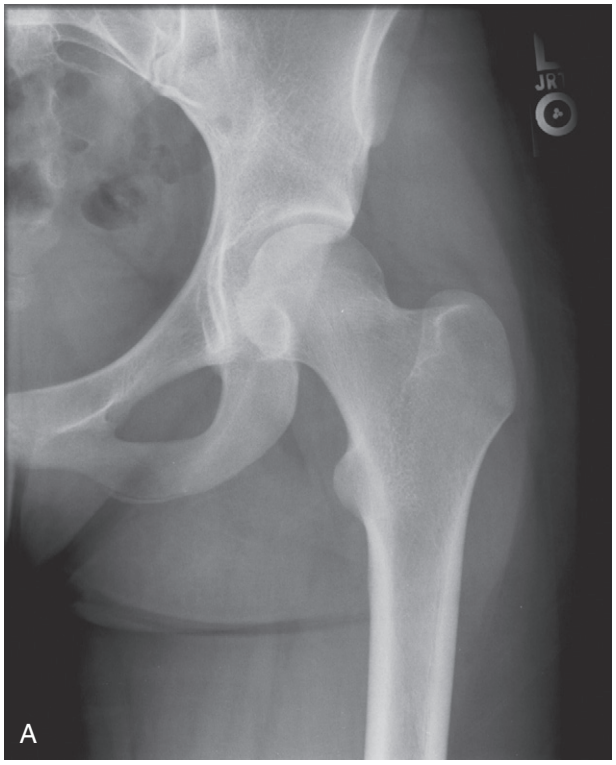
MANAGEMENT

Patients with traumatic fracture of the hip or femur should have blood typed and crossmatched for administration of at least 2 units of blood. Hemodynamic instability may result from dehydration and blood loss of up to 3 units into the fracture site. The potential for significant blood loss and the multiple common associated injuries constitute important justification for this recommendation. Currently, treatment of these fractures is hemiarthroplasty or open reduction and internal fixation for femoral neck fractures. Internal fixation with a sliding compression screw generally is used to treat intertrochanteric fractures. The goal is to promote immediate postoperative mobilization. It has become widely accepted that the risks of surgery in elderly patients are minimal when compared with the risks of prolonged bedrest, deep vein thrombosis, pulmonary embolism, pneumonia, and urosepsis from an indwelling Foley catheter. If possible, the repair is conducted with use of spinal anesthesia to decrease the operative risk. Care of an elderly patient with a hip fracture requires a multidisciplinary approach and often involves coordination of the efforts of the emergency physician, orthopedist, internist, neurologist, and cardiologist to stabilize the patient before surgery. Operative repair should be performed after the patient is resuscitated and is in optimal preoperative condition.

Traction and Immobilization

Emergency rescue personnel often place a Hare splint or similar device that applies traction to the leg before transport if they suspect a femoral fracture. Although such management may provide pain relief and limit blood loss, great care must be given to the proper use of these devices. Prolonged traction during the assessment and management of other injuries can cause or worsen serious neurologic injury in the thigh. The traction used in the field for transport may produce potentially damaging tension on the nerve.

The femoral and sciatic nerves are much more likely to be injured from traction or during surgery than they are from a femoral fracture. Injuries considered to represent contraindications to the use of traction splints include pelvic injuries, patellar fractures or ligamentous knee injuries, and tibia or fibula fractures. Nonhospital health care and emergency rescue personnel should be instructed that traction should not be applied to any open fracture that has exposed bone. Such reduction pulls grossly contaminated bone fragments back into the wound before adequate débridement can be undertaken in the operating room. In patients with a suspected vascular



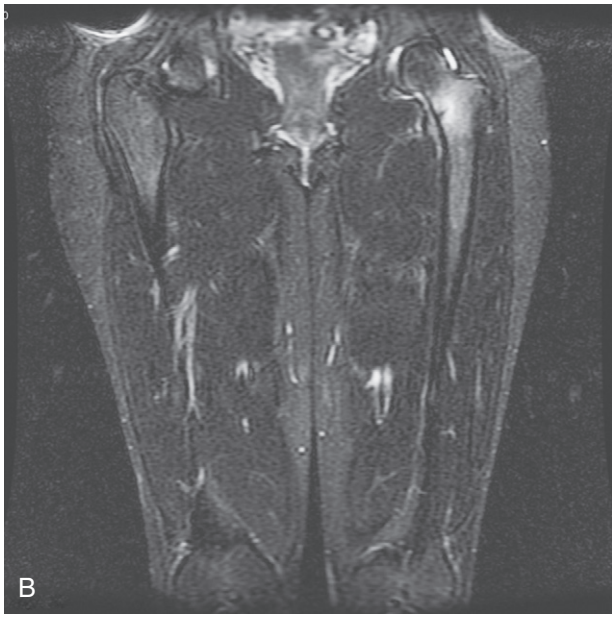


Figure 53-12. The patient complained of hip pain and could not ambulate. **A,** Initial radiographs failed to demonstrate a fracture. **B,** A magnetic resonance image revealed a femoral neck fracture through the compressive trabecular fibers.

injury, traction may potentially decrease the impingement of the fracture fragments on the vessels. A study evaluating patients with multisystem trauma in whom traction splints were placed in the field for femur fractures found concomitant contraindicating injuries in 38% of the cases.[28]

The injured extremity should be immobilized without traction when the patient is moved. The leg may be supported in a position of comfort with a pillow placed under the thigh.

Maintaining the leg in flexion at the hip reduces intracapsular pressure, whereas extension of the leg increases pressure and potential for ischemic necrosis of the femoral head. Accordingly, traction for proximal femur fractures should be discontinued once the patient arrives in the ED. The theoretical advantages for use of traction in the ED are pain control and fracture reduction, making operations easier to perform. A Cochrane systematic review looking at preoperative traction for fractures of the proximal femur in adults found no evidence to support these proposed advantages.[29]

Table 53-2 Classification of Open Fractures

CRITERION	TYPE I	TYPE II	TYPE III*
Wound size	<1 cm	1 to 10 cm	>10 cm
Soft tissue damage	Minimal, if any	Moderate, without nerve, arterial, or periosteal stripping	Extensive muscle devitalization; nerve and arterial involvement often classified as type IIIb
Mechanism of injury	Bone edge pierces outward	Variable	High-energy shotgun blast, high-velocity gunshots

Type I: endosteal or periosteal callus without a definite fracture line on plain radiographs; type II: a definite fracture is identified on plain radiographs, but no displacement; type III: the fracture is displaced.

*Any shotgun wound, high-velocity gunshot wound, segmental fracture, farmyard injury, vascular injury, or crush injury is classified as type III, regardless of wound size.

From Morris JM, Blickenstaff LP: Fatigue Fractures. Springfield, Ill, Charles C Thomas, 1967.

Open Fracture Care

By definition, an *open fracture* is any fracture in which a break in the integrity of the skin and soft tissue allows communication with the fracture and its hematoma. Any nearby wound or break in the skin must be considered to communicate with the fracture. Open fractures are divided into three categories (Table 53-2). *Type I* is characterized by the presence of endosteal or periosteal callus without a definite fracture line on plain radiographs; in *type II*, a definite fracture is identified on plain radiographs, but with no displacement; in *type III*, the fracture is displaced. Type III open fractures may be subdivided according to the amount of nerve, arterial, or periosteal injury present. A bone piercing from the inside outward often causes only a small wound. The contaminated bone tip may then slip deceptively back into the soft tissue; therefore, any break in the integrity of the skin makes the fracture an open one. Open wounds should be irrigated and then covered with sterile saline–moistened gauze.

For all type I open fractures, a first-generation cephalosporin should be administered intravenously. Types II and III require additional gram-negative coverage because of the amount of devitalized tissue and increased gram-negative skin flora found in the groin.[30] This additional coverage could be provided by an aminoglycoside such as gentamicin or tobramycin. The use of perioperative first-generation cephalosporins has been shown to reduce postoperative infection even in closed fractures in patients who are to undergo surgery.[23]

Great care should be taken to identify tetanus-prone wounds so that appropriate prophylaxis can be provided with tetanus immune globulin when indicated. Immunization status should be verified. especially in immigrant populations.

Compartment Syndrome

Because of the thigh's larger volume, compartment syndrome within the thigh is far less common than in the lower part of the leg. When compartment syndrome does occur, only 50% of the cases are associated with a femur fracture.[31] A large amount of bleeding into the compartment is required before the pressure rises above capillary perfusion pressure. It is difficult to clinically differentiate the expected swelling after an injury from early compartment syndrome. Clinical examination and the use of direct compartment pressure measurements can detect the development of compartment syndrome at an early stage.

Pain Management

Systemic Analgesia

It is well known that control of pain in EDs often is inadequate.[32] Clinicians may be more reluctant to administer adequate doses of analgesics in elderly patients because of the potential for respiratory depression with narcotic medications. Nevertheless, pain control should be a high priority during the initial management period.

Femoral Nerve Block

Femoral nerve blocks have been used to treat femoral shaft fractures for more than 50 years. Despite proven effectiveness and a low complication rate, this technique has not been widely embraced by emergency physicians or surgeons.[33] Femoral nerve block is invaluable as an adjunct or alternative to systemic analgesics in patients at risk for hypotension. It has been shown to significantly decrease time to lowest pain score as compared with intravenous narcotics, and patients have been found to require significantly lower doses of narcotics in conjunction with femoral nerve blocks.[33,34] The block can be performed with the assistance of a peripheral nerve stimulator to localize the nerve; however, it also has been shown to be effective when performed by newly trained emergency physicians without the assistance of peripheral nerve stimulators.[34] If a long-acting anesthetic such as bupivacaine is used, the expected onset of analgesia is 15 to 30 minutes, and its duration is 6 to 8 hours.[35]

Careful neurovascular examination should be undertaken and documented before performing the femoral nerve block. After the nerve block procedure, continued assessment of the femoral muscular compartments is advisable to check for the development of compartment syndrome.

Hip Arthroplasty

Background and Epidemiology

Sir John Charnley first described the modern form of total hip arthroplasty (THA) in 1961. Despite many changes in both the design and materials used, Charnley's essential design has been established as the standard.[36] The number of THA procedures performed annually in the United States rose from 65,000 in 1982 to more than 234,000 in 2004. Women account for 62% of THAs in the United States. The most common indication for THA is joint failure resulting from severe osteoarthritis. Other indications include rheumatoid arthritis, certain types of hip fracture, AVN, and certain tumors. Arthritis associated with Paget's disease, trauma, ankylosing spondylitis, and juvenile rheumatoid arthritis also are relative indications for THA or partial hip arthroplasty.

Figure 53-13. Dislocation of the femoral prosthesis in a patient who had undergone a total hip arthroplasty. The femoral head often becomes caught on the rim of the acetabular cup, thereby preventing reduction. Reduction may disrupt or dislocate the acetabular cup.

Outcomes and Complications

THA provides an immediate, substantial reduction of pain and improvement in functional ability and overall quality of life. A 10-year follow-up study of patient outcomes, including gait, perception of pain, physical mobility, sleep patterns, and energy scores, showed positive results in more than 90% of cases.[37] Despite the tremendous success of THA, numerous complications have been reported, aseptic loosening of the prosthesis being the most common. Other complications include component wear, infection, surrounding femoral fractures, and deep vein thrombosis. Postoperative dislocation of the femoral component occurs in 1 to 3% of patients who have had primary THA and in 5 to 20% of patients who undergo revised THA. Generally, flexion past 90 degrees, adduction, and internal rotation place the hip at risk for dislocation. This combination can occur when patients bend at the waist (e.g., to sit on a normal low toilet or to get out of a chair) or cross the legs[38] (Fig. 53-13).

■ SPECIFIC INJURY PATTERNS

Fractures of the Hip and Femur

Avulsion Fractures

The pain of avulsion injuries of the hip may be manifested as referred pain to the thigh; these fractures are most common in adolescents and young adult athletes. The incidence of avulsion fractures is increasing as a result of the growth of competitive sports participation, especially in 14- to 17-year-olds.[39] The muscular origin of this type of injury commonly involves the pelvic apophyses, which may not fully ossify until age 25. Avulsion at the site of the growth plate is the result of sudden

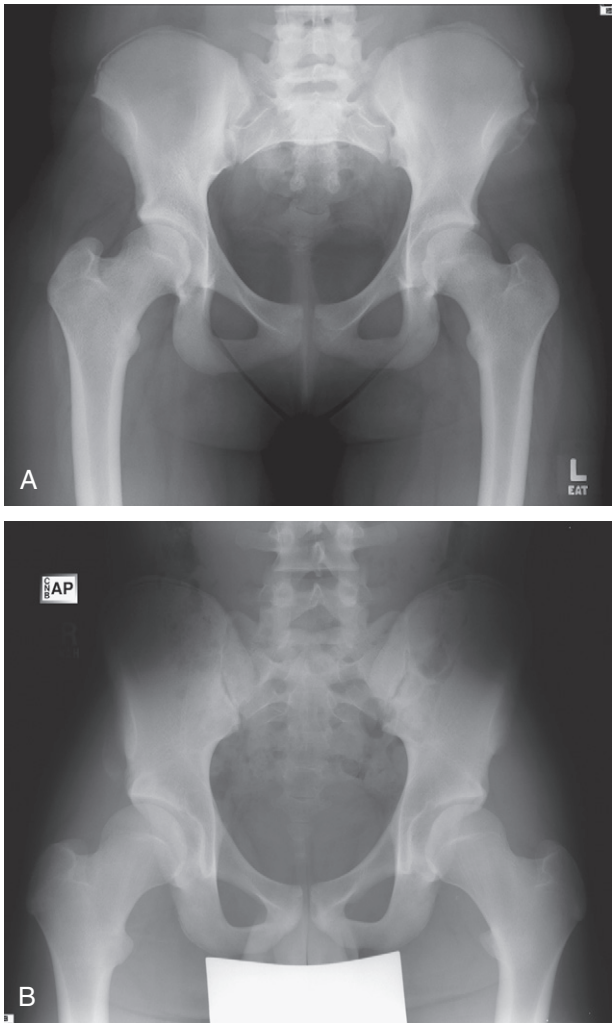


Figure 53-14. **A,** Avulsion fracture of the anterior superior iliac spine by the sartorius muscle. **B,** Avulsion fracture of the anterior inferior iliac spine by the rectus femoris.

maximal muscular exertion. It may occur with rapid acceleration or sudden changes in speed or direction. The athlete classically experiences a sudden piercing pain at the site of injury, along with a "snapping" or "popping," and frequently falls to the ground because of the intensity of this pain. As depicted in Figure 53-14, avulsion at the anterior superior iliac spine (ASIS) involves the separation of a thin piece of bone as the sartorius muscle suddenly contracts (see Fig. 53-14A). The anterior inferior iliac spine (AIIS) is avulsed by the rectus femoris, and the hamstring group may pull off the ischial tuberosity (see Fig. 53-14B). Avulsion fractures of the ASIS and AIIS are managed nonoperatively with conservative treatment. Treatment of avulsion fractures of the ischial tuberosity is more controversial. Most experts recommend conservative treatment for avulsion injuries with less than 2 cm of displacement. Fractures with more than 2 cm of displacement may benefit from operative fixation to prevent nonunion, as well as union with exuberant callus formation.[40]

Proximal Femoral Fractures

Classification Systems

Fractures of the proximal end of the femur have been classified on the basis of their relationship to the hip capsule (e.g., intracapsular and extracapsular), geographic location (neck, trochanteric, intertrochanteric, subtrochanteric, and shaft fractures), and degree of displacement. A working knowledge of the classification system will allow the emergency physician to communicate with the consulting orthopedist regarding the fracture's pattern, stability, and treatment options.

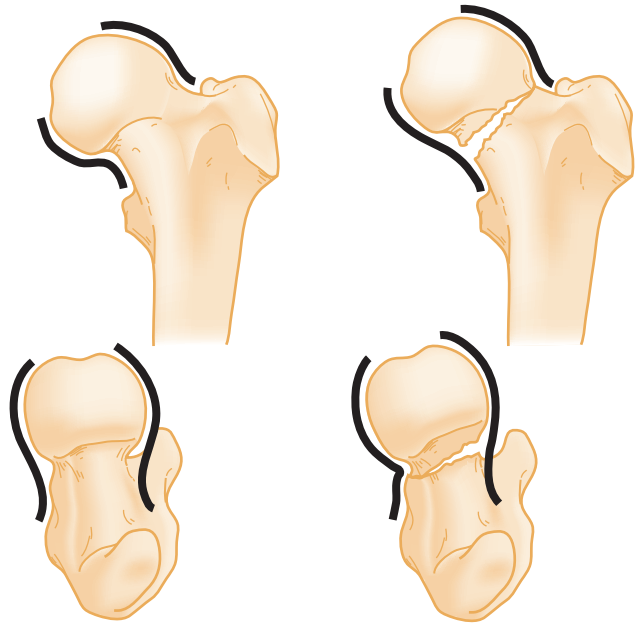


Figure 53-15. Lowell[20] described the normal anatomic x-ray appearance of the femoral head as smooth S and reverse S lines drawn above. The concave outline of the femoral neck meets the convex outline of the femoral head as shown here in various views. Any tangential angle suggests a fracture.

Femoral Neck Fractures

Pathophysiology. Many experts now refer to femoral neck fractures as *insufficiency fractures* in acknowledgment of the major role played by osteoporosis. Age-related bone loss is believed to be the most important etiologic factor in femoral neck fractures.[41] The theory that these fractures result from primary skeletal pathology is supported by the fact that minimal or no injury is associated with most of these fractures. Pathologic fractures from metastatic carcinoma are well described.

Classification. Fractures of the femoral neck originally were divided by location into subcapital and transcervical types. The subcapital fracture line lies just under the dome of the femoral head's articular surface. Although several classification systems formerly were used to describe these fractures, they have been abandoned because of poor inter-rater reliability and limited clinical utility. Currently, femoral neck fractures should be classified as either nondisplaced or displaced fractures.

From 15 to 20% of all femoral neck fractures are *nondisplaced fractures*. The fracture line often may be very subtle. Techniques described for detection of subtle fracture lines may be useful for this reason. Evaluation of the continuity of the subcapital cortical lines, search for an indistinct broad band of increased subcapital density, and identification of the S and reverse S curves (Fig. 53-15) will lead to the correct diagnosis in most cases. In impacted femoral neck fractures, the neck cortex is driven into the cancellous femoral head. Bone impaction lends a certain inherent stability (Fig. 53-16). Because of this inherent stability, two different management approaches have been advocated: early ambulation and internal fixation. AVN, the most common complication, occurs in 20% of

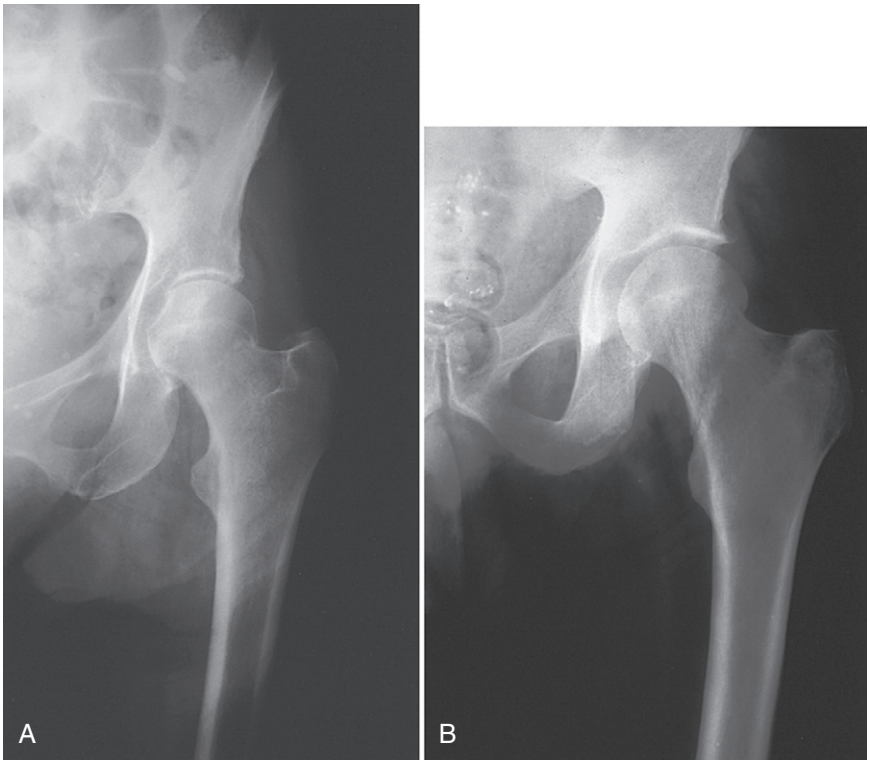


Figure 53-16. **A,** Subtle nondisplaced impacted femoral neck fracture. Use of Lowell's S curves aids in identification. **B,** A nondisplaced femoral neck fracture possesses no stability without impaction.

patients regardless of the type of management. The prognosis for nondisplaced fractures is excellent; 96% of patients heal without complication. Without impaction, a nondisplaced femoral neck fracture possesses no inherent stability and will become displaced without internal fixation.

On initial evaluation, a patient with a *displaced fracture* of the femoral neck lies with the limb externally rotated, abducted, and slightly shortened. The diagnosis is confirmed with plain hip films. To avoid further disruption of the blood supply to the femoral head, range of motion should be deferred unless radiographs fail to reveal a fracture. In all displaced femoral neck fractures, the femoral head is rendered largely avascular, and signs of AVN and collapse may develop over the ensuing several years.

Treatment of these displaced fractures consists of either open reduction with internal fixation, hemiarthroplasty, or THA.

Outcome and Complications. The mortality rate during the first year after a femoral neck fracture is 14%, as compared with 9% for the control population. Factors affecting mortality include age, male sex, psychiatric illness, end-stage renal disease, and congestive heart failure.[42] Institutionalized patients have a death rate three times higher.[43] Complications can be minimized by early reduction, stable internal fixation, and early ambulation.

AVN and nonunion are the two major complications of femoral neck fractures. AVN is the most common complication, despite optimal treatment, because of the complex arterial anatomy. Deep infection in the form of osteomyelitis or septic arthritis is more common with femoral neck fractures because the fracture line extends into the joint. The rate of infection has been dramatically reduced with the use of perioperative antibiotics. Pulmonary embolism is another significant complication and is the leading cause of death 7 days after fracture in all orthopedic patients. Anticoagulation is recommended for at least 10 days after any hip surgery in patients without significant contraindications. Fondaparinux has been shown to be the most effective anticoagulant in this setting.[44]

Intertrochanteric Fractures

Anatomy. The fracture line of intertrochanteric fractures extends between the greater and lesser trochanters of the femur. These injuries are considered to be extracapsular fractures. The fracture line extends through cancellous bone, which has an excellent blood supply. The hip's short external rotators remain attached to the proximal femoral neck, and the internal rotators are attached to the distal end of the femur, thus explaining the position that the leg assumes with this fracture.

Pathophysiology. An intertrochanteric fracture in younger adults usually is the result of high-speed collisions or high-energy trauma, such as falls from heights. An elderly person may sustain this injury during a fall from any height. The fracture lines are the result of both direct and indirect forces. The direct forces act along the axis of the femur and on the greater trochanter as it strikes the ground. Indirect forces are produced as the iliopsoas pulls the lesser trochanter and the abductors pull the greater trochanter; these forces often cause fractures at the site of insertion.

Classification. A large number of classification systems for intertrochanteric fractures have been proposed to predict the possibility of achieving and maintaining stable reduction.[45] A useful system, as borne out by our own clinical experience, designates the fracture according to the number of separate bone fragments produced (Fig. 53-17).

Management. Intertrochanteric fractures carry particular management pitfalls for the emergency physician. Great care must be taken to maintain focus on the entire patient and not on the fracture alone. Hemodynamic instability may result from

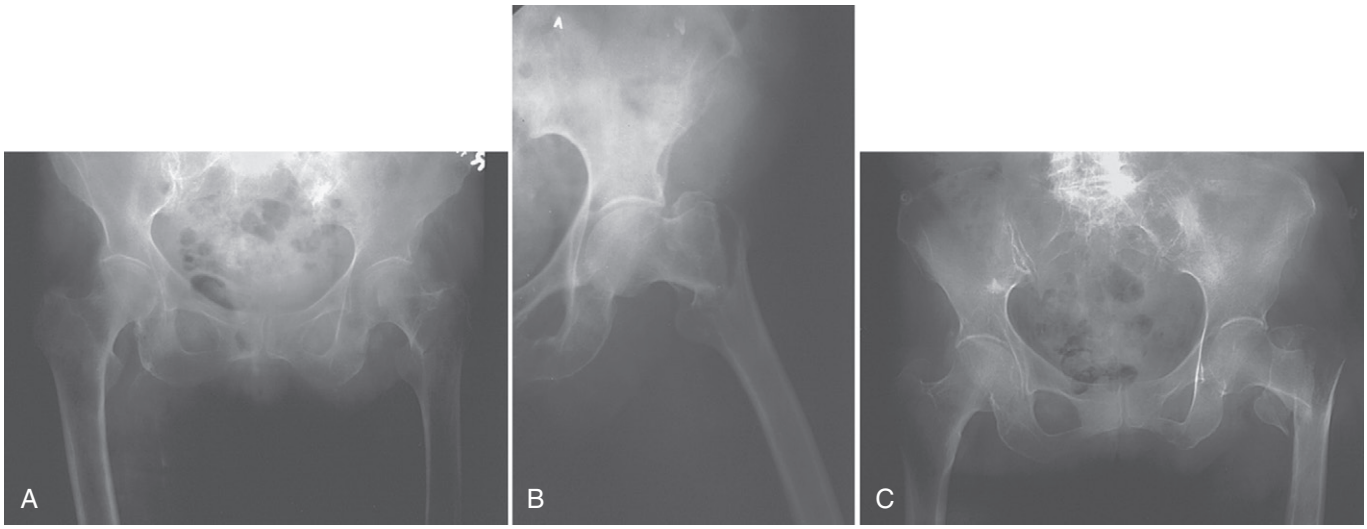


Figure 53-17. The number of parts that the fracture produced classifies intertrochanteric fractures. **A,** Two-part fractures have one part connected to the femoral head and a second part attached to the shaft. **B,** The greater or lesser trochanter also is fractured with three-part fractures. A greater degree of instability is produced because the attached muscles continue to act on the fractured trochanter. **C,** Four-part intertrochanteric fractures involve both trochanters.

dehydration and blood loss of up to 3 units into the fracture site.[46] Poor nutrition before the fall, chronic diuretic use, and decreased oral intake in patients who have to wait until they are found will contribute to the level of dehydration. Up to 70% of these patients are under-resuscitated.[22] Associated distal radial, proximal humeral, and rib fractures and compression fractures of the lumbar and thoracic spine often are overlooked because the femoral fracture distracts the attention of both patient and physician. Spinal compression fractures most commonly involve T12 and L1.

A substantial majority of intertrochanteric fractures will require some type of internal fixation. Such fixation allows rapid mobilization, decreased hospital length of stay, reduced mortality, and improved function.[23] The procedure should be performed on an urgent rather than an emergency basis. Mortality is increased when the patient is taken to the operating room on the day of injury; however, early repair within 24 to 48 hours is associated with a 1-year mortality reduction.[47]

Outcomes. Intertrochanteric fractures have an associated mortality rate of 10 to 30% in the first year. Life expectancy returns to normal among patients who survive that year. Survival is most commonly related to the patient's age and preexisting medical conditions. Additional risks associated with operative treatment include mechanical failure (1 to 16%), implant migration (2 to 10%), and infection (2% to 8%).[48] Mechanical failure and nonunion are much more common in unstable fractures and those that were not adequately reduced. Approximately only one half of patients sustaining these fractures are able to eventually regain their original level of ambulation. Yearly infusion of zoledronic acid beginning within 90 days of hip fracture repair reduces the incidence of new fractures and decreases mortality.[49]

Pathologic Intertrochanteric Fractures

Aggressive treatment is indicated for patients who have pathologic intertrochanteric fractures or impending fractures if their life expectancy is more than a few months. Such treatment with subsequent radiation therapy improves the patient's quality of life, decreases pain, and improves mobility.

Isolated Fractures of the Greater or Lesser Trochanter

Fractures of the greater or lesser trochanter are rare. They occur in women more often than in men and are the result of a fall directly onto the trochanter or avulsion by the iliopsoas muscle. There may be a comminuted fracture involving only part of the greater trochanter or more subtle impaction of the lateral cortex. If avulsed, the fragments are displaced superiorly and posteriorly[23] (Fig. 53-18).

Treatment consists of pain control and early mobilization with crutches; weightbearing is allowed as tolerated by pain. Outpatient management of this injury is possible with satisfactory support for home convalescence. The prognosis is good, and healing generally is excellent.

Subtrochanteric Fractures

Anatomy and Pathophysiology. Subtrochanteric fractures occur between the lesser trochanter and the proximal 5 cm of the femoral shaft. They may accompany intertrochanteric fractures. The subtrochanteric region is composed almost entirely of cortical bone, which lacks the vascularity important to new bone growth and repair. When fractured, it is more likely to be comminuted than bone with a higher cancellous content. Additionally, the greater portion of the biomechanical forces of the femur is transmitted down the curved medial cortex of the femoral shaft. If this cortex is disrupted, the metal hardware undergoes the majority of the stress. This mechanism accounts for the increased incidence of hardware failure when the medial cortex is largely involved.

These fractures characteristically are deformed because of the unbalanced muscle forces. The attachments of the iliopsoas, gluteal, and external rotator muscles consistently produce flexion, abduction, and external rotation of the proximal fragment.

Epidemiology. Subtrochanteric fractures account for 11% of all fractures of the proximal end of the femur. Although 10% of these fractures are caused by gunshots, the usual mechanism of injury is direct blunt trauma.[50] A bimodal distribution for these injuries has been recognized. The first group consists of

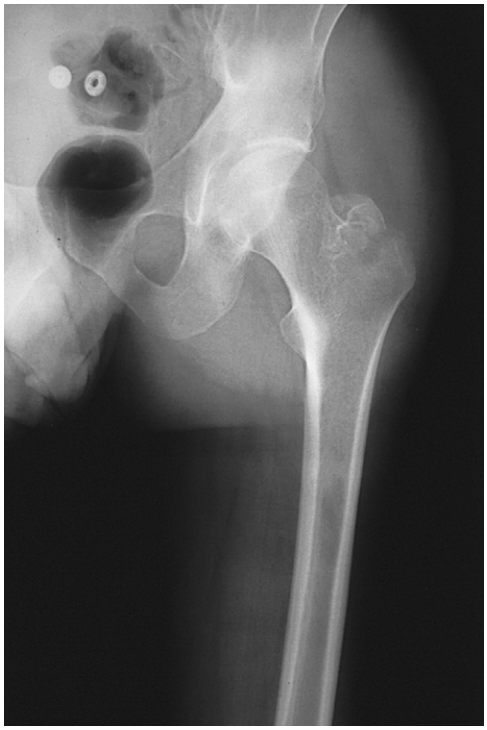


Figure 53-18. Isolated fracture of the greater trochanter. Note that the trochanter is displaced in the typical posterior and superior direction.

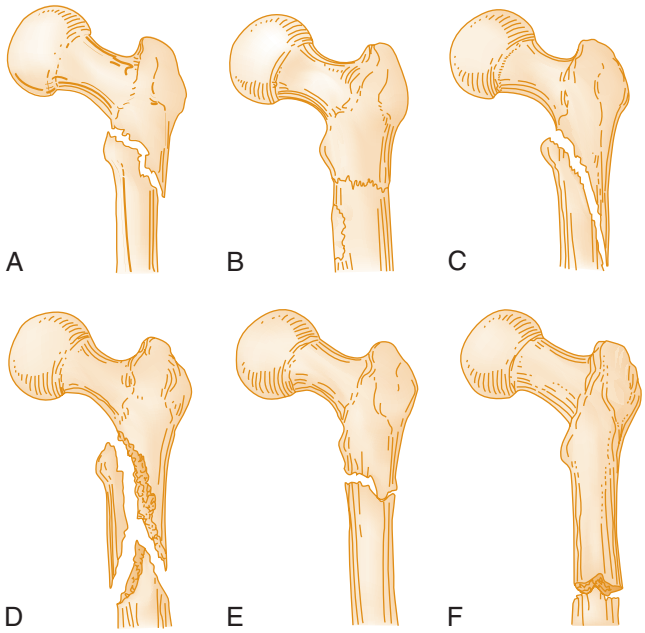


Figure 53-19. Variants of subtrochanteric fractures. **A**, Short oblique fracture. **B**, Short oblique fracture with comminution. **C**, Long oblique fracture. **D**, Long oblique fracture with comminution. **E**, High transverse fracture. **F**, Low transverse fracture.

elderly patients who experience a fall, in whom the fracture occurs through an area of weakened cortical bone. Pathologic fractures from metastatic lesions, Paget's disease, renal osteodystrophy, osteogenesis imperfecta, and osteomalacia are well-recognized clinical entities in these patients. The second group comprises victims of extreme high-energy trauma. In these patients, the subtrochanteric fracture is rarely an isolated injury because of the tremendous force required to produce it. Associated thoracic and abdominal injuries are common and must be aggressively sought to ensure adequate management. From 30 to 50% of patients with subtrochanteric fractures have associated fractures of the pelvis, spine, or other long bones. Stress fractures can occur in this region but are extremely uncommon.

Classification. A variety of classification systems for these fractures have been proposed, although none are widely accepted.[45] From a practical standpoint, it is best to define and describe these fractures by location (*proximal* or *distal*), angle (*transverse*, *oblique*), and the presence of comminution (Fig. 53-19).

Management. Hemodynamic instability may result from blood loss of up to 3 units into the fracture site.[46] Although such blood loss can lead to hypovolemic shock, other causes of hypotension in a trauma patient must be investigated. Open fractures are rare and, when present, are accompanied by significant soft tissue injury. Vascular and neurologic injuries also are uncommon.

Definitive management of subtrochanteric fractures is a complex issue. Maintaining limb length and controlling rotation are difficult. Open reduction with internal fixation generally is the treatment of choice. However, in the rare case with severe comminution or an open, grossly contaminated fracture, nonoperative management may be preferable.[51] Children younger than 10 years also may be managed nonoperatively. The amount of remodeling and growth stimulation occurring in children of this age usually ensures good results without internal fixation.

Outcomes. The bone in the subtrochanteric region is largely cortical and relatively avascular when compared with the cancellous intertrochanteric region. It logically follows that healing is comparatively slow. Comminution is common and increases the likelihood of nonunion. Comminuted and distal subtrochanteric fractures carry a worse prognosis.

Complications include fat embolism in all patients and the adverse effects of prolonged immobilization in the elderly. Reported mortality rates from subtrochanteric fractures range from 9.6 to 13.3%.[51] The violent force and common associated injuries contribute to the high mortality among patients who sustain these fractures.

Femoral Shaft Fractures

Pathophysiology. Femoral shaft fractures are common injuries in young adults after high-energy trauma. As is the case with other femoral cortical fractures, considerable violent force is required to produce a fracture in a normal shaft. Automobile and motorcycle accidents, falls, and pedestrian accidents account for a majority of femoral shaft fractures. The femoral shaft usually fails under tensile strain, and a transverse fracture results. Higher forces produce varying degrees of segmentation or comminution. Open fractures of the femoral shaft are less frequent and are often the result of a gunshot wound. Pathologic fractures occur from a torsional stress that produces a spiral fracture.[52]

Classification. There is no commonly accepted or easily remembered classification for femoral shaft fractures. Location and geometry of the fracture line should be used to describe these fractures. *Transverse*, *oblique*, *spiral*, *wedge*, and *comminuted* are useful terms for describing these fractures.

Clinical Features. Patients often arrive in the ED with the injured extremity immobilized by traction devices, which should be removed while maintaining immobilization of the limb. Neurovascular injuries are rarely associated with closed femoral shaft fractures.[53] Significant hemorrhage into the thigh can occur with a femoral shaft fracture, just as it can with

intertrochanteric and subtrochanteric fractures. Injuries commonly occurring in the presence of femoral shaft fractures include hip fractures, fracture-dislocations, femoral neck fractures, supracondylar femoral fractures, and patellar fractures.[54] Almost half of femoral shaft fractures have associated ligamentous damage in the knee. If the patient has a femoral fracture, pain often prevents adequate evaluation of knee stability. Any attempt to evaluate the stability of the knee acutely will result in additional pain and hemorrhage without providing useful, reliable information.

Management. Internal fixation with intramedullary rods has been demonstrated to shorten both hospitalization and total disability time with most femoral shaft fractures. The vast majority of femoral shaft fractures heal well in time, regardless of the mode of treatment. Severely comminuted fractures are more likely to be treated by closed reduction.

Outcomes. Femoral shaft fractures have close to a 100% union rate, and most patients are able to return to work after approximately 6 months. Even a minor degree of limb shortening or malalignment can lead to posttraumatic arthritis.[55] Refracture is a rare occurrence that is most likely at two times during the healing process: during early healing and callus formation or during the brief period after the hardware is removed. After the hardware removal, the unsupported bone is required to bear the entire weight of axial loading and is at risk for refracture.

Fractures with Minimal or No Trauma

Most patients who arrive in the ED with hip or thigh pain will provide a clear history of a traumatic event. Hip or knee pain in the young, in athletes, and in the elderly deserves investigation, even when minimal or no trauma has been reported. This patient population commonly has occult hip pathology and occasionally femoral pathology. Although senile osteoporosis is the leading cause of femoral neck fractures after minor trauma, pathologic fractures of the femur may result from metastatic, metabolic, or endocrinologic disease.[56] The incidence of fracture in patients with hyperthyroidism is 12%.[57]

Stress Fractures

Pathophysiology. Stress fracture of the femoral neck was first reported in 1905 by Blecher.[58] Stress fractures occur when normal bone is repeatedly subject to submaximal forces. This recurring stress stimulates the bones to remodel and strengthen. In a stress fracture, osteoblasts are unable to lay down new bone and remodel fast enough, so the bone fails. Stress fractures can also occur in diseased bone when it is subjected to repeated minimal stress.[59]

Clinical Features. The symptoms of a stress fracture of the femoral neck often are so subtle that they may be mistaken for muscle strain or an overuse injury. Early symptoms frequently include morning stiffness and aching in the hip on the first steps after a period of rest. The pain gradually increases during prolonged exercise and may reach the point at which bearing weight becomes impossible. Pain is felt in the groin or along the medial aspect of the thigh toward the knee.

On examination, a painful limp is obvious. This painful or *antalgic* gait is characterized by shortening of the stance phase of the injured extremity. No obvious external rotation or shortening of the leg is seen; the patient experiences only minor discomfort with active or passive motion, except at the extremes of flexion and internal rotation. Tenderness is minimal because of the large amount of soft tissue coverage at the femoral neck.

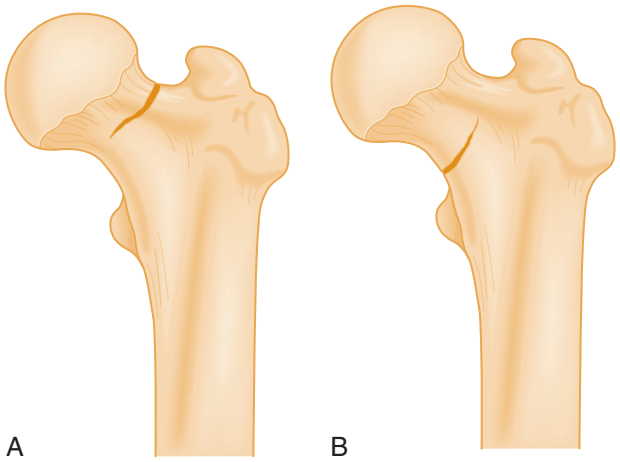


Figure 53-20. Schematic illustrating femoral neck fractures through the tensile (**A**) and compressive (**B**) trabecular fibers.

Diagnostic Strategies. Radiographs are helpful if they demonstrate a fracture, but findings often are negative until 10 to 14 days after the injury.[23] Endosteal or subperiosteal callus develops at the fracture site during this period. In addition to the standard anteroposterior and lateral views of the hip, oblique views may delineate the fracture line. Close attention should be paid to the trabecular fibers of the femoral neck. A stress fracture often can be identified as an isolated disruption of either the tensile (lateral aspect of the femoral neck) (Fig. 53-20A) or the compressive (medial aspect of the femoral neck) (Fig. 53-20B) trabecular fibers. If a fracture is suspected clinically but radiographic findings are negative, the next step is MRI.[27] If a fracture is found, the contralateral hip should be extensively evaluated because of the significant incidence of bilateral stress fractures.

Management. Treatment of stress fractures of the femoral neck is determined by the involvement of the compressive or tensile aspect. Compressive-side fractures involving less than half of the cortex are inherently stable and can be treated conservatively with partial weightbearing with crutches. Tension-side fractures and compressive-side fractures involving more than half the cortex are considered unstable and at risk for displacement. These fractures should be treated operatively with screw fixation.[60]

Other Causes of Pain

Considerations in the diagnosis of atraumatic pain of the hip and thigh are listed in Box 53-1.

Dislocations and Fracture-Dislocations of the Hip and Femur

Injury Patterns

Epidemiologists have identified injury patterns in victims according to the mechanism of injury.[61] Pedestrians who are struck by a car have head, chest, pelvic, arm, and femur injuries. Motorcyclists tend to sustain pelvic and ipsilateral leg injuries. A person who stumbles and falls seldom has major associated injuries. Each of these main categories of injury is discussed next.

Hip Dislocations

Dislocations and fracture-dislocations of the hip are two of the few true orthopedic emergencies. The hip joint possesses

BOX 53-1 DIFFERENTIAL DIAGNOSIS OF A PAINFUL HIP WITHOUT OBVIOUS FRACTURE

Referred pain (lumbar spine, hip, or knee)
Avascular necrosis of the femoral head
Degenerative joint disease or osteoarthritis
Herniation of a lumbar disk
Diskitis
Toxic synovitis of the hip
Septic arthritis
Bursitis
Tendonitis
Ligamentous injuries of the knee or hip
Occult fracture
Slipped capital femoral epiphysis
Perthes' disease
Tumor (lymphoma)
Deep venous thrombosis
Arterial insufficiency
Osteomyelitis
Iliopsoas abscess
Retroperitoneal hematoma
Inguinal hernia
Inguinal lymphadenopathy
Genitourinary complaints
Sports-related hernia

impressive inherent strength and stability; thus, considerable force is required to produce these injuries. With this understanding, a hip dislocation serves as a "red flag" for multisystem injury and should prompt a diligent search for other occult injuries. Serious associated injuries are found in up to 95% of patients with a dislocated hip.[62,63] Knee fractures, ligamentous injuries, and dislocations are present in up to 30% of patients sustaining a hip dislocation.[64] It is highly recommended that in the presence of this type of injury, patients be managed as major trauma victims.

Mechanism and Biomechanics. Traumatic hip dislocations occur primarily in patients sustaining severe multisystem trauma, most often as a result of high-speed motor vehicle crashes. Failure to use seat belts is a significant risk factor. Other less common mechanisms include falls, sports injuries, and pedestrians struck by automobiles.

Posterior dislocations are almost always the result of motor vehicle crashes. A seated vehicle occupant typically has the hip adducted, flexed, and internally rotated at the time of impact. As the knee strikes the dashboard, the force is transmitted through the femoral shaft to the femoral head. With sufficient force, the femoral head dislocates posteriorly. Anterior dislocations result from forceful extension, abduction, and external rotation of the femoral head. These forces lever the head up out of the acetabular cup. Such dislocation most often occurs after a motor vehicle crash when the occupant has the hip abducted and externally rotated at the time of impact. It may also result from a fall or sports injury when the hip is forcefully hyperextended.

Classification. The relationship of the femoral head to the acetabulum is used to classify dislocations into anterior, posterior, central, and inferior types. A fracture-dislocation includes an associated fracture of the acetabulum or femoral head. Posterior dislocations (Fig. 53-21) account for 80% to 90% of cases. Anterior dislocations (Fig. 53-22) are seen in 10 to 15% of patients. In anterior dislocations, the femoral head may dislocate medially toward the obturator foramen (obturator dislocation) (Fig. 53-23) or laterally toward the pubis (pubic dislocation). Central dislocations, which occur in 2 to 4% of cases, are not true dislocations because the entire femoral head is forced centrally through a comminuted fracture of the acetabulum. Inferior dislocation (luxatio erecta) of the hip is a very rare condition that occurs almost exclusively in children younger than 7 years of age.

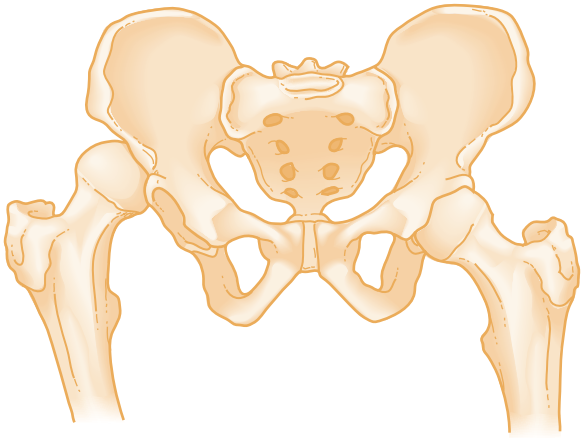


Figure 53-21. In a posterior dislocation, the hip is internally rotated and the lesser trochanter is superimposed on the femoral shaft. Failure to visualize the lesser trochanter on the anteroposterior projection identifies a posterior dislocation.

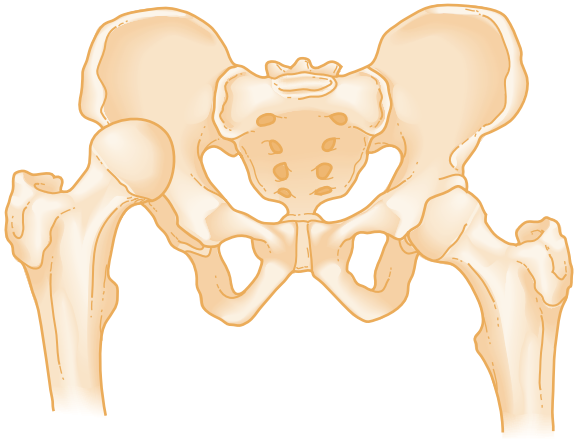


Figure 53-22. In an anterior dislocation, the hip is externally rotated and the lesser trochanter appears in profile. The hip is farther from the x-ray cassette than the unaffected side and may appear larger because of the beam's projection.

Clinical Features. The position of the injured extremity may provide valuable clues in the evaluation of a hip dislocation. A patient with a posterior dislocation typically holds the hip flexed, adducted, and internally rotated. The knee of the affected extremity rests on the opposite thigh. The extremity generally is shortened, and the greater trochanter and buttock may be unusually prominent. By contrast, a patient with an anterior dislocation holds the hip in abduction, slight flexion, and external rotation. These physical findings may be absent in patients with an associated ipsilateral femoral shaft fracture.

The neurovascular examination should focus on the sciatic nerve and femoral vessels. Sciatic palsy is present in approximately 10% of patients with hip dislocation and most commonly involves the peroneal nerve branch. The most sensitive clinical sign of peroneal nerve palsy is weakness of the exten-

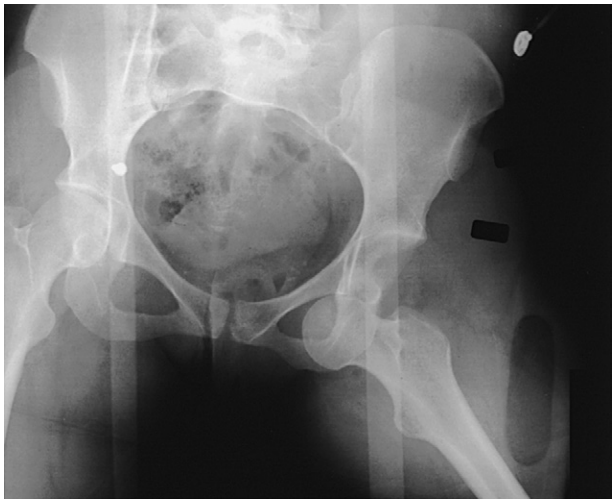


Figure 53-23. Radiograph of obturator dislocation.

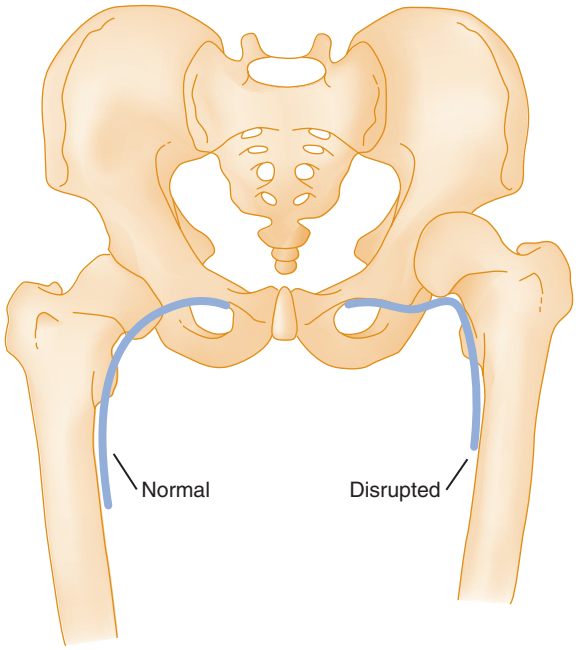


Figure 53-24. Shenton's line is a smooth curved line drawn along the superior border of the obturator foramen and medial aspect of the femoral metaphysis. Disruption of this line should raise suspicion of a femoral neck fracture or hip dislocation.

sor hallucis longus; other signs include weakness of dorsiflexion and numbness or tingling over the dorsum of the foot. The femoral vessels and nerve are particularly prone to injury after an anterior dislocation.[65]

Diagnostic Strategies. Radiologic investigation begins with an anteroposterior view of the pelvis. This view alone will identify a majority of hip dislocations. An anteroposterior pelvis film should be obtained in all trauma patients with the aforementioned deformities. The anteroposterior radiograph should include the entire pelvis and the proximal third of the femur to allow comparison of both hips. When a dislocation is found or suspected, a lateral view of the hip will provide additional definition of the injury.

Although most hip dislocations are seen clearly with these two views, several more subtle radiographic signs may assist physicians in making a confident diagnosis. The first indicator involves the position of the lesser trochanter. Because a posteriorly dislocated hip is internally rotated, the lesser trochanter is superimposed on the femoral shaft and is not seen on the anteroposterior projection. By contrast, an anteriorly dislocated hip is externally rotated and the lesser trochanter appears in profile. The second clue is found in the size of the femoral head. Because a posteriorly dislocated hip is closer than the unaffected side to the x-ray cassette, it appears smaller. The converse is true in anterior dislocations, in which the hip is farther from the x-ray cassette than the contralateral side is and thus appears larger. The third finding relates to the integrity of Shenton's line (Fig. 53-24). This line is a smooth, curved line drawn on the radiograph along the superior border of the obturator foramen and medial aspect of the femoral metaphysis. Disruption of this line should raise suspicion for a femoral neck fracture or hip dislocation.[66]

An obvious dislocation may distract the emergency physician from a search for concomitant fractures. Examination of the trabecular pattern can identify associated fractures of the acetabulum and femoral head, neck, or shaft. It is important to identify acetabular fractures before closed reduction is attempted because intra-articular bone fragments may interfere with effective reduction.[67] Although these fractures may make the reduction more difficult, their presence is not a contraindication to reduction.

Management. Hip dislocations constitute a true orthopedic emergency, and reduction should be performed within 6 to 12 hours. The earlier the reduction, the better the results. The incidence of AVN, traumatic arthritis, permanent sciatic nerve palsy, and joint instability logarithmically increases with the length of time for which the hip remains dislocated.[67,68]

The timing and method of reduction are dependent on the overall condition of the patient, the type of dislocation, and the presence or absence of associated fractures. In cases of simple dislocation, closed reduction should be attempted first. Although some clinicians recommend that this procedure be performed with the patient under general anesthesia, this delay, with its associated increase in the rate of AVN, is not warranted when moderate sedation in the ED is readily available. If the emergency physician chooses to attempt closed reduction, the principles of moderate sedation and monitoring should be followed. The primary contraindication to closed reduction is the presence of a femoral neck fracture. Another relative contraindication is the presence of fractures in the dislocated extremity, because such fractures preclude application of traction to the limb. Techniques of closed reduction are described next.

Reduction Techniques. The Stimson technique and the Allis technique are the methods most commonly used for reduction of posterior hip dislocations[23] (Fig. 53-25). The Allis technique usually is effective for both posterior and obturator dislocations (Fig. 53-26). It is perhaps the most commonly used method for hip reductions in the ED.

Allis technique for reduction of posterior hip dislocation

1. The patient is placed in the supine position, and the pelvis is stabilized by an assistant.
2. With the knee flexed, the operator applies steady traction in line with the deformity.
3. The hip is slowly brought to 90 degrees of flexion while steady upward traction and gentle rotation are applied.
4. The assistant pushes the greater trochanter forward toward the acetabulum.
5. Once reduction is achieved, the hip is brought to the extended position while traction is maintained.

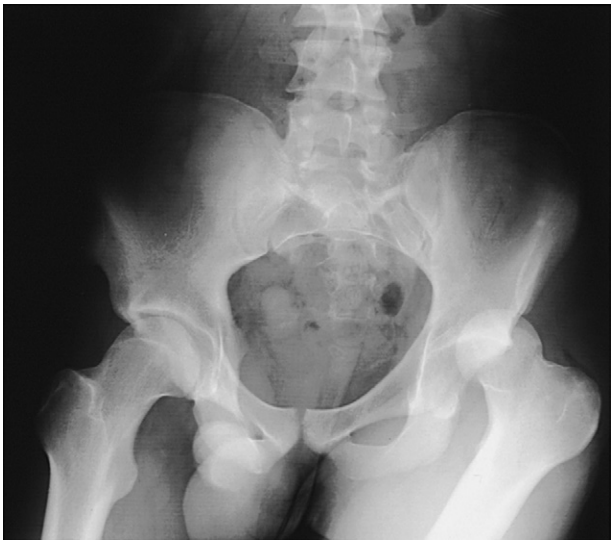


Figure 53-25. Radiograph of posterior dislocation identified by loss of the lesser trochanter on the anteroposterior view.

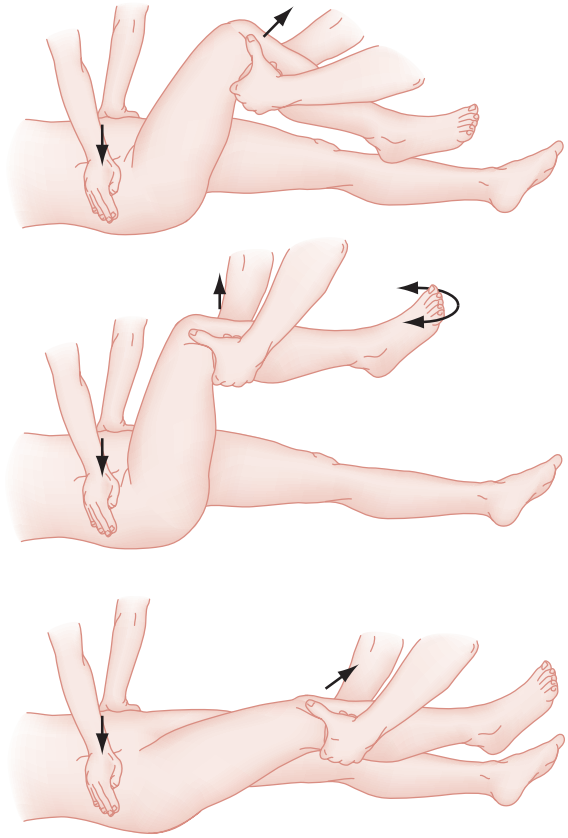


Figure 53-26. The Allis technique for hip reduction. See text for a description of this method.

The Stimson technique (Fig. 53-27) uses the weight of the limb and the force of gravity to reduce the dislocation and is relatively atraumatic. Although the Stimson technique generally is effective, placing an acutely and often multiply injured trauma patient in the required prone position may be a challenge. Adequate radiographic clearance of the spine usually has not yet been accomplished, and the administration of sedatives and analgesics in a prone patient has inherent risks.

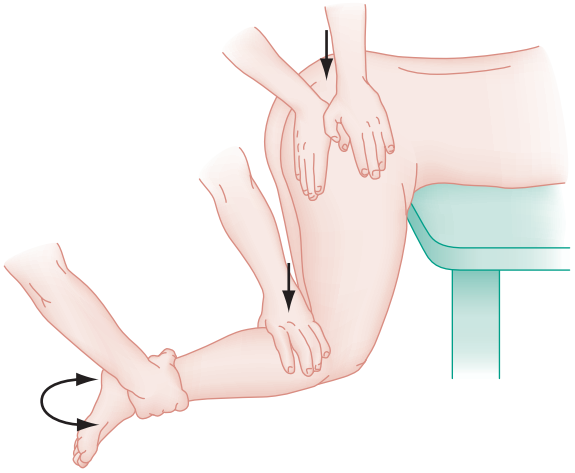


Figure 53-27. Stimson's technique for hip reduction. See text for a description of this method.

Stimson technique for reduction of posterior hip dislocation

1. The patient is placed prone with the leg hanging over the edge of the bed. The hip and knee are flexed at 90 degrees.
2. An assistant stabilizes the pelvis.
3. The operator applies steady downward traction in line with the femur.
4. The femoral head is gently rotated, and the assistant pushes the greater trochanter anteriorly toward the acetabulum.
5. Once reduction is achieved, the hip is brought to the extended position while traction is maintained.

Other recently described techniques for closed reduction of posterior hip dislocations include the Rochester method,[69] the Whistler method,[70] and the traction-countertraction technique.[71]

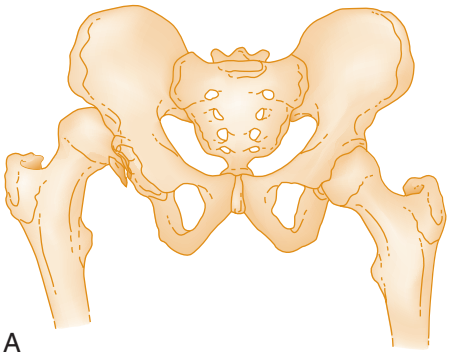
Closed reduction of a pubic dislocation can be quite difficult. The anterior position of the femoral head will resist flexion, making the Allis technique impossible. We recommend reduction with the following sequence of maneuvers.

Technique for reduction of pubic dislocation

1. The patient is placed in the supine position.
2. Longitudinal traction is applied in line with the deformity.
3. The hip is hyperextended and internally rotated as an assistant applies downward pressure on the femoral head.

Although prompt anatomic reduction is clearly desirable, multiple attempts at reduction in the ED should be avoided. Difficulty with reduction usually is the result of incarceration of a tendon, a capsular structure, or an unrecognized osteochondral fragment that is blocking reduction. In the case of an irreducible dislocation, closed reduction with the patient under general anesthesia or an open reduction procedure often is required.

Postreduction Management. After closed reduction, the hip should be tested for stability, which is accomplished by gently taking it through a full range of motion to see whether it will redislocate. After testing has ensured stability, the injured extremity should be placed in a knee immobilizer and an abduction pillow should be applied to prevent repeat dislocation. An anteroposterior radiograph of the pelvis should be obtained to verify the adequacy of reduction. The radiograph should be carefully inspected to verify that the femoral head is in the acetabulum, the shaft of the femur is in neutral position, Shen-



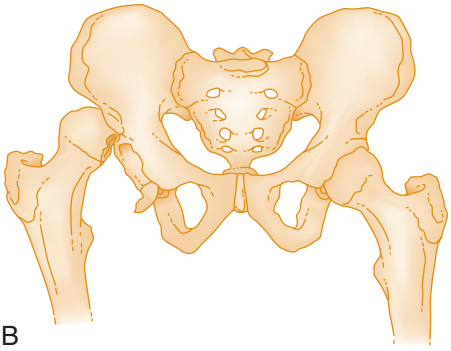
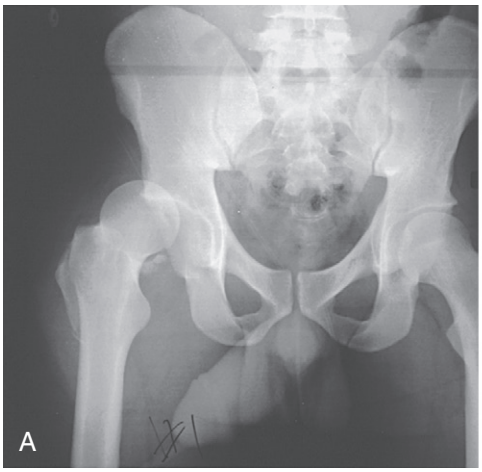


Figure 53-28. **A**, A fracture through the femoral head is seen with this anterior hip dislocation. **B**, Incomplete reduction is identified by examination of the joint space. This space should be the same width as in the unaffected joint. Asymmetry signals an entrapped intra-articular fragment, which should be verified by computed tomography scan.



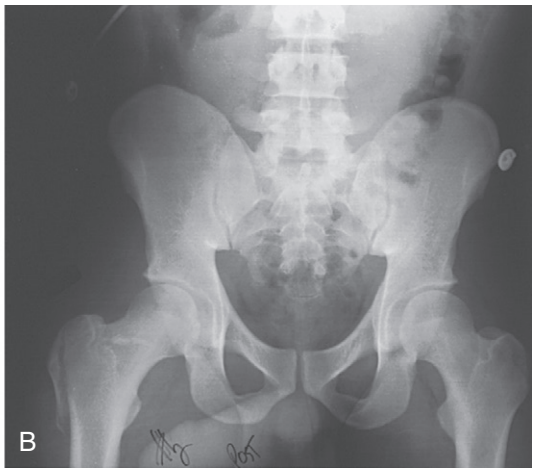


Figure 53-29. **A**, Anterior hip dislocation is identified as the lesser trochanter is brought into profile. Note the fracture of the lateral aspect of the greater trochanter. **B**, A postreduction radiograph demonstrates adequate reduction with symmetrical joint spaces.

ton's line is intact, and the profile of the lesser trochanter is well visualized. The intra-articular space should be symmetrical and, when measured, of the same depth as in the unaffected joint. Asymmetry signals an entrapped intra-articular fragment and is an indication for CT scanning (Fig. 53-28).

Outcomes. The precarious blood supply to the femoral head is particularly important with regard to the long-term consequence of hip dislocations. The development of AVN of the femoral head has been reported in 1 to 17% of dislocations.[68] Other risk factors for the development of AVN include the total dislocation time, the severity of the injury, the number of reduction attempts, and presence of comorbid conditions.

Fracture-Dislocation of the Femoral Head

Epidemiology and Mechanism. A small subset of hip dislocations are associated with fractures of the femoral head (Fig. 53-29A). Femoral head fracture occurs in 22 to 77% of anterior hip dislocations and in 10 to 16% of posterior hip dislocations.[72] These injuries are almost always the result of high-speed vehicular trauma. Because of the tremendous force required to produce this injury pattern, coexistent multisystem trauma is the rule.

When a femoral head fracture and hip dislocation coexist, patients assume the position typical for the dislocation. Hip mobility is markedly reduced, and pain usually is severe. After initial stabilization, the involved extremity should be carefully examined for associated fractures of the femoral shaft and knee. The neurovascular examination should assess for femoral or sciatic nerve injury. Radiographs should be evaluated carefully for any femoral head fracture in all patients with hip dislocations. Evidence for fracture of the femoral head can be subtle. These fractures may be detected on radiographs by following the curve of the dislocated head and the acetabular cup to search for a small fragment that may otherwise be overlooked. Known or suspected injuries can be further defined by CT or MRI.[72]

In most cases, satisfactory results can be obtained with closed reduction (see Fig. 53-29B).[67] Several experts recommend obtaining a CT scan of the hip before closed reduction to further define the injury and locate fracture fragments.[67] If the hip cannot be reduced by manipulation or if reduction of the femoral head fragment is unsatisfactory, open reduction will be required.

Dislocation of Hip Prosthetics

An increasing number of patients have undergone hip arthroplasty. In addition to those procedures performed for treatment of femoral neck fractures, more than 230,000 patients undergo elective primary THA each year.[73] Postoperative dislocation of the prosthesis is a common complication that occurs in 1 to 3% of patients with primary THA and in 5 to 20% of patients with a revised THA.[74] Although most dislocations take place within 3 months of surgery, "late dislocations" have been reported up to 10 years after the operative procedure; such dislocations can result from major trauma or from trivial events (e.g., rising from a seated position). Posterior dislocations account for 75 to 90% of cases (see Fig. 53-13).[63] Reduction techniques for prosthetic hip dislocations are identical to those described earlier. Consultation with an orthopedic surgeon is essential for safe reduction and development of a

long-term treatment plan for the patient. Reduction of the prosthesis does not carry the same urgency as for reduction of a dislocated hip because there is no risk for the development of AVN once the femoral head has been replaced. Traction on the sciatic nerve can occur, however, making early reduction more compelling. In addition, the reduction itself carries the unique dangers of loosening of the components, fracturing of the surrounding bone, and movement of the acetabular cup; reduction is best performed with an orthopedic consultant.

Soft Tissue Injuries

Soft tissues may be subject to muscle or tendon strain or contusions from misuse, overuse, or accidental trauma. Rupture, hemorrhage, or myositis ossificans may develop in muscles.[75]

Muscular Injuries

Strenuous exercise in a poorly conditioned person, sudden exertion, and direct trauma all may traumatize soft tissues. Cold temperature, vascular or infectious disease, fatigue, and poor training are known predisposing conditions for this injury.[76] Predisposing infectious diseases include trichinosis, tuberculosis, and typhoid fever.

A detailed classification system of muscular injuries has been devised, but it is of little clinical significance for the emergency physician. Classification of complete and partial tears is reasonable and of greater clinical utility. Partial tears are reversible injuries that are aggravated by movement or tension. Mild spasm, swelling, ecchymosis, and tenderness cause minor loss of function and strength. Complete tears produce a palpable depression, and the torn muscle edge also is often palpable. Other possible findings include severe spasm, swelling, ecchymosis, tenderness, and loss of muscle function. In significant muscle strains, radiographs are needed to evaluate for the possibility of an accompanying bone avulsion injury.

Initial management of incomplete tears traditionally includes the local application of ice for the first 48 hours, followed by heat.

Compressive wraps cause distal venostasis with the potential for distal venous clot formation and do not significantly decrease recovery time. A regimen of nonsteroidal anti-inflammatory agents to achieve sufficient analgesia is important for recovery and patient satisfaction. Muscle relaxants may be useful when the injury is accompanied by muscular spasm. In general, complete rest of the affected muscle should be maintained, with the recommendation of "weightbearing as pain tolerated." This progressive muscle loading can be started within 3 to 5 days once sufficient scar has formed. In order to prevent reinjury, the muscle loading should be limited by the patient's pain. Any patient with significant injury should be referred for physical therapy.

A complete muscle tear is a serious condition. Consultation plus follow-up care with an orthopedic surgeon or sports medicine specialist is vital for these patients.

Sports Injury Patterns

Athletes commonly experience muscular injury from accidents and overtraining. The two most common injuries involve the hamstrings and the quadriceps.

The Hamstrings

Hamstring muscle strains are common in sports involving running and sudden acceleration. The injury is accompanied by sudden intense pain in the posterior of the thigh. Any active or passive motion at the hip is poorly tolerated because of the intense pain that movement causes. Ischial avulsion fractures can occur, and pelvic radiographs should be obtained if the exam reveals bony tenderness. Crutches and toe-touch weightbearing are recommended until the patient is evaluated by a physician trained in sports medicine. *Toe-touch weightbearing* refers to walking with crutches while the toes of the injured extremity rest on the ground without placing any weight on it. Appropriate weight-training programs have been shown to speed rehabilitation of this injury.[75] Complete recovery from a hamstring muscle strain may take weeks to months.

The Quadriceps

The quadriceps is the most common muscular group to sustain complete tears. This injury occurs when the muscles are contracted suddenly against the body's weight, as may occur when an athlete slips or stumbles and attempts to avoid a fall. Ambulation is significantly affected. There is pain with active and passive knee extension. In significant tears, the patient may be unable to actively extend the knee or maintain its extension against gravity. A palpable depression just proximal to the superior pole of the patella suggests a complete tear. It is imperative to document an intact patellar mechanism on exam, because a complete tear of the quadriceps most often requires surgical repair and extensive rehabilitation.

Iliopsoas Strain

Gymnasts and dancers are the group of athletes most likely to experience an injury to the iliopsoas as a result of sudden forceful hip flexion against resistance. Severe pain often is experienced in the groin, thigh, or low back region. Severe intra-abdominal pain is common at the muscle origin and may dominate the clinical picture. Examination reveals groin tenderness and pain with active hip flexion. Radiographs of the femur should be obtained to identify an avulsion fracture of the lesser trochanter. CT frequently will demonstrate a large hematoma. Bedrest with partial flexion at the knee and hip generally is required for 7 to 10 days. With severe strains, symptoms may persist for 2 to 3 months.

Hip Adductor Strain

Injury to the hip adductors occurs as the thigh is forcefully abducted, as in a straddle injury. The patient complains of pain in the groin, the pubic region, and the medial proximal aspect of the thigh. Abduction and adduction often are limited because of pain. Swelling and skin discoloration may confirm presence of the tear. If the tear is complete, a defect in the muscle may be felt by the examiner along the medial aspect of the thigh near the groin. Treatment is conservative, with patients initially benefiting from rest, with gradual progression in a stretching and strengthening program.

Gluteus Muscle Strain

The gluteus muscles may be injured with vigorous or forced hip extension, as seen in track-and-field jumping events. The pain typically is less severe than that associated with injuries to other muscle groups. The hip is tender when extended or abducted.

Tendon Injuries

Clinically, tendon strains tend to have a more insidious onset than that typical for muscle strains. These strains may occur at the attachment of the muscles to the superior or inferior pubic ramus, the pubic symphysis, the ischium, and the femur.

A *groin pull* is the lay term for an injury to the tendons of the hip adductors. One study found adductor strains to be the most common groin injury in athletes, with 62% of the cases

involving the adductor longus muscle.[76] The adductor magnus and brevis and the pectineus often are involved as well.[77] It commonly occurs in skaters and cross-country skiers when an accidental stress abducts the thigh during a powerful contraction of the adductors. These muscles also may be injured from overuse in an unconditioned patient. Local pain is noted at the inferior pubic ramus and the ischial tuberosity. Extension, abduction, and adduction of the hip are painful. The pain may radiate to the back of the thigh.

Pain over the greater trochanter may represent tendon strain of the attachments of the gluteus medius, gluteus minimus, tensor fasciae latae, or piriformis. The pain is aggravated by resisted abduction. Tenderness in the groin and painful hip movement suggest a strain of the iliopsoas tendon at its attachment to the lesser trochanter. Trochanteric bursitis, peritendinitis, AVN, neoplasm, and other causes should be considered.

Treatment of a tendon strain is similar to that for other soft tissue injuries. The use of crutches with weightbearing as tolerated by pain is helpful for the first 2 weeks. Opioid analgesics and a short course of anti-inflammatory agents should be given. Complete tendon disruption may require surgical repair.

Osteitis Pubis

Osteitis pubis is a poorly understood disorder. It is characterized by pubic symphysis pain and joint disruption and is most common in distance runners and soccer players.[78] The adductor muscles act as a "compression strut," displacing forces across the hip. The most likely mechanism is repetitive pulling of the adductor muscles, causing increased shearing at the pubic symphysis.

Clinically, patients present with groin pain of insidious onset, with most reporting pain at the symphysis and adductor muscles.[79] Pain usually can be elicited on palpation of the symphysis and also can be provoked by adduction of the hip or by sit-ups. Plain radiographs show widening of the symphysis, irregular contour of the articular surfaces, or periarticular sclerosis (a late finding) (Fig. 53-30). These features are not specific and in one study were seen in 76% of asymptomatic soccer players.[80] MRI is the imaging study of choice and will show marrow edema on T_2 images early in disease. Osteitis pubis has been associated with spontaneous cases of pubic symphysis osteomyelitis and should be considered in the differential diagnosis.[79]

Figure 53-30. Plain radiograph showing irregular articular surfaces and periarticular sclerosis consistent with osteitis pubis.

Treatment is conservative, and in most cases the process is self-limited. Patients benefit from activity modification, good shoe wear, and therapy addressing flexibility and strength of the pelvic and hip musculature. Average time to heal has been reported at 9 months.

Vascular Injuries

Hip dislocations and the various types of femoral fractures may have an associated arterial injury. The vessel may be partially lacerated, completely severed, or thrombosed. Lack of distal arterial flow may also represent a stretched vessel in spasm. The superficial femoral artery is most commonly injured with trauma to the hip and thigh. The common and the deep femoral arteries are less frequently injured. In the acute setting, penetrating trauma is the usual mechanism of injury.

Arterial injury with femoral shaft fractures is rare. Anterior- and superior-type dislocations may produce femoral artery injury.[23]

Comparative blood pressures obtained by Doppler examination in the injured and uninjured extremities may be useful in suspected arterial injuries. If the systolic pressure in the affected extremity is 90% or less (index less than 0.9) than that in the unaffected extremity, additional diagnostic studies should be undertaken. The ankle-brachial index also can be similarly determined by comparing the systolic pressures of the affected extremity and of the ipsilateral arm. An index less than 0.9 necessitates further diagnostic studies.[23] Additional diagnostic studies include Doppler flow ultrasound imaging, CT angiography, and angiography alone. CT angiography, however, is becoming more prevalent, with recent studies showing 96% and 97% sensitivity and specificity, respectively, when compared with conventional radiography.[81]

Diagnostic evaluation must not delay surgical exploration when clinical signs and symptoms of vascular injury are obvious.[82] These hard signs and symptoms of injury include active or pulsatile hemorrhaging, expanding or pulsatile hematoma, diminished or absent pulses, auscultated bruit or palpable thrill, and evidence for limb ischemia. Early restoration of blood flow is essential to prevent ischemic damage to the leg.

Neurologic Injuries

Trauma, infectious agents, and degenerative disease all may injure peripheral nerves. In trauma, nerves may be injured by a blunt object that causes a contusion, by a sharp penetrating object that produces a partial or complete tear, or by the stretch of a missile as it passes in proximity. Nerves are particularly vulnerable to prolonged ischemia, which can lead to necrosis. Compression of the nerve from a hematoma or a dislocated femoral head may also appear as a neurapraxia manifested by transient loss of conductivity. The femoral and sciatic nerves are rarely injured with femoral shaft fractures because they are encased in muscle throughout the length of the thigh.

Treatment of neurovascular compromise from a hip dislocation or a displaced femoral fracture consists of immediate reduction to ensure limb viability. Whenever possible, reduction should be accomplished before transfer of the patient to another treatment center.

Femoral Nerve

When the femoral nerve is injured, the iliac and femoral arteries are commonly involved because of their anatomic proximity. If injured, the femoral nerve most often is traumatized in penetrating trauma of the pelvis, groin, or thigh. Femoral neuropathy occasionally can result from compression by a hematoma within the abdominal wall or the iliopsoas as a complication of hemophilia, anticoagulant therapy, or trauma.[83]

The motor deficit in complete femoral neuropathy is manifested as marked weakness of knee extension. The patient is able to walk on level ground yet has extreme difficulty walking up stairs or an incline. Patients cannot rise from a sitting position because of significant proximal muscle weakness. The sensory deficit varies but is localized along the anterior aspect of the thigh and medial lower aspect of the leg. The most reliable spot for testing for a sensory deficit is just superior and medial to the patella. The deep tendon reflex of the knee will be diminished or absent with such deficits.

If a traumatic neuropathy is suspected, immediate orthopedic consultation should be obtained. Nerve exploration and repair generally are preferred for penetrating trauma and when direct impingement on the nerve by bone fragments or hematoma is suspected. Surgical exploration and drainage of a hematoma that is impinging on the femoral nerve are appropriate.

Progressive nontraumatic neuropathies warrant urgent neurologic consultation. With a chronic neuropathy, atrophy of the anterior aspect of the thigh will already have developed. The motor deficits have been discussed previously.

Sciatic Nerve

Sciatic injury is rare with femur fractures, but it may be the result of traction used to stabilize the fracture during the initial management period. Complete traumatic injury may result from a deep penetrating wound in the hip, thigh, or buttock. Sciatic nerve palsy either from inadvertent injection into the nerve or secondary to intraneural or extraneural hemorrhage in patients taking anticoagulants has been described. Posterior hip dislocations and fracture-dislocations produce sciatic neurapraxia in 10 to 14% of these injuries.[23,65] Patients with complete sciatic neuropathy have paralysis of the hamstring muscles and all muscles below the knee. With partial injury, a peroneal palsy with weakness of the extensor hallucis longus muscle is the most sensitive clinical sign. There is sensory loss below the knee and along the posterior of the thigh. The deep tendon reflex at the ankle is absent or diminished.

Sciatic injury from posterior dislocations often consists of only transient loss of conductivity, particularly in motor fibers. Unfortunately, the other injury patterns to the sciatic nerve carry the worst prognosis of all peripheral nerve injuries. The prognosis is poorest when the injury is proximal and complete. Even with optimal repair, recovery often is inadequate. Sciatic neuropathy is a disabling problem. Obvious atrophy of the lower part of the leg and foot develops, followed by ulceration of the sole of the foot and infection. A below-the-knee amputation frequently is necessary in these cases.

SPECIAL PEDIATRIC CONSIDERATIONS

Anatomy

Development of the femoral head and neck with its growth plates and two primary ossification centers is illustrated in Figure 53-31. A significant proportion of the pediatric hip is radiopaque cartilage and developing new bone. For this reason, almost any type of trauma in this location carries the potential for premature growth arrest. Recognition that large portions of the pediatric hip are radiolucent will counter the tendency to focus attention on the ossified elements.

Hip Dislocation

The incidence of hip fractures and dislocations is increasing in young patients, often as a result of high-energy trauma. Up to 50% of children with a hip dislocation also will have fractures elsewhere. In small children, dislocation of the hip is more common than femoral neck fractures. The force required to dislocate a pediatric hip is much less than that required in an adult because the acetabulum is less completely developed than in adults. Seemingly negligible trauma, such as tripping or a minor fall, may dislocate the femoral head in a young child. In a school-age child, athletic injuries are the major cause of traumatic hip dislocation. In the teenage years, motor vehicle collisions predominate as the cause of hip dislocations.

Hip and Femur Fractures

The vast majority of pediatric hip fractures result from high-energy violent trauma. These fractures usually are the result of falling from heights, jumping out of a swing, being struck by a car, or a bicycle accident. Nonaccidental trauma also must be considered. Whereas a car commonly strikes an adult pedestrian at the tibial level, a smaller child most often is hit at the level of the hip, which results in a fracture there.

The Salter-Harris classification of fractures in the pediatric population is not used for hip fractures. The Delbet classification is a well-accepted system used for pediatric femoral fractures.[84] This system separates fractures through the physis and the transcervical, cervicotrochanteric, and intertrochanteric regions (Fig. 53-32).

Spiral Shaft Fractures

If seemingly trivial trauma has resulted in a spiral femoral shaft fracture in a child, nonaccidental trauma and pathologic frac-

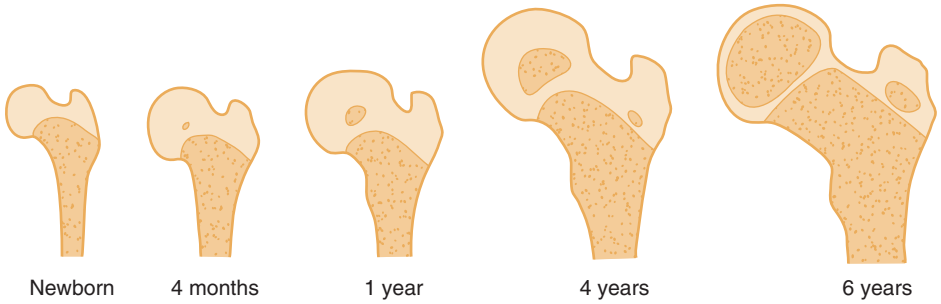


Figure 53-31. Development of the femoral head and neck with its growth plates and two primary ossification centers.

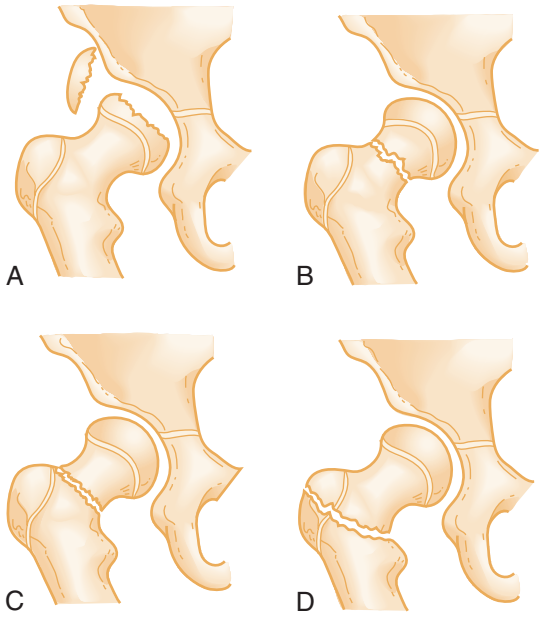


Figure 53-32. Pediatric proximal femoral fractures are classified by a system that separates fractures in the physis (**A**), the transcervical area (**B**), the cervicotrochanteric area (**C**), and the intertrochanteric region (**D**). (From Canale ST, Beaty JH: Fractures of the pelvis. In Rockwood JC Jr, Green DP, Bucholz RW [eds]: Rockwood and Green's Fractures in Children, vol 3, 5th ed. Philadelphia, JB Lippincott, 2001, pp 883–911.)

ture must be considered.[85,86] Common causes of pathologic fracture include unicameral bone cysts, fibrous dysplasia, osteogenesis imperfecta, and malignancy.[86,87]

Management. Femur fractures in children are so rare that most orthopedists treat only three or four in a career.[84] Although these pediatric injuries are extremely rare, their complications are significant. Unlike in an adult, a child's femur has growth potential, and any disruption carries the possibility of lifetime disability. Treatment of femoral shaft fractures in adults is aimed at prevention of the complications of prolonged immobilization. Unlike adults, children tolerate bedrest well, which allows more treatment options. The primary goal in children is prevention of the many complications common with femoral fractures. Premature closure of the physeal plate results in a valgus deformity of the hip. AVN, malunion, nonunion, and limb length discrepancy all are complications frequently seen with pediatric femoral fractures. For these reasons, referral to a pediatric orthopedist is recommended.[84]

The Child with a Limp

A child who comes to the ED with a limp presents a diagnostic challenge. Both life-threatening and benign disease processes can produce a limp. When the child is too young to give an adequate history, the etiology becomes more elusive. The attending physician should inquire about the chronology of the symptoms, the child's development (i.e., social milestones, weight gain, physical development), and diet. Associated illness and a family history may be helpful. Although identifying a specific causative disorder is challenging, the history and physical examination, combined with appropriate diagnostic modalities, will allow definitive diagnosis in most patients. An important point is that in the pediatric population, the knee is a common site for referred hip pain. Proper follow-up care is crucial to avoid additional morbidity in these children.

Evaluation of the Child's Gait

Gait is a learned, complex combination of motions produced through coordination of the musculoskeletal, peripheral, and central nervous systems. A limp is produced by anything that alters this process; the numerous clinical entities that may be associated with a limp can be divided into categories according to the underlying abnormality. Pain, muscle weakness, structural alteration, peripheral sensory deficit, and cerebellar or vestibular imbalance are major categories. A limp caused by pain is referred to as an "antalgic" gait. Conditions that disturb the biomechanics of the hip or cause the child pain may affect any of the elements of gait. Other conditions such as cerebellar pathology or disease of the knee or foot are discussed in their respective chapters.

Etiology of the Limp

Inflammation and Infection

Inflammation of the articular surface, the intra-articular synovium, or the joint capsule creates pain. Weightbearing increases the pain. The child limps in an attempt to limit the time during which the affected hip bears the body's weight.

Toxic synovitis is a common nonbacterial inflammatory clinical entity that can cause a limp. Little is known about its etiology. It develops most frequently in boys between 3 and 10 years of age. Clinically, the synovitis is manifested as pain in the hip or knee. An antalgic gait is present, with minimal systemic symptoms. There is restriction of hip motion and associated muscle spasm, and the child often will refuse to bear weight on the hip. As the disease progresses, the joint capsule is increasingly stretched, and intra-articular pressure rises. The potential volume of the joint capsule is largest with the hip flexed, abducted, and externally rotated. The child prefers to lie in this position as the capsule begins to bulge, to minimize the tension and intra-articular pressure.

The diagnosis of toxic synovitis must be one of exclusion of more serious diseases that mimic this condition. Acute joint inflammation and pain may be associated with juvenile rheumatic arthritis, systemic lupus erythematosus, Perthes' disease, septic arthritis, and tuberculous arthritis. Ultrasound imaging of the hip joint will detect an effusion in 78% of cases of toxic synovitis but cannot distinguish this condition from septic arthritis.[88] Joint aspiration may be required when the diagnosis is in doubt.

Distinguishing between toxic synovitis and septic arthritis can be a diagnostic dilemma. Recent work has illustrated four key predictors: temperature higher than 38.5° C in the preceding week, non-weight-bearing (refusal or inability to bear weight even with support), erythrocyte sedimentation rate higher than 40 mm/hour, and a white blood cell count greater than 12,000/mL. These four predictors were developed in a retrospective study and then validated in a prospective study.[89,90] Based on the validation study, the probability of septic arthritis was 2% for zero predictors, 9.5% for one predictor, 35% for two predictors, 73% for three predictors, and 93% for four predictors.[91]

The use of C-reactive protein (CRP) assay is becoming more prevalent in the evaluation of septic arthritis. Levine and coworkers studied the test characteristics of CRP in septic arthritis and determined the likelihood ratio for a CRP value greater than 10.5 mg/dL to be 2.75 and for a value less than 0.9 mg/dL to be 0.36.[92] When CRP evaluation (positive result defined as a value greater than 2.0 mg/dL) was added to the aforementioned four predictors, the probability of septic arthritis was 97.5% when all five were present; however, when all

of the predictors were absent, the probability was still 16.9%.[93] Taken together, all of these predictors should be used in conjunction with clinical assessment.

Acute bacterial infections of the hip and femur require early identification and intervention to minimize subsequent morbidity and disability.[91] Unfortunately, the diagnosis often is missed initially because the child may appear relatively nontoxic in the early phases of infection. Signs and symptoms of systemic illness usually accompany infection of the femur or hip. Fever, malaise, decreased oral intake, a limp, and refusal to bear any weight are common.[94] Whereas osteomyelitis most commonly develops in the metaphysis in adults, the physeal region often is the infected site in children. Pyarthrosis (septic arthritis) may result from hematogenous seeding or direct extension of osteomyelitis. The hip and the knee are the most commonly infected joints.

The causative agent in osteomyelitis and pyarthrosis is nearly always a gram-positive organism, usually *Staphylococcus*. The incidence of *Haemophilus influenzae* infection has fallen as a direct result of addition of the relevant vaccine to the childhood immunization regimen. Neonates, asplenic children, and children with sickle cell anemia are at risk for infection with gram-negative organisms. *Salmonella* infection also is more often seen in patients with sickle cell disease–related osteomyelitis. Viral and rickettsial diseases (e.g., Lyme disease) have been known to be present in subacute cases.

Identification of acute osteomyelitis on plain radiographs is difficult until 2 to 3 weeks after onset of infection. Pyarthrosis may be manifested by widening of the space between the femoral head and the acetabular roof and bulging of the joint capsule and surrounding soft tissues. This is seen as a change in the contour of the gluteus minimus and iliopsoas fat stripes (Fig. 53-33). Care should be taken to identify the normal shadow of the muscles and the joint capsule, as described earlier in this chapter (see Fig. 53-11). Plain radiographs are seldom useful in the initial identification of infection because visualization of a joint effusion has low sensitivity for pyarthrosis. Bone scan, MRI, CT, and ultrasound-guided joint aspiration are appropriate to diagnose a septic joint.

The inflammatory process involved in the immune system's attempt to eradicate the intruder also begins to destroy the body's own articular surfaces. Even with treatment, most children experience some arthritic disability.

Slipped Capital Femoral Epiphysis

Anatomy. The capital femoral epiphysis appears during the first year of life. The epiphysis of the greater trochanter appears by the age of 5 years and that of the lesser trochanter during the 13th year of life. All of these structures unite between the ages of 17 and 19 years. The anatomic relationship has been compared with a scoop of ice cream sitting on a cone. This relationship remains symmetrical on both anteroposterior and frogleg lateral radiographs (Fig. 53-34A and B). Asymmetry in any view represents either SCFE or a subcapital fracture (Fig. 53-35).

Epidemiology and Pathophysiology. SCFE is the most common hip disorder in adolescents, with an incidence of approximately 5 per 100,000 population per year. From 25 to 50% of the cases are bilateral.[39,95] SCFE occurs twice as frequently in boys as in girls, with the respective peaks of incidence at the ages of 13 and 11 years.

Epidemiologic data have provided clues to the pathophysiology of this injury. SCFE is associated with the onset of puberty and is rare before the age of 10 years. It most commonly is seen boys 10 to 17 years of age during their period of rapid growth. It is believed to be the result of a structural weakness in physeal cartilage associated with pubescence.[96]

The specific cause of SCFE is not well understood, and most cases are idiopathic. SCFE occurs more frequently in male African Americans than in the white population, lending support to the presence of a genetic element in the pathophysiology of the condition.[96] Other risk factors identified are obesity, previous irradiation or chemotherapy, renal osteodystrophy, hypothyroidism, and neglected septic arthritis.[97]

Clinical Features. SCFE usually is an insidious process extending over a period of several weeks to months. Initially, the only complaint may be slight discomfort in the groin, thigh, or knee after activity. Shear stress combined with a weaker physeal plate leads to slippage of the epiphysis inferiorly and posteriorly in the direction of weight-bearing force. Pain worsens as slippage progresses, and eventually pain may occur at rest as well. Referred pain to the knee is a classic manifestation, and patients frequently present with groin, thigh, or knee pain rather than hip pain. This presentation often causes delay in diagnosis, potentially increasing displacement, and a worsened prognosis.[98] Parents often bring the child in for medical evalu-

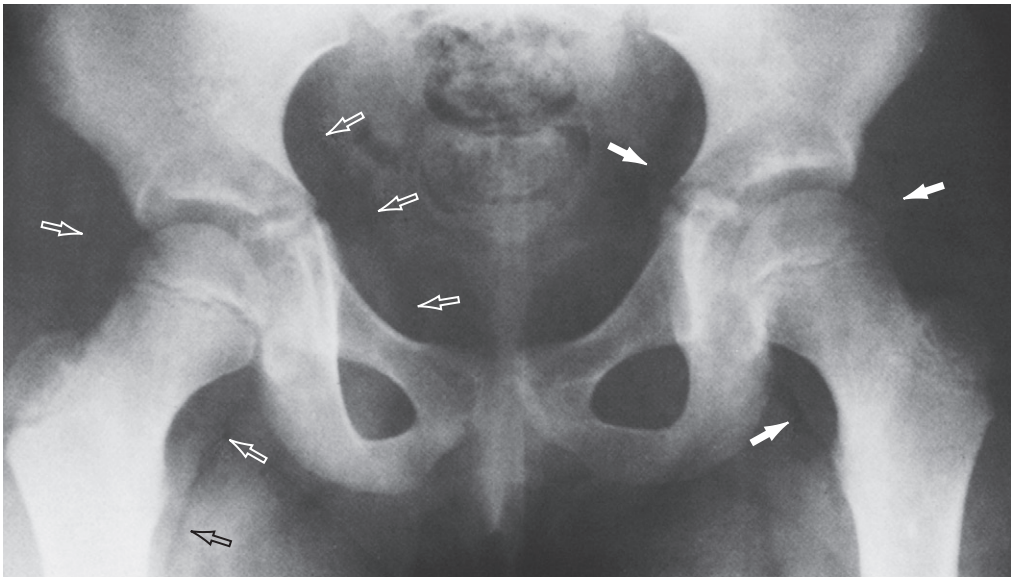
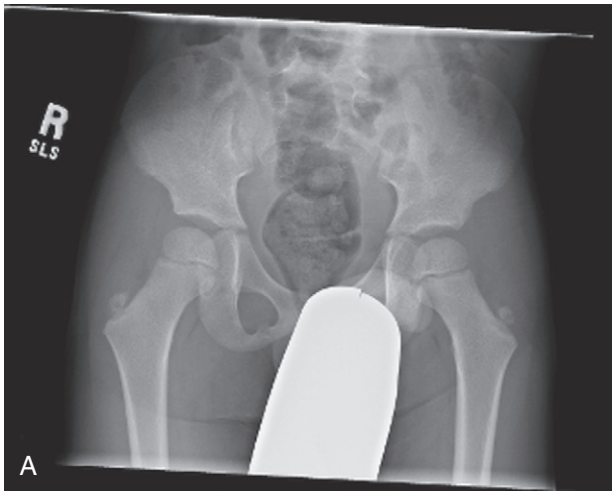


Figure 53-33. Prominence of the soft tissue shadows about the right hip, including bulging of the obturator internus muscle and its aponeurosis *(open arrows)*, indicates distention of the joint capsule. The opposite hip shows the normal soft tissue shadows, indicated by the *solid arrows*. (From Harris JH, Harris WH, Novelline RA: The Radiology of Emergency Medicine, 3rd ed. Baltimore, Williams & Wilkins, 1993.)



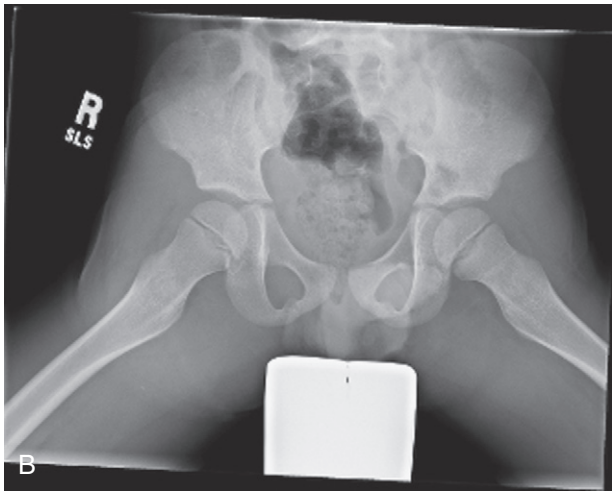


Figure 53-34. Anteroposterior (**A**) and frogleg lateral (**B**) radiographs obtained in a young boy demonstrate the normal anatomic relationship of the capital femoral epiphysis, the proximal physis, the apophysis of the lesser trochanter, and the triradiate synchondrosis.

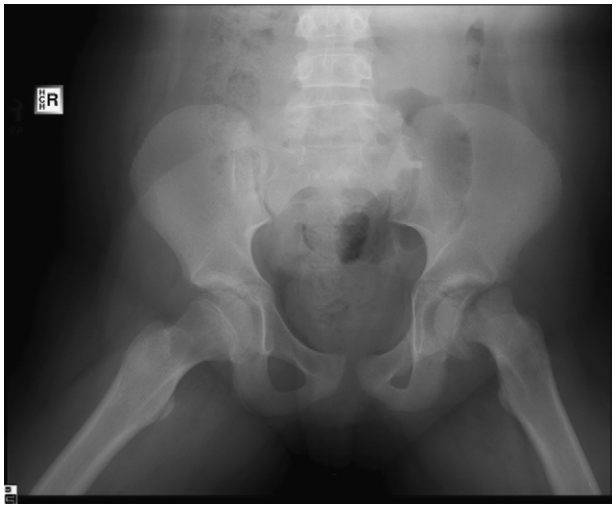


Figure 53-35. Frank slippage of the capital femoral epiphysis of the left hip. The capital femoral epiphysis is displaced medially, inferiorly, and posteriorly.

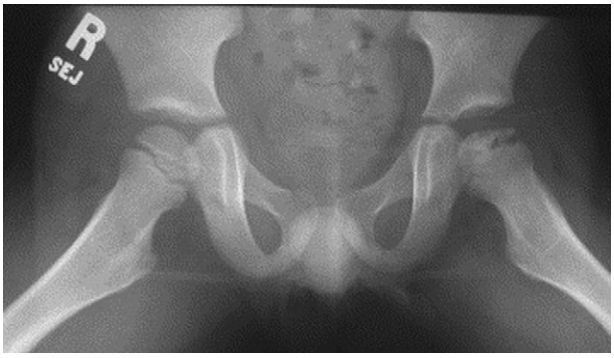


Figure 53-36. Perthes' disease affecting the left hip. Similar collapse of the femoral head as seen in adults. (From Kocher MS, Tucker R: Pediatric athletic hip disorders. Clin Sports Med 25:241, 2006.)

ation when they notice the child beginning to limp. Physical examination may reveal hip tenderness, decreased hip range of motion, and an abducted, externally rotated thigh.

Diagnostic Strategies and Treatment. Children with unexplained hip or knee pain merit clinical as well as radiographic evaluation. Initially, anteroposterior, lateral, and frogleg lateral radiographs of the hip should be obtained. The frogleg lateral projection shows the hip in a plane midway between the anteroposterior and lateral views. The earliest radiographic findings are subtle, with the abnormality visualized on only one projection. The most reliable initial finding with SCFE is asymmetry of the femoral epiphysis in relation to the neck. Small amounts of slippage can be detected by examining the epiphyseal edge as it becomes flush with the superior border of the femoral neck. This can be visualized as "the scoop slipping off the ice cream cone." The dome of the epiphysis may be flattened. On the radiograph, a line drawn along the superior margin of the femoral neck (Klein's line) should intersect some part of the normal femoral head. Failure of this line to intersect the head indicates medial and posterior movement of the head on the epiphysis.[95] Comparative views of the two hips are indicated if initial radiographic findings are equivocal. If occult fracture is suspected, MRI or CT should be performed.[25,99] The goal of treatment is to prevent further slippage and subsequent injury to the physis. The patient should be made non-weight-bearing and referred for orthopedic management. Surgery is required to anchor the epiphysis and prevent further slippage.

Perthes' Disease

Perthes' disease is the name given to AVN of the pediatric femoral head (Fig. 53-36). It also has been called *Legg-Calvé-Perthes disease* and *Calvé-Perthes disease*. It occurs at a younger age than SCFE does. A majority of cases are diagnosed between the ages 4 and 8, with the peak incidence at 6 years. It occurs five times more often in boys than in girls and affects both hips 15 to 24% of the time.[100]

Patients classically present with unilateral, oftentimes painless limp of insidious onset. As the disease progresses, pain becomes nearly constant and typically is exacerbated with activity and exercise. Treatment is controversial and determined by progression of disease and age at diagnosis.

Isolated Fracture of the Greater or Lesser Trochanter in Children

An isolated fracture of the greater trochanter is a rare injury. In children, this fracture occurs when the entire greater trochanteric epiphysis is avulsed from the femur. Children and adolescents between 7 and 17 years of age are most commonly affected. The mechanism of injury generally is a powerful

Figure 53-37. Forceful contraction of the iliopsoas muscle results in avulsion of the lesser trochanter. (From Kocher MS, Tucker R: Pediatric athletic hip disorders. Clin Sports Med 25:241, 2006.)

muscular contraction of the lateral rotators of the hip joint during a twisting fall. If the fragment is large and displaced by more than 1 cm, open reduction and internal fixation may be indicated.

An isolated fracture of the lesser trochanter occurs when a forceful contraction of the iliopsoas muscle avulses the lesser trochanter from the physis during sudden hip flexion (Fig. 53-37). Eighty-five percent of all cases occur in patients younger than 20 years, with a peak incidence between the ages of 12 and 16 years.[101] Marked tenderness can be elicited in the femoral triangle, and hip flexion against resistance is painful. Clinically, the seated patient is unable to lift the foot of the affected leg from the floor. Treatment of an isolated lesser trochanter avulsion fracture usually involves bedrest and early mobilization. Painless active hip motion is achieved within 3 weeks.

KEY CONCEPTS

- *Hip dislocation*: Hip dislocation constitutes one of the few orthopedic emergencies. The likelihood of its complication, AVN, is related to both the initial degree of trauma and the amount of time the femoral head remains out of joint. Reduction of the hip within 6 to 12 hours after dislocation significantly decreases the incidence of AVN. The only true contraindication to hip reduction is the presence of an ipsilateral femoral neck fracture.
- *Hip fracture*: When a painful hip makes ambulation difficult and plain radiographs do not reveal a fracture, MRI should be performed.
- *Intertrochanteric fracture*: Hemodynamic instability may result from dehydration and blood loss of up to 3 units into the fracture site. Up to 70% of patients with these injuries are under-resuscitated.
- *Acetabular fracture*: It is important to identify acetabular fractures before closed reduction is attempted because intra-articular bone fragments may interfere with effective reduction.
- *Slipped capital femoral epiphysis*: This condition is most commonly seen in African American boys 10 to 17 years of age; 25% of cases are bilateral. The most reliable initial finding with SCFE is asymmetry of the femoral epiphysis in relation to the neck, wherein small amounts of slippage give the appearance of "the scoop slipping off the ice cream cone."

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 54 Knee and Lower Leg

Daniel J. Pallin and Everett T. Lyn

KNEE

PERSPECTIVE

More than 1 million patients presenting with acute knee injuries are seen annually in North American emergency departments (EDs).[1] These injuries range in severity from minor contusions to limb-threatening injuries to the popliteal artery. The knee joins the longest mechanical levers in the body, the femur and tibia, and is thus subject to high forces. It is the largest and most complex joint in the body that functions through a complicated interaction of flexion, extension, rotation, gliding, and rolling. Its large synovial space frequently is involved in infections and other inflammatory conditions.

The main goal in emergency evaluation of the traumatized knee is to prevent further damage by identifying reparable vascular injuries, reducing dislocations, stabilizing fractures, and administering antibiotics when indicated. Definitive treatment of less urgent problems is deferred to other settings, such as primary care offices for chronic knee pain and orthopedic clinics for ligamentous injuries.

PRINCIPLES OF DISEASE: ANATOMY AND PATHOPHYSIOLOGY

The knee is a modified-hinge diarthrodial synovial joint that consists of the tibiofemoral and patellofemoral joints.[2] The head of the fibula, although not part of this articulation, is closely approximated laterally and provides a site for the attachment of muscles and ligaments. Joint stability is provided by ligaments, although surrounding muscles and the joint capsule contribute as well (Fig. 54-1).

The distal femur terminates in the medial and lateral condyles. The femoral condyles protrude anteriorly, leaving a vertical groove between them. Together, these condyles with their groove form the femoral trochlea—*trochlea* being the term for an anatomic structure that resembles a pulley. The patella slides up and down in the groove during knee extension and flexion. Poor patellar tracking results in lateral subluxation of the patella, causing patellofemoral pain syndrome (discussed later on in greater detail), the most common cause of knee pain in young adults.

The femoral condyles articulate with the superior surface of the tibia and the tibial condyles. Within the joint, medial and lateral menisci are interposed between the femoral and tibial condyles, where they prevent damage to the articular cartilage from friction and impact.

The tibia is anchored to the femur by four strong ligaments, the anterior and posterior cruciate ligaments (ACL and PCL, respectively) and the medial and lateral collateral ligaments (MCL and LCL). The ACL and PCL are located deep within the knee. The ACL arises from the posterior aspect of the femoral intercondylar notch and inserts on the anterior surface of the tibial plateau within the tibial intercondylar notch. It prevents anterior displacement of the tibia relative to the femur. The PCL arises from the anterior aspect of the femoral intercondylar notch and inserts on the posterior surface of the tibial plateau within the tibial intercondylar notch. It prevents posterior displacement of the tibia relative to the femur. The cruciate ligaments have a rich blood supply, and injury typically results in a hemorrhagic knee effusion.

The MCL and the LCL connect the femoral epicondyles to the tibial condyle and the head of the fibula, respectively. The MCL prevents *valgus* deviation. Valgus deviation refers to abnormal lateral flexion of the tibia relative to the femur when the leg is straight—that is, hinging of the right tibia to the right or hinging of the left tibia to the left. The LCL prevents *varus* deviation, which is abnormal medial flexion of the tibia relative to the femur.

Functionally the knee joint can be divided into three compartments: patellofemoral, medial tibiofemoral, and lateral tibiofemoral. These compartments, defined anatomically by the articulation of the bones, are contained within the same joint capsule. The *patellofemoral* compartment, located anteriorly, contains the quadriceps tendon, which envelops the patella, continues inferiorly as the patellar tendon, and terminates on the tibial tubercle. The fibers of the medial and lateral retinacula are found on either side of the patella, originating from the vastus medialis and vastus lateralis. The patella increases the mechanical advantage of the quadriceps tendon. The quadriceps tendon is a continuation of the quadriceps femoris muscle, which consists of the rectus femoris, vastus medialis, vastus lateralis, and vastus intermedius, comprising the important extensor structures of the knee.

The *medial tibiofemoral* compartment is located on the medial aspect of the knee and consists of the medial femoral condyle, concave medial tibial condyle (plateau), medial meniscus, MCL, adductor tubercle, and pes anserinus. The pes anserinus (literally, "goose foot") is a three-pronged tendinous structure that is the conjoined insertion of the sartorius, semitendinosus, and gracilis muscles.

The *lateral tibiofemoral* compartment encompasses the lateral half of the knee joint and includes the lateral femoral

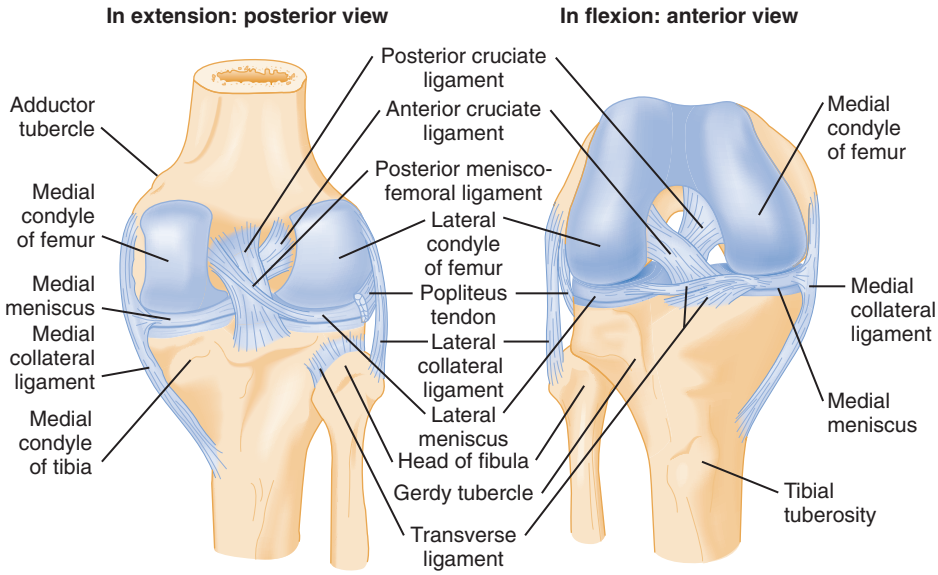


Figure 54-1. Posterior and anterior views of the right knee.

condyle and epicondyle, lateral tibial condyle (plateau), LCL, lateral meniscus, and popliteus tendon. The fibular head can be palpated posterolaterally and inferiorly to the joint line but is not usually considered a structure of the lateral tibiofemoral compartment.

The knee is surrounded by a thick ligamentous sheath composed largely of tendons and their expansions. The capsule of the knee joint is reinforced at multiple sites: anteriorly, by the ligamentum patellae; medially and laterally, by the medial and lateral patellar retinacula; and posterolaterally, by a combination of structures referred to as the posterolateral corner. The posterolateral corner includes the IT band, biceps femoris, fibular collateral ligament, popliteus complex (tendon, tibial attachment, popliteofibular ligament, lateral meniscal attachments), arcuate complex, fabellofibular ligament, capsular ligament, and joint capsule. The popliteofibular ligament has been identified as an important contributor to posterolateral stability. The synovial capsule of the knee works in unison with the ligamentous structures in strengthening the knee. The tibiofemoral joint communicates with the suprapatellar bursa, which expands in conditions that cause knee effusion. The prepatellar bursa is anterior to the patella and does not communicate with the tibiofemoral joint. It is important not to confuse prepatellar bursitis with a septic knee (i.e., septic arthritis of the tibiofemoral joint).

The popliteal fossa is a rhomboid hollow in the posterior aspect of the knee. It is bounded by the biceps femoris laterally, the semimembranosus and semitendinosus muscles medially, and the two heads of the gastrocnemius muscle inferiorly. Found within the popliteal space are the popliteal artery, the popliteal vein, and the peroneal and tibial nerves.

The popliteal artery is found deep within the popliteal fossa and represents the direct continuation of the femoral artery beyond the adductor hiatus. The popliteal artery descends across the posterior aspect of the knee joint and terminates at the level of the tibial tubercle, where it divides into the anterior and posterior tibial arteries. The popliteal artery is anchored firmly at the proximal and distal ends of the popliteal fossa, which explains the high incidence of arterial injury with knee dislocations. Blood supply to the knee joint comes from the popliteal artery by way of the geniculate arteries. Branches of the geniculate arteries interconnect with other vessels, forming a complex anastomosis around the knee. The circumflex fibular artery is a branch from the anterior tibial artery and constitutes the main blood supply to the head of the fibula. Blood supply to the head of the tibia is derived in part from two branches of the anterior tibial artery: the anterior and posterior recurrent tibial arteries.

The tibial nerve, along with one of its branches, the common peroneal nerve, is responsible for innervation of the knee. The tibial nerve joins the artery and vein in the popliteal fossa. It is not tethered proximally and seems to be injured less often than the popliteal artery. The common peroneal nerve wraps around the head of the fibula and continues inferiorly as the deep and superficial peroneal nerves. Common peroneal nerve injury may occur in association with injury to the fibula head or may be due to prolonged compression, as when the flexed knee hangs over the edge of a hard surface such as an operating room table. This causes footdrop, in which dorsiflexion strength at the ankle is reduced.

Depending on the population studied, management of knee and leg fractures commonly requires immobilization, which can result in deep vein thrombosis in up to 19% of the cases. Prophylactic treatment with low-molecular-weight heparin can substantially reduce this risk.[3]

CLINICAL FEATURES

Presentation

Patients with knee injuries present with pain, tenderness, deformity, limited range of motion, effusion, warmth, or redness. Knee pain without an immediately apparent knee abnormality should prompt a careful evaluation of the entire femur and hip, injuries of which frequently manifest with pain referred to the knee. Patients with radiculopathy of the third, fourth, or fifth lumbar roots also may complain of knee pain. Children with slipped capital femoral epiphysis, toxic tenosynovitis, or septic hip frequently complain of knee pain.

A knee effusion may result from infection, hemarthrosis, lipohemarthrosis, or inflammatory arthritis, and arthrocentesis is commonly required for diagnosis.

High-energy trauma without knee swelling should raise suspicion for disruption of the joint capsule with expulsion of joint fluid and hemorrhage into the thigh or lower leg. Lower-energy injuries are more commonly associated with meniscal tears, patella dislocations, and less severe ligament injuries; in particular, activities with twisting and turning are associated with anterior cruciate and meniscal tears. Immediate deformity, hemarthrosis, or instability suggests intra-articular frac-

BOX 54-1 EXAMINATION OF THE KNEE

1. Assess neurovascular integrity of the foot.
2. Determine whether a knee effusion is present, and assess for gross deformity.
3. Identify signs of infection (redness, warmth, and effusion out of proportion to mechanism of injury).
4. Localize tenderness.
5. Assess range of motion and perform stability testing and meniscal evaluation when feasible.

ture, cruciate ligament injury, or vascular injury. By contrast, a torn meniscus more commonly is associated with delayed onset of swelling over 12 to 24 hours and intermittent locking associated with joint line pain.

Locking of the knee is manifested clinically by inability to extend the joint fully. It typically results from either a meniscal tear or trapping of a loose body within the joint, thereby preventing full extension. A complaint of "giving way" may indicate instability or involuntary muscle inhibition secondary to pain. This is a nonspecific symptom and may be reported in association with arthritis or patellofemoral disorders when inhibition of quadriceps function occurs in association with episodic pain. Although pain remains a helpful indicator of injury, its absence should not be interpreted as proof that only minor injury is present. Complete ligament tears may be less painful than partial tears because the completely disrupted ligament has no tension across injured fibers.

Dislocation is among the most serious of knee injuries, because the popliteal artery is commonly injured. Because many knee dislocations reduce spontaneously before the patient arrives at the ED, normal findings on physical examination and radiographs do not rule out a recent dislocation.[4] If a history of knee dislocation is suspected or when a trauma patient has unexplained vascular insufficiency of the foot, thorough evaluation of the neurovascular status of the feet is an integral part of the secondary trauma survey.

Physical Examination

Proper examination of the knee requires the patient to be supine with both legs exposed. The evaluation should begin with an assessment of the neurovascular integrity of the foot. The question of whether knee pain may be the result of hip or spine pathology should be raised early. Examination of the knee begins with visual inspection (Box 54-1), followed by palpation (Fig. 54-2). Any obvious deformity, swelling, effusion, or ecchymosis is noted. Localized swelling must be distinguished from the presence of a joint effusion, which may obliterate the normal contour of the knee. If a large effusion is present, the patella is elevated from the femur by fluid, and the patella can be "ballotted" against the femur. Loss of the medial peripatellar concavity may be the only sign of a small knee effusion. A small knee effusion may be accentuated by milking the suprapatellar pouch inferiorly to force fluid into the knee joint. An effusion in the prepatellar bursa is found just beneath the skin anterior to the patella; this should not be confused with a knee effusion.

Palpation for areas of tenderness is performed last because eliciting pain early in the examination may cause the patient to refrain from cooperating fully. The patella and the extensor mechanism should be palpated with attention to the superior pole. In the absence of trauma, tenderness localized here is consistent with quadriceps tendinitis. Warmth, erythema, and swelling over the anterior patella may result from prepatellar bursitis. Tenderness along the inferior pole of the patella is

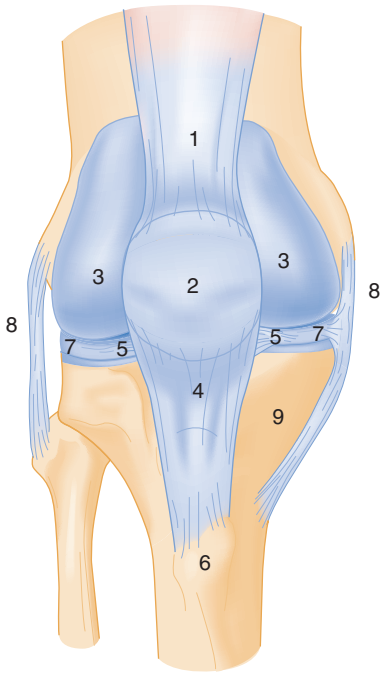


Figure 54-2. Sites for palpation of tenderness in the knee: 1, quadriceps tendinitis; 2, prepatella bursitis, patella pain; 3, retinacular pain after patella subluxation; 4, patella tendinitis; 5, fat pad tenderness; 6, tibial tubercle pain due to Osgood-Schlatter disease; 7, meniscus pain; 8, collateral ligament pain; 9, pes anserine tendinitis-bursitis. (Adapted from Cailliet R: Knee pain. In Soft Tissue Pain and Disability, 3rd ed. Philadelphia, FA Davis, 1976, p 411.)

seen with peripatellar tendinitis. The insertion of the patellar tendon onto the tibial tubercle should be palpated. Pain at this location in an adolescent is the hallmark of Osgood-Schlatter disease. In an adolescent, pain along the femoral or tibial epiphysis after trauma may represent a Salter-Harris type I fracture (i.e., a nondisplaced fracture through the physis). The joint line should be palpated carefully. Pain along the joint line may indicate meniscal pathology. The posterior aspect of the knee should be examined for fullness, which may indicate a Baker's cyst, or popliteal artery pseudoaneurysm. Tenderness over the medial or lateral heads of the gastrocnemius may indicate tendinitis or muscle strain.

Accurate diagnosis of soft tissue knee injuries often is impossible in the acute phase because of pain and swelling. In the *acute setting*, the main goals are to relieve pain, stabilize the joint, rule out vascular injury, and determine the need for radiography. In the *subacute setting*, range of motion should be assessed. The normal range is from slight hyperextension to approximately 135 degrees of flexion, but the patient's unaffected knee should be used for comparison. With knee flexion, it is normal for the tibia to glide posteriorly as much as a few millimeters and to rotate internally up to 40 degrees. Similarly, the tibia moves anteriorly and rotates externally during extension. In the extended position, tautness of the ligaments prevents rotary motion. Loss of active extension of the knee and inability to maintain the passively extended knee against gravity are the hallmarks of quadriceps and patellar tendon rupture, which otherwise may be clinically occult.

Tests for Specific Injuries and Disturbances

Stability Testing

Although range of motion is important for documentation of disability, it is stability testing that provides the most specific

diagnostic information. Stability testing seeks to identify tears of the four major ligaments of the knee—ACL, PCL, MCL, and LCL. Results of stability testing often are inaccurate in the acute phase, owing to splinting and effusion, and such testing may be deferred to the subacute setting. When the acute phase has passed, the goal of stability testing is to determine whether a patient may benefit from orthopedic referral for surgical diagnosis and repair.

Anterior Drawer Test

The *anterior drawer test* seeks to identify tears of the ACL. A positive test result is defined as greater anterior movement of the tibia as compared with the other knee. The test is performed with the patient in a supine position, the hip flexed at 45 degrees, and the knee flexed at 90 degrees. The examiner may stabilize the patient's tibia by sitting on the patient's foot. The examiner then determines the amount of step-off between the femoral condyle and the tibial plateau by placing the thumbs over the joint line while exerting a smooth, gentle pull anteriorly on the tibia. The amount of forward displacement is compared with that on the normal side. Significant laxity relative to the contralateral knee is fairly specific for ACL disruption, although a false-positive result can be caused by PCL insufficiency, which allows the tibia to slip back on the femur, showing an abnormal amount of displacement when pulled forward. The test is not sensitive, with only 10% sensitivity in the acute phase, rising to 50% when performed with the patient under general anesthesia.[5] False-negative findings may be due to an effusion preventing knee flexion to 90 degrees, insufficient force applied during the test, or simply the strength of the knee flexors and extensors preventing abnormal movement.

Lachman's Test

Lachman's test is the most accurate physical test for anterior cruciate ligament damage, with a sensitivity of 80% when performed acutely and 100% when performed with the patient under general anesthesia.[5] Lachman's test is done with the knee flexed 20 to 30 degrees while the examiner uses one hand to grasp the thigh and stabilize it. The tibia is pulled forward with an anteriorly directed force, and the examiner notes tibial excursion. The examiner records "firmness" or a "soft endpoint." The endpoint can be graded as 1+ (0 to 5 mm more displacement than on the normal side), 2+ (5 to 10 mm), or 3+ (greater than 10 mm). The knee should be in a neutral position before manipulation, and the PCL must be intact for the test results to be valid. In an acute injury, any difference in translation or the feeling of a soft or indistinct endpoint may indicate a ligament tear. A PCL injury results in a false-positive test result as the knee is pulled forward. Potential causes of false-negative test results include hamstrings that are very strong or in spasm, meniscal tears, and third-degree MCL tears with posterior medial extension. Specific limitations of Lachman's test include difficulty quantitating the amount of anterior translation and inability to limit motion of the femur. In addition, the detection of partial tears of the ACL is problematic and less reliable. Lachman's test also may be difficult to perform if the examiner's hands are small relative to the patient's thigh.

Posterior Drawer Test

The *posterior drawer test* assesses for PCL injury.[5] The posterior drawer test can be accomplished with the patient's knee flexed at 90 degrees and the foot stabilized by the examiner's thigh. A smooth backward force is applied to the tibia. Posterior displacement of the tibia more than 5 mm, or a "soft endpoint," indicates injury to the posterior cruciate ligament. A normal knee should exhibit no significant posterior excursion. The posterior drawer test result may be positive in only 85% of patients with PCL insufficiency documented operatively.

Posterior Sag Sign Test

The *posterior sag sign test* is a second method of determining PCL integrity. Sensitivity in the acute phase is 79%.[5] The test is done as follows. The patient is placed in a supine position, and a pillow is placed under the distal thigh for support while the heel rests on the stretcher. The knee is flexed to either 45 or 90 degrees, depending on which position provides the greater muscle relaxation. If the tibia sags backward, the test result is considered to be positive, indicating PCL insufficiency. If the posterior sag sign is not appreciated before the different drawer tests are performed, a false-positive result on the anterior drawer test is misinterpreted as an ACL injury. Posterior sag also may be shown by passive elevation of the leg in a fully extended position, with the examiner applying the elevating force at the ankle. As the leg is elevated, the tibia may fall back on the femur if the PCL is ruptured.

Pivot Shift Test

The *pivot shift test*, also called subluxation provocation or the "jerk" test, is performed to detect anterolateral rotatory instability associated with an injury to the ACL or lateral capsular structure. This test must be done carefully, if at all, in the acutely injured knee because the test maneuvers can exacerbate the initial injury. Sensitivity in the acute phase is only 27%, but the test is highly specific for ACL tear.[6]

The pivot shift test is performed with the patient supine. The knee is examined in full extension. The tibia is internally rotated while the examiner grasps the foot with one hand and applies a mild valgus stress at the level of the knee joint with the other hand. Then, with flexion of the knee to approximately 20 to 30 degrees, a jerk is suddenly felt by the examiner at the anterolateral corner of the proximal tibia. With a positive result, the tibia subluxates when the knee is extended and relocates when it is flexed to 20 to 30 degrees. Grading of the relocation event is as follows: absent (0), rolling (1+), moderate (2+), or momentary locking (3+). Because of pain or spasm, the pivot shift test is unreliable without use of anesthesia.

Instrument Testing

Arthrometers are devices that quantitate anterior displacement of the tibia relative to the femur and are far more accurate in diagnosing ACL tears than the anterior drawer and Lachman's tests, although these devices are rarely used in the ED setting. Studies using commercially available arthrometers indicate that a side-to-side difference exceeding 3 mm anterior displacement at 20 pounds is predictive of ACL injury with high accuracy.[7]

Collateral Ligament Stress Test

The *collateral ligament stress test* is used to test the integrity of the MCL and LCL. With the patient lying supine, the examiner applies varus and valgus stress with the knee at 0 and 30 degrees of flexion. *Joint line opening* is the amount of movement (i.e., hinging) produced between the tibia and the femur; this can be palpated and estimated in millimeters. The normal knee should be subjected to the same amount of valgus and varus stress and joint line opening and then compared with

that in the injured knee. Isolated collateral ligament tears are detected only with the knee in slight flexion, because in extension, the cruciate ligaments, capsule, and lesser ligaments of the knee provide significant lateral stability. Laxity in full extension implies complete collateral ligament tear and also injury to the cruciate ligaments or other structures. Laxity may be graded as follows: grade I, some laxity; grade II, marked laxity; and grade III, total laxity.

Assessing for Meniscal Tears

Meniscal tears are difficult to diagnose in the acute setting, and these assessments are best reserved for the convalescent phase. Even then, small meniscal tears can cause significant symptoms but may not be detected on physical exam, and MRI or arthroscopic evaluation may be required for diagnosis. However, meniscal tears are likely to limit activity, rather than leading to further damage, so there is less urgency. By contrast, failure to diagnose a nondisplaced fracture can lead to displacement and severe consequences.

McMurray's Test

McMurray's test is used to help identify meniscal tears. The patient is placed in supine position with the knee hyperflexed. The examiner grasps the foot with one hand and the injured knee with the other. The examiner flexes and extends the knee while simultaneously internally and externally rotating the tibia on the femur and providing slight varus and valgus stress. A positive test result is the occurrence of clicking palpable along the joint line, or locking of the knee. Internal rotation of the leg tests the posterior segment of the lateral meniscus. External rotation tests the posterior segment of the medial meniscus. In the acute setting, limitation of range of motion may not allow sufficient hyperflexion to perform McMurray's test, and the test may be falsely negative.

Apley's Test

Apley's test also aids in diagnosing meniscal tears. With the patient prone, the knee is flexed 90 degrees, and the leg is internally and externally rotated with pressure applied to the heel. Pain elicited by downward pressure suggests meniscal pathology. The pain should be relieved with distraction of the knee and rotation of the leg back to a neutral position. Although relatively specific, the Apley test has a low sensitivity for detecting meniscal tears.[6]

DIAGNOSTIC STRATEGIES

Radiologic Evaluation

Plain Radiographs

In acute knee trauma, the goal of radiography is to rule out fracture. Radiographs are not 100% sensitive, however, and sometimes severe symptoms or physical findings suggest the need for CT or MRI to rule out fracture definitively. One study found a negative predictive value of only 49% for plain films in diagnosing knee fracture, with CT as the gold standard.[8] However, all knee and tibial fractures should be managed with non-weight-bearing instructions, and in the case of suspected fracture with negative plain film, the same approach may be pursued, with further imaging at a later time, in the absence of a clinical indication for emergent CT/MRI.

Plain films are useful for diagnosing fracture, effusion, foreign bodies, joint space narrowing, and lipohemarthrosis. Evaluating plain films begins with an assessment of bone anatomy and alignment. Nonobvious fractures are best detected by careful inspection of the cortex of all visualized bones. Any disruption of the continuous line of the cortex should raise suspicion for fracture. Subtle cortical disruptions indicate either nondisplaced fractures or draining cortical veins. The next step is to evaluate for the presence of an effusion, seen as a radiolucent area (of density similar to that of fat) distending the joint capsule. Presence of a linear interface between two different densities within an effusion suggests lipohemarthrosis (see Fig. 54-5), in which the effusion contains not only blood but also fat. This feature results from entry of marrow fat into the joint cavity and is diagnostic of fracture.

The traditional standard of care was to obtain anteroposterior and lateral radiographic views of the knee in all cases of acute knee trauma. More recent work has led to validation of clinical decision rules that help decrease unnecessary radiography.[9-11] The *Ottawa Knee Rule* states that radiography is necessary only if any one of five conditions is present: (1) age older than 55 years, (2) inability to transfer weight from one foot to the next four times at the time of injury and in the ED, (3) inability to flex the knee to 90 degrees, (4) patellar tenderness with no other bone tenderness, or (5) tenderness of the fibular head. Initial tests found that this rule detected 100% of fractures while allowing significantly fewer radiographs to be done.[10,11] The *Pittsburgh Knee Rule* similarly was found to be 100% sensitive.[12] This decision rule states that radiography is necessary only if the patient fell or sustained blunt trauma to the knee, and if either of two conditions is present: (1) age younger than 12 or older than 50 years or (2) inability to walk four full weight-bearing steps in the ED.

In a study comparing these two decision rules, both had good sensitivity, but the Pittsburgh rule was more specific, allowing fewer radiographs to be done without sacrificing sensitivity; in this study, the sensitivity of the Ottawa rule was 97% (95% confidence interval, 90 to 99%), and the sensitivity of the Pittsburgh rule was 99% (95% confidence interval, 94 to 100%).[13] Either rule may be used, but patients should be told that this approach is associated with an approximately 1% chance of a missed fracture and that they should seek reevaluation in the event of persistent or progressive symptoms.

One study validated the Ottawa Knee Rule in children older than 5 years of age, finding a sensitivity of 100%. The Ottawa Knee Rule permitted a 31% reduction in the number of radiographic evaluations.[14] In another pediatric study, 1 of 13 fractures was missed, implying a sensitivity of only 92%, so application of the rule in children still requires clinical judgment.[15]

In another approach, investigators asked whether a single lateral radiograph could replace the traditional three-view "knee series" (anteroposterior, lateral, and tunnel views). These investigators found that a single lateral view could detect 100% of fractures identifiable on the full series.[16]

Joint space narrowing, as seen in osteoarthritis, is easily discernible on erect standard views. Lateral views may reveal an abnormally low-riding or high-riding patella. Tangential, "sunrise," or "skyline" views are especially good for delineating the patellofemoral joint. Tangential views are useful to assess patella tracking or subluxation. Oblique radiographic studies are used when tibial plateau fractures are suspected but not seen on routine views, although MRI is far more sensitive. "Tunnel" views, which image the intercondylar notch, are used to detect tibial spine fractures and loose bodies within the notch. Although most ligamentous injuries cannot be diagnosed by plain radiography, avulsion of the attachment site can be seen occasionally and provides indirect evidence of ligament disruption. Stress radiographs may aid in the diagnosis of collateral ligament disruption but generally are not used in the initial evaluation.

Computed Tomography

Computed tomography (CT) is most useful in detecting and classifying tibial plateau fractures and usually is done when the diagnosis is unclear or if operative intervention is being considered. CT angiography is an excellent tool for detecting injury to the popliteal artery, although its sensitivity relative to traditional angiography has not been quantified.[17]

Ultrasound Imaging

Ultrasound imaging is useful in assessing the integrity of ligaments, tendons, and muscles of the knee and can localize and quantify joint effusions. It is particularly useful when MRI is contraindicated.[18] It has gained wide acceptance in the diagnosis of popliteal deep vein thrombosis and Baker's cyst, which appears as a nonechogenic mass with smooth walls lying medially within the popliteal fossa. The popliteal artery is the most common site for peripheral aneurysms, yet the clinical diagnosis can be difficult. The aneurysm typically occurs just distal to the adductor hiatus in the proximal segment and midsegment of the artery and is bilateral in up to 64% of cases. Coexistent aneurysms of the aorta (reported in 62% of the cases) and femoral artery (in 40%) are common, and screening for these conditions is appropriate.[19]

Contrast Arteriography and Color Flow Doppler Studies

Contrast arteriography and color flow Doppler ultrasonography are used to evaluate the arteries of the knee and leg. Traditionally, arteriography was deemed mandatory in all cases of tibiofemoral knee dislocation and in all cases of penetrating trauma in close proximity to major arteries. More recently, serial examination and Doppler scanning have been studied and found to be acceptable alternatives to arteriography in patients with normal findings on distal neurovascular examination.[4] As mentioned previously, CT angiography may replace these modalities.[17]

Radionuclide Bone Scan

A radionuclide bone scan can be used to detect osteomyelitis or occult bony injuries, such as stress fractures, osteochondritis dissecans, and avascular necrosis.

Magnetic Resonance Imaging

MRI has replaced contrast arthrography in the workup of occult fractures and ligamentous and meniscal injuries. Contrast arthrography involves injection of radiopaque contrast material into the joint, followed by radiography. Double-contrast arthrography involves injection of both air and contrast. These techniques are rarely performed when MRI is available.

MRI is highly accurate for diagnosis of fractures and ligamentous injuries, although it can miss small meniscal tears. It has proved to be superior to other imaging modalities in the evaluation of osteonecrosis, osteochondritis dissecans, occult fractures, and bone contusion.[20] Its advantages are that it is noninvasive and painless and does not involve exposure to ionizing radiation. MRI of the knee is rarely performed on an emergency basis, because immobilization and non-weight-bearing instructions are always an option, pending outpatient orthopedic evaluation.

Arthroscopy

Arthroscopy of the knee is the most commonly performed orthopedic surgical procedure in the United States. This nonemergent procedure is useful in diagnosis and treatment of knee injuries, including injuries of the meniscus, cruciate ligaments, articular cartilage, capsule, and synovium. The superior diagnostic accuracy of arthroscopy compared with the clinical knee examination has been well documented. In particular, arthroscopy has increased the accuracy of diagnosis of ACL injuries and small capsular tears. It is especially helpful for children, in whom diagnosis can be difficult because developing skeletal changes can obscure pathology. Difficulties in visualization arise when the capsular structures are tight and when meniscal tears are situated posteriorly. Arthroscopy is superior to MRI for diagnosis of meniscal tears and other soft tissue injuries, and the diagnosed problem can be repaired immediately. The need for arthroscopy is established in the convalescent phase of injury and need not be determined in the emergent setting, so long as appropriate referral to an orthopedist is made.[21]

Arthrocentesis

Aspiration of fluid from the knee joint can be diagnostic and can reduce pain from a tense effusion. Arthrocentesis should be performed if the injured knee is greatly distended with a tight effusion and when the cause of the joint effusion is unknown. Aspiration of the joint and subsequent analysis can distinguish among simple effusion, hemarthrosis, lipohemarthrosis, and septic arthritis. As noted earlier, lipohemarthrosis refers to an effusion containing blood and fat globules and is diagnostic of fracture.

Patient-controlled continuous infusion of various combinations of intra-articular local anesthetics, opiates, tramadol, magnesium, and clonidine has been used with success in reducing postoperative knee pain, although no regimen is clearly superior.[22-24]

KNEE INJURIES

Dislocation

Anatomy and Pathophysiology. True knee dislocation is tibiofemoral dislocation, and this should not be confused with patellofemoral dislocation, a relatively minor injury. Knee dislocation is a limb-threatening emergency, because popliteal artery injury often is present. It requires significant force; two thirds of these injuries result from motor vehicle collisions, with the remainder occurring from falls, sports injuries, and industrial accidents. Knee dislocation is uncommon but should be considered in the setting of an appropriate injury mechanism, because one half of all knee dislocations are reduced before the patient arrives at the ED.[25] Reduction before ED arrival does not lessen the likelihood of vascular injury, and vascular injury should be considered in patients with severe ligamentous injuries and high-energy mechanisms.

Dislocations are always associated with significant ligamentous injury. There is disruption of the joint capsule with accompanying trauma to the muscles and tendons. Vascular injury to the popliteal artery is the most severe complication and is the primary cause of morbidity and limb loss.

The neurovascular bundle, which is composed of the popliteal artery, popliteal vein, and common peroneal nerve, runs posteriorly behind all bony and ligamentous structures in the popliteal fossa. The popliteal artery is fixed in the fibrous tunnel of the adductor magnus hiatus proximally and traverses

the fibrous arch of the soleus and interosseous membrane distally. In essence, it is tethered to the femur and the tibia, and its inherent immobility renders it susceptible to injury during dislocation. Because of the parallel course of the popliteal vein and the peroneal nerve, they are vulnerable to simultaneous injury.

Traumatic dislocation of the knee can be characterized by the mechanism of injury and the type of dislocation. The injury is most commonly sustained in high-velocity accidents, such as motor vehicle and motorcycle collisions, or in severe crush injuries. Anatomically, dislocations are described according to the displacement of the tibia relative to the femur. They are classified into five types: anterior, posterior, medial, lateral, and rotary. More than half of all dislocations are anterior and result from hyperextension. Posterior dislocations are the second most common type and usually result from high-velocity direct trauma to the flexed knee, often in association with vehicular trauma (dashboard-type injury). The remaining dislocations are lateral, medial, or rotary dislocations and result from direct or indirect trauma producing valgus, varus, or rotary forces, respectively.[23]

Clinical Features. The diagnosis of knee dislocation is based on the mechanism of injury and clinical and radiographic findings. Clinical deformity should be easily palpable when a dislocation is present. Swelling may be absent, however, because of the associated tearing of the capsular structures and dissipation of the acute hemarthrosis into the adjacent soft tissue. The initial evaluation may not reveal an obvious gross deformity because of the variable occurrence of spontaneous reduction. Some experts have advocated expanding the definition of knee dislocation to include bicruciate ligament (i.e., ACL and PCL) injuries, even when the knee is reduced on initial presentation.[25] For this reason, patients with grossly unstable knees but no proven dislocation and patients who have a bicruciate ligament injury should be evaluated for concomitant injuries, as with patients with proven dislocation.[4]

Vascular injury is a catastrophic complication of knee dislocation, and popliteal artery injury is reported in 4.8 to 65% of these patients.[4,26] The collateral geniculate arteries around the knee also may be damaged directly or secondarily compressed by hematoma formation after the dislocation. Direct arterial injury, decreased collateral circulation, and elevated compartment pressures all may compromise limb perfusion. In addition to being clinically occult, vascular injury in blunt trauma is more difficult to manage because of associated soft tissue injury and edema.

Evaluation of the limb vascular status is the most important part of the initial physical examination of knee dislocation. All knee dislocations may warrant vascular surgery consultation, but the "hard" signs of vascular injury necessitate immediate surgical consultation. These signs include absence of pulse, limb ischemia, rapidly expanding hematoma, pulsatile bleeding, and bruit or thrill over the wound, especially in penetrating injuries. When popliteal artery repair is delayed, the amputation rate increases with time, nearing 90% after 8 hours.[27] The posterior tibial and dorsal pedal pulses should be evaluated. Doppler pressure measurements and peripheral pulse determinations have high specificity but poor sensitivity, because approximately 10% of popliteal artery injuries are associated with a normal pedal pulse.[28]

Minor vascular injuries, such as isolated intimal tears, often are treated conservatively, but a vascular surgeon should be consulted when possible. Isolated intimal tears are identified by arteriography and undetectable on physical examination. Injuries to small branches of the popliteal artery can be managed by observation and serial examinations.[25] Vigilance is necessary because apparently minor injuries can lead to compartment syndrome.

Neurologic integrity in the limb also should be assessed, because peripheral nerve injury may be associated with all types of dislocation. Peroneal nerve injury is the most common major neurologic problem associated with knee dislocation; some degree of dysfunction occurs in 20 to 40% of patients and is permanent in approximately 80% of these.[1,25,29] The peroneal nerve should be evaluated by determining sensation of the dorsum of the foot and by having the patient dorsiflex the ankle. Less commonly, the posterior tibial nerve may be injured, manifesting as diminished plantar sensation and plantar flexion of the foot. Complete nerve palsy in the acute setting has been associated with a poor prognosis for recovery.[29]

Diagnostic Strategies. Radiographic examination usually confirms the clinical findings (Fig. 54-3). In rare posterolateral and rotary dislocations, radiographic interpretation may be more difficult. Radiographic examination also serves to document associated fractures.

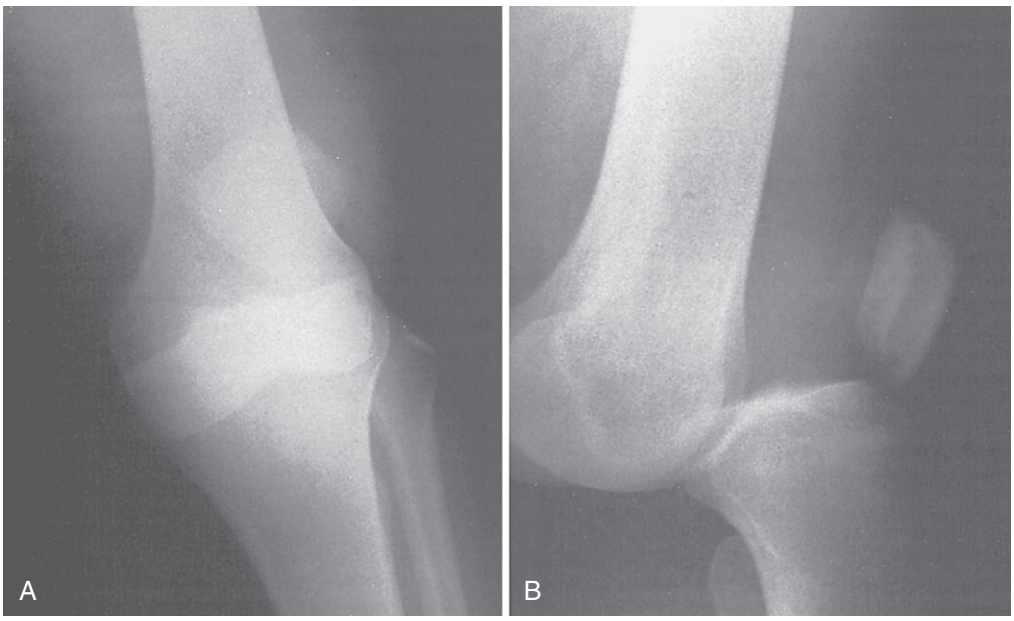


Figure 54-3. Anterior dislocation of the knee. **A,** Anteroposterior view shows overlap of the femur and tibia, which is never seen under normal circumstances. The anteriorly displaced tibia is magnified. **B,** Lateral view shows anterior displacement of the tibia in relation to the femur. The patella also is anteriorly displaced. (From Rosen P, et al: Diagnostic Radiology in Emergency Medicine. St. Louis, Mosby, 1992, p 194.)

Contrast arteriography has been the standard of care modality for diagnosis of injuries to the popliteal artery. More recently, however, debate has emerged in the trauma literature regarding whether all patients with knee dislocations require arteriography. Some studies have found that serial examinations can detect all clinically significant injuries, whereas others have emphasized the occasional occurrence of an occult arterial injury. Meta-analysis indicates that absence of normal pulses has only 79% sensitivity for a surgical popliteal artery injury after knee dislocation, suggesting that the default strategy should still be to perform angiography in these patients.[4,30] Color flow Doppler ultrasonography is gaining acceptance as an alternative to arteriography in some treatment centers, but it may not be as readily available during off-hours. Many trauma patients today have CT scans with intravenous contrast, and this is likely to replace angiography after further research.[17,31,32]

Management. The dislocated knee should be reduced immediately. For patients being transferred from nontrauma centers to trauma centers, reduction should be attempted before transfer. Reduction usually can be accomplished with simple traction-countertraction, preferably with use of intravenous moderate ("conscious") sedation; general anesthesia is rarely necessary. Radiographic confirmation is not required before reduction but is desirable if readily available. Neurovascular status should be documented before and after reduction is achieved. The limb should be immobilized in a long leg posterior splint with the knee in 15 to 20 degrees of flexion. Circumferential casting is avoided in the acute setting. When vascular injury is suspected or if immediate exploration is not planned, a Doppler flow ultrasound study, CT angiography, or standard angiography should be considered, in consultation with a vascular surgeon. Current indications for immediate surgery include obvious vascular injury with a cool, cyanotic ischemic lower extremity and irreducible or open dislocations. Arthroscopy is contraindicated in the acute setting because of the risk of fluid extravasation secondary to capsular deficiencies.

Loss and disability are minimized by expedient revascularization and primary arterial repair, heparinization when not contraindicated, repair of popliteal venous injury, aggressive wound débridement, and early soft tissue coverage. In the absence of vascular injury, early operative intervention does seem to confer an advantage.[33] Four-compartment fasciotomy is recommended by some clinicians, to minimize the consequences of reperfusion edema in patients who undergo vascular repair.

If the neurovascular structures remain intact after dislocation, the knee joint is reduced and allowed to rest for 2 to 3 days before reconstruction of the torn ligaments is considered. In follow-up studies, clinical instability generally is not a problem, but chronic pain and discomfort are present in nearly one half of the patients. Loss of motion is a common complication, and extensive damage to the articular surfaces at the time of injury increases the risk of early osteoarthritis.

Failure to achieve a closed reduction is uncommon. Delayed complications associated with traumatic knee dislocations include deep vein thrombosis, compartment syndrome, pseudoaneurysm, and arterial thrombosis. Compartment syndromes generally develop within 24 to 48 hours of the initial injury. Pseudoaneurysms are rare; they may form several hours to months after popliteal artery injury.[34] Heterotopic ossification is a poorly understood syndrome of calcification of the soft tissues of the knee. It has been observed in uninjured knees of patients who sustained major trauma. In its most severe form, heterotopic ossification can cause dramatic decrease in knee mobility. Almost one half of dislocated knees are found to have subsequent heterotopic ossification, although the most function-limiting form may be limited to patients with a history of severe trauma.[35]

Distal Femur Fractures

Anatomy and Pathophysiology. Distal femur fractures are uncommon, comprising approximately 4% of femur fractures.[36] A high-energy mechanism of injury is required. An isolated fracture of the femoral condyle may occur, or the fracture may extend in a T or Y pattern to include the intercondylar or supracondylar region of the femur. Condylar fractures are intra-articular and may result in disruption of the articular surface with subsequent arthritis.

Clinical Features. Patients with condylar or intercondylar fractures have pain and swelling in the distal femur and suprapatellar region and often are unable to bear weight. Examination may reveal shortening, rotation, and angulation of the extremity and tenderness to palpation along the medial or lateral joint line. Acute hemarthrosis is common and may be secondary to intra-articular extension of the fracture or associated ligamentous injury. Careful assessment of the circulation and motor function of the limb should be documented. Any soft tissue defect in the region of the fracture is considered to be an open fracture until proven otherwise. A fracture (or other injury, for that matter) thought to enter the knee joint can be evaluated with methylene blue injection. Using sterile technique, methylene blue is injected into the tibiofemoral joint at a site distant from the skin injury, until the joint is distended. Emergence of methylene blue from the skin lesion confirms an open joint. If methylene blue does not emerge from the skin injury, an open joint is highly unlikely; the methylene blue should be reaspirated. Some authorities recommend use of normal saline rather than methylene blue, as the latter can stain cartilage and make arthroscopy difficult.

Diagnostic Strategies. The diagnosis of a distal femur fracture is made from radiographs. Routine anteroposterior and lateral views should be obtained and usually show the fracture pattern and any significant displacement of fragments. In high-energy injuries, radiographs of the ipsilateral hip and tibia are required to exclude associated fractures. Occasionally, CT or MRI may be required to diagnose a nondisplaced fracture. MRI is more sensitive, although CT is more readily available. If signs of vascular impairment are present, a vascular study should be obtained promptly when surgical exploration is not being considered.

Management. After the initial examination, the leg should be splinted to prevent excessive motion of the fracture site. Early orthopedic consultation is advised. In a stable patient with an uncomplicated fracture, reduction may be done with skeletal traction followed by immobilization. Intra-articular fractures generally are treated with open reduction and internal fixation. Distal femoral fractures may be associated with thrombophlebitis, fat embolus syndrome, delayed union or malunion if reduction is incomplete or not maintained, intra-articular or quadriceps adhesions if the fracture is intra-articular, angulation deformities, and osteoarthritis, particularly affecting the patellofemoral articulation.

Tibial Plateau Fractures

Anatomy and Pathophysiology. The proximal end of the tibia is expanded into the medial and lateral condyles, the former having the greater surface of the two. Together they make up approximately three quarters of the proximal tibial surface, and their integrity is important for normal knee alignment, stability, and motion. The plateau normally slopes 10 degrees

from anterior to posterior; on a straight anteroposterior view, the anterior and posterior portions of the plateau may not appear to be at the same level. In addition, the lateral plateau is slightly convex upward, whereas the medial is slightly concave upward.

Tibial plateau fractures often are intra-articular and result in loss of joint congruity. The forces that normally act on the tibial condyles include axial compression and rotation. The most common mechanism of injury is a strong valgus force with axial loading. Severe high-energy tibial plateau fractures occur primarily in younger patients and are often the result of motor vehicle collisions or falls from heights. These fractures occur in concert with many other injuries and may be open. Fatigue stress fractures of the tibial plateau occur mostly in elderly persons. These low-energy fractures are the result of compression forces in osteoporotic bones.

Tibial plateau fractures encompass many differing degrees of articular depression and displacement. Because the initial injury mechanism usually is a valgus stress with an abduction force on the leg, 55 to 70% of condylar fractures involve the lateral plateau. Medial plateau fractures typically result from adduction forces on the distal leg and account for 10 to 23% of these fractures; both plateaus are involved 11 to 31% of the time.[36] If the knee is extended at the time of injury, the fracture tends to be anterior. Posterior condylar fractures usually occur when the knee is flexed at the time of impact.

The *Segond fracture* represents a bone avulsion of the lateral tibial plateau (Fig. 54-4). The avulsion occurs at the site of attachment of the lateral capsular ligament. On radiographs, an oval-shaped fragment can be seen adjacent to the lateral tibial plateau; this injury must be differentiated from an avulsion from the adjacent fibular styloid. The Segond fracture is an important marker of ACL disruption and anterolateral rotatory instability. Most Segond fractures are caused by sports injuries, and the mechanism is almost always knee flexion with excessive internal rotation and varus stress. Segond fractures can be detected on radiographs (lateral capsule sign) or even ultrasound images, but MRI usually is performed in the acute phase to delineate the expected soft tissue disruption.[37]

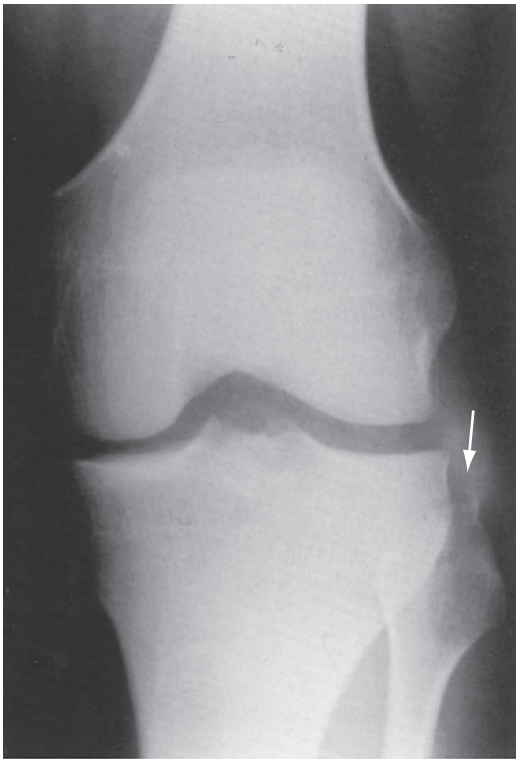


Figure 54-4. Anteroposterior view of the left knee shows lateral curvilinear avulsion fracture *(arrow)* and joint effusion. (From Kerr HD: Segond fracture, hemarthrosis, and anterior cruciate ligament disruption. J Emerg Med 8:29, 1990.)

Clinical Features. Clinical manifestations of knee fractures are the presence of an effusion, inability to bear weight, severe joint line tenderness, ecchymosis, and localized soft tissue swelling and pain. A common associated finding is acute hemarthrosis with decreased range of motion. Tenderness is present over the fracture but also may be found near torn collateral ligaments. A valgus or varus limb deformity may be present and usually indicates a depressed fracture or concomitant ipsilateral leg fracture. The most important aspect of the initial examination is assessment of neurovascular status. Tibial plateau fractures produce a high percentage of vascular complications. The popliteal artery is immobile in this region and branches into the anterior and posterior tibial arteries at the upper edge of the interosseous membrane. The popliteal artery may be injured by fragments from bicondylar or comminuted fractures involving the subcondylar area. Vascular impairment may result in distal circulatory compromise. Displaced fractures of the lateral condyle may produce peroneal nerve paralysis in addition to injury to the anterior tibial artery. Stretch of the peroneal nerve is the usual cause of injury.

Soft tissue injuries also may involve the capsuloligamentous structures of the knee. Ligamentous injuries accompany tibial plateau fractures in up to 66% of cases, most often involving the ACL and MCL.[38] Although ligament injuries can occur with any type of tibial plateau fracture, they occur more commonly with local compression and split compression fractures (see Fig. 54-4).[29]

Cruciate ligament injuries associated with tibial plateau fractures are associated with an increased incidence of late traumatic arthritis and a poor prognosis. Regardless of the type of treatment, operative or nonoperative, tibial plateau fractures with significant residual laxity fare poorly in comparison with stable fractures.[39]

Most experts agree that four factors determine the prognosis of tibial plateau fractures: (1) degree of articular depression, (2) extent and separation of the condylar fracture lines, (3) diaphyseal-metaphyseal comminution and dissociation, and (4) integrity of the soft tissue envelope (i.e., open versus closed). Fractures of the tibial plateau generally carry a good prognosis, with good to excellent results reported in 90% of patients more than 20 years after injury; however, high-energy tibial plateau fractures generally are associated with a more guarded prognosis.[40] In high-energy fractures, a large degree of articular depression, multiple displaced condylar fracture lines, and diaphyseal-metaphyseal extension and comminution in association with open injuries or an extensive internal degloving injury may occur and are poor prognostic signs.[41]

Diagnostic Strategies. Lipohemarthrosis, seen as a fat-fluid level on a plain film, suggests an occult fracture and is due to entry of marrow fat into the joint space[42] (Fig. 54-5). Lipohemarthrosis also is detected when fat globules are found on aspiration of a hemarthrosis. All knee radiographs should be examined closely for bone avulsion fragments from the fibular head, femoral condyles, and intercondylar eminence, because these may indicate ligamentous injury. Widened joint spaces associated with a fracture of the opposite condyle also may indicate concomitant ligamentous injury.

CT and MRI are more sensitive than plain radiography, help localize occult lesions, and help quantify the amount of depression in displaced fractures and the extent of articular surface involvement in comminuted fractures.[38] These studies

need not be undertaken emergently, because the knee can be immobilized pending orthopedic consultation. MRI is more sensitive than CT and should be consider the gold standard.

Several classification systems have been proposed. Most such systems depend on the mechanism of injury (i.e., the location and force with which the femoral condyle is driven into the plateau). The *revised Hohl classification* is in common although not universal use.[36] As shown in Figure 54-6, this system divides the plateau fractures into two categories: minimally displaced (less than 4 mm of depression or displacement) and displaced. Displaced fractures are subdivided into six distinct types: local compression, split compression, total depression, splint, rim, and bicondylar.

Management. All patients with a tibial plateau fracture should be referred for evaluation by an orthopedist. In the acute phase, the fracture should be immobilized in a noncircumferential splint and the patient should not bear weight on the limb until seen by an orthopedist. The therapeutic goals include precise reconstruction of the articular surfaces, stable fragment fixation, and early knee motion to prevent stiffness. Weightbearing generally is delayed until healing is complete, usually 6 to 8 weeks. Stable nondisplaced fractures may be

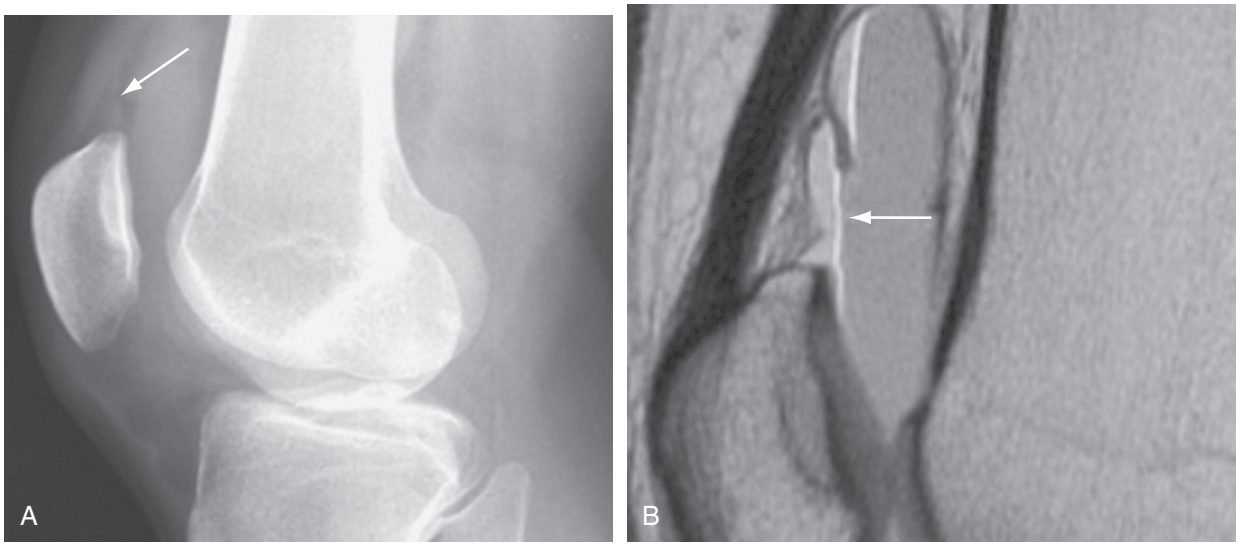


Figure 54-5. Lipohemarthrosis. **A,** A lateral plain film of the knee of a young woman with a nondisplaced patella fracture. The only radiographic abnormality is an effusion that contains a linear interface *(arrow)* between two soft tissue densities, suggesting lipohemarthrosis. **B,** A magnetic resonance image from the same patient shows plainly the presence of blood and fat in the effusion *(arrow)* (the nondisplaced patella fracture is not seen).

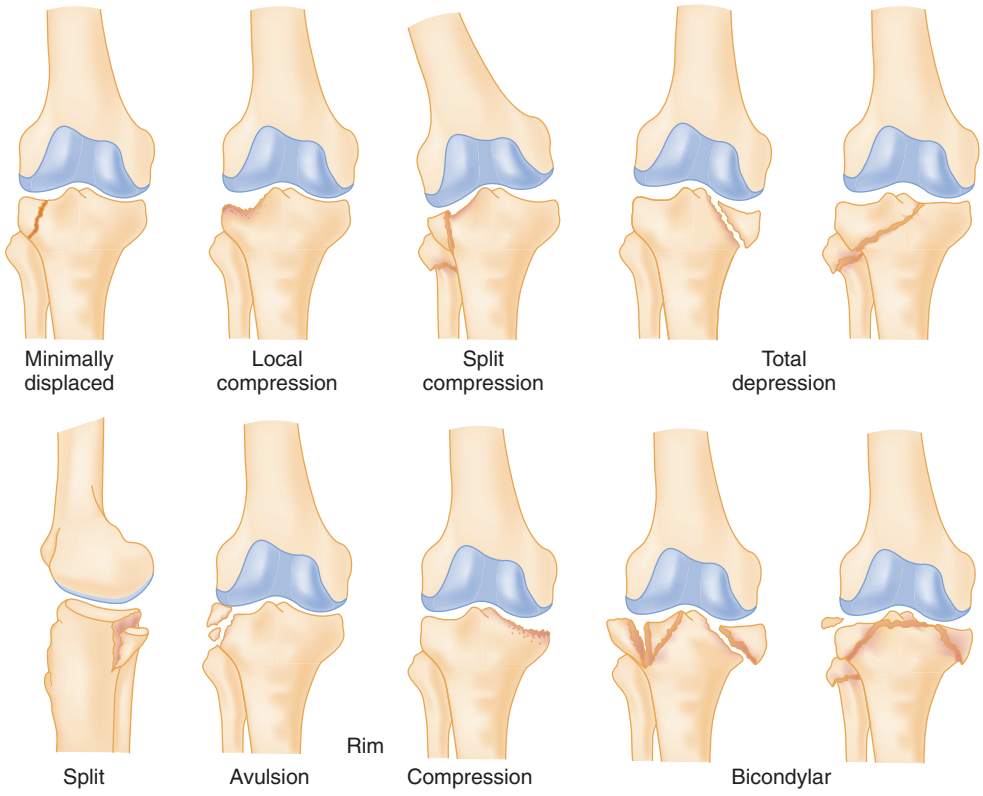


Figure 54-6. Hohl's revised classification of tibial plateau fractures: minimally displaced (accounting for 22% of such fractures), local compression (28%), split compression (18%), total depression (13%), split (3%), rim avulsion or compression (5%), and bicondylar (11%). (Modified from Watson JT, Wiss AA: Fractures of the proximal tibia and fibula. In Rockwood CA Jr, Green DP [eds]: Fractures, vol 3, 5th ed. Philadelphia, JB Lippincott, 2001.)

treated with immobilization alone, but instability or significant depression or disruption of the joint surface will necessitate surgical management.[36]

Early complications of tibial plateau fractures include wound infection, loss of reduction, and development of compartment syndrome. Compartment syndromes most commonly occur with high-energy fractures, typically within the first 24 to 48 hours after injury. Deep vein thrombosis also may occur, and prophylactic anticoagulation should be considered in consultation with an orthopedist. The most common late complication is the development of osteoarthritis in the affected compartment.

Fractures of the Intercondylar Eminence (Tibial Spine)

Anatomy and Pathophysiology. The intercondylar eminence, or tibial spine, is the central portion of the proximal tibial surface. The spine has two prominences: the medial and the lateral tubercle. The medial tubercle is larger and located more anteriorly than the lateral tubercle. Two intercondylar fossae are present on the proximal tibial surface, one anterior to the intercondylar eminence and one posterior to it. The ACL and the anterior horns of the medial and the lateral menisci attach in the anterior intercondylar fossa. The PCL and the posterior horns of the menisci attach in the posterior intercondylar fossa.

Tibial spine fractures are commonly seen in children and adolescents, but a study suggests that these fractures occur more frequently in adults than was previously thought.[43] The injury is more common in children than in adults because the ligaments are stronger than the adjacent physeal plates in the immature skeleton. A fracture of the anterior tibial spine in children usually is associated with an ACL rupture, as is the case in adults.

Most tibial spine fractures occur as the result of violent knee twisting, hyperflexion, hyperextension, or valgus-varus forces generated during motor vehicle collisions or athletic activities. The tibial spines are fractured by twisting knee movements, whereas hyperextension or hyperflexion forces may cause avulsion of the intercondylar eminence or of the cruciate ligaments from their tibial attachments.

Clinical Features. After tibial spine fracture, the patient complains of pain and swelling of the knee and may be unable to bear weight on the affected extremity. Examination confirms acute hemarthrosis and may reveal a block to full knee extension. Tense effusion may limit range of motion, hinder physical examination, and mask ligament disruption. Definite ACL laxity is associated with this injury, and patients may exhibit an anterior drawer sign, a positive result on Lachman's test, or other signs of ligamentous laxity. In the presence of open physes, tibial spine fractures usually are isolated injuries. Adults are more likely to have an associated tear of the MCL or associated intra-articular fracture, which is associated with a worse prognosis.[38]

Diagnostic Strategies. Radiographic evaluation should include standard anteroposterior and lateral views, and a tunnel view provides a clearer look at the intercondylar area and may reveal the diagnosis. Joint margins should be examined closely for evidence of collateral ligament or capsular bone avulsions. CT sometimes is required to show the location and displacement of the fracture. The fabella, present in some patients, is a sesamoid bone located in the lateral head of the gastrocnemius muscle, which should not be mistaken for an intra-articular loose body or fracture fragment.

The classification of tibial spine fractures is based on the degree of displacement (Fig. 54-7). Type I involves incomplete avulsion of the tibial spine without displacement. In type II, an incomplete avulsion is associated with minimal displacement of the anterior third of the fracture fragment, but the posterior portion remains adherent. Type III is characterized by complete separation of the fragment from its fracture bed and has a higher associated rate of collateral ligament injuries and peripheral meniscal tears. Type III may be subdivided into type IIIA, fractures with complete displacement, and type IIIB, fractures with displacement and rotation (see Fig. 54-7).

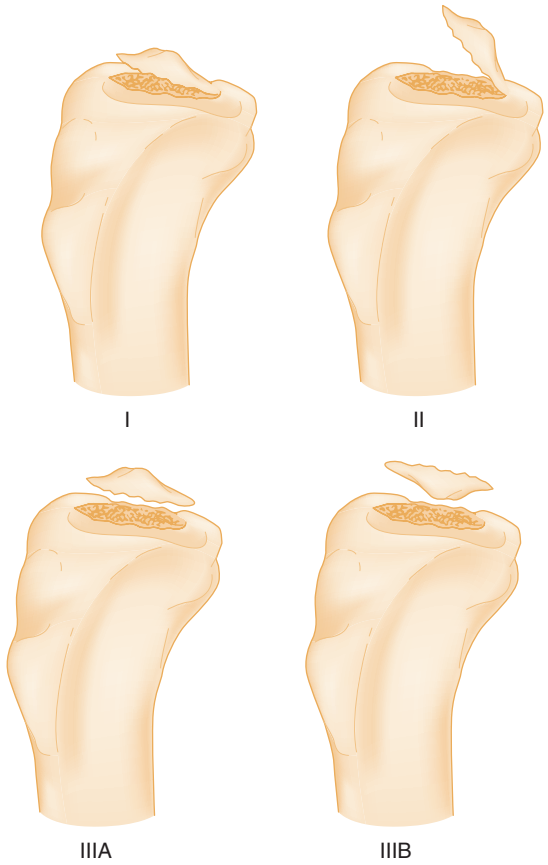


Figure 54-7. Tibial eminence fracture classification. *Type I*: The fracture fragment is elevated anteriorly only slightly; *type II*: the anterior fracture fragment is elevated with only minimal posterior attachment; *type IIIA*: the fracture fragment is completely separated from the tibia; *type IIIB*: the fracture fragment is completely separated and rotated. (Modified from Meyers MH, McKeever FM: Fracture of the intercondylar eminence of the tibia. J Bone Joint Surg Am 41-A(2):209–220, 1959.)

Arthroscopy is useful for diagnosis and treatment of tibial spine fractures. This modality allows drainage of tense hemarthrosis and enables precise diagnosis and classification, especially for children, in whom the diagnosis can be difficult because of developing skeletal changes.

Management. Conservative treatment is effective for all type I injuries. Nondisplaced or incomplete tibial spine fractures generally heal well when treated with cast immobilization in full extension for approximately 6 weeks. Type I and II fractures may require arthroscopy for lavage and accurate classification. If satisfactory closed reduction cannot be obtained or there is associated ligamentous injury, open or arthroscopic reduction and internal fixation should be performed. To restore normal function of the ACL, displaced or rotated fragments must be reduced. Type III fractures usually require arthroscopic or open reduction; screws and tension band wiring techniques have yielded excellent results.[36] With most uncomplicated fractures of the tibial spine, a good result can be expected

when the fracture heals and restores function to the avulsed ACL. A poor outcome, with residual pain and instability, may be associated with additional intra-articular fractures and damage to the MCL.

Epiphyseal Fractures

Anatomy and Pathophysiology. The physes, which occur at the end of the long bones, are primarily responsible for longitudinal growth through the process of endochondral ossification. From birth to skeletal maturity, the distal femoral growth plate contributes 70% of the growth of the femur and 37% of the growth of the lower extremity.[44] Likewise, the upper tibial epiphysis accounts for most of the long growth of the tibia.

Biomechanical data and clinical studies in children and adolescents have confirmed that the ligaments and articular capsule are firmer than the bone and epiphyseal plate.[45] As a result, trauma to this region of the maturing skeleton usually injures the cartilaginous epiphyseal plate. In this way, the physis protects the joint surface from the grossly comminuted fractures seen in adults.

Despite data showing that the physis is the weakest link in the immature skeletal unit, only 15 to 20% of all fractures in children occur through the growth plate.[46]

The proximal tibial physis is far more resistant than other physes as a result of the unique anatomic features of this site.[44] The proximal tibial physis has no significant attachments to the collateral ligaments of the knee. The LCL inserts into the head of the fibula and has no tibial attachment, and the MCL has only a minor attachment to the epiphysis. The major portion of this ligament is attached to the tibial shaft well below the epiphysis. Varus or valgus stress is more likely to injure the distal femoral physis or the tibial metaphysis. Fracture-separation of the distal femoral growth plate and proximal tibial epiphysis most often is caused by an indirect mechanism, commonly related to sports injuries.[44] The Salter-Harris classification of epiphyseal injuries is described in Chapter 46.

Clinical Features. Epiphyseal injuries should be suspected in a child or adolescent who has juxta-articular (growth plate) tenderness, limps, or refuses to or cannot bear weight. The degree of discomfort varies, but the pain often is severe. Depending on the mechanism of injury, the overlying soft tissue may be abraded or lacerated. Swelling is usual in the overlying soft tissue, and an effusion may be present. If the separation is displaced, an angular deformity may be noted.

Epiphyseal growth plate fractures in the lower extremity carry a high incidence of associated injury. Physeal fractures in the region of the knee may be associated with ligament injuries, especially to the ACL and MCL, in one half of the patients. The most serious injury associated with a proximal tibial physis fracture is neurovascular trauma. In particular, popliteal artery injuries have been associated with these fractures, especially when posterolateral or posteromedial displacement is a feature. Peroneal nerve injury also has been reported and may range in severity from neurapraxia to complete disruption.[44]

Diagnostic Strategies. Plain radiography remains the primary means for evaluating epiphyseal injuries. Diagnosis is based on epiphyseal displacement, widening of the physis, and obliteration or haziness of the normal sharply defined, fine, sclerotic opposing margins of the metaphysis and epiphysis. The latter may result from angulation at one or both sites. Oblique views may be required to show nondisplaced fractures of the epiphysis. CT or MRI can evaluate more fully or classify injuries that already are established on the basis of plain radiography.

Management. The most common complication of fractures through the proximal tibial physis is growth disturbance.[45] When growth arrest occurs (approximately 1% of cases), it usually is partial and results from formation of a bridge of bone from the metaphysis to the epiphysis, crossing the growth plate. Although shortening or deformity is less well tolerated in the lower extremity because of weightbearing, many of the growth disturbances do not prove to be clinically significant because of the ability of the immature skeleton to remodel; few such cases are reported to be of sufficient severity to interfere with function.

With regard to treatment, important differences exist between fractures in children and fractures in adults. In general, fractures in children heal rapidly. The younger the child, the more rapidly the fracture heals. In newborn infants, callus forms within 1 week after a birth injury. During the first year, callus is established within 2 weeks; callus takes slightly longer to form in toddlers. Fracture modeling also is more extensive in younger children and when the fracture is closer to the end of the bone. Modeling is less perfect in fractures of the mid-diaphysis in older children. Reduction of fractures near the proximal or distal end of the bone need not be perfect.

If a child has juxta-articular tenderness with negative radiographic findings, a growth plate injury (Salter-Harris type I) should be assumed. If it is difficult to determine whether a line on the radiograph is an epiphyseal line or fracture, a comparison view of the contralateral limb should be obtained. Because growth centers ossify at different times, this technique of comparing the uninvolved limb is often of great assistance in confirming a suspected physeal injury. In such cases, when a physeal injury is suspected, the extremity should be immobilized for approximately 2 weeks and reevaluated with radiographic study, looking for periosteal new bone or physeal thickening. Generally, emergency management of most epiphyseal fractures of the distal femur or proximal tibia includes ice, elevation, immobilization with a long leg posterior splint, with early orthopedic consultation. Anatomic reduction is desirable for displaced fractures of the distal femur and proximal tibial epiphysis. Open reduction usually is required only for patients in whom closed reduction fails.[47]

Late complications include angular deformity, leg length discrepancy, stiffness, quadriceps atrophy, and persistent instability of the knee. Delayed union or nonunion is almost never a problem except in patients with an underlying neuropathy.[34] Because growth inhibition may follow even nondisplaced physeal fractures, long-term orthopedic follow-up care is advisable.

Bone Bruise

Bone bruise is a radiographic diagnosis, involving areas of cancellous bone with high signal intensity on MRI fat suppression sequences. Bone bruise may be present in approximately one half of acutely injured knees.[48] A high proportion of patients with a bone bruise have significant soft tissue injury. Nearly all bone bruises resolve after 1 year.[49]

Osteochondritis Dissecans

Osteochondritis dissecans is a rare orthopedic disorder of unknown etiology (Fig. 54-8). The disorder is found mainly in adolescents and results in partial or total separation of a segment of articular cartilage and subchondral bone from the underlying bone. It is commonly unilateral, involving the nonweight-bearing lateral aspect of the medial femoral condyle, and is thought to be related to acute or chronic trauma. Occasionally the lateral femoral condyle or inferior patella pole is involved. Patients often have pain, swelling, and giving-way

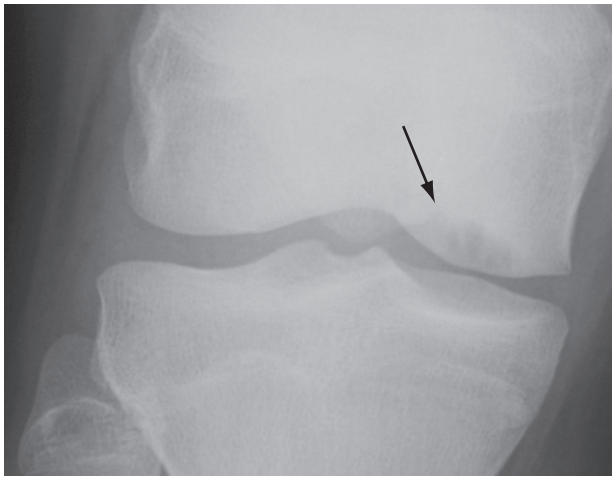


Figure 54-8. Osteochondritis dissecans. The *arrow* indicates a subcortical radiolucency in the knee of an adolescent female with chronic medial knee pain.

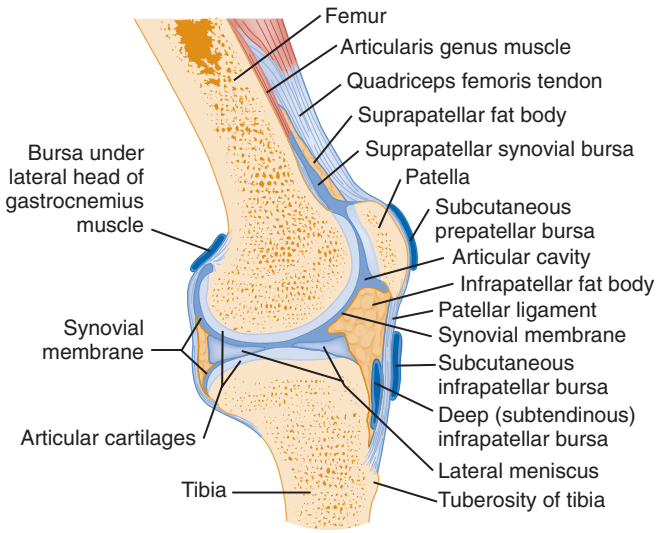


Figure 54-9. Parasagittal section (lateral to midline) of the knee showing extensor mechanisms and relevant structures.

episodes without a history of trauma. Localized tenderness of the condyle often is the only physical finding. Routine radiographic views usually are diagnostic: A subcortical lucency (see Fig. 54-8) can be appreciated, and an osteochondral fragment may be seen separated from the underlying bone. MRI or CT may aid in determining the exact location and extent of the osteochondrotic lesion. Emergency department patients with suspected osteochondritis dissecans should be non-weight-bearing until seen by an orthopedist.

The management of these patients is based on the stability of the osteochondral fragment and the maturity of the skeleton.[48] If the epiphyses are open, conservative treatment with protective weightbearing usually results in healing of the lesion. When the epiphyses are closed, the prognosis for healing is guarded. If the fragments are detached, the loose fragments require surgery for removal or fixation. Protected range of motion with non-weight-bearing activity for 6 to 10 weeks generally is advised.

Osteonecrosis

Osteonecrosis occurs when disruption of the blood supply to the bone causes infarction. The knee is a common site of involvement, particularly the weight-bearing surface of the medial femoral condyle.[50] Spontaneous osteonecrosis usually affects middle-aged and elderly patients, whereas secondary osteonecrosis may occur in younger patients related to corticosteroid therapy or in association with sickle cell disease, lupus, or renal transplantation, among many other risk factors.[51] The exact etiology is unknown. A common clinical presentation is spontaneous onset of severe localized knee pain that may be accompanied by an effusion and loss of joint motion. The physical examination reveals point tenderness over the involved femoral condyle or tibial compartment. Radiographs obtained at the onset of symptoms usually are normal in appearance, and the diagnosis is confirmed with technetium bone scanning, which shows increased activity. MRI also is diagnostic of acute osteonecrosis. Subchondral marrow signal abnormality is the earliest change noted; subchondral collapse and fracture may be seen in more advanced cases.[52]

Initially, most patients can be managed with conservative treatment consisting of rest, protected weightbearing, and nonsteroidal anti-inflammatory drugs (NSAIDs). The outcome depends on the percentage of the weight-bearing surface involved with the process. If the lesion is small, no surgical treatment is required. Over the long term, degenerative changes will develop in most patients, but initially the changes are not severe. For more advanced stages of femoral osteonecrosis, various surgical treatments have been proposed, including arthroscopic débridement, proximal tibial osteotomy, prosthetic replacement, and allografting.[51]

Extensor Mechanism Injuries

Anatomy and Pathophysiology. The extensor mechanism consists of the quadriceps muscles, quadriceps tendon, medial and lateral retinacula, patella, patellar tendon, and tibial tubercle (Fig. 54-9). Passive and dynamic stabilization of the patella are aided by the surrounding soft tissue. Although this anatomic complex encompasses the most superficial aspect of the knee, ruptures of the extensor mechanism are infrequent injuries relative to other types of injuries of the knee joint. Disruptions of the extensor mechanism may occur at any level from the quadriceps muscle to the insertion on the tibial tubercle. Injury generally occurs as a result of sudden vigorous contraction of the quadriceps muscle with the knee in a flexed position, laceration, or a direct blow. Rupture of the quadriceps tendon usually occurs at or just proximal to the patellar insertion. Occasionally the rupture may extend into the vastus intermedius tendon or transversely into the retinaculum. Most patellar tendon ruptures occur at the site of origin on the inferior pole of the patella.

Tendons of the extensor mechanism are extremely resistant to tensile loads and do not rupture under normal physiologic conditions, even with significant degrees of stress. Chronic systemic conditions, including rheumatoid arthritis, gout, systemic lupus erythematosus, hyperparathyroidism, and iatrogenic immunosuppression in organ transplant recipients, may render the tendon vulnerable to rupture.[53] Several studies have implicated use of steroids or fluoroquinolones in tendon rupture.[54] Age also seems to be a factor, with quadriceps tendon rupture usually occurring in patients 40 years of age or older and patellar tendon rupture occurring in patients younger than 40. In children, quadriceps and patellar tendon ruptures are rare, and muscle tears seem to predominate. In adolescents, patellofemoral dysplasia, chronic tendinitis, and the use of steroids seem to be predisposing factors. Dysplasia may cause extensor mechanism injury by repetitive tensile overloading, and corticosteroids seem to weaken collagen ultrastructure and impair the reparative process.

Clinical Features. Clinical evaluation can elicit the correct diagnosis in most cases of complete disruption of the extensor mechanism.[55] Patients with extensor disruption may have the following signs and symptoms: (1) acute onset of pain, swelling, and ecchymoses over the anterior aspect of the knee and a palpable defect in the patella, quadriceps tendon, or patella tendon; (2) loss or limitation of ability for active leg extension (extension lag usually is seen when the last 10 degrees of extension is performed haltingly or with difficulty); (3) high-riding patella (patella alta) with patellar tendon rupture and superior retraction; and (4) low-riding patella (patella baja) with quadriceps tendon rupture and inferior retraction. Partial disruptions may be difficult to diagnose on clinical examination and may require MRI for confirmation.

Diagnostic Strategies. Standard anteroposterior and lateral radiographs should be obtained and may reveal characteristic findings, possibly including obliteration of the quadriceps or patella tendon, a poorly defined suprapatellar or infrapatellar soft tissue mass, soft tissue calcific densities, or a displaced patella (Fig. 54-10). Patella alta may be sought on the lateral radiograph using a ratio of patellar length to patellar tendon length (the Insall-Salvati ratio). If this ratio is less than 0.8, patella alta is present.[56,57] The degree of flexion should not affect this ratio, which relies on the inelasticity of the patellar tendon. In patients with quadriceps rupture, degenerative spurring of the patella (tooth sign) commonly is seen on tangential views. Obliteration of the extensor tendons may be caused by a frayed tendon and surrounding hematoma. A soft tissue mass represents proximal or distal retraction of the torn tendon. Calcific densities may represent avulsed bone fragments of the patella or tibial tubercle or dystrophic calcifications in the substance of the tendons. Despite these multiple radiographic signs, the correct diagnosis is infrequently made by plain radiography in cases of incomplete quadriceps tendon rupture. MRI shows the entire extensor mechanism and is the best imaging modality for diagnosing pathology in this system, even in the acute phase. MRI usually is reserved for patients with possible incomplete disruption or for those with a complication of intra-articular derangements.

Management. Treatment of acute extensor mechanism injuries produces a much better clinical outcome if instituted early, within 2 to 6 weeks of the initial injury. Accurate diagnosis at the time of injury is essential. Patients with delayed diagnosis of patellar tendon rupture may experience significant retraction of the patella proximally and subsequent development of quadriceps contractures or adhesions. If the tear is only partial, immobilization with the knee in full extension for 4 to 6 weeks is the treatment of choice.[58] Surgical intervention is required for reattachment of complete tendon ruptures, and repair should be performed as soon as possible after injury to obtain the best results. Numerous techniques have been described for early and late repairs, and the choice of procedure depends on several factors, including location of the tear, lag time between injury and repair, and presence or absence of adhesions. After primary repair, the knee is immobilized in full extension with a long leg cast until healing is complete. Gradually progressive active and passive range-of-motion exercises are indicated for optimal results.

Patellar Fractures

Anatomy and Pathophysiology. The patella is the largest sesamoid bone in the body. It is held in place by the quadriceps tendon, the patellar ligament, and the medial and lateral retinacula. As an integral part of the extensor mechanism, the patella increases the effective lever arm of the quadriceps by providing anterior displacement of the quadriceps tendon.[27] All fractures of the patella, except for small avulsion fractures of the rim, are intra-articular.

Patellar fractures constitute approximately 1% of all skeletal injuries and occur in all age groups.[59] Patellar fractures are classified as transverse, stellate, or comminuted; longitudinal or marginal; proximal pole or distal pole; and rarely osteochondral. They may be either displaced or nondisplaced and occur either from direct or indirect forces or from dislocation. The most common fracture pattern is the *transverse* fracture (accounting for 50 to 80% of cases).[59] This type often is seen in young adults and usually results from a powerful contractile force transmitted from the quadriceps tendon. This force may pull the superior portion of the patella upward, leading to wide displacement. In such cases, the medial and lateral retinacula are usually disrupted, resulting in significant functional dis-

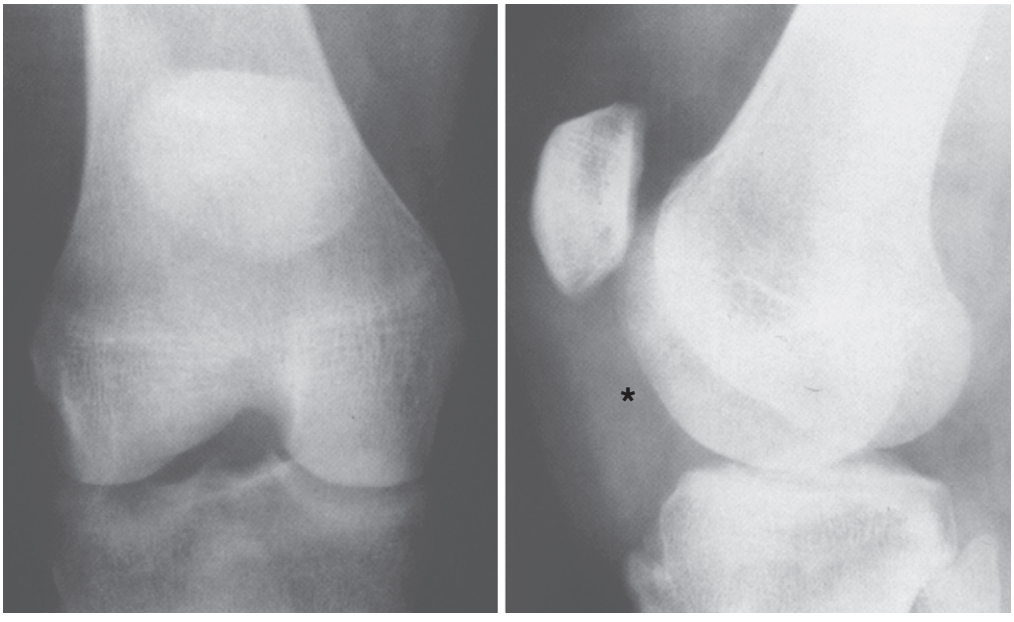


Figure 54-10. Rupture of the infrapatellar tendon, resulting in the high-riding patella in frontal (**A**) and lateral (**B**) projections. In **B,** the normally lucent infrapatellar portion of the joint space is dense *(asterisk)*, representing blood within the anterior compartment. (From Harris JH, et al: The Radiology of Emergency Medicine, 3rd ed. Baltimore, Williams & Wilkins, 1993.)

ability; active extension is impossible. Nondisplaced transverse patellar fractures usually are caused by a direct blow to the anterior aspect of the patella (e.g., a fall on the knee or a direct blow sustained in vehicular trauma). The retinaculum and extensor mechanism usually remain intact, and the patient retains limited functional ability for active extension. *Stellate* and *comminuted* fractures account for 30 to 35% of all patellar fractures and commonly result from a direct impact.[59] The fracture elements often appear as separated fragments on plain radiographs, but they are held in place and supported by the medial and lateral retinacula and the overlying soft tissues. Small proximal fragments are at risk for avascular necrosis because the patellar blood supply is central and inferior. *Longitudinal* or *marginal* vertical patellar fractures are less common, usually are the result of direct injury, and involve the lateral facet.

Clinical Features. On physical examination, tenderness, swelling, and ecchymosis over the patella and prepatellar bursa are noted. Active extension may be limited or absent, depending on the fracture pattern and amount of fragment displacement. Associated injuries may include fractures of the femoral neck, dislocation of the hip, and acetabulum fractures.

Diagnostic Strategies. Radiologic evaluation of patellar fractures should include standard anteroposterior, lateral, and sunrise views. Most patellar fractures are obvious on plain radiographs, but vertical marginal fractures may be difficult to identify; they are obscured by the femur on the anteroposterior view and not seen at all on the lateral view.[60] Close examination of sunrise (or equivalent) views may reveal an osteochondral avulsion fragment or marginal fracture (Fig. 54-11). Bipartite and multipartite patellae are common normal variants and should not be confused with fractures. Ossification centers are found at the upper outer quadrant of the patella and have smooth cortical margins. Comparison radiographs may be helpful because these anatomic anomalies often are bilateral. In some cases, MRI or arthroscopy may be needed to identify occult marginal fractures or free osteochondral fragments.

Management. If the patient can actively extend the knee without displacing the fracture, the retinaculum is intact, and the fracture may be treated nonoperatively. Nondisplaced patellar fractures usually are treated with a long leg cast for 4 to 6 weeks, with uniformly good results. Casting the knee in full extension relieves the patella of almost all stress during the healing period. For initial management, a knee immobilizer may be used. Patients should be instructed to use crutches, with partial weightbearing as tolerated, and should be referred for orthopedic or primary care follow-up.

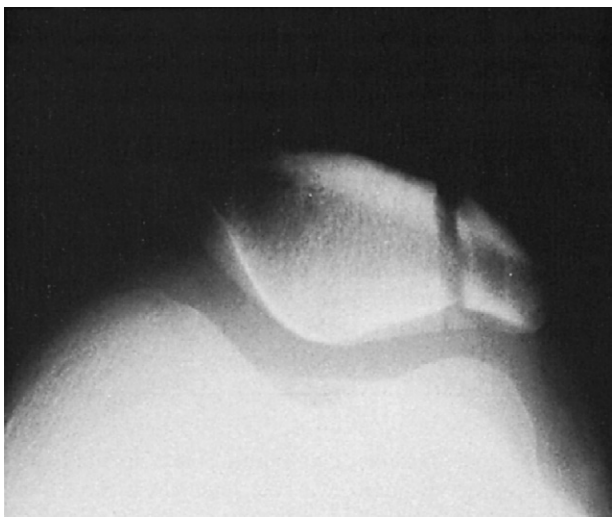


Figure 54-11. Patellar fracture, sunrise view. The sharp nonsclerotic margins identify this as an acute fracture and not a congenital finding. (From Rosen P, et al: Diagnostic Radiology in Emergency Medicine. St. Louis, Mosby, 1992, p 196.)

For widely displaced transverse fractures, open reduction and internal fixation are necessary for optimal results. Although operative techniques vary among surgeons, tension band wire and suturing of the retinaculum often are used. A knee immobilizer or long leg posterior splint can be used initially to immobilize the extremity before definitive care is provided. Treatment options for displaced comminuted fractures include open reduction and internal fixation and partial or complete patellectomy.

Fracture fragment separation and dehiscence of the fracture repair are uncommon. They generally result from inadequate internal fixation or, in some cases, an inadequate period of immobilization. Avascular necrosis is rare. Range of motion generally is good after all procedures. Persistent patellofemoral pain and osteoarthritic symptoms are reported as late sequelae of patellar fractures in 56% of patients.[59]

Patellar Dislocation

Anatomy and Pathophysiology. Traumatic patellar dislocation is a relatively common knee injury and can lead to recurrent patellar subluxation and dislocation. It is more common in children than in adults. Most cases are lateral extra-articular dislocations, and the mechanism of injury usually is a direct blow to the anterior or medial surface of the patella. It may occur from an athletic injury caused by a valgus stress combined with flexion and external rotation. In nearly all cases, disruption or sprain in the medial patellar retinaculum results from stretching of this structure as the patella subluxates laterally; subluxation usually indicates a stretched medial retinaculum, and dislocation suggests a tear. Although extra-articular patella dislocations are common, intra-articular dislocations are rare occurrences that must be considered in any patient with a locked knee.

The quadriceps angle (Q angle) is measured with the quadriceps contracted. The angle is formed by lines drawn on an anterioposterior radiograph from the tibial tubercle to the center of the patella and from the center of the patella to the anterior superior iliac spine. Normally this angle is 10 degrees or less in men; it may be 15 degrees in women. A Q angle exceeding these dimensions may predispose the patient to patellofemoral problems.[61]

Clinical Features. Patients with lateral patellar dislocation may complain of the knee giving out accompanied by pain and swelling. Inability to bear weight and inability to flex the knee are common complaints. There may be a history of previous dislocation. Examination reveals a defect anteriorly with the patella deviated laterally. Tenderness along the medial joint line usually can be elicited by palpation, and an effusion may be present. Acute hemarthrosis is seen most commonly if there is an associated osteochondral fracture. Osteochondral fractures typically occur on the articular surface of the patella and may involve only cartilage (chondral fractures) or include a piece of underlying cortical bone. Patellar dislocations may reduce spontaneously, or the patient may self-reduce the dislocation, usually followed by formation of a large effusion.

The patellar apprehension test is used to aid the clinical identification of patients at risk for patellar dislocation or subluxation. The *apprehension sign* refers to the combination of manifestations of anxiety and anticipatory reactions observed in the patient when the examiner attempts to slide the nondisplaced patella laterally. As a more objective element of this reactive pattern, the patient may forcefully contract the

quadriceps femoris muscle in an attempt to prevent such displacement and its associated pain. A positive result on the apprehension test indicates a tendency for patellar subluxation or dislocation. This test has no proven value and is not necessary in a patient with acute patellar dislocation, but it may be useful in establishing the diagnosis in patients who report an "event" that resolved spontaneously.

Diagnostic Strategies. Standard anteroposterior and lateral radiographic views generally are adequate for diagnosis. Obtaining a sunrise (skyline) view usually is not possible because of pain and inability to flex the knee. Radiographic findings include lateral deviation of the patella out of the trochlear groove, usually with an effusion. Radiographs should be examined for evidence of avulsion fractures.

Management. After dislocation is diagnosed, closed reduction should be attempted. Force or pressure should be directed anteromedially on the lateral patellar margin while gentle extension of the leg is attempted simultaneously. Uncommonly, patellar reduction may be difficult. Closed reduction can be achieved by applying downward pressure to the lateral aspect of the patella, creating an external rotational force that unlocks the medial patellar facet.[62] Postreduction radiographs are recommended and should reveal the patella in the trochlear grove. Osteochondral avulsion fragments may be visualized radiographically, and postreduction radiographs should be examined carefully for their presence. Radiologically evident intra-articular loose bodies may require arthroscopic removal.

Typically, traumatic patellar dislocations occur with disruption of the medial retinaculum but an intact lateral retinaculum, preventing internal rotation. Dislocations that are irreducible by conventional methods may be associated with significant internal rotation and lateral retinaculum pathology.

After successful reduction, the knee should be immobilized in full extension for 3 to 6 weeks, to allow adequate time for the medial retinaculum to heal. Ice, elevation, nonweight bearing, and analgesia provide additional benefit in the acute setting. The patient can be discharged with referral for orthopedic or primary care follow-up within 2 weeks. Although the incidence of recurrence may be decreased with appropriate therapy and proper patient selection, up to 44% will experience a recurrent dislocation, and more than one half of all patients with a primary patellar dislocation will continue to have symptoms of instability or anterior knee pain.[63] Patellar dislocations often recur and sometimes require surgery, involving arthroscopic release of the lateral retinaculum.

Soft Tissue Injuries

The knee is the most commonly injured joint. The ligaments of the knee function in conjunction with the joint capsule to limit varus-valgus (medial-lateral) bending of the knee and both anterior-posterior and varus-valgus translations of the knee. Ligament injuries to the knee may involve any or all of the ligaments and may range in severity from mild sprain to complete tears. Collateral ligament injury usually causes tenderness and pain along the joint line. Cruciate injuries pose more of a diagnostic dilemma because they are intra-articular structures.

Cruciate Ligament Injuries

The cruciate ligaments are the primary stabilizers for anterior and posterior displacement of the tibia on the femur. They are so named (Latin *crus* means "cross") because they cross each other between their attachments. The ACL extends obliquely upward, medially, and backward from the anterior intercondylar area of the tibia to the medial aspect of the lateral femoral condyle. The ACL prevents excessive anterior displacement of the tibia on the femur and helps control rotation and hyperextension of the knee during cutting, twisting, and turning activities. It is the most commonly injured major ligament of the knee, with more than 100,000 new ACL tears occurring in the United States annually.[64] The PCL passes upward, laterally, and forward medial to the ACL from the posterior intercondylar area of the tibia to the lateral aspect of the medial condyle of the femur. The PCL prevents excessive posterior displacement of the tibia on the femur, especially during flexion. The PCL is extremely strong, and injuries are relatively uncommon. Cruciate ligament injury is uncommon in children with open physes.

The ACL is commonly injured in sports. Numerous mechanisms of injury produce ACL disruption. Although ACL injuries can be caused by contact, they are more common in noncontact sports, with the plant-and-pivot and stop-and-jump mechanisms predominating. A direct blow to the flexed knee, as may occur in motor vehicle crashes (from the dashboard), and turf injuries with the knee flexed and the ankle plantarflexed also can result in an ACL injury.

One half of ACL injuries are associated with meniscal tears. The lateral meniscus is torn more commonly than the medial meniscus in acute ACL injuries, but in chronic ACL tears, the medial meniscus is more commonly involved. The classic "unhappy triad" of ACL, MCL, and medial meniscus injury may actually be less common than the association of torn ACL, torn MCL, and torn lateral meniscus.

The diagnosis of ACL injury often can be made from the history alone. Pain is the most common complaint with ACL rupture and usually is immediate. An audible "pop" at the time of injury is an important clue and is reported by approximately 70% of patients with ACL rupture. Patients also may report buckling, locking, or collapse of the knee and its inability to bear weight. The anterior drawer test is used to diagnose ACL injuries (see above).

PCL injuries are comparatively rare. Mechanisms include a fall onto the ground with the foot plantar-flexed (striking the tibial tubercle), a direct posterior blow to a flexed knee (e.g., a dashboard injury), hyperflexion, hyperextension, severe varus or valgus loads after failure of the collaterals, and knee dislocations. Nearly all PCL injuries are associated with other ligament injuries, including concurrent injuries of the MCL, ACL, or posterolateral complex.[64,65] PCL injuries are classified as partial (grade I or II) or complete (grade III) tears. Pain and swelling are common complaints with isolated PCL tears and with PCL tears having combined capsuloligamentous disruption. Popping or tearing sensations are infrequently noted, and instability usually is not immediately appreciated. Later, the patient may complain of feeling the femur "fall off" the tibia. The posterior drawer test (see above) is commonly done to assess for the integrity of the PCL.

Clinical evaluation is moderately sensitive for ACL tears and other intra-articular injuries with sensitivity for ACL injury ranging from 62 to 100% and 64 to 82% for meniscus injury.[66] The lesions most difficult to diagnose are chondral fractures, tears in the ACL, loose bodies, and fibrotic fat pads.

Collateral Ligament Injuries

The medial stabilizers of the knee are the joint capsule and the MCL. The semimembranosus and pes anserinus are medial dynamic stabilizers. These structures resist valgus laxity and medial rotary instability. The MCL is a two-part structure with both a long superficial and a deep capsular component; the latter attaches to the medial meniscus and acts as a stabilizer for this structure. The MCL usually is injured

by a direct blow or impact to the lateral aspect of the knee, which imposes a valgus stress. Overall, MCL injury is the most common isolated knee ligament injury, and it is the injury most commonly associated with ACL injury. MCL injury usually does not require surgical treatment.

The lateral stabilizers of the knee are the LCL and the lateral joint capsule. Secondary contributors to lateral stability are supplied by the IT band, biceps tendon, and popliteal arcuate complex in the posterolateral corner of the knee. Resistance to varus stress is provided mainly by the LCL. Fibers descend from the lateral femoral condyle and insert at the fibula head. The lateral ligaments are under tension during standing and walking, when they are at or near maximal extension. The LCL usually is injured by a mechanism of hyperextension with varus stress, commonly accompanied by a direct blow or rotation. Injuries to the LCL are less common but more disabling than injuries of the medial aspect. The lower incidence of injury is attributed to the greater mobility of the LCL and overall greater stability of the lateral compartment. Varus injury is uncommon because the inner aspect of the knee is protected by the opposite leg. The forces necessary to produce LCL injury usually are greater than the forces required for medial injury, which partially explains the high frequency of associated injuries accompanying LCL injury. The tendon of the biceps femoris muscle attaches to the head of the fibula, just inferior to which the peroneal nerve passes. Because of this relationship, common peroneal nerve injury and biceps femoris tendon injury must be considered in patients with LCL injury.

The accuracy of the knee examination for ligamentous damage is enhanced if it is accomplished soon after injury and before the onset of swelling and pain, but the patient may not tolerate the examination in any case, and muscle spasm can obscure findings. In any case, ligamentous injuries are not emergencies and can be diagnosed definitively after the acute phase has passed. Focal tenderness at the origin or insertion sites suggests collateral ligament trauma but also can occur with muscular injury, osseous pathology, or meniscal tear. Range of motion should be documented and stability testing done to assess ligamentous injury as outlined previously.

Diagnostic Strategies. Plain radiography may be used before stress testing in cases of suspected ligamentous injury to rule out the possibility of an associated fracture. Although patients with isolated collateral ligament strain rarely show acute osseous pathology, the yield increases in cases with radiographic evidence of traumatic effusion and in cases in which cruciate ligament injury is suspected. The initial radiographic evaluation should include anteroposterior, lateral, intercondylar notch, and sunrise views. Each radiograph should be evaluated for possible osteochondral injuries, loose bodies, or avulsion injuries at the attachment sites of ligaments. The lateral capsular sign, associated with the Segond fracture (see Fig. 54-3) and fracture of the posterior aspect of the lateral tibial plateau, commonly are associated with ACL tear.

Arthroscopy is the "gold standard" modality for diagnosis of soft tissue injuries of the knee (ligaments or menisci). MRI is useful but may miss small tears and anatomic abnormalities, and even if findings are normal, arthroscopy may still be necessary if symptoms persist. Moreover, abnormalities discovered at arthroscopy can be repaired. Therefore, many orthopedic surgeons recommend arthroscopy rather than imaging for diagnostic workup of knee pain when the causative disorder is not apparent on physical examination.

Management. Isolated collateral ligament injuries of all grades usually are managed nonoperatively, provided that the ACL is intact. The nonoperative approach should focus on controlling pain, restoring range of motion, regaining muscle strength, and protecting the knee from further injury. Appropriate initial therapy includes ice, NSAIDs, and immobilization if needed to control pain. Patients may be placed on a regimen of partial weightbearing or nonweightbearing using crutches. Orthopedic or primary care follow-up is advised, and a rehabilitative exercise program for quadriceps and hamstring strengthening may be instituted when the acute injury resolves.

Management of an ACL tear is controversial, because short-term disability and long-term arthritic sequelae are difficult to predict. Most young patients with a complete ACL tear who are active in sports require reconstructive surgery to stabilize the knee. Surgical repair usually is performed arthroscopically after a delay of 2 to 3 weeks to allow swelling to subside. Older patients and patients who do not participate in active sports may be managed conservatively with muscle strength training. If recurrent functional instability subsequently develops, reconstruction may be considered at a later date.

Isolated PCL injuries are unusual and typically are managed nonoperatively. These injuries often are painful but usually do not lead to instability. Rehabilitation involves quadriceps strengthening and functional bracing. Over 10 to 20 years, degenerative changes of the articular surface may result in stiffness and pain.

Meniscal Injuries

Anatomy and Pathophysiology. The medial and lateral menisci are crescent-shaped fibrocartilaginous cushions that sit on the superior articular surface of the tibia and provide a gliding surface for the femoral condyles. They function as shock absorbers and aid in the distribution of stress across the joint surface by providing a larger area of contact. They also act as secondary stabilizers by deepening the tibial plateau. Normal tibiofemoral articulation and function depend on meniscal integrity; damage or loss leads to osteoarthritis. The medial meniscus is firmly attached anteriorly and posteriorly to the joint capsule. The lateral meniscus is less firmly attached to the capsule and more mobile. The menisci move slightly forward with extension and backward with flexion. Because of its greater mobility, the lateral meniscus is less vulnerable to injury. The meniscus is avascular except at the peripheral third, which has the greatest potential to heal after injury.

Meniscal injury classically manifests with pain and tenderness at the joint line, effusion, and clicking or locking of the knee. Significant hemarthrosis is less likely and suggests cruciate ligament injury. Intermittent locking results from a meniscal fragment blocking joint movement. By contrast, persistently decreased range of motion results from prevention of knee movement by effusion and pain. Injury to the menisci may be from a single traumatic episode or a degenerative process, or a combination. The mechanism usually involves a twisting maneuver on a weight-bearing knee. The force required sometimes can be as slight as arising from a chair while turning. Most meniscal tears are posterior.

Clinical Features. Meniscal injuries are unusual in children but become increasingly more common in adolescents and adults. An isolated meniscal tear should be suspected in a patient with a history of intermittent locking, effusion, giving way, and pain and physical examination findings of joint line tenderness and a positive result on McMurray's test. Cruciate tears invariably result in immediate hemarthrosis; meniscal tears usually result in development of an effusion over 12 to 24 hours. A second, more common presentation is that of a patient with an unstable knee who has chronic ACL insufficiency and similar history and physical findings.

The cardinal sign of a meniscal tear is local pain and tenderness along the joint line. Joint line pain and tenderness are

especially apparent with extremes of flexion and extension. Not all tears of the menisci are symptomatic. Degenerative lesions of the posterior horn are relatively common in middle age and later and may be asymptomatic. The differential diagnosis for a torn meniscus is extensive and includes loose bodies, osteochondrotic lesions, tibial spine fractures, patellofemoral pain syndrome, popliteal tendinitis, plica syndromes, inflammatory arthritis, and discoid menisci with or without a tear. Meniscal tears commonly accompany ACL tears.

Diagnostic Strategies. Diagnosis of acute meniscal injury is difficult, and more so in the presence of any acute knee injury, especially ACL tear.[67] Meniscal injury cannot be diagnosed by plain radiography or CT scanning. Arthroscopy is the gold standard for diagnosis, and MRI is an alternative but may miss meniscal tears.

Management. Definitive treatment of a meniscal injury is not urgent. Unless the knee is locked and cannot be extended or flexed, a patient with a meniscal tear should be managed with analgesics, immobilization, ice, nonweightbearing, and referral for orthopedic or primary care follow-up. Surgery is reserved for cases with persistent symptoms that limit activity. Surgery involves arthroscopic exploration. The torn meniscal fragment is reattached if it is well vascularized; otherwise, it is resected.

Overuse Syndromes

Overuse syndromes result from repetitive trauma and inflammation. The typical complaint is knee pain, often localized to one of three particular areas: the medial aspect, the lateral aspect, or the peripatellar region. Medial knee pain may be caused by subluxation of the patella, a stress fracture of the upper third of the tibia, anserine bursitis or tendinitis, and MCL strain related to excessive foot pronation. Lateral knee pain may be caused by iliotibial or popliteal tendinitis, LCL strain, or stress fracture of the fibula. Anterior pain is typical of lateral patellar compression syndrome, peripatellar tendinitis, and patellofemoral syndrome, the most common cause of knee pain.

Patellofemoral Pain Syndrome

Anatomy and Pathophysiology. The *patellofemoral pain syndrome* refers to the clinical presentation of anterior knee pain related to changes in the patellofemoral articulation. *Chondromalacia patellae* describes softening of the articular cartilage. Correlating pathologic changes on the surface of the patella and clinical symptoms has been difficult, and the pain mechanism has not been precisely defined.

Clinical Features. As noted, the patellofemoral pain syndrome is the most common cause of knee pain. Affected patients generally are 10 to 20 years of age and often have difficulty describing their symptoms clearly. The pain usually begins gradually and commonly is not related to trauma. One knee usually is more affected than the other. The knee is more painful with prolonged flexion (e.g., from sitting in a movie theater), and the discomfort typically is accentuated by stair climbing and kneeling. The patient may have instability related to patellar subluxation or dislocation. The syndrome occurs both in athletes and in elderly patients who have arthritis affecting the patellofemoral joint. Considerations in the differential diagnosis include tears of the menisci, plica syndrome, inflammatory or degenerative arthritis, ligament injuries, and overuse syndromes (e.g., prepatellar bursitis, patella tendinitis).

The physical examination should begin with observation. The patient may ambulate with an antalgic gait. A tibiofemoral joint effusion may be present. The patellar facets may be tender. Classically, compression of the patella against the femur, with the knee extended, causes pain. There may also be apprehension to medial or lateral sublaxation.

Diagnostic Strategies. Plain films are typically normal, and other more advanced studies should be undertaken only if other diagnoses are being considered.

Management. Most patients, regardless of the cause of their condition, respond to a rehabilitation program. Conservative treatment for patellofemoral pain usually is effective, with most patients responding to one or more of four types of treatment: (1) exercises to strengthen the quadriceps, (2) brace support of the patellofemoral mechanism, (3) activity modification limiting flexion, and (4) medications such as NSAIDs for pain. The initial goal is to reduce pain and improve function, with emphasis placed on strengthening the vastus medialis oblique muscle. The patient should receive appropriate referral to ensure that an optimal rehabilitative scheme is designed.

Iliotibial Band Syndrome

The IT band is a strip of fascia lata that extends from the iliac crest to the lateral tibial tubercle. It connects the lateral femoral condyle and the lateral tibia and stabilizes the knee joint in extension. Irritation due to overuse can cause inflammation of a bursa underlying the IT band at the lateral femoral epicondyle, resulting in lateral knee pain. The syndrome is most common in distance runners and is more likely in hyperpronators. Physical findings include localized tenderness of the lateral femoral epicondyle and IT tightness or pain, elicited by Ober's or a related test.[67] In Ober's test, the patient lies on the side with the unaffected leg down, flexed to 90 degrees at the hip and knee. The affected hip is abducted, the knee extended, and then the hip is allowed to return to neutral adduction with gravity. Failure of the hip to adduct fully with gravity or reproduction of pain at the lateral knee indicates IT tightness or inflammation, respectively. Radiographs are normal in appearance. Considerations in the differential diagnosis include early degenerative joint disease, cystic or torn lateral meniscus, lateral capsular strain, lateral tibial or femoral condyle osteonecrosis, stress reactions, chondromalacia, and popliteus tendinitis. Treatment involves rest, ice, and NSAIDs during the acute phase, followed by an IT band stretching regimen, improved footwear and orthotics when indicated, and gradual return to previous levels of activity. Steroid injections are helpful for refractory cases, and surgical release is uncommonly required.

Peripatellar Tendinitis

Peripatellar tendinitis, or jumper's knee, refers to a spectrum of patellar tendon and extensor mechanism abnormalities that result from chronic repetitive stress from jumping, running, or cutting. Microscopic tears occur in the tendon. Treatment involves NSAIDs, rest, and activity modification. Local steroid injections are not recommended. For highly competitive athletes and patients in whom conservative treatment fails to effect improvement, surgery with débridement of abnormal tissue may be performed.

Plica Syndrome

Plicae, or redundant folds of synovium, are normal embryologic structures that persist in the adult knee. Repetitive bouts of synovitis within the plica may result in a tight inelastic band that interferes with knee motion. Patients typically complain

of pain over the region of the medial femoral condyle brought on by activity but also occurring after sitting for prolonged periods. A snapping sensation is another commonly reported symptom as the plica sweeps across the femoral condyle. Other nonspecific symptoms include intermittent swelling, locking, weakness, and stiffness. The physical examination often elicits tenderness over the medial femoral condyle but not the medial joint line; the latter finding would be more typical of a medial meniscal lesion. An effusion, crepitus, loss of motion, quadriceps atrophy, and a positive result on McMurray's test may be noted as well.[68]

Plain radiography is necessary to exclude other causes of knee pain but is of no value in diagnosing plica syndrome, for which arthroscopy usually is required. Most plicae are incidental arthroscopic findings unrelated to underlying knee pathology. Medial patella pain is more likely to be related to patellofemoral maltracking than to plica syndrome. Likewise, anteromedial joint line tenderness is more likely to be related to a meniscal tear than to a pathologic plica.

Treatment involves rest and NSAIDs. When the acute symptoms have resolved, a rehabilitation program is instituted to emphasize quadriceps strengthening and stretching. Arthroscopic excision of pathologic plica may be necessary if conservative treatment fails.

Popliteus Tendinitis

The popliteus is a small, flat muscle that originates on the lateral femoral condyle and inserts on posteromedial tibia, capsule, and lateral meniscus. It passes beneath the lateral head of the gastrocnemius. Its tendon is surrounded by a bursa that separates it from the fibular collateral ligament, femoral condyle, and capsule. Functionally, it prevents external rotation of the tibia and withdraws the lateral meniscus during flexion to prevent impingement between the femur and the tibia. A third function, along with the quadriceps and PCL, is to stabilize the knee by preventing forward displacement of the femur on the tibia. Popliteal tendinitis usually occurs in athletes and often causes localized pain over the posterior or posterolateral aspect of the knee. Running and walking downhill exacerbate symptoms. Usually there is no history of effusion, locking, or giving way.[69]

On physical examination, tenderness is noted at the insertion point of the muscle, medial to the insertion of the lateral head of the gastrocnemius. Because of its close relationship to other soft tissue structures, the diagnosis may be difficult. The *Webb test* is performed with the patient supine and the knee flexed to 90 degrees. The leg is rotated internally, and the patient is asked to resist the examiner's attempt to externally rotate the leg. Reproduction of symptoms suggests the diagnosis. Considerations in the differential diagnosis for popliteus tendinitis include injury of the biceps femoris insertion, lateral meniscus, lateral gastrocnemius, and IT.

Treatment involves rest, ice, NSAIDs, and quadriceps strengthening and stretching. Most athletes can gradually return to activity in 10 to 14 days.

Bursitis

The knee has several bursae, which decrease friction between moving structures. They usually are thin but with repeated stress may become thickened and fluid-filled. The *prepatellar bursa* is located between the patella and the skin. The *superficial infrapatellar bursa* is located between the tibial tubercle and the skin. The *deep infrapatellar bursa* is located between the posterior margin of the distal part of the patellar tendon and the anterior aspect of the tibia. The *suprapatellar bursa* is not a true bursa but rather is an extension of the tibiofemoral joint capsule. The *anserine bursa* separates the pes anserinus from the distal portion of the MCL and the medial tibial condyle. As noted previously, *pes anserinus* means "goose foot," and *anserine* means "related to the pes anserinus." The term derives from the fact that the bursa underlies the anserine tendon, a three-forked structure constituting the insertion of the gracilis, sartorius, and semitendinosus muscles.

Bursitis is caused by repeated stress, infection, local trauma, crystal deposition, or systemic inflammatory arthropathy. Bursitis must be differentiated from knee effusion. Prepatellar bursitis is characterized by swelling with effusion of the superficial bursa overlying the lower pole of the patella. Passive motion usually is fully preserved, and the pain generally is mild. The disorder usually is caused by pressure from repetitive kneeling on a firm surface ("housemaid's knee"). The prepatellar bursa also is a common site of septic bursitis, and a common error is to confuse this entity with a septic knee (involving the tibiofemoral joint).

Anserine bursitis involves pain and tenderness at the proximal medial tibia, a few centimeters inferior to the medial joint line. It occurs most commonly in obese women in association with osteoarthritis of the knee but also may occur from overuse, especially in runners. It is characterized by a relatively abrupt onset of knee pain with localized tenderness and puffiness at the pes anserinus. It can be confused with a medial meniscal or MCL tear.

Radiographic studies may reveal soft tissue swelling. Ultrasound imaging also may detect the fluid collection. MRI may be helpful but is not required on an urgent basis. With any uncertainty regarding the possibility of infection, the bursa fluid should be aspirated, and Gram staining, culture, cell count, and crystal analysis of the aspirate should be performed.

Septic (bacterial) bursitis requires antibiotic treatment, with operative drainage in refractory cases. Aseptic (inflammatory) bursitis is treated with ice, rest, anti-inflammatories, and injection of bupivacaine and corticosteroids—the last, of course, being contraindicated in the presence of infection. All of the bursae of the knee may be injected with steroids; in the ED, steroid injection of the anserine and prepatellar bursae is most common.

Osteoarthritis

Osteoarthritis is joint inflammation due to degeneration. The incidence increases with age, obesity, trauma, and meniscectomy. Pain usually is the initial complaint and typically is aggravated by activity and relieved by rest. Locking, giving way, and a sensation of instability may be associated complaints. The physical examination may reveal a gross angular deformity—either genu valgum (knock-knee) or genu varum (bow-leg)—and an antalgic gait may be noted. The joint line of the involved compartment usually is tender. Osteoarthritis may involve one or all compartments of the knee.

Standard anteroposterior weight-bearing radiographs may reveal narrowing of the joint spaces, peripheral osteophyte formation, subchondral sclerosis, and cyst formation; they also may show angular deformity of the knee. Lateral and oblique views may show the presence of peripheral osteophytes and loose bodies. Tangential sunrise views are needed to evaluate the patellofemoral joint for osteophytes, sclerosis, and maltracking.

Treatment consists of activity modification, NSAIDs, bracing, and strengthening exercises. A cane may be helpful

to unload the affected extremity and provide symptomatic relief. If the patient is obese, weight reduction is recommended. Surgical treatment is reserved for severe cases and may involve osteotomy, hemiarthroplasty, or total knee arthroplasty.

Septic Arthritis

The knee is the most common joint affected with septic arthritis. Hematogenous seeding is the most common route of spread, but joint trauma also is a frequent cause. Bacterial spread usually affects the vascular synovial membrane and then extends into the joint. *Staphylococcus aureus* is the most common pathogen, but *Neisseria gonorrhoeae* also must be considered, because the typical treatment is vancomycin for the former and ceftriaxone for the latter. Moreover, the latter is a reportable disease requiring contact tracing. To prevent septic arthritis in the ED setting, all open joint injuries should be treated by operative washout and antibiotics, and clinicians should avoid performing arthrocentesis through infected skin, which can seed the joint.

Baker's Cyst

Baker's cyst (popliteal cyst) is a herniation of the synovial membrane through the posterior aspect of the capsule of the knee (Fig. 54-12). It results from an enlarging knee effusion of any cause. A mass is palpable in the posteromedial corner of the knee and often produces pressure, pain, and limitation of range of motion. Rupture of the bursa with resultant escape of fluid into the calf may produce a clinical picture similar to that of deep vein thrombosis or compartment syndrome.[70] In this circumstance, ruptured Baker's cyst is a diagnosis of exclusion (i.e., thrombosis should be ruled out). Treatment is directed at the underlying intra-articular pathology.

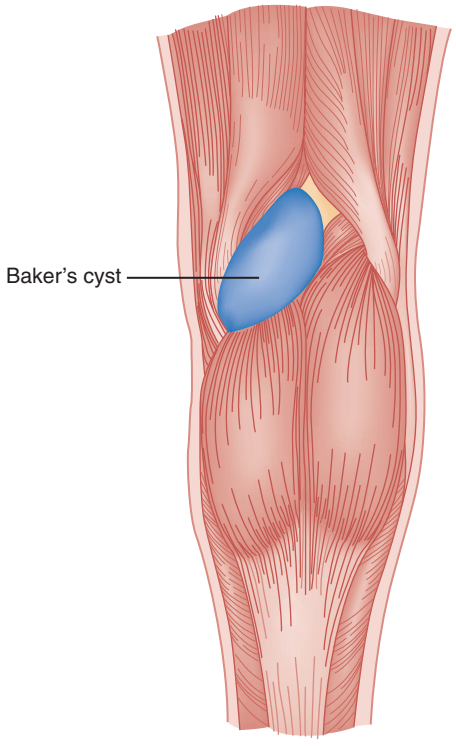


Figure 54-12. Baker's cyst is an extension of the semimembranosus bursa posteriorly. This bursa often is connected with a joint cavity.

LEG

PERSPECTIVE

Anatomically, the *leg* comprises the tibia, fibula, and associated soft tissues, whereas the *thigh* comprises the femur and its soft tissues. Bearing the full weight of the body, the leg is subject to enormous stress, and the tibia is the most commonly fractured long bone. Moreover, the tibia is poorly covered by soft tissue anteriorly, making infection and delayed healing common.

PRINCIPLES OF DISEASE: ANATOMY AND PATHOPHYSIOLOGY

The bony structure of the lower leg is relatively simple, consisting of the tibia and fibula. The fibula stabilizes but does not bear weight. The shaft of the tibia is triangular in cross section and poorly covered with soft tissue over its anteromedial aspect. It is the most common long bone to be fractured and to sustain open fracture. The lack of overlying soft tissue results in a tenuous blood supply, which increases the rate of osteomyelitis and contributes to delayed union and nonunion, which are common in tibial fracture.

The distal end of the tibia is expanded and bears an additional surface feature, the fibular notch, for the lower tibiofibular joint. The medial malleolus projects from the distal medial aspect of the tibia and has a posterior groove for the tibialis posterior tendon. The inferior surface of the distal tibia is covered with articular cartilage and forms the tibial plafond, the upper anterior surface of the ankle joint. The fibula, in contrast with the tibia, is covered by soft tissue except at the ankle, where it is subcutaneous and easily palpable. The fibula is composed of the head with its styloid process, the neck, the shaft, and the lateral malleolus of the ankle.

The tibia and fibula are connected by a superior and an inferior tibiofibular joint and a strong interosseous membrane or syndesmotic ligament. The latter is a fibrous band that has particular importance at the distal portion of the lower leg, where it is responsible for keeping the tibia and fibula closely approximated to provide a stable ankle mortise.

The vascular supply of the lower leg derives from the popliteal artery, which trifurcates to form three branches: the anterior tibial artery, the posterior tibial artery, and the peroneal artery. The anterior tibial artery can be assessed by palpating the dorsalis pedis artery pulse over the dorsum of the foot, and the posterior tibial artery pulse can be palpated posterior to the medial malleolus.

The lower leg is divided into compartments by deep partitions of the investing crural fascia. Each compartment has a sensory nerve running through it, an anatomic feature that can be used to help diagnose compartment syndrome. The compartments are anterior, lateral, superficial posterior, and deep posterior. The *anterior compartment* contains the tibialis anterior, the long toe extensor muscles, the anterior tibial artery, and the deep peroneal nerve, which supplies sensation to the first web space of the foot. The *lateral compartment* contains two muscles that evert the foot, the peroneus longus and brevis, and the superficial peroneal nerve, which supplies sensation to the dorsum of the foot. The *superficial posterior compartment* contains the gastrocnemius, plantaris, and soleus muscles, and the sural nerve, which supplies the lateral side of the foot and distal calf. The *deep posterior compartment* contains the tibialis posterior muscle, the long toe flexor muscles, the posterior tibial and peroneal arteries, and the tibial nerve, which supplies sensation to the plantar aspect of the foot.

MECHANISMS OF INJURY AND MANAGEMENT

Proximal Extra-articular Tibial Fractures

Subcondylar Tibial Fractures

Subcondylar tibial fractures usually are associated with tibial plateau fractures, especially bicondylar fractures. Subcondylar fractures involve the proximal tibial metaphysis and typically are transverse or oblique. The mechanism of injury involves a rotational or angular stress accompanied by vertical compression. Examination reveals tenderness and swelling of the involved area. A hemarthrosis may indicate extension of the fracture into the joint or associated ligamentous injury. Routine radiographic views usually are adequate in showing the fracture line. ED management includes ice and immobilization with a long leg posterior splint. Stable extra-articular nondisplaced transverse fractures usually are treated conservatively with a long leg splint, followed by delayed casting on the outpatient basis. In children, casting (with adequate padding) is sometimes performed acutely. Comminuted fractures or fractures associated with an intra-articular component require open reduction and internal fixation and may be treated in the acute setting.

Tibial Tubercle Fractures

Anatomy and Pathophysiology. The tibial tubercle is located at the proximal anterior border of the tibial shaft and is the insertion point of the patellar ligament. The proximal tibial epiphysis and the tibial tuberosity develop from two separate ossification centers that coalesce during adolescence. Epiphyseal ossification terminates in late adolescence.

Avulsion fractures of the tibial tubercle are uncommon. They occur predominantly in adolescent boys.[71] The injury typically occurs near the end of growth, when endochondral ossification of the physeal cartilage of the tibial tubercle occurs. Avulsion fractures mainly occur as an indirect injury during activity. The mechanism of injury has been described as a violent flexion of the knee against a tightly contracted quadriceps muscle, which also can cause patellar tendon rupture. The *Watson-Jones classification* describes three grades of injury depending on the extent of displacement (Fig. 54-13). In type I injuries, the tubercle is hinged upward without displacement from the proximal base. The type II injury has a small portion of the tubercle avulsed, but it is retracted proximally; the articular surface is not involved. Type III fractures are more severe and extend across the articular surface; displacement of the fragment and often comminution are features.

Clinical Features. Physical examination reveals acute tenderness and swelling at the anterior aspect of the knee and proximal tibia. Depending on the type of injury, functional disability may range in severity from extensor lag to complete loss of active extension. Hemarthrosis is evident with type III injury because of intra-articular fracture extension across the proximal epiphysis.

Diagnostic Strategies. Plain radiographs usually are adequate for diagnosis. The lateral view shows the avulsion fracture, number of fragments, and amount of displacement. Swelling of the overlying soft tissue is evident. Comparison views may be necessary when a type I injury is suspected.

Management. Treatment depends on the degree of displacement and the presence of joint involvement. Nondisplaced type I avulsions are treated with cast immobilization with the knee in extension until healing results. Minimally displaced type II avulsions may be treated similarly if the displacement can be reduced by external manual maneuvers. Displaced type III fractures are treated by open reduction and internal fixation to restore proper biomechanics and joint congruity. Fixation screw and tension band wiring techniques have yielded excellent results. After a period of immobilization and progressive rehabilitation, most patients are able to return to full activity.

Complications of tibial tubercle fractures are rare and include genu recurvatum (backward curvature of the knee), patella alta, meniscal tears, failure of surgical fixation, and subsequent heterotopic ossification and osteonecrosis of the tubercle.[72] If the involved growth plates are closing at the time of injury, premature physeal closure can rarely result in a significant recurvatum deformity.

Osgood-Schlatter Disease

Anatomy and Pathophysiology. Adolescents are susceptible to the development of Osgood-Schlatter disease, also known as osteochondritis of the tibial tuberosity or apophysitis of the tibial tuberosity. This common condition results from traction of the distal patellar tendon on the tibial tubercle, causing repetitive microtrauma with subsequent healing of the physis

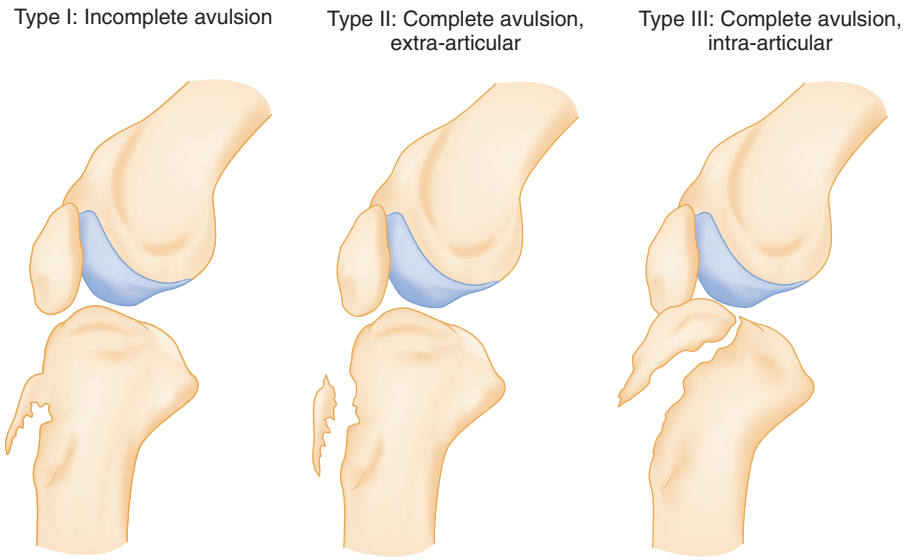


Figure 54-13. Tibial tuberosity fractures.

of the tibial tuberosity. This traction apophysitis occurs during the adolescent growth spurt, usually in athletically active children.

Clinical Features. The disease is characterized by painful swelling over the tibial tubercle, which is exacerbated by activity, is relieved by rest, and is usually of several months' duration. The tubercle may appear abnormally prominent, often on both sides. Pain is elicited on resisted extension of the flexed knee, and occasionally an extensor lag may be noted. Tenderness is most pronounced at the insertion of the patellar tendon. Bilateral involvement is noted in 20 to 30% of patients.[73]

Diagnostic Strategies. The diagnosis of Osgood-Schlatter disease is based on clinical signs and symptoms. Plain radiography of the knee may be useful to exclude other pathologic entities (e.g., tumors, infection, avulsion fractures) but generally is not required. Radiographs are normal in appearance or reveal pretibial soft tissue edema or prominence of the tubercle, with no other bone abnormalities.

Management. Treatment varies according to the acuteness of the symptoms and the skeletal age of the patient. Initially, rest, ice, and analgesics are the mainstays of therapy. As symptoms subside, a rehabilitation program that stretches and strengthens the quadriceps should be instituted. Knee orthoses are used to damp the pull of the extensor mechanism on the weakened tibial apophysis. Immobilization is reserved for the unreliable patient who will not or cannot comply with the program of relative rest in which aggravating activities are avoided. For children with severe symptoms, immobilization for 2 to 3 weeks may be used. Surgical repair may be required if the conservative treatment fails, but it cannot be implemented until the epiphysis is closed, at which time the problem usually is resolved.

Tibial Shaft Fractures

Anatomy and Pathophysiology. The tibia and fibula are tightly bound to each other by the syndesmotic ligament. This strong band of tissue can transmit energy such that the tibia and fibula may be fractured at nonadjacent sites. The fibula remains intact in only 15 to 25% of tibial shaft fractures. Tibial shaft factures are associated with a high incidence of infection, delayed union, nonunion, and malunion, in part because of the poor soft tissue coverage of the anterior tibia.

Transverse tibial diaphyseal fractures typically result from high-energy direct trauma. Low-energy rotatory and compressive forces often result in spiral or oblique fractures.

The *toddler's fracture* is a nondisplaced spiral fracture of the distal tibia in a child 9 months to 3 years of age. The classic distal fracture often relates to accidental trauma, as opposed to a midshaft fracture, which suggests abuse.

Tibial fractures also may occur without trauma. Stress fractures occur most commonly in the tibial shaft. Pathologic fractures may be caused by metabolic bone disease, osteomalacia, or neoplasm.

In children, buckle fractures and greenstick fractures are common in the tibia and fibula. A *buckle fracture* is manifested radiographically as an often subtle buckling without angulation, in contrast with the smooth line formed by the normal cortex. A *greenstick fracture* is a bending fracture, with a break in the periosteum and cortex of the convex side of the angulated bone, while the concave side of the bone is spared. Both of these fractures are stable with an intact periosteum so that swelling, crepitance, and mobility at the fracture site are minimal.

Clinical Features. Tibial shaft fractures cause pain, swelling, and localized deformity, usually angulation or rotation of the foot. Determination of vascular integrity is the priority. Distal dorsalis pedis and posterior tibial pulses should be assessed; however, vascular injury is a rare complication of these fractures. Neurologic injury, by contrast, is common, particularly injury of the peroneal nerve. Motor function of the peroneal nerve is checked by testing active ankle and toe dorsiflexion (deep peroneal nerve) and active foot eversion (superficial peroneal nerve). Sensory function of the peroneal nerve is documented by testing sensation in the first dorsal web space in the foot (deep peroneal nerve distribution) and sensation of the dorsal lateral foot (superficial peroneal nerve distribution). Integrity of the posterior tibial nerve is assessed by checking for the presence or absence of plantar sensation. Significant soft tissue damage also may accompany tibial shaft fractures. Compartment syndrome may be a complication of tibial fractures and usually develops within the first 24 to 48 hours.

Diagnostic Strategies. Anteroposterior and lateral radiographic studies document the fracture, define the fracture pattern, and identify any associated bone loss (Fig. 54-14). The knee and ankle should be included in both views, and radiographs of the pelvis and ipsilateral femur may be required to assess for associated injuries. Postreduction views should be taken after any manipulation of the extremity and should include the knee and ankle joints so that alignment of the proximal and distal joint surfaces can be determined.

Management. The initial management of closed tibial shaft fractures consists of immobilization in a long leg posterior splint applied with the knee in 10 to 20 degrees of flexion. The splinting procedure may require analgesia and sedation. Generally, after fractures are immobilized, pain decreases. If the patient complains of continued severe pain after immobilization, a complication such as compartment syndrome, nerve root compression, or limb ischemia should be considered. Circumferential casts generally are avoided in the acute setting because of the risk of compartment syndrome, although some orthopedists will cast pediatric fractures in the acute phase. Initial hospitalization is indicated for most patients with significant tibial shaft fractures to allow adequate pain control and observation for compartment syndrome.

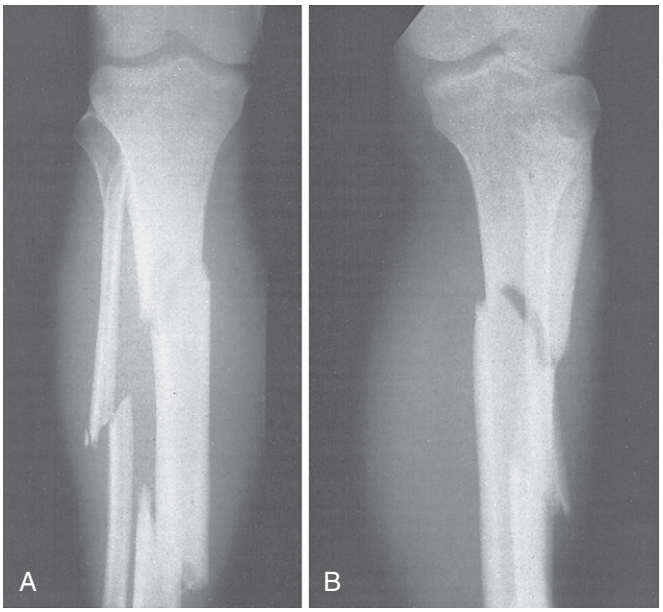


Figure 54-14. Tibiofibular fracture. **A,** Anteroposterior view. Comminuted fractures of the tibial and fibular shafts are present. Note the obliteration of the normal soft tissue planes secondary to edema or hemorrhage. **B,** Lateral view. (From Rosen P, et al: Diagnostic Radiology in Emergency Medicine. St. Louis, Mosby, 1992, p 198.)

Open fractures should be covered by a sterile dressing. Antistaphylococcal antibiotics (typically cefazolin) should be given, with consideration of agents active against multidrug-resistant *Staphylococcus areus* (MRSA). Gentamicin is added for severely contaminated wounds.[74] Tetanus vaccination status should be updated as indicated. A long leg posterior splint should be applied. (This applies to all open fractures.)

Emergency operative débridement with external or internal fixation is recommended as soon as possible for open tibial fractures with significant soft tissue disruption. Osteomyelitis is more likely with open fracture, significant soft tissue disruption, and longer time from contamination to definitive surgical management.

In general, tibial fractures are slow to heal. The average time to union is approximately 20 weeks for stable tibial shaft fractures caused by a low-energy mechanism and more than 30 weeks for unstable fractures caused by a high-energy mechanism.[75] *Delayed union* describes fracture segments that have not united after 24 weeks or that show no radiographic evidence of callus formation for 3 consecutive months. *Nonunion* is a radiographic diagnosis, with a finding of rounded, well-corticated edges of the major fracture fragments. It is much more common in adult long bone fractures than in childhood fractures, which generally heal rapidly. Delayed vascular injuries of the shank vessels, including pseudoaneurysm, arteriovenous fistula, and deep vein thrombosis, also may occur as a complication of tibial shaft fractures. Fat embolism also may occur acutely, especially after reamed nailing. Additional late complications include malrotation of the leg, refracture, and reflex sympathetic dystrophy.

Figure 54-15. Maisonneuve fracture, anteroposterior view. The rotatory force involved in this injury has caused fractures of the distal tibia and the proximal fibula *(arrows)*. (From Rosen P, et al: Diagnostic Radiology in Emergency Medicine. St. Louis, Mosby, 1992, p 197.)

Proximal Fibula Fractures

Anatomy and Pathophysiology. Isolated fibular fractures are relatively unimportant because the fibula is non-weight-bearing. The mechanism of injury usually is a direct blow to the lateral aspect of the leg or an indirect varus stress to the knee. An important exception is *Maisonneuve fracture* (Fig. 54-15). This injury involves a medial ankle disruption (deltoid ligament tear or medial malleolar fracture), with complete tearing of the syndesmotic ligament joining the tibia and fibula, and fracture of the proximal fibula. Consequently, the fibula floats free relative to the tibia, resulting in an unstable ankle mortise, for which surgical fixation is required. The possibility of this injury mandates examination of the proximal fibula in all medial ankle injuries.

Clinical Features. Isolated fibular shaft fractures cause lateral leg pain that is exacerbated by walking. Local pain, swelling, and tenderness at the fracture site may be elicited, although signs and symptoms can be subtle. A thorough evaluation should be done to exclude serious associated occult neurovascular or ligamentous injuries. The common peroneal nerve courses around the neck of the fibula and may be contused or lacerated at the time of injury. The LCL of the knee may be ruptured or strained in association with the fracture, and anterior tibial artery injury with thrombosis may occur.

Diagnostic Strategies. Anteroposterior and lateral radiographic views should include the knee and ankle joints.

Management. Isolated fibular shaft fractures are treated symptomatically with ice, analgesia, and nonweightbearing. Immobilization in a long leg cast is rarely done but may provide symptomatic relief beginning 2 days after the acute injury. Weightbearing may be advanced progressively as tolerated; pain should be avoided. Patients with nondisplaced or minimally displaced fractures may have little pain and tolerate crutch walking without casting. In general, isolated fibula shaft fractures can be managed on an outpatient basis and heal without complication.

For severely displaced fibular shaft fractures or fractures with associated peroneal nerve deficit (i.e., footdrop), orthopedic consultation is indicated. Cast immobilization is not recommended in cases with concomitant nerve damage, and follow-up is scheduled at a shorter interval from injury. Elective surgical repair may be indicated if function does not return. Maisonneuve fracture results in an unstable ankle, and open reduction and internal fixation usually are required.

Proximal Tibiofibular Joint Dislocations

Anatomy and Pathophysiology. The proximal tibiofibular joint is a small synovial joint between a circular or oval facet on the head of the fibula and a similar facet on the inferior aspect of the lateral tibial condyle. The proximal tibiofibular joint is stabilized by the joint capsule and the anterior and posterior tibiofibular ligaments. Dislocation of the proximal tibiofibular joint is rare, occurring most commonly in adolescents and young adults because of its association with motor vehicle crashes and sports injuries.[76] Several types of dislocations of the joint have been described; anterolateral dislocation is the most common and usually is caused by a fall on a flexed, abducted leg. Posterior medial dislocation generally is caused by a direct blow to the flexed knee and is more often associated with peroneal nerve injury. Superior dislocation is associated with ankle diastasis and typically occurs simultaneously with an ankle fracture.

Clinical Features. The patient may complain that the knee feels "out of joint," or if the problem is intermittent, the knee may lock or give way periodically. Physical examination reveals tenderness and swelling over the proximal fibula and tibiofibular joint. In the absence of associated injury, findings on knee

examination are otherwise normal, with full range of motion and no joint line tenderness or effusion.

Diagnostic Strategies. Plain radiography may confirm the diagnosis, although CT may be required. On the anteroposterior view, the fibular head is displaced laterally, and the interosseous space is widened. Comparison views of the uninjured knee may be necessary to appreciate these findings.

Management. Traumatic proximal tibiofibular dislocation is treated initially with closed reduction. If the patient seeks treatment within a few days of injury, reduction of an anterolateral dislocation can be accomplished in the ED by flexing the knee to 90 degrees, everting the ankle, and applying direct pressure to the head of the fibula.[76] Orthopedic referral and immobilization of the knee for a minimum of 3 to 6 weeks are necessary after reduction. If closed reduction fails, the patient may require open reduction, with repair of the torn capsule ligaments and pinning. For recurrent dislocations or injuries that do not respond to initial treatment, resection of the proximal fibula or arthrodesis may be effective.

Stress Fractures

Anatomy and Pathophysiology. The tibia is a common site of stress fracture. Usually the stress fracture occurs on the tibial shaft. Fractures typically are horizontal or oblique and uncommonly longitudinal.[77] Other sites of stress fracture include the femur, fibula, tarsals (especially navicular), and metatarsals. Stress fractures result from overuse. Stress fractures, which occur as a result of excessive repetitive force to normal bone, are distinguished from pathologic fractures, which occur as a result of normal forces acting on abnormal bone (due to osteoporosis or tumor, for example).

Clinical Features. Bone pain and tenderness without a history of direct trauma are characteristic. The most important historical information includes a recent increase in physical activity, training on hard surfaces, and inadequate footwear. The pain usually is insidious in onset and progressive but may be sudden. Pain is usually relieved with rest. The differential diagnosis for lower leg pain also includes shin splints, exercise-induced compartment syndrome, contusion, muscle strains, tendinitis, periostitis, and interosseous membrane strains. The physical examination may reveal localized bone tenderness and swelling of the overlying soft tissues. Usually there is no muscle atrophy, weakness, or restriction of joint range of motion.

Diagnostic Strategies. The radiographic findings vary depending on the location of the fracture and stage of healing. Approximately one third of stress fractures are evident radiographically at the time of initial diagnosis, compared with one half after 2 to 6 weeks. The radiographic findings often are subtle and may include periosteal new bone, sclerosis, and a lucent line perpendicular to the cortex. MRI can diagnose the condition earlier and more accurately than plain films.[77]

If a stress fracture of the lower extremity is suspected and findings on initial plain radiography are unremarkable, follow-up evaluation at 10 days to 2 weeks may detect radiographic signs of fracture after a period of inactivity. Evidence of healing (periosteal reaction) in response to treatment usually is sufficient to confirm the diagnosis.

Management. Most tibial and fibula stress fractures can be treated nonoperatively. Activity should be decreased for 3 to 6 weeks to allow for healing, and serial radiographs should be obtained. In those rare instances in which walking causes pain, a cast and nonweightbearing may be required. Serial radiographs are used to evaluate healing. Rare cases of nonunion require surgery.

Compartment Syndrome

Compartment syndrome is due to increased pressure within a fascial compartment, leading to necrosis of muscle and nerve and is discussed in Chapter 46.

Soft Tissue Injuries Involving the Lower Leg

Strains

Gastrocnemius Strain

The medial head of the gastrocnemius muscle often is strained in athletics and sometimes ruptures. On physical examination, a palpable gap may be identified in the substance of the muscle, and point tenderness may be elicited in the medial and inferior borders of the muscle belly. Any attempted active or passive ankle dorsiflexion elicits pain.

Gastrocnemius strain or rupture may be confused with rupture of the plantaris tendon, which causes tenderness, swelling, and ecchymosis in the proximal calf; rupture of a Baker's cyst, which may result in the escape of fluid into the calf; thrombophlebitis; and Achilles tendon rupture, which typically results in a palpable gap just proximal to the calcaneus. The diagnosis is made clinically, although a soft tissue defect may be seen on plain radiographs of large ruptures. MRI can confirm the diagnosis but is rarely necessary.

A mild partial rupture of the medial head of the gastrocnemius can be treated with rest and nonweightbearing for several days. Treatment for more extensive incomplete ruptures involves casting for 8 weeks with the ankle plantarflexed. For a complete tear, most orthopedists recommend surgical repair to restore normal length and tensile strength. Acute compartment syndrome can complicate gastrocnemius strain.

Plantaris Strain and Rupture

The plantaris is a small, variable muscle that originates at the lateral condyle of the femur and passes beneath the soleus to insert on the Achilles tendon. It is a feeble flexor of the knee and plantar flexor of the ankle joint with little functional significance. Rupture may occur at the myotendinous junction with or without an associated partial tear of the medial head of the gastrocnemius muscle. A strain of the more proximal plantaris muscle also may occur as an isolated injury or in conjunction with injury to the ACL of the knee. The patient may describe a sudden sharp snap in the posterior calf followed by a duller deep ache, which may be disabling. Tenderness is greatest just lateral to the midline of the posterior calf. Treatment is symptomatic.

Shin Splints

Shin splints refers to anterior tibial pain occurring during or after exercise. The most common causes are a tibial stress reaction or periostitis. Tibial stress reactions are microfractures caused by stress placed on the tibia and are distinct from gross stress fractures, which predispose the affected bone to complete fracture.

The physical examination reveals localized tenderness over the tibia, usually at the junction of the middle and lower thirds. Radiographic studies are not helpful in the diagnosis of shin splints and also cannot exclude a tibial stress fracture with certainty. Treatment is symptomatic: rest, NSAIDs, ice, and

supportive footwear. The patient should be referred for outpatient evaluation, where conservative therapy can be continued or further diagnostic workup can be pursued.

Foreign Bodies

Foreign bodies such as plant matter (e.g., thorns) are commonly encountered in the leg. Missed retained foreign bodies to the lower leg can be the cause of cellulitis, abscess, necrotizing fasciitis, and gangrene. Plain films are a necessary part of evaluation but will be unhelpful when the foreign body is radiolucent. Ultrasound imaging is superior for diagnosis and localization, and fluoroscopy and MRI are alternatives.[78] Surgical exploration is sometimes necessary. Extraction is difficult, and deep foreign bodies should be removed by a surgeon, often in the operating room.

Acknowledgments

We are grateful for the previous contributions of Dr. Robert Antosia and for the assistance of Dr. James Andruchow with preparation of this chapter for the present edition.

KEY CONCEPTS

- Knee injuries are the most common orthopedic injury seen in the ED.
- The most commonly injured ligament is the MCL. ACL injuries also are common and are more serious. Approximately 50% of patients with ACL injury have a concomitant meniscal tear.
- Knee dislocation often causes vascular injury to the popliteal artery. The presence of a distal pulse does not preclude vascular injury, and angiography or CT angiography may be required to exclude significant injury. Early revascularization is crucial.
- The most common long bone fracture is that of the tibial diaphysis, and compartment syndrome is an infrequent but serious complication.
- Toddler's fracture is a spiral fracture of the distal tibia and usually is not related to abuse. Midshaft or transverse tibial fractures, however, should trigger suspicion.
- The prepatellar bursa should not be confused with the knee (tibiofemoral) joint.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 55 Ankle and Foot

Riyad B. Abu-Laban and Kendall Ho

To him whose feet hurt, everything hurts.

Socrates

The ankle and foot are highly evolved structures designed to support the body's weight and to facilitate locomotion over varied terrain. Findings related to ankle and foot injuries often are subtle, and diagnosis may be delayed or missed, particularly in cases of multiple trauma.

The ankle and foot are best approached clinically as a single functional unit. Although they are discussed sequentially in this chapter, their mechanisms of injury overlap, and a pathologic condition in one location may accompany an associated pathologic condition in another.

ANKLE

PRINCIPLES OF DISEASE

Anatomy

The ankle joint is the articulation of the tibia and fibula with the talus. The dome of the talus fits securely into the "mortise" formed by the medial malleolus, the horizontal articular surface of the tibia (the plafond), and the lateral malleolus. The stability of the ankle depends on the bony and ligamentous integrity of the mortise. The calcaneus also is important to the motion and stability of the ankle.

The ankle comprises three primary articulations: the inner surface of the medial malleolus with the medial surface of the talus; the distal tibial plafond with the talar dome; and the medial surface of the lateral malleolus with the lateral process of the talus. These three articular surfaces are contiguous, lined with cartilage, and enclosed by a single joint capsule. The distal tibia also articulates with the distal fibula just proximal to the talus, forming the distal tibiofibular joint. Collectively, these articulations are called the *talocrural joints*.

Three sets of ligaments—the syndesmotic ligaments, the lateral collateral ligaments, and the medial collateral ligaments—support the ankle joint and are essential to its stability (Figs. 55-1 and 55-2).

Tendons course through the ankle in four geographic groups. The flexor retinaculum tethers the tendons of the tibialis posterior, the flexor digitorum longus, and the flexor hallucis muscles behind the medial malleolus. The peroneal retinaculum and tendon sheath tether the peroneus longus and brevis tendons behind the lateral malleolus. The extensor retinaculum tethers the tendons of the tibialis anterior, extensor digitorum longus, extensor hallucis longus, and peroneus tertius over the anterior aspect of the ankle. Posteriorly, in the midline, lie the Achilles and plantaris tendons.

Pathophysiology

Ankle movements are complex, often involving more than one joint. It is best to consider the group of joints about the ankle as one unit, the ankle joint complex. This complex, which is made up of the talocrural joints and the talocalcaneal joints, or the subtalar joints, allows movements along several axes of motion.[1] *Dorsiflexion* (extension) and *plantar flexion* (flexion) of the ankle joint complex occur primarily at the talocrural joints, rotating about the horizontal axis that passes through the medial and lateral malleoli (Fig. 55-3; see also Fig. 55-5). Motions of the ankle joint complex in conjunction with the midtarsal joints include *inversion* and *eversion*, which are rotational movements about the oblique subtalar axis involving the subtalar joint (see Fig. 55-3A), and *abduction* (external rotation) and *adduction* (internal rotation), which are rotational movements about the longitudinal axis of the tibia (see Fig. 55-3B).

The components providing stability to the ankle are best conceptualized as a ringlike structure surrounding the talus[2] (Fig. 55-4). Disruption of one element of this ring does not, by itself, induce instability. Injury to one ring element, however, should prompt careful scrutiny for a second injury. Any disruption of two or more elements causes ankle instability and can significantly affect the proper functioning of the joint.[2]

Clinical Features

The presence of immediate swelling and severe pain suggests serious ligament disruption, hemarthrosis, or fracture. Inability to bear weight immediately after an injury often implies a significant pathologic condition.[3] Patient recollection of a "pop" sound mandates consideration of ligament, tendon, or retinacular rupture but does not necessarily increase the probability of a fracture. Rapid progression of symptoms may represent more severe injury.

The patient with a subacute or chronic ankle problem may be unable to correlate symptom onset with a particular traumatic event. Inquiry should elicit the type and extent of physical activities and whether the ankle gave way. Finally, ankle injuries or fractures in elderly patients may manifest as subacute problems, which may reflect either misdiagnosis of a

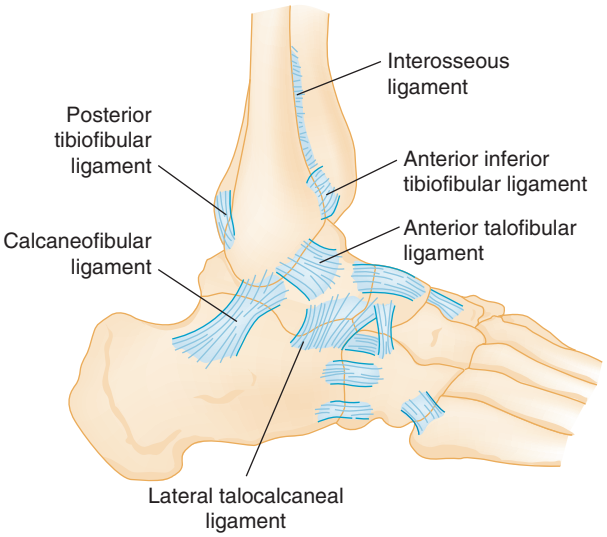


Figure 55-1. Anatomy of the lateral collateral ligaments and the syndesmotic ligaments of the ankle. (From Nicholas JA, Hershman EB [eds]: The Lower Extremity and Spine in Sports Medicine, 2nd ed. St Louis, Mosby, 1994.)

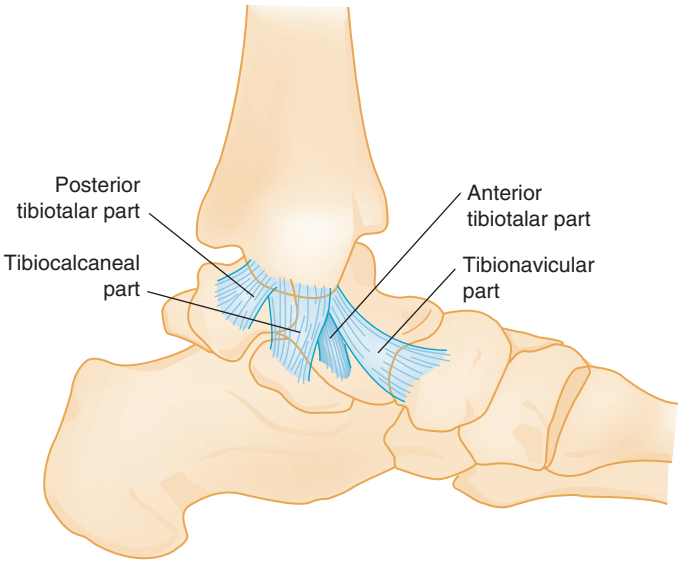


Figure 55-2. Anatomy of the medial collateral ligaments of the ankle. (From Nicholas JA, Hershman EB [eds]: The Lower Extremity and Spine in Sports Medicine, 2nd ed. St Louis, Mosby, 1994.)

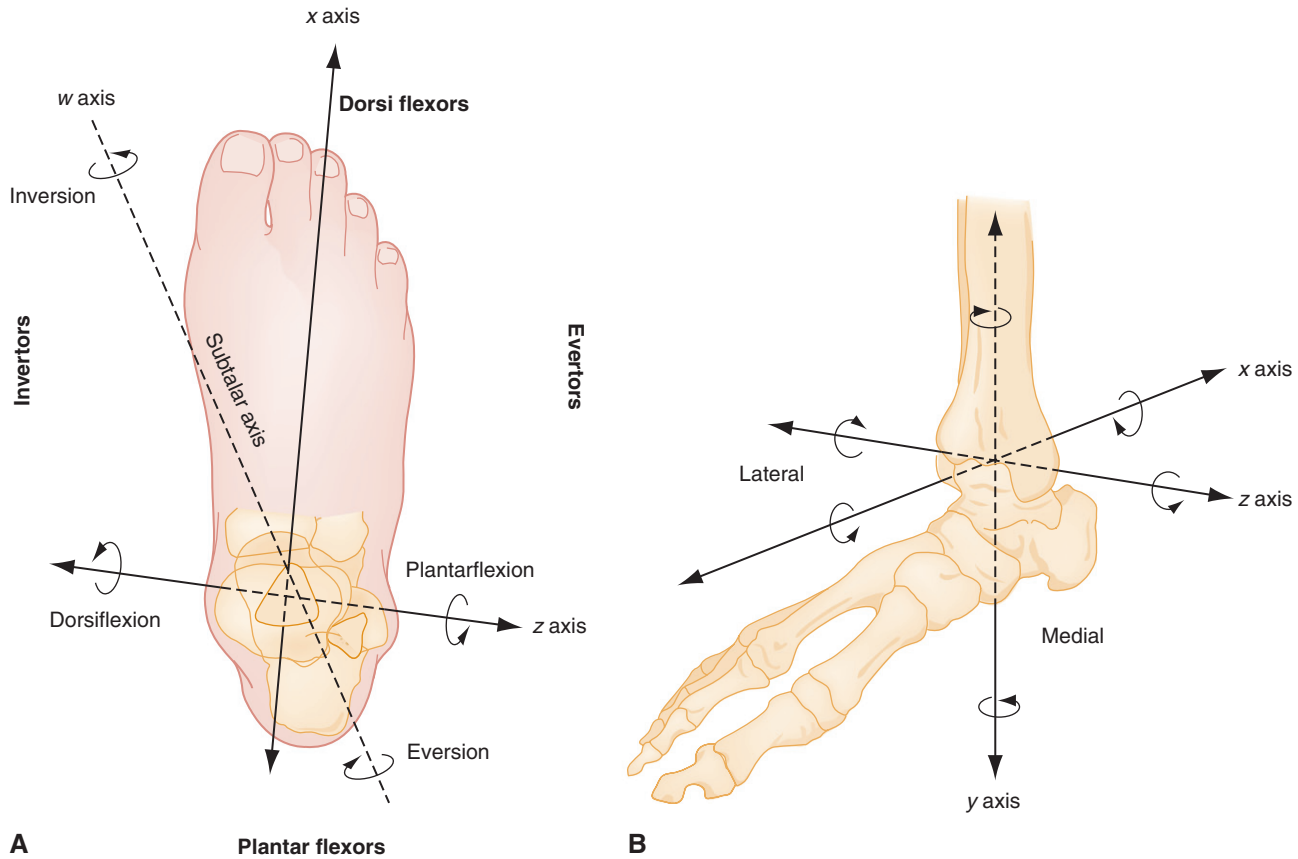


Figure 55-3. Four axes of the ankle joint complex. **A,** The horizontal axis passing through the two malleoli (*z* axis); the longitudinal axis of the foot (*x* axis); the oblique subtalar axis (*w* axis). **B,** The longitudinal axis of the tibia (*y* axis) and two additional views of the *x* and *z* axes. (**A,** From the American Academy of Orthopedic Surgeons: Atlas of Orthotics. St. Louis, Mosby, 1975; **B,** modified from the Department of Orthopedics, Mayo Clinic and Mayo Foundation, Rochester, Minn. Reproduced in Storment DM et al: Am J Sports Med 13:296, 1985.)

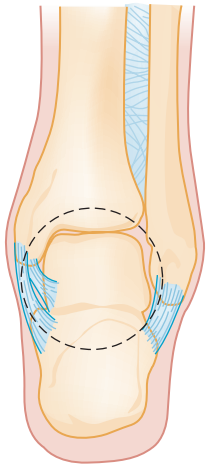


Figure 55-4. The ring structure surrounding the talus is made up of the tibial plafond, medial malleolus, deltoid ligaments, calcaneus, lateral collateral ligaments, and syndesmotic ligaments. The integrity of this ring determines the stability of the ankle. (From Simon RR, Koenigsknecht SJ: Emergency Orthopedics: The Extremities, 2nd ed. Norwalk, Conn, Appleton & Lange, 1987.)

serious condition as a simple sprain or neglect by the patient or caregiver.

Physical Examination

The examination of the ankle starts with an assessment of deformity, ecchymosis, edema, and perfusion, followed by active and passive range of motion. Assessment of point tenderness may localize ligament, bone, or tendon injuries, particularly when the patient is seen early. Palpation should include the medial and lateral collateral ligaments, the syndesmotic ligaments, the inferior and posterior edges of the medial and lateral malleoli, the entire length of the fibula and tibia, the anterior plafond, the medial and lateral dome of the talus (palpable with the ankle in plantar flexion), the base of the fifth metatarsal, the calcaneus, the Achilles tendon, and the peroneal tendons behind the lateral malleolus. Stress testing of the ankle joint, which is discussed later, should not be performed until a fracture has been excluded. An evaluation of weight-bearing ability should proceed only if clinical suspicion of a fracture is low, the locations of tenderness do not indicate the need for plain radiography, or radiographs have ruled out a fracture.[3]

■ DIAGNOSTIC STRATEGIES

Radiology

The anteroposterior, lateral, and mortise views make up the standard three-view radiographic series of the ankle. Although two-view ankle series have been studied, the likelihood of missing a subtle fracture is reduced with three views.[4] The anteroposterior view identifies fractures of the malleoli, distal tibia or fibula, plafond, talar dome, the body and lateral process of the talus, and the calcaneus. The lateral view identifies fractures of the anterior and posterior tibial margins, talar neck, posterior talar process, and calcaneus, and any anterior or posterior displacement of the talus. On this view, any incongruity of the articular space between the talar dome and the distal tibia suggests ankle instability, particularly if narrowing of the anterior joint space is present. The lateral view also is useful in identifying an ankle effusion, which appears as a teardrop-shaped density displacing the normal fat adjacent to the anterior or posterior margin of the joint capsule (Fig. 55-5). Its presence suggests the possibility of a subtle intra-articular injury, such as an osteochondral fracture of the talar dome.[5]

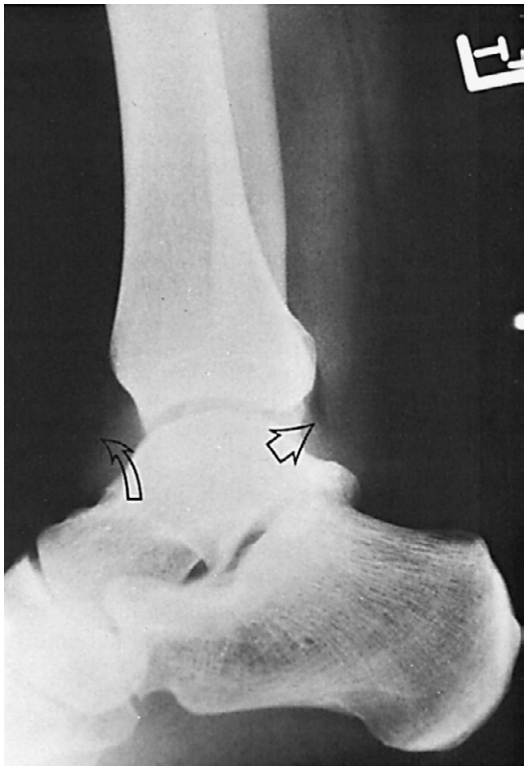


Figure 55-5. Lateral radiographic view showing an ankle effusion. The *arrows* depict the distention of the joint capsule anteriorly *(curved arrow)* and posteriorly *(straight arrow)*. (From Nicholas JA, Hershman EB [eds]: The Lower Extremity and Spine in Sports Medicine, 2nd ed. St. Louis, Mosby, 1994.)

The mortise view, which is taken with the ankle in 15 to 25 degrees of internal rotation, is most important for evaluating the congruity of the articular surface between the dome of the talus and the mortise. The lines formed between the articular surfaces should be parallel and the joint space should appear uniform throughout the tibiotalar and talofibular components of the joint, and the medial clear space should not exceed 4 mm[6] (Fig. 55-6).

In most cases of isolated blunt ankle trauma evaluated within 48 hours of injury, the Ottawa Ankle Rules (OAR) should be used to determine whether ankle or foot radiographs are necessary.[3,7] The OAR state that an *ankle radiographic series* is required if there is pain in the malleolar region with any of the following findings:

- Bone tenderness at the posterior edge of the distal 6 cm or the tip of the lateral malleolus, *or*
- Bone tenderness at the posterior edge of the distal 6 cm or the tip of the medial malleolus, *or*
- Inability to bear weight for at least four steps both immediately after the injury and at the time of evaluation

The OAR further state that a *foot radiographic series* is required if there is pain in the midfoot region with any of the following findings:

- Bone tenderness at the navicular bone, *or*
- Bone tenderness at the base of the fifth metatarsal, *or*

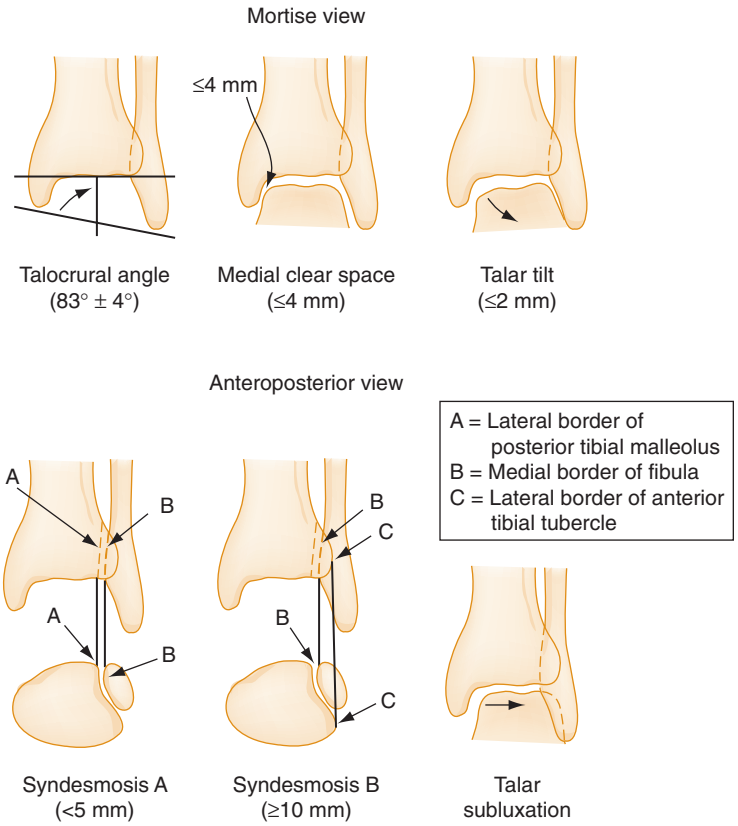


Figure 55-6. Radiologic criteria for evaluating syndesmosis. (From Stiehl JB: Ankle fractures with diasthesis. Instr Course Lect 39[III]:79, 1990.)

- Inability to bear weight for at least four steps both immediately after the injury and at the time of evaluation

The OAR have a sensitivity approaching 100% in detecting malleolar zone ankle fractures and midfoot zone fractures.[3,7] The OAR were derived in an adult population and are not applicable in subacute or chronic injuries. The OAR appear to perform well in pediatric patients; however, results have varied, leading some groups of researchers to propose alternative rules to address the unique aspects of this population.[8-14] The decision rules for foot radiography, although applicable to blunt ankle trauma, apply only to the midfoot zone and only to the mechanism of injury defined by the studies. The OAR were not designed to be general guidelines for foot radiography and certainly do not apply to the hindfoot or forefoot. Finally, the OAR are not applicable to intoxicated patients or those who are difficult to assess because of head injuries, multiple injuries, or diminished sensation related to neurologic deficits. The OAR have been found to have efficacy comparable to that accorded to physician judgment when used by specialized emergency and triage nurses.[15-17] Although the OAR are well validated, their adoption and application by emergency physicians remain variable.[18,19]

Other Imaging Techniques

Although plain radiography is the initial imaging modality of choice for ankle injuries, it can miss subtle ankle fractures, osteochondral fractures, stress fractures, or ligamentous injuries. When unexplained symptoms persist after negative or inconclusive findings on plain radiography, other imaging modalities or orthopedic consultation may be advisable on a semiurgent or elective basis.[20]

Radionuclide imaging (bone scanning) can detect soft tissue injuries such as distal syndesmotic disruptions, stress fractures, and osteochondral fractures.[21] Bone scan abnormalities typically appear 1 to 2 weeks before radiographic evidence of a stress fracture, and negative findings on bone scan can effectively rule out the diagnosis. Bone scan abnormalities are nonspecific, however, because infections and tumors also can lead to positive results (see further discussion on stress fracture imaging in the "Foot" section of this chapter), and bone scanning is not useful for follow-up because abnormalities can persist for up to 1 year after recovery.[21]

Computed tomography (CT) scanning provides superior bone imaging and is an excellent modality to delineate abnormalities identified by another imaging modality.[21,22] CT can detect very small fractures, subtle stress fractures, and ligamentous injuries and can facilitate surgical planning.[21,22] Newer CT image reformatting techniques can be extremely helpful, including two-dimensional multiplanar reformatting to identify small fractures, three-dimensional volume rendering to show relationships between tendons and underlying bones, and shaded surface display to provide disarticulated views of joint surfaces and enhance diagnostic accuracy.[22,23]

Magnetic resonance imaging (MRI) provides unprecedented clarity in depicting soft tissue structures such as ligaments and tendons and also can delineate bone marrow changes associated with stress fractures before radiographic abnormalities appear.[21] MRI can be helpful both in guiding management decisions and in following the patient's response to therapy.[24]

Additional imaging techniques such as MR or CT arthrography can be useful in the evaluation of chronic ankle pain to detect loose bodies, cartilaginous abnormalities, impingements, or osteochondral defects.[25] The decision to perform specialized imaging of this nature typically is made through orthopedic and radiologic consultations; such studies are not performed in the emergency department (ED).

■ SPECIFIC PATHOLOGIC CONDITIONS

Ankle Fractures

Pathophysiology. Fractures occur when a deforming force is sufficient to overcome the structural strength of a bone. A bone under tension breaks transversely along the axis of the deforming force[26] (Fig. 55-7). Alternatively, ligamentous rupture or a chip avulsion fracture can occur at either end of a stressed ligament.

Management. The management of ankle fractures consists of identification and classification, assessment of stability, immediate reduction of fracture-dislocations that threaten neurovascular or soft tissue viability, and specific treatment and disposition.

To date, there is no ideal system for the classification ankle fractures. The classic Danis-Weber (see Fig. 55-8) and Lauge-Hansen classification systems are based on mechanism and fracture location.[27] Both systems have limitations, however, and neither accurately predicts clinical outcome in all situations. The Danis-Weber classification has predictive value in unimalleolar fractures, but not in more complex bimalleolar and trimalleolar fractures.[28] Moreover, the Danis-Weber system does not adequately classify isolated medial malleolar fractures or pilon fractures.[28] By contrast, the Lauge-Hansen classification was intended to characterize ligamentous injury patterns based on the radiographic appearance of ankle fractures. According to a recent MRI study of ankle fractures, however, this system was unable to predict patterns of ligamentous injuries in 53% of cases (26 of 49), and 17% of cases (10 of 59) could not be classified at all.[29] This study also found that more than 65% of patients had a complete ligamentous disruption associated with a related malleolar fracture, calling into question the stability of their fracture.[29] It is clear that the Lauge-Hansen system is inadequate in isloation for classifying all fractures and has particular limitations in predicting soft tissue injuries. Modifications to these two classification schemes have been proposed to better describe ankle fractures and, of more importance, to predict outcome.[27-29]

The injured ankle should be immobilized, elevated, and iced promptly to minimize swelling and further soft tissue damage. The presence of gross deformity with neurovascular compromise or skin tenting necessitates immediate intervention.[30,31] Plain radiography before reduction can be helpful but should not be allowed to delay reduction in injuries with vascular compromise.

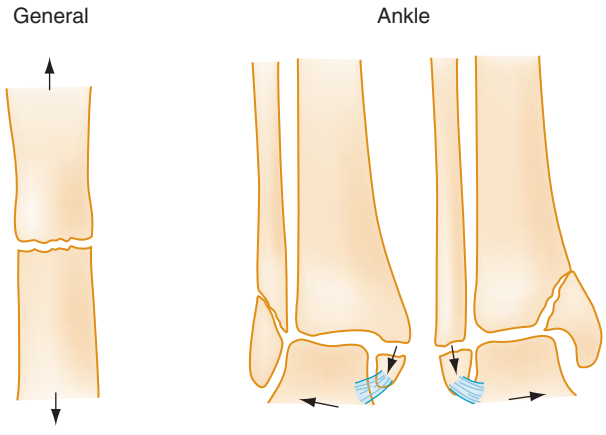


Figure 55-7. The mechanics of bone failure in tension and types of tension ankle fractures. *Arrows* indicate the direction of distracting forces. (From Dahners LE: The pathogenesis and treatment of bimalleolar ankle fractures. Instr Course Lect 39[III]:85, 1990.)

Appropriate procedural sedation and analgesia techniques should be used for reduction. The fundamental principle of closed reduction is to reverse the deforming forces. For example, reduction of a fracture-dislocation caused by an adduction injury would require an abduction force. The initial application of a distraction force often is helpful. After reduction, neurovascular status should be reassessed, the lower leg should be immobilized and elevated, and postreduction radiographs should be obtained. The overarching goal in the definitive treatment of ankle fractures is to achieve perfect reduction.

Disposition. In general, all displaced or potentially unstable ankle fractures require orthopedic consultation in the ED (Box 55-1). These injuries include all bimalleolar and trimalleolar fractures and unimalleolar fractures with contralateral ligamentous injuries (e.g., a lateral malleolar fracture with deltoid ligament disruption or a medial malleolar fracture with lateral collateral ligament disruption).[32] In addition, all intra-articular fractures, especially those with step deformity of the articular surface, require early orthopedic involvement.

Extra-articular fractures that disrupt only one ring element generally can be treated with casting for 6 to 8 weeks. Orthopedic follow-up on an outpatient basis within 1 to 2 weeks of the injury is ideal in case operative intervention is required. The presence of any abnormal measurement on the mortise view (see Fig. 55-6) suggests instability and the need for orthopedic consultation in the ED. Chip avulsion fractures in which the avulsed fragment is less than 3 mm in diameter and minimally displaced can be treated as for an ankle sprain.

The outcome of ankle fractures depends on the extent of injuries, the number of malleoli fractured, ankle stability, and patient age.[27,28] For ankle fractures that require surgery, outcome is better in unimalleolar fractures over trimalleolar fractures, in isolated lateral malleolar fracture over isolated medial malleolar fractures, in multimalleolar fractures without medial malleolar fracture over those with malleolar fractures, and in cases with posterior fragments involving less than one third of the articular surface over larger fragments.[33]

BOX 55-1 ANKLE FRACTURES FOR WHICH ORTHOPEDIC CONSULTATION IN THE EMERGENCY DEPARTMENT IS RECOMMENDED

- Unimalleolar fractures
  - Displaced medial malleolar fracture
  - Medial malleolar fracture with lateral collateral ligament rupture
  - Displaced lateral malleolar fracture
  - Lateral malleolar fracture with deltoid ligament rupture
  - Lateral malleolar fracture with widened medial clear space
  - Unimalleolar fracture with syndesmotic diastasis
  - Fibula fracture at or proximal to the tibiotalar joint line
  - Displaced posterior malleolar fracture
  - Posterior malleolar fracture involving more than 25% of articular surface
- All bimalleolar fractures
- All trimalleolar fractures
- All intra-articular fractures with step deformity
- All open fractures
- All pilon fractures

Unimalleolar Fractures

Lateral Malleolar Fractures

The stability of an isolated lateral malleolar fracture depends on the location of the fracture in relation to the level of the tibiotalar joint, and the Danis-Weber classification (Fig. 55-8) is useful and predictive of outcome in this type of unimalleolar fracture.[28] Fractures below the tibiotalar joint rarely disrupt other bony or ligamentous structures (a Danis-Weber type A1 injury). In the absence of medial injury, lateral malleolar fractures are unlikely to affect the dynamic congruity of the ankle joint.[32] The management of uncomplicated lateral malleolar fractures involves casting for 6 to 8 weeks, with no weight bearing for at least the first 3 weeks, and ongoing follow-up to ensure proper healing. Concomitant tenderness over the deltoid ligament, which suggests a biomechanical disruption of both malleoli, an associated fracture of the medial malleolus (a Danis-Weber type A2 injury), or an associated fracture of the posterior malleolus (a Danis-Weber type A3 injury) warrants orthopedic consultation in the ED, especially if the medial clear space on the mortise view is widened (see Fig. 55-6).[14]

Fibular fractures proximal to the tibiotalar joint line (a Danis-Weber type C injury; see Fig. 55-8) frequently, but not always, disrupt the distal tibiotalar syndesmosis and the medial structures and commonly require orthopedic consultation in the ED. Treatment of an isolated fracture at the level of the tibiotalar joint (a Danis-Weber type B injury; see Fig. 55-8) is controversial because 50% of these injuries are accompanied by an injury to the distal tibiofibular syndesmosis. Distal tibiofibular space measurements on plain radiography have a sensitivity of only 31% and a specificity of 83%, compared with CT scan, in detecting tibiofibular syndesmosis injuries.[34] Tenderness on palpation of the syndesmotic ligament or a widening of the medial joint space on the mortise view adds further support to the need for emergency consultation.

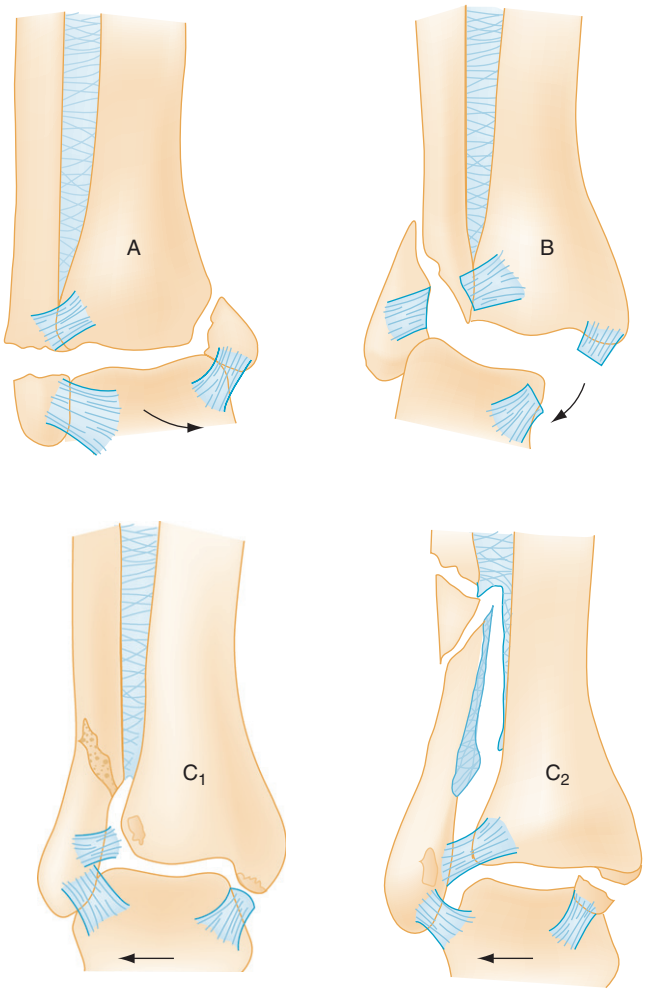


Figure 55-8. The Danis-Weber classification of ankle fractures focuses on the location of the fibular fracture in relation to the tibiotalar joint. See text for explanation. (From Wilson FC: The pathogenesis and treatment of ankle fractures: Classification. Instr Course Lect 39[III]:79, 1990.)

Medial Malleolar Fractures

Medial malleolar fractures usually are the result of eversion or external rotation. These two forces exert tension on the deltoid ligament, causing an avulsion of the tip of the medial malleolus or a rupture of the deltoid ligament. Although they can occur in isolation, medial malleolar fractures commonly are associated with lateral or posterior malleolar disruption. Because of this association, the identification of a medial malleolar fracture mandates a careful examination of the entire length of the fibula for tenderness, the presence of which warrants radiographic evaluation to rule out a proximal fibular fracture (Fig. 55-9).

An isolated nondisplaced medial malleolar fracture can be treated with casting for 6 to 8 weeks, with no weight bearing for at least the first 3 weeks, with close orthopedic follow-up. Any displacement or concomitant disruption of the lateral components of the ankle warrants orthopedic consultation in the ED for consideration of operative management.[32]

Posterior Malleolar Fractures

Isolated fractures of the posterior malleolus are rare and imply an avulsion of the posterior tibiofibular ligament. These injuries can be associated with proximal fibular fractures and medial and lateral collateral ligament sprains. Treatment usually consists of casting for 6 weeks, provided that no associated injury or ankle instability is present.[35] Fractures involving more than 25% of the posterior tibial surface usually require open reduction and internal fixation.[32]

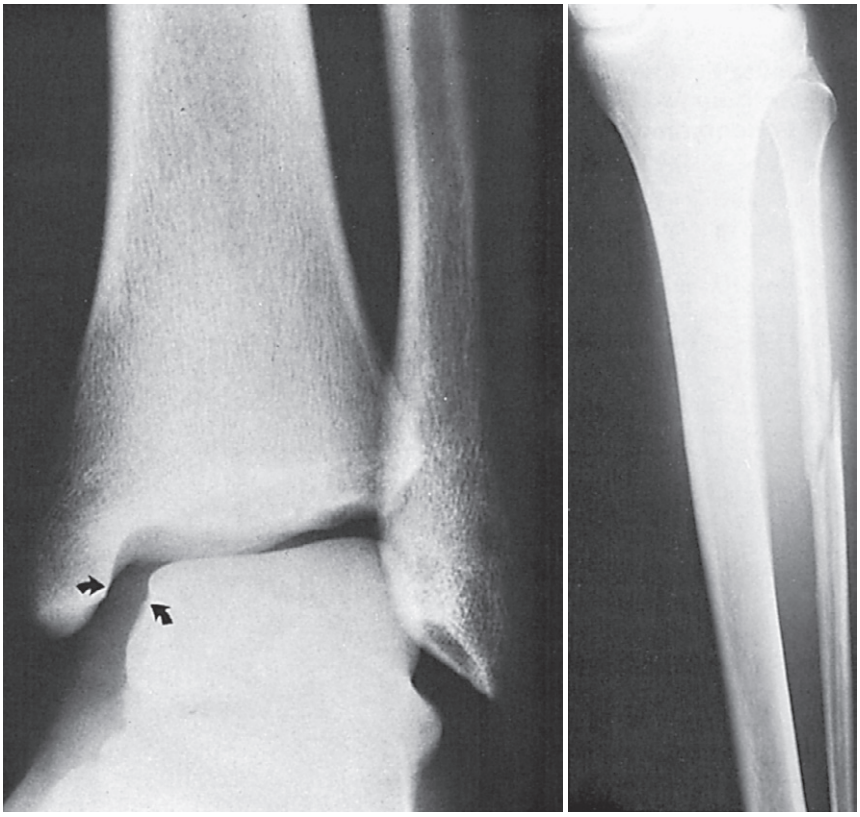
Bimalleolar Fractures

Bimalleolar fractures involve the disruption of at least two elements of the ankle ring and therefore are unstable. These fractures result from adduction or abduction forces, although the latter are more common.[26] Rotational injuries also can cause bimalleolar fractures, as well as trimalleolar fractures if the posterior malleolus is involved.

The mechanism of injury often can be deduced from the appearance of the fractures.[26] An abduction injury exerts tension on the medial malleolus, causing a horizontal fracture, and bends the lateral malleolus, causing an oblique shear or a comminuted fracture (see Fig. 55-7). An adduction injury causes the reverse, leading to a horizontal fracture of the fibula and an oblique shear fracture of the medial malleolus. A rotational injury causes oblique or spiral fractures of the fibula or medial malleolus. Associated damage to other soft tissue structures (e.g., the syndesmosis) is common with bimalleolar fractures.

Controversy exists about whether such injuries should be treated closed or surgically.[26,36] Unstable bimalleolar fractures require surgical intervention, however, and one study found that outcomes at 1 year after surgery were worse with bimalleolar fractures than with lateral malleolar fractures with deltoid ligament disruption.[37]

Stress fractures of the medial malleolus and distal fibula rarely can be seen in athletes and runners. Plain radiographs



A B

Figure 55-9. Maisonneuve fracture. **A,** Anteroposterior view shows a slight widening *(arrows)* of the ankle mortise and the medial clear space. **B,** Lateral view shows an oblique fracture at the proximal shaft of the fibula. (**A** and **B,** From Nicholas JA, Hershman EB [eds]: The Lower Extremity and Spine in Sports Medicine, 2nd ed. St. Louis, Mosby, 1994.)

may be nondiagnostic, but radionuclide bone scanning or MRI can establish the diagnosis.[38] Most such injuries can be treated nonoperatively, but orthopedic consultation and follow-up are prudent.

Trimalleolar Fractures

Trimalleolar fractures involve fractures of the medial, lateral, and posterior malleoli. Closed treatment of trimalleolar fractures often leads to unsatisfactory results, so operative reduction and internal fixation constitute the treatment of choice.[39]

Open Fractures

Open ankle fractures usually occur with severe isolated ankle injuries or multiple trauma and require immediate orthopedic consultation. After documentation of the neurovascular status and the extent of soft tissue trauma, the injured leg should be splinted and saline-soaked sterile gauze applied to the wound.[30] Swabbing an open wound for bacterial culture and sensitivity testing is unnecessary. If gross deformity is present (indicating a fracture dislocation), immediate reduction before splinting is indicated.[30] Tetanus immunization should be administered as appropriate. Because all open fractures are contaminated with bacteria, patients with these injuries should receive intravenous antibiotics.[40] For low-energy injuries with mild to moderate contamination, a broad-spectrum cephalosporin usually is sufficient.[30,40] Heavily contaminated wounds require the addition of gram-negative bacterial coverage, typically with an aminoglycoside.[40] Adding penicillin G as a third antibiotic is necessary for farm- or soil-related crush injuries, where contamination with *Clostridium perfringens* can be present.[40] In addition to the ankle radiographs, radiographs of the foot, tibia, and fibula should be obtained.

All open fractures benefit from early surgical intervention for débridement and thorough irrigation.[30] Therefore, identification is crucial, and emergency orthopedic consultation must be sought for such injuries.

Complications. Early operative complications of closed and open ankle fractures include pin site infection, delayed skin necrosis, skin graft rejection, and osteomyelitis. Delayed complications of both operative and nonoperative treatment include malunion, nonunion, osteopenia, traumatic arthritis, chronic instability, ossification of the interosseous membrane, and complex regional pain syndrome.[2,41]

Pilon Fractures

Pilon fractures involve the distal tibial metaphysis and usually are the result of high-energy mechanisms such as falls from a significant height. These injuries often are comminuted and associated with significant soft tissue trauma, devastation of joint architecture, and leg shortening (Fig. 55-10).

Pathophysiology. Destot first coined the term *hammer fracture* to describe the way the head of the talus drives itself into the tibial plafond and causes a pilon fracture. The primary deforming force is one of axial compression, and the position of the foot at the time of injury determines the fracture location and pattern[42] (Fig. 55-11). Secondary rotational or shear forces may cause increased comminution and fragment displacement with more extensive soft tissue injuries. One fourth of pilon fractures are open, and associated injuries include fractures of the calcaneus, tibial plateau, femoral neck, acetabulum, or lumbar vertebrae, as well as trauma to other major systems.

Management. Radiographic examination should include the entire tibia and fibula, as well as the ankle. The emergency management principles for open fractures, as outlined previously, should be applied. Treatment involves restoration of

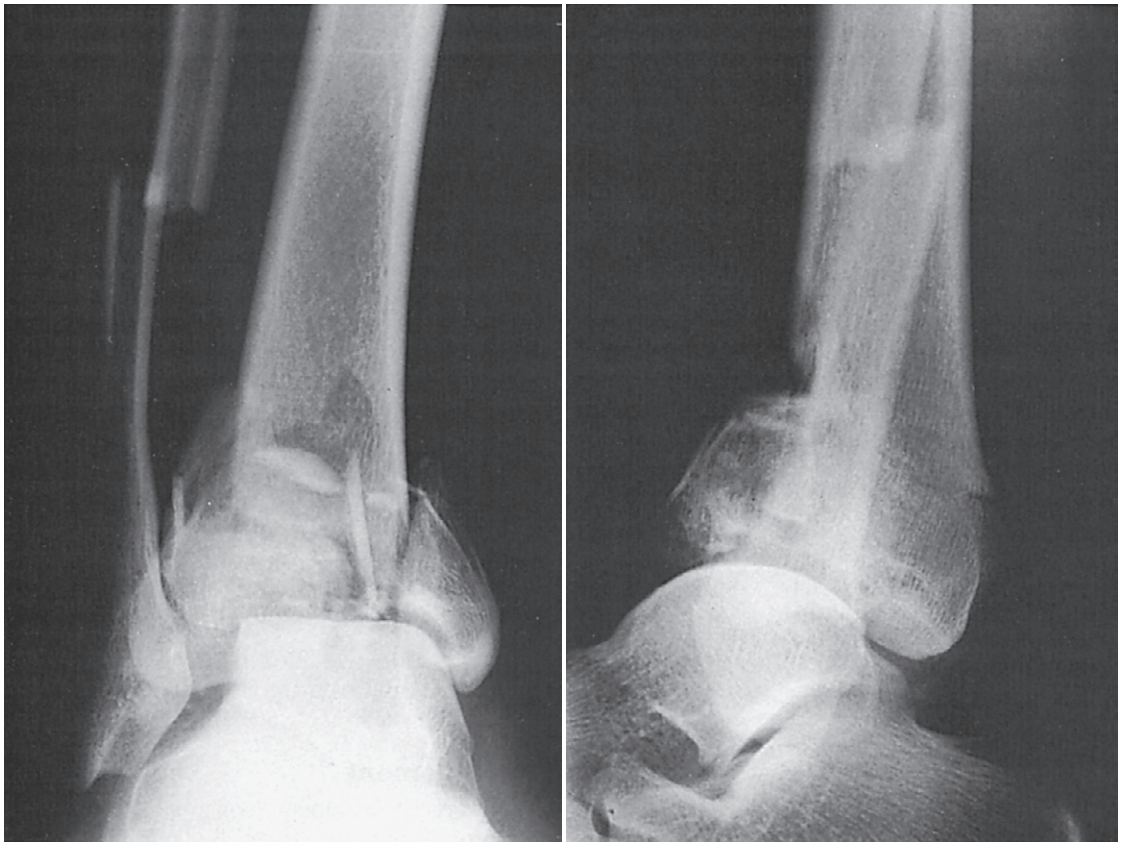


Figure 55-10. Anteroposterior (**A**) and lateral (**B**) radiographic views showing a pilon fracture. (**A** and **B,** From Gustilo RB, et al [eds]: Fractures and Dislocations. St. Louis, Mosby, 1993.)

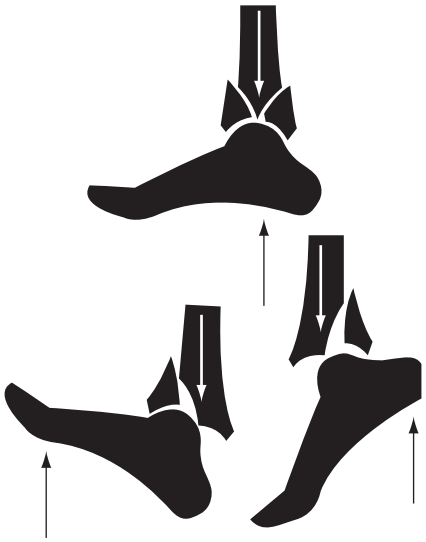


Figure 55-11. Schematic diagram of the pathophysiology of pilon fractures. The position of the foot at the time of impact determines the fracture pattern. (From Gustilo RB, et al [eds]: Fractures and Dislocations. St. Louis, Mosby, 1993.)

the articular surface and fibular length, combined with meticulous management of soft tissue injuries.[42,43] Because surgical management is required, orthopedic consultation in the ED is necessary. Primary open reduction and internal fixation constitute appropriate management of pilon fractures with low-grade soft tissue damage.[43,44] In severe pilon fractures with extensive soft tissue damage, however, results are better with a two-stage approach involving initial length restoration and external fixation followed by anatomic reduction and internal fixation after soft tissue swelling has subsided.[44-46]

Complications. Complications of pilon fractures are common, particularly in more severe cases.[43] Early complications include wound infection, skin sloughing, pin site infection, and wound dehiscence. Delayed and late complications include malunion, nonunion, leg shortening, post-traumatic arthritis, avascular necrosis, and protracted pain. Some patients with severe pilon fractures ultimately require arthrodesis.

Soft Tissue Injuries

Ligament Injuries

Ankle sprains are commonly seen in EDs, with a recent series estimating an annual incidence of 52.7 to 60.9 cases per 10,000 population.[47] Ankle sprains also are one of the most common injuries in young athletes.[48] The term *ankle sprain* refers to a potpourri of ligamentous and nonligamentous injuries.[49] Even when ligamentous injury is certain, the ideal treatment approach remains controversial, and significant variation in clinical practice exists.[47,50,51]

Pathophysiology. Most ankle sprains occur from extreme inversion and plantar flexion. Usually the anterior talofibular ligament is injured first, followed by the calcaneofibular ligament if the deforming forces are sufficiently strong. Approximately two thirds of ankle sprains are isolated anterior talofibular ligament injuries, whereas 20% involve both anterior talofibular and calcaneofibular ligament injuries. In addition, the lateral

talocalcaneal ligament may be stressed with an inversion injury, leading to avulsion fractures at either end of the attachment sites.[52] Isolated calcaneofibular or posterior talofibular ligament injuries are rare.

Isolated injury of the deltoid ligament occurs in less than 5% of ankle sprains. Rupture of this ligament occurs most commonly in conjunction with malleolar fractures, especially when an external rotational force is involved.

Injuries of the distal tibiofibular syndesmotic ligaments are uncommon in the general population but may represent 10 to 20% of injuries in competitive athletes.[53] Dorsiflexion and external rotation forces usually are responsible for this injury, the presence of which may significantly prolong the recovery time with lateral collateral ligament sprains.[53]

Ligamentous injuries are classified into three grades based on functional and presumed pathologic findings. A *grade I* injury involves ligamentous stretching without grossly evident tearing or joint instability. A *grade II* injury involves a partial tear of the ligament with moderate joint instability, often accompanied by significant localized swelling and pain. A *grade III* injury involves a complete tear of the ligament with marked joint instability and severe edema and ecchymosis. This classification system, although commonly used, fails to characterize ankle injuries involving two or more ligaments, and it does not consider nonligamentous injuries. These limitations have led to the proposal of other, more comprehensive classification systems.[52]

Clinical Features. Although desirable, an accurate history of ankle position and injury mechanism often is unavailable. Inversion followed by external rotation of the ankle suggests the potential for deltoid or syndesmotic injury. Forced dorsiflexion with snapping may indicate peroneal tendon displacement. Previous injuries to the same ankle or symptoms of recurrent ankle instability or pain suggest the presence of a subacute or chronic pathologic process.

On physical examination, the presence of edema, ecchymosis, and point tenderness over the medial or lateral collateral ligaments or the syndesmotic ligaments suggests a ligamentous injury. With inversion injuries, point tenderness also may be present along the distal fibula, the lateral aspect of the talus, the lateral aspect or anterior process of the calcaneus, or the base of the fifth metatarsal. Deltoid ligament tenderness demands palpation of the full length of the fibula to rule out a proximal fibular fracture (a type C Danis-Weber or Maisonneuve fracture; see Figs. 55-8 and 55-9). The *fibular compression test*, also known as the squeeze test, reveals fibular and syndesmotic injuries.[53] To perform this test, the examiner places the fingers over the fibula and the thumb over the tibia at midcalf and squeezes the two bones. The elicitation of pain anywhere along the length of the fibula suggests a fibular fracture or an interosseous membrane or syndesmotic ligament disruption at that location.[53] Finally, the Achilles tendon should be assessed.

Diagnostic Strategies: Radiology. Standard ankle radiographic views are useful to exclude fractures and to detect instability by the measurement of joint spaces (see earlier discussion and Fig. 55-6).[6] Presence of avulsion fractures, which can be located at the bases of the malleoli, the lateral process of the talus, the lateral aspect of the calcaneus, the posterior malleolus, the lateral aspect of the distal tibia, or the base of the fifth metatarsal, constitutes an important clue to the location of ligamentous injuries.

In addition to the standard mortise measurements previously discussed, two measurements on the anteroposterior radiograph further evaluate the distal tibiofibular syndesmosis (see Fig. 55-6).[6] At the distal overlap between the fibula and the tibia, the distance between the posterior edge of the lateral tibial groove and the medial fibular cortex (syndesmosis A) should not exceed 5 mm.[6] Furthermore, the amount of tibiofibular bony overlap (syndesmosis B) should be at least 10 mm.[6] Measurements outside of these values suggest a syndesmotic diastasis.

Stress testing is the application of a deforming force to assess joint motion beyond the physiologic range, the presence of which suggests ligament disruption or mechanical instability. Indications for stress testing are few and may include an acute and severe ankle injury in which rupture of two or more ligaments is suspected; a fracture suspected to be isolated in which the presence of an additional ligament rupture would influence management; the possibility of a concomitant syndesmotic injury; follow-up evaluation of an acute ankle injury after pain and swelling subside; and a chronically symptomatic ankle. With the exception of these scenarios, stress testing is not indicated because it is painful and does not alter management. The normal ranges for stress tests are controversial, so the uninjured side should be examined for comparison.

Common ankle stress tests include the anterior drawer test, the inversion stress test, and the external rotation test. The *anterior drawer test* primarily assesses the integrity of the anterior talofibular ligament. To perform this test, the patient is comfortably seated, with the knee in 90 degrees of flexion and the ankle in a neutral position or 10 degrees of plantar flexion. The examiner then pulls on the heel with one hand and pushes the leg posteriorly with the other. Anterior displacement of the talus, the perception of a "clunk," and the induction of a sulcus anteromedially over the joint indicate partial or complete tear of the ligament.

The *inversion stress test*, or talar tilt test, evaluates both the anterior talofibular ligament and the calcaneofibular ligament. It is performed by inverting the heel with the knee in 90 degrees of flexion and the ankle in neutral position. Palpation of the head of the talus laterally or a finding of increased laxity compared with the uninjured side suggests partial or complete tear of these ligaments.

The *external rotation stress test* is indicated when injury to the distal tibiofibular syndesmotic ligaments is suspected. It is done by externally rotating the foot with the knee in 90 degrees flexion and the ankle in a neutral position. Pain at the syndesmosis or the sensation of lateral talar motion suggests partial or complete tear of the ligaments.

Stress radiographs, which are radiographs taken during stress testing of the ankle, generally do not influence the emergency management of ankle sprains and are not recommended.[54]

Many injuries can masquerade as ankle sprains.[49] Box 55-2 lists conditions to be considered in the differential diagnosis; Figure 55-12 shows locations of common fractures in or near the ankle.

Management. Most ligament sprains, regardless of severity, heal well and result in a satisfactory outcome. To date, compelling evidence for a significant difference in outcomes with

BOX 55-2 DIFFERENTIAL DIAGNOSIS FOR PRESUMED ANKLE SPRAIN

Lateral collateral ligament sprain
Peroneal tendon dislocation
Osteochondral fracture of the talar dome
Fracture of the posterior process of the talus
Fracture of the lateral process of the talus
Fracture of the anterior process of the calcaneus
Midtarsal joint injury
Fracture of the base of the fifth metatarsal

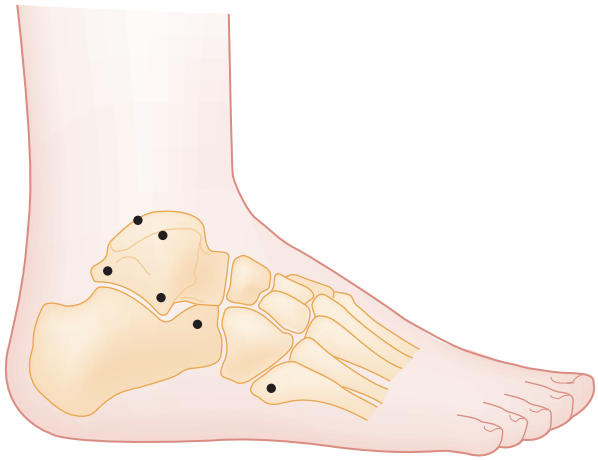


Figure 55-12. Differential diagnosis of a presumed ankle sprain: potential locations of fractures. (From Gustilo RB, et al [eds]: Fractures and Dislocations. St. Louis, Mosby, 1993.)

surgical and with nonsurgical (functional) treatment is lacking. Limited data suggest that recovery times may be longer and complications more frequent with surgical treatment.[55] Most patients with acute sprains of the ankle should start with functional treatments.[56] For the minority who fail to respond, delayed operative repair of ruptured ligaments, sometimes years after the injury, has been shown to yield results equivalent to those with primary repair.[56,57]

Functional treatment starts in the ED with RICE therapy (rest, ice, compression, elevation); however, significant variability exists in how this combination is applied, and the optimal methods remain unclear.[51,52,58] The evidence to date suggests that lace-up ankle support is more effective in short-term edema reduction than semirigid ankle support, elastic bandaging, and taping. Elastic bandaging causes fewer complications than taping but appears to correlate with slower return to work and sports.[51] A more recent study suggests that compared with elastic bandaging, ankle bracing with a lace-up brace such as the Air-Stirrup Ankle Brace (Aircast, DJO Inc., Vista, California) leads to improved functioning at both 10 days and 1 month.[59]

For grade I or II injuries, short-term protection with a tensor bandage, taping, a laced-up support, or a commercial walking boot or brace, with the optional use of crutches for a few days, is appropriate.[56,58] For patients with first-time ankle sprains, treatment with a lace-up stirrup brace combined with elastic wrapping results in an earlier return to function compared with use of a brace alone, elastic wrap alone, or a walking cast.[60] For severe grade II or grade III injuries, splinting or casting for up to 3 weeks occasionally is necessary. Because there is no evidence for a more favorable outcome with immobilization than with functional treatment, the use of a lace-up support or air cast that permits some ankle motion generally is preferable.[56,61] Such patients also should a use crutches to avoid weight bearing until they can stand and walk a few steps on the injured ankle without pain. How long crutches will be required varies significantly, ranging from a few days to 2 or 3 weeks. Follow-up care with the patient's primary physician within the first 2 weeks is appropriate for minor sprains, whereas orthopedic referral on an outpatient basis is prudent for severe sprains.

Analgesics often are necessary for acute pain management in ankle injuries, and studies suggest that nonsteroidal anti-inflammatory agents, acetaminophen, or oral opioids for severe cases are efficacious.[62-64] Topical diclofenac gel also has been shown to have efficacy in pain reduction.[55,65,66]

After the acute management phase, the next two phases of functional treatment involve appropriate early rehabilitation and occur outside the ED.[67] Phase two, which begins after swelling has subsided and the patient is able to bear weight easily, involves strengthening the peroneal and dorsiflexor muscles by isometric, concentric, and eccentric exercises. The final phase begins when full range of motion has been reestablished and the patient can exercise painlessly. This starts with exercises to rebuild motor coordination, recondition the muscles, and increase endurance. The patient uses an ankle tilt board or disk to develop coordination and performs increasingly demanding functional activities (e.g., brisk walking, running, and figure-of-eight running to hopping, jumping, and cutting) to build up the muscle groups.[67,68] With severe sprains, the patient may benefit from the use of air casts, braces, or taping during the latter two phases of functional treatment.[67] The entire treatment program usually lasts 4 to 6 weeks, depending on the injury's severity.[52,58,69]

Disposition. Rarely, orthopedic consultation in the ED is indicated for an acute ligament sprain. Primary surgical repair of acute ligament rupture is controversial, and possible indications include sprains with displaced osteochondral fractures, complete tears of both the anterior talofibular and calcaneofibular ligaments in a young athlete, a ligament sprain associated with a fracture causing instability (e.g., a deltoid ligament rupture with a lateral malleolar fracture), and an acute severe sprain in a patient with a history of recurrent and severe sprains.[52] Failure of nonoperative treatment also constitutes an indication for surgical repair; however, an orthopedic referral on an outpatient basis is adequate ED management.[57]

Small avulsion fractures of the fibula with minimal or no displacement can be treated as for an ankle sprain. If the chip fragment is larger than 3 mm or significantly displaced, splinting and referral for orthopedic follow-up on an outpatient basis are justified.

Despite appropriate treatment, chronic problems develop in 10 to 30% of patients with ankle sprains.[58] These include functional instability, mechanical instability, chronic pain, stiffness, and recurrent swelling.

Functional instability refers to the patient's subjective sensation that the ankle gives way during activity. Although this may be a minor nuisance for some people, it can be devastating and debilitating for persons whose activities demand a high degree of ankle stability. *Mechanical instability* results from ligamentous laxity, which allows ankle joint movements beyond the physiologic range. In contrast with functional instability, mechanical instability can often be demonstrated clinically by the anterior drawer or talar tilt test and stress radiographs.[52]

Soft tissue abnormalities that cause chronic pain include synovial impingement, peroneal tendon subluxation or dislocation, loose bodies, anterior tibiofibular syndesmotic ligament injuries, and degenerative arthritis. Bone-related causes of chronic pain include osteochondral fractures, fractures of the anterior process of the calcaneus, fractures of the lateral process of the talus, and anterior and posterior impingement.[49,70]

Patients with any of these chronic conditions should be referred for orthopedic follow-up care because they may require further imaging or arthoscopy for diagnosis or definitive treatment.

Tendon Injuries

Achilles Tendon Rupture

Achilles tendon rupture is most common in middle-aged men, and its causes are multifactorial.[71] This condition can easily be misdiagnosed, leading to delay in therapy and a worse prognosis.

Achilles tendon rupture results from direct trauma or indirectly transmitted forces, including sudden unexpected dorsiflexion, forced dorsiflexion of a plantar-flexed foot, and strong push-off of the foot with simultaneous knee extension and calf contraction (as in a runner accelerating from the starting position). Factors predisposing to Achilles tendon rupture include preexisting disease such as rheumatoid arthritis, systemic lupus erythematosus, gout, hyperparathyroidism, or chronic renal failure; steroid use or injection; and fluoroquinolone antibiotic therapy.[72,73]

The diagnosis of an Achilles tendon rupture is primarily clinical. Patients usually describe a sudden onset of pain at the back of the ankle associated with an audible "pop" or "snap." Although the pain can resolve rapidly, weakness in plantar flexion persists. On examination, a visible and palpable tendon defect may be noted 2 to 6 cm proximal to the calcaneal insertion in acute presentations but will be less apparent in delayed presentations because of hematoma or edema. Even in cases of complete Achilles tendon rupture, weak plantar flexion may still be possible because of the actions of the tibialis posterior, toe flexors, and peroneal muscles. This retained ability for plantar flexion often leads to the misdiagnosis of ruptures as strains or partial tears.

The classic maneuver to assess the integrity of the Achilles tendon is the *Thompson test*.[74] This is performed with the patient prone and the knee flexed at 90 degrees. Alternatively, the patient kneels on a chair with both knees flexed at 90 degrees and the feet dangling over the edge. Squeezing the calf muscles in these two positions should cause passive plantar flexion of the foot. Absence of this motion or a weakened response compared with the uninjured side suggests complete rupture. Another diagnostic test involves wrapping a sphygmomanometer cuff around the calf while the patient is prone. With the knee flexed to 90 degrees and the foot relaxed, the cuff is inflated to 100 mm Hg. Dorsiflexion of the foot by the examiner should cause an increase in pressure to approximately 140 mm Hg. Failure to induce a rise in pressure or a significant diminution compared with the uninjured side suggests rupture.[75]

Lateral radiographic views of the ankle may confirm rupture by showing opacification of the triangular fatty tissue–filled space anterior to the Achilles tendon (Kager's triangle) or an irregular contour and thickening of the tendon.[76] Ultrasonography or MRI also can demonstrate partial or complete tendon ruptures, but these studies are indicated only in rare cases in which diagnostic uncertainty exists.[76] Portable ED ultrasound imaging is occasionally used to confirm the diagnosis, but its accuracy is operator-dependent. The choice of operative repair versus nonoperative management involving a series of casts is controversial.[71,77,78] Surgical repair is commonly performed owing to its lower incidence of rerupture, but surgery carries higher rates of other complications such as superficial or deep wound infections in comparison with nonoperative management.[77,79] In both types of management, early mobilization improves functional recovery without increasing rerupture rates.[77,78] Minimally invasive surgery combined with early rehabilitation with postoperative functional bracing may further improve outcome.[80,81] Achilles tendon rerupture after initial nonoperative treatment usually necessitates surgical repair. ED orthopedic referral of patients with Achilles tendon rupture is necessary to determine the appropriate management.

Peroneal Tendon Dislocation or Tear

The peroneal muscles are the primary evertors and pronators of the foot and also participate in plantar flexion. The peroneus longus and brevis tendons use the posterior peroneal sulcus (the fibular groove), located behind and underneath the lateral malleolus, as a pulley for their midfoot insertions. The peroneus brevis tendon inserts onto the tuberosity of the fifth metatarsal, and the peroneus longus tendon courses beneath the cuboid to insert onto the medial cuneiform and base of the first metatarsal. The superior peroneal retinaculum (Fig. 55-13), a fibrous structure running from the distal fibula to the posterolateral aspect of the calcaneus, maintains the peroneal tendons against the fibular groove.

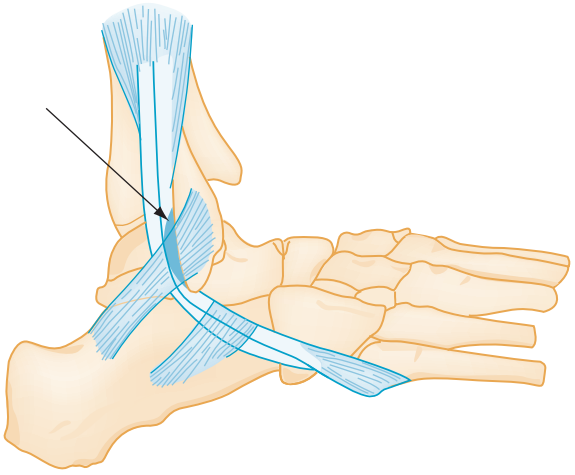


Figure 55-13. The locations of the superior *(arrow)* and inferior peroneal retinaculum in relation to the fibula and the peroneal tendons. (From Arrowsmith SR, et al: Traumatic dislocations of the peroneal tendons. Am J Sports Med 11:142, 1983.)

Anterior subluxation or dislocation of the peroneal tendons occurs as a result of a tear of the superior peroneal retinaculum attachment from the fibula.[82,83] This infrequent injury commonly is misdiagnosed as an ankle sprain and can occur in isolation or concomitant with other sprains or fractures. The mechanism of injury usually is forced dorsiflexion with reflex contraction of the peroneal muscles, resulting in avulsion of the retinaculum and anterior displacement of the peroneal tendons.[82]

Patients with a peroneal tendon dislocation complain of sudden pain and a snapping sensation over the posterolateral ankle associated with weakness of eversion. Tenderness and swelling over the lateral retromalleolar area (a location not typically involved in ankle sprains) are characteristic. When accurate examination is not precluded by swelling, the dislocated tendons also may be palpable near the inferior tip of the lateral malleolus. Inability to actively evert the foot when it is held in dorsiflexion or frank subluxation of the tendons with this maneuver confirms the diagnosis. Findings on plain radiography often are normal; however, between 15% and 50% of patients will be found to have an associated avulsion fracture of the lateral ridge of the distal fibula. An MRI study or CT scan can be helpful in confirming the diagnosis. All patients with a suspected or confirmed peroneal tendon dislocation should be referred for orthopedic follow-up, because these injuries require surgical repair.[83,84] Spontaneous healing is rare in untreated cases, and chronic ankle instability and pain are common sequelae. Peroneal tendons also can tear longitudinally; such injuries manifest either acutely or subacutely with recurrent pain and swelling during activities.[84,85]

Tibialis Posterior Tendon Rupture

The tibialis posterior is primarily responsible for plantar flexion and inversion along the subtalar joint. Its tendon uses the

posteroinferior surface of the medial malleolus as a pulley and inserts onto the navicular, the medial cuneiforms, and the bases of the second through the fifth metatarsals. The peroneus brevis opposes the action of the tibialis posterior. With rupture of the tibialis posterior tendon, the peroneus brevis becomes unopposed and the medial longitudinal arch loses its muscular support, leading to valgus deformity of the hindfoot and a unilateral flatfoot.[86]

The mechanism of traumatic tibialis posterior rupture involves forced eversion.[86] In addition to a unilateral flatfoot, pain and swelling on the medial aspect of the ankle are seen. Tenderness is present over the navicular, and the patient cannot perform a toe raise on the affected side. In addition, the patient with a tibialis posterior tendon rupture is unable to invert the foot when it is in plantar flexion and eversion. With a unilateral flatfoot, an observer standing behind the patient can see "more toes" on the lateral aspect of the affected side—a classic sign.[86] Plain radiography can exclude other bone abnormalities. Ultrasonography and MRI are useful imaging modalities to diagnose this condition.[86] Orthopedic consultation is indicated for tibialis posterior tendon ruptures, because surgical repair often is necessary.

Other Tendon Injuries

The tibialis anterior is the primary dorsiflexor of the foot. Its tendon courses under the superior extensor retinaculum and inserts onto the navicular, the medial cuneiform, and the base of the first metatarsal. Tenosynovitis of the tibialis anterior tendon is associated with overuse and characterized by swelling, tenderness, and crepitus along the tendon. Treatment involves RICE therapy, analgesia, and close follow-up. Rupture of the tibialis anterior is rare and often is misdiagnosed as lumbosacral radiculopathy or peroneal palsy because of the footdrop it produces. This condition requires orthopedic consultation in the ED because surgical repair usually is necessary.

The flexor hallucis longus is responsible for flexion of the great toe and participates in plantar flexion of the foot. Its tendon courses behind the medial malleolus through a fibro-osseous canal and inserts onto the distal phalanx of the great toe. Flexor hallucis longus tendinitis, also called *dancer's tendinitis*, most often occurs at the fibro-osseous canal.[87] On examination, tenderness and edema posterior to the medial malleolus are noted, and passive extension of the first metatarsophalangeal (MTP) joint causes significant pain when the foot is in neutral position. Initial treatment involves rest, nonsteroidal anti-inflammatory drugs, and a short course of immobilization. Orthopedic follow-up on an outpatient basis should be arranged to ensure proper resolution. Rarely, surgical intervention may be necessary.[87]

Ankle Dislocations

Ankle dislocations are described according to the direction of displacement of the talus and foot in relation to the tibia. Thus, dislocation may be upward, posterior, medial, lateral, posteromedial, or anterior. Medial dislocation is the most common. Most dislocations involve associated ankle fractures; rarely, however, dislocations can occur without fracture. The mechanism in all dislocations begins with axial loading of a plantar-flexed foot, which forces the talus either anteriorly or posteriorly from the ankle mortise. The eventual position of the dislocation depends on the position of the foot at the time of injury and the direction of the displacing force. Ankle dislocations can be closed or open and most commonly result from significant falls, motor vehicle collisions, or high-speed sports.[31] The neurovascular supply to the foot usually is intact but may be compromised in open dislocations.[88]

ED management involves the assessment of neurovascular status and tendon function, followed by rapid reduction. Radiographs are helpful but should not delay reduction in obvious cases or when neurovascular compromise or skin tenting is present.[31] After appropriate procedural sedation and analgesia, the patient is placed supine and the knee is flexed to 90 degrees. Distraction of the foot, followed by a gentle force to reverse the direction of the dislocation, usually accomplishes the reduction.[89] Splint immobilization, elevation of the ankle, reassessment of the neurovascular status, and postreduction radiography should follow. Open dislocations require the same management as previously discussed. The prognosis with an ankle dislocation usually is good, although open fractures are associated with an increased incidence of complications.[88,89]

FOOT

PRINCIPLES OF DISEASE

Anatomy

The foot is composed of 28 bones and 57 articulations (Fig. 55-14). It can be divided into three anatomic and functional regions: the hindfoot, which contains the talus and calcaneus; the midfoot, which contains the navicular, cuboid, and cuneiforms; and the forefoot, which contains the metatarsals, phalanges, and sesamoids. The midtarsal joints (Chopart's joint) join the hindfoot and midfoot, and the tarsometatarsal joints (Lisfranc's joint) join the midfoot and forefoot. The inferior aspect of the talus has three articulations with the calcaneus that are collectively known as the *subtalar joint*.

The foot's bones interlock in a manner that is often likened to the blocks and keystones of a bridge, forming a complex system of arches and beams tethered by ligaments and intrinsic muscles. Extrinsic muscles, originating in the leg, are responsible for most of the foot's movements, as well as for

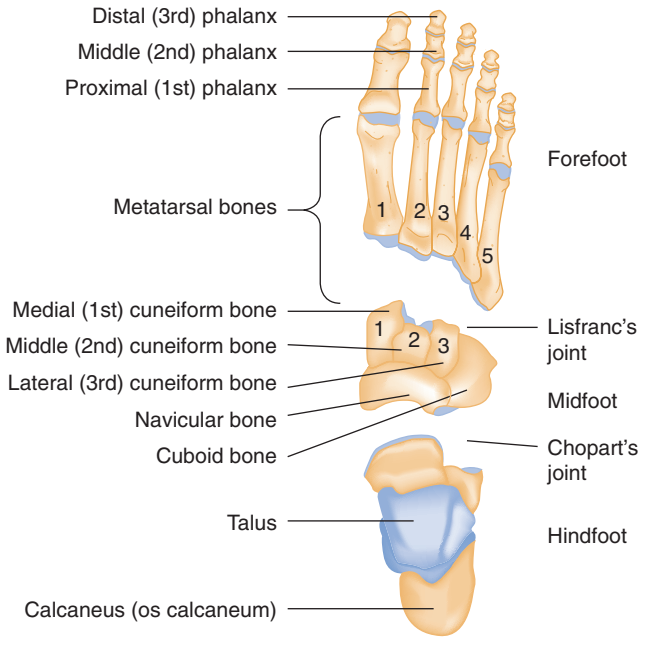


Figure 55-14. Bones and joints of the foot. (From Rockwood CA, et al [eds]: Rockwood and Green's Fractures in Adults, 3rd ed. New York, JB Lippincott, 1991.)

maintenance of the arch and beam structure. The course and insertion of these extrinsic muscles are important in their actions and in their association with specific avulsions and injuries. The arterial supply to the foot is from the anterior and posterior tibial arteries and the peroneal artery, a proximal branch of the posterior tibial artery. Motor and sensory innervation comes from branches of the deep and superficial peroneal, posterior tibial, saphenous, and sural nerves.

The foot is capable of numerous weight-bearing and nonweight-bearing motions (see Fig. 55-3), which vary at each articulation. Inversion and eversion of the hindfoot occur primarily through the subtalar joint, adduction and abduction of the forefoot through the midtarsal joints, and flexion and extension through the MTP and interphalangeal (IP) joints. The relative importance of specific bones in supporting the body's weight varies with changes from the static to the mobile state. The biomechanics of walking and running are extremely complex, and significant forces are imparted to the foot's structures during these precisely coordinated activities.[90]

Clinical Features

An accurate history is essential in the setting of foot trauma because many mechanisms are associated with specific injury patterns. Mechanisms can be broadly divided into direct and indirect (torsional) forces. Falls, twisting injuries, dropped objects, overuse injuries, burns, and penetrating wounds each suggest different potential pathologic conditions. Patient complaints may involve any combination of pain, swelling, deformity, reduced function, or altered sensation. The location of pain, along with a description of its quality, duration, and precipitants, focuses the differential diagnosis. The combination of increasing pain with decreasing sensation is particularly compelling because this may indicate neurovascular compromise requiring immediate intervention. Along with obtaining general information, the history should identify underlying pertinent medical conditions, medications, and previous foot problems.

The structures of the foot are uniquely accessible to palpation and assessment. A directed examination, specific for the patient's complaint, is most useful in the ED.[91]

If the patient is ambulatory, observation of the gait provides information on the degree of disability and pain and the potential for serious injury. Formal examination begins with observation of the foot in its position of rest, normally one of slight plantar flexion and inversion. Swelling, deformity, ecchymosis, open wounds, color, and temperature should be noted. The use of ecchymosis to localize injuries can be misleading because of pooling of blood in dependent areas after tracking through tissue planes. All patients should have a neurovascular examination with assessment of the dorsalis pedis and posterior tibial pulses, sensation, and motor function. Precise localization of pain or crepitus, when not precluded by swelling, is extremely valuable and facilitates appropriate use of further diagnostic tools. The entire foot should be gently palpated over both the dorsal and plantar surfaces, methodically progressing from the heel to the toes. Particular attention should be paid to areas in which injuries commonly occur, such as the base of the fifth metatarsal.

In some situations, an evaluation of range of motion is indicated. This begins with an assessment of active motion with the foot dependent. Next, if active motion is well tolerated, passive motion is assessed, beginning with the subtalar joint in the hindfoot and moving distally to the midtarsal and forefoot joints. Subtalar motion is evaluated by holding the lower leg with one hand and the heel with the other. Then, with the foot in neutral position, the heel is inverted and everted. Normally, there should be at least 25 degrees of mobility in each direction. Midtarsal motion is evaluated by stabilizing the heel with one hand while the other hand grasps the forefoot at the bases of the metatarsals. The forefoot can then be pronated, supinated, abducted, and adducted. Normally, there should be at least 20 degrees of adduction and 10 degrees of abduction.

Forefoot motion is evaluated by flexing and extending the MTP and IP joints individually. The first MTP joint has a particularly wide passive range of motion, with 45 degrees of flexion and 70 to 90 degrees of extension. Throughout the physical examination, findings can be compared with those for the opposite foot.

Diagnostic Strategies: Radiology

Plain radiography of the foot may be indicated by history, physical examination, or both. Standard three-view radiographs of the foot consist of anteroposterior, lateral, and 45-degree internal oblique projections. The lateral projection gives the best imaging of the hindfoot and soft tissues, whereas the anteroposterior and oblique projections give the best imaging of the midfoot and forefoot. The numerous overlapping bones of the foot demand this complete radiographic series in all patients for whom radiographic examination is indicated.[92] Injuries to the hindfoot also warrant the addition of standard ankle projections and, when indicated, calcaneus views.

Foot radiographs can be difficult to interpret.[93] Moreover, foot fractures often are minimally displaced, or nondisplaced, increasing the challenge of radiographic diagnosis. Several additional views improve the imaging of specific areas of the foot. Coned views, weight-bearing radiographs, or a 45-degree external oblique projection can be useful, particularly for detection of midfoot and forefoot pathology. The most commonly obtained atypical view is the Harris (axial) view for visualizing the calcaneus and subtalar joints. Special magnification radiographs or stress radiographs also may be useful in selected cases.

Interpretation of plain radiographs can be complicated by the numerous accessory centers of ossification and the presence of sesamoid bones (unipartite and multipartite) that exist as normal variants in up to 30% of the population (Fig. 55-15). The most commonly seen accessory bones are the os trigonum, os tibiale externum (also called an accessory navicular bone), os peroneum, and os vesalianum.[94] These can be differentiated from fractures by their smooth corticated surfaces. Comparison radiographs of the opposite foot may be helpful, although such variants are not inevitably bilateral. Accessory bones themselves can also fracture or cause pain syndromes.[95]

Because of the limitations of plain radiography, other imaging techniques have gained importance for specific foot injuries. Radionuclide imaging (bone scanning) can be useful for evaluating unexplained foot pain or pain in athletic injuries.[96] In the setting of acute foot trauma, this modality often can demonstrate subtle fractures not visible with plain radiography. Bone scanning has been the "gold standard" modality for the diagnosis of stress fractures; however, MRI has comparable sensitivity and better specificity and is emerging as the imaging modality of choice for this diagnosis.[21]

The CT scan can be valuable when complex articulations and overlapping bones make standard radiographs difficult to interpret, particularly in the midfoot and hindfoot.[97,98] As a result of the wide availability and superiority of CT scanning, plain film tomography is now rarely performed. CT is an excellent modality for imaging complex anatomy, including the subtalar joint, the calcaneus, and the tarsometatarsal (Lisfranc)

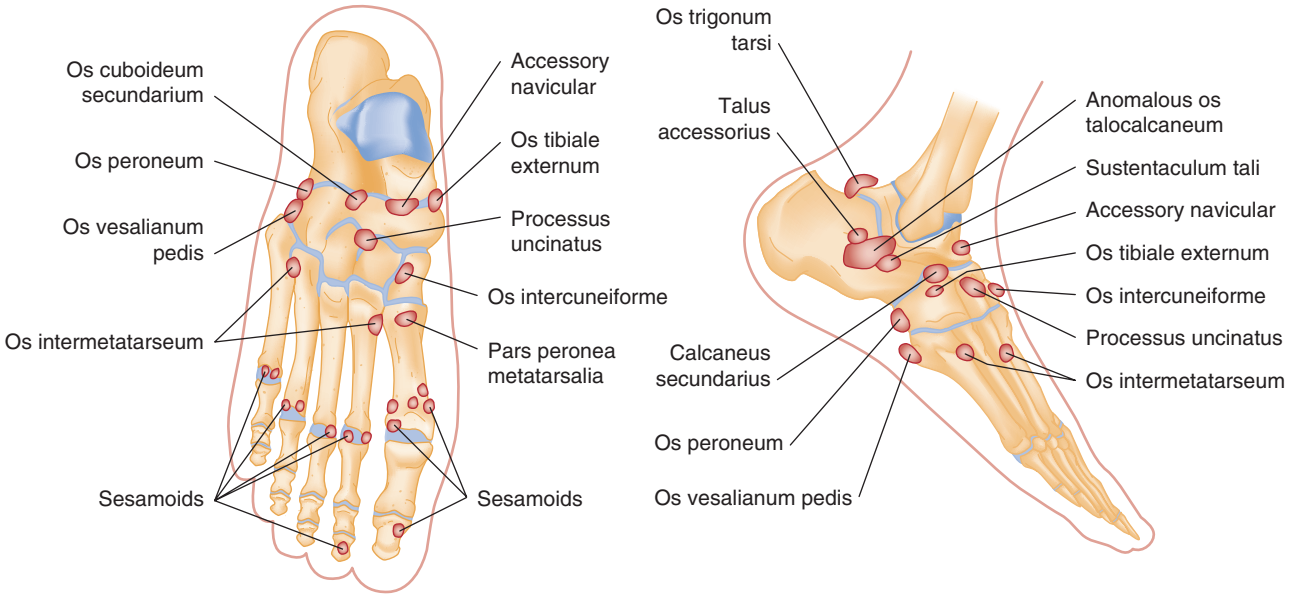


Figure 55-15. Accessory ossicles of the foot. (From Berquist TH [ed]: Radiology of the Foot and Ankle. New York, Raven Press, 1989.)

joint complex. Three-dimensional CT images provide unprecedented clarity and detail.[99]

MRI has been used in investigation of many of the same fractures and dislocations imaged by CT, and the two modalities can be used in a complementary manner.[100-103] As in the ankle, the most significant role of MRI is in delineating soft tissue conditions, such as athletic injuries and tendon ruptures, where it has become the imaging modality of choice. In some conditions involving the ankle joint, MR arthrography can be useful.[104]

SPECIFIC PATHOLOGIC CONDITIONS

This section covers the major fractures and dislocations seen in the foot, progressing anatomically from the hindfoot through to the forefoot. This order corresponds with the sequence of physical examination in patients with foot trauma. Any of these fractures or dislocations may be open, necessitating appropriate wound management.

Hindfoot Injuries

The hindfoot commonly is involved in foot injuries and is a difficult area to image. Fractures or dislocations in this region can masquerade as ankle sprains and, if not considered in the differential daignosis, can be missed.

Talar Fractures

Principles of Disease: Anatomy. The word *talus* is related to the Latin *taxillus*, meaning "dice," and dates back to the Roman Empire, when soldiers made dice out of the ankle bones of horses. An appreciation of the unique anatomy of the talus is crucial to an understanding of the pathophysiology and treatment of talar fractures and dislocations. The talus is the second largest tarsal bone and has seven articulations making up 60% of its surface. It is divided into three regions: the head, which articulates with the navicular and calcaneus; the body, which articulates with the tibia, fibula, and calcaneus; and the neck, which joins the head and body and is the only portion of the talus that is predominantly extra-articular. The talus is the only bone in the lower extremity with no muscular attachments and is held in position by the malleoli and ligamentous attachments. The anterior width of the talus is greater than the posterior, causing it to be less stable and more prone to dislocation when the foot is plantar flexed.

The blood supply to the talus is from a vascular ring formed by branches of the anterior and posterior tibial arteries and the perforating branch of the peroneal artery. Vessels enter the talus from three main sites, any or all of which can be disrupted by fractures or dislocations. Because of the tenuous nature of these vessels and the inconsistency of collateral circulation, the risk of avascular necrosis is significant with many talar fractures.

Pathophysiology. Talar fractures are the second most common tarsal fracture after the calcaneus. They are best grouped into minor and major fractures, with minor fractures being the more common.[105] Stress fractures of the talus also can occur. *Minor* talar fractures include chip and avulsion fractures of the superior neck and head, and the lateral, medial, and posterior aspects of the body.[106] These fractures often involve the same mechanism as that for ankle sprains (see Fig. 55-12 and Box 55-2): a combination of plantar flexion or dorsiflexion and an inversion force. Lateral process fractures, a previously uncommon injury, may be associated with snowboarding and can be occult on plain radiographs.[107] Osteochondral fractures of the talar dome also fall into the minor fracture category.

Major talar fractures usually are produced by significant forces and occur in the head, neck, or body. Talar head fractures are uncommon, making up 5 to 10% of all talar fractures. Their mechanism is a compressive force applied on a plantar-flexed foot and transmitted up through the talonavicular joint. Comminution is common, and associated navicular fractures can occur, further disrupting the talonavicular articulation.

Talar neck fractures account for 50% of major talar injuries. Their mechanism usually is an extreme dorsiflexion force, as generated in falls or motor vehicle collisions. Associated fractures are common; the most common is an oblique or vertical fracture of the medial malleolus, which is seen in up to one fourth of cases. Other associated injuries include calcaneal fractures and vertebral compression fractures.

Hawkins classified talar neck fractures into three categories (Fig. 55-16): Type 1 fractures are nondisplaced; type 2 frac-

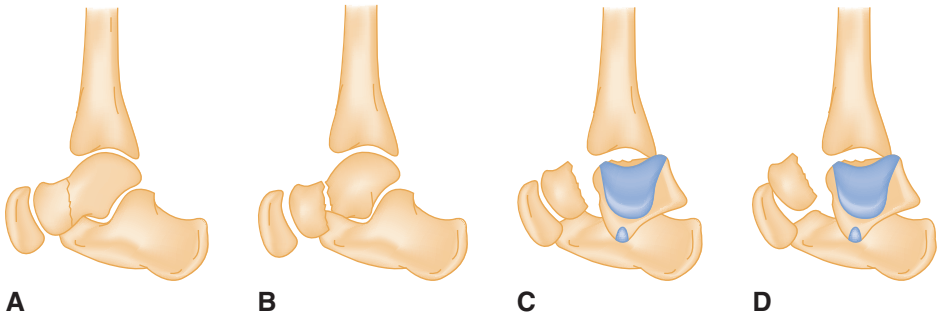


Figure 55-16. **A, B,** and **C,** Hawkins' type 1, 2, and 3 fractures, respectively. **D,** Canale and Kelly's type 4 fracture of the talar neck. (**A–D,** From Gustilo RB, et al [eds]: Fractures and Dislocations. St. Louis, Mosby, 1993.)

tures show subtalar subluxation; and type 3 fractures, 50% of which are open, involve a dislocation of the talar body from the ankle and subtalar joint. A fourth type that has been added to this classification involves the additional distraction of the talonavicular joint. This classification is important descriptively and because the type of fracture influences both treatment and outcome. Complications are more common with increasing displacement of talar neck fractures.

Talar body fractures include many of the minor talar fractures previously listed.[108] Major talar body fractures are uncommon and usually result from falls with axial compression of the talus between the tibial plafond and the calcaneus.

Clinical Features. Talar fractures range from obvious open fractures to subtle fractures requiring special imaging techniques to diagnose. Typically, a history of a twisting injury, fall, or high-energy impact can be elicited. Dorsal swelling and tenderness over the talus are characteristic findings. Although ankle motion may be preserved, inversion and eversion of the hindfoot often are painful.

Diagnostic Strategies: Radiology. With minor talar fractures, radiographs can be misinterpreted as normal in appearance. Even when supplemental views are obtained, other fractures may be occult on plain radiography and require CT or MRI for visualization. Standard foot and ankle radiographic views usually demonstrate major talar fractures (Figs. 55-17 and 55-18), with the anterior and oblique projections showing talar alignment within the mortise and the lateral projection showing the talar neck and alignment of the posterior aspect of the subtalar joint. Normal variants, such as an os trigonum or os supratalare (see Fig. 55-15), are occasionally encountered and must be differentiated from fractures. Specialized imaging by CT, or MRI often is required for complete assessment of talar fractures.

Management. Major talar fractures require precise reduction because more weight per unit area is borne by the superior surface of the talus than by any other bone. Most talar fractures involve multiple articular surfaces, and adequate repair often necessitates open reduction and internal fixation. Many minor talar fractures heal with casting, and the initial treatment should be with a non-weight-bearing below-knee cast or posterior plaster slab. Fragments larger than 5 mm in diameter may require excision. Other minor fractures, such as displaced lateral process fractures, require operative fixation because of their articular involvement.

The treatment of major talar fractures is controversial. Any significantly displaced fracture, particularly if associated with neurovascular or cutaneous compromise, requires an early attempt at closed reduction in the ED. Even if nonoperative reduction is impossible, as is common in type 3 and type 4 neck fractures with an intact medial malleolus, alignment often can be improved. With neurovascular or cutaneous compromise, reduction should not be delayed by waiting for radiography or consultation. After appropriate procedural sedation

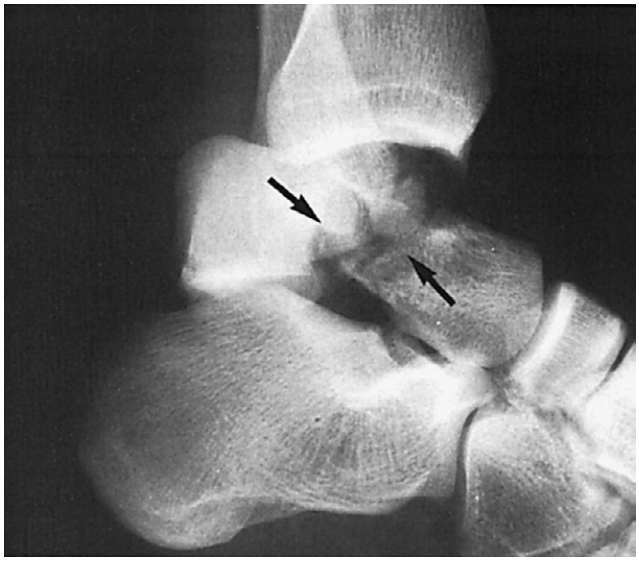


Figure 55-17. Comminuted fracture of the talar body *(arrows)*. (From Rosen P, et al [eds]: Diagnostic Radiology in Emergency Medicine. St. Louis, Mosby, 1992.)

Figure 55-18. Fracture of the talar neck *(arrow)*. (From Rosen P, et al [eds]: Diagnostic Radiology in Emergency Medicine. St. Louis, Mosby, 1992.)

and analgesia, reduction is performed by grasping the hindfoot and midfoot and applying longitudinal traction with plantar flexion. This is followed by realignment of the foot as reduction is achieved. Posterior slab immobilization and postreduction radiographs should then follow.

Displaced talar head fractures or those involving more than 50% of the articular surface usually require open reduction and internal fixation followed by non-weight-bearing casting. Smaller fragments may require excision. Type 1 fractures of the talar neck usually are treated with non-weight-bearing casting for 8 to 12 weeks. Most type 2 and all type 3 and type 4 fractures require open reduction and internal fixation. The management of talar body fractures varies with location.

Disposition. All patients with talar fractures require orthopedic consultation in the ED or referral for early orthopedic follow-up on an outpatient basis. Most minor talar fractures are suitable for outpatient follow-up care.

Although most minor talar fractures heal well, some result in post-traumatic arthritis. Major talar fractures have a high incidence of complications, the most significant of which is avascular necrosis.[1] Outcome depends on the degree of anatomic reduction attained and preservation of the vascular supply. Avascular necrosis can occur and presents treatment challenges.[109] The risk of avascular necrosis increases with increasing talar displacement, ranging from 10% for type 1 neck fractures to 70% or more for type 3 neck fractures. Major fractures of the talar body also are prone to avascular necrosis, the risk of which doubles if an associated dislocation is present. Other potential complications include skin infection, skin necrosis, post-traumatic arthritis, malunion, delayed union, nonunion, and predisposition to peroneal tendon dislocation. The incidence of each complication varies with the type of fracture and the aggressiveness of ED and operative management.

Osteochondral Fractures of the Talar Dome

Osteochondral fractures of the talar dome account for 1% of talar fractures and are usually diagnosed late in the clinical course after ankle trauma.[110] These injuries involve both the cartilage and subchondral bone. Many synonyms for this entity, including *transchondral fracture*, *dome fracture of the talus*, and *chip* or *flake fracture*, are in use. Mechanisms identical to those causing ankle sprains are the most common cause; however, a significant number of these injuries cannot be ascribed to an acute traumatic event.

An osteochondral fracture should be considered in any patient with ligamentous ankle injury accompanied by gross edema and an effusion on plain radiographs.[5] The diagnosis often is missed initially and not made until the patient returns with chronic ankle discomfort.[111] Physical findings usually are nonspecific, although localized tenderness over the posteromedial aspect of the talus and increasing pain with exertion, weight bearing, or passive plantar flexion may be noted. Standard-view radiographs commonly are normal in appearance or show subtle and easily overlooked abnormalities (Fig. 55-19). Bone scanning is useful in identifying talar dome abnormalities. CT or MRI studies often are required for further evaluation and classification.

When an osteochondral fracture is diagnosed or suspected, outpatient orthopedic referral is advised. The natural history of osteochondral fractures is poorly defined; however, chronic ankle discomfort and osteoarthritis are potential sequelae. Osteochondritis dissecans, a subacute or chronic talar dome defect, may develop after inadequate treatment or failure to treat an osteochondral fracture. In general, however, with appropriate treatment, either by cast immobilization for up to 6 weeks or by excision, the prognosis is good, particularly if treatment begins within 12 months of symptom onset. The benefit of excision, often done arthroscopically, varies with the type of lesion and its location.[112] The previous discussion underscores the necessity for orthopedic evaluation when a patient is seen with persistent unexplained ankle pain after a previous "sprain."

Figure 55-19. Anteroposterior view of an ankle showing an osteochondral fracture over the lateral dome of the talus *(arrow)*. (From Baxter DE [ed]: The Foot and Ankle in Sport. St. Louis, Mosby, 1994.)

Subtalar Dislocations

Principles of Disease: Pathophysiology. Subtalar dislocation, also called *peritalar dislocation*, is the simultaneous disruption of both talocalcaneal and talonavicular joints without disruption of the tibiotalar joint (Fig. 55-20). This occurs when the talonavicular and talocalcaneal ligaments rupture while the stronger calcaneonavicular ligament remains intact. Subtalar dislocations are rare and are classified by the direction the foot takes in relation to the talus.[113] Anterior and posterior dislocations occasionally occur; however, most subtalar dislocations are either medial or lateral, with medial dislocations accounting for a majority of cases. Dislocation of the calcaneus is an exceptionally rare event that is distinct from subtalar dislocation and involves disruption of the talocalcaneal and calcaneocuboid articulations.

Subtalar dislocations are caused by severe torsional forces such as those generated in motor vehicle crashes or falls. Medial dislocations result from inversion and plantar flexion, whereas lateral dislocations arise from the combination of eversion and plantar flexion. Ten percent of subtalar dislocations are open, and associated fractures are present in one half of the cases, particularly those with lateral dislocations.

Clinical Features. Obvious deformity typically is present, often with tension of the skin on the side opposite the direction of dislocation. Neurovascular status should be carefully assessed, although it is rarely compromised. Swelling can mask the extent of the injury, so that diagnosis can be further delayed or missed if only ankle radiographs are obtained.

Diagnostic Strategies: Radiology. Although standard foot radiographic views are diagnostic, these may be difficult to obtain because of deformity. Inadequate films due to incorrect patient positioning can delay diagnosis and treatment. The single most helpful radiograph is an anteroposterior view of the foot, which will demonstrate the talonavicular dislocation.

Management. Subtalar dislocations require expeditious reduction.[114] More than 80% of closed subtalar dislocations can be

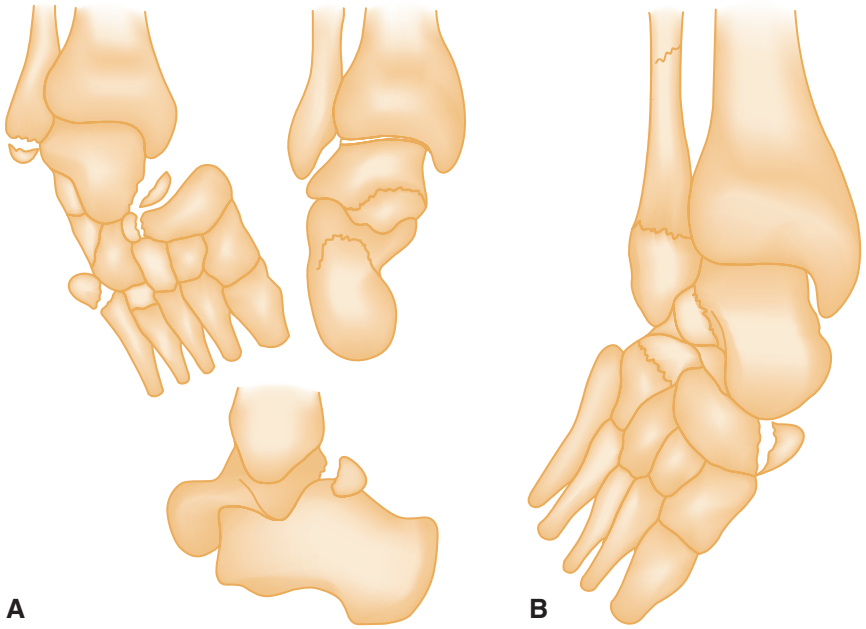


Figure 55-20. Subtalar dislocations with associated fractures. **A,** Medial subtalar dislocation resulting from an inversion force. **B,** Lateral subtalar dislocation resulting from an eversion force. (**A** and **B,** From McGlamry ED, et al [eds]: Comprehensive Textbook of Foot Surgery, vol 2, 2nd ed. Baltimore, Williams & Wilkins, 1992.)

treated with closed reduction, either with use of moderate sedation ("conscious sedation") in the ED or with the patient under general anesthesia. Closed reduction is performed by flexing the knee and applying longitudinal traction to the foot with initial accentuation, followed by reversal of the deformity (using eversion for medial dislocations and inversion for lateral dislocations). Sometimes direct pressure over the head of the talus aids in reduction. Closed reduction may be impossible because of buttonholing of the talus through the extensor retinaculum, entrapment in the peroneal tendons, or associated fractures. After reduction, immobilization in a below-knee cast for 4 to 6 weeks is indicated.

Disposition. Urgent ED orthopedic consultation is indicated for subtalar dislocations. Although serious complications are uncommon in cases of closed subtalar dislocation, most patients have limitation of subtalar motion, a sequela that can affect gait. Avascular necrosis is uncommon.

Total Talar Dislocation

Total talar dislocation is an extremely rare and devastating injury requiring orthopedic consultation in the ED. In these injuries, which are the end result of the same forces that produce subtalar dislocation, the entire talus is distracted from all of its articulations. Most are open, and infection and avascular necrosis are common complications.[115]

Calcaneal Fractures

Principles of Disease: Anatomy. The calcaneus is the largest bone in the foot and the most commonly fractured tarsal bone.[116] It articulates with the talus superiorly (forming the subtalar joint) and with the cuboid anterolaterally.

Pathophysiology. Falls with direct axial compression cause most calcaneal fractures. Because of this high-energy mechanism, associated injuries are common: 7% of calcaneal fractures are bilateral, 25% are associated with other lower extremity injuries, and 10% are associated with spinal injuries, typically vertebral compression fractures.

Numerous classification schemes have been developed for calcaneal fractures. Perhaps the most intuitive is simple categorization of the fracture as either extra-articular or intra-articular. Extra-articular fractures usually involve the addition of a rotatory mechanism and include fractures of the sustentaculum tali and the tuberosity and oblique fractures of the body. Avulsion fractures of the anterior process by the bifurcate ligament (which joins the calcaneus, navicular, and cuboid) also are included in this category. Up to 75% of calcaneal fractures are intra-articular, ranging in severity from nondisplaced single fractures to severely crushed, comminuted fractures. Because of the cancellous nature of the calcaneus, fractures are frequently comminuted. Calcaneal stress fractures may occur as well.

Clinical Features. The typical history is one of a fall resulting in a direct impact on the heel or heels. Physical examination reveals pain, swelling, and tenderness over the affected heel, and weight bearing on the hindfoot usually is impossible. In cases of significant fracture, the heel may be deformed when viewed from behind, appearing short, wide, and tilted. Ecchymoses may extend over the entire sole, a finding not seen in isolated malleolar fractures. The presence of compartment syndrome or associated injuries such as vertebral compression fractures should be considered.

Diagnostic Strategies: Radiology. Standard radiographic views of the foot and ankle should be obtained. The anteroposterior view of the foot shows the calcaneocuboid joint and the anterosuperior calcaneus, whereas the lateral view shows the posterior facet and can demonstrate compression of the calcaneal body (Fig. 55-21). In addition, a Harris (axial) view, when not precluded by pain, should be obtained to image the calcaneal tuberosity, subtalar joint, and sustentaculotalar joints. Anterior process fractures require differentiation from a calcaneus secundarius (see Fig. 55-15).[117]

Two assessments are critical to the management of calcaneal fractures: whether the fracture involves the subtalar joint and the degree of depression of the posterior facet.[118] Compression fractures are not always obvious, and measurement of Boehler's angle (Fig. 55-22) can be helpful. Boehler's angle is more useful for determining prognosis than diagnosis, however, because the angle may be normal even in the presence of severely comminuted calcaneal fractures. Boehler's angle is measured on the lateral view as the angle between two lines, one between the posterior tuberosity and the apex of the posterior facet and the other between the apex of the posterior

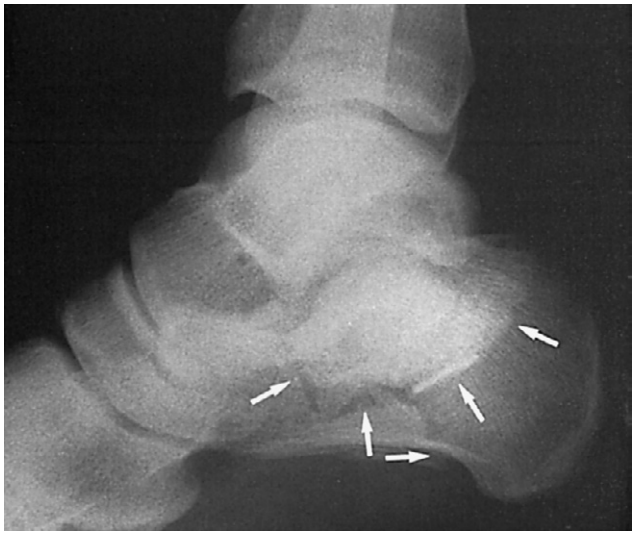


Figure 55-21. Comminuted body fracture of the calcaneus with subtalar involvement *(arrows)*. (From Rosen P, et al [eds]: Diagnostic Radiology in Emergency Medicine. St. Louis, Mosby, 1990.)

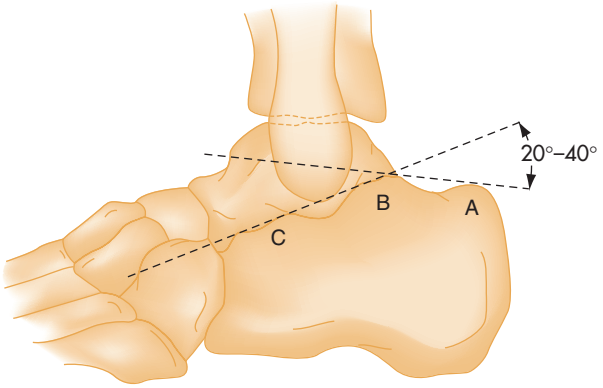


Figure 55-22. Boehler's angle is obtained by measuring the angle formed by two lines, one between the posterior tuberosity (A) and the apex of the posterior facet (B) and the other between the apex of the posterior facet (B) and the apex of the anterior process (C). A value less than 20 degrees suggests a calcaneal compression fracture. (From Rosen P, et al [eds]: Diagnostic Radiology in Emergency Medicine. St. Louis, Mosby, 1990.)

facet and the apex of the anterior process. Although several ranges for this measurement have been cited, an angle of 20 to 40 degrees gives the best diagnostic performance for fracture detection.[119] An angle of less than 20 degrees suggests a compression fracture, and comparison measurement of the uninjured side is helpful in questionable cases.

Imaging of the calcaneus can be difficult because of the complex three-dimensional nature of its articulations. Plain radiography can underestimate injury severity, and the CT scan has revolutionized the assessment of calcaneal fractures, with good correlation of findings with outcome.[118,120] MRI also is an excellent modality for imaging the hindfoot and has a role in assessment of selected calcaneal fractures.

Management. The management of intra-articular or displaced calcaneal fractures is controversial, with many operative and nonoperative approaches described.[118] If operative fixation is performed, reduction must be as precise as possible to obtain results superior to those with nonoperative treatment. The treatment of nondisplaced extra-articular fractures usually involves casting for 6 to 8 weeks.

Disposition. Intra-articular or displaced calcaneal fractures require orthopedic consultation in the ED. Outpatient orthopedic follow-up care can be arranged for more innocuous injuries, provided that this approach is consistent with local practice and no associated injuries that warrant hospitalization are present. In considering outpatient follow-up, it is important to bear in mind that the extent and severity of calcaneal fractures often are significantly underestimated from plain radiographs. Minor extra-articular fractures usually heal uneventfully; however, with significant calcaneal fractures, complications, including compartment syndrome, are frequent. In both conservatively and surgically treated patients, the incidence of long-term pain, loss of joint mobility, and functional disability approaches 50%.

Midtarsal Joint Injuries

The midtarsal joint (Chopart's joint) is composed of the talonavicular and calcaneocuboid joints. Injury in this area, although rare, can occur with any ankle, hindfoot, or midfoot trauma. Midtarsal joint injuries usually result from forced dorsiflexion and often are associated with other significant fractures. Sprains, fracture-subluxations and fracture-dislocations, and an isolated "swivel dislocation" (a variant of a subtalar dislocation) all can occur at the midtarsal joint. Pain, swelling, inability to bear weight, and tenderness over the midtarsal joint are usual findings. Although standard radiographs often are abnormal in appearance, the diagnosis frequently is overlooked or delayed, with symptoms ascribed to an ankle sprain (see Fig. 55-12 and Box 55-2). The possibility of a midtarsal joint injury should be considered with any isolated midfoot fracture,[121] particularly those of the navicular tuberosity. MRI can be helpful in the evaluation of midfoot tendon and ligamentous injuries.[122] Undisplaced injuries may heal with casting, but operative fixation often is required. Complications are common and include persistent pain, arthritis, and long-term disability.

Midfoot Injuries

The midfoot is an inherently stable region of the foot and is not commonly injured. Fractures and relationships of the midfoot tarsals often are difficult to visualize on standard radiographic views because of underpenetration and the oblique orientation of the bones and joints. A compounding factor is that pain associated with midfoot injuries often is ill-defined and poorly localized. Delay in diagnosis is frequent with midfoot injuries. Although isolated fractures of the midfoot tarsals occur, associated injuries, including significant sprains, subluxations, and spontaneously reduced dislocations, often are present.

Navicular Fractures

Principles of Disease: Anatomy. The navicular has a curved shape—hence the derivation of its name from the Latin *navis*, "ship." Because of the navicular's extensive articular surface, its blood supply can enter only through a small waist of cortex, and the middle third is relatively avascular. As a result, the navicular is at particular risk for avascular necrosis after fractures, as with the scaphoid bone of the wrist.[123]

Pathophysiology. Navicular fractures, although relatively rare, are the most common midfoot fracture and are classified into dorsal avulsion fractures, tuberosity fractures, and body fractures. *Dorsal avulsion* fractures account for one half of navicular fractures and usually occur when an eversion stress causes bony avulsion from either the talonavicular capsule or the deltoid ligament. These fractures usually do not involve a significant amount of articular surface. *Tuberosity* fractures also

occur from eversion forces, leading to an avulsion at the insertion of the posterior tibial tendon. A tuberosity fracture may be the only clue to the presence of a midtarsal joint injury. *Body* fractures are uncommon and result from an axial loading mechanism. They often are comminuted, intra-articular, and associated with other midtarsal pathologic conditions. Stress fractures of the navicular can occur as well.

Clinical Features. Navicular fractures cause localized tenderness over the dorsal and medial aspects of the midfoot. The navicular tuberosity may be tender and is located by first identifying the sustentaculum tali, a shelf of bone on the medial aspect of the ankle approximately 2.5 cm below the tip of the medial malleolus. The tuberosity is then easily palpable just anterior to this landmark. In the case of tuberosity fractures, pain may be exacerbated by passive eversion or active inversion of the foot.

Diagnostic Strategies: Radiology. Standard foot radiographs usually demonstrate navicular fractures; however, CT or radionuclide bone scans may be required. Care must be taken not to confuse the commonly occurring os tibiale externum, also called an accessory navicular bone, with an acute fracture (see Fig. 55-15).

Management. Dorsal avulsion and tuberosity fractures not involving a significant amount of articular surface usually are treated with a walking cast worn for 4 to 6 weeks. Body fractures and displaced fractures involving more than 20% of the articular surface often require operative fixation.

Disposition. Most navicular fractures are suitable for outpatient orthopedic follow-up care; however, significant fractures, particularly if intra-articular, warrant orthopedic consultation in the ED. Navicular tuberosity fractures can be complicated by nonunion. Avascular necrosis and arthritis, particularly in body or other intra-articular fractures, are potential late sequelae.

Cuboid Fractures

Isolated cuboid fractures are uncommon and usually result from lateral subluxation of the midtarsal joint in a Lisfranc injury. Cuboid fracture has been termed a *nutcracker fracture* because the cuboid is crushed between the bases of the fourth and fifth metatarsals and the anterior calcaneus.[124] These fractures also are associated with fractures of the posterior malleolus.

The cuboid is best evaluated by the oblique view of a standard foot radiographic series because this demonstrates both the calcaneocuboid and the cuboid-metatarsal relationship. The possibility of a Lisfranc injury should be considered with any cuboid fracture. Treatment of isolated injuries ranges from casting for minor nondisplaced fractures to operative fixation.[125] Extra-articular cuboid fractures may still lead to serious disability from dysfunction of the peroneus longus tendon at the level of the peroneal groove. All cuboid fractures warrant orthopedic assessment.

Cuneiform Fractures

Fractures of the cuneiforms are extremely uncommon and usually result from direct trauma. As with cuboid fractures, the patient should be assessed carefully for the presence of a Lisfranc injury. Treatment usually is by casting; however, displaced fractures require orthopedic assessment.

Dislocations of the Navicular, Cuboid, and Cuneiforms

Isolated dislocations of each of the midfoot bones have been described. These are uncommon injuries that often require open reduction. Orthopedic consultation in the ED is required for any of these injuries.

Lisfranc (Tarsometatarsal) Fractures and Dislocations

Principles of Disease: Anatomy. Collectively, the tarsometatarsal joints (see Fig. 55-14) commonly are called *Lisfranc's joint*. Any injury to this area, whether dislocation or fracture-dislocation, is termed a *Lisfranc injury*. Knowledge of the anatomy of the Lisfranc joint complex is central to an understanding of these injuries.

The Lisfranc joint is made up of the articulations of the bases of the first three metatarsals with their respective cuneiforms and the fourth and fifth metatarsals with the cuboid. In concert, the tarsometatarsal joints act to allow supination and pronation of the forefoot. The intrinsic stability of Lisfranc's joint is provided by the bone architecture and associated ligaments. When viewed end on, the metatarsals have a trapezoidal shape and combine to form a transverse arch with the second metatarsal acting as the "keystone." The second metatarsal is essential for the stability of the entire complex and is further buttressed by its snug articulation in a recess created by the three cuneiforms. Strong transverse intermetatarsal ligaments join the bases of the second through fifth metatarsals, and Lisfranc's ligament joins the medial cuneiform with the second metatarsal base (see Fig. 55-23). Lisfranc's joint is further supported by dorsal and plantar ligaments, the plantar fascia, and the insertions of the tibialis anterior and peroneus longus tendons at the first metatarsal base.

Pathophysiology. Lisfranc injuries are uncommon because tremendous energy is required to disrupt this complex. Such injuries arise from three mechanisms: rotational forces, whereby the body twists around a fixed forefoot; axial loads, whereby the weight of the body drives the hindfoot into the bases of the metatarsals; and crush injuries. Because of the mechanisms involved, associated injuries, such as MTP joint dislocations, can occur. Most Lisfranc injuries are incurred in motor vehicle crashes. Sports involving fixation of the forefoot (e.g., equestrian activities, windsurfing) also are associated with these injuries. Of note, one third of Lisfranc injuries arise from seemingly trivial mechanisms such as stumbles or falls. Most Lisfranc injuries are closed.

Lisfranc injuries are classified by the direction of the dislocation in the horizontal plane (Fig. 55-23).[126-128] In *homolateral* injuries, all five metatarsals are displaced in the same direction. In *isolated* injuries, one or more metatarsals are displaced away from the others. In *divergent* injuries, the metatarsals are splayed outward in both the medial and the lateral directions. These injuries usually occur between the first and second metatarsals because of their lack of an intermetatarsal connection. A component of dorsal displacement also is commonly present in Lisfranc injuries, whereas plantar displacement is uncommon because of the joint's bone architecture and the strength of the plantar ligaments and fascia.

Because of ligamentous attachments, Lisfranc injuries almost invariably involve associated metatarsal fractures, usually of the second metatarsal base. Fractures of the cuboid, cuneiforms, and navicular also are common, occurring in more than one third of cases. Lisfranc injuries may be complicated by vascular injury because a critical branch of the dorsalis pedis artery dives between the first and second metatarsals to form the plantar arch. Trauma to this vessel can cause significant hemorrhage and, uncommonly, vascular compromise.

Clinical Features. Most Lisfranc injuries are obvious; however, injuries may be subtle, and the true extent of the pathologic condition can easily be missed or misdiagnosed.[129]

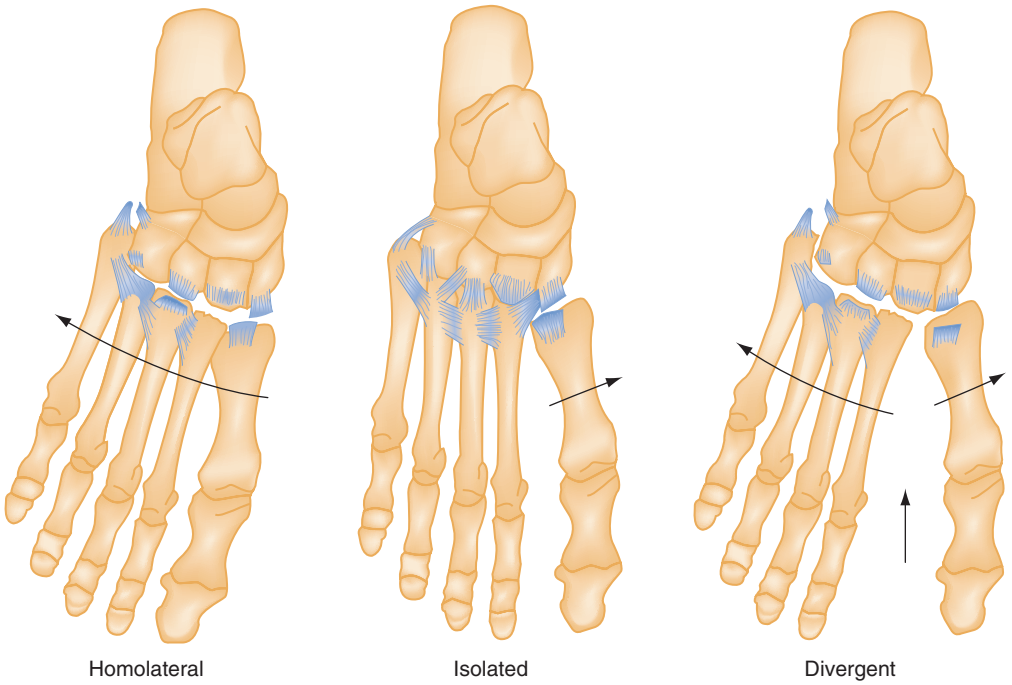


Figure 55-23. Classification of Lisfranc injuries. The ligamentous anatomy of the Lisfranc complex also is depicted. (From Hardcastle PH, et al: Injuries to the tarsometatarsal joint: Incidence, classification and treatment. J Bone Joint Surg Br 64:349, 1982.)

Apparently trivial fractures, if viewed in isolation, fail to reflect the serious soft tissue disruption that can be present.

The clinical presentation varies with the extent of injury and displacement. Severe pain in the midfoot and inability to bear weight, particularly on the toes, are usual features. Paresthesias occasionally are present, and examination usually reveals edema and ecchymosis. In severe injuries, obvious deformity with forefoot abduction, equinus, and prominence of the medial tarsal area can be present. In addition, anteroposterior shortening and transverse broadening may be found. The dorsalis pedis pulse can be absent, or evidence of vascular compromise of the forefoot may be present. Typically, tenderness along the affected tarsometatarsal joints and pain with passive abduction and pronation of the forefoot are present, sometimes with pathologic mobility.

Diagnostic Strategies: Radiology. Standard radiographic views of the foot usually are sufficient to diagnose injuries to the Lisfranc complex (Fig. 55-24). The anteroposterior view identifies fractures and alignment, with the oblique view greatly aiding this assessment by eliminating overlap at the metatarsal bases. The lateral view shows the soft tissues and identifies any dorsal or plantar displacement. When possible, weight-bearing lateral radiographs are obtained because they may be useful to look for flattening of the longitudinal arch in subtle injuries.[130] Comparison views are extremely helpful, and a 30-degree oblique view, in addition to the standard 45-degree oblique view, also may be of value. CT scanning can be helpful for diagnosis or to assess severity.

An appreciation of normal radiographic anatomy is essential to assess Lisfranc injuries. Radiographs should be methodically examined, with assessment of alignment, bones, and soft tissues. The first four metatarsals should each line up with their respective tarsal articulation along their medial edge on anteroposterior and oblique radiographic views. The most consistent relationship is the alignment of the medial edge of the base of the second metatarsal with the medial edge of the middle cuneiform. Dorsal alignment of the tarsals with their respective metatarsals should be assessed on the lateral view.

Findings suggestive of a Lisfranc injury include widening between the first and second or second and third metatarsal bases and any fracture around the Lisfranc joint. Fracture of the second metatarsal base (called a *fleck sign*), cuboid fractures, and cuneiform fractures are particularly common. A fracture of the second metatarsal base is virtually pathognomonic for occult tarsometatarsal joint disruption.

If a suspicious fracture is present and alignment appears normal, a spontaneously reduced dislocation may be present. In addition, plain radiographs may be normal in appearance in the setting of a typical history and tenderness over the tarsometatarsal joints, suggesting a sprain of the Lisfranc complex. In either case, stress radiographs may be diagnostic.

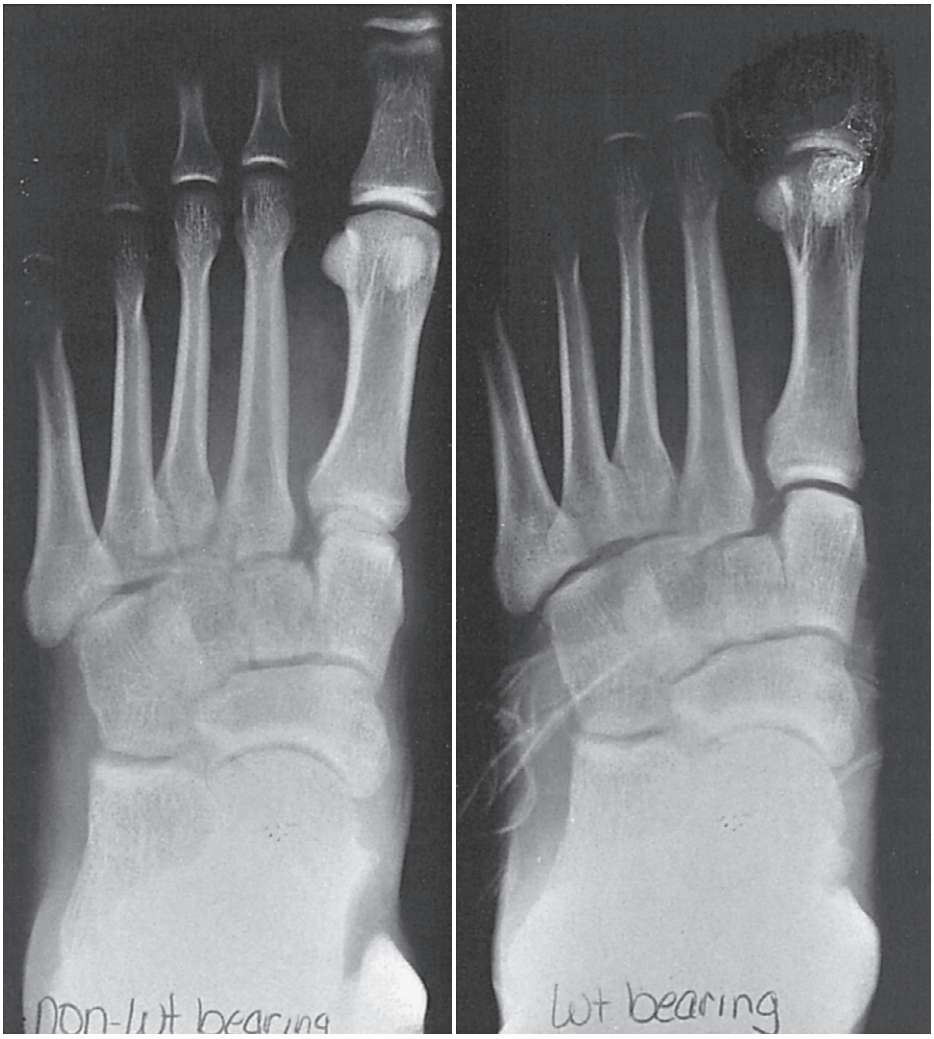
Management. Lisfranc injuries usually are treated with closed reduction and internal fixation with percutaneous Kirschner wires. This is followed by non-weight-bearing casting for 12 weeks and wearing of an orthotic for 1 year. Treatment of a Lisfranc "sprain" usually is by immobilization for 6 weeks in a below-knee walking cast.

Disposition. Any obvious or suspected Lisfranc injury requires orthopedic consultation in the ED. Patients suspected of having a Lisfranc sprain require casting and orthopedic assessment on an outpatient basis, because operative fixation can be required. The incidence of complications with Lisfranc injuries depends on the timing of diagnosis and the degree of anatomic reduction achieved. Aggressive surgical management clearly improves outcome.

Degenerative arthritis is a common complication of Lisfranc injuries. Other potential complications include compartment syndrome, residual pain, unequal metatarsal pressure, loss of the metatarsal arch, and complex regional pain syndrome. Because of their instability, Lisfranc sprains can result in biomechanical problems if untreated, and delayed presentations pose management challenges and often result in complications.[131]

Forefoot Injuries

Traumatic forefoot conditions are commonly underdiagnosed and often consist of more than one fracture or dislocation occurring simultaneously. As occurs elsewhere in the foot, forefoot trauma may lead to prolonged disability and dysfunction.



A B

Figure 55-24. Lisfranc injury diagnosed by step-off at the base of the second metatarsal and middle cuneiform and widening between the bases of the first and second metatarsals. **A,** Non-weight-bearing radiograph. **B,** Weight-bearing radiograph (note increase in step-off). (**A** and **B,** From Baxter DE [ed]: The Foot and Ankle in Sport. St. Louis, Mosby, 1994.)

Metatarsal Fractures

Metatarsal fractures are common and account for one third of foot fractures. The best approach is first to classify the injury anatomically as occurring in the shaft, the head and neck, or the base. Management is then dictated by the metatarsal involved, the specific location and type of fracture, and the nature of any associated injuries.[132]

Metatarsal Shaft Fractures

Principles of Disease: Pathophysiology. Metatarsal shaft fractures arise from either direct trauma (e.g., a crush injury from a heavy object) or indirect trauma (e.g., a twisting force applied to a fixed forefoot). Because of the nature of the mechanism of injury, associated phalangeal fractures often occur. Direct trauma may be highly disruptive, resulting in multiple metatarsal fractures and severe complications. The third metatarsal is the most commonly fractured, and metatarsal shaft stress fractures are common.

Biomechanics are an important consideration in the approach to metatarsal shaft fractures. During stance, weight is distributed equally between the heel and forefoot, where it is spread across the metatarsals, with the first metatarsal carrying twice its share of the load. Great toe metatarsal fractures, although uncommon, require more aggressive management because of this load-bearing function. Alignment of fractured metatarsals is important because dorsal or plantar displacement can lead to pain or functional disability by altering the transverse arch and load distribution. Dorsal angulation commonly occurs at the site of metatarsal fractures from the action of intrinsic muscles and toe flexors. Medial or lateral displacement, although less critical, can lead to the development of painful bony prominences or neuromas.

Clinical Features. Metatarsal shaft fractures cause weight-bearing difficulty and tenderness, which usually is maximal on the plantar surface and can be difficult to localize if swelling is significant. Axial compression of the involved toe often is painful, and ecchymosis usually appears within 12 hours of injury. Rotational alignment should be assessed by evaluating the position and plane of the involved digit.

Diagnostic Strategies: Radiology. Standard radiographs are sufficient to diagnose most metatarsal shaft fractures; however, radiographs usually are exposed for visualization of the talar bones, and the forefoot may be overpenetrated. Adjustment of penetration or coned views may be required for visualization of subtle fractures. Displacement and angulation, in both the sagittal and mediolateral planes, should be assessed.

Management. Most undisplaced metatarsal shaft fractures of the second through fifth metatarsals are treated with a below-knee walking cast for 2 to 4 weeks. Early casted ambulation may be beneficial to healing and reduce the incidence of complex regional pain syndrome. Although some practitioners recommend a non-weight-bearing cast for 4 to 6 weeks for

these fractures, others suggest that a metatarsal pad, stiff shoes, and crutches, if needed, are sufficient. These various approaches attest to the fact that most nondisplaced metatarsal shaft fractures heal well regardless of the treatment.

The great toe metatarsal requires more aggressive management because of its biomechanical role and the stresses imposed on it during gait. Nondisplaced first metatarsal fractures should be treated with casting for 4 to 6 weeks.[133] At least the first 3 weeks of this immobilization, if not the entire period, should be non-weight-bearing.

Reduction should be considered in any metatarsal shaft fracture with more than 3 mm of displacement or 10 degrees of angulation. Closed reduction, with toe traps and countertraction at the ankle, often is successful. Non-weight-bearing casting for 4 to 6 weeks should follow. The indications for open reduction are controversial but generally include the presence of compartment syndrome, unstable fractures, open fractures, fractures that have failed closed reduction, and multiple fractures. These are treated with fixation using either Kirschner wires or plates.[133] In particular, displaced first and fifth metatarsal shaft fractures are commonly treated operatively. Major forefoot trauma, with crushing and multiple open metatarsal fractures, requires an aggressive approach with staged operative management.

Disposition. Most undisplaced metatarsal shaft fractures are suitable for management without orthopedic referral. Orthopedic consultation in the ED should be obtained for patients with multiple or displaced fractures. Complications are rare in nondisplaced or minimally displaced metatarsal shaft fractures. Complex regional pain syndrome can occur and may be related to the unnecessary use of non-weight-bearing casting. Inadequate reduction, particularly in the sagittal plane, can lead to biomechanical problems and formation of painful callosities or metatarsalgia. Malunion in the mediolateral plane, particularly if involving the first or fifth metatarsal, can lead to development of pressure points, neuromas, or biomechanical problems. Delayed union, nonunion, compartment syndrome, and soft tissue complications occur uncommonly.

Metatarsal Head and Neck Fractures

Metatarsal head and neck fractures, although similar in their pathophysiology and assessment to shaft fractures, commonly are multiple and often result from direct trauma. Nondisplaced fractures may be treated with a walking cast for 4 to 6 weeks. Often these fractures are displaced, with the distal fragment pulled in a plantar and lateral direction by the flexor tendons, a finding best appreciated on oblique and lateral radiographic views. Precise realignment of neck and head fractures is important to maintain the transverse arch. Although reduction may be successful with toe traps, instability is common, and operative fixation is required more commonly than with shaft fractures. Most of these fractures should warrant orthopedic consultation in the ED, particularly if they are displaced or intra-articular. Complications are similar to those seen with shaft fractures.

Metatarsal Base Fractures

Principles of Disease: Pathophysiology. Isolated fractures of the first through fourth metatarsal bases are uncommon. Most are nondisplaced transverse fractures within 1 cm of the tarsometatarsal articulation and arise as a result of direct trauma. An indirect mechanism is more suggestive of the presence of an occult Lisfranc injury. The most commonly encountered metatarsal base fractures occur at the fifth metatarsal.

Fifth Metatarsal. *Jones fracture* is a term often erroneously applied to any fracture of the fifth metatarsal base. The eponym is in reference to Sir Robert Jones, a physician who in 1902 described a fracture he sustained while dancing and a series of similar injuries. In reality, two distinct fractures can occur in the region of the fifth metatarsal base, and debate continues regarding which one Jones actually described.[134] More important than the terminology, these two fractures differ dramatically in their mechanism, treatment, and prognosis.[135]

The more common, and benign, fracture at the fifth metatarsal base is of the tuberosity. Also called the *styloid*, the tuberosity is the bulge of the fifth metatarsal that is easily palpated over the lateral edge of the foot. It is fractured by a sudden inversion of a plantar-flexed foot; for decades, this fracture was thought to be caused by an avulsion at the insertion of the peroneus brevis tendon. Cadaveric studies, however, have implicated the lateral band of the plantar aponeurosis in the location and nature of this fracture. Tuberosity fractures range from tiny flecks to lesions involving the entire tuberosity and usually are extra-articular, although they may extend into the cubometatarsal joint. Often these injuries masquerade as ankle sprains (see Fig. 55-12 and Box 55-2), making the fifth metatarsal base an important area to palpate in any twisting injury.

The more serious acute fracture at the base of the fifth metatarsal is a transverse fracture occurring at least 15 mm distal to the proximal end of the bone.[135] This diaphyseal fracture probably is a true Jones fracture and involves the fourth and fifth intermetatarsal articulations but not the cubometatarsal articulation. Diaphyseal fractures result from a complex combination of forces generated when a load is applied to the lateral forefoot in the absence of inversion.[135] Typically, these occur in running and jumping sports. Further subclassification of proximal diaphyseal fractures has been done and can be helpful in determining management.

Clinical Features. The assessment of metatarsal base fractures is similar to that described for fractures of the metatarsal shaft. Pain often is diffuse and difficult to localize in these injuries, with the exception of the easily palpable fifth metatarsal tuberosity. Passive inversion also may be painful with a fifth metatarsal base fracture.

Diagnostic Strategies: Radiology. Standard radiographic views easily demonstrate most metatarsal base fractures. Radiographs should be carefully assessed for fracture angulation, displacement, and articular extension. If the fracture is intra-articular, an estimation of the percentage of articular surface involved is essential in determining management. In difficult cases, CT studies may be helpful.

With fractures of the first through fourth metatarsal bases, it is important to search for other radiologic clues to a Lisfranc injury. A fracture of the second metatarsal base is virtually pathognomonic for occult tarsometatarsal joint disruption. In assessment for a fifth metatarsal base fracture, differentiation between the tuberosity and diaphysis is essential (Fig. 55-25). Care should be taken not to misinterpret an os vesalianum or os peroneum for a fifth metatarsal base fracture (see Fig. 55-15). Standard ankle radiographs also demonstrate the fifth metatarsal base, and this area should be routinely scrutinized.

Management. Nondisplaced extra-articular fractures of the first through fourth metatarsal bases usually are managed with a below-knee cast. Displaced fractures should be reduced and often require fixation. Intra-articular fractures, especially those of the first metatarsal, often lead to complications. Operative fixation may be required, even in nondisplaced intra-articular first metatarsal base fractures, if more than 25% of the articular surface is involved.

The management of fifth metatarsal base fractures depends on the type of fracture. Extra-articular tuberosity fractures, regardless of their size or degree of displacement, heal well

A

B

Figure 55-25. **A,** Diaphyseal fracture of the fifth metatarsal *(arrow)*. This is the more serious of the two fractures occurring at the fifth metatarsal base. **B,** Tuberosity fracture of the fifth metatarsal base *(arrow)*. This is the more benign of the two fractures occurring at the fifth metatarsal base. (**A,** From Rosen P, et al [eds]: Diagnostic Radiology in Emergency Medicine. St. Louis, Mosby, 1990.)

and are managed symptomatically with a walking cast for 2 to 3 weeks, compression wrap, or stiff shoes.[134] Intra-articular tuberosity fractures involving more than 30% of the articular surface, or with more than 2 mm of displacement, may require fixation.[134] Nondisplaced intra-articular fractures usually are treated initially with non-weight-bearing casting for 6 to 8 weeks, followed by radiographic reassessment.[134] Immobilization for up to 6 months may be required for complete healing, and immediate fixation may be advisable in athletes.[135] Displaced fifth metatarsal diaphyseal fractures usually are managed operatively, and prolonged treatment may be necessary.

Disposition. Because they are rare and treatment varies, most first through fourth metatarsal base fractures require orthopedic assessment. Nondisplaced extra-articular fractures of the

first through fourth metatarsal bases are suitable for management by orthopedic follow-up on an outpatient basis. Orthopedic consultation in the ED should be obtained in any other first through fourth metatarsal base fracture or if a Lisfranc injury is suspected. Significant or displaced intra-articular fifth metatarsal tuberosity fractures or diaphyseal fractures should warrant orthopedic evaluation in the ED.

Intra-articular metatarsal base fractures involving the first through fourth metatarsals can lead to post-traumatic arthritis requiring arthrodesis. Complications are rare in cases of fifth metatarsal tuberosity fractures, although fibrous nonunion of the fracture fragment can occur. Fifth metatarsal diaphyseal fractures often are complicated by delayed union, nonunion, or recurrence owing to poor healing subsequent to disruption of the metatarsal vascular supply. These complications occur in more than 50% of patients treated conservatively and often require aggressive surgical therapy and prolonged healing times.

Phalangeal Fractures

Principles of Disease: Pathophysiology. Phalangeal fractures are the most common forefoot fracture. They usually arise from direct trauma, often the result of dropped heavy objects or stubbing the toe. Less commonly, indirect mechanisms involving twisting of the forefoot can lead to phalangeal fractures. Proximal phalanges are more commonly fractured than middle or distal phalanges, and the proximal phalanx of the fifth toe is most commonly injured. Fractures of the hallux often are displaced, whereas fractures of the lesser phalanges are often comminuted but less commonly displaced.

Clinical Features. Although phalangeal fractures generally are considered minor injuries, they can lead to disabling sequelae and merit careful assessment.[136] The patient with a phalangeal fracture has acute pain and swelling of the affected toe, often with difficulty ambulating or wearing shoes. Examination may reveal tenderness, crepitus, and reduced range of motion. A subungual hematoma often is present if the distal phalanx is involved, and open fractures are common.

Diagnostic Strategies: Radiology. Standard radiographic views usually are sufficient to demonstrate phalangeal fractures, with the lateral view being most sensitive. Often the uninjured toes must be positioned out of the way to obtain adequate radiographs, and magnification radiographs occasionally are required. Angulation and joint involvement should be assessed.

Management. Most phalangeal fractures are easily managed and heal well. A subungual hematoma should be evacuated, and nail bed repair may occasionally be required. Nondisplaced lesser phalangeal fractures should be stabilized by "buddy taping"—splinting the injured toe to an adjacent toe with adhesive tape. Placement of gauze between the splinted toes is advisable to prevent skin maceration. Phalangeal fractures often remain painful for 2 to 3 weeks until stabilized by callus.

If significant displacement or angulation is present, reduction should be performed with manual traction or toe traps after digital block anesthesia. Moderate persistent angulation or displacement is acceptable if the clinical appearance of the toe remains satisfactory. Rarely, operative fixation of lesser phalangeal fractures is indicated, particularly in cases with severe rotatory deformity or in open fractures requiring débridement.

Nondisplaced phalangeal fractures involving the hallux are treated by buddy taping, with a walking cast worn for 2 to 3 weeks if the toe is painful. Alternatives to standard casting techniques, such as the slipper cast, have also been described for phalangeal fractures.[137] Displaced phalangeal fractures of the hallux require reduction. If the reduction is inadequate or unstable, operative fixation may be indicated. Unless completely nondisplaced, most intra-articular fractures involving the hallux are treated with operative fixation, although this is an area of controversy.

Disposition. Most phalangeal fractures do not require orthopedic evaluation; however, if displacement persists or causes cosmetic or functional concern, consultation is advised. Orthopedic consultation in the ED is advised for poorly reduced or intra-articular hallux fractures.

Complications of phalangeal fractures are uncommon. With intra-articular phalangeal fractures, particularly those involving the hallux, arthritis may be a late sequela, or fragments may require operative removal. Symptomatic angular malunion and osseous deformity can occur with phalangeal fractures, and exostectomy is sometimes required.

Sesamoid Fractures

The sesamoids are two flat oval bones found within the tendon of the flexor hallucis brevis, under the head of the first metatarsal. Their name comes from the Greek word *sesamoeides*, meaning "resembling a sesame seed." Ten percent of the population has sesamoid bones under the fifth metatarsal head, and uncommonly, sesamoids are found under the second, third, or fourth metatarsal (see Fig. 55-15). Sesamoid fractures are uncommon and usually are caused by direct trauma from falls. Hyperextension of the great toe can indirectly lead to a sesamoid fracture.[138] Sesamoid fractures also can be found in association with MTP joint dislocations. The medial sesamoid is more commonly fractured than the lateral, and a suspected fracture must be differentiated from partition of sesamoids, which occurs in up to one third of the population and also is more common on the medial aspect. Stress fractures of the sesamoids also occur. Sesamoid fractures generally require a below-knee walking cast for 3 to 4 weeks. Most heal without complications and do not require orthopedic consultation.

Metatarsophalangeal Dislocations

Principles of Disease: Pathophysiology. Dislocations of the MTP joint are uncommon injuries because of the protection footwear provides and the inherent stability of MTP and IP joints. MTP joint dislocations can occur in any joint and in any direction. First MTP joint dislocations require large forces and usually result from motor vehicle collisions. These injuries often are open and typically involve dorsal dislocations of the distal component caused by hyperextension of the MTP joint. Associated sesamoid fractures may be present. Complex dislocations, in which the sesamoids or local tendons prevent closed reduction, can occur. Second through fifth MTP dislocations usually are medial or lateral displacements that occur when the toe strikes or hooks an object. The most common is a lateral dislocation of the fifth MTP joint.

Clinical Features. Dislocations of the MTP joint cause pain, swelling, and difficulty bearing weight on the ball of the foot. First MTP joint dislocations usually are obvious on clinical examination because the toe is angled upward with dorsal and proximal displacement of the proximal phalanx. This deformity leads to a striking prominence of the metatarsal head over the plantar surface. Skin tenting or a dimple may be present. Rarely, the sesamoids are palpable dorsal to the metatarsal, indicating a complex dislocation. Dislocations of the lesser toes often are more subtle in presentation, and comparison with the uninjured foot may be helpful. Neurovascular compromise is rare.

Diagnostic Strategies: Radiology. Dislocations of the MTP joint are well visualized on standard radiographic views of the foot. In first MTP joint dislocations, a double density often is present, caused by superimposition of the base of the proximal phalanx over the metatarsal head. Radiographs should be scrutinized for signs suggesting complex dislocation, such as the sesamoids lying between the two articular surfaces or dorsal to the metatarsal head.

Management. Most MTP joint dislocations, particularly of the lesser toes, are easily reduced with longitudinal traction. Appropriate analgesia or local anesthesia should be administered before reduction is attempted. Dorsal dislocations of the first MTP joint can be more challenging and may require initial accentuation of the deformity during reduction. Joint stability should be assessed and repeat radiographs obtained after reduction of an MTP joint dislocation. After reduction, a walking cast with a toe plate is worn for 3 weeks, followed by physiotherapy to ensure adequate range of motion. Alternatively, buddy taping and an aluminum splint can be used for immobilization.

Disposition. Most MTP joint dislocations can be managed without orthopedic consultation. If crepitus or obvious instability is present or postreduction radiographs show joint incongruity or an intra-articular fracture, orthopedic consultation should be obtained for possible fixation. First MTP joint dislocations that are open, show radiographic evidence of complexity, or do not easily reduce require orthopedic consultation in the ED, because open reduction may be required. Very rarely, MTP joint dislocations of the lesser toes require open reduction.

Complications are uncommon after MTP dislocations. Arthritis and reduced range of motion, particularly of the hallux, may occur. Dislocations for which the diagnosis is delayed for more than 3 weeks often are not amenable to closed reduction and may require metatarsal head excision.

Interphalangeal Joint Dislocations

IP joint dislocations are much less common than MTP joint dislocations and are sometimes overlooked. Most IP joint dislocations occur in the great toe and are a result of axial loading. IP joint dislocations usually involve dorsal displacement of the distal component and are easily managed without orthopedic consultation. Reduction is performed with longitudinal traction after digital block anesthesia is obtained. Initial accentuation of the deformity may be necessary if reduction is unsuccessful with simple traction. If the dislocation involves the great toe, a walking cast with a toe plate for 3 weeks is indicated after reduction. Lesser toes require only buddy taping. As with the MTP joint, complex dislocations involving the first IP joint can occur, and orthopedic consultation in the ED for open reduction may be necessary. Very rarely, lesser toe IP joint dislocations are irreducible with closed methods and will require open reduction.

Foot Pain

Perspective. Foot pain, particularly in the absence of obvious trauma, poses a diagnostic and therapeutic challenge. Plain radiographs commonly are normal in appearance, so that the history and physical examination assume increased importance. Although a definitive diagnosis often is difficult to obtain in the ED, a structured approach aids in appropriate patient management and disposition. Most causes of foot pain are minor and self-limited, but the possibility of serious pathologic conditions (e.g., infection, arthritis, tumor) must be considered. Although orthopedic consultation in the ED is rarely required, orthopedic follow-up on an outpatient basis is indicated for selected cases.

Foot pain can be classified as acute, acute on chronic, or chronic and is best approached anatomically by localizing symptoms to the hindfoot, midfoot, or forefoot. Three conditions warrant specific mention.

Complex regional pain syndrome is a condition involving pain in the presence of trophic changes and vasomotor instability from inappropriate sympathetic nervous system activity and was previously termed "reflex sympathetic dystrophy." Complex regional pain syndrome occurs months after trauma, which may be major, as in a Lisfranc injury, or relatively innocuous. It has many synonyms, including *causalgia* and *Sudeck's atrophy*, and produces pain of a diffuse burning, aching, or searing nature, together with evidence of vasomotor instability. Complex regional pain syndrome should always be considered in the differential diagnosis for foot pain after trauma.

Another important consideration in patients with previous penetrating trauma is a *retained foreign body*. Foreign bodies can be a source of chronic drainage or chronic pain. The inciting trauma may have occurred years previously, and a history of the event may be difficult to extract, or such an event may be unknown to the patient.

Finally, *stress fractures* are an important consideration in the differential diagnosis for foot pain, particularly in athletes.

Hindfoot Pain

Hindfoot pain is a common complaint that usually is the result of overuse rather than acute trauma.[139] Bone pain in the hindfoot necessitates consideration of talar or calcaneal stress fractures. A calcaneal stress fracture may be suspected when pain is elicited on squeezing the calcaneus mediolaterally. Another cause of bone pain is impingement by an os trigonum (see Fig. 55-15) or prominent lateral posterior talar process. The *os trigonum syndrome* involves pain during plantar flexion of the foot and is particularly common in ballet dancers. A bone scan may be required for diagnosis, and treatment is surgical.

Most patients with hindfoot pain describe subcalcaneal heel pain, a complaint with an extensive differential diagnosis.[140] The literature on this topic is conflicting and fraught with inconsistent terminology. The most common causes of subcalcaneal pain are plantar fasciitis, subcalcaneal bursitis, acute rupture of the plantar fascia, and nerve compression.

The plantar fascia is a tough layer of the sole that is functionally significant during foot strike and the early stance phase of walking. Plantar fasciitis, an overuse injury of insidious onset, usually begins with pain on first weight bearing in the morning or after prolonged sitting.[141] This progresses to persistent pain during gait. Pain and tenderness are localized to the medial aspect of the heel. Plantar fasciitis is particularly common in cavus feet, although the nature of this association is unclear.[142] Plain radiography is not diagnostic but shows a calcaneal spur in 50% of patients with plantar fasciitis. This is a stress-related ossification with a 16% incidence in asymptomatic persons and is not considered the primary cause of pain in plantar fasciitis. Rarely, fascial ossification (an os subcalcis) may be seen.

Plantar fasciitis is distinct from subcalcaneal bursitis, a condition with an identical presentation in which the pain is localized to the bursa directly below the calcaneus. Differentiating these two conditions can be difficult and usually is academic, because initial treatment is identical: a combination of avoiding precipitating conditions, rest, padding, orthotics, and nonsteroidal anti-inflammatory drugs. Shock wave therapy can be beneficial in refractory cases.[143] Very rarely, surgical release of the plantar fascia is required, a therapy that can be beneficial in either condition.

Plantar fascial rupture is a tear of the origin of the plantar fascia at the calcaneus. This injury usually occurs during the push-off phase of gait. Swelling may be noted, and typically pain is elicited by passive dorsiflexion of the hallux. Treatment is nonsurgical, often with a period of cast immobilization for symptomatic relief.

Compression of either the abductor digiti quinti nerve or the posterior tibial nerve (the so-called tarsal tunnel syndrome) can cause subcalcaneal heel pain.[144] Diagnosis of these conditions is difficult and is sometimes facilitated by assessing the impact of selective nerve block with local anesthesia. Initial treatment of these conditions is similar to that for plantar fasciitis, although local steroid injections or surgical release may be required. Other nerve entrapments also can occur in the hindfoot area.

Many tendons course through the hindfoot, particularly the anteromedial aspect, and tendinitis can occur. Other tendon pathologic conditions (e.g., ruptures, dislocations, retinacular injuries) must be considered because they can result in significant functional disability.

Midfoot Pain

Isolated midfoot pain is less common than forefoot or hindfoot pain. Stress fractures are uncommon in the midfoot and most commonly involve the navicular. Other causes of midfoot pain include symptomatic accessory bones, particularly the os tibiale externum or os peroneum (see Fig. 55-15). An os tibiale externum is present in up to 14% of the normal population and is asymptomatic in most cases. This accessory bone can produce debilitating pain on the medial aspect of the midfoot. A bone scan facilitates diagnosis, and surgical excision may be necessary. An os peroneum is one of several conditions that can cause lateral plantar pain in the midfoot region. Localization of tenderness is aided by resisted plantar flexion, and treatment ranges from immobilization to surgical excision.

Forefoot Pain

The forefoot is the site for a myriad of painful problems. Bunions, painful bursae, blisters, corns, calluses, hammertoes, and ingrown toenails all are diagnostically obvious but can pose therapeutic challenges. Many are the result of poor footwear or a biomechanical problem with the foot and respond to appropriate padding, avoidance of precipitants, and occasionally surgical intervention.

Metatarsalgia is an often used, although loosely defined, term referring to pain in the region of the metatarsal heads.[145] This is a common presenting complaint with many potential causes. Metatarsal stress fractures are extremely common and must be considered in the differential diagnosis for any unexplained forefoot pain. Flexor or extensor tendinitis also can produce metatarsal area pain and is suggested when plain radiographs show areas of tendinous calcification. Arthritis, sesamoiditis, or a sesamoid stress fracture should be considered when pain occurs in the area of the hallux. "Turf toe" is MTP joint inflammation of the hallux resulting from repeated hyperextension stress.[98] It usually responds to symptomatic measures.

An important cause of unilateral metatarsalgia is a perineural fibrosis of the intermetatarsal plantar digital nerve, more commonly known as *Morton's neuroma*.[145] This neuropathy of unknown cause was first described in 1876 and usually involves the second-third or third-fourth inter-metatarsal space, causing lancinating pain with weight bearing. The pain may be associated with paresthesias and can radiate into the toes. In addition, "afterburn" pain can persist during rest. The pain of Morton's neuroma is reproduced when structures of the affected interspace are pinched or when the metatarsal heads are compressed together. Hence, pain may occur intermittently with tight-fitting footwear (e.g., rock-climbing shoes, ski boots). Crepitus or a nodule may be palpable. Treatment usually involves surgical excision or neurolysis.[146]

Freiberg's disease is an osteochondrosis of the metatarsal head, usually involving the second metatarsal, and is another cause of pain in this area. *Ingrown toenails* are a common affliction that can occur in any toe, most commonly the hallux. Often the abnormality is perpetuated by short nail trimming, which affords the opportunity for a spicule of nail to grow under the nail fold.[147] Allowing the nail to grow out and providing local care usually will lead to resolution of the condition. Antibiotics are indicated if infection is present. Chronic or recurring ingrowth necessitates partial or complete excision of the nail and germinal ablation.[147]

SPECIAL CONSIDERATIONS

Stress Fractures

Principles of Disease: Pathophysiology. Stress fractures can occur anywhere in the appendicular skeleton but are particularly common in the lower extremity. Athletic activities, particularly running, account for most stress fractures. Predisposing factors include training errors, poor footwear, a previous period of inactivity, or a change in running surface. Anatomic variations may play a role, with cavus feet being more prone to stress fractures than flat feet.

Pedal stress fractures may occur anywhere but are most common in the second or third metatarsal shaft. It is not generally appreciated that calcaneal stress fractures occur almost as often as metatarsal stress fractures. Midfoot stress fractures are uncommon and usually occur in the navicular. The type of sport or activity is related to the location of stress fractures, with navicular stress fractures most often seen in basketball, metatarsal shaft stress fractures in running, and fifth metatarsal diaphyseal stress fractures in football.

Clinical Features. Although the history is variable, most stress fractures produce localized pain of insidious onset, usually with aching over a period of weeks.[148] The pain may be anywhere in the hindfoot, midfoot, or forefoot but is most common along a metatarsal. Initially symptoms occur after athletic activities, but later they limit such activities. Often a predisposing factor, such as a training regimen change, is present. A menstrual history should be obtained in female patients because amenorrhea, often a result of training, can predispose to stress fractures.[149]

Physical examination may reveal swelling, point tenderness, or percussion tenderness. In most patients, however, these findings are absent, and the diagnosis must be suspected by history alone.

Diagnostic Strategies: Radiology. Initial plain radiographs are commonly normal because bone reaction in stress fractures depends on the length of time from symptom onset. Radiographic abnormalities in the metaphyses can take up to 4 weeks to develop, and those in the diaphyses can take 6 weeks.[21] Although plain radiographs have low sensitivity for stress fractures, their specificity is high. The three important findings are periosteal new bone, endosteal thickening, or a radiolucent line. Radiographic findings vary with location: Metatarsal fractures usually show callus or periosteal reaction, whereas navicular fractures show a lucent line, and calcaneal fractures show curvilinear sclerosis.

The diagnosis of a stress fracture is easily missed because only 50% of patients develop plain radiographic abnormalities. Until recently, radionuclide bone scanning was the imaging modality of choice for stress fractures. Bone scans are nonspecific but extremely sensitive for stress fractures, usually

showing abnormal uptake within 24 hours of injury. Rarely, a bone scan may be falsely negative if pain occurs before the onset of a demonstrable pathologic condition. MRI scanning has been found to be more specific and is emerging as the new "gold standard" for this condition.[21]

Management. Athletic stress fractures are overuse injuries and necessitate an evaluation of training habits, equipment, and techniques. Most pedal stress fractures resolve in 4 to 6 weeks simply with limitation of impact activities and do not require immobilization unless symptoms are severe. Two locations, however, are unique and deserve specific discussion.

Navicular stress fractures are uncommon and often delayed in diagnosis. Healing is hampered by the relative avascularity of the middle third of the bone, and initial treatment is with non-weight-bearing casting for 6 to 8 weeks. Stress fractures of the fifth metatarsal base are also problematic. Fifth metatarsal diaphyseal stress fractures (also called chronic Jones fractures) are usually initially treated with nonweightbearing and casting. As with acute diaphyseal fractures, delayed healing is common, and casting for up to 20 weeks may be required.[134]

Disposition. Any patient diagnosed with or suspected of having a stress fracture should have orthopedic follow-up on an outpatient basis. Delayed union or nonunion can occur with stress fractures, particularly those of the navicular or fifth metatarsal base. Bone grafting or hardware fixation may be required. Most other pedal stress fractures heal without complications.

Contusions and Sprains

Contusions of the foot, usually from dropped objects, are a common injury. Sprains can occur in the foot, particularly with athletic injuries. The calcaneocuboid and intermetatarsal ligaments are common sites of injury. Localizing such injuries is difficult, and these are often diagnoses of exclusion made after appropriate clinical and radiographic assessment. Both contusions and sprains usually respond rapidly to symptomatic therapy. Sprains of the Lisfranc joint complex are unique and require orthopedic consultation in the ED.

Tendon Injuries

Acute tendon ruptures in the foot, apart from the Achilles and posterior tibial tendons, are rare. Although isolated ruptures of the flexor hallucis longus and anterior tibial tendons have been described, most tendon transections are the result of lacerations. These typically arise from one of two mechanisms: penetrating wounds to the sole of the foot or major trauma from such sources as dropped objects, lawn mowers, or motor vehicle crashes. Plantar penetrating trauma usually results in flexor tendon injuries, whereas most major mechanisms involve extensor tendons.

Orthopedic or plastic surgery consultation in the ED is indicated for any patient known or suspected to have a tendon injury in the foot. It is clear that flexor and extensor hallucis longus tendons should be repaired primarily; however, the need to repair other tendons is controversial. In general, an attempt should be made to repair any tendon transection, because apparently minor injuries can lead to complications such as claw deformity. Tendon injuries associated with innocuous lacerations are easily missed if not carefully sought. Splinting for 2 to 6 weeks is required after tendon repair.

Crush Injuries, Amputations, and Major Vascular Injuries

Rapid assessment, stabilization, and immediate consultation are priorities in the ED management of a major crush injury, amputation, or vascular injury of the foot. The injured limb must be handled gently and can be irrigated with sterile saline solution to remove debris. Use of other irrigating solutions, exploration, or débridement is contraindicated.[150] Antibiotics should be administered, as with any open fracture. Compartment syndrome must always be considered. Many factors enter into surgical decision-making for patients with such injuries, and objective measures such as the "mangled extremity score" have been developed to predict the need for amputation.[151] Local crush injuries often heal better than diffuse crush injuries.[150] A surgical goal is preservation of as much length as possible to maintain a longitudinal arch. In the presence of a major vascular injury, the likelihood of permanent disability is high.

Compartment Syndrome

Principles of Disease: Pathophysiology. *Compartment syndrome* is defined as an increase in pressure within a confined osseofascial space that impedes neurovascular function, resulting in tissue damage.[150] Compartment syndrome in the foot, as elsewhere in the body, constitutes a medical emergency. Classically, four foot compartments—medial, central, lateral, and interosseous—are described, although studies using dye injection have suggested that there may be as many as nine foot compartments.[150]

Pedal compartment syndrome is most commonly caused by significant crush injuries, fractures, or dislocations. Other causes include bleeding disorders, burns, postischemic swelling after arterial injury or thrombosis, drug or alcohol overdose, excessive exercise, and venous obstruction. Damage is related to the duration and magnitude of compartment pressure rise and the arteriovenous gradient. Compartment syndrome can develop anywhere from 2 hours to 6 days after an insult, although the peak incidence is at 15 to 30 hours.

Clinical Features. Compartment syndrome typically causes pain out of proportion to that expected for the injury. The pain is not decreased by immobilization and can be described as a feeling of tautness within the foot.[152] In the case of calcaneal fractures, the pain often is a relentless burning involving the entire foot. Physical examination may reveal tense swelling and sensory deficits. Pain is exacerbated by any movement (active or passive) that stretches the muscles of the involved compartment. Passive dorsiflexion of the toes often is painful. Peripheral pulses and capillary refill usually are normal in compartment syndrome and thus offer no reassurance when present. Presence of an open wound does not guarantee that all compartments are decompressed.

Diagnostic Strategies: Special Procedures. The only way to diagnose a compartment syndrome is to measure intracompartmental pressure. The decision to perform this maneuver relies on appropriate clinical suspicion. Techniques of pressure measurement are well described, with a pressure greater than 35 mm Hg generally considered diagnostic.[152,153] Compartment syndrome can occur at lower pressures in hypotensive patients. The needle localization and distinguishing of foot compartments is challenging because of their small size. For this reason and because of its importance in surgical decision-making, measurement of pedal compartment pressures usually should be left to an orthopedic surgeon.

Management. Early identification and prevention of further tissue damage are important considerations in any patient with a mechanism consistent with the development of compartment syndrome. Circumferential bandages and casts should be avoided during early management. In diagnosed or suspected cases of compartment syndrome, the limb should be positioned at the level of the heart. Limb elevation beyond

this point is contraindicated because it would decrease arterial flow, thereby narrowing the arterial-venous pressure gradient.

Disposition. If compartment syndrome is suspected, immediate orthopedic consultation is indicated because the only treatment is decompressive fasciotomy.

KEY CONCEPTS

- Ankle dislocations with skin tenting or neurovascular compromise should be reduced promptly, before radiographs are obtained.
- The entire fibula should be examined if an isolated medial malleolar fracture is present, to rule out a proximal fibular (Danis-Weber type C or Maisonneuve) fracture.
- Before diagnosis of an ankle sprain, other injuries that may mimic an ankle sprain should be ruled out.
- Patients with Achilles tendon rupture are still capable of weak plantar flexion. The Thompson test should always be performed if an Achilles tendon rupture is suspected.
- The presence of accessory ossicles may explain unexpected radiologic "lesions" in the foot.
- The possibility of a Lisfranc injury should always be considered with any fracture or dislocation in the tarsometatarsal region, particularly fractures of the second metatarsal base.
- The tuberosity should be carefully differentiated from the diaphysis in all fifth metatarsal base fractures.
- The possibility of a stress fracture should always be considered in patients with long-standing foot pain, particularly if symptoms are in the metatarsal region.
- Compartment syndrome of the foot can occur, with potentially devastating results if it is not diagnosed early.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 56

Wound Management Principles

Barry Simon and H. Gene Hern, Jr.

PERSPECTIVE

The goals of emergency wound treatment are to restore function, repair tissue integrity with strength and optimal cosmetic appearance, and minimize risk of infection. Risk of infection depends on the location, mechanism, host, and care. The risk for a clean facial wound produced by incision is less than 1%, whereas a dirty crush injury to the lower extremity may have more than a 20% risk. Wound infection generally results in delayed healing, decreased strength, and a poor cosmetic result. These facts highlight the need for high-quality wound care. Understanding the biology of wound healing and the technical aspects of wound treatment facilitates emergency management of these patients.

Emergency physicians must also be aware of the medicolegal risk associated with soft tissue injuries. Including injuries to the hand, wound-related complaints are the fourth most common cause of malpractice claims against emergency physicians. Missed foreign body, wound infection, and missed tendon or nerve injury are the most common complications leading to these claims.

PRINCIPLES OF DISEASE

Anatomy of Skin and Fascia

An understanding of skin anatomy leads to better appreciation of wound closure concepts and techniques. The skin is a complex organ that protects the body against bacterial invasion and ensures thermoregulation. The skin also helps to regulate water content and register sensory stimuli.

The skin and fascia vary in thickness from 1 to 4 mm, depending on the part of the body. The *epidermis*, the outermost layer, is several cell layers thick. The most important parts of the epidermis are the *stratum germinativum* (basal layer), where new cells originate, and the *stratum corneum*, the outermost cell layer that gives the skin its cosmetic appearance. The layer of skin directly beneath the epidermis is the *dermis*. The much thicker dermis is primarily composed of connective tissue. The dermis is the key layer for the ultimate healing of skin wounds. Optimal healing and minimal scar formation depend on the removal of debris and devitalized tissue from the dermis. The dermis also functions to anchor sutures placed percutaneously or subcutaneously.[1]

The *superficial fascia* lies directly beneath the dermis and encloses the subcutaneous fat. This space must be irrigated and débrided to decrease the risk of infection. The *deep fascia* lies beneath the fat and is a strong, off-white sheath that covers and protects the underlying muscles and helps prevent superficial infection from spreading to deeper tissues. The deep fascia must be closed to maintain its protective and functional roles.

Wound Biology

Normal wound healing is a well-choreographed sequence of biologic events. It is described as an orderly process, but it actually represents multiple phenomena that seem to occur simultaneously. These events include coagulation, inflammation, collagen metabolism, wound contraction, and epithelialization.[1,2] Maintaining the balance of these events is crucial for normal healing. Delaying any of the stages may result in a weak closure and dehiscence. Prolonging segments of the process may affect the ultimate scar appearance.

Soon after tissue integrity is altered, the process of *coagulation* begins. Platelet release factors initiate and enhance a response from inflammatory cells. Capillary permeability increases to allow white blood cells to migrate into the wound. Neutrophils and monocytes act as scavengers to rid the wound of debris and bacteria. Monocytes transform into macrophages, which seem to have a major role in subsequent healing phenomena. In addition to providing wound defense, macrophages release chemotactic substances, calling on other monocytes to stimulate fibroblast replication and trigger neovascularization.[1]

Collagen is the principal structural protein of most tissues of the body. Normal tissue repair depends on collagen synthesis, deposition, and cross-linking. Fibroblasts synthesize and deposit collagen compounds 48 hours after injury. Immature collagen is highly disorganized because it exists in a gel-like consistency.

After a series of enzymatic processes, characteristic fibrils are produced. Subsequent intermolecular cross-links are responsible for a major portion of the strength of the collagen fibril. The entire process depends on tissue lactate and ascorbic acid and is directly related to tissue arterial carbon dioxide partial pressure. In the absence of vitamin C, prolyl and lysyl hydroxylase do not activate, and oxygen is not transferred to proline or lysine. Underhydroxylated collagen is produced, and characteristic collagen fibers are unable to form. Wound healing is poor, and capillaries are fragile. Without oxygen to hydroxylate proline and lysine, a local condition resembling scurvy tends to occur.

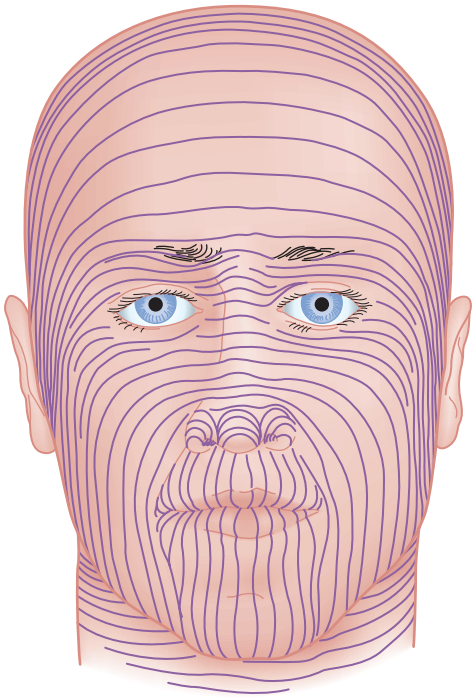


Figure 56-1. Skin tension lines of the face. Incisions or lacerations parallel to these lines are less likely to create widened scars than those that are perpendicular to these lines. (Modified from Simon R, Brenner B: Procedures and Techniques in Emergency Medicine. Baltimore, Williams & Wilkins, 1982; as published in Trott A: Wounds and Lacerations: Emergency Care and Closure, 2nd ed. St. Louis, Mosby, 1997.)

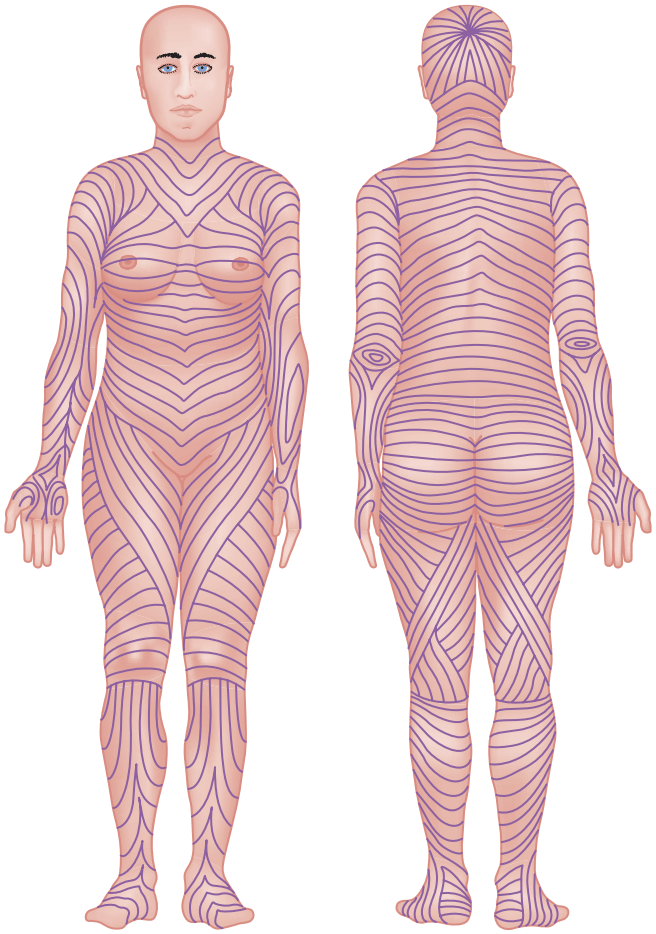


Figure 56-2. Skin tension lines of the body surface. (Modified from Simon R, Brenner B: Procedures and Techniques in Emergency Medicine. Baltimore, Williams & Wilkins, 1982; as published in Trott A: Wounds and Lacerations: Emergency Care and Closure, 2nd ed. St. Louis, Mosby, 1997.)

Under normal conditions, collagen synthesis peaks by day 7, coincident with rapid increases in tensile strength. The healing wound has the greatest mass at 3 weeks but remodels itself during the next 6 to 12 months. However, the wound achieves less than 15 to 20% of its ultimate strength by 3 weeks and only 60% by 4 months.[3]

Wound contraction is the movement of whole-thickness skin toward the center of the skin defect. Immediately after injury, the wound edges retract and increase the size of the defect. Normal skin tension along the lines of minimal tension produces this retraction (Figs. 56-1 and 56-2). Wounds perpendicular to these lines are under greater tension and result in a larger scar.[1,4]

During the next 3 or 4 days, the wound size shrinks as its edges move toward the center. This phenomenon is independent of epithelialization, and the presence of collagen is not necessary for it to occur. This process is considered beneficial to healing and should not be confused with contracture that results from scar shortening.[1,3]

Contracture becomes more apparent when the normal healing process is prolonged. The effect is a disfiguring hypertrophic scar. Optimizing the duration of the inflammatory phase and minimizing wound tension help to produce a more "appealing" scar.

Epithelialization is a mechanism in the healing process whereby epithelial cells migrate across the wound. Mitosis appears at the wound edge near the basal cell layer within hours of injury. Eschar or other debris impedes this process. When a wound is properly cleansed and débrided and kept moist and protected, epithelialization proceeds at a maximum rate.[3]

In a surgically repaired laceration, epithelialization bridges the defect by 48 hours. The new tissue proceeds to thicken and grow downward, beginning to resemble the layered structural characteristics of uninjured epidermis within 5 days. Simultaneously, keratin formation loosens the overlying scab.

Biomechanical Properties of Skin

Various forces (lines of tension) exist as a result of skin elasticity from collagen fibers. These static forces may vary more than fivefold with the respective area of body skin surface, but the static tension of a given area of skin remains constant. These static forces are shown clinically by the gaping of wounds after incision. The magnitude of static skin tension is directly related to ultimate scar width.[1,4]

Uneven, jagged wounds have greater surface area than do linear lacerations. The skin tension is distributed over a greater area and is less per unit length of tissue. Meticulous reapproximation of the jagged edges results in a more appealing scar. Sharp débridement, converting a jagged wound to a linear laceration, is often unwise because it may cause too much tissue loss and produce a wider, more visible scar.[4]

Skin forces produced by muscular contraction and movements of flexion and extension influence healing and scar size. These dynamic forces are greatest where skin elasticity is necessary for function. Lacerations parallel to skin folds, lines of expression, and joints do not impair function or produce unattractive scars. Wounds that traverse the skin lines heal with conspicuous scars and may impair function.[4] Knowledge

of these lines and forces is necessary for optimal wound repair. In addition, the patient should be educated about wound healing and scarring potential.

CLINICAL FEATURES AND DIAGNOSTIC STRATEGIES

History

A detailed history should be obtained as part of routine wound evaluation. Serious complications can result when basic information is not obtained. If the patient has significant peripheral vascular disease, is immunocompromised, or has a high risk of retained foreign body, wound care decisions may be changed. Essential historical information includes medical history, mechanism and setting of injury, and tetanus status.

Risk Factors

Risk factors for wound morbidity include prolonged time since injury; crush mechanism; depth of the wound; age of the patient; high-velocity missiles; and contamination with saliva, feces, soil, or other foreign matter (Box 56-1).[1,4,5] Three hours after acute trauma, bacteria proliferate to a level that may result in infection. Standard wound care guidelines for the routine wound recommend closure within 8 to 12 hours of injury. Yet all risk factors must be considered before adopting specific timeline guidelines, and flexibility is required. Lacerations produced by fine cutting forces resist infection better than crush injuries. Reduction of blood flow to wound edges in the latter may increase the infective concentration of bacteria by 100-fold.[4] High-velocity missile injuries produce damage remote from the missile tract. The extent of injury may not be apparent for several days. Clean, finely cut lacerations on the face may be safely closed in some patients 24 or more hours after injury, whereas blunt lacerations to the leg or thigh may be treated with delayed primary closure as early as 4 to 6 hours after injury. For sutured wounds, location appears to have the strongest association with infection. Lacerations repaired on the leg and thigh may have an infection rate greater than 20%, those on the torso and other extremities greater than 10%, and those on the face and scalp less than 4%.[5]

Wounds contaminated by foreign matter are at high risk of infection, despite adequate therapeutic intervention. Saliva and feces are composed of a concentration of bacteria (approximately 10^{11} per gram wet weight) that greatly exceeds the numbers needed to produce infection ($\geq 10^6$ bacteria per gram tissue).[4]

The presence of any foreign matter in the wound decreases resistance to infection. Soil fractions, which include organic components and inorganic clay particles, damage host defenses with adverse interactions between charged soil particles and white blood cells. The presence of these soil fractions greatly increases the infective potential of bacteria.[4]

Optimal physical assessment of wounds requires patience, diligence, and an organized approach. Wound closure decisions must be individualized for each laceration. Sharp, clean lacerations of the face may be safe to close up to 24 hours after the time of injury, whereas highly contaminated blunt injuries to the feet should never be closed primarily. When the distal neurovascular evaluation is completed, the examination may proceed. All of these risk factors have to do with the injury, but there are three additional areas of concern: (1) immunocompetence of the host, (2) physical characteristics of the host (e.g., peripheral vascular disease), and (3) structural defects that invite bacterial seeding (e.g., damaged or prosthetic heart valves).

BOX 56-1 RISK FACTORS FOR WOUND INFECTION

1. Injury >8–12 hours old (varies depending on the following factors)
2. Location: leg and thigh, then arms, then feet, then chest, then back, then face, then scalp
3. Contamination with devitalized tissue, foreign matter, saliva, or stool
4. Blunt (crush) mechanism
5. Presence of subcutaneous sutures
6. Type of repair: risk greatest with sutures > staples > tape
7. Anesthesia with epinephrine
8. High-velocity missile injuries

Physical Examination

Physical examination errors are minimized with optimal visualization and anesthesia. When the injury occurs on an extremity, use of a sphygmomanometer may help to ensure a bloodless field. The blood pressure cuff is placed proximal to the injury, and the extremity is elevated above the heart for at least 1 minute. Exsanguinating the extremity may be hastened by wrapping the limb tightly with an Ace bandage, beginning distally and ending at the base of the cuff. The sphygmomanometer is inflated to a pressure greater than the systolic pressure of the patient. Although this process causes the patient significant discomfort after 1 minute, the cuff can safely remain inflated for 2 hours. A Bier block should be used if inflation longer than several minutes is contemplated.

A thorough examination of the wound requires that the tissues be adequately anesthetized. Subcutaneous tissues quickly reapproximate after injury, giving the appearance of a shallow wound. In addition, significant subcutaneous swelling lends to this appearance and renders examination of the laceration more difficult, as in wounds of the scalp and face. Careful probing and examination are needed to avoid missing damage to structures deep to the skin and subcutaneous tissue. This warning is more crucial for wounds on the distal aspects of upper and lower extremities. Finger lacerations are rarely gaping, but crucial structures (e.g., tendons, nerves, and vessels) are often damaged. The examiner must pry the wound margins apart, ensure a blood-free field, and examine the tissues as the digit or extremity is placed through range of motion. The injured section of tendon may have been in a different state of tension and in a more proximal or distal location at the time of injury. Wounds that cannot be explored adequately and wounds with probable trauma to underlying tissues or with foreign matter require additional studies. It may be appropriate to extend the laceration to enable improved visualization of wound depth and extent.

Sterile gloves may not be a necessary part of wound closure. Although data are limited, one study found that the use of sterile gloves makes no difference with respect to the incidence of infection.[6] Clean nonsterile gloves should be worn to offer some protection for both the patient and the provider.

Foreign Body Assessment

No single method can guarantee the identification and removal of all foreign matter from wounds. The key is to document all efforts and to explain to the patient the possibility of a foreign body. Good follow-up can protect the patient as well as the health care provider.

Attempts to visualize foreign matter by standard radiography are not as helpful as might be expected. The radiodensity of an object depends on the relative density of the matter and the adjacent tissue. Pieces of glass greater than 1 mm thick are visible when appropriate views are ordered.[7] Many organic substances, such as wood, are not visible on plain films, but specifically requested soft tissue views may increase the yield. A radiolucent shadow may be seen on close inspection because the foreign substance displaces tissue in its path. Xerograms are better than plain radiography but still miss some plastics and organic matter. A computed tomography (CT) scan is excellent for identifying all foreign substances but is expensive and results in significant exposure to radiation. Ultrasonography is a good technique, but the small size of many foreign bodies and pockets of air, edema, pus, and some calcifications may produce confusing echoes, limiting its clinical utility.[8,9] When simpler, standard methods fail to locate a foreign body that is likely or definitely present, ultrasonography or a CT scan should be considered.

MANAGEMENT

Anesthesia

After an appropriate neurovascular examination is documented, the involved tissue should be anesthetized. Careful physical examination and thorough cleansing, irrigation, and débridement require that the patient be free of pain. Regional anesthesia may be preferable for wounds innervated by one superficial nerve. Injections at the wound site produce swelling and further distortion of landmarks. With a regional block, more than one laceration may be repaired in the same nerve distribution without additional anesthesia. Lacerations on the face, hands, fingers, feet, and toes and in the mouth are often well suited for regional anesthesia.

Anesthetic Agents

Lidocaine (Xylocaine) is the most common agent used for local and regional anesthesia.[10] It is safe and fast acting. Onset of action for direct infiltration occurs within seconds and seems to last 20 to 60 minutes. When lidocaine is administered as a regional nerve block, onset occurs in 4 to 6 minutes and generally lasts 75 minutes, although it may remain effective for 120 minutes. A 1% lidocaine solution contains 10 mg/mL. It is safe to use 3 to 5 mg/kg, not exceeding 300 mg at a single injection. More volume can be added safely every 30 minutes. When epinephrine is added, the resulting vasoconstriction prolongs the effect for 2 to 6 hours and the safe dose is increased to 5 to 7 mg/kg. However, the addition of epinephrine has been shown to delay healing and lower resistance to infection. Lidocaine with epinephrine should be avoided in wounds with higher risks of infection and when tissue viability is of concern.[11] Traditional teaching has been to avoid epinephrine in the fingers and toes because of the risk of vasoconstriction in small arterioles. However, recent literature suggests that with careful screening epinephrine can be safely used in digital blocks. Digital artery vasospasm, accidentally induced by local injection of epinephrine, can be reversed successfully with a local injection of 0.5 to 2 mg of subcutaneous phentolamine or by applying topical nitroglycerine.[12]

Bupivacaine (Marcaine) provides anesthesia that is equal to that of lidocaine. Onset of action is slightly slower than that of lidocaine, but the duration of anesthesia is four to eight times longer.[13] These benefits suggest that bupivacaine is the preferred local anesthetic agent for the care of most wounds. In adults, the maximal reported safe dose is approximately 2.5 mg/kg without epinephrine and 3.5 mg/kg with epinephrine.[1] The dose can be repeated every 3 hours, not exceeding a total of more than 400 mg in a 24-hour period. The maximal intraoral dose is 90 mg.

Local injection of lidocaine should be done with a 27-gauge needle; the slower the injection, the less pain produced.[1] The rate of injection through a 30-gauge needle is far too slow, and the thin needle is difficult to control. A 25-gauge needle is acceptable, but the more rapid injection can result in greater patient discomfort. The needle should be introduced through the cut margin to minimize the pain of the injection. Concerns of spreading bacteria into the adjacent uninvolved tissue and increasing the frequency and severity of wound infections are unfounded. The pain of injecting lidocaine can be ameliorated with the addition of bicarbonate to buffer the solution.[14] The shelf life of the lidocaine-bicarbonate mixture decreases but it remains effective for 1 week at room temperature and for 2 weeks if refrigerated. Adding sodium bicarbonate in a 1:10 volume ratio to lidocaine (1 mL bicarbonate and 10 mL lidocaine) decreases the pain of injection without compromising the quality of anesthesia. A much smaller dose of bicarbonate must be added to bupivacaine because the alkalinization results in precipitation. A 1:100 volume ratio (0.1 mL of bicarbonate and 10 mL of bupivacaine) has been found to be effective.[15] Warming the anesthetic solution is also an effective means of decreasing the pain of injection.[16]

Topical anesthesia may be an effective painless alternative. Studies show that a combination of tetracaine, adrenaline (epinephrine), and cocaine (TAC) (0.5% tetracaine, 1:2000 adrenaline, and 11.8% cocaine) can function effectively on skin lacerations. The solution is administered by soaking a cotton ball with 5 mL of the combined drugs (25 mg of tetracaine, 25 mg of adrenaline, and 590 mg of cocaine) and applying it to the wound for 10 to 20 minutes. TAC is similar to infiltrative lidocaine in all respects, including risk of complications. It is more effective on the face and scalp than on extremities.[17] Data suggest that half-strength TAC solution is effective and may reduce the potential for toxicity.[18] The tetracaine component may be superfluous and can be eliminated without compromising the quality of anesthesia.[19] By using a topical combination, time to repair is reduced, patient acceptance improves, and landmarks are left undisturbed. Although experimental studies show that TAC increases the infection rate in contaminated wounds, this is not the case with routine wound care.[11] The proven benefits and enhanced patient compliance, especially in pediatric patients, make TAC an excellent medication to use alone or in conjunction with another local anesthetic. The potential toxicity from TAC has been documented by (1) measurable plasma cocaine levels[20] and (2) a case report of a child's death from exposure to TAC.[21] The child's wound was on the upper lip between the vermilion border and the nares. The solution apparently dripped onto the nasal and oral mucosa, increasing the systemic absorption of the drugs. Until further studies are done, TAC should be avoided in the repair of highly contaminated wounds and in lacerations near mucous membranes. In children, a half-strength solution can be used to reduce potential toxicity.

The potential serious adverse effects of TAC have led to the increasing use of other topically applied anesthetic combinations. A mixture of lidocaine (1–4%), epinephrine (1:1000 to 1:2000), and tetracaine (0.5–2%) has been used successfully in place of TAC. This mixture avoids the untoward side effects of cocaine.[22] EMLA (eutectic mixture of local anesthetics) is a cream used to produce anesthesia of wounds. Although the onset of anesthesia is longer than for the other mixtures (1 hour vs. approximately 30 minutes), one study showed that the

need for supplemental local anesthesia was reduced.[23] Because the time to onset is greatly delayed with EMLA, its utility may vary with emergency department patient volume.

A newer technique that uses topical anesthesia in a progressively layered approach appears to be safe and effective.[24] Although time to anesthesia was significantly longer (a mean of 29 minutes compared with 5 minutes), efficacy was equivalent. Patient satisfaction was much greater with the layer topical approach, and the elimination of the risk of a hollow-bore needle puncture is a major benefit.

Allergy

Allergy to local anesthetics is uncommon. Two distinct groups of "caine" anesthetics exist. The esters include procaine, tetracaine, and benzocaine. The second group, including lidocaine and bupivacaine, belong to the amide family. Allergy to the esters is uncommon. True allergy to agents in the amide family is rare. Good history taking is the best way to document a true allergic reaction.[25] Many patients labeled as allergic have suffered uncomfortable drug effects or autonomic responses to the pain and the overall setting.

The subject of allergy is complicated further because multidose vials contain the preservative methylparaben, an ester related structurally to anesthetics in the ester family. Apparent allergic reaction to lidocaine or bupivacaine may be a reaction to the methylparaben. Cardiac lidocaine does not contain preservatives, is a standard drug in the emergency department, and can be used for wound anesthesia when there is concern about potential allergic reactions.

When allergy to a local anesthetic is known or strongly suspected, alternatives are available. No cross-reactivity occurs between the amide and ester families, so an agent from a different group may be chosen. Single-dose vials of lidocaine or cardiac lidocaine are not mixed with methylparaben and may be used.[26] A test dose of 0.1 mL may be administered intradermally before proceeding. The patient should be observed for 30 minutes, and as with any allergy testing, the emergency physician should be prepared to treat all complications. Aqueous diphenhydramine (1%) has also been shown to provide effective local anesthesia.[27]

Skin Preparation

Disinfection of the skin (not the wound itself) may be accomplished with several different agents. The ideal agent is fast acting, has a broad spectrum of antimicrobial activity, and has a long shelf life. Povidone-iodine (Betadine) and chlorhexidine (Hibiclens) satisfy all three characteristics. Although excellent as skin disinfectants, both products are toxic to wound defenses and may increase the incidence of wound infection. Povidone-iodine is effective against gram-positive and gram-negative bacteria, fungi, and viruses. Chlorhexidine is less effective against gram-negative bacteria, and its efficacy against viruses is unknown. Care must be taken to avoid spilling these substances into the wound. Exposure of the eye to these agents can be disastrous. Chlorhexidine has been shown experimentally and in case reports to produce serious permanent corneal opacification.[28]

Body, facial, and head hair is usually removed to clean and examine the wound, although this is not necessary to diminish the risk of wound infection. Removal of the hair makes it easier for the patient to keep the area clean and ultimately facilitates accurate suture placement and removal. Exceptions are parts of the body where hairlines provide important landmarks for the accurate reapproximation of tissue margins, most notably the eyebrow. Reports of inconsistent or absent eyebrow hair regrowth suggest that eyebrow hair should not be shaved.

Surgical studies show that hair removal with a razor is three to nine times more likely to result in a wound infection than is clipping the hair. It seems that the razor damages the infundibulum of the hair follicle.[29] The wounded follicle provides access for bacterial invasion and ultimately infection. For wounds considered to be at high risk of infection, clipping may be done with electronic shears or scissors because close shaving is not necessary. Another option is to apply a petroleum-based product to the hair adjacent to the wound margins, allowing the provider to keep the hair away from the surgical field.

Wound Preparation

Débridement

Débridement is the removal of foreign matter and devitalized tissue from the wound. With respect to ultimate wound healing and risk of infection, débridement is the most important consideration in wound care.[30] The presence of any devitalized tissue in the wound delays healing and significantly increases the risk of infection. However, the benefits of débridement have to be weighed against the consequences of producing a larger tissue defect. The resultant closure is exposed to higher tension and may result in a wider scar. Skin edges that are clearly devitalized must be débrided before wound closure. On the trunk, where there is little concern for specialized tissue, wide excision and débridement are feasible. On the face and hands, where all tissue must be saved if possible, the process is more difficult. Meticulous sharp excision of small fragments of nonviable tissue should be performed only by experienced physicians. When the viability of large areas of skin or muscle is a significant concern, the wound should be prepared for delayed primary closure.

Wound Cleansing

An ideal wound cleanser has broad antimicrobial activity with a rapid onset. It is nontoxic to the tissue and does not reduce tissue resistance to infection, delay healing, or decrease the tensile strength of the healing wound. Many antiseptic solutions have been used clinically and studied in great detail (Table 56-1). Much debate exists regarding which agent comes closest to possessing these qualities. Povidone-iodine in various concentrations, saline, and, more recently, tap water have received the most attention.[31-34]

Evidence suggests that a 0.9% normal saline solution or tap water may be effective irrigants when used with high-pressure syringe irrigation.[35,36] Saline is the traditional wound-irrigating fluid of choice. However, tap water has consistently produced equivalent rates of infection and cosmetic outcomes. Tap water irrigation allows a large volume of irrigation rapidly and inexpensively and is especially suited to upper extremity and scalp injuries.

Free iodine, although possessing broad, rapid antimicrobial activity, is too toxic to tissue and its defenses to have therapeutic value in the open wound. An iodophor is a complex of iodine with a carrier to increase its solubility and decrease the availability of free iodine. The most widely used iodophor is povidone-iodine, in which the carrier molecule is povidone (formerly polyvinylpyrrolidone). It is generally available in a 10% solution, which is 1% free iodine. The clinical benefit of this complex is a solution that maintains broad antimicrobial activity and eliminates most local and systemic toxicity. It is well documented that even a 5% povidone-iodine solution is toxic to polymorphonuclear neutrophil leukocyte activity and

Table 56-1 Antiseptic Solutions

AGENTS	ANTIMICROBIAL ACTIVITY	MECHANISMS OF ACTION	TISSUE TOXICITY	INDICATIONS AND CONTRAINDICATIONS
Povidone-iodine solution (iodine complexes) (Betadine)	Available as a 10% solution with polyvinylpyrrolidine (povidone) containing 1% free iodine with broad rapid-onset antimicrobial activity	Potent germicide in low concentrations	Decreases PMN migration and life span at concentration >1% May cause systemic toxicity at higher concentrations; questionable toxicity at 1% concentration	Probably a safe and effective wound cleanser at a 1% concentration 10% solution is effective to prepare skin around the wound
Povidone-iodine surgical scrub	Same as the solution	Same	Toxic to open wounds	Best as a hand cleanser; never use in open wounds
Nonionic detergents Pluronic F-68 Shur Clens	Ethylene oxide is 80% of their molecular weight No antimicrobial activity	Wound cleansers	No toxicity to open wounds, eyes, or IV solutions	Appear to be effective, safe wound cleansers
Hydrogen perxoide	3% solution in water has brief germicidal activity	Oxidizing agent that denatures protein	Toxic to open wounds	Should not be used on wounds after initial cleaning; may be used to clean intact skin
Hexachlorophene (polychlorinated bisphenol) (pHisoHex)	Bacteriostatic (2–5%) Greater activity against gram-positive organisms	Interruption of bacterial electron transport and disruption of membrane-bound enzymes	Little skin toxicity; the scrub form is damaging to open wounds	Never use scrub solution in open wounds Very good preoperative hand preparation
Alcohols	Low-potency antimicrobial most effective as a 70% ethyl and 70% isopropyl alcohol solution	Denatures protein	Kills irreversibly and functions as a fixative	No role in routine care
Phenols	Bacteriostatic >0.2% Bactericidal >1% Fungicidal 1.3%	Denatures protein	Extensive tissue necrosis and systemic toxicity	Never use >2% aqueous phenol or >4% phenol plus glycerol

IV, intravenous; PMN, polymorphonuclear neutrophil leukocyte.

may increase the infection rate. A 1% solution is safe and effective with little or no toxicity.[28,34] Detergent-containing cleansers, such as povidone-iodine scrub, may be excellent for skin preparation but are toxic to tissue defenses and should never be allowed to contaminate open wounds.

Although many different irrigation solutions may be beneficial, it seems that the key to cleansing is high-pressure irrigation rather than the type of solution used. Tap water irrigation soon may become the preferred method of irrigation because it is safe, effective, requires no preparation, and is less expensive. Wounds close to the eye, where pressure irrigation may be impossible, may be cleaned with a sponge with fine-pore cells and a surfactant, such as poloxamer 188.

Irrigation

The quality of mechanical cleansing is one of the most important determinants of wound prognosis. The most effective form of wound cleansing is high-pressure irrigation. Irrigating with pressures greater than 7 pounds per square inch (psi) significantly decreases the number of bacteria and the incidence of infection.[37,38] Although several commercial devices are available, attaching an 18-gauge needle to a 35-mL syringe yields a force of 7 or 8 psi. High pressures of 50 to 70 psi may be obtained by using a commercial water pick. These pressures may cause some tissue damage, but the beneficial effect of ridding the wound of bacteria and debris outweighs this risk. Simply soaking the wound in an antiseptic solution is not beneficial and may be harmful. Scrubbing the wound with a sponge with large-pore cells inflicts tissue trauma and impairs the ability to resist infection. Tissue damage can be decreased by using a sponge with a fine size of pore cell. Adding a surfactant further minimizes the mechanical trauma inflicted by the sponge. Flooding the wound under low pressure using a bulb syringe or gravity alone does not reduce the incidence of infection, regardless of the agent used.

At least one study has shown little benefit to any irrigation in facial and scalp lacerations. This study prospectively compared outcomes of almost 2000 immunocompetent patients. Infection rates and cosmetic outcomes were similar in the irrigation and the nonirrigation groups.[39]

Wound Closure

Decision-Making

The first determination required is whether the wound should be treated open or closed. Each wound, patient, and clinical circumstance must be handled individually. Certain lacerations, such as a fine linear laceration to the face, can be closed primarily 24 hours or more after injury. Other injuries may necessitate open management, regardless of the extent of delay.[40] A large stellate laceration to the foot produced by blunt force and contaminated with dirt and grease should not be closed primarily; in addition, human and animal bites to the hand should not be closed primarily. Physician judgment is

often the best method for deciding when it is safe to close a wound. In one study in which hand wounds were described as dirty, 22% became infected. When the injury was documented to be clean, the incidence of infection was 7.1%.[39]

Three wound closure options are available. The wound may be (1) closed primarily in traditional fashion, (2) closed in 4 or 5 days (delayed primary closure) or (3) left open and allowed to heal on its own. *Delayed primary closure* is a safe alternative to traditional primary closure.[2,40] Overall healing time is not affected, and the risk of infection is greatly decreased if proper technique is used. When a wound is slated for delayed primary closure, it must be prepared, débrided, and irrigated in the same manner as for immediate closure. The wound should be packed to prevent it from closing on its own. If the wound is on an extremity, the injury should be splinted and dressed, and appropriate wound care instructions should be given. The patient should return for a wound check and packing change in 24 hours and should be instructed to follow up in another 72 hours for definitive repair, with wound closure 96 to 120 hours after injury. No studies offer guidelines for prophylactic antibiotic use when delayed primary closure is the treatment option. Extrapolation from other wound studies strongly suggests that antibiotics offer no benefit.

Individuals who do not seek medical care after an injury select the option of leaving a wound open to heal on its own. Most patients who present to an emergency department with a laceration undergo some form of wound closure. Yet one study that examined unsutured hand lacerations less than 2 cm long followed patients for 3 months and found that there was no significant difference in cosmetic appearance, and there was no difference in time to resume activities of daily living.[41,42]

Closing a wound loosely is occasionally discussed as an option in the treatment of contaminated wounds. This choice should rarely be considered. The loosely closed wound approximates the tissue margins enough to allow the wound to seal itself completely within 48 hours. The infection risk when using this method is the same as when closing the wound traditionally.

Wound Tension

The goal of wound closure is optimal anatomic and functional reapproximation of tissue with minimal risk of complication. Consideration must be given to the wound's size, shape, location, depth, and degree of tension. Wounds with high static and dynamic tension that require meticulous closure cannot be closed with tape or staples. Delicate approximation of wound edges under tension can be accomplished only with suture.

Several techniques may be used to reduce wound tension. Deep sutures may be placed in subcutaneous tissue to help bring the wound margins closer together. In this manner, forces on the skin are reduced, and potential dead space can be closed. Care should be taken to avoid suturing adipose tissue because it may become necrotic and increase the likelihood of infection. The number of dermal sutures depends on the characteristics of the wound. Generally, the number should be kept to a minimum because suture material acts as foreign matter in the wound and can increase the risk of infection. Subcutaneous sutures should never be placed in the hand or foot because of the major structures that reside near the surface. Another method of ameliorating static tension from cut edges of the wound is to undermine at the lacerated margin. Undermining helps free the dermis from its deeper attachments, allowing the skin edges to be approximated with less force. Care must be taken to preserve the blood supply to the wound margins and not increase dead space in the process.

Suture Technique

Careful surgical technique is important to optimize the ultimate repair. If possible, pickups, hemostats, or forceps should not be used, especially on wound margins. Blind clamping in a wound can damage a nerve, artery, or tendon. Wound margins should be everted and the sutures tied just tightly enough to allow the edges to approximate lightly. The edges can be everted by ensuring that the needle enters and exits perpendicular to the skin. Wounds with opposing margins of different thickness can be difficult to close. If this difference is not considered and corrected, the ultimate scar has uneven margins that cast a shadow on the skin and is unsightly. To close these wounds, the needle should be pulled through the cut margin of one side before entering the opposite edge. This method gives the emergency physician the best opportunity to take an equivalent amount of tissue on both sides of the wound. Viable edges of a jagged wound must be meticulously reapproximated. Because of the greater surface area and the ultimate contraction of the wound, preserving the jagged edges results in a more "natural" scar.

Most lacerations are closed with running or interrupted percutaneous suture. The running technique is appropriate for linear lacerations under minimal tension when there is a low risk of infection. This technique is more rapid, requires less suture material, and yields equivalent cosmetic results. Curvilinear or jagged wounds are best closed with interrupted sutures to distribute tension properly. Because tensile strength of interrupted sutures may be superior, wound edges subjected to higher levels of tension should be closed with interrupted sutures.[43-45]

Basic and Advanced Techniques

Simple Sutures. Wound closure with simple interrupted sutures is the most common method of laceration repair in emergency departments. The placement of simple sutures yields excellent cosmesis and a low infection rate.

Procedure. The needle is placed to one side of the laceration margin and enters the skin at approximately 90 degrees. To pass the needle through the tissue, the clinician's wrist is supinated and guides the needle deep but parallel to the skin surface. Wrist supination is extended as the needle exits the skin on the opposite side perpendicular to the surface. Proper technique produces wound edges that are slightly everted and are lightly touching. The art of the process takes into consideration swelling while being careful not to secure the suture too tightly because necrosis of the wound margin tissue can seriously compromise healing.

Intradermal (Buried) Sutures. Placing cutaneous sutures in wounds under tension can lead to ischemia of the wound margin and an unsightly scar. Proper placement of buried intradermal sutures helps to approximate dermal margins and reduce wound edge tension. Buried sutures should not be used in contaminated wounds because they increase the risk of wound infection. Sutures through adipose tissue also increase infection and do not relieve skin tension.

Procedure. Placement of buried sutures differs from traditional suturing because of the need to bury the knot deep to the skin. Failure to do this can interfere with dermal healing and can leave a small lump under the surface of the skin. The needle is introduced deep in the wound in the subcutaneous tissue and emerges from the dermis below the skin surface. The needle is reintroduced in the dermis on the opposite wound

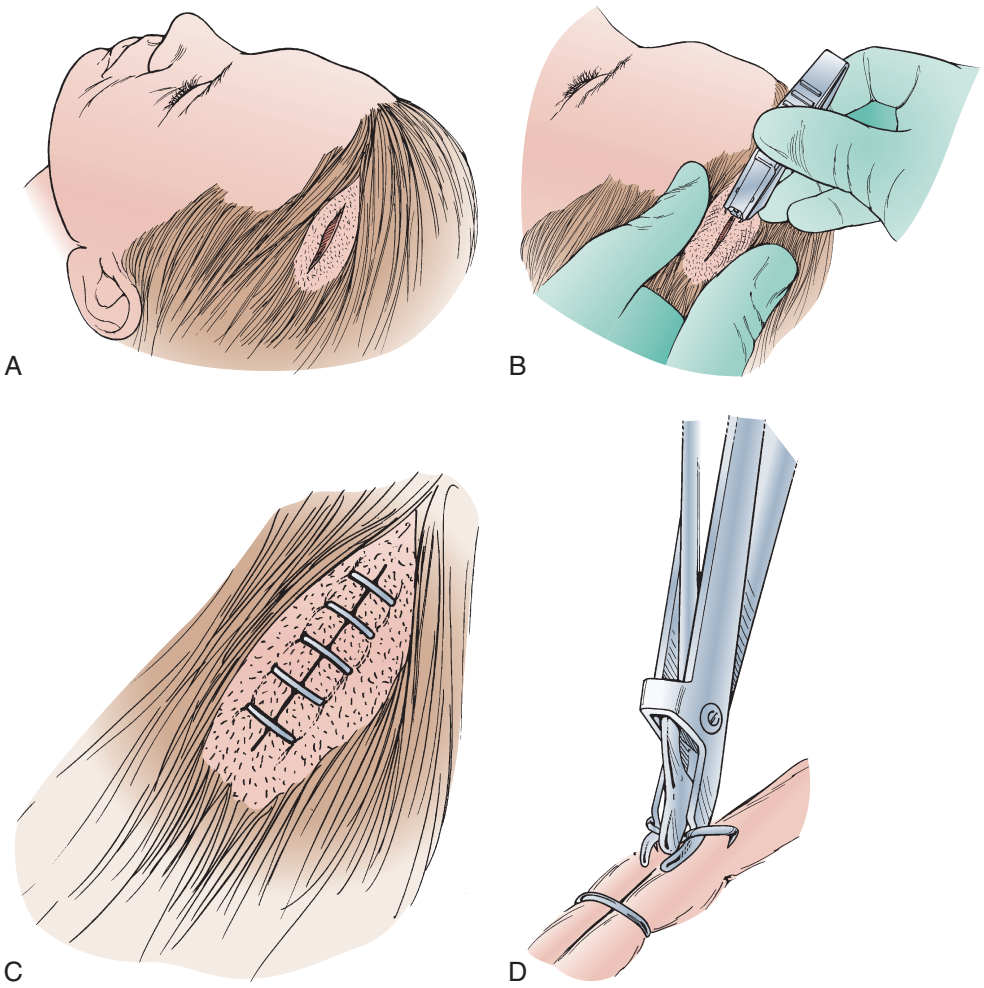


Figure 56-3. Scalp laceration repair. (Modified from Simon BC: Skin and subcutaneous tissue. In Rosen P, et al (eds): Atlas of Emergency Procedures. St. Louis, Mosby, 2001.)

margin and emerges from the subcutaneous tissue at the same level on the opposite side. The knot is secured and remains buried deep below the skin surface.

Scalp Laceration Repair. In contrast to small lacerations elsewhere on the body, most scalp lacerations require repair because of the propensity to bleed profusely. The dense connective tissue beneath the skin tends to hold vessels open and delay hemostasis. Frontal scalp lacerations in young men should be considered to be a cosmetically significant wound. Although the scalp laceration currently may be well hidden by hair, most men experience some balding. Care must be taken to explore the laceration thoroughly to look for a defect in the galea, an injury that requires repair with deep sutures. Staples may be ideal for the skin closure of simple linear scalp lacerations. Hair is less of a problem when placing staples, staples can be placed more quickly than traditional suture, and staples are easier to see and can be removed 1 to 3 days earlier than traditional sutures (Fig. 56-3). Staples may produce artifact on CT scan, but useful information may still be obtained if CT is necessary. Staples may move during magnetic resonance imaging and should not be placed if this imaging modality is being considered. Lightweight stapling devices are available. Most devices come preloaded with five or more staples and are easy to use.

Traditional sutures are used to repair most scalp lacerations, usually with standard nylon suture. Absorbable chromic gut can be used in children and in adults who may not return for suture removal.

Procedure. Anesthesia with epinephrine is recommended to help control bleeding. Hair removal is necessary only if the hair makes closure difficult. A defect in the galea is closed with 3-0 or 4-0 absorbable suture. Failure to repair the galea can lead to a cosmetic deformity related to frontalis muscle function. Linear superficial scalp lacerations that do not require deep sutures can be closed with staples or with monofilament nylon sutures applied using a simple interrupted or running technique. Jagged or macerated lacerations may require some débridement and horizontal mattress sutures. When one chooses to staple a scalp laceration, the adjacent skin margins are pinched together with forceps to evert wound margins. The "mouth" of the stapler is placed gently on the skin surface, taking care not to indent the skin. The handle of the stapler is squeezed carefully to eject the staple into the tissue. Ideally, the staple closely approximates the wound margins without indenting the surface of the skin. To release the staple, the wrist must be pulled back to disengage itself from the last staple.

Vigorously bleeding scalp lacerations often need temporizing measures to control bleeding while the patient is being evaluated and resuscitated. An anesthetic agent with epinephrine should be used and may be helpful to control some bleeding. Blindly clamping in an attempt to control bleeding is unwise and not likely to be successful. Raney scalp clips can be rapidly applied to the wound margins to quickly gain control of the bleeding. An applicator is used to apply and remove the clips so that they can be replaced with sutures once the patient

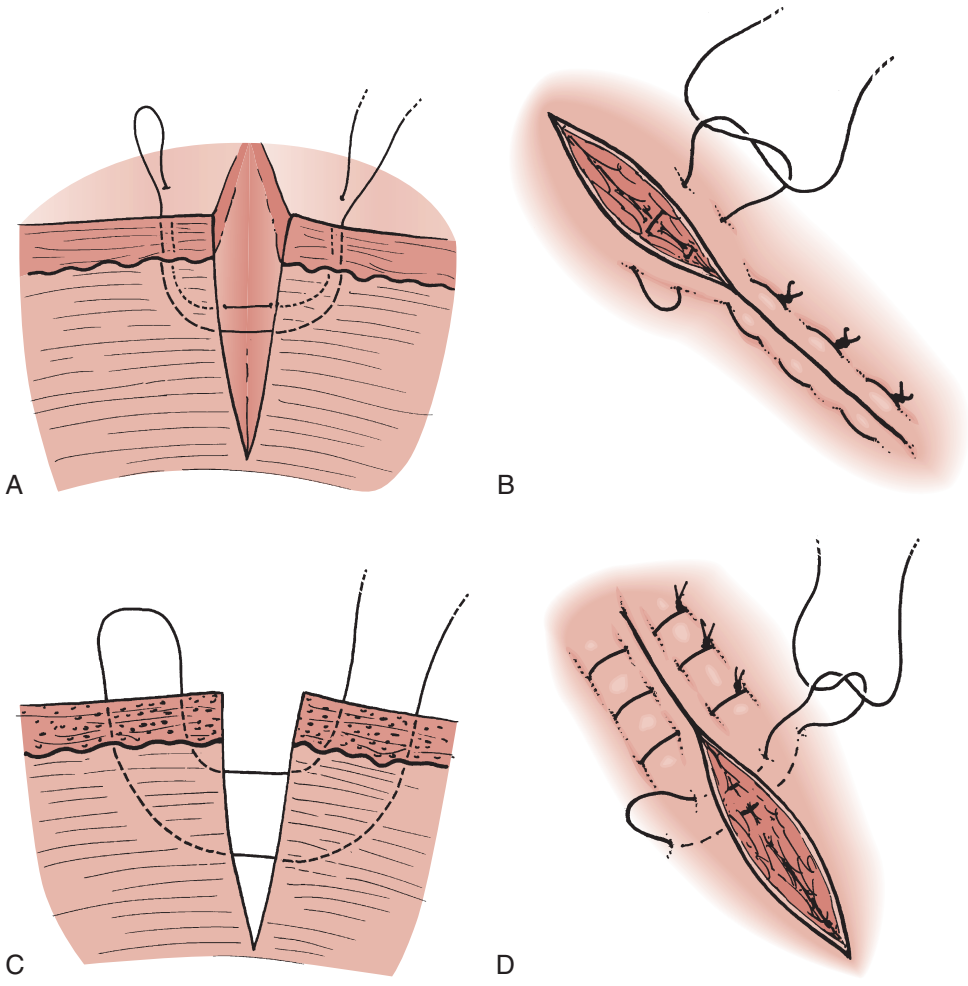


Figure 56-4. Mattress suture. (Modified from Simon BC: Skin and subcutaneous tissue. In Rosen P, et al (eds): Atlas of Emergency Procedures. St. Louis, Mosby, 2001.)

has been stabilized. The clips are plastic and will not interfere with CT or magnetic resonance imaging.[43]

Staple removal is simple, especially if the patient has kept the wound clean and free of dried secretions. The dual prongs on the disposable staple remover slide under the staple crossbar. As the handle is squeezed and the horizontal aspect of the staple is depressed, the sharp edges are eased out of the tissue for removal.

Vertical Mattress Sutures. Vertical mattress sutures improve wound edge eversion. They are also used for the closure of gaping wounds and deep lacerations that may need more than simple sutures to close potential dead space. Areas of lax skin tension, generally where maximal skin mobility is needed such as over joint surfaces, may need assistance to ensure eversion of the wound margins. Vertical mattress sutures may be ideal to accomplish both tasks.

Procedure. A vertical mattress suture is a combination of deep and superficial components. The needle is introduced at a 90-degree angle approximately 1 cm from the wound margin. The needle courses through the depth of the wound and emerges on the opposite side, 1 cm from the laceration margin at a 90-degree angle. The needle is reintroduced 1 or 2 mm from the epidermal edge for final approximation of the wound.

Horizontal Mattress Sutures. Horizontal mattress sutures are useful to help disperse excess skin tension and to evert wound edges. The scalp, which has minimal skin mobility, is one area where gaping lacerations may benefit from this tension-reduction method. Horizontal mattress sutures may also be beneficial in thin, fragile skin of elderly people and for lacerations that have lost tissue from the injury or débridement.

Procedure. The initial step is to pass the needle as for a simple interrupted stitch (Fig. 56-4). On exiting the skin, however, the needle is reintroduced approximately 0.5 cm adjacent to the exit point. This second "bite" re-emerges 0.5 cm adjacent to the initial insertion point and is tied. In contrast to the vertical mattress, each bite is always the same distance from the wound margin.

Dog-Ear Deformity Repair. Some redundant tissue may result on one side of the repair as the closure nears completion, especially in the closure of curvilinear lacerations. This redundant tissue generally can be avoided by placing the initial suture in the middle of a curvilinear wound. If the clinician has limited experience, excising and undermining tissue are likely to result in complications and should not be attempted.

Procedure. The laceration repair begins in a traditional manner and continues to approximately the final 1 cm of the wound (Fig. 56-5). A short incision (approximately 1 cm) is made from the end of the laceration at a 45-degree angle. The angle is cut toward the side of the redundant, bunched tissue. In most cases, the subcutaneous tissue from the start of the dog-ear defect to the newly created end of the wound must be gently undermined to mobilize the skin. The next step, the final step before suturing, is the most important. The work that has just been completed leaves a small triangular piece of excess tissue. The redundant piece is gently lifted with the tissue forceps and excised in a line parallel to the incision made above. The wound can now be closed with simple interrupted suture technique. Poor technique can result in a more unsightly repair. If too much tissue is undermined, the edge of the skin can lose its blood supply and necrose.

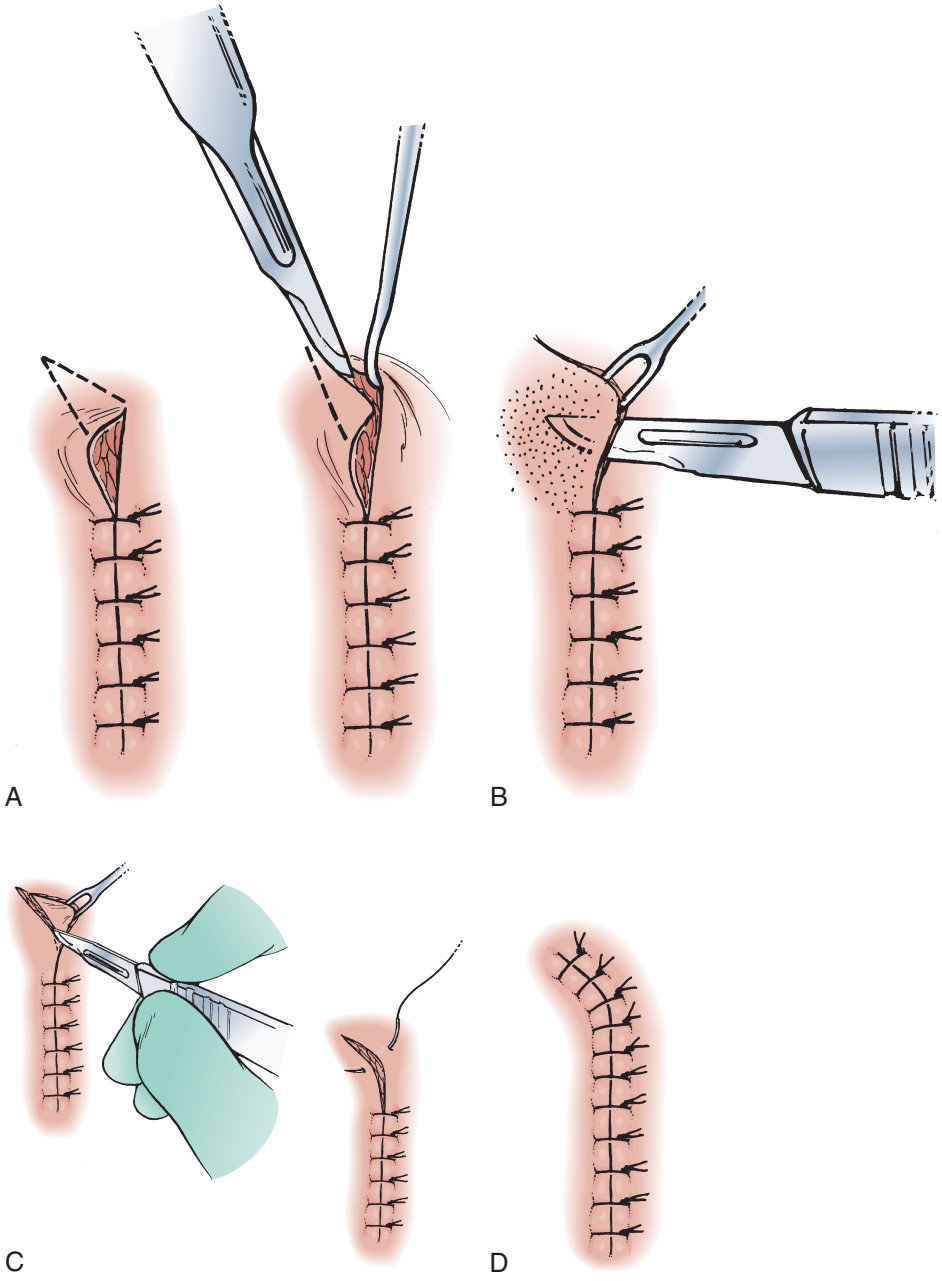


Figure 56-5. Dog-ear repair. (Modified from Simon BC: Skin and subcutaneous tissue. In Rosen P, et al (eds): Atlas of Emergency Procedures. St. Louis, Mosby, 2001.)

Corner Stitch (Half-Buried Horizontal Mattress Sutures). Jagged and triangular-shaped wounds create corners that can be difficult to repair. The clinician must avoid placing the suture directly in the tip of the flap. This practice may "stretch" the tissue and further compromise blood flow to the wound margin. The corner stitch allows optimal tissue approximation with minimal tension.

Procedure. The needle is introduced percutaneously through the nonflap side of the wound a few millimeters from the corner of the wound (Fig. 56-6). The needle is passed horizontally through the dermis of the flap. The final step is to pass the needle into the dermis of the nonflap aspect of the wound a few millimeters from the opposite side of the corner. The suture is led out through the epidermis and tied. This technique can also be used to encompass multiple flaps either individually or simultaneously if the tips are adjacent to one another. The most difficult but important aspect of the corner stitch is to take bites of equal depth with each pass of the needle. Failure to take equal bites of tissue results in a wound with opposing sides that do not lie flat; this leads to a more obvious scar. When the corner has been repaired, the remaining two sides of the wound may be closed with simple interrupted or running suture technique.

V-Y Wound Closure. The V-Y closure is indicated for the repair of V-shaped wounds with tissue loss or with nonviable margins that must be trimmed. The tissue loss is such that the adjacent mobile tissue is not sufficient to close the remaining defect.

Procedure. Nonviable tissue is trimmed with fine iris scissors (Fig. 56-7). The long V-shaped portion of the wound is sutured with simple interrupted percutaneous stitches. This first step brings the tip of the flap closer to the newly created corner of the wound. A corner stitch is used to secure the tip of the flap. The remaining limbs of the Y can be repaired with simple interrupted stitches. Some degree of undermining is likely to be needed to mobilize tissue to close the defect. Débridement of too much tissue can make the final repair more difficult and can distort adjacent anatomy.

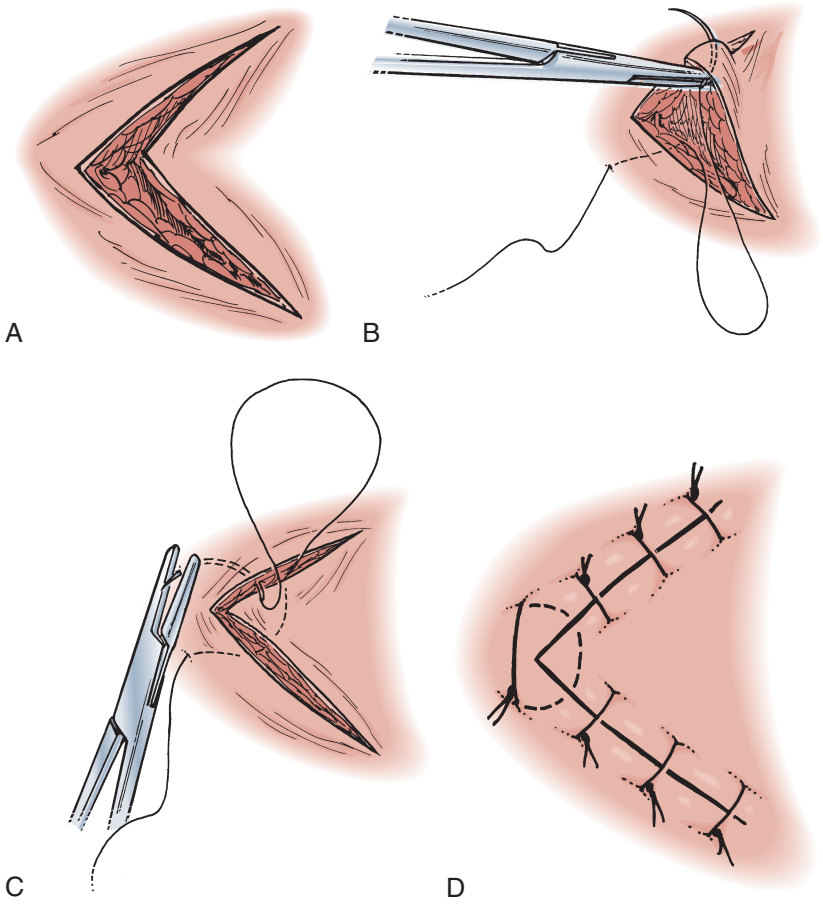


Figure 56-6. Corner stitch (half-buried horizontal mattress). (Modified from Simon BC: Skin and subcutaneous tissue. In Rosen P, et al (eds): Atlas of Emergency Procedures. St. Louis, Mosby, 2001.)

Materials

In the Middle Ages and earlier, materials used to close wounds included flax, hemp, fascia, hair, linen strips, pigs' bristles, reeds, grasses, and even the mouth parts of the pincher ant. In the early 1900s, natural organic protein products, including silk, cotton, and catgut, were the only available substances. Polyester (Dacron) and nylon were the first synthetic materials available in the 1940s. Since then, a host of other synthetic materials have become available.

Suture. The ideal suture is inert to metabolism, is resistant to infection, has great tensile strength, does not tear tissue, is easy to work with and tie, and is available in convenient colors with a variety of cutting and noncutting needles (Table 56-2).[46] A common classification of suture material relies on relative *absorbability*. In general, the materials that maintain their tensile strength for more than 60 days after implantation have been defined as *nonabsorbable*. Materials that undergo rapid degradation in tissue and lose their strength in less than 60 days are considered *absorbable*. A second classification considers the source and nature of the material. *Biologic* substances, which include catgut, collagen, silk, linen, and cotton, generally produce the greatest tissue reaction and have the lowest relative tensile strength but have good knot security. These characteristics are in contrast to *synthetic* materials, such as polyester (Dacron), polyamide (nylon), polypropylene (Prolene), polyglycolide and polylactide polymers (Dexon and Vicryl), polydioxanone (PDS), and steel, which usually have less tissue reactivity, greater strength, and less knot security.[47,48]

Knotting properties and handling characteristics tend to vary inversely. Knot security is of particular importance in maintaining wound closure and the patient's confidence in the physician. Sutures with smooth or slippery surfaces produce little friction and glide effortlessly through tissue and are easy to tie. Smoother materials are more difficult to handle and more likely to untie spontaneously. Certain monofilament synthetic materials tend to return or spring back to their original shape. To overcome this suture memory, the first part of the tie should be a "double throw" pulled tightly enough to approximate the tissue, taking care not to strangulate the margins. The second throw locks the tension of the first part into position. A third throw is used for added security. If done properly, additional knotting is not needed after the third throw.

The presence of any suture material in a wound increases the likelihood of infection. Subcutaneous sutures bear the greatest risk.[47] The degree of risk depends on characteristics of the substances used. Braided multifilament materials, such as the polyesters, polyamides, polyglycolides, and silk, yield the highest infection rates, whereas monofilament synthetic substances have the lowest risk of infection. There are several nonabsorbable monofilament synthetic sutures and one absorbable monofilament (PDS). The degree of infectivity of PDS compares well with the low rates of infectivity of similar materials.[48]

Consideration of patient comfort in suture selection is important. Although silk is highly reactive, it ties well, is easy to handle, and is comfortable for the patient. It is an excellent choice in and around the lips, where comfort is a major concern. PDS is a comfortable absorbable suture and can be left in intraoral mucosa to be absorbed, with apparently low risks of infection, or it can be removed in 5 to 7 days. Staples or metallic sutures are excellent when strength is needed, but they may be uncomfortable for the patient. Nylon and polypropylene, which are the most common sutures used on skin, produce

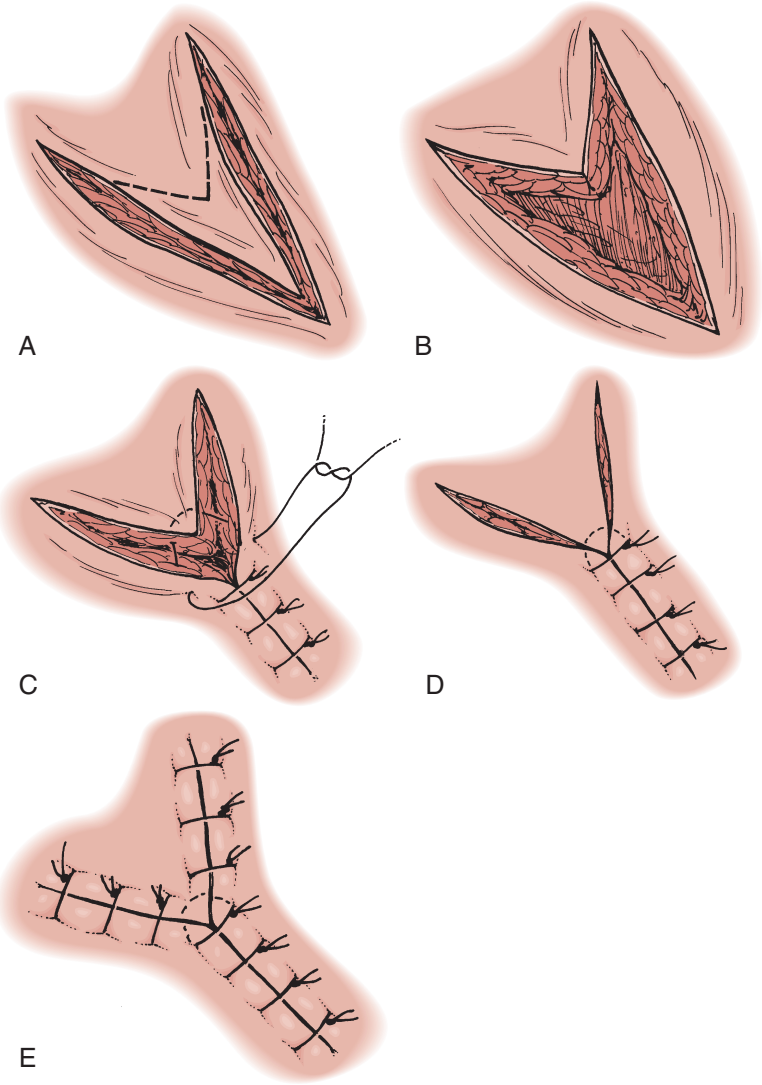


Figure 56-7. V-Y closure. (Modified from Simon BC: Skin and subcutaneous tissue. In Rosen P, et al (eds): Atlas of Emergency Procedures. St. Louis, Mosby, 2001.)

little tissue reaction and offer good tensile strength. They tend to be stiff, produce discomfort near the lips, have poor knot security, and may be difficult to work with. A braided, coated polyester nonabsorbable material, such as Ethibond, is easier to work with and has better knot stability. Although Ethibond is more expensive than nylon, its characteristics and added patient comfort suggest that it may be preferable. Absorbable suture materials, such as polyglycolide and polylactide polymers (Dexon and Vicryl), have been used strictly for subcutaneous and mucosal closures. Their highly reactive nature allows them to be broken down and absorbed over weeks. Chromic catgut, another absorbable material, has been shown to be safe and effective for the closure of scalp wounds in children.[49]

Needles. Surgical needles are available in a variety of sizes and shapes with a myriad of other characteristics. Cutting needles may be reverse cutting, conventional cutting, taper cut, or precision point. Most emergency wounds may be closed using a conventional cutting needle. In addition to its sharp point, it has two opposing cutting edges, with a third on the inside curve. Precision point needles are similarly shaped but are honed 24 extra times and maintain their added sharpness longer. These needles are used for delicate plastic or cosmetic surgery. Noncutting needles are reserved for organ repair and subcutaneous suturing. Cutting needles may also be used to repair subcutaneous tissue. Needle nomenclature is confusing and varies by manufacturer.

Tape. Tape closure may be superior to sutures and staples if applied in the appropriate circumstances. Generally, the laceration should be linear and subjected to weak static and dynamic forces. Tape is not considered for wounds requiring meticulous tissue approximation. Compared with other closure materials, application of tape is associated with lower risk of infection, less expense, and less physician time. In addition, a painful injection of local anesthetic is not needed.

The ideal wound closure tape must allow water and gas exchange and possess elasticity, strength, and optimal adhesiveness. To maximize adhesive properties, tincture of benzoin should be painted on the skin adjacent to the wound. Care must be taken to avoid introducing benzoin compound in the wound. A nonwoven, microporous tape, which is not reinforced, has been found to best meet these requirements.[50,51]

Staples. Staples offer several advantages over sutures. Monofilament stainless-steel staples offer less risk of infection than even the least reactive suture.[52] The time necessary to accomplish closure may be significantly lessened. Acceptable wounds must be linear and subjected to weak skin forces. Wounds requiring accurate approximation of tissue are not candidates for staple closure. Staples are also uncomfortable while in situ and on removal. Stapled wounds gain tensile strength sooner,

Table 56-2 Suture Materials for Wound Closure

TYPE	DESCRIPTION	SECURITY	STRENGTH	REACTION	WORKABILITY	INFECTION	COMMENT
Nonabsorbables							
Silk		++++	+	++++	++++	++	Suitable around mouth, nose, or nipples, but too reactive and weak to be used universally
Mersilene	Braided synthetic	++++	++	+++	++++		Good tensile strength; some prefer for fascia repairs
Nylon	Monofilament	++	+++	++	++	+++	Good strength; decreased infection rate; knots tend to skip, especially the first "throw"
Polypropylene (Prolene)	Monofilament	+	++++	+	+	++++	Good resistance on infection; often difficult to work with; requires an extra throw
Ethibond	Braided coated polyester	+++	++++	++½	+++	+++	
Stainless-steel wire	Monofilament	++++	++++	+	+	+	Difficult to use; painful to patient; some prefer for tendons
Absorbables							
Gut (plain)	From sheep intima	+	++	+++		+	Loses strength rapidly and quickly absorbed; rarely used today
Chromic (gut)	Plain gut treated with chromic salts	++	++	+++		+	Similar to plain gut; can be used to close intraoral lacerations
Dexon	Braided copolymer of glycolic acid	++++	++++	+		++++	Braiding may cause it to "hang up" when tying knots
Vicryl	Braided polymer of lactide and glycolide	+++	++++	+		+++	Low reactivity with good strength; suitable for subcutaneous healing; good in mucous membranes
Polydioxanone	Monofilament	++++	++++	+	Excellent	Unavailable	First available monofilament synthetic absorbable sutures; appears to be excellent

From Swanson NA, Tromovitch TA: Suture materials, 1980s: Properties, uses and abuses. Int J Dermatol 21:373, 1982.

and the staples can be removed 1 to 3 days earlier than sutures. After removal, the staples should be replaced with wound closure tape for continued reinforcement.

Various stapling devices are available. The device must allow good visual access and flexible positioning for difficult angles. A precocking mechanism is necessary to allow the physician to hold the staple securely during its placement. The angle of staple delivery is important. One brand releases the staple perpendicular to the wound with its crossbar flush with the skin; this can result in cross-hatching on the skin or tissue strangulation if placed too deeply. The device needs an ejector spring for smooth staple release and must handle without producing fatigue.

Tissue Adhesives. European and Canadian physicians have used tissue adhesives (butyl 2-cyanoacrylates) for many years. In 1998, octyl-2-cyanoacrylates were approved for use in the United States. Tissue adhesives offer many advantages over traditional sutures. The emergency physician can apply the adhesive quickly and easily with a minimum of patient discomfort. In addition, suture removal in 7 to 10 days is unnecessary because the adhesive sloughs off the skin in approximately the same amount of time. Evidence indicates that adhesives not only provide their own dressing but also have antibacterial properties and may decrease the rate of wound infections.[53] Considering time and materials, closing wounds with adhesives is less expensive than traditional suturing and carries no risk of needle-stick injuries.[54]

Tissue adhesives achieved cosmetic results similar to those of traditional sutures in randomized trials.[55,56] Tissue adhesive may be applied in high-tension areas, but only if used in conjunction with subcutaneous or subcuticular sutures. If used alone, tissue adhesives are not recommended for lacerations longer than 4 cm or in areas of higher tension or frequent repetitive movements, such as joints or hands.[55]

Other disadvantages of tissue adhesives include the inability to use antibacterial or other petroleum-based products on the wound, the recommendation not to swim to limit forces that may prematurely remove the adhesive, and the greater risk of dehiscence. The tensile strength of tissue adhesives is significantly less than that of sutures. Despite these disadvan-

tages, tissue adhesives represent a tremendous advance in the management of routine uncomplicated lacerations in nontension areas. Patients routinely prefer tissue adhesives over traditional sutures.[56]

Application of tissue adhesive begins with routine skin and wound preparation. The area must be dried and adequate hemostasis achieved before application of the adhesive. The wound margins should be approximated as meticulously as possible, and care should be taken to prevent adhesive from getting between the wound margins. Applying tape (Steri-Strips) prior to application will facilitate wound margin approximation and make it easier to apply. Adhesive between the wound margins delays healing and increases the likelihood of wound dehiscence. The adhesive should be applied to the entire length of the wound sufficient to cover 5 to 10 mm of skin adjacent to the margins. Three layers of adhesive are to be applied. The physician should allow 30 to 45 seconds for the first layer to polymerize and then apply the subsequent two layers, allowing approximately 10 seconds between applications. Special care must be taken to ensure that the adhesive does not run off and disturb adjacent tissues. Lying the patient on the affected side will help avoid contamination of the eye near the wound and the opposing eye. Newer, high-viscosity formulations are now available that help limit this risk. Wounds may get wet but should not be immersed in water and should be blotted dry and not vigorously rubbed. An additional dressing may be desired by the patient but is not necessary.[56,57]

Antibiotic Prophylaxis

Routine antibiotic prophylaxis for simple wounds has no scientific basis. A meta-analysis compared the rates of infection in patients with simple, nonbite wounds receiving antibiotics with those of control groups. Of 1734 patients enrolled in the seven studies, patients treated with antibiotics had a slightly greater incidence of infection. The authors concluded that prophylactic antibiotics had no role in simple, nonbite lacerations.[58] Routine antibiotic use also has complications: Increasing resistance to antibiotics, gastrointestinal side effects, and allergic reactions are common and may result in significant morbidity and unnecessary cost.

Although irrigation and débridement are the most important means of preventing wound infections, antibiotic prophylaxis is recommended in some circumstances. Prophylaxis must be tailored to each patient. Some recommendations are supported by scientific data, whereas others have few data to support their use and are based on custom.

Contamination, Crush, and Host Factors

Antibiotic prophylaxis is often provided for patients with wounds with gross contamination, patients with severe crush injuries, and immunocompromised patients. Some authors recommend not closing these wounds and instead using delayed primary closure. If circumstances require wound closure despite the infection risk, many emergency physicians recommend prophylaxis despite scarce data.[59]

Some authors believe that a patient with significant crush injury requires antibiotics. Crush injuries are high-risk wounds because they produce more devitalized tissue.[60] A definitive answer may not be forthcoming because it would be difficult to complete a well-controlled prospective, blind study.

Patients with certain risk factors have increased wound infection rates. A prospective study of more than 23,000 surgical wounds showed an increased rate of wound infection in patients with diabetes, obesity, malnutrition, chronic renal failure, advanced age, and chronic steroid use.[59] Because of higher rates of infection, some authors suggest the use of antibiotics in these patients, again based on individual circumstances.[60] No controlled studies of antibiotic prophylaxis in these patients exist, however. Finally, some authors advocate prophylaxis for other host factors, such as prosthetic joints or risk for endocarditis.[61,62] Little evidence exists to support either recommendation.

Open Fractures, Joint, and Gunshot Wounds

Wounds that involve joints or open fractures need prophylactic antibiotics. Prospective randomized controlled studies have documented decreased infection rates in patients receiving antibiotics compared with placebo. Indeed, the time to antibiotic administration in these wounds was found to be the most important factor in decreasing wound infection rates.[63] Open fractures without evidence of significant soft tissue damage (avulsions and crushed or devitalized tissue) require antibiotics for 24 hours. Open comminuted fractures or fractures with significant tissue damage require 72 hours of antibiotics.[64] For gunshot wounds, which are classified as a type of open fracture, the recommendations vary with the type of missile wound. Low-velocity missile wounds not treated with antibiotics showed no increased infection rate in a randomized controlled trial of 67 patients with fractures treated with a closed technique.[65] High-velocity wounds with fracture, on the other hand, are associated with an increased risk of infection, and antibiotic therapy should be initiated early and maintained for 48 to 72 hours.[66] In addition, shotgun wounds with fracture should have prophylaxis as well. Appropriate antibiotic therapy would be a cephalosporin with or without an aminoglycoside plus penicillin (to cover *Clostridia* species).[67]

Bites and Puncture Wounds

Antibiotics are indicated for through-and-through intraoral lacerations, cat bites, some dog bites, some human bites, and some puncture injuries to the foot.

Cat Bites. Prophylaxis is required for patients with cat bites. These bites tend to be deep puncture wounds that are difficult to irrigate adequately. These wounds also tend to become infected at a much higher rate than other types of bites. Cat bites have been reported to cause infections in 10 to 40% of all wounds. In one study, 12.9% of patients had signs of infection when they presented to the emergency department, and 15.9% eventually developed infection. Other authors report that 80% of these bites become infected, although obvious selection bias limits this interpretation. Antibiotics seem to decrease the incidence of infection.[68]

The organisms found in cat bites include *Staphylococcus* species, *Streptococcus* species, and, most often, *Pasteurella multocida*. *Pasteurella multocida* is usually found in infected cat bite wounds and is present in the normal oral flora of 70% of all cats. *Pasteurella multocida* is sensitive to penicillin, but the infection is often polymicrobial. *Pasteurella multocida* is resistant to dicloxacillin, cephalexin, and clindamycin, and there are many erythromycin-resistant strains. Amoxicillin with clavulanate is the current recommendation for antibiotic prophylaxis for cat bites.

Dog Bites. Antibiotic prophylaxis for dog bites is more controversial. The infection rate has been reported as 6 to 16% for patients not receiving antibiotics. Dog bites tend to be more crush injuries with tearing and avulsions rather than puncture wounds. As such, dog bites are usually more amenable to irrigation and débridement. Seven of eight randomized trials of dog bite wounds showed no benefit with antibiotics. However,

pooled data for meta-analysis did show a small but statistically significant benefit from antibiotics.[69] It may be logical to limit the use of antibiotics to high-risk wounds, such as hand injuries, deep puncture wounds, and wounds in older or immunocompromised patients.

Hand Bites. In addition to the previous bite wound recommendations, antibiotic prophylaxis of injuries to the metacarpophalangeal joints is advised. These wounds are assumed to be human bites until proved otherwise. Also known as "fight bites," these wounds have a high incidence of infection. Patients without signs of infection may be managed as outpatients. Close inspection after anesthesia is applied is necessary to thoroughly evaluate the area for tendon involvement and/or penetration of the joint. If the joint is involved, aggressive irrigation is required. Some institutions take all these patients to the operating room for a thorough washout. Patients with early signs of infection must be admitted for intravenous antibiotics and aggressive débridement and irrigation. The choice of antibiotics reflects the predominant organisms of hand bite infections. *Streptococcus* and *Staphylococcus* species are common, but *Eikenella corrodens* and *Bacteroides* species are also typical pathogens. Because *Eikenella* is often resistant to clindamycin, first-generation cephalosporins, and erythromycin, patients with early infection should receive amoxicillin with clavulanate. Patients with later infection should receive intravenous extended-spectrum antibiotics (e.g., ampicillin with sulbactam).

Intraoral Lacerations. Lacerations of the oral mucosa involve bacteria-rich oral secretions and may become infected slightly more often (6–12%) than other wounds. Although few data suggest a clear indication for prophylactic antibiotics, one study showed that patients benefit from antibiotics if they are compliant with their regimen. Rates of infection for through-and-through lacerations may be twice the rates for simple mucosal lacerations. It may be reasonable to limit antibiotic use to these patients. Penicillin is an appropriate choice of antibiotic.

Puncture Wounds of the Foot. Puncture wounds of the foot are seen frequently in the emergency department. These wounds are often caused by common nails, although other objects (e.g., glass, metal, and wood) must be considered. Despite their simple appearance, these wounds may produce significant morbidity. The infection rate for puncture wounds has been reported to be 15%.[70,71] Most wounds occur on the plantar surface, from the neck of the metatarsal to the toes. Simple cellulitis accounts for half of these infections. More significant infections include septic arthritis, abscesses, and osteomyelitis. *Pseudomonas* organisms cause 90% of osteomyelitis cases from puncture wounds. No data suggest a benefit from prophylactic antibiotics, but given the high risk of infection and serious complications, their use should be strongly considered in select puncture wounds. Consideration of *Pseudomonas* organisms when the puncture went through a rubber-soled shoe is essential. Patients with puncture wounds to the foot require early follow-up. Ciprofloxacin is the drug of choice to treat outpatients with suspected wound infection when *Pseudomonas* is of concern. Cephalexin (keflex) or dicloxacillin is adequate for staph and strep coverage unless methicillin-resistant *Staphylococcus aureus* (MRSA) is likely. In cases suspicious for MRSA, sulfa/trimethoprim or doxycycline is recommended.

Drains, Dressings, and Immobilization

Drains

Drains probably have no role in emergency department wound care. In general, drains are placed when a collection of fluid exists or may develop. The presence of a drain reduces the wound's resistance to infection, regardless of the materials used in its construction, and the use of drains should be avoided.[72] In wounds likely to collect fluid (e.g., around the elbow or knee), it is preferable to place the extremity at rest with a plaster splint or perform delayed primary closure.

Dressings

Various dressing materials are available. The microenvironment created by a dressing affects the biology of healing. The optimal wound climate must not interfere with the activity of fibroblasts and macrophages. The production of granulation tissue and migration of epithelial cells across the wound must be optimized.

Several factors should be considered when choosing the appropriate dressing. Dressings that prevent evaporation of water and keep tissues moist are helpful. A drying wound produces a thick, hardened scab that impedes the process of epithelialization. Excess fluid can lead to maceration of tissue and may be a potential culture medium for bacterial proliferation. Gaseous permeability is essential because epithelialization is accelerated greatly in the presence of oxygen. The wound-covering product should be impermeable to bacteria and other particulate matter that can contaminate the wound. It is important not to traumatize newly established tissue during dressing changes. The optimal dressing should have a nonadherent surface, be permeable to gases, and have a capacity to absorb some fluid but not allow desiccation. The outer barrier of the product should be impermeable to bacteria but permeable to water vapor. These products include films, hydrocolloids, foams, and hydrogels. The choice of dressing for emergency department wounds is primarily based on the amount of drainage that is expected.[73-75]

Film dressings are thin membranes that are transparent, adhesive, and waterproof but are not absorptive. They are best reserved for wounds with low levels of drainage. Film dressings may be left in place for up to 7 days as long as they do not leak or separate from the wound bed. For wounds with a moderate amount of drainage, moderately absorptive hydrocolloid dressings may be indicated. These dressings are thicker than films, semiocclusive, waterproof, and very comfortable for the patient. Like films, they can be left on for up to 7 days. Foam dressings are more absorptive and made of a soft cushion sponge-like material. Some may require a secondary dressing for adhesion and need to be removed every 3 days. Hydrogel dressings are moisture-donating water-based gels that are available in sheets attached to a semipermeable film. These dressings do not absorb fluids, so they must be used on relatively dry wounds. Patients often find these dressings to be the most comfortable, but they need to be changed every 1 to 3 days. The least expensive and simplest method of dressing a straightforward, uncomplicated laceration is to use a Vaseline-impregnated gauze or gauze on top of a thick layer of antibiotic ointment. These should be changed daily to prevent dessication.

Immobilization

Wounds in proximity to joints must be immobilized as part of routine care. Splinting the injured body part places the injury at rest and hastens healing. Failure to splint appropriately exposes the healing tissue to the dynamic forces of muscular contractions, ultimately slowing the healing process and increasing scar size. In addition, immobilization decreases lymphatic flow and minimizes spread of microflora from the wound.

DISPOSITION

Wound Care Instructions

It is difficult for patients to identify and recognize the signs of infection (Box 56-2).[76] Discharge instructions must be clear, understandable, and reasonably comprehensive. Instructions should include daily care, observation for signs of infection, suture removal dates, and a follow-up source. During the first 24 to 48 post-traumatic hours, the injured extremity should be elevated. Elevation lessens edema, hastens healing, and mollifies pain. The wound should be protected as described previously or should be cleaned daily to remove crust formations. It is safe to bathe and get the wound wet 24 hours after injury.[77] Daily swabbing with half-strength hydrogen peroxide rids the wound of debris and any blood clot that forms between the sutured edges. Hydrogen peroxide should not be used after separation of the scab because it is toxic to the epithelium and may produce bullae.

Wound infection is difficult for the untrained observer to distinguish from the inflammatory response of injury and subsequent healing. Patient education in this regard should be cautious and straightforward (e.g., return or follow-up for redness, swelling, increased pain, fever, pus, or red lines progressing up an extremity). An injury classified as high risk must be reexamined 48 hours after the trauma, regardless of its appearance.

Suture removal times vary, but generally they are approximately 4 days for the face and 7 to 14 days for other body parts (see Box 56-2). Considerations include cosmetics, dynamic forces in proximity to the injury, static skin tension, blood supply, and anticipated healing rates.

BOX 56-2 WOUND CARE INSTRUCTIONS

A. Elevate the injured extremity above the level of the heart. Wear a sling when appropriate.
B. Cleanse daily in a gentle manner to remove debris and crusting that develops. Use dilute hydrogen peroxide.
C. Immobilization should be maintained at least until suture removal.
D. Signs of infection
   1. Redness
   2. Increasing pain
   3. Swelling
   4. Fever
   5. Red streaks progressing up an extremity
E. Wound check
   1. As needed to check signs of infection
   2. Routine at 48 hours for high-risk wounds
F. Suture removal (*Note*: Suture may be removed earlier if Steri-Strips reinforce the wound.)
   1. Face: 3–5 days (always replace with Steri-Strips)
   2. Scalp: 7–10 days
   3. Trunk: 7–10 days
   4. Arms and legs: 10–14 days
   5. Joints: 14 days

Tetanus Immunization

The reported incidence of tetanus in the United States in 2005 was 0.011 per 100,000 population (27 cases reported).[78] Most tetanus patients are older than age 50 years. Immunization status needs to be considered in all patients with wounds, regardless of severity. Forty percent of all cases of tetanus occur in individuals who have either minor wounds or no recollection of injury. These numbers raise serious questions regarding the validity of separating immunization recommendations according to clean and tetanus-prone wounds. Studies show that many people are inadequately immunized, especially patients older than age 70 years, immigrants, and people with no education beyond grade school.[79] Also, patient immunization histories are often unreliable. Given the inability to predict which wounds are high risk, all wounds should be approached with suspicion.

The usual incubation period for tetanus is 7 to 21 days (range, 3–56 days). Immunization should be given as soon as possible but can be given days or weeks after the injury. The dose of tetanus toxoid (T) or diphtheria, pertussis, and tetanus toxoids (dTap) is 0.5 mL intramuscularly, regardless of the patient's age. Inadequately immunized patients need a dose of dTap and tetanus immune globulin (TIG). The TIG dose is 250 U in patients 10 years old or older, 125 U in children 5 to 10 years old, and 75 U in children younger than 5 years old (Table 56-3). A single injection of TIG provides protective levels of passive antibodies for at least 4 weeks. The immune globulin and toxoid may be given during the same visit but should be administered with a different syringe at separate sites. Emergency physicians need to be more diligent because data suggest that TIG is rarely administered even when indicated.[80]

Because studies suggest that 10 to 40% of the U.S. population is inadequately immunized against diphtheria, diphtheria vaccination should be given along with tetanus toxoid.[81] Immunity to pertussis wanes approximately 5 to 10 years after vaccination. Since the 1980s, the number of reported pertussis cases has steadily increased, especially among adolescents and adults. In 2005, a total of 25,616 cases of pertussis were reported in the United States. In 2005, a tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine, adsorbed (Tdap) product formulated for use in adults and adolescents was licensed in the United States for people age 11 to 64 years. When possible, it is recommended that this triple combined formulation be used in the emergency department. Although all four injections (T, dt, TIG, and dTap) are considered safe and effective in pregnancy, because of limited experience during pregnancy the recommendation is to use dt. However, dTap is recommended immediately postpartum, including for breast-feeding women.[82]

SUMMARY

Box 56-3 summarizes the principles of wound care management.

Table 56-3 Tetanus Prophylaxis for All Patients with All Wounds*

IMMUNIZATION HISTORY	DTAP (0.5 ML)	TIG (250 IU)
Fully immunized <10 yr since booster	No	No
Fully immunized >10 yr since booster	Yes	No
Incomplete series (<3 injections)	Yes†	Yes

*Consider more frequent immunization for elderly patients. dTap recommended for ages 11–64 years (dt to be used in those older than 64 years).
†Refer these patients to complete their series; dTap in 6 weeks and 12 months.
dTap, diphtheria, pertussis, tetanus toxoids; TIG, tetanus immune globulin. All injections are intramuscular.

BOX 56-3 SUMMARY OF WOUND CARE

A. Stabilize patient
B. History (include tetanus immunization and allergies)
C. Physical examination
   1. Neurovascular examination
   2. Anesthesia: bupivacaine 0.5% without epinephrine, regional or local
   3. Bloodless field: tourniquet or sphygmomanometer for extremities
   4. Sterile examination of anatomic structures, skin, nerves, tendons, blood vessels, bones, muscles, fascia, other (ducts, cartilage)
   5. Consult if indicated
D. X-ray films to detect injury to bone or the presence of foreign bodies (xeroradiograph or ultrasound)
E. Wound preparation
   1. Cut—do not shave—surrounding hair
   2. Prepare surrounding skin with povidone-iodine (Betadine) solution
   3. Sharp débridement of foreign matter and devitalized tissue
   4. High-pressure irrigation with saline, 1% Betadine, an antibiotic solution, or a nonionic solution
F. Wound closure
   1. Tape, staples, or suture
   2. Do not use subcutaneous sutures unless the wound is under high tension
G. Antibiotics
   1. Apply topical antibiotics
   2. No systemic antibiotics unless wound is very high risk
H. Dress and immobilize: Consider a transparent gas-permeable dressing
I. Wound care instructions (see Box 56-2)
   1. Signs of infection
   2. Elevation
   3. Wound check if necessary
   4. Suture removal as soon as possible

KEY CONCEPTS

- Risk factors for wound infection include prolonged time since injury; crush mechanism; deep penetrating wounds; high-velocity missiles; and contamination with saliva, feces, soil, or other foreign matter.
- The most effective intervention to decrease infection is thorough cleansing, using saline irrigation at approximately 8 psi. Attaching an 18-gauge needle to a 35-mL syringe creates an irrigant force of 7 or 8 psi, which decreases bacterial counts.
- Soaking wounds in povidone-iodine (Betadine) is more toxic than beneficial to healthy tissue.
- Antibiotics are indicated for through-and-through intraoral lacerations, cat bites, some dog bites, some human bites, puncture injuries to the foot, open fractures, and wounds involving exposed tendons or joints.
- High-risk wounds should not be sutured primarily but may be repaired in 4 or 5 days (i.e., delayed primary closure).
- Tetanus immunization should be given soon after injury but can be given days or weeks later. The usual incubation period for tetanus is 7 to 21 days (range, 3–56 days).

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 57 Foreign Bodies

Stephen H. Thomas and Benjamin A. White

PERSPECTIVE

History

When people ingest or insert foreign bodies, a brief history may be sufficient to guide management and predict the process required for definitive resolution. The technical intervention required for foreign body removal may be more complex, sometimes requiring substantial expertise. Cases involving persistent cough after ingestion of peanuts in a toddler or abdominal pain and a history of ingesting foreign objects in a psychiatric patient should be diagnosed rapidly and easily. Sometimes, however, diagnosis and management of a foreign body may require a meticulous history and insightful care. Persons at higher risk of having a foreign body include neurologically impaired patients, edentulous persons, patients with certain psychiatric diagnoses, incarcerated persons, and patients at the extremes of age. In these same groups, definitive history often is elusive. Sometimes the clinician must use situational clues: A toddler left alone with an infant may have inserted a foreign body, or a prisoner with abdominal cramps may have ingested a foreign body for secondary gain. Even when patients are fully cooperative, the diagnosis of foreign body ingestion or insertion can be difficult. The presentation may be for a seemingly unrelated problem, and sequelae of foreign bodies may be delayed by months, years, or even decades.[1]

PHYSICAL EXAMINATION

Depending on the location of the foreign body, the physical examination can provide direct or indirect evidence of foreign bodies or their complications. Specifics are presented for each category of foreign body described later in the section on management, but with a recurring theme: Meticulous examination frequently aids in providing a diagnosis.

DIAGNOSTIC IMAGING

Plain radiography, classically the primary technique used for foreign body detection, often is the test of first choice. In appropriate circumstances, plain films can aid in determination of the location, size, and number of foreign objects. Even when objects are not visualized, radiographs may show secondary changes (e.g., pulmonary air trapping) providing clues to foreign body presence. To assist in the localization, two views—anteroposterior and lateral—usually are necessary. Objects such as metal or gravel, which are denser than the tissue in which they are embedded, usually are easy to visualize on plain radiographs. Organic material, may have a density similar to that of human tissue, may not be seen on plain films.

PRINCIPLES OF DISEASE

When the foreign body is localized, it usually is removed, either in the emergency department (ED) or in specialized areas such as interventional radiology, endoscopy, or operating suites. Although foreign body removal is not always feasible or desirable, extraction is indicated in most cases. Removal frequently is vexing for both physician and patient, so an initial discussion outlining the need for the procedure is recommended.

When the foreign body represents an immediate threat to the patient, as is the case with an airway foreign body, the need for urgent extraction is obvious. Trauma-related foreign bodies, such as knives and bullets, pose important management issues (see other chapters on trauma). Even in cases in which no immediate life threat exists, some foreign bodies should be removed because of the threat of injury from their nature or constituents. For instance, cocaine can kill a body packer,[2] an impacted button battery can cause fatal electrochemically induced tissue damage,[3] and an insect can damage otic structures.[4]

In the absence of immediate life threat or constituent-related foreign body danger, additional complications can occur. In cases involving luminal obstruction, the foreign body may become lodged and may exert pressure on adjacent tissue, with the potential for necrosis and perforation. The object also may serve as a nidus for infection that is recurrent or refractory to treatment until removal of the foreign body is accomplished. In such cases, the patient often seeks medical attention for secondary symptoms. Specific recommendations for foreign body removal are presented in the following section.

FOREIGN BODY MANAGEMENT BY SPECIFIC ANATOMIC LOCATION

Eye

Clinical Features. Although wooden and metallic fragments are found most frequently, ophthalmic foreign objects vary widely, from dust particles to lost contact lenses to missiles associated with penetrating trauma.[5] The diagnosis usually is self-evident. With both extraocular and intraocular foreign bodies, however,

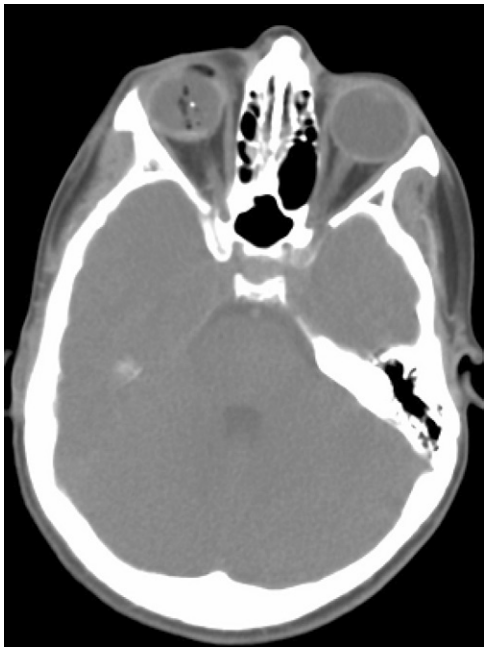


Figure 57-1. Computed tomography scan shows a right intraocular foreign body (a BB pellet) in an intoxicated patient without a known history of trauma.

the clinical presentation may be subtle, with mild symptoms and uncharacteristic history involving seemingly trivial trauma, such as brushing against a bush or falling. In some cases, foreign bodies are identified in intoxicated patients who present with abnormalities on ocular examination and no known history of trauma (Fig. 57-1). ED presentation can be delayed by days or even years after the initial incident.[5,6] Early diagnosis and appropriate care and follow-up minimize the risks of delayed sequelae, such as endophthalmitis (which may develop within 48 hours after foreign body introduction) or sight-threatening siderosis bulbi.[7,8] Controversy about foreign body removal (and its timing) does not diminish the importance of making the initial diagnosis.

History. Most patients complain of "something in the eye" (often on blinking) and cannot see the foreign body either when looking in a mirror or on scanning the visual field. If the object is corneal, however, it may be seen by the patient from within or from without. The patient also may complain of tearing and conjunctival reddening. Foreign bodies that create corneal injury and are no longer present may account for symptoms identical to those noted in the presence of a foreign body. Additionally, patients may present with symptoms in the absence of any history of known foreign body. In these cases, the occupational and social history, including pets and hobbies, may shed light on the diagnosis. Another important component of the history is whether radial keratotomy has been performed. This procedure is associated with potential for foreign body entrapment in the corneal incisions, which can gape as long as 6 or more years after the procedure.[9]

Physical Examination. The initial survey should include standard elements of ED eye examination. Early visual acuity is an important predictor of final visual outcome in cases of intraocular foreign body.[10] Slit-lamp examination may reveal a corneal foreign body by means of the shadow it casts on the iris. This examination also can facilitate identification of rust rings, and application of fluorescein can aid in detecting abraded corneal epithelium. The inner aspects of both lids must be examined. The upper lid should be everted by instructing the patient to look downward while upward traction on the eyelashes is applied; an applicator stick is placed on the proximal edge of the tarsal plate, to act as a fulcrum. After localization and removal of a foreign body, complete examination should seek presence of other ocular objects.

Diagnostic Strategies. The foreign body may have penetrated the anterior eye structures and entered the globe (see Fig. 57-1). If the history and mechanism of injury are compatible with ocular penetration by radiopaque material, or if a small wound of the globe is noted, obtaining anteroposterior and lateral radiographic views of the orbit is a reasonable initial step.[11] However, the multiple advantages of computed tomography (CT) render this latter technique the modality of choice when intraocular penetration is strongly suspected.[7,12] Compared with plain radiography, CT delivers less radiation to the lens. Multiplanar reconstruction minimizes streak artifacts, affording better localization of intraorbital objects. When globe penetration is strongly suspected, staining with fluorescein is best avoided owing to its obscuration of anatomic features on the physical exam. In cases in which perforation is judged unlikely and fluorescein is administered, identification of rivulets of fluorescein tracking from the puncture (i.e., positive result on a Seidel test) is helpful in identifying the fact that intraocular penetration has occurred.

Ultrasound imaging is a useful adjunct to CT scanning in patients with foreign bodies that are difficult to localize.[13] When CT will be delayed, or if ionizing radiation is a concern, two ultrasound techniques can be useful in searching for foreign bodies. Standard B-scan ultrasonography has been shown to detect foreign bodies missed on ophthalmologic examination, as well as objects that are not seen or incompletely characterized on other imaging studies.[6,8] The more advanced technique of ultrasound biomicroscopy, more likely to be available in ophthalmologic specialty centers than in general EDs, also has been shown to be helpful in foreign body imaging. The sensitivity of this modality is sufficient to detect foreign bodies not visible by direct or indirect ophthalmologic examination, traditional B-scan ultrasonography, or CT.[11] In light ofthe lack of reported case series and justifiable concerns about eye damage from mobilization of ferromagnetic foreign objects,[14] use of magnetic resonance imaging (MRI) for ophthalmologic foreign body imaging remains controversial.[7]

In some cases, orbital trauma is associated with central nervous system injury. When the workup indicates potential for injury or foreign body involving the brain, imaging of the intracranial compartment should be performed.[15]

Management. In nearly all cases, appropriate therapy consists of removal of the foreign body. If the object is located on the bulbar or palpebral conjunctiva (*not* the cornea), it often can be removed easily by sweeping the site with a moist cotton-tipped applicator. Usually, other instruments are required (Fig. 57-2). Occasionally, if the foreign body is large, it may be extracted with forceps. For small corneal foreign bodies, after application of a topical anesthetic, it is often necessary to use an eye spud or small-gauge needle, inserted gently underneath one end of the object, to pick it out; magnification usually is helpful. If this is unsuccessful or if the foreign body is deeply embedded, the patient should be referred for object removal by an ophthalmologist within 24 to 48 hours. This is particularly true with metallic foreign bodies, early removal of which decreases the size of the rust ring. Overly vigorous attempts at removal may lead to anterior chamber perforation. Avoidance of significant corneal procedures is prudent in patients who have had a laser-assisted in situ keratomileusis (LASIK) procedure to correct nearsightedness.

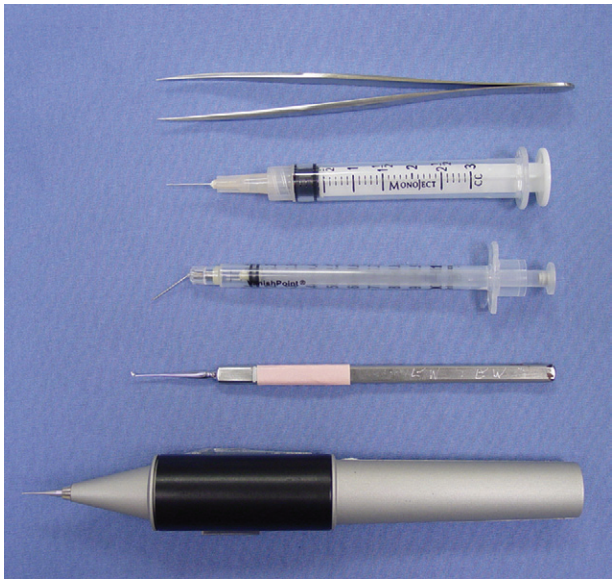


Figure 57-2. Instruments for removal of an ocular foreign object. *Top to bottom*: Forceps, needle (straight or bent) mounted on a syringe "handle," angled eye spud, and rotating straight-tip eye spud.

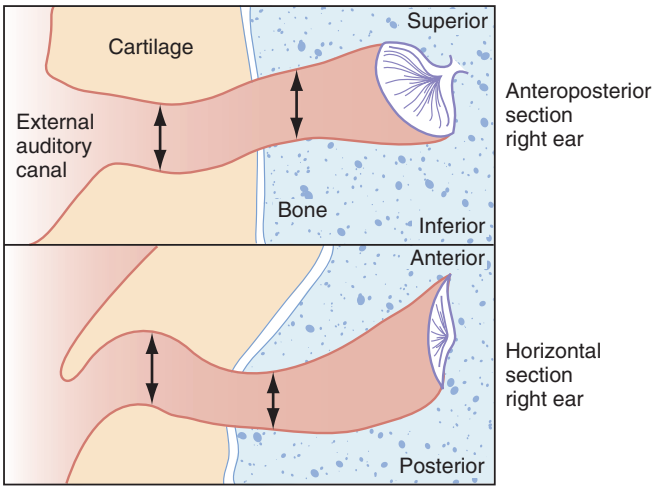


Figure 57-3. Horizontal and vertical cross sections of the external ear canal showing points of anatomic narrowing *(arrows)*.

After the removal of a corneal foreign body that leaves no rust ring, treatment is essentially the same as for corneal abrasion. In cases in which foreign bodies may have elicited an allergic response, topical steroids have been used. Therapy for patients with a rust ring is controversial. ED management should be dictated either by standing protocol (designed in collaboration with ophthalmologists) or by in-hospital ophthalmologic consultation. Otherwise, it is prudent to recommend evaluation within 24 to 48 hours by an ophthalmologist to consider removal of retained rust.

Ear

Clinical Features. Foreign bodies of the ear are more likely to prove problematic for ED management than foreign bodies in other locations. The difficulty has little to do with diagnosis. Rather, the problem is the need to remove objects from a sensitive anatomic area in an often uncooperative patient population.[16] In terms of specific objects found in ears, different series list varying culprits, but common findings include insects, beans, plastic toys, and small spherical objects such as pearls, pebbles, or beads.[17]

History. Patients usually state that something is in the ear. If the foreign body is an insect, the patient may feel motion or hear buzzing, although less specific complaints may include itching, discharge, or otalgia. Similar secondary symptoms may be reported when noninsect foreign bodies are lodged in the ear canal. This type of presentation is especially common in children, who may fear telling of foreign object insertion into the ear; the problem is ignored until secondary problems prompt a visit to the ED.

In patients with ear complaints and travel or camping history or poor living conditions, geographic information may suggest insects inhabiting the external ear canal. Infestation with Korean or Middle Eastern mites, Malaysian ticks, and Omani beetles has been associated with various degrees of morbidity in patients spending time in those regions.[4,18,19] In most U.S. cases, the cockroach is the culprit.[16,18,20]

Patients with foreign bodies in the ear may present with secondary symptoms related to pathologic changes in adjacent structures. Malocclusion may be the chief complaint if the foreign body erodes to the temporomandibular joint.[21] Similar erosion has caused otic foreign bodies to manifest as eustachian tube dysfunction, parapharyngeal abscess, or mastoiditis with progression to fatal brain abscess and meningitis.[22,23] Such events are rare.

It is important to ask patients about previous attempts at foreign body removal, because these efforts may have caused further problems. Poorly executed attempts at foreign body removal may injure the ear canal, perforate the tympanic membrane, or merely push the foreign body deeper into the canal. Irrigation may cause enlargement of the foreign object, especially if it is vegetable matter.

Physical Examination. The external auditory canal is cylindrical with an elliptical cross section (Fig. 57-3). A thin layer of sensitive epithelium covers an outermost cartilaginous portion and an inner bony segment. Two anatomic points of narrowing (and foreign object lodging) are present within the canal: (1) near the inner end of the cartilaginous portion of the canal and (2) at the point of bony narrowing called the *isthmus*.

The first factor crucial to successful examination is adequate lighting that can be directed by the operator. This may be a strong light source and a head mirror, a headlamp, an operating otoscope, or an operating microscope. A large-size speculum is essential to obtain an adequate field of view and to enable four-quadrant injection of local ear canal anesthesia when necessary for foreign body removal. As with any examination involving the external auditory canal, the pinna of the ear is grasped and then retracted in a posterosuperior direction to straighten the canal and afford a more complete view.

Inspection of the tympanic membrane is important because it may have been ruptured by the foreign object or by previous removal attempts.[4,24] If so, medical documentation should indicate that this injury was present before attempts at foreign object removal. As in other body locations (especially the nose), the risk of multiple foreign objects is such that if one foreign object is identified, a search for additional material is warranted.[24,25]

Diagnostic Strategies. Diagnostic imaging rarely plays a role in the ED workup of suspected otic foreign bodies. The primary indication is to identify complications from foreign body presence. CT or MRI may be performed to characterize infectious or erosive sequelae of ear canal foreign objects.

Management. In most cases, foreign body removal attempts may be instituted in the ED. Neither presence of the foreign

body for more than a day nor very young patient age (younger than 4 years) constitutes an independent risk factor for foreign body removal failure or complications; the emergency physician may thus proceed with removal efforts if not otherwise contraindicated.[26] The patient should be informed about the extreme sensitivity of the auditory passage and the likely discomfort and potential for minor bleeding. Sedation may be important to minimize patient discomfort and reduce risks of iatrogenic trauma. Lidocaine instillation may aid in topical anesthesia; liquid 1 or 2% solution is preferred to gel preparations, which impair visualization. Less often, foreign body removal requires local anesthesia of the external ear canal. The anesthesia instillation procedure, which may cause patient discomfort and iatrogenic injury, is performed by injecting all four quadrants of the canal with lidocaine using a tuberculin syringe inserted through an otic speculum. In cases of a refractory foreign body and an uncooperative patient, definitive management should be performed with procedural sedation or even general anesthesia. Although the evidence is not universally consistent, available data suggest that approximately 95% of aural foreign bodies can be removed without the need for general anesthesia.[17,26]

When the ear canal is inhabited by an insect, it is important to kill or immobilize the creature to facilitate its removal. Such precautions reduce the chance of patient discomfort or ear damage caused by an insect attempting to evade forceps introduced into the ear canal. Different immobilizing agents have different reported success rates. Efficacious formulations include lidocaine as a 10% spray or less concentrated liquid, 2% lidocaine gel, mineral oil with 2% or 4% lidocaine, and alcohol.[4]

Any of several extrication methods may prove effective, and various instruments may be useful (Fig. 57-4). Small objects often can be removed by the application of suction with a small plastic catheter. With soft or irregularly shaped objects, it often is possible to grasp the foreign body with forceps (alligator forceps may be best) and remove it either in one piece or in fragments. If the object cannot be grasped, removal may be possible by passing a blunt-tipped right-angle hook beyond the foreign body and then gently coaxing it out. Alternatively, a balloon-tipped catheter can be passed distal to the object, with subsequent attempts to withdraw the (inflated) balloon and extract the object. Any balloon-tipped catheter design may be used, so long as its caliber is small enough (approximately 18 gauge or less) to allow comfortable introduction into the ear canal; a typical commercial device is shown in Figure 57-5.

Indirect methods for foreign body removal also have been used with some success. The irrigation technique takes advantage of the elliptical shape of the external ear canal. A stream of room-temperature water or saline should be directed at the (nonvegetable) foreign body periphery, using a 20 mL syringe and a 14- or 16-gauge catheter (this setup is safe in terms of pressure on the tympanic membrane).[27] The hope with irrigation is that the jet of water will be directed past the object, against the tympanic membrane, and finally against the posterior aspect of the foreign body, driving it out of the canal. In a study examining the use of an electric ear syringe for removal of foreign bodies from the ear canal, the syringe outperformed the other techniques used for comparison.[28] No significant complications were reported with use of this technique, and it was well tolerated by children and adults. This modality should not be used in patients with a known history of or clinically suspected tympanic membrane perforation.

Removal of objects from the middle ear with cyanoacrylate adhesive–tipped swabs has been recommended in the past. This technique carries the risk, however, of contaminating the ear canal with a substance that is difficult to remove and has been associated with tympanic membrane rupture.[29,30] Insufficient evidence exists to condone or condemn this technique.

If these methods are unsuccessful or if the patient, especially a child, is uncooperative or in undue distress even with procedural sedation, removal efforts should cease and the patient should be referred to an otolaryngologist. In most cases, the patient should be discharged directly to the otolaryngologist's office. If the clinical scenario (e.g., acceptable patient comfort level, low-risk foreign body) seems to be amenable to nonemergent follow-up, arrangements should be made for the patient to see the otolaryngologist in a day or two. Rates of operative intervention vary in published series. Studies' case mix differences probably are responsible for the varying rates (from 5 to 33%) of reported need for surgical removal of otic foreign bodies.[17,20,26]

Inappropriately prolonged efforts at foreign object removal can result in wasted time, unnecessary patient discomfort, and high potential for complications as previously noted. Patient apprehension, distal foreign body movement, or damage to the ear canal (including induction of edema) may prompt surgical intervention that would have been otherwise unnecessary.[16,31]

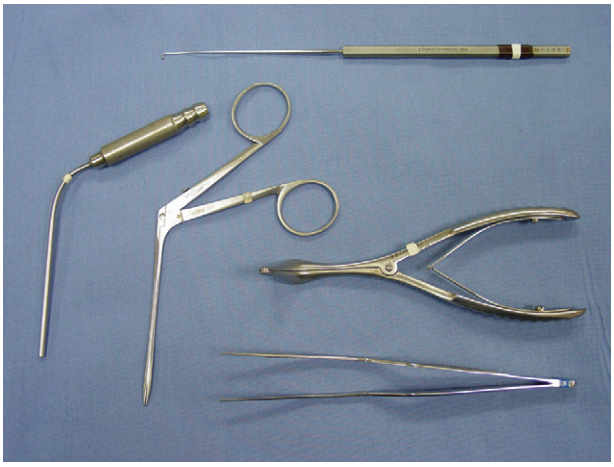


Figure 57-4. Instruments that may be useful for removal of a foreign body from ear canal or nares. *Clockwise from left:* Right-angle probe, suction catheter, alligator forceps, nasal speculum, and bayonet forceps.

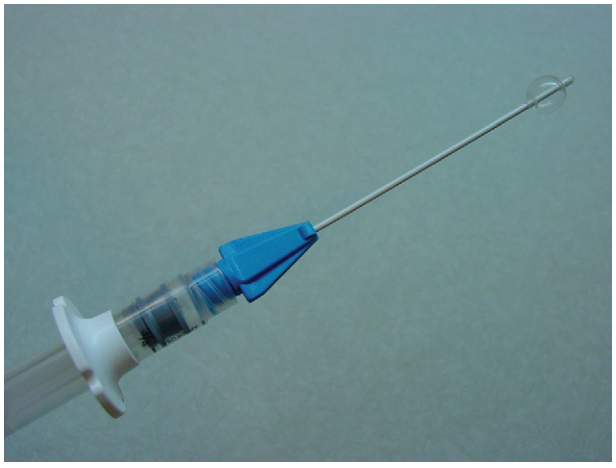


Figure 57-5. Balloon-tipped catheter, which can be used for removal of otic or nasal foreign bodies.

Otic foreign bodies are associated with many sequelae, but these usually are not serious. The most commonly occurring complications in pediatric series are external ear canal bleeding (approximately 16%), otitis externa (6%), and tympanic membrane perforation (2%).[17] One large series suggests that, perhaps as a result of relative delay in seeking medical attention, otitis externa is significantly more likely in adults than in children.[32]

After removal of the foreign body, canal examination should be repeated to ensure the absence of retained material and to evaluate otic anatomy. In cases in which the tympanic membrane is ruptured and the middle ear is at risk for infection, appropriate oral antibiotics are recommended. Topical antimicrobial therapy decreases the risk of external otitis; one method packs the meatus with ribbon gauze impregnated with a broad-spectrum antibiotic.[4] Follow-up evaluation should occur within 2 to 3 days for cases involving tympanic membrane rupture, or those in which foreign body removal was traumatic (to assess for external otitis).

Nose

Clinical Features. The nose is perhaps the most common site for the insertion of foreign bodies by children.[33] Among the nasal objects found most frequently are beans, sponge pieces, pebbles, plastic toy fragments, and other small round objects.[34] Perhaps because most people are right-handed, most nasal foreign bodies are right-sided.[25,35] Compared with patients with ear canal foreign bodies, children with nasal foreign bodies tend to be younger (most commonly younger than 5 years of age).[24,25]

Nasal foreign bodies are less problematic than foreign bodies in other locations. ED removal is nearly always successful, and with proper technique (e.g., care to avoid aspiration), serious sequelae are rare.[35] The infrequently encountered cases involving intranasal insertion of an alkaline button battery, which may cause electrical or chemical burns with liquefaction necrosis or may be accidentally aspirated during attempts at removal, constitute an exception to this rule.[24,34,36,37]

History. Although most patients seek medical attention within 24 hours, patients with nasal (versus otic) foreign bodies are more likely to present with secondary symptoms and delays of 1 week.[24] In fact, nasal foreign bodies may be asymptomatic, identified as incidental findings on imaging studies obtained for other purposes.

Patients seen in the ED with a nasal foreign body usually have one of two histories. With the first type of presentation, the patient admits to, or is seen, placing an intranasal object. This is the most common history. Other patients present with a constellation of signs and symptoms: purulent, unilateral, malodorous nasal discharge or even persistent epistaxis. These patients often are misdiagnosed and treated with antibiotics for supposed sinusitis. Unresolving sinusitis despite appropriate antibiotic therapy should alert the emergency physician to the possibility of nasal foreign body.[24]

Foreign objects placed intranasally may purposefully or inadvertently end up in the sinuses. These foreign bodies require more invasive intervention, and psychiatric evaluation of the patient may be indicated when self-injury is suspected. When the history suggests a foreign body but none is identified on nares examination, imaging the sinuses should be considered.

Physical Examination. As with foreign bodies of the ear canal, it is important to prepare the patient (and the parents) for examination and subsequent removal attempts. Because of risks of iatrogenic movement of the foreign body further posteriorly or into the airway, children may need to be restrained to permit the examination. Physical examination sometimes can be delayed until after insufflation of the nares is attempted. The nasal mucosa normally is quite sensitive, and this sensitivity is increased by any infection or irritation. Examination is facilitated by provision of topical anesthesia and vasoconstriction to the nasal mucosa. Examination should include both nares, with adequate lighting and visualization using a nasal speculum. The presence of the foreign body and any secondary tissue damage should be noted. Necrosis of the nasal mucosa and septum may accompany button battery impaction.[37] During the examination, care is taken not to dislodge or drive the foreign body posteriorly into the nasopharynx and risk aspiration. In some circumstances, it may be prudent to place patients in lateral decubitus, perhaps with additional Trendelenburg positioning, to help prevent aspiration of objects that are pushed into the posterior pharynx.

Diagnostic Strategies. Diagnostic imaging does not play a major role. When intrasinus foreign bodies are suspected, CT can be helpful. Rarely, CT or MRI may be indicated to visualize suspected foreign bodies or their complications.

Management. In most cases, removal of a nasal foreign body is readily and safely accomplished in the ED. Although the avoidance of iatrogenic injury is paramount, the structures local to an intranasal foreign body are not as sensitive or easily damaged as structures in other body cavities (e.g., the ear canal) that may harbor foreign objects. Accordingly, the need for subspecialty consultation and operating room removal is rare.[24,25,34]

Occasionally, positive pressure applied to the patient's mouth achieves rapid foreign body dislodgment while obviating the need for restraint, sedation, and other requirements attendant to more invasive removal techniques. This technique is a quick and safe primary intervention. The underlying principle is that a short burst of air blown into the mouth of a child, with finger occlusion of the nonobstructed naris, may force the foreign object out of the nose. Pretreatment with vasoconstrictive spray may improve the chances of success.[38] The insufflation, preferably applied as a "kiss" from a parent, also can be provided by a manual ventilation bag. The insufflation technique is quite useful, particularly in preschoolers, who are likely to be uncooperative with other removal modalities. Many children can be instructed to take a deep breath and blow hard through the nose as a parent closes the unaffected naris. An otherwise troublesome removal often can be accomplished quickly and easily by this method.[33,38,39]

When positive-pressure insufflation is not warranted or is unsuccessful, use of instruments and specialized removal techniques may be required (see Figs. 57-4 and 57-5).[34] Regardless of the method, the patient (usually a child) may benefit from some combination of restraint, sedation, and pretreatment with vasoconstrictive (e.g., nebulized racemic epinephrine) and anesthetic (e.g., benzocaine spray) agents.[38] Adequate illumination is essential. Necessary instruments include a blunt-tipped right-angle probe, suction catheter, and alligator forceps. The forceps is used when the foreign body is to be directly grasped, and the right-angle probe is used in an attempt to reach proximal to the foreign object and displace it forward. Other useful instruments include Fogarty (vascular) and Foley catheters; "specialized" balloon-tipped catheters also are available in many EDs (see Fig. 57-5).[25,34] Suction is necessary primarily for removing purulent secretions and any blood that may obscure the field. In some cases, suction can be used to withdraw foreign bodies directly. Suction may be useful with hard-to-grasp objects or small soft objects not tightly lodged in place. The use of cyanoacrylate-tipped swabs may be useful in certain circumstances. As noted previously with respect to

otic foreign bodies, the available evidence is insufficient to permit definitive conclusions about this approach.

Airway

Clinical Features. Although improved diagnostic and therapeutic techniques have markedly reduced fatality rates from foreign body inhalation, airway tract foreign objects still cause a significant number of deaths and cases of anoxic brain damage annually. In a large-city series of ambulance-transported patients with an airway foreign body, a 3.3% mortality rate (an average of one patient per month) even before arrival at the ED was reported.[40]

Alternatively, airway foreign objects can manifest less dramatically than acute respiratory distress and can go undiagnosed for years. Delayed diagnosis is common. Only one half of the patients in a pediatric series of lower respiratory tract foreign body presented within 1 day of aspiration; an additional 20% presented during the first week, and another 20% presented after a delay of more than 1 week.[41] Patients with uncharacteristic presentations may have unusual foreign body introduction mechanisms, such as ingestion or penetrating trauma.[1] Patients with altered mental status from a variety of causative disorders are at risk for occult aspiration, which may be difficult to diagnose.

The most common airway foreign bodies in one series were ingestible agents, primarily meats and medications.[40] Airway foreign body series also identify pins, needles, jewelry, thermometers, pencils, and metal and plastic toys. The primary reason to characterize the type of airway foreign object is to determine the likelihood of radiopacity. Most airway foreign bodies are not visible on plain films.[42-45] In an 8-year pediatric series of foreign body aspiration, the most commonly identified objects were nuts (59%) or other vegetable material (23%) not likely to be visualized on plain films. In another classic paper describing childhood asphyxiation with foreign bodies, nearly one half of fatal choking cases were due to food aspiration, with hot dogs (17%), candy (10%), nuts (9%), and grapes (8%) most prominent.[44] In a third report, the foreign body was organic (usually nut) in nature in more than 90% of cases of pediatric aspiration.[45]

Airway foreign bodies are seen more commonly in pediatric patients.[46] In a case series covering 2 decades, 75% of patients were younger than 9 years of age.[45] Peak incidence of aspiration is in the second year of life, with a brisk decline after the age of 3 years.[45,46] Mastication difficulty secondary to premature molar teeth contributes to pediatric food aspiration.[41] Also, the fact that children explore their environment with their hands and mouth translates into aspiration of nonfood objects. In adults, the peak aspiration incidence is in the elderly.[40] Some evidence suggests that adults are more likely than children to have nonfood items aspirated into the airway.[47]

Children and adults also differ with respect to anatomic location of aspirated foreign bodies. Recognition of this difference is crucial because foreign body location plays a major role in determining associated morbidity or mortality risk. In adults, 75% of foreign bodies lodge in the proximal airways (larynx, trachea, main bronchi). In children, less than one half of foreign objects are located proximally, with bronchial tree locations the most common.[45,46]

Foreign bodies can be located as proximally as the oropharynx, with retained intraoral bodies found in the medial pterygoid space.[48] The foreign object can be slightly distal, causing airway obstruction at the laryngeal or subglottic level. Foreign body impaction at this level often is caused by inappropriately executed attempts to finger sweep an oropharyngeal foreign body.[47] Subglottic foreign bodies are difficult to identify and may be associated with diagnostic delay in most cases.[49] It is important to recognize relevant historical clues to differentiate epiglottitis, asthma, and laryngotracheobronchitis from subglottic foreign body.

Airway foreign bodies usually pass beyond the laryngeal inlet[47] and may cause drastic obstruction. Unfortunately, tracheal foreign bodies are associated with a surprisingly high incidence of lack of symptoms or worrisome clinical findings.[43] Foreign bodies that pass beyond the trachea are less likely to cause acute hypoxic crisis but can lead to substantial respiratory embarrassment and can be difficult to remove. In adults, bronchial foreign bodies are found more often in the right bronchial tree. In one large series, 69% of bronchial foreign bodies were right-sided.[45] Because the main bronchi branch from the trachea at more equal angles in children, occurrence rates for the left-right distribution of lower airway foreign bodies are approximately equal.[41,43] Foreign objects can be bilateral, with 3.6% of patients in one series found to have foreign bodies in right and left main bronchi.[45]

History. Clinical presentation can range from chronic nonspecific respiratory complaints to acute airway obstruction.[50] In most aspiration cases, foreign body presence is suspected after a thorough history. The most dramatic cases typically involve a history of what is commonly termed the "café coronary": The patient attempts to swallow a food (usually meat) bolus larger than the esophagus can accept. The bolus lodges in the hypopharynx or trachea. Often there is confusion over whether the patient is having a myocardial infarction or has an obstructing foreign body, but the conscious cardiac patient is able to speak. Patients with airway foreign bodies may exhibit noisy breathing, inspiratory stridor, vomiting, and possibly slight hemoptysis.[40]

Some patients may give a history similar to that in café coronary, with resolution of major symptoms. These symptoms—a choking sensation accompanied by respiratory distress with coughing, wheezing, and dyspnea—occur in up to one half of patients who aspirate and are collectively known as the *penetration syndrome* (object penetrates airspace).[45] Symptom resolution may result from spontaneous clearance of the foreign body by coughing. In some cases, coughing does not eject the foreign body completely but rather results in its impaction in the subglottic region.[47] A retained airway foreign object should be considered in cases in which the patient history is one of perceived foreign body followed by cough with incomplete (or even complete) post-tussive symptom resolution.

In a 20-year series of adult and pediatric patients with suspected foreign body aspiration, sudden onset of choking and intractable cough were present in one half of the cases, with eventual foreign body identification.[45] In addition to coughing and choking, stridor is a frequent component of an acute aspiration episode in patients of all ages.[47] Symptom distribution is similar in adult and in pediatric patients,[45] but choking and wheezing appear more prominently in the pediatric literature. In a series of 87 pediatric patients with suspected foreign body, 96% had a history of a choking crisis.[43] Wheezing is common, having been reported in up to 75% of patients from 8 to 66 months of age with airway foreign bodies.[41,46]

Most patients who have aspirated objects have persistent symptoms (e.g., cough, wheezing, dyspnea) after manifesting penetration syndrome, but 20% have no ongoing symptoms.[45] Many patients have a history of alarming symptoms followed by few ongoing complaints; an aspirated foreign body should not be dismissed from consideration in such patients. With dyspnea and odynophagia of sudden onset, subglottic impaction of the object should be suspected. If the object is known to be sharp and thin, the possibility that it has become embedded between the vocal cords or in the subglot-

tic region, with resultant partial obstruction, also should be considered.[47]

Other components of the history may provide clues to airway foreign body presence and location. Even when the history cannot be obtained directly or does not suggest an aspirated foreign object, the presence of a foreign body can be inferred in certain patients. Trauma patients who present to the ED with injured, loose, or missing teeth may have aspirated in the field, or during emergency laryngoscopy and oral intubation.[45] Besides the intubated or obtunded patient with only indirect historical evidence of aspiration, conscious and alert patients may not give a direct history of aspiration owing to lack of dramatic airway symptoms or remoteness of the aspiration event and onset of secondary problems (e.g., pneumonia). In some cases, such as penetrating trauma or blast injuries, the patient may be unaware of the potential for aspiration and not attribute symptoms to this entity.[42] Patients who aspirate needles may have minimal or no symptoms, with chronic hemoptysis or odynophagia the only manifestation of these or similar foreign bodies.[45,47]

The available evidence is conflicting regarding the role of neurologic disease in aspiration. Patients with deficits may be unaware of or unable to report problems such as denture displacement; this inability has been associated with disastrous results in the case of airway obstruction from dental hardware.[51] Neurologic impairment may result in atypical or absent history in cases of foreign body aspiration.[42] Reports of adult[45] and pediatric[43] series have identified little role, however, for neurologic impairment in foreign body aspiration. An atypical history is a concern in neurologically impaired patients, but the problem of foreign body aspiration with atypical history is uncommon in this patient population.

Onset of respiratory difficulty after eating in a child can present a diagnostic dilemma. Children with stridor or other respiratory symptoms may have esophageal bolus impaction. The pediatric trachea is soft, especially posteriorly, and may be compressed by a large esophageal body pressing anteriorly on the trachea. In addition, the trachea itself may be displaced anteriorly and kinked, causing a partial obstruction.

Other components of the history can help diagnose and characterize foreign bodies in patients with aspiration of nonfood objects. These items may be aspirated by children who are exploring their environment, by psychiatric patients, or by persons who normally "store" small items in their mouths. The last group includes repairmen, construction workers, seamstresses, and others who may keep nails, pins, and other paraphernalia in the mouth for quick access.

Regardless of the nature of the foreign body, patients with a retained airway foreign object may present only with infectious complications. A foreign object may cause retropharyngeal abscess. With pathology located more distally in the airway tract, a patient with atypical or recurrent pneumonia may have pulmonary infection secondary to persistence of a foreign object serving as a nidus of infection. In some cases, the respiratory infection associated with retained pulmonary foreign body is silent but seeds distant organs with organisms, raising suspicion for an airway foreign body. In patients with *Eikenella corrodens* brain abscess, clinically occult respiratory foreign bodies have been found.[52]

Patients may present to the ED with a diagnosis of a disease thought to be infectious but actually may have foreign bodies in the airway. A careful history should be obtained in the setting of suspected croup or epiglottitis because a foreign body in the trachea or larynx may have a clinical presentation similar to that with these infectious entities.

Physical Examination. Physical findings depend on degree of airway obstruction and duration of the object's presence in the respiratory system. Small objects causing no obstruction may produce no findings or may manifest as infectious complications. In many cases, however, the physical assessment is helpful in diagnosis and characterization of airway foreign bodies.

Cyanosis is present in 10% and coughing, audible wheezing, or overt respiratory distress is noted in 25 to 37% of patients with aspirated objects.[45,46] Unilateral diminution of breath sounds, when present, is a useful identifier of aspirated foreign body.[50] Patients with upper airway foreign objects may be stridorous or hoarse, and sternal retractions may be noted in patients with intratracheal foreign bodies.[40] More than one half of children in one series had initial oxygen saturation values of 95% or less.[45] Patients with secondary infection may have fever.

Oropharyngeal examination may reveal a foreign body posteriorly or "donor sites" of fractured teeth. The examination should include a search for fractured or missing dental prostheses, which sometimes can be lodged in pharyngeal areas for days and can account for sudden deterioration in status when the airway suddenly becomes occluded, as can occur after coughing.[51] Oropharyngeal examination frequently can be augmented by indirect or direct laryngoscopy or nasopharyngoscopy, but these procedures should be performed only if the associated stress is unlikely to pose undue risk of airway compromise. Furthermore, laryngoscopy or nasopharyngoscopy should be undertaken only if definitive airway management equipment and expertise are readily available. The advantage of these modalities is that they allow excellent visualization of the proximal airway, which is important diagnostically and therapeutically. Indirect laryngoscopy can be useful in detection of radiolucent structures.

Assessment of the neck may reveal accessory muscle use. Tracheal palpation may reveal a thud, indicating movement of a mobile foreign body against the tracheal wall. Abnormal inspiratory sounds may be heard on tracheal auscultation.[47] Coughing may result from local irritation caused by bronchial foreign bodies. Localized or apparently generalized wheezing is frequently auscultated in patients with lower respiratory tract foreign bodies.[46] It is important to keep in mind the dictum that "all that wheezes is not asthma." If a main bronchus is completely obstructed, breath sounds are absent on the involved side. Occasionally a foreign body acts as a one-way valve, allowing air into the lung during inspiration but permitting none to exit during expiration. The involved lung becomes hyperexpanded, which may be detected as hyperresonance to percussion.

Diagnostic Imaging. In the stable patient, plain radiography of the neck and chest remains the mainstay of airway foreign body imaging.[42] Air trapping may be shown when inspiratory and expiratory films are compared.[46] Other imaging techniques of potential usefulness are fluoroscopy, CT, and MRI, although bronchoscopy and microlaryngoscopy (with an operating microscope) remain the ultimate diagnostic maneuvers.[46]

A normal radiographic appearance cannot rule out an aspirated foreign body in a patient with a suggestive history. Series of patients undergoing endoscopy for suspected foreign body aspiration demonstrate mediocre sensitivity and specificity for plain radiography.[43,45,50] The radiographic evidence is indirect (as discussed in the next paragraph) in most cases; radiopaque foreign bodies were found uncommonly (less than a fourth of patients on one series).[53] This series included foreign bodies in the upper airway (at the level of the trachea); findings on plain radiographs in these patients frequently were negative.[43] If the radiopacity of the suspected foreign body is in doubt, and if the patient has brought a piece of the object, it may be

tested for radiodensity by placing it over the shoulder during taking of the radiographs.

Specific findings on plain radiography are categorized as *direct* (i.e., identification of the foreign body itself) or *indirect* (e.g., hyperinflation). Direct foreign body identification is relatively uncommon.[47] When subglottic foreign body impaction is suspected, plain soft tissue radiographic studies of the neck constitute the best initial step, provided that they are performed under the close supervision of a physician trained in provision of airway management. In some of these patients, plain radiography may definitively show an intratracheal foreign body and can provide a rapid diagnosis.[47]

Indirect or secondary signs, such as narrowing of the subglottic space from an embedded foreign object, are an important aid in foreign body radiography.[47] Air trapping and atelectasis are the most common early clues to presence of a foreign body in the airway, with bronchiectasis and bronchial stenosis developing later.[42] In air trapping, a comparison of inspiratory and expiratory films shows a flat, fixed diaphragm on the involved side, with shift of the heart and mediastinum to the uninvolved side during expiration (Fig. 57-6). In one pediatric series, air trapping was found in 90% of patients with lower airway foreign bodies, but it appears that indirect signs of airway foreign body are easily missed on initial interpretation of radiographs.[41,54,55] The small caliber of the airways may explain the relatively higher frequency of air trapping in children compared with adult patients.[45] If obstruction becomes complete, the involved lung becomes atelectatic; patients with persistent atelectasis should have foreign objects considered as the explanation. An additional indirect radiographic sign of more proximal foreign bodies is prevertebral swelling or soft tissue emphysema seen on neck films.[42]

When a foreign body is seen on the chest radiograph but its exact location (airway or esophagus) is in doubt, the anteroposterior orientation of the object may help (Fig. 57-7). Esophageal foreign bodies usually are oriented in the coronal plane, with airway objects oriented in the sagittal plane (Fig. 57-8). Radiographs also can provide useful information by showing whether the object is within or outside of the tracheal air column (Fig. 57-9).

Fluoroscopy was used historically but has been largely supplanted by bronchoscopy as a result of advances in this modality. Fluoroscopy has identified air trapping, but one case series reported a relatively low 77% sensitivity for foreign body presence using this finding.[41,42] CT, especially helical, is useful in evaluating patients with suspected airway foreign bodies when findings on plain films are negative. Even when an aspirated object is radiolucent, and often when the object cannot be identified by standard thoracic CT, helical CT has visualized the foreign body when it is of greater density than surrounding tissues. Helical CT can obviate the need for diagnostic flexible bronchoscopy, allowing direct progression to therapeutic rigid bronchoscopy for foreign object retrieval. CT also can be useful in delineating specific anatomic changes caused by foreign bodies. MRI may be useful in cases of aspiration of nuts, especially in children. The high fat content of the nut translates to its relatively easy visualization on MRI.[42]

Management. Management of an airway tract foreign body is removal, which generally leads to rapid recovery of the patient.[45] The emergency physician can accomplish removal in some patients. When the foreign object is distal to the oropharynx, however, subspecialty consultation is the safest and most expeditious means for foreign body removal. As a general rule, early bronchoscopy in any patient with a suspected foreign body is key to minimizing morbidity and mortality, and the role for endoscopic management remains important in light of limitations of other diagnostic methods.[46,50,53]

A patient with critical airway obstruction and impending or actual respiratory arrest may require immediate and definitive intervention in the ED. The three management options in such cases are (1) to attempt to extract the foreign body with maneuvers, (2) to perform laryngoscopy with attempts at removal under direct visualization, and (3) to control the patient's airway.

Some maneuvers to remove foreign bodies acutely are accomplished without direct visualization. These attempts may be directed at the proximal or distal respiratory tract. Proximal foreign body removal without direct visualization is attempted using the finger sweep, but this technique is losing favor in pediatric and adult patients. In infants, the larynx is higher, at the level of the fourth cervical vertebra; by age 4 years, it is at the C5–6 level. Blind finger sweeping has resulted in conversion of partial to complete airway obstruction when objects are displaced into the subglottic space. Finger sweeping also is less preferable in adults; abdominal thrusts and back blows are safer and at least as efficacious.[47] These procedures produce increased intraluminal pressure in the trachea, thereby forcing objects out into the pharynx, from which they are easily removed.[56]

The optimal management of a choking infant is controversial regarding whether back blows, chest thrusts, or abdominal thrusts should be the initial intervention. Data are limited, but

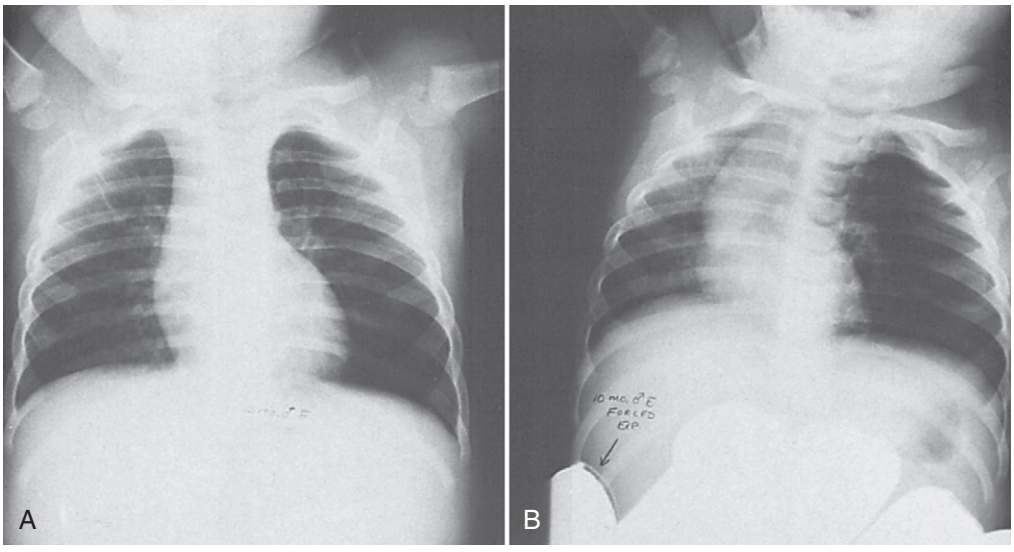


Figure 57-6. **A,** Normal-appearing inspiratory chest film obtained in a child with a foreign body in the left main bronchus. **B,** Forced expiratory view shows expanded lung on the left, with shift of the mediastinum to the uninvolved right side.

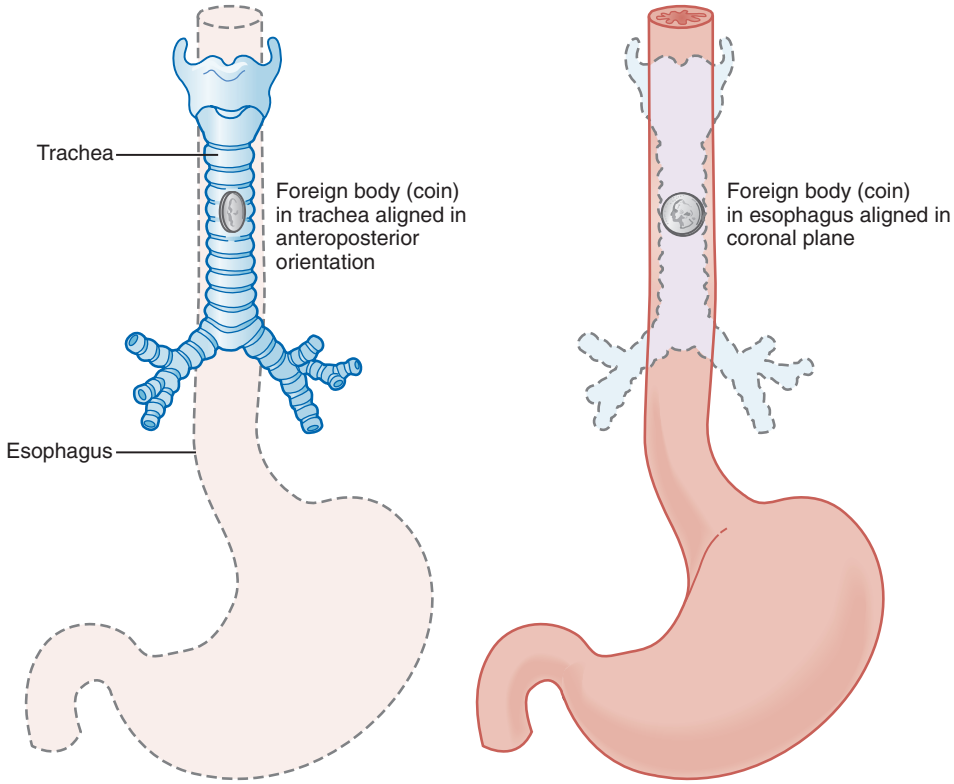


Figure 57-7. Coronal orientation of esophageal foreign object *(left)* and sagittal orientation of tracheal foreign object *(right)*.

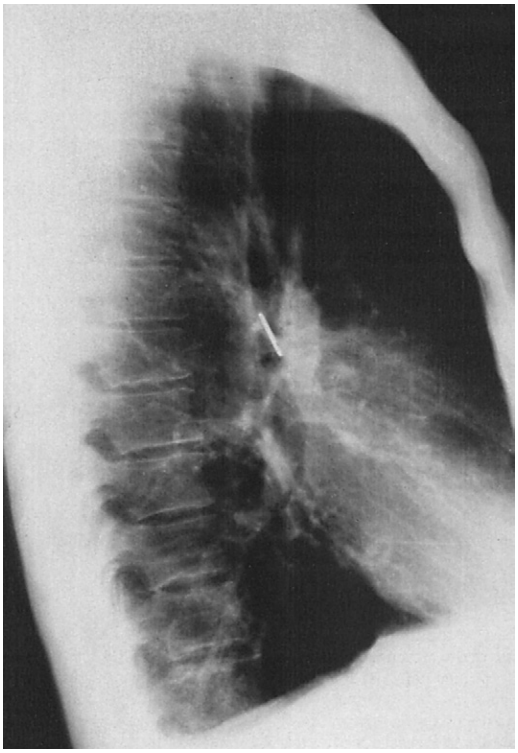


Figure 57-8. Lateral radiographic view of the chest shows an aspirated coin in the tracheal air column.

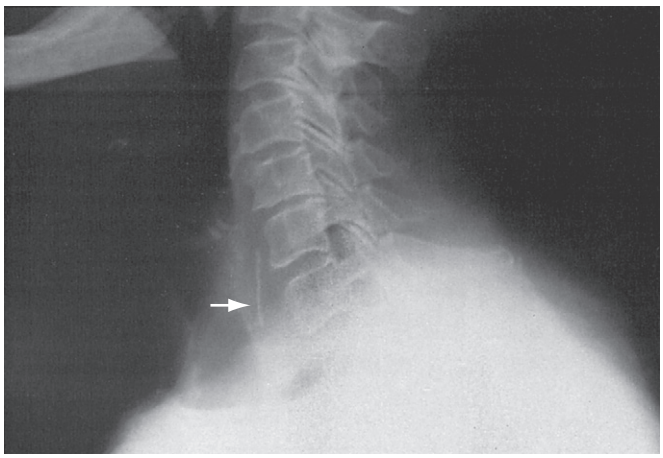


Figure 57-9. Lateral radiographic view of the neck shows a foreign body (a chicken bone) within the esophageal soft tissue shadow *(arrow)*.

the American Heart Association, the National Academy of Science, the American Academy of Pediatrics, and the American Thoracic Society recommend up to five back blows with the patient in a head-down position, followed by chest thrusts. Intubation or needle cricothyroidotomy may be performed if consistent with the setting.[57]

If indirect efforts fail to remove foreign bodies from patients in extremis, direct laryngoscopic visualization during intubation may reveal a proximal foreign object that can be removed with Magill forceps.[40] If a foreign body is not visualized on laryngoscopy, intubation of the patient may be indicated. Intubation may force the foreign body distally, especially if the endotracheal tube tip is passed beyond the carina. Placement of the endotracheal tube into the right main bronchus may displace the foreign body into the right bronchus, allowing oxygenation and ventilation through the left-sided pulmonary tree when the endotracheal tube is withdrawn back to normal position proximal to the carina. In cases in which intubation fails because of positioning of the foreign object, surgical cricothyrotomy (needle cricothyrotomy in young children) is indicated. Cricothyrotomy may bypass proximal obstruction,

allowing sufficient oxygenation to bridge the time gap to definitive care by surgical subspecialists.

Patients who do not require immediate intubation or cricothyrotomy for complete airway obstruction may benefit from airway management for other indications. These patients may have poor oxygenation or may require assisted ventilations during transport to surgery. In either case, if airway obstruction is not too proximal or too complete, placement of a laryngeal mask airway should be considered. The laryngeal mask airway offers easy airway access, excellent visualization, and safe respiratory management during bronchoscopic procedures. The laryngeal mask airway allows use of larger bronchoscopes than those employed in intubated children. Especially in pediatric patients requiring bronchoscopy, the laryngeal mask airway may be an appropriate airway.[45]

In noncritical situations, the only airway foreign objects generally amenable to removal in the ED are those in the oropharynx, which are best removed by forceps under direct laryngoscopic visualization after topical anesthesia is achieved. Care should be taken when foreign objects appear to be impaled in the oropharynx because postremoval hemorrhage is a possibility. Also, special care should be taken to prevent posterior displacement of oropharyngeal foreign objects or dropping of incompletely grasped foreign bodies into the airway. These mishaps are more likely to occur in patients who are uncooperative; in these patients, subspecialty consultation for removal in the operating room is the best course. Removal of a laryngeal foreign object, even with the patient under general anesthesia, can be dangerous. Operative risks include hemorrhage, laryngeal trauma, and airway obstruction from the mobilized foreign object; subspecialty consultation also is indicated for laryngeal foreign body removal.[47]

The management decisions for endoscopic evaluation and treatment depend on the clinical presentation. An emerging standard is initial use of rigid bronchoscopy in time-critical airway obstruction, with flexible instrumentation used for diagnostic purposes in less acute situations.[46] The emergency medicine specialist may have requisite expertise to perform flexible bronchoscopy in occasional low-risk cases, but consultants have broader experience, as well as facility with potentially useful adjuncts such as cinefluoroscopy.[58] In patients in whom overall clinical suspicion is low, fiberoptic bronchoscopy may be indicated, but rigid bronchoscopy is the optimal first step when clinical suspicion is high.[41] Foreign body removal usually is achieved using rigid bronchoscopy with the patient under general anesthesia, but in unusual circumstances, flexible bronchoscopy with use of local anesthesia may suffice for foreign body location and removal.[45]

Even after foreign body removal, late complications may occur. Injury from airway fish bones, even after removal, can lead to deep tissue infection, such as cervical spondylodiskitis.[59] Patients in whom an airway foreign body was removed should be observed for development of sequelae, with postdischarge follow-up evaluation within a few days for reassessment. In pediatric patients, education should focus on preventive efforts to reduce the likelihood of a repeated aspiration episode.

Gastrointestinal Tract

Foreign bodies in the gastrointestinal tract can be seen in all age groups, although most cases occur in pediatric patients.[60] No predisposing anatomic or pathologic conditions have been identified. Series have noted, however, that in addition to younger persons, those at highest risk include edentulous, incarcerated, and psychiatric patients.[61-63]

Complications associated with foreign body ingestion account for an estimated 1500 deaths annually in the United States.[64] Perforation occurs in approximately 3% of cases and most frequently involves the esophagus or the ileocecal region.[65] Because ingested objects are expected to pass spontaneously in the vast majority of patients with normal anatomy, initial management usually is expectant, with radiographic and stool follow-up examinations to confirm passage.[65,66] Direct foreign body removal using surgical intervention usually is unnecessary, although some treatment centers pursue early operative intervention for impacted esophageal objects including coins.[67] In pediatric series, endoscopy—including esophagoscopy, laryngoscopy, and anoscopy—tends to be successful in removing the foreign body in nearly all cases.[66-68] Early endoscopy usually should be undertaken in cases of potential toxicity (e.g., button battery ingestion), altered anatomy (e.g., previous abdominal surgery), or sharp foreign bodies.

Pharynx and Esophagus

Foreign bodies lodged in the pharynx and esophagus are usually a sharp object (e.g., fishbone) that is impaled in the wall of the pharynx, hypopharynx, or esophagus or a larger bolus, usually a coin or food, that cannot pass beyond the anatomic points of esophageal constriction. Pediatric series analyzing both witnessed and unwitnessed ingestion of esophageal foreign bodies report that coins are the most common culprit, typically accounting for more than one half of the cases.[66,67] Esophageal constriction locations, where foreign objects tend to lodge, are (1) the proximal esophagus at the level of the cricopharyngeal muscle and thoracic inlet or, radiographically, the clavicular level; (2) the midesophagus at the level of the aortic arch and carina; and (3) the distal esophagus just proximal to the esophagogastric junction, or radiographically a level two to four vertebral bodies cephalic to the gastric bubble. Foreign bodies may lodge at any level of the esophagus (or remainder of the gastrointestinal tract) with abnormal anatomy. The complication rate for esophageal foreign body ingestion is estimated at less than 2%, but the sequelae can be severe. Complications become more likely with increasing impaction time and include esophageal erosion or perforation, tracheal compression, mediastinitis, esophagus-to-airway or esophagus-to-vascular fistulas, extraluminal migration, and formation of strictures or false esophageal diverticula.[67,69]

History. A useful history usually is available from the patient or a caregiver. Because natural curiosity leads them to ingest myriad nonfood items, children are particularly likely to present with esophageal foreign bodies. The object most often encountered is a coin.[66,67] Other common objects are foods, toys, bones, batteries, wood, and glass.[70,71] In a series of 104 consecutive cases, one third of the esophageal foreign bodies were sharp objects.[64] In situations in which the history is unclear, ingested foreign body should be considered in the differential diagnosis for atypical chest pain.[72]

Esophageal rupture is a particular risk with ingestion of a button (disk) battery.[3] These batteries cause pathologic changes through pressure, electrical current, corrosive leakage, or heavy metal poisoning.[60] Batteries containing potassium can produce liquefaction necrosis, and batteries containing mercury can cause mercury poisoning.[73] The identification of button batteries has both prognostic and therapeutic ramifications—esophageal button battery impaction is an indication for prompt endoscopic intervention.[60] Although not as likely as button batteries or sharp foreign bodies to cause esophageal rupture, practically any ingested foreign body (e.g., meat) can cause rupture if patients experience repeated vomiting after impaction.[74]

Retention of an ingested object in place for longer than 24 hours is more likely to cause mucosal erosion, and management plans for ingested bodies are different when the objects have been in the gastrointestinal tract for a long time.[70] Children usually present to the ED within 6 hours of foreign object ingestion. The most frequent presenting manifestations are dysphagia, drooling, retching, and vomiting. Pain, usually odynophagia, may be the major complaint. Anorexia, wheezing, and chest or neck pain also may be features. Patients may complain that they can feel the object in the throat or chest and are unable to pass it any further. The victim often is able to localize the foreign body accurately, particularly in the upper esophagus, and should be asked to indicate the level of obstruction.[75] Drooling is consistent with high-grade obstruction. Patients rarely may complain of shortness of breath or air hunger resulting from a large foreign body in the esophagus impinging anteriorly and compressing the trachea. Infants and children may experience coughing, choking, and significant respiratory compromise from foreign bodies lodged in the upper esophagus.[67]

Patients may present with late sequelae. Foreign bodies serving as a nidus for infection result in complaints (e.g., fever) consistent with the infectious process.[67] Signs of mediastinitis indicate esophageal perforation. Perforation of the esophagus with erosion into the vasculature or pulmonary tree can result in presentations ranging in severity from hemoptysis to pulmonary abscess to life-threatening hemorrhage.[76,77]

The history should include any known esophageal anatomic abnormality or previous instrumentation. A patient with a history of esophageal stenting should be considered to have stent migration when the presenting complaint is dysphagia. Migration typically occurs within the first week of placement but has been reported up to 1 year after initial placement.[78]

Physical Examination. Examination begins with a careful search of the pharynx and hypopharynx. This search may reveal the foreign body or identify an oropharyngeal mucosal scratch that can cause foreign body symptoms even in the absence of an impacted object. Oropharyngeal examination also may provide indirect clues; for example, a missing dental plate should suggest the possibility of its presence as a gastrointestinal tract foreign object.[79] The base of the tongue, vallecula, supraglottic area, epiglottis, and piriform sinus should be examined. Topical anesthesia facilitates the examination. If adequate visualization is not obtained with the indirect laryngoscopy mirror, fiberoptic nasopharyngoscopy or direct laryngoscopy should be performed.

Subcutaneous emphysema found by neck palpation indicates probable esophageal perforation. Drooling and inability to handle secretions are secondary indicators of esophageal impaction; wheezing can be a manifestation of airway compression.[67] Esophageal object detection generally necessitates esophagoscopy, however, because these foreign bodies are not otherwise amenable to detection by physical examination.[80]

Diagnostic Imaging. Because of the limitations of clinical presentation and examination in excluding a foreign body, radiography is a routine part of the assessment and contributes to diagnosis and management in approximately one half of the cases.[71,81] The initial step generally is to obtain posteroanterior and lateral chest radiographs and lateral cervical spine films made using soft tissue technique. The primary utility of plain radiography lies in detection of radiopaque objects, although some series report that retrospective review of lateral neck films identifies indirect signs (e.g., soft tissue swelling) in most patients with proximal aerodigestive tract foreign body.[81] Overall, the sensitivity of plain radiography for detection of esophageal foreign bodies is relatively poor.[82] Plain radiography has identified metal foreign objects missed on direct (including endoscopic) examination, however.[83] In patients who are transferred to the ED from an outlying hospital, repeat radiography may be useful to assess whether the foreign object has passed into the stomach in the interval since previous studies[70] (Fig. 57-10).

Figure 57-10. Plain radiograph obtained in a child who had swallowed a coin, located in the stomach.

Esophageal foreign objects usually align themselves in the coronal plane and are posterior to the tracheal air column on a lateral radiographic view. Coins in the esophagus lie in the coronal position in virtually all cases because the opening into the esophagus is much wider in this orientation.[70] Certain common foreign bodies are not radiopaque; for example, fish and chicken bones are frequently ingested, are difficult to visualize directly or radiographically, and often scratch the esophageal mucosa. Plain films of the neck and chest have sensitivity of roughly 25% for impacted fish bones.[80] Although some studies suggest that technique variation improves fish bone detection, plain radiographs remain insufficiently sensitive as a means to rule out these foreign bodies.[84] In various studies, false-negative results were reported in at least 30 to 55% and false-positive results in approximately one fourth of the cases.[80,85,86]

When plain films fail to visualize foreign bodies and suspicion remains high, one option is contrast esophagography, which can be useful with radiopaque and sometimes with radiolucent foreign bodies.[42,70] If perforation is not a concern, barium may be used as the contrast medium because it provides higher-quality images. If an esophageal leak is suspected, water-soluble contrast solution should be used; a barium follow-up study may be considered if findings on the initial contrast study are equivocal or suspicion remains high. When initial contrast films are not definitive, patients may be asked to swallow a contrast-soaked cotton ball, which may localize the foreign body by lodging proximal to the object. Contrast studies, even when performed with barium, have limitations when the suspected object is an impacted bone.[82] In one series using barium-soaked cotton balls, false-positive and false-

negative rates were 26.9% and 40%, respectively.[86] Barium swallow yields better results but risks aspiration and coats the object and esophagus, reducing effectiveness of subsequent endoscopy.[70,87]

CT scans with coronal and sagittal reconstructions are useful in identifying foreign bodies or in further characterizing objects seen on plain films.[68,83,88] CT has been recommended as the primary diagnostic modality because it can give information about foreign body size, type, location, and orientation with respect to other anatomic structures.[62,88] In one study, non–contrast-enhanced CT scans interpreted by resident physicians detected all impacted bony foreign bodies found by esophagoscopy; the one false-positive result was due to esophageal calcification, and no false-negative results were reported. Overall, CT use reduced the incidence of negative results on esophagoscopy. These study findings portend a potentially important role for CT in imaging of impacted bony foreign objects.[70] CT also can assist with identification of complications. CT identified a fistulous (subsequently fatal) esophagoaortic tract in a patient who had swallowed a bone splinter 1 week earlier.[77] Also, CT may be used in patients with positive findings on plain films and negative results on esophagoscopy to search for objects that have migrated from the intraluminal to the extraluminal space.[62]

A relatively inexpensive and noninvasive modality reported to be useful in detection and characterization of metal foreign bodies is scanning with a hand-held metal detector. Use of a commercial hand-held metal detector (e.g., Super Scanner, Garrett Security Systems, Garland, Texas) has been studied in large adult and pediatric series of patients with suspected esophageal metallic foreign bodies, with positive and negative predictive values approximating 90 to 100% (and no complications).[89,90] The hand-held metal detector easily detects aluminum foreign bodies missed by radiography. The hand-held metal detector avoids time, radiation exposure, and costs associated with radiography and may obviate the need for radiography in patients with suspected coin ingestion in whom no foreign body is detected or an object is detected below the diaphragm.[71,89]

Management. Pharyngeal foreign bodies visualized by direct or indirect laryngoscopy usually can be removed with a forceps or clamp. It is important to guard against the possibility of inducing trauma as well as airway obstruction during extraction attempts.

Management of esophageal foreign bodies depends on many factors. With esophageal food bolus or coin, the emergency physician often can provide appropriate treatment. With sharp objects, displaced esophageal stents, or impacted button batteries, more invasive techniques are necessary.[70,91] Management strategy depends on the nature of the foreign body, the length of time the object has been lodged, and the expertise and experience of the treating clinician.[70] In addition, the patient's age and previous medical and surgical history may be relevant.[68] The overall success rate for nonsurgical removal of objects from the esophagus is greater than 95%.[86]

The first basic strategy for esophageal foreign body management is applicable only if the object is known to be an impacted food bolus. In these cases, pharmacologic maneuvers may be tried to move the bolus into the stomach. Glucagon (0.5–2 mg) given intravenously has been used to relieve distal food obstructions. The drug acts by lowering the smooth muscle tone at the lower esophageal sphincter without inhibiting normal esophageal peristalsis. A concern is that too-rapid administration of glucagon may cause vomiting, posing a risk of rupture of an obstructed esophagus. Other pharmacologic agents have been used with mixed success. Gas-forming agents also have been used, and although supporting evidence is sparse, some practitioners suggest that this approach should be attempted first or in combination with glucagon.[87] Patients who complain of chest pain at presentation should not be given gas-forming agents because they may have esophageal perforation. Two other agents used for management of distal food bolus impaction that probably are not as useful as glucagon are nitroglycerin and nifedipine. Both of these agents have a relaxing action on the lower esophageal sphincter and are safe and roughly equally (if only marginally) effective agents for management of impacted food bolus. A last approach, enzymatic degradation of an impacted meat bolus using the proteolytic enzyme papain, has fallen into disfavor because of risks of esophageal perforation.

The preferred strategy for esophageal foreign body removal is endoscopy. Flexible endoscopy does not require general anesthesia, can be performed in a sedated (nonintubated) patient, and may be both diagnostic and therapeutic in the case of foreign bodies such as coins.[68] The high overall success rate for endoscopy has prompted some experts to recommend that patients with symptoms that started within 48 hours of ED presentation be taken directly to the endoscopy suite if no suspected complication is evident.[70]

Another removal strategy, best suited for smooth, nonimpacted, and blunt objects, uses a contrast-filled balloon catheter and fluoroscopy. A Foley catheter is introduced into the esophagus, and the balloon is passed beyond the foreign body, inflated with radiographic contrast material, and withdrawn under fluoroscopic monitoring; the object is extracted along with the catheter. To minimize risk of foreign body aspiration, this procedure should be performed with the patient in a steep, head-down position in lateral decubitus; the procedure is contraindicated in patients with airway compromise, complete esophageal obstruction, or inability to cooperate.

The final strategy for active foreign body removal, bougienage, involves pushing the foreign object into the stomach. Strict criteria determine eligibility for this procedure, which generally is not performed by the emergency physician. Compared with endoscopy, bougienage appears to be at least as safe and much more time- and cost-efficient.[92,93] Although patient eligibility for bougienage may be limited by factors such as presentation delay, when performed, the procedure appears to be successful in up to 95% of attempts.[93]

The fifth approach, expectant management awaiting spontaneous passage of the foreign object into the stomach, is often successful. This approach is best for patients presenting within 24 hours of ingestion and who have a radiographically identified "safe" (e.g., coin) object in the distal esophagus.[70,94] The button battery is associated with specific expectant management issues. If a disk battery has been ingested, its location must be ascertained, with immediate removal if it has lodged in the esophagus. If the button battery has passed distal to the esophagus, the patient can be observed, with serial radiographic follow-up studies to confirm spontaneous passage through the gastrointestinal tract.[95]

After the removal of an esophageal foreign body, regardless of the method used, a follow-up esophagogram frequently is necessary to evaluate esophageal anatomy and patency. Referral to investigate cause of dysphagia and obstruction should be made.

Stomach and Bowel

Foreign bodies that reach the stomach rarely cause major difficulties, although problems such as perforation may occur even with ingestion of blunt objects.[54] Observation with expectant management usually is appropriate[95] because ingested foreign bodies reaching the stomach generally are

propelled by peristalsis through the length of the gastrointestinal tract, with expulsion in a few days. Objects may pass beyond the esophagus and still become impacted, however, most often at the gastric outlet or the ileocecal valve, although complications can arise at any point throughout the intestinal portion of the gastrointestinal tract.[96,97] If the foreign body is a *bezoar*, a mass of undigestible food or nonfood material, a palpable mass may be noted on abdominal examination. Otherwise, the physical examination is relatively unhelpful, only rarely revealing indirect evidence of foreign body presence or complications.

History. Signs and symptoms of intraluminal objects range from none to vague abdominal pain to obstruction or perforation-associated peritonitis.[97] Most patients have a specific history of ingesting a nonfood item, however, or the circumstances indicate the likelihood and character of an intestinal foreign object. Patients with psychiatric or secondary-gain reasons for foreign body ingestion occasionally may be encountered in the ED.

Hiding of illicit drugs is an important motivation for foreign body ingestion. Rupture of these drug-containing packets, especially when cocaine is involved, may have rapid and fatal consequences. Less often, one or more packets can cause bowel obstruction. Even when obstruction is not present, vomiting may be reported. *Body packing*, which entails systematic gastrointestinal tract placement of previously prepared drug packets (Fig. 57-11), should be clinically differentiated from *body stuffing*, which denotes hurried ingestion of hastily prepared packets in the face of imminent police presence.[98] Body stuffers are more likely to experience toxicity because of the poor packaging of drugs and are less likely to exhibit positive plain radiography findings.[99] Drugs most often involved in body packing or body stuffing are cocaine and heroin, with amphetamines and cannabinoids involved less frequently.

Another important component of the history is placement of a dental implant or of a medical implant in the gastrointestinal tract. Dental implants can migrate to the distal gastrointestinal tract, where they may cause complications.[79] Expandable esophageal stents migrate in some patients, and biliary stents also have been become malpositioned, with resulting complications.[100]

Patients with gastrointestinal tract foreign bodies should be asked about history and behaviors possibly related to the development of bezoars. A habit of chewing hairs can result in formation of trichobezoars, which infrequently extend from the stomach into the small intestine as a "tail" (Rapunzel syndrome). Phytobezoars (composed of vegetable matter) and lactobezoars (from milk curds) also have caused complications, usually in the stomach.[101] Infants with lactobezoars from undigested formula may have a history of prematurity and often are receiving formulas with a high casein-to-whey ratio. Other bezoars may be composed of infectious (e.g., fungal bezoar) or inorganic (e.g., lithobezoar) material.[102]

Other specific intestinal foreign bodies, previously mentioned in the discussion of esophageal impaction, are of clinical importance in the distal gastrointestinal tract. Button batteries can rupture in the intestine, and fish bones have penetrated through the gastric mucosa. Ingested toothpicks can lodge in the bowel wall, causing gastrointestinal complications and erosions or compression of nearby structures.[88]

Diagnostic Imaging. The initial imaging modality is plain radiography, which often is diagnostic (Figs. 57-12 and 57-13). Two-view plain radiography has proved useful in clinical situations ranging from coin ingestion to body packing (see Figs. 57-10 and 57-11). Plain radiographic findings are positive in approximately 90% of body packers but are nearly always negative in body stuffers and usually are negative in patients who have ingested crack vials.[99,103,104] Plain radiography usually identifies drug packets, but false-negative results do occur, and follow-up contrast radiography or CT is recommended.[105] Ultrasound imaging has been reported to be useful in drug packet cases in which plain radiography is nondiagnostic, but this modality is most helpful when it yields positive findings (i.e., a negative result is insufficient to rule out presence of an ingested packet).[106]

Figure 57-11. Plain radiograph obtained in a patient after body packing. Note the appearance of previously prepared drug packets.

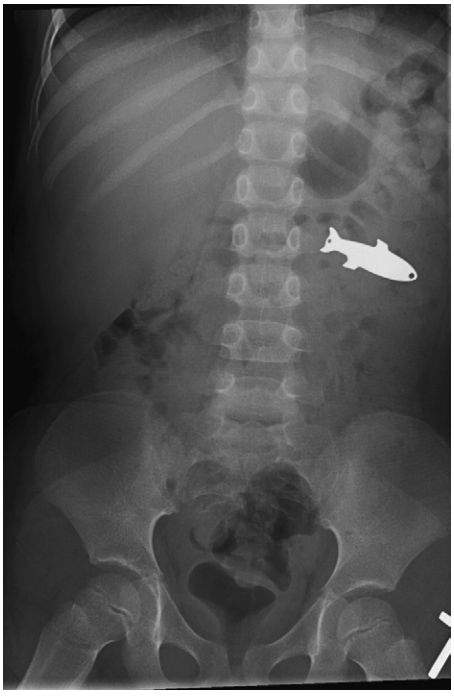


Figure 57-12. Plain radiograph obtained in a child who had ingested a fishing lure (without hooks).

Figure 57-13. Plain radiograph obtained in a child who had ingested a nail (which ultimately passed after observation).

Contrast-enhanced upper gastrointestinal tract radiography has intermediate success in patients with suspected body stuffing or body packing. Contrast administration also has proved useful in outlining bezoars. CT can identify foreign bodies in the stomach and intestines and can help diagnose packet ingestions in body stuffers. In these patients, contrast-enhanced CT outlines the bag containing the illicit drug; contrast administration also can help by identifying air trapped in the packet. CT has yielded false-negative results, however, in detection of drug packets.[101] CT also has proved useful in determining whether complications of foreign body perforation are present.[84]

Management. The general rule for the management of gastric or intestinal foreign bodies is observation, although some treatment centers favor early endoscopy and report this approach to be nearly universally successful.[66] Management decisions are based in part on the nature of the ingested object. Blunt objects can be expected to pass easily through the bowel, with expulsion verifiable by stool examination. If confirmation of passage is of particular concern, serial radiographs may be obtained after 5 to 7 days.[60] Sharp objects may be recovered using fiberoptic gastroscopy, although they traverse the gastrointestinal tract without incident in 90% of cases.[68] Early removal generally is required for objects wider than 2 cm because they do not pass the pylorus, or for those longer than 5 to 6 cm because they do not clear the duodenal sweep.[60] Overall, surgery is required in less than 1% of cases of intestinal foreign body, but in certain instances (e.g., bowel obstruction), clinical circumstances prompt early operative intervention.[96,97]

When chosen, observation should be continued until (1) the object is found in the patient's stool; (2) the object causes bowel obstruction or perforation, requiring immediate surgical intervention; or (3) the object shows no evidence of progression through the gastrointestinal tract on two radiographic examinations performed 24 hours apart, indicating impaction and mandating active removal. In some cases, the identity of the foreign body dictates management. In a body packer or body stuffer, regardless of external (e.g., law enforcement) pressures, only interventions that are justified medically as reasonable steps to prevent injury from the ingested object or substance should be performed. If urgent drug packet retrieval is unnecessary, the patient should be admitted for close observation for packet passage or signs of toxicity. Monitoring of drug levels can be helpful. Usually the packet passes through the gastrointestinal tract spontaneously. This passage can be facilitated with polyethylene glycol solution or laxatives or both. If cocaine-containing packets have been ingested, alkalinization of gastric contents (to enhance hydrolysis of cocaine to its inactive metabolite benzoylecgonine) may be of therapeutic assistance.

Immediate removal of drug-containing packets should be considered in patients in whom intestinal obstruction or drug intoxication develops. Most experts, citing risks of packet rupture and drug toxicity, contend that endoscopic removal of cocaine-containing packets is never indicated. Endoscopic removal has been reported to be safe and effective, however, in an asymptomatic patient who ingested a single packet.[107]

As noted earlier, button batteries represent another foreign body type with specific management implications. Intact batteries ingested into the stomach can be observed without the immediate removal necessary in cases of esophageal impaction. Repeat radiographs should be taken the next day to ensure movement of the battery into the intestinal tract, with films obtained every 3 to 4 days thereafter to confirm continued distal movement. As with illicit drug–containing packets, administration of polyethylene glycol solution may speed distal movement. If the foreign body has not been passed after the first few clear liquid stools, repeat radiography may identify the battery in the rectum, where it may be digitally evacuated.[95] Surgery is indicated for failure of the battery to progress, for radiographic signs of battery rupture, or for development of symptoms such as abdominal pain.[70] Endoscopy is increasingly reported to be useful for removal of gastric button batteries, with success in 14 of 16 cases in one series (the other two batteries were endoscopically moved into the intestine and subsequently were passed spontaneously).[66]

Management of bezoars depends on type and location. Dietary therapy, endoscopic removal, and enzymatic dissolution frequently are used.[97] For some bezoars, specific therapy has been identified. Infants with lactobezoars should be changed to elemental diets and observed, because most cases resolve without surgery.

Rectum

Most anorectal foreign bodies result from retrograde introduction, typically as a result of sexual practices that patients may be reluctant to discuss. Obtaining the history also may be difficult owing to presence of a mental disorder, reported in more than one third of patients with rectal foreign bodies in an 8-year series.[108] Prompt diagnosis is crucial because delay in definitive treatment is strongly associated with complications.

History. Patients with anorectal foreign bodies often are hesitant to give an accurate history. Studies have found that many patients with self-introduced anorectal foreign bodies do not initially admit to insertion but rather present with anal pain or simply constipation (which is in fact the most common complaint).[108] Other complaints include rectal pain, bleeding, and inability to void when large objects impinge on the urethra. History also may be lacking in body packers, who may present with toxicity symptoms; fatal cardiovascular collapse can occur with ruptured cocaine packets.

It is possible for ingested food or objects to lodge in the rectum after passing through the proximal gastrointestinal

tract. Rectal foreign masses of fish bones have been noted in many patients, all of whom strenuously denied transanal insertion, and in a series characterized by a high proportion of mental patients, oral ingestion accounted for nearly half of the of rectal foreign bodies.[108] If patients do admit to transanal foreign body placement, more accurate information about size, shape, and physical characteristics to plan imaging and extraction may be obtained. The duration of retention of the object in the anorectum has implications for mucosal failure and rupture.

Physical Examination. In patients with anorectal perforation, examination may reveal evidence of peritonitis or abdominal tenderness. On digital rectal examination, the foreign body may be directly palpated; this is the method of diagnosis in a large number of cases. In the absence of direct foreign body palpation, findings on digital rectal examination (e.g., bloody discharge, loose sphincter tone) may raise suspicion for anorectal foreign body.

When findings on digital rectal examination are negative or when better visualization is required, anoscopy is the next step. Although the anoscope's diameter limits the size of foreign bodies that may be extracted through the instrument, anoscopy affords an improved view of the nature and positioning of the object. Similarly, rigid sigmoidoscopy may be performed, with special care taken to minimize pressure on possibly ischemic anorectal mucosa. In many patients, especially those in whom multiple examinations or removal attempts have been made, sedation and analgesia may be required to enable invasive examination techniques. With any doubt about the integrity of the anorectal mucosa, invasive examination is best done in the operating room with the patient under general anesthesia.

Diagnostic Imaging. The foreign body may be detected on a plain abdominal radiograph (Fig. 57-14; see also Fig. 57-16). An important secondary finding is free intra-abdominal air secondary to anorectal perforation. If the object is not visualized on plain films, a contrast study can be performed, with care taken to minimize hydrostatic pressures on potentially compromised mucosa. Water-soluble contrast material should be used if perforation is suspected. Specialized imaging such as CT is not usually part of the imaging workup but may be indicated if complications are suspected.

Management. With patience and judicious use of sedation and analgesia, the emergency physician often can remove rectal foreign bodies. Surgical intervention may be necessary on occasion and was in fact required in a majority of patients in some series.[109] Depending on the nature of the foreign body and the presence of damage or perforation of the rectal wall, transanal removal (with or without sedation and local anesthesia) is successful in roughly half of the patients, with general anesthesia required in the remainder.[108] Attempts to retrieve objects that pose a high risk for rectal injury due to sharp edges or likelihood of dangerous breakage (e.g., lightbulbs) are not recommended.

Initial efforts at foreign body removal in the ED should begin with the examiner's digit. Small rectal objects occasionally can be hooked by a finger and withdrawn; this is the initial technique in patients who do not have signs of peritoneal irritation from bowel wall perforation. The digit should be lubricated with lidocaine jelly, and abdominal pressure may be applied in an attempt to mobilize foreign objects distally.

When digital extraction fails, an anoscope or small vaginal speculum can be used in an attempt to visualize the foreign body. A ring forceps is placed through the visualizing apparatus to grasp and remove the object. Sometimes the mucosa may become tightly adherent to the distal end of the foreign body, creating a vacuum that prevents object withdrawal. Passage of a Foley catheter beyond the foreign object (sometimes through a rigid sigmoidoscope) with proximal air inflation usually breaks the vacuum and permits retrieval.[110] Passage of the catheter, followed by air inflation and balloon filling, may allow object removal with gentle catheter traction.

When the appropriate expertise and equipment are available in the ED, or if subspecialists are available for consultation, the next step may be removal with a vacuum device, well suited for use with some foreign bodies (Figs. 57-15 and 57-16), or with forceps; sigmoidoscopy may be a necessary adjunct to such an approach. As with other removal means, careful technique is essential to minimize risk of anorectal perforation. Removal of occult anorectal foreign objects after administration of an enema for symptomatic relief of anal pain was successful in 10% of patients in one series. Experts caution against possible perforation, however, when enemas or cathartics are

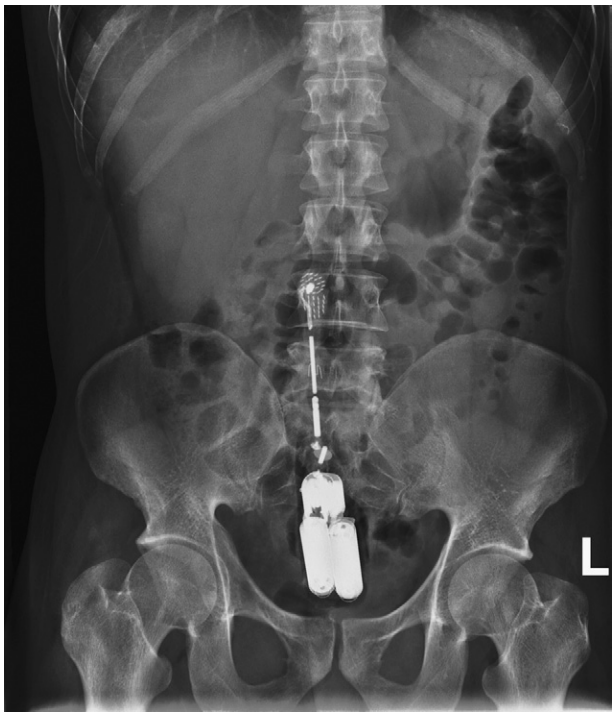


Figure 57-14. Plain radiograph obtained in a patient who had inserted an electric toothbrush into the rectum. The device was removed during proctoscopy.

Figure 57-15. Vacuum device used to remove a difficult-to-grasp rectal foreign body, such as this bottle.

Figure 57-16. Plain radiograph obtained in a patient who had inserted an aerosol can into the rectum.

administered to patients with known rectal foreign bodies, especially those with sharp edges.

After removal of the foreign object, the possibility of rectal trauma should be considered. When foreign body retrieval has been simple and the patient does not show increased pain, tenderness, or rectal bleeding, further evaluation for rectal trauma probably is unnecessary. If any of these is present, postremoval sigmoidoscopy may identify small abrasions requiring close follow-up, but generally hospitalization is necessary only if a rectal laceration or perforation is found. An appropriate antibiotic regimen is indicated in all cases of suspected bowel wall perforation and peritonitis. Long-term follow-up study has identified few or no sequelae in patients with rectal foreign bodies.[108] In one study tracking patients for more than 5 years, the investigators found no problems with fecal incontinence or recurrence of rectal foreign objects.[111]

Genitourinary Tract

The literature describes a wide variety of genitourinary tract foreign objects, ranging from easily extracted tampons and condoms to penile rings removed only with great difficulty.[112,113]

History. An accurate history may not be readily obtained because most foreign bodies are placed by the patients themselves. Reports have validated the occasional value of a history, however, as a means to diagnose some genitourinary objects such as those associated with genital body piercing (in patients or their sexual partners).[114,115] In children who fear parental disapproval of foreign object placement, secondary signs constitute the usual presentation. They are brought to medical attention when parents note foul-smelling, purulent discharge or bleeding from the urethra or vagina or both.[116] Another common infant presentation is penile constriction caused by inadvertent wrapping of hairs around the shaft, usually just proximal to the corona.[117]

In older children, rubber bands or string may be placed around the genitalia. In adolescents and adults, metal objects are placed for autoerotic stimulation. Constricting bands may be placed proximal to the scrotum or, more often, on the penile shaft. These patients frequently have presentations delayed by 12 hours or more. The swelling that renders these constricting bands so difficult to remove also hinders the physical examination, emphasizing the need for an accurate history.[117]

Occasionally an inserted object (e.g., a tampon) is forgotten until it causes purulent discharge. Secondary symptoms also can bring foreign bodies to medical attention in rare cases of genitourinary tract perforation by foreign bodies from the genitourinary tract or elsewhere. Migration of an intrauterine device into the bladder has occurred, with associated cystolithiasis. In another unusual case, a sewing pin caused perforation through the appendix and into the bladder.

Genitourinary tract foreign bodies may be infectious. The term *bezoar*, traditionally considered to delineate indigestible material in the gastrointestinal tract, also has been used to describe foreign collections in the bladder. A common urinary tract bezoar is the *Candida* bezoar, seen in immunodepressed patients or in patients with diabetes mellitus, neurogenic bladder, antibiotic use, or an indwelling urinary catheter.[118]

Physical Examination. Patients of all ages require a careful, gentle examination because they often are anxious about the anatomic region being examined. In a pediatric patient, a nasal speculum may be used to help visualize a vaginal foreign body. Thorough vaginal examination is indicated in patients with symptoms of vaginitis, with the search directed to look for infectious agents and foreign bodies. A vaginal foreign body may be palpated during digital rectal examination.

In children and adults, the presence of blood or discharge at the urethral meatus or vagina should be noted. Patients with intraurethral foreign objects also may have perineal induration and a high incidence of associated infection, which may progress to sepsis syndrome.[112] In males with penile shaft swelling, careful inspection for constricting objects is indicated. In an infant with penile swelling, a coronal constricting hair should be sought.[117]

In patients with penile rings, especially most who present after some hours' delay, examination may reveal a swollen penis with mottling, duskiness, and excoriation. The interruption of venous and lymphatic outflow results in increasing penile enlargement with the risk of tissue damage. Damage is especially likely if the patient previously has tried removal of the constriction.[117] Urethrocutaneous fistulas, relatively common in infants and children, should be sought in any patient with a constricting band.

Examination may reveal only indirect evidence of other genitourinary objects as well. Multiple abscesses in an enlarged scrotum have been reported in a patient presenting with acute infection from embedded metallic objects placed (by the patient) decades before ED presentation.[114] Any genitourinary examination abnormalities should prompt questioning of the patient about possible foreign bodies.

Diagnostic Imaging. Often, no imaging is necessary, but plain films may be obtained to look for urethral or bladder radiopaque foreign bodies. Plain radiography also has proved useful in unusual cases of embedded metallic objects not palpable because of pain.[114] Urethrocystography may be useful in identifying and locating genitourinary tract foreign objects and has been an aid to surgical planning for affected patients.[112] Intravenous urography may reveal a filling defect in the case of a bladder foreign body, or it can reveal delayed renal excretion as a general finding suggesting foreign object–related renal function impairment. Ultrasound imaging is useful to investigate for hydronephrosis. Acoustic shadowing may or may not be seen, depending on the nature of the foreign body: *Candida* bezoars, for example, do not produce acoustic shadowing. These bezoars and other genitourinary tract objects generally are identifiable on CT.[118]

Management. Vaginal foreign bodies usually are removed easily. If the object has been present for some time, any associated vaginitis should be treated. In males or females, foreign bodies located just inside the urethral meatus usually can be grasped with a clamp and removed. The overriding goal is to avoid causing further damage to the already traumatized urethra. After failure of one or two attempts at removal in the ED, the best course is early consultation with the appropriate subspecialist. Objects located in the proximal urethra or bladder usually require cystoscopy for extrication. One exception is the *Candida* bezoar, for which management generally consists of treatment with antifungal agents.[118] Penile urethral foreign bodies may be associated with urinary retention and secondary infection; early endoscopic intervention is necessary for these patients.[113]

Constricting penile foreign bodies must be removed as early as possible because progressive swelling makes removal more difficult. Sedation and analgesia may be necessary. Also, care must be taken in removing constricting objects with instruments such as ring cutters; penile shaft lacerations may result because of the tautness of the thin underlying skin. Hair and string foreign bodies are removed relatively easily with forceps and scissors or scalpel. Wrapping the penis with string followed by distal mobilization of the ring (as is done for digital foreign bodies) has been successful.[117] Other approaches have been used to remove penile constricting bands. A cast saw, the vibrating blade of which reduces risk of skin damage, may be useful for removal of some objects, such as acrylic rings. After penile ring removal and confirmation of ability to void, patients usually can be discharged with close follow-up.[117] Subspecialty consultation should be obtained for patients with penile trauma.

Soft Tissues

Soft tissue foreign bodies present unique diagnostic and management dilemmas. Foreign bodies may be present not only in patients with known wounds but also in patients with secondary symptoms who are unaware of or uncertain about foreign body entry.

History. All patients with wounds should be considered for soft tissue foreign body contamination, and evaluation of soft tissue injury should include a search for foreign objects. In straightforward cases, patients present with symptoms such as pain or foreign body sensation and may report presence of a specific foreign body. In more difficult cases, patients present with symptoms related to complications. Soft tissue infections, especially recurrent, should suggest a foreign body serving as a nidus. Careful history in patients with soft tissue complaints should include a search for antecedent trauma, no matter how remote, which may have resulted in foreign body entry.

Physical Examination. The diagnosis frequently is obvious on visual inspection or standard wound evaluation. For smaller objects, use of loupe magnification may be a significant aid in foreign body identification and removal.[119] Besides location of the foreign body, the examination should assess for injuries collateral to the object's presence. Distal neurovascular function should be tested.

Diagnostic Imaging. Anteroposterior and lateral radiographs of the involved area of the body are valuable. Plain radiography has been shown to be more than 98% sensitive when the foreign body is metal or another radiopaque material, such as gravel.[120,121] If silver nitrate sticks were used to achieve hemostasis before imaging, the deposited metal can be expected to appear on plain radiographs.[121]

One common foreign body is glass, which has shown radiopacity.[120,121] In one cadaver study, nonleaded glass was visualized with 90% sensitivity and a false-positive rate of 10%; glass color and location were unimportant, but a volume of less than 15 mm^3 was associated with a greater likelihood of failed visualization.[122] Other items are not easily seen on plain radiographs, which are insensitive for detection of vegetable (e.g., wooden) material or plastic objects.[120,121] Xeroradiography, recommended in the past, has no advantage over plain radiography and has been discarded in favor of other modalities (e.g., CT) when plain film findings are negative and suspicion remains.[120,121,123] In EDs in which digital radiography and image manipulation are available, the use of "soft tissue" exposures is not necessary. For EDs in which hard-copy radiographs are used, specification for "soft tissue" exposure should be indicated when films are requested.

Fluoroscopy has received attention as a diagnostic and therapeutic tool. In an ex vivo beef model, emergency physician–conducted fluoroscopy had 100% sensitivity for gravel, metal, and glass; sensitivity was 90% for graphite and zero for plastic and wood.[124] Another evaluation of C-arm imaging in a chicken leg model also found 100% of gravel, metal, and glass objects, although sensitivities for wood and plastic were low.[125] One advantage of fluoroscopy is that it can guide removal and later confirm absence of foreign objects.

When plain radiographic findings are negative yet suspicion for foreign body remains, ultrasound imaging or CT is the next step.[123,126,127] Ultrasonography is readily available in many EDs and has been the subject of intensive but ultimately unconvincing study. Even radiologists, interpreting scans done in an animal model, had low detection rates for gravel (40%), metal (45%), glass (50%), cactus spine (30%), wood (50%), and plastic (40%); overall, false-negative and false-positive rates were 50% and 30%, respectively.[120] In another study, using a cadaver hand model, ultrasound imaging proved 93% sensitive for wood and 73% sensitive for plastic foreign bodies, but specificity was only 59%.[128] A third study, using credentialed sonographers and radiologist interpretations in a chicken breast model, found some utility for ultrasound imaging in the ED. The investigators concluded that a 7.5-MHz probe was better at shallow depths and that a 5-MHz probe should be used for deeper searching.[129] The study found that wood had the best acoustic shadow, followed by plastic; other materials investigated (paper clip, glass, needle) had lesser shadowing and were more difficult to detect. In another artificial setting, ultrasound imaging was the only modality among plain radiography, CT, and xeroradiography that clearly identified wood and plastic foreign bodies.[130] Overall, in view of the general availability of ultrasound imaging in the ED and the case reports of its clear occasional utility in foreign body localization and removal, it is reasonable to use this technique with the understanding that a positive test result is much more useful than a negative one.[131,132]

In addition to characterizing objects seen on plain films, CT is useful for detecting items (e.g., plastic, wood) not evident on plain radiographs.[121,133] CT also is valuable in localizing small or deep objects and delineating anatomic positioning.[123,126] Newer-generation image viewers increase the utility of CT; higher detection rates for wood and plastic are reported with on-screen image viewing and manipulation than with hard-copy CT film.[133,134] CT also is useful for identifying foreign body sequelae (e.g., abscess).

MRI can assist in identifying foreign body complications.[126] Soft tissue objects can induce a chronic inflammatory reaction and lytic or blastic osseous changes that allow MRI localization.[135] In other cases, MRI is less useful. Gravel, readily detected on images obtained with most modalities, causes MRI streaking because of ferromagnetic material. MRI also has identified foreign objects of wood and plastic; however,

CT usually is adequate for detection of these types of foreign bodies.[121]

Management. The most important determinant of successful foreign body removal is knowledge of the object's precise location. Standard radiopaque markers can aid in wound localization. For small objects, needles placed in the soft tissues can help pinpoint the location of foreign bodies seen on radiographs. Fluoroscopy may allow simultaneous visualization and removal. When objects are not radiopaque, judicious probing of wounds with fine-gauge needles or forceps may allow tactile detection of the foreign body.

To remove a foreign body, it may be necessary to extend the original wound or, if it is located away from the entrance site, to make a separate incision. The emergency physician can perform limited wound extension or make separate incisions in regions in which adequate analgesia and a bloodless field can be achieved. Retrieval of foreign bodies, especially those linear in shape, is best achieved after recognition of the orientation of the object. Then the proximal end of the foreign body is grasped, and extraction is accomplished gently, following the plane of orientation. This allows easier removal and helps avoid breaking the object into multiple foreign bodies.

When objects are deeply embedded, it may be better to leave them in place, rather than creating large surgical wounds to effect removal. Depending on foreign body location, operative intervention may be necessary for safe foreign body extraction.[136]

After foreign body removal, tetanus prophylaxis and antibiotic coverage may be given when warranted by clinical circumstances. Patients with contaminated hand wounds and wooden splinters may be candidates for prophylaxis. Patients with suspected vascular or neurologic injuries require early evaluation, possibly but not invariably in the ED, by appropriate subspecialists. Some soft tissue foreign bodies may go undetected, leading to infectious sequelae. Careful discharge instructions and timely follow-up are crucial in these patients.

KEY CONCEPTS

- If the history and mechanism of injury are compatible with ocular penetration or if a small puncture wound of the globe is noted, obtaining anteroposterior and lateral radiographic views of the orbit is an appropriate initial step when the foreign body is thought to be radiopaque. CT and ultrasound imaging are complementary diagnostic studies.
- Inappropriately prolonged ED efforts at removal of otic foreign bodies can result in wasted time, unnecessary patient discomfort, and potential for complications, including tympanic membrane damage.
- Unresolving sinusitis despite appropriate antibiotic therapy should alert the emergency physician to the possibility of nasal foreign body.
- Most airway foreign bodies are seen in pediatric patients and may not be visible on plain films. A normal radiographic appearance does not rule out an aspirated foreign body.
- Esophageal foreign bodies (e.g., coins) usually are oriented in the coronal plane; airway objects usually are oriented in the sagittal plane, parallel to the tracheal rings.
- The patient with critical airway obstruction and impending or actual respiratory arrest requires one of three options: (1) forced expulsion of the foreign body; (2) direct laryngoscopy with attempted manual removal; or (3) cricothyroidotomy, other transtracheal ventilation, or intubation while the foreign body is pushed distally.
- Esophageal foreign bodies typically are found at one of the three constriction locations: (1) proximal esophagus at the level of the cricopharyngeal muscle and thoracic inlet—radiographically, the clavicular level; (2) midesophagus at the level of the aortic arch and carina; and (3) distal esophagus just proximal to the esophageal-gastric junction—radiographically, a level two to four vertebral bodies cephalic to the gastric bubble.
- In cases involving body packing or body stuffing, regardless of external (e.g., law enforcement) pressures, only those interventions justified medically as reasonable steps to prevent injury resulting from the ingested object or substance are indicated.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 58 Mammalian Bites

Ellen J. Weber and Hugh H. West

ANIMAL BITES

Perspective

Epidemiology

The incidence of animal bites has been difficult to determine because many are not reported. The Centers for Disease Control and Prevention (CDC) has provided the best epidemiological data available, but data sources are heterogeneous and have varied over time. In 1994, for example, based on a telephone survey, it was estimated that 756,000 people sought medical attention for dog bites.[1] A CDC estimate for the year 2001, based on the National Electronic Injury Surveillance System–All Injury Program (NEISS-AIP), suggested that 368,000 people in the United States were treated in emergency departments (ED) during that year for dog bite-related injuries.[2] The incidence thus varied by about 50% over a period of 7 years. The latter estimate of dog bite injuries is probably more accurate. Data from a surveillance network in Switzerland suggested that there were 190 dog bites per 100,000 persons in that country for the year 1995.[3] By comparison, the U.S. numbers for 2001 of 133 per 100,000 fall somewhat below that range.[2]

Estimates of bites from other species, including humans and cats, are far more difficult to estimate as the CDC groups these in a category with reptile and insect bites, as well as stings from coral, jellyfish, and plants.

Dog bites represent approximately 0.4% of all ED visits and account for 60 to 90% of bite injuries treated in the ED.[4] Cat bites represent 1 to 15% of treated bites, rodents up to 7%, and other species (monkeys, ferrets, raccoons, foxes, livestock, bats, minks, kinkajous, other wild animals) less than 2% of bites.[5,6]

Children are the most frequent victims of dog bites, and below the age of 15, males are bitten more often than females. For patients 15 or older, the difference in bite occurrence between the rate for males and females was not statistically significant.[2,6,7] Most cat bites occur in or near the home of the victim. In the United States more than half of dog bites occur at home and about one third in a public place.[4] Cat bite victims are more frequently female than male.[8] In one study from Austria, approximately 82% of children sustaining dog bites were familiar with the dogs.[9] This is not the case elsewhere. In Bangkok, for instance, dog bites are more likely to be inflicted by stray or "community" dogs and to occur in public places.[7]

About 200 fatal attacks by dogs occur each decade in the United States.[10] The majority of the victims are children younger than 10 years of age. The highest incidence has been reported in 1-year-old patients and decreases with increasing age.[9] The breeds most frequently responsible are pit bulls, Rottweilers, and German shepherds. In at least half the cases, the attack involves an unrestrained dog on the owner's property. For most of the fatalities in children younger than 1 year of age, the attack involved a pet dog and a child who was sleeping or in a crib.[10]

Animal bites can usually be treated on an outpatient basis. Hospitalization is most often required for plastic surgery or repair of deep structures in fresh wounds, or for subsequent infection. Approximately 2% of victims who seek care for dog bites are hospitalized.[2] Patients with dog bites are usually hospitalized at the time of the injury for operative repair, whereas most hospitalizations for cat bites are a result of infection that occurs several days after the initial bite.[11]

PRINCIPLES OF DISEASE

Bites are traumatic injuries that can cause damage to skin, muscle, nerves, blood vessels, tendons, joints, and bones. Wounds may be lacerations, contusions, scratches, tears, or deep punctures. Contamination with oral flora from the biting animal makes local wound infection the principal treatment concern, and to a far lesser degree, the prospect of rabies or tetanus.

Dogs

Injury

The jaws of adult dogs can exert approximately 200 pounds per square inch (psi), enough to perforate sheet metal, but the teeth generally are not sharp. Most dog bites are large, relatively superficial crush injuries which damage skin and muscle but rarely reach tendon, bone, joint, or nerve. The wounds may be contusions with ecchymosis and hematoma, without any break in the skin, or large gaping wounds. Punctures occur less often. The large wound and emotional trauma of a dog bite typically precipitate an early visit for medical attention.

The lower extremities are most frequently injured in dog bites, but face, neck, and scalp wounds are common sites for dog bites in young children.[2-4,9,12-15] In children up to 2 years old, dog bites can perforate the cranium, resulting in depressed skull fractures, brain laceration, intracranial abscess, and meningitis.[16] Fractures of facial bones may also occur. In adults, dog bites rarely result in fracture, vascular injury, or tendon and nerve damage. However, bites from police dogs that are trained to hold their grasp until given the command to release

pose a significant risk of complications, in particular vascular injury. Infection, fracture, and nerve or tendon injury are also more common in bites from police dogs than those from civilian dogs.[17]

The overall incidence of infections from dog bites is 5 to 10%, only slightly higher than the 3 to 7% infection rate for nonbite lacerations sutured in the ED.[18-20] However, dog bites on the hand have a higher risk of infection (12–30%). Dog bites of the face have a lower risk of infection (1–5%) than bites elsewhere.[3,14,21-27] There is an obvious selection bias here, as the numbers refer to patients seen in the ED rather than all patients with dog bites, a good number of whom probably do not seek medical attention.

Bacteriology

More than 100 different organisms have been isolated from infected dog bites. Most infected wounds are polymicrobial.[11,22,28,29] No one organism is responsible for more than 30% of infections.[22,29] The organisms found in infected wounds are common mouth flora from the biting animal. *Staphylococcus aureus*, alpha-hemolytic and beta-hemolytic streptococci, *Capnocytophaga canimorsus*, *Klebsiella*, *Bacillus subtilis*, *Pseudomonas*, and Enterobacteriaceae are among the more frequently isolated aerobic organisms.[28,30] NO-1, a gram-negative rod sensitive to β-lactams, quinolones, aminoglycosides, tetracycline, and sulfonamides, has recently been identified as a rare source of localized infection from dog and cat bites.[31] Anaerobic organisms isolated from infections include *Bacteroides*, *Fusobacterium*, *Peptostreptococcus*, and other species. Anaerobic organisms are most often recovered along with aerobic species in cultures of infected wounds.[28,30]

Although much attention is focused on *Pasteurella multocida*, its role in causing infections in dog bites may be overestimated.[22,32] *P. multocida* is found in the mouths of 77% of cats but in only 13% of dogs.[33] *Pasteurella* species are isolated in 25 to 50% of infected dog bite wounds in some studies, although one study of infected dog bites found no *Pasteurella*.[11,28,29] However, the *Pasteurella* species that have usually been isolated from dogs, such as *Pasteurella stomatis*, *Pasteurella canis*, and *Pasteurella dagmatis*, are less virulent varieties.[28,33] When *P. multocida* is isolated from infected dog bites, it is frequently found in mixed culture with other organisms; when isolated from infected cat bites, *P. multocida* is often the sole pathogen.[11]

Capnocytophaga canimorsus. *C. canimorsus*, formerly known as dysgonic fermenter 2 (DF-2), is a fastidious gram-negative rod that can cause overwhelming sepsis. It is part of the normal oral flora of both dogs and cats. More than 100 cases have been documented since the organism's discovery in 1976.[34-36] About 90% of cases are attributed to contact with a dog, primarily through bites or scratches, but for approximately one quarter of infections, only dog contact (without a bite) was documented. A few infections have resulted from contact with cats. About 10% of cases are unrelated to any animal exposure. The disease tends to strike patients with alcoholic liver disease, functional or surgical asplenia, lung disease, or those taking corticosteroids. However, in 40% of victims, no underlying illness is identified.[34-38]

The illness begins within 2 to 3 days of exposure and is characterized by hypotension, disseminated intravascular coagulation (DIC), and renal failure. Purpura, particularly on the face, and petechiae are frequent findings and may progress to symmetrical peripheral gangrene.[39] Cutaneous gangrene at the site of the bite strongly suggests *C. canimorsus*.[40] Waterhouse-Friderichsen syndrome (adrenal hemorrhage with cutaneous ecchymoses) occurs, as well as metastatic infection, resulting in endocarditis, meningitis, peritonitis, and pneumonitis. The mortality rate is 30%, with 70% of deaths occurring in immunocompromised patients.[40]

C. canimorsus grows slowly and requires special media and growth conditions. In the event of sepsis where contact with a dog or cat has occurred and this organism is suggested, the laboratory should be notified to prevent cultures from being misidentified or discarded prematurely. Although cultures may take up to 14 days, the organism can sometimes be identified in the patient's blood smear at the time of presentation, or in blood culture media before macroscopic growth.[38,40,41]

Cats

Injury

The typical cat bite is a puncture wound caused by sharp teeth. Abrasions, lacerations, and avulsions may also result.[42] Cats have long, slender, pointed teeth that can penetrate tendons, joints, and bone, inoculating bacteria deep into these tissues. The majority of these bites occur on the hand.[3,42] Cat scratch injuries may also become infected, and when this occurs the same organisms are found due to the propensity of cats to lick their paws.

Wound Infection

The reported incidence of infection in cat bites is 30 to 50%, although this may be an overestimate since many patients present for treatment of cat bites only after an infection develops.[3,5,6,42] In a prospective ED study of patients with cat bites, the overall infection rate was 16%, and most infections were present when the patient first sought care.[42] Nevertheless, 24% of the infections required admission to the hospital. Cat bites have a substantially higher risk of infection than dog bites. The puncture wound itself is difficult to explore, irrigate, or débride. Location on the hand increases the risk of infection.

Pasteurella multocida. Another important factor in the development of wound infection after cat bites involves the presence of *P. multocida*, a highly virulent, gram-negative, facultatively anaerobic rod found in the oral cavity or nasopharynx of 70 to 90% of healthy cats.[33] Wound infections and abscesses caused by *P. multocida* have occurred after cat scratches as well as bites and less often from dog bites or from open wounds that had been licked by dogs.[32] *P. multocida* infections have also been reported after the bite of an opossum, rat, lion, rabbit, pig, wolf, monkey, and cougar.[43-45]

P. multocida wound infections appear to have a distinctly earlier onset, causing a rapidly progressive cellulitis that may be apparent within 6 hours and easily identifiable within 24 hours, whereas infections from other pathogens are usually not evident for 2 to 3 days. Presenting features include erythema, warmth, swelling, and tenderness. Purulent drainage, lymphangitis, and adenopathy may also occur. In addition to cellulitis, *P. multocida* can cause abscess, tenosynovitis, joint infections, and osteomyelitis at the site of a bite and can seed arthritic joints and prosthetic valves, causing septic arthritis, endocarditis, and osteomyelitis at sites distant to the bite. Meningitis and pericarditis due to *P. multocida* after a bite have also been reported.[46,47]

In vitro, *P. multocida* is sensitive to penicillin, ampicillin, tetracycline, fluoroquinolones, amoxicillin-clavulanate, second- and third-generation cephalosporins, and trimethoprim-sulfamethoxazole (TMP-SMZ).[48,49] The organism is resistant to vancomycin and clindamycin and shows borderline susceptibility to aminoglycosides. Oral first-generation cephalosporins may not be effective.[50] Semisynthetic penicillins such as

oxacillin and dicloxacillin have been reported to have only minimal activity against *P. multocida* in vitro.[50] Erythromycin is a relatively poor agent against *P. multocida*, but the extended-spectrum macrolide azithromycin shows good in vitro activity against this organism.[48,49] However, the relevance of these in vitro data to wound care is occasionally unclear as culture-proven *P. multocida* infections have resolved after treatment with erythromycin, and oral cephalothin has been used to successfully treat a *P. multocida* infection that failed to respond to erythromycin.

Rodents

Rodent bites result in small puncture wounds with a low risk of local wound infection. These bites are frequently seen in laboratory workers, in children in lower socioeconomic areas who are bitten while sleeping, and occasionally in pet owners.[52] A number of diseases may be transmitted by rodent bites or scratches, including rat-bite fever, leptospirosis, tularemia, sporotrichosis, murine typhus, and plague, although nonbite contacts are the more common routes of transmission of systemic disease to humans. Rat-bite fever, caused by *Streptobacillus moniliformis* or *Spirillum minus* is rare, but can result from any rodent bite. It usually presents 1 to 3 days after the bite with abrupt onset of fever, chills, myalgias, and headache followed by a rash. Abscesses form in many tissues, including brain and myocardium and soft tissues. Involvement of joints occurs in 50% of patients, resulting in an asymmetrical migrating polyarthritis.[53,54] Hantavirus pulmonary syndrome (HPS) is a rare febrile illness characterized by bilateral pulmonary infiltrates and respiratory decompensation resembling acute respiratory distress syndrome and is usually fatal. HPS is caused by viruses of the Hantavirus genus, for which rodents are the natural reservoir. Transmission usually occurs from the inhalation of aerosolized material but may occur from bites or direct contact.[55]

Primates

Monkey and other primate bites are said to have a high wound infection rate. The infecting organisms have not been well described, with the exception of one case of wound infection due to *Eikenella corrodens* and a case of osteomyelitis due to *P. multocida*.[45,56] Old World macaque monkeys (Rhesus macaques, cynomolgus, and other Asiatic macaque monkeys) may harbor Cercopithecine herpesvirus 1, also called Herpesvirus simiae or more simply, B virus, which is fatal to humans if not treated early. Most victims of B virus infection in the United States were laboratory workers who were bitten or scratched by monkeys or who sustained scratches from cages; many of the exposures were considered trivial at the time.[57,58] This virus has been found to be highly prevalent in adult macaque monkeys, making them unsuitable pets.[59]

The disease in monkeys resembles that of human herpesviruses; monkeys may shed virus without symptoms but are more likely to shed when ill, under stress, immunocompromised, or breeding. Virus can be found in the conjunctiva, buccal mucosa, and genital areas, but most infected monkeys do not display any lesions.[57] B virus can enter host cells within 5 minutes, making immediate wound care at the scene the most important step in prevention of transmission. Deep puncture wounds that are difficult to clean; inadequately cleansed wounds; and wounds of the face, neck, or thorax may pose greater risks of infection.

The incubation period is 2 days to 5 weeks, with most cases presenting within 5 to 21 days. The illness usually, but not always, is heralded by the appearance of vesicles at the site of the injury, sometimes associated with tingling, pain, or numbness. In some cases, the illness starts with peripheral or central nervous system symptoms, or it may begin as a flulike illness Eventually, paresthesias at the site ascend along the infected extremity, and the victim develops headache, confusion, cranial nerve palsies, hemiparesis, and ultimately, coma and death. The case fatality rate is approximately 70%.[57] Treatment is most successful if begun when vesicles first appear.[58] With aggressive treatment, however, survival is possible even after central nervous system symptoms develop.[57]

Ferrets

The European ferret (*Mustela putorius furo*) is now the third most popular pet in the United States, with an estimated 5 to 7 million pet ferrets in 4 to 5 million households. The ferret is descended from the polecat, a member of the weasel, mink, and wolverine family. In the past, hunters bred ferrets to hunt rats and rabbits; they are extremely ferocious and tenacious with their prey. Although domesticated for more than 2000 years, the ferret appears to retain its instinctive propensity for attacking suckling animals and an attraction to the neck of its victim. Ferrets are known to attack infants and young children suddenly and without provocation, even in the presence of an adult. They usually attack around the face and neck, and often have to be pried off the victim. Extensive cosmetic repair after such attacks has been required.[60,61] Locking ferrets in a cage may not be an adequate safeguard; ferrets have been known to escape and hide for several days.

Little is known about the bacteriology of ferret bites. Rabies, though uncommon, has been documented in ferrets, but there has not been a documented case of transmission to humans.[62] In experimentally induced rabies, ferrets develop clinical signs (ataxia, paresis, anorexia, fever, hyperactivity) within 16 to 96 days after inoculation and secrete rabies in their saliva from 2 days before to 6 days after the onset of overt illness, which is similar to the way the illness behaves in other animals.[63] The CDC recommends a management strategy of ferret bites similar to that for other domestic animal bites with regard to rabies, allowing a 10-day observation period after the bite, rather than immediate sacrifice and testing.[64] A rabies vaccine for ferrets is available.[65] Ferrets should be vaccinated at 3 months and yearly thereafter.

Pigs

Pig bites are often deep, but may be deceptively small on the surface.[66] They require careful exploration and débridement. Pathogens include *Pasteurella aerogenes, P. multocida, Escherichia coli, Bacteroides, Proteus,* and alpha-hemolytic and beta-hemolytic streptococci.[43,66] Despite antibiotics and appropriate wound care, pig bites have a high risk of infection.

Domestic Herbivores

The bites of horses result in severe soft tissue contusions, but virtually all heal uneventfully. Cattle do not have upper incisors, so they virtually never bite. Camels are well known for biting their handlers, particularly in the winter, reportedly in sudden vengeance for offenses committed previously. Unlike most other herbivores, the camel has canine teeth and can cause deep wounds, fractures, and amputations, most involving the handler's upper limbs. These wounds are reported to have a very high rate of infection.[67,68] Most domestic herbivores carry *Pasteurella multocida*. Because antibiotics are added to the feed of most domestic herbivores, bacterial isolates from these animals are frequently resistant to common antibiotics.

Wild Animals

Human encounters with large wild animals, such as wolves, coyotes, large cats, elephants, or bears, usually result in massive trauma and often death, from some combination of biting, swiping, throwing, goring, and trampling. Attacks by animals may result in major blunt or penetrating trauma, with major arterial blood loss, airway damage, intracranial and subarachnoid penetration, broken ribs and vertebrae, pneumothoraces, and intraperitoneal bleeding.[16,69] Hyenas are known for their tremendously strong jaws and their frequency of attacks on humans in Africa. Hyenas target the face and can literally rip off a face or a head with one clean massive bite. Bites of bears usually result in a series of punctures, with crushing and tearing of soft tissues, and underlying fractures, particularly of facial bones and those of the upper extremity. Big cats tend to go for the nape of the neck; their teeth may enter the pharynx, esophagus, and intervertebral space.[69] A common killing mechanism is to shake the victim by the neck, which results in hyperextension injuries. The wounds grow *P. multocida*, staphylococci, and streptococci.

Systemic Infection

Approximately 150 systemic diseases of mammals can be transmitted by some route and in some form to humans. Leptospirosis, rat-bite fever, cat-scratch disease, tularemia, erysipelas, hepatitis B, bubonic plague, rabies, tetanus, and sporotrichosis have been transmitted through bites or scratches, but with the exceptions of rabies and tetanus, this mode of transmission is rare.[70] Patients with these systemic illnesses present weeks or months after the exposure, so a history of animal contact must be elicited.

Infection Risk Factors

Location of Wound

In studies of nonbite lacerations, wounds on the hand and those below the knee have a greater propensity for infection and a higher morbidity than those in other areas of the body[71-73] (Table 58-1). The hand contains many poorly vascularized structures that do not resist infection well. The fascial spaces and tendon sheaths communicate, so an infection quickly spreads throughout the entire hand. For dog bites the infection rate of hand wounds is as high as 30%, regardless of suturing, whereas the infection rate of dog bites elsewhere averages only 9%.[22,24,25] In a series studying cat bites, hand wounds had an infection rate of 19%; lower extremity wounds 20%; and arm, neck, or trunk wounds 5% or less.[42] In contrast, nonbite lacerations of the head and neck have a lower risk of infection than wounds elsewhere on the body.[71,72] Similarly, dog bites of the face and neck (including punctures) have an infection rate of only 0 to 5% even when sutured.[21,22,27] Severe facial wounds that warrant hospital admission and operative repair have a substantially higher infection rate.

Table 58-1 Risk Factors in Bite Wound Infections

FACTOR	HIGH RISK	LOW RISK
Species	Cat Human Probably primate Pig	Dog Rodent
Location of wound	Hand Below knee Through-and-through oral Over joint	Face Scalp Mucosa
Wound type	Puncture Extensive crush Contaminated Old	Large Superficial Clean Recent
Patient	Elderly Diabetic Prosthetic valve Peripheral vascular disease Asplenic Alcoholic Steroids, cytotoxic drugs	

Delay in Care

The age of the wound may be one of the most important factors contributing to the risk of infection. In studies of nonbite wounds, delay in seeking care is associated with a higher risk of infection and complications.[71,73] Dog bites in patients who delay care by 10 to 24 hours have a substantially increased risk of becoming infected.[21,23] Time to presentation, presence of infection at presentation, and subsequent morbidity are strongly correlated in human bites of the hand.[74,75]

Host

Patients with underlying illnesses (e.g., diabetes, peripheral vascular disease) or those taking steroids are at increased risk for infection and poor healing.[72,73] Immunocompromised patients are probably at a higher risk for infection. Elderly patients in general have a higher risk of infection than other age groups for nonbite lacerations and dog bites.[14,76]

MANAGEMENT

First Aid and Wound Preparation

Animal bites should be treated as contusions, with immediate ice and elevation (Box 58-1). Direct pressure with a clean cloth or gauze for 10 minutes will stop most bleeding. Washing the wound with soap and water, ideally with a fine-pore sponge to minimize additional tissue trauma, substantially decreases the risk of rabies infection if done within 3 hours, so this should be carried out before the patient arrives at the hospital if possible.[64]

History

Practitioners should elicit the circumstances of the bite, the biting animal, and whether the animal is in captivity and has been immunized against rabies. Specific inquiry should be made about risks for poor wound healing (e.g., diabetes, peripheral vascular disease) and risks for increased susceptibility to *C. canimorsus*, specifically immune status, lung disease, steroid use, splenectomy, or alcoholism. Tetanus immunization status, allergies to medications, and availability and reliability of follow-up care should also be assessed.

Evaluation and Repair

Radiographs of the injured area may be indicated to detect possible fracture, foreign body, or joint penetration, although they are rarely necessary in dog bites in adults and older children. Infants and small children (up to 2 years old) who sustain substantial bite wounds to the scalp should have skull films or

BOX 58-1 Basic Wound Care for Bites

Arrival at Emergency Department
Elevate
Ice
Evaluate
- Airway-breathing-circulation
- History
  - Circumstances of bite, biting animal, captivity status
  - Diabetes, alcohol, spleen, peripheral vascular disease, steroids, tetanus
- Neurovascular examination distal to wound
- Radiographs as indicated

Wound Preparation
Clean skin; do not shave
If rabies is a concern, scrub wound with soap and water and rinse
Anesthetize
Irrigate, explore, debride

Wound Closure Factors
Species
Type of wound
Location of wound

Aftercare
Dressing
Splint extremities
Tetanus prophylaxis
Prophylactic antibiotics in selected cases
Rabies prophylaxis as indicated

Table 58-2 Recommendations for Wound Closure and Antibiotics in Bite Cases

SPECIES	SUTURING	PROPHYLACTIC ANTIBIOTICS
Dog	All (± hands and feet)	High risk only*
Cat	Face only	All
Rodent	Yes (rarely needed)	No
Monkey	No	Yes
Human		
Hand bites	No	Yes
Other locations	Yes	Not necessary unless other high risk concerns are present*
Self-inflicted		
Mucosa	Yes	No
Through-and-through	Yes	Yes

*Hand wounds; deep punctures; heavy contamination; significant tissue destruction; >12 hours old; joint, tendon, or bone involvement; patients with diabetes, peripheral vascular disease, or corticosteroid use.

preferably a computed tomographic scan.[16] Evidence of skull perforation should prompt neurosurgical consultation and admission to the hospital.

Following a careful neurovascular examination of the injured area, the wound should be anesthetized and explored, looking for foreign bodies and injuries to nerves, tendons, arteries, and joint space violation or injury to other deep structures. After cleaning with soap and water, wound irrigation followed by débridement is recommended. There is no compelling evidence that extension of the wound to promote irrigation diminishes the chance of infection (see Chapter 56).

Much controversy and little data surround the question of suturing animal bites. Sound practice dictates that when a wound is at high risk for infection, it should not be sutured unless there is strong experimental evidence of the safety of the practice. To date, only dog bites have undergone controlled studies.[23] The infection rate in 169 wounds was the same for sutured bites as for those left to heal by secondary intention (7.7%). This was true even for dog bites on the hand, which had a higher infection rate (12%), but with no significant difference between sutured and unsutured wounds. Observational studies demonstrate an equivalent infection rate for sutured dog bites and unsutured wounds.[14,21,22,77] Sutured dog bites of the face have a very low infection rate, even when punctures are sutured and no prophylactic antibiotics are used.[27] Sutured cat bites primarily on the face developed no infections in one study, whereas another study of selectively sutured cat bites found an infection rate of 4.4%. In both studies, patients received antibiotic prophylaxis.[42,77]

The following guidelines are suggested, even though data are limited (Table 58-2). Thorough wound cleansing and irrigation are presumed. Bite wounds of the face and scalp from any species that are less than 12 hours old may be cleansed well and sutured. It is probably safe to suture most uncomplicated dog bites. Lower extremity and hand wounds are at higher risk for infection and should be handled with extra caution (i.e., rarely sutured). Cat bites and primate bites on the face or scalp can be considered for suture repair, but sutures should be avoided in other locations. Puncture wounds from any species should not be closed. Contaminated wounds, wounds more than 12 hours old, or wounds infected at presentation should not be sutured. Most bite wounds that are going to be closed ought to have this done within 6 hours. Patients at risk for infection or poor wound healing should be treated conservatively, with sutures avoided in higher risk wounds. Proper alternatives include delayed primary closure or allowing healing by secondary intention. Patients and physicians may be reassured when small wounds are left open; a study comparing suturing with conservative treatment of uncomplicated, full-thickness hand wounds smaller than 2 cm demonstrated no difference in functional or cosmetic outcome.[78] No current evidence shows that use of topical adhesive results in a lower infection rate than sutures.

A simple, sterile dry dressing is sufficient to protect the wound. Delayed primary closure requires that the wound be kept moist, usually with a wet saline dressing. Abrasions should be covered with a topical antibiotic and dry sterile dressing. Bites of the hands or over joints should be immobilized with a bulky soft dressing or a splint. Bite wounds are considered tetanus-prone (see Table 58-5).[79] It is prudent to encourage patients to have wound checks within 1 to 3 days after the bite. Early follow-up is particularly important when the risk of a *Pasteurella* infection is high.

Prophylactic Antibiotics

Dog Bites

Prophylactic antibiotics are not indicated for most routine dog bite wounds, except of the hand.[22,24,25,80,81] Other high risk wounds (e.g., deep structure injury) and patients at high risk have traditionally been excluded from studies on prophylactic antibiotics and would probably benefit.[25] Therefore a reasonable approach is to give prophylactic antibiotics to victims of

Table 58-3 Suggested Regimens for Prophylactic Antibiotics in Bite Wounds

SPECIES	NONALLERGIC PATIENT	PENICILLIN-ALLERGIC PATIENT
Dog, most other animals	Dicloxacillin Cephalexin	Erythromycin TMP-SMX†
Cat	Cefuroxime	Extended-spectrum quinolone*
	Amoxacillin-clavulanate Dicloxacillin penicillin	Azithromycin TMP-SMX†
Dog, cat; patient who is without spleen or is alcoholic or who has lung disease (*Capnocytophaga canimorsus*)	Penicillin Amoxacillin-clavulanate Azithromycin or clarithromycin	Clindamycin Erythromycin
Human (CFIs),‡ monkey	Cefuroxime	Extended-spectrum quinolone*
	Cefaclor Amoxacillin-clavulanate Ampicillin first-generation cephalosporin Ampicillin dicloxacillin	TMP-SMX†
Human: not CFI	Dicloxacillin or cephalexin	Erythromycin
Human: through-and-through	Penicillin	Clindamycin

CFI, closed-fist injury; TMP-SMX, trimethoprim-sulfamethoxazole.
*Includes levofloxacin, moxifloxacin, sparfloxacin. Quinolones not approved for children and pregnant women.
†Sulfonamides should not be given to pregnant women.
‡Anaerobic coverage not necessary unless established infection; 50% of human mouth anaerobes resistant to penicillin.

high risk dog bite wounds but not to those with low risk wounds (see Table 58-2).

For prophylaxis, 5 days of an antibiotic that covers *S. aureus* and streptococcus is likely sufficient (Table 58-3).

On the other hand, for treatment of established dog bite infection, coverage of *P. multocida* should be included. A second- or third-generation cephalosporin or amoxicillin-clavulanate are all excellent first-line agents. For the adult allergic to penicillin, a combination of clindamycin plus sulfamethoxazole can be used. Doxycycline and fluoroquinolones are also effective but should not be used in children. For penicillin-allergic children, clindamycin plus trimethoprim-sulfamethoxazole (TMP-SMX) is acceptable.

Capnocytophaga canimorsus. There are no studies on prevention of *C. canimorsus* infection, but it is prudent to give patients with known risks prophylactic antibiotics after a dog or cat bite.[35,40] It would be logical to include in this population immunocompromised patients, including those with diabetes. In vitro, *C. canimorsus* is susceptible to penicillin G, ampicillin, carbenicillin, cephalothin, ceftizoxime, clindamycin, erythromycin, tetracycline, fluoroquinolones, vancomycin, and chloramphenicol, although one clinical case of resistance to penicillin, erythromycin and clindamycin has occurred.[38] *C. canimorsus* displays variable susceptibility to TMP-SMX, and it appears to be resistant to all aminoglycosides. For prophylaxis, consider amoxicillin/clavulanate or penicillin for 5 days. For treatment of established infection, an intravenous second- or third-generation cephalosporin, amoxicillin/sulbactam or clindamycin plus a fluoroquinolone (in adults) are acceptable (see Table 58-3).

Cat Bites

One small controlled study on the use of prophylactic antibiotics in cat bites has been published, demonstrating reduced infection with prophylaxis.[51] No other randomized studies on cat bites have been conducted. A Cochrane review, however, concluded that there was no evidence that the use of prophylactic antibiotics are effective for cat bites, although it did conclude that animal bites on the hands benefit from prophylaxis. Because cat bites have been reported to have a high likelihood of infection and infected cat bites often require hospitalization, it may be prudent to consider prophylactic antibiotics for cat bites in certain circumstances such as hand wounds, but sufficient data on this question is lacking.[6,81]

P. multocida should be specifically covered if prophylaxis is given, as well as *S. aureus* and *Streptococcus* species. *P. multocida* may be resistant to semisynthetic penicillins (dicloxacillin, methicillin) as well as erythromycin, clindamycin, first-generation cephalosporins, and aminoglycosides. These antibiotics should not be used to treat *Pasteurella* soft tissue infections and should be avoided in terms of prophylaxis considerations. *Pasteurella* is usually sensitive to penicillin, although some β-lactamase-producing strains have been recovered. *Pasteurella* is also usually sensitive to ampicillin, ticarcillin, amoxicillin-clavulanic acid, tetracyclines, second- and third-generation cephalosporins, fluoroquinolones, and TMP-SMZ.[49] For prophylaxis, excellent coverage and convenience are afforded by a second-generation cephalosporin such as cefuroxime, which needs to be taken only twice a day. Amoxicillin-clavulanate is also a good choice, although it requires more frequent dosing and has substantial side effects.

Extended-spectrum fluoroquinolones cover *P. multocida* and have good staphylococcal and streptococcal coverage.[82] Given the many other alternatives for prophylaxis, however, the use of fluoroquinolones as first-line agents is not recommended because of cost, lack of clinical experience, and concerns that overuse will result in resistance. Additionally, these drugs are not approved for children or pregnant women.

TMP-SMX offers reasonable coverage against *P. multocida* as well as staphylococci and streptococci and is a low-cost, although not ideal, alternative (see Table 58-3). Tetracycline is not advisable for *P. multocida* coverage because it achieves low tissue levels at a very slow rate and is not very effective against common bite pathogens, including streptococci, staphylococci, diphtheroids, *Bacteroides*, and anaerobic gram-positive cocci.[50,82,83] When used together, however, tetracycline and erythromycin have a synergistic effect against *Pasteurella*.[84]

For very high risk bites, such as cat bites on the hands, patients should receive an antibiotic in the ED. Intravenous (IV) treatment is preferable because it achieves detectable levels in the wound much sooner than by the oral (PO) or intramuscular (IM) route. However, even a PO dose of antibiotic at the time of treatment is preferable to giving patients a prescription that may not be filled for 24 hours. The usual course for prophylaxis is 5 days.

Other Animal Bites

Patients who sustain pig bites or camel bites, especially on the hand, should receive antibiotic prophylaxis. Prophylaxis should include coverage against *Pasteurella*. Rodent bites and most

other species have a lower risk of wound infection, so prophylaxis generally is not indicated.

Monkey Bites

Monkey bites are considered to have a high risk for bacterial infection. Although there are no data on the use of prophylactic antibiotics, antibiotics are advisable for full-thickness bites, particularly those on the hand.[56] Management of these wounds involves selection of antibiotics to cover the most common pathogens for animal bites, *Staphylococcus aureus*, anaerobic cocci, and *Bacteroides*. A good choice would be amoxicillin and clavulanic acid (875/125 mg PO bid for 5 days). An acceptable alternative is ciprofloxacin (500 mg PO bid for 5 days) plus metronidazole (500 mg PO tid for 5 days).[85]

Prevention of B virus infection requires *rapid* local wound care; this should be performed at the scene of the exposure before medical evaluation is sought.[57] The wound should be washed with povidone-iodine, chlorhexidine, or a detergent soap solution for at least 15 minutes; eyes or mucous membranes should be irrigated with sterile saline or running water for at least 15 minutes. It is recommended that workers with potential exposures be referred by their occupational health care provider to a person knowledgeable about B virus, as treatment decisions are complex; however, most laboratories provide workers with written information and appropriate kits for specimen collection if they are referred to an ED.

Clinicians examining patients with fresh monkey bites from macaque monkeys, in particular Rhesus and cynomolgus, should determine the risk of exposure by evaluating the time, source, location, and type of exposure, as well as the timeliness and adequacy of cleansing and examination of the wound. Cleansing should be repeated. The health status of the monkey should be determined, and if it can be done safely, the facility should examine the monkey for active lesions. Cultures of bite or scratch wounds or splashes should never be done prior to cleansing but are often negative after cleansing. However, a positive culture for B virus would prompt prophylaxis if not previously given. Prophylaxis with antiviral therapy is recommended only where the risk of transmission is high (Table 58-4) because human cases of infection are extremely rare, despite thousands of potential exposures each year and treatment may interfere with seroconversion, confounding diagnostic testing. The recommended therapy is valacyclovir, (1 g PO q8 for 14 days) or alternatively, acyclovir (800 mg PO 5 times daily for 14 days). Prophylaxis, when indicated, can be given up to 5 days after the exposure.[57] Patients should be counseled about the signs and symptoms of B virus infection and told to immediately seek care if any occur. Patients with high risk exposures should be told to avoid activities that involve exchange of bodily fluids, including saliva. Close follow-up for the next 4 weeks is essential.

Table 58-4 Recommendations for Postexposure Prophylaxis for Persons Exposed to B Virus (Herpesvirus simiae)

Prophylaxis Recommended
Skin exposure (with loss of skin integrity) or mucosal exposure to a high risk source: macaque that is ill, immunocompromised, or known to be shedding virus or has visible lesions compatible with B virus
Inadequately cleaned skin or mucosal exposure
Laceration of head, neck, or torso
Deep puncture bite
Needlestick associated with tissue or fluid from the nervous system, lesions suspicious for B virus, eyelids, or mucosa
Puncture or laceration after exposure to objects (a) contaminated with fluid from monkey oral or genital lesions or with nervous system tissues or (b) known to contain B virus
Postcleaning culture-positive B virus
Prophylaxis Considered
Mucosal splash that has been adequately cleaned
Laceration (with loss of skin integrity) that has been adequately cleaned
Needlestick involving blood from an ill or immunocompromised macaque
Puncture or laceration occurring after exposure to either objects contaminated with body fluid (other than from a lesion) or potentially infected cell culture
Prophylaxis Not Recommended
Skin exposure in which the skin remains intact
Exposure associated with nonmacaque species of nonhuman primates

Modified from Cohen JI, et al: Recommendations for prevention of and therapy for exposure to B virus (Cercopithecine herpesvirus 1). Clin Infect Dis 35:1191, 2002.

DISPOSITION

Patients with life-threatening or limb-threatening injuries or with severe cosmetic defects requiring operative repair, particularly children, should be admitted to the hospital. Most other patients may be discharged with close follow-up. Many U.S. cities and counties have animal bite-reporting laws. These require the ED to obtain details on the biting incident, the animals involved, and names of owners and submit a report shortly after the victim is treated. Public health officials may be able to locate escaped animals or those that are potentially ill based on these reports, as well as to provide consultation regarding the need for rabies prophylaxis and animal management.

Treatment of Infected Bites

Patients who present or return with infected bites should be assessed for complications such as retained foreign body, tenosynovitis, joint infection, or fracture. Abscesses should be drained. Patients with wound infection and fever, systemic symptoms, lymphangitis, or deep structure involvement should be hospitalized for administration of IV antibiotics and surgical consultation as needed. In addition, high risk patients (e.g., diabetic, immunosuppressed, elderly) with localized infections, those with peripheral vascular disease, and those likely to be noncompliant with therapy require hospitalization, although IV antibiotic treatment in a short-stay unit or at home with a visiting nurse may be a suitable alternative. Empiric, broad-spectrum antibiotic coverage should be started and the affected area elevated and immobilized. Anaerobic coverage, should be included for infected bite wounds. Wound or blood cultures are usually not necessary unless the patient fails to respond to the first line of therapy.[86,87] Healthy patients with localized infections may be treated with oral antibiotics at home with close follow-up. The infected area should be immobilized with a splint; the patient should be instructed in strict elevation of the infected area and assessed daily until the infection has resolved.

HUMAN BITES

PERSPECTIVE

Epidemiology

Human bites of the hand, especially the clenched-fist or closed-fist injury (CFI), or fight bite, are associated with a high incidence of infectious complications. These include septic

arthritis, tenosynovitis, and osteomyelitis, as well as surgical amputation necessitated by infection.[74,75] Most simple human bites elsewhere on the body are probably no more significant than ordinary lacerations. The reported rate of infectious complications in human bites of the hand is 25 to 50%.[88] The majority of infections already exist when the patient first presents for care.[74,75] The high infection rate results from a combination of factors: the location on the hand, the position of the hand at the time of injury, the mechanism of entry, associated injuries, the bacteriology of the human mouth, and a delay in seeking care.

PRINCIPLES OF DISEASE

Fight Bites

The CFI is a ragged laceration most often found over the metacarpophalangeal joints of the middle finger and ring finger. It results when an individual strikes another person's mouth with a closed fist. Associated traumatic injuries include the *boxer's fracture* (distal ring or small finger metacarpal fractures), amputations, foreign bodies, and extensor tendon lacerations. Penetration of the joint occurs in up to 62% of wounds; up to 58% involve injury to the bone.[89] The presence of an extensor tendon laceration is highly predictive of joint penetration. Patients who have deep structure involvement have significantly more morbidity than those who do not. Another type of fight bite is an actual bite, usually on the finger, which may penetrate the proximal or distal interphalangeal joint; this can result in a traumatic amputation.

Bacteriology

Information on the bacteriology of human bites comes almost exclusively from hand bites, with the vast majority of these being CFIs. Infected wounds are polymicrobial. *Streptococcus* species and *Staphylococcus aureus* are the most common aerobic pathogens. Gram-negative rods and anaerobes are more frequently isolated from infected human bites than other types of hand infections, including those from animal bites. The presence of anaerobes in mixed infection may be associated with a worse outcome.

Eikenella corrodens, a facultatively anaerobic gram-negative rod harbored in human dental plaque, is found in 25 to 29% of CFI infections.[90] It acts synergistically with aerobic organisms, most frequently streptococci, and is thought to account for greater morbidity in these wounds.[91] *E. corrodens* is susceptible to penicillin, ampicillin, second- and third-generation cephalosporins, carbenicillin, tetracycline, and the fluoroquinolones.[82,83] Resistance to penicillin has been reported.[92] *E. corrodens* is resistant to penicillinase-resistant penicillins, methicillin, nafcillin, aminoglycosides, clindamycin, vancomycin, and metronidazole.[50] Susceptibility to first-generation cephalosporins and erythromycin is suboptimal.[83,92]

Other Human Bites

Human bites in locations other than the hand have about the same rate of infection as ordinary lacerations, if proper local wound care is administered. Human bites of the face have about a 2.5% infection rate.

In children, approximately 70% of human bites are abrasions, which generally do not become infected. The reported infection rate of human bites in children is 9 to 12%. Most of these infections are already established at the time of the initial visit, usually in patients who have delayed care for more than 12 to 18 hours.[93,94]

Wounds from the victim's own teeth, usually a result from a fall or a seizure, may be considered bites. Wounds that only involve the mucosa or tongue have a low infection rate, from 0 to 12%. Mucocutaneous (through-and-through) lacerations have an infection rate of up to 30% in the absence of prophylactic antibiotics. Organisms cultured from these infected wounds include *Streptococcus*, *Staphylococcus aureus*, *Epidermidis*, *Bacteroides*, *Corynebacterium*, *Neisseria*, and *Haemophilus haemolyticus*.[95]

Transmission of Disease

Human bites have resulted in the transmission of actinomycosis, syphilis, tuberculosis, herpes, hepatitis C, and hepatitis B.[96,97] Herpetic whitlow, infection of the distal phalanx from herpes simplex virus, is a well-known occupational hazard for nurses, physicians, dentists, and oral hygienists. Although HIV is secreted at some time in the saliva of up to 44% of infected patients, the CDC does not consider human bites to carry a risk of transmission unless there is exposure to blood in the process.[98-100] HIV is not often present in the saliva of most infected patients, and when it is, the titer of virus is very low.[97] Cases in which HIV has convincingly been transmitted through a bite involved significant amounts of blood mixed with the saliva.[101,102] Nevertheless, when a significant bite has occurred, and particularly if the biter is known to be HIV-positive, it is reasonable to consult with infection control experts locally or at the CDC. The potential risk of HIV transmission to the person inflicting the bite should also be considered.

MANAGEMENT

The approach to the human bite depends on the location and the mechanism of injury. Any laceration or puncture in the vicinity of the metacarpophalangeal joint should be considered a CFI unless proved otherwise. Full-thickness bites on the hand should be considered high risk. Hand radiographs should be obtained, looking for fractures, dislocations, retained tooth fragments or other foreign bodies, or air in the joint space.[74,75] A "skyline" view, but not standard finger views, may demonstrate vertical articular fractures of the metacarpals.[103]

The wound should be assessed for signs of established infection and a careful neurovascular examination performed, paying particular attention to the extensor function. The wound should then be anesthetized and explored in a bloodless field to look for foreign bodies, tendon laceration, or joint penetration. It is essential that the wound be examined through the full range of motion, including the position at the moment of injury. The wound should be irrigated and débrided. Wounds that demonstrate tendon lacerations should be presumed to have joint involvement as well, and this finding should prompt consultation by a hand surgeon.

Although there are no controlled studies on suturing human bites, the high rate of infection and complications of human bites on the hand suggest that they should be left open rather than sutured. The wound should be covered with a dry sterile dressing and the hand splinted in a position of function either with a plaster splint or by packing the palm with bulky gauze and wrapping the hand in a mitten-type dressing. Human bites are considered to be tetanus-prone wounds (Table 58-5).[79,104] Human bite injuries elsewhere on the body should generally be treated as typical lacerations. Treatment includes irrigation,

Table 58-5 Guidelines for Tetanus Prophylaxis

HISTORY OF ADSORBED TETANUS TOXOID (DOSES)	CLEAN, MINOR WOUNDS		ALL OTHER WOUNDS*	
	Td†	*TIG*	*Td*†	*TIG*
Unknown or <3	Yes	No	Yes	Yes
≥3‡	No§	No	No¶	No

*Such as, but not limited to, wounds contaminated with dirt, feces, soil, and saliva; puncture wounds; avulsions; and wounds resulting from missiles, crushing, burns, and frostbite.
†For children <7 years old, DTP (DT, if pertussis vaccine is contraindicated) is preferred to tetanus toxoid alone. For persons ≥7 years of age, Td is preferred to tetanus toxoid alone.
‡If only three doses of *fluid* toxoid have been received, a fourth dose of toxoid, preferably an adsorbed toxoid, should be given.
§Yes, if >10 years since last dose.
¶Yes, if >5 years since last dose. (More frequent boosters are not needed and can accentuate side effects.)
DTP, diphtheria, tetanus, and pertussis antigen; Td, tetanus, diphtheria antigen; TIG, tetanus immune globulin.
From the Centers for Disease Control and Prevention: Diphtheria, tetanus, and pertussis: Recommendations for vaccine use and other preventive measures—recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 40:1, 1991.

aggressive débridement, and suturing if anatomy permits and cosmetic considerations are important.[105]

Antiviral Agents

Victims of bites from persons potentially infected with HIV or hepatitis should receive exceptionally rapid, vigorous, and thorough wound cleansing with soap and water, to remove saliva, followed by irrigation with virucidal agents such as 1% povidone-iodine. A baseline HIV blood test and hepatitis antibodies at the time of injury should be obtained or arranged, along with a follow-up test in 6 months. If the bite involved blood, hepatitis B and HIV prophylaxis may be warranted. Consultation with the CDC's postexposure prophylaxis hotline regarding possible blood-borne exposures is available 24 hours a day (1-888-448-4911; http://www.ucsf.edu/hivcntr/).

Prophylactic Antibiotics

Antibiotic prophylaxis is recommended for full-thickness human bite wounds of the hand (see Tables 58-2 and 58-3). One randomized, placebo-controlled study of hospitalized patients with uninfected human bites on the hand found no infections in patients who received antibiotics, whereas those who received placebo had a 47% infection rate.[88] Although good results have been achieved historically in selected situations without prophylactic antibiotics when patients presented early and received appropriate wound cleansing, this is probably not optimum management today.[74,75] Antibiotics are also indicated for high risk wounds elsewhere on the body, including deep punctures, severe crush injuries, contaminated wounds, older wounds, and wounds in patients with underlying illnesses. The antibiotic selected should offer coverage for gram-positive organisms and *E. corrodens*, such as with a second-generation cephalosporin or amoxicillin-clavulanate, and should be given for 5 days.

Mucosal lacerations from a person's own teeth, including those of the tongue, should be irrigated well. Suturing is advisable only for deeper and larger wounds. Although such wounds may have a higher risk of infection, prophylactic antibiotics do not necessarily reduce the incidence.[95] Through-and-through lacerations, from a tooth puncture through the skin of the lower lip, may require a layered closure and are at high risk for infection. Prophylactic antibiotics probably reduce the risk.[95] Penicillin for 5 days remains the regimen of choice.

BOX 58-2 Indications for Hospital Admission for Human Bites of the Hand

Wound >24 hours old
Established infection
Penetration of joint or tendon sheath
Bone involvement
Foreign body
Unreliable patient or poor home situation
Diabetic or suppressed immune status

Infected Wounds

Infected human bites of the hand require both aerobic and anaerobic cultures, and the patient should be treated with IV antibiotics that cover gram-positive organisms, *E. corrodens*, and anaerobes. Anaerobes isolated from human bite wounds produce β-lactamase and are often resistant to penicillin. Treatment options include amoxicillin-sulbactam, cefoxitin, and ticarcillin-clavulanate. Penicillin-allergic patients may receive clindamycin plus TMP-SMX or clindamycin plus a fluoroquinolone, although data for these regimens are limited.

DISPOSITION

Patients with Infection

All patients with infected human bites of the hand should be hospitalized (Box 58-2). Localized infections of human bites not on the hand can usually be treated without hospitalization in immunocompetent patients with no evidence of lymphangitis or systemic symptoms for whom appropriate follow-up can be arranged.

Patients without Infection

Reliable, otherwise healthy patients who present within 24 hours without infection and have no tendon, joint, or bone damage may be treated at home with close follow-up, preferably within 1 or 2 days.[74,75] Discharge instructions should include immobilization, elevation, and sterile dressing changes every 6 hours.

Patients at high risk, such as those with delayed presentation or deep structure involvement, require prophylactic parenteral antibiotics and close evaluation. Consultation with a hand surgeon is highly recommended, and hospitalization is generally prudent. Although many human bites are a consequence of mutual aggression, the physician must keep in mind that the patient may be the victim (or perpetrator) of child, spousal, or elder abuse.[106] All states require reporting of suspected child abuse; laws vary for spousal or elder abuse. In all cases, details of the incident should be documented and the wound carefully described in the record. Counseling or referral should be offered when appropriate.

KEY CONCEPTS

- *Dog bites*: Prophylactic antibiotics are not indicated for routine dog bite wounds but are recommended for dog bites of the hand and for high risk patients. Coverage should be aimed primarily at staphylococci and streptococci.
- Patients at risk for *C. canimorsus* infection should receive prophylactic antibiotics for this organism after a dog bite.
- *Cat bites*: Cat bite wounds have a high rate of infection and warrant consideration of prophylactic antibiotic administration in high risk situations.
- *Suturing bites*: In general, when a wound is at high risk for infection, it should not be sutured.
- *Human bites*: Prophylactic antibiotics are recommended for all human bites of the hand as well as for high risk wounds, including deep punctures, severe crush injuries, contaminated wounds, older wounds, and wounds in patients with underlying illnesses. Ordinary human bites, such as those exchanged among children (nonpercutaneous, superficial, minimal tissue trauma), do not represent a high risk for infections or complications and do not require prophylaxis.
- All bites are considered tetanus-prone wounds.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 59

Venomous Animal Injuries

Edward J. Otten

Young primates appear to be born with only three inborn fears—of falling, snakes, and the dark.

C. Sagan[1]

PERSPECTIVE

Epidemiology

Venomous animals account for considerable morbidity and mortality worldwide. Snakes alone are estimated to inflict 2.5 million venomous bites annually, with approximately 125,000 deaths. The actual numbers may be much larger. Southeast Asia, India, Brazil, and areas of Africa lead the world in snakebite mortality.[2] It is impossible to estimate the worldwide morbidity and mortality resulting from other venomous animals such as bees, wasps, ants, and spiders.

Approximately 45,000 snakebites occur annually in the United States; 7000 to 8000 are inflicted by venomous snakes, and 5 to 10 result in death. Table 59-1 categorizes fatalities caused by venomous animals in the United States for the 20-year period from 1950 to 1969.[3-6] Insects were responsible for 52%, snakes for 30%, and spiders for 13%. Specifically, bees were responsible for the most fatalities, followed by rattlesnakes, wasps, and spiders. Historically, most of the recorded spider deaths were caused by the black widow, although the brown recluse spider has been implicated in an increasing number of deaths.

The American Association of Poison Control Centers began collecting data in 1983 on deaths caused by venomous animals. Their 20-year experience shows a significant number of exposures by bite or sting but relatively few deaths (Table 59-2).[7] Although these data include most of the United States, there is no requirement that hospitals, emergency departments, coroners, or public health agencies report deaths or exposure to Regional Drug and Poison Information Centers. This decline may be caused by an actual decrease in mortality or may be due to inadequate reporting. Meaningful morbidity data, such as the number of amputations, hospitalizations, and disabilities, do not exist. The number of exposures and deaths from exotic snakes seems to be increasing, possibly because of interest in collecting so-called hot or venomous varieties such as cobras, mambas, and vipers. The morbidity from marine animal injuries is increasing in proportion to the number of people exposed to the ocean and the number of private collectors, but the mortality has not increased dramatically. An increase in outdoor recreational activities such as camping, scuba diving, and wilderness trekking puts more people in proximity to venomous animals and increases the risk of envenomation. Most exposures occur from April to October, when animals are most active and potential victims are outdoors and involved in activities that might increase their risk for envenomation. Of course, many spider bites and exotic animal envenomations that occur indoors can take place at any time. Most deaths seem to occur in very young, elderly, and/or inappropriately treated patients.

Venom Delivery

Animals that have developed specific venom glands and venom delivery systems can be found in every class, including, most recently, birds.[8] The toxin and toxic apparatus vary from class to class. For example, the rattlesnake has modified salivary glands and maxillary teeth and uses this system primarily to obtain food. The bee has a modified ovipositor that is used mainly for defense. Poisonous and venomous animals are not the same and should be differentiated. Animals can be considered *poisonous* because of various toxins distributed in their tissues. For example, certain shellfish, toads, and barracuda have been known to cause death after ingestion. However, only animals with specific glands for producing venom connected to an apparatus for delivering that venom to another animal can be considered *venomous*.

Most venomous animal injuries seen in the emergency department are minor problems, but some injuries must be given priority. Venomous snakebites, black widow spider bites, certain marine animal envenomations, and anaphylactic reactions to insect stings are life-threatening emergencies requiring immediate attention.

VENOMOUS REPTILES

Snakes

Snakes first appeared in the late Cretaceous period, and venomous snakes evolved approximately 50 million years later in the Miocene epoch. Of the 3000 species of snakes, approximately 10 to 15% are venomous. Of the 14 families of snakes, 5 contain venomous species. Snakes are distributed throughout most of the earth's surface, including fresh and salt water. The major exceptions are the Arctic and Antarctic zones, New Zealand, Malagasy, and many small islands. Most snakebites occur in tropical and subtropical climates, especially in agricultural settings where the inhabitants go barefoot. Sea snakes are found only in the Pacific and Indian Oceans. Snakes are

Table 59-1 Venomous Animal Fatalities in the United States, 1950–1969

ANIMAL	FATALITIES
Hymenoptera	
Bees	175
Wasps	127
Yellow jackets	33
Hornets	12
Ants	5
Ticks	3
Spiders	92
Unidentified insects	53
Coelenterata	2
Stingray	1
Snakes	
Rattlesnakes	159
Water moccasins	9
Copperheads	2
Coral	3
Cobra	3
Unidentified	67
Animal, not coded	44
Total	790

Table 59-2 Venomous Animal Injuries and Deaths, 1983–2006

ANIMAL	ENVENOMATIONS	DEATHS
Coelenterates	13,846	0
Fish	23,866	0
Ants	45,019	0
Bees/wasps/hornets	327,268	22
Caterpillars/centipedes	40,768	0
Other arthropods	234,147	2
Copperheads	10,720	1
Rattlesnakes	17,382	23
Water moccasins	1,887	0
Coral snakes	1,055	0
Exotic snakes	1,994	3
Nonvenomous snakes	34,385	0
Unknown snakes	35,695	2
Black widow spiders	50,968	0
Brown recluse spiders	37,811	7
Other/unknown spiders	238,447	1
Scorpions	210,675	3

Data compiled from Watson WA, Litovitz TL, et al: American Association of Poison Control Centers data. *Am J Emerg Med* 2:1984–2005; Lai et al: *Clini Toxicolo* 44, 2006; and Bronstein et al: *Clini Toxicolo* 45, 2007.

poikilotherms, which accounts for their distribution and activity. Their inability to raise their body temperature above ambient levels restricts their activity to a fairly narrow temperature range, approximately 25° C to 35° C. All snakes are carnivorous, and their venom apparatus evolved for the purpose of obtaining food.

Epidemiology

The incidence of reported venomous snakebites is greatest in the southern United States, which has the largest number of venomous snakes. States having the highest death rates are North Carolina, Arkansas, Texas, and Georgia. The anatomic distribution of snakebites is not surprising. Of all snakebites, 97% occur on the extremities, with two thirds on the upper extremities and one third on the lower extremities. This is a reversal of the previous trend and may reflect bites being provoked rather than accidental. Bites that occur accidentally are considered "legitimate," whereas bites that occur when attempting to handle or disturb a snake are considered "illegitimate." Men are bitten nine times more frequently than women.[9]

Imported venomous snakes have recently been an increasing problem throughout the United States. In the past, only zoos, research centers, and herpetologists kept exotic venomous snakes. Today, however, hundreds of people are raising deadly venomous snakes without the necessary precautions, such as specialized cages, safe handling techniques, and rapid access to specific antivenin. They place not only themselves in danger but also their families and the general public.

Classification and Characteristics

The five venomous families of snakes are the Colubridae, Hydrophiidae, Elapidae, Viperidae, and Crotalidae. The Colubridae, although representing 70% of all species of snakes, have very few venomous members dangerous to humans; these include the boomslang and bird snake. The Hydrophiidae are sea snakes. The Elapidae are more common and include the cobras, kraits, mambas, and coral snakes. The Viperidae, or true vipers, are represented by Russell's viper, the puff adder, the Gaboon viper, the saw-scaled viper, and the European viper. The Crotalidae, or pit vipers, are sometimes considered a separate family and sometimes a subfamily of the Viperidae. Among the pit vipers are the most common American venomous snakes, such as rattlesnakes, water moccasins, copperheads, the bushmaster, and the fer-de-lance. Several species of Asian pit vipers are responsible for bites in Okinawa and bites by imported snakes in the United States.[10-12]

Pit vipers, the most prevalent venomous snakes in the United States, are native to every state except Maine, Alaska, and Hawaii. They are classified into three main groups: true rattlesnakes (genus *Crotalus*), copperheads and water moccasins (genus *Agkistrodon*), and pygmy or Massasauga rattlesnakes (genus *Sistrurus*). Pit vipers account for 98% of all venomous snakebites in the United States.[13,14]

The Colubridae and Hydrophiidae families have few venomous members and are responsible for even fewer injuries. Some colubrid species found in the United States that were previously thought to be harmless may indeed be venomous. Examples are the Lyre snake and the wandering garter snake. No deaths have been reported, but the problem has generated much interest among herpetologists and toxicologists.[15] The yellow-bellied sea snake (*Pelamis platurus*; family Hydrophiidae) has been found off the coast of southern California and western Mexico, but bites by this snake are rare.

The other major group of venomous snakes in the United States is the *coral* snakes. The eastern coral snake (*Micrurus fulvius*) is found in North Carolina, South Carolina, Florida, Louisiana, Mississippi, Georgia, and Texas. The western or Sonoran (*Micruroides euryxanthus*) coral snake is native to Arizona and New Mexico. Although both species are generally quite shy unless handled, the eastern coral snake is considered deadly. There are no records of fatalities caused by the western species.

Coral snakes can be readily identified by their color pattern. At first glance, they resemble one of several varieties of king

snake found in the southern United States. The coral snake can be differentiated from the king snake by two characteristics: The nose of the coral snake is black, and the red and yellow bands are adjacent on the coral snake but separated by a black band on the king snake. The popular rhyme is as follows:

Red next to yellow, kill a fellow.
Red next to black, venom lack.

This rhyme can be used only in the United States; Brazilian coral snakes have red next to black bands, and some coral snakes have no red bands.

Identification

In the identification of venomous snakes, two principles should be kept in mind: Only experts should handle live snakes, and even dead snakes can envenom careless handlers.[16] It is not difficult to differentiate between pit vipers and harmless snakes found in the United States (Fig. 59-1). Pit vipers, as their name implies, have a characteristic pit midway between the eye and the nostril on both sides of the head. This pit is a heat-sensitive organ that enables the snake to locate warm-blooded prey. Pit vipers may be identified through other methods, but this characteristic is 100% consistent. The triangular shape of the head, the presence of an elliptic pupil, the arrangement of subcaudal plates, the tail structure, and the presence of fangs are useful characteristics but are inconsistent. An individual specimen may not fit the classic description, depending on the age of the snake, the time of the year, and the condition of the tail and mouthparts. A person should never attempt to identify pit vipers by color or skin patterns (Fig. 59-2).[13,14]

Size is not an important factor in identifying various reptiles. Venomous snakes range in length from several inches to several feet. Although a 6-foot eastern diamondback rattlesnake is much more dangerous than a 10-inch copperhead, all venomous snakes are able to envenom from birth and should be treated as though they are dangerous.

Exotic snakes that are *not* pit vipers are not as easily identified. If possible, they should be safely transported to an expert for positive identification. Local zoos, herpetology groups, and colleges often have individuals who can identify unknown snakes. Usually, however, a person bitten by an exotic snake knows the type of snake or at least the common name of the snake.

Other Reptiles

Only two venomous lizards are found in the world, both in the southwestern United States and Mexico. They are the Gila monster (*Heloderma suspectum*) and the Mexican beaded lizard (*Heloderma horridum*). Fortunately, both these lizards are nonaggressive and rarely encountered. Bites usually result from handling the animals in captivity.[17] The Gila monster and the Mexican beaded lizard are easily identifiable. Both have thick bodies, beaded scales, and either white and black or pink and black coloration.

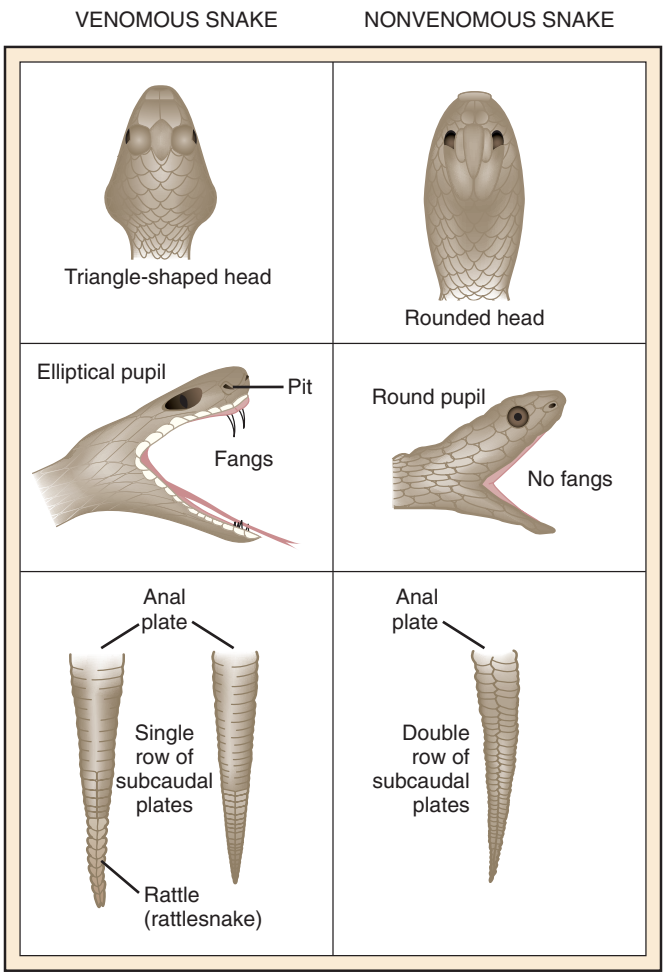


Figure 59-1. Identification of venomous and nonvenomous snakes.

Principles of Disease

Toxins

The two main factors influencing the pathophysiology of any venomous animal injury are the toxic properties of the venom and the victim's response to these toxins. In the past, snake venoms were classified as either neurotoxic or hematotoxic, depending on the observed response of the victim to the various venoms. Modern toxicologic investigation has shown that this classification is inadequate because most snake venoms studied contain compounds that have many toxic properties. It is true, however, that the venom of a particular species of snake may show a clinical response, predominantly neurotoxic or hematotoxic.[18]

Figure 59-2. Western diamondback rattlesnake (*Crotalus atrox*).

The toxic components of snake venom can be classified into four broad categories: enzymes, polypeptides, glycoproteins, and low-molecular-weight compounds. They can also be classified as protein and nonprotein compounds. *Proteins*, which account for most of the toxic manifestations, make up 90 to 95% of venom. Symptoms can generally be classified as local or systemic. Local effects are usually caused by enzymatic action on the various cellular and noncellular structures in the victim's tissues. These enzymes can cause coagulation, anticoagulation, cell lysis, hemorrhage, hemolysis, and the destruction of nucleic acid, mitochondria, and other organelles.

Polypeptides are structurally smaller and more rapidly absorbed than proteins and may account for the venom's effects on presynaptic and postsynaptic membranes and other organ systems.

Phospholipase A can inhibit electron transfer at the level of cytochrome *c* and render mitochondrial-bound enzymes soluble. It can hydrolyze phospholipids in nerve axons, break down acetylcholine vesicles at the myoneural junction, cause myonecrosis, and induce lysis of red cell membranes. This single enzyme has been identified in all venoms of Hydrophiidae, Elapidae, Viperidae, and Crotalidae thus far investigated.[19,20]

Elapidae and Hydrophiidae venoms have predominantly systemic effects, whereas Colubridae, Viperidae, and Crotalidae venoms have mainly local effects. There are many exceptions to this general division. For example, the venom of the Mojave rattlesnake (*Crotalus scutulatus*) may show minimal local effects and significant systemic effects, whereas the venom of the cobra (*Naja naja*) may cause extensive local tissue destruction.[19,21]

Venom Delivery

The mechanism for delivering venom is fairly standard among snakes. It consists of two venom glands, hollow or grooved fangs, and ducts connecting the glands to the fangs. The glands, which evolved from salivary glands, are located on each side of the head above the maxillae and behind the eyes. Each gland has an individual muscle and a separate nerve supply that allow the snake to vary the amount of venom injected. The venom duct leads from the anterior portion of the gland along the maxilla to the fangs. Pit vipers have fangs that are large anterior maxillary teeth. These teeth are hollow and rotate outward from a resting position to a striking position. The coral snake has fixed, hollow maxillary teeth that are much smaller than those of pit vipers. The fangs in most snakes are shed and replaced regularly, and it is not unusual to see a snake with double fangs on one or both sides of its mouth.[5,21,22]

The snake can control the amount of venom injected. In biting a human, a prey much too large to swallow, the snake may become confused or disoriented, especially if injured or surprised, and inject little or no venom (a "dry" bite). However, the snake may inject more than 90% of the contents of the gland for the same reasons.

Clinical Features

The signs and symptoms of a venomous snakebite vary considerably and depend on many factors. From 30 to 50% of venomous snakebites result in little or no envenomation. A person with impaired cardiovascular, renal, or pulmonary function is less able to cope with even moderately severe envenomation. Because of these multiple variables, the individual clinical response is the only way to judge the severity of a venomous snakebite.[11] Factors that influence the effects of a snakebite are the age, health, and size of the snake; the relative toxicity of the venom; the condition of the fangs; whether the snake has recently fed or is injured; the size, age, and medical problems of the victim; and the anatomic location of the bite.

Local envenomation, if left untreated, can cause serious systemic problems (e.g., disseminated intravascular coagulation, pulmonary edema, and shock) as the toxic products are absorbed. The victim's autopharmacologic response to the envenomation must also be taken into account. An IgE-mediated anaphylactic-type reaction may develop in victims of a previous snakebite when re-exposed to the venom. Many venoms contain enzymes that trigger the release of bradykinin, histamine, and serotonin from the patient's cells, which may cause fatal anaphylactic reactions. A wave of effects ranging from minimal pain to multisystem failure and death can occur over a period of several days.

Pit Vipers

The most consistent symptom associated with pit viper bites is immediate burning pain in the area of the bite, whereas pain may be minimal with bites of Elapidae and other exotic snakes. With pit vipers, the severity of pain is probably related to the amount of venom injected or the degree of swelling. Edema surrounding the bite that gradually spreads proximally is a common finding. This edema is usually subcutaneous, begins early, and may involve the entire extremity. Compartment syndrome has been described; however, it is unusual even with severe edema. It has been reported more frequently in models involving intracompartmental venom injection.[23] Most fangs do not penetrate into the fascial compartments, although muscle destruction may result from direct toxicity. Mortality is less frequent with distal bites to the toe and finger and is greatly increased with intravenous bites. An intravenous bite from any venomous snake is likely to be fatal. Petechiae, ecchymosis, and serous or hemorrhagic bullae are other local signs. Necrosis of skin and subcutaneous tissue is noted later and may result from inadequate doses of antivenin. Many systemic symptoms, such as weakness, nausea, fever, vomiting, sweating, numbness and tingling around the mouth, metallic taste in the mouth, muscle fasciculations, and hypotension, often occur after pit viper envenomation.

Death from pit viper bites is associated with disruption of the coagulation mechanism and increased capillary membrane permeability. Ultimately, these two processes lead to massive pulmonary edema, shock, and death. Heart and kidney damage occurs secondary to these mechanisms. Specific toxins in certain species may act directly on specific organs, such as the heart or skeletal muscle. An allergic type of reaction may add to this process through release of histamine and bradykinin.[24,25]

Coral Snakes

Signs and symptoms can vary considerably with bites of coral snakes, Mojave rattlesnakes, and many exotic snakes, especially cobras and Australian elapids. Little pain and swelling may occur. Many of these species' venoms contain compounds that block neuromuscular transmission at acetylcholine receptor sites and have direct inhibitory effects on cardiac and skeletal muscle. Ptosis is common and often the first outward sign of envenomation. Other signs and symptoms include vertigo, paresthesias, fasciculations, slurred speech, drowsiness, dysphagia, restlessness, increased salivation, nausea, and proximal muscle weakness. The usual cause of death is respiratory failure.[14]

Gila Monster

Gila monster bites are generally associated with pain, edema, and weakness. Hypotension is common with severe bites. Envenomation involves secretion of the venom from glands along the lower jaws. The venom is introduced into the victim through grooved teeth and a chewing mechanism. Gila monster bites are seldom fatal.[17]

Infection

Although snakebite envenomation has been stressed here, any bite or puncture wound carries a risk for bacterial contamination. Gram-negative organisms predominate when snake venom and mouthparts are cultured. Although several studies have shown that prophylactic antibiotics are not indicated for snakebite, tetanus, osteomyelitis, cellulitis, or gas gangrene may occur in cases of snakebite with or without envenomation. This is especially true when a large amount of local tissue destruction has occurred, treatment has been delayed, or inappropriate first aid was attempted.[26]

Management

Out-of-Hospital Care

All snakebites should be considered an emergency, and any victim should be medically evaluated. The initial 6 to 8 hours after a snakebite is critical. During this time, medical therapy can help prevent the morbidity associated with severe envenomation. Effective out-of-hospital care can be important.[27]

Out-of-hospital care is relatively simple if guided by four basic concepts. First, the estimated time until arrival at a medical facility, as well as the skill of the on-scene assistants, must be considered when instituting first aid. The victim should be separated from the snake if possible to prevent further bites. A stick, pole, or other object longer than the snake can be used to move the snake away from the victim or, if necessary, to kill the snake by striking it behind the head. Rapid transportation to a medical facility is the best first aid for a snakebite.

Second, spread of the venom should be slowed if possible; several methods are known. The patient's excitement and physical activity, movement of the bitten area, alcohol consumption, and greater depth of the bite increase the spread of venom. Except for the last factor, these issues can be addressed by calming the victim, immobilizing the bitten area, and not giving anything by mouth. A new method of first aid for venomous snakebites has been developed in Australia. The immobilization and compression technique, also called the Commonwealth Serum Laboratory technique, slows uptake of Elapidae venom and mock venom in humans. The bitten extremity is either wrapped in an elastic bandage or placed in an air splint. In another technique from Australia called the Monash method, a thick pad and bandage are placed over the bite wound and extremity. Both these techniques have similar postulated mechanisms of action: The lymphatic vessels and superficial veins are collapsed, and the proximal spread of venom is slowed. Although this method is successful as first-aid therapy for Elapidae bites, its use for pit vipers has not been demonstrated.[28-30] If less than 30 minutes has elapsed since the bite, a constricting band applied tightly enough to impede superficial venous and lymph flow, but not arterial blood flow, may be used. The band should be loose enough to admit a finger between the band and the skin after application. It should be used with caution to prevent the development of a tourniquet effect under swollen tissue, which may cause more destruction than the snakebite.[31] Incision of bite wounds should be avoided because of lack of proven efficacy and potential danger to underlying structures. The use of ice is not helpful in slowing the spread of venom, but an ice bag wrapped in a towel and applied to the bite area helps relieve pain. Ice water immersion and packing of the extremity in ice are dangerous and only contribute to tissue destruction. The use of suction devices has not been shown to be beneficial.[32,33]

Third, when feasible, the snake should be identified or brought to the treating facility with the victim. This should be done safely; usually, only experts should handle live snakes. Dead snakes can be placed in a hard container such as a bucket or ice chest. Care should be taken to not touch the head of the snake because envenomation can occur even after death. Live snakes should not be pursued to capture them. It is more important to get the victim to definitive medical care. Fourth, additional medical interventions should be initiated, if available. Cardiac monitoring, intravenous fluids, analgesics, and blood samples may be helpful, especially with signs of envenomation.

Emergency Department Care

Many snakes do not envenomate their victims when they bite, which has provided false support for the historical use of whiskey, clam juice, or split chickens for snakebite. The only proven therapy is antivenin. Emergency department care of a snakebite must focus on supportive care and rapid treatment with the appropriate antivenin. Rapid decision-making is required to determine the optimal type, amount, and route of administration of the antivenin. By the time the emergency physician examines a snakebite victim, the venom may have already caused much damage both locally and systemically. In this case, the emergency physician must be prepared to support the victim's cardiovascular and respiratory systems.

The snake should be identified if possible, but this may not be easy. The presence of pits is the most consistent factor in identifying pit vipers, and the color pattern can help identify a coral snake. Most large cities have either zoos or herpetologic societies whose members can help identify exotic or unknown snakes. Fortunately, most victims of exotic snakebite are collectors and can positively identify the snake.

Patient History. Specific historical information should include time elapsed since the bite, the number of bites, whether first aid was administered and what type, location of the bite, and any symptoms (e.g., pain, numbness, nausea, tingling around the mouth, metallic taste in the mouth, muscle cramps, dyspnea, and dizziness). A brief medical history should include the last tetanus immunization, medications, and cardiovascular, hematologic, renal, and respiratory problems. An allergy history with emphasis on symptoms after exposure to horse or sheep products, previous injection of horse or sheep serum, and a history of asthma, hay fever, or urticaria should be obtained if considering antivenin treatment.

Patient Examination. The bite area should be examined for signs of fang marks or scratches and local envenomation (e.g., edema, petechiae, ecchymosis, and bullae). The area distal to the bite should be checked for pulses. A general physical examination should be performed with emphasis on the cardiorespiratory system. A thorough neurologic examination should be performed and recorded, especially if a Mojave rattlesnake, coral snake, or exotic snake is suspected. If the bite involves an extremity, the circumference of the extremity at the site of the bite and approximately 5 inches proximal to the bite should be measured and recorded. These data aid in objectively estimating both spread of the venom and the effect of antivenin (Fig. 59-3).

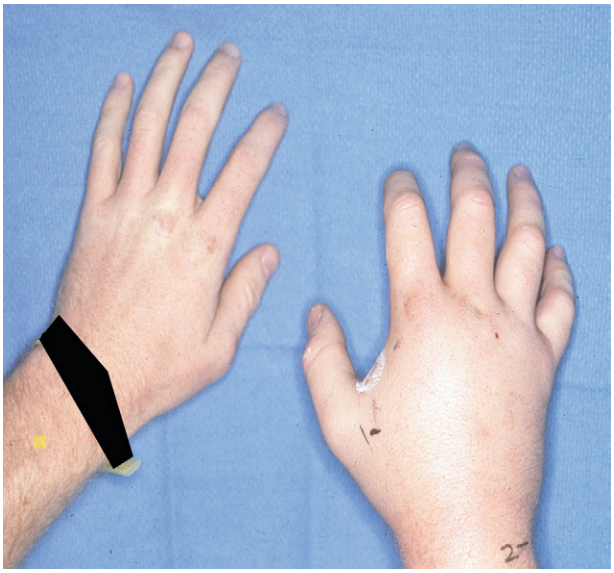


Figure 59-3. Northern copperhead (*Agkistrodon controtrix mokasen*) bite on right hand with normal left hand for comparison.

Initial Medical Care. If the bite occurred less than 30 minutes before arrival in the emergency department, first-aid measures can be instituted, including a constricting band until antivenin can be obtained. Snakebite victims with clinical evidence of envenomation should have an intravenous line with normal saline placed in an unaffected extremity. An electrocardiogram, complete blood count, urinalysis, protime, and levels of fibrinogen, fibrin split products, electrolytes, blood urea nitrogen, and creatinine should be obtained. The patient's blood should be typed and crossmatched for 4 U of packed red blood cells.

The patient's vital signs must be monitored closely. Snakebite victims are often hypotensive because of third-space losses and hemorrhage. In an edematous extremity, the distal pulse may have to be examined with a Doppler instrument. If a compartment syndrome is suspected, a pressure monitor should be inserted and surgical consultation obtained. If signs and symptoms of compartment syndrome are present, pressure greater than 30 mm Hg may require fasciotomy.

At this point, the emergency physician should determine the severity of the bite and decide whether to administer antivenin. The more distal the bite on the extremity, the less toxicity associated with the bite.[34] Intravenous bites may be rapidly fatal.[25] Bites occurring on the trunk, neck, and face have increased risk because of rapid transit of the venom.

Antivenin. The emergency physician should determine the type of antivenin to administer, how much, and over what period.[14] If the bite is from a pit viper, the problem is not too difficult. Envenomation may be classified according to severity into five grades, from grade 0 (no sign of envenomation) to grade IV (very severe envenomation). The amount of antivenin to be given is correlated with the grade of envenomation (Table 59-3). Bites by copperheads usually cause a moderate amount of edema but generally do not require antivenin. Dart and colleagues have advocated slightly different grading systems and higher doses of antivenin. Grades 0 and I correspond to *minimal* envenomation, grade II represents *moderate* envenomation, and grades III and IV correspond to *severe* envenomation.[35]

Grading Envenomation

- *Grade 0 (minimal).* There is no evidence of envenomation, but snakebite is suspected. A fang wound may be present. Pain is minimal, with less than 1 inch of surrounding edema and erythema. No systemic manifestations are present during the first 12 hours after the bite. No laboratory changes occur.
- *Grade I (minimal).* There is minimal envenomation, and snakebite is suspected. A fang wound is usually present. Pain is moderate or throbbing and localized to the fang wound, surrounded by 1 to 5 inches of edema and erythema. No evidence of systemic involvement is present after 12 hours of observation. No laboratory changes occur.
- *Grade II (moderate).* There is moderate envenomation, more severe and widely distributed pain, edema spreading toward the trunk, and petechiae and ecchymoses limited to the area of edema. Nausea, vomiting, and a mild elevation in temperature are usually present.
- *Grade III (severe).* The envenomation is severe. The case may initially resemble a grade I or II envenomation, but the course is rapidly progressive. Within 12 hours, edema spreads up the extremity and may involve part of the trunk. Petechiae and ecchymoses may be generalized. Systemic manifestations may include tachycardia and hypotension. Laboratory abnormalities may include an elevated white blood cell count, creatine phosphokinase, prothrombin time, and partial thromboplastin time, as well as elevated fibrin degradation products and D-dimer. Decreased platelets and fibrinogen are common. Hematuria, myoglobinuria, increased bleeding time, and renal or hepatic abnormalities may also occur.
- *Grade IV (severe).* The envenomation is very severe and is seen most frequently after the bite of a large rattlesnake. It is characterized by sudden pain, rapidly progressive swelling that may reach and involve the trunk within a few hours, ecchymoses, bleb formation, and necrosis. Systemic manifestations, often commencing within 15 minutes of the bite, usually include weakness, nausea, vomiting, vertigo, and numbness or tingling of the lips or face. Muscle fasciculations, painful muscular cramping, pallor, sweating, cold and clammy skin, rapid and weak pulse, incontinence, convulsions, and coma may also be observed. An intravenous bite may result in cardiopulmonary arrest soon after the bite.

Table 59-3 Antivenin Dosage for Pit Viper Envenomation*

ENVENOMATION	FABAV†	WYETH AV
Moderate	4–6 vials	4–6 vials
Severe	8–12 vials	5–10 vials
Very severe	12–18 vials	10–20+ vials

*Dosage based on initial findings and clinical response to antivenin.
†If this dose elicits a clinical response, it is recommended to give an additional two vials at 6, 12, and 18 hours.

Onset of symptoms may be delayed and manifested as a variety of neurologic symptoms, including weakness, ptosis, stupor, bulbar paralysis, and other cranial nerve dysfunction, as well as nausea, abdominal pain, and headache.

Administration of Antivenin. Any victim of a venomous snakebite with moderate or severe envenomation is a candidate for antivenin. The choice of antivenin depends on the species of snake, and the antivenin may be horse serum- or sheep-derived Fab fragments. Wyeth Laboratories, producer of the polyvalent antivenin for Western Hemisphere pit vipers, no longer manufactures that antivenin. Many zoos and hospitals still maintain vials of this antivenin until it can be replaced with the ovine-derived Fab antivenin (FabAV). This antivenin is

derived from four species of U.S. pit vipers and has not been studied with regard to bites from Mexican, Central American, or South American pit vipers. The Wyeth antivenin was derived from two U.S. species, one Mexican and Central American species, and one South American species and was efficacious against most of the world's pit vipers. Most antivenin for exotic snakes is derived from horse serum, and the eastern coral snake antivenin is also horse serum derived. Skin testing was commonly performed before administering horse serum-derived antivenin, but it is not medically indicated because of the inaccuracy of the test. Moreover, testing with normal horse serum may precipitate an allergic reaction, and even a positive test may not preclude treatment if a patient has sustained severe envenomation.

Dosage and Precautions

1. Because anaphylaxis may occur whenever antivenin is administered, appropriate therapeutic agents (e.g., oxygen supply, airway support, epinephrine, and other pressors) must be ready for immediate use. Any patient requiring antivenin should have two intravenous lines inserted. If an allergic reaction occurs, the line with the antivenin can be clamped and the other line used for resuscitation. Administering 0.3 mg of 1:1000 epinephrine subcutaneously before administration of antivenin may prevent allergic reactions from horse serum-derived antivenin and, if not contraindicated, should be used.
2. The initial dosage of antivenin is prepared (see Table 59-3). The smaller the body of the patient, the larger the relative initial dose that may be required. A bitten child usually receives more venom in proportion to body weight and thus requires more antivenin to neutralize it. Because children seem to have less resistance and less body fluid with which to dilute the venom, they may require twice the adult dosage of antivenin. The total fluid requirements of children are less, however, so the antivenin should be given in a more concentrated solution. All antivenin should be administered intravenously.
3. Pregnancy is not a contraindication to antivenin therapy.
4. Administration of antivenin at or around the site of the bite is not recommended.
5. The need for subsequent doses is based on the patient's clinical response. The patient is monitored closely after the initial dose, and local and systemic symptoms, as well as laboratory findings, are determinants of the need for further antivenin. Additional injections of one to five vials of antivenin are administered every 1 or 2 hours if symptoms progress. Most pharmacies do not stock large amounts of antivenin, and the pharmacy should be notified to obtain additional antivenin for treating a severe bite.
6. Even with a history or signs of allergy, patients with severe envenomation should be treated with a dilute form of antivenin and epinephrine.

Current treatment of pit viper envenomation in the United States is to use an FabAV polyvalent antivenin rather than the horse serum product. This is designed to limit the allergic reactions associated with horse serum antivenin by using antigen-binding fragments (Fabs) of sheep (ovine) immunized against four species of venomous snake found in the United States. CroFab has been shown to be as effective as the Wyeth antivenin, with fewer allergic reactions. Because of more rapid clearance of smaller Fab fragments by the kidney, however, a repeat dose regimen must be used to prevent the recurrence of coagulopathy. The duration of action of the venom may be longer than the therapeutic effect of the antivenin. Initial studies have shown promise for a new affinity-purified, mixed monospecific ovine Fab antivenin. This product has been tested with favorable results in humans after minimal to moderate crotalid envenomation.[36-39] Its efficacy in pit vipers from South America or Asia has not been proved, nor has its usefulness for copperhead bites. Purification of antivenin by separation of active fractions may lead to safer administration of horse serum-derived antivenin. In the next decade, snakebite management will probably change radically throughout the world. Phytotherapy (botanical therapy) and other non-antivenin drug therapies for snakebite have been shown to be efficacious in experimental animals, and some centers have successfully treated snakebite with medical support only.[40-47]

The use of enzyme-linked immunosorbent assay in the diagnosis of Viperidae and Elapidae bites, especially in Australia, Asia, and Africa, has led to more certain criteria for identifying the responsible snake in a patient with suspected envenomation. Active immunization against specific snakes, similar to that for certain jellyfish and hymenopterans, is being attempted in the Amami Islands.

Coral and Exotic Snakes. All victims of bites by the *eastern coral snake* (*Micrurus fulvius*) should be given antivenin (also manufactured by Wyeth) even before any symptoms develop. The toxicity of this venom has a rapid onset, and once symptoms develop, it may be too late to reverse the effects with antivenin. The recommended dose is three to five vials in 300 to 500 mL of normal saline.[42] Antivenin should be given based on the clinical response. No antivenin exists for the venom of the *Arizona* (*Sonoran*) *coral snake*, which fortunately is less dangerous. Treatment of this type of snakebite is supportive.

The problems with bites of exotic snakes are threefold: Positive identification of the specimen is sometimes difficult, even for experts; specific antivenin is not always readily available; and even if the antivenin is available, the instructions for reconstitution and dosage may not be written in English. Many zoos maintain a supply of antivenin for their venomous snakes, and this may be the best source of antivenin for an exotic species. Some collectors keep appropriate antivenin on hand for the species that they collect. The Antivenin Index at the Arizona Poison Center (602-626-6016) can assist in identifying sources of exotic antivenin or in obtaining more pit viper antivenin. As with coral snakes, many patients do not show any early signs after envenomation by exotic snakes. The antivenin should be administered before neurologic changes develop.[35]

Wound Care. The wound should be cleansed and immobilized. Elevation at or above heart level may relieve some of the pain. If the snake is a pit viper and the wound is on an extremity, a constricting band that does not occlude arterial blood flow may be applied proximal to any swelling caused by the bite. A constricting band should not be applied, however, if more than 30 minutes has elapsed since the bite occurred. Some authors have previously advised excision of the bitten area, but such management is no longer recommended. As with any puncture wound, patients should be immunized against tetanus. Broad-spectrum antibiotics have not been shown to be useful in uncomplicated snakebites. If there has been a long delay in treatment or if signs of secondary infection develop, ampicillin-clavulanate can be administered. Analgesics should be given as needed to relieve severe pain.[11] The wound should be examined for remains of embedded fangs or teeth, and these should be removed.

Patients admitted to the hospital should have the previously mentioned laboratory tests performed and then serial determinations of platelets, fibrinogen, prothrombin time, and urinalysis every 4 hours to check for myoglobin and hemoglobin. Blood products should be administered, including packed red

blood cells, fresh frozen plasma, and other coagulation factors as needed. Usually, it is best to wait until antivenin therapy has been started, or the use of the blood products may be futile. Daily comprehensive laboratory tests should be performed. Awake patients who have no nausea or abdominal pain can be given oral fluids. Local wound care should involve daily cleansing with soap and water and the application of a sterile dressing. Surgical consultation should be obtained for débridement or skin grafting. Fasciotomy is not usually indicated unless compartment pressures are elevated above 30 mm Hg and signs of compartment syndrome are present. Débridement should probably not be performed earlier than 3 days after the bite, until the coagulopathy has resolved. Surgical exploration of the bite wound is not necessary and may be harmful. Skin grafts are occasionally necessary after bites by pit vipers that produce large necrotic areas. Physical therapy is often needed and should begin soon after the acute phase of the envenomation is complete.[6,10,11,30]

Serum Sickness. In most patients who receive more than 10 vials of horse serum-derived antivenin and in approximately 15% of those who receive FabAV, serum sickness develops up to a week later. The administration of diphenhydramine plus cimetidine, and in severe cases a tapering dose of steroids, can be used to treat this problem. Serum sickness is the only indication for the use of steroids with snakebite.[43-45]

Other Envenomation. Gila monster and Mexican beaded lizard bites are treated similar to pit viper bites with regard to first aid. No definitive medical treatment exists. Antivenin is currently not available. Local wound care, tetanus prophylaxis, the use of antibiotics and analgesics, and supportive care are the extent of emergency department treatment available for this type of envenomation.[17]

Envenomation by the yellow-bellied sea snake causes severe muscle necrosis with the release of large amounts of myoglobin and neurologic symptoms. Although a polyvalent antivenin is available from Australia, maintenance of adequate urine output, alkalinization of urine, and general supportive care are usually sufficient.[10,35]

Disposition

If no envenomation is evident after clinical examination and the snake was either nonvenomous or a pit viper, the victim can be observed for 6 to 8 hours. With some snakebites, however, toxicity may be delayed by up to 8 hours. If no sign of envenomation is seen after 8 hours, the patient may be discharged. These patients should be given tetanus immunization and wound care instructions and referred for follow-up within 24 to 48 hours. They should be told to return to the emergency department immediately if any symptoms of envenomation develop.

If only local pain and minimal edema have occurred and the snake is thought to be nonvenomous or a pit viper, the patient should be closely watched for 12 hours in the emergency department. Then, if the pain and swelling have decreased and no systemic symptoms have developed, the patient may be treated with the same precautions as a patient with no signs of envenomation. Any patient with moderate or severe envenomation should be admitted to an intensive care unit for constant monitoring during antivenin therapy. Depending on the severity of the bite, blood products, vasopressors, and invasive monitoring may be necessary.

Any patient bitten by a coral snake, a Mojave rattlesnake, or an exotic snake is at risk for severe neurologic sequelae that may not become evident for many hours. As a result, the patient should be admitted to the hospital, preferably to an intensive care unit where he or she can be monitored closely. Arrangements should be made to have a ventilator, Swan-Ganz catheter, and dialysis equipment available if necessary. Appropriate antivenin should be obtained and treatment initiated at the earliest onset of symptoms. Some experienced clinicians may wait until symptoms develop before administering antivenin.

VENOMOUS ARTHROPODS

Arthropods are animals with segmented bodies and jointed appendages. This phylum (Arthropoda) contains approximately 80% of all known animals. Arthropods first appeared in the Cambrian period of the Paleozoic era 600 million years ago. The living members of this phylum are categorized into 12 classes. Two classes, the Insecta and the Arachnida, are of particular interest because numerous venomous species have evolved that are harmful to humans. Many species have developed venom glands and an apparatus for delivering the venom to obtain food. Others have developed venom delivery systems used solely for defense, most of which are found in the order Hymenoptera.[18]

Arthropods account for a higher percentage of deaths from envenomation than do snakes. They are found inside dwellings, as well as in deserts, forests, and lakes. Although most arthropods are more active in April through October, many are active throughout the colder months. Arthropods are also active 24 hours a day, and many can fly, thus increasing their range. This high level of contact results in millions of cases of envenomation annually. Most fatalities result from an autopharmacologic response by the victim rather than the toxicity of the venom. An individual stung by a bee may have a small amount of pain and local swelling or, in severe cases, an anaphylactic reaction and death.

Arthropods use three main methods of delivering venom: stinging, biting, and secreting venom through pores or hairs. Some arthropods combine two systems, one for offense and the other for defense. Generally, venom systems found on the oral pole of an animal are used for offensive purposes or food acquisition, whereas systems found on the caudal pole are used for defense. Humans are not considered prey for any venomous animal, and therefore bites from venomous animals are defensive, accidental, or reflexive. Many venomous arthropods are omitted from this discussion because of their infrequent contact with humans or the relative impotence of their venom.[21,48,49]

Hymenoptera

Hymenoptera is a familiar order of arthropods that is composed of the families of bees, wasps, hornets, yellow jackets, and ants. Many of these species are social insects, and their defense response is related to protection of the group rather than the individual organism. Although most members of this order are stinging insects, several species of ant can bite and sting simultaneously.

Bees and wasps have similar mechanisms of delivering venom. Female insects of this type have modified ovipositors that protrude from the abdomen and act as hypodermic needles to administer the venom. The barbed stinging apparatus of the bee is quite prominent. The stinging action pulls the stinger from the bee, thereby eviscerating the insect and killing it.[50]

The wasp, which has an unbarbed stinger, may inflict many stings without damaging itself or its stinging apparatus. The venom is produced in one or two tubular glands that empty into a venom reservoir. The venom reservoir has a duct that connects to the stinger. The venom is composed of several classes of substances varying in composition among different species. Proteins, as in snake venom, make up most of the

venom by dry weight. Peptides, amino acids, carbohydrates, lipids, and other low-molecular-weight substances are also found. The most common enzymes are phospholipase A and hyaluronidase. Peptides are common in some species and comprise up to 50% of the dry weight. Most of the toxicity of the venom results from substances of low molecular weight (e.g., bradykinin, acetylcholine, dopamine, histamine, and serotonin). Many other antigenic substances have been identified in bee and wasp venom, and they account for the induction of hypersensitivity and anaphylaxis in humans.[21,51-53]

Clinical Features

The signs and symptoms of bee and wasp stings vary, depending on the degree, type, and location of envenomation, as well as the characteristics of the victim. Bee and wasp venom can cause serious injury other than allergic types of reactions, depending on the number of stings, the species of insect, the size and previous health of the victim, and the anatomic area stung. For example, a sting in the tongue or throat may quickly compromise the airway. Honeybee venom causes a much greater release of histamine per gram than does other hymenoptera venom and thus is more dangerous. Certain species of honeybee release a pheromone, isoamylacetate, when the ovipositor is pulled from the abdomen after stinging a victim. This pheromone attracts other bees to the victim and thus incites multiple stings.

There is little antigenic overlap between species, which may explain the variability in reaction to stings reported by victims. Victims who are allergic to honeybees and who mistakenly identify a yellow jacket as a honeybee may not have a systemic reaction and thus may think that they are no longer allergic to honeybees.[54-56]

The most consistent finding is immediate pain at the site of the sting, followed by local swelling, redness, and itching. A sensitive victim may experience swelling, urticaria, coughing, wheezing, coma, and respiratory arrest. Some large and especially venomous hornets have been known to cause muscle necrosis and renal damage. Most serious reactions to bee stings occur in the first 30 minutes; however, the local effects of a sting may persist for 2 or 3 days. Delayed hypersensitivity may occur 7 to 10 days after the sting.

"Killer Bees." Health officials have been concerned about a particularly aggressive species of bee imported from Africa to Brazil in 1956 that has been known to attack humans and cattle with fatal results. This bee has managed to compete with native species and is gradually replacing some of these species while still retaining its aggressive behavior. Envenomation from these aggressive arthropods is most dangerous to very young or elderly patients and those with concomitant medical conditions.[57] Killer bees have colonized northern Mexico and have moved into the southern United States, including California, Arizona, and Texas, where the mean high temperature is at least 60° F.[58,59] This type of bee is not more toxic, only more aggressive.

Fire Ants. Another unwelcome import to the United States is the fire ant. This insect is a member of the family Formicidae and is another of the Hymenoptera that is harmful to humans. Several species of fire ant are known, some native to North America and some imported. The species responsible for 95% of clinical cases, *Solenopsis invicta*, was imported from Brazil to Alabama in the 1930s. This ant is now found in nine southern states and is replacing many native species and inhabiting new niches. The only limiting factor keeping the fire ant from progressive migration seems to be cold winters. This ant is small and light reddish brown to dark brown. Its venom is unique to the animal kingdom in that it is 99% alkaloid. The remaining 1% is quite immunogenic and can sensitize an individual to the venom. Properties of this venom include hemolysis, depolarization of membranes, activation of the alternative complement pathway, and general tissue destruction. The sting is produced when the ant bites the victim with its jaws and, while holding tight, pivots around and stings the victim with its ovipositor. The sting usually produces a sterile pustule within 24 hours. Other symptoms include local burning, redness, and itching. With multiple stings and in sensitive individuals, urticaria, angioedema, dyspnea, nausea, vomiting, wheezing, dizziness, and respiratory arrest may occur. Approximately 10% of victims have some degree of hypersensitivity reaction.[60-62]

Management

Home Care. First aid for Hymenoptera envenomation depends on the degree of reaction to the sting. With simple stings, an ice bag wrapped in a towel and applied to the sting area usually relieves the pain and swelling. In the event of an anaphylactic reaction, basic life support should be administered until further medical help can be obtained. Many people allergic to Hymenoptera envenomation carry an emergency insect sting kit containing a tourniquet, epinephrine in a 1:1000 dilution, and an antihistamine. These kits are readily available, and both the patient and the patient's family should be instructed in the treatment of a severe allergic reaction.

Emergency Department Care. No specific antivenin exists for Hymenoptera stings. Treatment consists of local wound care and general supportive measures. A history of any previous allergic reactions to bee stings, hay fever, asthma, or drug reactions should be obtained. The circumstances surrounding the sting and the number and location of stings should be noted. A patient with a single sting and only a local reaction should have the sting area inspected for evidence of a venom apparatus, which is removed by scraping the edge of a scalpel blade parallel to the skin and lifting the apparatus away from the skin without squeezing the venom sac. An ice bag wrapped in a towel may then be applied and the patient given an oral antihistamine (e.g., 50 mg of diphenhydramine). The patient should be monitored and, if no further reaction is observed, may be discharged with instructions to return to the emergency department if wheezing, dyspnea, hives, dizziness, and/or dysphagia occurs.

Adults in whom a severe urticarial reaction, dyspnea, or hypotension develops should be given 0.3 mL of epinephrine in a 1:1000 dilution intramuscularly, 50 mg of diphenhydramine intravenously, and 50 mg ranitidine intravenously. Patients with severe hypertension, cerebrovascular disease, or heart disease should be given epinephrine cautiously because of the potential for adverse reactions. Children should be given 0.01 mL/kg based on their body weight of a 1:1000 dilution of epinephrine intramuscularly and 1 mg/kg of diphenhydramine intravenously. These patients must be watched closely for signs of respiratory problems and treated accordingly. After 1 hour, these individuals should be totally free of symptoms (except for some itching around the sting site). Any patient requiring epinephrine should be watched for 24 hours due to recurrent allergic reaction. There is a possibility of recurrence of the reaction up to 72 hours and patients should be warned of this. They should be given the same instructions as patients with a minor reaction. Patients with allergic reactions to a single sting should be given an emergency insect sting kit and instructed in its use. They may be referred to an allergist for desensitization.

Wheezing should be treated with a beta$_2$-agonist given by hand-held nebulizer and repeated as necessary. A second

large-bore intravenous line with normal saline should be established. These patients should be monitored closely and given an intravenous steroid plus 50 mg of diphenhydramine and 50 mg of ranitidine intravenously. Admission is warranted for any severe anaphylactic reaction. Patients who have life-threatening reactions (hypotension, respiratory arrest, and cardiac arrest) may be given 0.1 mg of epinephrine in at least a 1 : 10,000 dilution, very slowly intravenously. The intramuscular route should be used for all but the most extreme reactions.

Treatment of allergic reactions to fire ant stings is the same. The skin lesions should be kept clean with soap and water. Ice bags may be applied initially to relieve burning and pain. Prophylactic antibiotics are not needed.

Of patients who have a systemic reaction to an insect sting, 60% can have a future allergic reaction if they have a positive skin test. These patients should be desensitized to any specific venom to which they are allergic. Purified insect venom is currently available for most Hymenoptera, including fire ants.[63] Patients seen in the emergency department with systemic reactions to stings should be referred for skin testing and desensitization. These patients should be given emergency insect sting kits with instructions for use and should avoid activities that place them in proximity to Hymenoptera species.[54-56,64]

Spiders and Scorpions

The class Arachnida contains the largest number of venomous species known, with approximately 34,000 species of venomous spiders and 1400 species of venomous scorpions. Virtually all known species are venomous, but most are not harmful to humans. Only approximately 50 species of arachnids in the United States cause human illness because most species do not have fangs or stingers sufficiently long to penetrate human skin. Humans fear spiders and scorpions, which is well founded in certain cases. Ticks, which also belong to this class, are less feared but probably cause more morbidity because of transmission of infectious diseases such as Rocky Mountain spotted fever and Lyme disease. Some spider bites are never diagnosed because of lack of significant symptoms and the fact that they occur while the victim is sleeping. Many non-spider bites are incorrectly diagnosed as spider bites, and unfortunately, there is no gold standard for making the diagnosis.

Black Widow Spider

The black widow spider, *Latrodectus mactans*, may be the most recognized venomous spider in the world. Several other closely related species of *Latrodectus*, or widow spiders, are found throughout the United States, including *Latrodectus hesperus*, which is common in Arizona and other western states. The diagnosis and treatment of the bites of all species are the same.

The black widow is found throughout the United States (except Alaska) and in southern Canada. The female is approximately twice as large as the male, and although both are venomous, only the female is able to envenomate humans. The black widow is glossy black, occasionally with red stripes, and has a bright red marking on the abdomen. This marking may have an hourglass shape or may appear only as two spots. Abdominal markings may vary, and related *Latrodectus* species may be similar in appearance and toxicity. The combined length of the black widow's head and abdomen is approximately 0.5 inch, and the spider is approximately 1.5 inches long, including the legs. It is found in protected places such as under rocks, in woodpiles, and in outhouses and stables. The female is not aggressive except when guarding her eggs.

The venom apparatus of the black widow is a modified first appendage of the head known as the chelicera. The spider is able to control the amount of venom injected into its prey. The venom of the black widow is complex and contains both protein and nonprotein compounds.

Spiders normally use the venom to paralyze their prey and also to liquefy the tissues of the prey for digestion. The venom probably evolved from digestive glands analogous to the salivary glands in snakes. The ingredient most toxic to humans is thought to be a neurotoxin. This toxin destabilizes neuronal membranes by opening ionic channels, causing depletion of acetylcholine from presynaptic nerve terminals and increasing the frequency of spontaneous miniature endplate potentials at neuromuscular junctions.[21,65]

Clinical Features. The classic symptomatology of the black widow bite is initially a pinprick sensation that may be followed by minimal local swelling and redness. If the area is examined closely, two small fang marks may be noticed. Sometimes the bite is not felt, especially if the victim is working when the bite occurs. From 15 minutes to 1 hour later, dull crampy pain develops in the area of the bite and gradually spreads to include the entire body. Usually, the pain is concentrated in the chest after upper extremity bites or in the abdomen after lower extremity bites. The abdomen may become boardlike, and the patient may complain of severe crampy pain. The abdominal manifestation may mimic pancreatitis, a peptic ulcer, or acute appendicitis, except that abdominal tenderness is usually minimal. Pregnant women may go into premature labor and precipitous delivery. Associated symptoms include dizziness, restlessness, ptosis, nausea, vomiting, headache, pruritus, dyspnea, conjunctivitis, facial swelling, sweating, weakness, difficulty speaking, anxiety, and cramping pain in all muscle groups. The patient is usually hypertensive, and cerebrospinal fluid pressure is sometimes elevated. There may be electrocardiographic changes similar to those produced by digitalis.[18,21,66]

In adults, the signs and symptoms begin to abate after several hours and usually disappear in 2 or 3 days. A small child bitten by a black widow spider, however, may not survive.[67] As with snake envenomation, the volume of distribution of black widow venom is much smaller in children than in adults. A dose that may cause only a few hours of pain in an adult may lead to complete cardiac decompensation and respiratory arrest in a child. Adult patients with preexisting hypertension, cerebrovascular disease, or cardiovascular disease are also at greater risk for complications. Symptoms usually persist for 8 to 12 hours and then subside, although in severe cases muscle cramps may continue for several days.

Management. First aid for a black widow spider bite consists of applying an ice pack to the bite area for relief of pain and transporting the victim to a hospital where supportive, symptomatic, and definitive treatment can be administered. The rescuer should obtain the specimen if possible because many dangerous spiders resemble harmless species and vice versa. The patient should be monitored closely en route to the hospital and basic life support initiated if necessary. Bites in the neck or mouth area may cause airway compromise through muscle spasm. Emergency department care consists of obtaining a history of the circumstances surrounding the bite, a description of the appearance of the spider, any significant past medical history, current medications, and allergies to insect bites, horses, or horse serum.

The wound site should be inspected for fang marks and cleansed with soap and water. As with any puncture wound, tetanus immunization should be instituted. The patient should

be observed for approximately 6 hours. If symptoms do not develop and the spider was not positively identified as a black widow, the patient may be discharged with instructions to return to the emergency department if any symptoms develop.

All patients with symptoms of moderate envenomation, pregnant women, children, and those with preexisting cardiovascular disease or hypertension should be admitted to the hospital, have intravenous lines inserted, and have a complete blood count, electrolytes, blood urea nitrogen, creatinine, coagulation studies, urinalysis, and an electrocardiogram performed. Acute hypertensive problems should be treated with nitroprusside if diastolic pressure rises above 120 mm Hg.

Symptomatic treatment usually involves controlling the muscle cramps responsible for most of the discomfort associated with the bite. Diazepam or other benzodiazepines given intravenously are useful for relieving muscle spasms. Dantrolene sodium has been used both orally and intravenously to provide muscle relaxation for *Latrodectus* envenomation.[68] Parenteral analgesics may be necessary to control pain. These drugs may affect an already compromised respiratory condition; thus, their use must be closely monitored. Patients with moderate symptoms should be admitted to the hospital and monitored until symptoms subside; usually 1 day is sufficient. Pregnant women should undergo fetal monitoring, and those with severe symptoms should be admitted to an intensive care unit with cardiovascular monitoring.

Latrodectus *Antivenin.* In general, pediatric patients, pregnant women, and the elderly may need to be given *Latrodectus* antivenin (Lyovac), which is derived from horse serum. Clinical judgment must be used to adjust for the age and category of patients needing antivenin. Antivenin should be administered to patients with severe envenomation manifested as seizures, respiratory failure, or uncontrolled hypertension; to pregnant women; and to patients not responding to other therapy. The dose of the antivenin is one vial diluted in 50 mL of normal saline and administered intravenously over a period of 15 minutes. Precautions for allergic reactions should be taken before administering antivenin. A dose of subcutaneous 1 : 1000 epinephrine may prevent allergic reactions when given before horse serum antivenin. This antivenin is also useful with other species of the *Latrodectus* genus.[66]

Brown Recluse Spider

Several deaths were attributed to the brown recluse spider, *Loxosceles reclusa*, in the 1950s, primarily in the south-central United States, thus drawing the attention of the medical community. Many species of *Loxosceles* are venomous to humans, and at least five are found in the United States. These spiders are approximately 1 inch long, including leg span, and range in color from tan to dark brown. The most distinguishing mark is a violin-shaped darker area found on the cephalothorax. Close examination may reveal that the brown recluse has three pairs of eyes rather than the usual four.[18,69]

These spiders, as their name implies, are not aggressive and are usually found under rocks, in woodpiles, and occasionally in attics and closets. Their range is concentrated in the south-central United States, especially Missouri, Kansas, Arkansas, Louisiana, eastern Texas, and Oklahoma. However, they have been reported in several large cities outside this range.

The venom apparatus is similar to that of most spiders, including the black widow. The composition of brown recluse venom has not been completely determined, but sphingomyelinase D is a primary component. The local tissue destructive effects are thought to be primarily caused by hemolytic enzymes and a levarterenol-like substance that induces severe vasoconstriction. The systemic symptoms seem to be an allergic phenomenon and vary according to the individual's immune response to the venom.[70,71]

Clinical Features. The symptoms of a brown recluse spider bite are both local and systemic. Initially, they are similar to those caused by bites of many other spiders and other conditions, including pyoderma gangrenosum, furuncles, viral and fungal infections, and foreign body reactions. The victim may notice some burning pain in the area of the bite. Some victims do not notice the initial bite at all. Pain usually develops within 3 or 4 hours, and a white area of vasoconstriction begins to surround the bite. A bleb then forms in the center of this area, and an erythematous ring arises on the periphery. The lesion at this stage resembles a bull's-eye. The bleb darkens, necroses over the next several hours to days, and continues to spread slowly and gravitationally, with involvement of skin and subcutaneous fat. The most common mimic of *Loxosceles* or other necrotic spider bite is a methicillin-resistant *Staphylococcus aureus* (MRSA) skin infection.

Systemic symptoms include fever, chills, rash, petechiae, nausea, vomiting, malaise, and weakness. Hemolysis, thrombocytopenia, shock, jaundice, renal failure, hemorrhage, and pulmonary edema are the usual signs of severe envenomation. Fatalities are more common in children, most often the result of severe intravascular hemolysis.[71,72]

Management. First aid for a brown recluse spider bite is simple. The specimen is secured if possible and the victim transported to a medical facility. Because the lesion develops over a period of days, there may not be any local treatment of the lesion that is effective. The physician should try to determine whether any systemic toxicity is present. A history of the circumstances surrounding the bite, the time elapsed since the bite, and any past history of allergic reactions, medications, or medical problems should be obtained. If a specimen is available, an attempt should be made to identify it. The assistance of a local entomologist should be obtained if necessary. If signs of systemic toxicity develop, an intravenous line should be placed in an unaffected extremity, and a complete blood count, electrolyte levels, blood urea nitrogen level, and creatinine level should be determined and coagulation studies and urinalysis performed. The patient who presents several days after the bite due to tissue injury should have the wound cultured to rule out MRSA and washed with soap and water, and tetanus prophylaxis should be given. Vital signs and urine output should be monitored closely. Excision of the lesion has not been shown to aid healing and may be detrimental.[73] Lesions have been known to cause extensive scarring, infection, and necrosis. Bites that are in fatty areas, such as the thigh or buttocks, may cause more extensive necrosis.

Dapsone, 50 to 200 mg/day, has been shown to be helpful in preventing local effects of the venom.[74] If used within 48 hours, it may limit the size of the lesion that develops. However, dapsone may cause methemoglobinemia and hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency. Hyperbaric oxygen has been shown to decrease lesion size in animals.[75-77] Analgesics and antibiotics should be used as indicated during the course of the disease, although infection is not common. All patients with signs of systemic envenomation should be admitted to the hospital and monitored closely with daily blood counts, urinalysis, and urine output. Dialysis may be necessary if acute renal failure develops, and surgical consultation should be obtained for evaluation of the wound.

The Instituto Butantan in Sao Paulo, Brazil, produces an antivenin for *Loxosceles* bites, but it is not available in the United States. Research is being conducted to produce a rabbit serum antivenin against *Loxosceles*, but it is not yet commercially available.[78]

Other Spiders

Several other spiders can cause envenomation but are uncommon in the United States. Some of these spiders are large and can be quite aggressive. Most are imported either intentionally or as stowaways on cargo ships. Tarantulas, wandering spiders, funnel-web spiders, pallid spiders, and crab spiders are a few of the imported venomous spiders. Many of these species can cause envenomation similar to that of the brown recluse spider, and some produce neurotoxins.

Antivenin is produced for some of these groups (e.g., Brazilian *Phoneutria* spp. and Australian *Atrax* spp.) but is usually available only in the country where the species is generally found.[79] Emergency care therefore involves symptomatic and supportive treatment. An outbreak of bites by a species of *Tegenaria*, known as the hobo or aggressive house spider, has been reported. This species was imported from Europe to the Pacific Northwest. This spider is a small brown spider with a herringbone pattern on its abdomen. The lesions are similar to those caused by the brown recluse spider, but systemic symptoms include headache and weakness. Treatment is largely supportive.[69]

Tarantulas are popular pets in the United States, and most native species are relatively nontoxic. Tarantulas are unusual in that the abdominal hairs can be thrown by the spider and embedded in human skin and the eye. These hairs can cause allergic reactions and severe conjunctivitis and must be removed under a slit lamp or by an ophthalmologist. A recent import from Thailand, the cobalt blue tarantula, *Haplopelma lividum*, is a very aggressive spider with toxic venom.

Scorpions

Scorpions are arachnids that resemble crustaceans and are among the oldest terrestrial animals. Scorpions are found throughout the world, and several species are located in the southwestern United States. Only one species, *Centruroides exilicauda*, which is found in Arizona, is particularly dangerous. Scorpions are nocturnal predatory animals that usually spend the day under rocks, logs, or floors and in crevices. *Centruroides exilicauda*, or the "bark scorpion," is found on or near trees (Fig. 59-4).

The scorpion has a tail-like structure that is actually the last six segments of its abdomen. The last segment, or the telson, contains the two venom glands and stinger. The toxicity of scorpion venom varies greatly from species to species. Generally, the less dangerous species produce more local reactions, and the more dangerous species cause more systemic reactions. Several proteins have been identified in their venom; some cause hemolysis, local tissue destruction, and hemorrhage. The venom of *C. exilicauda* is predominantly a neurotoxin that causes or enhances repetitive firing of axons by activation of sodium channels.[18]

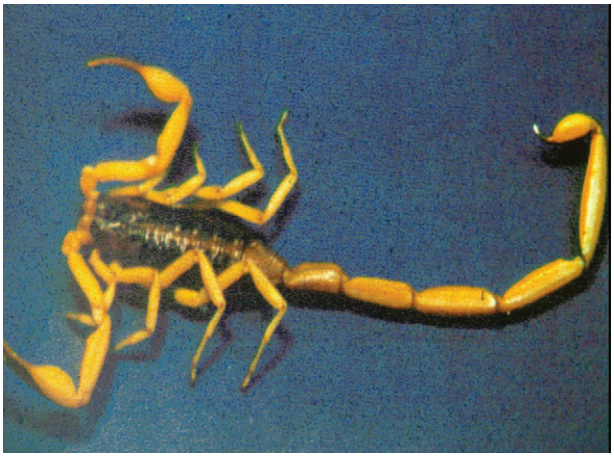


Figure 59-4. Arizona bark scorpion (*Centruroides exilicauda*).

Clinical Features. Envenomation causes severe and immediate pain at the sting site. Local edema and erythema may or may not be present, depending on the species. After envenomation by *C. exilicauda*, the victim may have heightened sensitivity to touch in the area of the sting along with local numbness and weakness. The diagnosis is often made by tapping on the site of the sting and causing an increase in pain at the site. Systemic symptoms may then develop, including anxiety, restlessness, muscle spasms, nausea, vomiting, excessive salivation, sweating, itching of the nose and throat, hyperthermia, blurred vision, myoclonus, hypertension, hemiplegia, syncope, cardiac dysrhythmias, and respiratory arrest. Various systemic complications may occur, depending on the species of scorpion. *Tityus trinitatus* scorpion stings cause pancreatitis to develop in 80% of its victims. A wave of symptoms sometimes occurs over a 24-hour period, or respiratory failure may develop in the first 30 minutes. As with most envenomation, children are at a greater risk for severe reactions. A grading system has been developed to guide management of bark scorpion stings.

Management. First aid for a scorpion sting consists of applying an ice bag to the area of the sting and transporting the victim to the hospital. A history of the circumstances surrounding the bite, any previous medical problems, and a description of the scorpion if no specimen is present should be obtained. It is relatively difficult for a layperson to differentiate the various scorpions. For *C. exilicauda* envenomations that occur in Arizona, a goat-derived non–Food and Drug Administration–approved antivenin is available from the Antivenom Production Laboratory of Arizona State University.[80] Expert advice should be obtained before the use of this antivenin. A new antivenin is currently being evaluated in children. Narcotic analgesics and barbiturates have been reported to increase the toxic effects of the venom and should be avoided.

Antivenin should be given in all cases of severe envenomation. All victims should be observed for 24 hours, and children should be admitted to the hospital and monitored closely. Intravenous diazepam or another benzodiazepine may be used for myoclonus and muscle spasms. Phenobarbital, previously used in large doses in children, may be more dangerous than efficacious and may have contributed to deaths in the past. Atropine may be administered to control hypersalivation and bradycardia. Nitroprusside and prazosin have been used to control hypertension. Ventilatory assistance may be necessary, especially in children.[81]

Other Arthropods

Ticks have been known as vectors of human disease for some time. Certain female ticks also secrete a toxin that causes a progressive ascending paralysis in humans and animals. The precise mechanism and structure of the toxin are unknown. The two species responsible in the United States are *Dermacentor andersoni* (wood tick) and *Dermacentor variabilis* (dog tick). The bite of the tick is usually painless, but the victim later has difficulty walking, weakness, flaccid paralysis, slurred speech, and visual disturbances. The victim is usually a child, often with a history of recent outdoor activity. Treatment is removal of the offending tick before the paralysis has progressed too far. Any patient seen with ascending paralysis

should be closely examined for the presence of a tick, especially on the head and back.

Several species of beetle, millipede, and caterpillar secrete irritating substances that cause severe burning pain, numbness, pustular contact dermatitis, edema, nausea, vomiting, and headache. Oropharyngeal exposure can cause mucosal edema and irritation.[82] No deaths have been reported. Treatment consists of washing the area thoroughly with soap and water and removing any spines or hairs present. Spines can be removed with adhesive tape or by applying white glue or facial peel. Locally applied ice bags and baking soda and water paste may be of benefit. Analgesics should be used as needed, and supportive therapy may be necessary for severe envenomation.

Centipedes can inflict bites causing erythema and edema. Treatment is usually local soaks and the use of analgesics. Conenose bugs, or "kissing bugs," may cause severe local and systemic allergic reactions. Treatment with antihistamines and supportive care, depending on the degree of reaction, are all that is necessary. Many other arthropods can cause local skin reactions and severe allergic reactions, depending on the individual's sensitivity. These patients should be treated symptomatically with local steroid creams, antihistamines, and other symptomatic supportive measures.[83]

VENOMOUS MARINE ANIMALS

Epidemiology

Almost 2000 species of animals found in the ocean are either venomous or poisonous to humans, and many can produce severe illness or fatalities. An estimated 40,000 to 50,000 marine envenomations occur annually. In recent years, the number of injuries caused by these animals has increased dramatically because of the greater number of scuba divers, snorkelers, surfers, and others engaging in water sports. These animals are not usually aggressive, and many are completely immobile. Most of the venomous marine animals injure humans with defense or food-procuring devices. Most venomous marine animals in the United States are found along the California, Gulf of Mexico, and southern Atlantic coasts. These animals range in complexity from sponges to bony fishes and contain some of the most complex and toxic venoms known.[20]

Venom Delivery

In general, venomous marine animals may be divided into three main classes according to the mechanism of venom delivery: bites, nematocysts, and stings.

Bites

Biting animals include several species of cephalopods, most often octopi. Although popular media portray a giant deadly creature that squeezes its victims to death, the most dangerous octopi are seldom larger than 20 cm. Several fatalities have been reported after a bite by the blue-ringed octopus, *Hapalochlaena maculosus*. Most victims are bitten on the upper extremity as they disturb this normally nonaggressive creature. The octopus has a pair of modified salivary glands that secrete venom into the wound produced by the animal's beak.[21] The venom contains a potent vasodilator and an inhibitor of neuromuscular transmission similar to tetrodotoxin.[84,85] No known antivenin exists, and treatment is largely supportive, with respiratory support the most important lifesaving intervention.[86-88]

Nematocysts

The second type of venom mechanism is the nematocyst found in coelenterates (Cnidaria). This group of animals includes the Portuguese man-of-war, true jellyfish, fire corals, stinging hydroids, sea wasps, sea nettle, and anemones. Most of these organisms are sessile, but some are free floating. Because of their large numbers, this group accounts for the greatest number of envenomations by marine animals.[18]

Many different types of nematocysts are known, but the basic mechanism is a "spring-loaded" venom gland that can, on mechanical or chemical stimulation, suddenly evert and discharge a structure that penetrates the prey and delivers the venom through a connecting tube. These nematocysts, found on the animal's tentacles, can number in the hundreds of thousands. Tentacles can be up to 100 feet long in some giant species. Nematocysts can still function even if the animal is dead or if the tentacles are separated from the animal's body. These stinging cells can remain active for weeks after an animal becomes beached. Often, not all nematocysts fire on initial contact but may discharge later during attempted rescue and treatment. Certain marine species have evolved methods of using ingested nematocysts for their own defense.

Toxicity. Nematocyst venom contains various peptides, phospholipase A, proteolytic enzymes, hemolytic enzymes, quaternary ammonium compounds, serotonin, and other toxic compounds. The venom of the coelenterates is antigenic, and allergic reactions are often seen. The severity of the envenomation is related to several factors. First, the severity of the injury is directly proportional to the number of nematocysts discharged. Second, the toxicity varies from species to species. It is unlikely that the victim or the treating physician will be able to identify the species from the appearance of the wound. Symptoms may range from simple isolated stinging to respiratory paralysis, cardiovascular collapse, and death. Therefore, the diagnosis must be made according to the clinical findings. Third, the victim's autopharmacologic response to the venom may turn a relatively minor envenomation into a fatal anaphylactic reaction. Any clinician who regularly treats this type of injury should become acquainted with the common species in the particular area.[89]

Although lethal and potentially lethal jellyfish occur worldwide, the extremely toxic specimens are found off the coast of Australia and in other Indo-Pacific waters. Probably the most notable and most toxic coelenterate is the box jellyfish (*Chironex fleckeri*), also known as the "sea wasp." More dangerous than the famed great white shark, this small animal causes several deaths along the Australian coast annually.[90] Cardiac arrest may occur within minutes, and early aggressive resuscitation offers the best chance of recovery. Intravenous verapamil and box jellyfish antivenin are advocated for use in treatment.[91,92]

Another north Australian jellyfish, *Carukia barnesi*, also produces a devastating envenomation known as *Irukandji syndrome*. This causes major catecholamine release, hypertensive crisis, and passive death.[93]

The Portuguese man-of-war (*Physalia physalis*) is found along the southern U.S. coastline. This organism is not a true jellyfish but a hydroid colony and is most often included in the jellyfish literature. Envenomation is usually limited to local pain and paresthesias, but it may progress systemically to nausea, headache, chills, and even cardiopulmonary collapse. This organism has also been responsible for several deaths.[94,95]

Most other envenomations are minimal, and the danger is either drowning after being stung or an allergic reaction to the venom. The symptoms resulting from coelenterate

envenomation usually consist of a severe burning sensation accompanied by raised erythematous lesions where nematocysts have discharged into the skin. The symptoms may progress, depending on the species and the number of nematocysts, to include nausea, vomiting, chest pain, muscle cramps, dyspnea, diarrhea, cough, convulsions, angioedema, and respiratory arrest. The initial pain and redness may last from a few hours to 2 or 3 days, depending on the therapy.

A related type of envenomation is caused by various species of coral, particularly fire coral (*Millepora*). These injuries combine nematocyst envenomation with wound contamination. Animal protein and calcareous material left behind in these wounds cause infection and chronic inflammation.

Stings

Some marine animals cause a "sting" that is produced by a specialized apparatus that punctures the victim's skin and then introduces venom. Common examples of this type of animal are sea urchins, cone shells, bristle worms, sea snakes, crown-of-thorns starfish, stingrays, scorpion fish, weever fish, catfish, stonefish, rabbit fish, and zebra fish. Sea urchins, cone shells (*Conus californicus*), catfish, scorpion fish, and stingrays account for most of the venomous marine animal injuries in the United States.[96]

Sea Urchins. Sea urchins belong to the Echinoderm family along with starfish and sea cucumbers. These animals produce injury and envenomation mostly through toxin-coated spines. These spines often break off and introduce calcareous material and debris into the wound, thereby potentiating severe infection. Symptoms most often include severe local burning, pain, and discoloration, but they may progress systemically in some patients. The degree of envenomation is usually related to the number of spines involved and the species of animal encountered.

Cone Shells. Cone shells are much more toxic than sea urchins, and some species have been responsible for fatalities in the Indo-Pacific region. The venom apparatus is a tubular gland that connects to several teeth at the end of a retractable proboscis. All envenomations reported have occurred in persons handling the shells. The venom contains several proteins, protein-carbohydrate complexes, and 3-indolyl derivatives that act mainly on skeletal muscle and cause variably spastic and flaccid paralysis.[97] Symptoms may or may not include pain, depending on the species. Severe envenomation may cause diplopia, slurred speech, numbness, weakness, paralysis, and respiratory arrest. Onset and regression of symptoms may vary from minutes to days. No antivenin is available for cone shell envenomation.

Stingray. The stingray is a member of the shark family. It is a broad, flat fish with a long, whiplike tail that may have one or more stings with barbed ends. They vary in size from a few inches to several feet, and the stings are proportional to the size of the fish. The sting is encased in an integumentary sheath and contains venom glands. Stingrays bury themselves in the sand of shallow water, where they can be easily stepped on inadvertently. The sheath and sting are often broken or left in the wound. The victim experiences an immediate, intense pain in the area of the wound, which may spread to the entire extremity. Systemic symptoms include salivation, nausea, vomiting, diarrhea, syncope, muscle cramps, fasciculations, dyspnea, cardiac dysrhythmias, and convulsions. The exact composition of the venom is unknown. Enzymes, proteins, serotonin, and a cholinergic substance have been identified, but the exact toxin responsible for most of the severe symptoms is yet to be isolated. The presence of foreign material may also impair healing and cause infection.

Bony Fishes. Bony fishes inflict their wounds through spines located on their fins. The spines and venom glands are encased in a sheath, and grooves along the spines act as channels for the venom. These fish injuries are typically encountered when the fish are stepped on in shallow water or handled by fishermen. The venom is made up of several classes of proteins, most of which are heat labile. The family Scorpaenidae includes three groups of species categorized by venom apparatus: zebra fish, scorpion fish, and stonefish. Zebra fish include the popular aquarium resident, the lionfish. Scorpion fish produce intense pain that can spread to the entire affected extremity within minutes.[98] Stonefish envenomation may cause serious and even life-threatening systemic illness, but manifestations such as cardiac and respiratory symptoms can be prevented by early administration of the appropriate antivenin.[21,99] Saltwater and freshwater catfish produce envenomation through contact with dorsal and pectoral spines.[100]

Management

Much of the venom can be neutralized at the scene, and most fatalities can be prevented. The most important step is to remove the victim from the water. Drownings after minimal envenomation may account for more fatalities than the end effects of severe envenomation. The patient should be questioned about the circumstances of the bite, allergies, and systemic symptoms. If a severe allergic reaction has occurred, the victim should be treated for this emergency before attending to the wound. The type of wound care largely varies according to the type of venom apparatus involved. As with all wounds encountered in the emergency department, appropriate cleansing, débridement, and tetanus prophylaxis are paramount. Prophylactic antibiotics such as ciprofloxacin should be given when indicated and when residual foreign body is suspected. Specific antivenins are available for some species, such as the box jellyfish and stonefish.

Bite injuries should be treated with basic life support measures and general wound care consisting of cleansing, débridement, and irrigation. Systemic signs and symptoms are treated accordingly, with aggressive attention paid to the cardiac and respiratory systems.

Nematocysts

Nematocyst injuries are treated by first removing the nematocysts without allowing them to discharge. Tentacles should be removed with a gloved hand or forceps. The remaining nematocysts should be fixed by pouring vinegar (dilute acetic acid) over the wound area. Baking soda and alcohol have also been shown to be effective, and deactivation of nematocysts may be species specific. Fresh water should not be used because it may stimulate continued nematocyst discharge.[101] Other methods include scraping off residual material with the use of a shaving cream or baking soda slurry. The affected area should then be débrided and cleansed. Hot water immersion may relieve pain. Most lifeguard stations in areas where coelenterate stings are common have the necessary materials for this regimen. Supportive pharmacologic therapy (e.g., analgesics, antihistamines, and steroid creams) is indicated for all but the most trivial envenomation. Delayed cutaneous reactions may persist despite optimal therapy.[102,103]

Fish

Puncture injuries are treated by removing the spine or sting if possible. An x-ray film should be taken of the involved area because many spines and sheaths are radiopaque. Sea urchin

spines usually break off in the wound; they are so fragile that removing them is difficult without the proper instruments. The sting of the stingray should be removed with forceps, although these stingers with their sheaths have been known to penetrate body cavities and require surgery for removal. Although not usually present in the wound, the fish spines of bony fish should be removed with forceps. In all cases, the wound should be copiously irrigated. Most venoms injected through puncture wounds are heat labile. Significant analgesia can be achieved by submersion of the wound in hot (110° F) water for 30 to 90 minutes or until symptoms improve.[98]

Patients envenomed by unknown or unfamiliar organisms should be observed for systemic signs and symptoms. Careful discharge instructions should warn the patient to return for increasing pain, numbness, difficulty breathing, and signs of infection.

KEY CONCEPTS

- Snake venom exhibits neurotoxicity and hematotoxicity, but one usually predominates, depending on the species of snake.
- The amount of crotalid antivenin given depends on the grade of envenomation, from 0 (minimal or no sign of envenomation) to IV (severe envenomation).
- Pit vipers have a characteristic pit found midway between the eye and the nostril on both sides of the head.
- Arthropods account for more deaths from envenomation than snakes, usually due to allergic reactions.
- Nematocyst (jellyfish) stings should be immediately neutralized with vinegar, and fish stings should be neutralized with hot water.
- Spider bites may be difficult to diagnose without identification of the offending spider.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 60

Thermal Burns

Adam J. Singer, Breena R. Taira, Christopher C. Lee, and Harry S. Soroff

INTRODUCTION

Burns are injuries to the skin resulting from contact with heat, electrical current, radiation, or chemical agents. The common denominator in all burns irrespective of the source of the energy is protein denaturation. With thermal burns, the degree of injury sustained is dependent on the amount of heat or temperature, the duration of the exposure, and the intrinsic structure of the burned tissue that determines its heat conductivity.[1–3] Temperatures less than 44°C can generally be tolerated for prolonged periods without causing burns. As the temperature rises, there is an exponential decrease in the duration of contact required to produce injury, since the proportion of unfolded protein molecules increases dramatically at supraphysiologic temperatures.[4] At temperatures above 60°C, most tissue proteins are denatured. The lipid bilayer and membrane-bound adenosine triphosphatases are the proteins most predisposed to thermal denaturation, and the thermal alteration of the plasma membrane is likely to be the most significant cause of the tissue necrosis.[4]

The young and elderly are more likely to sustain deep burns because their skin is generally thinner than that of adults. The blood supply of the skin may also affect the susceptibility to injury, since blood flow dissipates heat. Epidermal appendages within the dermis (e.g., sebaceous glands and hair follicles) also help to dissipate heat and reduce the degree of injury.

BURN EPIDEMIOLOGY

According to the American Burn Association, 500,000 burn injuries are treated in medical facilities each year.[5] This includes 4000 deaths, which occur mostly in residential fires. Of the 40,000 burn admissions each year, more than 60% are admitted to specialized burn centers. The majority of burns occur from fire/flame (46%), scalds (32%), contact with hot objects (8%), electricity (4%), or chemical agents (3%). Over one third of admissions (38%) exceed 10% total body surface area (TBSA), and 10% exceed 30% TBSA. Most admissions include severe burns of such vital body areas as the face, hands, and feet. The overall survival rate from burns in the years 1995 to 2005 was 94.4%.

The National Center for Health Statistics indicates a decreasing trend in the number of burn visits from 1996 to 2000, with no further changes in trends from 2000 to 2005.[6] Half of patients presenting to the emergency department (ED) were between the ages of 19 and 44 years. The most commonly affected body areas were the upper extremities (41%), lower extremities (26%), and head and neck (17%). Most of the burns were partial-thickness injuries, and less than 5% were full thickness.

BURN PATHOPHYSIOLOGY

Traditionally the burn injury has been divided into three concentric zones.[7] At the center of the burn is a zone of irreversible coagulative necrosis that is formed immediately after injury. Surrounding this central core is a zone of ischemia in which there is a reduction in the dermal microcirculation, putting this area at risk for subsequent necrosis if the perfusion is not improved. The zone of ischemia has been the focus of intense research, which is directed toward reversing or preventing the conversion to necrosis. The third and outermost zone is the zone of hyperemia, characterized by an immediate and transient increase in perfusion. The ability of the skin to regenerate itself without scar formation is highly dependent on the level of injury.[8] Regeneration of the damaged epidermis occurs from two primary sources. The basal layer of cells from the uninjured adjacent epidermis can give rise to re-epithelialization of the burn; however, this is limited to 1 cm from the wound edges. With large burns, the major source of regenerative epidermal cells comes from the dermal skin appendages: hair follicles and sebaceous glands. More damage to the epidermal appendages increases the likelihood that the burn will heal with scar formation.

Injury to the skin results in the activation of a number of complex hematologic cascades, which include the clotting and the compliment system,[9] and results in the local activation and recruitment of inflammatory cells such as leukocytes and monocytes to the site of injury. In order to facilitate passage of the inflammatory cells from the systemic circulation through the blood vessels and into the site of injury, glycoproteins known as the β_2 integrins, including CD11b and CD18, are expressed on the surface of the neutrophils, allowing them to adhere to the endothelial cells. Administration of monoclonal antibodies aimed against CD18 in an animal model results in a reduced area of burn injury and more rapid healing.[10] Intercellular adhesion molecule-1 is also expressed on the endothelial cell surface, which binds to integrins on leukocytes, allowing them to marginate or adhere to the vessel walls.

Once activated inflammatory cells are in the area of injury, they release a large number of inflammatory mediators or cytokines as well as cytotoxic reactive oxygen and nitrogen species,

which results in lipid peroxidation of cell membranes, damaging their integrity.[11,12] The accumulation of leukocytes, red blood cells, and platelets in the blood vessels of the injured area results in the formation of microthrombi, which further reduce local perfusion. The extent of the burn injury is often exacerbated by recurring cycles of ischemia and reperfusion that result in increased formation of reactive oxygen species.[13] The presence of prostaglandins, histamine, and bradykinin increases the permeability of the blood vessels, leading to hypoperfusion secondary to edema-related fluid shifts from the intravascular compartment into the interstitial space.[11,14]

The cytokines released after injury (such as tumor necrosis factor alpha, interleukin-1 [IL-1], and endotoxin) activate nuclear factor kappa beta,[15] which induces the synthesis of inducible nitric oxide synthase, which leads to further production of nitric oxide, an important reactive nitrogen species.[16] Reactive oxygen species results in damage to DNA, proteins, and lipids. Lipid peroxidation is thought to cause oxidative damage to the cellular membrane and eventually result in cell death.[16] Reactive nitrogen species (such as nitric oxide) also inhibit T cells, thus participating in the immunosuppression associated with large burns.[17]

Abnormal and denatured proteins accumulate as a result of exposure to heat, causing a stress response that increases the expression of heat shock proteins.[18] These proteins play an important role in protein assembly, transport, and repair. The production of the heat shock proteins is induced by a number of transcription factors termed heat shock factors, which are activated by the stress response. The heat shock proteins in turn help attenuate the production of proinflammatory cytokines such as tumor necrosis factor alpha, IL-1, and IL-6, which tend to increase the extent of the burn injury.

A predisposition to infection, metabolic derangements, and other factors predispose partial-thickness burns to progress to deeper burns.[11] Lack of adequate fluid resuscitation and hypoperfusion contribute to the deepening of the burn wound.[19] Impaired ability to combat infection is common in patients with large burns and appears to be cytokine mediated.[20] In particular, IL-12 has been shown to depress immune function. Abnormal compliment activity is another factor in large burns that predisposes to infection.

Pathophysiology of Inhalation Injury

Injury to the airways can be the direct result of thermal injury from steam[21] or more commonly from the products of incomplete combustion such as the aldehydes and oxides of sulfur and nitrogen.[22] Other toxic compounds released from burning of common household materials such as polyvinylchlorides include hydrochloric acid and carbon monoxide.[23] Upper airway obstruction that occurs within the first few hours after injury is generally caused by chemical irritation. In up to one third of burn patients with inhalation injury, acute upper airway obstruction occurs due to the rapid progression of pharyngeal and supraglottic edema.[24]

The upper and lower airway pathology is secondary to airway edema and de-epithelialization of the injured tracheobronchial mucosa, with progressive shedding of the necrotic lining of the airway and the formation of pseudomembranous casts that partially or completely obstruct the airway. These casts consist of necrotic epithelium, mucus, cellular debris, fibrinous exudate, polymorphonuclear leukocytes, and clumps of bacteria.[25] In addition, there may be severe edema and congestion of the pulmonary parenchyma with infiltration of leukocytes that release additional inflammatory mediators and reactive oxygen species that further contribute to bronchospasm, tissue inflammation, and destruction. Damage to the mucociliary function of the endobronchial mucosa reduces the ability to eliminate excess mucus and secretions. The increase in extravascular water content and pulmonary lymph flow causes a marked decrease in the compliance of the lungs.[26] Inhalation injury also results in deactivation of pulmonary surfactant, leading to areas of microatelectasis causing ventilation perfusion mismatch and pulmonary shunting, and results in progressive hypoxemia and ultimately the clinical syndrome of acute respiratory distress syndrome.[27]

CLASSIFICATION AND DIAGNOSIS OF BURNS

Burns can be classified by mechanism of injury, depth, extent, and associated injuries and comorbidities. Determination of the depth of injury is crucial as appropriate treatment is contingent on the depth of injury (Table 60-1). The current burn classification system is several hundred years old and was first described by the French barber surgeon Ambroise Paré. First-degree burns are limited to the epidermis and characterized by erythema and pain. They generally heal within several days to a week. Second-degree, or partial-thickness, burns extend through the epidermis and into the dermis. They may be divided into superficial and deep partial-thickness injuries depending on the depth of dermal injury. Superficial second-degree burns extend into the superficial (papillary) dermis. The skin is erythematous and forms blisters, and the surface can be moist (Fig. 60-1). The wound blanches on pressure and is painful. Deep second-degree burns extend through the epidermis into the deep (reticular) dermis. They appear white with some erythematous areas and exhibit less blanching and moisture than the superficial second-degree burns (Fig. 60-2). The distinction between superficial and deep second-degree burns is important in that deep second-degree burns often do not heal within 2 to 3 weeks and often result in severe scarring and contractures, especially in children. As a result, deep second-degree burns that do not heal within 21 days require excision and skin grafting in order to minimize scarring. Deep second-degree burns may also progress to third-degree burns over the course of several days after injury. Third-degree burns extend through both the epidermis and the entire dermis and are referred to as "full-thickness" burns. Their appearance is stiff and white or tan. They are dry or may have a charred

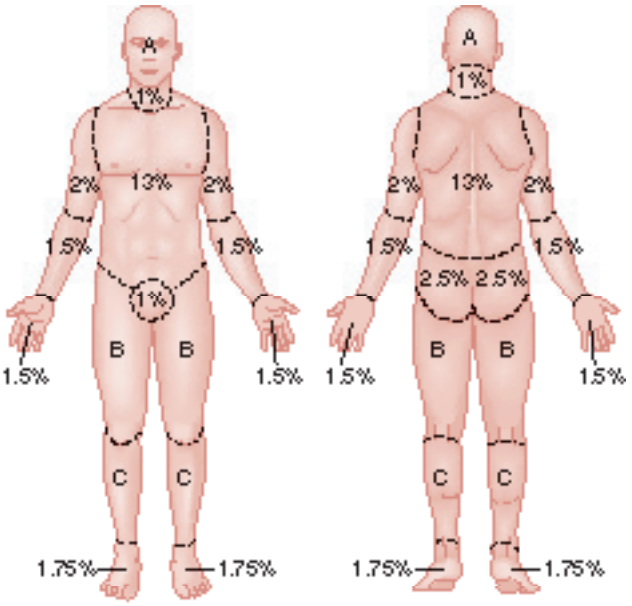
Table 60-1 Burn Depth Classification

	APPEARANCE	SURFACE	SENSATION	TIME TO HEALING
1st degree	Pink or red	Dry	Painful	Days
Superficial 2nd degree	Pink, clear blisters	Moist	Painful	14–21 days
Deep 2nd degree	Pink, hemorrhagic blisters, red	Moist	Painful	Weeks, or may progress to 3rd degree and require graft
3rd degree	White, brown	Dry, leathery	Insensate	Requires excision
4th degree	Brown, charred	Dry	Insensate	Requires excision

Figure 60-1. Superficial second-degree burn.

Figure 60-2. Deep second-degree burn.

Figure 60-3. Third-degree burn.



Relative percentages of areas affected by growth

Age	Half of head (A)	Half of one thigh (B)	Half of one leg (C)
Infant	9.5	2.75	2.5
1 yr	8.5	3.25	2.5
5 yr	6.5	4	2.75
10 yr	5.5	4.25	3
15 yr	4.5	4.25	3.25
Adult	3.5	4.75	3.5

Figure 60-4. Lund-Browder chart.

appearance (Fig. 60-3). They do not blanch, and due to destruction of the nerves are not painful. Finally, fourth-degree burns extend through the skin and subcutaneous fat into the underlying muscle and bone. Fourth-degree burns are stiff and charred and have visibly thrombosed vessels. Most burns are not uniform in depth and have areas of varying depth of injury.

Clinical estimation of the depth of the burn is often inaccurate.[28] It is particularly difficult to distinguish superficial partial-thickness burns that heal spontaneously from deep partial-thickness injuries that require excision.[29,30] Many tools exist that help determine burn depth (such as laser Doppler and magnetic resonance imaging); however, these are not generally available in the ED.[31] Clinical examination remains the most frequently used means of diagnosis. Serial assessments are necessary to distinguish between deep and superficial burns as the injury is dynamic and often continues to evolve after initial presentation.

The extent or surface area of the injury must be evaluated. The ability to estimate the percentage of total body surface area burned is often inaccurate on initial inspection.[32–34] Clinical rules and charts are commonly used for more precise estimation of the percentage of TBSA involved. Careful estimation is critical because the volume of fluid administered is based on this evaluation and an overestimation of the extent of injury can lead to inappropriate fluid administration.[35,36] In addition, the criteria for referral to a burn unit are dependent on the surface area of the burn. In general, only second- and third-degree burns contribute to the calculation of the percentage of TBSA affected. A useful clinical rule for smaller burns or scattered areas of burn is that the area of a patient's palm and fingers is approximately equivalent to 1% TBSA.[37] For larger burns, the "rule of nines" is used. This rule states that the allocation of percentage of TBSA in an adult patient can be estimated as follows: 18% for the front and 18% for the back of the trunk, 18% for each lower extremity, 9% for the head and 9% for each upper extremity, and 1% for the perineal area. A Lund-Browder chart is useful for estimating the extent of burns in children (Fig. 60-4). The rule of nines should not be

Table 60-2 Classification of Burn Severity

	MILD	MODERATE	SEVERE
Children	<5% TBSA	5–10% TBSA	>10% TBSA
Adult	<10% TBSA	10–20% TBSA	>20% TBSA
Elderly	<5% TBSA	5–10% TBSA	>10% TBSA
All	<2% full thickness	2–5% full thickness, high voltage, inhalation, circumferential, comorbid disease	>5% full thickness, high voltage, significant burn to face, eyes, ears, genitalia, or joints, significant associated trauma
Disposition	Outpatient	Admission	Burn unit

TBSA, total body surface area.

used for children as their head is larger and their extremities smaller in proportion compared with adults.[38]

Finally, burns are classified by severity into minor, moderate, and severe based on the TBSA burned, the percentage of full-thickness injury, and the involvement of specific areas such as the face, hands, feet, or perineum (Table 60-2). In addition, consideration is given to the presence of inhalation injury, high-voltage electric burns, associated major trauma such as fractures, extremes of age, and comorbid conditions.

MANAGEMENT OF BURNS PRIOR TO ED ARRIVAL

The goal of care before ED arrival is to deliver the burn patient to the hospital in the best possible condition. The first priority is to stop the burning process and to protect the patient from additional injury. If clothing is burning, extinguish the flames with water or smother the flames with a blanket and gently remove the involved clothing. If chemical injury has occurred, immediate and copious dilution of the chemical agent with tap water and prompt removal of all involved clothing are necessary while still protecting those aiding the patient from exposure. After the burning process has been stopped, the priorities of care are assessment of adequacy of airway and ventilation and assessment of the cardiac status and peripheral perfusion. If the patient has a compromised airway, orotracheal intubation should be performed. If the patient is alert and oriented and the areas of unburned skin are warm and dry, it may be assumed that the patient is adequately perfusing his or her vital organs. If there is a suspected inhalation injury or carbon monoxide intoxication, the patient should be placed on 100% oxygen delivered by a non-rebreather mask. The possibility of a concomitant traumatic injury, particularly a cervical spine injury, should be considered and necessary spinal precautions should be addressed. Prehospital infusion of intravenous fluid is beneficial in those patients with extensive burns (greater than 20% TBSA) in whom intravenous access can be established expeditiously. Whenever possible, the intravenous fluid should be initiated through unburned skin. Lactated Ringer's (LR) solution is the intravenous fluid of choice since it may reduce the risk of hyperchloremic acidosis associated with use of normal saline. The amount of LR solution required for the first hour can be rapidly estimated using the Parkland formula by multiplying the estimated TBSA of the second- and third-degree burn by body weight in kilograms and dividing by 4. When preadmission protocols allow use of opioids, morphine sulfate should be administered intravenously during transport to the hospital using frequent 2- to 4-mg intravenous boluses.

Burns should be covered with a clean dressing. Cooling with tap water or a commercially available cooling blanket[39,40] helps reduce pain. Care should be taken to minimize hypothermia, especially when ambient temperature is low. Topical antimicrobial agents should not be used in the prehospital phase of burn care because they offer few significant benefits during transport and must be removed when the patient arrives at the hospital.

EMERGENCY DEPARTMENT MANAGEMENT OF BURNS

Severely burned patients are among the most critical patients seen in the ED. Burn injuries are extremely painful and dramatic, and there is a tendency to focus on the burn wounds. However, all burn patients must be approached in a systematic manner focusing on the ABCs first. Some burn patients have associated traumatic injuries or comorbidities that must be identified and addressed.

Airway Management

Management of the upper airway in burn patients may be extremely challenging. After exposure to superheated steam and toxic fumes, rapid and progressive upper airway edema may develop within minutes.[21] If there is doubt regarding the presence of upper airway compromise, fiberoptic laryngoscopy should be performed. Endotracheal intubation guided by fiberoptic laryngoscopy/bronchoscopy is a useful technique, and if attempts at intubation are unsuccessful, surgical cricothyrotomy or needle cricothyrotomy may be necessary. After placing an endotracheal tube, several devices are available to help secure the tube.[41] With circumferential neck burns, the stiff burn eschar may compress the airway (as well as the major neck vessels) and require laterally placed escharotomies on either side of the neck.

General Measures for Moderate to Severe Burns

All patients with moderate to severe burns and those with suspected inhalation injury should receive supplemental humidified oxygen to maintain an oxygen saturation greater than 92%. With severe burns, intravenous access should be obtained with at least two large-bore intravenous catheters in peripheral veins, preferably in a noninjured limb. If peripheral access cannot be obtained, central venous access will be required. Patients with severe burns require a urethral catheter to monitor urine output and evaluation for rhabdomyolysis and myoglobinuria. A nasogastric tube should be placed in order to prevent gastric distention that would compromise ventilation. Patients should also have continuous cardiac and oxygen

saturation monitoring, as well as frequent assessment of the arterial blood pressure.

Recognizing Inhalation Injury

Smoke inhalation injury affects between 5 and 35% of hospitalized burn patients.[42] With improvements in fluid resuscitation, inhalation injury has become one of the two causes of morbidity and mortality in burn patients.[43] The presence of inhalation injury increases the mortality from burns by 20% and when combined with pneumonia by 60%.[44]

Traditionally, inhalation injury was diagnosed based on clinical findings such as facial burns, singed nasal vibrissae, carbonaceous sputum, and a history of injury within a closed space. However, these findings are neither highly sensitive nor highly specific.[45] Similarly, wheezing, crepitations, hypoxemia, and abnormalities on the initial chest radiograph may or may not be present in the ED, except in the most severely injured.[45]

The diagnosis of inhalation injury in the ED is best made by direct visualization of the airways with fiberoptic laryngoscopy (before intubation) and bronchoscopy (after intubation).[46] Findings of inhalation injury include the presence of soot, charring, and mucosal inflammation, edema, or necrosis.[46] While bronchoscopy is useful in identifying injury to the airway, it cannot exclude parenchymal injury. Diagnosis of injury to the parenchyma of the lung is best made using xenon ventilation scanning,[47] which demonstrates areas of decreased alveolar gas washout secondary to small airway obstruction. However, xenon scanning is rarely, if ever, used in the ED setting.

Carbon monoxide levels should be based on measurement of serum carbon monoxide levels using co-oximetry. Cyanide, a frequent combustion product of plastics, should be suspected in patients in a closed space fire with elevated carbon monoxide and elevated lactate levels.

Management of Inhalation Injury

Deciding when mechanical ventilation is required is critical. In addition to securing the upper airway, there are several other indications for endotracheal intubation and mechanical ventilation (Table 60-3). Alveolar lavage may be required to help remove thick secretions and improve pulmonary toilette. This has been simplified by smaller and more flexible bronchoscopes.[45]

There are many modes of mechanical ventilation, each having their own advantages and disadvantages. In the ED most patients who are intubated will require heavy sedation with or without paralysis, and therefore, the assist control mode, in which the ventilator cycles automatically at a preselected rate, is most appropriate. The goals of mechanical ventilation should include achieving an acceptable oxygen saturation (>92%) and limiting the plateau airway pressures to 35 cm H_2O or less to reduce the incidence of barotrauma.[47] This may require allowing the partial pressure of carbon dioxide (P_{CO_2}) levels to rise to 35 to 55 mm Hg (permissive hypercapnia) as long as the pH remains greater than 7.25. A recent randomized trial found that low tidal volumes (6 mL/kg of predicted weight) reduced mortality.[48] Therefore, starting tidal volumes should be set at 6 to 8 mL/kg of predicted body weight. Larger tidal volumes may be required if oxygenation is not adequate. Positive end expiratory pressure may also help support oxygenation. In order to reduce hyperoxic lung injury, oxygen concentrations should be titrated to the lowest concentrations that maintain adequate oxygenation. A sample of initial ventilator settings is presented in Table 60-4. High-frequency percussive ventilation may be used to obtain adequate oxygenation while minimizing airway pressures. This mode of ventilation administers high-frequency, time-cycled, pressure-limited subtidal volumes, which may reduce the incidence of barotrauma.[49,50]

Patients with inhalation injury may develop bronchospasm, and therefore bronchodilators should be used in patients with wheezing. Bronchodilators may improve mucociliary function. Frequent airway suctioning and chest physiotherapy are also helpful at removing secretions. Aerosolized *N*-acetylcysteine with or without aerosolized heparin has also been shown to help break down thick mucous secretions.[51,52] An example of a treatment protocol for patients with inhalation injury may include 5000 to 10,000 units of heparin and 3 mL of normal saline nebulized every 4 hours, alternating with 3 to 5 mL of 20% *N*-acetylcysteine.[45]

Circulation and Fluid Resuscitation

Fluid resuscitation is one of the most important elements in the treatment of burn patients. Prior to World War II, many burn patients died of hypovolemic shock and renal failure. The first formal fluid resuscitation protocol was developed treating the burns that occurred during the Cocoanut Grove nightclub fire in Boston in 1942.[53] Since then, many fluid resuscitation regimens have been described; however, the Parkland formula described by Baxter remains the most popular.[54]

Burn injury results in the activation of the compliment system and the release of a large number of inflammatory mediators such as histamine, prostaglandins, and leukotrienes. These mediators increase the permeability of the local and systemic vasculature, resulting in the extravasation of intravascular fluids and proteins into the interstitial space, contributing to fluid depletion and soft tissue edema.[55] The leakage of plasma proteins during the first 3 to 5 hours reduces the intravascular oncotic pressure and increases the interstitial oncotic pressure, which leads to an increase in edema formation.[56] With large burns, half of the fluid requirements are due to extravasation into unburned areas.[57]

Table 60-3 Indications for Endotracheal Intubation and Mechanical Ventilation in Burn Patients

Upper airway obstruction
Inability to handle secretions
Hypoxemia despite 100% O_2
Patient obtundation
Muscle fatigue suggested by a high or low respiratory rate
Hypoventilation (a P_{CO_2} > 50 mm Hg and a pH less than 7.2)

P_{CO_2}, partial pressure of carbon dioxide.

Table 60-4 Recommended Initial Ventilator Settings

Tidal volume	6–8 mL/kg
Respirator rate	8–12 in adults 12–45 in children
Plateau pressures	<35 cm H_2O
I/E ratio	1:1–1:3
Flow rates	40–100 L/min
PEEP	8 cm H_2O

I/E, inspiratory/expiratory; PEEP, positive end expiratory pressure.

Patients with small burns (less than 20% TBSA in adults and less than 10–15% TBSA in children) can be successfully treated with oral fluids only.[58] With larger burns, intravenous fluid resuscitation is required to restore intravascular volume and prevent the development of hypovolemic shock. One of the oldest controversies in the management of burn patients is the role of colloids for the resuscitation of burn patients. Since capillary leakage of proteins lasts at least 12 to 24 hours after injury, the consensus is that colloids should not be used during the initial fluid resuscitation unless the burn is very deep.[59] A recent systematic review of 23 trials that included 7754 patients concluded that there is no evidence that resuscitation with colloids reduces the risk of death compared with crystalloids in patients with trauma, burns, or following surgery.[60]

In 1968, Baxter reported that resuscitation of dogs with 50% TBSA burns with a volume of LR solution equal to 24% to 32% of their body weight corrected physiologic and metabolic derangements within 24 hours.[61] The results were optimal when half of the volume was administered within the first 8 hours after injury. These findings were then evaluated in 11 patients with burns covering 30 to 85% TBSA, demonstrating that the required fluid volume of LR was between 3.5 and 4.5 mL/kg/%TBSA. These findings led to the Parkland formula that called for a volume of 4 mL/kg/%TBSA of LR to be given over the first 24 hours, with half of the volume given over the first 8 hours.[62] Later studies demonstrated that most adults and children were successfully resuscitated with 24-hour fluid volumes from 3.7 to 4.3 mL/kg/%TBSA.[63] Other fluid resuscitation formulas have been described (Table 60-5); however, the Parkland formula remains the most commonly used.

It is important that all fluid resuscitation formulas should be used as a general guide and that adjustments must be made to maintain adequate tissue and organ perfusion. Thus, burn patients should be resuscitated with only as much fluid as is necessary to maintain organ perfusion. Organ perfusion can be estimated by heart rate, blood pressure, level of consciousness, capillary refill, and a urine output of at least 50 mL/hr in adults or 0.5 to 1.0 mL/hr in children. Certain patient groups may require additional fluid, including patients with inhalation injury, electrical burns, and those in whom resuscitation is delayed. Patients with inhalation injury require 35 to 65% more fluid than patients with similar sized burns without inhalation injury[64] and do not develop pulmonary edema.

A study of transferred burn patients found that smaller burns tended to be overestimated and over-resuscitated, while larger burns tended to be underestimated and under-resuscitated.[65] This further emphasizes the need for careful monitoring of the volume of urinary output and clinical signs of tissue turgor and adequate resuscitation.

In contrast, there have been rising concerns that overly aggressive fluid resuscitation, often termed "fluid creep," may have adverse outcomes.[59] In a study of 72 patients, increased fluid volumes were associated with pneumonia, sepsis, adult respiratory distress syndrome, multiorgan failure, and death.[66] Patients who receive more fluid than needed are at risk for the abdominal compartment syndrome, which may lead to acute renal failure. Factors associated with fluid creep include a lack of careful, frequent observations by clinicians, increasing use of opioids (termed "opioid creep"), and the emergence of goal-directed resuscitation. While clinicians are often eager to increase fluid administration in patients with poor urine output and unstable vital signs, they are less likely to reduce fluids in patients with adequate or increased urine output.[67] Goal-directed therapy is aimed at achieving supranormal levels of cardiac output, oxygen delivery and/or consumption, and normal acid-base status. In contrast, restoration of normal physiologic and metabolic conditions in severely burned patients generally requires at least 24 to 48 hours to occur, and "pushing" these parameters prematurely may be detrimental.[59] We believe that excessive initial resuscitation should be avoided, and fluid infusions should be adjusted downward to avoid overhydration and subsequent cardiac failure, especially in the elderly.

Children have a larger TBSA relative to weight when compared with adults and therefore have larger fluid requirements. Fluid resuscitation in children is often calculated based on body surface area instead of weight. The Galveston formula is used to calculate resuscitation needs and gives LR 5000 mL/m^2 TBSA burned + 2000 mL/m^2 TBSA over the first 24 hours, with half of the volume given over the first 8 hours. The body surface area can be estimated with the Mosteller formula: ([Height (cm) × Weight (kg)]/3600)$^{1/2}$. Infants should have dextrose 5% added to their fluids since they lack adequate carbohydrate reserves.

Table 60-5 Burn Resuscitation Formulas

FORMULA	FIRST 24 HOURS	NEXT 24 HOURS
Parkland	LR 4 mL/kg/% burn ½ within first 8 hr	Colloids in amount of 20–60% of plasma volume; glucose in water added to maintain urine output 0.5–1.0 mL/kg/hr in adults and 1 mL/kg/hr in children
Modified Parkland	LR 4 mL/kg/% burn in adults	Colloid infusion of 5% albumin at the amount (0.3–1 mL/kg/% burn)/16 per hr
Evans	Crystalloids in the amount of 1 mL/kg/% burn, plus colloids at 1 mL/kg/% burn, plus 2000 mL glucose in water	Crystalloids at 0.5 mL/kg/% burn, colloids at 0.5 mL/kg/% burn, and the same amount of glucose in water as first 24 hr
Brooke	LR 1.5 mL/kg/% burn, plus colloids at 0.5 mL/kg/% burn, plus 2000 mL glucose in water	LR 0.5 mL/kg/% burn, colloids at 0.25 mL/kg/% burn, and the same amount of glucose in water as first 24 hr
Modified Brooke	LR 2 mL/kg/% burn in the adult and 3 mL/kg/% burn in children	Colloids 0.3–0.5 mL/kg/% burn, glucose in water to maintain urine output
Monafo	Solution containing 250 mEq Na, 150 mEq lactate, 100 mEq Cl; amount adjusted to urine output	Solution titrated with 1/3 NS according to urine output
Galveston	LR at 5000 mL/m^2 TBSA burned plus 2000 mL/m^2 TBSA, ½ within 8 hr	3750 mL/m^2 TBSA burned plus 1500 mL/m^2 TBSA

LR, Ringer's lactate; TBSA, total body surface area; NS, normal saline.

■ LOCAL BURN WOUND CARE

All burns are considered contaminated and require thorough cleansing with soap and water. Obvious debris or necrotic tissue should be gently removed. Care of the burn wound generally requires administration of an oral or intravenous analgesic agent. Patients may need a tetanus toxoid booster (dT or aPdT toxoid 0.5 mL IM) with tetanus immune globulin if necessary.

Cooling of the Burn

The benefits of cooling the burn surface have been recognized for many years. There is controversy regarding the best cooling agent and the optimal timing, duration, and temperature of cooling. Classic studies suggest that the optimal cooling temperature is in the range of 10° to 25° C,[68] but cooling of large burns with ice water can result in hypothermia and increased mortality. Venter et al. found that ice water (1°–8° C) resulted in more necrosis than no cooling at all, and that when tap water at 12° to 18° C was used, there was the least necrosis and fastest healing.[40] The beneficial effects of cooling were still present when treatment began up to 30 minutes after injury. External cooling with tap water is associated with a reduction in pain and may reduce the progression of tissue necrosis and limit the requirement for skin grafting.[69,70] If the patient is made comfortable by the cooling, it should be continued until the pain is reduced. Ice and ice water may lead to increased tissue injury and are contraindicated.[40]

Management of Burn Blisters

The management of burn blisters is a controversial topic. Some suggest that the fluid confined by the necrotic skin can lead to a closed space infection, while others have argued that the intact blister creates a moist wound environment that is beneficial to wound healing. In vitro studies show both positive and negative effects of the burn blister fluid; however, clinical studies show that intact blisters heal faster and are less likely to become infected.[71,72] A porcine study of deep second-degree burns evaluating the effects of débridement demonstrated faster healing, fewer infections, and less scarring when the burn was left intact.[73] There have been no large trials, however, to confirm this. With blisters that have already ruptured, any necrotic epidermis should be gently removed while leaving adherent epidermis intact.

Burn Dressings

The purposes of a burn dressing are to protect the wound, to reduce pain, to absorb wound exudate, and, finally, to reduce evaporative heat loss.[74] The use of systemic antibiotics is not supported in the literature.[75] Local care for first-degree burns is not required other than optional topical anesthetics, aloe vera, and/or topical nonsteroidal anti-inflammatory drugs (NSAIDs).[76,77] There are two general methods of treating second-degree burns: (1) the open method, which consists of topical antimicrobials; and (2) the closed method, which uses synthetic occlusive dressings.

The open method is most appropriate for contaminated, large burns with large amounts of exudate. Topical antimicrobials should be used until the burn is completely re-epithelialized to prevent bacterial colonization of the wound. The burn is re-epithelialized when there is a pearly opalescent coating and it is dry to the touch. Antimicrobials used for burn dressings include bacitracin, neomycin, mupirocin, silver sulfadiazine, and mafenide.[78] After the antimicrobial is applied, a nonadherent dressing can be used to cover the wound. With this method the dressings should be removed daily and the burns cleansed with water and soap followed by reapplication of the antimicrobial agent and dressing. Traditionally, silver sulfadiazine and mafenide were the mainstays of treatment. However, there are rare adverse reactions. Silver sulfadiazine should not be used in patients with sulfa allergy, and rarely it has also caused reversible bone marrow suppression.[79] Experimentally, silver sulfadiazine has been shown to adversely affect keratinocytes and fibroblasts,[80] and in large burns, mafenide acetate is associated with metabolic acidosis.[81]

The second method of dressing partial-thickness burns is with occlusive dressings. Occlusive dressings support a moist wound healing environment that is optimal for healing. A moist environment has been shown to enhance re-epithelialization and angiogenesis and to reduce pain, partly since these dressings do not need to be changed daily.[82] Occlusive dressings are most appropriate for superficial second-degree burns with little exudate. There are six major types of materials used for occlusive dressings: polyurethane films, hydrocolloids, alginates, silver impregnated dressings, hydrogels, and composites (Table 60-6). The development of products containing nanocrystalline silver has renewed interest since silver has potent antimicrobial properties against both gram-negative and gram-positive organisms as well as fungi such as *Candida*. Nanocrystalline silver is less rapidly deacti-

Table 60-6 Dressings

CATEGORY	EXAMPLES	ADVANTAGES	DISADVANTAGES
Absorptive			
Gauze, nonadherent	Telfa (Kendall, Mansfield, MA)	Nonadherent, inexpensive	Requires daily dressing changes
Occlusive			
Hydrocolloid	Duoderm (Convatec, Skillman, NJ), Tegasorb (3M, St. Paul, MN)	Absorbs exudates, protective cushioning of wound	Opaque, no antimicrobial properties
Alginate	Seasorb (Coloplast, Holtedam, Denmark), Algiderm (Bard, Murray Hill, NJ)	Absorptive	Frequent dressing changes
Nanocrystalline silver	Acticoat, (Smith & Nephew, Largo, FL) Aquacel Ag (Convatec, Skillman, NJ)	Antimicrobial, creates a moist environment, less frequent dressing changes	Need to keep dressing moist
Hydrogel	Curagel (Kendall, Mansfield, MA), Flexigel (Smith & Nephew, Largo, FL) Nu-Gel (Johnson & Johnson, Arlington, TX)	Rehydrates dry wounds	Nonabsorptive
Polyurethane foam	Tegaderm (3M, St. Paul, MN), Opsite (Smith & Nephew, Largo, FL)	Transparent, inexpensive	Nonabsorptive

vated than the ionic form of silver and thus does not require frequent dressing changes and reapplication. Nanocrystalline silver has been incorporated into many new sustained delivery dressings[80] that have been shown to reduce pain, but also are more cost effective with less frequent dressing changes.[83] Examples of such products include Acticoat (Smith & Nephew, Hull, United Kingdom) and Aquacel Ag (Convatec, Skillman, NJ).

Multiple trials have compared silver sulfadiazine with the newer occlusive dressings for the treatment of partial-thickness injuries. There is faster re-epithelialization, lower cost, and reduced length of hospital stay with burns treated with Aquacel Ag.[84,85] Absorptive hydrocolloids (such as DuoDerm [Convatec, Skillman, NJ]) have also been shown to be effective and less painful than traditional silver sulfadiazine. Biosynthetic composite dressings such as biobrane, Apligraft (Organogenesis, Inc., Canton, MA), and transcyte are generally limited to use by burn specialists.

Most patients with minor burns can be treated in the ED and discharged home. If the burn is limited in size and has a blister, the patient should be reexamined within 48 hours by a primary care physician. However, if the burn is extensive, or involves the face or the hands, or appears to be dry and deep, the patient should be referred to a surgeon experienced in the care of burns or a burn center that same day.

For patients with superficial partial-thickness burns who go home, the discharge instructions should describe washing the wound with mild soap and tap water, applying the prescribed topical agent, and a dressing (the patient should receive a prescription for additional dressings and topical agents). If a synthetic occlusive dressing is applied, it should not be removed by the patient unless it is saturated and/or malodorous, at which time the patient will need to be seen by a physician. The patient should be instructed to immediately return to the ED or his or her physician if fever, swelling, or increased pain occurs in or around the burn injury.

If a patient with a third-degree burn will be transferred to a burn center, it is best to simply cover the wound with a petrolatum-type dressing for transfer. Silver sulfadiazine should not be applied as this has the potential to change the appearance of the wound prior to evaluation by a burn specialist.[74]

Escharotomy

Releasing the constriction of a burn eschar with a scalpel or cautery at the bedside is called an escharotomy. Although infrequently needed in the ED, escharotomy can be a limb- or life-saving procedure. The dead skin hardens and forms an eschar that appears as a hard covering. Patients with a large eschar require careful monitoring, especially those with circumferential burns or extensive burns to the chest or neck, since there is the danger of the development of edema beneath the eschar, which leads to constriction and eventual interruption of arterial inflow. In the chest, the increased pressure impairs respiration. Pain, loss of sensation, and delayed capillary refill may be early signs of reduced perfusion. Traditionally, decreased Doppler signals in the extremity have been used as an indication for escharotomy, but one recent study suggests that pulse oximetry of less than 90% with or without Doppler signals in the involved extremity is an indication for escharotomy.[86] Further, an increase in peak airway pressure or difficulty with ventilation in a mechanically ventilated burn patient may be a sign that escharotomy of the chest is required.

The procedure is performed by making a longitudinal incision down to the fat in the constricting eschar (Fig. 60-5). Care should be taken to avoid underlying vessels and nerves. One study of patients transferred to burn centers found that escharotomy incisions were frequently not made deep enough to relieve the obstruction of flow.[87] It is important to check that an adequate incision has been made by reassessing Doppler signals and pulse oximetry in the extremities and ensuring that the peak airway pressures are decreased after the procedure. Use of cautery to perform escharotomy is preferred by some to minimize bleeding.

Figure 60-5. Performing an escharotomy on the lateral lower extremity.

PAIN MANAGEMENT

Burns are among the most painful injuries[88]; however, many patients do not receive analgesia while in the ED.[89] In addition to being inhumane, inadequate pain management may contribute to an exaggerated inflammatory and stress response, increased pain due to a "wind up" phenomenon, long-term chronic pain and dysesthesias, and the post-traumatic stress disorder.[90–92] The release of second messenger proteins such as protein kinase C-epsilon and neurotrophins such as nerve growth factor may mediate acute-burn hyperalgesia and priming, resulting in a predilection toward the development of chronic hyperalgesia.[93] Inadequate analgesia may be due to the distraction of the often dramatic burn wound or other associated injuries, or concern that potent analgesics may impair ventilation. Pain management should be of primary concern for all burn patients.

There are three phases of burn recovery, each with a characteristic and different type of pain, and each requiring specific assessment tools and management strategies. These three phases include the emergent or resuscitative phase, the healing phase, and the rehabilitative phase.[88] This chapter will only focus on the emergent phase of pain management.

During the emergent phase of management, patients may suffer from three major types of pain. Background pain describes the underlying pain that results directly from the injury. The amount of background pain is highly variable and also depends on the amount of patient anxiety. This pain is usually described as a continuous sensation of burning or throbbing that exists even when the patient is immobile. Background pain may be substantially reduced simply by covering the burn with a moist cool dressing. Breakthrough pain occurs when the patient experiences a sudden increase in the pain intensity, usually as the analgesic level decreases with time. Shortening of the analgesic dosing interval usually addresses this type of pain. Procedural pain refers to the pain experienced when the burn wound is manipulated or débrided.

This pain is generally very severe but transient in nature. Adding anxiolytic medication to parenteral opioids is useful during this phase of management.[94]

Nonpharmacologic Methods to Reduce Pain

Cooling of burns with cold water can significantly reduce pain. The optimal cooling temperature is around 10° to 25° C, which is approximately the temperature of tap water.[69,70,95] Cooling with ice or ice water increases the severity of injury and should be avoided.[96] Cooling is most effective when administered immediately after injury. However, cooling may still be effective up to 30 minutes after injury.[40,69] Burns may be cooled by holding the wound under running tap water or by applying moist dressings. Commercially available cooling blankets are also available and are useful, especially in the setting prior to hospitalization.[39]

Covering the burn with a moist occlusive dressing also reduces pain.[82] This effect is probably explained by reducing stimulation of the underlying nerves from air currents and other direct stimuli.

Pharmacologic Therapies

Morphine sulfate and acetaminophen are the most commonly used analgesics in burn patients.[97] Minor pain from burns may be managed with oral acetaminophen (1 g in adults or 15 mg/kg in children) every 4 to 6 hours or an NSAID such as ibuprofen (400–800 mg in adults or 10 mg/kg in children) every 6 to 8 hours. The pain of minor burns may also be treated with a topical NSAID or aloe vera.[77,98]

Moderate to severe burn pain is managed with parenteral opioids (such as morphine sulfate 0.05–0.1 mg/kg) titrated to effect. The intravenous route is recommended due to its rapid and reliable effects and consistent absorption. Due to its short half-life, fentanyl 0.5 to 1.0 μg/kg may be used for managing breakthrough and procedural pain. Intranasal fentanyl at a dose of 1.4 μg/kg may be as effective as oral morphine in both children and adults.[99] Intravenous infusion of lidocaine (1 mg/kg bolus followed by 2–4 mg/min infusion) can reduce the severity of pain in burn patients.[100,101]

Anxiolytics, particularly the benzodiazepines, have been useful adjuncts to pain therapy in burns. Care must be exercised in administering opioids and benzodiazepines together as they may act synergistically to induce hypoventilation and hypotension. Lorazepam (1 mg IV or PO) and midazolam (1 mg IV or intranasally) are both widely used in burn patients.[102,103]

Other drugs (including gabapentin, stimulants, beta-blockers, and antidepressants) are useful in managing chronic pain and burn pain in the burn unit; however, there is no evidence to support their use in the ED.[104,105]

Table 60-7 Burn Prevention Recommendations

Flame burn prevention	Check that smoke detectors are functional Create an escape plan for the home and practice with the family Safety device around fireplace Matches, lighters in secure place away from children
Scald prevention	Use splash guards on stove Lower hot water heater maximum temperature to 49°–54° C Use thermometer for bath water

BURN PREVENTION

The ED visit offers a unique "teachable moment" for physicians to educate patients and their families on preventing burns in the future. Prevention programs and safety legislation have made substantial contributions to decrease the incidence and severity of burn injury, especially for parents or school age children. Areas where burn prevention programs were implemented have a significant decrease in admissions for burn injury.[106]

In addition, recent initiatives are targeting vulnerable segments of the population for prevention efforts.[107,108] Mothers with less than a high school education who are less than 20 years old, and with more than two other children are at much higher risk for a fatal fire event.[109] Every visit to the ED provides an opportunity for education. While prevention initiatives are reaching increasing numbers of the population, there is still the need for further education of the public and in particular, those subsegments of the population at high risk for burn injury. Specific recommendations are listed in Table 60-7.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 61 Chemical Injuries

Michael Levine and Richard Zane

PERSPECTIVE

During the past century, there has been a dramatic increase in the number of chemicals produced. Worldwide, there are at least 5 to 6 million known chemicals, with an additional 10,000 to 20,000 new chemicals developed each year.[1] Furthermore, an estimated 500,000 unique shipments of hazardous materials occur daily throughout the United States,[2] resulting in thousands of exposures to hazardous materials annually.[3] These chemicals, which include acids, alkalis, and other highly reactive substances, not only are found throughout industry but also are ingredients in many household products. Exposure to these substances can result in injuries to many organs, including the eyes, skin, and lungs.

Despite myriad potential exposures to chemicals each day, the number of actual exposures is relatively low, due largely to sound industry practices and state and federal regulations. The Superfund Amendments and Reauthorization Act contains extensive provisions for emergency planning.

The Hazardous Substances Emergency Events Surveillance (HSESS) system collects information on chemical exposures from several states. According to the HSESS database, from 1993 to 2001, the manufacturing sector accounted for nearly half of all chemical exposures in the United States. Transportation, communication, and other public utilities accounted for slightly less than one third of all exposures. Employees working with the chemicals were the most likely to be injured, followed by the general public.[3] Both the current and the past HSESS reports can be found online at http://www.atsdr.cdc.gov/HS/HSEES.

The most commonly released hazardous substances are volatile organic compounds, herbicides, acids, and ammonia. Various household products, such as cement, drain cleaners, and gasoline, are also potentially quite hazardous, and exposure can result in severe disability or death.

PATHOPHYSIOLOGY

Most chemical agents cause skin damage by producing a chemical reaction rather than a hyperthermic injury. Certain chemicals can generate significant heat production following an exothermic reaction. Nonetheless, the majority of dermal injuries result from direct damage to the skin rather than from a hyperthermic injury.[4] The type of chemical reaction produced depends on the properties of the individual agent. In general, however, the degree of damage is directly correlated with the concentration of the toxic agent and the amount of time in contact with the toxic agent. Several other factors also contribute to the degree of injury. Areas of the body where the skin is particularly thin are more at risk than areas of the body where the skin is thicker. In addition, skin that is particularly thin (i.e., elderly skin) or broken (e.g., preexisting abrasions and lacerations) can contribute to more severe injury.

When acidic compounds interact with skin, protein denaturation and coagulative necrosis ensue. This coagulative necrosis produces an eschar, which limits the depth to which the acid can penetrate. Various acids produce characteristic color eschars. For example, nitric acid burns result in a yellow eschar, whereas sulfuric acid burns result in a black or brown eschar. Hydrochloric acid and phenol burns produce a white to gray/brown eschar.

Unlike the coagulative necrosis produced from acids, alkalis produce saponification and liquefactive necrosis of body fat. Because there is no eschar to limit penetration, alkali burns tend to penetrate deeper into the tissues, which results in significant tissue damage.

COMMUNITY PREPAREDNESS AND HAZMAT RESPONSE

A hazardous material (HAZMAT) is a substance that can cause physical injury or environmental damage if handled improperly. These substances can be found in residential, urban (e.g., manufacturing), and rural (e.g., agricultural) settings. Furthermore, because these substances are often transported on highways and railroads, a HAZMAT exposure could potentially occur almost anywhere. Nearly three fourths of all HAZMAT incidents involve fixed buildings, whereas the remaining one fourth are transportation-related incidents.[5] Accidents involving fixed locations are most likely to occur during weekdays between 12:00 and 6:00 PM, whereas no time predominance has been shown for transportation-related incidents.[5]

Following a HAZMAT accident, many people may be exposed to the agent. Employees working with the agent are at highest risk of injury,[3] but first responders are also in danger because they frequently arrive before the scene is contained. As a community develops its plans for responding to HAZMAT incidents, it is imperative to know the type of agents that are most likely to be involved.[6,7]

Identify and Assess Hazardous Environment

The paramedics and members of the HAZMAT response team must work together to identify toxic chemicals and assess hazardous environments. Placards, shipping papers, United Nations chemical identification numbers, and markings on shipping containers help identify the offending agent. In some cases, chemical analysis may be required to assist in the identification of the agent. The presence of carbon monoxide, cyanide, hydrogen sulfide, oxygen, and combustible gases can be detected using different instruments. Calorimetric detector tubes can approximate the concentrations of chemicals in the air. Alpha, beta, and gamma radiation detectors can record radioactive contamination. CHEMTREC (Chemical Transportation Emergency Center) in Arlington, Virginia, maintains a 24-hour telephone hotline (1-800-424-9300) to assist in the rapid identification and management of chemical agents. The staff at CHEMTREC can provide emergency responders in the field with shipper or product information for most chemicals. On average, CHEMTREC handles 22,000 HAZMAT incidents annually.

Contingency Plan

The contingency plan for HAZMAT management can be divided into two parts: initiation of the site plan and evacuation. Initiation of the site plan begins after the specific offending agent has been identified and the surrounding environment has been assessed. Only after the substance has been identified can the risks to the public and the environment accurately be identified. A central command post should be used to coordinate the activities of the HAZMAT team with those of the emergency medical services personnel, firefighters, police officers, and other relevant personnel.

Coping with HAZMAT Incidents

When dealing with a HAZMAT incident, two distinct processes must occur simultaneously. First, the scene must be secured, which involves containing the substance, extinguishing fires, and controlling other environmental hazards. All exposed individuals, injured or not, should be decontaminated before they are permitted to leave the scene. In addition, people who are not exposed to the hazardous material must be kept away from the scene to prevent subsequent exposure. Lastly, all injured persons must be treated.

At the outset of any contamination event, the offending agent may not be known. Therefore, first responders and those having direct contact with ill patients must wear personal protective equipment (PPE). Once the first responder is dressed appropriately, decontamination should begin by removing the patient's contaminated clothes. Dry (anhydrous) chemicals can be brushed off the patient's skin, followed by copious irrigation with water delivered under low pressure. Liquid chemicals can be copiously irrigated directly. The water used for decontamination should be collected, but decontamination of symptomatic individuals should not be delayed for this process. Ideally, decontamination should occur before arrival in the emergency department (ED). If decontamination has not yet occurred, the patient must be decontaminated prior to entering the ED. The primary and secondary survey can occur simultaneously with decontamination.

Although the exact requirements for PPE among hospital personnel are somewhat controversial, at a minimum, all personnel involved with decontamination should wear chemical-resistant clothing with a hood, boots, eyewear, at least two layers of gloves, and some form of respiratory protection.

MANAGEMENT

The initial management of the chemically burned patient involves removing the individual from the hostile environment. All clothing must be promptly removed and placed in plastic bags, if not already done. Dry chemical agents, such as lye, should be brushed away prior to instituting hydrotherapy. The priority of decontamination should progress from cleansing of contaminated wounds to eyes, mucous membranes, skin, and hair.

Hospital personal involved in decontamination should wear chemical-resistant clothing, with built-in hood and boots, at least two layers of gloves, protective eyewear, and some form of respiratory protection. The minimum level of respiratory protection for hospital personnel during decontamination has not been clearly established.

Chemical burns continue to destroy tissue until the causative agent is inactivated or removed.[7] Therefore, the quicker the agent is removed from the skin, the less severe the injury. Prompt treatment results in a return of the skin pH to normal or near-normal conditions.

Hydrotherapy

Hydrotherapy involves the application of large amounts of water or saline to the affected skin. Gentle irrigation of a large volume of water under low pressure for a prolonged time dilutes the toxic agent and washes it out of the skin. High-pressure irrigation should not be used because it is possible to drive the chemical deeper into the skin. Furthermore, the use of high-pressure irrigation can result in splattering of the chemical into the eyes of the patient or rescuer.

Elemental metals (e.g., sodium) may produce profound exothermic reactions when combined with water. To minimize the exothermic reaction from such compounds, mineral oil should be applied to the skin first, if it is immediately available. However, hydrotherapy should not be delayed while waiting for mineral oil. In addition, some have argued that phenol (carbolic acid) should not be irrigated with water due to concern for enhanced skin penetration after exposure to water. However, use of a substance that has both hydrophobic and hydrophilic properties (i.e., polyethylene glycol) does not demonstrate clear benefit over water alone; therefore, hydrotherapy should not be delayed while waiting for polyethylene glycol.[8]

After exposure to strong alkalis, prolonged hydrotherapy is especially important to limit the severity of the injury. In experimental animal models, the pH of chemically burned skin does not approach a normal concentration unless continuous irrigation has been maintained for more than 1 hour, and the pH often does not return to normal for 12 hours despite hydrotherapy. In contrast, with hydrochloric acid skin burns, the pH usually returns to normal within 2 hours after initiation of hydrotherapy.[9] The mechanism by which NaOH maintains an alkaline pH despite treatment is related to the by-products of its chemical reaction to skin. Alkalis combine with proteins or fats in tissues to form soluble protein complexes or soaps. These complexes permit passage of hydroxyl ions deep into the tissue, limiting their contact with the water diluent on the skin surface. On the other hand, acids do not form complexes, and their free hydrogen ions are easily neutralized.

Water is the agent of choice for decontaminating dermal burns due to either acidic or alkali substances. The deleterious effects of attempting to neutralize acid and alkali burns were first noted in experimental models in 1927.[10] In nearly every instance, animals with either acid or alkali burns that under-

went initial irrigation with water survived longer than animals treated with chemical neutralizers. The striking difference between the results of these two treatment methods is attributed to the additional trauma of the heat generated by the neutralization reaction superimposed on the existing burn. Although the same effect may occur when certain chemicals come in contact with water, large volumes of water tend to limit the exothermic reaction.

However, scientists are beginning to question the belief that neutralization of an alkaline burn of the skin with acid does indeed increase tissue damage because of the exothermic nature of acid-base reactions.[11] Using an animal model with 5% topical acetic acid (i.e., household vinegar), researchers demonstrated that the application of acetic acid to alkaline burns resulted in rapid neutralization of the tissue and reduction of the tissue injury in comparison with water irrigation alone.

Ocular Injury

Chemical burns to the eye necessitate emergent management. Alkali burns are more common than acidic burns, and unilateral involvement is more common than bilateral involvement.[12] Common etiologies include inadvertent handling of chemicals with resultant splash injury, exploding batteries, airbag deployment, and intentional assaults. Alkali burns can initially appear trivial, but because of an interaction with lipids in the corneal epithelial cells, a coagulative necrosis results, and deep penetration through the corneal stroma can ensue. The injury can occur rapidly. For example, anhydrous ammonia can penetrate into the anterior chamber in less than 1 minute, resulting in complete blindness.

Similar to cutaneous burns, ocular burns can be classified into four grades, with grade IV being the most severe. Grade I and II burns are associated with hyperemia, conjunctival ecchymosis, and defects in the corneal epithelium. Grade III and IV burns are associated with deeper penetration and, as such, are associated with mydriasis, a gray discoloration of the iris, and rapid cataract formation.

Grade II burns can be differentiated from grade I burns by the hazy appearance of the cornea in the former. Blood vessel thrombosis in the anterior chamber occurs in both grade III and grade IV burns, and as a result limbus ischemia occurs. The degree of ischemia differentiates grade III from grade IV burns: ischemia occurs in less than half of the limbus in grade III, whereas ischemia occurs in more than half of the limbus in grade IV. In addition, grade IV burns are associated with necrosis of the bulbar and tarsal conjunctiva and significant limbal ischemia.[12,13]

Treatment

When a chemical injury to the eye is suspected, copious irrigation should be started immediately. At the scene, the victim should submerge the eyes in running tap water and continuously open and close the eyes. The head should be turned such that the affected eye is lower than the unaffected eye to minimize any contamination into the unaffected eye. In the emergency department, tap water irrigation can be continued while preparing for a more definitive irrigation system. The repeated application of topical anesthetics such as proparacaine can decrease pain and facilitate irrigation. Hydrotherapy can also be accomplished by connecting IV tubing to a bag containing normal saline or lactated Ringer's solution. The initial therapy should consist of continual irrigation of the eye with 2 L of normal saline during the first 30 minutes. A Morgan lens can be used for irrigation, but there is a theoretical risk of trapping the chemical between the conjunctiva and the Morgan lens, thereby increasing the burn. If a Morgan lens is used, we recommend replacing the lens between saline applications. After 2 L has been infused, litmus paper should be inserted into the conjunctival sac and the pH tested. Irrigation should continue until the pH is at a physiologic level (approximate pH of 7.4). Alkali burns are likely to require more irrigation than are acidic burns. For very severe acid or alkali burns, prolonged irrigation may be needed regardless of a normal ocular pH. It is important to also double-evert the upper eyelid and visually inspect the area for any lodged particulate matter, which may be hidden.

Previously, some experimental settings have found benefit from the application of *N*-acetylcysteine or cysteine. These collagenase inhibitors are thought to prevent loss of the corneal stroma by limiting the amount of collagenase released from the injured tissue. In one retrospective study, the application of steroids, ascorbate, citrate, and antibiotics resulted in improved outcomes in grade III, but not grade IV, burns compared with steroids and antibiotics alone.[13] It is hypothesized that the citrate suppresses neutrophils and inhibits collagenase, thereby reducing the inflammatory response. Ascorbate has been hypothesized to promote new collagen deposition. Topical antibiotics (e.g., sulfacetamide, gentamicin, and ciprofloxacin) are indicated for any corneal injury. Mobility of the eye should be encouraged to minimize the formation of adhesions (symblepharon). With the exception of the antibiotics, there are insufficient data to recommend using any of the pharmaceutical agents mentioned in this paragraph as part of routine practice.

Immediate ophthalmologic consultation and close follow-up are indicated for all significant exposures. Patients with grade I and II injuries can often be managed as outpatients, but patients with higher-grade injuries should be admitted to the hospital. All but the mildest burns should be treated with a long-acting cycloplegic, a mydriatic. A carbonic anhydrase inhibitor may be used for 2 weeks (or until the pain disappears), after discussion with an ophthalmologist. These medications decrease the potential for pupillary constriction, increased intraocular pressure, and early glaucoma. Procedures such as amniotic membrane patching, anterior chamber paracentesis, and corneal transplant have been used for chemical injuries to the eye, and these are undertaken by the ophthalmologic consultant.

Hydrofluoric Acid

Hydrofluoric acid (HF) is an acidic aqueous solution made from the element fluorine. It is commonly used in the petroleum industry to manufacture high-octane gasoline. It is also commonly used in the production of microelectronics and for etching glass, removing rust, and cleaning cement and bricks. Absorption of HF can occur following exposure to the lung, skin, and eyes. In an 11-year review of all HF deaths reported to the Occupational Safety and Health Administration, four deaths resulted strictly from dermal exposure and five deaths resulted from both inhalational and dermal exposure. Several of these deaths were associated with inadequate medical therapy, and all of the cases were associated with unsafe workplace practices.[14]

HF is unique in its mechanism of action. When in a concentrated solution, it can act as a strong proton donor, thereby inducing a coagulative necrosis similar to other strong inorganic acids. However, the free fluoride ion is actually responsible for most of the damage associated with HF exposure.[15] The free fluoride ion scavenges cations, such as calcium and

magnesium, thereby resulting in systemic hypocalcemia and hypomagnesemia. In addition, the free fluoride ions can inhibit sodium/potassium/ATPase and the Krebs cycle. The combination of cellular destruction and inhibition of sodium/potassium/ATPase can also result in hyperkalemia. The severity of injury depends on the concentration of the substance and the length of exposure.

Inhalation

Inhalation of HF is rare, and it almost always occurs in the industrial setting. Patient outcomes vary considerably depending on the concentration and duration of exposure to HF. Inhalation and skin exposure to 70% HF can result in pulmonary edema and death within 2 hours.[11] However, delayed pneumonitis and adult respiratory distress syndrome can also occur, and once symptoms occur, they can be present for months. Pneumonitis can be severe and require ventilatory support.

Ocular Exposure

Despite the fact that HF is an acid, exposure of the eye to HF can result in a severe burn with penetration and necrosis of the structures throughout the anterior chamber.[16,17] As with other ocular injuries, immediate and copious irrigation of the eye is indicated. Systemic absorption is possible.

Dermal Exposure

Dermal exposure is perhaps the most common route of injury. Relatively dilute solutions of HF (0.6–12%) are available to the general public in the form of rust removal and aluminum cleaning products. During handling of containers storing HF, contamination of inadequately protected fingers and hands often results in a chemical burn injury. The HF skin burn has a distinct characteristic: the exposure causes progressive tissue destruction. Intense pain can occur quickly or be delayed for several hours, but it can persist for days if untreated. The skin at the site of contact develops a tough coagulated appearance. Eschar formation can occur.[18] If untreated, the burn can progress to an indurated, whitish appearance with vesicle formation. In the digits, HF has a predilection for subungual tissue. Severe untreated burns can progress to full-thickness burns and can even result in loss of digits.

Initial Therapy

The initial treatment of HF skin exposure is immediate irrigation with copious amounts of water for at least 15 to 30 minutes. Most exposures to dilute solutions of HF respond favorably to immediate irrigation. Severe pain or any pain that persists after irrigation denotes a more severe burn that requires detoxification of the fluoride ion. Detoxification is accomplished when an insoluble calcium salt is formed.

All blisters should be removed because necrotic tissue may harbor fluoride ions. The fluoride ions can then be detoxified through topical treatment, local infiltrative therapy, or intra-arterial infusion of calcium. Calcium gluconate (2.5%) gel is the preferred topical agent.[19,20] However, this gel is often not available in most hospital pharmacies, but it can be made by mixing 3.5 g calcium gluconate powder in 150 mL of a water-soluble lubricant (e.g., glycerin-hydroxyethyl cellulose [K-Y] jelly). The gel should be secured by an occlusive cover (e.g., powder-free latex glove). Because the skin is impermeable to calcium, topical treatment is effective only for mild, superficial burns.

Infiltration Therapy

Subcutaneous. Infiltrative therapy is necessary to treat deep, painful HF burns. Calcium gluconate is the agent of choice and can be administered by either direct infiltration or intra-arterial injection. A common technique involves injecting 0.5 mL/cm^2 of 10% calcium gluconate subcutaneously through a 27- or 30-gauge needle.[17] The use of an equal volume mixture of 5% calcium gluconate and 0.9% normal saline has been shown to reduce irritation of tissues and decrease subsequent scarring.[21] Patients treated in this manner should be hospitalized for observation and toxicologic consultation.

Despite its wide acceptance, the infiltration technique has disadvantages, especially when treating digits. A regional nerve block is recommended because the injections may be very painful. Removal of the nail to expose the nail bed is required if subungual tissue is involved. Vascular compromise can occur if excessive fluid is injected into the skin exposure sites, and unbound calcium ions have a direct toxic effect on tissue. Because of these disadvantages with subcutaneous infiltration, intra-arterial infusion of calcium is now recommended in most instances.

Intra-arterial. An intra-arterial catheter is placed in an artery close to the site of the HF exposure (e.g., radial, ulnar, or brachial artery). Various dilute solutions of calcium have been used, but perhaps the most commonly used solution is a mixture of 10 mL of solution of 10% calcium gluconate in 40 to 50 mL of normal saline infused over 4 hours.[22-24] If more than 6 hours has elapsed since the time of HF exposure, tissue necrosis cannot be prevented, even through pain relief can occur up to 24 hours after exposure.

The intra-arterial infusion technique also has potential disadvantages. Arterial spasm or thrombosis may result in significant skin loss. The intra-arterial procedure is more costly because it requires hospitalization for the use of the infusion pump and the monitoring of serum calcium concentrations if repeated infusions are used.

Systemic Toxicity

HF binds calcium and magnesium ions with strong affinity. Systemic manifestations of fluoride toxicity are at least partly related to hypocalcemia and include abdominal pain, muscle fasciculations, nausea, seizures, ventricular dysrhythmias, and cardiovascular collapse.[17,24] Consequently, patients with significant HF exposure should be hospitalized and monitored for cardiac dysrhythmias for 24 to 48 hours. Hypocalcemia can occur after significant exposure to HF and should be corrected with the intravenous administration of a 10% calcium gluconate infusion. Calcium chloride can be used, but requires central access to administer. In addition, fluoride ion accumulation has cardiac and neurotoxic effects.[25] Burns as small as 2.5% of the total body surface area have proven fatal in concentrated HF exposure.[26]

Formic Acid

Formic acid is a caustic organic acid used in industry and agriculture. It causes cutaneous injury by inducing a coagulative necrosis. Systemic toxicity occurs after absorption and is manifested by acidosis, hemolysis, and hemoglobinuria. Hemolysis is the result of the direct effect of formic acid on the red blood cells.

Copious wound lavage should be instituted immediately. Acidosis should be treated with sodium bicarbonate. Mannitol may be used to expand plasma volume and promote osmotic diuresis in patients with hemolysis. Exchange transfusion and

hemodialysis may be needed in patients with severe formic acid poisoning.

Anhydrous Ammonia

Anhydrous ammonia is a colorless, pungent gas used extensively as a fertilizer in the agricultural setting.[27] It can also be used in the manufacture of explosives, petroleum, plastics, and synthetic fibers. In addition, a newer method utilizing anhydrous ammonia has become popular. This method, called the "dry cook" or the "Nazi" method, utilizes anhydrous ammonia as a precursor to methamphetamines.[28] As a result of the use of this new method, there has been an increasing number of anhydrous ammonia burns associated with illicit methamphetamine production.[29,30] In one study, the incidence of anhydrous ammonia exposure from methamphetamine production was three times greater than that from agricultural production.[29]

The sudden release of liquid ammonia can cause injury through two distinct mechanisms. First, anhydrous ammonia has an extremely low temperature (−33° C) and freezes any tissue it touches. Second, the ammonia vapors readily dissolve in the moisture in skin, eyes, oropharynx, and lungs to form hydroxyl ions that cause chemical burns by liquefaction necrosis, which can result in full-tissue skin loss. The severity of injury is directly related to the concentration and duration of ammonia exposure. In general, acute exposure to anhydrous ammonia produces the greatest injury to the proximal airway rather than the distal airway.[29]

Treatment consists of prompt irrigation of the eyes and skin with water and management of inhalation injury. If necessary, the airway should be secured through standard intubation methods. A large-diameter tube should be used to prevent distal airway obstruction from sloughing of mucosa. After intubation, lower airway injury should be managed with positive end-expiratory pressure ventilation.

Cement

Cement is a solid material composed of salicylates and calcium aluminates. When dry cement is combined with water, hydrolysis occurs, resulting in a solution of basic lime hydrate. This solution has a pH of 10 to 12. As hydrolysis continues, however, the pH can increase up to 14, which is comparable with that of sodium or potassium hydroxide or lye.

There are three types of cement burns. The most common burn is a chemically abrasive form, and heat-related or blast-induced burns can also occur.[31] Heat-related and blast-induced burns are more common in the industrial setting and are associated with severe burns, often involving the respiratory tract.

The treatment of a cement burn should attempt to eliminate the toxic component via hydrotherapy. All clothes should be removed, and copious irrigation should occur. Early excision and grafting are often necessary.[31]

Phenol and Derivatives

Phenols are used industrially as starting materials for many organic polymers and plastics. They are widely used in the agricultural, cosmetic, and medical fields. Because of their antiseptic properties (first appreciated by Lister), they are also used in many commercial germicidal solutions. A number of phenol derivatives (e.g., hexylresorcinol and resorcinol) are more bactericidal than phenol.

Phenol (carbolic acid) is an aromatic acidic alcohol. Both phenol and its derivatives are highly reactive, corrosive poisons that damage cells by inducing cell wall disruption, protein denaturation, and coagulative necrosis. Their characteristic odor usually signals their presence. After penetrating the dermis, phenol produces necrosis of the papillary dermis. This necrotic tissue may temporarily delay its absorption. Therefore, when skin comes in contact with phenol, treatment must be instituted immediately. The exposed area should be irrigated with large volumes of water delivered under low pressure. Because dilute phenol solutions are more rapidly absorbed through skin than concentrated solutions, gentle swabbing of the skin surface with sponges soaked in water should be avoided. Any hair, including a beard or mustache, that has come in contact with a phenol should be removed as soon as possible because the phenol can become trapped in hair.

In animal studies, it was found that exposure to as little as 0.625 mg/kg of phenol could be lethal.[7] Systemic toxicity of phenol primarily affects the central nervous system (CNS) and cardiovascular system. In the CNS, toxicity can manifest as stimulation, lethargy, seizures, or coma.[32] Conduction disturbances can be either tachycardic or bradycardic in nature. Marked hypotension may occur as a result of central vasomotor depression, in addition to a direct toxic effect on the myocardial cells and small blood vessels. Also, hypothermia can result from phenol exposure because the phenols are a powerful antipyretic and thus decrease body temperature. Metabolic acidosis can result from both the direct acidic nature of certain phenols and lactate accumulation as a result of cellular dysfunction in shock.

A number of substituted phenols have unique systemic actions that are distinct from those of other phenols. For example, resorcinol can cause CNS stimulation. Picric acid can cause hemolysis, acute hemorrhagic glomerulonephritis, and acute liver injury.

Dilute solutions of phenol are used by plastic surgeons for chemical face peels.[33,34] Phenols are usually mixed with water, soap, and croton oil. This solution can produce a partial-thickness burn of a predictable depth in a controlled manner. It has been the standard for many years and is now also being used for skin resurfacing to remove wrinkles, irregular pigmentation, and actinic keratosis. The concentration is kept sufficiently low to reduce the occurrence of systemic complications. Interestingly, higher concentrations of phenol result in a shallower burn depth because of increased coagulation of the keratin, thereby preventing deeper penetration. Histologic studies have demonstrated that 100% concentrations of phenol produce 35 to 50% less penetration than a 50% solution.

The physician performing phenol chemical peels should be concerned about the possibility of rapid phenol absorption. Even in a controlled setting, ventricular dysrhythmias occur as a result of the phenol application.[34,35]

Polyethylene Glycol Therapy

Experimental studies indicate that water alone is effective in reducing the severity of burns and preventing death in animals with skin exposed to phenol and its derivatives. The most effective treatment is undiluted polyethylene glycol (PEG) of molecular weight 200 to 400 or isopropanol (isopropyl alcohol).[36,37] Adequate supply of either PEG or isopropanol should be stocked in hospitals located near areas of phenol use, and these can often be found in the chemical section of hospital pharmacies. A quick wipe of the skin with PEG solutions reduces mortality and burn severity in experimental animals. These solutions can be used in phenol burns of the face because they are not irritating to the eyes.[38] Decontamination with water should be performed until a PEG solution is

obtained. Large amounts of water must be used, however, because small amounts are detrimental, enhancing dermal absorption of phenol. Removal of phenol should be undertaken in a well-ventilated room so that hospital personnel are not exposed to high concentrations of phenol fumes.

Treatment of Systemic Toxicity

The treatment of systemic symptoms is primarily supportive. Respiratory depression may require ventilatory support. Hypotension should be treated initially with crystalloid fluids. If fluid resuscitation is inadequate, vasopressors might be needed. Metabolic acidosis can be treated with sodium bicarbonate. The alkalinization can also help prevent hemoglobin precipitation in the nephron as a result of hemolysis. Benzodiazepines may be required to treat seizures caused by CNS stimulation.

White Phosphorus

White phosphorus is widely used in munitions manufacturing and in civilian settings as an ingredient in fertilizers, rodenticides, and fireworks. It has a relatively low melting point of 44° C (111° F). The autoignition temperature (the temperature at which spontaneous combustion can occur) is 30° C (86° F).[39] When white phosphorus comes in contact with air at temperatures above the autoignition point, the phosphorus will spontaneously oxidize, forming phosphorus pentoxide. Phosphorus pentoxide is very hygroscopic—that is, it has the ability to combine with small amounts of moisture in the air. After combining with water, phosphoric acid is formed. In wounds, oxidation of phosphorus pentoxide will continue until it is débrided, neutralized, or consumed.[1]

Tissue injury from white phosphorus appears to have both thermal and chemical causes. The corrosive action of the phosphoric acid results in an exothermic reaction, thereby liberating heat and causing a thermal burn. The hygroscopic action of the phosphorus pentoxide, however, is also responsible for causing a chemical burn.[1] Ultimately, a profound thermal injury can occur, which frequently results in a partial-thickness or full-thickness burn.

Metabolic derangements can also occur following white phosphorus exposure. Hypocalcemia and hyperphosphatemia can occur. Conduction system disturbances can occur as well, which are at least partially explained by the electrolyte derangement. These electrocardiographic abnormalities include bradycardia, QT prolongation, and ST or T wave abnormalities.[1,40] These electrocardiogram changes may explain the sudden early death that occasionally occurs in patients with relatively minor white phosphorus burns.

Following oral ingestion of white phosphorus, three stages of toxicity occur. The first stage is characterized by gastrointestinal tract irritation, including vomiting, abdominal pain, diarrhea, and gastrointestinal bleeding. Hypovolemic shock can result. As many as one third of patients who ingest significant quantities of white phosphorus will die during this stage. The first stage can last 8 to 24 hours. The second stage, which lasts 1 to 3 days, is a latent phase in which symptoms appear to improve. However, the third stage is characterized by multisystem organ failure, including hepatic failure, renal failure, and CNS depression. Renal failure is usually present between days 1 and 4, whereas jaundice typically manifests between days 3 and 5.[41]

The out-of-hospital management involves the immediate removal of contaminated clothing, followed by submersion of the injured skin in cool water. Warm or hot water should be avoided because white phosphorus becomes liquid at 44° C (111° F). Phosphorus particles should be removed from the victim's skin and submerged in water. The burned skin should be covered with towels soaked in cool water during transport to the emergency department.

After the patient arrives at the emergency department, the burned skin should be washed copiously with normal saline. Previously, some advocated use of a suspension of 5% sodium bicarbonate, 3% copper sulfate, and 1% hydroxyethyl cellulose. Other similar solutions containing copper sulfate have also been described. The use of 0.9% normal saline solution, however, has demonstrated better effects than copper-containing solutions.[42] Although there are some conflicting recommendations in the literature,[43] given that saline is probably at least as efficacious as copper sulfate solutions and has less associated toxicity, saline irrigation should be considered the preferred irrigating solution.[1,40,44]

Phosphorus particles can be identified with either ultraviolet light or copper-containing solutions. When using a Wood's lamp, the phosphorus will fluoresce under an ultraviolet light.[44] Unlike copper-containing solutions, the use of a Wood's lamp is not associated with any adverse or detrimental effects. The use of the copper-containing solutions causes the phosphorus particles to become coated with black cupric phosphide. These black particles are more easily identified and thus more easily removed. Copper sulfate also decreases the rate of oxidation of the phosphorus particles, thus limiting their damage to the underlying tissue. However, because the blackened particles can still cause tissue damage, they must be removed. If a copper solution is used, after 30 minutes of exposure to the burned skin, the copper-containing solution must be thoroughly washed from the skin, thereby limiting the development of systemic copper toxicity. Systemic copper toxicity manifests with gastrointestinal irritation with bluish discoloration of the emesis, hepatotoxicity, hemolysis, methemoglobinemia, CNS depression, hypotension, and cardiovascular collapse. Skin burns can also occur at the site of the copper contact.

After hydrotherapy and treatment of associated electrolyte disturbances, definitive management of the skin burns is accomplished as with any other burn wound. Serum calcium and phosphate levels should be monitored for 24 to 48 hours.[43]

Nitrates and Nitrites

Both nitrates (NO_3^-) and nitrites (NO_2^-) are abundant in modern society. Both sodium nitrate and sodium nitrite are used in food preservatives for their antimicrobial effects. Nitrites also have many uses in medicine for their vasodilatory properties. Nitrates are commonly used in electroplating, engraving, and metal casting. Nitrates are also commonly used as fertilizing agents. Exposure to either nitrates or nitrites has been associated with methemoglobinemia.[45]

Reduced hemoglobin contains four heme groups, each with a ferrous (Fe^{2+}) ion. Methemoglobinemia results when the ferrous ion becomes oxidized to the ferric (Fe^{3+}) state.[46] At physiologic levels, there is usually 1 or 2% methemoglobinemia in circulation at any given time. In nonanemic patients, methemoglobin levels less than 20% can produce cyanosis, but the patients are otherwise usually fairly asymptomatic. Levels greater than 20% are associated with headache, anxiety, dyspnea, and tachycardia. Confusion, lethargy, and acidosis typically occur with methemoglobin levels approaching 40 to 50%. Coma, seizures, hypotension, dysrhythmias, and death occur when levels exceed 70%.[47] The diagnosis of methemoglobinemia should be sought in any cyanotic patient who is unresponsive to oxygen therapy and whose blood appears

chocolate brown in color. Asymptomatic patients can be treated simply by removing the offending agent. For symptomatic patients without G6PD deficiency, 2 mL/kg of 1% methylene blue can be administered over 3 to 5 minutes. Symptoms typically improve within 20 minutes. Severe cases can be treated with exchange transfusion. Candidates for exchange transfusion include patients with G6PD dificiency with significant toxicity from methemoglobinemia and patients who fail to respond to methylene blue.

Hydrocarbons

Hydrocarbons are a heterogeneous group of organic compounds that are derived from carbon and hydrogen molecules. They have become an integral part of modern society; they are found in fuels, solvents, paints, paint and spot removers, dry cleaning solutions, lamp oil, rubber cement, and lubricants.

Hydrocarbons can be classified as aromatic, in which the carbon moieties are arranged in a ring, or aliphatic, in which the carbon moieties are arranged in a linear or branched chain. Halogenated hydrocarbons are a subgroup of aromatic hydrocarbons in which one of the hydrogen molecules is substituted with a halogen.

The toxicity from hydrocarbons can affect many different organs, but the lungs are the most commonly affected organ. The toxicity of hydrocarbons is directly related to the volatility and inversely related to the viscosity and surface tension. The primary toxicity from hydrocarbons occurs from aspiration following ingestion. Thus, substances with high volatility, low viscosity, and low surface tension are most likely to be aspirated.

Systemic toxicity from dermal exposure to a hydrocarbon is relatively rare. Significant dermal exposures can result in local pain, erythema, blistering, and local edema. Treatment should involve removal of the patient from the source and removal of any contaminated clothing. Copious irrigation with warm water should be performed, and burns should be managed as with other burns.

Chronic dermal exposure can result in a perioral or perinasal dermatitis with pyoderma. This so-called "huffer's rash" is primarily seen with recreational abuse.[48] The hydrocarbon inhalant can dry the skin, thereby causing microscopic cracks and allowing bacteria to enter, causing a bacterial superinfection.

Significant toxicity from inhaled (nonaspiration) exposure to hydrocarbons is also unlikely to produce serious effects. Some patients may develop mild headache, dizziness, nausea, or wheezing. These symptoms should be treated by removal of the patient from the contaminated environment and administration of oxygen. Wheezing can be treated with beta-agonists.

Ingestion of hydrocarbons can result in aspiration and systemic toxicity. Following ingestion of hydrocarbons, patients should be monitored for 6 hours. A chest radiograph should be obtained 6 hours postexposure. If there are neither radiographic abnormalities nor clinical findings suggesting aspiration (e.g., coughing, gagging, vomiting, wheezing, tachypnea, or hypoxia), the patient can be discharged home. If any of these symptoms is present, admission is mandatory because a hydrocarbon-induced pneumonitis can occur, resulting in severe difficulties with oxygenation. Endotracheal intubation is often required for severe hypoxia. Neither corticosteroids nor empiric antibiotic administration is indicated. Antibiotics may be warranted, however, if a superimposed bacterial infection develops, which will typically occur several days after the pneumonitis develops.

Tar

Burns from hot tar present a treatment challenge. When hot, liquefied tar comes in contact with skin, heat is transferred and thermal injury results. The tar cools and solidifies on the skin, making removal difficult. There are two types of hot tar: coal tar pitches and petroleum-derived asphalts. Both products are heated to maintain a liquid form. Roofing tar needs to be heated to temperatures of at least 232° C in order to achieve desirable viscosities.[49] Deeper burn injuries are associated with burns from roofing asphalt.

When hot tar touches skin, it rapidly cools, solidifies, and becomes enmeshed in the hair. It is important to facilitate this cooling process by adding cold water to the tar at the scene of the accident. Cooling tar with cold water limits the amount of tissue damage and prevents the spread of tar. Tar should be continually washed with water until it has cooled and hardened. After cooling, the skin should be dried with towels to prevent systemic hypothermia.

Adherent tar should not be removed at the scene of the accident. In the emergency department, definitive care of tar burn injury involves early removal of tar because it occludes injured skin and encourages bacterial growth. Tar adheres to skin because it is enmeshed in the hair, not because of a direct bond between epidermis and tar.

Solvents used to remove tar ideally should have a close structural affinity to tar. Both petroleum-based aromatic hydrocarbon solvents and surface-active agents such as polyoxyethylene sorbitan (Tween 80) and polysorbate (De-Soly-It) have been used to facilitate tar removal. These latter two agents are more water soluble and may remove tar more easily than the petroleum-based products. Use of these surface-active agents is an effective, safe, and inexpensive means of removing tar from skins. Sunflower oil, NISA baby oil, mayonnaise, and butter have also been used to remove adherent tar from skin, requiring 30 to 90 minutes for complete removal. Sunflower oil has proved effective and safe in removing tar without causing further skin damage.[50]

Asphalts are susceptible to both aromatic (e.g., naphthalene) and aliphatic (e.g., hexade) hydrocarbon solvents, whereas coal tars are susceptible only to aromatic hydrocarbons. Broad-spectrum antibiotic ointments can be used to both help with removal and to help prevent infection. If used, they must be removed and a new coating applied every hour until all the tar is removed. This process typically takes 12 to 48 hours. Commonly used antibiotic ointments include bacitracin (400 μg/g), polymyxin B (5000 U/kg), and neomycin (5 mg/g). Antibiotic ointment has been used successfully to remove even tar layered over the cornea and conjunctiva.

Elemental Metals

The elemental metals, such as lithium, sodium, and potassium, are harmless unless they come in contact with water. When this happens, a violent exothermic reaction occurs, which produces heat, hydrogen gas, and hydroxide. The evolved heat is sufficient to ignite the hydrogen gas, which results in further heat production and thermal burns. The formation of the hydroxide compound may also result in significant chemical injury to tissue. The reaction occurs more rapidly with elemental potassium than with sodium. These deleterious effects of potassium have been attributed to trace amounts of potassium superoxide released on exposure to room air.[4] Water lavage is therefore contraindicated in these circumstances.

In the out-of-hospital setting, only a class D fire extinguisher (containing sodium chloride, sodium carbonate, or graphite

base) or sand should be used to suppress the flames. Once the flame is extinguished, the metal should be covered with an oil (mineral oil is preferred). The oil will isolate the metal from air and water. The patient should be transported to the emergency department for wound débridement and cleansing. Small pieces of metal that cannot be brushed away should be débrided from the skin. Metal fragments can be placed in mineral oil for safe deposit.

CHEMICAL TERRORISM

Following the terrorist attack on September 11, 2001, the public has become increasingly aware of this type of attack.[51] Despite being banned by the 1925 Geneva Convention, chemical weapons have been used in both the military and the civilian arenas for many years, including the decades preceding the September 11th attack. In the 1980s, Saddam Hussein's cousin, Ali Hassan al Majid, also known as "Chemical Ali," was responsible for attacking up to 30 villages in the Jafati valley with chemical weapons. In 1995, Aum Shinrikyo, a Japanese cult, released VX nerve gas in the Tokyo subway, causing 12 deaths and more than 5000 casualties.[52] As terrorist organizations continue to use nonconventional weapons such as chemical and biologic agents, the civilian medical community needs to better understand their characteristics and pathophysiology.

Response

The U.S. government recognizes the emerging threat of terrorism and the potential for terrorist organizations to use nonconventional weapons. In 1997, the U.S. Congress appropriated $52.6 million for the Defense Against Weapons of Mass Destruction Act.[53] Subtitle A of this document established the Domestic Preparedness Program to enhance the government's capability to respond to terrorist attacks with these weapons. The act also focuses on improving local and state agencies to address these threats and to train communities.

The government's direct response was delineated by Presidential Decision Directive 39 (PDD-39), signed by President Clinton in 1995.[54] For all cases of domestic terrorism, the Federal Bureau of Investigation is assigned to oversee crisis management and to investigate the case for eventual prosecution. The Federal Emergency Management Agency (FEMA) is to coordinate assistance to state and local governments, provide emergency relief, and protect public health and safety. In March 2003, FEMA joined 22 other federal agencies, programs, and offices to form the Department of Homeland Security. The Office of National Preparedness, a division of FEMA, is currently responsible for ensuring that the nation's first responders are trained and equipped to deal with weapons of mass destruction.

Appropriate casualty triage remains a critical component when dealing with nonconventional weapons. Triage should be performed by specially trained emergency medical personnel who are familiar with these agents and with the use of PPE.[55] The emergency department could be quickly overwhelmed with masses of non-critically injured survivors. Ideally, triage would be conducted both at the scene of the attack and again at a second point before emergency department arrival.

Emergency Department Preparedness

Following a chemical attack, triage should be started outside the emergency department. Appropriate decontamination measures should be performed prior to the patients entering the treatment areas of the emergency department. These steps are critical to ensure that other patients and staff are not secondarily exposed. For those directly handling the casualties, PPE such as a full-face respiratory mask, self-contained breathing apparatus, and impermeable suits should be available. The greatest challenge for emergency departments in caring for these individuals is the sudden increase in patients presenting for treatment.[56] The use and location of decontamination showers should be well known, and negative-flow isolation rooms should be available. In emergency departments with only one or two negative-flow isolation rooms, it is possible to put two patients in the same room if they have both been exposed to the same agent. Otherwise, one of the patients might need to be placed outside but in a well-ventilated area. A surveillance system should be established to identify groups at high risk and to evaluate medical interventions. Many of these agents can cause long-term adverse health outcomes, and registries should be established to facilitate appropriate follow-up.

Chemical Agents

Chemical agents can be classified as (1) nerve agents, (2) vesicants, (3) choking agents, or (4) cyanide and related toxins (Table 61-1). The first nerve agent documented was tabun, which was synthesized by German chemist Gerhard Schrader in 1937. Schrader developed tabun (military symbol: GA) while researching new insecticides. The following year, sarin (GB) was created. Other popular nerve agents include soman (GD) and VX. Although nerve agents were stockpiled for use during both World Wars, the first documented use in a war was in the 1980s during the Iran-Iraq War.[57] The largest use of

Table 61-1 Classification of Chemical Agents

CLASS	EXAMPLE*	TREATMENT
Nerve agents	Tabun (GA) Sarin (GB) Soman (GD) Cyclosarin (GF) VX	Atropine and pralidoxime
Vesicants	Mustard agents Mustard/sulfur mustard (H) Distilled mustard/sulfur mustard (HD) Nitrogen mustard (HN1, HN2, HN3) Organic arsenical agents (e.g., lewisite; L) Halogenated oxime agents (e.g., phosgene oxime; CX)	Hydrotherapy Moist dressing on blisters Supportive care
Choking agents	Phosgene (CG) Chlorine (CL) Military smoke (HC) Chloropicrin (PS)	Supportive care
Cyanide agents	Hydrogen cyanide	Cyanide kit Amyl nitrite Sodium nitrite Sodium thiosulfate Hydroxocobalamin

*Chemical or common name (military chemical symbol).

nerve agents by terrorists was by the Aum Shinrikyo cult of Japan, which produced both VX and sarin.

Vesicants, also known as blistering agents, are a class of drug that produce blisters at the site of contact. Despite their discovery in the 1800s, their introduction to warfare did not occur until the 20th century. Since World War I, however, sulfur mustard (also known as mustard gas, mustard, or CAS No. 505-60-2) has remained a constant threat in modern warfare. Other vesicants include lewisite (dichloro-2-chlorovinylarsine), which is an organic arsenical, and phosgene (dichloroformoxime), which is a halogenated oxime. Although phosgene is often listed as a vesicant, technically it is not because its urticarial lesions that develop after contact are not fluid-filled.

Choking agents have been used in both military and civilian settings. Although there are many different agents and uses, the collective term *choking agent* refers to a chemical that can potentially induce pulmonary edema. Phosgene and chlorine are two agents that were used in World War I. Although chlorine is no longer used as a warfare agent, it is still used widely in the industrial setting. Zinc-containing smoke is another choking agent that is used in conventional warfare. Other agents are used for riot control.

Cyanide agents, such as hydrogen cyanide or sodium azide, are cellular toxins. Cyanide was discovered in the 18th century by the Swedish chemist Carl Wilhelm Scheele.[58] Although Scheele gave no indication of its lethal characteristics, today hydrogen cyanide is one of the most toxic chemicals known, with potential deadly consequences if used by a terrorist organization.

Nerve Agents

The nerve agents can be classified as either "G" agents or "V" agents. The nerve agents are all derived from phosphoric acid and are volatile liquids at room temperature. As such, they must be aerosolized or evaporated in order to be used as an inhalational weapon. Because the vapors are heavier than air, they tend to remain close to the ground and will travel downwind and downhill. However, various weather conditions, such as wind, can result in unpredictable dispersal.[59]

The nerve agents work by affecting acetylcholine (ACh). ACh receptors are found on the postsynaptic receptor of cholinergic synapses. These receptors can be either nicotinic or muscarinic. Activation of the nicotinic receptors results in depolarization of the postsynaptic neuron or skeletal muscle cell, whereas muscarinic activation affects exocrine glands and smooth muscle, primarily in the CNS. Under normal conditions, the enzyme acetylcholinesterase hydrolyzes ACh in the synapse, thereby inactivating ACh. The primary mechanism of action of the nerve agents is to prevent acetylcholinesterase from hydrolyzing ACh. As a result, ACh accumulates in excess. The effects at the muscarinic receptors include excess secretions and smooth muscle contractions.[60] The mnemonics DUMBELS (diarrhea, urination, miosis, brochoconstriction/bronchorrhea, emesis, lacrimation, and salivation) and SLUDGE (salivation, lacrimation, urination, defecation, and gastrointestinal emesis) are often used to describe these effects. The nicotinic manifestations include muscle fasciculations and weakness. The primary clinical toxic effects are respiratory, however, and treatment should be aimed at correcting these effects.

Victims of dermal exposure should be undressed and thoroughly decontaminated with water using large-volume, low-pressure irrigation. Following decontamination, the initial treatment should be aimed at maintaining an airway and restoring adequate oxygenation and ventilation. If rapid sequence intubation is desired for airway management, the paralytic succinylcholine should be used with great caution because its duration of action will be significantly prolonged since the nerve agent will likely inhibit its breakdown. Atropine is a direct-acting antagonist of the muscarinic receptor. It is important to note, however, that because atropine does not work at the nicotinic receptors, all nicotinic effects, including muscle weakness or paralysis, will not be reversed with atropine. The initial recommended dose is 2 mg of atropine for adults, although much larger doses will likely be required. The endpoint for stopping atropine administration is not improvement in heart rate but, rather, drying of bronchial secretions. Pralidoxime should also be administered to patients with suspected or known ingestion with significant symptoms. The traditional dose of pralidoxime is 600 to 1200 mg intramuscularly. Pawars and colleagues examined a high-dose strategy of pralidoxime for organophosphate poisoning. In their study, all patients received 2 g of pralidoxime intravenously as a loading dose. Patients were then randomized to receive either 1 g (over 1 hour) every 4 hours for a total of 48 hours or a continual infusion of 1 g/hr for 48 hours. The continual infusion strategy had lower morbidity and mortality compared with the intermittent bolus group.[61] Lastly, benzodiazepines should be given both to prevent and to treat any seizure activity. Exact dosing and treatment strategies should be discussed with a medical toxicologist.

For pediatric patients, if accurate weight-based dosing is not available, children younger than 1 year can receive 0.5 mg atropine, whereas children older than 1 year can receive the standard adult dose of 2 mg atropine as a starting dose.[62]

Vesicants

At temperatures below 14° C, mustard exists in the solid form. Once in the liquid or gaseous form, mustard gas can be recognized by its unique garlic or fishlike odor.[63] Mustard vapor is also much heavier than air and, as a result, tends to remain close to the ground. When stored as an oil-based liquid, it can be readily aerosolized and attached to a bomb or shell. Because vaporization occurs slowly, the risk of injury is much greater in cool environments and closed spaces. Several minutes of exposure can result in skin and eye injury, whereas exposure for more than 30 minutes can lead to respiratory injury and death.

Mustard gas can enter the body following inhalational, dermal, or oral exposures. After entering the body, it functions as an alkylating agent. The altered molecules then interact with proteins and nucleic acids, forming covalent bonds. Mustard is the only vesicant that does not cause immediate pain.[63] Several hours after exposure, manifestations of exposure occur. Following exposure to aerosolized mustard gas, cutaneous manifestations appear after a latent period of up to 24 hours.[64] Initial dermal symptoms include burning, itching, and erythema, followed by hyperpigmentation, vesicle formation, and, later, bullae.[65] Electrolyte depletion and secondary bacterial infection can occur if the affected body surface area is large. In addition, inhaled mustard gas can lead to vomiting and diarrhea. Myelosuppression can occur within 3 to 5 days of exposure, resulting in leukopenia and thrombocytopenia.[64] Direct mucosal damage in the respiratory tract can occur, resulting in bronchiolar damage and hemorrhage.[63] The systemic manifestations can occur with any route of exposure.

Treatment consists first and foremost of removing the patient from the environment and decontamination of the vesicant. Water can be used for decontamination if that is all

that is available, but it might not be the preferred agent.[66] Some advocate using a 0.5% hypochlorite solution (diluted household bleach [1:9]). Currently, the U.S. military recommends using an alkaline hypochlorite solution (pH 10 or 11) as the decontamination method of choice.[67] However, this solution should not be used on open abdominal or chest wounds. No specific antidote exists. British anti-lewisite (BAL; 2,3-dimercapto-1-propanol; dimercaprol) was originally developed as an antidote for lewisite. Although BAL is currently available as a chelator for several heavy-metal poisonings, it should be used cautiously, if at all, for mustard poisonings.

Choking Agents

Chlorine (CL) and phosgene (CG) were both used in World War I as part of chemical warfare. However, most contact with choking agents today comes from accidental industrial exposures to chlorine. Phosgene is still used in the production of polyurethanes. In addition, riot control agents, such as pepper spray and tear gas, can be considered choking agents. Chemicals are collectively considered choking agents if they induce the sensation of choking and have the potential to induce upper airway damage and pulmonary edema.

Chlorine is a heavy greenish-yellow gas or liquid with a characteristic odor. Today, chlorine is used for plastic production (mostly for polyvinyl chloride), dry cleaning, pharmaceuticals, textile or paper bleaching, water purification, and as a disinfectant.[68,69] The clinical effects observed following chlorine exposure are directly related to the time and concentration of the exposure. Mild exposure may simply cause nasal irritation, whereas more severe chlorine exposure will induce edema of both the upper airway and the lung parenchyma. In large doses, this edema results in cellular exudates, pulmonary congestion, and hemorrhage.[68,69] In addition, increased secretions, a sensation of coughing, dyspnea, and chest tightness can be observed. Because chlorine is primarily reactive only at a local level, absorbed systemic effects are not commonly observed.[69]

In contrast to chlorine, phosgene is much less water soluble. As a result, there is less upper airway edema but more alveolar damage, resulting in more severe noncardiogenic pulmonary edema.[70]

The first step in treating an exposure to any choking agent is to remove the individual from the environment. No specific antidote exists, and supportive care is indicated. Following significant exposure to these agents, the ABCs (*A*irway *B*reathing and *C*irculation) should be assessed, with particular attention paid to ensuring an adequate airway and oxygenation. Endotracheal intubation may be required. Any bronchospasm can be treated with beta-agonists such as albuterol. Irritation of the eyes can be handled with copious irrigation of water or saline, and the cornea should be examined for any abrasions.

Cyanide

Cyanide salts and hydrocyanic acid are commonly used for metal cleaning, precious metal extraction, photographic processes, electroplating, laboratory assays, and jewelry cleaning. In addition, cyanide gas is often liberated from the combustion of plastic-containing compounds. There is considerable concern that cyanide can be used by terrorists as a weapon.[71]

Cyanide is considered a cellular toxin. It binds to both Fe^{3+} and cobalt. By binding and inactivating the enzyme cytochrome oxidase, which is part of cytochrome a3 on the electron transport chain, cyanide inhibits oxidative phosphorylation.[71] This inhibition results in profound cellular hypoxia and death.

Following ingestion of cyanide, many patients will experience sudden cardiovascular collapse. Hypotension and altered mental status can frequently be observed. A characteristic odor of bitter almonds may be noted.

Although cyanide levels can be confirmatory, they are rarely immediately available. However, most patients with significant cyanide exposure will have a profound lactic acidosis. In addition, because the cellular utilization of oxygen is blocked, venous blood is highly oxygenated. As such, an elevated mixed venous O_2 saturation, or an elevated peripheral venous partial pressure of oxygen (Po_2) may be observed.[72,73] In these cases, the pulse oximeter reading may be near normal, despite significant cellular hypoxia.

A diagnosis of cyanide poisoning requires careful consideration. The initial treatment should be focused on maintaining the ABCs. Standard antiarrhythmic medications are appropriate for the treatment of cyanide-induced arrhythmias. Vasopressors may be required.

Any potentially exposed skin or eyes require prompt decontamination by copious irrigation with saline or water. Currently, two specific types of antidotes can be used to treat known or suspected cyanide intoxication. One method of treatment involves the administration of amyl nitrite, sodium nitrite, and sodium thiosulfate. Using this combination of medications, amyl nitrite pearls should be broken open and the patient allowed to breathe a pearl for 30 seconds of each minute. A new pearl is needed every 3 or 4 minutes. Once intravenous access has been established, 300 mg of sodium nitrite (one 10-mL ampule of 3% solution for adults and 0.12–0.33 mL/kg for pediatrics) can be administered. Because sodium nitrite is a potent vasodilator, hypotension can ensue. Thus, the sodium nitrite should be administered over a minimum of 5 minutes. Following sodium nitrite administration, sodium thiosulfate should be administered at a dose of 12.5 g (one 50-mL ampule of a 25% solution for adults and 1.65 mL/kg for pediatrics). The function of the nitrites is to induce methemoglobinemia. Thus, in patients who have a suspected simultaneous intoxication of cyanide and carbon monoxide, the nitrites should not be used.

In December 2006, the Food and Drug Administration approved hydroxocobalamin (Cyanokit) for treatment of cyanide intoxication.[74] Hydroxocobalamin binds to cyanide to form cyanocobalamin, which subsequently undergoes renal excretion.[75] Hydroxocobalamin appears to be safe for use in both the hospital and the out-of-hospital setting, although there may be a reddish discoloration of the skin.[76,77] In addition, its use is associated with alteration in laboratory measurements of magnesium, iron, aspartate aminotransferase, total bilirubin, and creatinine.[78] If treating a patient for known or suspected cyanide toxicity, either the Taylor Kit (amyl nitrite, sodium nitrite, and sodium thiosulfate) or the Cyanokit (hydroxocobalamin) should be used, but not both.

Acknowledgments

The authors acknowledge the contributions of Richard F. Edlich, Marcus L. Martin, and William L. Long III, who wrote the chapter on chemical injuries for the previous edition.

KEY CONCEPTS

- For chemical injury, the degree of skin destruction is determined mainly by the concentration of the toxic agent and the duration of its contact.
- Chemical injuries are commonly encountered after exposures to acids and alkalis.
- HAZMATs are substances that can cause physical injury and damage the environment if improperly handled.
- In dealing with HAZMAT incidents, two distinct goals must be achieved: (1) The HAZMAT must be contained, fire and explosions must be extinguished, and the site must eventually be cleaned, and (2) people exposed to the HAZMAT must be treated.
- For more than 30 years, CHEMTREC has provided crucial information needed to assist emergency response personnel in handling HAZMAT incidents in the safest possible manner.
- Alkali burns tend to penetrate deeper than acidic burns; as a result, alkali burns tend to be associated with greater morbidity.
- HF burns can be associated with significant hypocalcemia.
- Nonconventional chemical weapons may be categorized into four major classifications: nerve agents, vesicants, choking agents, and cyanide agents.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 62

Forensic Emergency Medicine

William S. Smock

PERSPECTIVE

Clinical forensic medicine is the application of forensic medical knowledge and techniques to live patients in a clinical setting. European and British physicians—known as police surgeons, forensic physicians, forensic medical examiners, or forensic medical officers[1]—have performed clinical forensic examinations for more than 200 years,[2] including evaluations on prisoners and victims of physical and sexual assault.[3]

All patients who are victims of physical or sexual assault, abuse, trauma, or a terrorist event have forensic needs. When treating injuries without considering the forensic issues, physicians may misinterpret wounds, miss victims of abuse or domestic violence, and inadequately document the nature of injuries. During the provision of patient care, evidence that can be of critical significance to criminal or civil proceedings can be lost, discarded, or inadvertently washed away.[4-16] Wound evaluation and evidence collection are critical for victims of a terrorist incident. Their wounds may contain radioactive materials, trace evidence, or bomb fragments that will be an important component of the criminal investigation.[17]

In 1991, the University of Louisville School of Medicine and the Kentucky Medical Examiner's Office established a clinical forensic medicine training and consultative program in the United States.[7,9,15,16] In 2006, the American College of Emergency Physicians established the Forensic Medicine Section to provide additional forensic resources and training[18] and to include forensic training within residency programs.[7,8,19]

Forensic examinations are conducted with the consent of the patient, legal guardian, or court, or by implied consent. The evaluation includes a history and physical examination, photographs, and anatomic diagrams.[17,20] Evidentiary material, including clothing, hair, blood, saliva, bullets, and bomb fragments is collected when indicated or when ordered by the court. If a patient has been admitted from the emergency department to surgery, an evaluation is done in the operating suite with the trauma surgeons.

Evaluations of gunshot and stab wounds, physical or sexual abuse, domestic violence, explosion-related injuries, and motor vehicle-related trauma should be adequately documented and include a photograph as well as a narrative and diagram for possible use in future legal actions.[5-11,13-17,20] However, in one trauma center, 70% of cases had improper or inadequate documentation, and 38% of cases had potential evidence improperly secured, incorrectly documented, or inadvertently discarded.[6] Former U.S. Surgeon General Dr. Richard Carmona reported that emergency and trauma physicians "usually have little or no training in the forensic aspects of trauma care and therefore necessary evidence may often be overlooked, lost, inadvertently discarded or its admissibility denied because of improper handling or documentation."[6]

Misinterpretation of physical injuries and evidence may be recorded in the medical record and may pose a problem in future legal proceedings.[2,4-16,20-24]

THE FORENSIC ASPECTS OF GUNSHOT WOUNDS

Firearm-related deaths—30,694 in 2005—are the second leading cause of injury-related deaths in the United States after motor vehicle trauma.[25] Emergency physicians treat more than 115,000 victims of gunshot wounds each year, principally from handguns.[26] The direct and indirect cost associated with gunshot wounds is $36 billion annually.[27]

Errors of Interpretation and Terminology

The emergency physician is in the ideal position to evaluate and document the state of a gunshot wound before it is disturbed, distorted, or destroyed by surgical intervention.[4-11,15,20,21,24] Documentation of gunshot wounds should include the anatomic location, size, shape, and characteristics of the wound. Wounds should be described according to the standard anatomic position with the arms to the side and palms up.

Clinicians should not describe wounds as "entrance" or "exit" but should document a detailed description, using appropriate forensic terminology, of the appearance, characteristics, and location of a wound without speculating on an interpretation or the caliber of the bullet (projectile).[15,28-31] Exit wounds are *not* always larger than entrance wounds, and wound size does not correspond to bullet caliber.[15,21,17,28-31]

The size of any wound (entrance or exit) is determined by five factors: the size, shape, configuration, and velocity of the projectile at the instant of impact with tissue and the physical characteristics of the impacted tissue. If the projectile is slowed and its shape unchanged on exiting the skin, the exit wound may be the same size as or smaller than its corresponding entrance wound.[15,28,32] If the projectile increases its surface area by fragmenting or changing its configuration while maintaining a substantial velocity, the exit wound may be significantly larger than the entrance wound.[15,28-36] If the bullet strikes bone,

fragments may extrude from the exit wound and contribute to the size and shape of the wound. Tissue elasticity also affects the wound size so that entrance or exit wound size may be smaller, equal to, or larger than the projectile that caused it.[15,34-36] Palmar or solar wounds may appear as slits and are easily mistaken for stab wounds.[28,35,36]

Inappropriate terminology should not be used to describe wounds.[6,36,37] An example is the use of the obsolete term *powder burns*, rather than *soot*, to describe the carbonaceous material associated with close-range wounds.[28,29,35,36] Powder burns are literally the burns associated with flaming black powder used in muzzle loaders, antique weapons, and blank cartridges. This does not occur with the smokeless powder used in modern ammunition.

It is unnecessary to document in the medical record the manner of a gunshot victim's death. The determination of whether a death is accidental, suicidal, or homicidal is the responsibility of the coroner or medical examiner and only after a detailed investigation of the scene and circumstances of the incident. The patient's position at the time of injury can be determined only after an examination of the scene and collection of all forensic evidence.

A treating physician may be requested to render "factual" testimony, "expert" testimony, or both in a criminal case. Expert forensic testimony not based in science and rendered without an appropriate forensic examination or adequate forensic training may mislead the criminal justice system (e.g., "the exit wound is always larger than the entrance"). Opinions related to entrance versus exit or the range of fire can affect the determination of innocence or guilt.[15,20,21,23,24,35] The speculation about the wounds in the assassination of President Kennedy is one example of the legal implications of the forensic evaluation.[23,24,38]

Forensic Aspects of Handguns

The Weapon

There are four categories of handguns: (1) the single shot weapon (usually a target pistol); (2) the derringer (a small, concealable weapon, usually with two barrels); (3) the revolver (a weapon with a rotating cylinder that advances with the pull of the trigger); and (4) the autoloading or semiautomatic pistol (which fires with each pull of the trigger), which is the most popular because the magazine, or clip, can hold up to 17 cartridges compared to the 5 or 6 cartridges for revolvers.

An automatic submachine gun fires pistol ammunition as long as the trigger is held until its ammunition is exhausted. A submachine gun's magazine may hold up to 60 cartridges. Weapons such as the Israeli Uzi and the Heckler & Koch MP-5 use 9-mm or 40-caliber ammunition and are commonly used by police Special Weapons and Tactics (SWAT) teams. Semiautomatic versions of the submachine gun are available to the general public, and kits to make these weapons fully automatic, although illegal, are sold through gun magazines.

Handgun Ammunition

The cartridge, or round, is composed of the primer, the cartridge case, the powder, and the bullet (Fig. 62-1). The bullet is the projectile that is propelled out of the muzzle.

The primer is a small explosive charge in the base of the cartridge that ignites the gunpowder. The primer may contain lead, barium, or antimony, which may be deposited on the hands of the shooter, on the victim of a close-range assault, and on objects within a room in which the weapon is discharged.

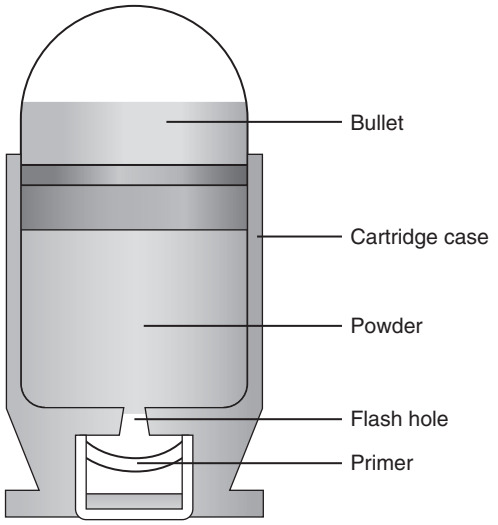


Figure 62-1. A cartridge consists of several distinct components: bullet, cartridge case, gunpowder, flash hole, and primer.

The cartridge case is typically made of brass, although other materials may be used. The function of the cartridge case is to slightly expand and seal the chamber against the escaping gases.[35] On detonation, a cartridge case is imprinted with unique microscopic marks that are valuable evidence and should be preserved for law enforcement.

The gunpowder found in all commercial cartridges except blanks is smokeless powder made with a single base (nitrocellulose) or a double base (nitrocellulose and nitroglycerine).[35] When a weapon is discharged, not all of the gunpowder is consumed. A percentage of the unburned gunpowder will travel out of the end of the muzzle for a distance, depending on the physical characteristics of the powder.

Blank cartridges, muzzleloaders, and other antiques or replicas may use black powder. Black powder (a combination of potassium nitrate, charcoal, and sulfur) does not burn as efficiently as the smokeless powder and results in a large flame and white smoke.

The bullet is forced from the muzzle of a handgun at velocities ranging from 700 to 1600 feet/second (in magnum loads). The term *magnum* indicates that additional gunpowder has been added to the cartridge case, increasing the velocity of the projectile. The most common bullet types include the round nose, the full metal jacket, the hollow point, the wadcutter, and the semi-wadcutter. Bullets generally have a solid core of lead or steel and have a jacket if the bullet core is covered with a metal, usually copper or aluminum. If the jacket covers the entire projectile, it is called a full metal jacket, and if the jacket leaves some portion of the core exposed, it is semijacketed.

The term *hollow point* denotes a hole in the tip of the bullet that causes expansion on contact with tissue, which increases tissue damage due to an increased surface area.

Bullet caliber is described in hundredths of an inch or in millimeters. Handgun bullets range from the .22 caliber or 5.56 mm to the .45 caliber or 11.3 mm. A bullet's weight is measured in grains, with 7000 grains/pound.

Handgun Wound Ballistics

Wound ballistics is the study of the effects of penetrating projectiles on the body.[33,39,40] Many misconceptions surround the science of wound ballistics.[33,40-44]

Wound severity is directly related to the amount of kinetic energy transferred to the tissue and direct tissue damage, not to the total amount of kinetic energy possessed by the

bullet.[33,35,39] Bullets fired from rifles generally have a higher velocity—1500 to 4000 feet/second versus 700 to 1600 feet/second in handguns. Therefore, rifled bullets have more kinetic energy and a theoretically higher wounding potential, but wound severity is the result of many variables, such as bullet velocity, weight, deformation, fragmentation on impact with tissue, and the characteristics and location of the impacted tissue.[32,37,39,40]

The principal mechanism for tissue damage is by crushing. A bullet traveling through tissue generates two cavities, one permanent and the other temporary. The temporary cavity, a result of tissue stretching, lasts 5 to 10 milliseconds from its generation until its collapse and leaves behind the permanently crushed tissue and the permanent cavity.[33,35,39] The size of the permanent cavity varies with the size, shape, and configuration of the bullet. A hollow-point bullet that mushrooms can increase its diameter 2.5 times on impact and will increase the area of tissue crush 6.25 times compared with a nondeformed bullet.[35]

The Forensic Evaluation of Handgun Wounds

Entrance Wounds

Range of fire is the distance from the muzzle to the victim and can be divided into four general categories: contact, near-contact or close range, intermediate or medium range, and indeterminate or distant range (Table 62-1). The size of the entrance wound does not correlate with the caliber of the bullet[15,34,35] because the entrance wounds over elastic tissue will contract around the tissue defect and have a diameter much less than the caliber of the bullet.[28,35]

Contact Wounds. In contact wounds, the barrel or muzzle is in actual contact with the skin or clothing. With tight contact, the muzzle is pushed hard against the skin, whereas with loose contact, the muzzle is incompletely or loosely held against the skin or clothing.

In a tight contact wound, all material—the bullet, gases, soot, the incompletely burned pieces of gunpowder, and metal fragments—is driven into the wound. These wounds can vary from a small hole with seared blackened edges from the discharge of hot gases and an actual flame to a gaping stellate wound (Fig. 62-2). Large wounds occur when the wound is

Table 62-1 Range of Fire

RANGE	INCHES (BARREL TO SKIN)	PHYSICAL PROPERTIES
Contact	0	Soot, seared skin, triangle-shaped tears
Close	0–6	Soot, abrasion collar (abrasion collar may be obscured by soot)
Intermediate	<48	Tattooing, abrasion collar
Distant or indeterminate	Any distance	Abrasion collar (intermediate objects will prevent soot and gunpowder from contacting the skin)

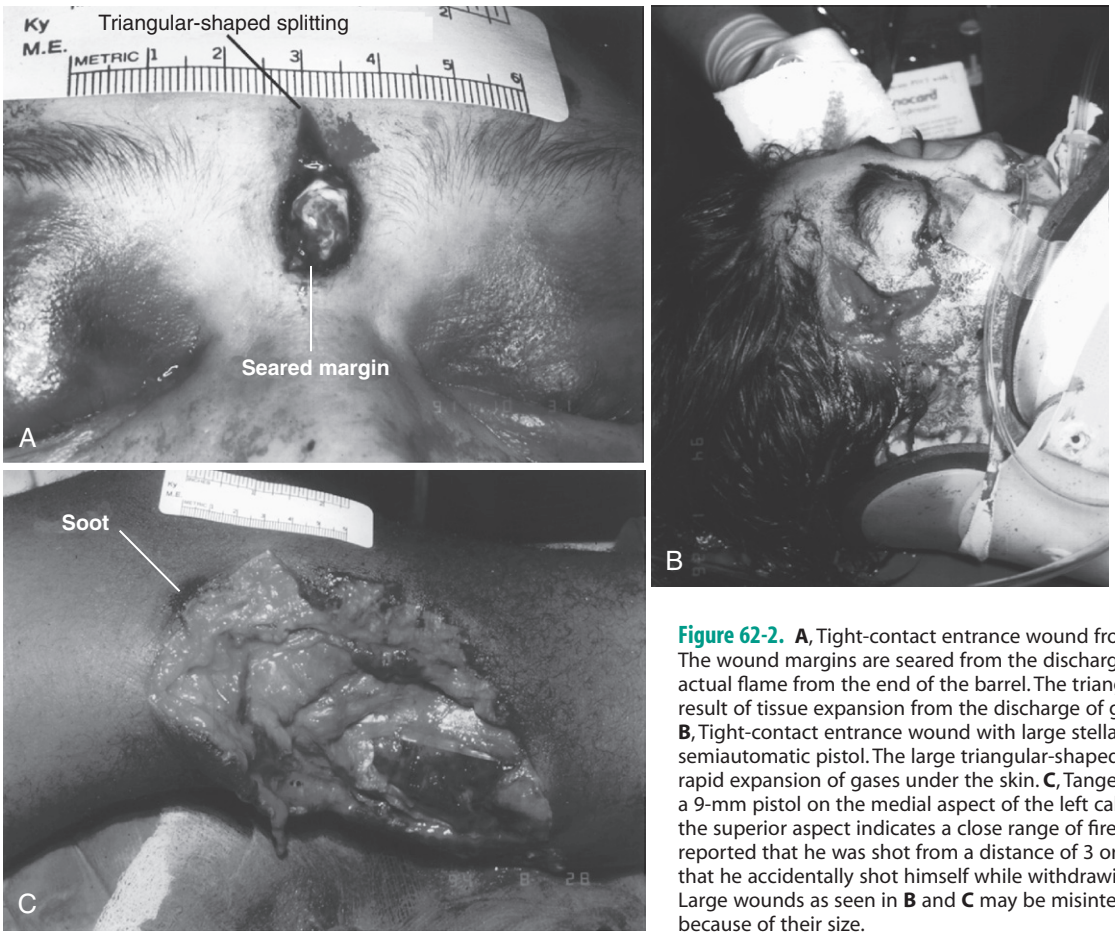


Figure 62-2. **A**, Tight-contact entrance wound from a .38-caliber revolver. The wound margins are seared from the discharge of hot gases and an actual flame from the end of the barrel. The triangular-shaped tear is the result of tissue expansion from the discharge of gases into the tissue. **B**, Tight-contact entrance wound with large stellate tears from a .380 semiautomatic pistol. The large triangular-shaped tears are the result of rapid expansion of gases under the skin. **C**, Tangential-contact wound from a 9-mm pistol on the medial aspect of the left calf. The presence of soot at the superior aspect indicates a close range of fire. The patient initially reported that he was shot from a distance of 3 or 4 feet and later admitted that he accidentally shot himself while withdrawing his pistol from his boot. Large wounds as seen in **B** and **C** may be misinterpreted as exit wounds because of their size.

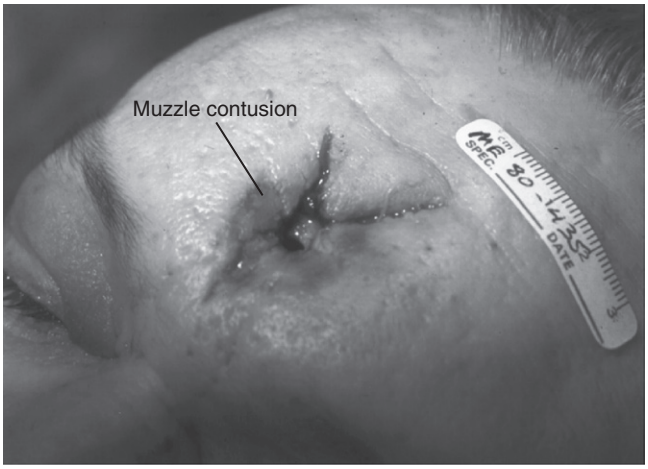


Figure 62-3. A "muzzle contusion" is a contusion caused by skin expansion against the barrel of the weapon. Muzzle contusions are associated with contact wounds.

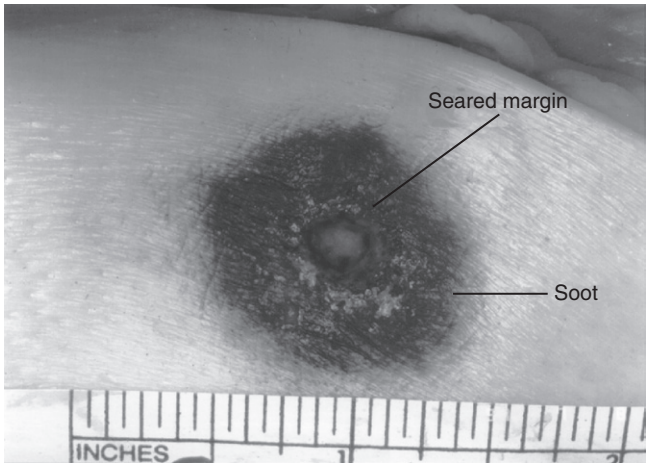


Figure 62-4. Close-range wound with soot deposition. Soot is associated with a range of fire of 6 inches or less.

inflicted over thin or bony tissue, and the injected hot gases cause the skin to expand until it stretches and tears. These tears will have a triangular shape, with the base of the triangle overlying the entrance wound. Tears are generally associated with .32 caliber or greater, or magnum loads. Large stellate contact wounds are easily misinterpreted as exit wounds if based solely on their size (see Fig. 62-2B and C).[15,28,35]

Stellate tears are not pathognomonic for contact wounds, however. Tangential wounds, ricochet or tumbling bullets, and some exit wounds may also be stellate, but these differ from a tight contact wound by the absence of soot and powder within the wound and a lack of seared wound margins.[15,28,35,36]

In some tight contact wounds, expanding skin is forced back against the muzzle of the gun, leaving a characteristic muzzle contusion (Fig. 62-3).[15,28,35,36] Patterns such as these should be documented before wound débridement or surgery because they are helpful in determining the type of weapon (revolver or semiautomatic).[15,20]

When a gun's muzzle or barrel is in loose contact or is angled to the skin, the soot and gunpowder residues are present both within and surrounding the wound. The angle between the muzzle and the skin determines the soot pattern. A tangential, loose, or near-contact wound produces an elongated searing and soot deposit surrounding the wound.

Close-Range Wounds. Close range is the maximum range at which soot is deposited on the wound or clothing, usually with a muzzle-to-target distance of less than 6 inches but as far away as 12 inches.[34-36] Beyond 6 inches, the soot usually falls away and does not reach the target. The concentration of the soot varies inversely with the muzzle-to-target distance and is influenced by the type of gunpowder and ammunition, the barrel length, and the caliber and type of weapon (Fig. 62-4).

A precise range of fire (e.g., 1 cm vs. 10 cm) cannot be determined from examining the wound. A forensic crime laboratory can attempt to reproduce the patient's soot pattern on a target by test-firing the offending weapon at different ranges using ammunition similar to that which caused the wound (Fig. 62-5). The accuracy of this test depends on an exact and detailed description of the patient's soot pattern. Because soot can be removed with débridement or wound cleansing, its presence and configuration around the wound should be noted and photographed unless the patient's clinical condition precludes this attention to detail.[15,20]

Intermediate-Range Wounds. "Tattooing," or "stippling," is pathognomonic for an intermediate-range gunshot wound. It appears as punctate abrasions and is caused by contact with partially burned and wholly unburned pieces of gunpowder (Fig. 62-6). Tattooing or stippling cannot be wiped away. Tattooing rarely occurs on the palms of hands or soles of feet because of the thickness of the epithelium.[35]

Tattooing may occur as close as 1 cm and as far away as 1 m from the weapon but is generally found at distances of 60 cm or less.[34-36,45] The density of the tattooing and the associated pattern depend on the length of the barrel, the muzzle-to-skin distance, the type of gunpowder, the presence of intermediate objects, and the caliber and type of ammunition. Clothing, hair, or other intermediate barriers may prevent tattooing from occurring. The presence of partially or entirely unburned pieces of gunpowder and gunpowder residues on clothing or skin aids in determining the range of fire. If gunpowder penetrates even thin clothing, it will generally lack the energy to penetrate the skin.

Distant-Range Wounds. The distant or long-range wound is inflicted from far enough away that only the bullet makes contact with the skin. There is no tattooing or soot. As the bullet penetrates the skin, the skin is indented, resulting in the creation of an "abrasion collar," also called an "abrasion margin," "abrasion rim," or "abrasion ring" (Fig. 62-7). This collar is an abraded area of tissue that surrounds an entry wound, the result of friction between the bullet and the epithelium. The width of the abrasion collar varies with the angle of impact. Most entrance wounds will have an abrasion collar. Entrance wounds on the palms and soles are exceptions because they usually appearing slitlike.[35]

The abrasion collar is not the result of thermal changes associated with a hot projectile. The edges of a contact or close-range wound may be seared by the release of hot gases and flame. This clinical finding may overlap or obscure the abrasion collar. When an abrasion collar is the only superficial clinical finding present, *indeterminate range* describes the range of fire. A wound from 10 feet will appear the same as a wound inflicted from 100 feet. An exact range cannot be determined with a distant wound.

Determining the range of fire may be complicated by clothing that prevents the deposition of soot and powder on the skin. When such a wound is examined without the overlying clothing or without information regarding the crime scene, the wound may appear to be from a distant range of fire. In reality, the range may have been close or intermediate. Conversely, a projectile discharged from a distant range of fire may mimic an intermediate range if it strikes an object, such as glass, which fragments. As with unburned gunpowder, when the

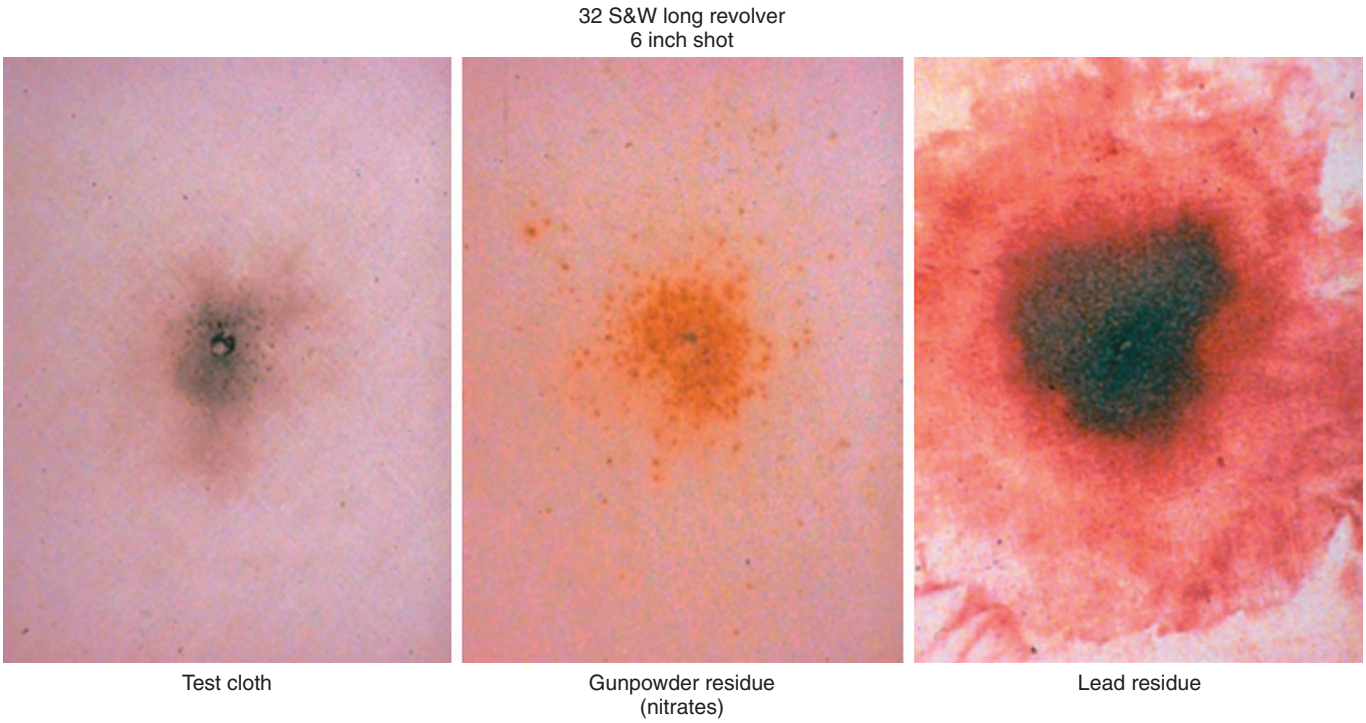


Figure 62-5. Gunshot residue testing conducted at 6 inches with a .32-caliber revolver. The testing searches for the presence of soot (burning of gunpowder), nitrates (unburned gunpowder), and vaporized lead residue. These tests determine the range of fire from the barrel to the clothing.

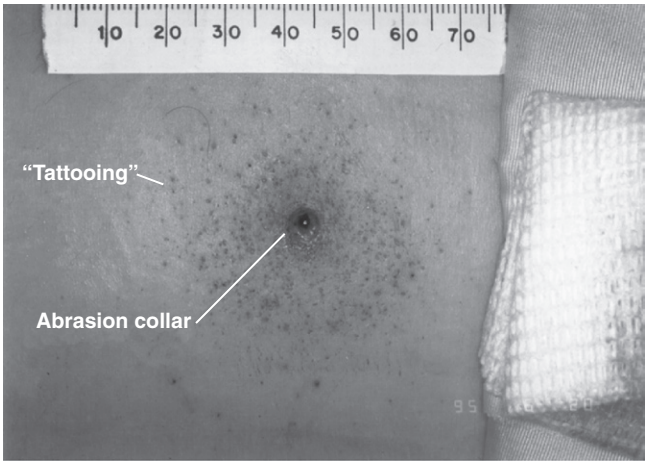


Figure 62-6. "Tattooing" results from contact with pieces of unburned gunpowder. These punctate abrasions are associated with an intermediate range of fire, generally less than 36 inches. The density of these abrasions depends on the length of the gun's barrel, the distance from the muzzle to the skin, the type of gunpowder used, and the presence of any intervening objects.

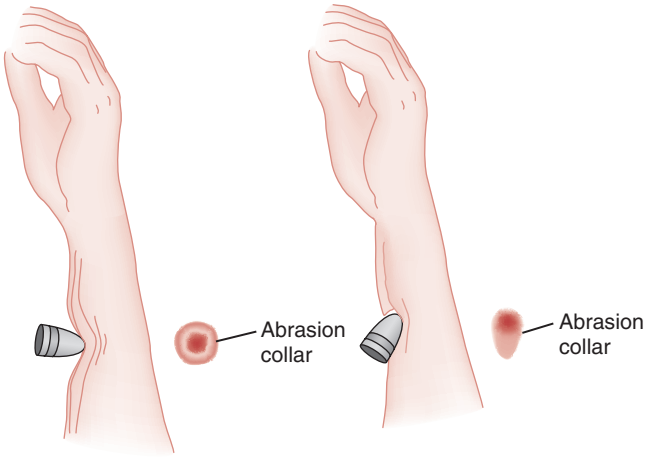


Figure 62-7. An "abrasion collar" is the abraded area surrounding the entrance wound created by the bullet when it indents and passes through the epithelium. The collar or rim is the result of friction between the bullet and the epithelium. The width of the abrasion collar will vary with the angle of impact.

glass fragments strike the skin, they may also cause punctate abrasions, resulting in pseudotattooing (Fig. 62-8).[35,46]

Atypical Entrance Wounds. Atypical entrance wounds are indicative of a bullet having encountered an intermediate object, such as a window, wall, or door, before striking the victim. The intermediate object may change the bullet's size, shape, or path. Such changes can result in entrance wounds with large stellate configurations that mimic close-range or contact wounds.[47,48] Ricochet bullets may also present with atypical entrance wounds.

Graze wounds are atypical wounds from tangential contact with a passing bullet. Directionality of the bullet may be determined from a close examination of the wound.[35,49,50] The bullet produces a trough with formation of skin tags on the lateral wound margins. The bases of these skin tags, when present, point toward the weapon and away from the direction of bullet travel.[49]

Exit Wounds

Exit wounds are the result of a bullet pushing and stretching the skin from inside out. The skin edges generally are everted with sharp but irregular margins. Abrasion collars, soot, and tattooing are never seen.

Figure 62-8. **A** and **B**, "Pseudotattooing" or punctate abrasions from glass fragments, not unburned gunpowder, on the medial aspect of the thigh associated with a gunshot wound. The leg was showered with glass fragments after the round penetrated the windowpane.

The size of the exit wound is determined by the energy possessed by the bullet as it exits the skin and by the bullet's size and configuration (Fig. 62-9).[15,35,36] On entering the skin, a bullet's configuration may change from its usual nose-first attitude to tumbling and yawing. A bullet with sufficient energy to exit the skin sideways, or one that has increased its surface area by mushrooming or transferred its energy to underlying bone, will have an exit wound larger than its entrance wound.[15,28,35]

Atypical Exit Wounds. A "shored-exit" wound is a wound that has an associated false abrasion collar. If the skin is pressed against or supported by a firm object or surface at the moment the bullet exits, the skin can be compressed between the exiting bullet and the supporting surface (Fig. 62-10).[15,35,36,51] Examples of supporting structures include belts, floors, walls, doors, chairs, and mattresses.

Rarely, soot may also be present at an atypical exit wound site.[52] If a contact entrance wound is located close to its associated exit wound, soot can be propelled through the short wound track and appear faintly on the exit wound surface.

Forensic Evaluation of Centerfire Rifle Wounds. Projectiles discharged from centerfire rifles have the potential to inflict massive tissue damage (Fig. 62-11). A bullet's wounding potential is based on the kinetic energy it possesses. The calibers of centerfire bullets, .223 to .308, are similar in diameter to handgun ammunition, but their wounding potential is greatly enhanced by the velocity of the round,[35] based on the formula kinetic energy = mass × velocity^2/G. Injuries result from the transference of energy from the projectile to organs and bony structures. With high-velocity rounds (velocities >2000 feet/second), a temporary cavity is formed along the wound tract and may be 11 or 12 times the diameter of the bullet and can result in tissue damage away from the physical tract taken by the projectile.[39] Due to the amount of energy possessed and transferred to underlying tissue, exit wounds associated with centerfire rifles, in contrast to those associated with handguns, are generally larger than their corresponding entrance wounds (Fig. 62-12).[35,36]

Entrance wounds associated with high-velocity, centerfire projectiles do not significantly differ from those of handguns. Entrance wounds will generally exhibit abrasion collars or microtears on the skin surface (Fig. 62-13). Wounds will also have associated soot deposition and tattooing, but because of a number of variables, such as muzzle length, amount of power in a given cartridge, muzzle configuration, and type of gunpowder, the range of fire in rifle wounds is not as clearly defined as in handgun wounds. The determination of an exact range of fire for rifles and shotguns is best established through controlled testing performed by a firearms examiner at a crime laboratory.

High-velocity lead core and jacketed bullets generally break up into hundreds of fragments, called a "lead snowstorm," upon entering tissues, creating significant tissue damage (Fig. 62-14).[35] If the tissue is deep, the bullet fragments may fail to exit and be embedded. Thus, it is possible to sustain an injury with a high-velocity round and not exhibit an exit wound. High-velocity rounds with steel cores will almost uniformly exit intact.

Microscopic Examination of Wounds

The débrided epithelial margins of wounds should be submitted to the pathology department for a histologic examination to help determine wound entrance, exit, and range of fire.[52-55]

Evidence

A victim's clothing may yield information about a bullet's range of fire and help distinguish entrance from exit wounds.[5,13,15,17,37-39,56] Clothing fibers will deform in the direction of the passing projectile.[35] Gunpowder residues and soot will deposit on clothing as they do on skin. Residue may be invisible to the naked eye but can be visualized using standard forensic staining techniques for nitrates and vaporized lead. Some bullets, as they make initial contact with clothing, leave a lead or lubricant residue that is termed *bullet wipe*. Articles of clothing removed from a wounded patient need to be placed in separate paper bags to avoid cross-contamination of evidence.[13]

A gunshot residue (GSR) test may determine whether a victim or suspect has fired a weapon.[36,56-65] The GSR test checks for the presence of invisible residues from the primer: barium nitrate, antimony sulfide, and lead peroxide. The presence of residue can be checked by (1) swabbing the palms and the dorsum of the hands with a 5% nitric acid solution and then analyzing using atomic absorption spectrophotometry or (2) placing tape or an adhesive disk on the hands and then removing it for examination under a scanning electron microscope.

The specificity and sensitivity of the GSR test are unclear.[36,51,64,65] Residue will deposit on the hands of the individual who fired the weapon in only 50% of cases.[36] Residue

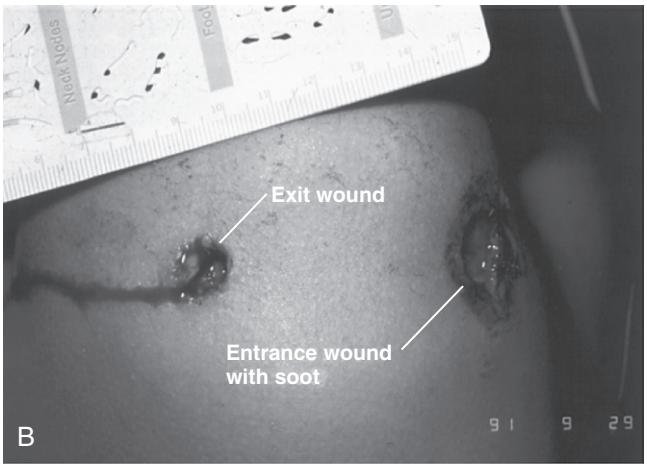


Figure 62-9. **A**, Slitlike exit wound from a .22-caliber bullet. **B**, Perforating gunshot wound to the left deltoid area with soot deposition around the larger entrance wound. No soot is present around the smaller exit wound. Exit wounds are *not* consistently larger than their corresponding entrance wounds.

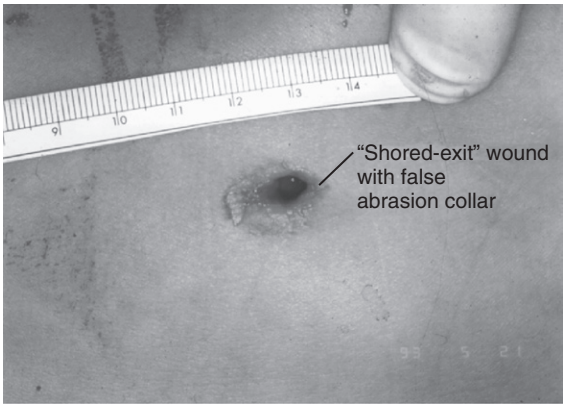


Figure 62-10. "Shored-exit" wound with a false abrasion collar. This type of wound occurs when the skin in the region of the exiting bullet is in contact with a supporting structure (e.g., a wall, floor, or mattress). The skin is slapped against the supporting structure, which results in a false abrasion collar.

Figure 62-11. This patient sustained a high-velocity gunshot wound to the forehead. High-velocity rifle rounds, due to their kinetic energy, can cause massive damage when the energy is transferred to underlying tissue.

may spread throughout a crime scene, and secondary contact with the weapon or furniture on which residue was deposited will result in a false-positive test. The transferring of residue from police officers to suspects has also been reported.[65] The sensitivity of the test decreases with time, and law enforcement agents may not have access to a patient during the "golden hour."[35] Factors that decrease sensitivity include washing the skin with alcohol or betadine, placing tape on the skin, rubbing the hands against clothing, and placing plastic bags over the patient's hands, which precipitates moisture on the skin. If a GSR test is to be performed or if soot is noted on the patient's hand, paper bags should be placed over the hands early in the treatment.

The bullet, the bullet jacket, and the cartridge case are invaluable when identifying or excluding a weapon.[15,34,35] When a weapon is discharged, it imprints multiple unique microscopic marks on the side of a bullet and on the bottom or side of the cartridge case.[15,34,35] The bullet's markings result

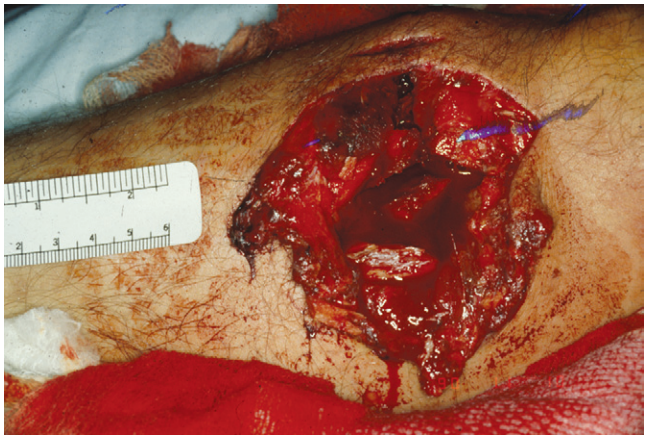


Figure 62-12. An exit wound from a high-velocity rifle round. Exit wounds from high-velocity rounds are generally larger than their corresponding entrance wounds. The large size is due to energy transfer from the projectile to underlying tissue with the expelling of tissue, principally bone.

Figure 62-13. An entrance wound from a high-velocity rifle round. Entrance wounds of high-velocity projectiles will also display an abrasion collar.

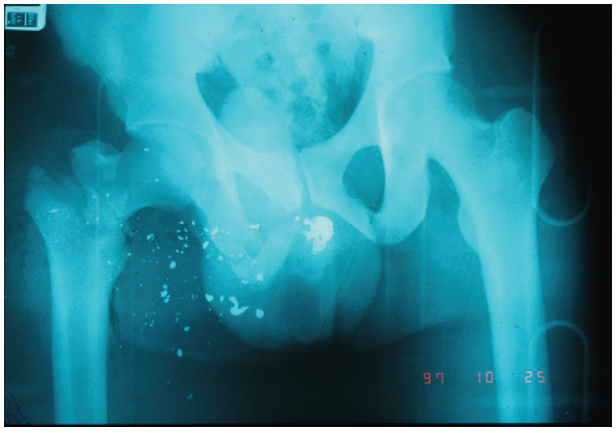


Figure 62-14. A "lead snowstorm" from a high-velocity rifle round. High-velocity projectiles have a tendency to fragment into hundreds of tiny particles upon contact with bone. This fragmentation contributes to the massive tissue damage associated with these projectiles.

Figure 62-15. Hemostats should be covered with gauze when removing bullets. Metal-to-metal contact destroys the microscopic marks, which are used to identify the weapon from which the bullet was discharged.

from its contact with the tool marks or "rifling" in the gun's barrel. The marks on the cartridge case are from contact with the firing pin, the breechlock, the magazine of semiautomatic weapons, and extractor and ejector mechanisms. These microscopic fingerprints and markings can be obliterated by removing a bullet with hemostats or pickups.[13,15,35] Bullets should be handled with gloves and surgical instruments covered with gauze (Fig. 62-15) to ensure the preservation of these microscopic "fingerprint" marks. It is not necessary to place initials or other markings on the bullet if adequate notes are made in the patient's medical record regarding the chain of custody.[13]

Radiographs also help locate retained projectiles and may be of evidentiary value when determining the number of projectiles and the direction of fire.[33-35,45,66]

FORENSIC ASPECTS OF PHYSICAL ASSAULT

Identifying Assault Victims

Studies estimate that 22 to 33% of patients in an urban emergency department are victims of domestic violence, yet very few are recognized as such.[18,67-81] In a study of victims of domestic violence, 43% of patients with acute trauma presented to the emergency department 6 or more times before they were identified as victims of abuse; nearly half of these patients presented at least 12 times.[78] Also, those admitted to the trauma service also go unrecognized.[79]

Every weapon leaves a mark, design, or pattern stamped or imprinted on or just below the epithelium. The epithelial imprints of these weapons, called *pattern injuries*, are consistently reproducible.[15,82] These injuries are classified into three major categories according to their source: blunt force, sharp force, and thermal.

BOX 62-1 COMMONLY INFLICTED PATTERN INJURIES

Slap marks with digits delineated
Looped or flat contusions from belts or cords
Circular contusions from fingertip pressure
Parallel contusions with central clearing from linear objects
Contusions from shoe heels and soles
Semicircular contusions and abrasions from bite marks

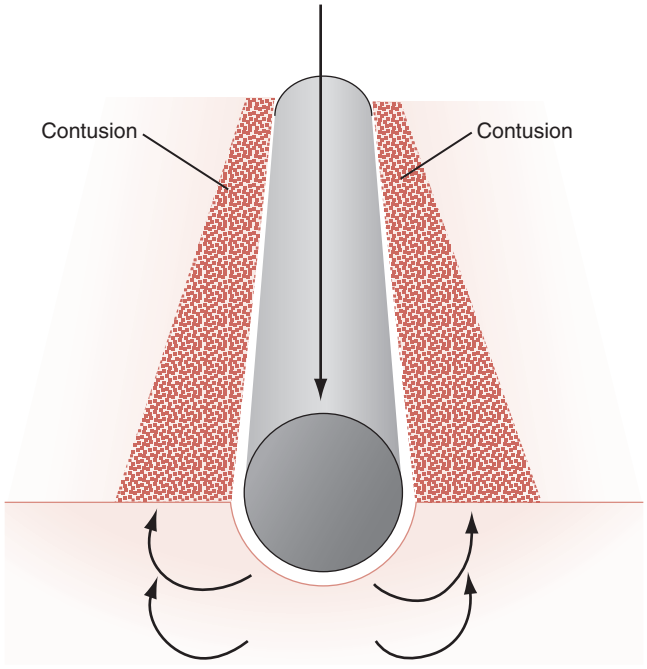


Figure 62-16. A direct blow from a linear object results in a pattern contusion with central clearing surrounded by parallel linear contusions. The blood directly beneath the impacting object is displaced laterally and accounts for the distinctive contusion.

Accurate documentation of the anatomic location of the injuries makes it easier to determine the implement, tool, or weapon responsible for producing each wound.

Blunt Force Pattern Injuries

The most common blunt force injury is the contusion, along with abrasions and lacerations. A weapon with a unique shape or configuration may stamp a mirror image of itself on the skin (Box 62-1).[15,82]

Pattern Contusions. A blow from a linear object leaves a contusion that is characterized by a set of parallel lines separated by an area of central clearing (Fig. 62-16).[15,82] The blood underlying the striking object is forcibly displaced to the sides, which accounts for the pattern's appearance (Fig. 62-17).

Circular or linear contusions should suggest abuse or battery. Circular contusions 1.0 to 1.5 cm in diameter are consistent with fingertip pressure and grab marks (Fig. 62-18). One commonly overlooked anatomic location for fingertip pressure contusions is the medial aspect of the upper arm.[82] The sole of a shoe from a kick or stomp may also leave a pattern contusion that can assist in identifying the assailant (Fig. 62-19).

Some injuries allegedly occur while in police custody. Specific pattern contusions can include parallel contusions from a flashlight or night stick. Handcuff or shackle marks present as narrow parallel contusions or abrasions on the wrists or ankles.

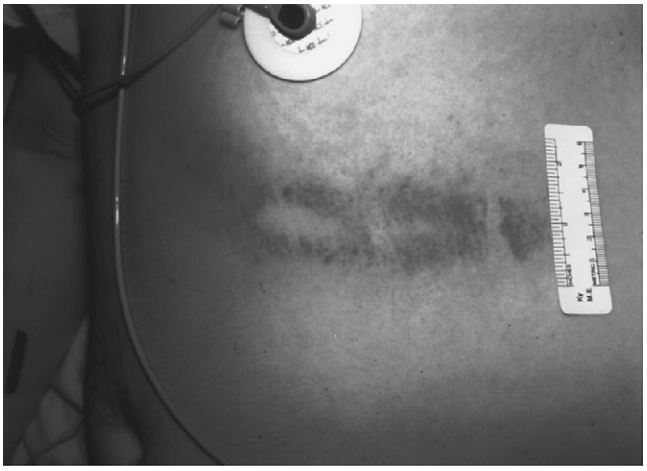


Figure 62-17. Pattern contusion with parallel lines and central clearing from contact with a baseball bat.

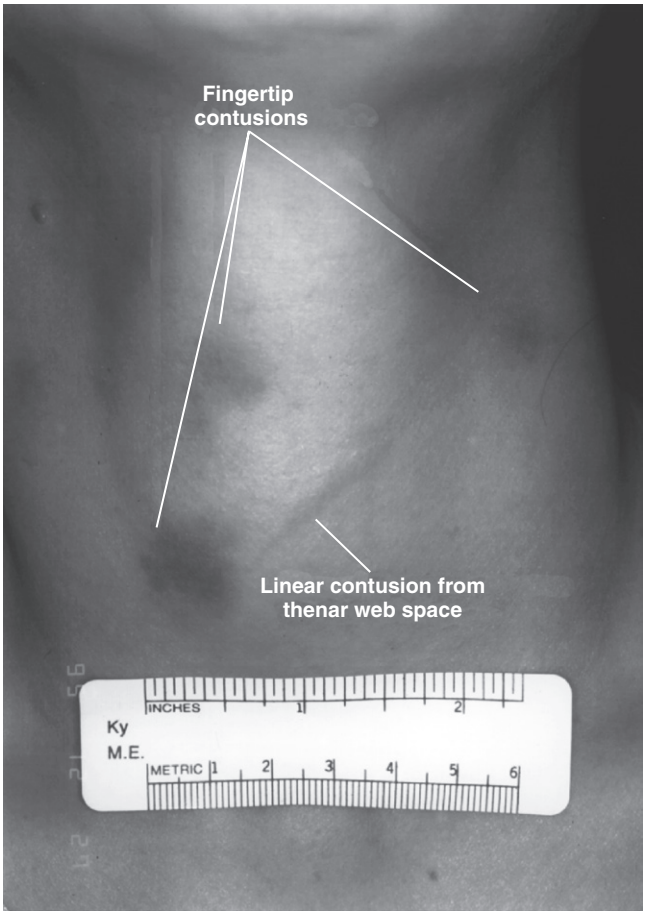


Figure 62-18. Three somewhat circular contusions and a linear contusion on the anterior aspect of the neck. These injuries resulted from hand and fingertip pressure applied during an attempted strangulation.

Handcuff and shackle marks are generally more prominent on the lateral aspects of the extremity.[36]

The history should be recorded and injuries documented with diagrams and photographs, when possible. The incident is best reviewed by an internal affairs unit of the investigating law enforcement agency and not by the emergency physician. Conclusions regarding the alleged perpetrator and mechanism should generally be avoided.

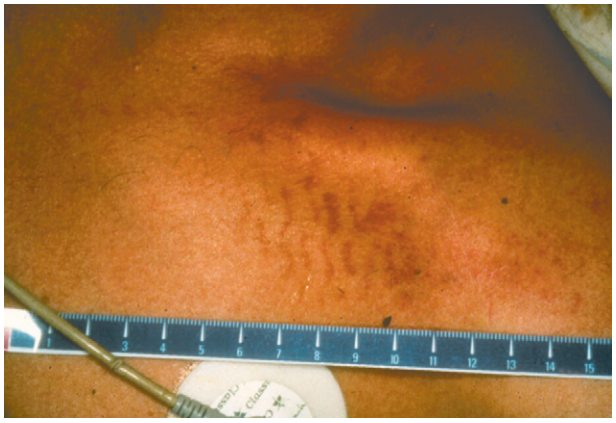


Figure 62-19. A pattern contusion on the patient's upper chest from the sole of a tennis shoe after a kick. This type of pattern injury can assist in the identification of a suspect and provide a physical connection between the victim and the attacker.

Figure 62-21. A laceration is the result of blunt trauma and characteristically displays tissue bridges and crushed wound margins.

Figure 62-20. Bite mark with two semicircular arched contusions over the anterior lateral aspect of the patient's neck. A bite mark can be used to identify the assailant if the injury is correctly documented by a forensic photographer or forensic odontologist. A circular contusion on the right lateral aspect of the neck was the result of fingertip pressure.

A bite mark may appear as a pattern contusion, an abrasion, or a combination of both (Fig. 62-20). Bite marks vary greatly in the quality of their identifiable features, depending on the location of the bite and the motion of the teeth relative to the skin. Some bite marks may not be readily identifiable as a bite and appear as a nonspecific contusion, abrasion, or contused abrasion.

When an acute bite mark is identified, care should be taken not to wash away potential evidence. The skin surface should be swabbed with a sterile cotton-tipped applicator moistened with sterile saline. This may detect the presence of the assailant's saliva. Such evidence is short-lived because of rapid degradation of blood group antigens and should be collected and sent to the crime laboratory as quickly as possible. Eighty percent of the population secretes an ABO blood group protein antigen in saliva. DNA from buccal cells may also be deposited over an acute bite mark.[13,15]

When available, a forensic odontologist can evaluate a bite wound with accuracy. The use of alternative light sources, such as ultraviolet or infrared, may reveal a pattern contusion within or under the epithelium that is not visible to the naked eye.[36] These light sources are routinely used by the forensic odontologist on faint, old, or difficult bite marks. Assailants have been identified from bite marks up to 6 months after injury.

The emergency physician may be asked to render an opinion regarding the age of a contusion. The development of a contusion is based on a number of variables: the amount of blunt force applied to the skin, the vascularity of the tissue, the fragility of the blood vessels, the density of the tissue, and the amount of blood that escapes into the surrounding tissue.[83-85] As a result, no reproducible standard for the dating of a contusion is possible based on its color.[83-85] New techniques based on reflectance spectrophotometry are currently being tested.[86] A tissue biopsy examining the hemosiderin breakdown may be the only scientifically accepted method to determine the approximate age of a contusion.[87]

Pattern Abrasions and Lacerations. A *pattern abrasion* is a rubbing or scraping away of the superficial layers of the epidermis (see Fig. 62-18), which is not important for treatment but may be invaluable from a forensic and injury reconstruction perspective.[82]

A *laceration* is defined as a tear produced by blunt trauma and should not be confused with an incised wound produced when a sharp-edged implement (knife or scalpel) is drawn across the skin.[15] A laceration has characteristically abraded or crushed skin edges and unique "tissue bridges" (Fig. 62-21).

Sharp Force Pattern Injuries

An *incised wound* is longer than it is deep, and the *stab wound* is defined as a puncture wound that is deeper than it is wide. The wound margins of sharp force injuries are clean and lack the abraded edges and tissue bridges of injuries resulting from blunt forces.

Forensic information can be gathered during the examination of a stab wound. Some of the characteristics of a knife blade, single edged or double edged, can be determined from visual inspection (Fig. 62-22A and B).[15,82] Additional blade characteristics, such as serrated versus sharp, can be seen if the blade was drawn across the skin during its insertion or withdrawal (see Fig. 62-22C). Serrated blades do not always leave these characteristic marks.[15,82]

Thermal Pattern Injuries

A thermal pattern injury is a common form of abuse or battery. The history should include the position of the patient relative

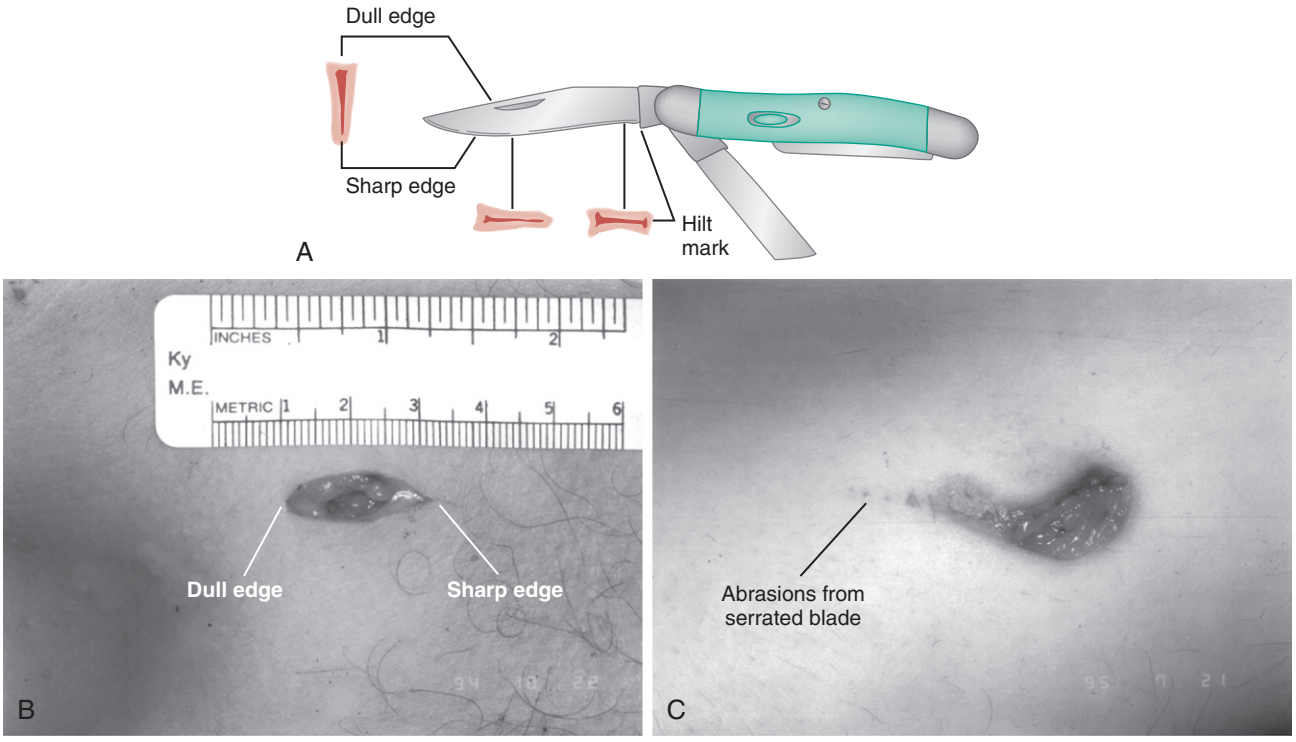


Figure 62-22. **A**, A single-edged knife blade will cause a wound to be formed with a sharp edge and a dull edge. If the blade penetrates to its hilt, a "hilt mark" may be seen overlying the sharp edge. **B**, Single-edged stab wound. **C**, Single-edged stab wound made by a serrated blade. Abrasions from the blade's serrated edges are seen on the left margin of the wound.

to the thermal source. This information will help determine whether the injury was intentional or accidental.[82]

Immersion or dipping burns are characterized by a sharp or clear line of demarcation between burned and unburned tissue. In contrast, splash burns are characterized by an irregular or undulating line or by isolated areas of thermal injury, usually round or oval in shape, caused by droplets of hot liquid.

The severity of thermal or scald injury depends on the contact length of time and the temperature. Water causes full-thickness damage in 1 second at 158° F (70° C) and in 600 seconds at 120° F (48.9° C) (Fig. 62-23).[88] Law enforcement routinely measures the household's or institution's water temperature in any investigation involving a scald injury.

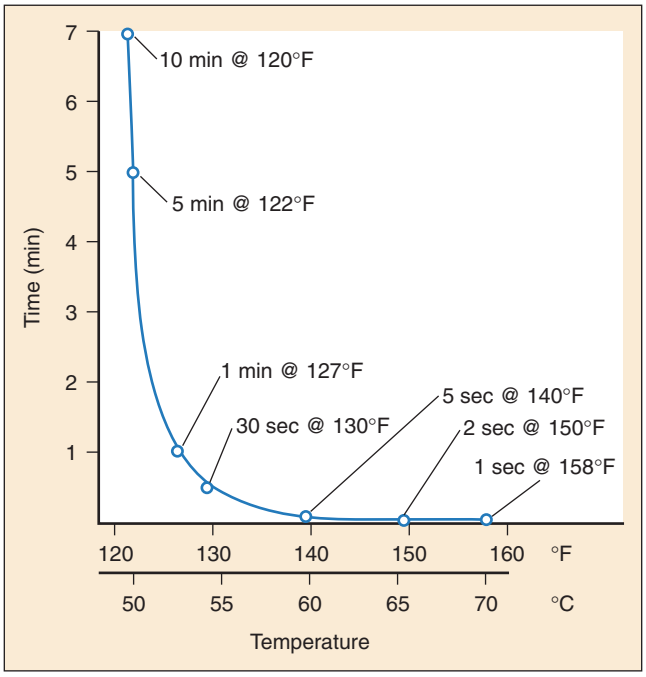


Figure 62-23. Relationship between water temperature and the duration of contact required to produce a full-thickness thermal injury. (From Katcher ML: Scald burns from hot tap water. JAMA 246:1219, 1981.)

FORENSIC ASPECTS OF MOTOR VEHICLE TRAUMA

Law enforcement officials investigating an incident involving serious or fatal injuries from a motor vehicle or pedestrian collision may benefit from information regarding injury patterns and the collection of trace evidence from the victim. This information can help determine whether an occupant was a driver or passenger. It may help to identify a suspect vehicle involved in a hit-and-run pedestrian collision or a pedestrian's position (standing or lying) when struck in the roadway.

Determination of a vehicle occupant's role may be simple, if the driver is pinned behind the steering wheel, or complex, if the vehicle's occupants are ejected. Many impaired drivers claim to be passengers. Short-lived evidence or pattern injuries that might be destroyed or altered in the delivery of patient care should optimally be preserved.[89,90]

An opinion on an occupant's position should be avoided because the position is difficult to determine based solely on the statements and physical findings in the emergency department.[89,90] Such an opinion is better based on an examination of the scene, the vehicle, other occupants, and information regarding trace evidence only after forensic examinations, including postmortem examinations, have been performed on all of the vehicle's occupants and all forensic evidence has been evaluated (Box 62-2).[35,89-91]

BOX 62-2 EVIDENCE COLLECTION—DRIVER VERSUS PASSENGER

Victim

Examine for Pattern Injuries
Steering wheel contusion
Radio knob contusion
Window crank contusion
Striated incised facial wounds
"Dicing" wounds

Examine Clothing for Transferred Material[*†]
Glass (front and side windows)
Fibers
Pedal imprint on shoe
Dashboard components

Collect Biologic Standards[†]
Hair
Blood

Collect Clothing Standards[†]
Damage

Vehicle

Examine for Pattern Damage
Steering wheel
Radio/knobs/dashboard
Window crank/side door
Windshield (laminated glass)
Side/rear window (tempered glass)

Collect Standards
Glass
Carpets and seats
Gas and brake pedals
Broken dashboard components

Examine for Transferred Material of Pedestrian
Hair on windshield/components
Blood on windshield/components

Examine for Transferred Material on Car Occupants
Fabric fibers
Imprinted fabric pattern

*Each article of clothing should be collected in a separate paper bag. This avoids cross-contamination, and wet material will dry. Do not collect evidence in plastic bags because moisture will condense within the bag and may degrade biologic material.

†Each article should be marked with the patient's name, item collected, date and time collected, location of collection, name of the collector, and name of law enforcement official to whom the evidence was given. This information will preserve the "chain of custody."

Pattern Injuries

Matching pattern injuries with components within a vehicle often reveals an occupant's position during a portion of the vehicle's collision sequence.[89-91] Common pattern contusions, abrasions, and lacerations are seen from steering wheels, air bags, air bag module covers, window cranks, radio knobs, door latches, dashboard components, and front and side window glass.[89-93] An occupant's movement and subsequent contact with a vehicle's components are dictated by the forces applied to the vehicle through its interaction with the environment. Vehicle occupants, restrained or unrestrained, will initially move toward the primary area of impact.[89,90] This movement within the vehicle, called occupant kinematics, is described as a motion parallel to and opposite from the direction of the force developed by the impacting object[89,90] and can predict the direction a particular occupant will move and therefore what component will be struck.

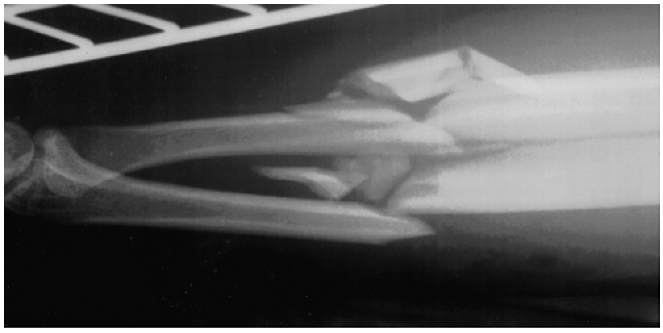


Figure 62-24. Comminuted, bending-type fracture of the radius and ulna from impact with a deploying air bag module cover.

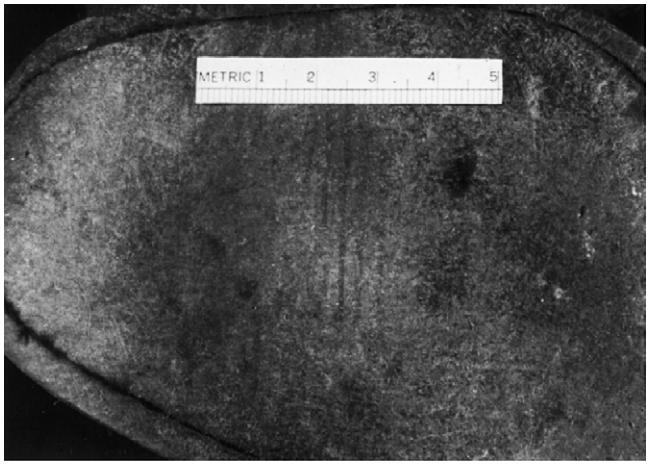


Figure 62-25. Imprint of a brake pedal on a leather-soled shoe. This information will assist in determining the occupant's role and whether the patient's foot was on the brake or accelerator pedal at the moment of impact.

A deploying air bag may induce a pattern abrasion to the face, cornea, forearms, or other exposed tissue. Pattern lacerations, specific fracture patterns, and amputations are seen when the deploying air bag module cover impacts the hand or forearm (Fig. 62-24).[92,93] The correlation of these injuries to the driver or passenger air bag system is helpful in assessing an occupant's role.[92,93]

Laminated (windshields) and tempered (side and rear windows) glass produce pattern injuries. The windshield is composed of two layers of glass laminated together with a thin layer of clear plastic sandwiched between. Laminated glass breaks into shards on impact and causes linear incised wounds. Tempered or "safety" glass is a single layer of glass that breaks into small cubes when fractured, imparting a "dicing" pattern to the skin.[36]

Trace Evidence

Clothing, shoes, and biologic standards (hair and blood) may determine an occupant's role.[89-93] The soles of leather shoes may reveal the imprint of the gas or brake pedal (Fig. 62-25). Preservation of clothing permits comparison of clothing fibers with those fibers transferred to vehicle components during the collision.[89-94] Imprints of fabric may also be transferred to components within the vehicle, including the steering wheel. Contact with the windshield often transfers hair and tissue to the glass. Glass collected from within a patient's wound can

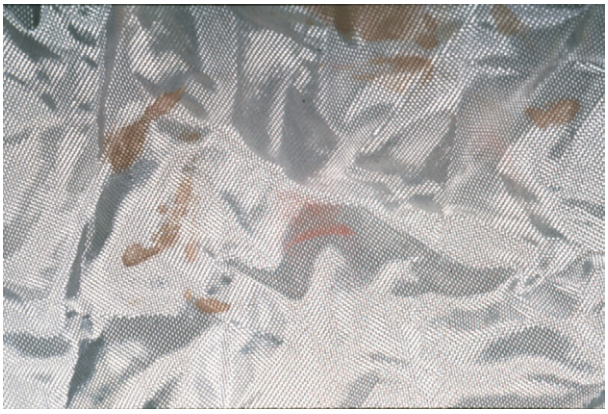


Figure 62-26. Occupant contact with the air bag often results in the transfer of trace evidence. The presence of blood, tissue, hair, and makeup will assist in the determination of the seating arrangement of a particular occupant.

be matched with a particular window within the vehicle. Airbags are also a tremendous source of trace evidence including skin, blood, makeup, and hair (Fig. 62-26).[93]

Evaluation of Pedestrian Collisions

Pattern Injuries

Approximately 66,000 people are killed or seriously injured annually in pedestrian collisions[95]; 87% are struck by a vehicle's front bumper/grill area.[95] When struck by the front of a vehicle, a standing adult will sustain "bumper injuries," which include open and closed fractures of the tibia and fibula, soft tissue damage, and pattern injuries from vehicle components and hardware.[36]

The height of bumper injuries, measured from the heel and including the height of the patient's shoe, can be correlated with the height of the vehicle's bumper to determine whether the vehicle was braking at the moment of impact. Application of the brake results in the dipping of a vehicle's front end. The presence or absence of braking may help determine the driver's intent. The presence of bumper injuries at one height on one leg and at another height on the other may indicate that the pedestrian was walking or running at the moment of impact, with one leg elevated. Examination of the soles may show lateral striations when a patient has been dragged.

A victim who is struck from behind may have pattern contusions on the calf or thigh (Fig. 62-27), whereas pattern contusions from a grill on the anterior aspect of the thigh indicate the pedestrian was standing and facing the vehicle. Pedestrians stuck by a glancing portion of a vehicle may also display a pattern injury (Fig. 62-28). Victims who are run over may display a tire tread pattern. Tire marks and the absence of bumper injuries may indicate that the patient was supine or prone in the roadway (Box 62-3).

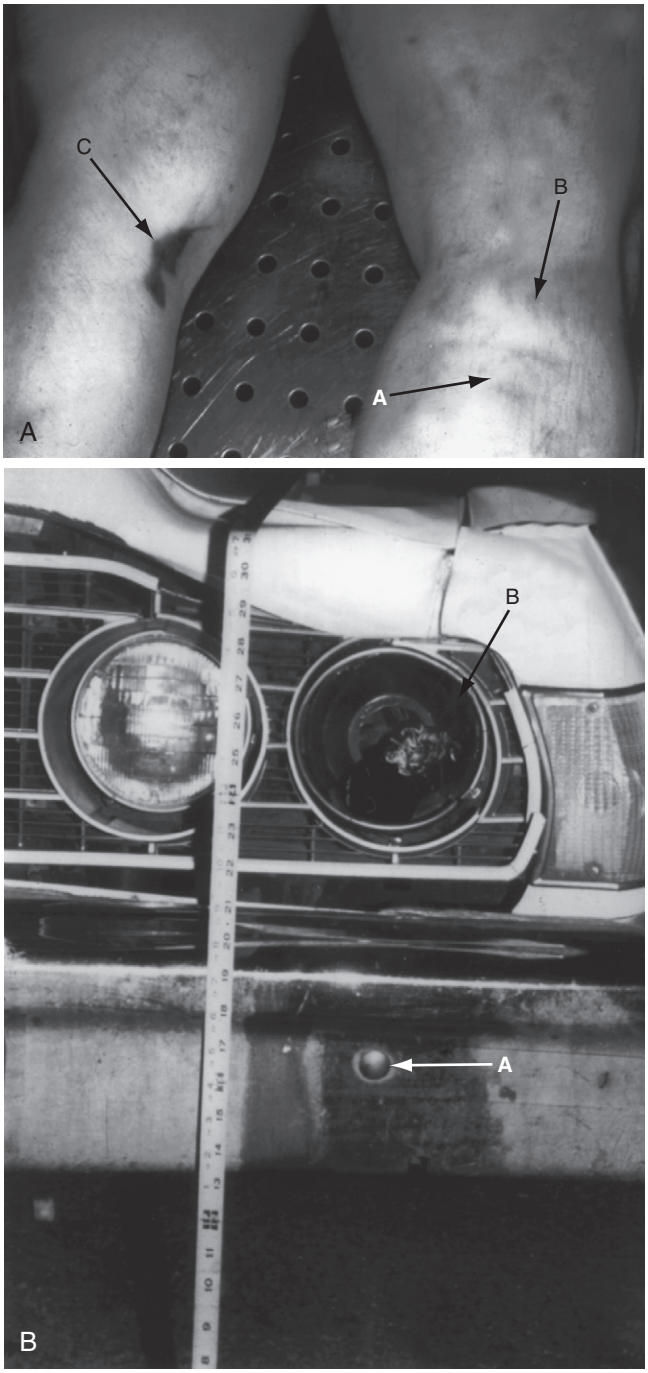


Figure 62-27. **A**, A circular pattern contusion on the posterior aspect of a pedestrian's left calf was the result of contact with the head of a bolt. The location of the contusion provides information about the configuration of the patient at the moment that the car struck him. The patient was struck from the rear. **B**, A puncture wound on the posterior aspect of the left thigh resulted from contact with the headlight filament.

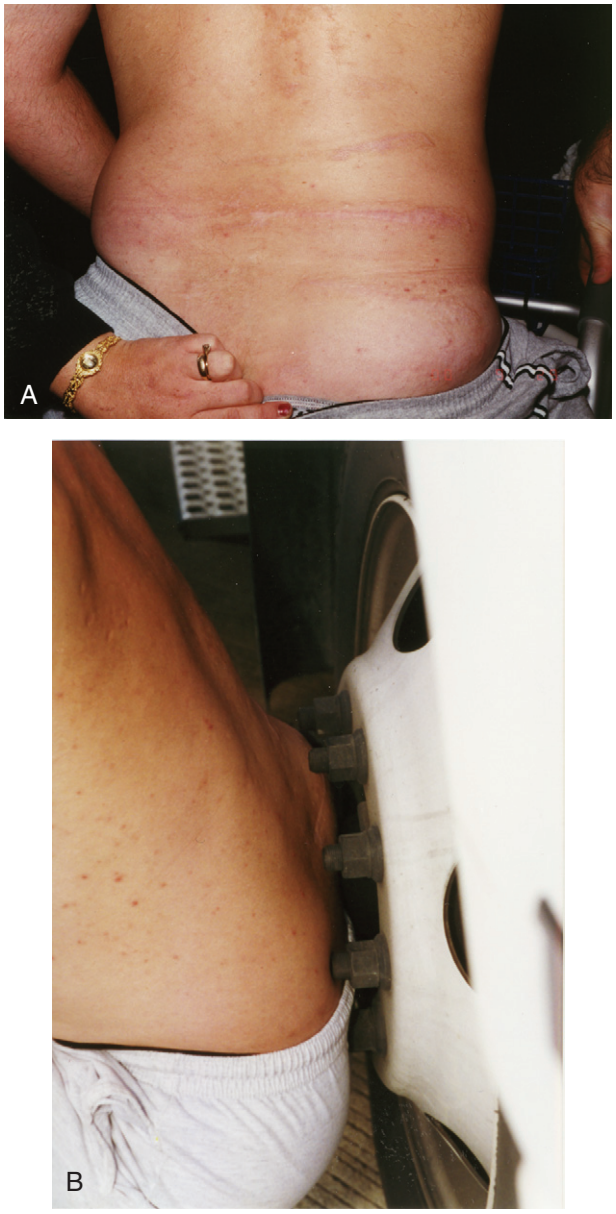


Figure 62-28. **A,** Three horizontally oriented wounds were noted on the back of a pedestrian struck by a semi-tractor trailer on a highway while changing a flat tire. **B,** The pattern injury was matched to the lug nuts of the front right wheel.

BOX 62-3 EVIDENCE COLLECTION—PEDESTRIAN COLLISIONS

Victim

Examine for Pattern Injuries

Height of bumper injuries
- Contusion
- Fracture
- Head/neck injuries
- Crush injuries

*Examine Clothing for Transferred Material**†*

Paint
Glass (windshield, headlight)
Oil or grease

Collect Biologic Standards†

Hair
Blood or tissue

Collect Clothing Standards†

Damage or tears

Vehicle

Examine for Pattern Damage

Bumper height and damage
Specific components
Windshield damage
Wheels and undercarriage

Collect Standards

Paint
Glass
Oil or grease

Examine for Transferred Material of Pedestrian

Hair
Blood or tissue

Examine for Transferred Material on Vehicle

Fabric fibers
Imprinted fabric pattern

*Each article of clothing should be collected in a separate paper bag. This avoids cross-contamination, and wet material will dry. Do not collect evidence in plastic bags because moisture will condense within the bag and may degrade biologic material.

†Each article should be marked with the patient's name, item collected, date and time collected, location of collection, name of the collector, and name of law enforcement official to whom the evidence was given. This information will preserve the "chain of custody."

KEY CONCEPTS

- Knowledge of wound mechanics and production, as well as wound appearance, can provide practicing emergency physicians with important clues to the forensic interpretations of injuries.
- Wounds and injuries should be diagrammed and photographed.
- The medical record should accurately document objective findings but should not speculate on the cause or mechanism.
- Any evidence collected in the course of treatment must be documented in the medical record, including to whom the evidence was given, in order for the chain of custody to be preserved.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 63 Child Maltreatment

Carol D. Berkowitz and Sara T. Stewart

PERSPECTIVE

Background

Child maltreatment is an all-encompassing term that includes all forms of child abuse: physical abuse, sexual abuse, emotional abuse, child neglect (physical, emotional, educational), and factitious disease by proxy (also known as Munchausen syndrome by proxy).[1] Although the recognition of these conditions by the medical community has occurred at different times, the pivotal report describing child physical abuse occurred in 1962 with the publication of the article "The Battered Child Syndrome" by Kempe and colleagues.[2] The article noted the presence of a complex of physical findings, including fractures, cutaneous bruises, and internal injuries. Since that time, multiple articles and books have described the spectrum of the disorders. During the 1980s, much of the literature focused on child sexual abuse, including the refinement of understanding of normal anogenital anatomy of prepubescent children.[3] *Child sexual abuse* is defined as the involvement of children and adolescents in sexual activity to which they cannot give consent based on their developmental level, involving an age disparity between the victim and the perpetrator, and for the sexual gratification of the older individual. Child sexual abuse may involve physical contact between the child and the adult or the involvement of the child in other activities, such as photography or the production of pornographic material.

The role of the physician in caring for an abused child is multifold. Most importantly, the physician should recognize which presenting complaints are attributable to child abuse and initiate medical management of diagnosed medical conditions, some of which may be life-threatening. Differentiating between inflicted injuries, noninflicted injuries, and other medical conditions is paramount to the correct diagnosis and the proper management of the case. In addition, the clinician has the primary responsibility for reporting the suspicion of child abuse to the appropriate authorities, which usually include child protective services and law enforcement.

Epidemiology

There are over 1 million suspected child abuse and neglect cases noted annually in the United States. Table 63-1 summarizes the data by category of abuse or neglect as noted by the 2005 Child Maltreatment report from the U.S. Department of Health and Human Services.[4] Although child abuse occurs across the spectrum of race, ethnicity, and socioeconomic class, certain factors are associated with an increased prevalence of abuse, including poverty, social isolation, parental alcohol and substance abuse, parental mental illness, and domestic violence.[5,6]

PRINCIPLES OF DISEASE

Child Physical Abuse

Child physical abuse refers to the infliction of injury on any part of a child's body. Injuries may be manifest in myriad forms to include cutaneous bruises, burns, skeletal fractures, internal hemorrhage, organ perforation, and brain injury.

Bruises may appear as petechiae or ecchymoses. They occur at the point of impact between the striking object, such as the hand, and the child's body. Often they mirror the form of the inflicting object and may appear as a hand print, belt outline, or other object (Fig. 63-1). These bruises are referred to as *patterned injuries*. When the blow occurs at high velocity, the bruising may resemble the outline of the object as the soft tissue in the center of the impacted field moves laterally (negative image). When the thrust of the strike is slower, the central portion of the skin also may be discolored (positive image). The extent of an injury is influenced by many factors, including the force of blow and the area struck. Frequently the struck area initially may be only erythematous, swollen, or tender, and 24 hours may lapse before bleeding into the skin and subsequent discoloration are noted. The degree of discoloration and the rapidity of resolution of the discoloration are influenced by the location of the injury; large muscle masses, such as the buttocks, can hold larger volumes of blood, and resolution takes longer. In general, extravasated blood goes through a predictable color change pattern as it resolves, progressing from purple to green to yellow and eventually to brown. However, the color of a bruise should not be used as a tool to estimate the age of a bruise.[7–9] Accidentally incurred bruises tend to occur over bony prominences, such as the shin and forehead. In addition, nonambulatory children (<1 year old) do not readily sustain accidental cutaneous injuries ("those who don't cruise, don't bruise").[10] Bites also produce a patterned injury. The distance between the maxillary canine teeth helps establish whether the perpetrator was a child (<2.5 cm), which is often alleged, or an adult (>3 cm).[11]

Burns may be inflicted through contact with a dry hot object or through immersion in hot water. Commonly inflicted burns

Table 63-1 Overview of Incidence of Child Abuse

TYPE	NO. OF CASES
Physical abuse	149,319
Sexual abuse	83,810
Psychological maltreatment	63,497
General neglect	564,765
Medical neglect	17,637
Other	138,367
Total	*1,017,395*

Data from U.S. Department of Health and Human Services, Administration on Children, Youth and Families: Child Maltreatment 2005. Washington, DC, U.S. Government Printing Office, 2007. Available at http://www.acf.hhs.gov/programs/cb/stats_research/index.htm#can.

Figure 63-1. Electrical cord bruising on a child's back. (Courtesy of Dr. Marianne Gausche-Hill.)

are secondary to contact with a cigarette, as opposed to inadvertent contact with a lit cigarette, which tends to create less severe or linear burns. Inflicted cigarette burns are usually circular, measuring 8 to 10 mm (Fig. 63-2). Initially they have a blistered appearance but then become ulcerated and crust over. Burn injuries also may assume a patterned appearance resembling the configuration of the hot object, such as a heating grid or an iron. Immersion burns occur when a child or infant is placed in hot water. Such burns often involve the anogenital area and may represent punishment for toilet training accidents, or they involve the hands or feet (glove-stocking distribution) that have been dunked in hot water. Immersion burns are usually second-degree burns (Fig. 63-3). The extent of the burn is influenced by the temperature of the water, the body site exposed (the skin is thinner in certain areas, such as the anogenital region), the age of the individual (younger children and elderly adults have thinner skin), and the duration of the contact between the hot object and the skin (Table 63-2).[12] Patients with burns of the hand and feet or anogenital region require specialty care and for many emergency medical service systems, once stabilized in the emergency department will be transported to a burn center. Escharotomy may be required in selected cases when the burns are circumferential and severe.

Table 63-2 Time to Cause First-Degree or Second-Degree Burn with Various Water Temperatures

WATER TEMPERATURE °F (°C)	EXPOSURE (S)
125.6 (52)	70
129.2 (54)	30
132.8 (56)	14
136.4 (58)	6
140 (60)	3
143.6 (62)	1.6
147.2 (64)	1

Figure 63-2. Cigarette burns on the soles of the feet of a child. (Courtesy of the EMSC Slide Set, National EMSC Resource Alliance.)

Figure 63-3. Immersion burn. (Courtesy of the EMSC Slide Set, National EMSC Resource Alliance.)

Accidental burns can occur in children and usually involve scald injuries, which happen when children spill hot liquids such as coffee down their shirts. Spill burns have a characteristic drip appearance, with more extensive and severe injury proximal to the point of contact and less extensive and milder injury more distally. Disposable diapers are very absorbent of heat as well as of liquids. Scald burns in the anogenital area that are attributed to hot beverages falling into a child's diaper should be scrutinized carefully, and if there is any concern of abuse a report should be made.[13]

Table 63-3 Suspicious Fractures

Long bone fracture in a preambulatory infant
Metaphyseal fractures (classic metaphyseal lesions)
Rib fractures
Scapula fractures
Spinous process fractures
Skull
Multiple
Wide (>3 cm)
Growing
Involving >1 cranial bone
Occipital

Figure 63-4. Complex skull fracture associated with child maltreatment. (Courtesy of Sara T. Stewart, MD, MPH.)

Figure 63-5. Metaphyseal fracture, "bucket handle type," associated with child physical abuse. (Courtesy of Sara T. Stewart, MD, MPH.)

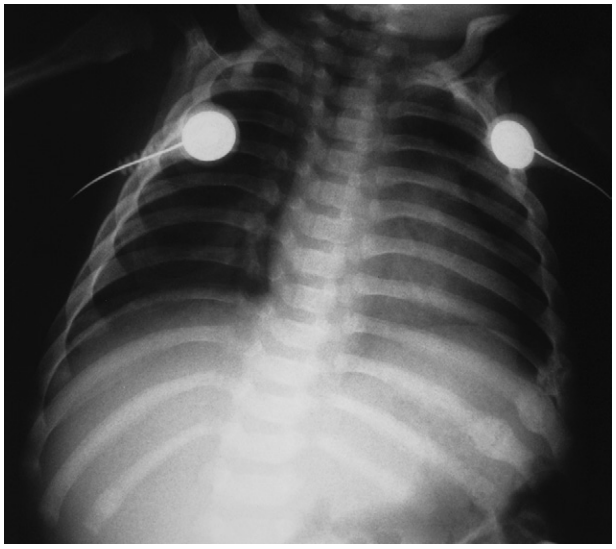


Figure 63-6. Posterior rib fractures caused by compression of the ribs from child physical abuse. (Courtesy of Sara T. Stewart, MD, MPH.)

Skeletal injuries may involve any of the bones in the body. Although approximately 42% of boys and 27% of girls have sustained a fracture before the age of 16 years, certain fractures are highly suspicious of an inflicted injury (Table 63-3).[14] In particular, metaphyseal fractures, rib fractures, and certain types of skull fractures should raise concern about inflicted trauma (Fig. 63-4). Metaphyseal fractures (i.e., classic metaphyseal lesions) occur because of yanking or pulling on an extremity. On radiographs, they may appear as chips or what is referred to as a *bucket-handle injury* of the long bone (Fig. 63-5). They usually are noted in children younger than 2 years. Rib fractures, particularly posterior rib fractures in a small infant, are virtually pathognomonic for inflicted injury[15] (Fig. 63-6). The rib cage, because of its archlike structure, must be subjected to a good deal of force to cause disruption. Rib fractures are extremely uncommon as a consequence of cardiopulmonary resuscitation.[16] The presence of multiple skull fractures and skull fractures in the occipital region are unusual in cases of accidental trauma and should raise concern for inflicted trauma. Fractures that are diastatic (>3 mm in width), grow in size, or involve more than one cranial bone are less specific as markers for nonaccidental trauma; however, they are usually associated with mechanisms of injury that involve greater traumatic forces.

Head injuries, including those associated with the classically described "shaken baby syndrome," account for most child abuse–related fatalities. The syndrome includes evidence of head trauma in association with retinal hemorrhages and skeletal injuries and occurs generally in infants younger than 1 year but may be seen in children up to 3 years old. Often, there is no evidence of an impact injury to the head, such as a scalp hematoma or skull fracture.[17] The impact may be against a soft or compressible surface, such as the mattress of the crib. Such an impact results in a rapid deceleration of the head, and the brain experiences a coup-contrecoup injury by moving back and forth within the confines of the skull. Shaking of an infant or young child subjects the brain to rotational acceleration, which is capable of generating greater force and speed than linear acceleration, the type of acceleration that occurs with a fall. It has been postulated that severe repeated shaking of an infant or young child can lead to disruption of

the neuronal cells, with or without the presence of either subarachnoid or subdural hemorrhage. Hemorrhage is a marker for the event but may be of limited clinical significance, and death, when it occurs, may not be related to bleeding, brain compression, or brain displacement. Injury to the brain cells is referred to as *traumatic axonal injury*. This injury results in disruption of the cell membrane and subsequent cerebral edema. Cerebral edema impedes the cerebral circulation, which results in further hypoxic damage to the brain.[18] At autopsy, special staining techniques allow for the recognition of axonal injury, which may be diffuse (diffuse axonal injury).[19]

Retinal hemorrhages are another common associated finding and are reported to be present in about 75% of cases of shaken baby syndrome.[20] The pathophysiology of retinal hemorrhages is uncertain. It is unclear whether bleeding is a result of increased intracranial pressure that is transmitted to the eye or occurs directly within the eye itself, perhaps through increased pressure along the retinal vein with subsequent disruption of the vessel. Additional theories propose a potential role of hypoxia and of direct vitreal traction on the retina with rotational head movement, resulting in torn retinal vessels. Retinal hemorrhages may involve the area in front of the retina (preretinal hemorrhages), the vitreous, and the subretina in addition to the retina. Hemorrhages may be described as "dot and blot" hemorrhages or flame or splinter hemorrhages. Clinically, the hemorrhages may be localized or extend to the ora serrata (the retinal edge). Retinal hemorrhages have been shown to not result from typical resuscitation efforts but could result from a severe blunt force mechanism such as a motor vehicle collision or a fall from a great height.

Abdominal trauma accounts for about 10% of injuries in abused children and carries a sixfold higher mortality rate than abdominal trauma due to accidental means.[21,22] Trauma is often blunt and includes blows and kicks to the abdomen. Frequently, there is no external evidence of the injury because the force has been transmitted to the intra-abdominal structures. Injuries can include lacerations to the liver (more commonly) or the spleen. In addition, children may develop duodenal hematomas, an injury that leads to symptoms of upper intestinal obstruction. Perforations of the intestine or other hollow viscera can follow a blow to the abdomen with subsequent progression to secondary peritonitis. Pancreatitis is also a sequela of inflicted abdominal trauma, and the latter is said to be the most common mechanism of non–medication-associated pancreatitis in children.

Child Sexual Abuse

Physical findings present when a child or adolescent has been sexually abused depend on the nature of the abuse, the time since the abuse, and whether the abuse was repetitive or isolated. Acute injuries include disruptions (tears) of the hymen, petechiae, hematomas, or rarely vaginal tears. The prepubescent hymen is significantly more fragile and more easily traumatized than the postpubertal hymen, which thickens and becomes redundant under the influence of estrogen. Physical changes in the anogenital area also may be noted when there has been prior or recurrent sexual abuse. Changes include loss of hymenal tissue and the appearance of U-shaped disruptions in the hymenal contour. Anal findings include the presence of scars and changes in anal tone and the anal contour.[23] Evidence of recent trauma also may be visible in the anal area. Acutely, there may be lacerations that appear as perianal fissures, which are characteristically wider distal to the anus. There may be post-traumatic dilatation, or alternatively anal spasm may occur in response to submucosal injury. In abused boys, the penis rarely has a noticeable injury. More recent studies have evaluated genital healing that occurs after traumatic injury.[24]

CLINICAL FEATURES

Signs and Symptoms

Child Physical Abuse

Children who have been physically abused may have complaints related to the abuse, or injuries may be noted during the course of an evaluation for an unrelated medical condition. Infants with head injuries may present with nonspecific symptoms that go unrecognized as being related to inflicted head trauma. These symptoms may include apnea, altered mental status, an apparent life-threatening event, vomiting, or a seizure. Clinicians should remain alert that these symptoms may be related to intracranial bleeding or elevated intracranial pressure. A careful physical examination should include an attempt to visualize the eye grounds to determine if there is any evidence of retinal hemorrhages. Bruises on a young infant's face are suspicious for head injury.

Refusal to use an extremity or to bear weight may be an indication of a fracture. Similarly, swelling of an extremity may be a sign of a skeletal injury.

Children with abdominal injuries may present with abdominal pain, vomiting, abdominal distention, or shock. In cases of inflicted trauma, the history may be unrevealing or may be inconsistent with the medical findings. It is common for a parent to state that he or she is uncertain how a child sustained the injury, or that the child was well at bedtime and awoke in the morning refusing to walk or with severe abdominal pain. Caregivers should be queried about how they think the injury was sustained. In cases of inflicted head trauma, the scenario often includes a young infant left in the care of a male friend or partner of the mother who has gone to work or to run errands. The male companion asserts that the infant was fine, sleeping in the crib when he went to take a shower or make some coffee, and when he returned to check on the infant, the infant was not breathing or was seizing. Often the mother is called before calling 911, or the infant is scooped up by the individual and carried to a hospital. The part of the history that is omitted is that the infant was crying, and the companion shook the infant and thrust the infant back into the crib. The infant sustained acute traumatic axonal injury and stopped crying. The infant is then left unattended, seemingly asleep. As bleeding and cerebral edema develop, other symptoms intervene. Sometimes a family member fallaciously relates a history of a fall, usually from a height (<25 inches from the ground) to a floor that is often carpeted. Or the family member may relate that a young sibling, for instance an 18-month-old, hit or jumped on the infant. Such events are not consistent with severe intracranial injuries.

Histories of falls also are related in children presenting with severe inflicted abdominal trauma. Although falls may lead to bruises of the abdominal wall and rarely damage to solid organs, they are unlikely to cause intestinal injury such as duodenal hematomas or intestinal perforations.[25] In addition to obtaining a history of the current event, past medical, developmental, and social histories are important. In children presenting with acute injuries consistent with physical abuse, there is the possibility that the findings or their severity may be related to an underlying medical condition. A careful medical history may help exclude such conditions or bring these disorders into consideration. A history of epistaxis and bleeding gums in a child who presents with bruises suggests an underlying coagulopathy. A family history of fractures raises the possibility of a bone disorder, such as osteogenesis

imperfecta. Documenting a developmental history is important when attempting to assess the likelihood that children's injuries were related to their own activity. It is crucial to be suspicious of injuries in young infants who have limited motor skills. A caregiver may allege that a 3-week-old infant sustained a head injury when he or she fell after having been placed in the center of the bed, but a 3-week-old infant is developmentally unable to scoot or roll from the center to the edge of the bed. The developmental history should document major milestones, such as age of rolling over, sitting unsupported, crawling, and walking.

A social history also is important. It may be helpful for a social worker to assist with a comprehensive social interview, but the clinician can obtain basic information, such as family financial resources (e.g., are the parents working?), where the family lives, what the family's support system is (is there extended family around?), whether there has been domestic violence within the family unit, whether there is substance abuse, and whether the family has ever been reported to child protective services.

A comprehensive physical examination should be conducted. Growth parameters should be obtained and plotted to determine if there is evidence of growth impairment or failure to thrive. It is helpful to have a diagram or outline of the body to allow for precise documentation of the size and location of bruises. In addition to the routine examination, there should be a thorough inspection of the infant to detect areas of swelling or tenderness as might occur with fractures. The abdomen should be palpated carefully for tenderness or masses. A careful ophthalmologic examination should be carried out. It is frequently difficult to visualize the fundi of young infants without the benefit of pupil dilation and an indirect ophthalmoscope. Specialized retinal cameras allow for documentation of the findings; often ophthalmologic consultation is requested to assess the fundi.

Child Sexual Abuse

Children who have been sexually abused may present with complaints related to an abusive event (e.g., "my Uncle Joey touched me"), anogenital injuries, or other related anogenital physical findings, such as a vaginal discharge. Some children present with stress-related symptoms, such as recurrent headaches or abdominal pain. Concerns about sexual abuse may be raised by divorcing parents when child custody is in dispute. Other patients, particularly older children and adolescents, may be brought to the emergency department by investigative agencies for a physical examination because of a disclosure about recent or prior abuse, even in the absence of any physical or medical complaints.

The medical evaluation should include a history of the events surrounding the alleged molestation. If the child is verbal and willing to disclose to the clinician, this information should be obtained and recorded in the medical record using the patient's own words as much as possible. The report with the disclosure is admissible as evidence. In other cases, the history may be related by other individuals, such as parents, social workers, or law enforcement officers, who are accompanying the patient. The history should include who did what, when, where, and how often. To facilitate communication and understand what the child is discussing, inquiring about the terms the child uses for different parts of the body can be helpful.

Past medical history also should be noted, including previous anogenital injuries, surgeries, or symptoms such as the presence of vaginal discharges or recurrent urinary tract infections. Stool patterns should be noted and, if constipation is reported, whether any anal medications (suppositories or enemas) are used. In postpubertal girls, a menstrual history, including age of menarche and type of sanitary protection, as well as a sexual history, should be recorded.

The physical examination should include a full head-to-toe assessment to determine if there are acute nongenital injuries (e.g., grip marks or oral injuries) or dermatologic conditions, such as lichen planus, which may explain changes in the anogenital area. The anogenital examination should note the level of pubertal development, recording if the child is prepubertal or at a more advanced stage of sexual maturity. Prepubertal children should be examined using a multimethod approach.[26] Initially, children should be evaluated in the supine position. The labia majora and surrounding tissues should be assessed for evidence of injuries or other abnormalities. Separation or traction should be applied to the labia to visualize the structures covered by the labia majora.[27] In prepubertal children, the labia majora are large and full and cover the underlying area. The labia minora are small and delicate and do not fully encircle the vaginal orifice. The clitoris and urethra should be examined. The hymen should be inspected visually for evidence of disruptions and irregularities. The hymen should be precisely described—the phrase "hymen intact" is not sufficiently descriptive for the purposes of a forensic medical assessment. An appropriate description would be "hymen pink, annular, with smooth thin edge and no disruptions." The hymenal diameter is difficult to measure reliably and an enlarged hymenal orifice without other changes in the hymen is not thought to have forensic significance. Prepubertal girls also should be examined in the prone knee-chest position. The hymen often relaxes more fully in this position, allowing for a more thorough assessment. Speculum examinations are neither indicated nor appropriate for a prepubertal child. If intravaginal trauma is suspected on the basis of vaginal hemorrhage, examination of the child in the operating room under anesthesia is mandatory. Postpubertal adolescents should be examined using a traditional pelvic examination table with stirrups. In cases of acute sexual assault, a full evidentiary assessment, including speculum examination for the purpose of evaluation and collection of forensic material, is indicated.

DIAGNOSTIC STRATEGIES

Child Physical Abuse

Diagnostic studies should be done to determine the extent of the injuries, detect occult injuries, and exclude medical conditions that may account for the findings. If there is evidence of hemorrhage, such as cutaneous bruises or intramuscular hematomas, coagulation studies are indicated. As a baseline, these studies would include a platelet count, prothrombin time, and partial thromboplastin time. It would be appropriate also to obtain a complete blood count to rule out a blood dyscrasia, such as leukemia in a child who presents with multiple ecchymoses. Occasionally, rarer coagulation deficiencies may present with bruising; the detection of such disorders requires more specific diagnostic studies. In a child with suspected burn injuries, skin cultures are appropriate to rule out infections with *Staphylococcus aureus*, such as occur with bullous impetigo.

In general, children younger than ages 2 to 3 years with suspected inflicted injuries should be evaluated with a skeletal series, sometimes referred to as a *trauma X* or *trauma series*. A trauma series includes radiography of the skull, long bones, ribs, and vertebrae. The presence of multiple fractures, particularly ones in different stages of healing, is the hallmark of the battered child syndrome. Acutely, some fractures, such as

rib injuries, may not be readily visible. Repeat radiography in 1 to 2 weeks shows evidence of callus formation and makes the fracture more readily appreciated. Alternatively a radionucleotide bone scan can detect subtle injuries and should be obtained if there is a skeletal injury but a negative skeletal survey.

Urinalysis, liver function studies, and serum amylase and lipase levels should be considered in children with symptoms of abdominal injury, such as vomiting, abdominal pain, or guarding.[28] Plain x-rays are rarely helpful but should be considered if clinical findings suggest perforation or obstruction. Computed tomography scan of the abdomen is a more precise way of delineating any abdominal injury. Computed tomography scan of the head is indicated when symptoms are consistent with head trauma or in an infant with facial bruising. Computed tomography scans may reveal extra-axial hemorrhage or findings consistent with cerebral edema. If the child is sufficiently stable, magnetic resonance imaging is helpful in determining the age of the hemorrhages and in assessing whether there has been prior intracranial hemorrhage.

In recent years, certain metabolic disorders have been described that also may be associated with intracranial hemorrhage. In particular, glutaric aciduria type I may be mistaken for inflicted head trauma.[29] Urinalysis for organic and amino acids would detect this condition.

A careful ophthalmologic examination is crucial. The examination is best done by a pediatric ophthalmologist. Photographic recording of the retinal findings is an important part of the diagnostic workup. Photographing cutaneous injuries is also important and frequently can be carried out by a police criminalist, whose equipment includes color bars for accurate documentation of the coloration of the bruising.

Child Sexual Abuse

Child sexual abuse assessments are sometimes best done with equipment that allows for magnification of the genital tissue. An otoscope or hand-held magnifier is usually available in an emergency department. Centers that evaluate sexually abused children often use colposcopes with photographic or video capability or both to allow for recording of the physical findings. Magnification allows for the detection of microtrauma or small changes in the hymen that may not be readily apparent to the naked eye. Toluidine blue is a stain that is used to increase the ease with which minor injuries are detected. The dye is selectively taken up by exposed endothelial cells. The collection of forensic specimens for the detection of sperm or for the retrieval of DNA of the alleged perpetrator is indicated in cases of acute sexual assault.

Evaluating a child or adolescent for the presence of a sexually transmitted infection depends on many factors, including disease prevalence in the community, patient symptoms, and the nature of the abuse. In cases of acute assault, the recommendation is often to treat the patient prophylactically against sexually transmitted infections such as gonorrhea and chlamydia. The decision to offer prophylaxis against human immunodeficiency virus is often based on disease prevalence and other risk factors (Table 63-4).

Part of the assessment of a sexually abused child may include a detailed interview. Forensic interviews are carried out by an individual with expertise in interviewing children, such as a social worker or clinical psychologist. Although the preliminary interview may be carried out in an emergency department, a more in-depth interview often takes place in a diagnostic center where it may be videotaped or observed (through a one-way mirror) by other individuals, such as law enforcement officers or criminal prosecutors, to minimize the number of times a child or adolescent needs to be questioned about the alleged abusive events.

Table 63-4 Sexually Transmitted Infection Prophylaxis or Treatment After Sexual Abuse/Assault

DISEASE	TREATMENT
Child, or Weight <45 kg	
Gonorrhea	Ceftriaxone 125 mg IM (1 dose) Spectinomycin 40 mg/kg IM (1 dose)
Chlamydia	Erythromycin base 50 mg/kg/day divided qid × 14 days
Trichomonas	Metronidazole 15 mg/kg/day PO divided tid × 7 days
Syphilis	Benzathine penicillin 50,000 units/kg IM (1 dose; maximum dose 2.4 million units)
HSV (first clinical episode)	Acyclovir 80 mg/kg/day divided tid × 7–10 days
Hepatitis B*	HBIG 0.06 mg/kg IM vaccine series
HIV	Contact local infectious disease specialist
Adolescent, or Weight >45 kg	
Gonorrhea	Ceftriaxone 125 mg IM (1 dose) or cefixime 400 mg PO (1 dose)
Chlamydia	>8 years of age: azithromycin 1 g PO (1 dose), or doxycycline, 100 mg PO bid × 7 days <8 years and >45 kg: azithromycin 1 g PO (1 dose)
Bacterial vaginosis	Metronidazole 500 mg PO bid × 7 days or metronidazole gel 0.75% 5 g intravaginally daily × 5 days or clindamycin 300 mg PO bid × 7 days
Trichomonas	Metronidazole 2 g PO (or 500 mg PO bid × 7 days)
Syphilis	Benzathine penicillin 2.4 million units IM (1 dose)
HSV (first clinical episode)	Acyclovir 400 mg PO tid × 7–10 days, or valacyclovir 1 g PO bid × 7–10 days
Hepatitis B*	HBIG 0.06 mg/kg IM vaccine series
HIV	Contact local infectious disease specialist

bid, twice daily; HBIG, hepatitis B immunoglobulin; HIV, human immunodeficiency virus; HSV, herpes simplex virus; tid, three times daily.
*Unimmunized child and perpetrator with acute hepatitis B infection.
Adapted from Workowski KA, Berman SM: Sexually transmitted diseases treatment guidelines, 2006. MMWR 55:1, 2006.

DIFFERENTIAL CONSIDERATIONS

Child Physical Abuse

The major differential diagnosis when considering child abuse is unintentional injury. Differentiating between inflicted and noninflicted injuries requires the consideration of multiple factors, including the developmental stage of the child, the extent of the injuries, whether the injuries appear to have occurred over a period of time, whether there were witnesses to the alleged event, whether medical care was sought in a timely manner, and whether the injuries could have been sustained in the stated manner. It is important for the evaluating clinician to have an understanding of normal child development, particularly the acquisition of motor skills. Children who are ambulatory, particularly toddlers and young school-age children, are prone to bruises over bony prominences, such as the shins and forehead. Noninflicted bruises are usually unilateral, occurring on the side where a fall or collision with a solid object has occurred. Bruises on the buttocks and flank must be explained by the mechanism of injury and are unusual in noninflicted trauma.

Figure 63-7. Mongolian spots in an infant. (Courtesy of the EMSC Slide Set, National EMSC Resource Alliance.)

Mongolian spots are bluish discolorations that are seen normally over the buttocks and lower spine in children with darker complexions (Fig. 63-7). Mongolian spots can appear on other parts of the body, such as the face and upper arm. They are usually present from birth but may not appear until the infant is several weeks old. When seen in a typical location, they are readily recognized as Mongolian spots. When located elsewhere on the body, they may be mistaken for bruises. Bruises resolve over time, Mongolian spots remain unchanged (do not go through purple-green-yellow-brown transformation) because they are undistributed melanocytes.

Phytophotodermatitis also may be mistaken for bruises. This is a condition that develops on sun-exposed areas of the body that have been in contact with certain fruits or juices, such as lime or lemon juice. The lesion appears as a brown discoloration, which may take the shape of the dripped juice or the object with which the juice came in contact. For instance, if a mother is making lemonade, has the lemon juice on her hand, and holds her child, a brown discoloration in the form of a handprint may appear if the child is in the sun. These lesions fade over time, and with a careful history and physician familiarity with the condition, the correct diagnosis can be made.

Burns also may occur unintentionally. Unintentional burns are usually secondary to spills and may take the form of drip marks down a child's chest. Bullous impetigo can be mistaken for second-degree burns because of its blister-like appearance. Culturing the lesion reveals the presence of *S. aureus* in the case of bullous impetigo. Certain dermatologic conditions, such as epidermolysis bullosa, also may cause bullous lesions that may resemble second-degree burns. The history and generalized appearance of these lesions help establish the correct diagnosis.

Fractures may occur unintentionally. In young infants, fractures may be a result of birth-related injuries. The most common fractures sustained during birth are clavicular and humeral fractures. These fractures may not be appreciated immediately after birth but become apparent when callus formation is noted. Ambulatory children may sustain fractures related to falls. A toddler's fracture, also referred to as a *CAST fracture* (*c*hildhood *a*ccidental *s*piral *t*ibial fracture), occurs when there is a twisting injury to the tibia as the child falls on it.[30] In general, the fracture is a nondisplaced distal fracture of the tibia that is detected when a child presents with a limp. Sometimes the fracture may not be apparent on the initial radiograph, but delayed radiographs (1–2 weeks after injury) may show callous formation or a bone scan may show the presence of increased bony uptake.

Fractures occur with increased frequency and with lower amounts of force in certain conditions. Premature infants may experience osteopenia of prematurity (sometimes referred to as *rickets of prematurity*), the radiographic appearance of which can be mistaken for a metaphyseal fracture.[31] In addition, osteopenic bones may fracture more easily. More advanced cases of osteopenia can be noted on a plain film of the bones. Osteogenesis imperfecta is a condition in which the bone is more brittle and easily disrupted.[32] There are four types of osteogenesis imperfecta, each with a different gene frequency. The overall incidence of osteogenesis imperfecta is 1 in 20,000. Generally, osteogenesis imperfecta is associated with other clinical findings, such as blue sclerae and brown discoloration of the teeth (dentogenesis imperfecta). Rarely, bone fragility may be present in isolation. Scurvy, congenital syphilis, and congenital rubella are associated with bony changes that may be misinterpreted as evidence of prior bony injury.

Cerebral edema may occur with infection, such as encephalitis and meningitis, or after a hypoxic event. The history and the presence of associated medical findings help with the differentiation of these conditions.

Child Sexual Abuse

Numerous medical conditions may be misdiagnosed as child sexual abuse. Accidental trauma, most commonly straddle injuries, may occur after a fall onto the perineum. Such falls occur with climbing on monkey bars, riding on boys' bicycles, or exiting from a swimming pool. Straddle injuries usually involve the labia minora, labia majora, or periurethral area. The hymen remains uninjured. Lichen sclerosis et atrophicus is a dermatologic condition of unclear etiology affecting prepubertal girls and boys and postmenopausal women. The hymen is unaffected, but the adjacent skin becomes atrophic and may sustain blood blisters or petechiae. Characteristically the skin in the perianal and perihymenal areas becomes hypopigmented and surrounds these orifices with a pale figure-of-eight configuration.

Urethral prolapse characteristically affects African American girls between the ages of 5 and 8 years. The mucosal lining of the urethra slides forward and protrudes from the urethral orifice, appearing as an erythematous, edematous mass. Symptoms include pain and bleeding. Management may involve sitz baths, antibiotic ointment, or referral to a urologist for ligation. Vaginal discharge may occur secondary to conditions other than sexually transmitted infections. *Shigella*, group A beta-hemolytic streptococcis, *Candida*, pinworm infestation, and vaginal foreign bodies can cause a vaginal discharge.

Penile swelling may occur with priapism (often secondary to sickle cell disease), paraphimosis, or an infestation with chiggers. Fissures and tags in the perianal area may result from trauma, but also may be associated with constipation and inflammatory bowel disease. Group A beta-hemolytic streptococcis can cause painful inflammation with erythema in the perianal area. Affected children may be febrile and experience pain with defecation. Hemorrhoids are rare in children and are associated with conditions that lead to an elevation of intra-abdominal venous pressure as occurs with cirrhosis of the liver.

MANAGEMENT

The focus of management is to attend to serious or life-threatening injuries, such as significant head or abdominal trauma, and stabilize the patient. Physical problems requiring medical intervention, such as fractures, lacerations, burns, or sexually transmitted infections, should be managed

appropriately. Key to the ultimate management of the abused child is the precise recording of the pertinent history, particularly any disclosure made by the child, and the physical findings. Most states require the completion of a specific child abuse reporting form as a means of notifying the authorities about the suspected case of child abuse. In addition, many jurisdictions require immediate telephonic notification to initiate an investigation of the circumstances surrounding the abuse.

Disposition

Admission to the hospital may be warranted because of the patient's injuries, to complete the medical evaluation, and to protect the child while the evaluation is occurring. Many hospitals have suspected child abuse and neglect (SCAN) teams. These teams can offer expert consultation either in the emergency department or after the child has been admitted. SCAN teams usually have unique expertise in assessing the genital findings in prepubertal girls.

Issues may arise with the family regarding "allowing" the child to be admitted to the hospital once the concerns of the emergency physician are related to the family. A strong security presence is advised during both disclosure of the intent to file a report of possible child abuse and when the decision is made to admit the child to the hospital. If security is not available to provide support to the emergency physician, and there is concern for personal safety, the addition of other hospital personnel should be solicited.

The outcome for an abused child varies with the nature, extent, and duration of the abuse. Some children die as a result of their inflicted injuries. Others have irreversible brain damage and may spend the remainder of their lives confined to wheelchairs or be blind or otherwise disabled. For other children, intervention and therapy for themselves and their offending parents may help reverse the adverse psychological effects of the abuse. The emergency physician has a key role in the early detection of the problem. The entire medical team, along with social services, law enforcement, and the judicial system, is responsible for implementing a treatment plan that prevents recidivism.

KEY CONCEPTS

- The emergency physician is mandated to report suspicion of child physical or sexual abuse.
- In infants and young children presenting with any injury, the emergency physician should consider child physical abuse as a diagnosis and especially with certain injuries, such as unusual facial bruising; skull, rib, or metaphyseal fractures; patterned bruises or burns; and injuries in preambulatory infants.
- Children who have been sexually abused may present with vague complaints, such as poor sleep pattern or abdominal pain, or may present with vaginal bleeding or discharge.
- Numerous conditions mimic child abuse and should be considered in the differential diagnosis, such as Mongolian spots, lichen sclerosis, impetigo, or urethral prolapse.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 64 Sexual Assault

Laura Slaughter

PERSPECTIVE

Background

Sexual violence is a significant problem in the United States. The Centers for Disease Control and Prevention have defined it as sexual activity where consent is not obtained or freely given. It pertains to a wide variety of sexual conduct and may entail, but does not require, penetration, completion, or, in certain cases, physical contact (e.g., voyeurism). Referred to in statute as sexual assault, it is explicated more precisely by state and local governments. Emergency physicians must be aware of their local laws because they are mandated reporters and may be involved in the evaluation, treatment, evidence collection, and documentation of sexual assault.[1]

Major advances in the evaluation and management of sexual assault victims (SAVs) have occurred over the past 30 years. The formation of community-based multidisciplinary teams that first took hold in California is probably the most important. The development of a sexual assault response team (SART) with representatives from the District Attorney's office, law enforcement, crime laboratory, medical personnel, including both physicians and nurses, social service agencies, and victim advocates came together as a group. These major players have sought to solve the logistical, medical, psychological, legal, and social problems incurred by SAVs. The commitment and mutual cooperation of the SART led to the development of standardized protocols for the care and treatment of SAVs. These protocols specify the procedures for interviewing and examining the SAV, collection, preservation, and storage of evidentiary materials, and include the evidence kit and forms for documentation. Many jurisdictions have adopted this standardized system, and in 2004 the first national protocol was released by the U.S. Department of Justice.[2] With a protocol in place, the necessity of having trained forensic examiners (FEs), irrespective of academic credentials, is evident.[3] Currently, this role subsumes the sexual assault nurse examiner (SANE); these ubiquitous, mostly hospital-based SANE programs have contributed substantially to our knowledge and understanding of SA and improved the care of these victims.[4,5] Additionally, because of the use of special technologies, including colposcopy, digital photography/videography, and the alternative light source, the establishment of designated examination centers for sexual violence is increasingly popular.[6] Much information about the characteristics, physical examination findings, and correlates of injury in SAVs is now available. This information facilitates the management of the SAV, improves the experience of the victim, and, ultimately, will assist in the identification of the perpetrator.

Epidemiology

Sexual assault does not seem to be declining at the rate of other violent crimes; nearly every category of crime was significantly lower in 2001–2002 than in the preceding 2 years except for SA.[7,8] Importantly, the cost of sexual violence to the health care system is high because it may include not only the initial visit for the crime but also subsequent visits for other health issues.[6]

Women remain the predominant victims (94%). Historically, SA has been a largely unreported crime, with only about a third of SAVs coming forward. The major reasons given for not reporting include that the matter was personal, fear of reprisal, or fear of police bias. The closer the relationship between the victim and offender, the less likely the SAV has been to report the crime; the relationship between SAV and perpetrator is often absent in the medical record, yet it is critical for safety planning.[9] A substantial proportion of SAVs report at or after 72 hours, and they are typically adolescents. There is a high positive correlation between reporting to the police and receiving medical treatment.[10]

SA is an extremely common crime, with estimates of one in three females and one in seven males being assaulted during a lifetime.[11] The mean age of the victim is approximately 20 years. She is most often single. Adolescents account for less than half of all victims seen, yet the incidence of SA peaks in the age group of 16 to 19 years.[12] For nearly 40% of victims, SA is the first sexual experience.[13] A person known to the victim commonly perpetrates the assault. Former and current boyfriends are equally common as perpetrators, lending support to the position that leaving a violent partner does not always end the terror.[9] The younger the victim, the more likely the perpetrator is to be a relative. The location of the SA varies with the victim and the type of perpetrator. In general, adults are usually assaulted in their own home, whereas adolescents are more likely to be assaulted in the assailant's residence.[14] Stranger assaults are less common; they are more likely to involve adults, occur outdoors, and include the use of a weapon and a greater likelihood of injury.[15–18] Alcohol and drug use in both the assailant and the victim are common accompaniments to SA.[19,20]

Most assaults involve penile-vaginal penetration,[11,21] and penile penetration is significantly associated with genital injury in females.[22,23] Typically, digital-vaginal penetration is the second most common sexual act reported. Oral-genital contact occurs in less than 30%, with anal assault slightly less common[11,13,24,25] The use of a foreign object is unusual (10%).[11,21] Anal assault is associated with increased violence,[13,15,22] offender preference for anal sex,[26] and offender problems with sexual dysfunction.[27,28]

Injury is not an inevitable consequence of SA.[18,29–31] Adolescent SAVs have been shown to sustain more anogenital injuries than their adult counterparts.[17,21,24,32]

Nongenital trauma occurs in 40 to 81% of SAVs, and its presence is associated with anogenital injury.[13,22,31] The extremities are most commonly injured, followed by the head and neck.[33] Serious injury involving hospitalization occurs in about 5%,[6,10] and death associated with SA is estimated at 1% or less, although this latter figure is probably a gross underestimate. Psychological distress and interpersonal difficulties are the major sequelae after an SA. These problems are exacerbated in SAVs with known attackers who delay reporting.[34]

DISTINGUISHING PRINCIPLES OF DISEASE

Emergency Department Preparation

A standardized approach to the management of the SAV is important. This should include, if at all possible, the development of a multidisciplinary team that works together under a protocol. That protocol should address every detail, from the handling of the SAV's first call to dispatch to the referral for psychological support. The SAV should be taken out of the medical triage system that typifies the emergency department not only to provide privacy and security for the SAV but also to prevent the deterioration of evidence. This approach assures a consistent process of evaluation, treatment, and collection of evidence. The medical team should receive forensic training on interviewing and examination techniques; collecting, preserving, and storing evidence; and chain of custody issues. The team should be trained to use the examination form and be thoroughly familiar with the SA kit (rape kit) provided by the state or local crime laboratory. Advocates, whether provided through law enforcement or by a separate entity, need to receive training from the SART about examination procedures and staff roles so they can best advise and counsel the SAV. A SART program cannot be successful unless advocates feel that the SAV will be treated with respect and receive the best treatment available. Because the SART examiner is the first person on the medical team to greet the victim, a kind, calm, knowledgeable, and professional demeanor is of the utmost importance.

The emergency department should also be prepared for the unusual victim with significant or life-threatening injuries. In this instance, the emergency physician needs to delegate the forensic responsibility to another forensically trained staff member whose sole purpose is to collect the evidence and, if required, follow the SAV to surgery. In cases in which there is substantial injury, following the patient from intake allows the examiner to understand better and document the nature and extent of the trauma and continue the forensic process with little further distress to the patient.[35]

Obtaining the History and Consent

Numerous consents should be obtained from the SAV, depending upon state and local laws (Box 64-1). The FE should be knowledgeable about all statutes governing consent, including whether minors need parental consent. In some states, even if parental consent is not required, the FE may still be required to contact the parents and document the success or failure of this attempt. Although not part of the official consent process, most SAVs are concerned about access to the SART record and photographs, particularly when the SART examination facility is within the hospital setting. Keeping these records separate from the primary hospital chart system helps protect the privacy of the victim and has a precedent in the similar handling of psychiatric records. Surveys of SAVs have identified that they desire information about sexually transmitted diseases (STDs), pregnancy, emergency contraception, follow-up care, and physical and psychological health effects of SA.[36] Providing written information on these topics to the patient with his/her signature confirmation documents the patient's receipt of follow-up recommendations. Before getting started with the history, the SAV's immediate privacy and personal needs should be addressed. Box 64-2 outlines some of the issues that may make the interview more comfortable for the patient and ensure reliable historical information from the patient. The group taking the history may include a law enforcement officer, patient advocate, medical assistant, and FE.

A detailed history is important. California was the first state to mandate a uniform examination protocol and specific training for examiners (Fig. 64-1).[37]

text continued on p. 806

BOX 64-1 CONSENT ISSUES IN SEXUAL ASSAULT CASES

Consents Should Specify that the SAV Signature Acknowledges:

That hospitals and health care professionals are mandated reporters
Receipt of information about victim compensation funds
Specific understanding of the examination and evidence collection procedures
Specific understanding of the use of photography in documenting physical and genital injuries
That information collected will be sent to law enforcement and is obtainable by defense counsel
That data without patient identity can be collected for valid educational and scientific interest
That consent may be withdrawn at any time

BOX 64-2 PRELIMINARY ISSUES AND STRATEGIES IN PREPARING FOR TAKING THE HISTORY FROM AN SAV

Provide quiet, confidential, safe environment.
Briefly review the interview and examination process in private with the SAV.
Explain sensitive/personal/embarrassing nature of questions and right to be interviewed without family or friends.
Show concern for immediate comfort (e.g., if thirsty, take oral swabs first so SAV may drink).
Provide advocacy.
Always conduct interview the same way.
Leave difficult questions until the end.
Explain why you are asking the question and the possible responses.
Explain that all questions must be asked.

FORENSIC MEDICAL REPORT: ACUTE (<72 HOURS)
ADULT/ADOLESCENT SEXUAL ASSAULT EXAMINATION

STATE OF CALIFORNIA
California Emergency Management Agency

CalEMA 2-923

Confidential Document **Patient Identification**

A. GENERAL INFORMATION (print or type) Name of Medical Facility:

1. Name of patient — Patient ID number

2. Address — City — County — State — Telephone (W) (H)

3. Age	DOB	Gender M F	Ethnicity	Arrival Date	Arrival Time	Discharge Date	Discharge Time

B. REPORTING AND AUTHORIZATION Jurisdiction (☐city ☐county ☐other):

1. Telephone report made to law enforcement agency
Name of Officer — Agency — ID Number — Telephone
Reported by: Name — Date — Time

2. Responding Officer — Agency — ID Number — Telephone

3. I request a forensic medical examination for suspected sexual assault at public expense.

Law enforcement officer — ID number — Agency

Telephone Authorization
Agency:
Authorizing party:
ID number:
Date/time:

Telephone — Date — Time — Case Number

C. PATIENT INFORMATION

- I understand that hospitals and health care professionals are required by Penal Code Sections 11160-11161 to report to law enforcement authorities cases in which medical care is sought when injuries have been inflicted upon any person in violation of any state penal law. The report must state the name of the injured person, current whereabouts, and the type and extent of injuries. _____ (Initial)
- I have been informed that victims of crime are eligible to submit crime victim compensation claims to the State Victims of Crime (VOC) Restitution Fund for out-of-pocket medical expenses, psychological counseling, loss of wages, and job retraining and rehabilitation. _____ (Initial)

D. PATIENT CONSENT

Minors: Family Code Section 6927 permits minors (12 to 17 years of age) to consent to medical examination, treatment, and evidence collection for sexual assault without parental consent. See instructions for parental notification requirements for minors.

- I understand that a forensic medical examination for evidence of sexual assault at public expense can, with my consent, be conducted by a health care professional to discover and preserve evidence of the assault. If conducted, the report of the examination and any evidence obtained will be released to law enforcement authorities. I understand that the examination may include the collection of reference specimens at the time of the examination or at a later date. I understand that I may withdraw consent at any time for any portion of the examination. _____ (Initial)
- I understand that collection of evidence may include photographing injuries and that these photographs may include the genital area. _____ (Initial)
- I hereby consent to a forensic medical examination for evidence of sexual assault. _____ (Initial)
- I understand that data without patient identity may be collected from this report for health and forensic purposes and provided to health authorities and other qualified persons with a valid educational or scientific interest for demographic and/or epidemiological studies. _____ (Initial)

Signature _____ ☐ Patient ☐ Parent ☐ Guardian

DISTRIBUTION OF CalEMA 2-923

☐ Original - Law Enforcement ☐ Copy within evidence kit - Crime Lab ☐ Copy - Child Protective Services (if patient is a minor) ☐ Copy - Medical Facility Records

E. PATIENT HISTORY

1. Name of person providing history: — Relationship to patient: — Date — Time

2. Pertinent medical history:
- Last menstrual period _____
- Any recent (60 days) anal-genital injuries, surgeries, diagnostic procedures, or medical treatment that may affect the interpretation of current physical findings? ☐ No ☐ Yes
If yes, describe: _____
- Any other pertinent medical condition(s) that may affect the interpretation of current physical findings? ☐ No ☐ Yes
If yes, describe: _____
- Any pre-existing physical injuries? ☐ No ☐ Yes
If yes, describe: _____

3. Pertinent pre- and post-assault related history:

	No	Yes	Unsure
• Other intercourse within past 5 days?	☐	☐	
If yes,			
anal (within past 5 days)? When _____	☐	☐	
vaginal (within past 5 days)? When _____	☐	☐	
oral (within past 24 hours)? When _____	☐	☐	
If yes, did ejaculation occur?	☐	☐	☐
If yes, where? _____			
If yes, was a condom used?	☐	☐	☐
• Any voluntary alcohol use within 12 hours prior to assault?	☐	☐*	
• Any voluntary drug use within 96 hours prior to assault ?	☐	☐*	
• Any voluntary drug or alcohol use between the time of the assault and the forensic exam?	☐	☐*	

* If yes, collection of toxicology samples is recommended according to local policy. ☐ Blood ☐ Urine

4. Post-assault hygiene/activity: ☐ Not applicable if over 72 hours

	No	Yes
Urinated	☐	☐
Defecated	☐	☐
Genital or body wipes	☐	☐
If yes, describe: _____		
Douched	☐	☐
If yes, with what _____		
Removed/inserted tampon ☐ diaphragm ☐	☐	☐
Oral gargle/rinse	☐	☐
Bath/shower/wash	☐	☐
Brushed teeth	☐	☐
Ate or drank	☐	☐
Changed clothing	☐	☐
If yes, describe: _____		

5. Assault-related history:

	No	Yes
Loss of memory? If yes, describe:	☐	☐*
Lapse of consciousness? If yes, describe:	☐	☐*

*If yes, collection of toxicology samples is recommended according to local policy. ☐ Blood ☐ Urine

Vomited? If yes, describe:	☐	☐
Non-genital injury, pain and/or bleeding? If yes, describe:	☐	☐
Anal-genital injury, pain, and/or bleeding? If yes, describe:	☐	☐

Patient Identification

F. ASSAULT HISTORY

1. Date of assault(s): — Time of assault(s):

2. Pertinent physical surroundings of assault(s):

3. Alleged assailant(s) name(s)	Age	Gender	Ethnicity	Relationship to patient: Known	Relationship to patient: Unknown
#1.		M F			
#2.		M F			
#3.		M F			
#4.		M F			

4. Methods employed by assailant(s):

	No	Yes	If yes, describe:
Weapons	☐	☐	
Threatened?	☐	☐	
Injuries inflicted?	☐	☐	
Type(s) of weapons?	☐	☐	
Physical blows	☐	☐	
Grabbing/holding/pinching	☐	☐	
Physical restraints	☐	☐	
Choking/strangulation	☐	☐	
Burns (thermal and/or chemical)	☐	☐	
Threat(s) of harm	☐	☐	
Target(s) of threat(s)	☐	☐	
Other methods	☐	☐	

Involuntary ingestion of alcohol/drugs ☐ No ☐ Yes ☐ Unsure
If yes, ☐ Alcohol ☐ Drugs
If yes, ☐ Forced ☐ Coerced ☐ Suspected
If yes, toxicology samples collected: ☐ Blood ☐ Urine ☐ None

5. Injuries inflicted upon the assailant(s) during assault? ☐ No ☐ Yes
If yes, describe injuries, possible locations on the body, and how they were inflicted.

G. ACTS DESCRIBED BY PATIENT

- **Any penetration of the genital or anal opening, however slight, constitutes the act.**
- **Oral copulation requires only contact**
- **If more than one assailant, identify by number.**

Patient Identification

	No	Yes	Attempted	Unsure	Describe:
1. Penetration of vagina by:					
Penis	☐	☐	☐	☐	
Finger	☐	☐	☐	☐	
Object If yes, describe the object:	☐	☐	☐	☐	
2. Penetration of anus by:					Describe:
Penis	☐	☐	☐	☐	
Finger	☐	☐	☐	☐	
Object If yes, describe the object:	☐	☐	☐	☐	
3. Oral copulation of genitals:					Describe:
Of patient by assailant	☐	☐	☐	☐	
Of assailant by patient	☐	☐	☐	☐	
4. Oral copulation of anus:					Describe:
Of patient by assailant	☐	☐	☐	☐	
Of assailant by patient	☐	☐	☐	☐	
5. Non-genital act(s):					Describe:
Licking	☐	☐	☐	☐	
Kissing	☐	☐	☐	☐	
Suction injury	☐	☐	☐	☐	
Biting	☐	☐	☐	☐	
6. Other act(s):	☐	☐	☐	☐	Describe:
7. Did ejaculation occur?	☐	☐		☐	Describe:

If yes, note location(s):
- ☐ Mouth
- ☐ Vagina
- ☐ Anus/Rectum
- ☐ Body surface
- ☐ On clothing
- ☐ On bedding
- ☐ Other

	No	Yes	Unsure	Describe Type/Brand, if known:
8. Contraceptive or lubricant products:				
Foam used?	☐	☐	☐	
Jelly used?	☐	☐	☐	
Lubricant used?	☐	☐	☐	
Condom used?	☐	☐	☐	

H. GENERAL PHYSICAL EXAMINATION

Record all findings using diagrams, legend, and a consecutive numbering system.

1. Blood Pressure	Pulse	Resp	Temp	2. Exam Started Date	2. Exam Started Time	Exam Completed Date	Exam Completed Time

3. Describe general physical appearance	4. Describe general demeanor

Patient Identification

5. Describe condition of clothing upon arrival.

6. Collect outer and underclothing if indicated. ☐ Not indicated
7. Conduct a physical examination. ☐ Findings ☐ No Findings
8. Collect dried and moist secretions, stains, and foreign materials from the body. Scan the entire body with a Wood's Lamp.
☐ Findings ☐ No Findings
9. Collect fingernail scrapings or cuttings according to local policy.

Diagram A

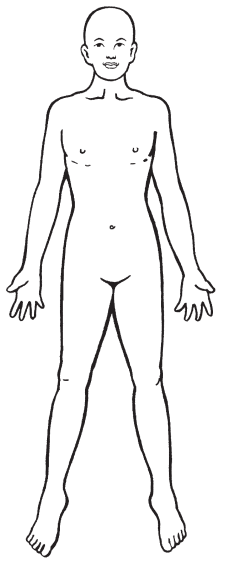
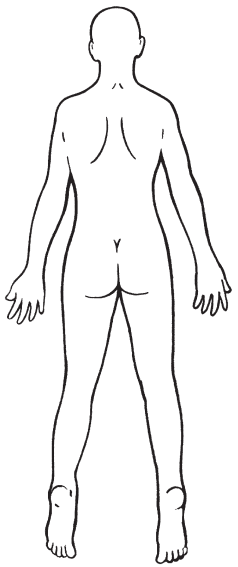


Diagram B



LEGEND: Types of Findings

AB	Abrasion	**DF**	Deformity	**FB**	Foreign Body	**MS**	Moist Secretion	**PE**	Petechiae	**TB**	Toluidine Blue ⊕
BI	Bite	**DS**	Dry Secretion	**IN**	Induration	**OF**	Other Foreign Materials (describe)	**PS**	Potential Saliva	**TE**	Tenderness
BU	Burn	**EC**	Ecchymosis (bruise)	**IW**	Incised Wound			**SHX**	Sample Per History	**V/S**	Vegetation/Soil
CS	Control Swab	**ER**	Erythema (redness)	**LA**	Laceration	**OI**	Other Injury (describe)	**SI**	Suction Injury	**WL**	Wood's Lamp ⊕
DE	Debris	**F/H**	Fiber/Hair					**SW**	Swelling		

Locator #	Type	Description	Locator #	Type	Description

RECORD ALL CLOTHING AND SPECIMENS COLLECTED ON PAGE 8

Figure 64-1. Forensic Medical Report Acute (<72 hours) Adult/Adolescent Sexual Assault CalEMA 2-923 from the State of California Emergency Management Agency. This form is available at www.CalEMA.ca.gov.

I. HEAD, NECK, AND ORAL EXAMINATION

Record all findings using diagrams, legend, and a consecutive numbering system.

1. **Examine the face, head, hair, scalp, and neck for injury and foreign materials** ☐ Findings ☐ No Findings
2. **Collect dried and moist secretions, stains, and foreign materials from the face, head, hair, scalp, and neck.** ☐ Findings ☐ No Findings
3. **Examine the oral cavity for injury and foreign materials (if indicated by assault history). Collect foreign materials.** **Exam done:** ☐ Not applicable ☐ Yes ☐ Findings ☐ No Findings
4. **Collect 2 swabs from the oral cavity up to 12 hours post assault and prepare one dry mount slide from one of the swabs.**
5. **Collect head hair reference samples according to local policy.**

Patient Identification

Diagram C

Diagram D

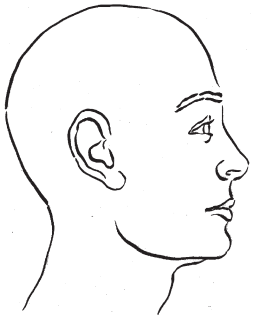


Diagram E

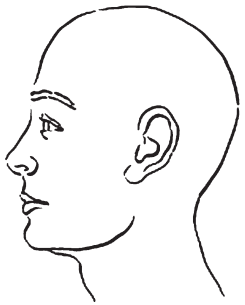
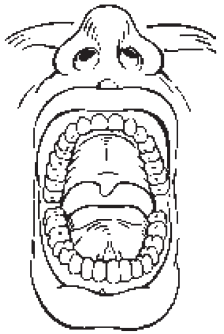


Diagram F



LEGEND: Types of Findings

AB	Abrasion	**DF**	Deformity	**FB**	Foreign Body	**MS**	Moist Secretion	**PE**	Petechiae	**TB**	Toluidine Blue ⊕
BI	Bite	**DS**	Dry Secretion	**IN**	Induration	**OF**	Other Foreign Materials (describe)	PS	Potential Saliva	**TE**	Tenderness
BU	Burn	**EC**	Ecchymosis (bruise)	**IW**	Incised Wound			**SHX**	Sample Per History	**V/S**	Vegetation/Soil
CS	Control Swab	**ER**	Erythema (redness)	**LA**	Laceration	**OI**	Other Injury (describe)	**SI**	Suction Injury	**WL**	Wood's Lamp ⊕
DE	Debris	**F/H**	Fiber/Hair					**SW**	Swelling		

Locator #	Type	Description	Locator #	Type	Description

RECORD ALL SPECIMENS COLLECTED ON PAGE 8

J. GENITAL EXAMINATION - FEMALES

Record all findings using diagrams, legend, and a consecutive numbering system.

1. **Examine the inner thighs, external genitalia, and perineal area. Check the box(es) if there are assault related findings:**
   ☐ No Findings
   ☐ Inner thighs ☐ Periurethral tissue/urethral meatus
   ☐ Perineum ☐ Perihymenal tissue (vestibule)
   ☐ Labia majora ☐ Hymen
   ☐ Labia minora ☐ Fossa navicularis
   ☐ Clitoris/surrounding area ☐ Posterior fourchette
2. **Collect dried and moist secretions, stains, and foreign materials. Scan the area with a Wood's Lamp.** ☐ Findings ☐ No Findings
3. **Collect pubic hair combing or brushing.**
4. **Collect pubic hair reference samples according to local policy.**
5. **Examine the vagina and cervix. Check the box(es) if there are assault related findings.** ☐ No Findings ☐ Vagina ☐ Cervix
6. **Collect 4 swabs from the vaginal pool. Prepare one wet mount slide and one dry mount slide.**
7. **Collect 2 cervical swabs (if over 48 hours post assault).**
8. **Examine the buttocks, anus, and rectum (if indicated by history).** **Exam done:** ☐ **Yes** ☐ **Not applicable** **Check the box(es) if there are assault related findings:**
   ☐ No Findings
   ☐ Buttocks ☐ Anal verge/folds/rugae
   ☐ Perianal skin ☐ Rectum
9. **Collect dried and moist secretions, stains, and foreign materials.** ☐ Findings ☐ No Findings
10. **Collect 2 anal and/or rectal swabs and prepare one dry mount slide.**
11. **Conduct an anoscopic exam if rectal injury is suspected or if there is any sign of rectal bleeding.** Rectal bleeding ☐ No ☐ Yes If yes, describe:_____
12. **Exam position used:** ☐ Supine ☐ Other Describe:

Patient Identification

Diagram G

Diagram H

Diagram I

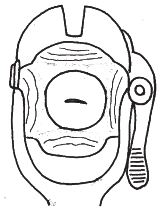
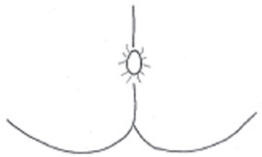


Diagram J



LEGEND: Types of Findings

AB	Abrasion	**EC**	Ecchymosis (bruise)	**MS**	Moist Secretion	**SI**	Suction Injury				
BI	Bite	**ER**	Erythema (redness)	**OF**	Other Foreign Materials (describe)	**SW**	Swelling				
BU	Burn	**F/H**	Fiber/Hair			**TB**	ToluidineBlue ⊕				
CS	Control Swab	**FB**	Foreign Body	**OI**	Other Injury (describe)	**TE**	Tenderness				
DE	Debris	**IN**	Induration	**PE**	Petechiae	**V/S**	Vegetation/Soil				
DF	Deformity	**IW**	Incised Wound	**PS**	Potential Saliva	**WL**	Wood's Lamp ⊕				
DS	Dry Secretion	**LA**	Laceration	**SHX**	Sample Per History						

Locator #	Type	Description

RECORD ALL SPECIMENS COLLECTED ON PAGE 8

K. GENITAL EXAMINATION – MALES

Record all findings using diagrams, legend, and a consecutive numbering system.

1. **Examine the inner thighs, external genitalia, and perineal area. Check the box(es) if there are assault related findings:**
   ☐ No Findings
   ☐ Inner thighs ☐ Glans penis ☐ Scrotum
   ☐ Perineum ☐ Penile shaft ☐ Testes
   ☐ Foreskin ☐ Urethral meatus
2. **Circumcised:** ☐ No ☐ Yes
3. **Collect dried and moist secretions, stains, and foreign materials. Scan the area with a Wood's Lamp.** ☐ Findings ☐ No Findings
4. **Collect pubic hair combing or brushing.**
5. **Collect pubic hair reference samples according to local policy.**
6. **Collect 2 penile swabs, if indicated by assault history.** ☐ N/A
7. **Collect 2 scrotal swabs, if indicated by assault history.** ☐ N/A
8. **Examine the buttocks, anus, and rectum (if indicated by history)**
   Exam done: ☐ **Yes** ☐ **Not applicable**
   Check the box(es) if there are assault related findings:
   ☐ No Findings
   ☐ Buttocks ☐ Anal verge/folds/rugae
   ☐ Perianal skin ☐ Rectum
9. **Collect dried and moist secretions, stains, and foreign materials.**
   ☐ Findings ☐ No Findings
10. **Collect 2 anal and/or rectal swabs and prepare one dry mount slide.**
11. **Conduct an anoscopic exam if rectal injury is suspected or if there is any sign of rectal bleeding.**
    Rectal bleeding: ☐ No ☐ Yes
    If yes, describe: _____
12. **Exam position used:**
    ☐ Supine ☐ Other Describe:

LEGEND: Types of Findings

AB Abrasion	**EC** Ecchymosis (bruise)	**MS** Moist Secretion	**SI** Suction Injury
BI Bite	**ER** Erythema (redness)	**OF** Other Foreign Materials (describe)	**SW** Swelling
BU Bum	**F/H** Fiber/Hair		**TB** ToluidineBlue⊕
CS Control Swab	**FB** Foreign Body	**OI** Other Injury (describe)	**TE** Tenderness
DE Debris	**IN** Induration	**PE** Petechiae	**V/S** Vegetation/Soil
DF Deformity	**IW** Incised Wound	**PS** Potential Saliva	**WL** Wood's Lamp⊕
DS Dry Secretion	**LA** Laceration	**SHX** Sample Per History	

Locator #	Type	Description

RECORD ALL SPECIMENS COLLECTED ON PAGE 8

Patient Identification

Diagram K

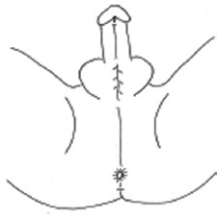


Diagram L

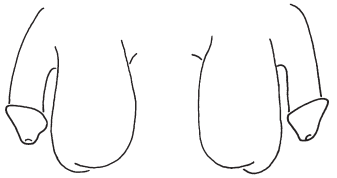


Diagram M

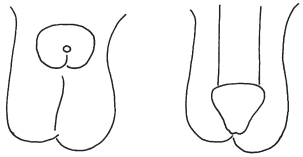
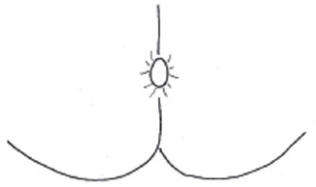


Diagram N



L. EVIDENCE COLLECTED AND SUBMITTED TO CRIME LAB

1. Clothing placed in evidence kit	Other clothing placed in bags

2. Foreign materials collected

	No	Yes	Collected by:
Swabs/suspected blood	☐	☐	
Dried secretions	☐	☐	
Fiber/loose hairs	☐	☐	
Vegetation	☐	☐	
Soil/debris	☐	☐	
Swabs/suspected semen	☐	☐	
Swabs/suspected saliva	☐	☐	
Swabs/Wood's Lamp⊕ area(s)	☐	☐	
Control swabs	☐	☐	
Fingernail scrapings/cuttings	☐	☐	
Matted hair cuttings	☐	☐	
Pubic hair combings/brushings	☐	☐	
Intravaginal foreign body	☐	☐	
If yes, describe: _____			
Other types	☐	☐	
If yes, describe:			

3. Oral/genital/anal/rectal samples

	# Swabs	# Slides	Time collected	Collected by:
Oral				
Vaginal				
Cervical				
Anal				
Rectal				
Penile				
Scrotal				

Aspirate/washings (optional) ☐ No ☐ Yes

4. Vaginal wet mount slide

	No	Yes	Time	Examiner:
Slide prepared				
Motile sperm observed				
Non-motile sperm observed				

M. TOXICOLOGY SAMPLES

	No	Yes	Time	Collected by:
Blood alcohol/toxicology (gray top tube)				
Urine toxicology				

N. REFERENCE SAMPLES

	No	Yes	Collected by:
Blood (lavender top tube)			
Blood (yellow top tube)			
Blood Card (optional)			
Buccal swabs (optional)			
Saliva swabs			
Head hair			
Pubic hair			

O. PHOTO DOCUMENTATION METHODS

	No	Yes	Colposcope/ 35mm	Macrolens/ 35mm	Colposcope/ Videocamera	Other Optics
Body	☐	☐	☐	☐	☐	☐ _____
Genitals	☐	☐	☐	☐	☐	☐ _____

Photographed by:

Patient Identification

P. RECORD EXAM METHODS

	No	Yes		No	Yes
Direct visualization only	☐	☐	Toluidine Blue Dye	☐	☐
Colposcopy	☐	☐	Anoscopic exam	☐	☐
Other magnifier	☐	☐	Anal speculum exam	☐	☐
Other	☐	☐			

If yes, describe: _____

Q. RECORD EXAM FINDINGS

☐ **Physical Findings** ☐ **No Physical Findings**

R. RECORD ASSESSMENT OF FINDINGS

☐ Exam consistent with history
☐ Exam inconsistent with history

S. SUMMARIZE FINDINGS

T. PRINT NAMES OF PERSONNEL INVOLVED

History taken by:	Telephone:
Exam performed by:	
Specimens labeled and sealed by:	
Assisted by: ☐ N/A	
Signature of examiner	License No.

U. EVIDENCE DISTRIBUTION

	GIVEN TO:
Clothing (item(s) not placed in evidence kit)	
Evidence Kit	
Reference blood samples	
Toxicology samples	

V. SIGNATURE OF OFFICER RECEIVING EVIDENCE

Signature: _____

Print name and ID #: _____

Agency: _____

Date: Phone:

Figure 64-1, cont'd

Table 64-1 Useful Information Not Routinely Found on the Sexual Assault Forms

Positions used during the assault	Affects the location of injury
Positions used during the examination	Helps to orient pictures
Sexual dysfunction in the suspect	Associated with increased violence and anal attack
Repeated thrusting by suspect	May explain loss of seminal product
Victim assistance with insertion of penis	May explain lack of genital injury
Did penis remain in vagina after ejaculation?	May explain loss of seminal product
How do you know ejaculation occurred?	Helps determine where semen may be found
Prior sexual experience	Lack of sexual experience associated with increased hymenal trauma
Gravity and parity	May be a factor in genital injury
History of prior victimization	At increased risk for post-traumatic stress disorder; need triage for counseling
Mental health problems	Increased severity of attack and worsening mental health problems
Past medical history	May explain physical or laboratory findings

History of Type of Sexual Assault

Questions about sexual acts need to be explicit and phrased in terms understandable to the SAV. Unless specifically asked, many victims will not disclose that injuries are a result of the assault.[9] Language used by the SAV to describe sexual acts should be documented in the medical record. Importantly, the FE should ascertain if the victim voiced her lack of consent and whether that terminated the behavior. The victim's own words should be used as often as possible and recorded in quotation marks to preserve the integrity of the interview. The experienced FE also gathers information about the sequence and type of sexual acts that occurred during an assault, including not only kissing, fondling, use of foreign objects, and digital manipulation, but also fetishism, voyeurism, or exhibitionism on the part of the suspect. Table 64-1 lists additional information, which may be useful for the investigation.

Drug and Alcohol Use

Inquiry about drug and alcohol usage is important and necessary.[20,38–41] Like driving under the influence, an SA may be the first indicator that the victim has a drug or alcohol problem.[42] Recent data indicate that drug and alcohol abuse by the victim is associated with a concurrent increased risk of an additional assault in the next 2 years; assaulted drug users are at risk for an escalation of drug abuse postassault.[43] These victims need prompt referral for counseling and drug rehabilitation programs. Further, the use of drugs and alcohol are relevant to issues of consent, credibility, and corroboration.[44,45] In the past, studies have not found a correlation between substance use and injury,[13,16,21,32,46] but recent studies indicate an increase in nongenital[17,18] and anogenital trauma.[23] The FE should order drug screening if the victim reports loss of consciousness or forced ingestion, appears confused, is amnesic, or has other changes in physical or vital signs that are suspicious for drug use. National drug screening data from SAVs show that the prevalence of drugs used is higher among SAVs than the general population.[47,48] Moreover, drugs are frequently used in combination. The two most popular combinations are alcohol and marijuana, followed by alcohol and benzodiazepines.[19] Routine surveillance of drugs and alcohol is recommended.

History of Child Abuse

A history of childhood abuse increases the risk of repeat assault. Researchers now believe that identification of this vulnerable group is a prerequisite for prevention.[49] The SA examination may be the one time during which the question of prior abuse is raised; a positive answer provides additional justification for referral for psychological services.

Mental Illness

About a quarter of the victims presenting for SA evaluation will have mental health problems. A history of mental illness has been shown to increase the severity of the sexual and physical attack. Moreover, the SA often results in an exacerbation of the mental illness and higher rate of post-traumatic stress disorder.[50]

Prior Sexual Experience

Knowledge about the victim's prior sexual experience is pertinent. New information has emerged that women without sexual experience are more likely to sustain genital trauma[23,51] and specifically more likely to have hymenal tearing.[13,21,52] Because hymenal and vaginal tears are usually associated with the dramatic presentation of bleeding, it is incumbent upon the examiner to ascertain the source of hemorrhage. The lack of visible genital injury in the female who has not had prior sexual experience does not exclude the possibility of intercourse.

SAVs are reluctant to report that they assisted the suspect in any way. Some suspects ask the victim to assist with insertion of the penis. If the SAV does this, she does so in order to avoid harming herself; this may explain the lack of the typical entry injury seen in most victims. Positioning may be another factor in the location of injury; anterior injury is more common when rear entry or female superior positions are used.[22]

Methods of Controlling the Victim

Much can be gleaned about the suspect from a careful interview of the SAV. Areas of interest for the examiner include the methods of approach and control of the SAV, the offender's reaction to resistance by the victim, and the occurrence of sexual dysfunction in the suspect. While the approach to the victim is usually easy to obtain, understanding how the suspect controlled the victim may not be immediately clear, as the mere presence of the suspect may be perceived by the victim as a threat to life and result in control of the victim's actions. Most protocols inquire about verbal threats and weapons, but getting the exact context of these (verbatim if possible) and determining whether the threats were carried out are important. Similarly, with a weapon, it should be noted whether the victim saw the weapon or whether it remained a verbal threat only. Was it a weapon of choice (brought with the suspect) or one of opportunity? Did the suspect relinquish it at any time

or use it? The examiner should inquire into the amount and timing of the force used by the assailant along with the use of any derogatory or profane language. The examiner should inquire about strangulation; SAVs typically do not volunteer this information. Strangulation tends to occur late in abusive relationships and has been associated with a higher risk for major morbidity and mortality.[53,54] The FE should take special care to ask questions in a manner that does not implicate that the victim should have done something to protect herself or to prevent the occurrence of the SA. In some cases, resistance may provoke an alternative demand, compromise, negotiation, and threat of force or use of force. If force is threatened, the examiner should be clear about whether it was used and understand how much and how long it was applied.

Sexual Dysfunction in Offenders

Nearly 34% of convicted rapists have a sexual dysfunction, and this information is obtainable from the SAV. Sexual dysfunction includes impotence, premature ejaculation, retarded ejaculation, or conditioned ejaculation (Box 64-3). This knowledge improves the examiner's ability to understand and collect the evidence. A premature ejaculator may have left semen on clothing or in the environment rather than intravaginally. Retarded ejaculation is associated with multiple sex acts, including anal intercourse and a more violent attack, including both genital and nongenital trauma. Serial rapists have been identified based upon language and demand for a specific order of sexual acts from several SAVs. Additionally, the SAV can be asked about any unique lesions or pathology of the perpetrator's genitalia or other identifying characteristics.[55]

Methods Used by the Offender to Avoid Detection

The FE should inquire about the methods used to avoid detection and escape, such as masks, gloves, blindfolds, or disabling the phone. An experienced assailant may also attempt to destroy evidence, such as forcing the victim to shower. Lastly, the FE should ask about missing items. Valuables or personal items retained as souvenirs have evidentiary value. The FE should ask the victim if the assailant is known to him or her; even if unknown to the victim, he or she may have a wealth of information about characteristics and behavior of the assailant.[27]

A complete history, which is temporally related, is crucial. The preprinted checklist forms provided by the state or local government are a good start, but unfortunately they do not elicit a specific narrative recall of events by the SAV. In every case, a dictated narrative summary is strongly recommended.

BOX 64-3 Definitions of Sexual Dysfunction Commonly Seen in Perpetrators of Sexual Assault

Erectile insufficiency: formally impotence; difficulty obtaining or maintaining an erection
Premature ejaculation: ejaculation that occurs immediately before or immediately after penetration
Retarded ejaculation: difficulty in ejaculating or failure to ejaculate
Conditioned ejaculation: able to ejaculate only after certain conditions (e.g., particular sex acts) have been met

PERFORMING THE PHYSICAL EXAMINATION AND EVIDENCE COLLECTION

The physical examination should be meticulous and include the collection of trace evidence and reference standards (see Fig. 64-1). There is a positive association between SAV injury and the filing of charges,[56] successful prosecution,[57,58] and sentencing.[59] In general, the sequence of observation, photography in situ, collection of evidence, and written documentation should be followed (Box 64-4). All items should be dry and placed in paper containers (no plastic), labeled (Box 64-5), and sealed. Each container should be sealed securely with tape, and the examiner should initial or sign across the tape and onto the container/bag.

To preserve the integrity of the evidence, the SAV should not be left alone in the room with it, and the FE should wear powder-free gloves to prevent contamination of the evidence. If the evidence is stored, a locked unit should be available. Preserving the chain of custody, a fundamental principle in the criminal justice system, should be understood by all personnel (Box 64-6). A complete examination and historically relevant evidence collection should be performed, irrespective of the time between the assault and examination. One investigator documents the retrieval of salivary DNA from a bite mark on a body even after the body had been submerged in water for more than 5 hours.[60] The FE should not second-guess what the laboratory may or may not recover based upon rigid time frames. If there is a history of loss of consciousness or significant memory impairment, then all specimens should be collected.

Examination of the Skin

The FE needs to describe the SAV's demeanor and general appearance. The examiner should be especially careful to use specific terms and note responsiveness and ability to cooperate and give a history. All clothing worn during the assault should

BOX 64-4 Documentation of Findings During Sexual Assault Examination

Findings/evidence to be documented include:
Preexisting injuries
Acute injuries
Tenderness or induration
Foreign material
Wood's lamp/alternate light source–positive areas
Secretions and stains
Potential saliva/semen (per history)
Swab collection sites (evidence and controls)
Indicate any site where moist swab collection occurred

BOX 64-5 Information to Document on Standard Evidentiary Label

On each item in the rape kit:
Full name of patient
Medical record or case ID number
Date of collection
Time of collection
Brief description of item with sampling site
Initials of the examiner

BOX 64-6 CHAIN OF CUSTODY

Record of signatures, dates, and times that:
- Document handling, transfer, and storage of evidence from the time of collection
- Provide sequential accountability of everyone who handled the evidence
- Document the location of the evidence at all times
- Ensure there has been no tampering, alteration, or loss of evidence prior to trial

For all transfers of evidence, documentation should include:
- Signature of person transferring custody
- Signature of person receiving custody
- Date of transfer
- Time of transfer

Documentation is written on sealed and packaged kit

BOX 64-7 WOOD'S LAMP AND ALTERNATE LIGHT SOURCE (ALS)

Wood's Lamp

Screening tool for detection of stains, secretions, and injuries
Long-wave UV light (310–400 nm)
Dried semen will usually fluoresce bright green/yellow or white
Moist semen fluoresces poorly or not at all
Other body fluids and substances may be seen
Room must be dark to use

ALS

High-intensity, tunable light source
Uses four narrow bands: 450, 485, 525, and 570 nm
Two wide bands: white light, all wave lengths <530 nm
Colored goggles used to block the reflected light and pass only the fluorescent light
Because of absorptive differences between normal and damaged tissues can detect injuries not seen with the naked eye
More accurate for certain body fluids and substances than Wood's lamp

be inspected, collected, and photographed. A Wood's lamp or alternate light source should be used to detect dried secretions and to document the findings (Box 64-7).

The SAV should undress on the large square of paper from the rape kit after removing shoes. Another sheet of paper should be placed underneath this square to prevent contamination from the floor. The square paper is used to catch trace evidence and should be folded carefully and placed into evidence.

When the SAV is undressed, the FE uses the Wood's lamp or ALS over the body and documents positive fluorescence. Dried secretions should be removed with a cotton swab moistened with sterile, distilled water. If one side of the swab is flattened and only that side is used to collect the specimen, the material is effectively concentrated. Conversely, wet secretions should be taken in the same manner using a dry swab. Swabs should be taken from areas of contact indicated by the SAV, even if there is no fluorescence or crusting seen. A double swab technique is used to collect saliva from skin (Box 64-8).[61] Bite marks need special attention (Box 64-9).[62] Control swabs should be taken in areas adjacent to the material removed and

BOX 64-8 DOUBLE SWAB TECHNIQUE FOR THE RECOVERY OF SALIVA FROM HUMAN SKIN

First swab: completely wet with sterile distilled water
- Roll over the surface of the skin using moderate pressure and circular motions.
- Rotate swab on long axis to assure maximal contact.
- Air dry completely (≥30 min).

Second swab: used dry
- Apply with the same action as above to pick up all the moisture left behind.
- Allow to dry completely (≥30 min).

Label each and submit with other evidence.

BOX 64-9 COLLECTION OF BITEMARK EVIDENCE

Take an orienting photograph before swabbing.
- Then be certain to take close-up photographs, and use a scale
- If the bite mark is on a rounded surface, you will need more than one photograph to avoid distortion.

Notify law enforcement immediately, so that they can contact a forensic odontologist who may take additional photographs and collect impressions.
Serial photographs are recommended at 24-hour intervals for up to 5 days.
Use the double-swab technique to obtain saliva sample.

labeled as such. All swabs should be dried in a stream of cool air at least 60 minutes before packaging. Swab-drying machines are available with locks to facilitate this process. To prevent contamination, only one person's evidence should be in the dryer at a time, and the drying chamber should be cleaned after each use with a 10% bleach solution. The location of all foreign material should be documented on the body diagrams and packaged in the standard fashion. Fingernail clippings or scrapings should be collected according to local custom and only if there is historical relevancy. All preexisting injuries and acute trauma need to be documented in the report.

Diagrams of the body should be large enough to allow documentation to remain clear. If need be, copies of the state/local diagrams should be available in full-page format to accomplish this. The documentation process in some states is artistic, which means the FE draws the injury on the diagram. California has switched to a purely descriptive approach for uniformity and clarity (see Fig. 64-1).

Head, Neck, and Oral Cavity

In examining the head, neck, and oral cavity, special attention should be given to the integrity of the frenula, buccal surfaces, gums, and soft palate. The SAV should not be allowed to eat or drink before this examination. If the SAV gives a history of oral copulation with ejaculation, then the upper and lower lips should be wiped using two moistened swabs. Next the examiner should swab from the gum to the tonsillar fossae, the upper first and second molars, behind the incisors, and in the fold of the cheek. If more than one swab is used to swab these areas, each should be labeled appropriately. Lastly, using a 16-inch piece of unwaxed floss, with two knots tied about 2 to 3 inches apart in the center of the floss, the SAV should floss her teeth using only the section between the knots. While flossing, the patient should lean over a clean 8 × 10 piece of

paper to catch any debris. The paper and floss are dried and bundled together. If the SAV is unable to use the floss, the examiner, wearing gloves and goggles, can perform this procedure.[63]

Hair matted with secretions or debris should be cut out and packaged. Signs of manual or ligature strangulation may include neck injuries with petechiae of the skin and conjunctiva. Reference samples for head hair and saliva should be taken according to local custom, including buccal swabs made for DNA analysis. Reference standards are used to determine whether the evidence specimens are of victim origin or are foreign. Additionally, they may help identify or eliminate potential suspects.

Anogenital Examination

The anogenital examination should begin with gross visualization of the inner thighs, external genitalia, and perineal area and anus, followed by Wood's lamp or alternate light source visualization. All trauma, secretions, and foreign material should be noted and appropriately handled. Gross visualization yields positive findings in 20 to 30% of cases (range 5–65 %).[11,28,30,51,52,56,64] Genital trauma associated with SA is considered to be a mounting injury because it occurs at the point of first contact of penis to vagina. This area, the posterior fourchette (soft tissue) or the perineal body (the juncture of the tendons of the superficial transverse perineal and the bulbocavernosus muscles) is inherently weak, and continued pressure will result in tearing. The position of restraint, male straddling female, will also effectively prevent the victim from accommodating the erect penis. The angle of the erect penis is not the same as the angle the vagina makes with the vestibule (approximately 45 degrees). Moreover, the vagina is considered a potential space. The lateral walls are more rigid than the anterior and posterior walls, so that in its normal state the anterior wall is collapsed onto the posterior wall; hence the use of the speculum to lift the anterior wall during the gynecologic examination.[65] During voluntary intercourse, the changes that occur with sexual stimulation, the human sexual response, remove these normal anatomic barriers and the female voluntarily tilts her pelvis.[66]

Typically, genital injury involves more than one site, is external, and is located posteriorly between 3, 6, and 9 o'clock (Fig. 64-2). The posterior fourchette is the most common site of injury.[11,13,21,22,52] Injuries are usually the result of blunt force trauma, which produces tears, ecchymosis, abrasions, redness, and swelling. The latter two may be difficult to recognize without a follow-up examination, and some investigators have suggested not reporting redness or swelling if a second examination is not performed.[13] Hymenal trauma is not the first site of injury, as myth would have it. Hymenal trauma is more common in adolescents and those without sexual experience.[13,22,51,52] Genital injury shows consistent topologic features, varying with the site and nature of the tissue. Tears are most commonly seen in the posterior fourchette and fossa navicularis. Abrasions typically occur on the labia minora. The hymen usually sustains damage in the form of ecchymoses or tears.[21,22]

Many factors affect the prevalence of genital injury, and the FE should be familiar with them (Box 64-10). Even though genital injury is statistically significantly associated with a history of nonconsent, the FE should not forget that genital trauma is not inevitable. Colposcopic magnification should be employed to photodocument these areas and to better identify the type of trauma seen. Colposcopy has been the standard of care and is the best method for determining genital injury.[67,68] Currently, many centers are using digital photography and videography with excellent results and less cost. Certain environmental factors have been identified with colposcopically recognized genital changes; this is particularly true with intravaginal findings (Table 64-2).[69] Frequently, trace evidence is seen only with the colposcope. We use adhesive note paper (Post-It) to capture such tiny particles while visualized under the scope. The Post-It is then folded and inserted into an envelope. Examiners should check with their local crime laboratory to see if this methodology is acceptable. Pubic hair brushings are collected by placing a sheet of paper under the patient's buttocks and brushing the pubic hair downward. The paper and brush should be bundled together and packaged. A pubic hair standard may be obtained according to local custom.

A warm speculum moistened with water should then be inserted into the vagina. Inspection of the vagina and cervix should be performed first grossly, then with colposcopic

BOX 64-10 Correlates of Genital Injury Found at Time of Sexual Assault Examination

Time to examination*
Nongenital injury is associated with genital trauma
Penile penetration
Sexual inexperience and hymenal tearing
Postmenopausal
History of anal contact
History of stranger assault
History of nonconsensual intercourse
SAV use of alcohol
SAV college graduate

*Increase in time since injury decreases likelihood of findings; other factors listed increase the likelihood of physical findings at time of sexual assault examination.

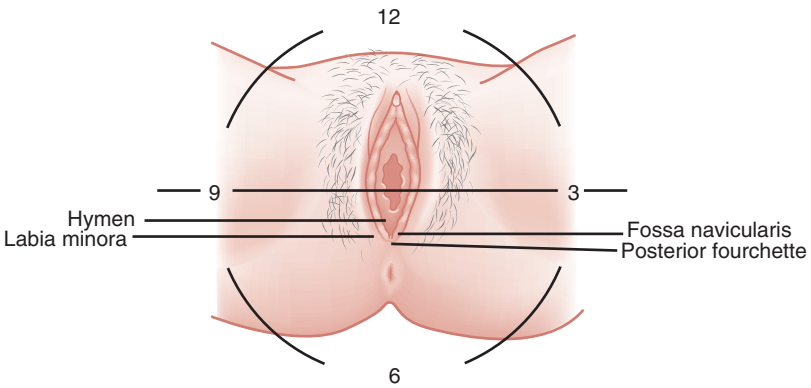


Figure 64-2. Typical genital injury between 3, 6, and 9 o'clock.

Table 64-2 Environmental Factors Associated with Intravaginal Epithelial Changes Seen with Visual Inspection, Colposcopy, or Acetic Acid Application

FACTOR	FINDINGS
Smoking	Edema, erythema, petechiae, abrasion
Tampon use at the time of examination	Erythema, petechiae, abrasion
Speculum manipulation	Laceration
Consenting intercourse	Erythema, petechiae, abrasion, ecchymosis
Herpetic infection	Microulcerations

Table 64-3 Maximum Reported Time Intervals for Sperm Recovery

BODY CAVITY	MOTILE SPERM	NONMOTILE SPERM
Vagina	6–28 hr	14 hr–10 days
Cervix	3–7 days	7.5–19 days
Mouth	—	2–31 hr
Rectum	—	4–113 hr
Anus	—	2–44 hr

Table 64-4 Factors Influencing Loss of Sperm and Seminal Fluid

FEMALE FACTORS	MALE FACTORS
Prior trauma to birth canal	Condom use
Lost upon withdrawal of penis	Vasectomy
Vaginal hygiene (e.g., douching, wiping)	Azoospermia
Repeated penile thrusting	Drug and alcohol abuse
Penis remains in the vagina after coitus	Sexual dysfunction
Change of posture	Failure to ejaculate

photography. If the SAV reported bleeding, the source needs to be determined. Bleeding is commonly associated with hymenal, vaginal, or combined tears. Swabs from the vagina and cervix should be obtained, air-dried for 60 minutes, and packaged. Cervical specimens augment those from the vaginal pool because the cervix acts as a reservoir and provides evidence of seminal products for longer periods of time[70] (Table 64-3). To check for motile sperm, the FE should inspect a wet mount slide. This method is useful because it gives a time frame for the assault, and sufficient numbers of sperm (60–100) allow for identification of a suspect. Semen is found about 50% of the time.[71] The FE should communicate this information to the investigator as soon as possible. The wet mount slide is then dried and prepared for deposit into the rape kit. Aside from time and site of deposition,[72–74] female and male factors influence the ability to find semen (Table 64-4). Typically, a bimanual examination is not performed.

A rectal examination is performed if indicated by the history. Because SAVs are reluctant to report this type of activity, however, the FE should always inspect the anus for signs of injury and reinquire about anal contact. Asking the patient to bring her knees up to her chest allows this examination to be done easily and quickly. If trauma is seen or the history suggests anal penetration, rectal bleeding, or that a foreign object was used in the assault, a rectal examination, including anoscopy, should be performed. To avoid contamination with vaginal secretions, the perianal region is swabbed thoroughly with a moistened swab or 2×2 gauze, which is dried, labeled, and included in the rape kit. This procedure should be done after all vaginal samples, external secretions, and foreign material have been collected. A warm water–moistened anoscope is used to perform the procedure. The examiner observes grossly, colposcopically, and photographs are taken. Swabs are collected under direct visualization beyond the tip of the scope. The source of any bleeding needs to be determined.

Special Staining Techniques

The use of special staining/lubrication techniques should be reserved until all photography and specimens are collected. On areas that are painful, 2% lidocaine gel can be used to obtain better visualization and pictures. Toluidine blue dye is a nuclear stain that has been shown to enhance gross visualization of external genital (vulvar) injuries (Fig. 64-3). Toluidine blue dye has some spermicidal activity[75] and was shown, in one small study, not to influence DNA analysis.[76] Stain results depend upon the presence or absence of a nucleated cell population at the exposed surface. Positive stain results can be seen with trauma, cancer, and areas of inflammation with a nucleated cellular infiltrate. Acutely, with tissue swelling and transudation, the dye may lift off quickly. Twenty-three categories of benign disease, along with columnar epithelium, and mucus will take up this stain.[77] Toluidine blue dye is nonspecific and should be used to enhance trauma seen with the colposcope or as an adjunct for gross visualization. It should not be used to date injuries. Diffuse staining or patchy uptake should not be reported.[78] Uptake should not be reported when no findings are seen with colposcopy.[67]

Photographic Documentation

Photodocumentation has become the standard of care. It eliminates the problem of hyperbole and understatement in the FE's description and allows the court to see a visual representation of findings on examination. Importantly, photodocumentation makes each case available for peer review and consultation, alleviating the need for repeated examinations by defense experts.[79] The entire examination should be photographically documented if at all possible, not just the positive findings. All photographs should be correctly labeled to show patient identification, date, time, and examiner. Frequently this information can be combined with a color guide and ruler. Jurors usually want to know how pictures are identified. The FE should develop a standard photographic technique, making certain that the plane of the film is parallel with the injury to minimize distortion. Photos of skin are enhanced if the background is blue or green because the automatic lens adjusts according to the lightest part of the picture. The examiner should take pictures of lesions first without magnification, then take closer views as needed. The full extent of the injury needs

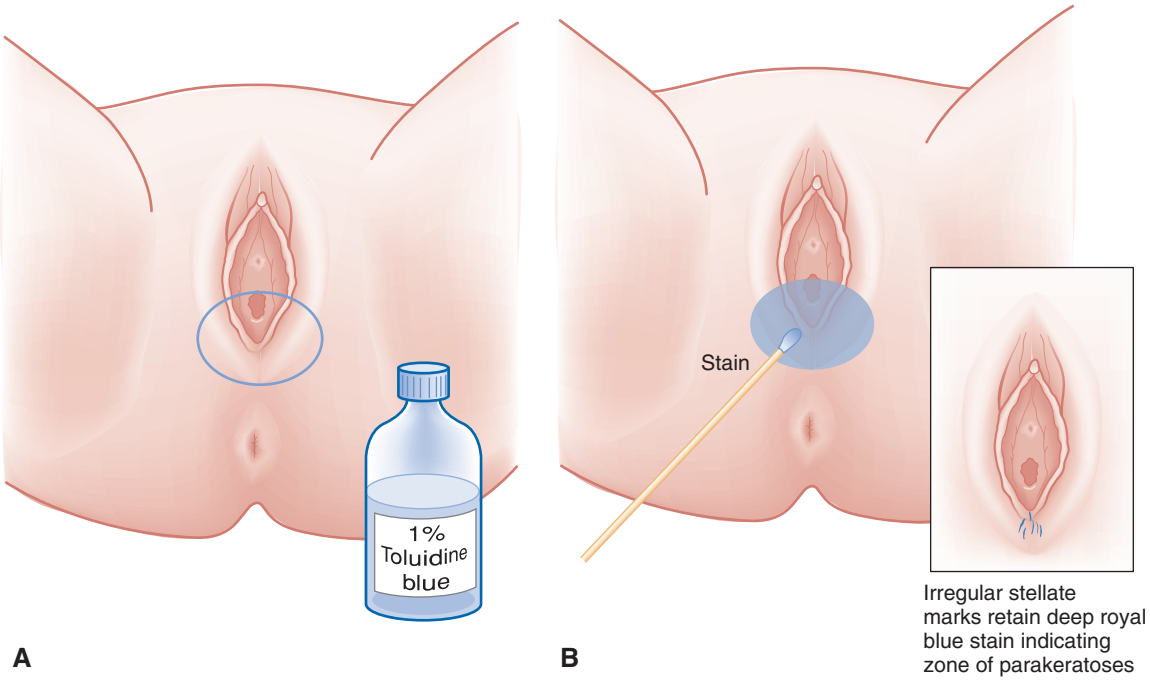


Figure 64-3. Application of toluidine blue dye with example of results.

to be captured. Using magnification usually requires more than one shot. The examiner should take many pictures because he or she has this opportunity only once (Box 64-11 outlines tips on performing photographic documentation in SA cases). Pictures are also a concern for SAVs. Most SAVs worry about where the pictures are kept and whether their name will appear on the pictures. Keeping the SART record separate from the medical record is reassuring. Some groups go a step further and separate the pictures from the written reports.

SEXUALLY TRANSMITTED DISEASES AND PREGNANCY

The risk of acquiring an STD after an SA is small but will vary by region and number of assailants (Table 64-5).[80] Testing for STDs is expensive, requires a reassessment of the patient, which is often difficult, and has no forensic value. Most protocols no longer require or pay for this type of assessment. Additionally, many SAVs have preexisting STDs. Most providers prefer preventative therapy (Box 64-12),[81–83] and it offers the SAV the psychological benefit of immediate protection from infection. For updated information and alternative therapies for patients who are pregnant or have specific allergies, the physician can consult www.cdc.gov and enter "std treatment." The efficacy of these regimens in preventing gonorrhea, trichomoniasis, bacterial vaginosis, and *Chlamydia trachomatis* genitourinary infections after SA has not been evaluated. The FE should counsel patients about the possible toxicity of any regimen; gastrointestinal problems are especially common, and the FE should consider antiemetic medication, particularly if emergency contraception is also prescribed. All patients should be advised to abstain from alcohol for 24 hours after metronidazole use and from sexual intercourse until the treatment is completed.[83]

Hepatitis B

Hepatitis B vaccination, without hepatitis B immune globulin, is recommended for those SAVs who are unimmunized (Box 64-13). Risk factors for hepatitis B virus include multiple sexual partners (more than one sex partner in a 6-month period), a recent history of an STD, men who have sex with men, correctional facility inmates, and intravenous drug users. Currently, testing to determine antibody levels in immuno-

BOX 64-11 TIPS IN PHOTODOCUMENTATION OF SEXUAL ASSAULT FINDINGS

Lens
Best all around for photographing bodily injury macrolens with focal length 100–105 mm.

Documentation
Do not photograph more than one victim per roll.
Begin each roll with facial shot and ID number.

Technique
Background
- Avoid clutter.
- Avoid reflective or bright background.
- Use blue or green surgical towels for extremity shots.

Positioning
- The plane of the film should be parallel to the plane of the finding.
- For textured findings (e.g., swelling, indentation), take additional shots at a variety of tangential or oblique angles.

Anatomic context and scale
- Every finding should appear in at least three pictures, including a regional shot that orients the viewer to the finding's general location.
- Close-ups should zoom in on the finding with the camera orientation the same as for the regional shot.
- At least one close-up shot should include a scale/color with victim's ID number on it.

Review your photos to make certain you took pictures of all findings and all areas of the anogenital anatomy.

Table 64-5 Risk of Sexually Transmitted Disease after Sexual Assault

Gonorrhea	6–18%
Chlamydia	4–17%
Syphillis	0.5–3%
HIV	<1%

BOX 64-12 CDC Prophylaxis for Sexually Transmitted Disease in Adult SAVs

Ceftriaxone 125 mg IM in a single dose
PLUS
Metronidazole 2 g orally in a single dose
PLUS
Azithromycin 1 g orally in a single dose
OR
Doxycycline 100 mg orally twice a day for 7 days.

BOX 64-13 Hepatitis B Infection Prophylaxis for SAVs

Serologic testing is not required.
Give vaccination if SAV is unimmunized or uncertain.
Follow-up doses should be given at 1–2 months and 4–6 months (total of three doses).

competent persons is not necessary because most fully vaccinated persons have long-lasting protection, and relatively high rates of protection are achieved following each vaccine dose. The FE should give the vaccination even if the completion of the series is not assured.[83] Note that some protocols may not cover this cost.

Human Immunodeficiency Virus

Although HIV exposure is of great concern to SAVs, the risk of seroconversion is likely low. The risk for HIV transmission is 0.1 to 0.2% for consensual vaginal intercourse and 0.5 to 3% for receptive rectal intercourse, with transmission rates from oral sex substantially lower. The FE needs to be familiar with the local epidemiology of HIV and acquired immunodeficiency syndrome; state guidelines for postexposure prophylaxis for SAVs, if any; the nature of the assault; and any HIV risk behaviors exhibited by the assailant, such as high-risk sexual practices or injection drug or crack cocaine use. Specific circumstances affecting the SAV and assailant, if known, can increase the probability of transmission (Table 64-6). The rate of HIV transmission in SA is likely to be higher than in consenting intercourse because of the possible presence of genital trauma. The effectiveness of postexposure prophylaxis is based solely on the treatment results of health care workers who have had occupational exposure, and these data have been extrapolated to SAVs. The Centers for Disease Control and Prevention recommends that therapy be considered in cases in which the risk for HIV is likely high and that all such cases are referred for consultation with an HIV specialist. Costs may not be covered by local protocols, and postexposure prophylaxis needs to be provided in the context of a comprehensive counseling, treatment, and follow-up program. To maximize the likelihood of success, therapy should be initiated as soon as possible or up to 72 hours following the assault, so that expeditious referral is prudent.[83]

Table 64-6 Factors Influencing the Probability of HIV Transmission

SAV FACTORS: SUSCEPTIBILITY	ASSAILANT FACTORS: INFECTIOUSNESS
Type of sexual contact* anal > vaginal	Presence of foreskin*
Presence of STDs*	Late stage of infection*
Presence of genital lesions*	Primary HIV infection*
Presence of genital/anal trauma*	Viral load in the genital tract*
Exposure to ejaculate on mucous membranes*	Presence of STDs or genital lesions*
Cervical ectopy*	Antiretroviral therapy†
Contraceptive method	Multiple offenders*
Barrier†	Offenders with history of incarceration, homosexuality, or bisexuality*
Intrauterine device§	
Nonoxynol 9†	
Pills‡	
Menstruation*	
Currently pregnant§	

*Increased probability.
†Decreased probability.
‡Evidence to support both increased and decreased probability.
§Unknown effect.
STD, sexually transmitted disease.

Assistance with postexposure prophylaxis decisions can be obtained by calling the National Clinician's Post-Exposure Prophylaxis Hotline (PEPLine), telephone: (888)-448-4911.

Follow-up Testing

For SAVs who do not want postexposure prophylaxis, repeat HIV testing is recommended at 6 weeks and 3 and 6 months. If a suspect is apprehended, HIV testing can be done with his consent or a blood sample held and tested at a later date after a court order has been obtained on the victim's behalf. Some states permit testing of the suspect at the victim's request in cases of SA. Many protocols do not require serologic testing and do not cover this cost.

Pregnancy Prophylaxis

There is a 2 to 4% risk of pregnancy from random unprotected intercourse; this figure reaches nearly 50% in women 19 to 26 years old, who are at their most fertile period, when combined with midcycle exposure. Before any medication is given to an SAV, pregnancy testing should be done. This includes patients already taking oral contraceptives, those fitted with an intrauterine device, or those who have undergone tubal ligation. The immediate use of an emergency contraceptive can reduce the risk of pregnancy to 1 to 2%. Its effectiveness depends on the regimen used and the time interval between exposure and treatment (Table 64-7). Data show that an emergency contraceptive should be offered up to 5 days after unprotected sex. There are no absolute contraindications to the use of hormonal emergency contraception, even for women who have contraindications to the long-term use of combination hormonal contraception. In those who have active migraine headaches with neurologic symptoms or a history of stroke, pulmonary embolus, or deep vein thrombophlebitis, progestin-only emergency contraception or the insertion of an intrauterine device should be considered first. The latter device offers the advantage of up to 10 years (depending on the device) of effective contraception.[84] Evidence suggests that there is not an increase in ectopic pregnancy with emergency contraceptive

Table 64-7 Types of Emergency Contraception

CLASS	DOSE	BRANDS	COMMENTS
Combined oral	100 U of ethinyl estradiol + 0.5 mg levonorgestrel twice 12 hr apart	Preven Ovral*	Decreases risk to 2% 50% nausea 20% emesis Requires antiemetic
Progestin only	1.5 mg levonorgestrel once or 0.75 mg twice 12 hr apart	Plan B	Decreases risk to 1% 22% nausea 8% emesis Effective up to 5 days FDA approved OTC 2004
Copper T intrauterine device		ParaGard T 380A	Decreases risk to 0.1–0.2% Indicated for postcoital period >72 hr Effective up to 5 days
Antiprogestins	10 mg of mifepristone	RU-486	Decreases risk to 1.5% 19% nausea 4.3% emesis Effective up to 5 days

*Other hormonal contraceptives that are useful can be found at www.not-2-late.com
FDA, U.S. Food and Drug Administration; OTC, over the counter.

use. Although there are no studies large enough to quantify the teratogenicity of hormonal emergency contraceptives, no increase in birth defects has been detected among infants exposed to daily oral contraceptive use.[85–88]

DEBRIEFING

Regardless of any physical injury, psychological distress is always present following an SA, and the FE needs to acknowledge that from the beginning of the examination. Establishing a quiet and calm place for the examination and evidence collection reassures the SAV and gives back to her a sense of control and safety. At the termination of the examination, the FE should spend time reviewing the physical and genital injuries and address modes of therapy as appropriate. The examiner should discuss any pending laboratory data and how results will be communicated (phone, written, or both) with the SAV. The method of communication should be acceptable to the SAV. The examiner should review all medication and vaccinations (e.g., tetanus), discuss side effects, and provide contact phone numbers in case of problems or questions. The examiner should review the common psychological problems (Box 64-14) and reinforce the need for counseling. The advocate who has been present during the examination can be a personal contact already established with the SAV. Nonetheless, contact numbers for rape crisis, local crisis intervention, social services, drug and alcohol services, HIV services, and emergency psychiatric services should be reviewed in detail, and all referrals should be discussed prior to departure. Compensation for victims of crime should be discussed and appropriate referrals made.

A forensic follow-up examination of all patients with genital injury should be scheduled.[83,89–91] This examination is particularly important for SAVs with genital injury. It documents the healing of injury and differentiates those findings that can be confused with trauma, such as hypervascularity, telangiectasis, and cherry red spots.[22,79] Its utility extends to nonspecific injuries such as swelling or redness, which are difficult to detect and create frequent interobserver disagreements.[13] This examination also gives the FE an opportunity to review any problems and encourage counseling, if it has not already begun. All of these plans should be in written format because most SAVs do not remember what is said during a time of crisis.

BOX 64-14 RAPE TRAUMA SYNDROME

Acute Phase
Expressed
- Crying
- Anger
- Restlessness

Controlled
- Calm, quiet
- Emotionless

Somatic and emotional reactions are prominent
- Increased muscle tension
- Headaches
- Genitourinal disturbances
- Fear/guilt
- Fatigue
- Gastrointestinal disturbances
- Anger/self-blame

Outward Adjustment Phase
Alteration of daily routines
Change of residence
Change of phone numbers
Seeking family support (often without giving reason)
Fears and phobic reactions
Daytime anxiety
Nightmares

Integration Phase
Survivor accepts the rape as part of her life
Survivor begins to integrate the crisis into her life experiences

ELDERLY VICTIMS

Two to six percent of all SAVs are over 50 years of age. The risk of being sexually assaulted or physically assaulted is further increased for homeless women in this age group.[92] Older women are less likely to report sex crimes due to self-blame and humiliation. The asexual stereotype attributed to them by family, caretakers, and other professionals often prevents detection. While most elderly SAVs present within 72 hours, delayed reporting is seen. This is especially true when the perpetrator

is a caregiver.[93,94] In 2005, A Perfect Cause, advocates for disability and elder rights, documented that 795 registered sex offenders were living in long-term care facilities and 5 were employees.[95] Elder SAVs present unique challenges to the FE. The history should be expanded to include medical problems, medications, surgical procedures, history of dementia, and neurologic problems. Obtaining the history may be difficult. Some patients may present in a disorganized state without a diagnosis of dementia. Others may have hearing impairment, cognitive disabilities, or psychiatric disturbances; the latter conditions, considered important vulnerabilities, often require special interviewing skills, and the examiner may need to obtain the history from other reliable sources.[96] Positioning should be thoughtfully performed with regard to limitation of motion for both natural and artificial joints and the need to prevent cardiovascular problems that attend anxiety and stress in this frail population. Skin changes related to aging, infection, and trauma can be difficult to discern, and a follow-up examination, including photodocumentation, will help to resolve these important issues.[97] Bruising not may be seen initially.[98]

Usually the SAV lives alone and the assault occurs at her home; the assailant is almost always a stranger. Sexual dysfunction and substance use are commonly seen in these perpetrators, and robbery is often involved. The most common type of assault is penile-vaginal intercourse, and genital injury is more frequent and severe than in younger SAVs, requiring hospitalization and even surgery. Clinically, lacerations, abrasions, and edema to the perineum and vagina are present. Physical restraint is common and usually in excess of what is required for restraint.[99] The aftermath of assault is particularly devastating for this age group. Older adults have high morbidity and mortality rates, even when they have sustained relatively minor injury; this may be attributed to concurrent medical conditions, decreased physiologic reserve, or adverse reactions to and between medications. Psychologically, post-traumatic stress with subsequent illness is more frequent and severe and leads to diminished functional capacity; this is devastating to this population, in which resources and support are limited.

MALE VICTIMS

Male SA is vastly underreported. Most victims seen come from institutional settings, with very few indeed from the nonincarcerated population. Factors that act as barriers to reporting this crime include societal beliefs that a man can defend himself and fear that his sexual orientation is suspect. The need to maintain emotional control makes disclosure very stressful. Men need to be accorded the same sensitivity and support as their female counterparts.[100]

Except for their anatomic differences, the procedures for the history, physical examination, evidence collection, and medical treatment are the same. Certainly, because of the typical location of injuries, some researchers have emphasized the increased risk of exposure to HIV, hepatitis B, and hepatitis C.[101] Some notable differences in the assault characteristics from those seen in female victims include a predilection for anal and oral sexual contact, with subsequent injury seen in 50 to 67%, more common use of the prone position during the assault, a higher incidence of nongenital trauma (80% in one study), use of a weapon, assault by a stranger or multiple assailants, and a history of abduction. Injuries to the penis and scrotum occur less often and may be the result of a non–sexually related injury (e.g., kicks).[102] In one study, the use of colposcopy, in addition to anoscopy, allowed the discovery of increased physical examination findings in men. As with female SAVs, colposcopy is recommended because of its additional utility for photodocumentation and collection of trace evidence.[103]

MALE SUSPECT EXAMINATION

The importance of the male suspect examination should not be overlooked. The SAV and suspect are the two pieces of the forensic puzzle in an SA. If they are evaluated and treated in the same location, it is critical that they not come in contact with each other. Expectations about this examination should be tempered by the FE's knowledge of the suspect's rights and the time elapsed between the assault and the examination. Presumed innocent, the suspect should be handled with the same courtesy and respect as any other patient.

If the FE is the same for both SAV and suspect, the examination is facilitated by the examiner's knowledge of the SAV's history. If a different examiner is used, he or she should know the history as given by the victim, and this usually can be obtained from law enforcement. The history obtained from the officer is *not* the history that is recorded on the suspect evaluation form. The history on the examination form should come from the suspect, but he has the right to remain silent on the events surrounding the assault. If, after understanding his rights, he chooses to give information about the events under inquiry, the examiner should have him sign the consent and record his statements on the suspect form. Most suspects will voluntarily give this information. For suspects in custody, the consent is not necessary because state law provides for the collection of perishable evidence. The FE should be knowledgeable about local laws, and a protocol should be developed to handle suspects who resist the collection of evidence. The interview and examination, for security reasons, are performed with law enforcement present at all times. The FE needs to record suspect statements verbatim, using quotation marks just as is done with the SAV. Medical information about preexisting conditions and hygiene is focused upon factors that could influence interpretation of current findings. If there is a history indicating the possible transfer of biologic material between the SAV and suspect, appropriate specimens should be collected irrespective of hygiene or timing.

The physical examination follows the same format as the SAV examination. Injury to the suspect occurs less often than to the SAV; however, swabs of the penis, including the glans, shaft, base (but excluding the urethral meatus), scrotum, and sulcus of the foreskin, if present, are taken. In contrast to the SAV examination, identifying features such as tattoos and scars should be noted and documented photographically. Reference samples, including blood, saliva, and hair, should be taken in accordance with local protocol. Typically, STD cultures and serology are performed, although they may not be required or paid for in current state protocols, and information about pending results and treatment is given as indicated.

KEY CONCEPTS

- The role of the FE is to provide a thorough examination as the basis for a report.
- Physical examination findings should be accurately, reliably, and clearly documented.
- The SAV should be offered emergency contraception and prophylaxis for sexually transmitted infection, including hepatitis B and in select cases HIV.
- Ultimately, the FE should be able to report findings and medical information in an understandable format for the court.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 65

Intimate Partner Violence

Deirdre Anglin and Connie Mitchell

PERSPECTIVE

Background

Emergency medical specialists, by nature and by necessity, focus their problem-solving skills on the presenting health complaint or bodily symptom that motivated the patient to seek relief at that particular moment. In the case of intimate partner violence (IPV), such focus may lead to blinding tunnel vision and missed opportunity to lift the veil of shame and empower a victim to consider options to reduce future harm and restore emotional and physical well-being. Most physicians, especially the younger ones, consider partner violence in the differential diagnosis of a physically injured woman. IPV is a shame-based disease not readily disclosed or discussed with the health provider, let alone anyone else. Patients who present acutely with an IPV injury represent the "tip of the iceberg." Emergency physicians are probably treating many more victims of IPV who present for other problems that may actually be comorbid to IPV or are complications of prior physical, sexual, or emotional abuse. The portion of the iceberg beneath the water level is the most dangerous—the breadth of its menace is difficult to ascertain, yet the urgency to safely navigate the turbulent waters is paramount. The intent of this chapter is to educate emergency medicine specialists about the health problem of IPV so that they can move beyond the obvious and improve IPV identification, facilitate earlier intervention, and reduce morbidity and mortality for victims and their children.

Epidemiology

Definition and Types of Intimate Partner Violence

In 2002, the World Health Organization (WHO) declared that "violence is a leading, world-wide public health problem" and then further declared that violence is not an intrinsic part of the human condition and it can be prevented. Gro Harlem Brutland, the Director General of the WHO, wrote, "to many people, staying out of harm's way is a matter of locking doors and windows and avoiding dangerous places. To others, escape is not possible. The threat of violence is behind those doors—well hidden from public view."[1] The WHO report distinguishes three general categories of violence—individual, interpersonal, and collective—and then further divides interpersonal into familial or stranger violence. IPV is a form of interpersonal, familial violence (Fig. 65-1).

Intimate partner violence has been defined by the Centers for Disease Control and Prevention (CDC) as the threat or infliction of physical or sexual violence by a current or former adolescent or adult intimate partner or spouse. This violence is often accompanied by psychological abuse.[2] The physical, sexual, and psychological forms of IPV occur as a pattern of assaultive and coercive behaviors. Physical violence consists of behaviors such as pushing, hitting, slapping, punching, kicking, biting, burning, strangulation, using objects and weapons, and controlling access to health care, medications, food, or shelter. Sexual violence includes behaviors such as forced sex, coerced sex with a partner or other persons, violence in association with sexual assault and rape, preventing the use of birth control, and refusing to use condoms to prevent the transmission of sexually transmitted infections and HIV. Psychological abuse includes behaviors such as intimidation, degradation, humiliation, isolation from family and friends, violence or threats of violence against family members, stalking, attacks against pets, destruction of property, controlling access to food, shelter, clothing, transportation, and money, and controlling employment and social or professional activities.

In the past, IPV has been referred to by a number of different terms. These include domestic violence, spouse abuse, wife abuse, battering, battered woman, and wife beating. However, the use of the term *intimate partner violence* is recommended as it is a more inclusive term and applies equally to adolescents and adults, females and males, opposite- and same-sex intimate partners, married and unmarried individuals, and current and former intimate partners.

State penal codes may utilize slightly different definitions of IPV from those of the CDC, especially as pertain to the nature of the relationship between the two individuals, and the forms of abuse that have transpired. In addition, the term domestic violence is generally used by the criminal justice system when referring to partner violence.

Prevalence

There are numerous population-based and health care–based studies that report prevalence rates of IPV victimization. Due to the different types of IPV (i.e., physical, sexual, psychological/emotional), the pattern of the violence (i.e., first episode, ongoing, intermittent, previous experience), and the population being surveyed, the reported IPV victimization prevalence rates vary widely. The prevalence of IPV victimization is often expressed as either a 1-year prevalence (the proportion

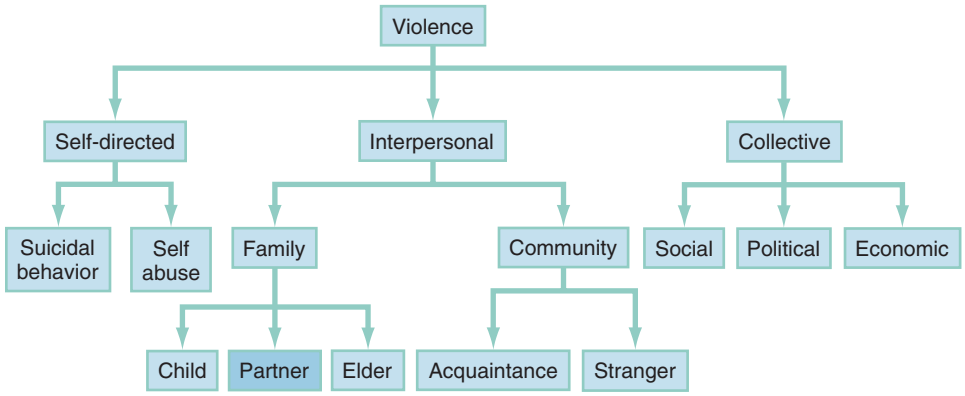


Figure 65-1. World Health Organization categories of violence.

of the population experiencing IPV in the past year) or as a lifetime prevalence (the proportion of the population who have ever experienced IPV). In order to fully understand the meaning of reported IPV prevalence rates, or to be able to compare IPV prevalence rates between studies, one should look at the population being studied, the types of abuse being measured, and the period of time being studied. The variation in research methodology between studies makes IPV surveillance challenging. In an attempt to improve IPV surveillance, the CDC published recommended uniform definitions and data elements for IPV research.[2]

The National Crime Victimization Survey (NCVS) and the National Violence Against Women Survey (NVAWS) are two large population-based surveys. In the NCVS, a randomized telephone survey of 42,000 households and 76,000 males and females 12 years and older, 20% of violent crime against women was IPV and 85% of IPV victims were women.[3] In the NVAWS, a random telephone survey of 8000 men and 8000 women 18 years and older, 22% of women and 8% of men reported being physically or sexually assaulted by an intimate partner during their lifetime; 1.5% of women and 0.9% of men reported being physically or sexually assaulted by an intimate partner within the previous year.[4] According to the NVAWS, women in same-sex relationships reported lower rates of IPV (11%) than women in opposite-sex relationships (20%). On the other hand, men in same-sex relationships reported increased rates of IPV (23%) compared to men with female partners (8%).[5]

The prevalence rates of IPV among emergency department (ED) patients are greater than those of population-based studies. While numerous IPV prevalence studies have been conducted in the ED, they are difficult to compare due to differing methodologies. The majority of ED-based studies have examined IPV prevalence rates among women. In general, ED-based studies report the incidence of acute abuse, 1-year, and lifetime prevalence rates. Based on several ED-based surveys, 1 to 7% of all adolescent and adult females who presented to the ED did so on account of an acute episode of physical abuse.[6] Moreover, 14 to 22% of all female patients in the ED disclosed that they had experienced IPV in the prior year.[7,8] The lifetime prevalence of IPV among female ED patients may be as high as 54%.[9] Few studies have investigated the prevalence rate of IPV among male ED patients, and those that did did not consider whether the relationship was homosexual or heterosexual IPV, did not specify whether injuries were sustained in the course of partner retaliation, defense, or retribution, and did not differentiate the force used and nature of injuries sustained.[10,11] The chief concern in comparing male and female victimization is that the dynamics of the abuse may be very different.

Health care providers (HCPs) will care for fatal or near-fatal cases of IPV in the ED, although the relationship between the victim and perpetrator may not be apparent at the time. Two studies found that up to 43% of female homicide victims had presented to an ED within the 2 years prior to their deaths.[12,13] According to the Federal Bureau of Investigation, 60% of fatal IPV victims are women, and 34% of women are killed by an intimate partner.[14] Unfortunately, in most homicide cases, the relationship between victim and perpetrator is never determined.

Finally, the annual economic cost to society in the United States is estimated at $8.3 billion dollars, in 2003 U.S. dollars, for direct medical and mental health services as well as lost productivity.[15] In one study, Wisner found that women patients experiencing IPV cost their health care plan $1775 more annually compared with the general female enrollees.[16] Other studies found that women patients with documented IPV have higher health care utilization and costs than those without IPV.[17,18] Rivara's research showed that even 5 years after abuse, IPV patients' health care costs were 19% higher than those of nonabused women.[19] Further, higher health care utilization and costs were seen in children whose mothers experienced IPV, even if the abuse ceased prior to their birth.[20]

Risks for Victimization

A few individual factors have been identified that appear to place persons at risk for IPV victimization: gender, age, exposure to violence in family of origin, use of alcohol, and being physically or mentally disabled. Most victims of IPV are young women, usually less than 35 years of age,[21] and single, separated, or divorced. Violence in the family of origin, such as witnessing IPV between caretaking adults, is one of the primary risk factors for victimization,[22–24] but direct childhood physical or sexual victimization also has been linked with adult IPV victimization.[23] Alcohol use also plays a role in both victimization and perpetration of violence, probably due to its disinhibitory effects. In Caetano's study, 30 to 40% of men and 27 to 34% of women arrested for IPV perpetration were drinking at the time of the event.[25] If men were drinking at the time of the physical assault, female victims were more likely to sustain a serious physical injury.[26,27] Victims with disabilities appear to experience rates of physical and sexual abuse at rates greater than or equal to women without disabilities.[28]

Other factors appear to contribute to the risk for IPV either because they contribute to relationship stress or they heighten victim vulnerabilities. IPV appears to occur at increased rates among relationships with lower socioeconomic status, where the abuser is unemployed or of lower levels of academic achievement.[29–32] Homeless women, in general, have higher

cumulative rates of violence over a life span than women with stable housing,[33,34] and fleeing domestic violent homes has been noted to be one of the causes of homelessness in women.[35] Immigrant women are another vulnerable population, and while IPV may not be occurring at higher rates among this group than in the native population, they may be reticent to disclose IPV, fearing deportation of themselves and/or their spouse. Immigrant women may be further isolated from services due to language barriers, lack of social support, or lack of economic independence.

Certain presentations should provoke consideration of IPV as an underlying or comorbid condition. One presentation is the woman with injuries to the head, face, or neck. According to a study by Ochs, a woman with head, neck, or facial injury was 11.8 times more likely to be a victim of IPV than women who had other types of injuries.[36] Muelleman et al. found facial contusions to be the most common injury type among battered women, with sensitivity of 40.5% but low predictive value.[37] Le et al. performed a retrospective review of patients treated for injuries due to IPV. Eighty-one percent presented with maxillofacial injuries in which the middle third of the face was the most commonly injured area (69%). Facial fractures occurred in 30%, and most of the facial fractures (40%) were nasal fractures.[38]

Another presentation that should prompt consideration of IPV is the female patient who has attempted suicide. Abbott found that among female patients with a lifetime history of a suicide attempt, 81% also had a history of IPV.[9] Over 90% of women hospitalized following a suicide attempt reported current severe IPV.[39,40] In addition, Abbott found that among women patients who abused alcohol, 71% also experienced IPV.[9]

Finally, Warshaw found that 67 to 83% of HIV-positive women patients in a hospital clinic had male partners who were abusive and refused to use condoms.[41]

Risks for Perpetration

Most of the research on persons who abuse their intimate partner is done on men who have committed violence of sufficient severity to have been arrested. While batterers are a heterogeneous group, some researchers have postulated three typologies: (1) the borderline/dysphoric, (2) the antisocial generally violent, and (3) the family only, no psychopathology.[42] The men in the first group, "borderline/dysphoric," are often described as both charming and moody with "Dr. Jekyll–Mr. Hyde" personality changes from one extreme (complacent) to another (rageful). High rates of alcohol and drug use appear in this group,[43] as well as increased contacts with police for violent or disorderly conduct offenses, and increased concerns about rejection or abandonment.[43,44] The antisocial generally violent male is described as "self-centered, self-absorbed and lacking in empathy."[42] Intimate partners are viewed as objects or possessions that serve the perpetrator's needs. While he may appear confident and exciting, he also manipulates and imposes his values on others. Antisocial batterers usually commit both physical and sexual violence that is more severe than the other two types, as well as committing more violence outside the family.[42] The third type is composed of men described as the "guy next door," not violent outside the home but usually with evidence of passive dependency or obsessive-compulsive personality style. They are rigid, rule bound, and conventional, and any deviation from "the rules" can become internalized resentments that occasionally erupt in aggressive outbursts of hostility and violence.

Other factors seem to have some association with IPV perpetration: younger age, lower socioeconomic status, exposure to violence in the family of origin, alcohol abuse, history of traumatic brain injury (anger flares and poorer impulse control), and highly or abnormally spouse-specific dependency.

Risks to Children Living in Intimate Partner Violence Homes

In one study of police responses to IPV, about half the women reported that their children witnessed the violence.[45] In another study of police calls, police or IPV advocates documented that children had witnessed the assault in 76 to 85% of the cases.[46,47] Younger children appear to be more likely to be exposed to the violence, because older children leave when they sense escalation of tension in the home. Children initiate calls to police in about 10% of IPV emergency calls.[48]

Children who live in IPV homes can suffer physically and emotionally, and the health impact can be acute or can lead to long-term health risks. The risk of exposure begins in the prenatal period. Pregnant women who are abused are more likely to smoke, consume alcohol, and use illicit drugs than nonabused pregnant women.[49–51] Pregnant women who experience IPV physical abuse experience miscarriage, premature rupture of membranes, preterm labor, and placental abruption at higher rates than pregnant women who have abdominal trauma due to other causes.[52–55]

Children in IPV homes are at increased risk for direct physical abuse by the IPV abuser and less often by the IPV victim.[56–59] Some state child welfare data have demonstrated that IPV appears to be associated with the most severe and fatal cases of child abuse.[60] Children can also be caught in the crossfire, and one study showed that small children are injured while being held in their mothers' arms while older children get injured during their attempts to intervene.[61]

Of great interest is the neurobiologic impact of exposure to violence at a young age. It has been demonstrated that chronic stress can cause the emotional, more primitive parts of the developing infant or toddler brain to become overly active or reactive to the environment. Stress can affect myelination and synaptogenesis and can result in problems in learning, memory, and behavior.[62]

HCPs who care for victims of violence should recognize the interrelated nature of various forms of violence and abuse. In the case of IPV, when an adult victim is identified, an assessment of the well-being of children should also be done. If the HCP suspects a child is being neglected or physically or sexually abused, there is a good chance that IPV is also occurring. Intervention programs should be prepared to address the health and safety needs of both child and adult victims that may co-occur in one family. Exposure to violence and abuse is a health risk factor that should be routinely addressed in a primary care practice, and emergency HCPs will encounter high rates of exposure in ED pediatric patients. Clinicians should interview older children alone and younger children in the presence of a guardian. Children's medical records can be sealed by court order from a guardian parent if the physician can document sufficient concern for the health and safety of the child.

Special Considerations for Adolescents in Abusive Relationships

In a nationally representative sample of 7500 adolescents who responded to the National Longitudinal Study of Adolescent Health, 12% reported an experience of physical violence in an opposite sex relationship in the previous 18 months. If the question included sexual, physical, or psychological abuse, the rate rose to 32%.[63] In a 2005 survey conducted by the CDC, 9.2% of male and female high school students reported an

episode of dating violence in the preceding year.[64] Higher rates are found in rural populations and when youth from lower socioeconomic groups were surveyed.[65,66] Surveys show that boys and girls both report acts of physical aggression; however, girls report more serious acts such as strangulation or use of a weapon in the assault or rape.[67–70] Girls are more likely to be worried or scared of relationship violence, while boys minimize the psychological impact of the aggression; however, this may be more of an enculturated response than a true reflection of boys' anxiety.[71] Complicating understanding regarding prevalence of relationship violence in teens is the fact that in some states it is reported as child abuse and in others as IPV.

Pregnant teens seem to be a high-risk population for prior exposure to violence. In one study of 724 pregnant adolescents, 12% had been assaulted by the man who had impregnated them, and of those who had experienced relationship violence, 40% also reported experiencing violence by a family member or other relative.[72]

By age 15 years, most males and females have some dating experience, and by age 18, 89% have had dates. Adolescents are more likely to endorse stereotyped gender roles (dominant/aggressive males and submissive/supportive females) and are more likely to interpret jealousy, violence, or controlling behaviors as signs of love or devotion.[73–75] Adolescents are also less likely to disclose abuse to parents from whom they are trying to individuate and separate and less likely to disclose abuse to peers for fear of being considered odd or rejected by the peer group.[76] This stew of vulnerability, immaturity, and privacy places teens at risk for suffering that goes unsuspected and undetected. Homosexual teens have the additional anxiety of being "outed" should they disclose the abuse.[77]

Health professionals should routinely spend time alone with adolescents in the course of the history or physical examination in order to explore health issues such as reproductive and relationship health and prior exposures to violence, threats of violence, or bullying. The health professional should be familiar with the rights of minors regarding confidentiality, state laws regarding mandatory reporting of relationship violence, and sexual assault. Many states have enacted legal exemptions that allow minors as young as 12 years to seek a domestic violence protective order.

■ ETIOLOGY

Intimate Partner Violence Social Ecology Model

In order to prevent IPV or intervene effectively, one must understand its etiology. There are multiple theoretical explanations for why two people who shared some level of affection as dating, cohabitating, or married partners would become emotionally, physically, or sexually abusive relationships. These can perhaps best be organized using the Social Ecology Model that nests individual, family, community, and cultural factors (Fig. 65-2). IPV may arise with multiple factors from various levels or may arise due to one pervasive etiologic force.[78]

The "Individual" layer includes the biologic, ontogenic, or experiential make-up of a person. There appears to be an association between witnessing IPV in one's family of origin and both IPV perpetration and victimization.[78] Being a victim of child abuse also appears to increase the risk of IPV perpetration.[78] There are certain personality psychopathologies that appear more often in IPV perpetrators, such as borderline, attachment, or antisocial personality disorders.[42] A small number of studies have shown a relationship between mild traumatic brain injuries and increased anger and aggression, poor impulse control, and decreasing marital satisfaction.[42]

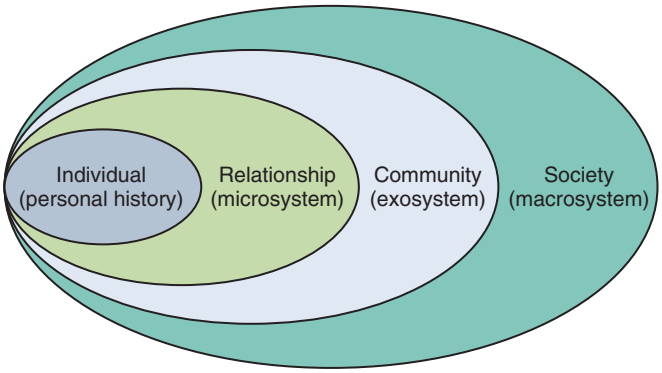


Figure 65-2. Intimate partner violence Social Ecology Model.

The second nested layer is the "Family" or the relationship itself with its own style of communication, decision making, and conflict resolution, also referred to as the "microsystem." Male dominance and male control of financial decision making in a family have been predictors of societies that have high rates of violence against women.[78] Not surprisingly, couples with high levels of conflict also have a greater risk of physical violence, and this risk increases when there is an asymmetrical power structure within the relationships.[78]

The third nested layer is "Community" or "exosystem" and refers to the neighborhood, institutions, local services, and social structures that surround the family. While IPV occurs across all socioeconomic strata, it appears to be more common in families with low income and in unemployed men.[78] It is likely that income level is not the critical variable but the stress of poverty, crowding, or hopelessness that actually contributes to increased violence. Lack of social support for women and delinquent peer associations for men have both been associated with victimization and perpetration, respectively.[78]

Finally, the individual, family, and community all function within a society or culture with rules, laws, taboos, attitudes, and biases that is also referred to as the "macrosystem." The predominant cultural theory is Feminist Theory, which states that violence against women results from gender inequity, both ideologic (belief, norms, values) and structural (access to and positions within social institutions).[79] The more unequal women are to men, the more likely men are to be violent to women.[80] This theory has found some validity when macro-level measures of women's status across multiple countries were compared with the prevalence of violence against women.[81] Dutton and Starzomski compared violent and non-violent men on a measure to assess different forms of abuse and control. Although the use of male privilege did not appear to distinguish the two groups, violent men were more likely to employ emotional abuse or children as a way to control their partner's action and also were more likely to minimize or deny the abuse.[82]

Forms of Intimate Partner Violence

It has been suggested that there may be two distinct forms of IPV: intimate terrorism and situational couple violence.[83,84] Researchers Johnson and Leone (2005) essentially differentiated the two based upon the use of power to control and defined intimate terrorism as "the attempt to dominate one's partner and to exert general control over the relationship" and situation couple violence as "violence that is not connected to a general pattern of control."[85] Johnson further described situation couple violence as usually less injurious and severe and more likely to be engaged in by either member of the couple.

Intimate terrorism was characterized as more injurious, more frequent, and almost exclusively perpetrated by men against women. Johnson further postulated that victims of intimate terrorism were more likely to be seen in clinic and ED settings; however, couple violence was thought to be more common overall.

Frye and Manganello in 2006 conducted an analysis to assess the prevalence of both intimate terrorism and couple violence as well as identify further characteristics of each.[86] They concluded that there may not be a sharp demarcation between the two hypothetical forms of IPV and that IPV relationships might be defined along a continuum based on the level of control. The research team created a five-item index to measure controlling behavior: (1) partner tries to limit your contact with family or friends, (2) partner insists on knowing who you are with and where you are at all times, (3) partner becomes jealous and doesn't want you to talk to other people, (4) partner prevents you from knowing about or having access to family income even if you ask, and (5) partner controls most or all of your daily activities (alpha = .72). They found evidence that controlling behaviors are present in 69% of physically violent relationships but present in only 11% of nonphysically abused controls. Their results further showed that primarily male characteristics differentiated the two forms of IPV. The ability to assess levels of control in relationships may have future utility in planning for appropriate safety and therapeutic interventions.

CLINICAL FEATURES

Patients who are currently experiencing or have previously experienced IPV may present to the ED for a wide range of health care issues. In several studies, women experiencing IPV generally reported their health to be poorer than those not exposed to IPV.[18] IPV patients may present for care of an acute physical or sexual assault, or for the chronic sequelae related to a previous injury. They may present for treatment of an acute medical condition, or for the care of a chronic illness exacerbated by IPV. In addition, IPV patients present for mental health care, and with conditions related to alcohol and substance abuse. IPV patients' presentations may be obvious, such as a geometrically patterned physical injury, or subtle, such as headaches due to repetitive blunt head trauma. Therefore, it is important that the HCP is aware of the broad possibility of IPV presentations as well as the comorbid conditions that are associated with IPV (Fig. 65-3).

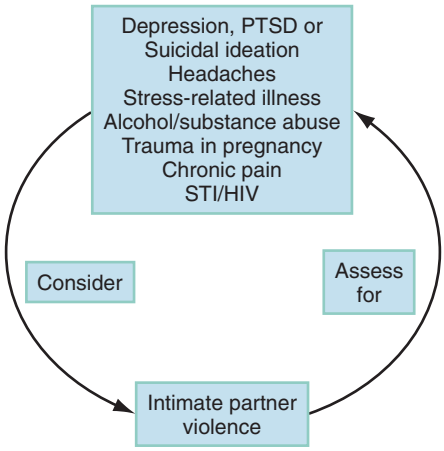


Figure 65-3. Intimate partner violence and associated comorbid conditions.

Medical History

When HCPs are eliciting a history from a patient with injuries, they should always attempt to determine the mechanism of injury. If the patient reveals that the injuries are as a result of interpersonal violence, the identity of the other person as well as that person's relationship to the patient should be ascertained, if possible, principally because the intervention for a victim who lives with the assailant will be very different from the intervention for a victim of an assault by a stranger. In order to make the patient feel more comfortable, the HCP may begin by asking whether the other individual was a stranger or an acquaintance. If the injury is due to IPV, the patient may be reluctant to divulge the information. Additional historical clues that an injury may be as a result of IPV are a changing history, a history that is inconsistent with the injuries, a statement by the patient that he or she is "accident prone," and a past history of injuries.

Many IPV patients seek care for chronic conditions that are due to previous injuries or are comorbid conditions of the abuse. If the patient exhibits comorbid conditions of IPV, the HCP should consider the possibility of IPV. Likewise, if the patient has experienced IPV, he or she should be questioned about the presence of any comorbid condition (see Fig. 65-3). Other findings in the medical history that may be suggestive of IPV include a delay in seeking medical care or noncompliance with medications and/or medical appointments, and this may be due to the abuser's controlling the patient's access to care. Frequent visits to the ED and alcohol and substance abuse are also highly associated with IPV.

Physical Examination

IPV patients frequently present to the ED on account of acute injuries. When examining an injured patient, the HCP should look for clues that the injury may be an intentional injury. Signs of an intentional injury include a central location (e.g., trunk, breasts), bilateral injuries (both arms or both legs), defensive injuries (e.g., ecchymoses on the back of the hand because of protecting the face), and patterned injuries (having the markings of an object such as the sole of a shoe or a burn with the imprint of an iron). Common locations for IPV injuries are the head, face, and neck. Types of injuries may include facial contusions, lacerations and fractures, traumatic alopecia, concussion, skull fractures, and intracranial hemorrhages. Injuries of varying severities to the eyes, ears, mouth, and teeth also occur commonly. Extremity injuries with "grab" marks (fingertip contusions) to the upper arms are suggestive of IPV. Anogenital injuries should alert the HCP to the possibility of sexual assault. Abdominal trauma in pregnancy should also heighten the HCP's concern about underlying IPV. If the injuries are incidental findings, the HCP should be prompted to ask additional questions about IPV. Injuries should be assessed for location, size, swelling, tenderness, coloration, evidence of healing, and any pattern present. In noting the color of each ecchymosis, the HCP should be careful not to make a determination as to the age of each one, as this may vary depending on the force, the vascularity of the tissue injured, the age and health status of the victim, and the presence of medications or use of alcohol that can alter coagulation profiles.

Other common medical presentations of IPV patients other than injuries include cardiorespiratory illnesses (palpitations, chest pain, asthma exacerbations, shortness of breath), gastrointestinal disorders (functional bowel disease), gynecologic conditions (chronic pelvic pain, dyspareunia, sexually transmitted infections, HIV, urinary tract infections), neurologic conditions (headaches, vertigo), as well as general constitu-

tional complaints (weakness, fatigue, dizziness, chronic pain). For this reason, the HCP should perform a thorough physical examination, including a neurologic examination, due to the possibility of repetitive blunt head trauma or anoxic brain injury due to strangulation from IPV.

Mental Status Examination

The HCP should assess any patient known or suspected of being exposed to IPV for mental health conditions associated with IPV. IPV victims frequently suffer from depression, suicidal ideation, homicidal ideation, post-traumatic stress disorder (PTSD), insomnia, eating disorders, and alcohol and substance abuse. In a meta-analysis of mental health disorders among women who had experienced IPV, the weighted mean prevalence was 50% for depression, 61% for PTSD, and 20.3% for suicidality. Higher prevalence rates were seen in women with more severe abuse or who were in shelters or court programs.[87] These rates are all significantly higher than those of individuals who have not experienced IPV. IPV patients should also be questioned about alcohol and substance abuse, a common coping mechanism or form of pain control for IPV patients.

Other Intimate Partner Violence Injuries

Strangulation, mild traumatic brain injury, and intimate partner sexual abuse are three forms of injury that occur frequently in IPV but historically have been underrecognized by HCPs.

Strangulation

Strangulation is a type of asphyxia caused by the compression of the veins and arteries in the neck or the trachea. The compression can be applied using a body part of the perpetrator such as one or two hands, forearm, or knee, or a ligature such as a necklace or piece of clothing worn by the IPV victim. When asking patients if their partner attempted to strangle them, it is suggested that the lay term "choked" be used because more people associate strangulation with a rope or object and associate the word *choking* with compression by the hands. Patients may complain of a hoarse voice, pain or difficulty swallowing, neck pain, difficulty breathing, loss of consciousness, incontinence, or confusion, or they may have no symptoms. On examination they may have a hoarse or muffled voice, difficulty swallowing, neck tenderness, respiratory difficulties, stridor, laryngeal fracture, facial petechiae, subconjunctival hemorrhages, ecchymoses or ligature marks on the neck, or altered mental status. They may also have a normal examination that does not show any specific signs of strangulation.[88] Direct laryngoscopy, computed tomography, or magnetic resonance imaging should be considered in any symptomatic patient in order to determine the extent of the injuries, and longer periods of observation are recommended as airway swelling can progress over time. The post-strangulation patient should be referred for early follow-up upon ED discharge.

Mild Traumatic Brain Injury

According to one study, 71% of women experiencing IPV have incurred traumatic brain injury (TBI) due to a physical assault and 51% had incurred multiple episodes of TBI from repetitive assaults.[89] In another study, approximately three fourths of IPV victims had symptoms of TBI.[90] Yet, TBI in IPV victims is underrecognized. Female IPV victims appear to be more at risk for postconcussive syndrome than men.[91] Female IPV victims are also at risk for second impact syndrome, a form of TBI in which cerebral edema occurs due to repeated blunt head trauma days to weeks after an initial episode of TBI but prior to the patient's recovering from the initial injury.[92] IPV patients may also sustain TBI due to "shaken adult syndrome," resulting in diffuse axonal injury. They may present with retinal hemorrhages, subdural hematomas, and ecchymoses of the upper arms and chest, much like the shaken babies demonstrate.[93] IPV patients frequently report difficulty concentrating, memory problems, headaches, depression and anxiety, and confusion, and problems with judgment, problem solving, and decision making. These IPV patients are often labeled as having borderline personalities, post-traumatic stress, or depression. The sequelae of TBI, which is frequently undiagnosed and under-recognized, include neurocognitive deficits and long-term disability. It has been postulated that perhaps TBI interferes more with a patient's ability to make safer choices than has been previously recognized. The IPV patient with mild TBI should be referred to neurology for a comprehensive neurocognitive assessment.

Intimate Partner Sexual Abuse

Approximately 8 to 14% of women are sexually abused during their lifetimes by an intimate partner, with this number being even higher in clinical populations.[29] While societal biases consider intimate partner sexual abuse as less severe and blame the victim more often than in stranger sexual assault, the sequelae of intimate partner sexual abuse are at least as serious as those of stranger sexual assault. In addition, victims of intimate partner sexual abuse were more likely to suffer from greater nongenital injuries than victims of stranger assault.[94] When questioning IPV patients about intimate partner sexual abuse and rape, the HCP should ask the patients whether they have ever been forced by their partner to do sexual activities they did not want to do, rather than asking if they have been raped or sexually assaulted. Many IPV patients do not consider that they have been raped or sexually assaulted, if it was their partner, husband, or boyfriend who was the perpetrator. Many IPV patients also do not recognize that sexual activity under coercion or threat is a form of sexual assault.

DIAGNOSTIC STRATEGIES

The ability of a clinician to identify and diagnose IPV in the ED largely relies on the interaction between the clinician and patient, and the rapport the patient has with the clinician. In addition, because IPV is a shame-based health care problem, the more comfortable the environment and the clinician-patient interaction, the more likely the clinician will be able to have a conversation about IPV with a patient.

Milieu Considerations

Two important concerns of IPV patients related to disclosure of IPV are safety and privacy.[95] While privacy and safety are issues for all patients, they are particularly critical for IPV patients, where the consequences of a breach of either could result in further injury or death. Specific provider behaviors that foster disclosure by IPV patients have also been identified. In addition, there are institutional barriers, professional and personal HCP barriers, and patient barriers that should be addressed and minimized in order to support the disclosure of IPV.

Privacy

One key behavior that promotes privacy is having a patient-only interview policy for at least part, if not all, of the interview, as patients who have experienced IPV may choose not to disclose their abusive relationship in the presence of their family, children, or friends, due to shame and embarrassment. Research has shown that women experiencing IPV prefer to talk to their physicians alone about the abuse.[95] In the case where a partner is reluctant or refusing to leave, the HCP may need to be creative in finding an opportunity to talk to the patient alone, such as when a patient is in the radiology department. In addition, if an interpreter is needed, only hospital employees or a nationally based telephone interpreter service should be utilized. In smaller communities, prior to using a hospital employee to interpret, the patient should be asked if he or she knows or is related to the employee. If this is the case, a telephone interpreter service should be used, in order not to jeopardize the patient's privacy. If a patient is asked to complete a written or computer-based questionnaire prior to being assessed by the HCP, he or she should be provided with a private, safe location in which to do this. Prior to questioning a patient about activities that must be reported to law enforcement, such as IPV in some states, the HCP should inform the patient about the limits of confidentiality. This is discussed further in the later section regarding Ethical Considerations.

Safety

The HCP needs to inquire of the patient as to the current location of the abusive partner as a first step to ensuring patient safety in the ED. An abusive partner may be in the waiting room, or may unexpectedly show up at the ED. In either case, the department should have a security protocol to protect patients when the threat level is high or if the batterer suddenly appears on the premises. Both IPV and sexual assault patients may feel that a room with a door is both protective of their safety and their confidentiality.

Provider Behaviors that Foster Disclosure

Numerous qualitative studies, primarily consisting of focus groups and surveys of women who are survivors of IPV, have been conducted to identify HCP behaviors that foster disclosure of IPV by patients. Women reported that they were more likely to disclose IPV to HCPs who listened attentively, conveyed compassion and concern, were nonjudgmental, and respected the woman's right to autonomy in decision making.[96–99] In addition, posters and patient brochures in the clinical setting made patients feel that the health care setting was a safe environment to discuss IPV with their HCP. Some women reported feeling more comfortable talking with a female HCP.[100]

HCPs' responses to surveys indicate that they are reluctant to ask patients about IPV for several reasons, including a lack of training about IPV, belief that there are no effective IPV interventions, time constraints, a perception that IPV patients are frustrating to deal with and do not follow the HCP's advice, concerns about mandated reporting to law enforcement in some states, and a reluctance of potentially having to go to court. In addition, HCPs' personal experiences with IPV, their biases about victims and batterers, and their belief that IPV is not a health care problem are all barriers that may limit an HCP's ability to diagnose IPV in the ED.[101]

Overcoming Barriers to Care

By finding ways to overcome barriers to the care of IPV patients, ED HCPs will be creating an environment that fosters disclosure and a feeling of safety for patients. Ways to overcome two institutional barriers to care of IPV patients, namely, safety and privacy concerns, have been discussed above. HCPs frequently state that they do not have time to spend assessing the IPV patient, given the complex nature of IPV. Having other trained personnel or a multidisciplinary response team to assist with assessment, referrals, and reporting can lessen this problem. In addition, partnering with a community advocacy organization that can provide crisis response and counseling benefits the HCPs and the patients. In addition, IPV patients who do not have injuries or positive responses to the Danger Assessment (Fig. 65-4) can be referred for further evaluation at a later time.

IPV patients are often embarrassed and ashamed about their situation, preventing them from feeling comfortable disclosing. By having patient awareness posters and information cards in the bathrooms, the message is made clear that patients can feel safe about talking about IPV with the HCPs. In addition, educating the HCPs not only helps them to understand the impact of IPV on the health of their patients, but will enable them to feel more comfortable talking about IPV with patients. The team approach is a very important one, as it provides good care for the IPV patients while providing support for all members of the ED.

Identification Through Disclosure and/or Pattern Recognition

Intimate partner violence is either disclosed to the HCP or is suspected by the HCP based on pattern recognition of signs and symptoms associated with IPV. The term *disclosure* means the act or process of revealing or uncovering.[102] In relation to IPV, disclosure refers to the acknowledgment by a patient that she or he has experienced IPV. Disclosure may be spontaneous or prompted.

Spontaneous Disclosure

A patient may spontaneously disclose IPV either when being questioned about his or her chief complaint, or during the history of the presenting illness. While being triaged, a patient might state in response to a question as to why she came to the ED, "I was punched in the nose by my husband." This is an example of spontaneous disclosure of IPV. Similarly, a patient being evaluated for decreased hearing might respond to a question about when the symptoms began, saying, "Ever since my partner slapped me across my ear."

Prompted Disclosure

A prompted disclosure of IPV occurs when the patient reveals or affirms IPV when asked by the HCP. The HCP may ask about IPV in the process of routine inquiry (scan mode), such as in the social history, or may consider IPV in the differential diagnosis. Prompted disclosure may occur during the course of the medical history or physical examination when patterns in the history or physical examination arouse concerns (search mode). Pattern recognition is a cognitive process that clinicians use when diagnosing a condition. It involves sorting through findings from the history and physical examination, as well as the patient presentation, to arrive at a particular diagnosis, suggested by the clinical findings associated with that diagno-

DANGER ASSESSMENT

Jacquelyn C. Campbell, Ph.D., R.N.
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Several risk factors have been associated with increased risk of homicides (murders) of women and men in violent relationships. We cannot predict what will happen in your case, but we would like you to be aware of the danger of homicide in situations of abuse and for you to see how many of the risk factors apply to your situation.

Using the calendar, please mark the approximate dates during the past year when you were abused by your partner or ex-partner. Write on that date how bad the incident was according to the following scale:

1. Slapping, pushing; no injuries and/or lasting pain
2. Punching, kicking; bruises, cuts, and/or continuing pain
3. "Beating up"; severe contusions, burns, broken bones
4. Threat to use weapon; head injury, internal injury, permanent injury
5. Use of weapon; wounds from weapon

(If **any** of the descriptions for the higher number apply, use the higher number.)

Mark **Yes** or **No** for each of the following. ("He" refers to your husband, partner, ex-husband, ex-partner, or whoever is currently physically hurting you.)

_____ 1. Has the physical violence increased in severity or frequency over the past year?
_____ 2. Does he own a gun?
_____ 3. Have you left him after living together during the past year?
3a. (If have *never* lived with him, check here_____)
_____ 4. Is he unemployed?
_____ 5. Has he ever used a weapon against you or threatened you with a lethal weapon?
(If yes, was the weapon a gun?_____)
_____ 6. Does he threaten to kill you?
_____ 7. Has he avoided being arrested for domestic violence?
_____ 8. Do you have a child that is not his?
_____ 9. Has he ever forced you to have sex when you did not wish to do so?
_____ 10. Does he ever try to choke you?
_____ 11. Does he use illegal drugs? By drugs, I mean "uppers" or amphetamines, "meth," speed, angel dust, cocaine, "crack," street drugs or mixtures.
_____ 12. Is he an alcoholic or problem drinker?
_____ 13. Does he control most or all of your daily activities? For instance: does he tell you who you can be friends with, when you can see your family, how much money you can use, or when you can take the car? (If he tries, but you do not let him, check here: _____)
_____ 14. Is he violently and constantly jealous of you? (For instance, does he say "If I can't have you, no one can.")
_____ 15. Have you ever been beaten by him while you were pregnant? (If you have never been pregnant by him, check here:_____)
_____ 16. Has he ever threatened or tried to commit suicide?
_____ 17. Does he threaten to harm your children?
_____ 18. Do you believe he is capable of killing you?
_____ 19. Does he follow or spy on you, leave threatening notes or messages on answering machine, destroy your property, or call you when you don't want him to?
_____ 20. Have you ever threatened or tried to commit suicide?

_____ Total "Yes" Answers

Thank you. Please talk to your nurse, advocate or counselor about what the Danger Assessment means in terms of your situation.

Figure 65-4. Danger Assessment instrument. (From Campbell JC: Danger Assessment. Available at http://www.dangerassessment.org. Copyright 2003. Permission to use this instrument in clinical settings has been universally granted by its creator. Dr. Campbell requests notification if the instrument is used in formal research studies.)

sis. As discussed previously, there are signs and symptoms that suggest the diagnosis of physical, sexual, or psychological IPV. By questioning a patient who has a pattern of signs and symptoms suggestive of IPV about current or past abuse, prompted disclosure by the patient may reveal IPV.

Routine Inquiry versus Screening for Intimate Partner Violence Identification

Due to the high prevalence rates of IPV in health care settings and the varied presentations of patients to the health care setting, numerous professional medical organizations, regulatory bodies, as well as advocacy organizations have recommended routine "screening" of patients to identify those who are experiencing IPV. These organizations include the American Medical Association,[103] the American College of Emergency Physicians,[104] the American College of Obstetricians and Gynecologists,[105] and the American Academy of Family Practice.[106] However, the American College of Emergency Physicians has recently revised its policy to recommend that emergency HCPs assess patients for IPV.[107] In the National Consensus Guidelines on Identifying and Responding to Domestic Violence Victimization in Health Care Settings, the Family Violence Prevention Fund, a national advocacy organization, also recommends routine "screening" in the health care setting.[108] The term *screening* has been used in the IPV

literature to refer to a process of asking about past or current exposure to violent or abusive behavior at some point in the clinical interaction with every patient.

However, *screening* is actually a public health term with a very specific meaning and refers to the use of a specific test, examination, or procedure to identify an unrecognized condition or illness in an asymptomatic person.[109] Early identification through screening enables early referral to effective interventions, resulting in decreased morbidity and mortality. The screening tests are validated, and the diagnosis is verified with a gold standard confirmatory test, such as a biopsy.

In 2004, the third United States Preventive Services Task Force (USPSTF) reported on their evaluation of the evidence regarding screening for family violence and IPV in the health care setting. In their report they stated that there was insufficient evidence for or against routine screening for IPV.[110] These findings were largely due to a paucity of evidence in this field. They were also due to the evaluation of the available evidence relative to traditional screening methodology, which entails a burden to prove the effectiveness of the test questionnaire to decrease the morbidity and mortality due to IPV.[111] In addition, the task force noted the lack of research to determine whether screening for IPV did more harm than good. This is an area that requires further study to determine whether potential harms are actual or not. In a recent study, Houry did not find any adverse effects from questioning patients about IPV.[112] It is important when interpreting the USPSTF report to realize that there was no evidence that providers should *not* ask patients about IPV. Exposure to ongoing IPV is likely to result in continued physical and sexual violence and psychological abuse.

When HCPs ask patients about IPV, they are identifying patients along the entire spectrum of IPV—those who have not been exposed to IPV and are not at risk for IPV, those who have not experienced IPV but are at risk for IPV, those who have experienced IPV but do not yet have health-related sequelae, and those who have experienced IPV and are very symptomatic with severe adverse physical and mental health sequelae due to the violence. Most patients who are experiencing IPV are fully aware of the violence and abuse, even if they choose not to disclose the violence to their HCP or the IPV goes unrecognized by the HCP. Further, there is no gold standard test against which to verify patient responses. While several questionnaires have been validated for use in identifying IPV, most have only been validated for use with female patients, and with select populations and clinical situations. Further, HCPs will only be able to identify IPV using a questionnaire if the patient chooses to disclose IPV at that particular time. So while the goal of being able to screen for IPV is a worthy one, the clinical reality is that we are carrying out a diagnostic assessment or routine inquiry.[113]

Assessment for Intimate Partner Violence

The opinion of experts in the field, supported by practice-based evidence, is that HCPs should assess patients for IPV due to the adverse physical and mental health effects of IPV, the morbidity and mortality of IPV, the economic cost, and the effect on children. In addition, failure to ask about IPV may lead to misdiagnosis, inappropriate workups, excessive costs, and increased morbidity and mortality. Due to the varied presentations of IPV in the clinical setting, routine inquiry is recommended. In addition, several studies questioning women and IPV patients have found that they also support routine inquiry for IPV by HCPs.[98,114,115] Routine inquiry may also be preventive; it may increase the patient's awareness of the impact of IPV on health, decrease the violence if referrals and interventions are provided, and lessen the impact of sequelae due to violence.

Prior to the HCP asking patients about IPV, the HCP should ensure that the patient is in as private an environment as possible, without family or friends nearby. Patients should be questioned in their primary language, using an interpreter service or hospital employee if needed. It is important that patients are informed if the HCP is legally required to report to law enforcement should the IPV patient disclose physical abuse. Routine inquiry about IPV may be conducted using a person-to-person interview or written or computerized questionnaires.[116,117] The inquiry may consist of a few questions about IPV, or may be part of a larger health risk assessment, which is usually a written or computerized questionnaire completed by the patient prior to being evaluated by the HCP. There are advantages and disadvantages to each of these methods of inquiry. Some patients prefer responding to a written or computerized questionnaire. However, others may have literacy difficulties or may be intimidated by a computer. When conducting a person-to-person interview, framing statements can be helpful. These statements help to normalize the questions about IPV and make them seem routine and not prejudicial (e.g., "Because of the impact of violence on women's health, I ask all my female patients these questions"). The HCP should use inclusive terms, such as partner or boyfriend. In addition, the HCP should make use of both direct and indirect questions (e.g., "Were you hit or hurt?," "Is there anything else you would like to tell me?"). Rhodes found that when the HCP asked at least one additional related question, patients were more likely to disclose abuse.[117] Brief instruments for use in asking about IPV are preferred by some HCPs, as they find standard questions easier to ask and remember. The Abuse Assessment Screen (AAS)[118,119] (Box 65-1) and Partner Violence Screen (PVS)[120] (Box 65-2) are both brief instruments for clinical use. The AAS has been validated in a variety of clinical settings, multiethnic populations, and in Spanish. The PVS was developed and validated in the ED.

An extensive list of IPV assessment tools is provided in compendiums published by the CDC.[121,122] Ultimately, whether the routine inquiry is verbal, written, or computerized, the HCP will need to have an individualized conversation with the IPV patient, being sensitive to the presenting medical problems, race/ethnicity, language barriers, cultural

BOX 65-1 Abuse Assessment Screen

Have you ever been emotionally or physically abused by your partner or someone important to you?
Within the last year, have you been hit, slapped, kicked, or otherwise physically hurt by someone? If yes, by whom?
Within the last year has anyone forced you to have sexual activities? If yes, by whom?
Are you afraid of your partner or anyone mentioned above?

BOX 65-2 Partner Violence Screen

Have you been hit, kicked, punched or otherwise hurt by someone within the past year? If yes, by whom?
Do you feel safe in your current relationship?
Is there a partner from a previous relationship who is making you feel unsafe now?

beliefs, gender, and sexual orientation. A successful encounter with an IPV patient or a suspected IPV patient is one in which the patient is treated with compassion, feels safe, and is provided with information, resources, and referrals regardless of whether he or she disclosed IPV or not.

MANAGEMENT

While patients may disclose IPV, they may be unwilling to pursue any suggestions for addressing the IPV. The reasons are myriad, but generally, the first and foremost factor is fear. Victims may fear for their own safety, fear for the well-being of their children, fear because they lack any means for economic independence, fear they will be deported if their spouse is arrested for a crime, fear they will be abandoned by family, friends, church, or community, and fear that the unknown could be worse than the known risks they are willing to endure. The cost of disclosure or the cost of making change may simply exceed the possible benefits. Patients may negotiate their options or reject any options presented to them. Patients sometimes make choices that physicians believe may increase their risk for a poorer outcome, but the physician's role is to provide recommendations for care, fully discuss the potential benefits and risks, document the discussion, and verify the patient's capacity for noncoerced decision making. While a patient may not make the decisions the provider would prefer, a respectful interaction that leaves the door open for reconsideration or a return visit may be more powerful than appreciated at first glance. Revictimizing an IPV patient through abusive use of professional power or disparaging remarks may be more harmful than realized.

Emergency departments need to plan for IPV patients as their care is multifaceted, often requiring social services, law enforcement, mental heath services, and occasionally child welfare services. The preplanning for a routine response or a crisis response should the threat of violence escalate is not only important for patient care, but also may increase the willingness of health care staff to address IPV in their patients. Hospital policy may need to allow for short-term admissions to provide for a safe haven in the rare case that emergency shelter services are not available and the patient has no other recourse.

Initial Intervention Assessment

Once IPV is identified, the patient should undergo a brief assessment by any member of the IPV response team that answers the following questions:

- What are the nature, scope, and consequences of the abuse in terms of its impact on physical and mental health?
- What is the level of danger and risk of a lethal outcome?
- What strategies have been tried and what are possible sources of support or major barriers that need to be addressed today in order to assist patient safety?
- If there are children, is the parent becoming concerned for the children's safety and well-being?
- How does the patient view his or her current situation and desire for change?

The assessment then directs the intervention (Table 65-1).

Table 65-1 Five Components of Intimate Partner Violence (IPV) Assessment

ASSESSMENT ISSUE	TOPIC TO EXPLORE OR CONSIDER	IMPLICATIONS FOR INTERVENTION
Nature, scope, and consequences of abuse	Types of abusive behaviors: physical, sexual, emotional, financial Continued problems from prior injuries? Possibility of pregnancy or sexually transmitted disease from coerced or forced sex? Is the victim being physically or psychologically stalked?	Directs the physical and forensic examination and any additional imaging or laboratory assessment or any needs for referral to appropriate care.
Danger Assessment	Threats of homicide/suicide, battering during pregnancy, access to a firearm; previous strangulation and others (see Fig. 65-4)	Patient may be unaware of the danger. If patient is at risk for fatal outcome, obtain additional consultation and explore with the patient the possibility of contacting police, obtaining an emergency protective order, or seeking emergency placement in a shelter or other safe haven.
Strategies and barriers to greater safety	Are there family members or friends to confide in; or a place to go in an emergency? Are there any cultural or religious barriers to consider? Does the patient have a source of income, any money, health insurance, etc., if she decided to separate? Does he/she understand his or her legal rights?	Many IPV community agencies provide individual and peer counseling, legal advice, and job training to help the victim gain confidence and support to make changes to become safer and healthier.
Safety of children	Are any of the children showing signs of distress such as behavior change at home, deterioration in school performance, depression, or acting out behavior? Are they harshly punished or verbally berated, or is there any possibility of sexual abuse?	A judgment must be made as to whether children are endangered or also being victimized, and if so, child protective services should be notified.
Process of change	How does the patient perceive the relationship? Is there a sense that the relationship may not be healthy or safe? Is the patient considering options? Has the patient tried to make a change or separate? Does the patient want immediate assistance for herself and her children?	Victim intervention can be tailored to the victim according to his or her position in the change process as determined in the assessment process. It is possible to use the brief negotiated interview to effect movement from one stage to another.

Of these, assessing for the risk of a lethal outcome has been the most extensively researched. Women are killed by current or former intimate partners almost nine times more often than by a stranger.[123] Contrary to the reporting by the lay press, IPV fatalities don't usually occur as a freak event in an otherwise happy family. IPV is a precursor to the homicide in 65 to 75% of cases.[124–126] Of even greater concern for health professionals is that 43 to 47% of IPV homicide victims saw an HCP within a year prior to their death.[12,13] IPV homicide is the seventh leading cause of premature death for women and is the second leading cause of death for African American women 15 to 34 years of age.[124] The incidence of fatal IPV due to homicide has continuously decreased since the mid-1970s, and this is attributed to societal shifts to more openly address family violence and to improvements in criminal justice, social service, and health system responses to both victims and perpetrators.

Twenty risk factors have been validated as highly associated with an IPV homicide. Campbell and colleagues—in a multicity, retrospective, case-controlled study using police files, surrogate interviews, and survivor interviews—compared case histories of fatal and nearly fatal cases with women who had been physically abused but without a life-threatening assault. Variables that significantly differentiated fatal and nearly fatal cases from controls became the elements of the Danger Assessment.[124] Some of these elements include stalking and harassment of the victim, estrangement (physical or legal separation), perpetrator access to a gun or prior threats with a gun, history of forced sex, and physical abuse during pregnancy. This is a two-part assessment that begins with a severity ranking that stimulates recall, and the second part consists of 20 dichotomous items that are validated risk factors for IPV homicide (see Fig. 65-4). A brief online training program (www.dangerassessment.org) provides instructions for weighted scoring, and then the copyrighted tool can be used for free. However, even without the weighted scoring, more affirmative responses indicate a greater risk of a fatal outcome. Assessing risk factors for a possible fatal outcome is good medical care and may be protective. Fifty-four percent of women killed and 45% of attempted homicide victims did not accurately perceive their risk of being killed by their partner.[124] In all likelihood, health and criminal justice professionals have also previously underappreciated the risk of a fatal outcome when caring for IPV victims.

Clinical Intervention for Intimate Partner Violence Victims

Clinical intervention for IPV in the ED is just like intervention for any other potentially life-threatening disease. System readiness coupled with practitioner skill is believed to lead to improved outcomes.

System Readiness

System readiness should address procedures to promote patient privacy and safety within a multidisciplinary team approach. On the rare occasion of a battered victim who remains in danger, a "code black and blue" would require the response of appropriate medical and surgical personnel, social services, IPV experts, site security, and community law enforcement. At a bare minimum, system readiness in the ED refers to ongoing professional education, established quality improvement measures to monitor quality of care, protocols for intervention, patient education, and established means for safe follow-up.

Emergency departments can take advantage of a tool developed by the Agency for Healthcare Research and Quality (AHRQ) to assess if processes are in place to respond to IPV (www.ahrq.gov/research/domesticviol/).[127,128] The tool addresses (1) hospital policies and procedures, (2) the physical environment, (3) the cultural environment, (4) provider education, (5) screening and safety assessment, (6) documentation, (7) intervention services, (8) evaluation and quality improvement measures, and (9) collaborative agreements. Inter-rater reliability was very high (Kronbach's alpha ranging from 0.97 to 0.99 in the experienced coders and 0.96 to 0.99 in the inexperienced coders). The instrument can be used for assessment and to set benchmarks for quality improvement. Instructions for use and scoring are available from AHRQ.

Three models of system intervention have been identified and they may be blended in various ways: Advocacy Partnering, Forensic Medicine, and a Specialty Care Model. The Advocacy Partnering Model is based on negotiated agreements between health clinics or hospitals and community IPV service providers. Trained peer counselors respond to provide bedside or telephone consultation, speaking directly with patients and providers to conduct a needs assessment and plan for initial intervention, or in some places, for ongoing case management and more chronic care. The Forensic Medicine Model also incorporates advocacy partnerships and provides, in the case of physically or sexually abused victims, nurses or physicians who have received advanced training in the retrieval, documentation, and storage of physical evidence, forensic photography, presentation of evidence in the courtroom, and expert interpretation of findings. In Specialty Care Models, patients can be referred to clinical experts or centers that specialize in trauma recovery. In pediatrics, child abuse is now a recognized subspecialty given the scope of both knowledge and skills the care of abused children requires. Some departments (e.g., behavioral health) or individuals have established IPV care as an area of expertise, and once the patient is medically stabilized, referral for bedside or delayed consultation is made just as for any other ED problem.

Health Care Provider Intervention

Intimate partner violence is a socially stigmatized issue and, as such, requires concerted effort on the part of the clinician to establish trust and convey empathy. An empathic and nonjudgmental assessment and respectful discussion of options with a trusted HCP are postulated to have potential therapeutic benefit in and of themselves. The assessment guides decision-making regarding the needs for immediate or delayed intervention. In addition, the emergency HCP might consider a brief intervention for substance abuse and brief interventions to ameliorate PTSD. The ED HCP will encounter five levels of patients, based on IPV exposure and risk. Each level requires varying intervention strategies and critical elements for documentation (Table 65-2).

Safety planning is a harm reduction intervention in that the patient may be returning to a dangerous situation but certain behavior changes may contribute to a less negative outcome. Needle exchange programs are examples of a harm reduction effort to prevent additional illness in intravenous drug users. Emergency preparedness for disaster events is another example of a harm reduction intervention. IPV patients may be discharged to a situation with risk of continued violence. Strategies for avoiding further harm may be both protective and empowering. Planning for safety during a violent outburst (getting to a room with a lockable door and exterior window) or for immediate escape (placing a suitcase in the safekeeping of a trusted other with clothes, documents, and extra cash) are examples that can be developed with the patient.[129]

Table 65-2 Intervention Strategies Based on Intimate Partner Violence (IPV) Exposure and Risk Level

PATIENT TYPE BASED ON ASSESSMENT	INITIAL INTERVENTION STEPS	CRITICAL DOCUMENTATION FOR THE ENCOUNTER
I. No history of IPV or suspicion of abuse	Provide basic message that IPV is a health problem	"No history of IPV; no suspicion of IPV"
II. Prior history of IPV but no current exposure	Assess for sequelae of prior abuse; provide educational message that patient is at risk of future IPV relationship	Add history of IPV to problem list (can be coded as a V-code); describe medical and mental heath impact and any referrals made
III. Recent or current abuse but no injuries and no elements on Danger Assessment	Assess for sequelae of abuse; provide referrals to IPV resources	Add IPV to problem list; describe health sequelae from abuse; note referral for urgent follow-up provided to patient
IV. Recent or current abuse with injuries or positive findings on Danger Assessment	Crises, bedside response by social services or IPV advocate; discuss possibility of an order for protection; notify police if required by law	Add IPV to problem list; describe health sequelae; summarize follow-up plan as outlined by social services or IPV advocate; complete reporting mandates; describe injury findings using narration, diagrams, and photos
V. Suspicion of current abuse but patient denies IPV	Provide basic message that IPV is health problem; request bedside consultation by social services or IPV advocate; provide referrals to IPV resources	Document IPV as a suspected health problem; note that bedside consultation done and resources provided; if injured, describe injury findings using narration, diagrams, and photos

In the past 20 years, community agencies or victim advocacy organizations have been developed in every state to provide services for IPV victims and their children. The federal Violence Against Women Act provides considerable funding to support these service providers. While most of the time patients are referred to such agencies for follow-up, more and more agencies now respond to health care requests for bedside or telephone consultation. Information about what agencies are available in a specific community is easily available through the National Domestic Violence Hotline at 1-800-799-SAFE or (TTY) 1-800-787-3224. Sullivan examined the effect of community-based advocacy services after a shelter stay and found that at 2-year follow-up, IPV victims who had received the advocacy intervention experienced less physical abuse, increased quality of life, and accessed more community IPV resources compared with the control group. Of note, 25% of the intervention group, compared with 10% of the control group, had experienced no further violence following the intervention.[130]

Bedside consultation was started in EDs in Kansas City, Missouri, and analysis showed that patients who received bedside counseling with a victim advocate were more likely than those who had social service consultation alone to call the police for a subsequent event (18% vs. 39%, 95% confidence interval [CI] difference 1–40%), seek emergency shelter (11% vs. 28%, 95% CI difference 6–27%), or obtain counseling (1% vs. 15%, 95% CI difference 7–21%) than controls.[131] In a study by McFarlane, telephone follow-up calls for harm reduction counseling resulted in the increased adoption of safety behaviors that remained even 2 years after counseling ended.[132] However, further research is needed. Canadian researchers examined 22 published reports involving IPV interventions to which a primary care clinician could refer a patient. Each study was rated using the Canadian Task Force on Preventive Health Care Levels of Evidence and Quality Ratings of Individual Studies assigning both a research design rating and a quality rating. They concluded that that no IPV intervention programs to which a primary care physician could refer a patient had been adequately evaluated and none, whether targeting the victim or the perpetrator, had yet been found to be effective in decreasing the violence.[133,134]

Most IPV intervention for victims centers around theoretical constructs of the Health Belief Model, Social Cognitive Theory, and self-efficacy. The Health Belief Model's core assumption is that a person will take a health-related action if the individual believes that a negative health condition can be avoided (perceived susceptibility), has a positive expectation about taking the recommended action (perceived benefit), and believes that he or she can successfully take the recommended action (self-efficacy).[135] Both perceived susceptibility and self-efficacy have been demonstrated to be strong predictors of behavioral change.[136] Social Cognitive Theory has a strong emphasis on cognition, then posits that cognitions change over time. According to this theory, people develop perceptions about their own abilities and characteristics that guide their behavior by determining what a person tries to achieve.[137] One's perceived self-efficacy for a given behavior dramatically affects one's self-motivation for performing that behavior. These are the theoretical constructs that underlie IPV victims' interventions, and they remain to be tested in large, controlled trials.

Interventions and Referrals for Perpetrators

Interventions for IPV perpetrators have not been shown to be as effective as hoped.[138–141] The problem is that a "one-size-fits-all" approach appears to be inadequate for the known typologies of violent offenders. The current treatment modalities are organized according to etiologic theories[142]: (1) cognitive-behavioral treatment focuses on deficient thought patterns such as rigid beliefs and limited problem solving; (2) psychodynamic treatment addresses unresolved physical and emotional trauma; and (3) feminist models focus on educational efforts to increase awareness of oppressive, sexist attitudes and foster nonoppressive, egalitarian behaviors. Conjoint treatment for couples remains controversial, and the primary objections center around safety concerns for victims. In the primary care setting, researchers found that 13% of men who participated in the study disclosed IPV perpetration.[143] Right now, patients who disclose histories of interpersonal violence, with partners, acquaintances, or strangers, should all be referred to social services for further evaluation and appropriate referral. Once arrested, the criminal justice system does not generally conduct comprehensive assessments, so offenders do not have as many treatment options. Unfortunately, that usually means that recidivism for offenders is quite high.

Cultural Issues

The phrase *cultural competency* has been previously misinterpreted to mean knowledge of another culture. While knowledge is valuable, the ability to be open and learn about other cultures and moving beyond the restrictive perspective of one's own culture manifests competency and has also been termed "cultural humility." In regards to IPV, beyond assessing for possible strengths or barriers within a given culture for an IPV patient, a few special considerations are worth mentioning:

- Language interpreters should be professionals and nonfamily members, with some training and background in the dynamics of IPV. There are some languages that do not readily translate the phrases or the concepts for family violence.
- Immigrant victims fear deportation for themselves should they disclose IPV and, in most cases, fear deportation for their partners. There are protections within the federal Violence Against Women Act that allow victims to remain in this country even if their legal spouse and/or sponsor is deported.
- Some victims of color may be reluctant to contact law enforcement due to apprehension regarding racism. While the desire to be safe and free from violence is real, the fear of brutal or unfair treatment for their partner is also real.

While not a distinct cultural group, health professionals should appreciate the barriers faced by IPV patients from rural areas (fewer resources, less privacy), the disabled (few shelter programs with full access, need and expense for sign language interpreters), and gay and lesbian IPV victims (few shelter services for gay men, "outing" or disclosing a person's gender orientation as a coercive threat). Socioeconomic status may also be a barrier for intervention. The lack of independent financial resources or educational/vocational training limits options for change at all socioeconomic levels.

Interface with the Criminal Justice System

Intimate partner violence impacts patient health both acutely and with exposure over time and is considered to be a public safety issue. As such, domestic violence is a crime in all 50 states, as is spousal rape. A criminal justice response can be helpful. Mandatory arrest policies provide a "cooling off" period that provides time for patients to implement safety plans or safer shelter. Orders of protection may be useful in helping victims to feel safer, although at least one study among African Americans reported heightened fear of retaliation when protective orders were obtained. Protective orders can be written such that they allow for immediate search and seizure of firearms, and protective orders link into databases that restrict firearm purchase by the perpetrator. Finally, victims of crime restitution programs can assist patients to buy and install home security systems, change residences, or pay for uncompensated medical or mental health care for victims and/or their children.

In most states, HCPs negotiate with patients to determine how and when to contact law enforcement. In some states, health care professionals are required by law to report any patients who have sustained injury with a weapon, and a few states require reports to law enforcement, regardless of patient consent for any patient who has injuries that appear to be intentionally inflicted. The most restrictive reporting mandates have been implemented because the IPV victim is perceived as a "vulnerable person" just as in child and elder abuse, and proponents advocate that victims be assisted with the full resources of the health and safety system. Unfortunately, there is neither sufficient evidence *for* nor sufficient evidence *against* mandatory reporting laws by health professionals to law enforcement in the case of IPV. There are survey data that reveal physician anxiety about proceeding without patient consent, and there are mixed results from victims themselves, some seeing the law as helpful and other seeing it as potentially harmful.

Ethical Considerations

Certain ethical issues will need to be addressed in designing ED intervention protocols.

Confidentiality

Despite all the increase in public awareness, IPV as a shame-based disease and bias, both professional and institutional, still remains. Breaches of confidentiality could put the victim at heightened risk. Some of the questions to be addressed in this regard are:

- What if the principal insured party is the abusive partner? What procedures are in place between the provider and the third party insurer to protect the confidentially and safety of IPV victims?
- Are there any routine follow-up processes in place, such as patient satisfaction surveys, that might inadvertently contact a patient and alert the abusive partner to a health care visit?
- What if a minor discloses IPV occurring in the home and the abusive parent seeks access to the medical record?
- If IPV is noted on the medical record, could this be grounds by health or home insurance companies to cancel insurance?
- What if the patient discloses IPV as the cause of injuries and now the provider, by law, must notify law enforcement of possible criminal behavior?

All of these have been addressed in various ways, some at the institutional level, some through collaborative agreements, and some through state legislation. Regardless, the potential for breach of confidentiality must be recognized, and limits to confidentiality, including any reporting mandates, should be communicated to patients during ED registration or as soon possible.

There are some protections for IPV patients within the Health Information and Portability and Accountability Act (HIPAA). Under HIPAA, physicians may not generally share confidential health information without the written approval of patients unless mandated by state law. However, physicians may disclose protected health information to government authorities or social services in the case where abusive behavior has been suspected to have occurred. Likewise, unless mandated by law, a physician has discretion to withhold information when he or she believes the notification will place the patient at "serious risk of harm." HIPAA also allows patients to specifically request nonrelease of protected health information to specific persons or agencies, and patients can request that they be notified of any release that does occur. IPV patients can request their names be withheld from any registry system when hospitalized, or hospitals can routinely admit IPV patients as a "Jane Doe" to ensure both safety and confidentiality. These are HIPAA protections that an IPV response team should know and routinely discuss and facilitate with IPV patients.

Table 65-3 Key Elements in Medical Record Documentation for Intimate Partner Violence (IPV) Cases

KEY ELEMENTS IN THE HISTORY	KEY ELEMENTS IN THE PHYSICAL EXAMINATION	KEY ELEMENTS IN THE DISCHARGE PLAN
A verbatim or near verbatim statement of the patient regarding etiology of injuries	Brief description of state of mind or demeanor of patient	Care instructions for medical or traumatic complaints
The relationship of the assailant to the victim	Mental status examination, including brief cognitive assessment for mild traumatic brain injury	Arrangements for follow-up for medical and IPV intervention
The current whereabouts of the assailant (immediate safety check)	Post-strangulation: results of direct or indirect laryngoscopy	Safety planning: Where should patient go now that is safe? What to do if safety is placed at further risk?
Detailed account of how current assaultive injury occurred	Narrative description of new injuries	How to access victim advocate?
Symptoms of current and past abuse-related injuries	Narrative description of sequelae of old injuries, such as chronic pain or decreased range of motion	How to apply for victims of crime restitution?
Post-strangulation: patient description of voice change, if any	Diagrammatic and/or photographic documentation of injuries (digital photography is acceptable for medical or forensic use)	If law enforcement notified, badge name and number of officer contacted
IPV assessment as outlined above by physician or consultant		

If a patient discloses violent or abusive behavior, the physician operates under obligation of confidentiality and cannot disclose to police unless required by law. The duty of a citizen to report criminal behavior is a communal value and appears to clash with the duty to maintain patient confidence. However, this duty to confidentiality is also a communal value, and unless over-ridden by legal mandates, the HCP cannot report criminal behavior but can warn intended victims if there is a perceived threat to their safety.*[144]

Informed Consent and Autonomy

Reporting, when required by law, is permissible by HIPAA and does not require patient consent, although addressing any concerns to safeguard the patient is an obligation of the health provider or the institution that receives the report. For example, California mandates physicians and surgeons to report patients with injuries suspected to be assault related to law enforcement. However, the reporting physician can request immediate bedside response rather than a delayed home response, and the report can indicate safe strategies for contact that the patient has identified.

IPV patients are not always free to act of their own will in health care decision-making. Coercive decision-making is not autonomous decision-making. Fear may be so profound that decision-making is impaired, thus jeopardizing informed consent. In a Montana malpractice suit, the ED physician and hospital were sued for failure to accurately diagnose and failure to provide for patient safety when an IPV patient was discharged to home only to suffer devastating physical injury by her abusive partner.[145] According to the plaintiff's attorney, the ED physician testified in deposition that IPV was discussed and safety issues addressed; however, the patient testified that she was at the hospital under coercion of her boyfriend, who had made specific violent threats to her should the IPV be disclosed (personal communication with C. Mitchell). While this case was settled prior to court judgment, the coercive nature of extreme fear and its impact on informed consent and clinical decision-making are challenges for both clinicians and ethicists alike.

*Tarasoff v. Regents of University of California (1976) 17 Cal. 3d 425.

Documentation

Medical Record

The ED physician cares for victims of violence and abuse on a daily basis. Because violence and abuse are both health and criminal justice problems, there is increased likelihood that the medical record may be introduced or referred to in criminal or civil proceedings. In addition, many states have evidence rules that allow the introduction of prior evidence of physical abuse (e.g., the medical record) to demonstrate a pattern of behavior even if the actual criminal charges or civil litigation is pursued many years later.

In IPV cases there are key elements in the history of the presenting illness, physical examination, and discharge instructions that should be addressed and documented (Table 65-3).

Diagnostic Coding

Intimate partner violence is the preferred term for health surveillance and research as defined by the CDC. *Domestic violence* is commonly used by the general public to refer to IPV but is specifically used by criminal justice to refer to physical abuse by a current or former intimate partner. Adult Maltreatment is the coding term used in the International Classification of Diseases (ICD) (995.8_). The last digit varies for different types of adult maltreatment: physical abuse (995.81); emotional/psychological abuse (995.82); sexual abuse (995.83); neglect (995.84); and other abuse or multiple forms of abuse (995.85).

In the 10th version of the ICD, a prefix can be given for Adult Maltreatment to designate suspected (T4) or confirmed (T7) IPV. The reason for this is that practitioners have been hesitant to document suspicions of abuse due to the desire to protect patient confidentiality and safety; however, failure to document adult maltreatment has impeded both continuity of care and surveillance. In the past, victims often received a psychological diagnosis that not only failed to recognize the primary etiology but also failed to recognize the relational aspect of IPV and appeared to be victim blaming, further stigmatizing patients.

Documenting suspicions of abusive behavior in the differential diagnosis is important because confirmation of shame-based health issues may take time and repeat discussions are not usually within the purview of the ED physician. In addi-

tion, hospital information managers should include E codes as to the cause or means of injury, as this is vital not only to ED research but for public health planning and population-based interventions.

Forensic Documentation

The medical record becomes a forensic record when it becomes part of a legal process. The word *forensic* means "pertaining to the law." However, a medical record does not need the degree of detail or scope in the history or physical examination that a formal forensic examination does. Sexual assault and child abuse patients have, for many years, benefited from the additional service and care of medical forensic teams that can coordinate with law enforcement and then follow meticulous protocols to collect and document detailed findings. Other members of the team can provide interventions for medical and mental health needs and establish care for longer term needs. These programs have served as models for IPV forensic care. California has developed clinical guidelines, a forensic protocol, and a form for the forensic medical examination of victims, which is available online (www.oes.ca.gov/WebPage/oeswebsite.nsf/Content/5B3A31407BB2C92D882574BF005A603E?OpenDocument). Multiple law enforcement agencies now contract with forensic medical personnel to conduct the forensic examination, collect physical evidence, and present courtroom testimony. Of note, forensic examinations are only done with the full consent of patients, which differs from some state laws regarding reporting. Forensic examinations are usually time consuming and detailed, while reporting seeks to capture critical elements for either public health surveillance or to alert public safety departments of a possible violent crime.

Participation in Public Health Intimate Partner Violence Activities

Emergency department HCPs play a critical role in surveillance of IPV both through accurate diagnosis and documentation of patients who have suffered IPV. In addition, ED physicians serve as valuable members of fatality review teams that examine the events leading up to a domestic violence fatality and attempt to identify either missed opportunity for prevention or strategies for an improved response to family violence. Given the multidisciplinary nature of IPV, community coordinating councils examine components of the system response components and work to improve interagency relationships. Other opportunities to improve health policy exist within organizations such as the Injury Control Committee with the American College of Emergency Physicians, the American Medical Association's National Advisory Council on Violence and Abuse, the Family Violence Prevention Forum within the American Public Health Association, and many others.

KEY CONCEPTS

- IPV is pervasive and difficult to diagnose. It can impact children, adolescents, adults, and elders. The ED HCP will care for both victims and perpetrators.
- Identification of IPV is through a process of patient disclosure and pattern recognition by the HCP. Just as with other medical problems, accurate diagnosis relies on interview, physical examination skills, and pattern recognition.
- Comorbid conditions. Some conditions are highly associated with IPV, and when identified should prompt the HCP to consider IPV. When a patient discloses IPV, the HCP, in turn, should assess for comorbid conditions.
- Readiness to intervene. A coordinated multidisciplinary team response using existing services (e.g., community advocacy agencies, forensic teams) will facilitate patient access to multiple resources that are often needed to promote the safety of victims and children. Having a response system in place will be time saving for the ED HCP.
- Documentation. After identifying or diagnosing IPV, the HCP should document the diagnosis Adult Maltreatment on the medical record. Further, all interventions, referrals, and mandatory reports should be documented. In addition to the medical record, the patient may have a forensic record in which evidence is documented for the purposes of legal proceedings.
- Patient disclosure of IPV is not necessary for a successful encounter with a patient. The goal of the HCP should be to provide a caring, compassionate environment in which the patient feels safe to talk about IPV now or in the future. All patients, whether they disclose IPV or the HCP suspects they are experiencing IPV, should be provided with written information and appropriate resources for IPV.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 66

Elder Abuse and Neglect

Deirdre Anglin and Diana C. Schneider

PERSPECTIVE

Background

Currently, 12.4% of the population in the United States is estimated to be 65 years of age or older.[1] The elderly segment of the population is expected to increase to 16.3% of the population by 2020[2] and 20.7% of the population by 2050.[2] Further, the "oldest" old (85 years of age and older) will make up an increasing proportion of the population.[2] At this time, older patients comprise about 15% of emergency department visits. This number is expected to increase to 25% by the year 2030, with 5% being over 85 years of age.[3]

With advanced age, vulnerabilities increase, such as significant physical and cognitive decline, expended financial resources, and uncertain medical insurance. As the U.S. population ages, maltreatment of elders is increasingly identified. Further, the World Health Organization has recognized that abuse and neglect of elders are global health problems.[4]

The first reports of "granny battering" appeared in the medical literature in 1975.[5,6] In 1978 the U.S. House of Representatives Select Committee on Aging held hearings on elder abuse. This committee concluded that elder abuse was a nationwide problem that suffered from severe underreporting. The committee recommended that the federal government assist states to develop agencies responsible for collecting reports and identifying and managing cases of elder abuse.[7] In 1981 the Prevention, Identification and Treatment of Elder Abuse Act was introduced into Congress to standardize definitions of elder abuse. In spite of being introduced numerous times, it was never passed. In 1990, the House Select Committee met to determine what progress had been made in the problems related to elder abuse. They concluded that elder abuse was increasing and that it continued to remain woefully underreported, even though 80% of states had statutes mandating reporting of elder abuse. Further, the committee noted that the federal government had not passed legislation to provide assistance to the states to deal effectively with the national problem of elder abuse.[8] In 1991, the National Institute on Elder Abuse was established to focus increased attention on the issue of elder abuse. An amendment to the Older Americans Act in 1992 established a national elder abuse policy and provided some funding to states. In the same year, the Joint Commission on Accreditation of Healthcare Organizations set standards for emergency departments that included having criteria for the detection and management of elder abuse among patients.[9]

Elderly individuals may be isolated from society as a result of physical illness, disability, mental illness (e.g., dementia), and age. Visits to physicians by elderly persons may provide their only contact outside the family. Elderly persons frequently present to the emergency department for medical care. Therefore, emergency physicians have the opportunity to diagnose suspected elder abuse and initiate further evaluation by elder abuse teams and Adult Protective Services.[10] However, one survey suggests that emergency physicians may lack awareness and adequate training about elder abuse. In this survey, 79% of emergency physicians reported they had treated a case of elder abuse in the previous year, but only 50% said they had reported the abuse. Of respondents, 28% believe elder abuse is rare and 84% rarely ask their patients directly about elder abuse. Only 31% of emergency physicians responded that they are aware of a written protocol for elder abuse in the emergency departments where they practice, and just 38% said they are familiar with their state laws pertaining to elder abuse. In addition, only 40% responded that they are aware of types of community services available for victims of elder abuse, and only 25% could recall education during their residencies about elder abuse.[11] Hopefully, through education and increased awareness, these numbers will increase markedly as the emergency department often serves as the first step in the detection of an abusive or neglectful situation.[12]

Epidemiology

It has been estimated that 2 million elders are neglected or abused annually in the United States.[8] In a survey of Adult Protective Services throughout the United States, between 2000 and 2004 there was a 19.7% increase in reports of elder abuse and a 15.6% increase in substantiated cases of elder abuse.[13] According to the National Elder Abuse Incidence Study, the median age of victims of elder abuse is 77.9 years, and two thirds of victims are women. Of the identified elder abuse victims, 66% are white, 19% black, and 10% Hispanic. More than two thirds of perpetrators of elder abuse are family members, primarily spouses and grown children, and the overwhelming majority of victims live with the perpetrators. A total of 77% of victims are unable or only somewhat able to care for themselves; 60% of victims are either very confused or occasionally confused. In addition, 37% of elder abuse victims are moderately depressed and 6% are severely depressed.[14] Surveys of noninstitutionalized elderly people in the community have revealed that between 3 and 5% had

experienced elder abuse or neglect, and the rates of psychological abuse were even higher.[15] Numerous studies have shown that as few as 1 in 14 cases of elder abuse is actually reported.[15]

DEFINITIONS AND TYPES OF ELDER ABUSE

Some of the difficulty in establishing the true incidence and prevalence of elder abuse stems from the lack of uniformity of definitions of elder abuse, both among researchers and in legislation. Definitions vary from state to state and often lack objective criteria for reliably establishing a medical diagnosis. Elder abuse is a form of family violence, along with child abuse and intimate partner violence. There are three main categories of elder abuse: domestic elder abuse, institutional elder abuse, and self-neglect or self-abuse. *Domestic elder abuse* includes any form of elder abuse that occurs in the elder's home or the caregiver's home by a family member or the caregiver. *Institutional abuse* includes any form of elder abuse that occurs in a residential facility for elderly persons, usually by individuals who are hired to provide care. *Self-neglect* or *self-abuse* is the result of the behavior of an elderly person and threatens the well-being of that individual. Self-neglect usually involves the refusal or failure of elderly individuals to provide themselves with basic necessities, such as food, water, shelter, medications if indicated, and appropriate personal hygiene. In 45% of cases of self-neglect, elders 80 years of age or older are involved.[16] Self-neglect does not include mentally competent elderly individuals who understand the consequences of their decisions.

In addition to the three main categories of elder abuse, 33 forms of elder abuse have been described.[17] These forms of elder abuse can be grouped into six types: physical abuse, sexual abuse, emotional or psychological abuse, neglect, abandonment, and financial or material exploitation.[16] In a study of substantiated cases of elder abuse, 58% involved neglect, 11% physical abuse, 15% exploitation, 15% emotional abuse, and 1% sexual abuse.[13] Victims of elder abuse are often subjected to multiple types of elder abuse.

Physical abuse is defined as the intentional use of physical force that may result in bodily injury, physical pain, or impairment.[16] Physical abuse is the most readily detected type of elder abuse. It includes slapping, hitting, kicking, pushing, pulling hair, and burning. Physical abuse may include overmedication or undermedication, the use of physical restraints, or force-feeding. It may also involve the use of household objects as weapons, as well as the use of firearms and knives.

Sexual abuse is defined as any type of sexual contact with an elderly person that is nonconsensual.[16] It may include sexual assault, sexual coercion, verbal and physical sexual advances, and indecent exposure. Sexual abuse also occurs if an elderly individual is incapacitated and therefore incapable of giving informed consent.

Emotional or *psychological abuse* is defined as intentional infliction of suffering, pain, and distress through verbal or nonverbal means.[16] Emotional abuse may include such acts as insulting or demeaning comments, name calling, threats of deprivation, isolation, and humiliation. Emotional abuse may accompany physical abuse or other forms of abuse.

Neglect is defined as the failure or refusal of caregivers to fulfill any of their duties or obligations to an elderly individual, which has resulted or is likely to result in serious harm to the elderly individual.[16] Neglect is the most common type of elder abuse.[18] Neglect may be either unintentional or intentional. However, intent is often very difficult to prove. Unintentional neglect may result from the inability of the caregiver to carry out responsibilities because of physical or mental inability or a lack of knowledge of how to care properly for the elderly individual. Neglect may consist of withholding of food, water, clothing, shelter, medications, medical equipment (e.g., walker, cane, glasses, hearing aids, dentures), or medical appointments.

Abandonment is defined as the desertion of an elderly person by the caregiver, custodian, or an individual who is responsible for providing care.[16] As many emergency physicians are aware, elderly patients may be abandoned in the emergency department. One survey reported that a median of 24 elderly patients were abandoned annually per emergency department, with 46% living alone and no longer being able to look after themselves and 41% being left in the emergency department by family members or a caregiver.[19] Abandonment may be considered a form of neglect.

Financial or *material exploitation* is defined as the illegal or improper use of an elderly person's money, property, or assets.[16] Financial exploitation includes denying an elderly person his or her home; stealing money or belongings; and coercing an elderly individual into signing contracts, changing a will, or assigning durable power of attorney to someone against his or her wishes.

In this chapter the term *abuse* will be used to encompass any of the types of abuse described above.

ETIOLOGY AND RISK FACTORS FOR ELDER ABUSE

There are several theories of the etiology of elder abuse.[20] More recent focus has been directed toward the abusing relative or caregiver. The social learning or transgenerational violence theory proposes that children who grow up in an abusive household may go on to be abusive against their own children and perhaps parents. Another theory, the stressed caregiver theory, proposes that as a caregiver becomes increasingly stressed (from caregiving or other causes), elder abuse is more likely to occur. Some researchers theorize that it is the psychopathology of the abuser that leads to elder abuse. Proponents of the isolation theory contend that as elderly individuals become more socially isolated as a result of illness, disability, and age, they are at increased risk for abuse. Those who adhere to the dependency theory believe that increasing frailty is the underlying etiology for elder abuse, whereas others contend that frailty only prevents many elders from protecting or defending themselves and the true etiology lies with the abuser.[21] It is now recognized that no single theory can account for all situations of abuse or neglect. An integrated theoretical model may describe all potential factors involved, and each circumstance may involve some components to a greater degree than others.[21]

Although numerous risk factors for elder abuse have been proposed, research is lacking and the list is far from definitive (Table 66-1). Therefore, emergency providers should be alert to the possibility of abuse among all elderly patients. Risk factors for elder abuse may be divided into four main categories: caregiver risk factors for abusing, elder risk factors for being abused, environmental risk factors, and institutional abuse risk factors.

CLINICAL FEATURES

In addition to the risk factors stated previously, other findings suggestive of elder abuse are abandonment of the patient in the emergency department by the caregiver, frequent visits to the emergency department, lack of compliance with medical appointments and medications, and the use of numerous phy-

Table 66-1 Potential Risk Factors for Elder Abuse[20,22]

Caregiver Risk Factors
Alcohol or drug abuse
Mental illness
Financial stress
Stress resulting from caring for the elder (e.g., a lack of resources)
Outside factors resulting in stress (e.g., unemployment)
Financial dependence on the elder
Unrealistic expectations regarding caregiver responsibilities
Lack of caregiving skills
Long duration of time as a caregiver

Elder Risk Factors
Physical/functional impairment
Financial dependence on the caregiver
Cognitive impairment/dementia
Social isolation
History of family violence
Aggressive behavior
Female
Advanced age
Incontinence
Frequent falls

Environmental/Family Factors
Shared living situation
Overcrowded living conditions
Lack of family/community support
Socially isolated

Risk Factors for Institutional Abuse
Poor working conditions
Inadequate training, experience, and supervision of caregivers
Low wages
Low staff-to-patient ratio

Table 66-2 Questions for Use in Asking Patients about Elder Abuse[22,26]

General
Do you feel safe where you live?
Are you afraid of anyone where you live?
Who assists you if you need help?
Who makes your meals?
Who helps you take your medications?
Who manages your checkbook?
Do you have frequent arguments with your family/caregiver?
What happens when you argue?

Physical Abuse
Have you been hit, slapped, or kicked?
Have you ever been locked in a room?
Have you ever been tied down?
Have you ever been forced to eat?

Sexual Abuse
Has anyone ever touched you sexually without your consent?

Psychological or Emotional Abuse
Do you feel alone?
Are you yelled at where you live?
Has your family/caregiver ever threatened to punish you or have you put in an institution?

Neglect
Are you left alone often at home?
Do you need to use hearing aids, glasses, and dentures, a walker, or a cane? Are they readily accessible to you?
Does your family/caregiver ever fail to help you when you need help?

Financial or Material Abuse
Has anyone ever taken anything from you without asking?
Have you been forced to sign a will, power of attorney, or any documents that you did not understand?
Does your family/caregiver rely on you for housing or financial support?

sicians and emergency departments for care rather than one primary care physician ("doctor hopping").

Elderly patients are four times more likely to present to the emergency department by ambulance than nonelderly patients.[23] When elders present to the emergency department by ambulance, the emergency medical technicians or paramedics may be invaluable in identifying at-risk elders on the basis of their assessment of the home situation and the family dynamics at the home.[24] Prehospital care providers should be questioned about the cleanliness and upkeep of the home; the availability of electricity, heat, water, and sanitation; infestation by rodents or vermin; and the safety of the interior of the home for the older patient.

The American Medical Association (AMA) has recommended that all health care providers routinely ask their older patients about abuse, even in the absence of signs of abuse.[25] Patients should always be questioned in as private a situation as possible, after the family or caregiver has left the room. If the patient suffers from dementia or is unable to answer questions for other reasons, individuals who have knowledge about the patient, other than the caregiver, should be questioned, such as other family members, visiting home nurses and assistants, therapists, primary care physician, or neighbors. If a translator is needed, someone other than a family member or the caregiver should be utilized. To broach the subject of elder abuse, the emergency health care provider should begin by asking about the patient's care in general and then focus on abuse and specific types of abuse (Table 66-2). Factors that have been shown to have a significant association with suspected elder abuse include a brittle support system, feeling lonely, expressing conflict with family or friends, alcohol abuse, short-term memory problems, and psychiatric illness.[27] One study has determined that emergency department nurses can be trained to routinely ask older patients about neglect and appropriately refer them for care.[28] There are now several instruments that can be used to assist medical personnel in inquiring about and identifying abuse and neglect. These tools involve direct questioning of the elder, recognizing possible physical signs, or identifying risk factors. No single test has been found to be optimal, but the use of multiple approaches may be most helpful in recognizing abuse victims.[29] If elder abuse is identified, the patient should be questioned further about the duration and frequency of the abuse, the nature of the abuse, and whether there has been intervention or assistance in the past because of the abuse.

There is increasing evidence that elder abuse is associated with adverse health outcomes, including increased dementia, depression, and premature death.[30,31] Therefore, a thorough, well-documented medical history and physical examination should be performed.[25] When the medical history of an elderly patient is taken, it should be elicited from the patient and caregiver separately and alone. Potential historical indicators of abuse are listed in Table 66-3. As part of the medical history, the patient and caregiver should be asked about routine medications. The discovery of caregivers who are unfamiliar with daily medications and other necessary medical care of the elderly patient (e.g., dressing changes) should raise the suspicion of elder neglect. If injuries are noted, the patient should be questioned about how the injuries occurred. Patients should be asked directly whether anyone has hit, punched, or kicked them. If the injuries occurred as a result of interpersonal vio-

Table 66-3 Indicators from the Medical History of Possible Ongoing Elder Abuse

Implausible history of injury mechanism
Inconsistent history of injury mechanism between the patient and caregiver
Delay between onset of medical illness or injury and seeking medical attention
Unexplained injuries
Elderly patient referred to as "accident prone"
Past history of frequent injuries
Noncompliance with medications, appointments, or physician directions
Caregiver not able to give details of the patient's medical history or routine medications
Caregiver answers the questions regarding the patient
Patient or caregiver reluctant to answer questions
Strained patient-caregiver interaction
Poor living conditions according to paramedics or others

Table 66-4 Signs of Physical Abuse, Sexual Abuse, and Neglect that May Be Noticed on the Physical Examination

Physical Abuse
Contusion
Contusions on bilateral upper arms (grab marks)
Abrasions
Burns (e.g., from cigarettes, irons, immersion)
Sprains
Patterned injuries (e.g., marks consistent with the shape of a belt, fingers, electrical cord)
Traumatic alopecia
Bite marks
Restraint marks (e.g., involving wrists, ankles, and torso)
Fractures
Multiple injuries in various stages of healing
Blunt head trauma
Intra-abdominal injuries (e.g., liver, spleen)
Gag marks
Ocular injuries (e.g., hyphema, retinal detachment)
Physical Signs of Sexual Abuse
Evidence of genital, rectal, or oral trauma (e.g., contusions, lacerations, erythema)
Evidence of sexually transmitted disease
Physical Signs of Neglect
Dehydration
Evidence that the patient has been lying in urine and stool
Malnutrition
Clothing inappropriate for the climate; dirty or severely worn
Poor body hygiene
Untreated injuries and medical problems
Poor oral hygiene
Skin breakdown (e.g., decubitus, pressure sores)
Elongated toenails

lence, the relationship between the patient and abuser should be ascertained. Providers should inform their patients if they are mandated to report abuse when it is disclosed by a patient. However, most states mandate reporting elder abuse even if it is only reasonably suspected. Because elders may be afraid to disclose abuse, it is important that providers reassure their patients that the goal is to provide a safer living environment for the elderly patient, not primarily to punish the caregiver. When a patient expresses fear about a report, the health care provider should give this information to Adult Protective Services in the report so that risk to the patient can be minimized.

When performing a physical examination of an elderly patient, the emergency provider should look for signs of physical abuse, sexual abuse, and neglect (Table 66-4). The provider should use clinical skill and judgment to decide whether physical findings are suspicious for elder abuse or represent pathology. Illnesses that may resemble elder abuse occur frequently in older patients (e.g., easy bruising, fractures resulting from osteoporosis or osteopenia, dehydration). Elder abuse is included in the differential diagnosis of numerous conditions that occur frequently in the geriatric population. Elderly patients with multiple clinical findings consistent with elder abuse have a higher likelihood of being victims than patients with isolated findings. In addition, injuries and medical conditions for which no underlying etiology can be determined are more likely to be a result of abuse.

During the physical examination, the general appearance (e.g., cleanliness, hygiene, and dress) and behavior (e.g., agitated, fearful, withdrawn) of the patient should be noted. The skin should be examined for unexplained bruises, particularly of the head, face, torso, back, bilateral upper arms, inner aspect of the arms, or inner aspect of the thighs. Additionally, bruising on the neck, ears, genitalia, buttocks, or soles of the feet is suspicious in an elder.[32] Attention should be paid to the state of care of decubitus, if present. (Figs. 66-1 and 66-2) Head and facial injuries, including broken teeth, lacerations, or the absence of hair, may reflect abuse. If the genitourinary examination reveals evidence of trauma or vaginal bleeding and sexual abuse is suspected, a complete sexual assault examination, including collection of evidence, should be carried out as for other cases of sexual assault. The extremities should be examined for evidence of contractures that may indicate confinement for long periods, burns in a glove-stocking distribution related to immersion, and wrist and ankle lesions from restraints (Fig. 66-3). The patient's gait should be observed. If there has been a recent change in the patient's ability to ambulate, further imaging studies should be performed to rule out an occult fracture (e.g., hip fracture). A thorough neurologic examination should be performed with careful attention to an alteration in the patient's mental status, focal neurologic findings, and dementia. The recent development of focal neurologic deficits may be a result of blunt head trauma. Longstanding focal neurologic deficits, such as hemiparesis from a cerebrovascular accident, suggest increased needs for care of the elder. The elderly patient's mental status should be assessed. Subtle changes in the elder's mental status may be the only signs of ongoing abuse. Dehydration and malnutrition are the most frequent physical findings of neglect.

An elderly patient who is being emotionally or psychologically abused may display deterioration in mental health and show signs of post-traumatic stress disorder. The patient may demonstrate fear, anxiety, or infantile behavior in the presence of the caregiver and may also exhibit poor self-esteem. On questioning, the elderly patient may admit to ambivalent feelings toward the family member who is the caregiver, as well as express feelings of mistrust related to the caregiver. The caregiver may also be emotionally abusive in the presence of the emergency health care provider. Elderly patients who are being physically abused, sexually abused, or neglected may also demonstrate findings similar to those of emotionally abused elderly patients.

DIAGNOSTIC STRATEGIES

When elder abuse is suspected, laboratory investigations and imaging studies should be obtained as indicated by the history

Figure 66-1. Case 1: A 72-year-old woman was brought to the emergency department by paramedics for "not eating for 5 days" according to her family. The paramedics noted she was covered in urine and feces. The following signs were of concern for neglect: elongated toenails (**A**), pressure sores (**B**), poor hygiene, and a delay in seeking medical care. (Courtesy of Dr. D.C. Schneider.)

Figure 66-2. Case 2: A 70-year-old man was brought from his caregiver's home to the emergency department by police after his daughter found him severely bruised. He had multiple contusions at varying stages of healing on his chest and arms, as well as a linear patterned injury across his left anterior chest. The central and bilateral locations of the contusions, varying colors, and linear pattern of the bruise on his left chest are highly suggestive of physical abuse. (Courtesy of Dr. D.C. Schneider.)

Figure 66-3. Case 3: A 65-year-old developmentally delayed but ambulatory woman was brought to the emergency department by her family on account of "unruly behavior." Examination of her left heel revealed a pressure ulcer and her left ankle revealed an erythematous rash in a circumferential pattern. This may represent the use of a restraint, resulting in the pressure ulcer. (Courtesy of Dr. D.C. Schneider.)

and physical examination. The emergency provider should have a lower threshold for ordering imaging studies for elderly patients secondary to difficulty in obtaining a history in some cases, the increased frequency of osteopenia and osteoporosis, and the tendency of some elders to minimize pain (Fig. 66-4). Metabolic laboratory tests may be helpful in determining electrolyte, nutritional, or endocrine abnormalities. Toxicologic studies may be helpful to document compliance with medications, overmedicating or undermedicating by the caregiver, and, in severe cases of elder abuse, evidence of poisoning.

DOCUMENTATION

Accurate and thorough documentation of the history and physical examination in cases of suspected elder abuse is essential.[22,26] The history of any suspected types of abuse, as well as the mechanism of injury, should be documented in the patient's own words, if possible. Documentation should include details of the pertinent social history (e.g., caregiver's identity, living arrangements, functional status). A description of any injuries should include types of injuries (e.g., fractures, lacerations, and contusions), number, size, location, color, and stage of healing, or approximate ages of the injuries. When possible, photographs of the injuries should be taken before rendering treatment. In addition to photographs, the locations and types of injuries should be documented on a body map or diagram. In California, a statewide form has been developed for the purpose of documenting a forensic examination in cases of elder abuse.[33] At this time, its use is not mandated. The explanation given by the patient for the mechanism of each injury should be included in the history, as well as whether the explanation seems appropriate. If the explanations for the injuries seem reasonable, a statement reflecting that the physical examination is compatible with the history may be included in the medical record. The results of laboratory investigations and imaging studies should also be recorded. Follow-up plans, referrals, and interventions should be documented in the medical record. If a report is made to Adult Protective Services, the name of the individual contacted or the case number should be recorded. In addition, if law enforcement is contacted, the name and badge number of the officer taking the report should be documented. In cases of suspected elder

Figure 66-4. Case 4: An 87-year-old white woman was brought by the paramedics to the emergency department from a skilled nursing facility on account of swelling of her right ankle. A phone call to the nursing facility determined that at baseline, the patient had dementia and was nonverbal and nonambulatory, needing to be lifted from her bed to a chair. Radiographs of her left ankle revealed a fracture of her medial malleolus and distal fibula, suspicious for physical abuse. The hospital's Adult Protection Team was consulted and contacted the Long-Term Care Ombudsman to investigate the nursing facility.

abuse that result in legal action, thorough documentation may be critical in determining the outcome and ultimate care of the patient.

CAREGIVER INTERVIEW

Part of the assessment of a suspected victim of elder abuse involves interviewing the caregiver or suspected abuser. The needs of both the caregiver and the elder should be addressed. To obtain beneficial information and not create a confrontational situation with the caregiver or suspected abuser, questioning should proceed in a nonthreatening and nonjudgmental manner. The goal is not to punish the caregiver but rather to stop the abuse. Accusations are likely only to curtail the amount of information the caregiver provides to the emergency physician. The caregiver or suspected abuser should be interviewed separately from the patient. Conducting separate interviews may reveal discrepant histories between the caregiver and the patient. Initially, questioning should be directed at the reason for presenting to the emergency department. Subsequently, questions should be directed at the patient's medical conditions and the daily care requirements, including routine medications and assistance with activities of daily living. Caring for an individual with chronic illness who frequently requires assistance with basic activities of daily living is a difficult and tiring task.[34] Therefore, verbal expressions of sympathy, explicit recognition of the challenges, and demonstrations of support can be beneficial for the caregiver and also promote information sharing. Statements such as "Caring for your mother must be a difficult task. Do you ever feel anger or resentment toward her?" may actually allow the family member or caregiver to express valid frustrations. Questions should also explore whether any recent stresses have occurred in the household, whether the caregiver feels that the patient is a financial burden, and whether any respite services or other home help services have been made available.

INTERVENTIONS AND REFERRALS

When elder abuse is suspected or identified, provision for immediate care needs, situational assessment, long-term care planning, and steps to prevent future abuse are all required. Emergency department interventions in elder abuse differ from those in child abuse primarily because the physician must respect the wishes of the mentally competent elderly adult. The older adult should be able to live in the least restrictive environment possible, and institutionalization should not automatically be regarded as a solution to ending the abuse. For many elders, the prospect of being institutionalized is worse than continuing to live in an abusive situation. In addition, providing home care assistance, respite care, and other in-home resources to the caregiver and elderly patient is more cost effective than institutionalization.[26] Therefore, one of the goals of management of elder abuse is to keep the family unit together, when possible, rather than have the elder removed from the home.

If there is immediate danger, the patient should be prevented from having any contact with the suspected abuser, which may involve being removed from the home. Hospitalization may be required for injuries and ongoing medical problems. However, in the absence of an acute medical illness, medical insurance companies and third-party payers may not cover the cost of hospitalization, and a safe-house placement may be required.[35] Physicians should be aware of the diagnosis and diagnostic codes that should be used in cases involving suspected or confirmed elder abuse and neglect, Adult Maltreatment (unspecified) (ICD-9: 995.8; ICD-10: suspected T76.91, confirmed T74.91) and the additional codes for specific types of abuse.[36,37]

If the patient refuses intervention, the emergency provider must determine whether the patient is capable of making his or her own decisions. In some instances a psychiatric consultation for the determination of capacity may be required. If the elderly patient is found not to have the capacity to make his or her own decisions, Adult Protective Services should be notified to arrange court-ordered guardianship. The wishes of a competent elderly patient must be respected even if the patient desires to return to an abusive situation.

In suspected cases of elder abuse that pose a less imminent threat, interventions should be individualized.[25] If the patient wants to return home and may be safely discharged from the emergency department, a follow-up plan should be established. This is best accomplished by a multidisciplinary team consisting of the patient's primary care physician, nurses, social workers, and occupational therapists or a geriatrics assessment team. Another approach includes Adult Protective Services caseworkers as members of the geriatric team.[38] The follow-up assessment should consist of an evaluation of the patient's functional, cognitive, medical, and emotional status. Social and financial resources should also be determined. The frequency, severity, and intent of the abuse should be assessed. At least one home visit should be included as part of the assessment.

The needs of the caregiver should also be assessed. Support services such as in-home services, respite care, psychological

counseling, employment referrals, and alcohol and drug abuse rehabilitation program referrals should be provided, as needed. For the short term, the emergency health care provider may assist the caregiver by obtaining increased involvement from other family members or friends, close follow-up with the patient's primary care physician, a social services consultation, home nursing assistance, and the involvement of Adult Protective Services. Other referrals that may be beneficial for both the elderly patient and the caregiver include senior centers, medical transport services, Medicare referral, Meals-on-Wheels, senior's housing, Social Security benefits, religious communities, home health, adult day care, hospice care, and victim assistance. Addressing behavioral issues in the elderly may also be very helpful to an overwhelmed caregiver.[39] Ultimately, if the caregiver has severe personal problems that cannot be resolved, the only solution may be separation of the elder from the caregiver. If the elderly patient is competent and does not wish to accept interventions, he or she should nonetheless be educated about elder abuse and given referral materials. Some cases of elder abuse are actually intimate partner violence, committed by the elder's spouse.[15] In these cases, intimate partner violence advocacy services should be consulted.

Elderly victims should be educated about elder abuse and the likelihood that it will increase in frequency and severity over time. All emergency departments should have protocols for the management of suspected cases of elder abuse to facilitate management and ensure appropriate care for these elderly patients.[40] This recommendation has been made by the AMA, the American College of Emergency Physicians, and other professional medical organizations.[25,40] Some emergency departments also have access to in-house elder abuse response teams that can be mobilized to assist the emergency physician with the management of these complex cases.[41]

REPORTING REQUIREMENTS

In all 50 states and the District of Columbia laws have now been enacted that pertain to the reporting and investigation of elder abuse. However, the definitions of elder abuse and requirements of the laws vary from state to state.[42] In most states, physicians are mandated to file a report if they know or reasonably suspect that elder abuse has occurred, and in several additional states physicians are mandated to report only if the suspected victim resides in a nursing home.[43] Many of the states with mandatory reporting requirements also grant immunity to physicians who report suspected elder abuse. Most state laws also have a penalty for failure to report.[44] These penalties usually consist of a fine or a jail sentence, or both. In most states, Adult Protective Services is designated as the agency responsible for receiving and investigating all reports of suspected elder abuse. The laws vary widely concerning the age at which "elder" is defined, with most states defining it as 60 years or older. In addition, the laws vary in their definitions of the circumstances of the abuse, types of abuse, the reporting and investigation of the abuse, and specifics regarding domestic and institutional abuse. Additional criminal laws regarding assault and battery, theft, fraud, rape, and murder may also pertain to elder abuse. Laws concerning guardianship and conservatorship, durable powers of attorney, intimate partner violence, and family violence may also be related to elder abuse. Emergency providers should become familiar with state laws pertaining to elder abuse and their duty to report in the state in which they practice.

There are several issues regarding the mandatory reporting laws for elder abuse. Some physicians are concerned that reporting elder abuse constitutes a breach of confidentiality with their patients. Others are concerned that mandatory reporting may deter elders from seeking medical care. The AMA has stated that health care providers should inform their patients if they have a legal obligation to report elder abuse and the medical necessity to intervene in cases of elder abuse. The AMA also emphasizes that the goal is to end the abuse by facilitating access to resources for the patient and their family.[25] There is a great need for standardization of legislation and increased funding to provide adequate service delivery to elder abuse victims and their families.[42]

Elder abuse is often underrecognized or underreported by emergency physicians. Reasons include[20,26] a lack of awareness of the prevalence of elder abuse, ageism (discrimination against the elderly), lack of knowledge of the appropriate management of suspected elder abuse, lack of an emergency department protocol for suspected elder abuse, lack of time to conduct a time-consuming evaluation of the suspected abuse, the emergency physician's concern about litigation, the emergency physician's concern about having to take time away from the practice to testify in court, and the ethical issue of not wanting to breach physician-patient confidentiality. One study found that only 2% of reports of elder abuse were made by physicians.[45] Physicians were most likely to report physical abuse and least likely to report exploitation.[45] It is unclear whether this was due to underrecognition of the abuse by the physicians or the use of other team members in making the report of abuse.

Elderly patients may also contribute to the difficulty in identifying elder abuse, willingly or unwillingly, because of isolation resulting from illness or age; inability to report abuse; reluctance to disclose the elder abuse owing to embarrassment or guilt; fear of retaliation by the abuser; wanting to protect the abuser, who is often a spouse or a child; fear of the consequences of the discovery of the abuse; fear of institutionalization; cultural or ethnic beliefs and backgrounds; and feeling that they are a burden to their families.

INSTITUTIONAL ABUSE

Approximately 5% of all elderly individuals reside in institutions such as nursing homes, board and care homes, and other assisted-living facilities.[46] With the growing elderly population, this percentage is estimated to increase significantly in the future. In 1976, the Older Americans Act established the Long-Term Care Ombudsman Program to monitor nursing homes and board and care facilities and to investigate cases of suspected elder abuse. This program is present in all 50 states. In 1987, the Nursing Home Reform Act included the right to be free from physical, sexual, and emotional abuse as well as isolation. Elderly residents of institutions may be subjected to abuse by other patients, visitors, and staff. A random survey of staff in long-term care institutions in one state revealed that 10% of nurses' aides reported committing at least one act of physical violence in the previous year and 40% at least one act of psychological abuse.[47] Risk factors for institutional abuse are shown in Table 66-1. A study examining ombudsman data from six states found that a higher percentage of complaints lodged on behalf of minorities were verified, but a lower percentage were fully resolved.[48] When patients from long-term care facilities present to the emergency department for medical care, emergency providers should be alert to signs of possible abuse. These cases should be reported to the state long-term care ombudsman for further investigation.

ABUSE OF PERSONS WITH DISABILITIES

In most states, the laws protecting elders from abuse also protect persons with disabilities, often referred to as

"dependent adults," "vulnerable adults," or "disabled adults." Included are persons aged 18 or older who have developmental, mental, or physical disabilities. Little is known about abuse and neglect of persons with disabilities; however, adults with disabilities are reported to be at higher risk for abuse than persons without disabilities.[49] In particular, persons with developmental disabilities are at high risk for abuse. The best conservative estimate is that people with developmental disabilities are four to ten times more likely to be victims of crime (or abuse) than people without disabilities[50]; the most pronounced are robbery (12.7 times higher) and sexual assault (10.7 times higher).[51] Emergency providers should have a heightened awareness of the greater likelihood of abuse when managing patients with disabilities and understand the mandated reporting laws and resources available to disabled victims in their state.

FUTURE DIRECTIONS

Residency training should include education in identifying and managing elder abuse and the reporting requirements for elder abuse. Emergency providers should also educate their patients and the community about the problem of elder abuse and the resources available in the community to assist elders and their caregivers. They should advocate for increased availability and funding of in-home services for elders. Further, they should engage in research on elder abuse to increase the understanding of risk factors for elder abuse, develop validated questions for the detection of elder abuse, determine effective management protocols, and evaluate effective preventive interventions.

KEY CONCEPTS

- Emergency health care providers should routinely ask all elderly patients about abuse, even in the absence of signs and symptoms of abuse. All emergency providers should be alert to the possibility of elder abuse.
- The needs of the caregiver should be assessed and support offered.
- An elderly patient who is in immediate danger should be hospitalized or prevented from having any contact with the suspected abuser, which may involve being removed from the home. If the patient is not in imminent danger, assistance may be provided to the caregiver. The family unit should be preserved whenever possible.
- The wishes of a competent elderly patient must be respected, even if the patient is not willing to accept interventions.
- In most states emergency physicians are mandated to report cases of known or suspected elder abuse to Adult Protective Services.
- The diagnostic term "Adult Maltreatment" should be used in cases of suspected or confirmed elder abuse or neglect. The use of this ICD diagnosis may facilitate hospitalization, if necessary, and will improve the accuracy of clinical prevalence data.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 67

Youth, Street Gangs, and Violence

H. Range Hutson and Jared Strote

PERSPECTIVE

Presently, there are approximately 82 million children and adolescents under the age of 20 in the United States. This population is increasingly composed of older adolescents and ethnic minorities. Adolescents are particularly vulnerable to violence and injury because of developmental issues, including independence and autonomy, curiosity leading to experimentation (e.g., alcohol, drugs, sex), peer group pressure, immaturity, impulsivity, the feeling of invincibility, narcissism, and problems with self-identity.[1] Other factors that increase the vulnerability of adolescents to violence include the breakdown of family and community structure, media violence, and easy accessibility to lethal weapons (e.g., firearms).[2] Data from the Federal Bureau of Investigation estimate that 16% of violent crimes are perpetrated by youths under the age of 18 years.[3]

Contrary to popular belief, violence is a learned behavior, and is predictable and preventable.[4] A child's initial exposure to violence usually occurs in the home (e.g., intimate partner violence, child abuse, elder abuse, corporal punishment) and increases an adolescent's predisposition to violence. The degree to which adolescents are exposed to violence in the home, community, school, media, sports, and peer groups and the extent to which they are victims of violence are associated with their own use of violence.[5,6] Except for rape, adolescent males are exposed to more violent acts than females and perpetrate more violence than females, with inner city youth having greater exposure to violence than others.[5,6]

Historically, injuries have been mistakenly called "accidents" because they have been viewed as unpredictable and uncontrollable. Epidemiologic research now shows that injuries, like other diseases, occur in highly predictable patterns and are controllable and preventable. Every year in the United States, approximately 16 million children and adolescents are treated in the emergency department (ED) for injuries, 600,000 are hospitalized, and 30,000 sustain permanent physical and neurologic sequelae from their injuries.

Injury is the leading cause of death during the child and adolescent period, causing more deaths than all other diseases combined.[7] For every death attributable to violent injury involving children and adolescents, there were 8 hospitalizations and 108 ED visits.[8] Assault is a leading cause of injury, particularly in adolescents, and this is the most common group victimized by violent crime.[9] Physical fighting is one of the most important risk factors for homicides, particularly for male adolescents.[10,11] Homicide is the second leading cause of death for those between 15 and 24 years of age. In addition, homicide is the leading cause of death among African American males, who are six times more likely to die from homicide than white males in this age group.[7,12] Further, homicide rates for children and adolescents are peaking at progressively earlier ages.[1] Adolescents are disproportionately represented as perpetrators and victims of violence,[5] while one third of individuals arrested for violent crimes (e.g., assault, rape, and homicide) are adolescents.

VIOLENCE IN SCHOOLS

Many adolescents report that their greatest fear is school violence.[13] In a national survey, 6% of students had not gone to school due to feeling unsafe at school and 6.5% had carried a weapon in the prior 30 days due to feeling unsafe at school. The study also noted that 13.6% of students had been in a physical fight on school property and 7.9% had been threatened or injured with a weapon in the prior 12 months.[14] Although the rates of physical fighting and weapon carrying have decreased from 1993 to 2003,[15] the availability of firearms to urban adolescents is pervasive and not limited to gangs or others at high risk for violence.[5,16]

Half of all school-associated violent deaths occur during transition periods during the school day (beginning of school, lunch period, end of school day). Most firearms used in school-related deaths are obtained from the perpetrator's home.[17]

Although other school violence is decreasing,[15] bullying is now being increasingly recognized. Bullying is designed to intimidate or harm an individual or group of individuals. Verbal intimidation, and increasingly, electronic harassment (e.g., text messaging, social network sites) are the most common forms; however, an association with physical violence is growing.[18–20] Bullying commonly starts in elementary school and continues throughout junior high and high school. Although bullying occurs among girls, it is a much larger male phenomenon, especially when it is associated with physical violence.[15,21–26]

In the National Crime Victimization Survey, 21% of students report that street gangs are present in their schools, and they are likely to fear being assaulted in school or on their way to and from school.[15] Gang members are seven times more likely to own a firearm than children and adolescents not in gangs.[27] For these reasons, many children and adolescents are fearful about going to school, resulting in more weapons being brought to school for personal safety.[28] During the 1999–2000 school

year, 32 school-associated violent deaths occurred, 9% of elementary and secondary school teachers were threatened with injury by a student, and 4% of teachers were physically attacked by a student.[15]

MEDIA VIOLENCE AND ITS EFFECT ON CHILDREN AND ADOLESCENTS

Children and adolescence are exposed to increasing amounts of media violence in movies, video games, youth-oriented music, the Internet, and especially television. By age 18, children have seen approximately 200,000 violent acts portrayed on television and approximately 20,000 homicides, and spend more hours watching television than attending school.[29] When today's children and adolescents reach age 70, they will have spent 10 years watching television.[30] Saturday morning children's programming still contains 20 to 25 violent acts per hour. Before age 8, children cannot consistently discriminate between real life and fantasy in entertainment. Through television and other forms of media violence, children and adolescents learn and imitate violent behavior, particularly if the aggressor is the hero or the heroine.[30,31] The more realistic the violence portrayed, the greater the probability the violence will be imitated by children and adolescents. Of young men incarcerated for violent crimes (e.g., homicide, rape, and assault), 22 to 34% consciously imitated crimes learned from television. In the media, violence is a quick, effective ending for disagreements and does not show the importance of patience, negotiation, and compromise in resolving conflicts and disagreements.[32] Media violence does not portray the true physical and psychological consequences of violent acts. This may lead children and adolescents to accept violence as a normal way of life, desensitizing them to future acts of violence and making them less likely to intervene when violent acts occur.[32]

Media violence has consistently been associated with significant increases in aggressive and criminal behavior. The most important factors are how much violence is viewed, identification with violent characters, and the perception that TV violence is real.[33,34] On television, one fourth of all violent scenes involve use of a handgun.[35] Forty percent of top-grossing movies rated for "general audience" and "parental guidance suggested" feature at least one character carrying a firearm.[36] Studies have shown that eighth and ninth graders who play video games frequently get into more arguments with teachers, get into more physical fights, and see the world as a more aggressive place.[37] Further, research shows that school shootings often relate to first-person shooter video games (e.g., Doom, Halo).[38] Studies also note the large amounts of violence in "Everyone"-rated video games.[39] In fact, 94% of games rated for teens contain violent acts.[40]

Short-term effects of viewing include excitement and imitation; long-term effects include desensitization to violence outcomes and socialization of violent behavior.[41] Mediators of these effects include justification for the behavior and consequences of aggression, perceptions of realism and identification with aggressive characters, age, gender, aggressiveness and intelligence of viewer, socioeconomic status, and parental influence.[41]

ADOLESCENTS, DRUG ABUSE, AND VIOLENCE

In the United States, 3 million adolescents have alcoholism, and another 400,000 adolescents require treatment for drug abuse. Illicit drugs cost $75 billion per year for law enforcement, incarceration, legal costs, medical treatment/hospitalization, and drug prevention programs, in addition to $70 billion per year spent for the purchase of illicit drugs. Illicit drugs account for almost half of the 1 million individuals incarcerated, requiring an enormous amount of time for law enforcement and almost 50% of judiciary work time.[42] In youth 12 to 17 years of age, 5.4% are dependent on alcohol and 4.6% are dependent on illicit drugs; 350,000 require treatment for alcohol or drug use each year. Two million are dependent on or abuse alcohol or drugs.[43]

From ages 10 to 13 years, children begin experimenting with a wide range of new behaviors. Cigarettes, alcohol, and other types of drugs are a normal part of the "coming of age" for many children, regardless of race, culture, socioeconomic status, or geographic location. Substance use follows a predictable pattern, beginning with experimentation with cigarettes and alcohol, followed by marijuana, then cocaine. Other drugs, including opioids and hallucinogens, typically occur later in the sequence. This does not mean that an adolescent necessarily progresses beyond a particular stage. Initially, the adolescent associates drugs with euphoria and pleasure. With regular use, tolerance and the need for particular drugs develop. At this stage, the adolescent is drug dependent and now uses the drug to prevent withdrawal symptoms, which may be physiologic or psychological in nature. For adolescents, any use of a drug is commonly perceived as drug abuse. Adolescents at greatest risk for lifelong substance abuse typically begin using drugs before age 15. Adolescents who are the most seriously affected by substance abuse are usually those who are least involved in school or other meaningful activities.[44]

The precise relationship has not been completely elucidated, but drugs and violent behavior are related to drug use (pharmacologic violence), to drug procurement (economic violence), and to the illicit sale of drugs.[45–48] Alcohol is the most commonly used drug associated with violence. The pharmacologic effects of alcohol contribute significantly to the prevalence of adolescent fighting, suicide, homicide, unintentional injury and death, rape, and physical assaults.[49] Cocaine, barbiturates, phencyclidine (PCP), amphetamines, and anabolic steroids also play a role in such violence.[47,48] Medications used for attention deficit disorder, hyperactivity, and the like are increasingly available for abuse. Economic violence can lead to intentional injury and death during the process of obtaining money to finance drug use. The illicit sale of drugs leads to several types of violence between buyers and sellers: robbery for money or drugs, arguments over quality or quantity of the drug, competition for territory or markets for the sale of drugs, and violence as a management strategy to discipline drug-selling subordinates.

FIREARMS

In the United States, eight children and adolescents are killed every day by firearms.[50] For every child killed, three children sustain a firearm-related injury.[51] Sixty percent of firearm assaults are fatal, compared with 4% of knife assaults and fewer than 1% of assaults with blunt objects.[52] There are approximately 218 million privately owned firearms, of which 85 million are handguns.[53] Handguns are involved in most firearm injuries and deaths, although they make up less than one third of all firearms. About half of all households in the United States contain a firearm.[53] Most privately owned firearms are purchased with the idea that firearms increase personal safety and home security, but the risks of firearms kept in the home are often unrecognized.[54] A firearm in the home is 43 times more likely to kill a family member or friend than an intruder.[55] When a gun is fired in the home by an adolescent, the victim

most often is the adolescent (35%), a friend (34%), a sibling (25%), or a parent or relative (6%).[1] Many firearms in the home are stored unlocked and loaded.[56] In one survey, three fourths of children younger than 14 knew exactly where the firearm in their house was located and one third had handled it.[57] Before 8 years of age, few children can distinguish between a toy gun and a real gun.[58]

Death caused by firearms occurs 90 times more frequently in the United States than in any other industrialized nation.[5] The availability of firearms increases the lethality of violent behavior,[59] and easy accessibility plays a major role in the morbidity and mortality of children and adolescents. In the past 20 years, there has been a 75% increase in child and adolescent firearm deaths.[52] The firearm homicide rate for boys is three to four times that for girls. The firearm death rate among U.S. children age 14 and younger is approximately 12 times greater than the firearm death rate among children in 25 other industrialized nations combined.[60] Firearm homicide rates are highest among African American adolescent boys in urban areas in the United States.[61] For African American male adolescents, firearm injury is the leading cause of death. Among adolescents, homicides occur most often in urban areas, and suicides occur most often outside urban areas. Among children, those in the most deprived socioeconomic quintile had a 159% higher homicide rate compared with those in the least deprived quintile.[62] A handgun is the weapon used in 82% of adolescent homicides[63]; most adolescent homicides are not premeditated but are impulsive, unplanned, and, in most cases, instantly regretted.[52]

NONPOWDER FIREARMS

Modern technology has transformed the BB gun from a toy to a potentially lethal weapon with a muzzle velocity in the range of small-caliber, low-velocity powder firearms. Other nonpowder firearms include pellet guns and air pistols that use spring-loaded, manual pump compression or pressurized carbon dioxide instead of gunpowder and can cause severe injury or death at close range.[64]

Nonpowder firearms are used predominantly by children and adolescents, with 80% of all injuries by nonpowder firearms in these age groups.[65] These injuries account for 23,000 ED visits per year.[66] Victims of nonpowder firearm injuries are overwhelmingly male.[67] Injuries to the extremities are the most common, with 33% of injuries to the eyes, head, face, or neck.[67] The most serious injuries are intracranial penetration in the region of the orbit or thin regions of the skull. Nonpowder firearm injuries are a common cause of blindness in adolescent boys; other complications include embolization and lead poisoning. Penetration of the heart and aorta occasionally results in death.[68] Overall, nonpowder firearm injuries are more numerous and less severe than powder firearm injuries, but head, chest, and abdominal wounds from these weapons may be erroneously regarded as trivial, with catastrophic results.[64]

PREVENTION STRATEGIES FOR YOUTH VIOLENCE

Children and adolescents lack judgment and experience and cannot be expected to avoid violence and injury by their own accord.[69] Factors associated with youth violence include history of violence victimization, exposure to violence, access to weapons, substance abuse, antisocial beliefs, low parental involvement, low income, poor academic performance, social rejection, low levels of community participation, and high levels of community transience. Factors associated with protection from violent behavior include high grade point average, strong religious beliefs, connectedness to family, ability to discuss problems with parents, and large amounts of social capital in the community.[70] To identify youths at risk for violence, physicians should screen for these risk factors.[71,72]

Many medical associations, including the American College of Emergency Physicians, have policy statements calling for physicians to incorporate youth violence prevention into their practices. To decrease youth violence, physicians and other health care providers should urge the media to do the following: (1) decrease the violence, use of weapons, and pain and suffering depicted in the media; (2) accurately portray the true consequences of violent acts; and (3) decrease the amount of violent lyrics and violent scenes in music videos and video games. Physicians should advise parents to monitor and limit their children's viewing of television, video games, music videos, movies, and the Internet.[73]

Health care providers can encourage schools to address youth violence.[5,74–76] Schools should be encouraged to teach conflict resolution and anger management skills, which represent an empowering step toward avoiding violence. Further, schools can make the learning environment physically safe by decreasing weapons among students. Students should be advised of the risk and legal consequences of carrying weapons to school. Depending on the school and local community, metal detectors and school safety police may be necessary. Schools should work jointly with local communities to decrease violence that occurs on the way to and from school and the overall level of violence in the community. Emergency physicians and other health care providers should encourage school-based counseling concerning violence and injury prevention.[77] This may be a cost-effective method of preventing childhood and adolescent violence.[78–80]

Physicians should educate children, adolescents, and their parents about drug use leading to abuse and dependency and the association between drugs and violence.

Physicians should educate parents about the risk of firearms kept in the home and, if a firearm is present, the proper storage, i.e., unloaded, separated from ammunition, and in a locked box or cabinet. Parents should ask about firearms when their children visit other homes and allow their children to use nonpowder firearms only with goggles, chest protection, and adult supervision.

The hospital and ED medical records of victims of violence should include the circumstances of the violent event leading to the injury. The emergency physician should also document the victim's relationship to the perpetrator of the violent event, the use of alcohol or drugs by the victim, and whether the victim has a previous history of injuries caused by violence. Most importantly, the emergency physician should determine whether the victim plans to seek revenge and provide immediate counseling emphasizing a cooling-off period to prevent further acts of violence. The risk of reinjury or death to the patient and others and the risk of criminal prosecution should be discussed. Health care providers should check with local laws to determine if they may be legally bound to report to law enforcement officers if the patient threatens a specific individual.[81,82] All individuals at risk for reinjury caused by violence should be counseled by either health care providers or social services while in the ED.

VIOLENCE BY STREET GANGS

Street gangs are mainly composed of inner-city adolescents from the same socioeconomic background. Adolescents join street gangs for a sense of belonging, protection, status, adventure, and illegal monetary gain. The vast majority of inner-city youth do not join street gangs.

In the 1950s, street gang violence typically involved fistfights, blunt objects, knives, and occasionally firearms. There was a much lower probability of serious injury or death to gang members or innocent bystanders. Modern-day street gangs are larger, more numerous, more widespread, more violent, and no longer confined to the inner city. More gang members and innocent bystanders are injured or killed since firearms have become the weapons of choice.[83] Drug use and selling, violence, and vandalism significantly increased the likelihood of joining a gang.[84] Gang members, as the ultimate defenders of intrusions in their neighborhood or on their turf by rivals, are willing to die, risk imprisonment, kill rivals, or unintentionally injure or kill innocent bystanders. If a rival street gang insults, challenges, injures, or kills a member of another street gang, it is highly probable that an episode of violence will occur. Being injured, imprisoned, or killed defending the gang or turf often enhances a gang member's reputation and standing in the gang. The more violent the street gang, the greater the reputation of the gang members. Gang members commonly do not testify in court against rival gang members but prefer to enforce their own brand of justice, violently, against rival street gangs. Common reasons for street gang violence include retaliation for previous shootings, rivalry, turf fights, arguments, and, at times, control over an illegal criminal enterprise. Injuries and homicides by violent street gangs occur in many ways, including walk-up shootings, drive-by shootings, stabbings, use of blunt force weapons, and arson. In most instances, street gang violence is intraracial (e.g., African American vs. African American, Hispanic vs. Hispanic).

Violent street gangs are active in 94% of U.S. cities with a population greater than 100,000,[85] yet are also present in many small cities and towns. It is estimated that there are 26,000 gangs and approximately 840,000 gang members nationwide.[86,87] Modern street gangs nationwide have patterned themselves after the street gang subculture in the Los Angeles area (African American street gangs [e.g., Crips, Bloods] and Hispanic street gangs). The street gang subculture has created its own style of dress, form of verbal and nonverbal communication, music, camaraderie, and funeral rituals, which has made it possible for adolescents of any ethnic group or background to identify with the gang lifestyle.[88,89] There are African American, Hispanic, Asian, and white gangs. Some white gangs differ from other ethnic gangs in that they are consistently involved in acts of hate violence.[87]

Life in the gang typically begins around age 13 as a "wannabe," with most adolescents joining the gang at around age 15. The peak ages for violent street gang activity are between 15 and 21 years,[90] after which gang members begin to migrate out. Some members stay active in the gang into their early 30s.[91]

The most likely reasons for increasing gang violence include the growth in the number of gang members, the appeal of the bravado and violent image of gang members, greater levels of intergang violence, an increase in the sophistication of firearm weaponry in gang violence, an increasingly violent society, increased economic despair in urban communities, a breakdown in sociocultural institutions, and an increase in marginalization of urban children and adolescents.[92–94]

Drive-By Shootings

One of the most common violent acts committed by street gangs is the drive-by shooting, defined as gang members shooting at suspected rival gang members from a vehicle. Violent street gangs perpetrate more than 90% of all drive-by shootings. The primary purpose of a drive-by shooting is to create fear, terror, and intimidation among members of rival street gangs. The secondary intent is to kill.[95] Drive-by shootings mainly occur at night in the inner city and generally last 5 to 15 seconds.[91] Most frequently, drive-by shootings occur on public streets, with gang members shooting into cars of suspected rival gang members. Drive-by shootings also include shooting into the homes of suspected rival gang members, in parks, and around public schools.[96] In many drive-by shootings, gang members flash their gang hand sign (a form of nonverbal gang communication) and yell their gang name. This makes it known to all rival gang members which gang actually was shooting at them. Most drive-by shooters are not apprehended by law enforcement.

Drive-by shootings are not random events.[96] No longer confined to the inner city, drive-by shootings are now a national phenomenon and in some regions of the United States have become endemic.[97] Drive-by shootings are a major public health problem because many individuals can be injured or killed in one incident.[98] In one study, 63% of children and adolescents who were shot at sustained a firearm injury, and 5.3% died from their injuries. Thirteen people are injured for each individual killed in a drive-by shooting.[96] For adolescents and young adults, the lower extremity is the most frequently injured body region, followed by the upper extremity. The most frequent fatal injuries are to the chest and head.[96] Small children who are victims of drive-by shootings frequently sustain fatal firearm injuries to the head, neck, and chest. Most small children injured or killed in drive-by shootings are unintentionally caught in the crossfire of gang shootings.[99]

The weapon of choice in a drive-by shooting is a 9-mm semiautomatic handgun. Some semiautomatic handguns may fire 15 or more bullets before reloading. The high-capacity, rapid-fire mechanism of a semiautomatic firearm helps to explain why many individuals may be injured or killed in a single drive-by shooting.[91]

Firearms and Violent Street Gangs

For many gang members, firearms fulfill the need for power, status, protection, and progression from adolescence into adulthood that is no longer being met by traditional sociocultural institutions. Firearms are used in 95% of gang homicides[83] compared with 70% of all homicides.[100] Handguns—particularly semiautomatic handguns—are the most commonly used weapon in gang shootings, followed by shotguns, which are used in 8% of all gang homicides.[83] Rifles are involved in 5% and assault weapons in 3% of gang homicides.[83]

Psychological Effects of Street Gang Violence on Children and Adolescents

Some urban communities have higher exposure to street gang violence than others.[5,101] In one group of inner-city adolescents, nearly 85% had witnessed at least one violent act, and 43.4% had witnessed a murder.[102] Children and adolescents living in the inner city are exposed to chronic, pervasive violence rather than isolated episodes of violence. The reactions of these children to this pervasive violence are consistent with those of children and adolescents living in war zones.[103]

On exposure to repetitive or extreme acts of violence, children and adolescents may show signs of sleep disturbance, difficulty concentrating in school, flashbacks, hypervigilance, increased risk-taking behavior, and a nihilistic, fatalistic orientation to the future.[104] Many of these children may also suffer from post-traumatic stress disorder. The severity of a child's or adolescent's reaction to a gang shooting is related to the proximity to the shooting, the threat to the child or adoles-

cent's own life, his or her relationship to others who may have been injured or killed in the shooting, and whether or not gang violence is endemic in their community.[104]

Children and adolescents who live in communities where there are large numbers of street gangs receive little or no counseling for the physical and psychological sequelae resulting from gang violence. The net psychological effect of exposure to gang violence on children and adolescents is unknown but potentially desensitizes children and adolescents to violence and may lead to carrying a weapon out of fear for their own personal safety.

Preventing Gang Violence in the Emergency Department

With the increase in gang violence nationwide, emergency physicians and other health care providers have become vulnerable to injury and death resulting from gang incidents in the hospital environment. The development of guidelines for the prevention of gang violence is recommended to safeguard emergency physicians, other health care providers, patients, and visitors.[105]

In the past, recognition of local street gangs was determined by tattoos, "colors" (e.g., blue for Crips, red for Bloods), typical clothing (e.g., baggy pants, athletic team jackets), and accessories (e.g., sneakers, caps, belt buckles, bandannas), in addition to hand signs. This style of clothing and tattoos has now become popular in all segments of society, however. Information about local gangs may be obtained from community activists involved in gang prevention programs or local law enforcement agencies. All health care providers should know the root causes of violent street gang formation, the effects of gang violence on the community, and the prevention of street gang violence.

Emergency Department Guidelines

1. On the arrival of injured known or suspected gang members, hospital security should be immediately involved, should be stationed in the ED and waiting area, and should secure the hospital perimeters.
2. Consistent with the primary survey examination, the patient should be undressed and searched for concealed weapons.
3. The evidence of previous major trauma (e.g., exploratory laparotomy, thoracotomy, thoracostomy scars) or tattoos may be indicative of previous gang injuries.[106,107]
4. In a calm, nonjudgmental fashion, emergency health care providers should ask the patient whether he or she is a gang member.
5. ED staff should not challenge or insult known or suspected gang members. In the street gang subculture, perceived disrespect often leads to a violent confrontation.
6. While the patient is in the ED, visitation should be limited, preferably to the patient's parents. Other visitors (e.g., friends and relatives) should be kept informed by periodic updates from the ED staff.
7. If admission is required, gang members should be admitted under "John or Jane Doe" status to protect their identity and avoid an outbreak of gang violence in the hospital.
8. Hospital security should be available 24 hours a day and should maintain high visibility and vigilance when injured gang members are present in the ED.
9. When large numbers of gang members (in particular, rival gang members) are present in the ED or waiting area, hospital security should be present and local law enforcement should be advised.
10. Although concerned for their personal safety, ED personnel should not arm themselves with firearms or other weapons while on duty. Health care providers with weapons potentially could escalate the level of violence in the ED. Gang members might view health care providers as adversaries.
11. Community leaders who are experienced with local street gangs may act as mediators between the ED staff and members of violent street gangs. These mediators should be summoned to help decompress any hostile situations that may arise.
12. Hospitals should have lock-down or evacuation plans for ED personnel and visitors in the event that violence erupts within the ED.
13. The ED staff should be educated in the recognition and de-escalation of previolent aggressive behavior.
14. The ED should keep a log of all violent incidents that occur within the ED. This strategy helps to quantify the severity and weapon use in violent incidents and could help determine the necessity for other security measures (e.g., video cameras, metal detectors, bullet-proof glass, armed safety police).

As long as gang violence exists in the community, spillover of the violence into the ED is inevitable. Although concerned about their own safety, ED personnel should deliver compassionate care to all members of violent street gangs, while minimizing their own risk of injury.

Prevention of Street Gang Violence

Law enforcement and the criminal justice system alone cannot solve the violence perpetrated by members of street gangs. The United States should develop a national policy on the issue of violent street gangs, with an emphasis on alleviating the root causes of violent street gang formation. The root causes of violent street formation include poverty, stressed families, lack of education, unemployment, underemployment, racism, marginalization, and a breakdown of sociocultural institutions. Although incarceration is a part of the solution, primary prevention through alleviating the root causes of violent street gang formation would be more effective. For truces among violent street gangs to be effective, they should be supported by concerted efforts to alleviate the root causes of violent street gang formation.[83]

Some gang members are receptive to leaving the gang after being injured or after a fellow gang member has been injured or killed in violent street gang activity.[108] Accordingly, preventive measures to break the cycle of gang membership should occur when injured gang members present to the ED. Hospital-based interventions should begin in the ED and continue throughout their hospitalization. When discharged from the hospital, counseling should continue to intervene further in breaking the cycle of violent street gang involvement. Because many individuals in the community, particularly children and adolescents, may experience the physical and psychological effects of violence, counseling should be made readily available.

Any prevention strategy with a unilateral focus would be unsuccessful in decreasing violent street gang activity and breaking the bonds of gang membership. The solution to street gang violence should involve a multifaceted approach.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

PART III

Medicine and Surgery

CHAPTER 68 Oral Medicine

James T. Amsterdam

PERSPECTIVE AND PRINCIPLES OF DISEASE

Anatomy

The stomatognathic system comprises the musculoskeletal unit of the mandible, maxilla, and muscles of mastication; the dental unit (teeth); the attachment apparatus that anchors teeth; and other soft tissues of the oral cavity.

Musculoskeletal Unit

The *mandible* is formed by two rami that divide into a horizontal and an ascending portion. The horizontal portion forms the body of the mandible. The ascending ramus divides into the coronoid process anteriorly and the condylar process posteriorly. The temporomandibular articulation is unique because it consists of a bilateral joint, or diarthrosis, between the mandibular fossa and articular eminence of the mandible's temporal bone and condyle (Fig. 68-1). An intervening layer of fibrous connective tissue separates the articulating surfaces. A fibrous capsule also surrounds the temporomandibular joint (TMJ) and is reinforced by capsular ligaments that help limit mandibular range of motion. Functionally, when the mandible opens, the condyles move inferiorly and anteriorly down the eminence; during closure, the mandible moves posteriorly along the eminence and superiorly into the fossa.[1]

The muscles of mastication are divided into the mandibular elevators (the supramandibular group) and depressors (the inframandibular group). The elevators, or "masseteric sling," consist of the masseters, medial pterygoids, and temporalis. The posterosuperior movement of the condyle during mandibular closure is the result of bilateral, simultaneous movement of this group. The muscles involved in the opening or depression of the mandible include the lateral pterygoid, digastric, geniohyoid, and mylohyoid. Bilateral activity of these muscles results in opening; unilateral contraction causes the mandible to deviate to the opposite side. At rest, the mandible assumes a position in which the mandibular and maxillary teeth are separated by a few millimeters of space. During functional activity, mandibular closure occurs as the action of the elevators predominates.

Teeth

The *pulp* is the tooth's center and serves as its neurovascular supply. The primary purpose of the pulp is to provide sensation and to produce dentin, a microtubular structure that hydrates and cushions the tooth during mastication. The part of the tooth normally visible in the oral cavity is the *coronal portion* covered with enamel, the hardest substance in the body. The part that is not normally visible and anchors the tooth is called the *root*. The root is covered with cementum, which is much softer than enamel and not designed for exposure in the oral cavity (Fig. 68-2).[2]

The normal primary, or deciduous, dentition consists of 10 mandibular and 10 maxillary teeth. The primary dentition is important for mastication, cosmesis, and growth and development and functions as a "physiologic space maintainer." Starting at the midline and moving posteriorly in any quadrant, the normal dentition consists of a central incisor, lateral incisor, canine, and two primary molars. The lower central incisor is the first tooth to erupt, at approximately 6 months of age; all primary teeth should be present by 3 years of age. If not, further investigation for developmental or endocrine abnormalities is warranted. The permanent dentition begins to erupt at approximately 5 to 6 years of age with the appearance of the first molar. Normally, the permanent dentition consists of 32 teeth: the central incisor, lateral incisor, canine, two premolars, and three molars. The third molars are the last to erupt, appearing at approximately 16 to 18 years of age, and are commonly called "wisdom teeth." The primary molars are replaced by the permanent premolars (Fig. 68-3). There are many numbering systems for teeth, but none are universal. Perhaps the most common system for the permanent dentition consists of numbering the teeth from 1 to 32, starting with the upper right third molar (1) to the upper left third molar (16) to the lower left third molar (17) to the lower right third molar (32). The starting point for this numbering system can be recalled by the mnemonic "upright." Because there may be congenital absence of teeth or additional, supernumerary teeth, it is perhaps best for practitioners to describe anatomically which tooth is involved (e.g., the upper left second premolar or the lower right second molar).[1]

Specific terminology is used to describe aspects of dentition. The *labial* or *buccal surface* faces outside the oral cavity; the *oral*, *palatal*, or *lingual surface* faces the tongue; the *medial surface* is toward the midline; and the *distal surface* is toward the ramus of the mandible. The *interproximal surface* refers to the contacting area of adjacent teeth, and the *occlusal surface* refers to the biting area. Finally, *apical* is in the direction of the root, whereas *coronal* is toward the crown of the tooth.

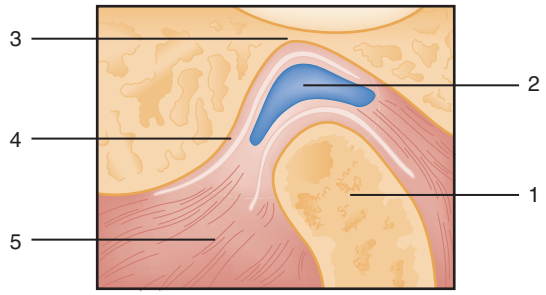


Figure 68-1. Temporomandibular joint structures in sagittal section: *1,* condyle; *2,* disk; *3,* mandibular (temporal-fossa); *4,* eminence; *5,* lateral pterygoid. (Redrawn and modified from Weisgold AS, et al: Dental medicine. In Kaye D, Rose LF [eds]: Fundamentals of Internal Medicine. St. Louis, Mosby, 1983.)

Periodontium

The periodontium consists of the gingival unit and the attachment apparatus. The *gingiva* is covered with keratinized, stratified, squamous epithelium and invests the tooth and alveolar bone. Apical to the gingiva is the alveolar mucosa, which is covered by nonkeratinized epithelium and is more subject to trauma. In healthy individuals, the gingiva is attached firmly to the tooth by connective tissue fibers inserting into the cementum, extending coronally from the alveolar bone to the cementoenamel junction. A 2- to 3-mm cuff of tissue, the *gingival sulcus,* is bordered by the enamel surface of the tooth, the gingival epithelium, and the junctional epithelium at its base (see Fig. 68-2). In a disease state, such as in the presence of the loss of alveolar bone, this cuff increases in depth and is called a "pocket."[3,4]

The *attachment apparatus* refers to the cementum on the tooth, the periodontal ligament, and the alveolar bone. The *periodontal ligament* is a fibrous structure that surrounds the root of the tooth. It is the key structure that anchors the tooth because it serves as a double periosteum that lays down cementum on the tooth on one side and alveolar bone on its other side.

Fascial Planes of the Head and Neck

The fascial planes of the head and neck are defined as potential spaces filled with loose areolar tissue that separates the layers of fascia of the head and neck. The deep cervical fascia is most important in a discussion of the extension of oral infection to the head and neck (Fig. 68-4). The *deep cervical fascia* consists of the superficial and investing layer, the pretracheal layer, the prevertebral layer, and the carotid sheath. The superficial and investing layer surrounds the entire neck; it splits as it attaches to the inferior border of the internal pterygoid muscles at the mandible's ascending ramus. This split forms the masticator space. This space communicates superiorly above the level of the zygomatic arch with the superficial and deep temporal pouches.[5]

Other spaces of importance in the neck to which dental infection may spread include the *lateral pharyngeal* or *parapharyngeal space,* which is lateral to the pharynx and medial to the masticator space; the *retropharyngeal space,* which is between the deep cervical and prevertebral fascia; and the *prevertebral space,* which is posterior to the retropharyngeal space. The pharyngomaxillary space extends from the base of the skull to the hyoid bone and is especially important because it communicates with all deep spaces.

The mandible itself may be divided further. The *mylohyoid muscle* divides the superior sublingual and inferior submaxillary spaces.

Pathophysiology

Nontraumatic Dental Emergencies

Two pathophysiologic processes affect the dental health of most of the population: (1) dental caries and (2) periodontal disease. Variables related in both disease states include the oral environment, consisting of the teeth and attachment apparatus; the presence of local factors such as bacterial plaque and oral microflora, and substrate; and host states, including immunocompromising diseases and nutritional status. Factors such as water fluoridation, fluoride supplements, and plaque control techniques (e.g., flossing, brushing, and dental surgical procedures) have decreased significantly the prevalence of dental caries and periodontal disease.[6,7]

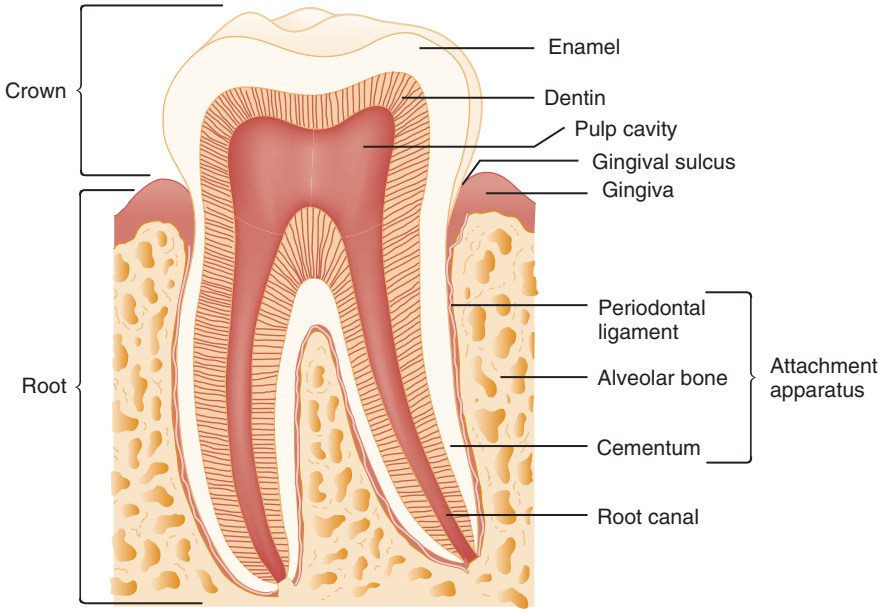
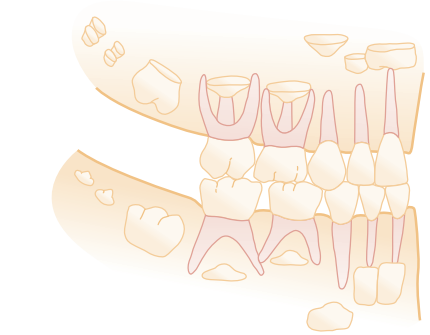


Figure 68-2. The dental anatomic unit and attachment apparatus.



1 Upper right 3rd molar
2 Upper right 2nd molar
3 Upper right 1st molar
4 Upper right 2nd premolar
5 Upper right 1st premolar
6 Upper right canine
7 Lateral incisor
8 Central incisor
25 Lower right central incisor
26 Lower right lateral incisor
27 Lower right canine
28 Lower right 1st premolar
29 Lower right 2nd premolar
30 Lower right 1st molar
31 Lower right 2nd molar
32 Lower right 3rd molar

Dental age	Erupting	Exfoliating
0–1	b a | a b b a | a b	
1–2	c | c d d c | c d	
2–3	e | e e | e	
3–4		
4–5		
5–6		
6–7	6 | 6 6 1 | 1 6	a | a
7–8	1 | 1 2 | 2	a | a b | b
8–9	2 | 2	b | b
9–10		
10–11	4 | 4 4 3 | 3 4	d | d d c | c d
11–12	5 3 | 3 5 5 | 5	e c | c e | e
12–13	7 | 7 7 | 7	
16–24	8 | 8 8 | 8	

B

Figure 68-3. **A,** Numbering and naming of deciduous and permanent dentition on the right side. Tooth numbering is in the more conventional upper right third molar (1) to lower right third molar (32). **B,** Most common pattern of dental development. a–e, Primary teeth; 1–8, secondary permanent teeth. (**B,** Redrawn from Belanger GK, Casamassio PS: Dental emergencies. In Barkin R [ed]: Pediatric Emergencies. St. Louis, Mosby, 1987.)

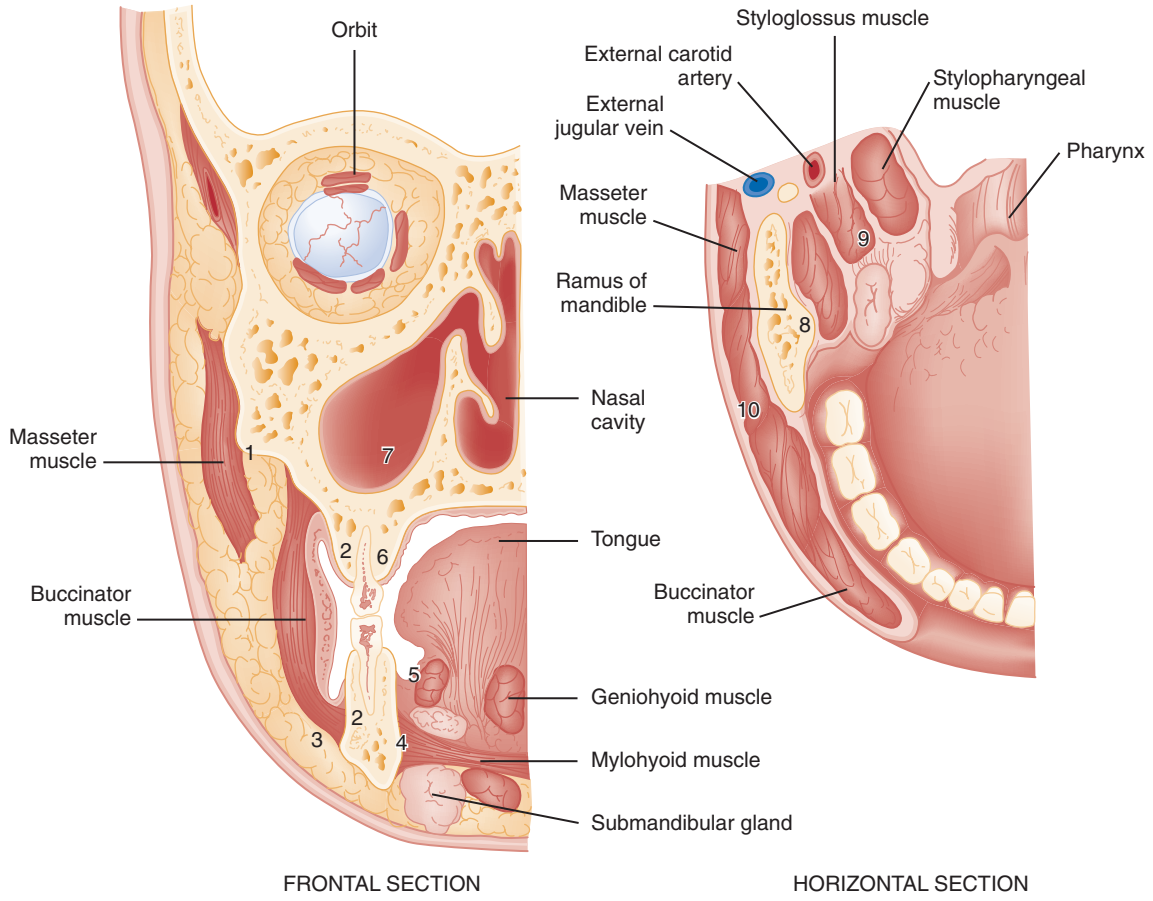


Figure 68-4. Natural progression of dental infection. The pathways by which such infections may travel are (1) postzygomatic (from canine fossa in cuspid and bicuspid region; pterygomaxillary fossa communicates from rear); (2) vestibular; (3) facial; (4) submandibular; (5) sublingual; (6) palatal; (7) antral; (8) pterygomandibular; (9) parapharyngeal; (10) masseteric. (Redrawn from Rose LF, Hendler BH, Amsterdam JT: Temporomandibular disorders and odontic infections. Consultant 22:125, 1982.)

Dental Caries

Dental caries is a multifactorial disease involving a susceptible host, cariogenic oral flora, and a substrate. In 1890, it was proposed that caries resulted from the decalcification of enamel by the production of acids from bacteria.[5-7] In the presence of saliva and a carbohydrate, cariogenic oral flora are able to develop a matrix called *dental bacterial plaque*. The bacteria metabolize the carbohydrate to form acids that decalcify the enamel. After the carious process has invaded the enamel, the microporous dentin is able to transmit saliva, by-products of the bacteria, and the bacteria themselves to the pulp. The pulp initially reacts with a hyperemic response, which continues to an inflammatory state, progressing to total degeneration and necrosis.

Pus leaks from the apex of the root and forms an abscess; this is termed a *periapical abscess*. Periapical abscesses are confined within the alveolar bone (Fig. 68-5). The abscess may break through the cortical plate of either the mandible or the maxilla and spread subperiosteally. Subperiosteal extensions are generally well confined anatomically by muscle attachments; however, if the muscle attachments are violated, either during a surgical procedure or by the natural extension of an infective process, the bacteria can gain access to the fascial planes of the head and neck.[8-11]

Infection extending to the submaxillary, sublingual, and submental spaces with elevation of the tongue is called *Ludwig's angina*. Ludwig's angina is one of the most serious mandibular infections because of its potential for airway obstruction.

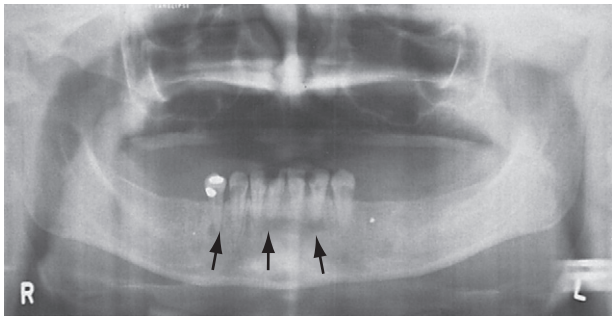


Figure 68-5. Periapical abscesses *(arrows)* as seen on Panorex film.

Space infections also may involve the face. The canine space is bounded by the orbicularis oris, the levator labii superioris, and the buccinator; abscessed anterior maxillary teeth commonly involve this space. Infection can extend to the periorbital area. The most serious complication of such space infections is cavernous sinus thrombosis resulting from contamination of the (valveless) facial venous system. The buccal space is superficial to the buccinator and limited by the anterior border of the masseter; maxillary molar infection com-

monly spreads to this space. The mental space is located at the anterior table of the mandible and often is infected by abscessed lower anterior teeth.[11]

CLINICAL FEATURES

Examination of the Oral Cavity

The examiner should wear eye protection, a mask, and gloves in compliance with universal precautions when examining the oral cavity. Ideally the patient should be placed in a dental/ear, nose, and throat chair or on a cart at a 45-degree angle. Because pediatric patients are unlikely to cooperate with the examination, the following technique is used by some experienced practitioners. The child is first placed in the parent's lap facing the parent. The examiner then sits in front of the parent. While the parent gently restrains the child's arms and legs, the emergency physician can lean the child backward and lock the child's head between the physician's legs.

An overhead examination light, headlight, or flashlight can be used for illumination. Other ancillary aids include a tongue depressor, 2×2 gauze, and possibly a dental mirror. To prevent the mirror from fogging, it should be warmed under hot water or a flame or moistened with the patient's saliva.

Examination of the oral cavity should be systematic, beginning with the soft tissues and including the tongue. The base of the tongue is examined for lesions, and Wharton's duct is milked. Stensen's duct, opposite the maxillary molars, should be examined on each side. The teeth should be examined next. Percussing a tooth with a tongue blade or handle of a mirror is a good way to elicit tenderness.

Radiographic evaluation of teeth is best accomplished using dental (periapical) films. These films are generally not available in the emergency department (ED), however. A panoramic radiograph is a useful alternative (see Fig. 68-5).

Signs and Symptoms

Dental Caries

Dental caries are the most common cause for pain of odontogenic origin. The patient may give a variable history of a sudden or gradual onset of a sharp to dull, throbbing pain. In most cases, the patient can indicate the specific tooth involved, but at times the pain may be generalized. An early pulpitis is sensitive to changes in temperature and aggravated by lying down; a more advanced pulpitis is worsened by any stimulus, including air. Pain may be referred to the ear, temple, eye, neck and, rarely, the opposite jaw.

Physical examination may reveal a grossly decayed tooth; however, if the carious process is interproximal or did not result in destruction of the outer table of enamel, the offending tooth may not be obvious. Localization of the involved tooth may be accomplished by percussing the teeth with a tongue blade or by having the patient bite on a piece of a tongue blade. Exquisite pain to percussion suggests an underlying periapical abscess, especially if the tooth is not sensitive to hot or cold. Palliative management is indicated for most odontalgia. Systemic analgesics, such as nonsteroidal anti-inflammatory drugs (NSAIDs) or synthetic opioid agents, are indicated. Although NSAIDs should be sufficient for most pain resulting from carious teeth, a therapeutic dental block also may be helpful. Synthetic opioids also are useful and are indicated in some cases but should not be used in chronically carious teeth without acute tooth fracture, filling crack or expulsion, or abscess because of their propensity for abuse.[12,13]

A dental anesthetic nerve block is helpful.[14,15] A limited quantity of analgesics should be dispensed, which encourages follow-up with a general dentist.

Patients with dental pain should be examined carefully for swelling caused by abscessed teeth. A periapical abscess or a localized swelling of the gingiva adjacent to the apex of the tooth (called a *parulis*) may cause pain from distention of the tissues. More commonly, fluctuant abscesses are a result of periodontal abscesses and are best treated with an incision and drainage. The gingiva and tooth are anesthetized by apical nerve block or block of the major nerve supplying the area (e.g., superior alveolar, inferior alveolar), or the gingiva is anesthetized superficially with 2% lidocaine with 1:100,000 epinephrine. A stab incision is made toward the alveolar bone and must extend through the periosteum; blunt dissection is carried out with a mosquito hemostat. In contrast to other abscess drainage, it is unnecessary to open the abscess from end to end—such a large incision exposes too much alveolar bone. In the dental office, a simple curettage between the tooth and the gingiva would establish drainage. For physicians not trained in dental scaling and curettage, the simple stab incision is sufficient. The cavity is irrigated, and, assuming there is sufficient space, a Penrose or iodoform drain is placed and secured with a No. 4-0 silk suture.[1]

The patient is started on phenoxymethylpenicillin (penicillin V) or erythromycin and warm saline rinses and is referred to an oral maxillofacial surgeon or general dentist. Drains are removed in 24 to 48 hours, and antibiotics are continued for 7 to 10 days.

The presence of cellulitis or swelling in the contiguous spaces of the head and neck indicates the spread of a localized infection. In the early stages of such an infection, the upper half of the face is generally involved, with extension of infection from maxillary teeth; cellulitis from mandibular teeth generally involves extension to the lower half of the face and the neck (Fig. 68-6). More advanced infections may extend into any of the fascial planes of the head and neck down to the mediastinum. In the nondebilitated host, untreated dental infections tend to localize and drain spontaneously and extraorally. In the presence of a compromised host or aggressive microorganisms, spread into the fascial planes is more common, with a potential for greater morbidity and mortality. General indications for admission include suggested spread of infection to fascial planes, high fever, toxic appearance, trismus, and an immunocompromised host.

The potential sequelae of sepsis and airway obstruction must be appreciated. Computed tomography of the head and neck can be useful if the diagnosis is in doubt. Airway management should be undertaken when indicated, particularly if signs or symptoms of impending airway obstruction are present or developing (altered voice, drooling, stridor). The intubation should be approached as a difficult airway, as outlined in Chapter 1. An ear, nose, and throat specialist or oral maxillofacial surgeon should be consulted for ongoing management, including determining the site of the initial focus so that pus can be evacuated.

Signs of infection peak in 3 to 5 days. Fever usually is present. Any irritation of the internal pterygoid or masseter muscles results in trismus. *Trismus* is the inability to open the mouth because of involuntary muscle spasm. Trismus limits visualization of the pharynx and may make diagnosis of lateral or retropharyngeal space involvement difficult. Trismus is muscular in origin, not a result of impaired or augmented neuromuscular transmission, and so is often minimally improved or not improved at all after administration of a neuromuscular blocking agent (e.g., succinylcholine) for intubation. All patients with trismus must be presumed to be difficult

Figure 68-6. Extensive spread of infection of odontogenic origin involving masseteric, sublingual, submental, and submandibular spaces with extension to mediastinum. **A,** Preoperative. **B,** Postoperative. Note drainage from mediastinum. (From Guernsey LH: Practical problem solving in oral surgery. In Cohen DW [ed]: Continuing Dental Education, vol 2, suppl 10. Philadelphia, University of Pennsylvania School of Dental Medicine, 1979.)

intubations. Difficulty swallowing or handling secretions increases the likelihood of retropharyngeal or parapharyngeal infection. Respiratory distress may be apparent, or the airway may occlude rapidly after a period of minimal signs of impending obstruction.

Ludwig's angina is a bilateral, boardlike swelling involving the submandibular, submental, and sublingual spaces with elevation of the tongue. The most serious immediate sequela is airway obstruction. A characteristic brawny induration is present; there is no fluctuance for incision and drainage. Hemolytic streptococcus is most commonly responsible for the infection, although a mixed staphylococcal-streptococcal flora is common, and both may lead to an overgrowth of anaerobic gas-producing organisms, including *Bacteroides fragilis*. Treatment consists of airway management as indicated, followed by admission to a unit capable of observing and managing the airway after airway maintenance. Although oral intubation can be attempted, an "awake" technique is recommended (see Chapter 1) because inability to displace the tongue into the submandibular space with a laryngoscope may make oral intubation impossible; cricothyrotomy may be necessary in these patients for emergent airway control.[5]

High-dose antibiotic therapy, such as 15 to 20 million U of intravenous penicillin daily, is necessary to achieve good tissue penetration. *B. fragilis* infections may be highly resistant, and a second-generation or third-generation cephalosporin, clindamycin, or metronidazole may be required to eradicate them.[16] If antibiotic therapy is not helpful, surgery is performed to eliminate causative factors and to explore for pockets of pus.

In general, the most important therapeutic treatment of orofacial infections is surgical drainage and removal of necrotic tissue. Involved teeth require endodontic therapy if they are restorable or extraction if they are nonrestorable or have lost all alveolar support. Antibiotic therapy is useful for halting the spread of cellulitis and preventing hematogenous dissemination, but it is no substitute for the prompt evacuation of pus.

Penicillin is the antibiotic of choice for treatment of orofacial infections. Minor infections respond to 250 to 500 mg of penicillin V potassium (Penicillin VK) four times a day. More serious infections, such as Ludwig's angina, require 12 million U of penicillin G intravenously a day. Most oral bacteria are sensitive to penicillin, with the exception of some *Bacteroides* species. Second-generation or third-generation cephalosporins are useful in these cases or in penicillin-allergic patients, although care must be exercised for the potential of crossover sensitivity. Clindamycin also is effective when there is a predominance of anaerobes in a penicillin-allergic patient or a patient in whom penicillin or third-generation cephalosporins seem ineffective. Potential side effects should be monitored carefully. Erythromycin is a potential alternative because it is active against most oral bacteria, but it is less active against anaerobic and microaerophilic streptococci, fusobacteria, and anaerobic gram-negative cocci. Long-term intravenous administration can also pose a problem because of its irritant effects.[7]

Periodontal Disease

Periodontal disease represents a continuum of pathology. Early periodontal disease is manifested by inflammation of the gingiva, termed *gingivitis*. Gingivitis is generally the result of an inflammatory response to an irritant, such as dental bacterial plaque and calculus. With extension of inflammation, alveolar bone is ultimately lost, a condition termed *periodontitis*. A physiologic space from the crest of the alveolar bone to the base of the junctional epithelium is maintained for the insertion of gingival fibers into cementum. In response to a loss of alveolar bone, the gingiva migrates down the root of the tooth, a condition termed *gingival resorption*. This is often accompanied by formation of gingival pockets. Advanced periodontitis results from a continuation of this process and causes marked mobility of the teeth and eventual loss as the attachment apparatus is destroyed.[1,3,4]

Space infections of the head and neck occasionally result from periodontal disease. The combination of periodontal lesions and resultant pulpal pathology can create periapical abscesses with the same sequelae as those caused by dental caries alone.

Gingivitis and periodontitis in themselves rarely cause a patient to come to the ED, unless there is sudden alarm at seeing blood on a toothbrush or the realization that certain teeth are loose. Occasionally, a patient complains about sensitive teeth. The patient can be advised to improve home care and see a dentist as soon as possible.

More commonly, a patient presents with pain from a periodontal abscess or swelling of the gingiva when food or pus becomes trapped in a "pocket." In the dental office, a periodontal abscess is treated with curettage to establish drainage. In the ED, treatment consists of a small conservative stab incision at the most fluctuant point to establish drainage, saline rinses, and antibiotic coverage. Use of tetracycline in patients older than 8 years of age is preferable because it provides better coverage for the gram-negative and anaerobic organisms found in the gingival pocket. The patient should be referred to the general dentist or periodontist for further treatment.[1,3,4]

Acute Necrotizing Ulcerative Gingivitis

In contrast to gingivitis, in which the gingiva becomes inflamed in response to an irritant such as bacterial plaque but is not invaded by bacteria, acute necrotizing ulcerative gingivitis (ANUG) is a periodontal lesion in which bacteria actually invade non-necrotic tissue. ANUG lesions commonly are accompanied by systemic manifestations of fever, malaise, and regional lymphadenopathy.[1,3,4] ANUG is characterized by painful edematous interdental papillae. The normally pointed interdental papillae are blunted and ulcerated. A gray pseudomembrane covers the tissue and leaves a bleeding surface when removed. The lesions can involve any part of the gingiva but are more common in the anterior incisor and posterior molar regions. The patient complains of pain, a metallic taste, and foul breath (Fig. 68-7).

Gingival crevices in ANUG show a predominance of fusobacteria and spirochetes. Electron microscopy reveals a layering pattern showing fusobacteria in superficial layers with spirochetes invading in deeper layers. Other necrotizing ulcerative oral diseases, such as Vincent's angina (extension of ANUG to the fauces and tonsils), cancrum oris (extension of ANUG to the lips and buccal mucosa, eroding through the teeth), and some pulmonary abscesses, also are caused by fusospirochetes.[17]

Because ANUG results from an overgrowth of bacteria normally present in the gingival crevice, immunologic factors probably contribute to the disease. ANUG has been associated with immunocompromised hosts, fatigue, local trauma, emotional stress, and smoking. ANUG has the name "trench mouth" from its occurrence in large populations living in close quarters under significant stress, such as in the trenches in World War I, military barracks, and college dormitories.[17] Despite this occurrence, there is no evidence that ANUG is communicable.

Figure 68-7. Acute necrotizing ulcerative gingivitis involving lower anterior teeth.

ANUG treatment consists of prescribing warm saline rinses; systemic analgesics so that the patient can improve oral hygiene; and systemic antibiotics, such as penicillin, erythromycin, or tetracycline. Topical local anesthetics, such as viscous lidocaine, may provide some relief. Antibiotics provide dramatic relief within 24 hours, as do dilute (3%) hydrogen peroxide rinses. Although the patient feels better, he or she should be advised to see a general dentist or periodontist for follow-up (this should be documented on the chart). The soft tissue and alveolar bone destruction from ANUG predisposes the patient to further periodontal disease; corrective procedures are necessary to create an environment conducive to maintaining periodontal health.[3,4]

Oral Pain

Although dental caries is the most common source of oral pain, the following disease entities also may cause oral or facial pain.

Root Canal Pain. Endodontic or root canal therapy involves opening the pulp chamber of the tooth, removing pulp tissue from the chamber and the root portion of the tooth to the apex, irrigating and effectively sterilizing the canal, and sealing the pulp chamber to prevent ingress of saliva and contamination. After surgery, the patient may experience exquisite pain caused by irritation beyond the apex of the tooth from instrumentation or from the buildup of gas from the irrigation solutions. Swelling may cause the tooth to be elevated slightly out of the socket so that premature contact during chewing causes extreme pain. These patients may have no relief with either systemic analgesics or anesthetic nerve blocks, presumably from the sensation of intense pressure. Treatment may consist of opening the canal to allow the gas or fluid to escape and of occlusal adjustment to take the tooth out of contact; the patient's general dentist or endodontist may have to be contacted.[18]

Cracked Tooth and Split Root Syndromes. Patients with cracked teeth or a split root may report having a toothache. Pain occurs primarily with chewing or forced closure. The patient may have had an extensive dental restoration, previous endodontic therapy, or a history of having received an upward blow to the jaw. In the ED, the diagnosis is made from history and from having the patient bite on a piece of wood. In the dental office, the diagnosis is made by removing a restoration and inspecting the cavity floor. Management is similar to that for carious teeth, including symptomatic pain medication and referral back to the dentist to consider possible causes.[2]

Maxillary Sinusitis. Dental pain often is referred to the area of the sinuses; similarly, congested or inflamed sinuses in the proximity of the apices of the maxillary teeth may cause apparent odontogenic pain. The patient may complain of throbbing pain unrelated to changes in temperature and aggravated by lying down. On examination, there is no apparent dental cause. There may be tenderness over the maxillary sinuses or periorbital regions. Nasal discharge may be present. The Panorex film can screen for dental and sinus pathology.

Atypical Odontalgia

Atypical odontalgia describes dental pain for which there is no dental cause. The patient may have a history of multiple dental procedures with no relief. The pain is chronic and occurs spontaneously. Percussion may elicit pain, and there may be thermal sensitivity as if a vital tooth were present. If paroxysmal pain of neuropathic origin is excluded, atypical odontalgia can be entertained. Similar to many chronic pain syndromes, treatment with tricyclic antidepressants may be

efficacious. Such management is best left to the dentist or pain management consultant who would follow the patient on a long-term basis.

Postextraction Pain

Pain after an extraction (i.e., immediate periosteitis) is common for approximately 24 hours. Systemic analgesics are usually adequate for pain control. Aspirin-containing compounds and NSAIDs are effective analgesics but are thought by some to contribute to postoperative bleeding and oozing.

A much more painful condition, acute alveolar osteitis or dry socket, may occur approximately 3 to 4 days after an extraction. The patient has a pain-free interval followed by sudden onset of excruciating pain associated with a foul odor. The pathophysiology involves premature loss of the healing blood clot from the socket with a localized infection of the bone.[19]

Treatment of a dry socket consists of an anesthetic nerve block, gentle irrigation of the socket, and packing the socket with iodoform gauze saturated with a medicated dental paste, such as Sed-A-Dent, or barely dampened with eugenol (oil of cloves). The packing affords almost immediate relief. Patients with a dry socket require daily follow-up for pack changes until the condition resolves. Most dentists include oral antibiotic (e.g., penicillin or erythromycin) coverage, analgesics, and NSAIDs with this regimen until the condition resolves. Although the condition is secondary to premature loss of the blood clot from the socket, no attempt should be made to stir up bleeding in the socket to form a new clot because this procedure is associated with a higher incidence of osteomyelitis.[19]

Paroxysmal Pain of Neuropathic Origin

Paroxysmal pain of neuropathic origin is most commonly caused by tic douloureux, or trigeminal neuralgia. The diagnosis is made principally on the basis of history. The patient complains of paroxysmal episodes of an excruciating, lancinating pain, also described as recurrent bursts of an electric shock. The pain follows the anatomic distribution of the involved division of the fifth cranial nerve. On physical examination, the pain sometimes can be elicited by tapping specific areas of the face (the so-called trigger zones) in the region of the distribution of the nerve involved.[20]

Medical management for tic douloureux consists of carbamazepine, although some patients may be afforded no relief. When medical management fails and the patient is in significant distress, he or she may be a candidate for neurosurgical procedures that ablate the nerve. Close follow-up is required if treatment for tic douloureux is initiated in the ED. Patients taking carbamazepine require adjustment of the dosage to achieve therapeutic effect and require monitoring for toxicity. Patients in whom the diagnosis is considered need additional evaluation to exclude the presence of multiple sclerosis, cerebellopontine angle tumor, acoustic neuroma, or nasopharyngeal carcinoma. Patients with this condition commonly require a full dental, otolaryngologic, and neurologic evaluation to investigate correctable causes.

Other causes of orofacial pain of the paroxysmal type include headaches (see Chapter 16). Vascular headaches such as migraine and cluster headaches may have facial pain as their principal manifestation. Rheumatologic disorders, such as giant cell arteritis and polymyalgia rheumatica in the elderly, can result in facial pain. Dull pain in the lower jaw is not always of dental origin. Myocardial ischemia may cause isolated jaw pain.

Temporomandibular Myofascial Pain Dysfunction Syndrome

The TMJ is a bilateral joint subject to almost continuous use. It is extremely sensitive to proprioceptive stimuli and can react to interferences in occlusion of only fractions of a millimeter. TMJ syndrome results from anatomic disharmony (see Fig. 68-1) and occlusal disturbances. The condition is aggravated by trauma, clenching of the teeth, or bruxism. Patients complain of pain in the region of the TMJ, usually unilateral. The pain is dull, worsens during the course of a day, and in extreme cases may result in trismus with palpable masseter and internal pterygoid spasm.[20-23]

TMJ radiographs are not helpful. Treatment consists of the external application of heat for 15 minutes four to six times per day, soft diet, analgesics including NSAIDs, and a muscle relaxant such as diazepam. Patients should be referred to a dentist specializing in TMJ disorders, such as a periodontist or a periodontal prosthodontist. Treatment at this stage consists of continued physiotherapy, bite appliances that put the musculature at rest, and occlusal adjustment.[24] Although certain anatomic abnormalities are amenable to surgical correction, most oral maxillofacial surgeons consider surgery only for the most intractable cases.[22]

Pericoronitis

Pain from the eruption of the third molar teeth (i.e., wisdom teeth) in an adult is common. Trapped food and plaque cause the gingiva surrounding crowded, malerupted, or impacted third molar teeth to become inflamed and swollen. This condition is called *pericoronitis* and is extremely painful because of repeated trauma from the opposing third molar biting on tender tissues and from distention of retromolar tissue on opening of the mandible. Pericoronitis is treated locally with warm saline irrigation, with or without hydrogen peroxide rinses. If the condition is severe or if there is a fever, an antibiotic is recommended. If fluctuant pus is present, an incision and drainage should be performed, exercising care not to track the infection posteriorly or to dissect deeply into distorted tissues, possibly encountering the internal carotid artery. Definitive treatment involves removal of the opposing third molar tooth for immediate relief and removal of the involved third molar tooth after the infection is resolved.[1] These patients should be referred to an oral maxillofacial surgeon.

Oral Manifestations of Systemic Disease

Although the oral manifestations of many systemic diseases are nonspecific, several diseases have distinct oral presentations. In certain instances, recognition of the oral signs aids in the specific diagnosis. In other disease states, the oral condition is a contributing factor to the overall pathophysiology.[25]

Diabetes Mellitus. Oral manifestations of diabetes mellitus are associated primarily with periodontal lesions. Diabetic patients seem to be more susceptible to periodontitis. Acute gingival abscess and sessile or pedunculated gingival proliferations have been described as being caused by or intimately associated with diabetes.[25]

Similar to other systemic manifestations of diabetes, the degree of control of diabetes seems to correlate with its effects on the periodontium. Uncontrolled diabetes generally results in greater periodontal disease. Control of diabetes helps decrease periodontal severity, although irreversible damage, such as bone loss, may result.

Although the severity of periodontal disease in diabetic patients is a function of the response to local factors, such as plaque and calculus, there is also evidence to support the role

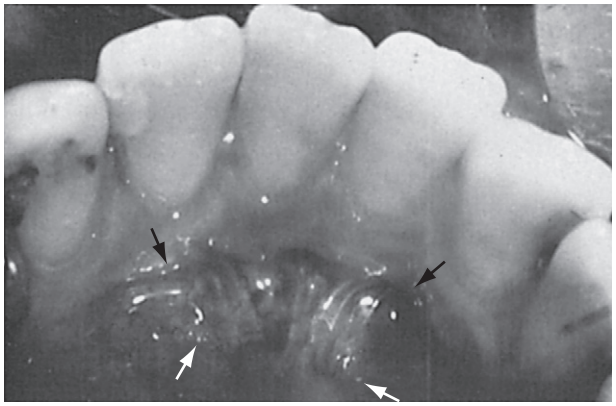


Figure 68-8. Lesion *(arrows)* secondary to systemic lupus erythematosus involving the floor of mouth.

of vascular changes and alterations in the role of polymorphonuclear leukocytes, monocytes, oral microflora, the patient's immune response, and genetic variables. Patients with diabetes who have advanced retinal changes also have been found to have more periodontal manifestations.

Maintenance of a healthy periodontium is important in a diabetic patient. Just as the degree of diabetic control affects the periodontium, so too does periodontal disease affect the degree of control. Patients with brittle diabetes or those subject to repeated episodes of ketoacidosis might be thrown out of control from a simple periodontal abscess. The presence of advanced periodontal disease in a young patient, especially in the absence of local factors, should lead one to exclude the diagnosis of diabetes. A sudden change from a healthy periodontium to a diseased state suggests a similar diagnosis in an adult. HIV infection also should be ruled out.

Collagen Vascular Diseases. Systemic lupus erythematosus is the most common collagen vascular disease to have oral manifestations. Patients commonly have large ulcerated intraoral lesions with necrotic borders. The lesions are usually secondarily infected and painful (Fig. 68-8).

Scleroderma usually is recognized by the characteristic facies. The periodontal ligament may appear thickened on dental radiographs. Characteristic microscopic changes can be seen on gingival biopsy specimens. Rare entities, such as the midline lethal granuloma or Wegener's granulomatosis, present with large intraoral ulcerative lesions, usually involving the hard palate.[25]

Granulomatous Diseases. Oral manifestations of granulomatous diseases are fairly rare today but are still seen. Tuberculosis may give rise to lesions of the tongue or tonsillar area. These lesions are confused most commonly with syphilitic ulcerations or infections caused by actinomycosis. A more common and benign entity is pyogenic granuloma,[4] which is a proliferation of highly vascular connective tissue in response to an irritant. The lesions range from sessile to pedunculated and have a warty texture. Pyogenic granulomas in the oral cavity are usually gingival in origin. They are especially common in pregnancy and are called "pregnancy tumors." Pregnancy tumors generally resolve 2 to 3 months after delivery; tumors that do not resolve require surgical excision.

Blood Dyscrasias

The gingiva may be massively infiltrated by leukemic cells in acute leukemic states, especially acute granulocytic leukemia. The gingiva is edematous and bluish red and may cover the teeth. These gingivae are compromised and may allow for the ingress of bacteria, leading to sepsis. Chronic leukemic states have no specific gingival lesions, and leukemic states in remission are associated with normal gingiva. In addition to sepsis, gingival hemorrhage is a serious sequela. Gingival sequelae are more severe with underlying periodontal disease; during remissions, it is imperative to maintain good periodontal health. Acute hemorrhage is controlled with the application of gauze pressure and hemostatic agents, such as topical thrombin, absorbable gelatin powder, and oxidized regenerated cellulose.[1]

Thrombocytopenic purpura commonly presents with oral manifestations. Spontaneous gingival bleeding from trauma is characteristic. Acute hemorrhage is managed in a fashion similar to that discussed for acute leukemia. Less serious persistent oozing responds to treatment of the underlying state.

Drug-Induced Gingival Hyperplasias

Some degree of gingival hyperplasia is present in 40% of patients receiving long-term phenytoin therapy. Younger patients seem to be affected more often than older patients. The degree of gingival hyperplasia does not seem to be related to dosage. The disease ranges from slight enlargements of the interdental papillae to massive enlargement of the gingiva, which covers the crowns of the teeth and may move the teeth. The hyperplastic tissue is subject to infection. The presence of local irritants seems to make the hyperplasia worse.[26-29] Treatment of the condition includes removal of local irritants and surgical excision of the hyperplastic tissue. If the drug is not discontinued, hyperplasia is likely to recur, although less severely if good oral hygiene is maintained.

Aphthous Stomatitis

Patients may complain of recurrent small oral mucosal ulcers. The ulcers are approximately 2 to 3 mm in size with a white center. The lesions tend to be tender but rarely become infected. Multiple ulcers that have coalesced can create an impressively large lesion. One third of the population may be affected by this condition, which is believed to be related to stress, nutrition, oral trauma, and hormonal etiologies. The condition is self-limiting, and treatment is symptomatic (hydrogen peroxide rinse; topical dental preparations such as benzocaine and an emollient gel; 50:50 mixture of diphenhydramine [Benadryl] and Kaopectate or Maalox; or prescription regimens, such as steroid-antibiotic ointment [Kenalog in Orabase] or sucralfate), with oral antibiotics reserved for secondary infection. A topical sulfuric acid phenolic, Debacterol, available only by prescription, is applied to the ulcer and appears to seal the ulcer and promote rapid healing. Ulcers that may appear similar to aphthous ulcers are those on the soft palate associated with hand-foot-and-mouth disease or lesions on the gingivae and tongue from herpetic stomatitis.[30,31]

TRAUMATIC DENTAL EMERGENCIES

Fractures of Teeth

The anterior teeth are commonly injured from falls or blows directly to the teeth. Forceful blows to the mandible directed superiorly may result in fractures of the premolars and molars caused by a wedgelike effect of the cusps of the mandibular teeth in the central fossae of the maxillary teeth. Many children have an anterior overbite, which makes this part of the dentition more prone to injury. Blunt trauma to the dentition may result in damage to the neurovascular supply to the tooth, bleeding within the tooth, fractures of the root or crown, loos-

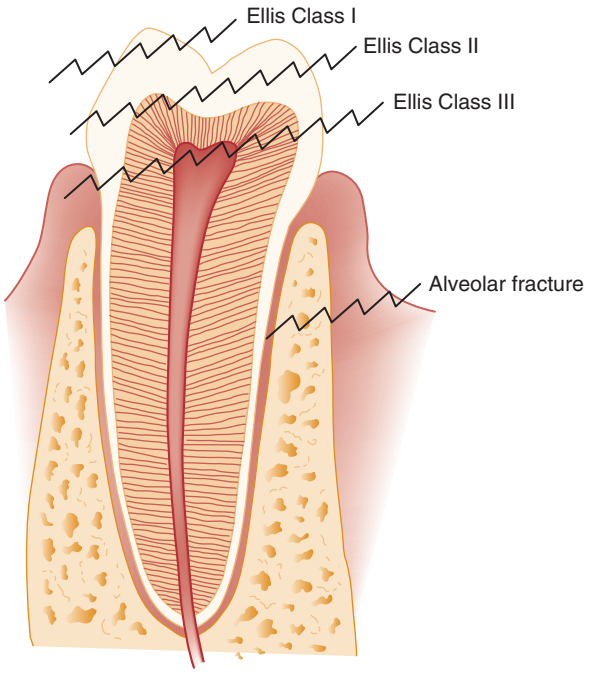


Figure 68-9. Ellis classification for fractures of anterior teeth. (Redrawn from Tintinalli JE, et al: Emergency Medicine: A Comprehensive Study Guide, 4th ed. New York, McGraw-Hill, 1996.)

ening of the tooth, or actual expulsion of the tooth from its socket. A long-term sequela of blunt trauma or reimplantation of teeth is resorption of the root.[1,32,33]

Fractures of the anterior teeth are managed based on the type of fracture, its relation to the pulp of the tooth, and the patient's age. The Ellis classification system was used to describe fractures of anterior teeth; however, now it is the accepted practice simply to describe the anatomy involved.[34] Fractures involving enamel; enamel and dentin; and enamel, dentin, and pulp exposure traditionally have been referred to as Ellis classes I, II, and III (Fig. 68-9).

The simplest and most common dental fracture involves only the enamel portion of the tooth, leaving a chalky-white appearance. These injuries are usually minor, unless a sharp portion of the tooth causes soft tissue trauma, in which case the sharp edge may be smoothed with an emery board. The patient or parents usually are concerned about the cosmetic deformity, but they can be reassured that the tooth can be restored to its natural appearance with the use of enamel-bonding plastic materials. Referral to the dentist is necessary but not urgent.

Fractures involving the dentin have an ivory-yellow appearance. The pulp continually lays down dentin throughout the life of the tooth in response to normal and noxious stimuli. In a child, the pulp is relatively large in size, and there is less dentin; the inverse is true in the adult. Because dentin is a microtubular tissue capable of allowing bacteria to percolate into the pulp chamber, fractures involving dentin are more serious in children and adolescents as there is little dentin to protect the pulp after it is exposed to the oral cavity.

In younger patients, the management of dentin fractures involves the immediate placement of a dressing of calcium hydroxide paste over the exposed dentin covered with dry foil, a metal band or, more commonly, an enamel-bonded plastic. Early intervention may prevent contamination of the pulp and the need for subsequent root canal treatment. A pediatric or general dentist should be notified as soon as possible. Exposed dentin may be exquisitely sensitive, so the patient should avoid extremes in temperature. In an adult, who has a greater thickness of dentin compared with pulpal tissue, there is less need for urgent referral to a dentist. A dressing can be placed on the tooth for comfort. Referral should be made to a dentist for the next working day.

Fractures of teeth resulting in pulp exposure are the most serious class of fractures of anterior teeth because the pulp chamber is immediately contaminated. Care should be taken to differentiate dentin exposure from the pulp. The tooth is wiped clean with a piece of gauze and examined for a pink blush or a drop of blood, indicating a pulpal exposure. There may be excruciating pain from exposure of the nerve, or the shock of the trauma may have disrupted the neurovascular supply at the apex of the tooth, eliminating most sensitivity. This injury is often accompanied by serious fractures of the tooth, possibly involving the entire crown or root.[35]

Pulp exposures are true dental emergencies. In the primary dentition, exposure of the pulp can be treated by performing a pulpotomy, in which the pulp in the chamber is removed, the remaining tissue is mummified with formocresol and covered with a layer of calcium hydroxide, and the tooth is restored. In most cases, if there has been minimal contamination, the primary tooth lasts its natural lifetime. In an adult, the pulpotomy is not a successful procedure, and all pulpal tissue from the crown and root must be completely removed. Although management of pulp exposures is more urgent in a child, endodontic therapy is less complicated and more successful in an adult if there is also a minimum of contamination; in the case of a pulpal exposure from a dental fracture, a general dentist, pedodontist, or endodontist should be notified immediately if possible, or the patient should be instructed to follow up the next working day. If no dentist is available, a piece of moist cotton can be placed over the exposed pulp and covered with a piece of dry foil or sealed with a temporary root canal sealant (e.g., Cavet). Although some authors have advocated removal of the exposed pulpal tissue with a dental endodontic instrument called a barbed broach, this procedure is not recommended because this instrument breaks easily, even in the hands of a skilled endodontist.[35] In cases of extreme pain, a dental anesthetic nerve block might be helpful.

Subluxed and Avulsed Teeth

Teeth that are loosened in their sockets as a result of a force are called *subluxed*. There may or may not be associated fractures. The diagnosis of subluxation can be made by gently tapping a tooth with two tongue blades. Any perceptible mobility is evidence for subluxation. A ring of blood may surround the gingival crevice. Minimally mobile teeth respond well to a soft diet for several days. Markedly mobile teeth require stabilization as soon as possible for 10 to 14 days. Teeth can be stabilized (generally by a dentist) by means of Erich arch bars, wire ligation, enamel bonding plastics, or a combination of modalities. Most of these techniques require an oral maxillofacial surgeon, hospital dentist, or pedodontist. They should be performed as soon as possible.[35]

As a temporizing measure, the patient can bite gently on a piece of gauze, or the teeth can be stabilized for 24 to 48 hours with the application of a periodontal pack (e.g., Coe-Pak).[36] A resin and catalyst paste are mixed together in equal quantities to a firm consistency and molded over the anterior and posterior aspects of the involved tooth and two or three adjacent teeth on each side. The patient is asked to close the mouth while the mixture hardens (Fig. 68-10). The patient is advised to avoid hot liquids that would soften the pack, eat a liquid to soft diet, and see a dentist as soon as possible.

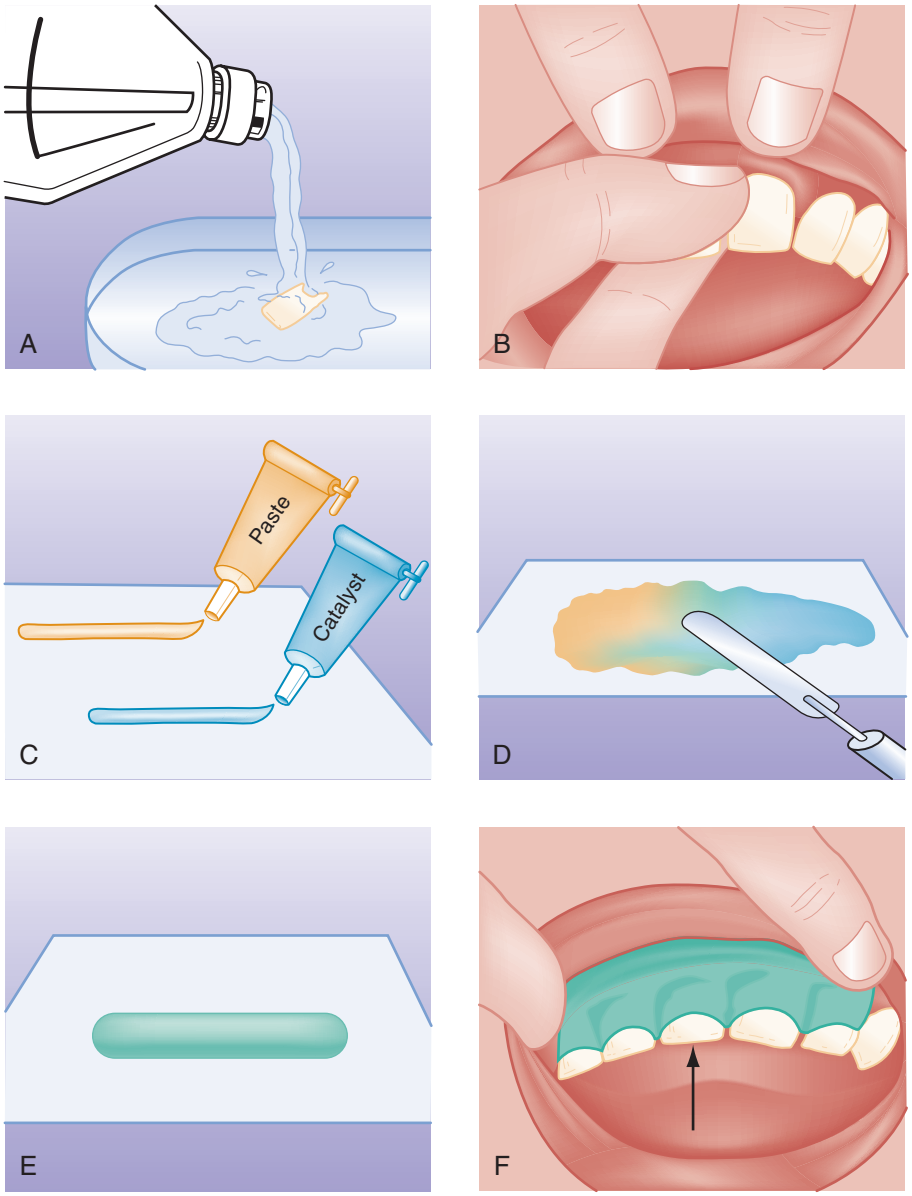


Figure 68-10. Reimplantation and stabilization of an avulsed tooth. **A,** Tooth is rinsed. **B,** Tooth is placed back into socket. **C** and **D,** Periodontal pack is mixed. **E,** Splint material is ready for application. **F,** Packing is molded over reimplanted tooth and two adjacent teeth to either side.

Avulsed teeth are completely torn from the socket and are a true dental emergency. If teeth are unaccounted for, the possibility of aspiration or entrapment in soft tissues should be considered.[37] Management of recovered avulsed teeth depends on the age of the patient and the length of time that the tooth has been absent from the oral cavity.[38] Avulsed primary teeth in a pediatric patient age 6 months to 6 years are not replaced in the socket. Reimplanted primary teeth ankylose or fuse to the bone so that although the dentofacial complex grows downward and forward, the reimplantation site does not. There also may be interference with the eruption of the permanent tooth. Cosmetic deformity results in either case. Such patients should be referred to a pedodontist for consideration of a space maintainer or cosmetic appliance.

Avulsed permanent teeth require prompt intervention. When a tooth has been avulsed from its socket, the periodontal ligament fibers are torn; fragments remain attached both to the cementum on the root of the tooth and to the alveolar bone in the socket. Ideally, the best environment for an avulsed tooth is its socket, and it has been known since the mid-1960s that an avulsed tooth can be successfully replanted if it is returned to its socket within 30 minutes of the avulsion.[37,39,40] A 1% chance of successful reimplantation is lost for every minute that the tooth is outside of its socket; however, there is often difficulty with immediate reimplantation. On-site personnel (parents, teachers, trainers, paramedics) may be unfamiliar or uncomfortable with tooth reimplantation. The tooth may be soiled, or the patient may be uncooperative. Occasionally, other, more serious life threats may preclude immediate reimplantation. Because of these factors, investigations were undertaken to find the ideal medium for transport and storage of an avulsed tooth.

The worst situation is to allow the tooth to be transported in a dry medium. Storage in plain water is not much better.[41] Although saliva is a reasonable storage medium, milk is preferable because of its osmolarity and essential ion concentration of Ca^{2+} and Mg^{2+}.[42] The best storage and transport medium is Hank's solution, a balanced pH cell culture medium.[43] This solution is commercially available as the "Save-a-Tooth" system (3M). Hank's solution can maintain the viability of the cells for 12 to 24 hours or more.[44] If the tooth has been avulsed for more than 30 minutes or has been allowed to dry, place-

ment of the tooth in Hank's solution helps restore the periodontal ligament cells.[45,46] With the "Save-a-Tooth" system, the tooth is simply dropped into the basket and the lid replaced. For removal, the lid is removed, the basket is lifted out of the solution, and the tooth is retrieved by tipping the basket over onto the padded lid.

If a call is received about an avulsed tooth, it first should be determined whether the tooth is permanent. If it is, the caller should be instructed to rinse the tooth off in saline or water and reimplant it immediately into the socket. If this cannot be performed for technical or emotional reasons, the patient should be instructed to place the tooth under his or her tongue or in the buccal pouch so that it is bathed in saliva. If the patient is too young, the tooth can be placed in the parent's mouth. If this is unacceptable to the parent or if there is concern about aspiration or swallowing of the tooth, it should be transported in a cup of milk. If milk is unavailable, saline should be used.[46] Ideally, the tooth should be transported in Hank's solution.

When the patient arrives in the ED, the tooth should be reimplanted at the earliest opportunity. If this cannot be done, the tooth can be placed in Hank's solution or a "Save-a-Tooth" system (especially if avulsion has been longer than 30 minutes or if the patient has other life threats that are being managed). If Hank's solution is not available, the tooth is rinsed with saline, the socket is suctioned if necessary, and the tooth is immediately implanted. Local anesthesia may be necessary. The tooth should be manipulated only by the crown, if possible, so that the remaining periodontal ligament fibers are not damaged. Stabilization must be performed immediately, or the tooth will exfoliate. Stabilization is performed as described for markedly subluxated teeth (see Fig. 68-10). The status of tetanus immunization should be checked, and the patient should be treated according to the standard for a nontetanus-prone wound (i.e., 10-year immunization update). The patient should be started on phenoxymethylpenicillin or erythromycin.[1,47]

The patient is placed on a liquid diet for several days and advanced to a soft diet for 1 week. Stabilization is maintained for approximately 2 weeks, and the tooth is gradually brought into function to prevent ankylosis. Teeth that have been avulsed for longer than 30 minutes invariably require endodontic therapy.[38] Although there may be concern about the anatomic orientation of the tooth or more confusion about which socket to use when several teeth are avulsed, each tooth should be placed into a socket with the best fit so that the tooth remains in a good physiologic environment. The dentist can make any necessary readjustments before final stabilization.

Alveolar Bone Fractures

Dental fractures and subluxated or avulsed teeth may be associated with fractures of the alveolus. Alveolar fractures may be apparent clinically from exposed pieces of bone or diagnosed radiographically. In massive facial trauma, care should be taken to conserve as much of the alveolar bone as possible, unless there is a tremendous danger of aspiration. Indiscriminate loss of alveolar bone results in tremendous cosmetic deformity that is difficult to restore with prosthetic devices.[42]

An arch bar stabilizes alveolar fractures. An alveolar fracture requires 6 weeks of stabilization for adequate healing; if there is an associated subluxed or avulsed tooth, stabilization is maintained at the expense of possible ankylosis of the tooth. The loss of alveolar bone ultimately results in more cosmetic deformity for the patient. A permanently ankylosed tooth can remain functional for some time, and although it may be difficult for an oral and maxillofacial surgeon to remove, it can be reconstructed more easily than supporting alveolar bone. The dental materials, including local anesthesia supplies and the "Save-A-Tooth" system, are conveniently assembled in a commercial package called "The Dental Box" (Dental Box Co.®, Pittsburgh, Penn).

Soft Tissue Injuries

Dentoalveolar trauma is commonly associated with soft tissue injuries of the lips, intraoral mucosa, and tongue. Wounds always should be examined for debris and tooth fragments. As with any surgical wound, débridement and irrigation should be performed. Final closure of soft tissue injuries should await the initial management of fractured teeth or the procedures necessary for stabilizing teeth because manipulation of the soft tissues is required. Carefully placed sutures may be torn and have to be replaced in already compromised tissue if soft tissue closures are performed first.[48]

Gaping intraoral lacerations tend to become ulcerated, secondarily infected, and painful. Fibrotic healing results in a cumbersome scar that is subject to repeated trauma during chewing. A well-prepared mucosal wound is closed with No. 4-0 absorbable or black silk suture. Gingival and tongue lacerations are best closed with No. 4-0 black silk because this material is less irritating to the touch. Absorbable suture, such as 4-0 chromic, is excellent for children. Large tongue lacerations should be well approximated or a cleft will form during healing, necessitating a revision. Anesthesia can be achieved by either direct local injection or lingual block. Small (<1 cm) lacerations are best left alone, especially in children. The management of through-and-through lacerations involving skin and oral mucosa is controversial. With proper preparation, mucosa can be closed as described previously. Subcutaneous sutures (absorbable) are placed to close the subcutaneous tissues from the outside, removing tension from the skin. Skin is closed with No. 6-0 or No. 7-0 synthetic nonabsorbable sutures that are removed in 3 to 4 days, depending on the amount of muscle tension on the wound. Intraoral silk closures are removed in approximately 7 days.[48]

Through-and-through lacerations and other significant intraoral wounds may benefit from prophylactic antibiotics (penicillin is the drug of choice).[47] The patient is advised to maintain oral hygiene, use saline rinses six times a day, place a triple-antibiotic ointment over the skin closure, and watch carefully for infection. These patients should be seen in 48 to 72 hours to check for infection. Normal postoperative soft tissue swelling should not be mistaken for an infected wound.

Temporomandibular Joint Dislocation

The mandibular condyles may dislocate from trauma, but more often dislocation follows extreme opening of the mandible such as occurs after a yawn or laughter. TMJ dislocation occurs when the condyle travels anteriorly along the eminence and becomes locked in the anterosuperior aspect of the eminence. The masseter, internal pterygoid, and temporalis go into spasm attempting to close the mandible; trismus results, and the condyle cannot return to the temporal fossa. Mandibular dislocation is painful and frightening for the patient. Patients prone to mandibular dislocation include individuals with anatomic disharmonies between the fossa and articular eminence, weakness of the capsule and the temporomandibular ligaments, or torn ligaments. Dystonic reaction to drugs may result in mandibular dislocation. Patients who have had one episode of mandibular dislocation are predisposed to further dislocations. If a unilateral dislocation has occurred, the

jaw deviates to the opposite side. More commonly, a symmetrical dislocation occurs. In cases of traumatic dislocation, a mandibular series, Panorex, or TMJ radiographs should be taken to exclude the possibility of a fracture.[1,42,47,49]

Reduction of a dislocated mandible is straightforward, although often difficult because the strength of the masseter contraction must be overcome. The patient requires procedural analgesia and sedation as for any other dislocation. Either facing the patient or from behind, the emergency physician grasps the mandible with both hands; the thumbs rest on the ridge of the mandible intraorally, posterior to the molars, and the fingers wrap around the outside of the jaw. It is best to have the patient sitting up, with a firm surface behind the head, so that posterior and inferior pressure can be exerted without accompanying movement of the patient's entire head. Some physicians prefer to place the thumbs on the occlusal surfaces of the teeth; in this case, the thumbs must be wrapped with gauze to protect them when reduction is accomplished because the masseter muscles can contract with tremendous force. Firm, progressive, downward pressure is applied on the mandible to free the condyles from the anterior aspect of the eminence; the mandible is guided caudally, then posteriorly and superiorly back into the temporal fossae (Fig. 68-11). The patient is advised to avoid extreme opening of the mandible such as occurs during laughing and yawning, to begin a soft diet for 1 week, and to apply warm compresses in the TMJ area. NSAIDs and muscle relaxants may be helpful. Patients with chronic dislocation may be helped initially with the application of a Barton bandage (elastic fabricated bandage that wraps around the top of the head and mandible). Intermaxillary fixation with wire and elastics may be necessary. Patients who have difficulty reducing themselves or who are plagued by recurrences may require surgical revision of the eminence for relief.[1]

Hemorrhage

Oral hemorrhage is a common complication of dental scalings, periodontal surgery, and dental extractions. Hemorrhage is controlled easily with local measures postoperatively. Patients may have sustained or recurrent hemorrhage after these procedures, however, and present to the ED. History should be obtained for recent dental procedures, drugs with antiplatelet activity such as aspirin, underlying coagulopathy, or a history of spontaneous bleeding. Spontaneous gingival hemorrhage without an inciting factor warrants a screen for coagulopathy and a complete blood count and differential. Diseases that result in spontaneous gingival hemorrhage are discussed in the section on oral manifestations of systemic disease. Management of coagulopathies caused by factor deficiencies requires factor replacement and administration of aminocaproic acid if there has been a recent dental extraction or periodontal surgery.[1]

Bleeding after extraction is the most common cause for oral hemorrhage. History of cigarette smoking, excessive spitting, or using straws is helpful information because each behavior

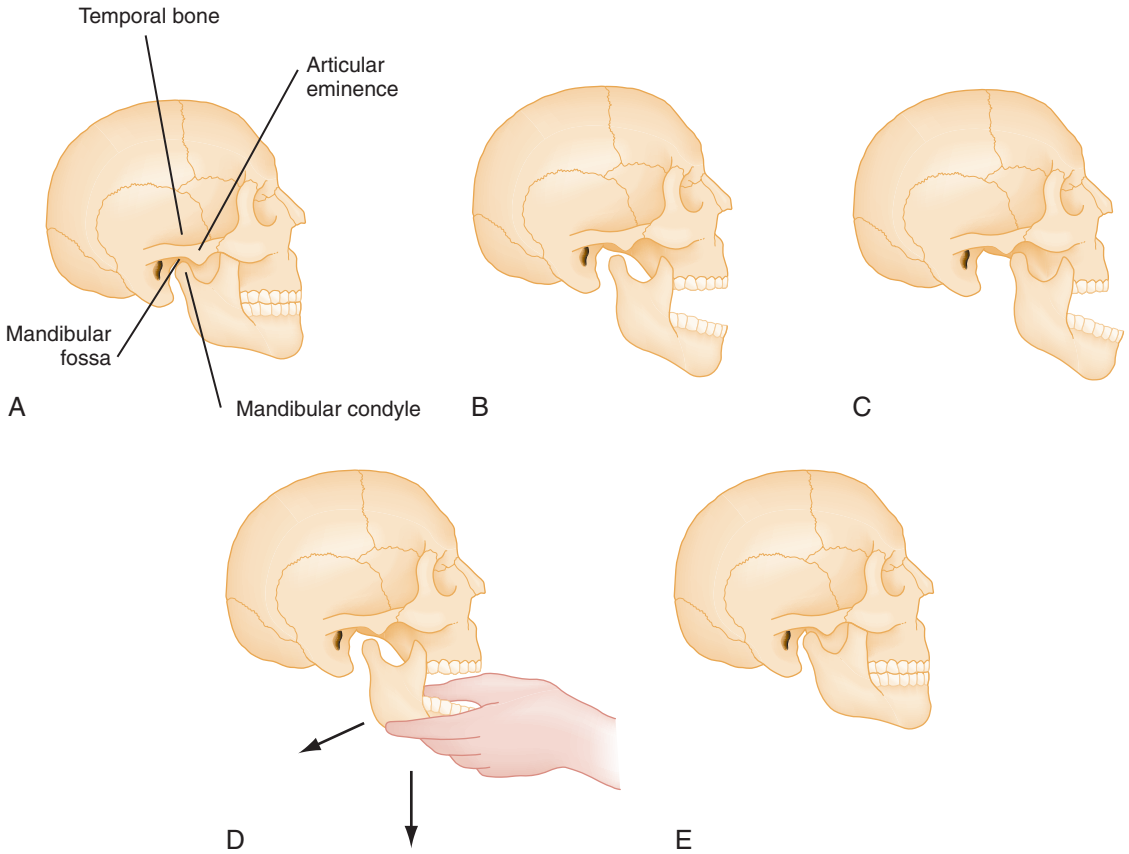


Figure 68-11. Reduction of temporomandibular joint dislocation. The temporomandibular joint is illustrated in normal and dislocated positions. **A,** Closed position, with the mandibular condyle resting in the mandibular fossa behind the articular eminence. **B,** In maximally open position, the mandibular condyle is just under and slightly behind the articular eminence. **C,** In dislocated position, the mandibular condyle moves forward and upward slightly above the articular eminence; muscle spasm then occurs. **D,** To reduce dislocation, the thumbs are placed intraorally and lateral to the lower molars and pressure is applied to the lower molar ridge area near the jaw angle in a downward and backward direction. **E,** When the mandibular condyle has cleared the articular eminence, muscle contraction returns the jaw to a normal closed position. (Redrawn from Rose LF, Hendler BH, Amsterdam JT: Temporomandibular disorders and odontic infections. Consultant 22:125, 1982.)

creates negative pressure in the oral cavity, which dislodges blood clots from the socket. Excessive clots should be removed from the oral cavity. The patient should be allowed to bite on gauze for 20 minutes. If bleeding has not stopped, the extraction site should be infiltrated with 2% lidocaine with 1 : 100,000 epinephrine so that the tissue blanches. Gauze pressure should be repeated for another 20 minutes. If bleeding continues, the socket should be packed with an absorbable gelatin sponge or oxidized regenerated cellulose and secured with a No. 4-0 silk suture. Gauze pressure is applied again. Failure to respond to these measures warrants an evaluation for an underlying coagulopathy. Patients who have had multiple extractions without adequate bone recontouring and soft tissue closure may require revision of the surgical site to achieve hemostasis.[1]

Patients who have bleeding after periodontal surgery usually respond to local measures and continued application of gauze pressure. Patients who are bleeding excessively after a deep scaling may be helped by injection of local anesthetic with epinephrine or the placement of a periodontal pack. Patients who recently have undergone periodontal surgery involving gingival flaps may have dislodged the periodontal packs that were placed to ensure proper tissue alignment and wound healing. The periodontist should be informed if possible so that the pack can be replaced as soon as possible to ensure appropriate healing.

KEY CONCEPTS

- The most common nontraumatic dental emergencies are pain from dental caries, periodontal abscesses, and spread of infection of dental origin.
- The most important concern of dental infection is any compromise of the airway.
- Fractures of teeth are managed differently depending on which structures are involved—enamel, dentin, or pulp exposure.
- Avulsed teeth must be reimplanted as quickly as possible and are best preserved in Hank's solution.
- Soft tissue injuries, such as lip lacerations, when involved with dental injuries should be managed after the teeth have been stabilized.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 69 Ophthalmology

Rahul Sharma and Douglas D. Brunette

PERSPECTIVE

Background and Epidemiology

Two percent of emergency department (ED) patients have eye complaints, including primary ophthalmologic pathology, infectious problems, and traumatic injuries. Eye injuries account for 3.5% of all occupational injuries in the United States, and about 2000 U.S. workers injure their eyes each day.[1] The majority of eye complaints can be treated without ophthalmologic consultation, but a few require ophthalmologist involvement as well as immediate action.[2] Some specific problems such as central retinal artery occlusion and caustic exposure require emergent therapy, even as assessment proceeds. Many other ophthalmologic conditions can be evaluated with a history and examination before treatment by the emergency physician.

Figures 69-1 and 69-2 are provided as brief reviews of normal ocular anatomy and funduscopic appearance.

OCULAR TRAUMA

Perspective

A systematic evaluation of the periorbital and orbital structures aids in the evaluation of patients with ocular trauma. Many extraocular structures are found in close proximity, and concomitant, nonocular injury is common. Penetrating and blunt ocular trauma may involve several eye structures.

Nonpenetrating Trauma

Orbit and Lid

Clinical Features and Management

Contusion. Blunt injury to the orbits and surrounding tissues results in ecchymosis, swelling, and an often dramatic appearance. Related significant injury must be considered. Basilar skull fractures may occur with bilateral ecchymosis (raccoon eyes). Underlying globe injury may be present, and complete examination may be impeded by swelling. The emergency physician should attempt to visualize and examine all structures underlying the eyelids and obtain an accurate visual acuity. This should be done soon after the patient presents, before further swelling occurs. Examining the structures underlying severely swollen eyelids is difficult. A Desmarres retractor may help avoid global pressure.

Treatment of isolated soft tissue injury to the eyelids and surrounding area is symptomatic. Head elevation and intermittent cold compresses started in the ED can be continued for 48 hours to decrease the pain and swelling. Complete resolution takes 2 to 3 weeks. Patients should be instructed to seek follow-up care for any increase in pain or swelling, decreased vision, double vision, or significant flashing lights or "floaters."

Orbital Wall Fractures. When blunt force causes an acute rise in intraorbital pressure, the thin walls of the orbit frequently fracture. Prolapse of orbital soft tissues into the maxillary sinus may result because the orbital floor is generally the weakest point.[3] Entrapment of the inferior rectus and inferior oblique ocular muscles, orbital fat, and connective tissues results in enophthalmos, ptosis, diplopia, anesthesia of the ipsilateral cheek and upper lip, and limitation of upward gaze. Subcutaneous orbital emphysema may be palpable. Associated globe injuries occur in 10 to 25% of patients with orbital floor fractures.[4] Radiographic examination of the face can help but is imperfect. A computed tomography (CT) scan of the orbits with axial and coronal views is preferred (Fig. 69-3). Plain x-ray films have limited utility given the lower sensitivity to delineate soft tissue structures and extent of bony deformity.[5] On x-ray film, the teardrop sign, a bulge extending from the orbit into the maxillary sinus, and an air-fluid level in the maxillary sinus are indirect signs of orbital floor injury. If the fracture involves an infected sinus, treatment consists of nasal decongestants, broad-spectrum oral antibiotics, and ice packs to the orbit for 48 hours. Some ophthalmologists use steroids to reduce swelling. Surgical repair is only for persistent diplopia or cosmetic concerns and is generally not performed until swelling subsides in 7 to 10 days.[6,7] Patients can usually be discharged to be reevaluated by an ophthalmologist in 1 to 2 weeks.

Medial orbital wall fractures, through the lamina papyracea of the ethmoid bone, involve entry into the ethmoid sinus. Clinical features include orbital emphysema and epistaxis. Diplopia from medial rectus impingement can occur.[3] The finding of orbital emphysema should prompt a search for associated injury.[8] Rarely is orbital emphysema significant enough to compress the optic nerve and result in acute visual loss.[9,10] In most cases, orbital emphysema is a benign finding that resolves with time. Prophylactic antibiotics are not needed unless the fracture involves an infected sinus.[8] Patients with orbital floor and medial orbital wall fractures should avoid blowing their noses and performing Valsalva maneuver to limit the extent of emphysema.

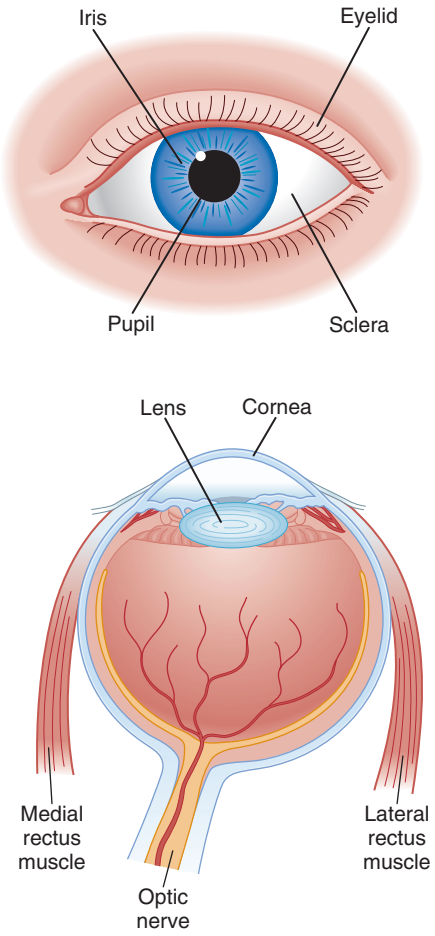


Figure 69-1. Normal eye anatomy.

Figure 69-2. Normal fundus. (Image courtesy of www.tedmontgomery.com)

Orbital rim fractures are also common. They are a result of direct force.

Retrobulbar Hemorrhage. Orbital hemorrhage in the potential space surrounding the globe may occur after blunt trauma and injury to the orbital vessels. Significant hemorrhage results in an acute rise in intraorbital pressure that is transmitted to the globe and optic nerve. This may result in occlusion of the central retinal artery. Clinical findings include proptosis, limitation of ocular movement, visual loss, and increased intraocular pressure. An orbital CT scan demonstrates a hematoma.

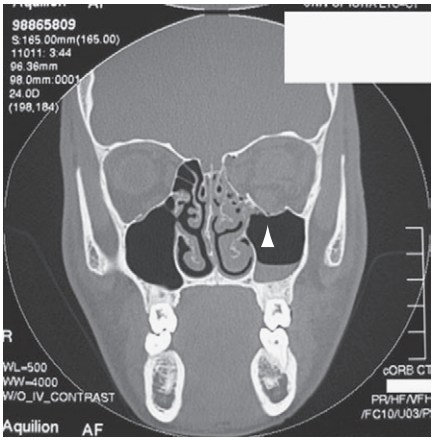


Figure 69-3. Facial CT scan showing left inferior orbital fracture with blood in maxillary sinus. (Image courtesy of http://webeye.ophth.uiowa.edu/eyeforum/Images/floorfx_08232004.jpg)

When a retrobulbar hematoma compromises retinal circulation, immediate ophthalmologic consultation for decompression is warranted. Treatment of increased intraocular pressure includes carbonic anhydrase inhibitor, topical beta-blocker, and intravenous (IV) mannitol. A lateral canthotomy can be done in the ED as a temporizing measure before definitive decompression.[3]

Cornea and Conjunctiva

Clinical Features and Management

Chemical Burns. Exposure of the eye to chemicals is a true ocular emergency. Exposure to strong alkaline chemicals, found in drain cleaners, chemical detergents, industrial solvents, and as lime in plaster and concrete, produces a liquefactive necrosis that penetrates and dissolves tissues until the alkaline agent is removed. Acid burns tend to be less devastating than alkali burns because acidic exposure causes coagulation necrosis and the precipitation of tissue proteins limits the depth of the injury.

Treatment should begin at the scene with immediate irrigation using copious amounts of water. Irrigation should continue for at least 30 minutes before any attempt to transport the patient to the hospital. Any particles should be removed from the fornices using a cotton swab.

Upon hospital arrival, irrigation should continue. Use of irrigation devices, such as a Morgan® Lens (Mortan Inc., Missoula, Mont), can assist in delivering continuous irrigation to the affected eye. Topical anesthetics and manual lid retraction may be needed for proper irrigation. Irrigation is needed until the pH of the tear film is neutral as tested by Nitrazine paper dipped into the inferior conjunctival fornix. If the pH tested immediately after irrigation is still alkaline, irrigation should be reinstituted. A normal pH should be checked again 10 minutes after the cessation of irrigation and periodically thereafter. Treatment after irrigation consists of a cycloplegic (avoid phenylephrine), topical antibiotics, treatment of increased intraocular pressure, and pain management.

Ophthalmologic consultation is indicated in all significant chemical exposures. Identification of the substance and its pH value is important. Alkaline substances with a pH less than 12 and acidic substances with a pH greater than 2 are thought not to cause significant injury, although high concentration and prolonged contact time can alter this general rule and may cause injury.[11,12]

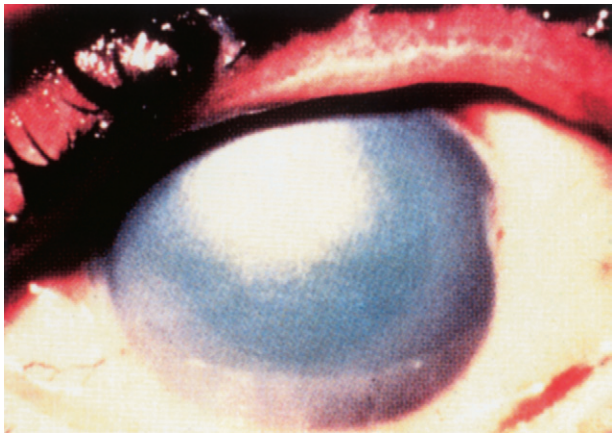


Figure 69-4. Severe alkali burn. Note scleral whitening and the cloudy cornea.

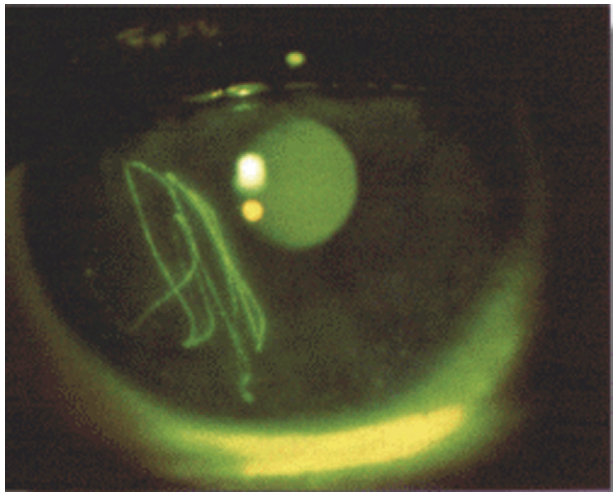


Figure 69-5. Corneal abrasion demonstrated by slit-lamp examination. (Image courtesy of http://www.perret-optic.ch/optometrie/symptomes_diagnostiques/symptomes/opto_symfor_gb.htm)

Severity can be judged by the degree of corneal cloudiness and scleral whitening (Fig. 69-4).[13] Long-term complications include perforation, scarring, and neovascularization of the cornea; adhesions of the lids to the globe (symblepharon); glaucoma; cataracts; and retinal damage.

Miscellaneous Irritants, Solvents, Detergents, and Glues. Unknown exposures should initially be treated as though they were an alkali or acid exposure, prompting immediate irrigation. Detergents generally cause conjunctival irritation only. More irritating substances may denude the corneal epithelium and cause anterior chamber inflammation. After copious irrigation, these injuries should be treated as corneal abrasions.

Aerosol exposures are common. Intraocular foreign bodies may result from the propellant. Exposure to the compounds found in personal defense devices (e.g., Mace) should be treated in the same manner as other chemical injuries.

Super glue (cyanoacrylate adhesive) exposure is also common. These glues harden rapidly, and typically the eyelids are sealed shut. Misdirected lashes and the hardened super glue may act as a foreign body and cause corneal defects.[14] Gentle traction on the eyelids and separating glued eyelashes may open the eyelids. If the eyelids are sealed shut in a normal anatomic position and cannot be opened with gentle traction, the eye may be left alone, allowing time for the super glue to dissolve by physiologic mechanisms over several days.[15] If the eyelids are inverted and sealed shut, surgical intervention may be needed. Attempts to dissolve the super glue with other substances should be avoided. Ophthalmic consultation should be obtained for super glue exposures.

Thermal Burns. Thermal burns affect the eyelids more than the globe because of reflex blinking and Bell's phenomenon. Superficial eyelid burns can be treated by irrigation and topical antibiotic ophthalmic ointment. Second- or third-degree eyelid burns need ophthalmic consultation. Hot liquid splashes and cigarette ashes to the cornea usually result in a superficial corneal epithelial injury and are treated as corneal abrasions. Molten metals and other hot objects may result in globe perforation.

Radiation Burns (Ultraviolet Keratitis). Ultraviolet light from sun lamps, tanning booths, high-altitude environments, snow or water reflection, or a welder's arc results in direct corneal epithelial damage. After a latent period of 6 to 10 hours, patients develop a foreign body sensation, tearing, intense pain, photophobia, and blepharospasm.[16] Topical ophthalmic anesthetics facilitate physical examination. Examination reveals decreased visual acuity, injected conjunctiva, and diffuse punctate corneal lesions, often with a discrete lower border defining the cornea protected by the inferior lid. Treatment consists of a short-acting cycloplegic and a topical broad-spectrum antibiotic ointment, although evidence for the latter is scant. Oral opioids are commonly needed. Patients should not be prescribed topical anesthetics because frequent use retards healing and can lead to corneal ulcer formation.[17] Patients should be counseled on the adverse effects of ultraviolet radiation and should be educated on using various protective devices.[18] Patients should have ophthalmologic or ED follow-up in 24 hours if their symptoms are not resolved.

Mechanical Corneal Abrasions. Patients complain of a foreign body sensation, pain, photophobia, and decrease in visual acuity. The degree of relief afforded by topical anesthesia can differentiate corneal injury from other causes of acute eye pain.[19] Physical examination reveals injected conjunctiva, decreased visual acuity if the defect is large or lies in the visual axis, and demonstration of the epithelial defect with slit-lamp examination using fluorescein (Fig. 69-5). Aqueous humor leaking from the anterior chamber during fluoroscein examination suggests a corneal perforation (Seidel's test). Foreign bodies of the lid conjunctiva must be identified. Treatment consists of cycloplegia and topical antibiotics. Recent data also suggest that treatment with topical nonsteroidal anti-inflammatory medications reduces the pain patients experience with corneal abrasions.[20] Patients with contact lenses should be treated with topical antibiotics with antipseudomonal coverage. Eye patching should be avoided, especially in injury involving vegetable matter or contact lens use. Data suggest that eye patching confers no benefit in healing small, uncomplicated corneal abrasions.[21,22] Patients with corneal abrasions should not wear their contact lenses. Oral pain medications may be needed. There are no known cases of clinical tetanus developing from a simple corneal abrasion.[23] Given the lack of evidence, simple corneal abrasions should not require tetanus immunization. However, tetanus immunization should be considered in any tetanus-prone injury such as corneal perforation or injuries containing dirt and organic matter. Patients should not be prescribed topical anesthetic agents as these may lead to corneal ulcer and bacterial infection. Patients should have ophthalmologic or ED follow-up in 24 hours if their symptoms have not resolved.

Corneal Foreign Bodies. Patients with corneal foreign bodies experience pain, foreign body sensation, injected conjunctiva, tearing, and blepharospasm. Administration of a topical ophthalmic anesthetic facilitates physical examination. Diagnosis

Figure 69-6. Corneal foreign body seen by slit-lamp examination. (Image courtesy of www.tedmontgomery.com)

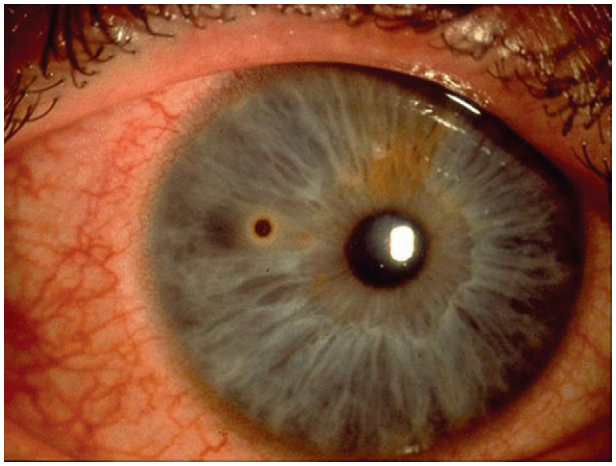


Figure 69-7. Corneal rust ring after removal of iron-containing foreign body demonstrated by slit-lamp examination. (Image courtesy of www.tedmontgomery.com)

is made with slit-lamp examination (Fig. 69-6). After a topical anesthetic is applied, the initial attempt at removing corneal foreign bodies should be with a stream of sterile saline solution. If this fails, the foreign body should be removed using a commercial eye spud or 25-gauge needle with a 1- to 3-mL syringe as a handle and magnification, generally the slit lamp. The patient must be totally cooperative and the patient's head firmly stabilized within the slit lamp. Alternatively, a short plastic 20-gauge catheter can be placed on a syringe and, with slit-lamp visualization, the foreign body can sometimes be irrigated out of the cornea.

Iron-containing corneal foreign bodies leave a residual rust ring (Fig. 69-7). Removal of the rust ring should be left to the ophthalmologist or a return visit to the ED for 24-hour follow-up because the affected cornea gradually softens, and the rust migrates toward the corneal surface, making removal easier.

Ophthalmologic consultation for corneal foreign bodies is recommended if a large area of the visual axis is involved, the object is deeply embedded within the cornea, the risk of perforation is increased for any reason, or there are multiple foreign bodies.

Treatment after foreign body removal is similar to that for corneal abrasion, with ophthalmologic or ED follow-up within 24 hours for patients who require rust ring removal or who remain symptomatic.

Use of high-speed drills, saws, grinders, and pounding objects or involvement in explosions should alert the emergency physician to the likelihood of an intraocular foreign body with perforation. CT can be used to rule out the diagnosis of an intraocular foreign body.

Conjunctival Foreign Body. Conjunctival foreign bodies can be removed under topical anesthesia with a cotton-tipped applicator or fine forceps. Topical phenylephrine can be used to reduce the conjunctival bleeding.

Subconjunctival Hemorrhage. Rupture of small subconjunctival blood vessels is common and occurs as a result of trauma or Valsalva maneuver or without apparent cause. Patients complain of its appearance. Pain, diminished visual acuity, or photophobia suggests a more serious pathologic condition. Subconjunctival hemorrhage is flat, bright red, smooth, limited to the bulbar conjunctiva, and sharply demarcated at the limbus (Fig. 69-8). Subconjunctival hemorrhage must be distinguished from bloody chemosis, which is indicative of more serious globe pathology. Bilateral or recurrent subconjunctival hemorrhage may require workup for bleeding diathesis.

Figure 69-8. Subconjunctival hemorrhage. (Image courtesy of www.tedmontgomery.com)

Treatment consists of local cold compresses for 24 hours, with resolution in 2 to 3 weeks.

Anterior Chamber and Iris

Clinical Features and Management

Traumatic Hyphema. Disruption of blood vessels in the iris or ciliary body results in hyphema, blood in the clear aqueous humor in the anterior chamber. If the patient is sitting, the blood often layers and forms a meniscus with the aqueous humor. Hyphemas range from minimal blood seen only with the slit lamp to the "eight ball" or total hyphema with blood that has clotted. Patients complain of pain, photophobia, and decreased visual acuity. The emergency physician sees the blood directly or with the aid of the slit lamp (Fig. 69-9). There is generally no afferent pupillary defect (or Marcus-Gunn pupil) present. An afferent pupillary defect occurs when the abnormal eye paradoxically dilates rather than constricts when light is directed to that eye. Intraocular pressure may also rise.

Management of hyphema must be individualized for a given patient. Selected low-grade hyphemas in reliable patients may be managed on an outpatient basis; all other patients should be admitted. General therapy includes elevating the bed 30 to

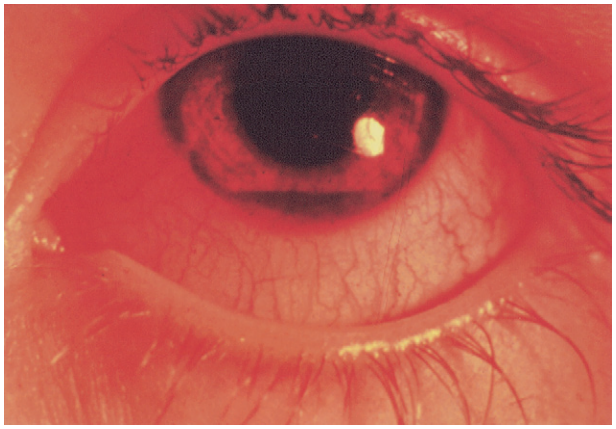


Figure 69-9. Small hyphema layering out in the inferior portion of the anterior chamber.

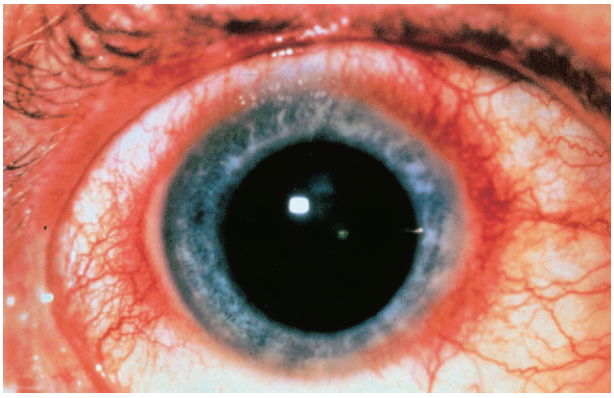


Figure 69-10. Ciliary flush. Note that conjunctival injection is most prominent immediately around the limbus.

45 degrees, bed rest, and limiting eye movement such as reading.[13] The affected eye should also be protected with a patch and shield. Analgesics are appropriate, but the patient should avoid taking aspirin and other platelet inhibitors.[24] Antiemetics and sedatives should be used cautiously. Increased intraocular pressure occurs as a result of aqueous flow blockage from the blood present. In patients without sickle cell disease, initial treatment is a topical beta-blocker; a topical alpha-agonist or topical carbonic anhydrase inhibitor is added if needed. Oral acetazolamide or IV mannitol may also be used.

Specific treatment for hyphema with miotics, mydriatics, cycloplegics, steroids, and antifibrinolytics such as aminocaproic acid varies depending on the specific clinical situation and is best left to the ophthalmologist.[13,25–27] Failure of medical therapy to control high intraocular pressure, failure of a large clot to resolve, and corneal blood staining are indications for surgical intervention.[26] There are case reports on the use of anterior chamber thrombolytics in those whose large clot fails to resolve.[24]

The major complication of hyphema is rebleeding, which occurs after 2 to 5 days when the initial clot retracts and loosens.[28] Rebleeding is more common in those with visual acuities of 20/200, initial hyphema covering more than one third of the anterior chamber, medical attention delayed more than 1 day after injury, and elevated intraocular pressure at the initial examination.[29] Other complications include corneal blood staining, acute or chronic glaucoma, and anterior or posterior synechia formation.

Patients with hemoglobinopathies (e.g., sickle cell disease, thalassemia) are at increased risk for hyphema complications. Red blood cells in the anterior chamber sickle in the relatively acidic and hypoxic environment,[30] which leads to decreased aqueous humor outflow and a rapid rise in intraocular pressure. Increased intraocular pressure in a sickle cell patient with a hyphema should be treated with topical beta-blockers. All other anti-glaucoma medications should be prescribed by an ophthalmologist. If needed, methazolamide by mouth, and not acetazolamide, may be used.

Traumatic Iridocyclitis. Blunt injury of the globe may contuse and inflame the iris and ciliary body, resulting in ciliary spasm. Patients complain of photophobia and deep, aching eye pain. Examination reveals perilimbal conjunctival injection (ciliary flush), cells (white or red blood cells) and flare (protein content) in the anterior chamber, and a small, poorly dilating pupil (Fig. 69-10). These symptoms indicate white blood cells and protein as a result of the inflammation. Patients may also experience direct photophobia, when the light is directed to the affected eye, and consensual photophobia when light is directed in the uninvolved eye.

Treatment consists of paralyzing the iris and ciliary body with a long-acting cycloplegic agent, such as homatropine hydrobromide 5%, given four times daily for 7 to 10 days.[31] Prednisolone acetate 1% may be given to help relieve the inflammation if there is no improvement after 5 to 7 days but should be avoided in patients with a corneal epithelial defect. Resolution occurs within 1 week.

Traumatic Mydriasis and Miosis. Blunt injury may result in either pupillary dilatation or constriction and may persist for days. For significant head trauma and altered mental status, a cranial nerve palsy must be ruled out before ascribing pupillary mydriasis to local contusion.

Permanent pupillary mydriasis may result from small radial tears in the pupillary sphincter muscle. The pupil margin may look irregular or scalloped. No specific ED treatment is warranted.

Iridodialysis. Traumatic iridodialysis is a tearing of the iris root from the ciliary body, leading to the formation of a "secondary pupil." This injury is often the cause of a hyphema. If no associated hyphema is present, no specific ED treatment is needed. Large tears can lead to monocular diplopia and may require surgical correction. Immediate ophthalmologic consultation is warranted when iridodialysis has caused a hyphema or a decrease in visual acuity.

Anterior Chamber Angle Recession. Blunt injury to the ciliary body may cause posterior displacement of the iris and surrounding tissues, deepening the anterior chamber, widening the anterior chamber angle, and causing potential damage to the trabecular meshwork that drains the aqueous humor. Severe damage can cause acute glaucoma.

Scleral and Lens Injuries

Clinical Features and Management

Cataract. If the lens capsule is disrupted by either blunt or penetrating trauma, the relatively dehydrated stroma absorbs fluid, swells, and becomes cloudy. Acute glaucoma may develop from blockage of the aqueous humor flow through the pupil, necessitating surgical intervention. In less severe injury, cataract formation may occur over weeks to months.

Lens Subluxation and Dislocation. Complete disruption of the lens zonule fibers by blunt trauma may result in anterior or posterior dislocation of the lens. Incomplete disruption of the lens zonule fibers results in subluxation of the lens. Lens dislocation may occur with minor trauma in patients with Marfan's syndrome, homocystinuria, tertiary syphilis, and

other predisposing conditions. Patients complain of monocular diplopia or visual distortion with subluxation and marked visual blurring with dislocation. Examination reveals decreased visual acuity. The edge of a subluxated lens can be seen when the pupil is dilated. Iridodonesis is a trembling or shimmering of the iris after rapid eye movements and is a helpful sign of lens dislocation. Treatment ranges from observation to surgical removal and is dictated by the location of the dislocated lens and associated eye injury. Immediate ophthalmologic consultation is warranted.

Scleral (Globe) Rupture. Blunt trauma causes scleral rupture by suddenly elevating intraocular pressure. Ruptures are most common at the insertions of the intraocular muscles or at the limbus, where the sclera is thinnest.[32] The diagnosis of scleral rupture is obvious when intraocular contents are visualized; however, occult global rupture can be difficult to diagnose. Patients complain of eye pain and decreased vision. Examination may reveal a bloody chemosis or severe subconjunctival hemorrhage overlying the scleral rupture site. When the rupture occurs at the limbus, an irregularly shaped (teardrop) pupil may also be seen. Uveal prolapse through the scleral wound, appearing as a brownish black discoloration, can also be seen (Fig. 69-11). Although a lower than normal intraocular pressure is a good indication of rupture, tonometry should not be performed in suspected globe rupture. Any maneuvers that increase intraocular pressure need to be avoided. A CT scan, ultrasonography, and indirect ophthalmoscopy all play a role in the diagnosis of occult globe rupture but may be left to the ophthalmologist.

Treatment in the ED for a known globe rupture includes avoidance of further examination or manipulation and the placement of a protective metal eye shield to prevent accidental pressure on the globe. The patient should be kept with nothing by mouth and a tetanus injection given as needed. Antiemetics should be given if the patient is nauseated. Broad-spectrum IV antibiotics should be instituted.[33]

Theoretical classical teaching states that the use of succinylcholine is contraindicated in the presence of a penetrating ocular injury because of the rise in intraocular pressure and potential for ocular extrusion, but a search of the literature does not identify a single report of this occurring. One study reported on the use of succinylcholine after pretreatment with nondepolarizing agents in 100 patients with penetrating eye injury; no adverse events were found.[34] Given the need for rapid airway management in a patient with penetrating ocular injury, rapid sequence intubation with succinylcholine and an induction agent is appropriate. Succinylcholine may be preceded by pretreatment with a defasciculating dose of a nondepolarizing neuromuscular blocking agent (e.g., 0.01 mg/kg of vecuronium or pancuronium), but there is no evidence that this definitely improves outcome.

Ophthalmologic consultation is required for all patients with suspected or proven globe rupture.

Figure 69-11. Scleral laceration with penetrating globe injury. Note care being taken not to increase intraocular pressure with examiner's fingers.

Posterior Segment Injuries

Clinical Features and Management

Vitreous Hemorrhage. Bleeding into the vitreous may occur from injuries to the retina and uveal tract and their associated vascular structures. Patients complain of decreased visual acuity and floaters. Floaters, described by the patient as dark dots or strands moving in the visual field in the direction of the preceding eye movement, are caused by vitreous blood. There is a diminished red reflex and an inability to visualize the fundus clearly with the direct ophthalmoscope. With vitreous hemorrhage caused by blunt trauma, B-scan ultrasonography is used to search for retinal injury and determine the need for operative repair.[35]

Treatment of vitreous hemorrhage includes elevating the head of the bed to allow settling of the blood and avoiding platelet-inhibiting drugs and Valsalva maneuver. Vitrectomy is performed for vitreous hemorrhage with an associated retinal detachment. Ophthalmologic consultation is warranted for acute traumatic vitreous hemorrhage.

Retinal Injuries. Blunt injury to the retina may result in hemorrhage, a tear or detachment, or commotio retinae.

Hemorrhage can occur in the preretinal (subhyaloid), superficial retinal, or deep (subretinal) spaces. Preretinal hemorrhage appears as boat shaped, superficial retinal hemorrhage as flame shaped, and deep retinal hemorrhage as rounded and grape-purple in color.

Tears and detachments from blunt trauma are common. Symptoms include floaters from bleeding, flashing lights from stimulation of retinal neurons, and visual field cuts or decreased visual acuity. Retinal tears or detachments do not cause pain. Examination may reveal the hazy gray membrane of the retina billowing forward (Fig. 69-12), but many tears are peripherally located and not seen with direct ophthalmoscopy. Visual acuity may be normal unless the macula is involved. Indirect ophthalmoscopy is warranted if historical clues to the presence of retinal tears are present.

Ophthalmologic consultation is warranted in all cases of suspected or proven retinal detachment. Treatment includes photocoagulation or operative repair; prognosis depends on the condition of the macula.

Commotio retinae occurs after recent ocular trauma. Patients may have decreased visual acuity or be asymptomatic. Examination reveals a cloudy whitening of the involved area that

Figure 69-12. Retinal detachment. Note large portion of retinal billowing forward. (Image courtesy of www.tedmontgomery.com)

subsides in a few weeks with no specific treatment. Serial follow-up is necessary to ensure that retinal tear or detachment has not occurred.

Optic Nerve Injury. Significant blunt force to the orbital contents may avulse, transect, compress, or contuse the optic nerve. Fractures may extend into the orbital canal and cause optic nerve damage. Patients complain of visual field cuts or decreased visual acuity. Examination reveals an afferent pupillary defect, assorted visual field cuts, a decrease in visual acuity, or total blindness. The optic disk is normal initially, but pallor eventually develops.[3] An orbital CT scan can help define the location and extent of injury. Management of traumatic optic neuropathy is controversial. High-dose methylprednisolone and surgical decompression have been used with varying degrees of success.[3] When edema or bleeding within the optic nerve is visualized, or with significant reduction in visual acuity, high-dose steroids can be used. Surgical decompression should be considered when decreasing visual acuity is occurring from a known orbital canal fracture.

Penetrating Trauma

Lacerations of the Eyelids

Clinical Features and Management. Any laceration involving the eyelids should prompt a search for penetrating globe injury and, if indicated, a thorough search for a foreign body. Soft eye pads should be avoided to prevent increases in intraocular pressure.

Emergency physicians can manage simple horizontal or oblique partial-thickness lid lacerations. These can be closed primarily using 6-0 or 7-0 nylon interrupted sutures. Sutures should be removed in 3 to 5 days.

Several lid lacerations have a high likelihood of cosmetic or functional complications and should be managed by ophthalmologists or plastic surgeons skilled in this area. The following lid lacerations fall into the category of complex lid lacerations and need immediate referral.

1. Lacerations involving the lid margins.
2. Lacerations involving the canalicular system. Injury to the canalicular system should be suspected in any laceration involving the medial lower eyelid area (Fig. 69-13).
3. Lacerations involving the levator or canthal tendons.
4. Laceration through the orbital septum. Orbital fat protrudes through septal lacerations into the wound. Because eyelids have no subcutaneous fat, the appearance of fat in a lid laceration confirms this diagnosis. These wounds are associated with a high incidence of globe penetration and intraorbital foreign bodies.
5. Lacerations with tissue loss.

Conjunctival Lacerations

Clinical Features and Management. Lacerations of the bulbar conjunctiva commonly involve intraocular foreign bodies or underlying scleral perforation. Slit-lamp examination can distinguish superficial from deeper lacerations. Small, superficial lacerations require no suturing and heal quickly. Topical prophylactic ophthalmic antibiotics are advisable. Larger (>1 cm) and deeper lacerations may require repair by an ophthalmologist.

Corneal and Scleral Lacerations

Clinical Features and Management

Corneal Lacerations. Signs of corneal perforation (full-thickness corneal lacerations) include loss of anterior chamber depth, teardrop-shaped pupil caused by iris prolapse through the corneal laceration, and blood in the anterior chamber (Fig. 69-14). Small corneal lacerations can be difficult to diagnose. If aqueous humor is leaking from the corneal wound, it appears as streaming fluorescent dye surrounded by an orange pool of solution on slit-lamp examination (Seidel's test).[36] Full-thickness corneal lacerations are managed as described for blunt traumatic globe rupture.

Superficial partial-thickness corneal lacerations without a widened wound can be treated with a cycloplegic, topical antibiotic, and a pressure patch. Repairs of partial-thickness corneal lacerations requiring suture closure are performed in the operating room.

Scleral Lacerations. Penetrating scleral lacerations occur with the signs and symptoms of blunt globe rupture. Globe perforation may be unrecognized in the absence of significant physical examination findings.

Orbital and Intraocular Foreign Bodies

Clinical Features and Management. Any orbital and intraocular penetration should be approached with the possibility of intracranial injury.

Small intraocular and intraorbital foreign bodies can occur with any perforating injury and be difficult to diagnose. Physical examination of the eye may be completely normal at initial presentation. Occult foreign bodies should be suspected with

Figure 69-13. Facial laceration near the medial canthus. (Image courtesy of http://www.mdchoice.com/photo/img/img0212.jpg)

Figure 69-14. Teardrop-shaped pupil demonstrating anterior chamber perforation through corneal laceration.

Figure 69-15. Centrally located corneal ulcer. (Image courtesy of www.tedmontgomery.com)

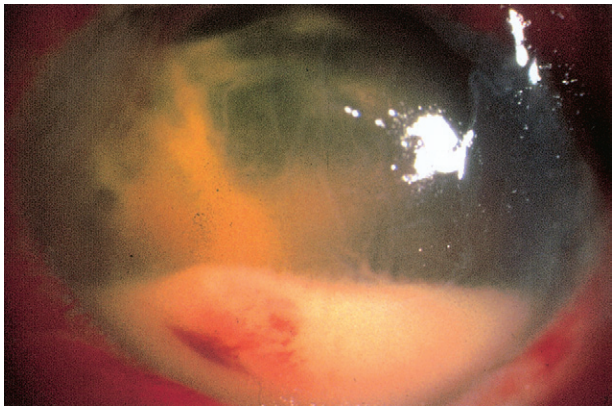


Figure 69-16. Endophthalmitis resulting from globe rupture.

any penetrating injury associated with mechanical grinding, sanding, drilling, and hammering. Plain orbital films, orbital CT scan, magnetic resonance imaging (MRI) scans, and ultrasonography aid in diagnosis. Although the decision to use one modality over another is dictated by individual clinical circumstances, an orbital CT scan is probably the most useful diagnostic tool. The MRI scan should not be used when an iron-containing foreign body is suspected.

Treatment of intraocular foreign bodies is dictated by clinical circumstances and is left to the ophthalmologist. Patients with acute intraocular foreign bodies should be hospitalized, have nothing by mouth, have a protective shield placed, and be given antibiotics. Generally speaking, acute intraocular foreign bodies are surgically removed.[32] Plastic, glass, and many metals are relatively inert, and their nonacute removal is sometimes likely to cause more damage than their permanent presence. Organic foreign bodies are more important to remove because of their propensity for infection. Siderous oxidation of ocular tissues is a late complication of iron-containing intraocular foreign bodies that can lead to visual loss. Chalcosis, a sterile inflammatory reaction to copper-containing compounds, may occur, requiring removal of the offending object.

Complications of Ocular Trauma

Clinical Features and Management

Post-traumatic Corneal Ulcers. Any defect in the corneal epithelium may become infected with bacteria or fungi. Ulcerations are surrounded by a cloudy white or gray-appearing cornea (Fig. 69-15). A reactive sterile hypopyon (pus or pus-like fluid) may be present in the anterior chamber. Emergent ophthalmologic consultation is needed. Treatment includes cycloplegia, topical antibiotics, and often admission to the hospital. Corneal perforation is a complication.

Endophthalmitis. Endophthalmitis is an infection involving the deep structures of the eye, namely the anterior, posterior, and vitreous chambers. Patients complain of pain and visual loss. Examination reveals decreased visual acuity, chemosis, and hyperemia of the conjunctiva, and the infected chambers are hazy or opaque (Fig. 69-16). Endophthalmitis is a complication of blunt globe rupture, penetrating eye injury, foreign bodies, and ocular surgery. Prompt diagnosis and early treatment with intraocular and systemic antibiotics are important in the successful management of post-traumatic endophthalmitis.[37] Common pathogens are *Staphylococcus*, *Streptococcus*, and *Bacillus*.[38] Topical, intravitreal, and systemic antibiotics are all used.

Sympathetic Ophthalmia. This is an inflammation that occurs in the uninjured eye weeks to months after the initial insult to the injured eye. It is thought to be an autoimmune response to the normally sequestered uveal tissues of the injured eye becoming exposed with injury. Patients have pain, photophobia, and decreased visual acuity. Treatment includes steroids and other immunosuppressive agents.[38] Enucleation of the blind injured eye can reduce symptoms even after the sympathetic ophthalmia has developed.

DISEASE OF THE CONJUNCTIVA

Clinical Features and Management

Conjunctivitis

Conjunctivitis is an inflammation of the bulbar and palpebral conjunctiva caused by various viral, bacterial, mechanical, allergic, and toxic agents. When the cornea is also involved, it is known as keratoconjunctivitis. Multiple viral and bacterial pathogens are responsible for acute conjunctivitis. Adenovirus, coxsackievirus, and enteroviruses have been isolated as causes of conjunctivitis. Common bacterial agents include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus* organisms, *Moraxella catarrhalis*, and *Neisseria gonorrhoeae*. Less common bacterial causes are *Klebsiella* and *Pseudomonas*.

Acute Bacterial Conjunctivitis. Patients complain of pinkeye, redness, a foreign body sensation, lid swelling, drainage, and eye crusting in the morning. Photophobia and visual loss are notably absent.

Treatment of acute bacterial conjunctivitis includes warm compresses and topical ophthalmic antibiotics. In uncomplicated acute bacterial conjunctivitis, topical trimethoprim and polymyxin are a good initial selection.[39] Other agents commonly used include sodium sulfacetamide, ciprofloxacin, ofloxacin, gatifloxacin, and erythromycin. Neomycin ophthalmic solutions should be avoided because of the high incidence of hypersensitivity reactions.[39] Ophthalmic ointments provide a soothing effect and have prolonged contact with the ocular surface while ophthalmic drops do not interfere with vision. Medications should be continued for 7 days. Corticosteroids and eye patching should be avoided.

Cultures are indicated when symptoms are severe or when prior treatment has been inadequate or unsuccessful.[39] Complications of acute bacterial conjunctivitis include corneal ulcer formation, keratitis, and corneal perforation. Patients

with complicated bacterial conjunctivitis should be referred to an ophthalmologist.

Acute bacterial infection caused by *N. gonorrhoeae* is uncommon but important because of its significant complications. Infection results from direct contact with individuals infected with urethritis or pelvic inflammatory disease. Signs and symptoms are markedly increased, including a copious purulent discharge. Gram's stain may reveal the diagnosis, although cultures are more sensitive.

Treatment is more aggressive than with other causes of bacterial conjunctivitis. Hospital admission for IV antibiotics, saline irrigation, and topical ophthalmic antibiotics is warranted in moderate and severe cases and any patient with corneal involvement. Outpatient management may be used in selected mild cases with ceftriaxone 1 g intramuscularly as a single dose, topical erythromycin ointment, and saline solution irrigation of the conjunctiva.[39] A substantial proportion of patients have concomitant *Chlamydia trachomatis* infection and should be treated with oral doxycycline, tetracycline, or erythromycin (20 mg/kg) or a single dose of 1 g of azithromycin.[39]

Viral Conjunctivitis. Viral infection is the most common cause of conjunctivitis. Several types of viruses can cause conjunctival infection; however, adenovirus is the most common viral cause. Viral conjunctivitis generally produces more redness, itching, eye irritation, a clear watery discharge (which can become purulent appearing), preauricular lymphadenopathy, and lasts longer than does bacterial conjunctivitis (Fig. 69-17). It commonly occurs in the setting of other viral symptoms (e.g., fever, myalgias, malaise). The patient usually complains of initial eye irritation in one eye that spreads to the other eye a few days later.

Viral conjunctivitis is very contagious for 10 to 12 days after onset, and appropriate preventive measure, such as frequent handwashing, should be taken. Treatment consists of artificial tears and cool compresses. A vasoconstrictor and antihistamine combination can be used if itching is severe. Sometimes it may be difficult to differentiate between viral and bacterial conjunctivitis. The emergency physician can use some clues in the history and physical examination to point to one direction. Not all patients with an erythematous eye need antibiotics. The emergency physician should use his or her clinical judgment to decide which patients may need antibiotics. Topical antibiotics should be given only to patients in whom bacterial superinfection is suspected. Since viral conjunctivitis is a self-limited and benign condition, the majority of patients require only supportive care with artificial tears, cold compresses, and decongestants.

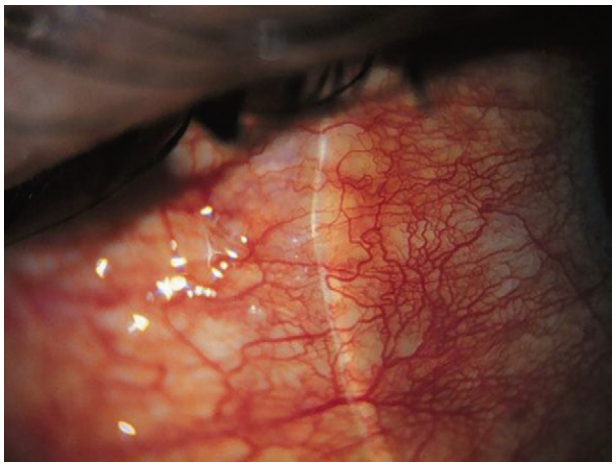


Figure 69-17. Conjunctival injection resulting from viral conjunctivitis. (Image courtesy of www.tedmontgomery.com)

Ophthalmia Neonatorum. Conjunctivitis that occurs within the first month of life is termed ophthalmia neonatorum and has several causes. A bacterial cause should be investigated with Gram's stain and cultures within the first 2 weeks of life. *N. gonorrhoeae* and *Chlamydia* are both transmitted from mother to infant through the birth canal.[39]

Infection with *N. gonorrhoeae* is manifest within 2 to 4 days after birth. The infant should be carefully examined for evidence of systemic gonococcal infection. Hospitalization and blood and cerebrospinal fluid examination may be indicated. Nonsystemically infected neonates can be effectively treated with a single dose of ceftriaxone, 125 mg intramuscularly, topical polymyxin B-bacitracin ointment, and saline washes.[39] These patients should also be treated for ocular chlamydial infection. Close follow-up is needed.

Infants with chlamydial infection develop symptoms between 5 and 13 days after birth. Topical erythromycin ointment and oral erythromycin are the antibiotics used.[40] Treatment is for 14 days.

Chemical conjunctivitis from antibiotic ointment administration immediately after delivery occurs within 1 to 2 days of birth but should not be the diagnosis if the infant has significant symptoms, the time course is inappropriate, or other historical and physical examination parameters are not classic. In such cases, a bacterial cause should be assumed.

In neonates with no information from stains or cultures and in whom an organism is not known or suspected, topical erythromycin ointment and oral erythromycin are utilized.

Miscellaneous Conjunctivitis. Allergic conjunctivitis is common. Allergens include drugs, cosmetics, and environmental agents. Eye itching is generally more pronounced in patients with allergic conjunctivitis and tends to be bilateral. Artificial tears, cool compresses, combination topical ocular decongestants, topical vasoconstrictor-antihistamine combinations, and topical nonsteroidal agents may be used for treatment. Other types of conjunctivitis include toxic conjunctivitis from topical ocular medications (aminoglycosides, antivirals, and preservatives), molluscum contagiosum, and chronic conjunctivitis.

DISEASE OF THE CORNEA

Differential Considerations

Clinical Features and Management

Pterygium and Pinguecula. A pterygium is a wedge-shaped area of conjunctival fibrovascular tissue that extends onto the cornea. Pterygium is associated with increased exposure to ultraviolet light exposure, especially in subtropical and tropical climates. Patients usually present with eye irritation as well as visual changes if a significant portion of the cornea is involved. A pinguecula is white or yellow, flat to slightly raised tissue on the conjunctiva, immediately next to but not on the cornea. Pinguecula can also be associated with ultraviolet light exposure or dryness. Patients can be asymptomatic or present with irritation and redness. Treatment of pterygium and pinguecula includes protection from wind, dust, sunlight, and artificial tears. An inflamed pinguecula can be treated with a short course of a topical nonsteroidal agent. Nonemergent referral to an ophthalmologist is recommended. Surgical removal is possible for selected individuals.

Superficial Punctate Keratitis. Superficial punctate keratitis consists of superficial, multiple, pinpoint corneal epithelial defects. Patients present with pain, photophobia, redness, and a foreign

body sensation. Superficial punctate keratitis is a nonspecific finding that is seen in many conditions. The most common precipitating conditions are ultraviolet burns (welders or sun lamps), conjunctivitis, topical eye drug toxicity (neomycin, gentamicin, and drugs with preservatives, including artificial tears), contact lens disorders, dry eye and exposure keratopathy, blepharitis, mild chemical injury, and minor trauma. Specific treatment is aimed at the underlying offending cause. Nonspecific treatment for a significant non–contact lens–associated superficial punctate keratitis includes nonpreserved artificial tears, topical antibiotics such as trimethoprim-polymyxin drops, and cycloplegia. Patients with a significant contact lens–associated superficial punctate keratitis should stop wearing their contact lenses and be treated with a topical fluoroquinolone or tobramycin drops during the day and ointment at night. Patients should have ophthalmologic follow-up the next day.

Corneal Ulcers and Infiltrate from Infection. Corneal infiltrates arise as a focal white opacity without an epithelial defect. Corneal ulcers have an overlying corneal epithelial defect that stains with fluorescein in addition to the corneal infiltrate. Patients present with pain, redness, photophobia, and decreased vision. The most common cause is bacterial, but fungal and herpes simplex infections are also possible. Patients should be immediately referred to an ophthalmologist for corneal culturing before treatment is initiated.

Herpes Simplex Infections. Infection with herpes simplex may be either primary or reactivation of preexisting disease. Symptoms include foreign body sensation, tearing, photophobia, clear discharge, and decreased visual acuity. Physical examination reveals a red eye and may or may not include the classic herpetic vesicles located on the lids or conjunctiva. Corneal involvement is seen on slit-lamp examination and may appear as a superficial punctate keratitis, ulcer, or the classical dendritic lesions (Fig. 69-18). Treatment for epithelial keratitis consists of topical antiviral agents such as trifluridine 1% every 2 hours for 14 to 21 days.[41] Topical prophylactic antibiotics and cycloplegia are also employed. Topical steroids are contraindicated in corneal epithelial disease but have proved to be beneficial in stromal disease.[41] Emergent ophthalmologic consultation is advised.

Herpes Zoster Infection. Herpes zoster keratoconjunctivitis occurs as a result of activation of the virus along the ophthalmic division of the trigeminal nerve. The rash follows dermatomal patterns, involves the forehead and upper eyelid, and produces significant pain. Involvement of the nasociliary branch of the trigeminal nerve, manifested by zoster lesions on the tip of the nose (Hutchinson's sign), is associated with a 76% risk of ocular involvement versus 34% risk if the nerve is not involved.[42] Ophthalmic herpes zoster accounts for approximately 10 to 20% of all zoster cases and mandates emergent ophthalmologic consultation.[43] Treatment is complex and depends on the type, location, and degree of ocular involvement. Antiviral agents (acyclovir, valacyclovir, or famciclovir), topical steroid agents, as well as topical antibiotics are used.[44,45] Early treatment with antiviral therapy within 72 hours of the onset of the rash has been shown to reduce acute pain and ocular complications.[46] Some patients may require admission for IV antiviral therapy while many can be treated as outpatients with close ophthalmologic follow-up. In a recent study, orally administered valacyclovir resulted in substantial vitreous penetration of this antiviral agent and was as effective as IV acyclovir treatment.[47]

Contact Lens Complications. The common complications of contact lens use involving the cornea include mechanical damage such as abrasions, corneal neovascularization, infections producing corneal ulcers, hypersensitivity or toxicity reactions to preservatives in solutions, and contact lens deposits. *Pseudomonas* is an important pathogen in contact lens–acquired infections.[18] If infection or abrasion is suspected, a topical fluoroquinolone is used six to eight times daily in the affected eye to cover for *Pseudomonas*. If no significant signs or symptoms exist that indicate corneal infection, the patient should discontinue contact lens use and follow up with his or her ophthalmologist. When corneal infection is present or suspected, immediate ophthalmologic consultation is indicated.

DISORDERS OF THE LIDS AND OCULAR SOFT TISSUES

Differential Considerations

Clinical Features and Management

Hordeolum and Chalazion. Hordeolums and chalazions are localized, nodular, inflammatory processes of the eyelids. Hordeolums, also known as styes, are acute inflammations of the glands of Zeis or hair follicles caused most commonly by *Staphylococcus* species. A chalazion is the result of an obstructed meibomian gland that results in swelling within the lid surface with the lid margin being normal.[18] Symptoms and signs include pain, swelling, and redness (Fig. 69-19). Spontaneous rupture may occur, and most resolve with warm compresses applied for 15

Figure 69-18. Herpes simplex keratitis infection. Note typical dendritic pattern on cornea. (Image courtesy of www.tedmontgomery.com)

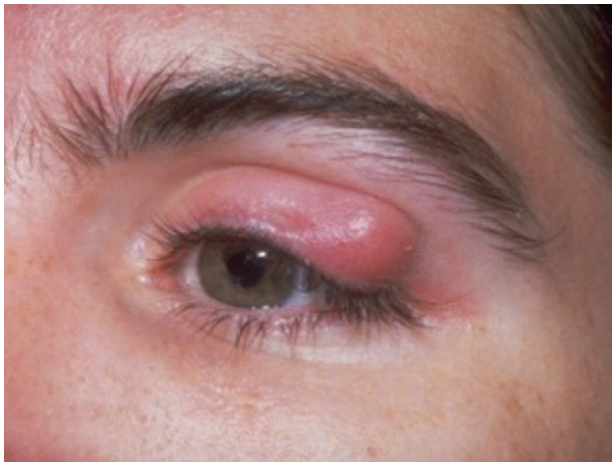


Figure 69-19. Chalazion of the upper eyelid. (Image courtesy of www.tedmontgomery.com)

Figure 69-20. Dacryocystitis.

minutes four to six times each day. Topical antibiotics (erythromycin) may be used, but there is no evidence for benefit. Incision and drainage are indicated for chalazia unresponsive to conservative therapy.[48]

Dacryocystitis. Dacryocystitis is an acute infection of the lacrimal sac from nasolacrimal duct obstruction. The most common organism is *Staphylococcus aureus*. Symptoms and signs include pain, tenderness, swelling, and erythema over the lacrimal sac (Fig. 69-20). Pressure over the sac may express purulent material from the puncta. Treatment includes topical ocular and oral anti-staphylococcal antibiotics and warm compresses. Gentle massage of the area during warm compress application may help decompress purulent material and relieve symptoms. Systemically ill patients should be hospitalized.

Blepharitis. Patients present with thickened, mattered, red eyelid margins with pronounced blood vessels. Patients complain of burning, itching, tearing, foreign body sensation, and morning crusting of the eyelids. Treatment includes rubbing the eyelid margins with a mild shampoo using a cotton-tipped applicator or cloth twice per day, warm compresses, and artificial tears. Severe blepharitis can also be treated with topical antibiotic ointment applied at night.

Preseptal Cellulitis. Patients present with lid erythema and warmth, tenderness, and swelling and may have a low-grade fever. Preseptal cellulitis is more common in younger children, with sinusitis being the most common cause.[49] It may also occur after minor skin trauma such as an insect bite or spread from a focus of impetigo.[50] It is important to note the absence of findings associated with orbital (postseptal) cellulitis (i.e., proptosis, restriction of extraocular movements, pain with eye movement, and patient's toxicity). If any of these findings are present, orbital cellulitis or abscess should be suspected and the patient managed more aggressively with imaging studies (CT scan of brain and orbits) and hospitalization. Orbital cellulitis can result in meningitis and cavernous sinus thrombosis if it is not recognized or left untreated.[18] Preseptal cellulitis is characterized by a continuum of disease, and treatment is tailored to the degree of the patient's toxicity. Mild disease can be treated on an outpatient basis with oral antibiotics, but hospitalization with IV antibiotics may be needed for moderate to severe disease and for younger children. The choice of antibiotic should include coverage for *Streptococcus* and *Staphylococcus* species, since these are the most common pathogens.[51] Adults should be treated with amoxicillin/clavulanate 500 mg PO three times daily for 10 to 14 days as outpatients or an IV second- or third-generation cephalosporin, such as cefuroxime or ceftriaxone, for inpatient treatment. Children should receive amoxicillin/clavulanate 20 to 40 mg/kg PO divided into three doses for 10 to 14 days for outpatient treatment or an IV second- or third-generation cephalosporin for inpatient treatment. Due to the increased incidence of community-acquired methicillin-resistant *S. aureus*, empirical coverage with vancomycin or clindamycin should also be considered. If the patient is admitted and shows improvement with IV antibiotics within 48 to 72 hours, a trial of oral antibiotics as outpatient therapy can be considered with close follow-up.

GLAUCOMA

Clinical Features and Management

Aqueous humor is produced by the ciliary processes. In addition to providing structural support to the eye, aqueous humor delivers oxygen and nutrients to the avascular lens and cornea and removes their waste products. This fluid passes from the posterior chamber to the anterior chamber through the pupillary aperture. The aqueous humor is transported into the trabecular meshwork located at the anterior chamber angle formed by the junction of the root of the iris and the peripheral cornea. The trabecular meshwork serves as a one-way valve and filter for the aqueous humor into the canal of Schlemm, which in turn drains into episcleral veins.

Intraocular pressure is determined by the rate of aqueous humor production relative to its outflow and removal. Normal intraocular pressure is between 10 and 20 mm Hg.[52]

Glaucoma is an optic neuropathy caused by increased intraocular pressure. Irreparable optic nerve damage can result. The simplest classification is to divide the glaucomas into primary or secondary and open angle or closed angle. Secondary glaucoma is associated with another ocular or nonocular event, whereas primary glaucoma is not. Closed-angle glaucoma is caused when the anterior chamber angle is narrowed, reducing the outflow and removal of aqueous humor, whereas open-angle glaucoma occurs with a normal anterior chamber angle.

Patients vary in their susceptibility to a given level of intraocular pressure. Some may develop significant optic nerve findings despite a relatively low intraocular pressure (low-tension glaucoma), whereas others may have scant optic nerve changes despite relatively high intraocular pressure (ocular hypertension).[53]

Primary Open-Angle Glaucoma

Primary open-angle glaucoma is the most common form of glaucoma and is a leading cause of blindness in the United States. There is increased resistance to aqueous humor outflow through the trabecular meshwork. Primary open-angle glaucoma is generally insidious, slowly progressive, chronic, bilateral, and painless. Advanced disease occurs before symptoms. Symptoms begin as visual field loss at the periphery that progresses centrally. Signs include an optic cup to optic nerve ratio of greater than 0.6.[54] Other findings include vertically oval, deep, and pale optic cups, with nasal displacement of blood vessels.

The three treatment options are medications, argon laser trabeculoplasty, and guarded filtration surgery. Initial treatment is generally with one or more topical agents. Beta-blockers, selective α_2-receptor agonists, carbonic anhydrase inhibitors, prostaglandin agonists, miotics, and sympathomimetics are all used.

Topical ocular medications are absorbed and may produce significant systemic side effects.[55] Topical beta-blockers have produced asthma, heart block, congestive heart failure, hypoglycemia, and depression. Adrenergics have produced hypertension and cardiac dysrhythmias, whereas carbonic anhydrase

inhibitors have produced renal calculi and hypokalemia. Complications may arise as a result of drug interaction. Prolonged apnea, for example, has resulted when succinylcholine has been given to a patient receiving topical ophthalmologic acetylcholinesterase inhibitors.[56]

Secondary Open-Angle Glaucoma

Secondary open-angle glaucoma can have a number of causes, including lens induced, inflammatory, exfoliative, pigmentary, steroid induced, traumatic, angle recession, and ocular tumor.

Treatment is directed to the offending mechanism and includes the methods used for primary open-angle glaucoma.

Primary Angle Closure Glaucoma

Primary angle closure glaucoma occurs in patients who have anatomically small and shallow anterior chambers. This anatomic variation results in the iris being nearly in contact with the lens, resulting in resistance to aqueous humor flow from the posterior to anterior chamber. This is called pupillary block.[57]

Attacks of primary angle closure glaucoma are precipitated by pupillary dilatation. Dimly lit rooms, emotional upset, and various anticholinergic and sympathomimetic medications are common precipitating events. The dilatation of the pupil increases the degree of pupillary block, leading to an accumulation of aqueous humor in the posterior chamber. The iris bulges forward, obliterating the angle between the cornea and iris, obstructing the trabecular meshwork, decreasing outflow, and leading to a rapid rise in intraocular pressure.[58]

A second, less common mechanism of acute angle closure glaucoma, produced without pupillary block, is caused by a flat or plateau iris. This leads to a narrow angle recess. Dilatation of the pupil causes the iris to fold and bunch over the angle, blocking aqueous humor outflow into the trabecular meshwork.

Symptoms are abrupt in onset and include severe eye pain, blurred vision, headache, nausea, vomiting, and occasionally abdominal pain. Patients see a halo around lights. Signs include conjunctival injection and a cloudy (steamy) cornea with a midpositioned to dilated pupil that is sluggish or fixed (Fig. 69-21). Visual acuity may be significantly decreased, and intraocular pressures are markedly elevated.

Treatment should begin promptly. If visual acuity is markedly reduced (hand movements or less), a combination of all topical glaucoma medications with IV osmotics and acetazolamide should be utilized.[44] Intraocular pressures less than 50 mm Hg without significant visual acuity change can be managed without the IV medications.[44] Topically administered timolol 0.5% decreases intraocular pressure within 30 to 60 minutes.[59] Pilocarpine, a miotic agent, 1 to 2% is topically administered, one drop every 15 minutes for two doses, and one drop may be placed prophylactically in the unaffected eye. A topical α_2-agonist (apraclonidine 1.0%) for one dose and topical steroid (prednisolone acetate 1% every 15 minutes for four doses) should be given.[44] In the setting of a severe attack, acetazolamide, a carbonic anhydrase inhibitor, is given in an IV dose of 250 to 500 mg, and mannitol 1 to 2 g/kg over 45 minutes.[60] Sedatives and antiemetics may be administered as needed. Emergent ophthalmologic consultation is warranted.

The definitive therapy for primary angle closure glaucoma is surgical.

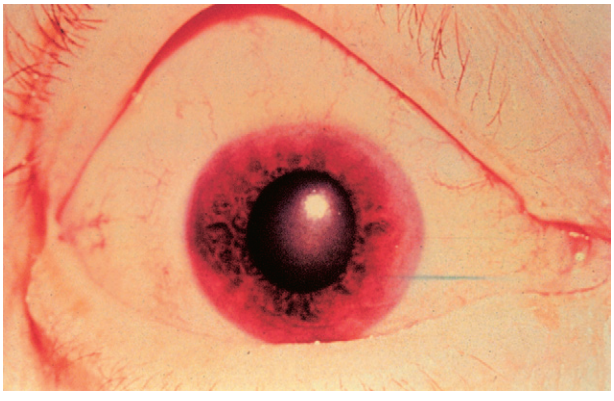


Figure 69-21. Acute narrow angle glaucoma. Note steamy appearance of cornea with a midpositioned and sluggish pupil.

Secondary Angle Closure Glaucoma

Pupillary block may develop from a swollen or dislocated lens or posterior synechiae (adhesions between the iris and lens). Secondary angle closure glaucoma, without pupillary block, can be caused by intraocular tumors, central retinal vein occlusion, or postoperatively. Treatment is directed at the offending cause.

■ ACUTE VISUAL LOSS

Differential Considerations

Acute visual loss, usually in only one eye, occurs over a period ranging from a few seconds to a day or two. The vision is generally reduced to 20/200 or worse. Patients need to be quickly evaluated to determine whether a treatable cause exists. The differential diagnosis of acute visual loss not related to trauma includes vascular occlusion, retinal detachment, vitreous hemorrhage, macular disorders, neuro-ophthalmologic disease, and hysteria. Most of these patients need ophthalmic or neurologic referral for a complete workup.

Patients may complain of acute visual loss when they may have neither an acute process nor a visual loss caused by the eye itself. For example, a patient with a visual field cut secondary to a neuro-ophthalmologic lesion may have an acute visual loss when the patient discovers the field cut. A patient with a hemianopsia usually has normal visual acuity even though both eyes are affected. An accurate history of how the patient discovered the visual loss, as well as the timing of that loss, is vital.

Clinical Features and Management

Central Retinal Artery Occlusion. Acute visual loss as a result of vascular occlusion of the central retinal artery is typically painless.

The ophthalmic artery is the first intracranial branch of the internal carotid artery and the central retinal artery is the first intraorbital branch of the ophthalmic artery. Central retinal artery occlusion causes an ischemic stroke of the retina. It occurs most commonly in those between 50 and 70 years of age, and 45% have carotid artery disease.[61] Risk factors include hypertension, cardiac disease, diabetes, collagen vascular disease, vasculitis, cardiac valvular abnormality, and sickle cell disease. Patients with increased orbital pressure are also at risk, including patients with acute glaucoma, retrobulbar hemorrhage, and endocrine exophthalmos. Patients complain of a severe loss of vision that develops over seconds. Examination reveals a markedly reduced visual acuity with a prominent afferent pupillary defect. On funduscopic examination, the

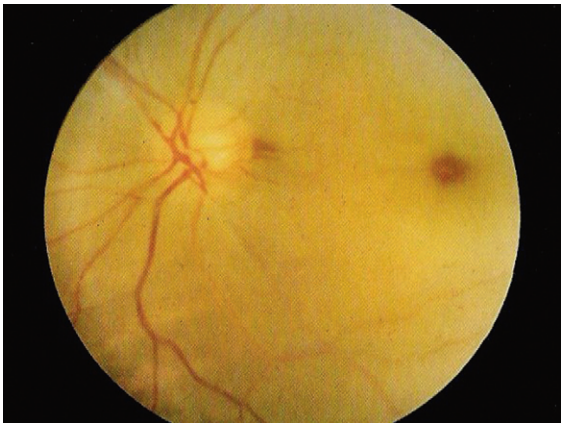


Figure 69-22. Central retinal artery occlusion. Note cherry-red spot (fovea). (Image courtesy of www.tedmontgomery.com)

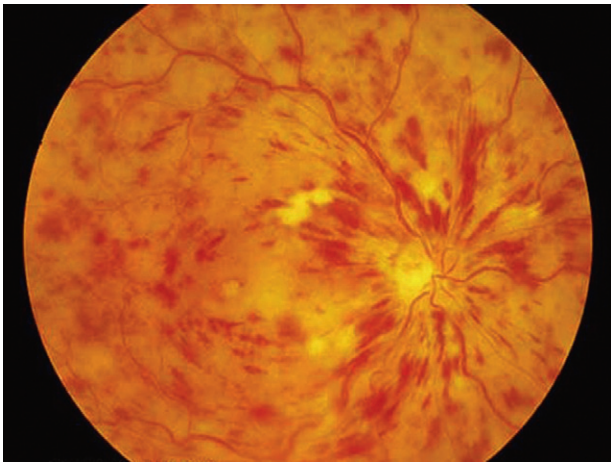


Figure 69-23. Central retinal vein occlusion. Note "blood and thunder" appearance. (Image courtesy of www.tedmontgomery.com)

retina is edematous with a pale gray-white appearance, and the fovea appears as a cherry-red spot (Fig. 69-22).

Therapy should be instituted immediately and should be directed at dislodging the embolus, dilating the artery to promote forward blood flow, and reducing intraocular pressure to allow an increase in perfusion gradient. Digital global massage should be begun immediately in the ED. Global massage is performed by applying direct digital pressure through closed eyelids. The pressure can be applied for 10 to 15 seconds and followed by a sudden release.[62] Increases in carbon dioxide pressure (P_{CO_2}) lead to retinal artery vasodilation and increased retinal blood flow. Increases in P_{CO_2} are obtained by either rebreathing into a paper bag for 10 minutes each hour or inhaling a 95% oxygen, 5% carbon dioxide mixture (carbogen). Intraocular pressure may be reduced by instilling timolol maleate 0.5% topically. Acetazolamide, 500 mg IV or PO, lowers intraocular pressure as well as increases retinal blood flow.[63] Emergent ophthalmologic consultation should be obtained as anterior chamber paracentesis may be attempted to facilitate the lowering of the intraocular pressure. One study, however, failed to find any therapeutic benefit for patients who received anterior chamber paracentesis and inhaled carbogen.[64] Thrombolytic agents have been studied, but no clear guidelines for their use exist.[62] One recent study showed improvement of visual acuity in 10 of 12 patients who were given IV tissue plasma activator for central retinal or ophthalmic artery occlusion. However, all of these patients had residual visual field defects.[65] A complete medical evaluation is necessary because central retinal artery occlusion is usually an embolic event.

Central Retinal Vein Occlusion. A painless loss of vision, central retinal vein occlusion leads to edema, hemorrhage, and vascular leakage. The wide spectrum of clinical appearances depends on the degree of venous obstruction present. Loss of vision can range from minimal to recognition of hand motion only. There are two types of central retinal vein occlusion, ischemic and nonischemic. The nonischemic type involves mild fundus changes and does not have an afferent pupillary defect. These patients tend to have less severe visual loss, with two thirds of the patients having 20/40 or better visual acuity without therapy.[66] Patients with ischemic central retinal vein occlusion have a marked decrease in visual acuity and often an afferent pupillary defect. Appearance can vary but classically includes dilated and tortuous veins, retinal hemorrhages, and disk edema. Hemorrhages can cover the entire fundus, giving a "blood and thunder" appearance (Fig. 69-23). Branch retinal vein occlusions occur just distal to an arteriovenous crossing, and hemorrhages occur distal to the site of occlusion. The differential diagnosis of central retinal vein occlusion includes hypertension, diabetes mellitus, hyperviscosity syndromes, and papilledema. All of these are bilateral processes, whereas central retinal vein occlusion is generally unilateral. Neovascular glaucoma is the major complication of ischemic central retinal vein occlusion. Treatment is complex and includes lowering of intraocular pressure, topical steroids, cyclocryotherapy, and photocoagulation.[66,67] Underlying medical disease should be managed as well. The prognosis depends on the degree of obstruction and resultant complications.

Retinal Breaks and Detachment. The retina has two layers, the inner neuronal retina layer and the outer retinal pigment epithelial layer, which can be separated by fluid accumulation.

A retinal break is a tear in the retinal membranes and may or may not lead to retinal detachment. Retinal detachments occur by three mechanisms: rhegmatogenous, exudative, and tractional. Rhegmatogenous retinal detachment occurs as a result of a tear or hole in the neuronal layer, causing fluid from the vitreous cavity to leak between and separate the two retinal layers. Rhegmatogenous retinal detachment, the most common type of retinal detachment, generally occurs in patients older than 45 years, is more common in men than women, and is associated with degenerative myopia.[68] Trauma may be associated with rhegmatogenous detachment by causing tears in the retina or by causing a disinsertion of the retina from its attachment at the ora serrata anteriorly. Traumatic retinal detachment can occur at any age. There is greater risk with severe myopia.

Exudative retinal detachment occurs as a result of fluid or blood leakage from vessels within the retina. Conditions leading to exudative retinal detachment include hypertension, toxemia of pregnancy, central retinal venous occlusion, glomerulonephritis, papilledema, vasculitis, and choroidal tumor.

Traction retinal detachment is a consequence of fibrous band formation in the vitreous and contraction of these bands. These fibrous bands result from the organization of inflammatory exudates or blood from prior vitreous hemorrhage.

Typically, patients complain of flashes of light related to the traction on the retina, floaters related to vitreal blood or pigmented debris, and visual loss. The visual loss is commonly described as a filmy, cloudy, or curtain-like appearance. Pain is absent. Visual acuity can be minimally changed to severely decreased. Visual field cuts relate to the location of the retinal detachment, and an afferent pupillary defect occurs if the

detachment is large enough. When the detachment is visualized by ophthalmoscopy, the retina appears out of focus at the site of the detachment. In large retinal detachments with large fluid accumulation, the bullous detachment, with retinal folds, can easily be seen (see Fig. 69-12). Retinal detachment cannot be ruled out by direct funduscopy. Indirect ophthalmoscopy is needed to visualize the more anterior portions of the retina. Bedside ED ultrasonography has been shown to be helpful in confirming the presence of a retinal detachment.[69]

Acute rhegmatogenous and tractional detachment that threaten the fovea should be urgently surgically repaired.[44] Acute retinal breaks are surgically repaired within 24 hours. All other acute rhegmatogenous and tractional retinal detachments can be repaired within a few days.[44] Treatment of exudative detachment is aimed at the underlying cause or use of laser photocoagulation. Any patient suspected of having retinal break or detachment requires immediate ophthalmologic consultation.

Posterior Vitreous Detachment. Posterior vitreous detachment is a common occurrence in patients older than 60 years. With aging, the vitreous gel pulls away from the retina, which can lead to symptoms similar to those of retinal break, vitreous hemorrhage, and retinal detachment. No specific treatment is indicated for posterior vitreous detachment unless it is accompanied by a retinal break, vitreous hemorrhage, or retinal detachment.[44] Patients with a new posterior vitreous detachment should have prompt evaluation by an ophthalmologist to rule out these surgically amenable complications.

Vitreous Hemorrhage. Vitreous hemorrhage results from bleeding into the preretinal space or into the vitreous cavity. The most common causes are diabetic retinopathy and retinal tears. Additional causes include neovascularization associated with branch vein occlusion, sickle cell disease, retinal detachment, posterior vitreous detachment, trauma, age-related macular degeneration, retinal artery microaneurysms, trauma, and intraocular tumor. Symptoms begin with floaters or "cobwebs" in the vision and may progress over a few hours to severe visual loss without pain. Direct ophthalmoscopy reveals a reddish haze in mild cases to a black reflex in severe cases. Details of the fundus are usually difficult to visualize. Vitreous hemorrhage by itself does not cause an afferent pupillary defect, which, if present, indicates a retinal detachment behind the vitreous hemorrhage. The hemorrhage may be evenly distributed throughout the vitreous or focal. Long-standing preretinal hemorrhage can become a white mass that may be misdiagnosed as a tumor, exudate, or infection. Initial therapy consists of bedrest with elevation of the head of the bed and avoidance of anticoagulative medications. Definitive therapy is targeted at the underlying cause. Vascular retinopathy is managed with laser photocoagulation or cryotherapy, and retinal tears and detachments are repaired. If the cause of the hemorrhage is unknown, prompt diagnostic workup is indicated to look for surgically correctable lesions. Ultrasonography can be used to determine whether a retinal detachment is present and may also determine the cause.[70] Vitrectomy is indicated in certain patients.

Macular Disorders. Many disease processes cause acute changes in the macula leading to acute visual loss. The role of the emergency physician is to recognize the maculopathy and refer the patient to an ophthalmologist. Keys to the diagnosis of macular dysfunction include loss of central vision with preservation of peripheral vision, complaints of central visual distortion, and anatomic changes in the retina.

Degenerative maculopathies occur as the result of trauma, radiation exposure, inflammatory or infectious disease, vascular disease, toxins, or hereditary disease, or may be idiopathic in nature.

The most common form is age-related macular degeneration after the age of 65 years.[71] It is a leading reason for legal blindness in the United States. Patients present with either a gradual or rapid onset of visual loss. Funduscopy reveals scattered drusen. Drusen are small, sharply defined yellow-white masses. Some patients with age-related macular degeneration and drusen develop a choroidal (subretinal) neovascular membrane, which appears as a grayish-green membrane beneath the retina. If this membrane is left untreated, hemorrhage, transudation, scar formation, or exudative detachment of the retina can result. If a large hemorrhage occurs from the neovascular membrane, it can cause severe central visual loss and may break through the retina into the vitreous, causing peripheral visual loss. Laser photocoagulation is the treatment for choroidal neovascular membrane formation and should be performed as soon as possible.[71]

Inflammatory processes involving the retina may also cause visual loss, especially if the macula is involved. Bacterial, viral, and protozoal agents have been shown to cause maculopathy. The presenting symptoms and signs vary according to the disease process and severity. Inflammatory debris from exudative processes may fill the vitreous, leading to a cloudy appearance. Infections within the eye are often associated with severe pain, redness, and periocular edema. If the retina and choroid are obliterated, the lesions appear white. Patients suspected of having an inflammatory maculopathy need emergent consultation and thorough medical evaluation.

Neuro-ophthalmologic Visual Loss. Visual loss not readily explained by an obvious abnormality on physical examination is called neuro-ophthalmologic visual loss. Patients can be divided into those who complain of decreased vision and have reduced visual acuity and those who complain of visual loss but have normal visual acuity. It is important to conduct careful visual field testing in the latter group.

Neuro-ophthalmologic visual loss can be further divided into prechiasmal, chiasmal, and postchiasmal anatomic areas.

Prechiasmal Visual Loss. Patients with prechiasmal disease have decreased visual acuity or visual field loss in the eye on the affected side. Prechiasmal disease may be a unilateral or bilateral process. The swinging flashlight test reveals an afferent pupillary defect on the side involved unless the process is bilateral. In such cases, the relative degree of afferent defect determines the results. Visual field testing demonstrates a field defect that does not respect the vertical meridian and is often localized to the center of the visual field. Causes of prechiasmal visual loss include optic neuritis, ischemic optic neuritis, compressive optic neuritis, and toxic and metabolic optic neuritis.

Optic Neuritis. Optic neuritis is an acute monocular loss of vision caused by focal demyelination of the optic nerve. The patients' ages range from 15 to 45 years. Symptoms include a progressive loss of vision over several hours or days and ocular pain with eye movement. Visual acuity can range from minimal loss to no light perception. An afferent pupillary defect is always present, and direct ophthalmoscopic examination reveals a normal or swollen disk.[72] The natural history of optic neuritis is for visual acuity to reach its poorest within 1 week and then slowly improve over the next several weeks. Approximately 30% of patients presenting with acute optic neuritis develop multiple sclerosis within 5 years.[73] In an initial study of patients with acute optic neuritis, treatment with a 3-day course of IV methylprednisolone reduced the rate of development of multiple sclerosis over a 2-year period.[74] However, 5-year follow-up of the same cohort of patients revealed no significant differences among treatment groups in the development of multiple sclerosis.[73] Use of oral steroids for hastening optic neuritis is controversial. The Optic Neuritis Study Group

showed an increased risk of optic neuritis recurrences in patients treated with oral prednisone.[73,74] However, a randomized and controlled study of high-dose oral methylprednisolone in acute optic neuritis showed improved recovery from optic neuritis at 1 and 3 weeks but no effect at 8 weeks or on subsequent attack frequency.[75] Long-term visual outcome is no different from that with observation alone.

Ischemic Optic Neuropathy. Ischemic optic neuropathy is the most common optic neuropathy and one of the most common causes of visual loss past middle age. Ischemic optic neuropathy can be giant cell arteritis or idiopathic. Temporal arteritis (giant cell arteritis) is characterized by weight loss, malaise, jaw pain, headache, scalp tenderness, polymyalgia rheumatica, low-grade fever, and severe painless visual loss. It is extremely rare in people younger than 50 years, but the incidence rises with each subsequent decade. A significant proportion of patients sustain visual loss, which can be sudden, severe, and bilateral.[76] Occasionally, visual loss is preceded by episodes of amaurosis fugax. In one series of patients, visual loss was unilateral in 46%, sequential in 37%, and simultaneously bilateral in 17%.[77] There is a large afferent pupillary defect, visual loss, and a visual field defect that may respect the horizontal meridian. The optic disk shows pallor and swelling. The diagnosis can be aided with an elevated erythrocyte sedimentation rate (ESR), but can be seen with normal sedimentation rates.[78] A guide to the upper limit of normal ESR is age/2 for men and (age + 10)/2 for women.[44] The diagnosis is confirmed by temporal artery biopsy, although biopsy results have been normal early in the disease. Treatment for temporal arteritis should be instituted when typical signs and symptoms, particularly visual loss, exist. The standard treatment is high-dosage corticosteroids, which should be started as soon as the diagnosis is suspected. Treatment should not wait for biopsy results. Biopsy should be performed within 1 week of diagnosis. Patients treated with oral prednisone were less likely to have visual improvement and more likely to develop fellow eye involvement than those receiving high-dose IV methylprednisolone.[77] Patients with visual loss had a 34% chance of improvement with IV methylprednisolone.[77]

Nonarteritic Ischemic Optic Neuropathy. Nonarteritic ischemic optic neuropathy is much more common than temporal arteritis. These patients lack the classic symptoms of temporal arteritis and do not have an elevated ESR. Most of these patients have systemic vascular disease, diabetes, or hypertension, and they tend to be younger. They have painless visual loss, afferent pupillary defects, disk swelling, and visual field defects that respect the horizontal meridian. The visual loss is less severe than with temporal arteritis, and improvement occurs in one third of patients. Steroids have been advocated, but the results are unclear. If there is doubt about whether a particular patient has temporal arteritis or an idiopathic form of ischemic optic neuropathy, treatment with steroids should be started until a temporal artery biopsy is performed.

Compressive Optic Neuropathy. Compressive optic neuropathy occurs at any age and can be caused by tumor, aneurysm, sphenoid sinusitis or mucocele, blunt trauma, or thyroid disorders. Although defined as a prechiasmal disorder, compression can occasionally occur far enough posteriorly to affect the optic chiasm. Patients with compressive optic neuropathy have visual loss that continues to progress beyond 7 days. Compressive optic neuropathies require neuroradiographic evaluation and rapid medical and surgical intervention. Optic neuritis can be difficult to distinguish from a compressive optic neuropathy, but compressive syndromes tend to involve other cranial nerves. If the signs and symptoms do not closely fit optic neuritis or ischemic optic neuropathy, a compressive lesion exists until proved otherwise.

Toxic and Metabolic Optic Neuropathy. A large number of toxic and metabolic neuropathies exists. Common toxic causes include barbiturates, chloramphenicol, emetine, ethambutol, ethylene glycol, isoniazid, heavy metals, and methanol. Causes of metabolic optic neuropathies include thiamine deficiency and pernicious anemia. These processes are bilateral, progressive, and symmetrical. Visual loss can be severe, and visual field testing reveals central defects. Treatment is aimed at the underlying toxin or metabolite involved.

Chiasmal Visual Loss. Chiasmal disease is the second category of neuro-ophthalmologic visual loss, most commonly caused by chiasmal compression from pituitary tumors, craniopharyngioma, or meningioma. Visual loss is gradual and progressive. Although formal visual field testing is necessary to stage the condition, the diagnosis can usually be made by confrontation visual field testing. The classic defect is a bitemporal hemianopsia; however, tumors often compress the optic chiasm and optic nerves asymmetrically, resulting in combined central and temporal defects. When a visual field defect respects the vertical meridian from a neuro-ophthalmologic visual loss, the lesion is out of the globe and must be either chiasmal or postchiasmal.

Postchiasmal Visual Loss. Postchiasmal disease represents the third category of neuro-ophthalmologic visual loss. The most common causes are infarction, tumor, arteriovenous malformation, and migraine disorders. Patients complain of difficulty in performing a certain task, such as reading. Lesions can be located from the immediate postchiasmal optic tract to the occipital cortex. The classic visual field defect is homonymous hemianopsia. Patients with such lesions have a focal neurologic deficit and need neurologic consultation. Cortical blindness is a special cause of neuro-ophthalmologic visual loss that is most commonly caused by bilateral occipital infarction. Cortical blindness is often mistaken for functional blindness because patients have both normal funduscopic examinations and intact pupillary reflexes. Anton's syndrome is characterized by bilateral blindness, normal pupillary reflexes, bilateral occipital lesions, and, interestingly, denial of blindness. It is this denial of blindness that may be incorrectly assumed to be evidence for a functional process.

Functional Visual Loss. Patients with functional visual loss fall into two categories: hysterical conversion reactions and malingering. Patients with hysterical conversion reactions have a nondeliberate, imagined visual loss. The patient has a flatter affect than one would expect under the circumstances of acute visual loss. The patient might appear completely unaffected emotionally by the acute visual loss. The malingerer, on the other hand, is a patient who is well aware that no visual loss exists, yet deliberately feigns visual loss for secondary gain. This patient is typically overemotional concerning the visual loss.

Examination of a patient with a suspected functional visual loss should be conducted in the same manner as every other ophthalmologic examination, with particular attention to possible neuro-ophthalmologic deficits. Normal pupillary reflexes and the absence of an afferent pupillary defect, together with a normal funduscopic examination, point toward functional visual loss. Multiple tests can ascertain whether a visual loss is organic or functional. Patients with feigned visual loss are hesitant to try to appose the index fingers of each hand and often write their names in a disorderly fashion, whereas genuinely blind patients can sign their names without difficulty. One effective test involves placing a large mirror directly in front of the patient's face and asking the patient to look straight ahead. The mirror is then tilted slightly back and forth. Most patients follow the reflection of their eyes in the mirror as it changes position, proving feigned visual loss. Another test commonly used is the optokinetic nystagmus (OKN) drum.

The drum should be turned in front of the patient's open eyes. If the patient is properly seeing, the eyes will automatically follow the stripes of the drum.[79] Some difficult cases require more sophisticated tests. Definitive treatment of functional visual loss should include a collaborative effort by the emergency physician, ophthalmology, and psychiatry.[18] If the diagnosis of feigned visual loss cannot be definitively made, consultation is required to rule out neuro-ophthalmologic visual loss.

■ ANISOCORIA

Clinical Features

Anisocoria in a patient with head trauma or decreased level of consciousness requires immediate and aggressive evaluation and intervention because it may result from increased intracranial pressure. If a patient is awake and alert, has no signs of trauma, and has anisocoria of unknown cause, less urgency exists. The first step is to determine which pupil is abnormal. If one pupil constricts poorly to a light stimulus, it is likely to be the abnormal one. Anisocoria greater in dark suggests that the abnormal pupil is the smaller pupil, whereas anisocoria greater in light suggests that the abnormal pupil is the larger pupil. If anisocoria exists in a patient with a normal afferent visual system, either an innervational or structural defect in the iris sphincter exists. Most structural defects in the iris can be diagnosed by slit-lamp examination. If both pupils react well to light and no iris abnormalities are seen with slit-lamp examination, the next step is to determine whether the anisocoria increases in light or darkness. Adie's tonic pupil, pharmacologic blockade, and third-nerve palsy are associated with anisocoria that increases in light, whereas benign anisocoria and Horner's syndrome are associated with anisocoria that increases in darkness.[44] Comparing pupillary size in a brightly and dimly lit room is the easiest method to evaluate the effect of lighting on anisocoria.

Adie's Tonic Pupil

With Adie's tonic pupil, patients complain of blurred near vision but have normal distant vision. Adie's syndrome is seen in young women 70% of the time and has associated symmetrically reduced deep tendon reflexes. Examination reveals poor accommodation with a very slow constriction to near testing. The pupil redilates slowly when the vision is again made distant. Slit-lamp examination reveals sector palsies of the iris. The diagnosis is confirmed when a weak cholinergic agent (pilocarpine 0.1%) causes an intense pupillary constriction as a result of cholinergic supersensitivity in the affected pupil compared with the normal pupil. These patients need to be referred to an ophthalmologist on a nonemergent basis for cholinergic agent therapy.

Pharmacologic Mydriasis

Pharmacologic mydriasis can be caused by deliberate or inadvertent local administration of both sympathomimetic and parasympatholytic agents. Phenylephrine and cocaine are two sympathomimetic substances commonly used as a nasal premedicant for nasotracheal intubation; careless administration may lead to anisocoria. Parasympatholytic agents, such as atropine and scopolamine, have been implicated in the development of anisocoria. The transdermal scopolamine patches placed for the prevention of motion sickness can cause anisocoria. Pilocarpine 1.0% can be used in special circumstances to help differentiate a third-nerve palsy from pharmacologically mediated mydriasis. The administration of pilocarpine 1.0% rapidly constricts the pupil that is dilated secondary to a third-nerve palsy but does not produce miosis in a pupil dilated from anticholinergic agents.

Third-Nerve Palsy

Patients with anisocoria that increases in light, without evidence of Adie's tonic pupil or pharmacologic medication, should be suspected of having a third-nerve palsy. They almost always have other signs of third-nerve involvement, including ptosis and extraocular muscle dysfunction. Patients complain of diplopia, and the involved eye is turned down and out. Patients may have ptosis and extraocular dysfunction with or without pupil dilatation. Any patient who has a new-onset third-nerve lesion involving the pupil should be admitted to the hospital to rule out aneurysm.

Horner's Syndrome

Horner's syndrome consists of ptosis, miosis, and facial anhidrosis resulting from an interruption of sympathetic innervation. The dilatation lag, a classic finding, results from the Horner's pupil requiring up to 15 seconds to dilate fully. The anisocoria is greater at 3 to 5 seconds of darkness than at 15 seconds of darkness, although the anisocoria is still more pronounced than in light. Topical ophthalmologic cocaine 10% can be used to aid the diagnosis. A Horner's pupil dilates less than a normal pupil in reaction to topical cocaine. Central nervous system strokes and tumors, lung carcinomas, thyroid adenomas, Pancoast's tumors, headache syndrome, carotid dissection, herpes zoster, otitis media, and trauma to brachial plexus during delivery are all causes of Horner's syndrome. Hydroxyamphetamine 1% administered 24 hours after the cocaine test can be used to determine the level of sympathetic interruption and dictate the type of workup indicated. In general, patients with new-onset Horner's syndrome should receive a thorough and immediate workup to determine the etiology.

Physiologic Anisocoria

Twenty percent of the population may have anisocoria of greater than 0.4 mm at any given examination.[80] This anisocoria may be transient or prolonged and may alternate pupils. Although the anisocoria increases in darkness, there is no dilatation lag as seen with Horner's syndrome. No associated features, such as loss in vision and diplopia, are seen and no further treatment is required.

■ ABNORMAL OPTIC DISK

Clinical Features and Differential Considerations

An important acquired cause of an abnormal optic disk is papilledema. Papilledema refers to the changes in the optic disk from increased intracranial pressure. The subarachnoid space of the brain is continuous with the optic nerve sheath. Any increase in the cerebrospinal fluid pressure can be transmitted to the optic nerve, resulting in swelling of the optic nerve head. Causes include intracranial tumor, pseudotumor cerebri, intracranial hematomas from trauma, subarachnoid hemorrhage, brain abscess, and meningitis or encephalitis. There is swelling of the optic disk and blurring of the disk margins, hyperemia, and loss of physiologic cupping (Fig. 69-24). There may be obliteration of spontaneous venous pulsations.

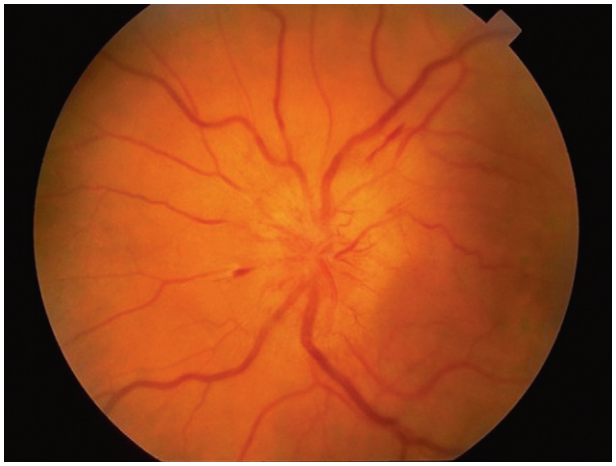


Figure 69-24. Papilledema. Note the blurred disk margins. (Image courtesy of www.tedmontgomery.com)

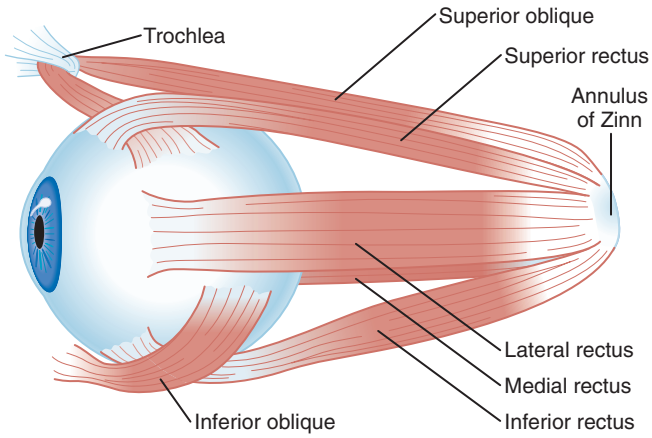


Figure 69-25. Extraocular muscles. (Image courtesy of www.tedmontgomery.com.)

Flame-shaped hemorrhages and yellow exudates appear near the disk margins as the edema progresses. Patients may have significant headaches or be completely asymptomatic. Visual acuity is not affected until the papilledema is long standing. Brief obscurations of vision, enlargement of the physiologic blind spot, and inferior nasal visual field loss are common. Papilledema is a bilateral process but may be asymmetrical. A patient with newly diagnosed papilledema should receive immediate neuroradiographic evaluation.

Many conditions may mimic papilledema, including central retinal vein occlusion, papillitis, hypertensive retinopathy, ischemic optic neuropathy, optic disk vasculitis, and diabetic papillitis with retinopathy.

NYSTAGMUS

Clinical Features and Differential Considerations

Clinically significant nystagmus is an oscillation of the eyes that occurs within 30 degrees of the midline. Pendular nystagmus is of equal velocity in both directions. With jerk nystagmus, the velocity is faster in one direction. The pathologic component is the slow movement, but the nystagmus is named according to the direction of the fast component. Nystagmus can also be divided into monocular or binocular, conjugate (both eyes moving in the same direction), or disconjugate (eyes moving in opposite directions), and primary gaze position or gaze position nystagmus. Important questions include the presence of tinnitus, nausea, vomiting, oscillopsia, and vertigo.

Congenital nystagmus is noted at birth or within the perinatal period and is usually horizontal, conjugate, bilateral, symmetrical, and pendular. On lateral gaze, this nystagmus may become jerky in nature but remains horizontal despite upward or downward gaze. Congenital nystagmus is damped by convergence, increased with fixation, accentuated by covering one eye, and abolished with sleep. These patients do not have oscillopsia, nor do they have other neurologic complaints. Almost all of these patients have recognized their nystagmus previously, and the diagnosis is generally straightforward.

There are many causes of acquired nystagmus. General categories of disease that result in nystagmus include toxic exposure, defective retinal impulses, diseases of the labyrinths or of the vestibular nuclei, and lesions of the brainstem or cerebellum controlling ocular posture. The workup includes drug and toxic screening and neuroradiologic testing with a CT or MRI scan.

DISORDERS OF EXTRAOCULAR MOVEMENT

Clinical Features and Differential Considerations

Patients complain of diplopia produced or exacerbated by certain eye movements. A knowledge of the anatomy of the extraocular muscles is useful (Fig. 69-25). The first step is to determine whether the diplopia is monocular or binocular. Binocular diplopia disappears with either eye covered. Monocular diplopia is less concerning, caused most commonly by refractive errors, a dislocated lens, iridodialysis, or feigned disease.

Binocular diplopia from misalignment of the eyes has a multitude of causes. Local mechanical defects such as hematoma, orbital floor fractures, or abscess and palsy of cranial nerve III, IV, or VI can lead to motility problems. Thyroid disease, progressive ophthalmoplegia, extraocular muscle fibrosis syndrome, multiple sclerosis, and myasthenia gravis can all lead to newly acquired extraocular movement dysfunction.

The most common cause is cranial nerve palsy. Patients with brainstem disease often have involvement of other cranial nerves, disturbances in level of consciousness, and sensorimotor loss. Isolated third-nerve lesions produce a palsy in which the patient develops ptosis, an inability to turn the eye inward or upward, and pupillary mydriasis. The causes of third-nerve palsy are varied and require aggressive and immediate neurologic and radiologic examination.

Isolated fourth-nerve palsy is an easily missed disorder. Patients complain of double vision, which is made worse in downgaze, or gaze away from the paretic side. These patients typically have a head tilt to the opposite shoulder to compensate for the vertical extorsion and have weakness in downward gaze. Trauma and vascular disease account for most cases of isolated fourth-nerve palsy, but aneurysm, intracranial tumor, and myasthenia gravis have been implicated.

Sixth cranial nerve palsies are the most commonly reported ocular motor palsies. Patients with sixth cranial nerve palsies have an esotropia that is worsened by lateral gaze and often turn their heads laterally toward the paretic side to compensate. Sixth-nerve palsy is caused by a variety of diseases. Wernicke-Korsakoff syndrome, aneurysm, vascular disease (diabetes, hypertension, atherosclerosis), trauma, neoplasm, multiple sclerosis, meningitis, thyroid eye disease, and increased intracranial pressure may all cause dysfunction. Workup consists of careful neurologic and radiologic examination.

■ MANAGEMENT

Ophthalmic Drugs

General Considerations

Most ocular medications are administered as drops, which have the advantage of concentrating drug delivery to the anterior segment of the eye and reducing unwanted systemic side effects. Eye drops have the additional advantages of rapid absorption, brief effect, and minimal interference with the visual media.

Unfortunately, the eye retains only a small amount of the drug; the remainder is cleared by the rapid turnover of tears.

To improve absorption, patients who are taking more than one eye drop should ideally wait 10 minutes between drops to prevent the second drop from washing out the first. Patients should apply digital pressure at the medial canthus of the eye to prevent drainage of drug through the nasolacrimal duct and keep their eyes closed for several minutes after instilling their drops to halt the lacrimal pumping mechanisms. Ointments increase the contact time of the medication with the anterior segment of the eye. Ointments blur vision but provide a pleasant lubrication to the eye that has been traumatized and patched and do not seem to interfere with corneal wound healing.

Drug Classification

Ophthalmologic medications can be classified into several categories, including anesthetics, antibiotics, antivirals, corticosteroids, and others. The emergency physician should be familiar with some common agents that are part of these categories and should be familiar with indications of each type of medication.

Local anesthetics block neurotransmission along sensory nerve fibers. Ocular procedures facilitated by topical anesthetics include direct inspection, foreign body removal, irrigation, tonometry, and contact lens removal. Topical anesthetics inhibit wound healing, and severe keratopathy can result from indiscriminate use of topical anesthetics. Local anesthetic drops should not be prescribed as pain medicine for self-administration by patients.

Antibiotics and antiviral agents are commonly prescribed. The choice of antibiotic agent should be guided by culture, Gram's stain, or suspected bacteria or virus. Antiviral agents are generally prescribed after consultation with an ophthalmologist.

Corticosteroids are used by ophthalmologists for many ocular conditions, but their use by emergency physicians should be limited. Corticosteroids can accelerate the activity of herpes simplex virus and should not be given to a patient when the diagnosis is uncertain. Post-traumatic iridocyclitis is one of the few conditions in which an emergency physician might consider prescribing a topical steroid agent, but close follow-up with an ophthalmologist is highly recommended.

Cycloplegics block the muscarinic receptors, producing paralysis of the ciliary muscle, which always causes mydriasis. Cycloplegics are useful in relieving pain and photophobia secondary to ciliary spasm related to corneal abrasion, ocular trauma, and iridocyclitis.[9] Mydriatics dilate the pupil, but not all mydriatics are cycloplegics. Mydriatics are contraindicated in any patient with a history of glaucoma, evidence of increased intraocular pressure, presence of a shallow anterior chamber, suspicion of a ruptured globe, or if a lens implant is present. Atropine has a long duration of action (1–2 weeks) and should be prescribed only by an ophthalmologist. Decongestants and antiallergy ocular medications are commonly prescribed and lessen allergic ocular symptoms.

A number of agents are used to treat glaucoma. It is important to know that these are absorbed and can have systemic effects. For example, topical beta-blocker agents can result in symptomatic bradycardia or increased bronchospasm.

Nonsteroidal anti-inflammatory agents are useful in alleviating the symptoms of inflammation in a wide variety of ocular conditions and provide symptomatic improvement in corneal abrasions.

Artificial tears relieve symptoms related to dry eyes and protect the corneas of unconscious patients as well as patients suffering from Bell's palsy.

KEY CONCEPTS

- *Orbital floor fractures*: Surgical repair is only for persistent diplopia or cosmetic concerns and is generally not performed until swelling subsides in 7 to 10 days. CT scan is the imaging choice.
- *Retrobulbar hematoma*: When a retrobulbar hematoma compromises retinal circulation, immediate treatment of increased intraocular pressure includes carbonic anhydrase inhibitor, topical beta-blocker, and IV mannitol. A lateral canthotomy can be done in the ED as a temporizing measure before definitive decompression.
- *Corneal abrasions*: Data suggest that eye patching confers no benefit in healing small, uncomplicated corneal abrasions.
- *Globe rupture*: Treatment includes avoidance of further examination or manipulation and placement of a protective metal eye shield to prevent accidental pressure on the globe. Antiemetics should be given if nausea is present. Broad-spectrum IV antibiotics should be instituted.
- *Retinal detachments*: Retinal tears or detachments do not cause pain. Examination may reveal the hazy gray membrane of the retina billowing forward, but many tears are peripherally located and not seen with direct ophthalmoscopy. Visual acuity may be normal unless the macula is involved. Indirect ophthalmoscopy is warranted if historical clues to the presence of retinal tears are present.
- *Bacterial conjunctivitis*: In uncomplicated acute bacterial conjunctivitis, neomycin ophthalmic solutions should be avoided because of the high incidence of hypersensitivity reactions. Corticosteroids and eye patching should be avoided.
- *Glaucoma*: Attacks of primary angle closure glaucoma produce symptoms that are abrupt in onset and include severe eye pain, blurred vision, headache, nausea, vomiting, and occasionally abdominal pain. Signs include conjunctival injection and a cloudy (steamy) cornea with a midpositioned to dilated pupil that is sluggish or fixed. Intraocular pressures are markedly elevated.
- *Topical anesthetics*: These should not be prescribed for painful eye disorders as prolonged use may result in corneal ulcer formation.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 70 Otolaryngology

James A. Pfaff and Gregory P. Moore

OTITIS MEDIA

Perspective

Background

Otitis media (OM) is the most common diagnosis made by U.S. physicians for children younger than 15 years old.[1] In 2002, 16.7 million visits were made to physician offices across the country for OM with an estimated 2.65 million visits made to emergency departments (ED), making it the sixth most common ED discharge diagnosis.[2] Over 80% of children will have at least one episode of acute otitis media (AOM) during their lifetime, and by age 3 up to 40% will have at least three episodes during the first 3 years of life.[3] The financial repercussions are enormous; one estimate is that $5 billion per year is spent on the evaluation, treatment, and socioeconomic effects of OM.[4] The most frequent outpatient use of antimicrobials in the United States is for OM, with the number of prescriptions increasing from 12 million in 1980 to more than 23.6 million in 1992.

Epidemiology

Male gender, day care attendance, parental smoking, pacifier use, and a family history of middle ear disease have been implicated as risk factors.[5,6] Children with anatomic abnormalities, such as cleft palate and Down syndrome, have a higher rate of OM, probably because of eustachian tube abnormalities. Some immunocompromised patients, including patients with HIV, may have recurrent OM as an initial symptom of their underlying disease. OM and upper respiratory infections occur primarily in the winter. Breast-feeding seems to be protective.[7]

Definitions

Otitis media is broadly defined as inflammation of the inner ear and is a continuum of disease. *Acute otitis media* is defined as the signs and symptoms of an acute infection, with evidence of effusion; this has also been called *acute suppurative*, or *purulent*, OM. *Otitis media with effusion* (OME) has effusion without signs or symptoms of an acute infection; additional descriptive terms include *serous*, *mucoid*, *nonsuppurative*, or *secretory* OM. OME is classified further into acute (<3 weeks), subacute (3 weeks to 3 months), and chronic (>3 months). Chronic OM, or *chronic suppurative otitis media*, refers to chronic discharge from the ear through perforation of an intact membrane. *Recurrent* OM is defined by three or more episodes over 6 months or four episodes in 1 year.

Principles of Disease

Pathophysiology

Eustachian tube dysfunction is the central theme of most theories of AOM pathogenesis. The eustachian tube, between the middle ear cavity and the nasopharynx, ventilates the middle ear to equilibrate pressure, allows for middle ear drainage, and provides protection from nasopharyngeal secretions. In children, it measures approximately 18 mm and is almost horizontal. As individuals age, the eustachian tube widens, doubles in length, becomes more vertically oriented, and stiffens (which may explain the decreased incidence of AOM in adults). Normally, the tube is collapsed, but it opens during yawning, chewing, and swallowing.

The eustachian tube may become either mechanically or functionally obstructed, decreasing middle ear ventilation. Examples of mechanical obstruction include inflammations from an upper respiratory infection, hypertrophied adenoids, and a cleft palate.[8] Functional obstruction from persistent tubal collapse occurs primarily in young children, who have less fibrocartilage support of the medial eustachian tube than older children or adults.[8] It has been postulated that this dysfunction results in negative middle ear cavity pressure, causing a transudate of fluid that combines with the reflux of nasopharyngeal secretions and bacteria.

Etiology

The most common causes of bacterial infection in children are *Streptococcus pneumoniae*, *Haemophilus influenzae* (primarily nontypeable), and *Moraxella* (*Branhamella*) *catarrhalis*. *Streptococcus pyogenes*, *Staphylococcus aureus*, and gram-negative bacteria are much less common.[9] Adult infection involves similar organisms. In OME, there is a greater proportion of *H. influenzae* and a higher percentage of sterile effusions.[10] Viruses also have been found in the middle ear aspirates of children with OM and are found in anywhere from 5 to 16%.[11-13] The advent of reserve transcriptase polymerase chain reaction technology for viral identification has improved, and it is likely that an even greater number of viral agents will be found. Some authors believe that viral infection is the cause of the inflammatory reaction in most cases and antibiotics are not necessary. Respiratory syncytial

virus is the most common virus, but parainfluenza, influenza, enterovirus, rhinovirus, and adenovirus have also been found in the middle ear aspirates of children.[10,11] Viruses have contributed to poor treatment outcome by increasing middle ear inflammation, decreasing neutrophil function and decreasing antibiotic penetration into the middle ear.[14]

In young children, it was believed that gram-negative organisms and *S. aureus* were the causative organisms. Although these bacteria may be the causes in intubated patients or patients in the neonatal intensive care unit, healthy newborns tend to be infected by the same pathogens as healthy older children.[15] Bullous myringitis presents with bullae on the tympanic membrane and may be present in up to 5% of cases of OM in children less than 2 years.[16] Although previously thought to be caused by *Mycoplasma pneumoniae*, culturing middle ear aspirates in this condition generally grows the usual organisms that cause AOM and *M. pneumoniae* is uncommon.[16,17]

Over 70% of children presenting with purulent conjunctivitis may have OM, a symptom complex described as the otitis-conjunctivitis syndrome,[18] which is predominantly caused by *H. influenza*.[19] Other, less likely organisms that can cause AOM include *Mycobacterium tuberculosis* (primarily in children) and *Chlamydia trachomatis* (most commonly seen in children younger than 6 months old with pneumonia).[20]

Conjugate pneumococcal vaccine has been effective in markedly reducing invasive disease in young children and decreasing the incidence of OM.[21] It is estimated that its use would decrease the number of visits to the pediatrician for OM by 1 million, and the number of children receiving tympanostomy tubes might decrease by 500,000.[22] The vaccine may be responsible for an increase in gram-negative and virulent β-lactamase-producing organisms in middle ear effusions, primarily in patients who have recently been treated.[23-25]

Up to 5 to 10% of the general pediatric population may be at risk for developing four or more episodes of OM in the first year of life; these children are generally called otitis-prone.[26] They may have subtle immunologic abnormalities[26] or a greater baseline colonization of virus and bacteria than the general population.[27]

Clinical Features

OM may be manifested by a multitude of symptoms, such as cough, poor appetite, diarrhea, vomiting, fever, and pulling at ears, all of which are nonspecific. Older children may be able to verbalize pain, but otalgia is not universally present. In OM, pain usually precedes otorrhea, in contrast to OME, in which pain accompanies the drainage. Children often have associated upper respiratory tract infections. Fever may be present, but in one large series, a temperature of 38.3° C or greater was present in only 26% of the episodes, with only 4% having a fever of 40° C or greater.[28] Some authorities have modified the definition to include otoscopic findings of acute inflammation regardless of symptoms; with this definition, one third of cases are not accompanied initially by acute symptoms.[29]

The auricle and external canal should be inspected for signs of erythema, discharge, or tenderness. If the canal is occluded with cerumen, an ear curette with direct visualization may be successful in clearing the canal. If not, the placement of 3% hydrogen peroxide or emulsifying drops, followed by gentle irrigation, may cleanse the canal.

The tympanic membrane (TM) may be bulging (as in AOM), neutral, or retracted as seen in chronic OME.[30] The color may be red, pink, yellow, or a normal pearly gray or translucent. The presence of erythema in itself does not indicate infection because crying or fever may cause hyperemia; however, a TM that is distinctly red (defined as *hemorrhagic*, strongly or moderately red) suggests AOM.[30]

Landmarks that should be visible include the pars flaccida, the malleolus, and the light reflex below the umbo.[30] The TM may have air-fluid levels, may have bubbles behind the TM, or may be completely opacified, all of which indicate middle ear effusion. The lack of mobility is one of the most sensitive indicators of middle ear effusion. In fact, mobility in response to insufflation should raise serious doubt as to the diagnosis of AOM. A TM that is cloudy, bulging, and distinctly immobile indicates AOM.[30] In OME, the TM often is retracted, with the malleolus being particularly prominent. The landmarks all may be obscured in the presence of significant fluid. A comparison examination of the other ear may help in confirming suspected infection.

In neonates, the TM appears thickened and opaque normally in the first few weeks of life, and the TM is in a highly oblique position. With tympanostomy tubes, in the absence of infection, the TM may have decreased mobility, altered landmarks, opacity, or dullness. If the tube is patent, erythema and discharge may indicate infection. If not, erythema, bulging of the TM, and immobility indicate AOM.

Complications

Before the use of antibiotics, there was a 20% incidence of complications from AOM, with mastoiditis and otic meningitis being relatively common.[31] Complications are either intratemporal or intracranial, occurring in both adults and children. The development of either complication of OM is thought to occur by one of three mechanisms: (1) direct extension of infection through bone weakened by osteomyelitis or cholesteatoma; (2) retrograde spread of infection by thrombophlebitis; or (3) extension of infection along preformed pathways, such as the round or oval windows or through dehiscences that are the result of congenital malformations.[32] The use of antibiotics has led to a reduction of all complications to less than 1%.[33]

Intratemporal. Hearing impairment is the most common complication in OM. Almost all children with OM have a temporary conductive hearing loss; sensorineural deficit occurs less commonly, probably as a spread of infection through the round window. This deficit may contribute to the association of OM with decreased or delayed speech, language, or cognitive development.

TM perforation occurs most commonly at the pars tensa and usually resolves spontaneously. It may persist for a longer period, resulting in a chronic perforation, chronic OM, or both.[20] Chronic OM refers to inflammation of the middle ear that persists for 6 weeks or longer[34] accompanied by discharge through perforation of an intact membrane. It *may* occur spontaneously or through tympanostomy tubes. The pathogenesis is multifactorial, and the most commonly involved causal organisms are *Pseudomonas aeruginosa*, *S. aureus*, gram-negative organisms, and anaerobes. Whereas acute otitis and its complications are more common in younger children, complications secondary to chronic OM are more common in older children and adults.[35] Topical antibiotics are an effective treatment.[36] Systemic treatment should be reserved for patients showing signs of complicated or invasive infections or signs of systemic disease.[34] Cholesteatoma is an accumulation of keratin-producing squamous epithelium in the middle ear and may result in erosion of bone within the middle ear cavity. It is seen most often in OME, in which retraction of the TM is a common problem and its presence may alter the courses of some treatment therapies.

Labyrinthitis occurs when infection spreads to the cochlear and vestibular apparatus, usually through the round or oval

windows. Serous labyrinthitis results when bacteria from the middle ear spread into the labyrinth space, resulting in a mixed conductive-sensorineural hearing loss and vestibular symptoms. Suppurative labyrinthitis is the development of purulence directly into the labyrinth as a result of bacterial invasion through the round window or around the annular ligament of the round window. It generally begins suddenly with mixed hearing loss and vestibular symptoms and is generally more severe than the serous form.[32]

The facial nerve courses through the middle ear, and facial paralysis is a known complication in OM. The exact mechanism is unknown, but it may be due to infection, surrounding osteitis, facial nerve swelling, demyelination of the facial nerve from bacterial toxins, or facial nerve ischemia.[37] Infectious eczematoid dermatitis may result from the otorrhea of OM, with perforation or tympanostomy tubes infecting the external auditory canal. Treatment involves otic suspension (*not* solution). Although caution is urged with these products, the incidence of adverse effects is small.[38]

Intracranial. Meningitis is the most common intracranial complication for AOM, resulting from hematogenous spread and direct invasion. Brain abscesses are most commonly due to chronic otitis and are the second most common intracranial complication.[39] They generally result from hematogenous extension secondary to thrombophlebitis but can result from erosion as well.[35] Causative organisms include *Proteus*, *Pseudomonas*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, and anaerobes.[40,41] Symptoms include headache, fever, vomiting, and mental status changes.

An extradural abscess may result from destruction of bone adjacent to the dura by cholesteatoma, infection, or both. Subdural empyema is a collection of fluid between the dura and arachnoid membrane as a result of infection or venous thrombophlebitis. Focal otic encephalitis is an edematous or inflamed area in the brain from a complication of OM, extradural abscess, or sinus dural thrombophlebitis.

Lateral venous sinus thrombosis occurs when the mastoid infection comes in contact with the sinus wall, which inflames the adventitia and penetrates the venous wall. Thrombosis and embolization occur. The classic presentation is the presence of high spiking fevers in a "picket fence" pattern, chills, earache, headache, and mastoid and neck tenderness.

Antibiotics are the primary treatment for all complications of OM. Myringotomy with or without tympanostomy tube placement ensures drainage of the middle ear and makes specimens available for culture.[42] Operative treatment may be required in the presence of intratemporal complications with abscess formation or intracranial complications, or when chronic OM or cholesteatoma is a cause of the acute complications.[42,43]

Diagnostic Strategies

Pneumatic otoscopy to confirm immobility of the TM is an important part of diagnosis in all cases (see earlier discussion). Tympanocentesis is aspiration of the middle ear effusion to identify causative organisms and is rarely indicated in the ED. Indications include patients with AOM who are seriously ill or appear toxic, are unresponsive to therapy, are younger than 4 weeks old, are immunocompromised, are receiving antimicrobials, or have suppurative complications.

Differential Considerations

OM usually does not cause a significantly high fever; in approaching a febrile, ill-appearing infant, the physician should investigate other causes for the fever. If a child or adult complains of otalgia, additional considerations or possibilities include OME, trauma, foreign bodies, and complications of OM such as mastoiditis. Ear pain also may be referred from the teeth, sinuses, throat, or temporomandibular joint.

Management

Although more than 16 antibiotics have been approved by the Food and Drug Administration for OM, few have shown efficacy against all of the main causative pathogens.[4] Concern about the rising rates of antibacterial resistance and the growing costs of antibacterial prescriptions has focused the attention of the medical community and the general public on the need for judicious use of bacterial agents.[44] Based on this and other factors, the American Academy of Pediatrics, the American Academy of Family Physicians, the Agency for Healthcare Research and Quality, and the Southern California Evidence Based Practice Center met to develop guidelines for the diagnosis and management of AOM to assist physicians in providing a framework for clinical decision making. These guidelines apply specifically to an otherwise healthy child between the ages of 2 months and 12 years without underlying conditions that may alter the natural course of acute AOM (Table 70-1).[4] Making a diagnosis of AOM requires three findings: (1) history of acute onset, (2) signs of middle ear effusion (including TM immobility), and (3) signs or symptoms of middle ear inflammation (see Table 70-1).

Because over 80% of cases of AOM resolve spontaneously,[45] the use of observation versus antibiotics has been advocated.[46] Several European countries have practiced this approach of "watchful waiting" for 48 hours for a number of years, with a resulting lower rate of antibiotic-resistant bacteria.[47] Although somewhat controversial, this approach has been met with acceptance by a majority of patients and physicians.[47,48] It has been successful in an ED setting[49] but has not yet become standard practice.[50]

The decision to treat is based on the age of the patient and certainty of the diagnosis.[44] The guidelines recommend an age-stratified approach that incorporates the age with a combination of diagnostic certainty and illness severity. Observation is an option in children older than 2 years, unless the child has severe otalgia or temperature of 39° C or greater (Table 70-2). In children 6 months to 2 years old, treatment recommendations are based on the certainty of the diagnosis and severity of illness, with recommended observation if the diagnosis is uncertain. The guidelines recommend treatment in children younger than 6 months old. Observation recommendations are based on the degree of severity, reliability of the caregivers, and ability for close follow-up. If there is concern about the ability to get follow-up, parents can be given a prescription to be filled if the patient does not improve in 48 hours—a so-called safety net.[51]

There is evidence that immediate antibiotic therapy for children younger than 2 years with severe symptoms results in a more rapid resolution of symptomatic disease and a reduced rate of treatment failure or relapse.[52,53] The potential risk of complications must be balanced against the side effects of antibiotic use, which may include allergic reactions, gastric upset, accelerated bacterial resistance, and unfavorable changes in the bacterial flora.[54]

Amoxicillin's cost, efficacy, safety profile, and palatability continue to make it a good first-line agent. It can be given twice a day at a dosage of 80 to 90 mg/kg/day. This higher concentration is effective against susceptible and intermediate resistant strains of *Streptococcus pneumoniae*. In patients who are allergic to penicillin, the guidelines distinguish between those

Table 70-1 Clinical Practice Guidelines: Diagnosis and Management of Acute Otitis Media

1. To diagnose acute otitis media, the clinician should confirm a history of acute onset *and* identify signs of middle ear effusion (bulging of the TM, limited or absent mobility of the TM, air-fluid level behind the TM, otorrhea) *and* signs or symptoms of middle ear inflammation as indicated by either distinct erythema of the TM or distinct otalgia.
2. The management of AOM should include an assessment of pain. If pain is present, the clinician should recommend treatment to reduce pain.

3A. Observation without use of antibacterial agents in a child with uncomplicated AOM is an option for selected children based on diagnostic certainty, age, illness severity, and assurance of follow-up.

3B. If a decision is made to treat with an antibacterial agent, the clinician should prescribe amoxicillin for most children. When amoxicillin is used, the dose should be 80–90 mg/kg/day.

4. If the patient fails to respond to the initial management option within 48–72 hr, the clinician must reassess the patient to confirm AOM and exclude other causes of illness. If AOM is confirmed in the patient initially managed with observation, the clinician should begin antibacterial therapy. If the patient was initially managed with an antibacterial agent(s), the clinician should change the antibacterial agent(s).
5. Clinicians should encourage the prevention of AOM through reduction of risk factors.

AGE	CERTAIN DIAGNOSIS	UNCERTAIN DIAGNOSIS
<6 mo	Antibacterial therapy	Antibacterial therapy
6 mo–2 yr	Antibacterial therapy	Antibacterial therapy; Observation option if nonsevere
>2 yr	Antibacterial therapy	Observation option if severe illness; observation option if nonsevere illness

AOM, acute otitis media; TM, tympanic membrane.

Note: Nonsevere illness is mild otalgia and fever <39° C in the past 24 hours. Severe illness is moderate to severe otalgia or fever >39° C. A certain diagnosis meets all three criteria: (1) rapid onset, (2) signs of middle ear effusion, and (3) signs and symptoms of middle ear inflammation.

From American Academy of Pediatrics Subcommittee on Management of Acute Otitis Media: Diagnosis and management of acute otitis media. Pediatrics 113:1451, 2004.

with type I sensitivity (urticaria or anaphylaxis) and those with non-type I sensitivity, but second- and third-generation cephalosporins have little cross reactivity.[55] Patients should be reevaluated in 3 days if the treatment fails. Treatment failure is defined by lack of clinical improvement in signs and symptoms, such as ear pain; fever; and TM findings of redness, bulging, or otorrhea. Treatment should include agents effective against the β-lactamase-producing organisms *H. influenzae* and *M. catarrhalis*. Recommended agents include amoxicillin-clavulanate (using 80–90 mg/kg/day of the amoxicillin component), oral cefuroxime axetil, and intramuscular ceftriaxone. Although ceftriaxone has been as effective as amoxillicin in patients with a history of vomiting, poor compliance, and a lack of follow-up,[56] a 3-day regimen may improve its effectiveness.[57] If treatment failure occurs within the first 28 days, recommended antibiotics are the same as at 3 days.

Patients who have been on antibiotics in the prior month should receive high-dose amoxicillin, high-dose amoxicillin-clavulanate, or cefuroxime axetil as the initial treatment. Cefdinir may be preferred over cefuroxime because of its more pleasing taste, which can equate to improved compliance.[4] Treatment failures at 3 days should be treated with intramuscular ceftriaxone or clindamycin, with tympanocentesis strongly encouraged. Clindamycin should be used only for treatment of *S. pneumoniae* because it is not effective against either *H. influenzae* or *M. catarrhalis*.[4,9] Treatment failures within 1 month should be treated with high-dose amoxicillin-clavulanate, cefuroxime axetil, or intramuscular ceftriaxone.[57]

Trimethoprim-sulfamethoxazole and macrolides traditionally have been second-line agents, but resistance is increasing—40% for trimethoprim-sulfamethoxazole and 30% for macrolides.[4] In addition, there is substantial cross-resistance between these drugs and the β-lactams, resulting in further treatment failures in children finishing a course of amoxicillin.[57,58] Fluoroquinolines may be effective, but their use in children is not approved.[57]

Response to antibiotics is only one of a number of factors that affect clinical outcome. Other factors include impairment of endothelin [ET](B) function, co-infection with nonbacterial pathogens, and host immune response.[58,59] Local practice patterns and antimicrobial sensitivities may also play a role in the types of treatment given. Other antibiotics available for treatment include erythromycin-sulfisoxazole, azithromycin, clarithromycin, cephalexin, cefaclor, cefprozil, loracarbef, cefdinir, cefixime, cefpodoxime, and ceftibuten. These were not included in the Centers for Disease Control and Prevention guidelines primarily because there was a lack of data on their efficacy.

Treatment historically involved a 10-day course. Numerous studies have compared traditional treatment courses with shorter therapy, which is most appropriate for uncomplicated AOM.[60,62] Patients with TM perforations and patients at high risk for treatment failure or those with chronic or recurrent OM probably are more appropriately treated with a longer course.[58] Shorter courses also are not appropriate for children younger than 2 years old.[60,62] The antibiotic treatment of AOM in adults is the same as in older children. There is no indication for the use of antihistamines, decongestants, steroids, or tympanostomy tubes for an acute episode of AOM.

AOM can cause substantial pain and should be appropriately addressed. Acetaminophen, ibuprofen, and benzocaine-antipyrine, a local anesthetic, may be helpful in some patients with an intact TM. Recurrent AOM occurs primarily in the winter months, often in conjunction with upper respiratory infections. Individuals at risk include children younger than 2 years old, children in day care, and Native American children.[60] These children may benefit from prophylaxis with amoxicillin (20 mg/kg).[63]

After a 10-day treatment with antibiotics, 50% of children may exhibit OME, but 90% of cases resolve within 3 months.[64] However, about 30 to 40% of children have recurrent OME and 5 to 10% of cases last 12 months or longer.[65] The treatment of OME is controversial, but OME may interfere with hearing and subsequent development of speech and language. OME is, by definition, asymptomatic, and the effusion may be sterile or contain infectious agents. Clinical guidelines developed by the Agency for Health Care Policy recommend observation or the use of antibiotics in patients with acute or subacute OME, although some experts recommend observation alone, given increasing antibiotic resistance.[1,60] Antihistamines, decongestants, steroids, or surgical procedures are not beneficial in patients with acute or subacute OME.[65] Myringotomy and tympanostomy tubes may be beneficial in children for whom medical treatment has failed, those who have had OME for 4 to 6 months, and those with a greater than 20-dB hearing loss.[1]

Table 70-2 Treatment Guidelines for Otitis Media

	AT DIAGNOSIS FOR PATIENTS BEING TREATED INITIALLY WITH ANTIBACTERIAL AGENTS		CLINICALLY DEFINED TREATMENT FAILURE AT 48–72 HOURS AFTER INITIAL MANAGEMENT WITH OBSERVATION OPTION		CLINICALLY DEFINED TREATMENT FAILURE AT 48–72 HOURS AFTER INITIAL MANAGEMENT WITH ANTIBACTERIAL AGENTS	
TEMPERATURE ≤ 39° C OR SEVERE OTALGIA OR BOTH	RECOMMENDED	ALTERNATIVE FOR PENICILLIN ALLERGY	RECOMMENDED	ALTERNATIVE FOR PENICILLIN ALLERGY	RECOMMENDED	ALTERNATIVE FOR PENICILLIN ALLERGY
No	Amoxicillin (80–90 mg/kg/day)	Non-type I: cefdinir, cefuroxime, cefpodoxime Type I*: azithromycin, clarithromycin Ceftriaxone—1 or 3 days	Amoxicillin (80–90 mg/kg/day)	Non-type I: cefdinir, cefuroxime, cefpodoxime Type I*: azithromycin, clarithromycin Ceftriaxone—1 or 3 days	Amoxicillin-clavulanate (90 mg/kg/day of amoxicillin with 6.4 mg/kg/day of clavulanate)	Non-type I: ceftriaxone—3 days Type I*: clindamycin
Yes	Amoxicillin-clavulanate (90 mg/kg/day of amoxicillin with 6.4 mg/kg/day of clavulanate)		Amoxicillin-clavulanate (90 mg/kg/day of amoxicillin with 6.4 mg/kg/day of clavulanate)		Ceftriaxone—3 days	Tympanocentesis—clindamycin

*Type I sensitivity—urticaria or anaphylaxis.
From American Academy of Pediatrics Subcommittee on Management of Acute Otitis Media: Diagnosis and management of acute otitis media. Pediatrics 113:1451, 2004.

Tonsillectomy is not beneficial, but adenoidectomy may be helpful in older children. Tympanostomy tubes have also been used in recurrent AOM unresponsive to prophylactic antibiotics; complications of AOM, and complications of eustachian tube dysfunction, including TM retraction with hearing loss, ossicular erosions, or retraction pocket formation.[64]

Disposition

Children normally are seen in 10 to 14 days for follow-up. This follow-up appointment may not be necessary in children older than 2 years in whom symptoms have resolved and who have no recurrent risk factors.[66] Infants younger than 2 months old with OM should be evaluated with blood, cerebrospinal fluid, and urine cultures.[8] Patients with complications need ear, nose, and throat (ENT) referral. Adults who have persistent OME need ENT referral to rule out nasopharyngeal carcinoma.

OTITIS EXTERNA

Principles of Disease

External otitis is an inflammation of the external auditory canal. There is a lifetime incidence of 10%, and it accounts for 7.5 million annual ototopical prescriptions in the United States.[67] The external auditory canal is lined with squamous epithelial cells and cerumen glands that provide a protective lipid layer.[68] This protective layer may be disrupted by high humidity, increased temperature, maceration of the skin after prolonged exposure to moisture, and local trauma (e.g., cotton swabs or the use of hearing aids), resulting in the introduction of bacteria. Otitis externa is a bacterial disease, most commonly caused by *P. aeruginosa*, *S. aureus*, and other gram-negative organisms often occurring as polymicrobial infection.[69] Occurring most often in the summer and in tropical climates, it is also known as swimmer's ear or tropical ear.

Clinical Features

The diagnosis is made clinically. The external auditory canal may be initially pruritic and become erythematous and increasing swollen. Symptoms include otalgia and ear fullness, as well as possible hearing loss or jaw pain. Physical findings include erythema or edema of the canal and reproduction of the discomfort with pulling on the auricle or tragus. There may be associated lymphadenitis, TM erythema, or local cellulitis. The disease may progress to a chronic form with itching, eczema, and flaking of the epithelium, which may be from bacterial, fungal, or dermatologic conditions. In children, it is usually secondary to chronic OM.

Differential Considerations

It may be difficult to distinguish otitis externa from OM, particularly in children. The TM may be erythematous in both conditions, and the edema may preclude diagnosis. The discharge may be from otitis externa or a perforated TM, and in equivocal cases it is prudent to treat for both conditions.

Otomycosis or fungal infection can occur as a primary or secondary infection and accounts for 10% of cases of otitis externa.[70] Itching is the prominent symptom, often with minimal pain or otorrhea. Aspergillosis is the cause in most cases. Otomycosis appears most often in individuals in tropical climates, in patients with diabetes, in immunocompromised patients, and in patients on immunosuppressive therapy. Treatment involves cleansing and acidifying and antifungal eardrops, such as thimerosal or gentian violet. Specific antifungal agents, such as clotrimazole and itraconazole, also are effective.[70]

Furunculosis is a small, erythematous, and well-circumscribed infection of the cartilaginous portions of the external canal, usually caused by *S. aureus*.[32] There is usually no drainage, and treatment involves incision, drainage, and an oral antistaphylococcal antibiotic. Cellulitis of the auricle and canal may cause erythema, induration, and other systemic signs. Treatment is with antibiotics directed at the offending organisms.

Herpes zoster oticus, also known as the *Ramsay Hunt syndrome,* is a viral manifestation of disease affecting the auricle, with resulting facial paralysis that may involve multiple cranial nerves. It initially causes pain, with erythema, swelling, and vesicles developing approximately 3 to 7 days later.[34] These patients need ENT referral. Treatment consists of analgesia, warm compresses, and acyclovir.

Management

Historically, combination drugs containing neomycin, polymyxin B, and hydrocortisone (e.g., Cortisporin otic suspension) four times a day have been effective for treatment, although there has been a problem with hypersensitivity to the neomycin component. The new fluoroquinolones are less reactive, have minimal toxicity, and are taken twice a day.[70,71] The addition of steroid drops may decrease the formation of granulation tissue in the canal.[67] Management may involve cleansing the external canal with a combination of gentle suctioning and irrigation, depending on the amount of obstructing exudate. Cleansing solutions include tap water, sterile saline, 2% acetic acid, and Burow's solution. In severe infections, a wick of cotton, gauze, or compressed hydroxycellulose facilitates medication delivery. The wick is placed 10 to 12 mm into the canal, moistened with antibiotic drops, and left in place for 2 to 3 days. Having the patient lie down for 5 minutes after the solution is placed may obviate the need for packing.[67] There is no evidence that systemic antibiotics alone or in combination with topical preparations improve treatment outcome compared with topical antibiotics alone,[72,73] but systemic medication may be indicated in immunocompromised patients with diabetes or HIV or in infections involving the skin and periauricular areas.[70] Otitis externa can be extremely painful, and severe symptoms may require opiate analgesia. Topical anesthesia such as benzocaine with or without antipyrine may also be used for pain relief, but benzocaine may cause a contact dermatitis that can worsen the disease.[67]

NECROTIZING (MALIGNANT) EXTERNAL OTITIS

Previously known as *malignant otitis externa* because of its associated high mortality rate, necrotizing external otitis is an extremely aggressive form of otitis externa. Patients affected include elderly patients with diabetics, AIDS patients, and, rarely, immunocompromised children. *Pseudomonas* is the predominant pathogen, but *Staphylococcus aureus*, *Streptococcus epidermidis*, *Proteus mirabilis*, *Klebsiella*, *Aspergillus*, and *Salmonella* all have been described.[74] The infection begins in the external canal and progresses through the periauricular tissue and cartilaginous bony junction of the external auditory meatus. It then spreads into the adjacent tissues along clefts in the floor of the meatus known as the *fissures of Santorini*.[75] It may spread to the base of the skull at the temporal bone, with a resultant skull-base *osteomyelitis,* another term often used to describe this entity. The facial nerve is the first cranial nerve affected, but additional nerves may be involved. The pathogenesis is uncertain but may be related to vascular insufficiency or immune dysfunction.[76]

Patients may present with persistent otorrhea unresponsive to topical medications, otalgia, headache, and periauricular pain and swelling. It should be considered in patients at risk who have a prolonged course of otitis externa. The clinical finding characteristic for the disease is granulation tissue in the floor of the ear canal at the bony cartilaginous junction. Cranial nerve VII is most often involved and manifests in facial paralysis, which occurs when the stylomastoid foramen is involved. Further extension can result in involvement of the glossopharyngeal, vagal, spinal accessory, hypoglossal, trigeminal, and abducens nerves.[77,78] Cranial nerve involvement does not affect mortality rates.[79] Additional complications include meningitis, brain abscess, and thrombosis of the sigmoid sinus.

There is no single diagnostic criterion for necrotizing external otitis. The diagnosis is made from a range of clinical, laboratory, and radiographic findings.[77] Bone scanning (technetium 99 m) is sensitive but is often positive in patients with otitis externa. Gallium scans are more specific, but computed tomography (CT) and magnetic resonance imaging (MRI) are better for detecting infratemporal spread of the disease, bony erosions, and abscess formation.[75,80] The bioavailability of oral ciprofloxin and its penetration to bone have made it the ideal treatment for necrotizing external otitis, eliminating the need for hospitalization in all but the most recalcitrant cases.[77] Treatment may be required for 6 to 8 weeks. Although extensive surgical treatment was previously required, its use is now limited to diagnostic confirmation or débridement of granulation tissue.[81] Hyperbaric oxygen may be used as an adjunct treatment for advanced disease with significant skull base or intracranial involvement, recurrent cases, and infections secondary to antibiotic treatment.[81,82]

MASTOIDITIS

The incidence of acute and chronic mastoiditis has decreased significantly since the advent of antibiotics, though there is concern about an increase in its frequency.[83,84] Although it is still associated primarily with OM, many patients have not had an episode of OM.[85,86] Mastoiditis also has been described as a complication of leukemia, mononucleosis, sarcoma of the temporal bone, and Kawasaki disease.[59]

Pathophysiology

Acute mastoiditis is a natural extension of middle ear infections because the mastoid air cells are generally inflamed during an episode of AOM. The aditus ad antrum is a narrow connection between the middle ear and mastoid air cells. If this connection becomes blocked, a closed space is formed, with the potential for abscess development and bone destruction. The infection may spread from the mastoid air cells by venous channels, resulting in inflammation of the overlying periosteum. Progression results in the destruction of the mastoid bone trabeculae and coalescence of the cells, resulting in acute mastoid osteitis or coalescent mastoiditis. The resulting pus may track through many routes: (1) through the aditus ad antrum with resultant spontaneous resolution; (2) lateral to the surface of the mastoid process, resulting in a subperiosteal abscess; (3) anteriorly, forming an abscess below the pinna or behind the sternocleidomastoid muscle of the neck, resulting in an abscess (often called a *Bezold abscess*); (4) medial to the petrous air cells of the temporal bone, resulting in a rare condition known as *petrositis*; and (5) posterior to the occipital bone, resulting in osteomyelitis of the calvaria or a Citelli abscess.[59,85,86]

Chronic mastoiditis is generally a complication of chronic OM. There may be extensive invasion of granulation tissue

from the middle ear into the mastoid air cells. Another entity, latent, or "masked," mastoiditis, also has been described. It is indolent in nature, with minimal signs and symptoms, little or no fever, and a history of otalgia. The TM may be intact or perforated. Suspicion should be raised in the presence of intracranial complications without an apparent source.[87] Patients at risk include newborns and immunosuppressed patients (those who have undergone recent chemotherapy or steroid administration or diabetic or geriatric patients).

Etiology

S. pneumoniae is the most common organism found in mastoiditis, but other organisms involved do not always mirror those of acute otitis.[85] Mixed cultures of aerobes and anaerobes are common. Common aerobes include group A streptococci, *S. aureus*, and *S. epidermidis*. Chronic mastoiditis also often has mixed cultures, with *P. aeruginosa* as the predominant organism.

Diagnostic Findings

Clinical findings in acute mastoiditis include fever, headache, and erythema. Pain is universally present.[85] Physical findings include postauricular or supra-auricular tenderness, with late edema. The TM is similar to AOM (erythema, bulging, and decreased mobility) but may be normal in 10% of cases.[85] Suspicions should be heightened if symptoms of AOM have lasted longer than 2 weeks.[87,88] In chronic mastoiditis, symptoms include persistent drainage through the perforated TM, redness, edema, and retroauricular sensitivity.[89]

Ancillary Testing

CT scans can identify the evidence of bony erosions, whereas MRI may be more useful in cases of possible intracranial complications.

Management

Antibiotics are the initial treatment of choice, with most cases responding without the need for surgical drainage.[84,90,91] If indicated, surgical procedures may range from myringotomy and tympanostomy tube placement (for drainage and identification of the offending organism) to mastoidectomy and drainage for more extensive disease progression.

SUDDEN HEARING LOSS

Hearing loss has a multitude of causes (Box 70-1).[92-94] Idiopathic sudden sensorineural hearing loss is an otologic emergency.[92] It is defined as the idiopathic loss of hearing of 30 dB over at least three test frequencies occurring within 3 days.[95] The overall incidence ranges from 5 to 20 per 100,000 people a year.[96] Severity ranges from difficulty with conversation to complete hearing loss.

A sudden onset may be from trauma or a vascular complication; gradual hearing loss suggests a tumor.[93] A history of trauma, medications, illnesses, physical activity at the time of the event, and unilateral or bilateral involvement all are helpful diagnostic clues. The presence of tinnitus, vertigo, and neurologic symptoms ranging from cranial nerve abnormalities to brainstem or cerebellar dysfunction is suggestive. In conductive hearing losses, such as otosclerosis, individuals hear better in noisy environments.[93]

Physical examination should include a thorough inspection of the external canal and TM integrity. Weber's test for hearing and Rinne's test may help in distinguishing conductive versus sensorineural deficits. A comprehensive neurologic examination including cranial nerves and cerebellar testing may localize brainstem involvement. CT may reveal trauma or tumors, and neurologic and chemical screening should be based on the history and physical findings.[94] Oral steroids are the most common treatment though their efficacy is debated.[95] Additional treatments have included intratympanic steroids, hyperbaric oxygen, antiviral therapy, vasoactive and hemodilution therapies, dextran, and magnesium, all with mixed results.[95,97-100]

Box 70-1 Causes of Sudden Hearing Loss

Infectious
Mumps
Measles
Influenza
Herpes simplex
Herpes zoster
Cytomegalovirus
Mononucleosis
Syphilis

Vascular
Macroglobulinemia
Sickle cell disease
Berger's disease
Leukemia
Polycythemia
Fat emboli
Hypercoagulable states

Metabolic
Diabetes
Pregnancy
Hyperlipoproteinemia

Conductive
Cerumen impaction
Foreign bodies
Otitis media
Otitis externa
Barotrauma
Trauma

Medications
Aminoglycosides (gentamicin, neomycin, vancomycin, kanamycin, streptomycin)
Loop diuretics (furosemide, ethacrynic acid)
Antineoplastics
Salicylates

Neoplasm
Acoustic neuroma

Data from references 92–94.

EPISTAXIS

Perspective

Epidemiology

Epistaxis is a common otolaryngologic problem, with 15 per 10,000 people requiring physician care annually and 1.6 per 10,000 requiring admission to the hospital.[101] Most cases occur

in children younger than age 10 years, and the incidence decreases with age. Some studies have found a bimodal distribution of patients younger than age 25 and those older than 50.[102] It is more common in males than females.[102] Epistaxis is more common in colder seasons and in northern climates because of decreased humidity and subsequent drying of the nasal mucosa. Nasal bleeding is a frightening condition for patients but is seldom life-threatening. A solid understanding of physiology and treatment allows for prompt and efficient management of the disorder.

Anterior epistaxis accounts for 90% of all nosebleeds and usually involves Kiesselbach's plexus on the anteroinferior nasal septum.[3] Epistaxis is unilateral and can be controlled with anterior packing. Posterior epistaxis accounts for 10% of nosebleeds and usually arises from a posterior branch of the sphenopalatine artery.[103] It cannot be controlled with a well-placed anterior pack. Posterior bleeding is rare in children.[103]

Principles of Disease

Anatomy

Three arteries with anastomoses between them supply the nasal area. The sphenopalatine artery supplies the turbinates and meatus laterally and the posterior and inferior septum medially. The anterior and posterior ethmoidal arteries from the ophthalmic branch of the internal carotid artery supply the superior mucosa medially and laterally. The superior labial branch of the facial artery provides circulation to the anterior mucosal septum and anterior lateral mucosa (Fig. 70-1).

Etiology

There are many reasons for epistaxis, but the most common are upper respiratory infection with concomitant mucosal congestion and vasodilation and trauma, either accidental or iatrogenic (i.e., nose picking) (Box 70-2).

Diagnostic Strategies

Patients initially should have their hemodynamic status evaluated, with resuscitation and laboratory studies performed as needed based on possible causes mentioned in Box 70-2.[103] Patients often are anxious and hypertensive. Elevated blood pressure is usually from stress and anxiety and resolves with treatment. Hypertension has never been shown to cause epistaxis, although it can worsen the bleeding when present.[103] Sedation with benzodiazepines or narcotics may help these patients.

The key to successful management is identifying the site of nasal bleeding and whether it is anterior or posterior. If the nose is actively bleeding, the patient should clear clots by blowing the nose, then apply bilateral pressure on the nasal septum by compressing the cartilaginous part of the nose for 10 to 15 minutes. This simple maneuver also educates the patient on how to self-manage further episodes. It is important to optimize the exam. The patient must have the floor of the nose parallel to the floor. If the head is tilted, only the anterior and upper aspect of the nares can be visualized. The nasal speculum should be opened in an upper-lower direction rather than side to side in the nares. During this time, materials for illumination, suction, visualization, and treatment should be assembled. Discharge without identification and treatment of

Box 70-2 ETIOLOGY OF EPISTAXIS

Local
Nasal or facial trauma
Upper respiratory tract infections
Nose picking
Allergies
Low home humidity
Nasal polyps
Foreign body in the nose
Environmental irritants
Nasopharyngeal mucormycosis
Traumatic internal carotid artery aneurysm
Chlamydial rhinitis neonatorum
Postoperative

Idiopathic
Habitual
Familial

Systemic
Atherosclerosis of nasal blood vessels
Hypertension (controversial)
Anticoagulant therapy
Pregnancy
Abrupt changes in barometric pressure
Hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber disease)
Blood dyscrasias (e.g., hemophilia, leukemia, lymphoma, polycythemia vera, anemias, idiopathic thrombocytopenic purpura, granulocytosis, inherited platelet disorders, acquired platelet disorders [i.e., aspirin])
Hepatic disease
Rupture of internal carotid artery aneurysm
Diabetes mellitus
Alcoholism
Vitamin K deficiency
Folic acid deficiency
Chronic nephritis
Chemotherapy
Blood transfusion reactions
Migraine headache
Drug-induced thrombocytopenia

From Wurman LH, et al: The management of epistaxis. Am J Otolaryngology 13:193, 1992.

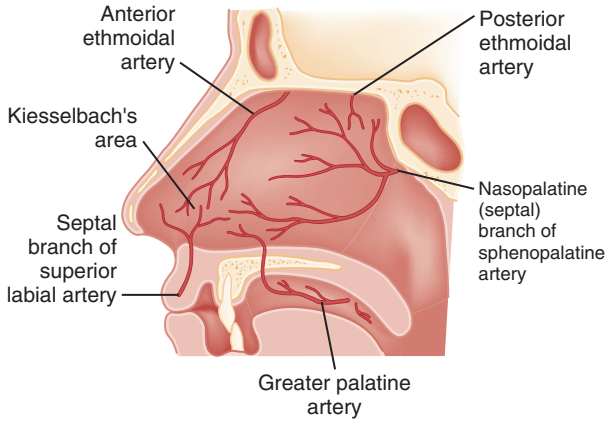


Figure 70-1. Arterial supply to medial wall of nose.

the bleeding site often results in recurrences. Anterior clots and obstructions may give the appearance of a posterior epistaxis if the blood runs posteriorly. Persistent bleeding should be controlled with pledgets soaked in cocaine, lidocaine-epinephrine, or phenylephrine (Neo-Synephrine) to promote vasoconstriction and anesthesia.

Management

Anterior Epistaxis

After having identified the site of bleeding in anterior epistaxis, the clinician has several treatment options. Application of silver nitrate chemically cauterizes the area but is directly unsuccessful during active bleeding. With 4 to 5 seconds of application, nitric acid is formed and coagulates tissue. Coagulation should never be maintained longer than 15 seconds because septal damage may occur.[103] The area should be cauterized peripherally to centrally and superiorly to inferiorly to avoid blood, which renders the sticks ineffectual. Bilateral application of silver nitrate to the septum is not advised because it may deprive the septum of a blood supply and theoretically could lead to necrosis. Cautery should not be done in the presence of coagulopathy.[103]

An alternative treatment is the application of topical agents, such as absorbable gelatin sponge (Gelfoam) and absorbable knitted fabric (Surgicel), with light packing. If bleeding persists, anterior tamponade with a commercially available nasal tampon or balloon or a formal anterior nasal pack may be necessary. Occasionally, for uncontrolled bleeding despite the presence of tampon, an second tampon can be inserted adjacent to the first. These work by three mechanisms. Direct pressure is applied, resultant mucosal irritation from the foreign body decreases bleeding, and surrounding clot formation adds further pressure. A recent study of 42 patients found no difference in efficacy or discomfort when the Merocel Sponge was compared with the Rapid Rhino; however, patients experienced greater subjective discomfort from the latter on insertion and removal.[104] When placed, anterior packs should be left in place for about 48 hours. Discomfort caused by anterior packs may require sedatives and opioid pain medication. Bilateral packs usually are required to obtain adequate compression when the patient has significant septal deviation.

It is customary to place patients on antibiotics to prevent sinusitis from obstruction. There is no proof, however, that this is effective. Toxic shock has also been reported in patients with nasal packing and is due to *S. aureus*.[105] Patients should be instructed on proper nose compression techniques and, after packing is removed, to keep mucosa moist with antibiotic ointment. Patients may be counseled to avoid closed-mouth sneezing, nose picking, coughing, nose blowing, and aspirin.

Posterior Epistaxis

Posterior epistaxis is suggested when posterior bleeding occurs with a properly placed anterior nasal pack. A posterior pack is therefore necessary, with either a commercially available device or basic Foley catheter. A standard Foley catheter may be inserted into the nasopharynx, partially inflated, and then pulled anteriorly, creating pressure posteriorly. A small amount of fluid can be added to the balloon, but caution should be exercised to avoid pressure necrosis. It is recommended that plain water rather than saline be used because saline can crystallize and cause problems with balloon deflation later.[106] Vaseline gauze should be packed around the catheter anteriorly. Commercially available balloons, such as the Nasostat and Epistat, are more comfortable than the posterior pack. The packs are left in for 2 to 5 days to minimize rebleeding and also avoid tissue necrosis associated with prolonged placement.[107] Antibiotics, such as cephalexin and amoxicillin-clavulanate, are traditional medications. If these techniques do not provide successful control, ENT consultation is necessary. Definitive care may require internal maxillary artery ligation or embolization with Gelfoam or posterior endoscopic cautery.

Patients with posterior nasal packs should be admitted to the hospital and may require sedation and supplemental oxygen. The partial pressure of oxygen (Po_2) may decrease 10 mm Hg, and partial pressure of carbon dioxide (Pco_2) may increase 10 mm Hg after posterior packing. This is thought to be secondary to a postulated nasopulmonary reflex. Dysrhythmias, bradycardia, myocardial infarction, stroke, and aspiration also have been reported after posterior nasal packing.[108]

Newer Agents in Epistaxis

The following three agents have recently become available. To this date, no large studies have examined their efficacy.

QuikClot hemostatic agent is a molecular sieve, sifting molecules by size. When QuikClot comes into contact with blood in and around a wound, it rapidly absorbs the smaller water molecules from the blood. The larger platelet and clotting factor molecules remain in the wound in a highly concentrated form. This promotes extremely rapid natural clotting. The particles provide key surface chemistry, rapidly enhancing the coagulation process. It is available over the counter and is being actively used by police, fire, sports, and military personnel. No clinical trials have been done, but case reports are available. It has been successfully used on a 60-year-old man with uncontrollable bleeding after a punch biopsy of the nasopharynx.[109] Thermal release due to an exothermic reaction of the product can cause discomfort.

Recombinant factor VIIa has been used to treat severe, uncontrolled, life-threatening bleeding. Recently it was used in two patients with Bernard-Soulier syndrome who had life-threatening epistaxis, and it may prove to be useful in uncontrolled epistaxis.[110]

Floseal Hemostatic Matrix is a combination of human thrombin (from pooled plasma), calcium chloride, and a gelatin matrix, which are mixed together and placed at a bleeding site. The manufacturer claims that bleeding, whether it is oozing or pulsatile, ceases within 2 minutes. Bleeding must be active for this method to be effective. Injection into blood vessels or open lacerations is contraindicated. After application, the volume swells approximately 20% and excess volume other than the induced clot should be gently irrigated away. Preparation of the material requires mixing of the materials and then passing the liquid back and forth between two connected syringes 20 times. It may not be used for at least 30 seconds. After mixing it is active for 2 hours.[111]

SIALOLITHIASIS

Stones of the salivary glands occur in 1% of the population.[112] They are found most commonly in people between ages 30 and 50 years. Although they are less common in children, a recent study of 210 stones found that 14% occurred in children younger than 18 years. Pediatric stones were more likely to be distal in the duct and smaller.[113] The most common gland affected is the submandibular (submaxillary) gland, accounting for 80 to 95% of cases.[112] They are found in

the sublingual gland about 6% of the time and in the parotid gland in 2%.

The stones occur when calcification occurs around an organic nidus. The patient has pain and swelling of the gland. Differential diagnosis includes infections, inflammation, as well as granulomatous and neoplastic processes. The most common viral pathogen is mumps. *Staphylococcus*, *Streptococcus viridans*, *S. pneumoniae*, and *H. influenzae* predominate in bacterial infections. Stones may be confirmed by palpation or purulent discharge from the glandular duct with massage. Ultrasonography is rapidly becoming the diagnostic modality of choice as it avoids radiation and may reveal diagnoses other than stones, although CT provides more accurate sizing and location within the duct.[114]

Treatment consists of antibiotics (covering penicillinase-resistant organisms), moist heat, massage, sialagogues (tart hard candies to promote glandular secretions), and sialolithotomy, if necessary, using probes or endoscopy.[115] Lithotripsy treatment is also used and works better for parotid rather than submandibular stones. A recent study of 323 submandibular and 132 parotid stones found lithotripsy to be successful in 39.4%, basket retrieval in 74.7%, and intraoral surgical removal in 95.8% of patients attempted.[116] Procedures are chosen based on stone size and location. For recalcitrant cases, the entire gland may require removal, but this may lead to chronic decreased function and morbidity. Follow-up within 24 hours should be arranged for patients who had stones that were not removed in the ED and 4 to 5 days if the removal is successful in the ED.

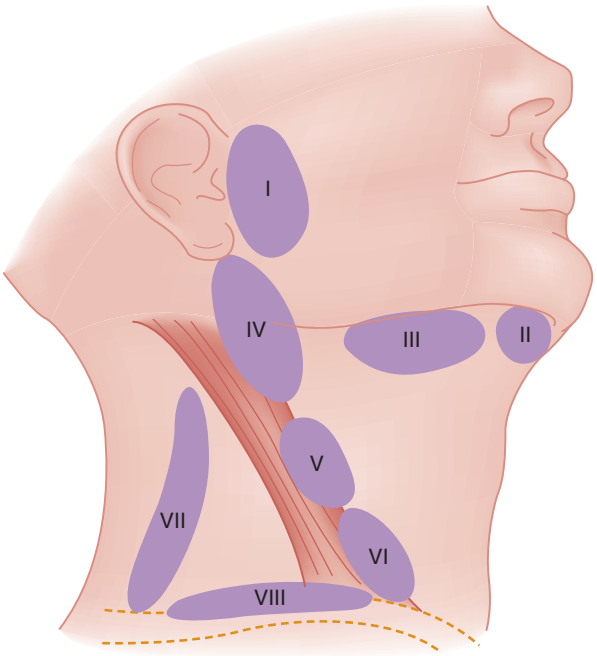


Figure 70-2. Major lymph node groups in the head and neck: *I,* parotid nodes; *II,* submental nodes; *III,* submandibular nodes; *IV,* jugulodigastric nodes (superior jugular nodes); *V,* midjugular nodes; *VI,* lower jugular nodes; *VII,* spinal accessory nodes; *VIII,* subclavian nodes. Groups VI and VII are often termed "scalene nodes." (Redrawn and modified from Moloy PJ: How to (and how not to) manage the patient with lump in the neck. In American Academy of Otolaryngology–Head and Neck Surgery Foundation: Common Problems of the Head and Neck Region. Philadelphia, WB Saunders, 1995, p. 134.)

NECK MASSES

Perspective

Neck masses are a relatively common clinical finding and are usually the result of inflammation but may be an indicator of head and neck malignancy as well. An extensive discussion of head and neck cancer is beyond the scope of this chapter, but some basics are discussed. Children and young adults are more likely to have benign disorders, such as inflammatory or developmental abnormalities, including thyroglossal or brachial cleft cysts. Adult neck masses are more likely to be neoplastic. In general, 80% of nonthyroid neck masses in adults are neoplastic, of which 80% are malignant.[117] In children, however, more than 80% of neck masses are benign. This is often referred to as *the rule of 80*, or the *80% rule*. Risk factors that may predispose patients to ENT malignancies include alcohol and tobacco use, viruses such as herpesvirus, sunlight exposure, genetics, diet, exposure to dust, and inhalation exposures.[118]

Principles of Disease

Identifying the location of the parotid and submandibular glands and thyroid cartilage and thyroid gland can help avoid confusion when evaluating a neck mass. In addition, knowing where the lymph nodes are can help distinguish lymph nodes from other types of masses (Fig. 70-2).

Clinical Features

Important associated symptoms include dysphagia, odynophagia, otalgia, stridor, speech disorders, and globus phenomena. *Dysphagia* is difficulty swallowing and may be caused by physical obstruction or neurologic disorders. *Odynophagia* is pain on swallowing and can be caused by many entities, such as tonsillitis or carcinoma of the pharynx. *Otalgia* is pain felt in the ear that may be referred from the larynx, pharynx, and cranial nerves V, IX, and X. Referred ear pain is considered an ominous sign in adults and should be presumed to be cancer until proved otherwise.[119] Unilateral OME in older adults should be considered nasopharyngeal carcinoma until proved otherwise. Stridor, specifically inspiratory stridor, is diagnostic of upper airway obstruction. It localizes a lesion to above or at the level of the larynx and, when present in adults with a neck mass, should increase the possibility of carcinoma. Speech disorders, particularly "hot potato" speech, are suggestive of space-occupying lesions above the oropharynx, a classic example being peritonsillar abscess. The globus symptom is a lump in the throat. It has occurred in almost everyone at one time or another, is localized to the pharynx, and is often a functional complaint.[119] Hoarseness, the final symptom, is a fairly common complaint, with a myriad of causes, ranging from viral pharyngitis to laryngeal cancer. Also, similar to the term *dizziness*, hoarseness has many descriptions, including breathiness, muffling, harshness, scratchiness, or unnatural deepening of the voice.[120] Hoarseness lasting longer than 2 weeks needs investigating.

Physical Examination

The head and neck examination may identify masses, lesions, mucosal ulcerations or discolorations, and cranial nerve abnormalities. The mass itself should be palpated for location, size, and consistency. Lymph nodes are generally smaller than 1 to 1.5 cm, so any nodes larger than 1.5 cm should be considered abnormal.[121] Lymph nodes are also mobile, soft, and fleshy. Decreased mobility and firmness are warning signs of malignancy.[121]

Box 70-3 Differential Diagnosis of Neck Masses

Inflammatory
Adenitis
- Bacterial (*Streptococcus, Staphylococcus*)
- Viral (HIV, EBV, HSV)
- Fungal (coccidioidomycosis)
- Parasitic (toxoplasmosis)

Cat-scratch disease
Tularemia
Local cutaneous infections
Sialoadenitis (parotid and submaxillary glands)
Thyroiditis
Mycobacterium avium-intracellulare
Mycobacterium tuberculosis

Congenital/Developmental
Brachial cleft cyst
Thyroglossal duct cyst
Dermoid cyst
Cystic hydromas
Torticollis
Thymic masses
Teratomas
Ranula
Lymphangioma
Laryngocele

Neoplastic
Benign
Mesenchymal tumors (lipoma, fibroma, neural tumor)
Salivary gland masses
Vascular abnormalities (hemangiomas, AVM, lymphangiomas, aneurysm)

Malignant
Primary tumors
Sarcoma
Salivary gland tumor
Thyroid or parathyroid tumors
Lymphoma

Metastasis
From primary head and neck tumors
From infraclavicular primary tumors (e.g., lung or esophageal cancer)

AVM, arteriovenous malformation; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus; HSV, herpes simplex virus.
Data from references 121–123.

Diagnostic Strategies

The diagnostic strategy should be tailored to results of the history and physical examination. Hoarseness for longer than 2 weeks should be investigated, generally with fiberoptic examination. Serologic and skin tests may be helpful in certain instances but are best performed by the referring specialist. Chest radiography may identify lung carcinoma as the source of metastasis. Ultrasonography, CT, MRI, and needle biopsy can aid in the diagnosis but usually are not required in the ED.

Differential Considerations

Box 70-3 lists common possibilities for the differential diagnosis of neck masses.[121-123]

Management and Disposition

Most masses in children are inflammatory; it is a reasonable strategy, therefore, to start the patient on antibiotics with a 2-week follow-up. If inflammation is considered in adults, a similar strategy can be used.[122] Adults generally need ENT referral if the mass does not resolve in 2 weeks, the mass is enlarging, the mass is fixed, cervical lymph nodes are matted, or masses are noted in the parotid or thyroid gland.[123]

KEY CONCEPTS

- Most cases of AOM resolve spontaneously. Children older than age 2 years may be observed for 3 days to determine whether antibiotics are required. When indicated, amoxicillin is the initial choice for treatment of AOM at a dose of 80 to 90 mg/kg/day.
- Necrotizing otitis externa should be considered in immunocompromised patients who have a persistent otitis externa.
- Patients with epistaxis with posterior nasal packing should be admitted to the hospital. Antibiotic therapy typically is prescribed.
- All neck masses that do not respond to antibiotics or persist for more than 2 weeks or hoarseness lasting for more than 2 weeks needs ENT referral.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 71 Asthma

Richard M. Nowak and Glenn F. Tokarski

PERSPECTIVE

The word *asthma* is derived from the Greek ασυμα, signifying panting, and was used initially as a synonym for "breathlessness." In 1698 Floyer published "A Treatise of the Asthma," in which he attempted to differentiate asthma more clearly from other pulmonary disorders. Subsequent definitions of asthma highlight concepts of airway hyper-responsiveness, bronchospasm, and reversible airway obstruction but fail to encompass the many facets of this disease.

The National Heart, Lung, and Blood Institute summarizes our current understanding of asthma as "a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role … this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing … episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyperresponsiveness to a variety of stimuli. Reversibility … may be incomplete in some patients."[1] Asthma is thus a chronic inflammatory disease, and control of symptoms ultimately depends on ameliorating the inflammatory reaction that produces alterations in airway function and structure. Irreversible structural airway changes occurring in response to chronic airway inflammation may influence emergency department (ED) asthma therapies.

EPIDEMIOLOGY

Lifetime asthma (defined as having ever being diagnosed with asthma by a physician) was reported by 26.7 million persons in the United States from 1980 to 1999,[2] 31.3 million in 2001,[3] 32.6 million in 2005[4] (Fig. 71-1), and 34.1 million in 2006.[5] The *current prevalence of asthma* (defined as individuals who have been diagnosed and currently have asthma) in 2006 was 22.5 million (15.7 million adults and 6.8 million children), and the *asthma attack prevalence* (the number of persons who had at least one asthma attack in the previous year) was 12.4 million representing 54% of persons currently having asthma.[5] Puerto Ricans have a current asthma prevalence 125% higher than non-Hispanic whites and 80% higher than non-Hispanic blacks. Females have a 40% higher prevalence rate than males (this pattern is reversed in children).

Asthma was responsible for more than 1.8 million ED visits in the United States in 2004[4] (Fig. 71-2) and a similar number in 2005.[6] African Americans had an ED visit rate 350% higher than that for whites. Children accounted for over 754,000 ED visits, and the ED visit rate was highest among children age 0 to 4 years. There were 488,594 asthma hospitalizations in 2005.[5] Children age 0 to 17 years accounted for 40% of asthma hospitalizations. The asthma hospitalization rate was 240% greater in African Americans than whites and was 35% greater in females than males. Since 1991 hospitalization rates have been highest in children younger than 15 years. Decreases in hospitalization rates have been noted in those older than 45 years from the late 1980s into the early 2000s.[7] From 2003 to 2005 there was a 16.2% decrease in hospitalization discharge rates for asthma.[5]

The estimated financial burden of asthma totaled $19.7 billion in the United States in 2007,[5] with approximately 75% attributable to direct costs (hospital inpatient, outpatient, ED and physician services). Prescription drugs represented the highest single direct cost at $6.2 billion. Less than 20% of asthma patients account for 80% of the direct costs.[8] Indirect costs attributable to asthma are reflected by decreased productivity. In 2006 asthma accounted for an estimated 10.1 million lost work days in adults and 12.8 million lost school days in children.[5] Asthma ranks within the top 10 prevalent conditions causing limitation of activity.

Disturbing increases in mortality related to asthma were reported in the 1980s, with a disproportionate number of deaths occurring in the age range 5 to 34. In the United States, moderation of this trend was noted in the mid-1990s and continued into the present millennium. The United States had one of the lowest rates of asthma mortality in the world in 2004, bettered only by the Netherlands, Finland, and Spain. In the United States in 2003, 4055 deaths from asthma were reported, which decreased to 3816 in 2004.[4,5] The number of asthma deaths has decreased by 18% since 1999. Despite these positive indicators, asthma mortality is 40% higher for females than for males and three times higher for the black than white population.[5] New Zealand, Australia, Great Britain, and Canada all reported increases in asthma prevalence,[9] hospitalizations, and deaths during the 1980s, with reversal of these trends during the 1990s. Developed nations have higher rates of asthma, which suggests that urbanization and westernization are correlated with increased asthma prevalence. Interestingly, migrants who move from an area of low asthma prevalence to an area of high asthma prevalence assume an increased asthma prevalence, suggesting that environmental factors play a role. Urban areas in the United States (New York City, Los Angeles, and Chicago) have high mortality rates associated with asthma,

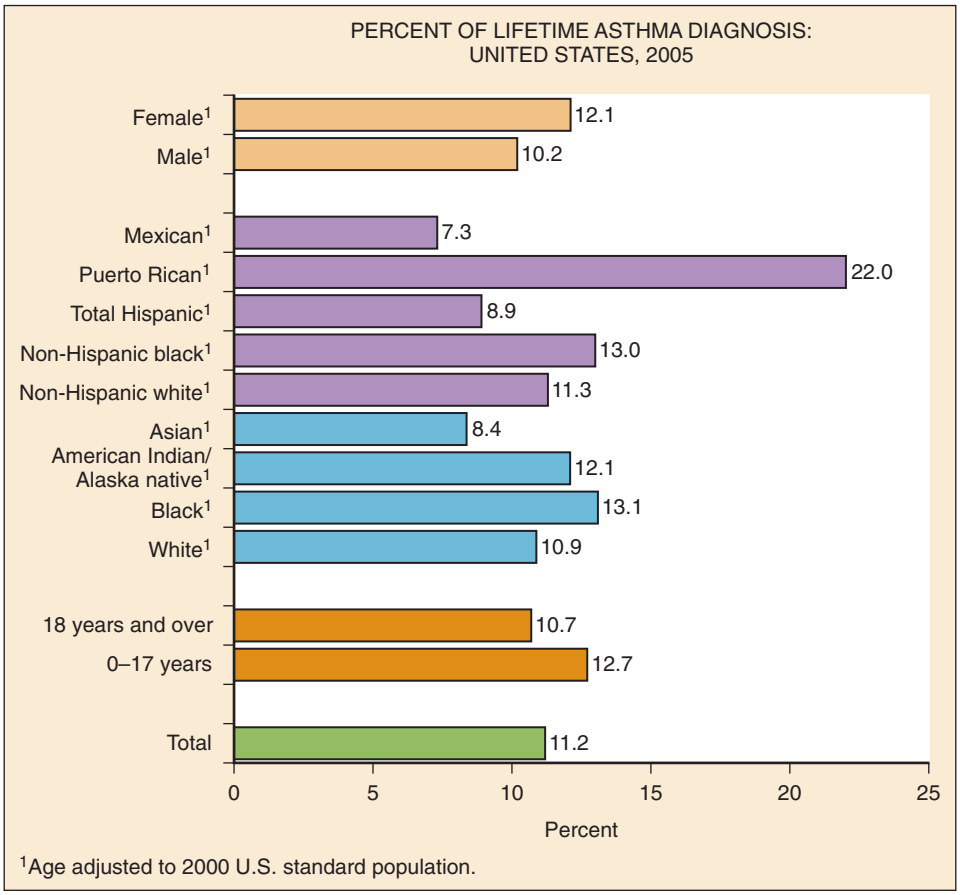


Figure 71-1. Percent of lifetime asthma diagnosis: United States, 2005. (From Figure 3 in National Center for Health Statistics: Asthma Prevalence, Health Care Use and Mortality: United States, 2003–2005. http://www.cdc.gov.nchs/products/pubs/pubd/hestats/ashtma03-05/fig3.png.)

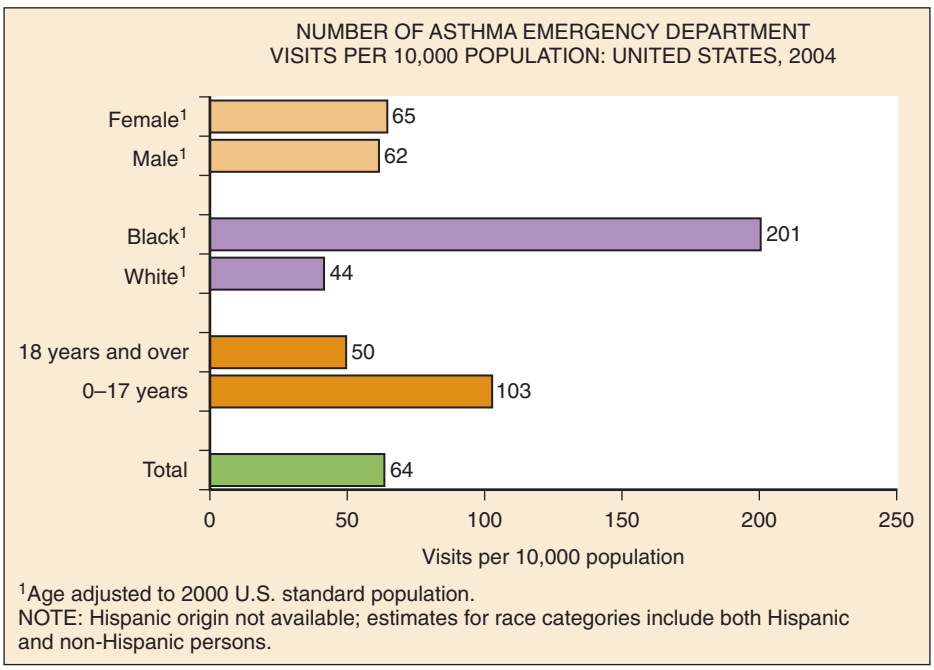


Figure 71-2. Number of asthma emergency department visits per 10,000 population: United States, 2004. (From Figure 5 in National Center for Health Statistics: Asthma Prevalence, Health Care Use and Mortality: United States, 2003–2005. http://www.cdc.gov.nchs/products/pubs/pubd/hestats/ashtma03-05/asthma03-05/fig5.png.)

indicating that poverty and lack of access to medical care may also be major determinants of asthma complications.

Factors that contribute to asthma morbidity and mortality include inadequate patient and physician assessment of an acute episode resulting in undertreatment, overuse of prescribed or over-the-counter medications leading to delays in seeking treatment, failure of physicians to consider previous hospitalizations or life-threatening episodes of asthma, and failure to initiate corticosteroid therapy early in the course of an exacerbation. Socioeconomic factors, environmental influences, and over-reliance on emergency facilities for all asthma care are also contributing factors. Initiatives to educate physicians and patients about asthma pathophysiology, monitoring, and therapy (e.g., National Asthma Education and Prevention Program [NAEPP], Global Initiative for Asthma) may be in part responsible for the moderation of asthma mortality rates.

PRINCIPLES OF DISEASE

Pathophysiology

A variety of airway alterations occur in asthma, but airway inflammation is the final common pathway limiting airflow. Bronchoconstriction occurs due to allergic or nonallergic stimuli. Allergens induce bronchoconstriction via release of mediators and metabolic products from inflammatory cells, but nonallergic mechanisms also trigger airway inflammation in exercise, aspirin-induced, and menstrual-related asthma. Compared with healthy individuals, patients with asthma show bronchial hyper-reactivity (hyper-responsiveness) in response to bronchoconstricting stimuli (e.g., methacholine). This hyper-responsiveness of the airways is characteristic of asthma and correlates with the severity of the disease and the need for treatment. Edema, inflammation, mucus production, and airway smooth muscle hypertrophy contribute to bronchoconstriction and hyper-reactivity and further airway obstruction and airflow limitation. Permanent structural airway changes (*airway remodeling*) may contribute to increased airway obstruction and hyper-responsiveness and decrease the response to therapy.[10] The interaction of these features determines the clinical manifestations and severity of asthma and significantly influences the response to therapy.

Evidence that inflammation is a component of asthma physiology was initially derived from autopsy findings in patients with fatal asthma. The airways revealed infiltration by neutrophils, eosinophils, and mast cells and the presence of subbasement membrane thickening, loss of epithelial cell integrity, goblet cell hyperplasia, and mucous plugs.[11] Subsequent antemortem bronchial biopsy findings in patients with even mild degrees of asthma also demonstrate inflammatory changes in the central and peripheral airways that correlate with disease severity.[12-14] Inflammatory and chemotactic cytokines produced by both resident airway and recruited inflammatory cells are identified in bronchoalveolar lavage washings and pulmonary secretions. Some cytokines initiate inflammatory responses by activating transcription factors that act on genes encoding for proteins that induce and perpetuate inflammation. Cytokines also induce expression of molecules that provide for the adhesion of inflammatory cells to the pulmonary vascular endothelium and allow migration of these cells through the vessel wall into the lamina propria, epithelium, and airway lumen.[11] Others participate in initiation, propagation, and amplification of the local inflammatory response.

Epidemiologic and clinical observations link immunoglobulin E (IgE) to the severity of asthma and the initial and sustained responses of the airways to allergens.[15,16] IgE synthesis is triggered[17,18] when inhaled allergens such as environmental

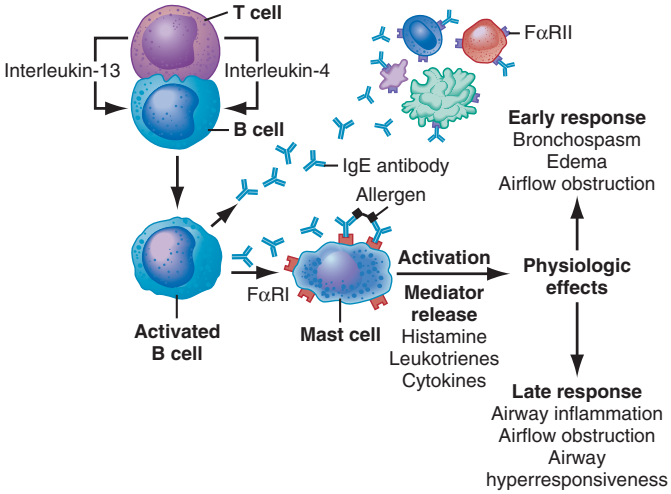


Figure 71-3. Cellular interactions involved in immunoglobulin E (IgE) and inflammatory reactions in asthma.

antigens (pollen, dander, mites), occupational antigens, and viruses encounter dendritic cells lining the airways.[19] Airway dendritic cells process the antigenic stimulus and migrate to local lymph nodes where antigen presentation to T and B lymphocytes occurs. The cytokines interleukin-4 (IL-4) and IL-13 induce differentiation of activated B lymphocytes that synthesize and release IgE in response to the antigenic stimulus (Fig. 71-3). IgE circulates briefly in the blood before binding to surface receptors on airway mast cells and peripheral blood basophils, lymphocytes, eosinophils, and macrophages. Further interaction of antigen with membrane-bound IgE activates and then releases preformed and generated mediators from these cells.

Mast cells reside in the mucosa and submucosa of the airways. Cross-linking of antigen and surface-bound IgE on the mast cells induces release of preformed mediators such as histamine and initiates the production of prostaglandins (PGs) and leukotrienes (LTs). Antigen-induced IgE cross-linking on mast cells also stimulates synthesis and subsequent release of other cytokines that induce further differentiation and proliferation of inflammatory cells, have chemoattractant properties, and increase adhesion of inflammatory cells to pulmonary vascular endothelial cells.[20] Thus, mast cells may contribute to both the acute and chronic inflammatory reactions occurring in the airways.

Release of preformed histamine from mast cell granules constricts bronchial smooth muscle and causes airway edema, resulting in wheezing and airflow obstruction. This reaction usually resolves within an hour and is referred to as the *early asthmatic response*. Similar clinical manifestations occur 4 to 6 hours later as a result of cytokines generated and released by mast cells and other local and recruited inflammatory cells. The airflow obstruction and bronchospasm may be prolonged and together are referred to as the *late asthmatic response*.

Eosinophils are major effector cells in asthma, and their presence is evidence of the allergic nature of this disease. Increased numbers of eosinophils are found in the airways of most but not all asthmatics.[21] They contain granules that release inflammatory mediators including major basic protein, cationic protein, and LTs. Major basic protein causes constriction of airway smooth muscle and desquamation of the airway epithelium. This effect exposes nerve endings, provides submucosal access for inflammatory cells and mediators, and negates epithelial cell regulation of the inflammatory process. Eosinophil cationic protein increases airway mucous produc-

tion and can cause histamine release from mast cells. LTs are potent bronchoconstrictors produced by eosinophils that are more potent than methacholine.[22] LTs also promote the secretion of thick viscid mucus, leading to airway plugging, and enhance airway vascular permeability, leading to airway edema. Eosinophil-produced ILs and granulocyte-macrophage colony-stimulating factor (GM-CSF) stimulate eosinophil proliferation and enhance pulmonary vascular endothelial cell adhesion, which locally amplifies the inflammatory process. Platelet-activating factor, superoxides, and free radicals produced by eosinophils also cause bronchospasm and bronchial tissue destruction.[23] Although eosinophils appear to be pivotal in airway allergic and inflammatory processes, the role of the eosinophil as the central effector cell in asthma is challenged by studies with anti-IL-5 treatment that significantly reduced sputum and blood eosinophilia but did not affect asthma control.[24]

Preformed mediator and cytokine release from other airway inflammatory cells following the triggering stimulus also contributes to bronchial smooth muscle spasm, edema, and mucus production. Extensive intercellular communication and widespread activation of the immune system occur with the lung and tracheobronchial tree as the target organ.[17] Ongoing synthesis and release of cytokines (e.g., IL-1 to IL-18, GM-CSF), PGs, and LTs (Fig. 71-4) are responsible for propagation and intensification of airway inflammation[11] and disruption of the airway epithelial border. The end result of persistent and self-reinforcing inflammation is airway smooth muscle stimulation and structural alterations evidenced by wheezing and airflow obstruction.

Airway epithelial cells are involved in asthma physiology. Inflammatory cells, mediators, and airway viruses can stimulate airway epithelium to produce inflammatory mediators or directly damage the epithelial barrier itself. Abnormal repair processes may further airway obstruction. Nitric oxide (NO) is produced by airway epithelial cells. It is a potent vasodilator and may reflect the presence of inflammation in asthma. Measurements of fractional exhaled nitric oxide (FENO) may prove useful for monitoring the response to asthma therapy.[25] Airway smooth muscle cells may be a contributor to airway dysfunction and obstruction as well as a target by producing proinflammatory mediators and responding to airway inflammation by proliferation, contraction, and hypertrophy.[1]

Airway remodeling is distinctive in chronic asthma and is likely due to the presence of repetitive or chronic airway inflammation. It consists of airway wall thickening, subepithelial fibrosis, mucous gland metaplasia, increases in airway smooth muscle, myofibroblast hyperplasia, and epithelial hypertrophy.[26] Basement membrane thickening may be protective by preventing inflammatory cells and proteins from entering the airway submucosa through a damaged epithelium; simultaneously, this process may be counterproductive by reducing the elasticity of the small airways. Airway remodeling may explain the resistance to therapy observed in patients with prolonged asthma histories and the decline in pulmonary function noted with age.[27,28] Finally, if asthma is improperly treated, airway remodeling induced by chronic inflammation may lead to the development of chronic irreversible airflow limitation and a shortened life expectancy.[29]

The clinical implications of the immune and inflammatory nature of the early and late asthmatic responses are crucial because therapy may be directed differently toward each phase. Mast cell stabilizers (e.g., beta$_2$-agonists) are more effective in the early asthmatic response but are of less use later in the course of an exacerbation. Anti-inflammatory therapy (e.g., corticosteroids, LT antagonists) is more effective in the late asthmatic response. Interference or inhibition of cytokine activities, suppression of chronic inflammation, and modulation of airway remodeling are potential therapeutic targets. Recognition of asthma phenotypes is assuming an increasing importance as different phenotypes (e.g., severe asthma) may have unique patterns of cytokine release and airway remodeling requiring specific therapies that are not useful in milder forms of asthma.

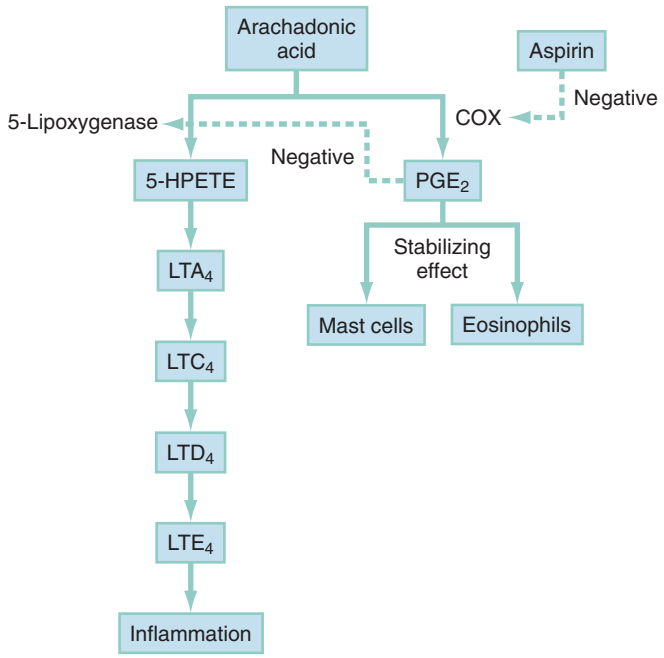


Figure 71-4. Mechanism of aspirin-exacerbated respiratory disease. Inhibition of COX (cyclooxygenase) decreases production of PGE_2 (prostaglandin E_2). PGE_2 has an inhibitory effect on leukotriene (LT) synthesis. 5-HPETE, 5-hydroperoxyeicosatetraenoic acid.

Miscellaneous Situations

Aspirin-exacerbated respiratory disease (AERD) was first described more than 100 years ago. The triad of aspirin sensitivity, asthma, and nasal polyps was described in 1922 and popularized in 1968. The prevalence of AERD is 21% in adult and 5% in childhood asthmatics.[30] It occurs more often in women. Nonsteroidal anti-inflammatory drugs (NSAIDs) also precipitate AERD. AERD is a common precipitant of life-threatening asthma—one survey notes that 25% of asthmatics requiring mechanical ventilation have AERD.[31]

Clinically, most patients with AERD develop symptoms in the third decade, frequently after a viral respiratory illness. Over several months, chronic nasal congestion, rhinorrhea, nasal polyps, and anosmia develop often followed by chronic pansinusitis. Bronchial asthma and sensitivity to aspirin (acetylsalicylic acid, ASA) then result. After ingestion of aspirin or a nonsteroidal drug, acute asthma symptoms occur within 3 hours, usually accompanied by profuse rhinorrhea, conjunctival injection, periorbital edema, and occasionally a scarlet flushing of the head and neck. Definitive diagnosis is made by provocation challenges. In most patients 30 to 150 mg of ASA (mean 60 mg) evokes respiratory reactions.[32]

The pathogenesis of AERD is detailed in Figure 71-4. ASA inhibits cyclooxygenase (COX),[33] of which two isoforms are identified. COX-1 produces PGs that are involved in normal physiologic maintenance of renal function, gastric mucosal integrity and hemostasis, and inflammatory states. COX-2 is not expressed in normal physiologic circumstances but pro-

duces PGs only in response to inflammatory stimuli. AERD occurs as a result of ASA inhibition of COX that decreases the production of PGE_2. The end result is inflammatory mediator release from mast cells and eosinophils, and an increase in LT production; some of which substances are potent bronchoconstrictors. Most patients with AERD benefit from anti-LT treatment. These agents block synthesis of LTs (e.g., zileuton) or block specific LT receptors (e.g., zafirlukast, montelukast). Desensitization with slowly increased doses of oral aspirin may be used when aspirin avoidance is not possible (e.g., cardiovascular disease).

COX-2 inhibitors have the advantage of inhibiting inflammation without renal, gastrointestinal, or hematologic side effects. AERD is not reported after administration of COX-2 inhibitors. These agents provide a potentially safe alternative for treatment of inflammatory conditions in patients with AERD.[34]

Exercise-induced asthma (EIA) has been recognized since the first Olympic games. It occurs in 5 to 20% of the general population, 30 to 70% of elite winter and summer endurance athletes, and in up to 90% of patients with persistent asthma.[35] Atopy is strongly associated with EIA, and up to 40% of patients with allergic rhinitis have EIA.[36] Although EIA was thought to be a distinct clinical manifestation of asthma, most asthmatic patients develop symptoms after a suitable exercise challenge, and EIA may be another reflection of chronic airway inflammation. Clinically, EIA is usually preceded by 3 to 8 minutes of exercise. Peak symptoms usually occur 8 to 15 minutes after exercise is complete and then begin to remit spontaneously; recovery occurs within 60 minutes.

The etiology of EIA remains unclear. In the "osmotic" hypothesis, airway cooling leads to mucosal drying and increased surface osmolality that causes mast cell degranulation and release of inflammatory mediators. The "thermal" hypothesis suggests that airway cooling during exercise followed by rapid rewarming after exercise causes airway vascular congestion and increased permeability, resulting in airway edema and obstruction. Another exercise-specific factor is autonomic deregulation associated with prolonged high-intensity physical training. The predominantly parasympathetic drive of athletes (evidenced by low heart rates) may also increase bronchomotor tone and increase the risk of EIA.[35]

Prophylaxis for EIA with warm-up and a short-acting inhaled $beta_2$-agonist is the therapy of choice. Pretreatment with cromolyn and LT antagonists is also effective. Breathing through the nose may allow warming and humidification of cool dry air during exercise. Long-acting $beta_2$-agonists are usually effective, but tachyphylaxis and loss of efficacy may occur if these agents are used regularly.[37]

Menstruation-associated asthma affects up to 40% of asthmatic women yet receives little emphasis in asthma treatment guidelines.[1] The ratio of female-to-male asthma prevalence increases dramatically after puberty, and health care for asthma increases in the perimenstrual phase. Perimenstrual reductions in peak expiratory flow rates of 35 to 80% are reported. Fluctuations in estrogen and progesterone levels are postulated as causal factors.[38] Estradiol inhibits eosinophil degranulation and suppresses LT activity—estrogen withdrawal in the luteal phase may enhance these actions. In animals, estrogen withdrawal down-regulates beta-receptors and increases cholinergic-induced bronchoconstriction. Progesterone may also have bronchodilator and anti-inflammatory activity, and the rapid decline in progesterone levels prior to menstruation may contribute to increased bronchospasm. Beneficial therapies for perimenstrual asthma include LT antagonists, long-acting beta-agonists, estradiol, progesterone, and gonadotropin-releasing hormone analogues.[39]

Psychological factors may precipitate bronchospasm. Panic disorder and generalized anxiety disorders are more common in asthmatics than the general population. An association between asthma and depression is noted in children. The mechanisms of bronchospasm associated with psychological factors may be related to autonomic nervous system activation or hyperventilation. Compliance may be adversely affected by psychological factors. Relaxation as a therapy for asthma has inconsistent effects[40]; hypnosis may be beneficial.[41] The actual influence of psychological factors in the induction or continuation of an episode of asthma is unknown but probably varies from patient to patient and episode to episode.

Genetics and Asthma

It is likely that asthma is not a single disease but a syndrome with various phenotypes. Clinicians have long recognized various asthma phenotypes (e.g., environmental, occupational, severe asthma), and researchers suspect that different pathophysiologic mechanisms may be responsible for the various manifestations of this disease. Since no biomarker exists to identify the various asthma phenotypes, categorization based on clinical characteristics (e.g., age at onset, treatment resistance), triggers (e.g., environmental/occupational allergens, ASA-induced, exercise-induced), and inflammatory characteristics (e.g., eosinophilic, neutrophilic) is suggested.[42] Understanding that different phenotypes may have different biologic alterations as their basis may enhance our understanding and treatment of these groups. Overlap may occur among the phenotypes, but it is hoped that recognition of various asthma phenotypes can enhance biomarker development, improve genetic assessment, and focus therapies for these distinct groups.

Pathology

Airway secretions evaluated by bronchoalveolar lavage and sputum analysis in patients with mild to moderate asthma reveal increased numbers of mast cells, eosinophils, lymphocytes, and airway epithelial cells. Their presence supports the concept of chronic inflammation in the airways. Endobronchial biopsies may be normal, show only mild histologic changes between attacks, or reveal chronic alterations. Microscopy demonstrates submucosal infiltration with eosinophils and other inflammatory cells along with viscous mucous plugs in the bronchi and bronchioles, increased numbers of goblet cells, and mucous gland hyperplasia. Airway epithelial cells may be damaged or denuded. Immunohistochemistry demonstrates disruption of the tight junctions in the columnar cells,[43] allowing allergens and infectious agents to penetrate into the submucosal area, thereby facilitating toxic, immune, and inflammatory responses. Airway remodeling is evidenced by squamous metaplasia, thickening of the basement membrane due to collagen and fibronectin deposition, and smooth muscle thickening.[44] Neutrophils are the dominant cell type in the airways of some asthmatics,[45] and noneosinophilic asthma may represent a distinct asthma phenotype that is associated with a reduced responsiveness to corticosteroid therapy.[46]

In contrast to patients with mild to moderate asthma, patients with acute severe asthma have inflammatory cells in the airways that consist of more neutrophils than eosinophils and elevated levels of IL-8 responsible for neutrophil activation.[47] Patients with severe asthma and no evidence of inflammation on endobronchial biopsy have been identified, which suggests a pathologic mechanism that may explain resistance to conventional asthma therapies.[48]

Necropsies of patients with status asthmaticus reveal grossly inflated lungs that may fail to collapse on opening of the pleural cavities. Histologic examination reveals luminal plugs consisting of inflammatory cells, desquamated epithelial cells, and mucus. Marked thickening of the airway basement membrane, submucosal inflammatory cells, increased deposition of connective tissue, mucous gland hyperplasia, and hypertrophy of airway smooth muscle are also observed. Bronchiectasis is described in 15 to 20% of asthmatics.[44] Reports of patients experiencing sudden-onset fatal asthma demonstrate less mucus in the airway lumens, suggesting that terminal events in this group may be dominated by bronchoconstriction without excessive luminal plugging; however, the putative roles of bronchoconstriction versus mucous plugging in sudden-onset fatal asthma are unclear.[49,50]

CLINICAL FEATURES

National and International Guidelines for the Diagnosis and Management of Asthma

In response to the increasing prevalence, morbidity, and mortality of asthma in the industrialized world, many countries publish guidelines that improve detection and treatment. Some of these, including the U.S. National Asthma Education and Prevention Program (National Institutes of Health) Expert Panel Report 3 (EPR-3), devote specific portions to the management of acute exacerbations of asthma.[1,51] The EPR-3 is further condensed as a practical summary for emergency physicians[52] but has not yet been independently critically analyzed by our specialty, as with the previous EPR-2.[53] The EPR-3 recommendations are graded from levels A through D based on the strength of the scientific evidence. These national asthma guidelines provide a common set of recommendations for management.[54] The American Heart Association has guidelines regarding the management of near-fatal asthma, filling a void in the EPR-3 regarding the management of the sickest acute asthmatics.[55]

Symptoms

Most patients with acute asthma have a constellation of symptoms consisting of cough, dyspnea, and wheezing. Cough often begins early in the attack, may be the sole manifestation of the disease in cough-variant asthma and elder patients, can be associated with sputum production, and is probably the result of subepithelial vagal stimulation. Nocturnal worsening is common, with most patients reporting cough or wheeze at least once per week. Nighttime mortality is higher than in the general population.

Although increased airway resistance, diminished flow rates, and increased bronchial hyperactivity are contributing factors, asthmatic patients who present nocturnally to the ED have disease severity similar to that of other asthmatics. Up to 40% of asthmatic women suffer from premenstrual worsening of symptoms, which peak 2 to 3 days before menses and are associated with more severe disease.[56] ED visits increase during the preovulatory and perimenstrual intervals.

There are interindividual differences in the dyspnea perceived by asthmatic subjects for the same level of airway narrowing. This difference results in poor correlation of symptoms with airway obstruction as determined by pulmonary function testing (PFT), both chronically and on presentation to the ED. Patients with a blunted perception of dyspnea (the "poor perceivers") have more ED visits, hospitalizations, and near-fatal and fatal asthma attacks.[57]

Wheezing that develops reflects air movement velocity and turbulence, and its intensity varies according to the radius of the bronchi. With severe airway obstruction, it decreases or vanishes because air movement velocity is insufficient to produce sound.

Many asthmatics report symptoms of gastroesophageal reflux that may cause airway narrowing through a vagally mediated pathway or microaspiration. Proton pump inhibitor therapy decreases asthma symptoms in these patients. Approximately 80% of patients with asthma have symptoms of rhinitis. Approximately 5 to 15% of patients with perennial rhinitis have asthma, and control of sinonasal inflammation can lead to asthma improvement. Overweight (BMI = 25 kg/m^2) asthmatics have higher admission rates and risk of complications, possibly secondary to a difference in the perception of dyspnea or in response to asthma controller agents.[58,59]

Lastly, as asthma can appear at any age, including the ninth decade, wheezing and dyspnea may be misascribed by both patients and physicians to heart failure, bronchitis, chronic obstructive pulmonary disease (COPD), occupational lung disease, or poor exercise capacity.

Historical Components

Slow-onset asthma with progressive deterioration over a period of at least 6 hours (usually days) occurs in over 80% of cases. This type has a female predominance, is triggered by upper respiratory tract infections, and has an airflow inflammation mechanism that results in a slower response to treatment. Sudden-onset asthma with rapid deterioration in under 6 hours occurs in less than 20%. This type has a male predominance, is triggered by respiratory allergens, exercise and psychosocial stress, and has a bronchospastic etiology resulting in more severe airway obstruction with a faster response to therapy.[60]

Risk factors for death from asthma are important to determine and are listed in Box 71-1.[1,61,62] In urban areas, heroin and cocaine abuse are commonly associated with the need for intubation in the ED.[63]

BOX 71-1 RISK FACTORS FOR DEATH FROM ASTHMA

Asthma History
- Previous severe exacerbation (intubation or ICU admission for asthma)
- Two or more hospitalizations for asthma in the past year
- Three or more ED visits for asthma in the past year
- Hospitalization or an ED visit for asthma in the past month
- Use of >2 MDI short-acting beta$_2$-agonist canisters per month
- Current use of or recent withdrawal from systemic corticosteroids
- Difficulty perceiving asthma symptoms or severity of exacerbations

Social History
- Low socioeconomic status or inner-city residence
- Serious psychosocial problems
- Illicit drug use, especially inhaled cocaine and heroin

Comorbidities
- Cardiovascular disease
- Other chronic lung disease
- Chronic psychiatric disease

ED, emergency department; ICU, intensive care unit; MDI, metered-dose inhaler.

The brief history pertinent to the current exacerbation should include onset and possible triggers, severity of symptoms especially as compared with previous exacerbations, and other comorbidities (especially those that may be worsened by systemic corticosteroids such as diabetes, peptic ulcer, hypertension, and psychosis). In addition, all current asthma medications should be noted, including times and amounts recently used, and any potential asthma exacerbators such as aspirin or NSAIDs, beta-blockers (including topical agents used for glaucoma), and angiotensin-converting enzyme inhibitors.

Physical Assessment

Those who suffer from mild acute asthma usually speak in sentences, moderate in phrases, and severe in words. Although alterations in mentation or consciousness indicate severe asthma, restlessness and agitation do not reliably indicate hypoxia or hypercapnia. Patients who sit upright have severe airway obstruction; cyanosis is uncommon because of the left shift of the oxyhemoglobin dissociation curve produced by respiratory alkalosis. Diaphoresis can be seen secondary to the work of breathing, but if profound it is usually accompanied by a decreasing level of agitation and interaction with caregivers and may be preterminal.

Tachypnea and tachycardia greater than 120 beats/min are associated with severe obstruction, but a lower rate does not rule out severe asthma. The respiratory rate correlates poorly with PFT and indicates severe obstruction only if it is more than 40 breaths/min.[64]

A pulsus paradoxus or inspiratory fall in systolic blood pressure greater than 10 mm Hg usually signifies severe disease, but its absence does not exclude it, and it rarely is contributory when taken in the context of the patient's overall evaluation. Its use predated common availability of bedside spirometry, which is a more accurate and reliable test. When pulsus paradoxus is present, it may disappear with minimal improvement in airflow through larger airways.[64] Similarly, use of accessory muscles of respiration (sternocleidomastoid and scalenus muscles) is not prognostic.

Wheezing does not designate the presence, severity, or duration of asthma. It correlates poorly with the degree of functional derangement and may be absent when maximal effort produces minimal airflow. Physical examination may help to identify such complications of asthma as pneumonia, pneumothorax, or pneumomediastinum that may arise atypically as subcutaneus emphysema or simulate upper airway obstruction.

DIAGNOSTIC STRATEGIES

Pulmonary Function Studies

Because the severity of airflow obstruction cannot be accurately assessed from symptoms and physical exam alone,[65] physicians tend to underestimate the degree of airway obstruction in acute asthma, particularly on initial assessment. Therefore, routine PFTs should be part of ED assessment and monitoring. The forced expiratory volume in 1 second from maximal inspiration (FEV_1) or the peak expiratory flow rate (PEFR) in liters per second starting with fully inflated lungs and sustained for at least 10 msec may be used. Both measurements require the patient's cooperation for maximal effort and are effort-dependent. Whenever possible, the best of three consecutive values should be recorded. Any patient not able to perform a pulmonary function study should be considered to have severe airway obstruction.

Most asthmatic assessments in the ED use single-patient-use portable peak flow meters because PEFR is easier to measure. There is wide limit of agreement between different devices, so a single device should be used to assess then reassess an individual patient, and different portable meters should not be used interchangeably.[66] Lastly, although generally similar, the FEV_1 and PEFR measurements do not appear to be interchangeable in assessing acute airway obstruction, which is not addressed in all management guidelines.[67]

Although absolute PFT measurements can be used,[68] percentage of predicted performance (% predicted) values are preferable because they account for the individual's age (now to age 85), sex, and height. Ideally, the percentage of the patient's personal best effort individualizes the assessment and treatment.

Arterial Blood Gas Analysis

Using pulse oximetry, changes in equilibration of oxygen saturation with supplemental oxygen occur in 3 to 4 minutes during an acute asthma attack. With initial onset of an asthma attack, stimulated hyperventilation leads to a modest fall in the partial pressure of carbon dioxide in arterial blood ($Paco_2$). As airway obstruction increases, the $Paco_2$ normalizes (PFT 15–25% predicted) and then increases (PFT < 15% predicted) with worsening hypoxemia. Because neither pretreatment nor post-treatment arterial blood gases (ABGs) correlate with PFTs or predict clinical outcome, ABG determination is rarely clinically useful in acute asthma exacerbations unless oxygen saturation cannot be obtained reliably using pulse oximetry. ABG determination is of no value in determining the need for tracheal intubation.

ABG sampling, if used, should be limited to a subset of patients with predicted PFTs of less than 30%, whose clinical course is perplexing and for whom capnography is not available. Occasionally, despite PFTs improving with bronchodilator therapy, some patients have a transient fall in the Pao_2 secondary to pulmonary vasodilatation and worsening ventilation-perfusion mismatch.[69] The assessment of ventilation may be simplified since there is a high concordance between end-tidal partial pressure of CO_2 (Pco_2) measured by capnography and the $Paco_2$ obtained with ABG measurements.[70]

Other Blood Testing

Leukocytosis is common in patients with acute asthma exacerbation, but is not of discriminatory value in determining whether patients with fever or purulent sputum have acute superimposed pulmonary infection. Of note, corticosteroid and epinephrine therapy demarginate polymorphonuclear leukocytes after 1 to 2 hours, and patients on chronic steroid therapy may have normal or significantly elevated WBC counts.

Serum electrolytes are not primarily altered unless the patient is on corticosteroids or diuretics or has cardiovascular disease and is receiving aggressive $beta_2$-agonist therapy. Frequent albuterol treatments can cause transient hypokalemia, hypomagnesemia, and hypophosphatemia, but this is rarely of clinical significance. The few remaining patients who are receiving chronic theophylline therapy should always have serum levels measured to assess for possible toxicity and for appropriate further dosing if deemed necessary.

In the older asthmatic with cardiovascular comorbidities who presents with wheezing, measure the B-type natriuretic peptide (BNP) level to determine the contribution of unrecognized congestive heart failure to the clinical picture.

Radiology Studies

A chest radiograph is of little value in most acute asthma exacerbations, and its use should be restricted to patients thought to have a complicating cardiopulmonary process such as pneumonia, pneumothorax, pneumomediastinum, or congestive heart failure. Also, patients who do not respond to optimal therapy and require hospital admission have a higher likelihood of radiographically identifiable, unsuspected, clinically significant pulmonary complications of asthma (15% of cases).[71]

Electrocardiogram and Cardiac Monitoring

The electrocardiogram (ECG) need not be routinely obtained, except in patients older than 40, those with a separate complaint (e.g., chest pain) that would prompt an ECG, or those with a history of significant cardiovascular disease, in whom the asthma attack may be a form of physiologic stress test. In patients with severe asthma, the ECG may show a right ventricular strain pattern that reverses with improvement in airflow. Older patients, especially those with coexistent heart disease or with severe exacerbation, may require continuous cardiac monitoring to detect dysrhythmias. All patients with severe hypoxemia, and those for whom intubation is contemplated, should have continuous cardiac monitoring.

Future Monitoring Strategies

Noninvasive monitoring of bronchial inflammation may customize the ED assessment of acute asthma. This may include measurement of biologic biomarkers such as cytokine profiles in the blood, evaluation of LTE_4 in the urine, and the monitoring of exhaled pentane, hydrogen peroxide, nitric oxide, or carbon monoxide levels. Of these measurements, exhaled nitric oxide shows the most promise in chronic asthma management[72] but provides little aid in assessing the severity of acute exacerbations.[73]

Assessment Summary

The severity of airflow obstruction cannot be accurately judged by patients' symptoms, physical examination, and laboratory tests. Serial measurements of airflow obstruction (FEV_1 or PEFR) are key components of disease assessment and response to therapy. A more detailed analysis between commonly measured variables and patients with severe asthma ($FEV_1 < 1$ L) is shown in Table 71-1.

Table 71-1 Objective Findings in Asthma Assessment

FACTOR	SEVERE ASTHMA ($FEV_1 < 1.0$ L)
Pulse rate (beats/min)	≥120, but may be less with equally severe asthma
Respiratory rate (breaths/min)	≥40, but most are >20, therefore nondiscriminating
Pulsus paradoxus (mm Hg)	≥10, but may be absent with equally severe asthma in 50% of cases
Pulse rate ≥120, respiratory rate ≥20, pulsus paradoxus ≥10	If all three abnormal, 90% with severe asthma, but only 40% with $FEV_1 < 1.0$ L have all three abnormal
Use of accessory muscles of respiration	If present, may indicate severe asthma; if absent, may have equally severe asthma in 50% of cases
ABG analysis (mm Hg)	$Pa_{O_2} \leq 60$ or $Pa_{CO_2} \geq 42$ indicates severe asthma; all other values difficult to interpret unless PEFR or FEV_1 known
Pulmonary function studies	PEFR and FEV_1 measure directly the degree of airflow obstruction; most useful in assessing severity and guiding treatment decisions

ABG, arterial blood gas; FEV_1, forced expiratory volume in 1 second; Pa_{CO_2}, partial pressure of CO_2 in arterial blood; PEFR, peak expiratory flow rate.

DIFFERENTIAL CONSIDERATIONS

See Box 71-2.

BOX 71-2 The Differential Diagnosis of Asthma

Cardiac Conditions
Valvular heart disease
Congestive heart failure

COPD Exacerbation
Pulmonary Infection
Pneumonia
Allergic bronchopulmonary aspergillosis
Löffler's syndrome
Chronic eosinophilic pneumonia

Upper Airway Obstruction
Laryngeal edema
Laryngeal neoplasm
Foreign body
Vocal cord dysfunction

Endobronchial Disease
Neoplasm
Foreign body
Bronchial stenosis

Pulmonary Embolus

Carcinoid Tumor

Allergic/Anaphylactic Reaction

Miscellaneous Conditions
GERD
Noncardiogenic pulmonary edema
Addison's disease
Invasive worm infection

COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease.

MANAGEMENT OF ACUTE EXACERBATIONS

Home and First-Responder Strategies

Patients should be educated to monitor their symptoms, signs, and PEFR to recognize early deterioration and should be provided with a written action plan in the event of an exacerbation. Early therapy can prevent progression to severe attacks. Home management includes increased use of inhaled $beta_2$-agonists, early administration of systemic corticosteroids (not simply doubling the dose of current inhaled corticosteroids), and specific instructions on when and how to seek emergency care.[1] Ideally, emergency medical service providers should

Table 71-2 Initial Severity Assessments and Therapies in the Emergency Department

	MILD TO MODERATE	SEVERE
FEV_1 or PEFR (% predicted/personal best)	≥40%	Unable or <40%
Oxygen therapy	Maintain Sao_2≥90%	Maintain Sao_2 ≥ 90%
Nebulized albuterol solution		
Levalbuterol (optimal)	1.25 mg q 20 min for up to 3 doses	1.25 mg q 20 min × 3 doses Continuous for 1 hr if severe
Racemic albuterol	2.5 mg q 20 min for up to 3 doses	5.0 mg q 20 min × 3 doses Continuous for 1 hr if severe
Albuterol MDI with VHC		
Levalbuterol (45 µg/puff) (optimal)	6–12 puffs q 20 min for up to 3 doses WS	Same × 3 doses (if able to do), WS
Racemic albuterol (90 µg/puff)	6–12 puffs q 20 min for up to 3 doses WS	Same × 3 doses (if able to do), WS
Ipratropium therapy		
Nebulized solution	If previous response (same dose as for severe)	0.5 mg q 20 min × 3 doses (may mix with albuterol solution)
MDI (18 µg/puff) with VHC	If previous response (same dose as for severe)	8 puffs q 20 min x 3 doses
Systemic corticosteroids		
Oral (preferred)	40–80 mg/day prednisone/prednisolone if no immediate response to albuterol	40–80 mg/day prednisone/prednisolone
IV (unable to take PO or absorb)	40–80 mg/day methylprednisolone	40–80 mg/day methylprednisolone
IV magnesium sulfate	Not indicated	2–3 g over 20 min (or at rates of up to 1 g/min) if FEV_1 ≤ 25% predicted

FEV_1, forced expiratory volume in 1 second; MDI, metered-dose inhaler; PEFR, peak expiratory flow rate; Sao_2, oxygen saturation in arterial blood: VHC, valved holding chamber; WS, with supervision.

provide albuterol inhalation therapy by protocol during transport to the hospital. Basic emergency medical technicians can be authorized to administer the patient's own inhaler.[74,75]

Management of Acute Asthma in the Emergency Department

The goal in the ED is to reverse the acute airflow obstruction safely, and the rapidity of this reversal is directly predictive of the outcome of the attack.[76] Effective bronchodilation often results in a decreased need for hospitalization with significant cost savings.[77] As outlined in Table 71-2, the severity of attack as measured by PFTs determines the aggressiveness of the therapy.

Oxygen Administration

All patients should receive supplemental oxygen to maintain an arterial oxygen saturation above 90% (>95% in pregnant women and those with coexistent heart disease) rather than using predetermined concentrations or flow rates. Serial oxygen saturation monitoring is essential during the acute phase. Humidification of the inspired air-oxygen mixture is not essential, although studies suggest that active airway rehydration should be revisited.[78]

Adrenergic Medication

Controversies in Use. Epidemiologic studies report an association between death and near death from asthma and the use of inhaled $beta_2$-agonists, with use of more than one canister per month increasing this risk that doubles for each additional monthly canister used.[79] This relationship does not imply causality but may be a marker for more severe disease, particularly if anti-inflammatory treatment is underused. Guidelines for chronic use of inhaled $beta_2$-agonists, however, recommend limited daily use in a rescue-only mode.[1]

One form of albuterol is a racemic mixture of equal amounts of R and S isomers. Data from animal and human studies suggest that the S isomer, which contributes no bronchodilator activity, is proinflammatory, spasmogenic, and induces bronchial hyper-reactivity. This possibly explains the adverse effects of increased morbidity and mortality rates associated with regular or excessive use of this drug.[80]

Some investigations of the beta-adrenergic receptor polymorphisms show differential responsiveness to inhaled albuterol, a possible explanation for the widely varying responses seen clinically when treating patients with acute disease.[81]

Short-Acting Inhaled $Beta_2$-Agonist Choice and Dosing Schedule. Racemic albuterol has been the main $beta_2$-agonist used in the ED for over 30 years. It is more $beta_2$-selective, longer acting, and has fewer side effects than other previously available drugs such as metaproterenol or isoetharine.

Levalbuterol, the R isomer of racemic albuterol, is commercially available as a preservative-free nebulizer solution (unit doses of 0.31, 0.63, or 1.25 mg) for prevention and treatment of bronchospasm. In chronic asthma, levalbuterol provides a better therapeutic index than the standard dose of racemic albuterol, further fueling the debate on the potential adverse effects of the S isomer of beta-agonists.[82] Clinical studies in acute disease report that levalbuterol on a milligram for milligram basis is a better bronchodilator than similar amounts of *R*-albuterol delivered with the S isomer in the racemic mixture.[83-85] This reinforces the notion that the S isomer has a negative rather than neutral effect.

The amount and frequency of delivery of levalbuterol and racemic albuterol depend on the initial severity and response to therapy, as shown in Table 71-2 and Table 71-3. Patients with more severe obstruction with a poor response to initial therapy should receive higher dosing schedules and possible continuous administration.[86] When patients are stable but require nonintensive care unit (ICU) admission, it may be possible to dose nebulized levalbuterol at 1.25 mg every 8

Table 71-3 Response after 1 Hour of Initial Treatment

	MODERATE EXACERBATION	SEVERE EXACERBATION
FEV_1 or PEFR (% predicted)	40–69%	<40%
Oxygen therapy	Unnecessary	Maintain Sao_2 ≥90%
Albuterol therapy		
Levalbuterol (optimal)	Reassess as may need < than with racemic dosing	Reassess as may need < than with racemic dosing
Racemic albuterol	Q 1–3 hr, admit decision in <4 hr	Q 1 hr or continuous
Ipratropium therapy	Unnecessary	Q 1 hr or continuous
Corticosteroids	Every 6–8 hr	Every 6–8 hr

FEV_1, forced expiratory volume in 1 second; PEFR, peak expiratory flow rate; Sao_2, oxygen saturation in arterial blood.

hours as opposed to racemic albuterol at 2.5 mg every 4 to 6 hours.[87]

Nebulizer versus Metered-Dose Inhaler and Valved Holding Chamber. A metered-dose inhaler (MDI) plus a valved holding chamber, used often and frequently (see Table 71-2), provides similar bronchodilation and side effects, even in severe asthma, when compared with wet nebulization.[88] This therapy requires more supervision because some patients have difficulty firing the canister before inhalation, breathing slowly, and holding their breath for 5 seconds, which may explain the infrequent use of canisters in the ED.[89,90] Wet nebulization by mouthpiece or mask requires no coordination and minimal cooperation and is less expensive.[91]

Intravenous Use of Adrenergic Agonists. Most international asthma guidelines, with the exception of those in the United States, recommend the use of intravenous (IV) beta-agonists for severe nonresponsive acute asthma. IV albuterol (not available in the United States) is given as a loading dose of 4 µg/kg for 2 to 5 minutes followed by an infusion of 0.1 to 0.2 µg/kg/min, with close cardiopulmonary monitoring.[92]

Some reviews conclude that evidence is lacking to support the use of IV beta-agonists in ED patients with severe acute asthma because the potential risks are warranted only when inhaled therapy is not feasible.[1,92] Epinephrine is used cautiously in patients older than 40 years of age or those with suspected cardiovascular disease, because it might provoke myocardial ischemia. Epinephrine IV titrated to effect (average 1.5 µg/min with a range of 0.5–13.3 µg/min) is associated with a low rate of major (3.6% of cases) and moderate or minor adverse events.[93]

Subcutaneous Adrenergic Agents. Subcutaneous use of adrenergic agents does not have an advantage over aerosol delivery. They may be considered in patients who cannot adequately inhale albuterol or who experience severe bronchospasm.

Epinephrine has been a mainstay for almost 100 years. It has both alpha and beta effects and can produce tachycardia, hypertension, dysrhythmias, and vasoconstriction, especially in older asthmatics with heart disease. Given the potential for increased side effects, it can be given subcutaneously (1:1000 solution 0.2 to 0.5 mL every 20 to 30 minutes as needed for three doses).

Terbutaline is a longer-acting $beta_2$-agonist with bronchodilating properties equivalent to those of epinephrine in acute asthma. It can cause skeletal muscle tremor and tachycardia. A 0.25-mg dose can be given subcutaneously every 20 minutes for three doses.

Long-Acting $Beta_2$-Agonists and Acute Disease. Salmeterol is a long-acting (12 hours) $beta_2$-agonist that is an effective additional medication for management of daytime and nocturnal symptoms that are not adequately controlled by regular and adequate doses of effective controller medications such as inhaled steroids. It has an onset of action of 20 minutes and thus is not indicated for the treatment of acute attacks. Regular use of this drug without concomitant use of inhaled steroids results in greater asthma-related deaths, resulting in a black box warning on the package insert. The controversies regarding regular use of short-acting beta-agonists extend to the long-acting classes.

Racemic formoterol dry powder and solution and single-isomer arformoterol are other long-acting $beta_2$-agonists that have an onset of action within minutes (similar to albuterol) and maximal effect within 2 hours. These drugs could evolve as acute rescue medications with extended length of action (12 hours) and similar safety profiles.[94,95] Patients receiving chronic long-acting beta-agonists but with acute asthma attacks are treated in the same way as all other asthmatics.

Corticosteroids

Corticosteroids have been used to treat asthma for approximately 50 years, and there is general agreement about their effectiveness. Their main action in the airways is inhibition of recruitment of inflammatory cells and inhibition of release of proinflammatory mediators and cytokines from activated inflammatory and epithelial cells. Corticosteroids activate cytoplasmic glucocorticoid receptors to regulate directly or indirectly the transcription of certain target genes resulting in the synthesis of new proteins.

Despite the long history of corticosteroid use, the resolution of fundamental acute care issues remains uncertain. These include the types and quantities required to induce a rapid remission, the time needed for drug action, the route of administration, the existence of dose-response effects, and the determination of which patient populations respond to this therapy.[96]

Systemic Corticosteroids in the Emergency Department. These medications should be given promptly to all patients with moderate to severe attacks or those experiencing an incomplete response to initial beta-agonist therapy. In addition, early systemic corticosteroids should be considered for patients who are taking oral or inhaled corticosteroids, have relapsed after a recent exacerbation, or have prolonged symptoms. Steroid effects begin within hours (not minutes) in acute asthma and increase to peak over 24 hours. Use of systemic steroids speeds the resolution of airflow obstruction, reduces the rate of relapse and may decrease admissions in severe, but not in mild to moderate attacks.[1,96] The PEFR may improve within 2 hours of steroid therapy in those not responding to initial albuterol inhalation.[97]

Many studies have clearly demonstrated that oral corticosteroids are as beneficial as IV corticosteroids in the ED management of an acute asthma exacerbation. Initial oral dosing is usually 60 mg of prednisone. If IV methylprednisolone is used, the dose is 40 to 80 mg/day in one or two divided doses until the patient can be switched to oral therapy, or PEFR reaches 70% of predicted or personal best.

Continuing therapy with oral prednisone or prednisolone is given in an adult dose of 40 to 80 mg/day, usually as a single dose. No study demonstrates the superiority of IV corticosteroids over oral preparations. Oral steroid therapy is preferred unless the patient is very ill, is unable to swallow or is vomit-

ing, or is thought to have impaired gastrointestinal transit or absorption.

Side effects of short-term (hours or days) steroid use include reversible increases in glucose (important in diabetics) and decreases in potassium, fluid retention with weight gain, mood alterations including rare psychosis, hypertension, peptic ulcers, aseptic necrosis of the femur, and rare allergic reactions.

Inhaled Corticosteroids in the Emergency Department. Using inhaled corticosteroids (ICS), either alone or in addition to systemic steroids, to treat acute asthma has the potential benefits of reducing systemic side effects, directly delivering medication to the airway, and reducing airway reactivity and edema more effectively. Patients treated with ICS are less likely to be admitted whether they received systemic steroids or not, and no increased cough or bronchospasm is seen with their use.[98,99] Patients treated with these agents have early improvement in outcomes (<3 hours) because of their topical effects. High doses of ICS given over hours may be necessary for them to be effective.[100] The optimal agents, delivery system, and dosing regimens, however, need to be determined, as well as whether these agents can replace systemic steroids in any patients.

Corticosteroids and Discharged Patients. Discharged patients who have received systemic corticosteroids in the ED should continue oral outpatient "burst" therapy to control disease and prevent relapse. Any need for additional steroids should be determined at the patient's follow-up outpatient visit. An acceptable regimen is 40 to 60 mg of prednisone (or equivalent) in single daily dose for a total of 5 to 10 days. Dose tapering to prevent asthma rebound or out of concern for adrenal suppression is unnecessary[101] unless the patient was already receiving systemic steroids or a prolonged course of therapy (more than 2 weeks) is deemed necessary. An alternative approach, if compliance may be an issue, is to give an equally efficacious single depot dose of triamcinolone diacetate (40 mg) or methylprednisolone (160 mg) before ED discharge.[102,103]

Patients who present to the ED for acute exacerbations of asthma may be taking insufficient amounts of chronic controller medications based on their symptoms and excessive use of beta$_2$-agonists.[1] If the patient is not taking oral or ICS, the addition of inhaled high-dose budesonide (400 µg, two puffs twice per day) to the patient's regular asthma medications on ED discharge improves symptoms and decreases relapse by approximately 50% in the ensuing 3 weeks.[104] Thus patients with a history compatible with persistent asthma but not taking any ICS should be given a prescription (1–2 month supply). Suggested regimens include budesonide dry powder inhaler (DPI) 1200 µg, flunisolide MDI 2000 µg, fluticasone DPI 500 µg, mometasone DPI 400 µg, or triamcinolone MDI 1500 µg in daily divided doses (twice per day) in addition to their prednisone. Patients already taking ICS therapy should continue it. Patients should use a spacer device if using an MDI and be reminded to rinse their mouths after steroid inhalation to decrease the side effects of dysphonia and oral or esophageal candidiasis.

Corticosteroid-Resistant Asthma. Chronic asthma is considered a steroid-responsive disease. A small proportion of asthmatics do not respond to even high doses of oral and inhaled glucocorticoids, which complicates management. The mechanism of this steroid resistance may be related to abnormalities in the glucocorticoid receptor number or binding properties. These patients are usually receiving alternative therapies such as cyclosporine, methotrexate, troleandomycin, hydroxychloroquine, azathioprine, gold, IV immune globulin, or (if with severe allergic asthma) maintenance anti-IgE recombinant humanized monoclonal antibody (omalizumab).

Anticholinergic Agents

The atropine-containing botanicals *Datura stramonium* (stinkweed or thorn apple) and *Atropa belladonna* (deadly nightshade) were smoked centuries ago in India for treatment of asthma. In the 19th century smoking leaves of the *Datura* species was common in England, and by the middle of the last century Salter's treatise on asthma listed *D. stramonium* as one of asthma's truly effective remedies. Atropine-containing cigarettes or powders smoked in pipes were available into the 20th century.

The anticholinergic drugs available for inhalation therapy include atropine sulfate, atropine methylnitrate, glycopyrrolate, and ipratropium bromide. They are all bronchodilators that override the smooth muscle constrictor and secretory consequences of the parasympathetic nervous system, blocking reflex bronchoconstriction and reversing acute airway obstruction. Since atropine use is associated with side effects and glycopyrrolate is not well studied, the discussion is limited to ipratropium bromide (Atrovent), a quaternary derivative of atropine that is poorly absorbed from the mucosal surfaces of the lung, resulting in decreased side effects.

The maximum effect with inhaled ipratropium is in 30 to 120 minutes, with the effect lasting for up to 6 hours. Its bronchodilating potency is lower and onset of action slower than those of the beta$_2$-agonists; hence, it should not be used alone in patients with acute asthma. Reviews of trials assessing the role of this drug in combination therapy with beta$_2$-agonists for acute disease found that ipratropium provides a modest improvement in PFTs and a reduction in hospitalizations.[105,106] This benefit is higher in patients with more severe disease.[107] There is wide interpatient variability in response to anticholinergic therapy, implying that cholinergic mechanisms play a varied and unpredictable role in acute attacks.

Treatment recommendations (see Table 71-2) include adding ipratropium (0.5 mg) with the first three albuterol treatments in severe acute asthma (<40% predicted). The equivalent MDI dose is approximately eight puffs (18 µg/puff) every 20 minutes three times. Data suggest that less ipratropium might be needed in patients treated with levalbuterol nebulizations. Ipratropium can be given to anyone, both acutely and at discharge, who has documented improvement with its past use. There is evidence that ipratropium may be more effective in patients older than 40 years, should be used in reversing bronchospasm secondary to beta-blocking agents, and might help those in whom psychological factors contribute to their disease.

Magnesium Sulfate

Magnesium relaxes bronchial smooth muscle in vitro and dilates asthmatic airways in vitro. Mechanisms for this direct relaxing effect on bronchial smooth muscle include calcium channel-blocking properties, inhibition of cholinergic neuromuscular transmission, stabilization of mast cells and T lymphocytes, and stimulation of nitric oxide and prostacyclin. Intracellular magnesium levels are lower in acute asthma,[108] and the level correlates with airway reactivity in chronic disease.

There is some evidence that IV magnesium therapy for severe attacks might obviate the need for intubation. Clinical trials and meta-analyses show that magnesium adjunctive administration in severe asthma attacks (FEV_1 < 25% predicted) improves airflow obstruction and decreases the need for hospital admission.[109-111] The optimal dose and rates of infusion are unclear, but it is reasonable to administer 2 to 3 g of IV magnesium sulfate over 20 minutes or at rates of up to

1 g/min to patients with severe refractory asthma while continuing aggressive inhalation therapy.

Uncommon and manageable side effects of magnesium infusion are dose-related and include warmth, flushing, sweating, nausea and emesis, muscle weakness and loss of deep tendon reflexes, hypotension, and respiratory depression. Inhalation magnesium in acute asthma may also have a role as an isotonic vehicle for nebulized bronchodilator therapy in improving the PFT response[112,113] or even be nebulized alone for bronchodilation.[114] The doses needed, delivery systems required, and timing of magnesium nebulizations remain under investigation.

Methylxanthines

The naturally occurring methylxanthines caffeine and theobromine (in coffee, tea, and cacao) have been used by asthmatics for hundreds of years to treat wheezing. Theophylline is the main oral methylxanthine used to treat asthma; aminophylline (80% theophylline by weight) is used intravenously. The mechanism for theophylline's bronchodilatory effects is unclear, and current therapeutic approaches capitalize on its nonspecific arousal properties in COPD (increased ventilatory drive) rather than bronchodilation. Theophylline also enhances diuresis, cardiac output, mucociliary clearance, ventilatory drive, and contractility of the diaphragm while inhibiting the release of inflammatory mediators and suppressing microvascular permeability. A number of studies of chronic asthma demonstrate additional potential anti-inflammatory and immunomodulatory activity[115] and may explain the usefulness of theophylline in nocturnal asthma[116] and moderate asthma managed with ICS. A small subset of ambulatory asthma patients may benefit from the chronic administration of theophylline.[117,118] Theophylline has a narrow therapeutic window. Significant side effects can affect the cardiovascular, gastrointestinal, CNS, and metabolic systems.

It is important to recognize that the NAEPP EPR-3 does not recommend the use of methylxanthines for treatment of acute disease in the ED or in the hospital because of their lack of demonstrated efficacy and increases in adverse events.[1]

Leukotriene Modifiers

The cysteinyl leukotrienes (LTC_4, LTD_4, and LTE_4) are highly potent mediators of inflammation thought to play a large role in the pathogenesis of asthma. Zafirlukast (20 mg twice a day) and montelukast (10 mg daily) are rapid-acting, safe, asthma controller drugs, taken orally, that are potent and highly selective antagonists of type 1 cysteinyl LT receptors.

Asthmatics generally produce elevated levels of LTs, and in acute attacks the levels in the urine can be markedly increased. The addition of either 7 or 14 mg of IV montelukast (not available in the United States) to standard therapy for acute asthma causes a 15% non-$beta_2$-mediated increase in FEV_1 over placebo with no increase in side effects.[119] Oral zafirlukast, when given as adjunctive therapy (20 or 160 mg) for acute asthma in the ED, improved PFTs and dyspnea but did not decrease admissions to the hospital.[120] The acute non-beta-mediated bronchodilating effects of these relatively safe medications could be very useful in managing acute disease.

Other or Future Therapies

In patients without signs of dehydration or hypovolemia, there is no evidence that vigorous administration of fluids aids in clearing airway secretions. Mucolytics may worsen cough or airflow obstruction, and chest physical therapy is not beneficial. Sedatives are contraindicated in acute disease because of their respiratory depressant effect.

Bacterial, chlamydial, and mycoplasmal respiratory tract infections infrequently contribute to acute asthma. The decision to administer antibiotics should generally be reserved for patients with fever, purulent sputum, pneumonia, or evidence of bacterial sinusitis.

Future asthma therapies may include the second-generation antihistamines, even though earlier compounds were considered contraindicated in the disease.[121] Neurokinin antagonists, inhaled loop diuretics (furosemide in acute attacks), and lidocaine may inhibit neurogenic inflammation, and heparin may have a role in the inhibition of mast cell products. Infused BNP can cause significant bronchodilation in patients with asthma.[122] Lastly, specific cytokine antagonists, agonists, inhibitors of T-cell function, selective inducible nitric oxide synthetase inhibitors, and possibly gene-directed therapies may become novel treatments.

Pregnancy and Acute Asthma

The maternal and fetal risks of uncontrolled asthma are high, and acute disease should be maximally treated with the prevention of maternal and fetal hypoxia as the principal goal. Maternal asthma is not associated with preterm birth or birth defects. Many complications of pregnancy (e.g., hypertensive disorders, antepartum hemorrhage, low birth weight, need for cesarean section), however, are reported.[123] Asthmatic African American women are more likely to require an ED visit, inpatient hospitalization, or a course of corticosteroids due to asthma during pregnancy.[124] Pregnant asthmatics receive corticosteroid therapy in the ED less often than nonpregnant women, resulting in continued exacerbation at 2-week follow-up after discharge.[125] Inhaled beta-agonists and corticosteroids should be continued during pregnancy. Although conflicting data regarding the use of systemic corticosteroids during pregnancy exists, their use is suggested in severe uncontrolled exacerbations as the risk to mother and fetus far outweighs the potential complications.[126] Continuous electronic fetal monitoring should be considered at delivery. Recommendations for managing asthma during lactation are the same as those for managing the disease during pregnancy.

Severe, Near-Fatal, and Fatal Asthma

The American Thoracic Society has developed a consensus definition for identifying severe and refractory asthma[127,128] that is unresponsive to conventional therapies (Fig. 71-5). Termed *severe asthma*, patients with these symptoms represent only about 10% of all asthmatics yet account for 30% of asthma-related health care costs and have the highest morbidity and mortality rates associated with this disease. To satisfy the definition of severe asthma, medical conditions that mimic asthma must be excluded, exacerbating factors (e.g., allergens) identified and treated, and patients must be generally compliant with therapies. Although these criteria may not be satisfied in individuals using EDs for asthma, important insights into the mechanisms of severe asthma influence emergent care in this important subgroup.

Cellular features of severe asthma include persistent eosinophilic inflammation that is unresponsive to high-dose corticosteroids along with the presence of neutrophilic inflammation in the distal airways. The latter is not seen in milder forms of asthma but is similar to that of other inflammatory conditions (rheumatoid arthritis, ankylosing spondylitis, Crohn's disease)

Major characteristics
- Treatment with continuous or near-continuous (≥50% of year) oral corticosteroids
- Requirement for treatment with high-dose intravenous corticosteroids

Minor characteristics
- Requirement for additional daily treatment with a controller medication (e.g., long-acting beta-agonist, theophylline, or leukotrienes antagonist
- Asthma symptoms requiring short-acting beta-agonist use on a daily or near-daily basis
- Persistent airway obstruction (FEV_1 < 80% predicted, diurnal peak expiratory flow variability > 20%)
- One or more urgent care visits for asthma per year
- Three or more oral steroid bursts per year
- Prompt deterioration with ≤25% reduction in oral or intravenous corticosteroid dose
- Near-fatal asthma event in the past

Figure 71-5. American Thoracic Society workshop consensus for definition of severe/refractory asthma (requires one or both major and two minor criteria and that other conditions have been excluded, exacerbating factors have been treated, and patient is generally compliant).

and is associated with greater airway tissue destruction and remodeling with changes suggestive of ongoing epithelial injury and repair.[127,129]

Tumor necrosis factor alpha (TNF-α), an inflammatory cytokine produced by mast cells, is present in increased concentration in bronchoalveolar lavage fluid of patients with severe asthma. Treatment with the TNF-α antagonist etanercept decreases the expression of membrane-bound TNF-α by peripheral blood monocytes, improves airway hyperresponsiveness, FEV_1 and asthma-related quality of life, and may be a future therapeutic target for this subset of asthmatics.[130,131]

Clinical features of severe asthma (compared with mild to moderate disease) include a lesser prevalence of atopy, a history of aspirin sensitivity, and a higher incidence of sinusitis and use of nasal corticosteroids (suggesting involvement of the upper as well as lower respiratory tract). Exacerbations are also associated with menses.[132] Other clinical features that distinguish severe asthma from milder forms are being identified in order to focus therapy in this small but important group of asthmatics.[133]

Status asthmaticus refers to severe bronchospasm that does not respond to aggressive therapies within 30 to 60 minutes. *Near-fatal asthma* is identified by respiratory arrest or evidence of respiratory failure ($Paco_2$ > 50 mm Hg).[134]

Two types of near-fatal asthma are recognized. Slow-onset near-fatal asthma typically reflects a gradual deterioration of asthma symptoms over several days, usually superimposed on chronic poorly controlled asthma. Rapid-onset near-fatal asthma is characterized by symptom onset and progression to life-threatening status in 3 hours or less. Clinically, rapid-onset near-fatal asthma is characterized by greater hypercapnia than occurs in the slow-onset type. Interestingly, the hypercapnia in rapid-onset near-fatal asthma is more responsive to therapy than that in the slow-onset type, and these patients require shorter durations of mechanical ventilation. Deaths associated with the slow-onset mechanism are thought to be preventable in many cases because the gradual progression of symptoms allows patients to seek medical evaluation before succumbing.

Risk factors for death from asthma are identified (see Box 71-2). Other risk factors linked to near-fatal and fatal asthma include a decreased use of corticosteroids,[135] hospital admission for asthma treatment within the past 12 months, low socioeconomic status (related to increased allergen exposure and less access to health care), environmental exposures (air pollution, cigarette smoking), and psychosocial and emotional problems. Patients with an episode of near-fatal asthma are also likely to depend on EDs for asthma crisis management. Patients who succumb to fatal asthma commonly tend to be African American, live in inner-city areas, and are between 15 and 34 years of age. Most deaths occur outside or on the way to the hospital, at night, and within 24 hours of the onset of symptoms.

Clinical Approach to the Critically Ill Asthmatic

The critically ill asthmatic appears agitated (hypoxemic), assumes an upright position, and appears to be in severe respiratory distress. Tachypnea, diaphoresis, and accessory muscle use are evident. Speech is fragmented into single or short bursts of syllables or words. Absence of wheezing indicates severe expiratory obstruction and minimal air movement. Peak expiratory testing is difficult for the patient to perform but, when possible, indicates severe expiratory obstruction. Alterations in consciousness and bradypnea indicate hypercarbia and impending respiratory arrest.

No laboratory markers identify patients with near-fatal asthma. In critically ill patients, elevated lactic acid levels reflect tissue hypoxemia and anaerobic metabolism; persistent elevations of arterial lactate levels are often associated with a poor prognosis. An elevated lactic acid level is not predictive of respiratory failure in critically ill asthmatics, and blood lactate levels are not informative.

Noninvasive Strategies. Therapy must be initiated immediately (see Table 71-2). Attempts to abort the episode should include high-dose frequent or continuously nebulized $beta_2$- and anticholinergic agents. If parenteral adrenergic therapy is desired, terbutaline is preferred because of its $beta_2$ selectivity. IV use of magnesium sulfate or $beta_2$-agonists (where available) may be of benefit. Oral prednisone, 60 mg, or IV methylprednisolone, 125 mg, should be administered early. Use of a helium/oxygen delivery system (heliox) is controversial. Helium is an inert gas with one eighth the density of nitrogen. When 60 to 80% helium is blended with 20 to 40% oxygen, the resulting gas mixture has a threefold reduction in density compared with air. Heliox reduces the resistance associated with gas flow through airways with nonlaminar flow and reduces respiratory muscle work; it also increases the diffusion of carbon dioxide and may improve alveolar ventilation.[136] Although heliox is not intrinsically therapeutic, it may decrease the work of breathing long enough to abort intubation by allowing bronchodilators and anti-inflammatory agents to achieve their effects. Studies have claimed beneficial effects when heliox is used to drive nebulized beta-agonist therapies in both children and adults.[137,138] No data indicate that heliox reduces the need for intubation or hospital admission, length of hospital stay, or mortality rates.[139-141] Heliox is administered by nonrebreather mask and may be an adjunctive strategy to mechanical ventilation in selected asthmatics. Close monitoring of oxygen saturation and continuous capnography are advisable. Considerations for heliox include cases of severe airflow obstruction (PEFR <30% predicted and a rapid onset of symptoms <24 hours), a history of labile asthma or previous intubation, and inability to be adequately mechanically ventilated.[136] Heliox use is discontinued when clinical improvement occurs.

Noninvasive positive-pressure ventilation may benefit carefully selected patients (see Chapter 2). Continuous positive airway pressure improves oxygenation and reduces respiratory muscle fatigue by increasing functional residual capacity and lung compliance and supplying some of the inflating pressure required during inspiration. Biphasic positive airway pressure

(BiPAP) provides continuous positive airway pressure but delivers higher pressure during inspiration than expiration. BiPAP is well tolerated by children with status asthmaticus and may decrease the need for intubation and mechanical ventilation.[142] BiPAP may also decrease the need for intubation and ICU care in adults with status asthmaticus, although the literature is not conclusive.[143-146]

BiPAP is not a substitute for endotracheal intubation and mechanical ventilation. Patient considerations for BiPAP include an alert mental status and intact airway reflexes. Providers should be familiar with BiPAP use in other medical conditions (e.g., COPD, CHF) and close monitoring of consciousness and vital signs is mandatory. Frequent ABG monitoring after institution of this therapy identifies nonresponders. Endotracheal intubation should be performed immediately if respiratory distress persists or if clinical or laboratory signs of deterioration are observed.

Ketamine is an IV dissociative anesthetic with potent bronchodilator effects. Some case reports and small series have suggested benefit when used in acute asthma, but no randomized trials have been conducted. Adverse effects include increased airway secretions and emergence reactions. At present, ketamine is not recommended for therapy of acute asthma in the nonintubated patient.

Intubation and Ventilator Strategy. Endotracheal intubation is required in 2% of all asthma exacerbations and 10 to 30% requiring ICU admission.[147-149] With the exception of apnea or coma, there are no absolute indications for intubation in the asthmatic patient, but intubation should occur in the failing patient before the patient develops profound acidemia or hypoxemia. Exhaustion, hypoxemia, and depression of mental status strongly mandate prompt intubation.

Orotracheal rapid sequence intubation utilizing induction agents and muscle paralysis is preferred (see Chapter 1). Ketamine (1–2 mg/kg) is the preferred agent for induction in rapid sequence intubation of the asthmatic patient. Succinylcholine (1.5 mg/kg) or a competitive neuromuscular blocking agent, such as rocuronium (1 mg/kg) can be used for intubation paralysis. Pretreatment with lidocaine (1.5 mg/kg), given 3 minutes before the succinylcholine and ketamine, may mitigate the exacerbation of bronchospasm by the upper airway instrumentation and the endotracheal tube. After intubation, additional ketamine may be given as a small number of intermittent boluses of 0.5 to 1.0 mg/kg, and a benzodiazepine should be administered to keep the patient sedated and to prevent a ketamine emergence reaction. Alternatively, propofol (1.5–2 mg/kg) offers rapid-onset deep sedation and also possesses bronchodilating properties. Continued deep sedation with propofol or an equivalent agent (e.g., long-acting benzodiazepine) usually avoids the need for muscle paralysis. After intubation, an opioid that does not release histamine, such as fentanyl, can be used to improve the patient's comfort with the ventilator.

A ventilator strategy providing adequate oxygenation and ventilation while minimizing high airway pressure, barotrauma, and systemic hypotension must be instituted. The technique of *permissive hypercapnia* (also known as controlled hypoventilation) is common (see Chapter 2). Oxygenation is maintained by using a high fraction of inspired oxygen (F_{IO_2}); hypercarbia and respiratory acidosis (pH maintained at 7.15–7.2 using sodium bicarbonate) are tolerated. Airway pressure is kept low by providing low tidal volumes (6–8 mL/kg), thus preventing excessive increases of intrinsic positive end-expiratory pressure, stacking of ventilations, and barotrauma. Low ventilation rates (<10 breaths/min) and high inspiratory flow rates provide prolonged time for expiration. Adjunctive therapies (in-line $beta_2$-agonists and anticholinergics, IV corticosteroids, IV ketamine, and possibly magnesium) to decrease airway pressure and airway obstruction are delivered simultaneously.

Continuous capnography is advisable. Moderate levels of hypercapnia are well tolerated and have few deleterious effects. Elevated CO_2 levels have vasodilatory effects on cerebral vessels. Cerebral blood flow reaches its maximum at a P_{ACO_2} level of 120 mm Hg, which may increase intracranial pressure. Although there is no consensus on what constitutes a safe level of hypercapnia, P_{ACO_2} levels above 100 mm Hg should be avoided.[148] Hypercapnia can decrease cardiac contractility and produce cardiovascular collapse; thus, permissive hypercapnia should be supplemented by generous repletion of intravascular volume through IV fluid administration.

Neuromuscular blockade, once widely used for ventilation of asthmatic patients, is now used only in cases where deep sedation with adequate analgesia fails to provide sufficient patient relaxation for successful mechanical ventilation (see Chapter 1). Myopathy attributed to the prolonged use of competitive neuromuscular blocking agents occurs in about 30% of asthmatic patients with neuromuscular blockade.[147] Intubation and mechanical ventilation may be lifesaving in near-fatal asthma attacks. Although hazards of mechanical ventilation (nosocomial infection, barotrauma) may occur, the treatment of critically ill asthmatics with mechanical ventilation is associated with low or zero mortality and few complications. Most asthmatics requiring mechanical ventilation improve rapidly and require short ICU stays.

Complications of mechanical ventilation in the asthmatic patient include hypotension and barotrauma. Hypotension is almost uniformly secondary to increased intrathoracic pressure with a subsequent decrease in venous return and cardiac output. Pneumothorax should be considered whenever sudden clinical deterioration occurs or when hypotension is accompanied by a significant rise in peak inspiratory ventilator pressures and falling oxygen saturation.

Treatment of the Refractory Critically Ill Asthmatic. If the intensively treated, intubated critically ill asthmatic continues to have elevated airway pressures, persistent hypoxemia, and continued bronchospasm, general anesthesia should be considered in the operating room. Isoflurane, a bronchodilator, has lower arrhythmogenic and hypotensive properties than halothane.[150]

External lateral chest compression may be of assistance when patients cannot exhale. Chest compression is delivered by bilateral squeezing of the lower chest walls immediately after end inspiration occurs. Compression delivered too early (i.e., during inspiration) may increase airway pressure and result in barotrauma. In children, this technique decreases peak airway pressure and P_{ACO_2} and increases pH.[151]

Cardiopulmonary arrest may result from unrecognized barotrauma. Empirical bilateral tube thoracostomy should be performed if unexplained cardiac arrest occurs, especially in the context of dramatic increases in peak inspiratory pressure. IV epinephrine is a logical agent to use in the setting of cardiopulmonary arrest because it has both cardiostimulatory and bronchodilatory properties.[152] Isoproterenol, a pure beta-agonist, may increase heart rate and provide bronchodilatation, but it decreases coronary perfusion pressure. Cardiopulmonary bypass and extracorporeal lung assist are also used in the treatment of near-fatal asthma.

DISPOSITION

Prediction of Relapse

Asthmatic patients discharged from the ED have rates of relapse that vary from 11% over 3 days to 45% at 8 weeks. In

Table 71-4 ED Disposition Decision-Making Guidelines

	GOOD RESPONSE	INCOMPLETE RESPONSE	POOR RESPONSE
FEV_1 or PEFR (% predicted/ personal best)	≥70%	≥40% but <69%	<40%
Disposition site			
Home	Yes	Individualized decision (see text)	No, continue therapy
Clinical decision unit	No	Yes, if available	Yes, if available and appropriate
Hospital ward	No	Yes, if no CDU	Yes, if appropriate and available
Critical care unit	No	No	Yes, if with respiratory insufficiency/ failure

CDU, clinical decision unit; FEV_1, forced expiratory volume in 1 second; PEFR, peak expiratory flow rate.

BOX 71-3 INSTRUCTIONS FOR METERED-DOSE INHALER USE

1. Remove cap from the MDI container.
2. Assemble the MDI and hold it upright.
3. Shake the canister.
4. Place the mouthpiece loosely between the teeth (or hold it 3–4 cm in front of the open mouth).
5. Exhale fully (to functional residual capacity).
6. Actuate the inhaler at the beginning of a slow and full inhalation (as if sipping hot soup) lasting 5 or 6 seconds.
7. Hold breath for at least 10 seconds.
8. Wait 1 minute before reuse.

a multicenter study, the relapse rate was 17% in the 2 weeks after ED discharge. The risk for relapse increases in those with numerous asthma-related ED visits within the last year, with more outpatient medications, and with longer duration of symptoms before the ED visit.[153] Other studies find similar out-of-control indices predicting relapse but have also included insufficient improvement in PFTs with hospital-based treatment for an attack.[154]

Inpatient versus Observation or Clinical Decision Unit

Patients requiring extended care who are without life-threatening exacerbations, pregnancy, or complications of asthma can generally be treated in a clinical decision unit (CDU) for 12 hours with 8-week outcomes equal to those of patients treated in a hospital ward but with significant cost savings.[155] The ability to predict discharge from the CDU can be assessed by the ED PEFR response to the third $beta_2$-agonist treatment (PEFR > 40% predicted is often associated with successful CDU discharge).[153] Lastly, patients prefer CDU treatment of acute attacks over routine inpatient care.[156]

Table 71-4 summarizes disposition guidelines for asthmatics on the basis of their response to therapies in the ED.

Planning Discharge from the Emergency Department

An asthma exacerbation does not end on ED discharge; airway inflammation and peripheral obstruction may take hours to days to resolve. Patients are likely to need continued $beta_2$-agonist rescue therapy during this time, and it is important that they can demonstrate the correct use of their inhalers (Box 71-3). If the patient is having difficulty coordinating the canister activation with inhalation, a breath-activated inhaler or spacer device can be prescribed or the need for a home nebulizer discussed. A patient using a portable, preloaded, multidose dry-powder inhaler must be able to inhale from the mouthpiece in a rapid and forceful inhalation to total lung capacity.

Patients receiving systemic corticosteroids in the ED must continue these orally for 5 to 10 days. Asthma patients treated in the ED are more likely to have moderate to severe disease; not receive controller therapy; and be younger, poorer, and less educated. They have reduced asthma management skills and are more likely to miss school or work. If the patient is not using controller medications and experiences persistent disease, moderate-dose inhaled steroids or a combination inhaled steroid and long-acting beta-agonist (e.g., salmeterol xinafoate-fluticasone propionate) should be started. A less preferred option is to prescribe an LT modifier (e.g., zafirlukast 20 mg twice a day or montelukast 10 mg daily) to decrease relapse and improve asthma control.

Patients should be encouraged to contact their physician or a respiratory specialist nurse[157] for asthma-related problems within the next 3 to 5 days and to make a follow-up medical appointment within 1 to 4 weeks. At this visit it can be decided whether the control drug regimen needs to be adjusted. Interventions that include free medications, transportation vouchers, and appointment assistance significantly increase the likelihood that discharged asthma patients will obtain primary care follow-up. These assistances, however, may not affect long-term outcomes.[158] Since the follow-up visit with a primary care physician does not ensure the prescribing of ICS, emergency physicians must evaluate chronic asthma management.[159]

The asthma patient can be provided written education about discharge medications, medication adjustment if the condition is not improving, and a peak flow meter for daily measurements, especially for those who have difficulty perceiving airflow obstruction or who have symptoms of worsening asthma. Lastly, smoking is surprisingly common (up to one third) in asthmatics presenting to the ED, and smoking asthmatics have more respiratory symptoms, lower lung function, and more parenchymal abnormalities noted on chest computed tomography.[160]

KEY CONCEPTS

- IgE-mediated immune responses, airway inflammation, and airway remodeling are concepts crucial to our understanding of asthma and are the targets of current and future therapies.
- Inhaled and systemic steroid medications are effective in controlling airway inflammation and have important roles in management of asthma exacerbations.
- Single-isomer albuterol (levalbuterol), the result of improving isomer technology, is a better bronchodilator in acute asthma than the traditional racemic form.
- Severe and refractory asthma exacerbations require rapid identification. Treatment must be aggressive and may employ strategies not used in mild to moderate exacerbations.
- The ED's management of acute asthma is expanding (up to 24 hours) as more noncritically ill asthmatics are treated in the clinical decision units.
- Integration of discharged acute asthmatics into chronic management strategies to prevent relapse requires that asthma patients' physicians be familiar with controlling medications such as ICSs and LT modifiers.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 72

Chronic Obstructive Pulmonary Disease

Stuart P. Swadron and Diku P. Mandavia

PERSPECTIVE

Chronic obstructive pulmonary disease (COPD) is one of the most common causes of death worldwide.[1-3] Epidemiologists agree that the prevalence of COPD is underreported and that its burden is increasing. Regardless of the success of smoking cessation programs, smoking behavior in the past several decades and the delay of the appearance of symptoms in an aging population virtually guarantee an increase in prevalence. Although in the United States the mortality rate among men is leveling off, the rate for women is still increasing. It has been estimated that COPD will be the seventh leading cause of lost disability-adjusted life years (DALYs) worldwide by 2030.[2] The financial burden of COPD is enormous, accounting for billions of dollars every year for treatment and lost productivity.[4] The majority of these costs are related to hospitalization for acute exacerbations.[5] Despite its enormous effects, COPD has received relatively less attention from basic medical researchers and clinicians than other diseases. This trend has begun to reverse.[6] Large multinational collaborations, such as the Global Initiative for Chronic Obstructive Lung Disease (GOLD) sponsored jointly by the National Heart, Lung, and Blood Institute and the World Health Organization, are designed to help reinvigorate the scientific and medical communities frustrated by the unrelenting progressive nature of COPD and its poor response to existing therapies.[7]

The definition of COPD is imprecise and incorporates advances in our understanding of its underlying mechanisms and natural history. In their consensus statement, the GOLD collaborators define COPD as "a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible." They also state that "the airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases."[7] This definition reflects new data underscoring the systemic nature of the disease, as well as a deliberate optimism with respect to new prevention and treatment strategies. It specifically avoids mention of chronic bronchitis and emphysema, two entities that have been traditionally included in the definition of COPD. Chronic bronchitis, defined as the presence of cough and sputum production for at least 3 months in each of two consecutive years, can occur *without* airflow limitation. Emphysema, the destruction of alveoli, is a pathologic term, not one that pertains to clinical diagnosis. Unlike many earlier definitions of COPD, the GOLD collaborators also specifically exclude asthma, which is *reversible* airflow limitation.[7] Whether reversible airflow limitation is considered to be part of COPD itself or due to coexisting asthma is of limited significance to the emergency physician, who will continue to make every attempt to identify and reverse airflow limitation.

As many as 50% of all acute COPD exacerbations are not reported to physicians. In addition, not all reported exacerbations require hospitalization.[8] Nonetheless, in 1998, almost 2% of all hospital admissions in the United States were directly attributed to COPD, and it was considered a contributory factor in another 7%. In patients older than 65, the percentage of all hospitalizations related to COPD approaches 20%.[9] As the severity of the underlying disease progresses, so does the frequency of exacerbations. Moreover, in a subset of patients, incomplete recovery from acute exacerbations may reflect a contribution of exacerbations to the pathophysiology of relentless disease progression.[10]

PRINCIPLES OF DISEASE

Pathophysiology

In the past two decades, the discovery that chronic airway inflammation plays a central role in the pathophysiology of asthma led to an important change in its management, specifically, the liberal use of corticosteroids for treating moderate to severe disease. Airway inflammation is also at the center of the pathophysiology of COPD, but the inflammatory process of COPD differs from that of asthma. In COPD, neutrophils, CD8+ lymphocytes, and macrophages predominate in bronchial washings, whereas in asthma, the cellular response is characterized by the presence of eosinophils.[11] The inflammatory mediators differ in COPD, and several mediators, such as tumor necrosis factor, leukotriene B4 (LTB_4), and interleukin-8 (IL-8), are linked to the destruction of parenchyma.[12] These differences in the nature of the inflammatory response in COPD may account for its relatively poor response to current anti-inflammatory treatment compared with asthma.

Pathologically, the abnormalities in COPD are found throughout the lungs. Although certain changes may be more or less prominent in a given patient, most patients have at least some component of the two main pathologic entities: chronic obstructive bronchitis and emphysema. Evidence of airway inflammation is found from the trachea down to the smallest

peripheral airways, which become progressively scarred and narrowed. An increase in both the number and size of mucus-secreting goblet cells results in the formation of mucous plugs that further contributes to airflow obstruction. Damage to the endothelium impairs the mucociliary response that clears bacteria and mucus. The lung parenchyma is progressively destroyed over time, usually in a pattern of centrilobular emphysema. This consists of a destruction of alveoli, loss of lung elasticity, and the closure of small airways, which rely on the radial support of surrounding connective tissues to maintain their patency during expiration.

The combination of airway obstruction and obliteration of the pulmonary vascular bed results in a failure of gas exchange. Thus, arterial blood gases (ABGs) may reveal both hypoxemia and hypercapnia. As the overall size of the pulmonary vascular bed decreases with time, chronic hypoxia induces a thickening of the vessel walls. Both of these factors contribute to the development of pulmonary hypertension, polycythemia and, eventually, right-sided heart failure (cor pulmonale).[6,12,13]

The pathophysiology of COPD reflects the apparent imbalance between proteases and antiproteases that favors the destruction of connective tissue in the lungs. In one small subset of COPD patients with congenital α_1-antitrypsin deficiency, a lack of α_1-antitrypsin, an enzyme that inhibits neutrophil elastase, leads to the pathology of severe panacinar emphysema.[14] In the majority of patients, however, the specific genetic factors are less well elucidated.[15,16] Oxidative stress, the imbalance of oxidant to antioxidant activity in favor of oxidants, is another important facet of the pathophysiology of COPD. External oxidants are found in cigarette smoke, whereas the products of the inflammatory process result in intrinsic oxidants. Not only may oxidants cause direct parenchymal damage, but oxidative stress indirectly fuels further inflammation and protease activity.[17]

Cigarette smoking, the most significant risk factor for the development of COPD, exerts its effects at multiple points in the inflammatory cascade of COPD, negatively affecting both the protease to antiprotease and oxidant to antioxidant balances.[12,17,18] Although smoking cessation slows the progression of the disease, it does not end the chronic inflammatory process within the airways, indicating that mechanisms independent of smoking are involved.[12] Moreover, although a majority of COPD patients have a significant smoking history, only a minority of smokers ever develop airflow limitation. This suggests the importance of other factors, both environmental and genetic.[19] Other identified causative factors include heavy occupational exposure to dusts and air pollution from indoor cooking, particularly in the developing world.[20-22] Long-term passive exposure to tobacco smoke also appears to be contributory, but the role of urban air pollution is not established.[23] Although there is an association between early childhood lower respiratory tract infections and later development of COPD, a causal relationship is less certain.[24-27]

Compensatory physiologic responses in COPD vary according to the balance of underlying pathologic derangements seen in individual patients. In a minority of patients, ventilatory drive is increased to maintain a near normal partial pressure of oxygen (P_{O_2}), preventing any cyanosis. The resultant tachypnea may also cause a slightly low partial pressure of carbon dioxide (P_{CO_2}). In such patients with relatively normal blood gases, pulmonary hypertension and cor pulmonale may not occur until very late in the course of the disease.

Although the precise mechanisms are ill-defined, the pathologic processes of COPD extend beyond the cardiac and pulmonary systems. The effects of circulating inflammatory mediators, oxidative stress, and protease antiprotease imbalance may be responsible for the weight loss, muscular wasting, metabolic derangements, and depression often seen in the later stages of disease.[18,28,29] These features of COPD are partly responsible for the influence of COPD as a comorbid illness, even when the presenting complaint is nonpulmonary. COPD influences a variety of management decisions in the emergency department (ED), ranging from the choice of agents for procedural sedation and rapid sequence intubation to the appropriate disposition of patients with nonpulmonary diagnoses.

Table 72-1 The GOLD Classification of Severity of COPD

STAGE	CHARACTERISTICS
I: Mild COPD	$FEV_1/FVC < 70\%$ $FEV_1 \geq 80\%$ of predicted Symptoms may or may not be present
II: Moderate COPD	$FEV_1/FVC < 70\%$ $50\% \leq FEV_1 < 80\%$ predicted Usually symptomatic with SOB on exertion or acute exacerbations, or both
III: Severe COPD	$FEV_1/FVC < 70\%$ $30\% \leq FEV_1 < 50\%$ predicted Increasingly symptomatic with frequent exacerbations and deleterious effects on quality of life
IV: Very Severe COPD	$FEV_1/FVC < 70\%$ $FEV_1 < 30\%$ of predicted or $FEV_1 < 50\%$ with chronic respiratory failure (P_{aO_2} <60 mm Hg ± P_{aCO_2} > 50 mm Hg) May or may not have clinical signs of right heart failure

COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; P_{aco_2}, arterial partial pressure of carbon dioxide; P_{ao_2}, arterial partial pressure of oxygen; SOB, shortness of breath.

Adapted from Rabe K, Hurd S, Anzueto A, et al: Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 176:532, 2007.

Staging the Severity of Disease

Most classifications of disease severity are based on quantitative measurements of airflow limitation, such as the forced expiratory volume in 1 second (FEV_1) and FEV_1/forced vital capacity (FVC) ratio. These indices are measured after any *reversible* airflow limitation is addressed by treatment with bronchodilator medications. The GOLD collaborators define four stages, beginning with a mild stage (stage 1), when spirometry is abnormal, but symptoms may not yet be apparent, and ending in very severe COPD (stage 4), when FEV_1 is less than 30% of predicted (Table 72-1). Frequent exacerbations are usually seen when the FEV_1 falls below 50% predicted (stages 3 and 4).[7,30]

Acute Exacerbations

Unlike asthma exacerbations, COPD exacerbations are not necessarily associated with major reductions in peak flow and FEV_1 measurements. Like COPD itself, the definition of an acute exacerbation is imprecise and relies on clinical parameters that are often subjective. The definition adopted by the GOLD collaborators is "an event in the natural course of the disease characterized by a change in the patient's baseline dyspnea, cough, or sputum that is beyond day-to-day variations, is acute in onset, and may warrant change in regular medication in a patient with underlying COPD."

Acute exacerbations are more common in the winter months, which most likely reflects the importance of viral pathogenesis. As with asthma, viral infection appears to be a frequent inciting agent in COPD exacerbations. Commonly implicated viruses include rhinovirus, respiratory syncytial virus (RSV), coronavirus, and influenza virus.[31-33] Exacerbations associated with a viral etiology are longer and more severe than those without an apparent inciting agent.[33,34]

Controversy remains regarding the role of bacterial pathogens in acute exacerbations of COPD, since the evidence for the role of bacteria in the pathogenesis remains indirect. Almost one half of all exacerbations are associated with negative cultures for the typical respiratory pathogens such as *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella (Branhamella) catarrhalis*, and *Pseudomonas aeruginosa*. In addition, these organisms are recovered from the tracheobronchial tree of patients in their chronic, steady state, suggesting that bacteria may play a more important role in the pathogenesis of chronic COPD than in acute exacerbations.[35-38] Although molecular typing shows that recent colonization with new serotypes of the common pathogens is associated with an exacerbation, there is a possibility that this relationship is not causal.[35,38,39] Experimental evidence of specific immunologic responses to bacteria in exacerbations suggests, however, that they do play a significant role.[40,41]

Environmental factors, such as air pollution, are also implicated in COPD exacerbations. Indirect evidence for this relationship is largely derived from hospitalization rates for exacerbations during periods of increased air pollution.[42] Finally, in as many as one third of all COPD exacerbations, no specific cause can be identified.[43]

In addition to acute exacerbations, patients with COPD may present with worsening symptoms due to comorbid conditions such as pneumonia, congestive heart failure (CHF), pneumothorax, pulmonary embolism (PE), lobar atelectasis, pleural effusion, or dysrhythmias. All of these are associated with COPD and may mimic or coexist with an acute exacerbation.

CLINICAL FEATURES

Symptoms and Natural History

COPD patients have a long premorbid course during which decreases in air flow indices can be measured in the absence of early symptoms. Intermittent cough or shortness of breath on exertion may be easily misattributed to poor physical conditioning. Moreover, patients may remain asymptomatic for many years by gradually limiting their activities in proportion to their pulmonary reserve. After several years, a daily productive cough frequently develops and periods of dyspnea, the cardinal symptom of airflow limitation, increase. The clinical progression of COPD is slow and insidious, with gradual decreases in airflow punctuated by increasingly frequent and debilitating exacerbations. Eventually, the patient becomes truly incapacitated by dyspnea on minimal or no exertion. Profound muscle wasting and weight loss and the emergence of cor pulmonale or chronic ventilatory failure are characteristic of end-stage disease. Figure 72-1 depicts the progression of COPD over time.

Physical Examination

The division of patients with COPD into two phenotypes, the "blue bloater" (for the patient with chronic obstructive bronchitis) and the "pink puffer" (for the patient with emphysema), is outdated because many patients with COPD do not conform to these descriptions. Nonetheless, these classical images do highlight some of the important clinical features that may be encountered in the patient with COPD and have implications for management. Most patients present with some combination of chronic obstructive bronchitis and emphysema and appear with a mixture of the syndromes described below. The precise identification of which process is predominant is less important than the evaluation of each patient and formulation of a specific treatment plan based on the individual clinical findings. In particular, the degree of chronic hypoxemia and dependence on home oxygen therapy, the presence of cor pulmonale, and evidence of comorbid illness, such as ischemic heart disease, should be determined.

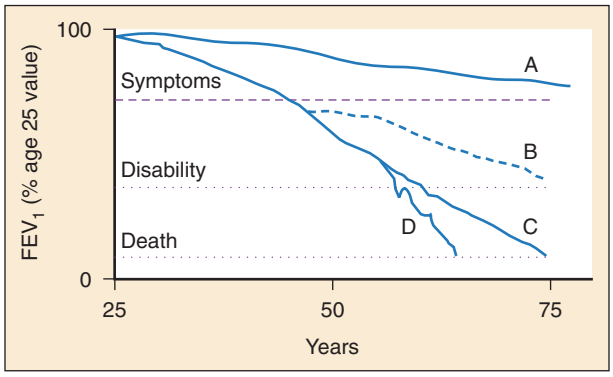


Figure 72-1. The progression of COPD over time. Natural history of COPD as measured by FEV_1 as a percentage of the baseline value at age 25. Normal nonsmoking individuals (A) have a progressive loss of FEV_1 but never become symptomatic with airway obstruction. Patients with COPD who quit smoking (B) experience an FEV_1 decline that parallels a nonsmoking, age-matched person. Patients with progressive COPD (C) can develop a loss of FEV_1, which may eventually produce symptoms, disability, and death. Some COPD patients (D) have steep declines in lung function during discreet clinical episodes. (From Heffner JE: Chronic obstructive pulmonary disease on an exponential curve of progress. Respir Care 47:586, 2002.)

In patients in whom chronic obstructive bronchitis predominates, the findings are those of chronic respiratory failure and cor pulmonale. Little air hunger or anxiety is present, and the combination of polycythemia and hypoxemia creates a plethoric, cyanotic appearance. Cough, as the clinical hallmark of bronchitis, is prominent and, when vigorous, causes expectoration. If acute ventilatory failure is present, the patient's consciousness is clouded. This often can be described as "irritable somnolence," and asterixis may be present. Chronic ventilatory failure and cor pulmonale account for the prominent peripheral edema and chronic jugular venous distention. If there is relatively little emphysema, the thoracic anteroposterior diameter is normal and the diaphragm is not abnormally low. The presence of severe bronchopulmonary secretions is evidenced by scattered rhonchi and rales, especially at both lung bases posterolaterally. These patients often have chronic CO_2 retention, requiring close monitoring of O_2 therapy because of their relative dependency on hypoxemic drive for ventilation.

When emphysema predominates, the patient is often thin, anxious, alert and oriented, dyspneic, tachypneic, and utilizing accessory muscles of breathing. The patient often self-administers positive end-expiratory pressure (PEEP) by using a pursed lip exhalation pattern to increase intraluminal bronchial pressure and provide internal support for bronchial walls that have lost their external support. Such patients usually assume a sedentary existence, chronically hunched forward.

Gross lung overinflation occurs, with a low immobile diaphragm and an increased anteroposterior diameter of the thorax. Percussion of the chest reveals hyper-resonance, and auscultation demonstrates diminished breath sounds with faint end-expiratory rhonchi. Despite air hunger caused by the extensive lung parenchyma destruction, the patient maintains adequate oxygen saturation and often has near-normal ABG levels. The heart is small and hypodynamic, and the blood pressure is usually low.

Cardiac examination in a patient with suspected COPD is crucial in the diagnosis of cor pulmonale and coexisting left ventricular failure. A subxiphoid or retrosternal heave suggests chronic right ventricular hypertrophy (RVH), an S_4 suggests decreased left ventricular compliance, an S_3 indicates left ventricular failure, and a holosystolic blowing murmur of tricuspid insufficiency is secondary to right ventricular and tricuspid ring dilation. Accentuation of the pulmonic component of the secondary sound reflects pulmonary hypertension. Chronic visceral congestion causes hepatomegaly, hepatojugular reflex, and sometimes prominent abnormalities of liver function.

DIAGNOSTIC STRATEGIES

Pulse Oximetry, Arterial Blood Gas Analysis, and Waveform Capnography

Pulse oximetry is part of the evaluation and monitoring of every patient with a COPD exacerbation. Comparison with prior values, both in crisis and in baseline state, helps to interpret measurements obtained during an acute exacerbation. The change in pulse oximetry from baseline or in response to emergency therapy is generally more important than absolute levels.

The stages of COPD severity correlate with arterial gas tensions. Abnormal ventilation-perfusion relationships of COPD produce only modest decrements in Pa_{O_2} in its early stages (80–100 mm Hg). Later in the course of the disease, hypoxemia below 60 mm Hg stimulates respiratory centers, producing hyperventilation ($P_{CO_2} < 35$) and acute respiratory alkalosis. As pulmonary dysfunction progresses, the work of hyperventilation becomes cost-ineffective; that is, more CO_2 is produced by the effort than is cleared by the increased ventilation. Eventually, alveolar hypoventilation impairs gas exchange, leading to CO_2 retention and acute respiratory acidosis. With renal compensation through bicarbonate retention, the pH normalizes. Finally, when acute ventilatory failure is superimposed at this stage of the disease, an elevated P_{CO_2}, lowered pH, and elevated bicarbonate are found.

ABG values, once a mainstay of ED evaluation of COPD patients, are of limited value. A direct measurement of ABGs may be considered in patients with severe exacerbations for whom hospitalization is anticipated. The presence of respiratory failure unresponsive to therapy (defined as $Pa_{O_2} <$ 40 mm Hg, $Pa_{CO_2} >$ 60 mm and pH < 7.25 Hg) warrants consideration of admission to an intensive care unit, but clinical evaluation is much more important than any particular blood gas values.[7] When baseline blood gas levels are not available, the utility of the ABGs is even more limited, and interpretation should be based on the degree of acidosis present, which likely represents the extent of acute CO_2 retention. ABGs should not be used to determine whether a patient requires intubation or noninvasive ventilatory support (NIVS). These decisions should rather be guided by the overall state of the patient, progression of fatigue, comorbid illness, and response to therapy. Patients with very poor blood gas values may do well without intubation or NIVS, but others with mildly disturbed values may require urgent airway intervention. Thus, ABGs should not be performed routinely in the ED and should only be undertaken in response to specific circumstances, such as irregular or apparently unreliable pulse oximeter values.

Waveform capnography represents the continuous quantitative measurement of exhaled CO_2. It has emerged as a potential diagnostic and monitoring tool in patients with acute respiratory distress. The appearance of the waveform may assist the clinician in differentiating acute exacerbation of COPD from other causes of acute dyspnea such as CHF. In patients with obstructed airways, the plateau phase of the waveform typically steepens in proportion to the severity of the obstruction. Unfortunately, in patients with COPD, the actual end-tidal P_{CO_2} measurements obtained from capnography do not correlate well with arterial P_{CO_2} measurements, especially in more severe disease. Nonetheless, the patterns and trends from capnography may be helpful in guiding management.[45]

Chest Radiography

In patients who are known to have COPD, the primary role of the chest radiograph is to determine whether there is an acute, treatable cause for clinical deterioration, especially pneumothorax or parenchymal consolidation (atelectasis secondary to mucus plugging, pneumonia, or obstruction by tumor). Otherwise, the chest radiograph is of limited use and may exhibit a range of chronic changes, depending on disease severity and the relative degree of the various pathologic processes. Findings may include hyperinflated lung fields, decreased vascular markings, and a small cardiac silhouette, or in contrast, normal inflation, with increased vascular markings and an enlarged heart.[44] In cor pulmonale, impingement on the retrosternal airspace by the enlarged right ventricle can be seen on the lateral film.

Bullae may also be present and resemble or mask a pneumothorax. In addition, chest radiography may reveal important coexistent pathology including CHF, effusions, and tumors. Routine chest radiography, although challenged, is appropriate in patients with acute exacerbations of COPD.[45-47]

Forced Expiratory Volume and Peak Expiratory Flow Rate

Pulmonary function tests (PFTs) are more useful in asthma, where there is a significant reversible component of airway obstruction. In addition, the patient in acute respiratory distress is often unable to cooperate, making testing unreliable. Thus, PFTs add little to decision making in cases of acute COPD exacerbation.

Sputum Examination

During acute exacerbations of bronchitis, sputum may be thicker and grossly purulent, but neither Gram's stain nor culture of sputum has been shown to be of value in acute COPD exacerbation.[48]

Electrocardiogram and Cardiac Monitoring

The classic descriptions of P pulmonale (peaked P waves in leads II, III, and aVF), low QRS voltage, clockwise rotation, and poor R wave progression in the precordial leads are interesting correlates of COPD but are both insensitive and nonspecific. The presence of electrocardiogram (ECG) criteria for RVH suggests established cor pulmonale. These findings,

however, can be easily obscured on the ECG by other processes and the absence of criteria for RVH cannot be relied on to rule out cor pulmonale.[49]

In severely ill patients, or those with concomitant chest pain, continuous ECG monitoring may be helpful, at least for the initial phase of the patient's evaluation and treatment. ECG monitoring can detect dysrhythmias associated with COPD exacerbations and changes of rate and rhythm in response to therapy. The most common dysrhythmias associated with COPD are atrial tachydysrhythmias, such as atrial fibrillation and multifocal atrial tachycardia. Although atrial fibrillation may require treatment with rate control or conversion, multifocal atrial tachycardia often resolves with the treatment of the COPD exacerbation itself.[50]

Blood Tests

Routine hematologic evaluation adds little to the treatment of the patient with COPD and acute exacerbation. A complete blood count may reveal polycythemia associated with chronic hypoxia. An elevated white blood cell (WBC) count is nonspecific and should not be interpreted as indicative of coexistent infection; nor should a normal range WBC count support a contention that no infection is present. Elevations in WBCs in COPD are more often related to the hyperadrenergic state of acute dyspnea. Although its use has declined markedly in recent years, if the patient is on a theophylline preparation, obtaining a theophylline level is warranted since many patients take additional medications when their breathing deteriorates, and toxicity may be seen. Patients may have symptoms or effects of theophylline toxicity even with a "normal" level, since the therapeutic margin of this agent is so narrow.[51]

The measurement of B-type natriuretic peptide (BNP) is a tool to differentiate acute CHF from other disease processes, mainly COPD and asthma, that may similarly present with acute dyspnea. BNP is a naturally occurring peptide that is released by the ventricles in response to volume expansion and stretch. It plays a central role in the neurohormonal response to "unload" the ventricles in CHF through natriuresis, diuresis, vasodilation, and suppression of the renin-angiotensin system. It is a sensitive marker for both acute and chronic CHF, and correlates well with the functional class of patients as well as their prognosis.[52,53] Both rapid bedside (whole-blood) and plasma assays are available. Using a cutoff value of 100 pg/mL to exclude the diagnosis of CHF, BNP is significantly more accurate in excluding CHF in acutely dyspneic patients than a conventional clinical assessment by general internists and emergency physicians. As the cutoff value is lowered, the assay is more sensitive for detecting CHF, but at the expense of overall accuracy.[54] Moreover, the utility of BNP is debated in patients for whom it is most likely to be helpful, such as those with equivocal clinical evaluations.[55] Thus, BNP measurements may be helpful in revealing patients with unsuspected CHF, but its role in the management of acute COPD exacerbations is yet to be fully delineated (see Differential Considerations).

DIFFERENTIAL CONSIDERATIONS

The differential diagnosis of the acutely dyspneic and hypoxic patient is broad. The condition that is most commonly mistaken for COPD is cardiogenic pulmonary edema, which may present with dyspnea and wheezing ("cardiac asthma"). Other serious cardiac etiologies include myocardial ischemia and pericardial effusion. Important pulmonary diagnoses include pneumothorax, PE, pneumonia, asthma, acute respiratory distress syndrome, bronchiectasis, pulmonary fibrosis, pleural effusions, and tuberculosis. In addition, metabolic acidosis and shock may manifest as dyspnea and ventilatory failure.

In most cases, differentiation of COPD exacerbation from acute CHF can be made on clinical grounds. Nonetheless, a significant percentage of patients presenting to the ED with acute dyspnea and an established diagnosis of COPD are ultimately diagnosed with acute CHF despite having no prior history of heart failure. The addition of a BNP assay to the ED evaluation of such patients likely identifies the majority in whom a new diagnosis of CHF was not suggested.[56] Although this strategy will potentially result in a greater number of patients being treated in a timely fashion for CHF, due to the limited specificity of BNP measurements, it will also falsely identify a substantial number of patients as having CHF at any cutoff value used.

Conversely, because of the high negative predictive value of a very low BNP (<100 pg/mL), acutely dyspneic patients with very low BNP values despite a moderate degree of clinical suspicion for CHF should be considered to have COPD.[57]

Because BNP can be elevated in association with right ventricular stretch, incautious interpretation of an elevated BNP may lead to the clinician to favor the diagnosis of acute left sided CHF and overlook cor pulmonale and PE, both critical considerations in the patient with COPD.[52] Moreover, acute CHF and COPD often coexist, and even severe elevations in BNP do not obviate the identification and treatment of acute pulmonary pathology.[58] Thus, although BNP measurement may be helpful in the evaluation of the acutely dyspneic patient, it cannot be interpreted in isolation.

Acute pneumothorax can occur with COPD. This diagnosis should be actively pursued in patients presenting with worsening respiratory status, especially when its onset is abrupt. In older patients with COPD, chest pain is often absent. A small pneumothorax cannot be excluded by physical examination and can be very difficult to detect on inspiratory chest films, especially in patients with bullous emphysema. Bedside ultrasound is a useful modality for diagnosing pneumothorax in the ED, particularly in major trauma. The presence of COPD, however, may result in false-positive results, and data in this setting are limited.[59] Ultimately, it is appropriate to perform chest computed tomography (CT) when clinical suggestion of a pneumothorax remains high and results of plain films and ultrasound are nondiagnostic.

Patients with COPD are often sedentary, and consequently at increased risk for venous thromboembolic disease.[60] The patient with cor pulmonale is at even higher risk because of increased blood viscosity, high peripheral venous pressure, and venous stasis. Pulmonary embolus (PE) should be considered when an acute exacerbation is more severe than prior episodes, particularly if deterioration occurs quickly, with no other apparent cause.[61] Unfortunately, because there is significant overlap in their patterns of presentation, differentiating a PE from a COPD exacerbation can be extremely difficult. Prophylaxic measures to prevent venous thromboembolic disease are important considerations in the inpatient management of an acute exacerbation of COPD.

A negative screening test with a sufficiently sensitive D-dimer assay (enzyme-linked immunosorbent assay [ELISA] or whole-blood agglutination) excludes venous thromboembolic disease in all but high pretest likelihood situations.[62] Pretest probability can be assessed using any one of several structured, validated scoring systems. If either the D-dimer is elevated or the pretest probability for PE is high, CT pulmonary angiography should be performed.[63] This requires multislice CT capability and may include indirect CT venography to evaluate the lower extremities for deep vein thrombosis or lower limb duplex ultrasonography.[64-68] A more detailed discussion

of the diagnostic evaluation and treatment of PE can be found in Chapter 86.

Lobar atelectasis occurs as a result of mucous plugging of bronchi and can be lethal. Similar to pneumothorax and PE, it may present abruptly. The chest film may show linear horizontal streaking or small flarelike shadows; more often, it is normal. Hypoxemic reactive airway patients with a protracted course unresponsive to bronchodilators should be presumed to have either PE or atelectasis. If PE is excluded, such patients often require endotracheal intubation and aggressive interventional pulmonary toilet.

Pneumonia is a common, devastating complication of COPD that leads to mortality in many patients. Its clinical appearance is more muted than the classically described lobar pneumonia of young adults. Classic symptoms of cough, fever, and toxicity are seen less often than the more nonspecific and subtle symptoms of malaise, weakness, decreased activity, and anorexia. Leukocytosis may or may not be present, and its presence should not be taken as indicative of infection, because of its low specificity. An infiltrate may or may not be seen, and correlation with previous radiographic studies may be necessary.[69]

Rib fractures occur in patients with COPD secondary to trauma, but in patients receiving steroid therapy, they can be due to vigorous cough alone. When rib fractures are identified, secondary pulmonary contusion and pneumothorax must also be considered. An intercostal nerve block may relieve enough discomfort to restore baseline pulmonary function.

Electrolyte disturbances, such as hypokalemia, hypomagnesemia, hypocalcemia, or hypophosphatemia may impair the contractility of muscles.

There are other treatable chronic, *nonobstructive* pulmonary diseases. For example, bronchiectasis is an often overlooked cause of purulent expectoration. It may accompany and contribute to COPD exacerbations. Although its pathologic characteristic is dilation, not constriction, of airways, the secretions that accompany it may result in an obstructive component. Active tuberculosis must be considered in patients with infiltrates (not only apical), a chronic wasting course, and risk factors for active disease, such as immunodeficiency virus (HIV) disease and homelessness. Sarcoidosis, which can present with chronic cough and constitutional symptoms, usually causes a dry cough and may be suggested on the basis of the chest film appearance.

Finally, there are some iatrogenic causes of acute decompensation in COPD. Many agents, such as beta-blockers and cholinergic agents, may directly or indirectly produce bronchospasm. A second group of potentially deleterious drugs are sedatives. It is important not to confuse hypoxic agitation with anxiety because patients with chronic respiratory failure are abnormally sensitive to the respiratory depressant effect of sedatives, and even small doses may significantly worsen hypoventilation.

Box 72-1 summarizes the causes of acute decompensation in the patient with COPD.

MANAGEMENT

The only modalities that alter the progression of COPD and reduce mortality rates are smoking cessation and chronic oxygen therapy for those with severe disease.[70-72] Vaccines, both against influenza and pneumococcus, are another important aspect of ongoing outpatient care. An overview of the emergency assessment and management of COPD exacerbations is provided in Box 72-2.

BOX 72-1 Causes of Acute Decompensation in the Patient with Chronic Obstructive Pulmonary Disease

I. Acute exacerbations
  A. Infectious
    1. Viral
       Rhinovirus, respiratory syncytial virus, Coronavirus, influenza virus
    2. Bacterial
       Haemophilus influenza, Streptoccocus pneumoniae, Moraxella (Branhamella) catarrhalis, Pseudomonas aeruginosa
    3. Atypical bacteria
       Chlamydia pneumoniae, Legionella
  B. Air pollution
    1. NO_2
    2. Ozone
    3. Particulate particles
II. Other critical events
    1. Pneumothorax
    2. Pulmonary embolism
    3. Lobar atelectasis
    4. Congestive heart failure
    5. Pneumonia
    6. Pulmonary compression (e.g., obesity, ascites, gastric distention, pleural effusion)
    7. Trauma (e.g., rib fractures, pulmonary contusion)
    8. Neuromuscular and metabolic disorders
    9. Unrelated treatable chronic pulmonary disease (bronchiectasis, tuberculosis, sarcoidosis)
    10. Noncompliance with prescribed treatment regimens
    11. Iatrogenic
       a. inadequate therapy
       b. inappropriate therapy (e.g., deleterious drugs)

BOX 72-2 General Therapeutic Guidelines for COPD Exacerbations

Life-Threatening	Moderate/Severe	Mild
Address ABCs	Oxygen to maintain O_2 saturation near 90%	Oxygen to maintain O_2 saturation near 90%
Bag-valve ventilation/preoxygenation	Nebulized beta-agonist/anticholinergic	MDI or nebulized beta-agonist/anticholinergic
Intubation ± via rapid sequence technique	Noninvasive ventilation if severe	Consider oral or IV corticosteroid
Inline beta-agonist/anticholinergic	IV corticosteroid	Consider oral antibiotic on discharge
IV corticosteroid	IV antibiotic	
IV antibiotic		

It is important to consider an inciting or aggravating factor and provide specific therapy as discussed in text.
ABC, airway, breathing, and circulation; COPD, chronic obstructive pulmonary disease; IV, intravenous; MDI, metered dose inhaler.

Ventilation and Oxygenation

All COPD patients in acute respiratory distress need continuous ECG and pulse oximetry monitoring. The patient in terminal ventilatory failure is cyanotic, speechless, lethargic, usually confused, and has gasping, ineffective respirations. Such patients require immediate endotracheal intubation and mechanical ventilation. Since these patients have exhausted all pulmonary reserve, rapid sequence technique should be performed with the goal of rapid paralysis and unconsciousness (see Chapter 1). For induction and paralysis, a combination of a hemodynamically stable sedative-hypnotic such as etomidate and a rapidly acting paralytic such as succinylcholine is an appropriate regimen.

Initial ventilator settings should include a fraction of inspired oxygen (FIO_2) of 100%, tidal volume in the 6- to 8-mL/kg range, and respiratory rate of 8 to 10 breaths/minute in an assist control mode with an inspiratory flow rate of 80 to 100 L/minute.[73] Sedation and analgesia are indicated to facilitate ventilation. Neuromuscular blockade is not routinely required and should be avoided when possible (see Chapter 1). Increased air trapping and resultant high intra-alveolar pressures physiologically induces intrinsic positive end-expiratory pressure (iPEEP) that can cause barotrauma. In addition, increased intrathoracic pressure decreases cardiac filling and output; therefore, peak flow pressures and systemic blood pressures must be carefully monitored. If continuous capnography is not available, ABGs should be drawn after 15 to 20 minutes to ensure that ventilation is appropriate. In some settings, placement of an arterial line is helpful for monitoring blood pressure and ABG tensions. After intubation, *permissive hypercapnia* is essential to the ventilatory treatment of these patients, and subsequent normalization of pH and P_{CO_2} should be gradual over many hours. Low volume and rate settings will result in hypercapnia and respiratory acidosis, but this approach helps prevent associated barotrauma often seen in treating these patients.[74] Moreover, hyperventilation alkalosis must be scrupulously avoided, particularly because patients may have preexisting chronic metabolic alkalosis. This alkalosis can result in seizures and dysrhythmias, especially with coexisting hypokalemia.[75]

Noninvasive ventilatory support (NIVS) is an accepted alternative to invasive ventilation in many patients with ventilatory failure (see Chapter 2). NIVS can be highly effective in avoiding intubation, increasing pH, reducing P_{CO_2} and dyspnea in the first 4 hours of treatment, and reducing mortality rates.[76,77] Selection of patients for NIVS continues to be challenging. Patients likely to benefit from NIVS are those with moderate to severe ventilatory failure and elevated P_{CO_2}, but without marked hypoxemia.[78] NIVS cannot substitute for invasive ventilation in those patients who are hemodynamically unstable or in whom respiratory arrest appears inevitable. On the opposite end of the spectrum, it remains unclear whether NIVS should be instituted in patients with mild to moderate exacerbations. Although the Cochrane Systematic Review stresses early NIVS therapy to prevent the development of worsening acidosis and need for intubation, there is insufficient evidence to recommend the routine use of NIVS in mild exacerbations.[77,79] Table 72-2 outlines inclusion and exclusion criteria for the use of NIVS.

NIVS can be delivered by either a nasal or a full-face mask. Modes of ventilation include continuous positive airway pressure (CPAP) and biphasic positive airway pressure (BiPAP).[80] Patients with COPD and respiratory distress have significant intrinsic PEEP (iPEEP), and this acts as an inspiratory threshold for the patient and increases the work of breathing.[81] Both modes of NIVS help to counteract this iPEEP and thereby decrease the work of breathing. Nasal CPAP is a simple technique, and 5 to 10 cm H_2O pressure is required. When using BiPAP ventilation, expiratory positive airway pressures are typically set at 2.5 to 5 cm H_2O, while inspiratory pressures range between 7.5 and 15 cm H_2O.

If the patient experiences relief of dyspnea, has stronger respirations, and becomes more alert, intubation may be averted, but the patient must be diligently observed for deterioration. Increasing respiratory rate, lethargy, exhaustion, speechlessness, paradoxical abdominal breathing movements, and falling oxygen saturation despite therapy mandates invasive ventilation.

The most important factor in the decision to intubate is the patient's clinical status, not ABG measurements. Even in the face of a significant rise in P_{CO_2} with oxygen administration, intubation may be unnecessary if the patient's clinical status has stabilized. Similarly, improving ABG values should not overrule the clinical impression of deterioration. Temporary improvement may be followed by exhaustion and respiratory failure. Table 72-3 outlines indications for invasive mechanical ventilation. Several of these criteria, adapted from the GOLD collaborators, are subject to interpretation, underscoring

Table 72-2 Suggested Selection and Exclusion Criteria for the Use of NIVS

SELECTION CRITERIA (ONE OR MORE MAY BE PRESENT)	EXCLUSION CRITERIA (ANY MAY BE PRESENT)
Moderate to severe dyspnea with use of accessory muscles and paradoxical abdominal motion	Respiratory arrest
Respiratory rate > 25 breaths/minute	Cardiovascular instability
Moderate to severe acidosis (pH < 7.35) and hypercapnia ($Paco_2$ > 45 mm Hg)	Uncooperative patient (agitated or severely somnolent)
	Upper airway obstruction
	High aspiration risk
	Recent facial or gastroesophageal surgery
	Craniofacial trauma, fixed nasopharyngeal abnormalities
	Nonfitting mask

NIVS, noninvasive ventilatory support; $Paco_2$, arterial partial pressure of carbon dioxide.

Adapted from Rabe K, Hurd S, Anzueto A, et al: Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 176:532, 2007; and Soto F, Varkey B: Evidence-based approach to acute exacerbations of COPD. Curr Opin Pulm Med 9:117, 2003.

Table 72-3 Proposed Indications for Mechanical Ventilation

Respiratory arrest
Worsening level of consciousness despite maximal therapy*
Cardiovascular instability (shock, heart failure)*
NIPPV failure or exclusion criteria (see Table 72-2)
Severe dyspnea with use of accessory muscles and paradoxical abdominal motion*
Severe tachypnea*
Life-threatening hypoxia
Severe acidosis and hypercapnea*
Other complications (metabolic abnormalities, sepsis, pneumonia, pulmonary embolism, barotraumas, massive pleural effusion)*

*For several of these parameters, criteria are deliberately imprecise; clinical decisions must be individualized in each case.

NIPPV, nasal intermittent positive-pressure ventilation.

Adapted from Rabe K, Hurd S, Anzueto A, et al: Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 176:532, 2007.

the critical role of clinical judgment in airway management decisions.

Physicians have an inherent anxiety about using oxygen therapy in patients with COPD because of the fear of inducing apnea by removing the hypoxic drive to breathe.[83,84] Although controversy surrounds the appropriate use of oxygen in exacerbations of COPD, the risks of hypoxemia need to be weighed against the risk of reducing ventilation. At no time, because of fear of reducing hypoxic ventilatory drive, should a patient be subjected to continued, severe hypoxemia, with its attendant risk of myocardial or tissue ischemia, worsening metabolic acidosis, and muscular fatigue. Despite intervention, including oxygen therapy, intubation is often ultimately required. Although P_{CO_2} rises in response to oxygen therapy, minute ventilation changes little.[85,86] Thus, titrated oxygen therapy to maintain an oxygen saturation close to 90%, while avoiding an unnecessarily high Fio2, is recommended. This can be done more reliably with the use of Venturi masks than with nasal cannulae. A patient with partial correction of hypoxia, who has mild respiratory acidosis, continues to have a high respiratory drive.[87] It is the patient who is breathing inappropriately *slowly* who is at highest risk of apnea with oxygen therapy.[88]

In patients who have compensated better, hypoxemia is avoided by hyperventilation. Administering low-flow oxygen by nasal cannulae at 1 to 2 L/minute in such patients raises the F_{IO_2} by a few percent, relieving the sensation of dyspnea. The patient then usually stops hyperventilating, thus reducing the work of breathing and oxygen consumption. This intervention may have significant benefits, especially in the setting of multiple comorbidities, such as myocardial ischemia or sepsis.

General Drug Therapy

Bronchodilators

Although bronchospasm is not the primary inciting event in acute COPD exacerbation, both beta-agonists and anticholinergic agents are considered first-line agents. The choice of agent for treating a given patient may depend on the respective side effect profiles of these two classes of drugs.[8,89,90]

Although many choices are available, inhaled albuterol, which is short-acting with selective $beta_2$-receptor action, is the beta-agonist of choice. The nebulization dose of albuterol is 2.5 to 5.0 mg (0.5–1.0 mL of 0.5% solution). Most patients tolerate two to three rapid successive doses of oxygen-nebulized beta-agonist with little difficulty. Therapy must occasionally be titrated if the side effects of tremor, tachycardia, or ventricular ectopy are significant.

Anticholinergic agents block muscarinic receptors and prevent smooth muscle contraction while decreasing the release of secretions from submucosal glands. Nebulized anticholinergic agents are as effective as $beta_2$-agonists in COPD and can be used alone or in conjunction with $beta_2$-agonists as first-line therapy in acute exacerbations.[91-93] Although evidence regarding the efficacy of their coadministration is controversial, for moderate to severe exacerbations presenting to the ED, these drugs should be given together for their possible synergistic effects.[7,8,46] Anticholinergics can be administered by nebulization or metered dose inhaler (MDI) and are also effective for intubated patients. Ipratropium bromide, a quaternary ammonium compound, is extensively studied in COPD. It has few systemic effects, yet has powerful bronchodilating properties. It is available as a nebulization solution and is prepared in MDI form as well. The nebulization dose is 0.5 mg, which may be repeated every half hour for a total of three doses and subsequently every four hours.

Long-acting bronchodilator agents such as salmeterol ($beta_2$-agonist) and tiotropium (anticholinergic) are added to treatment recommendations for chronic stable COPD.[7] Although these agents may reduce the frequency of COPD exacerbations, no role for their use in ED management of acute exacerbation has yet been defined.

The COPD patient with a mild to moderate exacerbation may be able to self-administer bronchodilator agents using an MDI with a spacer device, which is equally effective as nebulized treatment.[94-96] Studies also demonstrate the efficacy and cost benefit of MDI therapy over nebulization in acutely hospitalized patients.[97] Because of the smaller dose delivered with single MDI puffs, MDI protocols often involve multiple puffs at each dosing interval. This mode of therapy should be considered only for stable cooperative emergency patients. The intubated patient should receive bronchodilator therapy via in-line nebulization.

Methylxanthines, principally aminophylline, were once prominently used in COPD exacerbations. They do not improve outcomes, even when combined with beta-agonists and anticholinergic agents. Evidence does not support the use of methylxanthines for COPD exacerbations. Recommendations that include methylxanthines as a second-line therapy when other modalities have failed are tempered by concerns about toxicity, which may outweigh the theoretical positive effects of these agents.[98] Patients taking methylxanthines on a chronic, ambulatory basis, should likewise not receive additional methylxanthines in the course of treatment of acute COPD exacerbation in the ED. Continuation of oral therapy, if deemed desirable to stimulate ventilation, can be undertaken on the inpatient service.

Corticosteroids

The anti-inflammatory effects of steroids provide a strong rationale for their use in acutely ill patients with COPD. Although steroids may not alter the immediate ED course, evidence points to a modest decrease in the relapse rate of acute exacerbations and improvement of dyspnea.[99,100] For severe exacerbations requiring admission, IV methylprednisolone (125 mg) or oral prednisone (60 mg) is given early in treatment and continued daily. Oral prednisone (40 mg once daily) is appropriate for discharged patients. Recommended doses of corticosteroids vary widely in the published studies. Consensus guidelines emphasize using doses on the lower end of the accepted range to minimize common adverse effects, such as hyperglycemia, myopathy, and immune suppression.[7] Inhaled steroid preparations have significantly less systemic absorption and potential for adverse effects. Although there is some evidence for their role in acute exacerbations, this has yet to be fully delineated.[101,102]

Antibiotics

In contrast to acute bronchitis in the setting of normal lung function, where antibiotics are clearly of no benefit, some COPD patients with an acute exacerbation appear to benefit from antibiotic therapy.[103,104] The GOLD collaborators recommend administering antibiotics in patients with an increase in sputum purulence and either increased dyspnea or increased sputum volume, as well as for any patients requiring invasive or noninvasive ventilation (see discussion below on pneumonia).[7] Furthermore, some patients may have clinical pneumonia without radiographic evidence, which may also warrant antibiotic therapy. Since antibiotics are generally benign and potentially beneficial, they should be considered for acute exacerbations in patients presenting to the ED.

Most of the randomized, controlled trials suggesting a treatment benefit with antibiotics were conducted prior to the emergence of widespread resistance. Amoxicillin, tetracycline, and trimethoprim-sulfamethoxazole were the most common antibiotics used in these studies. Although antibiotics with broader spectrum coverage such as the fluoroquinolones and third-generation cephalosporins are commonly prescribed, the evidence for the superiority of these newer agents is indirect.[45] The GOLD collaborators recommend using antibiotics that reflect local patterns of antibiotic sensitivity to *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*.[7] Azithromycin has the added advantage of once-a-day doses for only 5 days. Ampicillin alone is not recommended because of high rates of resistance.[105]

For outpatient therapy of pneumonia in patients with COPD, an advanced macrolide, such as azithromycin or clarithromycin, can be used in patients who have not recently received antibiotic therapy. In patients who have recently received an antibiotic, a respiratory quinolone, such as levofloxacin, gatifloxacin, or moxifloxacin, can be used or a β-lactam, such as a cephalosporin, can be added to the macrolide. Oral therapy should last for at least 10 days, with longer therapy (2 weeks) if *Mycoplasma* or *Chlamydia pneumoniae* are possible causal organisms. For inpatient therapy, no distinction is made for patients with COPD. A more extensive discussion of antibiotic therapy in pneumonia is found in Chapter 74.

Other Therapeutic Agents

Mucokinetic Medications and Mucus Clearance Strategies

Mucus production and cough are cardinal symptoms of COPD. Unfortunately, little objective evidence exists that mucokinetic agents are successful, and they are not recommended.[8,45,46] Nebulized saline, oral expectorants, and chest physiotherapy have all failed to demonstrate benefit.[46,106]

Respiratory Stimulants

Several respiratory stimulants have been studied in patients with COPD, including opioid antagonists, progesterone, acetazolamide, doxapram, and almitrine.[107,108] Doxapram and almitrine appear to be the most effective of these agents. Although doxapram can effect small, temporary improvements in blood gas exchange in the first hours of treatment, it is less effective than other techniques, such as NIVS.[109,110] Almitrine, which may have a role in chronic therapy, does not have a role in acute respiratory failure.[111] Respiratory stimulants are therefore not recommended for routine use in the ED.

Heliox

Helium-oxygen mixtures decrease the work of breathing and improve airflow by virtue of their low density. Such mixtures, however, fail to demonstrate a benefit in either ventilated or nonventilated patients with COPD exacerbations.[112]

Table 72-4 General Guidelines for Admission of the Patient with COPD

Significant worsening of symptoms from baseline
Inadequate response of symptoms to ED management
Significant comorbid condition (e.g., pneumonia, heart failure)
Worsening hypoxia or hypercarbia (from baseline)
Inability to cope at home or insufficient home resources

COPD, chronic obstructive pulmonary disease; ED, emergency department.
Adapted from Rabe K, Hurd S, Anzueto A, et al: Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 176:532, 2007.

DISPOSITION

Significant deterioration from baseline is the general guideline for admission of patients with COPD. Important factors in the decision include the presence of coexisting conditions, failed outpatient management for the current exacerbation, and lack of improvement while in the ED. The GOLD collaborators propose guidelines for admission, and these are adapted in Table 72-4. If the decision is made to discharge the patient, attention should also be directed to the patient's vaccination status, proper technique of inhaler use, evaluation of outpatient support systems, appropriate referrals and, perhaps most importantly, smoking cessation.[7,113]

KEY CONCEPTS

- BNP can be elevated as a result of right ventricular stretch. The clinician may mistakenly assume the cause is left-sided CHF and overlook cor pulmonale or pulmonary embolus.
- Beta-agonists, anticholinergics, and corticosteroids are the mainstay of drug therapy of acute COPD exacerbation.
- Noninvasive ventilatory support (NIVS) is an important therapeutic option in the COPD patient with respiratory failure. It has significant advantages over traditional mechanical ventilation and should be considered when significant dyspnea, acidosis, hypercapnia, and elevated respiratory rate are present.
- Acute complications are common aggravating factors and need consideration during evaluation. These include pneumonia, pneumothorax, and pulmonary embolism.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 73

Upper Respiratory Tract Infections

Frantz R. Melio

PHARYNGITIS (TONSILLOPHARYNGITIS)

Perspective and Principles of Disease

Tonsillopharyngitis (from this point on referred to as pharyngitis) is an inflammatory syndrome of the oropharynx. Transmission is mainly through contact with respiratory secretions, but transmission through food and fomite contact is also possible. Although most cases of pharyngitis are uncomplicated and self-limited, the swelling may threaten airway patency or preclude ingestion of adequate liquids, thereby resulting in dehydration.

Etiology

Viruses are responsible for most cases of pharyngitis. Group A beta-hemolytic streptococcus (GABHS) is the most common bacterial cause of pharyngitis in children, with a peak incidence of 30%.[1,2] Common causes of acute pharyngitis in adults are beta-hemolytic *Streptococcus*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*.[1-6] Pharyngitis can also be caused by sexually transmitted diseases. Diphtheria is a potentially serious cause of pharyngitis.

Cultures obtained in cases of chronic or recurrent pharyngitis often grow mixed aerobic and anaerobic bacteria. Commonly isolated aerobic organisms include streptococcal species, *Staphylococcus aureus*, *Haemophilus influenzae*, and *Moraxella (Branhamella) catarrhalis*. The anaerobic bacteria most commonly isolated include *Bacteroides*, anaerobic gram-positive cocci, and *Fusobacterium*. β-Lactamase production is extremely common in bacteria responsible for chronic pharyngitis. Epstein-Barr virus (EBV) and *Actinomyces* are also implicated in chronic or recurrent pharyngitis. Rare causes of bacterial pharyngitis include *Francisella tularensis*, *Yersinia pestis*, and *Yersinia enterocolitica*.[1-3]

Clinical Features

The most common symptom is pharyngeal pain that is aggravated by swallowing and may radiate to the ears. Examination usually reveals fever, pharyngeal erythema, pharyngeal or tonsillar exudate, and tonsillar enlargement (Fig. 73-1). The infection tends to localize to lymphatic tissue and produces suppuration and swelling of the tonsils, along with tender cervical adenopathy. Occlusion of the eustachian tubes may result in secondary otitis media. Clinical differentiation of the etiologic organisms is virtually impossible.[1-5]

Viral pharyngitis usually occurs in conjunction with cough, rhinorrhea, myalgia, headache, stomatitis, conjunctivitis, exanthem, and odynophagia. Low-grade fever and pharyngeal exudates may be present. Cervical lymphadenopathy is generally absent.[1,2] Mild pharyngeal edema and erythema associated with a "scratchy" throat are present in 50% of patients with the common cold. Systemic viral infections, including measles, cytomegalovirus (CMV), rubella, and human immunodeficiency virus (HIV), may initially manifest as mild pharyngitis.[1-3] HIV and CMV pharyngitis may be clinically indistinguishable from infectious mononucleosis.[1,2]

Influenza occurs in epidemics and is associated with high fever, myalgia, and headache. Although 50 to 80% of patients with influenza experience pharyngeal discomfort, pharyngeal exudate and cervical lymphadenopathy are rare. Adenovirus may cause severe exudative pharyngitis with cervical adenitis similar to that in streptococcal pharyngitis. Thirty percent to 50% of cases of adenoviral pharyngitis are associated with a follicular, usually unilateral, conjunctivitis.[1] Coxsackieviruses are the most frequent cause of hand-foot-and-mouth disease and herpangina.[1,2]

Pharyngitis is a common manifestation of infectious mononucleosis (caused by EBV) in young adults.[1-3] Symptoms develop after an incubation period of 4 to 7 weeks. Fever and a tonsillar exudate or membrane (that is cheesy or creamy white) are often present. Cervical as well as generalized lymphadenopathy (90–100%) and splenomegaly (50%) are usually noted, and palatal petechiae may be present. Hepatomegaly is present in 10 to 15% of cases. Periorbital edema and rash are rare findings. In up to 90% of patients with mononucleosis who are inadvertently given ampicillin or amoxicillin, a diffuse macular rash develops that may be misdiagnosed as an allergic reaction.[1,2]

Patients with early (days to weeks) HIV infection can develop acute retroviral syndrome. This is manifested by fever, sore throat, generalized nontender lymphadenopathy, a diffuse maculopapular rash, arthralgias, mucocutaneous ulcerations, and, commonly, diarrhea. A nonexudative pharyngitis is present in 50 to 70% of patients. Oral thrush and ulcers may be present. Acute HIV infection can be differentiated from infectious mononucleosis by its more acute presentation, the absence of tonsillar hypertrophy or exudates, the frequent occurrence of rash, and the presence of oral ulcerations.[1]

Herpes simplex also causes pharyngitis. These infections typically affect young adults. The presence of painful vesicles with erythematous bases is characteristic of herpes

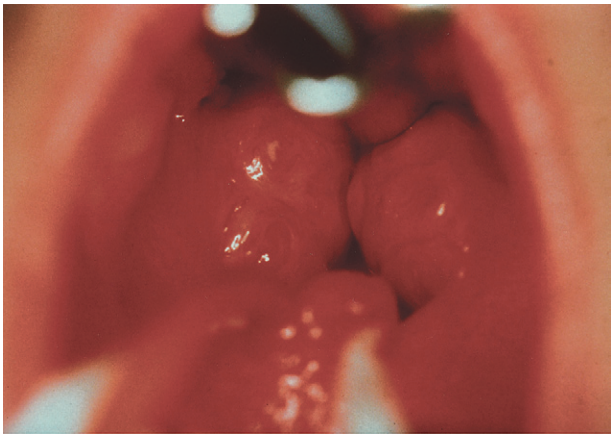


Figure 73-1. Bilateral tonsillopharyngitis.

pharyngitis. Ulcers may be present on the pharynx, lips, tongue, gums, and buccal mucosa. Pharyngeal erythema and exudate, fever, and tender lymphadenopathy are common for 1 to 2 weeks. In an immunocompromised host, large painful ulcers may be present. Herpes pharyngitis can be due to primary infection or reactivation. Concomitant bacterial superinfection may occur.[1,2]

GABHS pharyngitis is primarily a disease of children 5 to 15 years old and, in temperate climates, occurs in winter and early spring.[1,2] It is responsible for less than 15% of cases of pharyngitis in patients older than 15 years and is rare in patients younger than 3 years. In epidemics, the incidence may double.[1,2] GABHS pharyngitis is associated with sudden-onset sore throat, fever over 38.3° C (101° F), tonsillar erythema and exudates, palatal and uvular petechiae, uvular edema and erythema, and tender anterior cervical lymphadenopathy. Headache, nausea, vomiting, and abdominal pain may be present, especially in children. Cough, rhinorrhea, coryza, or other viral symptoms are usually absent. GABHS pharyngitis associated with a fine sandpaper erythematous rash that subsequently desquamates is termed *scarlet fever*. These findings, however, cannot be used to reliably diagnose or exclude streptococcal pharyngitis. Patients with recent exposure to others at risk for GABHS pharyngitis or in whom it has been diagnosed are more likely to become infected.[1-5] Non–group A beta-hemolytic streptococcal species can cause pharyngitis indistinguishable from GABHS.[1]

Diphtheria is a potentially lethal cause of pharyngitis that is uncommon where adequate vaccinations are administered. U.S. serologic surveys indicate that a large percentage of adults and adolescents lack immunity to diphtheria toxin.[1] Following a 2- to 4-day incubation period, patients develop malaise, sore throat, fever, and dysphagia. Examination early in the disease process may reveal pharyngeal erythema and isolated spots of gray or white exudate that later coalesce to form a pseudomembrane. This gray-green pseudomembrane is usually well demarcated and covers the nares, tonsils, soft palate, pharyngeal mucosa, and, occasionally, the uvula. The membrane may extend to involve the larynx and tracheobronchial tree, leading to hoarseness, cough, stridor, and airway obstruction. Tender and at times painful cervical lymphadenopathy may be found. Severe inflammation and edema can produce dysphonia and a characteristic "bull neck" appearance. Some strains of *Corynebacterium diphtheriae* produce a systemic toxin that may cause myocarditis, polyneuritis (at first autonomic and then peripheral), vascular collapse, diffuse focal organ necrosis, and death. Asymptomatic carriers may transmit the disease.[1,2] *Corynebacterium ulceras* is an animal pathogen passed on by consumption of raw milk that can produce infection indistinguishable from *C. diphtheriae*.

Arcanobacterium haemolyticum (previously called *Corynebacterium haemolyticum*) typically affects the 10- to 30-year-old age group and can be indistinguishable from streptococcal pharyngitis. Most patients have an associated rash that may be scarlatiniform, urticarial, or erythema multiforme (occasionally skin manifestations may be the only complaint). Patients complain of a moderately severe sore throat and are usually nontoxic and afebrile. *A. haemolyticum* may cause a membranous pharyngitis that strongly mimics diphtheria; it is also associated with chronic tonsillitis.[1-3]

Anaerobic pharyngitis, or Vincent's angina, is characterized by superficial ulceration and necrosis that often results in the formation of a pseudomembrane. Foul-smelling breath, odynophagia, submandibular lymphadenopathy, and exudate are often present. Patients typically have poor oral hygiene.[3]

Gonococcal pharyngitis is a sexually transmitted disease that may occur independently of genital infection. Those at highest risk are persons who practice receptive oral sex, especially men who have sex with men (in whom the incidence has been reported to be as high as 15%). Its severity is variable and it may result in an exudative or nonexudative pharyngitis. These differing manifestations can be explained in part by the lack of symptoms during the latent period of infection. Asymptomatic carriers are described, as is chronic and recurrent pharyngitis. Gonococcal pharyngitis is an important source of gonococcemia.[1-3] Syphilitic pharyngitis is a manifestation of primary or late (tertiary) syphilis and presents with painless mucosal lesions. *Chlamydia trachomatis* pharyngitis is a sexually transmitted disease. Similar to gonococcal infection, *C. trachomatis* pharyngitis is associated with orogenital sex. Urogenital culturing is necessary along with treatment of sexual contacts. Patients are usually asymptomatic or may have only mild symptoms.[1,2]

Tuberculous pharyngitis usually occurs in patients with advanced disease. Symptoms and signs include hoarseness and dysphagia with pharyngeal ulcerations. Candidal pharyngitis is usually found in immunocompromised adults. Patients have dysphagia, odynophagia, and adherent white plaques with focal bleeding points.

Mycoplasma pneumoniae infection usually causes a mild pharyngitis. *Mycoplasma* infection occurs in epidemics and in crowded conditions and can be responsible for approximately 10% of cases of adult pharyngitis. Pharyngeal and tonsillar exudates, cervical lymphadenopathy, and hoarseness are common. Lower respiratory tract infection may also be present.[1-3]

Chlamydia pneumoniae pharyngitis resembles *M. pneumoniae* pharyngitis. It also occurs in epidemics or crowded conditions. Severe pharyngitis with laryngitis is suggestive of *C. pneumoniae* infection. Swelling and pain in the deep cervical lymph nodes may be prominent. Lower respiratory tract and concomitant sinusitis occur. The hallmarks of chlamydial pharyngitis are recurrence and persistence.[2,3]

Diagnostic Strategies

Monospot tests may be negative in up to 10% of patients with infectious mononucleosis, especially in the early stages of the illness. Immunoglobulin M (IgM) antibodies to EBV capsid antigen develop in 100% of cases. EBV nuclear antigens develop within 3 to 6 weeks and are useful if an initial negative test becomes positive at a later date. Peripheral blood smears demonstrate atypical mononuclear cells in 75% of patients, with the peak incidence occurring in the second to third week of illness.[1,2] Herpes pharyngitis may be diagnosed by culture,

cytopathologic tests on scrapings of lesions, and serologic tests. Enzyme-linked immunosorbent assay testing for HIV can be falsely negative during the first 3 to 4 weeks of illness. During this period of time, quantitative assays for plasma RNA should be performed.[1]

Diagnosis of GABHS infection is important to prevent complications, particularly rheumatic fever. Even the most experienced practitioner has difficulty clinically diagnosing streptococcal pharyngitis.[1-5] Several authors propose scoring systems based on clinical findings,[2-5] but the only valid method of determining acute GABHS infection is by acute and convalescent antistreptolysin O titers, which is not practical in the emergency department. A single throat culture has a sensitivity of 90 to 95% in detecting *Streptococcus pyogenes* in the pharynx. Variables that affect the accuracy of throat cultures include collection and culturing technique, as well as the recent use of antibiotics.[1,3-5]

Rapid diagnostic tests for GABHS detect streptococcal antigens. Rapid streptococcal tests (RSTs) have a reported specificity of 70 to 100% (with most being >95%) and a sensitivity of 31 to 100% (with most being 60–95%). Sensitivity and specificity in actual practice are lower than in controlled trials.[1] Patients with positive cultures or RSTs may actually be carriers who may not need treatment and are at low risk for transmission and complications. The use of RSTs in patients without clinical findings consistent with GABHS may increase false-positive results. A positive RST seems to reliably indicate the presence of *S. pyogenes* in the pharynx. In contrast, RSTs are often negative in the setting of pharyngitis with a low bacterial count (these patients are still at risk for complications, including rheumatic fever). It is recommended that a negative RST in a child be followed by a confirmatory culture.[1,3-5]

Diagnosis and treatment of GABHS in adults is controversial and the subject of two expert panel recommendations.[3-5] It is agreed that antibiotics are overused in the treatment of pharyngitis, the use of clinical criteria in conjunction with RSTs improves the accuracy of RSTs, adults with negative RSTs do not require confirmatory cultures (because of the lower incidence of GABHS infection and the extremely low risk for complications), and neither testing nor antibiotic treatment should be used in patients who are clinically at low risk for GABHS infection. Both panels agree that the most useful clinical criteria for determining GABHS pharyngitis are the Centor criteria (Box 73-1).[3-5]

The position of the Infectious Disease Society of America is that a positive throat culture or RST in addition to clinical symptoms and signs is needed to confirm the diagnosis of GABHS pharyngitis. The society stresses that clinical criteria alone are appropriate to determine which patients do not need testing but are insufficient, without bacterial confirmation, to diagnose GABHS pharyngitis.[1]

Though controversial, we recommend that: Patients with none or one Centor criterion not be tested or treated. Treat patients with all four criteria without testing. Perform RSTs in patients with two or three criteria, and treat only those who have positive results (Box 73-2).[4,5]

These recommendations apply only to immunocompetent patients with no underlying comorbid conditions or a history of rheumatic fever. They do not apply in settings of outbreaks of GABHS infection or rheumatic fever, nor are they appropriate in situations in which the endemic rate of rheumatic fever is higher than that in the United States. It is important to consider local epidemics and be prepared to revise the approach to treatment if evidence of GABHS infection or complications exists.[3-5] Non–group A streptococcal pharyngitis should also be treated, since the same suppurative complications occur as with group A. Pharyngitis caused by other treatable organisms must also be considered and is associated with serious complications.[1,2,4] Confirmation of diphtheria requires culturing on the proper media and immunologic testing (polymerase chain reaction). Toxigenicity testing must also be performed.[1,2] The diagnosis of *A. haemolyticum* infection should be considered if rash, including erythema multiforme, accompanies pharyngitis. The diagnosis of Vincent's angina is based on clinical findings and Gram's stain. In cases of possible gonococcal infection, a sample should be plated on Thayer-Martin agar. Tuberculous pharyngitis is diagnosed by acid-fast staining. Syphilitic pharyngitis is diagnosed with darkfield microscopy, direct immunofluorescence, and serologic testing. Candidal pharyngitis is diagnosed by noting yeast on potassium hydroxide preparations of throat swabs or Sabouraud's agar.[2] The diagnosis of mycoplasmal pharyngitis can be confirmed serologically or by culture. Rapid antigen tests for *Mycoplasma* are available. Chlamydial pharyngitis can be diagnosed by serologic testing, by culture, or by antigen detection tests. Studies of patients with chronic pharyngitis find that surface cultures do not correlate well with the causal pathogens, which are often concealed within the tonsillar crypts.

Differential Considerations

The differential diagnosis of adult pharyngitis includes deep space infections, tumors, foreign bodies, pemphigus, Stevens-Johnson syndrome, drug reactions, allergic reactions, uvulitis, angioneuropathic edema, chemical and thermal burns, esophagitis, gastroesophageal reflux disease, cricoarytenoid arthritis, thyroiditis, and epiglottitis.[5]

Management

Patients with pharyngitis should be treated symptomatically with topical anesthetic rinses or lozenges and with acetaminophen or ibuprofen. Oral hydration and saltwater gargles are helpful. Most cases of pharyngitis are self-limited and follow a benign course.[1,3-5]

Treatment of infectious mononucleosis is supportive (see Chapter 128). Patients should avoid contact sports for 6 to 8 weeks to minimize the small risk of splenic rupture. Corticosteroids are indicated for patients with tonsillar hypertrophy that threatens airway patency, severe thrombocytopenia, or hemolytic anemia.[1,2] Acyclovir, valcyclovir, or famciclovir is indicated in immunocompromised patients with herpetic pharyngitis and may be beneficial in the treatment of acute

BOX 73-1 Centor Criteria for Determining Group A Beta-Hemolytic Streptococcal Pharyngitis

Tonsillar exudates
Tender anterior lymphadenopathy or lymphadenitis
Absence of cough
History of fever

BOX 73-2 Centor Criteria Scoring for Determining Testing and Treatment for Group A Beta-Hemolytic Streptococcal Pharyngitis

Centor Score	Testing/Treatment
0–1	None
2–3	Treatment based on results of RST
4	Treat without testing

herpetic pharyngitis.[1,5] The use of antiretrovirals is indicated in acute HIV infection.[1]

Although many studies focus on GABHS pharyngitis, proper treatment of nonstreptococcal pharyngitis can also avoid serious complications. Because clinical judgment is insufficient and rapid diagnostic tests are not always accurate and diagnose only GABHS, this disease process is often treated empirically. The choice of antibiotic for the empirical treatment of adult pharyngitis is not fully elucidated. It is unclear how effective antibiotics are in uncomplicated cases of non-GABHS pharyngitis in adults. Antibiotics may modestly shorten the course of the disease process, but they are also associated with increased recurrence, increased bacterial drug resistance, decreased immune response, and patient expectations for antibiotics with subsequent episodes of pharyngitis.[1,3-6]

GABHS pharyngitis in children and adolescents must be treated adequately (within 9 days) to prevent rheumatic fever. The incidence of rheumatic fever parallels that of GABHS and has markedly diminished with the use of antibiotics. Patients with mild cases of GABHS pharyngitis may develop rheumatic fever. Current estimates show that rheumatic fever complicates 0.3% of cases of GABHS pharyngitis, but in epidemics the incidence increases to 3%. More troubling is an increase in sporadic outbreaks of rheumatic fever.[3-5] The incidence and course of poststreptococcal glomerulonephritis caused by nephritogenic strains are unaffected by antibiotic therapy.[1,3-5] Antibiotic therapy is extremely effective in eradicating GABHS and its other complications. Untreated, GABHS pharyngitis is a self-limited illness that lasts 3 to 4 days. Early antibiotic treatment of streptococcal pharyngitis leads to a 13% earlier resolution of symptoms and shortens the course of illness by about 1 day. Antibiotic therapy also decreases transmission, and patients are no longer infectious after 24 hours of antibiotic treatment.[1,3-6]

The antibiotic regimen of choice in adults for GABHS pharyngitis is either a single intramuscular injection of 1.2 million U of benzathine penicillin or a 10-day course of penicillin V, 500 mg orally twice a day. Less frequent dosing is less effective in preventing rheumatic fever.[1,3-5] Intramuscular penicillin may be more effective than oral penicillin and ensures compliance, but allergic reactions are more severe as a result of procaine allergy, and treatment is more expensive. Penicillin failure usually reflects noncompliance, reinfection, or the presence of β-lactamase-producing organisms. Erythromycin is recommended for patients who are allergic to penicillin. A 1-g total daily dose must be given for 10 days, but dosing intervals of two, three, and four times a day are equally effective in preventing rheumatic fever.[1,3-5] Cephalosporins or clindamycin are also acceptable for penicillin-allergic patients. Once-daily amoxicillin therapy may be effective in children.[1,7] Oral cephalosporins may be more effective than penicillin in eradicating GABHS pharyngitis and some authors argue for their use as first-line agents.[7] These alternative regimens should be used for patients not responding to penicillin or unable to tolerate either penicillin or erythromycin.[1,3,6,7]

Patients whose symptoms return within a few weeks of treatment may have been noncompliant with oral therapy or may have acquired a new infection (at times from asymptomatic close contacts). Evaluation and treatment should be similar to that of the first episode, with consideration given to treatment with intramuscular penicillin. Further recurrences mandate more extensive evaluation. Pharyngeal cultures should be obtained and consideration given to evaluating and treating close contacts for GABHS infection.[3]

Successful treatment of diphtheria is inversely related to the duration of disease. When diphtheria is strongly suspected on the basis of clinical findings, treatment must begin immediately. Airway collapse may occur suddenly and without warning. The mainstay of therapy is antitoxin (a horse serum product), that should be administered immediately on clinical suggestion of diphtheria. The dose of antitoxin varies widely and depends on the site of infection and the duration of symptoms. Antibiotics have little effect on the resolution of systemic toxicity, but they are useful in eradicating *C. diphtheriae* infection and preventing transmission. Infected patients should remain in strict isolation to prevent transmission. The antibiotic of choice is penicillin G for 5 days, followed by penicillin VK for 5 days, or erythromycin, 500 mg four times a day for 10 days. A small percentage of patients require an additional 10-day course of erythromycin for persistent infection. Rifampin, 600 mg/day for 10 days, is also effective in eradicating the carrier state of *C. diphtheriae* and treating erythromycin-resistant diphtheria. Diphtheria toxoid should be administered during convalescence and to unvaccinated close contacts.[1,2,8]

A. haemolyticum may be resistant to penicillin. Erythromycin, 250 mg orally four times a day for 10 days, is the treatment of choice.[1,2] Vincent's angina is treated with penicillin or clindamycin and rinses with an oral oxidizing agent (hydrogen peroxide).[8] Gonococcal pharyngitis is often more difficult to eradicate than genital infections. Treatment is similar to that for gonococcal urethritis and consists of ceftriaxone (125 mg intramuscularly) or single-dose oral treatment with either ciprofloxacin (500 mg), ofloxacin (400 mg), or gatifloxacin (400 mg). Concomitant treatment of chlamydial infection with a single oral dose of 1 g of azithromycin or doxycycline, 100 mg orally twice a day for 7 days, is also recommended.[2,8] Tuberculous pharyngitis is seen with disseminated disease. Patients should be isolated and treated with a multidrug regimen. Pharyngitis caused by primary syphilis is treated with 2.4 million U of benzathine penicillin (long-acting), with 14 days of tetracycline or doxycycline used as an alternative. Candidal pharyngitis is treated with systemic fluconazole or itraconazole. Alternative therapy includes nystatin (suspension or tablets) or oral clotrimazole for 14 days. Chronic suppression therapy with ketoconazole, clotrimazole, or fluconazole is usually required for HIV pharyngitis.[8]

M. pneumoniae is treated with erythromycin, tetracycline, or doxycycline for 7 to 14 days.[2,8] Chlamydial pharyngitis is treated with doxycycline, trimethoprim-sulfamethoxazole, or a macrolide antibiotic. *C. pneumoniae* pharyngitis should be treated for 7 to 10 days to prevent treatment failure and recurrence. *C. trachomatis* pharyngitis may require prolonged or repeated courses of antibiotics.[2,8]

Treatment of recurrent or chronic tonsillitis should include β-lactamase-resistant antibiotics active against aerobic and anaerobic organisms. Choices include oral cephalosporins, amoxicillin-clavulanic acid, penicillin with rifampin or metronidazole, or clindamycin.[2]

Steroids given in conjunction with oral antibiotics in adults with acute pharyngitis may significantly shorten the duration of symptoms and provide a greater degree of pain relief without increasing complications. Oral (40-60 mg of prednisone per day for 1-5 days) or intramuscular (a single dose of 10 mg of dexamethosone) have been found to be equally effective.[9,10]

Disposition

Although most cases of pharyngitis follow a benign course, life-threatening complications can occur. Airway compromise from tonsillar enlargement, local and distant spread of infection, deep neck abscesses, necrotizing fasciitis, sleep apnea, bacteremia, sepsis, and death are reported.[1,3]

Infectious mononucleosis may lead to hepatic dysfunction, splenic injury, neurologic disorders, pneumonitis, pericarditis, and hematologic disorders, including thrombocytopenia and hemolytic anemia.[1,2] Complications of GABHS pharyngitis are both suppurative and nonsuppurative. Suppurative complications include peritonsillar abscess, deep space abscesses, suppurative cervical lymphadenitis, otitis media, sinusitis, mastoiditis, bacteremia, sepsis, osteomyelitis, empyema, meningitis, and soft tissue infections. Nonsuppurative complications include scarlet fever, rheumatic fever, poststreptococcal glomerulonephritis, nonrheumatic perimyocarditis, erythema nodosum, and streptococcal toxic shock syndrome. In contrast to rheumatic fever, other complications of GABHS pharyngitis are increasing in incidence and severity. A chronic carrier state of streptococcal infection exists and can persist for several months despite treatment. These patients are asymptomatic, at low risk for rheumatic fever, and not considered highly contagious. Non–group A streptococcal pharyngitis may be complicated by the same suppurative complications as group A infections. Scarlet fever and acute glomerulonephritis, but not rheumatic fever, are linked to group C and G pharyngitis.[1-3,5]

LINGUAL TONSILLITIS

Lingual tonsillitis is a rarely diagnosed cause of pharyngitis that predominantly occurs in patients who have had palatine tonsils removed. The lingual tonsils are a collection of nonencapsulated lymphoid tissue most commonly (size and location are highly variable) located symmetrically on either side of the midline just below the inferior pole of the palatine tonsils and anterior to the vallecula at the base of the tongue. This lymphoid tissue may enlarge after puberty, repeated infection, and tonsillectomy.[11] Patients with lingual tonsillitis have a sore throat that worsens with movement of the tongue (including tongue depression) and phonation. The patient may have a classic "hot potato" voice (the muffled voice one has when eating very hot food) and complain of feeling a swelling in the throat. Dysphagia, fever, respiratory distress, and stridor may be present. Chronic or recurrent lingual tonsillitis may also cause a chronic cough or sleep apnea. Physical findings often include a normal-appearing pharynx with mild hyperemia. Direct or indirect laryngoscopy reveals an edematous lingual tonsil covered with a purulent exudate. Lateral soft tissue neck films aid in the diagnosis. These films demonstrate a normal-appearing epiglottis and arytenoepiglottic folds, with a scalloped appearance on the anterior surface of the vallecula caused by an enlarged lingual tonsil (Fig. 73-2).[11]

Management includes maintenance of airway patency, antibiotics, and supportive therapy. Rarely, acute lingual tonsillitis may be a life-threatening condition. Airway management includes warmed humidified oxygen, hydration, and corticosteroids. Nebulized epinephrine can relieve the acute respiratory distress and stridor. Antibiotics of choice are similar to those used for the treatment of pharyngitis.[11]

LARYNGITIS

Laryngitis is manifested as hoarseness and aphonia. It is usually caused by viral upper respiratory tract infections. In up to 10% of cases, bacteria (including streptococci and diphtheria) may be responsible. Other infectious causes include tuberculosis, syphilis, leprosy, actinomycosis, and fungal infections. These patients should be evaluated for epiglottitis. Noninfectious causes include tumors, caustic or thermal injuries, trauma, and esophageal reflux disease.[12,13] Antibiotics are not indicated unless signs of bacterial infection are present.[14] Steroids may hasten resolution of symptoms.[15]

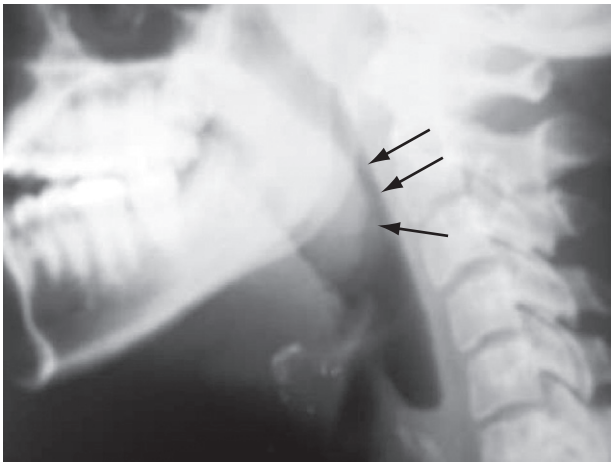


Figure 73-2. Lingual tonsillitis. Notice the "scalloped" appearance of the lingual tonsil on the anterior surface of the vallecula (*arrows*) with a normal epiglottis and aryepiglottic fold.

ADULT EPIGLOTTITIS

Perspective

Adult epiglottitis can lead to rapid, unpredictable airway obstruction. Before the introduction of *H. influenzae* vaccine, epiglottitis was primarily a pediatric disease. Although the incidence of pediatric epiglottitis has diminished, there is an increase in adult epiglottitis. Whether the increase is due to increased recognition or prevalence is unknown.[1,4,16,17]

Principles of Disease

Adult epiglottitis is a localized cellulitis involving the supraglottic structures, including the base of the tongue, vallecula, aryepiglottic folds, arytenoid soft tissues, lingual tonsils, and the epiglottis. Inflammation does not extend to the infraglottic regions. Some adults have a normal epiglottis in the setting of severe supraglottic involvement. The term *supraglottitis* is a more accurate description of this disease process. Adults with epiglottic involvement are prone to epiglottic abscesses.[16,17]

The most commonly isolated bacterial pathogen causing adult epiglottitis is type b *H. influenzae*, but it is only isolated from a minority of affected patients. *H. influenzae* infection is associated with a more aggressive disease course. In many cases, no organisms can be cultured from either blood or the supraglottic structures, which suggests that respiratory viruses may play an important etiologic role. The predominant organisms isolated from epiglottic abscesses are *Streptococcus* and *Staphylococcus* species. Adult epiglottitis may also result from thermal injury.[1,16,17]

Clinical Features

Adult epiglottitis has no age or seasonal prevalence. Males and smokers are more commonly affected. Adults with epiglottitis typically experience a prodrome resembling that of a benign upper respiratory tract infection. The duration of the prodrome is usually 1 to 2 days but may be as long as 7 days or as short as several hours. Patients who have a rapid onset of the disease as well as those with comorbid conditions (especially diabetics) are more likely to require airway intervention.[1,16,17]

Patients typically have dysphagia, odynophagia, and a sore throat. Pharyngeal pain may be severe and is often disproportionate to the clinical findings. Dysphonia and a muffled voice

are common, while hoarseness is unusual. Fever is absent in up to 50% of cases and may develop only in the later stages of the disease. Tachycardia disproportionate to fever correlates with severe disease. Tenderness to palpation of the anterior aspect of the neck in the region of the hyoid and when moving the larynx side to side is a reliable finding in epiglottitis. Ear pain may be a manifestation of adult epiglottitis.

Concomitant uvulitis, pharyngitis, tonsillitis, Ludwig's angina, peritonsillar abscess, and parotitis can occur; therefore, these findings on pharyngeal examination do not exclude the diagnosis of epiglottitis. The classic symptoms and signs of imminent airway obstruction may not appear until immediately before complete obstruction occurs, thus the earlier signs of drooling and dysphonia are more compelling indicators of impending airway compromise. Patients who assume a classic sniffing position are at imminent risk for rapid airway obstruction. These patients should not be laid flat, and immediate preparations must be made to rapidly secure the airway (see Chapter 1).[1,16,17]

Diagnostic Strategies

Although severe cases of adult epiglottitis are easily recognized, a large number of less severe cases are initially misdiagnosed. In up to a third of adult patients, epiglottitis is present but not diagnosed within 48 hours of admission.[4]

Adult patients without respiratory distress should undergo fiberoptic or rigid direct laryngoscopy, or indirect laryngoscopy, but preparations should include the ability to provide immediate bag-mask ventilation, intubation, or cricothyrotomy. Laryngospasm and complete obstruction can occur during instrumentation of the inflamed airway. Flexible fiberoptic laryngoscopy is the preferred approach as it provides direct, minimally invasive examination of the upper airway and can be used to determine the need for, and imminence of, airway management. Laryngoscopy reveals a swollen epiglottis and surrounding structures (Fig. 73-3). The epiglottis may appear "cherry red" but is often pale and edematous. In patients with respiratory distress, drooling, aphonia, or stridor, indirect laryngoscopy is contraindicated and direct laryngoscopy should be undertaken only as part of a "double setup" with the ability to proceed immediately to cricothyrotomy.[1,17]

Lateral cervical soft tissue radiographic films have a sensitivity of up to 90% compared with direct laryngoscopy; however, normal soft tissue plain films do not exclude mild or moderate adult epiglottitis. Adults with possible epiglottitis and normal soft tissue radiographic films should undergo laryngoscopy as described earlier. Radiologic findings include obliteration of the vallecula, swelling of the arytenoids and aryepiglottic folds, edema of the prevertebral and retropharyngeal soft tissues, and "ballooning" of the hypopharynx and mesopharynx. The edematous epiglottis appears enlarged and thumb-shaped (Fig. 73-4). An epiglottic width greater than 8 mm or an aryepiglottic fold width greater than 7 mm is suggestive of epiglottitis.

Differential Considerations

Adult epiglottitis is often misdiagnosed as streptococcal pharyngitis. Other entities that must be considered include mononucleosis, deep space abscesses, lingual tonsillitis, diphtheria, pertussis, and croup. Noninfectious considerations include angioedema, allergic reactions, foreign body aspiration, laryngospasm, tumors, toxic inhalation or aspiration, and laryngeal trauma.

Management

Most adults with epiglottitis do not require intubation, but all patients with epiglottitis should be treated with extreme care because of the possibility of unpredictable sudden airway obstruction. Endotracheal intubation should always be performed under direct visualization. Awake fiberoptic intubation is the optimal method, but awake orotracheal intubation by direct laryngoscopy is also safe and effective.[1,17] Blind nasotracheal intubation can lead to airway obstruction and is contraindicated in the setting of epiglottitis.

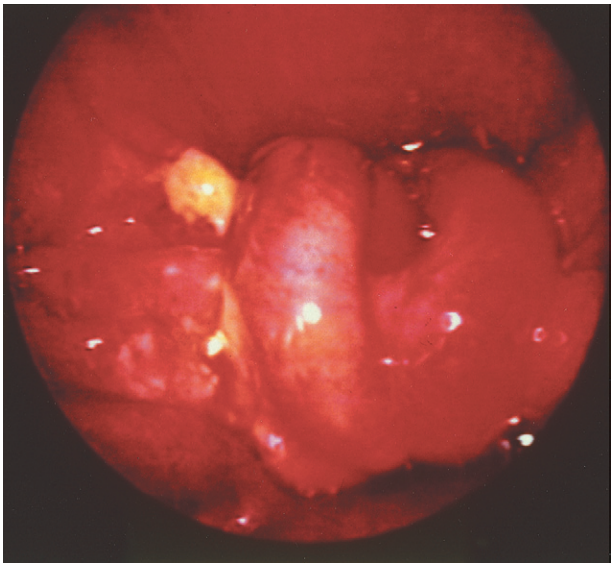


Figure 73-3. Epiglottitis.

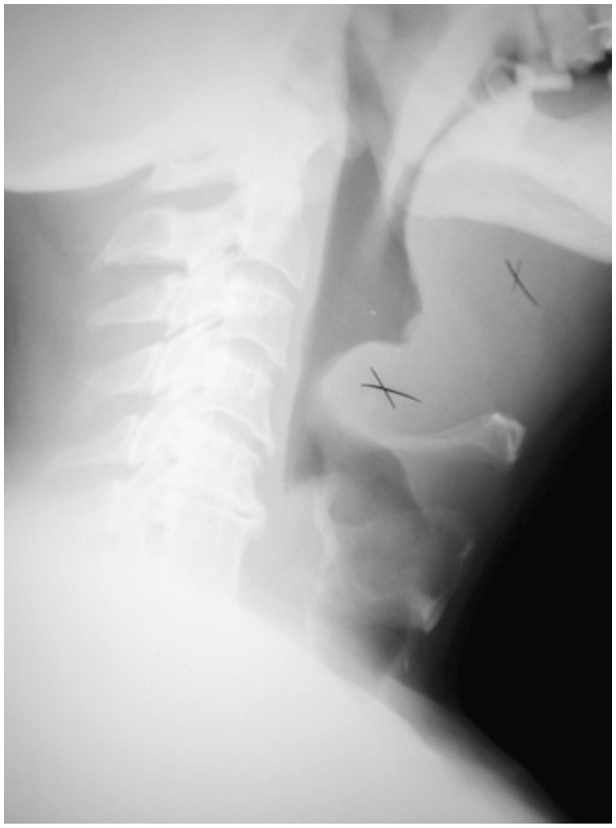


Figure 73-4. Radiograph of epiglottitis.

Antibiotics should be initiated against *H. influenzae* and other likely bacterial pathogens. First-line agents pending culture and sensitivity results are cefotaxime and ceftriaxone. Alternative antibiotics include ampicillin-sulbactam and trimethoprim-sulfamethoxazole.[1,8,9] The role of steroids and racemic epinephrine is unresolved.

Disposition

Stable patients, particularly those who present more than 24 hours after onset of symptoms, who are without respiratory distress, and who are handling their secretions can be safely observed without intubation in the emergency department observation unit or a higher level inpatient unit (intermediate or intensive care unit). Such patients include those with mild swelling on laryngoscopy and without drooling, stridor, or dyspnea. Patients who have a rapidly progressive course, are immunocompromised or diabetic, or have an epiglottic abscess or significant epiglottic enlargement on plain film study or laryngoscopy are at high risk.[1,16,17]

Extraepiglottic infections are less likely to occur in adults than children. Meningitis, retropharyngeal abscess, pneumothorax, empyema, pneumonia, sepsis, acute respiratory distress syndrome, necrotizing fasciitis, mediastinitis, and pulmonary edema occur in conjunction with epiglottitis.

DEEP SPACE INFECTIONS OF THE LOWER PART OF THE FACE AND NECK

Patients with deep space infections of the head and neck (Fig. 73-5) can decompensate rapidly. The incidence and complications of deep space infections have decreased dramatically because of improved dental hygiene and the advent of antibiotics.[18]

The submandibular space comprises two spaces: the sublingual and submaxillary spaces. The submandibular space is involved in Ludwig's angina.[19] Five potential communicating spaces in the neck are clinically relevant: the peritonsillar, parapharyngeal, retropharyngeal, "danger," and prevertebral spaces. The parapharyngeal space contains the carotid artery, the jugular vein, the cervical sympathetic chain, and cranial nerves IX through XII. The retropharyngeal space lies in the midline (medial to the parapharyngeal space) and extends from the base of the skull to the superior mediastinum (at about the level of T2). Retropharyngeal abscesses tend to occur lateral to the midline. Posterior to the retropharyngeal space lies the "danger space," which extends from the base of the skull to the diaphragm. The prevertebral space extends from the base of the skull to the coccyx. Danger space and prevertebral abscesses are located in the midline. Infections in the retropharyngeal, danger, and prevertebral spaces easily access the mediastinum.[18,20]

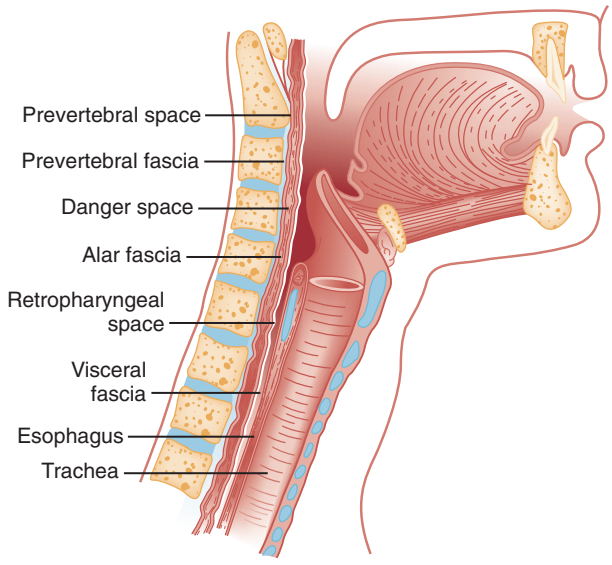


Figure 73-5. Lateral view of the neck showing the relationship of fascia to the prevertebral, "danger," retropharyngeal, and submandibular space.

The primary pathologic process of deep space infection is regional cellulitis. The fasciae may confine infections within their boundaries, thereby leading to abscess formation. Infections are most commonly a polymicrobial disease of mixed aerobic-anaerobic bacteria of oral origin. The most frequently isolated organisms are streptococci, staphylococci, and *Bacteroides* species. β-Lactamase-producing organisms are isolated in up to two thirds of cases. Other organisms include *H. influenzae*, *Pseudomonas aeruginosa*, *Klebsiella* species, and *Candida albicans*.[18,19,21]

Computed tomography (CT) and magnetic resonance imaging (MRI) can help distinguish cellulitis from abscess formation and guide therapy. Patients with cellulitis usually respond well to high-dose antibiotic therapy. Patients with small abscesses may be successfully treated with high-dose intravenous antibiotics or needle aspiration. The presence of an abscess, however, usually requires surgical incision and drainage. With the exception of patients with uncomplicated peritonsillar abscesses, patients with deep space abscess usually require admission, intravenous (IV) antibiotics, and consultation with otolaryngologists for possible surgical intervention.[22]

There is little anatomic resistance to spread of infection within the fascial planes and spaces, which allows rapid spread of infection. Life-threatening complications can occur rapidly.

Airway distortion and trismus may complicate intubation attempts. Neuromuscular blockade is generally ill-advised, unless as part of a "double setup" with the ability to proceed directly to cricothyrotomy, because both intubation and bag-mask ventilation may be impossible. Awake techniques are preferable. Fiberoptic-guided intubation can be useful in this setting.[18,19,23] Blind nasotracheal intubation can cause abscess rupture and further compromise and is thus contraindicated.[19,23] Should it be necessary to secure an airway surgically, cricothyroidotomy is generally the procedure of choice, except in some cases of Ludwig's angina, in which anatomic distortion may necessitate tracheostomy.

PERITONSILLITIS (PERITONSILLAR CELLULITIS AND PERITONSILLAR ABSCESS)

Perspective

Peritonsillar cellulitis and abscess should be regarded as the clinical continuum of peritonsillitis. Peritonsillar abscess, also termed *quinsy*, is the most common deep infection of the head and neck in adults.

Principles of Disease

Peritonsillitis may occur as a result of acute tonsillitis. Infection in either Weber's glands or the tonsillar crypts invades the peritonsillar tissues and thereby leads to cellulitis and abscess formation. Fibrous fascial septae divide the peritonsillar space into compartments and direct the infection anteriorly and superiorly.[1,18]

Dental infections, chronic tonsillitis, infectious mononucleosis, smoking, chronic lymphocytic leukemia, and tonsilloliths are predisposing factors. Peritonsillar abscess occurs in patients who have undergone complete tonsillectomy and is seen in all age groups. Peritonsillitis recurs in up to 50% of patients, with the incidence of recurrent peritonsillar abscess of approximately 10%. The highest incidence of recurrence is seen in patients younger than 40 years and in those with a history of chronic tonsillitis.

Most peritonsillar abscesses are polymicrobial. In patients who have received antibiotics in whom peritonsillar abscesses develop, fewer aerobes and more β-lactamase-producing organisms are isolated.[1,18]

Clinical Features

There is often a delay of 2 to 5 days between abscess formation and local and systemic symptoms. Symptoms and signs include odynophagia, dysphagia, drooling, trismus, and referred otalgia. Patients may have a characteristic muffled, hot potato voice and rancid breath. Systemic manifestations include fever, malaise, and dehydration. Patients often relate a history of recurrent tonsillitis with multiple trials of antibiotics but without resolution.

The examination of the pharynx may be limited by trismus. Physical findings of peritonsillitis include inflamed and erythematous oral mucosa, purulent tonsillar exudates that obscure the tonsil, and tender cervical lymphadenopathy. Peritonsillar cellulitis mimics peritonsillar abscess. Peritonsillar abscess is characterized by a greater frequency of drooling, trismus, and dysphagia, whereas peritonsillar cellulitis is more commonly bilateral. The distinguishing feature of peritonsillar abscess is inferior medial displacement of the infected tonsil (at times involving the soft palate), with contralateral deviation of the uvula (Fig. 73-6). The abscess is generally unilateral and located in the superior pole of the tonsil. Bilateral peritonsillar abscesses occur occasionally.[1,18]

Diagnostic Strategies

Aspiration of pus establishes the diagnosis of peritonsillar abscess. Because patients with peritonsillar abscess have a 20% incidence of mononucleosis, laboratory testing for mononucleosis should be considered.

Roentgenographic examination in uncomplicated cases contributes little to the diagnosis. Contrast-enhanced CT and ultrasonography (both intraoral and transcutaneous) aid in differentiating peritonsillar abscess from cellulitis, especially when patients are unable to cooperate with needle aspiration. These modalities are also useful in diagnosing posteriorly and inferiorly located abscesses and in guiding needle aspiration.[18,22,24]

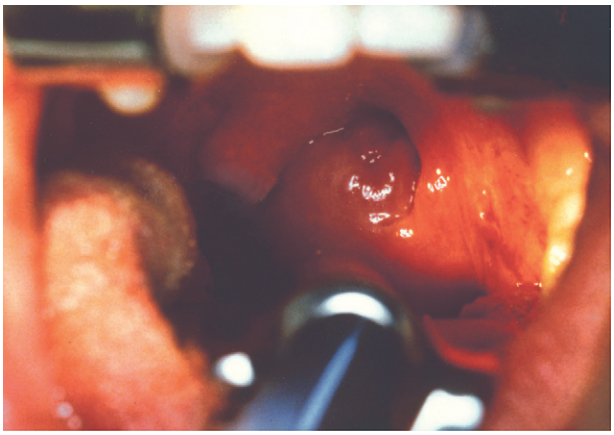


Figure 73-6. Peritonsillar abscess with uvular displacement to the right.

Differential Considerations

The differential diagnosis of peritonsillitis includes hypertrophic tonsillitis, infectious mononucleosis, tubercular granuloma, diphtheria, other deep space infections of the neck, cervical adenitis, congenital or traumatic internal carotid artery aneurysms, foreign bodies, and neoplasms.

Management

Emergency abscess aspiration is necessary in cases of complete or impending airway obstruction. Antibiotics alone may control peritonsillar cellulitis. Regimens include high-dose penicillin plus metronidazole, cefoxitin, ampicillin-sulbactam, and clindamycin. Alternative antimicrobial agents include a carbapenem, high-dose penicillin and rifampin, ticarcillin-clavulanate, or piperacillin-tazobactam.[1,8,18] β-Lactamase-producing bacteria and poor penetration of antibiotics into the abscess limit the effectiveness of antibiotics. The use of steroids may be beneficial.[25]

Drainage of the abscess is curative. Needle aspiration of abscesses by both emergency physicians and otolaryngologists is diagnostic (although false-negative aspirations occur in approximately 10% of cases, and another 10% may require repeated aspirations) and therapeutic. This immediately relieves symptoms and is more cost-effective, less painful, and easier to perform than incision and drainage.[1,18,24,25] Intraoral ultrasound-guided needle aspiration is a useful adjunct in the presence of trismus.[24,25] Immediate tonsillectomy under general anesthesia may be needed in extremely young or uncooperative patients.

Disposition

Hospital admission is indicated for patients who have underlying disease, are dehydrated, appear toxic, are unable to tolerate oral fluids, are in severe pain, or have other significant complications. The most dangerous immediate complication of peritonsillitis is pharyngeal obstruction with upper airway compromise. Other complications include sepsis, abscess rupture and pulmonary aspiration leading to pneumonia, empyema, and pulmonary abscess formation. Infection can spread contiguously to the parapharyngeal and retropharyngeal spaces. Ludwig's angina, mediastinal involvement (including mediastinitis, pneumonia, empyema, and pericarditis), myocarditis, carotid artery erosion, jugular vein thrombophlebitis, septic embolization, abscess formation, Lemierre's syndrome (postanginal septicemia), and cervicothoracic necrotizing fasciitis can complicate peritonsillitis. Intracranial extension of peritonsillitis may result in meningitis, cavernous sinus thrombosis, and cerebral abscess.[18]

■ LUDWIG'S ANGINA

Perspective and Principles of Disease

Ludwig's angina is a potentially fulminant disease process that can lead to death within hours.[19,21,26] This is a progressive cellulitis of the connective tissues of the floor of the mouth and neck that begins in the submandibular space. Dental disease is the most common cause of Ludwig's angina. An infected or recently extracted lower molar is noted in most affected

patients.[19,21,26] Dentoalveolar abscesses easily break through the relatively thin cortex of the mandible below the mylohyoid ridge and infect the submandibular space. Other causes of Ludwig's angina include a fractured mandible, foreign body or laceration in the floor of the mouth, tongue piercing, traumatic intubation and bronchoscopy, secondary infections of an oral malignancy, osteomyelitis, otitis media, submandibular sialadenitis, peritonsillar abscess, a furuncle, infected thyroglossal cyst, and sepsis.[19,21]

Clinical Features

Infection of the sublingual and submaxillary spaces leads to edema and soft tissue displacement, which may result in airway obstruction. The most common presentation in patients with Ludwig's angina includes dysphagia, odynophagia, neck swelling, and neck pain. Other symptoms and signs include dysphonia, a hot potato voice, dysarthria, drooling, tongue swelling, pain in the floor of the mouth, restricted neck movement, and sore throat. Patients should be questioned regarding recent dental extraction and disease. A foul taste in the patient's mouth, feeling air release at the time of extraction, rapid development of crepitus, and unilateral pharyngitis in patients with recent dental extractions should suggest the diagnosis of Ludwig's angina.[19,21,26]

The most common physical findings in Ludwig's angina are bilateral submandibular swelling and elevation or protrusion of the tongue. Other findings include elevation of the floor of the mouth, posterior displacement of the tongue, and a "woody" consistency of the floor of the mouth. The combination of tense edema and brawny induration of the neck above the hyoid may be present and is described as a "bull neck." Marked tenderness to palpation of the neck and subcutaneous emphysema may be noted. Trismus and fever are usually present, but generally no palpable fluctuance or cervical lymphadenopathy. Tenderness to percussion may be elicited over the involved teeth.[19,21,26]

Diagnostic Strategies

The diagnosis is made clinically by examination. Soft tissue plain films of the neck may confirm the diagnosis by showing swelling of the affected area and airway narrowing and by identifying gas collections. CT and MRI aid in the diagnosis of Ludwig's angina and its complications. Ultrasonography is also useful in diagnosing abscesses and edema in the setting of Ludwig's angina.[19,21,26]

Differential Considerations

The differential diagnosis includes deep cervical node suppuration, peritonsillar and other deep neck space abscess, parotid and submandibular gland abscess, oral carcinoma, angioedema, submandibular hematoma, and laryngeal diphtheria.

Management

Sudden asphyxiation is the most common cause of death in patients with Ludwig's angina.[21] Stridor, tachypnea, dyspnea, inability to handle secretions, and agitation are all indications of impending airway compromise. Fiberoptic-guided oral or nasotracheal intubation under sedation with topical anesthesia is the preferred method of airway control. Endotracheal intubation may be difficult because of distortion of the upper airway, trismus, pooled secretions, the cephalad and posterior displacement of the tongue, inability to displace the tongue into the submandibular space, and a tendency for the development of laryngospasm.[21] Cricothyrotomy may be difficult and opens tissue planes that increase the risk of spreading infection into the mediastinum, but is the procedure of choice if fiberoptic intubation is not available.[23]

Emergent antibiotic regimens are similar to those for peritonsillar abscess.[8,18,21,26] The value of corticosteroids in the setting of Ludwig's angina is unclear. With the exception of dental extractions, surgery is reserved for patients who do not respond to medical therapy and those with crepitus and purulent collections.[19,21,26]

Disposition

The mortality rate resulting from Ludwig's angina is less than 10% with early aggressive antibiotic therapy and adequate protection of the airway. Infection can easily spread into other deep spaces of the neck and into the thoracic cavity and cause empyema, mediastinitis, mediastinal abscess, and pericarditis. Aspiration may lead to pneumonia and the formation of lung abscesses. Other complications include internal jugular vein thrombosis, carotid artery infection and erosion, bacteremia and sepsis, pneumoperitoneum, subphrenic abscess, cervicothoracic necrotizing fasciitis, and spontaneous pneumothorax.[19,21,26]

RETROPHARYNGEAL ABSCESS

Perspective and Principles of Disease

Retropharyngeal swelling reflects expansion of the retropharyngeal, danger, or prevertebral spaces. This discussion refers to infections in these spaces collectively as retropharyngeal abscesses.

Retropharyngeal abscess was previously a disease of childhood, with 96% of cases occurring in patients younger than 6 years. Adults are now increasingly affected. Children younger than 4 years have prominent retropharyngeal lymph nodes that may become infected and lead to retropharyngeal cellulitis and abscess formation. The increased use of antibiotics to treat pharyngitis in children has led to a declining incidence of retropharyngeal abscess in this age group. These retropharyngeal nodes atrophy after 4 to 6 years of age, and thus the incidence and pathophysiology of this entity differ in adults.[18,22,27]

In adult patients, cellulitis develops in the retropharyngeal area.[22] Once the retropharyngeal space is involved, the infection spreads rapidly and an abscess may form. Nasopharyngitis, otitis media, parotitis, tonsillitis, peritonsillar abscess, dental infections and procedures, upper airway instrumentation, endoscopy, lateral pharyngeal space infection, and Ludwig's angina are all implicated in the development of retropharyngeal abscess. Other causes include blunt and penetrating trauma (usually from foreign bodies, commonly fish bones), ingestion of caustic substances, vertebral fractures, and hematologic spread from distant infection.[18,27] Vertebral osteomyelitis and diskitis may lead to infection of the prevertebral space. Danger space infections are caused by extension of infection from either the retropharyngeal or prevertebral spaces. Underlying systemic disorders (e.g., diabetes and depressed immune system) may predispose individuals to retropharyngeal infections.[18,27]

Retropharyngeal abscesses are most commonly polymicrobial with a mixture of aerobes and anaerobes. β-Lactamase-producing organisms are present in two thirds of the cases. Tuberculosis is rarely reported in the United States as a cause of retropharyngeal abscess. *Staphylococcus* is currently the most common cause of pyogenic vertebral osteomyelitis

leading to the formation of retropharyngeal abscess. Disseminated coccidioidomycosis may also cause retropharyngeal abscess.[18,22,27,28]

Clinical Features

Patients typically have a sore throat, dysphagia, odynophagia, drooling, a muffled voice, neck stiffness, neck pain, and fever. Dysphonia is usually present and is described as a duck "quack" (*cri du canard*). Patients may complain of feeling a lump in their throat. Patients with a retropharyngeal abscess may appear quite ill and generally prefer to hold their necks extended and remain in the supine position. This position keeps the swollen posterior pharynx from compressing the upper airway. Forcing the patient to sit may lead to increased dyspnea.[18,26]

Physical examination may reveal tender cervical lymphadenopathy, tender cervical musculature, neck swelling, torticollis, and often a high fever. Trismus may be present and make visualization of the pharynx difficult. In cases of retropharyngeal cellulitis, diffuse edema and erythema of the posterior pharynx are present.[18,26] Once an abscess develops, palpation of the pharynx may demonstrate a unilateral mass if the retropharyngeal space is affected and a midline mass if the abscess is in the prevertebral or danger space. Palpation of a fluctuant mass is unreliable and carries a risk of inadvertent rupture of the abscess. Tenderness on moving the larynx and trachea side to side (tracheal "rock" sign) is commonly present. A retropharyngeal abscess may also cause pain in the back of the neck or shoulder that is precipitated by swallowing. Cold abscesses (caused by tuberculosis) are characterized by insidious onset, chronicity, constitutional symptoms, and less of a febrile response. Symptoms disproportionate to the findings should prompt further evaluation.[28]

Diagnostic Strategies

Diagnosis rests on the clinical findings and lateral cervical radiographs, CT, and MRI (Fig. 73-7). The soft tissue along the anterior bodies of C1-C4 should be less than 40% of the diameter of the vertebral body just behind it; an increase in this tissue thickness suggests infection or abscess. Inspiratory lateral neck films often demonstrate thickening of the retropharyngeal soft tissues with forward displacement of the larynx and esophagus.[20] The soft tissue swelling may be diffuse in the case of cellulitis or more focal if an abscess cavity is present. A pathologic process is suggested if the retropharyngeal space on lateral neck films (measured from the anteroinferior aspect of the second vertebral body to the posterior pharyngeal wall) is wider than 7 mm in both children and adults or the retrotracheal space (measured from the anteroinferior aspect of the sixth vertebral body to the posterior pharyngeal wall) is more than 14 mm in children and 22 mm in adults. True lateral films with the neck fully extended during deep inspiration are the most reliable. Other radiographic findings include reversal of the normal lordosis of the cervical spine, air-fluid levels in the abscess cavity, foreign bodies, and vertebral body destruction.

Plain films may not be sufficiently sensitive to diagnose retropharyngeal abscess. CT or MRI should be performed in these instances. These studies not only aid in the diagnosis and differentiation between cellulitis and abscess but also determine the extent of the disease process and the presence of complications (Fig. 73-8).[20,22,28] Ultrasonography is useful for differentiating retropharyngeal cellulitis from retropharyngeal abscess.

Differential Considerations

The differential diagnosis includes retropharyngeal tumors, foreign bodies, inflammation, hematoma, aneurysms, hemorrhage, lymphadenopathy, and edema. Other considerations

Figure 73-7. Radiograph of a retropharyngeal abscess demonstrating retropharyngeal soft tissue swelling.

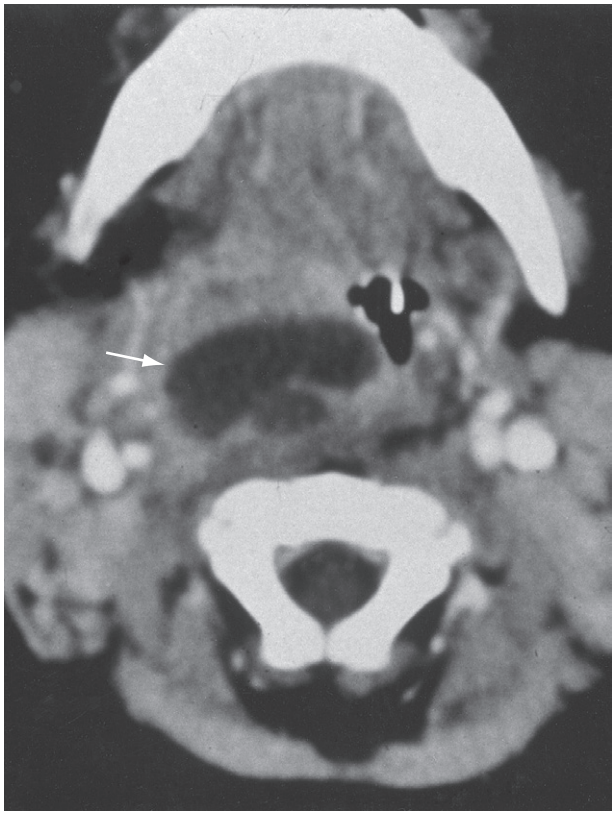


Figure 73-8. Computed tomographic scan demonstrating a right-sided retropharyngeal abscess (*arrow*).

include tendinitis of the longus colli muscle and retropharyngeal thyroid tissue.[20]

Management

Patients with retropharyngeal cellulitis are best treated with high-dose IV antibiotics. Appropriate regimens are similar to those used for peritonsillar abscess. Tuberculosis and fungal infections must also be considered. Resolution of retropharyngeal cellulitis is possible without surgical intervention.[8,18,22,26,28]

Generally, retropharyngeal abscesses are treated with antibiotics, in conjunction with operative incision and drainage. In selected cases, retropharyngeal abscesses can be treated successfully with antibiotics alone or in combination with needle aspiration. Cold abscesses should only be drained extraorally, unless the patient is in acute respiratory distress.[22,26,28]

Neck immobilization may be necessary in patients with vertebral body destruction caused by osteomyelitis or atlantoaxial separation. These patients need neurosurgical or orthopedic evaluation and may require internal or external fixation.

Disposition

Airway compromise can be caused by anterior displacement of the pharyngeal tissues. Pulmonary complications include abscess rupture with aspiration and subsequent pneumonia, empyema, and asphyxiation. Extension of the infection along tissue planes and through other deep spaces may lead to mediastinitis and mediastinal abscess formation, pericarditis, pleuritis, and empyema. In addition, abscesses may track into the back of the neck and into the axilla. Vascular complications occur from the extension of the retropharyngeal abscess into the lateral pharyngeal space. Atraumatic atlantoaxial separation is due to damage to the transverse ligament of the atlas by the abscess. These patients may have neurologic symptoms and a widened predental space on plain films, CT scan, or MRI. Acute transverse myelitis and epidural abscesses also occur, and both can result in quadriplegia. Other complications include internal carotid pseudoaneurysm, erosion into the esophagus and auditory canal, necrotizing fasciitis of the neck, acute respiratory distress syndrome, sepsis, and death.[18,28]

PARAPHARYNGEAL ABSCESS

Perspective

The parapharyngeal space, also known as the lateral pharyngeal and pharyngomaxillary space, is divided into two compartments by the styloid process. The anterior compartment contains connective tissue, muscle, and lymph nodes. The carotid sheath (which contains the carotid artery, internal jugular vein, vagus nerve, cranial nerves IX through XII, and the cervical sympathetic chain) runs in the posterior compartment.[18]

Principles of Disease

Parapharyngeal abscesses are most often polymicrobial infections. Odontogenic and pharyngotonsillar infections are the most common causes of parapharyngeal space abscesses. Parapharyngeal space infections can also arise by contiguous spread from other surrounding deep neck space infections. Other causes include parotitis, sinusitis, spread from infected neck tumors, infected branchial cleft cysts, suppuration of local lymphadenitis, iatrogenic introduction of organisms during a mandibular nerve block or anesthesia for tonsillectomy, nasal intubation, dental extraction, chronic otitis with cholesteatoma, and mastoiditis.[18]

Clinical Findings

Pain and swelling of the neck are the most common complaints. Odynophagia is present in most patients. A history of an antecedent sore throat may be elicited in some patients. Torticollis caused by irritation of the sternocleidomastoid muscle is also reported.[18]

The classic physical findings of infection involving the anterior compartment of the parapharyngeal space are medial tonsillar displacement and posterolateral pharyngeal wall bulging. Other findings include fever, trismus (caused by irritation of the muscles of mastication), edema, and swelling at the angle of the jaw. An erythematous, tender, nonfluctuant swelling at the angle of the mandible is a consistent finding in patients with an anterior parapharyngeal abscess.[18]

Involvement of the posterior space is associated with many of these same signs. If the anterior compartment is spared, however, little or no trismus occurs. Instead, posterior displacement of the tonsillar pillar and retropharyngeal swelling may be present.[18]

Diagnostic Strategies and Differential Considerations

The diagnosis of parapharyngeal abscess is suggested by the presence of a severe sore throat with the characteristic physical findings. Blood cultures are usually sterile unless jugular vein thrombophlebitis is complicating the parapharyngeal space infection. Ultrasonography, CT, and MRI are more useful than lateral radiographs in diagnosing parapharyngeal abscess and its complications. Angiography, Doppler flow studies, and magnetic resonance angiography may also be helpful in evaluating vascular complications.[18,22,29]

The differential diagnosis includes infections in other deep spaces of the neck, tumors and metastatic lymph nodes, thyroiditis, branchial cleft cyst, and carotid artery aneurysms.

Management

Treatment includes high-dose IV antibiotics and consultation with an otolaryngologist for surgical drainage of the abscess cavity. Appropriate antibiotic regimens are discussed in the section on the treatment of peritonsillar abscess. Intravenous antibiotics alone will cure parapharyngeal space infections in selected patients and should be started on an emergency basis.[8,18,22,29,30] Successful resolution of parapharyngeal abscesses with high-dose IV antibiotics and needle aspiration is reported.[22,29]

Disposition

Complications of a parapharyngeal abscess include airway obstruction and abscess rupture with subsequent aspiration, pneumonia, and empyema. Infection can spread to surrounding spaces and into the mediastinum and pericardium. Such spread may lead to mediastinitis, mediastinal abscess, pericarditis, myocardial abscess, and empyema. Other complications include osteomyelitis of the mandible, cervicothoracic necrotizing fasciitis, parotid abscess, cavernous sinus thrombosis, and meningitis.[18]

Posterior parapharyngeal space infections are particularly dangerous. These infections may affect the cervical sympathetic chain, carotid artery, or internal jugular vein. Ipsilateral

Horner's syndrome and neuropathies of cranial nerves IX through XII may occur. Carotid artery erosion may lead to hemorrhage and the formation of aneurysms. Oral, nasal, and aural warning bleeding is common with carotid artery erosion, with aural bleeding being particularly ominous. Any unexplained bleeding associated with parapharyngeal or other deep neck space infection should be investigated thoroughly. Persistent peritonsillar swelling despite resolution of the parapharyngeal abscess or a tender unilateral pulsatile mass may indicate an arterial aneurysm. Aspiration or incision of a carotid artery aneurysm thought to be a parapharyngeal abscess may have disastrous complications.[18]

Involvement of the internal jugular vein may lead to septic thrombosis and Lemierre's syndrome.[1,31] This entity, also called postanginal septicemia, affects primarily young healthy patients and is easily confused with right-sided endocarditis or aspiration pneumonia. The manifestation is one of a pharyngitis that initially improves but is then followed by severe sepsis. It is thought that the pharyngeal infection spreads to the parapharyngeal space and causes septic thrombophlebitis of the jugular vein. Patients usually appear ill and are febrile. Metastatic infections involve primarily the lung and are manifested by bilateral nodular infiltrates, pleural effusion, and pneumothorax. Septic arthritis, osteomyelitis, soft tissue cellulitis and abscesses, meningitis, and a vesiculopustular rash are also reported as a result of septic embolization. Leukocytosis and elevated bilirubin and liver function test values, with and without hepatomegaly and jaundice, are often present. Albuminuria, hematuria, and elevations in serum creatinine and blood urea nitrogen are reported. Septic shock rarely develops, although acute respiratory distress syndrome, transient coagulopathies, and hypotension commonly occur. The most frequent cause of this entity is *Fusobacterium* (primarily *Fusobacterium necrophorum*), although *S. aureus* is the most common pathogen in IV drug users. Treatment consists of parenteral antibiotics and incision and drainage of abscesses. Jugular vein ligation and resection are necessary in patients with uncontrolled sepsis and respiratory failure caused by repeated septic pulmonary emboli. The value of anticoagulation is unknown.[1,31]

RHINOSINUSITIS

Perspective and Principles of Disease

It is estimated that 0.5 to 2% of viral upper respiratory tract infections are complicated by rhinosinusitis. Since sinusitis usually involves the nasal cavity, the term *rhinosinusitis* is preferred. These terms will be used interchangeably in this section.[32,33]

The paranasal sinuses (frontal, maxillary, ethmoid, and sphenoid) are named for the facial bones with which they are associated. Pneumatization may involve other bones but represents extension from the main sinus. The maxillary, anterior ethmoid, and frontal sinuses drain into the medial meatus, located between the inferior and middle nasal turbinates. This area is named the ostiomeatal complex and is the focal point of sinus disease. The posterior ethmoid sinus drains into the superior meatus and the sphenoid sinus just above the superior turbinate.[32,33]

A healthy sinus depends on a patent ostium with free air exchange and mucus drainage. A healthy sinus is sterile and does not accumulate mucus. Viral upper respiratory tract infections and allergic rhinitis are the most common causes of ostial obstruction with resultant sinusitis. Ciliary abnormality or immobility inhibits drainage and is another important cause of sinusitis. Ciliary dysfunction can be temporary (e.g., upper respiratory infection) or permanent (e.g., syndromes associated with cilial structural abnormalities). Infection leads to increased mucus viscosity, thus further impeding drainage. Bacteria are introduced into the sinus by coughing and nose blowing. These processes lead to increased inflammation and bacterial overgrowth. Other factors predisposing to rhinosinusitis include immunocompromised status, nasal septal deviation and other structural abnormalities, nasal polyps, nasal tumors, trauma and fractures, rhinitis medicamentosa, rhinitis secondary to toxic mucosal exposure, barotrauma, foreign bodies, nasal cocaine abuse, and instrumentation (including nasogastric and nasotracheal intubation).[32,33]

Sinusitis can be classified into acute viral, acute bacterial, chronic, and recurrent acute variations. Approximately 90% of patients with colds have an element of the acute viral form. Acute viral sinusitis may lead to the development of the acute bacterial variety. *S. pneumoniae*, nontypable *H. influenzae*, and *M. catarrhalis* are the primary pathogens responsible for acute bacterial and recurrent acute sinusitis. *P. aeruginosa* is associated with sinusitis in the setting of HIV infection and cystic fibrosis. Anaerobic bacteria, streptococcal species, and *S. aureus* are more prominent causes of chronic sinusitis. Fungi also have a role in CS. *Rhizopus*, *Aspergillus*, *Candida*, *Histoplasma*, *Blastomyces*, *Coccidioides*, and *Cryptococcus* species, as well as other fungi, may cause sinusitis, primarily in immunocompromised hosts. It is important to distinguish infectious from allergic sinusitis. Allergic sinusitis is associated with sneezing, itchy eyes, allergen exposure, and previous episodes.[32-35]

Clinical Features

Frontal sinusitis can cause severe headache localized to the forehead and orbit. Sphenoid sinusitis, may cause vague headaches and focal pain almost anywhere in the head. Maxillary sinusitis may be seen with pain over the zygoma, in the canine or bicuspid teeth, or periorbitally. Ethmoid sinusitis can cause medial canthal pain and periorbital or temporal headaches.[32,33]

The cardinal symptoms of acute rhinosinusitis are mucopurulent nasal discharge, nasal obstruction or congestion, and facial pain, fullness, or pressure lasting less than 4 weeks. Other symptoms and signs include postnasal drip (that may lead to coughing), pressure over the involved sinus, malaise, hyposmia, anosmia, fever, maxillary dental pain, and ear fullness or pressure. Acute sinusitis typically progresses over a period of 7 to 10 days and resolves spontaneously. During the first 3 to 5 days of illness, it may be difficult to differentiate acute viral from acute bacterial sinusitis. The bacterial origin is suggested by worsening symptoms within 10 days, persistent symptoms after 10 days, or "double sickening," which refers to patients who improve initially, only to have worsening sinus congestion and discomfort. Bacterial infection is also associated with more severe presentations and extrasinus manifestations of infection.[32,33]

Chronic sinusitis is slow in onset, prolonged in duration (greater than 12 weeks), and recurrent in frequency. Symptoms can be nonspecific but are generally similar to those of acute disease. Symptoms of chronic disease may also include chronic cough, fetid breath, laryngitis, bronchitis, and worsening asthma. Recurrent acute sinusitis is diagnosed when four or more episodes of acute bacterial infection, without its signs or symptoms between episodes, occur per year. The presentation and treatment of recurrent acute disease is similar to that for acute bacterial sinusitis.[32,33]

Invasive fungal sinusitis (mucormycosis) is an aggressive opportunistic rhinocerebral infection that affects immunocompromised hosts. Mucormycosis (*Rhizopus*) is generally associ-

ated with fever, localized nasal pain, and cloudy rhinorrhea. On examination, the affected tissue (usually the turbinates) appears gray, friable, anesthetic, and nonbleeding because of infarction caused by mucormycotic angioinvasion. In advanced cases the affected tissues are necrotic and black, and the infection spreads beyond the sinus.[34,35]

Diagnostic Strategies

Physical examination is best performed after the application of a topical decongestant. Mucosal erythema and edema are usually present. Purulent discharge from the nasal meatus may be observed if the sinus ostia are not completely obstructed. In the setting of acute sinusitis, nasal and nasopharyngeal cultures correlate poorly with cultures of sinus aspirates and cultures obtained at the time of open antrostomy and do not differentiate between acute viral and acute bacterial infections. Culture and biopsy are indicated in suggested chronic, recurrent acute, and fungal sinusitis.[32,33] Radiographic examination should be limited to diagnosis of chronic or recurrent acute sinusitis, cases of questionable diagnoses, those with unresponsive disease, or investigation of complications. Axial and coronal CT is the imaging modality of choice. CT findings suggestive of sinusitis include air-fluid levels, sinus opacification, sinus wall displacement, and mucosal thickening (Fig. 73-9). CT is sensitive, though not specific. Incidental sinus mucosal thickening is seen in 40% of asymptomatic patients, and abnormal CT findings can also be noted in just half of patients with seasonal allergies. CT with IV contrast or MRI may be required to evaluate complications of rhinosinusitis (central nervous system, orbital, or other extrasinus infections) and are helpful in determining alternative diagnoses. Plain films have limited utility in the diagnosis of rhinosinusitis; positive findings are similar to those of CT. Sinus endoscopy is another option.[32,33]

Differential Considerations

Rhinitis can be differentiated from sinusitis by the increased response of nasal obstruction to treatment, clear nasal discharge, and absence of pain. Rhinitis does not lead to ostial obstruction, and thus patients do not complain of facial pain. Malignancy, tension headache, vascular headache, foreign body, dental disease, brain abscess, epidural abscess, meningitis, and subdural empyema may also present in a manner similar to sinusitis.

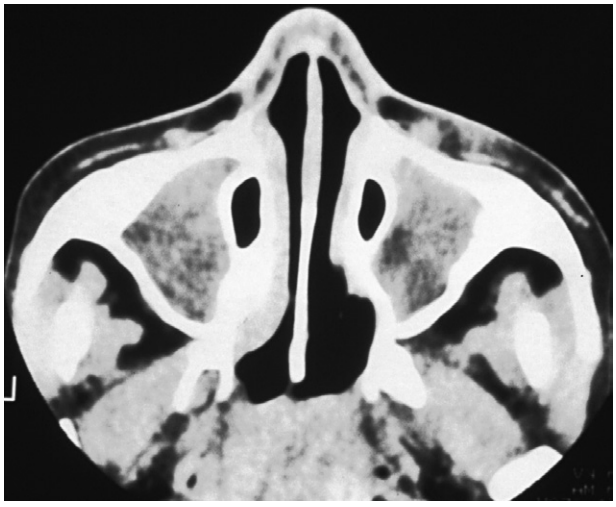


Figure 73-9. Computed tomographic scan showing bilateral maxillary sinus opacification.

Management

Analgesics, antipyretics, and decongestants play important roles in the symptomatic management of sinusitis. A large proportion of cases of viral and bacterial sinusitis resolve spontaneously, and antibiotic therapy offers only modest incremental benefit.[32,33,36] Most patients do not require antibiotics, and antibiotics should be reserved for those with symptoms and signs of sinusitis who have not improved after 7 days, who worsen despite adequate symptomatic treatment, or who have moderate to severe symptoms, including fever and purulent discharge, strongly suggestive of bacterial sinusitis, regardless of the duration of symptoms.[32,33,36] Patients who are at high risk for severe infection or complications should also be considered for antibiotic therapy. The choice of antibiotics must consider β-lactamase production and multidrug-resistant pneumococci. Amoxicillin administered for 7 to 10 days is still the first-line agent, but benefits are limited and treatment failures occur in areas with a high percentage of β-lactamase-producing bacteria.[8,32,33] High-dose amoxicillin should be considered for patients who have a child in daycare in the household. Penicillin-allergic patients may be treated with trimethoprim-sulfamethoxazole or a macrolide antibiotic. A 3-day course of trimethoprim-sulfamethoxazole or azithromycin and decongestants may be as effective as the standard 10-day antibiotic course.[32,33] Failure of symptoms to resolve after 7 days of therapy, or antibiotic usage in the past 4 to 6 weeks, necessitates a change to a broader spectrum antibiotic and reassessment of the patient to confirm the diagnosis of acute bacterial sinusitis. Appropriate management includes a 10- to 14-day course of high-dose amoxicillin-clavulanate, cefuroxime axetil, other second- or third-generation cephalosporins, clindamycin alone or in combination with ciprofloxacin, sulfamethoxazole, azithromycin, clarithromycin, or one of the respiratory fluoroquinolones (levofloxacin, moxifloxacin, gemifloxacin). Metronidazole may be added to any of these regimens to increase activity against anaerobic organisms. Antibiotics for chronic sinusitis should be effective against anaerobic and β-lactamase-producing bacteria. Treatment of life-threatening complications requires consultation and high-dose IV antibiotics, including cefuroxime, ceftriaxone, or ampicillin-sulbactam.[8,32,33,36] Antifungals may be beneficial in the treatment of chronic sinusitis.[34,35]

The goal of decongestant therapy is to reduce tissue edema, facilitate drainage, and maintain patency of the sinus ostia. Decongestants are available in topical and systemic preparations, both of which should be used simultaneously in conjunction with appropriate antibiotics.[32,37] Topical agents provide more relief than systemic decongestants. Topical agents include 0.5% phenylephrine hydrochloride and 0.05% oxymetazoline hydrochloride. Topical agents should be used for only 3 to 5 days. Extended use results in rebound vasodilation and nasal obstruction, a condition termed *rhinitis medicamentosa*. Systemic oral adrenergic agonists (e.g., phenylpropanolamine or pseudoephedrine) reduce nasal blood flow and congestion. These medications should be used cautiously in patients taking tricyclic antidepressants, monoamine oxidase inhibitors, and nonselective beta-adrenergic blockers.[32,33] Antihistamines should be reserved for the treatment of allergic sinusitis because these agents may impede sinus drainage. Second-generation H_1-antagonists are preferred due to their better side effect profile. Topical, but not systemic, steroids

are indicated for chronic and allergic sinusitis. Systemic steroids may be indicated in allergic and chronic sinusitis with nasal polyps.[32,34,38]

Saline nasal irrigation is beneficial for treating acute bacterial, recurrent acute, and chronic sinusitis. Saline irrigation may be efficacious for the prevention of sinusitis. Hypertonic saline preparations have superior anti-inflammatory properties and may be more effective than normal saline.[32,33]

Complications

Most cases of uncomplicated acute bacterial sinusitis can be treated on an outpatient basis with systemic decongestants, topical decongestants, and oral antibiotics. Failure of definitive antibiotic therapy suggests that the patient's sinusitis has extended to the chronic stage and necessitates referral to an otolaryngologist. Treatment of chronic sinusitis requires a prolonged (3–6 week) course of antibiotics.

Frontal or sphenoid sinusitis with air-fluid levels may require hospitalization. A previously healthy, nontoxic patient with good home support can be treated as an outpatient but should return immediately for any symptoms or signs of complications, including severe headache, neurologic changes, or visual changes. Patients who appear toxic, who are immunoincompetent, or who have poor home resources require hospital admission and IV antibiotics.

Sinusitis is associated with an increased incidence of bronchitis and asthma. Infectious processes of the sinuses can spread to the orbit or central nervous system and can be fulminant. Sinusitis may extend to involve the bones and soft tissues of the face and orbit. Facial and periorbital cellulitis, periorbital abscess, optic neuritis, blindness, and orbital abscess may develop. Patients with orbital complications may have marked swelling, proptosis, decreased ocular motility, and decreased visual acuity. Sinusitis may also lead to intracranial complications. Meningitis, cavernous sinus thrombosis, epidural or subdural empyema, and brain abscess occur. Intracranial involvement may result in headache, decreased sensorium, or focal neurologic deficits and has a rapidly progressive course. Acute fulminant fungal sinusitis requires IV antifungal therapy and aggressive surgical débridement.[32,33,35] Complications of mucormycosis are directly related to delay in diagnosis and treatment. This opportunistic fungal infection rapidly progresses to involve the central nervous system and is associated with high morbidity and mortality rates.

KEY CONCEPTS

- A severe sore throat with surprisingly minimal findings on examination of the oropharynx suggests serious soft tissue infection such as epiglottitis, retropharyngeal abscess, or peritonsillar abscess.
- Deep space cellulitis is difficult to differentiate from deep space abscess and may require needle aspiration after CT or MRI.
- Keep patients with upper airway infections in a position of comfort.
- Posterior parapharyngeal abscess may involve the cervical sympathetic chain, carotid artery, or internal jugular vein.
- Aspiration and incision of a carotid artery aneurysm thought to be a parapharyngeal abscess may be disastrous.
- Resolving pharyngitis followed by severe sepsis, right-sided endocarditis, or aspiration pneumonia should suggest septic thrombosis of the internal jugular vein.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 74 Pneumonia

Gregory J. Moran and David A. Talan

PERSPECTIVE

Pneumonia is the seventh leading cause of death and the leading cause of death from infectious disease in the United States.[1] The annual incidence of community-acquired pneumonia (CAP) in the United States ranges from 2 to 4 million, resulting in approximately 500,000 hospital admissions. Most cases of CAP are managed in the outpatient setting and the mortality is low (<1%), but pneumonia requiring hospitalization is associated with a much higher mortality rate (approximately 15%). Most deaths occur in elderly or immunosuppressed patients. Pneumonia remains challenging because of an expanding spectrum of pathogens, changing antibiotic resistance patterns, the availability of newer antimicrobial agents, and increasing emphasis on cost-effectiveness and outpatient management.

The epidemiology of CAP is changing. As the percentage of the population older than age 65 years continues to increase, the incidence of pneumonia is expected to increase. An increasing number of patients are taking immunosuppressive drugs related to treatment of malignancy, transplantation, or autoimmune disease, resulting in more cases of pneumonia due to other opportunistic pathogens. Patients with acquired immunodeficiency syndrome (AIDS) are at increased risk of infection with *Streptococcus pneumoniae*, *Mycobacterium tuberculosis*, or *Pneumocystis jirovecii* (previously known as *Pneumocystis carinii*). Antibiotic resistance is more common among *S. pneumoniae* and other pathogens. In addition, the threat exists of respiratory infections due to biologic terrorism or newly recognized pathogens that have the potential to spread quickly through international travel.

Identification of a specific etiology of pneumonia is extremely difficult within the time frame of an emergency department (ED) visit. Even after a thorough inpatient evaluation, a specific pathogen is never identified in many patients with pneumonia. When pneumonia is diagnosed, the priorities in the ED are to initiate appropriate empirical antibiotic therapy based on the most likely pathogens, provide appropriate respiratory support, assess the severity of disease, and recognize indications for hospitalization.

PRINCIPLES OF DISEASE

Despite the constant presence of potential pathogens in the respiratory tract, the lungs are remarkably resistant to infection. The alveolar surface of the lungs covers an area of approximately 140 m^2. Approximately 10,000 L of air passes through the respiratory tract each day, and typical ambient air can contain hundreds to thousands of microorganisms per cubic meter. Numerous potential respiratory tract pathogens may colonize the oropharynx and upper airways. Although the cough and laryngeal reflexes prevent most large particulate matter from entering the lower respiratory tract, aspiration of oropharyngeal contents may be a common occurrence during normal sleep. Despite these hazards, healthy lungs are usually a virtually sterile environment.

The development of clinical pneumonia requires a defect in host defenses, the presence of a particularly virulent organism, or the introduction of a large inoculum of organisms. If the challenge of invading organisms overwhelms host defenses, microbial proliferation leads to inflammation, an immune response, and clinical pneumonia. If host defenses are weak, a minimal challenge may lead to the development of pneumonia.

The mouth normally contains numerous microorganisms. Saliva contains approximately 10^8 bacteria/mL, with anaerobic organisms predominating. *Bacteroides* and *Fusobacterium* spp. are the most common anaerobic organisms. Streptococci are the most common aerobic organisms, but staphylococci, *Haemophilus* sp., *Moraxella catarrhalis*, and *Neisseria* sp. are also found. Anything that upsets the balance of normal oral flora may permit the growth of more virulent organisms. Systemic illness may alter epithelial binding of oral flora, leading to increased colonization with aerobic gram-negative bacilli. Antimicrobial therapy can also adversely alter normal oral flora.

Host defenses can be impaired in many ways. An altered level of consciousness (e.g., intoxication, stroke, seizures, and anesthesia) can suppress protective airway reflexes and lead to aspiration of oropharyngeal contents into the lower respiratory tract. Interventions that bypass the usual defenses of the upper airways, such as endotracheal intubation, nasogastric intubation, and respiratory therapy devices, predispose to infection. Cigarette smoking damages mucociliary function and macrophage activity. Viral infections of the respiratory tract may destroy respiratory epithelium and predispose it to bacterial infection. Increased risk of bacterial pneumonia after influenza or other viral respiratory infections is well described. The elderly are at increased risk of pneumonia related to decline of mucociliary clearance, elastic recoil of the lungs, and humoral and cellular immunity. Human immunodeficiency virus (HIV) infection impairs humoral and cellular immunity.

If an infectious organism reaches the alveoli and begins replicating, a series of host immune responses occurs that ultimately may lead to the development of clinical pneumonia. As antigens of the infecting organism are identified by the host, cytokines, such as interleukin-1, interleukin-8, and tumor necrosis factor, are produced that mediate the inflammatory response. Transudation of plasma fluids into the lung tissue allows entry of IgM and IgG for bacterial opsonization, complement activation, agglutination, and neutralization. Neutrophils are recruited into the lung to ingest and kill the infecting organisms. Cell-mediated immunity plays an important role in defense against certain pathogens, such as viruses and intracellular organisms such as *Mycobacterium* and *Legionella* spp. As fluids and inflammatory cells enter the alveolar spaces to combat the infection, the patient develops the clinical and radiographic signs of pneumonia.

Etiologic Agents

The challenge with pneumonia lies in identifying the etiologic agent rather than in diagnosis of pneumonia. It is extremely difficult to determine with a high degree of certainty the specific organism responsible for pneumonia, especially within the time frame of an ED evaluation. Empiric therapy must be chosen with activity against the spectrum of likely pathogens based on the overall clinical picture.

Difficulty in determining the specific etiology of pneumonia exists even with advanced microbiologic and serologic testing that is not generally available during an ED evaluation. In community-acquired pneumonia, a microbial etiology cannot be determined in one third to one half of cases, even after thorough investigation. In hospitalized adults with CAP, pathogens such as *S. pneumoniae* and *Haemophilus influenzae*, referred to as "typical" pathogens, account for approximately one fourth of cases. *Legionella*, *Mycoplasma*, and *Chlamydophila* spp. (previously known as *Chlamydia*), referred to as "atypical" pathogens, are also common.[2] Testing for common viral agents reveals a viral etiology in approximately 18% of cases, with influenza and parainfluenza viruses most common.[3] Adults who require intensive care unit (ICU) admission have *S. pneumoniae* as the most common pathogen, with even higher prevalence among fatal cases. *Legionella* sp., *Staphylococcus aureus*, and aerobic gram-negative bacilli also appear to be relatively more common among adults with severe CAP.[4] Atypical organisms such as *Mycoplasma* sp. or viruses account for a relatively higher proportion of pneumonia in patients who have milder illness that is amenable to outpatient therapy.[5] However, atypical organisms occur with significant frequency in patients with severe illness requiring hospitalization, particularly due to *Legionella* infection. Co-infection, such as with *Chlamydophila pneumoniae* and *S. pneumoniae*, is also well recognized.

Streptococcus pneumoniae is a gram-positive coccus that is the most common etiology of CAP among adults. It colonizes the nasopharynx in 40% of healthy adults. Although this organism can cause pneumonia in healthy people, patients with a history of diabetes, cardiovascular disease, alcoholism, sickle cell disease, splenectomy, and malignancy or other immunosuppressive illness are at increased risk. A vaccine containing the 23 capsular polysaccharides of pneumococcal types most commonly associated with pneumonia reduces the likelihood of serious pneumococcal infection. It is recommended for people at increased risk because of underlying illness or age older than 65 years.[6] Many ED patients have not received pneumococcal vaccine, and vaccinating eligible patients in this setting seems to be feasible and effective.[7] A heptavalent protein-conjugate pneumococcal vaccine effectively reduces invasive pneumococcal disease and pneumonia in infants and young children.[8]

Haemophilus influenzae, the second most frequently isolated organism in CAP among adults, is a pleomorphic gram-negative rod. It is a common pathogen in adults with chronic obstructive pulmonary disease (COPD), alcoholism, malnutrition, malignancy, or diabetes.

Although *Staphylococcus aureus* remains an uncommon cause of CAP, community-associated strains of methicillin-resistant *S. aureus* (CA-MRSA) are emerging as a cause of severe pneumonia in previously healthy adults and children. This is often associated with influenza.[9] Staphylococcal pneumonias are often necrotizing, with cavitation and pneumatocele formation. Intravenous drug users may develop hematogenous spread of *S. aureus* that involves both lungs with multiple small infiltrates or abscesses (e.g., tricuspid endocarditis resulting in septic pulmonary emboli). Other pyogenic bacterial etiologies include *Moraxella catarrhalis*, a gram-negative diplococcus that can be associated with lower respiratory tract infections in patients with COPD.

Klebsiella pneumoniae is a gram-negative rod that rarely causes disease in a normal host and accounts for a small percentage of CAPs. It may cause severe pneumonia in debilitated patients with alcoholism, diabetes, or other chronic illness. There is a high incidence of antibiotic resistance since the organism is often hospital acquired.

Mycoplasma pneumoniae is one of the most common causes of CAP in previously healthy patients younger than age 40 years. Another important organism in CAP is *C. pneumoniae*, an intracellular parasite that is transmitted between humans by respiratory secretions or aerosols. Seroprevalence studies indicate that virtually everyone is infected with *C. pneumoniae* at some time and that reinfection is common. *Chlamydophila pneumoniae* is a relatively common etiology of CAP, especially in older adults. It accounts for at least 8% of cases, although this is an underestimate due to difficulty in diagnosing infection with this organism.

At least 30 species of *Legionella* have been isolated since the 1976 convention-related outbreak in Philadelphia, from which the organism derives its name. At least 19 are known human pathogens. *Legionella* is an intracellular organism that lives in aquatic environments. There is no person-to-person transmission. Although it is implicated in point outbreaks related to cooling towers and similar aquatic sources, the organism also lives in ordinary tap water and is underdiagnosed as an etiology of CAP. *Legionella* prevalence seems to vary greatly by region.

Lower respiratory infections due to anaerobic organisms generally result from the aspiration of oropharyngeal contents with large amounts of bacteria. These infections are typically polymicrobial, including *Peptostreptococcus*, *Bacteroides*, *Fusobacterium*, and *Prevotella* spp. Presentation is often subacute or chronic and may be difficult to distinguish clinically from other etiologies of pneumonia. Clinical factors that suggest an anaerobic infection include risk factors for aspiration, such as central nervous system depression or swallowing dysfunction; severe periodontal disease; fetid sputum; and the presence of a pulmonary abscess or empyema.

Viral pneumonias are common in infants and young children and are recognized as an important cause of pneumonia in adults. Respiratory syncytial virus and parainfluenza viruses are the most common causes of pneumonia in infants and small children, occurring mostly during autumn and winter. Influenza viruses are the most common cause of viral pneumonia in adults. Winter influenza outbreaks, usually due to influenza type A, may cause 40,000 deaths annually in the United States. More than 90% occur in people age 65 years or older.[10]

Metapneumovirus is a paramyxovirus that seems to be an important cause of viral pneumonia in children and adults.[11] Cytomegalovirus (CMV) primarily causes pneumonia in immunosuppressed patients, such as transplant recipients. Varicella-zoster virus causes pneumonia that seems to be more common and more severe in adults. Predisposing factors include smoking or pregnancy. Severe acute respiratory syndrome (SARS) is a respiratory illness due to a coronavirus identified in Southeast Asia. SARS is associated with a high case fatality rate (approximately 10–15% overall and higher in the elderly).

Fungal infections due to organisms such as *Histoplasma capsulatum*, *Blastomyces dermatitides*, and *Coccidioides immitis* commonly present as pulmonary disease. These organisms are present in the soil in various geographic areas of the United States: *H. capsulatum* in the Mississippi and Ohio River valleys, *C. immitis* in desert areas of the Southwest, and *B. dermatitides* in a poorly defined area extending beyond that of *H. capsulatum*. These infections should be considered in people in appropriate geographic areas, especially in those who are near activities that disturb the soil, such as construction or dirt bike riding. Clinical presentation varies from an acute or chronic pneumonia to asymptomatic granulomas and hilar adenopathy.

Pneumocystis pneumonia (PCP) occurs in compromised hosts, principally people with AIDS or malignancy. Although *P. jirovecii* is often classified as a protozoan, biochemical evidence indicates that it is more closely related to fungi. PCP is one of the most common presentations leading to a diagnosis of HIV infection and AIDS. Patients with pulmonary complaints should be questioned about HIV risk factors, and clinicians should search for signs of HIV-related immunosuppression, such as weight loss, lymphadenopathy, and oral thrush. PCP typically presents subacutely with fatigue, exertional dyspnea, nonproductive cough, pleuritic chest pain, and fever.

Mycobacterium tuberculosis is a slow-growing bacterium transmitted between people by droplet nuclei produced from coughing and sneezing. *Mycobacterium tuberculosis* survives within macrophages as a facultative intracellular parasite and may remain dormant in the body for many years. Active tuberculosis (TB) develops within 2 years of infection in approximately 5% of patients, and another 5% develop reactivation disease at some later time. Reactivation is more likely to occur in people with impaired cell-mediated immunity, such as patients with diabetes, renal failure, immunosuppressive therapy, malnutrition, or AIDS. Approximately one third of the world's population is infected with *M. tuberculosis*. Approximately 8 million new cases of active disease develop annually, resulting in 3 million deaths worldwide. An estimated 10 to 15 million people in the United States (3–5% of the population) are infected with TB. Multidrug-resistant strains of *M. tuberculosis* are found in increasing numbers, especially among immigrants from Southeast Asia and AIDS patients.

Unusual Causes of Pneumonia

Hantaviruses are endemic in several areas of the United States and can cause a syndrome of severe respiratory distress and shock. Infection occurs from inhalation of aerosols contaminated with rodent urine and feces. Patients are typically healthy adults with a prodrome of fever, myalgia, and malaise followed several days later by the onset of respiratory distress. Hypoxia may progress rapidly, requiring ventilatory support. Characteristic laboratory findings include thrombocytopenia, hemoconcentration, and leukocytosis with atypical lymphocytes. Chest radiographs show bilateral interstitial lung infiltrates that are more pronounced in dependent areas. Treatment is supportive, including the use of extracorporeal membrane oxygenation. There is no known effective antiviral therapy.

Plague, caused by *Yersinia pestis*, is endemic in many areas of the world, including the southwestern United States. It is an agent that could be used for biologic terrorism,[12] but it also occurs naturally in people bitten by fleas from infected rodents or carnivores. Hematogenous spread may lead to pneumonia that is highly contagious and has a high mortality.

A number of zoonotic organisms cause pneumonia. Tularemia, caused by the bacterium *Francisella tularensis*, is spread by contact with body fluids of an infected mammal (especially rabbits) or the bite of an infected arthropod. Illness usually begins with an ulcerated skin lesion and painful regional lymphadenopathy. Some patients have a typhoidal form with only fever, malaise, and weight loss. Pneumonia may occur with either form, presenting as a nonproductive cough and patchy infiltrates on a chest radiograph. Psittacosis can spread to humans from birds infected with *Chlamydophila psittaci*. Illness often begins rapidly with chills, high fever, myalgias, and nonproductive cough. Severe headache is often the major complaint. Splenomegaly is often present. Q fever is caused by the rickettsial organism *Coxiella burnetii*. It is most common in people with occupational exposure to cattle or sheep or parturient animals, including cats. Severe headache occurs in approximately 75% of cases. Q fever is rarely fatal. Other zoonotic pulmonary infections include *Rhodococcus equi* associated with exposure to horses and *Bordetella bronchiseptica* associated with exposure to ill dogs ("kennel cough").

CLINICAL FEATURES

The ED evaluation should focus on establishing the diagnosis of pneumonia and determining the presence of epidemiologic and clinical features that would influence decisions regarding hospitalization and antibiotics. Key history includes the character and pattern of symptoms, the setting in which the pneumonia is acquired, geographic or animal exposures, and host factors that predispose to certain types of infections and are associated with outcome.

Pneumonia generally presents as a cough productive of purulent sputum, shortness of breath, and fever. In most healthy older children and adults, the diagnosis can be reasonably excluded on the basis of history and physical examination, with suspected cases confirmed by chest radiography. The absence of any abnormalities in vital signs or chest auscultation substantially reduces the likelihood of pneumonia. However, no single isolated clinical finding is highly reliable in establishing or excluding a diagnosis of pneumonia.[13]

Elder or debilitated patients with pneumonia often present with nonspecific complaints but not the classic symptoms. Pneumonia commonly presents in the elderly as acute confusion or a deterioration of baseline function. Elder patients are more likely to have advanced illness at the time of presentation and may present with sepsis in the absence of a previous syndrome suggestive of pneumonia. Rarely, patients with lower lobe pneumonia present with a complaint of abdominal or back pain. The diagnosis may be more difficult in infants and small children who are unable to give an adequate history. Pneumonia may present in infants as a fever associated with irritability, tachypnea, tachycardia, intercostal retractions, nasal flaring, or grunting. Cough may be minimal or absent.

Pneumonia can be divided based on clinical patterns into typical pneumonia caused by pyogenic bacteria, such as *S. pneumoniae* or *H. influenzae*, and atypical pneumonia caused by organisms such as *Mycoplasma* and *Chlamydophila* spp. This division is artificial, and a clear differentiation between these two types of pneumonia on clinical grounds alone is impossi-

ble. Certain clinical factors are often said to be suggestive of atypical organisms. Factors studied prospectively and found *not* to be more frequent with atypical pneumonias than with pyogenic bacterial etiologies include gradual onset, viral prodrome, absence of rigors, nonproductive cough, lower degree of fever, absence of pleurisy or consolidation, low leukocyte count, and an ill-defined infiltrate on a chest radiograph.[2] Although it is impossible to determine with a high degree of certainty the specific etiology of pneumonia without results of microbiologic or serologic tests, certain clinical factors suggest that a specific pathogen should be considered.

The classic presentation of pneumococcal pneumonia is the abrupt onset of a single shaking chill followed by fever, cough productive of rust-colored sputum, and pleuritic chest pain. Many patients do not exhibit the classic pattern. Patients often have a preceding upper respiratory illness, and the onset of pneumonia may be insidious, especially in the elderly or with underlying lung disease. Patients with a history of asplenia, sickle cell disease, AIDS, multiple myeloma, or agammaglobulinemia are at increased risk of pneumococcal bacteremia and sepsis with high mortality rates. Extrapulmonary complications (e.g., meningitis, endocarditis, or arthritis) may rarely be present. Adults with chronic lung disease who develop pneumonia due to *H. influenzae* typically present with an insidious worsening of baseline cough and sputum production, and bacteremia is rare. *Klebsiella pneumoniae* may cause severe pneumonia in elderly or debilitated patients. Sputum is often described as "currant jelly" because of the necrotizing, hemorrhagic nature of the infection. Abscess formation, empyema, and bacteremia are common with this organism, and mortality is high.

Atypical pneumonia is caused by organisms such as *M. pneumoniae*, *C. pneumoniae*, viruses, *Legionella* sp., or rickettsiae such as *C. burnetii*. Mycoplasmal infection usually begins as a flulike illness with headache, malaise, and fever. Cough is usually nonproductive but may sometimes produce clear or purulent sputum. Skin lesions, including maculopapular, vesicular, urticarial, or erythema multiforme-type rashes, are common, especially in younger patients. Although bullous myringitis is described as a classic finding, it is not specific for mycoplasmal infection and is present in only a few cases. Common physical findings include pharyngeal erythema, cervical adenopathy, and scattered rales and rhonchi. Rare extrapulmonary manifestations include pericarditis, glomerulonephritis, aseptic meningitis, and Guillain-Barré syndrome. Patients generally do not appear toxic, and most can be treated as outpatients. Although mucopurulent sputum generally indicates the presence of pyogenic bacterial pneumonia or bronchitis, it may also be present with mycoplasmal or viral pneumonia. Viral pneumonia in adults is often preceded by symptoms of upper respiratory infection, such as rhinitis or sore throat. Cough is usually nonproductive, and pleuritic chest pain is less common than with bacterial pneumonia.

Most *C. pneumoniae* infections in young adults cause a minor, self-limited upper respiratory illness that is subacute in onset. This organism is also associated with bronchitis, wheezing, sinusitis, pharyngitis, and atherosclerosis. Development of radiographically evident pneumonia is more common in the elderly, in contrast to the common perception that atypical pneumonias occur in the young.

Some patients with *Legionella* infection have a mild, self-limited atypical pneumonia presentation. Older patients, smokers, and those with chronic disease or immunosuppression are more prone to develop the more acute and severe systemic illness of legionnaires' disease. Gastrointestinal symptoms, such as diarrhea and abdominal cramping, are sometimes prominent.

In addition to age, the presence of underlying illness, and presenting symptoms, the setting of acquisition of pneumonia may provide clues to likely etiologies. CAP that occurs in otherwise healthy individuals is likely to be due to viruses, *Mycoplasma* sp., or *S. pneumoniae*. *Staphylococcus aureus*, including CA-MRSA, can cause severe pneumonia associated with influenza. Hospitalized patients may develop pneumonia due to agents that are uncommon in CAP, such as Enterobacteriaceae, *Pseudomonas aeruginosa*, and *S. aureus*. Healthy patients in an institutional setting, such as a dormitory or military barracks, are likely to have pneumonia due to *Mycoplasma* sp. or viruses.

Patients with underlying lung disease, especially COPD, constitute an important group likely to develop pneumonia. The lower respiratory tract of these patients is commonly colonized with organisms such as *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*. Cystic fibrosis patients are prone to pneumonia due to *P. aeruginosa* or *S. aureus*. Defective mucociliary clearance in both of these groups makes them highly susceptible to repeated episodes of pneumonia.

Patients with immunosuppression due to hematologic malignancy, patients receiving chemotherapy for malignancy, and transplant recipients are prone to pulmonary infections with a wide variety of organisms. In addition to the usual pathogens, these patients may develop pneumonia secondary to viruses such as CMV, varicella, or herpes simplex virus. They are also more likely to develop pneumonia due to aerobic gram-negative bacilli, fungi such as *Candida* sp. or *H. capsulatum*, and *P. jirovecii*.

Patients in nursing homes or other extended-care facilities are at increased risk for infection with resistant organisms such as *P. aeruginosa*, *K. pneumoniae* (including strains producing extended-spectrum β-lactamases), *Acinetobacter* species, and hospital-associated strains of MRSA. Other risk factors for infection with multidrug-resistant pathogens include (1) hospitalization for 2 or more days in an acute care facility within 90 days of infection; (2) patients who attended a hemodialysis clinic; and (3) patients who received intravenous antibiotic therapy, chemotherapy, or wound care within 30 days of infection. Any patient with pneumonia that fulfills any one of these historical features, including patients from a nursing home or long-term care facility, is designated as having health care–associated pneumonia (HCAP). HCAP is associated with a greater likelihood of resistant pathogens such as *Pseudomonas* and MRSA, and mortality is higher than that for CAP.[14]

DIAGNOSTIC STRATEGIES

Although many chest radiographs are obtained unnecessarily for patients with upper respiratory tract infections or bronchitis, it is difficult to identify a set of specific criteria to direct test ordering that is better than the clinical judgment of an experienced physician. A routine chest radiograph for all patients who present with cough is not necessary; chest radiography may be reserved for patients who have other suggestive findings (e.g., fever, tachycardia, oxygen desaturation, or an abnormal lung examination). Among patients suspected to have pneumonia, these clinical findings are prospectively validated and are better predictors of a radiographic infiltrate than physician judgment.[15] Patients with serious underlying disease, patients with severe sepsis or shock, and patients in whom hospitalization is considered should have chest radiography performed. Computed tomography (CT) of the chest is more sensitive than plain radiography for detecting the presence of pulmonary consolidation, although the natural history of CT-positive, plain radiograph-negative pneumonia is not clear.[16] Young, healthy adults with a presumptive diagnosis of pneu-

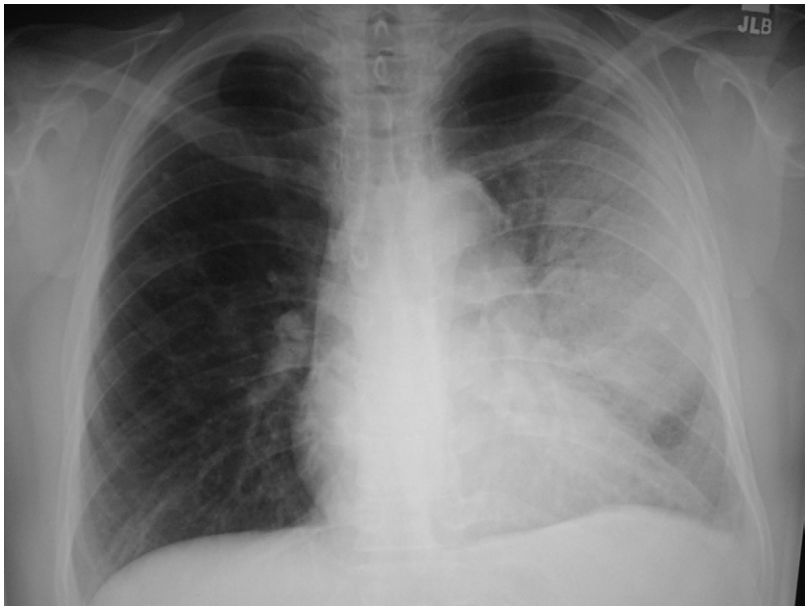


Figure 74-1. Posteroanterior chest radiograph reveals a left upper lobe pneumonia. A variety of organisms can produce this pattern, most commonly *S. pneumoniae*, *H. influenzae*, or gram-negative bacilli, but also *C. pneumoniae*, *Mycoplasma*, or *Legionella* sp.

monia, who will be treated as outpatients, may have a chest radiograph deferred unless there is a suspicion of immunocompromise or other unusual features of disease. A chest radiograph should be obtained subsequently if there is a poor initial response to treatment. Routine performance of chest radiography for patients with exacerbation of chronic bronchitis or COPD is of low yield and may be limited to patients with other signs of infection or congestive heart failure. Studies of infants with fever show that a routine chest radiograph is of low yield in the absence of other symptoms or signs of lower respiratory tract infection (e.g., abnormal auscultation or elevated respiratory rate).[17]

Although the causative agent cannot be determined solely by the results of chest radiography, certain radiographic patterns may suggest the possibility of specific pathogens. In pyogenic bacterial pneumonias, radiographs usually show an area of segmental or subsegmental infiltration and air bronchograms (Fig. 74-1). Lobar consolidation is present in a few cases of bacterial pneumonia, often due to pneumococcus or *Klebsiella*. A dense lobar infiltrate with a bulging fissure appearance on a chest radiograph is often described with pneumonia due to *Klebsiella*, but this finding is nonspecific, and most cases present as a subtler bronchopneumonia. Pneumonia resulting from spread of infection along the intralobular airway results in fluffy or patchy infiltrates in the involved areas of the lung. A wide variety of bacteria and agents such as *Chlamydophila* sp., *Mycoplasma* sp., *Legionella* sp., viruses, and fungi may cause this pattern.

An interstitial pattern on a chest radiograph (Fig. 74-2) typically is caused by *Mycoplasma* sp., viruses, or *P. jirovecii*. Tiny nodules disseminated throughout both lungs represent a miliary pattern typical of granulomatous pneumonias, such as TB or fungal disease. The location of infiltrates may also give a clue to the etiology. Aspiration pneumonia occurs in dependent areas of the lung, most commonly the superior segments of the lower lobes or posterior segments of the upper lobes. Pneumonias produced by hematogenous spread (e.g., *S. aureus*) tend to be peripheral. Apical infiltrates suggest TB.

The presence of additional radiographic features in association with infiltrates may suggest a specific etiology. An infiltrate associated with hilar or mediastinal adenopathy suggests the presence of TB or fungal disease or may indicate pneumonia associated with a neoplasm. Bacteria most likely associated with cavitation (Fig. 74-3) are anaerobes, aerobic gram-negative bacilli, and *S. aureus*. Cavitation also may be present in fungal disease or TB and with noninfectious processes (e.g., malignancy and pulmonary vascular disease). Pneumato-

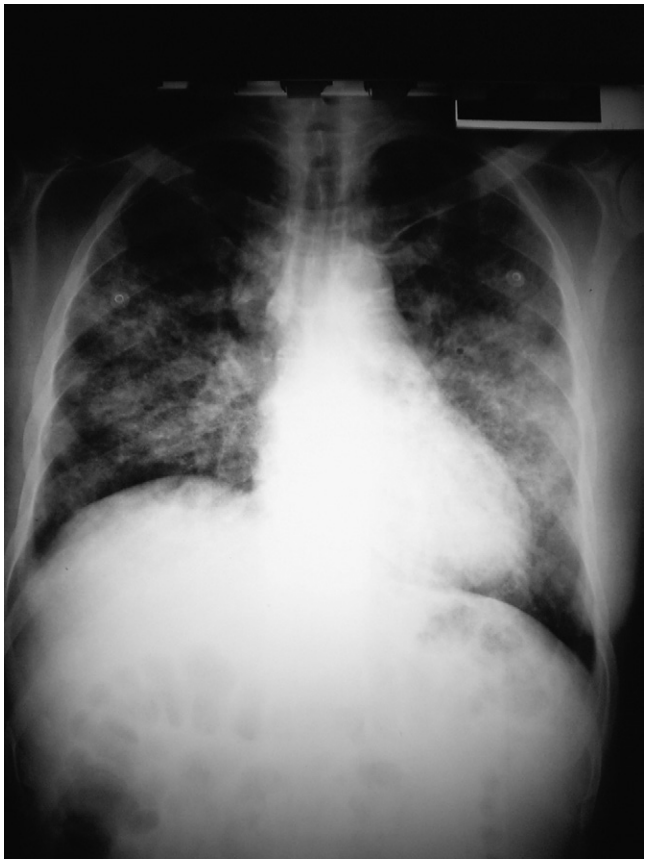


Figure 74-2. Posteroanterior chest radiograph reveals patchy interstitial infiltrates. Viruses and *Mycoplasma* are the most likely etiologies in an otherwise healthy patient, but many bacterial organisms may also produce this pattern.

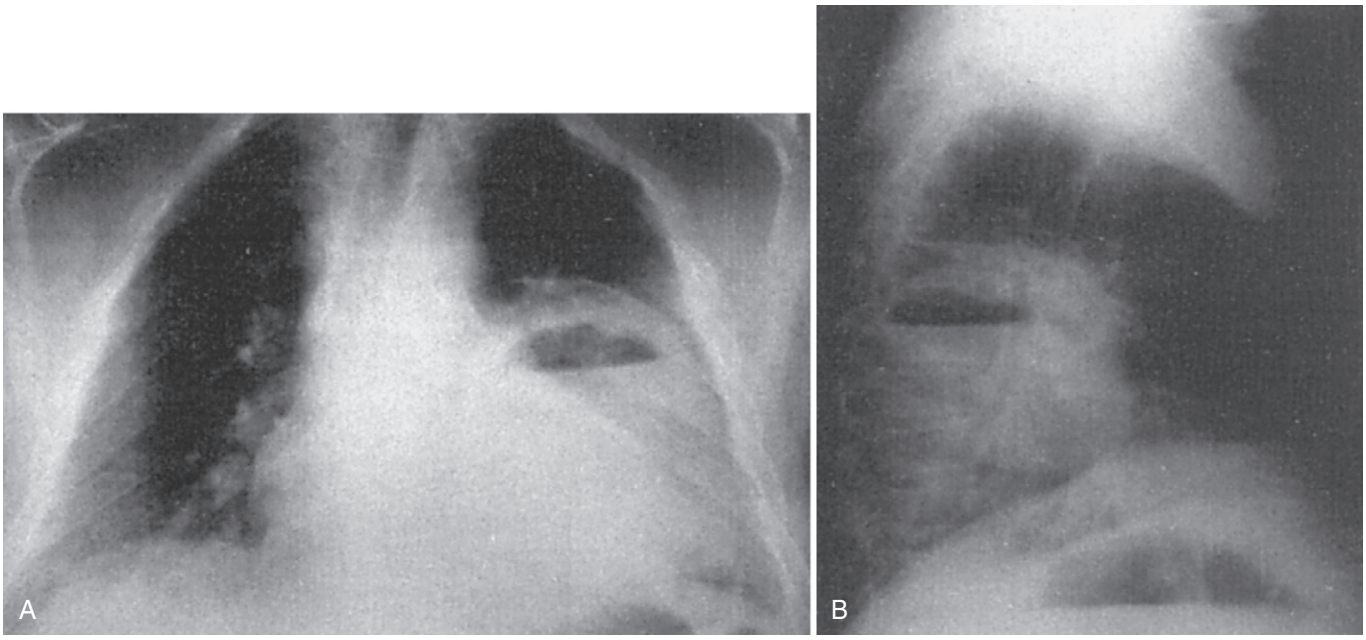


Figure 74-3. Posteroanterior (**A**) and lateral (**B**) chest radiographs reveal a lung abscess in the left lower lobe with a distinct air-fluid level.

celes or spontaneous pneumothorax may be seen in AIDS patients with PCP. Pleural effusions occur with a wide variety of organisms, including many types of pyogenic bacterial pneumonias, *Chlamydophila* sp., *Legionella* sp., and TB. Anaerobic infections associated with an effusion are especially prone to development of empyema. The diagnosis and aspiration of pleural effusions can be aided by use of ED bedside ultrasonography.

Radiographic findings are nonspecific for predicting a particular infectious etiology. *Mycoplasma* pneumonia may present as a dense infiltrate, or pneumococcal pneumonia may present as a diffuse interstitial infiltrate. Immunocompromised patients are particularly prone to having atypical radiographic appearances. Rarely, patients with a clinical picture strongly suggestive of pneumonia have a normal chest radiograph, and some are found to have an infiltrate within the next 24 to 48 hours. The absence of findings on a chest radiograph should not preclude the use of antimicrobial therapy in appropriate patients with a clinical diagnosis of pneumonia. Whether the state of hydration can affect the radiographic appearance of pneumonia is controversial. Although severe dehydration theoretically could result in a diminished exudative response by decreasing blood volume and hydrostatic pressure, this has not been shown experimentally.[18,19]

Laboratory studies also are nonspecific for identifying the etiology of pneumonia. Although the finding of a white blood cell count (WBC) greater than 15,000/mm^3 increases the probability of the patient having a pyogenic bacterial etiology rather than a viral or atypical etiology, the predictive value of this finding depends on the stage of the illness and likely prevalences of various etiologies. This is neither sensitive nor specific enough to aid decisions regarding therapy in an individual patient. A WBC may be helpful if it yields evidence of immunosuppression, such as neutropenia, or if it reveals lymphopenia that may indicate immunosuppression from AIDS. Basic metabolic panels may help identify patients with renal or hepatic dysfunction or metabolic acidosis associated with sepsis. These findings predict a complicated course and influence decisions regarding disposition, choice of antimicrobial agents, and dosages.

The assessment of respiratory function with pulse oximetry is important in the evaluation of patients with pneumonia since clinical assessment of oxygenation can be inaccurate.[20] Pulse oximetry should be obtained in any patient suspected to have pneumonia.

Sputum Gram's stain rarely results in a change in therapy or outcome. Correlation between identification of pneumococcus on Gram's stain and sputum culture results is poor, even when commonly used criteria for an adequate sputum specimen (<5 squamous epithelial cells and >25 WBC/high-power field) are applied. Gram's stains are even less likely to show gram-negative pathogens, such as *H. influenzae*, and should not be relied on to rule out a gram-negative etiology. Empirical antimicrobial agents are usually highly clinically effective if chosen based on clinical information without sputum analysis. Guidelines for management of CAP from the Infectious Disease Society of America (IDSA) and American Thoracic Society (ATS) support limiting sputum Gram's stain and culture to those patients with more severe disease or risk factors for unusual pathogens.[1]

Routine blood cultures are of essentially no value in nonimmunocompromised adults with pneumonia, in whom there is a very low prevalence of noncontaminant bacteremia, and management is rarely changed based on the results.[21,22] The follow-up of false-positive blood cultures is costly and labor-intensive, and it may lead to unnecessary use of antibiotics such as vancomycin or linezolid when results are initially reported as gram-positive cocci. Blood cultures should be obtained from immunocompromised patients, those with severe sepsis or shock, or those with risk factors for endovascular infection (e.g., prosthetic valves, intravenous drug use, or cavitary infiltrates).[1] When cultures are drawn, they should be obtained prior to the initiation of antibiotics (although antibiotics should not be delayed for this reason).

Patients with a pleural effusion greater than 5 cm on lateral upright posterior-anterior chest radiograph should have a diagnostic thoracentesis performed,[1] with fluid sent for cell count, differential, pH (pH < 7.2 predicts the need for a thoracostomy tube), Gram's stain, and culture. For most patients, thoracentesis can be safely deferred until after hospital admis-

sion. Patients in significant respiratory distress, however, or with evidence of tension and mediastinal shift require emergent diagnostic and therapeutic thoracentesis.

Serologic tests are available for the diagnosis of many organisms, including *C. pneumoniae*, *Legionella* sp., and fungi. The use of serologic tests to determine the etiology of pneumonia may be helpful retrospectively, but they usually require acute and convalescent serum titers and are of little use in the ED. Urine antigen tests for *S. pneumoniae* and *Legionella* are available, and in some facilities results can be obtained within the time frame of an ED evaluation. It is not clear, however, that a positive result should prompt a change of empirical treatment.[1] Rapid diagnostic tests for viral antigens are available for several viruses, including RSV and influenza. These tests may be useful for infection control decisions in hospitalized patients, and they may provide an indication for influenza therapy and family prophylaxis. In the future, rapid testing using technology such as the polymerase chain reaction may provide emergency physicians with a reliable method to determine the specific etiology of pneumonia.

Pneumonia Associated with Human Immunodeficiency Virus Infection

The approach to an HIV-infected patient with pulmonary complaints must consider the likelihood of opportunistic lung infections. Although the use of highly active antiretroviral therapy (HAART) is decreasing the incidence of opportunistic infections among HIV-infected patients, individuals who are not under regular care often present to the ED. In the setting of a patient with risk factors for HIV but an unknown serologic status, a decision must be made as to the likelihood of AIDS and the need to search aggressively for opportunistic pathogens.

Respiratory infections are the most common type of opportunistic infection in AIDS patients. In addition to *P. jirovecii*, there is also an increased incidence of pneumonia due to *M. tuberculosis* and common bacterial pathogens such as *S. pneumoniae* and *H. influenzae*. The incidence of pneumococcal pneumonia is 7 to 10 times higher in HIV-infected people and the incidence of *H. influenzae* pneumonia is approximately 100 times higher than in non-HIV-infected individuals. Other less important causes of pneumonia in HIV-infected patients include *Mycobacterium avium* complex, CMV, aerobic gram-negative bacilli, *Cryptococcus neoformans*, and *Rhodococcus equi*.

Although some patients have known HIV infection or AIDS, many patients are unaware of their HIV status, and many are reluctant to volunteer that they have risk factors for HIV. The first crucial step in the diagnosis of PCP is the recognition that a patient may be at risk. If the possibility of HIV infection is established, the likelihood of immunosuppression must be determined. The potential for opportunistic pulmonary infection can be predicted by a recent absolute CD4 lymphocyte count less than 200/mm^3. This count is often known by patients with recognized HIV infection or may be surmised by a peripheral total lymphocyte count less than 1000/mm^3.[23] In patients who do not know their HIV status, the presence of findings such as weight loss, hairy leukoplakia, and oral candidiasis strongly suggests immunosuppression.

Although patients with PCP may present with typical features of subacute onset of nonproductive cough, fever, shortness of breath, diffuse interstitial infiltrates on chest radiography, and arterial hypoxemia, 10 to 20% of patients subsequently proven to have PCP lack these findings. PCP usually has a subacute presentation characterized by nonproductive cough, exertional dyspnea, and weight loss. Tachypnea and tachycardia are usually present.

The classic radiographic findings in PCP are bilateral interstitial infiltrates that begin in the perihilar region. Radiographic manifestations of PCP can vary considerably, however, ranging from a normal appearance to dense consolidation. Lobar infiltrates, pleural effusions, hilar adenopathy, parenchymal nodules, and cavitary disease are also described. Hypoxemia, hypocapnia, and an increased arterial-alveolar oxygenation gradient are usually present. Serum lactate dehydrogenase is significantly elevated in AIDS patients with PCP compared to patients with non-PCP pneumonia. The demonstration of oxygen desaturation with mild exercise may be helpful in patients with more subtle presentations. Confirmation of the diagnosis of PCP requires sputum induction and staining and, in some cases, further invasive procedures, such as bronchoscopy with bronchoalveolar lavage or biopsy. In most settings, patients suspected to have PCP are admitted to the hospital and given presumptive therapy against PCP.

There is a broad differential diagnosis for pulmonary infiltrates in AIDS patients (Fig. 74-4). The bacterial pathogens most commonly responsible for pneumonia in these patients are the same pathogens most frequently encountered in immunocompetent individuals with CAP, but they may have an atypical appearance on chest x-ray. Because AIDS patients with pulmonary TB cannot be distinguished reliably from AIDS patients with other pulmonary infections at presentation, consider TB in all HIV-infected patients with respiratory complaints and initiate respiratory isolation. AIDS patients are also at risk for pneumonia due to other mycobacterial species (e.g., *M. avium* complex). Nevertheless, the finding of acid-fast bacilli in the sputum should prompt empirical therapy against *M. tuberculosis* until another mycobacterial species is definitively identified. AIDS patients are also at increased risk for pneumonia due to *Cryptococcus neoformans* or other fungi associated with geographic exposure. Kaposi's sarcoma may also present with pulmonary infiltrates.

DIFFERENTIAL DIAGNOSIS CONSIDERATIONS

The differentiation between upper and lower respiratory tract infections may be difficult. A chest radiograph helps differentiate between upper respiratory tract infection or bronchitis and pneumonia, but it is probably not necessary for all patients with cough and sputum production unless other factors are present that suggest the possibility of pneumonia or obscure its clinical diagnosis (e.g., toxic appearance, extremes of age, underlying illness, and abnormal chest examination).

Many noninfectious etiologies may result in inflammatory lung processes, including exposure to mineral dusts (e.g., silicosis), chemical fumes (e.g., chlorine and ammonia), toxic drugs (e.g., bleomycin), radiation, thermal injury, or oxygen toxicity. Immunologic diseases (e.g., sarcoidosis, Goodpasture's syndrome, and collagen vascular disease) or hypersensitivity to environmental agents (e.g., farmer's lung disease) may also result in pneumonia. Tumors may be confused with pneumonia radiographically or may present initially as a postobstructive infection or adenopathy with peripheral infiltrates. Lymphangitic spread of lung malignancy may resemble interstitial pneumonia.

Aspiration

It is important to recognize the distinction between the acute aspiration of gastric contents or other liquids and bacterial pneumonia that may develop later as a complication of

Figure 74-4. Posteroanterior chest radiograph of an HIV-infected patient reveals interstitial disease mixed with patchy alveolar infiltrates. *Pneumocystis jirovecii* is the most common etiology, but bacterial pathogens and tuberculosis must also be considered.

aspiration. Aspiration of liquids into the lung disrupts surfactant and causes an inflammatory response that may lead to hypoxia and respiratory failure. Aspiration of acidic gastric contents is particularly damaging to lungs and is common in patients who are unconscious from intoxication or anesthesia or who have neurologic deficits. Patients may present initially with coughing or shortness of breath or may appear well initially and then develop respiratory dysfunction during the next several hours.

Acute aspiration of acidic fluid into the lungs may produce fever, leukocytosis, purulent sputum, and radiographic infiltrates that mimic bacterial pneumonia. Although many of these patients go on to develop bacterial pneumonia, prophylactic administration of antibiotics is controversial. Some studies indicate that prophylactic antibiotics do not seem to be beneficial and may select for resistant organisms.[24] Antibiotics should be initiated if the patient develops signs of bacterial pneumonia, including new fever, expanding infiltrate appearing more than 36 hours after aspiration, or unexplained deterioration. Systemic corticosteroids for acute aspiration are of no benefit.

MANAGEMENT

The possibility of communicable disease should suggest early isolation.[25] Patients with a history of TB exposure, suggestive symptoms (e.g., persistent cough, weight loss, night sweats, and hemoptysis), or belonging to a group at high risk for TB (e.g., homeless, intravenous drug user, alcoholic, HIV risk, and immigrant from high-risk area) should be given a mask and placed in respiratory isolation before evaluation, including chest radiography.[26] EDs that frequently care for patients at risk for TB should consider triage protocols to identify these individuals rapidly before patients, visitors, or staff are unnecessarily exposed.[27]

Antimicrobials should be administered in the ED for patients who are being admitted to the hospital. Timely administration of antimicrobials has been associated with improved outcomes for hospitalized pneumonia patients[28], although confounding factors limit the conclusions of these studies. A rush to treatment without a diagnosis of pneumonia, however, can result in inappropriate antibiotic use. Although the Centers for Medicare and Medicaid Services have used specific time cutoffs for antibiotic administration as a quality measure, the IDSA/ATS guidelines for management of pneumonia do not support the use of a specific time cutoff. The antibiotics selected should cover the likely etiologies based on clinical, laboratory, radiologic, and epidemiologic information. However, the regimen should also be as selective as possible to avoid drug toxicity, emergence of resistance to broad-spectrum agents, and excessive cost.

The prevalence of drug-resistant *S. pneumoniae* (DRSP) is increasing. In most areas of the United States, high-level penicillin resistance occurs in approximately 15 to 20% of outpatient pneumococcal sputum isolates. DRSP that is resistant to penicillin is usually resistant to other β-lactams, macrolides, tetracyclines, and trimethoprim-sulfamethoxazole (TMP-SMX). Many extended-spectrum or "respiratory" fluoroquinolones are available, such as levofloxacin, moxifloxacin, and gemifloxacin. Because oral bioavailability of fluoroquinolones is high, oral therapy provides serum and tissue levels essentially equivalent to parenteral therapy.[29] These agents are active against DRSP and other typical or atypical pneumonia pathogens. It is not clear, however, that in vitro resistance is related to adverse clinical outcome. Most cephalosporins and macrolides achieve adequate levels in serum and tissues to successfully treat *S. pneumoniae* respiratory tract infections, even if the laboratory reports that the organism is resistant.

CA-MRSA has rapidly emerged as the most common pathogen isolated in community-acquired skin and soft tissue infections. It is also increasingly recognized as a cause of severe, rapidly progressing pneumonia with sepsis, often in children or healthy young adults with influenza.[9] Antimicrobials with consistent in vitro activity against CA-MRSA isolates include vancomycin, TMP-SMX, daptomycin, tigecycline, linezolid, ceftaroline, and ceftobipirole. Although vancomycin is used most often for documented MRSA infections, there is concern that vancomycin may be losing efficacy in light of increasing minimum inhibitory concentrations for vancomycin.[30] Daptomycin is inactivated by pulmonary surfactant and would not be appropriate for empiric therapy. Empirical coverage of

Table 74-1 Community-Acquired Pneumonia in Older Children and Adults: Outpatient Treatment

CLINICAL SETTING	ANTIBIOTIC REGIMEN*	COMMENTS
Previously healthy, no antimicrobials in last 3 mo	Doxycycline 100 mg PO bid	Preferred for adolescent/young adult when likelihood of mycoplasma is high; variable activity vs. *S. pneumoniae.*
	Azithromycin	Treats common typical bacterial and atypical pathogens. Variety of dosing regimens: 500 mg once followed by 250 mg daily for 4 days; 500 mg PO daily for 3 days; 2 g PO extended-release suspension once. Can substitute clarithromycin.
Comorbidities, or antimicrobials in last 3 mo	Levofloxacin 750 mg PO daily for 5 days	Can substitute moxifloxacin or gemifloxacin.
		Treats common typical and atypical bacterial pathogens; active vs. DRSP. Use if recently received β-lactam or macrolide.
	Cefpodoxime 200 mg PO bid + azithromycin 500 mg PO daily	Use if recently received fluoroquinolones. Can substitute cefdinir, cefprozil, or amoxicillin/clavulanate for cefpodoxime. Variable activity against DRSP.

*Doses are for 70-kg adult with normal renal and hepatic function.
DRSP, Drug-resistant *S. pneumoniae.*

MRSA should be strongly considered for patients with severe pneumonia associated with sepsis, especially those with concurrent influenza, contact with someone infected with MRSA, or radiographic evidence of necrotizing pneumonia.

Appropriate agents for outpatient treatment of adults with CAP include macrolides, doxycycline, and fluoroquinolones with enhanced activity against *S. pneumoniae* (Table 74-1).[1] In patients properly identified at low risk for complications and who will have careful outpatient follow-up, use of a macrolide or doxycycline is reasonable. For patients at higher risk of DRSP due to recent antibiotic use or comorbidities such as chronic heart, lung, liver, or renal disease, a respiratory fluoroquinolone should be considered.

For patients who have received a fluoroquinolone within the previous few months, a combination of a macrolide plus a β-lactam agent (e.g., high-dose amoxicillin [1 g three times daily], amoxicillin-clavulanate [2 g orally twice daily], or cefpodoxime) is appropriate. Except for the administration of fluoroquinolones, these recommendations also apply to school-age children and adolescents, in whom mycoplasmal infection is common.

For patients whose illness is severe enough to require hospital admission and parenteral antibiotics, options include a combination of a β-lactam agent (e.g., ceftriaxone, cefotaxime, ampicillin-sulbactam, or ertapenem) and a macrolide (e.g., intravenous or oral azithromycin) or an extended-spectrum fluoroquinolone alone. These regimens are associated with lower mortality in elderly patients hospitalized for CAP compared with monotherapy with a third-generation cephalosporin. These regimens treat the most common bacterial pathogens, such as *S. pneumoniae*, *M. catarrhalis*, and *H. influenzae*, and atypical pathogens, such as *Mycoplasma*, *Chlamydophila*, and *Legionella* spp. Intravenous azithromycin alone is another option, although this drug does not achieve significant serum levels and lacks significant activity against many aerobic gram-negative bacilli and DRSP. Azithromycin alone might be an appropriate choice for people with milder illness who are less likely to be bacteremic. If anaerobic organisms are suspected (e.g., aspiration), clindamycin or metronidazole could be added to the regimen, or the regimen could include an antibiotic with anaerobic activity, such as ertapenem, ampicillin-sulbactam, or piperacillin-tazobactam. Some quinolones, such as moxifloxacin, are also active against anaerobes (Table 74-2).

Seriously ill patients who present with severe sepsis or septic shock require aggressive fluid resuscitation and may benefit from more intensive management with vasopressors, transfusion, and inotropic agents as part of early goal-directed therapy.[31] Severely ill and compromised patients are at relatively greater risk of infection due to *S. pneumoniae*, aerobic gram-negative bacilli, *S. aureus* (including MRSA), and, in some areas, *Legionella* sp. For pneumonia patients admitted to an ICU, adequate activity against DRSP may be more important. Outcomes with severe pneumococcal pneumonia may be better with combination therapy compared with a single agent such as a fluoroquinolone alone.[32] A third-generation cephalosporin or β-lactam/β-lactamase inhibitor can be combined with a fluoroquinolone. Addition of an aminoglycoside should be considered if septic shock is present.

Patients with recent hospitalization, neutropenia, or underlying bronchiectasis are at increased risk of infection with *P. aeruginosa*. Empirical therapy should include two agents with extended gram-negative activity, including *P. aeruginosa*. Empirical regimens include cefepime, imipenem, meropenem, or piperacillin-tazobactam, plus either ciprofloxacin (high dose) or an aminoglycoside and a macrolide. For life-threatening pneumonia in populations at risk for MRSA, and for patients recently exposed to fluoroquinolones who may have fluoroquinolone-resistant *S. pneumoniae*, consider vancomycin or linezolid. The regimen should also cover atypical pathogens and gram-negative bacilli.

Since HCAP is associated with higher mortality and a greater likelihood of unusual pathogens, it is appropriate to give broader spectrum empirical therapy, usually with a combination of antimicrobials to increase the chance that at least one antibiotic will be active against the causative pathogen. Appropriate combinations include an antipseudomonal β-lactam agent, such as piperacillin-tazobactam, cefepime, imipenem, or meropenem, with either an aminoglycoside or a fluoroquinolone and vancomycin or linezolid for MRSA.[33]

For patients with AIDS, it is important to treat *P. jirovecii* and bacterial pathogens such as *S. pneumoniae*. TMP-SMX is the treatment of choice; the usual regimen is 20 mg/kg of TMP and 100 mg/kg of SMX daily in four divided doses, to be continued for 21 days.[34] For most adult patients, a regimen of three ampules (80 mg of TMP and 400 mg of SMX per ampule) every 6 hours is appropriate. For patients allergic to sulfa, pentamidine can be given, 4 mg/kg over 1 hour. Toxicities of pentamidine include acute hypotension and hypoglycemia. Because pentamidine has no activity against *S. pneumoniae* or other bacterial pathogens, it is important to add a cephalosporin or other antibacterial agent to the initial

Table 74-2 Community-Acquired Pneumonia in Older Children and Adults: Inpatient Antimicrobial Treatment

CLINICAL SETTING	ANTIBIOTIC REGIMEN*	COMMENTS
Community-acquired, nonimmunocompromised	Ceftriaxone 1 g q24h + azithromycin 500 mg q24h IV or PO	Could substitute cefotaxime, ampicillin-sulbactam, or ertapenem for ceftriaxone.
	Respiratory fluoroquinolone (levofloxacin 750 mg IV q24h or moxifloxacin 400 mg IV q24h)	Treats most common bacterial and atypical pathogens. Active vs. DRSP.
Severe pneumonia (ICU)	Ceftriaxone 1 g IV q24h + levofloxacin 750 mg IV q24h + vancomycin 1 g IV q12h	Can substitute cefotaxime, cefepime, ertapenem, or β-lactam/β-lactamase inhibitor for ceftriaxone. Can substitute moxifloxacin for levofloxacin. Can substitute linezolid for vancomycin.
Health care–associated pneumonia or severe pneumonia with neutropenia, bronchiectasis (risk for *Pseudomonas*)	Cefepime 2 g IV q12h + ciprofloxacin 500 mg IV q12h + vancomycin 1 g IV q12h	Can substitute other antipseudomonal β-lactam, such as piperacillin-tazobactam, imipenem, or meropenem, for cefepime. Can substitute aminoglycoside plus macrolide for ciprofloxacin.
Presumed PCP	Trimethoprim-sulfamethoxazole 240/1200 mg IV q6h	Add ceftriaxone to TMP/SMX if severe, until PCP confirmed. Alternatives for sulfa allergy include pentamidine + third-generation cephalosporin; clindamycin + primaquine; or atovaquone + ceftriaxone.

*Doses are for a 70-kg adult with normal renal and hepatic function.
DRSP, drug-resistant *S. pneumoniae*; ICU, intensive care unit; PCP, *Pneumocystis* pneumonia.

empiric regimen. Other options include clindamycin, 900 mg intravenously every 8 hours, plus primaquine, 15 mg orally daily; atovaquone; trimetrexate; or TMP plus dapsone. The addition of steroids (prednisone, 40 mg orally twice daily) reduces mortality and clinical deterioration in patients with partial arterial oxygen tension (Pao_2) less than 70 mm Hg or alveolar-arterial gradient greater than 35 mm Hg. *Mycoplasma*, *Legionella*, and *Chlamydophila* spp. are uncommon etiologies of severe pneumonia in AIDS patients, so empirical therapy with erythromycin or doxycycline is not routinely recommended.

Many EDs initiate outpatient therapy in moderately ill patients, for whom hospitalization might be considered, with an initial parenteral dose of a long-acting antibiotic, such as ceftriaxone, and employ extended observation (i.e., 12–24 hours) while administering supportive care, such as hydration, antipyretics, and bronchodilators, before discharge on an oral regimen. Certain patients may also be brought back to the ED for follow-up in 24 hours and receive a second parenteral or observed oral dose of antibiotics. An extended-spectrum fluoroquinolone (oral or parenteral) is another option that may be advantageous due to additional activity against atypical pathogens and DRSP.

There is little experimental evidence that directly addresses the question of duration of therapy for pneumonia. Outpatient treatment for pneumonia is generally 10 to 14 days. A 5-day treatment course is possible with azithromycin or levofloxacin (750 mg daily).

Patients with a positive influenza antigen test or culture may benefit from antiviral treatment. Empirical antiviral treatment is reasonable with compatible clinical findings when influenza is in the community, and it may be associated with reduced mortality when started early in the course of influenza.[35] Neuraminidase inhibitors such as oseltamivir are recommended instead of amantadine and rimantadine because they are active against influenza A and B and because many circulating strains are resistant to these older agents.[36] Inhaled zanamavir is not recommended for patients with underlying reactive airway disease because of concern about induced bronchospasm.

DISPOSITION

There is tremendous variability in physician admission decisions for pneumonia. The more common tendency is overestimation of disease severity, leading to hospitalization of patients at low risk for death or serious complications. The decision to hospitalize a patient with pneumonia does not necessarily mean that a prolonged inpatient stay is required. Observation for 12 to 24 hours in the ED or hospital may allow the early discharge of certain moderate-risk patients. Inpatient treatment of pneumonia is 15 to 20 times more expensive per patient than outpatient treatment, and most patients are more comfortable in a home environment.

Although no firm guidelines exist regarding hospital admission, a scoring system may assist with hospitalization decisions. One commonly used system is based on the Pneumonia Patient Outcomes Research Team study, a prospectively validated predictive rule for mortality among immunocompetent adults with CAP.[37] This model (also known as the Pneumonia Severity Index [PSI]) suggests a two-step approach to assess risk. Patients in the lowest risk class who are recommended for outpatient management are those younger than age 50 years, without significant comorbid conditions (neoplasm, congestive heart failure, cerebrovascular disease, renal disease, liver disease, and HIV), and without the following findings on physical examination: altered mental status, pulse 125 beats/min or greater, respiratory rate 30 breaths/min or greater, systolic blood pressure less than 90 mm Hg, or temperature less than 35°C or 40°C or greater. Patients who do not fit the lowest risk category are classified into categories based on a scoring system that accounts for age, comorbid illness, physical examination findings, and laboratory abnormalities (Table 74-3). Hospitalization is recommended for patients with a score greater than 91, and brief admission or observation may be considered for patients with a score of 71 to 90. Although this method of assessing the likelihood of successful outpatient management is helpful, it can be cumbersome, is not modeled to predict acute life-threatening events, does not take into account dynamic evaluation over time, and has many

Table 74-3 Scoring System for Pneumonia Mortality Prediction

PATIENT CHARACTERISTICS	POINTS
Demographic factor	
Age	
Male	No. years of age
Female	No. years of age −10
Nursing home resident	10
Comorbid illness	
Neoplastic disease	30
Liver disease	20
Congestive heart failure	10
Cerebrovascular disease	10
Renal disease	10
Physical examination finding	
Altered mental status	20
Respiratory rate ≥ 30	20
Systolic blood pressure ≤90 mm Hg	20
Temperature < 35° C or > 40° C	15
Pulse ≥ 125 beats/min	10
Laboratory or radiographic finding	
Arterial pH < 7.35	30
Blood urea nitrogen >30 mg/dL	20
Sodium <130 mEq/L	20
Glucose > 250 mg/dL	10
Hematocrit < 30%	10
Arterial Po_2 < 60 mm Hg	10
Pleural effusion	10

Adapted from Mandell LA, et al: Update of practice guidelines for the management of community-acquired pneumonia in immunocompetent adults. Clin Infect Dis 37:1405, 2003.

Table 74-4 Criteria for Severe Community-Acquired Pneumonia

Minor criteria*
Respiratory rate ≥30 breaths/min†
Pao_2/Fio_2 ratio ≤250†
Multilobar infiltrates
Confusion/disorientation
Uremia (BUN level, ≥20 mg/dL)
Leukopenia‡ (WBC count, <4000 cells/mm^3)
Thrombocytopenia (platelet count, <100,000 cells/mm^3)
Hypothermia (core temperature, <36° C)
Hypotension requiring aggressive fluid resuscitation
Major criteria
Invasive mechanical ventilation
Septic shock with the need for vasopressors

*Other criteria to consider include hypoglycemia (in patients who do not have diabetes), acute alcoholism/alcoholic withdrawal, hyponatremia, unexplained metabolic acidosis or elevated lactate level, cirrhosis, and asplenia.

†A need for noninvasive ventilation can substitute for a respiratory rate >30 breaths/min or a Pao_2/Fio_2 ratio <250.

‡As a result of infection alone.

BUN, blood urea nitrogen; Pao_2/Fio_2, arterial oxygen pressure/fraction of inspired oxygen.

Adapted from Mandell LA, Wunderink RG, Anzueto A, et al: Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 44:S27, 2007.

important exceptions (e.g., an otherwise low-risk patient with severe hypoxia would be discharged by strict interpretation of this rule). Clinical judgment should supersede a strict interpretation of this scoring system. However, a study in which physicians were educated and provided the patient's risk score revealed a significantly lower overall admission rate, cost savings, and similar quality-of-life scores compared to those for patients conventionally managed by their physicians.[38] Additional discharge criteria include improving and stable vital signs over a several-hour observation period, ability to take oral medications, an ambulatory pulse oximetry greater than 90%, home support, and access to follow-up.

A similar tool that is easier to use is the CURB-65 rule.[39] This rule uses only five simple criteria to determine patients at lower risk for adverse events: *c*onfusion, *u*remia (blood urea nitrogen >20 mg/dL), *r*espiratory rate greater than 30, *b*lood pressure less than 90 systolic or greater than 60 diastolic, and age *65* or greater. The risk of 30-day mortality increases with a greater number of these factors present: 0.7% with zero factors, 9.2% with two factors, and 57% with five factors. Patients with zero or one feature can receive outpatient care, those with two should be admitted, and ICU care should be considered for those with three or more. No randomized trials of hospital admission strategies directly compare the PSI to the CURB-65 score. In a comparison of scores in the same population of CAP patients, the PSI yields a slightly higher percentage of patients in the low-risk category, with a similar low mortality rate.[40]

The disposition of HIV-infected patients with possible PCP is dictated by the likelihood of progression to severe disease and by the feasibility of close outpatient follow-up. Factors associated with decreased survival in AIDS patients with PCP include a history of prior PCP, anemia, hypoxemia, and medical comorbidity.[41] Patients without multiple poor prognostic factors may be discharged from the ED with close outpatient follow-up, ideally within 2 or 3 days. Because of the potential toxicity of TMP-SMX, empirical treatment with this agent for well-appearing patients with a low probability of disease is not recommended. An empirical trial of a macrolide may be indicated for treatment of bronchitis or mild CAP in a patient at low risk for PCP (e.g., recent CD4 count >350/mm^3). Any deterioration on outpatient oral antibiotics should prompt admission for a more extensive evaluation. Some clinicians initiate oral outpatient therapy with TMP-SMX or an alternate drug for patients with a high probability of PCP and favorable clinical parameters, but this should be done only if the patient can be followed closely.

The decision to admit a patient to the ICU is straightforward when patients are intubated or require vasopressors. It is more difficult to identify patients who do not require these interventions initially but may be at greater risk for deterioration and require a level of monitoring that may be beyond that available on the typical hospital ward. Objective criteria using the PSI (class V) and CURB-65 are proposed but have not been prospectively validated for the ICU admission decision.[42] When similar criteria were retrospectively studied in a cohort of CAP patients, they did not perform better than actual physician decisions.[43] IDSA/ATS guidelines include criteria for defining severe CAP (Table 74-4), but these have not been validated.[1] The decision to admit a patient to the hospital largely reflects the potential for acute deterioration. Likewise, some rate of floor to ICU transfer is inevitable.

Most patients with CAP do not need respiratory isolation. Patients who could pose a threat of transmission to other patients (e.g., influenza, varicella, TB, and plague) should be isolated. People with fever and respiratory symptoms who have been traveling in an area with SARS or avian influenza should also be isolated. Neutropenic patients generally are placed in reverse isolation. HIV-infected patients who present with pneumonia should be isolated until TB can be evaluated by sputum acid-fast bacilli smears; this is particularly true for

patients with other risk factors for TB. The chest radiograph cannot exclude TB in AIDS patients because it often does not have the typical appearance of TB. Isolation should be strongly considered for others at high risk for TB, such as inner-city homeless people and intravenous drug users.

ACUTE RESPIRATORY DISTRESS SYNDROME

Acute respiratory distress syndrome (ARDS) is a form of noncardiogenic pulmonary edema that is a result of the nonspecific response of the lung to a variety of insults. ARDS is defined as respiratory failure indicated by a requirement for mechanical ventilation and Pao_2/fraction of inspired oxygen ratio 200 or less in the appropriate clinical setting with one or more recognized risk factors. This presentation is accompanied by new, bilateral, diffuse, patchy or homogeneous pulmonary infiltrates on the chest radiograph, with no clinical evidence of heart failure, fluid overload, or chronic lung disease (pulmonary artery occlusion pressure ≤18 mm Hg).[44]

Respiratory failure results from damage to the region of alveolar-capillary oxygen exchange with increased permeability to plasma fluid and protein. ARDS can be caused by a direct injury to the lungs (e.g., aspiration of liquids or inhaled toxins) or may result from circulating inflammatory mediators associated with multisystem trauma, sepsis, or numerous drugs (Box 74-1). A variety of mediators are implicated in the development of ARDS, including neutrophil production of proteases and oxygen radicals, interleukins and other cytokines, tumor necrosis factor, and complement factors. This syndrome most often develops in patients already seriously ill in the hospital.

Treatment of ARDS is primarily supportive. High inspiratory pressures and positive end-expiratory pressure are often required to maintain oxygenation, so it is difficult to avoid barotrauma. Peak airway pressures should be kept at less than 35 cm H_2O if possible. Outcome is improved with use of reduced tidal volumes, allowing permissive hypercapnia.[45] Other ventilator techniques that may be beneficial include inverse-ratio ventilation with prolonged inspiratory time and use of a high-frequency oscillatory ventilator.[46] Fluid balance must avoid increased pulmonary capillary pressure while maintaining organ perfusion. Prone positioning during ventilation may improve distribution of perfusion to ventilated lung regions, but improvement in oxygenation is variable. Inhaled nitric oxide, *N*-acetylcysteine, prostaglandin E_1, ketoconazole, and nonsteroidal anti-inflammatory drugs produce variable results.[47] Corticosteroids do not reduce mortality in early ARDS but may have benefit in the late fibroproliferative phase. Although mortality is high, most survivors recover normal or near-normal lung function. Research is focusing on preventive measures for ARDS that may be used in the ED for patients at risk. Agents under study include aerosolized surfactant, free radical scavengers, prostaglandin inhibitors, and agents that can modify interleukins and other inflammatory mediators.

BOX 74-1 CONDITIONS ASSOCIATED WITH ACUTE RESPIRATORY DISTRESS SYNDROME

Sepsis
Shock
Toxic gas or smoke inhalation
Aspiration
  Gastric contents
  Near-drowning
  Hydrocarbons/solvents
Pneumonia
Drug reaction
  Salicylates
  Opiates
  Tricyclic antidepressants
  Cyclosporine
  Amiodarone
  Cancer chemotherapeutic agents (e.g., bleomycin)
  Hydrochlorothiazide
Trauma
Burns
Transfusion reaction
Radiation injury
Pancreatitis
Thromboembolism
Fat embolism
Air embolism
Amniotic fluid embolism
Eclampsia
Neurogenic (e.g., subarachnoid hemorrhage, head trauma)
Disseminated intravascular coagulation
High-altitude exposure
Oxygen toxicity
Cardiopulmonary bypass

KEY CONCEPTS

- Empirical antimicrobial therapy should be started in the ED for patients admitted with pneumonia. Empirical therapy should treat the most likely pathogens, including *S. pneumoniae*, *H. influenzae*, *M. pneumoniae*, and *C. pneumoniae*.
- HIV or other immunosuppressive conditions should be considered in all patients in whom pneumonia is suspected.
- Communicable diseases should be considered and isolation initiated when appropriate, including suspected TB, SARS, or influenza.
- The disposition of patients with pneumonia is dictated by the patient's underlying medical conditions, the severity of illness and likelihood of clinical deterioration, and the feasibility of home care and outpatient follow-up.
- *Mycoplasma* pneumonia may present as a dense infiltrate, or pneumococcal pneumonia may present as a diffuse interstitial infiltrate.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 75 Pleural Disease

Joshua M. Kosowsky

Pleural disease is commonly encountered in the emergency department (ED). Presentations range in severity from asymptomatic pleural effusion to tension pneumothorax. This chapter reviews the two most common nontraumatic pleural problems: spontaneous pneumothorax and pleural inflammation with effusion. Pleural space problems associated with trauma are discussed in Chapter 42, and the approach to a patient presenting with pleuritic chest pain in Chapter 17.

SPONTANEOUS PNEUMOTHORAX

Perspective

Under normal conditions, the visceral and parietal pleurae lie in close apposition, with only a potential space between them. *Pneumothorax* is defined as the presence of free air in the intrapleural space. A *spontaneous pneumothorax* occurs in the absence of any external precipitating factor, either traumatic or iatrogenic. *Primary spontaneous pneumothorax* occurs in individuals without clinically apparent lung disease. *Secondary spontaneous pneumothorax* arises in the context of an underlying pulmonary disease process.

The incidence of primary spontaneous pneumothorax is approximately 15 cases per 100,000 population per year among men and 5 cases per 100,000 population per year among women. Primary spontaneous pneumothorax typically occurs in healthy young men of taller than average height. Factors associated with primary spontaneous pneumothorax include cigarette smoking and changes in ambient atmospheric pressure. Familial patterns suggest an inherited propensity in some cases of primary spontaneous pneumothorax. Mitral valve prolapse and Marfan's syndrome are associated with spontaneous pneumothorax in the absence of clinically apparent lung disease.

Approximately one third of spontaneous pneumothoraces occur in the context of underlying pulmonary disease (Box 75-1). The incidence of secondary spontaneous pneumothorax is three times higher in men. The most common condition associated with secondary spontaneous pneumothorax is chronic obstructive pulmonary disease (COPD), which accounts for nearly 70% of cases. Patients with severe COPD (e.g., with forced expiratory volume in 1 second <1 L) are at highest risk. The incidence of spontaneous pneumothorax among patients hospitalized for emphysema is 0.8% and for asthma 0.3%.

Spontaneous pneumothorax occurs in approximately 2% of patients with acquired immunodeficiency syndrome, almost always in the setting of *Pneumocystis jiroveci* (previously known as *Pneumocystis carinii*) pneumonia.[1] Bilateral pneumothoraces are common with *P. jiroveci* pneumonia, as are problems with delayed reexpansion and recurrences. Mortality in these patients is high.[2]

Malignancy is another common etiology of secondary spontaneous pneumothorax. The occurrence of spontaneous pneumothorax in a patient with known malignancy should suggest lung metastases. In developing countries, tuberculosis and lung abscess remain leading causes of secondary spontaneous pneumothorax.

Catamenial pneumothorax is a rare condition in which recurrent spontaneous pneumothorax occurs in association with menses (typically within 72 hours of onset).[3] Although it is termed *thoracic endometriosis syndrome* and often responds to ovulation-suppressing medications, the exact etiology of catamenial pneumothorax is uncertain.

Spontaneous pneumothorax is rare in childhood. The principles of diagnosis, imaging, treatment, and surgical management for pediatric primary spontaneous pneumothorax are similar to those for adult pneumothorax.[4]

Pathophysiologic Principles

Normally, intrapleural pressure is negative (less than atmospheric), fluctuating from −10 mm Hg to −12 mm Hg during inspiration to approximately −4 mm Hg during expiration. Intrabronchial and intra-alveolar pressures are negative during inspiration (−1 to −3 mm Hg) and positive during expiration (+1 to +3 mm Hg). The alveolar walls and visceral pleura form a barrier that separates the intrapleural and intra-alveolar spaces and maintains the pressure gradient. If a defect occurs in this barrier, air enters the pleural space until either the pressures equalize or the communication seals.

With the loss of negative intrapleural pressure in one hemithorax, the ipsilateral lung collapses. A large pneumothorax results in restrictive ventilation impairment, with reduced vital capacity, functional residual capacity, and total lung capacity. Shunting of blood through nonventilated lung tissue may result in acute hypoxemia, although over time this effect is mitigated by compensatory vasoconstriction in the collapsed lung.

In tension pneumothorax, the alveolar-pleural defect acts as a one-way valve, allowing air to pass into the pleural space during inspiration and trapping it there during expiration (Fig. 75-1). This trapping leads to progressive accumulation of intrapleural air and increasingly positive intrapleural pressure,

BOX 75-1 CAUSES OF SECONDARY SPONTANEOUS PNEUMOTHORAX

Airway Disease
Chronic obstructive pulmonary disease
Asthma
Cystic fibrosis

Infections
Necrotizing bacterial pneumonia/lung abscess
Pneumocystis jiroveci pneumonia
Tuberculosis

Interstitial Lung Disease
Sarcoidosis
Idiopathic pulmonary fibrosis
Lymphangiomyomatosis
Tuberous sclerosis
Pneumoconioses

Neoplasms
Primary lung cancers
Pulmonary/pleural metastases

Miscellaneous
Connective tissue diseases
Pulmonary infarction
Endometriosis/catamenial pneumothorax

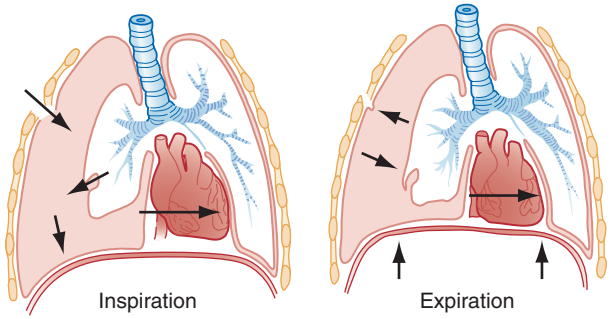


Figure 75-1. Tension pneumothorax with total collapse of the right lung and shift of mediastinal structures to the left. Air is forced into the pleural space during expiration and cannot escape during inspiration.

causing compression of the contralateral lung with asphyxia and worsening hypoxia. Intrapleural pressure exceeding 15 to 20 mm Hg impairs venous return to the heart. If allowed to progress, cardiovascular collapse and death ensue.

In primary spontaneous pneumothorax, disruption of the alveolar-pleural barrier occurs when a subpleural bulla (or bleb), typically located at the lung apex, ruptures into the pleural space. Subpleural bullae are found in almost all patients who undergo surgical treatment for primary spontaneous pneumothorax and are identified on computed tomography (CT) of the chest in 90% of cases.[5] The etiology of these bullae may be related to degradation of elastic fibers within the lung and an imbalance in the protease-antiprotease and oxidant-antioxidant systems.[6]

In the case of secondary spontaneous pneumothorax, the underlying lung disease weakens the alveolar-pleural barrier. In patients with *P. jiroveci* pneumonia, the cytotoxic effects of repeated episodes of inflammation lead to bullous and cystic changes. In patients with COPD, chronic exposure to cigarette smoke results in the development of large, thin-walled bullae that are at an increased risk for rupture. Other factors, including increased intrabronchial and intra-alveolar pressures generated by bronchospasm and coughing, also play a role.

Clinical Features

Symptoms of primary spontaneous pneumothorax typically begin suddenly while at rest. Ipsilateral chest pain and dyspnea are the most common symptoms. At the outset, the pain is typically "pleuritic" in nature (i.e., often described as sharp and made worse with deep inspiration), but it often evolves over time into a dull, steady ache. Although patients frequently describe shortness of breath, extreme dyspnea is uncommon in the absence of underlying lung disease or tension pneumothorax. Cough is present in a few individuals. Occasionally, patients are asymptomatic or have only nonspecific complaints. Patients may wait several days before they seek medical attention, and a significant number delay presentation for 1 week or more. Without treatment, symptoms often resolve spontaneously within 24 to 72 hours, although the pneumothorax is still present.

Physical findings tend to correlate with the degree of symptoms. A mild sinus tachycardia is the most common physical finding. With a large pneumothorax, decreased or absent breath sounds with hyperresonance to percussion may be present. Other classic signs include unilateral enlargement of the hemithorax, decreased excursion with respirations, absent tactile fremitus, and inferior displacement of the liver or spleen. Absence of any or all of these findings does not exclude pneumothorax, however, and a chest radiograph should be obtained when pneumothorax is suspected.

With tension pneumothorax, signs of asphyxia and decreased cardiac output develop. Tachycardia (often >120 beats/min) and hypoxia are common. Hypotension is a late and ominous finding. Distention of the jugular veins is common but may be difficult to detect. Displacement of the trachea to the contralateral side is classically described but is an uncommon finding, usually occurring only in the immediately preterminal phase of the pneumothorax, if at all. Its absence should not be considered evidence that a tension phenomenon is not present.

In patients with significant underlying lung disease, pneumothorax presents differently. Because of poor pulmonary reserve, dyspnea is nearly universal, even when the pneumothorax is small, and symptoms tend not to resolve on their own. Physical findings, such as hyperexpansion and distant breath sounds, often overlap considerably with the underlying lung disease, making the clinical diagnosis difficult. For this reason, the diagnosis of pneumothorax should be considered whenever a patient with COPD presents with an exacerbation of dyspnea.

Although suggested by the patient's history and physical examination, the diagnosis of pneumothorax is generally made with the chest radiograph. The classic radiographic appearance is that of a thin, visceral pleural line lying parallel to the chest wall, separated by a radiolucent band devoid of lung markings. The average width of this band can be used to estimate the size of the pneumothorax with a fair degree of accuracy (Fig. 75-2), but in general, it is more reasonable simply to characterize the pneumothorax as small, moderate, large, or total. The estimated size of the pneumothorax and the patient's clinical status can be useful in guiding management decisions.

Tension pneumothorax is a clinical diagnosis, and delaying treatment to obtain radiographic confirmation is inadvisable. When the diagnosis of tension pneumothorax is not apparent clinically and a chest radiograph is obtained, the classic appearance is one of complete lung collapse with gross distention of the thoracic cavity on the affected side and shift of mediastinal

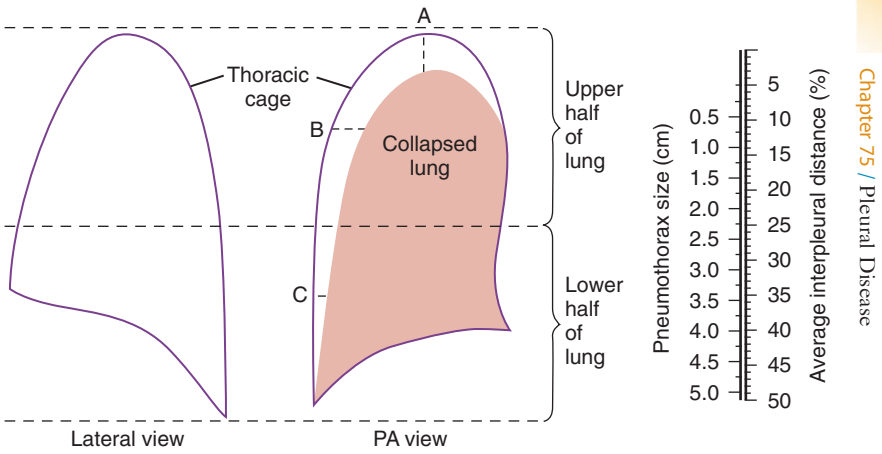


Figure 75-2. Determining the size of a pneumothorax. Calculation of average interpleural distance to predict pneumothorax size. PA, posteroanterior.

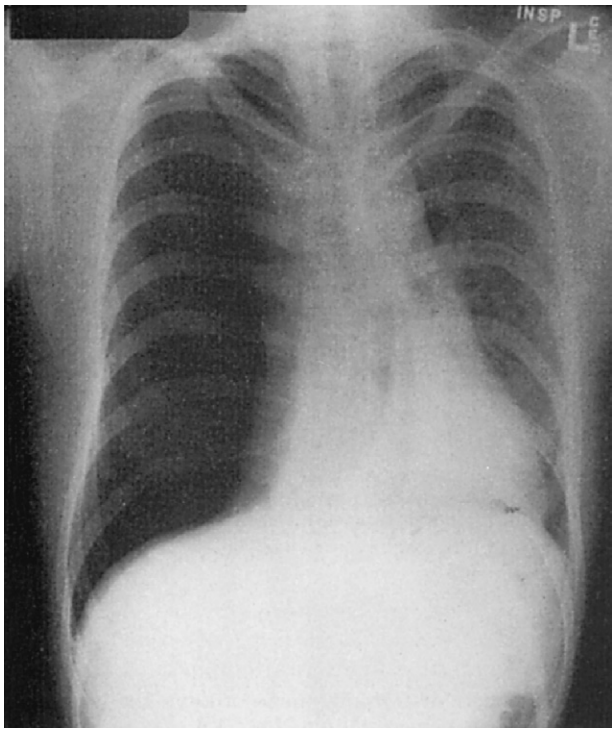


Figure 75-3. Radiograph of tension pneumothorax with mediastinal shift to left.

structures across the midline (Fig. 75-3). In patients with underlying pulmonary disease, however, pleural adhesions and lack of lung elasticity may mask the fact that a pneumothorax is under significant positive pressure.

When pneumothorax is suspected but not seen on a standard chest radiograph, an expiratory film may be obtained. Theoretically, the volumes of the lungs and the chest cavity are reduced during expiration so that the relative size of the pneumothorax is enhanced. Although occasionally helpful in identifying a small apical pneumothorax, routine use of expiratory films does not improve diagnostic yield.[7] In critically ill patients for whom only a supine chest radiograph can be obtained, the finding of a "deep sulcus" (i.e., a deep lateral costophrenic angle) can suggest the presence of pneumothorax on that side (see Fig. 75-3).

Special care should be taken when viewing the chest radiographs of patients with underlying lung disease. In patients with COPD, the relative paucity of lung markings makes pneumothorax more difficult to detect. At the same time, giant bullae may simulate the radiographic appearance of pneumothorax. A clue to differentiating a pneumothorax from a giant bulla is that the former tends to run parallel to the chest wall, whereas the latter tends to have a more concave appearance. When the diagnosis is unclear, computed tomography (CT) can differentiate between the two entities.[8]

While CT is considered the gold standard for the diagnosis of pneumothorax, it requires that patients be stable enough for transport. Bedside ultrasound is also a rapid and accurate diagnostic aid.[9,10] Assessment for pneumothorax begins over the upper anterior chest wall in the midclavicular line and proceeds inferolaterally toward the anterior axillary line. Once the pleural line is identified, the presence of lung sliding during respiration effectively rules out a pneumothorax in the area being scanned. The differential diagnosis of pneumothorax includes numerous conditions associated with chest pain and dyspnea. Among the most important of these is pulmonary embolism, which may present in similar fashion with unilateral pleuritic chest pain. Most pleural-based processes (pneumonia, embolism, tumor) have characteristic radiographic findings. Rarely, pneumothorax may mimic an acute myocardial infarction with electrocardiogram changes simulating an acute injury pattern.[11]

Spontaneous pneumomediastinum is a closely related clinical entity, diagnosed by the presence of subcutaneous emphysema and the finding of mediastinal air on chest radiography. In contrast to spontaneous pneumothorax, spontaneous pneumomediastinum typically occurs during exertion, particularly after a strenuous Valsalva maneuver. Most cases of spontaneous pneumomediastinum occur in the absence of known underlying disease and have a benign course. Secondary causes of pneumomediastinum (e.g., Boerhaave's syndrome) are more serious, and treatment is aimed at the underlying disorder.

Spontaneous hemopneumothorax is a rare but potentially serious condition that occurs when collapse of the lung is associated with rupture of a vessel in a parietopleural adhesion. The clinical presentation is similar to that of spontaneous pneumothorax but may be accompanied by symptoms and signs of hemorrhagic shock. Treatment entails large-caliber tube thoracostomy to evacuate the pleural space, reexpand the lung, and tamponade bleeding.

Pneumothorax has a readily available, highly reliable confirmatory diagnostic test (i.e., chest radiography). Absence of a pneumothorax on chest radiography should prompt a search for an alternate diagnosis.

Management

Whether in the field or in the ED, if the clinical circumstances suggest tension pneumothorax, treatment should not be delayed by awaiting further cardiovascular compromise or definitive diagnosis by chest radiography. As soon as tension pneumothorax is believed to be present, the pleural space should be decompressed. This decompression may be accomplished by insertion of an intravenous catheter or by immediate tube thoracostomy, depending on the availability of equipment and the expertise of the providers. The diagnosis is confirmed by the hiss of air escaping under positive pressure as the needle or chest tube enters the pleural space. Needle decompression is only a temporizing procedure, and definitive management requires prompt tube thoracostomy. In morbidly obese patients, the needle and catheter may be of insufficient length to reach the pleural space, and a longer needle may be required.

The management of spontaneous pneumothorax has two goals: (1) to evacuate air from the pleural space, and (2) to prevent recurrence. Pursuit of the latter goal extends well beyond the realm of the ED but may influence the initial approach to management. Therapeutic options for treatment of pneumothorax range from simple observation or aspiration with a catheter to video-assisted thoracoscopic surgery or thoracotomy. Decisions must be individualized and consider several factors, including size of the pneumothorax, severity of signs, presence of underlying pulmonary disease, other comorbidities, history of previous pneumothoraces, patient reliability, degree and persistence of the air leak, and available follow-up monitoring.

For otherwise healthy, young patients with a small primary spontaneous pneumothorax (i.e., <20% of the hemithorax), observation alone may be appropriate. The intrinsic reabsorption rate ranges from 1 to 2% per day, a rate that is accelerated by a factor of 4 with the administration of 100% oxygen.[12] By lowering the alveolar partial pressure of nitrogen, supplemental oxygen increases the rate at which air diffuses across the pleural-alveolar barrier. The disposition of patients managed noninterventionally for a small pneumothorax varies by institution. Most physicians admit these patients for at least 6 hours of observation, often in an ED-based observation unit. A repeat chest radiograph can be obtained before discharge to document that there is no increase in the size of the pneumothorax. Discharged patients should be able to obtain emergency medical services quickly and should have definitive follow-up evaluation in 24 hours. Air travel and underwater diving must be avoided until the pneumothorax has completely resolved. Unreliable patients are not candidates for this approach.

For primary spontaneous pneumothoraces that are larger in size (i.e., ≥20% of the hemithorax), aspiration with an intravenous catheter may be attempted. If 6 hours after aspiration the chest radiograph shows no reaccumulation of the pneumothorax, the catheter is removed, and the patient can be discharged home, with the same caveats that apply to patients managed with observation alone.

Although there is no universal agreement on the optimal treatment of patients presenting with a first episode of primary spontaneous pneumothorax, data suggest that aspiration may be equally effective as chest tube drainage.[13] Advantages of simple aspiration include low morbidity, lack of invasiveness, and overall cost savings, with reported rates of successful outcome ranging from 45 to 71%.[14–18] Success is less likely when the patient is older than 50 years or the volume of air aspirated exceeds 2.5 L, suggesting a continuing air leak. If aspiration fails to reexpand the lung fully, the catheter can be attached to a water-seal device or to a one-way Heimlich valve and managed like a small-caliber chest tube.

Most secondary spontaneous pneumothoraces should be managed with tube thoracostomy because less invasive approaches (i.e., observation or simple aspiration) are associated with significantly lower success rates.[18] Similarly, patients who present with respiratory distress, have tension pneumothorax, or are likely to require mechanical ventilation should undergo tube thoracostomy to reexpand the lung definitively. Also, if there is detectable pleural fluid (hemothorax or hydrothorax), tube thoracostomy is required. Finally, tube thoracostomy may be considered in uncomplicated cases of primary spontaneous pneumothorax either as a first-line intervention or after a less invasive approach (i.e., observation or simple aspiration) fails.

For most primary spontaneous pneumothoraces, placement of a small-caliber (7–14F) tube is generally sufficient because air leakage tends to be minimal.[19,20] Small-caliber tubes are easy to insert, are well tolerated by patients, and leave only a small scar after removal. Complications associated with small-caliber tubes include kinking, malposition, inadvertent removal, occlusion by pleural fluid or clotted blood, and large persistent air leaks. For secondary spontaneous pneumothorax, a standard size (20–28F) thoracostomy tube is recommended. When there is detectable pleural fluid or an anticipated need for mechanical ventilation, a larger tube size (≥28F) is required.

After insertion, the tube is attached to a water-seal device and left in place until the lung has reexpanded fully and the air leak has ceased. A Heimlich valve, which consists of a one-way flutter valve covered in transparent plastic, can be used in place of a water-seal device and allows unhindered ambulation. Specific complications associated with the use of a Heimlich valve include accidental disconnection and occlusion by fluid.

Routine application of suction neither increases the rate at which the lung reexpands nor improves patient outcome and is no longer recommended after standard tube thoracostomy.[21] Rather, the use of suction (with a pressure of 20 cm H_2O) is reserved for situations in which the lung fails to reexpand after drainage through a water-seal device or Heimlich valve for 24 to 48 hours.

In most cases, chest tube management requires hospital admission, although outpatient management of spontaneous pneumothorax with a small-caliber tube and Heimlich device is described.[22] Common complications of chest tube placement include incorrect placement, pleural infection, and prolonged pain. Reexpansion pulmonary edema and reexpansion hypotension are rare occurrences after rapid evacuation of large pneumothoraces.[23,24]

Outcome

Most spontaneous pneumothoraces resolve within 7 days of tube thoracostomy. Air leaks that persist for longer than 2 days are less likely to resolve on their own. If an air leak persists beyond 4 to 7 days, tube thoracostomy is considered to have failed, and surgical intervention generally is recommended.

Failure of tube thoracostomy is more common with secondary spontaneous pneumothoraces because these tend to be associated with larger and more persistent air leaks. In the setting of COPD, healing of the alveolar-pleural barrier may be impaired by chronic inflammatory changes and loss of vascularity in pulmonary tissue. The success rate also decreases substantially with recurrent episodes of pneumothorax, declining from 91% for treatment of a first pneumothorax to

52% for treatment of a first recurrence and to 15% for treatment of a second recurrence.[25]

Recurrences of spontaneous pneumothorax are common. The risk of recurrence after a primary spontaneous pneumothorax is approximately one in three, with studies reporting rates between 16 and 50%.[26] Younger age, lower weight-to-height ratio, and history of smoking are associated with an increased rate of recurrence. Recurrence rates after a secondary spontaneous pneumothorax are slightly higher (39–47%).[6]

Recurrences may be life-threatening for patients with serious underlying lung disease, and intervention is advocated to prevent recurrence as part of the initial approach to secondary spontaneous pneumothorax. In contrast, for patients with primary spontaneous pneumothorax, interventions typically are not considered until after a second ipsilateral pneumothorax. Preventive treatment also is recommended for patients who plan to continue activities such as flying or diving that increase the risk of serious complications if a pneumothorax recurs. CT can be used in primary spontaneous pneumothorax to detect emphysematous changes, predict the likelihood of recurrence, and guide intervention decisions.[27]

A variety of operative and nonoperative interventions prevent recurrences. One strategy promotes adherence of parietal and visceral pleura, which obliterates the pleural space. Pleurodesis can be accomplished by mechanical pleural abrasion or by instillation of sclerosing agents. Another strategy involves resection of apical bullae or other lesions at risk for causing recurrences. Often the two strategies are combined. Minimally invasive procedures, such as video-assisted thoracoscopic surgery, allow for resection of bullae and pleurodesis.[28] Patients with extensive bullae may require thoracotomy for wider visualization of lesions. Success rates are generally good, ranging from 86 to 100%.

PLEURAL INFLAMMATION AND EFFUSION

Perspective

Under normal circumstances, a thin layer of fluid lies between the visceral and the parietal pleurae. Pleural effusion implies the presence of an abnormally large amount of fluid in the pleural space. Pleural effusions are relatively common.[29] The most common cause of pleural effusions in Western countries is congestive heart failure, followed by malignancy, bacterial pneumonia, and pulmonary embolism.[29] In other countries, tuberculosis is the leading cause of pleural effusions. Other conditions commonly associated with pleural effusions include viral infections of the lung parenchyma or pleura, uremia, myxedema, cirrhosis, nephrotic syndrome, ovarian hyperstimulation syndrome, collagen vascular diseases (e.g., systemic lupus erythematosus, rheumatoid arthritis), and intra-abdominal processes (e.g., acute pancreatitis, subphrenic abscess, ascites). Esophageal perforation is a rare but uniquely morbid cause of a pleural effusion.

Pleuritis (also referred to as *pleurisy*) is a nonspecific term denoting inflammation of the pleura. Pleuritis can occur with or without significant exudation of fluid into the pleural space. Pleuritis is a common presentation for a range of disease processes, from self-limited viral syndromes to more serious acute conditions, such as pneumonia and pulmonary embolism, to chronic illnesses, such as systemic lupus erythematosus and other connective tissue diseases.

A pleural effusion associated with bacterial pneumonia, bronchiectasis, or lung abscess is called a *parapneumonic effusion*. The term *complicated parapneumonic effusion* refers to parapneumonic effusions that require tube thoracostomy for their resolution. Empyema (or pus in the pleural space) requires the presence of bacteria on Gram's staining of the pleural fluid.

Fluid anatomically confined and not freely flowing in the pleural space is termed a *loculated effusion*. Loculated effusions occur when there are adhesions between the visceral and the parietal pleurae. Hemothorax and chylothorax (i.e., from rupture of the thoracic duct) are special instances of pleural effusion that are approached separately.

Pathophysiologic Principles

Pleural fluid is produced from systemic capillaries at the parietal pleural surface and absorbed into pulmonary capillaries at the visceral pleural surface. Lymphatics also play an important role in removing pleural fluid. Movement of fluid across the pleural surfaces is governed by Starling's law. Under normal circumstances, the direction of pleural fluid flow is largely governed by the difference in hydrostatic pressure between the systemic and the pulmonary circulations (Fig. 75-4). Pleural fluid exists in a dynamic equilibrium in which influx equals efflux, with approximately 1 L of fluid traversing the pleural space in 24 hours. Under normal conditions, the amount of fluid that remains in the pleural space is small (~0.1–0.2 mL/kg body weight) and clinically or radiographically undetectable. Pleural effusion develops whenever influx of fluid into the pleural space exceeds efflux. Numerous disorders can lead to formation of a pleural effusion. Pleural effusions classically are

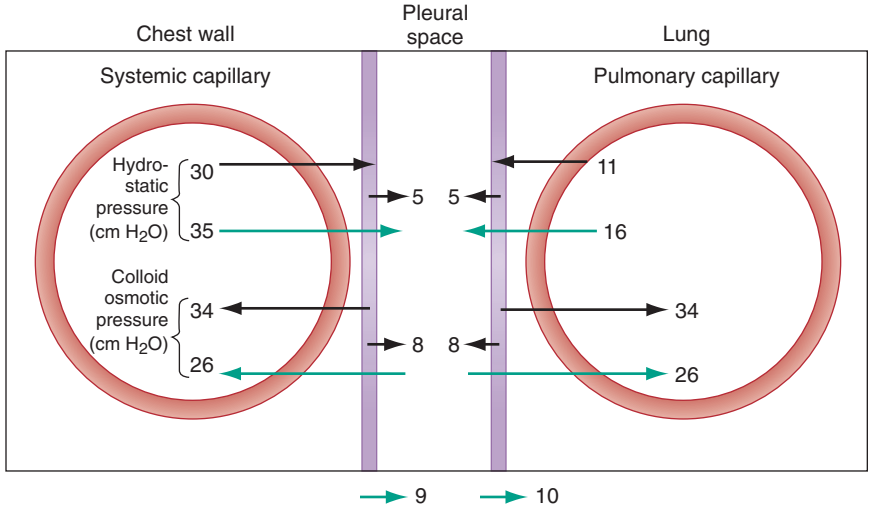


Figure 75-4. Diagram representing pressures involved in formation and absorption of pleural fluid. (Modified from Fraser RG, et al: Diagnosis of Diseases of the Chest, 3rd ed. Philadelphia, WB Saunders, 1988.)

BOX 75-2 CAUSES OF PLEURAL EFFUSION

Transudates
Congestive heart failure
Cirrhosis with ascites
Nephrotic syndrome
Hypoalbuminemia
Myxedema
Peritoneal dialysis
Glomerulonephritis
Superior vena cava obstruction
Pulmonary embolism

Exudates
Infections
Bacterial pneumonia
Bronchiectasis
Lung abscess
Tuberculosis
Viral illness
Neoplasms
Primary lung cancer
Mesothelioma
Pulmonary/pleural metastases
Lymphoma

Connective Tissue Disease
Rheumatoid arthritis
Systemic lupus erythematosus

Abdominal/Gastrointestinal Disorders
Pancreatitis
Subphrenic abscess
Esophageal rupture
Abdominal surgery

Miscellaneous
Pulmonary infarction
Uremia
Drug reactions
Postpartum
Chylothorax

divided into two groups—*transudates* and *exudates*—according to the composition of the pleural fluid (Box 75-2).

Transudates are essentially ultrafiltrates of plasma, containing very little protein. A *transudative effusion* develops when there is an increase in the hydrostatic pressure or decrease in the oncotic pressure within pleural microvessels. The primary cause of increased hydrostatic pressure is congestive heart failure, which is responsible for about 90% of transudative effusions. In hepatic cirrhosis and nephrotic syndrome, increased hydrostatic pressure is combined with loss of plasma oncotic pressure because of significant decreases in serum albumin. Patients with severe malnutrition may develop transudative effusions resulting from severe isolated hypoalbuminemia.

Exudates contain relatively high amounts of protein, reflecting an abnormality of the pleura itself. An *exudative effusion* is the result of increased membrane permeability or defective lymphatic drainage. Any pulmonary or pleural process associated with inflammation can result in an exudative effusion. In the absence of clinically apparent effusion, pleuritic symptoms may still be present. The most common form of exudative effusion is a parapneumonic effusion, in which infection of the adjacent lung elicits an intense inflammatory response in pleura, disrupting normal membrane permeability. Malignant effusions are the second most common form of exudative effusion and often reflect alterations in pleural permeability and problems with lymphatic drainage. Exudative effusions also may arise in response to inflammatory abdominal processes, such as pancreatitis or subphrenic abscess, presumably owing to altered permeability of the diaphragm itself. Exudative effusions may be reabsorbed or organize into fibrous tissue, resulting in pleural adhesions.

Some pleural effusions can present as either transudates or exudates or may have characteristics of both. In the case of pulmonary embolism, the pathogenesis of pleural effusion is often multifactorial, reflecting increased pulmonary vascular pressure (a transudative process) and ischemia and breakdown of the pleural membrane (an exudative process).

Massive effusions (>1.5–2 L) are most commonly associated with malignancy but also can arise in the setting of congestive heart failure, cirrhosis, and other conditions. Massive effusions may restrict respiratory movement, compress the lungs, and result in intrapulmonary shunting. In extremely rare cases, tension hydrothorax can develop, with mediastinal shift and circulatory embarrassment.

Clinical Features

Symptoms associated with pleural effusion are most often due to the underlying disease process and not the effusion itself. Small pleural effusions can be entirely asymptomatic. A new pleural effusion may be heralded by localized pain or pain referred to the shoulder. Viral pleuritis and pulmonary infarction commonly are associated with pleuritic chest pain. When the volume of pleural fluid reaches 500 mL, dyspnea on exertion or at rest may occur as a result of compromised pulmonary function.

The patient's history often helps to establish the diagnosis for pleural effusion or pleural inflammation. A history of congestive heart failure, liver disease, uremia, or malignancy can direct subsequent evaluation. The pain of viral pleuritis usually is preceded by several days of a typical viral prodrome, with low-grade fever, sore throat, and other upper respiratory or constitutional symptoms. In the absence of such prodromal symptoms, an alternate etiology for pleuritis such as pulmonary embolism must be sought.

Physical findings depend on the size of the effusion but are often either dominated or obscured by the underlying disease process. Classic physical signs of pleural effusion include diminished breath sounds, dullness to percussion, decreased tactile fremitus, and occasionally a localized pleural friction rub. The simple technique of auscultatory percussion (i.e., percussing the chest while listening for a dullness with the stethoscope) may be even more sensitive and specific for the physical diagnosis of pleural effusion. Egophony and enhanced breath sounds can often be appreciated at the superior border of the effusion because of underlying atelectatic lung tissue. In the setting of pleuritis, a pleural friction rub may be appreciated. With massive effusions, signs of mediastinal shift may be present.

Chest radiography confirms the clinical suspicion of pleural effusion and occasionally reveals a pleural effusion as an incidental finding. The classic radiographic appearance of a pleural effusion is blunting of the costophrenic angle on the upright chest radiograph. On a frontal (anteroposterior or posteroanterior) projection, a volume of 250 to 500 mL of pleural fluid is required before radiographic demonstration is possible. A lesser amount of fluid may be visible in the posterior costophrenic gutter on a lateral projection. With larger effusions, the hemidiaphragm is obscured, and an upwardly concave

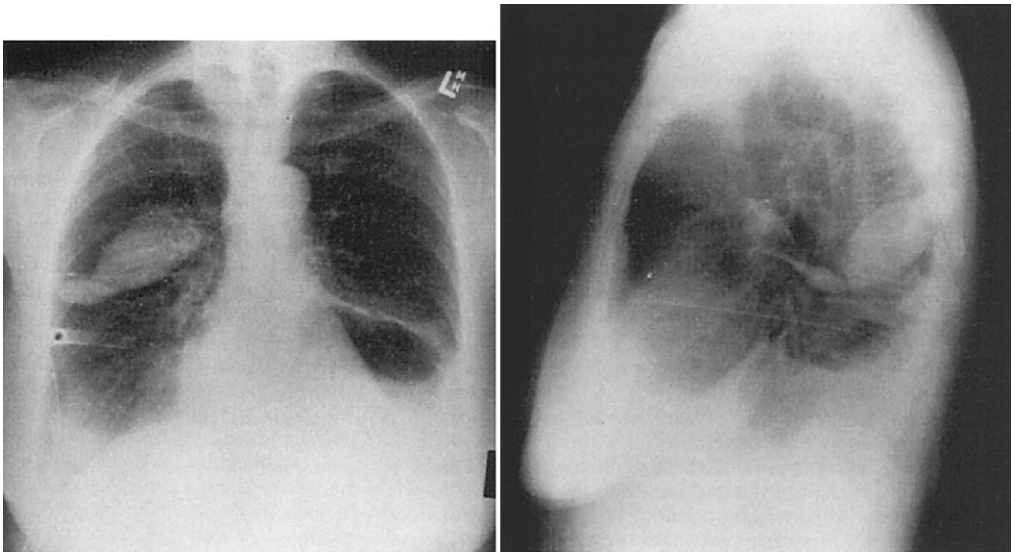


Figure 75-5. Radiographs of pleural effusion along major and minor fissures.

meniscus may be seen because pleural fluid has a tendency to layer higher laterally than centrally. Pleural fluid can extend up a major fissure and appear as a homogeneous density in the lower two thirds of the lung field. Massive pleural effusion can appear as a totally opacified hemithorax.

In the recumbent patient, free pleural fluid gravitates superiorly, laterally, and posteriorly and may not be clearly discernible on a supine radiograph. If the effusion is large enough, diffuse haziness or partial opacification of a hemithorax may be seen. Other findings on the supine radiograph may include apical capping, obliteration of the hemidiaphragm, and a widened minor fissure. The radiographic appearance of pleural effusions can be confusing. Subpulmonic effusions (fluid collections between the lung base and the diaphragm) can be difficult to diagnose, often simulating an elevated hemidiaphragm. Clues to the presence of a subpulmonic effusion include shifting of the apparent dome of the diaphragm toward the lateral chest wall and, when located on the left side, an increase in the distance between the gastric bubble and aerated lung. Fluid that loculates in a fissure may take on a fusiform appearance and can simulate a mass (Fig. 75-5). Such "fluid pseudotumors" are common in patients with congestive heart failure.

Other imaging techniques, such as ultrasound and CT, may be helpful in localizing effusions and characterizing underlying lung processes.[30] Ultrasound is particularly helpful, because it can be used to guide thoracentesis and decrease the risk of complications, particularly in the case of small or loculated effusions.[31] Sonographically, pleural effusion is demonstrated by the appearance of hypoechoic fluid located above the diaphragm with loss of the usual mirror-image artifact. Pleural effusions smaller than 500 mL, however, can be missed with bedside radiography.[32]

Pulmonary embolism is the most commonly overlooked disorder in the workup of a pleural effusion, and any patient with an undiagnosed pleural effusion should be evaluated for possible pulmonary embolism.[33] Pleural effusion resulting from pulmonary embolism usually occupies less than one third of the hemithorax, but dyspnea is frequently out of proportion to size.

An unexplained pleural effusion requires further investigation. Unless required to rule out an immediately life-threatening condition such as empyema or hemothorax, pleural fluid evaluation may be deferred to an inpatient or outpatient setting. The primary goal of pleural fluid analysis is to distinguish between transudative and exudative effusions. The presence of a transudate suggests an underlying process (e.g., congestive heart failure, nephrotic syndrome), whereas the presence of an exudate mandates a more extensive diagnostic evaluation. Although numerous alternative measurements are proposed, Light's criteria remain a widely accepted means of differentiating transudates and exudates (Box 75-3).[34]

BOX 75-3 Light's Criteria for Differentiating Transudates from Exudates

Pleural fluid is considered an exudate if one or more of the following hold true:

1. Pleural fluid protein level: serum protein level >0.5
2. Pleural fluid lactate dehydrogenase (LDH) level: serum LDH level >0.6
3. Pleural fluid LDH level >⅔ × (upper limit of normal for serum LDH level)

From Light RW, et al: Pleural effusions: The diagnostic separation of transudates and exudates. Ann Intern Med 77:507, 1972.

In the presence of an exudative effusion, additional pleural fluid analyses further classify the effusion. A pleural fluid pH of less than 7.3 is associated with parapneumonic effusions, malignancies, rheumatoid effusions, tuberculosis, and systemic acidosis. A pH of less than 7.0 strongly suggests empyema (or esophageal rupture). A pleural fluid pH of less than 7.0 and glucose less than 50 mg/dL are reasonable indications for tube thoracostomy.[35]

Normal pleural fluid contains less than 1000 white blood cells/mm^3; exudative pleural fluid may contain over 10,000 white blood cells/mm^3. Although the absolute cell count has limited diagnostic value, a predominance of neutrophils suggests an acute process, such as pneumonia, pulmonary embolus, or acute tuberculous pleuritis. A predominance of monocytes or lymphocytes suggests a more chronic process, such as malignancy or established tuberculosis. Pleural fluid from any patient with an undiagnosed exudative pleural effusion should undergo Gram's staining and culture for bacteria (aerobic and anaerobic), mycobacteria, and fungi.

In the absence of a traumatic tap, bloody fluid suggests trauma, neoplasm, or pulmonary infarction.[35] If the hematocrit of the pleural fluid is more than 50% that of the peripheral blood, the effusion is, by definition, a hemothorax. Atraumatic hemothorax is relatively rare but can occur with spontaneous rupture of a tumor or blood vessel (e.g., ruptured aortic aneurysm).

If the diagnosis of a malignant pleural effusion is being considered, pleural fluid should be submitted for cytologic examination. Contrary to popular perception, the sensitivity for diagnosis of pleural malignancy does not depend on the volume of pleural fluid extracted during thoracentesis.[36] Cytologic analysis provides the diagnosis of cancer in 40 to 87% of malignant effusions.[35]

Management

In patients with large effusions, urgent therapeutic thoracentesis may stabilize respiratory or circulatory status. The presence of empyema mandates insertion of a chest tube to drain the pleural space adequately and prevent the development of loculations. If an effusion is already loculated, streptokinase or urokinase can be injected by a thoracic surgeon, pulmonologist, or interventional radiologist into the pleural space in an attempt to dissolve adhesions and allow fluid to drain freely. Hemothorax requires tube thoracostomy to evacuate the pleural space, quantify bleeding, and allow apposition of the two pleural surfaces to tamponade hemorrhage. If bleeding exceeds 200 mL/hr, thoracotomy should be considered.

In most other cases, the decision to proceed with therapeutic thoracentesis in the ED can be individualized. For example, therapeutic thoracentesis may be considered in patients with known, recurrent malignant effusion, in whom symptomatic relief may permit discharge.

Pain relief is an important consideration in the management of patients with pleuritis, which may have a significant inflammatory component. Nonsteroidal anti-inflammatory drugs are relatively successful in treating pleural pain.[37] Opioid analgesia is safe and effective, but care should be exercised in debilitated patients or patients with severe lung disease because of potential respiratory depression.

Relative contraindications to thoracentesis include coagulopathy and other bleeding disorders. Thoracentesis may be safe with a prolonged prothrombin time in the absence of active bleeding.[38] Pleural adhesions, suggested by a prior history of empyema, represent a relative contraindication to thoracentesis because of the high risk of pneumothorax associated with blind needle insertion.

After thoracentesis is completed, a chest radiograph should be obtained to rule out iatrogenic pneumothorax. Other potential complications of thoracentesis include hemothorax, lung laceration, shearing of the catheter tip, and infection. Transient hypoxia caused by ventilation-perfusion mismatch often occurs, whereas unilateral, postexpansion pulmonary edema is rare except when large volumes (>1500 mL) are drained in one session. Hypotension also can occur after removal of a large volume of fluid, particularly in patients who are already intravascularly volume depleted.

Outcome

Some pleural effusions reflect little clinical significance. For example, small pleural effusions are common after abdominal surgery and in the postpartum state and resolve spontaneously within a few days. Effusions associated with viral pleuritis are generally self-limited and resolve without specific treatment.

For patients with congestive heart failure, pleural effusions generally respond well to diuretic therapy. If an effusion persists despite several days of aggressive diuresis, a diagnostic thoracentesis should be considered.

Pleural effusions associated with malignancy are a significant cause of morbidity in patients with advanced cancer. The presence of a malignant effusion indicates disseminated disease, and most of the malignancies that cause pleural effusions—mainly lung or breast carcinoma and lymphoma—are not curable by this stage. Therapeutic thoracentesis can relieve dyspnea in the short term, but malignant effusions tend to be recurrent, often rapidly so. Management strategies include chemical or mechanical pleurodesis to obliterate the pleural space or placement of a pleuroperitoneal shunt to provide continual drainage. Control of pleural effusions can improve quality of life in these patients.[39]

Parapneumonic effusions contribute significantly to the morbidity and mortality of pneumonia.[40] Therefore, the presence of a parapneumonic effusion may influence the decision to hospitalize a patient with community-acquired pneumonia.[41] Empyema can develop in 5 to 10% of patients with a parapneumonic effusion, but in most cases it responds well to parenteral antibiotics and pleural drainage. Early surgical drainage results in shorter hospital stays and may be more cost-effective than conservative management.[42] In nearly 20% of pleural effusions, no definitive diagnosis can be established even after extensive investigation. A sizable percentage of these effusions may be due to viral infections, and most resolve spontaneously without sequelae.

KEY CONCEPTS

- For healthy, young patients with a small (<20%) primary spontaneous pneumothorax, observation alone (with administration of 100% oxygen) is an appropriate treatment option; for larger symptomatic pneumothoraces, simple aspiration with an intravenous catheter is often successful.
- In most cases of secondary spontaneous pneumothorax, tube thoracostomy should be considered because less invasive approaches are associated with lower rates of success.
- Routine application of suction after tube thoracostomy is no longer recommended and does not accelerate lung reexpansion.
- The most common cause of pleural effusions in Western countries is congestive heart failure, followed by malignancy and bacterial pneumonia; however, the diagnosis of pulmonary embolism should not be overlooked in a patient with pleural effusion of unknown etiology.
- Therapeutic thoracentesis is indicated for the relief of acute respiratory or cardiovascular compromise.
- The clearest indication for diagnostic thoracentesis in the ED is to diagnose immediately life-threatening conditions, such as empyema or esophageal rupture in a toxic patient; in most other cases, diagnostic thoracentesis to distinguish between transudative and exudative processes can be deferred.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 76 Acute Coronary Syndrome

William J. Brady, Richard A. Harrigan, and Theodore C. Chan

Acute coronary syndrome (ACS) refers to the constellation of clinical diseases occurring as a result of acute myocardial ischemia. ACS includes a spectrum of clinical presentations ranging from unstable angina (UA) to non-ST segment elevation myocardial infarction (NSTEMI) and ST segment elevation myocardial infarction (STEMI). ACS and in particular acute myocardial infarction (AMI) remain the leading cause of death in much of the developed world. Tremendous progress, however, is occurring in the diagnosis and management of ACS.

HISTORICAL PERSPECTIVE

Several advances in the mid-twentieth century drastically changed the approach to acute coronary care. The development of external defibrillators and cardiac pacemakers, as well as new pharmacologic agents, provided physicians with an effective approach for treating life-threatening dysrhythmias. The introduction of selective coronary arteriography by Sones in 1959 revolutionized the management of patients with coronary artery disease (CAD). In 1960, Kouwenhoven inaugurated the era of cardiopulmonary resuscitation (CPR).

These developments led to the recognition that the time between onset of symptoms and the initiation of therapy is critical. Day organized a cardiac arrest team in 1960 and established the first coronary care unit 2 years later, reducing AMI mortality by half. In the 1980s, DeWood and colleagues performed coronary angiography early in the course of AMI and demonstrated coronary occlusion in the infarct-related artery. The early experience of Rentrop with the intracoronary administration of streptokinase in AMI ushered in the era of thrombolysis, now termed fibrinolytic therapy.

Recognition that the majority of sudden deaths from ischemic heart disease occur outside the hospital led to numerous advances for preadmission ACS care. In 1969, advanced prehospital cardiac care was initiated in Belfast with Pantridge's mobile cardiac care units. In 1970, Nagel and coworkers reported the benefits of preadmission telemetry for field advanced cardiac life support in patients experiencing dysrhythmias or sudden cardiac death. In the 1980s, portable 12-lead electrocardiograms (ECGs) were introduced into the emergency medical systems environment.

Although the ECG is the cornerstone for the diagnostic evaluation of ACS, diagnostic tools such as echocardiography, stress testing, nuclear imaging, and computed tomography (CT) play increasingly important roles, particularly when the diagnosis is not straightforward.

Fibrinolytic therapy and interventional, catheter-based techniques revolutionized the treatment of patients with STEMI during the 1980s. Combination therapies with antiplatelet, antithrombotic, and fibrinolytic agents continue to be studied for STEMI patients. Interventional success is improving with the use of newer stenting devices and glycoprotein platelet inhibitors. Current efforts focus on the establishment of regional cardiac centers, expansion of interventional capabilities to smaller hospitals, and the development of STEMI systems of care.

EPIDEMIOLOGY

Ischemic heart disease and CAD continue to be the leading causes of death among adults in many developed countries. Ischemic heart disease accounts for nearly 1 million deaths in the United States annually, of which approximately 160,000 occur in persons 65 years of age or younger. More than half of all deaths from cardiovascular disease occur in women, and CAD remains a major cause of morbidity and mortality in women beyond their middle to late fifties. The incidence of cardiovascular disease is expected to continue to increase due to lifestyle and behavioral changes that promote heart disease.[1]

A significant reduction in age-adjusted mortality from CAD has occurred in the United States over the past four decades.[2,3] In large part, the decline is accompanied by diminished mortality from AMI. This is due to a reduction in the incidence of AMI by 25% and a sharp drop in the case-fatality rate. Reduction in cigarette smoking, management of lipids, and improved management of hypertension and diabetes mellitus undoubtedly play a role, along with significant advances in medical treatment.

In 2005, 5.8 million patients were evaluated for chest pain or related complaints in the emergency department (ED) in the United States, comprising 5% of all ED visits that year.[4] In 2004, 4.1 million visits to the ED had a primary diagnosis of cardiovascular disease and over 1.5 million patients were hospitalized for a primary or secondary diagnosis of ACS.[4-7] In addition, approximately 2% of patients with ACS are discharged from the ED. In the United States, approximately 900,000 persons suffer an AMI, of whom 20% die before reaching the hospital, and 30% die within 30 days.[8,9] The majority of fatalities from CAD occur outside the hospital, usually from an ACS-related dysrhythmia within 2 hours of onset of

symptoms. For many patients who suffer a nonfatal AMI, their lives are limited by an impaired functional status, anginal symptoms, and a diminished quality of life. The economic cost for the evaluation and care of patients with an ACS is estimated to be $100 to $120 billion annually.[10]

SPECTRUM OF DISEASE

ACS includes the spectrum from asymptomatic CAD and stable angina to UA, AMI, and sudden cardiac death.

Stable Angina

Stable angina pectoris is transient, episodic chest discomfort resulting from myocardial ischemia. This discomfort is typically predictable and reproducible, with the frequency of attacks constant over time. Physical or psychological stress (physical exertion, emotional stress, anemia, dysrhythmias, or environmental exposures) may provoke an attack of angina that resolves spontaneously over a constant, predictable period of time with rest or nitroglycerin (NTG).

The Canadian Cardiovascular Society classification for angina is defined as follows: class I, no angina with ordinary physical activity; class II, slight limitation of normal activity as angina occurs with walking, climbing stairs, or emotional stress; class III, severe limitation of ordinary physical activity as angina occurs on walking one or two blocks on a level surface or climbing one flight of stairs in normal conditions; and class IV, inability to carry on any physical activity without discomfort as anginal symptoms occur at rest.

Unstable Angina

Unstable angina is broadly defined as angina occurring with minimal exertion or at rest, new-onset angina, or a worsening change in a previously stable anginal syndrome in terms of frequency or duration of attacks, resistance to previously effective medications, or provocation with decreasing levels of exertion or stress. Rest angina is defined as angina occurring at rest, lasting longer than 20 minutes, and occurring within 1 week of presentation. New-onset angina is angina of at least class II severity with onset within the last 2 months. Increasing or progressive angina is diagnosed when a previously known angina becomes more frequent, longer in duration, or increased by one class within the last 2 months of at least class III severity. Symptoms that last longer than 20 minutes despite cessation of activity are consistent with angina at rest and indicate the diagnosis of UA.

UA is often referred to as preinfarction angina, accelerating or crescendo angina, intermediate coronary syndrome, and preocclusive syndrome, underscoring its difference from stable angina. UA should be considered a possible harbinger of AMI and hence should be treated aggressively. A patient with a diagnosis of angina in the ED should be presumed to have UA until a thorough clinical evaluation reliably determines otherwise.

UA can also be defined from a pathophysiologic perspective. Plaque rupture accompanied by thrombus formation and vasospasm illustrate the intracoronary events of UA. This is frequently characterized by an electrocardiographic abnormality, including T wave and ST segment changes.

Variant angina—also known as Prinzmetal's angina—is caused by coronary artery vasospasm at rest with minimal fixed coronary artery lesions; it may be relieved by exercise or NTG. The ECG reveals ST segment elevation that is impossible to discern from AMI electrocardiographically and, at times, clinically.

Acute Myocardial Infarction

AMI is defined as myocardial cell death and necrosis of the myocardium. The four-decade-old World Health Organization (WHO) definition for AMI has been replaced by clinical criteria developed jointly by the European Society for Cardiology and American College of Cardiology (ACC) that focus on defining infarction as any evidence of myocardial necrosis. This definition for an acute, evolving, or recent MI requires a typical rise and fall of a cardiac biochemical marker, serum troponin, with clinical symptoms, ECG changes, or coronary artery abnormalities based on interventional evaluation.[11] The actual definition[11] includes the following; either one of these criteria satisfies the diagnosis for an *acute, evolving, or recent MI*:

1. Typical rise and gradual fall (troponin) or more rapid rise and fall (isoenzyme of creatine kinase with muscle and brain subunits [CK-MB]) of biochemical markers of myocardial necrosis with at least one of the following:
   a. Ischemic symptoms;
   b. Development of pathologic Q waves on the ECG;
   c. ECG changes indicative of ischemia (T wave changes or ST segment elevation or depression); and/or
   d. Coronary artery intervention.
2. Pathologic findings of an AMI.

Any one of the following criteria[11] satisfies the diagnosis for *established MI*:

1. Development of new pathologic Q waves on serial ECGs. The patient may or may not remember previous symptoms. Biochemical markers of myocardial necrosis may have normalized, depending on the length of time since the infarct developed; or
2. Pathologic findings of a healed or healing MI.

AMI is further classified by findings on the ECG at presentation, as either ST elevation MI (STEMI) or non-ST elevation MI (NSTEMI). Previous descriptors such as *transmural* and *non-transmural*, as well as *Q wave* and *non-Q wave MI* fail to adequately describe the coronary event and its related pathophysiology, electrocardiographic presentation, and pathologic outcome. The differentiation between STEMI and NSTEMI has important implications in terms of management, therapeutic intervention, outcome, and prognosis for patients with AMI. In fact, the American College of Cardiology and American Heart Association have developed separate clinical guidelines for the management of patients with UA/NSTEMI and those patents with STEMI.[6,7,12]

PATHOPHYSIOLOGY

The underlying pathophysiology of ACS is myocardial ischemia as a result of inadequate perfusion to meet myocardial oxygen demand. Myocardial oxygen consumption is determined by heart rate, afterload, contractility, and wall tension. Inadequate perfusion most commonly results from coronary arterial vessel stenosis as a result of atherosclerotic CAD. Usually, the reduction of coronary blood flow does not cause ischemic symptoms at rest until the vessel stenosis exceeds 95%. Myocardial ischemia, however, may occur with exercise and increased myocardial oxygen consumption when there is as little as 60% vessel stenosis.[13]

CAD is characterized by thickening and obstruction of the coronary vessel arterial lumen by atherosclerotic plaques. Although atherosclerosis is usually diffuse and multifocal, indi-

vidual plaques vary greatly in composition. Fibrous plaques are considered stable but can produce anginal symptoms with exercise and increased myocardial oxygen consumption because of the reduction in coronary artery blood flow through the fixed, stenotic lesions. Vulnerable or unstable fibrolipid plaques consist of a lipid-rich core separated from the arterial lumen by a fibromuscular cap. These lesions are likely to rupture, resulting in a cascade of inflammatory events, thrombus formation, and platelet aggregation that can cause acute obstruction of the arterial lumen and myocardial necrosis.[14]

Thrombus formation is considered an integral factor in ACS, including UA, NSTEMI, and STEMI. All of these syndromes are initiated by endothelial damage and atherosclerotic plaque disruption, which leads to platelet activation and thrombus formation. Platelets play a major role in the thrombotic response to rupture of coronary artery plaque and subsequent ACS. Platelet-rich thrombi are also more resistant to fibrinolysis than fibrin- and erythrocyte-rich thrombi. The resulting thrombus can occlude the vessel lumen, leading to myocardial ischemia, hypoxia, acidosis, and eventually infarction. The consequences of the occlusion depend on the extent of the thrombotic process, the characteristics of the preexisting plaque, the extent of the vessel obstruction, and the availability of collateral circulation.

In the setting of UA, acute stenosis of the vessel is noted; complete obstruction, however, is encountered in only 20% of cases. In these cases, it is likely that extensive collateral vessel circulation prevents total cessation of blood flow, averting frank infarction.[13,15] With AMI, the occlusive fibrin-rich thrombus is fixed and persistent, resulting in myonecrosis of the cardiac tissue supplied by the affected artery. Angiographic studies demonstrate that the preceding coronary plaque lesion is often less than 50% stenotic, indicating that the most important factors in the infarction are the acute events of plaque rupture, platelet activation, and thrombus formation rather than the severity of the underlying coronary artery stenosis.

Another important aspect of ACS is vasospasm. After significant coronary vessel occlusion, local mediators and vasoactive substances are released, inducing vasospasm, which further compromises blood flow. Central and sympathetic nervous system input increases within minutes of the occlusion, resulting in vasomotor hyperreactivity and coronary vasospasm. Sympathetic stimulation by endogenous hormones such as epinephrine and serotonin may also result in increased platelet aggregation and neutrophil-mediated vasoconstriction. Approximately 10% of MIs occur as a result of coronary artery spasm and subsequent thrombus formation without significant underlying CAD. This mechanism may be more prevalent during UA and other coronary syndromes that do not result in infarction.

Further myocardial injury occurs at the cellular level as inflammatory, thrombotic, and other debris from the occlusive plaque lesion are released and embolize into the distal vessel. Such embolization can result in obstruction at the microvasculature, leading to hypoperfusion and ischemia of the distal myocardial tissue, even after reopening of the more proximal, initial, obstructing lesion. In particular, the introduction of calcium, oxygen, and cellular elements into ischemic myocardium can lead to irreversible myocardial damage that causes reperfusion injury, prolonged ventricular dysfunction (known as myocardial stunning), or reperfusion dysrhythmias. Neutrophils probably play an important role in reperfusion injury, occluding capillary lumens, decreasing blood flow, accelerating the inflammatory response, and resulting in the production of chemoattractants, proteolytic enzymes, and reactive oxygen species.

CLINICAL FEATURES

Preadmission Evaluation

Appropriate pharmacotherapy for persistent anginal chest pain in the preadmission setting includes sublingual NTG, oral aspirin (acetylsalicylic acid [ASA]) that is preferably chewed, and intravenous morphine sulfate; the acronym MONA summarizes preadmission pharmacotherapeutic interventions (*m*orphine, *o*xygen, *n*itroglycerin, and *a*spirin). Establishment of the diagnosis of ACS in this setting is difficult, however, as chest pain is a poor predictor of the diagnosis and adjunctive tools are limited.[16] Preadmission 12-lead ECG offers high specificity (99%) and positive predictive value (93%) for AMI in patients with atraumatic chest pain while increasing the paramedic scene time by an average of only 3 minutes. This approach offers the advantages of earlier detection of STEMI and more rapid reperfusion therapy.[7,17] Preadmission 12-lead ECG would be necessary in the limited populations in whom preadmission fibrinolytic therapy might be applicable, such as those with prolonged out-of-hospital times (>90–120 minutes).[17]

Emergency Department Evaluation

The History

The character of the chest discomfort as well as the onset, location, radiation, duration, prior presence, and any exacerbating or alleviating factors should be sought. Associated symptoms, especially of a cardiac, pulmonary, gastrointestinal, and neurologic nature, should be elicited. Results from any prior cardiac testing should be obtained.

Traditionally, a history of risk factors for CAD is sought; these include male gender, age, tobacco smoking, hypertension, diabetes mellitus, hyperlipidemia, family history, artificial or early menopause, and cocaine abuse. Approximately 80% of a population of more than 122,000 patients with known CAD had at least one of the four conventional risk factors (diabetes mellitus, cigarette smoking, hypertension, or hyperlipidemia).[18] Cardiac risk factor burden has little impact on the ED diagnosis of ACS; however, in patients greater than 40 years of age, ACS is 22 times more likely if four of the five major risk factors (diabetes mellitus, smoking, hypertension, hyperlipidemia, and family history) are present (compared to none).[19] Nevertheless, Bayesian analysis indicates that risk factors are a populational phenomenon and do not increase or decrease the likelihood of any condition in any one patient. Thus, the presence of an individual risk factor, or a collection of risk factors, is far less important in diagnosing acute cardiac ischemia in the ED than the history of presenting illness, the presence of ST segment or T wave changes, or cardiac marker abnormalities.[20]

Risk assessment tools, such as the PURSUIT (The Platelet Glycoprotein IIb-IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy) risk model, the GRACE (Global Registry of Acute Coronary Events) risk model, and the TIMI (Thrombosis in Myocardial Infarction) risk score, can be used to determine risk of death and ischemia in NSTEMI and STEMI. These may aid in decision making and in risk stratifying patients so as to properly disposition them (telemetry bed vs. intensive care unit). The TIMI risk score assigns a point each for seven factors based on history, cardiac markers, and the ECG. It can be accessed at www.timi.org.[6]

There are several nontraditional risk factors for coronary disease. Antiphospholipid syndrome, rheumatoid arthritis, and particularly systemic lupus erythematosus (SLE) are each associated with a higher risk of cardiovascular disease.[21] Women

with SLE 35 to 44 years of age are over 50 times more likely to have an MI than a similar age- and gender-matched Framingham population.[22]

The Classic History

The term *angina* refers to "tightening," not pain. *Classic angina pectoris* may not be pain at all but rather a "discomfort," with a "squeezing," "pressure," "tightness," "fullness," "heaviness," or "burning" sensation. Classically, it is substernal or precordial in location and may radiate to the neck, jaw, shoulders, or arms. If the discomfort does extend down the arm, it classically involves the ulnar aspect. Discomfort in the left chest and radiation to left-sided structures is typical, but location and radiation to both sides or to only the right side may be consistent with angina. Radiation of the discomfort to the right arm or shoulder, or to both arms or shoulders, exceeds radiation to the left arm or shoulder in terms of likelihood of the chest pain being due to ACS, although all exceeded a positive likelihood ratio of 2.[23] Further, classic features of angina pectoris include exacerbation with exertion, a heavy meal, stress, or cold and alleviation by rest. The onset of pain at rest in no way excludes the diagnosis of angina. Anginal discomfort characteristically lasts from 2 to 5 minutes up to 20 minutes, and it is rare for it to last only a few seconds or to endure for hours or incessantly, "all day" (Table 76-1).

Symptoms characteristically associated with angina pectoris, or other entities of ACS, include the following: dyspnea, nausea, vomiting, diaphoresis, weakness, dizziness, excessive fatigue, or anxiety (Table 76-2). If these symptoms arise, either alone or in combination, as a presenting pattern of known ischemic coronary disease, they are termed *anginal equivalent symptoms*. Recognition that coronary ischemia may arise with an anginal equivalent, rather than a classic symptom is the key to understanding the atypical presentation of ACS. Complaints of "gas," "indigestion," or "heartburn" in the absence of a known history of gastroesophageal reflux disease or reproducible pain upon abdominal palpation should raise suspicion of ACS, and similarly if the heartburn is different from the patient's usual gastroesophageal reflux.

The Atypical History

A description of typical symptoms (crushing, retrosternal chest pain or pressure) is often lacking in ACS; this may be due to atypical features of the pain (e.g., character, location, duration, exacerbating and alleviating factors) or the presence of anginal equivalent symptoms (e.g., dyspnea, nausea, vomiting, diaphoresis, indigestion, syncope). Patients with an ultimate diagnosis of AMI or UA can have pain that is pleuritic, positional, or reproduced by palpation.[24] Some patients describe their pain as burning or indigestion, sharp, or stabbing (see Table 76-2).[25]

In a large study of nearly 435,000 patients ultimately diagnosed with AMI, one third did not have chest pain on presentation.[26] Multiple studies have identified risk factors for atypical presentation of ACS: diabetes mellitus, older age, female gender, nonwhite ethnicity, dementia, no prior history of MI or hypercholesterolemia, no family history of coronary disease, and previous history of congestive heart failure (CHF) or stroke.[26–31] In patients with AMI or UA, atypical presenting complaints include dyspnea, nausea, diaphoresis, syncope, or pain in the arms, epigastrium, shoulder, or neck.

Atypical features of ACS are present with increasing frequency in sequentially older populations. Before age 85, chest pain is found in the majority of patients with acute MI, although dyspnea, stroke, weakness, and altered mental status are notably present. In those older than 85 years, however, atypical symptoms are more common than chest pain, with 60 to 70% of patients older than 85 presenting with an anginal equivalent complaint, especially dyspnea.[28–30] Coincident ACS is more likely to occur in the elderly; patients who present with another acute condition (e.g., trauma, infection) should be scrutinized for concurrent ACS.[32]

Patients with *diabetes mellitus* are at heightened risk for ACS as well as an atypical presentation such as dyspnea, nausea or vomiting, confusion, or fatigue. Medically unrecognized AMI can occur in 40% of patients with diabetes mellitus compared with 25% of a nondiabetic population, and myocardial scar unaccompanied by antemortem diagnosis of MI is three times more likely in diabetics.[33]

As with age and diabetes, female gender is an important risk factor for MI without chest pain.[31] In some series, less than 60% of women reported chest discomfort at the time of their MI, with others reporting dyspnea, indigestion, or vague symptoms such as weakness, unusual fatigue, cold sweats, sleep disturbance, anxiety, or dizziness.[34,35]

Finally, nonwhite *racial and ethnic populations* may have atypical symptoms in ACS.[26] Compelling data demonstrate a disparity in treatment approach related to race in patients with acute manifestations of coronary heart disease.[36] Whether this is related to the atypical nature of presenting symptoms in different racial groups is not clear. Although certain features of the chest pain history serve to increase or decrease the likelihood of ACS, none of them is strong enough to endorse discharge of the patient based on the history alone.[23]

Table 76-1 Clinical Characteristics of Classic Anginal Chest Discomfort

CHARACTERISTIC	MORE LIKELY TO BE ANGINA	LESS LIKELY TO BE ANGINA
Type of pain	Dull, pressure	Sharp, stabbing
Duration	2–5 min, always <15–20 min	Seconds or hours
Onset	Gradual	Rapid
Location	Substernal	Lateral chest wall, back
Reproducible	With exertion	With inspiration
Associated symptoms	Present	Absent
Palpation of chest wall	Not painful	Painful, exactly reproduces pain complaint

Modified from Zink BJ: Angina and unstable angina. In Gibler WB, Aufderheide TP (eds): Emergency Cardiac Care. St. Louis, Mosby, 1994.

Physical Examination

The physical examination focuses on the cardiac, pulmonary, abdominal, and neurologic examinations, looking for signs of severe illness in patients with symptoms of ACS as well as other entities in the differential diagnosis of chest pain and the anginal equivalent syndromes (Table 76-3). Altered mental status, diaphoresis, and signs of CHF are all ominous findings in patients presenting with symptoms consistent with ACS. Historical studies using untrained physicians identified chest wall tenderness or "reproducible" chest wall tenderness in up to 15% of patients ultimately diagnosed with AMI, but these data are highly suspect. The real incidence of truly reproducible chest wall tenderness (i.e., when the patient reliably identifies to the examiner that the pain produced on palpation is

Table 76-2 Symptoms of Acute Myocardial Infarction: Typical and Atypical

SYMPTOM	BAYER ET AL*,†	TINKER‡	URETSKY ET AL§	PATHY‖
Typical				
Chest pain	515	51	75	75
Atypical				
Dyspnea	118	19	14	77
Syncope	72	4	1	27
Confusion	46	1		51
Stroke	32	6		26
Fatigue	36	2	4	10
Nausea or emesis	28		1	10
Sudden death	31			31
Giddiness	18	3		22
Diaphoresis	18			2
Arterial embolus	3			19
Palpitation	4			14
Renal failure				11
Pulmonary embolus				8
Restlessness				4
Abdominal pain			5	
Arm pain only			1	
Cough			1	
Silent				
No symptoms				
Total	777*	87¶	102**	387¶

*Patients able to report multiple symptoms; therefore, total exceeds 777.
†Bayer AJ, et al: Changing presentation of myocardial infarction with increasing age. J Am Geriatr Soc 34:263, 1986.
‡Tinker GM: Clinical presentation of myocardial infarction in the eldery. Age Ageing 10:237–240, 1981.
§Uretsky BF, Farquhar DS, Berezin AF, et al: Symptomatic myocardial infarction without chest pain: Prevalance and clinical course. Am J Cardiol 40:498–503, 1977.
‖Pathy MS: Clinical presentation of myocardial infarction in the elderly. Br Heart J 29:190–198, 1967.
¶Patients classified by principal symptom, although all patients with complaint of chest or epigastric discomfort were placed in typical group.
**Same as ¶ except patients with epigastric complaints were placed in atypical group.
Modified from Scott PA, Gibler WB, Dronen SC: Acute myocardial infarction presenting as flank pain and tenderness: Report of a case. Am J Emerg Med 9:547, 1991.

Table 76-3 Key Entities in the Differential Diagnosis of Chest Pain

Acute myocardial infarction	Unstable angina
Stable angina	Prinzmetal's angina
Pericarditis	Myocardial or pulmonary contusion
Pneumonia	Pulmonary embolism
Pneumothorax	Pulmonary hypertension
Pleurisy	Aortic dissection
Boerhaave's syndrome	Gastroesophageal reflux
Peptic ulcer disease	Gastritis or esophagitis
Esophageal spasm	Mallory-Weiss syndrome
Cholecystitis or biliary colic	Pancreatitis
Herpes zoster	Musculoskeletal pain

identical to the pain causing the patient's presentation) in ACS is probably vanishingly small. It has been suggested that chest pain that is fully *p*leuritic, *p*ositional, or reproducible by *p*alpation (the three P's) is at low risk (yet not no risk) for ACS.[23]

Outcomes in Atypical Presentations

Not surprisingly, atypical presentation of patients with ACS is linked to delay in diagnosis and poorer outcomes.[37] In the Second National Registry of Myocardial Infarction (NRMI-2) study, patients with MI presenting without chest pain were significantly more likely to die in the hospital (23 vs. 9% for patients with chest pain) and were more likely to experience stroke, hypotension, or heart failure that required intervention, possibly reflecting the older age and greater comorbidity in this group.[26] Patients with atypical symptomatology present for medical care later and are less likely to receive aspirin, beta-adrenergic blockers, heparin, fibrinolysis, and emergent reperfusion therapy.[26] Patients 65 years of age or less with NSTEMI have a 1% chance of dying during their hospitalization, but this risk is increased to 10% for patients ages 85 years and up.[32]

Missed Diagnosis of Acute Coronary Syndrome

Approximately 2 to 4% of patients with acute MI who present to the ED are discharged without diagnosis.[38] The highest mean payments for emergency physician medical malpractice claims are related to this population of patients. Atypical presenting symptoms are an obvious causative consideration. Patients with undiagnosed ACS discharged from the ED are significantly younger, more likely to be women or nonwhite, more likely to have atypical complaints, and less likely to have ECG evidence of acute ischemia.[38–40] Among all patients with cardiac ischemia, women younger than 55 years seem to be at highest risk for inappropriate discharge. With respect to ECG findings, 53% of patients with missed AMI and 62% of patients with missed UA have normal or nondiagnostic ECGs. In one

series, the emergency physician failed to detect ST segment elevations of 1 to 2 mm in 11% of the MI patients. Finally, the risk-adjusted mortality ratio for all patients with acute cardiac ischemia is 1.9 times higher among nonhospitalized patients.[38] Factors associated with misdiagnosis of ACS in medical malpractice closed claims analysis include physicians with less ED experience who document histories less clearly, admit fewer patients, and misinterpret the ECG.

Early Complications of Acute Myocardial Infarction

Bradydysrhythmia and *atrioventricular (AV) conduction block* occur in 25 to 30% of patients with AMI; sinus bradycardia is most commonly seen.[41–43] Symptomatic bradydysrhythmias in the first few hours following inferior AMI tend to be atropine responsive; conduction abnormalities that appear beyond 24 hours of MI tend not to respond to atropine.[44] Patients with AV block in the setting of anterior AMI tend to respond poorly to therapy and have a poor prognosis.

Tachydysrhythmias are quite common in the setting of AMI and may be atrial in origin (e.g., sinus tachycardia and atrial fibrillation) or ventricular (e.g., ventricular tachycardia and fibrillation). Not all require treatment, such as a compensatory sinus tachycardia in patients with AMI complicated by CHF. Primary ventricular fibrillation occurs in an estimated 4 to 5% of patients with AMI, with 60% of those cases occurring in the first 4 hours and 80% within 12 hours.

Cardiogenic shock is hypotension with end-organ hypoperfusion resulting from decreased cardiac output that is unresponsive to restoration of adequate preload. Patients at risk include those with large infarcts, prior MI, low ejection fraction on presentation (<35%), older age, and diabetes mellitus. Although some differential diagnoses can usually be reasonably excluded (e.g., sepsis, anaphylaxis, adrenal crisis, and hypovolemic or hemorrhagic states), other causes of shock with similar presentations should be considered, such as aortic dissection, pulmonary embolism, pericardial tamponade, and ventricular free wall rupture accompanying acute MI. Adjunctive diagnostic measures include bedside echocardiography and invasive hemodynamic monitoring, with the latter demonstrating systemic hypotension, low cardiac output, elevated filling pressures, and increased systemic vascular resistance. Therapeutic measures include vasopressor and inotropic support, intra-aortic balloon counterpulsation, and early revascularization; fibrinolytic therapy does not decrease mortality in cardiogenic shock.

Left ventricular free wall rupture is uncommon. Approximately one third of cases occur in the first 24 hours , and the remainder occur 3 to 5 days after transmural MI. Clinically, free wall rupture may occur with sudden death, pulseless electrical activity, or precipitous decline in the presence of AMI. Subacute presentations include agitation, chest discomfort, and repetitive vomiting. Signs of pericardial effusion on the ECG or echocardiogram are suggestive of the diagnosis in the setting of acute or recent MI. Free wall rupture is almost universally fatal, although prompt diagnosis followed by emergent surgical intervention may rarely be lifesaving; pericardiocentesis is indicated as an immediate temporizing intervention.

Rupture of the interventricular septum may also occur; it may arise similarly to cardiogenic shock and free wall rupture of the ventricle. The clue to this diagnosis on physical examination is the development of a new, harsh, loud holosystolic murmur heard best at the left lower sternal border. The diagnosis can be confirmed by echocardiography with color flow Doppler imaging. The presentation of acute, catastrophic deterioration with a new, harsh systolic murmur should prompt immediate cardiac surgery consultation for repair of a septal defect or ruptured papillary muscle of the mitral valve. Medical therapy including vasopressor and inotropic support, as well as intra-aortic balloon counterpulsation, is an important bridge to the definitive surgical treatments of valve repair or replacement.

Pericarditis, when associated with AMI, can occur early or in a delayed fashion; the former is termed infarct pericarditis, and the latter is known as post-MI syndrome or Dressler's syndrome. *Infarct pericarditis* is associated with transmural insult and thus principally involves the pinnacle of the infarct zone near the epicardium. Although the characteristic ST segment changes may be obscured by ST segment abnormalities related to the infarction itself, if they are evident, they are logically quite localized. Infarct pericarditis is a common cause of new chest pain in the first week after MI. This pain is characteristically pleuritic and worse in the supine position. Embolic complications are more common in patients with infarct pericarditis; linked to this is the higher rate of ventricular aneurysm development in this population.

Dressler's syndrome, unlike infarct pericarditis, does not require transmural involvement. It is a relatively uncommon, late complication occurring from 1 week to several months after the MI. Clinical features include fever, malaise, pleuropericardial pain, and at times the presence of a rub on cardiac auscultation. Laboratory findings are highly nonspecific and include an elevated sedimentation rate and leukocyte count. The ECG may show ST segment-T wave findings of pericarditis, although as with infarct pericarditis, these changes may be overshadowed by the evolving changes of the recent MI. PR segment depression is a telltale clue. Pericardial or pleural effusions may be evident and can be serous or bloody. Echocardiography assesses pericardial fluid and risk of tamponade. The pericardial reaction is believed to be immune mediated, and treatment includes anti-inflammatory agents.

Stroke may also complicate AMI, most commonly ischemic or thromboembolic. The major predisposing mechanisms with a recent MI are embolization from left ventricular mural thrombus with decreased ejection fraction, embolization from the left atrial appendage with atrial fibrillation, and hypercoagulability with concomitant carotid arterial disease. The rate of stroke is higher in the setting of MI (0.9% tapering to 0.1% at day 28 after MI) than in control subjects (0.014%).[45]

Hemorrhagic stroke is an obvious concern in the patient receiving fibrinolytic therapy. The rate of hemorrhagic stroke with varying fibrinolytic agents is under 1%, although the rate climbs in older patients. Percutaneous coronary intervention (PCI) lowers the overall risk of stroke compared with fibrinolytic therapy. Analysis of only fibrinolytic-eligible patients from the NRMI-2 database yields more than 24,000 patients treated with alteplase and more than 4000 who received primary angioplasty. The difference in stroke rate is highly significant (1.6% in the fibrinolytic group vs. 0.7% in the angioplasty group). Considering hemorrhagic strokes, the difference is again dramatic (1.0% in the fibrinolytic group vs. 0.1% in the angioplasty group).[46]

Hyperglycemia in the setting of AMI may be viewed as a complication, as well as a complicating disease process in AMI. Hyperglycemia is present in up to one half of all patients with STEMI, yet only one fifth to one fourth of those patients are recognized diabetics. Elevated glucose at the time of admission has independent negative implications for mortality rates in AMI patients. Although fasting blood sugar the day after presentation is a better predictor, an admission blood glucose greater than 200 mg/dL is linked to similar mortality rates among diabetics and nondiabetics. There is a 4% mortality increase for nondiabetic patients for every 18 mg/dL elevation in blood glucose level. Hyperglycemia seems to induce a

complex set of unfavorable cellular and biochemical circumstances, including negative effects on coronary flow and microvascular perfusion, as well as adverse effects on platelet function, fibrinolysis, and coagulation. Intravenous insulin therapy for glucose normalization is linked to improved outcomes in patients with STEMI as well as those in the medical intensive care unit. ACC/AHA guidelines acknowledge that tight control of blood glucose during and after STEMI decreases acute and 1-year mortality rates.[47]

DIAGNOSTIC INVESTIGATIONS

Electrocardiography

In patients with ACS, the ECG assesses the evolution of the syndrome and the response to treatment. The ECG is analyzed for signs of ST segment elevation AMI, evidence of cardiac ischemia, determination of cardiac rhythm, and possible evidence of a noncardiac cause of the chief complaint (e.g., in pulmonary embolism, pericarditis).

The ECG in ACS may manifest dynamic changes. Morphologic changes may occur in the T wave, the ST segment, the QRS complex, and even in the PR segment (e.g., ST segment depression in atrial infarction or infarct-related pericarditis). A variety of rhythm disturbances are also possible. Notably, the ECG may be normal or nonspecifically abnormal in the presence of ACS, including AMI. The ECG is limited by individual variations in coronary anatomy, preexisting coronary disease (e.g., previous MI, collateral circulation, coronary bypass surgery) and by the fact that it does not view the posterior, lateral, and apical left ventricular walls particularly well.[44] Thus, a single ECG must be evaluated in context. It is neither 100% sensitive nor 100% specific for AMI and reflects a single point in time. In addition, overreliance on a normal or nonspecifically abnormal ECG in a patient with anginal chest pain who is currently sensation free should be avoided. Patients with an initially nondiagnostic ECG who later develop AMI during that hospitalization more often are sensation free or minimally uncomfortable on presentation; these patients frequently also lack a past history of ischemic heart disease. Further, the total elapsed time from chest pain onset in patients with normal ECGs does not assist in ruling out the possibility of AMI in patients with chest pain with a single ECG. Although the negative predictive value is quite high, it is not 100%, even up to 12 hours after the onset of the patient's chest symptoms.[48] The patient's history of the event—and the physician's interpretation of the history—is the most important diagnostic study.

Electrocardiographic Abnormalities in Acute Coronary Syndromes

The earliest electrocardiographic finding in AMI is the *hyperacute T wave*, which maintains its vector but becomes tall and peaked within minutes of the interruption of blood flow. It is usually broad based and slightly asymmetrical. The hyperacute T wave progresses to ST segment elevation in classic MI. This hyperacuity may be missed on the initial ECG. The differential diagnosis of the tall T wave includes hyperacute T waves of ischemia, hyperkalemia, benign early repolarization (BER), left ventricular hypertrophy (LVH), left bundle branch block (LBBB), and pericarditis (Fig. 76-1).

As the AMI progresses, *ST segment elevation* may become evident. Morphologic variations of ST segment elevation can be seen from the J (or junction) point at the end of the QRS complex to the apex of the T wave. This upsloping portion of the ST segment usually progresses as it elevates from flat to convex or domed; if flat, it is characteristically horizontally or obliquely so. At times, the ST segment may be concave or scooped in its elevation with AMI[49]; this morphology may progress to a convex shape or may stay the same throughout the infarction. The concave morphology, if noted in all elevated ST segments, is atypical for AMI and more commonly seen with other ST segment elevation syndromes (Table 76-4 and Fig. 76-2).[50,51]

ST segment elevation is measured in millimeters; one block on the ECG tracing is equivalent to 1 mm in height. The baseline is usually considered to be the TP segment, although some clinicians advocate using the terminal point of the PR segment. In general, the most definable, constant baseline evident on the ECG should be used.

ST segment elevation, both benign and pathologic, is common (see Table 76-4). Most normal ECGs, especially those of men, may have some degree of ST segment elevation—indeed, upward of 90%. This elevation is seen in the precordial leads and it is usually 1 mm or more in men and 1 mm or less in women. The ST segment elevation is concave and is more prominent the deeper the corresponding S wave. Because of the common occurrence of this finding, it is not a normal variant but rather a normal finding.[51–54] A helpful point in differentiating normal ST segment elevation from the pathologic ST segment elevation of AMI is that the latter is a *dynamic* phenomenon; ECGs recorded sequentially over time with waxing and waning symptoms should demonstrate some fluctuation in the degree of ST segment deviation in the presence of ACS.

ST segment depression is generally considered to represent subendocardial or noninfarction ischemia. In addition, ST segment depression in ACS (1) may be seen in non-ST segment elevation AMI, (2) may precede ST segment elevation in ST segment elevation AMI, (3) may reflect a "mirror image" of ST segment elevation from posterior MI when found in the right-sided precordial leads (i.e., ST segment depression in V1 to V3 in posterior MI), and (4) may represent reciprocal ST segment depression seen with ST segment elevation AMI. With *reciprocal ST segment depression*, such changes are seen in leads on the "opposite" side of the heart from simultaneous ST segment elevation. Inferior MI with ST segment elevation more frequently manifests reciprocal ST segment depression than does its anterior counterpart. The reciprocal ST segment depression in inferior MI is best seen in lead aVL, which is 150 degrees removed from lead III when considering the positive poles of these leads in the frontal plane. Anterior ST segment elevation AMI may feature reciprocal ST segment depression in at least one of the inferior leads (II, III, or aVF). The ST segment depression seen in leads V1 to V3 with posterior MI is actually a reciprocal change from the ST segment elevation that would be recorded in

Table 76-4 Differential Diagnosis of ST Segment Elevation on the ECG

Acute myocardial infarction	Acute pericarditis
Left ventricular hypertrophy	Left ventricular aneurysm
Ventricular paced rhythm	Benign early repolarization
Normal variant	Osborn wave of hypothermia
Hyperkalemia	Brugada's syndrome
Pulmonary embolism	Acute cerebral hemorrhage
Prinzmetal's angina	Postelectrical cardioversion

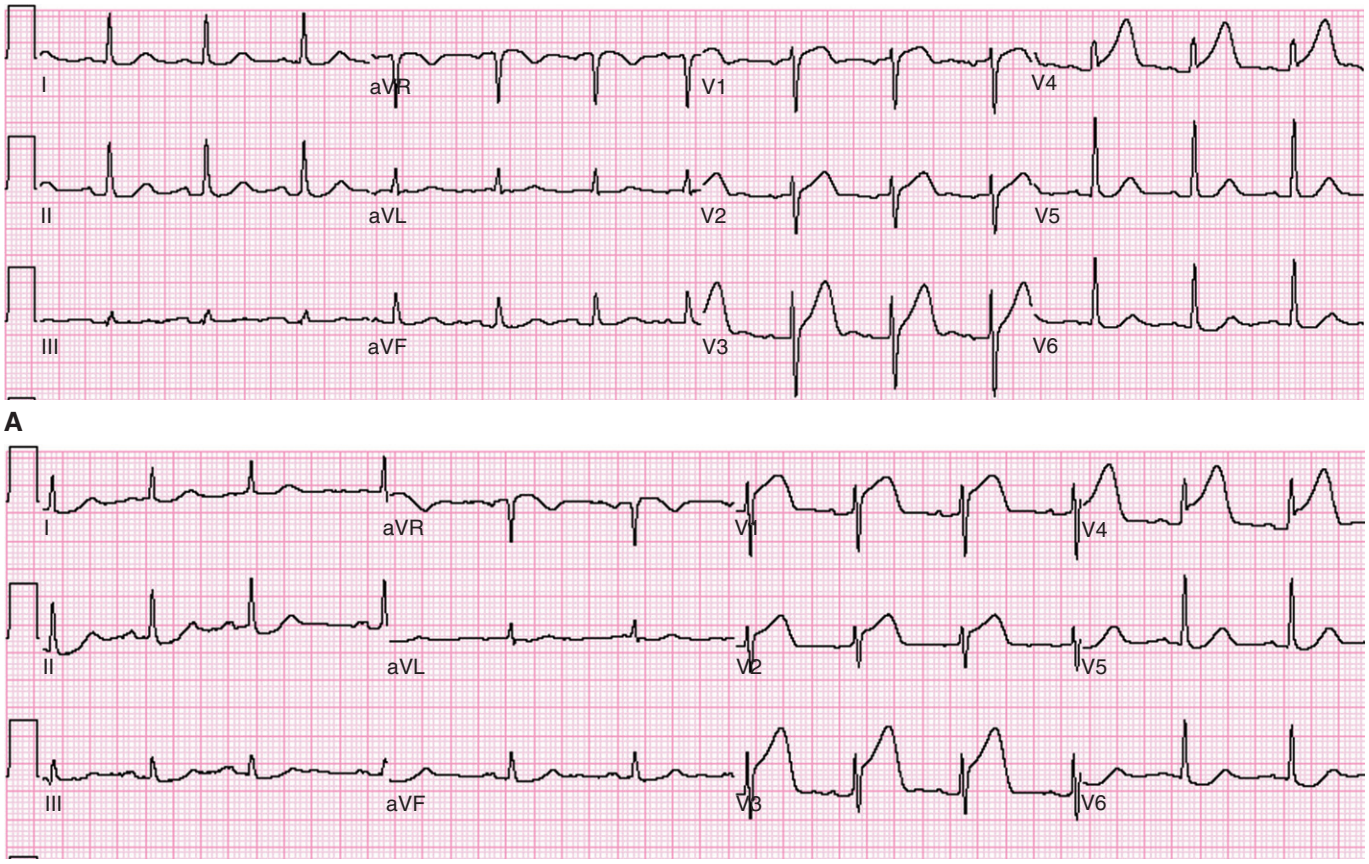


Figure 76-1. Hyperacute T wave of acute myocardial infarction. **A,** Note the broad, tall T waves in leads V3 and V4 in this patient with chest pain and diaphoresis. These are the hyperacute T waves of early ST segment elevation myocardial infarction. The ST segment is just beginning to rise in leads V3 and V4; leads V1 and V2 are also suspicious. **B,** This tracing is from the same patient, roughly 30 minutes after the electrocardiogram in **A**. Note the prominent ST segment elevation in leads V1 to V4.

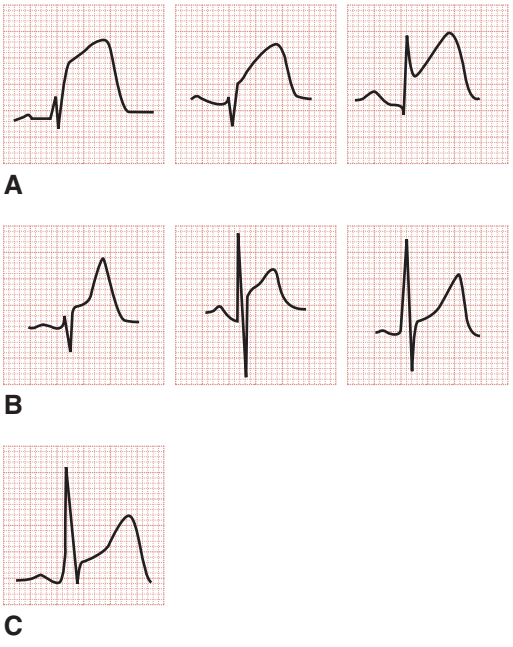


Figure 76-2. Analysis of ST segment–T wave morphology in acute myocardial infarction (AMI), benign early repolarization (BER), and acute pericarditis. An analysis of the ST segment–T wave morphology (from the beginning at the J point to the end at the apex of the T wave) may be particularly helpful in distinguishing among the various causes of ST segment elevation (STE) and identifying the AMI case. **A,** The initial upsloping portion of the ST segment is usually either flat (horizontally or obliquely) or convex in the patient with AMI. This morphologic observation, however, should be used only as a guideline; it is not infallible. **B,** Non-AMI causes of STE are seen here with concavity of the ST segment–T wave (left BER, middle pericarditis, right BER). **C,** Patients with STE related to AMI may demonstrate concavity of this portion of the waveform.

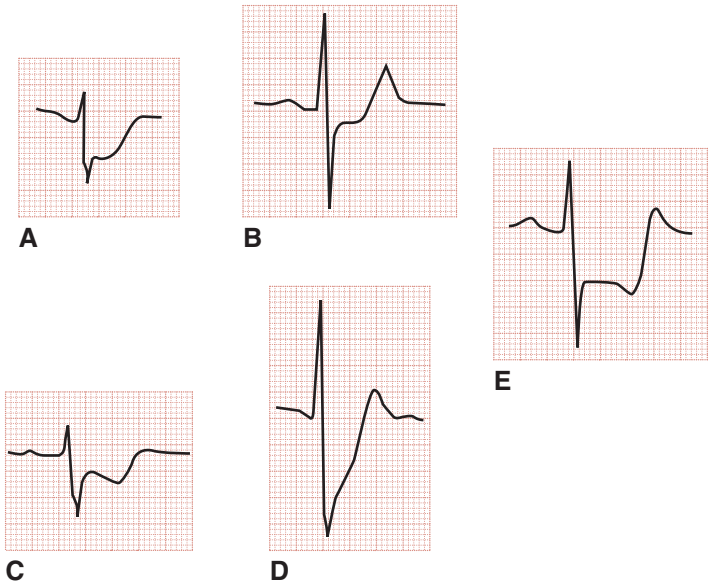


Figure 76-3. ST segment depression (STD) in acute coronary syndrome. **A,** Horizontal STD unstable angina pectoris (USAP). **B,** Horizontal STD (non-STE acute myocardial infarction). **C,** Downsloping STD (USAP). **D,** Upsloping STD (USAP). **E,** Horizontal STD as seen in lead III in a patient with anterior wall acute myocardial infarction, an example of reciprocal STD, also known as *reciprocal change*. STE, ST segment elevation.

posterior leads V8 and V9, were they to be employed. Reciprocal changes in the setting of STEMI increase the specificity and positive predictive value of the ECG in AMI.[52,53]

Ischemic ST segment depression is typically horizontal or downsloping; an upsloping contour may be seen but is less frequently associated with ischemia. Subendocardial ischemic ST segment depression may be diffuse, spanning anterior and inferior leads. The differential diagnosis of ST segment depression includes myocardial ischemia or infarction, repolarization abnormality of ventricular hypertrophy (the "strain" pattern), bundle branch block, ventricular paced rhythm, digoxin effect, hyperkalemia, hypokalemia, pulmonary embolism, intracranial hemorrhage, myocarditis, rate-related ST segment depression, postcardioversion of tachydysrhythmias, and pneumothorax (Fig. 76-3).

T wave inversions, although extremely nonspecific, should suggest possible myocardial ischemia. Normally, the T wave is upright in the left-sided leads I, II, and V3 to V6 and inverted in the right-sided lead aVR. T wave vectors are variable in leads III, aVL, and aVF. They are usually normally inverted in V1 and are occasionally normally inverted in lead V2. The T wave inversions of ACS are classically narrow and symmetrically inverted. The preceding ST segment is typically isoelectric and may be bowed slightly upward or concave. Associated ST segment depression may occur. T wave inversions are best viewed in comparison with the most recent prior ECG, given the multitude of normal variations (Fig. 76-4).

A notable subgroup of ischemic T wave inversions is associated with *Wellens' syndrome*, which classically manifests either deep symmetrical T wave inversions or biphasic T wave changes in the anterior precordial leads. The presence of biphasic T waves is suggestive of ischemic heart disease. Other electrocardiographic features include isoelectric or minimally elevated (<1 mm) ST segments and no precordial Q waves. This finding may manifest in the anginal or pain-free state and may or may not be accompanied by cardiac enzyme elevations, which is indicative of a lesion of the left anterior descending artery.

Although T wave inversion is sought as a harbinger of ACS, it can also occur as an evolutionary change after MI. In MI without culprit artery reperfusion, as the ST segments return to baseline, the T waves may invert, although not particularly deeply. In hearts that have been reperfused, T wave inversion may follow ST segment elevation, in either a biphasic or deeply inverted morphology, appearing much like the T wave changes of Wellens' syndrome.[55,56]

The clinician must also consider *pseudonormalization* of the T wave as a potential electrocardiographic indicator of ACS. Pseudonormalization occurs when, during an acute episode of chest discomfort or anginal equivalent, an apparently normal-appearing T wave on the ECG has replaced the "normally"

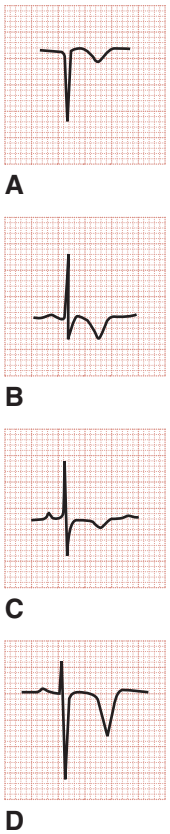


Figure 76-4. T wave inversions of acute coronary syndrome. **A** and **B,** T wave inversions in patients with ACS. **C,** T wave inversion in a patient with non-STE acute myocardial infarction. **D,** Deeply inverted T waves in a patient with proximal left anterior descending artery stenosis, Wellens' syndrome. STE, ST segment elevation.

inverted T wave that existed prior to the development of symptoms. The T wave has assumed a normal appearance and may indicate ACS at this presentation.

The differential diagnosis of T wave inversion is broad and includes ACS, ventricular hypertrophy, bundle branch block, ventricular paced rhythm, myocarditis, pericarditis, pulmonary embolism, pneumothorax, Wolff-Parkinson-White syndrome, cerebrovascular accident, hypokalemia, gastrointestinal disorders, hyperventilation, persistent juvenile T wave pattern, and normal variants.

Q waves are generally representative of irreversible myocardial necrosis but are rarely the sole manifestation of AMI. Pathologic Q waves may emerge within the first hour of infarction, but most commonly develop 8 to 12 hours into the infarction. It follows that ST segment elevation with concomitant Q waves does not preclude consideration of emergent reperfusion therapy. Q waves may persist after MI as enduring markers of previous infarction on the ECG; in some cases, however, Q waves disappear with time regardless of whether the infarcted territory was reperfused.

Anatomic Location of Acute Myocardial Infarction

The regional distribution of an AMI can be derived from noting the pattern of the various morphologic changes that are described (Table 76-5). *Anterior infarctions* are primarily evidenced by changes in the precordial leads V1 to V4 (Fig. 76-5). Septal involvement is reflected by changes in V1 and V2. Extension to the lateral wall (i.e., anterolateral MI) is evident if the pathologic changes extend beyond leads V1 to V4 to include leads V5, V6, I, and aVL. In anterior ST segment elevation AMI, reciprocal ST segment depression may occur in leads III and aVF. The anterior wall is served by the left anterior descending artery. The first diagonal branch of the left anterior descending artery is likely to be involved when the ST segment elevation extends to leads I and aVL. Isolated occlusion of the diagonal branch of the left anterior descending artery displays similar findings, but of smaller amplitude, to those seen with left anterior descending artery occlusion (ST segment elevation in leads V2 and V3, and possibly leads V1 and/or V4, along with ST segment depression in lead II and either III, aVF, or both).[57]

Lateral infarctions are frequently seen in concert with anterior infarction (anterolateral), inferior infarctions (inferolateral), or inferior infarctions with posterior extension (inferoposterolateral). This is due to the fact that the lateral wall of the heart is variably served by the left anterior descending, right coronary, and left circumflex coronary arteries. Thus, lateral involvement is manifested by changes in some or all of the lateral leads I, aVL, V5, and V6. So-called high lateral infarctions are restricted to leads I and aVL (Fig. 76-6) and are suggestive of occlusion of the left circumflex coronary artery; ST segment elevation in these leads may be accompanied by reciprocal ST segment depression in leads III, aVF, and V1. Based on cardiac magnetic resonance imaging localization of some of these lesions, new Q waves appearing in leads I and aVL (but not V6) indicate a "mid-anterior wall MI," previously referred to as a "high lateral MI."[6]

Inferior infarctions are characterized by morphologic changes in limb leads II, III, and aVF. The inferior wall of the heart and the AV node are served by the right coronary artery in roughly 90% of cases (right dominant); in the remainder, the left circumflex artery serves that function (left dominant). An inferior ST segment elevation AMI is present if two or more contiguous inferior leads (III, aVF, II) are involved; reciprocal ST segment depression is frequently seen in lead aVL, lead I, or both (Fig. 76-7) and perhaps in the anterior precordial leads: V1 less than V2 and V3. ST segment depression in leads V1 to V3 in the presence of inferior MI can be due to reciprocal change, to posterior extension, or to simultaneous anterior ischemia during inferior infarction. ST segment elevation inferiorly that is greater in lead III than in lead II, accompanied by ST segment depression in lead aVL, I, or both, is 90% sensitive and 71% specific for right coronary artery occlusion.[44] ST segment elevation in lead V1 in the presence of an ST segment elevation inferior MI (with elevation greater in lead

Table 76-5 Regional ST Segment Changes in Acute Myocardial Infarction

LOCATION	LEADS	ST SEGMENT
Anterior wall MI	V1 through V4	Elevation
Lateral wall MI	I, aVL, V5, and V6	Elevation
Inferior wall MI	II, III, and aVF	Elevation
Right ventricular wall MI	V4R	Elevation
Posterior wall MI	V8 and V9 V1 through V3	Elevation Depression

MI, myocardial infarction.
Modified from Aufderheide TP, Brady WJ: Electrocardiography in the patient with myocardial ischemia or infarction. In Gibler WB, Aufderheide TP (eds): Emergency Cardiac Care. St. Louis, Mosby, 1994.

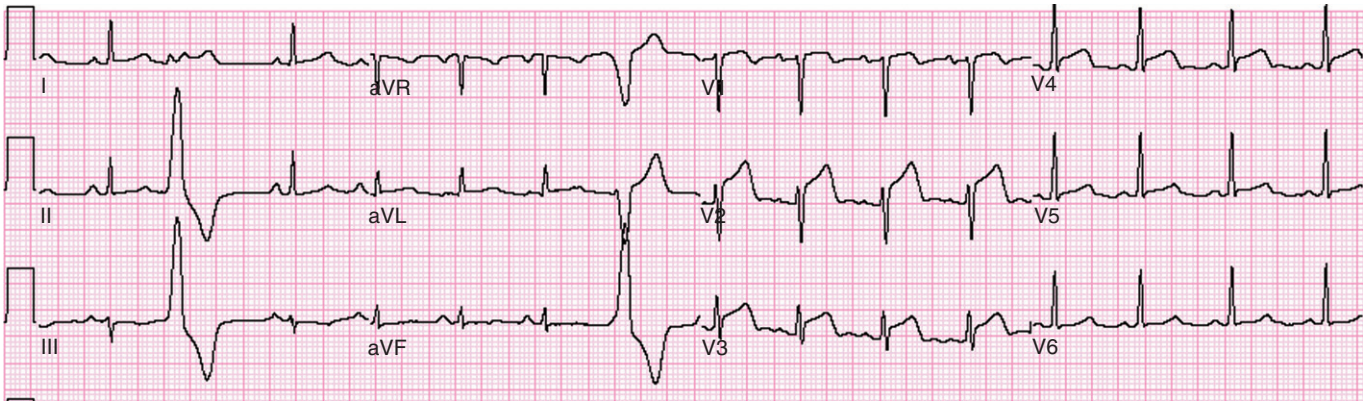


Figure 76-5. Anterior wall acute myocardial infarction (AMI). ST segment elevation is evident in leads V1 to V4. The morphology seems obliquely straight. Emergency cardiac catheterization revealed a 90% stenotic lesion in the left anterior descending artery; the patient did well after placement of a coronary stent but showed serum marker evidence of AMI.

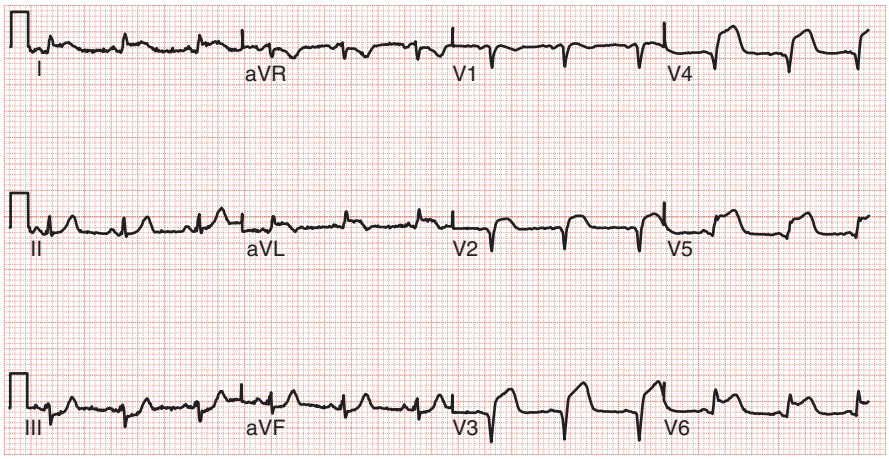


Figure 76-6. Anterolateral acute myocardial infarction. ST segment elevation is seen in leads I, aVL, V5, and V6. A proximal left anterior descending artery lesion with thrombus was noted at emergent percutaneous coronary intervention.

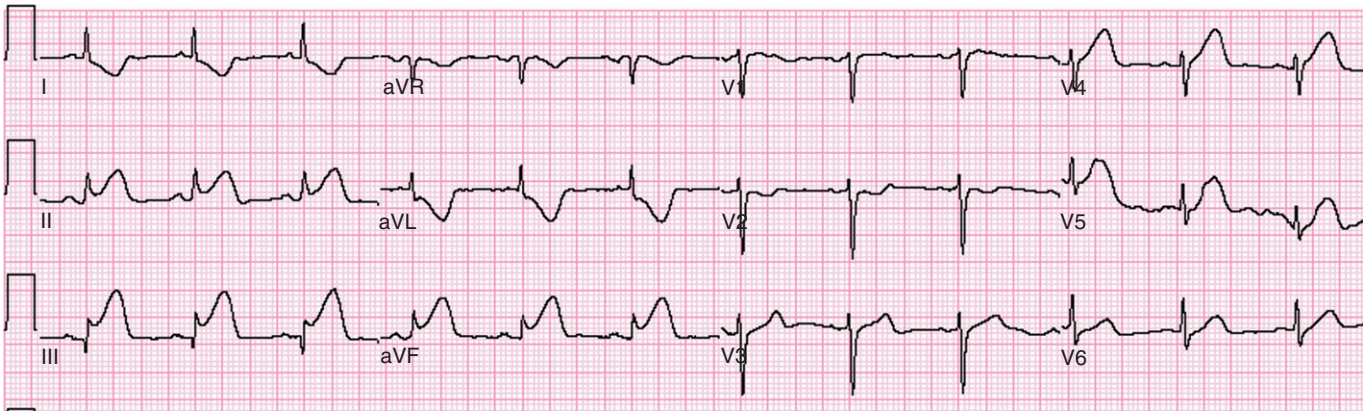


Figure 76-7. Inferior acute myocardial infarction with reciprocal changes. Marked ST segment elevation is seen inferiorly (leads II, III, and aVF). Classic reciprocal ST segment depression is evident in leads I and aVL.

III than in lead II) suggests concomitant right ventricular infarction. Coexistent reciprocal change with inferior STEMI is associated with larger infarct size and increased mortality. Occlusion of the left circumflex artery may be occult on the 12-lead ECG. If it is responsible for inferior ST segment elevation, expect the ST segment elevation in lead III not to be greater than that seen in lead II, and lead aVL may display an isoelectric or elevated ST segment.[44]

Posterior infarctions as isolated infarctions are estimated to contribute to 15 to 20% of all AMIs and are usually seen along with inferior or inferolateral infarctions. Posterior infarctions occur in isolation in about 4% of AMI cases (demonstrating elevated ST segments only in accessory leads V7 through V9).[6] The culprit lesion may be in the right coronary artery, its posterior descending branch, or the left circumflex artery. In that the 12-lead ECG features no electrodes placed directly over the posterior wall of the heart, one must infer acute STEMI of the posterior wall from what are actually reciprocal ST segment changes in the right precordial leads (V1 to V3). Findings include (1) horizontal ST segment depression; (2) a tall, upright T wave; (3) a tall, wide R wave; and (4) an R wave amplitude/S wave amplitude ratio greater than 1 (Fig. 76-8). The combination of horizontal ST segment depression with an upright T wave increases the diagnostic accuracy of the 12-lead ECG for posterior MI. In that the tall R wave in the right precordial leads is actually the mirror image of a posterior Q wave, its emergence may be delayed in posterior infarction. Additional leads (posterior leads V8 and V9) increase the sensitivity for detection of acute posterior MI. Patients with inferior MI who have either ST segment depression in leads V1 to V3 or ST segment elevation in the posterior leads V8 and V9 generally have larger infarction zones, lower resultant ejection fractions, and higher cardiovascular morbidity and mortality than patients with isolated inferior MI.[46] Cardiac magnetic resonance imaging suggests these "posterior" infarctions producing tall R waves in leads V1 and V2 are actually lateral left ventricular wall MIs.[6] A consensus document suggests reclassifying posterior infarctions as inferobasal infarctions.[58]

Right ventricular infarctions rarely occur in isolation and are usually associated with inferior or inferoposterior MI, although only about one third of inferior infarctions have associated infarction of the right ventricle. At times, an anterior MI involves some (but less than half) of the right ventricular wall. It follows that occlusion in any of the major coronary arteries may lead to right ventricular infarction, although the right coronary is most commonly involved. Clinically, right ventricular infarction features include elevated jugular venous pressure and hypotension in the setting of inferior wall MI. These findings, however, are also suggestive of pericardial tamponade. Nitrate-induced hypotension is also suggestive of right ventricular infarction, and of tamponade. Initial therapy for both would include volume loading and avoidance of vasodilators or other agents that may lower the blood pressure.

ST segment elevation in lead V1 in the setting of inferior MI (i.e., ST segment elevation in leads II, III, and aVF rather than in the setting of concomitant ST segment elevation in all anterior precordial leads) is suggestive of right ventricular infarction; this is not surprising in that lead V1 is the most rightward of the precordial leads. These changes occasionally extend into lead V2 with right ventricular infarction. ST

segment elevation is usually greater in lead III than in lead II when right ventricular infarction coexists with inferior AMI.[59] This logically follows in that (in the frontal plane) the positive vector of lead III is more rightward than that of lead II. Application of "right-sided" precordial leads is the best means to diagnose right ventricular infarction with the ECG. These leads, as a mirror image of the left precordial leads, demonstrate ST segment elevation with right ventricular infarction in leads V3R to V6R, with V4R having the highest sensitivity. ECG changes in the right-sided precordial leads with right ventricular infarction may be subtle owing to the smaller muscle mass of the right ventricle and the resulting diminution in QRS size (Fig. 76-9). Patients with inferior MI with concomitant right ventricular infarction have larger infarcts and experience more in-hospital complications and higher mortality rates.[60]

Left main coronary artery occlusion. In a patient with symptoms of ACS, ST segment elevation in lead aVR should prompt consideration of occlusion of the left main coronary artery. Pooled data from several studies demonstrate that ST segment elevation in lead aVR (>0.5 mV) is approximately 78% sensitive and 83% specific for left main disease; alternatively, this finding in lead aVR may represent multivessel disease, acute proximal left anterior descending occlusion, or (less commonly) left circumflex or right coronary occlusion.[61] If ST segment elevation occurs both in leads aVR and V1, greater elevation in the former lead favors left main disease, whereas if it is greater in the latter lead, occlusion in the left anterior descending artery is more likely.[62]

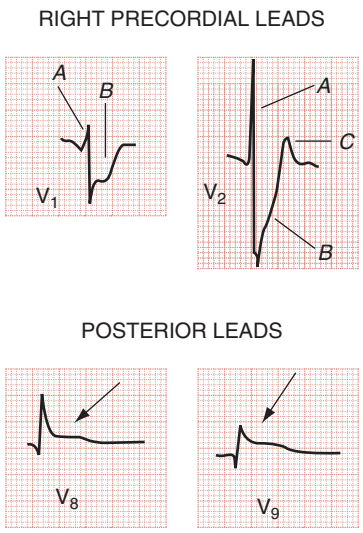


Figure 76-8. Isolated posterior wall acute myocardial infarction (PMI); complexes from right precordial leads and posterior leads. The right precordial leads V1 and V2 reveal typical findings of PMI with prominent R wave (**A**), STD (**B**), and upright T wave (**C**). The posterior leads V8 and V9 in the same case demonstrate STE *(arrows),* confirming isolated PMI. STD, ST segment depression; STE, ST segment elevation.

Electrocardiographic Differential Diagnosis of ST Segment Elevation

ST segment elevation on the ECG in the context of a presentation compatible with ACS is considered to represent acute myocardial ischemia until proved otherwise. Several other conditions, particularly left bundle branch block (LBBB) and LVH, also feature ST segment elevation that mimics infarction (see Table 76-4).[54] Caution is required when interpreting ST segment elevation as to the decision to administer systemic fibrinolytic therapy.[63]

Benign early repolarization is a normal electrocardiographic variant that does not imply, or exclude, CAD. BER includes the following electrocardiographic characteristics: (1) ST segment elevation; (2) upward concavity of the initial portion of the ST segment; (3) notching of the terminal portion of the QRS complex at the J point (i.e., junction of the QRS complex with the ST segment); (4) symmetrical, concordant T waves of large amplitude; (5) diffuse ST segment elevation on the ECG; and (6) relative temporal stability over the short term, although these changes may regress with old age. J point elevation is usually less than 3.5 mm, and the concave ST segment is usually elevated less than 2 mm (although it may be elevated as much as 5 mm in some cases) in the precordial leads and 0.5 mm in the limb leads. Maximal ST segment elevation in BER is typically seen in leads V2 to V5. Isolated BER in the limb leads is quite rare and should prompt reconsideration of AMI (Figs. 76-10A and 76-11). Reportedly 31% of predominantly white individuals less than 60 years of age who are resuscitated after idiopathic ventricular fibrillation have early repolarization changes in the inferolateral leads, as opposed to only 5% in a well-matched cohort of patients without syncope or heart disease. While significant malignant dysrhythmias may occur in patients with this electrocardiographic finding, there are many who do well over a lifetime.[64]

Pericarditis, in the acute phase, features diffuse ST segment elevation as well. In pericarditis, the ST segments are concave

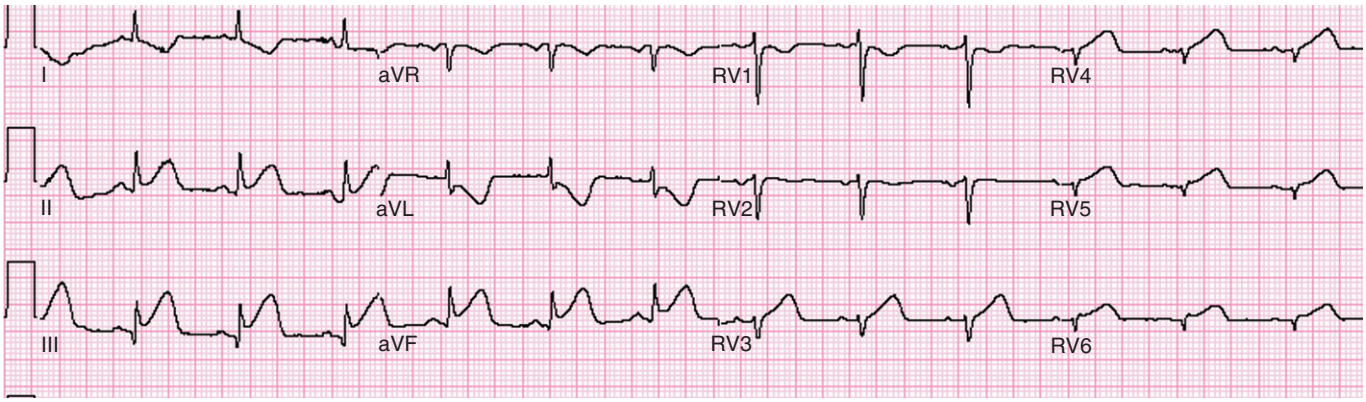


Figure 76-9. Right ventricular infarction demonstrated with right-sided precordial leads (RV1 to RV6). This tracing is taken from the same patient as in Figure 76-7. The ST segment elevation of inferior acute myocardial infarction is still present, as is the reciprocal ST segment depression in leads I and aVL. The precordial leads are right-sided chest leads, as might be inferred from the relatively low voltage. ST segment elevation is noted in leads V3R to V6R, consistent with right ventricular infarction.

with an initial upsloping contour and are usually less than 5 mm in height. Occasionally, the initial contour is obliquely flat, but convex or domed ST segment morphology is suggestive of AMI. The ST segment elevation is usually seen in all leads with the exception of aVR (where it is depressed); V1 is variable. Focal pericardial inflammation is manifest as a more accentuated change in the leads reflecting the affected region. PR segment depression is an insensitive yet specific associated electrocardiographic finding in pericarditis, which is typically best seen in the inferior leads and in lead V6; correspondingly, PR segment elevation may be evident in lead aVR (Fig. 76-12; see Fig. 76-10B).

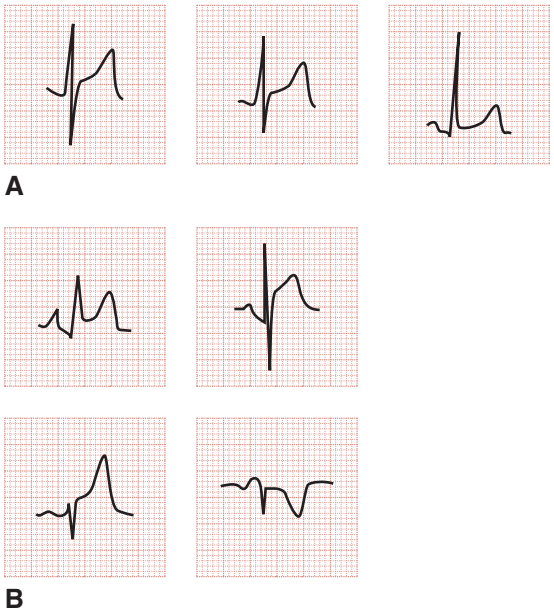


Figure 76-10. Noninfarctional ST segment elevation (STE). **A,** Benign early repolarization (BER) with concave STE. **B,** Acute pericarditis with concave STE and PR segment depression *(upper two examples)*; concave STE without PR segment abnormalities *(lower left example)*; and "reciprocal" STD and PR segment elevation in lead aVR *(lower right example)*.

Left ventricular aneurysm (LVA), wherein a focal area of myocardium paradoxically bulges outward during systole, has characteristic electrocardiographic changes that can be difficult to differentiate from those of AMI. Considerable overlap exists between populations of patients with potential for AMI and LVA, and the electrocardiographic changes of LVA tend to be regional rather than diffuse.[65] Anatomically, LVA is most commonly found anteriorly, and changes are most often seen in leads V1 to V6 as well as leads I and aVL. ST segment elevation may be of any morphology (e.g., convex or concave), and Q waves may be present (Fig. 76-13). The calculation of the ratio of the amplitude of the T wave to the QRS complex may help distinguish acute anterior MI from LVA. If the ratio of the amplitude of the T wave to the QRS complex exceeds 0.36 in any single lead, the ECG probably reflects acute MI. If the ratio is less than 0.36 in all leads, however, the findings are probably due to ventricular aneurysm.[66]

Left bundle branch block is a confounding pattern that reduces the ECG's ability to detect ACS. A new, or *presumably new*, LBBB is strongly suggestive of ACS when noted in the appropriate clinical presentation. Preexisting LBBB, however, shares many ECG similarities to various electrocardiographic findings of ACS. In the right-sided precordial leads, ST segment elevation and tall, vaulted, upright T waves mimic those seen in acute anterior MI. The QS pattern of LBBB in these leads resembles the Q waves seen in infarction. Depressed ST segments with T wave inversions are seen in some or all of the lateral leads (V5, V6, I, and aVL) in LBBB; both of these resemble ischemic changes seen in ACS. Yet, these findings in LBBB are merely expressions of the "rule of appropriate discordance." The ST segment and T wave vectors are expectedly discordant, or opposite in direction, to the major vector of the QRS complex in those leads. Since LBBB is a frequent finding on the ECG of a patient at risk for CAD, the normal findings in LBBB (Fig. 76-14) and the presentation of ST segment AMI in a patient with LBBB must be distinguished.

Sgarbossa[67] used the Global Use of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO-I) trial database to obtain a population of patients with LBBB and enzymatic evidence of AMI. Three independent electrocardiographic

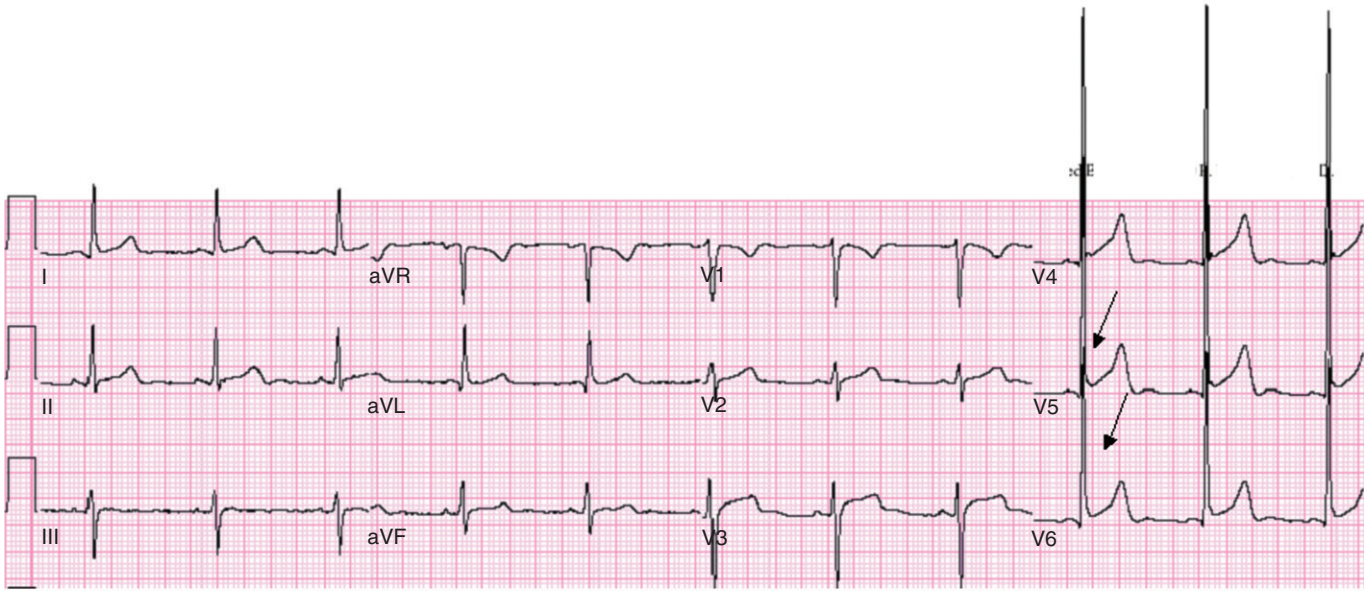


Figure 76-11. Benign early repolarization. Note the upwardly concave ST segment elevation, best seen in leads V4 to V6. The T waves are relatively large in the same leads. Subtle notching is also seen at the J point in leads V4 and V5. Prior electrocardiograms of this patient were unchanged.

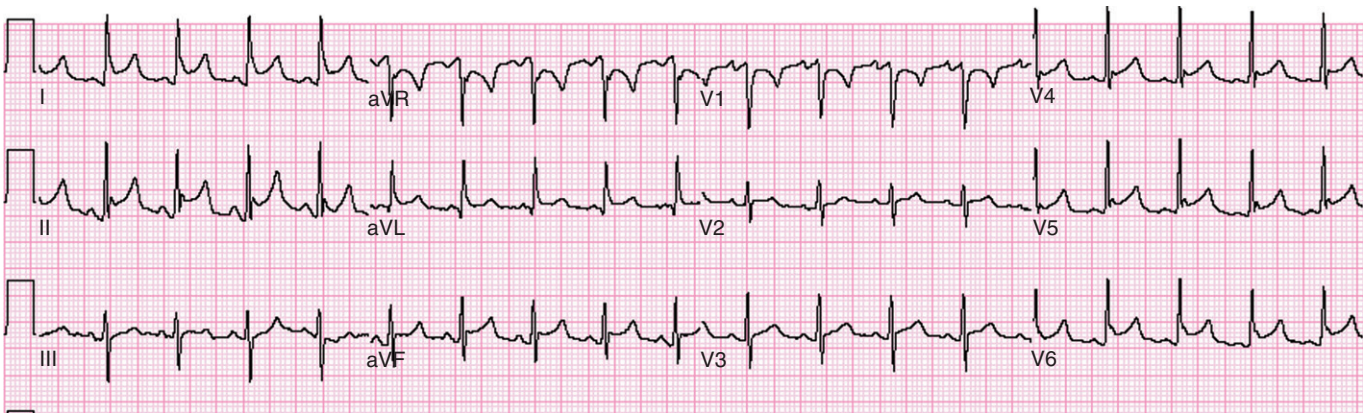


Figure 76-12. Pericarditis. This tracing demonstrates several classic signs of pericarditis: (1) sinus tachycardia; (2) diffuse, concave upward ST segment elevation; (3) PR segment depression, best seen in lead II; and (4) PR segment elevation in lead aVR.

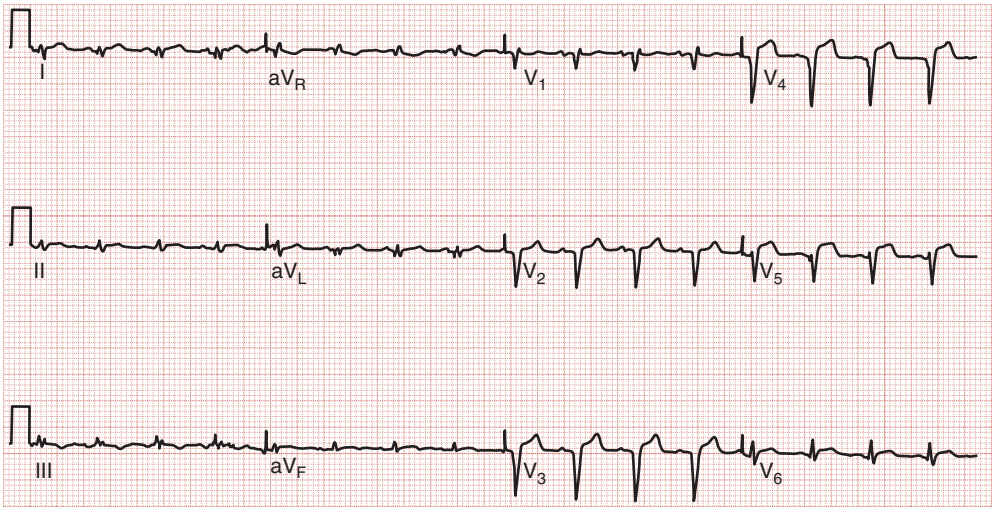


Figure 76-13. Left ventricular aneurysm: representative example of 12-lead electrocardiogram from patient with anterior left ventricular aneurysm. Note well-developed, completed Q waves in leads V2 through V5 and absence of reciprocal changes in contralateral leads. (Modified from Aufderheide TP, Brady WJ: Electrocardiography in the patient with myocardial ischemia or infarction. In Gibler WB, Aufderheide TP [eds]: Emergency Cardiac Care. St. Louis, Mosby, 1994, pp 169–216.)

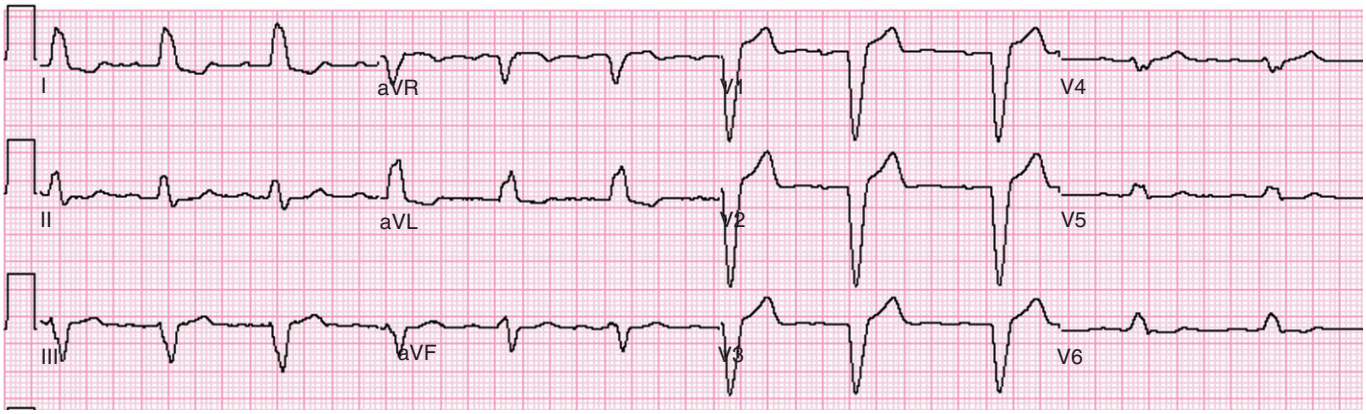
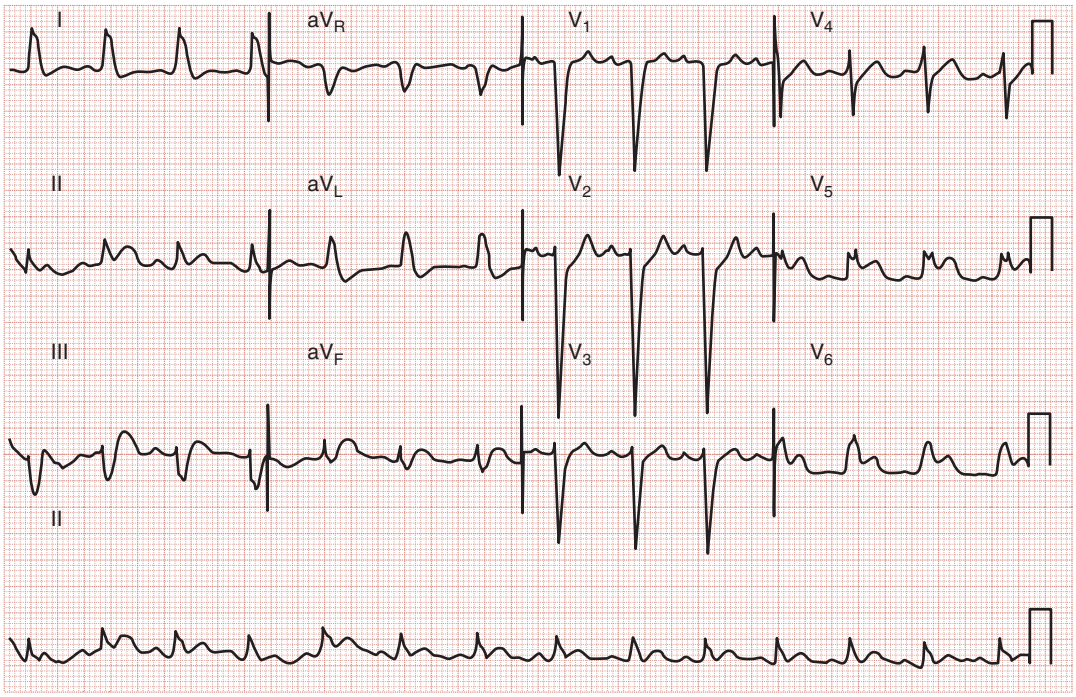
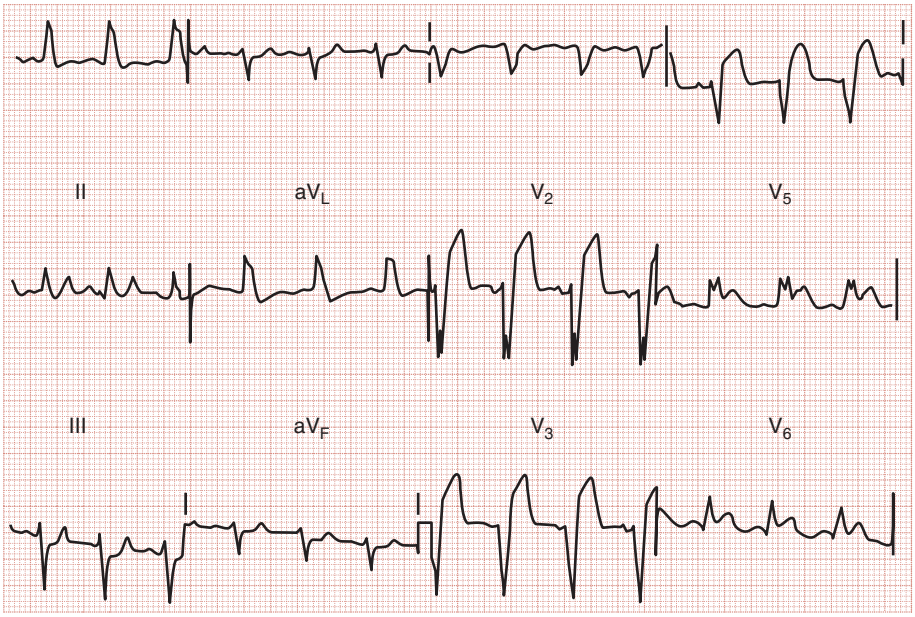


Figure 76-14. Left bundle branch block (LBBB) (normal). This tracing demonstrates the classic findings of LBBB: (1) QRS complex width greater than 0.12 second; (2) absence of Q wave in lead V6; (3) broad monophasic R wave in leads V5, V6, I, and aVL; (4) discordant ST segment–T wave changes in leads V1 to V3 (simulating acute myocardial infarction), I, and aVL. A first-degree atrioventricular block is also apparent.

predictors of MI in the presence of LBBB were identified: (1) ST segment elevation of at least 1 mm that is concordant with the QRS complex; (2) ST segment depression of at least 1 mm in lead V1, V2, or V3; and (3) ST segment elevation of at least 5 mm that is discordant with the QRS complex. These findings were assigned weighted scores of 5, 3, and 2, respectively. For accuracy in diagnosis, a specificity of 90% requires a score of at least 3. Thus, if an ECG features only discordant ST segment elevation of 5 mm or more but neither of the other two criteria, further testing is recommended before concluding that the ECG is indicative of AMI (Fig. 76-15).[67] Subsequent literature yields mixed reviews of the Sgarbossa criteria[67] for diagnosis of AMI in the presence of LBBB.[68] Ultimately, the approach to the patient with LBBB and possible MI remains



A

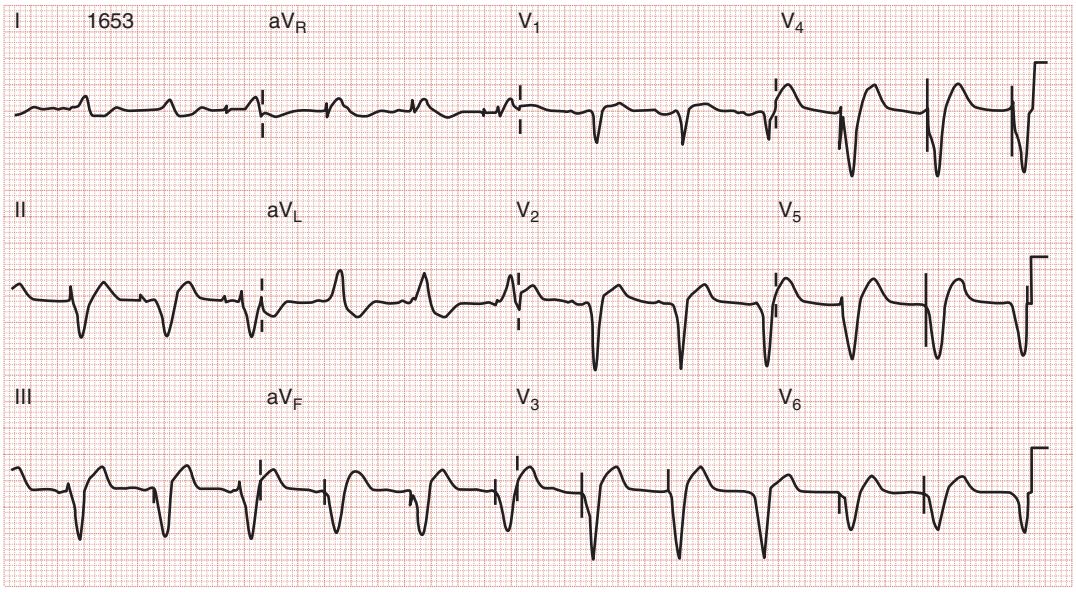


B

Figure 76-15. Acute myocardial infarction (AMI) in left bundle branch block (LBBB). **A,** Using the Sgarbossa criteria,[67] there is strong evidence of AMI because of the concordant ST segment elevation greater than 1 mm in leads II, V5, and V6; also suggestive is the ST segment depression seen in V2. **B,** Again, applying the Sgarbossa criteria[67] to this tracing with underlying LBBB, AMI is strongly suggested. There is concordant ST segment elevation in leads V5 and V6 that appears to exceed 1 mm; further, there is excessively discordant ST segment elevation in leads V2 and V3, probably greater than 5 mm.

complicated; diagnostic adjuncts to the history and physical examination (e.g., serial ECGs, comparison with prior ECGs, echocardiography, serum cardiac marker measurement) should be liberally employed when the ECG does not show obvious evidence of AMI as noted by the Sgarbossa criteria.[67] A new LBBB together with a clinical impression of AMI remains an indication for fibrinolytic therapy or PCI.

Ventricular paced rhythms (VPRs) can mimic and mask the manifestations of AMI. VPRs originating in the right ventricular apex create a wide QRS complex, with a pseudo-LBBB pattern. As with LBBB, the right precordial leads in VPR typically feature predominantly negative QRS complexes with discordant ST segments and T waves that are elevated and tall or vaulted, respectively. Unlike LBBB, however, VPR originating in the right ventricular apex often yields a predominantly negative QRS complex in leads V5 and V6 as well (which is oriented leftward and slightly downward, whereas the impulse generated from the pacemaker wire is oriented superiorly). Furthermore, small vertical pacemaker spikes immediately preceding the QRS complex should be a clue to VPR, although these deflections are at times hard to detect on the 12-lead ECG.



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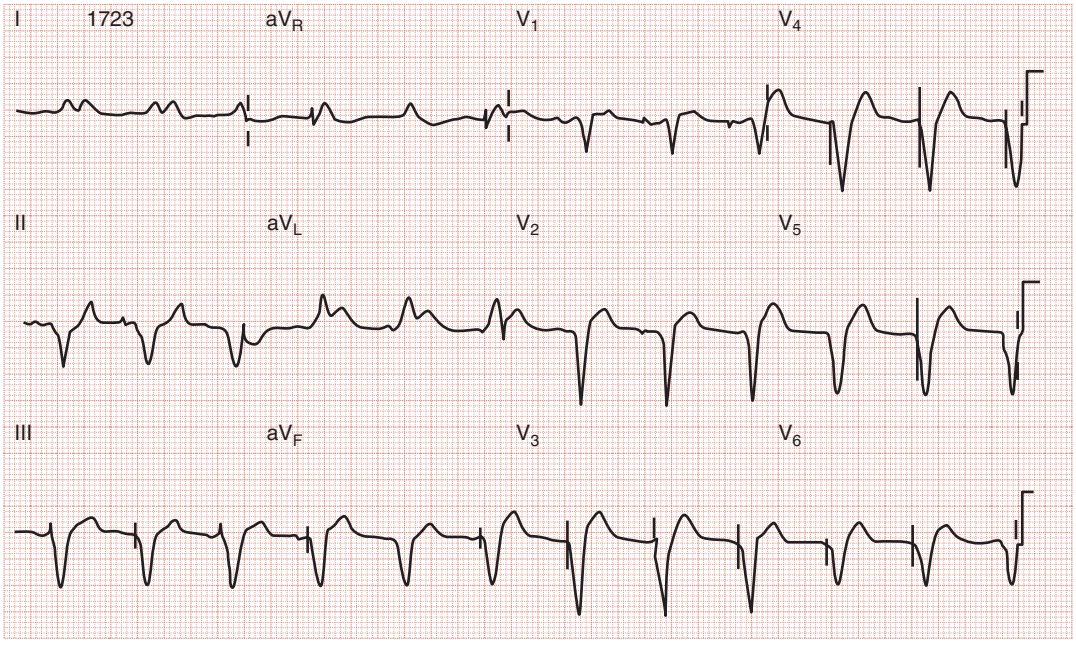


B

Figure 76-16. Permanent right ventricular paced pattern with acute myocardial infarction (AMI); ventricular paced rhythm. **A,** Appropriate ST segment–T wave findings in the patient with a paced rhythm. **B,** Serial electrocardiogram from the patient in **A,** revealing evolution of changes worrisome for AMI, including concordant ST segment elevation in leads I and aVL consistent with lateral wall AMI.

Limited data exist to guide the clinician in interpretation of the 12-lead ECG in this setting. As with the LBBB scenario, the VPR pattern represents a significant confounding variable in the evaluation of the patient with chest pain suspected of having ACS. Sgarbossa and associates advanced criteria for detection of AMI in the presence of VPR[69] that are similar to those for LBBB.[67] These, too, are derived from the GUSTO-I database, but from a smaller group of patients. The criteria are essentially the same as the LBBB criteria: (1) ST segment elevation of at least 5 mm that is discordant with the QRS complex; (2) ST segment elevation of at least 1 mm that is concordant with the QRS complex; and (3) ST segment depression of at least 1 mm in lead V1, V2, or V3[69] (Fig. 76-16).

Left ventricular hypertrophy may mimic or obscure ACS on the ECG. LVH may feature prominent left-sided forces, manifesting as large rS or QS complexes in the right precordial leads—yet these changes seldom extend beyond V1 and V2 in the case of LVH. Consistent with the rule of appropriate discordance, the leads demonstrating such a pattern feature discordant ST segment elevation and tall, vaulted T waves, paralleling the changes of AMI. The initial portion of the elevated ST segment in LVH is generally concave, as opposed to the obliquely straight or convex pattern that usually (but not always) is seen with ST segment elevation in AMI. In LVH, the left precordial leads (and at times leads I and aVL) may show evidence of repolarization abnormality (or strain pattern), with ST segment depression and asymmetrically inverted T waves. The presence of this strain pattern in the left precordial leads is reassuring when attributing ST segment elevation and tall T waves in the right precordial leads to LVH rather

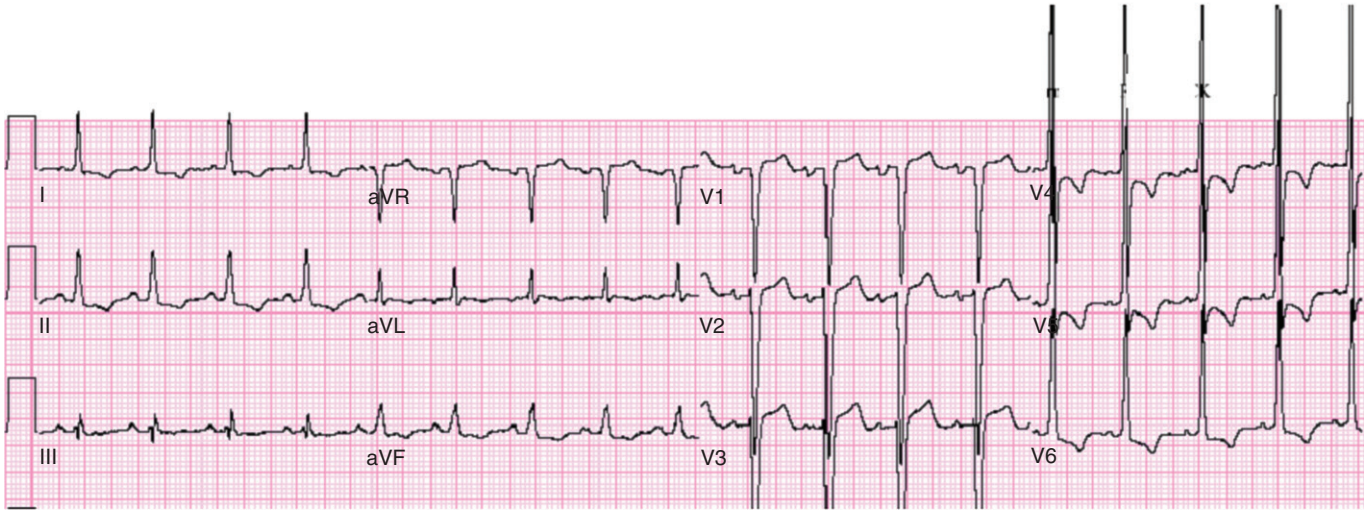


Figure 76-17. Left ventricular hypertrophy (LVH) with repolarization abnormality. This tracing demonstrates classic repolarization abnormality, with ST segment depression in the left-sided precordial leads following large-amplitude R waves. The T waves in these leads are asymmetrically inverted. The right precordial leads (V1 and V2) show a mirror image of the changes seen in V3 to V6, with slight ST segment elevation (contour initially concave) and asymmetric tall T waves. See Fig. 76-20B for evidence of evolving acute myocardial infarction in a patient with LVH and repolarization abnormality.

than to AMI because one is essentially the mirror image of the other. The changes in LVH should be static over time (Fig. 76-17).

Takotsubo Cardiomyopathy

Commonly referred to as left apical ballooning or "broken heart" syndrome, Takotsubo cardiomyopathy features ST segment elevation (or deep T wave inversions) without evidence of obstructive CAD. Positive serum markers for cardiac ischemia may be present, as well as hemodynamic compromise. It occurs principally in postmenopausal women and characteristically is triggered by intense emotional stress. Ballooning of the left ventricular apex is seen on ventriculography or echocardiography. Prognosis is excellent, typically with recovery of normal wall motion within a month or less.[6,69]

Non-ST Segment Elevation Acute Myocardial Infarction

This terminology supplants "non-Q wave MI," previously termed "subendocardial infarction." Precise terminology is difficult because Q waves may disappear with time and the criteria for "significant" Q waves vary. Moreover, transient ST segment elevation may simply be missed on ECG. Nonetheless, it is useful to describe the entity wherein there is serum marker evidence of MI in the appropriate clinical scenario but no captured ST segment elevation.

Pathophysiologically, total occlusion of the diseased artery may not have occurred, or the infarct zone may have been partially spared by collateral circulation or therapeutic intervention. ECG manifestations of non-ST segment AMI (NSTEMI) include ST segment depression and T wave inversion, which may be deep and symmetrical. Absence of STEMI, however, does not necessarily translate to better outcomes. A study analyzing over 250,000 AMI patients from the NRMI 2, 3, and 4 databases determined that patients with ST segment depression on the initial ECG have an in-hospital mortality rate of 15.8%—similar to that of patients with ST segment elevation or LBBB (15.5%).[70] ST segment depression may herald true posterior infarction on the 12-lead ECG. Acute posterior (inferobasal) MI is one entity wherein emergent fibrinolysis or PCI is indicated in the absence of ST segment elevation on the 12-lead ECG.

Electrocardiographic Adjuncts in the Diagnosis of Acute Coronary Syndrome

Additional lead ECGs can increase sensitivity for AMI by evaluating regions of the heart prone to electrical silence on the 12-lead tracing. Most commonly, additional lead ECGs use posterior (leads V8 and V9) and right ventricular (RV4) electrodes, thus constituting the 15-lead ECG (Fig. 76-18). Posterior leads V8 and V9 are placed under the tip of the left scapula and at the left paraspinal area, at the same level as leads V4 to V6. Morphologic changes in the posterior leads may be subtle, principally because of the increased distance between these electrodes and the posterior wall of the heart (Fig. 76-19).

Electrocardiographic imaging of the right ventricle is enhanced with the use of the right-sided chest leads V1R to V6R (also termed RV1 to RV6). These are placed in mirror image fashion across the right precordium. Of the right precordial leads, V4R has the highest sensitivity for right ventricular infarction and is the lead of choice to include in the 15-lead tracing. Morphologically, less pronounced changes can be expected in the right-sided chest leads because of the relatively thinner wall of the right ventricle.

Use of the 15-lead ECG may improve diagnostic precision but does not appear to affect the rate of AMI diagnosis, use of reperfusion therapy, disposition, or outcome in patients with chest pain evaluated for ACS.[71] In the subset of ED patients identified as candidates for admission to the cardiac care unit (i.e., high-risk patients), the 15-lead ECG increased the sensitivity of ACS detection by 12%.[72] Possible applications for additional lead ECGs include the following: (1) ST segment changes (depression or elevation) in leads V1 to V3, either in an isolated lead or in more than one; (2) equivocal ST segment elevation in the inferior (II, III, aVF) or lateral (I, aVL) limb leads, or both; (3) all inferior STEMI; and (4) hypotension in the setting of ACS.

Serial ECGs and ST segment trend monitoring overcome the limitations of the snapshot 12-lead ECG. The use of increased electrocardiographic surveillance demonstrates diagnostic benefit in patients with recurrent or continuous chest

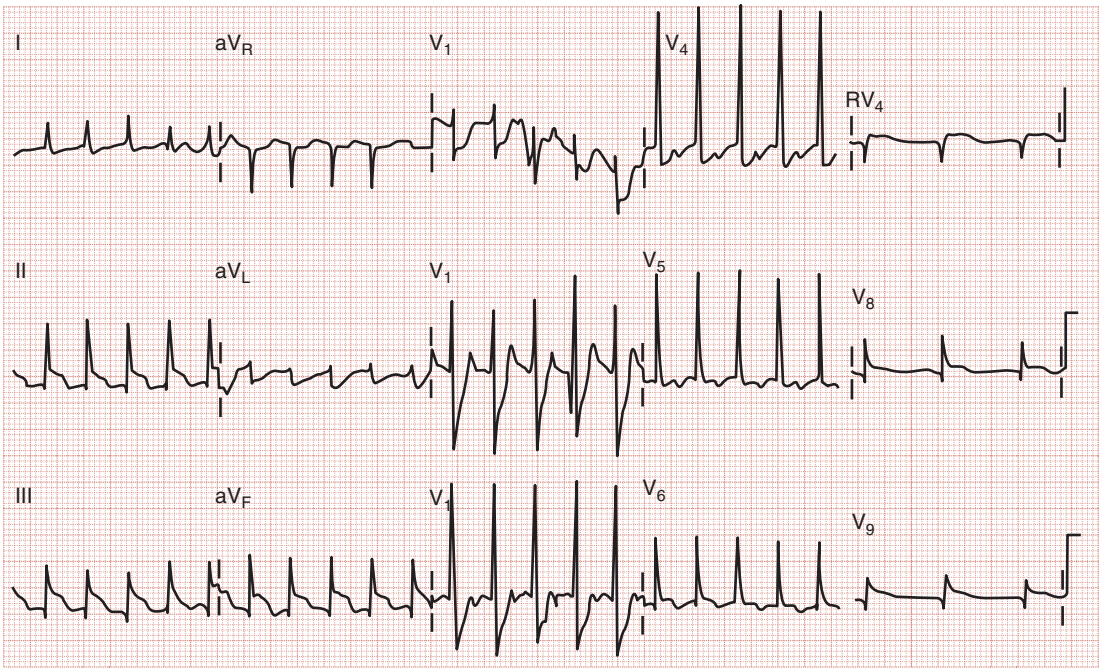


Figure 76-18. Fifteen-lead electrocardiogram (ECG) with inferior, lateral, posterior, and right ventricular acute myocardial infarction (AMI). The standard 12-lead ECG reveals the typical ST segment elevation (STE) in the inferior and lateral leads as well as ST segment depression (STD) with prominent R wave in the right precordial leads. Posterior AMI is indicated by both the right precordial STD with prominent R wave and the STE in posterior leads V8 and V9. Note that the degree of STE is less pronounced than that seen in the inferior leads because of a relatively longer distance from the posterior epicardium to surface leads. The right ventricular infarction is noted in this case using the simplified approach with only RV4, which demonstrates STE of relatively small magnitude.

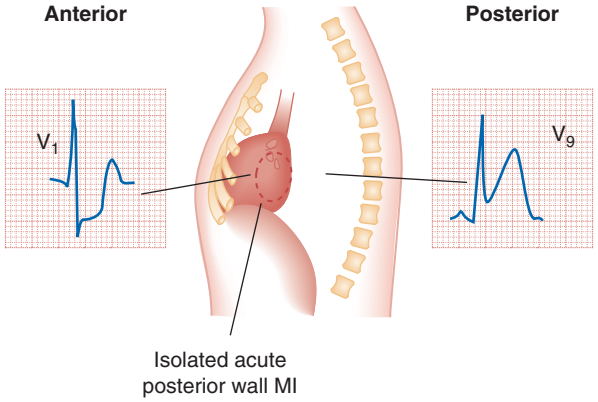


Figure 76-19. Schematic of thorax depicting single anterior and posterior complexes in posterior wall acute myocardial infarction (AMI). The standard electrocardiographic precordial (anterior) leads image the posterior wall of the left ventricle from the anterior perspective of the thorax. Acute infarction of this region manifests electrocardiographic changes that are frequently the reverse of the typical abnormalities of AMI. In this schematic example, lead V1 reveals ST segment depression with an upright T wave and prominent R wave. Use of the posterior lead V9 demonstrates ST segment elevation, consistent with AMI.

pain, particularly in patients with an initially normal nondiagnostic or possible ST segment mimicking syndrome (i.e., ST segment elevation potentially resulting from BER) ECG. Examining ST segment trends (measured every 20 seconds for at least the first hour) and automated serial ECGs (at least every 20 minutes) in ED patients with chest pain can significantly increase the sensitivity and specificity for detection of AMI (16%) and ACS compared with that of the initial ECG[73] (Fig. 76-20). In more than 600 patients admitted with nondiagnostic initial ECGs and symptoms consistent with ACS, 12 hours of continuous 12-lead ECG monitoring in a coronary care unit setting revealed that only serum cardiac marker elevation and presence of ST segment episodes (defined as ST segment elevation or depression more than 1 mm different from baseline that endured for at least 1 minute) predict cardiac death or MI.[74]

Measuring *QT dispersion* may facilitate risk stratification, assessment of therapeutic success, and monitoring of ongoing pharmacotherapy. *QT dispersion* is the calculated difference between the longest and shortest QT intervals on a 12-lead ECG. Ischemic myocardium has a prolonged repolarization time, and the QT interval measures time from ventricular depolarization to repolarization. Increased variability in measured QT intervals translates to greater QT dispersion, which reflects underlying regional ischemia. Comparing ACS or AMI patients with those found to be free of such disease reveals a difference between populations in QT dispersion values.

Body surface mapping increases the amount of electrocardiographic data for processing and decision-making. Whereas serial ECGs and ST segment trend monitoring increase the period of time over which data are collected on a 12-lead ECG, body surface mapping increases the number of electrodes used to gather data and increases the vantage points from which the heart is evaluated. Various devices use between 40 and 120 leads. With an 80-electrode device, 64 chest and 16 back electrodes are applied in a vest-like fashion with self-adhering strips. Recording from all electrodes simultaneously, the body surface map enters ST segment elevation and depression data into a computer, which transforms the data into a color-coded torso image. With red representing ST segment elevation, blue signifying ST segment depression, and green reflecting normal, degree of disease is also expressed in terms of color intensity.[75–77] Body surface mapping may increase sensitivity for MI, especially in areas that are relatively electrically silent

Figure 76-20. Serial electrocardiography. **A,** Representative example of lead III in a patient with chest pain and an initially nondiagnostic electrocardiogram depicting the evolution of ST segment elevation acute myocardial infarction (STE AMI). **B,** Representative example of lead V2 in a patient with the left ventricular hypertrophy pattern. Serial sampling of this patient with ongoing chest pain and a confounding electrocardiographic pattern reveals the progression to STE AMI. **C,** Representative example of lead V3 in a patient with left bundle branch block and evolving AMI. **D,** Representative examples of lead III in a patient with chest pain and noninfarctional STE; note the lack of change (degree of elevation as well as morphology of elevation) over time in this patient with benign early repolarization.

on the 12-lead ECG (e.g., posterior and lateral walls of the left ventricle and the right ventricle) and in patients with underlying LBBB.[75–77]

Limitations of Electrocardiography in Acute Coronary Syndrome

The sensitivity and specificity of a single ECG for AMI are approximately 60% and 90%, respectively. Serial ECGs in the setting of continued or recurrent pain increase the diagnostic utility.[78] The initial ECG is nondiagnostic in approximately half of the patients presenting to the ED who are ultimately diagnosed with AMI. Moreover, nondiagnostic and even normal ECGs do not exclude the diagnosis for AMI since around 20% of patients ultimately diagnosed with AMI have nondiagnostic ECGs earlier in their course. As time elapses from symptom onset to ECG recording, the ability of the ECG to exclude AMI does not markedly increase.[48] Thus, a single normal or nondiagnostic ECG does not ensure absence of ACS, even if the ECG was recorded well after the onset of symptoms. In patients being evaluated for ACS, only serial electrocardiography, combined with serial cardiac marker determinations, can exclude AMI, and even then UA without actual myocardial necrosis may be present.

Chest Radiography

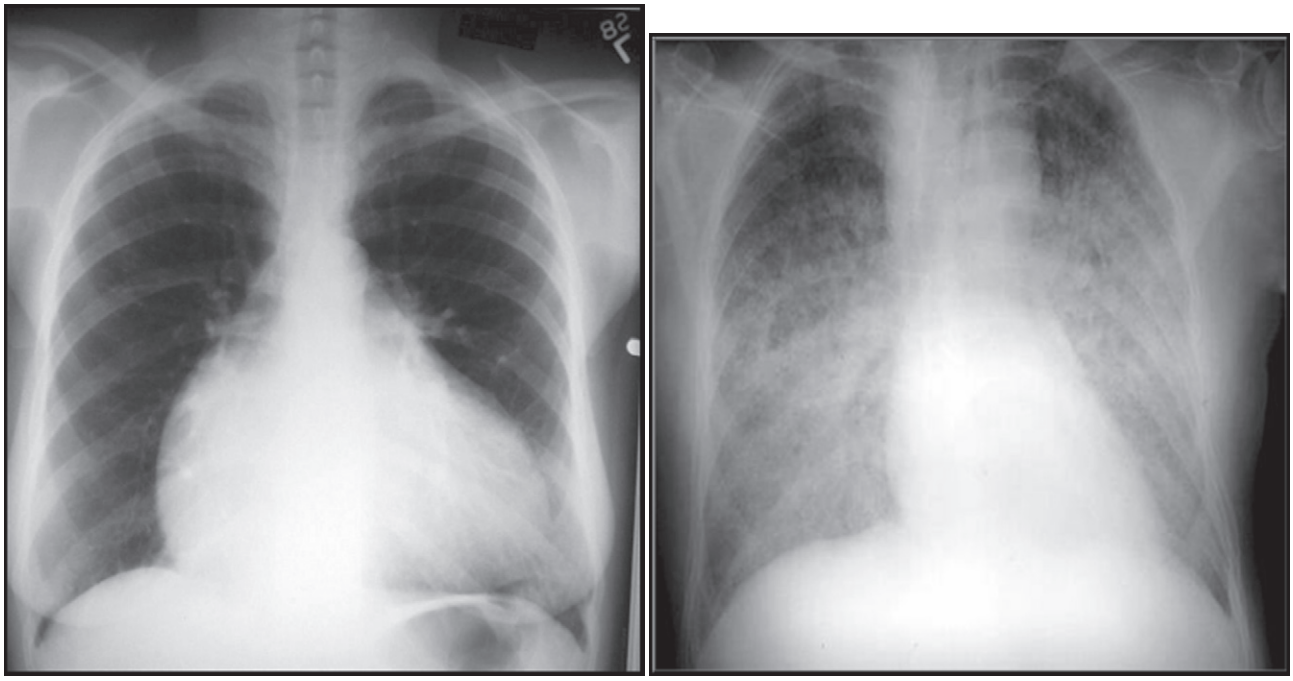
The chest radiograph provides information concerning the application of therapies (i.e., an evaluation of mediastinal width in the consideration of fibrinolytic agent use and the determination of pulmonary congestion in the consideration of acute parenteral beta-adrenergic blocking therapy). Further, the presence of CHF on the chest radiograph increases risk in AMI patients who may benefit from an aggressive therapeutic approach.

There is radiographic evidence of pulmonary congestion in approximately one third of AMI patients. AMI patients who develop CHF have increased mortality, as reported by the Killip classification. The chronicity of the CHF syndrome may also be suggested by the heart size. Patients who present with AMI complicated by pulmonary edema and have a normal heart size most often have no past history of CHF. In fact, AMI is the most frequent cause of pulmonary edema with a normal cardiac size. In other instances, patients with AMI and cardiomegaly with or without pulmonary edema frequently have a preexisting history of CHF, anterior wall infarct, and multiple-vessel CAD (Fig. 76-21).

Serum Markers

Biochemical markers play a pivotal role in the diagnosis, risk stratification, and guidance of treatment. The European Society of Cardiology and ACC define the criteria for AMI diagnosis on biochemical grounds since specific markers, particularly the troponins, indicate irreversible cell damage.[11] In the past, detection of AMI by characteristic enzyme elevations over 48 to 72 hours was sufficient to establish the diagnosis of AMI because there was essentially no specific therapy to reverse or prevent the developing myocardial necrosis. The evolution of fibrinolytic therapy and acute intervention create significant pressure to identify patients with AMI.

For patients with a nondiagnostic ECG, early elevation of serum markers of myocardial necrosis confirms a presumptive diagnosis of NSTEMI. Caution is advised, however, when a single serum marker is not elevated. This single test is too insensitive to be used to support a decision that the patient can be discharged, or that no acute coronary event has occurred. The patient's history remains the most vital portion of the diagnostic evaluation of potential ACS. Serial testing substan-



A B

Figure 76-21. Chest radiographs in patients with acute coronary syndrome. **A,** Cardiomegaly. **B,** Borderline cardiomegaly with pulmonary edema.

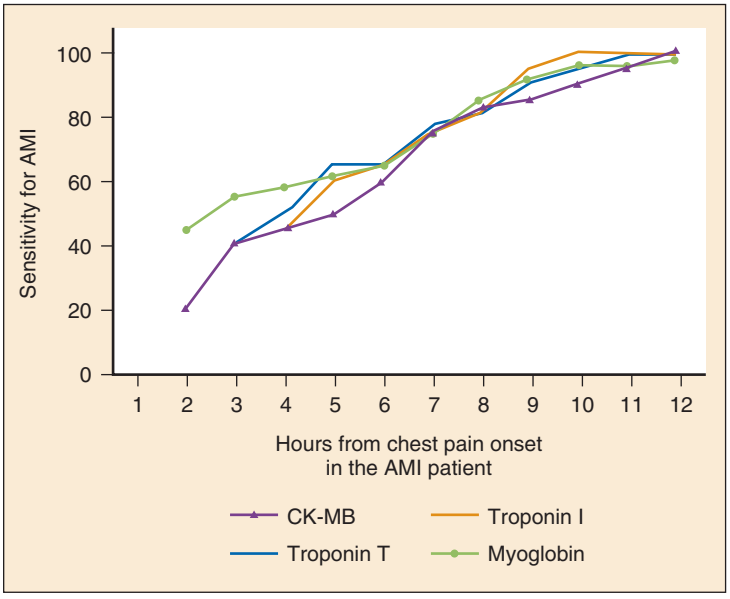


Figure 76-22. Serum marker sensitivity relative to the time of onset of chest pain in the patient with acute myocardial infarction. Data obtained from the medical literature. AMI, acute myocardial infarction; CK-MB, creatine phosphokinase MB fraction.

tially improves the sensitivity of these tests (Table 76-6 and Fig. 76-22).[79]

Troponins

Because of their superior sensitivity and specificity compared with CK-MB, cardiac troponins are the best markers for myocardial cell injury. Two myocardium-specific proteins, myocardial troponin I (TnI) and troponin T (TnT), precede the release of CK-MB into the serum. The cardiac troponins are genetically distinct from troponin forms found in other muscle tissue, rendering them highly cardiac specific. Monoclonal antibodies have little cross-reactivity with troponins from skeletal muscle. Troponins I and T are very similar in their diagnostic and prognostic utility as well as their serum kinetics and rates of rise and fall associated with myocardial ischemia, infarction, and ACS.

The biokinetics of troponin release relate to the location of the protein within the cell. Normally, small quantities of troponins are free in the cytosol, and the majority is entwined in the muscle fiber. After injury, a biphasic rise in serum troponins corresponds to early release of the free cytoplasmic proteins, followed by a slower and greatly prolonged rise with breakdown of the actual muscle fiber. The slow destruction of the myocardial cell contractile proteins provides a sustained release of the troponins for 5 to 7 days. Serum troponin concentrations begin to rise measurably in the serum at about the same time as CK-MB elevations become detectable, as early

Table 76-6 Summary of Test Performance Studies of Diagnostic Technologies for Acute Coronary Syndrome in the Emergency Department

TECHNOLOGY	DISEASE STUDIED	NO. OF STUDIES (SUBJECTS)	POPULATION CATEGORY OF STUDIES*	STUDIES PREVALENCE RANGE, %	DISEASE SENSITIVITY,† % (95% CI)	DISEASE SPECIFICITY,† % (95% CI)
Creatine kinase (single)	AMI	12 (3195)	I/II/III/IV	7–41	37 (31–44)	87 (80–91)
Creatine kinase (serial)	AMI	2 (786)	I	26–43	69–99	68–84
CK-MB (presentation)	ACS AMI	1 (1042) 19 (6425)	III I/II/III/IV	20 6–42	23 42 (36–48)	96 97 (95–98)
CK-MB (serial)	ACS AMI	1 (1042) 14 (11,625)	III I/II/III/IV	20 1–43	31 79 (71–86)	95 96 (95–97)
Myoglobin (presentation)	AMI	18 (4172)	I/II/IV	6–62	49 (43–55)	91 (87–94)
Myoglobin (serial)	AMI	10 (1277)	I/II/IV	11–41	89 (80–94)	87 (80–92)
Troponin I (presentation)	AMI	4 (1149)	II/III/IV	6–39	39 (10–78)	93 (88–97)
Troponin I (serial)	AMI	2 (1393)	III/IV	6–9	90–100	83–96
Troponin T (presentation)	AMI	6 (1348)	II/III/IV	6–78	39 (26–53)	93 (90–96)
Troponin T (serial)	AMI	3 (904)	I/III/IV	5–78	93 (85–97)	85 (76–91)
CK-MB and myoglobin combination (presentation)	AMI	3 (2283)	II/IV	9–28	83 (51–96)	82 (68–90)
CK-MB and myoglobin combination (serial)	AMI	2 (291)	IV	11–20	100	75–91
Exercise stress ECG	ACS	2 (312)	III	6–10	70–100	82–93
Rest echocardiography	ACS AMI	2 (228) 3 (397)	III I/III	3–30 3–30	70 (43–88) 93 (81–91)	87 (72–94) 66 (43–83)
Stress echocardiography	AMI	1 (139)	III	4	90	89
Sestamibi (rest)	ACS AMI	3 (702) 3 (702)	III 2–12	9–17 92 (78–98)	81 (74–87) 67 (52–79)	73 (56–85)

*Results from meta-analysis of several studies, with random effects calculations unless otherwise indicated.
†Point estimate from a single study or a range of reported values; meta-analysis not performed.
ACS, acute coronary syndrome; AMI, acute myocardial infarction; CI, confidence interval; CK-MB, creatine phosphokinase MB fraction; ECG, electrocardiogram.
Modified from Pope JH, Selker HP: Diagnosis of acute cardiac ischemia. Emerg Med Clin North Am 21:27, 2003.

as 3 hours after onset, but troponin levels remain elevated for 7 days or more.

The cardiac-specific troponins, determined serially, are highly sensitive for the early detection of myocardial injury. A positive test result is associated with significant risk, and serial negative results predict low risk.[80] A single troponin measurement on presentation, however, has limited utility in excluding AMI and no ability to detect UA without infarction because cell injury is required and because of the time delay in the rise in levels (which may not be detected until 10 hours after symptom onset in some AMI patients).[79] Serial measurements, particularly when performed at least 6 hours after symptom onset, markedly improve the sensitivity of the cardiac troponins for AMI, and the pattern of rise may assist in determining the acuity of the event. The sensitivity of TnT approaches 50% within 3 to 4 hours of the event. The test result is positive in about 75% of patients at 6 hours after onset of symptoms; at 12 hours, the test is almost 100% sensitive. A single troponin determination, however, may have utility in evaluating patients who present several days into a syndrome of atypical chest pain that is felt possibly, but unlikely, to represent an ACS event. Further, a single serum troponin value may also have utility in elderly patients with nonspecific presentations for AMI, such as weakness, confusion, or altered mentation.

Because cardiac troponins are not found in the serum of healthy individuals, an abnormally elevated level is defined as that which exceeds the 99th percentile in a healthy population. Sensitivity to detect abnormal low troponin levels, however, varies among the multiplicity of existing assays, particularly with respect to TnI. Physicians therefore must be familiar with the sensitivity and limitations of the particular assay used at their institution and the cutoff concentrations for clinical decisions.[6]

Multiple studies have indicated that even very low levels of troponin elevations are associated with significant adverse clinical prognosis.[81,82] In a number of studies, up to 33% of patients diagnosed with UA with normal CK-MB levels had elevated troponin levels, indicating the markers' improved sensitivity for myocardial cell injury.[83] The fact that the risk of these patients for cardiac events and mortality is similar to that of the patients diagnosed with AMI by traditional WHO criteria led to the redefinition of AMI on the basis of biochemical markers. On the basis of data from the Thrombolysis in Myocardial Infarction-IIIB study, there is almost a linear correlation between increasing troponin levels and risk of cardiac events and mortality, even in patients with a nondiagnostic ECG and normal CK-MB levels.[83,84] In a review of over 7000 NSTEMI patients, troponin levels identified patients at low mortality risk.[85] Small elevations of troponin may be used as an objective measure of "preinfarcts" that characterize UA and are associated with increased risk of infarction in the near term. Marked elevations in troponin consistent with AMI represent further progression along the continuum of ACS toward "traditional" AMI.[86]

Cardiac troponins may also guide ACS treatment. Data from the Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy-Thrombolysis in Myocardial Infarction (TACTICS-TIMI 18) trial suggest that patients with elevated troponin who are treated with an early invasive interventional strategy within 48 hours have a marked improvement in recurrent ischemia, infarction, and mortality both in the short term and at 6 months.

These studies included patients without major ECG criteria for immediate interventional reperfusion strategies.[70] The use of glycoprotein IIb/IIIa inhibitors (GPIs) in patients with elevated troponins may prevent early complications in patients with ACS. It is likely that the improved sensitivity of troponin has captured a high-risk ACS population not previously diagnosed or treated. Importantly, elevated troponin levels identify those patients with UA or NSTEMI who stand to gain the greatest benefit from an early invasive strategy with coronary angiography and revascularization.[81,87]

Elevated troponin levels occur in a variety of cardiac and noncardiac conditions unrelated to the typical ACS and AMI pathophysiology. Cardiac conditions that can result in significant increased troponin levels in patients without evidence for ACS include myocarditis, pericarditis, CHF, LVH, and nonpenetrating cardiac trauma. While the presence of elevated troponin levels in these conditions might be considered false-positive results, data support the contention that the source of these levels is underlying noninfarction myocyte injury that occurs with these conditions. Moreover, elevated troponin levels in these non-ACS cardiac conditions have prognostic significance.[88,89]

Troponin elevations can also be seen in noncardiac conditions including pulmonary embolism (PE), sepsis, and renal insufficiency. Troponin elevation may result from right ventricular dysfunction and myocyte injury in the case of submassive and massive PE, and is a significant predictor of adverse outcome.[88,89] Similar elevated troponin levels are reported in patients with sepsis and critically ill patients with multiple organ system failure.[90–92]

Elevated troponin levels are commonly seen in asymptomatic patients with end-stage renal disease. This finding may relate to the high prevalence of cardiac disease in this population rather than any reduced renal clearance, and may still represent evidence of subclinical myocardial damage.[92,93] The TnT isoform is associated with elevated levels in renal failure more than TnI, particularly in patients on hemodialysis. Elevated troponin levels in the setting of renal failure are associated with increased risk of death and major cardiac and vascular morbidity and should not be ascribed to chronic renal failure unless old records are present to corroborate that the elevated troponin level is actually the patient's normal baseline level.[93]

Creatinine Phosphokinase

Creatinine phosphokinase (CK) is found in large quantities not only in cardiac muscle but also in skeletal muscle, brain, kidney, lung, and the gastrointestinal tract. Myocardial cells are by far the most abundant potential sources of CK-MB; thus, the appearance of CK-MB in the serum is highly suggestive of MI.[94] The CK-MB fraction remains the best alternative to the troponins as a cardiac marker.[95] In the setting of AMI, CK-MB is released and is detectable in the serum as early as 3 hours after onset of the necrosis. CK-MB characteristically peaks at 20 to 24 hours and becomes normal within 2 to 3 days after injury. Elevated CK-MB values identify a patient at considerable risk for a poor outcome but do not correlate well with infarct size. Unfortunately, skeletal muscle does contain small amounts of CK-MB, particularly the pelvic musculature. Abnormal CK-MB elevations may be seen in trauma, muscular dystrophies, myositis, rhabdomyolysis, and after extremely vigorous exercise.

The sensitivity of a single CK-MB determination in diagnosing AMI is dependent on the elapsed time from chest pain onset. Values obtained within 3 hours of onset are poor diagnostic tools, with a sensitivity of only 25 to 50%. CK-MB determinations obtained beyond this 3-hour time period have increasing sensitivities for the diagnosis of AMI, ranging from 40% to nearly 100%, particularly when obtained 12 to 16 hours after onset.[79] As a result, the use of single determinations of CK-MB is of little value in excluding ACS. Serial sampling, even over relatively short time periods (12 hours), increases sensitivity considerably, particularly when considered with serial electrocardiography and repeated assessments of the patient. Diagnostic utility is also improved by requiring that the CK-MB value not only be elevated but also be at least 5% of the total CK value. False-positive elevations can occur with noncoronary conditions such as pericarditis, myocarditis, skeletal muscle disease, rhabdomyolysis, trauma, and exercise.

Myoglobin

Myoglobin, a small protein (17,000 daltons) found in muscle tissue, is rapidly released into the circulation after cellular injury. In cases of myocardial injury, myoglobin rises in the initial 1 to 2 hours, peaks at 5 to 7 hours, and returns to baseline by 24 hours. Because of its rapid rise, myoglobin is attractive as an early indicator of myocardial injury. Myocardial myoglobin, however, is not currently distinguishable immunologically from skeletal muscle myoglobin. Thus, myoglobin is elevated in any clinical situation involving the skeletal muscle, such as trauma, exercise, and significant systemic illness. In addition, myoglobin increases are seen in patients with renal failure because of reduced clearance.

The sensitivity of an initial myoglobin at presentation for AMI varies from as low as 21% to as high as 100%.[79] Serial testing at 2 to 4 hours after presentation significantly improves the assay's diagnostic power. A doubling of the level as soon as 1 to 2 hours after the initial measurement greatly increases the sensitivity for the diagnosis of AMI, but this approach is very nonspecific.[79] The value of myoglobin may be in its excellent negative predictive power for AMI and its early rise kinetics compared with other markers. Although some evidence suggests that a normal myoglobin value 2 hours after presentation may be used safely to rule out active AMI but not ACS, myoglobin has largely fallen out of favor.[79]

Other Cardiac Markers

Troponin, CK, and myoglobin are all measures of myonecrosis. Biochemical assays for potential new cardiac markers for necrosis are being developed in the hope of finding ones with improved sensitivity, risk determination capability, and prognostic power. One such new cardiac-specific myonecrosis marker is heart-type fatty acid–binding protein. Other potential markers for utility in ACS include those that may detect ischemia prior to actual necrosis, and plaque instability or inflammation.

Episodes of ischemia can result in biochemical changes prior to actual irreversible cell necrosis. Ischemic-modified albumin (so-called cardiac albumin) is a potentially useful ACS biomarker that reportedly detects early myocardial ischemia rather than the later myocyte necrosis, and may have even earlier elevation than myoglobin. Other potential ischemia markers include unbound free fatty acids and whole blood choline levels. Markers of hemodynamic status, including the natriuretic peptides, may also have utility in ACS.[96] These markers such as B-type natriuretic peptide (BNP) and NT-proBNP are released from cardiac myocytes in response to increases in ventricular wall stress. BNP is most commonly used as a marker for CHF, but is a useful adjunct to the standard cardiac markers, and has good predictive power for recurrent ACS events and cardiac-related deaths, as well

as CHF exacerbations, in patients with AMI.[97,98] Moreover, the natriuretic peptides are excellent predictors of both short- and long-term mortality in patients with UA, NSTEMI, and STEMI.[97,98]

Given the underlying pathophysiology of ACS, a variety of biochemical markers for inflammation and plaque instability may prove useful in evaluating risk of a cardiac event. Chief among these is the inflammatory marker C-reactive protein (CRP) and high-sensitivity CRP (hsCRP), which have long-term prognostic value for cardiac events in healthy individuals as well as potential short-term prognostic value when combined with other markers for ACS. Other inflammatory markers include interleukin-6 and tumor necrosis factor alpha. Elevated plasma levels of myeloperoxidase, an abundant leukocyte enzyme found in vulnerable coronary plaques that have ruptured, predict short-term risk of adverse cardiac events even with negative cardiac troponin and no evidence of myocardial necrosis.[99]

Multiple Marker Strategies

Diagnostic, risk stratification, and prognostic accuracy might be enhanced by the utilization of multiple markers for AMI and ACS.[100] The combination of CK-MB and myoglobin measurement has a sensitivity from 62 to 100% and specificity from 72 to 89% for AMI on presentation. Serial measurements of these markers significantly improve the performance of this combined marker approach.[79] McCord reported on the utility of a multimarker strategy using the early but noncardiac-specific marker myoglobin with the more specific and prognostic marker TnI. In 817 patients evaluated for ACS in the ED, the combined marker approach had a sensitivity of 96.9% and negative predictive value of 99.6% for AMI when applied at presentation and at 90 minutes.[101] Similarly, the utility of a three-marker approach (CK-MB, TnI, and myoglobin) in an accelerated critical pathway reported 100% sensitivity and 100% negative predictive power for AMI in 1285 patients assessed for ACS.[102] In a large series of ED chest pain patients with an initial nondiagnostic ECG, a 2-hour delta CK-MB combined with a 2-hour delta troponin I had a sensitivity of 93% and specificity of 94% for AMI.[103] Other multimarker strategies include combining measurement of a conventional marker for myocardial necrosis (troponin) with a marker for inflammation (CRP) and a hemodynamic marker (BNP). Many of these multimarker strategies, however, have low specificity. As a result, a positive multimarker test requires confirmation with later-appearing, more definitive cardiac biomarkers.[6] Thus, the multimarker approach does not offer substantial benefit over the individual biomarker determinations and is therefore not recommended.

Echocardiography

Two-dimensional echocardiography detects regional wall motion abnormality associated with ACS. Impaired myocardial contractility can range from hypokinesis to akinesis. Impaired myocardial relaxation during diastole results in decreased ventricular distensibility. After AMI, paradoxical wall motion and decreased ejection fraction observed during systole indicates the subsequent loss of muscle tone from necrosis.

Particularly in individuals with nondiagnostic ECGs, the presence of regional systolic wall motion abnormalities in a patient without known CAD is a moderately accurate indicator of acute myocardial ischemia or infarction, with a positive predictive accuracy of about 50%.[6] The age of wall motion abnormalities, however, often cannot be determined without prior echocardiograms.

The absence of segmental abnormalities (presence of either normal wall motion or diffuse abnormalities) has a significant high negative predictive value, as high as 98% for cases of suspected MI.[6] Moreover, segmental wall motion abnormalities can be seen not only in the zone of acute infarction but also in regions of ischemic stunning. Resting echocardiography provides an assessment of global and regional function, an important predictor of complications and mortality in patients with ACS. Data from the ACC/AHA task force indicate that patients with mild and localized as opposed to extensive wall motion abnormalities have a low risk of ACS complications.[6] In addition, echocardiography can help evaluate other causes of clinical presentations mimicking ACS, including valvular heart disease, aortic dissection, pericarditis, mitral valve prolapse, and pulmonary embolus. Finally, echocardiography is an important tool to assess for various complications of AMI, including acute mitral regurgitation, pericardial effusion, ventricular septal and free wall rupture, and intracardiac thrombus formation.

Technical limitations restrict the use of echocardiography in the ED. These limitations include the quality of the study and the expertise of the reader interpreting the study at the patient's bedside. Injury involving more than 20% of the myocardial wall is required before segmental wall motion abnormalities can be detected echocardiographically.[11] In addition, the inability of the two-dimensional echocardiogram to distinguish between ischemia, AMI, or old infarction and the potential absence of wall motion abnormality in nontransmural infarctions can further limit the usefulness of two-dimensional echocardiography.

Stress echocardiography, as opposed to resting echocardiography, can detect CAD as well as assess cardiac function early after an AMI. This can be performed with graded increases in cardiac workload, either by standardized exercise or pharmacologic adrenergic stimulating agents such as dobutamine. In addition, vasodilating agents, such as dipyridamole and adenosine, induce heterogeneous myocardial perfusion and reveal functional myocardial ischemia in susceptible patients. Stress echocardiography is superior to conventional treadmill testing for CAD in women. Graded dobutamine stress echocardiography assesses myocardial viability and ventricular function within the first few days after an AMI. Clinical studies of patients with nondiagnostic ECGs, negative markers, and negative rest echocardiography suggest a role for emergency pharmacologic stress echocardiography as a provocative test after a period of observation with at least two marker and ECG assessments in a chest pain or ED observation unit.[104,105]

Myocardial contrast echocardiography (MCE) uses microbubble ultrasonic contrast agents to assess microvascular perfusion and regional function with echocardiography. MCE evaluation of perfusion and regional function is able to accurately risk stratify ED patients with chest pain and nondiagnostic ECGs even before serum markers are available.[106] Other smaller studies have reported low rates of adverse cardiac events in chest pain patients with normal MCE findings following a nondiagnostic ECG and negative serum markers.[107] The clinical value of MCE in the ED, like resting and stress echocardiography, remains uncertain.

Myocardial Scintigraphy

Radionuclide tracer injection and scintigraphy, such as with single-photon emission computed tomography (SPECT), allows real-time assessment of myocardial perfusion and function. Technetium-99 sestamibi has a slow redistribution to ischemic myocardium. This property allows immediate injection and imaging, which detects altered distribution consistent

with some form of ischemic heart disease, followed by subsequent scanning, which provides more definitive data regarding the particular subtype of ACS. In patients with a normal initial study, the likelihood of ACS is extremely low. In patients with an initial study revealing abnormal distribution (i.e., reduced uptake) of the tracer, some form of ischemic heart disease is likely. Subsequent imaging then reveals one of two patterns: normal redistribution (normal uptake) or continued reduced uptake. The redistribution pattern is consistent with active coronary ischemia and the continued reduced uptake is found in patients with MI, either remote or recent. Myocardial scintigraphy has promising positive and negative predictive values for cardiac events with high sensitivity and a good specificity for CAD.[108,109]

Immediate myocardial scintigraphy is useful in detecting ACS and risk of cardiac events in selected patients presenting at the ED with atypical chest pain, nondiagnostic ECGs, and low to moderate risk of AMI. Multiple studies find a relatively high incidence of cardiac events, presence of AMI, and need for revascularization in patients with a positive nuclear scan. The probability of a cardiac event is 10-fold higher in patients with abnormal scans than in patients with a normal scan. The incidence of cardiac events with a normal scan is lower than 1% for the 30-day period following the index study.[110] Myocardial scintigraphy can reduce the number of patients admitted from the ED with chest pain who are ultimately determined not to have ACS without reducing appropriate admissions for patients with ACS.[111]

Myocardial scintigraphy studies are difficult to perform early after the patient's presentation to the ED. Radioisotopes and the personnel to administer them may not be immediately available and physician interpretation experience quite variable. Studies of ED perfusion imaging are resting studies, rather than more provocative stress (exercise or pharmacologically induced) perfusion studies.

Computed Tomography

Computed tomography imaging is a noninvasive imaging modality to assess for ACS. Electron beam computed tomography (EBCT) was introduced nearly two decades ago to screen for coronary calcium as a marker of underlying atherosclerotic heart disease and risk of ACS.[112] While calcium scoring systems exist to assess cardiovascular disease risk, there are few studies that have examined the role of EBCT in the assessment of patients with acute chest pain.[113] The few studies that examine EBCT demonstrate good sensitivity and excellent negative predictive value for subsequent cardiac events, but have design limitations.[114,115]

Technical advances in imaging include multidetector computed tomography (MDCT) with multislice 16-, 64-, and 256-slice CT scanning, as well as ECG-gated MDCT. These may revolutionize noninvasive cardiovascular imaging in the setting of ACS. These enhancements allow imaging of the beating heart with minimal motion artifact and accurate resolution to the level of the coronary vessels. Improvements in image reconstruction and reformatting software allow not only direct visualization of the coronary arteries, or CT angiography (CTA), but also can provide functional information on perfusion, wall motion, and left ventricular ejection fraction.

The utility of MDCT in the ED focuses on two potential protocols, a coronary CTA by MDCT and a more global "triple rule-out" thoracic or chest MDCT.[116,117] Noninvasive coronary CTA by MDCT performs well when compared with standard invasive coronary angiography.[116,117] Cardiac CT provides excellent detection of calcified and noncalcified coronary artery plaque and stenosis, indicative of atherosclerosis and risk of ACS.[112] CTA may be less useful, however, in a patient with preexisting CAD and extensive coronary calcifications, or those who have undergone prior interventions and have resulting imaging artifacts from coronary stents.[117]

The "triple rule-out" or global assessment protocol refers to the use of CT to assess for three life-threatening causes of chest pain, including pulmonary embolism and aortic dissection as well as ACS. The scanning protocol is a compromise between coronary CTA and pulmonary embolism/aortic dissection with larger field-of-view requirements and alterations in contrast delivery. A high-resolution, fast MDCT (64-slice or higher) is necessary so that adequate contrast enhancement, imaging, and visualization of the pulmonary vessels, coronary arteries, and aorta can all be obtained.

The literature regarding the use of cardiac CT in patients with acute chest pain is limited. A study of 69 ED patients with chest pain and nondiagnostic ECGs noted that an ECG-gated 16-slice MDCT had a 96% negative predictive value when compared to the final diagnosis of CAD. Three patients were diagnosed by CT with other causes for their chest pain, including pneumonia and pulmonary embolism.[118] A study of 64-slice MDCT coronary angiography in 92 low-risk ED patients for ACS reported a sensitivity of 86% and specificity of 92%, which is comparable with stress nuclear imaging.[119] Another report using a 64-slice MDCT in 103 patients admitted to the hospital for ACS with nondiagnostic ECGs and negative cardiac markers noted a 100% negative predictive power for CTA.[120]

The clinical indications for and utility of coronary CTA in the ED, as well as global assessment "triple rule-out" MDCT protocols, require further investigation. Impediments include the limited availability of high-end MDCT technology, the unknown economic and workflow impact of increased MDCT utilization, the lack of guidelines for the use of dedicated coronary CTA or the more global assessment "triple rule-out" MDCT for acute chest pain, and concerns regarding radiation exposure.

Graded Exercise Testing

Exercise stress testing for ED patients is feasible. In over 1000 patients with low-risk chest pain (5% incidence of CAD) who underwent exercise testing after negative serial markers and 9 hours of ECG monitoring in the ED,[121] stress testing had a negative predictive value of 98.7% for the diagnosis of ACS or cardiac event within 30 days. An abbreviated ED-based "rule out MI" protocol followed by mandatory stress testing appears to be an effective diagnostic method for the detection of symptomatic CAD in low- to moderate-risk patients.[122]

ACC/AHA guidelines on exercise testing state that such testing can be performed when patients are free of active ischemic or heart failure symptoms for a minimum of 8 to 12 hours.[123] Immediate stress testing without the rule-out MI evaluation, however, may be safe and cost effective in patients with chest pain felt possibly to be of cardiac origin, but with low suspicion of ACS. To determine the safety and utility of immediate exercise testing in the ED, 1000 low-risk patients underwent immediate exercise testing with no adverse effects.[124] Six hundred forty patients (64%) had negative exercise test results, all of whom were discharged home from the ED. The rate of CAD diagnosis or cardiac event within 30 days was 29% for the positive stress group, 13% for the nondiagnostic group, and 0.3% for the negative stress group. In total, 30-day follow-up was achieved in 888 (89%) patients and revealed no mortality in any of the three groups.

Graded exercise testing in the ED at most institutions is not available continuously. The mortality rate is extremely low (1 in 2500), but absolute contraindications include recent AMI (within 2 days), high-risk UA, uncontrolled cardiac dysrhyth-

mias causing symptoms or hemodynamic compromise, symptomatic severe aortic stenosis, uncontrolled symptomatic heart failure, acute pulmonary embolus or infarction, acute myocarditis or pericarditis, and acute aortic dissection.[123]

Patients with a high pretest probability of CAD have a significant rate of false-negative results, and patients with a low pretest probability have a significant rate of false-positive stress test results. The specificity of the test is decreased in the presence of underlying electrocardiographic abnormalities secondary to medications, electrolyte abnormalities, LVH, or artifact. A false-positive test outcome may result from aortic stenosis or insufficiency, hypertrophic cardiomyopathy, hypertension, arteriovenous fistula, anemia, hemoglobinopathies, low cardiac output states, chronic obstructive pulmonary disease, digitalis toxic states, LVH, hyperventilation, mitral valve prolapse, and bundle branch blocks. An increase in the rate of false-positive test results in women tends to decrease the usefulness of graded exercise testing in this population.

ED-BASED CHEST PAIN CENTERS

These specialized units for the lower-risk population are utilized in 30% of the EDs in the United States. The goal of the chest pain center (CPC) is to provide an integrated approach to patients with chest pain or potential ACS that includes rapid triage, early identification, and treatment of high-risk ACS patients and risk stratification for low-risk patients. Guidelines and critical pathways play an essential role in the CPC process. Staff, resources, and space are often dedicated for a CPC, but the unit can be part of an ED observation unit or a "virtual" unit located near or within the ED.

A CPC protocol should rapidly direct patients with possible ACS into a high-level treatment area where an ECG and clinical examination can be obtained within the first 10 minutes. Patients with STEMI requiring immediate reperfusion therapy or with UA in need of further intervention can be identified quickly. This goal can be combined with an efficient ED evaluation of patients with low to moderate risk of ACS. The greatest medical benefit from the CPC is the early identification of patients with AMI and UA; the most significant financial impact is the reduction of inappropriate hospital admissions.

The National Heart Attack Alert Program (NHAAP) of the National Heart, Lung, and Blood Institute (NHLBI) challenges clinicians to provide care for ED patients with clear symptoms and signs of AMI within 30 minutes of arrival. The NHAAP recommends (1) a specific area of the ED equipped for assessing and monitoring patients potentially having ischemia, including standing orders for initial diagnostic and therapeutic actions; (2) a standing protocol with inclusion and exclusion criteria for reperfusion therapies, including language authorizing the physician to administer fibrinolytic therapy or to mobilize the catheterization laboratory for prespecified cases; (3) a clear demarcation of responsibilities for all members of the reperfusion team; and (4) policies and procedures for the treatment and possible transfer of patients with ST segment elevation AMI who are ineligible for fibrinolytic therapy.

These recommendations highlight the advantages of a target "door-to-drug" time of 30 minutes (or less) or a door-to-catheter (where percutaneous procedures are available) time of 90 minutes (or less) for patients with typical presentations of AMI with ST segment elevation. For example, the CPC can have assigned nursing personnel who rapidly evaluate the patient with chest pain with a 12-lead ECG, as well as screening vital signs and cardiac monitoring, and deliver the ECG directly to a clinician capable of making a decision about activation of the catheterization laboratory or administration of fibrinolytic therapy.

The CPC may also be used as an observation and evaluation unit where patients with chest pain and low to intermediate clinical likelihood of ACS can be monitored with electrocardiography, ST segment trending, serial 12-lead ECGs, and sequential serum markers. In addition, many CPCs now employ further ACS evaluation with stress testing, echocardiography, or myocardial scintigraphy before disposition.[125] Significant cost savings occur, with typical charges and actual costs ranging from 20 to 50% of the costs for the usual inpatient approach.

The Chest Pain Evaluation in the Emergency Room (CHEER) investigators in a prospective, randomized trial compared a CPC with the traditional hospital admission to rule out MI.[126] Over a 16-month period, patients with chest pain at intermediate ACS risk on the basis of history, examination, and ECG were randomly assigned to either CPC or hospital admission. CPC patients underwent serial serum marker and ECG determinations over a minimum of 6 hours. If investigations were negative and the course was uncomplicated, patients were elevated with an exercise stress test, nuclear stress test, or stress echocardiography. If the results of this evaluation were positive, the patient was admitted; if negative, the patient was discharged with cardiology follow-up within 72 hours. In the CPC group, all events occurred among those with a positive stress test result; no cardiac events occurred in the negative stress test group after ED discharge. Admissions were reduced by 45.8%.

A chest pain accelerated diagnostic protocol approach to low- to intermediate-risk patients can be feasible, safe, and effective.[121] In a study of comprehensive diagnostic 9-hour evaluation (Heart ER Program) for 1010 patients with possible ACS, patients underwent serial testing with the following: CK-MB at presentation, 3, 6, and 9 hours; continuous 12-lead ECGs; and serial ST segment trend monitoring. Two-dimensional echocardiography and graded exercise testing were performed in the ED after the 9-hour evaluation.

Approximately 80% of patients with chest pain can be safely evaluated in the ED with ultimate discharge to home. The resources required for a successful CPC-based operation in which patients undergo rapid exclusion of ACS through serial testing, continuous monitoring, and immediate provocative stress testing are considerable. Although studies suggest that CPCs decrease the number of admissions, they may increase the number of patients seen in the ED for chest pain, and physicians may overuse the CPC accelerated diagnostic protocol approach in patients whom they would otherwise have discharged.[127] Other issues to consider include cardiologist support and the impact on primary care physicians.

MANAGEMENT OF ACUTE CORONARY SYNDROME

The pathophysiology of an acute coronary event includes (1) endothelial damage through plaque disruption, irregular luminal lesions, and shear injury; (2) platelet aggregation; (3) thrombus formation causing partial or total lumen occlusion; (4) coronary artery vasospasm; and (5) reperfusion injury caused by oxygen free radicals, calcium, and neutrophils. In patients with noninfarction ACS, spontaneous fibrinolysis of the thrombus occurs rapidly, minimizing ischemic insult; persistence of the occlusive thrombus, however, results in MI.

Relationship of Time to Treatment with Outcome

The beneficial effect of reperfusion is a function of the length of ischemic time. In the late 1970s, the wave front phenomenon of ischemic cell death hypothesized that myocardial

necrosis progresses from the subendocardium to the epicardium after coronary occlusion (Fig. 76-23).

Early patency resulting in myocardial salvage is the key benefit of emergent revascularization therapy using either fibrinolysis or primary angioplasty. Treatment within the first hours after symptom onset may result in substantial myocardial salvage. Delivered at a later time, from 2 to 12 hours after AMI onset, treatment may result in a modest yet significant benefit. The opening of the occluded artery causes less adverse ventricular modeling, reduces occurrence of ventricular aneurysm, increases blood flow to myocardium, and improves electrophysiologic stability. In the angiographic substudy of GUSTO, preserved left ventricular function and mortality at both the 24-hour and the 30-day end points related to angiographic patency at 90 minutes.[128] Fibrinolytic therapy of patients with AMI had significantly greater benefit for those treated within the first 1 or 2 hours compared with those treated later. In the Myocardial Infarction Triage and Intervention (MITI) trial, the mortality rate among patients treated within 70 minutes was 1.3% compared with 8.7% in those treated later.[129]

Substantial delays often occur between symptom onset and hospital-based initiation of fibrinolytic therapy. In 1991, the NHLBI launched the NHAAP to promote the rapid identification and treatment of AMI. The factors responsible for delay in the care of AMI patients are grouped by the NHAAP into three phases: patient-bystander, preadmission, and hospital. Patient-bystander factors are those that prevent immediate medical care through the emergency medical service (EMS) system. Median delays range from 2 to 6.5 hours; in fact, 26 to 44% of AMI patients delay more than 4 hours before seeking medical care. In all major studies evaluating patients' delay, the median time of arrival at hospital is delayed well beyond the critical first hour during the time period in which half of AMI deaths occur.

Preadmission delay factors occur from the time the patient decides to seek medical attention until the patient arrives at the ED. It is not uncommon for patients to call their primary care physician, which may delay definitive care significantly. Only half of patients with suspected AMI call the EMS system. Many transport themselves or wait for someone other than EMS personnel to take them to the hospital. Further complicating preadmission issues include wide variations in the availability and ability of EMS throughout the United States.

Further delays can occur between the time a patient arrives at the hospital and the initiation of acute revascularization therapy. Overall, the average time to fibrinolysis ranges from 45 to 90 minutes. The GUSTO trial demonstrated a median time from hospital arrival to treatment with fibrinolytic therapy of 70 minutes.[128] The AHA recommends that all patients with AMI receive fibrinolytic therapy within 30 minutes of arrival. Ideally, AMI patients who undergo primary PCI should have therapy initiated no later than 90 minutes after arrival.[7]

STEMI patients who receive hospital-based reperfusion therapies (fibrinolytic agent or PCI) progress through a sequence of steps that can define process time points (Fig. 76-24). Within each interval, various impediments to timely care can occur. Reducing delay times is applicable to all time points in the ED by addressing the four D's: door (events prior to arrival at the ED), data (obtaining the ECG), decision (arriving at the AMI diagnosis and deciding upon therapy), and "drug" (administering the fibrinolytic agent or passing the angioplasty catheter across the culprit lesion for PCI candidates).

Preadmission care providers may alert the ED to the impending arrival of a patient with a suspected AMI. A field 12-lead ECG may assist in diagnosis and decrease the reperfusion time. Self-transported patients with possible ACS should be evaluated by the triage nurse immediately. Development of hospital-based protocols and system response plans for identifying and rapidly treating patients reduces the amount of time to treatment. When using fibrinolysis in uncomplicated cases, the emergency physician should activate the hospital-based system for reperfusion. Checklists of inclusion and exclusion criteria for fibrinolytic therapy should be available. Fibrinolytic agents should be stored and administered in the ED. Nonconsultative communications prior to administration of the agent with family physicians, internists, or cardiologists may result in unnecessary delays. Medical consultative discussions prior to administration of therapy are warranted in complicated situations. In a system where fibrinolysis is the sole reperfusion therapy, the decision to administer is that of the emergency physician. In a system where the reperfusion strategy can involve either fibrinolysis or PCI, extremely rapid consultation with the treating cardiologist is ideal.

If the hospital offers primary PCI, many hospitals activate "STEMI alert" responses with an ST segment elevation AMI patient. Analogous to the "trauma alert," the cardiologist and catheterization laboratory personnel are immediately mobilized. Emergency physician activation of the catheterization laboratory demonstrates very high rates of accurate STEMI diagnosis with very low rates of false activation (i.e., the

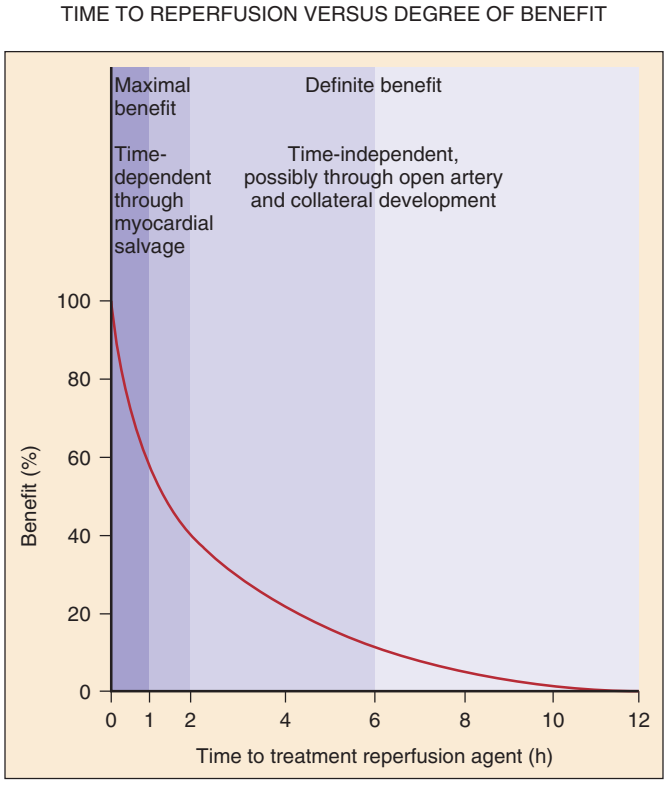


Figure 76-23. Relationship between time to reperfusion and benefit in ST segment elevation acute myocardial infarction. This figure depicts combined human and animal data and represents the time-dependent benefit anticipated, depending on the length of the interval between coronary artery occlusion and reperfusion. (Modified from Tiefenbrunn AJ, Sobel BE: Timing of coronary recanalization. Paradigms, paradoxes, and pertinence. Circulation 85:2311, 1992; Reproduced from U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Heart, Lung, and Blood Institute [NIH Publication No. 93-3278], September 1993, p 8.) ©1992 American Heart Association.

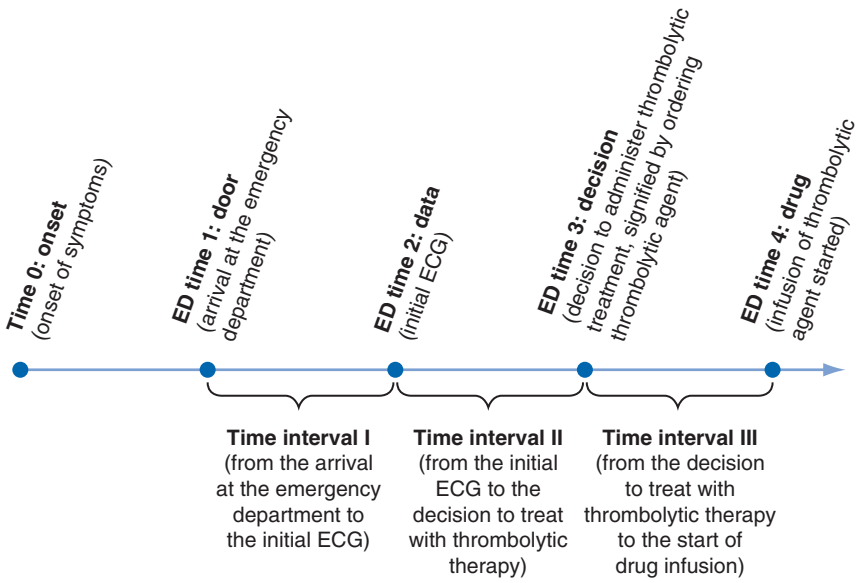


Figure 76-24. The four Ds of emergency department (ED)-based diagnosis and management of the patient with acute myocardial infarction (AMI). Shown are the process time points and intervals through which the patient with AMI passes until treatment in the emergency department. ECG, electrocardiogram. (From U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Heart, Lung, and Blood Institute [NIH Publication No. 93-3278], September 1993, p 10.)

STEMI mimicker) while markedly reducing the time to definitive therapy. Interhospital transfer of AMI patients for PCI, when they are also candidates for fibrinolysis, should be discouraged if definitive therapy (i.e., catheter placement across the culprit lesion) is likely to be delayed beyond 90 minutes.

Pharmacologic Intervention

Nitroglycerin

Nitrates decrease myocardial preload and, to a lesser extent, afterload. Nitrates increase venous capacitance and induce venous pooling, which decreases preload and myocardial oxygen demand. Direct vasodilation of coronary arteries may increase collateral blood flow to ischemic myocardium. Most studies of intravenous NTG in the setting of AMI are from the prefibrinolytic era. A meta-analysis of multiple small trials noted a 35% mortality reduction with intravenous NTG.[130]

Patients with possible ACS and a systolic blood pressure greater than 90 mm Hg should receive a sublingual NTG tablet (0.4 mg or 400 μg) on presentation. If symptoms are not fully relieved with three sublingual tablets, intravenous NTG should be considered. With bradycardia, hypotension, inferior wall AMI, and right ventricular infarction, a sudden decrease in preload associated with NTG can result in profound hypotension. Initial infusion rates at 10 μg/min are titrated to pain symptoms. The clinician should increase the infusion at regular intervals, allowing a 10% reduction in the mean arterial pressure if normotensive and a 20 to 30% reduction if hypertensive. Sublingual bolus therapy, the use of additional sublingual NTG in the setting of intravenous NTG infusions, more rapidly increases the serum level of the medication with delivery of 400-μg boluses. Maximal benefit is probably achieved at 200 μg/min, although certain patients may receive additional benefit at higher infusion rates.

Morphine

Morphine is a potent opioid analgesic with weak sympathetic blockade, systemic histamine release, and anxiolysis. If a patient with possible ACS is unresponsive to NTG or has recurrent symptoms despite maximal anti-ischemic therapy, administration of morphine sulfate is appropriate. The relief of pain and anxiety decreases oxygen consumption and myocardial work. Some vasodilatory effects are also noted with preload reduction. Standard doses of morphine sulfate are 2 to 5 mg delivered intravenously, repeated every 5 to 30 minutes as necessary. In addition to allergic reactions, the most significant adverse effect of morphine sulfate administration is hypotension, which is managed with intravenous fluid in bolus fashion.

Caution must be exercised with the administration of morphine in the ACS setting. A review notes an increase in the adjusted risk of death in chest pain patients suspected of ACS who receive morphine. This increased risk of mortality was noted in all patients who received morphine as well as in patients who received morphine versus NTG. While one study should not alter the standard medical approach, this must be given consideration.[131]

Beta-Adrenergic Blockers

Historically, beta-adrenergic blocking agents have been effective in ameliorating catecholamine-induced tachycardia, including ventricular fibrillation, increased contractility, and heightened myocardial oxygen demand. Beta-blockade is effective in decreasing mortality for patients with AMI. Although the impact of beta-adrenergic blockade in treating UA is less well studied, a meta-analysis showed a 13% reduction in the risk of subsequent AMI.

These observations occurred, however, when adjunctive therapies were few, and beta-adrenergic blockade was monotherapy in AMI. Current management strategies include highly effective reperfusion therapies coupled with potent anticoagulant and antiplatelet agents.

Two large reports suggest that the intravenous use of beta-adrenergic blockade should be reconsidered. The GUSTO-1 trial involved fibrinolytic agents for STEMI followed by early intravenous atenolol. The use of the early intravenous beta-adrenergic blocking agents in this study was associated with increased death, heart failure, shock, recurrent ischemia, and pacemaker use than when patients received early oral administration. This occurred despite exclusion of patients with obvious contraindication, including preexisting hypotension, bradycardia, or heart failure.[132] The Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) evaluated approximately 46,000 patients with suspected STEMI, comparing early intravenous beta-adrenergic blocking agent use

followed by continued oral therapy versus placebo. There was no significant difference between the two groups in terms of mortality. The group receiving beta-adrenergic blocking agents did demonstrate a minimal reduction of reinfarction (2.0 vs. 2.5%) and ventricular fibrillation (2.5 vs. 3.0%). Unfortunately, the group receiving beta-adrenergic blocking agents had a higher rate of developing cardiogenic shock (5.0 vs. 3.9%). This was more common in patients who are elderly, have a systolic blood pressure less than 120 mm Hg, a heart rate greater than 110 bpm, or mild, acute heart failure. Patients receiving the beta-adrenergic blocking agents also had an increased rate of developing heart failure requiring treatment, increased rate of developing persistent hypotension, and increased rate of developing bradycardia.[133]

The early *intravenous* use of beta-adrenergic blocking agents does not appear to offer significant benefit and, in fact, is associated with an increased rate of cardiovascular adverse effect.[134] Oral administration to patients without contraindication during the first day of management is more likely an appropriate approach to the ACS patient. Empirical therapy in the ED, however, should be reconsidered and reserved for patients who are felt to have adverse effect from significantly elevated heart rate, blood pressure, or both.

Angiotensin-Converting Enzyme Inhibitors

Angiotensin-converting enzyme (ACE) inhibitor agents benefit patients with CHF. ACE inhibitors may also reduce morbidity and mortality after AMI. In particular, patients treated with ACE inhibitors experience a reduction in cardiovascular mortality, decreased rates of significant CHF, and fewer recurrent AMIs. These benefits increase when ACE inhibitors are used in conjunction with other agents such as aspirin and fibrinolytics. The mechanism of action regarding a reduction in recurrent AMI is unknown but may involve a reduction in plaque rupture related to decreased intracoronary shear force or neurohumoral influences.

Captopril, enalapril, lisinopril, or ramipril may be used in this setting. The ultimate doses should be maximized after careful titration with these potent agents to avoid hypotension. Therapy should be initiated within the first 24 hours, although ED administration is usually not indicated. In patients with asymptomatic left ventricular dysfunction, therapy should continue for a minimum of 2 to 4 months. In patients with symptomatic CHF, ACE inhibitors should be administered indefinitely. Contraindications to ACE inhibitor therapy include hypotension, volume depletion, and borderline perfusion. Renal function must be monitored closely. The angiotensin receptor blockers also inhibit the renin-angiotensin system, thus representing possible alternatives to ACE inhibitors in patients status post myocardial infarction with or without heart failure.

Calcium Channel Blockade

As with beta-blockade, the primary benefit of calcium channel blockers appears to be with symptom resolution. Unfortunately, these agents may be accompanied by a significant vasodilatory effect resulting in hypotension and potentiation of the coronary ischemic process. Like beta-blocking agents, calcium channel blockers have a substantial negative inotropic effect. AV nodal blockade is also a significant side effect that may be exacerbated in patients previously treated with beta-blockers or with ischemia-related conduction disturbance. Unless specifically used for rate control of supraventricular dysrhythmia in a patient who cannot tolerate beta-blockade, calcium channel blocker agents are not recommended for ACS.

Antiplatelet Therapy

In non-AMI ACS patients, dramatic reductions in the progression to acute infarction are noted with aggressive antiplatelet therapy. The administration of antiplatelet therapy, particularly aspirin, is indicated in the ED for most ACS patients, since in AMI, antiplatelet therapy reduces mortality from 25 to 50%.

Aspirin. Aspirin, the prototypical antiplatelet agent, is the most cost-effective treatment. It irreversibly acetylates platelet cyclooxygenase, thereby removing all activity for the life span of the platelet (8–10 days). Thus, aspirin stops the production of proaggregatory thromboxane A2 and is an indirect antithrombotic agent. Aspirin also has important nonplatelet effects because it inactivates cyclooxygenase in the vascular endothelium, thereby diminishing formation of antiaggregatory prostacyclin.

The Second International Study of Infarct Survival (ISIS-2) trial provided the strongest evidence that aspirin independently reduces the mortality of patients with AMI without fibrinolytic therapy (overall 23% reduction), and is synergistic when used with fibrinolytic therapy (42% reduction in mortality).[135] The usual dose is 325 mg of non-enteric-coated aspirin, chewed and swallowed. Administration of aspirin in the ED is strongly recommended immediately upon identification of any patient with suspected ACS, either AMI or UA. It should be administered to all such patients unless significant allergy, hemorrhage, or other issue such as a potential aortic dissection contraindicates its use.

Glycoprotein IIb/IIIa Receptor Inhibitors. The GPI is another potent antiplatelet agent, which includes three current agents: abciximab, eptifibatide, and tirofiban. The GPI, however, demonstrates clinical utility in only a subset of ACS patients—those undergoing PCI. Therefore, the primary indication regarding GPI administration for the emergency physician is planned mechanical coronary intervention. The ideal location for administration may include the ED, catheterization laboratory, or coronary care unit. Early GPI administration in the ED, compared to the catheterization laboratory, demonstrates improvement in outcome in pilot studies.[136,137]

Numerous trials have demonstrated the effectiveness of these agents in the subset of ACS patients who are managed with PCI with or without an intracoronary stent, consistently showing reduced mortality, need for subsequent revascularization, and recurrent ischemia, although at the cost of an increase in hemorrhagic complications.[138–141] A meta-analysis of GPI use in ACS patients concluded that patients who undergo PCI benefit markedly from GPI administration.[142] In ACS patients who are managed medically without mechanical revascularization, consistent benefit with GPI therapy is not found, using either direct outcome measures or secondary markers of successful reperfusion, and hemorrhagic complications are increased.[142,143] None of the GPIs has demonstrated significant benefit in the treatment of ACS patients without PCI.[144] The Integrilin to Manage Platelet Aggregation to Combat Thrombus in Acute Myocardial Infarction (IMPACT-AMI) investigators[145] reported the results in AMI patients receiving fibrinolytic agents and varying doses of eptifibatide (i.e., nonmechanical means of reperfusion); they noted similar rates of death, recurrent MI, and the need for revascularization procedures but observed an increase in TIMI grade 3 flow at 90 minutes. Furthermore, using troponin values as an estimate of infarct size, investigators did not demonstrate benefit in eptifibatide-treated patients with non-ST elevation ACS presentations.[146]

GPI therapy, in the invasively managed patient, continues to offer improved outcome.[147,148] In one large series, patients

who received GPIs experienced lower in-hospital mortality (3 vs. 6.2%), which was noted in all STEMI risk groups managed.[147] Subsequent analysis of the subgroup of patients receiving stents during PCI noted both a lower mortality rate (10.9 vs. 14.3%) and a lower reinfarction rate (2.3 vs. 5.5%) in the treatment group; also, the composite endpoint (death and reinfarction) occurred much less frequently in the treatment group, with a relative risk reduction of 37%. In a large meta-analysis of similar construction, major bleeding was not significantly different.[148]

The issue of timing and location of GPI administration has recently been explored, with initial studies suggesting that early therapy in the ED is associated with more favorable outcomes.[149,150] Both of these studies are rather small and thus should not dictate management policy, yet their findings suggest that earlier therapy is "better" with no increased rate of adverse effect.

The glycoprotein IIb/IIIa receptor inhibitors have consistently demonstrated benefit in ACS patients treated with urgent mechanical revascularization; other groups of ACS patients, such as medically managed, combination fibrinolytic agent, or transferred patients, have not established an invariable positive effect. Consequently, the ACC/AHA has provided the following guidelines for GPI use in ACS patients:

1. For patients in whom an *initial invasive strategy* is selected, additional antiplatelet therapy beyond aspirin should be initiated before PCI with either clopidogrel or GPI (abciximab)—only if there is no anticipated, significant delay to coronary angiography and PCI is most likely to be performed. If a significant delay is anticipated to PCI in the invasively managed patient, either eptifibatide or tirofiban is the preferred GPI (class I).
2. For patients in whom an *initial noninvasive strategy* is selected, it may be reasonable to add eptifibatide or tirofiban to existing anticoagulant and oral antiplatelet therapies (class IIb). GPI (abciximab), however, should not be administered to patients in whom PCI (*initial invasive strategy*) is not planned (class III).
3. For patients in whom an *initial noninvasive strategy* is selected and who have recurrent ischemia, develop acute heart failure, or experience malignant dysrhythmias while receiving clopidogrel, ASA, and anticoagulant therapy, it is reasonable to add a GPI (eptifibatide or tirofiban) before diagnostic angiography (class I).[6]

Thienopyridine Antiplatelet Agents. The thienopyridines, ticlopidine and clopidogrel, are more potent platelet inhibitors than aspirin. The thienopyridines inhibit the transformation of the glycoprotein IIb/IIIa receptor into its high-affinity ligand-binding state, irreversibly inhibiting platelet aggregation for the duration of the life of the platelet. Ticlopidine has nonlinear kinetics and, after repeated dosing, reaches a maximal effect after 8 to 11 days of dosage. Clopidogrel, a ticlopidine analogue, has the advantages of a rapid onset of action and an intravenous route of administration.

Clopidogrel is the preferred agent of this class because of its more rapid onset of action and its safety profile. Ticlopidine is associated with a risk of neutropenia and agranulocytosis that is not encountered with clopidogrel; furthermore, it demonstrates a much slower onset of platelet inhibition. With clopidogrel, maximal platelet inhibition occurs after 3 to 5 days of clopidogrel therapy using 75 mg daily; an earlier onset of platelet inhibition is seen when a higher loading dose is used (300 to 600 mg). In fact, higher clopidogrel "loading doses" may produce benefit at an earlier time. For instance, there is clear benefit to clopidogrel administration (300-mg loading dose) occurring at least 6 hours before PCI in patients with STEMI; higher doses (e.g., 600 mg) in many studies demonstrate a trend toward improvement at slightly earlier time periods (i.e., 3 to 4 hours).

From the emergency medicine perspective, the most appropriate recommendation for clopidogrel in the ED is the patient with a high-risk ACS presentation who is truly allergic to ASA (ACC/AHA class I indication);[6] this high-risk presentation would be characterized by objective clinical abnormality, including a significantly abnormal serum marker and/or 12-lead ECG. Other indications are discussed below.

The considerations which must be kept in mind include the ultimate treatment strategy chosen (i.e., medical versus invasive) and the time to angiography if an invasive plan is elected. ACS patients managed medically (i.e., noninvasively) or invasively with coronary angiography deferred to a later time are the most appropriate, potential candidates for clopidogrel.[151–154] In the patient selected for invasive management, the time-to-the-procedure must be considered as a primary issue when considering clopidogrel—patients undergoing early angiography (less than 6 hours) are less likely to derive significant benefit, while deferred catheterization likely will gain advantage as a result of this treatment.

In the patient with unstable angina or NSTEMI, clinical benefit is confirmed in UA patients when treated with clopidogrel in a noninvasive strategy scenario, with an increase in major hemorhage.[151] As noted, invasively managed patients receiving the drug with less time to procedure performance do not benefit from such treatment. The NSTEMI patient demonstrates improved outcome with clopidogrel therapy when a conservative treatment scenario is initially followed.[153] Of note, a large portion of these patients will undergo PCI within the first 24 hours after admission; yet, this "delayed" PCI allows for benefit to occur from clopidogrel administered earlier in the course of management.

The STEMI patient who is managed medically (i.e., with a fibrinolytic agent) will also benefit from clopidogrel use. Clopidogrel therapy in conjunction with fibrinolysis followed by deferred cardiac catheterization occurring at least 2 days post-AMI—clearly beyond this 6-hour window—decreases the rates of death, recurrent ACS, and urgent coronary revascularization. This improvement occurs without a significant increase in hemorrhage.[154] Conversely, the use of clopidogrel does not appear to show benefit in the STEMI patient if the drug is given less than 6 hours prior to PCI performance, regardless of the clinical setting.

ACS (UA, NSTEMI, and STEMI) patients with PCI performed soon after arrival (i.e., less than the 6-hour interval from clopidogrel dosing) are less likely to benefit from early therapy. Thus, urgent PCI for the ACS patient is not associated with significant clopidogrel-derived clinical advantage. ACS patients urgently or emergently managed with PCI are less likely to benefit from clopidogrel use in the ED.

The potential need for urgent CABG must also be strongly considered. The higher risk ACS patient will more likely benefit from clopidogrel therapy, yet the same patient will more likely need urgent CABG. The emergency physician, however, is not able to reliably identify ACS patients requiring urgent CABG. Of the 60,000 patients in the CRUSADE registry, 14% underwent CABG, a reasonably frequent rate of surgical intervention;[155] most centers, however, report a 2 to 5% incidence of coronary surgery. Mehta and colleagues, in a review of ED ACS patients, were unable to demonstrate a single or combination of clinical features that reliably identified patients not requiring CABG.[156] Interestingly, an analysis of the CURE database suggests that, while these CABG patients had a greater incidence of bleeding perioperatively,

outcomes were not statistically different in clopidogrel versus placebo groups in this surgical subset.[153] It is likely that as the cardiovascular surgeon gains more experience with clopidogrel, this concern will cause less anxiety, much like ASA and heparin in years past.

The ACC/AHA suggests—in the form of a Class I recommendation—that clopidogrel should be withheld for at least 5 days before CAGB. If CAGB is performed within 5 days of clopidogrel use, patients have an increased incidence of operative and postoperative hemorrhage, increased need for transfusions, increased need for re-operation for hemostasis, and increased postoperative mortality. Nevertheless, the recommendation suggests that early clopidogrel therapy be considered in those patients who likely will not require CAGB.[6] The American College of Emergency Physicians Clinical Policy concludes that there is insufficient evidence to recommend any exact location or timing of clopidogrel administration in the ACS patient.[157] In that it does not appear possible for the emergency physician to reliably predict which patients will require urgent CABG, collaborative multidisciplinary pathways should be developed, with emergency medicine, cardiologist, and cardiovascular surgeons providing input.

Antithrombins

As with antiplatelet therapies in ACS patients, significant reductions in the progression to acute, recurrent, or extensive infarction and death are noted in individuals treated with aggressive antithrombin therapy. The antithrombins include unfractionated heparin, low-molecular-weight (fractionated) heparin (LMWH), and the direct thrombin inhibitors (hirudin and bivalirudin). Antithrombotic therapy is indicated in ACS patients with recurrent anginal pain, AMI (non-ST segment elevation and ST segment elevation), positive serum marker, and a dynamic 12-lead ECG.

Heparins. The term *heparin* refers not to a single structure but rather to a family of mucopolysaccharide chains of varying lengths and composition—hence, unfractionated—with pronounced antithrombotic properties. At standard doses, unfractionated heparin binds to antithrombin III, forming a complex that is able to inactivate factor II (thrombin) and activated factor X. This prevents the conversion of fibrinogen to fibrin, thus preventing clot formation. Heparin by itself has no anticoagulant property. This indirect effect on thrombin inhibits clot propagation; it prevents heparin, however, from having any effect on bound thrombin in a thrombus. Unfractionated heparin also assists in the inactivation of factors XIa and IXa through antithrombin and interacts with platelets.

Unfractionated heparin has a profound synergistic effect with aspirin in preventing death, AMI, and refractory angina in ACS patients, particularly those with AMI and, to a lesser extent, high-risk UA. Unfractionated heparin should be administered early in patients with the following ACS features: recurrent or persistent chest pain, AMI, positive serum marker, and dynamic ECG. In patients undergoing PCI, bleeding and mortality were higher in TIMI 14 in patients receiving an 80-U/kg bolus and 18-U/kg infusion compared to patients with lower bolus amount and infusion rate. Therefore, the weight-adjusted regimen recommended is an initial bolus of 60 U/kg (maximum 4000 U) and an initial infusion of 12 U/kg/hr. The activated partial thromboplastin time should be titrated to 1.5 to 2.5 times the control value.

LMW heparins constitute approximately one third of the molecular weight of heparin and are less heterogeneous in size. The LMW heparins inhibit the coagulation system in a fashion similar to that of unfractionated heparin. Approximately one third of the heparin molecules bind to both antithrombin III and thrombin. The remaining molecules bind only to factor Xa. The variable efficacy found among the LMW heparins is attributed to different ratios of antifactor Xa to antifactor IIa. High-ratio preparations have a clear advantage over standard heparin; enoxaparin has the highest ratio of available LMW heparins. LMWH was designed on the basis of the hypothesis that inhibition of earlier steps in the blood coagulation system would be associated with a more potent antithrombotic effect than inhibition of subsequent steps. This results from the amplification process inherent in the coagulation cascade; that is, a single factor Xa molecule can lead to the generation of multiple thrombin molecules.

Potential advantages of LMW heparin over unfractionated heparin include easier administration, greater bioavailability, more consistent therapeutic response among patients, longer serum half-life producing a more manageable dosing schedule, and reduced rates of adverse bleeding episodes, albeit at a higher cost.

The combination of aspirin, beta-blocker, and LMWH (dalteparin) significantly decreases the rate of nonfatal AMI or death at 1 week of therapy with a less pronounced effect at 40 to 150 days, but with an increase in minor bleeding episodes.[158] Studies comparing outcomes between LMWH and unfractionated heparin have shown mixed results, with some showing better outcomes with LMWH while others do not.[159,160] In summary, the LMWH enoxaparin demonstrates some degree of benefit compared to unfractionated heparin (UFH) in higher-risk NSTE-ACS patients treated conservatively without immediate PCI (i.e., beyond 24 hours).[161] Conversely, in patients managed aggressively with PCI within 24 hours, enoxaparin offers little benefit while major bleeding rates are increased.[162]

Enoxaparin is administered in a twice-daily regimen subcutaneously at a dose of 1 mg/kg. If patients have renal dysfunction with an estimated glomerular filtration rate less than 30 mL/min, the dose should be reduced to 1 mg/kg in a single daily administration. There are little safety data available for enoxaparin in ACS patients with renal insufficiency, and UFH may be preferable.

Contraindications to heparin therapy include known allergy, active ongoing hemorrhage, and predisposition to such hemorrhage. Further, patients who have their heparin therapy changed (UFH to LMWH and vice versa) during the active treatment phase of their ACS care experience higher rates of bleeding.

The vast majority of patients with AMI require therapy with heparin, whether it is fractionated or unfractionated. Non-AMI ACS, however, is an entirely different issue since UA is a heterogenous condition. For example, the stable patient with a classical description of new-onset angina who is sensation free with a negative serum marker and a normal ECG is still correctly diagnosed with UA.[163] In contrast, an individual who presents with ongoing pain, either intermittent or constant, with a dynamic ECG clearly represents an active, unstable coronary event. The latter patient, who is at higher risk, can benefit from heparin therapy more than the former. Heparin therapy, however, can be a major contributor to morbidity and mortality among hospitalized patients. Major bleeding develops in 1 of every 90 patients treated, and heparin-induced thrombocytopenia in 1 of 34 patients. LMWH is as effective as unfractionated heparin in patients with ACS and does not greatly increase the bleeding risk while decreasing the risk of thrombocytopenia.

Other Antithrombins (Hirudin, Bivalirudin, and Fondaparinux). The direct thrombin inhibitors hirudin and bivalirudin (formerly known as hirulog) are potent antithrombin anticoagulants providing significant theoretical advantages compared with heparin. Hirudin is a peptide derived from the leech salivary gland but is also synthesized as recombinant hirudin. It binds directly

with high affinity to thrombin and can inactivate thrombin already bound to fibrin (clot-bound thrombin) more effectively than UFH. Hirudin does not require endogenous cofactors such as antithrombin III for its activity. Also, unlike heparin, hirudin can inhibit thrombin-induced platelet aggregation. Hirudin demonstrates little significant benefit over other anticoagulants in ACS, with a possible increased rate of hemorrhage; thus, it offers little value in the ACS patient.

Bivalirudin is a bifunctional 20–amino acid peptide designed on the basis of the structure of hirudin. It has properties similar to those of hirudin but also interacts with the catalytic site of thrombin. Bivalirudin, however, is more effective than heparin in reducing death or reinfarction in patients with ACS, particularly in those patients undergoing very early PCI.[164]

Bivalirudin compared with heparin produces similar rates of ischemia and major bleeding at 1 month. Bivalirudin when used with clopidogrel is comparable to the combination of heparin and GPI prior to coronary angiography or PCI. When used alone, it is inferior to the combination of heparin and GPI.[165] Bivalirudin should be considered an acceptable alternative anticoagulant agent compared to the heparins in the ACS patient, and has a class I indication for the ACS patient.[6]

Fondaparinux is a synthetic oligosaccharide with a structure similar to the heparins. It is the first widely used selective factor Xa inhibitor. As with the other ACS anticoagulant agents, fondaparinux has a class I ACC/AHA recommendation.[6] With the increased emphasis on the reduction of hemorrhagic complications in ACS care, this drug appears to demonstrate similar efficacy to LMWH with fewer bleeding complications. The attendant reduction in mortality appears to be almost entirely explained by decreased bleeding complications, including patients selected for PCI, renal failure patients, and patients receiving other anticoagulation, including UFH.[166,167] Thus, when either invasive or noninvasive strategies are contemplated, fondaparinux is an effective anticoagulant for the ACS patient. It also may be ideal for the patient with significant renal dysfunction or at increased risk of hemorrhage. The dose is 2.5 mg subcutaneously once daily for all patients.

In the large Optimal Antiplatelet Strategy for Interventions (OASIS) trial, fondaparinux is similar to enoxaparin in the short-term reduction of ischemic events, yet substantially reduces major bleeding and improves long-term outcome.[167] The OASIS-6 investigators reviewed the use of fondaparinux in 5436 STEMI patients managed medically with fibrinolytic agents. Fondaparinux significantly reduced hemorrhage and the primary study outcome (death or myocardial infarction) as well as the individual occurrence of these endpoints at 30 days.[167]

Reperfusion Therapies

Reestablishing perfusion in the infarct-related coronary artery with the use of fibrinolytic therapy or PCI increases the opportunity for salvage of the ischemic myocardium. Pharmacologic and mechanical methods of reperfusion are both effective under specific clinical conditions. The importance of early coronary artery patency was affirmed by the GUSTO investigators in their angiographic substudy. They demonstrated that 90-minute patency predicts rates of survival and preserves left ventricular function more than in those patients not achieving normal coronary flow.[128]

Fibrinolytic therapy unequivocally improves survival in patients presenting with STEMI and remains an ACC/AHA class I recommendation.[6] Although fibrinolysis has widespread availability and a proven ability to improve coronary flow, limit infarct size, and improve survival in AMI patients, many individuals with acute infarction are not suitable candidates. Patients with absolute contraindications to fibrinolytic therapy, certain relative contraindications, cardiogenic shock, and UA may not be eligible. The temporal constraints and other limitations of fibrinolytic therapy suggest that *rapidly* performed PCI is often the treatment of choice in the STEMI patient. To provide the most significant benefit, PCI must be performed as soon as possible after the initial presentation. In other settings and situations, PCI that is delayed is inferior to rapidly administered fibrinolysis.

Fibrinolytic Therapy

Fibrinolytic Agent Selection. Three megatrials compared tissue-type plasminogen activator (t-PA) with streptokinase. The Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI-2) trial[168] and the closely related International Study[169] compared a 100-mg infusion of t-PA over 3 hours with streptokinase with or without heparin. The GISSI-2 study was the first large-scale mortality trial directly comparing t-PA and streptokinase in patients with AMI. The investigators found no difference in mortality between the two treatment groups. More strokes were reported with t-PA than with streptokinase (1.3 vs. 1%) in the International Study, yet the frequency of confirmed hemorrhagic stroke was similar for both agents. Similar results were found in the ISIS-3 trial,[170] the next fibrinolytic megatrial, which compared t-PA, streptokinase, and anisoylated plasminogen-streptokinase activator complex in approximately 40,000 patients. In marked contrast to current practice, the inclusion criteria allowed entry up to 24 hours after symptom onset and did not require diagnostic electrocardiographic change. All patients received adjunctive aspirin therapy, and approximately half of the patients were given delayed, unmonitored subcutaneous heparin. A significant difference in both 35-day mortality and intracranial hemorrhage was not found. The results of the ISIS-3 study[170] proved controversial because of the unmonitored, delayed subcutaneous heparin protocol, particularly with studies now proving improved infarct artery patency using early therapeutic intravenous doses of heparin.

Current fibrinolytic practice is highly affected by the results of the GUSTO-I trial.[128] The purpose of the GUSTO-I trial was to test the hypothesis that early and sustained infarct vessel patency was associated with better survival rates in patients with AMI.[128] More than 41,000 patients were randomly assigned to four different fibrinolytic strategies: accelerated t-PA given over 90 minutes plus intravenous heparin, a combination of streptokinase plus a reduced dose of t-PA along with intravenous heparin, and two control groups (streptokinase plus subcutaneous heparin and streptokinase plus intravenous heparin). Unlike previous trials, t-PA was given in a more aggressive, front-loaded 90-minute infusion (referred to as accelerated t-PA). In addition to a primary endpoint of 30-day mortality, the GUSTO investigators explored coronary artery patency and degree of normalization of flow in the angiographic substudy. This portion of the larger trial was designed to determine the relationship between early coronary artery patency and outcome. In this trial, accelerated t-PA, administered with intravenous heparin, reduced 30-day mortality significantly by 15% compared with streptokinase with either form of heparin or the combination of t-PA and streptokinase with intravenous heparin. The benefit was highly consistent across virtually all subgroups, including elderly patients, location of AMI, and time from symptom onset. These differences remained significant at 1 year of follow-up.

The angiographic substudy demonstrated a strong relationship between TIMI flow and outcome. Patients with strong forward flow (i.e., TIMI grade 3 flow) at 90 minutes had significantly lower mortality rates than patients with little to no

flow. The mechanism for this benefit was found to be earlier, more complete infarct vessel patency with accelerated t-PA; this early t-PA patency advantage over other agents was lost by 180 minutes after symptom onset. As would be expected, the patients with the higher risk derived the most substantial benefit with accelerated t-PA compared with streptokinase in this large study. Patients who received accelerated t-PA did suffer more hemorrhagic strokes than those who received streptokinase, but the combined endpoint of death and disabling stroke still favored the accelerated t-PA regimen.

Another important addition to the fibrinolytic agent literature base includes the GUSTO-III investigation.[171] This study compared accelerated t-PA with r-PA; r-PA is a mutant form of t-PA that can be administered in a fixed double-bolus dose with no adjustment required for weight, which simplifies administration. In this very large trial, r-PA was found to be equivalent to accelerated t-PA, and the overall results were nearly identical for the two drugs. The one exception is that of patients who present more than 4 hours after onset of symptoms—a significant number of patients in many institutions. In this group of patients, accelerated t-PA may be superior to r-PA because of its greater fibrin specificity.[171]

The Assessment of the Safety and Efficacy of a New Thrombolytic Agent (ASSENT-2) trial investigated the use of TNK, another mutant of wild-type t-PA. TNK has several potential benefits: (1) its longer half-life allows it to be administered as a single bolus, (2) it is 14 times more fibrin specific than t-PA and even more so than r-PA, and (3) it is 80 times more resistant to plasminogen activator inhibitor type 1 than t-PA. The ASSENT-2 trial[172] randomly assigned approximately 17,000 patients with AMI to single-bolus TNK (30–50 mg on the basis of body weight) or accelerated t-PA (100 mg total infusion). The investigators found no differences in mortality or ICH.[172] In a subgroup analysis, however, significantly lower 30-day mortality was noted among patients who presented more than 4 hours after onset of symptoms in those treated with TNK. Further, fewer nonintracranial major bleeding episodes were encountered in the TNK group. On the basis of these results, it is concluded that TNK is equally or minimally more effective, particularly in late presenters. Concerning adverse reactions, TNK also appears modestly safer than accelerated t-PA. Lastly, because of its single-bolus administration, TNK is markedly easier to use in preadmission environments and the ED.

Eligibility Criteria for Fibrinolytic Agent Therapy

The 12-Lead Electrocardiogram. Combined with the patient's history and physical examination, the 12-lead ECG is the key determinant of eligibility for fibrinolysis. The electrocardiographic findings include two basic issues: (1) ST segment elevation of 1 mm or more in two or more anatomically contiguous *standard limb* leads and elevation of 2 mm or more in two or more contiguous *precordial* leads, and (2) new or presumed new LBBB. No evidence of benefit from fibrinolytic therapy is found in patients with ischemic chest pain who lack either appropriate ST segment elevation or the new development of LBBB.[7]

Patients with LBBB and AMI are at an increased risk for a poor outcome and need rapid reperfusion therapy. The new development of LBBB in the setting of AMI suggests proximal occlusion of the left anterior descending artery and places a significant portion of the left ventricle in ischemic jeopardy. Unfortunately, patients with LBBB receive fibrinolytic agents less often than those with the more electrocardiographically alarming STEMI.

Patients with AMI in anterior, inferior, or lateral anatomic locations benefit from fibrinolytic therapy. The relatively favorable prognosis associated with inferior infarction without fibrinolytic therapy requires larger sample sizes to detect a significant survival benefit. The ISIS-2 trial[173] demonstrated a statistically significant mortality benefit for fibrinolytic therapy in patients with inferior AMI. Patients with inferior AMI with coexisting right ventricular infarction, as detected by additional lead ECGs, are likely to benefit because of the large amount of jeopardized myocardium. Acute, isolated posterior wall MI, diagnosed by posterior leads, may be another electrocardiographic indication for fibrinolysis. Although unproven in large fibrinolytic agent trials, patients with isolated posterior AMI may be considered for reperfusion therapy.

Fibrinolytic therapy should not be used routinely in patients with only ST segment depression on the 12-lead ECG, and the mortality rate may actually be increased. The TIMI-3 trial[174] demonstrated a significant difference in outcome in fibrinolytic-treated patients with only ST segment depression—7.4% incidence of death compared with 4.9% in the placebo group. These findings are further supported in the Fibrinolytic Therapy Trialists' (FTT) meta-analysis, which demonstrated that the mortality rate among patients with ST segment depression who received fibrinolytic therapy was 15.2% compared with 13.8% among control subjects.[175]

Patient's Age. Past trials do not provide evidence to support withholding fibrinolytic therapy or choosing one particular agent over another on the basis of the patient's age. In fact, the FTT Collaborative Group[175] concluded that "clearly, age alone should no longer be considered a contraindication to fibrinolytic therapy." Patients older than 75 years do have a higher incidence of hemorrhagic stroke than younger patients.

Time from Symptom Onset. The generally accepted therapeutic time window for administration of a fibrinolytic agent after the onset of ST segment elevation AMI is 12 hours. Patients treated within the first 6 hours of AMI have the best outcome. Later administrations, from 6 to 12 hours after AMI onset, also confer benefit, although of a lesser magnitude. The Late Assessment of Fibrinolytic Efficiency (LATE) trial, which compared fibrinolytic therapy with placebo, found a significant 26% decrease in 35-day mortality in patients treated with t-PA, heparin, and aspirin 6 to 12 hours after the onset of symptoms.[176] There was no significant decrease in mortality among patients treated 12 to 24 hours after symptom onset.

These studies clearly establish benefit from 0 to 12 hours in patients who are otherwise appropriate candidates for fibrinolytic therapy. Treatment beyond that time is not supported by the literature. The single exception may be a patient with a "stuttering" nature of chest pain between 12 to 24 hours after symptom onset, which emphasizes the importance of an adequate history.

Blood Pressure Extremes. Patients with a history of chronic hypertension should not be excluded from fibrinolytic therapy if their blood pressure is under control at the time of presentation or can be lowered to acceptable levels using standard therapy for ischemic chest pain. The admission blood pressure is also an important indicator of risk of intracerebral hemorrhage. The FTT meta-analysis[175] demonstrated that the risk of cerebral hemorrhage increases with systolic blood pressure greater than 150 mm Hg on admission and further increases when systolic blood pressure is 175 mm Hg or higher. Despite an increased mortality rate during days 0 and 1, the FTT meta-analysis demonstrated an overall long-term benefit of 15 lives saved per 1000 for patients with systolic blood pressures greater than 150 mm Hg and 11 lives saved per 1000 for patients with systolic blood pressures of 175 mm Hg or greater.[175] Although the FTT meta-analysis appears to indicate an acceptable risk-benefit ratio for patients with substantially increased systolic blood pressure, a persistently elevated blood pressure greater than 200/120 mm Hg is generally

considered to be an absolute contraindication to fibrinolytic therapy.

The benefit of fibrinolytic therapy in patients with hypotension is unclear. The GISSI-1 and GISSI-2 trials showed no apparent reduction of mortality rate with fibrinolytic therapy among patients classified in Killip class III or IV.[168] These findings have led to the suggestion that primary angioplasty, not fibrinolytic therapy, be used in patients with cardiogenic shock. The FTT meta-analysis, however, does not support this hypothesis.[175] In this meta-analysis, patients with an initial systolic blood pressure less than 100 mm Hg who were not treated with fibrinolytic therapy had a very high risk of death (35.1%), and those who were treated with fibrinolytic therapy had the largest absolute benefit (60 lives saved per 1000 patients).[175] On the basis of this evidence, the FTT Collaborative Group suggested that hypotension, heart failure, and perhaps even shock should not be contraindications to fibrinolytic therapy.[175] These data support immediate treatment followed by diagnostic angiography and further intervention as indicated.

Retinopathy. Active diabetic hemorrhagic retinopathy is a strong relative contraindication to fibrinolytic therapy because of the potential for permanent blindness caused by intraocular bleeding. There is no reason, however, to withhold the use of a fibrinolytic agent in a diabetic patient with evidence of simple background retinopathy. Patients with diabetes mellitus who sustain an AMI have an almost doubled incidence of mortality.

Cardiopulmonary Resuscitation. CPR is not a contraindication to fibrinolytic therapy unless CPR has been prolonged—more than 10 minutes—or extensive chest trauma from manual compression is evident. Although the in-hospital mortality rate is higher in AMI patients who experience cardiac arrest and then receive fibrinolytic agents in the ED, no difference is found in the rates of bleeding complications. Hemothorax and cardiac tamponade were not diagnosed in those receiving fibrinolytics who survived to admission. Even prolonged CPR beyond 10 minutes does not appear to be associated with higher rates of complication.[177]

Previous Stroke or Transient Ischemic Attack. A history of previous stroke or transient ischemic attack is a major risk factor for hemorrhagic stroke after treatment with fibrinolytic therapy. A history of previous ischemic stroke should remain a strong relative contraindication to fibrinolytic therapy, and previous hemorrhagic stroke an absolute contraindication.

Previous Myocardial Infarction or Past Coronary Artery Bypass Graft. In the setting of AMI, a previous MI should not preclude consideration for treatment with fibrinolytic agents. Without treatment, there is a potential for greater loss of function in the newly infarcting region of the myocardium. Although the GISSI-1 trial showed no treatment benefits for patients with previous MIs, the ISIS-2 trial demonstrated a 26% relative mortality rate reduction.[173] The FTT meta-analysis further demonstrated that patients with a history of past MI who receive fibrinolytic therapy for recurrent acute infarction have a mortality rate of 12.5% compared with 14.1% among control patients.[175]

Many studies report successful fibrinolysis in AMI patients with a prior CABG. Complete thrombotic occlusion of the bypass graft is the cause of AMI in approximately 75% of cases as opposed to native vessel occlusion. Because of the large mass of thrombus and absent flow in the graft, conventional fibrinolytic therapy may be inadequate to restore flow. These patients should be considered for direct angioplasty or combined fibrinolysis and rescue angioplasty.

Recent Surgery or Trauma. Recent surgery or trauma is considered a relative contraindication to fibrinolytic therapy. The term *recent* is subject to variable interpretation in fibrinolytic trials. In the GISSI-1 trial,[178] patients were excluded if they had surgery or trauma within the previous 10 days. In the Anglo-Scandinavian Study of Early Thrombolysis (ASSET) trial, patients were excluded for surgery or trauma within the previous 6 weeks.[179] Other fibrinolytic therapy trials do not define "recent surgery or trauma." Alternative interventions should be considered in patients with AMI within 10 days of surgery or significant trauma.

Menstruation. Since natural estrogen is partially cardioprotective, there is little experience with fibrinolysis among premenopausal women. Gynecologists indicate that any excessive vaginal bleeding that may occur after receiving fibrinolytic therapy should be readily controllable by vaginal packing and therefore can be considered as a compressible site of bleeding.

Contraindications. A list of absolute and relative contraindications is shown in Box 76-1.

BOX 76-1 Fibrinolysis in Acute Myocardial Infarction: Absolute and Relative Contraindications

- Recent (within 10 days) major surgery (e.g., coronary artery bypass graft, obstetric delivery, organ biopsy, previous puncture of noncompressible vessels)
- Cerebrovascular disease
- Recent gastrointestinal or genitourinary bleeding (within 10 days)
- Recent trauma (within 10 days)
- Hypertension: systolic BP ≥180 mm Hg or diastolic BP ≥110 mm Hg
- High likelihood of left heart thrombus (e.g., mitral stenosis with atrial fibrillation)
- Acute pericarditis
- Subacute bacterial endocarditis
- Hemostatic defects, including those secondary to severe hepatic or renal disease
- Significant liver dysfunction
- Diabetic hemorrhagic retinopathy or other hemorrhagic ophthalmic condition
- Septic thrombophlebitis or occluded AV cannula at seriously infected site
- Advanced age (older than 75 years)
- Patients currently receiving oral anticoagulants (e.g., warfarin sodium)
- Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location

AV, atrioventricular; BP, blood pressure.
Modified from Physicians' Desk Reference, 50th ed. Montvale, NJ, Medical Economics, 1996.

Percutaneous Coronary Intervention

Although fibrinolysis has widespread availability and a proven ability to improve coronary flow, limit infarct size, and improve survival in AMI patients, many individuals with acute infarction are not considered suitable candidates. Patients with absolute contraindications to fibrinolytic therapy, certain relative contraindications, cardiogenic shock, and UA may be ineligible to receive fibrinolytic therapy. The requirement of administering prompt reperfusion therapy to these patients, as well as the other limitations of fibrinolytic therapy, have led many clinicians to advocate PCI. PCI has many theoretical advantages over fibrinolysis, including an increased number of

eligible patients, a lower risk of intracranial bleeding, a significantly higher initial reperfusion rate, an earlier definition of coronary with rapid triage to surgical intervention, and risk stratification allowing safe, early hospital discharge. Potential disadvantages include operator expertise and numerous catheterization laboratory logistical issues, including local and regional availability as well as time to therapy application.

Several trials of varying sizes comparing primary PCI with fibrinolysis are reported. Interventions in the early trials were performed prior to the current widespread use of coronary stents with GPI. Despite a clear and consistent benefit of PCI in restoring patency of the infarct-related artery, differences in mortality in the individual trials were difficult to evaluate because of the smaller sample sizes. The Primary Angioplasty in Myocardial Infarction (PAMI) trial[180] enrolled 395 patients randomly assigned to undergo PCI or to receive t-PA. Compared with standard-dose t-PA, PCI reduced the combined occurrence of nonfatal reinfarction or death, was associated with a lower rate of intracranial hemorrhage, and resulted in a similar left ventricular function. The results of the Netherlands trial indicate that primary angioplasty is associated with a higher rate of patency of the infarct-related artery, a less severe residual stenotic lesion, better left ventricular function, and less recurrent myocardial ischemia and infarction than in patients receiving streptokinase.[181]

In a substudy of the GUSTO IIb trial,[182] the investigators randomly assigned 1138 patients with AMI to either PCI or accelerated t-PA. The composite endpoint of the study included death, nonfatal reinfarction, and nonfatal disabling stroke, all occurring within 30 days of the AMI. Of the patients assigned to PCI therapy, 83% were candidates for such treatment and underwent angioplasty 1.9 hours after ED arrival for a total elapsed time from chest pain onset to therapy of 3.8 hours. Ninety-eight percent of the patients assigned to fibrinolytic therapy received t-PA 1.2 hours after hospital arrival. The composite endpoint was encountered significantly less often in the PCI group (9.6%) than in the t-PA group (13.7%) at 30 days. When the individual components of the composite endpoint at 30 days were considered separately, death, infarction, and stroke occurred at statistically similar rates for both treatment groups. A meta-analysis[183] reviewed 10 major studies comparing fibrinolysis with primary PCI in more than 2600 patients. The 30-day mortality and stroke occurrence were significantly lower in the PCI group.

The second Danish acute myocardial infarction (DANAMI-2) trial comprehensively investigated the PCI strategy.[184] Investigators randomly assigned AMI patients to receive either PCI or accelerated treatment with alteplase (t-PA). Patients presented to hospitals without invasive capabilities (totaling 24) or those with angioplasty capability (totaling 5). Stents and GPI were available and used at the discretion of the treating physicians. For angioplasty-managed patients presenting to noninvasive centers, transfer to PCI-capable institutions had to occur within a 3-hour time period. Significant differences were observed in a composite endpoint of death, reinfarction, or disabling stroke at 30 days between the groups, with rates of 8.5% in the PCI group versus 14.2% in the fibrinolytic group. Transfer for PCI occurred within 2 hours in 96% of patients. These additional studies support the findings of the DANAMI-2 trial.[180–183]

The Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) investigators compared angioplasty and PCI using coronary stents in STEMI patients undergoing urgent reperfusion therapy; abciximab was added to portions of both treatment groups. At 6 months, the primary endpoint (a composite of death, recurrent infarction, stroke, and urgent revascularization) had occurred in 20% of patients after angioplasty, 17% after PCI with abciximab, 12% after stenting, and 10% after stenting with abciximab.[185]

The longer-term results with PCI, however, are less clear. The GUSTO IIb study[182] showed no overall mortality advantage of PCI at 6 months. Much of the literature comparing the acute reperfusion therapies in AMI does not include the use of coronary stenting during PCI.

The issue of long-term outcome in PCI-managed STEMI patients is further complicated by drug-eluting stents (DES). Early studies used bare metal stents (BMS), which, in the setting of an acute thrombotic event such as STEMI, raised concern regarding stent thrombosis with obstruction and recurrent AMI. A review of this issue compared BMS and DES with both angiographic and clinical outcome variables in STEMI patients treated with PCI using intracoronary stenting. Event-free survival at 12 months was significantly higher in the DES group, with 74% in BMS patients and 86% in DES patients. Furthermore, the target-vessel-failure-free (i.e., correctly functioning culprit artery stent) survival was also significantly greater in the DES patients compared to the BMS group. The rates of death, myocardial infarction, and stent thrombosis, however, were not significantly different between the groups. Also, a higher rate of stent malposition was noted in the DES group, despite a lower rate of event occurrence in this contingent.[186]

A meta-analysis of 7 randomized trials compared the effects of DES and BMS in 2357 AMI patients. This study reported that DES significantly reduces the need for revascularization without changes in death or myocardial infarction out to 1 year follow-up; no increased risk of thrombosis was found in the DES group.[187] Another group extended the follow-up period of patients managed with coronary stenting. This patient group, undergoing PCI with stenting in an elective setting, extended the period of observation out to 2 years. These investigators found that target vessel revascularization was needed less often in the DES group, yet the rates of AMI and death were similar.[188]

Thus, PCI with stenting appears to be superior to standard angioplasty. The addition of DES to the equation has produced less favorable results, however, with similar rates of myocardial infarction and death coupled with a lower rate of revascularization in the DES patients to several years postintervention.

Rescue PCI. Historically, rescue PCI has been considered advantageous in patients whose infarct-related arteries fail to reperfuse after fibrinolytic therapy.[189] These patients are profoundly ill, with a markedly worse outcome. Some centers routinely catheterize patients after fibrinolytic therapy to determine whether successful reperfusion has occurred and to perform angioplasty if feasible. Other centers catheterize patients after fibrinolytic therapy only if there is clinical evidence that the infarct-related artery fails to open, as suggested by continued chest pain or persistent ST segment elevation.[190–193]

The Middlesbrough Early Revascularization to Limit INfarction (MERLIN) trial compared outcomes after rescue PCI with a conservative management strategy in STEMI patients who fail fibrinolysis. Rescue PCI was not associated with improved survival at 1 month; further, increased rates of stroke and transfusion were noted in this group. At 1- and 3-year intervals, the lack of survivor benefit persisted.[190–192] In a meta-analysis of STEMI patients who did not achieve satisfactory reperfusion after fibrinolysis, rescue PCI was not associated with mortality reductions. In this very ill group,

however, the incidence of heart failure and recurrent infarction was reduced. Repeat fibrinolysis was not associated with significant improvements in mortality or recurrent infarction.[193] Although the decision to offer rescue PCI in the failed fibrinolytic patient remains controversial, evidence favors rescue PCI and does not support the use of repeat fibrinolysis.

Facilitated PCI. Facilitated PCI refers to the combination therapy involving fibrinolysis with urgent PCI. This concept originally was developed to maximize therapy in STEMI patients who would be transferred urgently for PCI; the patient would receive a fibrinolytic agent prior to transfer, thus optimizing therapy prior to arrival at the PCI-capable institution. Outcomes are less optimal in those patients undergoing facilitated PCI compared to either fibrinolysis or standard PCI. The ASSENT-4 PCI investigators considered this approach with tenecteplase in a facilitated PCI protocol for STEMI patients. The tenecteplase group had a higher rate of the primary endpoint (death, acute CHF, or shock) within 90 days as well as increased occurrences of stroke, ischemic cardiac complications, and need for repeat revascularization.[194] A larger meta-analysis of 17 trials compared facilitated PCI to standard PCI in the STEMI patient. Patients undergoing facilitated PCI experienced higher rates of poor outcome and complication compared to the standard PCI group. The facilitated PCI group fared less well, with a higher rate of nonfatal recurrent infarction, urgent need for revascularization, major bleeding, and stroke.[195]

Choice of Reperfusion Therapy

The principal choices for reperfusion therapy in the STEMI patient include fibrinolysis and PCI. Numerous recommendations, statements, guidelines, and protocols exist. Regardless of the reperfusion strategy selected, "... the systems goal should be a first medical contact-to-[therapy] time within 90 minutes."[7] The following recommendations should be considered by the emergency physician and other involved clinicians in determining the most appropriate reperfusion therapy for the STEMI patient. A fibrin-specific fibrinolytic agent is the preferred strategy in the patient without contraindication to such therapy who presents early in the time course of the infarction (i.e., <3 hours). In this fibrinolytic-preferred strategy, PCI is either not available (i.e., a noninvasive center) or delayed (transfer or other logistical problems). The system goal for fibrinolytic therapy is to deliver the drug within 30 minutes of patient presentation.[7]

PCI is the preferred reperfusion strategy in the STEMI patient who can arrive in the catheterization laboratory with placement of the catheter adjacent to the culprit artery lesion within 90 minutes of initial hospital arrival.[7] High-risk STEMI patients, "late presenters" (i.e., >3 hours since the onset of STEMI symptoms), and individuals with contraindication to fibrinolysis are also candidates for PCI. When the diagnosis of STEMI is in doubt, PCI is the most appropriate diagnostic and therapeutic strategy.

If applied early without time delay, PCI provides improved outcome over fibrinolysis in the STEMI patient. It must be initiated within 90 minutes of arrival at the initial hospital ED.[7] As noted in the DANAMI-2 study,[184] PCI initiated within 3 hours of initial hospital arrival is also superior to fibrinolysis. *Since many hospital systems do not have the capability of meeting the time goal for primary PCI, fibrinolytic therapy is preferred because of the critical importance of time to treatment from onset of symptoms of STEMI in reducing morbidity and mortality.*[7]

If the time required to mobilize staff and arrange for PCI is prolonged or delays in transfer are anticipated, the treating physician must consider fibrinolysis. Prior agreement between the ED and the cardiovascular physicians at institutions with invasive capability must be obtained so that PCI consideration does not introduce further delays in fibrinolytic drug administration. Consensus clinical pathways limit additional delays in the administration of fibrinolytic agents in patients who are considered for PCI in AMI.[196]

An elegant analysis of the "PCI vs. fibrinolysis" consideration in the STEMI patient asks: How long should the practitioner wait for PCI in a patient who is fibrinolytic eligible? Considerations include the important time-to-therapy question and also factors such as the time from onset to presentation, patient age, and infarct location. Time recommendations are also provided with respect to patient age, infarct duration, and MI anatomic location. The maximal elapsed times one should wait for PCI (the actual time to balloon inflation) at which point the survival benefit of the invasive strategy is lost and the patient should receive a fibrinolytic agent are suggested.[197]

In this complex analysis of 192,509 patients in a national STEMI registry,[197] a broad range of acceptable PCI "waiting times" range from approximately 40 to 180 minutes. For instance, the relatively younger patient who is experiencing an anterior STEMI and presents within 2 hours of symptom onset should be in the catheterization laboratory with the catheter across the lesion within 40 minutes or receive a fibrinolytic agent. Conversely, the "older" STEMI patient with an inferior or lateral STEMI who presents beyond 2 hours of symptom onset could wait up to 179 minutes (almost 3 hours) before any PCI survival benefit is lost. Patient presentations with the "maximal allowable" time to catheter placement across the lesion are as follows:

- For patients presenting within 2 hours of symptom onset —94 min
- For patients presenting beyond 2 hours of symptom onset —190 min
- For patients less than 65 years old—71 min
- For patients greater than 65 years old—155 min
- Anterior STEMI—115 min
- Nonanterior STEMI—112 min

Further analysis combined commonly encountered clinical variables in typical STEMI presentations:

- Patient presentation within 2 hours of symptom onset and …
  - Anterior STEMI with age less than 65 years—40 min
  - Anterior STEMI with age greater than 65 years—107 min
  - Nonanterior STEMI with age less than 65 years—58 min
  - Nonanterior STEMI with age greater than 65 years—168 min
- Patient presentation beyond 2 hours of symptom onset and …
  - Anterior STEMI with age less than 65 years—43 min
  - Anterior STEMI with age greater than 65 years—148 min
  - Nonanterior STEMI with age less than 65 years—103 min
  - Nonanterior STEMI with age greater than 65 years—179 min

The importance of symptom duration as well as patient age and infarct location affects reperfusion therapy decisions.

Patients who are not able to rapidly reach the PCI suite should be considered for fibrinolysis. This analysis does not represent the standard for treatment comparisons.[197]

Delays to reperfusion therapy are not without negative consequences, as noted in a subset of patients in the GRACE database. The investigators examined the outcome impact of treatment delays on STEMI patients receiving reperfusion therapy. This study involved 3959 patients from 106 hospitals in 14 countries who presented within 6 hours of chest pain onset and underwent either PCI (55%) or fibrinolysis (45%). Delays in reperfusion were associated with increased mortality for both treatment strategies and were more pronounced in those patients receiving fibrinolysis.[198]

A cooperative effort between all providers and units can reduce markedly the door-to-therapy time in STEMI patients. A "STEMI alert" system, analogous to the "trauma alert" approach, mobilizes hospital-based resources, optimizing the approach to the AMI patient. This system, whether activated by data gathered in the ED or in the field, has the potential to offer time-sensitive therapies in a rapid fashion. In fact, emergency physician activation of the catheterization laboratory demonstrates very high rates of accurate STEMI diagnosis while markedly reducing the time to definitive therapy with very low rates of false activation (i.e., the STEMI mimicker).[199–201] The ACC/AHA recognizes the numerous challenges and potential difficulties in achieving these reperfusion therapy time goals.[7]

Reperfusion Therapy in Cardiogenic Shock

Patients with AMI who present with cardiogenic shock, which occurs in up to 10% of cases, demand special consideration because of a mortality rate approaching 80%. Fibrinolysis is not effective in these patients, with a significantly lower coronary perfusion pressure. In shock, the occlusive thrombus is not exposed to the fibrinolytic agent, resulting in clinical failure of the drug. In large fibrinolytic trials such as GISSI-1[179] and ISIS-2,[174] AMI patients presenting in cardiogenic shock do not benefit from fibrinolysis. Conversely, primary PCI has been investigated in more than 600 patients in several small studies. A cumulative analysis revealed a significantly lower mortality rate (45%) compared with placebo or historical controls.[202] The SHould we emergently revascularize Occluded Coronaries in cardiogenic shocK? (SHOCK) trial[203] compared the outcomes of AMI patients presenting in cardiogenic shock. Patients were randomly assigned to emergency revascularization (PCI or emergent CABG) or initial medical stabilization, including fibrinolysis. The primary endpoint was mortality from all causes at 30 days; 6-month survival was the secondary endpoint. Overall mortality at 30 days did not differ significantly between the revascularization and medical therapy groups. Six-month mortality was lower in the revascularization group than in the medical therapy group. The investigators conclude that in AMI patients with cardiogenic shock, emergency revascularization does not significantly reduce overall mortality at 30 days. After 6 months, however, there is a significant survival benefit. Thus, when catheterization facilities are not available, fibrinolytic therapy should be given to eligible patients, and urgent transfer to an interventional facility should be strongly considered.[203]

Resuscitated Cardiac Arrest with STEMI

The management of the STEMI patient resuscitated from cardiac arrest includes strict blood pressure and serum glucose control as well as the consideration of therapeutic hypothermia. Specific STEMI issues to consider include not only the type of reperfusion therapy offered but also the extent and timing of such treatment. In a series of 186 patients who underwent immediate PCI after successful resuscitation for cardiac arrest complicating STEMI, PCI was successful in almost 90%, restoring adequate coronary perfusion. Interestingly, 54% survived beyond 6 months with a large proportion with intact neurologic function.[204] A second investigation reviewed 135 patients with resuscitated cardiac arrest complicated by STEMI. Among those patients who were conscious at the time of PCI, invasive therapy restored coronary perfusion in 96% of cases, and all of these patients survived without neurologic deficit. The outcome in the comatose patient subgroup was less favorable, with approximately a 50% survival rate demonstrating good neurologic outcome.[205]

Another study compared reperfusion strategies in cardiac arrest survivors who experienced STEMI in the immediate postresuscitation period. Regardless of the reperfusion method, approximately 65% of patients survived to 6 months, with 53% demonstrating good neurologic function. The rate of an adverse event such as significant hemorrhage in those patients who received greater than 10 minutes of CPR was similar in those patients who did and did not receive a fibrinolytic agent.[206]

Therapeutic hypothermia, when combined with PCI, in resuscitated cardiac arrest STEMI patients demonstrates an impressive rate of survival with good neurologic outcome. In a series of 40 such patients, therapeutic hypothermia coupled with PCI demonstrated a significantly improved survival.[207] These retrospective case series suggest that aggressive reperfusion therapy may contribute to a favorable survival rate in the resuscitated cardiac arrest STEMI patient with either fibrinolytic or PCI reperfusion therapy.

Transfer of a Patient with Acute Coronary Syndrome

There are several indications for the transfer of a patient with ACS to a facility with PCI capability. These include rapid access to PCI (catheter across the lesion within 90 minutes of arrival to the initial hospital), persistent hemodynamic instability or ventricular dysrhythmias, and postinfarction or postreperfusion ischemia. Hospital transfer for PCI is also suggested in patients with fibrinolytic contraindications who may benefit from PCI or CABG.

The urgent transfer of a fibrinolytic-eligible STEMI patient for PCI to another institution is not recommended until fibrinolytic therapy is initiated if a delay in PCI application is anticipated.[185] In fact, the ACC/AHA notes "in hospitals without PCI capability, immediate transfer for primary PCI is a treatment option when the expected door-to-balloon time is within 90 minutes of first medical contact."[7] If delays in PCI performance are anticipated and the patient is an acceptable candidate for fibrinolysis, the fibrinolytic should be started before or during transport to the receiving hospital.

Many institutions are not PCI capable. Thus, the decision for the emergency physician involves not only the relatively simple "lytic vs. PCI" issue but also the potential need for urgent transfer to a larger center. The Primary Angioplasty in patients transferred from General Community hospitals to specialized PTCA Units with or without Emergency thrombolysis (PRAGUE) investigators explored the potential benefit of PCI over fibrinolysis and the all-important impact of transfer in the STEMI patient presenting to a noninterventional hospital over a multiyear follow-up study. At the end of the 5-year period, the cumulative incidence of composite endpoint (death from any cause, recurrent infarction, stroke, and/or revascularization) was 53% in fibrinolytic patients compared with 40%

in the PCI group. The investigators concluded that the early benefit from a transfer-related invasive strategy is sustained over the 5-year follow-up period. The benefit is obtained largely due to a lower event rate in the first 30 days following presentation.[208]

The potential need to transfer the STEMI patient over long distances can also impact reperfusion therapy decisions. In a study of patients presenting to rural hospitals in central Illinois, a standard treatment protocol initiated by the emergency physician included rapid hospital transfer for PCI. Fibrinolysis was used at the discretion of the treating emergency physician when either unanticipated delays occurred or the physician felt such therapy was necessary. In this study, the median initial hospital arrival to transfer initiation time was 46 minutes; a large portion of this delay was due to the transport vehicle. The transferring and accepting hospital arrival to catheter median placement times were 29 minutes and 35 minutes, respectively. Overall, the initial hospital arrival to catheter placement times was 117 minutes. No transfer-related complications occurred. Sixty percent of STEMI patients received some form of reperfusion therapy in this rural system within 120 minutes.[209] This prolonged transport issue is also explored in an established treatment system involving 30 hospitals ranging up to 210 miles from the PCI center. Over a 2.5-year period, 1345 consecutive STEMI patients were managed, including 1048 patients transferred from non-PCI hospitals.[210] These two investigations suggest that rapid transfer for PCI in the STEMI patient can occur in the rural setting with acceptable time to therapy.

Potential Pharmacologic Management Approach

The patient with stable chest pain who presents with a normal to minimally abnormal ECG and a negative serum marker is best managed initially with NTG sublingually or topically in combination with aspirin. Resolution of the discomfort with continued stability probably does not warrant further ED pharmacologic management. Continued or recurrent pain in the ED may be treated with parenteral morphine sulfate. Continued pain may ultimately require intravenous NTG and heparinization with unfractionated or LMW heparin with additional antiplatelet therapy using either clopidogrel or GPI. The patient with "stable" UA (i.e., new-onset or altered pattern but now symptom free and lacking abnormal serum markers and ECG) does not require heparin or other more aggressive platelet inhibition therapy in most cases.

The ACS patient with an abnormal ECG, particularly ST segment and T wave abnormalities, or elevated serum markers may warrant numerous therapies, including ASA, heparin, and other antiplatelet agents. NTG may be administered by the topical or intravenous route. The patient with recurrent angina may also benefit from such an approach. Heparin therapy is generally indicated in this instance.

The AMI patient without ST segment elevation requires aspirin, NTG, heparin, and morphine sulfate. Depending on hospital protocols and the type of ACS, clopidogrel can be administered in the ED or in the coronary care area. The patient with ST segment elevation AMI is treated with the preceding medications as well as considered for urgent revascularization, achieved by either fibrinolytic agents, PCI, or, in the rare case, CABG. Patients who are to undergo acute PCI should receive GPI therapy, either in the ED or in the catheterization laboratory, depending on the local protocol.

KEY CONCEPTS

- Anginal equivalent symptoms that are not characteristically associated with ACS vary widely and often distract from the diagnosis. Consider the age, diabetes, ethnicity, and gender with an atypical history.
- Limitations of the 12-lead ECG in ACS include initial nondiagnostic findings, evolving fluctuations with ongoing symptoms, anatomic myocardial "blind spots," and confounding or obscuring patterns, such as LBBB.
- Biochemical markers for ischemia and infarction have a pivotal role for diagnosis, risk stratification, and treatment of ACS. Serial testing strategies substantially improve sensitivity when indicated.
- Functional testing strategies for ACS include graded exercise testing, echocardiography, myocardial scintigraphy, and coronary CT. Graded exercise testing with or without nuclear scintigraphy can be used in the patient with low to moderate suspicion for CAD who is able to exercise. Myocardial scintigraphy with pharmacologic stress can be used in the debilitated or older patient (i.e., unable to exercise). Echocardiography with pharmacologic stress is appropriate for the woman over age 45 years, the patient with diabetes mellitus, and in those patients with other forms of organic heart disease (valvular dysfunction and low cardiac output states). Coronary CT is still a new testing modality; its use is most appropriate in the younger patient yet its widespread application cannot be advised in that little data exist to appropriately guide its use.
- Advancements in other noninvasive imaging to assess ACS include coronary CTA and "triple rule-out" MDCT protocols; their role in the ED remains undefined.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 77 Dysrhythmias

Donald M. Yealy and Theodore R. Delbridge

The term *dysrhythmia* denotes any abnormality in cardiac rhythm. In this chapter, we review dysrhythmias outside of cardiac arrest and those secondary to toxidromes. The physiology of normal and abnormal cardiac impulse formation and conduction is summarized, and diagnostic tools including the history, physical examination, and surface electrocardiogram (ECG) are discussed. With each rhythm disturbance, treatment options are identified for care prior to and in the emergency department (ED).

CARDIAC CELLULAR ELECTROPHYSIOLOGY

The function of individual cells in the conductive and contractile tissues of the heart depends on an intact resting membrane potential. Na^+, K^+, and Ca^{2+} ions create the membrane potential and regulate conduction, hence contraction. The membrane potential is the result of a differential concentration of Na^+ and K^+ on each side of the cell membrane. The potential measures approximately 90 mV in normal resting nonpacemaker cells, with a relative net negative charge in the intracellular area (Fig. 77-1). This electrical gradient exists mainly due to the sodium-potassium exchange pump and the natural concentration-dependent flow of K^+ out of the cell. A Na^+-Ca^{2+} exchange also exists, regulating the intracellular concentration of Ca^{2+}, although this latter exchange contributes more to myofibril contraction than conduction.

Adenosine triphosphate (ATP) fuels Na^+ transport out to the extracellular fluid, with Mg^{2+} used as a cofactor (see Fig. 77-1). This process creates an osmotic gradient, allowing Ca^{2+} to be exchanged for Na^+ without energy expenditure. Disturbances in intracellular and extracellular ion concentrations from ischemia, electrolyte abnormalities, metabolic derangements, or drugs can alter the membrane potential and disrupt normal impulse generation, conduction, and myofibril contraction.

The remaining 90 mV of the resting membrane potential is generated from the flow of K^+ down a concentration gradient toward the extracellular fluid (see Fig. 77-1). The cell membrane is far more permeable to potassium than sodium ions, resulting in a greater loss of intracellular positive charge. Abnormalities in the K^+ gradient, as in extracellular hyperkalemia, can interfere with normal impulse formation and conduction.

In normal nonpacemaker cells, the application of an electrical stimulus causes the membrane potential to become less negative, termed *depolarization*. When the membrane potential reaches −70 mV, specialized channels open for Na^+ entry, causing a rapid influx of positive charge into the cell. This "fast" channel activity further decreases the membrane potential and is augmented at approximately −30 to −40 mV by a second "slow" channel that allows Ca^{2+} influx. When channels close, the resting potential is restored by the sodium-potassium pump and the K^+ concentration gradient, an event known as *repolarization*. This cycle can be traced with a cell microelectrode and is called the *action potential* (Fig. 77-2).

The microelectrode identifies the phases of cell energy change. Phase 4 represents electrical diastole, with the normal cell membrane at a resting potential of −90 mV. Nonpacemaker cells maintain this potential until an electrical stimulus arrives. When a stimulus arrives, abrupt membrane depolarization occurs (phase 0). Phase 1 is a short period of membrane repolarization, caused by the closure of the fast Na^+ channels and transient K^+ efflux from the cell. Phase 2 is the plateau phase of the action potential, in which the slow Ca^{2+} channels remain open, maintaining a near balance between ion influx and efflux. During this phase, an increase in the cytosol Ca^{2+} concentration occurs as both the extracellular and intracellular (within the sarcoplasmic reticulum) stores are mobilized. This increase in intracellular Ca^{2+} concentration facilitates mechanical coupling and myofibril contraction. Phase 3 represents the rapid membrane repolarization period as the slow channels close and K^+ flows down the concentration gradient. The ATP-driven pump exchanges Na^+ and K^+ until the phase 4 resting potential is reached.

In nonpacemaker cells, additional depolarization from a second electrical stimulus is not possible when the membrane potential is more positive than −60 mV (initially achieved during phase 0 and maintained until phase 3), irrespective of impulse strength. This period is termed the *effective refractory period* (Fig. 77-3). At a membrane potential of −60 to −70 mV, a strong impulse can cause a response that is likely to be propagated, although abnormally; this response represents the *relative refractory period* (see Fig. 77-3). At a membrane potential of −70 mV or less, virtually all fast channels are ready for activity if properly stimulated.

Pacemaker cells differ from non-impulse-generating cells in two ways: their resting membrane potential is less negative, and they can spontaneously depolarize via slow Na^+ influx during phase 4 (see Fig. 77-2). Pacemaker cells exist normally within the sinoatrial (SA) and atrioventricular (AV) nodes, with others found on the atrial surfaces of the AV valves and within the His-Purkinje system. Nonpacemaker cells may develop

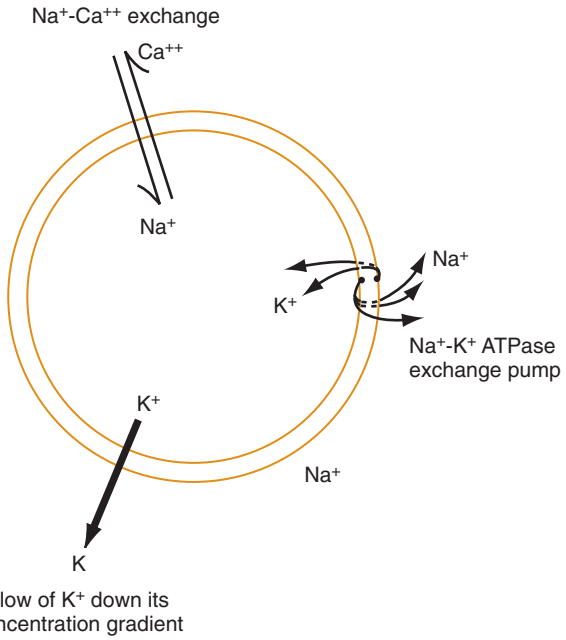


Figure 77-1. Flow of various ions across the myocardial cell membrane. Na^+-K^+ pump exchanges three Na^+ ions for each two K^+ ions, generating a net negative flow of 10 mV. The flow of K^+ down the concentration gradient *(dark arrow)* generates another 80 mV of current. The Na^+-Ca^{2+} exchange adds little to the resting potential. ATPase, adenosine triphosphatase. (From Marriott HJL, Conover MB: Advanced Concepts in Arrhythmias, 2nd ed. St. Louis, Mosby, 1989.)

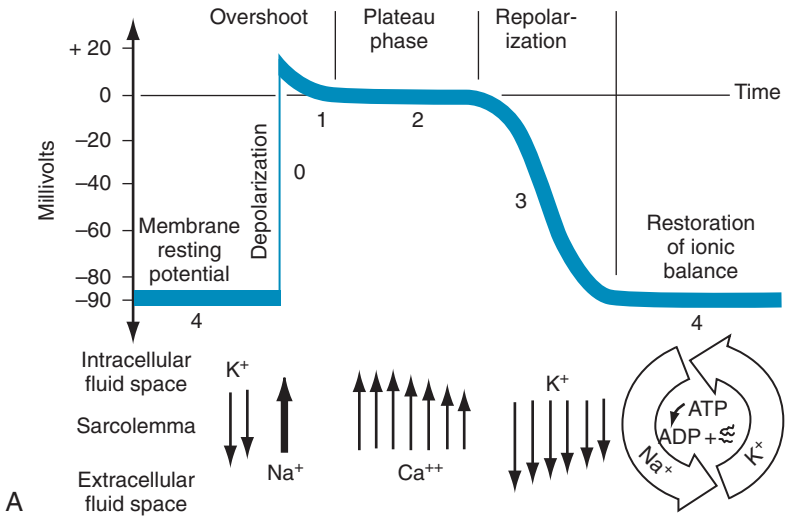
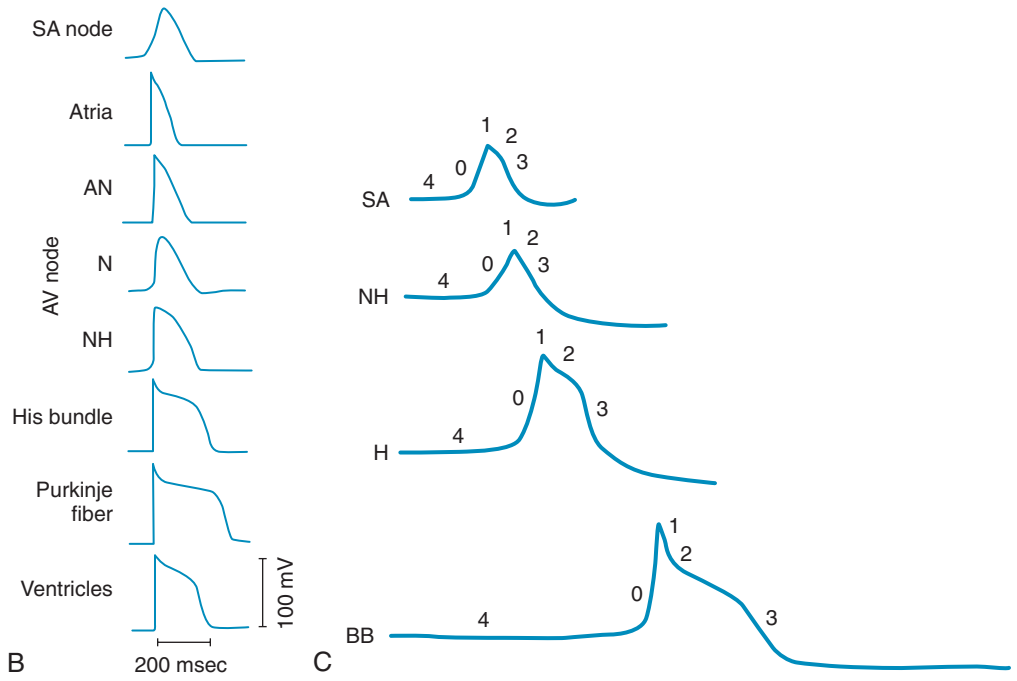


Figure 77-2. **A,** Action potential of a myocardial cell and its relation to ion flow. **B,** Action potentials of various myocardial tissues. **C,** Action potentials of various pacemaker cells. Note that phase 4 becomes flatter as location becomes more distal. AN, atria-nodal; AV, atrioventricular; BB, bundle branch fascicles; H, His bundle; NH, nodal-His; SA, sinoatrial. (**A** and **B,** from Calcium in Cardiac Metabolism. Whippany, NJ, Knoll Pharmaceutical Co., 1980; **C,** from Conover M: Understanding Electrocardiography, 5th ed. St. Louis, Mosby, 1988.)



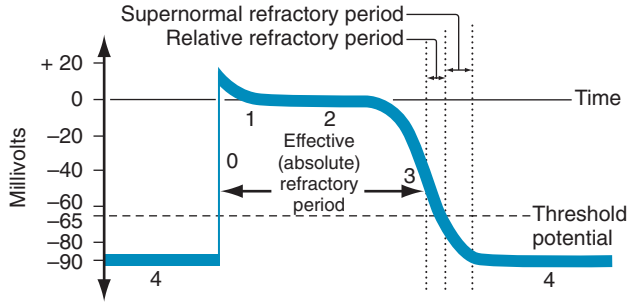


Figure 77-3. Action potential showing various refractory periods. (From Calcium in Cardiac Metabolism. Whippany, NJ, Knoll Pharmaceutical Co., 1980.)

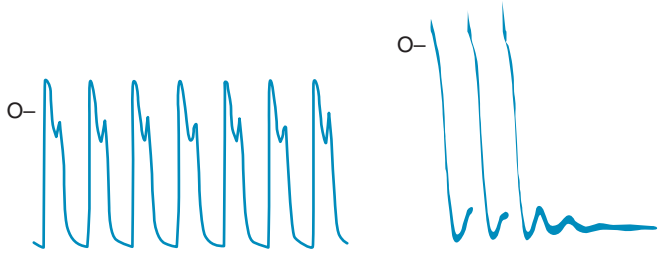


Figure 77-4. Early after-depolarizations *(left)* compared with delayed after-depolarizations *(right)*. (From Marriott HJL, Conover MB: Advanced Concepts in Arrhythmias, 2nd ed. St. Louis, Mosby, 1989.)

altered resting potentials and undergo spontaneous depolarization under pathologic conditions, especially during ischemia.

After-depolarizations are fluctuations in membrane potential that occur as the resting potential is approached. These fluctuations may precipitate another depolarization (Fig. 77-4). After-depolarizations can occur just before full resting potential (early after-depolarizations) or after full resting potential (delayed after-depolarizations) is reached. Delayed after-depolarizations can arise from ischemia, pump failure, catecholamine excess, or electrolyte disturbances (especially K^+, Mg^{2+}, and Ca^{2+}) and are enhanced by faster heart rates. Early after-depolarizations are associated with high resting membrane potentials and are more likely with slower heart rates.

■ ANATOMY AND CONDUCTION

The SA node is located at the junction of the right atrium and the superior vena cava. It is supplied by the right coronary artery (RCA) in 55% and the left circumflex artery (LCA) in 45% of patients. The normal SA node produces spontaneous depolarizations at a faster rate than other pacemakers and functions as the dominant pacemaker. When the SA node is injured or when other pacemakers generate impulses at a faster rate, nonsinus cardiac rhythms are observed. The SA node is normally under a slight parasympathetic dominance, which maintains the resting heart rate between 60 and 90 beats per minute in most adults. Patients whose parasympathetic tone is lost—after heart transplantation or with certain drugs—may have slightly higher resting heart rates. Hypothermia and increased relative vagal stimulation slow the rate of SA node impulse formation, whereas hyperthermia and increased relative sympathetic stimulation can increase the rate. Other pacemaker sites may be similarly affected by temperature and autonomic tone.

Figure 77-5 correlates the normal surface ECG events with those occurring at the electrophysiologic level. The impulse

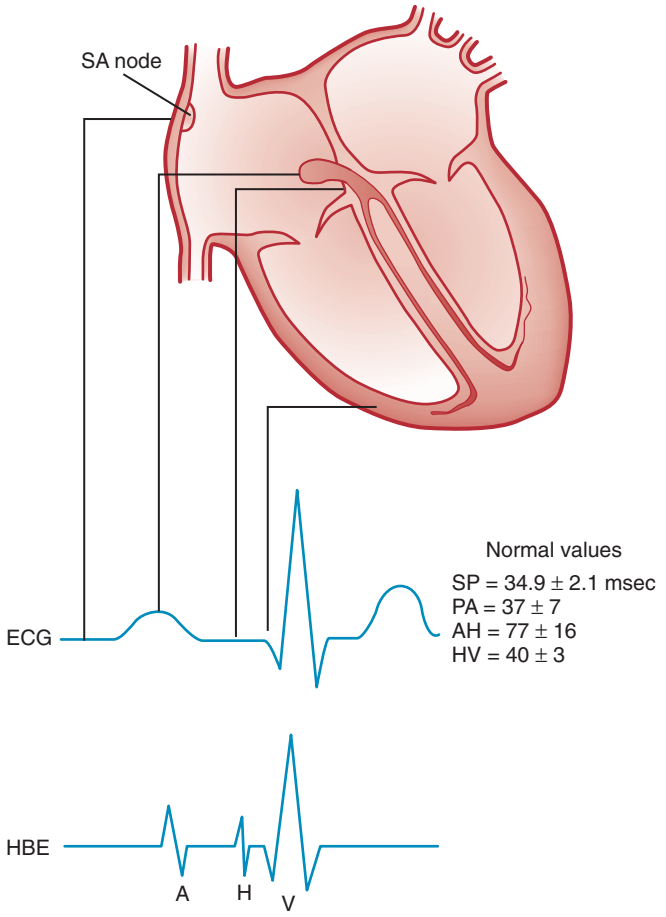


Figure 77-5. Electrical events in the heart related to surface electrocardiogram (ECG) and His bundle electrogram (HBE). Approximate relationship of sinus node discharge is also related to surface ECG. AH, atrioventricular nodal conduction time; HV, His-Purkinje conduction; PA, intra-atrial conduction time; SA, sinoatrial; SP, SA conduction time. (From Marriott HJL, Conover MB: Advanced Concepts in Arrhythmias, 2nd ed. St. Louis, Mosby, 1989.)

Table 77-1 Conduction Velocities in Various Heart Tissues

TISSUE	VELOCITY (M/SEC)
Atrium	1000
Atrioventricular node	200
His-Purkinje system	4000
Ventricles	400

generated from within the SA node, imperceptible on the surface ECG, is propagated through the atrial tissue to the AV node. The atrial depolarization wave is characterized by the P wave on the surface ECG. The AV node is supplied by a branch of the RCA in 90% (termed right-dominant circulation) and by the LCA in the remaining 10% of patients (left-dominant circulation). Transport of the impulse within the AV node is slower than other areas of the conducting system (Table 77-1) because of the dependence on slow-channel ion influx to depolarize the cell membranes. This delay limits the ventricular rate and allows complete atrial emptying, providing a greater ventricular diastolic volume and increased stroke volume.

The two functionally distinct pathways within the AV node are termed alpha and beta. The alpha pathway has relatively

slow conduction and a short refractory period, and the beta pathway exhibits faster conduction and a longer refractory period. These paths are important in sustaining a reentrant tachycardia. The PR interval (normally 0.10–0.20 second) represents the time needed for conduction of a sinus impulse through the atria and AV node. Impulses originating in the low atrial tissues, the AV junction, or other infranodal tissues are associated with a shortened PR interval, along with impulses conducted to the ventricles by accessory pathways. PR prolongation usually results from nodal or supranodal conduction system disease.

After entry into the AV node, the impulse propagates down through the His bundle to the three main bundle branch fascicles. The His bundle is the most distal portion of the AV node and derives its blood supply from the RCA and left anterior descending (LAD) artery. The bundle branch fascicles beyond the His area supply the right bundle branch (RBB), left anterior-superior bundle (LASB), and left posterior-inferior bundle (LPIB) ventricular myocardium. Before separating into the three fascicles, His bundle fibers assume a topographic distribution. Thus, the appearance of a specific bundle branch pattern on the ECG can be the result of injury within a specific bundle branch or fascicle. The RBB and LASB are supplied by the LAD artery, and the LPIB can be supplied by either the RCA or the LCA. Occlusion of these vessels can cause a variety of conduction abnormalities. Commonly, RCA occlusion causes AV node block, whereas LAD artery occlusion usually causes infranodal (bundle branch) block.

After conduction down the three main bundle branches, each impulse is delivered to the Purkinje fibers. These Purkinje fibers propagate the impulse to the ventricular myocardial tissues in a rapid and orderly fashion, allowing coordinated contraction and ejection of the ventricular contents. The QRS complex on the ECG is normally 0.09 second or less and represents ventricular depolarization; the T wave reflects repolarization. The total time of ventricular depolarization and repolarization is represented by the QT interval. The normal duration of the QT interval must be corrected for age, sex, and heart rate but is usually less than half of the R-R interval (between two surface beats).

The time required for complete conduction system repolarization is a function of the preceding cardiac cycle length. Shorter cycle lengths, represented as shorter preceding R-R intervals (i.e., faster heart rates), beget a shorter repolarization time. Conversely, longer cardiac cycles (slower heart rates) are associated with longer repolarization times. If an underlying slow sinus rhythm is present and an ectopic atrial impulse arrives between sinus impulses, the ectopic impulse may be conducted aberrantly (if bundles are relatively refractory), or it may be blocked (if the bundles are completely refractory). The preceding cycle is called the setup cycle because it dictates the refractory time of the infranodal conducting tissues.

The *Ashman phenomenon* refers to aberrant ventricular conduction of an atrial extrasystole after a long setup cycle, occurring in any irregular atrial dysrhythmia. Classically, the Ashman phenomenon is seen in atrial fibrillation, in which long-short cycle sequences are common. In normal subjects the RBB is the last part of the infranodal system to repolarize completely. Thus, aberrantly conducted impulses in the Ashman phenomenon usually assume a right bundle branch block (RBBB) appearance on the ECG.

Normally, the AV node is the preferred path for impulse delivery to the infranodal conducting system. In some patients, pathologic accessory pathways connecting atrial, infranodal conducting, and ventricular myocardial cells exist. These accessory pathways do not share the normal conduction delay of the AV node and may allow a rapid ventricular response rate and subsequent reduced cardiac output when supplanting the normal conduction system. *Preexcitation* refers to the early depolarization of ventricular myocardium when accessory paths are employed instead of the normal conduction system.

The AV node may serve as a subsidiary pacemaker in the absence of normal SA node activity; this node has an intrinsic impulse formation rate of 45 to 60 beats per minute. Infranodal pacemakers, found within the His bundle, the Purkinje system, and the bundle branches, usually function at a rate of 30 to 45 beats per minute. These rates may vary widely based on the underlying pathologic process present. In addition, as a result of ischemia or drug effect, atrial and ventricular nonpacemaker myocardial cells may become pacemakers.

MECHANISMS FOR DYSRHYTHMIA FORMATION

The three common causes of dysrhythmia formation are based on the electrophysiologic cause: altered automaticity, reentry, and triggered mechanisms. The history and ECG help distinguish between these mechanisms.

Altered automaticity can result from spontaneous phase 4 depolarization in nonpacemaker cells (abnormal automaticity) or an increase in the slope of depolarization in cells that normally undergo phase 4 depolarization (enhanced automaticity) (Fig. 77-6). Both types of altered automaticity occur in the setting of ischemia, electrolyte disturbances, and drug therapy.

Dysrhythmias caused by altered automaticity usually require a "warm-up" period. Clinically, a patient may report a gradual increase in palpitations versus an abrupt onset. A similar gradual increase in abnormal impulses on the ECG should accompany these symptoms. These dysrhythmias also tend to terminate gradually. Ventricular tachycardia within the first 24 hours after myocardial infarction is often the result of abnormal automaticity.

Enhanced automaticity occurs when catecholamine excess stimulates a non-SA nodal pacemaker source to become the dominant pacemaker. A typical enhanced automatic dysrhythmia is an idioventricular rhythm after myocardial infarction. Another enhanced automatic dysrhythmia is atrial or junc-

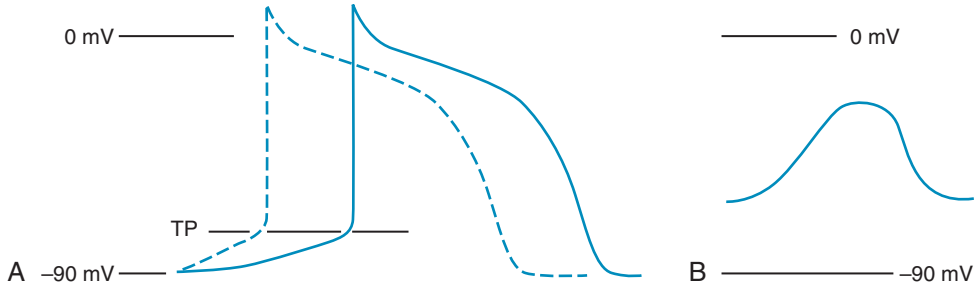


Figure 77-6. **A,** Enhanced normal automaticity *(dashed line)*. TP, threshold point. **B,** Abnormal automaticity. (From Marriott HJL, Conover MB: Advanced Concepts in Arrhythmias, 2nd ed. St. Louis, Mosby, 1989.)

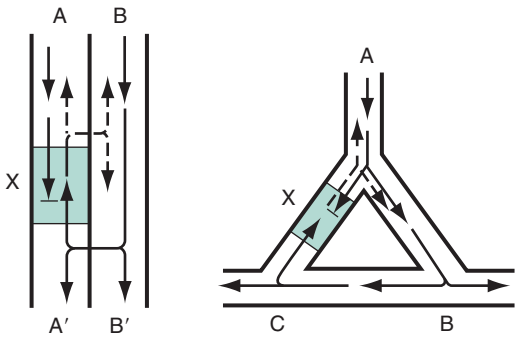


Figure 77-7. Mechanism of reentry.

tional tachycardia with digitalis toxicity. In this setting, digitalis interferes with SA node impulse conduction and increases phase 4 depolarization in other myocardial cells, resulting in this dysrhythmia.

Reentry mechanisms are a common cause of narrow-complex (QRS duration less than 0.10 second) tachydysrhythmias, accounting for 50 to 80% of these rhythms. Reentry dysrhythmias are the result of abnormal conduction, as opposed to the abnormal impulse formation that occurs with altered automaticity dysrhythmias (Fig. 77-7). For reentry to occur, three conditions must exist: two paths (or a circuit) must be available, they must have unequal responsiveness, and one path must be slower.

In a reentrant dysrhythmia, an impulse reaching a circuit finds one of the two limbs refractory. The impulse is conducted down the nonrefractory limb to the distal tissues. If the initial refractory limb recovers during the time required for the impulse to traverse the other limb, however, the impulse can then enter the distal end of the latter limb and travel in a retrograde direction. The unequal responsiveness of the limbs creates a functional unidirectional block of one. When the impulse exits the second (retrograde conducting) limb, it may then reenter the first limb. Each cycle can be repeated, creating a self-sustaining, or "circus movement," tachycardia. These cycles can be ordered or disordered (i.e., fibrillatory) and are termed *microreentry* when larger circuits are employed. In the AV node the *alpha* pathway usually serves as the anterograde limb and the *beta* pathway as the retrograde limb during a junctional reentrant tachycardia, although the converse can be seen in 10% of cases.

Reentry mechanisms are responsible for most regular narrow-complex tachycardias, some atrial and ventricular bigeminal and trigeminal rhythms, and many ventricular tachycardias. Clinically, these dysrhythmias start and terminate abruptly, without a warm-up period. Treatment is based on altering the refractoriness of the involved circuit by slowing or speeding conduction in one limb.

Triggered dysrhythmias are the result of after-depolarizations and are highly dependent on heart rate for propagation. Triggered dysrhythmias secondary to delayed after-depolarizations are associated with an intracellular Ca^{2+} overload and can occur during reperfusion therapy in myocardial infarction and with digitalis toxicity. Ectopic atrial and junctional rhythms are often the result of this mechanism, along with some forms of ventricular tachycardia and bigeminy. These dysrhythmias are enhanced by faster heart rates and are inhibited by drugs that slow the heart rate or interfere with calcium entry into the cell.

In contrast, triggered dysrhythmias from early after-depolarizations are enhanced by slower heart rates. The classic dysrhythmia associated with this mechanism is a specific form of acquired polymorphic ventricular tachycardia termed *torsades de pointes*. Increasing the heart rate by overdrive pacing or drug administration (especially beta-adrenergic agonists) can terminate triggered dysrhythmias from early after-depolarizations.

CLASSIFICATION OF DRUGS FOR DYSRHYTHMIA TREATMENT

On the basis of their effect on the action potential and on impulse conduction in myocardial tissue, the drugs used to treat dysrhythmias can be classified into four major categories (Box 77-1).

Class I agents are further subdivided into three categories (A to C). Some agents exhibit properties of more than one class; for simplicity, these agents are grouped according to their major effect. Other agents fall outside this classification system and are discussed separately.

Class I agents exert their major effects on the fast Na^+ channels, resulting in slowed conduction and membrane stabilization. The subclasses are based on specific effects on action potential duration and conduction. Class IA agents moderately slow depolarization, prolong repolarization and action potential duration, and slow conduction. Class IB agents cause minimal slowing of depolarization and conduction and shorten repolarization and action potential duration. Class IC agents markedly slow depolarization and conduction and prolong repolarization and action potential duration.

Class II agents are the beta-adrenergic antagonists (blockers); these agents slow the SA node rate and AV node conduction. Beta-blockers also prolong the action potential and can depress conduction in ischemic myocardial tissues, although the normal His-Purkinje system is unaffected.

Class III agents prolong the action potential and refractory period duration, thus exhibiting a clinical antifibrillatory effect.

Class IV agents are the slow Ca^{2+} channel entry antagonists, causing a depression of anterograde conduction through the AV node and suppression of other calcium-dependent dysrhythmias. Miscellaneous agents important in the emergency treatment of dysrhythmias include magnesium sulfate, digitalis, and adenosine.

Although all class I to IV drugs are used as antidysrhythmics, they are also associated with "prodysrhythmic" effects. The term refers to the exacerbation or the provocation of a dysrhythmia after institution of drug therapy.[1,2] Prodysrhythmia occurs most often in those with existing structural heart disease receiving new or high doses of inciting agents, although it can occur with any use of these drugs. The class I and III agents cause prodysrhythmic effects in up to 15% of patients, including ventricular tachycardia. In general, the class IB agents are associated with the least (<2% incidence) and the class IC agents the most frequent (5–15% incidence) prodysrhythmic effects. One investigational class IC agent, vernakalant, has atrial specific activity, offering potential advantages in treating atrial dysrhythmias and limiting ventricular prodysrhythmia.[3] For the classes II and IV agents, the prodysrhythmic effects are an extension of the electrophysiologic actions manifested as bradycardia and increasing AV nodal block.

Class IA Agents

All class IA agents slow conduction through the atria, AV node, and His-Purkinje system directly and decrease conduction in accessory pathways. Class IA agents also exhibit anticholinergic and negative inotropic effects, with disopyramide displaying the most prominent and procainamide the least effect on contractility. Both procainamide and quinidine have periph-

BOX 77-1 CLASSIFICATION OF ANTIDYSRHYTHMIC DRUGS

Class I
Sodium (fast) channel blockers. Slow depolarization with varying effects on repolarization. These "membrane-stabilizing" drugs have prominent antiectopic effects.

Class IA
Moderate slowing of depolarization and conduction. Prolong repolarization and action potential duration.
Quinidine
Procainamide
Disopyramide

Class IB
Minimally slow depolarization and conduction. Shorten repolarization and action potential duration.
Lidocaine
Phenytoin
Tocainide
Mexiletine
Moricizine*
Aprindine

Class IC
Markedly slow depolarization and conduction. Prolong repolarization and action potential duration.
Flecainide
Encainide
Lorcainide
Propafenone*
Vernakalant (atrial specific/investigational)

Class II
Beta-adrenergic blockers
Propranolol
Esmolol
Acebutolol
Nadolol
Metoprolol
Atenolol

Class III
Antifibrillatory agents. Prolong action potential duration and refractory period duration with antifibrillatory properties.
Bretylium (historical significance)
Amiodarone
Dofetilide
Ibutilide†
Sotalol†
Dronedarone
Azimilide

Class IV
Calcium (slow) channel blockers
Verapamil
Diltiazem

Miscellaneous
Digitalis
Magnesium sulfate
Adenosine

*Shares effects with class IA agents.
†Shares activity with class II agents.

eral vasodilatory actions as a result of alpha-adrenergic blockage, which contributes to hypotension after administration. Disopyramide has vasoconstrictor properties, which together with its marked negative inotropic effects limits its use for acute dysrhythmia treatment.

Each class IA agent has high oral bioavailability. This route may be useful in the emergency treatment of certain dysrhythmias when symptoms are minimal. All class IA agents, particularly quinidine and procainamide, prolong ventricular repolarization and lengthen the QT interval. These changes mirror an increased risk of acquired polymorphic ventricular tachycardia in some patients treated with these agents. The aggregate incidence of prodysrhythmic effects appears to be approximately 5% with this class.

Procainamide

Procainamide is the most commonly used class IA agent in the emergency treatment of selected ventricular and supraventricular dysrhythmias.[4,5] Intravenous procainamide at a rate of 20 to 30 mg/min is recommended until the dysrhythmia is terminated, hypotension occurs (defined as a drop in the mean blood pressure of 15% or greater of the pretreatment value, or to a systolic pressure below 90 mm Hg), the QRS complex widens (to >50% of the pretreatment width), or a total dose of 18 to 20 mg/kg is administered (12 mg/kg if congestive heart failure is present). For convenience, some clinicians routinely start with a loading dose of 1 g, though this arbitrary limit can impair the success of this agent.

As result of its anticholinergic properties, intravenous procainamide may cause a transient increase in heart rate when used to treat a supraventricular dysrhythmia. A decrease in heart rate from its direct effect on AV nodal conduction and depolarization may also occur and force the termination of its use because of bradycardia. If successful, intravenous maintenance therapy is at a rate of 1 to 4 mg/min, with the lower rate suggested for elderly, congestive heart failure, and renal failure patients.

Oral therapy can be started at 2 g daily in divided doses (depending on the preparation) and titrated to effects and serum levels of procainamide and *N*-acetylprocainamide (an active metabolite). In addition to prodysrhythmia, other complications include heart block, orthostasis, abnormal liver function tests, and a lupus-like autoimmune syndrome. All side effects improve when the drug is discontinued.

Quinidine and Disopyramide

Quinidine and disopyramide are rarely used in current practice. While available for emergent rhythm control, both are better suited for long-term oral therapy. Oral quinidine is well absorbed and is eliminated primarily by hepatic metabolism (50–80%), with some renal excretion. The initial daily oral dose for adults is 150 to 300 mg every 6 hours, with therapeutic serum levels of 3 to 8 µg/mL. Oral quinidine can also be used in the pharmacologic conversion of atrial fibrillation but requires extended (2–6 hours) observation (see Box 77-1). Quinidine may have a role in ventricular dysrhythmia prevention in Brugada's syndrome. Sustained-release preparations are best reserved for use after successful titration with short-acting preparations.

Intravenous disopyramide is not approved for use in the United States. Oral doses are well absorbed (80–95%) by the gastrointestinal tract and are eliminated by hepatic metabolism (50%) and renal excretion. Treatment begins with 400 to 800 mg/day in four divided doses, and the therapeutic serum level during long-term use is 2 to 4 μg/mL. Approximately 15 to 20% of patients treated with disopyramide develop new or increased clinical signs of congestive heart failure, limiting its long-term use.

Class IB Agents

Class IB agents slow conduction and depolarization the least of the class I agents, and they shorten repolarization and action potential duration instead of the prolongation seen with the classes IA and IC agents. These agents have little effect on accessory pathway conduction. The two class IB agents most commonly administered are phenytoin and lidocaine.

Lidocaine

Lidocaine is rapidly absorbed by the gastrointestinal tract but largely inactivated by first-pass hepatic metabolism, limiting oral utility. Lidocaine can suppress dysrhythmias secondary to enhanced automaticity, although it has little effect on abnormal automatic rhythms. When used for ventricular dysrhythmias, lidocaine successfully terminates 60 to 90%, depending on the specific rhythm encountered and the dose used.[6] Lidocaine can also depress SA and AV node conduction and slow the ventricular rate, usually in the presence of myocardial ischemia. These pharmacologic properties may disproportionately limit its clinical popularity, despite the small risk, ease of use, and effectiveness. In atrial fibrillation or flutter, lidocaine may cause a transient increase in conduction and heart rate. Otherwise, it is usually devoid of effects on autonomic and vascular tone, myocardial contractility, and the surface ECG in therapeutic doses.

Phenytoin

Phenytoin is mostly used for the treatment of generalized seizures, but it can have a limited role in the emergency treatment of dysrhythmias. Phenytoin is 70 to 90% protein bound and is eliminated primarily by hepatic metabolism, with only 5% excreted by the kidneys. During long-term outpatient use, the daily dose often must be lowered as metabolism slows. Many drugs increase or decrease phenytoin levels through their effects on protein binding and metabolism.

Intravenous phenytoin should be infused at a rate no greater than 50 mg/min (25 mg/min in those with heart failure). In therapeutic doses, phenytoin has little effect on the ECG aside from mild shortening of the PR and QT intervals.[7] Intravenous loading should be discontinued if the dysrhythmia is controlled, hypotension or conduction delays develop, or after a total dose of 18 mg/kg is administered. Although serum phenytoin levels between 10 and 20 μg/mL are therapeutic for seizure prophylaxis, lower serum levels may be adequate for rhythm controls. In terms of rhythm management, phenytoin is useful only in the setting of concomitant seizures and ventricular dysrhythmia.

Other Class IB Agents

Mexiletine and tocainide are not used in the ED and rarely employed elsewhere. A positive response to intravenous lidocaine predicts successful dysrhythmia control with either of these agents. Their side effects are similar to those seen with lidocaine, although the incidence of dizziness and paresthesia is slightly greater. Moricizine hydrochloride is a phenothiazine derivative that shares activity with classes IA, IB, and IC agents. Moricizine has no role in the initial management of ventricular dysrhythmias.

Class IC Agents

The class IC agents profoundly slow depolarization and conduction and have significant antidysrhythmic properties.[1,2] The true incidence of prodysrhythmic effects in this class is unclear because these agents are used primarily in patients refractory to more conventional therapies, creating a potential magnification of the effect. Up to 15% of patients treated with class IC agents experience new or increased ventricular dysrhythmias, with up to 5% developing polymorphic or sustained monomorphic ventricular tachycardia. The incidence of prodysrhythmia, especially polymorphic ventricular tachycardia, increases when IC agents are used in high doses in those with decreased ejection fraction. The total morbidity and mortality associated with any cardiac-related event (including dysrhythmias and shock) is also relatively high when these agents are used in the long term, even in patients being treated for mildly symptomatic dysrhythmias.[8]

Class IC agents are approved only for oral use in the United States and have a limited role in the initial management of dysrhythmias. In Europe, these agents are employed for emergent intravenous dysrhythmia treatment. Each agent can increase the PR, QRS, and QT intervals on the ECG, although this does not reliably predict the risk of polymorphic ventricular tachycardia.

Flecainide

Flecainide, in addition to the electrophysiologic effects shared with all class IC agents, increases the refractory period in most accessory pathways. It has a mild negative inotropic effect, with up to 4% of patients experiencing increased heart failure. Flecainide is well absorbed from the gastrointestinal tract, with 30% excreted unchanged in the urine and 70% metabolized by the liver. The mean although variable serum half-life is 14 hours.

Flecainide controls 60 to 90% of all ventricular dysrhythmias and between 40 and 100% of supraventricular dysrhythmias. Side effects may occur in up to 40% of patients but are usually minor, and respond to a decreased dosage. These include visual disturbances, dizziness, paresthesia, headache, and nausea. An increase in ventricular rate may occur in 10% and hypotension in another 10% of patients in addition to the previously mentioned risk of heart failure. Oral therapy requires ECG monitoring for both QRS and QT prolongation. Single-dose oral flecainide can terminate atrial fibrillation in outpatients.

Encainide

Encainide has an electrophysiologic profile similar to that of flecainide, with the advantage of a less negative inotropic effect. It is well absorbed from the gastrointestinal tract, with extensive hepatic metabolism forming two active metabolites. The serum half-life of all active forms is 3 to 12 hours. Treatment is usually begun with 75 mg/day in three doses and increased every 3 to 5 days on the basis of response and side effects to a maximal daily dose of 300 mg. It it is not approved for intravenous use. The side effects and success rates are similar to those seen with flecainide.

Table 77-2 Cardiac and Respiratory Beta-Adrenergic Receptors and Responses to Pharmacologic Manipulation

RESPONSE TO RECEPTORS	LOCATION	STIMULATION	ANTAGONISM
β_1	Heart	Increased heart rate and ectopy Increased contractility	Decreased heart rate and ectopy Decreased contractility
β_2	Airway (smooth muscle) Peripheral vasculature	Decreased tone (relaxation) Decreased tone (relaxation)	Increased tone (contraction) Increased tone (contraction)

Propafenone

This agent shares properties with class IA and IC agents, with intermediary effects regarding sodium channels. It also possesses some beta-adrenergic and calcium channel–blocking properties. It is not available for intravenous use but is available for the oral treatment of atrial fibrillation and ventricular dysrhythmias. Propafenone is effective in converting and maintaining sinus rhythm in 40 to 70% of patients with atrial fibrillation and flutter.[9] Compared with other class IC agents, propafenone has a lower observed prodysrhythmic rate in therapeutic doses. Its side effects are usually related to conduction disturbances on the ECG, dizziness, dysgeusia, or blurred vision.

Vernakalant

This investigational class IC agent has atrial specific activity and converts approximately 50 to 60% of patients with new-onset nonvalvular atrial fibrillation in doses of 2 to 3 mg/kg.[3,10] Vernakalant offers promise of effects similar to class IC agents in the target rhythms with less ventricular prodysrhythmia.

Class II Agents

In general, class II agents (beta-blockers) are best suited to control ventricular response rates and break a reentrant circuit in a supraventricular dysrhythmia than to treat a ventricular dysrhythmia. In the setting of acute myocardial infarction, limiting ventricular dysrhythmia and reinfarction are important indications for beta-blockers, especially metoprolol.

All beta-blockers are active at both β_1- and β_2-receptors (Table 77-2) but to varying degrees. Those with more prominent β_1 effects are termed *cardioselective*. Through their effects on β_1-receptors, all class II agents slow SA node impulse formation and depress myocardial contractility to varying degrees. β_1 selectivity is desirable because a lowered incidence of bronchospasm is observed with therapeutic antidysrhythmic doses. The usual effect of class II agents on the ECG is slowing of the heart rate and PR prolongation, with no effect on QRS and QT duration.

Relative contraindications for beta-blockers include asthma or chronic obstructive lung disease, advanced congestive heart failure, and third-trimester pregnancy. Beta-blockers should not be used in patients with bradycardia or greater than first-degree heart block. Although often used together during long-term oral therapy, intravenous beta-blockers should be given with great caution after recent intravenous calcium channel antagonist (class IV) use because of the increased risk of hemodynamic side effects. Acute side effects of beta-blockers include bronchospasm, heart failure, excessive bradycardia, hypotension, and vasospasm (especially with Raynaud's syndrome).

Propranolol

Propranolol is nonselective and well absorbed by the gastrointestinal tract. It undergoes extensive first-pass liver metabolism after oral intake, requiring a much higher dose by this route than an equipotent intravenous dose. The serum half-life is 3 to 6 hours, requiring a four times daily dosing regimen. Therapy is usually monitored by rhythm control and side effects, not serum levels. Oral dosages begin at 80 mg/day of a short-acting preparation in divided doses. Oral propranolol is better suited for maintenance therapy than intravenous propranolol for acute dysrhythmia treatment.

Propranolol is effective in terminating 30 to 80% of reentrant supraventricular tachycardias (SVTs), depending on the pathway, especially if the rhythm is catecholamine induced. Because of its relatively long effect, it is not commonly employed in emergency settings. Its use in other rhythms is associated with a lower success rate and increased side effects when compared with class I agents.

Esmolol

Esmolol is an attractive beta-blocker in the emergency treatment of supraventricular tachydysrhythmias. It is β_1 selective with a rapid onset of action, with a 5- to 10-minute duration of effect. The brief clinical effect is the result of its short elimination half-life (9½ minutes) because of metabolism by plasma cholinesterase. An intravenous bolus of 500 µg/kg esmolol is usually followed by a continuous infusion starting at 50 µg/kg/min. Discontinuance of the infusion results in a rapid decrease in therapeutic and toxic effects. If the dysrhythmia persists after the initial bolus and infusion, a repeated loading dose should be given and the infusion rate should be increased in increments of 50 µg/kg/min. Usually an esmolol infusion rate of 200 µg/kg/min or less is effective, and the maximal recommended rate is 300 µg/kg/min.

Metoprolol

Metoprolol is available in oral and intravenous preparations. Although not approved for initial dysrhythmia treatment in the United States, metoprolol (5–10 mg IV every 10–15 minutes titrated to response) will slow atrial and nodal fast rhythms and is often used for these purposes.

Nadolol and Acebutolol

Nadolol and acebutolol are used for oral dysrhythmia treatment but are not approved for intravenous use. The effectiveness and side effect profiles are similar to those of propranolol and metoprolol, aside from a lowered risk of bronchospasm with acebutolol, which has an intrinsic sympathomimetic effect.

Class III Agents

This class is called the *antifibrillatory* group for the treatment of atrial and ventricular fibrillation. All class III agents prolong the refractory period and action potential duration but have variable effects on the QT interval.[11] In general, class III agents are alternative drugs to the class I agents for the treatment of many ventricular and atrial dysrhythmias.

Bretylium

Bretylium was previously the most commonly used class III agent. Because of its profound hemodynamic effects and the emergence of newer class III drugs, it is no longer available in the United States.

Amiodarone

Amiodarone is approved for the treatment of both ventricular[12,13] and supraventricular dysrhythmias,[14] including atrial fibrillation or flutter and accessory pathway syndromes. In addition to features of all class III agents, amiodarone prolongs the action potential duration and refractory period, slows automaticity in pacemaker cells, and slows conduction in the AV node. It also displays a noncompetitive blockade of adrenergic receptors and causes smooth muscle relaxation. When given intravenously, amiodarone may cause a mild drop in blood pressure and heart rate along with a slight decrease in contractility. The recommended intravenous dose is 3 to 5 mg/kg over 10 to 15 minutes.

After an oral dose, absorption is slow and erratic, varying widely among subjects. The serum half-life is about 50 days during long-term oral use and approximately 25 hours after a single intravenous dose. Because of the unusual pharmacokinetics, oral dosing regimens vary widely, starting at 600 to 1000 mg/day initially for up to 7 days, followed by 400 to 800 mg/day for a maintenance dosage. The acute side effects of amiodarone are primarily limited to hypotension, bradycardia, and heart failure (Box 77-2).

Between 1 and 3% of patients experience prodysrhythmia with long-term amiodarone use, often without QT prolongation. Torsades de pointes is rare (<1% with long-term use and much less with acute use). Long-term amiodarone use is associated with significant side effects, including prominent extracardiac issues, forcing many patients to discontinue treatment. Amiodarone also causes an increase in the serum level of many agents, especially digoxin and warfarin. It can cause an additive risk of bradycardia and hypotension when used in conjunction with calcium channel or beta-adrenergic blockers. Long-term amiodarone use can cause pulmonary fibrosis, which can increase dyspnea. Also, amiodarone potentiates the rhabdomyolysis seen with simvastatin, a common cholesterol-lowering agent.

BOX 77-2 ADVERSE EFFECTS OF AMIODARONE

Acute
Hypotension
Slowing of heart rate
Decreased contractility

Long-Term
Common
Corneal deposits
Photosensitivity
Gastrointestinal intolerance

Less Common
Hyperthyroidism
Heart failure
Pulmonary toxicity/fibrosis
Hypothyroidism
Bradycardia
Prodysrhythmic effect

Drug Interactions
Increases levels
Quinidine
Phenytoin
Procainamide
Warfarin
Digoxin
Flecainide

Ibutilide

This agent is approved in the United States only for intravenous use. When it is given in a dose of 0.015 to 0.02 mg/kg, approximately 50 to 65% of patients convert from atrial fibrillation or flutter to a sinus rhythm, usually within 20 minutes.[15] Prolongation of the QT interval and prodysrhythmia, especially torsades, are more common than with amiodarone when used chronically (but similarly rare in acute use) with few other side effects. This drug is an alternative to intravenous procainamide for pharmacologic conversion of atrial fibrillation and flutter in the ED, with easier use and a good safety profile offset by higher cost.

Sotalol and Other Agents

Sotalol (a mixed class III–adrenergic blocking agent) has a limited ED role and is associated with a higher incidence of prodysrhythmia (especially polymorphic ventricular tachycardia) than other class III agents. It is used intravenously for conversion of atrial fibrillation but offers limited advantages over other regimens.[14] Dofetilide, dronedarone, and azimilide are investigational class III agents that possess other properties but have not clinically replaced the class I or III agents.

Class IV Agents

Class IV agents block the slow calcium channels in myocardial and vascular smooth muscle cells. Each agent exhibits activity at both the myocardial and peripheral vascular levels, with specificity for particular areas within the group. Verapamil and diltiazem exhibit the most potent effects on myocardial cell calcium entry, conduction, and contractility. Verapamil has the least effect on peripheral vascular tone, and diltiazem has an effect intermediary between that of verapamil and nifedipine. Both verapamil and diltiazem have a role in atrial and AV nodal tachycardias. Verapamil is often forgotten or shunned because of perceived relative side effect differences compared to diltiazem, yet both perform similarly well in practice. Nonetheless, diltiazem is the much more commonly used class IV agent currently.

Verapamil and diltiazem have little direct effect on accessory pathways, but since the native conduction system may participate in such a syndrome, these should be used only when anterograde conduction through the AV node exists (seen as narrow QRS complexes). Both slow conduction within the AV node (primarily at the atrial-His level) more than within the SA node. These actions are partially reversed by atropine. After an intravenous dose of either agent, the ECG is usually unchanged aside from a slower heart rate and prolonged PR interval. Intravenous class IV drugs should not be used in patients with second- or third-degree AV block and should be used with close monitoring in those with first-degree block.

Calcium chloride, 500 to 1000 mg (5–10 mL of a 10% solution), can reverse or prevent verapamil-induced hypotension.[16,17] Calcium salts attenuate the peripheral vasodilatory

actions without altering the chronotropic (antidysrhythmic) effects of verapamil. For patients with borderline hypotension, administering 500 mg of calcium chloride prior to verapamil is an alternative approach. If verapamil-induced hypotension persists after calcium administration and intravenous fluids, use a direct-acting vasopressor. Aside from AV block, hypotension, and congestive heart failure, verapamil can cause other side effects, including nausea, vomiting, constipation, dizziness, nervousness, and pruritus.

Diltiazem

Oral doses are rapidly absorbed, although a significant first-pass effect is seen. Intravenous diltiazem (0.25 mg/kg over 2 minutes, followed by 0.35 mg/kg 15 minutes later if the first dose is unsuccessful) controls the ventricular response rate in 90% of patients with atrial fibrillation and atrial flutter and is associated with minimal hypotension.[18] If the intravenous bolus is successful, a continuous infusion (5–15 mg/hr initially) or an oral dose (60–90 mg initially) may sustain the response.

Verapamil

Verapamil terminates or controls the ventricular response rate in 80 to 90% of tachycardic rhythms.[19,20]

Intravenous verapamil is given at a dosage of 0.1 mg/kg over 1 to 2 minutes; for the average healthy adult, this translates to a dose of 5 to 10 mg. In elderly patients or those with preexisting borderline hypotension (systolic blood pressure of 90–110 mm Hg), a smaller dose (0.05 mg/kg, or 2.5-mg increments) should be employed. Repeated doses (either the same or larger, up to twice the initial dose if there is no response in younger patients with cardiovascular stability aside from tachycardia) should be given every 10 minutes on the basis of response. Use of a longer dosing interval, especially if over 30 minutes, may interfere with successful treatment of a dysrhythmia because of redistribution.

Verapamil is rapidly absorbed from the gastrointestinal tract but undergoes extensive first-pass liver metabolism. The drug is 90% protein bound and is eliminated primarily by renal excretion. After an oral dose, the duration of effect is 4 to 6 hours, with a total elimination half-life of 3 to 12 hours. Daily maintenance with 120 to 720 mg of a short-acting preparation in four divided doses is recommended for prophylaxis from recurrent dysrhythmias. A long-acting preparation of verapamil is available but not approved for the treatment of dysrhythmias.

Miscellaneous Agents

Digitalis

Digoxin is the main form of digitalis used in the emergency treatment of cardiac dysrhythmias. In addition to their positive inotropic effects, digitalis compounds have variable effects on myocardial cells (Table 77-3). These electrophysiologic effects are both excitant and depressant. Digitalis excitant effects cause an increase in altered automatic and triggered ectopic impulses, particularly when it is given in toxic doses. Digitalis also depresses conduction and lengthens refractoriness in the AV node in therapeutic doses. Although the therapeutic effects are primarily the result of the depressive actions, toxic dysrhythmias may be the result of either or both of these mechanisms.

Digitalis inhibits the membrane-bound enzyme adenosine triphosphatase (ATPase), impairing the active transport of Na^+ out of and K^+ into the cell. Aside from increasing intracellular Na^+ concentration and decreasing intracellular K^+ concentration, the disruption of the pump indirectly causes a mild increase in intracellular Ca^{2+} concentration, which accounts for the positive inotropic effects of digitalis. At usual doses, digitalis slows the heart rate and decreases the QT interval slightly. Also, characteristic ST segment depression and shortening and T wave inversion occur with digoxin therapy.

Table 77-3 Effects of Digitalis on Heart Tissues

TISSUE AND PROPERTY	DIRECT THERAPEUTIC EFFECT	DIRECT TOXIC EFFECT	INDIRECT EFFECT*
Sinoatrial node automaticity	0	D	D
Atrial conduction	0	I	D
Atrial refractoriness	I (small)	I	D
Atrioventricular node refractoriness and conduction	I (small)	I	I
Purkinje fibers			
automaticity and conduction	I (small)	I	0
Refractoriness	I (small)	D	0
Conduction	0	I	I
Refractoriness	I (small)	D	0

*Indirect autonomic effects (vagotonic and sympatholytic).
D, decreases; I, increases; 0, minimal effect.

Digitalis controls the ventricular rate in narrow-complex tachycardias, including atrial fibrillation, atrial flutter, and paroxysmal supraventricular tachycardia (PSVT). Because of its slow onset of action and narrow therapeutic window, digitalis is not a first-line agent for emergency therapy. Digoxin is a complementary agent and useful in the outpatient management of these supraventricular rhythms, particularly when underlying heart failure is present.

Emergently, the first intravenous digoxin dose is commonly 0.5 mg in adults. A clinical effect may be seen within 30 minutes, but the peak effect does not occur until 1½ to 2 hours. To optimize, repeat doses of 0.25 mg IV every 4 to 6 hours may be needed up to a total dose of 1.5 mg. The latter ceiling is arbitrary; some patients may require a higher dose to control rate but risk increased side effects.

Digoxin is excreted 50 to 75% unchanged in the urine and is 25% protein bound with a large volume of distribution. The serum half-life is 24 to 48 hours, allowing a daily or every other day maintenance regimen. Side effects of digoxin are listed in Box 77-3 and are enhanced by hypokalemia, hypercalcemia, hypomagnesemia, increased catecholamines, and severe acid-base disturbances. The concomitant use of quinidine can increase the serum levels of digoxin by interfering with renal and nonrenal elimination.

Two misconceptions about digoxin persist. Often it is used in atrial fibrillation because of a belief that conversion to a sinus rhythm is more likely than after the use of other rate-controlling agents, which is a fallacy.[21] Furthermore, beta-adrenergic and calcium channel blockers are often better tolerated than digoxin in the absence of ventricular dysfunction.[22] Another concern is the safety of cardioversion during digoxin therapy and the possible development of ventricular dysrhythmias. If no clinical or laboratory evidence of toxicity is present, cardioversion of atrial fibrillation or flutter is safe, with little added risk of precipitating ventricular dysrhythmias compared with patients not receiving digoxin.[23]

BOX 77-3 ADVERSE EFFECTS OF DIGITALIS

Common
Gastrointestinal intolerance (nausea, vomiting, abdominal pain, diarrhea, anorexia)
Fatigue
Drowsiness
Visual color disturbances
Headache
Depression
Apathy

Less Common
Psychosis
Cardiac symptoms
Heart block
Increased ectopy
Combined block and ectopy (multifocal atrial tachycardia with block or complete atrioventricular block with accelerated junctional rhythm)
Ventricular tachycardia

Magnesium

Magnesium has been in use for over 50 years as an antidysrhythmic, controlling the ventricular response rate in a variety of narrow-complex tachycardias, including atrial fibrillation, multifocal atrial tachycardia, and reentrant SVT. Magnesium (2–4 g as a slow IV bolus) can also terminate ventricular tachycardia, including digoxin-induced and polymorphic ventricular tachycardia (especially torsades de pointes).[24] Aside from a central role in the latter rhythm, magnesium is generally a second- or third-line agent.

Adenosine

Adenosine is a naturally occurring purine nucleoside used for the intravenous treatment of narrow-complex tachydysrhythmias.[25,26] It causes a concentration-dependent slowing of AV conduction and a slowing of conduction in both anterograde and retrograde paths of a reentrant circuit. Adenosine shortens the action potential duration and is devoid of effects on ventricular contractility, although it may cause a decrease in atrial contractility. In extremely low doses, adenosine causes selective coronary vasodilation. As the dose is increased to the amount needed for a maximal antidysrhythmic effect, peripheral vasodilation occurs.

After an intravenous dose, adenosine has an onset of action of 5 to 20 seconds with a duration of effect of 30 to 40 seconds. It is eliminated primarily by deamination in endothelial and blood cells, with a 10-second serum half-life. Aside from a decreasing heart rate and an increasing AV block, adenosine has little effect on the ECG. Except in rare cases of catecholamine-induced ventricular dysrhythmias, adenosine has little effect on infranodal conduction. This fact, coupled with clinical data, prompted some to use adenosine as a diagnostic agent in the wide-complex tachycardias.[27,28] For most patients with ventricular tachycardia, adenosine will have no effect on rhythm or blood pressure due to the pharmacologic behavior of the drug, though a small number will experience dysrhythmia relief and, rarely, collapse.[29,30]

An initial dose of 6 mg as a rapid bolus for adults weighing 50 kg or greater is recommended with flush through a large peripheral vein. If no response is seen within 1 to 2 minutes, the dose is doubled (12 mg) and repeated. If no effect is seen after a third 12-mg dose, the rhythm should be reassessed and another agent employed. Pediatric doses are of 0.05 mg/kg initially with doubling at similar intervals up to a total dose of 0.25 mg/kg.[26]

Side effects coincide with the onset of clinical effects and occur in up to a third of patients but are usually minor. These include flushing, dyspnea, chest pressure, nausea, headache, dizziness, transient bradycardia or heart block, and hypotension (seen rarely, from the vasodilatory properties). All resolve rapidly without treatment, although many patients are intensely uncomfortable for a short period. Other rhythms rarely seen after adenosine use include atrial fibrillation and ventricular tachycardia. Aminophylline and the other methylxanthines, caffeine and theobromine, antagonize the effects of adenosine, and dipyridamole potentiates its effects. Digitalis, calcium channel blockers, and benzodiazepines can all augment the activity of adenosine.

In comparative studies of patients with narrow-complex tachydysrhythmias, adenosine has response rates equivalent to those of verapamil and diltiazem (85–90% overall, 60% with first dose) and few serious side effects. Because of its short duration of action, recurrence of the tachycardia occurs in many (~25%). Because of the short effect, adenosine is not a therapeutic agent for atrial fibrillation or flutter and nonreentrant rhythms, although it can help unmask these rhythms when not apparent on the initial ECG. Similarly, adenosine should not replace a careful search for a ventricular source or the rare but potentially lethal combination of atrial fibrillation with an accessory pathway. The use of *any* drug that depresses the AV node primarily in these settings (including adenosine, though given the short effect it is rare) can result in precipitous hemodynamic collapse.[29,31] Finally, adenosine often fails because it is used for the wrong reason, especially unrecognized atrial fibrillation or ventricular tachycardia.

APPROACH TO DYSRHYTHMIA RECOGNITION AND MANAGEMENT

Dysrhythmias are classified according to their electrophysiologic origin, ECG appearance, and underlying ventricular rate. Although overlap exists, the following categorization is useful:

- Bradycardias, sinus and atrial rhythms, SA and AV block
- Extrasystoles and parasystoles
- Narrow-complex (QRS < 0.12 second) tachycardias
- Preexcitation and accessory pathway syndromes
- Wide-complex (QRS ≥ 0.12 second) tachycardias

The treatment of specific dysrhythmias is divided into two broad categories on the basis of clinical stability, which is a continuum. *Unstable patients* have evidence of end-organ hypoperfusion from the dysrhythmia. Bedside ED symptoms and signs of unstable rhythms are:

- Hypotension
- Chest pain suggestive of myocardial ischemia
- Dyspnea or pulmonary edema
- Altered sensorium (from agitation to coma)

The latter three are more specific because absolute blood pressure values may vary widely. For example, a patient with chronic hypertension who has a blood pressure of 110/60 mm Hg and crushing chest pain with a wide-complex tachycardia at a ventricular rate of 180 beats per minute is "more unstable" than a young woman with a similar rhythm and a blood pressure of 88/50 mm Hg without other symptoms. Patients with an unstable rhythm deserve rapid pharmacologic or electrical therapy after a focused assessment, whereas stable patients can

be treated after a more thorough evaluation to identify the exact cause. In general, rapid unstable dysrhythmias aside from sinus tachycardia require sedation and cardioversion, especially when more than one symptom or sign of instability is present. Slow unstable dysrhythmias require temporary pacing, although atropine can be used while preparing for pacing.

The Initial Assessment of Stable Patients

The approach to the patient with a stable dysrhythmia is to gather subjective and objective data concerning the underlying rhythm. The following steps are key:

- Directed history
- Physical examination
- 12-lead ECG and rhythm strip
- Diagnostic and therapeutic interventions

When caring for a stable patient with a dysrhythmia, these steps are often taken concurrently (e.g., history taking during the initial physical examination and combined ECG monitoring with certain physical examination techniques). In the presence of clear or potential instability, it is important to obtain and interpret the ECG while preparing for pacing (slow rate) or cardioversion (fast rate).

In stable patients, one should elicit the nature of any symptoms, including the timing and velocity (gradual or abrupt) of symptom onset. It is valuable to ask each patient specifically about prior or recent palpitations, dizziness, chest pain, dyspnea, or syncope. Known previous dysrhythmia, ischemic or structural heart disease, and current medications will help better assess the underlying rhythm. For example, a 22-year-old man treated with propranolol for "palpitations" who seeks treatment for abrupt onset of a regular tachycardia with a QRS duration of 0.12 second at a rate of 200 complexes per minute is more likely to have a reentrant SVT with aberrant conduction than ventricular tachycardia. Conversely, a 55-year-old man with a history of a previous myocardial infarction and taking daily amiodarone who presents with palpitations and chest pain and a similar wide-complex regular tachycardia is more likely to have ventricular tachycardia. Occasionally, the family history can be helpful. The combination of deafness with paroxysmal palpitations, syncope, and a family history of sudden death strongly suggests a specific form of torsades de pointes. Early sudden cardiac death in family members also heightens the suspicion for Brugada's syndrome.

On physical examination, one must look for evidence of end-organ hypoperfusion or clues to the cause of the dysrhythmia. Alteration in cognitive function (from mild excitation to depressed consciousness), diaphoresis, or dusky skin are findings of hypoperfusion. Cannon waves in the neck and variation in the intensity of the first heart sound or arterial pulse suggest AV dissociation, a feature of ventricular rhythms. These are a challenge to detect in most ED patients. Close auscultation of the heart sounds may detect valvular disorders. Certain clinical toxidromes, such as organophosphate, anticholinergic, and cyclic antidepressant ingestion have prominent physical findings.

The most important ECG observations are listed in Box 77-4. Diagnosis using a single lead can be adequate, but multiple leads (especially a 12-lead ECG) best define the dysrhythmia accurately. Occasionally, an apparently narrow-complex rhythm is discovered to be a wide-complex rhythm when a different lead is examined, or evidence of AV dissociation is revealed when the rhythm strip does not demonstrate this finding. The paddles from a defibrillator and monitor unit can be helpful for short periods, because a modified chest lead from this application will optimize the appearance of the P wave and QRS complexes. Finally, since the most useful information about paroxysmal dysrhythmias occurs at the onset and termination of the rhythm, these tracings should be saved.

BOX 77-4 Basic Electrocardiographic Observations During Dysrhythmia Analysis

1. Ventricular rate: Fast (>100 complexes/min), slow (<60 complexes/min), or normal (60–100 complexes/min).
2. Rhythm: Regular, completely irregular (irregularly irregular or chaotic), regular with occasional irregularities, or grouped impulses. Calipers and long strips are recommended to detect subtle irregularities.
3. QRS width: Prolonged (>0.12 sec), borderline (0.09–0.12 sec), or normal. If done without ECG physically present (e.g., prehospital radio medical command), it is helpful to ask for QRS duration in number of small boxes from printed rhythm strip (each box equals 0.04 sec) to ensure accuracy.
4. P wave presence and relationship to QRS complexes: This may require mapping of P waves with calipers to detect those falling within QRS complex or T wave.
5. Rhythm changes: Examine these areas closely for clues.
6. Multiple leads, especially chest leads or esophageal lead if difficulties with P wave visualization.
7. Comparison with previous tracings (if available) is often valuable.

A long rhythm strip (up to a minute) may be needed to define a dysrhythmia. Other adjuncts to standard ECG monitoring include increasing the paper speed and the use of esophageal electrodes. Normally, a paper speed of 25 mm/sec is used; when it is increased to 50 to 100 mm/sec, the relationship of the P wave to the QRS complex may be better defined (Fig. 77-8). Esophageal leads can also help better define the P-QRS relationship but are not readily available in most settings (Fig. 77-9).

The use of maneuvers that alter autonomic tone can help uncover the cause of dysrhythmias and terminate selected rhythms. Carotid sinus massage and the Valsalva maneuver increase vagal (parasympathetic) tone. Vagal maneuvers transiently slow AV conduction, which may help terminate or uncover the primary rhythm disturbance on the ECG.[32] The use of ice packs or cold-water head dunking (with care to avoid aspiration) has similar effects, especially in children, through the diving reflex. Carotid sinus massage is best avoided in elderly patients because of the risk of embolic phenomena. Auscultation of the neck for bruits should be performed before carotid sinus massage is attempted. Ocular or rectal massage and inflation of MAST trousers are not recommended.

The effectiveness of any maneuver alone or in various combinations compared with pharmacologic treatment is unclear. Generally, reentrant dysrhythmias abruptly terminate or continue with little change in rate, whereas atrial fibrillation and tachycardia slow temporarily. Vagal maneuvers usually fail to terminate supraventricular dysrhythmias but rarely cause deterioration. The failure of vagal efforts may be from poor technique (carotid massage should not be performed upright and should target carotid body, not the base of carotid artery) or a selection bias (those who will respond to vagal maneuvers often do so before arrival).

Pseudodysrhythmias

Occasionally, an artifact on the ECG produces an apparent dysrhythmia. Muscle contraction or movement (especially

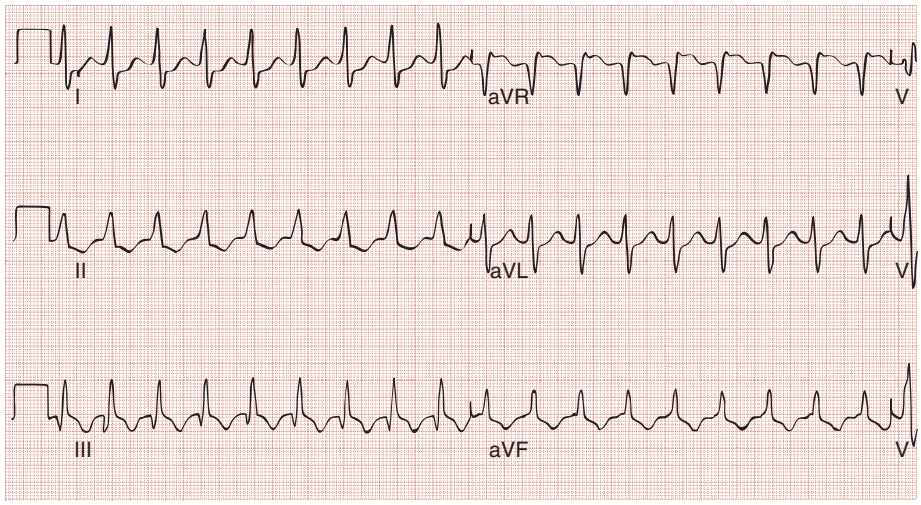


Figure 77-8. Note the P waves before the QRS complexes in lead aVF.

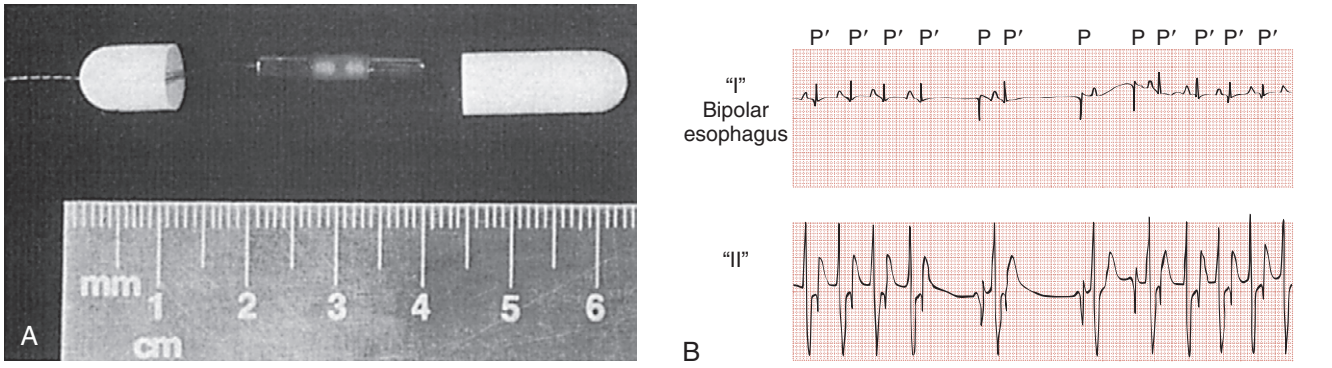


Figure 77-9. An esophageal pill electrode (**A**) and a representative tracing of a reentrant tachycardia with retrograde (P′) depolarization not appreciated on the simultaneously recorded lead II strip (**B**). (From Hammill SC, Pritchett ELC: In Campbell R, Murray A [eds]: Dynamic Electrocardiography. Edinburgh, Churchill Livingstone, 1985.)

shivering), loose leads, and stray external signals from other electrical equipment and monitoring devices can produce these artifacts, called *pseudodysrhythmias* (Fig. 77-10). These findings may often be mistaken for serious ventricular dysrhythmias, including ventricular fibrillation. Pseudodysrhythmias illustrate the need to avoid treating the ECG solely without incorporating bedside patient findings.

SPECIFIC DYSRHYTHMIAS

Bradycardia, Sinoatrial and Atrioventricular Block

Bradycardia, defined as a ventricular rate of less than 60 beats per minute, can be normal in well-conditioned subjects or the result of two basic disturbances. Depression of the dominant pacemaker, usually the sinus node, causes bradycardia. Another cause is conduction system block, in which the normal sinus node impulses are incompletely carried to the AV node and ventricular tissues. In both situations, a subsidiary pacemaker may assume the dominant role, with ventricular rates of 30 to 60 beats per minute. The rhythms seen with subsidiary pacemakers during SA and AV nodal block are called *escape* rhythms because they provide a physiologic escape from no impulse generation (asystole).

The treatment of bradydysrhythmias is based on the underlying cause and symptoms. The two options are intravenous atropine (0.5–1 mg for adults) and temporary pacing, either transcutaneous or transvenous. Bradycardias require emergency treatment only when the ventricular rate is less than 50 beats per minute with hypoperfusion or if the rhythm carries a high risk of progression to complete block. A transcutaneous pacemaker should be readily available if observation is planned. Asymptomatic bradycardia requires no therapy.

Sinus Bradycardia

Sinus bradycardia appears on the ECG as a regular rhythm at a ventricular rate below 60 beats per minute and a normal consistent P wave morphology and PR interval duration (Fig. 77-11). This pattern may be found in healthy adults, during sleep and periods of fright. Other causes include hypothermia, excessive parasympathetic or diminished sympathetic stimulation (often from drug therapy, especially beta-adrenergic and calcium channel blockers), and carotid sinus hypersensitivity. The last is sometimes seen in men with bradycardia or syncope while wearing a tight shirt collar. Sinus bradycardia may be seen in the early stages of an acute inferior wall myocardial infarction, resulting from parasympathetic stimulation. Generally, sinus bradycardia is a benign dysrhythmia and requires no specific treatment aside from that required for any underlying condition such as hypothermia or acute myocardial ischemia.

Sinus and Atrial Dysrhythmias

Sinus dysrhythmia is seen at variable rates in the normal ranges. The ECG features are similar to those of sinus bradycardia, aside from the varying and normal ventricular rate (Fig. 77-12). Atrial dysrhythmias have ECG features similar

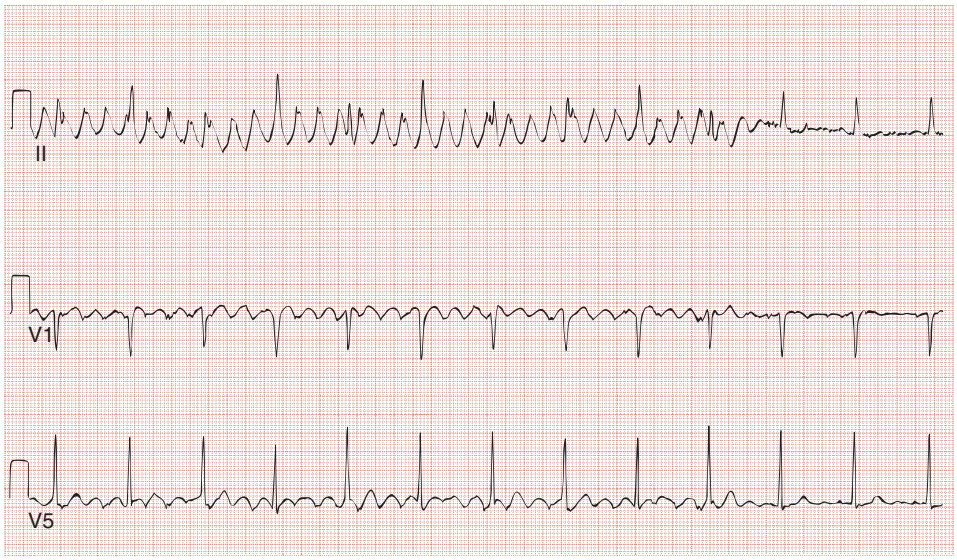


Figure 77-10. Pseudodysrhythmia. In this case, atrial flutter waves appear to be present but are recognized as an artifact when examining the patient and the right side of the electrocardiogram.

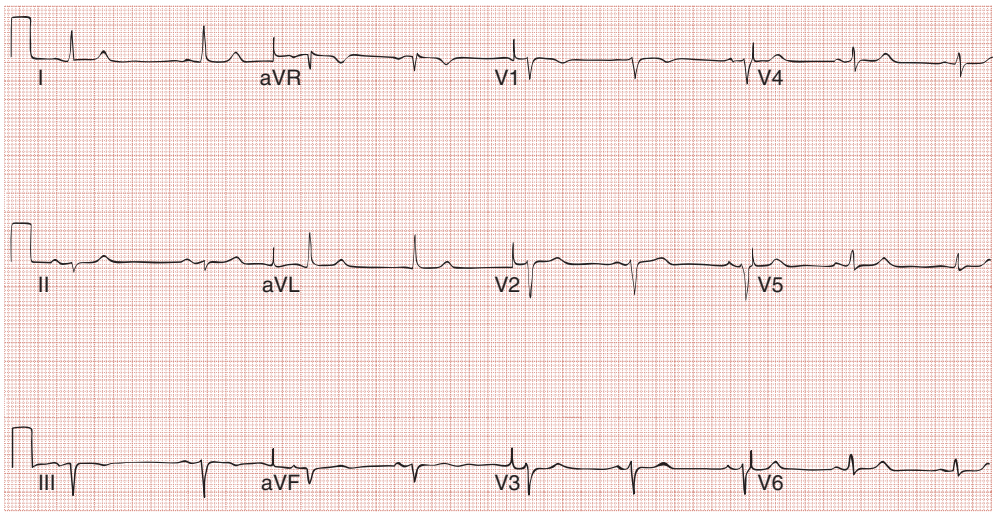


Figure 77-11. Sinus bradycardia.

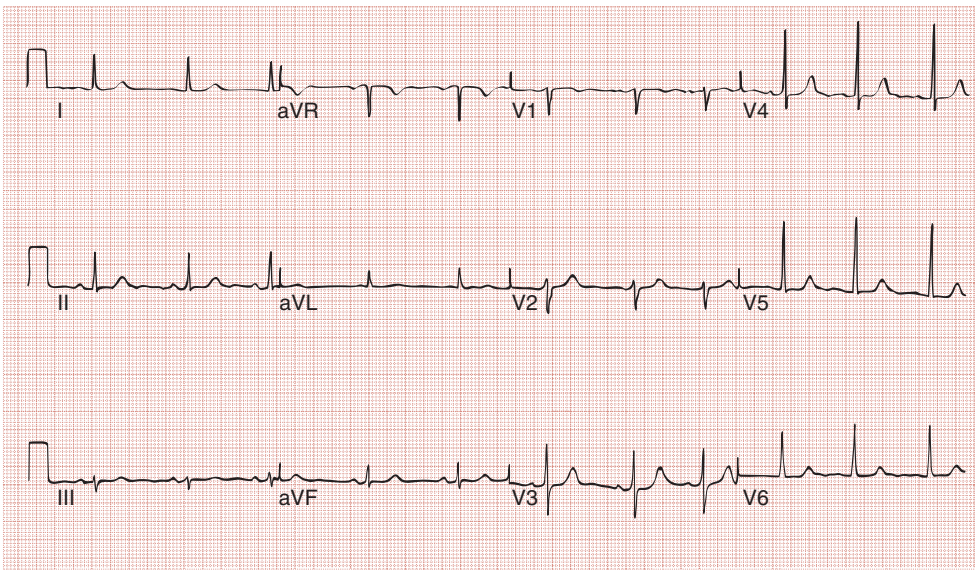


Figure 77-12. Sinus dysrhythmia (note slight irregularity).

to those of sinus dysrhythmias, except that an atrial source other than the sinus node serves as the pacemaker, producing P′ waves that are consistent in structure yet different from the sinus P waves. The P′R interval may also vary from the normal sinus PR interval, which distinguishes these rhythms. Both dysrhythmias may be normal variants, with sinus dysrhythmias often resulting from respiratory variation. Neither has clinical significance except that they may be confused with other dysrhythmias. No treatment is required for these rhythms.

Sinoatrial Block and Escape Rhythms

The underlying feature of SA block is absent atrial depolarization, characterized by missing P waves. This lack of atrial depolarization occurs for three reasons: (1) failure of the sinus node to generate an impulse, (2) failure of impulse conduction out of the SA node, or (3) failure of the impulse to activate the atria, from either inability of the atria to depolarize or an inadequate stimulus intensity. SA block can be the result of ischemia, hyperkalemia, increased vagal tone, or drug therapy including beta-blockers, calcium channel blockers, and digitalis.

Incomplete SA block is diagnosed when an occasional P wave is dropped from the normal P-QRS-T sequence on the ECG. There are no P waves on the ECG (Fig. 77-13) in complete SA block (sinus arrest). Usually, a lower pacemaker emerges in complete SA block. If this pacemaker is within the AV node, the QRS complex is narrow and results in an "idiojunctional" escape rhythm at a rate of 45 to 60 beats per minute. Pacemakers within the His-Purkinje system usually result in a wide-complex "idioventricular" escape rhythm at a rate of 30 to 45 beats per minute.

The treatment of SA block is based on symptoms and includes atropine (except in the setting of digitalis toxicity) and temporary pacing. Patients without evidence of hypoperfusion should be observed without treatment. Class I antidysrhythmics should be avoided because they may extinguish an escape rhythm that is supporting life.

Sinus Node Dysfunction (Sick Sinus Syndrome)

This syndrome refers to a myriad of overlapping pathologic states ranging from frequent sinus pauses and bradycardia to the tachycardia-bradycardia syndrome. The latter represents bursts of an atrial tachydysrhythmia, usually atrial fibrillation, alternating with periods of sinus or atrial bradycardia. The tachycardia-bradycardia syndrome usually occurs in elderly persons but is also associated with ischemia, inflammatory diseases, cardiomyopathy, connective tissue diseases, and drug therapy (especially beta-blockers, calcium channel blockers, digitalis, and quinidine).

The diagnosis is made when symptoms, such as palpitations or syncope, are correlated with the bradycardia or tachycardia, usually through ambulatory ECG monitoring. The ECG manifestations vary, depending on the rhythm at presentation. Treatment consists of rate stimulation (with atropine or a pacemaker) or rate control (with calcium channel blockers, beta-blockers, or digitalis) when symptoms of hypoperfusion coexist. Either modality should be attempted with caution because excessive bradycardia or tachycardia may result, although generally the response is blunted (i.e., the heart rate increases to 90 beats/min or less after atropine). Recognition and referral are the mainstays of ED management. Long-term management is often a combination of an antidysrhythmic agent to suppress the tachycardia and a demand pacemaker (to provide a "floor" against excessive bradycardia).

Atrioventricular Block

AV block is the result of impaired conduction through the atria, AV node, or proximal His-Purkinje system. Although electrophysiologic studies using His bundle tracings can pinpoint the area of conduction disturbance, the surface ECG can provide information and guide clinical decisions. There are three common grades of AV block based on the ECG and clinical characteristics. First- and second-degree AV blocks represent an incomplete conduction disturbance, whereas third-degree block indicates complete AV conduction interruption.

First-Degree Atrioventricular Block. First-degree AV block is prolonged conduction of atrial impulses without the loss of any single impulse. This can occur at the level of the atria, AV node (most common), or His-Purkinje system (least common). On the ECG, a regular narrow-complex rhythm at mildly slow to normal ventricular rates with a prolonged PR interval (>0.20 second) is seen (Fig. 77-14). First-degree AV block is often a normal variant without clinical significance, occurring in 1.6% of healthy young adults. This type of AV block requires no specific treatment, though nodal depressing agents should be given with caution in this setting.

Second-Degree Atrioventricular Block. Second-degree AV block is an intermediate step between every impulse being conducted (albeit slowly) and no impulses being conducted. On the ECG this type of block is manifested as one or more sinus impulses failing to reach the ventricles. The *conduction ratio* in all types of incomplete AV block is described as the ratio of the number of P waves to the number of QRS complexes (e.g., 3:2, 4:3). Second-degree AV block can be divided into two types on the basis of the ECG appearance and clinical characteristics (Table 77-4).

Table 77-4 Characteristics of Second-Degree Atrioventricular Block

FEATURE	TYPE I	TYPE II
Clinical	Usually acute	Often chronic
	Inferior myocardial infarction	Anteroseptal
	Rheumatic fever	Lenègre's disease
		Lev disease
	Digitalis or beta-blockers	Cardiomyopathy
Anatomic	Usually AV node	Infranodal
Electrophysiology	Increased relative refractory period	No relative refractory period
	Decremental conduction	All-or-none conduction
ECG features	RP/PR reciprocity	PR interval stable
	Prolonged PR interval	PR interval usually normal
	QRS duration normal	QRS duration prolonged
Response to atropine and exercise	Improves	Worsens
Response to carotid massage	Worsens	Improves*

*Primarily refers to conduction ratio.
AV, atrioventricular; ECG, electrocardiographic.

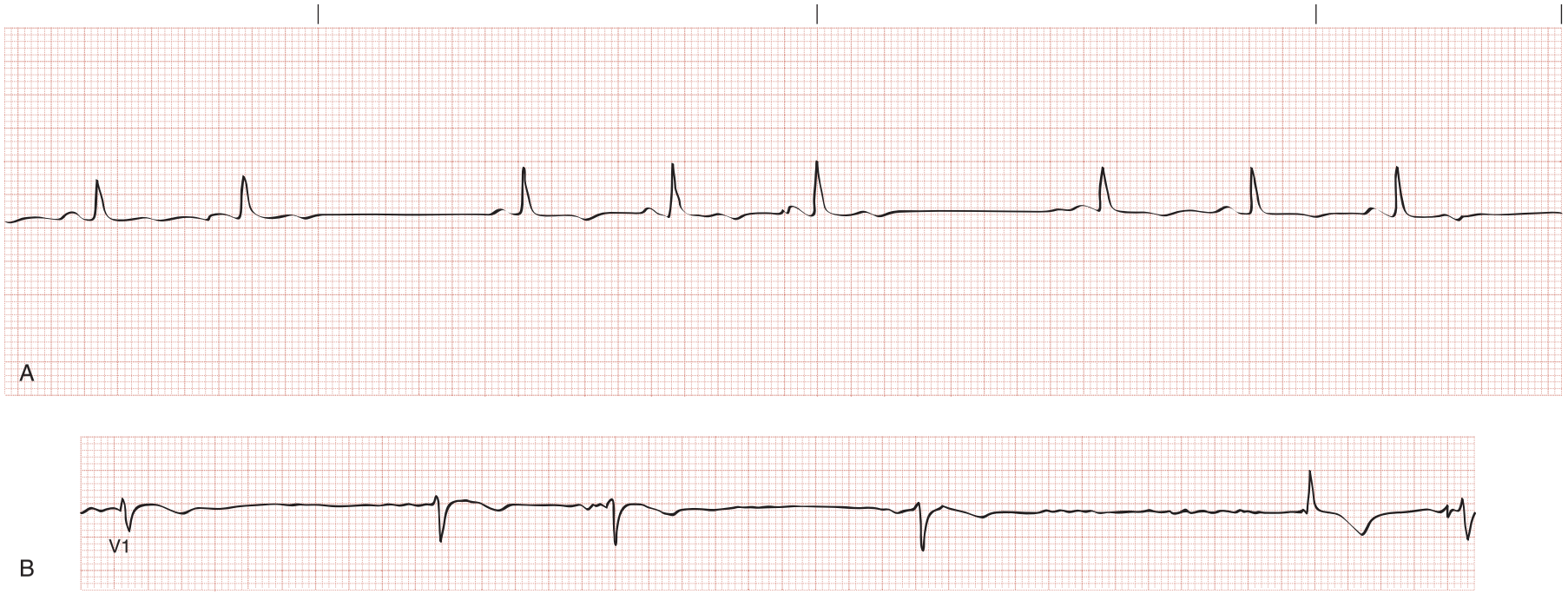


Figure 77-13. **A,** Incomplete sinus block. **B,** Complete sinus block (sinus arrest) with ventricular escape rhythm.

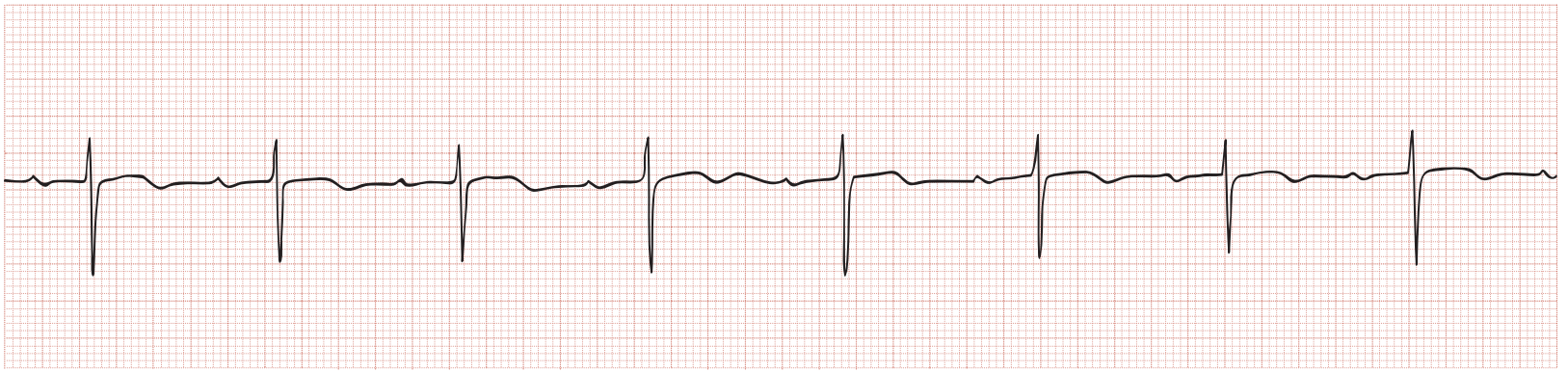


Figure 77-14. First-degree atrioventricular block.

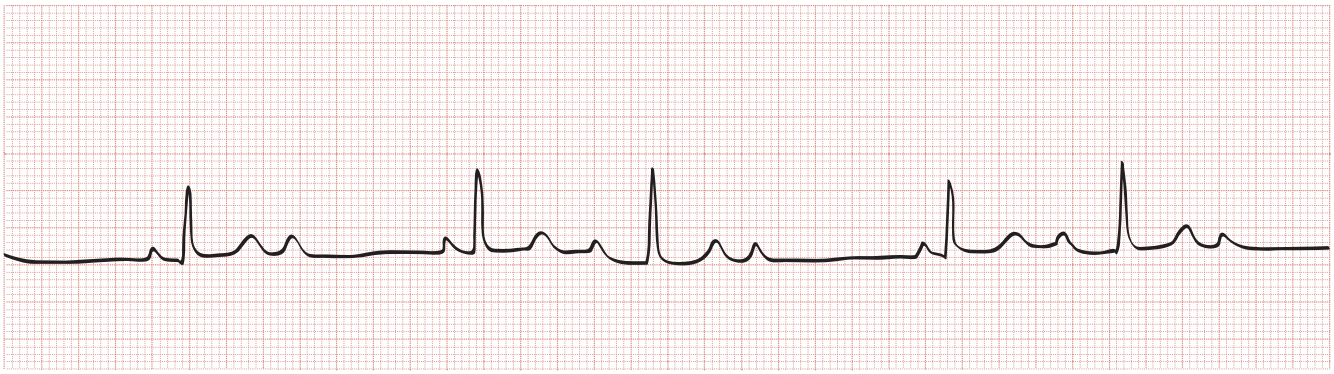


Figure 77-15. Second-degree atrioventricular block, type I (Wenckebach). Note the prolongation of the PR interval between the second and third beats followed by a nonconducted atrial impulse.

Type I Second-Degree Atrioventricular Block. Type I second-degree AV block, also called Wenckebach or Mobitz I AV block, is associated with a conduction deficit within the AV node. On the surface ECG, a narrow-complex rhythm with the following three basic characteristics is seen (Fig. 77-15):

- Grouped beating (especially pairs or trios, but occasionally larger groups).
- Progressive lengthening of the PR interval until an impulse is not conducted ("dropped beat").
- The longest cycle (of the dropped beat) is less than twice the length of the shortest (usually the impulse after the dropped beat).

The progressive lengthening of the PR interval gives the appearance of successive P waves retreating into the preceding QRS complexes. This highlights another feature of type I block, the concept of *RP/PR reciprocity*. This means that as the interval between the preceding R wave and the next P wave becomes shorter, the PR interval of the next cycle becomes longer until an impulse is dropped.

Type I second-degree AV block occurs in a variety of acute and chronic conditions (see Table 77-4) and usually requires no treatment. In the setting of acute myocardial infarction, this type of AV block is associated with inferior wall ischemia and a good outcome. Children with asymptomatic type I second-degree AV block may eventually develop complete heart block but usually remain asymptomatic because of adequate subsidiary pacemaker function. Carotid massage and increased vagal tone may worsen type I block, whereas atropine may improve conduction.

The Wenckebach phenomenon occurs in other conduction disturbances, including SA block, producing grouped impulses. Grouped impulses should always raise the question, "Is a Wenckebach mechanism present?" Not all grouped impulses are caused by this phenomenon (Box 77-5).

Type II Second-Degree Atrioventricular Block. Type II second-degree AV block, or Mobitz II block, is never a normal variant and implies a conduction block below the level of the AV node, usually in the His-Purkinje system. On the ECG, intermittent conduction of atrial impulses occurs without changes in the PR interval (Fig. 77-16). The QRS complex of conducted beats is often narrow, but wide-complex beats may result if infranodal conduction disturbances (e.g., bundle branch block) or escape impulses are present. Type II second-degree AV block is associated with a variety of acute and chronic diseases (see Table 77-4). Compared with type I second-degree AV block, type II block carries a worse prognosis. In acute myocardial infarction, type II AV block is associated with anterior wall ischemia and often progresses to complete AV block. This variety of block is further complicated by poor subsidiary pacemaker function and mandates that temporary pacing be readily available.

BOX 77-5 CAUSES OF GROUPED IMPULSES

Wenckebach mechanism (usually at atrioventricular node, but can occur elsewhere)
Atrial tachycardia or flutter with alternating conduction (e.g., 2:1 with 3:2 or 4:1)
Frequent extrasystoles (two or more impulses)
Nonconducted atrial trigeminy
Concealed or interpolated extrasystoles

When the conduction ratio is 2:1, it may be impossible to distinguish type I from type II AV block on the ECG. The response to autonomic manipulation, however, can aid in this task. Atropine usually has no effect on the His-Purkinje system and may worsen the conduction ratio in type II AV block by increasing the number of atrial impulses without improving conduction (although clinical deterioration is not likely). Carotid sinus massage may transiently improve the conduction ratio (but not the overall condition) in type II AV block by slowing the conduction in the proximal AV node, allowing the lower conductive tissues to recover and be less refractory.

Pharmacologic treatment of type II AV block is *not* indicated. In the out-of-hospital setting, symptomatic type II second-degree AV block should be treated with transcutaneous pacing; in the ED, transcutaneous or transvenous pacing can be used. Immediate cardiology consultation should be sought for all patients, and none should be discharged to home unless the condition is chronic and without new symptoms.

Third-Degree (Complete) Atrioventricular Block. Third-degree, or *complete*, AV block is characterized by absent conduction of all atrial impulses (Fig. 77-17) and complete electrical AV dissociation. Not all AV dissociation represents complete heart block. For complete heart block to exist, the underlying atrial or junctional rhythm must be of a rate sufficient to overcome the action of any subsidiary infranodal pacemakers. For example, an accelerated junctional focus at a ventricular rate of 80 beats per minute (as a result of enhanced automaticity from catecholamine excess) may usurp the sinus node and become the dominant pacemaker. In this situation, the underlying sinus rhythm of less than 80 beats per minute would be manifest as regular P waves unrelated to the source of ventricular depolarization, the junctional rhythm. This junctional rhythm is not complete heart block because no underlying AV nodal conduction disorder is present. In a similar fashion, com-

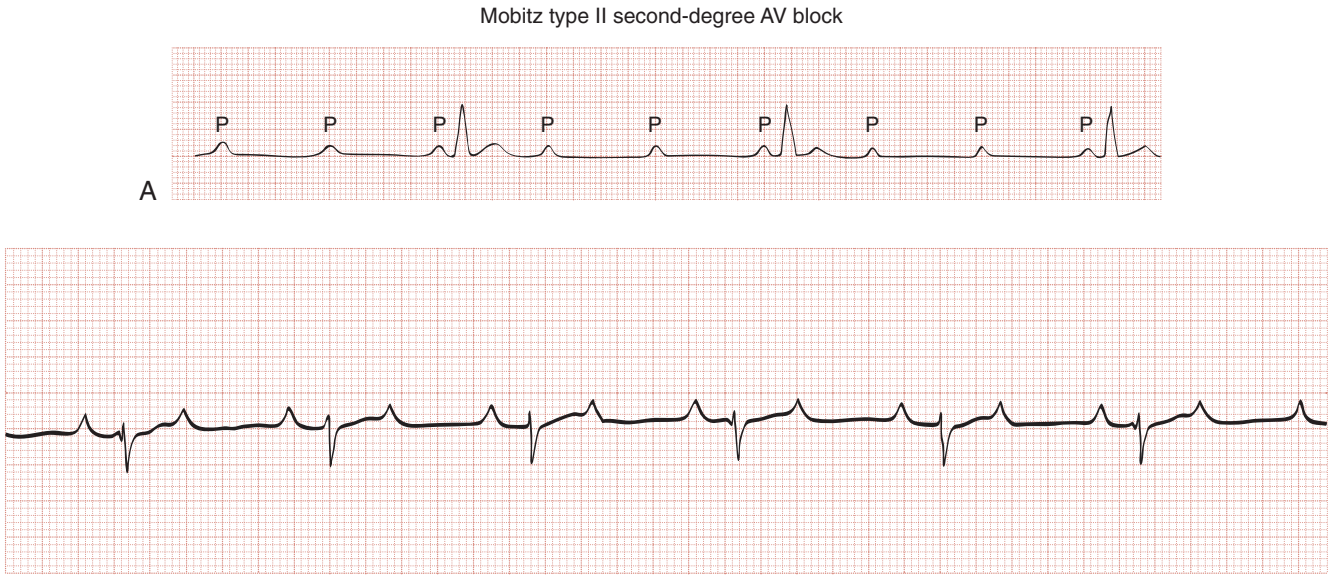


Figure 77-16. **A,** Second-degree atrioventricular (AV) block, type II. In this example, 3:1 conduction is seen. **B,** Second-degree AV block with 2:1 conduction. From the rhythm strip alone, it is difficult to categorize this as type I or II block. (**A,** from Goldberger AL, Goldberger E: Clinical Electrocardiography, 2nd ed. St. Louis, Mosby, 1981.)

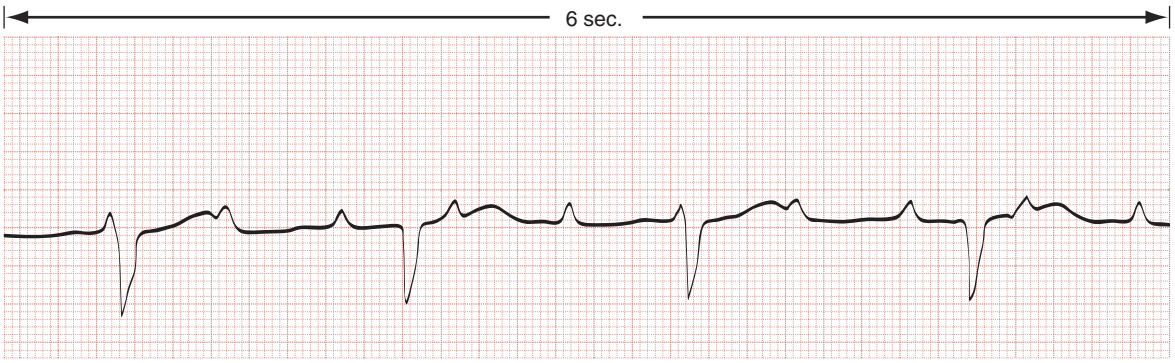


Figure 77-17. Complete (third-degree) atrioventricular block. Note that there is no constant relationship of P waves to QRS complexes even though some are noted in close proximity.

plete SA block coupled with a junctional or ventricular escape rhythm can be misidentified as complete AV block (see Fig. 77-13).

During complete heart block, the P waves and QRS complexes are present but are unrelated and occur at different rates. When the atrial and escape rates are similar, *isorhythmic AV dissociation* exists. This can be difficult to appreciate unless a long rhythm strip is examined and the P waves and QRS complexes are closely tracked. The duration of the QRS complex depends on the site of the escape rhythm pacemaker. Pacemakers above the His bundle produce a narrow complex, whereas pacemakers at or below the His bundle produce a wide-complex rhythm. The narrow-complex rhythms usually operate at a faster rate (45–60 beats/min) and respond to atropine and isoproterenol; the wide-complex escape rhythms are slower (30–45 beats/min) and are unaffected by autonomic drugs. When rapid P waves or fibrillatory waves are coupled with a slow and regular ventricular response, atrial tachycardia or fibrillation with third-degree heart block and an escape rhythm is present. This combination is commonly the result of digitalis toxicity.

Third-degree AV block can be congenital or acquired. In general, congenital third-degree AV block is associated with a narrow-complex escape rhythm and fewer symptoms. The fixed rate of the subsidiary pacemaker limits the ability to increase cardiac output, resulting in varying degrees of exercise intolerance. Acquired third-degree block is often the result of ischemia, drug therapy, or structural heart disease (alone or in combination). Acquired third-degree AV block often has a wide-complex escape rhythm and symptoms of hypoperfusion at rest or with minimal exertion.

In the field, the treatment of patients with third-degree AV block depends on the symptoms. Patients with clinical evidence of hypoperfusion are best treated with transcutaneous pacing. While atropine is often used in the field, it rarely helps or harms, usually simply altering conduction ratios without changing the escape rhythm. Asymptomatic patients should be rapidly transported with pacing readily available.

In the ED, the treatment includes close clinical assessment and pacing if there is any hypoperfusion. The patient should be admitted to an appropriate monitoring unit if acquired or symptomatic third-degree AV block is diagnosed. A transvenous temporary pacemaker is usually indicated but can be placed electively if the transcutaneous pacemaker is functioning well. Also, avoid type I antidysrhythmics since these can extinguish the escape rhythm.

This classification scheme has shortcomings. The conduction ratio depends on the atrial rate and the presence of under-

lying nodal pathology. A 2:1 conduction ratio does not mean worse conduction system disease than a 3:2 ratio, and not all 2:1 conduction is pathologic. For example, an atrial impulse rate of 300 complexes per minute (common in atrial flutter) presented to the AV node usually results in conduction of half the impulses, producing a ventricular rate of 150 beats per minute. This conduction ratio does not represent significant AV block because the AV node is responding normally and preventing excessive ventricular stimulation. Conversely, a sinus rhythm at a rate of 70 P waves per minute paired with a similar conduction ratio produces a ventricular rate of 35 beats per minute; this ratio clearly represents profound AV block. The term *high-grade second-degree block* is best applied to conduction disturbances that prevent physiologic ventricular response rates and not solely to higher conduction ratios.

Extrasystoles and Parasystole

Extrasystoles, defined as ectopic impulses that occur in addition to the underlying normal sinus rhythm, are present in most individuals when closely monitored. Certain specific extrasystoles may help identify patients with a poor prognosis when coupled with symptoms. Not all extra impulses are translated into mechanical contractions. Even without associated contractions, nonconducted impulses can trigger a secondary irregularity of the rhythm by interfering with conduction. In fact, the most common cause of a pause on the ECG is a nonconducted atrial extrasystole that resets the SA node.

The mechanism responsible for most extrasystoles is abnormal automaticity, although some can result from reentry or triggered automaticity. In general, ectopic impulses occur earlier in a cardiac cycle than the normal sinus impulse and are termed *premature*. By convention, the term *contraction* is applied to these extra impulses, although a true mechanical contraction may not always occur. The source of these ectopic impulses can be the atria, AV node, His-Purkinje system, or ventricles. *Bigeminy* occurs when an extrasystole follows every sinus beat, and *trigeminy* occurs when every third beat is extrasystolic (Fig. 77-18). These forms can occur with any of the three sources (atria, junction, or ventricles) and are usually benign rhythms.

The extrasystole and its preceding complex are referred to as the *couplet*, and the *coupling interval* refers to the period between these two beats. When the coupling interval in a given rhythm is constant (or "fixed"), a single focus is believed to be responsible for the extrasystoles. Although previously considered to be solely the result of reentry, fixed coupling does not reliably define the mechanism of ectopic impulse formation. There are three basic extrasystolic foci, along with a specific form of abnormal impulse generation and propagation called *parasystole*.

Premature Atrial Contractions

Premature atrial contractions (PACs) are often the precipitating event for a variety of dysrhythmias, including atrial fibrillation, atrial flutter, and SVT. Abnormal automaticity and atrial or AV nodal reentry are the most common causes of PACs. The diagnosis of PACs is made from the ECG, where an abnormal P′ wave is seen early within a cardiac cycle (Fig. 77-19). The P′ wave may be difficult to see if it is buried within the preceding T wave, although increasing the paper speed and use of an esophageal lead can help. Inverted P′ waves suggest an atrial source near the AV junction, where nearly normal P′ waves imply a focus near the SA node. If the P′ waves, P′R intervals, and coupling intervals are constant, a single focus is likely. Variations in these three characteristics are consistent with multiple foci. Either the left or right atrium can be the source of PACs.

Most PACs depolarize the sinus node, which resets the intrinsic sinus node rate. On the ECG, the P-P interval after a conducted PAC is equal to the P-P interval of the cycle preceding the PAC. Because of this adjustment of the sinus cycle, the R-R interval surrounding the ectopic beat is less than twice the intrinsic R-R cycle length (see Fig. 77-19). This is referred to as a *noncompensatory pause*, a hallmark of PACs. Occasionally, PACs do not depolarize the sinus node, and a compensatory

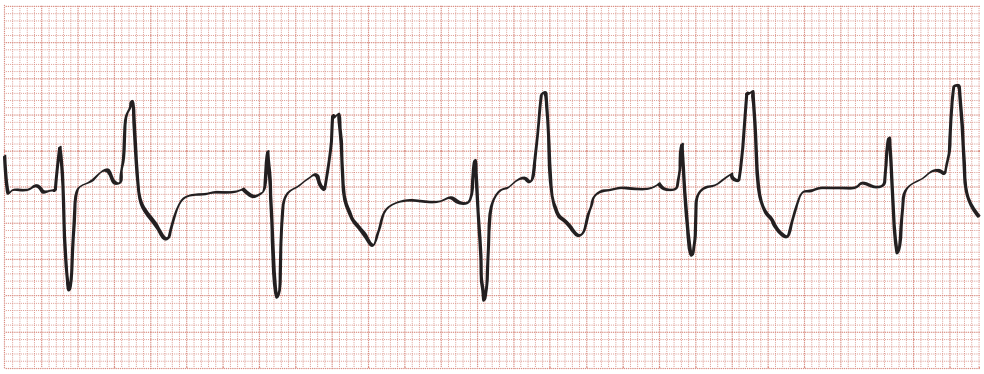


Figure 77-18. Ventricular bigeminy.

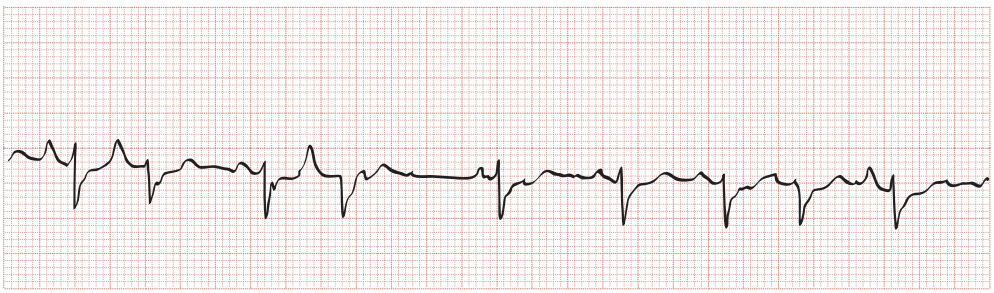


Figure 77-19. Premature atrial contractions.

pause may result. Fully compensatory pauses are more commonly seen with premature ventricular contractions (PVCs). Table 77-5 lists ECG features to help distinguish PACs from PVCs.

If it is conducted to the ventricles, a PAC results in a QRS complex that occurs earlier than the expected sinus QRS complex. The QRS complex from a PAC is narrow and identical to the sinus rhythm complex unless aberrant conduction occurs (Fig. 77-20). Aberrancy is likely to occur if a PAC arrives early within the cardiac cycle, with an RBBB pattern commonly seen on the ECG. Since bundle conductivity depends on the previous cycle length, a PAC that follows a long cardiac cycle (reflected as a preceding long R-R interval) may also be aberrantly conducted because the bundles require more time to repolarize. In the latter setting, aberrant conduction occurs because of the relatively early arrival of the PAC for the given cycle length. This "long/short" aberrant conduction is called the Ashman phenomenon and can occur with any irregular atrial rhythm, including PACs and atrial fibrillation.

A PAC is the most common cause of a pause on the ECG. Although the source of this type of pause is obvious when a PAC is conducted, nonconducted PACs are frequently responsible for pauses. In this situation, the sinus node is depolarized by the PAC, causing an interruption and resetting of the regular rate. If the same extrasystolic impulse reaches the AV node or infranodal conducting system during the refractory period, no ventricular depolarization is possible. This combined sinus node reset with a nonconducted atrial extrasystole creates the pause seen on the ECG. Often the PAC responsible for a pause falls within the previous T wave and is not visible on the ECG. On rare occasions an extremely late PAC can cause atrial depolarization in combination with the sinus node impulse. The P′ waves in these cases represent a *fusion complex* and have qualities of both impulses.

The management of PACs is based on recognition with no need for specific therapy. Underlying causes, such as catecholamine excess, hypoxemia, myocardial ischemia, heart failure, and acid-base or electrolyte imbalance, should be treated.

Premature Junctional Contractions

Premature junctional contractions (PJCs) result from either altered automaticity or nodal micro-reentry. On the ECG, a P′ wave from retrograde atrial depolarization is buried within the QRS complex, and the extrasystole appears as a lone additional QRS complex (from a high nodal focus) that may be seen as a result of retrograde conduction to the atria. If seen, the P′ waves from PJCs are usually inverted because of the opposite direction of the depolarization wave compared with the normal sinus impulses and can be difficult to distinguish from PACs emanating from a low atrial source. If a high nodal focus is involved, the QRS complex is narrow; wide QRS complexes imply a lower His source or abnormal infranodal conduction (bundle branch block).

Table 77-5 Features to Distinguish Premature Atrial Contractions with Abnormal Conduction from Premature Ventricular Contractions

PREMATURE ATRIAL CONTRACTIONS	PREMATURE VENTRICULAR CONTRACTIONS
No compensatory pause	Fully compensatory pause (unless interpolated)
Preceding P wave (different from sinus P wave; occasionally buried in T wave)	No preceding P waves (although retrograde atrial conduction can cause inverted P wave after QRS)
Usually classic right bundle branch block pattern (especially if long-short cycle sequence appears) identical to sinus QRS	Left bundle branch block, right bundle branch block, or hybrid pattern
QRS axis normal or near normal	Frequently bizarre QRS axis
QRS rarely >0.14 sec	QRS often >1.14 sec

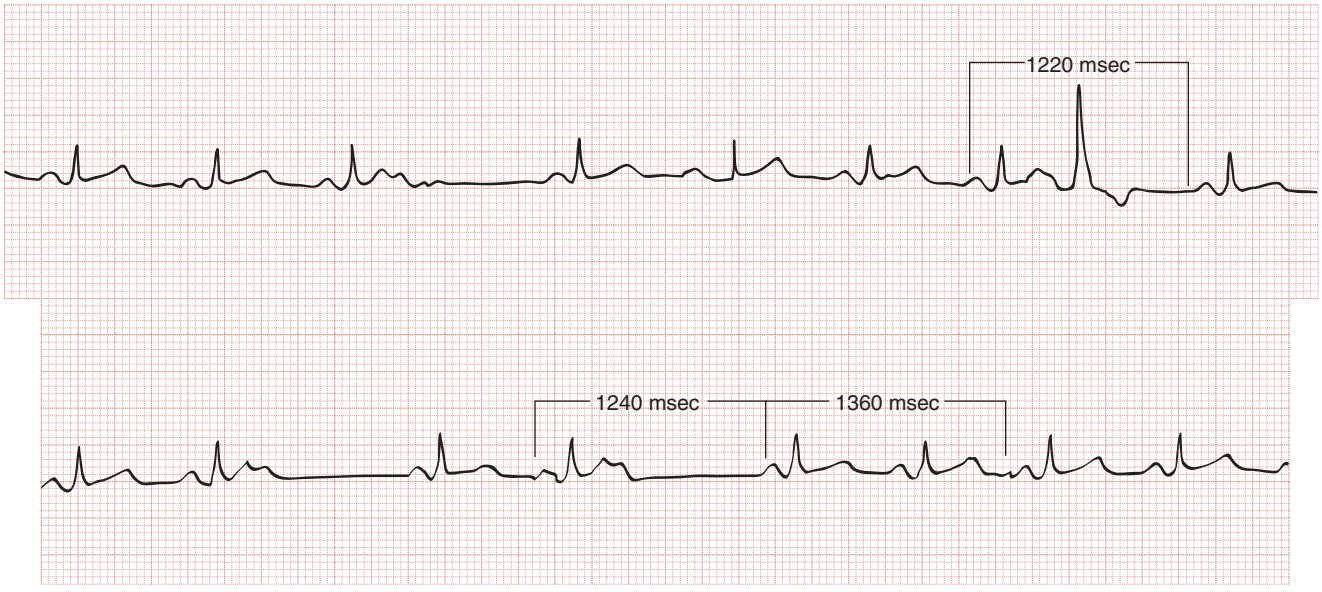


Figure 77-20. Premature atrial contractions (PACs) with noncompensatory pauses and one aberrantly conducted impulse *(upper strip)*. Note that both conducted and nonconducted PACs reset the sinus node, with the latter creating a pause.

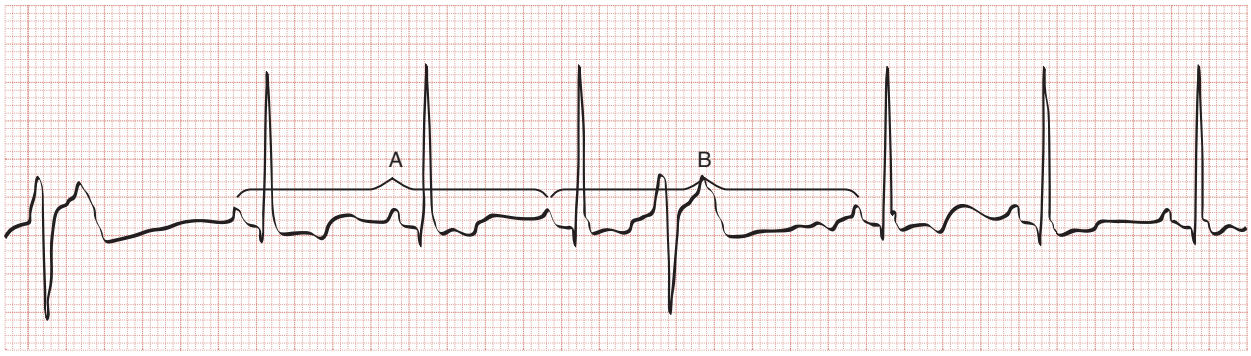


Figure 77-21. Premature ventricular contractions with compensatory pause. Note that a sinus P wave can be seen in the T wave of the extrasystolic beat. Also note the secondary T wave changes in beats 1 and 4 (T wave is opposite the main deflection of the QRS complex).

BOX 77-6 CAUSES OF PREMATURE VENTRICULAR CONTRACTIONS AND VENTRICULAR TACHYCARDIA

Acute or previous myocardial infarction/ischemia
Hypokalemia
Hypoxemia
Ischemic heart disease
Valvular disease
Catecholamine excess*
Other drug intoxications (especially cyclic antidepressants)
Idiopathic causes†
Digitalis toxicity
Hypomagnesemia
Hypercapnia
Class I/antidysrhythmic agents
Ethanol
Myocardial contusion
Cardiomyopathy
Acidosis
Alkalosis
Methylxanthine toxicity

*Relative increase in sympathetic tone from drugs (direct or indirect) or conditions that augment catecholamine release or decrease parasympathetic tone.
†Isolated premature ventricular contractions (PVCs) can occur in up to 50% of young subjects without obvious cardiac or noncardiac disease; however, multiform and repetitive PVCs and ventricular tachycardia are rarely seen in this population.

Fully compensatory pauses and aberrant conduction occur more often with PJCs than with PACs. The causes and treatment of PJCs are the same as those of PACs.

Premature Ventricular Contractions

PVCs can occur in a variety of pathologic and nonpathologic states. Their major importance is related to the clinical scenario accompanying their presence and the risk of more serious ventricular dysrhythmias, such as ventricular tachycardia and fibrillation. Extrasystoles that occur during ventricular repolarization (the R-on-T phenomenon) are believed to carry a higher risk of precipitating ventricular tachycardia, although the magnitude of this effect is debated. Other data suggest that PVCs occurring during the next atrial depolarization (the R-on-P phenomenon) carry as high or a higher risk of precipitating serious ventricular dysrhythmias than R-on-T PVCs.[33]

PVCs can be caused by varying mechanisms (Box 77-6), including reentry, abnormal automaticity, and triggered afterdepolarizations. Classically, PVCs appear on the ECG as wide

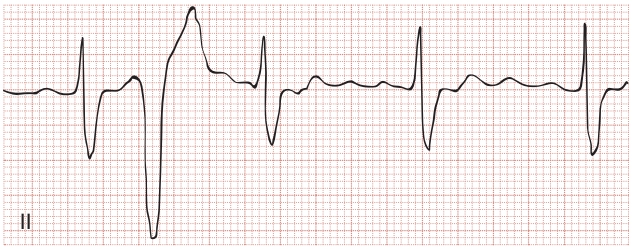


Figure 77-22. Interpolated premature ventricular contraction.

QRS complex extrasystoles (>0.12 second) unassociated with a preceding P wave (Fig. 77-21). In a single lead, a PVC may appear as a narrow QRS complex. This narrow complex occurs if the wave of depolarization is traveling directly perpendicular to the ECG lead and underscores the need to examine multiple leads to identify PVCs accurately. Although P waves from nonconducted sinus impulses may be seen on the ECG, these should have no consistent relationship with the QRS complexes from the PVCs. Rarely, retrograde conduction of PVCs can produce an inverted P′ wave after each QRS complex. PVCs usually cause a fully compensatory pause, with the resulting RR interval encompassing the PVC equal to twice the intrinsic RR interval length (see Fig. 77-21). Rarely, noncompensatory or subcompensatory pauses can be seen with PVCs and are associated with retrograde conduction and sinus node depolarization. *Interpolated PVCs* refer to another rare instance when the underlying sinus rhythm is unaffected by a PVC (Fig. 77-22).

The structure of the QRS complexes depends on the origin of the impulse. PVCs with a left bundle branch appearance result from a wave of depolarization beginning in a right ventricular source and vice versa. Multiform (or "multifocal") PVCs refer to ventricular extrasystoles from more than one source and appear as varying QRS complex structures. When a PVC depolarizes the ventricles at a similar time as a conducted atrial beat, a *fusion QRS complex* is seen (Fig. 77-23). Identification of fusion QRS beats indicates the presence of PVCs.

PVCs produce abnormal repolarization as a direct result of the abnormal depolarization of the ventricles. *Secondary T wave abnormalities* refer to the repolarization changes seen as a result of pathologic depolarization and are seen with PVCs along with bundle branch blocks and left ventricular hypertrophy. These secondary T wave changes consist of widening and deflection opposite of the main QRS deflection (see Fig. 77-21). *Primary T wave abnormalities* refer to changes in ventricular repolarization caused by underlying cardiac disease (such as ischemia) and are not solely the result of depolarization abnor-

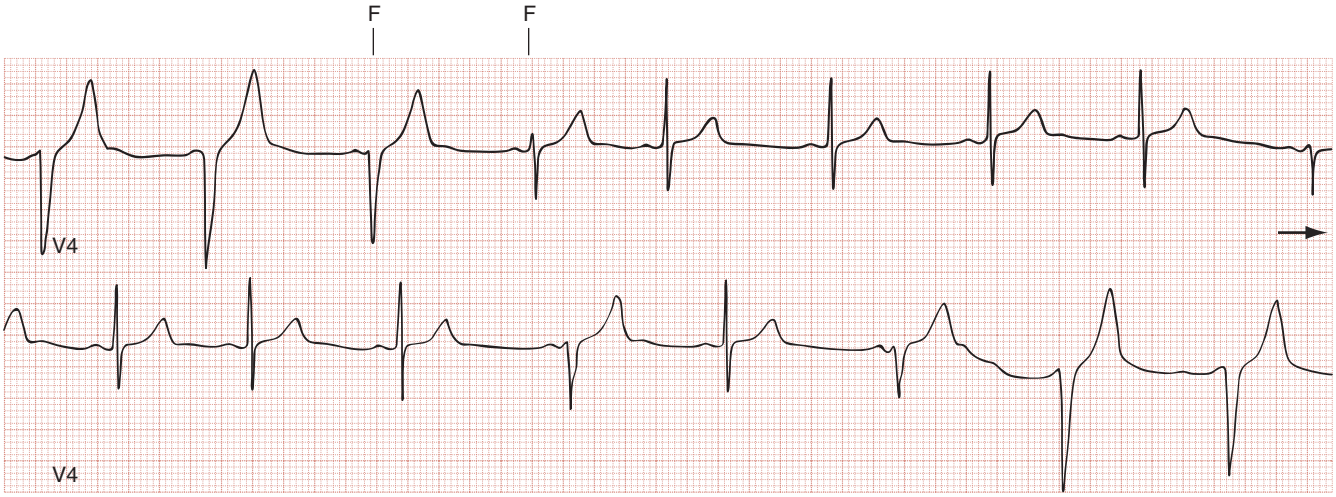


Figure 77-23. Sinus rhythm with run of accelerated idioventricular rhythm. Note fusion beats (F) displaying hybrid appearance of both morphologies.

Table 77-6 Lown Classification of Premature Ventricular Contractions

CLASS	DESCRIPTION
0	None
1	<30/hr
2	30 or more/hr
3	Multiform (or multifocal)
4A	Two consecutive
4B	Three or more consecutive
5	R-on-T phenomenon

BOX 77-7 ELECTROCARDIOGRAPHIC FEATURES OF VENTRICULAR PARASYSTOLE

- Protected pacemaker-fixed discharge rate (although all impulses may not be evident on ECG)
- Wide QRS complexes
- Interectopic intervals fixed or in multiples of shortest interval
- Fusion beats if simultaneous to conducted sinus impulse (not mandatory for diagnosis)
- Variable coupling intervals

malities. Primary T wave changes often consist of T wave deflection in the same direction as the main QRS vector.

The pattern of PVCs is commonly classified by the Lown criteria (Table 77-6). In general, these criteria are intended to distinguish benign PVCs from those likely to degenerate into ventricular tachycardia and ventricular fibrillation. After myocardial infarction, PVCs in Lown classes 3 to 5 carry a high risk for these malignant ventricular dysrhythmias and sudden death, with class 4 having the highest risk. The use of this classification system in other patients with PVCs does not predict the risk of morbidity and mortality. PVCs are found in healthy young patients and their frequency generally increases with age.

Therapy for PVCs is directed toward correcting the underlying cause, especially if ischemia, electrolyte imbalance, or drug overdose is evident. Often, PVCs are not symptomatic aside from a sensation of palpitations. In the absence of ischemia, asymptomatic PVCs alone rarely require antidysrhythmic therapy. Although lidocaine can lessen or abolish PVCs in the setting of acute myocardial infarction, it is recommended only when PVCs in Lown classes 3 to 5 are present or close monitoring and rapid defibrillation capabilities are not readily available. Even in ischemic settings, most clinicians only treat sustained PVC runs.

The need for intravenous delivery limits the use of all class I agents except lidocaine in the out-of-hospital setting. The treatment of PVCs is rarely indicated even in the field. In the ED, alternative agents such as amiodarone and procainamide are options for the few indications, although lidocaine remains an acceptable alternative despite the rare concern of heart block in ischemia. In selected cases, beta-blockers (e.g., for catecholamine-induced PVCs and those occurring after myocardial infarction) and calcium channel blockers (after reperfusion therapy) can diminish PVC frequency and decrease the risk of ventricular fibrillation and ventricular tachycardia. Magnesium sulfate (2–4 g IV over 10–20 minutes) can also diminish the frequency of PVCs, particularly in the setting of acute myocardial ischemia.

Patients with symptomatic or frequent PVCs and syncope, presyncope, dyspnea, or chest pain should be monitored. This can be done (with an ambulatory monitor if otherwise asymptomatic) after considering potential causes listed in Box 77-6.

Parasystole

Parasystole occurs when two separate pacemakers compete to produce ventricular depolarization in the absence of structural conduction disease. The latter distinguishes parasystole from high-grade incomplete or complete AV block. In addition to the sinus node, the usual source of the second pacemaker is the ventricular conductive or contractile tissues, although atrial and junctional pacemakers can also cause parasystole. The key point in identifying the competing pacemaker is that it functions like an artificial fixed-rate pacemaker, producing impulses irrespective of the sinus node activity. The second pacemaker displays an entrance block, which prevents any outside impulse from depolarizing the area and resetting the rhythm.

Ventricular parasystole has five characteristics on the ECG in addition to its wide QRS extrasystolic complexes and fixed rate (Box 77-7 and Fig. 77-24). One hallmark of parasystole is

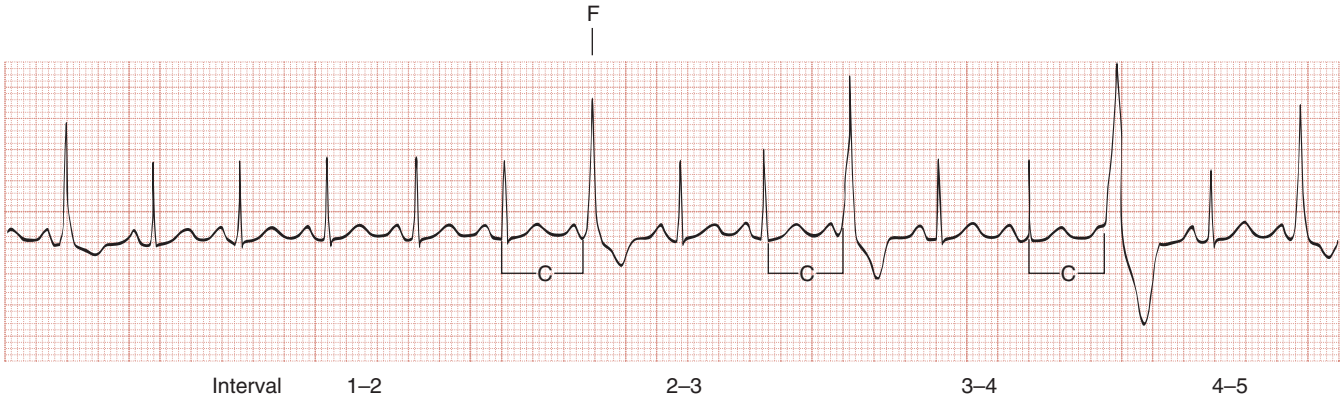


Figure 77-24. Ventricular parasystole. Fusion (F) beats are seen, and coupling intervals (C) vary. Interectopic intervals are all based on a common denominator (0.4 second).

a fixed interectopic interval. In this, the R′R′ intervals are the same throughout a rhythm strip or follow a similar denominator. This is a direct result of the protected parasystolic focus. If all impulses exiting this focus find the conducting system nonrefractory, a fixed interectopic interval is observed. If the conducting tissues are refractory (usually from recent conduction of a sinus impulse), no ventricular depolarization is seen on the ECG, yet the protected parasystolic focus continues to fire at the same rate. If the next impulse from the parasystolic focus finds nonrefractory conducting tissues, the interectopic interval is equal to two times the basic cycle length. If the first and second parasystolic impulses are not conducted but the third in a series finds nonrefractory tissues, the interectopic interval is three times the basic cycle length. For example, based on a 1-second interval, ventricular parasystole may have R′R′ intervals in multiples of this interval (e.g., impulses seen 1, 2, or 3 seconds apart at various times).

Ventricular parasystole is usually the result of an altered automatic mechanism and does not have the serious implications that frequent PVCs have even when an R-on-T phenomenon is seen. Ventricular parasystole may be difficult to distinguish from frequent PVCs in the field because it requires close observation of a prolonged rhythm strip with multiple leads. Fusion QRS complexes may be seen but are not essential to the diagnosis. Ventricular parasystole is usually a benign rhythm, with treatment similar to that of non-ischemia-related PVCs.

Atrial and junctional parasystoles are rare and are more difficult to diagnose. They can be identified when P′ waves or junctional impulses are seen throughout an underlying sinus rhythm with a fixed interectopic interval. As with ventricular parasystole, the P′-P′ intervals or junctional RR intervals should be the same or in multiples of a common interval. Atrial and junctional parasystoles are usually benign and require no specific emergency therapy.

Narrow-Complex Tachycardia

Narrow-complex tachycardias are rhythms with a QRS complex duration of less than 0.12 second and a ventricular rate of greater than 100 beats per minute. Although virtually all narrow-complex tachydysrhythmias originate from a focus above the ventricles (with the rare exception of a very high His bundle rhythm), the term *supraventricular tachycardia* is conventionally used to denote the rhythms aside from sinus tachycardia, atrial tachycardia, atrial fibrillation, and atrial flutter. The atrial depolarization waves may be difficult to appreciate on the ECG, especially if the ventricular response rate is over 150 beats per minute. The use of multiple-surface leads, increased paper speed, an esophageal lead, or vagal maneuvers can help identify the atrial depolarization waves and diagnose the source of the dysrhythmia. Also, atrial or junctional parasystole can create a narrow-complex tachycardia, termed *pseudotachycardia* because neither focus has a ventricular rate greater than 100 beats per minute.

BOX 77-8 CAUSES OF COMPLETELY IRREGULAR (CHAOTIC) RHYTHMS

Atrial fibrillation
Atrial tachycardia or flutter with varying conduction
Multifocal atrial tachycardia
Multiple extrasystoles
Wandering pacemaker (usually atrial)
Parasystole

One ECG feature that can help distinguish the source of a tachydysrhythmia is the location of the P waves and the regularity of the QRS complexes. If nearly normal-appearing atrial depolarization waves precede each QRS complex and the underlying pattern is regular, a sinus rhythm, atrial flutter, or single-focus atrial tachycardia is commonly present. If a completely irregular (or chaotic) pattern of QRS complexes is seen, atrial fibrillation, multifocal atrial tachycardia, or another atrial rhythm with varying conduction is possible (Box 77-8). The identification of atrial depolarization waves and the appearance of irregularity or regularity can be deceiving within any short rhythm strip.

The treatment of each narrow-complex tachycardia is based on the specific rhythm and symptoms. In general, class II (beta-adrenergic blockers) and IV agents (calcium channel blockers) are used to slow AV nodal conduction. These agents may terminate certain dysrhythmias, especially AV nodal reentry. Adenosine transiently slows AV nodal conduction and can help diagnose or treat certain rhythms. Classes IA and IC agents are useful in converting other narrow-complex tachycardias (e.g., atrial flutter and fibrillation) to a sinus rhythm.

After identifying the specific dysrhythmia during an episode, the underlying cause of the tachycardia should be sought. Hypovolemia is a frequent cause of a narrow-complex tachycardia, especially in the young. Fever, anemia, hypoxemia or impaired oxygen delivery (including abnormal hemoglobin states), relative sympathetic excess, drug intoxication, endocrinologic disease (especially thyroid), metabolic derangements, ischemia, infections, and inflammatory causes (including myocarditis and pericarditis) are other considerations.

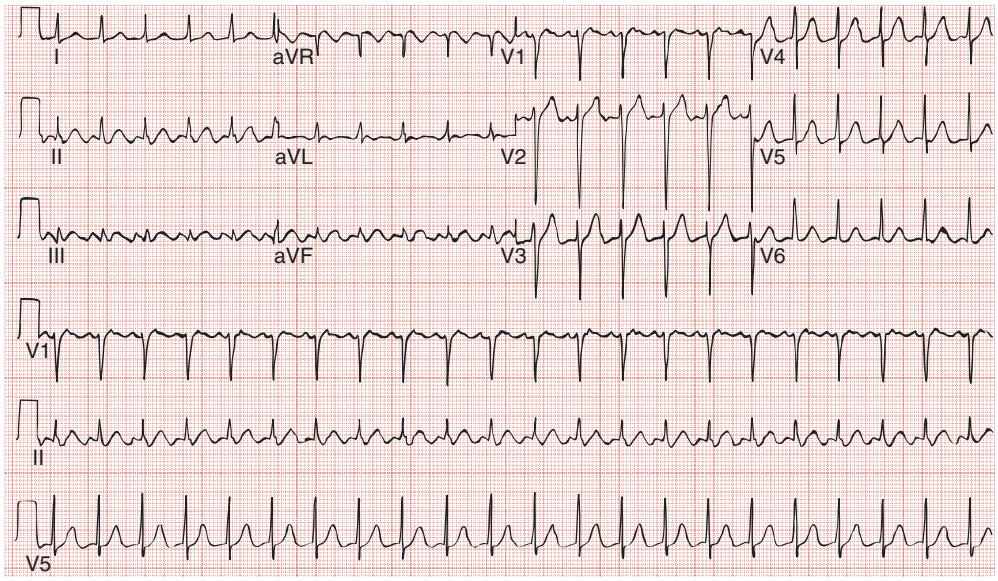


Figure 77-25. Sinus tachycardia.

Sinus Tachycardia

Sinus tachycardia is characterized by a narrow-complex regular rhythm at a ventricular rate of greater than 100 beats per minute. The P waves are upright in all leads but aVR and the appearance of each is consistent (Fig. 77-25). The PR and PP intervals are usually constant, but both may shorten as the rate increases. Increasing vagal or decreasing sympathetic tone decreases the rate of impulse formation and conduction in a graded continuous manner. Conversely, sinus tachycardia can result from increased catecholamine tone or decreased vagal stimulation.

Functionally, sinus tachycardia is a response to physiologic stress and is intended to increase cardiac output. This response can be compensatory for a relative lack of perfusion or oxygen delivery, such as congestive heart failure, pulmonary embolism, hypovolemia, anemia, or sepsis. It can also occur in non-hypoperfusion states when a relative sympathetic excess exists. Treatment is based on the recognition and treatment of the underlying cause. Although anxiety or pain can cause sinus tachycardia in patients, this is a diagnosis of exclusion after a careful search for evidence of the aforementioned physiologic causes of tachycardia.

Sinus tachycardia can be easily mistaken for other causes of a regular narrow-complex tachycardia, especially in young patients, and the converse can occur (e.g., regular atrial flutter at a rate of 150 beats per minute mistaken for sinus tachycardia). Infants and young children can easily attain ventricular rates of 170 to 225 beats per minute with an episode of hypovolemia-induced sinus tachycardia. This may be mistaken for a paroxysmal atrial or junctional tachycardia, with disastrous consequences if a rate-controlling drug is given. Adults do not often reach a rate above 170 beats per minute because of the braking properties of the AV node.

Specific antidysrhythmic therapy for sinus tachycardia is almost never indicated. If the patient is symptomatic or if the risk of precipitating myocardial ischemia is high, the use of a beta-blocker is warranted only after all possible primary causes are treated or eliminated from consideration.

Atrial Tachycardia and Multifocal Atrial Tachycardia

Atrial tachycardia refers to any rapid dysrhythmia from a non-sinus focus above the AV node. Atrial tachycardia can be gradual in onset (suggesting an abnormal automatic mechanism) or abrupt (suggesting a reentrant mechanism). The hallmark of this dysrhythmia on the ECG is a narrow-complex tachycardia at a ventricular rate above 100 beats per minute, with each QRS complex preceded by a P′ wave that is morphologically different from the sinus P wave (Fig. 77-26). If the P′ wave is inverted, a low atrial source is likely. The P′-R interval can be normal or abnormal and is usually constant unless more than one focus is involved. Generally, the conduction ratio is 1:1, but this can vary, especially as the atrial rate increases. If no ECG tracing of the normal sinus rhythm is available, single-focus atrial tachycardia can be indistinguishable from sinus tachycardia.

Paroxysmal atrial tachycardia (PAT) is an intermittent dysrhythmia with an abrupt onset and termination, often seen in children and young adults without concomitant SA node disease. PAT is usually reentrant in origin, as opposed to nonparoxysmal (sustained) atrial tachycardia (NPAT), which is often automatic in nature. PAT can be precipitated by a PAC, or rarely by a PVC, and often originates and terminates abruptly. Other causes of PAT and NPAT include electrolyte and acid-base disturbances, drug toxicity, fever, and hypoxemia. NPAT with varying or complete AV block is classically seen in digitalis toxicity.

Multifocal atrial tachycardia (MAT) is a subset of atrial tachycardia, with more than two foci of impulse formation. On the ECG, at least three distinctly different P waves with varying P′-R, R-R, and P′-P′ intervals are seen (Fig. 77-27). In addition to the causes just listed for PAT, MAT is often associated with pulmonary disease and hypoxemia, either directly from these conditions or as a result of beta-adrenergic agonist or chronic methylxanthine treatment. MAT often resolves when hypoxemia is resolved with supplemental therapy and when other therapies are optimized. MAT is easily confused for atrial fibrillation, since irregularity exists in both, with MAT being much less common.

Correcting the underlying primary disturbance treats PAT, NPAT, and MAT. If the patient is symptomatic and without evidence of instability, or if concerns about precipitating myocardial ischemia are present, treatment with a beta-blocker or calcium channel blocker can be begun in the absence of hypotension. Magnesium (2–4 g IV) is a second-line agent for PAT and MAT. Although adenosine may slow the ventricular rate or occasionally extinguish atrial tachycardias, these rhythms

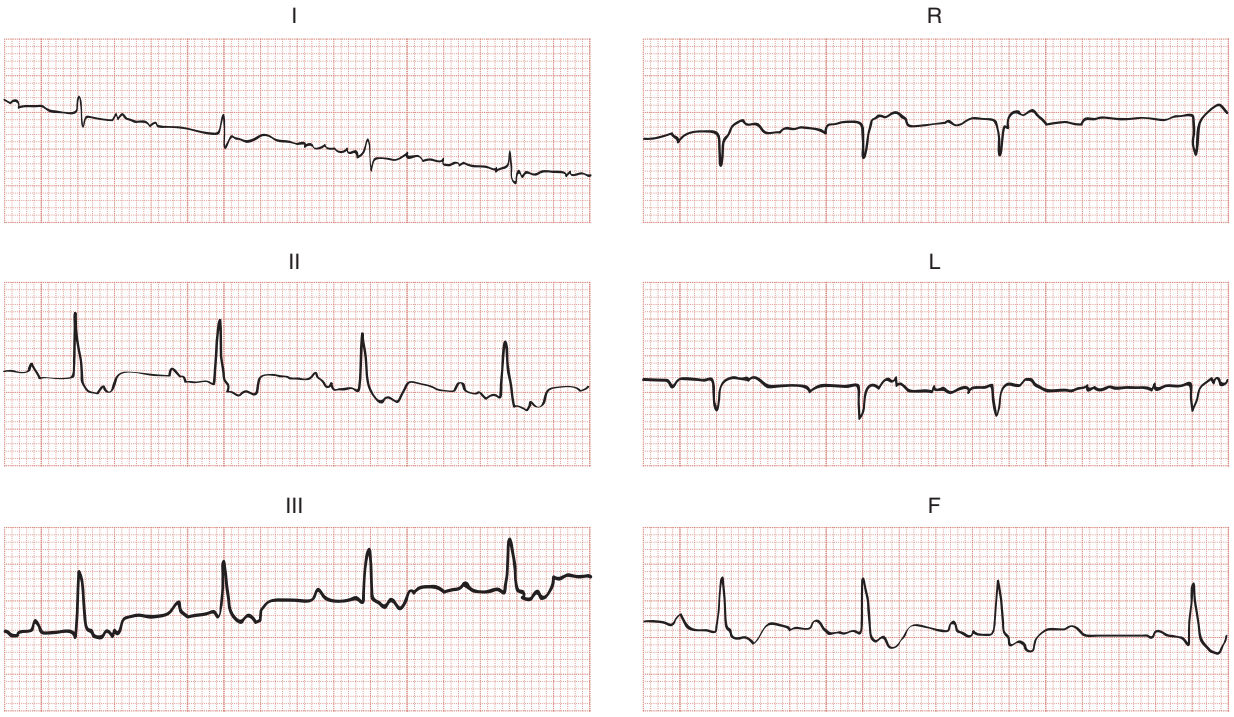


Figure 77-26. Atrial tachycardia (with 2:1 conduction) in a patient with digitalis toxicity. (From Marriott HJL, Conover MB: Advanced Concepts in Arrhythmias, 2nd ed. St. Louis, Mosby, 1989.)

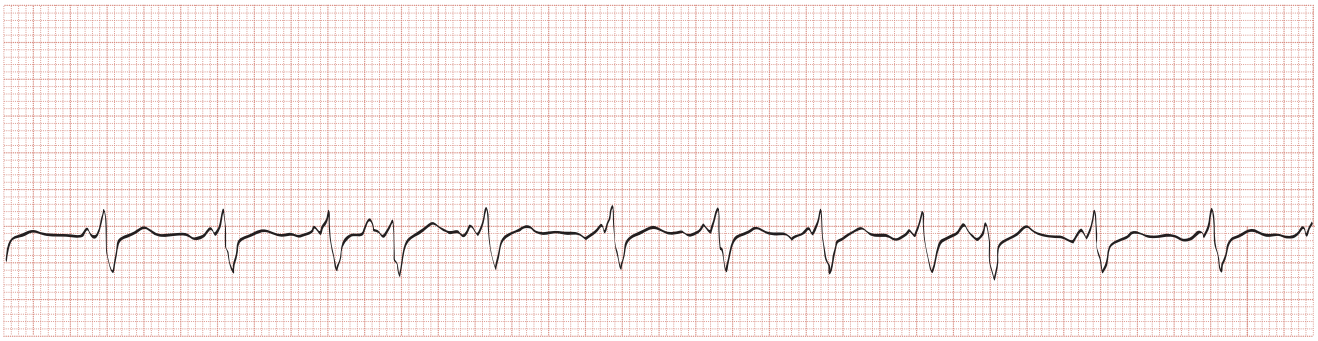


Figure 77-27. Multifocal atrial tachycardia. Note that although the rhythm is irregular, at least three distinct P wave morphologies are present.

often recur because of the short therapeutic effect of this drug. Overdrive transvenous atrial pacing can be used if a reentrant mechanism is suspected and drug treatment fails.

In general, electrical treatment is rarely needed in PAT and MAT. If hypotension or other manifestations of instability exist, synchronized cardioversion with sedation at 50 to 100 J can be performed. Cardioversion is not useful in refractory cases of MAT because the dysrhythmia is likely to recur if no other treatment is employed. When it is the result of digitalis toxicity, PAT and MAT should be treated by correcting hypokalemia if it exists, followed by administration of magnesium and digitalis antibody fragments. Emergency cardioversion should be avoided if possible in this setting.

Atrial Flutter

The most accepted characteristics of atrial flutter are (Fig. 77-28):

- A regular atrial depolarization rate of 250 to 350 atrial complexes per minute—a rate of 300 beats per minute is classic though not universally present.
- Distinct ECG manifestations of abnormal atrial depolarizations in a "saw tooth" appearance. These are referred to as *flutter waves* and are best seen in leads II, III, aVF, and V_{1-2}.
- Frequent 2:1 or 4:1 AV conduction ratio, although any ratio may be seen. The 2:1 ratio with an atrial rate of 300 beats per minute accounts for the classic (although not exclusive) ECG appearance of atrial flutter as a narrow-complex tachycardia with a regular ventricular rate of 150 beats per minute.

Most experimental data suggest a reentrant mechanism for atrial flutter, although some patients may display an abnormal automatic mechanism. In the ED, it is easy to mistake atrial flutter for sinus tachycardia, especially if the flutter waves resemble normal P waves or a nonclassic ventricular rate is present.

Atrial flutter is often associated with structural heart disease, heart failure, valvular dysfunction (especially mitral), or thyroid disease. The clinical importance of atrial flutter is primarily the result of symptoms caused by the ventricular response rate, including palpitations, syncope, presyncope, hypoten-

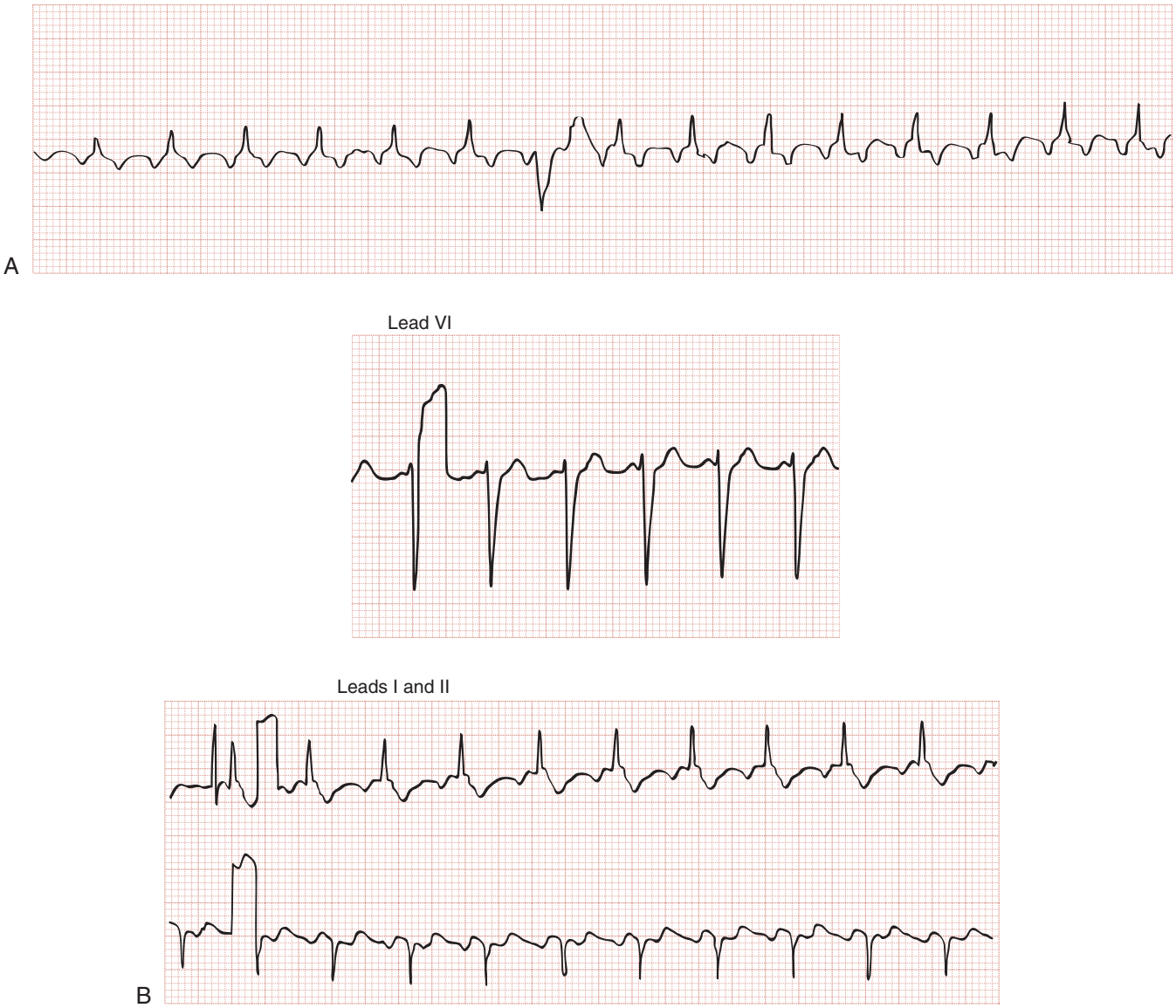


Figure 77-28. **A,** Atrial flutter with 2:1 conduction and isolated premature ventricular contraction. **B,** Atrial flutter with 2:1 conduction. In lead VI, diagnosis is unclear, but examination of other leads, especially lead II, helps identify characteristic flutter waves.

sion, chest pain, and heart failure. If accompanied with an AV block, especially a Wenckebach mechanism, atrial flutter may have irregular ventricular rates like atrial fibrillation. Rarely, high-grade AV conduction block can result in a very fast atrial rate but clinical bradycardia.

In stable patients, ventricular response rates can be controlled with an intravenous calcium channel blocker or a beta-adrenergic blocker. Diltiazem is often favored, although in practice there is little difference in the effects and complication rates among these agents in patients without overt ventricular failure. Digitalis can be used as a second-line agent or in those with mild tachycardia and preexisting congestive heart failure. Magnesium (2–4 g IV) is an adjunctive or third-line therapy to control the ventricular response rate. The major value of adenosine may be in unmasking flutter waves in a narrow-complex tachydysrhythmia, helping to identify the underlying rhythm correctly. Hence, its role may be diagnostic, but it is not therapeutic.

All AV nodal conduction slowing agents, including calcium channel blockers, beta-adrenergic blockers, adenosine, and digitalis, *should be avoided in patients with atrial flutter and a suspected accessory pathway* because these agents primarily block AV nodal conduction and may enhance anterograde conduction in the accessory path. Rapid ventricular response rates (especially >200 beats/min in an adult) are a clue to the possibility of an accessory pathway because normal AV nodal tissues rarely allow a ventricular response rate of more than 150 to 165 beats per minute. The use of any predominantly AV nodal blocking agent in the presence of an accessory pathway and atrial flutter or fibrillation may allow unbridled rapid ventricular response rates and precipitate ventricular fibrillation.

Type IA agents (especially procainamide) can convert atrial flutter if the previously mentioned drugs fail, or they may be used to prevent recurrence in an outpatient setting. The type III agents amiodarone and ibutilide are alternative primary converting agents. Finally, synchronized electrical cardioversion with sedation, beginning at 25 to 50 J, is effective in terminating atrial flutter in refractory or unstable patients. If electrical therapy is successful but atrial flutter recurs, a type IA or IC agent should be used before repeated electrical cardioversion to help prevent this from occurring again.

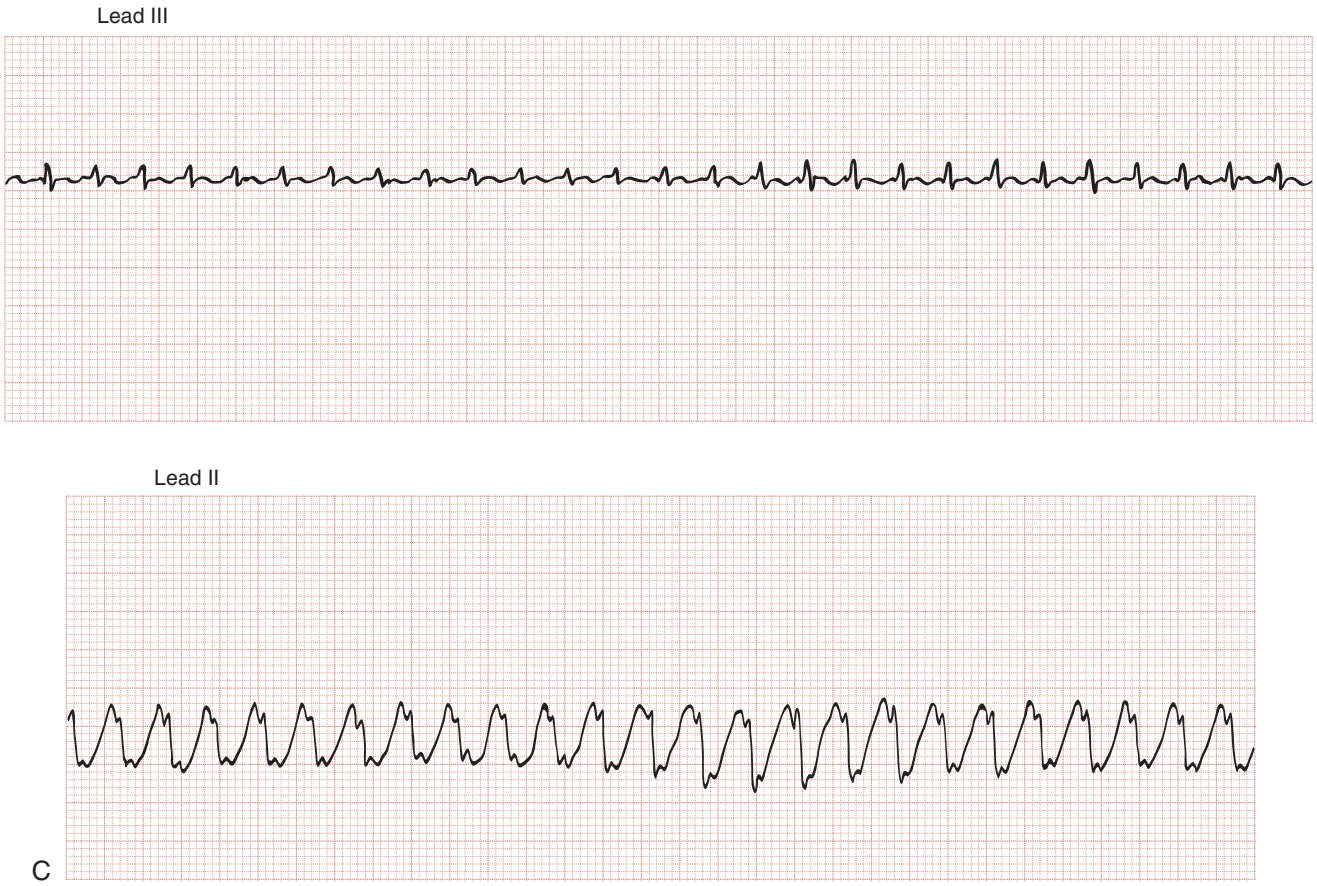


Figure 77-28, cont'd **C,** Atrial flutter with 1:1 conduction. This is rare and can be mistaken for ventricular tachycardia (lead II).

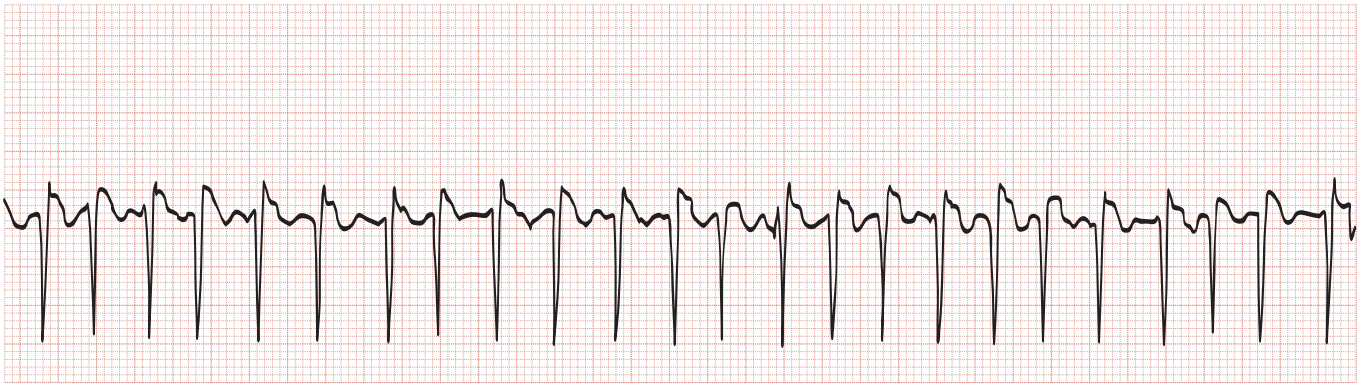


Figure 77-29. Atrial fibrillation with rapid ventricular response.

Atrial Fibrillation

Atrial fibrillation is the result of chaotic depolarization of atrial tissues. This chaotic activity can lead to reduced cardiac output from a loss of coordinated atrial contractions and a rapid ventricular rate, both of which may limit the diastolic filling and stroke volume of the ventricles. Atrial fibrillation may be paroxysmal or chronic; the paroxysms may last for minutes to days. On the ECG, fibrillatory waves are seen and accompanied by an completely irregular QRS pattern, the hallmark of atrial fibrillation (Fig. 77-29). These fibrillatory waves are best seen in the inferior leads or lead V_1 and are described as fine to coarse on the basis of their amplitude. Atrial fibrillation is the result of multiple microreentry circuits, creating 300 to 600 atrial impulses per minute.

The QRS complexes are usually narrow unless an underlying bundle branch block is present. The Ashman phenomenon can cause isolated or repeated aberrant ventricular conduction, usually in an RBBB pattern (Fig. 77-30). These Ashman beats can be mistaken for PVCs if the long-short cycle sequence is not recognized. The ventricular response rate depends on the conduction path and ratio, with the normal AV node maximal response rate being no greater than 150 to 170 beats per minute. As noted with atrial flutter, the presence of a chaotic rhythm (irrespective of the QRS duration) at a ventricular rate of more than 200 beats per minute strongly suggests atrial fibrillation coupled with conduction down an accessory pathway. This rhythm may deteriorate to ventricular fibrillation,[34] especially if the rate reaches 250 beats per minute or greater or an AV nodal blocking agent is administered.

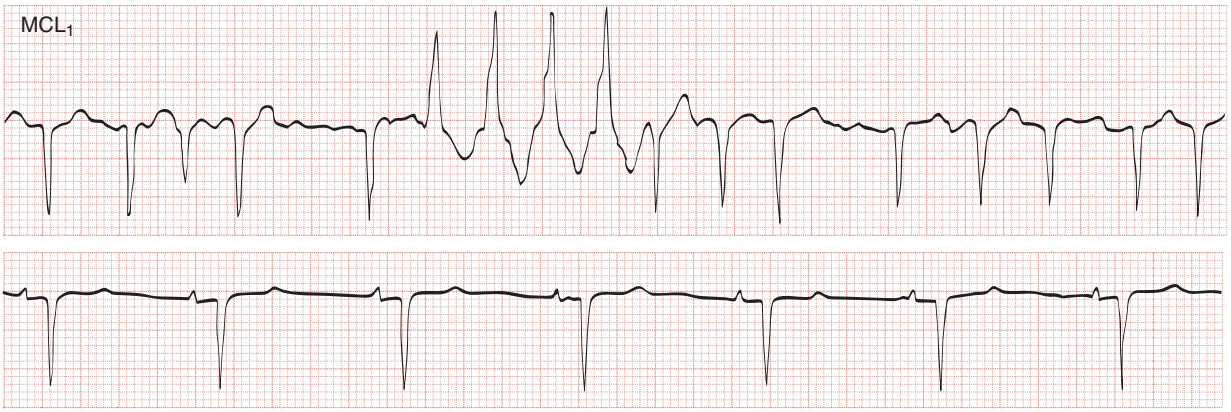


Figure 77-30. Atrial fibrillation with classical Ashman phenomenon series of beats. Note long-short cycle before aberrantly conducted impulses. (From Marriott HJL, Conover MB: Advanced Concepts in Arrhythmias, 2nd ed. St. Louis, Mosby, 1989.)

BOX 77-9 CAUSES OF ATRIAL FIBRILLATION

Ischemic heart disease*
Valvular disease (especially mitral)*
Pericarditis
Hyperthyroidism
Sick sinus syndrome
Myocardial contusion
Acute ethanol intoxication (holiday heart syndrome)
Idiopathic
Hypertensive heart disease*
Cardiomyopathy*
Cardiac surgery
Catecholamine excess
Pulmonary embolism
Congestive heart failure*†
Accessory pathway (Wolff-Parkinson-White) syndrome‡

*Related to increased left atrial size.
†Can also be a result of atrial fibrillation.
‡Especially in patients with a ventricular response rate greater than 200 beats per minute.

Atrial fibrillation often occurs in an otherwise normal heart (*lone atrial fibrillation*) but is also associated with a variety of underlying diseases (Box 77-9). One etiology of new-onset atrial fibrillation is the "holiday heart" syndrome. This can occur after an ethanol binge, producing atrial fibrillation, atrial flutter, or atrial tachycardia. These rhythms usually revert spontaneously to a sinus rhythm after 24 to 48 hours.

Atrial fibrillation may also result from the degeneration of atrial flutter, irrespective of the cause. In this case, an intermediary condition called *atrial fibrillation-flutter* shows characteristics of both rhythms on ECG. It may be manifested as fine fibrillatory waves with irregular QRS complexes intermixed with flutter waves and a stretch of regular QRS complexes. Rapid atrial fibrillation followed by sinus bradycardia in an elderly patient suggests the aforementioned *bradycardia-tachycardia syndrome*. Finally, irregular atrial fibrillatory waves coupled with regular narrow or wide QRS complexes may represent atrial fibrillation coupled with complete heart block and an accelerated junctional or ventricular rhythm; this syndrome strongly suggests digitalis toxicity.

The treatment of atrial fibrillation is based on distinguishing it from other chaotic rhythms (primarily MAT or other atrial rhythms with varying conduction) and the recognition of any underlying causes and symptoms. Asymptomatic atrial fibrillation at a ventricular rate of 100 beats per minute or less requires no specific emergency therapy. Patients who are unstable from acute rapid atrial fibrillation should receive sedation and synchronized cardioversion starting at 50 to 100 J. Electrical cardioversion is not associated with an increased risk of malignant ventricular dysrhythmias in patients receiving digitalis unless clinical or laboratory evidence of toxicity coexists.

In the ED, the therapeutic course chosen depends on the aforementioned principles plus the duration of the dysrhythmia. Both chronic and paroxysmal atrial fibrillation are associated with atrial thrombus formation and embolic events. Chronic but rapid atrial fibrillation is best managed by treating any trigger (notably volume deficits, infection, or decompensated heart failure) and rate control if needed. Embolic risk increases with the duration of atrial fibrillation and when there is underlying valvular disease or chamber enlargement. Prolonged outpatient attempts to establish or maintain a sinus rhythm in patients with recurrent atrial fibrillation do not offer a clear benefit compared with rate control.

Patients with new-onset atrial fibrillation of more than 72 hours' duration should receive ED rate control if needed. Before considering cardioversion in this group through any means, a search for atrial clot or empiric anticoagulation is needed. This usually occurs in an observation or formal admission setting. Clot and embolism can develop during fibrillation and for days after conversion, the latter related to stunned myocardium after restoration of a sinus rhythm.

In stable patients with new-onset atrial fibrillation for 72 hours or less, ventricular rate control first is recommended.[4,5,35] After carefully assessing the functional implications (seeking evidence of myocardial ischemia, heart failure, syncope, or other symptoms directly attributed to the dysrhythmia), cardioversion may be undertaken, often in consultation with a cardiologist.

Intravenous calcium channel blockers (diltiazem or verapamil) or beta-adrenergic blockers are first-line rate-controlling agents in atrial fibrillation. As in atrial flutter, the relative effectiveness and complication rates in clinical practice between these agents are similar absent overt heart failure; titration is the most important guiding principle.

Beta-adrenergic blockers are particularly effective in atrial fibrillation secondary to hyperthyroidism or catecholamine excess. Digitalis is a second-line agent for ventricular rate control because of its relatively slow onset of action. Calcium channel and beta-adrenergic blockers, adenosine, and digitalis are not indicated for patients in atrial fibrillation with an accessory pathway because of the risk of precipitating ventricular fibrillation.

Intravenous magnesium sulfate (2–4 g over 2 minutes) is an adjunctive or third-line therapy to decrease the ventricular response rate. As with its use in atrial flutter, adenosine is not indicated as a primary therapy because of its short duration of effect. For outpatient rate control, calcium channel and beta-adrenergic blockers are preferred over digitalis in patients without contraindications.

Again, despite intuition, there appears to be no long-term benefit of converting atrial fibrillation to sinus rhythm, as opposed to rate control alone. This is especially true for older patients. However, it may be appropriate to attempt pharmacologic cardioversion for younger patients who present with a first known episode of atrial fibrillation of less than 72 hours' duration. Pharmacologic cardioversion of atrial fibrillation is best accomplished with procainamide, amiodarone, flecainide, propafenone, or ibutilide.[4,5,15,36] Each has conversion rates around 50 to 70%, although there may be a modestly better success rate with ibutilide. Flecainide and propafenone are reserved for patients without significant structural heart disease, hypertension, ischemia, or heart failure. In other words, these agents may be used when the patient's only indication of heart disease is atrial fibrillation ("lone" atrial fibrillation). In all other cases, procainamide, amiodarone, or ibutilide is an appropriate choice. A calcium channel or beta-adrenergic blocker should be given before a type IA agent to control the ventricular rate, with a target of 100 to 120 beats per minute (Box 77-10). This approach may limit any increase in the ventricular rate from the type IA agent. Irrespective of the route and specific agents chosen, pharmacologic cardioversion requires close monitoring and observation. If a class IA or III agent fails, one should not switch to agents of another class for several hours to avoid complications.

Type IC agents (flecainide and propafenone) are not available for intravenous use in the United States (but are used in Europe for this indication) and therefore have a limited role for emergency management of atrial fibrillation. Vernakalant is an investigational, atrial-specific type IC agent that may become a useful tool for acute atrial fibrillation conversion,[3,10] with fewer conductive side effects. One European trial noted success with oral propafenone or flecainide in a single dose "pill in the pocket" method.[37] In this approach, patients with previous atrial fibrillation paroxysms are given a dose of either agent, taking it when symptomatic and irregular palpitations occur. This strategy can convert some overtly symptomatic patients to a sinus rhythm within hours and obviate an ED visit or hospitalization.

Electrical cardioversion (with 50–100 J) is indicated if the previously described measures fail to convert symptomatic atrial fibrillation and in unstable patients.[35] Although a synchronized countershock is recommended, the irregularity may require delivery of an unsynchronized countershock. Electrical therapy converts 85 to 90% of new-onset, stable, and nonvalvular atrial fibrillation.

Admission criteria for a patient with atrial fibrillation include instability, myocardial ischemia, worsened heart failure, or symptomatic recurrence in the ED. Traditionally, all patients with new-onset atrial fibrillation were admitted to "rule out" causes such as myocardial ischemia and pulmonary embolism. These diagnoses are rarely occult, and selective discharge of patients in the absence of clinical evidence of acute coronary ischemia, new valve dysfunction, acute lung illness (including pulmonary embolism), or thyroid disease is acceptable after ED observation and with close follow-up. While electrical conversion previously mandated admission, it may be possible to discharge after observation absent other admission triggers.

BOX 77-10 PHARMACOLOGIC APPROACH TO ATRIAL FIBRILLATION CONVERSION

Intravenous procainamide, 50 mg/min, up to a total dose of 18 to 20 mg/kg (12 mg/kg in patients with congestive heart failure) or until conversion or side effects occur

or

Amiodarone, 3 to 5 mg/kg IV, over 15 to 20 minutes

or

Ibutilide, 0.015 to 0.02 mg/kg IV, over 10 to 15 minutes (conversion usually occurs within 20 minutes if successful)

or

Oral propafenone 600 mg (contraindicated in setting of structural heart disease or ischemia)

or

Oral flecainide 300 mg (contraindicated in setting of structural heart disease or ischemia)

If needed:

A calcium channel blocker (verapamil, 40–80 mg PO or 5-10 mg IV, or diltiazem, 60–120 PO or 15–25 mg IV) can be given before the type IA agent (if no contraindications are present) to lower the ventricular response rate to <120 beats per minute and to attenuate further tachycardia from the vagolytic effects of these agents.

Supraventricular (Atrioventricular Nodal) Tachycardia

These dysrhythmias are often referred to as paroxysmal supraventricular tachycardia (PSVT or simply SVT), although the precise term is paroxysmal junctional tachycardia (PJT). For the purposes of this discussion, we will use the more common term, PSVT. ECG diagnosis is based on the presence of a narrow-complex regular tachycardia without preceding atrial depolarization waves (Fig. 77-31).

PSVTs produce retrograde atrial depolarization and a P′ wave, but these P′ waves are usually buried within the QRS complex. P′ waves may be located anywhere in relation to the QRS complex and assume either a normal or abnormal structure. The location of the P′ waves can be useful in defining the electrophysiologic source of a PSVT and help distinguish it from other causes of a regular narrow-complex tachycardia (Fig. 77-32).

Among all patients with a regular PSVT, reentrant PSVT (also termed *AV nodal reentry*) is the most common type. The alpha pathway within the AV node is used for anterograde conduction in 90% of cases of sustained PSVT and accounts for the common finding of P waves buried within the QRS complexes (see Fig. 77-32). Clinically, patients experience the abrupt onset of a regular tachycardia at a ventricular rate of 120 to 200 beats per minute. A PJC or PAC often initiates PSVT. Termination is also abrupt, from increased vagal tone, drug therapy, or spontaneous conversion. PSVT at a rate of more than 225 beats per minute is rare, and suggests an accessory pathway syndrome. All "regular" narrow-complex tachycardias (QRS duration <0.10 second) are treated in the same way, whether or not a PSVT or accessory pathway syndrome is responsible. As noted, sinus tachycardia may be mistaken for SVT or PSVT in infants and young children.

Nonparoxysmal (or sustained) junctional tachycardia (NPJT) is usually the result of an automatic mechanism, with gradual onset and termination. NPJT rarely exceeds a ventricular rate of 130 beats per minute. Compared with PJT, NPJT is more

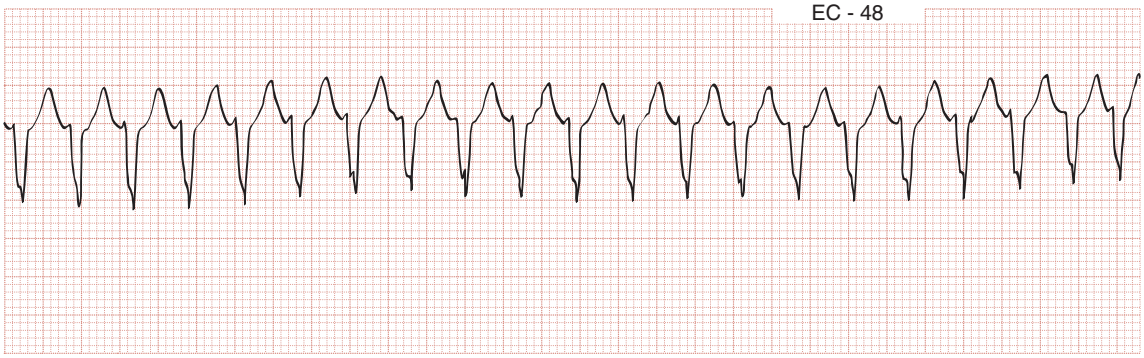


Figure 77-31. Paroxysmal supraventricular tachycardia. Note the narrow, regular QRS complexes.

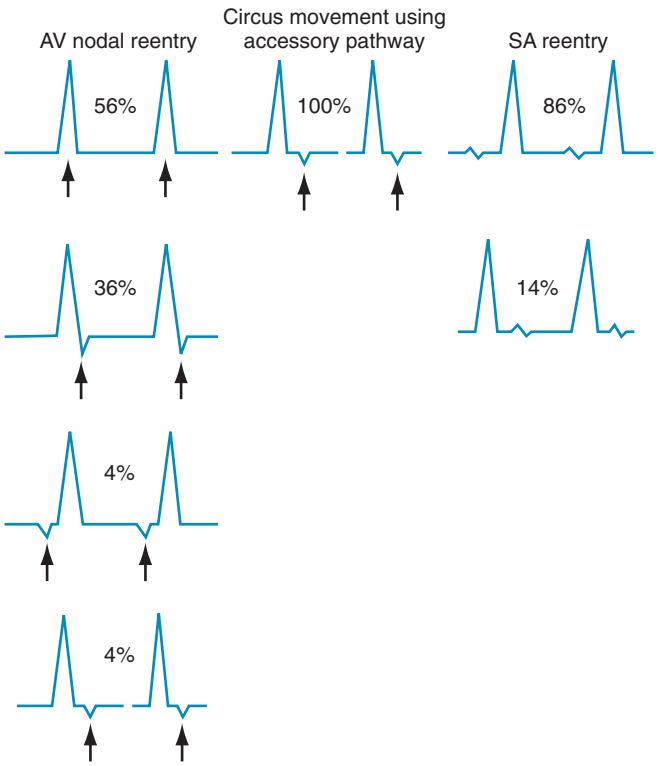


Figure 77-32. Location of P waves in common causes of regular narrow-complex tachycardia. AV, atrioventricular; SA, sinoatrial. (From Marriott HJL, Conover MB: Advanced Concepts in Arrhythmias, 2nd ed. St. Louis, Mosby, 1989.)

often associated with underlying heart disease, electrolyte imbalance, or excess catecholamine states.

Asymptomatic junctional tachycardia at a rate less than 120 beats per minute does not require specific therapy aside from correcting any underlying abnormalities. Stable symptomatic patients with rates greater than 120 beats per minute are most often treated initially with adenosine. The adult dose is 6 mg, followed by 12 mg, which can be repeated, if conversion does not occur. Conversion with adenosine is successful in 85 to 90% of cases. Similar results can be obtained with a calcium channel blocker or a beta-adrenergic blocker. Although adenosine produces initial success rates similar to those seen with diltiazem or verapamil, recurrence rates may be higher because of the short serum half-life (10 seconds; see Miscellaneous Agents, Adenosine). Calcium channel blockers and adenosine are safe and effective in out-of-hospital treatment of PSVT. Vagal maneuvers, especially Valsalva maneuver or carotid sinus massage, may effectively terminate the PSVT without pharmacologic intervention. In certain cases, patients can be taught how to do this at home.

Blood pressure must be monitored closely to avoid excessive hypotension, making electrical cardioversion a better choice in patients with severe hypotension during the PSVT. Type IA and IC agents may be used to prevent the recurrence of PSVT, particularly in individuals who cannot tolerate calcium channel or beta-blockers. Cardioversion (ideally synchronized) with 50 to 100 J is the best treatment for unstable patients with PSVT or NPJT.

Most patients can be discharged if the PSVT is terminated. Oral therapy with a class II or IV agent is an option for those with frequent symptomatic episodes of PSVT, but this decision is best made in consultation with the physician who will be providing ongoing care for the patient. Patients with serious underlying medical illnesses, recurrent or poorly controlled dysrhythmias, or evidence of instability or cardiac ischemia should be admitted to the hospital or ED observation unit. Some patients requiring electrical cardioversion may be admitted to the hospital, although an otherwise healthy patient who is easily cardioverted without recurrence can be considered for discharge with appropriate follow-up. Referral for thyroid testing, ambulatory monitoring, electrophysiology studies, and potential ablation may be considered if the problem is recurrent or associated with profound symptoms.

Preexcitation and Accessory Pathway Syndromes

Preexcitation refers to depolarization of the ventricular myocardium earlier than would occur by conduction of an impulse through the AV node. This implies the existence of a pathway from the atria to the ventricular myocardium in addition to the AV node, hence the term *accessory pathway*. These terms are related but not interchangeable because not all accessory paths are used to activate the ventricles early. Wolff-Parkinson-White (WPW) syndrome is the classic accessory pathway syndrome, although it probably represents a group of pathologic conditions. The clinical hallmark of this syndrome is paroxysmal tachycardia at a ventricular rate of 150 to 300 beats per minute, the direct result of the loss of the normal AV node conduction restraint. Any tachycardia in an adult at a ventricular rate greater than 200 beats per minute should raise the suspicion of an accessory pathway syndrome.

The classic WPW syndrome consists of tachycardia with the following three features (Fig. 77-33):

- A short P-R interval (<0.12 second)
- QRS duration greater than 0.10 second
- A slurred upstroke to the QRS complex, referred to as a *delta wave*

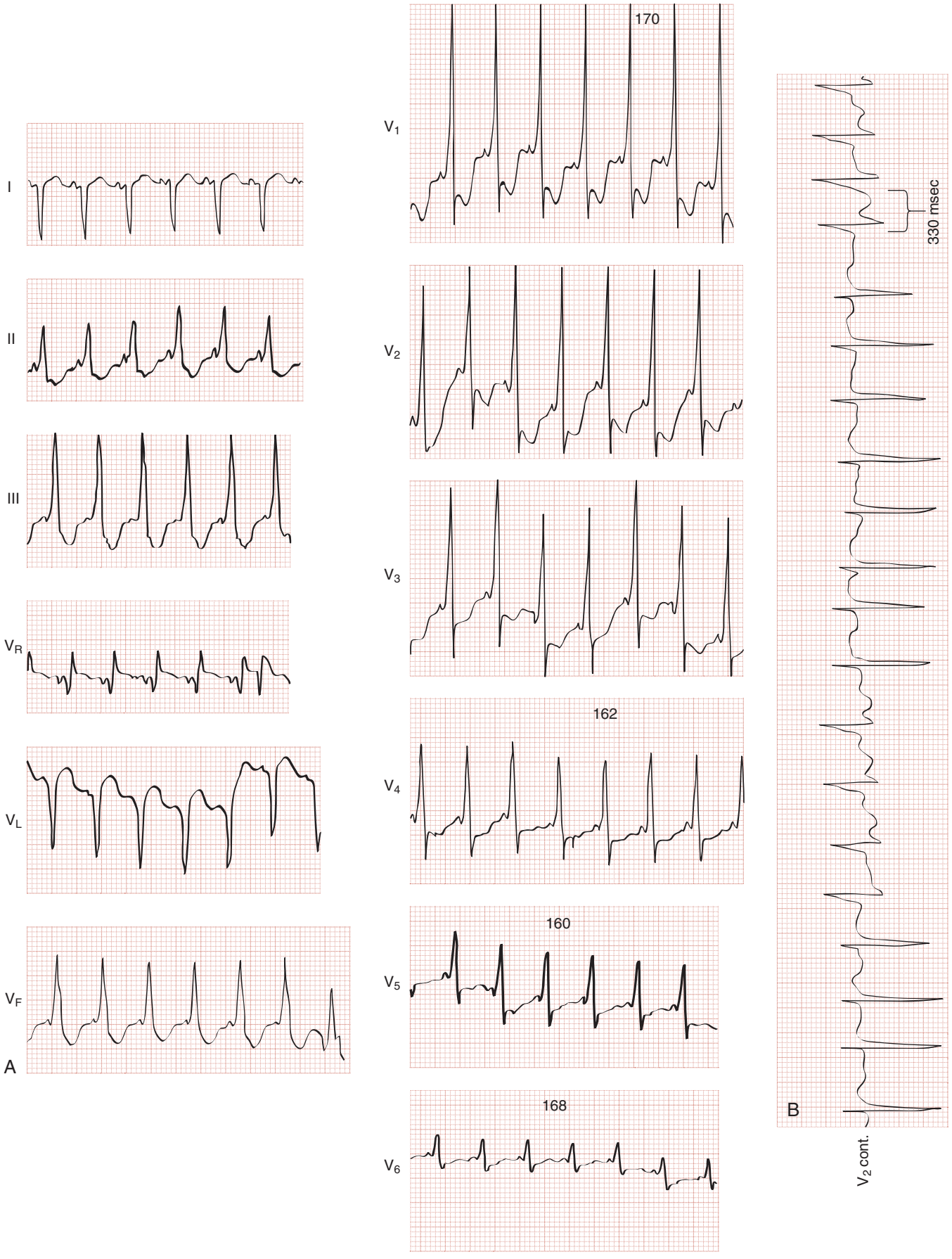


Figure 77-33. **A,** Wolff-Parkinson-White (WPW) syndrome. **B,** WPW syndrome with atrial fibrillation. Note short refractory period (330 msec). (**A,** from Watanabe Y, Dreifus LS: Cardiac Arrhythmias. New York, Grune & Stratton, 1977.)

The short P-R interval is the result of the absent AV node conduction delay, and the delta wave occurs because of early activation of the ventricular myocardium. Although the WPW syndrome typically has a prolonged QRS duration as a result of the delta wave, the QRS duration commonly varies with the location and conduction direction of the accessory pathway. Pathways inserting into infranodal conducting tissues can produce a near-normal QRS complex, whereas those inserting in the nonconductive tissues produce a wide QRS complex with an abnormal structure. If this classic triad is present, secondary T wave changes (a deflection opposite the main QRS vector) are seen.

Multiple possible connections between the atria and ventricles can create an accessory path in WPW syndrome (Fig. 77-34), with up to 13% of patients having more than one anomalous AV path. The Kent fibers are the single most common accessory pathway. Historically, WPW syndrome was divided into left-sided (QRS mostly positive in V_1, type A) and right-sided (QRS mostly negative in V_1, type B) paths, with the latter being more accessible to surgical ablation. With the advent of catheter radiofrequency ablation, this classification is no longer relevant.

The accessory path(s) participate in a reentry circuit that produces or sustains the tachycardia. The AV node often constitutes one limb of these circuits. When the QRS complex is narrow and a delta wave is absent, the AV node is being used for anterograde conduction to the ventricles and the accessory path is used for retrograde conduction, termed an *orthodromic tachycardia*. Conversely, if the QRS complex is wide and a delta wave is present, the accessory pathway is being used as the anterograde limb and the AV node as the retrograde limb of the reentry circuit, termed an *antidromic tachycardia*. The majority of symptomatic patients with WPW syndrome have a regular orthodromic tachycardia, making detection of the syndrome difficult in the ED. Conversely, asymptomatic WPW syndrome is usually discovered when a delta wave or waves and wider QRS complex of antidromic WPW syndrome are seen on the ECG.

Patients with WPW syndrome often have one or more of the classic features missing on the surface ECG, especially if a sinus rhythm is present at the time of evaluation. WPW syndrome is present in 0.1 to 0.3% of the population, with men affected twice as often as women. On the basis of this prevalence, it is estimated that only 25 to 50% of patients with WPW syndrome become symptomatic. WPW syndrome is associated with a variety of conditions, although up to 70% of patients have no underlying heart disease (Box 77-11). In those without underlying heart disease, especially if WPW syndrome is discovered in the absence of symptoms, the prognosis is excellent, with an extremely low risk of sudden death.

The presenting rhythm in symptomatic patients with WPW syndrome is usually a reentrant tachycardia (70–80%), although atrial fibrillation can be seen in 10 to 30% of patients. Emergency treatment depends on the following three observations:

- Symptoms of instability
- QRS duration or delta wave presence
- QRS regularity or irregularity

Unstable patients, irrespective of the QRS duration or regularity, should be cardioverted (synchronized preferred) with 50 to 100 J (0.5–2 J/kg for children) with sedation if time permits.

A regular orthodromic (narrow QRS complex) tachycardia is the single most common presentation of an accessory pathway syndrome (and often not recognized as an accessory pathway syndrome) and is treated in the same way as PSVT. Adenosine, calcium channel blockers, beta-adrenergic blockers, and procainamide are all suitable for first-line therapy if vagal maneuvers fail. Procainamide may be preferable as the primary therapy for all stable patients with the WPW syndrome with prolonged QRS complexes because of its effectiveness and safety irrespective of the conduction pathway. Digitalis, amiodarone, or class IC agents are alternative therapies for orthodromic regular tachycardias. All of these drugs except adenosine are suitable for outpatient prophylaxis after termination of the tachycardia. Lidocaine is unlikely to have any effect on orthodromic WPW-related tachycardia, and magnesium is not well studied in this syndrome.

Symptomatic patients with an antidromic (wide QRS complex) regular tachycardia or any irregular tachycardia (irrespective of QRS duration) have a more serious prognosis because of the high risk of ventricular fibrillation, especially when the RR interval is less than 0.20 second. In these situations, *AV nodal blocking drugs (calcium channel blocking agents, beta-adrenergic blocking agents, and digoxin) are contraindicated.* These agents may create a faster ventricular response rate from unopposed conduction through the accessory pathway, which can lead to ventricular fibrillation.[34] It is not clear whether adenosine, with its extremely short half-life, shares this risk, and adenosine has been used successfully in patients

BOX 77-11 DISEASES ASSOCIATED WITH WOLFF-PARKINSON-WHITE SYNDROME

Idiopathic*
Cardiomyopathy (especially hypertrophic)
Transposition of great vessels
Endocardial fibroelastosis
Mitral valve prolapse
Tricuspid atresia
Ebstein's disease

*Most common.

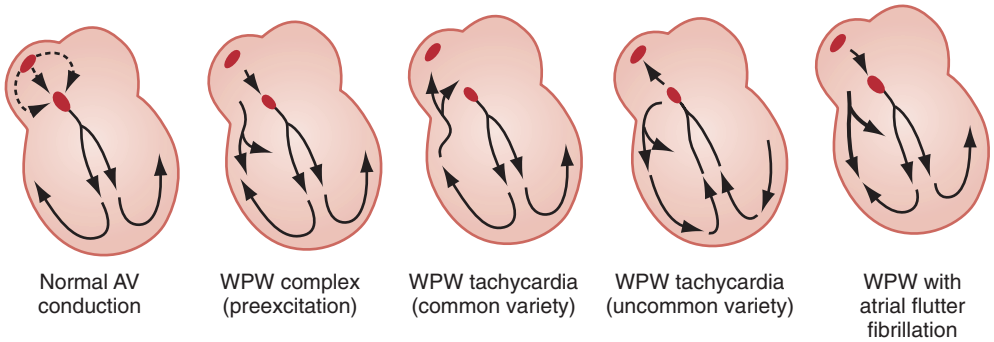


Figure 77-34. Wolff-Parkinson-White (WPW) paths and associated rhythms. AV, atrioventricular. (From Watanabe Y, Dreifus LS: Cardiac Arrhythmias. New York, Grune & Stratton, 1977.)

with wide-complex, regular tachycardias (see Wide-Complex Tachycardias). When a wide-complex, irregular rhythm is present, however, adenosine is contraindicated, along with the other nodal-blocking agents. Irregularity can be difficult to detect at extremely fast rates and should be assumed present when there is doubt. A wide-complex irregular tachycardia at a ventricular rate of 250 beats per minute or greater is highly suggestive of atrial fibrillation and WPW syndrome.

Procainamide and amiodarone are the drugs of choice in all antidromic or irregular WPW-related tachycardias. Electrical cardioversion is best any time the ventricular rate is 250 beats per minute or greater, drug therapy fails, or instability or clinical deterioration occurs. Lidocaine has limited utility in antidromic or irregular accessory pathway syndromes. It usually has little effect on conduction, although isolated reports of both decreased and enhanced conduction through the accessory pathway exist. For these reasons, lidocaine is not recommended for antidromic or irregular accessory pathway syndromes.

Patients who experience recurrence in the ED and those with underlying complicating diseases or symptoms (e.g., chest pain, congestive heart failure, electrolyte imbalance) should be admitted to the hospital or to an observation unit. Those without the aforementioned features in whom tachycardia is easily terminated can be discharged and referred as necessary for electrophysiologic studies to map the location of the pathway and potential radiofrequency ablation of the tract.

The Lown-Ganong-Levine syndrome is an uncommon accessory pathway syndrome associated with paroxysmal tachycardia, a short PR interval, and a normal QRS complex without a delta wave. Patients usually have a paroxysmal reentrant narrow-complex tachycardia. The treatment parallels that for the WPW syndrome.

Wide-Complex Tachycardias

Wide-complex tachycardia refers to dysrhythmias at a ventricular rate greater than 100 beats per minute and a QRS duration of 0.12 second or more. Wide-complex tachycardia can originate from foci in the ventricles (ventricular tachycardia) or above the ventricles (supraventricular tachycardia, SVT). Supraventricular foci can produce a wide-complex tachycardia if a conduction abnormality exists. The widened QRS seen in supraventricular rhythms occurs with a preexisting bundle branch block or an acquired bundle branch block (often related to fast or irregular heart rates and ischemia), or when conduction is through an accessory pathway. A focus below the level of the AV node results in ventricular tachycardia. The treatment of wide-complex tachycardia is based on the ability to distinguish ventricular tachycardia from SVT with abnormal conduction.

The approach to the differential diagnosis of a wide-complex tachycardia is based on systemic evaluation of evidence gained from a focused history, physical examination, and ECG tracing. The classic Wellens criteria[38] (Table 77-7) use multiple, unordered clinical data points to help estimate the likelihood of a ventricular or supraventricular source. As an improvement, the Brugada and the Griffith criteria use the ECG principles encased in the Wellens approach, surrounded in a decision tree approach (Fig. 77-35). The Brugada approach[39] uses four steps to identify ventricular tachycardia; if absent, an SVT is diagnosed. Griffith uses the opposite approach, identifying classic bundle block patterns to first identify SVT, then seeking AV dissociation to find ventricular tachycardia in the remainder. These two have similar performance in daily practice.[38–41]

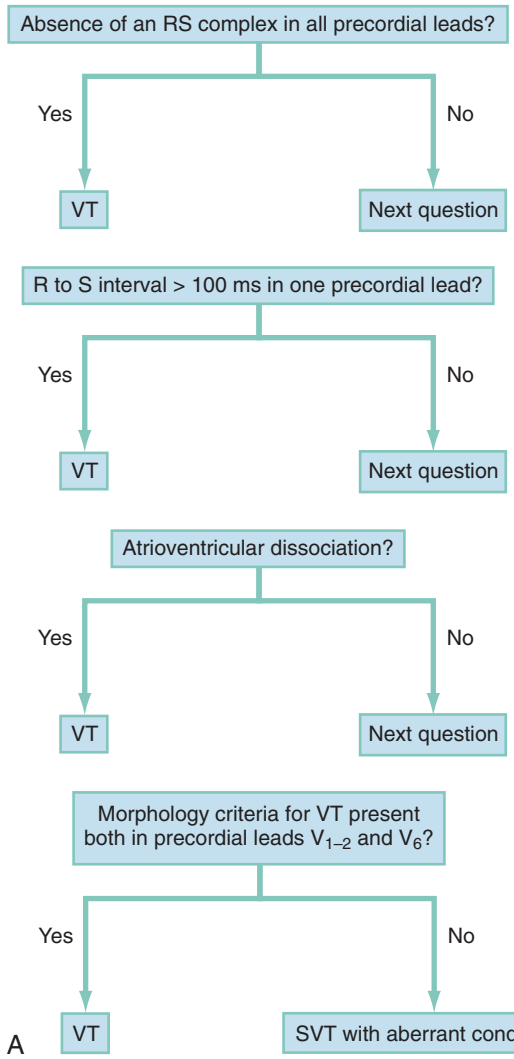
No one criterion or system that helps distinguish a supraventricular from a ventricular source is infallible. A careful collection of multiple data points usually leads to the correct diagnosis. The treating physician should *always initially assume that any new-onset symptomatic wide-complex tachycardia is ventricular tachycardia until proved otherwise* (which often can be done by history, examination, and evaluating the ECG).

Patients with a history of a previous myocardial infarction are more likely to have ventricular tachycardia than SVT with abnormal conduction. This historical point, coupled with the onset of a dysrhythmia after the infarction, strongly suggests the diagnosis of ventricular tachycardia. Other features more frequently associated with ventricular tachycardia are an age of 50 years or older, known ischemic or structural heart disease, congestive heart failure, family history of early or sudden cardiac death, and a previous history of ventricular dysrhythmias. Conversely, younger patients (younger than 35 years) and those with a history of SVT are more likely to have a supraventricular source with abnormal conduction.

Table 77-7 Features Helpful in Distinguishing Ventricular Tachycardia from Supraventricular Tachycardia (SVT) with Abnormal Conduction

	VENTRICULAR TACHYCARDIA	SVT PLUS ABERRANCY
Clinical features	Age 50 or older	Age 35 or less
	History of myocardial infarction, congestive heart failure, CABG, or ASHD	None
	Previous history of ventricular tachycardia	Previous history of SVT
Physical examination	Cannon A waves	Absent
	Variation in arterial pulse	Absence of variability
	Variable first heart sound	Absence of variability
Electrocardiogram	Fusion beats	None
	AV dissociation	Preceding P waves with QRS complexes
	QRS >0.14 sec	QRS usually <0.14 sec
	Extreme LAD (<–30 degrees)	Axis normal/near normal
	No response to vagal maneuvers	Slow or terminate with vagal maneuvers
Specific QRS patterns	V_1: R, qR, or RS	V_1: rSR′
	V_6: S, rS, or qR	V_6: qRs
	Identical to previous ventricular tachycardia tracing*	Identical to previous SVT tracing*
	Concordance of positivity or negativity†	

*If proven by electrophysiologic studies or by a preponderance of evidence.
†Main deflection of QRS complex either positive or negative in every precordial lead.
ASHD, arteriosclerotic heart disease; CABG, coronary artery bypass graft; LAD, left anterior descending artery.



A

	BBB pattern
Right	
V_1	rSR′pattern with R′>rRS (RS) pattern with R > S; Q wave
V_6	<40 ms and <2 mm (0.2 mV) were allowed
Left	
V_1	rS or QS pattern with time to 5 wave nadir <70 ms
V_6	R wave with no Q wave

BBB = bundle branch block.

If no classic BBB pattern as noted above that would define SVT with aberrancy, search for AV dissociation; if present, VT is diagnosed and if absent, SVT diagnosed by default.

B

Figure 77-35. A, Brugada four-step approach for differentiating ventricular tachycardia (VT) and wide-QRS supraventricular tachycardia. Only when a negative response to all four questions occurs is a supraventricular rhythm with abnormal conduction diagnosed. As soon as a single "yes" answer is noted, ventricular tachycardia is diagnosed. (From Brugada P, et al: A new approach to the differential diagnosis of a regular tachycardia with a wide QRS complex. Circulation 83:1649, 1991.) **B,** Griffith approach, where aberrant conduction is sought in leads V_1 and V_6 (right bundle branch block [RBBB] or left bundle branch block [LBBB] classic appearances), followed by a search for atrioventricular (AV) dissociation. If classic RBBB/LBBB patterns are absent, or if remainder have no AV dissociation, VT is diagnosed. (Redrawn from Griffith MJ, et al: Ventricular tachycardia as default diagnosis in broad complex tachycardia. Lancet 343:386, 1994.)

During the physical examination, clues about the source of a wide-complex tachycardia can be gleaned. Evidence of AV dissociation (variation in the first heart sound or in the systolic blood pressure beat to beat or cannon jugular waves) suggests a ventricular origin. The absence of these findings, however, does not imply a supraventricular source. Slowing or termination of a wide-complex tachycardia in response to carotid sinus massage and other vagal maneuvers suggests a supraventricular source.

One common error in the differential diagnosis of wide-complex tachycardia is the belief that the blood pressure and level of consciousness can be used to distinguish ventricular tachycardia from SVT with abnormal conduction. Although ventricular tachycardia is more often associated with reduced cardiac output, hypotension, and a depressed sensorium, the absolute blood pressure and level of consciousness are not useful in discriminating ventricular tachycardia from SVT with abnormal conduction. Many patients with ventricular tachycardia tolerate the dysrhythmia well.

ECG clues to the origin of a wide-complex tachycardia can be distilled into a few simple rules (see Table 77-7 and Fig. 77-35). Again, *evidence of AV dissociation strongly suggests a ventricular source for a wide-complex tachycardia*. Retrograde conduction to the atria during ventricular tachycardia can occa-

sionally produce a consistent P′ wave after the QRS complex, creating the appearance of AV association (though the P waves should look abnormal). Another strong indicator that ventricular tachycardia is present is fusion beats, occurring when an atrial impulse reaches the AV node and infranodal conduction system at the same time as the ventricular impulse, creating a hybrid QRS complex. This hybrid fusion QRS complex is often intermediate in duration and structure between the narrow atrial impulse and the wide ventricular impulse.

The appearance of specific QRS patterns in the precordial leads, especially leads V_1 and V_6, can also help identify the origin of a wide-complex tachycardia (see Table 77-7). A QRS duration of greater than 0.14 second is more commonly associated with ventricular tachycardia, especially when coupled with a history of previous myocardial infarction. A bizarre QRS axis, manifested as an extreme left-axis deviation, also suggests ventricular tachycardia. Finally, a previous ECG tracing can be helpful; QRS complexes that are identical to those seen on an old ECG strongly suggest the same source. If the QRS morphology during a wide-complex tachycardia is the same as the morphology of sinus rhythm with bundle branch block, it is more likely that the wide-complex tachycardia is supraventricular with aberration rather than ventricular tachycardia. This indicator is not without pitfalls; subtle changes in QRS morphology or duration can be difficult to see, yet may be important clues in separating ventricular tachycardia from SVT with abnormal conduction.

The Brugada ECG criteria[39,41] search for four pieces of evidence of ventricular tachycardia from among those listed previously; as soon as one is found, the diagnosis is made. *The rhythm must be regular for these to be employed* (chaos suggests atrial fibrillation with altered conduction). The sequential criteria are (see Fig. 77-35):

1. Absence of any RS complexes in the chest leads
2. RS duration (measured from beginning of R to deepest part of S wave) greater than 100 msec
3. AV dissociation (often present but overlooked may be best appreciated in inferior limb leads and $V_{1–2}$)
4. Specific ventricular tachycardia morphologic criteria (Fig. 77-36)

Only when none of the criteria are present is a supraventricular etiology diagnosed. Although the original investigators found excellent sensitivity (98.7%) and specificity (96.5%) in detecting ventricular tachycardia, follow-up investigations have not duplicated this level of accuracy in ED patients (sensitivity 92–94%). Often, physicians either cannot complete or agree on the findings.[42] In patients receiving class I agents, the Brugada criteria are less reliable.

The Griffith criteria[40,41] use a three-step approach seeking to identify aberrancy, first through classic RBBB or left bundle branch block (LBBB) morphologies in V_1 and V_6 to identify SVT, then seeking AV dissociation in the remainder to identify ventricular tachycardia (see Fig. 77-35). Like the Brugada approach, this has a real use sensitivity of 92%, although specificity may be less.

The regularity of the QRS complexes can be helpful in distinguishing ventricular tachycardia from SVT with abnormal conduction and in guiding treatment. Most episodes of ventricular tachycardia and SVT with abnormal conduction are completely or predominantly regular, although some irregularity can be seen with both. Nevertheless, *a wide-complex tachycardia with an underlying chaotic rhythm (irregularly irregular) is strong evidence of atrial fibrillation with abnormal conduction*. The conduction abnormality can result from a preexisting bundle branch block, an acquired bundle branch block (often in an RBBB appearance), or an accessory pathway syndrome. Atrial fibrillation with an accessory pathway syndrome, whether associated with a wide or narrow QRS complex, should not be treated with calcium channel blockers or digoxin because of the risk of precipitating ventricular fibrillation. Cardioversion, procainamide, or amiodarone should be used on accessory pathway syndromes.

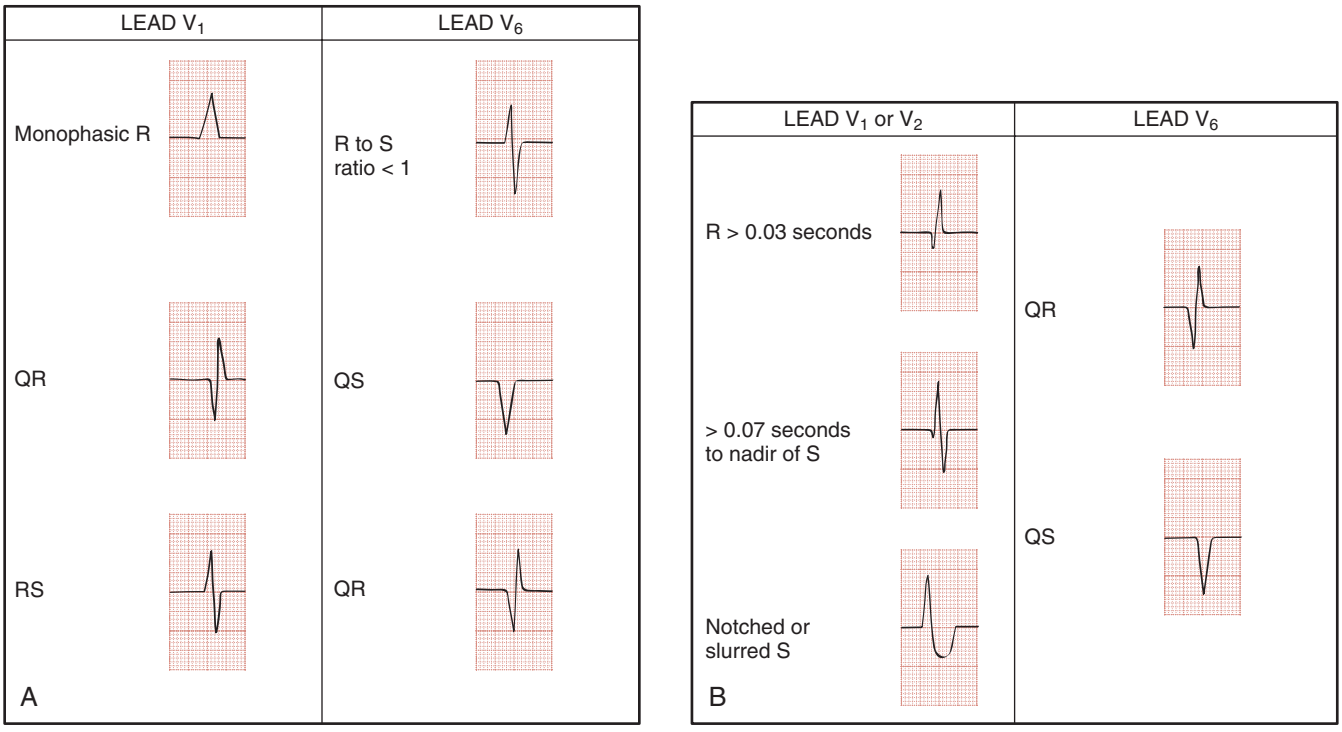


Figure 77-36. The morphology associated with the fourth criterion in the Brugada system. **A,** In patients with a right bundle branch–appearing complex. **B,** In patients with a left bundle branch–appearing complex.

Unstable patients with a wide-complex tachycardia should be treated as if ventricular tachycardia is present. Patients with pulseless wide-complex tachycardia should be treated as outlined previously in the discussion of pulseless ventricular tachycardia and fibrillation. For unstable patients with a wide-complex tachycardia and a palpable pulse, cardioversion with 50 to 100 J initially (after sedation if time permits, biphasic discharge preferred but not mandatory) is recommended. If the initial countershock is unsuccessful, repeated attempts with increased doses in 50- to 100-J increments (up to a maximum of 360 J) should be administered. Although a biphasic, synchronized countershock is preferred, unsynchronized monophasic countershock of ventricular tachycardia is acceptable.

If the patient is "borderline unstable" (only one nonextreme symptom or sign is present) or if the patient is stable yet the source of the wide-complex tachycardia is unclear, treatment should proceed assuming that ventricular tachycardia is present. Pharmacologic agents such as amiodarone, lidocaine, or procainamide are best.[43] Amiodarone is recommended as a first-line agent but may produce hypotension.[44] The advantages of lidocaine are that it can be given rapidly and terminates most cases of ventricular tachycardia. Lidocaine is unlikely to have an appreciable effect on an SVT with abnormal conduction, but is also likely to cause no harm. Procainamide and amiodarone are preferable as the initial agent in patients with a wide-complex tachycardia of uncertain origin because both can convert both SVT (including those associated with accessory pathways) and ventricular tachycardia. Electrical cardioversion remains an option in stable patients if pharmacologic treatment fails.

Because ventricular tachycardia does not usually respond to adenosine (only 5 to 10% of ventricular tachycardia cases terminate with this agent) and most SVTs are terminated or temporarily slowed, this agent can help differentiate the diagnosis of wide-complex tachycardia. Overall, this approach is relatively safe, although case reports of poorly defined hemodynamic collapse after adenosine administration in wide-complex tachycardia exist, tempering widespread enthusiasm for this approach.[29]

Although calcium channel blockers have little direct effect on most forms of ventricular tachycardia, many patients with this rhythm experience immediate cardiovascular collapse from the vasodilatory effects of these drugs. When a supraventricular source for a wide-complex tachycardia is verified, the principles of treatment parallel those outlined for narrow-complex tachycardia. While agents such as adenosine and calcium channel blockers may sometimes seem suited to aid in the diagnosis of rhythm disturbances, it is important first to carefully evaluate the ECG in the context of a patient's clinical and historical circumstances.

Ventricular Tachycardia with Pulses

Ventricular tachycardia (QRS rate ≥100 beats/min) originates within or below the His bundle. On the ECG, a minimum of three consecutive wide QRS complex beats is necessary to diagnose ventricular tachycardia. *Nonsustained* refers to short episodes (≤30 seconds) that revert spontaneously, whereas *sustained ventricular tachycardia* refers to more prolonged episodes. Reentry mechanisms are the most common cause of ventricular tachycardia, although automatic and triggered mechanisms also occur. Ventricular tachycardia can be precipitated by any extrasystole, with PVCs the most common inciting stimulus. Extrasystole that occurs during ventricular repolarization (the R-on-T phenomenon) may carry a risk of precipitating ventricular tachycardia, although the magnitude of this risk is debated. Most patients with ventricular tachycardia have underlying heart disease or ischemia.

Several groups of ventricular tachycardia can be identified on the basis of the ECG pattern and history. *Monomorphic ventricular tachycardia* can occur in the presence or absence of ischemic heart disease and appears as morphologically consistent QRS complexes, usually in a regular pattern and at a rate of 150 to 200 beats per minute (Figs. 77-37 and 77-38). An irregular rhythm and a rate greater than 200 beats per minute or less than 150 beats per minute may be seen. Monomorphic ventricular tachycardia associated with chronic coronary artery disease is the single most common form of ventricular tachycardia.

Polymorphic ventricular tachycardia is manifested as QRS complexes that vary in structure or duration and is associated with more severe underlying disease (Figs. 77-39 and 77-40). *Torsades de pointes* is a specific form of polymorphic ventricular tachycardia. *Bidirectional* (or *alternating*) *ventricular tachycardia* occurs most frequently in digitalis intoxication and appears as a ventricular tachycardia with a QRS structure and axis that change periodically (see Fig. 77-39). During all forms of ventricular tachycardia, the main vectors of the ST segment and T wave are usually in an opposite direction from the terminal portion of the QRS complex. This phenomenon is termed a *secondary repolarization abnormality*.

Treatment of stable monomorphic ventricular tachycardia is based on correcting any underlying cause (especially electrolyte imbalance, hypoxemia or hypercapnia, and myocardial ischemia) and intervening pharmacologically to terminate the dysrhythmia. Amiodarone (3–5 mg/kg over minutes) or lidocaine (1.0–1.5 mg/kg bolus, up to 3 mg/kg maximum and followed by an infusion) are first-line choices, with up to 90% of episodes successfully terminated. Procainamide can be used as a second-line agent. Magnesium sulfate (2–4 g IV as a slow bolus) can augment or serve as a third-line agent in the treatment of ventricular tachycardia, especially in the setting of ischemia. Unstable patients or those refractory to drug therapy should be cardioverted with 50 to 100 J (again, biphasic synchronized preferred but monophasic acceptable), with escalating doses (up to 200 J biphasic or 360 J monophasic) as needed.[45]

In the rare case of ventricular tachycardia caused solely by catecholamine excess, beta-adrenergic blockers may be useful in the primary treatment; otherwise, these agents are best suited for prophylaxis. Calcium channel blockers may prevent ventricular tachycardia associated with reperfusion but are not indicated for the treatment of ventricular tachycardia.

All patients with symptomatic ventricular tachycardia, new-onset ventricular tachycardia, or ventricular tachycardia requiring electrical therapy should be admitted. The rare patients eligible for discharge are those with chronic ventricular tachycardia who have no change in symptoms or evidence of acute ischemia. These patients should be released only after consultation with cardiologists familiar with their care and with close outpatient follow-up.

Many patients with ventricular tachycardia are candidates for an implanted defibrillator. The prognosis for patients with ventricular tachycardia depends on the symptoms and the presence of underlying heart disease. Those with structural heart disease and syncope have a poorer prognosis.

Polymorphic Ventricular Tachycardia and Torsades de Pointes

Polymorphic ventricular tachycardia implies more severe underlying cardiac disease and is usually treated in the same way as monomorphic ventricular tachycardia. One specific form of polymorphic ventricular tachycardia requires recogni-

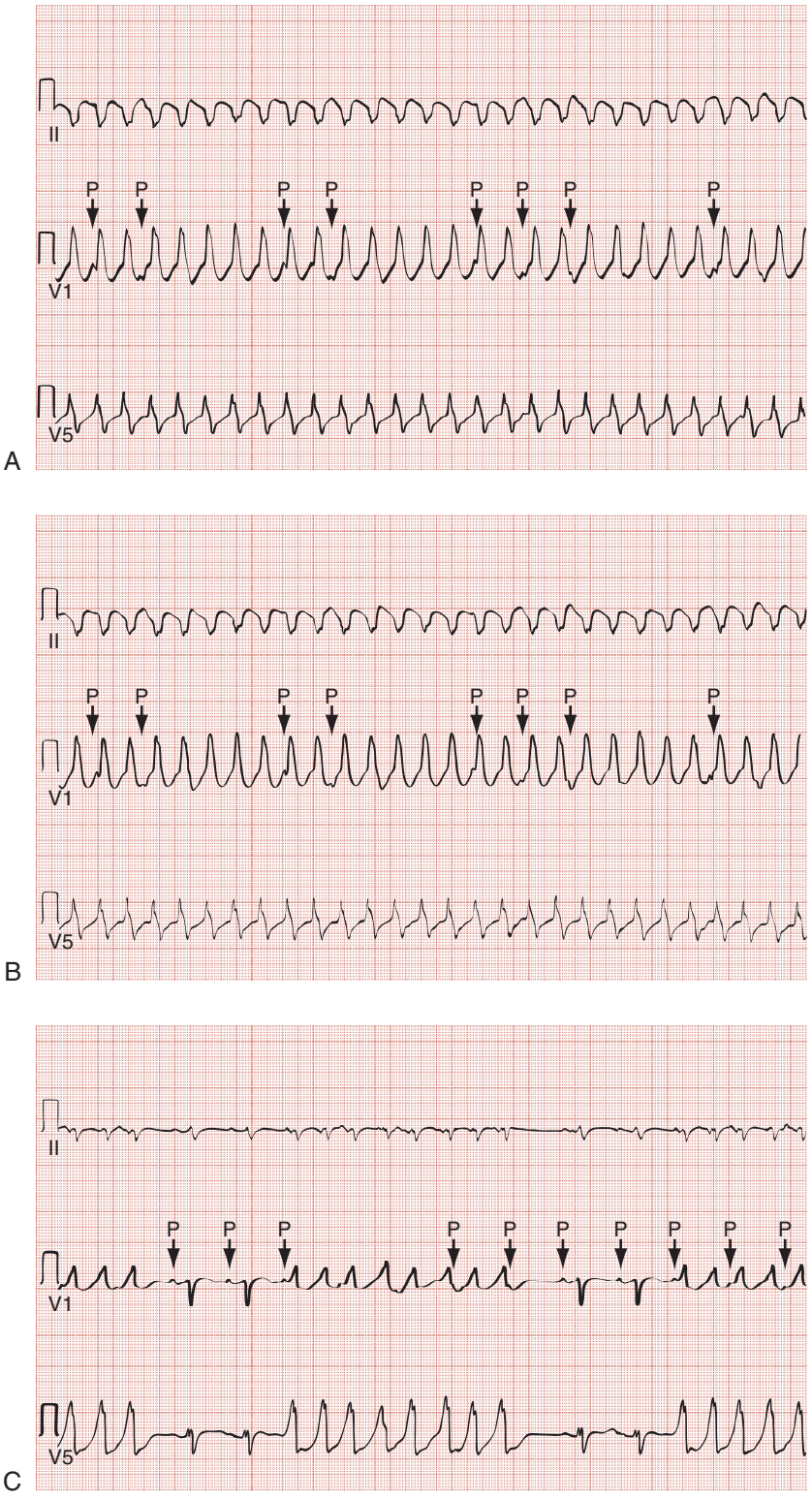


Figure 77-37. **A** and **B,** Ventricular tachycardia. Note atrioventricular dissociation. **C,** Intermittent, nonsustained ventricular tachycardia. Atrioventricular dissociation is evident. (Courtesy of Edward Curtis, MD.)

tion and specific therapy. Torsades de pointes, literally translated as "twisting of the points," is a paroxysmal form of ventricular tachycardia that meets the following clinical criteria (see Fig. 77-40):

1. Ventricular rate is greater than 200 beats per minute.
2. QRS structure displays an undulating axis, with the polarity of the complexes appearing to shift about the baseline.
3. Occurrences are often in short episodes of less than 90 seconds, although sustained runs can be seen.

Torsades often occurs in the setting of an existing prolonged QT interval during sinus rhythm, a reflection of abnormal ventricular repolarization. The normal range of QT duration must be corrected for age, sex, and heart rate. A QT interval of 500 msec or longer indicates an increased risk of torsades. Prolonged QT intervals can be congenital or acquired, with the latter being more common. Women have a greater risk of QT prolongation and torsades.

Acquired QT prolongation and torsades are often multifactorial, including interactions between drug therapy, myocar-

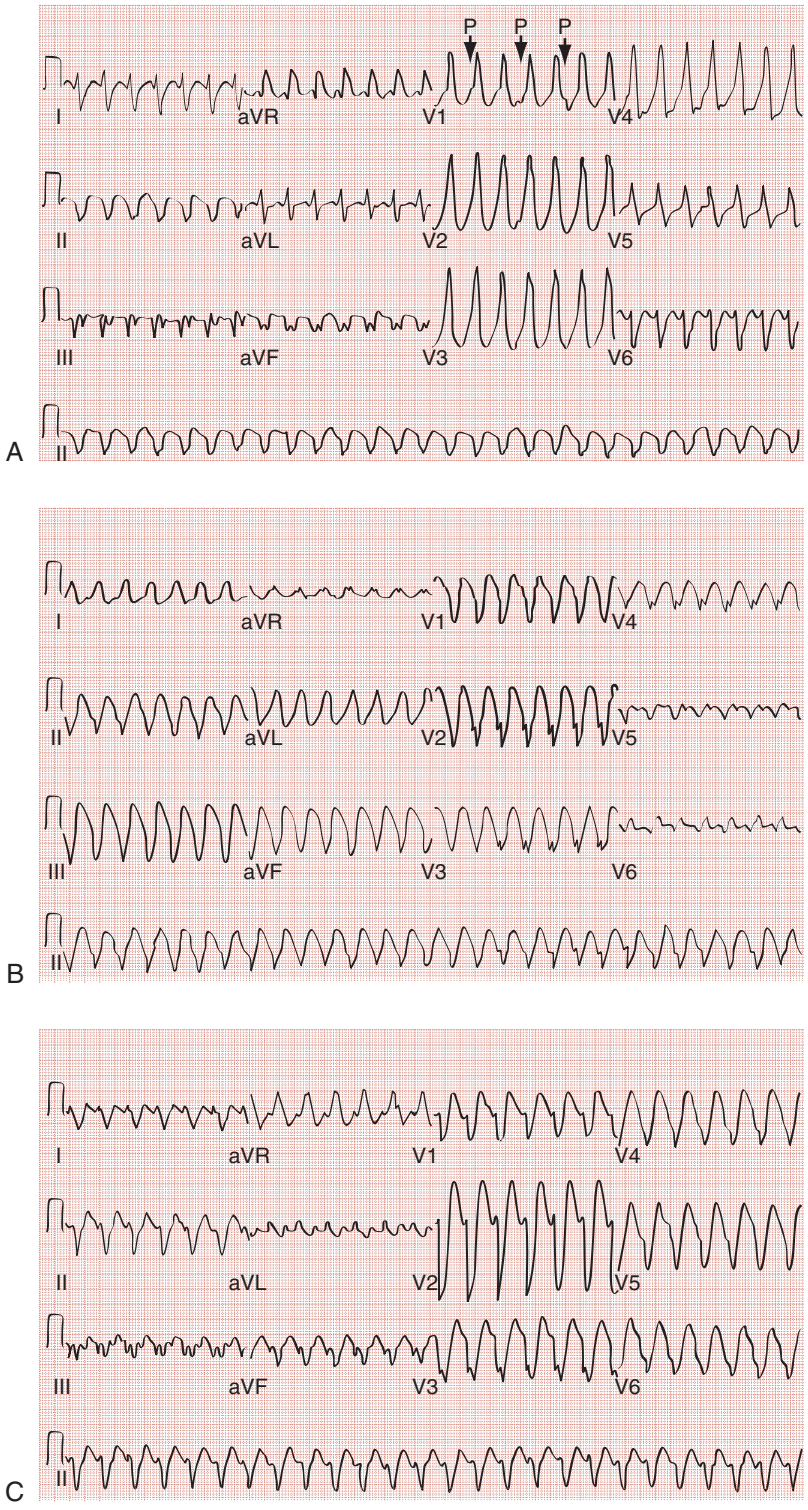


Figure 77-38. Ventricular tachycardia. **A,** RS complexes are present in chest leads, but RS duration is greater than 100 msec. Although Brugada criteria indicate that no further analysis is necessary, atrioventricular dissociation is also evident and QRS morphology (R:S ratio <1 in lead V_6) is consistent with ventricular tachycardia. **B,** Some RS complexes are present, RS duration is not greater than 100 msec, and atrioventricular dissociation is difficult to appreciate; morphologic criteria for ventricular tachycardia are fulfilled because S is notched in V_1 and QR is present in V_6. **C,** Diagnosis is based on morphologic criteria because S is notched in V_1 and V_2 and QS is present in V_6. (Courtesy of Edward Curtis, MD.)

dial ischemia, and electrolyte disturbances (hypokalemia and hypomagnesemia). Drugs (classes IA, IC, and III agents, plus many antibiotics, antifungals, antiemetics, antipsychotics, antiseizure medications, and a variety of other agents) can trigger prolonged QT intervals or torsades when new or in high concentrations, with abrupt infusion, or simply without warning. Delayed episodes (months after treatment is begun or altered) are often the result of an additive effect on ventricular repolarization, such as electrolyte imbalance, clearance issues (e.g., renal or liver failure), or addition of another drug implicated in this syndrome.

The majority of adult cases of torsades are acquired and *pause dependent* (Box 77-12). These episodes of torsades are precipitated by a slow heart rate. Treatment of intermittent torsades in stable patients is based on correcting any underlying metabolic or electrolyte abnormalities and increasing the heart rate to shorten ventricular repolarization. The latter can be done with overdrive pacing (external or transvenous) or beta-adrenergic infusion to achieve a ventricular rate of 100 to 120 beats per minute. Intravenous magnesium sulfate is also effective in treating paroxysmal torsades. Classes IA and IC agents are contraindicated because they may worsen the dys-

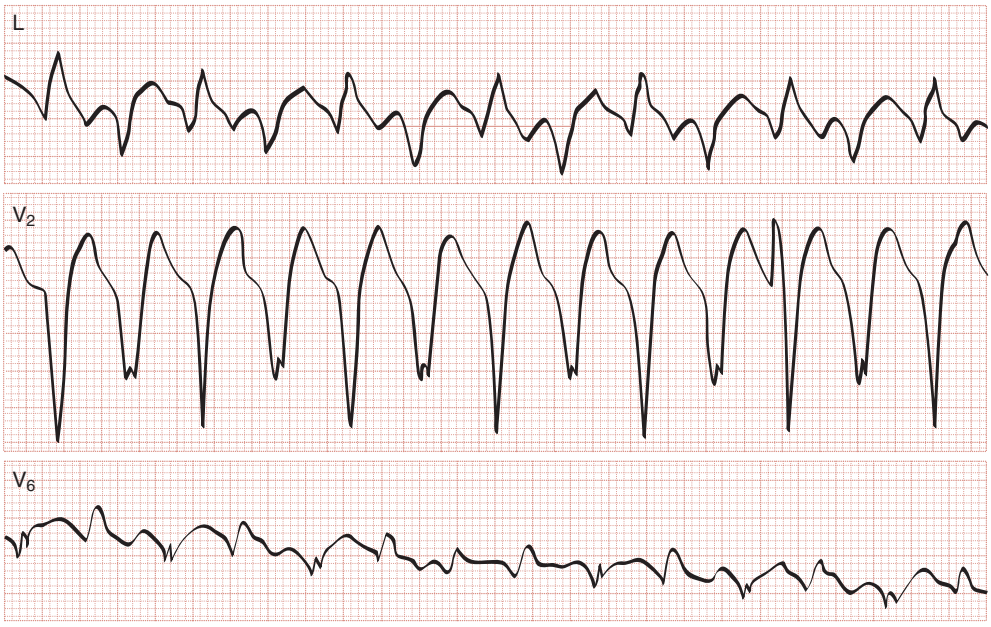


Figure 77-39. Bidirectional ventricular tachycardia in a patient with digitalis toxicity. (From Marriott HJL, Conover MB: Advanced Concepts in Arrhythmias, 2nd ed. St. Louis, Mosby, 1989.)

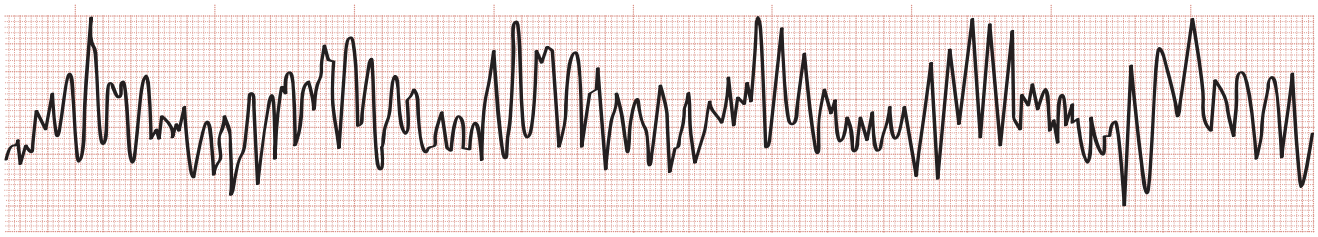


Figure 77-40. Torsades de pointes with classic spiraling of QRS complexes around baseline.

BOX 77-12 CLASSIFICATION AND CAUSES OF PROLONGED QT SYNDROMES THAT PRODUCE TORSADES

Pause Dependent (Acquired)

Drug induced: Class IA and IC antidysrhythmics; many phenothiazines/butyrophenones (notably haloperidol and droperidol), cyclic antidepressants, antibiotics (especially macrolides), organophosphates, antihistamines, antifungals, antiseizure and antiemetic agents
Electrolyte abnormalities: hypokalemia, hypomagnesemia, hypocalcemia (rarely)
Diet related: starvation, low protein
Severe bradycardia or atrioventricular block
Hypothyroidism
Contrast injection
Cerebrovascular accident (especially intraparenchymal)
Myocardial ischemia

Adrenergic Dependent (Tachycardia Prompted)

Congenital

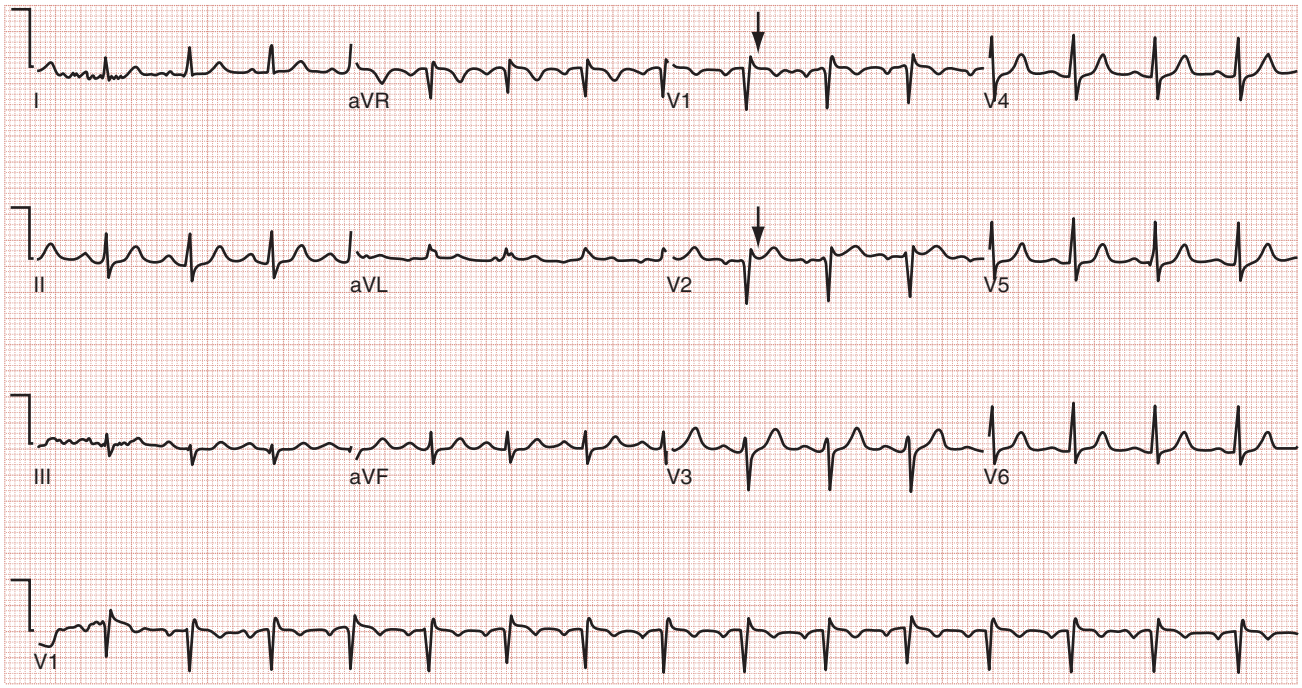
Jervell and Lange-Nielsen syndrome (deafness, autosomal recessive)
Romano-Ward syndrome (normal hearing, autosomal dominant)
Sporadic (normal hearing, no familial tendency)
Mitral valve prolapse

Acquired

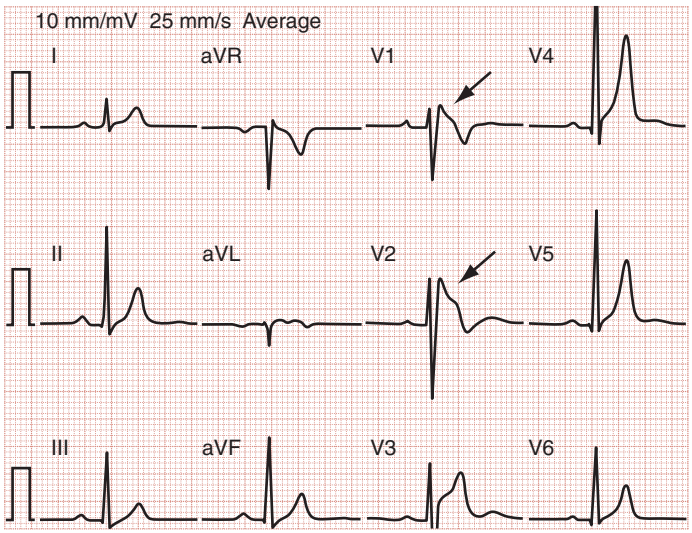
Cerebrovascular disease (especially subarachnoid hemorrhage)
Autonomic surgery: radical neck dissection, carotid endarterectomy, truncal vagotomy

rhythmia by further prolonging repolarization. The class IB agents (including lidocaine and phenytoin) shorten repolarization, but their overall success rate is low in these cases. Amiodarone is an alternative therapy, although rarely it can precipitate this rhythm.

Patients who are unstable or in sustained torsades should be electrically cardioverted as with any ventricular tachycardia; synchronization will usually not be possible. In contrast, torsades de pointes associated with a congenital QT prolongation syndrome is much rarer, usually arising in childhood or early adulthood. This form is precipitated by catecholamine excess (e.g., exercise or medications) and termed *tachycardia dependent*. Patients may present with syncope after exertion. Similarly, torsades after neck surgery and cerebrovascular accidents may also be precipitated by catecholamine excess. Treatment of all forms of catecholamine-induced torsades is based on slowing the heart rate, usually with beta-adrenergic blockers. Other agents, such as magnesium sulfate, calcium channel blockers, amiodarone, or phenytoin, have varying effectiveness and are second-line therapies.



A



B

Figure 77-41. Brugada's syndrome, with ST elevation in V_{1-2}. The ST elevation is coved (upper, **A**) or "saddle back" (lower, **B**) and may be transient.

Brugada's Syndrome

This syndrome (like prolonged QT syndromes) is associated with unpredictable ventricular dysrhythmias and syncope or sudden cardiac death, especially in those under 50 years old.[46] Brugada's syndrome results from an inherited disorder of sodium channels; it is most common in men and is most common in patients of Asian origin, although the syndrome has been reported in virtually every ethnic group. No structural heart disease accompanies this conductive disorder. It is appropriate to consider the possibility of Brugada's syndrome when children, teenagers, or young adults present with unexplained syncope or symptomatic palpitations. In the ED, Brugada's syndrome is diagnosed by its characteristic ECG pattern of elevation of the ST segment with a "saddle-back" or coved appearance in leads V_1 to V_3 (Fig. 77-41). Often, an RBBB pattern will coexist, and less commonly a first-degree AV block. The ST segment findings may be transient and variable, altering with time, drugs, or duress.

When Brugada's syndrome is noted or suspected, admission for electrophysiology testing and implanted defibrillator insertion is the key to long-term care. Drug therapy is poorly studied, with only quinidine showing promise. Other class IA, IC, and III agents can help unmask the syndrome but are not therapeutic.

KEY CONCEPTS

- Unstable patients should receive prompt electrical therapy—pacing if a slow heart rate and countershock if fast rate—after a brief examination and rhythm analysis.
- Any new-onset, symptomatic wide-complex tachycardia should be assumed to be ventricular tachycardia, allowing the clinical status and ECG features to confirm, refute, or prompt therapy.
- Type II second-degree AV block, or Mobitz II block, is never a normal variant and implies a conduction block below the AV node. When the conduction ration is 2:1, it may be impossible to distinguish from type I AV block.
- The possibility of an accessory pathway should be considered whenever ventricular response rates exceed 200 beats per minute in an adult.
- A regular narrow QRS complex tachycardia is the most common presentation for an accessory pathway syndrome.
- AV nodal blockers should not be administered when there is the possibility of an accessory pathway syndrome (e.g., any ventricular rate over 250 beats/min, especially if irregular and wide QRS complexes) or ventricular tachycardia (e.g., new wide-complex tachycardia that is mostly regular); cautious and judicious use of adenosine as a diagnostic aid should be reserved for those cases where ventricular tachycardia or atrial fibrillation and WPW are carefully considered and are not likely.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 78 Implantable Cardiac Devices

James T. Niemann and Benjamin Squire

PERSPECTIVE

Electrical cardiac pacing for the management of bradyarrhythmias was first described in 1952, and permanent transvenous pacing devices were introduced into clinical practice in the early 1960s.[1] The first devices for endocardial defibrillation were implanted in surviving victims of sudden cardiac death in 1980.[2] Currently implanted electrical devices for the management of cardiac dysrhythmias have changed rapidly over the years with both increasing complexity and miniaturization. In 1991, it was estimated that 1 million patients in the United States had permanent pacemakers, and survey data from 1989 indicated that approximately 425 new pacemakers per million population were implanted annually in the United States.[3] New indications for the use of permanent pacemakers in the management of congenital and acquired heart disease include cardiac resynchronization therapy for heart failure.[4-6]

A number of large clinical trials comparing implantable cardioverter-defibrillators (ICDs) with antiarrhythmic drugs for the prevention of sudden cardiac death resulting from ventricular dysrhythmias indicate that ICDs significantly improve survival.[7,8] Such studies have led to a dramatic increase in ICD implantations, and it is estimated that there are 125,000 new ICD implants annually in the United States.[9] The widespread use of these devices ensures that the emergency physician frequently encounters such patients, often with symptoms that may be related to malfunction of the pacemaker or ICD.

INDICATIONS FOR PERMANENT PACEMAKERS AND ANTIARRHYTHMIA DEVICES

Guidelines for the implantation of these devices have been developed by a joint task force of the American Heart Association and the American College of Cardiology (AHA/ACC) and are periodically updated.[10] Using an evidence-based approach, recommendations are categorized as class I, II, or III. Class I includes conditions for which there is general agreement that a device should be implanted. A class II recommendation includes conditions for which these devices are frequently used but for which there is disagreement about their need or benefit. Class III is reserved for conditions for which there is general agreement that a device is not needed.

In the case of pacemaker therapy, additional factors are considered when selecting the mode of pacing and include, but are not limited to, overall health, lifestyle, and occupation of the patient. Class I indications for a permanent pacemaker or ICD are listed in Boxes 78-1 and 78-2. In general, pacing is recommended for patients with symptomatic heart block, symptomatic sinus bradycardia, and atrial fibrillation with a symptomatic bradycardia (low ventricular response rate) in the absence of medications that affect atrioventricular (AV) conduction. Controversial indications include pacing in patients with syncope, heart block, or fatigue in the presence of some conduction disease or bradycardia. The likelihood of a patient's improvement after pacing can be assumed only if the symptoms can be closely correlated with inadequate rate.

Pacemaker Terminology

A letter code, initially established in 1974 and since revised as technology has advanced, standardized nomenclature for pacemakers.[11] Table 78-1 includes an explanation of the five-letter code scheme and the standard abbreviations in each category. The first three code letters are used most commonly. Using this table, one should be able to understand the features of any pacing mode. For example, a VDD pacemaker is capable of pacing only the ventricle, sensing both atrial and ventricular intrinsic depolarization, and responding by dual inhibition of both atrial and ventricular pacing if intrinsic ventricular depolarization occurs; a paced ventricular beat is triggered in response to a sensed intrinsic atrial depolarization. The codes of a permanent pacemaker that are used most frequently and the indications, advantages, and disadvantages of each are listed in Table 78-2. Detailed algorithms for matching a patient with a pacemaker have been developed.[10] The majority of permanent pacemakers are now dual chamber and often rate adaptive.[12]

Pacemaker Components

All pacemaker systems have three basic components: the pulse generator, which houses the power source (battery); the electronic circuitry; and the lead system, which connects the pulse generator to the endocardium.

Nearly all implanted pacemakers are lithium powered. Lithium-powered pulse generators function normally for 4 to 10 or more years, depending on the pacemaker features, such as single versus dual chamber, pacing threshold, and rate adaptiveness. This long "battery life" and the fact that the output voltage of the lithium-iodine cell decreases gradually rather than abruptly, as occurred with the early mercury-zinc cell,

BOX 78-1 CLASS I INDICATIONS FOR PERMANENT PACING IN ADULTS

1. Third-degree and advanced second-degree AV block at any anatomic level associated with any of the following:
   - Symptomatic bradycardia (including heart failure) or ventricular dysrhythmia presumed to be due to AV block
   - Symptomatic bradycardia secondary to drugs required for dysrhythmia management or other medical condition
   - Documented periods of asystole lasting more than 3 seconds or an escape rate of less than 40 beats/min or an escape rhythm originating below the AV Node in an awake, asymptomatic patient in sinus rhythm
   - Awake, asymptomatic patients with atrial fibrillation and bradycardia a documented pause of 5 seconds or longer
   - After catheter ablation of the AV node
   - Postoperative AV block that is not expected to resolve
   - Neuromuscular disease with AV block (e.g., the muscular dystrophies)
2. Symptomatic bradycardia resulting from second-degree AV block regardless of type or site of block
3. Asymptomatic, persistent third-degree AV block with awake ventricular rate >40 bpm with cardiomegaly or LV dysfunction or if block is below AV node
4. Chronic bifascicular or trifascicular block with intermittent third-degree AV block or type II second-degree AV block
5. Second or third-degree AV block with exercise in the absence of myocardial ischemia

AV, atrioventricular.

make sudden pulse generator failure an unlikely cause of pacemaker malfunction.

Permanent pacemakers have endocardial leads that are positioned in contact with the endocardium of the right ventricle and, in the case of a dual-chamber device, the right atrium, using a subclavian or cephalic vein approach for insertion. Occasionally, an epicardial lead may be implanted during open-heart surgery performed for another indication, such as prosthetic valve insertion or correction of a congenital cardiac defect. Pacemaker leads, like power sources, continue to undergo major technical improvements.[1] Innovations include resilient plastic insulation surrounding the electrodes that reduces the chance of complete lead disruption or breakage (resulting in failure to pace or sense) or the chance of partial fracture (resulting in a "make or break" contact with intermittent failure to sense or pace). Despite these advances, problems with the electrical circuitry remain the most common cause of pacemaker malfunction.[13] A lead capable of active fixation is more commonly used in patients with cardiomyopathies and right ventricular dilation complicated by tricuspid regurgitation.

BOX 78-2 CLASS I INDICATIONS FOR IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR THERAPY

1. Cardiac arrest resulting from VF or VT not caused by a transient or reversible event
2. Spontaneous sustained VT
3. Syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT or VF induced at electrophysiologic study when drug therapy is ineffective, not tolerated, or not preferred
4. Nonsustained VT with coronary artery disease, prior myocardial infarction, left ventricular dysfunction, and inducible VF or sustained VT at electrophysiologic study that is not suppressible by a class I antiarrhythmic drug

VF, ventricular fibrillation; VT, ventricular tachycardia.

Table 78-1 Five-Letter Pacemaker Code

LETTER 1	LETTER 2	LETTER 3	LETTER 4	LETTER 5
Chamber Paced	Chamber Sensed	Sensing Response	Programmability	Antitachycardia Functions
A = atrium	A = atrium	T = triggered*	P = simple	P = pacing
V = ventricle	V = ventricle	I = inhibited	M = multiprogrammable	S = shock
D = dual	D = dual	D = dual (A and V inhibited)	R = rate adaptive	D = dual (shock pace)
O = none	O = none	O = none	C = communicating	
			O = none	

*In the triggered response mode, the pacemaker discharges or fires when it recognizes an intrinsic depolarization. As a result, pacemaker spikes occur during inscription of the QRS complex. Because this mode results in high-energy consumption and a shortened battery life and because the sensing response can be misinterpreted as pacemaker malfunction, this sensing mode is not used with modern pacemakers.

Table 78-2 Common Permanent Pacemakers

CODE	INDICATION	ADVANTAGES	DISADVANTAGES
VVI	Intermittent backup pacing; inactive patient	Simplicity; low cost	Fixed rate; risk of pacemaker syndrome
VVIR	Atrial fibrillation	Rate responsive	Requires advanced programming
DDD	Complete heart block	Atrial tracking restores normal physiology	No rate responsiveness; requires two leads and advanced programming
DDDR	Sinus node dysfunction; for rate responsiveness atrioventricular block and need	Universal pacer; all options available by programming	Complexity, cost, programming, and follow-up evaluation

Pacemaker leads may be either bipolar or unipolar in configuration. A bipolar endocardial lead has both the negative (distal) and the positive (proximal) electrodes, separated by approximately 1 cm, within the heart. A unipolar lead has the negative electrode in contact with the endocardial surface, and the positive pole is the metallic casing of the pulse generator. Each lead system has potential advantages and disadvantages.[12] The unipolar configuration is not compatible with ICD systems, is prone to oversensing of myopotentials and electromagnetic interference, but is of smaller diameter and less susceptible to fracture. The bipolar configuration is compatible with ICD systems but is larger and more prone to lead fractures. Oversensing, however, is rarely a problem. The selection of lead configuration usually depends on the experience and preference of the operator.

The Standard Electrocardiogram During Normal Cardiac Pacing

The modern pacemaker has two basic functions: to stimulate the heart electrically and to sense intrinsic cardiac electrical activity. Additional functions are available and noted in the pacemaker code system (see Table 78-1, letters 4 and 5). The pacemaker delivers an electrical stimulus to either the atrium or the ventricle if it does not recognize (sense) any intrinsic electrical activity from that chamber after a selected time interval. This interval is usually programmed at the time of implantation and can be changed noninvasively at a later time, if necessary, using a programming and "interrogating" device provided by the pacemaker manufacturer. If the pacemaker recognizes or senses an intrinsic atrial depolarization (P wave) or ventricular depolarization (QRS complex), it inhibits or resets its output to prevent competition with the underlying intrinsic rhythm. The stimulus intensity and sensing threshold (amplitude of electrical activity that is detected as being intrinsic) are typically set at the time of implantation but can also be reprogrammed later.

The two basic functions of a pacemaker can be easily recognized and confirmed on a standard 12-lead electrocardiogram (ECG) or rhythm strip. The normal function of a single-chamber VVI pacemaker is most easily recognized (Fig. 78-1). After a programmed interval is surpassed during which intrinsic ventricular activity does not occur, a pacer "spike" or stimulus artifact appears. The pacer spike is a narrow deflection that is usually less than 5 mm in amplitude with a bipolar lead configuration and usually 20 mm or more in amplitude with a unipolar lead. A wide QRS complex appears immediately after the stimulus artifact. Depolarization begins in the right ventricular apex, and the spread of excitation does not follow normal conduction pathways. Characteristically, a left bundle branch block conduction pattern is seen. A right bundle branch pattern is abnormal and suggests lead displacement. In VVI pacing, the paced QRS complexes are independent of intrinsic atrial depolarization if present (AV dissociation).

The recognition of normal dual-chamber pacing is more complex due to the interactive sensing and pacing of the right atrium and ventricle (Fig. 78-2).[14] Pacing intervals are preprogrammed, may be changed noninvasively at a later time, and are generally specific to the patient's needs. Pacing rates and delay intervals typically vary from patient to patient. Dual-chamber devices are typically used in patients with nonfibrillating atria coupled with intact AV conduction. A normal-appearing QRS complex may follow an intrinsic "p" wave due to normal sinoatrial node discharge if the intrinsic atrial depolarization is conducted to the ventricles. The intrinsic p wave and QRS complex inhibit the atrial and ventricular circuitry. A normal QRS complex follows a paced p wave if the paced atrial beat is conducted through the AV node and the programmed AV delay period is not exceeded. If it is not conducted to the ventricles (AV delay period exceeded), the pacemaker stimulates the ventricle, resulting in a paced p wave and a wide, paced QRS complex with left bundle branch block configuration.

Recognition of the interactivity of the paced chambers is important. A paced p wave may be mistaken for failure to sense or pace, and malfunction may be diagnosed when it is not present (pseudomalfunction). In addition, if the programmed rate of the pacemaker approximates the patient's intrinsic heart rate, fusion of paced and native beats may occur and represents another common type of pseudomalfunction (Fig. 78-3).

Complications of Implantation

Infection

Pacemaker implantation is a surgical procedure and, like all surgery, carries a risk of infection, and the presence of a foreign body enhances this risk. The incidence of infection is small—approximately 2% for wound and subcutaneous pacemaker "pocket" infection and approximately 1% for bacteremia with sepsis. The presence of a foreign body complicates management, and few cases of bacteremia that develop after implantation can be managed with antibiotics alone. In most instances, reimplantation and replacement of the lead system are necessary.[15,16]

Pain and local inflammation at the site of the pacemaker are the first manifestations of a wound infection, cellulitis, or pocket infection. Approximately 20 to 25% of patients with a local infection have positive blood cultures. Bacteremia may occur in the absence of a focal infection and may arise with the typical manifestations of the systemic inflammatory

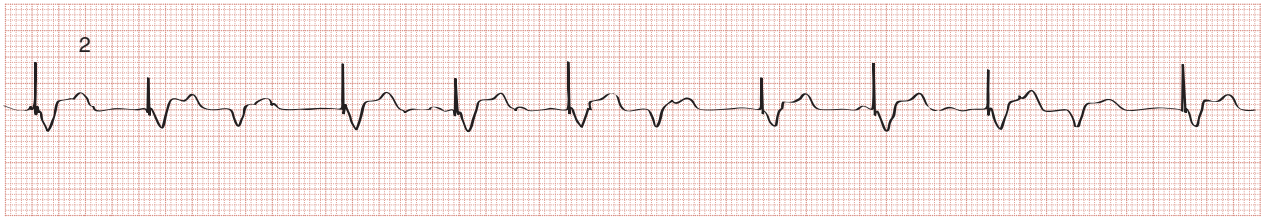


Figure 78-1. Normal VVI pacemaker (rhythm strip). This rhythm strip was recorded in a patient with a VVI pacemaker implanted for the treatment of symptomatic complete heart block. The pacing rate is approximately 75 beats/min (determined by measuring the time between consecutive pacemaker spikes). Each pacemaker spike is followed by a paced QRS complex. The third QRS from the left has a slightly different morphology than the paced QRS complexes. It is an intrinsic QRS complex that is sensed by the pacemaker, and a paced beat does not occur again until the programmed rate of the pacemaker is exceeded. The time interval between the spontaneous QRS and the next paced beat is approximately the same as the interval between consecutive pacemaker spikes. This sequence is subsequently repeated twice on this strip.

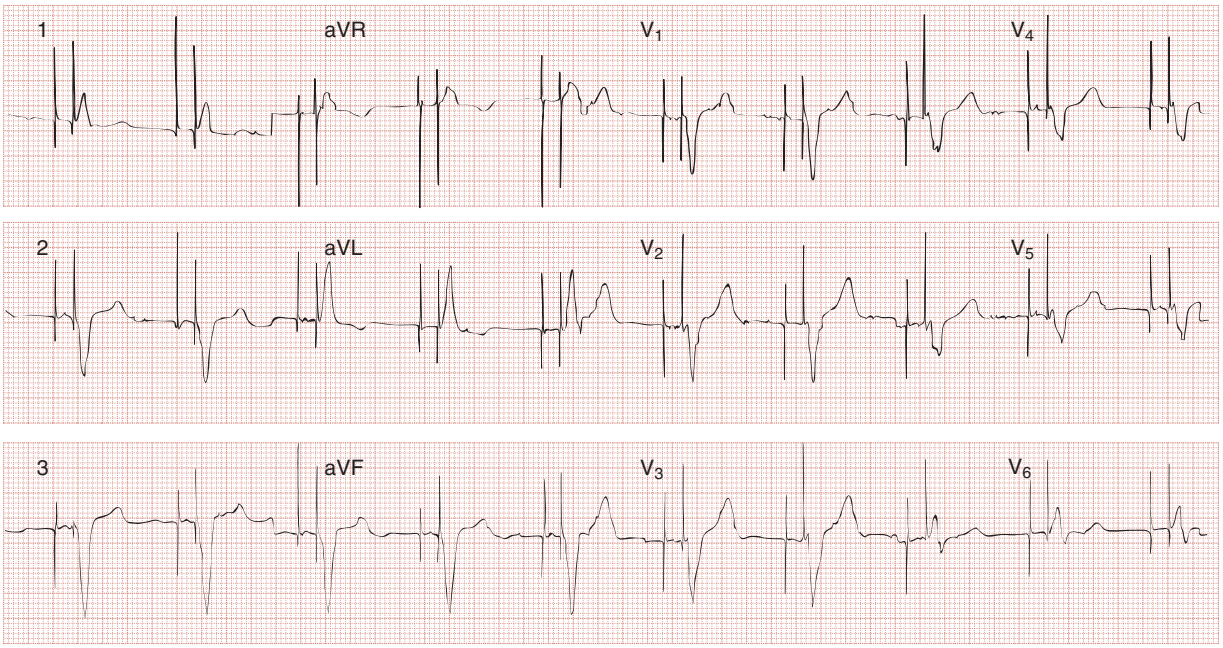


Figure 78-2. Normal DDD pacemaker (12-lead electrocardiogram). Each QRS complex is preceded by two pacemaker spikes. The first spike results in atrial depolarization, and the second produces a wide QRS complex. The QRS complex is conducted with a left bundle branch morphology, which is expected with endocardial pacing at the right ventricular apex.

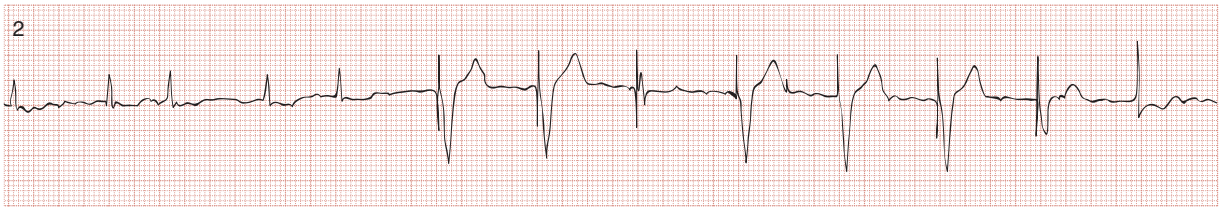


Figure 78-3. VVI pacemaker with fusion beats (pseudomalfunction). This VVI pacemaker was implanted in a patient with atrial fibrillation and intermittent symptomatic complete heart block. In the lead II rhythm strip, the first five QRS complexes are normal in morphology and irregular, as would be expected in atrial fibrillation. The next two QRS complexes are wide and preceded by a pacemaker spike. This represents normal sensing and pacing. The 8th QRS complex is narrow but preceded by a pacemaker spike. The spikes occur at a fixed and regular interval. In this instance, spontaneous ventricular depolarization had begun at approximately the time the pacemaker discharged. The 12th QRS complex in the sequence represents a fusion beat. Within the QRS complex of the 13th beat, a pacemaker spike is visible. Again, this represents nearly simultaneous conduction of a supraventricular beat and pacemaker electrical discharge. At first glance, this may appear to be failure to sense; however, the pacemaker is functioning normally and competing with the underlying rhythm.

response syndrome or sepsis. A hematoma of the pacemaker pocket may mimic a wound or pocket infection. Needle aspiration of the pocket should only be done under fluoroscopy because the needle may cut the insulation surrounding the pulse generator or the portion of the pacemaker lead that lies within the pacemaker pocket.

When a local infection or bacteremia is suspected, blood cultures should be obtained and intravenous antibiotic therapy initiated. *Staphylococcus aureus* and *S. epidermidis* are isolated in approximately 60 to 70% of cases. Empirical antibiotic therapy should include vancomycin pending culture and sensitivity data. If blood cultures are positive, the pulse generator and pacemaker lead are usually removed, temporary transvenous pacing is performed, and intravenous antibiotic therapy is continued for 4 to 6 weeks. The permanent pacemaker and lead are subsequently reimplanted.[17]

Thrombophlebitis

The incidence of venous obstruction associated with permanent transvenous pacemakers ranges from 30 to 50%, with approximately one third of patients having complete venous occlusion.[18] Thrombosis of varying degrees can involve the axillary, subclavian, and innominate veins or the superior vena cava (SVC). The site of insertion does not appear to affect the incidence of this complication. Chronic thrombosis of the veins of the upper arm is common and usually asymptomatic owing to extensive venous collateral circulation.

Because of extensive collateralization, only approximately 0.5 to 3.5% of patients develop symptoms usually indicative of acute thrombosis. These patients typically present with edema, pain, and venous engorgement of the arm ipsilateral to the site of lead insertion. Although rare, SVC syndrome resulting from pacemaker lead-induced thrombosis is reported. The symptoms and signs of lead-induced SVC syndrome are identical to those described in patients with SVC syndrome and malignancy. Whether pulmonary embolism is associated with pacemaker therapy and thrombosis is controversial.

Although symptoms might suggest thrombosis, definitive diagnosis of acute thrombosis usually requires duplex sonography of the jugular venous system, conventional venography, or contrast-enhanced computed tomography. The symptoms

typically respond to intravenous heparin therapy followed by long-term warfarin administration. Thrombolytic therapy is most effective if used early in management (within 7–10 days).

The "Pacemaker Syndrome"

After pacemaker implantation, a patient may present with new complaints or report a worsening of the symptoms that prompted evaluation and eventual pacemaker therapy. Such complaints often include syncope or near-syncope, orthostatic dizziness, fatigue, exercise intolerance, weakness, lethargy, chest fullness or pain, cough, uncomfortable pulsations in the neck or abdomen, right upper quadrant pain, and other nonspecific symptoms.

These symptoms are termed the pacemaker syndrome.[19] The etiology of this syndrome is the loss of AV synchrony and the presence of ventriculoatrial conduction, and it is most commonly encountered in the setting of VVI pacing. It is also described with the DDI mode. With VVI pacing, the ventricle is electrically stimulated and depolarized, resulting in ventricular systole. If sinus node function is intact, the atria can be depolarized by a sinus impulse and contract when the tricuspid and mitral valves are closed. This contractile asynchrony results in an increase in jugular and pulmonary venous pressures and may produce symptoms of congestive heart failure.

Atrial distention can result in reflex vasodepressor effects mediated by the central nervous system. Elevated levels of B-type natriuretic peptide and diuresis are considered markers for the syndrome in its more severe form. If the contribution of atrial contraction to late diastolic ventricular filling is important in maintaining an adequate cardiac output, basal and orthostatic hypotension may occur. DDI pacing in a patient with AV block may result in this syndrome if the sinus node discharge rate exceeds the programmed rate of the pacemaker.

Approximately 20% of patients report symptoms suggesting the pacemaker syndrome after pacemaker insertion. In most instances, symptoms are mild and patients adapt to them. In approximately one third of these patients, symptoms are severe. Treatment usually requires replacing a VVI pacemaker with a dual-chamber pacemaker or lowering the pacing rate of the VVI unit. If symptoms occur in a patient paced in the DDI mode, optimizing the timing of atrial and ventricular pacing is usually required. Patients appear to prefer dual-chamber pacing to the VVI modality.[20]

Although the pacemaker syndrome may be suspected in the emergency department in the patient with suggestive symptoms soon after pacemaker implantation, consultation with a cardiologist for interrogation of the pacemaker is recommended. The same symptoms may be observed in patients with true pacemaker malfunction, which may necessitate pacemaker reprogramming or replacement of the pulse generator or pacemaker lead.

Pacemaker Malfunction

The term *pacemaker malfunction* refers specifically to problems with the circuitry or power source of the pulse generator, the pacemaker lead (most commonly displacement or fracture), or the interface between the pacing electrode and the myocardium (pacing or sensing threshold). In addition, environmental factors such as extracardiac or extracorporeal electrical signals may interfere with normal pacemaker function.[21,22] Using the standard ECG, pacemaker malfunction can be separated into three broad categories: (1) failure to capture (no pacemaker spikes or spikes not followed by an atrial or ventricular complex), (2) inappropriate sensing (oversensing or undersensing spikes occur prematurely or do not occur even though the programmed interval is exceeded), or (3) inappropriate pacemaker rate. Symptomatic pacemaker malfunction after implantation occurs in less than 5% of patients and is rarely immediately life-threatening. Malfunction is most commonly due to inappropriate sensing, followed by failure to capture.[19] Typical presentations and etiologies of pacemaker malfunction are listed in Box 78-3.

BOX 78-3 CAUSES OF PACEMAKER MALFUNCTION

- Failure to capture
  - Lead disconnection, break, or displacement
  - Exit block
  - Battery depletion
- Undersensing
  - Lead displacement
  - Inadequate endocardial lead contact
  - Low-voltage intracardiac p waves and QRS complexes
  - Lead fracture
- Oversensing
  - Sensing extracardiac signals: myopotentials
  - T wave sensing
- Inappropriate rate
  - Battery depletion
  - Ventriculoatrial conduction with pacemaker-mediated tachycardia
  - 1:1 response to atrial dysrhythmias

When the emergency physician suspects pacemaker malfunction, knowledge of the pacing modalities (see Table 78-1) and what is normal for a given pacing modality are critical when reviewing the ECG. Fortunately, patients are provided with important identifying information, usually in the form of a wallet card, after pacemaker implantation. The most important information for the emergency physician is provided in the five-letter code. If this information is not available, a standard posteroanterior and a lateral chest radiograph can provide critical information. A single lead in the apex of the right ventricle indicates a VVI pacemaker. With VVI pacing, only one stimulus artifact or spike is seen with each stimulated ventricular depolarization (see Fig. 78-1). If sinus node activity is present, the paced QRS complex is dissociated from the intrinsic p waves. If separate leads are identified in the right atrium and right ventricle, the pacing modality is most often DDD or DVI, and paced p waves and QRS complexes (two spikes for each QRS complex) are seen (see Fig. 78-2). Although DDD and DVI units are capable of pacing both the right atrium and the right ventricle, only one spike may be seen (Fig. 78-4). Failure to identify two spikes with a DDD or DVI unit can represent normal pacemaker function.

A magnet placed externally over the pulse generator is frequently used in the assessment of pacemaker function. Magnet application causes closure of a reed switch within the pacemaker circuitry, converting the pacemaker to an asynchronous or fixed-rate pacing mode, and the pacemaker is no longer inhibited by the patient's intrinsic electrical activity. The technique is most commonly used when the patient's intrinsic heart rate exceeds the pacemaker's set rate and pacemaker function is inhibited. Magnet application then allows pacing to occur, despite the patient's native cardiac activity, and pacing rate and the presence of capture can be determined. Magnets are made by each manufacturer, but any cardiac pacemaker magnet will typically activate the reed switch within any of the devices.

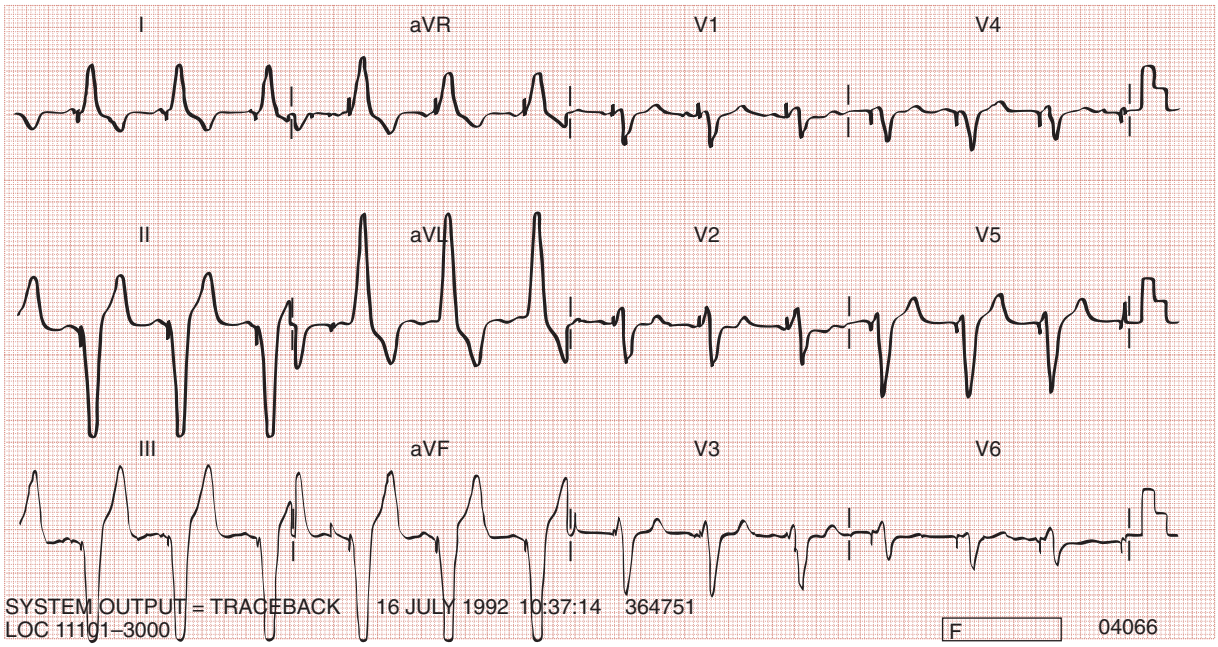


Figure 78-4. Normal DDD pacemaker (half-standard 12-lead electrocardiogram [ECG]). Three paced QRS complexes preceded by a stimulus artifact or spike are evident in leads I, II, and III. Paced QRS complexes occur after spontaneous or intrinsic p waves are sensed and atrioventricular (AV) conduction delay exceeds the pacemaker's programmed AV interval. The first QRS complex in the augmented leads, best seen in lead aVF, demonstrates both a paced p wave and a paced QRS complex. Although the pacemaker is a dual-chamber device, two spikes may not always be seen preceding every QRS complex and the presence of only one spike, or no spikes, should not be interpreted as evidence of pacemaker malfunction. Also evident on this ECG are the different amplitudes of the pacemaker spikes from lead to lead. When a single-lead rhythm strip is recorded, the selected lead should be the one in which the pacemaker spikes are most easily identified.

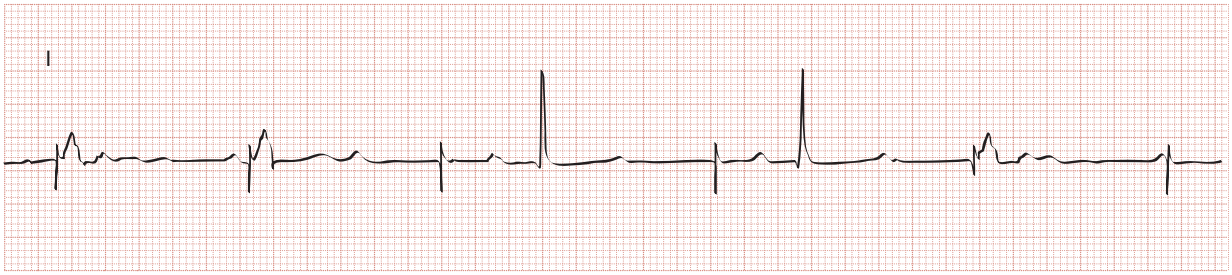


Figure 78-5. Intermittent failure to capture and slow pacing rate (lead I). This lead I rhythm strip demonstrates intermittent failure to capture of a VVI pacemaker. The first and second pacemaker spikes are followed by wide-paced QRS complexes; the third and fourth spikes are not. The pacemaker spikes occur at a rate of approximately 50/min. The device was programmed to pace at a rate of 75/min. This is a typical example of "end-of-life" pacing characteristics of a depleted battery.

Failure to Capture

Failure to capture may range from the complete absence of pacemaker spikes to spikes not followed by a stimulus-induced complex (Fig. 78-5). A complete absence of pacemaker spikes may result from battery depletion, fracture of the pacemaker lead, or disconnection of the lead from the pulse generator unit.

Current lithium-iodine batteries are not subject to sudden power failure, and they display typical end-of-life functional changes over a period of months to a year before complete depletion.[1] Usually, the first sign of voltage depletion is a decrease in the programmed pacing rate. This change is gradual and should be detected during the regular follow-up evaluations that pacemaker patients receive. When voltage output falls to a critical level, stimulus strength falls below the required threshold and failure to capture or intermittent failure to capture may be observed late in battery life. As a result, urgent or emergent battery replacement is rare.

Failure to capture, which may be complete or intermittent, is most commonly a lead problem. Lead displacement is the most common cause and is most likely to occur within the first month of pacemaker insertion. The chest radiograph may demonstrate the tip of the pacing catheter displaced from the right ventricular apex. The catheter tip is commonly found in the pulmonary outflow tract, where it may have intermittent contact with endocardium, resulting in intermittent failure to pace and sense. The atrial leads of dual-chamber devices are commonly displaced into the body of the right atrium, resulting in loss of contact between the pacing lead and the atrial endocardium.

Lead fracture, which is uncommon with the current polyurethane lead coating,[1] produces an insulation break, resulting in failure to capture as a result of current leakage. It can be detected as a change in pacing threshold. Lead fractures occur at predictable locations, usually at the site of attachment to the pulse generator or at abrupt angulations that serve as stress points. Inadequate contact of the lead with the pulse generator

can mimic a lead fracture. Occasionally, when a lead fracture is complete or nearly complete, a break in the catheter or its insulation can be detected on an overpenetrated posteroanterior chest radiograph. Loss of lead–pulse generator contact can be detected on the chest radiograph with close inspection of the pulse generator.

Exit block (the failure of an adequate stimulus to depolarize the paced chamber) can also result in failure to pace. Exit block should be considered when the preprogrammed pacing stimulus output fails to result in capture in the presence of a normally functioning pulse generator and an intact lead system. This problem is most commonly due to changes in the endocardium in contact with the pacing system. Etiologies include ischemia or infarction of the endocardium in contact with the electrodes; systemic hyperkalemia; and the use of class III antiarrhythmic drugs, such as amiodarone, which affect ventricular depolarization. Although other drugs are reported to alter pacemaker threshold, the effect is small and is rarely clinically important.[21] At the time of pacemaker insertion, stimulus strength, defined as the amplitude and duration of the electrical output, is always set substantially above the minimum required to result in an artificial electrical depolarization.

Inappropriate Sensing

For a pacemaker to function in a noncompetitive mode, it must be capable of sensing the intrinsic or "native" electrical activity of the heart. The electrical activity that is sensed is determined by the pacing modality (see Table 78-1). Sensing parameters are determined at the time of pacemaker insertion on the basis of the signal size of the intracardiac ECG and can be changed or fine-tuned externally at a later time if needed.

Undersensing

Failure to sense may be complete or intermittent. It may result from a change in the sensing parameters selected at the time of insertion. This is most commonly encountered after acute right ventricular infarction or during the progressive fibrosis that accompanies many cardiomyopathies, causing intracardiac signals to decrease in amplitude. Lead displacement, fracture, and poor contact with the endocardium may also cause undersensing.

Undersensing is typically recognized electrocardiographically as the appearance of pacemaker spikes occurring earlier than the programmed rate. The spike may or may not be followed by a paced complex, depending on when it occurs during the cardiac refractory period (Fig. 78-6). Failure of a stimulus spike to produce a complex when it occurs during the atrial or ventricular refractory period should not be interpreted as failure to pace.

Oversensing

In rare instances, the pacemaker may detect electrical activity that is not of cardiac origin. The result may be intermittent, irregular pacing or an apparent complete absence of pacemaker function. Myopotentials produced by the pectoralis muscle (Fig. 78-7) and extracorporeal electrical signals are frequently oversensed when a unipolar lead system is used. T waves following an intrinsic ventricular depolarization are the most common oversensed cardiac signals. Common medical sources of electrical interference include electrocautery, which can cause temporary pacemaker inhibition, and magnetic resonance imaging, which can alter pacemaker circuitry and result in fixed-rate or asynchronous pacing. Electromagnetic interference resulting from close proximity to a microwave oven should not cause pacemaker problems with currently implanted pacemaker units. Interference can be caused by the use of a digital cellular phone.[21,22] These devices may cause pacemaker inhibition, inappropriate ventricular tracking, or asynchronous pacing. Malfunction is most commonly seen when the phone is within 10 cm of the pulse generator and often occurs when the phone is applied to the ear ipsilateral to the site of the pacemaker pocket.

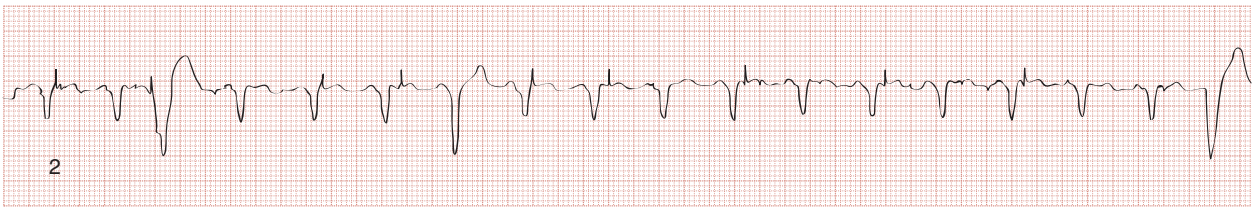


Figure 78-6. Failure to sense or undersensing (lead II). Pacemaker spikes are evident during inscription of the ST segment on this rhythm strip. These spikes do not produce QRS complexes because they occur during the ventricular refractory period of the preceding spontaneous QRS complex. The third QRS complex on the strip is a paced QRS complex. The device is capable of capture but is undersensing the spontaneous rhythm.

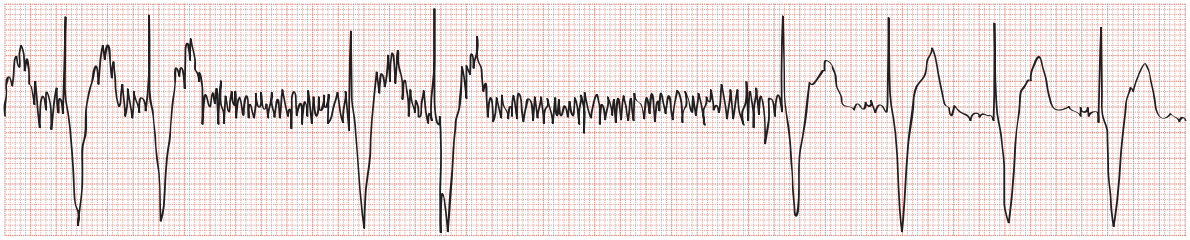


Figure 78-7. Oversensing (lead II). This VVI unipolar lead pacemaker is oversensing myopotentials produced by contraction of the pectoralis major. Myopotentials result in the undulating and irregular baseline seen in the middle of the strip. After muscular contraction ceases, normal pacing resumes (last four complexes on the strip).

Inappropriate Pacemaker Rate

A pacing rate below the programmed rate is a typical finding in pulse generator depletion and does not occur abruptly with lithium-iodine batteries. An extreme increase in pacing rate, the so-called runaway pacemaker, is rarely, if ever, encountered with current pacemaker technology and circuitry in which upper rate limits are set (typically <140/min). An "endless loop" tachycardia may develop during dual-chamber pacing when ventriculoatrial conduction occurs and the resulting retrograde atrial depolarization results in a stimulated or paced ventricular depolarization.[23] If atrial flutter develops during dual-chamber pacing, flutter waves may be sensed and tracked, resulting in a rapid, paced ventricular rate. In both instances, the ventricular rate does not exceed its set upper limit. Patients with such rhythms may complain only of palpitations or symptoms of hemodynamic compromise. When such rhythms are detected, magnet application usually converts the pacemaker to a fixed rate in a competitive mode and terminates the tachyarrhythmia.

Management

History

The patient should be asked for the pacemaker identification card. The information on the card explains why a pacemaker was placed and the pacing modality used.

Most patients with pacemaker malfunction present with symptoms reminiscent of those that prompted pacemaker therapy: syncope, near-syncope, orthostatic dizziness, lightheadedness, dyspnea, or palpitations.

The majority of pacemaker complications and most instances of pacemaker malfunction occur within the first few weeks or months of pacemaker implantation. After wound healing, palpation of the pulse generator site should not elicit tenderness. A wound infection or pocket infection typically arises with localized pain. Bacteremia secondary to infection of the pacing catheter, however, may arise only with fever and without other manifestations of the systemic inflammatory response syndrome. Pain in the arm ipsilateral to the site of insertion should suggest acute thrombophlebitis.

Patients who develop the pacemaker syndrome secondary to the loss of AV synchrony may present with nonspecific complaints of easy fatigability, generalized weakness, dyspnea, or an uncomfortable fluttering or "pounding" sensation in the neck or abdomen. Syncope or near-syncope may also occur, but these complaints should prompt an evaluation for true pacemaker malfunction. The pacemaker syndrome should be a diagnosis of exclusion.

Physical Examination

A pacemaker infection should be suspected in the presence of fever, even if another potential source of infection can be identified. Extremely low (<60) beats per minute or high pulse rates (>100 beats per minute in the resting patient) are suggestive of altered pacing parameters (battery depletion or pacemaker-mediated tachycardias). Hypotension may be present in either instance. Cannon "a" waves on inspection of the jugular venous pulse wave indicate AV asynchrony. Auscultation of lungs may reveal bibasilar rales if congestive heart failure is present.

During pacing, the first heart sound may vary in intensity as a result of AV dissociation (VVI mode), and the second heart sound may be paradoxically split when ventricular pacing occurs (the right ventricle is activated first). A pericardial friction rub may also be heard if the tip of the pacing catheter has perforated the wall of the right ventricle. Perforation, however, usually occurs at the time of pacemaker implantation and is usually recognized at that time. Although the pacing catheter traverses the tricuspid valve, tricuspid regurgitation is rarely heard unless there is myocardial disease such as right ventricular dilation that is common in the cardiomyopathies. Pedal edema may be present and is important if it is a new symptom or if chronic edema has recently worsened.

Chest Radiograph

A chest radiograph should be obtained to define pacing catheter tip position and to determine the number of pacing leads, unless this information is available from another source. A ventricular pacing catheter tip in the right ventricular outflow tract or an atrial catheter tip in the SVC or right ventricle is always abnormal. The pulse generator site should also be examined on the radiograph. Occasionally, disconnection of the lead from the pulse generator may be observed. In some cases, this is due to the patient's manipulation of the pulse generator ("twiddler's syndrome").[24]

12-Lead Electrocardiogram

A standard ECG and a long rhythm strip should be obtained in all patients. With bipolar pacing systems, the stimulus artifact may be extremely small and difficult to recognize in some leads (see Fig. 78-4). Inspection of the rhythm strip may reveal failure to sense or pace, a low pacing rate, or an abnormally rapid rhythm, suggesting a pacemaker-mediated tachycardia.

Disposition of the Emergency Department Patient with a Pacemaker

As a result of the current design of modern pacemakers and the frequent follow-up evaluation of patients with pacemakers, life-threatening emergencies resulting from pacemaker malfunction requiring immediate emergency department intervention are rare. Most instances of malfunction are subtle and difficult to recognize without interrogation of the pacemaker using manufacturer-specific devices by someone skilled in the technique. In all instances of suspected pacemaker malfunction, the patient's cardiologist should be consulted.

Advanced Cardiac Life Support Interventions

Electrical defibrillation at recommended shock strengths (200, 300, and 360 J) can be safely performed in the patient with a pacemaker.[19] If the sternal paddle is placed adjacent to the sternum, it is at a safe distance (≥10 cm) from the pulse generator. Alternatively, defibrillation electrodes can be placed in an anteroposterior configuration. A cardiologist should ensure that the pacing parameters of the unit have not been altered if the resuscitation is successful. A chest radiograph should also be obtained after resuscitation to ensure that the pacing catheter was not displaced during chest compression, although this is an extremely uncommon occurrence.

Immediate return of pacing (capture) may not occur after defibrillation; this is commonly the result of global myocardial ischemia and increased pacing threshold and is not an indication of pacemaker malfunction. Temporary transcutaneous pacing may be needed if the pacemaker cannot be reprogrammed. Transcutaneous pacing can also be safely used because the anterior and posterior pacing electrodes, if properly positioned, are distant from the pulse generator. Attempt-

ing temporary transvenous pacing is usually not necessary and is unlikely to be successful, especially if undertaken without fluoroscopic guidance. Chronic venous thrombosis, which is common and most often asymptomatic after pacemaker insertion, may preclude temporary catheter insertion through the neck veins. Insertion through the femoral vein is also difficult because the permanently implanted catheter may prevent entry into the right ventricle. Blind insertion may also dislodge the permanent catheter.

IMPLANTABLE CARDIOVERTER-DEFIBRILLATORS

The ICD was first used clinically in 1980. Technical refinements in this modality for treating ventricular dysrhythmias have progressed even more rapidly than refinements in the less complex standard pacemaker. A surge in the use of ICDs reflects improved survival with ICDs versus antiarrhythmic therapy in patients at risk for sudden death resulting from ventricular dysrhythmias. Generally accepted indications for ICD implantation are noted in Box 78-2. Many patients still require drug therapy after ICD implantation to suppress ventricular dysrhythmias, minimize the frequency of ICD shocks, improve patients' tolerance, and decrease energy use, which prolongs ICD life.

Terminology and Components

The majority of ICDs are now placed percutaneously in a manner similar to that of the standard pacemaker. A transvenous electrode system has largely replaced epicardial lead placement, which required thoracotomy. An epicardial defibrillation lead may occasionally be placed during coronary artery bypass surgery or in a few patients who cannot be defibrillated using existing transvenous electrode systems.

The typical modern ICD consists of components similar to those in the standard permanent pacemaker—namely, a power source, electronic circuitry, and lead system. In addition, the standard ICD has a high-voltage capacitor and complex microprocessor memory.[25] The power source is lithium chemistry based with a battery life of 5 to 10 years. The longevity is largely determined by the frequency of shocks. All ICDs are also ventricular pacemakers, providing pacing for bradyarrhythmias.

The right ventricular lead is used for sensing and pacing, and shocks are typically delivered between a coil in the right ventricular lead and the pulse generator. If dual-chamber pacing is required, a second lead is placed in contact with the endocardium of the right atrium. A biphasic waveform is currently the preferred waveform for internal defibrillation. The shape and characteristics of the shock waveform vary among manufacturers. The biphasic waveform is more effective at lower energies than earlier monophasic waveforms and allows a smaller capacitor to be used, thereby reducing the size and increasing the comfort of the ICD unit.

The diagnostic and treatment functions of the ICD are determined at the time of implantation. In most instances, the cardioversion and defibrillation thresholds are determined at the time of ICD insertion by inducing ventricular tachycardia (VT) and fibrillation and adjusting the shock strength at a level above the minimum required to terminate the induced rhythm. Optimally, the required shock strength for defibrillation is less than half the maximum output (approximately 30 J) of the device. VT is typically managed using either low-energy shocks or programmed pacing that interrupts the VT reentrant circuit. Programmed pacing is less likely to have proarrhythmic effects and requires less energy, thereby extending battery life. In the setting of ventricular fibrillation (VF), ICDs are capable of delivering up to five additional discharges if the first shock fails.

The patient with an ICD should have close follow-up monitoring by a cardiologist familiar with ICD programming. This allows the cardiologist to determine the frequency of ICD activation (programmed antitachycardia pacing or shocks) and to confirm the programmed functions of the device. The majority of patients with ICDs have underlying heart disease, most commonly extensive atherosclerotic coronary artery disease, that is complicated by a low ejection fraction and congestive heart failure. The patient's medications and metabolic status, such as electrolyte disorders that accompany diuretic usage, may also affect ICD function.

Complications of Implantation

Complications of ICD implantation are nearly identical in type and frequency to those of permanent pacemaker implantation. They include infection of the wound, the subcutaneous pouch fashioned for the device, and the lead system as well as acute thrombophlebitis and chronic thrombosis of the veins traversed for lead insertion. Management of these complications is similar to that for patients with permanent pacemakers.

Malfunction

Patients with ICD malfunction usually present to the emergency department with a limited number of specific symptoms (Box 78-4).

In contrast to patients with a permanent pacemaker, ICD patients are aware of when the ICD discharges to terminate VT or VF. The most common complaint of ICD patients is the occurrence of frequent shocks (i.e., occurring at a rate greater than they are accustomed to).[26] Increasing shock rate may be appropriate and not indicative of ICD malfunction if the patient is experiencing an increase in the frequency of VT or VF episodes. An increase in the frequency of episodes may occur in the setting of hypokalemia, hypomagnesemia, ischemia (with or without infarction) related to underlying coronary artery disease, or the proarrhythmic effect of drugs

BOX 78-4 CAUSES OF IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR MALFUNCTION

Increase or abrupt change in shock frequency
- Increased frequency of VF or VT (consider ischemia, electrolyte disorder, or drug effect)
- Displacement or break in ventricular lead
- Recurrent nonsustained VT
- Sensing and shock of supraventricular tachyarrhythmias
- Oversensing of T waves
- Sensing noncardiac signals

Syncope, near-syncope, dizziness
- Recurrent VT with low shock strength (lead problem, change in defibrillation threshold)
- Hemodynamically significant supraventricular tachyarrhythmias
- Inadequate backup pacing for bradyarrhythmias (spontaneous or drug induced)

Cardiac arrest
- Assume malfunction, but probably due to VF that failed to respond to programmed shock parameters

VF, ventricular fibrillation; VT, ventricular tachycardia.

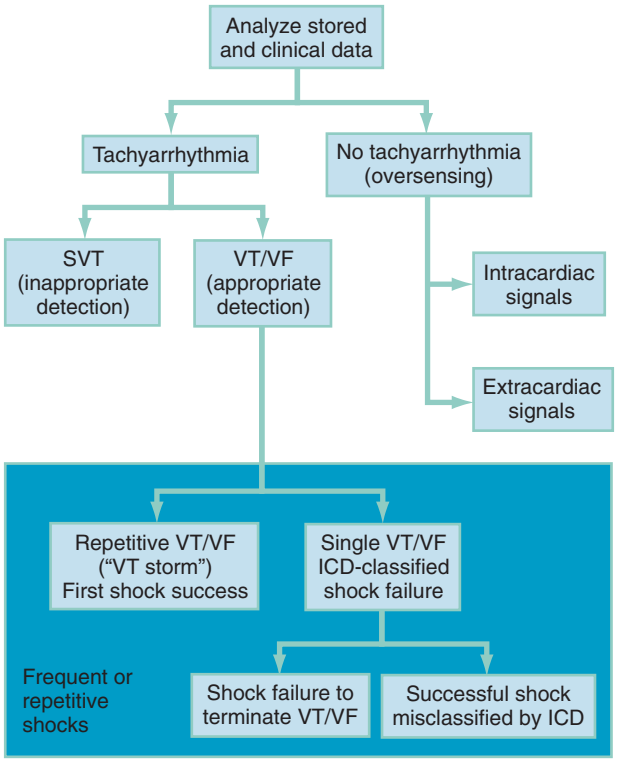


Figure 78-8. Approach to the patient with shocks. **Top,** Flow diagram for one or infrequent shocks. **Bottom,** Diagram for multiple or repetitive shocks. ICD, implantable cardioverter-defibrillator; SVT, supraventricular tachycardia; VT/VF, ventricular tachycardia/ventricular fibrillation. (Redrawn from Swerdlow CD, Zhang J: Implantable cardioverter defibrillator shocks: A troubleshooting guide. Rev Cardiovasc Med 2:61, 2001.)

administered to decrease the frequency of ventricular tachyarrhythmias. Many ICD patients, particularly those to whom the technology is new, present complaining that their device discharged, but subsequent device interrogation reveals that no discharge occurred.

An increase in the shock frequency is a manifestation of ICD sensing malfunction if (1) a supraventricular tachyarrhythmia is inappropriately sensed as VT, (2) shocks are delivered for nonsustained VT, or (3) intracardiac T waves detected by the ICD system are sensed as QRS complexes and the ICD interprets this as an increased heart rate. Temporary ICD deactivation with magnet application may be necessary if oversensing is the problem. Syncope, near-syncope, dizziness, or lightheadedness in the patient with an ICD may indicate undersensing of sustained VT or inappropriately low shock strength to terminate the rhythm. An approach to the evaluation of ICD malfunction is shown in Figure 78-8.

Advanced Cardiac Life Support Interventions

An ICD does not prevent sudden death in all patients at risk, and a patient with an ICD may present in cardiac arrest (2% annual incidence in implanted patients). Cardiac arrest is not necessarily an indication of ICD malfunction. Appropriate repeated shocks may have been delivered but were ineffectual. Alternatively, the ICD may not have sensed VF or the ventricular ectopic activity that typically precedes VF. Resuscitation efforts in the patient with an ICD should be undertaken in accordance with current recommendations. Transthoracic defibrillation can be performed in the standard manner with a monophasic or biphasic defibrillator if VF is the arrest rhythm. The sternal electrode or paddle should be placed in a parasternal location approximately 10 cm from the ICD subcutaneous pouch if the device has been implanted in the right deltopectoral area. If it has been implanted in the left deltopectoral region, this recommended safety distance is usually exceeded.

If the ICD discharges during manual chest compressions, the rescuer may feel a weak shock. There have been no reports of injury to rescuers from such discharges during resuscitation efforts. The device can be deactivated with magnetic application during resuscitation efforts. Deactivation is probably more important in the immediate postresuscitation period because recurrent ventricular dysrhythmias are common at this time following prolonged global myocardial ischemia during the arrest period, reperfusion, and the hyperadrenergic state worsened by the use of intravenous epinephrine during resuscitation. ICD malfunction should be assumed and these postresuscitation rhythms treated with standard pharmacologic agents (lidocaine and amiodarone). Although class 1 antidysrhythmic agents may raise the defibrillation threshold of the ICD, their impact on the defibrillation threshold during transthoracic countershock is clinically inconsequential due to the high shock strengths that are used.

Disposition of the Emergency Department Patient with an Implantable Cardioverter-Defibrillator

As a result of the difficulty in documenting or excluding ICD function or malfunction in the patient with transient symptoms, the device should be interrogated by the patient's cardiologist to guide further evaluation and therapy. In cases in which the patient reports a single ICD shock, an assessment for acute cardiac ischemia, worsening of chronic congestive heart failure, symptoms of new-onset heart failure, and electrolyte abnormalities should be performed. In the absence of a change in clinical status, such patients can be discharged in consultation with the managing or consulting cardiologist after assuring timely follow-up. For patients reporting multiple shocks, immediate consultation is required along with admission to a monitored setting for extended telemetric observation. If frequent ventricular ectopy is noted, intravenous amiodarone should be given.[26] ICD interrogation allows assessment of ICD function and preceding dysrhythmia episodes. Reprogramming may be necessary. If a lead problem is detected, reimplantation is required. A magnet can be placed over the ICD to inactivate the defibrillator. This should be done only if the emergency physician is confident that the ICD is delivering inappropriate shocks, such as a supraventricular tachycardia.

Biventricular Pacing

Biventricular pacing, also known as cardiac resynchronization therapy, is a new therapy for patients with left-sided heart failure and ventricular dyssynchrony. It is beneficial for patients with NYHA class 3 or 4 heart failure despite optimal medical therapy, a left ventricular ejection fraction of 35% or less, and sinus rhythm with QRS duration of 120 msec or greater.[27] Left bundle branch block causes an altered sequence of depolarization of the left ventricle such that the interventricular septum contracts before the left ventricular free wall, leading to inefficient mechanical pumping. Biventricular pacing "resynchronizes" the ventricles by simultaneously pacing the left and right ventricles, eliminating the delay in left ventricular free wall contraction, and improving systolic function.

The complications and malfunctions inherent with conventional cardiac pacing are also observed with biventricular pacing. In addition, biventricular pacing has unique complications related to placement of the left ventricular pacing lead through the coronary sinus. In large clinical trials, coronary sinus dissection occurred in 0.3 to 4.0% of patients and coronary vein or coronary sinus perforation in 0.8 to 2.0% of patients. Cardiac tamponade due to perforation of the coronary venous system is seen in less than 1% of patients. Dislodgement of the left ventricular electrode with resultant loss of pacing occurs as an early complication in approximately 10% of patients. Patients with malfunction of a biventricular pacing system frequently present with complaints of palpations or acute decompensation of chronic heart failure.

Left Ventricular Assist Devices

Mechanical ventricular assistance devices have been used as a "bridge" to transplantation since the 1960s.[28] These implanted devices replace or support the pump function of the left ventricle and were originally bulky and mechanically complex due to the pulsatile nature of the pump mechanisms. This usually resulted in extended in-hospital care while the patient awaited cardiac transplantation. Newer devices, such as the Jarvik 2000 and HeartMate II, are continuous flow pumps that are portable and powered with a comparatively smaller battery pack. Implantation is associated with fewer infectious complications and lower immediate postoperative mortality, and survival for more than 1 year is increasingly common. The greatest mortality is noted within the first 30 days after implantation and during hospitalization. Left ventricular assistance devices (LVADs) are commonly used as "destination" therapy in patients who do not qualify for cardiac transplantation.[29]

Patients with an LVAD typically require care at cardiac transplant centers. As technology progresses, emergency physicians not based at a transplant center may encounter a patient with an LVAD. The more common complications with this device include infection and embolic stroke. Device failure usually results in severe congestive heart failure. If necessary, dopamine, dobutamine, or a combination of these drugs may be given to treat congestive heart failure symptoms while the patient awaits transfer. LVAD patients in cardiac arrest should be provided standard advanced cardiac life support.

KEY CONCEPTS

- Pacemaker malfunction soon after implantation (within 6–8 weeks) is usually due to a lead problem, such as a lead displacement, or to pacemaker programming failure, such as a pacing rate too slow for the patient's needs.
- Pacemaker malfunction arises in a limited number of ways: failure to pace, oversensing, undersensing, and pacing at an inappropriate rate (too fast or too slow).
- With lithium-iodine batteries, abrupt failure is an unlikely cause of pacemaker malfunction.
- If a patient with a pacemaker presents with a fever of unclear etiology, pacemaker lead infection and endocarditis should be considered.
- Because paced ventricular complexes are conducted with a left bundle branch block pattern, a paced rhythm obscures the electrocardiographic diagnosis of acute myocardial infarction.
- Magnet application does not turn off a pacemaker. It does convert an inhibited or noncompetitive pacemaker to one that is not inhibited. Fixed-rate pacing and competition with the pacing underlying rhythm occur.
- Defibrillation is safe in patients with a pacemaker or ICD if paddles are placed at least 10 cm from the subcutaneous implant site of the device. Alternatively, anteroposterior defibrillation with adhesive defibrillation electrodes can be performed. There are no reports of injury to rescuers from ICD discharges during manual chest compressions.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 79 Heart Failure

John F. O'Brien and Jay L. Falk

Heart failure (HF) is a debilitating cardiac condition characterized by poor exercise tolerance and chronic fatigue along with high morbidity and mortality. *Heart failure* may be defined as the pathophysiologic state in which the heart is incapable of pumping a sufficient supply of blood to meet the metabolic requirements of the body or requires elevated ventricular filling pressures to accomplish this goal. The caveat that filling pressures must be normal acknowledges that a failing heart may continue to maintain systemic perfusion by using the compensatory Frank-Starling mechanism of preload reserve, resulting in the maintenance of normal stroke volume despite reduced ejection fraction. Conversely, low filling pressure with hypoperfusion indicates a pump-priming problem distinct from cardiac disease.

A complex neurohormonal regulatory relationship exists between the heart and multiple organ systems. Feedback loops mediated through a variety of vasoactive substances secreted by the kidneys, autonomic nervous system, adrenals, lungs, and vascular endothelium are most important. Perturbations of function in any of these organs affect the others (Fig. 79-1). Accordingly, the cardiovascular system must be viewed as a dynamic one, continually adapting to optimize organ perfusion. Dysfunction of the heart or any component of the system results in hormonal and other compensatory responses, some of which are not precisely titrated and may themselves be maladaptive over time.

HF is a progressive disease that begins long before symptoms and signs are evident. It is initially characterized by adaptive neurohormonal activation of the renin-angiotensin-aldosterone system, sympathetic nervous system, natriuretic peptides, endothelin, vasopressin, and other regulatory mechanisms. Various resultant inflammatory mediators are important in the pathogenesis of chronic HF by contributing to peripheral vascular disturbances and cardiac remodeling.[1,2] Neurohormonal activation initially compensates for circulatory system dysfunction, but these mechanisms eventually lead to increased mechanical stress on the failing heart, causing maladaptive electrical and structural events, further impairment of systolic and diastolic function, and progressive cardiac fibrosis and apoptosis.[3] In many circumstances, HF occurs as a consequence of pathologic conditions involving the renal, peripheral vascular, or pulmonary system. The degree of myocardial dysfunction depends on both the amount of primary myocardial disease and the functional status of these other organ systems. Increasing knowledge of these neurohormonal interactions is leading progressive improvement in the management of HF, with a shift from a hemodynamic to a neurohormonal model.

EPIDEMIOLOGY

HF represents the only significant cardiovascular disease that is increasing in prevalence in our society and is a common cause of poor life quality and premature death. Nearly 5 million people in the United States have been diagnosed with HF, and almost 550,000 new cases are diagnosed annually.[4-6] The incidence approaches 10 per 1000 in people older than 65 years. Decompensated HF is the most common reason for hospital admission in this age group[7] and also the most common reason for readmission within 60 days of discharge.[8] This prevalence results in an annual estimated health care cost of $20 billion to $50 billion. The aging population, coupled with improvements in the medical therapy of HF, will result in an increased prevalence of this disease.

HF carries a 50% mortality at 5 years after symptom onset.[9] One third of the patients with the most severe disease die within the first year after diagnosis.[10] Females have a survival advantage over males.[11-13] Progressive hemodynamic deterioration accounts for approximately 50% of deaths, but sudden death resulting from malignant ventricular dysrhythmias occurs in up to half of the patients.[14] Medical therapy has not significantly decreased sudden dysrhythmic deaths but has improved overall outcome from pump failure. Multiple medical therapies including beta-blockers decrease the death rate by improving functional status and slowing progression of pump dysfunction.[8]

The prognosis in HF is related to a number of factors, including age, left ventricular ejection fraction,[15,16] exercise tolerance, plasma norepinephrine and B-type natriuretic peptide (BNP) levels, cardiothoracic ratio on chest radiograph,[17] electrocardiogram (ECG) evidence of left ventricular hypertrophy[18] or atrial fibrillation,[19] renal function, and the presence of ventricular dysrhythmias. One third to one half of patients with HF have some degree of renal insufficiency,[20] which is one of the strongest predictors of mortality in patients with HF.[21-24] The American Heart Association (AHA) and American College of Cardiology (ACC) guidelines define HF related to systolic dysfunction as a left ventricular ejection fraction less than 40%. Diastolic dysfunction, a pathologic condition involving failure of diastolic ventricular relaxation with consequent high filling pressures, may exist in up to half of older populations with HF.

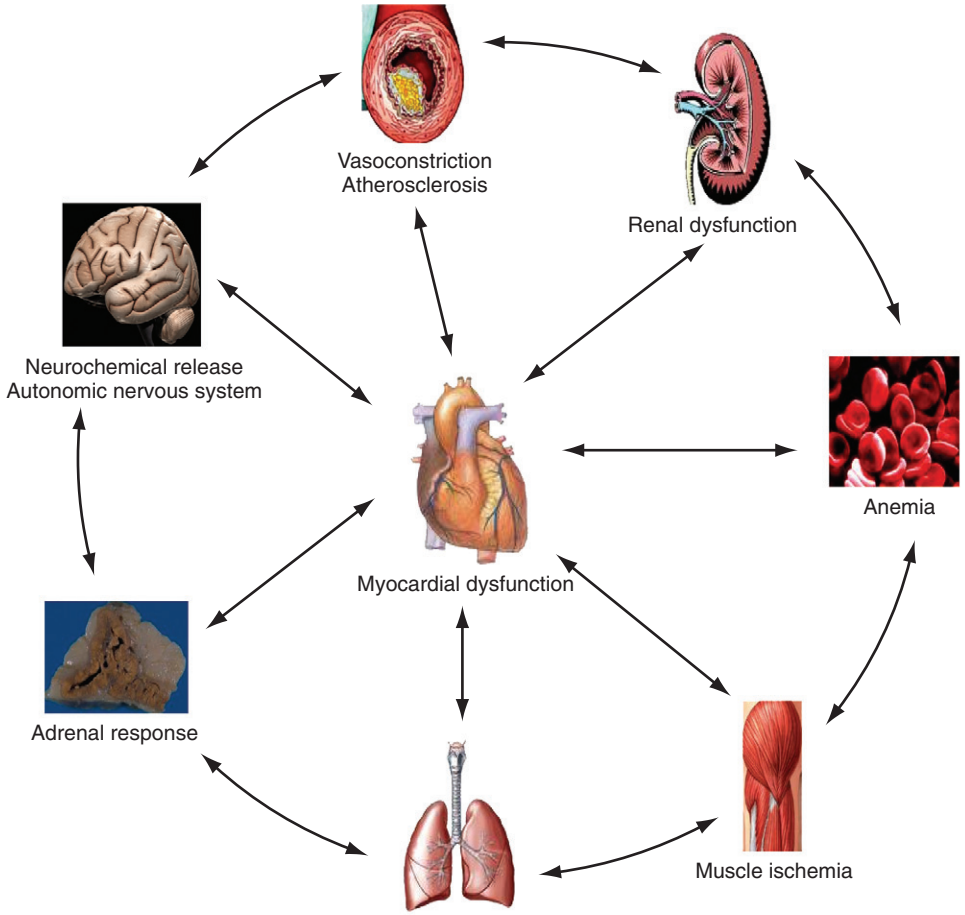


Figure 79-1. The neurohormonal model of HF describes a complex interdependence among many organ systems of the body in which functional disturbances in any one cause complex compensatory changes in the others that are eventually maladaptive. Correction of organ system dysfunction by medications and other interventions may result in the correction of these perturbations.

CELLULAR MECHANISMS

The heart is composed of a mass of individual striated muscle cells (myocytes) that form a branching syncytium. Each myocyte contains a central nucleus, mitochondria, an intracellular tubular system termed the *sarcoplasmic reticulum*, and numerous cross-banded strands termed *myofibrils* that traverse the length of the myocyte. The myofibrils, in turn, contain multiple subunits called sarcomeres. They form the basic functional unit of myocardial contraction and are arranged in series. Sarcomeres occupy approximately 50% of the mass of myocardial cells and are composed of the contractile proteins actin and myosin along with the regulatory proteins troponin and tropomyosin. These proteins are surrounded by invaginations of the myocardial cell membrane (sarcolemma) and the sarcoplasmic reticulum.

The sarcomere ranges in length from 1.6 to 2.2 μm, depending in part on the tension exerted on the muscle before contraction (preload). Sarcomere contraction occurs when the thin, double-helix actin is exposed to the thick myofilament myosin in the presence of Mg^{2+} and adenosine triphosphate (ATP). This interaction and thus myocyte contraction as well as relaxation are controlled by the intracellular Ca^{2+} level. When intracellular Ca^{2+} is increased, it binds to the contraction regulatory protein troponin, which causes a conformational change in tropomyosin that exposes actin to myosin. In the presence of ATP, linkages are rapidly made and broken between actin and myosin, causing the actin to slide along the myosin filaments. This process generates muscle tension and ultimately myocyte contraction. A decrease in intracellular Ca^{2+} level reconforms the troponin-tropomyosin complex in such a way that myosin and actin linkages are broken, allowing sarcomere relaxation. Intracellular ionic calcium is the principal mediator of the inotropic state of the heart and is mainly stored and regulated by the sarcoplasmic reticulum. Most positive inotropic agents, including digitalis and catecholamines, act by increasing the availability of intracellular calcium in the vicinity of the myofibrils.

The normal cardiac index is 2.5 to 4.0 L/min/m^2 at rest. It is determined by the contractility, preload, afterload, and heart rate. In normal hearts, the collective force of contraction of the cardiac chamber is the sum of the forces generated by the individual myocytes. Myocyte force is in turn a function of the ability of the contractile proteins to generate power (inotropic state or contractility) as well as the degree of sarcomere stretch at the start of contraction (preload). Stretching the sarcomere progressively toward its optimal length of 2.2 μm increases the force of contraction by allowing the maximum number of actin-myosin myofilament interactions. This forms the basis of the Frank-Starling relation, which states that within physiologic limits, the force of ventricular contraction is directly related to the end-diastolic length of cardiac muscle. Contractility may be affected by a host of factors.

Multiple physiologic depressants (e.g., hypoxia, hypercarbia, acidosis, and ischemia) and pharmacologic depressants (e.g., many cardiac antidysrhythmic agents, calcium channel blockers, beta-blockers, barbiturates, and alcohol) decrease myocardial contractility. Correcting physiologic myocardial depressant factors and discontinuing certain medications with negative inotropic properties are important first steps in managing patients with HF. Inotropic agents enhance contractility and may improve hemodynamics both acutely, such as with catecholamines, and chronically, with cardiac glycosides.

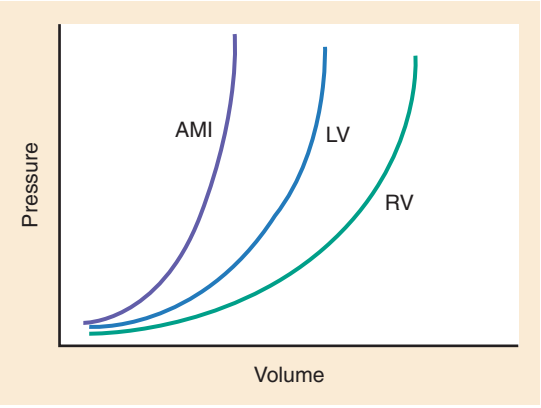


Figure 79-2. The end-diastolic pressure of the chamber is determined by the filling volume and the compliance characteristics of the chamber. The right ventricle (RV) is more compliant than the more muscular left ventricle (LV), which becomes stiffer still under conditions of ischemia or acute myocardial infarction (AMI).

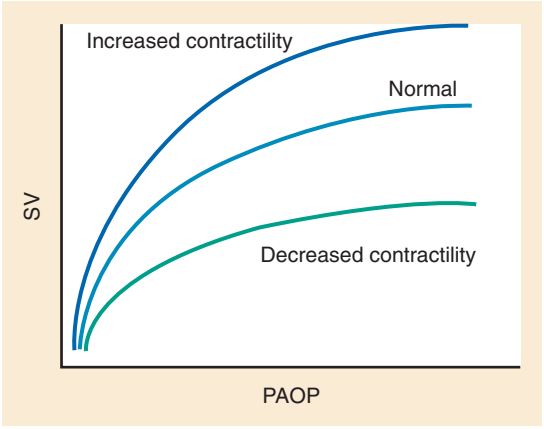


Figure 79-3. Increased preload, represented as pulmonary artery occlusion pressure (PAOP), results in increased stroke volume (SV) irrespective of the contractile state of the ventricle. At any level of contractility, an optimal PAOP is reached beyond which further increases in pressure may result in increased risk of pulmonary edema, with minimal incremental increase in SV.

Preload is the amount of force stretching the myofibril before contraction. In the intact ventricle, preload is produced by the venous return into the chamber resulting in stretch of the myofibrils constituting the chamber walls. The volume filling the chamber also results in the development of pressure that can be measured clinically in either ventricle. The pressure measured within a chamber is determined by both the volume stretching the chamber wall and the compliance characteristics of the muscle. For this reason, pressure is only an indirect reflection of the preload. Changes in compliance may occur acutely with ischemia or chronically with hypertrophy, and they may substantially alter the relationship between chamber volume, pressure, and preload (Fig. 79-2). These considerations notwithstanding, the bedside measurement of the pulmonary artery occlusion pressure (PAOP), an indirect measure of left ventricular (LV) filling pressure, by a balloon flotation pulmonary artery catheter remains an occasionally useful clinical tool in estimating preload of the left heart in complex clinical situations.

Optimal preload is the filling pressure that stretches ventricular myofibrils maximally and leads to the greatest stroke output per contraction. The actual optimal PAOP is unique for each patient because it is affected by the loading conditions and compliance characteristics. For example, patients with acute myocardial infarction tend to have stiffer, less compliant left ventricles. In these patients, optimal PAOP ranges are higher. Irrespective of the inotropic state of the ventricle, optimizing preload results in the maximum stroke output for that ventricle (Fig. 79-3). Ventricles with normal compliance accommodate larger volumes before the chamber pressure rises. Accordingly, if pressure is used to estimate preload, the normal ventricle has more dramatic increases in stroke output for similar increases in filling pressure (steeper Starling curve). The risk of pulmonary edema increases when PAOP rises significantly above normal ranges (6–12 mm Hg). In patients with low colloid osmotic pressures secondary to hypoalbuminemia, pulmonary edema may occur at even lower filling pressures.

Afterload represents the mural tension on myocardial cells during contraction. It is determined by the total peripheral vascular resistance and the cardiac chamber size. The peripheral resistance is affected by the total cross-sectional area of the circulation, the blood viscosity, and other factors. The arterioles are the major resistance vessels in the circulation. Flow is directly proportional to the fourth power of the vessel radius (Poiseuille's law). The larger the ventricular cavity, the

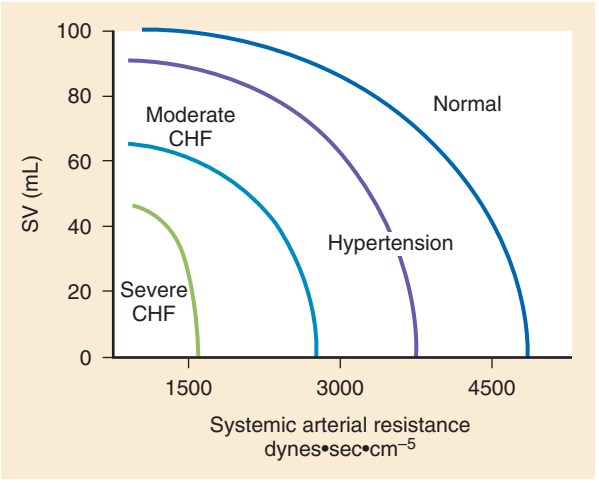


Figure 79-4. Normal hearts can perform pressure work against high peripheral resistance, maintaining cardiac output even in the presence of very high systemic arterial resistance. Failing hearts are more afterload sensitive and exhibit decreased stroke volume (SV) when confronted with high or high-normal resistances. CHF, congestive heart failure. (Modified from Weil et al: In Braunwald E (ed): Heart Disease: A Textbook of Cardiovascular Medicine, 4th ed. Philadelphia, Saunders, 1992.)

more mural tension and thus myocardial work is required during contraction (law of Laplace). Failing ventricles cannot overcome increases in peripheral resistance in order to eject blood (Fig. 79-4). In the presence of this afterload mismatch, these ventricles dilate further, increasing their end-diastolic volumes such that stroke volume is maintained, even with decreasing ejection fraction (preload reserve). Failing hearts are therefore extremely afterload sensitive.

For clinical purposes, afterload can be thought of as the pressure against which the heart must pump to eject blood. Blood pressure (BP) is determined by the product of the systemic vascular resistance and flow (BP = SVR × CO). Hypertension is a major cause of HF in 91% of cases.[25] Patients with HF and low cardiac output (CO) tend to maintain blood pressure by peripheral vasoconstriction mediated mainly by endogenous catecholamines and the renin-angiotensin-aldosterone system. Afterload reduction may be beneficial because it allows the conversion of pressure work into flow

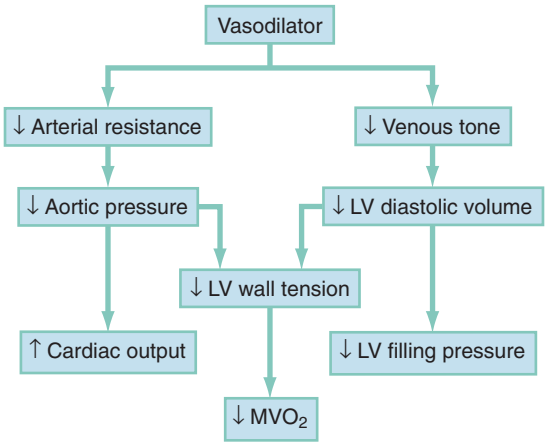


Figure 79-5. Arterial dilators decrease arterial resistance and result in increased cardiac output. Venodilators decrease venous return to the heart and relieve pulmonary congestion. Balanced agents (nitroprusside and angiotensin-converting enzyme inhibitors) do both. Decreased mural tension reduces myocardial oxygen demand (MVO_2) and may relieve ischemia. LV, left ventricular.

work (Fig. 79-5). When blood pressure is decreased, cardiac output increases as long as preload is maintained. Since flow work is proportionally less oxygen demanding, afterload reduction therapy has the additional benefit of decreasing myocardial oxygen demands.

Heart rate and rhythmic contraction are important determinants of optimal cardiac output. As heart rate increases to the range of 150 to 160 beats/minute in the adult, output increases progressively. Tachycardia above this level compromises diastolic filling time and leads to decreased cardiac output. Myocardial perfusion, which occurs during diastole, also becomes impaired by severe tachycardia. Stroke volume is maximized when atrial contraction "primes" the ventricular pumps before they contract. Accordingly, any derangement of intracardiac conduction or dysrhythmia can reduce stroke output. Loss of atrial priming (e.g., atrial fibrillation) can lead to marked deterioration in cardiac output, especially in diseased, stiffer hearts that require high filling pressures to optimize preload.

PATHOPHYSIOLOGY OF ACUTE PULMONARY EDEMA

Pulmonary edema is classified clinically into cardiogenic and noncardiogenic forms. Most patients in the emergency setting with pulmonary edema have the acute cardiogenic variety, which results mainly from elevated pulmonary capillary hydrostatic pressure. Most commonly, cardiogenic pulmonary edema occurs with acute myocardial ischemia or infarction, cardiomyopathy, valvular heart disease, or hypertensive emergencies. In contradistinction, noncardiogenic pulmonary edema generally results from an alteration in the permeability characteristics of the pulmonary capillary membrane. The alteration may have such diverse causes as systemic sepsis or septic shock, inhalation injuries, drugs and toxins, aspiration syndromes, the fat emboli syndrome, neurogenic causes, and high altitude.

Cardiogenic pulmonary edema results primarily from increases in pulmonary capillary hydrostatic pressure that force a protein-sparse plasma ultrafiltrate across the pulmonary capillary membrane into the pulmonary interstitium. As in all forms of pulmonary congestion, this increase in fluid flux immediately results in an increase in the lymphatic drainage of fluid from the lung. This compensatory mechanism may quickly become overwhelmed if large amounts of edema begin to accumulate in the pulmonary interstitium, ultimately leading to alveolar flooding.

The increase in left ventricular end-diastolic pressure that causes the rise in pulmonary artery occlusion pressure may have a variety of causes, particularly myocardial ischemia. Increases in left ventricular end-diastolic pressures do not always reflect increases in plasma volume, although they generally do in patients with chronic HF. In patients with chronic HF, neurohumoral mechanisms generally result in plasma volume expansion. In patients suffering from acute-onset cardiogenic pulmonary edema (as may result from acute myocardial ischemia, infarction, or abrupt increases in afterload), plasma volume is generally not expanded and may, in fact, be contracted. In this scenario, the acute challenge to a ventricle with minimal reserve results in an immediate decrease in ventricular compliance (diastolic dysfunction), with generation of high left ventricular pressures, although there is no change in volume (see Fig. 79-2). The pressures are reflected backward to the pulmonary capillaries, resulting in pulmonary edema. Volumes as large as 1 or 2 L may leave the plasma over a short time and create serious respiratory compromise.

Plasma volume studies in patients with acute cardiogenic pulmonary edema reveal that they have substantially lower plasma volumes than control patients. As therapy progresses, the plasma volume may expand as fluid is reabsorbed from the interstitial pulmonary space back into the vascular space. These changes are reflected by initial hemoconcentration as evidenced by higher hematocrits and colloid osmotic pressures.

It is important to understand this pathophysiologic scenario when treating patients with both acute pulmonary edema (APE) and systemic hypotension because despite the presence of pulmonary congestion, these patients may have low plasma volume (low preload) and be in need of fluid challenge to rapidly restore preload, cardiac output, systemic perfusion, and blood pressure. Thus, careful volume infusion with aliquots of normal saline is usually the most appropriate initial resuscitation response for the hypoperfusing patient with acute-onset cardiogenic pulmonary edema.

COMPENSATORY MECHANISMS

Increase in Stroke Volume

Increased stroke volume occurs in response to an increase in preload (Frank-Starling mechanism). This compensatory mechanism is immediate and effective in improving cardiac output in response to acute systemic demands. It is a limited response, however, because myofibril stretch to a sarcomere length beyond 2.2 μm does not further increase and may actually reduce stroke output. Also, this mechanism greatly increases myocardial oxygen demand, which may lead to dysfunction in the setting of significant coronary artery disease.

Increased Systemic Vascular Resistance

Increased systemic vascular resistance results in redistribution of a subnormal cardiac output away from skin, skeletal muscles, and kidneys to maintain normal blood flow to the brain and heart. This increased afterload also increases myocardial work greatly.

Development of Cardiac Hypertrophy

Development of cardiac hypertrophy is the primary chronic adaptation of the heart to compensate for pump failure. This hypertrophy occurs mainly by increasing the number of myo-

fibrils per cell, as the heart has very limited ability to produce new cells (hyperplasia). New myofibrils arrange in series in response to an increase in chamber volume (leading to dilation over time) and in parallel when responding to higher pressure loads (leading to increased chamber wall thickness). In addition to myofibril hypertrophy, mitochondrial mass expands, leading to additional ATP provision for the expanded myofibril mass.

Initially, hypertrophy leads to improved function of each myocardial cell but at a higher energy cost. Unfortunately, capillary mass may not increase significantly in response to myocyte hypertrophy. In addition, hypertrophy is associated with myosin synthesis shifts from V_1 to V_3 isoforms, with related slowing of the rate of contraction, prolongation of the time to peak tension, and reduced rate of relaxation. With the continued influence of volume overload, myofibril mass expands more than mitochondrial mass and relative capillary blood flow is reduced, leading to progressive myocyte death (apoptosis) with fibrosis and increased stress on the remaining myocytes. This process appears to be a particular problem with aging, in which substantial diffuse loss of myocytes, increased fibrosis, and reactive hypertrophy of remaining myocytes are demonstrated. Thus, the hypertrophic response, if allowed to continue, eventually becomes a destructive process that accelerates myocyte death and reduces pump function.

NEUROHORMONAL MECHANISMS

Neurohormonal mechanisms maintain blood pressure and vital organ perfusion and are activated by left ventricular dysfunction. Regrettably, these neurohormonal mechanisms also increase the hemodynamic burden and oxygen consumption of the failing ventricle and are counterproductive on a chronic basis.

Renal Neurohormonal Response

Decreased glomerular perfusion results in a reduction in the renal excretion of sodium. Renal arteriolar and adrenergic receptors stimulate renin release by the juxtaglomerular apparatus. Renin facilitates the conversion of the hepatically produced protein angiotensinogen to angiotensin I, which is further converted to angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II is a potent vasoconstrictor and also an important stimulus for aldosterone release by the adrenal cortex. Aldosterone increases renal sodium retention and potassium excretion.

Renal adaptation to hypoperfusion occurs mainly through production of vasodilatory hormones such as prostacyclin, along with prostaglandins PGI_2 and PGE_2. Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) interfere with prostaglandin synthesis by inhibiting cyclooxygenase. Accordingly, except for the useful antiplatelet effect of aspirin, NSAIDs optimally should be avoided in patients with chronic HF because they may contribute to acute renal insufficiency with concomitant salt and water retention.

Central and Autonomic Nervous System Neurohormonal Response

The heart and great vessels contain sensory receptors that detect changes in perfusion. Metabolic receptors in muscles also exert inhibitory and excitatory influences on brainstem vasomotor neurons. Arginine vasopressin (antidiuretic hormone) is released from the pituitary gland in response to decreases in perfusion. Elevated vasopressin levels in HF increase volume overload while decreasing osmolality. This adversely affects hemodynamics and cardiac remodeling while potentiating effects of angiotensin II and norepinephrine.[26] Vasopressin antagonists may hold promise in HF.[27]

HF results in a generalized stimulation of sympathetic activity and inhibition of parasympathetic tone. Increased sympathetic outflow results in the release of increased epinephrine and norepinephrine from the adrenal glands and norepinephrine at peripheral sympathetic nerve endings. These elevated catecholamine levels stimulate surface receptors in the heart and blood vessels, increasing cardiac contractility, heart rate, and vascular tone. The resulting increased venous tone augments preload, which tends to maintain stroke output (preload reserve). Increased arterial smooth muscle tone increases afterload, which is deleterious to a failing ventricle incapable of maintaining stroke output against this resistance to flow.

Afterload reduction improves stroke output as pressure work is converted to flow work (see Fig. 79-5). Adequate preload must be maintained to achieve optimal benefit. Acutely, arterial blood pressure is improved and cardiac output increased by catecholamines. Chronically, a decrease in the number and affinity of surface catecholamine receptors occurs in myocardial tissue, reducing responsiveness to epinephrine and norepinephrine. Elevated catecholamines adversely affect myocardial perfusion, leading to progressive apoptosis and cardiac fibrosis.

Cardiac Neurohormonal Response

Increases in myocardial wall stretch activate the release of cardiac natriuretic peptides, which are structurally related peptides that are important in volume and sodium homeostasis. They include atrial, BNP, and C-type natriuretic peptide. All are elevated in patients with left ventricular dysfunction. The natriuretic peptides promote water and sodium excretion, promote peripheral vasodilation, and inhibit the renin-angiotensin-aldosterone system. A variety of natriuretic peptide receptors exist on endothelial cells, vascular smooth muscle cells, renal epithelial cells, and in the myocardium. Circulating natriuretic peptides are greatly increased in HF as a result of increased synthesis. In early HF, they play a key role in compensation for left ventricular dysfunction. Attenuation of the renal response to natriuretic peptides occurs as HF progresses.

Vascular Endothelial Neurohormonal Response

Endothelial function locally regulates vasomotor tone. A family of endothelins—ET-1, ET-2, ET-3, and ET-4—are produced by endothelial and smooth muscle cells as well as neural, renal, pulmonary, and inflammatory cells. This occurs in response to hemodynamic stress, hypoxia, catecholamines, angiotensin II, and many inflammatory cytokines. ET-1 is the most important endothelin and exerts its main vascular effects, vasoconstriction and cell proliferation, through specific ET_A and ET_B receptors on vascular smooth muscle cells. ET_B receptor stimulation by ET-1 also increases prostacyclin and nitric oxide (NO) release, causing vasodilation. ET-1 plasma levels are elevated in patients with HF, correlate with symptoms as well as hemodynamic severity, and are associated with an adverse prognosis. Infusion of a mixed $ET_{A/B}$ antagonist, bosentan, improves systemic and pulmonary hemodynamics in both acute and chronic HF. Selective ET_A and mixed $ET_{A/B}$ receptor antagonists show promise for hemodynamic and symptomatic improvements in patients with HF.

Nitric oxide plays a critical role in the homeostasis of cardiac function.[28] Reduced synthesis or increased degradation of NO

at the endothelial level is detrimental in HF. Nitric oxide-mediated endothelial dysfunction may represent the earliest stage of target organ damage, which ultimately leads to hypertensive heart disease and HF.[29] Virtually all cell types constituting the myocardium produce NO. One of the three recognized nitric oxidase synthase isoforms, inducible NOS, may produce excessive NO and suppress cardiac myocyte function in HF.[30]

MYOCARDIAL PATHOPHYSIOLOGY

Understanding HF requires recognition of the underlying pathologic conditions resulting in progressive myocardial dysfunction as well as the adaptive responses to this disease process. If properly recognized, precipitating causes of acute decompensation of cardiac function can usually be more effectively treated than the underlying chronic condition. The short-term prognosis in patients who have an acute precipitating cause of HF is generally favorable, provided an effective therapeutic intervention is available. The prognosis is more guarded when the underlying disease process has progressed to a decompensated state.

PRIMARY DISEASE PROCESSES RESULTING IN HEART FAILURE

HF can result from primary disease of the coronary arteries, myocardium, cardiac valves, pericardium, peripheral vessels, or lungs. Often, determining the etiology of HF is simpler early in its course than during its later stages.

Coronary Artery Disease

In developed countries, atherosclerotic coronary artery disease remains the leading cause of HF, present in almost 70% of patients in multicenter HF trials.[31] Acute coronary thrombosis leads to focal myocardial necrosis, with resultant myocardial fibrosis and scarring. This process leads to areas of dyskinesis that result in a decreased ejection fraction. When approximately 40% of the left ventricular muscle mass is acutely infarcted, cardiogenic shock ensues. Aneurysmal dilation of infarcted areas with paradoxical motion during systole may disproportionately decrease the ejection fraction. Transient loss of contractile function may result from episodes of myocardial ischemia that do not cause frank necrosis or from an ischemic zone surrounding an infarct. This "myocardial stunning" may persist for several days. Due to improved treatment of acute coronary syndromes, the rates of death and HF are decreasing.[32]

Chronic coronary insufficiency leads to a more diffuse myocardial fibrosis termed ischemic cardiomyopathy. Revascularization of ischemic but not infarcted myocardial tissue provides a survival benefit in patients with HF related to ischemic left ventricular systolic dysfunction. Diseases affecting the coronary microcirculation, such as vaso-occlusive sickle cell anemia and diabetes mellitus, result in similar pathology. Compensatory mechanisms may occur after large myocardial infarction and progressive cardiac disease, which are collectively termed ventricular remodeling. They include cardiac dilation, reactive hypertrophy, progressive fibrosis, and changes in wall conformation. These may result from elevated chamber filling pressures as well as neurohumoral factors.

Cardiomyopathy and Myocarditis

The cardiomyopathies are a group of disease processes that primarily affect the myocardium (see Chapter 80). Myocardial diseases resulting from coronary, valvular, and pericardial pathologies are excluded. Cardiomyopathy is categorized as primary, in which the cause is unknown, or secondary to some identifiable cause. Clinically, patients with cardiomyopathy tend to present with three forms—dilated, hypertrophic, or restrictive—each of which is associated with heart failure. The specific cardiomyopathy syndromes and myocarditis, which may also cause heart failure, are discussed in Chapter 80.

Valvular Heart Disease

Cardiac valvular disease is the third leading cause of HF, after ischemic heart disease and dilated cardiomyopathy. Acute valvular dysfunction, such as acute mitral regurgitation secondary to papillary valve rupture, may precipitate fulminant HF. Most acute valvular dysfunction involves either the mitral or the aortic valve and usually results in fulminant regurgitation. Acutely stenotic lesions are predominantly restricted to mechanical catastrophes of prosthetic valves. Typical murmurs may be difficult to appreciate or even absent in acute valvular insufficiency because of early equilibration of pressures across the defective valve. Accordingly, patients may present in extremis with fulminant pulmonary edema. Valvular disease is discussed in Chapter 81.

Mitral insufficiency and aortic stenosis are most commonly associated with chronic HF. Knowledge of the precise valvular pathology may have important implications for emergent HF therapy. For example, patients with decompensated aortic stenosis should generally not receive vasodilator agents, which cannot increase flow across a fixed obstruction. Patients may become hypotensive due to reduced preload, with resultant decreased systemic and coronary perfusion. On the other hand, patients with mitral regurgitation benefit greatly from vasodilators, which improve antegrade flow by reducing afterload.

Pericardial Diseases

Pericardial diseases may significantly affect ventricular function, decreasing cardiac output and increasing intracardiac pressures, with cardiac tamponade occurring at the extreme. These are discussed in Chapter 80.

Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) has a 20 to 30% prevalence in HF and may obscure recognition of HF.[33] Pulmonary dysfunction reduces myocardial oxygen supply while increasing the demand for cardiac output by perfusing all tissues with suboptimally oxygenated blood. Hypoxia leads to pulmonary arteriolar vasoconstriction, which reduces lung vascular bed area, elevating pulmonary artery pressures. Chronic increases in pulmonary arterial pressure lead to right ventricular hypertrophy and dilation. When compensatory mechanisms fail, the patient develops right-sided HF (cor pulmonale), usually with left ventricular output preserved, at least at rest. Causes of acute cor pulmonale such as a large pulmonary embolus may precipitate sudden systemic hypotension and death caused by decreased left ventricular priming.

Distinguishing primary pulmonary disease causing predominantly right-sided HF from left ventricular failure with secondary right-sided dysfunction is clinically challenging. Wheezing or rhonchi may be seen in both entities. The chest radiograph may be difficult to interpret because both presentations cause interstitial changes. Hyperinflation depresses the diaphragm, which elongates the cardiac silhouette and may mask cardiomegaly. Competition for intrathoracic space reduces lung capacity in patients with chronic HF.[34] Natri-

uretic peptide levels may help distinguish primary pulmonary disease from HF[35] (see Chapter 72).

CLASSIFICATION OF HEART FAILURE

Many different methods of classifying HF exist, including high versus low output, acute versus chronic, right sided versus left sided, systolic versus diastolic, and forward versus backward. Early in HF, these may be useful clinical descriptors suggesting particular causes and treatment strategies. Late in the disease process, these distinctions blur.

High-Output Versus Low-Output Failure

High-output failure refers to a hyperdynamic state with supranormal cardiac output and low arteriovenous oxygen difference (decreased oxygen extraction ratio). Pulmonary congestion and peripheral edema occur as a consequence of elevated diastolic pressures. Diastolic dysfunction and circulatory overload contribute to the congestive symptoms. As the condition progresses, systolic myocardial dysfunction is superimposed on this background, and symptoms progress. At this point, cardiac output is normal or even low. Ultimately, untreated patients have classic HF indistinguishable from other end-stage cardiomyopathies.

A persistent hyperdynamic state results in myocardial damage over time. The hyperdynamic state may result from increased preload (e.g., renal retention of salt and water, and mineralocorticoids), decreased systemic vascular resistance (e.g., arteriovenous fistulas, pregnancy, cirrhosis, severe anemia, beriberi, thyrotoxicosis, Paget's disease, and vasodilator medications), increased beta-sympathetic activity, or persistent tachycardia. Early recognition of the hyperdynamic state may allow effective therapy of the underlying condition, thus avoiding the development of HF.

Low-output failure is the more typical variety of HF and occurs as a result of entities such as ischemic heart disease, dilated cardiomyopathy, valvular disease, and chronic hypertension. Low cardiac output (systolic dysfunction), high filling pressures (diastolic dysfunction), and an increased systemic oxygen extraction ratio (widened arteriovenous oxygen difference) characterize this more commonly encountered classic form of HF.

Acute Versus Chronic Heart Failure

The prototypical case of acute HF is that of the healthy person who develops a large myocardial infarction or acute valvular dysfunction. Chronic HF is best characterized by a disease state such as dilated cardiomyopathy, with gradual deterioration of cardiac function. In acute HF, the early presentation may be due to systolic dysfunction and hypoperfusion, often with APE resulting from the sudden reduction in chamber compliance (diastolic dysfunction) that accompanies acute ischemia or infarction. Chronic HF usually arises with symptoms related to fluid retention, with compensatory mechanisms adjusted so that normal perfusion exists, at least in the resting state.

Right-Sided Versus Left-Sided Heart Failure

The notion that one of the cardiac chambers can fail independently of the other is somewhat artificial. The right and left circulations are connected and, over time, output from the two chambers must be equal. Furthermore, the right and left ventricles share an interventricular septum, and dysfunction in one chamber may have immediate impact on the other. For example, acute right-sided HF from pulmonary hypertension secondary to acute respiratory failure causes bulging of the interventricular septum into the left ventricular chamber. This so-called septal shift results in decreased left ventricular preload and low cardiac output that is volume responsive. Chronic left-sided HF leads to pulmonary hypertension with resultant right-sided HF. In addition, cardiac biochemical changes such as an abnormal catecholamine response affect all chambers.

Nonetheless, the terms have some usefulness in identifying the predominant clinical presentation. Fluid accumulation "behind" the involved ventricle is responsible for many of the clinical manifestations of HF. For example, left ventricular failure leads primarily to pulmonary congestion with symptoms mostly of dyspnea and orthopnea. Patients with right-sided HF present with symptoms of systemic venous congestion, such as pedal edema and hepatomegaly.

When previously normal patients have acute pathology, the concept of left- versus right-sided HF may be clinically useful. Patients with acute myocardial infarction of the anterior wall may present with APE. Yet, unlike patients with chronic HF, they generally do not have jugular venous distention or pedal edema because the central venous pressure remains normal. A chest radiograph reveals evidence of pulmonary venous congestion, interstitial edema, and, in fulminant cases, alveolar edema. Since there has not yet been time for cardiac dilation, the cardiac shadow is of normal size.

Patients with acute right ventricular infarction typically have jugular venous distention and hypotension, but often without rales. Bulging of the interventricular septum into the left ventricular chamber results in decreased left ventricular preload. The low cardiac output and hypotension are often responsive to fluid challenge. Jugular venous distention is a sign of right-sided heart diastolic dysfunction. Failure to understand this may result in withholding of a therapeutic fluid challenge if distended neck veins are interpreted simply as a sign of HF.

Forward Versus Backward Heart Failure

Forward failure refers to inadequate systemic perfusion resulting from low cardiac output. The symptoms of forward failure include weakness, fatigue, oliguria, prerenal azotemia, and, in advanced cases, hypotension and cardiogenic shock. Backward failure refers to symptoms related to pressure that builds up "behind" a failing chamber. Pulmonary edema, hepatomegaly, and pedal edema are symptoms of backward failure.

Systolic Versus Diastolic Dysfunction

Systolic dysfunction refers to impairment of contractility. Stroke output is reduced and forward flow is compromised. Systolic dysfunction is typically caused by myocyte destruction such as occurs in myocardial infarction. Asymptomatic left ventricular systolic dysfunction in patients 45 years of age or older has an estimated prevalence of 6% and is more common than symptomatic systolic HF.[36,37] Diastolic dysfunction indicates a primary problem with the ability of the ventricles to relax and fill normally.[38] In many cases, normal or even supernormal systolic function is preserved. Most cases of systolic dysfunction also involve some degree of diastolic dysfunction.

Echocardiographic and nuclear imaging techniques demonstrate that 40 to 50% of patients with congestive symptoms have normal ejection fractions and suffer from diastolic dysfunction,[39,40] termed HF with a normal ejection fraction.[41] The proportion of HF that is primarily diastolic increases with age,

from 46% in patients younger than 45 years to 59% in patients older than 85 years.[42] Asymptomatic diastolic dysfunction is much more common than asymptomatic systolic dysfunction, occurring in 26% of patients 45 years of age or older in one study.

Diastolic dysfunction is the predominant pathophysiology in hypertrophic and restrictive cardiomyopathies, valvular aortic stenosis, and, most important, hypertension. Diastolic dysfunction occurs predominantly as a result of one of three mechanisms: impaired ventricular relaxation, increased ventricular wall thickness, or accumulation of myocardial interstitial collagen. Impaired relaxation (lusitropic) capacity of the myocardium leads to higher ventricular filling pressure, which results in congestive symptoms. Myocardial relaxation is an active, energy-requiring process. Failure of myocytes to relax may be secondary to low intracellular energy stores. Physiologic stresses causing increased cardiac demands can precipitate lusitropic abnormalities. In chronic renal disease, mortality is higher in diastolic than systolic HF.[43] In addition, systolic contractile dyssynchrony occurs in one third of diastolic HF patients, and diastolic dyssynchrony in more than half, with therapeutic implications.[44,45]

As with the other classification schemes, most patients with HF have components of both systolic and diastolic dysfunction. The classification of systolic and diastolic dysfunction allows specific treatment strategies.[46] Patients with predominantly diastolic dysfunction have the advantage of having intact myocardial contractile function. Stiffer hearts have steep pressure-volume curves; therefore, small reductions in diastolic filling volume, as may occur with aggressive vasodilator or diuretic therapy, may markedly decrease ventricular filling (see Fig. 79-3). This preload deficiency may compromise stroke output.

CLINICAL EVALUATION OF PATIENTS WITH SUSPECTED HEART FAILURE

The New York Heart Association (NYHA) classification system is a time-honored categorization for patients with chronic HF (Box 79-1). Patients who present in extremis require aggressive evaluation, monitoring, and management. Careful consideration of the differential diagnosis is symptom based. The most common manifestation of acute HF is acute respiratory distress caused by pulmonary edema. Accordingly, the differential diagnosis includes exacerbation of COPD or asthma, pulmonary embolus, pneumonia, anaphylaxis, and other causes of acute respiratory distress. Hypoperfusion may be caused by some of these as well as by sepsis syndrome, hypovolemia, hemorrhage, cardiac tamponade, and tension pneumothorax.

PRECIPITATING CAUSES OF HEART FAILURE

Various stresses may result in acute cardiac decompensation (Box 79-2).

BOX 79-1 CLASSIFICATION SYSTEM FOR CHRONIC HF: NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSES

I. Asymptomatic on ordinary physical activity
II. Symptomatic on ordinary physical activity
III. Symptomatic on less than ordinary physical activity
IV. Symptomatic at rest

Systemic Hypertension

Sudden elevation of arterial pressure acutely increases afterload, which may precipitate the rapid onset of HF. This is particularly common when antihypertensive therapy is abruptly discontinued. Malignant hypertension, pheochromocytoma, and other states associated with high sympathetic outflow may be implicated. Cocaine and other sympathomimetic drugs of abuse may precipitate HF.

Myocardial Infarction and Ischemia

A new ischemic event may precipitate HF by impairing contractility and decreasing left ventricular compliance. Pulmonary edema may occur rapidly in this setting, especially when large areas of myocardium are involved. In the compromised heart, even local ischemia may precipitate HF.

Dysrhythmia

Both tachydysrhythmias and bradydysrhythmias can severely affect cardiac output, especially when acute. Tachydysrhythmias compromise diastolic filling time and thus may reduce cardiac output. Concurrently, the shortened diastole impairs coronary perfusion and myocardial oxygen delivery while the tachycardia results in increased myocardial oxygen demand. These factors may precipitate ischemia, which may further impair contractility and exacerbate HF.

The prevalence of atrial fibrillation in patients with HF increases from less than 10% in NYHA functional class I to approximately 50% in NYHA functional class IV.[47] Neurohormonal alterations, electrophysiologic changes, and mechanical factors create an environment in which HF predisposes to atrial fibrillation and atrial fibrillation exacerbates HF. New-onset atrial fibrillation or other dysrhythmias that affect coordinated atrial priming of the ventricular pump may seriously reduce preload, especially in disease states with reduced ventricular compliance. Significant bradydysrhythmias may also reduce cardiac output simply by reducing the number of systolic ejections per minute (CO = stroke volume × heart rate).

Systemic Infection

Infection results in increased systemic metabolic demands. Pulmonary infection, which is common in patients with pulmonary vascular congestion, may add hypoxia to the metabolic stressors fever, tachycardia, and increased tissue perfusion. The sepsis syndrome is associated with a reversible form of myocardial depression, mediated by various cytokines,

BOX 79-2 COMMON PRECIPITATING CAUSES OF ACUTE HF

- Systemic hypertension
- Myocardial infarction or ischemia
- Dysrhythmia
- Systemic infection
- Anemia
- Dietary, physical, environmental, and emotional excesses
- Pregnancy
- Thyrotoxicosis or hypothyroidism
- Acute myocarditis
- Acute valvular dysfunction
- Pulmonary embolus
- Pharmacologic complications

including interleukins-1, -2, and -6, as well as tumor necrosis factor.[48]

Anemia

With chronic anemia, oxygen delivery to tissues is maintained by increased cardiac output (isovolumic hemodilution). Anemia increases in prevalence with increasing severity of HF, especially with declining renal function and increasing age. Anemia is associated with poorer survival in HF,[49-51] with greater disease severity, a greater left ventricular mass index, and higher hospitalization rates.[52] In anemic patients with HF, correction of anemia with erythropoietin and oral iron improved left ventricular systolic function, left ventricular remodeling, and BNP levels.[53] Abrupt exacerbations of anemia increase systemic perfusion demands and, especially if coupled with reduced coronary oxygen delivery, may prompt the onset or exacerbation of HF.

Dietary, Physical, Environmental, and Emotional Excesses

Increased sodium ingestion, plasma volume expansion such as with a transfusion, increased exertion, extremes of environmental temperature, and emotional upset are some of the important factors that may prompt cardiac decompensation.

Pregnancy

Cardiac output is normally increased significantly during pregnancy, which may lead to decompensation in women with underlying valvular disease or other cardiac pathology. Peripartum cardiomyopathy is a type of dilated cardiomyopathy that may occur late in pregnancy or more commonly in the early postpartum period, with more than 50% of patients having normalization of left ventricular function with pharmacologic therapy.[54]

Thyroid Disorders

HF may be a clinical manifestation in patients with previously compensated cardiac disease who develop hyperthyroidism. Hypothyroidism also adversely affects myocardial pump function. Restoration of normal thyroid function usually reverses the abnormal cardiovascular hemodynamics.[55]

Acute Myocarditis

A variety of infectious and inflammatory diseases, including viral agents and acute rheumatic fever, may precipitously impair myocardial contractility.

Acute Valvular Dysfunction

Almost all causes of acute HF resulting from cardiac valve dysfunction are secondary to aortic or mitral insufficiency. Mitral valve papillary muscle dysfunction or rupture may result from acute myocardial infarction, whereas acute aortic insufficiency is more commonly precipitated by acute bacterial endocarditis or aortic dissection. Occasionally, acute valvular stenosis may occur, usually as a consequence of acute dysfunction of a prosthetic valve.

Pulmonary Embolus

The acute pulmonary hypertension and hypoxia that accompany pulmonary embolus may cause acute HF. Accordingly, this diagnosis should be entertained in patients who have unexplained HF and risk factors for pulmonary embolism.

Pharmacologic Complications

Patients with ischemic heart disease are often receiving ambulatory treatment with beta-blocking and calcium channel-blocking agents. These drugs have negative inotropic effects and may precipitate overt HF at higher doses. Many of the current antidysrhythmic agents may have this effect as well. Glucocorticoids, NSAIDs, vasodilator drugs, and others may result in sodium retention with substantial increases in plasma volume that may precipitate HF.[56] NSAIDs in particular interfere with prostaglandin synthesis through cyclooxygenase inhibition, thereby impairing renal homeostasis in patients with HF. They also interfere with the effects of diuretics and ACE inhibitors. Noncompliance with medication regimens for hypertension, HF, or ischemia is the most common pharmacologic cause of acute HF decompensation. A careful medication history and evaluation of the patient's compliance with that regimen are important in a search for precipitating factors.

EVALUATION OF HEART FAILURE

History

The presence and character of chest pain, previous heart disease, cardiac catheterization, surgery, and other focused cardiac history should be explored. With patients unable to give a history, family members and old records are sources of information. A careful review of the patient's current medications may indicate ongoing disease processes. A more traditional history may be taken for patients who are less severely ill.

In patients with more gradual onset of HF, dyspnea on exertion is among the earliest complaints. Orthopnea is a type of dyspnea seen among patients with HF, in which supine position enhances venous return to the heart, precipitating increases in diastolic pressure. Symptoms abate when the patient props up the trunk and venous return decreases. Paroxysmal nocturnal dyspnea results from pulmonary congestion precipitated by plasma volume expansion that occurs as interstitial edema is reabsorbed into the circulation. Lower extremity venous hydrostatic pressure decreases during recumbency and is resolved by standing. Nocturia results from the same pathophysiologic process. Many historical features increase the likelihood of HF. Most predictive is a past history of HF or paroxysmal nocturnal dyspnea; the absence of dyspnea on exertion reduces the likelihood.[57]

Physical Examination

Clammy, vasoconstricted patients with a thready pulse and delayed capillary refill may have systemic hypoperfusion despite adequate blood pressure that is maintained by intense vasoconstriction. Noninvasive assessment of blood pressure in the vasoconstricted patient with low cardiac output can be inaccurate, but cuff pressures are also not reliable (see Chapter 3).[58] An accurate intra-arterial pressure may substantially influence the choice of therapeutic agent and should be obtained, whenever possible, before initiating inotropic or vasoconstrictor drugs. For example, a patient with a cuff pressure of 80 mm Hg might receive a catecholamine vasoconstrictor to maintain coronary perfusion pressure despite the negative impact of these drugs on afterload and ischemia. If it were known that the *mean* intra-arterial pressure was 80 mm Hg, the

same patient might more appropriately receive carefully titrated vasodilators such as intravenous nitroglycerin. Persistently hypotensive patients require intra-arterial pressure monitoring.

Physical examination of patients with APE resulting from acute myocardial infarction includes a search for surgically correctable lesions such as acute mitral regurgitation or ventricular septal defect. Patients with pulmonary congestion secondary to HF develop interstitial and alveolar pulmonary edema, causing reduced pulmonary compliance and decreased functional residual capacity. Crackles reflect alveolar flooding, often present in pulmonary edema. Peribronchial edema may cause wheezing, which can mimic bronchospastic disease and misdirect therapy. A positive response to bronchodilator therapy does not exclude HF. The presence of a third heart sound significantly increases the likelihood of HF, and the absence of rales decreases the likelihood.[57]

Diagnostic Testing in Heart Failure

The upright chest radiograph is a very useful tool to distinguish cardiogenic pulmonary edema from other causes of dyspnea, although the differentiation may be challenging in patients with COPD. Arrhythmia recognition and management are important, as is identification of acute coronary syndrome. A chest radiograph showing an enlarged cardiac silhouette with pulmonary congestion and an ECG showing atrial fibrillation, ventricular hypertrophy, or evidence of past ischemia or myocardial infarction greatly increase the likelihood of HF, whereas the absence of cardiomegaly on chest radiography and the absence of any abnormality on ECG greatly decrease the likelihood.[57]

The ESCAPE trial demonstrated that pulmonary artery catheterization in severe symptomatic HF increased anticipated adverse effects but did not affect overall mortality or duration of hospitalization.[59] It is nonetheless still used judiciously in some complex clinical situations. Noninvasive impedance cardiography appears to be an effective and developing technology to measure cardiac output and other hemodynamic variables in HF and may obviate the need for a pulmonary artery catheter.[60,61]

Echocardiography is a useful diagnostic test in the evaluation of HF[62] and can noninvasively provide measures of left ventricular function and determine structural heart disease.[63] Multidetector computed tomography coronary angiography can distinguish ischemic from other forms of cardiomyopathy, but it is rarely of use in the patient with acute HF.[64] Radionuclide imaging in patients with HF and significant coronary artery disease may be useful in myocardial viability testing and predicting survival response to coronary revascularization but is not of value in the management of acute HF.[65]

Serum levels of natriuretic peptides correlate with severity of HF and have prognostic significance.[66] BNP is a neurohormone synthesized in the ventricles in response to ventricular myocyte stretch that is released as pre-proBNP and then enzymatically cleaved to NH_2-terminal-proBNP (NT-proBNP) and BNP. Blood measurements of NT-proBNP and BNP help identify patients with HF[67] and may improve the management of patients presenting to the emergency department with dyspnea.[68] Rapid, whole-blood BNP assays to evaluate possible HF are approved for clinical use. The "breathing not properly" BNP Multinational Study is a prospective evaluation of patients who presented to the emergency department with acute dyspnea. BNP levels above 500 pg/mL were highly associated with HF (likelihood ratio [LR] = 8.1), and levels of 100 to 500 pg/mL were generally indeterminate (LR = 1.8). A low BNP level (<100 pg/mL) indicated that HF was highly unlikely (LR = 0.13).[60,69] Elevated BNP levels may also be seen in right-sided HF related to cor pulmonale or pulmonary embolism. BNP levels are not falsely elevated in patients with end-stage renal disease, and in this setting elevation reflects ventricular dysfunction.[70]

The NT-proBNP and BNP levels correlate with ventricular function, NYHA classification, and prognosis.[71-73] This screening modality may obviate the need for echocardiography, invasive monitoring, or both in selected clinical situations.[74-76] BNP also provides a means of evaluating response to therapy. BNP levels have strong prognostic significance in ischemic heart disease. Results for large clinical trials confirm that BNP levels are the strongest predictor of outcome in HF compared with other neurohormones and clinical markers.[77] There is often a disconnect between the perceived severity of HF by clinicians and the level of BNP elevation, yet BNP levels are better predictors of 90-day outcome than physician judgment.[78] Patients with indeterminant BNP levels have a better prognosis than expected when physicians clinically perceive them to have NYHA class III or IV chronic HF.[79] High predischarge BNP levels are a strong, independent predictor of death or rehospitalization after decompensated HF.[80]

Plasma levels of troponin T in stable HF predict adverse outcomes,[81] and admission BNP and cardiac troponin levels are independent predictors of in-hospital mortality in acute decompensated HF.[82] Concentrations of these and other biochemical markers of myocyte injury increase in the absence of discrete ischemic events in those patients with HF most likely to have adverse events.[83]

TREATMENT OF HEART FAILURE

Of the patients with HF presenting to the emergency department, 21% are experiencing their first episode of HF and 79% have had prior hospital visits for the same condition.[84] An organized approach that (1) identifies the underlying cardiac pathology, (2) recognizes the acute precipitating event or events, and (3) controls the acute congestive state must be developed. The immediate therapeutic goals are to improve respiratory gas exchange, maintain adequate arterial saturation, and decrease left ventricular diastolic pressure while maintaining adequate cardiac and systemic perfusion. The acute congestive state may be controlled by (1) reducing the cardiac workload by decreasing both preload and afterload, (2) controlling excessive retention of salt and water, and (3) improving cardiac contractility. Patients may have a wide spectrum of symptoms and signs ranging from mild dyspnea on exertion to full-blown cardiogenic shock with hypotension and concomitant respiratory failure. The specific presentation dictates the appropriate clinical approach (Table 79-1). In most patients, sitting upright while high-flow supplemental oxygen is administered and preload is decreased with nitrates, morphine, and furosemide results in prompt improvement.

Onset of pulmonary edema may occur over several days or even weeks, but in some cases it may develop rapidly over minutes to hours. This acute, fulminant pulmonary edema is often referred to as "flash pulmonary edema," although the origins of this term are not evident. Acute rupture of a papillary muscle during acute myocardial infarction can cause flash pulmonary edema, but it can also develop in the absence of an acute anatomic disturbance. The principles of treatment for flash pulmonary edema are the same as those for pulmonary edema of more usual onset, although the therapies may need to be delivered with greater alacrity.

Table 79-1 Agents Useful in the Treatment of HF

AGENT	ROUTE	ACTION					COMMENT
		MECHANISM	PAOP	CI	BP	HR	
Morphine	IV	Sympatholytic	↓↓↓	—	↓	↓	Excellent in APE, avoid in COPD
Nesiritide	IV	Natriuretic peptide	↓↓	↑↑	— or ↓	—	Potent reduction in neurohormonal activation
Nitroglycerin	Sublingual Transmucosal Transcutaneous	Direct smooth muscle dilator	↓↓	—	— or ↓	—	Venodilator or relieves ischemia
Nitroglycerin	IV		↓↓↓↓	↑	↓	—	Venodilator or vasodilator in larger doses, tachyphylaxis
Furosemide	Oral IV	Loop diuretic venodilator	↓↓	—	— or ↓	—	Electrolyte abnormalities
ACE inhibitors	Oral IV	ACE inhibition	↓↓	↑↑	↓↓	— or ↓	Improves outcome in chronic HF, antihypertension
Nitroprusside	IV	Direct smooth muscle dilator	↓↓↓↓	↑↑↑	↓↓↓	— or ↓	Intra-arterial monitoring required Thiocyanate and cyanide toxicity
Digoxin	Oral IV	Increased Ca^{2+} availability	↓	↑	—	↓	Most effective in atrial fibrillation with chronic HF
Dobutamine	IV	Beta-agonist	↓↓	↑↑	— or ↓	— or ↑	Safest catecholamine inotrope May cause hypotension
Dopamine	IV	Beta-, Beta-dopaminergic agonist	—	↑↑	↑↑	↑	Effects differ with dose range
Levarterenol	IV	Alpha-agonist	↑	↑	↑↑↑↑	↑	Most effective vasopressor
Epinephrine	IV	Alpha- and Beta-agonist	—	↑↑↑	↑↑↑	↑↑↑	High potential to induce ischemia
Amrinone	IV	Phosphodiesterase inhibitor	↓↓	↑↑	↓	↓	Nontitratable inotropic vasodilator
Beta-blockers	Oral IV	Beta blockade	↑↑	↓↓	↓↓	↓↓	May be useful chronically to treat diastolic dysfunction

ACE, angiotensin-converting enzyme; APE, acute pulmonary edema; COPD, chronic obstructive pulmonary disease; HF, heart failure; IV, intravenous; —, no effect; ↑ or ↓, increase or decrease on a relative scale of 1 to 4.

Acute Heart Failure

Common precipitants of rapid-onset HF include acute myocardial ischemia or infarction, medication noncompliance or toxicity, cardiac dysrhythmia, dietary indiscretion, acute hypoxia, severe hypertension, acute valvular dysfunction, and increased hemodynamic demand secondary to trauma or infection (see Box 79-2). Iatrogenic causes of HF must also be considered, especially in patients who have recently received intravenous fluids. Patients with known renal insufficiency most often experience pulmonary edema as a consequence of salt and fluid overload, which may require prompt hemodialysis. The presence of HF on admission in patients with acute coronary syndromes is associated with increased short- and long-term rates of death and myocardial infarction.[85-87]

Acute Pulmonary Edema

Many patients with rapid onset of pulmonary edema demonstrate adequate systemic perfusion with elevated blood pressure because of activation of various compensatory mechanisms. The ability of the left ventricle to generate systolic pressures above 160 mm Hg indicates the presence of considerable myocardial reserve. This group of patients must be quickly distinguished from those with pulmonary edema and evidence of hypoperfusion. Hypertensive pulmonary edema is easier to manage because afterload reduction with vasodilators is extremely effective.

Most patients with APE are diaphoretic because of intense sympathetic activation. Typical findings include diffuse moist rales or rhonchi, although both may be absent with decreased ventilation in more agonal patients. Jugular venous distention is present in approximately 50%, and one third of patients have peripheral edema. An S_3 gallop may be present in up to 25% but is often difficult to appreciate. An enlarged cardiac silhouette is seen in 70% of cases. These common clinical findings of chronic HF are prevalent among patients with APE because most patients have acute exacerbations superimposed on chronic underlying disease.[90] The absence of jugular venous distention, pedal edema, and cardiomegaly is expected in previously healthy individuals with pulmonary edema resulting from an initial episode of acute myocardial ischemia. Accordingly, a normal-size heart on chest radiograph may be consistent with acute cardiogenic pulmonary edema. In addition, normal heart size should suggest the possibility of diastolic dysfunction, COPD, or noncardiogenic pulmonary edema.

All patients with significant pulmonary edema have hypoxemia and require a high-flow oxygen face mask if spontaneously breathing. The typical acid-base disturbance of acute HF is mixed. Most patients with fulminant APE have lactic acidosis, and many also have concomitant respiratory alkalosis resulting from the tachypnea stimulated by metabolic acidosis, hypoxemia, and decreased pulmonary compliance. A substantial minority of these patients present with respiratory acidosis, even without chronic lung disease. The ratio of dead space to total ventilation (V_D/V_T) may be significantly increased directly

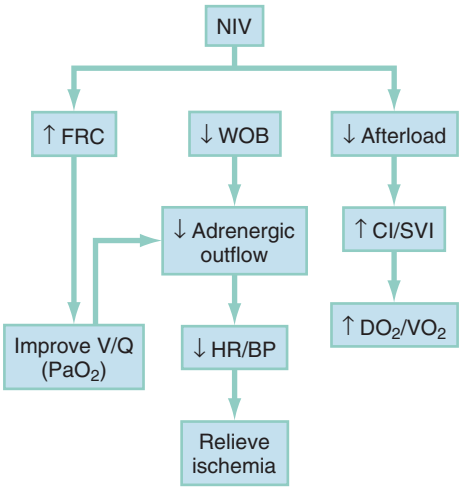


Figure 79-6. Noninvasive ventilation (NIV) techniques recruit collapsed alveoli and increase functional residual capacity (FRC), which improves oxygenation and reduces work of breathing (WOB). These factors tend to reduce sympathetic tone, heart rate (HR), and blood pressure (BP), relieving myocardial ischemia. NIV also acts as an afterload-reducing agent, which tends to directly improve cardiac index (CI) and systemic oxygen delivery (DO_2) and consumption (VO_2). Pao_2, partial pressure of oxygen in arterial blood; SVI, stroke volume index; V/Q, ventilation-perfusion ratio.

from the pulmonary edema. Respiratory muscle fatigue may supervene and result in frank hypoventilation. Patients with inadequate ventilation or with severe hypoxia require immediate ventilatory support with bag-valve-mask assisted oxygenation. Endotracheal intubation is reserved for apneic patients and those with respiratory distress, agitation, and hypoxemia not responsive to high-flow oxygen. Most spontaneously breathing patients respond rapidly to medical therapy, and most hypercarbic patients can also be managed without mechanical ventilation.

Noninvasive ventilation (NIV) techniques show promise in treating severely compromised, but not agonal, APE patients. Continuous positive airway pressure (CPAP), biphasic positive airway pressure, and CPAP plus inspiratory pressure support (noninvasive positive pressure ventilation [NIPPV]) applied by an adjustable, snugly fitting face mask increase functional residual capacity, improve oxygenation, reduce work of breathing, and result in decreased left ventricular preload and afterload by raising intrathoracic pressure (Fig. 79-6). These techniques result in more rapid restoration of normal vital signs and oxygenation than supplemental oxygen alone. Even in studies using only CPAP, fewer patients required endotracheal intubation than in control groups. The addition of pressure support (NIPPV) further reduces the work of breathing and more rapidly improves hypercarbia than CPAP alone. Selected patients may benefit greatly from these techniques when appropriately applied in conjunction with pharmacotherapy.[88-90] These ventilatory therapies do not increase the risk of myocardial infarction in acute pulmonary edema.[91] A large multicenter trial demonstrates that noninvasive ventilation provides earlier improvement in respiratory distress and related metabolic abnormalities than supplemental oxygen alone in acute pulmonary edema but does not improve short-term mortality.[92]

Acute Pulmonary Edema with Adequate Perfusion

Therapeutic interventions should decrease both preload and afterload. Excessive preload reduction may result in an abrupt decrease in cardiac output, which could cause hypotension. This occurs more readily in patients with less compliant hearts, such as those with diastolic dysfunction, aortic stenosis, or acute myocardial infarction. Fluid challenge generally restores blood pressure quickly in these patients. In general, the three initial pharmacologic therapies are nitrates, morphine sulfate, and diuretics. Minimal research exists concerning the role of ACEIs in APE but they may be useful in selected clinical circumstances.

Nitrates

Organic nitrates activate the enzyme guanylate cyclase, leading to accumulation of cyclic guanosine monophosphate (cGMP). cGMP relaxes vascular smooth muscle by sequestering calcium in the sarcoplasmic reticulum. At lower doses, nitrates are primarily venodilators. They effectively decrease PAOP and are therefore very effective in the initial therapy of APE. At higher doses, intravenous nitroglycerin also causes arteriolar dilation that decreases blood pressure and afterload. Thus, myocardial pump function is improved while myocardial oxygen demands are decreased. Nitroglycerin may further reduce myocardial ischemia by its direct coronary vasodilator effect. Prolonged nitrate therapy over hours to days leads to tachyphylaxis secondary to depletion of intracellular sulfhydryl groups. Intermittent therapy with the smallest effective dose and occasional nitrate-free intervals minimizes tolerance.

Nitroglycerin may be initiated most expeditiously by the sublingual route, but intravenous administration and titration should begin at the earliest opportunity. Hypotension from excessive preload reduction or vagally mediated idiosyncratic reactions may occur. Nitroglycerin should also be avoided in patients who have recently taken sildenafil or similar agents because it may precipitate refractory hypotension. Patients with APE are often diaphoretic, with poor skin perfusion. Transcutaneous absorption may be erratic, and ointment applied earlier might be absorbed later in the course when skin perfusion is improved, resulting in "unexplained" hypotension. Lastly, transcutaneous nitroglycerin patches may ignite during defibrillation. These factors mitigate the use of transcutaneous nitroglycerin in patients with APE.

Intravenous nitroglycerin is a titratable agent with rapid onset and offset of action. Dosing begins at 10 to 20 µg/min by infusion pump and may be rapidly titrated upward in increments of 10 µg/min every 3 to 5 minutes. Dosages of 50 to 80 µg/min provide an antianginal effect and decrease preload in most cases. Dosages as high as 200 to 300 µg/min may be needed for maximal antihypertensive effect. High-dose nitroglycerin is effective even in severely decompensated HF.[93]

Morphine Sulfate

This opioid analgesic reduces pulmonary congestion through a central sympatholytic effect and release of vasoactive histamine that causes peripheral vasodilation. The result is decreased central venous return and reduced preload, lowering PAOP. In addition, through reduced systemic catecholamines, morphine decreases heart rate, blood pressure, cardiac contractility, and myocardial oxygen consumption. Patients with APE tend to be agitated as a result of air hunger. The calming effect of morphine is advantageous in this setting. Morphine is administered in repetitive 2- to 5-mg intravenous doses titrated to effect. If oversedation results in hypoventilation, gentle stimulation usually restores ventilatory effort. In APE, mild CO_2 retention does not contraindicate morphine because it results from acute alveolar flooding that is improved by the mechanisms just delineated. Patients who are obtunded at presentation should not be given morphine prior to airway support.

Loop Diuretics

Loop diuretics inhibit sodium resorption from the renal filtrate in Henle's loop in the medulla. The result is significant increases in renal salt and water excretion. In patients with volume overload, this diuretic action lowers plasma volume, decreasing preload and pulmonary congestion. Although intravenously administered loop diuretics have a rapid onset of action (5–10 minutes), symptom relief in patients with APE often occurs much faster than it could from the diuretic effect alone. These improvements are probably the result of diuretic-induced neurohumoral changes. Furosemide is both a vasodilator, which promotes both renal PGE_2 and natriuretic peptide secretion, and a vasoconstrictor, which stimulates renin release. Loop diuretics (furosemide 1 mg/kg or bumetanide 1 mg/kg) should be administered to patients with hypertensive APE. The half-life of furosemide in patients with APE is double that in healthy volunteers, and caution is required with frequent dosing.

Patients with abrupt onset of APE who do not have underlying chronic HF may have low plasma volumes at presentation. Diuresis in this group of patients may be unnecessary. Patients who fail to respond to loop diuretic administration may have severely compromised renal perfusion. Invasive hemodynamic monitoring may be beneficial in these patients. Diuretic therapy causes depletion of the important cations K^+ and Mg^{2+}, which may be significant in patients already depleted by chronic diuretic therapy or other agents. High-dose diuretic therapy in acute pulmonary edema is associated with deterioration in renal function and increased mortality.[94,95]

Nesiritide

Nesiritide, a recombinant human B-type natriuretic peptide, is a balanced vasodilator that reduces aldosterone and endothelin levels while increasing sodium and water excretion without a resultant reflex tachycardia. The Vasodilatation in the Management of Acute HF (VMAC) trial[96] demonstrates that nesiritide is capable of symptom improvement similar to that produced by intravenous nitroglycerin in HF and, like nitroglycerine, nesiritide improves hemodynamic function while creating a diuresis (natriuretic vasodilator).[97] Nesiritide has not been shown to be superior to nitroglycerin, however, nor to provide additional benefit when added to a treatment regimen that includes intravenous nitroglycerin. These considerations and the high cost of nesiritide relegate its use to selected cases unresponsive to other vasodilator therapy. Meta-analyses of studies of the use of nesiritide in acute HF suggest there may be increased drug-related mortality.[98-100]

Nitroprusside

Nitroprusside is a potent direct smooth muscle relaxing agent that acts as a balanced vasodilator to reduce both preload and afterload. Continuous intra-arterial pressure monitoring is required in patients receiving this drug to avoid precipitous hypotension. Nitroprusside is an attractive drug for patients in hypertensive crisis with pulmonary edema if intra-arterial monitoring is available and can be combined with adequate nurse staffing to avoid an inadvertent hypotensive emergency precipitated by the drug.

In patients with acute myocardial ischemia or infarction, however, nitroglycerin is preferable because it avoids the coronary steal syndrome, in which less diseased vessels dilate and "steal" flow from more diseased vessels. These patients are also particularly vulnerable to unintended hypotension, an event more likely to occur with nitroprusside than nitroglycerin. Patients with renal failure may experience thiocyanate toxicity from high-dose infusions. Cyanide toxicity, recognized clinically by the presence of agitation and lactic acidosis, may occur in individuals with a genetic predisposition.

Other Therapies

Most patients with APE and adequate systemic perfusion respond promptly to treatment with oxygen, morphine, nitrates, and diuretics. Although newer therapies, such as endothelin receptor antagonists,[101,102] vasopressin receptor antagonists,[103-105] beta-endorphins,[106] adenosine antagonists,[107,108] and other agents, have therapeutic potential, further studies will be required to define their utility in acute HF. Ularitide, a synthetic renal natriuretic peptide, has utility in acutely decompensated HF.[109] Levosimendan, a calcium-sensitizing drug that opens ATP-dependent potassium channels, provides prompt hemodynamic improvement in acute HF.[110] In cardiogenic shock treated with percutaneous coronary intervention (PCI), levosimendan improves cardiovascular hemodynamics compared to conventional inotropic therapy.[111] Trials with a tumor necrosis factor antagonist fail to offer benefit in HF.[112] Other previous therapies (e.g., rotating tourniquets, phlebotomy, and theophylline) have no demonstrated efficacy in APE. Endotracheal intubation should be reconsidered if the patient develops severe respiratory deterioration unresponsive to NIV, significant cardiac dysrhythmias, low cardiac output, or has ongoing chest pain.

Treatment of Acute Pulmonary Edema in Hypotensive Patients

Patients with acute cardiogenic pulmonary edema and apparent systemic hypotension present a therapeutic dilemma. Coronary perfusion in patients with coronary artery disease depends on the pressure gradient between the aorta and left ventricular chamber in diastole. The combination of hypotension and elevated left-sided filling pressure dramatically decreases coronary perfusion and leads to further impairment of contractility from increased ischemia. Accordingly, vasopressor administration to maintain coronary perfusion pressure is necessary if this set of conditions truly exists. However, vasopressor therapy can increase afterload, decrease cardiac output, increase myocardial oxygen demand, exacerbate ischemia, and precipitate dysrhythmias. Patients with this clinical condition uniformly have low cardiac output and intense peripheral vasoconstriction. In this situation, noninvasive assessment of arterial pressure is often unreliable.[61] Significant gradients may exist between cuff systolic and true intra-arterial systolic pressures. Intra-arterial pressure monitoring should be instituted as early as is feasible in these patients, which may allow the judicious use of effective and myocardium-sparing vasodilator agents and avoid the use of potentially dangerous vasopressors.

If the patient is truly hypotensive, initial measures should aim to maintain or restore coronary perfusion pressure. In this setting, the patient is either in true cardiogenic shock (pulmonary edema, hypotension, and decreased peripheral perfusion) or volume depleted. Patients in true cardiogenic shock have lost as much as 40% of their ventricular muscle mass. They have both a low cardiac index (<2.2 L/min/m^2) and high left-sided filling pressures (PAOP >15 mm Hg). Patients with depressed perfusion and APE may also be plasma volume depleted, with a cardiac index less than 2.2 L/min/m^2 and PAOP less than 15 mm Hg. It is impossible to distinguish between these two subsets of patients by physical examination alone because both have signs of systemic hypoperfusion and

pulmonary edema. Pulmonary artery catheterization may be needed to accurately assess the hemodynamic status of these individuals.

Nearly 25% of patients with acute myocardial infarction and clinical evidence of systemic hypoperfusion have low PAOP, indicating the presence of hypovolemia. Fluid challenge alone in these patients results in restoration of hemodynamic stability in half the cases. Hypotensive patients with APE should receive a judicious fluid challenge in the form of 250-mL saline boluses over 5 to 10 minutes. If the respiratory status is not deteriorating, repeated aliquots may be administered. If hypovolemia is contributing to the hypotension, this intervention should restore blood pressure and systemic perfusion without the need for vasopressors. If the patient has true cardiogenic shock, more aggressive interventions, including inotropic and vasopressor therapy, intra-aortic balloon counterpulsation, and endotracheal intubation with mechanical ventilation, may be needed. Acute pulmonary edema with systemic hypoperfusion in the setting of acute coronary syndrome represents ischemic cardiogenic shock. Emergency coronary revascularization is the treatment of choice.[113]

Catecholamine Inotropic Agents

In truly hypotensive patients who are adequately volume repleted (cardiogenic shock), norepinephrine is probably the pressor of choice. It raises blood pressure and coronary perfusion pressure (α-vasoconstrictor effect) with a modest β effect for inotropy and the least overall increase in heart rate and contractility that could further increase myocardial oxygen demands. In cardiogenic shock, norepinephrine administration is a temporizing maneuver to maintain coronary perfusion pending rescue strategies such as angioplasty, intra-aortic balloon pumping, or cardiac surgery.

Intravenous inotropic agents with vasodilator properties should be reserved for hypoperfused patients with low cardiac output despite a high left ventricular filling pressure.[114] Dopamine is a naturally occurring catecholamine and a norepinephrine precursor. It has a dose-dependent effect on peripheral vascular tone and is a positive inotropic and chronotropic agent. Despite previous impressions, dopamine in HF has no clinically significant perfusion-sparing effect on the kidneys at any dose.[115,116]

Epinephrine is a potent α- and β-agonist that maintains blood pressure and increases cardiac output. In cardiac surgery patients, it combats myocardial stunning after cardiopulmonary bypass. Dobutamine is a synthetic catecholamine that is mainly a β_2-receptor agonist with some β_1- and α-agonist activity. It is an inotropic vasodilator at therapeutic doses and should be used with caution in patients with borderline hypotension because it occasionally reduces blood pressure further. Isoproterenol is a potent β-agonist that causes profound tachycardia and vasodilation, which would be dangerous in HF.

In patients with acute myocardial infarction or ischemia and severe left ventricular dysfunction, the use of a catecholamine may be counterproductive. Revascularization to reperfuse stunned or hibernating myocardium is preferable.

Digitalis

The cardiac glycosides inhibit the adenosine triphosphatase-dependent sodium-potassium pump in the cell membrane of the cardiac myocyte. This inhibition increases the availability of intracellular calcium to contractile proteins in myocardial cells, increasing the force of myocardial contraction, with modest inotropic effect. In the setting of acute myocardial infarction with pulmonary congestion, digitalis has minimal potency in improving hemodynamics compared with dobutamine. Digitalis preparations have little role in acute HF. Formerly, digitalis was used to control the ventricular response rate in atrial flutter or fibrillation. In this clinical situation, however, diltiazem is a more prompt and safe alternative to digoxin in normotensive patients.[117]

Other Cardiotonic Agents

Amrinone is the prototype of phosphodiesterase type III inhibitors, which produce increased levels of cyclic adenosine monophosphate in the myocardium and peripheral smooth muscle. Only intravenous forms of amrinone and milrinone are approved by the Food and Drug Administration for use in HF. These intravenous vasodilating inotropic agents increase cardiac output and reduce left ventricular pressures without producing significant changes in heart rate and blood pressure. The positive inotropic effects of amrinone and dobutamine are additive, and concomitant use of both drugs appears to be better tolerated than high dosing of dobutamine alone, with lower metabolic costs. Nevertheless, long-term use of phosphodiesterase type III inhibitors reduces survival in HF in functional NYHA classes III and IV.[118] These agents appear to be prodysrhythmic. Amrinone and milrinone may be useful on a short-term basis in patients awaiting heart transplantation. They should be used with caution in selected patients—in general in the context of invasive hemodynamic monitoring.

Treatment of Heart Failure without Pulmonary Congestion

Occasionally, HF may lead to hypoperfusion without significant pulmonary congestion. For example, patients with dysfunction because of congestive cardiomyopathy may have had excessive diuresis or developed a dysrhythmia that has negatively affected pump function without creating pulmonary edema. Other entities to consider include septic shock and massive pulmonary embolus. Hypotension in this situation may not be pathologic because chronic adaptive changes and medical therapies may leave patients with a low blood pressure that is well tolerated. Clamminess, cyanotic extremities, altered mental status, metabolic acidosis, and decreased urine output are some of the important findings that help define significant hypoperfusion. If hypoperfusion is present, cautious volume challenge is instituted with isotonic crystalloid. Invasive hemodynamic monitoring may be indicated because chamber filling pressures help define the cardiovascular pathology.

Acute right ventricular infarction is one important cause of hypoperfusion with jugular venous distention and absent pulmonary congestion. Approximately one third of patients with acute inferior infarction have significant right ventricular involvement, which leads to inadequate pulmonary perfusion and low left ventricular priming. These patients have hypotension that is often symptomatic. Jugular venous distention is prominent, but pedal edema is usually absent. These patients often have evidence of ST segment elevation or depression in the V_1 lead. Right-sided leads may provide further evidence of right ventricular infarction. Large volume crystalloid resuscitation followed by inotropic support with norepinephrine or dopamine may be required to provide adequate preload to the left ventricle and restore blood pressure.

Treatment of Chronic Heart Failure

Patients with chronic HF often have complex multiorgan dysfunction and polydrug medical regimens. In this clinical setting, the potential impact of any therapeutic intervention

Table 79-2 HF Management Recommendations for Patients in New York Heart Association Class I or II with Stage A, B, or C Disease

STAGE OF HF	MANAGEMENT RECOMMENDATIONS
A (High risk of developing HF)	Risk factor management (e.g., control of hypertension, diabetes, lipid disorders; smoking cessation; avoidance of alcohol and illicit drugs) Use of ACE inhibitor in patients with atherosclerotic disease, hypertension, diabetes, or other risk factors Control of ventricular rate in patients with supraventricular tachyarrhythmias Treatment of thyroid disorders Periodic evaluation for signs and symptoms of HF Recommendations for stage A
B (Left ventricular dysfunction without symptoms)	Use of ACE inhibitor in patients with history of myocardial infarction or reduced ejection fraction regardless of history of myocardial infarction Use of beta-blocker in patients with history of myocardial infarction or reduced ejection fraction regardless of history of myocardial infarction Valve replacement or repair in patients with hemodynamically important valvular disease Long-term use of systemic vasodilator in patients with severe aortic regurgitation Recommendations for stages A and B
C (Symptomatic left ventricular dysfunction)	Use of diuretic in patients with fluid retention Use of ACE inhibitor in all patients unless contraindicated Use of digitalis to treat symptoms unless contraindicated Discontinuation of drugs known to affect patient status adversely (e.g., nonsteroidal anti-inflammatory drugs, most antiarrhythmic drugs, calcium channel blockers) Use of spironolactone in patients with class IV symptoms, preserved renal function, normal potassium levels Exercise Use of angiotensin II receptor blocker in patients treated with digitalis, diuretics, or beta-blockers who cannot tolerate ACE inhibitors because of cough or angioedema Use of hydralazine-nitrate combination in patients treated with digitalis, diuretics, or beta-blockers who cannot take ACE inhibitors because of hypotension or renal insufficiency Addition of angiotensin II receptor blocker to ACE inhibitor Addition of nitrate, alone or with hydralazine, to ACE inhibitor, digitalis, diuretic, or beta-blocker

ACE, angiotensin-converting enzyme; HF, heart failure.

on the entire spectrum of disease and compensatory mechanisms should be considered. For example, adding an NSAID to the medical regimen of a patient with chronic HF may negatively affect renovascular function and precipitate increased fluid retention and pulmonary edema.[59] Chronic HF often involves a much more gradual onset of symptoms, with a slow increase in dyspnea with minimal exertion, progressive orthopnea, fatigue, and other symptoms.

U.S. guidelines approved by the AHA and ACC reflect a new classification system for chronic HF that includes four categories: patients at risk, patients with asymptomatic left ventricular dysfunction, patients with symptomatic HF, and those with refractory HF (Table 79-2). The number of patients with asymptomatic HF is approximately fourfold greater than the number of patients with symptomatic HF.[119] Echocardiography is a very useful modality in screening for asymptomatic left ventricular dysfunction in high-risk subgroups,[120] which has an estimated prevalence of 3 to 6% and is at least as common as systolic HF.[36]

A most important advance in the management of HF is to modify long-term maladaptive responses as well as achieve short-term functional improvement.[121] Ideally, treatment should be initiated in patients at risk to prevent disease progression. Atherosclerotic coronary artery disease, hypertension, diabetes mellitus, hyperlipidemia, cocaine and ethanol abuse, smoking, and obesity are significant risk factors for HF.[122] Hypertension precedes HF in 75% of patients, particularly in blacks. Approximately two thirds of patients with systolic HF have significant coronary artery disease. Control of hypertension reduces the risk of developing HF,[123] as does control of dyslipidemias among patients with atherosclerosis. Patients with diabetes mellitus have more than a threefold increased risk of cardiac ischemic events and HF.[124] High dietary sodium is associated with impaired diastolic relaxation.[125] Appropriate lifestyle changes, including smoking cessation, weight reduction, restriction of salt and water intake, and modest exercise, reduce symptoms in HF and may delay progression. Excessive lipid accumulation within the myocardium is directly cardiotoxic and causes left ventricular remodeling and dilated cardiomyopathy.[126] Substantial weight loss in patients with HF associated with obesity produces a reversal of many of the clinical manifestations and improves NYHA functional class in most patients.[127,128] In patients with persistent atrial fibrillation and mild to moderate chronic HF, rate control is not inferior to rhythm control.[129]

There is significant variability in the adherence to HF quality-of-care issues in the United States.[130] Initiation of proven therapeutic modalities at hospitalization leads to early benefits, including decreased risks of mortality and rehospitalization for HF.[131,132]

The left ventricular remodeling process is triggered by volume or pressure overload as well as loss of cardiac myocytes (e.g., myocardial infarction). Therapeutic interventions in HF aim to slow the remodeling process. Ventricular remodeling correlates with other clinical outcomes in HF,[133] and serial measurements of various neurohormones may serve as surrogate markers of ventricular remodeling.[134] Various antihypertensive therapies allow regression of left ventricular hypertrophy and reduce the rate of sudden cardiac death.[135] Reverse remodeling is a new concept in which progressive left ventricular dysfunction is not simply arrested but also partially reversed.[136] Beta-blockers, ACE inhibitors, aldosterone antagonists, and angiotensin receptor blockers are all able to inhibit or reverse remodeling.[137,138]

The mainstay of treatment for chronic HF and asymptomatic left ventricular dysfunction is vasodilator therapy, which benefits pump function by reducing both afterload and preload. The most important vasodilators for chronic HF are ACE

inhibitors, angiotensin II receptor antagonists, and nitrates. In general, exacerbations of chronic HF require admission if the cause of the exacerbation cannot be readily recognized and corrected, if the disease process has become unstable because of increased ischemia or new dysrhythmia, or if clinical deterioration of the patient appears likely.

Angiotensin-Converting Enzyme Inhibitors

ACE inhibitors provide the most effective therapy for left ventricular dysfunction. ACE inhibitors increase survival in all classes of chronic HF and are also useful to prevent the development of HF in patients with myocardial infarction and asymptomatic left ventricular dysfunction.[139-141] The actions of ACE inhibitors inhibit production of angiotensin II, producing direct vasodilation in addition to a natriuretic effect mediated by inhibition of aldosterone secretion. Additional ACE inhibitor effects include inhibition of the degradation of bradykinin and reduction of intrinsic endothelium-dependent vasoconstriction.[142] ACE inhibitors are natriuretic vasodilators that reduce diuretic and potassium supplement requirements. Unlike other vasodilators, they do not induce reflex tachycardia.

The main side effects of ACE inhibitors are hypotension, deterioration of renal function, chronic cough, and upper airway angioedema. ACE inhibitors should be initiated at low doses with careful attention to the potential for hypotension, with concomitant reduction in diuretic and potassium supplementation. Optimal ACE inhibitor dosing, however, appears to be neglected in many patients with HF, particularly elderly patients.[143,144] In patients with chronic HF, high-dose aspirin (>325 mg/day) may impair some clinical benefits of ACE inhibitors.[145]

Angiotensin II Receptor Blockade

In HF patients intolerant of ACE inhibitors, angiotensin type 1 (AT_1) receptor blockers (ARBs) have utility.[146] ARBs appear to avoid the side effects of cough and bradykinin accumulation. Two studies comparing AT_1 receptor antagonists with ACE inhibitors in symptomatic HF fail to show superiority of either drug type.[147,148] AT_1 receptor antagonists have theoretical utility in patients on ACE inhibitors because angiotensin II can be produced by pathways unaffected by ACE inhibitors, and chronic ACE blockade leads to upregulation of the AT_1 receptor. Addition of ARBs to maximally tolerated doses of ACE inhibitors improves hemodynamic features in patients with chronic HF and enhances peak exercise capacity while alleviating symptoms. In a meta-analysis of 17 trials comparing angiotensin II receptor blockers with ACE inhibitors, ARBs were not superior to ACE inhibitors in reducing mortality or hospitalization for HF.[149-151] The combination of an ARB and an ACE inhibitor was superior to an ACE inhibitor alone for reducing hospitalizations but not mortality. ARBs are most useful in patients intolerant of ACE inhibitors.[152,153] Both ACE inhibitors and ARBs allow reverse remodeling in HF.[154]

Nitrates

Nitrate therapy, by virtue of a direct vasodilator effect, improves exercise tolerance in chronic HF. When used in combination with the arteriolar dilator hydralazine, it also prolongs survival in patients with HF, but less so than ACE inhibitors. However, ACE inhibitors are less effective in African Americans. A fixed-dose isosorbide dinitrate/hydralazine regimen is particularly effective in chronic HF in African Americans,[155] reducing hospitalization by 39% and mortality by 43%,[156,157] with these positive effects sustained over time.[158,159] Nitrate therapy offers potential hemodynamic improvement in patients already taking ACE inhibitors.[160] The main problem with nitrate therapy appears to be rapid drug tolerance, which can be partially addressed by daily nitrate drug-free intervals.

Calcium Channel Blockers

First-generation calcium channel blockers (verapamil, diltiazem, and nifedipine) do not improve survival in chronic HF and may precipitate clinical deterioration.[161] Second-generation dihydropyridines (nicardipine and amlodipine) have more moderate negative inotropic effects. Amlodipine reduces fatal and nonfatal cardiac events in nonischemic but not in ischemic heart disease.[162] There is no compelling evidence for the use of calcium channel blockers in HF, although they may be used in patients intolerant of beta-blockers, ACE inhibitors, ARBs, and combined nitrates plus hydralazine.[163] Calcium channel blockers are indicated for the treatment of hypertension, angina, and dysrhythmias, but they should be used with caution, if at all, in patients with associated chronic HF.[164]

Beta-blocker Therapy

Despite the apparent paradox of using agents that reduce myocardial contractility, beta-adrenergic blocking agents have significant efficacy in chronic HF. Long-term activation of the sympathetic nervous system in HF, activation of the renin-angiotensin-aldosterone system, myocardial beta-adrenergic receptor downregulation, and direct cardiotoxicity because of elevated norepinephrine levels are associated with adverse effects. An extensive meta-analysis revealed that beta-blockers in chronic HF increase ejection fraction by 29%, reduce mortality by 30%, and reduce hospitalization by 40%.[165-167] The AHA/ACC guidelines recommend beta-blockers for all patients with symptomatic left ventricular systolic dysfunction.[168]

Beta-blockers should not normally be initiated in acute HF. They are most useful in chronic HF associated with other conditions in which there are indications for beta-blocker therapy, including hypertension, angina pectoris, and significant dysrhythmias. Slow upward titration of beta-blocker therapy facilitates maximal tolerability.[169] Carvedilol, a third-generation alpha- and beta-blocker with antioxidant properties, may be a particularly effective agent in chronic HF.[170-173] In one large study comparing metoprolol to carvedilol for HF, the number needed to treat was 15 to prevent one excess death at 5 years for carvedilol.

Diuretics

Patients with chronic HF exhibit a reduced ability to excrete a sodium and water load, with abnormal cardiac and hemodynamic adaptations to salt excess.[174] Low-dose diuretics are one of the most effective treatments to prevent the recurrence of HF.[175] Loop diuretics, although commonly used, are associated with significant side effects, including hypovolemia, electrolyte disturbances (low K^+, Mg^{2+}, and Na^+), hyperuricemia, and metabolic alkalosis. The use of potassium-sparing diuretics in HF is associated with a reduced risk of death. The hypokalemia and hypomagnesemia secondary to diuretic therapy are believed to be prodysrhythmic.

In patients hospitalized for HF exacerbation, admission serum sodium is an independent predictor for increased days of hospitalization for cardiovascular causes and increased mortality within 60 days of discharge.[176-178] Persistent hyponatre-

mia is an independent predictor of mortality, hospitalization for HF, and death or rehospitalization despite clinical and hemodynamic improvements similar to those in patients without hyponatremia.[179]

Spironolactone and eplerenone directly antagonize aldosterone. They significantly reduce mortality while improving left ventricular function in patients with severe HF (ejection fraction <35%) already being treated with an ACE inhibitor and a loop diuretic, with or without digoxin.[180] In the Randomized Aldactone Evaluation Study (RALES), in which patients were appropriately managed medically, 2-year mortality was 46% for the placebo group and 35% for the spironolactone group.[181] Spironolactone reverses remodeling in patients with mild to moderate chronic systolic HF.[182] Eplerenone, when used in addition to standard therapy, results in significant reduction in morbidity and mortality in patients post-acute myocardial infarction.[183-185] Aldosterone antagonists may lead to serious hyperkalemia in the presence of significant renal insufficiency or in patients taking supplemental potassium.

Cardiac Glycosides

Digoxin is of benefit in patients with all degrees of chronic HF by reducing symptoms and improving quality of life and exercise tolerance.[186] Digoxin reduces the rate of hospitalization in chronic HF, and it reduces mortality when added to ACE inhibitor and diuretic therapy.[187] Digoxin should be used for most persistently symptomatic HF patients whose treatment already includes ACE inhibitors, diuretics, and beta-blocker therapy when HF is caused by systolic dysfunction. Digoxin appears to have no beneficial effects in mild to moderate diastolic HF.[188]

Other Therapeutic Interventions in Chronic Heart Failure

Phosphodiesterase Inhibitors

There is no indication for long-term amrinone or milrinone therapy, which increases morbidity and mortality in patients with severe chronic HF.[189,190] Other agents in this class have limited efficacy associated with increased mortality. Phosphodiesterase inhibition with sildenafil, used commonly for erectile dysfunction, is safe in HF[191] and may have other beneficial effects, including improved cardiac output and exercise capacity.[192-194] Long-term use of sildenafil in chronic HF improves exertional ventilation and aerobic efficiency.[195]

Statins

Statins improve endothelial function and have anti-inflammatory, antioxidative, and immunomodulatory effects that are beneficial in patients with chronic HF.[196-202] Early use of statin therapy within 96 hours of acute myocardial infarction reduces the risk of HF.[203] Atorvastatin in nonischemic HF with moderately decreased cardiac function improved left ventricular ejection fraction, NYHA classification, and reduced serum levels of multiple inflammatory markers.[204,205] Simvastatin use reduced the risk of HF by 14% in a high-risk population and also decreased the risk of major vascular effects.[206] Statin therapy is associated with lower mortality among patients with severe HF.[207,208]

Ultrafiltration and Renal Dialysis

Ultrafiltration reduces volume overload when diuretic therapy is inadequate.[209,210] In decompensated HF, ultrafiltration may be more effective than intravenous diuretics in volume-overloaded states.[211,212] Renal dialysis is important for HF treatment in end-stage renal disease. Potential complications of renal disease that may require special consideration include fluid overload, severe hyperkalemia, iatrogenic hypermagnesemia, uremic pericardial effusion, and drug toxicity (especially digitalis).

Anemia

An aggressive approach to anemia in chronic HF using iron supplements and intermittent erythropoietin improves NYHA-class,[56,213] sleep-related breathing disorders,[214] cardiac and renal function, as well as need for hospitalization.[215]

Sleep Apnea–Related Respiratory Support

Obstructive sleep apnea is more prevalent in chronic HF than previously recognized, and treatment with CPAP can be therapeutic,[216-218] even improving left ventricular ejection fraction and heart transplant-free survival.[219,220] Continuous positive airway pressure for central sleep apnea and HF improves nocturnal oxygenation, ejection fraction, central sleep apnea, and exercise capacity but does not improve survival.[221]

Exercise Programs

Various exercise programs in chronic HF show mixed benefits in terms of functional status and quality of life, but they seem to reduce rehospitalization rates.[222-225]

Depression

Depression is common in patients with HF, and treatment can improve psychological aspects of quality of life,[226,227] although antidepressant medications may be associated with increased hospitalization and death.[228]

Coronary Artery Bypass Grafting and Angioplasty

Although there is little consensus regarding the role of revascularization in the management of ischemic cardiomyopathy, registry data suggest a benefit of coronary artery bypass grafting over percutaneous coronary intervention in HF.[229] Another study shows no advantage in preventing HF, death, or reinfarction in stable patients with occlusion of the infarct-related artery 3 to 28 days after myocardial infarction.[230]

Antidysrhythmic Therapy

From 70 to 95% of patients with cardiomyopathy and HF have frequent premature ventricular beats, and 40 to 80% develop nonsustained ventricular tachycardia.[231] An associated increased risk of sudden death exists in these patients. An extensive meta-analysis shows a 15% reduction in total mortality with amiodarone, with arrhythmic sudden death reduced by 29%.[232] In chronic HF, amiodarone prevents the development of atrial fibrillation and converts significantly more patients with atrial fibrillation to sinus rhythm.[233,234] Amiodarone is also useful in acute management of sustained ventricular tachyarrhythmias. Unfortunately, amiodarone and other antidysrhythmic agents have significant toxicities and may be prodysrhythmic. In a study of patients with post-myocardial infarction LV systolic dysfunction with or without HF, amiodarone was associated with increased early and late all-cause and cardiovascular mortality.[235]

Implantable Defibrillators and Pacemakers

Implantable cardioverter-defibrillators (ICDs) have a mortality advantage over antiarrhythmics in chronic HF,[14,236] although that advantage does not exist in nonischemic dilated cardiomyopathy with asymptomatic nonsustained ventricular tachycardia. In patients with previous myocardial infarction with ejection fraction below 35%, nonsustained ventricular tachycardia, and inducible ventricular tachycardia not suppressible by procainamide, ICD placement reduced sudden death by 54% at 2 years.[237] A follow-up study demonstrated a 29% reduction in all-cause mortality with ICDs in patients with a history of myocardial infarction and a left ventricular ejection fraction less than 30%. The economic as well as clinical impact of these studies awaits further clarification.[238]

Patients with severe HF with significant left ventricular dyssynchrony benefit from atrioventricular sequential pacing.[239-241] Right ventricular apical pacing is often used in chronic HF but creates abnormal left ventricular contraction, hypertrophy, and reduced pump function.[242] Left or biventricular pacing allows more physiologic LV contraction, and both were equally effective in one study.[243] Cardiac resynchronization therapy via left or biventricular pacing attempts to coordinate the activation of the interventricular septum and left ventricle free wall in HF with significant contractile dyssynchrony.

Optimal lead positioning using three-dimensional echocardiographic guidance maximizes the effectiveness of cardiac resynchronization therapy.[244,245] Cardiac resynchronization therapy improves HF symptoms and exercise capacity, and it can reverse chronic cardiac dilation.[246-254] Cardiac resynchronization therapy combined with implantable cardioverter-defibrillator greatly reduces the risk of sudden cardiac death.[255-260] Cardiac resynchronization therapy reduces functional mitral regurgitation at rest.[261] Intrathoracic impedance monitoring is available on some devices to continuously monitor hemodynamic status in HF.[262,263] Also, ventricular pacing after atrioventricular node ablation appears to be more effective than pharmacologic therapy for HF with chronic atrial fibrillation.[264]

Left Ventriculoplasty, Ventricular Assist Devices, and Transplantation

Batista and colleagues stunned the medical community in 1996 by reporting a pilot trial of partial left ventriculoplasty in the treatment of chronic HF.[265] Simplistically, the surgery is a mechanical method of reducing left ventricular chamber size, which by Laplace's law should make the residual myocardium more efficient by reducing left ventricular workload. After a promising beginning, left ventriculoplasty has largely been abandoned because of failure to demonstrate long-term efficacy in HF. It is still being performed with perceived benefit during coronary artery bypass grafting in patients with a dilated left ventricle.[266,267]

Multiple implantable left ventricular assist devices are in various trial stages for chronic HF as a bridge to transplantation and as a surgical alternative to chronic medical management.[268-273] An innovative elastic ventricular restraint device is reliably implantable in HF patients with severe left ventricular dysfunction, with apparent functional and clinical benefit.[274] Heart transplantation is still the most effective therapy for end-stage HF, with 84% survival at 1 year, 75% survival at 3 years, and a 10-year survival rate approaching 50%.[275,276] The limited availability of donors (2500 heart transplants per year in the United States),[277] however, makes alternative surgical techniques of interest in end-stage HF. Cell transplantation techniques using neonatal or fetal cardiac myocytes or even skeletal myoblasts may become viable techniques to repair the failing myocardium,[278] and there is increasing evidence that stem cell therapy may offer promise in chronic HF.[279-281] Skeletal myoblast transplantation in a post-myocardial infarction scar experimentally improves left ventricular election fraction but increases arrhythmic risk.[282] Autologous stem cell transplantation led to significant improvement in cardiac function in patients undergoing coronary artery bypass grafting for ischemic cardiomyopathy.[283]

SUMMARY

Diagnosis and management of patients with HF in the emergency department remain challenging aspects of emergency medicine. Advances in the chronic medical management of HF, including the routine use of beta-blockers, ACE inhibitors, diuretics including spironolactone, and occasionally digoxin and ARBs, have resulted in sustained symptomatic improvement and reduced 5-year mortality. Despite these advances, HF exacerbation remains among the most frequent conditions resulting in emergency department visits and hospital admissions. The increased pharmacologic armamentarium presents a challenge for emergency physicians to care for HF appropriately.

Abrupt-onset APE and cardiogenic shock also require deliberate consideration of all differential diagnostic entities. A sound understanding of the pathophysiology and pharmacotherapy allows rewarding results when caring for this frequently encountered and ever challenging diverse group of patients.

KEY CONCEPTS

- Hypoperfusing patients with acute pulmonary edema and systemic hypotension may have acute plasma volume depletion and require a fluid challenge.
- In HF, patients with decompensated aortic stenosis should not receive vasodilator agents; in contrast, patients with mitral regurgitation benefit greatly.
- Patients with acute right ventricular infarction may present with distended neck veins but require a fluid challenge.
- Patients with acute cardiogenic pulmonary edema have low cardiac output and intense peripheral vasoconstriction. Noninvasive assessment of arterial pressure is notoriously unreliable.
- Approximately 50% of cases of HF involve mainly diastolic dysfunction.
- Aggressive treatment of risk factors for HF may prevent the development of HF.
- Neurohormonal mechanisms are ultimately deleterious in HF. Chronic therapy to negate these effects is important even in asymptomatic myocardial dysfunction.
- Emergent BNP laboratory assays objectively quantify and treat acute HF.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 80

Pericardial and Myocardial Disease

Nicholas J. Jouriles

PERICARDIAL DISEASE (PERICARDITIS)

PERSPECTIVE

Knowledge regarding pericardial function and disease has increased greatly since Hippocrates described the pericardium in 460 BC as "a smooth tunic that envelops the heart and contains a small amount of fluid resembling urine." Galen provided the first description of a pericardial effusion and performed the first pericardial resection.[1] Lancisi first described the appearance of constrictive pericarditis at autopsy in 1728. Also in the 18th century, Laennec said, "There are few diseases attended by more variable symptoms and more difficult to diagnose than [pericarditis]."[1] In the 1930s, Beck described the clinical presentation of cardiac tamponade, which is known as *Beck's triad* (hypotension, jugular venous distention, and muffled heart sounds).[2] Despite the availability of many diagnostic tools, recognition of pericardial disease still presents a challenge.

ETIOLOGY

Each of the disorders listed in Box 80-1 can produce acute pericarditis, with or without pericardial effusion. In addition, most of these disorders can progress to cardiac tamponade or constrictive pericarditis.

Most cases of pericarditis are idiopathic. Even exhaustive clinical testing identifies a specific etiology in less than 20% of patients, with the remainder being considered idiopathic.

EPIDEMIOLOGY

Acute pericarditis is a syndrome caused by inflammation of the pericardium. Although the exact incidence is unknown, autopsy series show an incidence of pericarditis of approximately 5%. The incidence of pericarditis in the emergency department is not known.

PRINCIPLES OF DISEASE

Pericardial Anatomy and Physiology

The normal pericardium envelops the heart and attaches to the great vessels. It consists of parietal and visceral layers, with a narrow potential space between them. The visceral layer or epicardium adheres to the myocardium. It is separated from the parietal layer by a potential space. Each layer is 1 or 2 mm thick and is composed of elastic fibers. The position of the heart within the chest is stabilized by the attachment of the parietal pericardium to the sternum, to the diaphragm inferiorly, and to the vertebral column posteriorly. Its blood supply comes from the internal mammary artery and its nerve supply from the phrenic nerve.[3]

An ultrafiltrate of plasma, 15 to 35 mL of fluid, is normally contained in the pericardial space. Abnormal amounts of pericardial fluid can accumulate when the venous or lymphatic drainage of the heart is obstructed. The pericardium serves several functions: it maintains the heart's position, lubricates the heart's surface, prevents the spread of infection, prevents cardiac overdilation, augments atrial filling, and maintains the normal pressure-volume relationships of the cardiac chambers. Patients with congenital absence (or surgical removal) of the pericardium show few, if any, problems.

PATHOPHYSIOLOGY

The inflammation of pericarditis is characterized by a granulocytic and lymphocytic infiltration of the pericardium. There is an increase in the number of antibodies in the pericardial fluid.

IDIOPATHIC PERICARDITIS

Clinical Features

The classic symptoms of pericarditis include chest pain, pericardial friction rub, and electrocardiogram (ECG) abnormalities. A history of fever and myalgia is common. Pericarditis chest pain is usually sharp, pleuritic, and varies with respiration. It is typically relieved by sitting forward and is worsened by lying down, deep inspiration, or swallowing. It uncommonly may mimic myocardial infarction (MI) pain. Pericarditis pain is usually retrosternal, can radiate to the trapezius muscles, and may present as isolated shoulder pain. Pain can also be felt over the diaphragm.

The physical examination hallmark of acute pericarditis is the pericardial friction rub. The rub may be caused by friction between inflamed or scarred visceral and parietal pericardium or may result from friction between the parietal pericardium and adjacent pleura. It may be audible anywhere over the anterior chest wall but usually is best heard at the lower left sternal border. Friction rubs are best heard using the diaphragm of the stethoscope, with the patient in the sitting position holding his or her breath. The rub tends to be inter-

BOX 80-1 ETIOLOGY OF PERICARDITIS

Infectious
- Viral
- Bacterial
- Fungal
- Parasite
- Rickettsia

Post Injury
- Trauma
- Surgery
- Myocardial infarction
- Radiation

Metabolic Diseases
- Uremia
- Medications

Systemic Diseases
- Rheumatoid arthritis
- Systemic lupus erythematosus
- Sarcoidosis
- Scleroderma
- Dermatomyositis
- Amyloidosis

Tumors

Aortic Dissection

mittent, migratory, and difficult to hear in a loud emergency department.

Diagnostic Strategies

There is no single test that is diagnostic for pericarditis. The ECG is the most reliable diagnostic tool. It evolves through stages that occur over time, but there is rarely the luxury of performing serial tracings. The first stage occurs in the first hours to days of illness. It includes diffuse ST segment elevation seen in leads I, II, III, aVL, aVF, and V_2 through V_6 and also reciprocal ST segment depression in aVR and V_1. Most patients with acute pericarditis have concurrent PR segment depression (Fig. 80-1). In the next stages, the ST and PR segments normalize, but the T waves flatten, and then there is deep, symmetrical T wave inversion. At the last stage, the ECG reverts to normal, although the T wave inversions may become permanent.[4]

The early ECG findings of acute pericarditis may be difficult to distinguish from those of acute MI, coronary artery spasm, or benign early repolarization. The differentiation of acute MI from acute pericarditis is essential. Thrombolytic therapy is contraindicated in pericarditis because its use may precipitate hemorrhagic cardiac tamponade. In contrast to the ECG in acute MI, the ST segment elevations in stage 1 acute pericarditis are concave upward rather than convex upward, and simultaneous T wave inversions are not seen. Subsequent tracings do not evolve through a typical MI pattern, and Q waves do not appear.

Ventricular dysrhythmias are rare in pericardial disease. Patients with pericarditis who have ventricular dysrhythmias should be presumed to have concomitant myocarditis, another cardiac disease, or to have been misdiagnosed.

Echocardiography facilitates the definitive diagnosis of pericarditis with effusion, although it will be normal in patients without significant effusion, and a normal echocardiogram cannot be used to exclude pericarditis. In addition, cardiac tamponade, increased pericardial thickness, pericardial tumors and cysts, constrictive pericarditis, and the congenital absence of the pericardium can all be diagnosed by echocardiography.

Some patients with acute pericarditis have elevated cardiac markers caused by myopericarditis, myocarditis, or MI. The white blood cell count and erythrocyte sedimentation rate (ESR) may be elevated but are insensitive and nonspecific. Other laboratory studies should be directed at determining nonidiopathic causes of pericarditis.

Management and Disposition

If a specific cause of pericarditis is found, therapy should be specific for that etiology.[4] Otherwise, therapy of acute pericarditis is symptomatic. Control of inflammation will reduce pain, and a nonsteroidal anti-inflammatory drug (NSAID) is the treatment of first choice. Ibuprofen has the best side effect profile and is prescribed in anti-inflammatory doses (2400 mg/day in adults), but other NSAIDs should be equally effective. Ketorolac is expensive and has a poor anti-inflammatory effect, so it is not recommended. The patient will often report significant pain relief from the analgesic effect of the ibuprofen while in the emergency department, even before the onset of the anti-inflammatory effect. If the chosen NSAID is not effective within 1 week, a different class of NSAIDs is chosen. Oral prednisone is the therapy for chronic pericarditis and for acute pericarditis in patients who cannot tolerate NSAIDs. Methylprednisolone and colchicine are also effective for recurrent pericarditis.

Complications

The clinical course of pericarditis is variable: 60% of patients have complete recovery within 1 week, and almost 80% have complete recovery within 3 weeks. Eighteen percent of patients can have recurrent pericarditis, which may require serial echocardiography to exclude effusion or tumor.[5]

UREMIC PERICARDIAL DISEASE

Perspective and Etiology

Pericarditis may occur secondary to end-stage renal disease or may be associated with dialysis. It occurs more frequently in patients receiving hemodialysis than those receiving peritoneal dialysis. Acute renal failure is also associated with pericarditis. The etiology is unknown, but possibilities include toxic metabolites, bleeding of uremia, and infectious or immunologic mechanisms. The evaluation of a chronic renal disease patient with pericarditis requires a diligent search for infectious causes.

Clinical Features and Diagnostic Strategies

Patients with uremic pericarditis present with chest pain, unexplained fever, and possibly a coarse friction rub. They also may have significant effusions. The ECG in uremic pericarditis is often normal because little epicardial inflammation occurs.[6] In a dialysis patient, cardiac enlargement on chest radiograph in the absence of signs of volume overload or congestive heart failure (CHF) should prompt consideration of pericardial effusion, and an echocardiogram will provide a definitive answer. Uremic pericarditis has an effusion that is

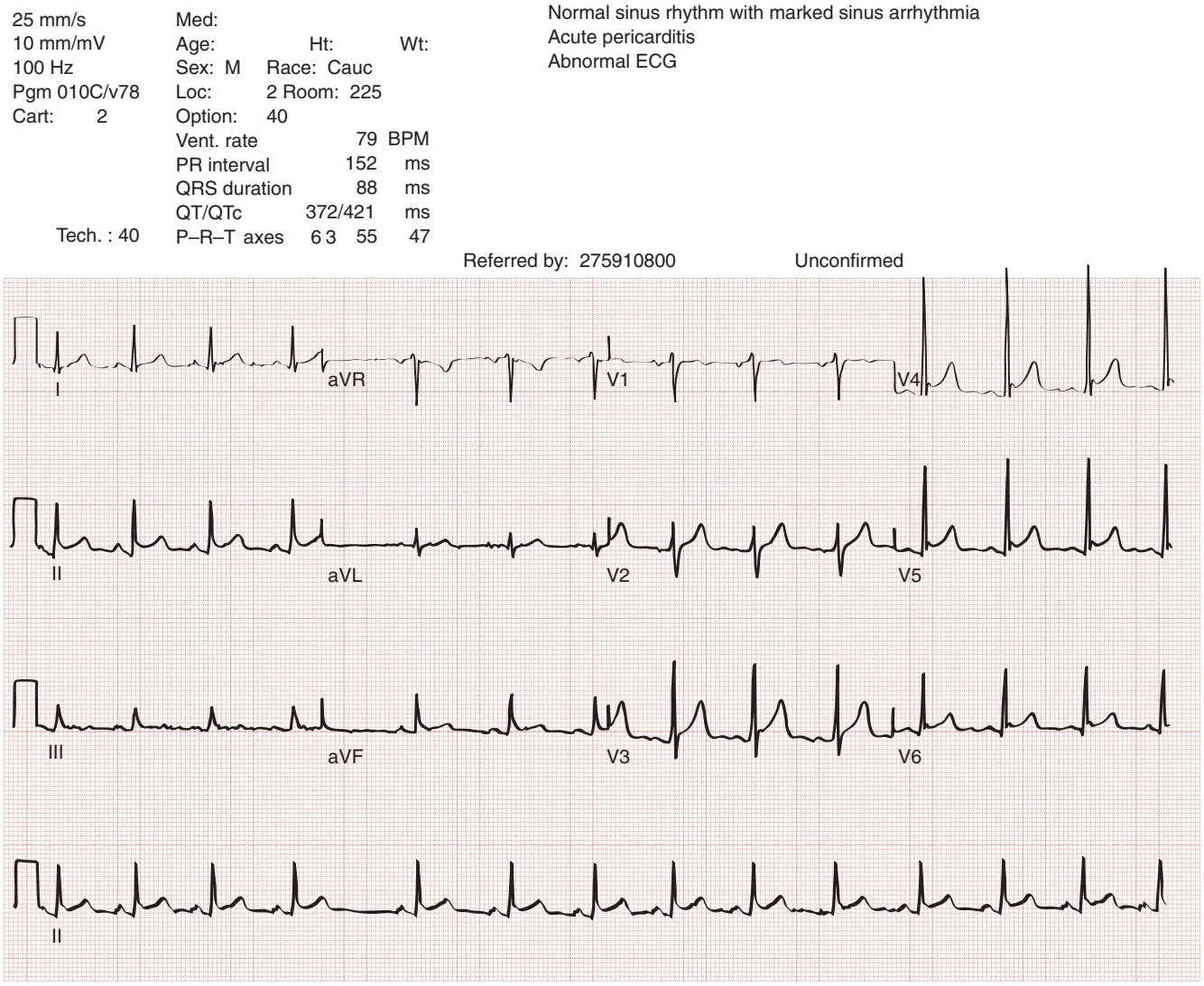


Figure 80-1. Electrocardiogram showing acute pericarditis. (Courtesy of the Ohio Chapter of the American College of Emergency Physicians.)

fibrinous and often grossly bloody. Diagnostic pericardiocentesis may be needed to exclude infection.

Management and Disposition

Uremic pericarditis is initially treated with intensive dialysis. NSAIDs are ineffective. Systemic steroids are often used but may require 1 or 2 weeks of therapy to produce a response.

Complications

Uremic pericardial effusions are among the most common causes of cardiac tamponade. Uremic pericardial effusions may be locular and difficult to drain fully with a catheter. Surgical options include a pericardial window or pericardiectomy.

POST-MYOCARDIAL INFARCTION PERICARDITIS

Approximately 20% of patients with transmural MIs experience a different quality of chest pain 2 to 4 days after infarction. This pain may represent early post-MI pericarditis. There is frequently low-grade fever and a transient pericardial friction rub. A large pericardial effusion is unusual. Early post-MI pericarditis is generally short-lived and disappears with 1 to 3 days of aspirin therapy.

The ECG changes of pericarditis usually are masked by the acute MI changes. Patients with early post-MI pericarditis have more dysrhythmias and heart failure. Pericarditis in acute MI may be an indicator of greater myocardial damage and a worse outcome.

Dressler[7] reported a syndrome of fever, pleuritis, leukocytosis, pericardial friction rub, and chest radiograph evidence of new pericardial or pleural effusions in 10 post-MI patients. Frequent relapses and a high incidence of friction rubs led Dressler to describe this syndrome as a delayed complication of MI in contrast to the well-known syndrome of early post-MI pericarditis. The etiology of late post-MI pericarditis (Dressler's syndrome) may be immunologic. It may also be seen with pulmonary embolus and after pericardiotomy. Anticoagulants should be discontinued to reduce the risk of hemorrhage. Delayed, post-MI pericarditis is treated with NSAIDs or aspirin; steroids and colchicine are alternatives.

POST-TRAUMATIC PERICARDITIS

Perspective

Post–cardiac injury syndrome is defined as pericarditis after MI, cardiac surgery, or trauma. The incidence ranges from approximately 5% after MI to 30% after thoracic surgery or trauma. Pericarditis develops in 20% of patients with a penetrating cardiac injury, few of whom have cardiac tamponade.

Principles of Disease

Injury to the pericardium in blunt trauma may range from contusion to laceration or rupture. Some degree of traumatic pericarditis is found during surgery or at autopsy in many patients sustaining severe blunt trauma of the chest.

Penetrating wounds to the heart usually cause laceration of the pericardium and the myocardium, with secondary pericarditis and pericardial infections. Although the exact incidence is unknown, infection, tamponade, myocarditis, and inflammatory pericarditis may occur.

An immune pathogenesis is suggested by the development of cardiac autoantibodies, although these autoantibodies are common after injury, even in patients who do not develop pericarditis. Constrictive pericarditis occurs secondary to trauma. It may be due to pericardial blood, possibly secondary to the decreased resorptive power of damaged pericardium, with secondary fibrosis and constriction.

Clinical Features

Symptoms and signs of post–cardiac injury syndrome include pericardial rub, fever, and chest pain. Although the diagnosis is usually established clinically, confirmation by echocardiography is helpful. The interval between injury and the onset of pericarditis ranges from 4 to 12 days. During hospitalization, purulent pericarditis should be considered as a possible source of febrile illness in a trauma patient with multisystem organ failure.

Management and Disposition

Most patients respond to aspirin or NSAIDs, and the use of steroids, if necessary, does not increase the likelihood of adverse effects. Uncomplicated pericarditis secondary to blunt trauma usually resolves. The patient should be observed until other life-threatening disease processes are excluded.

NEOPLASTIC PERICARDIAL DISEASE

Perspective

Malignant pericardial tumors typically present late, which complicates diagnosis and treatment. Malignant involvement of the pericardium is observed in 3.4% of general autopsies and 2 to 31% of cancer autopsies. The most common causes are lung cancer (30%), breast cancer (23%), leukemia (9%), non-Hodgkin's lymphoma (9%), and Hodgkin's disease (8%). Primary malignancies of the pericardium are rare.[8]

Principles of Disease and Pathophysiology

The pattern of cardiac involvement by a malignant tumor is determined by the heart's lymphatic drainage system. Small lymphatics drain into a few vessels, which perforate the myocardium and drain into an epicardial plexus. The epicardial lymphatics drain into larger vessels, which accompany the coronary arteries to the aortic root. There, they empty into the cardiac lymph nodes in the mediastinum between the innominate artery and the superior vena cava. The route of metastasis is usually retrograde from involved mediastinal lymph nodes to the relatively narrow passage at the root of the aorta. This is where obstruction to cardiac lymphatic drainage occurs.

Malignant pericardial effusions contribute directly to the patient's death in most cases. Cardiac tamponade is common. Although the underlying disease process is often advanced when tamponade develops, the patient's quality of life can usually be improved if tamponade is treated promptly.

Clinical Features

Primary cardiac neoplasms, such as angiosarcoma and teratoma, can present initially with symptoms consistent with pericarditis. The typical course is that of an acute pericarditis that resolves and subsequently recurs. Malignant pericardial disease is difficult to diagnose. Most patients are asymptomatic or have nonspecific symptoms, such as shortness of breath, cough, palpitations, ill-defined chest pain, weakness, dizziness, hiccups, or fatigue.

Diagnostic Strategies

The diagnostic workup for malignant pericardial effusion includes an echocardiogram, computed tomography (CT), or magnetic resonance imaging (MRI). When a pericardial effusion is identified, pericardial fluid cytology is recommended if the underlying malignancy is undiagnosed.

Management and Disposition

Malignant pericardial effusion is usually treated in the inpatient unit, and treatment may include pericardiocentesis, local instillation of sclerosing or chemotherapeutic agents, systemic chemotherapy, cardiac radiation, and pericardial window. The method chosen depends on the primary tumor and the patient's expected length of survival.

The prognosis for patients with malignant pericardial disease depends on the type and extent of the underlying cancer. Patients with a tumor diagnosed in the emergency department should be offered admission, as should all patients who are symptomatic or hemodynamically compromised.

RADIATION-INDUCED PERICARDITIS

Fewer than 5% of patients treated with radiation therapy develop pericarditis. The incidence has decreased with modern radiation therapy techniques. The percentage of pericardial volume irradiated and the dose help determine which patients develop pericarditis. Radiation-induced pericarditis is seen most commonly in patients with Hodgkin's lymphoma or breast cancer. Pericardial effusion and constrictive pericarditis are common. Tumor recurrence should be considered.

PERICARDIAL DISEASE RELATED TO SYSTEMIC CONNECTIVE TISSUE DISORDERS

Rheumatoid Arthritis

Pericarditis occurs in approximately one third of patients with rheumatoid arthritis (RA) during the course of their disease, usually within 3 years of the initial diagnosis. Rheumatoid pericardial disease is rarely clinically significant. Occasional

patients develop effusions, constrictive pericarditis, or cardiac tamponade. These patients usually have rheumatoid nodules, elevated circulating rheumatoid factor levels, and valvular heart disease. Pericardial involvement should be suspected in any RA patient experiencing the onset of right-sided CHF. There are no suggestive ECG or chest radiograph findings. Pericardial fluid may have rheumatoid factor or a low glucose level. Corticosteroid treatment is useful in symptomatic patients.

Systemic Lupus Erythematosus

Pericarditis is found in more than 50% of patients with systemic lupus erythematosus (SLE) at autopsy. The effusion is usually thick and fibrinous. Either cardiac tamponade or constrictive pericarditis may develop. Lupus erythematosus cells may be identified in pericardial fluid specimens. Corticosteroid therapy is indicated for pericardial involvement in SLE.

Other Connective Tissue Disorders

Approximately 33% of patients with Sjögren's syndrome show evidence of pericarditis. Giant cell arteritis produces granulomatous myocarditis that may respond to methylprednisolone. Cardiac abnormalities, particularly pericarditis, are seen in numerous patients with mixed connective tissue disease. Other connective tissue diseases that may cause pericarditis include ankylosing spondylitis, Reiter's syndrome, Behçet's disease, systemic sclerosis, and polyarteritis nodosa.

MISCELLANEOUS INFECTIOUS CAUSES OF PERICARDITIS

Other etiologies of pericarditis include *Rickettsia conorii*, which causes Mediterranean spotted fever (treated with doxycycline), *Mycoplasma pneumoniae* (treated with a macrolide), *Nocardia asteroides* (treated with pericardiectomy and long-term use of antibiotics such as sulfisoxazole), *Chlamydia trachomatis*, Epstein-Barr virus, cytomegalovirus infection, *Haemophilus actinomycetemcomitans* (treatment with chloramphenicol), and coccidioidomycosis (endemic in the southwestern United States). Viral and bacterial causes of pericarditis can coexist, such as varicella-zoster infection superinfected with *Staphylococcus aureus*. Bacterial superinfections associated with varicella are more common in children.

PERICARDIAL EFFUSION

Etiology and Clinical Features

The most common causes of pericardial effusion are viral or idiopathic pericarditis, malignancy, uremia, trauma, and radiation therapy. Drug reactions and autoimmune diseases are less common causes.

Pericardial effusion is often asymptomatic. Patients with known associated conditions (e.g., cancer or renal failure) who present with cough, fever, chest pain, or dyspnea may have an effusion.

Diagnostic Strategies

Pericardial effusion may present with an enlarged cardiac silhouette on chest radiograph, usually with normal pulmonary vasculature. A minimum of 200 to 250 mL of pericardial fluid is necessary to produce cardiomegaly on chest radiograph.

Echocardiography is the diagnostic modality of choice (Fig. 80-2). It easily differentiates pericardial fluid from cardiac

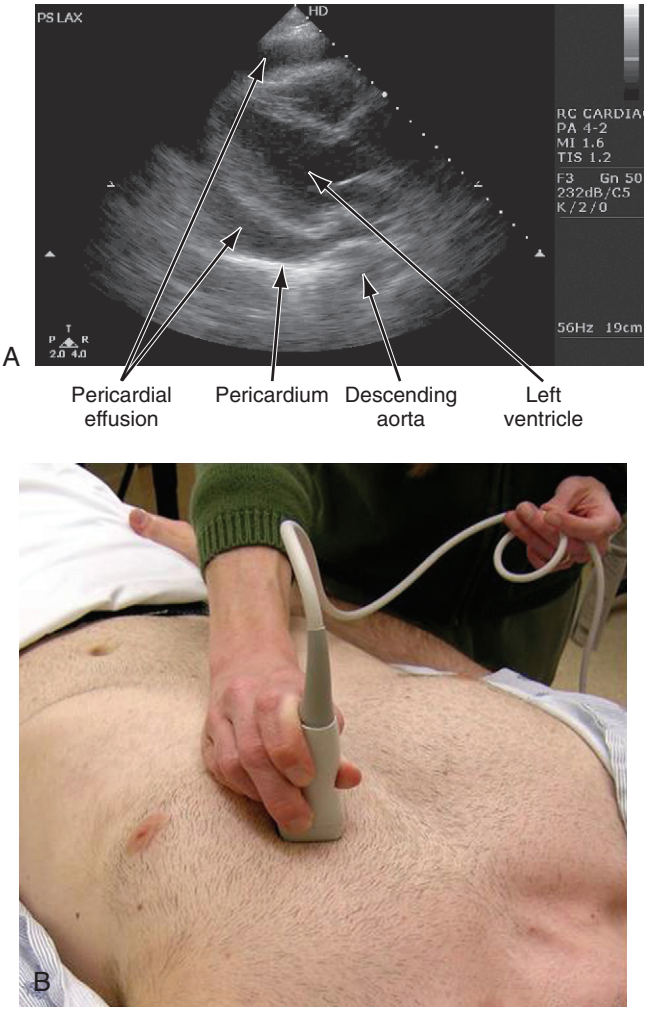


Figure 80-2. **A,** Bedside ultrasound showing a pericardial effusion. The effusion is best seen superior to the left ventricle at the top of the image. **B,** The proper technique for emergency department ultrasound of pericardial effusion. (Courtesy of Jessica Resnick, MD.)

chamber enlargement and provides information about myocardial wall motion.

CT may be useful in diagnosing pericardial effusion when the echocardiogram is technically unsatisfactory. MRI can also be diagnostic. Nuclear scans may be useful in detecting purulent pericardial effusions.

Pericardiocentesis may be performed for either diagnostic or therapeutic purposes. Elective diagnostic pericardiocentesis is indicated in cancer patients (to differentiate malignant effusion from postradiation pericarditis), for failure to respond to usual treatment, or when bacterial infection is suspected. Common complications of pericardiocentesis include induction of cardiac dysrhythmias, pneumothorax, perforation of myocardium, laceration of coronary or internal mammary arteries, and liver laceration. Echocardiographic-guided pericardiocentesis is the procedure of choice.

Pericardial fluid should be analyzed for protein, glucose, specific gravity, cell count and differential, Gram's stain, and culture. Other tests, depending on the clinical picture, include cytology, acid-fast stain, fungal smear, and connective tissue disease screening.

The gross appearance of the pericardial fluid provides a clue to the cause. Serosanguineous effusions are associated most commonly with neoplasms, tuberculosis, uremia, radiation, and idiopathic pericarditis. Grossly bloody effusions are caused

by blunt or penetrating trauma, postinfarction myocardial rupture, aortic dissection, coagulopathies, and iatrogenic cardiac perforation. Purulent pericardial fluid is seen with pneumonia, empyema, and sepsis.

CARDIAC TAMPONADE

Etiology and Pathophysiology

Ten percent of all patients with cancer develop cardiac tamponade.[9] Cardiac tamponade should be suspected in patients with penetrating chest wounds. It is also common in patients with uremic pericarditis.

Cardiac tamponade is the result of compression of the myocardium by the contents of the pericardium. This compression is usually caused by fluid, but it may be caused by gas, pus, blood, or a combination of factors.

Cardiac tamponade is a physiologic continuum reflecting the amount of fluid, the rate of accumulation, and the nature of the heart. The three stages necessary for tamponade to develop are fluid filling the recesses of the parietal pericardium, fluid accumulating faster than the rate of the parietal pericardium's ability to stretch, and accumulation that exceeds the body's ability to increase blood volume to support right ventricle filling pressure. The final result is increased pericardial pressure, which causes decreased cardiac compliance and decreased flow of blood into the heart, which leads to decreased cardiac output.[9]

The most important factor in the development of tamponade is the rate of fluid accumulation. The main pathophysiologic effect is reduction of blood inflow into the right ventricle that results in decreased stroke volume and decreased cardiac output. The heart initially responds to tamponade by increasing heart rate to maintain output. This compensatory mechanism is maintained until late in the course. Decompensation occurs quickly.

Symptoms and Signs

Cardiac tamponade symptoms are usually nonspecific. The patient may complain of chest pain, cough, or dyspnea. The classic triad of cardiac tamponade signs described by Beck is hypotension, distended neck veins, and muffled heart sounds.[10] These signs may not be present if tamponade develops quickly.

Diagnostic Strategies

The chest radiograph shows cardiomegaly only if there is a large accumulation of fluid (250 mL). The ECG classically shows decreased voltage or electrical alternans (Fig. 80-3), but the latter is rare. Echocardiography confirms the diagnosis when an effusion and paradoxical systolic wall motion are seen. Thermodilution catheters can also be diagnostic, showing equalization of right and left ventricular pressures.

Management and Prognosis

Initial treatment includes volume augmentation to the right ventricle with intravenous fluids to increase the filling pressure to overcome the pericardial constriction. Pericardiocentesis is the treatment of choice. Enough fluid should be withdrawn to stabilize the patient. If tamponade recurs, pericardiocentesis may be repeated, or a drainage catheter may be left in the pericardial space. A pericardiectomy ultimately may be necessary. Cardiac tamponade has a high mortality that depends on the severity and nature of the underlying disease, the time course of onset, and the rapidity of diagnosis and intervention. Traumatic cardiac tamponade is discussed in Chapter 42.

PURULENT PERICARDITIS

Epidemiology and Etiology

Purulent pericarditis is a life-threatening process that is seen most commonly in hospitalized patients with systemic illnesses who develop sepsis. It can occur in any age group. It can be caused by any type of infectious agent, with bacteria, especially *Streptococcus* and *Staphylococcus*, being the most common. *Candida* pericarditis is found in three groups of patients: in those after cardiac surgery, those with impaired host defenses, and those with severe debilitating underlying diseases. *Histo-*

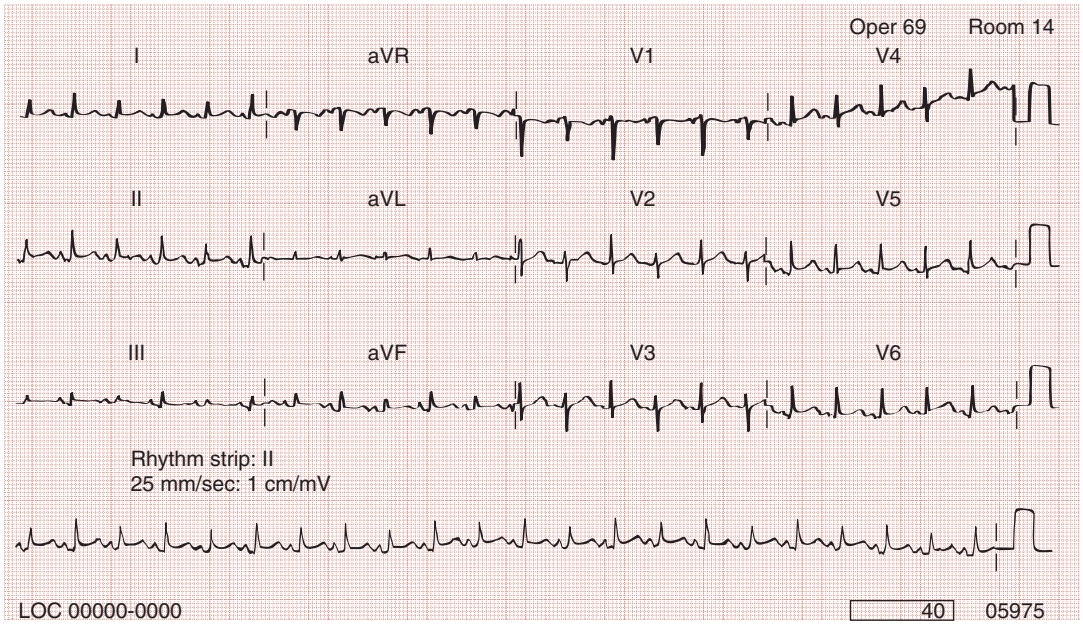


Figure 80-3. Electrocardiogram showing electrical alternans.

plasma infection of the pericardium occurs in endemic areas, including the Ohio and Mississippi River valleys.

Principles of Disease and Pathophysiology

Purulent pericarditis occurs by several mechanisms: (1) spread from an adjacent infection, such as pneumonia or empyema; (2) hematogenous spread from a distant site; (3) direct inoculation of bacteria (trauma or procedure); and (4) spread from an intracardiac source. The most common mechanism is spread from a distant site.

Clinical Features and Diagnostic Strategies

Purulent pericarditis usually presents as a febrile illness lasting 2 or 3 days. Common presenting signs include tachycardia, dyspnea, hepatomegaly, elevated central venous pressure, chest pain, friction rub, and a leukocytosis. The most common presentation is a hospitalized patient with a serious underlying disease who initially improves after treatment of the primary process but later develops fever, dyspnea, and chest pain.

The diagnosis should be suspected in any febrile patient with multisystem illness who has a pericardial effusion. Pericardiocentesis is necessary to establish the diagnosis, obtain fluid for microbiologic studies, and relieve cardiac tamponade.

Management and Disposition

Pericardiectomy is the traditional treatment of choice. Indwelling catheters, coupled with lavage, antibiotics, and fibrinolytics, may avoid the need for surgery. When intravenous antibiotics or antifungals are indicated, prolonged treatment is necessary.

The overall survival rate for purulent pericarditis is approximately 30% with antibiotic therapy alone and 50% when combined with early surgical drainage. In addition to the initial complications related to sepsis and tamponade, long-term sequelae of purulent pericarditis include the development of constrictive pericarditis.

TUBERCULOUS PERICARDITIS

Tuberculous pericarditis is estimated to occur in 1 or 2% of patients with pulmonary tuberculosis.[11] In Africa, it is the most common cause of pericarditis. In countries in which tuberculosis is not a major health problem, tuberculous pericarditis is most common in patients who are socioeconomically deprived or immunodeficient. Although rare, isolated tuberculous pericarditis still exists. Tuberculous pericarditis usually spreads to the pericardium by direct extension from the tracheobronchial tree, mediastinal or hilar lymph nodes, sternum, or spine.

In many patients, the chest radiograph shows an enlarged cardiac silhouette without a pulmonary infiltrate. Pericardial fluid aspirates reveal acid-fast bacilli by smear or culture (which may require 4–6 weeks to become positive) in approximately 50% of cases. Diagnostic workup should include assessment for human immunodeficiency virus (HIV).

Patients with tuberculous pericarditis should be hospitalized and observed for evidence of cardiac tamponade. Triple-drug therapy should be started in the hospital and continued for at least 9 months. Patients with chronic pericardial effusions may benefit from oral prednisone therapy. Those with evidence of pericardial thickening, constrictive pericarditis, or hemodynamic compromise should be referred for surgical treatment. The mortality rate is approximately 15% in HIV-negative patients and 20 to 35% in HIV-positive patients.[11]

OTHER CAUSES OF PERICARDITIS

Amyloid deposition can cause either restrictive cardiomyopathy (RCM) or constrictive pericarditis. Pericarditis can occur rarely as an extraintestinal complication of inflammatory bowel disease and is independent of the clinical course of the gut disorder.

Iatrogenic pericarditis can also occur as a complication of an implantable defibrillator or an atrial lead of a permanent pacemaker. A polymicrobial bacterial pericarditis can occur after transbronchial needle aspiration or as a complication of endoscopic variceal sclerotherapy. Rarely, pericarditis can also be caused by erosion of a foreign body, such as a sewing needle or toothpick, through the esophagus into the pericardium.

PERICARDITIS AND ACQUIRED IMMUNODEFICIENCY SYNDROME

Progressive dysfunction of multiple organ systems occurs in AIDS. Pericarditis is usually nonspecific in origin, but it can be associated with Kaposi's sarcoma, lymphoma, or any infectious pathogen.

Less than 1% of patients with HIV develop acute pericarditis, but 40% have asymptomatic pericardial effusion. In 33% of these patients, the effusion is moderate or large. Pericardial effusion is more frequent in patients in the more advanced stages of HIV infection. Although the etiology may differ, the clinical features and diagnostic evaluation of patients with AIDS-related pericarditis are the same as those in patients without AIDS.

PNEUMOPERICARDIUM

Perspective and Etiology

Pneumopericardium and pyopneumopericardium are rare. Pneumopericardium may be caused by diseases that can lead to formation of fistulae between the pericardial and pleural space, bronchial tree, or upper gastrointestinal tract (e.g., peptic ulcer disease, carcinoma of the esophagus or stomach, and esophageal diverticulum). It may result from bronchial carcinoma or infection with gas-producing microorganisms, or it can be idiopathic. Pyopneumopericardium may result from trauma, foreign body, ingestion of caustic substances, or invasive procedures (e.g., esophagoscopy, thoracentesis, and endotracheal intubation).

Spontaneous pneumopericardium may complicate asthma, labor, barotrauma from positive-pressure ventilation, or Valsalva maneuvers, such as might occur during weightlifting. Cocaine inhalation from positive-pressure devices can also cause pneumopericardium.

Pathophysiology

Pneumopericardium is caused most commonly by an increase in intra-alveolar pressure above atmospheric pressure, resulting in rupture of alveoli. Air dissects into the hilum and mediastinum, through the pericardial reflection on the pulmonary vessels, and into the pericardium.

Clinical Features and Diagnostic Strategies

Physical findings depend on the quantity of fluid and gas in the pericardial space. Heart sounds can be of variable intensity, change depending on body position, and have a metallic quality that may be accompanied by splashing sounds. *Hamman's sign* and *mediastinal crunch* are the terms used for a loud,

crunching sound associated with pneumopericardium or pneumomediastinum. This is best heard with the patient in a left lateral recumbent position and is diagnostic for the presence of mediastinal air. The diagnosis of pneumopericardium is confirmed by chest radiograph, CT scan, or echocardiography. Tension pneumopericardium presents with clinical findings of acute cardiac tamponade.

Management

Stable patients with uncomplicated spontaneous pneumopericardium can usually be observed. After all other life-threatening injuries and complications are excluded, there are no expected long-term sequelae. Tension pneumopericardium should be treated with emergency pericardiocentesis.

CONSTRICTIVE PERICARDITIS

Perspective and Etiology

Constrictive pericarditis may be a late consequence of viral pericarditis. Tuberculosis is still the leading cause of constrictive pericarditis in some countries. There is an increased incidence of constrictive pericarditis as a result of improved survival of patients with chronic renal disease. Other predisposing conditions include radiation, trauma, purulent pericarditis, actinomycosis, and postpericardiotomy adhesions.

Principles of Disease and Pathophysiology

Constrictive pericarditis usually results from fibrous reaction of the pericardium and is characterized by impaired diastolic filling from external cardiac compression caused by a thickened pericardium. In advanced cases, the visceral and parietal pericardial layers may be adherent. Impaired ventricular filling is the key pathophysiologic feature.

Since the pericardium limits volume, ventricular filling is rapid and completed within the first one third of diastole, after which left ventricular volume and pressure remain unchanged. Early ventricular filling followed by a period of unchanging pressure yields a corresponding dip and plateau pattern or square root sign on the left ventricular diastolic pressure curve. This suggests the diagnosis of constrictive pericarditis.

Clinical Features

The symptoms and signs of constrictive pericarditis are virtually indistinguishable from those of CHF. Dyspnea, fatigue, and weight gain are the most common complaints. Hepatomegaly, marked pitting lower extremity edema, and ascites can be seen on physical examination. The characteristic auscultatory finding of constrictive pericarditis is a pericardial knock in early diastole, and a friction rub may also be audible.

Diagnostic Strategies

The diagnosis is considered in a patient with right-sided heart failure symptoms. Heart size on the chest radiograph is typically small but may be increased by atrial enlargement. Pericardial calcification is suggestive when present on CT or MRI. Liver function tests are consistent with passive congestion. ECG findings include low QRS voltage, nonspecific ST-T wave abnormalities, and atrial dysrhythmias.

Doppler echocardiography may help differentiate constrictive pericarditis from RCM or cardiac tamponade.[12] Cardiac catheterization and simultaneous measurement of right ventricular and left ventricular end-diastolic pressures or endomyocardial biopsy may be necessary.

Differential Considerations and Management

Constrictive pericarditis is often confused with CHF. A history of viral or bacterial pericarditis, radiation therapy, tuberculosis, chest trauma, or cardiac surgery should suggest constrictive pericarditis. The diagnosis should also be considered with signs of elevated venous pressure but no history of myocardial dysfunction. Right ventricular infarction causes a hemodynamic picture similar to that of constriction, but the echocardiogram reveals abnormal right ventricular function and wall motion.

The hemodynamic picture in RCM is virtually identical to that of constrictive pericarditis: Both are associated with signs of elevated venous pressure and small heart size. The echocardiogram may reveal the presence of infiltrative myocardial disease in patients with RCM. Pericardiectomy is the therapy of choice for constrictive pericarditis.

MYOCARDIAL DISEASES (MYOCARDITIS)

PERSPECTIVE

The term *myocarditis* was coined initially by Sobernheim in 1837. Romberg reported the association with scarlet fever and typhus in 1891, and "isolated idiopathic interstitial myocarditis" was described by Fiedler in 1899. The 1995 World Health Organization/International Society and Federation of Cardiology classification of myocardial disease considers myocarditis an inflammatory cardiomyopathy, a subset of dilated cardiomyopathy (DCM).

EPIDEMIOLOGY AND ETIOLOGY

Some degree of myocarditis is detected in almost 10% of routine autopsies but is often not recognized clinically. The overall incidence is unknown and probably underdiagnosed.[13] Enteroviruses, especially the coxsackie B virus, and adenoviruses predominate as causative agents. Coxsackie B virus usually causes infection during the summer months, but outbreaks do not occur every year. Other organisms that may cause myocarditis include influenza A and B, *Streptococcus*, mononucleosis, *Chlamydia*, *Mycoplasma*, parainfluenza, mumps, cytomegalovirus, rubeola, rubella, rabies, lymphocytic choriomeningitis virus, hepatitis A and B, and varicella zoster. The etiology varies by patient age and region. Cytomegalovirus and *Toxoplasma gondii* have emerged as potential causes of myocarditis in cardiac transplant patients. Of patients dying of AIDS, 67% have myocarditis on autopsy. Worldwide, Chagas' disease is a leading cause of myocarditis, especially in South America. Mortality from myocarditis has not changed since before 1990. The mortality rate is approximately 20% at 1 year and 50% at 5 years.[14]

PRINCIPLES OF DISEASE AND PATHOPHYSIOLOGY

Myocarditis occurs by (1) necrosis from direct invasion of an offending infectious agent and its replication within or near myocytes, (2) destruction of cardiac tissue from infiltration of host cellular immune components or from cytotoxic effects of host immunity activated by the infectious agent, or (3) the toxic effect of exogenous or endogenous chemicals produced by a systemic pathogen. Three stages are proposed: acute

(early after infection), with viral cytotoxicity and focal necrosis; subacute, in which there is an increase in humoral factors, such as nitrous oxide synthetase, natural killer cells, and interleukin-2, which lead to autoimmune injury; and chronic, in which there is diffuse myocardial fibrosis and cardiac dysfunction that may lead to DCM.[13] In neonates, the pathologic changes are more often related to direct viral damage, whereas adults are more often injured by immunologic damage.

Adenoviruses and enteroviruses may be associated with most cases of myocarditis in all age groups. Isolation of a coxsackievirus-adenovirus receptor shows how these two types of viruses, one RNA and one DNA, may enter the heart.[15]

Cardiac autoantibodies develop after myocarditis. There is also a higher concentration of IgG anti-α-myosin antibodies in patients with myocarditis and DCM than in controls. Because myocarditis is linked to the development of DCM, idiopathic DCM after myocarditis may be predominantly autoimmune in origin, resulting from either shared antigens or molecular mimicry.[16] The amino acid sequences of the coxsackie B virus and β-myosin heavy-chain protein are more than 50% similar. An immune response to the former yields damage to the latter (molecular mimicry).

CLINICAL FEATURES

Flulike complaints, including fever, fatigue, myalgias, vomiting, and diarrhea, are usually the first symptoms and signs of myocarditis. Altered vital signs include fever, tachycardia, tachypnea, and, uncommonly, hypotension. Tachycardia disproportionate to the temperature or apparent toxicity may occur but is a nonspecific finding. No symptom or sign is sensitive or specific. Cardiac examination is often unremarkable. When chest pain or CHF occurs at initial presentation, there is an increased likelihood of parvovirus infection, greater cardiac damage, and a worse prognosis.[17] Other etiologies to consider include sepsis or MI.

In children, prominent physical findings include grunting respirations and intercostal retractions. Although the lungs are clear to auscultation in most patients, approximately 10 to 15% have rhonchi. This may be related to infection with RSV, which can cause these symptoms with or without associated myocarditis. Infants often have a fulminant syndrome characterized by fever, cyanosis, respiratory distress, tachycardia, and cardiac failure. When children have ventricular dysrhythmias, myocarditis and idiopathic DCM are commonly seen on endomyocardial biopsy, despite findings of a structurally normal heart by noninvasive studies.

DIAGNOSTIC STRATEGIES

Common ECG changes include sinus tachycardia and low electrical activity. There may be a prolonged corrected Q-T interval, atrioventricular block, or acute MI pattern abnormalities.

Cardiac troponin is usually elevated. The white blood cell count and ESR are nonspecific. The echocardiographic features of myocarditis, although nonspecific, include reduced left ventricular ejection fraction, global hypokinesis, and regional wall motion abnormalities. Contrast-enhanced MR may also be diagnostic. Indium-111 anti-myosin antibodies bind specifically to exposed myosin in damaged myocardial cells, providing a noninvasive approach for the diagnosis of myocardial necrosis. With nuclear scanning, myocarditis is usually characterized by a diffuse, faint, heterogeneous uptake of anti-myosin antibody because myocyte necrosis is typically widespread. Acute MI is almost always characterized by an intense, localized uptake of antibody in the region of the occluded coronary artery.[18]

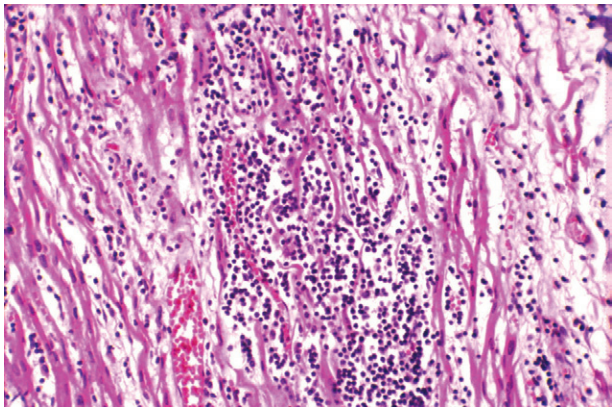


Figure 80-4. Myocardial biopsy showing myocarditis. Note the lymphocytic infiltrate.

Acute and convalescent viral titers are positive in less than 40% of cases.[15,19] A fourfold rise in viral titers or a high titer of viral-specific IgM may help establish a viral etiology.

Endocardial biopsy, long considered the gold standard, has variable sensitivity and specificity (Fig. 80-4). Histologic criteria for myocarditis are present in only 5 to 30% of patients with clinically suspected myocarditis and up to half of patients with DCM. Molecular genetic probes, such as polymerase chain reaction, are used to supplement standard histologic analysis. In addition, polymerase chain reaction analysis of tracheal aspirates of intubated patients with myocarditis shows a correlation with endocardial biopsy.[20]

DIFFERENTIAL DIAGNOSIS

Myocarditis can masquerade as acute MI with severe chest pain, ECG changes, elevated cardiac markers, and heart failure. Patients with myocarditis are usually young and have few risk factors for coronary artery disease. ECG abnormalities may extend beyond the distribution of a single coronary artery, or there may be global, rather than segmental, wall motion abnormalities on echocardiography. In myocarditis, chest pain continues, but there are no further ischemic ECG changes.

If the differentiation of myocarditis from MI is unclear, the emergency physician may refer the patient for catheterization. Coronary angiography is usually normal in myocarditis, which should prompt consideration of endomyocardial biopsy.

The diagnosis of myocarditis should also be considered in an otherwise healthy patient who presents with symptoms and signs of new CHF or dysrhythmias.

MANAGEMENT

The type of supportive care necessary is determined by the patient's clinical presentation and the stage and severity of disease. This may extend from simple limitation of activity to rhythm and CHF treatment, extracorporeal membrane oxygenation, ventricular assist devices (VADs), and eventual cardiac transplantation.

Therapy is stage specific, given the three distinct phases of the disease. In the first phase, demonstration of replicating enterovirus RNA suggests that early antiviral agents, such as pleconaril or ribavirin, may be effective. Agents active at the coxsackievirus-adenovirus receptor present an intriguing, theoretical approach.[14]

Hopes that the subacute phases of myocarditis might respond to immunosuppressive therapy are tempered by the

results of several multicenter trials, which do not establish efficacy.[14] Efforts to identify patient and treatment subsets in which immunosuppressive therapy may be beneficial are ongoing. High-dose gamma globulin therapy has been studied in a pediatric population. High-dose intravenous immunoglobulin may be associated with improved recovery of left ventricular function and better survival during the first year after presentation.

In the chronic stage, CHF symptoms predominate and standard pharmacologic treatment for CHF is indicated. In some cases, the deterioration of cardiac function is reversible with the aid of a VAD. These devices have been used successfully over extended periods, including up to 70 days. Their use should be considered before transplantation.[21]

DISPOSITION

All patients should be monitored, and those with hemodynamic instability require intensive care. Paradoxically, patients with fulminant myocarditis have the best prognosis. Complications of myocarditis include ventricular dysrhythmias, left ventricular aneurysm, and cardiac failure.

The mortality rate is 20% at 1 year and 50% at 5 years, despite optimal medical management. Ejection fraction and right ventricular function 1 year after initial presentation may be the best predictors of subsequent survival. The long-term prognosis in survivors is variable.

Patients who undergo transplantation because of myocarditis heart failure have decreased 1-year survival compared to patients transplanted for other reasons. They also have higher allograft rejection rates than other recipients. The overall 5-year survival rate for children is 70%.[13]

CHAGAS' DISEASE

Chagas' disease is one of the leading causes of myocarditis in many countries in Latin America, particularly in Central America. Chagas' disease is caused by the protozoan *Trypanosoma cruzi* with transmission by insect vectors.[22]

Approximately 75% of seropositive patients with Chagas' disease never have cardiac symptoms. One fourth have angina-like chest pain, dysrhythmias, embolic episodes, heart failure, conduction abnormalities, multifocal ventricular premature contractions, and abnormal ST segment and T wave abnormalities in the precordial leads. Ventricular tachycardia is common. Syncopal or near-syncopal episodes occur in nearly two thirds of patients.[23]

Serum parasites establish the diagnosis. Chagas' disease should be suspected in ED patients with new cardiac symptoms and a Latin American travel history.

In more than half of those patients who die of chronic Chagas' disease, autopsy reveals a unique left ventricular apical aneurysm or scar, which is a reliable marker of the disease.[23] Echocardiography may also be suggestive. The extent of tissue damage correlates with the parasite load, which also can be found in histologic sections of infected tissues.

Chagas' disease is treated with the antitrypanosomal drugs benznidazole and nifurtimox. Amiodarone may be useful to treat ventricular tachycardia. An angiotensin-converting enzyme inhibitor may be useful for CHF.

TRICHINOSIS

Trichinosis is caused by ingestion of the cysts of *Trichinella spiralis* in undercooked meat. The acute illness consists of fever, myalgias, muscle tenderness, neck stiffness, and a characteristic periorbital edema. Historically, in the United States, pork was the most commonly implicated meat, but trichinella has been eradicated from commercial domestic pork for many decades. Trichinosis in the United States is most likely to be caused by wild game, such as bear or cougar, although there are scattered reports from imported or home-raised pork. Larvae may be deposited in the myocardium, which incite an eosinophilic inflammatory reaction and necrosis of muscle fibers.

Myocardial involvement is present in approximately 20% of clinically diagnosed cases and appears in the second or third week of illness, when other symptoms are declining. Cardiac manifestations include chest pain, dyspnea, cardiomegaly, dysrhythmias, and CHF. ECG findings, such as nonspecific ST-T wave abnormalities and conduction blocks, may appear transiently, even in the absence of cardiac symptoms. Peripheral eosinophilia and an elevated ESR are common.

The diagnosis is usually established with serologic studies or biopsy of any symptomatic muscle group. Treatment usually involves corticosteroids together with antihelminthic drugs such as thiabendazole and albendazole.[24]

DIPHTHERIA

The incidence of diphtheria in the United States since 1980 is 0.001 cases per 100,000 population. Most diphtheria patients in the United States are immigrants. Individuals at risk include the nonimmunized and those in contact with farm animals and unpasteurized dairy products.[25]

Diphtheria is caused by the toxin of the gram-positive organism *Corynebacterium diphtheriae*. The principal manifestations are nasopharyngitis with membrane formation and respiratory obstruction, myocarditis, and polyneuritis. Myocardial involvement is clinically evident in 10 to 25% of cases and is the major cause of death. Early signs of myocarditis are tachycardia and faint heart sounds. Cardiac markers are often elevated. Prolongation of the P-R interval and ST-T wave abnormalities occur within the first 2 weeks of onset. Other ECG abnormalities, such as bundle branch block or complete heart block, precede total circulatory collapse and are associated with a poor prognosis.

Specific therapy involves high-dose penicillin and diphtheria antitoxin. Treatment with oral carnitine, a cofactor in the transport of fatty acids to mitochondria, is associated with a lower incidence of heart failure, severe conduction blocks, and decreased mortality.

LYME DISEASE

Epidemiology and Clinical Features

Lyme disease is caused by infection with the spirochete *Borrelia burgdorferi* and is discussed in Chapter 132. Lyme disease–related carditis occurs a median of 21 days after the onset of erythema migrans. Cardiac complications occur in 4 to 10% of patients. These include conduction disturbances; bundle branch block; first-degree, second-degree, and third-degree heart block; cardiac arrest; dysrhythmias; and left ventricular dysfunction.

Lyme disease-related carditis should be suspected in otherwise healthy persons with unexplained heart block and potential exposure to ticks in an endemic area. Lyme disease is diagnosed by identification of the spirochete with serologic testing. Silver staining of endomyocardial biopsy also identifies the spirochete. A screening ECG should be performed whenever the diagnosis of Lyme disease is suspected.

Atropine or isoproterenol may be used to treat first-degree or second-degree heart block or third-degree block that is

hemodynamically stable. Temporary placement of a pacemaker is often required in unstable patients. Antibiotic therapy with intravenous penicillin or oral tetracycline is effective and can reverse atrioventricular block. Erythromycin should be prescribed in place of tetracycline in young children. Ceftriaxone is also effective. The role of antibiotics in preventing Lyme disease–related carditis is unknown.

■ ACQUIRED IMMUNODEFICIENCY SYNDROME–RELATED MYOCARDIAL DISEASE

Epidemiology

The cardiac manifestations of AIDS are diverse and cause death in at least 6% of patients with HIV (HIV is discussed in Chapter 130). The prevalence of left ventricular dysfunction in adult AIDS patients is approximately 20%. Myocarditis is described in approximately 46% of AIDS patients undergoing postmortem examination. Most AIDS patients exhibit cardiac involvement as their underlying disease worsens.

Etiology

The pathogenesis of HIV-related heart muscle disease is multifactorial. The direct etiologic role of HIV infection in cardiomyopathy is controversial. Cytomegalovirus infection is a major cause of morbidity in AIDS and can cause myocarditis, as can infection with *Toxoplasma*. Of AIDS patients with toxoplasmosis, 28% initially have cardiac symptoms, such as cardiomegaly, CHF, dysrhythmias, pericarditis, pericardial tamponade, or chest pain. *Mycobacterium tuberculosis*, *Aspergillus fumigatus*, coxsackie B virus, cryptococcal, and *Histoplasma* myocarditis also occur.

HIV disease treatment may also lead to cardiac toxicity. Pentamidine, which is structurally similar to procainamide, can cause torsades de pointes ventricular tachycardia. Zidovudine and dideoxyinosine also can lead to cardiac dysfunction.

■ OTHER CAUSES OF MYOCARDITIS

Cardiac involvement with *Legionella pneumophila* is uncommon, although the heart may be the only affected organ. Clinical symptoms resemble pericarditis and myocarditis, including dysrhythmias and conduction blocks. After treatment with erythromycin, normal cardiac function may return.

Cardiac *Toxoplasma* infection may lead to clinically significant disease. Infection is well described in recipients of bone marrow and cardiac transplantation. Immunocompromised patients with toxoplasmic myocarditis may have bundle branch block, CHF, pericarditis, and dysrhythmias as a result of lesions in the conducting system. Untreated toxoplasmic myocarditis is fatal.

Myocarditis associated with *M. pneumoniae* may be caused by direct invasion of the myocardium, an autoimmune mechanism, or intravascular coagulation. Miliary tuberculosis, including tuberculosis myocarditis, can produce granulomas within the myocardial conduction system that can precipitate fatal dysrhythmias. Sudden death can also occur secondary to *Chlamydia pneumoniae* myocarditis. In addition, myocarditis, presumably mediated by exotoxin, is associated with *Shigella* infection.

Cardiac involvement of the conduction system and the pericardium also may occur in dermatomyositis and polymyositis. Patients are usually asymptomatic, but pericarditis, myocarditis, and dysrhythmias can occur.

■ PHARMACOLOGIC CARDIOTOXICITY

Cocaine has various cardiac effects in addition to ischemia, including myocarditis and DCM. Myocarditis is a common autopsy finding in patients with cocaine abuse. The mechanism responsible for the cardiotoxic effects of cocaine is largely unknown. Theories include the following: (1) cocaine may have a direct effect on lymphocyte activity; (2) intravenous cocaine can increase natural killer cell activity in blood, which may be cytotoxic to myocardial cells; (3) there is a cocaine-related eosinophilic infiltrate that suggests a hypersensitivity reaction; and (4) catecholamine administration can induce a focal myocarditis. Cocaine has a direct, negative inotropic effect on cardiac muscle.

Patients who die with detectable cocaine levels have myocarditis and myocardial contraction bands more often than controls. The severity of contraction-band necrosis correlates with the serum and urine concentrations of cocaine. Catecholamine excess caused by cocaine use may contribute to contraction-band necrosis, which may supply the anatomic substrate for ventricular dysrhythmias.

Lastly, acute and chronic cardiotoxicity occur secondary to the use of doxorubicin. Manifestations of acute cardiotoxicity include dysrhythmias, pericarditis, myocarditis, and left ventricular dysfunction.

■ KAWASAKI DISEASE

Kawasaki disease, or mucocutaneous lymph node syndrome, is of unknown etiology and primarily affects children. This self-limited vasculitis affects many organ systems. Twenty-five percent of all patients develop coronary artery abnormalities, usually several weeks after symptom onset. These are usually reversible but may lead to aneurysm formation or secondary thrombosis and myocardial ischemia. Myocarditis and pericarditis also occur during the initial phase of the disease.

CARDIOMYOPATHIES AND SPECIFIC HEART MUSCLE DISEASE

Cardiomyopathies are a heterogeneous group of diseases associated with mechanical or electrical dysfunction that usually exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that are frequently genetic. The diseases included are genetic (hypertrophic cardiomyopathy, arrythmogenic right ventricular cardiomyopathy, mitochondrial myopathies, and ion channel disorders), mixed (dilated cardiomyopathy and restrictive cardiomyopathy), and acquired (inflammatory, stress provoked or tako-tsubo, peripartum, and tachycardia induced).[26]

A variety of pathologic processes may initiate myocyte injury. When a threshold of injury occurs, common pathophysiologic pathways are activated. These pathways involve neurohumoral factors, immune factors, and cytokines. These factors contribute to myocyte dysfunction, which leads to remodeling. In response to disease, the heart remodels usually by hypertrophy or dilation. There is also an increase in interstitial fibrosis, which impairs ventricular filling; this leads to increased metabolic demands on the myocardium.[27,28] The ultimate pathophysiologic derangement may be the troponin complex, intracellular concentration of calcium, myocardial subproteins, or the sarcomere.[29] These lesions lead to alteration in the cardiac muscle's ability to contract, which eventually leads to clinical pathology.[30] There is also change in the cardiac microvascular circulation that is an independent predictor of morbidity and mortality.[31]

The traditional splitting of cardiomyopathies into subtypes may evolve into a unified theory that shows all types of cardiomyopathy to be variations of a common genetic, anatomic, and humoral pathophysiologic process.

Mutations of genes for myocardial protein components lead to molecular changes in heart muscle that lead to clinical cardiomyopathy. The correlation between genotype, phenotype, and clinical presentation is unknown when the molecular level changes transition from compensatory to pathologic.

DILATED CARDIOMYOPATHY

Epidemiology and Etiology

DCM is a spectrum of disorders that have in common a dilated and failing heart for which no cause can be established. The incidence of DCM is estimated to be 36 cases per 100,000 persons per year. The true incidence is probably underestimated because many asymptomatic cases remain undiagnosed. DCM is estimated to affect 5.5 million adults and 500,000 children in the United States, costing $10 billion.[32] It is estimated that 50% of cases previously thought to be of unknown etiology may be secondary to infection.[33] Myocarditis is the most common cause of DCM in children.[32]

DCM affects men more often than women, affects African Americans more than whites,[27] and may occur in any age group, with middle age (40–65 years old) being the most common. Risk factors include ethanol and tobacco abuse, pregnancy, hypertension, and infection. Among patients with DCM, approximately 25% have an inherited form.[34]

Pathophysiology

There are both primary and secondary etiologies for DCM. Possible pathophysiologic causes include myocardial inflammation mediated by cytokines, macrophages, and natural killer cells; local inflammation caused by the release of cytokines by infiltrating lymphocytes; direct reaction of antibodies with receptors on myocardial muscle; toxins, such as ethanol, impairing myocardial biochemical processes; and loss or dysfunction of myocardial matrix proteins.[35] Myocardial damage initiates a vicious cycle of hypertrophic cell death that increases the burden of the remaining cells; this leads to signaling, more work, and cell death.[36]

Identification of a genetic basis for the coxsackievirus-adenovirus receptor and efforts to correlate this with cases of DCM suggest that development of a vaccine against coxsackievirus and adenovirus may decrease these infections in myocarditis and DCM.[19]

Clinical Features

Symptoms of DCM have an insidious onset. Left-sided heart failure occurs as the initial manifestation in 75% of adults, with dyspnea (usually with exertion or while supine) the major symptom. Exacerbation of heart or renal disease, dietary indiscretion, and medication noncompliance are key contributors. CHF symptoms are the most common presentation in children. Chest pain on exertion is the initial symptom in 10% of adults, and systemic or pulmonary emboli are the initial manifestation in 4%. Right-sided heart failure is a late and ominous sign.

Diagnostic Strategies

ECG findings are nonspecific and may include poor R wave progression, intraventricular conduction delay, or left bundle branch block pattern. Holter monitoring may show frequent premature ventricular contractions and occasional ventricular tachycardia. Sudden death is uncommon. The chest radiograph reveals cardiomegaly.

Echocardiography shows left ventricular dilation, reduced systolic function, and variable wall motion abnormalities. Abnormal ventricular contractility defines DCM, and an ejection fraction less than 45% is required for diagnosis. End-diastolic and systolic volumes are increased, as are pulmonary capillary wedge pressure and central venous pressure.

Endomyocardial biopsy may also be necessary. Histologic abnormalities are nonspecific. New histochemical, immunologic, and molecular biologic techniques improve the diagnostic yield, especially for infectious causes.

Management and Disposition

Therapy includes supportive measures, such as adequate rest, weight control, abstaining from tobacco, moderate salt and ethanol consumption, and reduced physical activity. Medical treatment includes standard measures for CHF.

Angiotensin-converting enzyme inhibitors reduce morbidity and mortality.[36] Other afterload-reducing agents, such as isosorbide dinitrate and hydralazine, also prolong survival in patients with heart failure. Spironolactone and the angiotensin receptor-blocking agents also prolong survival.[27] Implantable defibrillators improve survival[37] and short-term statin therapy may help.[38] Antidysrhythmics are not usually effective.

Various beta-blockers can reduce symptoms and improve left ventricular function, functional capacity, and survival. In addition, the improvement in cardiac function associated with beta-blockers is also associated with changes in expression of genes encoding for α- and β-myosin heavy-chain and sarcoplasmic reticulum calcium adenosine triphosphate.[39]

Outcome

Since medical therapy usually fails, DCM is the leading indication for cardiac transplantation in adults and children. Mortality from DCM is 18% by 1 year, 35% by 5 years, and 50% by 10 years. Patients with DCM show progressive deterioration, with 75% of patients dying within 5 years of diagnosis.[27]

The clinical course for children is variable, with a better prognosis in young children. Most deaths occur within the first 2 years. Some children show delayed, spontaneous, and unexplained improvement.

HYPERTROPHIC CARDIOMYOPATHY

Perspective

Hypertrophic cardiomyopathy (HCM) is a complex disorder with variable clinical manifestations. The prevalence is estimated to be 1 in 500 persons in the general population. It affects all races, men and women equally, and can present at any age.[40]

Principles of Disease

Anatomy

HCM is a disease involving abnormalities of heart muscle at anatomic, cellular, and genetic levels. The defining anatomic feature of HCM is a hypertrophied left ventricle in the absence of another cause of left ventricular hypertrophy. The thickening is usually asymmetrical and involves the septum more than the free ventricular wall. The extent of hypertrophy at any

given site can vary greatly and bears significantly on the manifestation of the disease. The dimensions of the left ventricular and right ventricular cavities are small or normal. Atrial dilation is another feature.

Histologically, individual muscle cells are hypertrophied, with a disorganized, characteristic whorled pattern.[41] Sarcomere disarray is the histologic hallmark. Abnormal fibrous tissue is often found in the left ventricle, and the scarring mimics a healed MI.

Pathophysiology

HCM is an autosomal dominant disease caused by mutations in genes that encode for sarcomere contractile proteins. Ten genes encoding for cardiac sarcomere proteins and more than 200 different mutations of these genes are identified. Half the mutations involve three genes: those for β-myosin heavy chain (which constitutes 30% of myocardial protein), myosin-binding protein C, and troponin-T.[40]

β-Myosin heavy chain is a contractile protein with enzyme activity responsible for hydrolyzing adenosine triphosphate. Troponin-T constitutes approximately 5% of the total myofibrillar protein and is involved in regulation of calcium. A decreased quantity of stable cardiac troponin-T alters the stoichiometry of the sarcomere.

Genetic studies of families with HCM identify specific mutations that correlate with sudden cardiac death. In families with Arg403Gln mutation, less than half of affected family members survive past 45 years of age. Genetics alone does not account for the clinical manifestation of HCM, since patients with the same genotype differ in phenotypic expression and clinical course. This indicates that modifier genes and environmental factors are also important.

The hypertrophy in HCM may be a compensatory response to the cardiac protein abnormalities. In vitro studies show that mutant β-myosin heavy chain protein exhibits impaired contractility and disrupts formation of the normal sarcomere. The usual cardiac response to physiologic stress is hypertrophy, dilation, or a combination of both. A gene mutation may lead to mutant protein that impairs cellular structure and function due to fibrous changes in the sarcomere. This causes compensatory tissue hypertrophy that is manifest as HCM.

Clinically, patients with HCM have asymmetric left ventricular hypertrophy. They have an abnormal echocardiogram or cardiac magnetic resonance image that shows hyperdynamic ventricles. There may be an outflow obstruction, although this usually occurs with exertion. The thickness of the ventricle and degree of outflow obstruction correlate with disease severity. The pathophysiology involves impaired ventricular filling during diastole.

Clinical Features

HCM occurs at all ages. The average age at diagnosis is 30 to 40 years. Approximately 2% of cases are diagnosed in children younger than age 5 years, and 7% are diagnosed before 10 years of age. HCM gained notoriety after the sudden deaths of several young athletes and the attendant press coverage. There is advocacy for large-scale ECG screening of young athletes, but no studies demonstrate an appropriate strategy for effective screening for the condition. The presentation of HCM varies widely. HCM may be discovered by screening relatives of patients who have HCM.[41]

In many patients, the initial event is sudden death, which usually occurs during exertion. Ninety percent of patients have shortness of breath. Other symptoms include chest pain, syncope, near-syncope, and palpitations.

Physical examination may reveal a loud S_4 gallop and a harsh crescendo-decrescendo midsystolic murmur. This murmur is accentuated by the Valsalva maneuver or standing/squatting. Such position interventions change preload and afterload, which accentuates the murmur. Other physical findings may include a bifid arterial pulse, paradoxical splitting of the second heart sound, and, rarely, a mitral leaflet septal contact sound. Many dysrhythmias are seen in HCM, including premature atrial and ventricular contractions, multifocal ventricular ectopy, and ventricular and supraventricular tachydysrhythmias. In the ED, the diagnosis should be suspected in anyone with a family history, characteristic murmur, and cardiopulmonary symptoms (i.e., chest pain, dyspnea, and dysrhythmia) not explained by other life-threatening conditions.

Diagnostic Strategies

Patients with suspected HCM should have an ECG, chest radiograph, and echocardiogram. The ECG is abnormal in approximately 90% of patients. The most common abnormalities are left ventricular hypertrophy, ST segment alterations, T wave inversion, left atrial enlargement, abnormal Q waves, and diminished or absent R waves in the lateral leads. The chest radiograph may be normal or show left ventricular or atrial enlargement.

Echocardiography is the most important diagnostic strategy. Findings include asymmetrical left ventricular hypertrophy, left ventricular outflow tract narrowing, a small left ventricular cavity, and reduced septal motion. The dynamic characteristic of HCM distinguishes it from the discrete forms of obstruction to ventricular flow. Doppler techniques help assess the severity of this obstruction at rest and with provocative maneuvers.

Magnetic resonance is helpful when the echocardiogram is not. Nuclear studies can be used to assess systolic and diastolic ventricular function and ventricular scarring. Electrophysiologic studies may show dysrhythmias but are not more predictive of sudden death than clinical factors.[42] Genetic screening may be helpful to predict other family members at risk.

Differential Diagnosis

HCM mimics many disorders. In individuals who have a gradient and a loud systolic murmur, HCM may be confused with valvular diseases or ventricular septal defect. In the absence of a murmur, symptoms may suggest mitral valve prolapse, primary pulmonary hypertension, or coronary artery disease. ECG changes, without a history of preceding MI, may also suggest HCM. Echocardiography is often helpful, but ultimately cardiac catheterization may be necessary to confirm the diagnosis.

Management

Beta-blockers are the mainstay of therapy. They decrease the effect of catecholamines on the outflow gradient. This prolongs diastole, increases ventricular filling, and results in symptomatic improvement (primarily dyspnea and chest pain) and exercise tolerance.[43] Calcium channel blockers are also useful. Verapamil reduces obstruction, decreases contractility, and improves diastolic relaxation and filling. This improves exercise capacity, and the negative effects on heart rate and blood pressure decrease oxygen consumption and the incidence of angina. Verapamil is contraindicated when conduction blocks are present, but it should be considered when there is no response to beta-blockers. Another option is disopyramide.

Nitroglycerin, the traditional initial ED management for chest pain, is not indicated in HCM-associated chest pain because it decreases ventricular volume. Amiodarone is the drug of choice for treatment of ventricular dysrhythmias in HCM. Amiodarone may also control atrial fibrillation. Automatic implantable cardioverter defibrillators are indicated for patients with sudden death or a history of a sudden death risk factor.[44] It is probably not necessary to give prophylactic antibiotics in patients with HCM.[45]

Surgical treatment is reserved for patients with large (>50 mm Hg) systolic gradients, severe symptoms, and poor quality of life who do not respond to drug therapy. The most common procedure is septal myomectomy. Dual-chamber pacing decreases outflow gradient and improves symptoms, but it does not improve outcome.

Disposition

The natural history of HCM is variable and probably reflects the many different genetic etiologies. The annual mortality rate is 1%.

The onset of atrial fibrillation in patients with HCM may precipitate marked hemodynamic compromise and severe CHF. Cardioversion is indicated, as is rate control and anticoagulation to prevent thromboembolism.

Risk factors for sudden death include malignant genotype, unexplained syncope, sudden death in first-degree relatives, abnormal hemodynamic response to exercise, and greater than 30-mm ventricular thickening.[46]

Patients with HCM initially diagnosed in the ED should have strenuous physical activity specifically proscribed until evaluated by a cardiologist. Patients with HCM who have angina, syncope, near-syncope, dysrhythmias, and abrupt changes in cardiopulmonary status should be hospitalized.

RESTRICTIVE CARDIOMYOPATHY

Perspective

The hallmark of RCM is a gradual and progressive limitation of ventricular filling secondary to myocardial infiltration. RCM is the least common type of cardiomyopathy. The most common etiology is amyloidosis. Other etiologies include sarcoidosis, hemochromatosis, scleroderma, neoplastic cardiac infiltration, radiation heart disease, glycogen storage disorders, Fabry's disease, and Gaucher's disease.

The most common cause of RCM worldwide is tropical endomyocardial fibrosis, which is endemic to India, Africa, and Latin America. Symptoms include an initial viral-like illness followed by persistent fever, malaise, and the development of severe right-sided heart failure.

Principles of Disease

Restriction of ventricular filling results in low ventricular volumes, high end-diastolic ventricular pressures, and decreased cardiac output. Systolic function is maintained. Grossly, there is atrial enlargement with small ventricles. As the disease progresses, the ventricular cavities may become obliterated by fibrous tissue, scarring, or thrombus.

Clinical Features and Diagnostic Strategies

Symptoms are those of worsening diastolic dysfunction and include exercise intolerance (cardiac output cannot be increased because ventricular filling is compromised), elevated central venous pressure, peripheral edema, pulmonary edema, and S_3 and S_4 gallops on auscultation. Children can present with failure to thrive.

Differentiation from constrictive pericarditis requires CT, MRI, or Doppler echocardiography. Pericardial calcification favors a diagnosis of constrictive pericarditis over the diagnosis of RCM. Myocardial biopsy may be necessary.

Management and Disposition

Most of the underlying causes of RCM are untreatable.[12] The exception is hemochromatosis. Symptomatic treatment with vasodilators and diuretics may help. Patients with RCM should be maintained in sinus rhythm, since loss of the "atrial kick" is devastating. Transplantation is a possibility in some patients. RCM is relentless, with 90% of patients dying within 10 years of diagnosis.

PERIPARTUM CARDIOMYOPATHY

Perspective

Peripartum cardiomyopathy (PPCM) is uncommon. It represents less than 1% of the cardiovascular problems associated with pregnancy. PPCM is a form of DCM with symptoms and signs of heart failure that present initially during the last 3 months of pregnancy or the first 5 months postpartum.

Etiology and Epidemiology

The etiology of PPCM is unknown. Proposed etiologies include myocarditis, excessive use of tocolytics, preeclampsia, altered autoimmune response, selenium or nutritional disorders, or genetic predisposition. The incidence is estimated to be 1 case of PPCM per 3000 live births in the United States and is higher in other countries. It is more common in women who are older than age 29 years or African American.[47]

Clinical Features and Diagnostic Strategies

PPCM is clinically identical to DCM. Patients usually have symptoms of CHF but may also have chest pain, palpitations, or thromboembolism. Physical examination often reveals tachycardia, tachypnea, pulmonary rales, an enlarged heart, and an S_3 heart sound.

The ECG may show left ventricular hypertrophy or nonspecific ST-T wave changes. On echocardiography, all four chambers are enlarged with reduction in left ventricular systolic function.

Management and Disposition

Treatment of PPCM includes limitation of physical activity, beta-blockers, alteration of preload with nitrates and diuretics, increase in ventricular contractility, and afterload reduction.[48] Angiotensin-converting enzyme inhibitors are teratogenic and should be avoided, if possible, in pregnancy. Hydralazine and labetalol are effective and a good choice for treating PPCM in the ED.

Mortality for PPCM in the United States is approximately 2%.[47] Half of the survivors have complete or near-complete recovery of cardiac function within the first 6 months. Patients who do not recover completely show either continuous clinical deterioration or persistent left ventricular dysfunction. Subsequent pregnancies may be associated with a high risk of maternal mortality. In the ED, patients with signs of hemodynamic instability or failure to maintain oxygenation should be admitted for treatment and fetal monitoring.

ION CHANNELOPATHIES

Several uncommon dysrhythmic diseases are caused by mutations of genes for ionic channel proteins, which are cell membrane transport proteins for sodium and potassium. These include long QT syndrome, short QT syndrome, Brugada's syndrome, and catecholaminergic polymorphic ventricular tachycardia.[40]

SPECIFIC HEART MUSCLE DISEASES

Amyloidosis

Disorders of amyloid deposition are divided into two categories: primary amyloidosis (associated with a high incidence of cardiac involvement) and amyloidosis secondary to multiple myeloma, RA, tuberculosis, or lymphoma. In cardiac amyloidosis, the cells of the reticuloendothelial system are stimulated to deposit amorphous material in the ventricle, coronary arteries, or valves. Massive amyloid deposition results in an increased cardiac weight and the diastolic dysfunction of RCM. CHF occurs in most cases of cardiac amyloidosis. Treatment involves standard CHF and antidysrhythmic therapy, although the dysrhythmias in amyloid heart disease are often refractory to treatment. The prognosis is poor, with death often resulting from progressive heart failure within 1 year of symptom onset.[49]

Sarcoidosis

Cardiac granulomas occur in approximately 25% of cases of systemic sarcoidosis. Granulomas located in the septum cause severe conduction defects, those in the papillary muscles cause mitral regurgitation, and those in the ventricular walls produce scarring and wall motion abnormalities. Complete heart block is the most common conduction block. Ventricular dysrhythmias are often refractory to therapy. Myocardial involvement in sarcoidosis is an indication for systemic corticosteroid therapy. Refractory cardiac failure and dysrhythmias are indications for heart transplantation.

Connective Tissue Disorders and Disease of the Myocardium

Myocarditis associated with various connective tissue diseases occurs more often than is recognized clinically. Cardiac abnormalities occur in RA, juvenile RA, mixed connective tissue disease, and primary Sjögren's syndrome. SLE is the connective tissue disease most commonly associated with cardiac abnormalities. Cardiac involvement in SLE includes pericarditis, endocarditis, and myocarditis.

Primary myocardial involvement is a major complication of diffuse scleroderma and develops as scleroderma worsens. Estimates of the frequency of myocardial involvement in scleroderma vary widely. The clinical presentation includes CHF, angina, and dysrhythmias. Pericardial disease can also occur. Although prognosis is poor, azathioprine may be a beneficial adjunct to steroid therapy.[50]

Sudden Death

Approximately 25% of sudden deaths in patients younger than age 21 years can be attributed to disease of the myocardium. Cardiac etiologies include myocarditis, HCM, and anomalous coronary artery circulation. In patients with sudden death attributed to cardiac etiologies, prodromal symptoms are reported in more than half of the patients, most commonly chest pain (25%) in patients older than age 20 years and dizziness (16%) in patients younger than age 20 years. The distribution of sudden death etiologies by age is as follows:

- Age younger than 20 years—myocarditis 22% and HCM 22%
- Age 20 to 29 years—myocarditis 22% and HCM 13%
- Age 30 to 39 years—myocarditis 11% and HCM 2%

Coronary artery disease becomes the leading cardiac etiology (58%) in sudden death in people ages 30 to 39 years. HCM is the cardiac disease most commonly found on postmortem diagnosis of athletes with sudden death. HCM and anomalous coronary arteries are seen more often in sports-related deaths.

KEY CONCEPTS

- Pericarditis must be differentiated from acute MI. Thrombolytic therapy is contraindicated in pericarditis because of the potential for hemorrhagic pericarditis or tamponade.
- Cardiac tamponade must be suspected (distended neck veins, hypotension, and muffled heart sounds), diagnosed (echocardiography), and treated (pericardiocentesis) quickly. Pericardiocentesis may be diagnostic and therapeutic.
- Myocarditis should be considered in any patient with the combination of viral illness symptoms and signs of cardiac disease.
- The symptoms and signs of constrictive pericarditis are virtually indistinguishable from those of RCM.
- Patients with newly diagnosed hypertrophic cardiomyopathy should avoid strenuous exertion until evaluated by a cardiologist. Beta-blockers are the mainstay of therapy for HCM; avoid nitrates.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 81

Infective Endocarditis and Valvular Heart Disease

Joshua M. Kosowsky

INFECTIVE ENDOCARDITIS

Perspective

The term *infective endocarditis* (IE) has replaced the older classifications of *acute*, *subacute*, and *chronic* as they have become less meaningful in the antibiotic era. Although bacteria remain the most common etiology, virtually all organisms (including viruses, fungi, and rickettsiae) can cause endocarditis. Early diagnosis of endocarditis and treatment of the causative organism play a significant role in the clinical outcome.

Principles of Disease

Estimates of the incidence of IE in the United States vary widely, in part because of changing case definitions throughout the years but also because of differences in predisposing conditions among studied populations. For example, the incidence of IE among patients admitted to hospitals in Philadelphia was estimated to be 11.6 cases per 100,000 person-years from 1988 to 1990.[1] In contrast, the incidence of endocarditis in Olmsted County, Minnesota, during the period from 1970 to 2000 was 5.0 to 7.0 cases per 100,000 person-years.[2] Others report significantly lower rates.[3] IE is increasingly a disease of the aged, with more than 50% of cases occurring in individuals older than age 60 years. This reflects the pervasiveness of degenerative valve disease in the elderly and the increased prevalence of prosthetic heart valves.[4]

Most patients with bacterial endocarditis have a predisposing valvular abnormality. Among elderly patients, calcific or degenerative disease of the aortic and the mitral valve is the most common predisposing factor. Rheumatic heart disease, although less prevalent than in prior decades, remains an important predisposing factor for IE among individuals from developing countries. Congenital cardiac lesions involving high-pressure gradients (e.g., ventricular septal defects, pulmonary stenosis, and tetralogy of Fallot) also increase risk for IE. A history of previous endocarditis is a major risk factor for recurrence because infected valves heal with irregularities that become a nidus for future vegetations.

The incidence of IE associated with injection drug use is estimated at 150 to 200 per 100,000 person-years.[5] Although any valve can be affected, injection drug use is classically associated with right-sided endocarditis.

Prosthetic valve endocarditis is a unique and potentially devastating complication of valve replacement.[6] The incidence of endocarditis in prosthetic valve recipients ranges from 0.5 to 4% per year. Prosthetic valve endocarditis can arise early or late after surgery, and the timing of infection reflects different epidemiology and microbiology.

The 5-year mortality rate for native valve endocarditis is 20%, but in the presence of a prosthetic valve estimates range up to 60%.[7,8] The mortality for right-sided endocarditis in a patient with a history of injection drug use is approximately 10%.[9]

Pathophysiology

The classic lesion of endocarditis is the vegetation, originating as a sterile thrombus upon which microorganisms adhere and colonize. The initial thrombus may form at a site of mechanical damage induced by inflammation, degenerative changes, or abnormal turbulence. In injection drug users, contaminants such as talc can injure the previously normal valve leaflets and encourage bacterial implantation. Theoretically, the onset of bacterial endocarditis is preceded by a period of subclinical bacteremia. Dental procedures, cystoscopy, endoscopy, and other invasive procedures result in transient bacteremia, but more commonly there is no clear precipitant for community-acquired IE.

A number of microorganisms cause IE, with staphylococci and streptococci accounting for the majority of cases (Table 81-1). In a study of nearly 1800 patients with IE from 39 medical centers in 16 countries, staphylococci were the etiologic agents in 42% (commonly associated with injection drug use) and streptococci in 40%.[10]

The microbiology of prosthetic valve endocarditis relates to the time of onset: *Staphylococcus aureus* is by far the most prevalent pathogen in the first two months following valve replacement. Subsequently, the microbiology mirrors native valve endocarditis.[11]

Among injection drug users, the most common infecting organism by far is *S. aureus*, particularly in right-sided infections.[12]

The HACEK group (*Haemophilus aphrophilus*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*) are fastidious gram-negative bacilli that are difficult to isolate. *Bartonella* species are another group of fastidious organisms associated with IE immunocompromised patients.

Candida and *Aspergillus* species cause most cases of fungal endocarditis. Predisposing factors include indwelling IV catheters, immunocompromise, and injection drug use. Large

Table 81-1 Epidemiology of Infective Endocarditis

MICROORGANISM	%
Staphylococcus aureus	32
Viridans group streptococci	18
Enterococci	11
Coagulase-negative staphylococci	11
Streptococcus bovis	7
Other streptococci	5
Non-HACEK gram-negative bacteria	2
Fungi	2
HACEK	2
Other organisms	3
Polymicrobial	1
Culture negative	8

HACEK group, *Haemophilus aphrophilus*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*.

fungal vegetations can embolize, and histologic analysis of these emboli may be the only clue suggesting fungal endocarditis.

Clinical Features

Symptoms associated with IE are nonspecific and diverse. The most common symptoms are intermittent fever (85%) and malaise (80%). Other symptoms (e.g., weakness, myalgias, back pain, dyspnea, chest pain, cough, headaches, and anorexia) vary widely in their incidence and are also nonspecific. Many patients who present early during the bacteremic phase of the illness do not have a cardiac murmur and are indistinguishable from the large population of patients who present to the emergency department (ED) with a febrile viral illness. During the initial assessment, a careful history should be performed with attention to any preexisting cardiac pathology or clues suggesting a recent source of bacteremia, such as intravenous drug use, indwelling intravascular catheters, or invasive procedures. In the absence of specific risks, the diagnosis of IE may be suspected when infectious symptoms persist or do not follow a typical course for viremia. The classic triad of fever, anemia, and heart murmur is rare.

Almost all patients with IE have a cardiac murmur at some time during the course of their illness. A murmur, however, may be absent at presentation. For example, fewer than 35% of IV drug users with endocarditis present with a murmur.[13] In this population, unexplained fever alone is sufficient to raise concern about possible endocarditis. A substantial minority of patients exhibit some form of vasculitic lesion, including petechiae, splinter hemorrhages, Osler's nodes, and Janeway lesions. Approximately 30% of patients have splenomegaly. Ocular findings include conjunctival or retinal hemorrhages, the latter of which may have a characteristic pale center surrounded by a red halo (Roth's spots).

Diagnostic Strategies

Laboratory findings in bacterial endocarditis are nonspecific. Similar to other infectious conditions, leukocytosis is insensitive (occurring in approximately 50% of patients diagnosed with IE) and nonspecific. An elevated erythrocyte sedimentation rate or C-reactive protein may be present, but these are also nonspecific. Most patients have a mild anemia, and up to 50% have microscopic hematuria as a result of embolic lesions of the kidney. A chest radiograph may show signs of heart failure, and an electrocardiogram (ECG) may display conduction abnormalities if an abscess has formed in the myocardium.

Three blood cultures from three separate venipuncture sites should be obtained for all patients with a presumptive diagnosis of possible endocarditis, with the first and last culture drawn at least 1 hour apart. Approximately 90 to 95% of blood cultures are positive unless antibiotics have already been administered.[14] If the patient appears septic, cultures may be obtained more rapidly to permit initiation of early empiric therapy. Cultures need not be timed to the presence of chills or fever because patients with IE typically have a continuous bacteremia.

An echocardiogram should be performed in all patients with a moderate to high suspicion of endocarditis. Although transthoracic echocardiography (TTE) is highly specific for vegetations in IE, it may be nondiagnostic in up to 20% of patients because of obesity, chronic obstructive pulmonary disease, and chest wall deformities. Overall sensitivity of TTE is at most 60%.[15] Transesophageal echocardiography (TEE), on the other hand, although more invasive and time-consuming, is far superior to TTE in its sensitivity.[16] The negative predictive value for IE with a normal TEE without prosthetic valves approaches 100%.[17]

Explicit criteria for the diagnosis of IE are important since underdiagnosis can lead to serious morbidity and death, whereas overdiagnosis can result in weeks of unnecessary antimicrobial therapy. The Duke criteria are the most widely accepted, and they stratify patients with suspected bacterial endocarditis into three distinct categories: definite, possible, and rejected (Box 81-1).[18] The sensitivity and specificity of the Duke criteria are approximately 95% and 99%, respectively.[19-22]

Management

Once the diagnosis of IE is established, whether by clinical, echocardiographic, or microbiologic methods, antimicrobial therapy should be administered. Choice of antibiotics depends on the likely (or known) causative organism but is usually empiric. Guidelines for empirical antibiotic therapy in patients with suspected IE are provided in Box 81-2.

Febrile patients with suspected IE require admission for definitive diagnosis and initiation of empirical therapy. An exception might be an otherwise well-appearing injection drug user with transient fever that is attributed to an injected contaminant ("cotton fever").

Consultation with an infectious diseases specialist or a cardiologist may be useful. Also, early consultation with a cardiac surgeon should be obtained for all cases in which mechanical complications are observed or expected (such as in infections involving prosthetic valves).

With appropriate antibiotic therapy, most patients with IE will defervesce within 1 week. The duration of antibiotic therapy must be sufficient to eradicate microorganisms present within the valvular vegetations. This may require up to 6 weeks, depending on the organism and the type of vegetation. Historically, most patients with IE received the entire antimicrobial therapy while in the hospital. The development of home health care, however, has allowed selected patients with endocarditis to be treated as outpatients during much or all of their therapy. Patients selected for outpatient therapy should be hemodynamically stable, compliant, and capable of managing the technical aspects of IV therapy.

BOX 81-1 DUKE CRITERIA (CLINICAL) FOR DIAGNOSIS OF INFECTIVE ENDOCARDITIS

Definite Endocarditis
Endocarditis is considered definitely present if any one of the following combinations of clinical findings is present:

- Two major clinical criteria
- One major and any three minor clinical criteria
- Five minor clinical criteria

Possible Endocarditis
Possible endocarditis is defined as the presence of any one of the following combinations of clinical findings:

- One major and one or two minor clinical criteria
- Three minor clinical criteria

Rejected Endocarditis
The diagnosis of endocarditis is considered rejected if any of the following are present:

- A firm alternate diagnosis is made
- Resolution of clinical manifestations occurs after 4 days of antibiotic therapy or less
- Clinical criteria for possible or definite infective endocarditis not met

Major Criteria
Positive blood cultures (of typical pathogens) from at least two separate cultures
Evidence of endocardial involvement by echocardiography, such as the following:
Endocardial vegetation
Paravalvular abscess
New partial dehiscence of prosthetic valve
New valvular regurgitation

Minor Criteria
Predisposition: Predisposing heart condition or IV drug use
Fever: ≥38° C
Vascular phenomena: Arterial emboli, septic pulmonary infarcts, mycotic aneurysm, conjunctival hemorrhages, or Janeway lesions
Immunologic phenomena: Osler's nodes, Roth's spots, and rheumatoid factor
Microbiologic evidence: Single positive blood culture (except for coagulase-negative *Staphylococcus* or an organism that does not cause endocarditis)
Echocardiogram findings: Consistent with endocarditis but do not meet major criteria

BOX 81-2 INITIAL EMPIRICAL THERAPY FOR BACTERIAL ENDOCARDITIS

Native Valve
Penicillin G 5 million units IV q 4 hr + nafcillin 2 g IV q 4 hr
Or
Vancomycin 15 mg/kg IV q 12 hr
Plus
Gentamicin 1 mg/kg IV q 8 hr

Native Valve (+ Injection Drug Use)
Vancomycin 15 mg/kg IV q 12 hr

Prosthetic Valve
Vancomycin 15 mg/kg IV q 12 hr
Plus
Gentamicin 1 mg/kg IV q 8 hr

BOX 81-3 HIGH-RISK CONDITIONS FOR BACTERIAL ENDOCARDITIS

Prosthetic heart valve
History of endocarditis
Unrepaired cyanotic congenital heart disease, including palliative shunts and conduits
Completely repaired congenital heart defects with prosthesis during the first 6 months after the procedure
Repaired congenital heart disease with residual defect at or adjacent to the site of the prosthetic device
Cardiac valvulopathy in a transplanted heart

Prophylaxis

The American Heart Association has updated guidelines, limiting prophylaxis to conditions with the highest risk of adverse outcome from IE (Box 81-3).[23] Virtually all of the procedures that are routinely performed in the ED, including suturing of lacerations, endotracheal intubation, placement of central venous catheters, vaginal deliveries, and placement of Foley catheters (in the absence of infection), do not require prophylactic antibiotics.

RHEUMATIC FEVER

Perspective

From 1920 to 1950, acute rheumatic fever (ARF) was the leading cause of death in U.S. children and the most common cause of heart disease in individuals younger than age 40 years. During the 1960s and 1970s, the incidence of ARF in the United States and other developed countries declined dramatically because of widespread antibiotic treatment of streptococcal infections, declining prevalence of the more virulent strains of group A streptococci, and improved living conditions. Children between 4 and 9 years of age remain at greatest risk, with an incidence of ARF between 2 and 14 cases per 100,000.[24] In many developing nations, however, ARF continues to be a leading cause of childhood mortality.

Principles of Disease

ARF is a delayed, nonsuppurative complication of streptococcal pharyngitis. Although the pathogenesis remains obscure, ARF may result from a particular immunologic response to group A β-hemolytic streptococci that results in antibodies cross-reacting with tissues in the heart, joints, skin, and central nervous system.

Clinical Features

After the initial pharyngitis, there is a latency period ranging from 1 to 5 weeks (average, 18 days) before symptoms and signs of ARF appear. Up to one third of patients with documented ARF do not remember having pharyngitis in the preceding month. Fever is present during the acute phase of rheumatic fever. It rarely lasts more than 2 weeks and has no characteristic pattern. Along with fever, manifestations of ARF may include arthritis, carditis, chorea, subcutaneous nodules, and erythema marginatum.

Migratory polyarthritis is the most common manifestation of ARF. Arthritis tends to occur early in the course of ARF and often coincides with a rising titer of streptococcal antibodies. The polyarthritis classically affects larger joints, such as the knees, ankles, elbows, and wrists, and the pain can be more

severe than physical findings suggest. Analysis of the synovial fluid generally reveals a sterile inflammatory fluid.

Cardiac manifestations of ARF may be subtle and can include symptoms and signs of pericarditis, myocarditis, and endocarditis. The mitral valve is the most common valve affected in ARF, causing mitral regurgitation accompanied by a new, high-pitched, systolic murmur. Inflammation of the valvular endocardium can result in permanent deformity and impairment of one or more cardiac valves over the course of decades. Stenotic lesions of the mitral or aortic valves are unusual at presentation, but they are common late manifestations of rheumatic heart disease.

Chorea (Sydenham's chorea and St. Vitus' dance) is manifested by random, rapid, purposeless movements usually of the upper extremities and face. These can be associated with emotional outbursts. Chorea is relatively rare in ARF and tends to emerge after a longer latency period than some of the other manifestations. Erythema marginatum and subcutaneous nodules are found in fewer than 10% of cases of ARF. Their presence, however, should immediately suggest the diagnosis. Erythema marginatum is a nonpruritic, painless, evanescent "smoke ring" of erythema that commonly appears on the trunk and proximal extremities. Subcutaneous nodules are pea sized and nontender. They typically appear over the extensor surfaces of the wrists, elbows, knees, and occasionally the spine.

Diagnostic Strategies

In 1944, Jones[25] formulated major and minor criteria for the diagnosis of ARF. After multiple revisions, the Jones criteria remain the diagnostic basis for this disease (Box 81-4).[26] The diagnosis of ARF requires evidence of an antecedent streptococcal infection plus at least two major, or one major and two minor, manifestations from the Jones criteria. Although throat cultures are usually negative at the time of clinical onset of ARF, antistreptolysin antibody titers remain positive for 4 to 6 weeks from the time of infection. Erythrocyte sedimentation rate and C-reactive protein levels are typically elevated, and a prolonged P-R interval is common and suggestive in ARF.

Management

All patients with ARF should receive antibiotic therapy regardless of the clinical history of pharyngitis. Penicillin can be administered orally (250 mg for children and 500 mg for adults, two or three times daily for 10 days) or intramuscularly (600,000 U benzathine penicillin in children weighing <25 kg and 1.2 million U in adults as a one-time dose).

Treatment for arthritis consists of anti-inflammatory agents, most commonly aspirin, administered until symptoms are absent and the erythrocyte sedimentation rate and C-reactive protein concentration normalize. Patients with severe carditis are often treated with corticosteroids, but their effects show conflicting results.[27]

Patients with ARF should receive ongoing prophylactic antibiotics (generally penicillin) to prevent recurrences. The recommended duration of secondary prophylaxis varies depending on the presence and severity of cardiac involvement.[28]

BOX 81-4 JONES CRITERIA (REVISED) FOR THE DIAGNOSIS OF ARF

Major Manifestations
Carditis
Polyarthritis
Chorea
Erythema marginatum
Subcutaneous nodules

Minor Manifestations
Arthralgias
Fever
Increased erythrocyte sedimentation rate or C-reactive protein
Prolonged P-R interval

Evidence of Preceding Streptococcal Infection
Positive throat culture for group A β-hemolytic streptococci or positive rapid streptococcal antigen test
Elevated or rising streptococcal antibody titer, most often antistreptolysin O

VALVULAR HEART DISEASE

Valvular Anatomy

Of the four heart valves, three (tricuspid, pulmonic, and aortic) are composed of three cusps, whereas the mitral valve has only two cusps. Each cusp is a double layer of endocardium that is attached at its base to the fibrous skeleton of the heart. The margins of the cusps are attached to muscular projections from the ventricles (papillary muscles) via tendinous cords (chordae tendineae). Contraction of the ventricle and consequently the papillary muscle results in the opening or closing of the valve depending on its location.

Mitral Stenosis

The most common cause of mitral stenosis is rheumatic heart disease, with the majority of patients exhibiting mitral stenosis. Symptoms of valvular dysfunction typically present after a latency period of one to three decades. Many patients will not recall a history of ARF. Less common causes of mitral stenosis include congenital mitral stenosis and mitral annular calcification.

Pathophysiology

The normal cross-sectional area of the mitral valve orifice is 4 to 6 cm^2. Stenosis becomes clinically significant when the area falls below 2 cm^2. Impeded flow from the left atrium to the left ventricle results in left atrial hypertension, restricted cardiac output, and, ultimately, pulmonary congestion. As the disease progresses, patients may develop pulmonary hypertension and right ventricular failure.

The most common complication of mitral stenosis is atrial fibrillation, which in the absence of rate control is generally not well tolerated. Patients with underlying mitral stenosis will decompensate under other conditions associated with increased cardiac demand and reduced ventricular filling, such as pregnancy, anemia, infection, and hyperthyroidism.

Clinical Features

Early symptoms of mitral stenosis include reduced exercise tolerance and dyspnea on exertion. Patients with more advanced disease may present with orthopnea and, if right ventricular failure is present, peripheral edema. Hemoptysis, due to rupture of a bronchial vein, and hoarseness, due to compression of the recurrent laryngeal nerve, are classic but rare presentations. Aside from the typical signs of heart failure, findings that suggest the presence of mitral stenosis include a loud S_1 and an opening snap in early diastole accompanied by a low-pitched, rumbling diastolic apical murmur.

Although the chest x-ray may be normal, in more advanced cases left atrial enlargement may be suggested by straightening of the left heart border. Common ECG abnormalities in addition to atrial fibrillation include left atrial enlargement and, ultimately, right ventricular hypertrophy. Echocardiography is required to confirm the diagnosis and assess the severity of disease.

Management

Medical treatment for patients with mitral stenosis comprises diuresis for symptoms of vascular congestion and anticoagulation for atrial fibrillation.[29] Once symptoms have developed, however, median survival without intervention is 7 years. Several surgical options exist, ranging from balloon valvulotomy or open commissurotomy to valve reconstruction or replacement. Management of the patient with mitral stenosis in the ED centers on identification and treatment of underlying precipitants such as atrial fibrillation or anemia, diuresis, and referral for definitive intervention.

Mitral Regurgitation

Acute and chronic mitral regurgitation are two distinct disease entities. Acute mitral regurgitation is a true emergency. It can result from idiopathic rupture of chordae tendineae, papillary muscle dysfunction in the setting of acute ischemia (or rupture 2–7 days postinfarction), or, rarely, perforation of a valve leaflet in the setting of infectious endocarditis or trauma. Chronic mitral regurgitation, on the other hand, most commonly occurs either in the setting of dilated cardiomyopathy (due to enlargement of the mitral annular ring) or in the setting of rheumatic heart disease. This frequently coexists with mitral stenosis. Other causes of chronic mitral regurgitation include mitral valve prolapse and connective tissue disorders, such as Marfan's syndrome and Ehlers-Danlos syndrome.

Pathophysiology

Acute mitral regurgitation is associated with low left atrial compliance and thus sharply elevated left atrial pressure that results in acute pulmonary congestion. In contrast, chronic mitral regurgitation is characterized by high left atrial compliance and near-normal left atrial pressures with reduced forward output. Patients with chronic mitral regurgitation typically decompensate in the setting of volume overload.

Clinical Features

The characteristic presentation of acute mitral regurgitation is one of fulminant pulmonary edema. This is accompanied by a unique, harsh, midsystolic murmur that radiates to the base and not the axilla. Patients typically have no prior history of heart failure. The electrocardiogram may display signs of ischemia or infarction.

The presentation of chronic mitral regurgitation is similar to that of chronic systolic heart failure with clinical symptoms and signs of decompensated congestion. The murmur is classically described as holosystolic, heard best at the apex and radiating to the axilla. The ECG often reflects both left atrial and ventricular hypertrophy. Atrial fibrillation is common, and left atrial enlargement may be suggested by the chest x-ray. Echocardiography may demonstrate a normal or above-normal ejection fraction, but much of the diastolic flow is retrograde.

Management

When the diagnosis of acute mitral regurgitation is suspected, emergency echocardiography and cardiac catheterization will assess the degree of regurgitation and urgency for surgery. Initial stabilization should include treatment of pulmonary edema with nitrates and diuretics. In a hypotensive patient, a counterpulsation intra-aortic balloon pump may provide temporary stabilization as a bridge to surgery.

The natural history of chronic mitral regurgitation is generally a very slow progression with a 15-year survival approaching 70% with medical therapy, including diuretics and afterload reducing agents. Once the ejection fraction falls below 60%, valve repair or replacement is advisable before the development of irreversible left ventricular dysfunction.[30]

Aortic Stenosis

The most common cause of aortic stenosis is calcific degeneration, which is prevalent in the elderly with coronary artery disease. This also occurs in younger individuals with a bicuspid aortic valve. Aortic stenosis can also occur along with mitral stenosis in rheumatic heart disease.

Pathophysiology

The normal aortic valve area is greater than 3 cm^2. Significant obstruction occurs when the valve area is reduced by more than 50%. *Critical aortic stenosis* is defined as a valve area of less than 0.8 cm^2 or when the pressure gradient across the valve exceeds 50 mm Hg. Compensatory left ventricular hypertrophy can maintain cardiac output until the stenosis becomes severe. Further progression of disease is associated with left ventricular dysfunction, left atrial enlargement, and atrial fibrillation. Individuals with severe or critical aortic stenosis are preload dependent and have very little cardiovascular reserve. Disruption of the delicate balance between myocardial oxygen supply and demand (e.g., ischemia, rapid atrial fibrillation, dehydration, and acute blood loss) can result in precipitous decompensation.

Clinical Features

Classic symptoms of aortic stenosis progress from angina (increased demand due to wall stress and decreased supply due to reduction in perfusion pressure) to exertional syncope (fixed cardiac output and vasodepressor response) and congestive heart failure (diastolic and systolic dysfunction). In an older patient presenting with chest pain, particularly if seemingly preload dependent, the possibility of aortic stenosis should be considered.[31]

The classic auscultatory finding in aortic stenosis is a crescendo-decrescendo systolic murmur heard best at the base (right second intercostal space) that radiates into the carotids and is associated with the presence of an S_4 gallop and a soft aortic component of S_2. Importantly, as the severity of disease increases, the murmur peaks later and becomes less apparent. Carotid pulses may be delayed (*tardus*) and diminished in intensity (*parvus*). The ECG typically reveals left ventricular hypertrophy. Echocardiography is required for assessment of the severity of stenosis and the presence of left ventricular dysfunction.

Management

The natural history of aortic stenosis is one of slow progression without symptoms for years. Once symptoms develop, survival

is markedly reduced unless the valve is replaced, and medical management has a limited role. Management of decompensated aortic stenosis in the acute setting centers on judicious fluid resuscitation, blood transfusion, restoration of sinus rhythm, and avoidance of vasodilators and diuretics and inotropic agents if possible. When there is no response to medical therapy and the patient is a candidate for valve replacement, an intra-aortic balloon pump may provide a bridge to surgery.

Aortic Insufficiency

Aortic insufficiency, whether acute or chronic, may reflect valvular abnormalities caused by a congenital bicuspid valve, rheumatic heart disease, or infectious endocarditis. In addition, aortic root abnormalities such as ectasia, aneurysm, or dissection may be associated with a variety of connective tissue diseases, including Marfan's syndrome.

Pathophysiology

With acute aortic insufficiency, left ventricular compliance is low and left ventricular pressure increases rapidly, leading to acute pulmonary congestion. The pressure gradient between the aorta and the left ventricle is minimal. In chronic aortic insufficiency, the left ventricle dilates, allowing the heart to maintain normal or near-normal cardiac output despite significant regurgitation. The enhanced stroke volume results in a wide pulse pressure and the associated clinical signs. Congestion is typically associated with volume overload.

Clinical Features

Patients with acute aortic insufficiency may present with a history suggestive of aortic dissection or aneurysm or severe respiratory distress and even frank cardiogenic shock. Acute aortic insufficiency can present with subtle physical findings. The pulse pressure may not be widened, and the short, soft, diastolic murmur may be difficult to detect. Echocardiography, which may be required emergently, is diagnostic.

With chronic aortic insufficiency, a widened pulse pressure may be accompanied by a number of physical findings, such as a rapidly rising and falling carotid pulse (water-hammer or Corrigan's pulse), spontaneous nailbed pulsations (Quincke's sign), or a to-and-fro murmur over the femoral artery (Duroziez's sign). A high-pitched, blowing, diastolic murmur at the left sternal border is characteristic of chronic aortic insufficiency. An Austin-Flint murmur, a soft diastolic rumble caused by the regurgitant stream against the mitral valve, may also be present.

Management

Acute aortic insufficiency is a surgical emergency requiring immediate valve replacement. Medical stabilization entails the cautious use of vasodilators and diuretics. Intra-aortic balloon counterpulsation is contraindicated in the presence of an incompetent aortic valve. In contrast, chronic aortic insufficiency is managed like other types of decompensated heart failure. Valve repair or replacement should be contemplated before the development of left ventricular systolic dysfunction.[32]

Mitral Valve Prolapse

Mitral valve prolapse (MVP) is defined pathophysiologically as an abnormal movement of one or both of the mitral valve leaflets across the plane of the valve during systole. Although generally a benign condition, it is infrequently associated with more serious cardiac pathology such as mitral regurgitation, endocarditis, and arrhythmias. Echocardiographic studies report a true prevalence of less than 1% in both men and women versus the previously reported 5% with a female predominance.[33]

Pathophysiology

Structurally, MVP is characterized by myxomatous proliferation of the spongiosa layer within the mitral valve that results in abnormal billowing of the leaflet during systole. MVP may be associated with other connective tissue disorders, such as Marfan's syndrome and Ehlers-Danlos syndrome. Although any of the leaflets may prolapse, involvement of the posterior leaflet is more likely to be associated with mitral regurgitation and other cardiovascular complications.[34]

Clinical Features

MVP is associated with a wide variety of clinical symptoms, including chest pain, palpitations, dyspnea, lightheadedness, and fatigue. However, appropriately controlled clinical studies, such as the Framingham Heart Study, suggest that patients with MVP and control subjects may be equally symptomatic.[35] The classic auscultatory features of MVP are a midsystolic "click" followed by a midsystolic to late systolic murmur over the mitral area. This click results from snapping of the chordae tendineae during the prolapse of the valve.

Diagnostic Strategies

The typical auscultatory findings should suggest MVP that is confirmed by echocardiography. Symptoms attributed to MVP, however, are often not explained by the degree of prolapse or mitral regurgitation. In some of these patients, autonomic or neuroendocrine dysfunction may be a cause of nonspecific symptoms.

Management

Propranolol or cardioselective beta-blockers may control symptoms such as palpitations, chest pain, and anxiety. Lifestyle modifications, such as exercise, relaxation techniques, and avoidance of ethanol or caffeine and other stimulants can also be helpful. Often, simple reassurance about the benign nature of the disease will suffice. The 2007 American Heart Association endocarditis prophylaxis guidelines no longer require consideration of mitral valve prolapse as one of the conditions requiring antibiotic prophylaxis.

Complications of Prosthetic Valves

Prosthetic heart valves are classified as either mechanical, constructed entirely of synthetic material, or biologic. The latter category includes whole valve transplants (porcine or human) as well as bioprosthetic valves manufactured from bovine pericardium. All prosthetic heart valves are associated with complications ranging from structural failure and thrombosis to systemic embolization, hemolysis, and endocarditis. The diagnosis of a prosthetic valve complication can be challenging because symptoms and signs are often subtle. The overall incidence of complications is approximately 3% per year.[36]

Primary structural failure is extremely uncommon with modern mechanical valves. When it does occur, the presentation is one of acute severe regurgitation and shock, mandating emergent replacement. With biologic valves, in contrast, struc-

tural failure is less dramatic but relatively more common. At 10 years, 20 to 30% of bioprosthetic valves will exhibit evidence of structural failure, and most are replaced electively. Symptoms are characteristically insidious in onset and mimic native valve disease.

Prosthetic valve thrombosis has an incidence of approximately 2% per year, both with biologic valves and with appropriately anticoagulated mechanical valves. Symptoms are of variable duration, generally subacute, and typically mimic congestive heart failure. The diagnosis is often initially overlooked, and untreated mortality approaches 15%. On physical examination, the diagnosis is suggested by a decreased or absent valve click, a new regurgitant murmur, or a louder than expected stenotic murmur. Echocardiography may demonstrate the thrombus or restricted leaflet motion suggesting obstruction. Treatment options include fibrinolytic therapy and surgery.[37]

The incidence of systemic embolization from a prosthetic valve is approximately 1% per year. Compared to patients with aortic valve prostheses, those with mitral valve prostheses have twice the risk of systemic embolization, with an incidence roughly the same in the case of a biologic valve or mechanical valve in an appropriately anticoagulated patient. The target international normalized ratio is 3.0 to 3.5 with a mechanical mitral valve versus 2.5 to 3.0 with an aortic valve. The vast majority of diagnosed embolic events (85%) involve the central nervous system, and roughly half of these result in permanent impairment. In this context, the risk of continued anticoagulation and possible hemorrhagic conversion must be weighed against the risk of a second embolic event.

Hemolytic anemia resulting from sheer forces around a prosthetic valve is usually mild and subclinical, but it may be severe in up to 15% of patients with certain prostheses. Presenting features can be subtle and include dyspnea, fatigue, jaundice, or dark urine. Iron replacement is effective in the majority of patients, although transfusion can be required, and reoperation may be indicated if hemolysis is due to a periprosthetic leak or other structural failure.

The incidence of prosthetic valve endocarditis is highest during the initial months following surgery and is similar for both mechanical and bioprosthetic valves.[11] Early prosthetic valve endocarditis (within 60 days of surgery) is presumed to be caused by a pathogen acquired perioperatively and is associated with higher morbidity and mortality, whereas late prosthetic valve endocarditis is more likely related to transient bacteremia and is generally associated with a more benign course. As with other forms of endocarditis, fever is by far the most common presenting symptom, and other manifestations are quite variable. Echocardiography can identify vegetations, but a normal study does not rule out endocarditis. In the ED, the diagnosis of prosthetic valve endocarditis is presumptive since the definitive diagnosis requires blood cultures or biopsy. As such, prosthetic valve patients with no obvious extracardiac source of fever, particularly within 60 days of surgery, should be considered for inpatient admission.

KEY CONCEPTS

- Many patients who present early in the bacteremic phase of IE lack a murmur and are indistinguishable from those with a viremia.
- Patients with a moderate to high suspicion of endocarditis require blood cultures, echocardiography, and admission for definitive diagnosis and initiation of empiric therapy.
- Prophylaxis for IE is rarely if ever indicated for procedures performed in the ED.
- Acute rheumatic fever is a delayed, nonsuppurative complication of streptococcal pharyngitis characterized by arthritis, carditis, chorea, subcutaneous nodules, and erythema marginatum.
- Patients with valvular stenosis (mitral and aortic) typically present with advanced disease, often exacerbated by atrial fibrillation.
- In patients with critical aortic stenosis, excessive preload reduction is to be avoided.
- In patients with acute aortic insufficiency, classic physical findings may be absent.
- Complications of prosthetic heart valves range from structural failure and thrombosis to systemic embolization, hemolysis, and endocarditis.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 82 Hypertension

Richard O. Gray

PERSPECTIVE

For most of the 20th century, elevated blood pressure (BP) readings were thought to be associated with, but not causing, morbidity and mortality. Not until large population-based studies in the 1960s, such as the Framingham study, did physicians begin to focus on hypertension as a treatable risk factor for stroke, myocardial infarction (MI), peripheral vascular disease, congestive heart failure, and renal disease. Medical management of hypertension has reduced stroke mortality by 50% on an age-adjusted basis and has probably contributed to the decline in mortality from coronary artery disease. As a matter of public health, however, much remains to be done in the treatment of hypertension. Although approximately 75% of patients with chronically elevated BP are aware of their disease, as few as one half to one fourth of these patients are adequately treated and most surveillance data suggest this is not improving.[1-3] Although hypertension may be epidemic, it rarely represents an emergency condition for the individual patient. In the absence of acute end-organ damage, it is rarely, if ever, necessary to lower a patient's BP acutely in the emergency department.

Hypertension is frequently encountered in the emergency department (ED), where many factors can cause elevated BP. Patients may measure their own blood pressure in a retail pharmacy and present to the ED concerned that a symptom they are experiencing is caused by the blood pressure elevation. Anxiety and pain often cause transient hypertension, but evaluation of the patient for evidence of acute end-organ ischemia is important. Most patients, even those with an exacerbation of chronically elevated BP, show a substantial decrease in pressure without intervention during a short observation period in the ED.[4-6] Even if the patient's BP does remain elevated, urgent treatment is rarely beneficial or indicated, unless there is evidence of end-organ damage. Patient education and appropriate referral for long-term management should be provided.[7]

PRINCIPLES OF DISEASE

Definition and Determination of Hypertension

The Joint National Committee on Prevention, Evaluation, and Treatment of High Blood Pressure in its seventh report has dramatically changed how it classifies hypertension. In adults, a sustained systolic pressure less than 120 mm Hg and a diastolic pressure less than 80 mm Hg are considered normal. If the systolic pressure is between 120 and 139 mm Hg or if the diastolic pressure is between 80 and 89 mm Hg, the term *prehypertension* is applied, reflecting that the lifetime incidence of hypertension in these individuals is twice that of individuals in the "normal" range.[2] The patient with a sustained systolic pressure of 140 mm Hg or higher or a diastolic pressure higher than 90 mm Hg is considered to be hypertensive. If hypertension, as defined by these arbitrary values, is not controlled, the patient is at great risk for long-term morbidity and mortality.[2,8] The diastolic pressure is the primary determinant of future cardiovascular risk and is the most prevalent form of hypertension in patients younger than 50 years. In the two thirds of adults older than 65 years who have hypertension, systolic hypertension is more common and represents their greatest cardiovascular risk. Even isolated systolic hypertension in elderly patients is a significant risk factor for cardiovascular disease, especially when combined with other risk factors. In older patients, an elevated pulse pressure (determined by subtracting diastolic from systolic pressure) is an equally significant risk factor for stroke and MI.[9-11]

Proper technique is required to obtain accurate BP readings. In patients with large extremities, a standard-size cuff may give a falsely elevated BP. A larger cuff should be used. With rapid deflation, inertia causes a gap between the actual pressure in the cuff and the measured pressure on the gauge. The systolic pressure should be recorded when the first tapping sound is heard as the cuff is deflated. Although several endpoints have been used to define diastolic pressure, the most widely accepted is the total disappearance of sound. In patients who do not have complete disappearance of these sounds, the point of distinct muffling should be recorded as the diastolic pressure.

A single elevated BP does not necessarily mean that the patient has hypertension. This is especially true in children.[12] BP measurement should be repeated after the patient is in a reclining position for at least 10 minutes and should be checked in both arms. If the second reading is also elevated or close to the hypertensive range, the patient should be advised of the potential for hypertension and referred for repeated blood pressure determinations in an ambulatory care setting.

Pathophysiology

Hypertension is not a single disease but, rather, the result of a number of disease processes. By far the most common cate-

gory is *essential hypertension*. No specific cause of essential hypertension has been identified, although heredity, age, race, obesity, and the amount of dietary sodium may contribute to elevated BP.[12] Prehypertension has been intensely studied because patients who later become hypertensive may provide clues about the physiologic changes that eventually produce a fixed elevation of BP. Two major theories exist: (1) hypertension results from alterations in the contractile properties of smooth muscle in arterial walls, and (2) alterations of arterial smooth muscle are a response to chronically elevated BP resulting from a primary failure of normal autoregulatory mechanisms. Research has focused on the role of calcium ions in vascular smooth muscle. Vascular tone depends on a transmembranous supply of calcium ions, and calcium antagonists suppress virtually all vasoconstrictive responses of vascular smooth muscles, including the peripheral resistance vessels.

Most patients with established hypertension have elevated peripheral arterial resistance and normal cardiac output. The findings are similar in the majority of prehypertensive individuals, many of whom have decreased plasma volume and elevated heart rate. This tachycardia seems to be caused not by an increased sympathetic tone but by a decreased parasympathetic tone. Autoregulatory mechanisms are blunted, and pharmacologic autonomic blockade has minimal effect on BP.

Other patients with hypertension have a very different circulatory status with an elevated cardiac output and hyperkinetic circulation. The increase in cardiac output results from an increase in both heart rate and stroke volume. There appears to be a large sympathetic component with an increase in both cardiac beta-adrenergic and alpha-adrenergic tone. Autonomic blockade returns the BP readings to normal.

Renin, Angiotensin, and Aldosterone

The role of renin and angiotensin as a cause of essential hypertension is not clear. Renin is an enzyme produced by the kidney that splits off angiotensin I from a plasma globulin precursor.[13] Angiotensin I is converted by an enzyme in the lung to produce angiotensin II. Angiotensin II is a potent vasoconstrictor and also stimulates aldosterone production in the adrenal gland. Figure 82-1 depicts the renin-angiotensin-aldosterone axis. Patients with hypertension may be divided into clinical groups according to renin levels. Determining the renin-sodium profile, which is the plasma renin activity measured against the 24-hour urine sodium content, is especially useful in making this distinction.

In normal individuals, angiotensin effects depend on sodium levels. Inhibition of angiotensin-converting enzyme (ACE) has some effect on BP in normotensive individuals with normal total body sodium but greatly reduces BP in those with sodium depletion. When ACE inhibitors are administered to patients with hypertension, their acute effect on BP is closely related to the plasma renin activity. With chronic administration, however, the effect of ACE inhibitors on BP no longer correlates with pretreatment plasma renin activity.[14] Elevated renin and angiotensin levels are responsible for the hypertension seen in ischemic renal disease, and angiotensin is a major contributor to maintaining the progressive rise of BP in accelerated hypertension. In the latter condition, renin and angiotensin levels are increased because of areas of renal ischemia secondary to arteriolar necrosis. ACE inhibitors or angiotensin blockers are clearly the drugs of choice in hypertensive patients with diabetes or decreased left ventricular function or both.

The role of hyperaldosteronism in essential hypertension is debatable.[15,16] Primary hyperaldosteronism may affect 8 to 32%

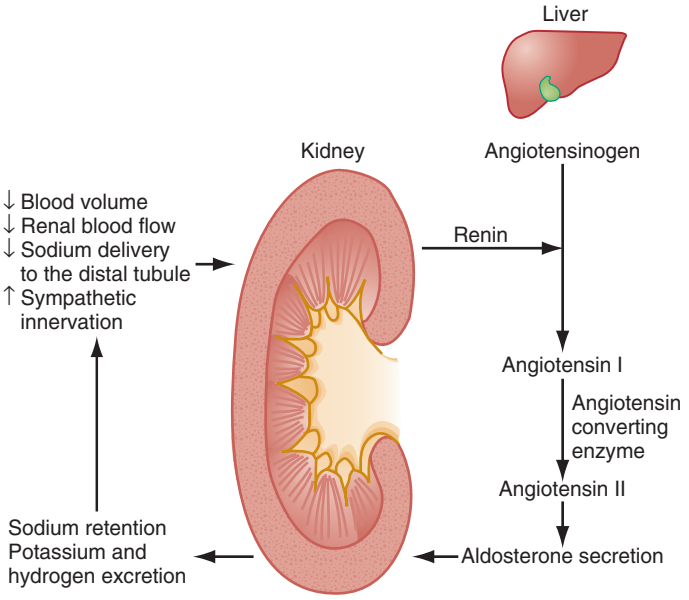


Figure 82-1. The renin-angiotensin-aldosterone axis. Solid lines represent stimulation, and dashed lines imply negative feedback mechanisms.

of patients, depending on the population of patients screened, and it should be investigated in patients with refractory hypertension.[17] Hyperaldosteronism may occur with an isolated adrenal aldosteronoma, bilateral microscopic multinodular adrenal hyperplasia, macroscopic adrenal hyperplasia, a genetic form called glucocorticoid remediable hyperaldosteronism, or even adrenal carcinoma. Spontaneous hypokalemia in a patient with hypertension should suggest primary hyperaldosteronism, but this is not invariably present. Catecholamine levels may also be abnormal. Primary hyperaldosteronism is usually investigated by a comparison of the ratio of plasma aldosterone concentration to plasma renin activity and confirmed by a failure to inhibit aldosterone levels in the urine or plasma with sodium loading.[18]

Renal Disease

Although essential hypertension is the most common form of hypertension, early identification of secondary hypertension is important because it may lead to cure or at least to a specific and much easier treatment regimen. Of these other causes, renal disease is the most prevalent. All types of renal disease are associated with hypertension, although a direct relationship can be demonstrated only in cases of unilateral renal disease, in which the removal of the affected kidney cures the hypertension. This is clear in unilateral renal arteriostenosis. *Renovascular hypertension* results from the overproduction of renin secondary to reduced blood flow through the stenotic renal artery. The increased levels of renin lead to activation of the angiotensin pathway and resultant hypertension. If the renin level in the affected kidney is more than 50% higher than the level in the normal kidney, a complete or partial cure of the hypertension can be anticipated with surgery.

Another vascular lesion associated with arterial stenosis and hypertension is fibromuscular dysplasia of the renal arteries.[19,20] This disease is predominant in young white women, and flank bruits are often present. The various types affect different areas of the renal arteries. The result is progressive hypertension. Neither pharmacologic therapy nor surgical revision offers a cure, but both treatments slow the disease process and help preserve functional renal mass.

Primary renal disease can produce hypertension, but the exact mechanism is unknown. Up to 70% of patients with chronic pyelonephritis have elevated BP. Local ischemia within the kidney is suspected as the cause of hypertension. Some authors suggest local microvascular renal disease as the final common pathway underlying essential hypertension.[17] Hypertension in patients with nonspecific glomerulonephritis may result from arteriolar lesions producing ischemia at the level of the individual nephron. With the exception of renin-secreting renal tumors, the exact cause of hypertension associated with the various nephropathies is unknown.

Arterial Disease

Abnormalities of the large arteries can also produce hypertension. Although uncommon, coarctation of the aorta is an important cause of secondary hypertension, and early surgical intervention can greatly improve the patient's prognosis.[21] The triad of upper extremity hypertension, a systolic murmur best heard over the back, and delayed femoral pulses should alert the examiner to the diagnosis of coarctation. Hypertension appears to result from the combined effects of mechanical obstruction and activation of the renin-angiotensin system.[22] Early diagnosis of coarctation is important because surgical repair results in a consistent and sustained lowering of BP. In adults, renal artery stenosis is an important cause of accelerated onset of significant hypertension, and renal artery ultrasonography or angiography is advisable (on an ambulatory basis) for patients with this type of onset of disease.

Loss of elasticity in the larger arteries associated with the aging process produces systolic hypertension as well as elevations in pulse pressure. Arteriosclerosis from the deposition of collagen and smooth muscle hypertrophy plays a major role in the age-dependent stiffness of the central vasculature. Previously, elevated systolic pressure was not considered significant and frequently was not treated. The current literature strongly suggests that isolated systolic hypertension is associated with an increased risk of stroke, heart disease, and renal failure and should be treated. The cause of reduced elasticity in the arteries associated with isolated systolic hypertension has not been fully determined. Endothelial dysfunction that develops over time with both aging and hypertension may play a critical role in this process. Other factors that decrease central vascular compliance include high dietary salt intake, tobacco use, elevated homocysteine levels, and diabetes.

Glucocorticoids

Excessive glucocorticoids are associated with hypertension, and the most common cause is iatrogenic steroid therapy. Endogenous overproduction is rare and results from excessive adrenocorticotropic hormone (ACTH) production by a pituitary tumor, ectopic ACTH production by a nonpituitary tumor, or glucocorticoid production by tumors of the adrenal cortex. These patients show other signs and symptoms of excessive glucocorticoids, including centripetal fat distribution, striae, easy bruising, muscular weakness, and poor healing. The hypertension associated with hyperadrenalism is usually not severe and can be controlled by treating the underlying disease process.

Thyroid and Parathyroid Disease

Both hyper- and hypothyroidism are associated with elevations in BP. In thyroid storm, patients are usually hypertensive and tachycardic, and beta-blockade is a mainstay of the acute management. Patients with hypothyroidism also present with hypertension as well as the other characteristic findings. Treatment of the hypothyroidism usually results in correction of the hypertensive state. Hypertension with hypercalcemia suggests hyperparathyroidism, which is another rare secondary cause of hypertension.

Sleep Apnea

Both obstructive and central forms of sleep apnea are associated with hypertension. Apnea itself is associated with a significant increase in BP. Approximately 50% of patients with sleep apnea have daytime hypertension, but many have other risk factors for hypertension, such as obesity or alcohol consumption. Studies suggest that treatment of nocturnal hypoventilation may improve daytime BPs.[23,24]

Pheochromocytoma

Pheochromocytomas are responsible for less than 1% of cases of hypertension. More than 90% of these patients are curable with early diagnosis. Pheochromocytomas produce catecholamines and arise from cells of the sympathetic nervous system. The most common site is the adrenal medulla. Patients with neurofibromatosis (von Recklinghausen's disease) have an increased incidence of pheochromocytoma. Pheochromocytoma, medullary carcinoma of the thyroid, and parathyroid adenomas form the triad of multiple endocrine neoplasia (adenomatosis), type 2.

The characteristic feature of pheochromocytoma is paroxysms of hypertension associated with palpitations, tachycardia, malaise, apprehension, and sweating. Many patients have a persistently elevated BP interspersed with episodes of greater hypertension that occur sporadically and vary greatly in severity, frequency, and duration. These episodes may be related to physical and emotional stress, eating, position, or even micturition. A prodrome of apprehension and nonspecific abdominal pain progressing to headache, palpitations, and angina may be seen. Because of the episodic nature of this syndrome, the patient is often dismissed with a diagnosis of hyperventilation syndrome or anxiety. An excessively elevated BP associated with these symptoms is enough to suggest a pheochromocytoma. Patients may also display increased BP when treated with beta-blocking agents (beta-blockers).

The diagnosis is confirmed with elevated urinary levels of catecholamines, metanephrines, and vanillylmandelic acid,[25] usually to more than twice the normal levels. Treatment consists of alpha-blockade to control hypertension and subsequent beta-blockade for the control of cardiac dysrhythmias. After the hypertension is adequately controlled, the tumor should be surgically removed.

Other Causes

Eating foods that contain large amounts of *tyramine* can cause episodic hypertension (Box 82-1). Tyramine causes release of norepinephrine stored in nerve endings. This response is normally transient; tyramine is rapidly destroyed by monoamine oxidase. Problems arise if a patient is being treated with a monoamine oxidase inhibitor (MAOI), which protects tyramine from destruction. Relatively small amounts of tyramine can cause severe and prolonged hypertension. A number of therapeutic agents can also induce a hypertensive crisis in patients taking MAOIs. These include meperidine, the amphetamines, ephedrine, reserpine, guanethidine, and tricyclic antidepressants. The hypertension can be controlled by using an alpha-blocking agent (alpha-blocker) such as phentolamine.

BOX 82-1 Foods and Drugs Causing Hypertensive Crisis in Patients Taking Monoamine Oxidase Inhibitors

Foods*
Natural or aged cheeses
Pickled herring
Chicken liver
Coffee in large amounts
Chocolate
Broad beans
Beer, wine
Snails
Yeast
Citrus fruits
Cream

Drugs
Sympathomimetic amines (e.g., amphetamines)
Methyldopa
Dopamine
Tryptophan
Reserpine
Guanethidine
Tricyclic antidepressants

*All contain significant amounts of tyramine except for broad beans, which contain dopamine.

BOX 82-2 Conditions Defining Hypertensive Crisis

Accelerated or Malignant Hypertension
Hypertensive encephalopathy
Microangiopathic hemolytic anemia
Acute renal failure

Aortic Dissection

Eclampsia/Preeclampsia

Severe Hypertension in the Setting of:
Myocardial ischemia
Left ventricular failure
Uncontrolled hemorrhage
Systemic reperfusion therapy for stroke or myocardial infarction
Postoperative state

Excess catecholamine effect can result from the acute withdrawal of clonidine or beta-blocker therapy.[26] *Clonidine* acts centrally as an alpha-adrenoreceptor agonist. The sudden withdrawal of this agent may result in catecholamine excess and severe hypertension 16 to 48 hours later. Many of the symptoms associated with clonidine withdrawal are similar to those of pheochromocytoma, including anxiety, tremor, palpitations, and severe headache. Urinary catecholamine levels are markedly elevated. Treatment consists of restarting clonidine therapy or using alpha-blockers. This characteristic limits clonidine's usefulness as an antihypertensive agent in noncompliant patients.

Alcoholism or alcohol withdrawal may precipitate hypertension. Use of nonsteroidal anti-inflammatory agents, including the selective cyclooxygenase-2 inhibitors, may inhibit the antihypertensive effects of diuretics and drugs that work on the renin-angiotensin system.[27,28]

Emergency Department Presentation

Hypertension is seen in the ED in the following four general ways:

1. "Hypertensive emergency" or "hypertensive crisis" with acute end-organ ischemia
2. "Hypertensive urgency," a historical term of no clinical value related to arbitrarily elevated BP with nonspecific symptoms. These patients probably are best referred to simply as having poorly controlled or inadequately controlled hypertension.
3. Mild hypertension without end-organ ischemia
4. Transient hypertension related to anxiety or the primary complaint

CLINICAL PRESENTATION OF HYPERTENSIVE EMERGENCIES

A small number of hypertensive patients present with a true hypertensive emergency. BP is usually markedly elevated and there is evidence of *acute* dysfunction in the cardiovascular, neurologic, or renal organ system (Box 82-2). These conditions are true medical emergencies and mandate early reduction of BP, preferably within 1 hour of identification of the condition.[2,29,30]

In the past, the range of hypertensive emergencies included patients who presented with any emergent condition associated with a marked elevation of BP. The elevated BP in these patients is often a physiologic response to an acute condition, and aggressive treatment for hypertension may actually *increase* morbidity and mortality. This is especially true for patients with acute intracranial events.[31]

Hypertensive Encephalopathy

Throughout the normal range of BP, cerebral blood flow is maintained by fluctuations in the vascular tone of the cerebral resistance vessels known as *autoregulation*. Hypertensive encephalopathy is an uncommon syndrome resulting from an abrupt, sustained rise in BP that exceeds the limits of cerebral autoregulation of the small resistance arteries in the brain. Above a mean arterial pressure (MAP) of approximately 160 mm Hg, autoregulation may be unable to control cerebral blood flow, resulting in vasospasm, ischemia, increased vascular permeability, punctate hemorrhages, and brain edema. Immediate reduction of BP by 30 to 40% reverses the vasospasm. Excessive reduction of BP must be avoided to prevent increasing cerebral ischemia. In normal humans, autoregulation operates above an MAP of approximately 60 mm Hg. In patients with uncontrolled hypertension, however, the level of autoregulation is elevated, cerebral ischemia may occur at a much higher MAP, and BP reduction should generally not take the MAP below 100 mm Hg.

Hypertensive encephalopathy is (1) acute in onset and (2) reversible. Patients present with severe headaches, vomiting, drowsiness, and confusion. Seizures, blindness, focal neurologic deficits, or coma may occur. Papilledema is usually present, along with significant hypertensive retinopathy. Differential diagnosis includes strokes and intracranial hemorrhage (ICH), meningoencephalitis, brain tumors, and metabolic coma. Careful neurologic examination often differentiates between a space-occupying lesion and hypertensive encephalopathy because focal deficits from hypertensive encephalopathy usually do not follow a singular anatomic pattern. They may occur on opposite sides of the body or may have multiple areas of involvement. Computed tomography is usually normal, and the electroencephalogram shows only nonspecific abnor-

malities. The cerebrospinal fluid is clear, with an increased opening pressure and normal or increased protein.

Hypertensive encephalopathy is a true medical emergency; untreated patients develop increasing coma, and death may ensue within a few hours. Rapid, controlled reduction of BP is essential with a careful reduction of the MAP by 25% or to a diastolic pressure of 100 to 110 mm Hg over 1 hour. The standard treatment regimen in the United States has long been intravenous (IV) nitroprusside, but labetalol is now widely used, and other agents, such as fenoldopam, nicardipine, and enalaprilat, have also proven effective. Clevidipine is a newer ultra-short-acting calcium channel blocker under investigation for the management of hypertensive emergencies.[32] Use of an oral or nontitratable agent may result in excessive reduction of BP and irreversible cerebral ischemia. Nifedipine was widely used in the past for rapid mitigation of hypertension, particularly in the context of heart failure, but it has largely fallen out of favor because of numerous serious adverse effects related to uncontrolled hypotension and sympathetic release.[30,33]

All patients with hypertensive encephalopathy should be hospitalized, and establishment of an arterial line for BP monitoring is desirable.

Malignant Hypertension

Malignant (*accelerated*) hypertension is severe hypertension associated with evidence of acute and progressive damage to end organs. This syndrome can occur at any time in the clinical course of hypertension. The diastolic BP is usually greater than 130 mm Hg. Readings below this level are seldom associated with either malignant hypertension or hypertensive encephalopathy, although rarely either can occur with diastolic pressures as low as 110 mm Hg. The vast majority of patients with diastolic pressures higher than 130 mm Hg do not develop either of these clinical syndromes. Malignant hypertension affects only 1% of the hypertensive population.[30]

The pathologic process begins when a rapid, sustained rise in BP overwhelms the high-pressure autoregulatory mechanism, causing the small arterioles to dilate. As these vessels dilate, pressure in the proximal capillary beds increases, and fluid leaks into the tissues. The arterioles may rupture and leak plasma and blood, resulting in fibrin deposition into their walls. This combination of necrosis of myofibrils in smooth muscle cells, leaking of plasma, and fibrin deposition in the walls of arterioles is *fibrinoid necrosis* and is responsible for end-organ damage. These changes within the small arterioles are directly visible in the retina as linear hemorrhages dissecting along nerve fibers. The disruption of the arteriolar wall causes obstruction of the vessel and ischemia downstream. In the retina, this produces a cotton-wool spot that consists of swollen, ischemic axons. The aggregation of materials within the ischemic axons produces a nuclear-like structure termed the *cytoid body*. Hard exudates, which consist of lipid deposits located deep in the retina, are also a common finding. These fine, punctate, shiny lesions can be distinguished from cotton-wool spots, which are larger and have blurred edges and a more diffuse appearance.

Patients with malignant hypertension appear ill and often present with complaints of severe headache, blurred vision, dyspnea, and chest pain or with symptoms of uremia. If untreated, it may result in acute renal failure, severe cardiac decompensation, MI, hypertensive cerebral hemorrhage, or hypertensive encephalopathy.

The diagnosis of malignant hypertension cannot be made on the basis of BP readings alone. In addition to elevated BP, these patients must have evidence of acute end-organ damage as a result of the hypertension. The physical examination may reveal an enlarged left ventricle and rales at the lung bases. Marked retinal findings are often present, including linear hemorrhages and cotton-wool patches. Acute elevation of blood urea nitrogen and serum creatinine or the presence of hematuria indicates involvement of the kidneys. Rarely, the blood smear reveals red cell fragments, and fibrin degradation products are elevated, giving a clinical picture compatible with microangiopathic hemolytic anemia. Left ventricular hypertrophy and strain are usually seen on the electrocardiogram (ECG). The chest radiograph may reveal cardiomegaly and evidence of congestive heart failure.

Malignant hypertension is treated in a manner similar to that for hypertensive encephalopathy by the judicious lowering of MAP by 25% of pretreatment levels over the initial minutes to hours and then toward a target of 160/100 over 2 to 6 hours, avoiding excessive decreases in pressure that may precipitate renal, cerebral, or coronary ischemia.[2,29,30]

All patients with malignant hypertension should be hospitalized, and invasive BP monitoring may be preferable. An easily titratable agent, such as labetalol, nitroprusside, or fenoldopam, is used, with the goal of avoiding any episodes of hypotension.

Stroke Syndromes

Hypertension is often associated with stroke syndromes.[34] In most of these patients, elevated BP is the physiologic response to the stroke and is not the immediate cause. Approximately 85% of strokes are nonhemorrhagic, and most patients who have embolic or thrombotic strokes without an associated hemorrhage do not sustain substantially elevated BP. These patients have mild to moderate hypertension that has little effect on the clinical course and may portend a better prognosis.[35] In patients with long-standing hypertension, rapid reduction of BP may further reduce cerebral blood flow and cause increased ischemia.

Except in cases of stroke caused by aortic dissection, antihypertensive therapy is not indicated and may be harmful. Some have recommended careful antihypertensive treatment for patients with persistent, extreme elevations of BP after a stroke (e.g., diastolic pressure >140 or MAP >130 mm Hg), but data do not support this approach.[36] The best current advice is to limit reductions in BP for acute stroke patients to circumstances in which the BP elevation is causing injury to another end organ, for example, myocardial ischemia. In these cases, BP should be lowered cautiously to mitigate the effects on the other end organ, but the ischemic neurologic deficit must not increase. When fibrinolytic therapy is administered, significant elevations of BP greatly increase the risk of secondary ICH, and patients with persistent pressures higher than 185/110 mm Hg should not receive thrombolytic therapy until their blood pressure is controlled.[36,37]

Patients with ICH often have a profound, reactive elevation of BP. In most patients with ICH, hypertension is secondary to the increased intracranial pressure (ICP) and to irritation of the autonomic nervous system. This type of hypertension often disappears rapidly and has little effect on clinical outcome. Deterioration in most patients with ICH results from hemorrhagic enlargement or edema. Data to support the pharmacologic lowering of BP in patients with ICH are lacking.[34] Persistent hypertension is associated with a poorer functional outcome after ICH, and traditionally many centers treat hypertension after ICH. Because cerebral perfusion pressure (CPP) depends on systemic pressure, this practice may not be beneficial. Although no conclusive evidence indicates that treating hypertension in the acute period after ICH is beneficial, modest reductions in BP (e.g., 20% reduction in MAP) have

not been clearly associated with a worse outcome and may be advisable after discussion with the vascular neurosurgery consultant.

If BP reduction is pursued in these patients, labetalol is the agent of choice. Labetalol and other adrenergic blockers shift cerebral autoregulation to lower pressures in patients with intracranial mass lesions. This shift preserves cerebral blood flow at lower pressures. Adrenergic blockers also preserve reactivity to carbon dioxide partial pressure (P_{CO_2}).[34] Nicardipine also has been used successfully to treat hypertension in the setting of acute intracerebral hemorrhage.[38] ACE inhibitors also shift autoregulation but have not been extensively studied in patients with ICH or elevated ICP. Vasodilators such as nitroprusside increase ICP, impair cerebrovascular reactivity to changes in P_{CO_2}, and exacerbate any decrease in CPP for a given level of BP reduction.

Pulmonary Edema

Most patients with congestive heart failure have some degree of increased peripheral vascular resistance (PVR) and resultant hypertension; this is a normal response. The degree of BP elevation is moderate and does not represent a medical emergency. When poorly controlled, however, long-standing hypertension produces myocardial hypertrophy, which continues until the hypertrophy can no longer overcome the increased PVR; then the left ventricle begins to fail and dilates.

In most patients with this combination, the hypertension results from increased PVR caused by elevated catecholamines associated with the stress of pulmonary edema. With standard treatment of pulmonary edema, including morphine, nitrates, oxygen, ACE inhibitors, and furosemide, catecholamine levels decrease and BP returns rapidly toward normal. In a small number of patients, pulmonary edema results from an abrupt, severe elevation of BP that precipitates acute left ventricular failure. The BP must be lowered to reverse this process. Nitroglycerin is usually the first drug used, but if it does not adequately reduce BP, nitroprusside should be the next choice. Nitroprusside does not cause sodium retention; it improves cardiac function, especially in the failing heart, and can be carefully titrated and rapidly reversed. ACE inhibition has also been used successfully as an adjunct in the acute treatment of pulmonary edema.[39,40] Although pressure often decreases significantly with treatment of congestive heart failure, stroke syndromes can occur as a consequence of hypotension occurring during the treatment of acute pulmonary edema.[41]

Cardiac Ischemia

Hypertension and angina are often found together. If severe hypertension is present with concurrent angina, immediate lowering of BP is indicated to prevent myocardial damage. In most of these patients, nitroglycerin and an IV beta-blocker, such as metoprolol, are the agents of choice. ACE inhibitors may be a useful adjunct and have also been shown to reduce mortality in patients with MI. Calcium channel blockers may be a useful alternative for patients unable to tolerate beta-adrenergic blockade because of bronchospasm. Nitroprusside may induce a reflex tachycardia and must be used with caution in patients with cardiac ischemia. With systemic fibrinolytic therapy, aggressive BP control is required due to the risk of ICH.[37]

Renal Failure

The most important cardiovascular complication of chronic renal failure (CRF) is hypertension.[42,43] Uncontrolled hypertension accelerates the development of cardiovascular problems, which are the most common cause of death in both dialysis and transplant patients. Hypertension also causes further damage to diseased kidneys. Hypertension may appear at any time during the course of CRF and occurs in more than 80% of patients with advanced renal failure. Glomerular disease is associated with a higher incidence of hypertension than is tubulointerstitial disease. In the absence of hypertension, CRF worsens more slowly; if hypertension is present but controlled, the progression of CRF can be delayed. Patients with renal failure secondary to malignant hypertension often demonstrate a transient worsening of renal function during their initial treatment period. After this initial period, renal function improves.

The primary cause of hypertension for patients with CRF is an actual or relative increase in extracellular volume secondary to sodium retention, as well as activation of the renin-angiotensin system in diseased kidneys. Glomerular disease is associated with greater sodium retention than is tubulointerstitial disease. Diuretics to improve fluid balance and ACE inhibitors, angiotensin receptor blockers, or calcium channel blockers should be the first-line agents to control hypertension in patients with renal failure.[44] Patients with CRF are frequently seen in the ED. If their BP is significantly elevated, the managing physician should be notified and the antihypertensive regimen adjusted.

Severe elevation of BP may lead to acute renal failure or may exacerbate CRF. Immediate reduction of BP is required. Fenoldopam is the drug of choice, although the IV calcium channel blocker nicardipine and nitroprusside are reasonable alternatives.[30]

Pregnancy

Hypertension is one of the most common complications of pregnancy, occurring in 5 to 10% of all pregnancies (see Chapters 176 and 177). Antihypertensive agents may be needed but in most patients can be delayed until hospital admission. The exceptions are those women with severe preeclampsia or eclampsia, both of which represent hypertensive emergencies and can occur without an extreme elevation of BP. Any acute elevation of the diastolic BP higher than 100 mm Hg in the pregnant patient represents a true hypertensive emergency. The treatment of hypertensive emergencies of pregnancy should include reduction of BP, prevention and control of seizures, and early obstetric consultation. Although it may cause tachycardia and hypotension, the classic antihypertensive agent of choice in preeclampsia has been IV hydralazine, but this is falling out of favor due to its relative unpredictable dose-response curve.[30,45] Alternative antihypertensives include labetalol and nicardipine. Nitroprusside is relatively contraindicated because of the potential for accumulation of cyanide in utero. Because of this potential complication, nitroprusside should be reserved for those patients in whom other agents have failed. Oral nifedipine has also been used in this setting, although, as in other conditions, overshoot hypotension has been observed.[46] Preeclampsia and eclampsia are true hypertensive emergencies and are discussed in Chapter 176.

Aortic Dissection

Aortic dissection is associated with a history of hypertension (see Chapter 83). Medical therapy consists of reducing BP to limit the extent of the dissection. The goals of medical therapy are to lower BP to a systolic level of 100 to 120 mm Hg and to reduce the ejection force of the heart. Classically, a beta-blocker such as esmolol is given to control reflex tachycardia,

whereas a vasodilator (nitroprusside, fenoldopam, or nicardipine) is used to reduce BP. Single drug management using the combined alpha/beta-blocker labetalol is commonly used and successful.[29,30]

MANAGEMENT OF HYPERTENSIVE EMERGENCIES

Vasodilators

Fenoldopam

Fenoldopam (Corlopam) is a peripheral dopamine-1 receptor agonist approved for the treatment of hypertensive emergencies. Dopamine-1 receptors are located postsynaptically in the systemic and renal vasculature and mediate systemic, renal, and mesenteric vasodilation as well as natriuresis. In contrast to treatment with nitroprusside, fenoldopam therapy improves renal function acutely in patients with malignant hypertension.[47] Fenoldopam does not cross the blood-brain barrier, has a rapid onset of action, and has an elimination half-life of 9 minutes.[48-50] Reflex tachycardia, flushing, and headache may be observed, but hypotension occurs less often than with nitroprusside therapy.

The initial dose of fenoldopam is 0.1 µg/kg/min, and the dose is titrated in 0.1 µg/kg/min increments every 15 minutes until the desired effect is seen. The maximum recommended dose is 1.6 µg/kg/min. Fenoldopam represents a reasonable alternative to nitroprusside in the treatment of hypertensive emergencies without the concerns of light sensitivity and cyanide or thiocyanate toxicity and also with fewer hypotensive episodes. Fenoldopam has been used in trials without invasive BP monitoring.[48]

Nicardipine

Nicardipine (Cardene) is a parenteral dihydropyridine calcium channel blocker that has become very popular in the treatment of postoperative hypertension. Nicardipine is titratable, has less negative inotropic effect, and induces less tachycardia than does nifedipine. Nicardipine acts predominantly as a vasodilator, but as with other calcium channel blockers, caution must be used when it is administered to patients with left ventricular failure. Nicardipine is administered as an infusion beginning at 5 mg/hr, increasing the infusion rate every 15 minutes until the desired reduction of BP has been achieved, to a maximum dose of 15 mg/hr. Onset of action is 5 to 15 minutes and duration of action 4 to 6 hours. As with labetalol, an oral form may facilitate the transition from acute to chronic therapy.

Nicardipine is heavily metabolized in the liver, and caution must be used in patients with cirrhosis. Nicardipine decreases the glomerular filtration rate in patients with compromised renal function, a trait shared by nitroprusside. As with the other vasodilators, headache, flushing, and tachycardia are the most common adverse reactions seen with nicardipine. Nicardipine has been best studied in pregnant patients and in the settings of postoperative and malignant hypertension, in which it appears to be a less toxic alternative to nitroprusside.[2,30,51]

Sodium Nitroprusside

Nitroprusside (Nipride and Nitropress) is a powerful vasodilator with a direct effect on the smooth muscle of both resistance and capacitance vessels. Nitroprusside has historically been the agent of choice for most hypertensive emergencies (Table 82-1). Its rate of onset is extremely rapid, and its duration of action is very short. Nitroprusside does not usually worsen angina, but a coronary steal phenomenon may occur.[30] The cardiac response depends on the state of myocardial function. Because of the reduction of preload by venous dilation, the cardiac output often improves if congestive heart failure or borderline myocardial function is present. Because nitroprusside is a cerebral vasodilator, it may increase ICP secondary to increased cerebral blood flow. Nitroprusside is metabolized to thiocyanate and is excreted slowly by the kidneys. Cyanide is an intermediate metabolite, and its metabolism requires functioning liver, kidneys, and adequate bioavailability of thiosulfate. In the presence of renal failure or during prolonged nitroprusside therapy, the thiocyanate concentration may reach toxic levels of 10 mg/dL, and a clinical picture of weakness, hypoxia, nausea, tinnitus, muscle spasm, disorientation, and psychosis may develop. The prolonged use of nitroprusside may produce hypothyroidism by inhibition of iodine transport, and methemoglobinemia has occurred.

Nitroprusside must be used as an IV solution. As capacitance vessels dilate, the patient must be kept recumbent to prevent profound orthostatic hypotension. Because of nitroprusside's short half-life, stopping the infusion returns the BP to pretreatment levels within 1 to 10 minutes. The amount of BP reduction is dose related. Elderly patients and those receiving antihypertensive medications are more sensitive to nitroprusside's effects. In all patients, the starting dose should be 0.25 to 1.0 µg/kg body weight per minute. The average dose required for the control of hypertension is 3.0 µg/kg/min. Dosages greater than 800 µg/min are seldom required and should not be used for long periods because of the accumulation of cyanide and thiocyanate. Patients treated with nitroprusside should be admitted to the intensive care unit for close monitoring of BP, preferably by an intra-arterial line. The drug should be diluted and given by an automatic infusion device. Nitroprusside is unstable in ultraviolet light, and the IV bag should be wrapped in opaque material. Only fresh solutions of nitroprusside less than 4 hours old should be used.

All types of hypertension respond to nitroprusside, although certain patients may not have an adequate response. Side effects are directly related to excessive vasodilation and resultant hypotension and can be avoided by careful monitoring of

Table 82-1 Summary of Drugs of Choice in the Treatment of Hypertensive Emergencies

EMERGENCY	DRUG(S) OF CHOICE	ALTERNATIVE OR SECOND-LINE DRUGS
Accelerated hypertension, hypertensive encephalopathy	Nitroprusside, fenoldopam	Labetalol or nicardipine
Intracranial hemorrhage	Labetalol	Nitroprusside, nicardipine
Acute pulmonary edema	Nitroglycerin, nitroprusside	Fenoldopam, ACE inhibitor
Cardiac ischemia	Nitroglycerin, beta-blockers	Nitroprusside, labetalol
Aortic dissection	Nitroprusside + beta-blockers	Labetalol
Adrenergic crises	Phentolamine, nitroprusside + beta-blockers	Labetalol
Eclampsia, preeclampsia	Labetalol	Nicardipine, hydralazine

ACE, angiotensin-converting enzyme.

BP and regulation of infusion rate. Extreme caution must be taken to avoid the extravasation of nitroprusside because local necrosis can be severe. Nitroprusside has not been proved to be safe during pregnancy and should be avoided because of the potential effect of thiocyanate on fetal thyroid tissue, the risk of cyanide poisoning to the fetus, and the possibility of fetal methemoglobinemia.

Nitroglycerin

Nitroglycerin is a vasodilating agent that acts predominantly on the venous system, decreasing left ventricular end-diastolic pressure. At normal doses, nitroglycerin has little effect on arterial vascular tone and reduces BP by reducing preload and cardiac output. These effects may be undesirable in patients with impaired cerebral and renal perfusion. Nitroglycerin use should be limited to patients with cardiac ischemia or pulmonary edema. Nitroglycerin may be administered either sublingually or intravenously. Care must be taken in patients with right ventricular dysfunction to avoid hypotension, which may exacerbate cardiac ischemia.

Hydralazine

Hydralazine (Apresoline) is a direct arteriolar vasodilator that was widely used in the past for the hypertensive emergencies of pregnancy. Recent studies, however, have shown that nicardipine and labetalol are superior agents in this setting, and hydralazine should not be considered first-line therapy for acute treatment of hypertensive emergencies in the ED.[52] The usual starting dose of hydralazine is 5 mg IV, with repeated doses of 5 to 10 mg every 20 minutes as needed to keep the diastolic pressure below 110 mm Hg. Typically, a latent period of 5 to 15 minutes is followed by a progressive and at times precipitous fall in BP lasting for up to 12 hours.[27] Hydralazine is also associated with significant reflex tachycardia, which may provoke angina in patients with coronary artery disease. Other common side effects are flushing, nausea, and headache. Chronic use is associated with a lupus-like syndrome that usually resolves with discontinuation of the medication.

Beta-Blockers

Labetalol

Labetalol (Trandate and Normodyne) is a selective $alpha_1$-blocker and nonselective beta-blocker with a ratio of alpha/beta-blockade between 1:3 and 1:7. It can be given orally or IV. Labetalol lowers BP by blockade of the $alpha_1$-receptors in vascular smooth muscle and the cardiac beta-receptors. Because of the simultaneous beta-receptor blockade, the usual reflex tachycardia associated with vasodilators does not occur. Labetalol does not cause the significant drop in cardiac output associated with other beta-blockers. Although oral labetalol is less likely to produce orthostatic hypotension, IV use is marked by profound orthostatic changes. After IV labetalol, the patient should be kept in the supine position for several hours. Labetalol does not affect cerebral blood flow or renal function.[34,53] With IV labetalol, BP generally decreases within 5 to 10 minutes, with maximum effect in 30 minutes.

The initial dose of labetalol is 20 mg infused over 2 minutes. The BP should be rechecked every 5 minutes, and if only minimal change occurs, an additional dose is given every 10 minutes in increments of 20, 40, or 80 mg to a total of 300 mg of labetalol, depending on BP response. A preferable approach may be to give the initial loading dose and then an infusion at 1 or 2 mg/min, which can be titrated upward.[54,55] When given in this manner, labetalol appears to be a safe agent, with minimal adverse reactions. Because labetalol is a beta-blocker, it is contraindicated in patients with congestive heart failure, heart block, and asthma. Labetalol also appears to be contraindicated for treatment of hypertension secondary to pheochromocytoma because it may result in paradoxical hypertension.

Labetalol therapy cannot be as closely controlled or as quickly reversed as nitroprusside or fenoldopam therapy. However, use of labetalol may not require admission to an intensive care unit. Labetalol does not appear to exacerbate coronary artery disease or cause uncontrolled drops in BP.

The transition to oral therapy is smooth. After initial control of BP with IV labetalol, oral labetalol should be started when diastolic pressure rises 10 mm Hg. Labetalol is an excellent alternative to nitroprusside when constant BP monitoring is not feasible. Labetalol is superior as a single agent in patients who have aortic dissection or cardiac ischemia with intact left ventricular function.

Esmolol

Esmolol (Brevibloc) is an ultra-short-acting, selective $beta_1$-blocker without intrinsic sympathomimetic activity. It typically has little effect on BP in normal individuals but may be very useful to control the reflex tachycardia seen with vasodilating agents such as nitroprusside. Esmolol is initiated with a loading dose of 500 µg/kg over 1 minute, followed by an infusion of 50 to 100 µg/kg/min. Maximal effect occurs in 5 minutes. If necessary, another bolus of 500 µg/kg is given, and the drip is increased by 50 µg/kg/min. This cycle may be repeated every 5 minutes until the desired heart rate response is seen, up to a maximum dose of 300 µg/kg/min. Because the elimination half-life of esmolol is 9 minutes, any effect resolves within 30 minutes of discontinuing the infusion, with substantial recovery from beta-blockade in 10 to 20 minutes. Contraindications are similar to those with labetalol, including cocaine overdose, pheochromocytoma, congestive heart failure, heart block, and reactive airway disease. Esmolol also causes tissue necrosis when extravasated into the soft tissue and may cause thrombophlebitis when infused into small veins.

Alpha-Blockers

Phentolamine (Regitine) is an alpha-blocking agent used for catecholamine-induced hypertensive crises (e.g., pheochromocytoma, MAOI crisis, and cocaine overdose). Phentolamine is usually given IV in 1- to 5-mg boluses, although it may be given as an infusion at a rate of 5 to 10 µg/kg/min.[51,53] The effect is immediate and may last up to 15 minutes. Reflex tachycardia may be seen. After BP is under control, oral phenoxybenzamine, a long-acting alpha-blocker, may be used.

Enalaprilat and Enalapril

Enalaprilat (Vasotec) is a parenteral active metabolite of the ACE inhibitor enalapril. This drug has been studied in limited numbers of patients with true hypertensive emergencies. Hypotension is rare with the use of enalaprilat, but caution should be used in patients who may be volume depleted. The acute dose is 0.625 to 5 mg administered as a single bolus. Peak effects generally occur in 15 minutes but may be delayed for hours. The response is not dose related, and one study showed an average drop in MAP of 35% at all doses and a 60% response rate.[56] Although no adverse effects were seen in this study, which excluded patients older than 80 years and with

known renovascular disease, such a significant drop in MAP might exceed the limits of vascular autoregulation in some patients. In fact, azotemia has been reported among older patients in studies of ACE inhibition after MI.[57]

Adverse effects seen with ACE inhibitors such as enalaprilat include idiopathic angioedema, cough, and renal failure. Renal failure has been classically described in patients with bilateral renovascular disease. ACE inhibitors are considered toxic in the first trimester of pregnancy.

CLINICAL PRESENTATION AND MANAGEMENT OF POORLY CONTROLLED HYPERTENSION

Elevated BP without evidence of progressive end-organ involvement does not require urgent treatment in the ED.[2] Historically, these patients, on the basis of arbitrarily defined BP elevations and the ill-conceived term "hypertensive urgency," were inappropriately treated with antihypertensive agents in the ED with little regard for the chronicity of the condition, potential adverse effects of acutely lowering their BP, or transition to a stable, oral, outpatient regimen for long-term control. It is unnecessary to lower BP acutely in the ED for these patients, and this practice may actually cause increased risk of adverse effects.[7,58] These patients are best managed with a long-term, ambulatory regimen, monitored and adjusted by their primary care provider.

Patients with elevated BP who are asymptomatic or have nonspecific symptoms require a thorough history and physical examination, paying special attention to the cardiovascular, funduscopic, and neurologic systems and findings. Depending on the presentation, laboratory testing may be helpful, including a urinalysis and electrolyte panel to evaluate renal function. In patients without any history of renal disease, a normal urinalysis obviates the need for blood tests of renal function.[59] A chest radiograph and ECG are obtained to evaluate patients with chest pain or symptoms of cardiac dysfunction. If initial evaluation fails to show any acute end-organ damage and myocardial ischemic symptoms are not present, the patient may be referred for outpatient evaluation within 7 days. Unfortunately, the evaluation for end-organ ischemia and referral for subsequent care occurs in a minority of patients with elevated blood pressures in most EDs.[60-62]

In some patients, it is evident that ongoing chronic pharmacologic therapy is indicated. In the ambulatory setting, the decision to initiate pharmacologic therapy for well-documented hypertension must be based on the degree of hypertension (Tables 82-2 and 82-3). These recommendations are not without controversy.[2,63-65] It is rarely advisable to initiate or substantially modify the outpatient treatment of hypertension in the ED, unless the patient has known (i.e., previously diagnosed and treated) hypertension, and treatment is restarted or modified in close consultation with the primary care provider. Large population-based studies comparing different classes of antihypertensive agents have established the thiazide diuretics, such as hydrochlorothiazide at 25 to 50 mg once a day, as the first-line agent of choice in the absence of compelling indications for other classes of antihypertensives.[2,66-68] These agents are inexpensive, well tolerated, and easy to take. Other more expensive agents have failed to show better efficacy in preventing the cardiovascular complications of hypertension.

Beta-blockers or calcium channel blockers are substituted or added as indicated.[2,9,66-70] Common starting doses of generic beta-blockers include atenolol 25 to 50 mg or metoprolol 50 mg once or twice daily. For patients with other health problems, specific classes of drugs have been shown to be particularly beneficial; the comorbid conditions should guide antihypertensive therapy. For patients with intact left ventricular function and a history of MI, a beta-blocker is the agent of choice. On the basis of evidence of increased mortality, such patients should not be treated with immediate-release dihydropyridine calcium channel blockers.[71] For patients with diabetes, ACE inhibitors or angiotensin receptor blockers (ARBs) have benefits with respect to the preservation of renal function beyond that seen with BP control alone. In diabetic patients as well as in those with a history of left ventricular failure, an ACE inhibitor or an ARB should be the drug of choice. Elderly

Table 82-2 Recommendations for Ambulatory Blood Pressure Therapy*

BLOOD PRESSURE CLASSIFICATION	SYSTOLIC BLOOD PRESSURE (MM HG)	DIASTOLIC BLOOD PRESSURE (MM HG)	LIFESTYLE MODIFICATION	INITIAL DRUG THERAPY	
				WITHOUT COMPELLING INDICATION	WITH COMPELLING INDICATION
Normal	<120	and <80	Encourage		
Prehypertension	120–139	or 80–89	Yes	No antihypertensive drug indicated	Drug(s) for compelling indications†
Stage 1 hypertension	140–159	or 90–99	Yes	Thiazide-type diuretics for most May consider ACEI, ARB, BB, CCB, or combination	Drug(s) for compelling indications† Other antihypertensive drugs (diuretics, ACEI, ARB, BB, CCB) as needed
Stage 2 hypertension	≥160	or ≥100	Yes	Two-drug combination for most‡ (usually thiazide-type diuretic and ACEI or ARB or BB or CCB)	

*Treatment determined by highest blood pressure category.
†Treat patients with chronic kidney disease or diabetes to blood pressure goal of <130/80 mm Hg.
‡Initial combined therapy should be used cautiously in those at risk for orthostatic hypotension.
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; CCB, calcium channel blocker.
Modified from the Seventh Report of the Joint National Committee on Prevention, Detection, and Treatment of High Blood Pressure. JNC7 complete report. Hypertension 42:1206, 2003.

Table 82-3 Antihypertension Drugs*

DRUG	TRADE NAME	USUAL DOSE RANGE, TOTAL MG/DAY AND INTERVAL	COMMON SIDE EFFECTS AND COMMENTS
Diuretics (Common)			Short-term: increases cholesterol and glucose levels; biochemical abnormalities: decreases potassium, sodium, and magnesium levels, increases uric acid and calcium levels; rare: blood dyscrasias, photosensitivity, pancreatitis, hyponatremia
Thiazides			
Chlorothiazide	Diuril	125–500 qd	
Chlorthalidone	Hygroton	12.5–50 qd	
Hydrochlorothiazide	Hydrodiuril, Microzide, Esidrix	12.5–50 qd	
Polythiazide	Renese	2–4 qd	
Indapamide	Lozol	1.25–5 qd	
Metolazone	Mykrox, Zaroxolyn	0.5–1 (b-tid), 2.5–5 qd	
Loop Diuretics			
Bumetanide	Bumex	0.5–4 b-tid	
Furosemide	Lasix	40–240 b-tid	
Torsemide	Demadex	3–100 q-bid	
Potassium-Sparing Agents			Hyperkalemia may occur
Amiloride hydrochloride	Midamor	5–10 qd	
Triamterene	Dyrenium	25–100 qd	
Aldosterone Receptor Blockers			
Spironolactone	Aldactone	25–100 qd	
Eplerenone	Inspra	50–100 q-bid	
Adrenergic Inhibitors			Postural hypotension
Central alpha-Agonists			Sedation, dry mouth, bradycardia, withdrawal hypertension
Reserpine		0.05–0.25 qd	
Clonidine hydrochloride	Catapres	0.2–1.2 b-tid	
	Catapres-TTS	0.1–0.3 weekly	
Guanabenz acetate	Wytensin	4–8 bid	
Guanfacine hydrochloride	Tenex	0.5–2 qd	
Methyldopa	Aldomet	250–1000 bid	
Alpha-Blockers			Hepatitis and lupus-like syndrome Postural hypotension
Doxazosin mesylate	Cardura	1–16 qd	
Prazosin hydrochloride	Minipress	2–20 b-tid	
Terazosin hydrochloride	Hytrin	1–20 qd	
Beta-Blockers			Bronchospasm, bradycardia, heart failure, may mask insulin-induced hypoglycemia; less serious: impaired peripheral circulation, insomnia, fatigue, decreased exercise tolerance, hypertriglyceridemia (except agents with intrinsic sympathomimetic activity)
Acebutolol[1,2]	Sectral	200–800 qd	
Atenolol[1]	Tenormin	25–100 q-bid	
Betaxolol[1]	Kerlone	5–20 qd	
Bisoprolol fumarate[1]	Zebeta	2.5–10 qd	
Metoprolol tartrate[1]	Lopressor	50–300 bid	
Metoprolol succinate[1]	Toprol-XL	50–300 qd	
Nadolol	Corgard	40–320 qd	
Nebivolol hydrochloride	Bystolic	5–20 qd	
Penbutolol sulfate[2]	Levatol	10–20 qd	
Pindolol[2]	Visken	10–60 bid	
Propranolol hydrochloride	Inderal	40–480 bid	
	Inderal *LA*	40–480 qd	
Timolol maleate	Blocadren	20–60 bid	
Combined alpha- and beta-Blockers			Postural hypotension, bronchospasm
Carvedilol	Coreg	12.5–50 bid	
Labetalol hydrochloride	Normodyne, Trandate	200–1200 bid	
Direct Vasodilators			Headaches, fluid retention, tachycardia Lupus syndrome Hirsutism
Hydralazine hydrochloride	Apresoline	50–300 bid	
Minoxidil	Loniten	5–100 qd	
Calcium Antagonists			Conduction defects, worsening of systolic dysfunction, gingival hypertrophy
Nondihydropyridines			
Diltiazem hydrochloride	Cardizem SR	50–300 bid	
	Cardizem CD, Dilacor XR, Tiazac	5–100 qd	
Verapamil hydrochloride	Isoptin SR, Calan SR	90–480 bid	Constipation
	Verelan, Covera HS	120–480 qd	

Table 82-3 Antihypertension Drugs—cont'd

DRUG	TRADE NAME	USUAL DOSE RANGE, TOTAL MG/DAY AND INTERVAL	COMMON SIDE EFFECTS AND COMMENTS
Calcium Antagonists			Pedal edema, flushing, headache, gingival hypertrophy
Dihydropyridines			
Amlodipine besylate	Norvasc	2.5–10 qd	
Felodipine	Plendil	2.5–20 qd	
Isradipine	DynaCirc	5–20 bid	
	DynaCirc CR	5–20 qd	
Nicardipine	Cardene SR	60–90 bid	
Nifedipine	Procardia XL, Adalat CC	30–120 qd	
Nisoldipine	Sular	20–60 qd	
ACE Inhibitors			Common: cough; rare: angioedema, hyperkalemia, rash, loss of taste, leukopenia
Benazepril hydrochloride	Lotensin	5–40 q-bid	
Captopril (G)	Capoten	25–150 b-tid	
Enalapril maleate	Vasotec	5–40 q-bid	
Fosinopril sodium	Monopril	10–40 q-bid	
Lisinopril	Prinivil, Zestril	5–40 qd	
Moexipril	Univasc	7.5–15 q-bid	
Perindopril	Aceon	4–8 q-bid	
Quinapril hydrochloride	Accupril	5–80 q-bid	
Ramipril	Altace	1.25–20 q-bid	
Trandolapril	Mavik	1–4 qd	
Angiotensin II Receptor Blockers			Angioedema (very rare), hyperkalemia
Candesartan	Atacand	8–32 qd	
Eprosartan	Tevetan	400–800 q-bid	
Losartan potassium	Cozaar	25–100 q-bid	
Valsartan	Diovan	80–320 qd	
lrbesartan	Avapro	150–300 qd	
Olmesartan	Benicar	20–40 qd	
Telmisartan	Micardis	20–80 qd	
Renin Inhibitors			
Aliskiren	Tekturna	150–300 qd	Rare angioedema, hyperkalemia (especially with ACE inhibitor use), hypotension, diarrhea, rash, renal stones

*This list is of single agents only; multiple combination agents are also manufactured.
[1]Beta$_1$ selective
[2]Intrinsic sympathomimetic activity; beta$_1$ selective with no related vasodilation
ACE, angiotensin-converting enzyme.

patients with isolated systolic hypertension may benefit from the addition of a long-acting calcium channel blocker when diuretic monotherapy fails. Patients with prostatism or dyslipidemia may benefit from alpha-blocker therapy, although a large prospective trial comparing the thiazide diuretic chlorthalidone with three other types of therapy showed an increased incidence of congestive heart failure and stroke in the group treated with the alpha-blocker doxazosin.[72] Regardless of the agent used, long-term reduction of BP to the target level remains the most important endpoint for the prevention of cerebrovascular, heart, and renal disease.

Mild or Transient Hypertension

A vast majority of the hypertension encountered in the ED is either transient or mild. The most common causes of transient hypertension are pain and anxiety. In these patients, end-organ ischemia does not occur, and attention is focused on treatment of the primary process. Patients with incidental hypertension identified during a visit for another purpose should simply be referred to their primary care physicians for repeated measurement in a few days to a few weeks. Most patients, even those with poorly treated chronic hypertension, show an improvement in their BP with watchful waiting.[4]

KEY CONCEPTS

- The presence or absence of acute target organ damage determines whether a hypertensive emergency exists and whether treatment of the BP elevation is indicated in the ED.
- All patients with persistent and marked elevations in BP (e.g., diastolic BP >110 mm Hg or systolic BP > 200 mm Hg) should be carefully evaluated for the presence of acute end-organ ischemia.
- The therapeutic goal for treatment of the majority of hypertensive emergencies is careful reduction of the BP with a titratable agent. Mean arterial pressure should be reduced by no more than 20 to 25% over minutes to hours. The diastolic pressure generally should not fall below 100 to 110 mm Hg. The exceptions to these rules may be patients with hypertensive complications of pregnancy, hypertensive emergencies of the pediatric population, and patients with aortic dissection.
- Patients without acute end-organ ischemia should not receive antihypertensive agents in the ED, and they may be safely referred for outpatient follow-up.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 83

Aortic Dissection

Felix Ankel

PERSPECTIVE

Aortic dissection is a longitudinal cleavage of the aortic media created by a dissecting column of blood. The term "dissecting aortic aneurysm" has been inaccurately applied to this entity since 1819, when Laënnec first used the term *aneurysme dissequant*. The term *aortic dissection* is preferred to dissecting aortic aneurysm because the affected aorta is only rarely aneurysmal. In 1955, DeBakey outlined the principles that remain the basis for the surgical treatment of this entity. Medical treatment of aortic dissection was first advocated in the 1960s and is indicated for certain types of dissections.[1-4] The in-hospital mortality rate for patients treated for aortic dissection is 27%.[4]

Epidemiology

Aortic dissection occurs more often in men and increases with age.[4,5] The incidence and prevalence are difficult to determine because of underreporting of this condition. Mortality is 1 to 5 per 100,000 population per year. Hypertension is the most common risk factor associated with aortic dissection and is seen in most patients.[4-6] A history of cardiac surgery is present in about 18%[4] and a bicuspid aortic valve in 14% of all patients with aortic dissections but more often in proximal dissections.[6] Atherosclerosis is rarely involved at the site of dissection. Patients with aortic dissection may have a positive family history.[7]

Aortic dissection is uncommon before age 40 except in association with congenital heart disease, Ehlers-Danlos or Marfan's syndrome, or giant-cell arteritis. As many as 44% of patients with Marfan's syndrome develop aortic dissection and account for about 5% of cases.[4,6,8] Women with Marfan's syndrome are at particular risk during pregnancy.[9] In patients without connective tissue disease and with an aortic root size of less than 40 mm, pregnancy does not appear to be an independent risk factor.[10,11] Acute aortic dissection also occurs with stimulant use,[12,13] exertion,[14] and trauma.[15] It may also be seen in patients who undergo cardiac surgery[4] or intra-aortic balloon pump insertion.[16]

Blunt trauma from a high-speed deceleration injury usually causes traumatic aortic rupture, which is an entity distinctly different from aortic dissection (see Chapter 42).

PRINCIPLES OF DISEASE

Anatomy and Physiology

With each contraction, the heart swings from side to side, resulting in flexion of both the ascending aorta and descending aorta. The descending aorta flexes just distal to the left subclavian artery, where the mobile aorta is tethered. At an average of 70 heartbeats per minute, this sequence occurs about 37 million times a year, causing a repetitive stress on the aorta.

The aortic wall has three distinct layers: the intima, the media, and the adventitia. The media is composed of elastic tissue and smooth muscle. Dissection occurs through a degeneration of the media characterized by loss of smooth muscle cells and elastic tissue, accompanied by scarring, fibrosis, and hyalin-like changes. Pathologic studies show that this process is neither cystic nor necrotic; therefore, the old term *cystic medial necrosis* is no longer used.[17]

Pathophysiology

Medial degeneration, previously thought to be specific for aortic dissection, is now considered to be part of normal aging, although it is augmented by hypertension and with aortic dissection. The anatomic differences between the "normal" aorta and a dissection are *quantitative* rather than qualitative.[17]

The repetitive hydrodynamic forces produced by the ejection of blood into the aorta with each cardiac cycle contribute to weakening of the aortic intima and to medial degeneration. These hydrodynamic forces primarily affect the ascending aorta. Sustained hypertension intensifies these forces and results in an increase in medial degeneration. A bicuspid aortic valve may disrupt laminar flow and reorient the flow of blood toward the aortic wall, producing local injury. In Marfan's and Ehlers-Danlos syndromes, normal hydrodynamic forces act on an aortic media that is already weakened.

As a result of medial degeneration and repeated flexion of the aorta, hydrodynamic stress tears the aortic intima and a column of blood gains access into the aortic media. An alternative theory suggests that these forces damage the vasa vasorum of the aorta, which rupture and hemorrhage into the aortic media,[18] which may explain the absence of an intimal tear in some cases of dissection. Regardless of which of these theories is correct, the depth of penetration into the media and the distance and direction of dissection are at least partially determined by the degree of medial degeneration.

Once a dissecting hematoma is established in the media, migration of the hematoma occurs in an antegrade or retrograde fashion, or both, forming a "false lumen." The false lumen forms in the outer half of the media and propagates until it ruptures back into the "true lumen" of the aorta, resulting in a rare "spontaneous cure," or through the adventitia into the pericardial sac or pleural cavity. Because the outer wall of the aorta that contains the hematoma is thin, rupture is much

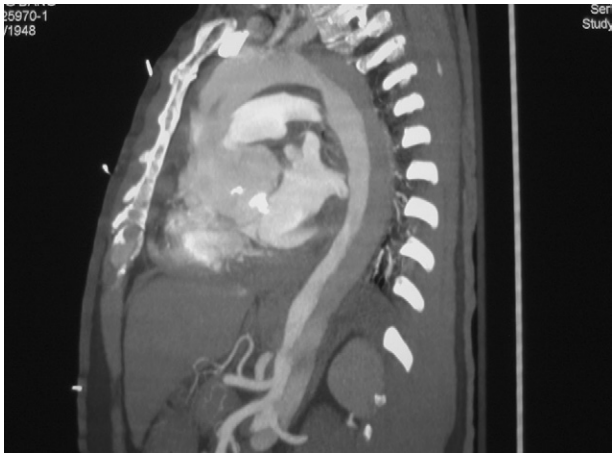


Figure 83-1. Computed tomographic reconstruction of Stanford type B or DeBakey type III dissection distal to the subclavian artery.

more likely to occur to the outside. The most important factors favoring continued dissection of the aorta are (1) the degree of elevation of blood pressure and (2) the steepness (slope) of the pulse wave (upstroke pattern on apex cardiogram, dP/dt). Both of these hemodynamic factors must be controlled to halt migration of the hematoma.

Classification

Anatomic classification is important for diagnosis and therapy. The *Stanford classification* is based on the involvement of the ascending aorta. Type A dissections involve the ascending aorta; type B dissections do not (Fig. 83-1). Dissections that involve the ascending aorta are much more often lethal than those limited to the distal aorta and call for a different therapeutic approach. In the International Registry of Acute Aortic Dissection (IRAD), 62% of dissections are type A and 38% are type B.[2-4] Patients with distal dissections tend to be older, heavy smokers with chronic lung disease, and more often have generalized atherosclerosis and hypertension compared with patients who have proximal aortic dissections.

Two other aortic conditions are closely related to aortic dissection: intramural hemorrhage[19,20] and penetrating aortic ulcer. Both groups of patients have clinical symptoms and management recommendations similar to those for patients with aortic dissection. An *intramural hemorrhage* is a contained hematoma within the aortic wall and occurs in about 10% of aortic dissections.[4] Rupture of the vasa vasorum is believed to be the initial event. *Penetrating atherosclerotic ulcers* of the aorta occur in older hypertensive patients with evidence of coronary artery disease. Computed tomography (CT) shows a focal ulceration without dissection, most commonly in the distal descending aorta. The progression of penetrating ulcers results in progressive aortic enlargement with saccular and fusiform aneurysm formation. Patients can have both an intramural hematoma and a penetrating atherosclerotic ulcer.[21]

A dissection is *acute* if it is of less than 2 weeks' duration and *chronic* if present for more than 2 weeks.

CLINICAL FEATURES

History

Pain is by far the most common presenting complaint, affecting more than 90% of patients.[4,6,8] Most cases of painless aortic dissection are chronic in nature.[6] The pain is usually excruciating, occurs abruptly, is most severe at onset, and is typically described as "sharp"[4] more often than "tearing" or "ripping."

The location of the pain may help localize the dissection. Anterior chest pain is associated with the ascending aorta, neck and jaw pain with the aortic arch, pain in the interscapular area with the descending thoracic aorta, and pain in the lumbar area or abdomen with involvement below the diaphragm. Migration of the pain consistent with propagation of the dissection suggests aortic dissection but occurs in only 17% of cases.[4] The onset of aortic dissection is often accompanied by visceral pain symptoms, such as diaphoresis, nausea, vomiting, lightheadedness, and severe apprehension.

Syncope occurs early in aortic dissection in approximately 9% of cases and may be the sole presentation in some patients.[4,8] It most often heralds dissection into the pericardium, causing pericardial tamponade, but may occur from transient interruption of blood flow to the cerebral vasculature. Other causes of syncope secondary to aortic dissection are hypovolemia, excessive vagal tone, and cardiac conduction abnormalities. Neurologic symptoms such as focal weakness or change in mental status occur in up to 17% of cases.[4,6,8]

Physical Examination

The presentation varies greatly, depending on the patient and the location and extent of the dissection. Generally, the patient appears apprehensive. Most of the patients have a history of chronic hypertension that may be exacerbated by a catecholamine release related to the acute event. Severe hypertension refractory to medical therapy may occur if the dissection involves the renal arteries with subsequent renin release. If hypotension is present, either the dissection has progressed back into the pericardium with resulting pericardial tamponade or hypovolemia has occurred from rupture through the adventitia. *Pseudohypotension*, a condition in which the blood pressure in the arms is low or unobtainable and the central arterial pressure is normal or high, may be present. This results from the interruption of blood flow to the subclavian arteries.

Aortic regurgitation occurs in up to 32% of patients and is more common with type A dissections.[4,6] The murmur of aortic insufficiency may have a musical, vibrating quality with variable intensity, and congestive heart failure may develop. The patient with presumed aortic dissection should be examined carefully for findings that suggest hemorrhage into the pericardium or tamponade, such as jugular venous distention, muffled heart sounds, tachycardia, and hypotension.

When the integrity of one of the branches of the aorta is compromised, the expected ischemic findings occur. Pulse deficits and discrepancies in blood pressure between limbs can be helpful if present[4,6,8] but have a sensitivity of only around 30%.[22] Usually these are present in the upper extremities and result from involvement of one or both of the subclavian arteries. Obstruction of one or both common iliac or superficial femoral arteries may produce pulse deficits in the lower extremities. Arterial obstruction may occur by either of two mechanisms. An intimal flap produced by the dissection may cover the true lumen of a branch vessel, or the dissecting hematoma may compress an adjacent true lumen. Frequent reexamination may detect transient pulse deficits.

Neurologic findings are related to the site of blood flow interruption. Proximal dissections are a more frequent cause of strokes or coma. Stroke treatment with a fibrinolytic agent in the patient with aortic dissection can be fatal. Distal dissections occluding the anterior spinal artery commonly cause ischemic paraparesis or ischemic peripheral neuropathy.[6]

Table 83-1 Characteristics of Aortic Dissection from the International Registry of Acute Aortic Dissection[4]

	CHEST PAIN (%)	SYNCOPE (%)	AORTIC INSUFFICIENCY MURMUR (%)	PULSE DEFICIT (%)	NORMAL CXR (%)	WIDENED MEDIASTINUM ON CXR (%)	NORMAL ECG (%)	ISCHEMIA (%)	LEFT VENTRICULAR HYPERTROPHY (%)
All (n = 464)	73	9	32	15	12	62	31	15	26
Type A (n = 289)	79	13	44	19	11	63	31	17	25
Type B (n = 175)	63	4	12	9	16	56	32	13	32

CXR, chest radiographic film; ECG, electrocardiogram.

In up to 3% of cases, a proximal dissection can dissect into the ostium of a coronary artery, most frequently the right coronary artery, and cause an acute myocardial infarction (MI), usually inferior to posterior.[4] Failure to identify the inciting aortic dissection with incorrect administration of a fibrinolytic agent occurs in about 0.1 to 0.2% of MIs.[23] Distal extension of aortic dissections into the abdomen can cause mesenteric ischemia, renal failure, femoral pulse deficits, and lower extremity ischemia.[24]

DIAGNOSTIC STRATEGIES

Routine laboratory tests are of little value in the diagnosis of aortic dissection. Unless massive hemorrhage has occurred, the hemoglobin is normal or only modestly reduced. The leukocyte count is commonly mildly elevated. Recently, there has been increasing interest in the biochemical diagnosis of acute aortic dissection.[25] Myocin heavy-chain concentrations, D-dimer levels,[26] and soluble elastin fragments are some of the newer tools that may be helpful to the diagnosis of aortic dissection and await prospective clinical trails to evaluate their usefulness. Historically, aortography was the "gold standard" against which other modalities were measured. With the advent of transesophageal echocardiography (TEE) and CT scanning, however, conventional aortography is rarely used as the initial diagnostic modality and is no longer the imaging modality of choice.[4]

Electrocardiography

The electrocardiogram (ECG) is often useful in excluding MI; however, 15% of patients with aortic dissection may have ECG abnormalities suggesting ischemia.[4,27] Proximal dissections that involve the right coronary artery may show an inferior wall MI, and the constellation of symptoms and signs (pain, diaphoresis, hypotension) may be difficult to distinguish from those associated with primary acute MI. The ECG typically shows left ventricular hypertrophy in 26%, reflecting long-standing hypertension. Other findings include nonspecific ST-T wave changes and prior Q wave infarction. No abnormalities are noted on the ECG in 31% of cases (Table 83-1).[4]

Chest Radiography

Routine chest radiographic studies are abnormal in 80 to 90% of patients, but the abnormalities are nonspecific and rarely diagnostic.[4,6,8,28] Mediastinal widening occurs in the majority of cases;[4,6] may occur in the ascending aorta, aortic arch, or the descending portion of the thoracic aorta; and may be difficult to differentiate from the aortic tortuosity that is associated with chronic hypertension. A plain chest radiograph is inadequate for ruling out aortic dissection. Up to 12% of patients with aortic dissection have a normal chest radiograph (see Table 83-1).[4,8]

Table 83-2 Sensitivities and Specificities of Imaging Modalities for Diagnosing Aortic Dissection

TEST	TEE	HELICAL CT	MRI
Sensitivity (%)	98	100	98
Specificity (%)	95	98	98

CT, computed tomography; MRI, magnetic resonance imaging; TEE, transesophageal echocardiography.
(From Shiga T, Wajima Z, Apfel CC, et al: Diagnostic accuracy of transesophageal echocardiography, helical computed tomography, and magnetic resonance imaging for suspected thoracic aortic dissection: Systematic review and meta-analysis. Arch Intern Med 166:1350–1356, 2006.)

The "calcium sign" is an uncommon radiographic manifestation of aortic dissection. Ordinarily, when intimal calcification is visible on a radiograph, it is butted up against the outer border of the aorta. With dissection of the aortic media, the calcium deposit becomes separated from the outermost portion of the aorta by more than 5 mm.

Other helpful radiographic signs include a double-density appearance of the aorta suggesting true and false channels, a localized bulge along a normally smooth aortic contour, a disparity in the caliber between the descending and ascending aorta, obliteration of the aortic knob, and displacement of the trachea or nasogastric tube to the right by the dissection. Previous chest roentgenograms, when available, are useful for comparison.

Echocardiography

Transthoracic echocardiography (TTE) is an insensitive tool for detecting aortic dissection because it does not visualize the aortic arch or much of the descending aorta, and imaging quality may not be optimal because of the patient's body habitus. While more sensitive imaging tests are being scheduled, however, TTE can provide valuable information about pericardial effusion or aortic regurgitation[29] and can help determine whether cardiac tamponade is the cause of hypotension in a patient with aortic dissection.

Transesophageal echocardiography (TEE) is highly sensitive[30] (Table 83-2) in the diagnosis of aortic dissection.[31] The proximity of the esophagus to the aorta and the ability to use higher transducer frequencies help to visualize the entire aorta and to detect pericardial effusion and aortic regurgitation.[30] TEE can be quickly performed at the patient's bedside with sedation or light anesthesia and requires no radiation or contrast

agent injection. Visualization of the distal ascending aorta and proximal arch used to be difficult because of the interposition of the air-filled trachea and left mainstem bronchus, but evaluation of this "blind spot" has been aided by biplane and multiplane probes.[30]

The diagnostic accuracy of TEE depends on the experience and availability of the echocardiographer. It is the primary diagnostic method in many institutions for detecting aortic dissection[4] and is the procedure of choice in unstable patients, in whom it can be done in the resuscitation area of the ED, or in the operating room coincident with induction of anesthesia.

Computed Tomography

CT aortography is a reliable test for diagnosing aortic dissection (see Table 83-2) and is the diagnostic test of choice in most institutions.[4] Findings suggestive of aortic dissection include dilatation of the aorta, identification of an intimal flap, and the clear demonstration of both the false and true lumina (Fig. 83-2). Dynamic scanning, in which rapid scans are obtained at multiple levels immediately after a bolus injection of an intravenous (IV) contrast agent, improves the accuracy of the CT scan in the diagnosis of aortic dissection by allowing detection of differential filling rates in the true and false lumina (see Fig. 83-1). Dynamic scanning performed with helical CT improves sensitivity and specificity.[32] Sixty-four-slice multidetector computed tomography (MDCT) may soon alter the approach to chest pain in the emergency department (ED). MDCT may reliably evaluate for coronary artery disease,[33,34] pulmonary embolus, and aortic dissection as a "triple" scan.[35,36]

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is an appealing option in the detection of low-grade aortic dissection in stable patients in whom the diagnosis is uncertain. Sensitivity and specificity are excellent (see Table 83-2).[37] MRI shows the site of intimal tear, type and extent of dissection, presence of aortic insufficiency, and differential flow velocities in the true and false channels and in the aortic side branches. It requires no contrast material or ionizing radiation and is noninvasive. It is particularly useful in the evaluation of chronic aortic dissection, in the follow-up of postoperative patients, and for monitoring nonoperative patients for progression of the dissection. Its availability, however, is limited and it is difficult to perform in unstable patients.

Choice of Diagnostic Test

Although aortic dissection can be suggested on the basis of history and physical examination, diagnostic imaging is necessary to establish the diagnosis. With a mortality rate in excess of 1% per hour after the onset of aortic dissection, a diagnostic study should be performed as soon as possible.[5] Frequently, more than one test is required to diagnose the condition and to assess associated complications.

The clinical services within the hospital involved in the diagnosis and treatment of aortic dissection should prospectively agree on a strategy.[38] This strategy should consider (1) the technology available at the institution, (2) the institution-specific sensitivities and specificities for the diagnostic tests, (3) the benefits of diagnosing nondissecting causes of chest pain, and (4) the ease of obtaining each test, especially "after hours." Some tests (e.g., CT, MRI, aortography) may require moving a potentially unstable patient outside the ED. In IRAD, the initial choice of diagnostic test was CT in 61%, TTE or TEE in 33%, aortography in 4%, and MRI in 2% of patients.[4] "Real-world" sensitivities of diagnostic tests in IRAD were CT 93%, TEE 88%, aortography 87%, and MRI 100%; and patients averaged 1.85 imaging studies.[39] A recent meta-analysis suggests that TEE, helical CT, and MRI yield similar diagnostic value in ruling aortic dissection in or out.[40]

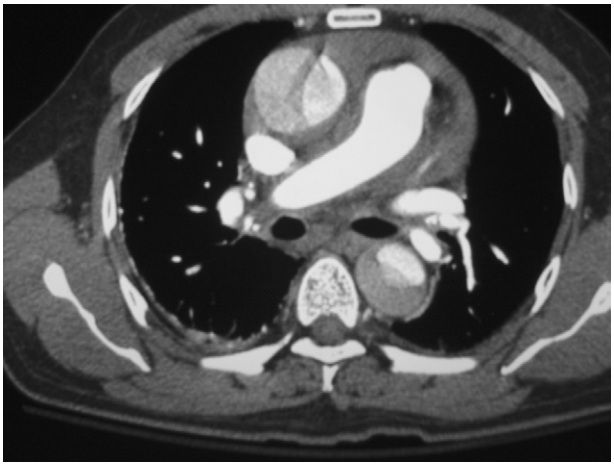


Figure 83-2. Computed tomography scan demonstrating the true lumen and false lumen.

DIFFERENTIAL CONSIDERATIONS

The differential diagnosis for the patient with symptoms suggestive of aortic dissection is extensive. Signs and symptoms associated with aortic dissection vary and depend on the extent of aortic and branch vessel involvement. Patients with the ultimate diagnosis of aortic dissection are often initially thought to have other conditions such as myocardial ischemia, congestive heart failure, or pulmonary embolus.[6] Several clinical syndromes are particularly suggestive of aortic dissection: sudden-onset chest pain, migratory pain, chest pain with concomitant neurologic deficits or syncope, and chest pain with pulse deficits.[41]

Although chest pain is the most common symptom of aortic dissection, it is also the most common presenting complaint of at least three other serious and more common clinical entities: acute MI, pulmonary embolus, and pericarditis. An ECG can be helpful in excluding MI, although aortic dissection and MI may coexist as a result of the dissection proceeding retrograde to the ostium of a coronary artery and causing infarction. In cases in which aortic dissection is excluded, CT may reveal other abnormalities that explain a patient's presentation (e.g., pulmonary embolus). TEE is helpful in identifying etiologies of chest pain other than aortic dissection (e.g., cardiac ischemia).

When the initial presentation of the aortic dissection is pain or dysfunction in an extremity resulting from disruption of the blood supply, peripheral neurologic diagnoses should be included in the differential diagnosis. An aortic dissection may involve the carotid artery with the initial presentation mimicking that of a primary central nervous system lesion such as a stroke. The diagnosis of aortic dissection should be entertained in any patient with a new diagnosis of pericardial effusion, pericardial tamponade, or aortic insufficiency.

MANAGEMENT

Emergency Department

Early therapy for aortic dissection is critical and should be initiated while diagnostic tests are being performed. Opioids should be administered in adequate amounts to control pain and decrease sympathetic tone.[42] Patients with aortic dissections are typically hypertensive. The two goals of medical management are to (1) reduce blood pressure and (2) decrease the rate of rise of the arterial pulse (dP/dt) to diminish shearing forces.[43] A target blood pressure of 100 to 120 mm Hg systolic and a heart rate less than 60 beats/min are recommended.[44] Beta-adrenergic blockers are the cornerstone of aortic dissection management. Because vasodilators such as sodium nitroprusside or fenoldopam reflexively increase the heart rate and may also increase the dP/dt, a beta-blocker must be started before or in conjunction with vasodilator therapy to lower the dP/dt.

Esmolol is an ultrashort-acting beta-blocker that is easily titrated. After mixing 5 g in 500 mL of 5% dextrose in water (D_5W), an initial bolus of 500 µg/kg is given, followed by an infusion of 50 to 200 µg/kg/min. *Labetalol* has both alpha- and beta-blocking activity and can be used as monotherapy. A suggested dose is an initial 20-mg IV bolus every 5 to 10 minutes, incrementally increased to 80 mg IV until a target heart rate is reached or a total of 300 mg is given. A maintenance infusion of labetalol is then given at 1 to 2 mg/minute. If a patient is normotensive, a beta-blocker should still be used to lower the dP/dt. In patients with a history of chronic obstructive pulmonary disease or at risk for bronchospasm, a selective beta-blocker such as metoprolol or atenolol should be considered.

Sodium nitroprusside can be used, in conjunction with a beta-blocker, to maintain the systolic blood pressure at 100 to 120 mm Hg or to the lowest level to maintain vital organ perfusion. Nitroprusside, 50 mg, is mixed in 500 mL of D_5W and initially infused at a rate of 0.5 to 3 µg/kg/min.

The calcium channel blocker *nifedipine* is not recommended to treat aortic dissection. Nifedipine has minimal inotropic or chronotropic effects and may reflexively stimulate sympathetic activity and increase shear stress on the aortic wall.[43] IV *nitroglycerin* is often used initially in patients with hypertensive chest pain and possible or uncertain aortic dissection. Nitroglycerin is a less effective arterial dilator than nitroprusside and less desirable than nitroprusside for the treatment of patients with aortic dissection. Nitroglycerin must, like nitroprusside, be accompanied by a beta-blocker. Some physicians prefer an infusion of fenoldopam over nitroprusside, but this has not been specifically studied in patients with aortic dissection.

Patients presenting with hypotension secondary to aortic rupture or pericardial tamponade should be resuscitated with IV fluids and immediately transported to the operating room if they are to have a chance to survive. Blood pressure should be measured in all four limbs, if necessary, to ensure that this is not a pseudohypotension caused by an intimal flap obstructing the extremity in which the blood pressure is measured. In patients with electromechanical dissociation or marked hypotension, pericardiocentesis may raise the blood pressure while awaiting definitive surgery.

Surgery

Type A acute aortic dissections require prompt surgical treatment. The aortic segment containing the original intimal tear is resected when possible, with graft replacement of the ascending aorta to redirect blood into the true lumen. If aortic insufficiency is present, it can be corrected through aortic valve resuspension or replacement. Patients with type A dissections have an in-hospital mortality rate of 27% when treated surgically versus an in-hospital mortality of 56% when treated medically.

Definitive treatment of type B acute aortic dissections is less clear.[45] These patients in general tend to be worse surgical risks. Uncomplicated distal dissections have traditionally been treated with blood pressure control, and patients have an in-hospital mortality of 10% when treated in this manner.[3] Surgery has been reserved for patients who have persistent pain, uncontrolled hypertension, occlusion of a major arterial trunk, frank aortic leaking or rupture, or development of a localized aneurysm. These patients have an in-hospital, 30-day mortality rate of 32%. A "deadly triad" of absence of chest pain, hypotension, and branch vessel involvement is an independent predictor of in-hospital death.[3]

Interventional Therapy

In general, interventional endovascular techniques are not applicable to type A dissections. Interventional stent-graft and fenestration techniques are replacing surgery for complicated type B dissections in some centers, especially for patients with renal and mesenteric ischemia.[46,47] Patients treated with interventional therapy have an in-hospital mortality rate of 6.5%.[3] Interventional therapy for stable type B dissections is currently under study, and treatment decisions should rest with the primary treating physician.[48]

DISPOSITION

Patients who present with chronic aortic dissection have already survived their period of greatest mortality risk and are usually treated by blood pressure control and close monitoring unless complications mandate surgery. All patients who have sustained and survived an aortic dissection, regardless of the type of definitive therapy used, require careful long-term treatment. Major complications that may occur with time are redissection, the development of a localized aneurysm, and progressive aortic insufficiency.

KEY CONCEPTS

- Risk factors for aortic dissection include advanced age, hypertension, and connective tissue disorders such as Marfan's or Ehlers-Danlos syndrome.
- Most patients with aortic dissection have chest pain, described as sudden-onset, sharp, and migratory. Chest pain associated with neurologic symptoms or syncope should increase the possibility of aortic disease.
- Physical examination findings may include pulse deficit, aortic insufficiency murmur, or neurologic findings.
- Diagnosis is difficult using only history, physical examination, and chest radiography. Computed tomography and transesophageal echocardiography are the confirmatory tests used most often.
- Treatment of type A proximal dissection is surgical. Treatment of uncomplicated type B distal dissection is usually medical, with a beta-blocker and nitroprusside to control blood pressure and dP/dt shearing forces. These agents are also used to control blood pressure and pulse in the preoperative phase for hypertensive patients with type A dissection.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 84 Abdominal Aortic Aneurysm

Howard A. Bessen

PERSPECTIVE

The abdominal aortic aneurysm (AAA) should be distinguished from other abnormalities of the aorta. Most AAAs are true aneurysms. A true aortic aneurysm is a localized dilatation of the aorta caused by weakening of its wall; it involves all three layers (intima, media, and adventitia) of the arterial wall (Fig. 84-1). AAAs should not be confused with aortic dissections, which are sometimes incorrectly called "dissecting aortic aneurysms." In aortic dissection, blood enters the media of the aorta and splits (dissects) the aortic wall (see Chapter 83). True aortic aneurysms and aortic dissections are very different diseases, with different clinical presentations, complications, diagnostic methods, and treatments.

A pseudoaneurysm (false aneurysm) is a collection of flowing blood that communicates with the arterial lumen but is not enclosed by the normal vessel wall; it is contained only by the adventitia or surrounding soft tissue. Pseudoaneurysms can arise from a defect in the arterial wall or a leaking anastomosis after AAA repair.

Aneurysms can develop in any segment of the aorta, but most involve the aorta below the renal arteries. The diameter of the normal adult infrarenal aorta is approximately 2 cm, and a diameter of 3 cm or more defines an AAA.[1,2]

Epidemiology

An AAA is a disease of aging, and the number of AAAs is expected to increase as the population of elderly patients grows. AAAs are rare before the age of 50 years but are found in 2 to 5% of men older than 50.[3,4] The average age at the time of diagnosis is 65 to 70, and men are affected much more often than women. The patient often has atherosclerotic occlusive disease involving the coronary, carotid, or peripheral vessels, which may influence the clinical presentations, complications, and management.

Certain groups are at greatest risk for AAAs (Table 84-1). An AAA can be found in 5 to 10% of elderly men who are screened with ultrasonography and in an even higher percentage of patients with coronary artery disease or peripheral vascular disease. A family history of an AAA is a very strong risk factor; those with an affected first-degree relative have a 10- to 20-fold increased risk of developing an AAA. Awareness of these high-risk groups can speed the recognition of AAAs in these patients.

PRINCIPLES OF DISEASE

Pathophysiology

AAAs have traditionally been attributed to atherosclerosis, but other factors probably contribute to their formation. Most patients with advanced atherosclerosis have occlusive disease, not aneurysms. Biochemical abnormalities leading to the loss of elastin and collagen, the major structural components of the aortic wall, have been identified in patients with AAAs.[2,13] The propensity to form aneurysms may have a genetic basis, but the exact mode of inheritance is uncertain. The Society for Vascular Surgery has recommended labeling the typical degenerative AAA as "nonspecific," rather than "atherosclerotic," to reflect this uncertain cause.

AAAs sometimes result from specific causes, such as infection, trauma, connective tissue diseases, and arteritis. Such aneurysms are rare compared with nonspecific, degenerative aneurysms.

Natural History

AAAs progressively enlarge, ultimately resulting in rupture of the aneurysm and fatal hemorrhage. Although other potential complications are possible, by far the most common and most important is rupture.

The most important factor determining the risk of rupture is the size of the aneurysm.[14-17] The rupture risk increases dramatically with increased aneurysm size, and most ruptured AAAs have diameters greater than 5 cm. Although rupture of aneurysms smaller than 4 cm is rare,[16] no aneurysm is completely "safe."[4,6] Any aneurysm can rupture and may be the source of the symptoms causing the patient's emergency department (ED) presentation.

Rupture of an AAA usually occurs into the retroperitoneum, where hemorrhage may be temporarily limited by clotting and tamponade at the rupture site. Of patients with ruptures, 10 to 30% have free intraperitoneal rupture, which is often rapidly fatal.[18,19] Occasionally, rupture occurs into the gastrointestinal tract or the inferior vena cava.

Complications can also arise from intact AAAs. The walls of AAAs are often lined with clot and atheromatous material, which can embolize and occlude distal vessels.[20] Aortic thrombosis may occur rarely. Patients can also have complications caused by impingement on adjacent structures.

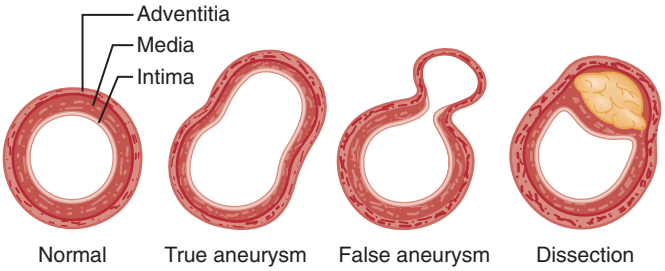


Figure 84-1. Types of aortic aneurysms. (Modified from LeRoy LL, et al: Imaging of abdominal aortic aneurysms. AJR Am J Roentgenol 152:785, 1989.)

Table 84-1 Prevalence of Abdominal Aortic Aneurysms (AAAs) in Selected Risk Groups

GROUP	INCIDENCE (%)
Autopsy subjects aged 50 years or older[5,6]	2–4
Men aged 65 years or older[4,7]	5–10
Patients with coronary artery disease[8] or occlusive peripheral vascular disease[9,10]	10–15
Brothers of patients with AAAs[11,12]	20–30

In approximately 5% of AAAs, a dense inflammatory and fibrotic reaction develops in the aneurysm wall and adjacent retroperitoneal tissue. In these "inflammatory" AAAs, the periaortic fibrosis may incorporate and obstruct adjacent structures, such as the ureters.[21,22]

The overwhelming concern in the patient with an AAA is the potential for rupture of the aneurysm. The natural history of expansion and rupture can be interrupted only by timely repair.

CLINICAL FEATURES

Unruptured Aneurysms

Because most AAAs cause no symptoms until they rupture, the prevalence of symptoms in patients with unruptured AAAs is unknown. Patients may have symptoms, such as pain in the abdomen, back, or flank; an awareness of an abdominal mass or fullness; or a sensation of abdominal pulsations, that lead to the aneurysm's discovery.[2,9,23] The pain associated with stable, intact aneurysms has a gradual onset and a vague, dull quality. It is usually constant but may be described as throbbing or colicky. Acute or severe pain is an ominous symptom that suggests imminent or actual aortic rupture.[2]

In many cases, an AAA is discovered incidentally on physical examination, on a radiologic study done for other reasons, or in an ultrasonography aneurysm screening program.[2,23] Symptoms usually do not develop until the aneurysm ruptures.

The most consistent physical finding is a pulsatile, expansile abdominal mass. The aortic bifurcation is at the level of the umbilicus, and an AAA can be palpated at or above this level. The mass may extend below the umbilicus if the iliac arteries are involved. The right border of an AAA may be palpable to the right of midline, whereas a normal or tortuous aorta is usually not. Most intact AAAs are nontender; tenderness suggests aneurysm expansion or rupture.[9]

Symptomatic aneurysms are usually fairly large and are often palpable. Likewise, the patient with an aneurysm large enough to warrant elective repair often has a palpable abdominal mass.[9,11,24] However, an AAA may be difficult to palpate if the aneurysm is small or the patient is obese. Published reports indicate that 30 to 60% of nonruptured aneurysms measuring 3.0 to 3.9 cm by ultrasonography can be detected by abdominal palpation; 50 to 70% of aneurysms measuring 4.0 to 4.9 cm and 75 to 85% of aneurysms 5 cm or larger can be palpated.[11,24] These reports are based on the examination of patients with intact, largely asymptomatic aneurysms, with the exam specifically directed at sizing the aorta. The sensitivity is likely much lower when the abdomen is not palpated deeply, and in hypotensive patients or those with significant abdominal guarding. There is virtually no risk of causing aneurysm rupture by abdominal palpation.[11]

When the physical examination is suggestive of an AAA, the aorta is often still of normal size.[11] A tortuous aorta may feel enlarged, and prominent aortic pulsations may simulate an aneurysm, especially in a thin patient. Aortic pulsations may be transmitted to an adjacent mass. Nonetheless, clinical suggestion of an AAA warrants further investigation.

An abdominal bruit is found in only 5 to 10% of patients with AAAs.[9] The presence of a bruit is a nonspecific finding because bruits can also originate in a stenotic renal, iliac, or mesenteric artery. A loud continuous bruit suggests the diagnosis of aortovenous fistula.[25]

Perfusion distal to an AAA is usually well maintained, and most patients have normal femoral pulses.[9] Diminished femoral pulses may result from iliofemoral occlusive disease or from hypotension in the patient with a ruptured aneurysm.

Thromboembolic complications can occur spontaneously or when atheromatous plaques are disrupted during invasive intravascular procedures. Large emboli can acutely occlude major vessels such as the iliac, femoral, or popliteal artery, causing acute painful lower extremity ischemia with absent distal pulses. Rarely, the aneurysm itself can thrombose, rendering both lower extremities acutely ischemic.

More often, microemboli consisting of cholesterol crystals or clot obstruct small distal vessels, such as the digital arteries of the toes and arterioles and capillaries of the skin. These patients have livedo reticularis; one or more cool, painful, cyanotic toes; and palpable pedal pulses.[20] This constellation of findings, often called the "blue toe" syndrome, is highly suggestive of a proximal source of emboli. When an AAA is the source, the aneurysm is often too small to palpate and may be discovered only after radiologic investigation.[20]

Rarely, an intact AAA causes atypical symptoms by compressing adjacent structures.[2] Large, long-standing aneurysms can cause vertebral body erosion and severe back pain. Compression of the duodenum between the superior mesenteric artery and an AAA can cause duodenal obstruction, vomiting, and weight loss.[26] Obstruction of the ureters in the patient with an inflammatory aneurysm can cause ureteral colic.[21,22]

Ruptured Aneurysms

Pain-Hypotension-Mass Triad

Although the classic triad of a ruptured AAA is pain, hypotension, and a pulsatile abdominal mass,[2] many patients have only one or two components of this triad, and an occasional patient has none of the classic features.

Rupture is often the first manifestation of an AAA. Some patients, however, have a previously diagnosed AAA, and a decision not to operate electively may have been made because the aneurysm was small or the patient was considered to be at too high a risk. If such a patient has acute symptoms, the presumptive diagnosis is aneurysm rupture.

Most patients with a ruptured AAA experience pain in the abdomen, back, or flank. Pain is usually acute, severe, and constant and can radiate to the chest, thigh, inguinal area, or scrotum. The history of pain may be unobtainable if the patient's mental status is compromised by severe hypotension.

The mechanism of the pain associated with aneurysm rupture is poorly understood. It may be caused by expansion of the aortic wall or by stimulation of sensory nerves in the retroperitoneum. Identical pain can occur with intact but acutely expanding aneurysms, which may be impossible to differentiate clinically from ruptured aneurysms.[27,28] Acute pain in the patient with an AAA should be considered a symptom of rupture or impending rupture.[2]

The duration of symptoms before presentation varies greatly. Some patients are seen shortly after severe pain and hypotension develop. In others, rupture is initially contained in the retroperitoneum, blood loss is small, and the presentation is delayed, sometimes for several days or even weeks.[29] A long duration of symptoms does not exclude the diagnosis of ruptured AAA.

Rupture of an AAA may be accompanied by nausea and vomiting, and sudden hemorrhage can cause syncope or near-syncope.[9,30] Compensatory hemodynamic mechanisms may then return the blood pressure and cerebral perfusion to normal. Transient improvement in symptoms is fairly common but will be followed by hemodynamic deterioration if diagnosis and treatment are delayed.[30]

Ruptured AAAs are often large, and most patients have palpable abdominal masses.[9,31] As with intact aneurysms, a ruptured AAA may not be palpable if the aneurysm is small or the patient is obese. The examination may be difficult if abdominal guarding is present or if an ileus causes significant distention. Aortic pulsations may not be prominent if the blood pressure is low.

Hypotension is the least consistent part of the triad, occurring in only one third to two thirds of patients, and is often a late finding.[18,31] When the initial blood loss is minor, vital signs are often normal. The patient with initially normal vital signs may deteriorate and become hypotensive suddenly and unpredictably.

Occasionally, rupture into the retroperitoneum is sealed and contained for many weeks or months.[32] Patients with this condition develop abdominal or back pain, presumably at the time of aneurysm leakage, that subsequently diminishes or resolves completely. If the diagnosis is made, evidence of chronic rupture (organized hematoma) is found at surgery. These patients can have chronic pain and may progress to free rupture and subsequent massive hemorrhage at any time.[32]

Aortoenteric Fistula

An AAA can rupture into the gastrointestinal tract (aortoenteric fistula) or inferior vena cava (aortocaval fistula). A primary aortoenteric fistula (AEF) is formed when an unoperated AAA erodes into the gastrointestinal tract,[33] usually the third or fourth portion of the duodenum. A secondary AEF, a communication between the site of previous aortic surgery and the gastrointestinal tract,[34,35] can occur as a late complication of AAA repair and should be considered as the leading diagnosis in any patient who presents with a severe gastrointestinal bleed and a history of aortic graft placement (see also Chapter 22).

Early in the formation of a primary AEF, the bowel wall is eroded from the outside by the adjacent AAA. This can lead to the leakage of intestinal contents, with local infection and sometimes abscess formation. Eventually, breakdown of the aortic wall leads to an AEF and gastrointestinal bleeding.

The patient with an AEF may have abdominal or back pain, fever or other signs of intra-abdominal infection, or gastrointestinal bleeding. Because most of these fistulas are into the duodenum, hemorrhage usually manifests as hematemesis or melena. The initial bleeding results from erosion of vessels in the bowel wall and is often minor.[35] Later, often after several days to a week or longer, massive bleeding results from rupture into the intestinal lumen.

The possibility of a primary AEF should be considered in any patient older than 50 years with unexplained gastrointestinal bleeding. If an AAA is diagnosed by history, physical examination, or any other modality, the patient should be presumed to have an AEF until proven otherwise.

Aortovenous (Aortocaval) Fistula

An aortovenous (usually aortocaval) fistula arises when periaortic inflammation causes adherence of the aorta to an adjacent vein, with pressure on the vessel walls causing the development of an arteriovenous communication. If concomitant extravasation of blood into the retroperitoneum occurs, the clinical presentation is similar to that of other patients with ruptured AAAs, often with hypovolemic shock. More often the aneurysm ruptures into the vena cava without leaking externally, and the signs and symptoms of a large arteriovenous fistula dominate the clinical picture.[25,36]

As in other patients with AAAs, a patient with an aortovenous fistula may have abdominal or back pain. An aneurysm that becomes fistulous with the vena cava is usually large, and 80 to 90% are palpable. A continuous abdominal bruit can be auscultated in approximately 75% of patients with aortovenous fistulas, and 25% of patients have a palpable abdominal thrill.[25]

Shunting of blood from the arterial to the venous system increases venous pressure, venous volume, and venous return to the heart. Signs and symptoms of high-output congestive heart failure (dyspnea, jugular venous distention, pulmonary edema) are often present.[25,36] The increased venous volume and pressure can cause lower extremity edema or cyanosis, and dilated superficial veins can be seen on the legs or abdominal wall. Distention and rupture of veins in the bladder mucosa can cause gross or microscopic hematuria, and rectal bleeding can occur for similar reasons. Because of shunting of arterial blood into the venous system, the lower extremities may be cool with diminished pulses.

The patient with an aortovenous fistula often has renal insufficiency caused by the decreased renal perfusion that accompanies high-output congestive heart failure and by increased renal venous pressure. Hematuria in these patients may originate from the kidneys or the bladder. Hematuria is common with an aortovenous fistula but not in other patients with AAAs.[25,37] With an AAA and hematuria, computed tomography (CT, preferably with CT angiography) can rule out aortovenous fistula formation.

DIAGNOSTIC STRATEGIES

Abdominal Radiography

Because of its low sensitivity compared with CT and ultrasound, plain abdominal radiography should rarely be used to investigate possible AAA—a normal plain film does not exclude the presence of an AAA and rarely identifies alternative pathology. However, symptomatic aneurysms are usually large and often calcified, and radiographs obtained to investigate other causes of pain (e.g., bowel obstruction or back pain) may reveal signs of an AAA. The most common findings are curvilinear

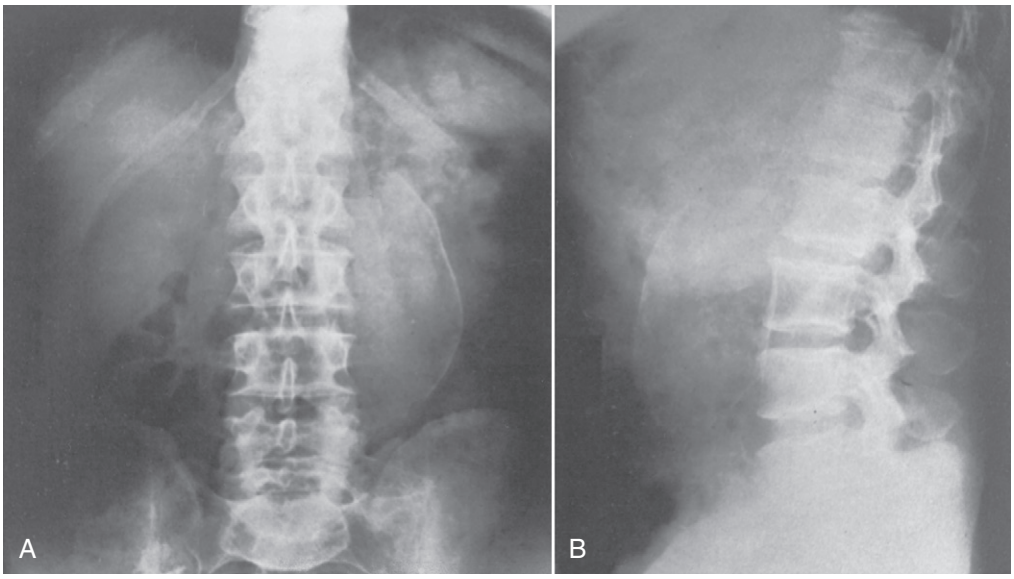


Figure 84-2. Anteroposterior (**A**) and lateral (**B**) views of large abdominal aortic aneurysms with calcification of the aortic wall. (From Juergens JL, et al: Peripheral Vascular Diseases, 5th ed. Philadelphia, WB Saunders, 1980; by permission of the Mayo Foundation.)

calcification of the aortic wall (Fig. 84-2) or a paravertebral soft tissue mass.

AAAs can be seen on both anteroposterior and lateral radiographs. In many cases, enough calcium is present in both lateral walls (on an anteroposterior view) or in the anterior and posterior walls (on a lateral view) to measure the aortic diameter and diagnose the presence of an aneurysm. Because the right border of the aneurysm may overlie the spine on the anteroposterior view, the lateral lumbar spine film is often the easiest to evaluate. If only the anterior wall is calcified (on the lateral view), the distance from the anterior wall calcification to the front of the vertebral bodies correlates well with the true aortic size.

Ultrasonography

Ultrasonography is virtually 100% sensitive in detecting AAAs (Fig. 84-3), provided that a technically adequate study can be obtained.[1] Measurements of aortic diameter are very accurate and reproducible. Because it is relatively inexpensive and requires no contrast agents or radiation exposure, ultrasonography is often chosen for nonemergency aneurysm diagnosis and used to follow patients with known aneurysms.

Ultrasonography has distinct advantages in the emergency evaluation of a patient with a possible ruptured AAA.[38] It can be performed very rapidly at the patient's bedside, obviating the need to take a potentially unstable patient to the radiology suite. If an aorta has a normal diameter visualized throughout its abdominal course, the patient does not have an AAA. Ultrasonography sometimes provides alternative explanations for the patient's pain by revealing conditions such as acute cholecystitis.

Ultrasonography is more operator-dependent than other diagnostic modalities and may be prone to technical or interpretive error.[39] Even with elective studies, the aorta is sometimes not well visualized because of obesity or excess bowel gas. If bedside ultrasonography is not immediately available, waiting for a radiologist or technologist is required. Importantly, although ultrasonography is extremely sensitive in demonstrating the presence of an AAA, it cannot be relied on to determine whether an AAA has ruptured.[29,40]

Rupture can be confirmed if free intraperitoneal or retroperitoneal blood is seen in the presence of an AAA.[39] However, the sensitivity of emergency ultrasonography in detecting extraluminal blood is very low.[29,40] The purpose of the study is to confirm or exclude the presence of an aneurysm; clinical information (or CT) must be used to determine the likelihood of rupture. Ultrasonography with the use of contrast agents may aid in the detection of leaking blood,[41] but the clinical utility of this modality remains to be determined. If ultrasonography reveals an AAA in an unstable patient, aneurysm rupture is presumed, and the patient requires immediate aneurysm repair.

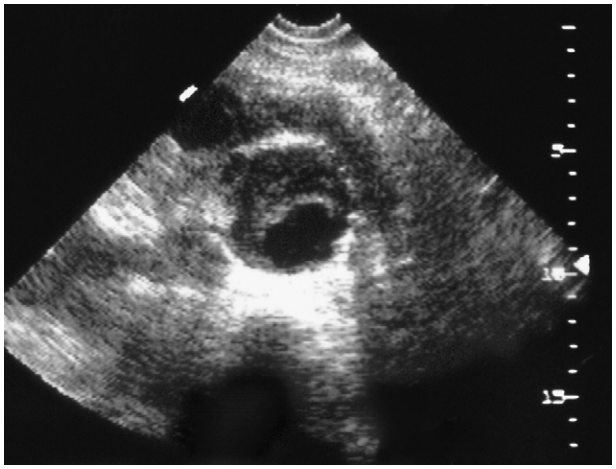


Figure 84-3. Cross-sectional ultrasound of a 6-cm abdominal aortic aneurysm. Note mural thrombus and eccentrically shaped patent lumen. (From Ma OJ, et al: Emergency Ultrasound, 2nd ed. New York, McGraw Hill, 2008, p 160. Courtesy of James Mateer, MD.)

Computed Tomography

As with ultrasonography, abdominal CT is virtually 100% accurate in determining the presence or absence of an AAA and provides accurate measurements of the aortic diameter.[42] CT is less subject to technical problems and interpretation errors than ultrasonography and is much more sensitive in detecting extraluminal blood.[39,43] CT is often used to help plan elective procedures because it can provide detailed anatomic information about the aneurysm.[44,45]

An intravenous (IV) contrast agent is usually administered in elective studies and is desirable, but not essential, in emergency situations.[42,43,46] With prolonged hypotension, it may be advisable to avoid IV contrast to prevent contrast-exacerbated nephropathy. An IV contrast agent will opacify the aortic lumen and distinguish the patent lumen from mural thrombus. It can demonstrate periaortic fibrosis because the soft tissue surrounding an inflammatory AAA is often enhanced.[21] IV contrast is not necessary to identify the aneurysm, however, and acute hemorrhage is well visualized on scans done without contrast.[42,43,46]

When evaluating a patient with a suspected ruptured AAA, a normal aortic diameter on CT excludes an AAA as the cause of the patient's symptoms. CT provides more information than ultrasonography about other retroperitoneal or intraperitoneal disorders and may reveal diagnoses such as ureterolithiasis, pancreatitis, or diverticulitis. However, CT takes longer than ultrasonography and requires moving the patient out of the ED. Therefore, obtaining CT is appropriate only in hemodynamically stable patients.

CT is much more sensitive than ultrasonography in detecting the retroperitoneal hemorrhage associated with aneurysm rupture. The reported sensitivity ranges from 77 to 100%[47] and is probably close to 100% with the use of current-generation scanning technology. Blood is seen as a retroperitoneal fluid collection adjacent to the aneurysm, often tracking into the perinephric space or along the psoas muscle (Fig. 84-4).

Although CT is sensitive in detecting retroperitoneal blood, the results are sometimes falsely reassuring. In these cases, an aneurysm is seen on the CT scan, without evidence of hemorrhage, but hemodynamic deterioration occurs a short time later, and a ruptured aneurysm is found at surgery. This situation can occur if hemorrhage is missed on the CT scan, or if rupture occurs shortly after the scan is completed. Although CT sometimes reveals signs of impending aneurysm rupture,[43,48] it cannot reliably determine whether an AAA is the cause of the patient's pain or whether rupture of the aneurysm is imminent.[49] Another cause of pain can be diagnosed only if the CT scan shows no aneurysm or shows an intact aneurysm and clearly demonstrates an alternative explanation for the patient's symptoms.

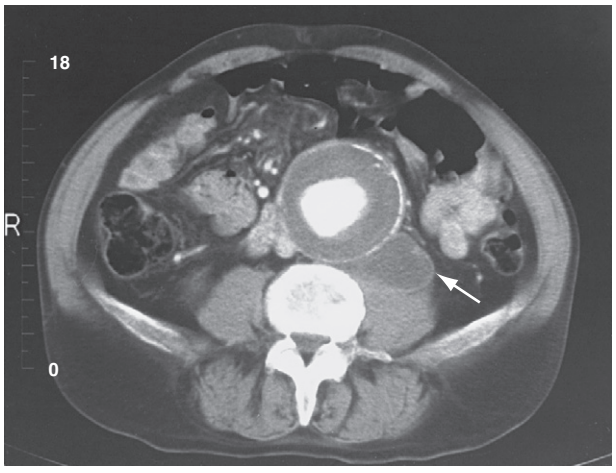


Figure 84-4. Computed tomography scan of ruptured abdominal aortic aneurysm, with calcification of the aortic wall and intraluminal thrombus. The patent lumen enhances with the administration of contrast material, but the periaortic hematoma *(arrow)* does not. (Courtesy of Richard Rensio, MD.)

Other Diagnostic Modalities

Conventional angiography has virtually no place in the emergency evaluation of the possible ruptured AAA. Because contrast opacifies only the patent lumen and not the mural thrombus, angiography often underestimates aneurysm size and can miss the aneurysm entirely.[42] In addition, angiography is time-consuming and performed away from the ED. If detailed information is needed about the anatomy of the aneurysm or its relationship to nearby vessels, a CT angiogram can provide the needed information.[23,43,50]

Magnetic resonance imaging and magnetic resonance angiography can be used for elective preoperative assessment, but not for the evaluation of possible aortic rupture. These procedures are very time-consuming, and the necessary monitoring equipment often cannot be used.[43]

DIFFERENTIAL CONSIDERATIONS

Because the patient with a ruptured AAA usually has abdominal, back, or flank pain, with or without hypotension, common misdiagnoses are other disease processes causing these symptoms (Box 84-1). The sudden onset of back pain often leads to the clinical suspicion of renal colic, with which AAA is often confused.[58] If a suspected kidney stone is investigated by CT, the abdominal aorta should always be evaluated. Abdominal pain and tenderness can suggest pancreatitis, intestinal ischemia, or other intra-abdominal disorders. The diagnosis of musculoskeletal back pain is especially dangerous because these patients are often discharged from the ED.

Epigastric pain and hypotension may lead to an admission diagnosis of acute myocardial infarction. Because the patient with a ruptured AAA often has coexistent coronary artery disease, blood loss from a ruptured aneurysm may diminish coronary perfusion and cause chest pain or electrocardiographic changes consistent with cardiac ischemia. These findings do not rule out the presence of a ruptured AAA.

To avoid missing the diagnosis, a ruptured AAA should be considered in middle-aged or elderly patients who show any part of the classic triad. The diagnosis of ruptured AAA should also be considered when making the diagnoses listed in Box 84-1, especially when the diagnosis is not clear-cut or the patient is at high risk for an AAA.

MANAGEMENT

Ruptured Aneurysms

The patient with a ruptured AAA is unstable until the aorta is cross-clamped in the operating room or stabilized with endo-

BOX 84-1 Common Misdiagnoses in Patients with Ruptured Abdominal Aortic Aneurysms

- Renal colic
- "Acute abdomen"
  - Pancreatitis
  - Intestinal ischemia
  - Diverticulitis
  - Cholecystitis
  - Appendicitis
  - Perforated viscus
  - Bowel obstruction
- Musculoskeletal back pain
- Acute myocardial infarction

vascular techniques. No patient with a known or suspected aortic rupture should be considered "stable," regardless of the initial vital signs or initial hemoglobin level. Patients taken to the operating room soon after arrival in the ED have a much higher survival rate than those for whom surgical care is delayed.[51]

When the patient arrives at the ED, large-bore IV access should be established and blood sent for crossmatching. Because patients with ruptured AAAs often have large transfusion requirements, at least 6 U of blood should be made available initially, with notification to the blood bank of the potential need for significantly more.[18] The surgical and anesthesia team should be notified immediately. Further management depends on the patient's current hemodynamic condition and the level of diagnostic certainty.

The hemodynamically unstable patient in whom a ruptured AAA has been diagnosed or is strongly suspected should be taken to the operating room as soon as possible (in this chapter, the term "operating room" includes other locations that may be used for endovascular aneurysm repair). Diagnostic testing should be kept to a minimum. The diagnosis can often be made from the clinical presentation and abdominal examination, and bedside ultrasonography can quickly confirm or exclude the presence of an aneurysm. CT is appropriate only if it can be obtained very quickly without compromising the patient's care. Time-consuming tests inappropriately delay definitive therapy and increase the risk of exsanguination. Hypotensive patients may have to be taken to the operating room based on a strong clinical presumption of the diagnosis, without definitive diagnostic imaging. Some of these patients will not have ruptured aneurysms, but they usually have other acute abdominal conditions requiring laparotomy.[52]

Attempts to resuscitate these patients fully in the ED and normalize the vital signs should be avoided. Hypotensive patients need to be taken to the operating room so that the aorta can be clamped or occluded with a balloon and hemorrhage stopped. If transfer is required, it should be initiated as soon as the diagnosis is known or strongly suspected. Attempts to stabilize the patient in the ED are often fruitless and waste valuable time.

Fluid Resuscitation

The appropriate degree of preoperative volume resuscitation is controversial. Preoperative hypotension is the strongest predictor of mortality in the patient with a ruptured AAA.[18,19,53] However, correcting the hypotension before clamping the aorta may not improve mortality rates and may even be harmful.

It has been argued that hypotension slows bleeding in patients with AAA and allows local clot formation and tamponade of the rupture site. Raising the intravascular volume and blood pressure before occluding the aorta may dislodge clots and cause further bleeding.[54] Large volumes of crystalloid solution may contribute to bleeding by causing a dilutional coagulopathy. These concerns are similar to those in trauma patients with uncontrolled hemorrhage.

Alternatively, delaying resuscitation of hypotensive patients until they reach the operating room may have deleterious effects. The patient with a ruptured AAA often survives the surgery but dies in the early postoperative period. These deaths are caused by complications of prolonged hypotension, such as myocardial infarction, respiratory failure, and renal failure. The patient with a ruptured AAA is usually elderly, often has coexisting conditions, and tolerates hypovolemia and hypotension poorly.

No prospective studies have compared different preoperative fluid regimens in hypotensive patients with ruptured AAAs, and the optimal resuscitation strategy has not been determined. The priority in these patients is expeditious transportation to the operating room for definitive control of aortic hemorrhage. In the out-of-hospital setting and in the ED before the availability of the surgeon and the operating room, the blood pressure should be raised with crystalloid or blood products only to a level that maintains adequate cerebral and myocardial perfusion. The goal is to prevent irreversible end-organ damage. An arbitrary blood pressure goal cannot be specified because the blood pressure necessary for vital organ perfusion varies among patients, but a reasonable target is a systolic blood pressure of 80 to 100 mm Hg.

Endovascular Approach

Until recently, ruptured AAAs were repaired almost exclusively via open surgical techniques. Endovascular repair of ruptured aneurysms is now feasible, even in unstable patients.[50,55,56] If necessary, the surgeon can stabilize the patient by placing an aortic occlusion balloon above the aneurysm after rapidly accessing the femoral artery. However, not all patients with ruptured aneurysms have an aorta that is anatomically suitable for endovascular repair.[50,55]

The method of repair is clearly the surgeon's decision. Planning for the care of such patients should include development of a well understood protocol that advises the ED staff about which services to mobilize and which diagnostic tests to obtain when patients with ruptured AAA present.[50,56]

Diagnostic Confirmation

In the patient with acute abdominal or back pain but without hypotension, more time can be taken to confirm the presence of an AAA. If an AAA can be diagnosed with bedside testing (abdominal examination or ultrasonography), the surgeon often proceeds immediately to the operating room with a clinical diagnosis of aneurysm rupture, because a delay in surgery places the patient with a ruptured AAA at risk for sudden and unpredictable hemodynamic deterioration. If the patient remains hemodynamically stable and an AAA cannot be identified with bedside testing, or if endovascular repair is being considered, abdominal CT can be obtained to confirm or exclude the presence of an aneurysm and define the aortic anatomy and the patient's suitability for endovascular repair. The patient who is sent for CT must be monitored closely and taken to the operating room immediately if hemodynamic deterioration occurs.

CT can also identify the retroperitoneal hemorrhage associated with rupture and confirm the need for an emergency procedure. The surgeon may want confirmation of rupture to avoid the problems of performing emergency surgery with an intact aneurysm. With emergency surgery, detailed anatomic evaluation and careful preoperative planning are often impossible, evaluation and optimization of the patient's cardiopulmonary and renal function may be precluded, and invasive hemodynamic monitoring may be unavailable. For these reasons, patients who are taken for emergency surgery and found to have intact, symptomatic aneurysms have a significantly higher mortality rate (20–25%) than patients undergoing elective aneurysm repair (approximately 5%).[9,27,28,57]

Once an AAA has been diagnosed, the decision to obtain CT to distinguish a ruptured from an unruptured aneurysm should be made very cautiously and in close consultation with a surgeon. If CT demonstrates an intact AAA and the decision is made to delay surgery, the patient must be closely observed

for signs of rupture in an intensive care setting, and a clear alternative explanation for the patient's presentation (e.g., hypotension, syncope) must be established.

Patients may be hypertensive on admission because of pain or underlying chronic hypertension. Unlike the situation with aortic dissection, no evidence exists that lowering the blood pressure is beneficial in the patient with a ruptured AAA, and these patients are at risk of developing precipitous hypotension.

Surgery and Mortality

Ruptured AAA is uniformly fatal unless treated surgically. Thus, once this diagnosis is made, repair should be attempted in almost all patients.[18] Attempts have been made to identify patients with a very low likelihood of survival, and it has been suggested that surgery can be withheld in patients with out-of-hospital or ED cardiac arrest. However, no variables (including cardiac arrest) that can be assessed in the ED are universally predictive of a fatal outcome.[5,18,19] Repair is indicated unless the patient's life expectancy is very short because of underlying illnesses or the patient's quality of life is so poor that repair is considered unreasonable.

Surgical mortality in patients with ruptured AAAs is approximately 50% and has shown little improvement in the past three decades.[58-60] Hypotension is the most important factor predicting a poor outcome.[18,19,53]

Operative mortality rates significantly underestimate the true lethality of the ruptured AAA. The patient with a ruptured AAA may die at home or may reach the hospital but die before surgery. When patients who do not reach the operating room are considered, the overall mortality rate is 80 to 90%.[61,62]

Intact, Asymptomatic Aneurysms

An incidental diagnosis of AAA may be made in the ED. The decision to repair an asymptomatic aneurysm depends on the risk of aneurysm rupture, the patient's life expectancy and likelihood of dying from other causes, and the surgical risk. The latter factors are determined by the patient's age and coexisting illnesses. The risk of rupture is largely a function of aneurysm size.

In two recent clinical trials, patients with small (<5.5 cm) aneurysms were randomized to early surgery or close follow-up with serial ultrasonography or CT, and surgery was performed only if symptoms developed, rapid expansion was documented, or a diameter of 5.5 cm was reached.[63-65] Both studies showed equivalent survival rates in the two groups. As a result, fewer small aneurysms are now repaired electively, potentially leaving a larger group of patients who may present to the ED with complications of an AAA. It is important to note that the "watchful waiting" approach is appropriate only for asymptomatic aneurysms, and rupture of the AAA must be strongly considered when evaluating any symptoms in these patients.

Traditional Repair

The conventional technique for repair of AAAs is an open approach with a laparotomy. The aneurysm is opened longitudinally and repaired from within (Fig. 84-5). A graft is inserted inside the aneurysm and anastomosed to uninvolved vessels above and below. When possible, a straight graft is used between the infrarenal and distal aorta. If the aneurysm involves the aortic bifurcation, or if iliac artery aneurysmal or occlusive disease is present, a bifurcation graft is used, with the distal anastomosis to the iliac or femoral arteries. The aneurysm wall is then closed around the graft to help separate it from adjacent structures.

Endovascular Repair

Many AAAs are now be repaired using endovascular techniques.[23,44,45,66] A stent graft (a fabric graft supported by an internal wire frame) is placed into the femoral artery percutaneously or through a groin incision and is advanced under fluoroscopic guidance to a position that spans the aneurysm (Fig. 84-6A). The contralateral iliac limb is placed to form a bifurcated graft (Fig. 84-6B). Once in position, the graft is expanded to fit tightly against the walls of the aorta. The stent graft may use hooks or barbs to secure it in place. Straight (tube) grafts, used earlier in the development of endovascular repair, are now rarely used because of their high failure rate.

Endovascular surgery avoids the morbidity associated with a laparotomy and allows the repair of AAAs in some high risk patients who would not tolerate conventional surgery. Periop-

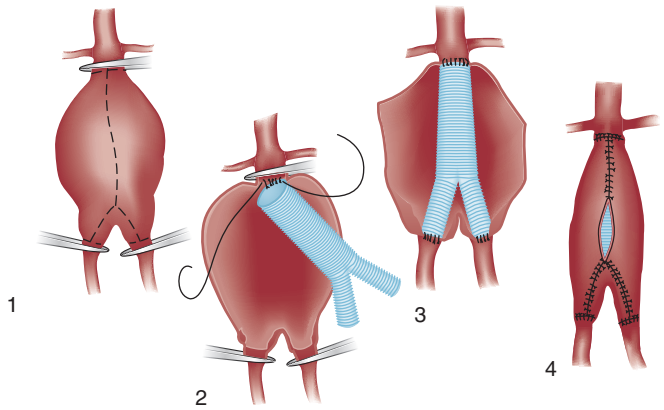


Figure 84-5. Steps in repair of an abdominal aortic aneurysm. (**1,** Incision sites; **2,** proximal anastamosis; **3,** completed anastamoses; and **4,** closure of aneurysm around graft.) (From Kent KC, et al: Surgical principles for operative treatment of aortic aneurysms. In Lindsay J Jr [ed]: Diseases of the Aorta. Philadelphia, Lea & Febiger, 1994, p 287.)

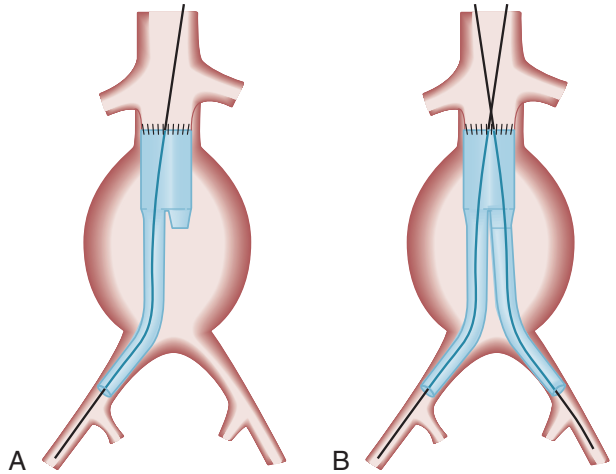


Figure 84-6. Endovascular repair of an abdominal aortic aneurysm. **A,** Aortic section with attached iliac limb. **B,** Addition of contralateral iliac limb. (From Blum U, et al: Endoluminal stent-grafts for infrarenal abdominal aortic aneurysm. N Engl J Med 336:13, 1997. Copyright © 1997, Massachusetts Medical Society. All rights reserved.)

erative mortality is lower than that with open surgery,[66-68] although a long-term survival advantage has not been demonstrated.

Not all aneurysms are anatomically suitable for endovascular repair. Detailed preoperative imaging and planning are often required to make this determination.[44,45] This technique has only recently been applied to patients with ruptured aneurysms.[50,55,56] In addition, patients who have had endovascular aneurysm repair remain at risk for several specific complications, including rupture of the aneurysm.[23,45]

Survival

The mortality rate of elective AAA repair is approximately 5%,[57,68] in stark contrast to the 50% operative mortality associated with ruptured aneurysms. Patients who survive the operation have an excellent prognosis, with a long-term survival close to that of the general population. After repair of the aneurysm, long-term survival is primarily limited by associated cardiac disease.

LATE COMPLICATIONS OF REPAIR

Graft infection, AEF formation, and anastomotic aneurysm (pseudoaneurysm) formation can occur at any time from weeks to many years after the surgery.[34,69] These complications often occur together, their clinical presentations overlap, and they are diagnosed by similar means. Endovascular aneurysm repair has several unique complications, the most important being endoleak.

Graft Infection

Graft infection can result from contamination of the graft at surgery, spread of a contiguous infection, or hematogenous seeding. Infection can disrupt the anastomosis between native artery and graft, leading to leakage of blood and pseudoaneurysm formation. The infection can be localized to a portion of the graft, most often the inguinal portion of an aortofemoral graft, or can involve the entire graft.[70]

Infection of the distal limb of an aortofemoral graft may be clinically evident, with local signs of infection or a palpable false aneurysm. Intra-abdominal graft infection is often subtle, with low-grade fever and vague abdominal or back pain.[70] Abdominal tenderness or a palpable mass may be present at the leaking anastomosis. CT should be performed to evaluate for possible graft infection.[43] Collections of fluid or gas around the graft provide evidence of infection, although CT scans are sometimes falsely negative.[43]

Aortoenteric Fistula

Graft infection may lead to secondary AEF formation. These fistulas, which are much more common than primary AEFs, can develop years after AAA repair or after aortoiliac or aortofemoral bypass surgery for peripheral vascular disease. Secondary AEFs usually form between the proximal aortic anastomosis and the distal duodenum. However, they can occur anywhere in the gastrointestinal tract and cause upper or lower gastrointestinal bleeding.[34,35]

The clinical presentation of the patient with a secondary AEF may be identical to that of a patient with graft infection alone, with fever and other signs of infection. More often, however, the patient with an AEF has gastrointestinal bleeding.[34,35] The bleeding can be acute or chronic, and ranges from minor to massive.

An AEF must be considered in any patient with gastrointestinal bleeding and a history of abdominal aortic surgery. Most of these patients, however, ultimately prove to have other, more common causes of gastrointestinal bleeding. The diagnostic approach depends on the patient's hemodynamic stability.

Diagnostic testing may be dangerously time-consuming if the patient with a possible AEF is unstable with massive bleeding. Emergency laparotomy may be necessary to control hemorrhage and diagnose or exclude the presence of an AEF.

Upper gastrointestinal endoscopy is sometimes recommended as the initial diagnostic test. Direct visualization of the fistula into the distal duodenum is sometimes possible. However, endoscopy cannot be relied on to identify an AEF, and its main value is in establishing another diagnosis. If an active bleeding site other than an AEF is clearly seen, emergency surgery can be avoided.

An abdominal CT scan can also be used to evaluate a suggested AEF.[34,43]Although imaging of the fistula may not be possible, graft infection is almost invariably present in patients with secondary AEFs, and CT can demonstrate the associated infection. Radiographically distinguishing an AEF from intra-abdominal graft infection alone may be difficult, but the distinction is not crucial because both need surgical management.

Pseudoaneurysm (Anastomotic Aneurysm)

Pseudoaneurysms can arise at the site of a leaking anastomosis.[71] They may be associated with graft infection or AEF formation but more often result from degeneration of the native vessel. The patient with an anastomotic aneurysm may have pain or a pulsatile mass in the abdomen or groin. The aneurysm may give rise to distal emboli or may rupture and cause life-threatening hemorrhage. Suspected pseudoaneurysms can be evaluated with angiography, CT, or ultrasonography.[71]

Complications of Endovascular Aneurysm Repair

The most serious of these complications is endoleak—blood flow outside of the graft lumen but within the aneurysm sac that potentially allows enlargement of the aneurysm. Endoleaks may be caused by separation of the proximal or distal end of the graft from the aortic wall, back-bleeding into the aneurysm sac from branch vessels such as lumbar arteries, leakage between the modular components of the graft, or leakage through the graft fabric itself (Fig. 84-7).[23,45] Importantly, the patient with persistent leakage of blood into the aneurysm sac is at risk for rupture of the aneurysm.[44,45,72]

Endoleaks may develop shortly after the procedure or much later. They have been reported in as many as 20% of patients who have had endovascular aneurysm repair;[73] this percentage is expected to decrease with improvements in device design and insertion techniques. Because many endoleaks resolve spontaneously, patients are sometimes observed for months before repair of the leak.

Patients sometimes sustain other complications such as graft migration, stenosis or thrombosis, and structural failure of various elements of the graft. These complications often lead to endoleak and the risk of rupture.

CT is used to investigate possible complications of endovascular repair. A specific imaging protocol may be desired;[43] this should be discussed with the radiologist or vascular surgeon.

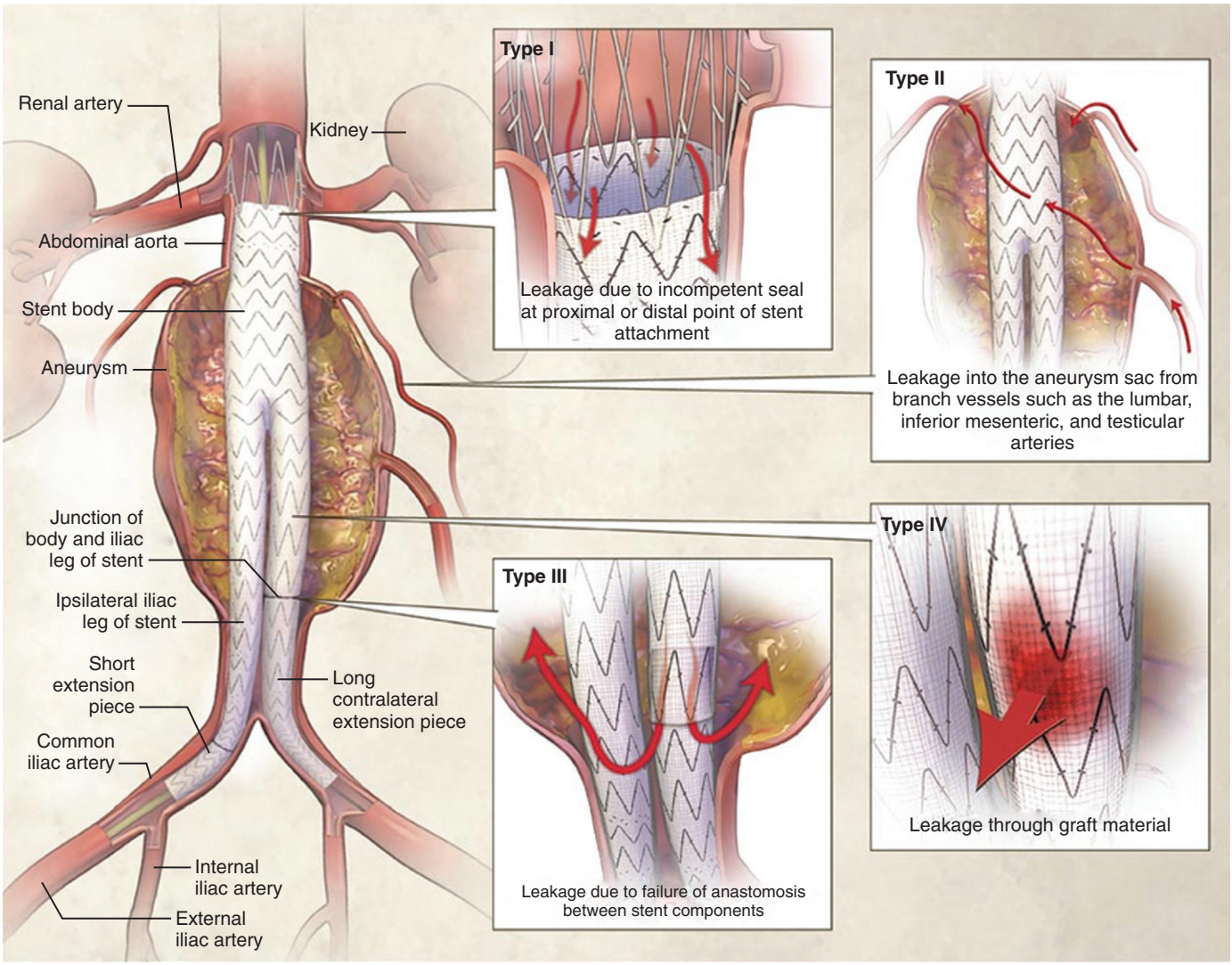


Figure 84-7. Types and causes of endoleaks. N Engl J Med 358:494, 2008. (Copyright © 2008, Massachusetts Medical Society. All rights reserved.)

Because of the many potential complications of endovascular aneurysm repair, these patients require close lifelong follow-up. Prompt surgical consultation should be obtained when patients present with any symptoms possibly caused by device malfunction.

DISPOSITION

A patient with an acutely symptomatic AAA requires hospital admission and urgent or emergency repair. A patient whose aneurysm is asymptomatic and discovered incidentally should be referred for consideration of elective repair. The patient with an AAA should be referred for an outpatient workup only if it is clear that the symptoms prompting the ED visit are unrelated to the aneurysm. If the patient is discharged, instructions should be given to seek medical attention immediately if abdominal, back, or flank pain develops.

In the patient who has had an AAA repaired, unexplained fever, abdominal pain, or gastrointestinal bleeding suggests the presence of a graft-related complication and the need for inpatient evaluation.

KEY CONCEPTS

- A ruptured AAA should be considered in any patient older than 50 years who presents with abdominal or back pain. The complete triad of pain, hypotension, and a pulsatile mass is often not present.
- In the patient with an AAA and acute symptoms, rupture is imminent or has already occurred.
- The patient with a ruptured AAA who appears to be hemodynamically stable can suddenly deteriorate at any time.
- The patient with a ruptured AAA should be moved expeditiously to the operating room and should receive only that testing essential to establishing the diagnosis.
- Resuscitation in the ED should not target normal blood pressure. A systolic blood pressure of 80 to 100 mm Hg is usually sufficient to perfuse the heart and brain.
- The patient who has had endovascular repair of an AAA remains at risk for aneurysm rupture.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 85

Peripheral Arteriovascular Disease

Tom P. Aufderheide

PERSPECTIVE

Treatments for peripheral arterial disease date from the late 18th century. In 1785, Hunter demonstrated complete thrombosis of an aneurysmal sac with a ligature proximal to a popliteal aneurysm.[1] In 1877, Eck reported the first successful anastomosis between two vessels, the portal vein and the inferior vena cava. In 1963, surgical embolectomy became widely established with the introduction of the Fogarty balloon catheter. Recent advances in noninvasive hemodynamic testing, imaging techniques, interventional devices, and chronic indwelling catheters present a wide range of new diagnostic and therapeutic challenges.

Arteries are classified into three categories on the basis of their size and histologic features: (1) large or elastic arteries (the aorta and its immediate proximal, larger branches, including the innominate, subclavian, common carotid, and pulmonary arteries); (2) medium-sized or muscular arteries (located just distal to elastic arteries, including the common femoral, axillary, and carotid arteries); and (3) small arteries (usually < 2 mm in diameter) that course in the substance of tissues and organs. This chapter considers diseases of medium and small arteries.

PRINCIPLES OF DISEASE

Arterial Anatomy

All arteries possess three layers: the tunica intima, tunica media, and tunica adventitia. As peripheral arteries diminish in caliber, these three layers become progressively indistinct and are no longer identifiable at the level of the arteriole (precapillary vessel containing smooth muscle).

The tunica intima has an inner lining of endothelial cells surrounded by subendothelial connective tissue. The outer limit of the tunica intima is demarcated by a longitudinally dispersed layer of elastic fibers known as the *internal elastic lamina*. The single layer of continuous endothelium is a unique thromboresistant layer between blood and the potentially thrombogenic subendothelial tissues. The integrity of the endothelium is a fundamental requirement for maintenance of normal structure and function of the entire vessel wall. Endothelial injury can result in intraluminal thrombosis and may contribute to the initiation of atherosclerosis.

The tunica media is made up primarily of circular or spiral smooth muscle cells arranged in concentric layers. The outer limit of this layer is marked by a well-defined, external elastic membrane. The elastic content of the tunica media gives resilience to medium-sized arteries. As part of the normal aging process, the elastic fibers deteriorate and are replaced by fibrous tissue. This loss of elasticity results in stretching and elongation and accounts for the progressive tortuosity and development of arterial aneurysms with aging. Vascular smooth muscle cells may be important in lipid accumulation in the vessel wall during atherosclerosis and participate in vasoconstriction and dilatation.

The tunica adventitia is a poorly defined layer of connective tissue in which nerve fibers and small, thin-walled nutrient vessels (vasa vasorum) are dispersed. Medium-sized arteries contain more nerve fibers than larger vessels, reflecting the importance of their role in the autonomic regulation of blood flow.

The peripheral arterial vascular system can be considered as a single end-organ subject to a variety of pathologic conditions. This chapter describes eight basic pathophysiologic processes: (1) atherosclerosis, (2) aneurysm, (3) embolism, (4) thrombosis, (5) inflammation, (6) trauma, (7) vasospasm, and (8) arteriovenous fistula. Two of these—atherosclerosis and thrombosis—are responsible for most peripheral arterial problems.

Pathophysiology

Atherosclerosis

Atherosclerosis is a disease of large- and medium-sized muscular arteries. The basic lesion, the *atheroma*, or fibrofatty plaque, is a raised focal plaque within the intima; it has a lipid core (mainly cholesterol, usually complexed to proteins and cholesterol esters) covered by a fibrous cap. As the plaques increase in size and number, they progressively encroach on the lumen of the artery and the adjacent media. Atheromas have two main effects: they compromise arterial blood flow and weaken the walls of the affected arteries.

The distribution of atherosclerotic plaques is rather constant. The abdominal aorta has more atherosclerotic disease than the thoracic aorta, and aortic lesions tend to be much more common and prominent around the ostia of major branches. Other vessels greatly affected by atherosclerosis are the aortoiliac, femoral, and popliteal arteries; the descending thoracic aorta; the coronary arteries; the internal carotid arteries; and the circle of Willis. Vessels of the upper extremities are usually spared.

As atherosclerosis progresses, atheromas almost always undergo calcification, resulting in hard, brittle vessels. Ulceration of the luminal surface and rupture of the atheromatous plaques may result in discharge of the debris into the bloodstream, producing atheroemboli (cholesterol emboli). Fissured or ulcerated lesions can produce in situ thrombosis, causing acute intraluminal occlusion.

Hemorrhage into the plaque may further compromise the arterial lumen. Although atherosclerosis primarily affects the intima, in severe cases, the tunica media undergoes pressure atrophy and loss of elastic tissue, with sufficient weakening to create aneurysmal dilatation.

Aneurysms

A *true aneurysm* is an abnormal localized dilatation of the intact vessel wall. In a pseudoaneurysm, the entire wall perforates or ruptures, and the extravasated blood is contained by the surrounding tissues, eventually forming a fibrous sac that communicates with the artery.

Mural and mechanical factors contribute to true aneurysm formation.[2] The major cause of aneurysms is a weakness or defect in the integrity of the arterial wall. The only aneurysms that develop in a normal arterial segment are poststenotic aneurysms, such as with coarctation. Acceleration of flow past a narrow point creates slower flow beyond the stenosis lateral to the jet stream, producing increased lateral pressure. Aneurysmal dilatation accelerates, increasing the risk of rupture as diameter increases, as predicted by Laplace's law: tension (lateral pressure) in the wall of a hollow viscus varies directly with its radius (tension = pressure × radius).

The most common cause of aneurysms is severe atherosclerosis resulting from thinning and destruction of the tunica media. Atheromatous ulcers covered by mural thrombi are common within an aneurysm. Such mural thrombi can form emboli that lodge in distal vessels. When an entire aneurysm is filled with thrombus material, arterial occlusion results.

Aneurysms cause clinical symptoms through (1) rupture with subsequent hemorrhage, (2) impingement on adjacent structures, (3) occlusion of a vessel by either direct pressure or mural thrombus formation, (4) embolism from mural thrombus, and (5) presentation as a pulsatile mass.

Arterial Embolism

An embolus is a blood clot or other foreign body that is carried by the blood to a site distant from its point of origin. Most emboli are the result of detached thrombus formation (thromboembolism). Less common sources include debris from ruptured atherosclerotic plaques, tumor debris, or foreign bodies. Unless otherwise specified, the term *embolus* in this chapter is defined as *thromboembolus*.

Thromboembolism. Most arterial emboli (85%) originate in thrombus formation in the heart. Left ventricular thrombus formation resulting from myocardial infarction accounts for 60 to 70% of arterial emboli. Atrial thrombi associated with mitral stenosis and rheumatic heart disease account for only 5 to 10% of arterial emboli.[3] Coexisting atrial fibrillation, often without mitral stenosis, is present in 60 to 75% of patients with peripheral arterial embolic events, since atrial fibrillation itself can predispose patients to intracardiac clotting.[4]

Acute arterial emboli often cause distal tissue infarction. Clinical outcome depends mostly on the amount of collateral circulation present but also on the size of the vessel and the degree of obstruction. Patients with long-standing atherosclerosis have well-developed collateral circulation, whereas sudden occlusion of a normal artery without collateral pathways results in severe ischemia. After acute obstruction, the embolus can propagate proximally or distally, fragment and embolize further to distal vessels, or precipitate associated venous thrombosis by initiating a localized inflammatory reaction.

Because vessel diameters change most abruptly at branch points, embolic occlusion most often occurs at major arterial bifurcations. The bifurcation of the common femoral artery is the most frequent site of arterial embolism, accounting for 35 to 50% of all cases.[3] The smaller femoral and popliteal arteries are involved twice as often as the larger aortic and iliac vessels, reflecting the small size of most emboli.

Cell death from arterial ischemia can produce high concentrations of potassium, lactic acid, and myoglobin in the extremity distal to an arterial occlusion. Their sudden release after revascularization can produce life-threatening hyperkalemia, metabolic acidosis, and myoglobinuria. This myonephropathic-metabolic syndrome accounts for approximately one third of the deaths from arterial embolism after revascularization.[5]

Atheroembolism. Atheroembolism refers to microemboli consisting of cholesterol, calcium, and platelet aggregates dislodged from proximal complicated atherosclerotic plaques that lodge in distal end arteries. In the central nervous system, atheroemboli cause transient ischemic attacks and strokes (cerebrovascular accidents). In the peripheral vascular system, atheroemboli characteristically present with cool, painful, and cyanotic toes, or the "blue toe" syndrome (see Fig. 85-2).[6]

Atheroemboli are caused by a proximally located arterial lesion, usually atherosclerotic plaques or aneurysms. Bilateral distal extremity involvement usually implies an aortic source, whereas unilateral atheroemboli usually arise from sites distal to the aorta. Distal lesions are most common in the femoropopliteal arteries (60%) and the aortoiliac arteries (40%). Aortic lesions (e.g., aneurysms, polytetrafluoroethylene grafts) are a less common source of microemboli.[6]

Atheroemboli tend to lodge in arteries, such as the digital arteries, which are 100 to 200 μm in size. Single atheroembolic events seldom result in tissue loss, but atheroemboli tend to cluster. If unrecognized, repeated events ultimately result in loss of collateral circulation, progressive symptoms, and extensive tissue infarction.[6]

Infectious emboli from bacterial endocarditis can produce septic infarcts that may convert to large abscesses. Rarely, cardiac and noncardiac tumors or foreign bodies may gain access to the arterial circulation and embolize. Primary or metastatic lung neoplasms, malignant melanoma, and bullet emboli have been reported. In patients with cyanotic congenital heart disease (e.g., patent foramen ovale), venous emboli may pass directly to the arterial circulation ("paradoxical" emboli). Although rare, this possibility should be considered in any patient with simultaneous arterial and venous emboli, particularly if a source of the arterial embolus is not evident.

Arterial Thrombosis

Thrombosis is the in situ formation of a blood clot within the noninterrupted arterial vascular system. Complicated atherosclerotic plaques are usually responsible for the two major factors that cause in situ thrombosis: endothelial injury and alterations in normal blood flow. Less common causes include acute vasculitis and trauma. Thrombosis is rare in normal arteries.[7]

Peripheral arterial thrombi are usually occlusive, although they may be limited to one wall (mural) in larger vessels. Peripheral arterial thrombi are usually firmly attached to the damaged arterial wall and infrequently embolize. The clot

may propagate proximally and distally, which intensifies the ischemia.

Inflammation

Inflammatory arterial injury can be caused by drugs, irradiation, mechanical trauma, or bacterial invasion. The major cause of arteritis is noninfectious systemic necrotizing vasculitis (see Chapter 116). Most cases of infectious arteritis are caused by direct invasion of the arterial wall. Septicemia, intravenous (IV) drug abuse, or infective endocarditis is most often responsible. Certain fungal infections, particularly aspergillosis and mucormycosis, are frequently associated with vasculitis and thrombosis.

Trauma

Different types of vascular injury result in characteristic pathologic syndromes.[8] Partial arterial lacerations continue to bleed because the intact portion of the vessel wall prevents retraction and closure of the arterial wound. This may form an expanding hematoma, causing progressive deformity, pain, and nerve compression. Complete arterial transection usually has only moderate or insignificant bleeding because of arterial spasm of the transected ends of the artery and the formation of a temporary thrombus. Delayed hemorrhage in completely transected arteries may result from relaxation of arterial spasm, eventual liquefaction of the thrombus, or displacement of the thrombus by arterial pressure. Blunt injury may produce partial or complete intimal disruption. Dissection of the distal intima can lead to progressive obstruction and thrombosis. Complete occlusion may not occur for hours or days after injury. Vasospasm can accompany injuries that are adjacent to blood vessels; spontaneous resolution always occurs in the absence of arterial disruption or intimal injury.

Vasospasm

Vasospastic disorders (Raynaud's disease, Raynaud's phenomenon, livedo reticularis, acrocyanosis, erythromelalgia) produce an abnormal vasomotor response in distal small arteries. The exact cause of these disorders is unknown but is thought to be related to the autonomic innervation of the peripheral arterioles. The vasospastic disorders are characterized by the presence of ischemic symptoms and the absence of tissue loss. True organic changes within the arterial wall are absent. In contrast, patients with digital ulceration and gangrene always have fixed arterial occlusions in the distal extremity arteries.

Arteriovenous Fistulas

Abnormal communication between arteries and veins may result from congenital defects, rupture of an arterial aneurysm into an adjacent vein, penetrating injuries, and inflammatory necrosis associated with neoplasms or infection. Arteriovenous fistulas can occur in any region of the body. The artery proximal to the fistula becomes distended, tortuous, and aneurysmal. Similar changes occur in the venous side of the fistula. Proximal and distal veins respond to alterations in hemodynamics with intimal proliferation and fibrosis, followed by a decrease in the internal elastic lamina, resulting in distention, tortuosity, and aneurysm formation. The resultant chronic venous hypertension may cause dermatitis and ulceration of overlying skin. The size of the opening between artery and vein generally increases with time.

Approximately 60% of arteriovenous fistulas are associated with a false aneurysm.[9] False aneurysm formation can occur as part of the fistulous tract or as the result of arterial or venous dilatation.[9]

The increase in cardiac output that occurs when blood switches from the arterial to the venous system can result in a widened pulse pressure or high-output cardiac failure.

CLINICAL FEATURES

History

Patients with peripheral arterial disease have pain, tissue loss (ulceration or gangrene), or a change in sensation or appearance (swelling, discoloration, or temperature change). Because the primary cause of peripheral arterial disease is atherosclerosis, related conditions providing evidence of atherosclerosis are cardiac disease, myocardial infarction, cardiac dysrhythmias (e.g., atrial fibrillation), stroke, transient ischemic attacks, and renal disease. Factors that increase the likelihood of atherosclerosis are cigarette smoking, diabetes, hypercholesterolemia, and hypertension. IV drug use can lead to arterial injury. Aortoiliac obstruction can cause sexual impotence in men (Leriche's syndrome).

Risk factors not related to atherosclerosis include prior injuries or surgeries, major illnesses, a history of phlebitis or pulmonary embolism, the presence of autoimmune disease or arthritis, and a history of prior coagulation abnormalities.

Acute Arterial Occlusion

The patient with acute arterial occlusion usually exhibits some variant of the "five P's": pain, pallor, pulselessness, paresthesias, and paralysis. Paresthesias and paralysis indicate limb-threatening ischemia that requires emergency surgical intervention regardless of the cause. In patients with non-limb-threatening ischemia, accurate differentiation between embolism and in situ thrombosis as the cause of acute arterial occlusion determines management. Arterial embolism is best managed by emergency Fogarty catheter embolectomy. Non-limb-threatening ischemia from in situ thrombosis is often aggravated by emergency surgical intervention and is therefore initially best managed nonoperatively, if possible (Fig. 85-1). Acute arterial embolism usually occurs in patients without significant peripheral atherosclerosis and without well-developed collateral circulation. For this reason, acute embolism usually presents as sudden limb-threatening ischemia. Patients describe a sensation of the leg's being "struck" by a severe shocking pain. Often the patient has to sit or fall to the ground during the event.

In situ thrombosis usually occurs in patients who have long-standing significant peripheral atherosclerosis and well-developed collateral circulation. For this reason, in situ thrombosis often is seen subacutely with non-limb-threatening ischemia. A history of claudication is common with in situ thrombosis and rare in patients with arterial embolism.

Chronic Arterial Insufficiency

Chronic arterial insufficiency causes two characteristic types of pain: intermittent claudication and ischemic pain at rest. The level of arterial occlusion and the location of intermittent claudication are closely correlated. Calf claudication is associated with femoral and popliteal disease. Patients complain of a cramping pain, reliably reproduced by the same degree of exercise and completely relieved by rest (usually 1–5 minutes). Aortoiliac occlusive disease typically causes claudication in the buttocks and hips, as well as the calves. The calf pain in aortoiliac disease is generally more severe than the buttock

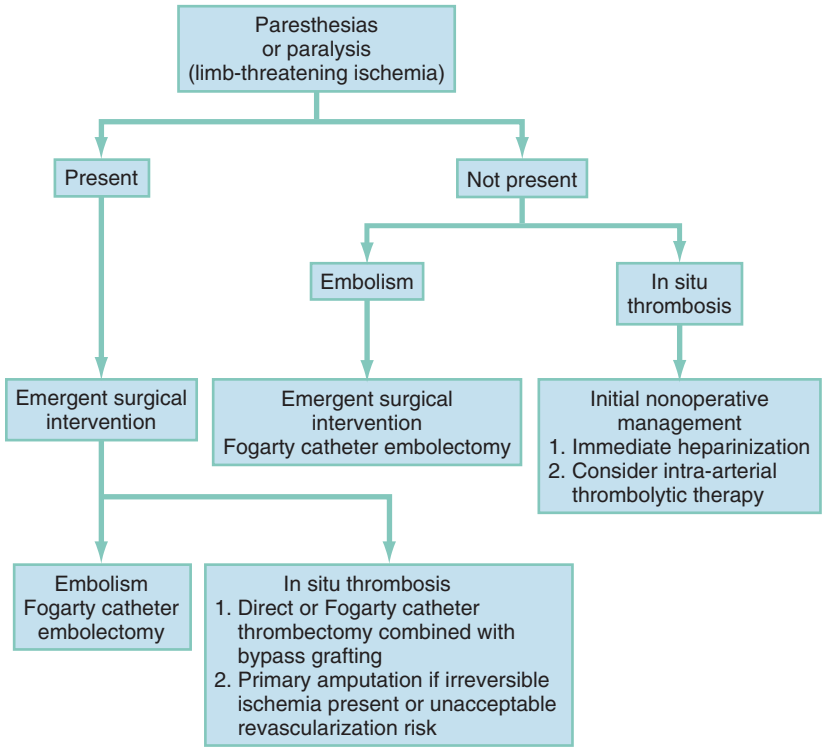


Figure 85-1. Clinical presentation and management of acute arterial occlusion.

and thigh pain, which is more often described as an aching, discomfort, or weakness. Some patients even deny pain, complaining only that the thigh or hip "gives out" with exercise. Aortoiliac occlusive disease severe enough to produce bilateral claudication is almost always associated with impotence in men (Leriche's syndrome). Even in the absence of impotency, bilateral hip or thigh pain in a man should indicate the possibility of aortoiliac occlusive disease.

Chronic arterial insufficiency may progress so that ischemic pain occurs at rest. Rest pain often begins in the feet and typically involves the foot distal to the metatarsals, awakening the patient from sleep. Ischemic rest pain is a severe, unrelenting pain aggravated by elevation and unrelieved by analgesics. Patients often sleep with the leg dangling over the side of the bed or sleep in a chair to improve perfusion pressure to the distal tissues. Patients have prompt relief of pain by any activity that involves a standing position.

Physical Examination

A systematic assessment of the peripheral vascular system includes palpation of the pulse volume in the pairs of brachial, radial, femoral, posterior tibial, and dorsalis pedis arteries documented on a scale of 0 to 4+. Carotid arteries should be gently palpated singly and findings similarly documented.

Approximately 10% of the population does not have one of the dorsalis pedis pulses.[10] The lower extremities should be examined for signs of chronic and advanced ischemia. Muscular atrophy, particularly in the lower extremities, and loss of hair growth over the dorsum of the toes and foot with thickening of the toenails resulting from slowness of nail growth are common signs of arterial insufficiency. As ischemia becomes more advanced, the skin becomes shiny, scaly, and "skeletonized" from atrophy of the skin, subcutaneous tissue, and muscle.

Any area in which ischemia is suggested can be tested by blanching with finger pressure; a delay in return of normal color on relieving the pressure (compared with that of the nonaffected extremity) implies reduced perfusion.

Buerger's sign provides reliable evidence of severe advanced ischemia. With the patient supine, the patient's feet are elevated more than 12 inches above the estimated level of the right atrium, and any change in the color of the feet is noted. If the color does not change, the patient dorsiflexes the feet five or six times; latent color changes induced by exercise are noted. With the patient sitting, the feet are then allowed to hang down over the side of the stretcher; the time of normal color return is recorded. Normal color should return within 10 seconds, and the veins should fill within 15 seconds. If the veins require more than 20 seconds to become distended, advanced ischemia is present.

With severely restricted arterial inflow and chronic dilatation of the peripheral vascular bed, the foot turns chalk white on elevation and intensely hyperemic after 1 minute of dependency. Localized pallor or cyanosis associated with poor capillary filling is usually a prelude to ischemic gangrene or ulceration.

Doppler ultrasonography should be used in the emergency department in all patients with questionable or absent pulses. Doppler testing is more sensitive than palpation in detecting peripheral pulses. An estimate of blood flow to the lower extremities can be made by measuring the systolic blood pressure at the level of the ankle and comparing it with the brachial systolic pressure. With the patient supine, a blood pressure cuff is applied just proximal to the malleolus, inflated above brachial systolic pressure, and then deflated slowly. Ankle systolic pressure can be accurately measured with a Doppler probe placed over the dorsalis pedis or posterior tibial artery. This pressure is normally 90% or more of the brachial systolic pressure; with mild arterial insufficiency, it is between 70 and 90%; with moderate insufficiency, between 50 and 70%; and with severe insufficiency, less than 50%.

The Allen test is helpful in assessing patency of the radial or ulnar artery distal to the wrist. The patient initially opens and closes the hand and then clenches the fist to expel as much

blood from the hand as possible; the examiner then compresses the radial and ulnar arteries. When the patient opens the fist, the hand is pale. The examiner then releases pressure from the radial artery but maintains it on the ulnar artery. If the radial artery distal to the wrist is patent, the hand becomes pink rapidly; if it is occluded, the hand remains pale. The maneuver is then repeated by maintaining pressure on the radial artery while releasing the ulnar artery. A comparison can be made with the opposite hand.

Arterial Embolism

The physical examination can assist in differentiating between arterial embolism and in situ thrombosis in patients who have acute arterial occlusion. The sudden loss of a previously present pulse is the hallmark of arterial embolism. It is difficult to recognize this finding, however, if the prior pulse status of the limb is unknown or is abnormal as the result of associated atherosclerosis. A bounding pulse may be felt initially at the location of an embolus as a result of transmitted pulsations through the fresh clot. In general, patients with arterial embolism have few physical findings suggestive of long-standing peripheral vascular disease with normal, proximal, and contralateral limb pulses. Occasional tenderness to palpation can be noted at the site of an embolic occlusion.

If arterial embolism is suspected, the physical examination should be directed to identifying its source. The two most common sites are a left ventricular mural thrombus secondary to a prior myocardial infarction and a left atrial thrombus in a patient with mitral valve disease. Coexistent atrial fibrillation is common.

The limb distal to an embolic occlusion is initially chalk white. Because of absence of blood from the venules of the subcapillary layer, the demarcation between ischemic and nonischemic tissue is sharp. With time, cyanosis may appear, indicating desaturation of blood with continued ongoing ischemia. Paresthesia or paralysis indicates limb-threatening ischemia. The presence of sensitivity to light touch is often the best guide to viability of the tissue. Complete anesthesia demands immediate surgical intervention. Paralysis represents severe skeletal muscle and neural ischemia, which may be irreversible. Involuntary muscle contracture with woody hardness represents irreversible ischemia.

Arterial Thrombosis

Physical findings of in situ thrombosis are often accompanied by evidence of atherosclerotic occlusive disease. Proximal or contralateral limb pulses are usually diminished or absent. An identifiable source of an embolus, such as mitral valve disease or atrial fibrillation, is usually not present. Because of collateral circulation, demarcation of limb ischemia is less well defined in these patients (Table 85-1).

Carotid, renal, and femoral arteries may have bruits, and there may be evidence of abdominal aortic aneurysm. If an occlusion of the upper extremity vessels is suggested, the subclavian artery should be evaluated by palpating for thrills and listening for bruits in the supraclavicular fossa.

A funduscopic examination allows direct visualization of retinal arterioles that may yield evidence of arteriosclerosis or hypertension. Hollenhorst plaques (atheromatous emboli containing cholesterol crystals in the retinal arterioles) may be detected. Roth's spots (round or oval white spots seen near the optic disk) may be present in patients with infective endocarditis.

Embolic phenomena can cause diverse end-organ damage: hemiplegia from cerebral emboli, flank pain with hematuria from renal emboli, left upper quadrant abdominal pain from splenic infarcts, and pleuritic pain with hemoptysis from pulmonary emboli. Septic pulmonary embolism from right-sided endocarditis may be confused with pneumonia.

Table 85-1 Differentiation of Embolus from Thrombosis

CLINICAL FINDINGS	EMBOLUS	THROMBOSIS
Identifiable source for embolus	Usual, particularly atrial fibrillation	Less common
History of claudication	Rare	Common
Physical findings suggestive of occlusive disease	Few; proximal and contralateral limb pulses normal	Often present; proximal or contralateral limb pulses diminished or absent
Demarcation of ischemia	Sharp	Diffuse
Arteriography	Minimal atherosclerosis; sharp cutoff; few collaterals	Diffuse atherosclerosis; tapered, irregular cutoff; well-developed collaterals

From Brewster DC, Chin AK, Fogarty TJ: Vascular Surgery. Philadelphia, WB Saunders, 1990.

Inflammation

Inflammatory vascular disease manifests primarily as skin involvement. Skin lesions typically appear as palpable purpura; other cutaneous manifestations of vasculitis include macules, papules, vesicles, bullae, subcutaneous nodules, ulcers, and recurrent or chronic urticaria. The skin lesions may be pruritic or even painful, with a burning or stinging sensation. Lesions more often occur in dependent areas: in the lower extremities in ambulatory patients or in the sacral area in bedridden patients. Edema accompanies some lesions, and hyperpigmentation often occurs in the areas of recurrent or chronic lesions.

Vasospasm

Vasospastic disorders cause a sharp border between ischemic and normal tissue. *Raynaud's disease* is characterized by intermittent attacks of triphasic color changes: pallor, cyanosis, and then rubor.[11] The most important element is pallor, during which the digits turn chalk white. Attacks generally last 15 to 60 minutes, and rewarming the hands restores normal color and sensation. Color changes do not occur above the metacarpophalangeal joints and rarely involve the thumb.

Two other vasospastic disorders have a characteristic appearance. *Livedo reticularis* is characterized by a persistent cyanotic mottling of the skin that has a typical "fishnet" appearance and may involve all parts of the extremities and trunk. *Acrocyanosis* is the least common vasospastic disorder and is characterized by persistent, painless, diffuse cyanosis of the fingers, hands, toes, and feet. Cyanosis usually intensifies with exposure to cold and decreases with warming. The involved parts are nearly always cold, exhibit excessive perspiration, and have normal arterial pulses.

Arteriovenous malformations and fistulas, although rare, must be distinguished from vascular bruits or aneurysms. True aneurysms and arterial stenoses are associated with a systolic murmur. Pseudoaneurysms generally have a loud systolic and sometimes a separate faint diastolic murmur. Arteriovenous fistulas have a constant systolic and diastolic (to-and-fro) murmur heard best directly over the lesion and often associated with a palpable thrill, precisely analogous to the findings of a therapeutic dialysis arteriovenous fistula. Unless congenital, arteriovenous fistulae occur at prior operative or trauma sites. The skin overlying the lesion may be warm, but distally the temperature is often decreased. Veins peripheral to the fistula are usually distended and varicose. Large and long-standing arteriovenous fistulas produce high cardiac output and widened pulse pressure. Tachycardia in these patients may suddenly decrease when the artery leading to the fistula or the fistula itself is occluded (Branham's sign).

DIAGNOSTIC STRATEGIES

An accurate diagnosis of peripheral arterial occlusive disease can be achieved in most patients by careful history and physical examination supplemented by bedside testing.

Noninvasive Assessment

Doppler ultrasonography measures blood flow velocity by detecting the frequency shift of sound waves reflected from red blood cells that move toward and away from the transducer. The Doppler signal generates a normal triphasic velocity waveform. Progressive arterial narrowing alters the triphasic waveform to biphasic and finally monophasic shape. Such Doppler ultrasonographic waveform analysis can detect significant arterial occlusive disease, although it is less accurate in determining exact location.

Ultrasound uses differences in sound wave reflection from the interfaces between tissues with different acoustic impedances to provide anatomic detail of underlying structures. Ultrasound is useful in detecting and evaluating atherosclerotic plaques and mural thrombi and in sizing aneurysms of the abdominal aorta and iliac, femoral, and popliteal arteries. B-mode ultrasonography is noninvasive, painless, less expensive than other modalities, and universally available. Bedside ultrasonographic studies can lead to rapid diagnosis of life-threatening conditions and reduce the number of delayed or invasive diagnostic procedures.[12] B-mode ultrasonographic imaging is the diagnostic procedure of choice for the initial evaluation and determination of the size of peripheral artery aneurysms.

Duplex scanning combines the image of B-mode ultrasonography and sophisticated online computer analysis of accurately sampled Doppler waveforms to allow simultaneous acquisition of both the image of a vascular structure and the characteristics of blood flow velocity within it. Duplex scanning permits noninvasive and accurate diagnosis of peripheral vascular, cerebrovascular, and venous disease.

Color imaging of blood flow has been combined with duplex scanning and is known as color-coded Doppler, Doppler angiography, or angiodynography. Color flow imaging is achieved by assignment of colors to the direction of blood flow detected by Doppler waveform signals. Red represents flow away from and blue represents flow toward the probe. Color-coded Doppler, the procedure of choice for most conditions, allows noninvasive and accurate detection of atherosclerotic plaques and stenoses, their effect on intraluminal blood flow, and the presence of venous thrombosis.

Invasive Contrast Arteriography

Angiography is the definitive test of abnormal peripheral artery anatomy but is often inconclusive about the physiologic condition of the tissues. Adverse effects of contrast media and catheter-related complications must be weighed against the benefits of this procedure. Contrast media have a direct toxic effect on vascular endothelium; can produce renal failure, especially in diabetic patients; may cause peripheral vasodilation with hypotension; may result in seizures and stroke in neurologic patients; and can cause severe idiosyncratic and allergic reactions. Catheter-related complications, including embolization, catheter breakage, and vascular disruption, vary with operator skill and anatomic location but average 0.5%. The overall mortality rate from angiography is 0.03%.[13] Emergency angiography is usually required in the following circumstances: (1) acute arterial embolus or thrombosis if the clinical diagnosis is uncertain, (2) consideration of emergency vascular bypass grafting, and (3) characterization of vascular abnormality before emergency surgical correction. A decision to proceed with angiography should be made with the vascular surgeon.

Computed Tomography and Magnetic Resonance Imaging

Angiography using spiral computed tomography (CT), called computed tomography angiography, is the most useful diagnostic modality for the evaluation of the abdominal aorta.[14] In the peripheral arteriovascular system, CT angiography is useful primarily for atherosclerotic, infected, and false aneurysms and for imaging the cerebral circulation. Magnetic resonance imaging (MRI) has the capability for angiography (magnetic resonance angiography) that has been particularly useful in delineating cerebrovascular problems (see Chapter 99) and is seeing expanded use in the evaluation of peripheral vascular disease. The ability to make axial, coronal, and sagittal sections provides accurate visualization of anatomy. MRI detects changes in the relaxation variables of tissues before obvious structural changes, uniquely differentiating blood, thrombus, fat, and fibrosis.

MANAGEMENT OPTIONS

The management of acute arterial occlusion depends on the degree and cause of ischemia. Patients with limb-threatening ischemia from embolism should have emergency Fogarty catheter embolectomy. Patients with limb-threatening ischemia caused by in situ thrombosis require direct or Fogarty catheter thrombectomy combined with vascular bypass grafting. Thrombectomy alone often fails because of recurrent thrombosis. Patients who have a lesion that cannot be bypassed, who have evidence of irreversible ischemia, or who are too ill to tolerate revascularization are treated with primary amputation.

A patient with non-limb-threatening ischemia from embolism still is treated with Fogarty catheter embolectomy. Non-limb-threatening ischemia from in situ thrombosis is best managed nonoperatively with immediate systemic heparinization and possibly with intra-arterial fibrinolytic therapy (see Fig. 85-1).

Elective surgical repair of an asymptomatic atherosclerotic peripheral arterial aneurysm is usually accomplished by excision of the aneurysm with end-to-end anastomosis or

graft interposition. Infected true and false peripheral aneurysms require aneurysm resection, débridement of infected tissue, and ligation of the proximal and distal uninfected arteries. Autogenous vein bypass through uninfected tissue planes is attempted, but prosthetic grafts carry a high risk for graft infection. The surgical approach to noninfected false aneurysms is similar to that of peripheral atherosclerotic aneurysms.

Patients with thoracic outlet syndrome who have cervical ribs, arterial involvement, or significant neurologic symptoms require surgical decompression with removal of anomalous fibromuscular bands and resection of the first rib, if present. Subclavian and subclavian-axillary aneurysms can be treated with resection and end-to-end anastomosis, graft reconstruction, or surgical revision. Patients with distal embolic occlusions are treated with Fogarty catheter embolectomy. Axillary and subclavian vein thromboses are best managed with surgical thrombectomy or systemic fibrinolytic therapy. Patients with only brachial plexus involvement and minimal signs and symptoms should be followed closely with conservative treatment.

Surgical treatment of peripheral arteriovenous fistulas requires interrupting the fistula tract and restoring both arterial and venous continuity with end-to-end anastomosis or graft interposition. If the anatomic location precludes surgical intervention, percutaneous transvascular embolization with liquid tissue adhesives (e.g., isobutyl 2-cyanoacrylate) is usually successful.

Noninvasive Therapy

Acute Anticoagulation with Heparin

Intravenous heparin is an important emergency department therapy for patients with acute arterial embolism, acute arterial thrombosis, and subclavian vein thrombosis. Heparin should be immediately and empirically started at standard IV doses (80 U/kg by IV bolus, followed by a maintenance infusion of 18 U/kg/hr). Heparin quickly reduces thrombin generation and fibrin formation, minimizing clot propagation, which can intensify limb ischemia and jeopardize tissues. Relative contraindications include recent neurosurgery (especially within 2 weeks), major surgery within 48 hours, childbirth within 24 hours, a known bleeding diathesis, thrombocytopenia, a potentially hemorrhagic lesion, and active bleeding.

Fibrinolytic Therapy

Low-dose intra-arterial fibrinolytic therapy is increasingly used for acute arterial occlusion. Patients with limb-threatening ischemia are not candidates because clot lysis generally takes 6 to 72 hours. Patients with an acute arterial embolism cannot tolerate several more hours of ischemia without tissue or limb loss. Fibrinolytic therapy is generally reserved for patients with in situ thrombosis and non-limb-threatening ischemia.

Intra-arterial fibrinolytic agents induce clot lysis in the small, distal runoff vessels, decreasing outflow resistance and enabling the native artery to remain open longer. Fibrinolysis often uncovers a critical stenosis that, untreated, may lead to another episode of thrombosis. After successful fibrinolytic therapy, most patients require secondary bypass grafting or percutaneous transluminal angioplasty. Streptokinase, urokinase, and tissue plasminogen activator have all been used successfully. Intravenous administration of a fibrinolytic agent is less effective than direct administration into the clot. Clots more than 30 days old are more organized and less likely to achieve successful lysis.

Invasive Therapy

Fogarty Catheter Thrombectomy

The Fogarty catheter is most frequently used for iliac, femoral, and popliteal embolectomy, often with only local anesthesia.[15] Aortic saddle embolus is removed by sequentially passing the Fogarty catheter through bilateral common femoral arteriotomies.

Newly formed in situ thrombosis can often be successfully removed with the Fogarty catheter. An older thrombus adheres more firmly to the damaged vessel wall, requiring direct surgical thrombectomy. The Fogarty catheter is not used in the venous system because of the venous valves.

Peripheral Percutaneous Transluminal Angioplasty

The initial success and long-term patency achieved by angioplasty depend on the location of the lesion and the extent of atheromatous disease. Proximal larger arteries (e.g., iliac, femoropopliteal) have the best initial and long-term results. Discrete stenotic lesions (<5 cm) have better long-term patency rates than those vessels that are diffusely involved or have multiple involved segments. Balloon angioplasty is the accepted treatment for isolated stenotic lesions in the renal, iliac, and superficial femoral vessels.

Transluminal angioplasty with intravascular stent is used in more distal vessels, including the popliteal and tibial circulation, in cases of more diffuse lesions, and for patients who are prohibitive surgical risks, although its value remains to be determined.[16]

Recanalization devices include the percutaneous atherectomy catheter, percutaneous angioscope, hot-tip laser, excimer laser, and high-speed rotating wire and drill.

Grafting

Vascular grafting is associated with a variety of complications that can be diagnosed in the emergency department. Autogenous vein grafts (usually a reversed greater saphenous vein) provide excellent long-term patency for small arteries. Vein grafts respond to arterial pressure with gradual intimal proliferation and medial fibrosis. They may develop atherosclerosis, which can lead to graft stenosis and thrombosis. False aneurysms can form along the suture line.

Polytetrafluoroethylene (Teflon) prosthetic grafts are widely used in medium and large arteries that are impossible to bridge with smaller vein grafts. Prosthetic grafts have a higher rate of thrombosis than venous grafts. Distal emboli may result from poor fixation of luminal fibrin. If the prosthetic graft has not been adequately covered by viable tissue, it can erode into adjacent structures and hollow viscera. Prosthetic graft infection is a devastating complication requiring removal of the entire graft.

Vascular grafts can be used to bypass arterial occlusions and reconstruct a diseased arterial bifurcation, or they can be interposed between sections of resected artery. The two most common complications of both prosthetic and vein grafts are thrombosis and development of a false aneurysm at one or more suture lines. Bypass grafting is most often used as palliative treatment for symptoms of atherosclerotic occlusive disease. Patients with localized unilateral stenosis (<3–5 cm in length) may have a comparable rate of success with percutaneous transluminal angioplasty with or without stent placement.[17]

Patients with calf claudication from superficial femoral or popliteal occlusive disease can avoid rapid progression of

disease if they stop smoking and maintain an active exercise regimen. Patients who have progression of disease, significant rest pain, or tissue loss require surgical revascularization.

Sympathectomy

Lumbar sympathectomy is no longer used for treatment of ischemia from arterial occlusion. The benefit of sympathectomy in patients with symptomatic Raynaud's phenomenon is unclear, but it remains a potential intervention to assist healing of superficial ischemic ulcers and relieve rest pain in patients with Buerger's disease.[18]

Hyperbaric Therapy

Scant objective evidence indicates that hyperbaric therapy alters the long-term course of chronic obliterative vascular disorders, presumably by accelerating formation of fine vessels. More success has been achieved with healing chronic diabetic ischemic ulcers and salvaging ischemic skin grafts and flaps.[19] Referral to a hyperbaric unit for chronic therapy should be made by the patient's primary physician or vascular surgeon and not in the emergency department.

SPECIFIC ARTERIOVASCULAR DISEASES

■ DISEASES OF CHRONIC ARTERIAL INSUFFICIENCY

Arteriosclerosis Obliterans

Arteriosclerosis obliterans (atherosclerotic occlusive disease, chronic occlusive arterial disease, obliterative arteriosclerosis) is the peripheral arterial presentation of atherosclerosis. Most often, arteriosclerosis obliterans affects the lower abdominal aorta, the iliac arteries, and the arteries supplying the lower extremities. Upper extremity manifestations are rare.

Arteriosclerosis obliterans is responsible for 95% of cases of chronic occlusive arterial disease. It is most common in persons older than 50 years, but as many as 19% of cases occur in patients between the ages of 30 and 49 years. Men are affected more often than women (5:1 to 10:1). Approximately one third of patients with arteriosclerosis obliterans have coexistent coronary artery disease. The incidence of diabetes mellitus is 20 to 30%.[20]

As with other atherosclerotic diseases, risk factors for arteriosclerosis obliterans include cigarette smoking, hyperlipidemia, and hypertension. Of patients with arteriosclerosis obliterans, 70 to 90% are smokers when first examined, 75% have hyperlipidemia, and 30% have hypertension.[20]

Clinical Features and Differential Diagnosis

Acute arterial occlusion from embolism, thrombosis, or trauma is ruled out primarily by history. Atheromatous emboli from proximal ulcerated plaques or aneurysms can cause small scattered ischemic lesions in the toes, feet, or legs, which may cause blue toe syndrome (Fig. 85-2). The peripheral pulses are present in the blue toe syndrome. Exercise-induced claudication must be distinguished from the nocturnal muscle cramps that frequently occur during rest in elderly patients. Aortoiliac occlusive disease must be differentiated from osteoarthritis of the hip, which tends to be more variable from day to day, is not relieved completely with rest, and is not reliably reproduced by the same amount of exercise. Pseudoclaudication from the cauda equina syndrome is caused by narrowing of the lumbar canal from spondylosis, disease of the intervertebral disks, or spinal cord tumor. Symptoms mimic intermittent claudication but are less closely related to exercise and rest than true claudication.

Figure 85-2. Clinical presentation of atheromatous emboli, or blue toe syndrome. (Courtesy of Gary R. Seabrook, MD.)

The cause of lower extremity ulcers should be carefully determined. Approximately 5% of lower extremity ulcerations are caused by arterial insufficiency.[21] These are usually located distal to the ankle, typically at the terminal portion of the digits, around the nail beds, or between the toes, caused by friction of one toe on another. Less common locations include the metatarsal heads, heel, and malleoli. Arterial insufficiency ulcers are painful but improve when the extremity is in a dependent position. They are associated with evidence of coexistent chronic arterial insufficiency (absence of hair growth on the dorsum of the feet, skin atrophy, absent pulses, and nail deformities). Ulcers are initially small, shallow, and dry. The base is gray, yellow, or black, with minimal or no granulation tissue. The rim of the ulcer is sharp and indolent, showing no signs of cellular proliferation or epithelialization.

Approximately 90% of lower extremity ulcers are caused by chronic venous insufficiency.[21] These typically occur proximal to or in the region of the ankle, especially near the medial malleolus. Venous stasis ulcers are only mildly painful and improve with elevation of the extremity. Evidence of long-standing chronic venous insufficiency, including edema, prominent superficial veins, and stasis dermatitis, is present. Ulcers are moderate in size, with a weeping base and extensive granulation tissue. A rapidly developing ulcer is more suggestive of venous insufficiency.

Most of the remaining lower extremity ulcers are caused by diabetic neuropathy, alone or with arterial insufficiency.[21] The location reflects sites of repeated trauma, including the toes, heels, and plantar surface of the feet, especially the metatarsal heads. Neurotrophic ulcers are typically painless. Patients may have evidence of coexistent peripheral arterial insufficiency.

The ulcers are deep and penetrating, often with suppurative drainage caused by an underlying infection or chronic osteomyelitis. Neurotrophic ulcers are usually surrounded by a rim of thick callus.

Hypertensive ulcers are rare and reflect long-standing, uncontrolled hypertension. These ulcers are typically near the lateral malleolus and start as painful, reddish blue areas of infarcted skin. A hemorrhagic bleb develops, then breaks down into a superficial ulcer, which can reach a size of 5 to 10 cm. The ischemic ulcer has sharply demarcated borders, little granulation tissue, and minimal drainage. The pain is the most severe of all lower extremity ulcers.

Multiple ischemic ulcerations above and below the ankle should suggest vasculitis or atheromatous embolization. Ulcers with regular edges in unusual locations may be factitial or may result from subcutaneous injection of illicit drugs. Thickened, rolled, and elevated edges with a central depression containing granulation tissue are characteristic of malignant ulcers.

Management

The first step is to identify patients whose symptoms are the sole result of arteriosclerosis obliterans without coexistent thromboembolic disease. Treatment is dictated by the classification of symptomatic patients into two groups: those with functional ischemia and those with limb-threatening ischemia.[22] Initial assessments and treatments should be made in conjunction with appropriate vascular surgery consultation.

Patients with limb-threatening ischemia constitute a surgical emergency. Angiography should be arranged to identify sufficiently localized disease to permit emergency bypass grafting.[22] Patients with functional ischemia should have outpatient arrangements for noninvasive vascular testing or elective invasive contrast arteriography to determine treatment options such as bypass grafting. Ischemic ulcers or skin lesions should be cultured in the emergency department. Systemic antibiotics to cover skin organisms should be instituted if infection is present. Wet to dry dressings may help débride ulcers containing fibrin, debris, or infection. Radiographs of the underlying bones should rule out osteomyelitis. Patients with ischemic rest pain require hospitalization even if they are not surgical candidates. Bedrest, a warm environment, and maintenance of the limb in a dependent position usually relieve pain.

Buerger's Disease (Thromboangiitis Obliterans)

First described by Buerger in 1908, thromboangiitis obliterans is an idiopathic inflammatory occlusive disease primarily involving the medium-sized and small arteries of the hands and feet.[23] Patients are usually men between 20 and 40 years of age who use tobacco, although recent reports indicate an increasing frequency of this disease in women. Buerger's disease affects all races but is more prevalent in the Middle and Far East. The incidence in the United States is 20 in 100,000.[24] The exact pathogenesis of Buerger's disease is unknown, but virtually all patients are smokers.

Thromboangiitis obliterans is characterized by segmental acute and chronic inflammation in the smaller arteries of both upper and lower extremities. The initial arterial inflammatory process progresses to affect the adjacent veins and nerves, often leading to associated venous thrombosis and progressive fibrous encasement of these structures. This is recognized clinically as painful, tender, reddened, or dark nodules over a peripheral artery with either a reduced or an absent pulse (phlebitis migrans).

Clinical Features

Clinical criteria for the diagnosis of Buerger's disease include (1) a history of smoking, (2) onset before the age of 50, (3) infrapopliteal arterial occlusive lesions, (4) either upper limb involvement or phlebitis migrans, and (5) absence of atherosclerotic risk factors other than smoking. A characteristic symptom of Buerger's disease is foot or instep claudication caused by infrapopliteal arterial occlusion. Intense rubor of the affected extremity, particularly with dependency, is also characteristic. Foot pulses may be absent in the presence of normal femoral and popliteal pulses. Involvement of the hands is often bilateral and symmetrical, leading to the development of hand claudication or fingertip ulcers. Phlebitis migrans occurs early in the disease. Approximately 50% of patients experience Raynaud-type triphasic color response to cold. In the upper extremities, the digital arteries are usually more involved than the radial or ulnar arteries.[24]

Diagnostic Strategies

Adherence to diagnostic clinical criteria should be sufficient for emergency department diagnosis of Buerger's disease. Noninvasive vascular laboratory testing can confirm the diagnosis and determine the extent of involvement. Although rarely required, angiography demonstrates multiple segmental occlusions.

Differential Diagnosis

Arteriosclerosis obliterans is most likely in patients older than 50 years who have signs of peripheral ischemia. In young women, autoimmune diseases such as scleroderma or systemic lupus erythematosus should be considered.[24]

Management

Permanent complete abstinence from tobacco is the only known effective treatment for Buerger's disease. If a patient does not completely stop smoking, alternating periods of quiescence are followed by exacerbations of severe arterial insufficiency. Patients who permanently abstain from smoking have a benign clinical course. Despite this, many individuals who have Buerger's disease continue to smoke even though they experience severe pain at rest, tissue loss, and eventually amputation.

With early symptoms without threat of tissue loss, patient education and follow-up with a vascular surgeon are sufficient. Vascular surgery treatment options are varied for patients with severe symptoms or threatened tissue loss. Intractable pain can be controlled with epidural anesthesia. Intra-arterial or IV prostaglandin E_1 and antithrombotic agents, including aspirin and heparin, have been used successfully.[24] Patients with large-vessel arterial occlusion may benefit from arterial reconstruction. Sympathectomy is a potential treatment in advanced cases for cutaneous ulceration or relief of rest pain.[18] Because patients with Buerger's disease have good healing, intensive conservative treatment is usually successful in avoiding surgical amputation.

DISEASES OF ACUTE ARTERIAL OCCLUSION

Arterial Embolism

Despite advances in diagnosis and treatment, acute arterial embolus continues to be associated with substantial morbidity

and mortality. Approximately 50% of acute arterial occlusions are caused by arterial embolism and the incidence appears to be increasing. The other 50% are caused by in situ thrombosis.[3]

Differential Diagnosis

Phlegmasia cerulea dolens is a massive iliofemoral deep venous thrombosis. The initial symptom may be acute onset of a swollen and painful leg. As swelling continues, secondary arterial insufficiency with associated pallor (*phlegmasia cerulea albens*) may occur. In cases of acute arterial embolism, leg swelling is not usually present, especially not at the onset of pain. In addition, acute embolism produces a sharply demarcated pallor; phlegmasia cerulea dolens causes a cyanotic-appearing leg.

Aortic dissection may involve the arteries of the upper or lower extremity and may mimic acute embolus. A history of progressive severe pain, the presence of aortic insufficiency, and involvement at multiple sites suggest dissection. Acute neurologic syndromes (e.g., transverse myelitis, spinal subarachnoid hemorrhage, ruptured intervertebral disk) may produce sudden onset of unilateral or bilateral lower extremity weakness or sensory loss that mimics an acute aortic saddle occlusion.

Cold, blue extremities may result from low-output states such as hypovolemia, decreased cardiac output, dehydration, myocardial infarction, and pulmonary emboli in patients with long-standing atherosclerotic disease.

Management

Acute arterial embolism is a surgical emergency. The likelihood of limb salvage decreases after 4 to 6 hours. On the basis of clinical diagnosis alone, full doses of IV heparin should be administered immediately to minimize clot propagation. Patients whose history and physical examination clearly indicate an acute arterial embolism should undergo immediate Fogarty catheter embolectomy without prior angiography. In these patients, preoperative ultrasonography and angiography are rarely useful diagnostically and prolong the limb's ischemic status.

If the differentiation of acute embolism and in situ thrombosis is uncertain, pretreatment angiography is required and usually diagnostic. Patients with acute emboli generally show minimal signs of atherosclerosis, occlusion at the site of an arterial bifurcation, sharply demarcated cutoffs, and lack of flow distal to the occlusion. In patients with in situ thrombosis, arteriography shows diffuse atherosclerosis, occlusion at sites other than arterial bifurcations, a tapered irregular cutoff, and well-developed collateral vessels. In general, emboli tend to lodge at arterial bifurcations, whereas arterial thrombi do not (see Table 85-1).

Intra-arterial thrombolytic therapy for acute embolism remains investigational. Immediate limb-threatening ischemia precludes consideration of treatment with thrombolytic therapy in most patients. Potential risks of thrombolytic therapy in arterial embolism patients with non-limb-threatening ischemia include partial clot lysis with further distal embolization or recurrent embolic events from the primary source of the initial embolus.[25]

Atheroembolism (Blue Toe Syndrome)

Atheroemboli are microemboli consisting of cholesterol, calcium, platelet aggregates, and hemorrhagic debris that break off from proximal atherosclerotic plaques or aneurysms and lodge in distal end arteries. In the central nervous system, atheroembolism causes transient ischemic attacks and strokes. In the peripheral vascular system, atheroemboli characteristically are found in the lower extremities with cool, painful cyanotic toes in the presence of palpable distal pulses (see Fig. 85-2).

Clinical Features

The typical presentation of atheroembolism is the sudden onset of a small painful (cyanotic and tender) area on the foot, typically the toe.[26] If bilateral involvement is present, the distribution is not symmetrical. Posterior tibial and dorsalis pedis pulses are present. The physical examination should be directed toward identification of a proximal source, such as an atherosclerotic aneurysm in the aorta or iliac, femoral, or popliteal artery.

Differential Diagnosis

A variety of conditions can mimic the blue toe syndrome. Acrocyanosis is painless, has a symmetrical distribution, and is located in the hands, nose, and lips. Poor peripheral perfusion as a result of low cardiac output must also be considered. Vasculitis, typically, has palpable purpuric lesions and is associated with constitutional symptoms of low-grade fever, myalgias, and weight loss. Previous frostbite may leave the extremities sensitive to cold. Local injury to the foot of the diabetic patient is easily differentiated.

Management

Treatment is directed toward identifying and removing the proximal source of atheroembolism. Angiography is the most accurate diagnostic method for determining the source of emboli. If the source is an aortic aneurysm and the patient is a surgical candidate, operative repair should be performed. Stenotic lesions in the iliac or femoral arteries can be treated with local endarterectomy, vascular bypass, or angioplasty.[16] Medical management with aspirin, dipyridamole, crystalline warfarin sodium (Coumadin), or steroids has variable results.

Arterial Thrombosis

Approximately 50% of acute arterial occlusions are caused by in situ thrombosis.[3] Acute arterial thrombosis is almost always superimposed on a complicated atherosclerotic lesion but can be caused by vasculitis or trauma. With limb-threatening ischemia, angiography can evaluate the feasibility of emergency bypass grafting. In patients with non-limb-threatening ischemia, angiography may be required if the clinical distinction of acute embolism and thrombosis is difficult (see Table 85-1).

Management

Systemic heparinization should be immediately established in the emergency department. Patients with severe limb-threatening ischemia require emergency direct or Fogarty catheter thrombectomy combined with bypass grafting. Simple thrombectomy alone often fails as a result of rethrombosis. Patients who have atherosclerotic disease not amenable to vascular bypass, who are too ill to tolerate revascularization, or who have irreversible ischemia require primary amputation. Patients with non-limb-threatening ischemia are best treated nonoperatively with heparin and low-dosage intra-arterial thrombolytic therapy.

PERIPHERAL ARTERIAL ANEURYSMS

A true aneurysm is an abnormal localized dilatation of the intact wall of any vessel caused by a combination of mural weakness and hemodynamic forces. Aneurysms enlarge at a rate governed by the cause of the lesion. Those caused by atherosclerosis progress slowly over years; those caused by trauma or infection enlarge over days, weeks, or months. The primary risk of central aneurysms (abdominal aorta, iliac arteries, and visceral arteries) is rupture (see Chapter 84). Peripheral arterial aneurysms rarely rupture; instead, they are complicated by thrombosis or embolism that jeopardizes distal tissues.[27]

The cause of an aneurysm depends on its anatomic location. Lower extremity aneurysms are most often atherosclerotic in origin. Upper extremity aneurysms are usually caused by localized trauma. Visceral aneurysms result from abnormal hemodynamics, atherosclerosis, or infectious causes.

Lower Extremity

Femoral and popliteal artery aneurysms almost always occur in older men with advanced atherosclerosis. Twenty-five percent of patients have distal atheroembolism or thromboembolism; an additional 15% have total occlusion from in situ thrombosis.[27]

Popliteal aneurysms are the most common peripheral aneurysms and occur bilaterally in approximately 60% of patients.[27] An abdominal aortic aneurysm occurs in almost 80% of patients with bilateral popliteal aneurysms. Most patients have claudication, thromboembolic events, atheroembolic events, or gangrene. Aneurysmal dilation can cause venous compression with associated deep venous thrombosis.

Femoral aneurysms are the second most common peripheral aneurysms and manifest similarly to popliteal aneurysms. Femoral aneurysm dilation can also compress the femoral nerve, producing anterior thigh pain or weakness.

Diagnosis of both popliteal and femoral aneurysms is made by palpation of a pulsatile mass. Plain radiographs may show unilateral or bilateral calcified aneurysms. Ultrasonography and CT are diagnostic. Arteriography yields definitive diagnosis and indicates involvement of distal vessels. Patients with a lower extremity aneurysm should be evaluated for the presence of other aneurysms.

Asymptomatic patients can undergo elective surgical excision of the aneurysm and end-to-end anastomosis or graft interposition. Simultaneous repair of coexisting abdominal aorta or contralateral extremity aneurysms combined with vascular bypass is typically done. Patients with limb-threatening thromboembolic events are first treated with Fogarty catheter embolectomy.[27]

Upper Extremity

Peripheral arterial aneurysms in the upper extremities are rare. Atherosclerosis generally spares the upper extremities, making localized trauma the most common cause.

The causes of proximal subclavian artery aneurysms are thoracic outlet obstruction, trauma, and, rarely, atherosclerosis. Subclavian aneurysms from atherosclerosis represent severe disease, and 30 to 50% of patients so afflicted also have aortoiliac or other peripheral aneurysms.[28] Symptoms depend on the aneurysm's anatomic location. Patients may have chest, neck, and shoulder pain from acute expansion. Compression of the right recurrent laryngeal nerve can lead to voice change. Compression of the trachea can lead to stridor or other respiratory complaints. The chest radiograph may reveal a superior mediastinal mass, easily confused with a neoplasm.

The subclavian artery can be compressed by a complete cervical rib that articulates with the first rib, producing a poststenotic dilation in the proximal subclavian and distal axillary artery. This syndrome occurs more often in women and in the dominant upper extremity. Cervical ribs occur in only 0.6% of the population.[29]

Axillary artery aneurysms are most often caused by blunt trauma from inappropriate and prolonged use of crutches. Humerus fracture and anterior shoulder dislocation are less common causes.[28]

Subclavian, subclavian-axillary, and axillary artery aneurysms share the common complications of thromboembolism and limb-threatening ischemia, neuromuscular and sensory dysfunction from brachial plexus compression, and central nervous system ischemia produced by retrograde thromboembolism in the vertebral and right carotid circulation. A systolic bruit with a palpable thrill is common.

Arteriography to confirm the diagnosis and determine involvement of distal vessels is the diagnostic procedure of choice. Surgical treatment consists of aneurysm resection, vascular grafting, and reestablishment of arterial continuity.

The rare syndrome of ulnar artery aneurysm (hypothenar hammer syndrome) is associated with occupational trauma in which the heel of the palm is used to hammer, push, or twist objects.[30] Patients are often mechanics, carpenters, and machinists.

The ulnar artery fits snugly into the bony canal at the hypothenar eminence under the hook of the hamate bone. Long-term repetitive damage to this region results in aneurysm formation.[30] The aneurysm may develop a mural thrombus that repeatedly embolizes to the superficial palmar arch or to a digital artery. Symptoms consist of paresthesias, pain, coolness, and cyanosis, most often in the little and ring fingers and occasionally in the middle and index fingers. The thumb is characteristically spared because of its radial artery blood supply. Diagnosis is easily made by finding a pulsatile or nonpulsatile tender mass in the hypothenar eminence of the dominant hand. The Allen test may demonstrate occlusion of the ulnar artery. Angiography of the distal vessels is diagnostic. Proximal angiography rules out the subclavian and axillary arteries as embolic sources. Treatment requires surgical resection of the aneurysm and reestablishment of ulnar artery continuity. Adjunctive preoperative fibrinolytic therapy may be helpful.[30]

Viscera

Splenic Artery Aneurysms

Splenic artery aneurysms account for 60% of all visceral arterial aneurysms. They are the only aneurysms that are more common in women, with a female-to-male ratio of 4:1.[31] The development of aneurysms in the splenic artery has been attributed to systemic arterial fibrodysplasia, portal hypertension, and increased splenic arteriovenous shunting that occurs in pregnancy.

Splenic artery aneurysms are most often asymptomatic. Symptomatic patients exhibit vague left upper quadrant or epigastric discomfort and occasional radiation of pain to the left shoulder or subscapular area. Most splenic artery aneurysms are less than 2 cm in diameter; therefore, a pulsatile mass is not palpable. Occasionally, a systolic bruit can be heard.

Only 2% of splenic artery aneurysms result in life-threatening rupture.[31] More than 95% of ruptures occur in

young women during pregnancy and can be confused with ectopic pregnancy or placental abruption.

Splenic artery aneurysms are usually an incidental discovery on the abdominal radiograph as signet ring calcifications in the left upper quadrant. Ultrasonography, CT, and MRI can distinguish aneurysms from other cystic lesions in the left upper quadrant.[31] An angiogram is usually required to confirm the diagnosis. Symptomatic splenic artery aneurysms require immediate operative intervention, particularly in pregnant women or in women of childbearing age. The rate of maternal mortality from rupture during pregnancy is approximately 70%. In asymptomatic patients, transcatheter embolization is an alternative to surgery.[32]

Hepatic Artery Aneurysms

Hepatic artery aneurysms represent 20% of visceral artery aneurysms. The lesions are caused by atherosclerosis, infection (most often as a complication of IV drug abuse), major abdominal trauma, and polyarteritis nodosa. Hepatic artery aneurysms affect men twice as often as women and usually occur in patients older than 60 years of age.

Most aneurysms remain asymptomatic, but unruptured symptomatic aneurysms generally produce symptoms consistent with cholecystitis: vague, persistent, right upper quadrant or epigastric pain radiating to the back. Large aneurysms can cause severe upper abdominal discomfort, similar to pancreatitis. Hepatic artery aneurysms may rupture into the common bile duct, peritoneum, or adjacent hollow viscera. The mortality rate associated with hepatic artery rupture is 35%.

An abdominal bruit or palpable pulsatile mass is usually not present on physical examination. Aneurysmal calcification may be seen on a plain abdominal radiograph, but the diagnosis can be made reliably by angiography. Ultrasonography and CT can detect asymptomatic hepatic artery aneurysms.[32]

Because of the high mortality rate with aneurysmal rupture, an aggressive approach to management is warranted. Surgical resection of the aneurysm is performed in operative candidates. Transarterial catheter occlusion can be used in patients who are high surgical risks.[33]

Superior Mesenteric Artery Aneurysms

Superior mesenteric artery aneurysms are the third most common visceral aneurysms. Nearly 60% are infected aneurysms caused by nonhemolytic streptococci from left-sided bacterial endocarditis. Atherosclerosis and trauma are much less common causes. Patients are usually younger than 50 years of age; men and women are affected equally.

Patients generally have intermittent upper abdominal pain consistent with abdominal angina. Fifty percent have a pulsatile abdominal mass on physical examination. The stigmata of subacute bacterial endocarditis may be present. Plain abdominal radiographs may show a calcified aneurysm. Angiography is necessary to confirm the diagnosis.

Management of superior mesenteric artery aneurysm should address any underlying infectious process. The surgical approach is difficult and varies with the condition of the patient, the shape of the aneurysm (saccular or fusiform), and the intraoperative assessment of bowel viability.

Infected Aneurysms

Mycotic Aneurysms

The term *mycotic aneurysm* has been a source of confusion in the medical literature. No direct association exists with fungal disease. Although the term has been used to describe any infected aneurysm regardless of cause, it should be reserved for infected aneurysms resulting from bacterial endocarditis, as originally described in 1885 by Osler.[34,35]

Septic emboli from infective endocarditis implant in one of two ways. First, hematogenous seeding of bacteria can occur in nonaneurysmal arteries whose vessel walls have been damaged by preexisting atherosclerosis. Second, septic emboli can also become lodged in the vasa vasorum of larger vessels, causing vessel wall ischemia and infection. In smaller vessels, septic emboli tend to lodge at arterial bifurcations, arteriovenous fistulae, or sites of arterial stenosis. Mycotic aneurysms are most common in the aorta, superior mesenteric artery, and intracranial and femoral arteries.

The infecting organism in mycotic aneurysms reflects the bacteriology of infective endocarditis. *Streptococcus viridans* is the most common organism, although IV drug abusers are most often infected by *Staphylococcus aureus*. Patients who have mycotic aneurysms tend to be 30 to 50 years of age. The mortality rate is reported to be 25% (Table 85-2).[34,35]

Atherosclerotic Arteries

Currently, the most common cause of an infected aneurysm is sepsis with hematogenous spread of bacteria, such as *Salmonella*, *Staphylococcus*, and *Escherichia coli*, to atherosclerotic

Table 85-2 Clinical Characteristics of Infected Aneurysms

	MYCOTIC ANEURYSM	INFECTION OF ATHEROSCLEROTIC ARTERIES	INFECTION OF EXISTING ANEURYSM	POST-TRAUMATIC INFECTED FALSE ANEURYSM
Cause	Endocarditis	Bacteremia	Bacteremia	Drug addiction Trauma
Age (years)	30–50	>50	>50	<30
Incidence	Rare	Most common	Unusual	Very common
Location	Aorta Visceral Intracranial Peripheral	Atherosclerotic Aortoiliac Intimal defects	Infrarenal Aorta	Femoral Carotid
Bacteriology	*Streptococcus viridans* *Staphylococcus aureus*	*Salmonella* Others	*Staphylococcus* Others	*Staphylococcus aureus* Polymicrobial
Mortality	25%	75%	90%	5%

From Wilson SE, Van Wagenen P, Passaro E Jr: Arterial infection. Curr Probl Surg 15:1, 1978.

arteries. Large vessels (especially the aorta) rather than peripheral arteries are the most common site. Patients tend to be older than 50 and to have well-established atherosclerosis. Perforation often occurs before diagnosis and carries a mortality rate of 75%.[35]

Preexisting Aneurysms

The incidence of infection in patients with preexisting atherosclerotic aneurysms is estimated at 3 to 4%, and patients with ruptured aneurysms have a higher incidence of positive bacterial culture results than those who have elective surgical treatment of an asymptomatic aneurysm. Gram-positive organisms, especially *Staphylococcus*, predominate (60%). The rate of mortality is extremely high (90%) because of aneurysm rupture.[34,35]

Post-traumatic Pseudoaneurysms

Post-traumatic infected aneurysms result from invasive hemodynamic monitoring, angiography, and IV drug use. The most common artery affected is the femoral because of its involvement in groin injection. *S. aureus* is isolated in 30 to 70% of cases. Because of the more peripheral location and early identification, the mortality rate is low (5%).[36]

The clinical presentation of an infected aneurysm varies with anatomic location and underlying pathophysiologic process. Patients with infected abdominal aneurysms are often misdiagnosed. Onset is usually insidious; low-grade fever may be present for several months. Common findings are fever (75%), back and abdominal pain (33%), and palpable aneurysm (53%). More peripheral aneurysms, especially infected femoral pseudoaneurysms, are characterized by a tender groin mass, some manifestation of sepsis, or bleeding.[37] Almost all are easily palpable. Although rare, fungal infections should be considered in patients who are chronically immunosuppressed, have been treated recently for disseminated fungal disease, or have diabetes mellitus.[37,38]

Positive blood cultures in a patient with a preexisting aneurysm should prompt treatment as an infected aneurysm until disproven. Bacteremia often is continuous, and blood culture findings are positive for bacterial growth in approximately 70% of cases, so negative blood cultures do not rule out this diagnosis. Angiography should be performed when an infected aneurysm is suggested.[38] Indium-111-labeled white blood cells are used to confirm or rule out infected aneurysms.[39]

Treatment includes both antibiotics and surgical repair. Antibiotic therapy is usually continued for at least 6 to 8 weeks, although some physicians advocate lifelong treatment after successful surgical repair.[40] The most important intervention is timely repair.[34,35] Without surgery, aneurysm rupture with exsanguinating hemorrhage is inevitable.[35]

Traumatic Aneurysms

Traumatic aneurysm refers to a pseudoaneurysm that follows perforation of the arterial wall, with formation of a perivascular hematoma. Chronic traumatic aneurysms may or may not be associated with an arteriovenous fistula. *Pseudoaneurysm* is a synonym for *false aneurysm*.

The usual presentation is a pulsatile mass found near the course of an extremity artery, with a history of trauma more than 1 month earlier.[41] The expanding aneurysm may compress associated peripheral nerves and produce neuropathy. Distal perfusion is usually well maintained, and thromboembolism is rare. A loud systolic and possibly a separate faint diastolic murmur are characteristic.

The diagnosis can be verified with many methods, including conventional angiography, digital subtraction arteriography, and CT. Surgical excision of the aneurysm is indicated as soon as possible to decrease the risk of complications, including rupture, thrombosis, or neurologic dysfunction caused by continued expansion.

VASOSPASTIC DISORDERS

Vasospastic disorders are characterized by an abnormal vasomotor response in the distal small arteries. Blood flow in the peripheral circulation is controlled by local, autonomic, and humoral mechanisms.[11] The cause of the heightened vasospastic response is unknown.

Raynaud's disease is the most common vasospastic disorder and occurs five or more times as often in women as in men. By definition, cases of Raynaud's disease have no evidence of an underlying cause. The diagnosis is correct in 95% of cases using these criteria: (1) episodes are precipitated by cold or emotion; (2) symptoms are bilateral; (3) gangrene is absent or is minimal and confined to the skin; (4) no disease or condition that could cause a secondary Raynaud's phenomenon is present; and (5) symptoms have been occurring for at least 2 years.[42]

The classic Raynaud's attack is triphasic: the fingers become white, then blue, and finally red. This is produced initially by complete closure of the palmar and digital arteries (and possibly arterioles), producing cessation of capillary perfusion. When a slight relaxation of arterial spasm occurs, a slight flow of blood returns into the dilated capillary bed, where it rapidly dissipates, producing cyanosis. Arterial spasm usually spontaneously resolves, arterial flow returns to baseline, but reactive hyperemia produces a red extremity. Attacks are often precipitated by cold and emotional stress. Raynaud's disease usually follows a benign course. True histologic changes within the vessel wall are absent. Reassurance, education, and continued primary care follow-up observation are the only treatment necessary for true Raynaud's disease.

Raynaud's phenomenon is Raynaud's disease that has an identifiable underlying disorder. Connective tissue disorders, including scleroderma, rheumatoid arthritis, and systemic lupus erythematosus, have the highest association with Raynaud's phenomenon. Treatment should be directed toward identifying the underlying disorder and minimizing threatened tissue loss if present.[42]

Benign livedo reticularis is caused by spasm of the dermal arterioles and may involve all parts of the upper and lower extremities, including the trunk. It is most common when skin is exposed to a cool environment. It is never associated with histologic vascular abnormality and quickly resolves when the exposed skin is covered or the environment is warmed. Other conditions, similar to the causes of Raynaud's phenomenon, can have secondary livedo reticularis along with other peripheral vascular disease manifestations.[42]

Acrocyanosis is the least common of the vasospastic disorders and is characterized by persistent, painless, symmetrical cyanosis of the fingers, the hands, and less often the feet. The disease is benign and not associated with either vascular abnormality or an underlying disorder. Pain, trophic skin changes, and ulceration do not occur. This disorder occurs more often in women, is intensified by exposure to cold, and decreases with warming. The diagnosis is made by the bilateral and persistent nature of the findings, localized to the hands or feet in the presence of normal arterial pulses. The involved extremities are nearly always cold and excessive perspiration is common. Except for reassurance and protection from cold, treatment is usually unnecessary.[42]

Primary erythromelalgia is a rare syndrome of paroxysmal vasodilation with burning pain, increased skin temperature, and redness of the feet and less often the hands. However, secondary erythromelalgia can occur in patients with underlying disease processes, most often systemic lupus erythematosus, myeloproliferative disorders, hypertension, venous insufficiency, or diabetes mellitus. Erythromelalgia is as common in children as adults, but in children it is less likely to be associated with an underlying systemic illness. Attacks are not triggered by cold and usually occur during modest ambient temperatures. Skin temperature of the involved digits is high compared with the patient's core temperature. Symptoms may remain mild for years or may become disabling. Tissue loss and trophic skin changes do not occur. Although rest, elevation of the extremities, and cold compresses or immersion in ice can provide temporary relief, no consistently effective treatment has been found for the multiple, often daily episodes of pain that occur with erythromelalgia.[42]

THORACIC OUTLET SYNDROME

Thoracic outlet syndrome involves compression of the brachial plexus, subclavian vein, or subclavian artery at the superior aperture of the thorax. Thoracic outlet syndromes were previously categorized by cause as scalenus anticus, costoclavicular, hyperabduction, cervical rib, and first thoracic rib syndromes. They are now most easily divided into three types—neurologic, venous, and arterial—depending on the predominant symptoms.

Compression of the brachial plexus causes the neurologic type of thoracic outlet syndrome and accounts for approximately 95% of all cases.[43,44] Symptoms begin between the ages of 20 and 50 years, with women predominating at a ratio of about 3:1. Compression or thrombosis of the subclavian vein constitutes the venous type of thoracic outlet syndrome and is responsible for 4% of all cases. It occurs most often in men 20 to 35 years of age. The arterial type of thoracic outlet syndrome is rare, occurring in approximately 1% of all cases, but is potentially the most serious of the three types. Men and women are equally affected in a bimodal age distribution of young adults (from cervical rib compression) and patients older than age 50 (from localized atherosclerosis caused by arterial compression). Figure 85-3 demonstrates the relationship between anatomic abnormalities and neurovascular compression.

Principles of Disease

Roos[45] has described four basic concepts of thoracic outlet syndromes: (1) patients who have a thoracic outlet syndrome develop an anatomic abnormality predisposing them to symptoms under certain conditions; (2) brachial plexus compression or irritation constitutes approximately 95% of all thoracic outlet syndrome cases and is rarely caused by compression of the subclavian artery; (3) bedside testing for thoracic outlet syndrome based on positional compression of the subclavian artery is insensitive and unreliable; and (4) in advanced or refractory cases, the causative anatomic abnormalities must be surgically corrected.

The subclavian artery courses over the first rib between the scalenus anticus muscle anteriorly and the scalenus medius muscle posteriorly. From this point, it passes under the

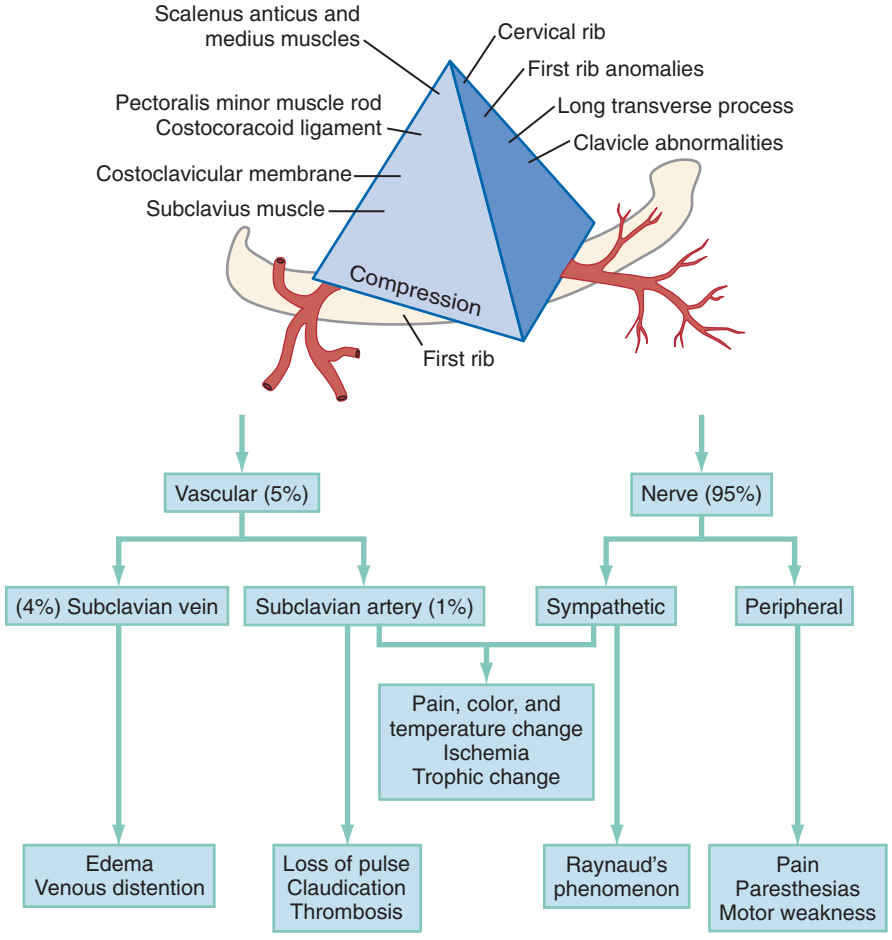


Figure 85-3. Inter-relationships of muscle, ligament, and bone abnormalities in the thoracic outlet that may compress neurovascular structures. (From Urschel HC Jr: Management of thoracic outlet syndrome. N Engl J Med 286:1140, 1972.)

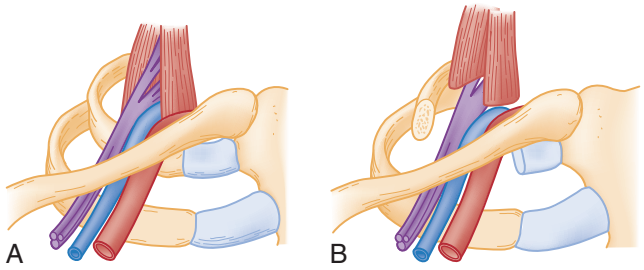


Figure 85-4. **A,** Thoracic outlet compression in costoclavicular space. **B,** Decompression of thoracic outlet by resection of first rib with disarticulation of the costochondral joint. (From Etheredge S, et al: Thoracic outlet syndrome. Am J Surg 138:175, 1979.)

clavicle to the axilla, where the brachial plexus lies posteriorly and laterally. Four anatomic abnormalities have been associated with thoracic outlet syndrome.

Cervical rib syndrome results from an uncommon abnormality (0.5–0.7% of all chest radiographs), which is bilateral in 70% of patients.[43,44] It occurs twice as often in women as men. Most cervical ribs are incomplete, attached to a fibrous band on the scalene tubercle of the first rib. The site of compression is the scalene hiatus, made up of the scalene anterior muscle frontally, the scalene medius posteriorly, and the cervical rib inferiorly.

Scalenus anticus syndrome results when the neurovascular bundle is compressed by various insertions of the anterior scalene muscle as it passes through the interscalene triangle. In some patients, the subclavian artery passes through the body of the muscle.

Costoclavicular syndrome results when the shoulders are moved backward and downward. Causes include hypertrophy of the subclavius muscle, abnormalities of the first rib, and past clavicular fractures.

Hyperabduction syndrome results from the neurovascular compression that occurs when the arms are placed in the hyperabducted position. The site of compression is in the retroclavicular space anterior to the first rib or at the point where the neurovascular bundle passes beneath the pectoralis minor muscle.

The neurologic and venous compression type of thoracic outlet syndrome can be associated with any underlying anatomic abnormality. Bony abnormalities (cervical rib, first thoracic rib, or clavicle) are the most common causes of the arterial type of thoracic outlet syndrome (Fig. 85-4A).

Clinical Features

Compression or irritation of the brachial plexus most often affects the lower two nerve roots, eighth cervical (C8) and first thoracic (T1), producing pain and paresthesias in the ulnar nerve distribution. The second most common anatomic pattern is involvement of the upper three nerve roots of the brachial plexus (C5, C6, and C7), with symptoms referable to the neck, ear, upper chest, upper back, and outer arm in the radial nerve distribution. Venous compression eventually progresses to intimal damage and subclavian vein thrombosis, with venous engorgement and swelling of the affected extremity. Persistent subclavian artery compression eventually results in poststenotic aneurysm formation and its sequelae.

Physical Examination

The Adson, costoclavicular, and hyperabduction maneuvers are unreliable as diagnostic tests.[43,45] The most reliable test in screening for thoracic outlet syndrome is the elevated arm stress test (EAST).[45] With the patient sitting, the arms are abducted 90 degrees from the thorax and the elbows flexed 90 degrees, with the shoulders braced slightly behind the frontal plane. The patient is asked to open and close the fists slowly but steadily for a full 3 minutes and to describe any symptoms that develop. Normal patients perform this test without symptoms other than mild fatigue. The patient with thoracic outlet syndrome, however, usually has early heaviness and fatigue of the involved limb, gradual onset of numbness of the hand, and progressive aching through the arm and top of the shoulder. Within the 3 minutes, the patient usually drops the hand to the lap for relief of the progressive, crescendo distress that becomes intolerable. Patients with carpal tunnel syndrome may experience dysesthesias in the fingers but do not have shoulder or arm pain. Patients with cervical disk syndromes may have pain in the neck and shoulder but have no arm or hand symptoms.

The EAST evaluates all three types of thoracic outlet syndrome: neurologic, venous, and arterial. Radial pulses can be palpated by the examiner during the test. The presence of a radial pulse and a positive EAST test result are strong indications that the basis of symptoms is neurologic involvement of the brachial plexus.

The hands should be observed for changes in skin color, warmth, moisture, or muscular atrophy. Triceps muscle strength (innervated by C7) should be tested bilaterally. Muscle strength of the interosseous muscles (innervated by C8 and T1) should be tested by asking the patient to spread the fingers apart against resistance. The muscles innervated by the radial nerve are tested by the patient hyperextending the thumb and dorsiflexing the wrist against resistance. The median nerve innervates the thenar muscles, which can be tested by asking the patient to abduct the thumb away from the palm with the thumb pointing straight to the ceiling. Tinel's sign ("electric shock" to tips of fingers) is an indication of carpal tunnel compression of the median nerve and is elicited by percussing the volar aspect of the wrist. Gentle pressure with the thumb in the supraclavicular fossa over the brachial plexus may reproduce thoracic outlet symptoms after several seconds. The cervical spine and upper extremity reflexes should be assessed.

A blood pressure difference between the two arms is a reliable indication of arterial involvement. The blood pressure in the affected arm is lower. Doppler ultrasonography may be helpful in demonstrating comparatively reduced pressure over the pairs of radial, ulnar, and brachial arteries. The supraclavicular area should be auscultated bilaterally for subclavian bruits.

Ancillary Evaluation

Cervical spine radiographs with oblique views and chest radiographs are indicated in each patient for evaluation of skeletal abnormalities (first rib, cervical rib, clavicle deformity), trauma, arthritis, scoliosis, Pancoast's tumor, or other pulmonary disease. Neurologic studies, including electromyography, nerve conduction times, and somatosensory-evoked potentials, are generally unreliable and do not provide objective evidence of thoracic outlet syndrome.[45] Patients thought to have cervical disk or spinal cord disease may require cervical myelography, CT, or MRI.

Arteriography is recommended with (1) obliteration of radial pulse on the EAST, (2) blood pressure 20 mm Hg less than that of the opposite asymptomatic limb, (3) possible subclavian stenosis or aneurysm (bruit or abnormal supraclavicular

pulsation), and (4) evidence of peripheral emboli in the upper extremity.[43] Venography is indicated if the patient has a history of intermittent or persistent edema of the hand or arm, peripheral unilateral cyanosis, or a prominent venous pattern over the arm, shoulder, or chest.[46]

Differential Diagnosis

The differential diagnosis of thoracic outlet syndrome includes herniated cervical disk, cervical spondylitis, spinal cord tumor, ulnar nerve compression at the elbow, carpal tunnel syndrome, orthopedic shoulder problems (sprain, rotator cuff injury, tendinitis), trauma, postural palsy, angina pectoris, and a variety of neuropathies, including multiple sclerosis, alcoholism, and diabetes.

Patients with a herniated cervical disk have more severe persistent pain radiating in a sharply demarcated dermatomal distribution (usually C4-5 or C5-6) and often have localized tenderness of the cervical spine at the affected level. Carpal tunnel syndrome is characterized by nocturnal symptoms of pain and paresthesias and an associated Tinel's sign on physical examination. Brachial plexus compression and irritation can be confused with other vascular conditions, such as Raynaud's disease, vasospastic disorders, vasculitis, or arterial ischemia.[43] Unilateral symptoms should suggest thoracic outlet syndrome, whereas bilateral symptoms suggest a systemic process. Subclavian or axillary venous thrombosis from thoracic outlet syndrome must be differentiated from thrombophlebitis or mediastinal venous obstruction from a benign or malignant process (Pancoast's tumor).

Management

Treatment varies, depending on whether the involvement is neurologic, arterial, or venous. In patients with only brachial plexus involvement and with minimal signs and symptoms, conservative treatment with physiotherapy and shoulder girdle exercises is sufficient. Surgery is reserved for patients with significant neurologic signs and symptoms. This includes intolerable pain or progressive loss of function and strength of the arm or hand. First rib and anomalous muscle or fibrous tissue resection is the surgical treatment of choice and provides consistent relief of symptoms and minimal morbidity (Fig. 85-4B).[43]

Patients with arterial complications of thoracic outlet syndrome (thrombosis, thromboembolism, or acute ischemia) require immediate heparinization and angiography; Fogarty catheter embolectomy, if appropriate; and emergency or urgent surgical exploration. Patients with axillary and subclavian vein thromboses require immediate heparinization and venography and are treated with surgical thrombectomy or systemic fibrinolytic therapy.[47]

Disposition

The correct diagnosis of thoracic outlet syndrome can be achieved in more than 90% of patients with a careful history, physical examination, and bedside testing alone.[45] Neurologic, orthopedic, or vascular surgery consultation is indicated according to the pathologic condition.

PERIPHERAL ARTERIOVENOUS FISTULAE

Acquired peripheral arteriovenous fistulas are most often caused by trauma (gunshot wounds, stab wounds, or surgery), with malignancy, infection, and arterial aneurysms as less common causes. Patients generally seek medical care several months after an invasive surgical procedure or penetrating injury.

Differential Diagnosis

The correct diagnosis of an arteriovenous fistula can usually be made with clinical examination alone. A constant systolic and diastolic (to-and-fro) murmur associated with a palpable thrill is characteristic. Sixty percent of arteriovenous fistulae are also associated with a coexisting false aneurysm. Patients with peripheral venous disease may have similar cutaneous manifestations (varicose veins and stasis pigmentation) but lack vascular bruits. Infection in the form of bacterial endarteritis may complicate large fistulae.

Management

Acquired peripheral arteriovenous fistulae usually increase in size with time if surgery is delayed. Vessel dilation, peripheral ischemia, and cardiac output increase.[48] Transcatheter embolization with detachable balloons and liquid acrylic tissue adhesives (e.g., isobutyl 2-cyanoacrylate) is used for surgically inaccessible fistulae.[49]

VASCULAR ABNORMALITY CAUSED BY DRUG ABUSE

Principles of Disease

The vascular complications of parenteral drug use have risen significantly in both frequency and severity since the late 1980s.[50] These IV or intra-arterial injuries can result in acute arterial ischemia, infected pseudoaneurysms, lymphatic obstruction, or direct neurologic injury.

Acute arterial ischemia results from direct drug effects or endogenous catecholamine release after injection. Endothelial wall damage can stimulate platelet aggregation and thrombus formation. Precipitated crystals, talc, or foreign body emboli can cause arterial occlusion. Necrotizing arteritis can produce ischemia and is especially prevalent in patients who abuse IV methamphetamines.

Infected pseudoaneurysms associated with arteriovenous fistulae result from a through-and-through puncture of the artery with simultaneous contamination from either skin flora or organisms inoculated by contaminated needles or drug. These fistulae are the most common vascular lesions resulting from IV drug abuse. Secondary infection of the vascular structure may be covered by a surrounding soft tissue infection (cellulitis or abscess). Infected aneurysms at sites distant from the injection can occur.

Intravenous drug abusers can develop unilateral hand edema or "puffy hand syndrome" because of gradual obliteration of the superficial venous vessels and chronic lymphatic obstruction. Direct injury to adjacent nerves, polyneuritis, and ischemic neuritis can result from IV drug abuse. Coexisting infections include cellulitis, septicemia, and bacterial endocarditis.[50]

Clinical Features

Patients may withhold information about the use of IV drugs, but objective evidence such as track marks may be present. Distal ischemia after intra-arterial injection most often occurs in the upper extremity after injection of the brachial or radial artery. The immediate onset of a severe, burning pain at the time of injection is a characteristic hallmark.[51] Patients have a painful, edematous upper extremity with patchy blue-purple

skin discoloration. Distal pulses are generally present, but the skin temperature of the involved extremity is decreased. Because patients tend to seek attention early, the site of injection may be identifiable over the radial or brachial artery. Evidence of gangrene, pregangrenous changes, or neuromuscular deficits may accompany this syndrome.

Patients with infected pseudoaneurysms have a painful mass develop several days to weeks after injection, with resultant bleeding or "hitting pink." The mass is usually pulsatile, and 50% have an associated bruit.[50] Infected pseudoaneurysm is part of the differential diagnosis of cutaneous abscess or cellulitis in an IV drug user. Infected pseudoaneurysms are most often encountered in the lower extremities (80%). All patients should be carefully evaluated for sepsis, metastatic infection, and bacterial endocarditis. A peripheral vascular examination with careful documentation of pulses should be performed. A radiograph of the affected extremity can detect subcutaneous needle or foreign body. Angiography is the diagnostic procedure of choice for suggested pseudoaneurysm or distal ischemia. Ultrasonography is often unable to distinguish an aneurysm from an abscess or cellulitis.

Management

Therapeutic considerations for acute ischemia from intra-arterial injection are primarily conservative. Intra-arterial vasodilators, heparin, low-molecular-weight dextran, fibrinolytic therapy, analgesics, systemic warming to stimulate vasodilation, antibiotics, elevation of the affected limb to promote venous drainage, and physical therapy have not significantly altered the outcome or amputation rate in this patient population. Surgical treatment is reserved for delayed amputation, with the goal of preserving as much tissue as possible. Gradual resolution of symptoms without surgical intervention is the most common outcome.

Patients with infected pseudoaneurysms require aneurysm resection, débridement of infected tissue, and ligation of the proximal and distal uninfected arteries. Autogenous vein bypass through uninfected tissue planes may require an extensive surgical approach.[52] Intravenous nafcillin is recommended for mild infections, nafcillin and a second- or third-generation cephalosporin for major infections, and vancomycin and a second- or third-generation cephalosporin or an aminoglycoside for patients who are bacteremic or overtly septic.[50] Methicillin-resistant *S. aureus* and gram-negative rods are increasing in frequency as the causative agents in infections and vascular injury resulting from drug abuse, and vancomycin should be added if these organisms are suggested.

PROBLEMS RELATED TO LONG-TERM CENTRAL VENOUS ACCESS

Hickman-Broviac Catheter

The Hickman-Broviac double-lumen catheter is in common use, with the smaller Broviac line used for the administration of IV therapy and the larger Hickman line reserved for additional venous access and blood withdrawal (Fig. 85-5; see also Fig. 85-7B). This catheter is generally inserted into the cephalic, subclavian, external, or internal jugular vein, with the distal tip just above the right atrium.[53] The proximal end exits through a subcutaneous tunnel from the lower anterior chest wall. A felt cuff (Dacron) is used to anchor it in place subcutaneously. The Hickman-Broviac catheter is made of polymeric silicone rubber that is of low thrombogenic potential but extremely flexible and soft. Because of the pliability of the material, the catheter must be treated gently. Clearing an obstructed catheter with a guidewire may perforate the catheter. Forcing fluid through the catheter by positive pressure carries the risk of catheter rupture or catheter embolus. For this reason, no syringe larger than 5 mL should be used for irrigation.

Routine Care and Use

The smaller Broviac line is most often used for the infusion of total parenteral nutrition or fat emulsions. This line should be irrigated with 6 mL of normal saline solution between different infusions to prevent mixing of incompatible solutions, development of precipitation, and resultant catheter occlusion. The larger Hickman line should be used to withdraw blood. This line should be irrigated with 6 mL of heparinized saline

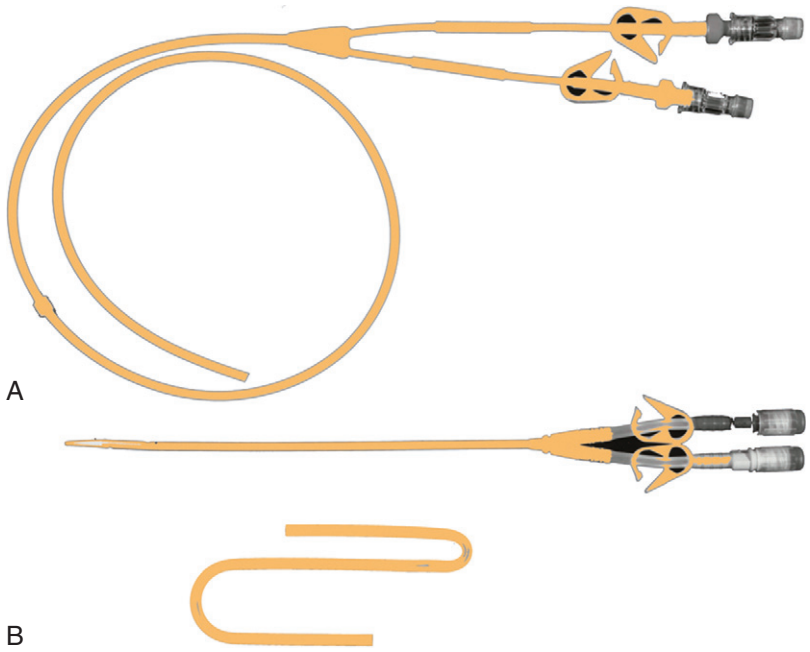


Figure 85-5. Selected catheters. **A,** Double-lumen Hickman-Broviac catheter. **B,** Quinton-Mahurkar catheter.

after blood withdrawal to prevent clot formation in the catheter lumen. When a clamp is used, it should be placed over a piece of tape wrapped around the line. The clamp should have a smooth surface, since teeth or prongs could sever or abrade the line.

Routine care and frequency of catheter dressing changes vary with the preference of the treating physician.[53,54] Most patients become skilled in routine catheter maintenance and are a reliable source of information. Absolute sterile technique is essential when manipulating the catheter.

Catheter Occlusion

Hickman catheters can exhibit complete or partial obstruction to flow in either line. Complete obstruction, in decreasing order of frequency, results from (1) clots within the catheter lumen, (2) precipitates within the catheter lumen, and (3) mechanical obstruction. In catheters that accept infusions at normal rates but cannot be aspirated, the causes, in decreasing order of frequency, are (1) catheter lodged against the wall of the vessel, (2) occluding fibrin sheath around the catheter tip, (3) ball valve or mural thrombus, and (4) central venous thrombosis. Patients who have intermittent complete occlusion and withdrawal occlusion have a type of mechanical obstruction called *pinch-off syndrome*, in which the catheter lumen is compromised from mechanical forces acting on it between the clavicle and the first rib. Clots within the catheter lumen, obstructing fibrin sheaths, and ball valve or mural thrombus often respond to low-dose intracatheter urokinase; central venous thrombosis, precipitants in the catheter lumen, and mechanical obstruction do not respond (Box 85-1).

Precipitants within the catheter lumen most often result from flushing the line with a heparin solution instead of saline after total parenteral nutrition. Heparin precipitates with total parenteral nutrition fluids. Clots within the catheter lumen usually result from failure to flush the line with a heparinized saline solution after blood aspiration.

A chest radiograph should be obtained in all patients with persistently occluded catheters to confirm catheter position and integrity. The catheter tip should be positioned just above the right atrium.[53] Persistent right atrial placement can cause perforation of this thin-walled heart chamber or result in a right atrial thrombosis. Comparison with previous radiographs may be necessary to ensure lack of movement or displacement. In patients with withdrawal occlusion but appropriate catheter position and without clinical evidence of subclavian vein thrombosis, the catheter may be lodged against the vessel wall. The patient's changing body position, raising the arms above the head, or performing the Valsalva maneuver may relieve withdrawal occlusion. If this is unsuccessful, some occlusions respond to low-dose intracatheter urokinase (see Box 85-1). Urokinase (5000 U) should be injected into the catheter and left for 30 minutes before aspiration is attempted. If this is also unsuccessful, a second dose of urokinase can be injected and the procedure repeated.[55] While contraindications to fibrinolytic agents should be considered, low-dose therapy for occluded catheters appears to be well tolerated.[55,56]

In the pinch-off syndrome the catheter is intermittently obstructed during both administration and withdrawal of fluids, typically within 3 weeks after catheter placement. A chest radiograph demonstrates narrowing of the catheter lumen as it passes between the clavicle and the first rib. The catheter must be removed because of fragmentation or embolization if left in place.[57]

Because engorged collateral circulation or swelling in the affected extremity is not universally present with subclavian vein thrombosis, this diagnosis should be considered in all patients who are unresponsive to declotting attempts. Catheter removal with systemic heparinization or catheter maintenance with high-dose fibrinolytic therapy is a therapeutic option for subclavian vein thrombosis.[58,59] Mechanical occlusion is rare and requires catheter replacement with a surgical approach. Because of variations in approach, early consultation is recommended in patients who have occluded central venous catheters (Fig. 85-6).

BOX 85-1 DIFFERENTIAL DIAGNOSIS OF OCCLUDED CHRONIC INDWELLING CATHETERS

Complete Occlusion
Clot in catheter lumen*
Precipitate in catheter lumen
Mechanical obstruction

Withdrawal Occlusion
Catheter against vessel wall
Fibrin sheath*
Ball valve/mural thrombus*
Subclavian vein thrombosis

Intermittent Complete Occlusion and Withdrawal Occlusion
Pinch-off syndrome

*Usually responds to low-dose intracatheter urokinase.

Catheter Laceration

If an external catheter laceration or fracture occurs, the catheter should be clamped over tape distal to the laceration close to the chest wall. The catheter can be repaired as long as the damage is more than 4 cm from the chest wall. After clamping, as an interim measure, the next step is to insert a 14-gauge, 2-inch shielded IV catheter (Angiocath) into the catheter; remove the stylus; tape securely; and flush with heparin. The catheter can then be used while a repair kit is obtained.[60]

Catheter-Related Infections

Catheter infections can be categorized as local or systemic. Local infections primarily involve the skin and subcutaneous tissues surrounding the exit site with erythema, tenderness, and no clinical or laboratory evidence of sepsis. Skin organisms are primarily responsible for local infections, especially coagulase-negative staphylococci.[54] Studies show that local infections usually do not require catheter removal and resolve with antimicrobial therapy alone.[61]

The source of systemic infection in patients with Hickman-Broviac catheters may be difficult to localize, particularly in immunosuppressed patients. The most common sites of systemic infection in any patient with a central venous catheter, in decreasing order of frequency, are the urinary tract, the anorectal area, the upper respiratory tract, and the catheter.[54] The most common organisms causing catheter infection are coagulase-negative staphylococci, *S. aureus*, and *Candida albicans*. In immunocompromised patients with Hickman-Broviac catheters, gram-positive organisms now are responsible for more cases of sepsis than gram-negative bacteria. Accordingly, initial empiric therapy should include an antistaphylococcal drug, in addition to the usual gram-negative coverage. A good empirical regimen is cefazolin (Ancef) (1 g) and gentamicin (1 mg/kg IV). All patients who have a possible vascular access infection should have two blood culture samples drawn. Comparison of blood culture samples drawn simultaneously through

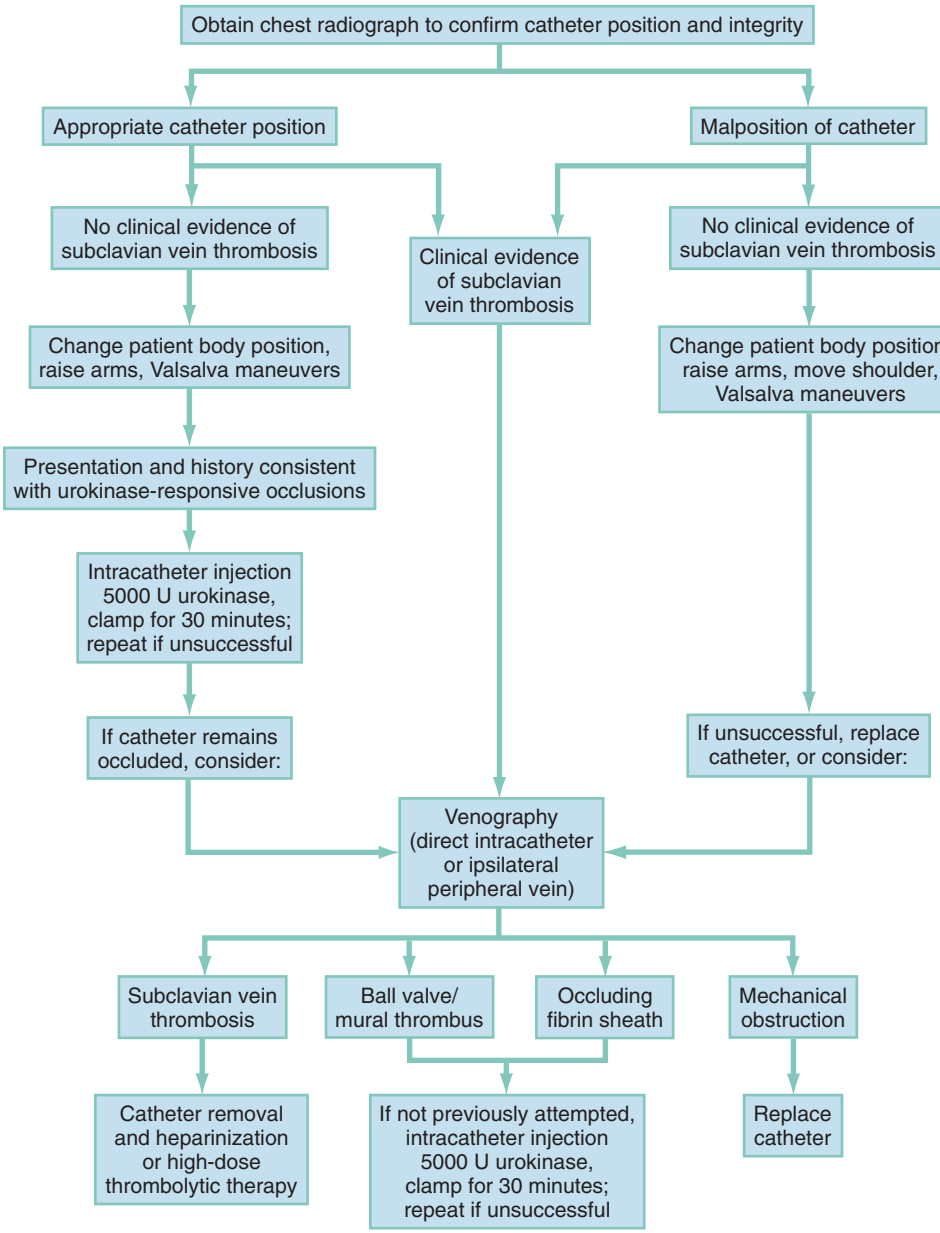


Figure 85-6. Approach to occluded indwelling catheter.

the catheter and from a peripheral blood vessel may assist in determining whether the catheter is the source of infection. Infections that do not extend through the vessel wall (pericatheter infections) can be successfully treated without catheter removal. Catheter removal is mandatory in patients with continued positive blood culture results despite therapy and in those with vascular access infections caused by *Candida* species.[61]

Catheter-related septic central venous thrombosis can progress through and around the vessel wall to cause a perivascular infection or abscess. This rare but devastating complication is associated with serious morbidity and a reported mortality rate as high as 83%. Because of the lack of specific clinical findings, the most prominent diagnostic feature is continued bacteremia after catheter removal. Diagnosis is confirmed by venography or CT.[62] Removal of the catheter, IV administration of antimicrobials, and anticoagulation constitute appropriate initial therapy. Surgical treatment with thrombectomy and possible abscess drainage are indicated after failure of an adequate course of antibiotics and anticoagulation. Fibrinolytic agents have been used as an adjunct for catheter-related septic venous thrombosis, but the risk-benefit ratio has not been established.[63] In patients who require catheter removal, a quantitative culture of the number of organisms on the catheter's surface correlates well with a positive blood culture result for the same organism. This technique involves rolling the catheter on a culture medium. Broth culture of catheter tips may be less reliable in determining whether the catheter is the source of infection.[64]

Groshong Catheter

The Groshong catheter is a single, thin-walled silicone rubber catheter designed for prolonged venous cannulation. It differs from the Hickman-Broviac catheter in insertion, design, and maintenance. A decreased outer diameter to inner diameter ratio allows insertion into a smaller vein through a smaller introducer sheath. The catheter can be inserted under local anesthesia without fluoroscopy, using the Seldinger technique and a peel-away catheter introducer sheath. After catheter placement in the subclavian, internal, or external jugular vein, a subcutaneous tunnel is created with a stainless steel

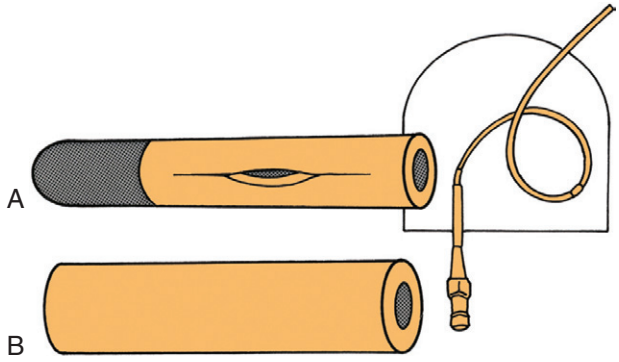


Figure 85-7. **A,** Groshong catheter with closed distal end and vocal cord–type valve. **B,** Hickman catheter with open distal end. (From Delmore JE, et al: Experience with Groshong long-term central venous catheter. Gynecol Oncol 34:216, 1989.)

tunneling device through which the catheter is threaded. A Dacron cuff stabilizes the catheter's placement in subcutaneous tissues and reduces the chance of inadvertent removal or retrograde infection.[65]

The Groshong catheter is constructed with a closed end and a vocal cord–type integral valve at the distal end (Fig. 85-7A). This pressure-sensitive two-way valve at the intravascular end minimizes back-bleeding, eliminating the need for heparin flushes or external clamping, but permits blood sampling with gentle negative pressure. Patency of the catheter is maintained with 5 mL of saline flush once a week. A 20-mL saline irrigation is necessary after any blood transfusion or if blood is observed in the catheter lumen. A 30-mL saline irrigation is performed before blood sampling after infusion of hyperalimentation solutions.

Groshong catheters offer the advantage of bedside placement, minimal back-bleeding, elimination of heparin flushes, and elimination of external clamping when changing injection caps or connecting tubing. A lower incidence of complete obstruction to flow from clots or precipitates within the catheter lumen, however, has not been shown.[66] Groshong catheters are otherwise subject to the same complications as Hickman-Broviac catheters.

Vascular Access for Hemodialysis

Quinton-Mahurkar Catheter

The Quinton-Mahurkar catheter is the preferred catheter for providing immediate and short-term vascular access for hemodialysis. Its advantages include bedside placement and a functional life up to 18 months.[67] This single, flexible, polyurethane cannula has two separate D-shaped channels, each connected by a molded Y piece to a color-coded external port (Fig. 85-5B). To protect against a disconnected cap, each limb of the Y piece has an attached clamp. The Quinton-Mahurkar catheter is placed by the Seldinger technique, most often in the subclavian vein and less often in the femoral vein.

The incidence of mortality from central venous catheter hemodialysis is low (0 to 1.25 per 1000 catheterizations), but the morbidity rate is high, with a reported overall complication rate near 30%.[68] The most common complications are catheter-related infections and thrombosis.

A Quinton-Mahurkar catheter can be used to obtain blood samples. After blood withdrawal, the line should be flushed with more than 10 mL of normal saline solution, followed by 5000 U of heparin in 1 mL of saline to prevent intracatheter clot formation. The catheter can also be used for the administration of IV therapy. Routine care and use are otherwise similar to that previously described for chronic indwelling central venous catheters.

Cimino-Brescia Fistula and Prosthetic Bridge Fistula

The subcutaneous Cimino-Brescia fistula is the preferred access for long-term hemodialysis. The fistula is created through a side-to-side and side-to-end anastomosis using the radial artery and the cephalic forearm vein. The high blood flow and pressure on the venous side of the fistula "arterialize" the veins, in 3 to 5 weeks. The Cimino-Brescia fistula is well tolerated by patients, has a low infection rate, and has the longest functional use of any vascular access method. The fistula has a 90% patency rate at 12 months, which gradually decreases to approximately 75% at 4 years.

An alternative to the Cimino-Brescia fistula is the *arteriovenous bridge fistula*. Formed by a prosthetic conduit, this fistula connects a superficial artery (usually the radial or brachial) with a large antecubital vein. The prosthetic material is usually expanded polytetrafluoroethylene. Arteriovenous bridges can be constructed in the leg between the superficial femoral or femoral artery and the saphenous vein. Lower extremity arterial bridges have a higher blood flow rate and are less likely to thrombose but also have a higher rate of infection because of their proximity to the bacteria-laden perineum.

Thrombosis

Thrombosis is the most common complication of a subcutaneous arteriovenous fistula or prosthetic graft. It is important to avoid circumferential bandages, tourniquets, or blood pressure cuffs in the fistula-bearing arm because restricted venous outflow may predispose to thrombosis. A tourniquet should not be used. The opposite arm or the fistula itself can be used to acquire blood or vascular access (without using a tourniquet). Normal graft flow is clinically verified by feeling a thrill or hearing a bruit on auscultation. A strong palpable pulse with no matching thrill suggests venous outflow obstruction or early graft thrombosis. Thrombosis of arteriovenous fistulae requires temporary vascular access and usually the creation of a new fistula proximal to the thrombosed shunt.

Blood Withdrawal

Ideally, an alternative peripheral venipuncture site should be sought first before using a Cimino-Brescia fistula for blood withdrawal. When an alternative site is unavailable, however, the arteriovenous fistula is a reasonable choice. An individual skilled in venipuncture techniques should maintain absolute sterility with antiseptic (e.g., povidone-iodine [Betadine]) skin preparation, sterile gloves, and sterile gauze. Tourniquets are contraindicated and unnecessary. Venipuncture should be performed on the well-developed venous side of the fistula. After blood acquisition, gentle pressure should be maintained for 5 minutes, with care taken not to occlude the vessel lumen. The site should then be observed for several minutes to ensure that bleeding does not occur. A prosthetic arteriovenous bridge fistula can also be used to obtain blood samples with careful perforation of the superficial wall of the prosthetic graft; otherwise, the technique is identical.

Clinically differentiating a Cimino-Brescia fistula from a prosthetic arteriovenous bridge fistula may be difficult. The prosthetic portion of an arteriovenous bridge fistula connects the arterial to the venous vessels in an H shape and is tunneled

for some distance beneath the skin, giving the appearance of a single, large blood vessel. The prosthetic fistula has a thrill but is not as pulsatile as a Cimino-Brescia fistula when gently palpated. If asked, most patients are knowledgeable about their fistula.

Peripheral IV access is best established at an alternative site. When an alternative site is unavailable and the patient requires timely IV access, the Cimino-Brescia fistula or bridge fistula can be used, following the guidelines for venipuncture. Careful attention to sterile technique, operator skill, and avoidance of tourniquets can provide timely venipuncture or IV therapy while preventing infectious or thrombotic complications. If an IV line is used in a fistula, early removal after alternative IV access is desirable.

Infection

Infections of an arteriovenous fistula or graft are potentially life-threatening and manifest with signs of septicemia and local inflammation. Once the diagnosis of infected fistula is considered, blood cultures should be obtained and IV antibiotics for gram-positive skin organisms administered. Prosthetic graft infection cannot be eradicated with IV antibiotics alone and requires prosthetic graft removal. Infections are the second leading cause of death of patients undergoing long-term dialysis.

Steal Phenomenon

Vascular steal from the ulnar artery via the palmar arch occasionally occurs in patients with atherosclerotic disease distal to the shunt, particularly diabetic patients. Symptoms of fingertip ischemia occur during periods of increased shunting (hemodialysis or increased activity). The steal phenomenon usually requires graft ligation with construction of a new fistula in the opposite extremity.

Venous Hypertension

Acute venous hypertension may occur in the first few weeks after fistula construction. This is a true surgical emergency. The early rise in venous pressure produces marked swelling of the extremity and severe venous stasis disease. Characteristic skin pigmentation, edema, and occasionally venous ulceration are seen. Management of venous hypertension requires hospitalization and urgent ligation of the vein immediately distal to the fistula before a potentially exsanguinating vessel rupture.

Bleeding

Patients also present to the emergency department with bleeding from their fistula after dialysis. Persistent, gentle pressure, with care taken not to occlude blood flow, usually resolves this problem.

KEY CONCEPTS

- Acute arterial occlusion is a limb-threatening emergency requiring early heparinization and Fogarty catheter embolectomy. The clinical diagnosis is based on some variant of the "five P's": pain, pallor, pulselessness, paresthesias, and paralysis. Confirmatory tests are unnecessary and increase the limb's ischemic status.
- Atheroembolism (blue toe syndrome) is associated with cool, painful cyanotic toes in the presence of palpable distal pulses. A proximal source should be localized, most often an atherosclerotic aneurysm in the aorta or the iliac, femoral, or popliteal artery.
- Popliteal aneurysms are bilateral in 60% of patients and often coexist with an abdominal aortic aneurysm.
- The classic Raynaud attack is triphasic: the fingers become white, blue, then red. Raynaud's disease has no detectable underlying cause and usually has a benign course. Raynaud's phenomenon has an underlying disorder, usually connective tissue disease.
- The only reliable clinical test for detection of thoracic outlet syndrome is the elevated arm stress test (EAST).
- The most common sites of systemic infection in patients with long-term central venous catheters are the urinary tract, the anorectal area, the upper respiratory tract, and the catheter, in that order. Local skin infection at the catheter site without systemic signs or symptoms usually responds to antibiotics and does not require catheter removal.
- Acute venous hypertension can occur in the first few weeks after construction of an arteriovenous fistula. Hospitalization is required for ligation of the vein before a potentially exsanguinating vessel rupture occurs.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 86

Pulmonary Embolism and Deep Vein Thrombosis

Jeffrey A. Kline and Michael S. Runyon

PERSPECTIVE

This chapter discusses the diagnosis and treatment of venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), from the perspective of the emergency physician and provides a functional resource for the evaluation and treatment of VTE in the emergency department (ED).

Pathophysiology of Thrombosis

Timely diagnosis and treatment of VTE can be facilitated by understanding the pathophysiology of thrombosis. VTE represents the end product of imbalanced clot formation versus clot breakdown. Fibrin represents the primary structural framework of embolized clots, and excessive fibrin deposition represents the primary nidus of VTE. Fibrinogen converts to fibrin in response to vascular injury and inflammation. Vascular injury exposes tissue factor that promotes fibrin formation, and inflammation increases the production of fibrinogen, stimulating fibrin deposition. Factors that enhance fibrin formation include systemic inflammation (which includes almost all so-called acquired states of hypercoagulability, such as antiphospholipid antibody syndromes) and genetic thrombophilias and neoplastic abnormalities that increase fibrin formation or decrease fibrinolysis. In particular, sluggish blood flow in large veins permits the process of fibrin deposition. Rudolf Virchow, a 19th-century pathologist, recognized the triad of venous injury, slow blood flow, and hypercoagulability as the cardinal factors that classify a patient as being at risk for excessive fibrin deposition relative to fibrin removal.[1] Most clinical decision rules for VTE incorporate these factors to help decide who has VTE and who does not. Despite its simplicity and elegance, from the perspective of diagnosis, Virchow's triad does not include the crucial issues of age or physiologic effects of VTE.

Epidemiologic studies show convincingly that age increases the likelihood of imbalanced clot formation.[2] Aging leads to venous valvular incompetence, which impairs venous return, and causes blood stasis; aging also increases the probability of an acquired hypercoagulability, such as malignancy. Older patients have more cumulative effects of inflammatory damage to venous endothelium; are more likely to be exposed to the independent risk factor of surgery; and may be predisposed to dehydration, which probably accelerates clot deposition. Older patients have more heart and lung disease, and when PE is present, older patients are far more likely to manifest the adverse physiologic consequences of PE than younger patients with the same degree of thrombosis.

DEEP VEIN THROMBOSIS

DVT represents a disease spectrum ranging from a minimally symptomatic isolated calf vein thrombosis to a limb-threatening iliofemoral venous obstruction. Although the true incidence is unknown in the ED population, DVT accounts for approximately 600,000 hospital admissions per year.

Anatomy

The venous anatomy of the lower extremity can be divided into the deep and superficial systems. The superficial venous system consists primarily of the greater and short saphenous veins and the perforating veins. The deep venous system includes the anterior tibial, posterior tibial, and peroneal veins, collectively called the *calf veins*. The calf veins join together at the knee to form the popliteal vein, which extends proximally and becomes the femoral vein at the adductor canal. The femoral vein sometimes is called the *superficial femoral vein*, and this nomenclature may contribute to some confusion when interpreting radiology reports. A clot in the superficial femoral vein is indeed a DVT and should be treated as such. The femoral vein joins with the deep femoral vein to form the common femoral vein, which subsequently becomes the external iliac vein at the inguinal ligament. *Proximal DVT* refers to a clot in the popliteal vein or higher, whereas *distal clot* refers to an isolated calf vein thrombosis.

Clinical Presentation

The initial symptoms of DVT can be as subtle and nonspecific as a mild cramping sensation or sense of fullness in the calf, without objective swelling, and may be difficult to differentiate clinically from myriad other unrelated disorders (Box 86-1). It is precisely at this early stage, however, that DVT can be treated most effectively to minimize the potential morbidity and mortality associated with VTE. Likewise, the clinical signs of DVT vary and may include unilateral swelling, edema, erythema, and warmth of the affected extremity; tenderness to palpation along the distribution of the deep venous system; dilatation of superficial collateral veins; and a palpable venous "cord." The classic Homan's sign (pain felt in the calf or posterior aspect of the knee on passive dorsiflexion of the foot

BOX 86-1 Differential Diagnosis of Deep Vein Thrombosis

Muscle strain/hematoma
Popliteal (Baker's) cyst
Lymphedema
Cellulitis
Vasculitis
Fracture
Superficial thrombophlebitis
Chronic venous insufficiency
Proximal venous compression (e.g., tumor, gravid uterus)
Congestive heart failure (swelling usually bilateral)
Hypoalbuminemia (swelling usually bilateral)

while the knee is extended) is insensitive and nonspecific for DVT and has no place in modern medicine.

Diagnosis

Estimation of the pretest probability (PTP) of DVT is the initial step in the diagnostic strategy. This estimation may be accomplished either by the clinical gestalt of an experienced practitioner or in conjunction with a clinical decision tool, such as that derived and validated by Wells and colleagues (Table 86-1) to determine which patient is at low risk.[3,4]

Laboratory Evaluation

The D-dimer is a protein derived from enzymatic breakdown of cross-linked fibrin, and an elevated plasma concentration indicates the presence of a clot formed somewhere in the body within the past 72 hours. D-dimer concentration may be elevated with any condition that causes fibrin deposition, including malignancy, pregnancy, advanced age, prolonged bedrest, recent surgery, infection, inflammation, new indwelling catheters, stroke, and myocardial infarction. D-dimer concentration is proportionate to the size of the clot and decreases as the clot matures, so the test is less sensitive with small or chronic clots. D-dimer analysis may be useful in the evaluation of suggested DVT, but differences in D-dimer assay methodology can greatly affect diagnostic accuracy.

The D-dimer protein can be measured in plasma using several techniques. All commercially available assays share the concept of antibody capture followed by detection. As of July, 2008, the FDA has approved 43 different D-dimer assays, which employ varying capture antibodies and detection methods. One way to categorize the D-dimer assay format is as quantitative or qualitative (which includes semiquantitative assays). The two most common detection methods for quantitative assays are the enzyme-linked immunosorbent assay (ELISA) and the immunoturbidimetric technique. Because of variable properties of the test capture antibody and differences in test standardization, the quantitative D-dimer assays vary regarding their cutoffs for the upper limit of normal. For many assays, a concentration of less than 500 ng/mL is a negative test, and this threshold generally carries an 88 to 97% diagnostic sensitivity for symptomatic proximal DVT and 83 to 94% sensitivity for calf DVT or asymptomatic proximal DVT. A negative quantitative D-dimer assayed by the ELISA or immunoturbidimetric technique may be used to exclude the diagnosis of DVT in patients at low or moderate risk without further evaluation. Qualitative D-dimer assays include whole-blood assays done on single-use cartridges that resemble home pregnancy tests and semiquantitative latex fixation assays that employ test cards containing several wells for plasma in various folds of dilution. Qualitative D-dimer assays have a diagnostic sensitivity of 78 to 93% for symptomatic proximal DVT. As a result, a negative qualitative D-dimer excludes proximal DVT only in patients deemed to have a low clinical possibility by the physician.[5]

Table 86-1 Clinical Model for Estimating the Pretest Probability of Deep Vein Thrombosis

CLINICAL FEATURE	SCORE*
Active cancer (treated within the previous 6 mo or currently receiving palliative treatment)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden for ≥3 days or major surgery within 12 wk requiring general or regional anesthesia	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling at least 3 cm larger than on the asymptomatic side (measured 10 cm below the tibial tuberosity)	1
Pitting edema confined to the symptomatic leg	1
Collateral superficial veins (nonvaricose)	1
Previously documented deep vein thrombosis	1
Alternative diagnosis at least as likely as deep vein thrombosis	−2

*A score of <2 indicates the probability of deep vein thrombosis is low.
Adapted from Wells PS, Anderson D, Bormanis J: Value of assessment of pretest probability of deep-vein thrombosis in clinical management. Lancet 350:1795, 1997.

Radiographic Evaluation

Contrast venography was once the gold standard for evaluating DVT, but it has largely been supplanted by a combination of D-dimer testing and duplex venous ultrasonography. Venography has the advantage of being able to differentiate between an acute and chronic thrombus, but clinical presentation usually provides this differentiation, so the test is rarely indicated on this basis.

Venous duplex ultrasonography, performed by a certified sonographer and interpreted by a board-certified radiologist or similarly credentialed expert, has a sensitivity and specificity of approximately 95% for proximal DVT and is the diagnostic test of choice in most centers.[6] A patient at low risk may have the diagnosis of DVT effectively excluded by a single negative venous duplex ultrasound. However, a negative ultrasound in a patient who is not at low risk should prompt further testing. A patient with a moderate or high PTP, a negative ultrasound, and a negative quantitative D-dimer has DVT excluded. If the D-dimer is elevated (or not performed), a patient with a moderate or high PTP and a negative ultrasound at the index visit can have DVT excluded after a repeat ultrasound that is negative for DVT in 2 to 7 days. An expertly performed and interpreted positive ultrasound is sufficient to confirm the diagnosis of DVT. Ultrasound cannot sufficiently image the pelvic veins or vena cava, but may identify a tangible alternative diagnosis, such as a ruptured Baker's cyst.

Many emergency physicians utilize bedside ED ultrasound in their daily practice for a variety of indications. A recent meta-analysis comparing emergency physician-performed

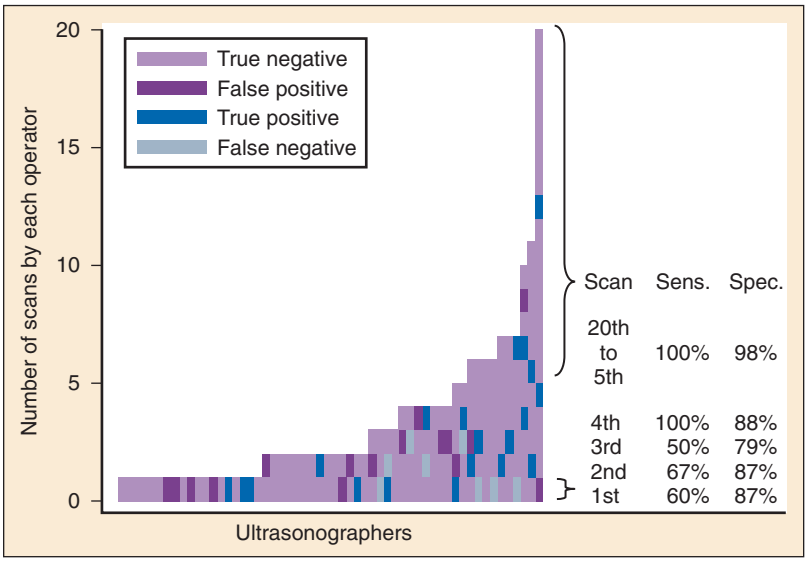


Figure 86-1. Graph showing the learning requirement for emergency physician-performed ultrasonography (EPPU). This figure plots the diagnostic results of each EPPU done by residents and attending physicians in a research study designed to measure the diagnostic accuracy for DVT. Each tile represents a unique clinician-participant (*x*-axis) who enrolled a unique patient-participant (*y*-axis), and each tile is color-coded to show the diagnostic result of the EPPU. The tiles are ordered from left to right in order of least to most number of patients enrolled per clinician. The tiles stack up vertically in temporal order. For example, the clinician to the far right enrolled a total of 20 patients: the first was a false positive, the fourth was a true positive, and the last seven were true negatives. This figure shows that the diagnostic sensitivity improved to 100% for clinicians who had enrolled at least three prior patients.

ultrasound (EPPU) for lower-extremity DVT with radiology-performed ultrasound studies calculated an overall sensitivity of 95% (95% confidence interval [CI] 87–99%) and specificity of 96% (95% CI 87–99%).[7] Although these results appear favorable, issues involving training and prior experience raise questions about the generalizability of these findings. A follow-up prospective study of EPPU performed by a heterogenous group of 56 emergency physicians revealed a sensitivity of 70% (95% CI 50–86%) and specificity of 89% (95% CI 83–94%), although the diagnostic accuracy was very good for operators who had performed more than three EPPU examinations (Fig. 86-1).[8]

Indirect computed tomography venography (CTV) is not a primary imaging modality for DVT, but may be performed in conjunction with CT pulmonary angiography (CTPA) of the chest during the evaluation of suggested PE. The technique involves imaging the pelvis and lower extremities during the venous return phase of the intravenous (IV) contrast material administered for the CTPA. Adding CTV to CTPA provides an incremental increase in the sensitivity for VTE, identifying DVT in approximately 2% of patients in whom the CTPA is read as negative for PE but at the expense of significant additional radiation exposure to the pelvis and lower extremities.[9,10] Interobserver agreement among radiologists interpreting CTV appears to be less than that for the CTPA portion of the study.[11] At this time, the overall clinical utility of CTV remains controversial.

Magnetic resonance imaging (MRI) can evaluate the pelvic vasculature and vena cava, which is not possible with ultrasound. MRI does not require exposure to ionizing radiation, making it an attractive option for pregnant patients with possible VTE. The clinical utility of MRI is currently limited by cost and availability.

Impedance plethysmography and strain-gauge plethysmography measure physical features of the leg (electrical resistance or girth) during venous outflow from the extremities to diagnose proximal DVT. The reported sensitivities are highly technique-dependent, and these tests are not recommended.

Treatment

When the diagnosis of DVT has been established, anticoagulation should be initiated, unless contraindicated, with weight-based unfractionated heparin (80 U/kg IV bolus followed by 18 U/kg/h infusion) or a low-molecular-weight heparin (e.g., enoxaparin, 1 mg/kg subcutaneously every 12 hours) assuming normal renal function. Both forms of heparin work equally well, and both are safe in the absence of contraindications to anticoagulation. Treatment requires transition to oral anticoagulation with warfarin for at least 3 months. Hospital admission is obviated by initiation of outpatient enoxparin therapy in the ED or ED observation unit, followed by self-administration at home (with appropriate patient teaching) or home administration by a visiting nurse. If admission is contemplated, the first dose of warfarin can be given in the ED to help reduce overall length of stay in the inpatient unit. Patients should be encouraged to ambulate after anticoagulation for DVT; bedrest represents an illogical measure for reducing the chance of clot dislodgement and development of PE because continued immobilization of the thrombosed extremity promotes DVT extension, increases the risk of embolization, and ultimately predisposes the patient to the postphlebitic syndrome.[12] Patients who cannot be given anticoagulants and those who have a recurrence of VTE despite anticoagulation therapy should be considered for vena caval interruption.

Superficial Thrombophlebitis

Although thrombophlebitis of the superficial veins uncommonly evolves into a thromboembolic event, many patients with clinically suggested superficial thrombophlebitis have a simultaneous DVT. Patients with a clot in the greater saphenous vein that extends above the knee are at risk for progression to DVT via the saphenous-femoral vein junction and should be considered for anticoagulation, although data are not available to quantitate the benefit (or harm). When DVT has been excluded, superficial thrombophlebitis should be treated symptomatically with nonsteroidal anti-inflammatory drugs, heat, and graded compression stockings (fitted to exert 30–40 mm Hg of pressure at the ankle). Increased ambulation and elevation of the extremity above the level of the heart while at rest help to decrease venous stasis. Routine anticoagulation is not indicated for superficial thrombophlebitis unless the patient is at extreme risk for developing clot extension, such as results in the presence of an external fixation device on the extremity, a proximal indwelling catheter, or from a very high risk thrombophilia such as an active adenocarcinoma or homozygous factor V Leiden genetic sequence variation.

Isolated Calf or Saphenous Vein Thrombosis

The optimal management strategy for thromboses of the saphenous, tibial, or peroneal veins remains controversial.[13] Isolated calf vein thrombosis was, previously, thought to carry a low risk of embolization that did not warrant anticoagulation. Longitudinal studies subsequently found that approximately 25% of isolated calf vein thromboses propagate proximally, prompting many experts to recommend treatment with anticoagulation as for DVT.[14] Others argue that a reasonable alternative in an otherwise healthy, ambulatory patient with an isolated calf thrombus and no other indication for anticoagulation is to prescribe antiplatelet therapy with aspirin (325 mg/day of enteric-coated acetylsalicylic acid) and arrange for close follow-up with serial duplex ultrasound scans at 2 to 7 days to evaluate for clot propagation.

Phlegmasia Cerulea Dolens (Painful Blue Leg)

Massive iliofemoral occlusion results in swelling of the entire leg with extensive vascular congestion and associated venous ischemia, producing a painful, cyanotic extremity. There may be an associated arterial spasm resulting in phlegmasia alba dolens (painful white leg or milk leg), which may mimic an acute arterial occlusion. Prompt consultation with a vascular surgeon should be obtained because patients with *phlegmasia cerulea dolens* may require emergent thrombectomy. If timely consultation is not possible, early thrombolytic therapy may be a limb-salvaging procedure in the absence of contraindications. One such strategy is to infuse alteplase (1 mg/min to a total dose of 50 mg) via a peripheral IV catheter placed distal to the thrombus.

Upper Extremity Venous Thromboses

DVTs of the upper extremity have become more common in association with increased prevalence of indwelling venous catheters and wires for electronic cardiac devices. Upper extremity DVT can cause PE, and all patients with DVT above the elbow require definitive treatment.[15-17] Axillary vein clots have recently become a topic of intense research activity. Several thematic points appear to be emerging: (1) About one half of all upper extremity DVTs are associated with an indwelling catheter. (2) DVT does not automatically warrant catheter removal if the catheter serves a vital purpose. However, these patients should receive anticoagulation if they do not have contraindications. The duration of anticoagulation following catheter removal for DVT remains controversial, but most published guidelines recommend at least 3 months. (3) The rate of PE from axillary vein DVT appears to be similar to that for femoral vein DVT, although many experts believe the severity of PE tends to be less with upper extremity DVT. (4) Isolated upper extremity DVT, especially axillary-subclavian vein thrombosis, also can be seen in relatively young, active, otherwise healthy patients. Although standard DVT risk factors, such as hypercoagulable state or malignancy may be present, most of these patients have no apparent predisposing condition. The most prevalent theory now is that these patients have abnormal anatomy related to their thoracic inlet and that direct or indirect pressure on the upper extremity venous system leads to eventual thrombosis. It is not known whether strenuous, repetitive activity (the condition was once called "effort DVT") causes the DVT by exacerbating the anatomic compromise through movement of the arm or hypertrophy of adjacent muscles, or whether effort simply brings out the symptoms of an otherwise occult upper extremity DVT. Many patients, however, engage in strenuous activities or sports involving the arm, and almost all will first experience their symptoms during a period of intense use of the arm and hand. Typically, patients present with an ill-defined ache or throbbing sensation of the affected extremity, distal swelling, or a sensation of arm heaviness, any or all of which are exacerbated by strenuous arm activity. Diagnosis is by a combination of clinical evaluation, D-dimer testing, and duplex ultrasonography. Venography is used primarily when surgical embolectomy or catheter lysis are contemplated. CT and MRI are of limited value. Treatment is by anticoagulation, possibly supplemented by catheter-directed fibrinolysis or embolectomy. Consultation with a vascular surgeon is advisable. Even with restoration of vein patency and long-term anticoagulation (as for a lower extremity DVT), many patients will remain symptomatic after 5 years, and some will have severe, permanent limitation of function.

Complications

Although the most feared complication of DVT is fatal PE, DVT damages venous valves, causing venous insufficiency. Venous insufficiency in turn, manifests as a spectrum ranging from painless varicosities to severe postphlebitic syndrome, which can cause unremitting pain and swelling, varicose veins, skin changes, and nonhealing ulcers.

PULMONARY EMBOLISM

PE results from a clot that formed hours, days, or weeks earlier in the deep veins that dislodges, travels through the venous system, traverses the right ventricle, and lodges in the pulmonary vasculature. During transit and after docking in the pulmonary vasculature, the embolism produces a highly variable set of symptoms and a wide range of physiologic perturbations. This variability contributes to the difficulty in diagnosing PE. No one knows exactly how many patients pass through the ED with PE because there is no reliable way of identifying missed cases. Assuming that ED populations have a risk for PE somewhere between hospitalized patients (who are at high risk for PE) and outpatients (who are at lower risk), approximately 1 in every 500 to 1000 ED patients has PE.[18] About 10% of ED patients with PE die within 30 days even when PE is promptly diagnosed and treated.[19,20]

Pathophysiology of Pulmonary Vascular Occlusion

The pulmonary vascular tree normally has a low resistance to fluid flow, and young persons without cardiopulmonary disease (e.g., congestive heart failure, chronic obstructive lung disease, advanced sarcoidosis, pulmonary fibrosis, scleroderma, and primary pulmonary hypertension) can tolerate at least 30% obstruction often with minimal trifling symptoms or signs. Pulmonary infarction is a more dramatic exception. Although a segmental pulmonary artery constitutes only about one sixteenth of the entire pulmonary vascular circuit, a clot lodged deeply in a segmental artery can obstruct blood flow to a sufficient degree to cause tissue necrosis. The patient can feel focal, sharp, pleuritic pain and exhibit a splinting response to breathing. Over several days, the infarcted segment becomes consolidated on chest radiography and exudes a pleural effusion, manifesting an intense underlying inflammatory process.[21] The exact physiology of this process is unknown, but probably results in part from the consequences of chemokine production and hyperinflammation stimulated by normoxic ischemia.[22] Chest pain from noninfarcting PE can be highly

BOX 86-2 PULMONARY EMBOLISM RULE-OUT CRITERIA (PERC RULE)

Low pretest probability for PE by the treating clinician's unstructured estimate, plus:
Age less than 50
Pulse rate less than 100 beats/min
Oxygen saturation greater than 94%
No hemoptysis
No unilateral leg swelling
No recent major surgery or trauma
No prior pulmonary embolism or deep venous thrombosis
No hormone use

PE, pulmonary embolism.

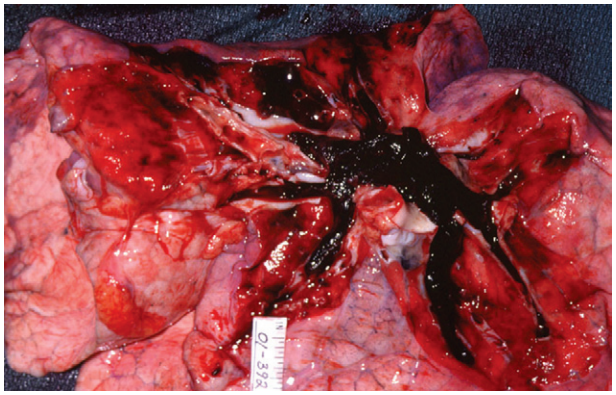


Figure 86-2. Massive pulmonary embolism on autopsy. This man died with a large clot burden that plugged the distal lobar arterial branches, eventually producing nearly complete obstruction to blood flow and subsequent cardiac arrest. This man had vague respiratory symptoms for 2 weeks, causing him to see a physician who diagnosed bronchitis.

variable and vague. About 30% of patients with definite PE have no perception of chest pain.

In contrast, if asked in a detailed and structured way, about 90% of patients with noninfarcting emboli admit to the sensation of dyspnea. The dyspnea may be constant and oppressive or may be intermittent and perceived only with exertion, possibly due to an exercise-induced increase in pulmonary vascular resistance. Rest dyspnea seems to be the clinical manifestation of distorted and irregular blood flow within the lung, referred to as *ventilation-perfusion inequality*. With each breath, a patient with PE wastes ventilation because of increased alveolar dead space (alveoli that are ventilated but not perfused). A lodged clot can redistribute blood flow to areas of the lung with already high perfusion relative to ventilation and as such cause more blue blood to pass through the lung without being fully oxygenated. This *venous admixture* is probably the primary cause of hypoxemia with PE and the increased alveolar-arterial oxygen difference (the A-a gradient). About 15% of patients with PE have a normal A-a gradient of oxygen (with normal defined as age in years/4 + 4), however, and the A-a gradient is abnormally high in most patients who are evaluated for PE, but ultimately found to not have PE.[23] In a multicenter registry of 348 patients with PE, 37 (10.6%) had a pulse oximetry reading of 100% at the time of arrival to the ED, while breathing room air. Despite its shortcomings as a single diagnostic step, the presence of hypoxemia (pulse oximetry <95%, breathing room air) that cannot be explained by a known disease process definitely increases the probability of PE. Conversely, a normal oxygen saturation can be used only when considered together with multiple other clinical features and should not alone or independently be used to support a decision to forego further testing for PE (Box 86-2).[24,25] Additionally, when PE is diagnosed, the severity of hypoxemia represents a powerful independent predictor of patient outcome.[19]

PE also causes highly variable hemodynamic effects. In the ED, about half of all patients with PE have a heart rate greater than 100 beats per minute.[26-28] Tachycardia from PE probably results from impaired left ventricular filling, leading to a pathophysiologic process that parallels that of hemorrhagic shock (see Chapter 4). When PE obstructs more than 50% of the vasculature, it usually causes an acute increase in right ventricular pressure. In contrast to the left ventricle, the right ventricle does not show an elastic response to acutely increased afterload; it quickly dilates, showing echocardiographic hypokinesis early in the course. In about 40% of cases, the right ventricular damage persists for at least 6 months and probably longer. Arterial hypotension represents an ominous hemodynamic consequence of PE; it occurs in only about 10% of patients, but signifies a fourfold increase in risk of death compared with normotensive patients.[20] In its most extreme form, PE can obstruct the right ventricular outflow entirely, either by casting the entire pulmonary vascular tree (Fig. 86-2) or by acutely occluding the main pulmonary artery. Pulseless electrical activity (PEA) is the most common electrocardiogram (ECG) result from obstructive PE.[29,30] The survival rate from cardiac arrest from PE is abysmally low, even if the arrest is witnessed and heroic treatment is initiated.

Clinical Presentation

Table 86-2 presents a listing of factors that significantly increase the probability of PE in a population of ED patients. As is the case for cardiac risk factors in the evaluation of acute chest pain, variables that increase the probability of PE in epidemiologic studies are not always useful for individual ED patients with signs and symptoms suggesting PE. For example, it is probably true from an epidemiologic standpoint that people who smoke are at a significantly higher risk for venous clots than are people who do not smoke. In the ED, however, the categorical presence of smoking in a given patient does not seem to increase that person's risk for PE over that of a nonsmoker with an otherwise identical clinical presentation. It is possible that smokers are simply more likely to have other lung problems that manifest a clinical presentation similar to PE.

As many as 50% of patients diagnosed with PE have no apparent clinical risk factors for VTE. As such, some have postulated that these "idiopathic" PEs might be associated with an increased frequency of thrombophilia-related genetic mutations that could be identified by laboratory investigation. However, a case-control study of 49 patients with idiopathic PE demonstrated no difference in the frequency of the thrombophilia genetic variants factor V Leiden G1691A or prothrombin G20210A compared with controls.[31]

Virtually any ED visit related to weakness, shortness of breath, dizziness or syncope, pain, extremity discomfort, or nonspecific malaise or functional deterioration could represent PE. A patient with PE typically presents with 2 to 3 days of shortness of breath, now worsened enough to seek care. The chest pain usually is vaguely described. A few patients have focal pleuritic chest pain, but many say nonspecifically that their chest hurts with breathing, usually on the lateral aspects. Purely substernal chest pain is a rare presentation for PE and in general suggests a cardiac or other origin. Although a sudden onset of the symptoms might prompt more serious consider-

Table 86-2 Classic Risk Factors and Physiologic Findings for Pulmonary Embolism

FACTOR	MECHANISMS	STRENGTH OF ASSOCIATION WITH PE IN ED POPULATIONS
Inherited thrombophilia	Hypercoagulability	++
Connective tissue disease	Inflammation	Unknown
Acquired thrombophilia	Hypercoagulability	Unknown
Carcinoma (all types, all stages)	Hypercoagulability	+
Limb or generalized immobility	Stasis	++
Prior PE or DVT	Multiple	+
Trauma within past 4 wk requiring hospitalization	Inflammation, venous injury and stasis	+++
Surgery within past 4 wk requiring general anesthesia	Inflammation, venous injury and stasis	++++
Smoking	Inflammation	Minimal
Estrogen	Hypercoagulability	++
Pregnancy/postpartum	Hypercoagulability	Minimal
Symptoms		
Chest pain	Ischemia, muscle strain	Minimal
Dyspnea	$\dot{V}/\dot{Q}$ mismatch	+
Hemoptysis	Infarction	+++
Syncope	Vascular obstruction	Minimal
Signs		
Pulse rate >100 beats/min	Cardiac stress, baroreceptors	+++
Pulse oximetry reading <95%	$\dot{V}/\dot{Q}$ mismatch	+++
Unilateral leg or arm swelling	Venous obstruction	++++

DVT, deep vein thrombosis; PE, pulmonary embolism; $\dot{V}/\dot{Q}$, ventilation-perfusion ratio.

ation of PE as the cause, many physicians use the inverse logic that if the symptoms did not start suddenly, this somehow reduces the probability of PE to a level that justifies no further workup. This perception is incorrect because less than half of outpatients with PE describe either their dyspnea or chest pain sensation as being of "sudden onset." When the antemortem histories of patients who die suddenly and unexpectedly from PE are reconstructed by interviewing family and examining medical records, most have complained of nagging symptoms for weeks before collapse, and 40% already had seen a physician for care.[30]

PE with lung infarction can present with a clinical picture that is similar to lobar pneumonia, including focal chest pain, fever, and unilateral rales on auscultation. However, a temperature greater than 103° F suggests infection rather than infarction. An occasional clue to pulmonary infarction is the onset of pain and blood-red hemoptysis on the same day, whereas lobar pneumonia usually presents with productive cough for a few days followed by rust-tinged sputum.

The physical examination can sometimes provide specific information about the presence of PE, including unilateral leg asymmetry, suggesting presence of DVT. Jugular venous distention in a patient with severe dyspnea and clear lung fields on auscultation suggests pure right heart failure. The presence of wheezing suggests bronchospasm, which is not common in PE and makes the diagnosis less likely (but does not exclude it). Bilateral rales suggest the diagnosis of left ventricular failure, although localized rales often are heard over infarcted lung tissue. Astute clinicians may hear an accentuated pulmonic component of the second heart sound, or a right ventricular S_3 sound.

Diagnosis

Chest radiography seldom provides specific information, but it is useful to suggest alternative diagnoses, such as pneumonia, congestive heart failure, or pneumothorax. Unilateral basilar atelectasis on chest x-ray increases the probability of PE.[32] If symptoms have been present for 3 days or more, pulmonary infarction sometimes shows an apex-central, pleural-based, wedge-shaped area of infiltrate, producing the "Hampton's hump" finding. Unilateral lung oligemia (Westermark's sign) is a rare radiographic manifestation of a large PE.

Likewise, a 12-lead ECG provides more information about the presence of alternative diagnoses, such as pericarditis or cardiac ischemia, than the presence of PE. When PE causes ECG changes, this is usually a result of acute or subacute pulmonary hypertension. The most common effects of pulmonary hypertension on ECG are rapid heart rate, symmetrical T-wave inversion in the anterior leads (V_1-V_4), the McGinn-White S1Q3T3 pattern, and incomplete or complete right bundle branch block (Fig. 86-3).[33]

After the history and physical examination (with or without ECG and chest film data), emergency physicians are often compelled to evaluate for PE mainly because there is no other explanation for symptoms or signs consistent with PE. Symptoms include dyspnea or atypical chest pain, syncope, or seizure; signs include respiratory distress, altered consciousness, tachycardia, tachypnea, or hypoxemia. In the ED, unexplained symptoms and signs are as important as predictors of the presence of PE as the triad described by Virchow. Since as many as 50% of patients diagnosed with PE have no identifiable classic risk factors for thrombosis, the decision to pursue the diagnosis of PE seems to be a complex process, based on that particular patient's presentation, which appropriately does not rely on the presence or absence of population risk factors.

In some cases, PE can be excluded with reasonable certainty based on data that are available at the bedside, gathered only by the medical history and physical examination. Multicenter studies of urban academic EDs have suggested that emergency physicians currently evaluate about 1 to 2% of all patients for PE.[34] Each year, more than 16 million patients

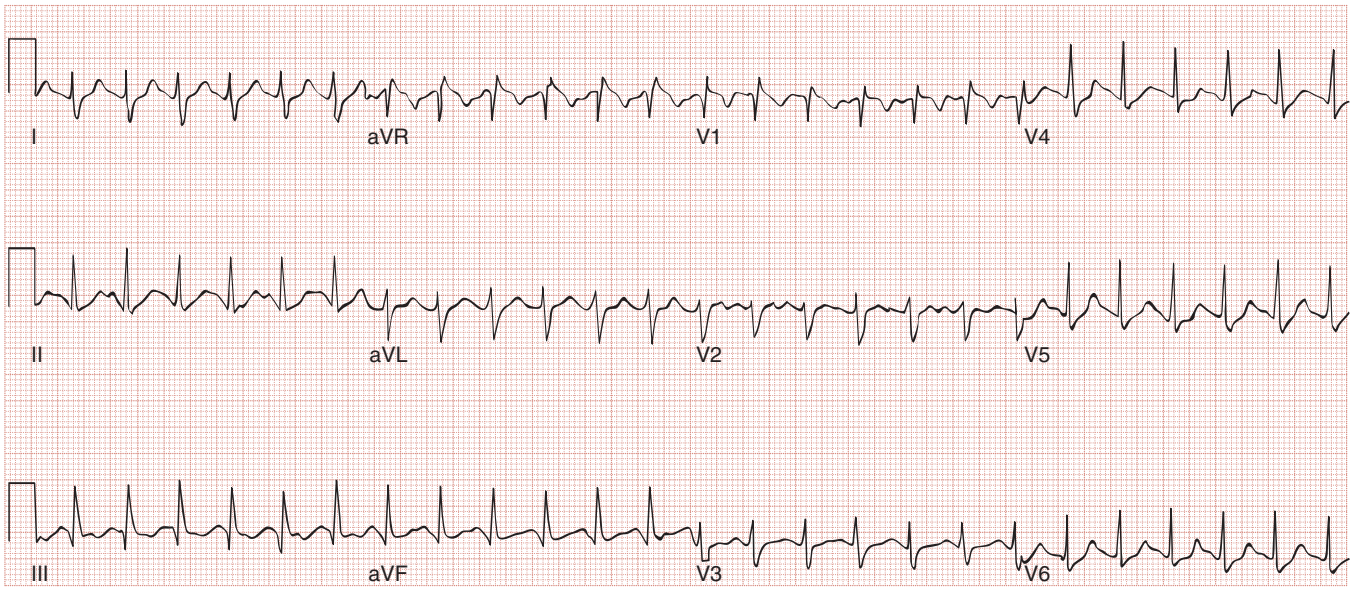


Figure 86-3. Initial electrocardiogram tracing from an 18-year-old woman on oral contraceptives who presented to the ED with syncope. Several findings consistent with pulmonary embolism are shown, including tachycardia, the S1Q3T3 pattern, and an incomplete right bundle branch block. Computed tomography angiography revealed extensive bilateral pulmonary emboli, and echocardiography showed severe right heart dysfunction.

present to the ED with chest pain or dyspnea. Although numerous cases of PE are probably still missed, overtesting for PE can also be harmful. Specific risks include exposure to the ionizing radiation and IV contrast necessary for CTPA-CTV and the risk of unnecessary anticoagulation. The appropriate use of D-dimer testing decreases the need for imaging in all but patients at high risk.

A single CTPA examination imparts a relatively large radiation dose that probably increases the lifetime risk of cancer, especially in young women.[35] Moreover, at least one third of all ED patients who receive one CTPA go on to have a second CTPA within 5 years.[36] The IV contrast required for CTPA can cause anaphylactoid reactions, local tissue damage from high-volume contrast injection through a dislodged catheter, and contrast-induced nephropathy. The frequency of post-CTPA contrast nephropathy is probably between 4 and 12%.[37]

Additionally, nonionic contrast material readily crosses the placenta, and the long-term effects of fetal contrast exposure are likewise unknown. Accordingly, there must be a rational, reproducible strategy to guide the decision-making and diagnostic processes. This strategy should begin with estimation of PTP. Methods for estimating PTP can be *implicit* (meaning the clinician's best guess) or *explicit* (meaning use of a scoring system or flow algorithm to categorize the probability).[38]

One approach to the workup for PE is to compare the PTP with the so-called test threshold for PE.[39] The test threshold represents the point above which some type of workup should be initiated and below which the clinician can justify not starting the workup. For PE, the test threshold is approximately 2%.[24] Patients with a PTP less than 2% are more likely to be harmed than benefited by a workup and vice versa for patients with a PTP greater than 2%.

The question becomes how to quantify the PTP accurately. One method is to use the implicit approach, in which the clinician draws from his or her own experience and surmises the probability of PE to be less than 2%. This method allows the inherent flexibility of human thought, but is subject to the conditions in the ED at the time (e.g., is one less likely to pursue a relatively low-likelihood diagnosis when the department is very busy), conditions of the clinician (e.g., fatigue, dysphoria, subjective feelings about the patient), and the availability of diagnostic studies (e.g., daytime versus nighttime, weekday versus weekend). In addition, there is the variability between clinicians who may not agree that a 19-year-old with cough and pleuritic chest pain, a normal chest radiograph, and no other risk factors has less than a 2% probability of PE.

Decision rules help to deal with these problems because they are structured and more transparent. Several rules have been derived and validated for the risk stratification of patients with possible PE; however, difficulty with spontaneous recall and a preference for gestalt reasoning by clinicians may effectively limit their use in clinical practice.[40] Fortunately, clinical reasoning appears to be comparable to at least two of the validated decision rules. In a large single-center study of 2603 ED patients evaluated for PE, the treating clinician's unstructured estimate of PTP was equivalent to that provided by the Wells score and the Charlotte rule. This finding was independent of training level, and interobserver agreement, measured in a subgroup of 154 patients, was good.[41]

Although gestalt reasoning and clinical decision rules may provide adequate stratification to guide the workup (i.e., D-dimer vs. pulmonary vascular imaging), they have not been able to reproducibly identify the "very low risk" population whose PTP lies below the 2% test threshold. In one validation study, patients with the Wells score less than 2 had a 1.3% probability of PE,[42] but this finding has not been repeated. To identify the very low risk group in whom PE could be safely excluded at the bedside with no diagnostic testing, the PE rule-out criteria (or PERC rule) were derived and prospectively validated in 8138 patients in 13 different hospitals across the United States and in New Zealand (see Box 86-2).[24,43]

When the clinical suggestion for PE is low *and* each of the eight elements of the rule is satisfied, the PERC rule identifies a very low risk population among whom no patient has a PTP for PE of greater than 2%. In the large validation series, the rule excluded PE at the bedside in 20% of cases and yielded a false-negative rate of 1% (95% CI 0.6–1.6%). This finding supports a rational and reproducible method for avoiding unnecessary testing in a low-risk patient with a sign or symptom

partially suggestive of PE. Patients with risk factors but without any symptoms or signs of PE (e.g., no chest pain, no shortness of breath, no dyspnea on exertion, normal or normalized vital signs, and no recent syncope) do not warrant workup for PE, unless there is some compelling clinical indication to the contrary.

PE also is less likely when some other disease process can explain the patient's complaints and findings (e.g., asthma causing bronchospasm proven by a low peak expiratory flow rate, or findings of wheezing and prolonged expiration on auscultation) and the patient is otherwise not believed to be at high risk for PE. The finding that a confirmed alternative diagnosis reduces the probability of coincident PE has been shown in multiple settings.

Because of variation in patient populations and availability of clinical testing differences, there is no single algorithm for the evaluation of PE. The flow algorithms provided here are predicated on the following goals: (1) to identify as many ED patients as possible who have PE; (2) to avoid mislabeling (and administering anticoagulants to) patients who do not have PE; and (3) to use available resources efficiently and effectively (Fig. 86-4).

For a patient with a relatively concerning clinical picture (e.g., implicit suspicion or explicit score suggesting a PTP > 40%), it makes little sense to start with a screening strategy that applies to a low or moderate risk population, such as the D-dimer. Because the half-life of circulating D-dimer is less than 8 hours, the sensitivity of the D-dimer may decrease if the patient's symptoms have been present for longer than 3 days. False-negative D-dimer measurements may also be seen with ingoing warfarin therapy and in the subset of patients with pulmonary infarction.

The type of D-dimer test influences the test sensitivity. Qualitative tests, such as the whole-blood agglutination assays (SimpliRED) or the immunofiltration assays (IL test, Simplify) and latex fixation tests, have sensitivities of 80 to 95% and specificities of 57 to 74% in ED populations and therefore may be inadequate to be considered diagnostic or exclusive of pulmonary embolism.[44-46] Meta-analyses have shown that quantitative tests, either ELISA or immunoturbidimetric tests using a cutoff of 500 FEU/mL (an *FEU* is a fibrinogen equivalent unit, usually reported by hospital laboratories as a mass value of 500 ng/mL or 0.50 µg/mL), have high sensitivities (about 94%) and specificities of about 55%.[47,48] Although high D-dimer concentrations (e.g., >2500 ng/mL) more strongly suggest the presence of PE, as opposed to a nonspecific cause, no cutoff of D-dimer concentration can be used to confirm the diagnosis.

The post-test probability to safely exclude the diagnosis of PE must be equal to 1%, which is at least equivalent to that of a normal $\dot{V}/\dot{Q}$ scan or a negative CTPA.[38] This combination can be achieved by the combination of a PTP assessment less than 40% and a quantitative D-dimer concentration less than 500 ng/mL. When the PTP is relatively high, or the screening D-dimer is positive, pulmonary vascular imaging by CTPA or, less commonly, $\dot{V}/\dot{Q}$ scanning is advised. Although CTPA is not perfect, it has multiple advantages over $\dot{V}/\dot{Q}$ scanning and usually can be considered to definitively confirm or exclude the presence of PE.

The relative accuracy and precision of the $\dot{V}/\dot{Q}$ scan were shown in the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study, which compared the results of $\dot{V}/\dot{Q}$ scanning with the most accurate criterion standard test available at the time—formal pulmonary angiography (Table

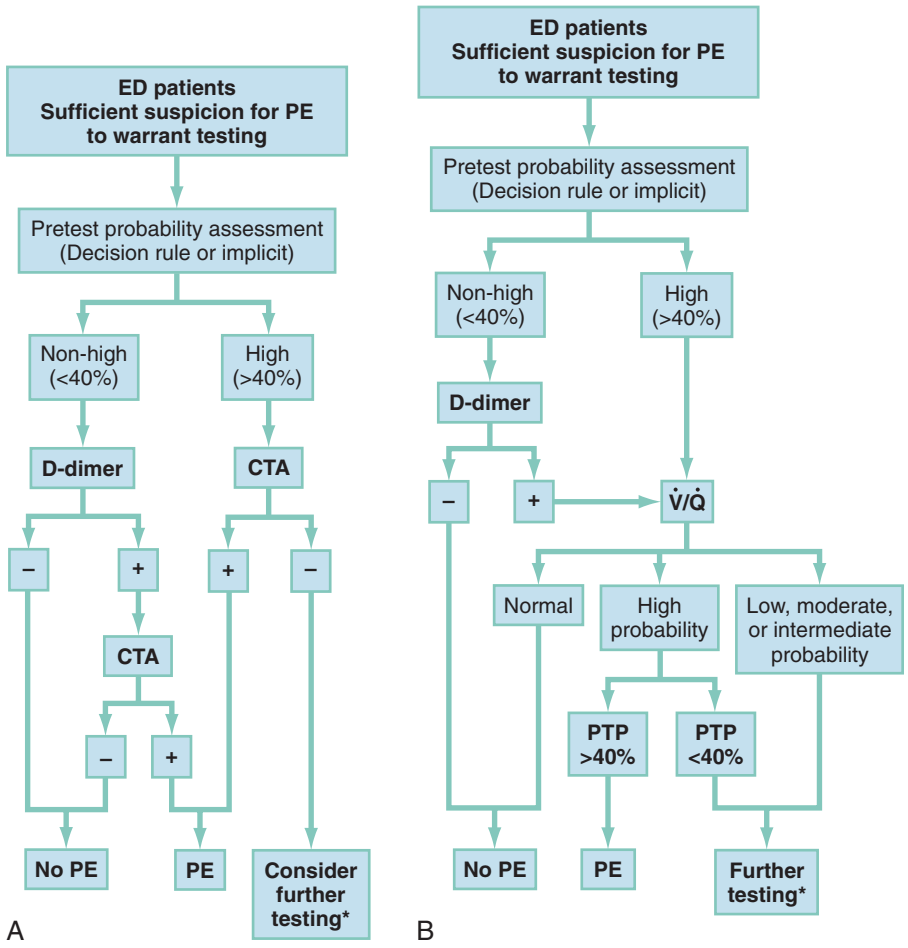


Figure 86-4. Suggested algorithms to evaluate for pulmonary embolism (PE) in the emergency department (ED). These algorithms include the use pretest probability (PTP), the enzyme-linked immunosorbent assay (ELISA) or immunoturbidometric quantitative D-dimer assay, and pulmonary vascular imaging (computed tomography angiography [CTA]). **A,** Algorithm incorporating contrast-enhanced CTA. A negative D-dimer is an immunoturbidimetric assay or ELISA that returns a concentration less than 500 FEU (ng)/mL. **B,** Algorithm incorporating ventilation-perfusion ($\dot{V}/\dot{Q}$) scanning. *May require patient admission. Additional testing: option 1: "crossover" to perform either $\dot{V}/\dot{Q}$ scanning or CT for algorithms **A** and **B;** option 2: perform lower extremity venous ultrasound, and if initial venous ultrasound is negative, repeat the lower extremity venous ultrasound in 1 week; option 3: perform formal pulmonary angiography.

Table 86-3 Prevalence of Pulmonary Embolism Stratified by Ventilation-Perfusion Scan Result and Pretest Probability Estimate

V̇/Q̇ SCAN RESULT	CLINICIAN ESTIMATE OF PRETEST PROBABILITY FOR PE			
	80–100%	20–79%	0–19%	ALL
High probability	28/29 (96%)	70/80 (88%)	5/9 (56%)	103/118 (87%)
Intermediate probability	27/41 (66%)	66/236 (28%)	11/68 (16%)	104/345 (30%)
Low probability	6/15 (40%)	30/191 (16%)	4/90 (4%)	40/296 (14%)
Near-normal/normal	0/5 (0%)	4/62 (6%)	1/61 (2%)	5/128 (4%)
Total	61/90 (68%)	170/569 (30%)	21/228 (9%)	252/887 (28%)

PE, pulmonary embolism; V̇/Q̇, ventilation-perfusion.
Adapted from the PIOPED Investigators: Value of the ventilation/perfusion scan in acute pulmonary embolism. JAMA 263:2753, 1990.

86-3).[49] This multicenter study showed that a high-probability V̇/Q̇ scan can be used to diagnose PE, and a normal V̇/Q̇ scan (i.e., no perfusion defect) excludes the diagnosis of PE with an acceptable degree of certainty. A moderate probability or indeterminate scan requires additional formal pulmonary angiography or a CTPA. Even in patients with a low PTP, a low-probability V̇/Q̇ scan usually indicates a need for additional testing, such as either CTPA or venous duplex ultrasonography of the legs. The latter should be repeated at least once, 2 to 7 days later, if negative at the initial presentation. In patients with a chest radiograph that shows airspace disease, the specificity of V̇/Q̇ scanning can be expected to decrease, and the relative diagnostic utility of CTPA can be expected to increase.

Most academic centers now employ CTPA as the primary method of evaluating for PE.[50] The PIOPED II study evaluated the test characteristics of CTPA for the diagnosis of PE in a prospective, multicenter study of 824 patients imaged primarily with four-row multidetector scanners.[51] CTPA images were deemed adequate for interpretation in 773 (94%), and the sensitivity in these patients was 83% (95% CI 76–92%) with a specificity of 96% (95% CI 93–97%). Among the 737 (89%) with adequate CTV images, isolated DVT was diagnosed in an additional 14 patients (2%), effectively increasing the overall sensitivity for VTE to 90% (95% CI 84–93%) with a similar specificity of 95% (95% CI 92–96%).

When CTPA fails to identify PE in a situation of high clinical suggestion, it is often worth the time to investigate issues of image acquisition quality that can affect the certainty of the radiologist's call on the presence or absence of PE. Good contrast enhancement of the pulmonary vasculature is probably the most important factor in determining the diagnostic quality of CTPA. Poor heart function complicates the timing of vascular opacification, but using bolus-timing software that is readily available on almost all modern CT scanners essentially should eliminate this factor. Obesity can compromise image quality and must be considered when determining the appropriate scanning parameters for each patient (i.e., milliampere-second [mAs], kilovoltage peak [kVp]). Motion artifact can severely degrade the quality of the images, as can severe intrinsic lung disease, such as stage 4 sarcoidosis or bulky carcinoma that can distort the vasculature and give false-positive appearances.[52] Technical aspects that seem associated with better accuracy of the interpretation include specialty training of the reader, review of images in cine mode on a picture-archiving and communication system (PACS), a greater number of detectors on the scanner, and thinner collimation of the x-ray beam. There is no quantitative method to fold these findings into the computation of post-test probability except to say that if the scan quality was good, this should inspire more confidence in the radiologist's interpretation. As with any imaging study, if CTPA quality was poor, and the results do not match the clinical picture, PE cannot be excluded or diagnosed with certainty, and more testing should be performed.

The importance of isolated subsegmental pulmonary embolus either missed or detected by CTPA can arise because of a radiologist's statement that "subsegmental clot cannot be excluded by CTPA." More recently, increased detection of isolated subsegmental filling defects occur with more thinly collimated images acquired with a higher number multidetector scanner. No firm evidence exists to guide these circumstances. When two radiologists independently evaluate CTPA, their agreement on the presence of isolated subsegmental filling defects is poor.[53,54] The same lack of agreement in subsegmental clots holds for formal pulmonary angiography.[55] Our opinion is that if the patient has no evidence of DVT, no signs of cardiopulmonary stress, and no ongoing major risk for thrombosis (e.g., active malignancy), isolated subsegmental findings or no findings together are a nonissue, and for either case, withholding anticoagulation would afford more benefit than harm. If a patient with negative CTPA has signs of pulmonary hypertension or hypoxemia without an apparent alternative cause, or has a known thrombophilia, further testing is advised. Subsequent testing after a negative CTPA is individualized by institution in consultation with radiology. Most commonly, if venous studies were not performed as part of the CTPA, duplex ultrasonography of both lower extremities should be undertaken. Positive sonographic evidence of DVT is considered confirmation of the presence of PE. A negative sonogram does not exclude the diagnosis, however, and should be repeated in 2 to 7 days.

CTPA can provide additional information to enhance its utility in the ED. First, without requiring any additional contrast injection, the legs can be scanned a few seconds later to provide a CTV, which can evaluate for DVT.[10] Whether CT protocols should routinely include CTV remains an area of controversy. CTPA often provides information about alternative processes that might explain the patient's symptoms (Box 86-3). Pneumonia is the most common alternative diagnosis found in ED patients.[56] In about 10% of ED patients evaluated for PE, CT as a single test could (1) show absence of PE; (2) provide evidence of alternative disease, which can be used with other evidence to reduce the probability of PE to a reasonably low level to stop the workup; and (3) facilitate treatment for the alternative disease.

Management

Anticoagulation

Anticoagulation therapy is initiated when there is a high-probability V̇/Q̇ scan, positive CTPA, or ultrasound evidence

Table 86-4 Predictors of Short-Term Complications from Pulmonary Embolism

PREDICTOR	CRITERIA	SENSITIVITY (%)*	SPECIFICITY (%)
Troponin I	>0.4 ng/mL or T > 0.04 ng/mL	60	85
Pulse oximetry	<95%, breathing room air	90	64
Brain natriuretic peptide	>90 pg/mL	85	75
Echocardiography	RV dilation or hypokinesis	86	39

*Sensitivity and specificity for the predication of circulatory shock requiring vasopressor treatment, need for intubation, or death during hospitalization.
RV, right ventricular.

BOX 86-3 Frequency of Non–Pulmonary Embolism Diagnoses Discovered on Computed Tomography

Pneumonia (6%)*
Unsuspected pericardial effusion (1%)
Mass suggesting new carcinoma (1%)
Aortic dissection (0.5%)
Pneumothorax (0.5%)

*Percentage of all 1025 emergency department patients who underwent computed tomography to evaluate for pulmonary embolism.

of DVT in a patient with a symptom or sign suggesting PE. Either unfractionated heparin (80 U/kg IV bolus, followed by 18 U/kg/hr IV infusion), fractionated heparin (e.g., enoxaparin, 1 mg/kg SC or IV every 12 hours), or the factor Xa inhibitor, fondaparinux (5–10 mg, depending on body mass) represents current standard treatment for most patients with PE. At present, no published evidence has proven the superiority of either form of heparin over the other. Both forms of heparin work equally well, and both are safe in the absence of contraindications to anticoagulation. Heparin provides several known benefits, including the reduction in formation of new clots (which can occur rapidly as clot volume increases exponentially with existing clot mass), and reduces the theoretical transient hypercoagulable effect of warfarin treatment, thought to be mediated by relative decrease in circulating protein C activity. Heparin also possesses anti-inflammatory properties that may help prevent pulmonary vasculitis associated with PE. As with DVT, administration of the first dose of warfarin in the ED can help shorten the time to therapeutic anticoagulation.

Heparin may be started before the results of imaging are known. In consideration of the risks and benefits of anticoagulation, empirical treatment seems to confer more benefit than harm when the PTP of PE exceeds 30%, the patient has no major contraindication to anticoagulation, and imaging would delay heparin initiation for greater than 24 hours.[57]

For a patient diagnosed with PE in the presence of a major contraindication to anticoagulation, such as a recent cerebral hemorrhage or large cerebral infarction, the appropriate consultant should be contacted for urgent placement of an inferior vena cava filter. If vena caval interruption cannot be performed within 12 hours, one option is to perform a baseline head CT scan, then start an unfractionated heparin infusion at 18 U/kg/hr (without a bolus) and admit the patient to the intensive care unit for close neurologic monitoring and frequent partial thromboplastin time determinations. The rationale for using unfractionated heparin is that it can be reversed more reliably (by discontinuing the heparin drip and administering protamine, 1 mg/kg IV) than fractionated heparin. One small case series of four patients suggests that inhaled nitric oxide might be helpful for patients with severe PE and an absolute contraindication to anticoagulation, but this treatment has not been subjected to rigorous study.[58]

Most patients with PE look and feel better the day after starting heparin anticoagulation, and more than half go on to a nearly full recovery of pre-PE health status. The in-hospital mortality rate of patients diagnosed with PE who remain hemodynamically stable while in the ED is about 10%. Another 10 to 20% complain of persistent dyspnea and exercise intolerance that permanently degrades their quality of life. Systolic hypotension (<90 mm Hg) represents a highly specific and moderately sensitive indicator of severe PE. In particular, persistent hypotension from PE increases the mortality rate dramatically.[20] In the absence of hypotension, several parameters available at the bedside can help with prognosis. A heart rate that is persistently above the systolic blood pressure indicates more severe clot, as does a pulse oximetry reading less than 95%.[19] Presence of prior congestive heart failure or advanced chronic obstructive pulmonary disease serves to magnify the severity of PE. Laboratory studies that portend a worse outcome include an elevated serum troponin measurement or an elevated brain natriuretic peptide or probrain natriuretic peptide concentration.[59-64] Echocardiography demonstrating right ventricular hypokinesis or dilatation also increases the probability of death from PE. Table 86-4 summarizes the diagnostic accuracy of these predictors for the outcome of in-hospital death, shock, or respiratory failure. Consideration of these criteria, in combination with the patient's hemodynamic status and comorbidities, may help guide the decision to place the patient in an ICU versus an intermediate or regular inpatient bed.

Thrombolytic Therapy

Thrombolytic therapy in PE is controversial. Administration of alteplase to patients with PE results in more rapid symptomatic improvement than standard antithrombotic therapy alone[65] and causes more rapid normalization of right ventricular function.[66] Alteplase also increases the risk of hemorrhage. It is not known how many patient lives would be saved, or definitively improved, by the addition of thrombolytic treatment to heparin therapy versus the number of patients who would experience a fatal or life-threatening bleeding event as a result of thrombolytic treatment.[67] On balance, the benefit-risk analysis suggests that fibrinolysis is of greatest value in the subset of patients with proven PE who are likely to die, develop circulatory shock, or progress to respiratory failure in the first week. Massive PE is defined by hypotension as evidenced by a systolic blood pressure less than 90 mm Hg for more than 15 minutes. In patients with preexisting hypertension, the threshold is adjusted to less than 100 mm Hg or a greater than 60 mm Hg reduction in the baseline systolic blood pressure. In the absence of contraindications, patients with proven massive PE probably benefit from fibrinolysis. It remains controversial if or when, based solely on clinical

Table 86-5 Food and Drug Administration–Approved Fibrinolytic Regimens for Acute Treatment of Pulmonary Embolism

Streptokinase	1 million U infused over 24 hr
Urokinase	1 million U bolus followed by 24-hr infusion at 300,000 U/hr
Alteplase	15-mg bolus followed by 2-hr infusion of 85 mg. Discontinue heparin during infusion.

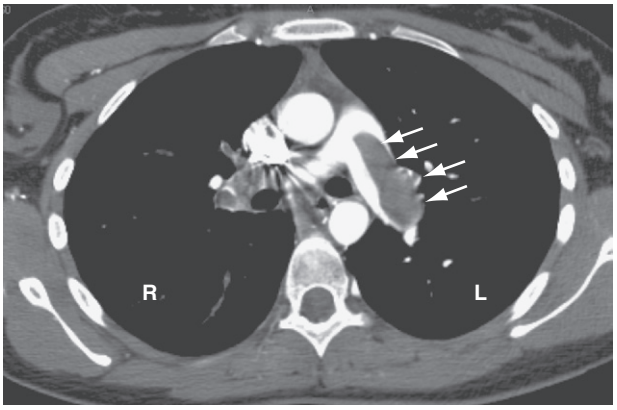


Figure 86-5. Massive pulmonary embolism on a contrast-enhanced computed tomography (CT) scan of the chest. This CT scan is at the level of the bifurcation of the main pulmonary artery. The left main branch of the pulmonary artery shows a massive filling defect (*arrows*). The patient was a young woman who recently began taking oral contraceptives who presented to the emergency department after passing out at work after a 1-week duration of dyspnea. The patient had cyanosis, hypoxemia, and worsened hemodynamic findings when supine but was normotensive when sitting upright. She was given anticoagulant therapy, had emergent surgical embolectomy, and survived with excellent outcome. Her DNA had factor V Leiden mutation, by polymerase chain reaction testing in both alleles.

suspicion of PE derived from information obtained at the bedside (i.e., empirical fibrinolysis in absence of pulmonary vascular imaging), to administer a fibrinolytic agent to a patient with profound shock. At the minimum, we recommend that fibrinolytics be used empirically only under the following circumstances: (1) the clinician can state that his or her clinical probability of PE exceeds 50%; (2) the patient is hemodynamically too unstable to leave the ED; and (3) a bedside cardiac ultrasound confirms a dilated, hypokinetic right ventricle. A subset of patients with submassive PE may benefit from fibrinolysis, including those with moderate to severe respiratory distress and hypoxia (oxygen saturation less than 95%) and those with echocardiographic evidence of right ventricular dysfunction. When echocardiography is unavailable in a timely manner, surrogate laboratory markers of right ventricular dysfunction may be useful, including an elevated troponin or a brain natriuretic peptide level greater than 90 pg/mL (see Table 86-4).[68]

Patients considered for fibrinolysis should be carefully screened for contraindications and counseled on the incremental increase in bleeding risk above that of anticoagulation alone. For the feared complication of symptomatic intracranial hemorrhage, the risk is approximately 2% with fibrinolysis, which represents a small, but important increase over the 1 to 1.5% rate associated with heparin anticoagulation alone. If possible, consultation with cardiology or cardiac surgery should be obtained before administering fibrinolytic therapy for patients with PE who are not in extremis. The Food and Drug Administration–approved regimens for thrombolysis are shown in Table 86-5.

Tenecteplase is a recombinant plasminogen-activating enzyme with several pharmacologic properties that may favor its use for fibrinolysis of acute PE, despite its lack of FDA approval for this indication. Tenecteplase differs from alteplase with a longer half-life, resistance to plasminogen activator inhibitor-1, and increased fibrin specificity, which results in less fibrinogenolysis and less coagulopathy.[69]

The clinical course of patients with obstructive PE can be unpredictable. Many patients with massive PE remain stable in the ED. Other patients "look fine" on arrival, but progressively deteriorate over hours as right ventricular function declines. Three percent of ED patients have no hypotension while in the ED, but experience cardiac arrest and die within 24 hours.[19] A patient can be stable and then hypotensive within minutes because of the effect of variable right ventricular outflow obstruction from a large clot perched in the main pulmonary artery (Fig. 86-5). Additional mechanisms of rapid instability include new embolization of clot material, release of mediators of pulmonary vasospasm, sudden brady-asystolic arrhythmias, or respiratory failure. Clues to oncoming cardiopulmonary decompensation include worsening respiratory distress and worsening hypoxemia, a rising shock index (the heart rate divided by the systolic blood pressure), systolic arterial blood pressure less than 90 mm Hg, and syncope or a seizure-like convulsive episode while in the ED. A particularly ominous finding is the evolution on ECG from a narrow-complex tachycardia to an incomplete right bundle branch block to a complete right bundle branch block (Fig. 86-6). This progression (or regression) is evidence of life-threatening pulmonary hypertension and incipient cardiac arrest.[33]

Clinical evidence of impending or actual respiratory failure indicates the need for prompt endotracheal intubation using standard rapid sequence intubation technique, preferably with either ketamine or etomidate for induction of anesthesia with neuromuscular blockade. Other induction agents that depress cardiac function or reduce preload may precipitate severe hypotension and as such they should be avoided or their dosage reduced. In the case of impending respiratory or cardiac arrest, fibrinolytic therapy should be strongly considered. For patients with known floating thrombi in the right heart or for patients with severe refractory hypotension, surgery is the most likely intervention to save the patient's life. Surgical embolectomy requires extracorporeal cardiopulmonary bypass and an experienced cardiothoracic surgeon. Surgery may be the best option for patients who have severe PE with a contraindication to fibrinolysis; however, extracorporeal perfusion requires intensive heparin anticoagulation, and the patient's mental status cannot be monitored during surgery—a key concern in patients with high risk of intracranial hemorrhage. Catheter thrombectomy also may be lifesaving, but requires that the patient be sent to the relatively uncontrolled environment of the interventional radiology suite.

PE can cause cardiac arrest. In the out-of-hospital setting, the arrest often appears to occur suddenly and unexpectedly. Most patients with incipiently fatal PE have overt respiratory distress, syncope or seizure-like activity, or a high heart rate relative to the systolic blood pressure before arrest. Compared with pure cardiac causes of arrest, a higher percentage of patients with arrest from PE have the initial arrest event witnessed, in particular by health care providers. First responders most commonly observe PEA as the initial cardiac arrest rhythm (>20 depolarizations per minute without palpable pulses). The mechanism for PEA seems to be pure right ventricular outflow obstruction complicated by impaired right ventricular contractility. Ultrasound performed during PEA

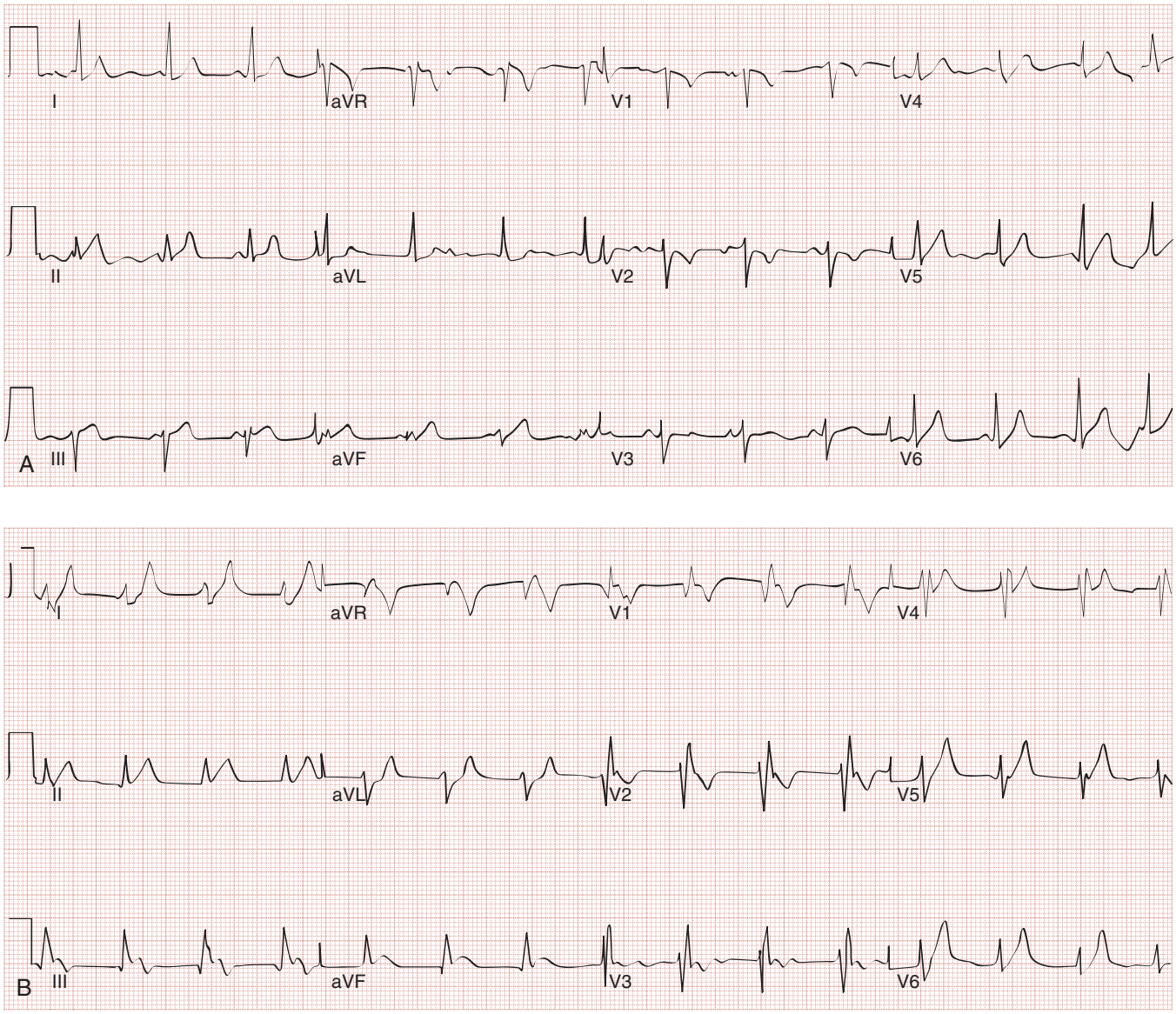


Figure 86-6. Serial electrocardiograms obtained 2 minutes apart show the progression from a narrow complex rhythm (**A**) to a right bundle branch block pattern (**B**) in a patient with massive bilateral pulmonary emboli. Shortly after the second tracing was obtained, the patient developed cardiovascular collapse refractory to vigorous resuscitation efforts.

arrest from PE usually shows weak cardiac contractions. The second most common rhythm after arrest from PE is asystole, or an agonal escape type rhythm with less than 20 complexes per minute. Mechanisms for brady-asystolic arrest include septal wall tension leading to ischemia or ischemic-equivalent effect on the atrioventricular node and infranodal conducting pathways.

Regardless of the initial rhythm, the development of pulselessness from PE imparts a mortality rate exceeding 70% in published studies. Numerous case reports have suggested heroic results from bolus administration of thrombolytic therapy to patients with cardiac arrest from PE. Notwithstanding these reports, the goal is to administer fibrinolytic therapy before cardiac arrest supervenes. The administration of fibrinolytic therapy does not absolutely preclude surgical intervention. Patients who have been treated with a fibrinolytic agent can undergo sternotomy or thoracotomy for embolectomy and survive without fatal hemorrhage. The decision to perform embolectomy ultimately resides with the cardiac surgeon.

Box 86-4 details questions that commonly arise regarding the diagnosis and treatment of PE in the ED.

BOX 86-4 UNIQUE QUESTIONS THAT COMMONLY ARISE IN THE ED

1. **I cannot get imaging at night. Is it reasonable to treat the patient with heparin until morning?** The short answer to this question is yes, if the patient has no contraindications. Many smaller hospitals routinely employ this method, using a single dose of enoxaparin.
2. **How do I manage the patient who is being treated for pulmonary embolism who returns to the ED for chest pain?** If the patient has a therapeutic international normalized ratio (1.5–2.5) and returns with symptoms only (e.g., chest pain, dyspnea) and without syncope, appears relatively comfortable, has normal vital signs, and has no new changes suggesting pulmonary hypertension on ECG (in particular, no S1Q3T3 pattern and no T wave inversion in leads V_1 through V_4), follow-up imaging is probably not needed. Other causes of chest pain (especially acute coronary syndrome) must be considered. In the absence of an identified alternative diagnosis, symptomatic care with an anti-inflammatory agent is safe and reasonable therapy for the return complaint of chest pain. Persistent dyspnea at rest raises more concerns of unresolved or recurrent thrombosis with secondary effects, including bronchospasm or, worse, pulmonary vascular hyperplasia with pulmonary hypertension. Repeat pulmonary vascular imaging may provide evidence of an unresolved or new clot. More importantly, a transthoracic echocardiogram can disclose evidence of persistent right ventricular dysfunction and pulmonary hypertension. Symptomatic patients with unresolved filling defects and pulmonary hypertension can progress to chronic thromboembolic pulmonary hypertension. To prevent this decline, patients who return to the ED with persistent rest dyspnea and have unresolved filling defects and pulmonary hypertension should be admitted or referred to a program that offers the option of pulmonary thrombectomy.
3. **How can I rule out pulmonary embolism in a pregnant patient without use of ionizing radiation?** One clinical conundrum is the fact the pregnancy is accompanied by both an increased risk of PE and a predictable elevation in D-dimer, even in the absence of PE.[70,71] Given that PE is the most common nontraumatic cause of death in pregnant women, clinicians are justified in adopting a liberal "rule-out PE" approach to all pregnant women with dyspnea.

   Pulmonary $\dot{V}/\dot{Q}$ scanning is safe in pregnancy and provides almost no risk to the fetus. A chest CT scan delivers about 250 mrad of energy, whereas the common threshold at which fetomaternal experts believe fetal teratogenicity becomes a concern is about 5 rad. The mother's abdomen can be shielded, but the fetus will still receive a small fraction of the 250 mrad. There is a rapidly growing body of literature that suggests that exposure of the young brain to even small amounts of radiation can produce subtle cognitive deficits later in life, and at present the long-term consequences of CT scanning of pregnant patients are unknown. It seems logical to try to rule out PE with the D-dimer in pregnant patients; if D-dimer is negative in a patient believed to be at low pretest probability, this excludes the diagnosis. However, coagulation systems are hyperactive in pregnancy, elevating the circulating D-dimer concentration. The D-dimer concentration increases linearly with duration of normal pregnancy, and about 75% of all pregnant patients evaluated for PE have a D-dimer concentration greater than the abnormal cutoff of 500 ng/mL.[72] As an additional margin of safety, a negative venous ultrasound of the lower extremities excludes DVT and helps reduce the probability of PE by about half. $\dot{V}/\dot{Q}$ scanning, if normal, excludes the diagnosis. A high-probability $\dot{V}/\dot{Q}$ scan establishes the diagnosis, and heparin (which does not cross the placental barrier) can be initiated. If neither normal nor high probability, the $\dot{V}/\dot{Q}$ scan is nondiagnostic, and further imaging (perhaps beginning with venous duplex ultrasound of the legs) is indicated.
4. **How do I evaluate the patient with possible pulmonary embolism who is too obese to fit in a CT or $\dot{V}/\dot{Q}$ scanner?** Each CT scanner has a maximum patient weight that it will accommodate. When a patient's weight exceeds the scanner limit, and a larger capacity scanner is not available, we recommend duplex venous ultrasonography of the lower extremities to rule out DVT. Although often technically suboptimal in a massively obese patient, venous ultrasound occasionally provides positive evidence of DVT, ostensibly clinching the diagnosis. Another option is to anticoagulate empirically based on a moderate-to-high pretest probability and a D-dimer concentration that exceeds 1000 ng/mL. The adequate regimen for anticoagulation is uncertain, but many experts recommend subcutaneous enoxaparin, 1 mg/kg of actual body weight up to a maximum of 200 μ/kg.

CT, computed tomography; ECG, electrocardiogram; ED, emergency department; PE, pulmonary embolism; $\dot{V}/\dot{Q}$, ventilation-perfusion ratio.

KEY CONCEPTS

- Deep vein thrombosis often presents as a nonspecific crampy sensation in the upper or lower extremity without obvious swelling.
- The absence of a "sudden onset" of symptoms is of no value in excluding PE as the cause of the patient's presentation.
- An ELISA or immunoturbidimetric D-dimer concentration <500 ng/mL can rule out PE or DVT in non-high-risk patients.
- A patient with a PTP <2% should not be tested for PE.
- A patient with PE and a pulse oximetry reading <95% has an increased risk for a bad outcome.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 87

Esophagus, Stomach, and Duodenum

Mark J. Lowell

ESOPHAGEAL OBSTRUCTION

Perspective

Ingestion of foreign objects and esophageal food bolus impactions occur commonly. Although most pass spontaneously, approximately 10 to 20% require a nonoperative intervention and less than 1% require surgical removal. Death as a result of foreign body ingestion or impaction is rare. Most foreign body ingestions occur in children between the ages of 6 months and 6 years, with coins being the most commonly impacted objects. In adults, foreign body ingestion tends to occur in prisoners, alcoholics, psychiatric patients, and mentally impaired patients; many have a tendency for repetitive ingestion. Most adult impactions are due to pieces of food, particularly meat and bones. Patients with preexisting esophageal abnormalities are at greater risk for foreign body impaction. Denture wearers are also at increased risk because of impaired oral sensation.

Principles of Disease

The adult esophagus is approximately 25 to 30 cm in length. Superiorly, it begins in the hypopharynx as a transverse slit posterior to the larynx and approximately at the level of the cricoid cartilage. On either side of this cephalad slit are the piriform recesses, which are blind pouches that may occasionally harbor a foreign body. The esophagus is distensible; an adult can usually pass an object up to 20 mm in size without difficulty. Throughout its course, the esophagus has four natural areas of narrowing that may cause impaction of a foreign body: at the cricopharyngeus muscle (the upper esophageal sphincter), the aortic arch, the left-mainstem bronchus, and the lower esophageal sphincter (LES) at the diaphragmatic hiatus. Most impactions occur in the mid to distal third of the esophagus. Large, proximal impactions can impinge on the trachea, leading to airway compromise presenting as choking, stridor, or cough.

The esophagus comprises two main bands of muscle: an inner circular layer and an outer longitudinal layer. The resting tone of these muscles causes the inner epithelium to fold in on itself, effectively obliterating the lumen. Elastic fibers enable the esophageal lumen to expand and allow passage of a food bolus. The upper one third of the esophagus, including the cricopharyngeus muscle, contains striated muscle to allow the voluntary initiation of swallowing. The middle portion of the esophagus is a mixture of skeletal and smooth muscle, and the distal third is composed only of smooth muscle.

Although it is relatively fixed at its origin, the esophagus becomes mobile as it traverses the mediastinum. Thus, it can be easily displaced by adjacent structures such as an enlarged left atrium or ventricle, a goiter, or a mediastinal tumor. Displacement of the esophagus may alter its shape enough to impede the passage of a food bolus or foreign body.

Clinical Features

Patients with an esophageal obstruction usually present with dysphagia (difficulty swallowing), odynophagia (painful swallowing), or chest pain. The obstruction may be partial or complete. The patient with complete obstruction is unable to swallow, is often drooling, and may be violently retching in an attempt to regurgitate the obstructing bolus. The patient may complain of pain from the neck to the substernal and epigastric area, although the perceived level of obstruction may not correlate with the actual site of the obstruction. Patients should be evaluated for the presence of stridor or signs of perforation or peritonitis.

A proximal obstruction may arise as a "café coronary," characterized by sudden cyanosis and collapse caused by food (usually an unchewed piece of meat) lodging in the upper esophagus or oropharynx leading to airway obstruction. Similarly, "steakhouse syndrome" results when a large piece of food, usually improperly chewed, is swallowed and causes esophageal obstruction in the distal esophagus. The obstruction may be transient with spontaneous passage of the bolus and may be complete or partial. Intense discomfort develops shortly after swallowing a large piece of meat, and the patient is usually unable to swallow anything else. Ingestion of alcohol and absence of teeth are predisposing factors. Although obstruction may occur in a patient with a normal esophagus, abnormalities such as carcinoma, peptic stricture, or a Schatzki ring are identified in almost 90% of patients with an esophageal obstruction. Schatzki's ring is a fibrous, diaphragm-like stricture near the gastroesophageal junction present in up to 15% of the population.

Aside from naturally occurring areas of anatomic narrowing, there are other pathologic causes of esophageal stenosis that may lead to symptoms of obstruction. Intrinsic causes of luminal narrowing include carcinoma and webs. An esophageal web is a thin structure composed of mucosa and submucosa. Although webs can occur in isolation, they are also seen in the Plummer-Vinson syndrome, which is characterized by anterior webs, dysphagia, iron deficiency anemia, cheilosis, spooning

of the nails, glossitis, and thin friable mucosa in the mouth, pharynx, and upper esophagus. Most patients with this syndrome are women between 30 and 50 years of age. Patients usually present with dysphagia that is initially intermittent and worse with solids. If untreated, it may progress and become constant.

Extrinsic compression of the esophagus can occur in a variety of conditions. In the neck, thyroid enlargement from goiter or carcinoma may cause dysphagia. Symptoms may also be seen with a pharyngoesophageal or Zenker's diverticulum, a progressive outpouching of the pharyngeal mucosa as a result of increased pressure generated by failure of proper relaxation of the cricopharyngeus muscle. Noisy deglutition, dysphagia, foul breath, and a palpable compressible mass in the neck may be present. Laryngotracheal aspiration when the patient is supine results from the emptying of contents from the diverticulum.

Congenital anomalies of the aortic arch may cause dysphagia in both children and adults. In children, respiratory symptoms are also usually present and commonly predominate. In adults, an anomalous right subclavian artery is the most common vascular cause for dysphagia, which often does not become symptomatic until the fourth decade of life. The most common symptoms in adults are dyspnea on exertion and dysphagia. Vascular compression of the esophagus with dysphagia may also occur with aneurysms of the aortic arch and great vessels. Bronchogenic carcinoma can cause dysphagia by direct involvement of the esophagus or by compression with nodes.

Esophageal foreign bodies can occur atypically in small children or mentally impaired individuals. They may present with choking, refusing to eat, vomiting, blood-stained secretions, or respiratory distress.

Diagnostic Strategies

Plain radiographs of the neck should be obtained if a foreign body in the throat is suggested. Chest or abdominal radiographs may provide additional information. Coins are easily visualized. Disk batteries have a characteristic radiographic "double-density" appearance. Small bones or radiopaque objects may occasionally be visualized. Air in the tissues may be present if perforation has occurred. However, failure to demonstrate a foreign body on radiographs does not rule out its presence. Traditionally, contrast studies have been performed next (see later discussion); however, computed tomography (CT) has been used successfully to identify foreign bodies, particularly chicken and fish bones, and may be more sensitive than plain radiographs or barium examinations.[1,2] Other nonorganic objects (e.g., Lego pieces) have also been successfully visualized with CT.[3] CT scans have the additional value of visualizing changes in the surrounding tissues associated with perforation.

Hand-held metal detectors have been reported to be useful screening devices for locating metallic foreign bodies in children. They may also be of use in finding radiolucent metallic foreign bodies such as aluminum pull tabs. They do not, however, pinpoint the object.[4]

If available, endoscopy is helpful in diagnosing and treating esophageal foreign bodies. When endoscopy is unavailable, a radiographic contrast study may help in diagnosis. However, in addition to the risk of aspiration, the presence of contrast agents may make endoscopy more difficult. It is therefore advisable to consult with the endoscopist before performing any study in a patient with a suggested esophageal foreign body. If an esophageal perforation is possible a water-soluble contrast agent (e.g., diatrizoate meglumine [Gastrografin]) should be used first because barium induces an inflammatory response in tissues. Caution should be used, however, since Gastrografin can cause pneumonitis if aspirated. Failure to visualize a clinically suggested perforation warrants a repeated examination using barium as the contrast agent. Because barium may obscure subsequent endoscopic visualization, a minimal amount of thin barium should be used. The use of a swallowed barium-soaked cotton ball to identify the site of obstruction is not recommended because it adds an additional foreign body that then needs to be removed. Plain radiographs followed by contrast studies have false-negative rates of less than 1% and false-positive rates of less than 20%.[5] Because of the risk of complications, a patient who may have ingested a sharp object should undergo evaluation up to and including endoscopy.

Differential Considerations

Esophageal foreign bodies must be distinguished from foreign bodies in the airway. This distinction can be especially difficult in small children. Radiographically, esophageal foreign bodies usually lie in the frontal plain and are best visualized in anteroposterior views. Tracheal foreign bodies tend to lie sagittally.

Patients with esophageal obstruction may present with retrosternal pain that can appear similar to that of an acute ischemic cardiac syndrome. The presence of odynophagia suggests an underlying mucosal lesion.

Management

Flexible endoscopy by an experienced endoscopist is the procedure of choice for removal of esophageal foreign bodies, as it is effective and relatively safe, with a complication rate of 8%.[6] A recent retrospective study demonstrated that bougienage was a successful and safe method for coin removal in selected patients.[7]

Upper Esophagus

Oropharyngeal foreign bodies can usually be removed with a Kelly clamp or McGill forceps under direct visualization. Smooth upper esophageal foreign bodies can often be removed with a Foley catheter. This procedure requires an experienced technician, a cooperative patient, and fluoroscopic guidance. The patient is placed in a prone position, and the catheter is passed into the esophagus past the point of the foreign body impaction. The balloon is then inflated and the catheter withdrawn, pulling the foreign body with it. Controversy exists regarding the safety of this technique because there is no direct control of the foreign body.[8-10] Prophylactic endotracheal intubation may be warranted to prevent the foreign body from entering the airway. When these maneuvers fail to dislodge the esophageal foreign body, consultation with a qualified endoscopist is indicated.

Lower Esophagus

Lower esophageal obstruction is usually the result of an impacted food bolus and can often be treated effectively in the emergency department (ED). Administration of 1 mg of glucagon intravenously (up to a total of 2 mg) may cause enough relaxation of the esophageal smooth muscle to allow passage of the bolus in approximately 50% of patients. Because glucagon affects smooth muscle only, it is only effective for impactions in the lower esophagus. Side effects of glucagon include vomiting, nausea, dizziness, and flushing. Glucagon should not be used in patients with sharp-edged, potentially

damaging foreign bodies or in patients with insulinoma, pheochromocytoma, or Zollinger-Ellison syndrome.[11]

Effervescent agents are sometimes effective in accelerating the passage of an obstructing food bolus. Although the mechanism of action is unclear, it is hypothesized that the carbon dioxide released from bubbles escaping the fluid acts to disrupt the impacted food bolus and to distend the distal esophagus. The administration of carbonated beverages (including soft drinks) results in the passage of the obstructing food bolus in 60 to 80% of patients treated.[12,13] Studies combining the use of glucagon and an effervescent agent show rapid relief of symptoms in 65 to 75% of patients.[14,15] It has been recommended that effervescent agents be avoided in cases of complete obstruction and cases in which an obstruction has been present for over 24 hours because of the theoretical potential of inducing perforation of a possibly ischemic distal esophagus. The use of meat tenderizer (papain) to soften a food bolus is not recommended. Although intact mucosa is resistant to papain's effects, an inflamed mucosa becomes much more inflamed when exposed to this proteolytic enzyme, and esophageal digestion or perforation may occur.

Patients with sharp-edged, distal foreign bodies, those who have contraindications to use of the aforementioned agents, and those who do not respond to treatment should be evaluated with endoscopy. It is unclear whether CT or contrast radiographic studies performed to document the presence of obstruction are of any benefit in symptomatic patients.

Endoscopy should be performed immediately for patients experiencing significant distress and for children with impaction of an alkaline button battery. These batteries contain concentrated sodium or potassium hydroxide in addition to metals such as zinc, lithium, and mercury. Leakage of any of these can lead to systemic toxicity. Larger batteries have a greater risk of impaction and leakage. Batteries that pass into the stomach should be followed radiographically and clinically to ensure passage. Assistance with the management of a patient with button battery ingestion can be obtained through the National Button Battery Ingestion Hotline at (202) 625-3333 or at www.poison.org/prevent/battery.asp.

Urgent intervention is also indicated for sharp objects, disk batteries, coins in the proximal esophagus, and impactions that impair the handling of secretions. It is unclear whether patients with mild to moderate symptoms of esophageal obstruction from a suspected food bolus require immediate endoscopy. In such cases, some experts believe that emergent intervention is unnecessary if the patient is still able to handle secretions because the bolus often passes on its own. Others believe that the softened bolus makes endoscopic removal more difficult and predisposes to complications. Any object remaining in the esophagus for more than 24 hours carries a higher risk of complications, including perforation, aortoenteric fistula, tracheoesophageal fistula, or abscess. These complications may occur up to years after the ingestion. Most experts advocate follow-up endoscopic evaluation in all cases after an esophageal obstruction to rule out underlying pathologic conditions.

Stomach

Certain foreign bodies that pass into the stomach still require endoscopic retrieval. Objects longer than 5 cm or wider than 2.5 cm in diameter (e.g., toothbrushes, spoons) rarely pass the stomach. All sharp and pointed foreign bodies (e.g., toothpicks, bones) should be removed before they pass into the stomach because 15 to 35% may cause intestinal perforation. Smaller objects that pass into the stomach can be followed with stool inspections and with serial radiographs if necessary to confirm passage. Surgical removal should be considered for objects that remain in the stomach for more than 3 to 4 weeks or that remain in the same intestinal location for more than 1 week.[16]

ESOPHAGEAL PERFORATION

Perspective

Esophageal perforation is a potentially life-threatening condition that must be identified and treated early to minimize morbidity and mortality. Although first reported by Boerhaave in the early 1700s as a result of forceful vomiting, it can also result from any Valsalva-like maneuver, including childbirth, cough, or heavy lifting. With its increased use over the past two decades, endoscopy has become the most common cause of esophageal perforation. Spontaneous perforation accounts for a minority of cases. Perforation has also been reported as a complication of both nasogastric tube placement and endotracheal intubation, including the use of the esophagotracheal Combitube.[17,18] Other causes of perforation include foreign body ingestion, caustic substance ingestion, severe esophagitis, carcinoma, and direct injury related to blunt or penetrating trauma.

Principles of Disease

More than 90% of spontaneous esophageal ruptures occur in the distal esophagus. In contrast, rupture resulting from blunt trauma to the neck or thorax usually occurs in the proximal and middle third of the esophagus. Most iatrogenic injuries occur at the pharyngoesophageal junction because the wall in this area is thin and there is no serosal layer to reinforce it, and force is frequently used to past the tube beyond the level of the cricopharyngeus. Another site of frequent iatrogenic injury is the esophagogastric junction. In this area, the esophagus curves anteriorly and to the left as it enters the abdomen, and an endoscope has a greater likelihood of perforating the posterior wall. This usually occurs during therapeutic dilatation for strictures or achalasia. Other factors predisposing to iatrogenic perforation include anterior cervical osteophytes, Zenker's diverticulum, esophageal strictures, and malignancies.

Perforation has been reported as a complication of most endoscopic procedures, including transesophageal echocardiography, sclerotherapy, or placement of a Sengstaken-Blakemore tube. When a perforation occurs, saliva and gastric contents can enter the mediastinum. Rapid spread of an infectious or inflammatory response to the surrounding tissues and organs occurs because of the thinness of the esophageal wall. Changes in intrathoracic pressure during respiration draw contaminants deeper into the mediastinum. The presence of gastric enzymes and other foreign material in the mediastinum induces an intense inflammatory response that may result in enough fluid buildup to displace adjacent structures.

Clinical Features

Clinical presentations vary and can depend on the cause, location, size, degree of contamination, and site of injury.[19] Signs and symptoms can therefore be vague and nonspecific. Patients with an upper esophageal perforation usually present with neck or chest pain, dysphagia, respiratory distress, and fever. Odynophagia, nausea, vomiting, hoarseness, or aphonia may also result.

Patients with perforation of the lower esophagus may present with abdominal pain, pneumothorax, hydropneumothorax, and pneumomediastinum. The pain often radiates into the back, to the left side of the chest, and to the left or both shoul-

ders.[20] Most patients have mediastinal or cervical emphysema, which may be noted by palpation or by a "crunching" sound heard during auscultation (Hamman's sign). Abdominal examination may reveal epigastric or generalized abdominal tenderness, often with guarding and involuntary rigidity. Patients with severe mediastinitis may present in fulminant shock.

Pain, fever, dyspnea, or crepitus following esophageal instrumentation should be considered an indication of perforation until proved otherwise. Symptoms related to iatrogenic perforation may not appear until several hours after the procedure.

Diagnostic Strategies

Radiographic studies are used to establish the diagnosis of an esophageal perforation. A chest and an upright abdominal radiograph are usually obtained first; soft-tissue neck radiographs should be considered if a proximal perforation is suggested. Radiographic abnormalities may be detected in up to 90% of patients with esophageal perforation and include subcutaneous emphysema, pneumomediastinum, mediastinal widening, pleural effusion, or pulmonary infiltrate.[21] Radiographic changes may not be present in the first few hours after the perforation.

Patients with possible perforation should have contrast radiographic studies performed. Controversy exists regarding the contrast agent of choice. Barium sulfate is superior in identifying small perforations; however, it may incite an inflammatory response in tissues. For this reason, some experts advocate the use of water-soluble agents (e.g., Gastrografin). However, the water-soluble agents are less dense and may not demonstrate the abnormality. Additionally, pneumonitis may result if these agents are aspirated. A prudent approach would be to attempt the study using a water-soluble agent first in patients who are not at risk for aspiration. If a clinically suggested perforation is not identified, the examination should be repeated using barium.

CT of the chest may be considered if a contrast study does not demonstrate a clinically suggested perforation. It can also be used in patients who cannot complete an esophagram. Findings such as mediastinal air, extraluminal contrast material, or fluid collections or abscesses adjacent to the esophagus confirm a perforation. These can be found after the initial perforation has healed. CT also allows evaluation of other adjacent areas that may suggest an alternative diagnosis. Endoscopy may be useful, especially in cases of trauma; however, small perforations may be difficult or impossible to visualize. Laboratory studies are not usually helpful soon after a perforation, although an elevated white blood count may be noted.

Differential Considerations

Misdiagnosis occurs in more than half of patients with esophageal perforation or rupture because the differential diagnosis includes the numerous causes of chest and abdominal pain, including pulmonary embolism, acute myocardial infarction, aortic dissection, perforated ulcer, pneumothorax, lung abscess, pericarditis, or pancreatitis. Esophageal perforations must be diagnosed as soon as possible because the morbidity and mortality associated with unrecognized perforations increases with time.

Management

Certain patients with esophageal perforation require rapid treatment. These include patients with Boerhaave's syndrome; clinically unstable patients; and those with perforations that contaminate the mediastinum or pleura, intra-abdominal perforations, and perforations with an associated pneumothorax.[22] Broad-spectrum intravenous (IV) antibiotics should be initiated early. The combination of a second-generation cephalosporin and an aminoglycoside usually provides adequate coverage. Patients should be kept with nothing by mouth (NPO), and a nasogastric tube should be considered to eliminate oral and gastric secretions. Early surgical consultation is warranted.

There is growing evidence that some iatrogenic perforations in certain patients at low risk can be managed conservatively with close observation. These include clinically stable patients, (minimal symptoms and fever with no clinical signs of shock), those whose perforation is contained, and those who present a long time after their procedure and have demonstrated no ill effects. They should be kept NPO and treated with broad-spectrum antibiotics and parenteral nutrition. These patients require diligent observation and assessment for failure of nonoperative therapy. Although not yet widely accepted, there is growing evidence for a role for endoscopic repair in selected patients.[23]

ESOPHAGITIS

Perspective

Esophagitis is defined as inflammation of the esophagus. The most common cause of esophagitis is gastroesophageal reflux disease (GERD). Other important causes include infectious esophagitis, pill esophagitis, and injuries from the effects of caustic ingestion, radiation, or sclerotherapy. Additionally, eosinophilic esophagitis, an new disease entity, is being diagnosed with increasing frequency.

Principles of Disease

Infectious Esophagitis

Esophageal infections in the immunocompetent host are relatively rare. If they do occur in healthy patients, there is usually an underlying esophageal abnormality or local area of immune compromise, as might occur with the use of inhaled steroids. Iatrogenic alterations in host defenses through the use of immunosuppressive agents, potent chemotherapeutic agents, and broad-spectrum antibiotics can predispose an individual to the development of esophageal infection The spread of the human immunodeficiency virus (HIV) has also led to an increase in esophageal infections, although the epidemiology has been changing as more effective antiretroviral agents have become available. In addition to iatrogenic immunosuppression, diseases that weaken immunologic defenses in otherwise normal hosts can predispose the esophagus to infections. These conditions include diabetes mellitus, alcoholism, underlying malignancy, use of corticosteroids, and advanced age. Changes that occur in the mucosal barrier of the esophagus as a result of these conditions lead to an increased susceptibility to infection. The *Candida* species (primarily *Candida albicans*) are the most common esophageal pathogens.

As empirical antifungal prophylaxis in immunosuppressive states has become more common, viral esophagitis has become more prominent. Herpes simplex 1 and cytomegalovirus are the most common viral pathogens. Human papillomavirus has been implicated as well. Bacteria, mycobacteria, other fungi, and parasitic organisms such as *Trypanosoma cruzi*, *Cryptosporidium*, and *Pneumocystis* are uncommon causes of infectious esophagitis and are usually diagnosed by culture or biopsy.

Pill Esophagitis

Pill esophagitis is estimated to occur in approximately 10,000 people per year in the United States.[24] However, because most cases are unrecognized and therefore unreported, the true incidence is unknown. The condition results when a pill or capsule fails to pass into the stomach and remains in contact with the esophageal mucosa for a prolonged period. The contents can become exposed, resulting in esophageal inflammation and injury. Pill esophagitis has been reported in all age groups. Predisposing factors include advanced age, decreased esophageal motility, and extrinsic compression. Large pills are more likely to be retained, as are those coated with gelatin. Pills can stick to a normal esophagus, especially when taken without water or while in the supine position. Any area of the esophagus can be affected, although sites of natural compression may be more susceptible. Sustained-release compounds may be more damaging than standard preparations. Injury can range from minor irritation to frank ulceration, hemorrhage, and ultimately stricture formation. Some of the more common offending medications include antibiotics (especially the tetracycline family) and antivirals, aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs), potassium chloride, quinidine, ferrous sulfate, alprenolol, alendronate, and pamidronate.

Eosinophilic Esophagitis

Eosinophilic esophagitis was first described in 1978 and is defined by the presence of eosinophils within the esophageal mucosa or deeper tissues. Initially thought to be a disease of children, it is being diagnosed in adults with increasing frequency. Although usually seen in patients with GERD, it has been identified as a cause of heartburn or dysphagia that is unresponsive to standard GERD treatment. The cause is unknown, although there is an association with allergies, especially in the younger age group.[25]

Caustic and Radiation-Induced Esophagitis

Esophagitis from caustic substance ingestion occurs most commonly in children, although adults may ingest a caustic substance in a suicide attempt. Strongly acidic or alkaline substances are the offending agents. The degree of injury depends on the concentration of the substance, the volume ingested, and the time in contact with tissue. Strong acids produce coagulation necrosis, which results in eschar formation that usually limits the damage. In contrast, alkali produces liquefaction necrosis, which continues to cause injury as long as the substance or its active breakdown products are in contact with tissue.

Patients undergoing radiation treatment for underlying malignancy may develop esophagitis. The degree of injury is related to the total dosage of radiation received. The mucosa becomes inflamed and friable. Agents used during sclerotherapy can also cause esophagitis.

Clinical Features

Esophagitis, regardless of cause, most commonly arises with dysphagia or odynophagia. Chest pain is frequently present and esophageal bleeding, ranging from localized oozing as a result of inflammation to frank hemorrhage, can occur. Ulceration and perforation can result in mediastinitis.

Infectious Esophagitis

Most commonly, infectious esophagitis causes severe odynophagia. Dysphagia of both solids and liquids may be present. Pain may be so severe that the patient refuses to eat or drink. Chest pain may also be present and may be described as acute in onset, constant, and not affected by antacid therapy. Heartburn (a burning sensation that begins in the subxiphoid area and radiates toward the neck) and nausea may be presenting symptoms. Some immunocompromised patients may have fever or bleeding without dysphagia or odynophagia.

Pill Esophagitis

Patients with pill esophagitis present with odynophagia. Most patients have no prior history of esophageal disease and present with sudden onset of pain worsened by swallowing. Dysphagia may be present. Although some patients may complain that a pill has become "stuck," the history of pill ingestion may be difficult to obtain because symptoms may begin hours after the offending pill is taken. Atypical presentations include a burning type of pain suggesting GERD as the cause.

Eosinophilic Esophagitis

Patients usually present with dysphagia, food impaction, or heartburn. Esophageal dysmotility may also result. The diagnosis is made by biopsy during endoscopy.

Caustic and Radiation-Induced Esophagitis

Patients with caustic injuries may present with pain in the mouth, chest, or epigastrium. Dysphagia and vomiting may be present. Patients may be drooling. Airway compromise may be present because of direct tissue injury or resulting edema. Later, perforation may occur, and strictures are a common long-term complication. Radiation-induced esophagitis usually causes odynophagia and dysphagia. Strictures may ultimately develop.

Diagnostic Strategies

Endoscopy is the best method of diagnosing both pill-induced and infectious esophagitis. With infectious esophagitis, direct visualization may reveal characteristic signs of infection, such as white plaques of *Candida* or herpetic vesicles. Definitive diagnosis can be made through brushings and biopsies. Radiographic studies are usually not helpful because the findings are nonspecific. A strong clinical suggestion is necessary to diagnose pill esophagitis. The other causes of esophagitis are usually clinically apparent.

Differential Considerations

Other causes of esophageal pain include GERD, esophageal motility disorder, foreign body, and perforation. Chest pain may also be a component, and therefore an acute coronary syndrome must be considered. Esophageal pain is more likely to be positional and related to swallowing.

Management

Infectious Esophagitis

For infectious esophagitis, therapy should be directed at the causative organism. Patients with normal immune systems and mild cases of candidal esophagitis can be treated with clotrimazole troches (10 mg dissolved in the mouth five times a day for 1 week) or nystatin (1–3 million units PO four to five times per day for 2 weeks). Some of the newer antifungal agents, such as fluconazole (200 mg PO daily for 3–4 weeks), ketocon-

azole (300–400 mg PO daily for 3–4 weeks), or itraconazole (100–200 mg PO daily for 3–4 weeks), may be used for more advanced infections in immunocompromised patients. They may also be used for a shorter duration in patients with less severe infections.

Initial treatment for herpes simplex esophagitis includes antivirals, such as acyclovir (400 mg PO five times per day for 7–14 days or 5–10 mg/kg IV every 8 hours for 7–14 days), famciclovir (500 mg PO three times a day for 7–14 days), or valacyclovir (500 mg PO twice a day for 7–14 days). For cytomegalovirus, initial treatment can begin with ganciclovir (5 mg/kg IV every 12 hours for 2–3 weeks) or foscarnet (60 mg/kg IV every 8 hours or 90 mg/kg IV every 12 hours for 2–3 weeks).[26]

If the causative organism cannot be adequately identified or if the patient is severely debilitated, admission to the hospital may be required. Patients discharged from the ED should receive appropriate follow-up with the relevant department (e.g., gastroenterology, infectious disease). In addition to therapy directed at the infecting organism, treatment with antacids, topical anesthetics, or sucralfate may provide symptomatic relief.

Pill Esophagitis

If a patient with suggested pill esophagitis has persistent symptoms, endoscopy may be necessary. It also helps to determine alternative causes. No data exist supporting any specific treatment, although, intuitively, antacid medication may prevent further erosion of damaged mucosa. Symptoms may take up to 6 weeks to resolve.

The best treatment for pill esophagitis is prevention. Patients should be instructed to drink at least 4 ounces of liquid with any pill. All medications should be taken when the patient is in an upright position, and the patient should remain upright for several minutes after medication ingestion. Patients with underlying esophageal abnormalities or those who are bedridden should avoid the use of pills whenever practical.

Eosinophilic Esophagitis

These patients usually present after standard antireflux measures have failed or if they develop a food impaction. The treating physician should consider the possibility of food impaction, ensure that appropriate antacid therapy is employed, and refer the patient to a gastroenterologist for further treatment. Although consensus has not yet been reached regarding an optimal treatment regimen, success has been reported with the use of topical (e.g., swallowed) corticosteroids.

Caustic and Radiation-Induced Esophagitis

Management of caustic injuries includes evaluation and management of possible airway injury, followed by assessment of the extent of esophageal involvement. Although the use of mild diluents like water or milk to limit the extent of chemical injury has been advocated by some authors, others warn against the possibility of inducing emesis, which reexposes the esophagus to the caustic substance. In general, it is probably best to avoid having patients ingest anything by mouth while undergoing evaluation. Likewise, gastric lavage and the administration of charcoal are not indicated. Symptomatic patients should be admitted to a monitored setting for observation, further evaluation with endoscopy, and treatment of complications, such as perforation. Asymptomatic patients who give a reliable history of a low-volume, accidental ingestion of a low concentration of an acidic or alkaline substance can be discharged after a period of observation and followed as outpatients.

Treatment of radiation esophagitis is supportive. Patients who cannot eat or drink because of radiation injury to the esophagus should be admitted for IV fluid therapy.

GASTROESOPHAGEAL REFLUX DISEASE

Perspective

Asymptomatic reflux of gastric contents from the stomach into the esophagus occurs in most people several times a day as a normal physiologic phenomenon. GERD occurs when reflux becomes symptomatic or causes histopathologic alterations in the upper gastrointestinal (GI) or respiratory tracts. In the United States, symptomatic reflux in the form of heartburn occurs daily in 7% of adults, weekly in 14%, and monthly in 40%.

Principles of Disease

Although the anatomic relationship between the cardia of the stomach and the left side of the esophagus prevents reflux of gastric contents into the esophagus, the major barrier to gastroesophageal reflux is the lower esophageal sphincter (LES). A defective LES is believed to be the primary mechanism in pathologic reflux by allowing a larger volume of refluxate to enter the esophagus.[27] When reflux does occur, gravity, peristalsis, normal swallowing of saliva, and secretions from esophageal glands help clear refluxed gastric contents back into the stomach. Factors also operate at the mucosal level to minimize the damage caused by refluxate.

Other mechanisms that may contribute to GERD include esophageal motility abnormalities, increased intragastric pressure (e.g., obesity, pregnancy), acid hypersecretion, gastric outlet obstruction, and conditions that cause delayed gastric emptying (e.g., gastroparesis, neuromuscular disease). The presence of a hiatal hernia (the prolapse of a portion of the stomach through the diaphragmatic esophageal hiatus), formerly thought to be synonymous with GERD, may be a factor in the initiation of GERD pathogenesis by interfering with the function of the LES. However, hiatal hernia is thought to play a greater role in sustaining GERD, as one is found in approximately 90% of patients with severe GERD and its complications.[28,29]

Clinical Features

Symptoms

The most common manifestation of GERD is reflux esophagitis, of which the most common symptom is heartburn, defined as a burning sensation that begins in the subxiphoid area and radiates toward the neck. Reflux may also cause a dull discomfort, localized pressure, or severe squeezing pain across the middle of the chest. This type of pain has been postulated to be a result of acid-induced esophageal spasm, but this is believed to be uncommon. The patient may appear comfortable or may have associated diaphoresis, pallor, nausea, and vomiting, leading to the consideration of an ischemic cardiac syndrome. A detailed history is often helpful in differentiating cardiac chest pain from reflux, although the distinction may not be possible in the ED.

Other symptoms of GERD include regurgitation (the spontaneous appearance of acid or bitter material in the mouth or pharynx) and water brash (a vagally mediated hypersalivation response that may produce as much as 10 mL of saliva in 1

BOX 87-1 Agents and Conditions Related to Gastroesophageal Reflux

Decreased Lower Esophageal Sphincter Pressure
Anticholinergic drugs
Benzodiazepines
Caffeine
Calcium channel blockers
Chocolate
Estrogen
Ethanol
Fatty foods
Nicotine
Nitrates
Peppermint
Pregnancy
Progesterone

Decreased Esophageal Motility
Achalasia
Diabetes mellitus
Scleroderma

Increased Gastric Emptying Time
Anticholinergic drugs
Diabetic gastroparesis
Gastric outlet obstruction

minute). Dysphagia and odynophagia may also be presenting complaints and may be associated with more serious complications. Bleeding, weight loss, or anemia in combination with any of these symptoms warrants prompt investigation.

Any condition or agent that decreases LES pressure, decreases esophageal motility, or prolongs gastric emptying predisposes patients to reflux (Box 87-1). Positions that place the esophagus in a dependent position to the stomach or increase intra-abdominal pressure tend to precipitate reflux. Stooping, bending, leaning forward, Valsalva-type maneuvers, and assuming a supine position are common precipitants.

GERD can manifest itself in extraesophageal locations. Reflux-induced asthma may result from either aspiration of gastric contents into the lung or activation of a vagal reflex arc from the gut to the lung. Although both asthma and GERD have been shown to coexist in many individuals, it is difficult to identify GERD as the cause of the asthma, and there is no diagnostic test to define which patients have GERD-associated asthma.[30-32] Chronic persistent cough (without wheezing) can also result from reflux.[33]

If the refluxate reaches the proximal esophagus, otolaryngologic manifestations may result, even in the absence of esophageal symptoms. Laryngeal and tracheal stenosis can result from repeated exposure to refluxate; it is postulated that subglottic stenosis in patients intubated for prolonged periods may be due to GERD.[34] GERD may also cause hoarseness, dysphonia, cough, globus sensation, repetitive throat clearing, and frequent sore throat or laryngitis.[35] Refluxate that enters the oropharynx may lead to gingivitis, halitosis, or dental problems such as erosion of the lingual sides of the teeth as a result of acid exposure. Otalgia and hiccups can also result from reflux.[36]

Complications

Repetitive exposure to acid can lead to changes in the esophageal mucosa. Continued reflux can lead to thinning of the normal stratified squamous epithelial layer. With the development of esophagitis, an inflammatory response occurs within the mucosa and submucosa with infiltration of polymorphonuclear leukocytes. The inflammatory response is the result of chemical irritation of the esophageal mucosa from reflux of gastric acid, pepsin, and bile acids. Both acid and alkaline refluxes produce the same pathologic changes. Continued exposure can lead to further endoscopically visible changes of erosion, ulceration, and scarring. Ultimately, stricture formation may result. The most severe histologic consequence of GERD is replacement of the normal stratified squamous epithelium with metaplastic columnar epithelium in a condition known as Barrett's metaplasia. Histologically, it is characterized by a villous architecture with goblet cells. There is a strong correlation between the development of Barrett's metaplasia and adenocarcinoma of the esophagus.

Diagnostic Strategies

GERD is a common problem, and additional diagnostic testing in the ED is rarely necessary, assuming other more serious causes of the patient's symptoms have been excluded. Patients with dysphagia, odynophagia, or bleeding should be referred for further study.

Differential Considerations

One should consider acute ischemic cardiac syndromes as a possible cause of chest pain in adults. Radiation of pain is an inconstant finding in both esophageal and cardiac chest pain. The pain seen with reflux may radiate into the neck, jaws, shoulders, back, arms, and abdomen. Radiation into the back is more often ascribed to the esophagus. Radiation of pain into one arm or into the neck or jaw is not helpful in distinguishing ischemic cardiac pain from esophageal pain. Radiation of pain into the abdomen is present approximately three times more often in reflux than in ischemic heart disease. Radiation into both arms is rarely seen in reflux, whereas it may be present in approximately one quarter of patients with ischemic heart disease. Precipitation of pain by exercise and relief by rest may occur in pain from reflux as well as in ischemic heart disease. Emotional precipitation of pain occurs in reflux, although it is also seen with coronary artery disease.[37] The occurrence of reflux after meals is another important feature in the history. A feeling of fullness after meals occurs commonly in reflux and is helpful in differentiating it from coronary artery disease.

Relief of chest pain from reflux by antacids is a key point in the history; however, one should not place too much weight on this point as evidence against a cardiac etiology. The relief is often short-lived, and pain may recur in a short time. Esophageal pain may be brought on by swallowing. The physical examination in patients with esophageal reflux is not usually helpful in diagnosis. Thus, the history is by far the most valuable aid. It is important to maintain an acute awareness of the diverse presentations of ischemic heart disease and to be cautious in attributing chest pain to esophageal causes solely on the basis of historical elements. Other GI disorders such as gastritis, esophagitis, peptic ulcer disease, and biliary tract disease should be considered in the differential.

Management

Earlier treatment guidelines for GERD recommended lifestyle modification solely as an initial approach; however, this approach has been shown to have little therapeutic benefit without concomitant medical management.[38,39] These recommendations are thought to decrease the number of reflux

episodes and facilitate the clearance of refluxate. Patients should be counseled to avoid the following: lying fully recumbent during sleep; eating before retiring; wearing tight garments; performing heavy physical exercise after meals; using anticholinergic drugs; consuming foods; or using agents that decrease LES tone, such as cigarettes and alcohol. Direct irritants to the esophagus such as coffee, citrus fruits, and tomato-based products should also be avoided.[40] Overweight patients may experience relief with weight loss. Avoidance of fatty foods and consumption of smaller meals may also help alleviate symptoms. A recent review demonstrated that weight loss and bed elevation are the only recommendations that have evidence-based support.[41]

The pharmacologic therapy of GERD includes agents that neutralize acids, decrease acid production, act on the LES or affect motility, and protect the mucosa. The most effective treatment for GERD is reduction of acid production. Many patients initially self-medicate with antacids or over-the-counter-strength H_2 receptor antagonists or proton pump inhibitors (PPIs), both of which have been demonstrated to relieve and prevent symptoms. Recent studies show that PPIs are more effective than H_2-blockers in eliminating symptoms and healing mucosal damage.[42] However, H_2-blockers are often effective in patients with mild to moderate GERD. These agents do not stop the reflux but rather reduce the potency of the refluxate.[43] Choices of H_2-blockers and PPIs are listed in Tables 87-1 and 87-2. All of these agents are now generally regarded as safe and effective.

Prokinetic agents treat GERD by increasing LES pressure. They may also be used for patients whose symptoms suggest a superimposed motility disturbance (e.g., regurgitation, choking, abdominal distention). In addition to improving propulsive activity of the stomach and small and large intestine, the increase in esophageal peristalsis and LES tone make an effective therapy for reflux by improving the clearance of refluxate.[44] Cisapride (Propulsid) was formerly used for this purpose but was withdrawn from the marketplace by the manufacturer because of adverse cardiac effects. Metoclopramide, a dopamine antagonist, may be used for these patients, but its efficacy has not been conclusively demonstrated and it has significant side effects, some of which are irreversible (e.g., tardive dyskinesia).[45] Baclofen has been used with some success in selected patients.[46] Candidates for this type of therapy are probably best chosen by a gastroenterologist.

Another agent that may be of benefit in refractory cases of symptomatic esophageal reflux is sucralfate, the salt of aluminum hydroxide and sucrose octasulfate. It may have an advantage in that it also absorbs and inactivates bile salts.[47] However, this indication for its use is not approved by the Food and Drug Administration.

Although the emergency physician can initiate antireflux therapy, the patient with clinically suggested reflux should be referred to a gastroenterologist to confirm the diagnosis and provide follow-up care. Further diagnostic evaluation, including esophageal pH monitoring, an upper GI radiographic series, esophageal manometry, or esophagoscopy may be necessary, especially for patients who fail to respond to all of the preceding measures. Patients whose condition is medically unresponsive may be candidates for antireflux surgery. Endoscopic therapies such as endoscopic sewing,[48] polymer injection,[49] and radiofrequency application[50] to the lower esophageal sphincter are currently being investigated.

Table 87-1 Summary of Histamine Receptor Antagonists

	GERD	PUD*
Cimetidine	800 mg bid or 400 mg qid	800 mg qhs or 400 mg bid
Famotidine	20 or 40 mg bid	40 mg qhs or 20 mg bid
Nizatidine	150 mg bid	300 mg qhs or 150 mg bid
Ranitidine	150 mg bid	300 mg qhs or 150 mg bid

*Maintenance dose for PUD is half the qhs dose.
GERD, gastroesophageal reflux disease; PUD, peptic ulcer disease.

Table 87-2 Summary of Proton Pump Inhibitors*

	GERD	PUD OR NSAID-INDUCED ULCERS†
Esomeprazole	20 mg qd or 40 mg qd	40 mg PO qd
Lansoprazole	30 mg qd or 30 bid	30 mg PO qd
Omeprazole	20 mg qd or 20 bid	20 mg PO qd
Pantoprazole	40 mg qd or 40 bid	40 mg PO qd
Rabeprazole	20 mg qd or 20 bid	20 mg PO qd

*All doses should be administered before breakfast; second doses (when necessary) should be administered prior to the evening meal.
†Patients with duodenal ulcer should be treated for 4 weeks; patients with gastric ulcer should be treated for 8 weeks.
GERD, gastroesophageal reflux disease; NSAID, nonsteroidal anti-inflammatory drug; PUD, peptic ulcer disease.
Adapted from Wolfe MM, Sachs G: Acid suppression: Optimizing therapy for gastroduodenal ulcer healing, gastroesophageal reflux disease, and stress-related erosive syndrome. Gastroenterology 118:S9, 2000.

GASTRITIS

Perspective

Strictly speaking, gastritis is a histologic diagnosis denoting inflammation of the gastric mucosa. Hence, the diagnosis of gastritis can be made only by endoscopy and biopsy. However, it is common practice for clinicians to use the term *gastritis* to refer to symptoms of dyspepsia. To confuse the picture further, gastroenterologists frequently use the term to refer to the endoscopic finding of an edematous, friable mucosa. However, without accompanying inflammation, this is more appropriately termed *gastropathy* rather than gastritis.[51] Controversy exists regarding how best to classify the entities that cause gastritis or gastropathy. This section considers gastritis and gastropathy together as one entity because the distinction makes little difference in the ED setting. Regardless of the cause, up to 50% of the population have endoscopic evidence of gastritis or gastropathy by age 50.

Principles of Disease

The most common cause of gastritis is infection with *Helicobacter pylori*. Although most patients are asymptomatic at the time of initial exposure, acute infection with *H. pylori* can cause severe gastritis and upper GI symptoms. Suppurative gastritis (also known as *acute phlegmonous gastritis*) can result from a bacterial infection of the stomach wall, usually from gram-positive cocci or gram-negative rods. Patients usually have an underlying mucosal abnormality such as cancer, ulcer, or preexisting gastritis. Less common infectious causes of gastritis include mycobacterial, viral, parasitic, and fungal organisms.

Gastritis can also result from exposure to drugs. Aspirin or other NSAIDs are the most common offending agents. Inflammation occurs as a result of prostaglandin inhibition both locally and systemically and is probably a precursor to gastric ulcer formation. Other drugs implicated in causing gastritis are

potassium preparations and iron supplements. Gastritis can result from both short- and long-term exposure to ethanol, although some authors feel that the long-term effects are more likely due to *H. pylori* rather than to the ethanol itself.

The presence of corrosive agents in the stomach can induce gastritis. Intrinsic substances such as bile or ingested substances such as acids, alkali, and corrosive agents can induce an inflammatory response and subsequent gastritis.

Any condition that causes hypovolemia or hypotension can lead to gastritis. Ulcer formation may ultimately result. This may be a major causative factor in the development of gastritis and upper GI bleeding in intensive care unit patients. Other causes of gastritis include radiation, autoimmune reactions, Crohn's disease, and sarcoidosis. These disorders can be diagnosed only by biopsy.

Clinical Features

No particular symptoms are characteristic of gastritis. Acute gastritis may cause abdominal pain, nausea, and vomiting, although most patients are asymptomatic unless ulcers or other complications develop. By definition, it is not possible to diagnose gastritis or gastropathy on the basis of clinical features alone. However, a good clinical history such as recent NSAID use or alcohol ingestion in the setting of the foregoing symptoms supports a presumptive clinical diagnosis of gastritis.

Acute infection with *H. pylori* may cause epigastric abdominal pain, nausea, and vomiting. Systemic signs such as fever are usually absent. Symptoms may last days to weeks. If the infection goes untreated, chronic gastritis may result. Patients with phlegmonous gastritis usually appear toxic. Patients with gastritis as a result of decreased mucosal blood flow may present with symptoms of abdominal pain and upper GI bleeding in addition to those of their underlying disease. Complications of gastritis include perforation and gastric outlet obstruction.

Diagnostic Strategies

Because the presumptive diagnosis of gastritis is made empirically, no specific diagnostic tests are necessary. Ancillary tests should be ordered as clinically indicated to rule out other possible diagnoses or to assess for complications of gastritis, such as bleeding, obstruction, or perforation.

Differential Considerations

Before making the diagnosis of gastritis, other diseases that cause nausea, vomiting, and upper abdominal pain, such as pancreatitis, biliary tract disease, and small bowel obstruction, must be excluded. The possibility of an acute coronary syndrome should also be considered, particularly in elders.

Management

Therapy of presumptive gastritis should be directed toward treating the suggested underlying cause. Acid suppression may improve symptoms of dyspepsia in patients taking NSAIDs. Patients with persistent symptoms should be referred to a gastroenterologist for further diagnostic evaluation.

PEPTIC ULCER DISEASE

Perspective

Gastric and duodenal ulcers are usually grouped together as peptic ulcer disease (PUD) because of the similarity in their pathogenesis and treatment. Approximately 4 million people in the United States are affected by PUD each year.[52] The annual cost to the health care system is estimated to be over $15 billion.[53] PUD is now considered to have two main causes: *H. pylori* infection and NSAID use. Approximately 1% of PUD is caused by increased levels of circulating gastrin from gastrin-secreting tumors (Zollinger-Ellison syndrome). These patients have increased parietal cell mass and hypersecretion of acid leading to ulcer formation. A small minority of patients have no identifiable cause for their ulcers.

Principles of Disease

Histologically, the stomach is composed of different types of cells with varying secretory functions. Mucous cells secrete acidic mucus, parietal cells secrete hydrochloric acid and intrinsic factor, chief cells secrete pepsinogens, and enterochromaffin-like cells release substances such as histamine and gastrin. Acid secreted by the over 1 billion parietal cells can generate a hydrogen ion concentration gradient of greater than 1 million to 1 within the lumen of the stomach.

Many mechanisms exist to protect the gastric mucosa from the digestive effects of the hydrochloric acid, proteolytic enzymes, bile, and other injurious substances to which it is exposed. Normally, a gastric mucosal barrier to intraluminal gastric acid is present and prevents the back-diffusion of hydrogen ions from the gastric lumen. Sodium ions are barred from moving in the opposite direction. This ionic impermeability protects the gastric mucosa from damage in a hostile environment. Damage to the gastric mucosal barrier from any cause (Box 87-2) allows hydrogen ions and digestive enzymes to make contact with the gastric mucosa, leading to inflammation, bleeding, and potential ulceration.

The identification of *H. pylori* has proved to be a landmark discovery that has changed our understanding of PUD. *H. pylori* is an spiral, flagellated, gram-negative rod whose natural habitat is the human stomach between the epithelial cell surface and the overlying mucus. Infection with *H. pylori* is a primary risk factor for development of PUD. It is estimated that 70 to 80% of patients with duodenal ulcer and 60 to 70% of patients with gastric ulcer are infected with *H. pylori*. *H. pylori* is more prevalent in lower socioeconomic groups and is probably spread by the fecal-oral route, although oral-to-oral and iatrogenic transmissions have also been suggested. It is estimated that 30 to 40% of the U.S. population is infected with *H. pylori*. It is found in all age groups, although it is believed that infection is acquired during childhood. Its presence is believed to cause mucosal inflammation that disrupts the normal defense mechanisms and leads to ulceration. It also increases the risk of gastric carcinoma and, less often, lymphoma. Not all people infected with *H. pylori* develop PUD,

BOX 87-2 SUBSTANCES AND CONDITIONS THAT DAMAGE THE GASTRIC MUCOSAL BARRIER

Bile
Cigarette smoking
Ethanol
Glucocorticoids
Helicobacter pylori
Nonsteroidal anti-inflammatory drugs
Pancreatic secretions
Shock conditions
Stress

and it is unclear what role environmental and host factors (such as diet) play. It is now accepted that almost all non-NSAID-related ulcers are due to *H. pylori*. Eradication of infection with *H. pylori* results in more rapid healing of ulcers, prevents relapse, and diminishes the rate of ulcer complications. The most effective means of diagnosis and optimal management, including the most effective antibiotic regimens, are still being defined. Currently available tests include a urea breath test, urea blood tests, antibody testing, stool antigen testing, and direct mucosal biopsy during endoscopy. As yet, none of these are of practical use for the ED patient.

The second most common cause of peptic ulcer formation is the use of NSAIDs. NSAIDs have both a direct and an indirect effect on the gastric mucosa. NSAIDs are weak acids that remain in the nonionized form in the acidic milieu of the stomach lumen. This allows free diffusion into the mucosal cells, where ionization occurs. Because ionized forms cannot cross the cell membrane, the NSAID becomes "ion-trapped" within the cell. The increased intracellular concentration of NSAID damages the cell, most likely as a result of uncoupling of oxidative phosphorylation. Because administration of enteric-coated NSAIDs that are not absorbed in the stomach does not diminish the incidence of ulcer formation, a second systemic mechanism of injury must also exist. It is believed that the inhibition of cyclooxygenase by NSAIDs leads to a diminished level of protective prostaglandins in the stomach. In addition, the antiplatelet aggregation effect of NSAIDs may increase the amount of bleeding associated with the development of NSAID-induced ulcers. NSAIDs differ in their ulcerogenic potential, with etodolac, nabumetone, and salsalate having lower risks of GI toxicity. The cyclooxygenase-2 specific inhibitors (celecoxib, rofecoxib, and valdecoxib) were initially felt to have a better GI safety profile than traditional NSAIDs. However, further studies refuted this belief and noted an increased risk of cardiovascular side effects. As a result, rofecoxib (Vioxx) and valdecoxib (Bextra) were withdrawn from the market. Celecoxib (Celebrex) is still available in the United States as a treatment for arthritis and familial polyposis, yet has a black box warning regarding an increased incidence of both GI side effects and increased cardiovascular risk. Certain patients are at high risk for NSAID-induced gastroduodenal toxicity. These include those with a prior history of an ulcer or hemorrhage, patients older than 60 years, those receiving higher doses of NSAIDS, and those currently using glucocorticoids or anticoagulants.[54] These patients should be considered for ulcer prophylaxis with a PPI or misoprostol. Other drugs with ulcerogenic potential include 5-fluorouracil, mycophenolate mofetil, and the bisphosphonates.

PUD also occurs in infants and children. Infants with PUD usually present with poor feeding, vomiting, or failure to thrive, but hematemesis may be the first sign. Toddlers and preschool children may have abdominal pain or vomiting and bleeding. Eighty percent of ulcers in this age group are stress ulcers. Older children and adolescents usually have primary PUD, with presentations similar to those of adults.

Clinical Features

Presenting Symptoms

Although 1 to 2% of patients with ulcers are asymptomatic, the most common symptom of PUD is abdominal pain. Classically, ulcer pain is described as nonradiating epigastric pain of a burning, gnawing, or "hunger-like" quality. However, patients may also describe pain in other areas of the abdomen, the chest, or the back; the pain may also be vague or crampy. It usually occurs 2 to 5 hours after a meal or at night. Pain that awakens a patient from sleep between midnight and 3 AM is a classic indicator of ulcer disease, because in most people gastric acid output is highest at about 2 AM. Ulcer pain is usually not present on awakening in the morning because gastric acid output is at its lowest at this time. Colicky pain is rarely gastric or duodenal in origin. Well-defined periods of exacerbation and remission are usually present with duodenal ulcer and aid in the diagnosis. A constant pain lasting from weeks to months is uncommonly caused by ulcer disease. Relief of pain after eating is another feature of gastric or duodenal ulcer. The pain from a duodenal ulcer is usually worse immediately preceding a meal, and the complex of pain-eating-relief is typical of duodenal ulcer.

Although some patients with ulcers may vomit, alternative diagnoses such as gastric volvulus, gastric outlet obstruction, small-bowel obstruction, pancreatitis, or biliary tract disease should be considered in patients who present with epigastric pain and vomiting. Relief of abdominal pain with antacids is an important aspect of the history. Antacids usually afford relief of pain in both PUD and gastritis. Ninety percent of patients with PUD have pain relief with antacids, and 75% with gastritis have relief. Patients with duodenal ulcer usually experience pain relief within 5 minutes after taking an antacid.

Physical findings in patients with PUD are usually minimal. Mild epigastric tenderness may be elicited. A positive stool guaiac test may be evidence of a bleeding ulcer, but other causes of occult bleeding must also be considered.

Complications

The most serious complications of PUD include hemorrhage, perforation, penetration, and gastric outlet obstruction. Hemorrhage is the most common complication, occurring in 15% of patients. Ulceration into an artery can lead to life-threatening hemorrhage. Older patients are at greater risk. Approximately 7% of patients experience perforation, which occurs when an ulcer erodes through the wall and leaks air and digestive contents into the peritoneal cavity. Penetration is pathologically similar to perforation, except that the ulcer erodes into another organ such as the liver (usually from a gastric ulcer) or the pancreas (usually from a duodenal ulcer) instead of into the peritoneal cavity. Gastric outlet obstruction occurs in 2% of ulcer patients as a result of edema and scarring near the gastroduodenal junction. Symptoms may manifest as gastroesophageal reflux, early satiety, weight loss, abdominal pain, and vomiting.

Pain patterns may be helpful in diagnosing some of the complications of PUD. Pain from a perforated duodenal ulcer is usually appreciated first in the epigastrium but becomes generalized within a short time. Vomiting is present in 50% of patients, and peritoneal findings usually result. Pneumoperitoneum commonly occurs after duodenal ulcer perforation, and the accumulated air under the diaphragm may cause referred pain to the shoulder. One or both shoulders may be involved, depending on the location of the free air.

A history of ulcer-like anterior abdominal pain that begins to radiate into the back suggests penetration of a duodenal ulcer. The pain is usually described as steady and is perceived at the level of the lower thoracic and upper lumbar vertebrae. Relief of the pain with antacids and food often vanishes, and the pain becomes refractory to treatment. Also, pain radiation may occur to the chest, right upper quadrant, and left upper quadrant in up to 20% of patients. The sudden onset of pain, especially if unrelated to eating, suggests either ulcer perforation or gastric volvulus.

Diagnostic Strategies

The initial diagnosis of PUD is usually made clinically. Upper endoscopy is the procedure of choice for confirming the diagnosis. Ancillary tests may be of benefit in evaluating possible complications of PUD in patients who present in distress. They may also be of benefit in providing indirect evidence of another disease. A complete blood count may diagnose anemia, and liver enzyme levels may help elucidate a hepatic or biliary tree etiology. Electrolytes may provide indirect evidence of disease, and assessment of amylase and lipase levels should be considered to rule out pancreatitis and may provide indirect evidence of a posterior penetrating ulcer.

Abdominal and chest radiographs should be ordered if obstruction, perforation, or penetration is suggested or if a pulmonary etiology is being considered, although negative radiographs do not definitively rule out these diagnoses. Electrocardiography should be performed in any patient thought to have a cardiac etiology for the pain. A pregnancy test should be performed on any woman of childbearing age.

As noted earlier, several methods exist for diagnosing infection with *H. pylori*, although at this time none is of practical application in the ED.

Differential Considerations

Fifty percent of patients with symptoms of dyspepsia have no identifiable cause. These patients are classified as having nonulcer dyspepsia (NUD). The official criteria for diagnosing NUD are chronic recurrent upper abdominal pain or discomfort for a period of at least 1 month, with symptoms present more than 25% of the time, and no evidence of organic disease.[55]

NUD may be caused by peptic ulcers that are not yet large enough to appear endoscopically. Gastritis related to hypersecretion of gastric acid, *H. pylori* infection, bile reflux, or viral infection may cause NUD, although these cases should be identifiable endoscopically or pathologically. Maldigestion or malabsorption of carbohydrates can arise as NUD in patients with lactase deficiency or in patients who consume large quantities of nonabsorbable sugars such as sorbitol, mannitol, and fructose. Intestinal parasites such as *Giardia intestinalis* or *Strongyloides stercoralis* may cause NUD, as can chronic pancreatitis. NUD may also be caused by gastric motility disorders, which have been reported in 25 to 60% of patients with NUD. Abnormalities in the biliary tract, such as increased resting pressure of the sphincter of Oddi, or incomplete relaxation of the sphincter on gallbladder contraction may lead to bile duct distention and pain.[56]

Many other disorders can produce epigastric pain that mimics the pain of an ulcer. It can be difficult to distinguish between gastritis and PUD. The discomfort associated with gastritis is often mild to moderate in severity and described as a hot, burning pain or bloating. In particular, burning pain is twice as common in gastritis as in PUD. Esophageal disorders such as GERD, esophagitis, or esophageal spasm can arise with abdominal symptoms. Mesenteric ischemia ("abdominal angina") should be considered, especially in elder patients and those with underlying vascular disease or atrial fibrillation. Aortic dissection, other intra-abdominal processes such as the biliary tract and pancreatic disease, and atypical presentation of an acute cardiac syndrome or other intrathoracic process should be considered in the differential diagnosis. Finally, abdominal pain may be the presenting symptom in psychiatric patients with somatoform disorder. These patients have an altered perception of visceral pain and have an increased sensation of pain when the stomach or small intestine is dilated.

Management

The initial treatment of presumptive PUD includes lifestyle changes (cessation of smoking and the use of alcohol and aspirin). Although the initiation of a bland diet with frequent small feedings is frequently recommended, no study has proven its effectiveness, and the only dietary recommendation should be to avoid foods that are known to exacerbate symptoms. Because PUD is a result of either infection with *H. pylori* or NSAID use, initial treatment should be based on the presumed cause. For NSAID-related ulcers, treatment should begin by discontinuing the offending agent and beginning a PPI.

If NSAIDs are not being used by a patient with suggested PUD, it is currently recommended to treat for *H. pylori* infection. Dyspeptic symptoms without proven ulcer may also be an indication for treatment, but that decision may best be left to a gastroenterologist. Antacid therapy may be started with a PPI or H_2-blocker. Nonendoscopic testing for *H. pylori* is available in the form of antibody detection, urea breath test, and fecal antigen tests; however, their role in the evaluation of ED patients is not yet defined.

Some recommended regimens combine antibiotics with acid-suppressing agents for treatment of *H. pylori* infection (Box 87-3). Commercially available combination products may also be prescribed that may assist in compliance (PrevPac, which contains lansoprazole, amoxicillin, and clarithromycin; and Helidac, which contains bismuth subsalicylate, metronidazole, and tetracycline). Most gastroenterologists recommend continued therapy with antisecretory agents following the antibiotic-containing regimens.

H_2-blockers have not been demonstrated to prevent the formation of ulcers when given concurrently with NSAID therapy; PPIs have been demonstrated to be of some benefit and should be used in patients with gastroduodenal ulcers who must continue using NSAIDs.[57]

BOX 87-3 SUGGESTED TREATMENT REGIMENS FOR *HELICOBACTER PYLORI*

Triple Therapy (10- to 14-day treatment regimen)
Clarithromycin 500 mg bid
Plus
Amoxicillin 1 g bid
Or
Metronidazole 500 mg bid (if penicillin allergic)
Plus
A PPI

Quadruple Therapy (10- to 14-day treatment regimen)
Bismuth subsalicylate (Pepto-Bismol) 525 mg PO qid
Plus
Metronidazole 250 mg PO qid
Plus
Tetracycline 500 mg PO qid
Plus
A PPI or ranitidine 150 mg PO bid

PPI, proton pump inhibitor.
From Chey WD and Wong BCI, American College of Gastroenterology Guideline for Management of *Helicobacter pylori* Infection, Am J Gastroenterol 102:1808, 2007.

■ GASTRIC VOLVULUS

Perspective

Gastric volvulus is a rare cause of severe abdominal pain that occurs when the stomach rotates upon itself more than 180 degrees, creating a closed-loop obstruction. Only 400 cases have been reported in the literature, although its true incidence is unknown because some types of volvulus are intermittent and resolve spontaneously. It most commonly occurs in persons 40 to 50 years of age and is usually associated with the presence of a paraesophageal hernia. Approximately 20% of cases occur in infants younger than 1 year and are due to congenital diaphragmatic defects.[58] If an acute volvulus is not identified and corrected early, it may lead to gastric ischemia, perforation, and death. The mortality rate from acute gastric volvulus is 15 to 20%.

Principles of Disease

The stomach is fixed at only two points: the esophagocardiac junction and the pylorus. The remainder of the organ is relatively distensible and mobile and can occupy various positions within the abdomen. When a person is supine, the stomach lies entirely above the umbilicus, whereas it descends below the umbilicus in the erect position. Regardless of its position, the stomach maintains its familiar morphology because of ligamentous attachments to the surrounding organs. A primary (or subdiaphragmatic) volvulus occurs when the stabilizing ligaments are too lax or are congenitally abnormal in such a way that the stomach is able to twist upon itself. Approximately one third of cases are of this type.

Secondary (or supradiaphragmatic) volvulus occurs in patients with diaphragmatic defects such as a paraesophageal hiatal hernia, an elevated diaphragm, gastric ulcer or carcinoma, diaphragmatic paralysis, extrinsic pressure on the stomach from other organs, or abdominal adhesions.[59] The combination of one of these factors and ligamentous laxity makes a volvulus more likely.

Gastric volvulus can be classified on the basis of its axis of rotation. The most common form is organoaxial volvulus, which occurs when the stomach twists on its long axis. Less commonly, the stomach folds on its short axis from the lesser to greater curvature and is classified as a mesenteroaxial volvulus. Approximately one third of cases of gastric volvulus are of this type.

Clinical Features

Presenting Symptoms

The presenting features of a gastric volvulus can vary, depending on the type. Primary volvulus may arise with the sudden onset of severe abdominal pain. The upper abdomen may demonstrate marked distention. Patients with secondary volvulus may experience predominant symptoms in the chest, with pain radiating to the back and shoulders along with accompanying dyspnea. The abdominal examination may be unremarkable. Vomiting is usually present and may be persistent and severe. The combination of severe epigastric pain and distention, vomiting, and inability to pass a nasogastric tube (Borchardt's triad) should increase the likelihood of a gastric volvulus.

A volvulus may be chronic if the rotation is minimal and there is no vascular compromise. Symptoms usually consist of mild intermittent upper abdominal pain. Early satiety, dyspnea, bloating, eructation, and upper abdominal fullness may be present. It is unknown how often a chronic volvulus can lead to an acute volvulus.

Complications

If not recognized, volvulus can lead to bowel ischemia and necrosis of the stomach. Untreated, this may lead to shock and death. Fortunately, the frequency of gastric infarction is low (reported between 5 and 28% for organoaxial volvulus) because of the redundant blood supply of the stomach. Other complications include ulceration, perforation, hemorrhage, pancreatic necrosis, and omental avulsion.

Diagnostic Strategies

A plain abdominal radiograph often demonstrates a large, gas-filled loop of bowel in the abdomen or chest. A barium swallow may help visualize the abnormality. There are no laboratory findings specific for volvulus, although elevations in amylase and alkaline phosphatase have been reported.

Differential Considerations

The differential diagnosis of gastric volvulus includes any disease that can arise with sudden upper abdominal pain and vomiting. Perforated peptic ulcer, gastric outlet obstruction, biliary tract disease, and acute pancreatitis should be considered. Symptoms of a volvulus may suggest an acute cardiac syndrome.

Management

The goal of treatment of an acute gastric volvulus is reduction. Mortality rates increase with delayed diagnosis because of complications of ischemia. Acutely, one should attempt passage of a nasogastric tube, which may occasionally reduce the volvulus. Although its role is somewhat controversial, patients without signs of gastric infarction may undergo an attempt at endoscopic reduction. Following reduction, recurrence is prevented by surgically repairing any predisposing defects.

■ DYSPHAGIA

Perspective

Precise motor control of the act of swallowing is necessary to ensure that food is successfully transferred from the mouth through the esophagus into the stomach. This includes the muscles of the oropharynx, the upper esophageal sphincter (UES), the body of the esophagus, and the LES. Failure at any one of these levels results in a motility disorder, the primary symptom of which is dysphagia, which literally means "difficulty swallowing."

Principles of Disease

Normal Physiology

Swallowing is a complex phenomenon requiring both voluntary and involuntary skeletal muscle activity. Control of swallowing is coordinated by the swallowing center in the medulla. Afferent sensory input involves the trigeminal, glossopharyngeal, vagus, and spinal accessory cranial nerves; efferent motor activity travels through the trigeminal, facial, glossopharyngeal, vagus, and hypoglossal cranial nerves. The act of swallowing begins a process of both simultaneous and sequential activity in all three esophageal zones. A rapidly progressive pharyngeal

contraction transfers the food bolus through a relaxed UES into the esophagus, where a moving ringlike contraction begins in the upper esophagus and propagates distally, making the transition from striated to smooth muscle, culminating with the propulsion of the bolus through a relaxed LES. Three mechanisms have been described that regulate the peristaltic wave, ensuring a smooth transition from the striated muscle in the upper esophagus to the smooth muscle of the middle and lower esophagus and coordination of UES and LES activity. These mechanisms are sequential firing of vagal afferents that begin in the brainstem, an intramural neural mechanism that responds to local stimuli, and myogenic propagation of the contraction through the myocytes themselves.[60]

Physiologically, swallowing can be divided into oral, pharyngeal, and esophageal phases. The oral phase involves preparation of the food bolus by mastication and lubrication. The tongue then propels the bolus into the pharynx by progressive anteroposterior contractions. In the pharyngeal phase of swallowing, events are initiated by delivery of the food bolus to the oropharynx. Voluntary contraction of the pharyngeal muscles seals the nasopharynx by elevation of the soft palate. The oropharynx is sealed by the upward movement of the tongue against the palate. The larynx and hyoid bone are elevated to seal off the respiratory passage. The cricopharyngeus muscle, or UES, relaxes, and the bolus is swept into the esophagus by sequential peristaltic waves initiated in the upper pharynx. During the esophageal phase, the bolus is propelled toward the stomach by sequential peristaltic waves. Peristalsis can be initiated by swallowing or in response to luminal distention of the gut or changes in the pH or osmotic environment of the mucosa. The lower sphincter normally maintains a degree of tone sufficient to prevent reflux of gastric contents. When the food bolus reaches the lower sphincter, the sphincter relaxes to allow passage of the bolus and then regains its degree of resting tone.

Pathophysiology

Disturbances of the interactions between the components of the upper GI tract lead to a motility disorder. The motor disorders of the body of the esophagus are only now beginning to be understood. The major primary esophageal motility disorders are achalasia, diffuse esophageal spasm, hypercontractile esophagus ("nutcracker esophagus"), and nonspecific motor disorder. Of these, the only two that are well defined are achalasia and diffuse esophageal spasm. Controversy exists about whether the other entities are true disease states because symptoms are not always associated with manometric abnormalities and correction of the abnormalities does not always result in symptom improvement. Motor disorders may be the primary cause of other esophageal abnormalities such as GERD or esophageal diverticula.

Clinical Features

Dysphagia at any age is abnormal and requires evaluation. The dysphagia should be classified into one of two types: oropharyngeal dysphagia (also known as transfer dysphagia), related to disease in the pharynx or upper esophagus, or esophageal dysphagia, which is due to disease in the esophageal body or lower esophageal sphincter. Although dysphagia has many causes, a thorough history reveals the diagnosis in most patients (Box 87-4). One should determine where the bolus sticks; the duration of the dysphagia and whether symptoms are intermit-

BOX 87-4 CAUSES OF DYSPHAGIA

Neuromuscular

Vascular
Cerebrovascular accident

Immunologic
Dermatomyositis
Multiple sclerosis
Myasthenia gravis
Polymyositis
Scleroderma

Infectious
Botulism
Diphtheria
Poliomyelitis
Rabies
Sydenham's chorea
Tetanus

Metabolic
Lead poisoning
Magnesium deficiency

Other
Alzheimer's disease
Amyotrophic lateral sclerosis
Brain tumor
Depression
Diabetic neuropathy
Familial dysautonomia
Metabolic myopathies (e.g., thyrotoxicosis)
Muscular dystrophies
Parkinson's disease

Obstructive
Aortic aneurysm
Esophageal motility disorder (e.g., achalasia, diffuse esophageal spasm, hypertensive LES, nutcracker esophagus)
Esophageal rings
Esophageal stricture
Esophageal webs
Esophagitis
Foreign bodies
Hypertrophic cervical spurs
Inflammatory lesions
Left atrial enlargement
Mediastinal mass
Neoplasm
Thyroid enlargement
Vascular anomalies (e.g., enlarged aorta, aberrant subclavian artery)
Zenker's diverticulum

Other
Alcoholism
Decreased saliva production (Sjögren's syndrome, post-irradiation)
Diabetes
Functional
Gastroesophageal reflux disease
Postoperative

LES, lower esophageal sphincter.

tent or progressive; whether solids, liquids, or both are involved; whether it is associated with pain; and whether the patient has any previous gastroesophageal history (e.g., esophageal reflux). Any family history of neurologic disease should be obtained.

The examination should include a thorough evaluation of the head and neck and a detailed neurologic examination. The patient should be observed while swallowing. Difficulty in initiating the swallow, misdirection of the bolus with regurgitation or aspiration, and unusual posturing of the patient when swallowing should be noted. Many patients with neuromuscular disorders depend on gravity to swallow, and having the patient swallow in the prone position may be helpful in diagnosis.

Oropharyngeal Dysphagia

Oropharyngeal causes of dysphagia inhibit the initiation of swallowing. Patients complain that "food gets stuck" on swallowing, often pointing to the cervical region when describing their symptoms. Coughing, choking, or drooling may be associated. Neuromuscular diseases cause approximately 80% of oropharyngeal dysphagias, with most remaining causes being localized structural lesions. Most neuromuscular causes of dysphagia result in misdirection of the bolus, sticking, and the need for repeated swallowing attempts. Patients may drool and turn the head and neck to the side to facilitate swallowing. Liquids, especially of extreme temperatures, usually cause dysphagia more commonly than solids, and symptoms are more often intermittent. Progressive unremitting dysphagia is usually not caused by neuromuscular disorders of the oropharynx. Cerebrovascular accidents are probably the most common cause of neuromuscular dysphagia, especially those involving the vertebrobasilar system and posteroinferior cerebellar arteries and when some degree of dysarthria is present. The mechanism in such cases is pharyngeal weakness, with failure of the cricopharyngeus muscle to relax. Weakness of the tongue may occur, resulting in poor transfer of the bolus, or weakness of the buccal muscles may produce drooling and difficulty initiating the swallow.

The second most common cause of neuromuscular dysphagia is polymyositis or dermatomyositis. These disorders are characterized by inflammatory and degenerative changes in striated muscle that can produce dysphagia from weakness of the palate, pharynx, and upper esophagus. Dysphagia is seen in approximately 25% of patients with these disorders at the time of treatment.[61]

A cause of oropharyngeal dysphagia that deserves particular mention is myasthenia gravis. Two thirds of patients with myasthenia gravis may have dysphagia, and occasionally it is the presenting symptom. The dysphagia becomes progressively worse with repeated swallowing attempts and is temporarily reversible with edrophonium.

Disorders in the pharyngeal phase of swallowing may lead to misdirection of the food bolus, pain, sticking, or multiple swallowing attempts. Tongue weakness can result in oral regurgitation. Inability to seal the nasopharynx because of obstruction or muscular weakness can cause nasal regurgitation. Inefficient laryngeal elevation from muscular weakness or a fixed larynx can result in laryngotracheal aspiration. Delayed aspiration can occur with pharyngeal weakness and with pooling of food in the piriform recesses or in a diverticulum. Inability to contract the pharyngeal muscles is often compounded by failure of the cricopharyngeus to relax. Failure of relaxation of the cricopharyngeus with or without pharyngeal weakness causes misdirection of the food bolus or necessitates repeated swallowing attempts. Inflammatory lesions of the tongue or oropharynx can result in odynophagia and even complete inability to swallow because of pain.

Esophageal Dysphagia

Dysphagia from upper esophageal lesions is usually perceived 2 to 4 seconds after the initiation of swallowing. Dysphagia that the patient localizes to the substernal or retrosternal area may be anatomically accurate, but localization to the neck may be referred from anywhere in the esophagus.

Esophageal dysphagia can be caused by mechanical lesions or a motility disorder. Mechanical lesions include strictures, webs, rings, tumors, esophagitis, or postsurgical changes. Pressure from extrinsic lesions such as osteophytes, mediastinal masses, or aortic aneurysms can also cause dysphagia.

Patients with esophageal dysphagia who have no readily identifiable cause may have a motor disorder. The motor disorders include achalasia, diffuse esophageal spasm, nutcracker esophagus, and hypertensive LES. Achalasia is a disorder of unknown cause in which the resting pressure of the LES is markedly increased and peristalsis in the body of the esophagus is absent. Although it can occur at any age, most patients are between 20 and 40 years of age. Dysphagia is the most common presenting symptom and usually begins insidiously with equal frequency for solids and liquids. Patients may report that maneuvers that increase esophageal pressure (raising arms above the head, standing erect with back straight) help pass the food. Odynophagia from esophageal spasm may also be seen early in the course of achalasia. The symptoms are often worse with rapid eating and during periods of stress. The patient may also report chest pain as a symptom. As dilation occurs above the sphincter, retention of undigested food in the esophagus occurs, and the patient may be aware of gurgling while eating. Regurgitation of the undigested material can occur after a meal (prompting consideration of the diagnosis of an eating disorder) or with changes in position or vigorous exercise. The regurgitated food usually has no acid taste, although bacterial contamination may lead to fermentation of the undigested food. Laryngotracheal aspiration may occur, especially at night, and may cause nocturnal coughing. Physical examination is usually unremarkable except for weight loss. Radiographically, a dilated esophagus is seen proximal to a narrowed gastroesophageal junction that has a beaklike appearance.

The second type of intrinsic motor disorder of the esophagus is diffuse esophageal spasm. Manometrically, simultaneous prolonged strong esophageal contractions are noted to be interspersed over normal peristaltic waves. If a barium swallow is obtained during a spasm, findings such as a "corkscrewing," or curling, of the esophagus may be noted. Diffuse spasm may be precipitated by swallowing very hot or cold liquids. Symptoms include chest pain, dysphagia, or both.

Nutcracker esophagus is the term used to describe prolonged, high-intensity peristaltic waves. Many experts feel that this represents a variant of diffuse esophageal spasm. Nonspecific motor disorder includes repetitive esophageal contractions, nontransmitted esophageal contractions, or low-amplitude esophageal contractions.[62]

Diagnostic Strategies

Given the myriad causes of dysphagia, a careful history and physical examination are essential. Patients with oropharyngeal dysphagia should have laboratory studies and central nervous system imaging as indicated. Nasopharyngoscopy may also be performed to rule out obvious structural abnormalities. If these are nondiagnostic, patients may be referred for a swallowing study (videoesophagram). Patients with esophageal dysphagia in whom carcinoma, radiation or caustic injury, or achalasia is suggested should undergo a barium swallow. If a

motor disorder is suggested, a swallowing study may prove helpful as well, but this may not detect intermittent dysfunction. In such cases, referral to a gastroenterologist for manometric examination may be required. At that time, additional provocative studies can be performed.

Differential Considerations

The differential diagnosis of lower esophageal dysphagia includes acute coronary syndromes. Substernal chest pain is the main symptom in 80 to 90% of patients with esophageal motility disorders. The chest pain can be similar to angina, described as crushing or squeezing with patterns of radiation similar to those of cardiac chest pain. Nitroglycerin may relieve the pain of spasm as well, further confusing the picture.

Symptoms that suggest an esophageal etiology of chest pain are pain that is prolonged and nonexertional, pain that interrupts sleep, pain related to meals, relief with antacids, and presence of other symptoms of esophageal disease such as heartburn, dysphagia, or regurgitation. Because of considerable overlap in symptoms, the emergency physician must exclude a cardiac diagnosis before attributing chest pain to an esophageal cause.

Management

Appropriate management of dysphagia is based on the identified or suggested cause. Most patients with no readily identifiable cause can be evaluated as outpatients; however, it is prudent to admit patients who are at high risk for aspiration. Patients in whom an esophageal motility disorder is suggested should be referred to a gastroenterologist because the diagnosis is usually made manometrically. Achalasia is the only motility disorder for which reasonably good studies support specific treatment. Pharmacologic therapy is directed at decreasing the tone of the LES. Nitrates and calcium channel blockers have been used with some success; however, reflux symptoms may be exacerbated.[63] Other therapies used with some degree of success have included botulinum toxin injection, pneumatic dilation, and surgical intervention.

Medical therapy of esophageal motility disorders is rather limited, and clinical results are usually minimal. Anticholinergic drugs such as hyoscyamine sulfate (Levsin) or dicyclomine (Bentyl) have been used because they decrease the amplitude of esophageal peristalsis and LES pressure. These drugs may also exacerbate reflux symptoms because they cause delayed gastric emptying and decreased esophageal peristalsis.

Calcium channel blockers decrease both LES pressure and the amplitude of esophageal contractions. Nifedipine has been used successfully in some patients.[64] Diltiazem has been shown to be effective in treating nutcracker esophagus.[65] Verapamil has been shown to decrease LES pressure when administered IV to healthy volunteers, but no effects have been noted with an oral dose.[66,67] Psychotropic medications such as alprazolam and trazodone have been used to treat some esophageal motility disorders. Although no study has demonstrated specific beneficial manometric effects, it is believed that the improvement may be secondary to treatment of an underlying functional disorder such as panic attacks or depression.[68]

PHARMACOLOGIC AGENTS FOR UPPER GASTROINTESTINAL DISORDERS

Antacids

By the time most patients present with upper GI complaints, most have already tried some form of antacid therapy because these agents are readily available as over-the-counter preparations. Antacids afford pain relief in most patients with PUD. Doses with low neutralizing capacity (as low as 30 mEq) promote ulcer healing. Antacids may also work by binding bile acids or inhibiting pepsin.

The choice of antacid should be individualized. The magnesium-containing antacids can produce diarrhea in up to 25% of patients. Magnesium-containing antacids can also lead to an increase in serum magnesium levels and should be avoided or used with caution in patients with impaired renal function. Aluminum-containing antacids may lead to constipation, and prolonged use may lead to phosphate depletion. Calcium-containing antacids have been marketed both as neutralizing acid and as a means of calcium supplementation, especially for postmenopausal women. Calcium-containing antacids have been traditionally believed to cause the most acid rebound, a paradoxical increase in gastrin secretion and acid production. Calcium antacids can also lead to constipation, and their excess consumption can lead to hypercalcemia, alkalosis, and renal insufficiency (the milk-alkali syndrome).

Antacids can also decrease the absorption of warfarin, digoxin, some anticonvulsants, and some antibiotics. The recommended dose of antacids in the treatment of PUD is 400 mmol/day divided over four doses, usually delivered 1 and 3 hours after meals and at bedtime. Antacids are the least expensive drugs available to treat PUD, but their use is somewhat limited by side effects and inconvenient dosing schedules.

Histamine Blockers

Histamine is the primary stimulus to gastric acid secretion. It binds to the type 2 histamine receptor (H_2) located on the basolateral portion of the parietal cell to stimulate the release of hydrochloric acid. The discovery of the ability of H_2-blockers to inhibit gastric acid production was a major advance in antiulcer therapy because ulcers cannot develop in the absence of acid. These drugs are highly selective competitive inhibitors of histamine for the H_2-receptor on parietal cells and reduce both the volume of gastric juice and its hydrogen ion concentration. All of the currently available H_2-blockers are rapidly absorbed after an oral dose, reaching peak levels within 1 to 2 hours. All have half-lives of approximately 2 to 3 hours, so the effects last for about 6 hours. Most are now available over the counter in lower dosage strength. H_2-blockers are effective in treating duodenal ulcer and, to a lesser extent, gastric ulcer, although they are not as effective as the PPIs. They are widely prescribed for symptoms of dyspepsia and work well in patients with episodic heartburn. All H_2-blockers are mainly hepatically and renally metabolized with the exception of nizatidine, which is almost exclusively renally metabolized. Dosages of all these agents should be reduced in patients with renal failure.

H_2-blockers are safe and generally well tolerated. Side effects are rare, including central nervous system effects such as somnolence, dizziness, and confusion. Transient increases in liver enzyme levels may be noted. Some patients may exhibit abnormalities in cardiac conduction, as there are H_2-receptors in the heart. Cimetidine has been shown to cause gynecomastia. Dosing of the various agents is summarized in Table 87-1.

Proton Pump Inhibitors

The H^+, K^+-ATPase (proton pump) is located on the apical portion of the parietal cell and is responsible for the production of hydrogen ions in gastric acid. PPIs are the most potent

inhibitors of gastric acid secretion. They work by irreversibly binding to stimulated proton pumps to block secretion of hydrogen ions. Although they have no effect on the volume of gastric juice produced, production of acid can be reduced by up to 95%. Both basal and stimulated gastric acid secretions are reduced. The antisecretory effects last up to 72 hours. PPIs should be administered before the first meal of the day, as the number of proton pumps is maximized after a fasting state. At the cellular level, additional proton pumps are continually recruited to produce more acid in response to stimulation; therefore, several doses of a PPI are necessary to achieve maximal antacid effect. The use of these medications on an as-needed basis would not be expected to provide a good clinical response. H_2-blockers are more suitable for this purpose.[69]

PPIs are hepatically metabolized, and dosage should be modified in patients with hepatic failure. Side effects are usually minimal. Although there are questions regarding the safety of long-term acid suppression leading to hypergastrinemia and hypochlorhydria, the 15-year experience with omeprazole has not demonstrated any clinically significant consequences.[70] PPIs may be used at significantly higher dosages in patients with Zollinger-Ellison syndrome. Dosing of the various agents is summarized in Table 87-2. Lansoprazole, pantoprazole, and esomeprazole are available as IV formulations.

Prostaglandins

Prostaglandins exert protective effects on the gastric mucosa by inhibiting acid secretion and decreasing the amount of cyclic adenosine monophosphate generated in response to histamine. Inhibition of gastric acid secretion, increased secretion of mucus and bicarbonate, and stimulation of mucosal blood flow have all been demonstrated.[71] Misoprostol (Cytotec) is an analogue of prostaglandin E_1 with a longer duration of action and greater potency than endogenous prostaglandins. It should be used only for prevention of NSAID-induced gastric ulcers in patients at high risk. The dose is 200 µg four times a day with food, but crampy abdominal pain and diarrhea may require the use of a somewhat less effective dose of 100 µg four times a day.[72] Misoprostol is an abortifacient and therefore is contraindicated in any female patient of childbearing age who is not using contraception.

Other Agents

Sucralfate (Carafate) binds to epithelial cells and especially to ulcerated surfaces, providing a protective layer that inhibits further acid damage. Its mechanism of action is not completely understood, although it has been shown to enhance epithelial growth, suppress acid secretion, and inhibit growth of *H. pylori*. The usual dose is 1 g four times a day given 30 to 60 minutes before meals.

Bismuth compounds such as bismuth subsalicylate (Pepto-Bismol) decrease pepsin activity, increase mucus secretion, and form a barrier to further acid damage in ulcer craters. They also increase prostaglandin synthesis and retard hydrogen ion diffusion through the mucosal barrier. Bismuth may also help heal ulcers through its bactericidal action on *H. pylori*. Bismuth compounds are not approved for the treatment of peptic ulcers.

KEY CONCEPTS

- The combined use of glucagon and an effervescent agent can cause rapid relief of acute lower esophageal obstruction in up to 75% of patients. Radiographic contrast studies of patients with suggested perforation of the esophagus or stomach should first be performed with water-soluble agents such as Gastrografin.
- There is a growing role for nonsurgical management of esophageal perforation for selected low-risk patients.
- GERD treatment includes lifestyle modification and therapy with an antisecretory agent, usually a PPI.
- Peptic ulcer disease results primarily from NSAID use or infection with *H. pylori*.
- Proton pump inhibitors are the most effective means of suppressing gastric acid secretion.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 88

Disorders of the Liver and Biliary Tract

David A. Guss and Leslie C. Oyama

HEPATIC DISORDERS

GENERAL PERSPECTIVE

The liver is one of the largest organs in the body, serving a multitude of critical functions. The average weight of the normal adult liver is 1500 g. It receives approximately 30% of the resting cardiac output by way of the portal vein and the hepatic artery.

The liver can be affected by a variety of disorders, and because of its varied synthetic and metabolic functions, liver disease may manifest with a broad range of clinical signs and symptoms. Acute and chronic diseases of the liver are common in the general population and represent a common cause for presentation to the emergency department (ED).

HEPATITIS

Perspective

Hepatitis is a generic term referring to inflammation of the liver. Hepatitis most commonly is a consequence of viral infection but can be secondary to bacterial, fungal, or parasitic infection; a result of toxic exposure; a side effect of prescribed medication; or a consequence of an immunologic disorder. Hepatitis in its generic context represents the most common variety of liver disease encountered by the emergency physician.

Viral Hepatitis

Although many viruses are associated with some degree of measurable liver inflammation, the most significant and potentially severe cases of viral hepatitis are caused by type A (infectious), type B (serum), type C (post-transfusion), and delta viruses. Although the Epstein-Barr virus, the causative agent of mononucleosis, is a common cause of hepatitis, it is more important clinically for its nonhepatic effects.

Epidemiology. The number of cases of hepatitis A has declined steadily, from a rate of 11.7 cases per 100,000 in 1997 to 1.5 per 100,000 population in 2005.[1,2] Western states had historically shown a higher incidence of hepatitis A, which in 1999 led to routine vaccinations of children from these areas. The greater decline in incidence of hepatitis A among children has resulted in an relative increase in the proportion of cases among adults.[3] The number of reported cases of hepatitis B declined by more than 80% in the interval between 1990 and 2005, again with the greatest decline occurring among children younger than 15 years of age.[3] The number of new cases of hepatitis C declined by approximately 80% during this period.[2] The reduced rates of hepatitis A and B are most likely to reflect today's broad use of effective vaccines.[4,5] Since the late 1980s, the incidence of acute of hepatitis C has declined, as a consequence of improved blood product screening. A majority of cases occur among adults, with injection drug use recognized as the most common risk factor.[3]

Hepatitis A virus (HAV), the causative agent of hepatitis A, is an RNA enteroviral picornavirus. It is spread by the fecal-oral route either directly or through contaminated water or foodstuffs. Transmission by blood is a theoretical possibility but is exceedingly rare. HAV can occur sporadically but is notorious for its association with epidemics generally linked to common source outbreaks. HAV infection is common worldwide; serologic evidence of previous infection exists in nearly 100% of the adult population in some regions. In the United States, close to one half of all urban-dwelling adults are seropositive for antibody for HAV.[5] High rates of seropositivity in association with the relatively small number of reported episodes support the notion that many cases may be asymptomatic. Occult disease appears to be more common in children, and 70% may be asymptomatic.[5] The incidence of hepatitis A infection varies among ethnic groups. In the United States, the incidence among different geographic areas and ethnic groups has changed notably since targeting of endemic areas with routine vaccination of children. In 2005, recommendations on immunization expanded to include routine vaccination of children in all 50 states.[6] These declines have shifted the pattern of reported risk factors, showing an increasing proportion of cases among adults—specifically, men who have sex with men (MSM), illicit intravenous drug users, and non–injection drug users. The most common risk factor for persons older than 15 years of age is travel.[2,6]

The typical incubation period for hepatitis A is 30 days, with a range of 15 to 45 days. Viremia is of relatively short duration and is most prominent before the onset of symptoms. Fecal shedding and maximum infectivity occur before the onset of symptomatic disease and generally have waned by the time jaundice appears (Fig. 88-1). HAV is not associated with a chronic carrier state.

Hepatitis B virus (HBV) is contained in a 42-nm structure called the *Dane particle*. Within this enveloped virion is the viral DNA, DNA polymerase, hepatitis B surface antigen

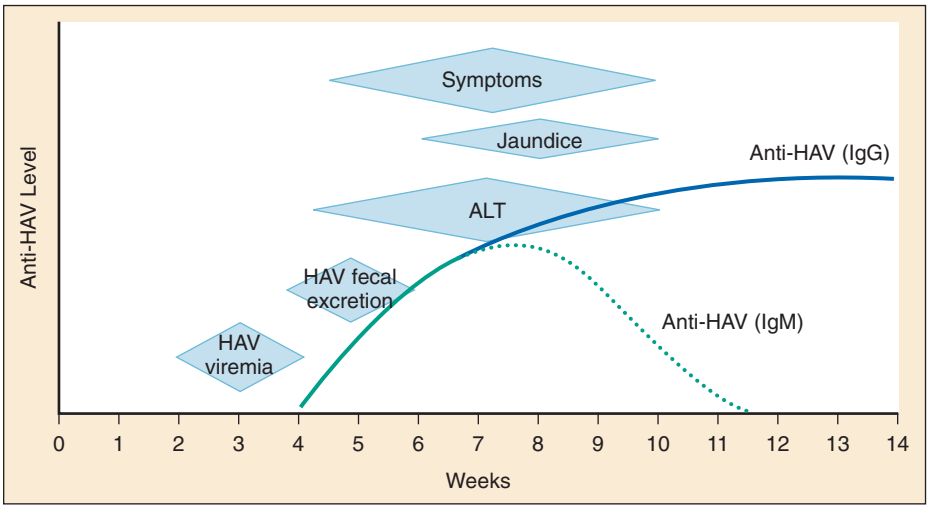


Figure 88-1. Acute hepatitis A virus (HAV) infection. ALT, alanine aminotransferase; IgG, immunoglobulin; IgM, immunoglobulin M.

(HBsAg), and hepatitis B core antigen (HBcAg). Hepatitis B e antigen (HBeAg), detectable in the serum of infected patients, is thought to be a degradation product of HBcAg.[7] In contrast with HAV, for which there is only a single antigenic variety, several genotypes of HBV, as defined by surface antigen, are recognized. HBV is transmitted principally by parenteral exposure but also can be transmitted through intimate contact. The highest rates of infection are among illicit intravenous drug users and homosexual men. Transmission by blood transfusion, previously a common source of infection, has been eliminated because of modern blood bank screening techniques.

HBsAg has been detected in a variety of bodily secretions, including saliva, semen, stool, tears, urine, and vaginal secretions. Although the presence of HBsAg is not synonymous with infectivity, HBV DNA has been identified in several of these fluids and is likely to be infectious. The typical interval between exposure and onset of clinical illness is between 60 and 90 days; however, serologic markers of infection generally appear within 1 to 3 weeks[8] (Fig. 88-2). Approximately 10% of adults and 95% of infected neonates with immature immune systems will become asymptomatic chronic carriers of HBsAg.[9,10] Health care workers who routinely come in contact with blood have a prevalence of HBsAg of 1 to 2%, and 15 to 30% show serologic evidence of previous infection.[11] Among emergency physicians, seropositivity rates of 12% and 15% have been reported.[12] The likelihood of becoming chronically infected with HBV varies inversely with the age at which infection occurs. HBV transmitted from HBsAg-positive mothers to their newborns results in HBV carriage in up to 90% of infants, whereas only 6 to 10% of acutely infected adults become carriers.[10,13] Approximately 3 to 5% of the cases of hepatitis B will progress to chronic hepatitis.

What was historically referred to as non-A, non-B hepatitis is caused by at least two distinct RNA viruses, hepatitis C virus and hepatitis E virus. Hepatitis C, linked to transfusions, is common in the United States. Hepatitis E, which is associated with fecal-oral transmission, is encountered most often in Asia, Africa, and Russia. The historical risk of hepatitis in patients receiving blood transfusions was approximately 0.45% per unit transfused. The screening of donor blood for surrogate markers (aminotransferases) and antibody to hepatitis C has decreased this risk to less than 1 per 1 million transfused units.[14] The estimated risk of transfusion-transmitted HCV is now 1 per 103,000 transfusions.[14,15] Although hepatitis C is most often associated with transfusions, only 10% of patients with this

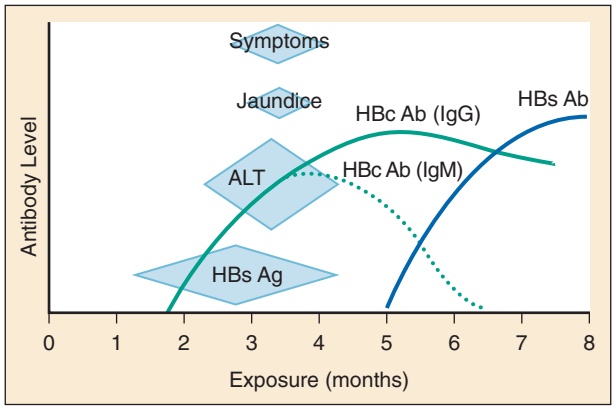


Figure 88-2. Acute hepatitis B virus infection. Ab, antibody; Ag, antigen; ALT, alanine aminotransferase; HBc, hepatitis B core; HBs, hepatitis B surface; IgG, immunoglobulin G; IgM, immunoglobulin M.

disease report a previous history of having received blood or blood products. Approximately 4 to 8% of cases are linked to occupational exposure in health care workers, and 23 to 42% are associated with intravenous drug use.[16] Among patients infected with HIV, the incidence of co-infection with hepatitis C is 15 to 30%. This rate approaches 50 to 90% in those who acquired HIV through intravenous drug use (IVDU).[17] Patients co-infected with HIV and HCV generally will have a more aggressive course of both their HIV and HCV infections.[18] In 40 to 57% of cases of hepatitis C, no source of infection is identified. The incubation period for hepatitis C is 30 to 90 days, with a mean of 50 days. Hepatitis E has an incubation period of 15 to 60 days. Approximately 90% of HCV infections go on to become chronic hepatitis. Long-term follow-up studies indicate that clinical liver disease develops in only 10 to 20% of those infected during a period of approximately 20 years after transfusion.[19] In the United States, it is estimated that 2.7 million people are chronically infected with HCV.[20,21]

Hepatitis delta virus (HDV) was discovered in 1977 in liver specimens from patients with chronic HBV infection.[22] It is a defective RNA virus that can infect only patients who are actively producing HBsAg, which is required for its viral coating. In the United States, the incidence of HDV antibody is between 4% and 30% of patients with chronic HBV infec-

tion.[23,24] As a consequence of the routine association with chronic HBV infection, it is likely that many cases of HDV infection are misdiagnosed as acute or reactivated hepatitis B. HDV infection is spread in a manner similar to that for hepatitis B, being most common among illicit intravenous drug users, promiscuous homosexual men, and patients with hemophilia. Infection with HDV can occur either concomitantly with HBV (co-infection) or subsequent to earlier HBV infection (superinfection), because HDV cannot replicate in the absence of HBV.[10] In cases of co-infection, the course of the illness generally is dominated by HBV; however, HDV seems to carry an increased risk for fulminant disease.[25] In cases of superinfection, the presentation may range from acute self-limited disease to fulminant hepatitis or chronic infection.

Hepatitis G virus (HGV), also referred to as hepatitis GB virus type C, is the most recently identified virus associated with hepatitis. It is a RNA virus in the Flaviviridae family. Transmission of HGV seems to occur through blood transfusion and parenteral exposure to blood or blood products and possibly during intimate sexual contact. The virus has been identified in patients with acute and chronic hepatitis. However, it generally is believed to be an "innocent bystander," with disease manifestations attributed to co-infection with another hepatitis virus.[26,27]

Principles of Disease. The pathophysiology of viral hepatitis is not completely understood. In the most common varieties of hepatitis, liver injury appears to be related to the development of the immunologic response to infection rather than to the cytopathologic effect of the virus. HDV appears to be an exception, having significant direct cytotoxic potential.

Clinical Features. The clinical presentation of viral hepatitis is highly variable. A significant number, possibly a majority, of cases are asymptomatic. The protean nature of symptoms and the common occurrence of anicteric disease can result in misdiagnosis. The most common symptoms and signs are malaise, fever, and anorexia, followed by nausea, vomiting, abdominal discomfort, and diarrhea. The first symptom leading to physician consultation typically is jaundice. A small number of patients with hepatitis B may experience a prodromal illness characterized by arthralgia or arthritis and dermatitis. The joint involvement typically is polyarticular; the small joints of the hands and the wrists are most commonly affected. Joint fluid usually is noninflammatory, but cell counts for aspirated fluid can be as high as 90,000/mm^3. The characteristic dermatitis is urticarial but may be macular, papular, or petechial.

Fulminant hepatitis is characterized by acute onset and progresses to hepatic failure and encephalopathy over a period of days. Although most often encountered with HBV and HDV, fulminant hepatitis can occur in association with all of the causative viruses.[28] The overall incidence of fulminant hepatitis is 1 to 2% of all cases. The hallmarks of fulminant disease are altered mentation and spontaneous mucosal bleeding.

Physical findings include elevated temperature, scleral or cutaneous icterus, and abdominal tenderness. If significant vomiting has occurred, tachycardia and supine or orthostatic hypotension may be noted. Hepatomegaly may be detected and generally is characterized by a smooth, homogeneous, and tender liver surface. Even if liver enlargement is not appreciated, the patient often exhibits tenderness to percussion over the lower right ribs. Scleral icterus is generally noticeable earlier than cutaneous discoloration, particularly in people of pigmented races. Muddy sclera, commonly found among African-American patients, may obscure or confuse this finding. An alternative in this setting is examination of sublingual or subungual surfaces. Scleral icterus usually is not clinically apparent until serum bilirubin is above 2.5 mg/dL. Spider angiomata and splenomegaly, although more commonly associated with cirrhosis, may be features in acute presentations. Gray or acholic stools are distinctly uncommon.

Diagnostic Strategies. Laboratory tests are critically important in diagnosing hepatitis and determining the specific cause. The most useful tests are measurements of the hepatic aminotransferases and bilirubin. Typically, hepatitis is associated with elevations (10- to 100-fold) of serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT), with ALT generally elevated in excess of AST. Bilirubin may be moderately increased (5 to 10 mg/dL) and occasionally is markedly elevated (15 to 25 mg/dL). Hyperbilirubinemia typically emerges several days to a week or more after the onset of clinical symptoms. Both direct and indirect bilirubin levels are elevated in close to equal proportions. Alkaline phosphatase and lactate dehydrogenase may be elevated but rarely are more than two to three times normal. Prothrombin time (PT) or international normalized ratio (INR) is useful in assessing the degree of hepatic synthetic dysfunction. Elevation of the PT or INR may be the first clue to a complicated course. The white blood cell count (WBC) generally is not useful in the diagnosis because values range from low overall counts with a lymphocytic predominance to marked polymorphonuclear leukocytosis.

Although determination of the precise cause of hepatitis can rarely be achieved in the ED, this evaluation should be initiated as soon as possible. Identification of the causative agent has significant impact on prognosis and public health issues. In this regard, it is important to be able to interpret the significance of certain serologic tests (Table 88-1).

Acute hepatitis A is diagnosed by the presence of immunoglobulin M (IgM) HAV antibody, whereas previous infection is determined by detection of an immunoglobulin G (IgG) antibody. Acute hepatitis B is characterized by the presence of HBsAg and IgM antibody to HBcAg. HBsAg alone does not establish the diagnosis of acute hepatitis B because it can be either absent late in the course of acute disease or present chronically unrelated to the cause of the current episode. Anti-HBcAg antibody generally is the best indicator of previous HBV infection, whereas anti-HBsAg antibody is the best marker for immunity to HBV.

Currently, the diagnosis of hepatitis C is based on the exposure history and the elimination of other causes. The serologic assay for an antibody to this virus facilitates a definitive diagnosis, but there can be a delay between the onset of symptoms and the development of assayable antibody.[29] Furthermore, the HCV test does not distinguish acute from chronic infection.

Diagnosing HDV infection requires an aggressive search because the disease can easily be mistaken for acute or chronic HBV infection. A serologic test for the antibody to HDV (anti-HDV) is available. The presence of this antibody in conjunction with IgM antibody to HBcAg suggests co-infection with HDV and HBV. Anti-HDV in association with IgG antibody to HBcAg supports the diagnosis of superinfection.

The temporal relationships among infection, clinical symptoms, and serologic responses for the two most common causes of viral hepatitis, HAV and HBV, are delineated in Figures 88-1 and 88-2.

Differential Considerations. The protean nature of the symptoms and signs associated with viral hepatitis makes the differential diagnosis of this disorder quite broad in scope. Beyond a variety of nonhepatic viral illnesses, all of the infectious, chemical, and immunologic causes of hepatic inflammation in addition to biliary tract disease must be considered. A viral cause often is suggested by the exposure and medical history but requires serologic tests for confirmation. Alcoholic hepatitis

Table 88-1 Serologic Markers in Hepatitis

SEROLOGIC MARKER	ABBREVIATION	INTERPRETATION
Antibody to HAV	Anti-HAV	A combination of IgG and IgM antibody defining infection with HAV, acute or past
IgM antibody to HAV	Anti-HAV IgM	Antibody to HAV, indicating acute infection
Hepatitis B surface antigen	HBsAg	Surface antigen associated with acute or chronic HBV infection
Hepatitis B e antigen	HBeAg	Antigen associated with active infection, acute or chronic, and indicative of high infectivity
Antibody to B surface antigen	HBsAb	Antibody indicative of acute or past infection or immunization
Antibody to B core antigen	HBcAb	A combination of IgG and IgM antibody defining infection with HBV, acute or past
IgM antibody to B core antigen	HBcAb-IgM	Antibody to B core antigen, indicating acute infection with HBV
Antibody to B e antigen	HBeAb	Antibody to e antigen, possibly representing resolving HBV infection and decreased infectivity
Antibody to HDV	Anti-HDV	Antibody defining infection with HDV; HBsAg should be present
Antibody to HCV	Anti-HCV	A new antibody that defines infection with HCV, acute or past

HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis delta virus; IgG, immunoglobulin G; IgM, immunoglobulin M.

usually is associated with a history of chronic or excessive alcohol consumption, less marked elevation of hepatic transaminases, and AST levels elevated above those of ALT. Extrahepatic obstruction, cholecystitis, and cholelithiasis are excluded by their lack of association with significant elevation of aminotransferases; however, abdominal ultrasound studies may be required to eliminate these other causes.

Management. Treatment of viral hepatitis is primarily symptomatic. It often is necessary to correct fluid and electrolyte imbalances secondary to poor oral intake or excessive diarrhea or vomiting. Antiemetics may allow resumption of adequate oral intake, thereby avoiding the need for hospital admission. In the anorectic or nauseous patient, fluid intake should be encouraged, with avoidance of solids until they are palatable. Medications requiring primarily hepatic metabolism generally do not need to be discontinued nor the dosage modified unless there is significant hepatic dysfunction. Nonessential drugs with hepatotoxic potential should be avoided. Alcohol consumption should be completely discontinued until signs of liver injury have disappeared. Although a variety of active interventions (e.g., corticosteroid administration) have been suggested, no reliable data suggest that such therapies offer clear benefit; they may even be harmful.

Complications of acute hepatitis are most commonly related to fluid or electrolyte imbalance as a result of inadequate oral intake or refractory emesis. Severe vomiting can result in upper gastrointestinal (GI) bleeding from an esophageal tear. The most severe complication of acute disease is the development of liver failure heralded by the emergence of hepatic encephalopathy. Most patients with viral hepatitis have self-limited disease, with symptomatic and histologic resolution in 2 to 4 weeks. Chronic disease will develop in approximately 10% of patients with hepatitis B and in as many as 50% of those with hepatitis C.[19] Clinical liver disease develops in only 10 to 20% of chronically infected patients approximately 20 years after becoming infected. Many of these patients will eventually die of cirrhosis secondary to their disease.[19]

Disposition. Hospital admission is rarely required for management of viral hepatitis and generally is reserved for the patient with significant fluid and electrolyte imbalance or refractory vomiting. Patients with less severe illness may require hospitalization for concomitant medical problems or if suitable living arrangements are not available. Altered sensorium, prolongation of the PT beyond 5 seconds or increase in the INR above 1.5 may suggest fulminant disease or an increased likelihood of a complicated course, necessitating hospitalization for observation. The emergence of fulminant disease should lead to consideration of transfer to a facility that can offer liver transplantation.

Treatment with interferon alfa-2b has resulted in a 35 to 45% remission rate after a 4-month course of treatment in selected patients with active immune responses in the symptomatic stage 2 period of hepatitis B infection.[10,30,31] Hepatitis C treatment recommendations suggest that duration of treatment with interferon and ribavirin should be based on the HCV genotype and pretreatment viral load. Polyethylene glycol added to interferon alfa (peginterferon alfa) extends the half-life and duration of the therapeutic activity of the interferon. Corresponding clinical benfits include both a higher rate of response than with conventional daily interferon monotherapy and feasibility of once-weekly administration.[32] Referral to a hepatic disease specialist is recommended.

Anxiety about disease communicability may affect the ease of disposition. Patients with possible HAV infection should be advised to practice meticulous personal hygiene, not to share toiletries, and to ensure cleaning of utensils and kitchenware between uses. In those patients with suspected HBV or HDV infection, the relatively low risk of transmission in lieu of intimate personal contact or parenteral exposure should be emphasized.

Viral hepatitis is a reportable disease requiring notification of the local health department. Immunoprophylaxis should be provided to the patient's family members and close personal contacts. Although the nature of prophylaxis depends on the specific viral cause, it is wise to offer gamma globulin to household contacts immediately unless they are known to have been previously immunized, pending serologic determination. Table 88-2 outlines the guidelines for immunoprophylaxis. Patients with HAV infection who process or handle food must not return to work while potentially infectious. Although infectivity is greatly diminished by the time jaundice emerges, it is best to delay return to work until after jaundice has cleared.

Special Considerations

Effective pre-exposure and post-exposure prophylaxis for HBV has been available for over 2 decades. The rates of seropositivity for HBV infection among health care workers have historically been high compared with those in the general

Table 88-2 Postexposure Hepatitis Prophylaxis

HEPATITIS A NATURE OF EXPOSURE	RECOMMENDED TREATMENT
Close personal contact	ISG 0.02 mL/kg IM
Daycare center	
Employee	ISG 0.02 mL/kg IM
Attendee	ISG 0.02 mL/kg IM
School contacts	None
Hospital contacts	None
Workplace contacts	None
Food-borne source	
Within 2 weeks of exposure	ISG 0.02 mL/kg IM
After 2 weeks of exposure	None
After common source outbreaks have begun to occur	None

HEPATITIS B			
		EXPOSED INDIVIDUAL	
NATURE OF EXPOSURE	SOURCE	UNVACCINATED	VACCINATED
Percutaneous/mucosal	HBsAG+	1. HBIG* 2. HB vaccine†	1. Test for HBsAb; if –, then give: a. HBIG b. HB vaccine
	Known source High-risk HbsAg+	1. HB vaccine 2. Test source; if +, then give HBIG	1. Test for HBsAb; if – and source HBsAg+, then give: a. HBIG b. HB vaccine
	Low-risk HBsAg+	1. HB vaccine	1. None
	Unknown source	1. HB vaccine	1. None
Intimate sexual	HBsAg+	1. HBIG 2. HB vaccine‡	1. None
Household/workplace	HBsAg+	1. None	1. None
Perinatal	HBsAg+	1. HBIG§ 2. HB vaccine	NA

HEPATITIS C
Unknown benefit from prophylaxis; ISG 0.06 mL/kg IM can be considered for parenteral exposures in patients with evidence of viral hepatitis and negative results on serologic studies

HEPATITIS DELTA
Same as for hepatitis B

*HBIG dose: 0.06 mL/kg IM.
†HB vaccine dose: 10 to 20 µg IM deltoid, depending on variety of vaccine used (adequate vaccination requires three injections, so all patients should be referred for follow-up care).
‡Vaccine required only if repeated sexual contacts are likely to occur over an extended period of time and the source becomes a chronic carrier.
§HBIG dose: 0.5 mL.
HB, hepatitis B; HBIG, hepatitis B immune globulin; HBsAg, hepatitis B surface antigen; ISG, immune serum globulin.
Modified from Protection against viral hepatitis. Recommendations of the Immunization Practices Advisory Committee (ACIP). MMWR Recomm Rep 39(RR-2):1, 1990.

population. Health care workers in an ED are at increased risk because of frequent contact with blood and interaction with high-risk patients. Historically, the seropositivity rate among ED nurses is 30% and among ED physicians is between 12% and 15%.[33,34] The 1-year risk of infection among nonimmunized emergency physicians is approximately 0.25%, with a 30-year risk approaching 7.5%. During a 30-year career, the risk of death from hepatitis B is estimated at 1/540.[35] Markers for hepatitis C were identified in 18% of patients in an inner-city ED; the potential associated health risk to staff is unknown.

All ED personnel involved in patient care or custodial work should be vaccinated for HBV before or soon after employment. The vaccine is highly effective and associated with minimal acute or delayed toxicity. A complete three-injection series of vaccine produces protective antibody in approximately 95% of persons. [36] Optimal immunologic response is obtained with deltoid injection.[37] HBV immune globulin (HBIG) is recommended for immediate passive immunization in persons not previously immunized but exposed to potentially infective material. HBIG alone diminishes the risk of HBV infection by 75%.[13] Unvaccinated, exposed people should receive HBIG 0.06 mL/kg IM in addition to the HBV vaccine. Concerns related to the potential risk of HIV infection from gamma globulin preparations are unfounded. Figure 88-3 outlines an approach for managing health care workers exposed to blood or other potentially infectious secretions.

A safe and effective vaccine for HAV is available; however, health care workers are not currently on the list of those recommended for routine immunization.[5]

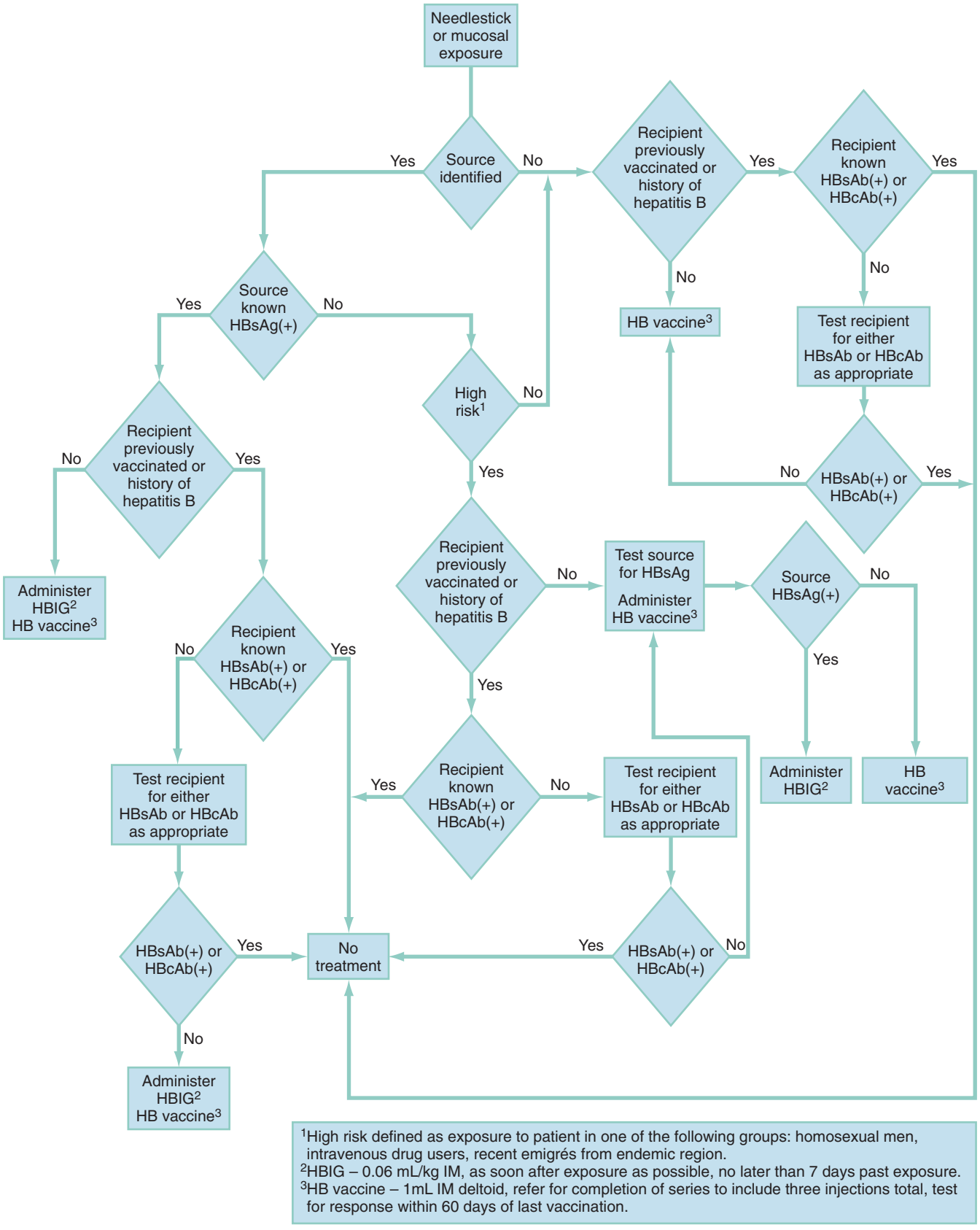


Figure 88-3. Management of health care workers exposed to blood or other infectious secretions. Ab, antibody; Ag, antigen; HB, hepatitis B; HBc, HB core; HBIG, HB immune globulin; HBs, HB surface.

The risk of seroconversion after percutaneous exposure from an HCV-positive source is approximately 1.8%[17] Despite the theoretical risk of blood-borne HCV exposure among health care workers, the prevalence of HCV infection in this group is approximately 1 to 2%, the same as in the general population.[17] No effective vaccine for HCV is available, and despite evidence to suggest effectiveness of interferon in acute hepatitis C, there is no accepted pre- or post-exposure prophylaxis regimen.[38]

Universal precautions—the use of gloves, masks, protective eye wear and gowns—constitute the first and best means of defense for persons who work in proximity to potentially infective bodily fluids.

KEY CONCEPTS

- Viral hepatitis is a common disorder that can be caused by several agents.
- Clinical presentation is highly variable, and many cases, particularly in children, are asymptomatic.
- The process of identifying the etiologic agent should be initiated in the ED because it affects both prognosis and public health interventions.
- Many of the etiologic agents of viral hepatitis represent a potential threat to health care workers, necessitating proper precautions in handling potentially infectious body fluids and pre- and post-exposure prophylaxis.

Alcohol-Related Liver Disease

Perspective. In the United States, an estimated 15 million to 20 million people are chronic alcoholics.[39] Alcohol and its metabolites are toxic to most organ systems and contribute to disease or death from many different causes. The liver is the most common site of injury from chronic ethanol ingestion. Alcoholic liver disease is ranked as the fourth leading cause of death among men aged 25 to 64 years living in urban areas. Cirrhosis, most commonly linked to chronic alcohol consumption, is a common cause of death and years of productive life lost.[40]

Principles of Disease. Alcohol is largely eliminated by metabolic degradation in the liver. Approximately 2 to 15% of alcohol is excreted unchanged in the urine or expired air.[41] The precise pathogenesis of alcoholic liver disease is unknown and probably is multifactorial. Coexistent malnutrition, accumulation of toxic metabolites (e.g., acetaldehyde), excessive production of nicotinamide adenine dinucleotide (NADH) and induction of microsomal enzymes due to the metabolism of alcohol, and alteration of immune function all may play a role.[41]

Regardless of the precise mechanism of injury, genetic heterogeneity in susceptibility to liver damage is likely. Women and possibly Native Americans appear to have an increased propensity for injury relative to white men.[42,43] A study of Portuguese adults identified certain histocompatibility antigens with increased risk of ethanol-related hepatic injury.[44] Although susceptibility to alcohol varies, a rough correlation is recognized between the amount of ethanol ingested and the risk of developing liver disease. The risk of liver injury increases as daily consumption exceeds 80 g of ethanol daily in men and 20 g in women. For men, this is equivalent to a six-pack of beer, four to six glasses of wine, or three to four mixed drinks daily.[39]

The most common variety of alcohol-induced liver disease is steatosis. Fatty infiltration of the liver is most likely a consequence of altered fatty acid metabolism resulting from a diminished NAD^+/NADH ratio, which favors triglyceride production. Fatty infiltration appears to depend on the duration and amount of alcohol consumed and, in general, is reversible when the patient stops drinking. Beyond enlargement of the liver, which usually is painless, this tends to be a benign process.

Clinical Features. Alcoholic hepatitis is a potentially severe form of alcohol-induced liver disease. Most cases probably are subclinical, but the spectrum of presentation can range from nausea, vomiting, and abdominal pain to acute liver failure.

Physical findings include tachycardia, fever, and supine or orthostatic hypotension. Abdominal tenderness usually can be elicited, especially in the right upper quadrant. Coexistent fatty infiltration may produce palpable hepatomegaly; cirrhosis from chronic disease may result in a small, nonpalpable liver. The characteristic physical signs of cirrhosis (gynecomastia, spider angiomata, muscle wasting, ascites, and palmar erythema) may be present. Jaundice can be noted in patients with a bilirubin level of at least 2.5 mg/dL.

Diagnostic Strategies. Laboratory tests reveal moderate elevations of AST and ALT. Values in excess of 10 times normal are unusual, even in severe cases associated with eventual liver failure. Compared with viral hepatitis, a relative predominance of AST to ALT is expected. Bilirubin is commonly elevated. The WBC count often is high, with a polymorphonuclear leukocytosis in the range of 10,000 to 20,000/mm^3. The PT and the INR provide a rough assessment of hepatic dysfunction. An acutely prolonged PT or elevated INR in a patient not suspected to have chronic cirrhotic disease suggests a complicated course. Electrolyte or acid-base disturbances may develop as a consequence of excessive vomiting or alcoholic ketoacidosis.

Differential Considerations. The differential diagnosis of alcoholic hepatitis is quite broad in scope and includes a variety of other alcohol-related GI maladies (e.g., gastritis, pancreatitis). Patients often have several ethanol-induced diseases simultaneously. Initially, all of the potential etiologic disorders must be considered; however, the clinical history and aminotransferase profile should facilitate accurate diagnosis. Mild aminotransferase elevation and marked bilirubin elevation is consistent with alcoholic hepatitis; ultrasonography will help differentiate this from common duct obstruction. Serum should be sent for testing for anti-HAV IgM and HBcAb IgM, but results usually are not available to establish these diagnoses in the ED.

Management. Management of alcoholic hepatitis is principally supportive. Fluid and electrolyte imbalance must be corrected, usually requiring parenteral fluid replacement; antiemetics may mitigate the need for intravenous treatment. Alcohol may suppress gluconeogenesis, thereby causing hypoglycemia. Blood glucose should be measured and supplemented as indicated. Many alcoholics are malnourished, and if thiamine deficiency is suspected, it should be given in a dose of 50 to 100 mg IM or IV before glucose administration to avoid inducing acute Wernicke's encephalopathy. Ethanol-induced magnesium wasting may not be apparent on serum magnesium measurement, and replacement should be given empirically unless the patient has a contraindication such as renal failure or known hypermagnesemia. Magnesium can be given as the sulfate salt in a dose of 1 g IV or IM or as an oxide, chloride salt, or amino acid conjugate for oral replacement therapy in a daily dose of 200 to 1000 mg.

The overall nutritional status of the patient should be addressed with the administration of a high-calorie, vitamin-supplemented diet. Protein content may require restriction if evidence of cirrhosis and incipient encephalopathy exists.

Coexisting gastritis should be treated with histamine H_2 antagonists, proton pump inhibitors, or antacids. The patient should be evaluated for GI bleeding and treated appropriately. Corticosteroids, propylthiouracil, and insulin-glucagon infusions have been investigated for treatment of alcoholic hepatitis and look promising in severe cases, but none of these agents have gained acceptance as part of routine management.[39,45-47]

Disposition. Disposition is determined by the patient's clinical state: the degree of fluid and electrolyte abnormality, the ability to retain oral intake, any coexistent illnesses or complications, and the patient's socioeconomic circumstances. Admission to the hospital generally is not required. All patients should be advised to abstain from further alcohol ingestion and should be provided referral for detoxification or alcohol dependency treatment.

KEY CONCEPTS

- The liver is one of the most common targets of alcohol toxicity.
- Alcoholic hepatitis, although generally a mild disease with minor clinical manifestations, can be a cause of fulminant hepatitis.
- Management of patients with alcoholic hepatitis should include referral for alcohol dependence treatment.

Cirrhosis

Principles of Disease. *Cirrhosis* is a generic term for an end stage of chronic liver disease characterized by destruction of hepatocytes and replacement of normal hepatic architecture with fibrotic tissue and regenerative nodules. *Laennec's cirrhosis* is a diffuse process that involves the entire lobule and most often is related to chronic alcohol ingestion. From 10 to 20% of chronic alcoholics develop this type of cirrhosis. Amount and duration of alcohol ingestion, heredity, and underlying nutritional status all seem to play some role in the development of this disorder. *Postnecrotic cirrhosis* usually is nonhomogeneous, characterized by regions of fibrosis and hepatocyte loss alternating with normal areas. It most often is a consequence of chronic hepatitis of various causes: infectious (viral, bacterial, fungal), drug-induced, or metabolic. *Biliary cirrhosis* is much less common and is a consequence of chronic extrahepatic biliary obstruction or a primary disorder of autoimmune mediated intrahepatic duct inflammation and scarring. Nonalcoholic fatty liver disease has become an increasingly recognized cause of *cryptogenic cirrhosis*. This still poorly understood disease, with features similar to those of Laennec's cirrhosis, is more common in obese patients and those with type 2 diabetes mellitus.[48]

Clinical Features. The clinical manifestations of cirrhosis are related to loss of hepatocytes, leading to metabolic and synthetic dysfunction, or to fibrosis and altered hepatic architecture, resulting in impaired portal vein blood flow and portal hypertension. Typically, the patient with cirrhosis complains of chronic fatigue and poor appetite. With the exception of those with biliary cirrhosis, many patients with cirrhosis can be asymptomatic until some dramatic complication develops, such as GI bleeding, ascites, or hepatic encephalopathy. Patients with biliary cirrhosis generally complain of pruritus or exhibit obvious jaundice before end-stage cirrhosis or complications develop. Primary biliary cirrhosis may be associated with other immune-mediated disorders; these patients may have signs and symptoms characteristic of scleroderma or the CREST syndrome (i.e., calcinosis cutis, Raynaud phenomenon, esophageal motility disorder, sclerodactyly, and telangiectasia).[49]

Physical examination may reveal muscle wasting, thinning of the skin with patchy ecchymosis, spider angiomata, palmar erythema, Dupuytren's contracture, and in men, gynecomastia or testicular atrophy. Jaundice generally is absent in mild cases or in early disease. The liver may not be palpable if it is extensively scarred, but a large regenerative nodule, tumor, or fatty infiltration can result in hepatomegaly. Ascites is common, particularly in advanced disease, and may be present in association with a characteristic pattern of abdominal wall vein distention known as *caput medusae*.

Diagnostic Strategies. Laboratory tests are not specific. Aminotransferase levels are rarely more than minimally elevated. Bilirubin may be increased but usually not until cirrhosis is far advanced. Elevation of alkaline phosphatase out of proportion to other liver enzymes is suggestive of biliary cirrhosis. Coagulation studies commonly show abnormalities, and the serum albumin level is low as a result of impaired hepatic synthetic function. Mild to moderate anemia and thrombocytopenia often are present in Laennec's cirrhosis. Elevated blood urea nitrogen (BUN) or creatinine suggests dehydration or hepatorenal syndrome.

Ancillary tests are rarely of use in the ED setting. Ultrasonography is highly sensitive for the detection of ascites, but a carefully performed physical examination generally can yield equivalent results. Patients with ascites and fever or abdominal pain should have paracentesis performed to rule out spontaneous bacterial peritonitis (SBP, see later section). Nuclear scintigraphy or computed tomography (CT) imaging may reveal a hepatic or splenic appearance characteristic of cirrhosis and portal hypertension, but in general, these tests should be deferred to an elective setting.

Management. Treatment of cirrhosis in the ED is limited. Fluid and electrolyte imbalances should be corrected, and vitamin and nutritional supplements should be provided. Most patients can be discharged with referral to a general internist for further evaluation and treatment. Ascites associated with respiratory compromise or significant discomfort can be treated with paracentesis and removal of 2 L of fluid or more. Removal of very large quantities of ascitic fluid can result in body fluid and electrolyte abnormalities and hemodynamic instability. If SBP is a consideration, diagnostic paracentesis should be done.

A low-sodium diet, in conjunction with an aldosterone antagonist, may be of use in the chronic management of ascites. A low-dose regimen of a thiazide or loop diuretic may accelerate resolution of ascites and probably is safe if the patient has coexistent peripheral edema and normal renal function. Coagulopathy noted before a planned invasive procedure or in conjunction with active bleeding should be corrected with fresh frozen plasma. With uncomplicated prolongation of PT or INR, treatment with vitamin K supplementation can be given but often is ineffective. GI bleeding should be treated aggressively. Early consultation with a gastroenterologist for endoscopy often will permit identification of a bleeding site and initiation of appropriate adjunctive treatment. An elevated creatinine level may herald the onset of hepatorenal syndrome and necessitates hospitalization of the patient for optimal fluid and electrolyte management.

Complications of cirrhosis include GI bleeding, ascites with or without infection, encephalopathy, and hepatorenal syndrome. Although GI bleeding often is related to esophageal or gastric varices, more than one half of the cases result from some other source (e.g., gastritis or a duodenal ulcer). Ascites

occurs as a consequence of portal hypertension, impaired hepatic lymph flow, hypoalbuminemia, or renal salt retention. Ascites generally causes few signs and symptoms beyond abdominal distention and discomfort. However, massive ascites can lead to respiratory embarrassment. SBP is an important and often subtle complication. Encephalopathy occurs as a result of impaired hepatic metabolic function and portal hypertension (see later on). *Hepatorenal syndrome* is defined as renal failure occurring in the setting of cirrhosis without obvious renal pathology. The mechanism of this almost universally fatal complication is not understood. An otherwise unexplained elevation of creatinine or BUN suggests an emerging hepatorenal state.

KEY CONCEPTS

- Cirrhosis is an advanced stage of liver disease from a variety of causes.
- Patients with cirrhosis most often present to the ED with complications of their disease: ascites, variceal bleeding, and hepatic encephalopathy.
- Impaired hepatic synthetic and metabolic function in patients with cirrhosis may require correction of coagulopathy before invasive procedures and modification of medication dosing.

Hepatic Encephalopathy

Principles of Disease. *Hepatic encephalopathy* is a clinical state of disordered cerebral function that may develop as a consequence of acute or chronic liver disease. The pathophysiology of hepatic coma is complex and related to the diseased liver's failure to adequately perform its normal metabolic functions. Ammonia, formed primarily in the GI tract by the action of bacteria on proteinaceous compounds, is a common marker of this process. Normally, absorbed ammonia is converted to urea in the liver. In severe hepatic disease, ammonia accumulates, crosses the blood-brain barrier, and combines sequentially with α-ketoglutarate and glutamate to form glutamine. Serum ammonia levels correlate inconsistently with the severity of encephalopathy, but a close association with cerebrospinal fluid (CSF) glutamine levels has been recognized.[50] Whether glutamine is itself toxic or simply represents a marker for disordered central nervous system (CNS) metabolism is unknown. Other agents presumed to play a role in the pathophysiology of this disorder include mercaptans, octopamine, γ-aminobutyric acid, and the aromatic amino acids, particularly tryptophan.

Clinical Features. The clinical manifestations of hepatic encephalopathy vary depending on the severity of the process, ranging from mild cognitive dysfunction, irritability, and confusion to profound coma. Table 88-3 summarizes the four stages of hepatic encephalopathy. Asterixis, a low-amplitude, alternating flexion and extension of the wrist occurring when it is held in extension, is characteristic of mild to moderate degrees of encephalopathy. A similar finding may be elicited in the dorsiflexed foot, or similar head movements may occur with extension of the neck. Fetor hepaticus, a musty breath odor presumably from mercaptans, may be detected in severe cases.

Physical examination commonly reveals signs of cirrhosis, including spider angiomata, testicular atrophy, muscle wasting, superficial bruising, gynecomastia, and ascites.

Diagnostic Strategies. Laboratory test results may be normal or indicate fulminate liver failure or chronic cirrhosis. Serum ammonia levels generally are elevated but do not necessarily correlate with the severity of encephalopathy. Results of tests reflective of hepatic synthetic function, serum albumin and PT, generally are abnormal. The electroencephalogram shows abnormalities in most cases, but the pattern of generalized slowing with high-voltage bursts of triphasic or delta waves characteristic of hepatic encephalopathy is not specific for this entity.[50]

Table 88-3 Grades of Hepatic Encephalopathy

GRADE	CLINICAL DESCRIPTION
I	Disordered sleep, irritability, depression, mild cognitive dysfunction
II	Lethargy, disorientation, confusion, personality changes, asterixis
III	Somnolence or marked disorientation, confused speech, inability to follow commands, possible asterixis
IV	Coma

Differential Considerations. The differential considerations in patients with suspected hepatic encephalopathy include all causes of altered sensorium. The scope of the differential can be narrowed if the patient's history includes previous episodes of hepatic encephalopathy or if the patient has severe underlying liver disease and physical signs are supportive. It may be useful to obtain a full electrolyte panel, glucose level, toxicology screen, and, if conditions warrant, a head CT scan and CSF examination to rule out potentially life-threatening conditions.

Management. Aggressive management of the patient with hepatic encephalopathy may reverse the condition. As with any comatose patient, the airway is assessed first, not only to determine the need for respiratory support but also for prevention of aspiration. Affected patients generally are hemodynamically stable but have an increased incidence of GI bleeding. Hypokalemia, alkalosis, and GI bleeding contribute to increased ammonia production or absorption, and the cause must be addressed when any of these abnormalities is detected. Relatively mild degrees of hyponatremia, hypoglycemia, azotemia, or dehydration often will have a disproportionate effect on cerebral function and require immediate correction. All CNS-depressant drugs must be discontinued, and care should be taken not to prescribe even mild sedatives.

Lactulose and neomycin are the principal therapeutic agents in the management of this disorder. Lactulose, an osmotic cathartic, is a poorly absorbed sugar metabolized to lactic acid by colonic bacteria. This causes acidification of the fecal stream, resulting in the trapping of ammonia as ammonium in the stool. The usual dosage of lactulose is between 30 and 60 g daily or in a quantity sufficient to result in several loose bowel movements daily.[51] The principal adverse effect is excessive diarrhea, with resultant fluid and electrolyte imbalance. Neomycin is a poorly absorbed aminoglycoside. It is believed to act by reducing colonic bacteria responsible for the production of ammonia. Neomycin is administered orally at a dosage of 0.5 g every 4 to 6 hours. Ototoxicity or renal injury may occur in patients with impaired renal function. In obtunded patients, lactulose and neomycin can be administered by nasogastric tube or rectal enema. Long-term management requires diet modification for significant protein restriction.

Alternative therapies, still undergoing clinical evaluation, include the antibiotics metronidazole and rifaximin (to decrease activity of urease-producing bacteria), *Lactobacillus acidophilus* (to increase non–urease-producing bacteria), eradication of *H. pylori* (urease-producing), zinc replacement

(because metabolism of ammonia is dependent on zinc, which often is deficient in liver disease), ornithine aspartate (which converts ammonia), benzoate (which metabolizes with glycine), and the benzodiazepine antagonist flumazenil.[51-56] The molecular absorbent recirculating system (MARS) uses albumin in a dialysis solution to bind and remove circulating toxins. This novel experimental approach to treat liver failure and hepatic encephalopathy appears to be safe and cost-effective.[57-59]

Disposition. Although most patients with hepatic encephalopathy will require hospitalization, those with grade I or II encephalopathy without complicating factors and a supportive home environment can be managed at home. In addition to a prescription for lactulose, a diet with limited amounts of protein is essential to effective ongoing management.

KEY CONCEPTS

- The differential diagnosis for hepatic encephalopathy should consider all causes of altered sensorium. The correct diagnosis may be determined by the clinical setting, but the broad scope of the differential may necessitate additional testing, including chemistry and CSF studies, toxicology, and a head CT scan.
- Management of hepatic encephalopathy includes correction of underlying electrolyte abnormalities, strict protein restriction, and administration of lactulose and neomycin.

Spontaneous Bacterial Peritonitis

Perspective. SBP is an acute bacterial infection of ascitic fluid in patients with liver disease, without an apparent external or intra-abdominal focus of infection. The syndrome is not new, but it was not until in the late 1960s and early 1970s that this potentially fatal disorder was commonly recognized. Although the disease occurs most often in patients with cirrhosis due to alcohol, it can occur in any patient with ascites secondary to cirrhosis.[60,61] Retrospective studies have identified SBP in 5 to 27% of patients hospitalized with cirrhosis and ascites.[62]

Principles of Disease. The pathophysiology of SBP remains speculative but is most likely to be related to a combination of impaired phagocytic function in the liver and portal systemic hypertension, which can cause bowel mucosal edema and transmural migration of enteric organisms. Additional contributing factors may include impaired activity of opsonins and complement in ascitic fluid. Gram-negative enteric organisms, primarily *Escherichia coli*, are the most frequently identified organism in SBP.[60,62] Newer invasive treatments of cirrhosis including variceal ligation, transjugular intrahepatic portosystemic shunt placement, and long-term antibiotic prophylaxis have changed the type and etiology of acute bacterial infections in cirrhosis.[63] Polymicrobial and anaerobic infections have been reported but are not common.

Clinical Features. The clinical presentation can be variable, ranging from the acute onset of severe abdominal pain, fever, chills, and hemodynamic instability to the slow, insidious onset of abdominal discomfort or low-grade fever, or hepatic encephalopathy. Although by definition, ascites must be present for SBP to develop, free peritoneal fluid may not always be clinically apparent. An elevated temperature may not be detected in 20 to 50% of cases.[64]

On physical examination, palpation may elicit only mild tenderness or may reveal abdominal rigidity and guarding with rebound tenderness. One study identified a positive peritoneal fluid culture rate of 3.5% among patients who were judged to have asymptomatic ascites.[65] This observation underscores the exceptionally broad spectrum of manifestations and often very minimal physical findings with this disorder and the need to consider the diagnosis of SBP in any patient with ascites who presents with abdominal pain or who exhibits unexplained clinical deterioration.

Diagnostic Strategies. Diagnosis is made by culture of the ascitic fluid, but treatment decisions should be made in advance of these results. An ascitic fluid granulocyte count greater than 500 cells/mm^3 correlates with positive cultures in more than 90% of cases; however, ED treatment for SBP should be initiated if the neutrophil count is greater than 250 cells/mm^3.[61,62,64,66,67] A positive result on urine reagent strip testing for leukocyte esterase has a high degree of correlation with a clinically significant elevation of neutrophil cell count.[68] If ascitic fluid is available for testing, a pH of less than 7.34 or a pH gradient between arterial blood and ascitic fluid of more than 0.10 also is a reliable early indicator of SBP.[66-69] Other laboratory parameters (e.g., aminotransferase, bilirubin, peripheral blood count) are commonly abnormal, but such findings are nonspecific and more often are a consequence of underlying liver disease than infection. A PT and INR should be measured in advance of paracentesis, and fresh frozen plasma should be administered if significant coagulopathy is identified.

Differential Considerations. The differential diagnosis for SBP includes all of those entities that may lead to peritonitis and abdominal pain in patients with or without liver disease.

Management. Treatment of SBP requires intravenous antibiotics. The choice of agents is driven by the anticipated bacteriology of the process. A third-generation cephalosporin such as cefotaxime is considered to be the agent of choice, with a demonstrated cure rate of 90%.[70] An alternative is an ampicillin-sulbactam combination. Ampicillin with an aminoglycoside also is effective but is associated with an increased risk of renal toxicity.

Disposition. Any patient with ascites is at risk for the development of SBP. This risk is markedly increased in patients with ascitic fluid protein levels less than 1 g/dL.[62,64,71] Other important risk factors include serum bilirubin level greater than 3.2 mg/dL, platelet count less than 98,000/mm^3, and a previous history of SBP.[72] Antibiotic prophylaxis for high-risk patients can reduce SBP incidence by 60 to 80% and can be cost-effective.[62,64,71,73] The preferred regimen consists of norfloxacin 400 mg daily.[62,64,74] The emerging problem of quinolone resistance has prompted investigation of trimethoprim-sulfamethoxazole as an alternative for prevention of SBP.[74,75] If a high-risk patient with ascites is identified in the ED and contraindications are absent, prophylactic therapy should be initiated. Referral to a primary care physician or gastroenterology specialist is recommended. Patients with diagnosed SBP require hospitalization.

KEY CONCEPTS

- SBP should be considered in any patient with ascites presenting with abdominal pain, fever, or unexplained clinical deterioration.
- The diagnosis is dependent on obtaining ascitic fluid for cell count and culture. An ascitic fluid granulocyte count greater than 250 cells/mm^3 is an indication for antibiotic treatment. Urine reagent strips that test for leukocyte esterase may provide a convenient means of bedside screening of ascitic fluid for SBP.
- Identification of a high-risk patient with ascites is an indication for initiation of SBP prophylaxis with an orthoquinolone antibiotic.

Drug-Induced Liver Disease

Perspective. In addition to alcohol, a variety of other chemical agents can induce injury to the liver. Most of these agents are commonly prescribed medicinals or drugs available over the counter. Although hepatic injury represents a relatively small proportion of all adverse drug reactions, it may account for up to 5% of hospital admissions for jaundice.[76] Drug-induced liver disease is one of the most common reasons for market withdrawal of drugs by the U.S. Food and Drug Administration (FDA) and is responsible for approximately 50% of the cases of fulminant liver failure in the United States.[77] For reasons not entirely clear, the incidence of liver injury related to drugs appears to increase with patient age. Notable exceptions include valproic acid and aspirin, which more often cause hepatic damage in children.

Principles of Disease. The pathogenesis of liver injury from drug exposure is variable. It may occur as a result of a direct cytotoxic effect of the primary agent or, as is more often the case, a major or minor metabolite. Alternatively, toxicity can be related to a hypersensitivity or allergic reaction. Antimetabolites (e.g., azathioprine, comfrey tea) have been associated with hepatic injury caused by veno-occlusive disease; oral contraceptives have been implicated in cases of hepatic vein thrombosis.[78,79] Antiretroviral drug therapy (ARVT) is a common cause of liver toxicity defined by elevations in alanine aminotransferase (ALT) greater than aminotransferase (AST). Increases in ALT or AST of 3.5-fold and 5-fold are considered to represent moderate and severe hepatotoxicity, respectively.[80] Mechanisms identified as leading to liver toxicity from ARVT include metabolic host-mediated factors, hypersensitivity, mitochondrial toxicity, and immune reconstitution.[80]

Not all agents commonly associated with hepatic toxicity will cause injury in all patients. This nonuniformity may be a consequence of variations in metabolic pathways, simultaneous ingestion of other substances that may facilitate toxicity, amount and duration of drug exposure, or patient idiosyncrasy. For example, isoniazid appears to have differential toxicity depending on both the patient's age and the rate of conversion to a particular toxic metabolite, acetyl hydrazine. Acetaminophen is relatively nontoxic when taken in the usually recommended amounts but universally toxic and potentially fatal when taken in significant excess (see Chapter 146).

In general, drugs that induce liver injury cause hepatocellular necrosis or cholestasis. Although specific agents tend to cause damage characterized by a particular pattern of injury, there is considerable overlap. Cellular necrosis commonly is associated with anesthetic agents (e.g., halothane, the antimicrobials amphotericin and ketoconazole, or the antidysrhythmic amiodarone). A cholestatic picture is characteristic of liver injury from chlorpromazine, haloperidol, anabolic or oral contraceptive steroids, or erythromycin estolate.

Clinical Features. Many patients with drug-induced liver disease will be asymptomatic, with injury manifested only by moderate elevations of aminotransferase levels. Other patients may experience painless jaundice resulting from agents associated with cholestatic pathology or as a result of acute hepatitis indistinguishable from virally induced disease.

Physical examination will vary depending on the nature of the underlying pathology. The liver can be enlarged and tender. A rash frequently is seen in halothane-induced hepatitis, consistent with its presumed allergic causation. Aminotransferase levels commonly are elevated but only mildly so in cholestatic cases. Bilirubin often is elevated, most dramatically in cases associated with cholestasis. Eosinophilia is a frequent finding in cases of chlorpromazine- or halothane-induced injury.

Table 88-4 Common Agents Involved in Hepatic Injury

AGENT	INJURY PATTERN
Acetaminophen	Cytotoxic
Amiodarone	Cytotoxic
Amphotericin	Cytotoxic
Anabolic steroids	Cholestatic, veno-occlusive
Azathioprine	Cytotoxic, cholestatic, veno-occlusive
Carbamazepine	Cytotoxic, cholestatic
Chlorpromazine	Cholestatic
Cis-platinum	Cytotoxic
Contraceptive steroids	Cholestatic, hepatic vein thrombotic
Cyclophosphamide	Cytotoxic
Erythromycin estolate	Cholestatic
Gold salts	Cytotoxic, cholestatic
Haloperidol	Cholestatic
Isoniazid	Cytotoxic
Ketoconazole	Cytotoxic
Lovastatin	Cytotoxic
Methotrexate	Cytotoxic
Methoxyflurane	Cytotoxic
Methyldopa	Cytotoxic
Phenobarbital	Cholestatic
Phenytoin	Cytotoxic
Quinidine	Cytotoxic
Salicylate	Cytotoxic
Tetracycline	Cytotoxic, fatty infiltrative
Valproic acid	Cytotoxic
Verapamil	Cholestatic

It can be difficult to differentiate drug-induced liver injury from infectious causes or extrahepatic biliary obstruction. A careful history in conjunction with knowledge of the drugs commonly associated with hepatic toxicity should facilitate diagnosis (Table 88-4). On occasion, particularly in cases with a cholestatic presentation, abdominal ultrasound imaging and liver biopsy may be necessary.

Management. The offending agent(s) should be discontinued and appropriate supportive measures instituted, as in the treatment of acute hepatitis. For patients with cholestasis and significant pruritus, a bile acid–sequestering agent such as cholestyramine may provide relief. If an allergic mechanism is suspected, corticosteroids may be of benefit. Although drug-induced liver disease generally is a benign disorder, it can be associated with fulminant hepatic failure or the development of cirrhosis.

Disposition. Mild cases of drug-induced hepatitis can be managed effectively on an outpatient basis. Telephone consultation with a gastroenterology specialist is recommended to aid in the diagnosis and ensure reliable follow-up. In severe cases, the patient should be hospitalized, and if signs of fulminant hepatitis are apparent, consideration should be given to transfer to a treatment center with the capacity to perform liver transplantation.

HEPATIC ABSCESSES

Hepatic abscesses fall into two broad categories, pyogenic and amebic. Although there may be similarities in clinical presentation, the pathophysiology and treatment differ significantly.

Pyogenic Abscess

Principles of Disease. Pyogenic hepatic abscess is uncommon, being reported in only 8 to 16 cases per 100,000 hospital admissions. The disorder increases in frequency with patient age and is distributed equally between men and women.[81] Liver abscesses are most commonly associated with biliary tract obstruction or cholangitis but also may be related to diverticulitis, pancreatic abscess, omphalitis, appendicitis, inflammatory bowel disease, or bacteremia of any cause.[82,83] In a significant number of cases, no underlying cause for liver abscess is identified.[84]

Solitary and multiple abscesses occur with approximately equal frequency, most often in the right lobe of the liver. Patients with multiple lesions tend to be more severely ill, with less favorable outcomes. Both anaerobic and aerobic organisms are causative; *E. coli*, *Klebsiella*, *Pseudomonas*, and *Enterococcus* species; anaerobic streptococci; and various *Bacteroides* species are the microbes most commonly isolated.[85]

Clinical Features. Clinical presentation is characterized by the onset of high fever, chills, right upper quadrant pain, nausea, and vomiting. Patients generally present acutely and appear quite ill, particularly if there is underlying cholangitis. A more insidious chronic presentation, although atypical, has been described. Physical findings include elevated temperature, right upper quadrant tenderness, hepatomegaly, and occasionally dullness to percussion and decreased breath sounds over the right lower chest. Jaundice may be apparent, especially if coexistent biliary tract obstruction is present.

Diagnostic Strategies. Laboratory findings include leukocytosis in 70 to 80% of cases, elevated alkaline phosphatase in up to 90%, and bilirubin in excess of 2 mg/dL in 50% of patients. Serum aminotransferase levels commonly are elevated to two to four times normal.[81] Chest radiographs may reveal a right pleural effusion, basilar atelectasis, or an elevated right hemidiaphragm.[86]

Many imaging techniques are useful in delineating hepatic abscesses, including ultrasonography, CT scan (Figs. 88-4 and 88-5), and magnetic resonance imaging (MRI). In the ED, ultrasonography and CT scan are the most sensitive and expeditious modalities.

Differential Considerations. The differential diagnosis of pyogenic hepatic abscess includes amebic liver abscess, hepatitis, and cholangitis, as well as pancreatic and subphrenic abscess. Although clinical evaluation may not allow definitive diagnosis, appropriate use of imaging techniques generally does.

Management. The initial treatment of a pyogenic hepatic abscess is hemodynamic stabilization, intravenous antibiotics, and pain control. Pending definitive microbial identification, broad-spectrum antibiotic coverage should be provided. Triple antibiotic coverage is warranted and should include an aminoglycoside or third-generation cephalosporin for gram-negative coverage, metronidazole or clindamycin for anaerobes, and ampicillin for streptococcal species.

Definitive treatment requires abscess drainage. This usually is done percutaneously, with open surgical drainage reserved for complex cases associated with intraperitoneal soiling, intestinal perforation, or biliary obstruction.[87-89] Complications include rupture of the abscess into the peritoneal cavity or an adjacent anatomic structure (e.g., the thoracic cavity, lung, pericardium).

Disposition. Patients with pyogenic hepatic abscess uniformly require admission to the hospital. Consultation with a general surgeon, gastroenterologist, or interventional radiologist will be necessary.

Amebic Abscess

Principles of Disease. Amebiasis is one of the most common protozoal infections worldwide. Up to 10% of the world's population and approximately 1 to 2% of the U.S. population may be infected. Transmission generally occurs by way of the fecal-oral route and usually is a consequence of ingesting contaminated water or foodstuffs. The illness is more common in homosexual men, presumably as a result of oral-anal contact during sexual activity. One limited but fatal outbreak of intestinal disease in the Midwest was traced to a contaminated colonic irrigation apparatus.[90] Although intestinal disease is by far the most common manifestation of infection, extraintestinal disease is not rare, with the liver most commonly affected. *Entamoeba histolytica* is the only ameba responsible for invasive disease, and evidently only certain varieties of *E. histolytica* are pathogenic.[89,91] Pathogenic amoebae reach the liver after invasion of the intestinal mucosa and transit through the portal vein. As with a pyogenic abscess, involvement of the right liver lobe is more common.

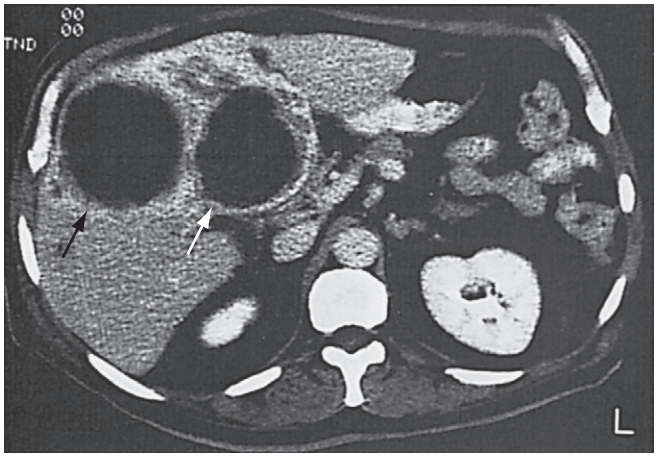


Figure 88-4. Contrast computed tomography scan of liver showing large cystic masses *(black arrow, white arrow)* with irregular, contrast-enhancing borders in a patient with pyogenic liver abscess caused by *Streptococcus milleri*.

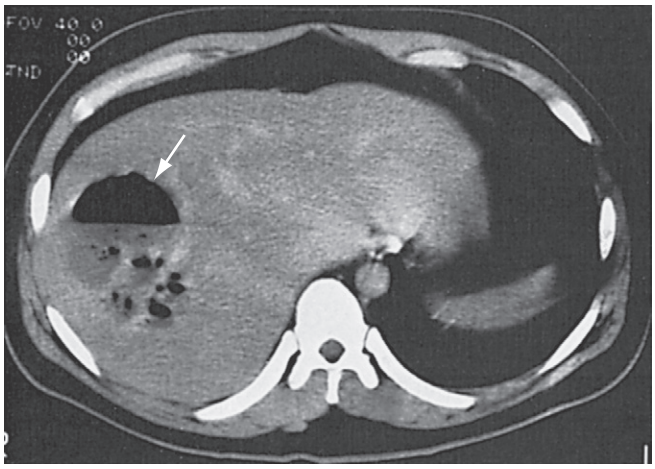


Figure 88-5. Contrast computed tomography scan of liver showing pyogenic liver abscess. Complex cystic mass with air-fluid level *(arrow)* caused by gas-producing *Klebsiella pneumoniae*.

Clinical Features. The clinical presentation generally is acute, with fever, chills, abdominal pain, nausea, and vomiting. Diarrhea is common in children but is present in less than one third of adults. Careful questioning of patients without diarrhea often yields a history of intestinal illness several weeks before. Many patients complain of cough, which can serve to direct attention away from the liver.

Chronic illness of several months' duration, although less common than the acute presentation, has been described.[92] Physical examination reveals an elevated temperature, right upper quadrant tenderness, hepatomegaly, and dullness with decreased breath sounds over the right lower chest.

Diagnostic Strategies. Laboratory parameters are not specific. Neutrophilic leukocytosis is common. Alkaline phosphatase is elevated in 75% of cases and aminotransferases in 50%. Hyperbilirubinemia is uncommon and when present is indicative of biliary obstruction. The chest radiograph may reveal a right pleural effusion, basilar atelectasis, or an elevated right hemidiaphragm. Ultrasound imaging of the liver can be diagnostic, revealing a peripherally based mass with well-circumscribed borders and a heterogenous hypoechoic center. Nuclear scintigraphy with technetium, CT scan, and MRI are alternative imaging modalities if ultrasonography is inconclusive.

Diagnosis is supported by identification of a pathogenic protozoan in the stool. Even in cases of invasive intestinal disease, however, the yield may be low. An enzyme-linked immunosorbent assay (ELISA) or a counterimmune electrophoresis generally is preferred. The indirect hemagglutination test remains positive for an extended period and is therefore not helpful in establishing the presence of acute infection.

Differential Considerations. In a review of 75 cases of amebic liver abscess seen in a single ED over 5 years, the correct diagnosis was made in the ED in only 31.5% of patients.[93] In order of their frequency of occurrence, considerations in the differential diagnosis of an amebic liver abscess include pyogenic abscess, biliary tract disease, hepatitis, pneumonia, appendicitis, and pancreatitis. Respiratory symptoms and abnormalities on the chest radiograph may cause confusion with pulmonary illnesses. Hepatic imaging is helpful in establishing the correct diagnosis; however, differentiation from pyogenic illness may still be difficult.

Management. Management consists of supportive therapy and initiation of amebicidal therapy. Metronidazole, 750 mg PO or IV three times daily for 7 days, is the therapeutic agent of choice. Most patients will respond to this regimen. Percutaneous catheter drainage is required only in refractory or complicated cases.

The most serious complication of amebic liver disease is rupture into adjacent anatomic structures. Involvement of the lung occurs in 20 to 35% of cases of extrahepatic disease, often manifesting with signs and symptoms of massive pleural effusion or consolidative pneumonia. With rupture into a bronchus, the patient can present with cough productive of an anchovy paste–like substance or necrotic debris, or with frank hemoptysis. Abdominal pain with peritonitis can result from rupture into the abdominal cavity. Involvement of the pericardium occasionally is seen with lesions in the left lobe of the liver and can be catastrophic, either acutely as a consequence of pericardial tamponade or chronically from constrictive pericarditis.

Disposition. Select patients with amebic liver abscess can be managed as outpatients. This approach is best suited for persons with mild clinical disease, stable living circumstances, and adequate access to medications as well as follow-up care. Patients with more severe disease, evidence of complications, or questionable social circumstances should be admitted to a medical service.

MISCELLANEOUS DISORDERS AND CONDITIONS OF THE LIVER

Chronic Hepatitis

Chronic hepatitis is defined as persistent inflammation of the liver for at least 6 months. *Chronic persistent hepatitis* (CPH) is characterized clinically by a lack of symptoms, persistent mild complaints, or intermittent episodes of moderate hepatitis. Despite persistent elevation of aminotransferases, CPH rarely progresses to hepatic failure or cirrhosis. *Chronic active hepatitis* (CAH), on the other hand, commonly progresses to cirrhosis. CAH initially may follow a clinical course indistinguishable from that of CPH; however, biopsy of the liver, even early in the disease, reveals diffuse inflammation, bridging necrosis, and evidence of scarring and macronodular cirrhosis.[94]

The causes of chronic hepatitis include all of the recognized causes of acute hepatitis; however, the chronic form is rare with HAV infection. It may occur in 5 to 10% of patients with HBV infection, in 50 to 60% of those with HCV infection, and probably in an even greater percentage of patients with HDV infection.[24,95-97] The incidence of chronic disease from other causes is closely related to the reversibility of the metabolic or immunologic disorder or to the duration of exposure to the incriminated toxic substance.

Chronic hepatitis, in its precirrhotic stage, rarely causes ED presentations. It is not unusual, however, for an elevated aminotransferase to be detected during the course of evaluation of some seemingly unrelated entity. Evaluation generally is limited to obtaining a careful history and ordering appropriate viral serologic studies (HBsAg, HBeAg, and anti-HCV assays). The active treatment of CAH goes beyond the bounds of the ED. Referral to an internist or gastroenterology specialist is advisable.

Liver Disease in Pregnancy

The two primary hepatic disorders associated with pregnancy are benign cholestasis and acute fatty liver. Cholestasis is common and appears to have a familial linkage. Onset is in the third trimester and is heralded by the development of progressive pruritus. Bilirubin may be elevated but not dramatically, so jaundice is uncommon. Laboratory tests reveal elevated alkaline phosphatase, 5′-nucleotidase, and bilirubin. Although the chief concern to the mother is discomfort from pruritus, the illness can bode poorly for the fetus, with increased incidence of prematurity, stillbirth, and fetal distress.[98] Malabsorption of vitamin K can result in serious coagulopathy in the fetus, predisposing to spontaneous intracranial hemorrhage.[99] Treatment is supportive and should include subcutaneous vitamin K for the mother ante partum and for the newborn after delivery. Cholestasis resolves without incident after delivery.

Acute fatty liver of pregnancy is a malignant disorder that, if unrecognized, can progress rapidly to maternal and fetal demise. The incidence is approximately 1 in 7000 live births.[100] The illness occurs in the latter part of the third trimester and is more common in primigravidas and twin pregnancies.[99] The initial clinical features include fatigue, anorexia, nausea, and vomiting. Abdominal pain may be present, most prominently in the midepigastrium and right upper quadrant. Physical examination may reveal mild jaundice and abdominal tenderness. The liver may not be palpable because of the enlarged uterus.

Abnormal laboratory findings include moderate elevation of aminotransferases (5 to 10 times normal) and bilirubin, hypoglycemia, and evidence of disseminated intravascular

coagulation (prolonged PT and partial thromboplastin time, hypofibrinogenemia, elevated fibrin split products, and thrombocytopenia). Treatment involves aggressive fluid and electrolyte support, glucose administration, and immediate delivery. Liver disease generally resolves without permanent sequelae after delivery.[100]

Budd-Chiari Syndrome

Budd-Chiari syndrome is a disorder of the liver due to hepatic venous outflow obstruction located anywhere above the level of hepatic venules. It is an uncommon disorder with a prevalence of 1/100,00 worldwide and is more common in females. The disorder is associated with hypercoagulable states such as factor V Leiden, protein S and C deficiency, thrombophilia, antithrombin III deficiency, myeloproliferative disorder, Behçet's disease, paroxysmal nocturnal hemoglobinuria, and oral contraceptive use.[101,102] In Asia, an association with a membranous obstruction of the inferior vena cava has been reported.[102]

Clinical presentation is variable, ranging from fulminant hepatic failure in acute high-grade obstruction to the insidious onset of jaundice and ascites in more subacute forms. Fulminant disease is clinically indistinguishable from acute hepatic necrosis from hepatocellular disease secondary to viral infection. It is important to make the distinction between these two causes of hepatic failure early, because treatment options differ. Prompt intervention in patients with Budd-Chiari syndrome offers the possibility of effective relief of signs and symptoms with potentially favorable outcome.

Doppler ultrasound imaging is reported to have sensitivity between 85% and 95% for diagnosis of Budd-Chiari syndrome and emerges as the diagnostic modality of choice in the ED setting.[101,103,104]

Management of Budd-Chiari syndrome relates to the severity and acuity of disease. Previously diagnosed disease with worsening ascites can be managed with modification of diuretics and therapeutic paracentesis followed by referral to a primary care physician or gastroenterology specialist. Newly diagnosed Budd-Chiari syndrome with acute decompensation will require immediate consultation and consideration for transjugular intrahepatic portosystemic shunt placement or percutaneous angioplasty or thrombolytic therapy. Portacaval shunting and liver transplantation are options for disease refractory to medical or other less invasive percutaneous interventions.[101,105,106]

Hepatic Cancer

Hepatocellular carcinoma is the most common primary hepatic malignancy. It is especially common in undeveloped areas of the world, particularly in regions in which chronic HBV infection is prevalent. In parts of Korea and Mongolia, the incidence of hepatocellular carcinoma approaches 48 to 98 per 100,000 population; in the United States, it is below 10 per 100,000.[107] It has been estimated that 75 to 80% of primary liver cancer is attributable to persistent viral infections with either HBV (50 to 55%) or HCV (25 to 30%).[107] Associations beyond HBV include infection with *Clonorchis* and schistosomiasis, chronic alcoholic liver disease, primary biliary cirrhosis, hemochromatosis, and several chemical agents (e.g., estrogens, androgens, the contrast agent Thorotrast, vinyl chloride, aflatoxins, tobacco).[108] Metastases to the liver from GI, lung, breast, or other tumors are more common than primary malignancy in the United States.

The clinical presentation of hepatic carcinoma or metastases is nonspecific. Symptoms and signs may include nausea, vomiting, jaundice, and right upper quadrant abdominal pain. Physical examination may reveal evidence of recent weight loss or cachexia. Hepatocellular carcinoma is linked with cirrhosis; many of these patients present with manifestations of that process. An enlarged liver, particularly in patients with a history of cirrhosis, is strongly suggestive of malignant transformation. Although results of laboratory tests (e.g., blood count, aminotransferase measurements, bilirubin assay) often are abnormal, these tests are nonspecific and generally are of little aid in diagnosis. Alpha-fetoprotein often is elevated in patients with a hepatoma but is nonspecific and of limited use in diagnosis. Ultrasound imaging, CT scan, and MRI of the liver all are effective means of identifying tumor. Liver biopsy is recommended for the definitive diagnosis of hepatoma; biopsy of an alternative site may be preferable in cases of metastatic disease.

Management in the ED is limited to supportive measures, provision of analgesic agents, and possibly nutritive supplementation. Hepatitis B and C serologic studies should be performed in cases of hepatoma to determine linkage with chronic HBV infection and to assess infection risk to family members.

Liver Transplantation

Human orthotopic liver transplantation was pioneered in the 1960s, and approximately 5000 liver transplant procedures are now performed annually in the United States. The 5-year survival rate generally is reported to be approximately 80%, but complications are common.[109,110] Early complications include bleeding, acute rejection, vascular and biliary tract problems, and infection. Delayed complications include malignancy, recurrence of underlying disease, infection, chronic rejection, medication toxicity, and renal failure. Many early complications will manifest during the immediate postoperative period while the patient is in the hospital or being closely followed by the transplantation team. Delayed complications may occur a year or more after transplantation.

The clinical signs that lead the transplant recipient to present for care in the ED are related to the nature of the underlying problem. The signs of malignancy or recurrence of underlying disease will mirror those in the patient who has not undergone transplantation. Infectious complications will be relatively straightforward when common pyogenic organisms are involved; however, liver transplant recipients are at increased risk for opportunistic infections as a consequence of their immunosuppressive therapy. Presenting signs and symptoms may be subtle. Chronic rejection manifests with low-grade temperature elevation, fatigue, and jaundice. Expected laboratory abnormalities include elevated bilirubin and transaminases, prolonged PT or INR, and low serum albumin. Renal failure may not be clinically apparent until the glomerular filtration rate has declined significantly. Routine serum creatinine measurement is the best means of identifying this disorder early, when successful intervention is still possible.

The most common immunosuppressive agents used after liver transplantation include corticosteroids, cyclosporine, tacrolimus, sirolimus, mycophenolate, and azathioprine. Corticosteroid toxicity may produce glucose intolerance, osteoporosis, gastric ulceration, and muscle wasting. Cyclosporine and tacrolimus can cause renal impairment, which is the most common dose-limiting effect of these agents. Azathioprine can be hepatotoxic but is more often associated with bone marrow suppression, placing the patient at increased risk for infectious complications and bleeding diathesis.

Management of patients with complications related to their liver transplant is directed by the nature of the problem. Infec-

tions are evaluated and managed in the usual fashion, with emphasis on evaluation of the patient's underlying immune function and a search for uncommon pathogens. Accordingly, assessment may include complete blood count and measurement of glucose, blood urea nitrogen, creatinine, serum electrolytes, transaminases, bilirubin, and albumin, as well as coagulation studies. Hepatobiliary imaging is indicated if tumor, vascular occlusion, or biliary tract obstruction is suspected. Ultrasound studies with Doppler interrogation can be particularly useful in the ED setting. Consultation with a transplantation specialist is recommended for any patient with a problem potentially related to the organ transplant or immune-modulating medications.

BILIARY TRACT DISORDERS

GENERAL PERSPECTIVE

The biliary tract is composed of the hepatic bile canaliculi, intrahepatic and extrahepatic bile ducts, the common bile duct, and the gallbladder. Bile, required for absorption of fats and fat-soluble nutrients, is produced in the canaliculi. During the fasting state, approximately 50% of the bile produced flows directly into the duodenum; the other half is stored in the gallbladder. The gallbladder serves to acidify and concentrate the bile and can store up to 50 mL of bile for immediate availability at the time of feeding. The presence of food in the stomach, in particular fat, results in both vagal impulses and the secretion of cholecystokinin-pancreozymin, which serve as potent stimuli for gallbladder contraction. Removal of the gallbladder generally is not associated with measurable changes in intestinal fat absorption or in clinical symptomatology.[111]

Biliary tract disorders constitute a relatively common cause of presentation to the ED. Signs and symptoms typically result from obstruction of the biliary tree. The clinical picture is variable but often includes abdominal pain, which may or may not be referred; nausea and vomiting; and jaundice.

SPECIFIC DISORDERS

Cholelithiasis

As noted, the principal cause of biliary tract disease is related to the development of gallstones. It is estimated that 20% of women and 8% of men have gallstones, resulting in approximately 500,000 operations annually.[112]

Principles of Disease. There are two categories of gallstones. *Cholesterol stones* most commonly occur as a consequence of an elevated concentration of cholesterol in bile relative to the other principal constituents, bile acids and phospholipids. Bile acids and lecithin, the primary bile phospholipid, act in concert to solubilize cholesterol. As cholesterol levels rise or bile acids and lecithin levels decline, cholesterol has an increasing tendency to form crystals. These crystals, particularly in an incompletely emptying gallbladder, serve as a nidus for stone formation. Factors associated with an enhanced risk of cholesterol stone formation include increased age, female gender, massive obesity, rapid weight loss, cystic fibrosis, parity, drugs (e.g., clofibrate, oral contraceptive agents), and familial tendency. The hereditary nature of cholelithiasis is most dramatically demonstrated by the high concordance for stone formation in monozygotic twins and the exceedingly high incidence of cholelithiasis among Pima Indians.[113]

Two varieties of *pigmented stones* have been identified: black and brown. Black stones occur exclusively in the gallbladder and contain a high concentration of calcium bilirubinate. They are more commonly encountered in elderly persons and have a strong association with disease causing intravascular hemolysis (e.g., sickle cell anemia, hereditary spherocytosis). Brown stones are associated with infection and can form in both the gallbladder and the intrahepatic and extrahepatic bile duct system. Although bacterial infections are most commonly incriminated, parasites (e.g., *Ascaris lumbricoides*, *Clonorchis sinensis*) also been linked to brown stone formation.[114] Both types of pigmented stones contain calcium bilirubinate and therefore may be visible on plain abdominal radiographs. For a stone to be radiopaque, it must contain at least 4% calcium by weight.

Clinical Features. The most common clinical manifestation of cholelithiasis is biliary colic. The pathophysiology of this process is not entirely clear, but it appears to be related to the passage of small stones from the gallbladder through the cystic duct into the common bile duct. The term *colic* is often misleading; affected patients commonly complain of steady pain, rather than intermittent or cramping discomfort. The pain most often is perceived in the right upper quadrant but may be localized over a wide region of the upper abdomen. Radiation of pain, if it occurs, generally is to the base of the scapula or shoulder. Associated signs and symptoms include nausea and vomiting, which may be severe enough to lead to fluid and electrolyte imbalance. Patients with biliary colic commonly report similar self-limited occurrences in the past and may offer an association between symptom onset and eating. A relationship between fatty food ingestion and symptoms is as likely to occur in patients with gallstones as it is in those without. Physical examination usually reveals mild tenderness to palpation without guarding or rebound in the right upper quadrant or epigastric region.

Diagnostic Strategies. No pathognomonic clinical laboratory findings are recognized; results of commonly performed tests typically are within normal limits. Important tests to perform include ALT and AST measurements to evaluate for the presence of hepatitis, bilirubin and alkaline phosphatase determinations to look for evidence of common duct obstruction, and lipase assay to assess for the presence of pancreatitis.

The diagnosis of biliary colic is made clinically in conjunction with demonstration of stones in the gallbladder. Plain radiography has little role in the evaluation of cholelithiasis because only 10% of stones have sufficient calcium to allow visualization.[115] Ultrasonography is the procedure of choice for investigating the gallbladder. Ultrasound imaging can be performed rapidly, is highly sensitive, and provides the added utility of permitting evaluation of surrounding structures (Fig. 88-6). Ultrasonography also can be used in the ED setting, adding further convenience to the patient and reducing turnaround times.[116] Oral cholecystography using ipanoic acid is an alternative when ultrasonography either is not available or cannot be performed successfully. This technique can identify gallstones in 95% of patients with cholelithiasis in whom visualization of the gallbladder can be achieved.

Differential Considerations. Considerations in the differential diagnosis of biliary colic include cholecystitis, peptic acid disease of the stomach or duodenum, pancreatitis, and hepatitis. Patients with cholelithiasis may occasionally present with chest pain, so cardiopulmonary syndromes must be considered as well. A compatible clinical history in conjunction with normal laboratory test values (ALT, AST, lipase, and alkaline phosphatase), gallstones on ultrasound imaging, and minimal or no tenderness in the right upper quadrant favors the diagnosis of cholelithiasis. If abnormalities are visualized, a chest radiograph or electrocardiogram may help differentiate between cardiopulmonary and biliary pathology.

Management. The initial management of biliary colic is directed at correction of fluid and electrolyte disturbances and

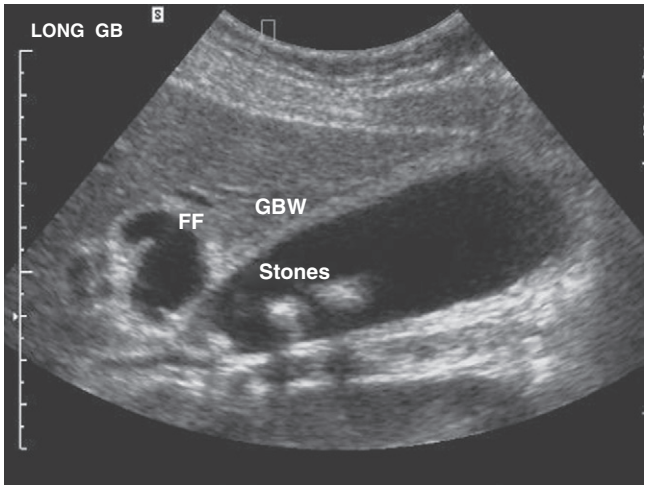


Figure 88-6. Gallbladder with gallstones (Stones), thickened gallbladder wall (GBW), and pericholecystic fluid (FF). Together these findings constitute the sonographic signs of cholecystitis.

relief of symptoms. Vomiting is managed with antiemetics and, if necessary, nasogastric suction. Pain often can be controlled with antispasmodics (e.g., glycopyrrolate), nonsteroidal anti-inflammatory agents, and opiate analgesic agents as needed. With clinical evidence of volume depletion, adequate intravenous fluid replacement is indicated.

The definitive management of cholelithiasis usually involves surgical removal of the gallbladder; however, other options are available. Oral administration of bile acid (e.g., chenodeoxycholate, ursodeoxycholate) over a period of months to years can result in dissolution of small to medium-size stones, whereas methyltert-butyl ether irrigation of the gallbladder has been shown to dissolve stones over a period of hours or days.[117,118] Extracorporeal shock wave lithotripsy may be successful in a select, technically suitable set of patients who have functioning gallbladders and ideally have a small number of stones.[119]

The most common complication of biliary colic is fluid and electrolyte imbalance secondary to vomiting. Other adverse consequences include Mallory-Weiss tear, from uncontrolled emesis, and cholangitis, from unrecognized and persistent common bile duct obstruction.

Special Considerations. Biliary colic is an uncommon symptom in children, in whom it most often is associated with an underlying hemolytic disorder (e.g., sickle cell anemia or spherocytosis). Acute management of biliary colic is the same for children as for adults.

Cholelithiasis may be encountered in pregnant women. Diagnosis in this population is made more difficult by the common occurrence of nausea and vomiting, particularly in the first trimester, and the presence of an enlarged uterus in later pregnancy, which alters anatomic relationships and interferes with abdominal examination. Ultrasound imaging is of considerable diagnostic use in this setting. Treatment in the ED is comparable with that for the nonpregnant patient; however, definitive therapy generally is delayed until after parturition.

Cholecystitis

Perspective. *Acute cholecystitis* is defined as sudden inflammation of the gallbladder. The incidence ranges from 5 to 19% among patients undergoing surgery for biliary tract disorders. The risk factors for cholecystitis are similar to those for cholelithiasis: female gender, increasing age and parity, and obesity.[120] Although gallstones play a prominent role in the pathogenesis of cholecystitis, approximately 2 to 12% of cases are categorized as acalculous.[121]

Principles of Disease. Obstruction of the cystic duct appears to be the critical factor in the development of gallbladder inflammation. Gallstones are identified in 95% of patients with cholecystitis and may be located in the common bile duct in many patients with acalculous cholecystitis. Causes of cystic duct obstruction unrelated to stone disease include tumor, lymphadenopathy, fibrosis, parasites, and kinking of the duct. Regardless of cause, obstruction of the cystic duct leads to filling and distention of the gallbladder. The ensuing inflammatory reaction may be related to mucosal ischemia from increased hydrostatic pressure or to the action of cytotoxic products of bile metabolism (e.g., lysophosphatidylcholine).[122] Although bacteria are isolated from the bile of inflamed gallbladders in a majority of cases, the role of infection in the pathogenesis of cholecystitis is not completely understood. Coliforms (e.g., *E. coli*) represent the most common isolates, but anaerobes have been identified in as many as 40% of cases.

Clinical Features. The most common presenting symptom of cholecystitis is pain, usually in the right upper quadrant. Although the pain initially may be described as colicky, it will become constant in virtually all cases. A previous history of similar but less severe and self-limited symptoms is a valuable diagnostic clue, as is documentation of previous gallstones. Radiation of pain generally is to the tip of the scapula on the right. Nausea and vomiting are typical features, and the patient may exhibit fever.

Physical examination reveals tenderness in the right upper quadrant or epigastric region, often with guarding or rebound. Murphy's sign (tenderness and an inspiratory pause elicited by palpation of the right upper quadrant during a deep breath) is compatible with, but not specific for, gallbladder inflammation. Fever and tachycardia are commonly absent, so cholecystitis should remain a diagnostic consideration in the absence of these findings in patients with abdominal pain and right upper quadrant pain and tenderness to palpation.[123]

Diagnostic Considerations. A polymorphonuclear leukocytosis with left shift is common, but the WBC count has been reported to be in a normal range in 27 to 40% of patients.[123,124] Serum aminotransferase, bilirubin, and alkaline phosphatase may be mildly elevated but more often are within normal limits. An elevated lipase should suggest the diagnosis of pancreatitis, either instead of or in addition to cholecystitis. Plain abdominal radiographs may reveal calcified stones, gas in the gallbladder, or an upper quadrant sentinel loop. These findings are so uncommon and nonspecific, however, that plain radiography is not recommended unless other diagnostic considerations are present.

Ultrasound imaging is the most useful test in the ED setting. Visualization of the gallbladder without identification of stones has an extremely high negative predictive value for cholecystitis, whereas the presence of stones, a thickened gallbladder wall, and pericholecystic fluid has a positive predictive value in excess of 90%[125] (Fig. 88-7).

Nuclear scintigraphy with technetium 99m–labeled iminodiacetic acid (IDA) generally is considered the most sensitive and specific imaging test for cholecystitis. IDA administered IV is taken up by hepatocytes and secreted into the bile canaliculi. Failure to obtain an outline of the gallbladder within 1 hour of administration of IDA in the face of hepatic and

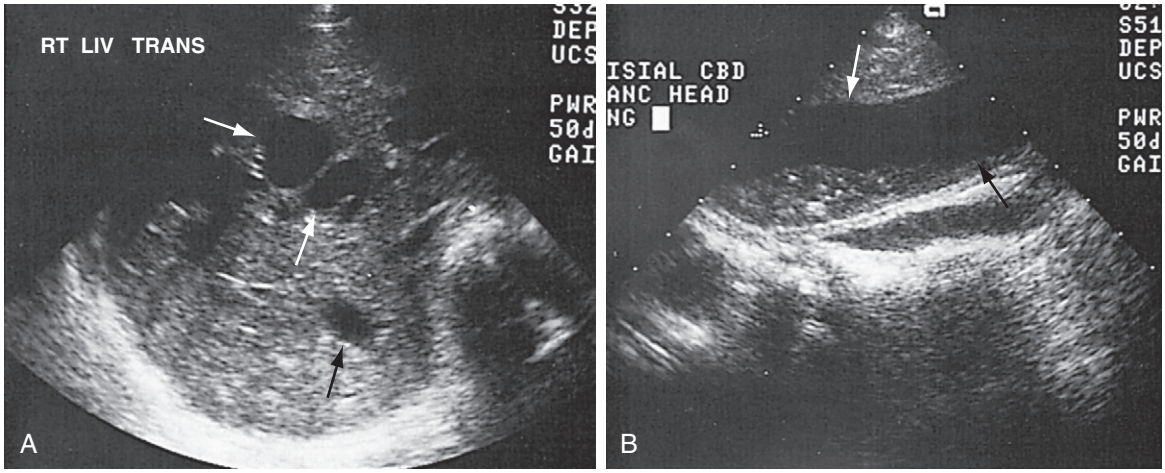


Figure 88-7. Abdominal ultrasound images from a patient with common bile duct obstruction. **A,** Multiple dilated intrahepatic ducts *(arrows)*. **B,** Significant dilated common bile duct *(arrows)*. The duct measures 2 cm in diameter.

common duct visualization proves cystic duct obstruction. In the appropriate clinical setting, this finding is diagnostic of cholecystitis. Conversely, visualization of the gallbladder and common duct within 1 hour of administration has a negative predictive value of 98%.[126] Scintigraphy with IDA loses its sensitivity as serum bilirubin rises above 5 to 8 mg; however, scintigraphy with diisopropyl IDA (diisopropyl iminodiacetic acid, or mebrofenin) allows visualization of the biliary tree in patients with total serum bilirubin in the range of 20 to 30 mg.[127] Although not the preferred imaging modality, CT can identify cholecystitis with a reported sensitivity of 92% and a specificity of 99%. It is of particular value in cases of emphysematous and hemorrhagic cholecystitis.[128]

Differential Considerations. Diagnostic considerations in the patient suspected of having cholecystitis include hepatitis, hepatic abscess, pyelonephritis, right lower lobe pneumonia or pleurisy, pancreatitis, peptic acid disease of the duodenum with perforation or penetration, and appendicitis. Up to 20% of patients with acute cholecystitis may be misdiagnosed when only clinical criteria are considered.[129] Accurate diagnosis often requires the use of sonographic or, less commonly, scintigraphic or CT studies.

Management. Basic supportive measures provide the foundation for initial management of acute cholecystitis. Volume status should be optimized with intravenous crystalloid administration. Emesis can be managed with antiemetics and nasogastric suction. Nasogastric suctioning may have the added benefit of diminishing the stimulus for biliary secretion and excretion, thereby adding to pain relief. Narcotic analgesic agents are useful for pain control. Despite the questionable role of microbial infection in the pathogenesis of cholecystitis, antibiotics are recommended. Unless clinical evidence of sepsis exists, coverage with a single broad-spectrum antibiotic (e.g., a second- or third-generation cephalosporin) is adequate.

The most serious complication of cholecystitis is gangrene of the gallbladder, with necrosis and perforation. Localized perforation may lead to pericholecystic abscess or fistula formation, the latter predisposing to gallstone ileus at a later date. Patients with diabetes mellitus are at increased risk for bacterial invasion of the gallbladder wall and for the development of emphysematous cholecystitis.

Disposition. Hospitalization for antibiotic therapy and pain management is required. Surgery is recommended for patients with cholecystitis; however, the best timing for operation is not certain. Surgery usually is performed after symptoms have subsided but while the patient is still hospitalized. Immediate cholecystectomy or cholecystotomy is reserved for the complicated case in which the patient has gangrene or perforation.

Special Considerations. Cholecystitis is uncommon in the pediatric age group; when it occurs, however, pediatric cholecystitis should be managed as in the adult. Cholecystitis in the pregnant woman poses challenges in both diagnosis and therapy. Initial therapy is identical to that for the nonpregnant patient, but the issue of surgical intervention requires an individualized consultation between surgeon and obstetrician.

Acalculous cholecystitis occurs in approximately 7 to 9% of cases.[130] It is more common in elderly persons and most often is encountered in patients who are recovering from non–biliary tract surgery. Over the past decade, acalculous disease has been increasingly encountered as a complication of advanced AIDS, usually secondary to infection with cytomegalovirus (CMV) or *Cryptosporidium*. In comparison with calculous disease, acalculous cholecystitis tends to have a more acute and malignant course, with a mortality rate as high as 41%.[130] The same techniques are used to diagnose acalculous disease as in other forms of cholecystitis but are less sensitive and specific for this entity. Sonographic findings include thickening of the gallbladder wall, pericholecystic fluid, and lack of response to cholecystokinin. Scintigraphic findings are the same as in calculous disease.

Emphysematous cholecystitis is an uncommon variant of cholecystitis, occurring in approximately 1% of cases. It is characterized by the presence of gas in the gallbladder wall, presumably consequent to the invasion of the mucosa by gas-producing organisms (e.g., *E. coli*, *Klebsiella* species, *Clostridium perfringens*). It is more common in diabetic patients, has a male predominance, and is acalculous in up to 50% of cases.[131,132] Clinical presentation and physical findings are similar to those in cholecystitis. Plain radiographs or CT scans of the abdomen will reveal gas in the gallbladder wall. Because of a high incidence of gangrene and perforation, emergency cholecystectomy is recommended.[123] Antibiotic coverage should include penicillin, an aminoglycoside, and clindamycin or an ampicillin-sulbactam combination agent. The mortality rate for emphysematous cholecystitis is approximately 15%.[132]

KEY CONCEPTS

- The vast majority of patients with cholecystitis have gallstones; however, approximately 7–9% have acalculous disease. This latter group of patients tend to have more severe disease and are at increased risk for complications.
- Despite an unclear relationship between bacterial infection and pathophysiology, antibiotic therapy is recommended.
- Patients with acalculous and emphysematous cholecystitis are at increased risk for gangrene and perforation and should have emergency cholecystectomy.

Cholangitis

Perspective. Acute obstructive cholangitis was first described by Charcot in 1877. In one large series, it was reported to occur in approximately 8% of patients admitted for biliary tract disease.[133] Cholangitis most often is a consequence of common duct blockage by a gallstone but may be associated with malignancy or a benign stricture.

Principles of Disease. The key factors in the pathogenesis of cholangitis are obstruction, elevated intraluminal pressure, and bacterial infection. Incomplete obstruction occurs more commonly than complete blockage.[133] Bacteria may gain access to the obstructed common duct either in a retrograde manner from the duodenum, by way of the lymphatics, or from portal vein blood. The most commonly encountered organisms are similar to those encountered in other varieties of biliary tract disease: *E. coli* and *Klebsiella*, *Enterococcus*, and *Bacteroides*.

Clinical Features. Patients most often experience fever, chills, nausea, vomiting, and abdominal pain. The classic triad of physical findings first described by Charcot consists of right upper quadrant pain, fever, and jaundice. Although these findings are compatible with cholangitis, they also can be seen with both cholecystitis and hepatitis. Sepsis is a common complication and may be heralded by tachycardia, tachypnea, and frank hypotension. The presence of Charcot's triad along with the clinical signs of sepsis—hypotension and altered sensorium—is referred to as Reynold's pentad.

Diagnostic Considerations. Common laboratory abnormalities include polymorphonuclear leukocytosis, hyperbilirubinemia, elevated alkaline phosphatase, and moderately increased aminotransferases. Arterial blood gas (ABG) measurements are useful to identify base deficit as an early sign of sepsis.

Sonography can be helpful if it demonstrates common and intrahepatic ductal dilatation, whereas identification of stones in the gallbladder or common duct suggests the underlying cause of obstruction (see Fig. 88-7). Although nuclear scintigraphy cannot determine the cause, it appears to be a more sensitive means to diagnose early obstruction. Several studies have demonstrated a high incidence of nonvisualization of the biliary tree with cholescintigraphy in patients with common duct obstruction when sonography failed to identify dilatation.[134,135]

Alternative imaging techniques include CT scan, percutaneous transhepatic cholangiography (THC), and endoscopic retrograde cholangiopancreatography (ERCP). Although these techniques may be more expensive and time-consuming, the latter two have the added benefit of offering potential therapeutic benefit. Endoscopic cholangioscopy can permit culture of bile, direct removal of obstructing stones, or decompression of the biliary tree by sphincterotomy or stent placement.[136]

Differential Considerations. Although patients with cholangitis generally have a higher fever and appear more ill than those with cholecystitis, considerable variability and overlap are possible. The presence of jaundice is the clinical sign most helpful in differentiating between these two disorders. An elevated bilirubin is characteristic of cholangitis and uncommon in cholecystitis. Ultrasonographic evidence of dilated common and intrahepatic ducts usually is required to distinguish cholangitis from cholecystitis.

Management. Treatment of cholangitis includes hemodynamic stabilization with crystalloid fluid and, if necessary, vasopressors. Broad-spectrum antibiotic coverage should be initiated immediately after blood culture specimens are obtained. The choice of antibiotics should be guided by local sensitivities and must provide coverage for enteric microbes. Single-agent therapies include piperacillin plus tazobactam, mezlocillin, imipenem, meropenem, ticarcillin plus clavulanate, and ampicillin plus sulbactam (which may be combined with metronidazole).[137] Combination therapy includes a regimen of extended-spectrum cephalosporin, metronidazole, and ampicillin. The key to successful treatment is early biliary tract decompression. This can be achieved with THC, ERCP, or surgery.

Disposition. Patients with cholangitis will require hospitalization, preferably to a monitored setting. Prompt consultation with a service that can provide for biliary tract decompression (surgery, interventional radiology, or gastroenterology) is necessary.

KEY CONCEPTS

- Cholangitis is an emergency condition resulting from extrahepatic bile duct obstruction and bacterial infection.
- Effective management requires prompt administration of broad-spectrum antibiotics and early biliary tract decompression.
- Biliary tract decompression can be achieved surgically, transhepatically, or by ERCP.

Sclerosing Cholangitis

Sclerosing cholangitis is an idiopathic inflammatory disorder affecting the biliary tree. It is characterized by diffuse fibrosis and narrowing of the intrahepatic and extrahepatic bile ducts. It is commonly associated with inflammatory bowel disease, particularly ulcerative colitis; however, in 25% of cases, it appears as an isolated disorder.

Patients usually present with complaints of weight loss, lethargy, jaundice, and pruritus. Rarely, infective cholangitis may develop. Prompt diagnosis may be more difficult in these cases because of the sclerotic nature of the bile ducts and the absence of duct dilatation on ultrasound imaging. Surgical exploration or ERCP often is required for diagnosis. The management of noninfected cases is primarily symptomatic. Cholestyramine, a bile acid sequestrant, may diminish pruritus.

AIDS Cholangiopathy

Manifestations of advanced HIV disease, generally associated with $CD4^+$ counts less than $200/mm^3$, may include any one of a group of disorders collectively referred to as *AIDS cholangiopathy*. These disorders include bile duct stricture, papillary stenosis, and sclerosing cholangitis.[138] The precise pathophysiology is not completely understood but is related to infection with either CMV, *Cryptosporidium*, microsporidia, or *Mycobac-*

terium avium complex. Clinical presentation may be similar to that in other causes of cholangitis, with fever and right upper quadrant pain. Laboratory test results include increased levels of alkaline phosphatase and minor elevation of transaminases. Bilirubin is less commonly elevated than in other disorders causing cholangitis. Ultrasonography generally is helpful in identifying bile duct stricture, thickening, or dilatation. IDA scans are useful, as they are in other causes of cholangitis. Management involves endoscopic sphincterotomy or stent placement in conjunction with treatment of the underlying infection.

Porcelain Gallbladder

The porcelain gallbladder is a dramatic radiographic finding caused by either linear or punctate calcifications within the gallbladder wall. Most patients are women, with a mean age in the 50s. Gallstones are commonly present. The gallbladder may be palpable in the right upper quadrant and is usually nontender to palpation. Patients with this disorder should be referred for cholecystectomy because of the high incidence of associated carcinoma.

Malignancy

Carcinoma of the biliary tract is uncommon. Gallbladder carcinoma is the most common malignancy of the biliary tract, accounting for 5% of all cancers found at autopsy. Gallbladder cancer is more frequent in patients with gallstones, especially if the gallstones are symptomatic and large. Other factors associated with gallbladder cancer include female gender, obesity, and high carbohydrate intake, all associated with gallstone disease.[139] Metastatic disease to regional nodes and the liver is common at the time of initial diagnosis because of the relatively silent nature of early disease. Symptoms include chronic right upper quadrant pain and jaundice. Physical examination may reveal a palpable mass in the right upper quadrant. These tumors will occasionally perforate, and the patient may have symptoms of pericholecystic abscess. Noninvasive imaging techniques may be of some aid in identifying the tumor. Ultrasound imaging is more sensitive than CT, but even the sequential use of both tests fails to identify malignancy in 49% of cases.[140]

Carcinoma of the extrahepatic bile ducts is less frequent than gallbladder malignancy and is more common in men. Jaundice is the most frequent finding. A palpable gallbladder (Courvoisier's sign) may be present on physical examination in one third of cases. The diagnosis is suggested by the presence of dilated intrahepatic and extrahepatic bile ducts on sonography. THC and ERCP may serve to delineate better the location and extent of tumor. Scirrhous carcinomas may have a radiographic appearance similar to that of sclerosing cholangitis, and the two conditions can be effectively differentiated only with surgical biopsy. Both gallbladder and ductal carcinomas carry a similarly dismal prognosis, with 5-year survival rates in the range of 5 to 10%.[139,141]Carcinoma of Vater's ampulla is more common in elderly persons and in males. The critical location of the ampulla results in relatively early symptomatology and thus more prompt diagnosis. Ultrasound imaging is the most useful initial imaging technique, but GI endoscopy and ERCP generally are necessary to provide a definitive diagnosis. Early detection contributes to the more favorable prognosis.[142]

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 89

Disorders of the Pancreas

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BACKGROUND

The pancreas is a retroperitoneal organ extending across the posterior abdomen in the epigastrium (Fig. 89-1). The head of the pancreas sits in the loop of the first part of the duodenum, whereas the tail lies against the hilum of the spleen. The main pancreatic duct (duct of Wirsung) goes from the tail through the body, to the head of the pancreas and where the common bile duct enters the second part of the duodenum through the sphincter of Oddi. Accessory ducts and anomalies are not uncommon. Anterior to the pancreas from right to left are the transverse colon, the lesser sac of the omentum, and the stomach. Posteriorly lie the bile duct, portal vein, splenic vein, vena cava, aorta, and superior mesenteric artery. To the left are the psoas muscle, kidney, and adrenal gland. Because of their close proximity, inflammation of the pancreas may not only injure these structures but also can mimic a variety of diseases.

The pancreas has both essential exocrine and endocrine functions. Exocrine products include amylase, lipase, trypsin, chymotrypsin, elastase, carboxypeptidase, phospholipase, and other enzymes. In addition, bicarbonate is produced in greatest quantity from this organ. The bicarbonate serves to neutralize gastric acids as well as the enzymes that break down proteins, carbohydrates, and fats. Cholecystokinin, pancreozymin, and secretin, as well as other factors, control secretion of these enzymes. The endocrine functions of the pancreas are managed by insulin, glucagon, pancreatic polypeptide, and somatostatin.

In the general population, diabetes is the most common disorder of the pancreas, followed by pancreatitis. *Acute pancreatitis* is an inflammatory process of the pancreas usually associated with abdominal pain, elevated pancreatic enzymes, and variable involvement of other regional tissues or remote organ systems. Both local and systemic complications may occur. Repeated bouts of pancreatitis of any cause may eventuate in chronic pancreatitis as a result of permanent alterations in function and morphology. *Chronic pancreatitis* is an ongoing inflammation of the pancreas, which may be interrupted by spells of acute pancreatitis.

Pancreatic tumors may develop from the endocrine or nonendocrine structures. These tumors may cause acute pancreatitis, but usually present in a more indolent fashion. The most common is adenocarcinoma originating from the pancreatic ducts.

ACUTE PANCREATITIS

Perspective

The first reports of pancreatitis date to the 1700s, whereas the first accurate study and description were completed by Fitz in 1889.[1] He noted that performing surgery in the early stages of this disease was "extremely hazardous." Since then, the understanding of pancreatitis has evolved; however, treatment remains largely supportive rather than curative. Advances in care have decreased hospital mortality for all patients with pancreatitis, from 10 to 15% as reported 20 years ago to 4 to 7% more recently.[2] Most patients with pancreatitis have a mild course; however, 10 to 15% of cases will progress to severe disease, with a mortality rate of 20 to 50%.[2,3] Children are at increased risk for death, with mortality rates of approximately 10%.[4] Severity also is increased in obese patients.[5,6]

Pancreatitis can be classified as mild or severe, the latter category of the disease being defined by the presence of organ failure or local complications, such as necrosis, pseudocysts, or abscess.[7] The gravity of the impending illness may not be apparent at the initial presentation, and in all patients, disease progression and outcome are difficult to predict at onset. Death in the first week usually is from pulmonary failure, multiorgan failure, or cardiovascular collapse.[8] Later deaths are more likely to be from infective complications.[9] In approximately 40% of cases, fatal pancreatitis on autopsy was undiagnosed. Therefore, pancreatitis should be suspected in moribund patients with multiorgan failure, particularly elderly persons.

The incidence of acute pancreatitis in the United States ranges from 4.8 per 100,000 to 40 per 100,000, varying with age, gender, and social characteristics of the population studied.[9-11] The incidence appears to be increasing, although the increase may be related to both improved diagnosis and greater prevalence of risk factors. Gallstones are the most common obstructive cause of pancreatitis and occur more commonly in women than in men, with peak symptomatic incidence between the ages of 50 and 60 years. Some variations of ductal anatomy are associated with increased risk of obstruction.[12] Many gallstones are asymptomatic; however, among people with gallstones, pancreatitis occurs with a frequency of between 8 and 20 per 1000 person-years.[11] Alcoholic pancreatitis is more common in men than in women. In most (but not all) populations, this is the second leading

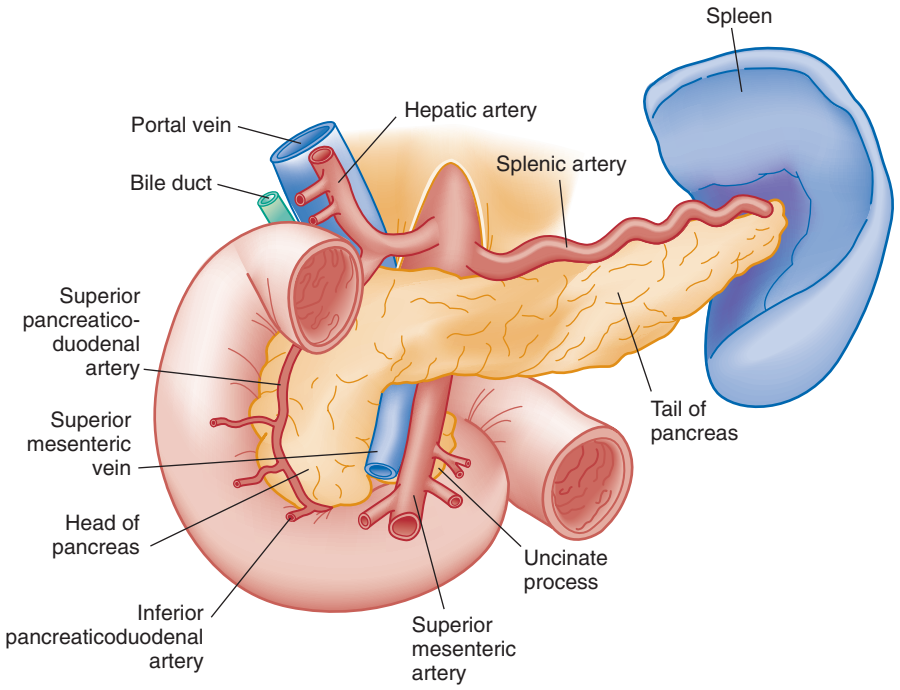

Figure 89-1. Diagrammatic representation of the pancreas, anterior view. (Redrawn from Feldman M, Friedman LS, Sleisenger MH [eds]: Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, Management, 7th ed. Philadelphia, Saunders, 2002.)

cause of pancreatitis after obstructive causes. In children, trauma is the most common identifiable cause of acute pancreatitis.[4,13]

Principles of Disease

Pathophysiology. Many of the pathobiologic responses such as edema, inflammation, and parenchymal cell death that occur in acute pancreatitis are easy to conceptualize. However, knowledge about the exact molecular mechanisms that go awry within the pancreatic cells and surrounding vasculature that ultimately leads to this cascade of events is still evolving. Intense research to further understanding of pancreatic intracellular digestive enzyme activation, pancreatic inflammatory response, and cell death responses such as necrosis and apoptosis is ongoing, with the aim of identifying new strategies for treatment.[14]

Acute pancreatitis may be divided into three phases that constitute a continuum of pathologic changes. The first phase is the local inflammation that is thought to result from obstruction of the pancreatic or bile ducts, direct toxicity of the pancreatic cells, toxins or infections, and trauma, as well as idiopathic causes. This first phase subsequently causes premature activation of pancreatic enzymes, such as trypsinogen and zymogen, either in the ducts or in the acinar cells.[5,12,15] This activation causes the release of enzymes that are intended to digest dietary proteins and fats that instead produce cellular breakdown and pancreatic tissue autodigestion. This is the generalized inflammatory stage. Initially the process is localized, creating focal pancreatic injury and edema. With increasing severity, the inflammation causes necrosis of the pancreas and spreads to the surrounding fat and tissues. There may be necrosis of the pancreatic ducts as well as the vascular structures, leading to hemorrhage.[16,17] Necrosis involving more than 30% of the pancreas increases both morbidity and mortality.[18]

The enzyme activation, inflammation, and necrosis cause a variety of localized complications. For example, fluid collections develop in 30 to 50% of patients with severe pancreatitis.[19] Over time, a fibrinous or granulation wall may form around this fluid collection, creating a pseudocyst. Thus, pseudocysts are not present in the initial phases of pancreatitis but instead develop over 4 to 6 weeks. Fluid collections, necrotic areas, or pseudocysts may become infected in 1% of cases, usually after several weeks.[19] Additionally, irritation of the surrounding bowel is common, creating bowel wall edema, ileus, and third spacing of fluid. Formation of ascites is common and, together with bowel edema, can lead to significant intravascular fluid loss and hypotension.

The third and final stage occurs with the development of multiorgan damage. Because of the release of inflammatory mediators, the initial localized inflammatory response may cause a systemic immune response syndrome (SIRS), resulting in multiple organ failure. This is a sepsis-like response, and any organ system can be involved, potentially resulting in myocardial depression, acute respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC), or renal failure.[20]

Etiology. Pancreatitis has a variety of causes, but the vast majority of cases (80%) will be due to either gallstones or alcohol, with gallstones the most common cause in most series (approximately 45% versus 35%)[5,21] (Box 89-1). The exact pathomechanism of biliary pancreatitis is not clear. Either a stone within the bile duct applies transmural pressure on the pancreatic duct, or a stone in the common channel of the pancreatic duct and common bile duct causes obstruction. Obstruction or pressure on the pancreatic duct causes bile reflux or increased pressure of pancreatic secretions. Either mechanism leads to the activation of pancreatic enzymes, setting off the cascade of pancreatitis. Many cases presumed to be idiopathic probably are due to small stones, sludge, or crystals that are too small to be detected on ultrasound examination but may be seen on endoscopic retrograde cholangiopancreatography (ERCP).[22] Missing this cause will increase the possibility of recurrence.

Alcohol is the cause of approximately 35% of pancreatitis cases. As with the other causes of pancreatitis, the mechanism by which alcohol is toxic to the pancreas is not well understood. Possible mechanisms include toxic effects of the ethanol metabolite acetaldehyde, ethanol-related lipid metabolism, or

BOX 89-1 ETIOLOGY OF PANCREATITIS

Toxic
Alcohol, methanol
Drugs
Scorpion bites (in Trinidad)

Metabolic
Hypercalcemia (often from hyperparathyroid)
Hyperlipidemia and hypertriglyceridemia (triglyceride levels >1000 mg/dL)

Obstructive
Biliary tract disease
Ampullary tumors
Pancreas divisum with obstruction of the accessory duct
Periampullary duodenal diverticula
ERCP and postpancreatography
Pancreatic neuroendocrine tumors
Pancreatic carcinoma
Sphincter of Oddi fibrosis, stricture, tumor, or hypertension

Infectious
Viral
Adenovirus
Coxsackievirus
CMV
EBV
Echovirus
Hepatitis A, B, C viruses
HIV
Varicella
Rubella

Other Infections
Aspergillus
Campylobacter
Clonorchiasis
Cryptococcus
Cryptosporidium
Dysentery
MAI
Mumps
Mycobacterium TB
Mycoplasma species
Legionella species
Leptospirosis
Salmonella typhimurium
Scarlet fever
Streptococcal food poisoning
Toxoplasma infection
Tuberculosis
Ascariasis

Other Causative Disorders/Conditions
Diabetic mellitus, DKA
Crohn's disease
Cystic fibrosis
Emboli (atherosclerotic)
Hemochromatosis
Hereditary pancreatitis
Hypothermia
Vasculitis
Lupus
Polyarteritis nodosa, malignant hypertension
Ischemia from hypoperfusion
Perforated ulcer
Postoperative
Pregnancy
Reye's syndrome
Trauma
Uremia
Idiopathic

CMV, cytomegalovirus; DKA, diabetic ketoacidosis; EBV, Epstein-Barr virus; ERCP, endoscopic retrograde cholangiopancreatography; HIV, human immunodeficiency virus; MAI, *Mycobacterium avium-intracellulare*; TB, tuberculosis.

spasm of the sphincter of Oddi. Patients with alcoholic pancreatitis have usually had 5 to 10 years of chronic alcohol use before the onset of pancreatitis.[5,23]

In addition to alcohol, a number of other medications and toxins may cause pancreatitis, including didanosine, pentamidine, oral contraceptives, and selected scorpion venoms. The list of definite and potential drugs causing pancreatitis is extensive (Box 89-2). Another cause of pancreatitis is hypertriglyceridemia, with levels more than 500 mg/dL being implicated, although the level is often above 1000 mg/dL. In pregnancy, both gallstones and increased triglyceride levels can cause pancreatitis.[5] When this occurs, both maternal and fetal mortality rates are high (20%).

Both blunt and penetrating abdominal trauma can disrupt the ductal system and the pancreatic cells, setting off the enzyme cascade that will result in acute pancreatitis. Pancreatitis also may result from iatrogenic ductal injury in 1 to 10% of ERCP procedures.[24] Likewise, postoperative pancreatitis is well recognized and carries a higher mortality than that associated with other causative disorders.

Although both viral and bacterial disorders may precipitate pancreatitis, the two most common viral causes of pancreatitis are mumps and coxsackievirus B infection. Pancreatitis is more common in patients with human immunodeficiency virus (HIV) infection than in the general population.[24] In addition to the common etiologic disorders, this population is at additional risk for opportunistic infections, toxicity from HIV-specific medications, and AIDS-related cancers.[25,26] Acute pancreatitis is ultimately classified as idiopathic in approximately 10% of cases.[16] Suspected but controversial causes include sphincter of Oddi dysfunction and pancreas divisum, which arises from a failure of the dorsal and ventral ducts to fuse. With this entity, most of the pancreatic juice flows through the minor pancreatic duct and papilla.[21]

The etiology of pancreatitis in adults and that in children are similar, although incidence rates for specific causative disorders are different. Trauma (including child abuse), infection, and idiopathic causes account for 70% of the cases in children.[3] Hereditary pancreatitis is an autosomal dominant trait, with onset frequently noted during childhood. Other causes include infections and congenital anomalies.[27] In elderly patients, gallstones are the most common cause of acute pancreatitis, accounting for up to 55% of the cases.[28]

Clinical Features

Pancreatitis should be suspected in all patients with epigastric abdominal pain, regardless of age. Once the diagnosis has been made, the underlying cause and presence of complications related to the disease should be sought.

BOX 89-2 DRUG-INDUCED PANCREATITIS

Definite	Possible
Acetaminophen	Bumetanide
Azathioprine	Carbamazepine
Cimetidine	Chlorthalidone
Cisplatin	Clonidine
Corticosteroids	Colchicine
Didanosine	Cyclosporine
Erythromycin	Cytarabine
Estrogens	Diazoxide
Ethyl alcohol	Enalapril
Furosemide	Ergotamine
L-Asparaginase	Ethacrynic acid
Mercaptopurine	Indomethacin
Metronidazole	Isoniazid
Methyldopa	Isotretinoin
Nitrofurantoin	Mefenamic acid
Octreotide	Opiates
Organophosphates	Phenformin
Pentamidine	Piroxicam
Ranitidine	Procainamide
Tetracycline	Rifampin
Salicylates	Thiazides
Sulfonamides, trimethoprim-sulfamethoxazole, sulfasalazine	
Sulindac	
Valproic acid	

By history, almost all patients have abdominal pain, most commonly in the midepigastric area; however, the pain also can be in the right or left upper quadrant. If significant inflammation is present, the pain may be diffuse and the patient may have difficulty localizing the discomfort. Typically, onset of symptoms is relatively rapid, increasing in severity over a few hours. The pain generally is described as constant and severe and may radiate to the mid-back. The degree of pain does not correlate with the severity of disease. Even though gallstones are frequently the cause of pancreatitis, the onset of pain is not usually related to eating. Nausea and vomiting often will accompany the pain. Although the discomfort may be lessened by lying on the side or sitting up, more typically little relief is obtained with position change, moving, eating, vomiting, or bowel movement. Colicky pain or pain that waxes and wanes suggests another diagnosis. Approximately 50% of patients will have a history of similar abdominal pain that may represent a previous episode of biliary colic or mild pancreatitis.[29]

On physical examination, vital signs may be stable but frequently are abnormal. Hypotension, tachycardia, and shock indicate severe disease with complications or an alternate diagnosis. Vital signs also may be influenced by pain (tachycardia, tachypnea, hypertension) or alcohol withdrawal (tachycardia, hypertension, fever). A low-grade fever is present in approximately one half of patients with pancreatitis, both at presentation and for the first several days thereafter in the absence of infection.[16,18] High fever is uncommon during the acute phase of pancreatitis because infection generally is a late complication. Ongoing evaluation should include pulse oximetry because acute hypoxia is an indicator of systemic complications and severe disease.

Patients with pancreatitis generally appear restless and in moderate distress as they search to find a position to relieve their discomfort. They may be jaundiced if an obstructing stone is present. The cardiopulmonary examination may be significant for rales or diminished breath sounds if the patient is hypoventilating from pain or if a pleural effusion (developing more commonly on the left) is present. On inspection, the abdomen may appear normal or may be notably distended. Only rarely will there be evidence of blood within the peritoneum or retroperitoneum resulting from severe hemorrhagic pancreatitis. Presence of blood within these areas is classically manifested as Cullen's sign (discoloration around the umbilicus) or Grey Turner's sign (discoloration of the flank). Auscultation of the abdomen may reveal normal, decreased, or absent bowel sounds, depending on whether the patient has a concomitant ileus. Because the pancreas is a retroperitoneal organ, palpation of the abdomen generally reveals epigastric guarding, rebound tenderness being a less common finding. Murphy's sign may be present if the pancreatitis is secondary to a biliary source. Very rarely the physician may see evidence of subcutaneous fat necrosis: red nodules most prominent on the extremities. Other physical findings, such as the stigmata of alcoholism or xanthomas of hyperlipidemia, may help point to the etiology of the pancreatitis.

Complications

The patient presenting with acute pancreatitis will often have fever, tachycardia, and leukocytosis; these findings represent three of the four criteria for SIRS. That such a patient might go on to suffer from complications such as fulminant sepsis or other problems related to the intense localized inflammation should not be surprising.

Shock may result from volume loss from multiple sources. Fluid sequestration occurs in both the pancreas and the bowel lumen and wall. Hemorrhage into necrotic pancreatic tissue also may be noted. Additionally, release of vasodilator and cardiodepressive substances may occur.

Approximately 18 to 30% of patients may have pulmonary complications, which may include degradation of surfactant by pancreatic phospholipases; pleural effusions (more commonly noted on the left and frequently with elevated amylase); hypoxia from atelectasis, hypoventilation, and intrapulmonary shunting; and ARDS. ARDS, due to the loss of surfactant as well as capillary leak caused by the inflammatory mediators, is rare but carries a 60% mortality rate.[6]

Metabolic complications of pancreatitis include both hyperglycemia and hypocalcemia. Hyperglycemia is caused by decreased insulin and increased glucagon. The mechanisms for hypocalcemia are (1) sequestration or saponification of calcium in areas of fat necrosis; (2) hypoalbuminemia, hypomagnesemia, hyperglucagonemia; and (3) inactivation of parathyroid hormone.

Coagulopathy develops from circulating proteases affecting the coagulation cascade. Acute tubular necrosis can cause acute renal failure and results from the effects of circulating inflammatory mediators or from hypotension and hypoperfusion. Ultimately, multisystem organ failure will occur if the balance of proinflammatory cytokine production overwhelms the anti-inflammatory response, which seeks to restrict the inappropriate movement of proinflammatory agents into the circulation.[30]

Late complications occur after the second week of illness and include involvement of local structures, abscess formation (1 to 4%), gastrointestinal bleeding from stress ulcers, splenic vein thrombosis, rupture of pancreatic pseudoaneurysms, fistula formation, splenic rupture, venous thrombosis, and right hydronephrosis.[5] Pancreatic pseudocysts develop in 1 to 8% of patients after 4 to 6 weeks and are more common with alcoholic pancreatitis[31] (Fig. 89-2). Long-term complications of pancreatitis include recurrent or chronic pancreatitis, diabetes mellitus, and digestive and malabsorption problems.

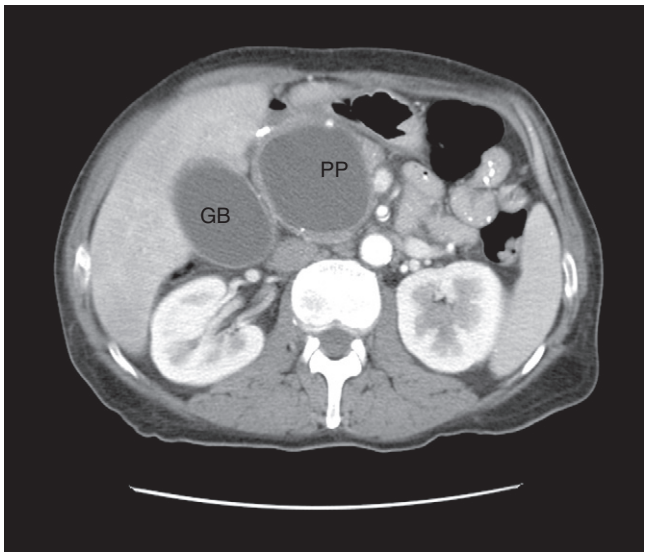

Figure 89-2. CT scan showing pancreatic pseudocyst (PP). In this patient, the pseudocyst was so large as to compress the common bile duct, causing obstructive jaundice. GB, gallbladder.

Diagnostic Strategies

Laboratory Tests

The diagnosis of acute pancreatitis and the differentiation from other abdominal disorders depend on careful clinical assessment in conjunction with abnormalities on certain laboratory tests and supportive radiographic findings. Three enzymes are derived from pancreatic acinar cells: amylase, lipase, and the proenzyme trypsinogen. Each has been tested as a biochemical marker of acute pancreatitis, but elevation of amylase remains the cornerstone of the diagnosis of pancreatitis, although it is an imperfect assay.

Amylase Assay. Amylase is an enzyme that cleaves carbohydrates. It is produced primarily in the salivary glands and pancreas, although it also also can be found in small amounts in the fallopian tubes, ovary, testis, muscle, intestines, and other organs. Elevations of amylase may be seen in normal persons as well as in ectopic pregnancy, macroamylasemia (amylase is bound to immunoglobulins or polysaccharides to form large-molecular-weight complexes), parotitis, renal failure (decreased clearance), mesenteric ischemia, bowel obstruction or infarction, perforated duodenal ulcer, acute peritonitis from other causes, and other diseases.[32] Pancreatic amylase can be differentiated from these other sources by electrophoresis, a test that is not readily available in the ED. Because of the other nonspecific sources of amylase, elevations of amylase lack specificity for the diagnosis of pancreatitis.[29,33] In acute pancreatitis, amylase rises within 6 to 24 hours and peaks in 48 hours, normalizing in 3 to 7 days. Thus, sensitivity of amylase decreases after the first 24 to 48 hours.[34]

In addition to the unclear origin of amylase, several other limitations are recognized for use of amylase assay to diagnose acute pancreatitis. The application of different assays and the lack of an international standard have led to designation of various measured levels as "normal" or "elevated" across institutions. Complicating matters is the lack of universal modality for the diagnosis of pancreatitis; amylase assay, autopsy, computed tomography (CT), and laparoscopy all have been used. Thus, amylase assay is commonly used as an imperfect standard with which to make the diagnosis of pancreatitis because of its low cost and rapid availability. However, it is difficult to determine the precise value of this test to the clinician trying to make the initial diagnosis, particularly in cases with an unclear clinical presentation. As reported by one study, the sensitivity of amylase for the diagnosis of pancreatitis ranges from 79 to 95%, depending on the comparative choice of standard test.[32] As expected, the sensitivity and specificity of amylase vary in accordance with the cutoff value selected to make the diagnosis of pancreatitis. With a cutoff value of total amylase that is at the upper limit of normal, the sensitivity is 91 to 100%, but the specificity is 71 to 98%. Increasing the cutoff value to approximately three times the normal value increases the specificity to nearly 100% but decreases the sensitivity to as low as 61%.[35] The higher cutoff for amylase gives a related drop in sensitivity, which is unacceptable for a serious disease such as acute pancreatitis. In up to 25% of patients with pancreatitis, especially in alcoholics and patients with hypertriglyceridemia (which interferes with the assay) or chronic pancreatitis, the amylase can be normal.[32] Of importance, mild amylase elevations in patients presenting with acute abdominal pain of unclear etiology, particularly in elderly persons, should raise suspicion for an acute surgical abdomen. Essentially, amylase levels alone, whether normal, mildly elevated, or extremely elevated, do not diagnose pancreatitis unless accompanied by the appropriate clinical picture.

Lipase Assay. Lipase is a pancreatic enzyme that hydrolyzes triglycerides and has been used both as an adjunctive test and an alternative test for the diagnosis of pancreatitis. Unfortunately, use of lipase assays is associated with many of the same pitfalls as for amylase assays. In the presence of pancreatic inflammation, lipase levels increase within 4 to 8 hours and peak at 24 hours. The levels stay elevated longer than with amylase, falling over 8 to 14 days,[32] thus giving greater sensitivity in patients with delayed presentation. Lipase, like amylase, is present in other tissues and tends to be elevated in similar clinical situations. Improved assays have rendered lipase more specific than amylase. Yet, there are still nonpancreatic causes of elevations of lipase, such as duodenal ulcers and bowel obstruction, as well as idiopathic elevations.[32,36] Comparisons between amylase and lipase are limited by the lack of a true "gold standard" modality for the diagnosis of pancreatitis, as well as the choice of cutoff values used for the diagnosis. Despite these limitations, lipase is at least as sensitive as and probably more specific than amylase (specificity of 80 to 99%). At values 5 times the upper limits of normal, lipase is 60% sensitive and 100% specific. The use of twice the upper limit of normal for lipase values has been recommended to decrease the possibility of missing the diagnosis of pancreatitis.[32] Using elevation of either amylase or lipase as evidence of disease will increase the sensitivity but decrease the specificity. Requiring both levels to be elevated does the reverse. Several experts recommend using lipase over amylase when seeking the diagnosis, and the United Kingdom recently released guidelines that recommend the use of lipase over amylase.[6,16,32,37,38]

The degree of elevation of amylase or lipase is not a marker of disease severity.[12,36] In a study of patients with pancreatitis, disease severity was equivalent in those with amylase elevation by less than 3 times normal and in those with higher elevations of amylase. In fact, compared with nonalcoholic patients, alcoholics will frequently have lower amylase levels but may have more severe disease.[39] In a patient with prolonged abdominal pain or a history of pancreatitis, an elevated amylase level for longer than a week may suggest pseudocyst or pancreatic abscess. Use of the amylase-to-lipase ratio has not proved helpful in the determination of a specific cause of pancreatitis.[33]

Other Tests. Several new tests still under development are aimed at improving diagnostic accuracy. Trypsinogen exists in

BOX 89-3 RANSON'S CRITERIA FOR PANCREATITIS-ASSOCIATED MORTALITY

At Admission	Within 48 Hours of Admission
Age >55 years	Hematocrit fall >10%
WBC >16,000/mm^3	BUN rise >5 mg/dL
Glucose >200 mg/dL	Calcium <8 mg/dL
LDH >350 IU/L	Po_2 <60 mm Hg
AST >250 SF units	Base deficit >4 mEq/L
	Fluid sequestration >6 L
Substitute if Gallstone Induced Admission:	**Within 48 Hours of Admission**
Age >70 years	Hematocrit fall >10%
WBC >18,000/mm^3	BUN rise >2 mg/dL
Glucose >220 mg/dL	Calcium <8 mg/dL
LDH >400 IU/L	Base deficit >5 mEq/L
AST >250 SF units	Fluid sequestration >4 L

Add the Total Number of Signs at 48 Hours:

Number	*Associated Mortality Rate*
0-3	1%
3-4	15%
5-6	40%
>7	100%

AST, aspartate transaminase; BUN, blood urea nitrogen; LDH, lactate dehydrogenase; SF, sigma-Frankel; WBC, white blood cells.

two major forms, with trypsinogen-2 present in high serum concentrations in acute pancreatitis. In a recent study, the sensitivity and specificity for urinary trypsinogen-2 dipstick testing were 93% and 92%, respectively. At present, however, neither this test nor any others have proved useful enough for inclusion in standard practice.[16,35,40]

Additional Laboratory Evaluation

In evaluating a patient with abdominal pain, amylase or lipase assays, along with other blood tests, are necessary to narrow the differential diagnosis, detect complications, and determine prognosis. Ranson developed a two-step list of primarily laboratory parameters, performed at hospital admission and after 48 hours, to determine the risk of death from pancreatitis[41,42] (Box 89-3). With this in mind, additional testing should consist of a complete blood count (CBC), lactate dehydrogenase (LDH) determination, and a comprehensive metabolic panel (including measurement of liver enzymes, calcium, renal function, and glucose). In patients with liver disease, coagulation studies should be performed to determine the degree of liver dysfunction. Arterial blood gas analysis should be done selectively in patients who are acidotic or hypoxic. This information can be used for treatment decisions and to determine prognosis based on Ranson's criteria. Magnesium should be checked in alcoholic patients and in those patients with electrolyte abnormalities. Both hypocalcemia and hyperglycemia are common in pancreatitis, with the hyperglycemia resulting from glucagon and insulin abnormalities. Calcium is best determined using the ionized calcium level. Serum calcium is falsely low in the presence of low albumin levels, as may be seen in patients with pancreatitis. Elevations of creatinine and blood urea nitrogen (BUN) may indicate the presence of hypovolemia or renal involvement, or both.

Elevation in liver enzymes may result from biliary-induced pancreatitis or from other diseases of the liver or biliary tract. In addition, liver enzyme levels may increase from the pressure on the common bile duct that results from the surrounding pancreatic inflammation. Mild elevations of bilirubin are common in all types of pancreatitis, as well as in many other liver disorders. For the patient diagnosed with pancreatitis, higher elevations of aspartate transaminase (AST) and LDH are related to worse prognosis according to Ranson's criteria.

Table 89-1 Sensitivity and Specificity of Liver Enzymes for the Etiology of Pancreatitis[35]

ENZYME/LEVEL	SENSITIVITY (%)	SPECIFICITY (%)	PPV (%)
ALT >150 mmol/L	48	96	95
AST >150 mmol/L	44	95	87
Alkaline phosphatase >300 units/L	24	95	87
Bilirubin 2.8 mg/dL	38	93	89

ALT, alanine aminotransferase; AST, aspartate transaminase; PPV, positive predictive value.

Data from Yadav D, Agarwal N, Pitchumoni CS: A critical evaluation of laboratory tests in acute pancreatitis. Am J Gastroenterol 97:1309, 2002.

When liver enzymes are elevated, the pattern of elevation may help determine the underlying cause of the pancreatitis (Table 89-1). Alanine aminotransferase (ALT) is the best single marker for a biliary etiology; levels greater than 3 times baseline support the diagnosis of biliary pancreatitis.[5,6,43] The higher the elevation of ALT, the greater the specificity and predictive value for gallstones. ALT levels more than 150 IU/L have 96% specificity, positive predictive value (PPV) of 95%, and 48% sensitivity for gallstone pancreatitis. Significant rises in AST, alkaline phosphatase, and bilirubin also are more likely to be related to biliary pancreatitis but are not as sensitive as ALT.[43]

The CBC may be notable for an elevated white blood cell count; the hematocrit may be either high or low. Early in the course, the hematocrit may be elevated because of third space volume loss. A decrease in hematocrit is a poor predictor of prognosis because it indicates intra-abdominal hemorrhage and severe pancreatitis. An electrocardiogram also should be done early to determine whether the patient's abdominal pain may be cardiac in origin.

Prognosis

At present, a variety of markers are available to aid in the detection of severe pancreatitis, including specific laboratory values that measure the systemic inflammatory response, scoring systems that tabulate the extent of inflammation or organ failure, and findings on imaging studies. The most commonly used scoring system is Ranson's criteria (see Box 89-3). In this system, the five criteria evaluated on hospital admission indicate the degree of local inflammation, whereas the six criteria assessed at 48 hours reflect the development of systemic complications. Ranson recognized that the model did not work well for patients with gallstone pancreatitis, so he revised the criteria to reflect the improved mortality. Although Ranson's criteria have an 89% negative predictive value, the obvious drawback to use of this system in the ED is that the scoring cannot be completed until 48 hours after diagnosis.[6,44] Furthermore, in patients with AIDS, Ranson's criteria may not be as accurate because of HIV-induced changes in the laboratory values such as those of calcium and LDH.[25,26]

BOX 89-4 ATLANTA CRITERIA FOR PREDICTING SEVERE ACUTE PANCREATITIS

Criteria for severe acute pancreatitis—one or more of the following:

1. Ranson score 3 or higher on admission (*or* during the first 48 hours)
2. APACHE II score 8 or higher at any time during course
3. Presence of organ failure
   - Shock (systolic blood pressure less than 90 mm Hg) *or*
   - Pulmonary insufficiency (PaO_2 60 mm Hg or less on room air) *or*
   - Renal failure (serum creatinine >2 mg/dL after fluid resuscitation)
4. Systemic complications
   - DIC (thrombocytopenia and hypofibrinogenemia and fibrin split products) *or*
   - Metabolic complications (serum calcium 7.5 mg/dL or less) *or*
5. Presence of one or more local complications (pancreatic necrosis, pancreatic abscess, pancreatic pseudocyst)

APACHE II, Acute Physiology and Chronic Health Evaluation II; DIC, disseminated intravascular coagulation.

From Bradley EL III: A clinically based classification system for acute pancreatitis. Summary of the International Symposium on Acute Pancreatitis, Atlanta, GA. Sept 11-13, 1992. Arch Surg 128:586, 1993.

Although Ranson's criteria constitute a simple and well-known scoring system, reliance on these criteria alone may result in delayed recognition of illness severity[23]; therefore, the Acute Physiology and Chronic Health Evaluation II (APACHE II) system also may be used to judge severity.[44-46] This system uses 12 physiologic variables, age, and chronic health status to generate a total point score. Scoring can be performed on admission and throughout the hospital stay. An APACHE score of 8 or higher indicates severe disease.[37,47] A score greater than 13 is associated with high likelihood of death.[5] An APACHE III scoring system also has been developed and includes additional physiologic variables, but this system has not proved to be better at predicting outcomes in patients with acute pancreatitis.[48]

C-reactive protein levels above 150 mg/L at 48 hours have proved to be a poor prognostic predictor 48 hours after symptom onset.[21,47] To account for the various factors that indicate the severity of disease in patients with acute pancreatitis, the Atlanta criteria for severity are widely accepted[49] (Box 89-4). Finally, a four-variable predictive model using BUN, age, LDH, and interleukin-6 has been proposed; initial analysis indicates that it is as accurate as other scoring systems.[50] This scoring system will need further validation, however.

Radiographic Studies

In pancreatitis, abdominal radiographs may show an ileus with a sentinel jejunal loop or spasm of the transverse colon and dilatation of the ascending colon. Pancreatic calcifications of chronic pancreatitis or gallstones may rarely be seen. The portion of the chest seen as part of the abdominal series may show left-sided or bilateral pleural effusions, atelectasis, or ARDS. Up to 80% of radiographs obtained in patients with pancreatitis will demonstrate some abnormality.[23] Unfortunately, many of these findings are nonspecific, and plain radiography has largely been replaced by more advanced imaging.

CT and ultrasound imaging are complementary studies in the evaluation of pancreatitis. Magnetic resonance imaging (MRI) offers imaging similar to that achieved with CT without significant advantages. Ultrasonography images the biliary tract with better accuracy than CT; however, the pancreas itself as well as local complications is less well visualized by this modality. It is recommended that an ultrasound study be performed within the first 24 hours of admission, particularly if a biliary etiology is suspected, to determine whether gallstones or dilation of the common bile duct is present.[7,38] In one study that compared the results of CT and ultrasonography among patients with pancreatitis, ultrasound findings resulted in a change in treatment in 55% of patients, compared with no changes after CT. CT was 39% sensitive for biliary disease, whereas ultrasonography was 83% sensitive.[51] In another study, ultrasound imaging was 94% sensitive for gallstones but only 19% for common duct stones and 38% for common duct dilatation.[52] Because of these limitations, when gallstone pancreatitis is highly suspected, an endoscopic ultrasound study may be more accurate and can help guide the emergency use of ERCP.[47,53] MRI cholangiopancreatography (MRCP) is a noninvasive test that can image the pancreas and may be used to help determine the cause of acute pancreatitis.[54]

Although ultrasound imaging is more sensitive for investigating biliary causes of pancreatitis, there are several reasons to perform CT in pancreatitis. The first is to rule out other causes of abdominal pain; the second is to evaluate for the presence of peripancreatic complications such as hemorrhage, pseudocyst, abscess, or vascular abnormalities; and the third is to help determine the extent of any pancreatic necrosis.[33,55] The Atlanta International Symposium recommended CT in patients with (1) an uncertain diagnosis; (2) severe clinical pancreatitis, abdominal distention, tenderness, fever with temperatures higher than 102°C, and leukocytosis; (3) a Ranson score greater than 3 or APACHE score greater than 8; (4) no improvement within 72 hours; and (5) acute deterioration.[49] If the diagnosis is clear and evidence of obstruction is lacking, CT or ultrasound imaging can be delayed until after the patient has been admitted to the hospital. The main indication for obtaining a CT in the ED is to exclude other diagnoses; however, if the patient is significantly ill and can tolerate the procedure, early CT may help determine if complications are already present.

If a CT scan is obtained, a dynamic helical CT study with oral and intravenous contrast is recommended. This study will help differentiate unopacified bowel from a pancreatic abscess or pseudocyst. Recent studies have shown that contrast does not aggravate pancreatitis in humans; however, if the patient cannot tolerate contrast, a noncontrast study will still be helpful.[33,56] CT also may be used to stage the severity and prognosis of acute pancreatitis.[5] Grades A (no abnormality) and B (focal or diffuse pancreatic enlargement) indicate lower levels of inflammation. Grade C shows mild peripancreatic inflammation and is associated with an increased risk of complication. Grade D (enlarged pancreas with fluid in the anterior pararenal space) and grade E (enlarged pancreas with two or more fluid collections) are associated with significant risk of infection, with mortality rates of up to 15%. The CT severity index is an additional grading system that uses the CT to evaluate how the pancreas looks, as well as evidence of fluid collections or gas adjacent to the pancreas.[57]

Differential Considerations

Pancreatitis must be differentiated from other abdominal processes, cardiopulmonary disorders, and systemic diseases (Box 89-5). An important point is that a number of acute surgical conditions may mimic pancreatitis in presentation and

BOX 89-5 DIFFERENTIAL DIAGNOSIS FOR PANCREATITIS

Abdominal Disorders
Perforated viscus
Peptic ulcer disease
Cholecystitis, gallbladder colic
Cholangitis
Gastroenteritis
Nephrolithiasis or pyelonephritis
Bowel obstruction
Mesenteric ischemia
Abdominal aortic aneurysm
Ectopic pregnancy

Cardiopulmonary Disorders
Myocardial infarction
Pericarditis
Pneumonia
ARDS
Pleural effusion

Systemic Disease
Sickle cell crisis

ARDS, acute respiratory distress syndrome.

also may cause elevated amylase. Examples are bowel perforation, peritonitis, ischemic bowel, small and large bowel obstruction, and ruptured ectopic pregnancy.

Management

The management of pancreatitis is primarily supportive; rehydration, pain and nausea control, nutritional supplementation, and monitoring for complications constitute the foundations of care. The supportive care given to the patient with acute pancreatitis has multiple objectives. The first is volume replacement. Because of vomiting and fluid sequestration, most patients with pancreatitis are dehydrated. Fluids should be replaced with normal saline; several liters may be required. Vital signs and urine output should be used to judge the adequacy of volume replacement. Electrolytes should be monitored and replenished.

A second objective is pain control. Abdominal pain associated with pancreatitis is severe and will generally require narcotic analgesia. Meperidine historically has been used in pancreatitis and biliary disease. Although morphine may increase the tone of the sphincter of Oddi, evidence that it worsens the disease process in pancreatitis is lacking.[58] Patient-controlled analgesia may be the most effective method of pain control.[38] Antiemetics are indicated to control nausea or vomiting.

A third objective is to ensure adequate nutrition. In the past, patients were allowed nothing by mouth and nasogastric suctioning was initiated out of concern that oral intake would stimulate the release of pancreatic enzymes. However, randomized clinical trials in patients with mild to moderate pancreatitis have shown no benefit from either fasting or use of nasogastric suctioning.[59,60] At this time, nasogastric suction is indicated only in cases of intractable vomiting or ileus, and some enteral feeding should begin as soon as it is tolerable. Some evidence suggests that early enteral nutrition may improve outcomes even in severe pancreatitis[61]; however, if oral feedings are not tolerated or are inadequate, then parenteral feedings should be initiated.[3]

Objective four is reevaluation for complications of pancreatitis. Hypotension should be corrected with large volumes of normal saline (up to 6 L). Invasive hemodynamic monitoring may become necessary. Airway control is appropriate for respiratory failure or continued shock. Hyperglycemia should be treated cautiously because it may self-correct as the pancreatitis resolves. Hypocalcemia may be the result of decreased albumin or hypomagnesemia, so ionized calcium and magnesium levels should be checked before replacement therapy is initiated. If true hypocalcemia is present and the patient is experiencing symptoms, then treatment is appropriate. Calcium gluconate should be used if the calcium must be replenished. The serum potassium should be normalized before calcium replacement, however, because calcium will cause intravascular potassium shifts.

In the case of gallstone pancreatitis, gastroenterology consultation is appropriate to discuss the use of ERCP. Early operative removal of gallstones and the gallbladder has been shown to increase mortality[62]; however, early removal of common bile duct stones by ERCP may reduce morbidity. At present, consensus is lacking regarding the optimal timing of ERCP in the presence of gallstone pancreatitis.[63] Early endoscopic sphincterotomy (in 24 to 48 hours) and stone removal are recommended in the setting of cholangitis, sepsis, and severe obstructive pancreatitis.[5,52,64] In mild pancreatitis, early ERCP has not consistently been shown to decrease morbidity. In addition, there is approximately a 5% rate of pancreatitis with ERCP and papillotomy, as well as other complications associated with the procedure (bleeding and perforation). In view of the ongoing controversy, it is appropriate to involve the consultant early in the case so that a well-coordinated plan can be created.

Theoretically, the following medications should moderate the course of pancreatitis: Histamine H_2 receptor blockers decrease the release of secretin by inhibition of gastric acid, glucagon directly suppresses pancreatic exocrine secretion, and octreotide inhibits pancreatic secretion. However, these therapies have not been shown to be clinically effective.[5,6] Other approaches using inhibitors of inflammatory mediators also have failed to show clinical improvement.[5,6,20] For patients with severe pancreatitis, an H_2 blocker, although not helpful for the acute disease, may decrease stress-induced ulcers.

Use of antibiotics in those patients with severe pancreatitis with or without evidence of necrosis of pancreatic tissue is controversial. Prophylactic antibiotics have been reported to be effective in reducing subsequent infection.[5,8,65] These positive effects have not been seen in all studies, however, and some evidence indicates that use of prophylactic antibiotics in any patient with severe pancreatitis may increase the risk of fungal infection.[66] A recent study with good methodology compared intravenous ciprofloxacin plus metronidazole with placebo and found no difference with respect to the development of infected pancreatic necrosis.[67] At this time, the literature regarding the use of early antibiotics remains unsettled, although there appears to be growing acceptance of withholding antibiotics until clear evidence of infection is present.[3,16,37,47,61,68] On the basis of this reality, early discussion with a consultant would be prudent, and in the absence of expert opinion, it remains reasonable to begin broad-spectrum antibiotics in those patients with severe acute pancreatitis.

Surgical intervention or percutaneous drainage may be necessary for cases of infected pancreatic necrosis, infected pseudocyst, or unresolved pseudocyst. Surgery is preferred when percutaneous drainage is not effective or not possible (as with extensive pancreatic necrosis or deteriorating clinical status).[18,39]

Disposition

The course of acute pancreatitis is unpredictable, and complications may occur hours or days after the onset of illness; therefore, almost all patients with acute pancreatitis should be admitted to the hospital. Patients with evidence of severe pancreatitis should be admitted to the intensive care unit (ICU), especially if findings include agitation, confusion, rising hematocrit, pulmonary insufficiency, or cardiovascular problems such as hypotension, progressive tachycardia, or poor urine output. Specifically, patients with a score greater than 2 on Ranson's criteria on admission or other evidence of organ failure, local complications, or significant comorbid illness will also require ICU management.[5]

In hospitals without appropriate intensive care facilities, patients with evidence of severe pancreatitis should be transferred to an appropriate treatment center. If the cause of pancreatitis is suspected or confirmed to be gallstones, discussion with a specialist (gastroenterologist or surgeon) is necessary. Pediatric patients have increased morbidity and mortality from pancreatitis and should be considered for early transfer to a pediatric specialty center.

CHRONIC PANCREATITIS

Principles of Disease

Chronic pancreatitis is an ongoing inflammatory process leading to irreversible structural damage and impairment of exocrine and endocrine pancreatic function. Normal pancreatic structure is replaced with fibrotic tissue, resulting in pancreatic ducts that are strictured in some areas and dilated in others. The incidence is approximately 4 per 100,000.[69] In 70 to 80% of cases, the cause is chronic alcohol use. The risk increases with the duration and amount of alcohol consumption. The ingestion of more than 150 g of alcohol per day for an average of 5 to 15 years is associated with the development of chronic pancreatitis; this form of the disease affects 3 to 15% of chronic alcoholics.[69-71] It is possible that chronic pancreatitis also may develop in persons sensitive to small amounts of alcohol. Three theories exist as to the mechanisms by which alcohol causes chronic pancreatitis have been proposed: (1) direct cellular toxicity, (2) alcohol-induced precipitation of proteinaceous fluid in the ductules, which causes obstruction and calcification, and (3) injury caused by recurrent acute pancreatitis leading to irreversible damage and chronic inflammation.[69,71,72] Chronic pancreatitis can continue even after the cessation of alcohol use, although it is more commonly associated with alcoholic relapse.

Other, less common causes of chronic pancreatitis include ductal obstruction, autoimmune pancreatitis, hereditary pancreatitis, cystic fibrosis, trauma, autoimmune, hyperparathyroidism, α_1-antitrypsin deficiency, hyperlipidemia, and tropical pancreatitis (cassava fruit is implicated).[69] Idiopathic chronic pancreatitis occurs in approximately 10% of patients. In the 25% of cases of unknown cause, occult alcohol use may be the culprit. In children the most common causes are cystic fibrosis and hereditary pancreatitis.[69,71]

The pathophysiology of chronic pancreatitis includes chronic calcific pancreatitis, usually seen in alcoholics and characterized by patchy fibrosis, ductal injury, intraductal protein plugs, stones, and chronic inflammatory pancreatitis with diffuse fibrosis and inflammatory changes. As in acute pancreatitis, chronic inflammation can cause local injury resulting in lesions such as pseudoaneurysms, splenic vein thrombosis, pancreatic ascites, or pancreatic fistulas. Pancreatic pseudocyst formation is seen in up to 25% of patients with chronic pancreatitis. Rarely, pseudocysts can erode into vascular structures or can become infected. Narrowing of the bile duct from extrinsic pressure or strictures may lead to elevation of liver enzymes and jaundice. In approximately 5% of patients, duodenal obstruction develops secondary to inflammation around the head of the pancreas. Thus, chronic pancreatitis in an acutely ill patient may be a manifestation of the primary disease or a complication.

The most common endocrine complication is the presence of glucose intolerance in many patients with chronic pancreatitis. Over years, insulin-dependent diabetes develops in 50 to 75% of patients.[69,72] Patients with chronic pancreatitis have an increased risk for the development of pancreatic carcinoma of approximately 4%, as do patients with hereditary pancreatitis.

Chronic pancreatitis is associated with considerable morbidity in terms of pain and complications. In addition, patients with chronic pancreatitis have an excess mortality of approximately 20%; however, the cause of death is more likely to be related to other consequences of alcoholism than to pancreatitis.

Clinical Features

Patients with chronic pancreatitis may present with near-constant and intractable chronic pain, or with complications from chronic pancreatitis, or may experience an acute flare of chronic underlying disease. These flares may be severe, and if the patient is relatively well during the interim it may be difficult to distinguish this episode from a recurrent bout of acute pancreatitis.[71] When present, the pain is epigastric, usually radiating to the back and associated with nausea and vomiting. Often, the pain is similar to that in previous attacks of acute pancreatitis or flares of chronic pancreatitis. Use of alcohol or eating exacerbates the pain. No correlation has been found between remaining pancreatic function and the degree of pain, although a few studies have shown that the pain may diminish over years of chronic disease. Patients may experience weight loss because of malabsorption or decreased intake secondary to nausea and vomiting or to the recognition that eating may precipitate the pain.

In approximately 15% of patients with chronic pancreatic disease, signs and symptoms of pancreatic exocrine function insufficiency, including malabsorption, diarrhea, steatorrhea, and weight loss, may develop over time. Malabsorption occurs after approximately 90% of the pancreas is nonfunctional. Functional endocrine insufficiency will develop in approximately one third to two thirds of patients with chronic disease. The symptoms primarily manifest as hyperglycemia; however, the development of diabetic ketoacidosis is rare. Hypoglycemia is multifactorial in origin, with causes including an insufficiency of glucagon, decreased liver glucose stores, malnourishment, and hypoglycemic medications.

On physical examination, patients may appear to be in significant discomfort. They frequently appear chronically ill from alcoholism, poor nutrition, and malabsorption. On abdominal examination, palpation frequently reveals tenderness without peritoneal signs. The abdomen should be carefully palpated for a mass that may represent a pseudocyst or tumor. Stigmata of chronic alcohol abuse also may be noted; however, jaundice may be from pressure on the common bile duct or from alcohol-related liver injury.

Diagnostic Strategies

The diagnosis of chronic pancreatitis frequently is made clinically rather than on the basis of laboratory testing. The serum

levels of amylase and lipase initially are mildly elevated in chronic pancreatitis, but as the disease progresses, these levels normalize. As in acute pancreatitis, the degree of elevation of amylase and lipase is not prognostic. In the patient with the appropriate clinical picture, normal amylase and lipase levels are consistent with a diagnosis of chronic pancreatitis.

Blood work should include a CBC and complete metabolic profile. The white blood cell count usually is normal. There may be elevations of hepatic enzymes (alkaline phosphatase, bilirubin, or transaminases) either from alcoholic hepatitis or from compression on the biliary duct from pancreatic inflammation or a mass in the head of the pancreas. Elevations in serum glucose also may be seen; hypoglycemia is less common. Decreases in albumin and calcium are common because of the chronic nature of the disease. If the diagnosis is in question, stool may be tested for fecal fat and pancreatic enzymes such as elastase, chymotrysinogen, and trypsinogen.[71]

Although abdominal radiographs are not necessary, presence of pancreatic calcifications is pathognomonic. Such calcifications are seen in 30 to 50% of patients, usually related to chronic alcohol-induced pancreatitis (Fig. 89-3). Patients with calcifications have had pancreatitis for an average of several years; therefore, these patients should be evaluated for long-term complications such as diabetes and malabsorption.

In patients with the clinical manifestations of chronic pancreatitis, including pain, malabsorption, and diabetes, the diagnosis is made by CT scan, ERCP, or endoscopic ultrasound.[71] In the ED setting, patients with known chronic pancreatitis do not need imaging except when the underlying cause of the pain is in question or if the pain is prolonged, significantly increased, or unresponsive to treatment. CT shows dilated intrapancreatic ducts, microcalcifications, pseudocysts, or other complications. CT is 90% sensitive for chronic pancreatitis and is the preferred modality when imaging is indicated. Although ultrasound imaging is useful in diagnosing the cause of acute pancreatitis, it is less useful in chronic pancreatitis, with a sensitivity of 75% and specificity of 80 to 90%. The primary ultrasound findings are pancreatic calcifications and ductal abnormalities.

Although endoscopic retrograde pancreatography (ERP) is not an ED procedure, it can be helpful in diagnosing pancreatic duct abnormalities and measuring pancreatic function. Some gastroenterologists consider the ductal abnormalities seen on ERP and endoscopic ultrasound to be pathognomonic for chronic pancreatitis. In the future, MRCP may assume a greater role in the evaluation of chronic pancreatitis.[72]

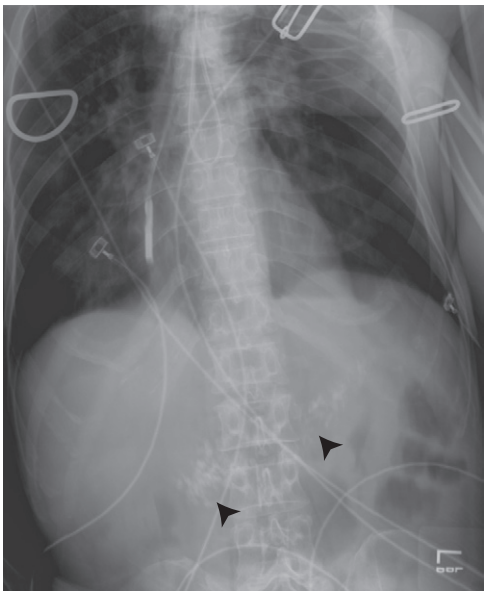

Figure 89-3. Pancreatic calcifications *(arrowheads)* throughout the pancreas as seen in chronic pancreatitis. (Incidental finding of feeding tube in main bronchus.) (Image courtesy of Ronald Arildsen.)

Differential Considerations

The diagnosis of chronic pancreatitis usually is straightforward in the alcoholic patient with hyperamylasemia who has chronic abdominal pain and a history of similar, previous flares of pancreatitis. The diagnosis may be more difficult when amylase and lipase levels are normal. However, the clinician should not be lulled into complacency and forget that other abdominal processes, unrelated to either the pancreas or the complications of pancreatitis, are legitimate considerations in the differential diagnosis (see Box 89-5). In addition, other chronic abdominal disease such as peptic ulcers, irritable bowel, gallstones, and endometriosis may manifest with recurrent abdominal pain. Finally, narcotic-dependent patients in withdrawal may experience vomiting and abdominal pain that may be difficult to differentiate from chronic pancreatitis.

Management

The initial management of chronic pancreatitis is supportive. Depending on the patient's clinical status and electrolyte values, replenishment of fluids and electrolytes may be necessary. An "alcohol cocktail" with thiamine, multivitamins, and folate often is indicated because patients frequently are malnourished. Antiemetics should be used to manage recurrent emesis.

Management of pain is one of the most important and most difficult aspects of treatment. Laboratory values may be normal despite significant pain, and patients with chronic pain syndromes may not exhibit signs of autonomic hyperactivity when experiencing exacerbations of their underlying disease. This lack of correlation may lead to a concern that the expressed need for pain medication constitutes drug-seeking behavior. Physicians should err on the side of treatment in most patients, except those with documented abuse. Nonsteroidal analgesics and acetaminophen are the preferred drugs for control of pain but often are not adequate. Either morphine or meperidine may be used and should be titrated to effect. Tramadol (Ultram) also has been used effectively.[73] The use of narcotics over extended periods may be necessary. Non-narcotic modulators of pain, such as selective serotonin reuptake inhibitors or gabapentin, may be helpful for chronic pain. In the ideal medical system, the primary care physician or a pain management specialist monitors the narcotic prescription, because narcotic dependence may become an issue.

The removal of inciting factors, especially alcohol, is important. Smoking also plays a role in the development of chronic pancreatitis that is independent of alcohol.[71] Patients with significant pain should have nothing by mouth, although as in acute pancreatitis, a nasogastric tube is not indicated. The use of oral pancreatic replacement enzymes increases the amount of trypsin in the duodenum and may decrease stimulation of the pancreas, with subsequent decrease in pain. Studies of the effectiveness of pancreatic enzyme replacement on pain have yielded contradictory results.[71] These enzymes should be used in patients with malabsorption or steatorrhea. In theory, proton pump inhibitors or H_2 receptor blockers also may reduce pancreatic stimulation; however, these agents have not been shown to decrease pain or hasten recovery. Octreotide lowers cholecystokinin levels and may inhibit pancreatic secretion.[71]

Beyond ED treatment, helpful adjuncts may include endoscopic dilation, ductal stone removal, extracorporeal shock wave lithotripsy, or stenting of the pancreatic ducts. Common bile duct stenting also may be necessary, because obstruction occurs in approximately 5 to 10% of cases.[71] Surgery such as pancreatic head resection, lateral pancreaticojejunostomy, or Whipple pancreatic duodenectomy is sometimes an option when conservative treatment has failed. One recent study showed improved pain and physical health summary scores in patients randomized to undergo surgery rather than endoscopy.[74] Pancreatic pseudocysts in chronic pancreatitis are less likely to resolve spontaneously and should be drained either endoscopically under ultrasound guidance or in an open procedure. Celiac plexus blocks also have been used with minimal success for pain control.

Disposition

In general, patients with chronic pancreatitis are managed as outpatients and present to the ED with exacerbations or complications. Because acute pancreatitis can occur in patients with chronic pancreatitis, the same prognostic indicators for severity of acute pancreatitis should be considered. Patients with severe disease should be admitted to the ICU. Patients with dehydration, abdominal pain unresponsive to medications, or questionable diagnosis should be hospitalized for evaluation and treatment. After a careful ED evaluation, in the absence of dehydration, unstable vital signs, or uncontrolled pain, the patient may be managed on an outpatient basis with close follow-up. After hospital discharge, it is important to stress lifestyle modifications of abstinence from alcohol and tobacco, as well as intake of frequent, small low-fat meals.

PANCREATIC CANCER

Perspective

Pancreatic cancer is a particularly lethal cancer, with a 5-year survival rate of 4% despite aggressive surgery and advances in chemotherapy. It is the fourth most common cause of cancer-related death in the United States. The disease is diagnosed in approximately 11 people per 100,000 per year, and the incidence has increased three-fold over the past 40 years. Because early symptoms are few, a minority of patients (less than 20%) are diagnosed at an early stage.[28,75,76]

Principles of Disease

Little is known about the etiology of pancreatic cancer. The most consistently reported risk factors are smoking, advanced age, and positive family history. Chronic alcoholism, chronic pancreatitis, and diabetes have been shown to be risk factors in some studies.[76-78]

Ductal adenocarcinomas account for 95% of malignant pancreatic tumors. The pancreatic head is the location of origin in 70% of cases. The tumor extends locally into adjacent structures and can metastasize by hematogenous or lymphatic spread to liver, peritoneum, lungs, bones, and brain. Neuroendocrine tumors, such as gastrinomas, vasoactive intestinal peptide (VIP)-omas, and glucagonomas make up the remaining cases.[79] These types of tumors carry a better prognosis.

Clinical Features

The presentation of pancreatic adenocarcinoma is variable because progression of the disease is indolent. The tumor usually has been present for several months before the cancer is diagnosed; therefore, patients may present with pain of long duration or with one of the many complications of the disease.[80] One of the most common presentations is weight loss, which usually is the result of anorexia rather than malabsorption. The patient may complain of dull, constant abdominal pain in the epigastrium that may radiate to the back. Alternatively, the patient may present with painless jaundice from common bile duct obstruction, and progressive jaundice develops in approximately 75% of patients. An enlarged, palpable, but painless gallbladder in the presence of jaundice is most commonly associated with pancreatic cancer (termed *Courvoisier's sign*). Glucose intolerance also may develop. As the tumor enlarges, patients may exhibit evidence of bowel obstruction. Pancreatic cancer (as well as other cancers) may render patients hypercoagulable, resulting in thromboembolic presentations. Varices and gastrointestinal bleeding may be caused by compression of the portal system.

Neuroendocrine tumors of the pancreas are rare and manifest with symptoms that reflect the hormones they produce. For example, with insulinomas, the presenting manifestation may be hypoglycemia. Gastrinomas are related to Zollinger-Ellison syndrome and recurrent peptic ulcers. VIPomas (also known as Verner-Morrison syndrome) manifest with extreme watery diarrhea, hypokalemia, and achlorhydria. Glucagonomas manifest with glucose intolerance and necrolytic migratory erythema. Some tumors produce multiple hormones.[79] Other, nonfunctional tumors also may be noted incidentally on CT scans as small pancreatic masses. Diagnosis is made by measurement of abnormal levels of hormones and recognition of the appropriate clinical syndrome. Fifty percent of pancreatic neuroendocrine tumors are malignant.[81]

Diagnostic Strategies

The diagnosis of pancreatic cancer may be made by ultrasonography, although CT scan provides better imaging of the cancer. MRI also may provide information. Percutaneous ultrasound-guided biopsy, endoscopic ultrasound examination and biopsy, or CT-guided biopsy can be used to obtain tissue diagnosis.[77] Histologic samples are needed to differentiate ductal adenocarcinoma from islet cell tumors, other metastatic cancers, and lymphoma. Serologic markers have not proved satisfactory for diagnosis or follow-up evaluation, although several oncogenes and tumor markers are under study (CA19-9 and CEA).

Management

Complete resection of the carcinoma is the only effective treatment. Unfortunately, few tumors (less than 20%) are diagnosed at a stage at which this may be possible.[77] In patients with unresectable tumors, the median survival period is approximately 6 months. Palliative surgery may be performed to relieve obstruction. Biliary drainage by percutaneously placed or ERCP-placed stents also may help to relieve jaundice. Chemotherapy and radiation therapy may decrease tumor size to ease pain and prolong survival in some patients.[77,82] Treatment of neuroendocrine tumors is aimed at limiting tumor growth by both excision and reversal of hormone excess.[82]

Patients may present to the ED with complications of the cancer such as bowel obstruction, jaundice, or problems with pain control. In view of the grim prognosis for this disease and the significant associated pain, narcotics should not be withheld, and end-of-life issues should be addressed by the oncologist.

KEY CONCEPTS

- Most cases of acute pancreatitis are caused by gallstones (45%) and alcoholism (35%). Other causes include medications, toxins, and trauma.
- The clinical spectrum of acute pancreatitis ranges from mild (epigastric discomfort often associated with vomiting) to life-threatening (severe abdominal pain in the presence of an acute abdomen and hemodynamic instability due to systemic complications). The mortality rate for severe pancreatitis approaches 30%.
- There is no perfect test for diagnosing acute pancreatitis. The most useful tests include serum amylase and lipase assays. Unfortunately, both tests can yield normal results in up to 25% of cases, and mild elevations are not specific for acute pancreatitis and can be seen in many other acute surgical disorders causing abdominal pain. Both tests are highly specific for pancreatitis when serum levels are elevated 5 times above the upper limits of normal.
- Emergent abdominal CT should be performed in patients with clinically suspected pancreatitis who appear acutely ill (to exclude peripancreatic complications such as hemorrhage, pseudocyst, or abscess) and in patients with an uncertain diagnosis (to exclude other surgical causes of acute abdominal pain).
- Because the course of acute pancreatitis is unpredictable, patients should be hospitalized for pain control, hydration, observation, and the management of complications. Patients with severe pancreatitis (i.e., those who have more than two of Ranson's criteria, an APACHE score over 7, or evidence of systemic complications) should be cared for in an ICU.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 90

Disorders of the Small Intestine

Susan P. Torrey and Philip L. Henneman

SMALL BOWEL OBSTRUCTION

Perspective

The signs and symptoms of intestinal obstruction have been recognized for centuries. This clinical entity has historically been treated with a variety of interventions, including enemas and inflation of the rectum, metallic mercury ingestion, therapeutic bleeding, and percutaneous intestinal puncture. By the late 19th century, proximal intestinal decompression was reliably used to provide temporary symptomatic relief of intestinal obstruction. Advances in the 20th century and beyond, including the development of antibiotics and improved surgical techniques, have significantly improved the prognosis for patients with small bowel obstruction (SBO).

Obstruction of the small bowel accounts for 15% of hospital admissions for acute abdominal complaints.[1] Approximately 300,000 operations are performed in the United States each year for relief of intestinal obstruction. Aggressive treatment has resulted in a current mortality rate of less than 5%, a substantial improvement over the expected 60% mortality rate for this disease in 1900. When strangulation complicates SBO, however, the mortality rate increases to as much as 30%. Death from SBO occurs most often in the elderly or in patients with significant underlying illness.

The term *mechanical obstruction* implies a physical barrier to the flow of intestinal contents. Within this definition, *simple obstruction* refers to the situation in which the intestinal lumen is partially or completely occluded at one or more points, thus producing proximal intestinal distention, but without compromise of the intestinal vascular supply. A *closed-loop obstruction* implies that a segment of bowel is obstructed at two sequential sites, usually by twisting about a constricting adhesive band or hernia opening. This mechanism of obstruction is associated with a high risk for compromise of intestinal blood flow with resulting intestinal ischemia, a condition referred to as *strangulation obstruction*. Not all closed-loop obstructions are associated with intestinal ischemia, and other types of obstruction may eventually involve vascular compromise.

In contrast with mechanical obstruction, *neurogenic* or *functional obstruction* occurs when intestinal contents fail to pass through the bowel lumen because of disturbances in gut motility rather than actual blockage. This entity also is commonly referred to as an *adynamic ileus*. When intestinal peristalsis fails, dilatation of the involved intestinal tract develops. Adynamic ileus most commonly is seen after abdominal surgery but can be caused by other common medical conditions (Box 90-1). Focal decrease in peristaltic activity may occur because of a localized inflammatory process (e.g., pancreatitis, cholecystitis, appendicitis) and result in gas and fluid accumulation in an isolated segment of bowel. This segmental ileus is called a *sentinel loop*.

Pseudo-obstruction refers to a poorly understood disorder of intestinal motility associated with a number of medical conditions, including amyloidosis, collagen vascular disease, diabetes, hypothyroidism, and several metabolic disorders—hypokalemia, hypocalcemia, and uremia. The signs and symptoms of intestinal obstruction are present, but evidence of an underlying lesion or cause is absent on diagnostic evaluation. Correction of any underlying disease process and supportive care are recommended, but the results of treatment often are disappointing.

Principles of Disease

A relationship between the progressive physiologic changes that occur in patients with SBO and the corresponding clinical manifestations is well documented. Mechanical SBO initially causes mild proximal intestinal distention that results from the accumulation of normal gastrointestinal secretions and swallowed air above the obstructing lesion. This distention stimulates peristalsis above and below the obstruction, which accounts for the frequent loose bowel movements that may accompany partial and even complete SBO in the early stages.[1] Early bowel distention stimulates epithelial cell secretory activity, resulting in the addition of more fluid, increasing bowel dilatation, and the creation of a self-perpetuating process. This situation is worsened by the inability of the distended bowel to absorb fluid and electrolytes at a normal rate. Further increases in intraluminal pressure result in capillary and lymphatic obstruction with subsequent edema of the bowel wall. Perforation occurs if this process continues uninterrupted. In addition, vomiting and intraperitoneal fluid sequestration further compound volume losses, leading to extracellular fluid depletion, hypovolemia, and, eventually, shock.

The rise in intraluminal pressure is much more abrupt with a closed-loop obstruction because the intestinal contents also are prevented from retrograde flow. Strangulation occurs, with subsequent development of venous congestion, small vessel rupture, intramural and mesenteric hemorrhage, and arterial insufficiency. It also is not uncommon for the loop of distended bowel to twist on itself further, resulting in large artery

BOX 90-1 Causes of Adynamic Ileus

Abdominal trauma
Infection (retroperitoneal, pelvic, intrathoracic)
Laparotomy
Medications (e.g., narcotics)
Metabolic disease (hypokalemia)
Renal colic
Skeletal injury (rib fracture, vertebral fracture)

BOX 90-2 Lesions Causing Small Bowel Obstruction

Intrinsic
Congenital (atresia, stenosis)
Inflammatory (Crohn's disease, radiation enteritis)
Neoplasms (metastatic or primary)
Intussusception
Traumatic (hematoma)

Extrinsic
Hernias (internal and external)
Adhesions
Volvulus
Compressing masses (tumors, abscesses, hematomas)

Intraluminal
Foreign body
Gallstones
Bezoars
Barium
Ascaris infestation

occlusion. Either sequence of events then progresses rapidly from intestinal ischemia to infarction.

Necrosis of the bowel and leakage of contaminated contents cause bacterial peritonitis and sepsis. Although the proximal small bowel normally contains few bacteria, this changes quickly during times of intestinal stasis. Simple intestinal obstruction has been shown to be associated with increased bacterial translocation to mesenteric lymph nodes. In one series, 59% of the patients undergoing laparotomy for simple SBO had bacteria (most commonly *Escherichia coli*) cultured from mesenteric lymph nodes, compared with only 4% of patients operated on for other reasons.[1,2]

The most common causes of SBO are listed in Box 90-2. In developed countries, postoperative adhesions are now responsible for more than 50% of all cases. It is estimated that as many as 15% of abdominal surgeries eventually result in SBO from adhesions. A particularly high incidence of SBO is found after gynecologic or intestinal surgery, as well as in patients who have previously undergone surgery in the presence of peritonitis or significant abdominal trauma.[3] Other important causes of SBO include hernias and neoplasms, each with an incidence of approximately 15%.[3,4] The incidence of obstruction related to hernias has been steadily decreasing in developed countries because of elective treatment of external hernias.[5] Although hernias account for a relatively small proportion of bowel obstructions, they are associated with a high rate of strangulation (28% with hernias versus 8% with adhesive obstruction). Anatomically, strangulation occurs because many obstructions caused by hernias are of the closed-loop type. When neoplasm is associated with SBO, the cause most often is colon cancer, followed by pancreatic, gastric, and gynecologic malignancies.

Several less common causes of SBO are pertinent to the practice of emergency medicine. *Gallstone ileus* is rare in the general population but accounts for 25% of nonstrangulated SBOs in patients older than 65 years.[6,7] In this entity, a gallstone erodes through an inflamed gallbladder wall into a loop of adjacent small bowel. The stone then passes through the bowel lumen until it meets some narrowing, typically at the distal ileum, where it produces mechanical obstruction. This problem occurs predominantly in elderly patients, so the associated 15 to 18% mortality rate is not surprising. Another unique cause of SBO is an *obturator hernia*. This hernia typically occurs in elderly emaciated women with significant concomitant medical illness but no previous abdominal surgery. It is believed that women with a wider pelvis and more oblique obturator canal are predisposed to the development of obturator hernia in the presence of decreased preperitoneal fat related to emaciation and chronic increased intra-abdominal pressure related to associated medical disease. This hernia is difficult to detect and often is diagnosed only when it arises as SBO. Both of these uncommon causes of SBO occur in the elderly, a group that is becoming an increasing percentage of the emergency department population.

Another uncommon but noteworthy cause of SBO is *small bowel volvulus*.[8] This condition results from abnormal twisting of a loop of bowel around the axis of its own mesentery. Although volvulus of the colon (sigmoid and cecum) is common, volvulus of the small bowel is rare. Primary small bowel volvulus occurs in an otherwise normal abdominal cavity and is seen most often in adult patients in Africa, the Middle East, and the Indian subcontinent. It is rarely seen in Europe and North America. Secondary causes of small bowel volvulus include malformation and malrotation of the intestine and tethering of the loop of bowel at its apex as a result of postoperative adhesions. Early surgical intervention is important because this classic form of closed-loop obstruction is associated with a high incidence of strangulation.

Intussusception occurs in all age groups but is primarily a disease of infancy and early childhood, constituting the most common cause of SBO in early childhood. Only 5% of all intussusceptions occur in adults, and intussusception accounts for only 5% of cases of SBO in adults.[9,10] An intussusception occurs when a segment of bowel telescopes into an adjacent segment, resulting in obstruction and ischemic injury to the intussuscepting segment. In contrast with the idiopathic nature of most childhood intussusceptions, a mechanical cause is present in more than 90% of adult cases. Tumors, either benign or malignant, act as the lead point of intussusception in more than 65% of adult cases. Several reports have described adult intussusception associated with acquired immunodeficiency syndrome (AIDS). In this setting, the lesions generally are in the ileum, and intussusception has been associated with lymphoma or unusual inflammatory processes, including atypical mycobacterial infection.

Clinical manifestations of intussusception in the adult patient are nonspecific and may occasionally be chronic or recurrent in nature. Abdominal pain is a prominent complaint, often associated with symptoms and signs suggestive of obstruction (nausea, vomiting, and abdominal distention). Radiographic features of intussusception also are nonspecific. Plain films may reveal evidence of partial or complete bowel obstruction. It has been recommended that ultrasonography may be useful in the diagnosis of adult and pediatric cases. The mainstay of diagnosis, however, remains contrast studies, typically abdominal computed tomography (CT) with an oral contrast agent. Although reduction of the intussusception may occur during contrast studies, surgery is recommended for adult patients because of the high incidence of pathologic lesions as a cause of intussusception.[10]

Finally, a fascinating and lengthy list of unusual causes of SBO has been reviewed and includes pharmacobezoars, *Ascaris lumbricoides* infection, and endometriosis. These reportable causes of SBO account for less than 6% of all cases.[11]

Clinical Features

History. Patients with SBO typically complain of regularly recurrent bouts of poorly localized abdominal pain lasting from seconds to minutes. The painful spasms occur every few minutes with proximal intestinal obstruction and less frequently with more distal obstruction. The pain is described as crampy in nature, and each episode has a characteristic crescendo-decrescendo pattern. A change in the description of the pain from intermittent and colicky to constant and severe may signal the development of complications, such as intestinal ischemia or perforation.

In general, the more proximal the obstruction, the greater the patient's discomfort and the shorter the delay between onset of symptoms and presentation. Several hours of severe colicky pain in association with bilious vomiting and mild abdominal distention are typical of proximal intestinal obstruction, whereas a day or two of progressively worsening pain and more prominent abdominal distention is typical of distal intestinal obstruction. When vomiting does occur with distal intestinal obstruction, it often is feculent from bacterial proliferation. With complete intestinal obstruction, obstipation eventually develops, whereas with early or partial obstruction, the patient may continue to pass stool or flatus.

Physical Examination. The physical examination should begin with a brief but thorough assessment of the patient's degree of distress, vital signs, and general condition. These important parameters determine the urgency of the evaluation and management of the patient.

Examination of the abdomen should include inspection for distention and a careful search for surgical scars and external hernias. Auscultation may reveal hyperactive bowel sounds—in particular, rushes or high-pitched "tinkles" produced by forceful peristaltic efforts. Late in the course of bowel obstruction, bowel sounds may become hypoactive or may be absent. Percussion may elicit tympany with distal obstruction and ileus. Palpation may reveal a tender mass, especially with a closed-loop cause of obstruction. A rectal examination should be performed to evaluate the rectal vault and to check for gross or occult blood. A prospective study of patients with abdominal pain defined six clinical variables that had high sensitivity and positive predictive value for the diagnosis of bowel obstruction[12]: a history of previous surgery, history of constipation, age older than 50 years, vomiting, abdominal distention, and increased bowel sounds.

The presence of peritoneal signs usually indicates late obstruction with complications, including strangulation. Of note, however, aggressive abdominal palpation in the setting of bowel dilatation can give the false impression of peritonitis, because quick compression-decompression of dilated bowel may elicit a significant pain response. Determining the presence of pain with cough or gentle shaking of the patient's pelvis along with percussion tenderness often is helpful in differentiating peritonitis from pain related to rapid decompression of dilated loops of bowel. Other clues to serious complications include alterations of the vital signs with tachycardia, hypotension, and fever indicating early sepsis. Unfortunately, a number of studies document that even experienced physicians cannot reliably distinguish between strangulation and simple intestinal obstruction on the basis of examination alone.[1,3]

Complications. Complications associated with SBO include hypovolemia, intestinal ischemia and infarction, peritonitis and sepsis, and respiratory compromise from elevation of the diaphragm or aspiration of gastrointestinal material. The incidence of complications will reflect in part the degree of intestinal dilation, which in most cases is directly related to delays in presentation, diagnosis, and initiation of appropriate treatment. Early diagnosis and management can prevent or minimize much of the preoperative morbidity associated with this disease.

Complications related to surgical management of SBO include recurrence of the obstruction, hemorrhage, wound infection, abscess formation, sepsis, and short bowel syndrome.[13-15] Much of the eventual postoperative morbidity and mortality is related to the patient's underlying medical condition. Whether the condition is treated surgically or conservatively, the long-term recurrence rate for adhesive SBO is significant—40% with nonoperative treatment and 27% with operative treatment.[16]

Diagnostic Strategies

Routine laboratory testing yields nonspecific findings. Leukocytosis is common with both simple and strangulated obstructions and is not a reliable marker for intestinal compromise. Serum markers of intestinal compromise and ischemia, including creatine kinase (CK), amylase, and lactate, are elevated late in the course of bowel obstruction. An electrolyte panel and renal function testing are appropriate if significant volume loss is evident.

Conventional and special radiographic examinations of the abdomen are the most useful diagnostic adjuncts for the evaluation of patients with suspected SBO. These studies may confirm or exclude the presence of bowel obstruction; identify the site, severity, and cause of the obstruction; and help distinguish simple obstruction from strangulation.[17-20] Characterization of the obstruction in this manner will determine the need for urgent surgical intervention versus a period of conservative, nonoperative management.

An adequate plain radiographic examination of the abdomen requires at least two films, one with the patient supine and the other with the patient in the upright or decubitus position. An upright chest film may be added to exclude the presence of free subdiaphragmatic gas, an uncommon finding in bowel obstruction. Plain radiographs demonstrate the presence of SBO in 50 to 60% of cases and delineate features suggestive of obstruction in another 20 to 30%.[17] The cause of obstruction is rarely demonstrated on conventional abdominal radiographs. The ability to predict the site of obstruction correctly often is limited by fluid-filled loops or abnormal positioning of small bowel. Despite these potential limitations, plain radiography is still the appropriate starting point for the diagnostic evaluation of a patient with suspected SBO.

Typical plain radiographic findings with SBO are distended loops of small bowel proximal to the site of obstruction followed by normal or collapsed bowel distal to the obstruction. The supine view may show dilated loops of bowel that are sharply angulated or arranged in a series of parallel segments reminiscent of a stepladder. Upright or decubitus films may demonstrate multiple intraluminal air-fluid levels (Fig. 90-1A and B). In general, the greater the number of dilated loops of bowel, the more distal the site of obstruction. Colonic gas usually is negligible in amount unless the films are obtained early in the course of the obstruction or in the presence of a partial SBO.

When the obstructed intestine contains more fluid than gas, the classic findings just described may be absent. In this setting, small pockets of gas may become trapped between the valvulae conniventes of the small bowel and may appear as an

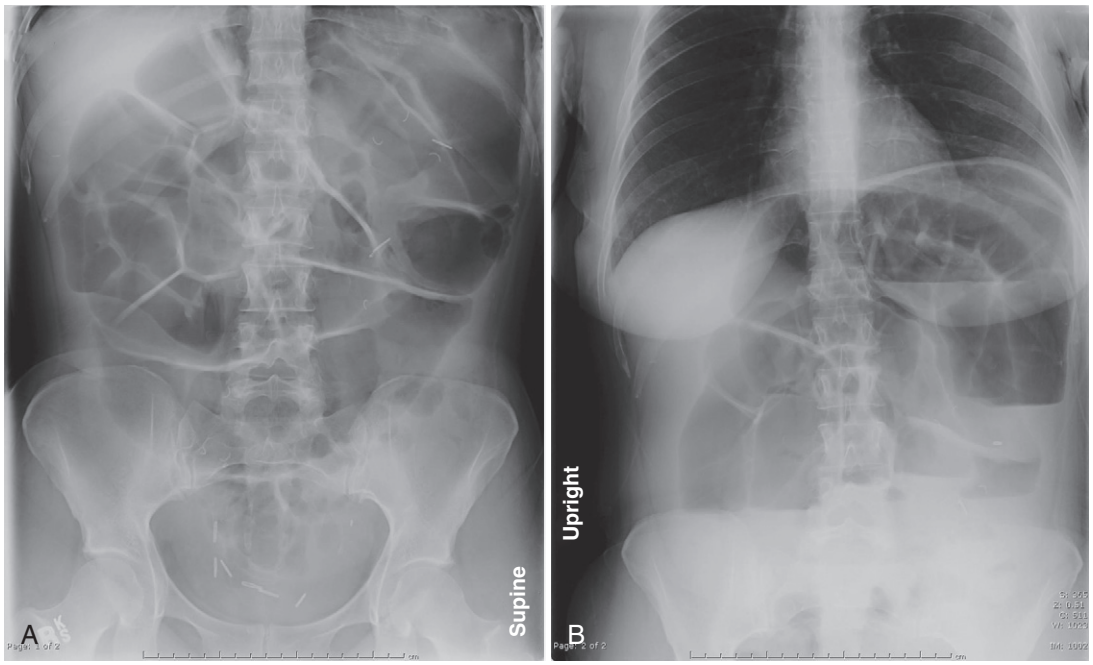

Figure 90-1. **A,** Supine film showing dilated loops of small bowel in a patient with small bowel obstruction. **B,** Upright abdominal film revealing multiple air-fluid levels and small bowel dilation, consistent with a diagnosis of small bowel obstruction.

oblique series of round radiolucencies on the upright film—the so-called string of pearls or string of beads sign, which is very suggestive of SBO.

In patients with adynamic ileus, plain film findings may be similar to those in patients with intestinal obstruction. With the former entity, however, the radiologic findings tend to involve the entire gastrointestinal tract, including the colon, and air-fluid levels are not as prominent as with mechanical obstruction. The air-filled loops of bowel also are not dilated in gastroenteritis or other causes of adynamic ileus.

Since the first reports describing the role of CT in bowel obstruction in the early 1990s, this modality has been increasingly used. It is considered complementary to standard radiography in the evaluation of SBO. CT has been shown to be an excellent modality for demonstrating intussusception, volvulus, and extraluminal lesions such as abscesses and tumors.[19] This modality is especially helpful and should be used as an early imaging technique in the setting of known abdominal malignancy or inflammatory bowel disease or when an abdominal mass is discovered on examination. CT scans have high sensitivity, specificity, and accuracy in the diagnosis of SBO.[17,18] In high-grade obstructions, in particular, these numbers are greater than 90%. CT can demonstrate both closed-loop obstruction and features suggestive of strangulation. In the vast majority of cases, CT is not required to make the diagnosis of bowel obstruction. Its main use is in better defining the site of obstruction and possible cause.[17-20]

Abdominal CT examination has increasingly been advocated for early diagnosis of complete obstruction and ischemia in SBO, both of which dictate early surgical intervention.[21,22] One recent study demonstrates the high sensitivity for CT for ischemia and further suggests that CT findings consistent with partial SBO predict a clinical condition that will resolve without surgery in more than 90% of cases.[22]

Another radiologic test for small bowel obstruction that may influence clinical outcome is the use of water-soluble contrast. Several studies have shown that water-soluble contrast radiography successfully predicts nonoperative resolution of adhesive SBO.[23,24] Although some early studies suggested that water-soluble contrast actually hastened resolution of the obstruction, a recent meta-analysis does not support a therapeutic benefit for this technique.[24]

Differential Considerations

The diagnosis of SBO should be considered in a patient with abdominal pain and vomiting, especially if the history includes previous abdominal surgery. It often is difficult to distinguish among mechanical obstruction, adynamic ileus, and pseudo-obstruction on clinical grounds alone.

Other clinical diagnoses that should be considered range from benign to life-threatening in nature and include pregnancy, gastroenteritis, cholelithiasis and cholecystitis, pancreatitis, peptic ulcer disease, appendicitis, ischemic bowel syndromes, and myocardial infarction. Each of these clinical entities has typical signs, symptoms, and diagnostic findings that help to differentiate it from SBO, but doing so may be challenging when patients present during the early stages of their particular disorder.

Management and Disposition

The initial management of SBO has remained largely unchanged for several decades and consists of aggressive fluid resuscitation, bowel decompression, and timely surgical consultation.

All patients with SBO should be admitted to the hospital. Intravenous hydration should be initiated with an isotonic crystalloid solution administered through a large-bore catheter. Enteral decompression by nasogastric suction should take place early in the clinical course to remove accumulated gas and fluid proximal to the obstruction. No convincing argument has been made for the use of a long intestinal tube (e.g., Cantor, Miller-Abbott) over a nasogastric tube.[1,16] Placement of a nasogastric tube is a noxious procedure for the patient. Application of topical anesthetic to the nasopharynx and posterior pharynx may improve tolerability of the procedure.

There is no convincing research to recommend routine use of antibiotics in the conservatively managed patient. However, the demonstration of bacterial proliferation during intestinal

stasis and obstruction suggests that broad-spectrum antibiotics are appropriate when surgery is planned and when the clinical picture suggests vascular compromise or intestinal perforation.[1] Antibiotic use should provide coverage for gram-negative and anaerobic organisms that colonize the intestinal contents (e.g., second-generation cephalosporins).

"Never let the sun set or rise on a bowel obstruction" is an oft-quoted surgical adage that has stood the test of time because of the preoperative difficulty in distinguishing strangulation from simple bowel obstruction. Proponents of early surgical intervention cite the similar clinical and radiographic presentations of simple and strangulated obstructions and argue that any delay in surgical therapy may increase morbidity. Although there is no debate about the need for surgery in patients with signs of peritoneal irritation or fever, most surgeons advocate a trial of conservative therapy in the absence of findings suggestive of strangulation. Up to 75% of patients with partial SBO and 35 to 50% of those with complete obstruction experience resolution of symptoms when treated with intravenous fluid and bowel decompression alone.[16,23] Patients with early postoperative bowel obstruction, adhesive obstruction, and obstruction secondary to Crohn's disease are more likely to respond to nonoperative management. Surgical intervention should be planned if substantial relief is not obtained within a short time after nasogastric tube placement or if symptoms persist after 48 hours of conservative treatment. A practical point is that obstruction occurring in a patient without a previous history of laparotomy is not likely to be caused by peritoneal adhesions. Such de novo obstruction and the underlying cause usually are not resolved without surgery.

Neither advanced age nor known abdominal malignancy is a contraindication to operative intervention. Patients with abdominal cancer who do not have widespread intra-abdominal metastases should be managed as for any other patients with SBO. They should receive a trial of bowel decompression followed by surgery if resolution of the symptoms is not evident. From 20 to 40% of patients with abdominal neoplasms and SBO have a benign cause of the obstruction.[1] In addition, the incidence of strangulation with obstruction related to malignancy is low. Therefore, a trial of tube decompression is a safe and often successful option.

A therapeutic approach that is gaining support for the management of SBO is laparoscopy.[25-28] Bowel obstruction traditionally has been a relative contraindication to laparoscopy because of the potential for bowel distention and the risk of enteric injury. However, as experience with this surgical approach has increased, surgeons have begun to demonstrate that this is a safe and effective method of diagnosing and treating acute bowel obstruction in selected patients, particularly in those with obstruction caused by adhesions.

KEY CONCEPTS

- More than 50% of SBO cases are caused by postoperative adhesions. Two other leading causes are various hernias (15%) and neoplasms (15%).
- The diagnosis of SBO usually is made on the basis of plain radiographic findings, with the upright abdominal radiograph revealing air-fluid levels and dilated loops of small bowel in a majority of cases.
- Initial management of SBO should include volume assessment and resuscitation, plain radiography, bowel decompression, and surgical consultation. A significant percentage of SBO cases caused by adhesions may be managed without surgery.

■ ACUTE MESENTERIC ISCHEMIA

Perspective

Acute mesenteric ischemia primarily affects patients older than 50 years, especially those with significant cardiovascular or systemic disease. The acute form of this disease results in the rapid development of intestinal injury and is much more common than the chronic form of mesenteric ischemia. Chronic mesenteric ischemia results when splanchnic blood flow is inadequate to support fully the functional demands of the intestines yet not so compromised as to threaten bowel viability. The incidence of acute mesenteric ischemia is difficult to determine but has been reported as 0.1% of hospital admissions, and increasing occurrence in today's aging population has been noted in several studies.[29] Acute vascular compromise of the intestine remains an important and life-threatening cause of acute abdominal pain in patients presenting to the emergency department.

Acute mesenteric ischemia was described in the 18th and 19th centuries in sporadic reports; however, an understanding of the underlying pathophysiology awaited the classical experimental work of Litten in 1875, when he described the results of ligation of mesenteric vessels in animals. In 1895, Elliot described the first patient to recover after resection of an infarcted intestine that probably was the result of mesenteric venous thrombosis. He created two stomas and reanastomosed the bowel segments 2 weeks later. Thus, the diagnosis of gangrenous bowel by laparotomy and its treatment by resection with anastomosis, a sequence of events that is still common today, were first performed more than 100 years ago.

The concept of mesenteric revascularization as the treatment for acute mesenteric ischemia was introduced in the 1950s. Even with the advent of this significant surgical advance, however, morbidity and mortality rates remained high. Today, most physicians use an aggressive approach to the patient with suspected acute mesenteric ischemia, as first proposed in the 1970s. The single most important step in this approach is early diagnosis.

The etiology of acute mesenteric ischemia actually has four distinct categories, each associated with a group of risk factors, signs and symptoms on presentation, and varying nuances in the evaluation and management of the patient. The most common cause of acute mesenteric ischemia is arterial embolus, which accounts for 40 to 50% of cases. Arterial thrombosis accounts for 25% of acute presentations, nonocclusive mesenteric ischemia for 20%, and the remaining 5 to 10% of cases are caused by mesenteric venous thrombosis.[29] The importance of early diagnosis and aggressive intervention in patients with suspected acute mesenteric ischemia is underscored by mortality rates that climb to 70% once intestinal infarction has occurred. The mortality associated with this lethal disease has changed little in the last several decades and probably will not decrease until a reliable screening test for the disease is found.[30]

Principles of Disease

The severity of intestinal injury is inversely proportional to mesenteric blood flow and is a function of the state of the systemic circulation, the number and caliber of involved vessels, the status of the collateral circulation in the region, and the duration of the ischemia.[29] The extent of the damage ranges from reversible impairments in mucosal function to transmural infarction and necrosis of part or all of the bowel served by the compromised vasculature.

Blood supply to the abdominal organs derives from three major vessels: the celiac artery trunk, the superior mesenteric

artery (SMA), and the inferior mesenteric artery (IMA). Abdominal organs receive their blood supply on the basis of embryologic development. The esophagus, stomach, proximal duodenum, liver, gallbladder, pancreas, and spleen are supplied by the celiac trunk. The SMA supplies the distal duodenum, jejunum, ileum, and colon to the splenic flexure. The descending and sigmoid colon and rectum are supplied by the IMA. There is an abundant system of collateral vessels with significant territorial overlap of blood flow that can be clinically significant.

Approximately 25% of the cardiac output is delivered to the small and large intestines, with two thirds going to the SMA distribution and one third to the IMA.[29] Eighty percent of this flow is destined for perfusion of the mucosa because of its high metabolic requirement. Accordingly, the visceral mucosa is very sensitive to decreased perfusion. With the onset of hypoperfusion, a redistribution of intramural blood flow favoring the superficial layers of the mucosa takes place. Below a critical level of blood flow, however, the intestinal villi become ischemic, and significant alterations in mucosal function occur.

The countercurrent exchange mechanism in the small intestinal villi initiates and perpetuates ischemic damage to the tissue. As epithelial cells become necrotic, endothelial factors are released that lead to the attraction and activation of neutrophils and macrophages into the ischemic tissue. These cells release protease enzymes, tissue necrosis factor, platelet activating factor, arachidonic acid by-products, and toxic oxygen radicals that cause further endothelial damage, increased vascular permeability, vasoconstriction, inflammation, and further necrosis. This initial ischemic insult is compounded if and when perfusion is reestablished, because restoration of blood flow permits further recruitment of inflammatory cells to the area. Ischemic disruption of the normally impenetrable mucosal barrier allows the release of bacteria, toxins, and vasoactive mediators into the systemic circulation. Cardiac depression, multisystem organ failure, septic shock, and death may occur even before the development of intestinal ischemia. Necrotic changes can be seen as early as 10 to 12 hours after the onset of symptoms but may develop in a more delayed fashion.

BOX 90-3 Factors Associated with Mesenteric Arterial Embolism

- Coronary artery disease
  - Post–myocardial infarction mural thrombi
  - Congestive heart failure
- Valvular heart disease
  - Rheumatic mitral valve disease
  - Nonbacterial endocarditis
- Arrhythmias
  - Chronic atrial fibrillation
- Aortic aneurysms or dissections
- Coronary angiography

BOX 90-4 Factors Associated with Nonocclusive Mesenteric Ischemia

- Cardiovascular disease leading to low-flow states
  - Congestive heart failure
  - Arrhythmias
  - Cardiogenic shock
  - Post–cardiopulmonary bypass
- Preceding hypotensive episode
  - Septic shock
- Drug-induced splanchnic vasoconstriction
  - Digoxin
  - Vasopressors
  - Ergot alkaloid poisoning
  - Cocaine abuse

Mesenteric Arterial Embolism

The median age of patients presenting with mesenteric arterial emboli is 70 years. Approximately two thirds of these patients are women. The vast majority of arterial emboli resulting in acute mesenteric ischemia involve the SMA. The source of SMA emboli usually is the heart, with fragmentation of either left atrial or ventricular thrombi during or after a dysrhythmia or valvular lesions. Emboli consisting of tumor and cholesterol also have been described. Emboli typically lodge 4 to 7 cm from the vessel's origin at a point of anatomic narrowing such as the takeoff of a major arterial branch. More than 50% of SMA emboli are found immediately distal to the origin of the middle colic artery. Risk factors for mesenteric arterial emboli include coronary artery disease, valvular heart disease, and arrhythmias—in particular, atrial fibrillation. A recent review of autopsy findings of thromboembolic occlusion of the SMA found a common association with acute myocardial infarction, cardiac thrombi, and synchronous emboli to other organs.[31] Risk factors are listed in Box 90-3. Recognition of these contributing factors is important to improve early diagnosis of this disease.

Mesenteric Arterial Thrombosis

The SMA, which originates from the ventral surface of the abdominal aorta at a 45-degree angle, commonly is narrowed by atherosclerosis. This is the most common site for thrombus formation in the mesenteric circulation. In contrast with arterial embolism, the more proximal nature of thrombus formation results in greater visceral damage and a less favorable prognosis. SMA thrombosis usually occurs in patients with chronic, severe visceral atherosclerosis. As many as 50% of these patients give a history of "abdominal angina," or abdominal pain after meals.[32] Thus, risk factors associated with mesenteric arterial thrombosis include older age, diffuse atherosclerosis (coronary, cerebral, or peripheral vascular disease), and hypertension.

Nonocclusive Mesenteric Ischemia

Nonocclusive mesenteric ischemia has been defined only in the last 50 years, as intraoperative and postmortem examinations have revealed ischemic bowel without obvious vascular obstruction.[29,33] The pathogenesis of nonocclusive mesenteric ischemia is multifactorial, but a common pathway involves mesenteric vasoconstriction, usually in response to low-flow states associated with decreased cardiac output or the administration of vasoactive medications. Factors contributing to the development of nonocclusive mesenteric ischemia include hypotension, which may be associated with many systemic diseases, and splanchnic vasoconstriction from various medications (Box 90-4). Nonocclusive mesenteric ischemia is seen in patients of all ages and often develops during hospitalization for other medical or surgical problems.

Mesenteric Venous Thrombosis

Mesenteric venous thrombosis is the least common cause of acute mesenteric ischemia. It occurs in a younger population

BOX 90-5 Factors Associated with Mesenteric Venous Thrombosis

- Hypercoagulable states
  - Polycythemia vera
  - Sickle cell disease
  - Antithrombin III deficiency
  - Protein C or S deficiency
  - Malignancy
  - Myeloproliferative disorders
  - Estrogen therapy/oral contraceptive pills
  - Pregnancy
- Inflammatory conditions
  - Pancreatitis
  - Diverticulitis
  - Appendicitis
  - Cholangitis
- Trauma
  - Operative venous injury
  - Postsplenectomy
  - Blunt or abdominal trauma
- Miscellaneous
  - Congestive heart failure
  - Renal failure
  - Decompression sickness
  - Portal hypertension

of patients, and the mortality rate is lower than that associated with other causes, ranging from 20 to 50%.[34,35] Mesenteric venous thrombosis rarely can be a primary diagnosis, but it often occurs in association with an underlying medical condition, including hypercoagulable states, inflammatory processes within the abdomen, local trauma, and conditions associated with relative venous stasis, including oral contraceptive use and inflammatory bowel disease[36,37] (Box 90-5). Historically, up to 60% of patients with mesenteric venous thrombosis have a history of peripheral deep vein thrombosis.

Clinical Features

History. The clinical findings associated with acute mesenteric ischemia, regardless of the cause of the vascular compromise, are fairly nonspecific. Nonetheless, the presentation is sufficiently characteristic that acute mesenteric ischemia should be considered in the population of patients at risk: In patients older than 50 years of age with any of the previously discussed risk factors for mesenteric ischemia, the sudden onset of abdominal pain severe enough to warrant medical attention and more than 2 hours in duration is highly suggestive of acute mesenteric ischemia.[30]

On initial presentation, the patient with acute mesenteric ischemia typically complains of severe, poorly localized, colicky abdominal pain. Associated symptoms and signs may include nausea, vomiting, and frequent bowel movements as the bowel attempts to empty itself. The most consistent finding is pain that is out of proportion to the physical findings. This characteristic finding is noted because only visceral structures are initially ischemic, and the parietal peritoneum is spared. Mesenteric ischemia also can be more subacute in its presentation, with the insidious onset of less severe and vague abdominal pain, abdominal distention, and occult gastrointestinal bleeding.

Physical Examination. In the early phases of mesenteric ischemia, physical examination findings may be nondiagnostic. As the disease process continues, abdominal distention develops and palpation reveals diffuse abdominal tenderness without guarding. Transmural intestinal injury leads to peritoneal signs (involuntary guarding and rebound tenderness). Late in the ischemic episode, the abdomen is grossly distended, with absence of bowel sounds and exquisite tenderness to palpation. Heme-positive stool is noted in 25% of patients and often is a relatively late finding.[29] Historical details and physical findings referable to other parts of the body may suggest the etiology of the acute impairment in mesenteric blood flow.

Complications. Delays in diagnosis permit progression of the disease process and the development of transmural intestinal ischemia, with its correspondingly high associated morbidity and mortality rates. Even with early diagnosis and aggressive management, however, a complicated course is to be expected. Secondary reperfusion injury is common, and bowel initially believed to be viable at the time of operation may become ischemic and infarct in the postoperative period. Other postoperative complications include wound infections, intraabdominal abscesses, sepsis, and pneumonia. This population of patients also is at risk for many life-threatening complications (including myocardial infarction, pulmonary embolism, and renal failure) because of significant concurrent illness.

Diagnostic Strategies

Routine laboratory and standard radiographic evaluations usually are not helpful in the diagnosis of mesenteric ischemia. An increase in the peripheral white blood cell count is a common but nonspecific finding, and although a normal count makes the diagnosis of acute intestinal ischemia less likely, it does not exclude the diagnosis. Hemoconcentration, metabolic acidosis with base deficit, and hyperamylasemia are present in more than one half of the cases of acute mesenteric ischemia but likewise are nonspecific findings. A significant emphasis has been placed on the role of serum lactate level determination in detection of ischemia, but a consensus regarding the utility of this test has yet to be reached. The sensitivity of this serum marker is high, approaching 100% when bowel infarction is present, but it has a disappointing specificity. A retrospective review of data on preoperative assessment for mesenteric ischemia noted an elevated serum lactate level at the time of diagnosis to be most useful as a significant predictor of mortality and suggested that the presence of unexplained acidosis in patients at risk should prompt a search for reversible causes of mesenteric ischemia. Levels of the seromuscular enzyme creatine kinase (CK) rise 3 to 4 hours after vascular occlusion, but the CK assay has limited specificity and sensitivity. Other seromuscular enzymes (lactate dehydrogenase, aspartate transaminase) and mucosal enzymes (alkaline phosphatase) are even less sensitive and specific than CK. Although it also has been suggested that a negative result on D-dimer assay may be useful for the exclusion of suspected mesenteric artery occlusion,[38] further evaluation of this laboratory screen needs to be accomplished before widespread application.

The first radiologic examination that should be done in a patient with suspected mesenteric ischemia is a plain abdominal radiograph series (supine and upright) to rule out bowel obstruction or presence of free air. Plain radiographs most often are normal in appearance in the presence of acute mesenteric vascular compromise. By the time any changes characteristic of acute intestinal ischemia are apparent, transmural damage has already taken place. Subtle signs of acute mesenteric ischemia on plain abdominal radiographs include adynamic ileus, distended air-filled loops of bowel, and bowel wall thickening from submucosal edema or hemorrhage (Fig. 90-2).[39] In advanced stages of ischemia, pneumatosis of the

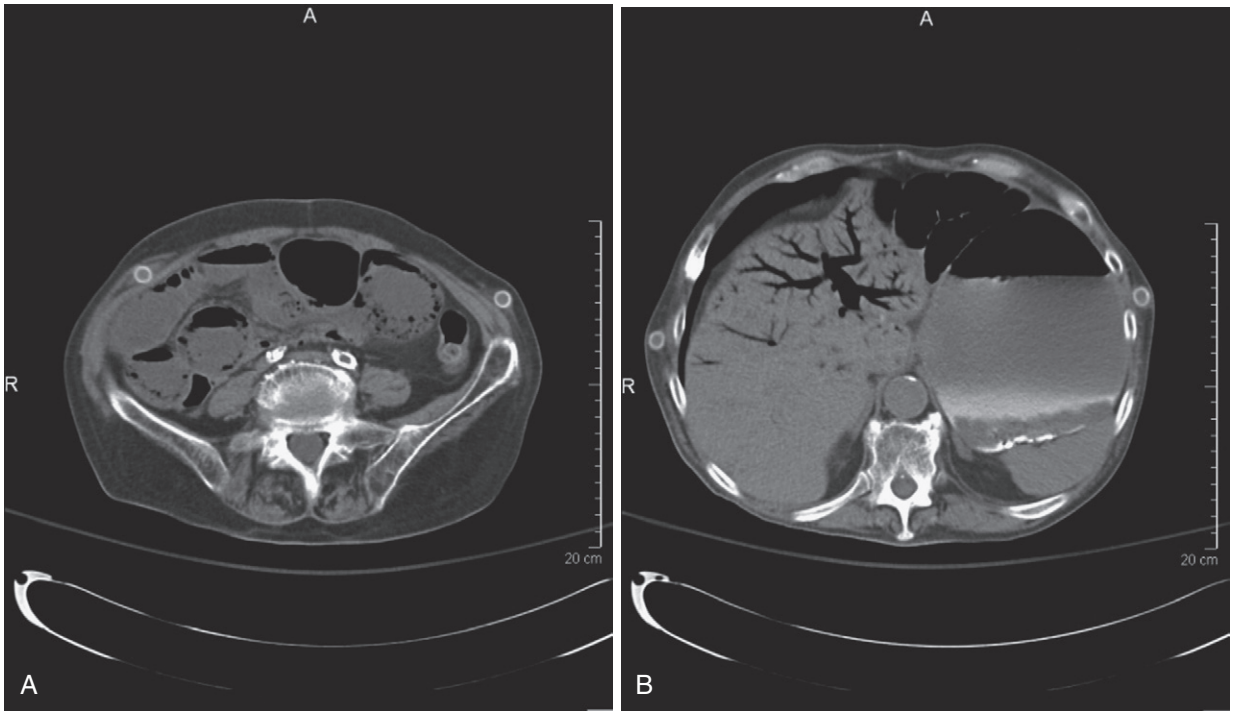

Figure 90-2. **A**, CT of abdomen showing pneumatosis intestinalis (note dependent air within wall of small bowel). **B**, CT of abdomen with air within portal venous system.

bowel wall may be detected as intraluminal gas dissects into the submucosa.[40] Another late, and often preterminal, sign of necrotic bowel is the presence of gas within the portal venous system. Further radiographic examinations should be selected judiciously. Intraluminal barium contrast evaluations are contraindicated because residual contrast material can limit visualization of the mesenteric vasculature during diagnostic angiography. Duplex ultrasonography may be of some benefit in visualizing blood flow in the SMA and celiac axis. Unfortunately, many patients suspected of having mesenteric ischemia often have dilated, air-filled loops of bowel, which makes ultrasonography extremely difficult.

Because of the availability, improved quality, and speed of CT, this radiologic test often is used for assessing undiagnosed abdominal pain in high-risk patients. In the setting of intestinal ischemia, a CT scan is capable of demonstrating edema of the bowel wall and mesentery, abnormal gas patterns, presence of intramural gas, ascites, and, occasionally, direct evidence of mesenteric venous thrombosis. The diagnosis of acute mesenteric ischemia often is made by CT imaging, reflecting the prevalence of this test in the evaluation of abdominal pain. Finally, an important consideration is that, as with plain radiography, a significant percentage of patients may have normal or nonspecific CT findings, so the diagnosis of mesenteric ischemia cannot be ruled out on the basis of normal findings on this study.

Angiography remains the "gold standard" modality for the diagnosis of mesenteric ischemia and is unique among imaging techniques in that it may assist with both diagnosis and therapy. Preoperative angiography is useful in the diagnosis of either mesenteric artery embolus or thrombus. It allows identification of the site and type of occlusion as well as evaluation of the splanchnic circulation, thus facilitating plans for prompt revascularization. Thrombosis of the SMA typically reveals an occlusion just distal to the origin of the vessel. In addition, angiography provides a definitive diagnosis of nonocclusive mesenteric ischemia. Arteriographic signs of nonocclusive disease include diffuse or focal tapering of mesenteric arterial branches, alternating segments of narrowing and dilatation of intestinal branches ("sausage sign"), poor intramural vessel filling, and mesenteric arcade vasospasm. Broad criteria for selection of patients must be used if early diagnosis and effective intervention are to be possible. Therefore, a significant number of "negative" angiograms should be accepted.

Helical CT scanning and CT angiography have progressed significantly in recent years and now offer reasonable alternatives to catheter angiography. Helical CT angiography should be considered the primary diagnostic modality for patients in whom clinical suspicion for mesenteric ischemia is high.[41,42] Conventional catheter angiography is reserved for equivocal cases of noninvasive imaging and also can be used for transcatheter therapeutic techniques.

Differential Considerations

Mesenteric ischemia occurs most often in patients older than 50 years, but the diagnosis should be considered in all patients, regardless of age, who experience sudden onset of severe abdominal pain. The severe and colicky nature of the pain also may suggest cholecystitis, peptic ulcer disease, perforation of bowel, nephrolithiasis, diverticulitis, or bowel obstruction. The significant pain, often out of proportion to the physical findings, also may suggest the possibility of pancreatitis and abdominal aortic aneurysm rupture. The urgency of efficiently identifying acute mesenteric ischemia would recommend that this diagnosis be considered in a large population of patients, particularly in patients at risk because of underlying illness or chronic medical therapy that produces vasoconstriction. In practice, the diagnosis of acute mesenteric ischemia often is made after other disorders have been excluded.

Management and Disposition

Early diagnosis achieved by aggressive use of angiography remains the key to a successful outcome. Therapeutic intervention should take place as soon as the diagnosis of acute mesenteric ischemia is made if tissue salvage is to be maximized and mortality minimized.

Initial resuscitative efforts should include correction of hypovolemia and hypotension as well as any accompanying metabolic abnormalities. In the population of patients at risk for mesenteric ischemia, successful resuscitation may require invasive hemodynamic monitoring. Control of arrhythmias, congestive heart failure, and other factors contributing to relative hypoperfusion of the bowel is a priority. Medications with vasoconstrictive properties should be discontinued immediately. If vasopressors must be used to support blood pressure, the lowest possible dose should be infused, and α-agonists should be avoided, with inotropes being the preferred agents. Enteral decompression by nasogastric tube placement is recommended. Broad-spectrum antibiotic therapy that provides coverage for bowel flora should be initiated early, particularly when surgery is anticipated.

When the patient's condition is stabilized, routine laboratory and plain radiographic examinations can be performed to exclude other, more common causes of abdominal pain. If an expeditious evaluation does not reveal an alternative diagnosis, angiography should be performed. Even when the decision to operate has been made on clinical grounds, preoperative radiologic studies, including some form of angiography, may improve management of the patient at laparotomy. In addition, when the diagnosis of acute mesenteric arterial compromise is confirmed, an infusion of papaverine through the angiography catheter directly into the SMA reduces or eliminates mesenteric vasoconstriction.[43] Papaverine is a potent inhibitor of phosphodiesterase, the enzyme necessary for degradation of cyclic adenosine monophosphate (cAMP). Increased cAMP levels cause vascular smooth muscle relaxation and relief of vasoconstriction. Because papaverine is 90% metabolized by the liver on its first pass, few if any systemic effects are noted during its use. Dosing consists of delivery of a 60-mg bolus into the SMA, followed by continuous infusion of 30 to 60 mg/hour at a concentration of 1 mg/mL. Use of this vasodilator in both nonocclusive and occlusive forms of mesenteric ischemia has improved survival.

The surgical management of acute mesenteric ischemia is both challenging and controversial. Treatment principles range from pharmacologic manipulation without operation to revascularization procedures to bowel resection. The underlying cause of intestinal hypoperfusion often is not amenable to surgical correction, as with mesenteric venous occlusion and nonocclusive disease, and the role of operative intervention may be limited to resection of already infarcted bowel.

If a revascularization procedure is to be undertaken in the presence of arterial occlusive disease, it is completed before any evaluation of bowel viability is performed. The reasoning behind this therapeutic sequence is that bowel that initially appears irreversibly damaged may exhibit significant recovery on restoration of blood flow. Obviously necrotic bowel is resected, but in the presence of extensive ischemic damage, the surgeon may choose to leave bowel of questionable viability in place and to reevaluate its viability during a subsequent operation.[44] This "second-look" operation, typically performed 12 to 24 hours after the initial procedure, may permit a more limited resection.

Percutaneous transluminal angioplasty has been described for both acute and chronic mesenteric ischemia from thrombosis of the SMA. In the acute setting, it appears to be associated with an increased risk of recurrence and potential for extensive bowel loss. With chronic intestinal ischemia, particularly in elderly patients who are poor surgical candidates, mesenteric angioplasty is a good option, with complete symptomatic improvement and continued relief of symptoms during follow-up observed in a majority of patients.

Intra-arterial infusion into the SMA of thrombolytic agents has been used successfully for mesenteric ischemia after acute embolism,[45] but only on a limited basis. The patients in the reported series were selected with emboli confirmed by angiography, with no peritoneal signs and no abdominal radiographic abnormalities including ileus. Close monitoring and frequent clinical reassessment, as well as serial angiograms, are necessary after the thrombolytic infusion. The main drawbacks to the use of thrombolytic agents are the difficulty in assessing bowel viability without laparotomy, the possible time delay of 12 to 18 hours before clot resolution, and the potential for clot fragmentation with involvement of more distal branches less amenable to surgical revascularization.

In patients surviving the initial episode of acute mesenteric ischemia, recurrent thrombosis is a potential problem requiring long-term anticoagulation. Warfarin (Coumadin) is started after mesenteric arterial embolism and mesenteric venous thrombosis. Antiplatelet therapy is begun after mesenteric arterial thrombosis and nonocclusive mesenteric ischemia. The 2-year mortality rate after mesenteric ischemia is as high as 70%. This grave prognosis, however, is related mainly to cardiovascular comorbidity, rather than to recurrent mesenteric ischemic events.

KEY CONCEPTS

- Four separate acute mesenteric ischemia syndromes are recognized. A majority of cases are caused by embolic occlusion of the SMA. The remainder are due to SMA thrombosis, venous thrombosis, and nonocclusive arterial ischemia. Each of the syndromes has a specific set of risk factors or associated medical conditions that are helpful in differentiating one from another.
- The diagnosis of acute mesenteric ischemia may be suggested by pain out of proportion to examination findings, heme-positive stool, elevated serum lactate levels, and classic findings on plain film or CT scan, but none of these provide enough sensitivity to ensure recognition of this entity before bowel infarction occurs.
- An aggressive approach to diagnosis and management, including early use of angiography, has provided some improvement in the prognosis for acute mesenteric ischemia, although the mortality rate for this disease is still greater than 50%.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 91 Acute Appendicitis

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PERSPECTIVE

Appendicitis is a common condition requiring emergency surgery. Approximately 7% of people will experience acute appendicitis during their lifetime. Most cases occur in adolescents and young adults, with a slightly higher incidence in men than in women.[1,2]

Historically, the earliest evidence of appendicitis is suggested by the presence of right lower quadrant adhesions in an Egyptian mummy from the Byzantine era. In 1492, Leonardo da Vinci drew pictures of the colon and the appendix, referring to the latter structure as an *orecchio*, which literally means "ear." Claudius Amyand removed the first appendix incidentally in 1735 during the repair of a scrotal hernia in an 11-year-old boy. The appendix had perforated, and a cutaneous fecal-draining fistula had developed.[3] The half-hour operation was done without anesthesia, and the boy fully recovered. In the early 1800s during the Lewis and Clark expedition, the only death during the trip was that of Charles Floyd, who is thought to have died from a ruptured appendix.[4]

In 1880 in Europe, Lawson Tait performed the first successful planned appendectomy by removing a gangrenous appendix from a 17-year-old girl. Six years later, Reginald Fitz, a pathologist, coined the term *appendicitis* when he presented his classic paper at the first meeting of the Association of American Physicians. Fitz correctly described many of the pathophysiologic changes associated with appendicitis and advocated early surgery. Three years later, Charles McBurney described a point "determined by the pressure of one finger" between "one and a half and two inches from the anterior spinous process" that, when palpated, was associated with maximal discomfort in patients with acute appendicitis (McBurney's point). The general acceptance that appendicitis was a surgical disease did not come until several decades later. Early surgical intervention became popular in the early 1900s around the time that King Edward VII was found to have a perforated appendix and was operated on days before his coronation.[5]

PRINCIPLES OF DISEASE: PATHOPHYSIOLOGY

The appendix is a hollow, muscular, closed-ended tube arising from the posterior medial surface of the cecum, approximately 3 cm below the ileocecal valve. Its average length is approximately 10 cm, and its normal capacity is 0.1 to 0.3 mL. The role of the appendix in human physiology is unclear, but some recent studies on biofilms suggest that the appendix may act as a repository for commensal bacteria that inoculate the large bowel and protect it against pathogens.[6] Innervation of the appendix is derived from sympathetic and vagus nerves from the superior mesenteric plexus. Afferent fibers that conduct visceral pain from the appendix accompany the sympathetic nerves and enter the spinal cord at the level of the tenth thoracic segment. This allows referral of pain to the umbilical area.

In a majority of affected patients, appendicitis is due to an acute obstruction of the appendiceal lumen. The obstruction often is from an appendicolith but also can be caused by a calculus, tumor, parasite, or enlarged lymph node. Of historical note, one of the more common causes of acute appendicitis from foreign objects in the early 19th century was ingestion of lead shells buried in quail flesh.[7] More recently, a lumen obstruction from a swallowed tongue stud has been reported.[8]

After acute obstruction, intraluminal pressures rise and mucosal secretions are unable to drain. The resulting distention stimulates visceral afferent pathways and is perceived as a dull, poorly localized pain. Abdominal cramping may occur as a result of hyperperistalsis. Next, ulceration and ischemia develop as the intraluminal pressure exceeds the venous pressure and bacteria and polymorphonuclear cells begin to invade the appendiceal wall. The appendix may appear grossly normal at this time, with evidence of pathology apparent only by microscopic examination. With time, the appendix becomes swollen, and factors elaborated in the pathologic process begin to irritate surrounding structures, including the peritoneal wall. The pain now becomes more localized to the right lower quadrant. If swelling does not abate, hypoxia leads to gangrene (presence of necrosis) and, ultimately, perforation through the appendiceal serosal layer. This can lead to abscess formation or diffuse peritonitis. The time required for the appendix to perforate is highly variable (and controversial—some experts believe that unless a virulent organism or genetic predisposition exists, many cases will spontaneously resolve), but perforation usually occurs within 24 to 36 hours. Elderly patients may be more prone to earlier perforation because of anatomic changes in the appendix associated with aging, such as a narrowed appendiceal lumen, thinner mucosal lining, decreased lymphoid tissue, and atherosclerosis.[9]

In approximately one third of cases, no direct cause of obstruction is noted. In these cases, it is surmised that inflammation is caused by viral, bacterial, or parasitic infection with subsequent mucosal ulceration or lymphoid hyperplasia.[2]

CLINICAL FEATURES

History

Appendicitis is classically described as starting with the vague onset of dull periumbilical pain and the development of anorexia, nausea, and vomiting. The pain then migrates to the right lower quadrant, and a low-grade temperature may develop. In most instances, the patient has not previously experienced pain similar to this episode.[2] Unfortunately, the presentation may be highly variable. If the appendix is retrocecal or retroiliac, the pain may be blunted by the presence of overlying bowel. If the appendix is elongated, the pain may be referred to the flank, pelvis, or right upper quadrant. Other, less typical symptoms seen with appendicitis are increased urinary frequency and the desire to defecate.[2]

Physical Examination

The most common finding on physical examination is localized abdominal tenderness, usually in the right lower quadrant. The pain may be noted over McBurney's point. The base of the appendix is within 5 cm of this point in only 35% of patients, however, so the pain of appendicitis also can be localized in other areas of the abdomen.[10]

Other physical findings include abdominal guarding and rigidity to palpation. Guarding usually is voluntary, and the patient often can be persuaded to relax. Rigidity is involuntary and implies more significant underlying pathology.[2] Both of these findings reflect the tensing of the abdominal wall musculature to protect the underlying bowel.

Rovsing sign is present when tenderness is referred to the right lower quadrant with palpation of the left lower quadrant. The *psoas sign* is the increase in pain when the psoas muscle is stretched as the patient is asked to extend the hip. The *obturator sign* is the elicitation of pain as the hip is flexed and externally rotated.

Rebound tenderness to palpation is a late finding in patients with appendicitis and usually is noted only after the appendix is significantly inflamed or ruptured. Rebound tenderness is detected by gradually pressing over the area of tenderness for 5 to 10 seconds and then quickly withdrawing the hand to just above the skin level. A positive response is when the patient reports increased pain as the hand is removed. Patients with rebound tenderness are very uncomfortable with this maneuver, and it should not be repeated unnecessarily. The sensitivity and specificity of rebound tenderness in diagnosing acute appendicitis range from 63 to 82% and from 69 to 90%, respectively.[2,11] The presence of peritoneal irritation also can be elicited by other maneuvers that cause the visceral and parietal peritonei to rub against each other, such as having the patient cough while observing for evidence of acute discomfort. A positive cough sign has been found to be 80 to 95% sensitive in diagnosing acute peritonitis.[12,13]

Isolated rectal tenderness rarely may be the only site of localized pain in patients with a low-lying or retrocecal appendix. In general, however, rectal tenderness has a very limited diagnostic value, especially if concurrent right lower quadrant pain and tenderness are present.[14,15] Although a single rectal exam may provide other important information, such as the discovery of a rectal mass or occult blood, multiple exams are not justified.

Although any of the foregoing signs may be present in patients with acute appendicitis, certain findings have a high positive likelihood ratio for identifying patients with appendicitis. These include right lower quadrant pain, rigidity, and migration of initial periumbilical pain to the right lower quadrant.[2] Conversely, the presence of pain for more than 48 hours, a history of previous episodes of similar pain, the lack of migration and of right lower quadrant pain, and the lack of worsening pain with movement or cough make appendicitis less likely.[2,14] A similar review of data on children with appendicitis concluded that fever and rebound tenderness were the most common associated findings.[16]

Vital signs often are normal, particularly early in the clinical course. A low-grade fever is present in approximately 15% of patients; this increases to approximately 40% if perforation has occurred.[17]

Special Considerations

Children

Acute appendicitis in young children often is diagnosed after perforation has occurred. Many common childhood illnesses are associated with nausea, anorexia, and vomiting, and young children may have difficulty communicating their discomfort.[18] Anatomically, children have a thinner appendiceal wall and a less developed omentum, which may predispose them to perforation and diffuse peritonitis.

Women

The diagnosis of acute appendicitis in women of childbearing age can be particularly challenging. Before the advent of imaging, as many as 45% of women with symptoms suggestive of appendicitis had a normal appendix at surgery, and as many as one third of women with true appendicitis were initially misdiagnosed. Gynecologic disease can easily masquerade as appendicitis because of the close proximity of the appendix to the right ovary and fallopian tube and the uterus.[19,20] Findings that may be more suggestive of abdominal pain of gynecologic origin are listed in Table 91-1. Of note, although cervical motion tenderness is more common in patients with pelvic inflammatory disease, it may be present in up to one fourth of women with appendicitis.[21] Because accurately diagnosing appendicitis in women is difficult, the use of ancillary imaging should be strongly considered.

Pregnant Women

In pregnant women, the overall risk for the development of appendicitis is similar to that in the general population.[22] Appendicitis appears to occur slightly more often in the second trimester than in the other two, for unknown reasons. The

Table 91-1 Abdominal Pain in Women

LIKELY ETIOLOGY	CLINICAL FINDINGS
More suggestive of appendicitis	Migration of pain and tenderness localized to the right lower quadrant Anorexia Normal or minimally abnormal findings on pelvic examination (e.g., isolated right adnexal tenderness)
More suggestive of pelvic inflammatory disease	Symptoms of several days' duration History of pelvic inflammatory disease Hunger Diffuse lower abdominal pain Bilateral adnexal tenderness Cervical motion tenderness Vaginal discharge

diagnosis of appendicitis during pregnancy can be particularly difficult. Nausea and vomiting occur frequently in a normal pregnancy, and the accuracy of the physical exam may be compromised because enlargement of the uterus may alter the location of the appendix. Nevertheless, a study of pregnant patients with appendicitis found that even when appendicitis occurred late in pregnancy, most women still had right lower quadrant pain.[23] Lab values are not helpful, because leukocytosis is common during pregnancy.

Although maternal death from appendicitis is extremely rare, spontaneous fetal abortion occurs in approximately 5 to 15% cases of simple appendicitis and in up to 37% of complicated cases.[24] Because of this high morbidity, extra caution should be taken in pregnant women with abdominal pain.

Elderly Patients

Elderly patients are three times more likely than those in the general population to have a perforated appendix at surgery. Multiple causes for this predisposition are recognized, including anatomic age-related changes in the appendix, delay in seeking medical care, atypical presentations, and minimally elevated values on laboratory tests.[9]

Complications

The complication rate after the removal of a normal or acutely inflamed appendix is approximately 3%, but this increases by three- to four-fold if perforation occurs.[17] The most common complication is infection. Localized wound infection occurs in approximately 2 to 7%, and deep intra-abdominal abscess occurs in 0.8 to 2%, with the higher percentages representing cases in which perforation had occurred.[25]

Other complications include a prolonged ileus, small bowel obstruction, pneumonia, and urinary retention and infection. In young women, perforation may cause obstruction of the fallopian tubes with subsequent fertility problems, although recent studies suggest that this sequela is not as prevalent as was once believed.[26,27] Pregnant patients with appendicitis have an increased risk of premature labor (15 to 45%) and fetal death.

The mortality rate for uncomplicated appendicitis is less than 0.1% but increases to 3 to 4% with perforation in patients with comorbid illness or advanced age. Although reported perforation rates vary significantly, the overall average is approximately 20 to 30%. This increases greatly at the extremes of age. Elderly persons have perforation rates as high as 60%, and children younger than 3 years of age can have perforation rates as high as 80 to 90%.[9,28]

The identification of factors that may increase a patient's risk for perforation is evolving. The traditional belief has been that the natural course of appendicitis is inflammation that, if surgery is delayed, ultimately progresses to necrosis and perforation. Many experts now feel that in most patients, the natural course of appendicitis is spontaneous resolution without perforation.[28] This view is supported by general autopsy reports from the presurgical era showing that in up to one third of cases not previously diagnosed, evidence of periappendiceal scarring was present, and by studies that report successful resolution of early appendicitis with nonoperative management.[29] It is hypothesized that a subset of the population is genetically predisposed to perforation by a characteristic early aggressive and exaggerated inflammatory response.[30] The evidence for such a predisposition is the relatively consistent population perforation rates, even with the advent of increased imaging and earlier diagnosis. In most patients so affected, perforation of the appendix occurs before medical evaluation, and hospital delays in operative management rarely appear to increase perforation rates.[31]

DIAGNOSTIC STRATEGIES

Laboratory Testing

Leukocyte Count

Approximately 80 to 90% of patients with acute appendicitis will have an elevated white blood cell (WBC) count above 10,000/mm^3. Unfortunately, the leukocyte count is nonspecific and often is elevated with other causes of abdominal pain.

C-reactive Protein

A meta-analysis suggests that the overall sensitivity of C-reactive protein is approximately 62% and its specificity is 66%. Accordingly, its usefulness as a diagnostic tool in patients with appendicitis is limited.[32]

Urinalysis

A urinalysis is helpful in differentiating urinary tract disease from acute appendicitis and is suggested in all patients. Mild sterile pyuria may be seen if the appendix is irritating the ureter. Significant pyuria (i.e., presence of more than 20 WBCs per high-power field) is highly suggestive of urinary tract pathology.

Pregnancy Test

A pregancy test should be performed in all women of childbearing age, because a positive result broadly expands the scope of the differential diagnosis for right lower quadrant pain.

Diagnostic Scores

Some retrospective studies have shown a benefit for use of diagnostic scoring systems for appendicitis that assign a numerical value to different aspects of the history and physical exam. Of note, however, these scoring systems yield inconsistent results when prospectively evaluated and appear to be particularly inaccurate when applied to female patients.[2,33]

Imaging Studies

Plain Radiography

Plain radiography is not useful in diagnosing appendicitis owing to its very low sensitivity and specificity and is not recommended in the evaluation of appendicitis unless there is a significant concern of bowel obstruction, free air, or pneumonia.[34]

Barium Enema

Barium enema has a sensitivity of approximately 80 to 90% for detecting appendicitis, and the diagnosis is essentially ruled out if the entire appendix is filled with contrast.[35] Unfortunately, a normal appendiceal lumen often is not visualized with this technique. Barium enema is most helpful when other colon pathologic processes are high on the list of considerations in the differential diagnosis.

The use of nuclear imaging with tagged WBCs has been well studied as a diagnostic tool for acute appendicitis.[36,37] The sensitivity of nuclear scans depends on the radiolabel used, and reported values ranges between 88% and 98%. The overall usefulness of these scans is limited because of poor specificity—any process causing inflammatory changes in the lower abdomen can lead to a false-positive result.

Ultrasonography

Graded-compression ultrasound imaging has been prospectively shown to improve the clinical accuracy of the diagnosis of acute appendicitis.[38] The reported sensitivity and specificity of ultrasound imaging for acute appendicitis in most studies are 75 to 90% and 85% to 95, respectively.[39] Some recent advances in ultrasound techniques have been described. One group of investigators reported an astonishing 98% rate for visualization (compared with the often cited 2 to 45%) of the appendix by adding simple maneuvers that repositioned this structure.[40] Similarly, small studies using contrast-enhanced Doppler or harmonic waves (which allow for better resolution) show promise of higher sensitivities while sparing the patient radiation exposure.[41-43]

On ultrasound examination, a noncompressible appendix with a diameter greater than 6 to 7 mm is considered diagnostic for appendicitis. Ultrasonography is inexpensive, requires no patient exposure to radiation or dye, adds no extra time for contrast filling, and has had long-standing success in diagnosing pelvic pathology in women. It also allows correlation of the patient's pain with direct visualization of underlying abdominal contents. The major disadvantage of ultrasonography is that visualization of the appendix—normal or abnormal—is operator-dependent, and the technique can be especially difficult if the patient is obese, has strictures from previous surgeries, or has a retrocecal appendix. A diagnostic ultrasound study also becomes more difficult to achieve after the appendix has perforated, and patients with significant right lower quadrant pain may not tolerate the graded compression.

Ultrasound findings suggestive of appendicitis have a very high positive predictive value (approximately 90%). Absence of abnormality on the ultrasound study, however, is not helpful unless the appendix is clearly visualized or alternative pathology is identified. Accordingly, with negative ultrasound findings, either in-hospital observation or a CT scan is indicated if the patient's symptoms have not abated.

Computed Tomography

Abdominal pelvic CT scanning has been prospectively studied and shown to improve the clinical accuracy of the diagnosis of appendicitis.[44,45] CT findings individually suggestive of appendicitis include an enlarged appendix (diameter greater than 6 mm), pericecal inflammation, the presence of an appendicolith (Fig. 91-1), and a periappendiceal phlegmon or abscess (Fig. 91-2). The sensitivity (87 to 100%) and specificity (89 to 98%) of CT scan vary by study and technique and by how investigators categorize inconclusive scans in their statistical analyses.

Of the different CT techniques, thin-cut, helical CT with rectal contrast appears to be the most sensitive, with sensitivity rates as high as 98%.[46] Use of rectal contrast confers a number of advantages: it may be better tolerated in nauseated patients; there is no delay in scanning due to contrast transit time; and more consistent cecal opacification is obtained, which aids in scan interpretation.[46-48] Although rectal contrast may not be conceptually or practically acceptable to some patients, at least in one study patient discomfort and satisfaction rates were similar regardless of type of contrast received.[47]

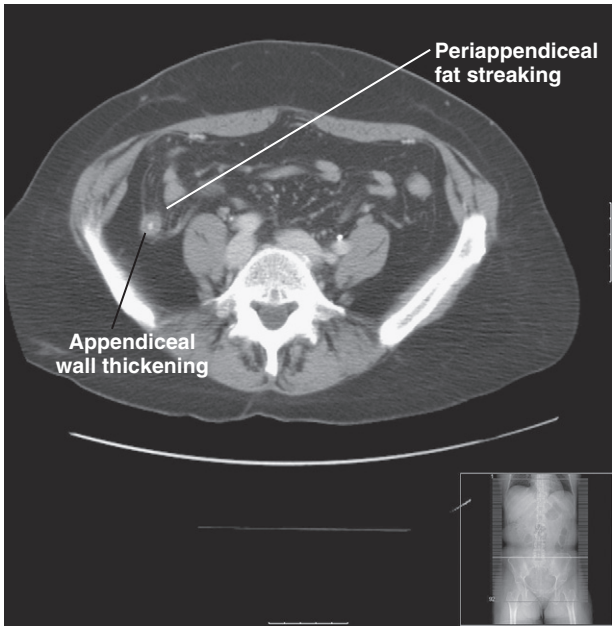


Figure 91-1. Oral contrast computed tomography scan showing evidence of acute appendicitis with periappendiceal fat streaking. (Courtesy of Jefferson Radiology.)

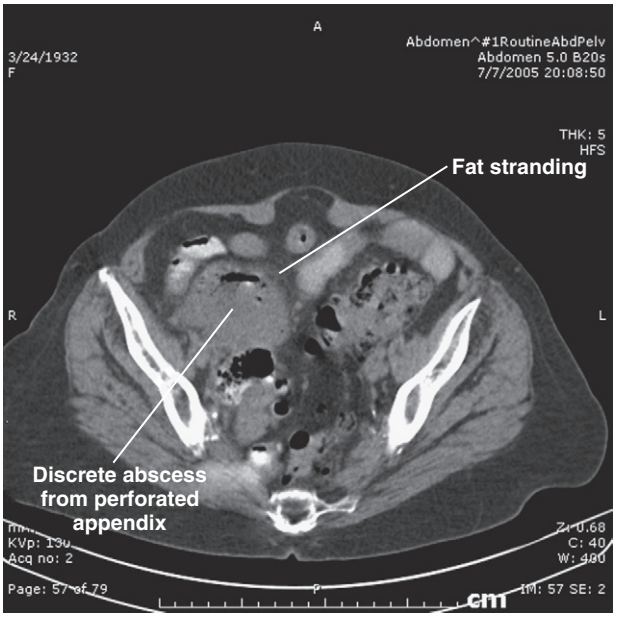


Figure 91-2. Oral contrast computed tomography scan showing discrete abscess from appendiceal perforation, with periappendiceal fat streaking. (Courtesy of Jefferson Radiology.)

Oral contrast abdominal pelvic CT is an alternative choice but requires a 60- to 90-minute delay after contrast administration for distal small bowel opacification and may be poorly tolerated in the patient with nausea or an ileus. A novel way to decrease transit time is to add polyethylene glycol to the oral contrast; in one study, this allowed good cecal opacification by 1 hour after ingestion.[49]

Although certain institutions have published high sensitivity and specificity rates with noncontrast CT scans, these

findings have not been reproducible in other settings.[50,51] Two recent studies found a 20 to 25% rate for inconclusive scan interpretation when no contrast was used.[52,53] Periappendiceal fat streaking can easily be missed on a noncontrast CT scan obtained in thin patients or children.

Intravenous contrast may help diagnose very early appendicitis by enhancing appendiceal wall inflammation, but in most instances it adds little additional information and increases the risk of adverse dye reaction.

CT scanning has some advantages over ultrasound in the diagnostic evaluation of appendicitis. With enteric contrast CT, the appendix usually can be visualized, the technique is standardized, and alternative pathology often is identified. An added benefit is that the identification of CT signs of appendicitis is relatively straightforward and can be easily learned. This is an important consideration because the initial interpretation of the CT usually dictates patient disposition, and in an academic teaching center, this scan often may be read by a junior radiology resident after hours.[54]

The biggest disadvantages of CT scanning are the radiation exposure and the expense. A routine full abdominal and pelvic CT study results in about 10 millisieverts of radiation exposure, which theoretically is carcinogenic. From analysis of data for World War II atomic bomb survivors, it has been suggested that the radiation from a single abdominal CT scan could cause a fatal cancer in 1 of every 500 children scanned.[55] Radiation exposure can be decreased by doing a focused 15-cm scan limited to the cecum and pelvis and by size-adjusting the scanner.

Finally, CT is not 100% accurate. Overall, approximately 5 to 10% of CT scans are considered inconclusive for appendicitis—for example, the appendix diameter may be enlarged but without wall thickening, or the appendix may not be visualized although surrounding fat streaking is evident. Care should be taken not to label these studies as "negative," because approximately 30% of patients with such equivocal findings will have histologic confirmation of appendicitis.[56]

In general, even patients with a true negative result on the CT scan should be explicitly told to return for reevaluation if their symptoms worsen or do not resolve in the next 24 to 36 hours. Such follow-up is particularly important in patients evaluated within the first few hours of symptoms, because early appendicitis may be missed on the initial CT scan.[57]

Magnetic Resonance Imaging

MRI is emerging as a useful tool in the evaluation of suspected appendicitis, with reported sensitivity similar to that for CT scan. Access to MRI is currently limited in most EDs, however, so its use often is confined to the pregnant patient with indeterminate ultrasound findings as an alternative to CT.[58-61]

Laparoscopy

Laparoscopy can be performed for diagnosis or definitive treatment. Historically, its greatest advantage was in the clarification of the diagnosis of appendicitis versus gynecologic disease in young female patients. Because an enteric contrast CT scan can now usually visualize the appendix, the use of diagnostic laparoscopy with its anesthetic risks has decreased significantly.

In-Hospital Observation

Despite the current increased tendency to pursue diagnostic imaging in patients with right lower quadrant abdominal pain, the recent literature suggests that most cases of appendicitis can still be accurately diagnosed by performing serial physical examinations.[62,63] A review of studies using active inpatient observation in patients with an equivocal diagnosis of appendicitis found a negative appendectomy rate of approximately 6% without an increase in perforation rates.[62]

Table 91-2 Differential Diagnosis for Appendicitis

ALL PATIENTS	WOMEN	CHILDREN
Nonspecific abdominal pain	Ovarian cyst	Henoch-Schönlein purpura
Gastroenteritis	Ovarian torsion	Testicular torsion
Ascending diverticulitis	Pelvic inflammatory disease	Epiploic appendagitis
Gallbladder disease	Ectopic pregnancy	Mesenteric adenitis/ileocolitis
Inflammatory bowel disease		Meckel's diverticulum
Renal colic		

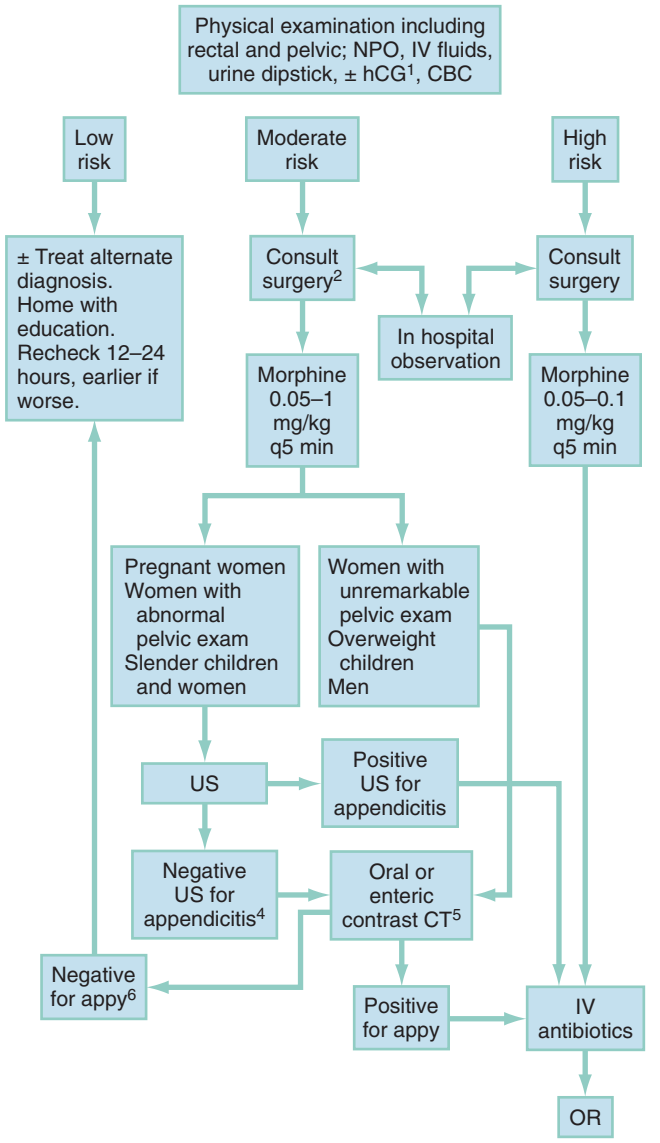
DIFFERENTIAL DIAGNOSIS

The differential diagnosis for appendicitis includes essentially any pathologic process that can cause abdominal pain. The more common diseases that can mimic appendicitis are listed in Table 91-2. Of note, the diagnosis of gastroenteritis should be made with caution and only in patients with vomiting and diarrhea.

MANAGEMENT

A strategy to manage patients with possible appendicitis is depicted in Figure 91-3. Patients should be kept on NPO (*nil per os*) status and undergo a complete physical examination, including a rectal and pelvic examination. Dehydrated patients should receive intravenous crystalloid fluids, parenteral antiemetics should be given to patients with nausea or vomiting, and patients with more than mild discomfort should be offered pain medication. Multiple studies have shown that giving opiate pain medicine to adults or children with signs of appendicitis does not mask important physical exam findings or impair surgical decision making.[64,65] Furthermore, a recent meta-analysis concluded that any changes in the physical examination due to administration of medications did not appear significant enough to alter management in patients with acute abdominal pain.[66] Depending on local surgical preference or institutional policy, surgical consultation before medication administration may be indicated, but only if it can be done in a timely fashion.

Controversy exists regarding when and how to best utilize advanced imaging techniques. Some experts have shown that CT scanning significantly decreases the rate of negative laparotomies, even in patients in whom clinical suspicion for appendicitis is high.[67-69] Others feel that diagnostic imaging is overused and has not improved patient care.[70,71] In any case, diagnostic imaging is likely to be most helpful if done in a select group of patients. After initial physical exam and laboratory tests, patients should be stratified by risk. Excessive imaging in patients who are at low risk for appendicitis will increase the frequency of false-positive results on relevant studies, because the prevalence of disease in this population is low. Patients may be considered to be at low risk if they have minimal physical findings and strong evidence for an alternative diagnosis, or if they have had multiple previous episodes of similar pain. The other distinct group of patients



1. Consult Ob/Gyn immediately if unstable pregnant patient. 2. Timing and type of surgical consultation will be dependent on local preferences. 3. Pain medication is considered safe and humane in patients with acute abdominal pain and should be offered to the uncomfortable patient as quickly as possible; if the surgeon requests to examine the patient unmedicated, the physical examination should be done in a timely fashion. 4. Failure to visualize a normal appendix on US does not rule out appendicitis. Unless other convincing pathology is found or the patient's exam has improved, enteric CT or in-hospital observation should be considered. 5. Rectal contrast abdominal pelvic CT is the preferred study. 6. Hospitalization should be considered in patients who have significant pain or have required substantial amounts of opiates.

Figure 91-3. Suggested emergency department management of patients with possible appendicitis. appy, appendectomy; CBC, complete blood count; CT, computed tomography; hCG, human chorionic gonadotropin; NPO, *nil per os* ("nothing by mouth"); OR, operating room; US, ultrasonography.

who may not benefit from imaging are patients who present within the first few hours of onset of symptoms. Imaging studies in these patients are more likely to yield false-negative results, and the "negative" scan may provide false reassurance. In both subsets, the best course of action probably is patient education about worsening signs of appendicitis, along with arrangements for immediate reevaluation if their symptoms progress, or for reexamination in 12 to 24 hours if they have not improved. Ideally, this conversation should be documented in the medical record.

Patients with "equivocal" signs of appendicitis should be considered for diagnostic testing or active observation. Surgical input by phone or formal consultation may be appropriate before imaging, depending on the preference of the consulting surgeon. "Equivocal" patients include most women (especially those of childbearing age). Historically, it has been very difficult to make an accurate diagnosis of appendicitis in women on clinical grounds alone, and negative laparotomy rates of 40 to 45% were common. Fortunately, imaging can dramatically decrease these rates and should be strongly considered in all women. Ultrasonography may be the most appropriate initial study if the history is strongly suggestive of gynecologic disease or if the pelvic examination reveals any abnormality. It also should be considered in very thin patients who have not previously had abdominal pelvic surgery; otherwise, an enteric contrast CT study is recommended.

If the patient is pregnant, ultrasound imaging is the first-line test to exclude other obstetric diagnoses. If the ultrasound findings are equivocal, MRI should be considered if it is readily available. Although CT is less desirable, owing to its considerable associated radiation exposure, after surgical and obstetric consultation, its use may still be justified when this drawback is balanced against the risks associated with potentially unnecessary anesthesia and surgery.

Other subgroups of "equivocal" patients are more difficult to define because of variable inclusion criteria among published studies. It appears reasonable that men and children with a clinical presentation suggestive of appendicitis but who lack at least one of its classic features (such as pain is new onset, migrates from periumbilical to right lower quadrant, and is associated with anorexia and tenderness) and have no clear alternative diagnosis be considered "equivocal."

Ultrasonography often is recommended as the preferred initial imaging study in children with equivocal findings of appendicitis because it does not expose them to radiation. This is a significant consideration because children are particularly vulnerable to the risks of radiation owing to their increased cell division and longer life expectancy.[55] A limited-cut helical CT study with enteric contrast (administered either rectally or orally) is an option in overweight children. If ultrasound imaging is chosen and the scan is interpreted as negative, a follow-up CT scan or admission for serial observation is indicated, unless the patient's clinical status has improved.[72]

Male patients with an equivocal presentation for appendicitis should be considered candidates for an enteric contrast CT examination (although US is a reasonable alternative for thin patients who can tolerate the US compression). Men with classic signs of appendicitis, however, are likely to have the disease more than 90% of the time, and imaging adds little to their workup.[73,74] Although the current practice in some institutions has evolved such that CT is almost mandated before surgical involvement, a recent well-done study suggests otherwise: with a decision for surgical involvement before CT, 65% of male patients went to the operating room without a CT scan, with a 4% negative appendectomy rate.[75] Emergency physicians should advocate institutional polices that prevent unnecessary radiation exposure in this group and in children with classic presentations; in these subsets, appendicitis is a clinical diagnosis.

Once the decision to operate has been made, prophylactic antibiotics should be given to provide coverage for gram-negative and anaerobic organisms; this strategy has been proved to decrease both superficial and deep postoperative

wound infections. Intravenous second-generation cephalosporins such as cefotetan or cefoxitin provide good coverage. In cases with a high likelihood of perforation, the traditional treatment has been a broad-spectrum triple antibiotic regimen; however, recent studies suggest that "single coverage" with a second-generation cephalosporin, mirapenam, or combination drug like pipercillin and tazobactam provides similar coverage, with easier administration.[76]

The timing of surgical intervention has recently been challenged, with several studies suggesting that complication rates are not adversely affected if surgery is delayed until daylight hours.[77] If this practice is to be adopted, it needs to be balanced by considerations including the condition of the individual patient and the potential for disrupting the morning operating room schedule and increasing the overall length of hospital stay.

The appendix can be surgically removed using either the traditional open technique or a laparoscopic approach. A Cochrane review of 45 randomized studies favored laparoscopic removal.[78] The investigators concluded that laparoscopic appendix removal resulted in less frequent wound infections, less postoperative pain on day 1, shorter length of hospital stay, shorter time to return to normal activity, and decreased overall costs. Laparoscopy may be most helpful in female patients, in whom it allows inspection for pelvic pathology that may masquerade as acute appendicitis.

Some institutions have begun to develop extensive operative and postoperative guidelines for the care of patients with appendicitis.[79,80] The use of these guidelines has decreased postoperative complications and costs and appears to be most helpful in the subgroup of patients with perforation.

For patients with evidence of obvious perforation and abscess formation, many surgeons prefer to drain the abscess nonoperatively and treat the condition with intravenous antibiotics and then perform an interval appendectomy 6 weeks later.[81] Recently, it has even been suggested that the appendix may not have to be removed after successful abscess resolution.[82]

DISPOSITION

If clinical suspicion for appendicitis is low, the patient may be sent home after extensive education has been provided and arrangements have been made for appropriate follow-up care. Discharged patients should be encouraged to start on a liquid diet and advance to solids if their symptoms abate.

Patients with abdominal pain of unclear etiology who require significant doses of opiates to control their pain should be considered for hospital admission.[83] In addition, if follow-up cannot be arranged, if patient or family reliability is in question, or if a significant language or transportation barrier exists, hospitalization for observation should be considered.

KEY CONCEPTS

- Classic appendicitis is a clinical diagnosis.
- Patients with a low risk for appendicitis may be sent home with close follow-up and education about progressive symptoms.
- Patients with equivocal findings should undergo advanced diagnostic imaging or in-hospital serial examinations.
- Men and children with classic signs and symptoms of appendicitis should undergo prompt surgical evaluation, because imaging may be unnecessary.
- Ultrasound examination is an appropriate initial test in pregnant patients, in women with a clinical presentation suggestive of pelvic pathology, and in thin children and women.
- Helical CT with enteric contrast is considered the initial imaging study of choice in all male patients with equivocal signs of appendicitis and in female patients without findings suspicious for gynecologic disease (although US is a reasonable alternative for thin patients who can tolerate the US compression).
- Pain medication should be offered to all patients with suspected appendicitis.
- Antibiotics should be given preoperatively.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 92 Gastroenteritis

Sandy A. Craig and David K. Zich

BACKGROUND

Gastroenteritis is defined as an inflammation of the stomach or intestines resulting in some combination of nausea, vomiting, and diarrhea. Although most affected patients will prove to have an infectious cause for their symptoms, the clinician also must consider noninfectious causes of vomiting and diarrhea, which are considered in detail in Chapters 20 and 23, respectively.

Infectious gastroenteritis is associated with dozens of causative pathogens. Most of these organisms cause benign and self-limited illness, but in a few cases, morbidity may be significant, necessitating prompt diagnosis and treatment. Diagnostic testing should be targeted to those patients who have clinically significant illness or suspected reportable disease. It is neither feasible nor necessary to identify the specific pathogen during the emergency department (ED) evaluation. Instead, the clinician should classify the gastroenteritis as *acute or chronic* and *invasive or noninvasive*, based on readily available clinical information. This classification narrows the differential diagnosis considerably and is a valuable guide to further testing.

Acute gastroenteritis lasts less than 2 weeks. The vast majority of ED patients will have acute gastroenteritis, and viral and bacterial pathogens should be the primary considerations in the differential diagnosis. *Chronic gastroenteritis* persists longer than 2 weeks. In such cases, the possibility of a parasitic pathogen should be added to the differential diagnosis.

Invasive gastroenteritis is a clinical diagnosis made in the presence of signs or symptoms of intestinal mucosal invasion, such as fever, gross or occult blood in the stool, tenesmus, or abdominal pain. When invasive disease is suspected, further diagnostic testing is indicated. Patients with *noninvasive gastroenteritis* do not exhibit fever, produce bloody stools, or experience significant abdominal pain. Noninvasive gastroenteritis suggests the presence of a viral pathogen or toxin-producing bacteria. This illness typically is brief and self-limited, and diagnostic testing is not likely to be of benefit.

ACUTE INVASIVE BACTERIAL ENTERITIS

Potential pathogens in acute invasive bacterial enteritis are summarized in Table 92-1.

Campylobacter Enteritis

Epidemiology. *Campylobacter* is the most common documented cause of bacterial enteritis in developed countries. In Canada, where the disease is reportable, campylobacteriosis was found in 30.2 persons per 100,000 in 2004, compared with 16 cases of salmonellosis per 100,000 population.[1] Most cases occur in children younger than 5 years of age or in male patients between the ages of 20 and 29 years, but people of all ages are affected. The disease is more common during the summer months. Opportunistic infections with *Campylobacter* species often are found in homosexual men or patients with acquired immunodeficiency syndrome (AIDS), even in the absence of symptoms of diarrhea or proctitis. *Campylobacter* species are a common cause of "backpacker's diarrhea," along with *Giardia*, both of which are frequently acquired by drinking from wilderness water sources.

Pathophysiology. *Campylobacter* organisms are small, spiral-shaped gram-negative bacteria. The most common species isolated are *Campylobacter jejuni* (94%), *Campylobacter coli* (1%), and *Campylobacter fetus*.[1] *Campylobacter cinaedi* and *Campylobacter fennelliae* are isolated almost exclusively from homosexual men. *Campylobacter* species produce disease primarily by direct invasion of the colonic epithelium and may induce inflammatory changes that are endoscopically indistinguishable from inflammatory bowel disease.

Most infections are acquired by handling raw poultry or eating raw or undercooked poultry meat. The primary reservoirs for *Campylobacter* organisms are chickens, with more than one half of U.S. flocks silently infected and well over one half of the chicken in U.S. supermarkets contaminated.[2] Other causes include consumption of tainted beef, pork, raw milk, or untreated water, or contact with infected pets and farm animals.[1]

Clinical Presentation. The incubation period for *Campylobacter* enteritis is approximately 2 to 5 days. Disease onset usually is rapid, with signs and symptoms of fever, cramping abdominal pain, and diarrhea. Constitutional symptoms of anorexia, malaise, myalgias, and headache are the rule, and some patients experience backache, arthralgias, and vomiting. The clinical picture can mimic that in acute appendicitis. Onset of diarrhea often lags 24 to 48 hours after the onset of fever and abdominal pain. Typically, the stools are loose and bile-colored but then become watery, grossly bloody, or melanotic approximately 40% of the time. Either gross or occult blood is found in the stool of 60 to 90% of patients with *Campylobacter* gastroenteritis. At the height of the illness, patients usually pass 8 to 10 stools or more per day.[3]

Most patients are well within a week or less; however, diarrhea can persist for weeks. Relapses are common although generally milder than the original episode. Fatalities are rare;

Table 92-1 Epidemiologic Aspects of Invasive Bacterial Enteritis

PATHOGEN	SOURCES/RISK FACTORS OR GROUPS	INCUBATION PERIOD (I); DURATION (D)	UNTREATED FEATURES
Campylobacter	Contaminated food/water, wilderness waters (backpacker's diarrhea), chickens, animals	I: 2-5 days D: 5-14 days	May cause bloody diarrhea May mimic acute appendicitis or inflammatory bowel disease; recurrence common
Salmonella	Grade A shell eggs, poultry, unpasteurized milk, domestic pets	I: 8-24 hr D: 2-5 days	Family and cafeteria-type food poisoning outbreaks common; increased incidence in patients with cancer or immunodeficiency
Shigella	Person-to-person, confined populations, poor hygiene, water-borne	I: 24-48 hr D: 4-7 days	Toxigenic watery diarrhea, followed by invasive picture; may produce severe dysentery
Yersinia	Food/water/milk, person-to-person, dogs, cats, pigs	I: 12-48 hr D: 5-14 days	Appendicitis/terminal ileitis-like syndrome; postinfection polyarthritis; long duration of fecal excretion of the organism
Vibrio parahaemolyticus	Raw or inadequately cooked seafood, especially shrimp	I: 8-24 hr D: 1-2 days	High attack rates, summer months; self-limited
Escherichia coli O157:H7	Raw ground beef, raw milk, meats, person-to-person, water-borne, travel	I: 3-8 days D: 5-10 days	Bloody diarrhea/hemorrhagic colitis; hemolytic uremic syndrome or thrombotic thrombocytopenic purpura
Plesiomonas	Uncooked shellfish, travel	I: 1-2 days D: 5-20 days	Severe abdominal cramps and vomiting, with dehydration
Bacillus anthracis	Infected herbivores, undercooked meat, bioterrorism	I: 1-6 days D: weeks	Oral ulcers, neck swelling, lymphadenopathy, fever, gastrointestinal hemorrhage, possible ascites

the Centers for Disease Control and Prevention (CDC) estimates 124 fatal cases in the United States each year.[3]

Diagnostic Strategies. Because the clinical presentation is similar to that with other invasive bacterial pathogens, the diagnosis of campylobacteriosis cannot be made on the basis of clinical presentation alone. Identification of the pathogen will require stool culture; specimens should be obtained in patients who present with acute enteritis associated with fever, abdominal pain, occult blood, or hematochezia. In borderline cases, stool methylene blue stain for fecal leukocytes is readily available and may help identify those patients who are likely to harbor an invasive pathogen. One study of outpatients with acute diarrhea found that the presence of fecal leukocytes (greater than 5 white blood cells per high-power field) was associated with a likelihood ratio (LR) of 5.0 for the presence of an invasive pathogen (95% confidence interval [CI], 2.9 to 8.6).[4] Blood culture results are rarely positive, so these studies are not routinely indicated. Sigmoidoscopy reveals a nonspecific inflammatory colitis, and *Campylobacter* infection must be considered before a new diagnosis of inflammatory bowel disease is made.

Differential Considerations. The differential diagnosis for suspected campylobacteriosis includes all infections with organisms that produce invasive diarrhea or fecal leukocytes, particularly salmonellosis, shigellosis, yersiniosis, and *Escherichia coli* O157:H7 infection.

Management. Empirical antibiotic therapy is not recommended for otherwise healthy patients who present with acute invasive diarrhea. (Travel-related diarrhea is an exception and is discussed later on.) Initial treatment of invasive diarrhea should focus on rehydration, and the decision to initiate antibiotic therapy should be deferred pending the result of stool culture. Treatment with antibiotics is not needed for patients who demonstrate clinical improvement by the time stool culture results become available. For those who are not improving, antibiotic therapy does shorten the duration of campylobacteriosis by approximately 1.3 days.[5] Erythromycin 500 mg twice a day for 5 days is the recommended first-line therapeutic regimen. Azithromycin 500 mg daily for 3 days is acceptable as well. Ciprofloxacin 500 mg twice a day can be used and was previously the treatment of choice, but alarming resistance to the fluoroquinolones has emerged, thought to be due mainly to antibiotic use in the poultry industry. Roughly 10% of *Campylobacter* strains are now resistant in the United States, and greater than 80% resistance has been documented in Thailand. *Campylobacter* organisms generally are resistant to trimethoprim-sulfamethoxazole (TMP-SMX) as well. Suggested antibiotic regimens for treatment of diarrhea are listed in Table 92-2. Relapses can occur, but the likelihood is decreased with appropriate antibiotic treatment.[3] Because *Campylobacter* infection is an invasive enteritis, antimotility agents are not recommended unless treatment with antibiotics also is given.

Complications of *Campylobacter* infection are rare. Cholecystitis, pancreatitis, and massive gastrointestinal bleeding all have been documented, as have meningitis, endocarditis, and osteomyelitis. In addition, a definite association has been made with Guillain-Barré syndrome. Guillain-Barré syndrome associated with *Campylobacter* infection tends to be more severe than Guillain-Barré syndrome from other triggers and can occur even with asymptomatic infections. Luckily, the incidence is estimated at less than 1 per 1000 cases.[2]

Salmonellosis

Epidemiology. *Salmonella* is the second most common cause of documented bacterial enteritis in the United States, with 36,184 cases (a rate of 12.2 cases per 100,000 population) reported in 2005. The actual number of cases is estimated to be greater than 1.4 million annually. U.S. surveillance systems found a 12% decrease in documented *Salmonella* infections in 2005 compared with 1995. Enteritis caused by this organism affects people of all age groups but particularly children, with those younger than 5 years of age accounting for 20% of cases.[6]

Table 92-2 Antibiotic Therapy for Diarrhea in Immunocompetent Adults

PATHOGEN	ANTIBIOTIC*†	DOSE
Campylobacter	1. Erythromycin 2. Azithromycin	500 mg PO bid × 5 days 500 mg PO qd × 3 days
Salmonella	1. Ciprofloxacin 2. Azithromycin	500 mg PO bid × 7 days 1 g PO × 1, then 500 mg qd × next 6 days
Shigella	1. Ciprofloxacin 2. TMP-SMX	500 mg PO bid × 3 days 160 mg/800 mg PO bid × 3 days
Yersinia	1. TMP-SMX 2. Ciprofloxacin	160 mg/800 mg PO bid × 3 days 500 mg PO bid × 3 days
Vibrio parahaemolyticus	Not recommended	
Vibrio cholerae	1. Ciprofloxacin 2. Doxycycline 3. TMP-SMX	1 g PO × 1 + IV fluids 300 mg PO × 1 + IV fluids 160 mg/800 mg PO bid × 3 days + IV fluids
Escherichia coli O157:H7	None recommended	
Enterotoxigenic *Escherichia coli*	*Mild symptoms*: ciprofloxacin 1. Ciprofloxacin 2. TMP-SMX	750 mg PO × 1 dose 500 mg PO bid × 3 days 160 mg/80 mg PO bid × 3 days
Plesiomonas hominis	1. TMP-SMX 2. Ciprofloxacin	160 mg/80 mg PO bid × 3 days 500 mg PO bid × 3 days
Clostridium difficile		
Diarrhea	1. Metronidazole 2. Vancomycin	250 mg PO qid × 10–14 days 125 mg PO qid × 10–14 days
Colitis	1. Metronidazole *or* vancomycin 2. Metronidazole	500 mg PO qid × 10–14 days 500 mg IV qid × 10–14 days
Aeromonas	1. TMP-SMX 2. Ciprofloxacin	160 mg/800 mg PO bid × 3 days 500 mg PO qid × 3 days
Bacillus anthracis	1. Ciprofloxacin 2. Doxycycline	400 mg IV q12h 100 mg IV q12h
Giardia lamblia	1. Metronidazole 2. Furazolidone	250 mg PO tid × 5 days 100 mg PO qid × 7–10 days
Entamoeba histolytica (confirmed by PCR assay or other test to be distinct from *Entamoeba dispar*)	1. Paromomycin 2. Iodoquinol 3. Diloxanide furoate *Severe symptoms*: start treatment with metronidazole	500 mg PO tid × 7 days 650 mg PO tid × 20 days 500 mg PO tid × 10 days 750 mg PO tid × 10 days followed by above
Cryptosporidium	1. Paromomycin 2. Indomethacin	500–750 mg PO qid × 14–21 days 500 mg PO tid
Isospora belli	1. TMP-SMX	160 mg/800 mg PO qid × 10 days, then bid × 3 wk
Cyclospora cayetanensis	1. TMP-SMX	160 mg/800 mg PO bid × 7 days
Strongyloides stercoralis	1. Ivermectin 2. Thiabendazole	200 µg/kg/PO day × 1–2 days 50 mg/kg/day in two doses × 2 days (max 3 g/day)
Enterobius vermicularis	1. Mebendazole *or* pyrantel pamoate 2. Albendazole	100 mg PO × 1 dose, repeated after 2 wk 11 mg/kg PO × 1 dose (max 1 g), repeated after 2 wk 400 mg PO × 1 dose, repeated after 2 wk

*Another quinolone agent, norfloxacin, can be substituted for ciprofloxacin in the treatment of diarrheas. The equivalent dosage is 400 mg bid.
†Listed drugs are numbered in order of preference: 1 indicates the drug of first choice; 2 and 3 indicate alternative drugs.
PCR, polymerase chain reaction; TMP-SMX, trimethoprim-sulfamethoxazole.

Almost all *Salmonella* infections are acquired from ingestion of contaminated food or drink.[7] Direct person-to-person transmission can occur, but most human infections are related to the vast reservoir of salmonellae in lower-order animals. Poultry products and beef constitute the most common sources of *Salmonella*. Unpasteurized milk, eggs, fish and domestic pets are other sources. Outbreaks also have been associated with consumption of fruits, vegetables, baked goods, rattlesnake meat, and medicinal preparations.[7] Approximately 10% of household dogs and cats excrete salmonellae, and pet reptiles, such as turtles, snakes, and iguanas, have been responsible for outbreaks of salmonellosis.[8]

Cooking contaminated foods decreases the possibility of infection but does not eliminate it. Salmonellae can survive cooking deep inside certain foods, where temperatures may not reach the lethal range. Very large outbreaks of *Salmonella* infection have been traced to contaminated, unbroken, grade A eggs.[8] Although the organism is present in the uncracked egg, thorough cooking usually eradicates or reduces the inoculum to clinically insignificant levels.

Common raw egg–based sources of *Salmonella* infections include homemade hollandaise sauce, eggnog, Caesar salad dressing, ice cream, mayonnaise, tiramisu, cookie dough (often consumed unbaked), frosting, and French toast mix.[8] *Salmonella enterica* subsp. *enterica* serovar Enteritidis (i.e., "*S.* Enteritidis") is the species universally associated with egg-related infections. Patients convalescing from *Salmonella*-related enterocolitis and persons with asymptomatic infection may continue to excrete *Salmonella* organisms for weeks or months, thus serving as ongoing sources of infection.[7]

Pathophysiology. Approximately 2000 *Salmonella* serotypes are known to cause human illness. Based on 2005 U.S. surveillance figures, the most common isolates are the *S. enterica* serovars Typhimurium (19%), Enteritidis (18%), Newport

(9%), and Heidelberg (5%).[6] Different *Salmonella* serotypes show marked variations in invasive potential and are associated with particular presentations: *S. enterica* serovar Typhi with enteric fever (typhoid fever), *S. enterica* serovar Choleraesuis with septicemia, *S.* Typhimurium with acute gastroenteritis, and *S.* Enteritidis infections from grade A shell eggs.[8]

Relatively large numbers of salmonellae must be ingested to produce illness. However, a carrier state can be induced with ingestion of 10 to 100 times fewer bacteria needed to induce carrier state relative to number needed to induce illness. In infants and adults with certain underlying diseases, a much smaller inoculum may produce illness. Decreased gastric acidity or an alteration of intestinal flora resulting from the administration of antibiotics can impressively reduce the size of the required inoculum.

Rates of invasive infection and disease severity are increased in infants, the elderly, and people with hemoglobinopathies such as sickle cell anemia, malignant neoplasms, or AIDS.[7] The CDC estimates that more than 500 fatal cases occur each year.[6]

Clinical Presentation. Family outbreaks and sporadic cases are more common than large epidemics. Ingested salmonellae penetrate the intestinal mucosal cells and lodge in the lamina propria. After an incubation period of 8 to 48 hours, the typical patient with *Salmonella* gastroenteritis presents with fever, colicky abdominal pain, and loose, watery stools, occasionally containing mucus and blood. Nausea and vomiting are common but rarely are severe or protracted. Mild to moderate diffuse abdominal tenderness can be elicited in most patients, but occasionally severe tenderness and even rebound tenderness may be noted. Symptoms usually abate within 2 to 5 days, and recovery typically is uneventful. Sustained or intermittent bacteremia may occur, especially in those with sickle cell anemia, malignancy, or AIDS. Focal infections are identified in 10% of those with *Salmonella* bacteremia.[7]

Diagnostic Strategies. The diagnosis of salmonellosis cannot be made on the basis of clinical presentation alone; stool cultures are needed for confirmation. Stool methylene blue staining for fecal leukocytes may help identify those patients who are likely to harbor an invasive pathogen. Blood culture results occasionally are positive, and samples should be obtained from severely ill or immunocompromised patients. The possibility of an underlying disease or immunodeficiency state should be considered in every patient with a severe *Salmonella* infection.

Differential Considerations. Family or communal outbreaks can suggest *Staphylococcus*-related food poisoning, but staphylococcal enteritis has a shorter incubation period, is not associated with fever, and produces the typical toxigenic, noninvasive, diarrheal picture. Vomiting is also much more prominent in cases of staphylococcal food poisoning than in most cases of *Salmonella* infection. The differential diagnosis for salmonellosis includes all organisms that produce invasive diarrhea or fecal leukocytes, particularly campylobacteriosis, shigellosis, yersiniosis, and *Escherichia coli* O157:H7 infection.

Management. Empirical antibiotic therapy is not recommended for otherwise healthy patients who present with suspected *Salmonella* enteritis. Antibiotic therapy does not shorten the duration of the disease and may prolong the duration of the carrier state. Although unproven, antibiotic therapy is recommended for patients with severe colitis and for infants younger than 3 months of age, adults older than 50 years, and other groups at risk for severe disease. Persons who represent a public health risk also should be treated in an attempt to eradicate the carrier state and prevent spread of the organism.[3,7] The choice of antibiotic should be based on sensitivities of the isolate. Any of the following antibiotic regimens typically is effective for outpatient management of *Salmonella* gastroenteritis: ciprofloxacin, 500 mg twice a day for 5 to 7 days; norfloxacin, 400 mg twice a day for 5 to 7 days; or azithromycin, 1 g by mouth and then 500 mg a day for the next 6 days.[3] TMP-SMX also can be used if the organism is susceptible. Ciprofloxacin is effective in the treatment of chronic *S.* Typhi carriers. However, treatment with fluoroquinolones can actually prolong shedding of non-Typhi organisms. Patients requiring hospitalization are best treated with intravenous ceftriaxone until results of sensitivity studies become available.[3]

Follow-up with the patient's primary care physician should be arranged. Food handlers and health care personnel should not be allowed to work until the carrier state has been eradicated. Repeated stool cultures and further decisions regarding job or school situations will be required. Personal hygiene should be emphasized, because untreated patients may continue to shed infective organisms in the stool for weeks or even months. As with other invasive pathogens, the use of antimotility drugs alone is contraindicated. These drugs prolong fever and diarrhea, increase the incidence of bacteremia, and promote development of a carrier state in patients with *Salmonella* enteritis. However, administration of loperamide is safe when it is given concomitantly with an appropriate antibiotic.

Prevention of salmonellosis depends on adequate cooking and minimizing the time that foods are allowed to stand at room temperature to reduce the chance of bacterial growth to an infectious inoculum. Careful personal hygiene, including hand washing, also is important. *Salmonella* infection is a nationally notifiable disease (Box 92-1).

Although most patients recover fully without long-term sequelae, up to 30% (primarily adults) will experience transient reactive arthritis. Reiter's syndrome, consisting of reactive arthritis, conjunctivitis, and urethritis, is a well-known complication and occurs in approximately 2% of patients.[7]

BOX 92-1 NOTIFIABLE FOODBORNE DISEASES AND RELATED CONDITIONS*

Bacterial
Botulism
Brucellosis
Cholera
Escherichia coli O157:H7—now listed as "Shiga toxin–producing *Escherichia coli* (STEC)"
Hemolytic uremic syndrome, postdiarrheal
Salmonellosis
Shigellosis
Typhoid fever
Vibriosis (with non-cholera *Vibrio* species)

Viral
Hepatitis A

Parasitic
Cryptosporidiosis
Cyclosporiasis
Trichinosis

*In the United States, additional reporting requirements may be mandated by state and territorial laws and regulations. Details on specific state reporting requirements are available from the Council of State and Territorial Epidemiologists (http://www.cste.org) and the Centers for Disease Control and Prevention (http://www.cdc.gov).

From Centers for Disease Control and Prevention: Nationally Notifiable Infectious Diseases—United States, 2007, revised. Available at: http://www.cdc.gov/epo/dphsi/phs/infdis2007r.htm (accessed 2007 November 8).

Shigellosis

Epidemiology. Shigellosis, or bacillary dysentery, is worldwide in distribution and particularly common in countries lacking effective sanitation. In the United States, a total of 10,484 cases of shigellosis were documented in 2005, representing a rate of 3.5 cases per 100,000 population.[9] The CDC estimates that there are actually approximately 448,000 cases each year.[10] *Shigella sonnei* is responsible for approximately 75% of the infections occurring in this country; *Shigella flexneri* causes most of the remaining cases, with *Shigella boydii* and *Shigella dysenteriae* responsible for less than 2% of cases.[9]

Shigella infections are common in confined populations, such as those in mental or penal institutions, in nursing homes or day care centers, or on Native American Indian reservations. Children younger than 5 years of age account for 30% of cases. An increased incidence has been documented among men who have sex with men and in the AIDS population.[11] Spread is by the fecal-oral route, and humans are the only natural hosts. Shigellae can be found in large numbers around the base of toilets used by infected persons, and the organism readily passes through toilet tissue onto the fingers. Shigellae can be recovered in cultures of samples taken as long as 3 hours after contamination. In the last few years, a number of large outbreaks have been associated with recreational water venues such as swimming pools, water parks, fountains, hot tubs, and spas.[10]

Pathophysiology. Unlike *Salmonella*, which requires a very large inoculum to produce disease, as few as 50 to 100 *Shigella* bacilli can cause infection. No other enteric pathogen is so efficient in producing overt disease in humans. Infection generally is superficial, localized to the epithelial lining of the colonic mucosa; therefore, bowel perforation or invasion into the bloodstream is extremely rare. Bleeding occurs from superficial ulcerations of the mucosa.

Clinical presentation varies among *Shigella* species. *S. sonnei* typically causes high-volume, watery diarrhea with relatively few systemic signs. Infection with *S. flexneri*, *S. dysenteriae*, or *S. boydii* typically causes low-volume bloody diarrhea and more severe systemic symptoms.[7]

Clinical Presentation. The usual incubation period is 24 to 48 hours, and the clinical manifestations vary considerably, often appearing in a bimodal fashion. Mild, watery diarrhea with few if any constitutional symptoms or asymptomatic infection occurs in a significant proportion of infected persons. It is estimated that fever occurs in 58 to 100%, abdominal pain in 75 to 100%, tenesmus in 55 to 96%, bloody stool in 46 to 73%, and nausea or vomiting in 63 to 100%.[3]

When true dysentery develops, it ordinarily is preceded by a recognizable period of watery diarrhea lasting a few hours to a few days. Patients with dysentery have grossly bloody diarrhea, tenesmus, and significant constitutional symptoms and signs, such as fever, nausea, vomiting, headache, and myalgias. If symptoms are severe enough, profound dehydration and even circulatory collapse can occur. Children younger than 2 years of age may have associated neurologic manifestations, most commonly seizures, although lethargy or frank coma develops in a small percentage of patients. *S. dysenteriae* type 1 infection, rarely diagnosed in developed countries, is associated with the hemolytic uremic syndrome.

Generally, shigellosis is a self-limited disease. Patients become afebrile in 3 to 4 days, and the abdominal cramping and diarrhea resolve within 1 week. A significant number of untreated patients will continue to shed organisms in the stool for 2 or more weeks, and approximately 10% of patients will have a relapse unless the infection is treated with antibiotics.

Diagnostic Strategies. As with other invasive pathogens, most cases of shigellosis remain undiagnosed. Patients with mild, watery diarrhea and few if any constitutional symptoms can be sent home with conservative management and no investigative procedures. However, shigellosis should be considered in every patient with an acute febrile illness associated with diarrhea, especially those patients who appear ill or who have dysenteric stools.

Fecal white blood cells are present, usually in large numbers, in 85 to 95% of the cases, regardless of the gross appearance of the stool.[3] Thus, finding leukocytes in watery stools can help identify shigellosis even in the absence of classic dysenteric stools. Occult blood usually is present in the stools of infected patients. Blood leukocytosis is common, and a significant leftward shift in the differential count is almost always seen. Results of blood cultures for *Shigella* are rarely positive. Sigmoidoscopic examination reveals diffuse mucosal inflammation, often with multiple ulcerations.

A definitive diagnosis of shigellosis is made with stool culture. Stool culture results are positive in more than 90% of cases when samples are obtained during the first 3 days of illness; however, results are positive in only approximately 75% if samples are obtained more than 1 week after the onset of diarrhea.[12]

Differential Considerations. Considerations in the differential diagnosis include salmonellosis, *Campylobacter* enteritis, yersiniosis, *E. coli* O157:H7 infection, amebic dysentery, and ulcerative colitis.

Management. Treatment primarily involves the correction of fluid and electrolyte abnormalities. If *S. sonnei* or *S. flexneri* is cultured from the stool, the decision to administer antibiotics is based on the patient's clinical condition and the feasibility of sanitary control. Asymptomatic or recovering patients do not need to be treated with antibiotics unless treatment is necessary for public health measures. Patients whose condition is not improving and those who are immunocompromised should be treated. Antibiotics shorten the clinical course and eradicate the pathogen from the stool, often within 48 hours.[12] Whenever *S. dysenteriae* is isolated, the patient should be treated to prevent outbreaks of dysentery, even if the patient is asymptomatic when the culture result returns from the lab.

In the United States, more than 80% of *Shigella* organisms are resistant to ampicillin, and 47% are resistant to TMP-SMX.[7] Significant resistance has not yet been found to the quinolone agents ciprofloxacin and norfloxacin, and one of these should be considered the drug of choice unless sensitivity studies demonstrate that the organism is sensitive to either ampicillin or TMP-SMX. Treatment is required for only 3 days in immunocompetent patients but should be extended to 7 to 10 days in the immunocompromised.[3]

Antimotility agents may prolong the fever, diarrhea, and excretion of *Shigella* in the stools and are contraindicated in patients with invasive shigellosis. However, they may be safe when used simultaneously with antibiotics. Follow-up stool cultures should be done in patients treated for *S. dysenteriae* infection to ensure eradication of the organism. Follow-up cultures, however, are not necessary after treatment for *S. sonnei* or *S. flexneri* infection, provided that the patient's condition improves clinically. Shigellosis is a nationally notifiable disease.

Yersinia enterocolitica Gastroenteritis

Epidemiology. *Yersinia enterocolitica*, a gram-negative facultatively anaerobic bacterium, is a member of the family Enterobacteriaceae. *Y. enterocolitica* is a relatively infrequent cause of enteritis in the United States, with FoodNet surveillance systems

documenting approximately 1 case of culture-verified yersiniosis per 100,000 population.[13] *Y. enterocolitica* infections are much more common throughout Scandinavia and Europe. In 2004, the incidence of human yersiniosis was 13.1 per 100,000 in Finland and 7.5 per 100,000 in Germany.[14] Yersiniosis is more prevalent in children and more common in the winter months.

Pathophysiology. After oral ingestion, the bacterium invades the intestinal epithelium and localizes to lymphoid tissue of the intestinal mucosa, particularly Peyer's patches. It then invades the regional mesenteric lymph nodes. Invasive enteritis is the clinical presentation in approximately two thirds of patients. Pseudoappendicitis and mesenteric adenitis account for the remainder of presentations. Infection originates from contaminated food or drink. The consumption of contaminated milk or contaminated raw pork has accounted for sporadic cases and several large outbreaks. Fecal-oral transmission to humans from a variety of animals, particularly dogs, cats, and pigs, and direct person-to-person spread probably occur, but communicability appears to be low.[13]

Clinical Presentation. The clinical picture with *Yersinia* enterocolitis often resembles that with infection by other invasive intestinal organisms: fever (68%); colicky abdominal pain (65%); watery, greenish, and sometimes bloody (26%) diarrhea; and constitutional symptoms of anorexia, vomiting (39%), and malaise.[3] However, in cases of *Y. enterocolitica* gastroenteritis, the abdominal pain and diarrhea usually persist for 10 to 14 days or longer.

In a substantial number of patients with yersiniosis, particularly adolescents and young adults, an ileocecitis may develop. In these cases, lower abdominal pain with little or no diarrhea is the predominant symptom, and the clinical presentation may perfectly mimic that in acute appendicitis. Large outbreaks have been traced to contaminated milk, largely because in the relevant series, physicians noticed an extraordinary rise in the number of negative appendectomies.[15]

Postinfection manifestations, such as erythema nodosum or a persistent polyarthritis, occur in as many as 2 to 5% of patients, mainly adults. Other presentations include sacroiliitis, ankylosing spondylitis, Reiter's syndrome, exudative pharyngitis, pneumonia, empyema, and lung abscess. *Y. enterocolitica* septicemia is rare but is known to occur, most often in patients with diabetes mellitus, severe anemia, hemochromatosis, cirrhosis, or malignancy.[15]

Diagnostic Strategies. Approximately 70% of patients with *Y. enterocolitica* infection will present with signs and symptoms of invasive enteritis. The diagnosis of yersiniosis cannot be made on the basis of clinical presentation; a positive stool culture is required. Methylene blue staining of stool for fecal leukocytes yields a positive result in approximately 48% of cases of yersiniosis.[3] Most laboratories do not routinely include *Y. enterocolitica* culture in the standard stool culture; *Yersinia* culture can be done by special request if clinically indicated (e.g., by history of *Yersinia* exposure, prolonged invasive enteritis despite a negative result on standard stool culture, or right lower quadrant pain with a normal appendix on imaging studies).

Stool cultures require special techniques and a long time for growth. Patients with *Yersinia* enterocolitis often continue to shed organisms in the stools well into convalescence, long after the diarrhea subsides. The mean duration of fecal shedding is approximately 6 weeks.

Differential Considerations. The diagnosis should be suspected in a patient with prolonged abdominal pain and diarrhea after what appears to be a common, usually self-limited gastroenteritis syndrome, or in a patient with symptoms similar to those of appendicitis or mesenteric adenitis. *Y. enterocolitica* infection also should be considered in the differential diagnosis of regional enteritis, which it can closely mimic.

Management. Generally, *Y. enterocolitica* infection is self-limited at the diarrheal stage and resolves without treatment. As with other invasive gastrointestinal pathogens, antiperistaltic drugs are not recommended unless the patient is simultaneously treated with antibiotics.

Treatment with antibiotics has not been proved to be essential or efficacious in the management of uncomplicated *Yersinia* enterocolitis or in the pseudoappendicitis syndrome. However, because *Yersinia* organisms take a long time to grow on culture, in most studies the duration of illness before antibiotics were started was 1 to 2 weeks. *Yersinia* organisms usually are susceptible to TMP-SMX, which is the agent of choice when antibiotic therapy is indicated.[3] Drug treatment does decrease the fecal shedding of the organism. Doxycycline in combination with an aminoglycoside is an alternative regimen, as is single-agent therapy with a quinolone.[3] In immunocompetent adults, a 3-day course is sufficient; the course is extended to 7 to 10 days if the patient is immunocompromised. Treatment should be considered in patients who are still significantly ill at the time culture results return, particularly if the patients are immunocompromised or have a significant underlying medical illness, or in cases in which the fecal shedding could represent a public health hazard. In those patients who interact with potentially susceptible persons, appropriate steps should be taken to ensure that they do not spread their infection.

Vibrio parahaemolyticus Gastroenteritis

Epidemiology. *Vibrio parahaemolyticus* is a halophilic (salt-requiring) gram-negative bacillus found naturally in warm marine environments such as the coastal seawaters of Japan, the United States, and other temperate-zone nations. In Japan, *V. parahaemolyticus* is the most common cause of bacterial enteritis, being responsible for approximately 70% of cases. The typical source is raw fish. In the United States, *V. parahaemolyticus* disease is much less common, with approximately 190 documented cases annually, or 0.25 per 100,000 population. The CDC estimates that approximately 3000 cases, 40 hospitalizations, and 7 deaths occur each year. U.S. cases typically are related to consumption of raw or undercooked shellfish, especially oysters (49%), although clams (38%), shrimp, lobsters, mussels, cockles, crabs, and scallops all have been implicated. Many cases occur as outbreaks on cruise ships or in persons who have patronized a common restaurant or seafood market. *V. parahaemolyticus* enteritis is much more common in the summer months, with 70% of cases occurring between the months of May and October, when warm seawater temperatures favor replication of the organism.[16] At such times, 100% of oysters in local beds have been shown to harbor the organism. Attack rates from a common-source exposure are fairly high, but little evidence is available for human-to-human spread among family members of infected patients.[17]

Pathophysiology. The mechanism by which *V. parahaemolyticus* causes human enteritis is poorly understood, but seems to be related to production of a thermostable direct hemolysin (TDH) enterotoxin. Serotypes that produce TDH attach to the colonic epithelium and induce a secretory diarrhea as well as local hemolysis. An infectious dose of *V. parahaemolyticus* is thought to be 100,000 colony-forming units (CFU) or more, and the sale of oysters with 10,000 CFU or less per gram of oyster product is allowed in the United States. Still, transmission has occurred from oyster beds in which the colony count was less than 200 CFU per gram of oyster meat.[17]

Although enteritis is the most common clinical presentation, accounting for 60 to 80% of cases, *V. parahaemolyticus* infections also manifest as wound infections (34%) and septicemia (5%). Serious wound infections and septicemia occur primarily in persons with underlying liver disease, alcoholism, or diabetes mellitus.[15]

Clinical Presentation. Signs and symptoms usually appear 8 to 12 hours after the ingestion of contaminated food, but the incubation period can range from 4 to 48 hours. The predominant manifestation is acute diarrhea, but the volume of fluid lost generally is not large. Moderately severe abdominal cramps occur in 88%, nausea in 52%, vomiting in 39%, and fever in 33%. Vomiting generally is not prominent. The illness is almost invariably self-limited and seldom lasts longer than 24 to 48 hours.[17]

V. parahaemolyticus infection should be suspected when a common-source outbreak of acute diarrheal disease occurs in persons exposed to fresh or frozen seafood. It also should be considered when fecal white blood cells are present in cases of acute invasive diarrhea linked to food poisoning.

Diagnostic Strategies. As with other types of acute invasive enteritis, the diagnosis of *V. parahaemolyticus* cannot be made on the basis of clinical presentation alone. The diagnosis is made by stool culture. Although blood agar and other nonselective media support the growth of this vibrio, isolation from the stool usually requires the use of a selective medium containing thiosulfate, citrate, bile salts, and sucrose (TCBS agar). This selective culture procedure is not part of the standard stool culture in most U.S. hospitals but can be obtained by special request in cases of outbreaks related to consumption of raw or undercooked shellfish, especially in coastal areas of the United States.[16]

Management. Because the disease is self-limited, most patients require no therapy. Although data on efficacy of antibiotic therapy are lacking, patients who still have diarrhea when culture results become available may benefit from treatment with tetracycline or fluoroquinolones or another antibiotic as guided by susceptibility testing.[15] An occasional patient may require fluid replacement. Antimotility agents are not indicated.

Because *V. parahaemolyticus* is widely present in coastal waters, the only effective preventive measures are adequate cooking, refrigeration, and hygienic practice in the preparation of seafood for human consumption.

Enterohemorrhagic (Shiga Toxin–Producing) *Escherichia coli* Gastroenteritis

Epidemiology. Enterohemorrhagic *E. coli* was first recognized as a human pathogen in 1982 after two outbreaks of hemorrhagic colitis were traced to undercooked ground beef contaminated with *E. coli* serotype O157:H7 and distributed at a fast food restaurant chain. It is now recognized that *E. coli* O157:H7 is 1 of more than 30 serotypes of *E. coli* known to produce *Shigella*-like toxins and that these "Shiga toxin–producing *E. coli*" (STEC) as a group constitute a major cause of hemorrhagic colitis, hemolytic uremic syndrome, and thrombotic thrombocytopenic purpura in humans.[15] The CDC estimates 110,000 cases and 2,100 hospitalizations per year in the United States and reports a 42% decrease in the incidence from 1996 to 2004, probably owing to improvements in food safety protocols.[18] STEC infections have been documented in more than 30 countries on 6 continents.

Inadequately cooked hamburger has caused many large outbreaks.[15] STEC, present in the intestines of healthy cattle, contaminates the meat during slaughter, and the grinding process then transfers the organisms from the surface of the meat to the interior. U.S. Department of Agriculture food safety regulations now require that hamburger be cooked thoroughly, to the point that the juices are no longer pink, to effectively kill *E. coli* organisms. Outbreaks also have occurred from consumption of venison, salami, pepperoni, cheese curds, apple cider, raw milk, and fruits and vegetables; from contamination of municipal water supplies; from animal contact in petting zoos; and from person-to-person spread in day care centers.[7] Food handlers with STEC-related diarrhea have contaminated meals responsible for institutional outbreaks. Enterohemorrhagic *E. coli* enteritis is more common in the summer months.

Pathophysiology. *Escherichia coli* O157:H7 is 1 of more than 30 serotypes of *E. coli* known to produce *Shigella*-like toxins called *verotoxins*, which are cytotoxic to the intestinal vascular endothelial cells and cause hemorrhagic colitis. STEC does not cause an invasive infection, but the clinical presentation is quite similar to that with an invasive bacterial infection. Bacteria attach to the surface epithelium of the cecum and colon and elaborate verotoxin. Clinical signs and symptoms correlate with presence of free verotoxin in the colon. Histologic changes include apoptosis in the surface epithelium, mucin depletion, and neutrophilic infiltration of the lamina propria and epithelium. The verotoxin-induced syndrome of pain and (often) bloody diarrhea closely mimics that caused by other invasive pathogens.

It appears that STEC serotypes are associated with two different Shiga-type toxins. The development of hemolytic uremic syndrome is associated primarily with serotypes that produce Shiga toxin 2. The CDC estimates that greater than 90% of cases of hemolytic uremic syndrome are associated with the serotype E. coli O157:H7.[19]

Clinical Presentation. After an incubation period of 3 to 4 days, patients initially produce watery diarrhea that becomes bloody hours to days later. Approximately 80 to 90% of patients report bloody stools.[3,19] The amount of blood varies, but stools passed may appear to consist wholly of blood, and the infection may masquerade as gastrointestinal bleeding from noninfectious causes. The bloody diarrhea typically is accompanied by severe abdominal cramps, pain, and often vomiting. Fever is a feature in fewer than one third of cases and, if present, usually is low grade.[7] This helps differentiate STEC infection from that due to other invasive organisms. Fecal leukocytes are found in approximately 50% of cases, but in small numbers, in contrast with the sheets of white blood cells seen in *Shigella* dysentery.[3] Endoscopic, histologic, and radiographic studies demonstrate only nonspecific changes consistent with an inflammatory hemorrhagic colitis and do not accurately distinguish STEC infection from other causes of colitis.[20]

Uncomplicated infection resolves spontaneously over 7 to 10 days. A carrier state may last another 1 to 2 weeks, but it also resolves spontaneously. Chronic diarrhea has very rarely been described.[21]

Complications. *E. coli* O157:H7 hemorrhagic colitis has been associated with two serious complications: hemolytic uremic syndrome and thrombotic thrombocytopenic purpura. These clinically similar disorders share the following features: microangiopathic hemolytic anemia, thrombocytopenia, fever, neurologic deficits, and renal dysfunction. In thrombotic thrombocytopenic purpura, neurologic findings predominate, and renal dysfunction is unusual. The opposite is seen with hemolytic uremic syndrome, which is more common in children, especially those younger than 4 years, occurring in approximately 8% of cases.[7,18,19] Of these, 3 to 5% are fatal.[18] Approximately 22 to 40% of elderly persons in nursing home outbreaks acquire hemolytic uremic syndrome, and 50 to 80% of these patients die. Thrombotic thrombocytopenic purpura

is seen in 2 to 3% of cases, most often in immunosuppressed patients. Hemolytic uremic syndrome and thrombotic thrombocytopenic purpura typically appear 5 to 20 days after the onset of infection, and the diarrhea can be totally resolved and forgotten by the time a diagnosis is established. Death from *E. coli* O157:H7 hemorrhagic colitis alone or from one of the complications occurs primarily among the elderly.[15]

Diagnostic Strategies. The CDC recommends that all patients who present with bloody diarrhea be tested for STEC infection and that E. coli O157:H7 be included in the standard stool culture in all clinical laboratories. Diagnosis requires specific stool culture techniques. In addition to the routine battery of media, specimens should be plated onto sorbitol-MacConkey (SMAC) medium. The O157:H7 strains of *E. coli* are sorbitol-negative at 18 to 24 hours of growth on this medium and can be rapidly identified using various serologic tests, such as latex agglutination or fluorescent antibody testing. A commercial Shiga toxin enzyme immunoassay (EIA) was introduced in 1995 in order to assist clinical laboratories in identifying non-O157 Shiga toxin–producing strains of *E. coli*. The CDC now recommends that all stools submitted for culture also be tested for STEC-associated verotoxin using EIA, and that non-O157 STEC be sent to the CDC for typing. As of 2007, only 9% of clinical laboratories in the United States test for STEC using EIA technology.[19]

Differential Considerations. Hemorrhagic *E. coli* infections may be misdiagnosed as ischemic colitis, inflammatory bowel disease, intussusception, or another infectious colitis. The examining physician should test for STEC when considering a diagnosis of one of these entities.

Management. Antibiotic therapy does not shorten the clinical course or eradicate the organism. Moreover, treatment with antibiotics to which the organism is resistant may increase the risk for hemolytic uremic syndrome by eliminating competing bowel flora. However, the degree to which antibiotic treatment truly increases the risk for hemolytic uremic syndrome remains controversial.[3,7,18] Retrospective studies in adults suggest an association between antibiotic use and the development of hemolytic uremic syndrome but may have been biased due to preferential use of antibiotics in the more serious cases. Because antibiotic treatment is of no clinical benefit and may increase the risk of hemolytic uremic syndrome, it is not recommended for patients with known infection with *E. coli* O157:H7.

Empirical antibiotic treatment for bloody diarrhea should be approached with caution. Empirical treatment is not recommended in children because of the increased incidence of hemolytic syndrome. In adults, empirical treatment is recommended only for those with a temperature above 38.5° C, since the presence of significant fever suggests a pathogen other than *E. coli* O157:H7.

Aeromonas Gastroenteritis

Epidemiology. *Aeromonas* organisms are gram-negative, facultatively anaerobic, rod-shaped bacteria of the family Vibrionaceae. *Aeromonas* species are ubiquitous worldwide in fresh and brackish water and also contaminate the food and water supply.[15,22] *Aeromonas* organisms grow at a range of temperatures but are isolated with increased frequency in summer months. No figures are available on the incidence of *Aeromonas* gastroenteritis in the United States. An association with human enteritis is difficult to confirm because no major outbreaks have been linked to *Aeromonas* species and the organism often is found in the feces of asymptomatic persons. Still, several small outbreaks have been documented in travelers and by case-control studies; it is likely that certain serotypes do cause gastroenteritis in humans.[23,24] Drinking untreated water, usually from private wells or springs, causes most cases of diarrhea from *Aeromonas* bacteria.[22] *Aeromonas* infection has not been associated with consumption of shellfish. *Aeromonas hydrophila* causes wound infection; septicemia occurs in persons of advanced age or with underlying gastrointestinal disease such as colon cancer, cirrhosis, or hepatobiliary or inflammatory bowel disease or history of recent hospitalization or antibiotic treatment. In some published series, *Aeromonas* infection causes 2 to 10% of all cases of diarrhea in children.[22,23]

Pathophysiology. The exact mechanism by which *Aeromonas* species produce diarrhea has not yet been explained. Both enterotoxins and cytopathic toxins may be produced, and the organisms may have some invasive characteristics.

Clinical Presentation

Typical signs and symptoms are watery diarrhea, abdominal cramps (50%), vomiting (25%), and fever in approximately one half of the patients.[24] Children tend to have a more acute, severe illness than that typical for adults. In untreated patients, diarrhea persists for 2 to 10 weeks, with more prolonged illness in adults than in children. Generally, leukocytes and occult blood are absent from the stool; however, patients can have a severe colitis, including fever, fecal leukocytes, and bloody diarrhea, which can mimic Crohn's disease or ulcerative colitis. Stool should be examined for the presence of *Aeromonas* infection before establishing a diagnosis of inflammatory bowel disease.

Diagnostic Strategies. Diagnosis is made by stool culture, but culture for *Aeromonas* species is not part of the standard stool culture, and the clinician must request that the laboratory culture specifically for this organism. *Aeromonas* infection should be suspected in children or immunocompromised patients with diarrhea associated with a history of drinking from untreated water sources.

Management. No controlled trials have been conducted that clearly demonstrate a benefit to antibiotic therapy. In most patients, *Aeromonas* enteritis is mild and self-limited, and antibiotic therapy probably is not warranted. In the case of severe disease, prolonged diarrhea, or an immunocompromised host, double-strength TMP-SMX is the drug of choice, but the quinolones also are effective.[3] A 3-day course is recommended.

Plesiomonas shigelloides Gastroenteritis

Epidemiology. *Plesiomonas shigelloides* is a gram-negative, facultatively anaerobic bacterium of the family Vibrionaceae. The organism is found in a variety of settings, including animals, soil, and in freshwater and dilute saltwater bodies including the Gulf of Mexico. Humans usually are infected by contaminated food or water or after contact with colonized animals. Worldwide, *P. shigelloides* enteritis is well documented in the tropical and subtropical areas of Africa, Asia, and Australia. In the United States and Europe, most cases occur after travel to tropical areas or after consumption of raw shellfish, especially oysters.[15] Sporadic diarrheal illness occurs in both normal and immunocompromised hosts. Large outbreaks have occurred, usually resulting from oyster consumption.[15]

Pathophysiology. Evidence supporting a pathogenic role for *P. shigelloides* includes documented outbreaks associated with contaminated shellfish, a very low asymptomatic carrier rate, and recovery from diarrheal illness after antibiotic therapy. The mechanism of disease production remains poorly under-

stood but probably involves enteroinvasion and elaboration of cytotoxins.

Clinical Presentation. The incubation period is only 1 to 2 days in duration. Abdominal pain is noted in 72% of patients. Diarrhea is watery in 73% of patients and grossly bloody in 24%. Occult blood is noted in 44%, emesis in 38%, and fever in 51%.[25] Symptoms resolve after 1 to 3 days in most cases but occasionally may persist for up to 8 weeks. The duration of illness usually is shorter in children.

Diagnosis of *P. shigelloides* infection should be considered in patients with a typical invasive-appearing diarrhea, especially if the stools are bloody or when the onset of illness occurs shortly after the ingestion of raw shellfish or foreign travel, particularly to Mexico. *P. shigelloides* is increasingly recognized as a pathogen in immunocompromised patients.

Diagnostic Strategies. Definitive diagnosis is obtained by stool culture. The laboratory must be notified when this organism is considered. Unless oxidase testing is done, *Plesiomonas* may be indistinguishable from Enterobacteriaceae on nonselective culture media. Patients with *Plesiomonas* infections should be evaluated for possible immunodeficiency.

Management. Antibiotic therapy usually is not necessary for *P. shigelloides* enteritis because of the brief duration of illness. In patients who are immunocompromised and those with severe or prolonged symptoms, antibiotic treatment may be of benefit. *P. shigelloides* usually is resistant to ampicillin but susceptible to TMP-SMX, the quinolones, cephalothin, gentamicin, and chloramphenicol. The current recommended treatment regimen is TMP-SMX, 160 mg/800 mg twice daily for 3 days; ciprofloxacin, 500 mg twice daily; or norfloxacin, 400 mg twice daily for 3 days.[3] Follow-up evaluation is not necessary unless the patient is immunodeficient or does not respond clinically.

Bacillus anthracis Infection

Epidemiology. Although gastrointestinal anthrax is rare in developed countries, large outbreaks still occur in agricultural regions throughout the world. Anthrax also has been used as a weapon of bioterrorism in regions not normally susceptible to the disease. As early as the 1930s, groups experimented with anthrax-impregnated chocolate as a weapon against their enemies.[26] Awareness of the spectrum of clinical presentations of gastrointestinal anthrax is important not only for the welfare of the patient but for prompt recognition of potential terrorist activity.

Traditionally, gastrointestinal infection has been estimated at less than 1% of all human anthrax cases. It was thought that 95% of cases involved cutaneous symptoms and 5% were limited to the respiratory tract. However, because gastrointestinal anthrax can cause only mild and self-limited symptoms, many persons with the gastrointestinal form may not seek medical treatment. Studies of several large outbreaks in Uganda and Thailand suggest that the gastrointestinal form is observed in 74 to 92% of patients who contract anthrax after eating the meat of infected herbivores.[26]

Areas endemic for anthrax exist in all continents containing tropical and subtemperate regions. Thailand, India, Iran, Gambia, and Uganda all have reported deaths from gastrointestinal anthrax.[26] Within the United States, naturally occurring anthrax exposure has been documented in several areas, including Minnesota.[26] Although no predilection for time of year in endemic areas has been documented, the disease is more common in animals after substantial rainfall following a period of drought, a pattern known as "anthrax weather."[27]

In the United States, gastrointestinal anthrax has not been reported, although cutaneous anthrax is reported once or twice each year.[28] Populations at risk for naturally occurring anthrax are persons living in rural, agricultural areas who have ingested undercooked meat contaminated with anthrax spores. As with many other organisms, the pediatric population seems to be most at risk for serious or fatal illness.

Pathophysiology. *Bacillus anthracis* is a nonmotile, rodlike, gram-positive anaerobic bacillus that produces central oval-shaped spores. It is introduced into the food chain most often after ingestion by herbivores such as cattle. The animal usually becomes visibly ill, and the meat often is identifiable as abnormal after slaughter, thereby preventing human exposure. Even when the meat reaches a consumer, adequate cooking usually reduces the inoculum to harmless levels. However, if the meat is undercooked, a high rate of infectivity results. Intentional placement of anthrax spores in the food or water supply could theoretically cause outbreaks of gastrointestinal anthrax, although this has not been reported.

When swallowed, anthrax spores stick to the gastrointestinal epithelium, where they germinate and create multiple superficial ulcerations. Lesions have been identified from the oral cavity to the cecum.[26] The vegetative cells may at times migrate into the bloodstream, where they rapidly multiply and can cause septicemia. *Bacillus anthracis* protects itself with an antiphagocytic capsule and produces two exotoxins, lethal and edema toxins.[28]

Clinical Presentation. A minority of patients who ingest anthrax spores remain asymptomatic, and in endemic areas, adults often are thought to have some natural immunity acquired through previous exposure. Of those in whom symptoms do develop, presentation can vary widely, ranging from mild watery diarrhea to fulminant upper and lower gastrointestinal bleeding, septicemia, and death. The incubation period for gastrointestinal symptoms ranges from 1 to 6 days, with larger inocula and more severe disease developing earlier. For disease confined to the oropharynx, patients usually present with complaints of sore throat, fever, dysphagia, hoarseness, and painful neck swelling. The swelling results from marked lymphadenopathy and tissue edema and can become severe enough to compromise breathing.[26]

Much information concerning intestinal anthrax has been derived from two large outbreaks in Uganda and Thailand, respectively.[26] A majority of the patients presented with isolated diarrhea. Nausea, vomiting, and severe abdominal pain with distention also developed in a minority of the patients. Most patients were febrile, with temperatures above 39° C, and blood in both the vomitus and diarrheal stool was common.

With this form of anthrax, lesions throughout the gastrointestinal tract often are surrounded by significant edema and can lead to obstruction, necrosis, and perforation. Intra-abdominal lymphadenopathy and splenomegaly develop as well. The lymphatic tissue often becomes hemorrhagic, and ascites may form, with fluid shifts large enough to cause shock and even death.

In cases of primary gastrointestinal anthrax, the superficial mucosa is always involved, with ulcerations visible on endoscopic examination. These findings are in contrast with those with disseminated infection from pulmonary anthrax, in which the lesions begin submucosally as a result of seeding from the bloodstream. These lesions can then secondarily ulcerate to the surface of the gastrointestinal tract epithelium. Untreated, gastrointestinal anthrax may last weeks and can be, but is not always, fatal.

Diagnostic Strategies. Diagnosis of *B. anthracis* in cases of oropharyngeal disease is best accomplished by swabbing the oral

lesions for culture. Blood cultures are recommended for all suspected cases of anthrax, but culture results usually are negative in patients with isolated oropharyngeal involvement. A Gram-stained smear from the lesions will demonstrate numerous polymorphonuclear leukocytes and gram-positive bacilli. Studies of serum antibody to anthrax antigens may confirm the diagnosis, but serologic testing is not widely available.

Diagnosis of the gastrointestinal variant of anthrax relies more on identifying *B. anthracis* DNA by PCR (polymerase chain reaction) assay and cultures of blood and, if possible, ascitic fluid. Culture of the diarrheal stool yields positive results in a minority of cases. Serum antibody tests for anthrax antigens can be helpful.

Differential Considerations. Oropharyngeal anthrax lesions are sometimes confused with peritonsillar abscess, although cervical swelling is unusually severe in cases of oropharyngeal anthrax. The marked swelling of the oral lesions is secondary to edema and should not yield pus if incision and drainage are performed. Gastrointestinal anthrax can cause enough upper gastrointestinal bleeding to be confused with variceal rupture. In patients with severe disease manifested as marked ascites and abdominal pain, the clinical presentation may be similar to that in patients with end-stage liver disease with peritonitis.

Management. Traditionally, penicillin has been used to treat gastrointestinal anthrax. Cases of penicillin resistance have been documented, however, and a logical assumption is that a resistant strain would be chosen for use as a weapon of bioterrorism. Therefore, current recommendations from the CDC are to treat gastrointestinal cases in the same manner as for cases of respiratory anthrax, with ciprofloxacin 400 mg IV every 12 hours or doxycycline 100 mg IV every 12 hours. Cephalosporins should not be used. Even with aggressive antibiotic therapy, the disease carries a 25 to 60% mortality rate, depending on host factors and the size of the inoculum.[28]

TOXIN-INDUCED BACTERIAL GASTROENTERITIS

Pathogens associated with toxin-induced bacterial enteritis are summarized in Table 92-3. In general, gastroenteritis due to toxin-forming bacteria and viral agents will manifest as an acute noninvasive enteritis, with watery diarrhea, minimal fever, little or no abdominal cramping, and absence of fecal leukocytes and erythrocytes. Treatment is primarily supportive, and diagnostic testing generally is not indicated in otherwise healthy patients. A specific diagnosis may be of help in attempting to identify a common source during large outbreaks.

Staphylococcal Food Poisoning

Epidemiology. *Staphylococcus*-related food poisoning occurs after multiplication of an enterotoxin-forming strain of *Staphylococcus* that is present in the food before its ingestion. Food contamination with *Staphylococcus* is extremely common because the organism is ubiquitous in the environment. It can be isolated from the hands of approximately 50% of persons in the general population. Most protein-rich foods support the growth of staphylococci, especially ham, eggs (even hard-boiled), custard-filled pastries, mayonnaise, and potato salad.[29] Temperatures between 45° and 140° F for only a few hours will allow proliferation of the organism in contaminated food and production of sufficient enterotoxin to cause disease. Foods

Table 92-3 Epidemiologic Aspects of Toxin-Induced Bacterial Enteritis

PATHOGEN/ILLNESS	SOURCE(S)	INCUBATION PERIOD (I); DURATION (D)	COMMENTS/UNTREATED FEATURES
Preformed Toxins			
Staphylococcus	Food handler–related; potato salad, mayonnaise, confections	I: 1-6 hr D: 6-10 hr	Very high attack rates, large outbreaks
Bacillus cereus			
Emetic toxin	Fried rice	I: 2-4 hr D: 10 hr	High attack rate, almost always after consumption of fried rice
Diarrheal toxin	Vegetables; meats, especially gravies	I: 6-14 hr D: 24-36 hr	Food reheated or sitting out for long periods
Scombroid fish poisoning	Mahi mahi, tuna, bluefish	I: 5-60 min D: 6 hr	Peppery or bitter taste, histamine intoxication, high attack rates
Ciguatera fish poisoning: ciguatoxin	Large, predacious coral reef fish	I: 2-6 hr D: 7-14 days	High attack rates, gastrointestinal and neurologic symptoms with paresthesias, cold allodynia, worse with alcohol
Toxins Produced after Colonization			
Clostridium perfringens	Meat, poultry, gravies, "steam table" meats	I: 6-24 hr D: 24 hr	Food reheated or sitting out for long periods
Vibrio	Seafood, especially raw shellfish	I: 24-48 hr D: 6-8 days	Summer months, dehydration common
Escherichia coli	Usually unsanitary drinking water	I: 24-72 hr D: 1-7 days	Travelers; dehydration common in children
Clostridium difficile	Overgrowth of normal flora	I: 5-14 days D: Variable	Antibiotic-associated colitis, cytopathic toxin
Aeromonas	Untreated drinking water	I: 1-5 days D: 2-10 wk	Common and severe in children, chronic watery diarrhea in adults, occasionally mimics inflammatory bowel disease

containing sufficient enterotoxin to produce violent illness usually are normal in appearance, odor, and taste. Large outbreaks are common worldwide, particularly in institutions such as school or hospital cafeterias, military bases, airlines, and restaurants.[29]

Pathophysiology. Although the bacterium itself is killed by cooking at temperatures above 140° F, *Staphylococcus* enterotoxin is heat-stable. Thus, once it is present in food, reheating or even boiling will not prevent illness. The toxin has no local effect on the digestive tract. It is a potent stimulator of T lymphocytes in the host, stimulating their proliferation and the release of various cytokines. The gastrointestinal effects are believed to be mediated by the release of histamine and leukotrienes from mast cells.[30]

Clinical Presentation. The illness has an explosive onset, beginning 1 to 6 hours after ingestion of the contaminated food. Cramping and abdominal pain, with violent and often-repeated retching and vomiting, are the predominant symptoms. Diarrhea is a variable feature; it usually is mild, occasionally absent entirely, and infrequently profuse. Fever occasionally is present. Staphylococcal food poisoning is short-lived, usually subsiding in 6 to 8 hours and rarely lasting as long as 24 hours. Patients often are recovering by the time they seek medical attention. Attack rates are very high, often greater than 75% of the population at risk.[31] The short incubation period and multiple cases among persons eating the same meal are highly suggestive of this disease. Examination of the stool is noncontributory, and no practical laboratory test is clinically available to confirm the diagnosis. The epidemiologic circumstances, however, usually provide adequate suggestive evidence.

Management. Rapid, uncomplicated, spontaneous recovery is the rule. Parenteral antiemetic agents help control vomiting. Intravenous fluids should be given to patients with significant dehydration and ongoing vomiting, particularly the very young, the elderly, and debilitated patients. Antibiotics are of no value because staphylococcal food poisoning is caused by preformed enterotoxin and not by viable microorganisms. Adherence to strict personal hygiene practices by food handlers and immediate refrigeration of foods not due for immediate consumption are the most important preventive measures. Ordinary refrigerator temperatures prevent production of the enterotoxin. Food should not be allowed to stand at room temperature for long periods before being served.

Clostridium perfringens Food Poisoning

Epidemiology. *Clostridium perfringens* food poisoning is one of the most commonly reported food-borne illnesses in the United States, with at least 10 to 20 outbreaks reported annually. Most cases occur in large groups, with dozens or even hundreds of persons affected. Illness is caused by the ingestion of meat or poultry heavily contaminated with *C. perfringens* type A heat-resistant spores.[32] The organism also is ubiquitous in the environment and in human and animal feces. Typically, poisoning results from ingesting food that is cooked more than 24 hours before consumption, allowed to cool slowly at room temperature, and then served either cool or rewarmed. During this period of incubation, spores that survived cooking germinate, and clostridia multiply to reach sufficient numbers to constitute an infectious inoculum.

Pathophysiology. Ingestion of live organisms is required to produce disease, but illness is not caused by infection; rather, it is from an enterotoxin produced by sporulation of the organism in the gastrointestinal tract. The enterotoxin is responsible for all of the symptoms of *C. perfringens* food poisoning.

Clinical Presentation. Symptoms usually appear within 6 to 12 hours but can occur up to 24 hours after ingestion of the contaminated food. Frequent passage of watery diarrheal stools and moderately severe abdominal cramping are the major symptoms. Fever, nausea, and vomiting are rare. The illness is self-limited and rarely lasts for more than 24 hours.

C. perfringens food poisoning should be considered in a patient who experiences an acute onset of abdominal cramps and watery diarrhea shortly after eating a suspect meat or poultry dish and when others who ate the same meal are similarly ill. Leukocytes and erythrocytes are not present on stool examination.

Complications. A rare type of *Clostridium* food poisoning termed *enteritis necroticans* (also known as "pig-bel") occurs after the ingestion of foods heavily contaminated with the type C strain of *C. perfringens*. The illness is characterized by an acute onset of severe abdominal pain, vomiting, diarrhea, prostration, and shock and may be rapidly fatal. Postmortem examination reveals a diffuse, hemorrhagic, necrotizing enteritis of the jejunum, ileum, and colon.[33]

Management. Occasionally, a patient will need intravenous fluid replacement. Antibiotics are of no value because of the toxigenic nature and brief duration of the disease. Food poisoning from *C. perfringens* can be prevented by avoiding long periods of warming or cooling of foods that have already been cooked.

Bacillus cereus Food Poisoning

Epidemiology. *Bacillus cereus* is an aerobic, spore-forming, gram-positive rod that is a common cause of food-borne illness. The organism is one of the most frequently isolated soil bacteria. Because of its abundance and the hardiness of its spores, *B. cereus* contaminates nearly all agricultural products and plays a major role in the spoilage of food items, including pasteurized milk and milk products. It commonly is isolated from pasta, rice, dairy and dried milk products, spices, dried foods, meat, chicken, vegetables, seafood, fruits, and grains. Because it is ubiquitous and tolerates extremes of temperature, control of this bacterium in the food-processing environment is very difficult to achieve.[34] It is estimated that *B. cereus* causes more than 27,000 cases of food poisoning in the United States each year.

B. cereus causes two distinct clinical syndromes: an emetic form produced by a heat-stable, *Staphylococcus*-like enterotoxin known as cereulide and a diarrheal form resulting from a heat-labile enterotoxin known as HBL, which is similar to that of *E. coli*. The emetic form usually is caused by the ingestion of contaminated fried rice, although beef, poultry, vanilla sauce, pasteurized cream, milk pudding, pasta, and infant formula also have been implicated. The diarrheal syndrome usually is associated with ingestion of HBL in meats or vegetables, but reported outbreaks also have involved fish, soups, sauces, and dairy products.[34]

Pathophysiology. The heat-resistant spores of *B. cereus* survive boiling and then germinate when boiled foods such as fried rice are left unrefrigerated. The vegetative forms then multiply and produce toxin. Flash-frying or brief rewarming of the food before serving often is not sufficient to destroy the preformed, heat-stable emetic toxin. Improper holding temperatures for cooked food is the most common feature of *B. cereus* food-borne illness.

Clinical Presentation. The emetic syndrome is clinically indistinguishable from that caused by staphylococcal enterotoxin. After an incubation period of 1 to 5 hours, profound vomiting and abdominal cramping occur in all patients. Diarrhea is present in approximately 25 to 30% of persons affected. The duration is short, usually less than 10 hours, and patients recover uneventfully.

The diarrheal syndrome begins after an incubation period of 6 to 14 hours and is characterized by diarrhea in all patients and by abdominal cramps in approximately 75%. Vomiting occurs in only 20% of cases. The duration of illness ranges from 12 to 36 hours. Symptoms are essentially the same as for food poisoning produced by *C. perfringens*, although vomiting is less common with *C. perfringens*.

Bacillus cereus food poisoning should be suspected whenever an illness localized predominantly to the upper gastrointestinal tract develops less than 6 hours after eating, or whenever a predominantly lower intestinal tract illness occurs 6 to 24 hours after a suspect meal, usually of meats or vegetables.

Diagnostic Strategies. Because of the brief and noninvasive nature of the illness, diagnostic testing typically is not performed. In response to large outbreaks, public health authorities may elect to test common food sources. Isolation of 10^5 colony forming units per gram from incriminated foods confirms the diagnosis. More recently, a real-time PCR assay has been developed that can detect the presence of *B. cereus* emetic toxin within 2 hours. This assay is not yet commercially available.[35]

Management. Both syndromes generally are mild and self-limited. Antibiotics are not indicated because symptoms are mediated by enterotoxins. Parenteral antiemetic agents provide effective relief in patients presenting with violent vomiting. *B. cereus* food poisoning is preventable if boiled rice or cooked foods are promptly eaten or refrigerated and not left to sit at room temperature.

Cholera and Gastroenteritis Due to Non-cholera Vibrios

Epidemiology. In addition to *V. parahaemolyticus*, other halophilic marine *Vibrio* species have increasingly been determined to be causes of acute gastroenteritis associated with seafood. Their epidemiology is identical to that of *V. parahaemolyticus*: ubiquitous presence in coastal seawater, outbreaks associated with the eating of raw or inadequately cooked shellfish, and an incidence markedly limited to the warmer months of the year.[15] Outbreaks of true cholera continue to occur sporadically along the Gulf Coast of the United States from inadequately cooked crabs or oysters. Other implicated foods include imported seafood, cooked rice, frozen or fresh coconut milk, and commercially prepared cut cantaloupe.[15] Cholera outbreaks in South America and India have led to an increasing number of cases of cholera imported into the United States. The CDC reports 0 to 5 cases annually.[36]

Pathophysiology. The difference between these species and *V. parahaemolyticus* lies in the mechanism of pathogenesis. *V. parahaemolyticus* produces disease directly by an invasive intestinal infection, whereas these strains produce an enterotoxin in vivo that is responsible for the diarrhea. Therefore, symptoms resemble those of other forms of enterotoxin-induced gastroenteritis and not those caused by invasive pathogens. The enterotoxin of the non-cholera vibrios is antigenically similar to *V. cholerae* enterotoxin and produces a similar diarrheal illness, although it is much less severe.[15]

Clinical Presentation. Patients with classic epidemic cholera experience copious "rice water" diarrhea, abdominal cramps, and often nausea and vomiting within 24 to 48 hours after ingesting contaminated seafood. A low-grade fever may be present. In these severe cases (cholera gravis), rates of diarrheal fluid loss can reach 1 L per hour. Nearly one half lose enough fluids to necessitate hospitalization, and fatality rates can reach 25 to 50% in untreated populations. The median duration of illness is approximately 7 days, quite unlike the 1- to 2-day course of *V. parahaemolyticus* infection.[15]

Despite the notoriety of the classic form of cholera, the CDC estimates that only 1 in 20 cases are associated with cholera gravis. A majority of affected patients experience a relatively mild diarrheal illness that may go undocumented. Cholera is extremely rare in the United States, even among returning travelers, with a documented incidence of 1 case per 1 million population annually.[36]

Another *Vibrio* species, *Vibrio vulnificus*, also is associated with eating raw seafood, especially raw oysters. *V. vulnificus* can cause self-limited gastroenteritis with onset approximately 16 hours after ingestion of contaminated food by healthy persons. In the compromised host, this organism causes serious wound infections after contact of seawater with open wounds, or a syndrome of primary septicemia characterized by hemorrhagic bullae of the skin and rapidly progressive septic shock. *V. vulnificus* infection is the leading cause of death in the United States associated with consumption of seafood. Septicemia carries a mortality rate of approximately 50% in patients with significant underlying disease, particularly chronic liver disease.[15] All patients with chronic liver disease, alcoholism, AIDS, other immunodeficiency states, and any significant chronic disease should be advised to avoid all raw shellfish.[37]

Diagnostic Strategies. Because these are noninvasive vibrios, unlike *V. parahaemolyticus*, stained fecal smears will not show leukocytes or erythrocytes. Stool cultures will quickly identify the organisms if plated on appropriate TCBS medium.[15]

Management. Patients with classic cholera often will lose enough fluids to require rehydration therapy. The World Health Organization oral rehydration formula has been used successfully to treat cholera worldwide.[7] The use of either oral or intravenous fluid hydration is dictated by the clinical picture. The role of antibiotics in the treatment of intestinal infections caused by noncholera vibrios is not clearly established. However, appropriate antibiotic regimens have been shown to decrease both the severity and the duration of cholera and may have the same effect on the diarrheal disease caused by these marine vibrios.[15] Choices include a single oral dose of either ciprofloxacin 1 g or doxycycline 300 mg; and a 3-day regimen of double-strength TMP-SMX twice a day.[3] Prevention, as with *V. parahaemolyticus* infection, depends on proper handling and avoidance of inadequately cooked seafood. Cholera is a nationally reportable infection.

A recently developed oral cholera vaccine is licensed and available in other countries. The oral vaccine appears to provide better immunity with fewer adverse effects than the previously available parenteral vaccine. The CDC does not recommend this vaccine for travelers, and it is not available in the United States.[36]

Scombroid Fish Poisoning

Epidemiology. Scombroid fish poisoning is a growing problem in the United States. The disease takes its name from the family Scombroidea (e.g., tuna, mackerel, skipjack, bonito, and related species) and results from the ingestion of a wide variety of dark-meat fish, including nonscombroid species such as herring, bluefish, anchovy, sardine, amberjack, black marlin, and mahi mahi. The fish species most commonly implicated are mahi mahi, tuna, and bluefish.[38] Restaurants serve these fish under various names such as mackerel, swordfish, bonito, dolphin, or amberjack, or they may make their appearance in the generic "tuna salad sandwich."

Most U.S. cases occur in Hawaii and Florida, followed in frequency by California, New York, Washington, and Connecticut. However, scombroid poisoning can occur in any location where "fresh fish" are flown in on a regular basis.

Pathophysiology. Implicated species naturally contain unusually high levels of histidine. Scombroid fish poisoning results from the ingestion of heat-stable toxins produced by bacterial action on the histidine present in the dark meat of the fish. The responsible bacteria are normal constituents of the surface marine flora, rather than contaminants. The histidine decarboxylase activity of these organisms produces histamine and histamine-like substances, which cause the symptoms of scombroid fish poisoning. High levels of histamine in the fish correlate directly with the occurrence of the illness. Formation of the scombrotoxins is directly related to improper preservation and refrigeration of the fish from the time they are caught until the time they are cooked. Generally, the problem is caused by improper refrigeration by the supplier, rather than being the fault of the restaurant serving the fish.

Clinical Presentation. The symptoms of scombroid fish poisoning resemble those of histamine intoxication. While eating the fish, the patient may note a metallic, bitter, or peppery taste, although many affected fish do not have an abnormal odor or taste. Symptoms usually develop abruptly within 20 to 30 minutes and consist of facial flushing, diarrhea, severe and throbbing headache, palpitations, and abdominal cramps. Other manifestations may include dizziness, dry mouth, nausea and vomiting, and urticaria. The facial flushing resembles a sunburn and can extend over the entire skin surface. The conjunctivae usually are injected. The duration of the major symptom complex generally is less than 6 hours, and although weakness and fatigue persist longer, the clinical course usually is benign. The attack rate is very high; most persons sharing the same toxic fish will become ill.

Management. Parenteral antihistamine therapy, such as diphenhydramine 50 mg IM or IV or cimetidine 300 mg IM or IV, usually promptly relieves all symptoms. Rarely, intravenous fluids are necessary. The disease is preventable if fish are properly handled, especially if they are refrigerated early and adequately. This is not an allergic reaction, so patients should not be told they are allergic to these fish, nor should they be prohibited from eating them again in the future.

Ciguatera Fish Poisoning

Epidemiology. Ciguatera fish poisoning is a common public health problem, with appreciable economic significance. It is endemic in tropical regions but is found worldwide. The CDC estimates that 50,000 to 100,000 people per year become ill from ciguatera poisoning.[38] Fish caught around Hawaii and Florida cause most of the cases, but because the responsible ocean fish are now commonly transported inland, cases can be seen virtually anywhere in the country.[38]

Ciguatoxin is produced by the marine dinoflagellate *Gambierdiscus toxicus*, which attaches itself to marine algae and is passed up the food chain. The lipid-soluble toxin accumulates in the tissues of the larger predacious coral reef fish, with the highest concentrations in the liver, intestines, head, and roe. It does not affect the fish in any way. Only humans suffer its ill effect when the toxin is ingested.

More than 400 fish species that frequent coral reefs have been implicated as ciguatoxin carriers, but fewer than 50 are commercially important. Those implicated in ciguatera poisoning include amberjack, barracuda, grouper, king mackerel, parrotfish, sea bass, snapper, sturgeon, surgeonfish, and ulua.[38]

Pathophysiology. Ciguatera fish poisoning results from the ingestion of the ciguatoxin neurotoxin. Ciguatoxin is heat- and acid-stable, odorless, and tasteless. It is not deactivated by cooking or freezing, nor is it eliminated by drying, salting, smoking, marinating, or pickling. It is not possible to predict whether a fish contains sufficient amounts of the toxin to produce illness.[39] Ciguatoxin has both anticholinesterase and cholinergic properties, but its neurotoxicity is mediated by its effect on sodium channels. Ciguatoxins cause a hyperpolarizing shift of the voltage dependence of channel activation such that sodium channels are open at resting membrane potential. Spontaneous firing of neurons occurs as tetrodotoxin-sensitive sodium channels are activated, giving rise to the typical neurologic signs and symptoms.[39]

Clinical Presentation. Ciguatera fish poisoning most commonly is seen in the spring and summer months. The incubation period is approximately 2 to 6 hours, but a delay of 12 to 24 hours is not unusual. Attack rates are very high; 80 to 90% of persons exposed become ill. Symptoms tend to be related to the amount of toxin ingested and vary considerably in their severity. If not fully recovered from an initial ingestion of ciguatoxin, affected persons are likely to have much more serious symptoms from a second ingestion.[39]

Classically, patients exhibit both gastrointestinal and neurologic symptoms. The gastrointestinal symptoms (e.g., nausea, vomiting, profuse watery diarrhea, crampy abdominal pain, and diaphoresis) tend to appear first and resolve over the first 24 hours. The constellation of neurologic symptoms consists largely of dysesthesias and paresthesias around the throat and the perioral area; "burning feet," which may resemble alcoholic peripheral neuropathy; "loose, painful teeth"; and sometimes central nervous system changes, such as ataxia, weakness, vertigo, visual hallucinations, and even confusion and coma.[39]

Distortion of temperature perception is vividly described by patients with ciguatera poisoning. *Cold allodynia*, defined as dysesthesia experienced on contact with cold water or cold objects, is almost pathognomonic of ciguatera poisoning and often is incorrectly referred to as "cold-hot temperature reversal." Another classic feature is either a return or a worsening of all of the symptoms after ingestion of alcohol.[39]

Ciguatera poisoning lasts an average of 1 to 2 weeks, but at least one half of its victims are still symptomatic at 8 weeks. The neurologic symptoms, particularly the paresthesias and dysesthesias, tend to persist longer than the gastrointestinal symptoms and have been reported up to years later.

Differential Considerations. Ciguatera fish poisoning should be strongly considered in patients with a combination of gastrointestinal and neurologic symptoms, particularly dysesthesias. Cold allodynia and marked worsening of the symptoms with alcohol ingestion are highly suggestive of ciguatera toxicity.

The disease sometimes is misdiagnosed as acute gastroenteritis with "hyperventilation syndrome" because of the combination of gastrointestinal symptoms and paresthesias, particularly when they occur about the mouth and acral areas. Similarly, manifestations of ciguatera toxicity sometimes have been ascribed to malingering because the paresthesias often are transient and vague and lack traditional dermatome patterns.

Other disorders that should be considered in the differential diagnosis include paralytic or neurotoxic shellfish poisoning, eosinophilic meningitis, botulism, organophosphate insecticide poisoning, and tetrodotoxin poisoning.[39]

Management. Treatment is primarily supportive. Intravenous fluids are given to replace volume losses from vomiting and diarrhea, and analgesics are given as needed. In severe cases, the toxin may exhibit some anticholinesterase activity, manifested as bradycardia and hypotension, which can be treated with atropine and dopamine. Patients must be told to abstain from alcohol in any amount until symptoms have completely resolved.

Pruritus may be managed with a histamine H_1 receptor antagonist such as cetirizine (Zyrtec) at a dosage of 10 mg once

daily. Amitriptyline, 25 mg twice a day, can bring about a dramatic reduction in both the pruritus and the dysesthesias, two of the most disturbing and protracted symptoms.

Intravenous mannitol has historically been an accepted treatment for ciguatera poisoning. The rationale for its use was based on data compiled from one uncontrolled study of 24 patients, one nonrandomized study, one nonblinded study, and anecdotal reports. More recently, a controlled, randomized double-blinded study of 50 adults found no difference in symptomatic improvement between patients who received normal saline and those who received mannitol. In addition, studies of ciguatoxin-intoxicated animals showed that mannitol did not reverse the effects of ciguatoxin. On the basis of this information, mannitol probably is not an effective therapy for ciguatera poisoning.[39]

Enterotoxigenic *Escherichia coli*

Epidemiology. Enterotoxin-producing *E. coli*, or enterotoxigenic *E. coli* (ETEC), is recognized as a major cause of acute diarrheal disease throughout most of the world. It is a major cause of diarrhea in persons traveling to underdeveloped areas. The disease has been most intensely studied in North American visitors to Latin America, where it occurs in 17 to 70% of travelers studied, often incapacitating them or forcing a change in their plans.[40] ETEC is increasingly recognized as a cause of food-borne illness in developed countries, including the United States.[41]

Infection is acquired from contaminated food or drink. Unpeeled fruits, leafy vegetables, unsanitary drinking water, and ice prepared from impure water are the most common sources. Most tourists are careful about their food and drink, but there seems to be a poor correlation between individual eating habits and the incidence of traveler's diarrhea.

Pathophysiology. For an *E. coli* strain to cause diarrhea, it must possess both a surface factor that allows colonization (although not invasion) of the small intestine and the ability to secrete an enterotoxin that causes the outpouring of fluids and electrolytes into the small bowel lumen. The enterotoxin-induced secretion occurs in the absence of any demonstrable histologic damage to intestinal epithelial cells or to the capillary endothelial cells.[42]

Escherichia coli produces both heat-labile and heat-stable toxins. The heat-labile enterotoxin is similar to cholera toxin in that it binds to specific receptors on the surface of the intestinal epithelial cell, allowing translocation of an A subunit into the cell. The A subunit modifies host cell signals, resulting in the dysregulation of sodium and chloride secretion, disturbances of ion transport, and intestinal water loss. The heat-stable toxin exerts its effect through the stimulation of guanylate cyclase in mucosal cells and tends to have a more rapid onset of action. Either or both toxins can be produced by any enterotoxic strain of *E. coli*. The intestinal fluid losses are qualitatively identical to those in cholera and other toxigenic diarrheas.[42]

Clinical Presentation. After an incubation period of 24 to 72 hours, an abrupt onset of watery diarrhea occurs. Severity varies, with the illness ranging from a fulminant, cholera-like disease to the much more common and milder *turista*, in which the symptoms of mild, watery diarrhea and abdominal cramps are more troublesome than life-threatening. Fever is unusual. Vomiting occurs in fewer than one half of affected adults and is seldom responsible for significant fluid losses. Even in severe cases, the diarrhea seldom lasts longer than 48 to 72 hours, and the response to either oral or intravenous fluids is uniformly good. Milder disease generally subsides more gradually, occasionally persisting for 1 week or longer. Virtually all persons recover completely without long-term sequelae.

E. coli enterotoxin–induced disease should be suspected when a child or adult has frequent, watery diarrhea and few other symptoms. It often is passed off as "mild, nonspecific gastroenteritis" and resolves spontaneously. Anyone who acquires toxigenic diarrhea while visiting a developing nation probably has this disease. ETEC is by far the most common cause of traveler's diarrhea.

Diagnostic Strategies. No easy, rapid means of laboratory diagnosis of ETEC infection exists. Methods that rely on identification of specific *E. coli* serotypes are unreliable because *E. coli* is part of the normal colonic flora, and its ability to produce enterotoxin is not restricted to any specific serotype. Methods based on detection of the heat-stable and heat-labile toxins using real-time PCR assay have been developed but are not clinically available. Stool preparations show no erythrocytes or leukocytes.

Management. Because ETEC infection is almost always a self-limited disease, no treatment other than maintaining hydration is required. However, if the organism is identified while symptoms are still active, or if the patient is traveling in an endemic area, antibiotics can give afford clinical relief. For milder symptoms, a single dose of ciprofloxacin 750 mg by mouth in addition to loperamide should be effective. For more severe symptoms, TMP-SMX 160 mg/800 mg or standard doses of a fluoroquinolone for 3 days should eradicate the organism.[3]

Clostridium difficile Antibiotic-Associated Enterocolitis

Epidemiology. *Clostridium difficile* is an anaerobic spore-forming gram-positive bacillus that was first linked to enteritis in 1978. It has been associated with a range of illnesses from asymptomatic colonization to severe diarrhea, pseudomembranous colitis, toxic megacolon, intestinal perforation, and death.[43] *C. difficile* can be cultured from the stool of up to 50% of healthy infants and approximately 3% of healthy adults.[7] The disease is unique in that an organism normally found in the colon causes illness primarily during or after the administration of antimicrobial agents. Colitis can occur as a result of oral or parenteral administration of most antimicrobial drugs, including quinolones, clindamycin, lincomycin, ampicillin, cephalosporins, tetracycline, penicillin, chloramphenicol, sulfa products, and erythromycin. Other risk factors, in addition to recent use of antimicrobials, include age older than 65 years, severe underlying illness, nasogastric intubation, use of antiulcer medications, and prolonged hospital stay.[43] Infection with this organism occurs primarily in adults. Most cases of *C. difficile* colitis occur in patients who are hospitalized or reside in long-term care facilities. Stool carriage rates reach 16 to 35% in hospitalized patients owing to transfer of organisms by the hands of hospital personnel or from patient to patient.[44] Occasional nosocomial infections occur in the absence of antibiotic therapy.[7]

During the past several years, an increase in the incidence and severity of *C. difficile*–associated colitis has been noted, along with recognition of a new strain designated NAP1/027 (toxinotype III, North American pulsed field gel electrophoresis type 1, PCR ribotype 027). This strain has been associated with outbreaks in Canada, Europe, and the United States. Data from the CDC indicate that hospitalizations with a discharge diagnosis of *C. difficile* colitis have increased, from 31 per 100,000 population in 1997 to 61 per 100,000 in 2003.[43]

Pathophysiology. *C. difficile* bacteria proliferate when the normal bowel flora is substantially reduced by antibiotic therapy. The organisms must then produce sufficient quantities of toxin for the disease to occur. *C. difficile*'s primary virulence factors are known as toxin A and toxin B. Toxin A attracts neutrophils

and monocytes, and toxin B disrupts colonic epithelial cells, both leading to watery diarrhea, colitis, and pseudomembrane formation. In persons who are colonized with *C. difficile* without experiencing colitis, higher levels of antibody to toxin A have been documented, and development of clinical disease is less likely. In those in whom colitis does develop, higher levels of anti–toxin A antibody are associated with a shorter duration of illness and decreased recurrence rate.[44] The incubation period has not been well established.[43]

On histologic examination, the mucosa is hyperemic and edematous. Raised, yellowish-white plaques, loosely adherent to the mucosa, occur in patches, primarily in the rectosigmoid area, but can occur in any part of the colon. The disease was previously named "pseudomembranous enterocolitis" because of these pseudomembrane-like plaques.

Clinical Presentation. Symptoms may appear during the course of antimicrobial therapy or commonly up to 3 or 4 weeks after discontinuation of antibiotics. Of interest, *C. difficile* has been reported to produce illness as late as 6 months after completion of antibiotic therapy. The clinical presentation is highly variable. Most often, patients present with mild to moderate nonbloody diarrhea associated with lower abdominal cramping and few systemic symptoms. Because the toxin alters the intestinal mucosa, the illness can manifest more like an invasive diarrhea than a toxigenic one, with fever, nausea, dehydration, severe crampy abdominal pain, distention, and profuse watery stools. Occult blood in the stool may be a feature, although hematochezia is uncommon. Fecal leukocytes usually are present. Children tend to have more severe infections than those seen in adults. *C. difficile* colitis is associated with a mortality rate of 6 to 30% when pseudomembranous colitis is present.[44]

Diagnostic Strategies. A variety of diagnostic tests are available for the detection of *C. difficile*. The historical "gold standard" modality is the cell cytotoxicity assay, in which stool is cultured on suitable medium and observed for the cytotoxic effect of toxin B. This test is 94 to 100% sensitive but requires 48 to 72 hours for completion. Stool toxin assays are now the primary method used to diagnose *C. difficile* infection.[7,43,44] Enzyme-linked immunosorbent assay (ELISA) for toxins A and B initially showed low sensitivity, but this has improved sufficiently that now most hospitals use ELISA testing, with a 2-hour turnaround time, as the preferred method. Stool cultures can confirm the presence of *C. difficile* in the feces of patients with antibiotic-associated enterocolitis (AAC). However, a positive stool culture result is not diagnostic because *C. difficile* often is present in the feces of normal subjects (especially infants) or in persons receiving antibiotics who do not have an enteritis. Cultures are seldom used clinically but often are part of epidemiologic studies.[7,43,44] In patients with typical history and physical examination findings, a tentative diagnosis can be made by sigmoidoscopy or colonoscopy.

Differential Considerations. It is important to differentiate *C. difficile* colitis from simple antibiotic-associated diarrhea. Three percent to 10% of all patients treated with antibiotics, particularly children, develop diarrhea not associated with *C. difficile* toxin. These patients experience mild, watery diarrhea and no associated constitutional symptoms or evidence of a cytopathic toxin–induced colitis.

Management. In early studies, 15 to 23% of patients who had *C. difficile* colitis experienced spontaneous resolution within 48 to 72 hours of discontinuing the offending antibiotic.[44] If discontinuing the antibiotic does not resolve the diarrhea, or if the diarrhea is severe, antibiotic treatment should be started promptly. Either oral metronidazole or oral vancomycin can be used. The dosage of metronidazole is 250 mg orally four times daily for 10 to 14 days. Metronidazole also is effective when administered by the intravenous route. Doses of vancomycin ranging from 125 to 500 mg orally four times daily have been equally effective.[44] Intravenous vancomycin generally is not effective because it does not reach effective intraluminal concentrations.

Initial trials comparing metronidazole and vancomycin found similar response rates of approximately 90%. In more recent studies, approximately 78% of patients treated with metronidazole had an initial response to therapy, and approximately one third of these had recurrence of disease, for an overall response rate of approximately 50%. Because vancomycin is much more expensive than metronidazole and because of concerns about emerging vancomycin resistance, oral metronidazole is the agent of choice for treatment in patients with mild disease, and oral vancomycin is reserved for patients who do not respond to metronidazole therapy or for those who are moderately to extremely ill at the time of presentation.[43]

Patients generally become afebrile and show clinical improvement within 36 to 72 hours; the diarrhea resolves over 5 to 7 days, even though results of toxin assays and stool cultures may remain positive for weeks. From 8 to 50% (average, 25%) of patients suffer a relapse regardless of the antibiotic chosen, its dosage, or the duration of treatment, and the recurrence rate is increasing. Risk factors for recurrent disease include new exposure to antibiotics, age older than 65 years, severity of underlying disease, low serum albumin, need for admission to an intensive care unit, and hospital stay of 16 to 30 days. Nearly all of these patients will respond to another course of antibiotic therapy.[44]

Adding the yeast *Saccharomyces boulardii*, 500 mg orally twice daily for 4 weeks, to antibiotic treatment has been shown to dramatically decrease the number of recurrences of *C. difficile*–associated disease in patients with previous episodes. However, no benefit is seen when *S. boulardii* is given to patients with an initial episode.[44] No serious adverse reactions have occurred with the use of *S. boulardii*.[44]

Although toxicity from parenteral vancomycin is common, no adverse effects have been reported with its oral use in the treatment of *C. difficile* colitis. Antimotility or constipating agents are contraindicated in these patients because of the risk of toxic megacolon and the possibility of increasing the level of cytopathic toxin in the colon.[44]

ACUTE VIRAL GASTROENTERITIS

Etiology and Epidemiology. Viral gastroenteritis is the second leading cause of illness in the United States. Although several virus families have been implicated, including caliciviruses, coronaviruses, and parvoviruses, two have predominated in the past decade. Noroviruses, which include the Norwalk virus, are primarily responsible for disease in adults and older children, whereas human reovirus–like agents, also called *rotaviruses*, cause most diarrheal disease in infants and young children. Worldwide, rotavirus infection causes 600,000 to 875,000 deaths annually and is responsible for 6% of deaths in children younger than 5 years of age. In the United States, rotavirus infection is the leading cause of hospitalization for gastroenteritis and precipitates 600,000 physician visits, 50,000 admissions, and approximately 20 deaths each year. Rotaviruses also cause epidemics in adults, especially those in contact with sick children.[7]

These viruses have a low infectious dose, and attack rates may reach 50%. The incubation period is short, so explosive outbreaks are common. Norovirus is transmitted by several routes and is relatively stable in the environment, making this infection particularly prone to spread of infection. It is esti-

mated that noroviruses are responsible for 68 to 80% of all outbreaks of gastroenteritis in industrialized countries.[7] Both viruses can be transmitted from person to person by the fecal-oral route, but water- or food-borne outbreaks also are common. Sources in large reported outbreaks of norovirus infection have included municipal or semipublic water supplies, bodies of water used in recreational swimming, stored water on cruise ships, cafeteria sandwiches, food handlers, and shellfish.[7,45] The ingestion of raw oysters has caused many large outbreaks. The CDC estimates that 50% of all food-borne outbreaks of gastroenteritis are attributable to noroviruses.[7] Nosocomial spread of infection also is common. Astrovirus and picornaviruses are common causes of diarrhea in HIV-infected patients.[7]

Pathophysiology. Viruses distort the absorptive cells of the microvilli of the small bowel, decreasing their absorptive surface and causing diarrhea from decreased absorption of fluid and electrolytes. Viral nonstructural proteins also may act as enterotoxins, promoting active chloride secretion into the bowel lumen. The histologic picture resembles that with tropical sprue, and transient malabsorption of fats and sugars, which may persist for a week or more after infection, occurs in patients with viral gastroenteritis.[45]

Diarrheal stools in viral disease contain more sodium, chloride, and bicarbonate than do normal stools, but these abnormalities are not comparable with the almost isotonic fluid loss of bacterial toxin–induced diarrhea. Potassium loss usually is not significant unless symptoms are prolonged.

Clinical Presentation. Viral gastroenteritis occurs primarily in two epidemiologically distinct clinical forms. Outbreaks caused by rotaviruses usually are sporadic, occasionally are epidemic, and typically occur in the winter months in infants and children 6 to 24 months of age. The incubation period is 24 to 72 hours, followed by abrupt onset of vomiting, watery diarrhea, and low-grade fever but little or no associated abdominal pain. Vomiting is a prominent and constant early manifestation of rotavirus enteritis but rarely persists beyond the first 36 hours. The diarrhea generally lasts for 4 to 7 days and may be followed by steatorrhea in approximately 20 to 40% of patients. Many children become significantly dehydrated, requiring hospitalization and intravenous fluid replacement, but the disease rarely is life-threatening in developed countries.

Overt clinical disease can occur among family and adult contacts of ill children, but it is uncommon. Most adults with rotavirus infections are asymptomatic. When symptoms do occur, they usually are mild, perhaps because these episodes represent reinfections; 60 to 90% of older children and adults have antibodies to rotaviruses.[45]

The second clinical entity is characteristically epidemic and is responsible for family and community-wide outbreaks of gastroenteritis among school-aged children, family contacts, and adults. This form generally is caused by the Norwalk virus. After an incubation period of 20 to 36 hours, diarrhea, nausea, and mild abdominal cramps occur. Vomiting is not prominent. Fever typically is absent. Anorexia, headache, malaise, and myalgias may be present. The illness is self-limited, usually lasting only 24 to 48 hours. Most affected adults have mild symptoms and do not seek medical attention.[7,45]

Diagnostic Strategies. The diagnosis of rotavirus gastroenteritis should be considered in children with significant vomiting, diarrhea, low-grade fever, moderate dehydration, and a normal white blood cell count, especially in those 6 to 24 months of age who become symptomatic during the winter months. An elevated blood urea nitrogen level and a compensated metabolic acidosis are common findings. Serum electrolyte studies indicate that the dehydration usually is isotonic.

In adults, the diagnosis of viral gastroenteritis usually is one of exclusion. Viral enteritis is the likely diagnosis when a patient has mild intestinal symptoms, does not appear ill, and further history and physical examination uncover no reason to suspect a bacterial pathogen, inflammatory disease, or any other cause. No investigation beyond the physical examination usually is required. Some of these patients may actually have mild bacterial infections, but these also generally are self-limited, and treatment is not different.

A laboratory diagnosis can be made by demonstration of the viruses in stools by electron microscopy or various methods used for the detection of viral antigens, such as latex agglutination, ELISA, or reverse transcriptase–PCR techniques. With rotavirus illness, large numbers of viruses are present in the stools, and these antigen detection methods are quite sensitive and specific. Rotavirus testing probably is indicated only in more serious cases of diarrhea. Fecal leukocytes and erythrocytes are not found in cases of viral gastroenteritis.[7]

Management. The most important aspect of therapy for acute viral gastroenteritis is fluid replacement. Many children require hospitalization for intravenous fluid and electrolyte repletion. No specific antiviral therapy is indicated. Use of antidiarrheal agents is not recommended in children. In adults, they generally are not needed but may provide some symptomatic relief. Because viral spread is primarily by the fecal-oral route, scrupulous hand washing and other hygienic practices are the best preventive measures.

A live tetravalent vaccine against rotavirus was approved for use in infants in 1998 but was withdrawn from the market in 1999 owing to a temporal association with intussusception. Rotateq is a newer oral, liquid live pentavalent vaccine that was licensed in the United States in 2006 and is now part of the annual recommended immunization schedule for all infants at ages 2, 4, and 6 months.

PARASITIC GASTROINTESTINAL INFECTION

Organisms that commonly cause protozoal enteritis are summarized in Table 92-4. As a group, parasitic pathogens are associated with more prolonged illness than that characteristic for bacterial or viral pathogens. The clinician should consider the possibility of a parasitic infection in patients with diarrhea that persists for longer than 2 weeks, especially in immunocompromised persons, travelers, and residents of developing countries.

Coccidial Infections

Cryptosporidium and *Isospora belli* Infections

Epidemiology. *Cryptosporidium* and *Isospora* are intestinal protozoal parasites that commonly cause diarrhea in the young of many animal species. In humans, cryptosporidiosis is a worldwide problem, most often seen in persons who handle animals, children in day care centers, healthy homosexual men, and immunocompromised patients.[7,46] *Cryptosporidium* has been the most common cause of chronic diarrhea in persons with AIDS, although the incidence has decreased in the U.S. AIDS population with the use of highly active antiretroviral therapy (HAART).[47] Congenital immunodeficiency and treatment with cancer chemotherapeutics or other immunosuppressive drugs are additional predisposing factors. The organism is highly infectious and is easily transmitted among nosocomial, household, and day care contacts or in any facility in which personal hygiene is poor.[47] In addition to zoonotic and person-to-person spread, indirect transmission occurs by exposure to

Table 92-4 Epidemiologic Aspects of Protozoal Gastroenteritis

PATHOGEN	SOURCES/RISK FACTORS OR GROUPS	INCUBATION PERIOD (I)	FEATURES
Entamoeba histolytica	Fecally contaminated food and water sources	3 wk to 4 mo	Infection may be commensal or intermittently symptomatic or produce severe dysentery
Giardia lamblia	Water-borne organisms, fecal-oral contact, day care centers, travelers, backpackers, AIDS, homosexual men	1-3 wk	5-10% of U.S. population, malabsorption syndromes or commensal
Coccidia			
Cryptosporidium and *Isospora*	Fecal-oral contact, water-borne organisms, animals, day care centers, AIDS	5-10 days	Profuse watery diarrhea, self-limited in the immunocompetent, persistent in the immunocompromised
Cyclospora cayetanensis	Fresh fruit, berries, lettuce, water supply	1 wk	Explosive, protracted, watery diarrhea; fatigue, weight loss
Strongyloides stercoralis	Occupational exposure to soil, travel to endemic areas in United States (Kentucky, Tennessee, West Virginia) or overseas	Weeks to months	Eosinophilia, sepsis, and hyperinfection syndrome in AIDS patients
Enteromonas hominis	Fecal-oral contact, homosexual men	?	Chronic watery diarrhea, especially in children

AIDS, acquired immunodeficiency syndrome.

fecally contaminated environmental surfaces, toys, food, and recreational water.[47] *Cryptosporidium* oocysts are highly resistant to chlorine and common disinfectants. Large outbreaks have originated from community swimming pools.[46]

The oocysts also are small (2 to 6 µm in diameter) and may not be removed from contaminated water by standard filtration systems used in the treatment of public water supplies. Ingestion of as few as 10 to 20 oocysts can cause illness in healthy persons. In a recent report, thousands of people contracted cryptosporidiosis from contamination of filtered public water systems that met federal and state standards for drinking water.[46] Contamination of rivers and streams by *Cryptosporidium* has been reported in a number of states.[47] In children, cryptosporidiosis is more common in the late summer and early fall and often is associated with intestinal infection with other organisms, particularly *Giardia*.

Isosporiasis generally is an opportunistic infection. It occurs primarily in patients with AIDS, especially Haitians with AIDS, and in homosexual men. In the homosexual community, isosporiasis is a sexually transmitted disease similar to giardiasis and amebiasis.[48]

Pathophysiology. The pathophysiology is the same for both *Cryptosporidium* and *Isospora*. Disease is acquired by ingestion of oocysts. Excystation occurs, and sporozoites attach to the surface of intestinal epithelial cells of the terminal ileum and proximal colon; no tissue invasion occurs. Profuse fluid loss results from a combination of active chloride secretion and malabsorption. A specific enterotoxin has not been identified, although up-regulation of a variety of proinflammatory cytokines, chemokines, and neuropeptides has been observed. In cryptosporidiosis, a biliary reservoir may contribute to chronicity of the infection and inability to eradicate the organism.[46]

Clinical Presentation. The clinical presentations of cryptosporidiosis and of isosporiasis are indistinguishable and highly variable. After an incubation period of approximately 1 week, symptoms may develop insidiously or suddenly. Infection is characterized by mild to profuse watery diarrhea, crampy abdominal pain, anorexia, nausea, malaise, weight loss, and flatulence. The diarrhea and abdominal pain often are exacerbated by eating. Immunocompromised patients (especially HIV-infected patients with $CD4^+$ counts less than 200/mm^3) can experience enormous stool fluid losses: 3 to 4 L/day is common, and losses may reach 10 to 20 L/day. Physical examination usually reveals only signs of dehydration. Minimal diffuse abdominal tenderness may be elicited by palpation, and fever and leukocytosis are uncommon. Eosinophilia is not a feature. Findings on stool examination for blood or leukocytes are almost uniformly negative in adults but occasionally are positive in children.[46,47]

The patient's immune status is the primary determinant of whether the infection is self-limited or persistent. Diarrhea in immunocompetent persons usually resolves after 1 to 3 weeks, but it can continue longer or become chronic. In immunodeficient patients, especially those with AIDS, chronic, persistent diarrhea is common, causing significant discomfort and morbidity unless the infection is responsive to treatment.[7,46,47]

Asymptomatic infections can occur from either *Cryptosporidium* or *Isospora*, and a carrier state has been demonstrated for *Cryptosporidium*.[47] In a U.S. study of immunocompetent patients who underwent upper endoscopy for a variety of reasons, 13% were found to harbor cryptosporidia in the second portion of the duodenum. None of the patients had diarrhea.

Diagnostic Strategies. The diagnosis of coccidial infection with either *Cryptosporidium* or *Isospora* is made by documenting the oocysts in the stool. Yeasts are similar in size and shape to coccidia but are not acid-fast. Before the development of antigen-based assays, acid-fast staining techniques were the preferred means of diagnosis. Such methods are insensitive for the diagnosis of cryptosporidiosis and require a high oocyst concentration and an experienced examiner. Immunofluorescent assays using monoclonal antibodies to the *Cryptosporidium* oocyst are commonly used and are 10 times more sensitive than acid-fast staining. ELISA-based detection kits also are commercially available, highly sensitive, and easy to use. Sensitivities and specificities of 94 to 100% have been documented

in several studies. A PCR-based assay for *Cryptosporidium* has been developed but is not yet available in clinical laboratories.[7,46]

Management. In immunocompetent persons, *Cryptosporidium* infection generally is self-limited; symptomatic therapy and fluid replacement are sufficient. Initial management should focus on replacement of fluid and electrolytes, by the oral route if possible. Antimotility agents such as loperamide or the combination diphenoxylate/atropine (Lomotil) can decrease stool output in persons with mild to moderate illness. For immunocompetent patients with persistent disease, nitazoxanide 100 to 500 mg every 12 hours has been approved by the U.S. Food and Drug Administration (FDA) and has proved to be effective in adults and children older than 1 year of age.[46] Immunocompetent patients shed oocysts in the stools when symptomatic and continue to do so for up to 6 weeks after resolution of their clinical illness, creating a public health risk. Oocyte shedding resolves more rapidly in those treated with nitazoxazide.[46]

Treatment of cryptosporidiosis in immunocompromised patients is more challenging. The most successful interventions occur when the underlying immunodeficiency can be reversed. In patients taking immunosuppressive agents, immune function generally recovers if the drugs can be discontinued. Patients with AIDS and $CD4^+$ counts below 200/μL sometimes respond dramatically if immune function is restored through institution of HAART. [46] Patients severely infected with *Cryptosporidium* often are fecally incontinent, with large numbers of infectious oocysts in the stool, so strict enteric precautions are necessary to prevent nosocomial spread. If enhancing the immune system fails and symptoms continue to be severe, nitazoxanide 0.5 to 1 g twice daily combined with antidiarrheals may be used, although evidence is lacking for the efficacy of nitazoxanide in HIV-infected patients. Paromomycin (Humatin, 500 to 750 mg three or four times daily) also is sometimes used to ameliorate cryptosporidiosis, particularly in combination with azithromycin, but no good evidence exists that these drugs are routinely effective.[46]

In contrast with cryptosporidiosis, isosporiasis responds promptly to antibiotic therapy. The treatment regimen of choice for isosporiasis in immunocompetent adults is TMP-SMX 160 mg, 800 mg twice daily for 10 days. In immunocompromised adults, the dosage is increased to four times daily for 10 days and then extended with twice-daily dosing for 3 weeks. In patients with sulfonamide sensitivity, pyrimethamine 50 to 75 mg daily may be effective.[3] Chronic suppressive therapy with either twice-daily doses of TMP-SMX or daily doses of pyrimethamine often is required, because *Isospora* infection recurs in more than 50% of patients.[3]

Patients seen in the ED in whom stool examination for parasites later reveals *Cryptosporidium* or *Isospora* should be contacted for appropriate management. Recovering patients require only an explanation of the diagnosis and its ramifications. Patients who are not recovering and those who are known or thought to be immunosuppressed should receive appropriate treatment and referral for follow-up care. Cryptosporidiosis is a nationally notifiable disease.

Cyclospora cayetanensis Infection

Epidemiology. *Cyclospora* is a coccidial parasite widely distributed throughout tropical and subtropical areas of the world that produces disease similar to that caused by *Cryptosporidium* and *Isospora*. In Nepal, *Cyclospora* organisms have been found in up to 11% of patients with diarrheal disease.[49] North American outbreaks have been traced to contaminated foods, primarily fresh fruit such as raspberries grown in Guatemala, fresh salads containing snow peas from Guatemala, fresh basil preparations, and mesclun lettuce; foreign travel; and contaminated water supplies.[50] *Cyclospora* infects all classes of vertebrates, reptiles, and rodents, and the vast majority of cases occur during the spring and summer seasons, often in large outbreaks.

Pathophysiology. The exact mode of *Cyclospora* transmission and mechanism of disease is not completely understood. The organism passes from the human gastrointestinal tract as an oocyst that must sporulate in order to become infective. Sporulation requires several days to weeks outside the human host; therefore, the disease is not transmitted from person to person and is not likely to be transmitted by infected food handlers. Recent work in Nepal suggests that domestic pets and farm animals may serve as intermediate hosts.[51] Histologic examination shows flattening of the villi and thickening of the basement membrane in the duodenum with intracellular parasites identified in jejunal biopsies, but it is unknown whether symptoms are toxin-induced or secondary to direct infection of the small bowel.[50] As with other parasitic diseases, immunocompromised patients are affected more frequently than immunocompetent hosts.[51]

Clinical Presentation. The average incubation period is 1 week.[50] Typically, the patient presents with an acute onset of explosive watery diarrhea and abdominal cramps. Thirty percent of patients report fever during this initial phase. Severe diarrhea subsides within 1 to 3 days and is followed by a period of intermittent mild diarrhea and marked anorexia and fatigue, which distinguishes this from other parasitic disorders. Weight loss is almost invariable, as is malabsorption of D-xylose.[50] Constitutional symptoms are relatively mild, and fever is uncommon. Fecal leukocytes are absent. The disease generally is self-limited in immunocompetent persons but may last as long as 2 to 6 weeks, and relapsing diarrhea is common. Sustained fatigue and weight loss are especially characteristic of cyclosporiasis. These findings are noted in approximately 90% of patients and should prompt consideration of the diagnosis in the setting of outbreaks or history of foreign travel.[51]

Diagnostic Strategies. The clinical picture may be suggestive, but finding oocysts in the stool is required to confirm the diagnosis. Stool specimens submitted for ova and parasite testing are not routinely examined for *Cyclospora* unless specifically requested. The oocysts measure 8 to 10 μm in diameter, approximately twice the size of *Cryptosporidium* oocysts. Oocysts can be identified by modified acid-fast stain, yet the inexperienced microscopist may overlook them or find *Cyclospora* difficult to distinguish from *Cryptosporidium*. False-negative and false-positive results on microscopic examination are common. Microscopic examination is greatly facilitated by stool concentration techniques.[50] *Cyclospora* also can be identified by stool PCR testing, although this technique is not widely available in U.S. hospitals.

Differential Considerations. The primary confusing organism is *Cryptosporidium*, because the symptoms of infection with the two pathogens often are indistinguishable. *Cryptosporidium* tends to be associated with animal contact, exposure in day care centers, and immunocompromised status. *Aeromonas hydrophila* infection also should be considered in the differential diagnosis.

Management. The disease tends to be self-limited in immunocompetent persons, but treatment with sulfa medications is very effective for cyclosporiasis, in contrast with cryptosporidiosis. The drug regimen of choice consists of double-strength TMP-SMX one tablet twice daily for 7 days in immunocompetent patients, and one tablet four times daily for 10 days, followed by one tablet three times per week, in patients with AIDS. The pediatric dose is TMP 5 mg/kg plus SMX

25 mg/kg twice daily for 7 days. Thorough washing of fresh produce before consumption decreases but does not eliminate the risk of transmission. Irradiation may be a future solution.[3,50,51] Cyclosporiasis is a reportable disease.

Giardiasis

Epidemiology. *Giardia* is one of the most common causes of parasitic diarrheal outbreaks in the United States.[7,46] The mode of transmission in large outbreaks is contamination of municipal water supplies with cyst-infested feces from humans or animals, particularly beavers or muskrats, but also dogs, raccoons, and other animals. Campers and backpackers commonly acquire giardiasis, called "backpacker's diarrhea," from drinking fecally contaminated water from the "pristine" mountain streams.[46] Only rarely is *Giardia* infection transmitted by contaminated food.

Giardia can be spread by sexual or other close person-to-person contact in which fecal contamination may occur, particularly among homosexual men, and in day care centers and institutions for the mentally challenged. The prevalence is 4 to 7% in the general U.S. population, 5 to 20% in homosexual men, and 25 to 50% in children attending day care centers.[46]

Many cases of acute symptomatic giardiasis in the United States are found in persons returning home from travel elsewhere. Travelers to any developing country can acquire giardiasis, but it is especially feared in those who visit the republics of the former Soviet Union, the Caribbean states, and Latin America, where the water supplies appear to be heavily contaminated with *Giardia* cysts.[52] Small groups traveling to the former Soviet Union, particularly the city of Leningrad, have experienced attack rates approaching 60%, and the disease is ruefully known among its victims as "the Trotskys." More recently, a Swedish study of giardiasis in returning travelers found that highest attack rates occurred in those returning from the Indian subcontinent, east Africa, and west Africa.[53]

Patients with decreased gastric acidity, for any reason, are more susceptible to *Giardia* infection. Giardiasis also is more frequent in patients with various immunoglobulin deficiencies; a relative deficiency of intestinal immunoglobulin A (IgA) may be the reason.

Pathophysiology. *Giardia* trophozoites infect the duodenum, jejunum, and upper ileum. Encystation occurs in the gut lumen, and cysts passed in the feces remain viable for long periods. After the cysts are ingested by the next host, excystation to the active trophozoites occurs in the proximal small bowel, completing the parasite's life cycle. The trophozoites multiply rapidly. A single diarrheal stool may contain billions of parasites or hundreds of millions of cysts. The trophozoites are capable of superficial invasion of the mucosa, but malabsorption probably causes most symptoms.

Clinical Presentation. Many patients harboring *Giardia* are asymptomatic. The most common symptoms of acute infection are abdominal distention (69%), colicky pain (70%), flatulence (74%), and frequent episodes of explosive diarrhea (89%) producing pale, loose stools that often are offensive-smelling. Audible borborygmi is a classic feature. The serum white blood count usually is normal, and eosinophilia is not seen. The onset typically is sudden, following an incubation period of 1 to 3 weeks. Symptoms may resolve within 7 to 10 days or continue intermittently and produce a malabsorption-like illness, particularly in patients with an immunoglobulin deficiency. The infection resolves spontaneously within 6 weeks in 85% of patients.

Diagnostic Strategies. Routine tests (e.g., blood counts, electrolyte panel, radiographic studies) generally are not helpful. Eosinophilia is not seen. Stool examination is the primary means of diagnosis. In the acute phase of *Giardia* infection, rapid bowel transit allows trophozoites as well as the more hardy cystic form of the parasite to appear in the stool. Trained observers using standard stool examination techniques will readily identify *Giardia* in more than 95% of acute cases if three or more stool specimens are studied. Detecting *Giardia* in cases of subacute, chronic, or asymptomatic infection, however, can be difficult. The trophozoites may be passed only intermittently and in small numbers. Concentration techniques should be used to improve the chance of finding the cysts in the stools. Diagnosis may require small bowel sampling techniques such as duodenal-jejunal aspiration by endoscopy or biopsy of duodenal-jejunal tissue. *Giardia* antigen tests using immunofluorescence ELISA, nonenzymatic immunoassays, or direct fluorescent antibody (DFA) techniques are replacing microscopic examination as the strategy of choice. The per-specimen cost is similar to that for microscopy; sensitivity is 85 to 98% and specificity 90 to 100%.[46]

Differential Considerations. *Enteromonas hominis*, a flagellate parasite like *Giardia*, can produce an intestinal infection that mimics giardiasis. *Enteromonas* infection most commonly affects children and homosexual men. Even when all techniques fail to confirm a clinically suspected case of giardiasis, an empirical diagnosis can be supported by a successful trial of appropriate antibiotics.

Management. The treatment regimen of choice has historically been metronidazole, a 5-nitroimidazole drug, 250 mg three times daily for 7 days for adults or 5 mg/kg three times daily (maximum 250 mg three times daily) for 7 days for children.[3,46] Metronidazole has an efficacy rate of 80 to 95%. Tinidazole is another 5-nitroimidazole agent that is FDA approved for the treatment of giardiasis. Some experts consider tinidazole a first-line agent because it can be given as single-dose therapy. When given in a single 2-g dose (50 mg/kg in children), tinidazole achieves a cure rate of approximately 90%. Furazolidone is the only alternative drug available as a suspension, which may be helpful in treating children. Its cure rates average only 80%, however. The recommended dosage is 100 mg four times daily for adults or 1.5 mg/kg four times daily for children, up to the adult dose, for a total of 7 to 10 days. Nausea and vomiting are common side effects, and rarely a hemolytic anemia develops in patients with glucose-6-phosphate dehydrogenase deficiency.[46]

Treatment of asymptomatic infections is controversial and best determined on a case-by-case basis. Asymptomatic cyst passers, especially children and food handlers, pose a threat of infection to others and are at risk for the development of intermittent chronic symptoms. Treatment of asymptomatic carriers can theoretically reduce the risk of spread. In heavily infected endemic populations, reinfection is practically universal after 3 months, and treatment is not useful or cost-effective.[54]

Giardiasis must be considered a family infection. Strict adherence to hand washing is important, especially after using the toilet, playing with pets, or changing diapers. To prevent reinfections, other household members and sexual contacts should be examined and, if found to harbor the parasite, treated appropriately.[46]

Acute Intestinal Amebiasis

Epidemiology. *Entamoeba histolytica* is a ubiquitous organism infecting at least 10% of the world's population but originally thought to cause clinical disease in only 10% of persons who carry it. This number probably is an underestimate, however, because recent studies have confirmed the presence

of a morphologically indistinguishable ameba, *E. dispar*, as a separate nonpathogenic species that also colonizes the human gut and probably is responsible for a majority of asymptomatic infections originally attributed to *E. histolytica*. Distinguishing between the two organisms can be accomplished using ELISA or PCR assay, with PCR testing slightly more reliable.[55] Worldwide, approximately 50 million symptomatic cases occur each year, resulting in 100,000 fatalities. In the United States, high-risk groups include travelers, homosexual men, patients with AIDS, and institutionalized persons. Most cases acquired in the United States are asymptomatic; acute amebic dysentery is rare and most often occurs in travelers returning from developing countries in which the disease is endemic.[56,57]

Entamoeba histolytica exists in trophozoite and cystic forms. The trophozoites infect the colon and may produce symptomatic disease. Infectious cysts are passed in the stool and are highly resistant to environmental factors. Transmission usually occurs through ingestion of cysts present in fecally contaminated food or water. Homosexual men commonly acquire amebic infection from cysts ingested through anal-oral sexual practices. When these patients present with diarrhea, a diligent search for other organisms should be completed before symptoms are ascribed to amebic infection. Co-infection with other enteric pathogens occurs frequently in homosexual men.[56,57]

Pathophysiology. The factors that determine whether infection with *E. histolytica* will be commensal or invasive are poorly understood. Variable strain virulence and host susceptibility are determinants. In young children, pregnant women, persons with malnutrition or underlying systemic disease, or persons taking corticosteroids, amebiasis often is more fulminant.[57]

Invasive trophozoites characteristically produce colonic ulcerations that on histologic examination are seen to have rounded or punched-out margins and are elevated by a submucosal inflammatory reaction from the advancing trophozoites. The ulcer bases are covered with whitish or yellowish exudate. Usually, no diffuse mucosal inflammation exists in areas between ulcers. Should diffuse inflammation occur, however, the picture becomes indistinguishable from that of idiopathic ulcerative colitis or Crohn's disease. Less than 1% of infections will spread outside the intestines. Gastrointestinal complications can include severe bleeding, toxic megacolon, intussusception, stricture, obstruction, and perforation. Extraintestinal complications include liver and brain infection, as well as pleural or pericardial effusions.[55,57]

Clinical Presentation. In many patients, *E. histolytica* lives as a commensal, without producing symptoms. Acute amebic dysentery manifests after an incubation period as short as 1 week or as long as 1 year. The onset is abrupt, with fever; severe abdominal cramps; profuse, bloody diarrhea; and tenesmus. Chronic amebic colitis is the common symptomatic form, for which the onset is gradual. Usually, intermittent diarrhea is present, with two to four foul-smelling stools daily, often containing blood-streaked mucus. Vague abdominal cramps, flatulence, weight loss, and low-grade fever are present. Symptomatic periods may alternate with asymptomatic periods lasting for months to years. The only physical finding may be slight right lower quadrant tenderness to palpation and occasional tender hepatomegaly. The diagnosis is elusive because cysts or trophozoites are difficult to detect; inflammatory bowel disease is a common misdiagnosis, and steroid therapy may exacerbate the symptoms.[57]

The stools of patients with symptoms contain mucus and leukocytes, although not in large quantity and numbers. Eosinophilia is not seen except in rare cases of ameboma. Liver function test results generally are normal unless the disease is complicated by liver abscess, which is the most common serious complication of amebic colitis.[56]

Diagnostic Strategies. Definitive diagnosis of intestinal amebiasis historically relied on microscopic identification of the organisms in the stools. Microscopic examination limited to a single stool sample can miss almost one half of infections; at least three fresh samples should be submitted. The examination must precede the administration of antibiotics, antidiarrheal agents, antacids, or enemas, or before the performance of radiographic procedures using barium sulfate. All of these agents destroy trophozoites or distort cysts, thereby interfering with the recovery of amebas. A rectal biopsy specimen or mucosal exudate obtained at sigmoidoscopy may reveal the amebas, even when multiple previous stool examinations have yielded negative results. To obtain mucosal exudate, a glass or metal pipette must be used, because amebas adhere to cotton swabs. Microscopy cannot distinguish *Entamoeba histolytica* from the nonpathogenic *E. dispar*. The presence of amebas on stool microscopy in an asymptomatic patient should suggest the presence of nonpathogenic *E. dispar*; treatment is not indicated.[55]

The diagnosis of amebiasis has been greatly improved by the development of stool antigen assays. Monoclonal antibody–based enzyme immunoassay for *E. histolytica* antigens has a sensitivity and specificity of approximately 95% and can distinguish *E. histolytica* from *E. dispar*. PCR techniques also have been developed but are not clinically available.[55,57]

Serologic tests are quite sensitive and specific for active amebic infection. Because administration of steroids to patients with amebic colitis is potentially fatal, and because identification of the parasite in stools is difficult, a serologic test for amebiasis should be done in all newly diagnosed cases of inflammatory bowel disease before initiation of steroid therapy.[57]

Differential Considerations. Amebiasis should always be considered in cases of acute dysentery-like colitis and in the differential diagnosis for any chronic diarrhea, especially when the stool contains blood-streaked mucus. Amebiasis also should be suspected in homosexual men with acute or chronic colitis. Among patients with AIDS, however, amebic dysentery is rare.[58] Patients with nondysenteric amebiasis often are misdiagnosed as having irritable bowel syndrome, diverticulitis, or regional enteritis.

Management. Substantial controversy previously existed over whether asymptomatic cyst passers should be treated. Today, however, advances in testing permit distinction between nonpathogenic *E. dispar* and *E. histolytica*, so an accurate diagnosis is now possible. Accordingly, it seems prudent to treat for *E. histolytica* infection in all patients in whom this organism is detected, even asymptomatic carriers. If only *E. dispar* is identified, treatment is unnecessary. When differentiation is not possible and the patient is asymptomatic, treatment is not recommended unless the clinical picture suggests an increased likelihood of *E. histolytica* infection. Such would be the case with patients with high specific antibody titers, a history of close contact with a patient with invasive amebiasis, or a patient with symptoms during an outbreak of amebiasis. In symptomatic patients who are diagnosed with *E. histolytica* or *E. dispar* infection, other pathogens should be ruled out before *E. histolytica* can be assumed to be the cause.[55]

For treatment of benign cyst passers, paromycin (aminosidine) 500 mg orally three times a day for 7 days should be effective. Other regimens include oral iodoquinol, 650 mg orally three times a day for 20 days, and diloxanide furoate, 500 mg orally three times a day for 10 days. For mild to moderate intestinal infection, metronidazole is added (see Table 92-2).[57] Treatment with metronidazole should precede treat-

ment with aminosidine. Aminosidine can cause diarrhea as a side effect, making it difficult to assess the patient's response to the metronidazole if both agents are given together.[59] Patients with severe infections and systemic illness such as dehydration or hypotension should be hospitalized. Therapy usually is effective, but relapses can occur. Standard precautions to prevent fecal-oral spread are the best preventive measures.

Enterobiasis

Epidemiology. *Enterobius vermicularis*, also known as *pinworm* or *seatworm*, is perhaps the most prevalent parasite in the United States. It is estimated that 20 to 30% of all children are infected with pinworms; 200 million people are infected annually worldwide, 40 million in the United States alone. Adult worms are small, spindle-shaped, white to yellowish roundworms that live in the cecum and adjacent portions of the large and small bowel. The female averages 10 mm in length, and the male is 3 mm long. The gravid female migrates through the anal canal at night and oviposits her eggs (up to 50,000) onto the perineal area. The eggs become infective larvae 4 to 6 hours after deposition. Once ingested, the eggs hatch in the duodenum, and the larvae mature as they migrate down to the cecum. Approximately 1 month from the time of ingestion, newly developed, gravid females are again discharging eggs.[57]

The human body is the only natural host of *E. vermicularis*. The most common means of infection, particularly in children, is by the direct transfer of eggs from the anus to the mouth on contaminated fingers. Retrograde infection, seen primarily in adults, may sometimes occur. In such cases, larvae hatch in the perineal region, reenter the anus, and migrate to the cecum. Spread within family and children's groups occurs readily, either by direct transfer of eggs or by airborne transmission. The eggs, which are relatively resistant to desiccation, also contaminate night clothes and bed linens, where they remain viable and infective for 2 to 3 weeks.

Pathophysiology. Because *E. vermicularis* does not penetrate the mucosa, no specific anatomic lesions are initially seen. The movement of the worms or the presence of the eggs on the perineum usually causes local tingling or itching. Scratching causes irritation of the skin, which can lead to excoriations, eczematous dermatitis, and secondary bacterial infections. In women, gravid female worms can migrate through the vagina and uterus into the fallopian tubes, where they may evoke vaginitis, endometritis, or salpingitis. Young girls with pinworms may have a much higher incidence of urinary tract infections than that typical for persons not infected.[60]

Clinical Presentation. The most common symptom is pruritus ani. This usually occurs at night in relation to the nocturnal migration and oviposition. Scratching may lead to secondary skin changes and bacterial infection. Restlessness, insomnia, and enuresis probably are a result of the pruritus. Alternative presentations include abdominal pain, rectal bleeding, diarrhea, and weight loss. In the absence of host autoinfection, infection typically lasts 4 to 6 weeks.

Diagnostic Strategies. Adult worms may be recognized in the perineal area, and in suspected cases, nocturnal examination of this area using a flashlight may confirm infection. Worms sometimes can be seen on the surface of stool as well. The most reliable way to diagnose infection is to examine material taken from the perineal area for ova. The cellophane tape test is simple and reliable. The tape is folded, sticky side out, over the end of a tongue blade, pressed firmly against the perineal area, and then spread on a glass slide with toluene and examined under the low-power objective lens of a microscope. The typical eggs are identified easily.

A single cellophane tape test will detect approximately 50% of infections. If done daily for 3 days, the test will detect 90% of infections; after 5 days, it will detect 99%. Examining stool specimens for ova is rarely helpful; only 5% of patients will have eggs in the stool. Scrapings from under the fingernails may reveal the ova.[57] Eosinophilia is not found because the worm does not have a tissue phase.

Management. All infected persons in a family or communal group should be treated simultaneously. It is accepted practice to treat empirically all other members of the same group at the same time, even if they are not infected. The drugs of choice are albendazole, 400 mg by mouth once; mebendazole (Vermox), in a single oral dose of 100 mg chewed well; and pyrantel pamoate (Antiminth), in a single oral dose of 11 mg/kg (maximum dose, 1 g). With all of these treatments, a second dose should be administered 2 weeks later. The repeat dose is needed because mature worms seem to be more vulnerable than young worms. Although the maturation process takes 1 to 2 months, a second dose is effective in eradicating the organism in all stages of the life cycle in 90 to 95% of infections.[57]

The ease of airborne dissemination of the eggs, their resistance to desiccation, and the poor hygienic practices of children all increase the likelihood of reinfection. Ova also are resistant to ordinary fumigants and disinfectants, making control in schools, institutions, and the home very difficult.

Diarrhea in Patients with AIDS

Epidemiology. Diarrhea is the most common manifestation of gastrointestinal disease in patients with AIDS and may be the presenting symptom or a life-threatening complication of the disease. The occurrence rate is greater than 90% in developing countries and historically 50 to 60% in the United States. With the widespread use of HAART, the incidence of infectious

Table 92-5 Causes of Diarrhea in Patients with AIDS

FREQUENCY	ORGANISM
Most common	*Cryptosporidium* Cytomegalovirus
Common	*Entamoeba histolytica* (probably commensal, not causative) *Giardia lamblia* *Mycobacterium avium-complex* *Salmonella* species, especially *Salmonella enterica* subsp. *enterica* serovar Typhimurium* *Aeromonas hydrophila* *Microsporidium* Astrovirus/picornavirus *Clostridium difficile* *Campylobacter jejuni*
Less common	Viruses—herpes simplex virus, rotavirus, adenovirus, Norwalk agent *Cyclospora* *Isospora belli* *Enteromonas hominis* *Strongyloides stercoralis* *Blastocystis hominis* *Shigella* species *Yersinia enterocolitica*

*Formerly *Salmonella typhimurium*.
AIDS, acquired immunodeficiency syndrome.

diarrhea has decreased dramatically in the United States and other developed countries, even among those with CD4+ counts less than 200/mm^3. It is believed that most cases of diarrhea in patients with AIDS in developed countries are now noninfectious in nature, most often related to the use of protease inhibitors; hence, the clinician should ask about recent changes in the HAART regimen in addition to considering infectious causes.[46,55]

Worldwide, patients who are HIV-positive and those with active AIDS are more susceptible to infection both from the usual enteric organisms and from opportunistic organisms. Diarrheal diseases are much more problematic in patients with AIDS because of their diminished immunity and underlying poor nutritional status.[58] A vastly expanded profile of pathogens may potentially cause diarrhea in patients with AIDS compared with immunocompetent persons. Also, the ramifications of the disease are significantly more serious, necessitating a much more aggressive diagnostic evaluation and treatment regimen.

Pathophysiology. The early concept of mucosal transmission of HIV was that it occurred through mucosal trauma that created breaches in the physical barrier of the genital or rectal epithelium, allowing introduction of viral particles directly to the bloodstream. It is now known that infection also occurs after atraumatic inoculation of mucous membranes. With gastrointestinal exposure, virions of certain HIV strains bind to particulate-sampling M cells (membranous epithelial cells) in the gastrointestinal mucosa and undergo receptor-mediated transport from intestinal lumen to lamina propria, with subsequent infection of CD4+ lymphocytes located in the gastrointestinal mucosa. Mucosal biopsy specimens in up to 40% of patients with AIDS demonstrate HIV virions, with depletion of CD4+ lymphocytes in the lamina propria and apoptosis of both HIV-infected and non–HIV-infected lymphocytes. It also has been observed that in a significant number of HIV-infected patients, diarrhea develops in the absence of an identifiable gastrointestinal pathogen, and that this pathogen-negative HIV-related diarrhea subsides with institution of HAART. These findings suggest that HIV itself can induce a primary enteropathy, although specific mechanisms have yet to be elucidated.[61]

In the population of homosexual men, unprotected receptive anal intercourse and anal-oral contact among multiple partners provide exposure to a diverse spectrum of enteric pathogens. In the heterosexual intravenous drug–abusing population, infection spreads primarily by water- and foodborne transmission of the organisms. Patients with AIDS are unable to combat these intestinal pathogens, probably because of a combination of T lymphocyte functional deficiency and underlying HIV-induced enteropathy.

Etiology. A known enteric pathogen can be identified in approximately 85% of patients with AIDS who are experiencing diarrhea. Multiple pathogens may be present in as many as 20 to 25% of patients. Homosexual men with AIDS experience diarrhea more often than do other patients with AIDS. Diarrhea also develops more often in patients who do not have access to or are not compliant with HAART and in those infected with resistant strains of HIV than in other AIDS patients.[62]

Cryptosporidium and cytomegalovirus infections are the two most common causes. The incidence of each is approximately 20%.[62,63] Chronic high-volume watery diarrhea most often is from one of the coccidia *Cryptosporidium* and *Isospora belli*. Although self-limited in the healthy host, coccidial disease often is persistent in patients with CD4+ counts less than 200/mm^3. Cytomegalovirus and *Mycobacterium avium-intracellulare* also produce a chronic illness in those with CD4+ counts less than 100/mm^3. Fever, weight loss, and abdominal pain are prominent; diarrhea is mild to moderate. Many patients die within 6 months of diagnosis. Microsporidia have emerged as a common cause of diarrhea in patients with AIDS in whom CD4+ counts are less than 100/mm^3. Worldwide, these organisms have been identified in 10 to 20% of patients with AIDS who are experiencing diarrhea. In one prospective study in the United States, microsporidia were identified in 39% of patients with AIDS undergoing small bowel biopsy for evaluation of diarrhea.[63]

Salmonella infections, especially with *S.* Typhimurium, are common in immunocompromised hosts.[63] Patients with AIDS who acquire *Salmonella* enteritis are at increased risk for bacteremia and metastatic focal infection compared with normal hosts. *Clostridium difficile* enteritis occurs more commonly in patients with AIDS owing to the common use of prophylactic antibiotic therapy and frequent hospitalizations. It is the most common bacterial enteritis in the AIDS population. Clinical presentation, response rate, and relapse rate are no different from those in the healthy host.[63] Giardiasis occurs with a frequency and severity that are unrelated to the degree of immune compromise.[55]

Entamoeba histolytica infection is neither more prevalent nor more severe in HIV-infected patients. When amebae are present, it is rare for these organisms to cause invasive disease in patients with AIDS.[63] For unknown reasons, *Yersinia*, *V. parahaemolyticus*, viruses (non-cytomegalovirus), *Neisseria gonorrhoeae*, and *Chlamydia trachomatis* are relatively unusual causes of diarrhea in patients with AIDS. Shigellosis and campylobacteriosis are more common among male patients with AIDS who have sex with men than among HIV-negative men who have sex with men.

Clinical Presentation. In patients with AIDS, diarrhea presents in one of three ways. First, at the time of HIV seroconversion, patients usually experience diarrhea, nausea, anorexia, and malaise in association with an acute infectious mononucleosis–like syndrome. Second, diarrhea may be the presenting symptom of full-blown AIDS, with associated fever, malaise, anorexia, and significant weight loss. The most common presentation, however, is for diarrhea to start well after AIDS has become clinically apparent and when the CD4+ count falls below 300/mm^3. In these cases, the patient typically has a chronic debilitating infection that rarely remits spontaneously unless CD4+ counts are normalized using HAART. Diarrhea often is accompanied by profound weight loss, major nutritional impairments, and a diminished sense of well-being. Many cases are refractory to antimicrobial treatment and persist until death, or may even be the cause of death.[55,63]

In patients with AIDS, the presenting signs and symptoms generally do not allow consistent classification of diarrheas, as is done for the immunocompetent host. This is so in part because many patients with AIDS have multiple, concomitant enteric pathogens. However, some clinical pictures are typical. Patients with a fulminating clinical course usually have a disseminated infection, such as infection with cytomegalovirus or *M. avium-complex*. Massive weight loss also is associated with diarrhea due to infection with those two organisms and the coccidia *Cryptosporidium* and *Isospora*. Voluminous, watery diarrhea usually is due to one of the coccidial organisms. Patients with a proctocolitis-like picture most often have herpes simplex virus or cytomegalovirus infection. Strongyloidiasis should be considered in any immunocompromised patient who experiences sudden clinical deterioration with eosinophilia, polymicrobial sepsis, meningitis, or adynamic ileus.[63]

Complications. The most common complications are dehydration, electrolyte abnormalities, and malnutrition resulting from

both fluid loss and malabsorption. Cytomegalovirus infection can produce gastrointestinal hemorrhage or perforation or toxic megacolon. *M. avium-complex* infection often manifests with severe anemia, weight loss, and a rapid downhill course of persistent weakness, malaise, and malabsorption. Bacteremia historically was found in as many as 40 to 45% of patients with AIDS and diarrhea, usually caused by *M. avium-complex* or *Salmonella* species. The incidence has decreased markedly over the past decade as the use of HAART has increased.[63]

Diagnostic Strategies. The diagnostic approach to patients with AIDS who are experiencing diarrhea is entirely different from that to an immunocompetent host. In 80 to 90% of cases, one or more enteric pathogens are found; of the pathogens identified, a majority are susceptible to appropriate antimicrobials.[55,62] Diarrhea in patients with AIDS in whom $CD4^+$ counts are less than 300/mm^3 generally is not self-limited and requires medical intervention to effect resolution. Therefore, each patient merits a diagnostic evaluation (Box 92-2). Infectious causes are detected less frequently in patients being treated with HAART.[62]

Patients with AIDS who are experiencing diarrhea should have up to three stool specimens cultured for enteric bacteria, because fecal shedding of pathogenic bacteria can be intermittent. Stool also should be examined for parasites, using antigen detection assays where available or microscopy of multiple samples for ova, parasites, and mycobacteria. The usual bacterial enteric pathogens are readily identified, but the protozoal infections can be difficult to detect if microscopy-based strategies are used. In patients with severe diarrhea from *Cryptosporidium*, the first stool examination usually yields a positive result, but in less severe cases, additional samples may have to be studied to make the diagnosis. Specialized techniques are necessary to detect most of the viral agents.

Blood cultures are a valuable diagnostic adjunct. Bacteremia may be found in up to 43% of patients, and a blood culture may yield a positive result when the stool cultures and examinations fail to reveal a pathogen.[64] The most common organisms detected by means of blood culture are *M. avium-complex*, cytomegalovirus, *Salmonella*, and occasionally herpes simplex virus. Most cases of *M. avium-complex* bacteremia occur in heterosexual intravenous drug abusers. A routine complete blood cell count demonstrating eosinophilia suggests parasitic infection with *Strongyloides stercoralis* or *Isospora*.[65]

If results of these diagnostic tests are negative, endoscopy should be performed to obtain mucosal biopsy samples from affected areas of the rectum or colon. Rectal biopsy, which can be performed easily even in seriously ill patients, is an indispensable tool in the diagnosis of cytomegalovirus infection. Viral inclusion bodies with clear halos typical of cytomegalovirus can be demonstrated or cytomegalovirus DNA can be detected using PCR techniques. Special staining examinations, DNA detection techniques, or culture of the biopsy tissue also may diagnose *M. avium-complex*, *Cryptosporidium*, or *Giardia* infections that were missed on stool examination. Herpes simplex virus infection can be identified microscopically by detecting multinucleated giant cells or through cultures obtained at the time of endoscopy.

Small bowel biopsy and duodenal aspiration are indicated when stool examination, cultures, and sigmoidoscopy fail to yield a definitive diagnosis. Small bowel studies are most helpful for detecting infection due to *Cryptosporidium*, cytomegalovirus, *M. avium-complex*, *Giardia*, or *I. belli*.[63]

Differential Considerations. Kaposi's sarcoma, even if it involves the bowel, rarely produces diarrhea. Symptomatic oral and esophageal candidiasis is common in patients with AIDS, but diarrhea from *Candida* has not been reported. Diarrhea can be a side effect of antiretroviral drugs used to treat AIDS, especially the protease inhibitors nelfinavir and the combination agent lopinavir plus rotinavir.[55]

Antibiotic-associated colitis from *C. difficile* should be considered when onset of the diarrhea follows antibacterial therapy or hospitalization. Ulcerative colitis can mimic or be mimicked by cytomegalovirus colitis.[63] Aphthous ulceration, particularly of the colon, should be considered when cultures and endoscopy biopsy specimens fail to reveal evidence of infection with common infectious pathogens, herpes simplex virus, or cytomegalovirus. Empirical corticosteroid therapy may lead to dramatic improvement in these patients.[63] Acute proctitis should be differentiated from diarrhea or acute colitis because the investigative evaluation and treatment regimens are distinctly different.

Management. The best strategy for treatment and prevention of acute and chronic infectious diarrhea is maintenance of $CD4^+$ counts through HAART. Treatment of diarrhea in patients with AIDS also includes diet, antimotility agents, and antimicrobial agents. Diets that are lactose-free and low in fat often diminish the diarrhea caused by malabsorption. Patients should avoid intestinal stimulants such as caffeine, raw or inadequately cooked seafood, rattlesnake preparations, and untreated water. Variable success has been reported with standard antimotility agents such as diphenoxylate or loperamide. In patients with cryptosporidiosis, these agents commonly cause a marked increase in crampy abdominal pain; long-acting

BOX 92-2 DIAGNOSTIC PROTOCOL FOR EVALUATING DIARRHEA IN PATIENTS WITH AIDS

Initial Evaluation

Indicated in all patients.

1. Stool cultures for enteric bacteria—*Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, STEC
2. Stool examination for *Giardia*, *Cryptosporidium*, *Isospora*, *Cyclospora*, amebas, and mycobacteria; *Clostridium difficile* toxin assay
3. Blood cultures
4. Proctosigmoidoscopy in patients with clinically severe colitis or a proctocolitis picture, especially homosexual men

Further Evaluation

Indicated if initial study results are negative or to look for multiple organisms present if a patient fails to respond to appropriate therapy for an identified pathogen.

1. Repeat stool cultures and examinations, possibly add culture for viruses
2. Colonoscopy or esophagogastroduodenoscopy performed to obtain duodenal fluid and small bowel and colonic biopsies, which are examined for:
   a. Duodenal fluid examination for ova and parasites
   b. Duodenal and colonic biopsy specimens cultured for mycobacteria, cytomegalovirus, and herpes simplex virus; colonic biopsy tissue also is cultured for bacterial enteric pathogens (add testing for gonorrhea and chlamydial infection in patients with acute proctitis)
   c. Biopsy specimens examined using multiple stains (e.g., acid-fast, hematoxylin-eosin, Giemsa, silver, periodic acid–Schiff) for protozoa, mycobacteria, and cells containing viral inclusion bodies

STEC, Shiga toxin–producing *Escherichia coli*.

morphine sulfate derivatives have provided better clinical relief.[46]

Specific antimicrobial therapy can lead to marked symptomatic improvement in 55 to 75% of patients in whom a pathogen has been identified (Table 92-6). Many patients show substantial improvement after therapy, even when the organism has not been eliminated or the diarrhea persists. Antimicrobial therapy should be dictated by the results of the diagnostic evaluation. Empirical use of antimicrobial agents is not indicated; no one antimicrobial agent can possibly provide reasonable coverage for the wide variety of causative organisms found in these patients. The possibility of infection by multiple organisms must always be considered, especially when patients do not respond to antimicrobial agents known to be effective aganst an identified pathogen.

Ganciclovir, a nucleoside analogue similar to acyclovir, is effective in inducing clinical remission in up to 90% of patients with gastrointestinal cytomegalovirus infection.[66] Foscarnet also is effective and typically is used in ganciclovir-resistant infections. The dosage of both drugs should be reduced in patients with low creatinine clearance. Treatment for the other most common cause of diarrhea in patients with AIDS, cryptosporidiosis, has improved with the use of nitazoxanide: in one study of HIV-positive patients with $CD4^+$ counts greater than 50/mm^3, 90% responded to a dose of 2 g/day, compared with 20% of those who received placebo.[46] Infection with *I. belli* and *C. cayetanensis* can be cured with TMP-SMX.[3] *M. avium-complex* infection is poorly responsive to therapy, and death generally ensues within 6 to 8 months of diagnosis. Virtually all of the other organisms listed in Table 92-5 are susceptible to the usual therapeutic agents, although higher dosages and longer courses of treatment often are required. Recurrences of diarrhea due to either the opportunistic organisms or the usual enteric organisms are common. Chronic suppressive antimicrobial therapy may be indicated to prevent relapse or reinfection.[3]

TRAVELER'S DIARRHEA

Epidemiology. It is said that "travel expands the mind and loosens the bowels." Diarrhea is by far the most common health problem among the 12 million people who travel from an industrialized nation to a developing country each year. Travel to high-risk areas is associated with diarrheal attack rates of 30 to 50%. Among travelers to industrialized countries, however, the development of diarrhea is infrequent. For visitors to the United States, the attack rate is less than 4%.[55]

Traveler's diarrhea is more common in young adults than in elderly persons. Travelers with inflammatory bowel disease, diabetes, or immune compromise and those taking antacids also are at increased risk.[67]

Pathophysiology. The syndrome is caused by an infection acquired by ingesting fecally contaminated food or water. High-risk items include raw leafy vegetables, raw or undercooked meats or seafood, unpeeled fruits, unpasteurized dairy products, tap water, and ice. Once an organism is ingested, rapid and dramatic change occurs in the traveler's intestinal flora. When the ingested inoculum overcomes host defense mechanisms, diarrhea develops. Most often, the pathomechanism involves elaboration of enterotoxins that produce a secretory diarrhea. When organisms are invasive, rather than toxigenic, a typical infectious enteritis results.

Etiology. Pathogens that commonly cause traveler's diarrhea are listed in Table 92-7. Bacterial enteropathogens cause approximately 80% of cases of traveler's diarrhea. Enterotoxigenic *E. coli* is the most common pathogen and can be acquired anywhere in the world, although the incidence of infection is higher in Latin America than in Africa, Asia, or the Middle East. *V. parahaemolyticus* is an increasingly common cause because of its association with consumption of raw or inadequately cooked seafood. The organism commonly causes diarrhea in persons traveling to Japan or Asia or in those vacationing on cruise ships.[15,55,68]

Plesiomonas shigelloides typically is associated with uncooked shellfish, especially oysters. It also is associated with travel to Mexico. *Plesiomonas* produces a typical invasive enteritis.[15] *E. coli* O157:H7 and enteroinvasive *E. coli* each cause up to 5% of cases of traveler's diarrhea.[68] Another type of *E. coli*, enteroadherent *E. coli*, may be the cause of a significant number of the previously undiagnosed cases of traveler's diarrhea. Viral agents cause up to 10% of cases of traveler's diarrhea.[68] Parasitic pathogens are implicated in approximately 10% of cases of traveler's diarrhea. *Giardia* is the most common parasite acquired by travelers; travelers to the former Soviet Union, particularly Leningrad and Moscow, have a very high risk for acquiring giardiasis. *Entamoeba histolytica*, *Cyclospora*, and *Cryptosporidium* are each implicated in less than 2% of cases.[68,69]

Clinical Presentation. Traveler's diarrhea typically begins abruptly, with production of four or five loose or watery stools per day for 1 to 3 days. Approximately one third of patients are temporarily confined to bed, and the symptoms last more than a week in 10% of patients.[68] Onset usually is within the first 3 to 4 days of travel but can occur at any time, including after the patient arrives home. Patients may not associate their diarrhea with recent travel because the incubation time for the infection, particularly if it is parasitic, may have been long enough to allow them to return home before the symptoms began.

Associated symptoms include abdominal cramps, nausea, bloating, urgency, and occasionally vomiting, fever, chills, headache, malaise, tenesmus, and bloody stools. Symptoms and signs depend on whether the pathogen is noninvasive or invasive. Traveler's diarrhea may ruin a trip, but it is rarely life-threatening.

Prevention.

Diet. Traditionally, instruction regarding food and beverage preparation has been touted to prevent traveler's diarrhea. Most travelers, however, do not follow such advice. Ideally, tourists should eat only foods that are freshly prepared and served piping hot. High-risk foods should be assiduously avoided, and travelers should follow the Peace Corps adage of "boil it, cook it, peel it, or forget it." Thirsty travelers should be advised to avoid ice and to drink beverages such as tea and coffee that are made with boiled water, canned or bottled carbonated beverages, and wine.[67,68] Boiling water is by far the most reliable method to make it safe for drinking and brushing teeth. Travelers and outdoor enthusiasts should be advised to bring the water to a vigorous boil and allow it to cool without adding ice. Boiling destroys virtually all bacteria, viruses, and parasitic cysts. A pinch of salt in each quart improves the taste. When boiling is not feasible, water can be chemically disinfected with 2% tincture of iodine drops or tetracycline hydroperiodide tablets, such as Globaline or Potable Aqua, available from pharmacies and sporting goods stores.

Nonantimicrobial Medications. The nonantimicrobial agent most studied in the prevention of traveler's diarrhea is bismuth subsalicylate (e.g., Pepto-Bismol). Taking two tablets, or 2 ounces, four times per day decreases the incidence of traveler's diarrhea by 65%. This dosage, however, contains the daily equivalent of eight 5-grain aspirin tablets. Bismuth subsalicylate should not be used in patients who are allergic to salicylates, those taking large doses of salicylates for arthritis, or

Table 92-6 Treatment Directed against Pathogens Causing Diarrhea in Patients with AIDS

ORGANISM/TREATMENT REGIMEN	COMMENTS
Cytomegalovirus Foscarnet 90 mg/kg IV q12h × 14–21 days (diluted in 100 mL D_5W, infused over at least 1 hr) for 3–6 weeks Ganciclovir 5 mg/kg q12h IV × 14 days (diluted in 100 mL D_5W, infused over 1 hr) for at least 21 days	Effective, but 75% recurrence rate within 8 to 9 weeks; maintenance therapy may be warranted
Cryptosporidium Paromycin 25–35 mg/kg/d PO in 2–4 doses × 4 wk Azithromycin 600 mg PO qd × 4 wk in combination with paromycin Nitazoxanide 1 g PO bid × 4 wk	Disease generally chronic, despite treatment
Cyclospora cayetanensis TMP-SMX 160 mg/800 mg qid PO × 10 days, then 1 tab PO 3×/wk	
Entamoeba histolytica Iodoquinol 650 mg PO tid × 20 days Diloxanide 500 mg PO tid × 10 days severe symptoms, add metronidazole 750 mg PO tid × 10 days Paromycin 25–35 mg/kg divided tid × 7 days	Treat only if distinguished from *Entamoeba dispar*, or for severe symptoms, which warrant search for other causes as well
Giardia lamblia Metronidazole 250–750 mg PO tid × 5–10 days Tinidazole 2 g PO as a single dose Furazolidone 100 mg PO qid for 7–10 days	Patient's symptoms may resolve despite continued enteric presence of *Giardia*
Mycobacterium avium-complex Clarithromycin 500 mg PO bid or azithromycin 500 mg PO qd plus ethambutol 15 mg/kg/d with or without rifabutin 300 mg PO qd until response Levaquin 500 mg PO qd	Mixed results with antituberculosis drugs, more drug-resistant than tuberculous strains of mycobacteria; little evidence that treatment prolongs life
Salmonella species Ciprofloxacin 500–750 mg PO bid × 10–14 days *or* azithromycin 1 g day 1, then 500 mg × 10 days *or* ceftriaxone 1–2 g IV q12h × 7–10 days	Bacteremia common; maintenance therapy often required
Herpes simplex virus Acyclovir 5 mg/kg PO or IV tid × 7–10 days Famciclovir 250 mg PO tid × 7–10 days Valacyclovir 1 gm PO bid × 7–10 days	Proctitis picture, especially in homosexual men
Campylobacter jejuni Erythromycin 500 mg bid × 7–10 days *or* azithromycin 500 mg qd × 5–7 days	40% recurrence rate; high rate of fluoroquinolone resistance
Isospora belli TMP-SMX 160 mg/800 mg PO qid × 10 days, then bid × 3 wk Pyrimethamine 50–75 mg qd × 10 days	50% recurrence rate; chronic suppressive therapy usually recommended
Aeromonas hydrophila Ciprofloxacin 500 mg PO bid × 3 days TMP-SMX 160 mg/800 mg PO bid × 3 days	Associated with drinking untreated water
Enteromonas hominis Metronidazole 250–750 mg PO tid × 10 days	Increasingly common in homosexual men, possibly commensal; treatment indicated when no other pathogens found in the presence of appropriate symptoms
Blastocystis hominis Metronidazole 750 mg PO tid × 10 days *or* furazolidone 100 mg PO qid × 7–10 days	Possibly more common in children
Shigella species Ciprofloxacin 500 mg PO bid × 7 days	Most species resistant to ampicillin, and increasing resistance is found to TMP-SMX
Yersinia Ciprofloxacin 500 mg PO bid × 7 days	Appendicitis-like picture; bacteremia possible
Strongyloides stercoralis Ivermectin 200 µg/kg/day × 1–2 days *or* thiabendazole 25 mg/kg PO bid × 2 days	Migration of the larvae through the bowel wall may be accompanied by gram-negative bacteremia and a hyperinfection syndrome in patients with AIDS; in disseminated strongyloidiasis, therapy should be continued for at least 5 days

AIDS, acquired immunodeficiency syndrome; D_5W, dextrose 5% in water; HAART, highly active antiretroviral therapy; TMP-SMX, trimethoprim-sulfamethoxazole.

Table 92-7 Causes of Traveler's Diarrhea

AGENT	ESTIMATED INCIDENCE (%)*
Bacteria (in approximately 80–85% of cases)	
Enterotoxigenic *Escherichia coli*	45–50
Shigella	8–12
Campylobacter	7–9
Enteroinvasive *E. coli* (hemorrhagic strain of O157:H7)	5–6
Salmonella	3–5
Others, such as *Vibrio*, *Aeromonas*, *Plesiomonas shigelloides*, *Yersinia*, other types of *E. coli*	1–5
Viruses (in approximately 5–10% of cases)	
Rotavirus	5–10
Norwalk agent and others	0–5
Parasites (in approximately 5–6% of cases)	
Giardia lamblia	4–5
Cryptosporidium	3–4
Entamoeba histolytica	0–1
Strongyloides stercoralis	0–1
Unknown	5–10

*Rough estimates, which vary depending on locales visited.

patients taking oral anticoagulants, uricosuric drugs, or methotrexate. Salicylates have antiplatelet effects, inhibit the activity of uricosuric drugs, and increase the toxicity of methotrexate by decreasing its renal clearance. Bismuth subsalicylate also turns the tongue and stool black and may cause mild tinnitus and interfere with the bioavailability of doxycycline.

Antiperistaltic agents such as diphenoxylate and loperamide are not effective prophylactic agents. Controlled studies have indicated that the prophylactic use of diphenoxylate actually increases the incidence of traveler's diarrhea: slowing of the gut allows more time for organisms to colonize and elaborate toxin or produce infection.[68]

Antimicrobials. The risks associated with prophylactic treatment with antibiotics include allergic reactions, skin rashes, photosensitivity reactions, serious hematologic reactions, Stevens-Johnson syndrome, and antibiotic-induced infections such as antibiotic-associated colitis or *Candida* vaginitis.[68] The main argument, however, against the widespread use of prophylactic antibiotics is the risk of emergence of resistant organisms. Resistance to doxycycline is now found in many parts of the world. TMP-SMX resistance is common in tropical areas. The quinolones are the most effective agents, but resistance rates of up to 80% have been reported for some organisms in parts of Southeast Asia.[68,69]

In addition, if the traveler is provided with a prescription for a suitable antibiotic based on regional resistance patterns, taking one dose in combination with loperamide immediately after the onset of diarrhea often will halt symptoms within hours. For these reasons, prophylactic use of antibiotics before the onset of symptoms is no longer recommended, except in cases of significant concurrent illness or immunocompromised status.[68,69]

If prophylaxis is indicated, a single daily dose of prophylactic antibiotics such as ciprofloxacin (500 mg), norfloxacin (400 mg), or rifamixin (200 mg), in combination with bismuth subsalicylate two tablets (262 mg/tablet) or 30 mL four times daily can effectively prevent traveler's diarrhea in up to 90% of persons. The regimen is started on the day before travel and continued until 2 days after returning home. TMP-SMX also can be used but is not recommended as a first-line agent because of significant resistance.

Management.

Diet. In most patients, fluid and electrolyte balances can be maintained by drinking potable fruit juices, bottled beverages, or caffeine-free soft drinks.

Nonantimicrobial Medications. Adsorbents such as kaolin or pectin are ineffective for treating traveler's diarrhea. They may give the stools more consistency but have not been shown to decrease cramping or the frequency of stooling, or to shorten the course of an infectious diarrheal illness. Nonantimicrobial agents such as bismuth subsalicylate, paregoric, codeine, diphenoxylate, or loperamide may provide prompt but temporary symptomatic relief.

Loperamide (initial dose 4 mg followed by 2 mg after each unformed stool for 2 days; total dosage no more than eight 2-mg capsules/day) has been shown to provide significantly more relief than that obtained with bismuth subsalicylate (30 mL orally every 30 minutes for 3 to 5 hours on each of 2 days, for a total dose of 240 mL/day).[68] Antimotility agents alone, however, should never be given to patients when an invasive bacterial infection is suspected, and they should be discontinued if symptoms persist longer than 48 hours.

Antimicrobials. Antibiotic therapy can provide prompt relief of symptoms, decrease the rate of stooling, and shorten a typically 1- to 3-day illness to a few hours.[67-69] In cases of mild toxigenic, nondysenteric traveler's diarrhea, a single dose of ciprofloxacin 750 mg PO in combination with loperamide often resolves the symptoms within an hour. When the course is extended to 3 days, response rates of up to 98% are attained. In patients with high fever, bloody stools, or the typical bacterial or invasive picture, the treatment of choice is norfloxacin, 400 mg twice daily, or ciprofloxacin, 500 mg twice daily, in combination with loperamide. The duration of treatment generally is 3 days, although one double dose may be all that is necessary.[68]

Persons with dysentery who fail to respond to one antibiotic should promptly be switched to another. Azithromycin may be effective in cases in which fluoroquinolones either cannot be used or are ineffective. The quinolone agents are not recommended for use in children and pregnant women.[68]

The antibiotic rifamixin was FDA-approved in 2004 for the treatment of traveler's diarrhea in adults and children older than 12 years of age. It is a nonabsorbable antibiotic that acts by inhibiting RNA synthesis, and the potential for development of bacterial resistance to this agent is believed to be low. Several studies demonstrate that oral rifamixin 200 mg three times daily for 3 days is an effective treatment for traveler's diarrhea.[68]

A summary of current recommendations for the prevention and treatment of traveler's diarrhea is outlined in Box 92-3. Further detailed information on traveler's diarrhea and the other medical problems of travelers can be found at the Center for Preventive Services section of the CDC's website, http://wwwn.cdc.gov/travel/default.aspx. The CDC's "Yellow Book," *Health Information for International Travel*, can be downloaded for free at http://wwwn.cdc.gov/travel/contentYellowBook.aspx, and the CDC provides up-to-the-minute travel information through its traveler's hotline telephone number, 877-FYI-TRIP.

BOX 92-3 Current Recommendations for the Prevention and Treatment of Traveler's Diarrhea

1. Provide instruction regarding sensible dietary practices and drinking water management.
2. Reserve prophylaxis for patients with special circumstances, including severe concurrent illness or immunosuppression. The basis of this recommendation is threefold: first, the potential for aspirin-related complications; second, the ramifications of widespread use of prophylactic antibiotics in terms of adverse medication reactions or the emergence of resistant organisms; and third, the availability of highly successful treatment strategies.
3. Other patients who request prophylaxis should be steered toward the use of bismuth subsalicylate rather than antibiotics.
4. For those requiring prophylaxis, one of the quinolones—norfloxacin, ciprofloxacin, or rifamixin—is recommended.
5. For all patients requiring prophylaxis, it is reasonable to institute prompt antimicrobial therapy once traveler's diarrhea occurs.
   a. Toxigenic/nondysentery: loperamide combined with one dose of ciprofloxacin 750 mg orally.
   b. Infectious/dysentery: norfloxacin, ciprofloxacin, or rifamixin—alone or in combination with loperamide twice daily for 3 days.
   c. The rare traveler with persistent symptoms, particularly fever, chills, or blood or mucus in stools, unresponsive to antimicrobial therapy within 24 to 48 hours, should seek immediate medical attention.

KEY CONCEPTS

- Contact isolation precautions should be followed for all patients with significant diarrhea that continues during the ED stay.
- Most otherwise healthy patients presenting with diarrhea do not require laboratory testing or antibiotic therapy.
- Fecal testing should be reserved for those patients who are systemically ill, are febrile, have significant comorbid disease, have bloody stools, or report recent antibiotic use, or in whom exposure to a treatable or reportable pathogen is strongly suspected.
- Empirical treatment of diarrhea in adults with a fluoroquinolone or TMP-SMX generally is not recommended but is acceptable for traveler's diarrhea and when severe inflammatory diarrhea is present with a low risk of *E. coli* O157:H7 as its cause. This indication includes bloody diarrhea in patients with a temperature greater than 38.5° C. "False-positive" blood in stools may come from aggravation of hemorrhoids or perianal irritation secondary to copious stooling. Fecal leukocytes or lactoferrin testing may help distinguish inflammatory diarrhea from that of other causes but has a low specificity. Stool testing should be performed before institution of all empirical treatment.
- Milk and other lactose-containing foods should be avoided because gastroenteritis often leads to transient lactose intolerance. Caffeine products also may worsen diarrhea. Bowel rest is not necessary or advantageous, however, and patients should be encouraged to eat and drink what they find palatable during the illness.
- Risks of empirical antibiotic treatment include adverse and allergic reactions, possible increase in the risk of hemolytic uremic syndrome in the case of *E. coli* O157:H7 infection, prolonged shedding of salmonellae of non-Typhi serotypes, and increased organism resistance.
- Treatment should be considered in patients who are still significantly ill when culture results are reported, particularly if they are immunocompromised or have a significant underlying medical illness, or in cases in which the fecal shedding could represent a public health hazard.
- Patients with sickle cell anemia, other hemolytic anemias, or AIDS are unusually susceptible to *Salmonella* bacteremia.
- Although risk associated with antimotility agents may be overstated, these agents are still not recommended for treatment of invasive enteritis unless antibiotics also are used.
- In patients with *Y. enterocolitica* gastroenteritis, the abdominal pain and diarrhea usually persist for 10 to 14 days or longer. in a substantial number of patients with yersiniosis, in particular adolescents and young adults, an ileocecitis may develop. In these cases, lower abdominal pain with little or no diarrhea predominates and may perfectly mimic the pain of acute appendicitis.
- The symptoms of scombroid fish poisoning, which resemble those in histamine intoxication and usually develop abruptly within 20 to 30 minutes of eating the fish, consist of facial flushing, diarrhea, severe, throbbing headache, palpitations, and abdominal cramps, and generally last less than 6 hours. The mainstay of therapy is antihistamine administration.
- Many cases of *C. difficile* antibiotic–associated enterocolitis are self-limited, provided that the offending agent is discontinued. When stopping the antibiotic does not resolve the diarrhea, or when the diarrhea is severe, empirical antibiotic treatment should be started promptly. Either oral metronidazole or oral vancomycin can be used to eradicate *C. difficile* colitis.
- *Giardia* is the most common cause of water-borne diarrheal outbreaks in the United States. Most patients harboring *Giardia* organisms are asymptomatic. The most common symptoms of acute infection are abdominal distention, colicky pain with audible borborygmi, flatulence, and frequent stools. All patients

with proven *Giardia* infection should receive treatment even if they are asymptomatic.

- Diarrhea is the most common manifestation of gastrointestinal disease in patients with AIDS and may be either the presenting symptom or a life-threatening complication of the disease. Diarrhea in patients with AIDS in whom $CD4^+$ counts are less than $300/mm^3$ generally is not self-limiting but requires medical intervention to effect resolution. Therefore, each patient deserves a diagnostic evaluation.
- ETEC is responsible for 40 to 50% of all cases of traveler's diarrhea, and these organisms can be acquired anywhere in the world. Prophylactic antibiotics are no longer recommended for otherwise healthy patients, but quick resolution of diarrhea is possible with prompt treatment.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 93

Disorders of the Large Intestine

Michael A. Peterson

IRRITABLE BOWEL SYNDROME

Perspective

Irritable bowel syndrome (IBS) is a chronic non–life-threatening disorder characterized by abdominal pain and alteration in bowel habits. IBS is an extremely common disorder; estimates put the prevalence in the North American population at 10 to 15%, with women affected twice as often as men.[1] Although only one third of patients who have the clinical syndrome ever seek medical attention, IBS accounts for more than 10% of all visits to primary care physicians and more than 25% of all visits to gastroenterologists.[2] IBS is said to contribute more impairment to quality of life than does either diabetes or renal failure.

No specific physical or laboratory abnormalities defining IBS have been identified. IBS is a functional asomatic syndrome that is defined by criteria and usually is diagnosed after other, more serious diagnoses are excluded. A new diagnosis of IBS may be difficult to make in the emergency department (ED) because many of the studies required to exclude other conditions are not readily available. Initially, patients usually are discharged with a diagnosis of "abdominal pain of unclear etiology" or the equivalent. Such patients and even patients with known IBS presenting with acute symptoms pose a diagnostic challenge. Symptoms of IBS overlap with those of other conditions, including some that are life-threatening, which must be excluded before hospital discharge.

Principles of Disease

Although the cause of IBS is unknown, it is associated with several pathophysiologic findings suggesting that it is a disorder of altered gut motility, gut sensation, and perception of intestinal activity. IBS initially was thought to be primarily a psychiatric disorder because there are no visible anatomic abnormalities, and because stress is an exacerbating factor. Physiologic testing has since shown that patients with IBS have disturbances in the rhythmic pattern of electrical activity in the intestine and in how the intestine responds to stimulation. Patients with IBS seem to be more attuned to activity in the abdomen as well, sensing different phases of intestinal motor activity and intestinal content movement more than people without IBS.

Psychiatric conditions often coexist with IBS, ranging from generalized anxiety disorder to major depression. An association with previous sexual abuse also has been reported.[2] In women, symptoms often are related to the menstrual cycle, suggesting a hormonal influence. A familial predisposition for the symptoms of IBS has been described, suggesting a genetic component.

Clinical Features

The diagnosis of IBS is defined by clinical criteria in a patient who has no other organic explanation for the symptoms. Several sets of clinical criteria have been published, one set of which is the Rome II criteria (Box 93-1). Patients with IBS experience symptoms intermittently, with the typical patient averaging symptoms on 1 of every 3 days. Complaints include abdominal pain, bloating, and constipation or diarrhea. Pain typically is relieved with defecation; pain that persists suggests another diagnosis. A mucoid discharge from the rectum often accompanies diarrhea. Upper gastrointestinal symptoms such as nausea and dyspepsia also can occur. Patients may present to the ED with an exacerbation of their previous symptoms or with a new abdominal complaint and often report that they are undergoing a period of stress. Physical examination may reveal mild abdominal tenderness that may be focal, often varying in location, or diffuse. IBS is subdivided into two categories: constipation-predominant and diarrhea-predominant.

Pain that is progressive, keeps the patient awake at night, or is associated with anorexia or significant abdominal tenderness suggests an alternate diagnosis. Fever, abdominal mass, and rectal bleeding also are atypical for IBS. In the absence of symptoms suggesting another diagnosis, the clinical criteria have a specificity ranging from 87 to 100%, although sensitivity may be only 60%.[2] In patients determined to have IBS through correct use of the clinical criteria, follow-up evaluation over many years rarely leads to a change in the diagnosis.[2]

Diagnostic Strategies

A final diagnosis of IBS usually is made in the primary care setting and not in the ED. A typical primary care evaluation for IBS may include a complete blood count, thyroid studies, stool exam for ova and parasites, evaluation for lactose intolerance, and possibly lower gastrointestinal endoscopy, although current approaches try to limit testing in cases in which the clinical picture is clearly IBS.[3] The ED evaluation seeks to exclude other, more urgent causes for the patient's symptoms. In this setting, testing for pancreatitis, hepatitis, biliary colic, or urologic disorders, including urolithiasis, may

BOX 93-1 Rome II Criteria for Irritable Bowel Syndrome

Abdominal pain or discomfort for 12 weeks or longer within the past year *and* two of the following:

1. Relief of discomfort with defecation
2. Association of discomfort with altered stool frequency
3. Association of discomfort with altered stool form

From Brandt LJ, et al: Systematic review on the management of irritable bowel syndrome in North America. Am J Gastroenterol 97:S7, 2002.

BOX 93-2 Differential Diagnosis in Irritable Bowel Syndrome

Constipation-Predominant
Bowel obstruction
Cancer
Adult-onset Hirschsprung's disease
Rectocele
Paradoxical closure of the anus during defecation

Diarrhea-Predominant
Bacterial/parasitic intestinal infection
Inflammatory bowel disease
Lactose intolerance
Malabsorption
Radiation proctocolitis

Painful
Inflammatory bowel disease
Ureteral colic
Bowel obstruction
Diverticular disease
Gastroesophageal reflux/ulcer
Liver or pancreatic disease
Lead toxicity
Porphyria

be appropriate as indicated by the pattern of the presenting complaints.

Differential Considerations

The differential diagnosis of symptomatic IBS depends on the predominant symptoms and includes a host of disorders (Box 93-2). Patients may present with pain, constipation, or diarrhea or any combination of the three.

Management

Not all patients with IBS require treatment. It is recommended that therapy be initiated only if symptoms diminish the quality of life.[1] Because no curative therapy is available, treatment is directed toward the relief of symptoms. Diet, behavioral, and pharmacologic therapies all are used in IBS. Specific therapy will be determined by the type of IBS: constipation-predominant, diarrhea-predominant, or constipation-plus-diarrhea combination. Dietary suggestions include a low-fat diet, reduced nondigestible sugars, and avoidance of gas-forming foods, although none of these has any proven benefit. Fiber supplementation may aid constipation-predominant IBS.

Medications with antispasmodic activity, such as anticholinergics and calcium channel blockers, are used for abdominal cramping, and peripherally acting narcotics, such as loperamide, are used to reduce diarrhea. Osmotic laxatives such as lactulose sometimes are helpful in constipation. Tricyclic antidepressants have been effective in certain classes of patients with IBS. Serotonin receptor antagonists, such as alosetron, and prokinetic agents also are used (Box 93-3). Nonsteroidal anti-inflammatory drugs (NSAIDs) may worsen symptoms.[3]

Behavioral therapy may benefit patients who are unresponsive to medication, but high-quality evidence of its effectiveness is lacking. A role for nontraditional therapies such as arrowroot, artichoke leaf, and some Chinese traditional herbal medicines is supported by limited scientific evidence.[2]

BOX 93-3 Medications Used in the Treatment of Irritable Bowel Syndrome

Osmotic laxatives
Antidiarrheals
Antispasmodics (anticholinergics and calcium channel blockers)
Tricyclic antidepressants
Serotonin receptor antagonists (e.g., alosetron)
Prokinetic agents
Female hormone–modulating agents
Tranquilizers

Disposition

IBS is not a life-threatening disease and can be managed on an outpatient basis so long as other disorders have been excluded. The search for optimal therapy usually involves empirical trials until the correct fit is found. This process is best accomplished through a well-established primary care relationship. The disorder is chronic, but with appropriate therapy, many patients experience significant improvement in their quality of life.

DIVERTICULAR DISEASE

Perspective

Diverticular disease is an affliction of middle age that seems to be a direct consequence of the diet of modern Western civilization. Diverticular disease was virtually unknown in the Western world before the 20th century and is still rare in other cultures. In 1925, only 9% of people older than 50 years of age in the United States had diverticula; by 1968, the percentage had increased to 30%.[4] Today it is estimated that 5 to 10% of people older than 45 years and 80% of people older than 85 years have diverticula.[5] Diverticula are less common in people younger than age 40, representing only approximately 2 to 5% of all patients with the disease. The proliferation of this disease was coincident with the invention and widespread use of the flour rolling mill, which removes the fiber-containing outer part of the wheat kernel. This coincidence has prompted the labeling of diverticulosis as a "modern deficiency disease," which is supported by the fact that adding fiber back into the diet seems to be protective against the development of diverticulosis.[4] In rural Africa and Asia, where the diet is high in fiber, diverticular disease is virtually unknown.[5]

Diverticulosis denotes the presence of diverticula in the colon. Most patients with this condition are asymptomatic. *Diverticulitis* denotes inflammation of diverticular tissue, which usually is painful. *Complicated diverticulitis* is defined by the

presence of more extensive disease, including abscess formation, peritonitis, intestinal obstruction, or fistula formation.

Principles of Disease

The wall of the colon is penetrated at regular intervals by blood vessels, collectively known as the *vasa recta*, that supply the internal intestinal layers. The site of vessel penetration is apparently the weakest part of the colon wall, because it is at these sites that diverticula form. Although the exact pathogenic mechanism is unknown, the current theory is that diverticula form in response to increased intracolonic pressures generated when the colon is processing smaller, non–fiber-containing stools. Higher pressures lead to a herniation of colonic mucosa through the intestinal wall at the vasa recta, creating small, sac-like appendages. These appendages (diverticula) typically measure 5 to 10 mm in diameter but on rare occasions can grow into huge sacs measuring many centimeters across *(giant colonic diverticula)*. Diverticula are asymptomatic in most affected persons, but symptoms are believed to develop when diverticula become obstructed, presumably with inspissated stool. When obstruction occurs, inflammation sets in and microperforations of the sac develop, resulting in inflammation of pericolonic structures and abdominal pain.

In the Western world, 85% of diverticular disease occurs in the left colon, usually the sigmoid.[5] This is not the case in Japan, where right-sided diverticular disease is more common. Japanese-Hawaiians consuming a low-fiber Western diet have a significantly increased incidence of diverticular disease, but it remains in the right colon.[4] This finding suggests that diet plays a significant role in the formation of diverticula but that the location of diverticula is genetically determined.

A spectrum of disease is observed in relation to diverticular inflammation. In *uncomplicated* diverticulitis, only the pericolonic fat is inflamed. With time, a phlegmon, abscess, or gross perforation may develop. Any extension of disease beyond the pericolonic fat is considered to represent *complicated* diverticulitis. The involved colonic segment may fistulize to any adjacent organ, most commonly the bladder (accounting for 65% of all fistulas).[6] Adjacent bowel may become obstructed by mass effect from an abscess or may incur an inflammatory ileus. Recurrent episodes of diverticulitis can lead to strictures in the colon with subsequent colonic obstruction.

Diverticula also can bleed, presumably from erosion into the mucosal wall by dried stool trapped in the diverticular sac. Severe hemorrhage occurs in 3 to 5% of all patients with diverticulosis and accounts for approximately 40% of all instances of lower gastrointestinal hemorrhage.[4] Bleeding notably occurs in the absence of inflammation and typically is painless. NSAID use is known to be associated with this complication.[6]

Clinical Features

Diverticulosis

Commonly asymptomatic, patients with diverticulosis sometimes have nonspecific abdominal complaints including bloating, crampy pain, excessive gas, or a change in bowel habits.[7] Diverticulitis will develop in approximately 10 to 30% of patients with diverticulosis; approximately 75% remain asymptomatic throughout their lifetime.[4,8]

Diverticulitis

Because most diverticula found in persons in the Western world form in the left colon, the typical presentation of diverticulitis is persistent left lower quadrant pain and tenderness. Pain may be felt first in the hypogastrium before localizing to the left lower quadrant. Referred pain may occur in the penis, scrotum, or suprapubic region. Right-sided diverticulitis may manifest as right lower quadrant pain and is impossible to distinguish clinically from appendicitis. Additional findings suggest various complications: Diffuse tenderness is associated with gross perforation or abscess rupture; dysuria, with a colovesical fistula; mass, with an abscess; and vomiting or abdominal distention, with intestinal obstruction. Fecal matter or gas emanating from the vagina suggests a colouterine fistula. Almost any adjacent organ can be involved in the inflammatory process. Patients recently diagnosed with diverticulitis who are being treated on an outpatient basis with oral antibiotics and who present to the ED with continuing or worsening symptoms should be evaluated for the possibility of an abscess.

Special care must be taken with elderly or immunocompromised patients, because clinical signs and symptoms are much less dramatic, even with more severe disease. Perforation is more common in these patients, manifests with less significant findings, and carries a high mortality rate.[5]

Diagnostic Strategies

Uncomplicated Diverticulitis

The clinical diagnosis of uncomplicated diverticulitis can be made in a patient in the appropriate age range exhibiting focal left lower quadrant pain and tenderness in the absence of symptoms or signs that suggest an alternative diagnosis. No mass or peritoneal irritation should be encountered on examination, and the patient should otherwise appear well. If the patient fits this clinical picture, treatment can be initiated on an empirical basis, and no laboratory tests or diagnostic imaging is required. Ancillary tests are performed primarily to exclude alternative diagnoses or the presence of complicated diverticulitis. When the diagnosis is unclear, studies to exclude gynecologic, renal, hepatic, biliary, or pancreatic disease may be indicated, depending on the patient's presentation and degree of distress. Computed tomography (CT) of the abdomen should be considered for elderly and immunocompromised patients to exclude the possibility of a subtle presentation of complicated diverticulitis.

Complicated Diverticulitis

Abdominal Computed Tomography. Abdominal CT is the preferred method of evaluation in complicated diverticulitis. CT has the advantage of evaluating the colon and the structures around it, so it can make the diagnosis of diverticulitis and simultaneously evaluate the extent of disease. CT also can be used to guide percutaneous drainage of diverticular abscesses. Findings on CT consistent with diverticulitis include the presence of diverticula, inflammation of pericolonic fat, thickening of the bowel wall to more than 4 mm, free abdominal air, and an abscess.[5,8,9] CT also can help make an alternative diagnosis when diverticulitis is absent. CT is relatively noninvasive and is well tolerated by ill patients. Sensitivity and specificity for diverticulitis range from 69 to 95% and from 75 to 100%, respectively.[6] Negative findings on CT scan cannot absolutely exclude diverticulitis. Small abscesses within the colon or mesocolon can be missed, as can the diverticula themselves. It also may be difficult to differentiate between carcinoma and diverticulitis on CT scan. Marked bowel wall thickening associated with diverticulitis looks like cancer; contrast enema or endoscopy may be required to differentiate between the two.

Barium Enema. Although double-contrast barium examination is the standard for the diagnosis of asymptomatic diverticula,

it should be avoided in the setting of diverticulitis. The potential for preexisting occult perforation and subsequent risk of barium peritonitis limits its usefulness. Barium enema may be used after the acute episode to exclude the diagnosis of carcinoma.

Water-Soluble Contrast Enema. A water-soluble contrast enema is the preferred method of imaging if a contrast enema study is needed in the acute setting. Water-soluble contrast material shows less detail than barium, but this modality is still useful. Findings consistent with diverticulitis include the presence of diverticula along with extravasation of contrast material into an abscess cavity or into the peritoneum. This study also can show a fistula or evidence of compression of the colon by an extrinsic mass. Because contrast material usually collects only in the intestinal lumen, contrast enemas give less information than CT about the extent of disease outside of the colon.

Ultrasonography. Ultrasound examination can detect various pathologic features characteristic of diverticulitis, including fluid collections around the colon, thickened hypoechoic bowel wall, or hyperechoicity adjacent to the bowel wall that suggest pericolonic inflammation. Tenderness to palpation over an abnormal-appearing colon suggests that the colon is the source of the patient's pain. Diverticula can occasionally be visualized by ultrasound exam. As is often the case, the sensitivity of ultrasound imaging for these findings varies significantly with the experience of the operator. Because gas interferes with ultrasound imaging, adequate visualization of the bowel can be a problem. Currently, the role for ultrasonography in the evaluation of diverticulitis is not well defined.

Endoscopy. Endoscopy is limited in the acute setting by its more invasive nature, the risk of perforation, and the logistics of arranging this procedure emergently.[10] Although the endoscope affords visualization of diverticula and other pathologic processes within the lumen of the colon, it does not permit evaluation of the extent of extracolonic disease.

Plain Radiography. Plain films of the abdomen are not likely to be helpful in the diagnosis of diverticulitis unless either intestinal obstruction or perforation is suspected.

Differential Considerations

In a patient who presents with more serious disease, making the correct diagnosis usually poses no great dilemma because more extensive laboratory testing and diagnostic imaging typically have been performed. In a patient with milder disease, in whom a tentative diagnosis of diverticulitis may be based on clinical grounds alone, the differential diagnosis presents more of a challenge. An important consideration is whether or not the patient has colonic carcinoma; however, it usually is safe to wait until after the acute episode has resolved to investigate this possibility. Additional diagnoses to consider include colitis (either inflammatory or ischemic); ureteral stones; inguinal hernia; and pelvic pathology, including ectopic pregnancy or pelvic inflammatory disease, and ovarian pathology with or without ovarian torsion. Appendicitis should be suspected when symptoms are predominantly right-sided. Diffuse abdominal pain should prompt an evaluation for other life-threatening problems, including leaking abdominal aortic aneurysm, peritonitis, hemoperitoneum from ectopic pregnancy, and bowel obstruction.

Management

Diverticulosis

All patients diagnosed with diverticulosis should be placed on a high-fiber diet, which has been shown to reduce abdominal symptoms and recurrent bouts of diverticulitis.[6] It is not known if the common advice to avoid foods that may obstruct diverticula, such as nuts and small seeds, is of any real merit.

Uncomplicated Diverticulitis

Uncomplicated diverticulitis in an immunocompetent, nonelderly patient can be managed on an outpatient basis with oral antibiotics[11] (Box 93-4). Coverage for gram-negative aerobic and anaerobic bacteria is required. Patients may be placed on a liquid diet for comfort, although this is not mandatory. NSAIDs or narcotics are appropriate for pain control, but many experts recommend avoiding morphine sulfate because it increases intraintestinal pressure, which theoretically can precipitate perforation.[5] A high-fiber diet prevents recurrent diverticulitis for 5 years in 70% of patients.

Patients with significant comorbid illness or other problems, including inability to tolerate oral liquids, poor social support, and inability to comply with follow-up in a reasonable time frame (2 to 3 days), should be considered for hospital admission. Hospitalized patients generally are treated with intravenous antibiotics (Box 93-5) and placed on bowel rest, although patients hospitalized for psychosocial reasons can be treated with oral medications.

Complicated Diverticulitis

Patients with complicated diverticulitis should be admitted to the hospital and treated with intravenous antibiotics. Emergent surgical intervention is indicated for all patients with peritonitis or perforation. Newer techniques using a laparoscopic approach with lavage and biologic glue have supplanted open surgical techniques in some patients.[12] Continuing clinical decline, sepsis resistant to medical management, or a high level

BOX 93-4 Oral Antibiotic Therapy for Uncomplicated Diverticulitis

- Trimethoprim-sulfamethoxazole, double-strength tablets bid, *and* metronidazole, 500 mg q6h *or*
- Ciprofloxacin, 750 mg bid, *and* metronidazole, 500 mg q6h *or*
- Amoxicillin-clavulanate extended-release, 1000/62.5 mg, 2 tabs bid *or*

All oral regimens should be taken for 7 to 10 days.

From Gilbert DN, Moellering RC Jr, Eliopoulos GM, Sande MA (eds): The Sanford Guide to Antimicrobial Therapy, 37th ed. Sperryville, Va, Antimicrobial Therapy, Inc, 2007.

BOX 93-5 Intravenous Antibiotic Coverage for Bowel Flora

Mild to Moderate Infection

- Ticarcillin-clavulanate, 3.1 g IV q6h *or*
- Ampicillin-sulbactam, 3 g IV q6h *or*
- Ciprofloxacin, 400 mg IV q12h, *and* metronidazole, 1 g IV q12h

Severe Infection

- Ampicillin, 2 g IV q6h, *and* metronidazole, 500 mg IV q6h, *and* (gentamicin, 7 mg/kg q24h, *or* ciprofloxacin) 400 mg IV q12h *or*
- Imipenem, 500 mg IV q6h

From Gilbert DN, Moellering RC Jr, Eliopoulos GM, Sande MA (eds): The Sanford Guide to Antimicrobial Therapy, 37th ed. Sperryville, Va, Antimicrobial Therapy, Inc, 2007.

of suspicion for carcinoma warrants urgent surgical consultation.[8] Small abscesses (less than 5 cm in diameter) are treated with intravenous antibiotics alone (see Box 93-5), whereas larger abscesses are drained either percutaneously with imaging guidance or surgically.[13] Bowel obstruction during an attack of diverticulitis usually is self-limited and resolves with conservative management. Chronic recurrent diverticulitis can result in stricture, which necessitates surgical intervention. Fistulas usually are repaired surgically. A significantly dilated cecum (to greater than 10 cm in diameter) or gas in the bowel wall should prompt early consultation with a surgeon about the possibility of bowel necrosis and impending perforation.[5]

Definitive Management

It is not known whether medical or dietary treatment is of benefit in diverticulitis. The only proven way to eradicate diverticula is to remove the affected segment of colon surgically. Most patients who recover from their first attack of diverticulitis are likely to remain asymptomatic for many years. With subsequent attacks, the likelihood of recurrence increases. Elective resection of diverticula generally is reserved for patients who have had more than one attack of diverticulitis. According to some experts, younger patients (i.e., younger than 40 years of age) should undergo elective resection after their first bout of diverticulitis because of concerns about a higher risk for a second attack, but this recommendation is controversial, with recent evidence suggesting that outcomes are better without surgery.[8,14] Most resections can be done laparoscopically with a single-stage procedure (no colostomy).[14] Estimates on recurrence of diverticular disease after resection vary, ranging from 3 to 27%.[5-7,14]

Disposition

Uncomplicated Diverticulitis

Nonelderly and immunocompetent patients may be sent home on oral antibiotics with referral for follow-up evaluation in 2 to 3 days to determine the success of treatment. Patients are cautioned to return to the ED if their condition worsens. Patients not significantly improved at follow-up should undergo diagnostic imaging to look for an abscess and be hospitalized for intravenous antibiotic therapy. Of patients treated medically for their first attack of diverticulitis, 95% remain symptom-free for the next 2 years, and 80 to 90% remain symptom-free permanently.[5,14] Patients with recurrent episodes of diverticulitis should be referred to a surgeon for outpatient consultation for elective resection. All patients should undergo an evaluation for colon cancer when the acute episode has resolved, because the incidence of coexistent cancer has been reported to be as high as 9%.

Complicated Diverticulitis

All patients require hospitalization for intravenous antibiotic therapy and bowel rest. Most patients (65 to 85%) recover with medical management alone; the rest require surgical intervention. Outcomes generally are good, with mortality rates ranging from 1 to 6% for all patients, increasing to 12 to 18% for patients requiring surgery.[4]

■ LARGE BOWEL OBSTRUCTION

Perspective

Large bowel obstruction (LBO) is much less common than small bowel obstruction, but LBO is a more ominous condition because it frequently is associated with malignant disease. One half of all operative cases involving LBO in the United States are the result of colorectal cancer. Adhesions, a common cause of small bowel obstruction, cause only 1 to 8% of LBOs.[15] Other causes of LBO include volvulus, diverticular disease, fecal impaction, strictures (often related to inflammatory bowel disease or chronic colon ischemia), adhesions, hernia, and pseudo-obstruction. Most causes are managed surgically, but pseudo-obstruction responds well to medical management alone.

Principles of Disease

When mechanical obstruction is secondary to an obstructing lesion, either inside the bowel (carcinoma) or outside the bowel (diverticular abscess, volvulus), the bowel becomes increasingly dilated with air, and fluid that cannot be passed distally. As the distention increases, the intraluminal pressure increases. When intraluminal pressure approaches systolic blood pressure, blood flow to the bowel wall is compromised and edema sets in, with subsequent transudation of fluid into the lumen. Transudation along with decreased resorption of intraluminal fluid leads to dehydration. Eventually, as arterial flow to the bowel wall is compromised, ischemia and gangrene develop. Translocation of bacteria from compromised bowel can lead to sepsis. Perforation of the bowel wall follows if the process is not interrupted.[15]

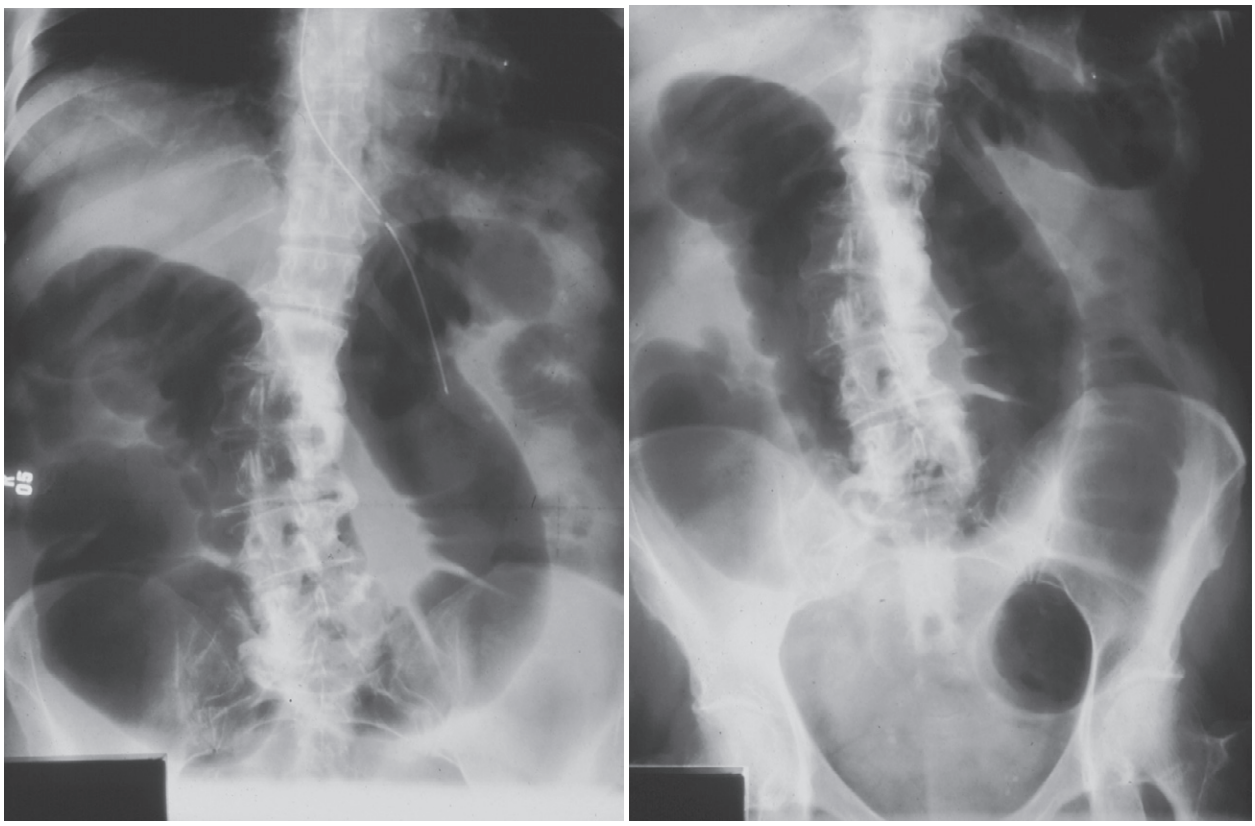
Pseudo-obstruction, also called *Ogilvie's syndrome*, occurs through a completely different mechanism. Pseudo-obstruction is defined as LBO in which no obstructing lesion can be identified. This condition usually is found in patients with significant acute comorbid conditions.[16] Patients typically have a history of significant spine or retroperitoneal trauma, severe electrolyte disturbances, or narcotic exposure. Although the exact mechanism is unknown, it is believed to involve malfunction of autonomic control of the bowel. Normal balance between parasympathetic and sympathetic input is disrupted, resulting in changes in motility that lead to obstruction. The pathophysiologic changes observed with pseudo-obstruction are the same as those described for mechanical obstruction.

Clinical Features

The typical presenting complaints in LBO are abdominal pain, abdominal distention, obstipation, and vomiting. The time frame within which these symptoms develop varies in accordance with the rapidity of onset of the obstruction. LBO associated with a volvulus can develop rapidly, whereas obstruction from cancer tends to be of gradual onset. Patients presenting later in the course of obstruction may be significantly dehydrated. Significant fever or tachycardia should prompt an investigation for gangrene and perforation. A palpable abdominal mass may represent a tumor, an abscess, or simply distended bowel. A rectal examination is helpful to look for an obstructing rectal mass or a large volume of hard stool in the rectal vault consistent with fecal impaction.

Diagnostic Strategies

Electrolyte measurements may be helpful in guiding fluid and electrolyte replacement therapy. A significantly elevated white blood cell (WBC) count should raise suspicion for gangrenous bowel, whereas anemia suggests the possibility of colorectal cancer.



A B

Figure 93-1. Plain radiographs showing large bowel obstruction at the sigmoid colon caused by carcinoma. **A,** Erect view. **B,** Supine view.

Plain Radiography. A distended colon is the hallmark of LBO (Fig. 93-1), although small bowel may be distended as well if the ileocecal valve is incompetent. In some cases, gas-filled small bowel may obscure visualization of the colon, leading to the misdiagnosis of small bowel obstruction. An abrupt cutoff at the distal end of the obstructed colonic segment suggests a possible pseudo-obstruction. A cecal diameter exceeding 12 cm is of concern because this finding is associated with a higher risk of perforation.[16] The actual location and cause of the LBO usually are not evident on plain films.

Computed Tomography. CT is a valuable tool for determining the cause of the obstruction, especially if the cause is a diverticular abscess or intussusception.[15] CT typically is less helpful in pseudo-obstruction, in which either colonoscopy or a water-soluble contrast enema study is needed to make the diagnosis.

Colonoscopy and Water-Soluble Contrast Enema Patients in whom the cause of obstruction is not known and who are not candidates for urgent surgical intervention should undergo either a water-soluble contrast enema study or colonoscopy to determine the etiology of the obstruction. This diagnostic strategy is much more accurate in ruling out pseudo-obstruction than imaging.

Differential Considerations

The most common causes of LBO are colorectal cancer (53%), volvulus (17%), diverticulitis (12%), and compression from metastatic disease (6%). Other, less common causes are strictures, incarcerated hernia, fecal impaction, adhesions, and pseudo-obstruction.

Management

Management in the ED is directed at relief of symptoms. Rehydration, electrolyte replacement, and pain management are the first concerns. Gastric decompression with a nasogastric tube may be helpful in cases in which vomiting is prominent or when there is evidence of significant fluid or gas buildup in the small intestine. No additional fluid or solids should be administered by mouth. Antibiotics are indicated if gangrene or perforation is suspected (see Box 93-5). Definitive management depends on the cause of the obstruction, which may or may not be determined in the ED. Select diverticular abscesses may be drained percutaneously, whereas a sigmoid volvulus or pseudo-obstruction can be decompressed endoscopically. Diverticular disease and sigmoid volvulus eventually necessitate an elective surgical procedure to prevent recurrence, although this often can be delayed. Carcinoma, cecal volvulus, strictures, intussusception, adhesions, and hernias are dealt with primarily surgically.

So long as the possibility of perforation is not an immediate concern, pseudo-obstruction is managed for the first 24 hours with bowel rest, hydration, and management of any acute comorbid conditions. If the colon fails to decompress, colonoscopic or pharmacologic intervention (neostigmine)[16] may be attempted, with surgery reserved for refractory cases.

Fecal impaction generally is managed definitively in the ED through digital disimpaction or an enema. Particularly helpful are retention enemas, for which the patient retains the enema fluid in the rectum for 15 minutes or longer. Occasionally disimpaction is technically difficult enough to warrant general anesthesia.

Disposition

Most cases of LBO require procedural intervention (surgical, endoscopic, or percutaneous abscess drainage) to achieve resolution. All patients require hospitalization and consultation with a specialist capable of performing the appropriate procedure. Emergent surgical consultation is warranted in patients with evidence of gangrenous bowel or perforation.

■ VOLVULUS

Perspective

Volvulus of the colon occurs when a loop of bowel twists and obstructs the intestinal lumen. If severe enough, the twist may involve and compromise the vascular supply to the loop of colon. The incidence of colonic volvulus is 2.65 cases per 100,000 population per year, accounting for 1 to 7% of all LBOs.[17] Volvulus occurs in all age groups, but older adults are affected most often, with a mean age of 60 to 70 years. One third of cases in the developed world involve institutionalized patients.[17] Most cases are divided roughly equally between the sigmoid colon and the cecum, although volvulus can occur in all other areas of the colon. Sigmoid volvulus typically is a disease of older persons. Mortality rates with sigmoid volvulus exceed 50% in patients who present with gangrenous bowel. In the absence of gangrenous bowel, the risk of death is approximately 10%.

Principles of Disease

Sigmoid Volvulus

The anatomic requirement for a sigmoid volvulus is a long, redundant section of sigmoid that is attached to the abdominal wall by a narrow strip of mesentery. The narrow attachment allows the mesentery to twist on itself, thereby obstructing the intestinal lumen. It is not clear whether this is a congenital condition or occurs as part of the aging process. After the colon twists on itself, the proximal colon continues to force gas and liquid into the obstructed segment, causing a sometimes massive dilation of the distal colon. Significant electrolyte disturbances can occur secondary to third spacing, and respiratory compromise occasionally occurs from massive abdominal distention. If the condition is left untreated, the vascular supply can become compromised, resulting in gangrene and perforation.

The exact precipitator of an acute episode of volvulus is not clear. A high-fiber diet has been implicated, because a significant increase in the disease is noted in patients who are switched to a high-fiber diet. Chronic constipation has been associated with volvulus, but it is unclear how the two conditions are related. Residents of long-term care facilities and patients with neurologic or psychiatric diseases also are predisposed to sigmoid volvulus, possibly as a result of alterations in colonic motility. No association with previous surgery has been observed. Women seem to be at a higher risk for cecal volvulus during pregnancy, presumably because of crowding of the abdominal cavity by the enlarged uterus. The condition is still rare, however, occurring in approximately 1 per 1 million pregnancies.[18]

Cecal Volvulus

As in sigmoid volvulus, a mobile segment of cecum is a prerequisite to the disease. This mobility seems to be due to a congenitally incomplete fusion of the cecal mesentery to the posterior abdominal wall. Cadaver studies show that 10% of the adult population have ceca that are mobile enough to cause torsion.[17] In 10% of the cases, cecal volvulus is due to a variant called *cecal bascule*, in which the cecum does not twist but merely folds over on itself; symptoms and management are the same.[15] The tendency for cecal volvulus may be related to "maneuvering room" available for the colon within the abdomen. Persons with less space in the abdomen for the colon to move about seem to be more predisposed to volvulus in general. Gangrene of the bowel is common and occurs in 20% of patients with cecal volvulus.[19]

Clinical Features

Sigmoid Volvulus

The hallmark of sigmoid volvulus is the triad of abdominal pain, distention, and constipation. The extent to which the sigmoid colon can twist on itself is recognized to vary, so the presentation of sigmoid volvulus will vary accordingly, from subtle to dramatic. The clinical picture may range from one of minor abdominal discomfort that has been present for many days to an acute onset of severe abdominal pain associated with gross abdominal distention and unstable vital signs. Sometimes the diagnosis of sigmoid volvulus is not made until the patient has been hospitalized for some time. In many instances, the history may be suggestive of previous episodes of volvulus that self-reduced.

The physical examination may reveal a distended tympanitic abdomen, often with most of the distention in the upper abdomen but primarily on one side. Patients may look remarkably well for the amount of distention that is encountered. Significant abdominal pain, fever, lack of bowel sounds, peritonitis, or cardiovascular instability suggests gangrenous bowel and should prompt immediate surgical consultation. The absence of these findings does not exclude gangrene, however. The duration of symptoms alone is not predictive of gangrene of the bowel.

Cecal Volvulus

The clinical triad of abdominal pain, distention, and constipation seen in sigmoid volvulus also is seen in cecal volvulus, but many patients with cecal volvulus lack one or more of these findings. Vomiting is seen in only approximately 50% of patients.

Diagnostic Strategies

Sigmoid Volvulus

The diagnosis of sigmoid volvulus can be made on the basis of findings on plain radiographs in most cases. A grossly distended loop of colon lacking haustral markings is typical and is seen just as often on the right side of the abdomen as on the left (Fig. 93-2). The bowel may have the appearance of a "bent inner tube." Free air may be seen on an upright chest film or lateral decubitus radiograph of the abdomen in patients who have a perforation. Gas backing up into the rest of the colon may obscure the typical appearance of sigmoid volvulus on plain radiographs, leading to a significant number of nondiagnostic studies. Cecal volvulus and bowel obstruction from other causes may have a similar radiographic appearance. When the diagnosis is in doubt, contrast enema may be helpful. Contrast material fills up the colon to the tapering point of torsion, giving a "bird's beak" appearance to the column of contrast material (Fig. 93-3). Sigmoidoscopy is diagnostic in many cases, visualizing a spiral sphincter–like twist

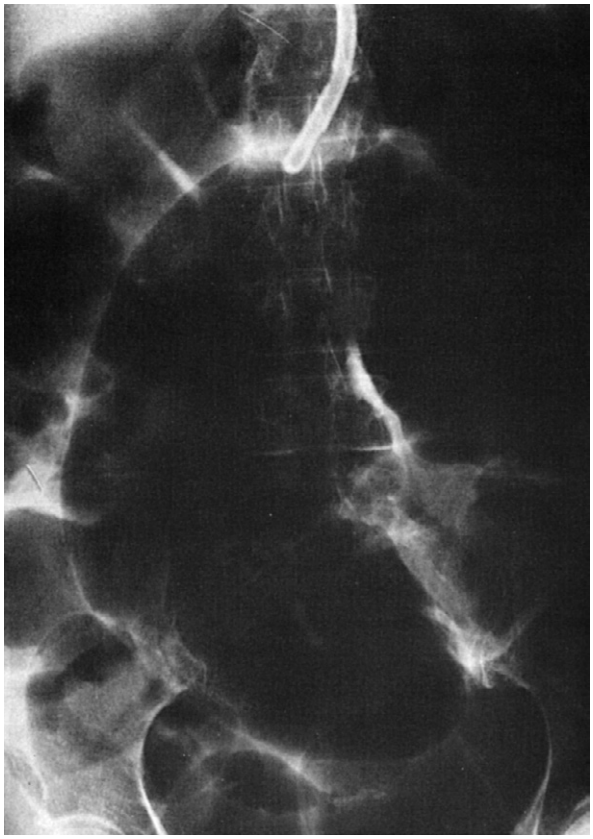


Figure 93-2. Plain film of abdomen shows a large dilated loop characteristic of sigmoid volvulus.

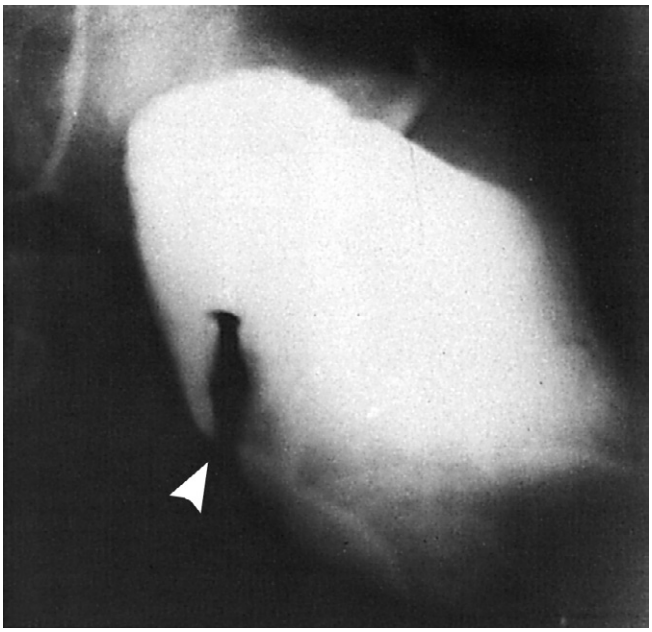


Figure 93-3. Characteristic "bird's beak" sign of volvulus *(arrowhead)* shown on this image from a barium enema study.

in the colonic mucosa.[20] CT scan, when used, also is highly accurate, but most diagnoses can be made without it.[20]

Cecal Volvulus

Plain radiographs often are helpful in establishing a diagnosis of cecal volvulus, but the findings are not definitive in 50% of

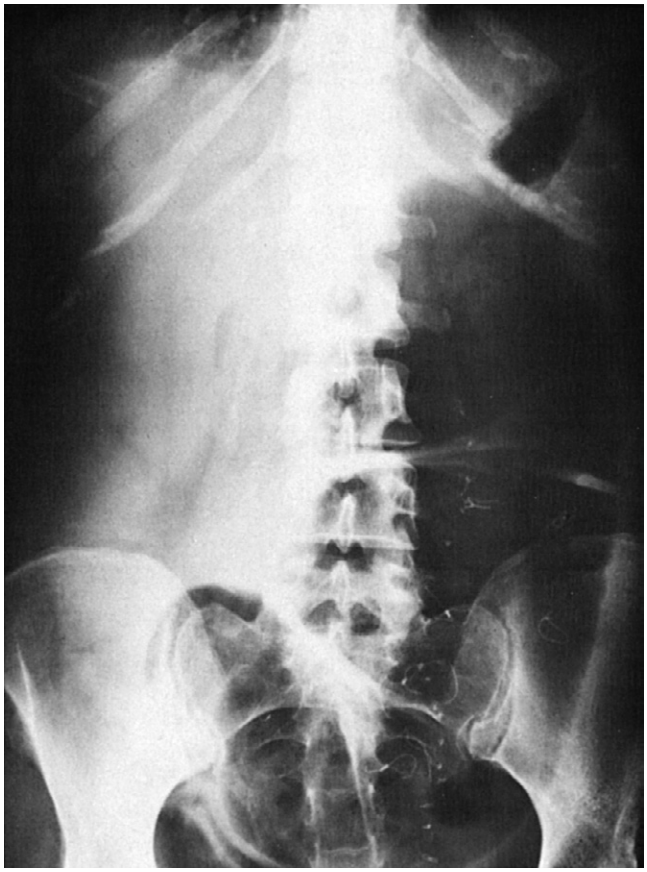


Figure 93-4. Plain film shows distended colon characteristic of cecal volvulus. Note presentation in the left lower quadrant and absence of right-sided gas shadows.

cases. The cecum should be markedly dilated and may contain an air-fluid level. The small bowel often is distended as well. In contrast with the picture in sigmoid volvulus, the distal colon should have a paucity of gas (Fig. 93-4). The classic "coffee bean" sign, a large oval gas shadow with a line down the middle representing bowel bent over on itself, may be seen in the midabdomen. Free air suggests perforation and requires emergent surgical consultation. A common mistake is misinterpreting the plain radiograph as showing a sigmoid volvulus. If the diagnosis is unclear, a contrast enema is helpful in showing the site of torsion. Ultrasound imaging generally is unhelpful.[18] On CT, a mesocolon "whirl sign" may be seen, indicating a twisted segment of mesentery.[21] In many cases, cecal volvulus is definitively diagnosed only at surgery.[19]

Differential Considerations

Any process that causes LBO may mimic volvulus.

Management

Sigmoid Volvulus

Although spontaneous reduction of a sigmoid volvulus can occur, it is infrequent enough to mandate a proactive approach to treatment. If clinical evidence of gangrenous bowel is lacking, endoscopic detorsion should be attempted by an experienced operator. Using the endoscope, the bowel is first examined for any signs of gangrene. If the bowel is healthy,

the twisted, obstructed proximal end of the bowel lumen is identified, and a lubricated rubber tube is inserted through the obstruction. With decompression of gas and liquid stool, the bowel is able to undergo self-detorsion. Endoscopic decompression is successful in 50 to 90% of cases.[15,20] If the patient has gangrenous bowel or the volvulus does not respond to endoscopic decompression, surgery is indicated. Recurrence rates are estimated at 60%; elective resection of the redundant sigmoid is recommended after resolution of the acute episode. The mortality rate for sigmoid volvulus is 20% overall and exceeds 50% in the subpopulation of patients with gangrene.

Cecal Volvulus

The proximal nature of the cecum makes it unavailable for endoscopic manipulation, so detorsion is done surgically. After detorsion, the cecum typically is fixed to the abdominal wall, or the redundant section is resected.[21] Recurrence is rare after resection.

Disposition

All patients with volvulus require hospitalization for detorsion and surgical intervention to prevent recurrence.

■ INTUSSUSCEPTION

Perspective

Intussusception in adults is rare, accounting for only 1 to 5% of cases of adult bowel obstruction. Most adult intussusceptions (80%) are of the small bowel. Although only 10% of children have a pathologic lesion as the cause of the intussusception, 90% of adults do. In the colon, these lesions are malignant 50 to 80% of the time, as opposed to the small bowel, in which malignant lesions are present approximately one third of the time.[22] In adults, the intussusception often is unsuspected before being revealed on a CT scan or during laparotomy. The condition occurs over a wide variety of ages, with a mean age at presentation of 65 years.[23]

Principles of Disease

The exact mechanism of intussusception is unknown, but it is believed that a lesion (the "lead point") changes the motility properties of the intestine, allowing a proximal segment to invaginate into a more distal segment. As peristaltic activity pushes the invaginated segment along with its mesentery and mesenteric blood vessels down the bowel, the blood supply to the segment can be compromised, and ischemia may occur. Edema associated with the intussusception can lead to a mechanical obstruction of the bowel.

Clinical Features

Intussusception in adults manifests in one of two patterns. The most common is that of acute partial intestinal obstruction. Less than 20% of intussusceptions cause complete obstruction.[24] With this pattern, the typical presenting complaint is abdominal pain. Vomiting, bleeding, and constipation may be present but often are not. The abdomen may be distended, and bowel sounds often are decreased. A mass is seldom palpated; the classic triad of abdominal pain, mass, and heme-positive stools noted in children is rarely found in adults. The second presentation is much more subtle, with intermittent abdominal pain for months or years. The diagnosis usually is made only when the pain becomes unrelenting or has been recurrent enough to prompt imaging.

Diagnostic Strategies

Plain Radiography. Plain radiography is a reasonable screening test in a patient suspected of having bowel obstruction, but the radiographs usually show only nonspecific large bowel dilatation.

Computed Tomography. Typically used in the evaluation of abdominal pain and bowel obstruction, CT usually is the most useful test in suspected intussusception but may not detect the actual intussusception in as many as one half of the cases.[22,23]

Ultrasound Examination. Ultrasonography also is helpful in detecting intussusception but is not as useful as CT in excluding other diagnoses. A transverse view of the intussusception has a donut or target shape, with multiple concentric rings. A longitudinal view of the intussuscepted segment has an ultrasound appearance similar to that of a kidney ("pseudo-kidney sign"), with a bright central area surrounded by a darker outer layer.

Barium Enema. Although a barium enema study can demonstrate intussusception and even reduce it, it is a less desirable study than either CT or ultrasound examination for initial diagnosis. In contrast with that in children, reduction of intussusception in adults is not desired before surgery because of concerns about spreading malignant cells from potentially malignant lead points. Barium enema should not be performed in patients suspected of having a bowel perforation.

Colonoscopy. Colonoscopy is helpful in defining the lesion causing intussusception but does not usually detect the intussusception itself.

Differential Considerations

The differential diagnosis includes other causes of bowel obstruction.

Management

Surgery is required in most cases. ED care is supportive and aimed at optimizing fluid status, recognizing gangrene or perforation, administering antibiotics if compromised bowel is suspected, and securing surgical consultation in the appropriate time frame. Because of the high incidence of malignancy, reduction often is not attempted in adults before surgical exploration.[23] Occasionally, intussusception may resolve spontaneously, but an evaluation to exclude a pathologic lead point still must be undertaken.

Disposition

Because of the surgical nature of this disease, all patients require hospitalization. Operative mortality tends to be minimal.[22]

■ INFLAMMATORY BOWEL DISEASE

Perspective

Inflammatory bowel disease (IBD) includes two clinically similar but distinct diseases: Crohn's disease (CD) and ulcerative colitis (UC). Both diseases are characterized by chronic and unpredictable relapsing inflammation of the gastrointestinal tract from causes that have not been definitively identified. Significant morbidity occurs from acute exacerbations of inflammation. It is estimated that more than 1 million people in the United States are affected by IBD.[25] Cases are divided approximately equally between CD and UC, with a combined

annual incidence of approximately 10 cases per 100,000.[26] The long-term management of IBD is a complex, stepwise process that involves multiple medications and surgery. The goals of the ED evaluation are to (1) recognize potential new cases of IBD, (2) consider and exclude serious complications in patients with IBD, and (3) identify those patients with IBD who need in-hospital care. Treatment plans are best developed in consultation with a physician experienced in the long-term management of IBD. Although life expectancy is slightly decreased for patients with CD, it is normal for patients with UC.[27]

Principles of Disease

Ulcerative Colitis

UC causes inflammation and ulceration throughout the colon and rectum, but spares the small intestine. Inflammation is more superficial than that found in CD. Typically, the inflammation exists as one continuous lesion originating in the rectum and extending a variable distance into the colon, although more recently, cases of discontinuous disease ("skip lesions") similar to that in CD have been reported in UC.[28] The concordance rate between identical twins is low (6 to 14%), suggesting that factors other than genetics are involved in the development of UC.[29] Stress can trigger exacerbations, and cigarette smoking has a protective effect, suggesting environmental factors at work. Appendectomy at an early age is protective, suggesting that the immune system may play a role. In animal models of IBD, the disease does not occur in animals that are devoid of normal bowel flora, suggesting that bowel flora are a necessary ingredient for disease.[30] One unifying theory is that UC represents a genetic predisposition to development of an inflammatory reaction to normal intestinal flora—in essence, losing the normal tolerance to these bacteria.

Crohn's Disease

The cause of CD is unknown, but genetic, environmental, immunologic, and infectious processes all have been implicated as possible causative or contributory factors.[26] Concordance between identical twins is 45 to 50%, suggesting a strong genetic predisposition that is modified by other factors.[29] Africans have a low incidence of CD, but African Americans have an incidence similar to that in white Americans.[26] The first genetic mutation associated with CD was described in 2001 and is associated with 10 to 20% of cases of CD.[30] An association between a strain of *Mycobacterium* and CD has been hypothesized, with the evidence being convincing enough to spur legislation in the United Kingdom to eradicate this potential pathogen from the food chain, but recent failures in a randomized controlled trial of antituberculosis medications in CD cast serious doubts on any causal relationship.[31,32] Although the onset of the disease can be at any time of life, CD affects primarily young patients, with onset of disease typically in the teens and 20s. Inflammation in CD is deep, involving the entire colonic wall. The disease is not limited to the colon and rectum as it is in UC but may affect any part of the gastrointestinal tract. CD most often involves the distal small intestine and colon and less commonly the esophagus, duodenum, or stomach.[33] Because of the transmural nature of the inflammation, the development of intestinal strictures or fistulas to adjacent organs is a potential complication.

Clinical Features

Typical presenting complaints in patients with IBD include abdominal pain, often crampy, and tenesmus with loose or diarrheal stools. Blood may be present in the stool. Patients with CD may have a history of nocturnal diarrhea, a complaint that helps differentiate CD from patients who have IBS. Weight loss is common. The physical examination may reveal significant abdominal tenderness or an abdominal mass representing an abscess. Patients with CD may have fissures, ulcerated hemorrhoids, strictures, or cutaneous abscesses around the anus. Extraintestinal manifestations include inflammatory conditions of the skin, eyes, and joints. In children, growth and sexual development may be affected. Onset of symptoms usually occurs before the age of 30 years,[25] although the diagnosis can be difficult to make in the early stages.

Patients often present to the ED with a known diagnosis of IBD and worsening abdominal symptoms. A common reason for relapse is interruption of the medications that have kept the disease in remission. Many patients become complacent during quiescent periods and stop taking such medications. IBD requires continuous, lifelong maintenance therapy. Adherence to therapy has been shown to reduce the risk of acute attacks and cancer.[25] Common complications of IBD include formation of fistulas, strictures, and abscesses; less common but life-threatening complications include fulminant colitis, toxic megacolon, and intestinal perforation.

Toxic Megacolon

Toxic megacolon is a pathologic dilatation of the colon resulting from inflammation of the smooth muscle layers of the intestine. Muscle inflammation leads to paralysis, dilation, and eventually perforation if left untreated. The hallmark of toxic megacolon is colonic dilatation in a patient with a known inflammatory condition of the colon who appears systemically toxic. Presence of inflammation and toxicity differentiates toxic megacolon from other disorders that cause colon dilatation, including mechanical obstruction, pseudo-obstruction, and congenital or acquired megacolon.

Toxic megacolon typically is associated with IBD or infectious colitis. The triggering event may be recent ingestion of anticholinergics, antimotility agents, narcotics, or antidepressants. Patients usually have experienced symptoms of colitis, which often are severe, for several days before the onset of toxic megacolon. Abdominal pain, fever, tachycardia, and abdominal distention are present. Plain radiographs are diagnostic and show a colon with a diameter of 6 cm or greater, although this feature may not be present in early stages. Treatment includes aggressive fluid hydration, intravenous corticosteroids, antibiotics covering bowel flora (see Box 93-5), and an evaluation for potential intestinal infections, especially in immunocompromised patients. The mortality rate has decreased over the past 4 decades to less than 2% as a result of the early recognition and aggressive treatment.

Diagnostic Strategies

No specific laboratory tests available to diagnose IBD are available, although recent tests targeting antibodies to *Saccharomyces cerevisiae* or antineutrophil cytoplasm help to differentiate between CD and UC.[27] Laboratory abnormalities may be due to a variety of reasons. Electrolyte abnormalities may be secondary to significant diarrhea, or anemia may occur from bloody stools. The erythrocyte sedimentation rate can be elevated and useful for categorizing the severity of the disease. Stools contain fecal leukocytes, but findings on stool cultures and ova and parasite examinations should be normal.

Plain radiography is not helpful in the diagnosis of uncomplicated disease but may show bowel obstruction, toxic megacolon, or free air from a perforation (Fig. 93-5). The use of plain films should be limited to patients suspected of having

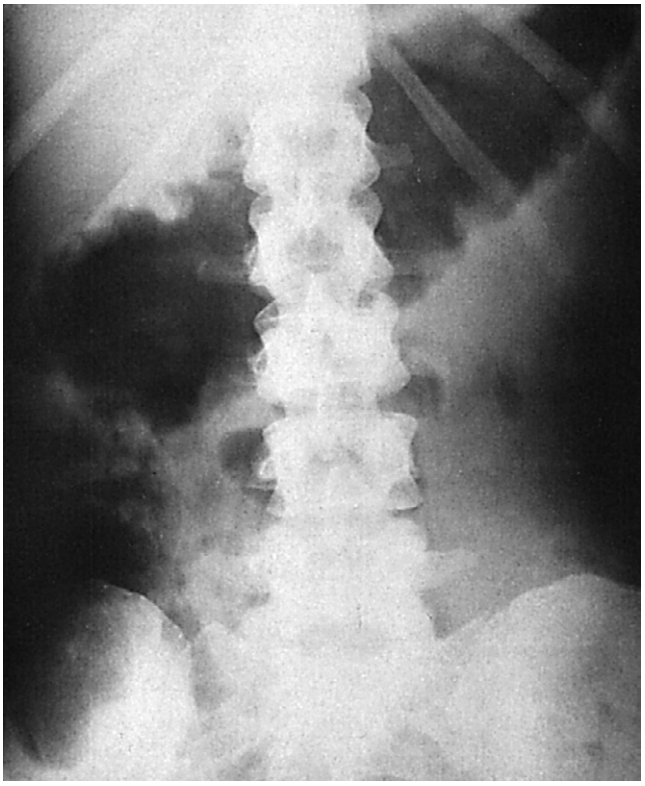


Figure 93-5. Toxic megacolon secondary to ulcerative colitis. The smooth indentations seen along the margin of the colon represent pseudopolyps.

these complications. Contrast studies can reveal lesions suggestive of IBD, including ulcerations of the mucosal surface, fistulas, and strictures. In Europe, where ultrasound technicians are more experienced in its application, ultrasonography is used to identify active disease and to look for complications.[28] Ultrasound imaging is used much less commonly in the United States. Magnetic resonance imaging can locate affected bowel segments and identify fistulas, stenoses, and abscesses. CT is the best study routinely available to evaluate extraluminal complications. CT colonography ("virtual colonoscopy"), although good at identifying cancerous lesions of the colon, does not show the typical lesions of IBD.[28] Endoscopic evaluation with biopsy usually is required to confirm the diagnosis.[27]

Differential Considerations

Symptoms and signs are protean and overlap with those of many common abdominal conditions, including appendicitis, infectious colitis, ischemic colitis, radiation colitis, diverticular disease, cancer, and bowel obstruction.

Management

Medical management is the mainstay of therapy for most patients with IBD. In general, patients are maintained on 5-aminosalicylic acid (5-ASA) agents while asymptomatic and then steroids are added once symptoms recur. Once remission is obtained, steroids are discontinued and the patient is once more maintained on 5-ASA agents. If remission is not obtained with steroids, other agents such as antimetabolites and immunosuppressants are used (Box 93-6). The choice of agents depends on classification of the disease as either *mild to moderate* or *severe* (Box 93-7). Surgery is reserved

BOX 93-6 MEDICATIONS USED IN THE TREATMENT OF INFLAMMATORY BOWEL DISEASE

5-Aminosalicylic Acid Agents
Sulfasalazine
Mesalamine

Antibiotics
Metronidazole
Ciprofloxacin
Rifaximin
Tobramycin

Corticosteroids
Prednisone
Hydrocortisone
Methylprednisolone
Budesonide

Antimetabolites
Azathioprine
6-Mercaptopurine
Methotrexate

Immunosuppressants
Cyclosporine

Anti–Tumor Necrosis Factor Antibodies
Infliximab

BOX 93-7 DISEASE SEVERITY CRITERIA IN INFLAMMATORY BOWEL DISEASE

Ulcerative Colitis

Mild Disease
- >4 stools per day
- Stools may contain some blood
- No systemic signs of toxicity (fever, tachycardia, anemia, elevated erythrocyte sedimentation rate)

Moderate Disease
- >4 stools per day
- Minimal signs of toxicity

Severe Disease
- >6 bloody stools per day
- Signs of systemic toxicity

Crohn's Disease

Mild
- Patient ambulatory and able to eat
- No toxicity
- No significant abdominal pain or mass

Moderate
- Mild disease that has failed to respond to treatment
- Patient may have some systemic toxicity

Severe
- Persistence of symptoms during corticosteroid therapy
- High fever, persistent vomiting
- Intestinal obstruction
- Rebound tenderness
- Cachexia
- Abscess

Adapted from Hanauer SB, Present DH: The state of the art in the management of inflammatory bowel disease. Rev Gastroenterol Disord 3:81, 2003.

for patients with severe disease who do not respond to medical therapy or for complications such as obstruction or fistula formation.

5-ASA agents are the first line of therapy for disease that is not severe. These agents can be administered orally, or rectally if the disease is in or near the rectum. Sulfasalazine, one of the original drugs in this category, is limited by sulfa toxicity at higher doses and has serious side effects including bone marrow suppression. A newer 5-ASA derivative, mesalamine, has less toxicity, allowing higher dosages. When IBD goes into remission after an acute flare, the patient may be continued on 5-ASA derivatives for maintenance therapy.

Antibiotics may be used for the primary treatment of IBD as well, but their use in IBD is controversial. Evidence supporting antibiotic use is stronger in CD than in UC. Metronidazole and ciprofloxacin are the most common antibiotics used, with some evidence suggesting that tobramycin or rifaximin may be beneficial as well.[34]

Oral corticosteroids are used in patients with moderate to severe disease or patients whose IBD is unresponsive to a 5-ASA agent. Steroids should be tapered when remission is achieved to avoid typical steroid side effects. Intravenous corticosteroids are reserved for hospitalized patients with severe disease. Budesonide, a newer oral corticosteroid, is degraded on its first pass through the bloodstream and has fewer systemic side effects.

The immunomodulating drugs azathioprine and 6-mercaptopurine are used in patients resistant to other therapies or to wean steroid-dependent patients off steroids. Patients on these medications should be assessed for bone marrow suppression and pancreatitis.[35]

The immunosuppressant agent cyclosporine is used in severe cases, often when patients are not surgical candidates. Although most patients tolerate it well, cyclosporine has significant potential toxicity, including myelosuppression, electrolyte disturbances, and hepatic and nephrotoxicity.[25] Opportunistic infections including *Pneumocystis* pneumonia have been known to occur.[29]

Infliximab, an antibody to human tumor necrosis factor-α, is useful in advanced cases of IBD. It generally has a benign side effect profile[26] but carries an increased risk of opportunistic infections, including tuberculosis and fungal infections. Surgery is reserved for patients with severe disease refractory to medical management or for patients with complications such as intestinal obstruction, significant bleeding, abscess, or fistula. A colectomy is curative for UC and improves quality of life, but there is no curative surgery for CD. Extraintestinal manifestations usually respond to therapy for intestinal disease.[27,36]

Disposition

Consultation with a gastroenterologist is recommended before patient disposition. Most patients with an uncomplicated mild to moderate exacerbation of IBD need only to restart their maintenance therapy if it was interrupted, or to add oral corticosteroids to their regimen. Patients with severe disease or those in whom oral corticosteroids have failed to effect improvement need hospitalization for administration of parenteral corticosteroids.[27] Bowel rest does not seem to be beneficial except as preparation for surgical intervention.[37] Emergent surgical consultation should be sought for life-threatening hemorrhage, evidence of perforation, or toxic megacolon. Urgent surgical intervention is indicated if the bowel is obstructed. Abscesses may be treated percutaneously with imaging guidance or surgically.[33] Chronic fistulas initially are treated medically.[35] After hospital discharge, close follow-up by the physician monitoring the patient's disease is indicated to ensure that remission is achieved in a timely fashion and that the patient complies with the suppressive therapy after the acute event. For patients in remission, endoscopic monitoring for cancer is required on an ongoing basis, although the optimal frequency of examination has not yet been defined.[35] The estimated prevalence of cancer among patients with CD is significant at 2%,[33] and patients with UC have a 15 times greater risk for the development of colorectal cancer than in the general population.[29]

COLONIC ISCHEMIA

Perspective

Colonic ischemia is the most common of the intestinal ischemic disorders. Estimates place the incidence of colonic ischemia at 1 of every 2000 hospitalizations. Its presentation overlaps with many other significant abdominal diseases, and it is difficult to diagnose without endoscopic visualization of the colonic mucosa. Although elderly persons are most at risk, with 90% of cases in those older than 60 years of age, the condition can occur in all age groups.[38] Both sexes are equally affected. In one study, more than 50% of persons admitted with colonic ischemia initially were diagnosed with IBD. Because there is no specific treatment and outcomes usually are good, the difficulty in making the diagnosis does not cause significant morbidity.

Principles of Disease

The exact cause of colonic ischemia is unknown. Isolated ischemia without small bowel involvement usually is due to nonocclusive microvascular disease of the colon and not to large vessel (mesenteric artery) occlusion. The primary insult is a low-blood-flow state associated with a variety of factors including congestive heart failure, vasoactive drugs, atherosclerosis, renal failure, and recent cardiac or vascular surgery.[38-40] Younger patients may suffer colonic ischemia in the setting of collagen vascular disease, hematologic disorders, long-distance running, or cocaine abuse. The colonic vascular system generally enjoys significant collateral flow, but in some patients this protective mechanism is tenuous, predisposing the affected person to ischemia from low-flow events.[38] In addition, colonic arterioles seem to be particularly sensitive to vasoconstrictive influences, and the rapid-growing intestinal mucosa is especially vulnerable to interruptions in blood flow. High intraluminal pressures that normally develop within the colon also can alter intestinal perfusion significantly. Colonic ischemia can occur in any part of the colon, including the rectum, but for unknown reasons it occurs most often in the left colonic segment.

Colonic ischemia represents a spectrum of disease whose manifestations vary with the extent of the ischemic insult. In most cases, the ischemic episode is self-limited and the condition resolves completely with conservative therapy, but in one third of patients, a prolonged or severe insult results in scarring or stricturing of the colon and chronic symptoms.[35] If the ischemia is transmural, gangrene and intestinal perforation are possibilities. Chronic mild inflammation results in intermittent symptoms similar to those of IBD.

Clinical Features

The presentation of colonic ischemia may vary but typically involves the acute onset of mild crampy abdominal pain in the left lower quadrant with abdominal distention and almost

always blood in the stool.[41] The typical patient has had recent surgery or has a significant medical illness. Some patients present without pain. Nausea and vomiting can occur with obstruction secondary to a stricture or an ileus. Tenderness over the affected colon may be present but often is not dramatic. Peritoneal findings, fever, and a significantly elevated WBC count suggest gangrenous bowel and perforation. Toxic megacolon is a recognized complication.

Diagnostic Strategies

No sensitive or specific biochemical markers for colonic ischemia are recognized, although biochemical abnormalities such as elevated serum lactate, phosphate, and alkaline phosphate levels may be present. These abnormalities may be absent in milder disease and often are not observed in more significant disease until after irreversible damage has occurred. A complete blood count to exclude significant anemia and to look for a leukocytosis suggestive of perforation is appropriate. Serum electrolytes should be checked if diarrhea or vomiting has been significant or prolonged. Stool blood and WBCs are common findings in several of the entities that present similarly to colonic ischemia, including IBD and infectious colitis. A positive occult stool guaiac test result should ensure that the patient is eventually evaluated for colonic carcinoma. Unfortunately, the definitive diagnosis of colonic ischemia rarely is made in the ED.[41]

Plain Radiography

Plain radiographs often show only nonspecific dilated bowel. Findings specific for colonic ischemia occur in only 20% of patients. The classic findings are intraluminal prominences, known as *thumbprinting*, representing submucosal hemorrhage and swelling. Thumbprinting also can be seen occasionally with other disorders, including IBD, colonic infections, or hemorrhage secondary to anticoagulants. Other findings consistent with colonic ischemia include wall thickening and ahaustral segments. Air in the portal venous system or bowel wall suggests imminent intestinal infarction.

Barium Enema

Thumbprinting is detected more often by barium enema than by plain radiography, but this study has largely been replaced by colonoscopy.

Colonoscopy

Colonoscopy with colonic biopsy is the preferred method to diagnose colonic ischemia because it visualizes the abnormal colonic mucosa better than barium enema and affords the opportunity to take biopsy specimens to differentiate between cancer and other non-ischemic causes of colitis. Colonoscopy also can detect necrotic bowel by its distinct cyanotic or black appearance. If colonoscopy is delayed, pathologic changes consistent with colonic ischemia may have already improved or resolved. The diagnosis may be missed on colonoscopy in up to one third of cases.[39]

Computed Tomography

Although CT does not allow the definitive diagnosis of colonic ischemia, it can exclude other disorders. CT features suggestive of colonic ischemia include thumbprinting, wall thickening, and luminal narrowing and inner wall hypoperfusion ("double halo sign").[38]

Angiography

Angiography usually is not helpful in either the diagnosis or the management of colonic ischemia. In most cases, the blood flow defect is at the microvascular level and has resolved by the time the patient presents for evaluation.[42] The exception is the case in which only the ascending colon is affected, suggesting a superior mesenteric artery thrombosis.

Differential Considerations

The symptoms of colonic ischemia are nonspecific and overlap with those of numerous other disorders including IBD, radiation proctocolitis, and infectious colitis, and of other causes of nonprofuse lower gastrointestinal bleeding. If strictures are present, the possibility of diverticulitis or colon cancer should be considered.

Management

In the absence of surgical complications, the treatment of colonic ischemia is supportive and includes hospitalization for bowel rest, hydration, and pain management, with some authors recommending antibiotic coverage.[38] NSAIDs are best avoided, as are oral cathartics or bowel preparation regimens that may lead to perforation. Broad-spectrum antibiotics covering bowel flora are indicated for patients with more significant symptoms (see Box 93-5). If colonic ischemia is precipitated by an episode of hypotension, the underlying cause of the hypotension must be sought and treated aggressively, and cardiac output must be maximized.[43] Vasopressors should be avoided to prevent worsening of ischemia, as should steroids, which may facilitate bowel perforation. Colonic distention if present can be relieved acutely through the use of a rectal tube; surgical consultation is recommended in these cases. Decompression of the colon may result in a lowering of transmural pressure and improved colonic perfusion. Sepsis, peritoneal changes, free abdominal air, significant fever, massive bleeding, and a significant leukocytosis suggest bowel necrosis or perforation and should prompt emergent surgical consultation.[38,40]

Disposition

Patients with mild symptoms and no significant abdominal tenderness or bleeding can be managed on an outpatient basis and referred for colonoscopy. Stool studies including cultures for bacteria, microscopy to look for ova and parasites, and a *Clostridium difficile* titer are helpful if the diagnosis is uncertain. Patients with more significant findings, especially if the diagnosis of gangrenous bowel cannot be excluded, require hospitalization. A high mortality rate (60%) is expected for patients undergoing emergent surgery, although deaths before the age of 50 years are rare.[40] Most patients improve without surgical intervention, and only 5% have a recurrence of colonic ischemia. Colectomy usually is curative.

■ RADIATION PROCTOCOLITIS

Perspective

Radiation proctocolitis is a common side effect of radiation therapy, occurring in 50 to 75% of patients receiving radiation to the pelvis. The disease has two distinct presentations: acute and chronic. *Acute radiation proctocolitis* begins during or shortly after a course of radiation therapy, usually is easily diagnosed, and is self-limited. *Chronic radiation proctocolitis* occurs in 5 to

10% of patients who have had pelvic radiation therapy and typically begins any time up to 2 years after the end of radiation therapy, although onset of clinical manifestations may be delayed beyond 2 years. Some cases have occurred decades later. Patients with more severe acute radiation proctocolitis seem to be prone to chronic proctocolitis.[44] Because of its nonspecific presentation and delayed appearance, the diagnosis of chronic radiation proctocolitis can be challenging. Patients at risk for chronic radiation proctocolitis seem to be those with more severe acute disease.

Principles of Disease

Radiation causes tissue injury through the creation of oxygen free radicals, which damage cellular DNA. The faster the growth rate of cells, the more this DNA damage affects their function. For this reason, radiation is an effective treatment for neoplastic disease, but it also damages rapidly growing normal tissue, such as intestinal epithelium. Radiation damage also may adversely affect anal sphincter function, leading to bowel incontinence.

Acute Radiation Proctocolitis

Intestinal epithelium normally is sloughed and replaced at a rapid rate. After the start of radiation therapy, growth of replacement epithelium is slowed, but sloughing continues at the preexposure rate. This mismatch leads to gaps in the epithelium, which over time coalesce into ulcerations. In addition, edema and inflammatory changes of the submucosa cause excessive mucus secretion and bleeding. When radiation therapy has ended, the cycle of damage stops, and healing occurs over the next few weeks.

Chronic Radiation Proctocolitis

The pathologic mechanism in chronic radiation proctocolitis is entirely different from that in acute radiation proctocolitis. Chronic radiation proctocolitis results from a progressive endarteritis with abnormal tissue collagen deposition. Affected intestine has a decreased microvascular density, with subsequent decreased perfusion.[45] Over time, affected bowel gradually becomes more ischemic, leading to ulceration, scarring, and narrowing of the bowel lumen. Frank necrosis and perforation, although uncommon, can occur. Long-term outcomes in chronic radiation proctocolitis have not been well studied, but it seems that patients in whom fistulas and persistent bleeding strictures develop have the poorest prognosis.[44]

Clinical Features

Acute radiation proctocolitis manifests with abdominal pain, bleeding, and tenesmus. Onset during the course of radiation therapy, typically after several treatments, suggests the diagnosis. Fecal urgency and incontinence can be devastating to quality of life.[45]

Chronic radiation proctocolitis has a more insidious onset with a variety of presentations, including ulcerative disease, stricture with or without obstruction, fistulas, and bowel perforation. Symptoms may be similar to those in acute disease, with tenesmus, diarrhea, and urgency. Bleeding can occur but usually is not hemodynamically significant. Decreased caliber of stool with increased straining or constipation suggests a stricture. Fistulas can develop between affected bowel and any adjacent organ, but the most common fistulas are rectovaginal. Some patients may exhibit anal sphincter dysfunction and loss of bowel control. Symptoms tend to have a significant negative impact on the quality of life.[44]

Diagnostic Strategies

The diagnosis of acute radiation proctocolitis is made clinically on the basis of the development of typical symptoms in the setting of radiation therapy. Further evaluation usually is not warranted.

Chronic radiation proctocolitis typically is a diagnosis of exclusion. Endoscopy can be suggestive, revealing pale, thickened, and friable mucosa with prominent telangiectasias. Biopsy specimens often show only nonspecific chronic inflammation. In some cases, endoscopy may be technically difficult because of scarring and reduced mobility of the intestine. Barium enema is an acceptable alternative when endoscopy is problematic, so long as bowel perforation is not a concern.

Differential Considerations

In chronic radiation proctocolitis, the possibility that symptoms are due to recurrence of the initial malignancy or a new malignancy induced by radiation exposure must be entertained. Symptoms of chronic radiation proctocolitis generally are clinically indistinguishable from those of other causes of bowel inflammation, including inflammatory bowel disease, infectious colitis, and ischemic colitis.[46]

Management

Treatment of acute radiation proctocolitis is symptomatic, and a therapeutic plan should be developed in conjunction with the patient's radiation therapist. Steroid enemas to reduce inflammation and water-absorbing stool softeners to reduce mucus-containing diarrhea are helpful. Reduction of the daily radiation dose also can reduce symptoms significantly.

Chronic radiation proctocolitis treatment also is symptomatic. If rectal involvement is significant, stool softeners, analgesics, anti-inflammatory agents (e.g., sulfasalazine, balsalazide), and sucralfate enemas are helpful. Metronidazole is beneficial when added to anti-inflammatory therapy. Minimally symptomatic strictures can be managed initially with stool softeners and enemas as needed. Some strictures have a reversible edema component, so the extent of narrowing may lessen after treatment. Fistulas and significant strictures generally require surgical repair. Approximately 20% of all patients with chronic radiation injury to the intestinal tract require some type of surgical intervention. Biopsy specimens from ulcerations associated with chronic injury should be obtained to exclude malignancy.

Disposition

Suspected perforation mandates emergent surgical consultation, and signs of bowel obstruction should prompt urgent surgical consultation. Unless symptoms are severe, patients with acute or chronic radiation proctocolitis usually can be managed on an outpatient basis under the care of their radiation therapist or gastroenterologist. With acute disease, symptoms typically resolve several weeks after radiation treatments have been completed. Mild chronic disease typically resolves with medical therapy, but more severe symptoms often require aggressive intervention.

KEY CONCEPTS

- New or atypical symptoms in a patient with known IBS should prompt an evaluation for other abdominal pathology.
- A new diagnosis of IBS should be left to the primary care setting; the purpose of the ED evaluation is to exclude other abdominal disorders.
- A positive result on testing for fecal occult blood should never be assumed to be due to diverticula. An appropriate investigation to exclude malignancy is essential.
- Uncomplicated diverticulitis can be diagnosed and treated without imaging in many patients.
- An LBO should prompt an evaluation for malignancy.
- Gangrene or perforation should be suspected in any patient with persistent unexplained tachycardia, fever, or remarkable abdominal tenderness that is associated with intestinal disease.
- Volvulus often appears as a nonspecific large bowel obstruction on plain radiographs.
- Although typically a disease of older persons, volvulus can occur at any age.
- Intussusception in adults most commonly is associated with a significant cause, often a malignancy.
- Intussusception in adults usually manifests as a partial small bowel obstruction and rarely is associated with the classic triad of abdominal pain, mass, and heme-positive stool that is seen in children.
- IBD is a lifelong relapsing disorder that can be treated with a variety of therapies. Management decisions are best made in consultation with the physician who will be providing ongoing care for the patient.
- Treatment of uncomplicated IBD depends on the clinical classification of disease severity (see Box 93-7).
- A new diagnosis of IBD in an elderly patient should be made only after the exclusion of colonic ischemia.
- Any evidence of blood in the stool should prompt an evaluation for colon cancer.
- Chronic radiation proctocolitis should be considered in any patient with a history of irradiation of the pelvis or abdomen who presents with symptoms of gastrointestinal inflammation. This is true regardless of how long ago the radiation therapy was received.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 94

Disorders of the Anorectum

Wendy C. Coates

PERSPECTIVE

Patients present to the emergency department (ED) with a variety of anorectal complaints. Such problems may be self-limited or may signify the presence of an underlying medical condition. A high degree of sensitivity and a professional demeanor should be maintained in interactions with these patients, who may find it difficult to discuss historical details openly and to describe physical complaints related to this area of the body and its function.

PRINCIPLES OF DISEASE

The anorectum marks the end of the alimentary canal. From its beginning at the rectosigmoid junction at the level of the third sacral vertebra (S3), the rectum follows the sacral curvature for 12 to 15 cm and then sharply turns posteriorly and inferiorly at the puborectalis muscle (Fig. 94-1). Here the anal canal begins its 4-cm course to the anal verge, the orifice whereby stool exits the body. It is supported by three muscle groups, the levator ani and the internal and external anal sphincters. Anal valves are located 2 cm proximal to the anal verge at the dentate line. Above the valves are the anal crypts, which contain mucous glands to provide lubrication during defecation. These constitute a nidus for abscess and fistula formation if occluded. Proximal to the crypts are the columns of Morgagni, where the epithelium of the anal canal changes from pink columnar (as in the rectum) to squamous.[1-3]

The superior, middle, and inferior hemorrhoidal arteries provide the blood supply to the anorectum. They arise from the inferior mesenteric, internal iliac, and internal pudendal arteries, respectively. The superior hemorrhoidal veins drain into the portal system, and the inferior hemorrhoidal veins drain into the caval system. Lymphatic drainage is to the inferior mesenteric nodes above the dentate line and to the inguinal nodes from all areas of the anorectum.[2]

Sympathetic and parasympathetic nervous systems function together to retain the contents of the rectum until evacuation is desired. Continence is maintained when sympathetic fibers from L1 to L3 (upper rectum) and presacral nerves (lower rectum) inhibit contraction of rectal smooth muscle and L5 fibers cause the internal sphincter to contract. Elimination occurs when parasympathetic fibers from the anterior roots of S2 to S4 cause the rectal wall to contract and the internal sphincter to relax. Voluntary external sphincter control is mediated by motor branches of the pudendal nerve (S2, S3) and the perineal branch of S4. The levator ani is supplied by the pudendal nerve and pelvic branches of S3 to S4 fibers. Sensory perception of rectal distention involves a signal pathway from extramural receptors to parasympathetic fibers from S2 to S4. The abundant sensory nerve endings of the distal anal epithelium perceive sensations that are transmitted by the pudendal nerve.[2]

Defecation begins as the rectum becomes distended, the internal sphincter relaxes, and stool enters the anal canal. At an appropriate time and place, the external sphincter is relaxed to complete the process of elimination. Sometimes voluntary straining is needed to assist in the passage of stool. When the Valsalva maneuver is performed, the abdominal muscles contract, the rectal angle straightens, and the pelvic floor descends. To postpone defecation, the external sphincter contracts voluntarily. This contraction relaxes the rectal wall and quells the urge to defecate unless there is an underlying sphincter disorder or an overwhelming volume of stool.[4]

CLINICAL FEATURES

History

A complete history of anorectal and gastrointestinal (GI) symptoms and the presence of systemic disease elucidates the diagnosis of most anorectal disorders (Box 94-1; Fig. 94-2). Common complaints include bleeding, swelling, pain, itching, and discharge. Standard historical questions about time and circumstances of onset, duration, quality, and exposure to radiation should be asked. Alterations in bowel habits should be noted. These include changes in color, frequency, or consistency of the stool and the presence of straining, flatus, and incontinence of solid or liquid stool. Persons with underlying GI disorders (e.g., Crohn's disease, cancer, polyps) are predisposed to atypical presentations of anorectal problems. Similarly, those with underlying systemic diseases such as acquired immunodeficiency syndrome (AIDS), cancer, diabetes mellitus, and coagulopathy are prone to develop more serious complications of standard anorectal conditions. Finally, patients should be asked directly about sexual practices involving the anus.[5]

Rectal Bleeding

The color, amount, and relationship to defecation are important factors in establishing the cause of rectal bleeding. Approximately 10 to 20% of the population experiences rectal bleeding at some time.[6] Pain and bright red blood signify anal

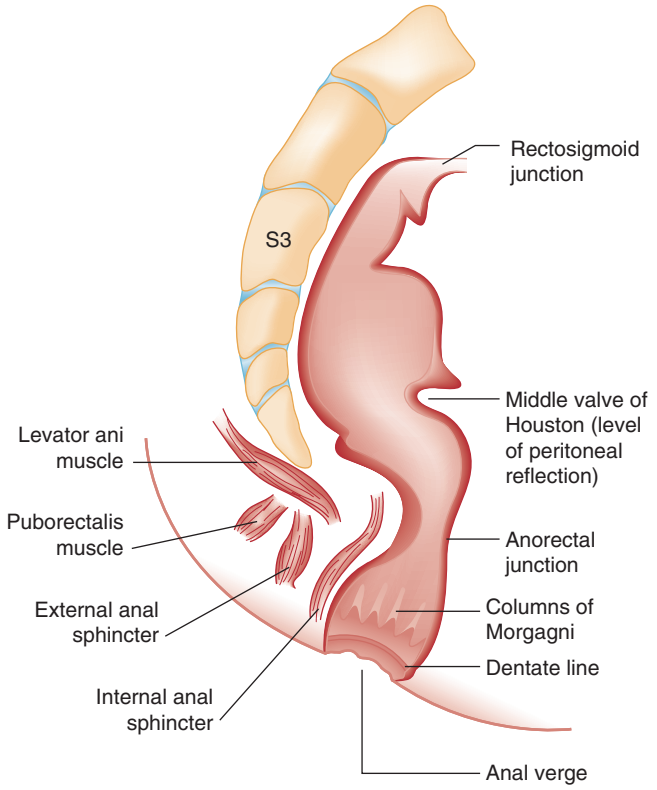


Figure 94-1. Anorectal anatomy.

BOX 94-1 MEDICAL HISTORY IN DIAGNOSIS OF ANORECTAL DISORDERS

Anorectal History
Pain
Bleeding
Swelling
Itching
Discharge
Urgency

GI History
Change in bowel habits (straining, flatus, color, consistency, frequency)
Nausea or vomiting
Incontinence of stool
Underlying GI disease (Crohn's disease, cancer, polyps)

Systemic Disease History
Diabetes mellitus
Coagulopathy
Cancer
HIV infection

Sexual History of the Anus
Penetration
Known STDs
Assault

GI, gastrointestinal; HIV, human immunodeficiency virus; STD, sexually transmitted disease.

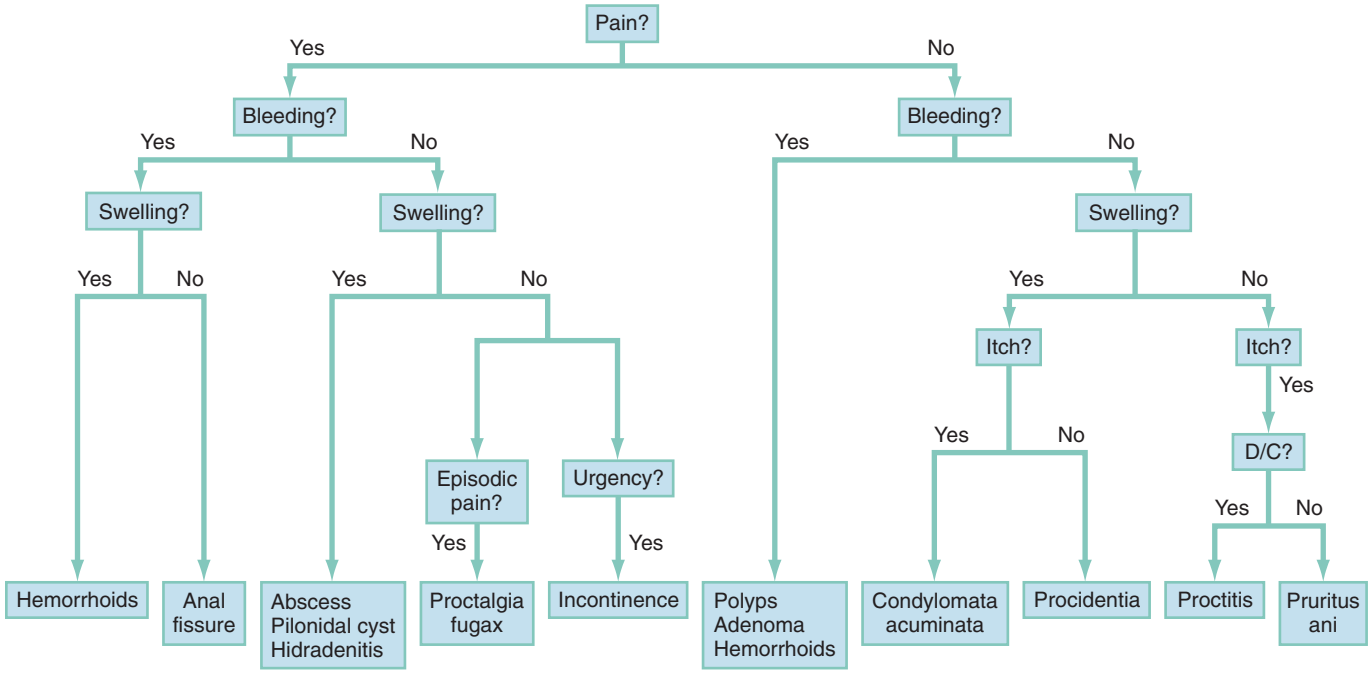


Figure 94-2. Algorithm for anorectal complaints. D/C, discharge.

fissures or hemorrhoids. Fissure pain is sharp, sudden in onset, and not associated with swelling, whereas pain from a prolapsed or thrombosed hemorrhoid is gnawing, continuous, and of more gradual onset. Painless rectal bleeding occurs with internal hemorrhoids, cancer, or precancerous lesions.

The relationship of bleeding to defecation is important. Visible blood on the toilet paper usually is caused by anal fissures or external hemorrhoids; however, minute quantities can result from any irritating condition. Bright red blood that drips into the toilet bowl or streaks around the stool is caused by internal hemorrhoids. Blood mixed with stool originates proximal to the rectum, whereas melena indicates a very proximal source. Bloody mucus is associated with cancer, inflammatory bowel disease, and proctitis.[1,6]

Swelling and Masses

Patients who complain of a swelling near the anus or have the sensation of rectal fullness often list hemorrhoids as their chief complaint. Painful swellings that bleed usually are thrombosed hemorrhoids, but other painful lesions such as abscesses, pilonidal disease, and hidradenitis suppurativa must be considered. Painless, itchy swellings may be caused by condylomata acuminata or secondary syphilis. A mass protruding through the anal orifice may signal rectal prolapse.[1] Perianal and rectal carcinoma should be considered in older persons and those with long-standing anorectal complaints.[5]

Pain and Itching

Severe, episodic anorectal pain that is not associated with bleeding or swelling may represent proctalgia fugax or levator ani syndrome. Perianal itching (pruritus ani) is caused by any lesion that makes hygiene difficult to maintain or may be attributed to certain foods or medications.

Physical Examination

The physical examination should take place in private, respecting the patient's modesty. The patient can then relax the external sphincter to facilitate a complete examination. The patient is placed in the left lateral decubitus position and covered with a sheet. The buttocks are inspected for dermatologic manifestations of disease and then gently spread apart to expose the anal orifice. Elements of personal hygiene are noted, in addition to anatomic disruptions such as fissures, skin tags, lesions, protruding hemorrhoids, or abscesses. The patient is asked to strain to assess the integrity of the pelvic floor and note prolapse of hemorrhoids or rectal mucosa. Next, a well-lubricated gloved finger is placed flat against the anal opening, exerting gentle pressure until the external sphincter relaxes and allows the finger to enter the anus. Anal sphincter tone can be assessed by asking the patient to squeeze the anal muscles against the examining finger. By sweeping the finger in a circumferential manner, accessible areas of the anorectum can be examined for masses and areas of tenderness. The cervix or prostate is palpated through the rectal wall. A bidigital examination reveals masses and tender areas at the distal portion of the anal canal and perineum. On withdrawal, the contents on the glove can be assessed for frank or occult blood, mucus, or pus.[1]

Direct visualization can be accomplished by anoscopy. With the patient positioned as described, the lubricated anoscope is inserted into the anus with the obturator in place. The obturator is removed to allow a circumferential view of the rectal mucosa. Attention is directed to sites of bleeding, hemorrhoids, masses, or abnormal tissue and finally the dentate line and anal epithelium.

SPECIFIC ANORECTAL PROBLEMS

Hemorrhoids

Perspective. When the Philistines defeated the Israelites, the book of I Samuel reports the fate of the avengers: "A deadly panic had seized the whole city, since the hand of God had been very heavy upon it. Those who escaped death were afflicted with hemorrhoids, and the outcry from the city went up to the heavens."[7] In 1815 the battle of Waterloo marked the defeat of Napoleon's army. Speculation purports that the great leader suffered from hemorrhoids at the time of his defeat.[8] Hemorrhoidal disease continues to afflict modern humans, with a 4.4% incidence in the U.S. population. Both sexes are affected, and an increased frequency has been documented among whites, rural dwellers, and those of high socioeconomic status.[9-11]

Principles of Disease. The cause of hemorrhoids is controversial. The anal vascular cushion theory is the most widely accepted. Rather than forming a continuous ring around the anal canal, the submucosa forms three distinct cushions of tissue that are richly supplied with small blood vessels and muscle fibers. Blood supply to these cushions is from the superior rectal artery, with some contribution from the middle and inferior hemorrhoidal arteries, which explains why hemorrhoidal bleeding is bright red. The muscularis submucosa cushions the anal canal during defecation to prevent injury and to aid in fecal continence.[12]

As the supportive tissue deteriorates, often starting in the third decade of life, venous distention, prolapse, bleeding, and thrombosis may occur. Some controversy exists about whether straining and constipation cause these changes by producing venous backflow when intra-abdominal pressure increases.[12,13] In pregnant women, direct pressure on a hemorrhoidal vein can produce symptomatic hemorrhoids. Up to one third of pregnant women experience hemorrhoids in the last trimester of pregnancy or the postpartum period. An increased incidence of thrombosed hemorrhoids is associated with traumatic deliveries.[14,15] Some familial predisposition is recognized, but whether this is a result of genetics or acquired factors such as diet is unknown.

Hemorrhoids are not varicose veins; they are normal structures that manifest symptoms when the muscularis submucosa weakens and the anal cushions are displaced distally.[12] Conditions that increase sphincter tone correlate with a higher prevalence of hemorrhoids.[10,13] Portal hypertension does not cause hemorrhoids. The incidence of symptomatic hemorrhoids is similar in patients with and in those without portal hypertension. Rectal bleeding in patients with portal hypertension may be caused by rectal varices, which are vascular communications between the superior and middle hemorrhoidal veins.[10,11] A major exception to this observation occurs in the pediatric population; children with portal hypertension are susceptible to hemorrhoidal exacerbations.[16,17]

Clinical Features. A careful history is needed to confirm the presence of hemorrhoids, because many patients use this term to refer to any perianal condition. Bleeding with defecation is the most common complaint, and unless the hemorrhoids are thrombosed, it usually is painless. Patients report variable amounts of bright red blood on the toilet paper or in the toilet bowl. Many complain of swelling, itching, mucoid discharge, or simply the presence of a moist perianal area. Further history should address recent stool patterns, such as diarrhea or constipation; chronic medical problems, such as portal hypertension or bleeding disorders; and a dietary and family history.

Hemorrhoidal symptoms are exacerbated by frequent bowel movements, prolonged sitting, heavy lifting, and straining while defecating. Although straining is cited as a cause of hemorrhoids, it also may be a result of them when the patient is constipated from delaying defecation because of fear of pain. Physical examination should ascertain the type and degree of hemorrhoids. This can be accomplished by a visual inspection at rest and during straining. Nonprolapsing hemorrhoids can be visualized on anoscopy as a focus of bleeding or as they bulge when the patient is asked to strain while the anoscope is removed. Anoscopy is painful and not useful in cases of prolapsed or thrombosed hemorrhoids.

Hemorrhoids are classified according to their location and severity (Table 94-1). *External* hemorrhoids originate *below* the dentate line and receive their blood supply from the inferior

Table 94-1 Types of Hemorrhoids

TYPE	ORIGIN	EPITHELIUM
External	Inferior hemorrhoidal plexus Proximal to dentate line	Modified squamous epithelium (anoderm)
Internal	Superior hemorrhoidal plexus Distal to dentate line	Transitional or columnar epithelium (mucosa)
Mixed	Superior and inferior hemorrhoidal plexus	Transitional, columnar, or modified squamous epithelium (mucosa and anoderm)

hemorrhoidal plexus. They are covered with modified squamous epithelium (anoderm) and resemble the surrounding skin. Two syndromes are common. First, the veins beneath the skin of the hemorrhoid become dilated and the surrounding subcutaneous tissue becomes engorged, causing swelling or pressure after defecation. Painless, bright red bleeding may occur. Second, the veins can become thrombosed as clots form within them (Fig. 94-3A). This produces acute pain and tenderness to palpation. A bluish discoloration often is noted.

Internal hemorrhoids originate *above* the dentate line and receive their blood supply from the superior hemorrhoidal plexus (Fig. 94-3B). They are covered with a mucosal surface consisting of transitional or columnar epithelium that looks very different from the surrounding anoderm. They are classified according to severity (Table 94-2). Symptoms and signs range from mild, painless bleeding with defecation to irreducible prolapse with unremitting and debilitating pain. *First-degree* internal hemorrhoids protrude into the lumen of the anal canal, causing a feeling of fullness. Because the mucosal wall lacks sensory nerve endings, these lesions do not cause pain. *Second-degree* internal hemorrhoids temporarily prolapse outside the anal canal during defecation but spontaneously return to their normal position at the end of the bowel movement. Both of these are amenable to medical management. *Third-degree* internal hemorrhoids prolapse spontaneously or during defecation and remain outside the body until they are manually replaced into the anal canal. A throbbing, pressure-like pain may accompany bleeding and subsides when the hemorrhoids are reduced. *Fourth-degree* internal hemorrhoids cannot be reduced and are permanently prolapsed. Continued prolapse leads to the formation of a thrombus with possible progression to gangrene. Definitive treatment for the intense pain and thrombosis is surgical.[1,13]

Management. The symptoms of nonthrombosed external and nonprolapsing internal hemorrhoids can be ameliorated by the standard regimen—warm water, analgesics, stool softeners, and high-fiber diet (WASH)—aimed at combating the problems that led to their formation (Box 94-2). Anal canal pressures decrease in warm water (40° C).[2] Patients can direct a shower stream at the area for several minutes or take sitz baths. Mild oral analgesic agents reduce the pain. Several over-the-counter preparations are available for the treatment of hemorrhoidal symptoms; however, their use is directed at improved hygiene and temporary symptom relief rather than correcting the condition.[18] The use of topical anesthetics, corticosteroids, astringents (e.g., witch hazel), mineral oils, and cocoa butter is controversial. Prolonged use of topical corticosteroids produces atrophic skin changes and is discouraged.[12] Stool softeners can make the passage of stool easier, to avoid straining. A high-fiber diet (consumption of 20 to 30 g of dietary fiber per day) produces stool that is passed more easily.[19]

Patients with second- or third-degree internal hemorrhoids also benefit from this regimen; however, permanent resolution

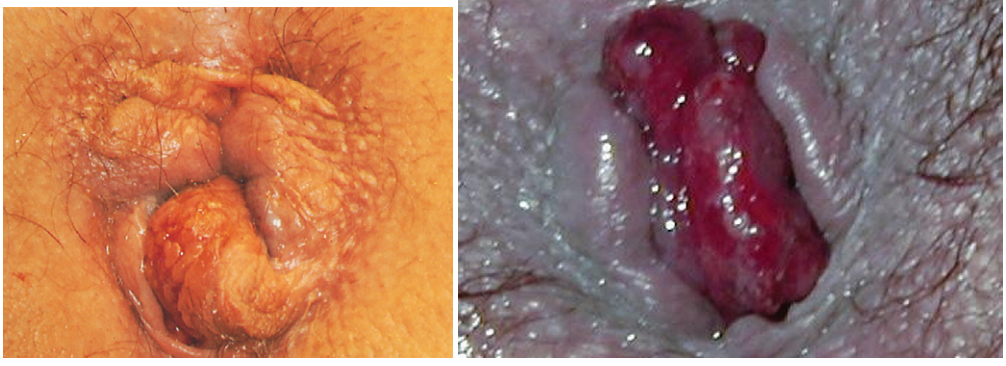
Table 94-2 Classification of Internal Hemorrhoids by Severity

TYPE	PROLAPSE	MODE OF REDUCTION	TREATMENT
First-degree	None	N/A	Medical management
Second-degree	During defecation	Spontaneous	Medical management
Third-degree	May be spontaneous or during defecation	Manual	Medical management Optional surgical repair
Fourth-degree	Permanently	Irreducible	Surgical repair

N/A, not applicable.

BOX 94-2 THE WASH REGIMEN FOR MANAGEMENT OF HEMORRHOIDS

Warm water
Analgesic agents
Stool softeners
High-fiber diet



A B

Figure 94-3. Thrombosed hemorrhoids. **A,** External. **B,** Internal. Note the engorged external hemorrhoids surrounding the thrombosed internal hemorrhoids. (**A,** Courtesy of Michelle Lin, MD, Harbor-UCLA Medical Center; **B,** courtesy of Gershon Effron, MD, Sinai Hospital of Baltimore. From Seidel HM, et al: Mosby's Guide to Physical Examination, 4th ed. St. Louis, Mosby, 1999.)

Table 94-3 Surgical Management of Hemorrhoids

CLASSIFICATION	MANAGEMENT
Thrombosed external hemorrhoids	Excision in emergency department
Second- and third-degree internal hemorrhoids	Elective surgical repair Banding Sclerotherapy Hemorrhoidectomy
Fourth-degree hemorrhoids (nonthrombosed)	Nonemergent hemorrhoidectomy
Thrombosed or gangrenous fourth-degree internal hemorrhoids	Emergent hemorrhoidectomy

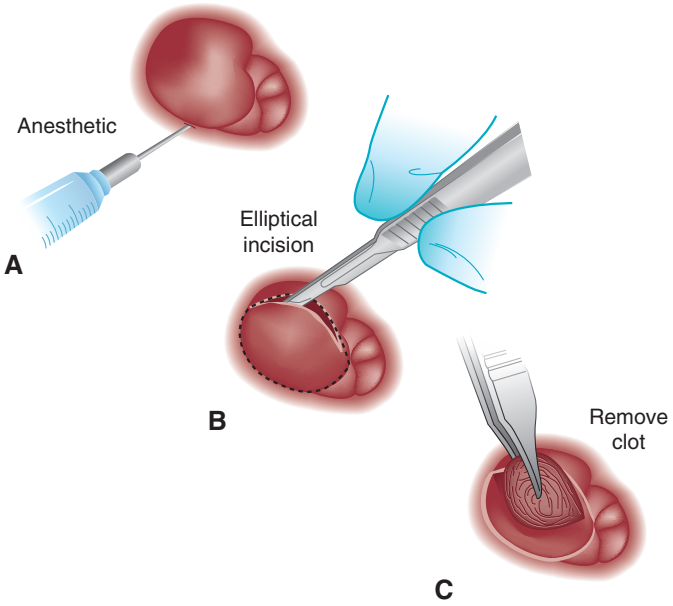


Figure 94-4. Excision of thrombosed external hemorrhoid. **A,** Field block with local anesthetic. **B,** An elliptical incision is made around the hemorrhoid. **C,** The thrombosed hemorrhoid is removed. (From Larson S, et al [eds]: Atlas of Emergency Procedures. St. Louis, Mosby, 2001.)

of their symptoms may require surgical intervention (Table 94-3). These patients can be discharged from the ED with the WASH regimen and referred to a surgeon for banding, sclerotherapy, or elective hemorrhoidectomy. Patients with acute, gangrenous, thrombosed fourth-degree internal hemorrhoids should be referred for emergent hemorrhoidectomy.

Acutely thrombosed external hemorrhoids can be excised (not incised and drained) in the ED to provide prompt relief within the first 48 hours after the onset of symptoms (Fig. 94-4). Incision results in incomplete evacuation of the clot, subsequent rebleeding, and swelling. Excision provides long-term relief and prevents subsequent formation of skin tags.[13,20] If not excised, the thrombosed external hemorrhoid will resolve spontaneously after several days when it ulcerates and leaks the dark accumulated blood, with relief of associated symptoms. Residual skin tags may persist. In the ED setting, this procedure is not commonly performed in pediatric patients, pregnant women, and immunocompromised patients.

Nonsurgical therapy with topical nifedipine (0.3%) with lidocaine (1.5%) gel has been shown to alleviate symptoms when applied twice daily for 2 weeks. The purported effectiveness of this regimen for treatment of thrombosed hemorrhoids is related to the ability of nifedipine to modulate resting

Figure 94-5. Lateral anal fissure. (Courtesy of Gershon Effron, MD, Sinai Hospital of Baltimore. From Seidel HM, et al: Mosby's Guide to Physical Examination, 4th ed. St. Louis, Mosby, 1999.)

sphincter tone and thereby reduce the associated pain and inflammation.[21]

Anal Fissures

Principles of Disease. The development of an anal fissure is the most common cause of intensely painful rectal bleeding of sudden onset. A superficial tear in the anoderm results when a hard piece of feces is forced through the anus, usually in patients who are constipated. Although anyone can experience an anal fissure, it is most common in the 30- to 50-year age bracket.[22] It is the most commonly encountered anorectal problem in pediatric patients, especially infants.[23,24] Males and females are affected equally. Most fissures occur along the posterior midline, where the skeletal muscle fibers that encircle the anus are weakest. Anterior midline fissures are more common in women than in men.[1,22] Fissures that occur elsewhere are more likely to be associated with systemic disease such as leukemia, Crohn's disease, human immunodeficiency virus (HIV) infection, tuberculosis (TB), or syphilis.[25]

Fissures not treated promptly may become chronic, with development of a classical "fissure triad" of deep ulcer, sentinel pile, and enlarged anal papillae (Fig. 94-5). A sentinel pile forms when the skin at the base of the fissure becomes edematous and hypertrophic. A resolving sentinel pile can form a permanent skin tag and may be associated with a fistulous tract.

Clinical Features. The patient complains of a sudden, searing pain during defecation that may be accompanied by a small amount of bright red blood on the stool or on the toilet paper. This is followed by a nagging, burning sensation that lasts for a few hours from internal sphincter spasm. Subsequent bowel movements are excruciating, and the external sphincter can exhibit a reflex spasm. Physical examination must be performed cautiously to avoid further spasm and pain. The depth of the fissure, its orientation to the midline, and the presence of a coexisting sentinel pile or edema are noted. Rectal examination during an acute exacerbation often is impossible because of pain and sphincter spasm.[22]

Management. Specific measures for the treatment of anal fissures are summarized in Box 94-3. Treatment using the WASH regimen (see Box 94-2) focuses on eliminating constipation

BOX 94-3 TREATMENT OF ANAL FISSURES

- WASH regimen*
- Nitroglycerin ointment (0.4%) bid or tid
- Nifedipine gel (0.2%) bid with lidocaine (1.5%)
- Botulinum toxin (Botox) 0.1–0.2 mL
- Anal dilation performed with the patient under general anesthesia
- Surgical excision

*See Box 94-2.

with a bulking agent, stool softener, and high-fiber diet. Warm sitz baths and limited use of topical anesthetics may be helpful. Parental encouragement to pediatric patients helps prevent encopresis that can result from a fear of painful bowel movements. Most acute, uncomplicated fissures resolve in 2 to 4 weeks. For adult patients who suffer from chronic anal fissures, application of various topical agents aimed at reducing sphincter pressures has been effective.[26,27] Hyperbaric oxygen has been used successfully for adjunctive therapy.[28]

Application of lidocaine ointment is effective in treating chronic anal fissures. In addition, nitroglycerin ointment applied topically to the anoderm two or three times daily has been shown to relieve the pain from anal fissures. Although it was not associated with more rapid healing, patients receiving this therapy reported a higher level of comfort during the healing process. The typical side effect of a vasodilatory headache may be experienced by some patients.[29,30]

Nifedipine gel (0.2%) in combination with lidocaine (1.5%) applied to the anal area twice daily is effective in promoting healing and reducing discomfort in the management of anal fissures. The mechanism of healing is thought to be the reduction of anal canal pressures by local calcium channel blockade.[31-33] When the efficacy of calcium channel blockers was compared directly with that of topical nitrates, the rates of healing and recurrence were similar; however, the incidence of side effects was lower in one study.[34]

Injection of botulinum toxin by colorectal surgeons (2.5 to 5.0 Units, 0.1 to 0.2 mL of Botox preparation) is effective in relaxing the sphincter tone by inhibiting acetylcholinesterase release but may cause temporary, reversible fecal incontinence.[32,35-39] Injection into the external (rather than internal) sphincter muscles may reduce this undesirable side effect. It has not yet been studied as a primary treatment in the ED or primary care setting. In comparison with the topical treatments, botulinum toxin is superior in its rate of permanent healing[40]; however, the first line of therapy is still topical agents because of their cost, ease of application, and benign side effect profiles.[39] Long-term treatment of recurrent fissures focuses on reducing resting anal pressures and may require anal dilation performed with the patient under anesthesia or surgical correction to reduce the tone of the internal sphincter.[29,35]

Abscesses and Fistulas

Principles of Disease. Anorectal abscesses and fistulas are most common in adults 30 to 50 years of age, and men are afflicted more often than women.[1,41] An increased incidence in infants (85% in male babies) has been reported to be associated with congenital abnormalities.[42-44]

One probable cause of anorectal abscesses is occlusion of the ducts of the mucus-producing anal glands at the base of the anal crypts (the cryptoglandular theory). Abscesses also are caused by inflammatory bowel disease, trauma, cancer, radiation injury, and infection (TB, lymphogranuloma venereum, actinomycosis).[1,41,43] Common causative bacteria are *Staphylococcus aureus*, *Escherichia coli*, *Streptococcus*, *Proteus*, and *Bacteroides*.

Management

General Approach. The various types of abscesses are the acute manifestations of a continuum of anorectal infections, whereas fistulas are the chronic sequelae. Symptoms vary depending on the site of infection, but incision and drainage constitute the curative treatment in all cases (Table 94-4). Delay of medical management may allow extension of the infection and eventual compromise of the sphincter mechanism.[45] Adjunctive antimicrobial therapy is indicated in patients who are immunocompromised or diabetic or have valvular heart disease. Tetanus immunization status should be verified. The sites of anorectal abscess formation are depicted in Figure 94-6. The difficulty in diagnosis is that pain often precedes physical findings of a mass or fluctuance. Approximately 34% of patients with AIDS develop anorectal abscesses and fistulas. In addition to the usual organisms, many are infected with opportunistic ones. HIV-infected patients appear to be more likely than their seronegative cohorts to have an incomplete fistulous tract. This condition prevents adequate spontaneous drainage, highlighting the urgency of treating these patients promptly. A small incision is desirable when possible because wound healing in general may be impaired.

Treatment of Specific Abscesses

Perirectal and Perianal Abscesses. Perirectal and perianal abscesses are the most common (40 to 45%) and produce painful swelling at the anal verge that is worsened by defecating or sitting. Most patients are afebrile. Physical examination reveals localized tenderness, erythema, swelling, and fluctuance. If tolerated, anoscopy may reveal pus in the anal crypts. ED management by incision and drainage with same-day discharge is possible in patients who do not have comorbidity (e.g., dia-

Table 94-4 Types of Abscesses of the Anorectum

FEATURE	PERIANAL	ISCHIORECTAL	INTERSPHINCTERIC	SUPRALEVATOR	POSTANAL
Incidence	40–45%	20–25%	20–25%	<5%	5–10%
Location	Outside and verge	Buttocks	Lower rectum	Above levator ani	Deep to external sphincter
Symptoms	Painful perianal mass	Buttock pain	Rectal fullness	Perianal and buttock pain	Rectal fullness Pain near coccyx
Fever, ↑WBCs	–	±	±	+	+
Associated fistula	++	+	+++	+++	–
ED incision and drainage	+	±	–	–	–

ED, emergency department; WBCs, white blood cells; –, does not occur; ±, occurs sometimes; ++, occurs often; +++, usually occurs.

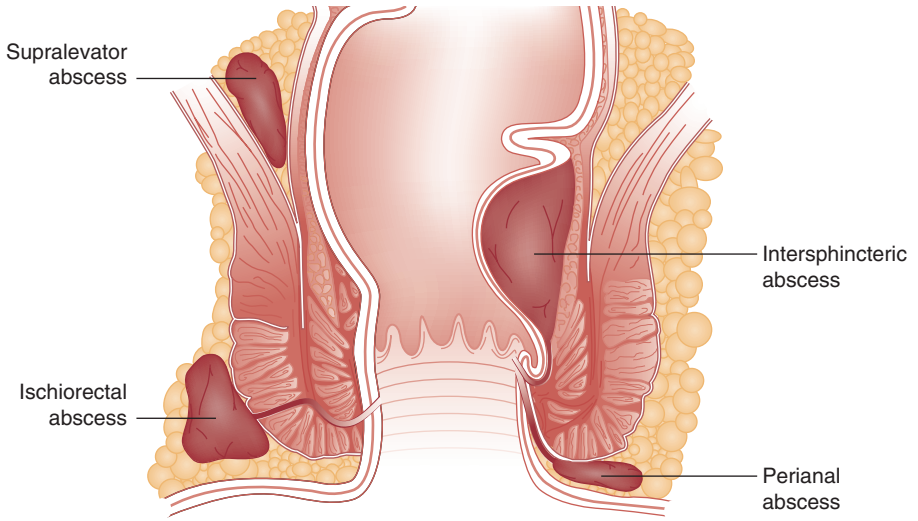


Figure 94-6. Location of common anorectal abscesses. (Modified from Gordon PH, Nivatvonghs S: Principles and Practice of Surgery for the Colon, Rectum, and Anus. St. Louis, Quality Medical Publishing, 1992.)

betes mellitus, extremes of age, compromised immune status). Some patients may be unable to tolerate the procedure without general or regional anesthesia. Incision and drainage should not take place in a sterile surgical procedure area. The WASH regimen (see Box 94-2) may alleviate postprocedure discomfort. Antibiotics are unnecessary in healthy adult patients except in cases involving associated cellulitis.[46]

Ischiorectal Abscess. Approximately 20 to 25% of abscesses form outside the sphincter muscles in the buttocks, and patients complain of severe pain. The diagnosis is obvious if an indurated mass is seen on the buttocks but is more difficult if the abscess is deep. Patients often have fever and leukocytosis. If there is no induration, a needle aspirate can confirm the presence of pus. Although many of these abscesses will require drainage performed with the patient under general anesthesia, superficial abscesses can be treated in the ED as for perianal abscess. If the patient is febrile, a short course of antibiotics, such as cephalexin, may be considered, beginning with a parenteral dose before drainage followed by 3 to 7 days of an oral agent.[47]

Intersphincteric Abscess. One fourth of abscesses form in the space deep to the external sphincter and inferior to the levator ani. The infection tracks cephalad and may appear to be a mass in the rectum and can be confused with a thrombosed internal hemorrhoid. Patients complain of continuous rectal pressure and a throbbing pain exacerbated by defecation or sitting. They may be febrile and have leukocytosis. External evidence of inflammation may be lacking, but rectal examination reveals an erythematous, indurated, sometimes draining mass. Associated fistulas and inguinal lymphadenopathy are common. Drainage in the operating room is required so that the entire abscess and fistula network can be evaluated and treated.[41]

Supralevator Abscess. Accounting for less than 5% of abscesses, supralevator abscesses cause perianal and buttock pain associated with fever and leukocytosis. External evidence of this disease usually is absent, which often delays the diagnosis. Approximately 23% of patients with this condition are obese or have diabetes mellitus, and others have concurrent disorders such as Crohn's disease, pelvic inflammatory disease, or diverticulitis.[1] A tender mass may be palpated on rectal or pelvic examination. Emergent surgical treatment is indicated.[41]

Postanal Abscess. Postanal abscesses are uncommon and occur posterior to the rectum, deep to the external sphincter, and inferior to the levator ani. Patients complain of severe rectal discomfort and coccygeal pain. They usually are febrile and have continuous pain that does not change with position. Rectal examination is painful, but anal drainage is rare. Many of these abscesses are missed on initial presentation, and the patient may be misdiagnosed as having lumbosacral strain, proctalgia fugax, sciatica, or coccygodynia. Patients often return in a few days with an abscess draining at the skin. Treatment is surgical.[1]

Horseshoe Abscess. Occasionally, a large, communicating, horseshoe-shaped abscess forms in the ischiorectal, intersphincteric, or supralevator space. Surgical management is necessary.

Necrotizing Infection. A delay in management of an anorectal abscess may lead to the destruction of tissue, especially in diabetic or immunocompromised patients. Widespread cellulitis, necrotic tissue, and gas on radiography suggest the possibility of necrotizing fasciitis, Fournier's gangrene, or tetanus. Wide surgical débridement, broad-spectrum antibiotics with anaerobic coverage, and tetanus prophylaxis are required.[1]

Treatment of Fistulas. A *fistula* (Latin for "pipe") is a connection between two epithelium-lined surfaces. Anorectal fistulas develop in 50 to 67% of patients with ischiorectal abscesses.[45] Other causes include Crohn's disease, trauma, foreign body reactions, TB, and cancer. Evidence to support these diagnoses should be sought because the anorectal complaint may be the presenting symptom of the fistula. Patients notice a recurrent or persistent perianal discharge that becomes painful when one of the openings becomes occluded. Bidigital rectal examination may reveal a tract in the perineum or canal. Probing of fistulous tracts is not recommended because the danger of creating a new tract outweighs the benefit of identifying the path of the existing fistula. Diagnostic evaluation may include intrarectal ultrasonography, fistulography with radiopaque dye, or radiolabeled white cell scanning during surgery.[41,43,48] Spontaneous resolution of fistula-in-ano is rare. Symptoms resolve when antibiotics are administered (e.g., ciprofloxacin, metronidazole) but commonly return as soon as therapy is discontinued. Other nonsurgical treatments that are effective for some patients, especially those with Crohn's disease, are administration of infliximab, a monoclonal antibody, or cyclosporine and hyperbaric oxygen therapy.[45] Because most fistulas produce recurrent abscesses if untreated, potentially leading to sphincter dysfunction, patients should be referred for surgical management. Immediate or delayed fistulotomy, fistulectomy, or repair with fibrin glue may be done.[41,48,49]

Pilonidal Disease

Principles of Disease. Little nests of hair in the sacrococcygeal area were first described in 1847 by Anderson (Latin *pilus*, "hair"; *nidus*, "nest"), who originally believed the lesions to be scrofula.[50] More than 150 years later, physicians have yet to agree on the cause and best mode of treatment. Pilonidal abscesses and subsequent sinus tracts afflict young adults with a 4:1 male predominance and are more common in obese and hirsute persons. The disease is rare in people older than 40 years, even among those who were afflicted in their youth. The lesions arise in the midline of the sacrococcygeal area in the natal cleft and should not be confused with anal fistulas, perirectal abscesses, hidradenitis suppurativa, or granulomatous diseases (syphilis, TB).[1] Much of the current understanding of pilonidal disease comes from the experience in World War II, when the condition was rampant among jeep drivers and was therefore dubbed "jeep-driver's disease."[4,51,52]

The debate between congenital predisposition and acquired disease seems to favor the latter.[51,53,54] This theory asserts that bacteria enter the usually sterile hair follicle and produce inflammation and edema, thereby occluding the opening to the skin surface. The contents expand until the hair follicle ruptures, and the material spreads into the subcutaneous fatty tissue, where a foreign body reaction leads to abscess formation. The purulent material subsequently tracks cephalad and drains to the skin through a laterally displaced, epithelialized tract. Diagnosis is made by establishing the presence of a painful, fluctuant area in the presacral skin. In chronic or recurrent disease, visible or palpable tracts of 2- to 5-cm length may be identified with openings approximately 5 cm above the anus. These sinuses usually contain hairs and cellular debris.[51,52]

Management. Treatment options vary, ranging from conservative therapy to extensive surgical management.[51,55,56] Antibiotics can supplement surgical drainage in cases accompanied by cellulitis but are not effective as the primary mode of treatment.[1] ED management of pilonidal disease involves drainage of the acute abscess for relief of symptoms. To prevent reaccumulation of debris and to minimize inflammation in the midline, a longitudinal incision lateral to the sacral midline should be made. To decrease the usual 40% recurrence rate, the patient can be referred for follicle removal and unroofing of sinus tracts after the acute inflammation subsides (usually 1 week). An alternate noninvasive strategy of shaving the hairs in the natal cleft every 3 weeks has been reported. For patients whose disease is recalcitrant, unroofing and marsupialization or wide excision techniques are used.[56]

Hidradenitis Suppurativa

Perianal hidradenitis suppurativa is an infection of the apocrine glands. It is most common in young adults and is related to poor skin hygiene, hyperhidrosis, obesity, acne, diabetes mellitus, and smoking. The condition commonly is misdiagnosed as pilonidal disease or fistula-in-ano. Other considerations in the differential diagnosis include sebaceous cysts, furuncles, granulomas (from TB or syphilis), and Crohn's disease. Occluded apocrine ducts may be infected with strains of *Staphylococcus*, *Streptococcus*, *E. coli*, or *Proteus*. Extension through the dermis spreads the infection to neighboring ducts, and a network of sinus tracts forms. This cycle leads to extensive scarring.[54,57]

Patients complain of a pustule in the perianal area, which may be associated with fever, leukocytosis, and malaise. One or more tender pustules may drain pus and be surrounded by cellulitis. Local lymphadenopathy is common. Treatment begins with careful attention to perianal hygiene, warm compresses, and broad-spectrum antibiotics. Recently, infliximab has been found to be effective, resulting in rapid clinical improvement.[58] Drainage of isolated lesions may provide symptomatic relief, but the recurrence rate approaches 40%. Referral to a surgeon for wide excision of tissue involved in advanced chronic disease may be necessary.[59-61]

Proctalgia

Perspective. Anorectal pain (proctalgia) that does not arise from one of the organic disorders described earlier can be severe and difficult to treat.[62] The two most common causes are levator ani syndrome and proctalgia fugax. These disorders can be distinguished by their patterns of affliction. Other causes of pelvic pain, such as tumors, cauda equina syndrome, and endometriosis, must be considered.[63,64]

Levator Ani Syndrome

A constant, dull pressure in the sacrococcygeal region that is precipitated by defecation or prolonged periods of sitting suggests levator ani syndrome. The patient usually has tenderness of the levator muscles, which may be firmly contracted on examination. It affects both men and women. No standard treatment regimen has been studied, but anecdotal reports indicate that sitz baths, levator ani muscle massage, and muscle relaxants can provide some relief.[58,62,63]

Proctalgia Fugax

Proctalgia fugax is an intensely painful spasm in the rectal area that begins abruptly and lasts for several minutes. It is attributed to a sudden spasm of the levator muscle complex or the sigmoid colon. People who frequently visit the toilet are at greatest risk, and women are more commonly affected than men. A psychogenic predisposition is described by Pilling and colleagues, who found that professionals, managers, and perfectionists are more likely to be afflicted.[65]

Proctalgia fugax can begin abruptly during sleep, defecation, urination, or intercourse. The nature of the pain has been compared to a "charley horse." It lasts less than 30 minutes and may radiate to the coccyx or perineum. Symptoms during recurrent episodes are consistent for the affected person, and each patient has a unique constellation of symptoms.[62] Treatment often is unrewarding, but recommendations include bowel cleansing regimens, upward manual pressure on the anus, diazepam, and topical nitrates.[63]

Fecal Incontinence

Perspective. Fecal incontinence is an embarrassing condition that affects parous women, elderly persons, and patients with a variety of neurologic or traumatic disorders. The pathomechanism involves disruption of the delicate balance among the pelvic floor muscles, sphincters, and anorectal sensation.[4] *Complete incontinence* is the inability to control passage of solid feces. *Partial incontinence* is characterized by loss of control of the passage of flatus or liquid feces.[66]

Principles of Disease. Multiple causes of fecal incontinence have been described[4,62,67] (Box 94-4). Injury to muscles and nerves may result from accidental trauma or surgery for anorectal disorders. Similarly, injury or stretching during childbirth can cause immediate or delayed problems. Spinal cord and cauda equina lesions and the autonomic neuropathy of diabetes mellitus can cause progressive incontinence. Liquid feces may seep around tumors or foreign bodies of the rectum or anal

BOX 94-4 CAUSES OF FECAL INCONTINENCE

Traumatic
Iatrogenic (surgical) nerve injury
Spinal cord injury
Obstetric trauma
Sphincter injury

Neurologic
Spinal cord lesions
Dementia
Autonomic neuropathy (e.g., diabetes mellitus)
Obstetric: pudendal nerve damage from stretching during surgery, Hirschsprung's disease

Mass Effect
Carcinoma of anal canal
Carcinoma of rectum
Foreign body
Fecal impaction
Hemorrhoids

Medical
Procidentia
Inflammatory disease
Diarrhea
Laxative abuse

Pediatric
Congenital
- Meningocele
- Myelomeningocele
- Spina bifida

After corrective surgery for imperforate anus
Sexual abuse
Encopresis

BOX 94-5 CAUSES OF PRURITUS ANI

Dermatitis
Fecal Irritation
Poor hygiene
Anorectal conditions: fissure, fistula, hemorrhoids, skin tags, perianal clefts
Systemic: caffeine, tea, beer, spicy foods, citrus fruits, quinidine, intravenous hydrocortisone, colchicine, tetracycline

Contact Dermatitis
Anesthetic agents, topical corticosteroids, perfumed soap

Systemic Diseases
Dermatologic
Psoriasis, seborrhea
Lichen simplex or lichen sclerosus

Nondermatologic
Chronic renal failure, myxedema, diabetes mellitus, thyrotoxicosis, polycythemia vera
Vitamin A or D deficiency, iron deficiency
Cancers: Bowen's, Paget's, Hodgkin's diseases

Infections
STDs
Syphilis
HSV infection
HPV infection

Other Infectious Processes
Scabies
Pinworm
Bacterial infection
Fungal infection

HPV, human papillomavirus; HSV, herpes simplex virus; STD, sexually transmitted disease.

canal. A common "foreign body" is a large impacted stool, as seen in elderly patients or those with underlying megacolon. Explosive diarrhea from laxative abuse, inflammation, or infection can temporarily overwhelm a normal sphincter mechanism. Partial incontinence after surgery to correct imperforate anus is common.[68] Incontinence is a common feature of congenital neurologic conditions such as meningocele, myelomeningocele, and spina bifida. Encopresis also may develop in young children (4 to 7 years) experiencing emotional stress.[22,69] In otherwise healthy children, sexual abuse involving the anus must be considered.[70]

Clinical Features. The physical examination should address the local and systemic factors described previously. The anorectum should be assessed for masses, hemorrhoids, evidence of previous surgery, and neuromuscular function. The anocutaneous reflex, or "anal wink," is elicited by touching the skin near the anus with a pin and observing the resulting constriction.[4] Sphincter function is assessed by asking the patient to "squeeze" the examiner's finger.

Management. The approach to management of fecal incontinence depends on the cause. Structural and inflammatory conditions may be diagnosed with anoscopy. In cases of transient incontinence caused by diarrhea, a high-fiber diet along with brief therapy with loperamide or opioids has been shown to solidify stool and enhance rectal compliance.[67]

Neuromuscular causes of fecal incontinence can be diagnosed by anorectal physiologic testing. In addition to conservative treatment measures described for transient incontinence, Kegel exercises, biofeedback training, or surgical repair may be necessary.[67,71]

Pruritus Ani

Principles of Disease. Patients with pruritus ani complain of an uncontrollable urge to scratch the perianal area. Approximately 1 to 5% of the population seek medical attention for this condition during their lifetime. Others rely on self-treatment to soothe less severe symptoms. The period of peak incidence is during the fifth and sixth decades of life, and it occurs more often in men.[72] The condition is more common in the summer months and is more noticeable at night. The sensation of itching arises when the richly innervated perianal skin becomes irritated. Patients scratch vigorously in an effort to relieve the itching, creating a vicious circle that results in greater irritation and excoriation. The causes of pruritus ani are summarized in Box 94-5.

The most common cause is the presence of feces on the perianal skin. Conditions ranging from poor personal hygiene to anatomic disorders of the anorectum allow feces to accumulate in the area. Patients may not clean the area thoroughly after defecation. Disruptions in the anorectal anatomy can lead to uncontrollable fecal accumulation on the perianal skin. Obesity, deep perianal clefts, copious hair, hemorrhoids, posthemorrhoidal skin tags, rectal mucosal prolapse, anal fissures, and fistulas make the area difficult to clean effectively. Decreased air circulation from wearing tight pants or undergarments of synthetic "nonbreathable" fabric may exacerbate symptoms.

Foods (e.g., caffeine, spicy or citrus foods, tea, beer) and drugs (e.g., quinidine, colchicine, tetracycline, intravenous

hydrocortisone) augment the irritant quality of the feces by altering its pH. Perfumed soaps and drugs, especially local anesthetic creams and ointments, can produce a contact dermatitis. Prolonged use of hemorrhoidal preparations containing local anesthetic and topical corticosteroid can exacerbate the symptoms. Other dermatologic conditions include psoriasis, seborrhea, lichen simplex, and lichen sclerosus.

Systemic diseases and local infections can produce perianal itching. Chronic renal failure, diabetes mellitus, thyrotoxicosis, myxedema, polycythemia vera, deficiency of iron or vitamin A or D, and certain cancers (Bowen's disease, Paget's disease, Hodgkin's disease) are systemic causes. Local conditions include pinworms (*Enterobius vermicularis* infection), scabies (*Sarcoptes scabiei* infection), bacterial or fungal infections, and dermatologic manifestations of sexually transmitted diseases (STDs) (e.g., syphilis or herpes simplex virus [HSV], cytomegalovirus, or human papillomavirus infection).

Management. A careful history and physical examination can identify the etiology of pruritus ani. Important considerations include hygienic care of the anus, coexisting anorectal or systemic conditions, diet, and sexual practices.[72]

Pinworms can be identified by applying transparent tape to the perianal area and attaching it to a glass slide. Visualization of eggs under the low-power objective of a microscope confirms the diagnosis. The first-line agent is mebendazole (Vermox), 100 mg orally. An alternative agent is pyrantel pamoate (Antiminth) 1 g orally (11 mg/kg, to a maximum of 1 g for pediatric patients). The dose of either may need to be repeated in 2 weeks. Scabies and pediculosis pubis should be treated with 1% lindane lotion or 5% permethrin cream. Dermatitis caused by a fungal infection is characterized by sharply demarcated borders and is treated with clotrimazole or nystatin cream. Definitive treatment of concomitant anorectal conditions (e.g., fissures, fistulas, hemorrhoids, skin tags, rectal prolapse) can prevent recurrence of pruritus ani.

Underlying systemic diseases that have perianal manifestations should be treated. Education on personal hygiene is of the utmost importance. Patients should be instructed to clean the area thoroughly with lukewarm water after each bowel movement and pat (rather than rub) it dry with a tissue or towel that is free of chemical irritants. Loose-fitting underwear and exposure to fresh air may aid in alleviating symptoms. The treatment of acute dermatitis includes a short course of topical corticosteroids,[73] calamine lotion, and systemic antihistamines.[72] Some success with topical application of capsaicin cream has been reported.[71,74] Prevention of recurrent bouts of pruritus ani requires compliance with impeccable anal hygiene and minimizing the factors that caused the initial exacerbation.

SEXUALLY TRANSMITTED DISEASES AND PROCTITIS

General Approach

The incidence of STDs has increased in the past few decades, and anorectal transmission is of particular concern in the patient with HIV infection. For patients who are sexually active, the history should ascertain whether sexual practices involve anal penetration and whether condoms are used. As a means of public health prevention of disease and patient safety, education regarding transmission of STDs and the efficacy of barrier methods is important.[75] Semen has a concentrated viral load, and the damaged epithelium of ulcerated anoderm makes an easy portal for entry of the virus.[76] The constellation of infectious diseases that afflicts the anus, rectum, and colon was historically referred to as "gay bowel syndrome," although it also affects women who engage in anal intercourse. In the past decade, a resurgence of syphilis, gonorrhea, and chlamydial infection has been documented among men who have sex with men. For this reason, more frequent STD screening is indicated in this population.[75] A summary of common infections and treatment guidelines is presented in Table 94-5.

Surgical repair for benign anorectal conditions in HIV-positive patients should be undertaken early in the course of the disease, when potential wound healing and overall patient health are at their best.[76] Empirical therapy is indicated for patients who have recently practiced anal-receptive intercourse and present with a rectal discharge. The recommended regimen is ceftriaxone 125 mg intramuscularly for one dose plus doxycycline 100 mg twice a day orally for 7 days.[75,77] All patients with anorectal infections should be referred for HIV testing. The possibility of sexual assault should be considered and managed appropriately.[75,78,79] The health care provider should report STDs and new diagnoses of HIV infection in accordance with state and local health department regulations.[75]

Treatment of Specific Sexually Transmitted Diseases

Gonorrhea

Gonorrhea is caused by the gram-negative diplococcus *Neisseria gonorrhoeae* and is most prevalent in young adults. Routine screening in homosexual men reveals that 55% have been infected, although not all experience symptoms.[76] It is postulated that gonorrhea is a cofactor for transmission of HIV.[80] Proctitis (inflammation of the rectum) results from anal intercourse or autoinoculation from vaginal secretions and becomes symptomatic after a 5- to 7-day incubation period. Symptomatic patients complain of pruritus ani, tenesmus, and bloody or thick, purulent yellow drainage. Anoscopy reveals proctitis and mucus in the anal crypts. Recovery of the organism directly from the crypts doubles the likelihood of identifying the organism on Gram stain. Only water should be used to lubricate the anoscope, because many lubricants contain an antibacterial agent. Signs and symptoms of disseminated gonococcal infection may include arthritis, skin lesions, perihepatitis, endocarditis, and meningitis.[81]

Chlamydial Infection and Lymphogranuloma Venereum

Infection with *Chlamydia trachomatis*, an intracellular organism that is endemic to the tropics, is the most common STD in the United States.[75,82] It causes proctitis in people whose sexual practices include anal intercourse or oral-anal contact. Common signs and symptoms include mucoid or bloody rectal discharge, tenesmus, and burning. Some people are asymptomatic carriers of the organism. Lymphogranuloma venereum is a more serious manifestation caused by specific strains of *C. trachomatis* that starts as a painful anal or perianal ulceration. Prominent unilateral lymph nodes coalesce to form a bubo, which must be distinguished from a granuloma of secondary syphilis. Patients often have systemic complaints of fever and malaise. Anoscopic examination reveals an erythematous, friable mucosa. Rectal cultures generally are unreliable because the organism is intracellular. Diagnosis is best achieved by immunofluorescent antibody testing. In its final stage, rectal strictures and rectovaginal fistulas may form.[66]

Table 94-5 Sexually Transmitted Diseases of the Anorectum

DISEASE/CONDITION (WITH SPECIFIC PATHOGEN WHEN KNOWN)	FINDINGS	TREATMENT
Ulcerative		
LGV	Unilateral inguinal adenopathy Fever, malaise Mucoid or bloody discharge	Doxycycline 100 mg PO bid × 21 days *For pregnant patients or those allergic totetracyclines*: Erythromycin 500 mg PO qid × 21 days
HSV infection	Rectal pain, tenesmus, constipation Bloody mucoid discharge Vesicles and ulcerations Fever, malaise, myalgias, paresthesias	*First episode*: PERIANAL: acyclovir 400 mg PO tid *or* Famciclovir 250 mg PO bid × 7–10 days *or* Valacyclovir 1 g PO daily for 7–10 days PROCTITIS: acyclovir 800 mg PO tid × 7–10 days *Recurrent*: acyclovir 400 mg PO tid for 5 days *or* Acyclovir 200 mg PO 5 times per day for 5 days *or* Acyclovir 800 mg PO bid for 5 days *or* Famciclovir 125 mg PO bid for 5 days *or* Valacyclovir 500 mg PO bid for 3–5 days *or* Valacyclovir 1 g PO daily for 5 days
Early (primary) syphilis (*Treponema pallidum*)	Chancre Tenesmus, pain, mucoid drainage Inguinal lymphadenopathy	Benzathine penicillin G 2.4 million units IM once *Alternatives*: doxycycline, erythromycin
Chancroid (*Haemophilus ducreyi*)	Inflammatory lesion progresses to ulcer Inguinal adenitis—bubo	Azithromycin 1 g PO once *or* Ceftriaxone 250 mg IM once *or* Ciprofloxacin 500 mg PO bid × 3 days *or* Levofloxacin 500 mg PO for 7 days *or* Erythromycin 500 mg PO tid × 7 days
CMV infection	Tenesmus, diarrhea, weight loss	Ganciclovir with appropriate disposition
Idiopathic (usually HIV^+)	Eccentric, deep, poor healing, multiple lesions	Symptomatic relief or surgical referral
Nonulcerative		
Condylomata acuminata (HPV)	Keratinized vegetative growths in anus or skin Asymptomatic, or pruritus ani, or bleeding	Podophyllin, topical, or cryotherapy Consider home therapy with podofilox 0.5% solution or gel for limited involvement
Gonorrhea (*Neisseria gonorrhoeae*)	Pruritus ani Tenesmus Purulent yellow discharge	Cefixime 400 mg PO once *or* Ceftriaxone 125 mg IM once *or* Ofloxacin 400 mg PO once *or* Ciprofloxacin 500 mg PO once *or* Levofloxacin 250 mg PO once *For pregnant patients*: Spectinomycin 2 g IM once *plus* Erythromycin 500 mg PO qid × 7 days
Chlamydial infection (*Chlamydia trachomatis*)	Mucoid or bloody discharge Tenesmus	Azithromycin 1 g PO once *or* Doxycycline 100 mg PO twice per day × 7 days *or* Ofloxacin 300 mg PO bid × 7 days *For pregnant patients*: Erythromycin 500 mg PO qid × 7 days
Syphilis (secondary)	Maculopapular rash Condyloma latum	Benzathine penicillin G 2.4 million units IM once *Alternatives*: doxycycline, erythromycin

CMV, cytomegalovirus; HIV, human immunodeficiency virus; HPV, human papillomavirus; HSV, herpes simplex virus; LGV, lymphogranuloma venereum.

Herpes Simplex Virus Infection

Herpes proctitis is caused by both HSV-1 and HSV-2, but HSV-2 is responsible for approximately 90% of cases.[81,83] The seroprevalence of HSV-2 in the HIV-positive population is 95%.[76] Herpes genital infections occur in people whose sexual practices include oral-anal contact or anal intercourse. Symptoms appear 1 to 3 weeks after exposure. Those with proctitis complain of severe rectal pain, bloody mucoid discharge, tenesmus, constipation, and sometimes sacral paresthesias and urinary difficulties. Systemic complaints may include fever, malaise, and myalgias.[81,83] Physical examination and anoscopy may be impossible without anesthesia. Single or coalesced vesicles and ulcerations occur in the perianal area and rectum, and anoscopy reveals an erythematous, friable, ulcerated rectal mucosa. Chronic mucocutaneous HSV infection is considered diagnostic for AIDS. Definitive diagnosis with viral or immunofluorescent staining relies on proper collection of fluid and scrapings from the base of the vesicle.[1,81]

Syphilis

The number of reported cases of syphilis is increasing. Up to 75% of homosexual men have been infected with *Treponema pallidum*, the motile spirochete responsible for the disease.[81] During anal intercourse, the organism enters the rectal mucosa or anoderm and causes an ulcer (chancre) to form within 2 to 6 weeks. The chancre heralds the primary phase of syphilis and may resemble an anal fissure that is not located in the midline of the perianal skin.[84] Most patients experience discomfort during defecation and tenesmus, with mucoid discharge; inguinal adenopathy also may be present. Primary

syphilis can be confused with lymphoma, but the diagnosis can be made by visualizing spirochetes on darkfield microscopy from scrapings taken from the base of the ulcer.[83] Serologic testing is useful several weeks after the appearance of the chancre. Treponemal tests such as the fluorescent treponemal antibody test yield a positive result earlier than does the Venereal Disease Research Laboratory (VDRL) or rapid plasma reagin (nontreponemal) test.[83] Patients infected with HIV may take longer to test positive, and in some cases test results remain negative despite infection.[81] Patients with AIDS have a high incidence of neurosyphilis regardless of the stage of syphilis at the time they seek treatment.[85]

In some patients the chancre goes unnoticed, and they are seen initially with secondary syphilis, marked by the appearance of a maculopapular rash that characteristically involves the palms and soles, or of condyloma latum. The latter is a spirochete-laden, weeping, verrucous lesion in the perianal area that emits a foul odor.[81] It is easily distinguishable from condyloma acuminatum, which has a drier, more keratinized appearance. Serologic testing results usually are positive. Tertiary syphilis is rare but may manifest as a rectal gumma with severe perianal pain and paralysis of the sphincters, which may initially cause it to be mistaken for cancer.[81]

Chancroid

Chancroid is caused by the gram-negative bacillus *Haemophilus ducreyi* and begins as an inflammatory pustule or macule that ruptures to form an irregularly shaped ulcer. In several days, painful inguinal adenitis develops. Chancroid often is a diagnosis of exclusion. All antimicrobial therapy regimens, especially single-dose ceftriaxone, are less effective in HIV-positive patients.

Condyloma Acuminatum

Condyloma acuminatum, the most commonly encountered anorectal STD, is caused by human papillomavirus. These lesions, also called genital warts, most often are found in homosexual men but can be seen in heterosexual men, women, and children. The mode of transmission is primarily through sexual intercourse, but transmission can occur through close personal contact, as often happens in pediatric cases in which an infected person is changing a diaper and transmits the virus to the infant because of poor hand-washing techniques. It is incumbent upon the evaluating physician to consider sexual abuse in such cases.[24] Because one half of HIV-positive patients have anal warts, HIV testing is recommended in patients with this diagnosis.[76,86]

The pink-to-gray warts are a result of hyperplastic epithelial growth and appear as vegetative papilliform growths (Fig. 94-7). They may coalesce to form a massive patch that obscures the anal verge.[39] Many patients are asymptomatic or complain of pruritus ani, a "hemorrhoid," or bleeding. Evaluation should include anoscopy because the warts often grow within the anal canal. Failure to treat the internal lesions results in recurrence.[1,39,70] The differential diagnosis includes the condyloma latum of secondary syphilis, which is flatter and more moist in appearance. Squamous cell carcinoma also should be considered if the lesions are indurated. Progression to intraepithelial neoplasia has been reported to be related to the level of immunosuppression.

Outpatient treatment with 0.5% podofilox solution or gel is limited to mild cases involving external lesions. The podofilox should be applied twice daily for 3 days followed by 4 days without therapy. This may be repeated for a total of four cycles per incidence. An alternative patient-applied regimen is imiquimod 5% cream applied at bedtime three times per week for up to 16 weeks.[71,75] Multiple applications of podophyllin resin, cryotherapy, intralesional interferon, or laser surgery by the physician may be required.[39]

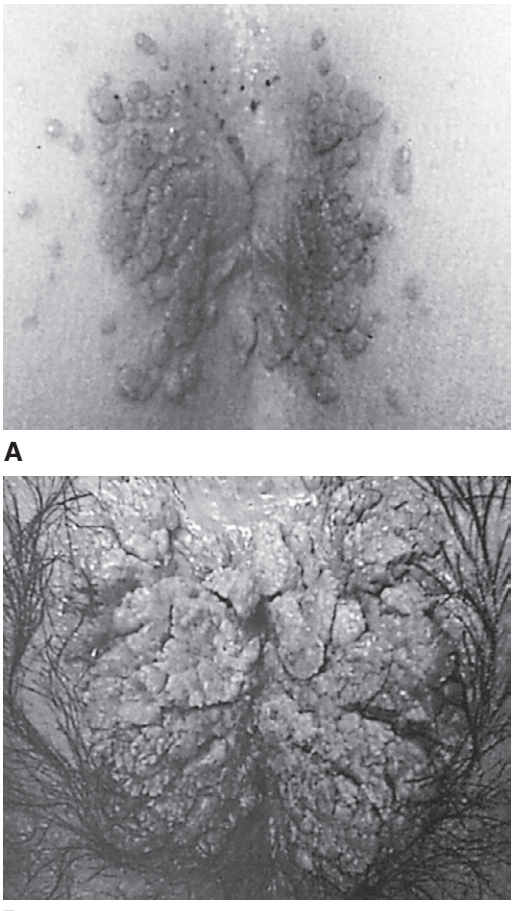


Figure 94-7. Condylomata acuminata in a child (**A**) and in an adult (**B**).

Ulcerative Lesions in the Patient with HIV Infection

The practice of anal intercourse has led to a proliferation of anorectal STDs. Most patients who are HIV-seropositive have current or past infection with an STD, which may be the initial reason for seeking medical attention. One third of anorectal complaints in this population fall into three categories: (1) routine proctologic conditions as seen in the general population, (2) STDs, and (3) opportunistic infections (Box 94-6). The treatment of routine conditions and common STDs is similar to that in other patients except that wound healing may be slower in HIV-infected patients.

In immunocompromised patients, the differential diagnosis of ulcerative anorectal lesions should include opportunistic infections, lymphoma, and Kaposi's sarcoma. In approximately 10% of patients with AIDS, cytomegalovirus proctitis with tenesmus, diarrhea, and weight loss develops. The only clue may be the presence of an anal ulcer that may be indistinguishable from a fissure. Further diagnostic testing and treatment are required. Patients with AIDS often exhibit idiopathic anal ulcerations with pain and bleeding. Before this diagnosis is made, other possible causes of the lesions must be considered (see Box 94-6). Symptomatic relief can often be achieved by the WASH regimen (see Box 94-2), but recalcitrant lesions may require surgical excision.[78,87,88]

BOX 94-6 ANORECTAL LESIONS IN THE PATIENT WITH HIV DISEASE

Common Conditions
Anal fissure
Abscess and fistula
Hemorrhoids
Pruritus ani
Pilonidal disease

Common STDs
Gonorrhea
Chlamydial infection
Herpes
Chancroid
Syphilis
Condyloma acuminatum

Atypical Conditions
Infectious: TB, CMV infection, actinomycosis, cryptococcosis
Neoplastic: lymphoma, Kaposi's sarcoma, squamous cell carcinoma
Other: idiopathic anal ulcer

CMV, cytomegalovirus; HIV, human immunodeficiency virus; STD, sexually transmitted disease; TB, tuberculosis.

Radiation Proctitis

Radiation-induced injury caused by treatment of gynecologic, urologic, and GI malignancies occurs most commonly in the rectum. Because of the ability to deliver localized radiation to organs in the pelvis, the dose of radiation for treatment of malignancies often is higher than for treatment of other forms of cancer.[89,90] Immediate radiation proctitis usually is self-limited and responds to symptomatic treatment. Delayed radiation proctitis can manifest up to 2 years after the exposure to radiation and may predispose the patient to subsequent rectal malignancies as a result of damage to DNA.[90]

Signs and symptoms of radiation proctitis include bleeding ranging in severity from spotting to hemorrhage, tenesmus, diarrhea, pain, fistula-in-ano, and rectal strictures.[91] Diagnosis is achieved by rectal mucosal biopsy, a procedure best performed with the patient under sedation or anesthesia.

Treatment regimens include the use of anti-inflammatory agents, botulinum toxin injection, enemas with short-chain fatty acids, oral sucralfate therapy, hyperbaric oxygen therapy, and sclerosing therapy.[92-94] Supportive therapy can be given for symptoms that the individual patient experiences.

Procidentia

Rectal prolapse, or procidentia, is a disease of persons at the extremes of age. Prolapse is *complete* if all bowel layers protrude and *incomplete* if only the mucosal layer is involved. In adults, complete procidentia is most common among older women with a history of excessive straining while defecating. The cause is a laxity of attachment structures, and the rectal prolapse often is accompanied by uterine prolapse or cystocele. Patients complain of an anal mass that protrudes during defecation, coughing, or sneezing. Findings may include fecal incontinence, bloody or mucoid discharge, and a foul odor. In some cases the patient is able to reduce the prolapse manually, while in others the tissue becomes edematous and they present with a red, ulcerated mass protruding from the anus (Fig. 94-8). Sphincter tone may be weakened. Reduction should be attempted; when this is successful, the patient should be discharged with agents to relieve constipation. Surgical repair often is necessary.[95,96]

Figure 94-8. Prolapse of the rectum. (Courtesy of Gershon Effron, MD, Sinai Hospital of Baltimore. From Seidel HM, et al: Mosby's Guide to Physical Examination, 4th ed. St. Louis, Mosby, 1999.)

In children up to 4 years of age, procidentia often is associated with chronic constipation or diarrheal disease. However, it may herald the presence of malnutrition, parasitic infection, or cystic fibrosis.[97] Children usually have a mucosal prolapse. The parent reports protrusion during defecation with small amounts of mucus or blood. This condition must be distinguished from a protruding juvenile polyp and intussusception. Gentle reduction may be attempted.[1] Conservative medical management aimed at the cause of procidentia often is successful because of the self-limited nature of the condition in children. Increasing the dietary fiber and fluid intake frequently is successful as a first line of therapy.[96,97]

Anorectal Foreign Bodies

Perspective. The incidence of anorectal foreign bodies is on the rise with the increasing popularity of the anus for sexual gratification. Rectal foreign bodies also are found in children, psychiatric patients, and victims of assault or as a result of iatrogenic injury. Most objects are introduced directly into the anus, but some become lodged there after oral ingestion. It is important to identify and remove foreign bodies to prevent mucosal lacerations, intestinal obstruction, sepsis, and peritonitis.[98] In many cases, removal can be done safely in the ED.

Clinical Features

Objects Inserted into the Anus. In a few cases, the foreign body is introduced iatrogenically. The two most common foreign bodies in this category are the enema tip and the broken rectal thermometer.[99] In most cases, however, the foreign body is placed deliberately by the patient or a partner for medicinal or sexual purposes. Objects that are commonly retrieved include fruits and vegetables; household items, especially those whose dimensions that resemble the penis; and those purchased specifically with an anal erotic intent.[100-102] By the time patients arrive at the ED, sometimes days after the introduction of the foreign body, they have most likely tried to remove it at home. The history of the injury often is reluctantly given or is vague and inconsistent. The initial ED evaluation, conducted in a nonjudgmental manner, attempts to ascertain the type of foreign body involved, how long it has been there, what attempts have been made to remove it, and whether the patient has fever, abdominal pain, or rectal bleeding. The possibility of assault should always be considered.[102]

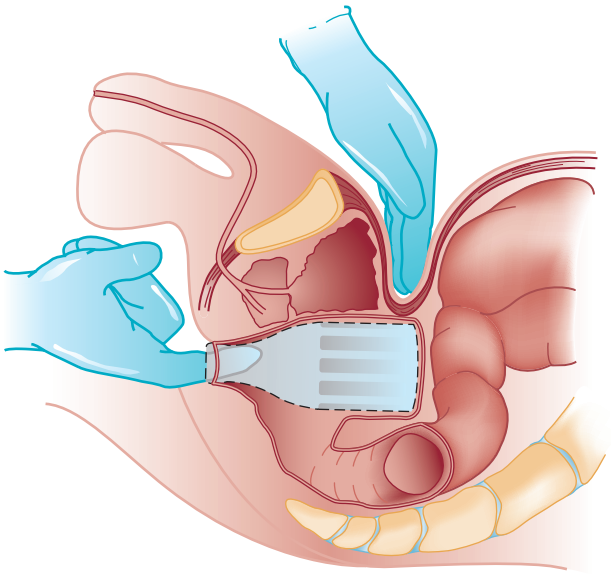


Figure 94-9. Removal of a foreign body from the rectum.

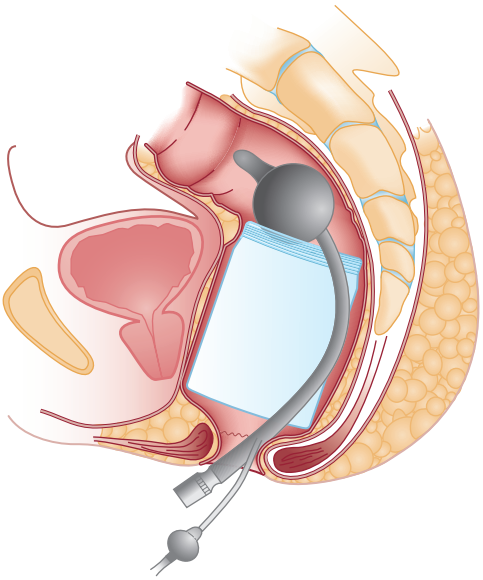


Figure 94-10. Foley catheter–assisted removal of a rectal foreign body.

Physical examination of the anorectum begins with an external examination for signs of trauma followed by digital rectal examination and anoscopy, which may reveal the foreign body, a lax sphincter, or a mucosal injury. Abdominal examination may demonstrate signs of perforation or obstruction. The foreign body may be visible on abdominal radiographs, or its presence may be inferred by a nonspecific gas pattern, free air, or signs of intestinal obstruction. If perforation is suspected, water-soluble contrast material can be introduced to delineate radiolucent foreign bodies.[99]

Orally Ingested Foreign Bodies. Some foreign bodies that are ingested orally, especially toothpicks and fish or chicken bones, pass through the GI tract and subsequently become lodged in the rectum or anal crypts.[102] Patients at highest risk for ingested foreign bodies are children, especially those in the first 2 years of life; psychiatric patients; and body packers who ingest condoms containing drugs.

Management. Optimal treatment depends on the location and type of object found.[98] Generally, objects that are soft and low-lying (less than 10 cm from the anal verge) can be removed safely in the ED. Large, hard, fragile objects and those that have migrated proximally are difficult to remove without anal dilation and instrumentation to assist in the passage through the sacral curve and sphincters. These are best performed with the patient under general anesthesia.[103] As a rule, however, the patient should remain awake to assist in expulsion by performing the Valsalva maneuver at the appropriate time, and premedication with a benzodiazepine is helpful to relax both the sphincter and the patient.[102] With the patient in the lithotomy position, suprapubic pressure can assist in removal (Fig. 94-9). Other positions may be more appropriate for a particular foreign body.

Several methods are effective for removal. The easiest is to grasp an edge of the foreign body with forceps and apply traction while the patient bears down. Most foreign bodies in the rectum do not have a convenient place to grasp, and other methods are needed. A Foley catheter can be placed beside the foreign body and the balloon inflated proximal to it (Fig. 94-10). This breaks the suction of the rectal wall mucosa and provides a way to guide the object out of the rectal vault. Hollow objects may be filled with plaster of Paris, with an inset, inflated Foley catheter to be used as a handle.[102]

Other creative ways to remove foreign bodies in the ED have been successful, and an individualized strategy for each patient is essential. After the removal of the foreign body, all patients should undergo sigmoidoscopy to look for mucosal tears and perforations.[98,101,102] Discharge instructions should warn the patient about signs and symptoms of perforation, peritonitis, and sepsis.

KEY CONCEPTS

- Patients who seek treatment for nonspecific anorectal complaints should be evaluated for the presence of underlying systemic disease (e.g., cancer, diabetes mellitus, immunodeficiency) because disorders of the anus may herald associated conditions.
- Patients with any STD should be evaluated for HIV infection and questioned about the use of the anus for sexual purposes.
- Anorectal conditions can be differentiated according to an algorithm (see Fig. 94-2) that addresses the presence or absence of pain, bleeding, swelling, and pruritus, in combination with an assessment of the patient's overall health.
- Most anorectal conditions can be symptomatically improved by adhering to the WASH regimen (warm water, analgesics, stool softeners, high-fiber diet).

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 95 Renal Failure

Allan B. Wolfson

EVALUATION OF RENAL FUNCTION

The evaluation of renal disease in the emergency department (ED) requires the intelligent use of urinalysis, serum and urine chemical determinations, and renal imaging studies to assess the degree of renal dysfunction and to take the first steps in determining its cause.

Diagnostic Strategies

Urine Volume

Because urine flow does not diminish until the glomerular filtration rate (GFR) is sharply decreased, urine volume is a poor indicator of renal dysfunction. In fact, urine volume often *increases* as concentrating ability is lost with advancing renal dysfunction; patients with renal failure typically produce urine that is isosmolar with serum. *Oliguria*, defined as a urine volume of 100 to 400 mL per 24 hours, may be seen with prerenal (blood flow–dependent), intrinsic (intrarenal), or postrenal (obstructive) causes of acute renal failure (ARF). Alternating oliguria and anuria, although uncommon, is a classic indicator of intermittent obstruction, which occurs as urine collects behind an obstructing stone or tumor and then is allowed to flow past as the obstructing material shifts position.

Urinalysis

The standard urinalysis consists of dipstick screening for heme pigment, protein, glucose, ketones, pH, leukocyte esterase, and nitrite and microscopic examination of a spun specimen of freshly voided urine.

Heme

The dipstick detects both free hemoglobin (or myoglobin) and the hemoglobin contained in red blood cells (RBCs) but is more sensitive to the former. Although as few as 3 RBCs per high-power field can be detected, the dipstick may fail to identify 10 to 15% of patients with microscopic hematuria, as defined by more than 5 RBCs per high-power field. A positive result on dipstick testing should prompt microscopic examination of the urine. If red cells are seen, the diagnosis of hematuria is confirmed. If the dipstick result is positive but findings on microscopic examination are negative, pigmenturia (myoglobin or free hemoglobin) should be suspected.

Protein

The dipstick test for protein, using the color change of tetrabromophenol blue, can detect protein at concentrations of 10 to 15 mg/dL but does not yield reliably positive results until the concentration is greater than 30 mg/dL. Moreover, the relation between color intensity and protein concentration is only approximate. The dipstick reagent is three to five times more sensitive to albumin than to globulins and immunoglobulin light chains (e.g., Bence Jones protein)—an important limitation.[1] False-positive results are caused by alkaline urine, hematuria, or prolonged immersion of the dipstick in the urine. False-negative results are seen with dilute urine.

Microscopic Examination

After dipstick testing of the urine has been completed, 10 mL of urine is placed in a conical test tube and spun at 2000 revolutions per minute for 5 minutes (higher speeds may break up casts). The supernatant is discarded. The sediment is resuspended in the residual urine, and a drop is placed on a slide and covered with a coverslip. Observations are recorded as the number of cells per high-power field. A level of 2 to 3 RBCs per high-power field in adult men or 2 to 4 RBCs per high-power field in adult women commonly is accepted as normal; in many studies, a finding of 5 RBCs per high-power field is considered to represent the threshold of abnormality.[2,3]

Casts are formed from urinary Tamm-Horsfall protein, a product of the tubular epithelial cells that gels at low pH and high concentration and when mixed with albumin, or from red cells, tubular cells, or cellular debris in the urine. The composition of a cast thus reflects the contents of the tubule. Casts are described and classified according to their appearance or constituents (e.g., hyaline, red cell, white cell, granular, or fatty casts) (Fig. 95-1). Hyaline casts, those that are devoid of contents, are seen with dehydration, after exercise, or in association with glomerular proteinuria. Red cell casts indicate glomerular hematuria, as seen in glomerulonephritis; the presence of even a few red cell casts is significant. White cell casts imply the presence of renal parenchymal inflammation. Granular casts are composed of cellular remnants and debris. Fatty casts, like oval fat bodies, generally are associated with heavy proteinuria and nephrotic syndrome.

Microscopic examination of the urinary sediment can be helpful in establishing the cause of ARF. A sediment without

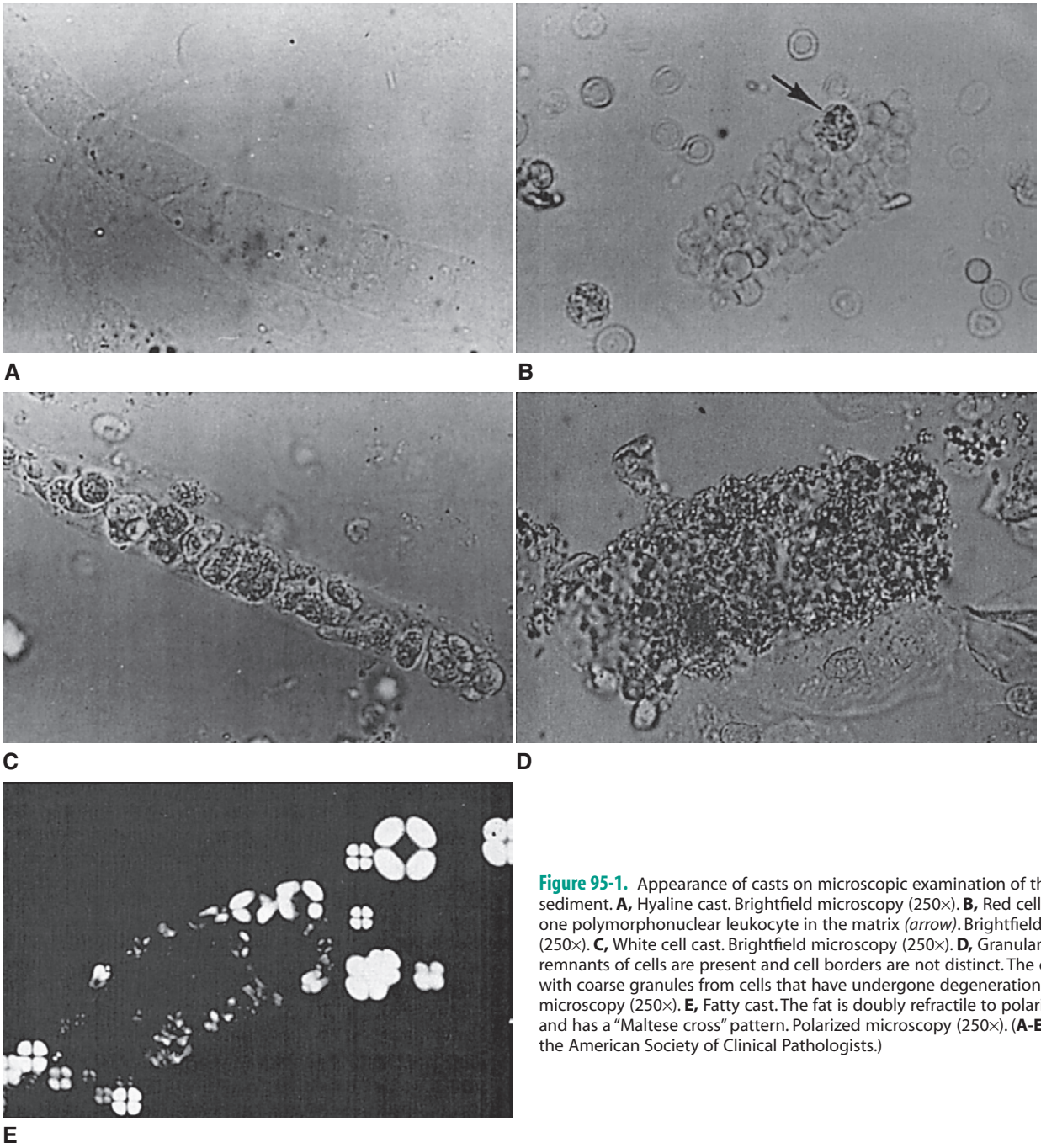


Figure 95-1. Appearance of casts on microscopic examination of the urinary sediment. **A,** Hyaline cast. Brightfield microscopy (250×). **B,** Red cell cast with one polymorphonuclear leukocyte in the matrix *(arrow)*. Brightfield microscopy (250×). **C,** White cell cast. Brightfield microscopy (250×). **D,** Granular cast. Only remnants of cells are present and cell borders are not distinct. The cast is filled with coarse granules from cells that have undergone degeneration. Brightfield microscopy (250×). **E,** Fatty cast. The fat is doubly refractile to polarized light and has a "Maltese cross" pattern. Polarized microscopy (250×). (**A-E,** Courtesy of the American Society of Clinical Pathologists.)

formed elements or with only hyaline casts is characteristic of prerenal azotemia or obstruction. Red cell casts suggest glomerulonephritis or vasculitis. Fatty casts also suggest glomerular disease. In acute tubular necrosis (ATN), the urinary sediment commonly shows granular casts and renal tubular epithelial cells. Large numbers of polymorphonuclear leukocytes are observed in interstitial nephritis, papillary necrosis, and pyelonephritis. Eosinophil-containing casts (appreciated only after staining of the sediment) are typical of allergic interstitial nephritis. Uric acid crystals suggest uric acid nephropathy but are extremely nonspecific; oxalic acid or hippuric acid crystals may be seen in ethylene glycol ingestion.

Serum and Urine Chemical Analysis

Creatinine and Blood Urea Nitrogen

The normal range for the serum creatinine level extends from 0.5 mg/dL in thin people to 1.5 mg/dL in muscular persons. Spurious elevations can be caused by acetoacetate (which cross-reacts with creatinine in commonly used assays) and by certain medications that either cross-react in the assay or reversibly inhibit tubular creatinine secretion despite a normal GFR. Serum creatinine concentration is a function of the amount of creatinine entering the blood from muscle, its volume of distribution, and its rate of excretion. Because the

first two usually are constant, changes in serum creatinine concentration generally reflect changes in GFR. Under steady-state conditions, if the GFR is halved, the serum creatinine doubles. Abrupt cessation of glomerular filtration causes the serum creatinine to rise by 1 to 2 mg/dL per day. Thus, a daily increment of less than 1 mg/dL suggests that at least some renal function has been preserved. Rhabdomyolysis releases creatine into the plasma and may cause the serum creatinine to increase by more than 2 mg/dL per day.

The blood urea nitrogen (BUN) level also rises with renal dysfunction but is influenced by many extrarenal factors as well. Increased protein intake, gastrointestinal (GI) bleeding, and the catabolic effects of fever, trauma, infection, and drugs such as tetracycline and corticosteroids all increase protein turnover and result in increased hepatic urea production and increased BUN. Conversely, BUN tends to be decreased in patients with liver failure or protein malnutrition.

When glomerular filtrate has been formed, renal urea clearance is largely a function of flow rate. Urea clearance is thus decreased in patients with prerenal azotemia or acute obstruction, despite preservation of tubular function. In such cases, the BUN/creatinine ratio usually is greater than the normal value of 10:1, whereas this ratio usually is not markedly increased in cases of uncomplicated intrinsic ARF.

Urine Sodium and Fractional Excretion of Sodium

Measurement of the urine sodium concentration provides information on the integrity of tubular reabsorptive function. Normally, urine sodium concentration parallels sodium intake. Low urine sodium concentration thus indicates not only intact reabsorptive function but also the presence of a stimulus to conserve sodium. The urine sodium concentration, as well as the fractional excretion of sodium (FENa), an additional measure of tubular sodium handling, helps distinguish between the two most common causes of ARF: prerenal azotemia and ATN (Table 95-1).

Urinary indices are most helpful in oliguric patients.[4] In general, an oliguric patient with a urine sodium concentration less than 20 mEq/L and FENa less than 1% should be considered to have prerenal azotemia, whereas urine sodium concentration greater than 40 mEq/L and FENa greater than 1% suggest ATN. Values in patients with prerenal azotemia overlap somewhat with those in patients with nonoliguric ATN, particularly if the renal injury is mild and some capability to retain sodium has been preserved. Thus, intermediate values for urine sodium concentration and FENa are of little help in differentiating between the two conditions. The administration of mannitol or a loop diuretic within the several hours preceding urine collection also may make interpretation of urine values difficult because the urinary sodium will tend to be higher and the urine less concentrated, causing the results in prerenal azotemia to resemble those in intrinsic renal failure (Box 95-1).

In glomerulonephritis, the urinary indices generally reflect intact tubular sodium handling, but the diagnosis is more accurately made by urine microscopy. In obstructive uropathy, the values of the urinary indices depend on the duration of obstruction and cannot be relied on to indicate either the presence or absence of obstruction.

Table 95-1 Typical Urinary Findings in Prerenal Azotemia and Acute Tubular Necrosis

LABORATORY TEST FINDING	PRERENAL AZOTEMIA	ACUTE TUBULAR NECROSIS
Urinalysis	Normal or hyaline casts	Brown granular casts, cellular debris
Urine sodium concentration (mEq/L)	<20	>40
Fractional excretion of sodium (%)	<1	>1
Urine-to-plasma creatinine ratio	>40	<20

Renal Imaging

General Considerations

Renal imaging often is helpful in evaluating the patient with kidney dysfunction, particularly when obstruction is suspected. Contrast-enhanced computed tomography (CT) scanning provides an anatomic image of the urinary tract but does not provide an evaluation of renal function. The classic findings of obstruction are kidneys that are normal to large in size, nephrograms that become increasingly dense, and delayed opacification of dilated collecting systems. However, contrast-enhanced CT subjects the kidneys of an already azotemic patient to the risk of an additional potential insult from the contrast agent (Fig. 95-2). Although the newer nonionic isosmolar contrast agents may have less potential for nephrotoxicity, techniques such as ultrasonography and CT scanning that do not involve contrast administration are much preferred in patients with preexisting renal insufficiency.

Computed Tomography

Noncontrast CT scanning may be useful in evaluating some azotemic patients. Hydronephrosis can be recognized without the use of contrast material. Often, dilated ureters also can be seen without contrast enhancement and the level of obstruction determined. Moreover, the cause of obstruction (e.g., lymphoma, retroperitoneal hemorrhage, metastatic cancer, retroperitoneal fibrosis) often can be delineated as well. Occasionally, obstruction severe enough to result in renal failure may not cause detectable proximal dilatation of the urinary tract. Bilateral ureteral obstruction produced by

BOX 95-1 Causes of High or Low FENa and UNa in Patients with Acute Renal Failure

UNa <20 mEq/L, FENa <1%
Prerenal azotemia
Acute glomerulonephritis
Acute obstruction
Contrast-induced ATN (some cases)
Rhabdomyolysis-associated ATN (some cases)
Early sepsis
Nonoliguric ATN (10% of cases)

UNa >40 mEq/L, FENa >1%
ATN (90% of cases)
Chronic obstruction
Diuretic drugs
Osmotic diuresis
Underlying chronic renal failure

ATN, acute tubular necrosis; FENa, fractional excretion of sodium; UNa, urine sodium concentration.
From Kelley WN (ed): Internal Medicine, 2nd ed. Philadelphia, JB Lippincott, 1992.

Figure 95-2. Computed tomography scan of bilateral hydronephrotic kidneys without intravenous contrast medium.

malignancy or retroperitoneal fibrosis is the most important cause of this nondilated obstructive uropathy. When noninvasive studies yield negative results, the diagnosis must be made by retrograde pyelography or by antegrade pyelography performed through a percutaneous nephrostomy.

Ultrasonography

Ultrasonography allows accurate measurement of renal dimensions and is a safe and reasonably reliable method of excluding obstruction as a cause of ARF. The normal kidney shows an echo-free renal parenchyma surrounding the echogenic central urothelium of the renal pelvis and calices. The sonographic appearance of the kidney in obstruction is that of an enlarged central sonolucent area that spreads the normal central echo densities. A similar pattern may be produced by renal cysts, but without associated ureteral dilatation. Dilatation of the collecting system generally is apparent within 24 to 36 hours of the onset of obstruction, but obstruction may be overlooked in patients who are evaluated early in the development of obstructive ARF.

HEMATURIA AND PROTEINURIA

Hematuria

Principles of Disease. Microscopic hematuria often is discovered incidentally on routine urinalysis, but as little as 1 mL of blood in 1 L of urine can cause grossly appreciable hematuria. Although not invariably a sign of disease, the finding of hematuria calls for an effort to rule out any treatable underlying disorder. Both gross and microscopic hematuria are caused by similar disorders, but the amount of blood in the urine does not correlate with the severity or the seriousness of the etiologic condition.[2,3]

The causes of hematuria can be divided into hematologic, renal, and postrenal causes; renal causes may be further classified as glomerular or nonglomerular[3] (Box 95-2). Overall, the most common causes of nontraumatic hematuria, in roughly descending order of occurrence, are kidney stones, carcinoma of the kidney or bladder, urethritis, urinary tract infection (UTI), benign prostatic hypertrophy, and glomerulonephritis. The scope of the differential diagnosis can be narrowed by taking into account the patient's age and sex (Table 95-2) and by distinguishing between upper and lower urinary tract sources. When gross hematuria is present, cystoscopy can determine whether blood is emerging from one or both ureteral orifices, thereby defining a source in the upper tract. Red cell casts indicate a renal source, as does associated proteinuria (excretion of greater than 500 mg of albumin in 24 hours). In differentiating between proteinuria due to renal parenchymal disease and that simply produced by admixture of urine with extravasated blood, a useful rule of thumb is that 1 mL of whole blood contains approximately 5 billion RBCs and approximately 50 mg of albumin.

ED evaluation of the patient with gross or microscopic hematuria should begin with a complete history to define the

Table 95-2 Most Common Causes of Hematuria by Age and Sex

<20 YR	20-40 YR	40-60 YR ♂	40-60 YR ♀
Glomerulonephritis UTI	UTI Stone Trauma Carcinoma (bladder, kidney)	Carcinoma (bladder) Stone UTI Carcinoma (kidney) BPH if >60 yr	UTI Stone Carcinoma (bladder, kidney)

BPH, benign prostatic hyperplasia; UTI, urinary tract infection.
Adapted from Restropo NC, Carey PO: Evaluating hematuria in adults. Am Fam Physician 40:149, 1989.

BOX 95-2 CAUSES OF HEMATURIA

Hematologic
Coagulopathy
Sickle hemoglobinopathies

Renal
Glomerular
Primary glomerular disease
Multisystem disease (e.g., systemic lupus erythematosus, Henoch-Schönlein purpura, hemolytic uremic syndrome, polyarteritis nodosa, Wegener's granulomatosis, Goodpasture's syndrome)

Nonglomerular
Renal infarction
Tuberculosis
Pyelonephritis
Polycystic kidney disease
Medullary sponge kidney
Acute interstitial nephritis
Tumor
Vascular malformation
Trauma
Papillary necrosis

Postrenal
Stones
Tumor of ureter, bladder, urethra
Cystitis
Tuberculosis
Prostatitis, urethritis
Foley catheter placement
Exercise
Benign prostatic hypertrophy

pattern and character of the hematuria. Blood noted only on initiation of voiding suggests a urethral source, whereas blood noted only in the last few drops of urine suggests a prostatic or bladder neck source. Hematuria present throughout urination suggests a source in the bladder, ureter, or kidney. Brown or smoky-colored urine usually has a renal source. Blood clots indicate a nonglomerular renal or lower urinary tract source of bleeding. Hematuria may rarely be cyclic or associated with menses, suggesting endometriosis of the ureter or bladder. Flank pain suggests calculus, neoplasm, renal infarction, obstruction, or infection as the cause. Symptoms of frequency, dysuria, and suprapubic pain suggest cystitis or urethritis; in adult men, perineal pain, dysuria, and terminal hematuria suggest prostatitis.

Other clues to the cause should be sought by careful questioning. Because glomerulonephritis or interstitial nephritis may be caused by a variety of bacterial, viral, and parasitic infections, a history of recent infection is important. Symptoms suggestive of a multisystem disorder (e.g., systemic lupus erythematosus) also should be sought, as should a history of human immunodeficiency virus infection.[5] Because drugs may cause acute interstitial nephritis (AIN),[6] papillary necrosis, or hemorrhagic cystitis, a complete medication history should be elicited. When hematuria is associated with anticoagulant use, significant underlying disease can be identified in at least 70% of patients.[7] The family history should be elicited because it may provide a clue to the presence of polycystic or other familial kidney disease, sickle cell disease, or renal calculi. A history of recent strenuous exercise is important to identify; 15 to 20% of normal persons exhibit hematuria after strenuous exercise. The mechanism is unclear, but the hematuria resolves spontaneously within a few days.

Clinical Features. On physical examination, findings of arthritis, skin lesions, hypertension, or edema suggest underlying glomerulonephritis. Examination of the external genitalia may reveal a urethral meatal lesion that may be the source of bleeding; in adult women, a pelvic examination should be performed to exclude vulvovaginal sources of blood. Because endocarditis or atrial fibrillation may cause renal embolism, the patient should be checked for a new heart murmur or an irregular rhythm. Costovertebral angle tenderness suggests pyelonephritis or stone disease, and a palpably enlarged kidney suggests polycystic kidney disease or renal malignancy. The prostatic examination may offer clues to the presence of prostatitis, benign prostatic hypertrophy, or cancer.

Laboratory Findings. Evaluation of hematuria in the ED setting should include assessment of the blood pressure and measurement of the BUN and serum creatinine levels to gauge the patient's underlying renal function, but urinalysis can be expected to provide more specific information. Red urine that is dipstick-negative and free of red cells on microscopy may be caused by ingestion of beets, red berries, or food coloring; by urate crystals; or by drugs such as phenazopyridine (Pyridium) and rifampin. A finding of red cell or other casts or lipiduria or significant proteinuria in combination with hematuria suggests intrinsic renal disease, and appropriate referral should be made. Microscopic hematuria usually does not produce a positive dipstick test result for protein, but gross hematuria may contribute enough protein to cause a positive result; thus, a finding of proteinuria should be confirmed and the amount quantitated in a 24-hour urine collection. Hematuria in combination with pyuria or bacteriuria suggests UTI; the infection should be treated and hematuria reassessed after therapy has been completed. Even if white cells or organisms are not seen on urinalysis, the urine should be cultured to rule out hemorrhagic cystitis, especially when lower tract symptoms are present.

Blood studies should be ordered only as necessary to gauge renal function and to confirm causes suggested by the clinical presentation. In the ED setting, routine ordering of the full gamut of chemical and serologic studies necessary to rule out all possible causes of hematuria is rarely appropriate. In particular, a platelet count and coagulation studies are extremely unlikely to be helpful in the absence of a suggestive history or other specific clinical clues.

Radiography and Ultrasonography. The role of urinary tract imaging studies in the immediate evaluation of hematuria also is limited. Visualization of the urinary tract generally is helpful only when the history suggests renal colic or other disorders of the upper urinary tract (e.g., polycystic kidney disease, tumor, obstruction). CT scanning without contrast has emerged as the imaging modality of choice.[8] Ultrasonography can be used to determine kidney size and shape and to detect renal masses or obstruction. Further imaging studies, if indicated, should be planned after urologic consultation.

If no upper tract lesions are identified on initial imaging studies, cystoscopy usually is the next step in evaluation because it is the most effective means of visualizing the bladder and the male urethra. It is the initial study of choice for patients with active gross hematuria; in fact, some urologists prefer to perform endoscopic procedures promptly during an acute bleeding episode to maximize the chance of localizing the source. In older patients in whom urinalysis shows only hematuria and the findings on the history and physical examination are otherwise unhelpful, urinary cytologic examination also may be undertaken.

Monitoring on an outpatient basis constitutes appropriate management in patients with hematuria who have no other abnormality revealed by urinalysis, who are otherwise asymptomatic, who are not azotemic, hypertensive, or severely anemic, and who have no evidence of intrinsic renal disease. (A possible exception may be the patient with a known bleeding disorder.) Extensive outpatient evaluation for an isolated episode of hematuria usually is not undertaken in patients younger than 40 years of age unless hematuria is persistent, but most patients older than 40 years should undergo a thorough evaluation after even a single episode of hematuria.

The cause of hematuria can be determined on initial medical and urologic evaluation in 70 to 80% of cases. In other cases, a diagnosis of small calculi, occult bladder tumor, arteriovenous malformation, or early glomerulonephritis is made only after repeated examination or the development of further signs or symptoms. In 5 to 10% of cases, no cause can be determined.

Proteinuria

Principles of Disease. Abnormal proteinuria is defined as excretion of more than 150 mg of protein (albumin) per 24 hours in adults, or more than 140 mg/m^2 per 24 hours in children. Patients with mild to moderate degrees of proteinuria commonly are identified incidentally on routine urinalysis; patients with more severe degrees of proteinuria often seek medical attention because of edema or other effects of hypoproteinemia.

With alteration in the glomerular capillary barrier (e.g., with the nephrotic syndrome and the many varieties of primary and secondary glomerulonephritis), albumin and globulins, which under normal circumstances are restricted from the glomerular ultrafiltrate because of their ionic charge and size, are lost into the urine. Persistent proteinuria is a marker for renal disease even in the absence of azotemia or an abnormal urine sediment.

Excretion of more than 2 g of protein in 24 hours is likely to be caused by a glomerular process. In the *nephrotic syndrome*, protein losses exceed the liver's capacity to synthesize albumin, resulting in hypoalbuminemia. This leads to decreased plasma oncotic pressure and accumulation of edema fluid in the extravascular interstitial space. Increased aldosterone secretion and further retention of salt and water ensue. Thus, edema is the clinical hallmark of the nephrotic syndrome and often is the initial complaint of patients who have significant proteinuria. Edema ranges in severity from mild dependent peripheral edema or periorbital swelling to frank anasarca with pleural effusions and ascites. *Nephrotic-range proteinuria* is defined arbitrarily as excretion of greater than 3.5 g of protein per 24 hours.

Patients with the nephrotic syndrome are at increased risk for thromboembolic events, including deep vein thrombosis of the lower extremity, renal vein thrombosis, and pulmonary embolism. The reason for this propensity appears to be a hypercoagulable state that may be related in part to urinary loss and decreased plasma levels of antithrombin III, proteins, and fibrinolytic factors.[1] Hyperlipidemia is another typical feature of the nephrotic syndrome; the mechanism is thought to be related indirectly to hypoalbuminemia and decreased oncotic pressure or viscosity. The major clinical significance of the nephrotic syndrome, however, is that it indicates the presence of an underlying renal process or systemic disease affecting the glomerulus (Box 95-3).

Clinical Features. Evaluation of the patient with proteinuria focuses not only on gauging the severity of proteinuria and the likelihood of complications but also on identifying any associated signs of underlying renal disease or systemic illness. Careful questioning will elicit a history of recent infections or use of medications or drugs or a past history of proteinuria, hypertension, edema, or renal disease. In young female patients, the possibility of pregnancy should be kept in mind because pregnancy can exacerbate previously inapparent renal disease; in late pregnancy, proteinuria may be the first sign of preeclampsia. Clues to the presence of systemic diseases that commonly affect the kidneys (e.g., diabetes, collagen vascular disease) should be sought as well. The physical examination should include evaluation of the blood pressure, determination of the presence or absence of edema, and assessment for signs of systemic disease or renal insufficiency.

Laboratory Findings. The laboratory evaluation in the patient with proteinuria should include urinalysis and measurement of the BUN and serum creatinine. Although the finding of isolated proteinuria may or may not be clinically important, proteinuria is almost always significant when it occurs in combination with hematuria. RBCs and red cell casts suggest glomerulonephritis; proteinuria with pyuria may be seen with AIN. The combination of proteinuria and glycosuria suggests diabetic nephropathy. A 24-hour urine collection should be ordered to provide an accurate measure of GFR and to quantitate protein excretion.

Abnormal findings on the history, physical examination, or laboratory evaluation greatly increase the probability of the presence of significant renal disease, and early referral to an internist or nephrologist is indicated. However, in the absence of edema, azotemia, hypertension, active urine sediment, or known systemic illness affecting the kidney, patients with proteinuria may be referred to their primary care provider for follow-up. Because transient, mild proteinuria is not uncommon in healthy persons, patients with mild proteinuria as indicated by dipstick testing (particularly if the urine is concentrated) should have dipstick testing repeated at follow-up visit before further evaluation is undertaken. Persistent proteinuria may require referral to a nephrologist; in some cases, renal biopsy will be necessary to establish a diagnosis and guide management.

BOX 95-3 CAUSES OF THE NEPHROTIC SYNDROME

- Primary renal disease
- Multisystem disease
  - Diabetes mellitus
  - Collagen vascular disease
    - Systemic lupus erythematosus
    - Rheumatoid arthritis
    - Henoch-Schönlein purpura
    - Polyarteritis nodosa
    - Wegener's granulomatosis
  - Amyloidosis
  - Cryoglobulinemia
- Drugs and toxins
  - Heroin
  - Captopril
  - Heavy metals
  - Nonsteroidal anti-inflammatory drugs
  - Penicillamine
  - Others
- Allergens
- Infection
  - *Bacterial*
    - Infective endocarditis
    - Poststreptococcal infection
    - Syphilis
  - *Viral*
    - Hepatitis B
    - Human immunodeficiency virus infection
    - Cytomegalovirus infection
  - *Protozoal*
    - Malaria
    - Toxoplasmosis
- Malignancy
  - Solid tumors
  - Multiple myeloma
  - Lymphoma
  - Leukemia
- Miscellaneous
  - Hereditary nephritis
  - Preeclampsia
  - Malignant hypertension
  - Reflux nephropathy
  - Transplant rejection

■ ACUTE RENAL FAILURE

The hallmark of ARF is progressive azotemia, which commonly is accompanied by a wide range of other disturbances, depending on the severity and duration of renal dysfunction. These include metabolic derangements (e.g., metabolic acidosis and hyperkalemia), disturbances of body fluid balance (particularly volume overload), and a variety of effects on almost every organ system (Box 95-4).

The causes of ARF may be divided into those that decrease renal blood flow (prerenal), produce a renal parenchymal insult (intrarenal), or obstruct urine flow (obstructive or postrenal). Identification of either a prerenal or a postrenal cause of ARF generally makes it possible to initiate specific corrective therapy; if these two broad categories of ARF can be excluded, an intrarenal cause is implicated. The renal parenchymal causes of ARF can be usefully subdivided into those primarily

BOX 95-4 CLINICAL FEATURES OF ACUTE RENAL FAILURE

Cardiovascular
Pulmonary edema
Arrhythmia
Hypertension
Pericarditis
Pericardial effusion
Myocardial infarction
Pulmonary embolism

Metabolic
Hyponatremia
Hyperkalemia
Acidosis
Hypocalcemia
Hyperphosphatemia
Hypermagnesemia
Hyperuricemia

Neurologic
Asterixis
Neuromuscular irritability
Mental status changes
Somnolence
Coma
Seizures

Gastrointestinal
Nausea
Vomiting
Gastritis
Gastroduodenal ulcer
Gastrointestinal bleeding
Pancreatitis
Malnutrition

Hematologic
Anemia
Hemorrhagic diathesis

Infectious
Pneumonia
Septicemia
Urinary tract infection
Wound infection

From Brady HR, Brenner BM, Clarkson MR, Lieberthal W: Acute renal failure. In Brenner BM: The Kidney, 6th ed. Philadelphia, Saunders, 2000, pp 1201–1246.

BOX 95-5 CAUSES OF PRERENAL AZOTEMIA

Volume Loss
Gastrointestinal: vomiting, diarrhea, nasogastric drainage
Renal: diuresis
Blood loss
Insensible losses
Third space sequestration
Pancreatitis
Peritonitis
Trauma
Burns

Cardiac
Myocardial infarction
Valvular disease
Cardiomyopathy
Decreased effective arterial volume
Antihypertensive medication
Nitrates

Neurogenic
Sepsis
Anaphylaxis
Hypoalbuminemia
Nephrotic syndrome
Liver disease

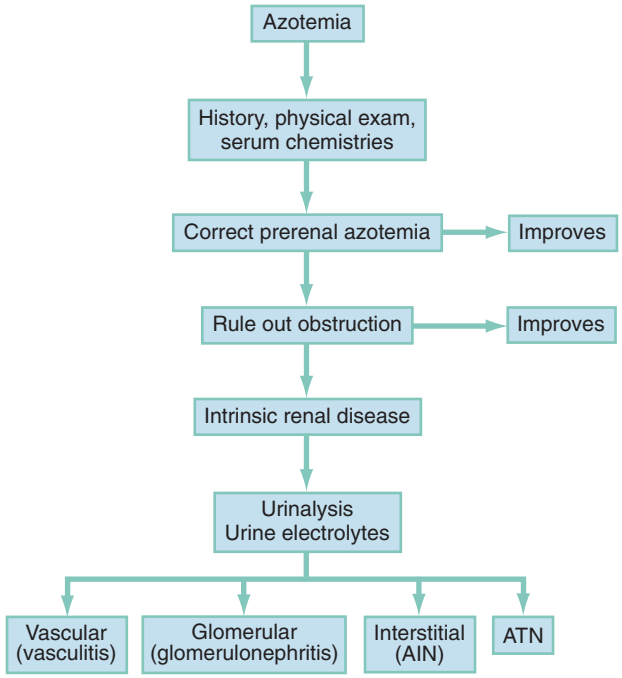


Figure 95-3. Evaluation of azotemia. AIN, acute interstitial nephritis; ATN, acute tubular necrosis.

affecting the glomeruli, the intrarenal vasculature, or the renal interstitium.[4] The term *acute tubular necrosis* denotes another broad category of intrinsic renal failure that cannot be attributed to specific glomerular, vascular, or interstitial causes[4] (Fig. 95-3).

Principles of Disease

Prerenal Azotemia

Decreased renal perfusion that is sufficient to cause a decrease in the GFR results in azotemia. The possible causes can be grouped into entities causing intravascular volume depletion, volume redistribution, or decreased cardiac output (Box 95-5). Patients who have preexisting renal disease are particularly sensitive to the effects of diminished renal perfusion.

Prerenal azotemia is characterized by increased urine specific gravity, BUN/creatinine ratio greater than 10:1, urine sodium concentration less than 20 mEq/dL, and FENa less than 1%. The condition generally can be corrected readily by expanding extracellular fluid volume, augmenting cardiac output, or discontinuing vasodilating antihypertensive drugs. However, severe prolonged prerenal azotemia can eventuate in ATN.

Patients who have congestive heart failure (CHF) or cirrhosis form an important subset of those with prerenal azotemia. These patients often are salt-overloaded and water-overloaded, yet their effective intra-arterial volume is decreased. Administration of diuretics has the potential to decrease intravascular volume further, resulting in decreased glomerular filtration and prerenal azotemia. For some patients with advanced CHF or hepatic disease, a state of chronic stable prerenal azotemia may be the best achievable compromise between symptomatic volume overload and severe renal hypoperfusion.[9]

Glomerular perfusion also may be decreased in patients with normal intravascular volume and normal renal blood flow who take angiotensin-converting enzyme (ACE) inhibitors or, more commonly, prostaglandin inhibitors. All nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, inhibit prostaglandin synthesis. Renal vasodilator prostaglandins are critical in maintaining glomerular perfusion in patients with conditions such as CHF, chronic renal insufficiency, and cirrhosis, in which elevated circulating levels of renin and angiotensin II act to diminish renal blood flow and GFR. In this setting, decreased production of vasodilator prostaglandins may result in acute intrarenal hemodynamic changes and a reversible decrease in renal function.[10] This phenomenon also is seen with the newer, selective cyclooxygenase-2 inhibitor class of NSAIDs.[11,12] Other risk factors include advanced age, diuretic use, renovascular disease, and diabetes. This entity is distinct from other renal complications of NSAIDs, including interstitial nephritis and papillary necrosis.

Renal insufficiency secondary to NSAIDs generally is reversible after withdrawal of the causative agent. For patients who are at increased risk but require treatment with NSAIDs, a short-acting preparation (e.g., ibuprofen) should be prescribed, and follow-up monitoring of renal function and serum potassium level should begin within days rather than weeks. If renal function is unchanged after a short course of treatment, adverse effects from continuing therapy are unlikely, although other potential mechanisms for the development of renal dysfunction (e.g., interstitial nephritis) should be kept in mind.

Postrenal (Obstructive) Acute Renal Failure

Obstruction is an eminently reversible cause of ARF and should be considered in every patient with newly discovered azotemia or worsening renal function. Obstruction may occur at any level of the urinary tract but most commonly is produced by prostatic hypertrophy or by functional bladder neck obstruction (e.g., secondary to medication side effects or neurogenic bladder) (Box 95-6). Intrarenal obstruction may result from intratubular precipitation of uric acid crystals (e.g., with tumor lysis), oxalic acid (as in ethylene glycol ingestion), myeloma proteins, methotrexate, sulfadiazine, acyclovir, or indinavir.[13] Bilateral ureteral obstruction (or obstruction of the ureter of a solitary kidney) may be caused by retroperitoneal fibrosis, tumor, surgical misadventure, stones, or blood clots. A sudden deterioration in renal function in the setting of diabetes mellitus, analgesic nephropathy, or sickle cell disease should suggest papillary necrosis.

Treatment of postrenal ARF consists of relief of the obstruction. In the absence of infection, full renal recovery is possible even after 1 to 2 weeks of total obstruction, although the serum creatinine level may not return to baseline for several weeks. Because the onset of irreversible loss of renal function with obstruction appears to be gradual, a few days' delay in diagnosis generally is considered acceptable. Still, common sense dictates that obstructions should be detected and relieved promptly.

BOX 95-6 CAUSES OF POSTRENAL ACUTE RENAL FAILURE

Intrarenal and Ureteral
Kidney stone
Sloughed papilla
Malignancy
Retroperitoneal fibrosis
Uric acid or oxalic acid crystal precipitation
Sulfonamide, methotrexate, acyclovir, or indinavir precipitation

Bladder
Kidney stone
Blood clot
Prostatic hypertrophy
Bladder carcinoma
Neurogenic bladder

Urethra
Phimosis
Stricture

Intrinsic Acute Renal Failure

Of the specific intrarenal disorders that cause ARF, glomerulonephritis, interstitial nephritis, and abnormalities of the intrarenal vasculature are amenable to specific therapy and thus should be carefully considered as possible causes. These entities are responsible for only 5 to 10% of cases of ARF in adult inpatients; most are due to ATN. In adults in whom ARF develops outside the hospital, the incidence of glomerular, interstitial, and small-vessel disease is much greater. In children, these entities account for approximately one half of the cases of ARF[4] (Box 95-7).

Glomerular Disease

Acute glomerulonephritis may represent a primary renal process or may be the manifestation of any of a wide range of other disease entities (see Box 95-7). Patients may have dark urine, hypertension, edema, or CHF (secondary to volume overload) or may be completely asymptomatic, in which case the diagnosis rests on an incidental finding on urinalysis. The hematuria associated with glomerular disease may be microscopic or gross and may be persistent or intermittent. Proteinuria, although often in the range of 500 mg/day to 3 g/day, not uncommonly is in the nephrotic range. Presence of hematuria, proteinuria, or red cell casts is highly suggestive of glomerulonephritis. In fact, red cell casts are essentially diagnostic of active glomerular disease, although occasionally they are seen with other types of renal disease. Conversely, the absence of red cell casts, proteinuria, and hematuria essentially excludes glomerulonephritis as the cause of ARF.

The specific diagnosis of acute glomerulonephritis caused by primary renal disease often is ultimately made by renal biopsy. However, when glomerulonephritis is secondary to a systemic disease such as systemic lupus erythematosus, the patient's clinical signs and symptoms, in combination with the results of laboratory assessment, aid considerably in narrowing the scope of the differential diagnosis. As a rule, extensive laboratory testing to identify the cause of acute glomerulonephritis is not indicated in the ED setting and is more appropriately performed as part of an inpatient evaluation.

Interstitial Disease

AIN most commonly is precipitated by drug exposure or by infection. Drug-induced AIN is poorly understood, but the

BOX 95-7 Intrinsic Renal Diseases That Cause Acute Renal Failure

Vascular

Large-Vessel Disease
Renal artery thrombosis or stenosis
Renal vein thrombosis
Atheroembolic disease

Small- and Medium-Vessel Disease
Scleroderma
Malignant hypertension
Hemolytic uremic syndrome
Thrombotic thrombocytopenic purpura
HIV-associated microangiopathy

Glomerular

Systemic Diseases
Systemic lupus erythematosus
Infective endocarditis
Systemic vasculitis (e.g., periarteritis nodosum, Wegener's granulomatosis)
Henoch-Schönlein purpura
HIV-associated nephropathy
Essential mixed cryoglobulinemia
Goodpasture's syndrome

Primary Renal Disease
Poststreptococcal glomerulonephritis
Other postinfectious glomerulonephritis
Rapidly progressive glomerulonephritis

Tubulointerstitial
Drugs (many)
Toxins (e.g., heavy metals, ethylene glycol)
Infections
Multiple myeloma

Acute Tubular Necrosis

Ischemia
Shock
Sepsis
Severe prerenal azotemia

Nephrotoxins
Antibiotics
Radiographic contrast agents
Myoglobinuria
Hemoglobinuria

Other
Severe liver disease[18]
Allergic reactions
NSAIDs[19]

ARF, acute renal failure; HIV, human immunodeficiency virus; NSAIDs, nonsteroidal anti-inflammatory drugs.

absence of a clear relationship to the dose and the recurrence of the syndrome on rechallenge with the offending agent suggests that an immunologic mechanism is responsible. The most commonly incriminated drugs are the penicillins, diuretics, anticoagulants, and NSAIDs. AIN has been reported in association with bacterial, fungal, protozoan, and rickettsial infections.

Patients with AIN classically have rash, fever, eosinophilia, and eosinophiluria, but it is common for one or more of these cardinal signs to be absent. Pyuria, gross or microscopic hematuria, and mild proteinuria are observed in some cases. A definite diagnosis sometimes can be made only on renal biopsy. Treatment of AIN is directed at removing the presumed cause; infections should be treated and offending drugs discontinued. Renal function generally returns to baseline over several weeks, although chronic renal failure has been reported to occur.

Intrarenal Vascular Disease

Vascular disease of the kidney can be classified according to the size of the vessel that is affected. Disorders such as renal arterial thrombosis or embolism, which affect large blood vessels, must be bilateral (or must affect a single functioning kidney) to produce ARF. Whether to attribute such cases of ARF to prerenal or intrarenal vascular causes is a matter of semantics. The most common cause of thrombosis probably is trauma; thrombosis also may occur after angiography or may be secondary to aortic or renal arterial dissection. Renal atheroembolism is thought to occur commonly—at least on a microscopic level—after arteriography but is an uncommon cause of ARF. Similarly, patients with chronic atrial fibrillation or infective endocarditis may experience embolization of the kidney but rarely suffer ARF as a result. Renal arterial embolism can cause acute renal infarction, generally manifested by sudden flank, back, chest, or upper abdominal pain. Urinary findings, including hematuria, are variable. Fever, nausea, and vomiting are not uncommon; in some cases, evidence of embolization to other vessels provides a useful clue. The diagnosis usually is made by renal flow scanning or arteriography. Surgical embolectomy has been reported to restore function when undertaken within several hours of occlusion, but significant return of function has been documented in patients operated on as long as 6 weeks after total occlusion. This outcome presumably is possible because collateral circulation has developed in association with a preexisting partial occlusion.

An interesting but relatively uncommon type of ARF occurs when an ACE inhibitor is given to a patient with underlying bilateral renal artery stenosis (or unilateral stenosis of a solitary functioning kidney). With inhibition of angiotensin synthesis, efferent arteriolar tone is not maintained and GFR decreases. The condition is reversible with cessation of therapy.

Several diseases that affect the smaller intrarenal vessels can cause ARF (see Box 95-7). Patients whose disease is severe enough to cause ARF also generally are found to have hypertension, microangiopathic hemolytic anemia, and other systemic and organ-specific manifestations. Infection with *Escherichia coli* O157:H7 has emerged as a major cause of hemolytic uremic syndrome, an important cause of ARF in children.[14]

Malignant hypertension, although much less common since the advent of more effective antihypertensive therapy, has by no means disappeared. Patients with scleroderma (systemic sclerosis) may have "scleroderma renal crisis,"[15] characterized by malignant hypertension and rapidly progressive renal failure. Whereas vasculitis associated with glomerular capillary inflammation typically causes gross or microscopic hematuria and formation of red cell casts, vascular involvement of the medium-size vessels, such as that produced by scleroderma, often spares the preglomerular vessels and tends not to produce an active urine sediment. Extrarenal manifestations (rash, fever, arthritis, pulmonary symptoms) are usually evident.

For malignant hypertension both as a separate entity and as a part of scleroderma renal crisis, appropriate treatment can produce a gratifying remission of ARF. Patients with malignant hypertension have been reported to recover renal function after aggressive antihypertensive therapy, with temporary maintenance with dialysis if necessary.[16] In patients with scleroderma renal crisis, specific therapy with ACE inhibitors

has been shown to result in improvement in renal function in a significant proportion of cases.[17]

Acute Tubular Necrosis

The term *acute tubular necrosis* refers to a generally reversible deterioration of kidney function associated with a variety of renal insults. Oliguria may or may not be a feature. The diagnosis is made after prerenal and postrenal causes of ARF and disorders of glomeruli, interstitium, and intrarenal vasculature have been excluded. These discrete categories do overlap in a few disorders. For example, ARF associated with multiple myeloma or ethylene glycol toxicity is associated with both intrarenal obstruction and interstitial disease, as well as probably having a direct toxic effect on the renal tubule itself.

The most common precipitant of ATN is renal ischemia occurring during surgery or after trauma and sepsis. The remainder of cases occur in the setting of medical illness, most commonly as a result of the administration of nephrotoxic aminoglycoside antibiotics or radiocontrast agents or in association with rhabdomyolysis. Multiple causes can be identified in some cases; in others, a definitive cause is never established.

Decreased renal perfusion results in a continuum of renal dysfunction that ranges from transient prerenal azotemia at one extreme to ATN at the other. Early during the period of renal ischemia, renal function can be restored completely by restoring renal blood flow, but at some point, continued hypoperfusion will result in renal dysfunction unresponsive to volume repletion and ATN will supervene. ATN may occur in the absence of frank hypotension; even modest renal ischemia may result in ATN in susceptible persons. Individual susceptibility to ATN may be related to the balance of prostaglandin-mediated vasopressor and vasodilatory influences on the renal vasculature.

Postischemic ATN can occur in the setting of volume loss from the GI tract (upper or lower), skin, or kidneys or can result from severe hemorrhage or major burns. Heatstroke commonly is associated with the development of ATN, which is thought to result from a combination of volume loss, hyperpyrexia, and rhabdomyolysis. Another cause of ATN is hyperglycemic hyperosmolar nonketotic coma, which can be associated with loss of as much as 25% of total body water. ATN also is seen in the setting of cardiogenic shock, sepsis, and third spacing of fluids in pancreatitis and peritonitis.

ATN is common in postoperative patients, although not all cases can be attributed to intraoperative hypotension or hemorrhage. Concomitant sepsis, increased age, preexisting renal disease, and other comorbid conditions are associated with a worse outcome.[18,19]

Nephrotoxins constitute the other major cause of ATN. Among the most prominent of these are the endogenous pigments myoglobin and hemoglobin. Rhabdomyolysis and ARF resulting from crush injuries first received widespread attention after their description in survivors of the London blitz during World War II, but many other causes of pigment nephropathy have been reported (Box 95-8). Hypotension secondary to fluid loss into damaged muscle is thought to worsen the effects of myoglobinuria on the renal tubule, as does acidosis. Hemolysis, resulting in the release of hemoglobin into the circulation and hemoglobinuria, can cause ATN but usually only in the presence of coexisting dehydration, acidosis, or other causes of decreased renal perfusion. ATN may be produced by the hemolysis of as little as 100 mL of blood.

ATN associated with rhabdomyolysis is often oliguric; it is characterized by rapid increases in the serum creatinine, potassium, phosphorus, and uric acid levels.[20,21] Creatine released from muscle is metabolized to creatinine, which may result in serum creatinine increases of more than 2 mg/dL per day, in contrast with the increase of 0.5 to 1.0 mg/dL per day typically seen in other forms of ARF. The BUN/creatinine ratio often is less than 10:1. Intracellular potassium released from damaged muscle may raise the serum potassium by 1 to 2 mEq/L in several hours. Likewise, phosphate released from muscle may cause dramatic increases in the serum phosphate level. Uric acid, produced by metabolism of purines released from damaged muscle, may accumulate to levels high enough to suggest acute uric acid nephropathy.

Urine dipstick testing yields a positive result for heme in only 50% of patients with rhabdomyolysis, because myoglobin is rapidly cleared from the serum and may therefore be undetectable in the urine at the time of presentation. Thus, a negative result on urine dipstick testing does not rule out the diagnosis. Serum creatine kinase (CK) is cleared much more slowly, so measurement of serum CK levels is a much more sensitive test.

No biochemical parameter can be used to predict which patients who have rhabdomyolysis will experience ARF. In one classic study of patients in whom alcoholism, muscle compression, and seizures were the most common causes of rhabdomyolysis, ARF developed in only one third. Neither the degree of serum CK elevation, the presence (or absence) of myoglobinuria, nor the degree of hyperkalemia correlated well with the development of ARF.[20]

Antibiotics and radiographic contrast agents are other nephrotoxins that commonly are implicated in the development of ATN. Aminoglycosides are the most commonly implicated antibiotics. Higher doses and longer duration of therapy are associated with higher serum drug levels, leading to greater accumulation of drug in the renal parenchyma and a greater likelihood of nephrotoxicity. Increased age, impaired renal function, dehydration, and exposure to other nephrotoxins are additional risk factors. Once-daily administration of a somewhat higher dose is associated with less nephrotoxicity but equal effectiveness.[22,23]

Aminoglycoside-induced ATN typically has a gradual onset. Clinically significant renal dysfunction usually occurs only after several days and often after more than a week of therapy. However, renal failure can develop as late as 10 days after a

BOX 95-8 CAUSES OF PIGMENT-INDUCED ACUTE RENAL FAILURE

Rhabdomyolysis and myoglobinuria
Vigorous exercise
Arterial embolization
Status epilepticus
Status asthmaticus
Coma-induced and pressure-induced myonecrosis
Heat stress
Diabetic ketoacidosis
Myopathy
Alcoholism
Hypokalemia
Hypophosphatemia
Hemoglobinuria
Transfusion reactions
Snake envenomation
Malaria
Mechanical destruction of RBCs by prosthetic valves
G6PD deficiency

G6PD, glucose-6-phosphate dehydrogenase; RBCs, red blood cells.

drug has been discontinued, an observation that appears to be explained by the prolonged tissue half-life characteristic of these agents. Renal function returns to normal after an average of 6 weeks, but the condition occasionally progresses to permanent renal injury.

Radiographic contrast agents constitute a common cause of hospital-acquired renal insufficiency. Renal failure produced by these agents may be defined as an increase in serum creatinine level of 25% over baseline with a temporal relation to contrast medium administration and in the absence of other identifiable causes. Radiocontrast agent–induced ATN encompasses a spectrum ranging from asymptomatic nonoliguric renal insufficiency to severe renal failure requiring dialysis, but most cases are mild. It can occur after any procedure involving intravascular administration of contrast material. Typically, an increase in the serum creatinine level is noted within 3 days of exposure, with a return to normal within 10 to 14 days.

The most important risk factors for radiocontrast agent–induced ATN are preexisting renal insufficiency, diabetes mellitus, multiple myeloma, age older than 60 years, volume depletion, and higher doses of contrast material. Among these, preexisting renal insufficiency is the most important.[24] Diabetic patients with a serum creatinine level less than 1.5 mg/dL are at low risk for the development of radiocontrast agent–induced ATN, whereas those whose serum creatinine is greater than 1.5 mg/dL are at significant risk.[25] Multiple myeloma, particularly in patients who are dehydrated, is another reasonably well-documented risk factor. Advanced age also appears to make ATN more likely, possibly because of decreased renal mass and cortical blood flow. Volume depletion appears to be an independent risk factor, and aggressive volume expansion before contrast exposure has been shown to have a protective effect.[26,27] Finally, large doses and repeated doses of contrast material are associated with increased risk of ATN, particularly if a second study is performed within 72 hours of the first. Use of low-osmolality contrast media appears to be associated with a lower risk of nephrotoxicity than that with use of standard high-osmolality agents.[28-30]

Oral *N*-acetylcysteine has been shown to have some protective effect when given prophylactically for 2 days before coronary angiography,[31] and in some studies when given much closer to the time of contrast exposure.[32] However, other analyses cast doubt on the feasibility and effectiveness of *N*-acetylcysteine in the ED setting.[33,34] A rapid-treatment regimen of modest volumes of intravenous $NaHCO_3$ (3 mL/kg over 1 hour, followed by 1 mL/kg per hour for 6 hours after contrast exposure) appears to be effective in decreasing the likelihood of nephrotoxicity and is more appropriate for use in the ED.[35,36]

Clinical Features

When the presence of azotemia or renal failure has been discovered, the first consideration in the ED evaluation should be the possibility of potentially life-threatening complications (e.g., hyperkalemia, pulmonary edema). Assuming these have been satisfactorily ruled out, the next step is to determine whether the condition represents ARF or is the result of preexisting renal disease. The clinical distinction between ARF and chronic renal failure often is difficult; old records and laboratory results are invaluable. The finding of small kidneys on abdominal radiography or bone changes of secondary hyperparathyroidism on hand films suggests that the renal failure is chronic. Anemia, hypocalcemia, and hyperphosphatemia, on the other hand, should not be relied on to identify patients who have chronic renal failure because these abnormalities can develop rapidly in ARF.

In evaluating the patient with azotemia, the history, physical examination, and laboratory studies should seek clues to the cause and identify signs and symptoms of uremia, volume overload, or other complications of renal failure. In attempting to identify the cause of azotemia, the general strategy is to rule out both prerenal and postrenal causes before considering the many intrinsic renal causes. First, potential sources of volume loss and causes of decreased cardiac output should be sought in the history, and the patient should be questioned about lightheadedness, bleeding, GI fluid loss, abnormal polyuria, or symptoms of CHF. In men, a history of nocturia, frequency, hesitancy, or decreased urinary stream suggests prostatic obstruction. A history of lower tract symptoms or of abdominal or pelvic tumor in either sex should likewise be elicited, as should a history of kidney stones or chronic UTI. As documented in the history, acute anuria (defined as the production of urine at less than 100 mL/day) most often is the result of high-grade urinary tract obstruction, although it also may accompany severe volume depletion, severe acute glomerulonephritis, cortical necrosis, or bilateral renal vascular occlusion. Intermittent anuria, on the other hand, is characteristic of obstructive disease.

The patient should be questioned about medication use and possible exposure to radiographic contrast agents or other exogenous toxins. A history of hypertension, dark-colored urine, rash, fever, or arthritis suggests intrinsic renal disease or a multisystem disorder. In older patients, presence of symptoms suggestive of multiple myeloma should be elicited.

The physical examination should focus on signs of volume depletion such as orthostatic hypotension, tachycardia, and decreased skin turgor. Documented short-term changes in body weight offer a valuable clue in assessing volume status, particularly in chronically ill patients. In addition, suspected bleeding should be specifically excluded. Similarly, volume overload should be sought by assessment of jugular vein distention and attention to the presence of rales, an S_3 gallop, or edema.

An attempt to percuss the bladder should be made. A distended bladder is percussible when it contains 150 mL of urine, and the dome is palpable abdominally when it contains 500 mL. Ultrasonography can be used to detect bladder distention or postvoid residual volume if there is a question of urinary retention.[37]

Prostate examination in adult men and pelvic examination in adult women should not be neglected. Rash, purpura, pallor, or petechiae should be noted, as should arthritis, musculoskeletal tenderness, or findings suggestive of infection or malignancy.

Diagnostic Strategy

Laboratory Findings. The laboratory evaluation should begin with a dipstick and microscopic urinalysis and measurement of urine output. BUN, serum creatinine, urine sodium, and FENa levels should be determined to help evaluate renal function and to provide clues to the cause of ARF. A complete blood count, serum electrolyte panel (expanded to include calcium, phosphorus, and magnesium determinations), electrocardiogram (ECG), and chest radiograph should be ordered to establish the patient's baseline status and to provide information about possible complications. Other studies may be of value in the ED setting when the history or physical findings suggest that they may have a specific role in immediate diagnosis or management.

Prerenal azotemia should be suspected in the setting of volume loss, volume redistribution, or decreased effective renal perfusion. It typically is associated with a normal urinaly-

sis, high BUN/creatinine ratio, increased urine osmolality, urine sodium concentration less than 20 mEq/L, and FENa less than 1%. A rapid response to volume repletion also is characteristic.

Urethral or bladder neck obstruction is documented by the finding of significant amounts of residual urine in the bladder (by catheterization or ultrasound examination) after the patient has voided or attempted to void spontaneously. An important point is that the ability to void does not rule out obstruction. In fact, the urine volume in the presence of obstruction may range from zero to several liters per day. Flank pain is likewise an insensitive marker for obstruction. Urine indices and the BUN/creatinine ratio tend not to be helpful, although an increase in the latter is common in obstruction. A renal parenchymal disorder often can be diagnosed by its manifestations on microscopic urinalysis or by associated extrarenal manifestations (e.g., with multisystem disease) or the clinical setting (e.g., recent exposure to a new medication). The absence of evidence for prerenal or postrenal causes in a patient with ARF may be taken as presumptive evidence of an intrarenal parenchymal process. Among these, the possibility of an acute or ongoing vascular insult should be kept in mind, because timely intervention may be important in preserving ultimate renal function.

Radiography and Ultrasonography. Significant hydronephrosis usually is readily demonstrable by ultrasonography and may indicate either upper or lower tract obstruction. In questionable cases, or if bilateral ureteral obstruction is strongly suspected on the basis of clinical findings, the next step is retrograde urography performed by a urologist.[38] CT imaging is less useful in this setting; in fact, intravenous radiocontrast material may compound the injury to the kidney.

Management

ED management of ARF is directed at reversing decreases in GFR and urine output (if possible) while minimizing further hemodynamic and toxic insults, maintaining normal fluid and electrolyte balance, and managing other complications of ARF as required. Because renal failure alters the metabolism and action of many drugs, often in ways that are not predictable, great care must be exercised in prescribing all medications. A compendium of guidelines for drug dosing in renal failure, such as the one by Brier and Aronoff,[39] is of great help for this purpose.

After ensuring that the vital signs are adequate and that the patient is in no immediate danger from volume or metabolic derangements, the next step is to correct prerenal and postrenal factors, if any are identified. Intravascular volume should be repleted in hypovolemic patients and maintained in euvolemic patients by matching input to measured and insensible output. Inadequate cardiac output should be augmented when possible. Postrenal or obstructive ARF is treated by restoration of normal urine outflow. Bladder outlet obstruction may be relieved by passage of a Foley catheter, whereas upper tract obstruction may require percutaneous nephrostomy.

When prerenal and postrenal factors have been ruled out, the challenge to the emergency physician is to identify the cause of intrinsic renal ARF, keeping in mind the multitude of known possible causes (see Box 95-7). The clinical setting and physical and laboratory findings often allow the scope of the differential diagnosis to be considerably narrowed. The clinical picture is often most consistent with the broad category of ATN.

It has been noted repeatedly that patients who have oliguric ARF have a significantly higher mortality rate and a much greater risk of complications than those who are not oliguric. The difference in prognosis may simply reflect a more severe renal insult in patients who are oliguric, however, and it is not clear that interventions aimed at converting oliguric to nonoliguric ARF have an effect on renal function or mortality.[40] Nevertheless, because nonoliguric patients are easier to manage, an attempt to increase urine flow is warranted.

Loop diuretics or mannitol often are effective in increasing urine flow when intravascular volume deficits have been corrected. Although furosemide has been shown to decrease dialysis requirements and complications caused by volume overload, it has not been shown to shorten the clinical course or affect mortality.[41-43] Mannitol appears to be most useful when given at the time of or shortly after the renal insult; the recommended dose is 12.5 to 25 g given intravenously. If urine output does not increase, further doses may cause hyperosmolality and clinically significant intravascular volume overload in patients with impaired renal function.[44]

Dopamine also has been used, with and without furosemide, in an effort to increase urine output, but efficacy has not been validated in prospective studies.[45-47]

Certain specific considerations apply to toxin-induced ATN. Pigment-induced ATN may be prevented by avoidance of hemolysis and muscle injury and by correction of the factors (e.g., dehydration, acidosis) that are known to predispose patients with pigmenturia to the development of renal failure. When hemolysis or rhabdomyolysis has occurred, treatment is directed at eliminating the cause and preventing the development of renal failure.

Mannitol has been shown to prevent ARF in experimental models of myoglobinuria, presumably by inducing osmotic diuresis and decreasing intratubular deposition of pigment. Furosemide, on the other hand, has not consistently shown a beneficial effect. Other studies have suggested that myoglobin precipitates in an acid urine but not in an alkaline urine. Thus, aggressive volume repletion, alkalinization, and mannitol infusion have traditionally been recommended after crush injuries to reduce the likelihood or severity of ARF.[48,49] This regimen also helps control hyperkalemia. Other evidence, however, suggests that aggressive volume resuscitation alone may be equally effective.[50] When ARF has occurred, management is similar to that of other forms of ARF, but early dialysis may be required to control rapidly developing hyperkalemia, hyperphosphatemia, and hyperuricemia.

Patients who have radiocontrast agent–induced ATN require only supportive therapy but should be hospitalized and seen by a nephrologist. A more significant aspect of ED management is *preventing* the occurrence of radiocontrast agent–induced ATN, particularly by identification of risk factors in patients for whom contrast studies are being considered. BUN and serum creatinine levels should be checked before contrast exposure in patients with risk factors. Moreover, before contrast medium is administered to a high-risk patient, it should be established that there is a compelling reason to perform the contrast study and that there is no adequate alternative to using a contrast agent. The patient should be volume-repleted before the study, the administered dose of contrast agent should be kept as low as possible, and multiple studies should be avoided, as should concomitant use of other nephrotoxins. Intravenous saline, given before and after radiocontrast agent administration, may be protective.[26,27]

Volume and Metabolic Complications

In addition to those general measures aimed at minimizing decreases in GFR and increasing urine output, an important component of the management of ARF is the prevention or

control of systemic complications. Of particular significance in this regard are metabolic derangements (e.g., hyperkalemia, hypocalcemia, hyperphosphatemia, metabolic acidosis) and complications of volume overload (e.g., hypertension, CHF).

Hyperkalemia, the most common metabolic cause of death in patients with ARF, results from an inability to excrete endogenous and exogenous potassium loads. In oliguric patients the serum potassium level typically increases by 0.3 to 0.5 mEq/L per day, but greater increases occur in catabolic, septic, or traumatized patients and in the presence of acidosis or exogenous potassium loads from diet or medication.

Hyperkalemia results in serious disturbances in cardiac electrophysiology that may culminate in cardiac arrest. Although some hyperkalemic patients note muscular weakness, most generally are asymptomatic until major manifestations of cardiotoxicity appear. Accordingly, detection of hyperkalemia should be a primary consideration in these patients. ECG changes correlate only roughly with the serum potassium level. Mild hyperkalemia (serum potassium less than 6.0 mEq/L) may be cautiously observed without specific treatment while all exogenous sources of potassium are eliminated. If the serum potassium level is greater than 6.5 mEq/L, and particularly if ECG changes are present, urgent intervention is necessary. When cardiotoxicity must be reversed immediately (e.g., when there is hemodynamic compromise), intravenous calcium (10 mL of 10% calcium gluconate or calcium chloride infused over 2 minutes) is the treatment of choice. Intravenous insulin (given with glucose to prevent hypoglycemia) and intravenous bicarbonate temporarily shift potassium to the intracellular space. Bicarbonate should be used with caution in patients with renal failure because of its potential to cause volume overload and to provoke hypocalcemic tetany or seizures. The safety and efficacy of inhaled albuterol in hyperkalemic patients with *chronic* renal failure have been well documented; like insulin and bicarbonate, this agent causes potassium to move into cells, thereby controlling hyperkalemia for 2 hours or more.[51,52] Elimination of potassium from the body is promoted by using a potassium-binding ion exchange resin (sodium polystyrene sulfonate [Kayexalate]), by enhancing urinary potassium excretion, or by dialysis.

Hypocalcemia is a common feature of ARF and can develop rapidly after its onset. Vitamin D–dependent intestinal absorption of calcium is decreased in ARF because of decreased renal synthesis of 1,25-dihydroxyvitamin D. Another factor promoting hypocalcemia is the complexing of calcium with retained phosphate. Rhabdomyolysis-associated ARF in particular often is associated with the deposition of complexed calcium in muscle and other tissues. Asymptomatic hypocalcemia requires no immediate treatment, but subtle or frank tetany should be treated with intravenous calcium (10 to 20 mL of 10% calcium gluconate infused over several minutes).

Hyperphosphatemia resulting from decreased renal elimination of phosphate is another common feature of ARF. The serum phosphorus level usually ranges from 6 to 8 mg/dL but may be much higher with rhabdomyolysis or in catabolic states. A calcium-phosphate product greater than 70 may result in metastatic soft tissue calcification. Hyperphosphatemia often is treated with oral calcium-based antacids that bind ingested phosphate in the gut.

Acids produced in normal metabolic processes accumulate in ARF and are buffered in part by serum bicarbonate, resulting in a decrease in the serum bicarbonate level and a high-anion-gap metabolic acidosis. Compensatory hyperventilation may be mistakenly attributed to primary cardiac failure or volume overload. The metabolic acidosis associated with ARF usually is mild, and treatment generally is not necessary if the serum bicarbonate level is greater than 10 mEq/L. Overzealous correction may result in hypokalemia, hypocalcemia, or volume overload.

Hypermagnesemia may complicate ARF when patients are given magnesium-containing antacids or laxatives. Thus, these products, as well as magnesium itself (e.g., when given for treatment of arrhythmia or wheezing), should be avoided in the setting of ARF.

Disturbances of volume regulation can be expected to occur in most patients with ARF. Some nonoliguric patients excrete enough salt and water that intravascular volume depletion can occur if adequate fluid replacement is not provided. Volume depletion prolongs recovery from ARF. Much more commonly, ARF is complicated by volume overload, because sodium and water excretion may be inadequate to match even modest intakes. Volume overload is largely responsible for the hypertension often seen in ARF and commonly leads to CHF and pulmonary edema. Iatrogenic volume overload is particularly common and can be prevented only by careful attention to fluid intake and output using prudent estimates of insensible loss. Volume overload can be treated with diuretics or intravenous nitroglycerin while preparations are being made to initiate dialysis.

Organ System Effects

The clinician should be alert to the numerous other important systemic and organ-specific effects of renal failure. Only the more prominent of these are mentioned here.

Uremia impairs host defenses, particularly leukocyte function. Infection occurs in 30 to 70% of patients with ARF and is a significant cause of morbidity and mortality. Thus, patients with fever require prompt investigation and aggressive treatment.

Pericarditis, which has a prevalence of 12 to 20% in dialyzed patients with end-stage renal disease (ESRD), also may occur in patients with ARF. Chest pain that is worse in a recumbent position is the most common symptom, and most patients have a pericardial friction rub. Fever is common. The ECG may show ST-T wave elevation, low voltage, electrical alternans, or atrial fibrillation. The presence of pericardial effusion is identified most accurately by echocardiography; tamponade, with typical clinical signs, occurs in some patients. In contrast with the situation in chronic renal failure, pericarditis or pericardial effusion in the setting of ARF generally is an indication for the urgent initiation of dialysis. Patients who have hemodynamically significant tamponade require surgical drainage of the effusion or, occasionally, emergency pericardiocentesis.

Neurologic abnormalities in ARF may be precipitated by electrolyte abnormalities, medications, or uremia. Common signs and symptoms in uremic patients include lethargy, confusion, agitation, asterixis, myoclonus, and seizures.

Anorexia, nausea, vomiting, gastritis, and pancreatitis also are associated with ARF. GI hemorrhage is seen in 10 to 30% of patients and is one of the leading causes of death in ARF.

Impaired erythropoiesis, shortened RBC survival, hemolysis, hemodilution, and GI blood loss all play a role in the normocytic normochromic anemia that usually accompanies ARF. Although mild thrombocytopenia may be present, it is the qualitative defect in platelet function associated with ARF that is more significant and that contributes to these patients' bleeding tendencies. In patients with active bleeding or those in whom an invasive procedure is being contemplated, the prolonged bleeding time can be corrected pharmacologically. Infusion of 10 units of cryoprecipitate normalizes the bleeding time in 1 to 2 hours, with a return to baseline in 24 hours. Administration of 1-deamino-8-D-arginine vasopressin (DDAVP) shortens the bleeding time within 30 minutes.

Disposition

Patients with new-onset ARF should be hospitalized. If nephrology consultation and dialysis facilities are not available, transfer to another institution is advisable, once volume and metabolic abnormalities have been adequately controlled and the patient is hemodynamically stable.

Decisions regarding dialysis generally are made by the nephrology consultant and take into account many factors, including laboratory test result abnormalities and the presence or absence of signs and symptoms of uremia (e.g., nausea, vomiting, change in mental status). Many nephrologists choose to initiate dialysis when the BUN level exceeds 100 mg/dL or the serum creatinine level exceeds 10 mg/dL. Intractable volume overload and life-threatening hyperkalemia are the two most common indications for emergency dialysis.

CHRONIC KIDNEY DISEASE

In contrast with the typical patient with ARF, the patient with chronic kidney disease has most commonly experienced a slowly progressive course of decreasing renal function over months or years and is likely to have either slowly progressive symptoms or acute problems brought on by superimposed illness, trauma, or other physiologic stress. The most common problems requiring emergent intervention are severe hyperkalemia and symptomatic volume overload.

Barring renal transplantation, chronic kidney disease is an essentially irreversible condition generally characterized by a relentless decrease in renal function. Thus, whereas preservation of renal function may be a high priority in the patient with known ARF, management need not as a rule involve efforts to reverse the process presumed to have caused chronic kidney disease, nor even perhaps efforts to determine the exact cause. On occasion, however, the kidney disease may have a reversible component. In some cases, the underlying pathologic process affecting the kidneys may be arrested or treated; more commonly, correctable extrarenal factors (e.g., volume depletion or urinary tract obstruction) may be identified.

In the patient with chronic kidney disease who has an acute problem, the focus must be the identification and treatment of an intercurrent illness that has caused clinical decompensation, with the goal of returning the patient to a stable, chronically compensated status.

Principles of Disease

The standard terminology for chronic renal failure has changed.[53] *Chronic kidney disease* denotes kidney damage or decreased renal function for 3 months or more and is characterized by irreversible nephron loss and scarring. *Chronic renal insufficiency*, which denotes a condition in which GFR has been moderately reduced but not to a degree sufficient to cause clear-cut clinical symptoms, has been replaced by an indication of the degree to which GFR is reduced. *End-stage renal disease*, now termed *kidney failure*, describes a condition in which renal function has diminished to a low level and in which serious, life-threatening manifestations can be expected to occur without dialysis or transplantation. At this stage, the kidneys often are shrunken and diffusely scarred to such a degree that it may be impossible to make an etiologic diagnosis, even on pathologic examination.

The causes of chronic kidney disease are numerous; their relative frequency depends primarily on the population studied. As with ARF, they can be conveniently classified (Box 95-9) as prerenal (vascular), intrinsic renal (glomerular and tubulointerstitial), or postrenal (obstructive). Glomerular disease accounts for approximately one third to one half of the cases of ESRD; in the United States, diabetic nephropathy forms the largest group of these. Hypertensive nephrosclerosis is another important cause, particularly among blacks, in whom it may be the cause of 25% or more of cases of ESRD. Among children and adolescents, reflux nephropathy is the most common cause of ESRD. Renal failure related to intravenous drug use or to human immunodeficiency virus disease is a major consideration in some populations. Clues to other specific causes may be gained from elements of the history, physical examination, or laboratory and imaging studies. Although determining the underlying cause of chronic kidney disease can permit the underlying disease to be treated and make possible some improvement in renal function in some cases, this is the exception rather than the rule.

BOX 95-9 MAJOR CAUSES OF CHRONIC KIDNEY DISEASE

Vascular
Renal arterial disease
Hypertensive nephrosclerosis

Glomerular
Primary Glomerulopathies
Focal sclerosing glomerulonephritis (GN)
Membranoproliferative GN
Membranous GN
Crescentic GN
IgA nephropathy

Secondary Glomerulopathies
Diabetic nephropathy
Collagen vascular disease
Amyloidosis
Postinfectious
HIV nephropathy

Tubulointerstitial
Nephrotoxins
Analgesic nephropathy
Hypercalcemia/nephrocalcinosis
Multiple myeloma
Reflux nephropathy
Sickle nephropathy
Chronic pyelonephritis
Tuberculosis

Obstructive
Nephrolithiasis
Ureteral tuberculosis
Retroperitoneal fibrosis
Retroperitoneal tumor
Prostatic obstruction
Congenital abnormalities

Hereditary
Polycystic kidney disease
Alport's syndrome
Medullary cystic disease

Uremia

Progressive loss of renal function eventually results in a recognizable syndrome termed *uremia*. Clinical manifestations do not generally appear, however, until GFR has been reduced to approximately 15 to 20% of normal.

As the patient becomes unable to excrete an ingested salt or water load promptly, external balance of sodium and water

is affected; volume overload or hypernatremia or hyponatremia may result. Inability to concentrate the urine is an early manifestation of renal insufficiency and may be manifested as nocturia. Potassium homeostasis is likewise disrupted, and a relatively small potassium load may lead to dangerous hyperkalemia. Acid-base balance is affected, because the kidney fails to clear the daily metabolic acid load owing to a decreased ability to excrete ammonium and phosphate; the result is a non-anion-gap acidosis in the earlier stages of chronic kidney disease and a superimposed anion-gap acidosis as GFR decreases further. Calcium and phosphate metabolism is affected as well; retention of phosphate and progressive loss of the kidney's capacity to synthesize 1,25-dihydroxycholecalciferol, the active form of vitamin D, lead to hypocalcemia, secondary hyperparathyroidism, and eventually the development of renal osteodystrophy.

Nitrogenous by-products of protein catabolism retained in the blood are the presumed cause of many of the diverse abnormalities of organ function in renal failure. Most patients with ESRD show decreased glucose tolerance, although it is rarely severe enough to require treatment unless the medical history includes established diabetes. In such cases, insulin or other hypoglycemic therapy may need to be continued but generally in a lower dosage than required before the onset of renal failure, because the normal kidney has a major role in insulin degradation. Alterations in lipid metabolism result in elevated low-density lipoproteins and hypertriglyceridemia in many patients with ESRD.

Clinical Features

Uremia has specific effects on a variety of organ systems. Many of these manifestations are relieved by dialysis, but others are not. A number have been attributed in some degree to the retention of nitrogenous wastes and to the previously noted derangements in vitamin D and parathyroid hormone metabolism.

Cardiovascular

The cardiovascular system is perhaps most dramatically affected in ESRD.[54-56] Many of the manifestations can be attributed to the effects of chronic volume overload, anemia, hyperlipidemia, alterations in calcium and phosphorus metabolism, and volume- and hormonally mediated hypertension.[56-60] Pericarditis, with or without pericardial fluid accumulation, also is common in ESRD, particularly among patients who have not had dialysis.

Pulmonary

Similarly, uremic pleuritis, with or without associated pleural fluid collections, may develop in some patients. So-called uremic lung, manifested radiographically by "batwing" perihilar infiltrates, represents pulmonary edema and is almost always caused by volume overload or myocardial dysfunction. Noninflammatory pleural effusion caused by volume overload also is fairly common. Of special importance in the ED evaluation is the fact that the radiographic appearance in pulmonary edema may at times be misleading, simulating an infectious lobar infiltrate or even assuming a nodular appearance in some cases.[61]

Neurologic

Neurologic dysfunction is common in advanced uremia and usually is manifested by lethargy, somnolence, difficulty concentrating, or frank alteration in mental status. Seizures also may occur, although causes other than uremia alone must be ruled out. Uremic encephalopathy also is commonly manifested by hiccups, asterixis, or myoclonic twitching. The last should not be confused with tetany caused by hypocalcemia, which also is common in untreated patients with ESRD. In the peripheral nervous system, uremia often causes cramps and a distal sensorimotor neuropathy. A troublesome and characteristic complaint is "restless legs syndrome," in which persistent neuropathic discomfort in the legs can be relieved only by movement.

Gastrointestinal

Anorexia, nausea, and vomiting are nearly constant features of uremia. These GI manifestations are thought to be caused by accumulation of nitrogenous wastes, because they often are relieved, even in the undialyzed patient, by introduction of a low-protein diet, and seem to correlate roughly with the BUN level.

Dermatologic

The skin of patients with chronic kidney disease has a characteristic yellowish tinge. "Uremic frost," the result of deposition of urea from evaporated sweat on the skin, is a classic finding that, like "uremic fetor," is seen only rarely now with the widespread use of dialysis (Fig. 95-4). Diffuse pruritus often is a major source of discomfort for the patient with ESRD; in some cases it may be caused by calcium deposition in the skin secondary to derangements in calcium metabolism.

The use of gadolinium-based contrast agents for magnetic resonance imaging (MRI) has been associated with the development of nephrogenic systemic fibrosis, a potentially fatal disorder of unknown etiology, in patients with chronic kidney disease.[62]

Musculoskeletal

The bones and joints are sites of problems for many of these patients, particularly those with long-standing renal disease.

Figure 95-4. Uremic frost. Note the fine white powder on the skin of this patient with kidney failure.

The complex disturbances of calcium and phosphate metabolism in ESRD result in renal osteodystrophy, a clinical entity encompassing several overlapping varieties of bone disease that can cause bone pain or frank fractures.[63] Patients with chronic kidney disease generally are treated with long-term oral calcium and vitamin D in an effort to prevent both secondary hyperparathyroidism and uremic osteodystrophy. Occasional patients will have a poor response to therapy and require parathyroidectomy.

A specific type of arthritis caused by deposition of calcium hydroxyapatite or calcium oxalate crystals in joints is seen in some patients,[64] as are periarticular calcium deposition, spontaneous tendon rupture, myopathy, and carpal tunnel syndrome.

Immunologic

Infection remains a leading cause of death associated with renal failure.[65] Uremic patients have long been noted to have an increased susceptibility to infection, even when not challenged by the invasive procedures associated with dialysis. Both humoral and cellular immunity have been shown to be affected. The relative importance of each in the pathogenesis of infection in renal failure has not been clarified, but defects in cellular immunity appear to be more significant clinically. Although patients with renal failure should be considered to be immunocompromised, most infections in patients with ESRD are caused by common pathogens rather than opportunistic organisms.

Hematologic

A rather severe normochromic normocytic anemia, with a hematocrit commonly in the range of 18 to 25%, is nearly universal in untreated ESRD, except among patients with polycystic disease. It is caused primarily by the kidneys' decreased production of erythropoietin, a hormone that stimulates red cell production by the bone marrow. Other contributing factors are increased red cell hemolysis, nutritional deficiencies, and increased bleeding secondary to platelet dysfunction.

Although platelet number generally is normal in uremia, the bleeding time is prolonged because of defective platelet adhesiveness and activation. Numerous ecchymoses, seen in many patients with chronic kidney disease, is a common manifestation.

Diagnostic Strategies

The patient with chronic kidney disease, particularly one who is not yet receiving dialysis, is likely to present to the ED with one of the manifestations previously noted. In cases in which the diagnosis of renal failure has not previously been made, patients' complaints most commonly are nonspecific and often of insidious onset, such as generalized weakness, poor appetite, or deterioration of mental functioning. The initial laboratory finding of a reasonably well-tolerated but rather severe anemia may be the first clue to the diagnosis, which is subsequently confirmed by elevated BUN and serum creatinine levels. A prudent next step is to check the ECG for evidence of immediately life-threatening hyperkalemia before further laboratory and radiographic investigations are undertaken.

Once it is determined that the patient is in no immediate danger, the ED evaluation should seek to establish that renal failure is indeed chronic rather than acute. An explicit history to that effect obtained from previous medical records or from the patient or family provides the most straightforward and reliable confirmation, as does the presence of a dialysis access device on physical examination. If such a history is unavailable, the finding of bilaterally small kidneys (readily detected on plain abdominal films or by ultrasonography) constitutes equally good evidence. However, the converse is not necessarily true—a finding of normal-sized or large kidneys does not rule out chronic kidney disease (Box 95-10). In such cases, additional diagnostic steps are required to establish the diagnosis. A convincing history of the long-standing presence of the presenting symptoms or of symptoms such as nocturia may be helpful in suggesting chronicity, as may a history of familial kidney disease such as polycystic kidney disease or Alport's syndrome. Laboratory abnormalities such as anemia, acidosis, hyperuricemia, hypocalcemia, and hyperphosphatemia can occur in patients with *acute* kidney failure as early as 10 days after onset. Although urinary findings likewise tend not to be helpful, the presence of broad waxy casts on microscopic examination is suggestive of chronic disease, whereas the finding of an "active" sediment (e.g., red cell casts) is good evidence for an acute process.

BOX 95-10 CAUSES OF CHRONIC KIDNEY DISEASE WITH NORMAL OR LARGE KIDNEY SIZE

Polycystic kidney disease
Amyloidosis
Diabetic nephropathy
Malignant hypertension
Multiple myeloma
Glomerulonephritis (some cases)
Obstructive uropathy (some cases)

Although as a rule chronic kidney failure is irreversible and slowly progressive, an essential component of the ED evaluation is to exclude the possibility of potentially reversible factors (in effect, ruling out "acute on chronic" renal failure), and to ensure that treatable causes of chronic kidney disease—disorders that if treated might allow for some return of renal function—have not been overlooked. These potentially reversible factors and treatable causes of chronic kidney disease are important to keep in mind because they represent the only potential opportunity to reverse the patient's disease rather than simply to manage its results (Box 95-11).

Primary among superimposed reversible factors are those that lead to decreased renal perfusion. Of these, the most common is volume depletion. Regardless of the initiating cause, the process is exacerbated by the diseased kidney's impaired ability to conserve sodium and to concentrate the urine appropriately. Decreased renal perfusion caused by cardiac dysfunction of any cause is another extremely common and potentially reversible factor. An uncommonly encountered but important vascular cause of reversible deterioration of renal function is scleroderma renal crisis, a syndrome of accelerated hypertension and severe vasoconstriction in patients with underlying scleroderma that can be reversed by timely treatment with ACE inhibitors.[17]

Increased catabolism caused by infection, trauma, surgery, corticosteroids, or GI bleeding is another reversible factor that often is responsible for worsening azotemia and the development of uremic symptoms.

Drugs and toxins constitute another important group of reversible factors. Not only may these agents exacerbate renal insufficiency by causing intravascular volume depletion (diuretics), decreased renal perfusion (antihypertensive agents), or increased catabolism (tetracycline); they also can cause ATN (radiographic contrast material), AIN (many drugs), or inhibition of renal prostaglandin synthesis (NSAIDs).

BOX 95-11 Reversible Factors and Treatable Causes of Chronic Kidney Disease

Reversible Factors
Hypovolemia
Congestive heart failure
Pericardial tamponade
Severe hypertension
Catabolic state/protein loads
Nephrotoxic agents
Obstructive disease
Reflux disease

Treatable Causes
Renal artery stenosis
Malignant hypertension
Acute interstitial nephritis
Hypercalcemic nephropathy
Multiple myeloma
Vasculitis (e.g., systemic lupus erythematosus, Wegener's granulomatosis, polyarteritis nodosa)
Obstructive nephropathy
Reflux nephropathy

BOX 95-12 Mechanisms of Drug Toxicity in Renal Failure

Excessive drug level
Impaired renal excretion of drug
Impaired renal excretion of active metabolite
Impaired hepatic metabolism
Increased sensitivity to drug
Changes in protein binding
Changes in volume of distribution
Changes in target organ sensitivity
Metabolic loads administered with drug
Misinterpretation of measured serum drug level (i.e., change in therapeutic range)

From Wolfson AB, Singer I: Hemodialysis-related emergencies: Part I. J Emerg Med 5:533, 1987.

Particularly noteworthy is the dramatic decrease in renal function produced when an ACE inhibitor is administered to a patient with renal insufficiency caused by bilateral renal artery stenosis (or renal artery stenosis in a solitary kidney).[66]

Postrenal reversible factors also are important because of their frequency, particularly obstructive disease in the older male patient and reflux nephropathy in the child. Papillary necrosis should remain a consideration in the diabetic patient, the patient with sickle cell disease, and the patient with a history of long-term analgesic use. Stone disease, retroperitoneal fibrosis, and even rarer entities such as ureteral tuberculosis also should not be overlooked.

Finally, treatment of the underlying disorder that has caused the chronic kidney disease can occasionally result in the return of some renal function, most notably in cases of myeloma kidney, some forms of secondary glomerulonephritis, and severe hypertensive disease. Although this consideration must relate to long-term care and follow-up, it is appropriate that ED management address this issue to ensure that appropriate evaluation and disposition are arranged.

Management

Persons with chronic kidney disease constitute a group of patients who merit special attention in the ED setting. These patients are susceptible to infection, bleeding, and the numerous other complications associated with renal failure, as well as those that may be associated with the underlying causative disorder. Moreover, these patients are more vulnerable to the effects of any intercurrent illness or trauma. Those who are maintained with chronic hemodialysis or peritoneal dialysis are subject to potential complications from the dialysis therapy itself.

Patients with chronic kidney disease also are uniquely susceptible to iatrogenic illness. First, they are less able to handle fluid and solute loads than are normal persons. Just as important, the presence of renal failure significantly alters the metabolism and action of many drugs, often in ways that are not predictable[67] (Box 95-12). Thus, the dose and schedule of every administered agent, even apparently innocuous ones such as antacids, laxatives, antiemetics, or multivitamin preparations, should be carefully considered. For this purpose, ready access to a compendium such as the one by Brier and Aronoff[39] or availability of a hospital pharmacist for frequent consultations is invaluable. In general, consultation with the patient's nephrologist is recommended on completion of the initial ED evaluation, because management and follow-up monitoring after the patient leaves the ED often are complex.

In the United States, most patients with advancing chronic kidney disease eventually will require dialysis, but several true emergencies may develop in the patient with ESRD before chronic dialysis has been instituted. Specific diagnostic and therapeutic considerations apply to the management of these conditions regardless of whether they occur in dialyzed or undialyzed patients.

Hyperkalemia

Potentially the most rapidly lethal complication of chronic kidney disease encountered in the ED setting is severe hyperkalemia. As a rule, this condition is clinically silent until it causes potentially life-threatening manifestations. Accordingly, hyperkalemia must be looked for in every patient with chronic kidney disease. These patients can become severely hyperkalemic when required to handle even modest exogenous and endogenous potassium loads; moreover, even drugs that have only minimal effects on the serum potassium in normal persons, such as β-blockers and ACE inhibitors, can cause hyperkalemia in these patients. The inadvertent use of succinylcholine in patients with ESRD can rapidly result in life-threatening hyperkalemia.

An ECG should be obtained whenever hyperkalemia is a possibility, and if signs of hyperkalemia are noted, appropriate therapy should be started immediately, even before laboratory confirmation of a high serum potassium level. ECG changes may be completely absent even when hyperkalemia is severe, however.[68] Thus, a normal ECG does not preclude the need for laboratory confirmation of a normal serum potassium level. A potassium level of 6 mEq/L should be considered potentially dangerous, even though many patients with ESRD chronically tolerate levels somewhat above this threshold without ECG changes. A patient with chronic kidney disease who is in cardiac arrest should be assumed to be hyperkalemic and treated accordingly while the usual resuscitative measures are taken.

The most rapidly effective treatment for hyperkalemia is intravenous calcium, which transiently reverses the cardiac manifestations of hyperkalemia without altering the serum potassium level or total-body potassium (Table 95-3). Calcium should be given to buy time in which more definitive measures can take effect. It makes little sense to administer calcium in

Table 95-3 Treatment of Hyperkalemia

AGENT/MODALITY	DOSE/REGIMEN	ONSET/DURATION OF ACTION	MECHANISM OF ACTION	COMMENTS
Calcium gluconate (10%) or calcium chloride (10%)	10 mL IV (may repeat × 2 prn every 5–10 min)	1–5 min/~1 hr	Antagonizes membrane effects of K^+	ECG monitoring required Do not mix with HCO_3^- *Beware*: Hypercalcemia
Sodium bicarbonate	50 mg IV (may repeat × 1 prn)	~10–15 min/1–2 hr	Intracellular movement of K^+	*Beware*: Volume overload Hypertonicity Alkalosis (Seizures)
Albuterol	10–20 mg (nebulized) by inhalation	30 min/2+ hr	Intracellular movement of K^+	Relatively free of significant side effects; tachycardia
Glucose/insulin	10–20 units regular insulin per 100 g glucose	30 min/while infusion continued	Intracellular movement of K^+	*Beware*: Hyperglycemia Hypoglycemia Infused volume may be decreased by giving $D_{10}W$, $D_{20}W$, or $D_{50}W$
Kayexalate	25 g in 25 mL 70% sorbitol PO q6h ± 50 g in 50 mL 70% sorbitol by retention enema q6h	Hours/while continued	Exchange of K^+ for Na^+	*Beware*: Na^+ overload Enema must be retained × 30–45 min
Dialysis	HD PD	Minutes/while continued	Removal of K^+ from blood	HD may remove 50 mEq/hr (*beware*: K^+ rebound) PD may remove 15 mEq/hr
Intravenous diuretics (intravenous fluid if patient is hypovolemic)		Minutes/while diuresis continued (depending on renal function)	Urinary K^+ excretion	Only in patients with some residual renal function

D, dextrose; ECG, electrocardiogram; HD, hemodialysis; PD, peritoneal dialysis.

response to an elevated serum potassium level in the absence of manifestations of hyperkalemia on the ECG.

In treating hyperkalemia, it also is important to keep in mind the ESRD patient's limited ability to tolerate volume and solute loads (see Table 95-3). Thus, repeated doses of intravenous sodium bicarbonate risk causing volume overload and precipitating pulmonary edema. Intravenous glucose and insulin act less rapidly and also entail volume administration. If the patient's condition permits, however, the latter method is preferred because sodium administration can be avoided and hyperkalemia can be controlled for as long as the infusion is continued. Another effective temporizing measure is the administration of inhaled albuterol to promote movement of potassium into cells while more definitive maneuvers are being instituted.[51,52]

To remove potassium from the body, sodium polystyrene sulfonate (Kayexalate), a resin that exchanges sodium for potassium ions, can be administered orally or rectally. This drug can continue to control the potassium for hours and, despite the modest sodium load it entails, can be effective as a temporizing measure until dialysis (if necessary) can be instituted. In patients who still retain some renal function, the most effective way to treat hyperkalemia may be to administer an intravenous diuretic such as furosemide (if the patient is not hypovolemic) and to give volume if necessary. Large doses of diuretic may be necessary to induce a satisfactory diuresis. In light of the potential for ototoxicity with the use of loop-active diuretics, these drugs should be administered by slow infusion rather than by bolus. They probably should be avoided in patients who also are receiving other potentially ototoxic agents. During the course of any of these therapeutic interventions, both the ECG and serum potassium levels must be monitored frequently.

Pulmonary Edema

Perhaps the most common ED problem in patients with chronic kidney disease is pulmonary edema secondary to volume overload. Surprisingly, the diagnosis is not always straightforward. The history may be suggestive of increasing dyspnea on exertion or paroxysmal nocturnal dyspnea, but physical examination may not reveal the expected signs of CHF, and even chest radiography may be deceptive[61] (Fig. 95-5). Recent weight gain or a body weight considerably over "dry weight" (typically more than 5 pounds) is the most reliable clue, and in the absence of convincing evidence of another cause for dyspnea, volume overload should be assumed to be the cause and the patient should be treated accordingly.

Treatment of pulmonary edema in the patient with chronic kidney disease is of necessity somewhat different from that in other patients[69,70] (Box 95-13). Arrangements for initiation of dialysis should be made as soon as possible because it is the most rapidly effective means to decrease intravascular volume in the absence of renal function. Other immediate measures should be instituted in the meantime. Although such measures may occasionally prove to be effective enough to avoid dialysis temporarily in patients who possess some residual renal func-

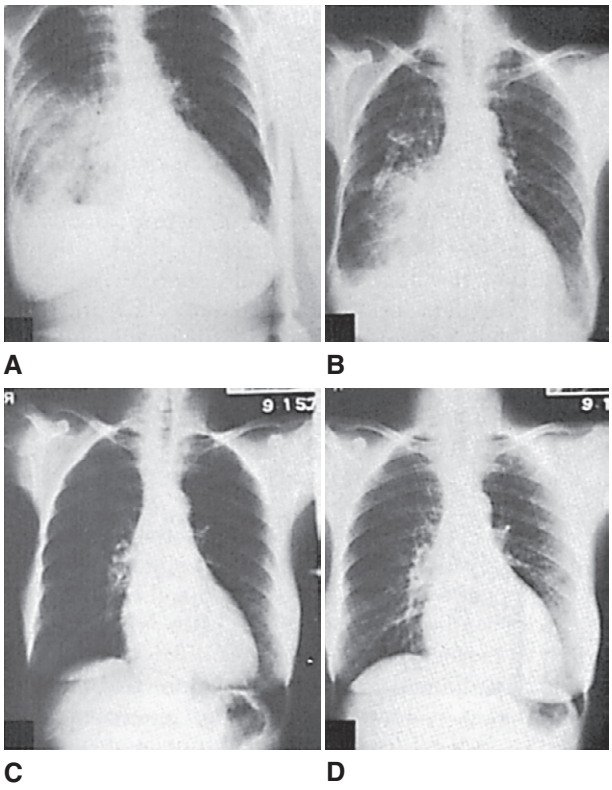


Figure 95-5. Pulmonary edema simulating right lower lobe pneumonia in a dialysis-dependent patient. Marked improvement with decreased infiltrate and return of heart to normal size were evident after dialysis and ultrafiltration. **A,** Chest x-ray film obtained immediately before dialysis shows cardiomegaly and right lower lobe infiltrate interpreted as pneumonia. **B,** Chest x-ray film at 5 hours after initiation of dialysis, with 2-kg weight reduction. The extent of the infiltrate has markedly decreased. **C** and **D,** Lung and heart have returned to normal size. (From Kjellstrand C, et al: In Drukker W, Parson FM, Maher JF [eds]: Replacement of Renal Function by Dialysis. Boston, Martinus Nijhoff, 1983, pp 536–568.)

BOX 95-13 TREATMENT OF PULMONARY EDEMA IN RENAL FAILURE

- Dialysis
  - Hemodialysis
  - Hemofiltration
  - Peritoneal dialysis
- Oxygen
- Nitroglycerin
- Morphine
- Diuretics
- Nitroprusside

tion, it should nevertheless be anticipated that the response to even extremely aggressive medical therapy short of dialysis will be inadequate.

The patient should be placed in the sitting position, and high-flow oxygen should be administered by mask. The use of continuous or bilevel positive airway pressure delivered by face mask has been reported to be a useful adjunct in patients with ESRD, as it is in patients without renal failure.[71,72] Sublingual or topical nitroglycerin, or both, can be administered immediately and functions rapidly to reduce both preload and afterload; an intravenous infusion can be begun promptly and titrated to effect. Intravenous nitroprusside may have an advantage in producing more arteriolar dilatation if the patient is hypertensive. Intravenous morphine increases venous capacitance, but as in patients without renal failure, its routine use as a first-line drug in pulmonary edema has become less common. Diuretics are not expected to be helpful unless the patient has retained a significant level of renal function.

Infection

Because infection is a major contributor to morbidity and mortality among patients with ESRD,[63,64] the possibility of serious infection should be entertained even when the expected classic findings are not all present.[63,65,67,73] For example, bacteremia may be manifested by fever alone, just as it is in other patients with impaired immunity. Patients with pneumonia may present with only vague dyspnea or malaise, symptoms that may be attributed to volume overload or uremia. Thus, all diagnostic possibilities should be pursued, and empirical broad-spectrum antibiotic coverage often is advisable until infection has been ruled out in the hospital. Bacteremia resulting from vascular access infection is quite common in patients receiving hemodialysis, as is peritonitis in patients undergoing peritoneal dialysis.

UTI can occur even in patients with minimal urine output or those with long-standing renal failure. Urinary stasis is undoubtedly a predisposing factor.[74] Upper UTI associated with a clinical picture typical of pyelonephritis or renal colic is seen most commonly in patients with polycystic kidney disease and necessitates parenteral therapy. A clinical diagnosis can be made presumptively in the ED, but invasive measures sometimes are necessary to document infection and guide therapy. For infected cysts, lipid-soluble antibiotics (e.g., clindamycin, trimethoprim-sulfamethoxazole) offer the best antibiotic penetration; surgical intervention for refractory infection sometimes becomes necessary, however.[75]

Dialysis

Dialysis can normalize fluid balance, correct electrolyte and other solute abnormalities, and remove uremic toxins or drugs from the circulation when the patient's kidneys are unable to do so. Dialysis also can, but generally to a lesser degree, reverse some uremic symptoms and permit better long-term control of hypertension, anemia, and renal osteodystrophy.

The two major dialysis modalities are hemodialysis and peritoneal dialysis. Each is based on technology wherein the patient's blood comes into contact with a semipermeable membrane on the other side of which is a specially constituted balanced physiologic solution. Water and solutes diffuse across the membrane by moving along concentration and osmotic gradients, effectively normalizing the blood's composition.

Hemodialysis requires special access to the patient's circulation, generally through a surgically created arteriovenous fistula or implanted artificial graft, or through a surgically placed tunneled catheter. The vascular access site must be treated with care because hemodialysis cannot be performed without it. Careless manipulation or puncture can result in bleeding, infection, or thrombosis that may result in loss of the access. The involved arm should not be used for blood pressure determinations, and a tourniquet should not be applied.

In general, blood should be drawn and intravenous lines established in other locations. In exceptional circumstances, if no other site is available and it is essential to obtain blood samples quickly, the fistula or graft may be used, but with precautions: A tourniquet should not be applied, the area should be cleansed scrupulously before the puncture, and extreme care should be taken not to puncture the back wall of the access opening. After the puncture, firm but nonocclu-

sive pressure should be applied for at least 10 minutes. The presence of a thrill both before and after the procedure should be documented. Similar precautions are taken in the exceptional cases in which the fistula or graft must be used for intravenous access. If this is done, an automated infusion pump is essential to control the infusion rate into these relatively high-pressure blood vessels.

In *peritoneal dialysis*, the patient's peritoneum functions as the dialysis membrane. Dialysate is infused through a surgically implanted Silastic catheter (Tenckhoff catheter) that penetrates the lower abdominal wall. As compared with hemodialysis, peritoneal dialysis offers the theoretical advantages of greater patient independence, avoidance of anticoagulation, and smoother control of volume and hypertension without the intermittent rapid shifts of solute typical of hemodialysis. Medications such as insulin and antibiotics can be administered intraperitoneally, allowing smoother absorption and more stable blood levels. The main disadvantage of peritoneal dialysis is a significant incidence of bacterial peritonitis, which is, however, usually readily treatable.

Indications for Dialysis

The decision to initiate chronic dialysis in the patient with ESRD generally is made by the patient's nephrologist in the setting of gradually decreasing GFR and slowly progressive manifestations of renal failure. The absolute value of the BUN or serum creatinine generally is used only as a rough guide to when chronic dialysis should be instituted. Provision of vascular or peritoneal access usually has been arranged weeks to months before the anticipated initiation of dialysis, to allow the access site to mature and to minimize any mechanical complications of the procedure.

For patients who comes to the ED with ARF, however, as well as for patients with chronic kidney disease in whom acute problems have developed, it is the emergency physician who must be prepared to make the decision to arrange for dialysis to be provided emergently (Box 95-14). How urgently dialysis must be initiated depends on not only the severity and acuteness of the presenting problem but also on the availability of technical facilities and trained dialysis personnel and the effectiveness of available temporizing measures for the problem at hand.

The most common problem requiring emergent dialysis, particularly in the patient with ESRD, is pulmonary edema secondary to volume overload. Generally, the inciting cause is overingestion of fluid and salt in excess of the patient's greatly diminished renal excretory capacity. Despite the effectiveness of temporizing measures, many of these patients require immediate dialysis—either emergency hemodialysis or, in the case of the patient maintained on peritoneal dialysis, intensification of the usual dialysis regimen.

A related problem that may require emergent, or at least urgent, dialysis is malignant hypertension, particularly when associated with hypertensive encephalopathy or cardiovascular decompensation. Because hypertension in most patients with renal failure commonly is volume-dependent, correction of volume overload, even if clinically inapparent, is a central component of therapy. Temporizing measures such as the administration of intravenous sodium nitroprusside or nitroglycerin often permit hypertension to be controlled sufficiently that dialysis can be delayed for several hours, but prolonged administration of sodium nitroprusside carries an increased risk of thiocyanate toxicity in patients with renal failure. In many cases, hypertension and associated symptoms are difficult to control until dialysis permits volume overload to be corrected. Because the blood pressure often is dramatically responsive to reduction of circulating volume, it is recommended that other antihypertensive agents with more prolonged effects be withheld until after dialysis has been able to reduce circulating volume.

Severe hyperkalemia is another common indication for emergent or urgent dialysis, particularly in the patient with ARF who is hypercatabolic. In the patient with chronic kidney disease, hyperkalemia usually is caused by excessive potassium intake, but endogenous causes such as hemolysis or rhabdomyolysis must be kept in mind as well. A variety of available temporizing measures can be used with variable degrees of effectiveness and for different durations to control the serum potassium level, but dialysis remains the most effective means of removing potassium from the body. For rapid control of the serum potassium, hemodialysis, with its high clearance rates, is preferred to peritoneal dialysis.

Other severe electrolyte and acid-base disturbances, including diabetic ketoacidosis,[76] may sometimes necessitate emergent dialysis. Occasional patients with renal failure and severe hypercalcemia uncontrollable by other modalities (e.g., patients with multiple myeloma causing both renal failure and hypercalcemia) may require dialysis. The occasional patient with renal failure in whom severe hypermagnesemia develops after inappropriate therapy or magnesium ingestion may require immediate dialysis to reverse life-threatening paralysis or cardiac dysrhythmia. Severe metabolic acidosis in the setting of renal failure is another indication for emergent dialysis, particularly if volume overload precludes the administration of reasonable amounts of bicarbonate. Of note, bicarbonate also can precipitate tetany and convulsions if administered intravenously (e.g., to treat acidosis or hyperkalemia) to a patient with hypocalcemia.

A somewhat unusual but related situation is one in which a patient with renal failure has taken an overdose or inadvertently been administered medication that ordinarily is cleared by the kidneys. If the agent is adequately dialyzable and its continued presence in the circulation poses a significant risk to the patient, immediate dialysis can be lifesaving. An example of such a situation is the ingestion of methanol or ethylene glycol by a dialysis patient. Similarly, ill-advised use of magnesium-containing cathartics or phosphate-containing enemas by patients with ESRD can lead to dangerous hypermagnesemia and hyperphosphatemia, respectively, and may necessitate urgent dialysis.

The serum creatinine and BUN levels themselves should not be considered indications for dialysis. A creatinine of 10 mg/dL or a BUN of 100 mg/dL often is used as a guideline for beginning chronic dialysis in the patient with progressive renal failure. In dialyzed patients, however, the serum creatinine often is considerably greater than 10 mg/dL but is a reflection more of total body muscle mass than the adequacy of dialysis. The BUN is a somewhat better indicator; the level in well-dialyzed persons generally is in the range of 50 to 80 mg/dL and is more than 100 mg/dL in less well-dialyzed patients. Neither blood level, however, correlates more than roughly with uremic symptoms even in undialyzed patients or

BOX 95-14 INDICATIONS FOR EMERGENCY DIALYSIS

Pulmonary edema
Severe uncontrollable hypertension
Hyperkalemia
Other severe electrolyte or acid-base disturbances
Some overdoses
Pericarditis (possibly)

has any direct bearing on how urgently dialysis should be initiated.

The occurrence of uremic symptoms or signs such as nausea, vomiting, lethargy, or twitching indicates a need for dialysis but does not necessitate immediate initiation of dialysis unless symptoms are severe. Pericarditis, even in the absence of cardiac tamponade, often is considered an indication for urgent dialysis,[77] but it is not uncommon for pericarditis to occur in well-dialyzed ESRD patients as well.[78,79] In a previously undialyzed patient with progressive renal insufficiency, the appearance of pericarditis indicates that it is time to initiate dialysis, although not necessarily on an emergency basis.

Complications of Dialysis Therapy

Optimal ED management of acute problems referred from the dialysis unit, or those occurring at home or in the interdialysis period, requires knowledge of and familiarity with the particular problems associated with ESRD and dialysis.[63,65,67,73] Consultation with the nephrologist or dialysis nurse is important in arranging a consistent care plan for the dialysis patient with an emergent condition and in ensuring appropriate further acute care or follow-up monitoring.

Complications of Hemodialysis

Vascular Access–Related Complications. The performance of hemodialysis depends on reliable vascular access, and it is the vascular access device that is responsible for complications of dialysis that most often require evaluation in the ED setting. These problems must be attended to promptly to minimize the risk of losing the patient's dialysis "lifeline."

Bleeding from the dialysis puncture site can occur hours after a hemodialysis treatment, either spontaneously or after inadvertent minor trauma to the site. Such bleeding almost always can be stopped by applying firm pressure to the access site; care should be taken not to occlude and possibly cause thrombosis of the vessel by compressing it too vigorously, and the presence of a thrill immediately after the procedure should be documented on the chart. It may be necessary to keep the patient in the ED for a time to ensure that bleeding does not recur. Recurrent bleeding, especially from an aneurysm or a pseudoaneurysm, should be evaluated by a vascular surgeon.

Similarly, if the patient reports that the thrill in the access has been lost, a vascular surgeon should be consulted immediately. Although thrombolytic agents sometimes are used, definitive treatment generally is surgical revision.[61,63] The access device should not be forcefully manipulated or irrigated, because rupture of the vessel or venous embolization may result.

Infection of the vascular access is not uncommon and can result in persistent or recurrent bacteremia as well as loss of the access. Infection appears to be a consequence of contamination at the time of puncture for dialysis; most infections are caused by staphylococci typical of skin flora. Infections are more likely to occur in grafts than in native fistulas.[64,65] The signs and symptoms of an access infection—redness, warmth, and tenderness over the site—often are obvious, but in many cases, localizing findings are absent and the patient has only fever or a history of recurrent episodes of fever and documented bacteremia.[63] For this reason, it is common practice to obtain blood cultures for all patients on hemodialysis who have a fever without an obvious source of infection and to treat them presumptively for an access infection. A careful search for other sources of infection should be made, however, before that inapparent access infection is concluded to be the cause. Infections such as odontogenic abscess, extremity cellulitis (particularly in diabetics), and perirectal abscess can easily be missed.

Although some nephrologists prefer to admit all dialysis patients with fever to the hospital, management of these patients on an outpatient basis often is possible, provided that they otherwise feel well and do not appear to be septic and provided that they can care for themselves at home and return promptly if their condition worsens. This course is made more practicable by the fact that they can be loaded with intravenous antibiotics that dependably maintain adequate blood levels until the time of the next scheduled dialysis treatment, at which time the culture and sensitivity test results can be checked and therapy adjusted accordingly. Vancomycin 1 to 1.5 g given intravenously as a single loading dose is the drug of choice in this situation, because most access infections are staphylococcal and because this drug is only minimally hemodialyzable and needs to be given only every 5 to 7 days in the chronic dialysis patient. If a gram-negative infection also is thought to be likely, as in a patient who has had recent episodes of gram-negative bacteremia, a loading dose of a second drug (e.g., a third-generation cephalosporin or an aminoglycoside) also can be administered. Patients can be reloaded with these drugs at the end of their next hemodialysis session if culture results prove to be positive.

Non–Vascular Access–Related Complications. The hemodialysis procedure itself, which entails invasion of the vasculature, anticoagulation, and often massive shifts of fluid and solutes, often is associated with acute complications such as hypotension, shortness of breath, chest pain, and neurologic abnormalities.

Hypotension. Hypotension that occurs after dialysis most commonly is the result of an acute reduction in circulating intravascular volume and the failure of the patient's homeostatic mechanisms to compensate for it. Because hemodialysis is episodic, each treatment must remove the excess fluid that has accumulated over the period since the last dialysis (generally 2 to 3 days), and patients often are relatively volume-overloaded at the beginning of each treatment. With rapid removal of extracellular fluid, there is inadequate time for transcellular fluid shifts to replace intravascular volume. Antihypertensive medications, particularly β-blockers, that are required when the patient is in a volume-expanded state, can contribute to the hypotension when intravascular volume is normalized.

Most episodes of hypotension that occur during hemodialysis will resolve spontaneously or can be readily managed by either a decrease in blood flow rate or the infusion of small volumes of saline (to effect transient volume expansion) or hypertonic solutions (to reverse transiently acute hypoosmolality). Patients with significant hypotension who do not respond to these maneuvers often are brought to the ED for further evaluation. Patients on dialysis should be considered to be at risk for acute myocardial infarction, acute dysrhythmias, and sepsis. These are common causes of hypotension among all patients presenting to the ED, and consideration should first be given to these entities[67] (Box 95-15).

Acute hemorrhage also is not uncommon in dialysis patients. Almost all of these patients are now routinely treated with epoetin or darbepoetin to prevent severe anemia,[80,81] but untreated patients typically have low baseline hemoglobin levels, and acute blood loss may result in symptomatic angina or CHF. Serum levels of clotting factors are normal in ESRD, but patients are routinely anticoagulated for each hemodialysis treatment. Although transient thrombocytopenia may occur during the dialysis procedure, the qualitative platelet defect characteristic of renal failure represents the most important factor in bleeding that continues beyond the peridialytic period.[82] This abnormality is only partially reversed by dialysis but can be corrected by administration of DDAVP, which

BOX 95-15 DIFFERENTIAL DIAGNOSIS OF HYPOTENSION IN HEMODIALYSIS PATIENTS

Hypovolemia
Excessive fluid removal
Hemorrhage
Septicemia
Cardiogenic shock
Dysrhythmia
Pericardial tamponade
Myocardial infarction
Myocardial or valvular dysfunction
Electrolyte disorders
Hyperkalemia or hypokalemia
Hypercalcemia or hypocalcemia
Hypermagnesemia
Vascular instability
Drug-related
Dialysate-related
Autonomic neuropathy
Excessive access arteriovenous flow
Anaphylactoid reaction
Air embolism

From Wolfson AB, Singer I: Hemodialysis-related emergencies: Part I. J Emerg Med 5:533, 1987.

increases release of factor VIII–von Willebrand factor (VWF) polymers from vascular endothelium. DDAVP has been used successfully to normalize the bleeding time in preparation for surgery in patients with chronic kidney disease. Cryoprecipitate and conjugated estrogen both have been shown to produce similar effects for a longer period.[82]

Overt bleeding from the GI tract, often caused by angiodysplasia or peptic ulcer disease, is common and can be dramatic. Occult hemorrhage in other locations, however, can present a diagnostic challenge, because symptoms and signs of volume loss tend to be overshadowed by local manifestations of bleeding into a closed space. Thus, spontaneous retroperitoneal or pleural hemorrhage tends to manifest with flank pain or with chest pain and shortness of breath, respectively.

Occasionally, acute hypotension may be caused by anaphylaxis or an anaphylactoid reaction to some component of the dialyzer or the dialysate; these possibilities should be considered if the history is suggestive. Acute pulmonary embolism and acute air embolism are two less likely possibilities. The former, although it does occur occasionally in dialysis patients, is unusual. The latter, although reported occasionally in the past, has been all but eliminated by improved dialysis monitoring equipment and safety mechanisms.

Two additional entities in the differential diagnosis for hypotension are of particular importance in the patient with ESRD—acute pericardial tamponade and severe, life-threatening hyperkalemia. *Acute pericardial tamponade* may be the result of either sudden pericardial hemorrhage or sudden worsening of a formerly compensated pericardial effusion after acute correction of elevated preload. The clinical features of tamponade in the dialysis patient are similar to those in other populations, but the common preexistence of cardiomegaly may make the chest film difficult to interpret unless it shows the typical "water bottle" shape and a definite increase in heart size from previous examinations.

Similarly, an elevated central venous pressure is of little use in differentiating tamponade from underlying right-sided heart failure. Even a bedside ultrasonographic examination that shows pericardial fluid, although suggestive, is not proof that tamponade is present, because many dialysis patients chronically have pericardial effusions that do not cause hemodynamic compromise.[78,79] Ultrasonographic demonstration of right ventricular diastolic collapse is more specific, but a definitive diagnosis of tamponade depends on the direct demonstration of equal pressures in the right and left atria on cardiac catheterization.

Emergency pericardiocentesis must occasionally be performed in the ED to relieve acute tamponade, but there often is enough time for the patient to be transported to the catheterization suite or operating room for safer and more definitive therapy in a controlled setting. If immediate pericardiocentesis is believed to be necessary, however, the emergency physician should not hesitate to perform this potentially lifesaving procedure, despite the many potential complications and the increased risk of bleeding in patients with ESRD. Similarly, in the case of a dialysis patient who is in cardiac arrest, pericardiocentesis generally should be attempted if initial resuscitative efforts have not been successful.

Severe, life-threatening hyperkalemia, although unusual in a dialyzed patient, can occur in the presence of underlying catabolic illness or with a prolonged period of hypotension and low flow. Patients who are hyperkalemic can have profoundly slow heart rates, particularly if they have been treated with β-blockers or calcium channel blockers. If a dialysis patient is in cardiac arrest, it should be assumed that hyperkalemia is present, and intravenous calcium should be given immediately.

Shortness of Breath. Shortness of breath in dialysis patients generally is caused by volume overload. In the patient who becomes short of breath while being dialyzed, however, other causes must be sought—primarily sudden cardiac failure, pericardial tamponade, pleural effusion or pleural hemorrhage. Air embolism and anaphylactoid reactions are unusual causes. Often, pneumonia or underlying reactive airway disease is responsible.

Chest Pain. Chest pain during dialysis must be taken seriously because cardiovascular disease is a leading cause of death in patients with ESRD, and most episodes of chest pain occurring during dialysis are likely to be ischemic in origin.[83,84] Most dialysis patients have risk factors for coronary artery disease, related to either ESRD itself or the underlying condition that led to renal failure, and many have well-documented coronary artery disease.[54] ESRD commonly is associated with hypertension, hyperlipidemia, carbohydrate intolerance, and disturbances of calcium and phosphorus metabolism. In addition, dialysis patients may be anemic, and many are chronically volume-overloaded. During hemodialysis, these underlying factors may be added to acute physiologic stresses such as transient hypotension and hypoxemia, which often are associated with the dialysis procedure, thereby increasing myocardial oxygen demand while decreasing oxygen delivery.

In evaluating presumed ischemic chest pain in a patient with ESRD, it is important to keep in mind the potentially reversible factors that may have precipitated the episode. Particularly when a patient whose angina has been stable begins to experience more frequent or more severe anginal episodes, it should be determined whether increasing anemia, poorly controlled hypertension, or uncorrected volume overload is a factor. Coronary artery disease appears to become symptomatic with a lesser degree of obstruction than that in other etiologic conditions.

Patients who repeatedly experience chest pain during dialysis should undergo a complete evaluation so that the extent of their coronary artery disease can be defined and optimal management planned. After repeated, frequent hospital

admissions to rule out myocardial infarctions because of chest pain during dialysis, it may be reasonable for the patient's nephrologist and cardiologist to set guidelines regarding further admissions.

The presence of renal failure and its associated electrolyte and acid-base disturbances does not in general obscure the usual ECG changes of angina or acute myocardial infarction. The pattern of the change of serum cardiac enzymes with acute infarction also is not altered by ESRD, although the baseline level of these enzymes may be higher than in the general population. Troponin appears to perform best as a marker of infarction in patients with ESRD.[85-87] Treatment of ischemic chest pain is the same as for other populations.

Among nonischemic causes of chest pain, pericarditis should always be a consideration, even in the well-dialyzed patient. The presentation is essentially the same as in nonrenal patients; fever, a friction rub, or atrial dysrhythmias may be associated findings, and signs of pericardial effusion or early tamponade should be sought. Indomethacin often is effective in relieving pain, but some patients eventually require further measures, such as pericardiocentesis with corticosteroid instillation or pericardial stripping. Patients with pericarditis often receive more frequent or intensified dialysis, because pericarditis is thought to be a marker for inadequate dialysis.[77]

Neurologic Dysfunction. Neurologic dysfunction manifesting during or immediately after hemodialysis often is caused by *disequilibrium syndrome*, a constellation of symptoms and signs that is thought to be due to rapid changes in body fluid composition and osmolality during hemodialysis. It usually occurs only in patients with high BUN levels who are just starting hemodialysis. The syndrome does not occur with peritoneal dialysis. Typically, patients have headache, malaise, nausea, vomiting, and muscle cramps, but features in more severe cases may include altered mental status, seizures, or coma. Symptoms resolve over several hours as fluid and solutes are redistributed across cell membranes.

It is dangerous, however, to attribute an altered mental status to disequilibrium syndrome unless other potential causes have been ruled out (Box 95-16), particularly when symptoms persist, fluctuate, or worsen during a reasonable period of observation.[73] Likewise, when seizures occur during dialysis, it is tempting but unwise to attribute them to disequilibrium syndrome without considering other, potentially serious causes, even in patients who have had seizures in the past. In particular, the finding of any new focal neurologic abnormality calls for, at a minimum, an immediate head CT scan to detect intracranial hemorrhage. Similarly, if fever or other evidence of infection is present, meningitis must be a serious consideration. Other considerations include hyperglycemia and hypoglycemia (especially in the diabetic patient), electrolyte abnormalities, hypoxic states, hypotension of any cause, and other toxic or metabolic causes. The treatment of seizures in patients with ESRD is essentially the same as in other populations.

BOX 95-16 Differential Diagnosis of Altered Mental Status in Dialysis Patients

Structural
Cerebrovascular accident (particularly hemorrhage)
Subdural hematoma
Intracerebral abscess
Brain tumor

Metabolic
Disequilibrium syndrome
Uremia
Drug effects
Meningitis
Hypertensive encephalopathy
Hypotension
Postictal state
Hypernatremia or hyponatremia
Hypercalcemia
Hypermagnesemia
Hypoglycemia
Severe hyperglycemia
Hypoxemia
Dialysis dementia

Complications of Peritoneal Dialysis

As with hemodialysis, most of the complications of peritoneal dialysis are related to the dialysis access device, in this case the peritoneal catheter.[65] In contrast with hemodialysis, however, the dialytic process in peritoneal dialysis occasions few immediate difficulties. Whatever volume or metabolic problems develop often are a consequence of the fact that the typical patient maintained on peritoneal dialysis is seen by a doctor or nurse only once a month.

Peritonitis is the most common complication of peritoneal dialysis. Fortunately, it is in general much less severe than other types of peritonitis and can be treated readily on an outpatient basis despite the continued presence of a foreign body—the Tenckhoff catheter—in the peritoneal cavity.[65,88,89] Occasionally, when an episode of peritonitis responds poorly to antimicrobial therapy or when a patient has repeated episodes of peritonitis caused by the same organism, the catheter must be removed and the patient sustained with hemodialysis until the infection is completely cleared and a new catheter can be placed. Repeated infections do, however, carry the risk of permanently altering peritoneal permeability or effective surface area and necessitating a permanent switch to hemodialysis.

Peritonitis in patients on peritoneal dialysis presumably is caused by inadvertent bacterial contamination of the dialysate or tubing during an exchange or by extension of an infection of the exit site or the subcutaneous tunnel into the peritoneal cavity. A majority of cases of peritonitis are caused by *Staphylococcus aureus* or *Staphylococcus epidermidis*, and most of the remainder (approximately 20%) by gram-negative enteric organisms.[88] Fungal infections are uncommon but generally are refractory to medical therapy and often are considered an indication for catheter removal. Polymicrobial infection suggests direct contamination from the GI tract and mandates a search for the site of perforation or fistula, although such a source is identified in only a minority of cases. No organism is identified in approximately 10 to 20% of cases of peritoneal dialysis–associated peritonitis.

The diagnosis of peritonitis usually is made by the patient when a cloudy dialysis effluent is noted, corresponding with the appearance of WBCs in the dialysate. Peritonitis often, but by no means invariably, is accompanied by nonspecific abdominal pain, malaise, or fever. Even in the absence of cloudy fluid, when a patient has fever or abdominal symptoms, it is advisable to consider peritonitis and to check the fluid, because early peritonitis may manifest atypically. In more severe cases, peritonitis is accompanied by nausea, vomiting, severe pain, and hypotension, necessitating hospitalization and consideration of the possibility of acute surgical disease.

In the ED setting, the diagnosis of peritonitis is confirmed by the finding of more than 100 WBCs/mm^3 in the peritoneal

fluid, with more than 50% neutrophils, or by a positive result on Gram staining. A sample of fluid should be obtained for analysis, preferably by a specialized dialysis nurse, if available. Fluid should be sent for cell count and differential, Gram's staining, and culture (using blood culture bottles).

Peritoneal dialysis–associated peritonitis usually can be treated with an initial intraperitoneal loading dose of antibiotic, followed by a 10- to 14-day course of intraperitoneal antibiotics, of which some may be administered by the patient on an outpatient basis. After the diagnosis has been confirmed, consultation with the patient's nephrologist or dialysis nurse specialist is indicated to determine antibiotic therapy as well as a plan for outpatient management and follow-up evaluation or occasionally, if peritonitis is severe or if outpatient management is precluded by psychosocial considerations, for hospitalization.

A common treatment regimen is a loading dose of vancomycin 30 mg/kg given intraperitoneally (IP), followed by further intraperitoneal doses every 4 to 7 days, plus ceftazidime or cefipime 1 g IP or gentamicin 0.6 mg/kg IP. The latter two regimens are given as a loading dose followed by maintenance doses administered intraperitoneally once daily at the time of an exchange. Heparin 500 to 1000 units also may be added to each bag of dialysate for the first few days of treatment to help reduce the formation of fibrin strands that may obstruct the catheter. Patients should be seen by the dialysis nurse in 24 to 48 hours to check on the response to therapy and to adjust antibiotic therapy as necessary after reviewing the results of culture and sensitivity testing.

Catheter contamination or leaks from the catheter, tubing, or dialysate bag should be managed in the same fashion as for frank peritonitis. The site and cause of leakage should be identified, and damaged elements should be replaced promptly. Occasionally, with leakage of peritoneal fluid from around the catheter, surgical correction of the underlying problem will be necessary.

Patients who have severe abdominal pain, vomiting, ileus, chills or high fever, or hypotension should be hospitalized. Likewise, patients with severe underlying illness and those who cannot reliably perform exchanges or administer antibiotics at home require inpatient management. Dialysis exchanges should be continued on the same schedule. The inpatient antibiotic regimen is essentially the same as that used for outpatients.

Perhaps the most serious potential pitfall in caring for the patient maintained on peritoneal dialysis with abdominal pain or other signs of peritonitis is to overlook other serious intra-abdominal conditions whose presentation may mimic that of peritonitis. Patients on peritoneal dialysis are at increased risk for abdominal wall or inguinal hernia because of chronically increased intra-abdominal pressures; previous abdominal surgery also places them at risk for hernia, as well as for obstruction secondary to adhesions. The manifestations of serious disorders unrelated to dialysis (e.g., acute appendicitis, diverticulitis, cholecystitis, acute pancreatitis, ischemic bowel, perforated viscus) also may be attributed to ordinary peritoneal dialysis–associated peritonitis, with the potential for disastrous consequences. The accessibility of the peritoneal fluid for examination may prove to be helpful in documenting the presence of an inflammatory process, but it also has the potential to mislead ED investigation of its cause. A finding of brownish or fecal material in the peritoneal drainage should suggest a ruptured viscus until proven otherwise, and immediate surgical consultation should be sought. Detection of localized tenderness, a palpable mass, or an incarcerated hernia on physical examination can be extremely helpful in making the diagnosis. Abdominal radiography may be useful for demonstrating the presence of ileus, but pneumoperitoneum may reflect only the introduction of air during a recent fluid exchange rather than a perforated viscus.[90] Thus, it is important to keep in mind the possibility that disorders other than peritonitis may underlie the patient's symptoms, and astute clinical judgment rather than specific criteria should dictate requests for surgical consultation or decisions regarding hospitalization of the patient for observation.

Infection of the catheter exit site is another relatively common problem for which the patient on continuous ambulatory peritoneal dialysis may seek care in the ED.[91] This infection tends to be caused by typical skin flora and is manifested by the usual local signs of infection. Although not serious in themselves, exit site infections should be taken seriously because they may lead to infection of the subcutaneous tunnel, which can cause repeated episodes of peritonitis and may ultimately necessitate removal of the catheter. Any visible exudate should be cultured and Gram stained, and therapy with an oral antibiotic such as trimethoprim-sulfamethoxazole should be started, pending the results of culture and sensitivity testing. The patient should be instructed to cleanse the site meticulously several times a day using povidone-iodine or peroxide solution.

Tunnel infections can be difficult to detect on physical examination and may be suspected only after the patient has several bouts of peritonitis caused by the same organism. As with other closed-space infections, they tend to be difficult to eradicate unless the tunnel is partially unroofed and drained.

Patients maintained on peritoneal dialysis also may present to the ED with any of several basically mechanical problems, of which the most common is failure of the dialysate to drain completely at the time of an exchange. Occasionally, this problem is caused simply by kinking or inadvertent clamping of the external catheter or tubing, but more often it is the result of catheter obstruction by fibrinous debris or kinking or migration of the catheter within the peritoneal cavity, often associated with constipation. Catheter position is best assessed initially by plain radiography of the abdomen. Specific intervention may be guided by a contrast "catheterogram." Fibrinolytic agents have been used successfully to open occluded catheters, but surgical intervention for catheter replacement often is required.

Severe metabolic disturbances are much less common among patients on peritoneal dialysis than patients on hemodialysis, because in the former group, dialysis is being performed essentially continuously and the blood remains in near-equilibrium with the dialysate. Significant disturbances do occasionally occur, usually in association with hypercatabolic states, major dietary indiscretions, or significant GI fluid loss. One interesting derangement that occurs occasionally in diabetic patients receiving peritoneal dialysis is a syndrome of severe hyperglycemia (sometimes even despite continuation of the usual insulin dose) resulting from absorption of glucose from hyperosmolar dialysate, with associated nonspecific symptoms of malaise, weakness, and headache. Although glucose levels may be as high as 1500 mg/dL in these patients, they cannot undergo an osmotic diuresis and remain clinically euvolemic. Correction of hyperglycemia must be undertaken carefully to avoid causing rapid osmolar and volume shifts.

KEY CONCEPTS

Acute Renal Failure

- The causes of ARF can be classified as prerenal, postrenal, and intrinsic renal disorders.
- Management of ARF should be directed first at potentially lethal complications such as hyperkalemia or volume overload and then at reversal of the underlying cause of renal dysfunction. It is important to avoid any further hemodynamic or toxic insults to the kidneys.
- The patient's impaired renal function must be considered when fluid is administered and drugs are prescribed.

Chronic Kidney Disease

- Patients with chronic kidney disease have a limited ability to handle fluid and solute loads and have altered metabolism of many drugs; therefore, as with ARF, fluid administration regimens and drug dosages should be checked carefully.
- The most rapidly lethal complication of chronic kidney disease is hyperkalemia. The possibility of this entity should always be considered, and appropriate diagnostic and therapeutic interventions should be instituted when indicated.
- Patients with renal failure often present with varying degrees of volume overload. Volume overload generally should be the first diagnostic consideration when dyspnea is the presenting complaint.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 96

Sexually Transmitted Diseases

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PERSPECTIVE

More than 300 million new cases of curable sexually transmitted diseases (STDs) are diagnosed worldwide each year, and these cases frequently are seen in emergency department (ED) settings. Nineteen million new STD cases are diagnosed annually in the United States,[1] for one of the highest rates of STDs in the industrialized world.

Because EDs often are used as a source of primary health care, the role of emergency departments in screening and treating STDs has been debated. A major area of difficulty with use of EDs for this purpose is that many test results are not available during the ED visit, and treatment decisions are therefore made presumptively. Errors are made in both overtreating and undertreating STDs in this setting. Although it has been shown that health care providers are significantly overtreating women who test negative for gonorrhea and chlamydial infection,[2] one third of patients who test positive for STDs in the ED are not treated during the initial visit, and a majority of untreated patients do not return for subsequent treatment.[2-4] As a result, providers must weigh the cost of overtreatment against the risk of untreated disease. Because these diseases pose a significant public health risk, it is recommended that patients be treated presumptively in the ED unless good follow-up for test results can be ensured. To help contain these diseases, many states allow expedited partner therapy, allowing physicians to prescribe treatment not only for the patients being treated but also for their partners. Information on expedited partner therapy and the states that allow it is available on the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov).

Patients with STDs present with a variety of symptoms and signs that most commonly involve the genitalia but also can include abdominal pain, dermatologic conditions, and systemic illness. To prevent both complications and spread of these diseases, accurate and timely diagnosis and treatment are crucial.

As with many other illnesses, history and physical examination provide much of the clinical information needed to diagnose STDs. Patients should be questioned about current and previous symptoms and their duration, as well as any previous history of STDs, recent sexual contacts, use of contraceptives (particularly barrier devices such as condoms), and types of sexual practices; women should additionally be questioned about their menstrual history. Physical examination should focus on the symptomatic area, often the genitalia. Evidence of skin lesions and their type as well as presence of discharge should be noted. Examination of the skin and lymph nodes may be an important component of the examination, particularly in the case of syphilis or gonorrhea. Evidence of septic arthritis on examination of symptomatic joints may indicate gonococcal arthritis and disseminated gonococcal infection.

The STDs can be split into two categories: those that manifest with genital ulcers, with or without adenopathy, and those that are nonulcerative, which most frequently manifest with genital discharge (Table 96-1).

DISORDERS CHARACTERIZED BY GENITAL LESIONS WITH OR WITHOUT ADENOPATHY

STDs constitute a common and well-recognized cause of genital lesions. As a point of clinical importance, however, patients who present with a "sore" on or near the genitalia may be using this term to refer to genital warts, scabies, premalignant lesions, or other conditions. If an STD is the cause, certain components of the history and physical examination can provide crucial information to help narrow the diagnosis to a specific infection (Table 96-2). History and physical examination should focus on the characteristics of the lesion or lesions, the presence or absence of adenopathy, and the presence or absence of systemic symptoms. In regard to the lesions, it is important to determine whether they are single or multiple, painful or painless, indurated or soft; whether they have irregular or regular borders; and how they began (e.g., as a vesicle or papule). If the patient has lymphadenopathy, it should be noted whether the condition is unilateral or bilateral, and the involved area should be evaluated for the presence of fluctuance and pain.

In evaluating a patient with genital ulcerative lesions, herpes simplex virus (HSV) testing and syphilis serologic studies should be undertaken; if feasible, a darkfield examination of the lesion scrapings also is useful. In addition, patients should be referred for human immunodeficiency virus (HIV) testing, because ulcerative genital lesions increase the risk of acquiring HIV infection.

Comprehensive test results often are not available during the patient's ED evaluation; therefore, treatment should be considered for the more likely diagnoses based on history and physical examination findings. The most common ulcerative diseases in the United States are herpes and syphilis; herpes occurs much more frequently than syphilis.[5] In rare outbreaks, chancroid may be the cause of the ulceration.[5]

HERPES

In the United States, genital herpes is the most common cause of ulcerative STDs, with 50 million people infected with the virus and 200,000 to 300,000 new symptomatic cases annually.[5] One in five sexually active adults is infected with the virus. Most commonly caused by herpes simplex virus type 2 (HSV-2), genital herpes also can be caused by HSV-1.[6] In pregnant patients, herpes can cause a devastating congenital infection, although the incidence of such infections has decreased. In addition, HSV infection plays a major role in the transmission of HIV, because herpetic lesions can increase the risk of both acquisition and transmission of HIV.

Clinically, genital herpes manifests as either primary herpes infection or recurrence. In primary infections, the degree of illness depends on whether the patient has preexisting circulating antibodies to either HSV-1 or HSV-2: those with antibodies tend to have a milder syndrome with initial genital infection than those without.[7] With primary infection in patients without antibodies, symptoms develop after a 2- to 7-day incubation period. The syndrome begins with genital lesions that tend to be painful, shallow, multiple, and grouped (Fig. 96-1); in women, they may coalesce into large ulcerations on the perineum (Fig. 96-2). Systemic symptoms may include low-grade fever, myalgias, headache, and fatigue. Adenopathy typically develops during the second or third week of the illness and is bilateral, mildly tender, and nonfluctuant. The local symptoms peak at approximately 8 to 10 days, and it takes 2 to 4 weeks for the lesions to completely heal. Viral shedding can last as long as 3 weeks. In some cases, sacral

Table 96-1 Differential Diagnosis for Sexually Transmitted Diseases

ULCERATIVE	NONULCERATIVE
Herpes genitalis	Gonorrhea
Syphilis (primary)	Chlamydial infection
Chancroid	Nongonococcal urethritis
Lymphogranuloma venereum	Secondary/tertiary syphilis
Granuloma inguinale (donovanosis)	Candidal vaginitis
Molluscum contagiosum	Trichomoniasis
Condylomata acuminata (genital warts)	Bacterial vaginosis
	Endometriosis
Pediculosis	
Scabies	
Pyoderma	
Trauma	
Excoriations	
Behçet's disease	
Fixed drug eruption	
Yeast infection	

Figure 96-1. Genital herpes lesions on the penile shaft.

Table 96-2 Characteristics of Ulcerative Sexually Transmitted Diseases

DISEASE	NATURE OF GENITAL ULCER	INCUBATION PERIOD	PAINFUL	INGUINAL ADENOPATHY	DIAGNOSTIC TESTS
Syphilis	Indurated, sharply demarcated, with red, smooth base; heals spontaneously	9–90 days; average 2–3 weeks	No	Firm rubbery nodes; nontender	Darkfield examination; serology
Herpes simplex	Multiple small grouped vesicles on a red base, which form shallow ulcers; may coalesce; resolve spontaneously but recurrence is common	2–7 days	Yes	Bilateral, firm, tender	Culture, serology
Chancroid	Irregular, sharply demarcated borders with undermined edges, shallow, often multiple	3–6 days	Yes	Unilateral most common; overlying erythema, fixed and tender; suppuration may occur	Culture
Lymphogranuloma venereum	Usually single lesion, papule or ulcer, transient, frequently not noticed	5–21 days	No	Unilateral most common; firm, tender, matted, fixed; may suppurate or form fistulas	Lymphogranuloma venereum complement fixation (serology)

Figure 96-2. Coalescent primary herpes lesions on the vulva.

radiculopathy may develop, with urinary retention, constipation, and sensory changes in the perineal region. Aseptic meningitis and transverse myelitis are relatively uncommon complications. In patients with circulating antibodies to the herpesvirus, genital lesions alone usually characterize the initial infection.

As the symptoms of primary infection recede, the virus takes residence in the spinal cord ganglia and becomes latent, residing there for the lifetime of the patient. Symptomatic recurrences are the rule, occurring in 60 to 90% of patients. In contrast with the prolonged syndrome and systemic symptoms of primary infection, recurrences are much shorter in duration and tend to cause only mild local symptoms. Many patients will be warned of an impending recurrence by a prodrome, often characterized by paresthesias, burning, or itching at the site of the subsequent lesions. Although it is known that viral shedding can occur during a recurrence, data suggest that in patients infected with HSV-2, shedding occurs during asymptomatic periods as well.

Population screening with serologic tests for HSV-2 suggests that many people become infected with the virus without symptoms or knowledge of having acquired the infection. Patients with only serologic evidence for past infection may be a potential reservoir for transmission of the virus.

Diagnosis

Although the diagnosis of genital herpes usually is made clinically, this diagnostic strategy is both insensitive and nonspecific. Confirmatory testing should be strongly considered, particularly in women of childbearing age. Several methods are available, including viral culture and antigen testing methods of the lesions, as well as new type-specific viral serologic testing of the blood; a positive result on any of these tests is considered definitive. The Tzanck test, used in the past for diagnosis of herpes infection, is no longer recommended because of its lack of sensitivity.

Although viral culture of a lesion traditionally has been and still is considered to be the "gold standard" diagnostic modality, this test takes 3 to 10 days to complete, and false-negative results, with rates ranging from 5 to 20%, are common, often as a consequence of improper specimen collection, storage, or transportation. Antigen testing has been disappointing, often found to be less sensitive than culture for identification of the virus. In addition, some antigen testing cannot distinguish between HSV-1 and HSV-2. Although the more recently available serologic testing is type-specific, patients with newly acquired viral infection may take up to 6 weeks to show positive antibodies.[8,9] This test is most useful in patients presenting with symptoms consistent with herpes but with negative results on culture or antigen testing.[5] In the newly presenting patient, culture for virus isolation is the recommended diagnostic test.

Treatment

Although genital herpes is incurable and outbreaks are self-limited, treatment decreases the duration of symptoms in patients with primary infection, can shorten or abort recurrences, and decreases the amount and duration of viral shedding and therefore potential infectivity. In patients with frequent recurrences (six or more per year), suppressive therapy can decrease the number of these episodes by up to 80%.[10,11] The mainstay of treatment is therapy with one of the antiviral drugs acyclovir, valacyclovir, and famciclovir[5] (Table 96-3). None of these agents can eliminate the virus, but their use can control symptoms, at least while the drug is being taken. Acyclovir has been shown to be safe for up to 6 years' continuous use as a suppressive agent; the other antivirals have been proved safe for 1 year.[5]

Patient education is critical in cases of genital herpes. The importance of testing the patient's sexual partner or partners should be emphasized, and the patient should be told that he or she can potentially transmit the virus and infect a sexual partner even during asymptomatic periods. If the patient is a woman of childbearing age, she must be instructed to inform her physician of her history of genital herpes if she becomes pregnant.

Neonatal herpes is a devastating and potentially fatal infection seen most often in women who acquire the infection during their pregnancy, whether or not the patient is symptomatic. Cesarean section is the preferred method of delivery if the patient has active lesions at the time of onset of labor. Because the antiviral agents used to treat genital herpes have not been proved safe during pregnancy, the decision to use these agents should be made in conjunction with both the patient and her physician.

BARTHOLIN CYST AND ABSCESS

The Bartholin glands are located inferiorly on either side of the vaginal opening. The glands normally secrete fluid through their openings on the sides of the vestibule. The ducts and glands are palpable or visible only when obstructed, infected, or inflamed. When the duct of the gland becomes obstructed, a simple cyst develops, which usually is painless. Patients with a Bartholin gland cyst typically report a lump at the lateral introitus, and on examination, an ovoid mass can be palpated on the mucosal surface of the lateral posterior introitus, just above the posterior fourchette. Treatment usually consists of incision and drainage using local anesthesia with Word catheter placement and sitz baths. Simple packing can be used, but the cavity may need repacking multiple times as the area heals.

A Bartholin abscess develops when a Bartholin cyst becomes secondarily infected. A majority of abscesses involve the

Table 96-3 Treatment Guidelines for Sexually Transmitted Diseases

DISEASE	RECOMMENDED TREATMENT REGIMEN	ALTERNATIVE(S)
Chlamydial infection	Azithromycin 1 g PO × 1 *or* Doxycycline 100 mg PO bid × 7 days	Erythromycin base 500 mg PO qid × 7 days *or* Ofloxacin 300 mg PO bid × 7 days *or* Levofloxacin 500 mg PO qd × 7 days *or* Erythromycin ethylsuccinate 800 mg PO qid × 7 days
Gonorrhea,* uncomplicated urethral, cervical, or rectal infection	Ceftriaxone 125 mg IM × 1	Spectinomycin 2 g IM × 1 Cefixime 400 mg PO in a single dose
Gonorrhea,* pharyngeal	Ceftriaxone 125 mg IM × 1	
Gonorrhea,* adult conjunctivitis	Ceftriaxone 1 g IM × 1 Normal saline irrigation Consider hospitalization	
Gonorrhea,* disseminated infection	Ceftriaxone 1 g IM or IV every 24 hours Strongly consider hospitalization	Cefotaxime 1 g IV q8h *or* Ceftizoxime 1 g IV q8h *or* Spectinomycin 2 g IM q12h
Syphilis, primary or secondary	Benzathine penicillin G 2.4 million units IM × 1	
Syphilis, late latent	Benzathine penicillin G 2.4 million units IM in 3 doses, 1 week apart	
Herpes simplex, first episode	Acyclovir 400 mg PO tid × 7–10 days *or* Acyclovir 200 mg PO 5×/day × 7–10 days *or* Famciclovir 250 mg PO tid × 7–10 days *or* Valacyclovir 1 g PO bid × 7–10 days	
Herpes simplex, recurrent	Acyclovir 400 mg PO tid × 5 days *or* Acyclovir 800 mg PO bid × 5 days *or* Acyclovir 800 mg PO tid × 2 days *or* Famciclovir 125 mg PO bid × 5 days *or* Famciclovir 1000 mg PO bid × 1 day *or* Valacyclovir 1 g PO qd × 5 days *or* Valacyclovir 500 mg PO bid × 5 days	
Herpes simplex, suppressive	Acyclovir 400 mg PO bid *or* Famciclovir 250 mg PO bid *or* Valacyclovir 500 mg PO qd *or* Valacyclovir 1 g PO qd	
Chancroid	Azithromycin 1 g PO × 1 *or* Ceftriaxone 250 mg IM × 1 *or* Ciprofloxacin 500 mg PO bid × 3 days *or* Erythromycin base 500 mg PO tid × 7 days	
Lymphogranuloma venereum	Doxycycline 100 mg PO bid × 21 days	Erythromycin base 500 mg PO qid × 21 days

*Because of resistance, quinolones are no longer recommended for the treatment of gonorrhea.

anaerobic and aerobic bacteria normally found in the vagina. However, they also can be due to sexually transmitted infections, including infection with *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. Other commonly implicated bacteria include *Bacteroides* species, *Escherichia coli*, and other gram-negative organisms. Patients with a Bartholin abscess present with swelling and pain at the lower lateral vaginal opening and may report a lump or mass near the affected labium. On examination, patients may have a swollen and painful labium, and a tender, fluctuant mass can be palpated on the posterolateral margin of the vaginal vestibule. Cellulitis may be present with surrounding edema and erythema.

Treatment options include incision and drainage, with the incision on the mucosal surface of the vestibule. Iodoform gauze can be used as a packing material to promote ongoing drainage, but it is preferable to use a Word catheter for this purpose. This small catheter is placed into the incision, and the balloon on the catheter is then inflated with 2 to 4 mL of water or saline. The catheter is left in place for 6 to 8 weeks until epithelialization along the catheter tract has occurred. Although this treatment is adequate in most patients, management of recurrent infections may require marsupialization, creating a permanent fistula that prevents recurrent abscess formation. Antibiotics usually are not necessary unless significant surrounding cellulitis is present. Patients are instructed to start sitz baths within 24 hours of ED discharge to promote drainage. Patients should be referred for follow-up for reexamination of the wound within 48 hours. Because some Bartholin abscesses are caused by sexually transmitted organisms, abscess drainage should be cultured and routine testing for STDs performed, and patients should be treated with appropriate antibiotic therapy to cover *Chlamydia* and *N. gonorrhoeae*.

SYPHILIS

Syphilis, also known as the "Great Imitator," is caused by the spirochete *Treponema pallidum* and earns its nickname from its ability to infect any organ of the body and cause multiple symptoms.

The organism is fragile and does not survive on dry surfaces. Transmission occurs during exposure of moist skin to an infected area. Although transmission usually involves the genitalia, inoculation can occur virtually anywhere on the

body. The incidence of this infection hit a nadir in 2000; since then it has been increasing steadily, and now nearly 10,000 cases of primary and secondary syphilis are reported annually in the United States.[5,12]

If untreated, syphilis typically progresses through several stages, as follows.

1. *Primary*. The primary lesion, called a *chancre*, occurs after an incubation period that varies from 9 to 90 days, averaging 2 to 4 weeks. This lesion occurs at the site of inoculation and begins as a papule that then becomes ulcerative. Typically, the chancre is painless and single and has a smooth, slightly raised edge, with sharply defined borders and a clean base (Fig. 96-3); occasionally, patients present with more than one lesion (Fig. 96-4). Without treatment, the chancre lasts for 2 to 6 weeks and resolves spontaneously, and the disease progresses to the secondary stage. Adenopathy is not a predominant feature of primary syphilis. If the chancre is on the genitalia, bilateral, painless, nonfluctuant, and slightly enlarged inguinal adenopathy may develop several days after appearance of the primary chancre.
2. *Secondary*. At 5 to 8 weeks after resolution of signs and symptoms of primary syphilis, the patient begins to exhibit manifestations of the secondary stage of the disease. The most common manifestation is a total body rash (Fig. 96-5). This rash begins on the trunk as a fine macular rash, which then spreads outward to the arms and legs and may involve the palms and soles (Fig. 96-6). As it progresses, it becomes papulosquamous and may appear slightly annular, often resembling the rash of pityriasis rosea. Mucous patches can be seen on the tongue, which are the oral manifestations of the skin rash. Condylomata lata (Fig. 96-7) also can develop; these lesions are broad-based papules with flat moist tops, occurring in the perineal region, which may involve the anus, the skin between the buttocks, and the labia. Constitutional signs and symptoms are common during this stage, including fatigue, low-grade fever, malaise,

Figure 96-3. Chancre of primary syphilis on the penis.

Figure 96-4. Two lesions of primary syphilis on the penile shaft.

Figure 96-5. The rash of secondary syphilis.

Figure 96-6. Palmar rash due to secondary syphilis.

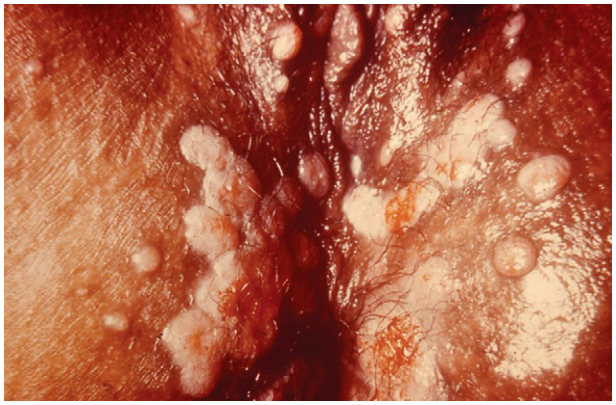

Figure 96-7. Condylomata lata of secondary syphilis.

headache, arthralgias, and generalized lymphadenopathy. Adenopathy may occur virtually anywhere in the body, including epitrochlear node involvement. The nodes are discrete, nontender, and rubbery. As with the primary stage, the manifestations of secondary syphilis will resolve spontaneously if the condition goes untreated, and the infection enters the latent or tertiary stage.

3. *Latent*. Once the clinical manifestations of secondary syphilis resolve, the patient's infection may become latent. There are no clinical signs and symptoms during this stage, and laboratory testing is the only means to identify infected persons. Latent syphilis is divided into two categories: *early latent* syphilis, acquired within the preceding year, and *late latent* syphilis, the designation for all other cases of latent syphilis or for latent syphilis of unknown duration.
4. *Tertiary*. After a latent period of at least 3 to 4 years, signs and symptoms of tertiary syphilis may appear. This stage predominantly involves the cardiovascular and nervous systems. Patients may present with a thoracic aortic aneurysm, meningitis, peripheral neuropathy (tabes dorsalis), or gummatous lesions of the mucous membranes. Although common in the preantibiotic era, tertiary syphilis is now uncommon in the United States.[5,13]

Diagnosis

The only rapid means of diagnosing syphilis is the darkfield examination. This method involves viewing scrapings or fluid from lesions of primary or secondary syphilis under a darkfield microscope to identify the spirochete. Unfortunately, the sensitivity of darkfield microscopy is approximately 80%, and many hospitals and clinics do not have this technique routinely available.[14]

Serologic testing is the current standard for diagnosing secondary, latent, and tertiary syphilis; for primary syphilis, one-time testing is less reliable, and follow-up testing may be necessary. The two types of serologic tests are *nontreponemal*—the Venereal Disease Research Laboratory (VDRL) and rapid plasma reagin (RPR) tests—and *treponemal*—(MHA-TP) and (FTA-ABS). Both tests are necessary for definitive diagnosis, although the nontreponemal test is used for screening, with treponemal testing used for confirmation. Nontreponemal tests measure nonspecific antibodies in serum from patients with syphilis, and the titers vary with the stage and activity of disease. These tests yield a positive result at approximately 2 weeks after the primary chancre appears and involve quantitative measurement of antibody. Titers are used to follow response to treatment. Because these tests are nonspecific for the treponeme and false-positive results can occur, positive test results should be confirmed with the more specific treponemal tests. Treponemal tests measure antibodies specific to the spirochete *T. pallidum*. These tests are more expensive and difficult to perform than the nonspecific tests, and because their titers do not predictably vary with treatment, the main value of these tests is in confirming positive findings on nontreponemal tests.[14]

Treatment

A one-time dose of the long-acting formulation of penicillin G benzathine, 2.4 million units IM, is the regimen of choice for treating primary and secondary syphilis[5] (see Table 96-3 for treatment of latent and tertiary syphilis). It is crucial that the long-acting form of penicillin G benzathine be used; the half-life of an alternative preparation comprising both penicillin G benzathine and penicillin G procaine (i.e., Bicillin C-R) is too short, which has resulted in treatment failures.[15] Sexual partners need to be evaluated; partners within the last 90 days should be tested but treated presumptively; and former partners from more than 90 days before diagnosis should be evaluated and treated if indicated. Because syphilis increases the risk of acquisition of HIV, all patients should be referred for HIV testing. To ensure response to treatment, patients should be reexamined clinically and serologically 6 and 12 months after treatment. Successful treatment is confirmed by either a nonreactive nontreponemal test or a fourfold or greater decrease in titers after 6 months. Because syphilis is a reportable disease, patients with positive test results should be reported to the public health department.

In the pregnant patient with syphilis, congenital syphilis with its devastating outcome is a significant concern. Parenteral penicillin G is the only agent with documented efficacy in these instances. In pregnant women with syphilis at any stage with a reported penicillin allergy, treatment with penicillin is still recommended after desensitization.[5]

LYMPHOGRANULOMA VENEREUM

Lymphogranuloma venereum is a chronic STD caused by specific serotypes of *C. trachomatis*. Although this disease is prevalent in many tropical countries, it is rare in the United States and is seen either in patients who have traveled to endemic areas or in localized outbreaks in patient populations such as men who have sex with men. The incubation period ranges from 3 days to 3 weeks. The initial infection manifests as a transient genital lesion that is small and painless and often goes unnoticed by the patient. The secondary stage, characterized by involvement of the lymphatic channels and nodes of the genitalia, pelvis, and rectum, begins at 7 to 30 days after the primary lesion disappears. The patient usually presents at this secondary stage, when regional lymphadenitis appears. Inguinal lymphadenopathy most often is unilateral, and enlargement of the glands above and below Poupart's ligament gives the characteristic lymphogranuloma venereum "groove sign." The enlarged nodes often are painful, with overlying erythema, but usually are not fluctuant. The nodes either eventually break down, with the formation of multiple draining sinuses, or form a hard inguinal mass without suppuration. The late complication of distal lymphedema results from the blockage of lymphatic channels.

Diagnosis

Diagnosis is based on the clinical picture, epidemiologic information, and the exclusion of other causes of inguinal lymphadenopathy and genital ulcers.

Treatment

Treatment is curative and prevents ongoing tissue damage. The preferred treatment is with doxycycline, 100 mg PO twice daily for 21 days; erythromycin base 500 mg PO four times daily for 21 days is an alternative regimen.[5] Patients should refer their sexual partners for evaluation and treatment, and all patients should be referred for HIV testing.

CHANCROID

Chancroid is caused by *Haemophilus ducreyi*, a small gram-negative bacterium. This disease is common in developing countries[13] but rare in the United States, with usually less than 100 cases reported annually to the Centers for Disease Control and Prevention (CDC).[5] Despite its being relatively rare, outbreaks of chancroid have been reported in the United States, and physicians should be aware of the characteristics of this disease to permit recognition of these occasional outbreaks when they occur.

Clinically, chancroid is characterized by multiple painful genital ulcerations and inguinal bubo formation (Fig. 96-8). After an incubation period of less than 1 week, a short-lived, small, tender red papule appears at the site of inoculation. This lesion rapidly ulcerates, followed by the formation of multiple shallow, painful ulcers with sharply demarcated edges and purulent bases that last 1 to 2 weeks; in some patients, these lesions coalesce. Inguinal lymph node involvement is seen in 50% of patients, manifesting 1 week after the ulcers appear. Typically, a unilateral large, painful, fluctuant lymph node (bubo) develops in the groin. Overlying skin is thinned and erythematous, and suppuration is common. These buboes can spontaneously rupture.

On a clinical basis, it may be difficult to distinguish chancroid from genital herpes. The presence of a large, fluctuant bubo strongly suggests chancroid. However, if only ulcers are present, the patient can have either disease. Because herpes is several orders of magnitude more common in the United States than chancroid (which tends to occur in isolated outbreaks), herpes should be the first diagnosis considered.

Diagnosis

H. ducreyi is difficult to culture, so the diagnosis is based on clinical presentation and often is one of exclusion, after other diseases such as herpes and syphilis are ruled out by testing. Definitive diagnosis requires isolation and identification of *H. ducreyi*, a fastidious organism requiring a special growth medium that is not routinely available. Because definitive diagnosis can be elusive, a "probable diagnosis" can be made if all of the following criteria are met: (1) The patient has one or more painful genital ulcers; (2) the patient has no evidence of *T. pallidum* infection on darkfield examination or serologic testing; (3) the clinical presentation, appearance of genital ulcers, and regional lymphadenopathy are typical for chancroid; and (4) results of HSV testing performed on the ulcer exudates are negative.[5] When local outbreaks are known, the microbiology laboratory can prepare the special medium required for growth of the organism to confirm specific cases, as well as to follow containment of the infection.

Figure 96-8. Ulcerative lesions of the penis from chancroid with accompanying fluctuant, tender, erythematous lymphadenitis (bubo).

Any of the following four curative treatment regimens may be used: a single dose of azithromycin 1 g PO; a single dose of ceftriaxone 250 mg IM; ciprofloxacin 500 mg PO twice daily for 3 days; and erythromycin base 500 mg PO three times daily for 7 days (see Table 96-3 for additional treatment options).[5] Co-infection with syphilis or HSV occurs in approximately 10% of patients who have chancroid acquired in the United States. Chancroid is associated with increased HIV transmission, so all patients should be referred for HIV and other STD testing. Sexual partners of patients with chancroid should be examined and treated if sexual contact with the patient occurred during the 10 days preceding the patient's onset of symptoms. To confirm response to treatment, patients should be referred for reexamination 3 to 7 days after initiation of therapy.

Drainage of buboes is not routinely recommended, because appropriate antibiotic treatment typically affects a good clinical response. If deemed necessary, needle aspiration of nodes in the superior cephalic aspect of the fluctuant area can be performed; reaspiration usually is not necessary because the adenopathy responds quickly to antimicrobial treatment.

GRANULOMA INGUINALE

Granuloma inguinale (donovanosis) is caused by *Klebsiella granulomatis* (formerly known as *Calymmatobacterium granulomatis*), an intracellular gram-negative rod. The disease is rare in developed countries but is endemic in tropical and semitropical regions, including India, Papua New Guinea, central Australia, and southern Africa. The disease is presumed to be sexually transmitted, with an incubation period of 8 to 80 days.

Clinically, the disease manifests as chronic, painless, progressive ulcerative lesions. The lesions are irregular, clean-based granulomatous ulcers that are highly vascular (giving the classic "beefy red appearance") and bleed easily on contact. The ulcer feels hard when palpated. Regional lymphadenopathy does not occur. As the lesion enlarges, it can be quite mutilating to the genitalia, causing urethral stenosis over a period of months to years. Without adequate treatment, it may result in lymphatic obstruction, producing genital edema and eventually lower extremity elephantiasis. In men, the sites of predilection are the prepuce, the coronal sulcus, and the frenulum. In women, lesions typically are found on the labia, but vaginal and cervical lesions also can occur.

Diagnosis is difficult and requires identification of the infectious agent, which appears as short, pleomorphic rods with bipolar staining. Donovan bodies may be seen within histiocytes on microscopy of tissue crush preparation or biopsy specimen. The causative organism is very difficult to culture, so visualization of the organism with appropriate staining is the primary means of diagnosing the disease.

Treatment halts progression of the lesions, but relapse can occur 6 to 18 months after apparently successful treatment. The CDC-recommended regimen is doxycycline 100 mg PO twice daily for at least 3 weeks or until the lesions have healed.

Alternative regimens include azithromycin 1 g PO once a week, ciprofloxacin 500 mg PO twice a day, erythromycin base 500 mg PO four times daily, and trimethoprim-sulfamethoxazole (Bactrim DS), one tablet PO twice daily; each regimen should be continued for 3 weeks or until the lesions have healed.

Clinical follow-up visits are recommended until signs and symptoms have resolved. Persons who have had sexual contact with the patient within 60 days of symptom onset should be examined and offered therapy. Patients should be screened for other STDs.

CONDYLOMATA ACUMINATA

Anogenital warts are caused by the human papillomavirus (HPV), and more than 30 types of HPV can infect the genital tract. HPV infections most often are sexually transmitted, and lesions are most common at the site of greatest trauma during sexual intercourse. Most cases of HPV infection are asymptomatic or subclinical, with only approximately 1% resulting in clinically apparent warts. Most visible genital warts are caused by HPV types 6 and 11 and are benign. Other HPV types have been associated with external genital squamous intraepithelial neoplasia, however, as well as with vaginal, anal, and cervical intraepithelial dysplasia and squamous cell carcinoma.

Warts may be single or multiple (Fig. 96-9). Warts on warm, moist, nonhairy skin tend to be soft and nonkeratinized, whereas those on dry, hairy skin are more firm and keratinized. The lesions can be broad-based, pedunculated, or pigmented. Depending on the size and location, warts can be painful, friable, or pruritic. Warts that are indurated, fixed, ulcerated, and darkly pigmented may require biopsy to rule out carcinoma.

Diagnosis usually is made clinically. In women, a speculum examination is indicated to evaluate the patient for intravaginal and cervical lesions. Occasionally, HPV infections may be confused with the condylomata lata of syphilis. If any doubt about the diagnosis remains, or if warts have high-risk characteristics, biopsy and darkfield microscopy of tissue are indicated, along with serologic testing for syphilis.

Figure 96-9. Genital warts due to human papillomavirus infection.

Treatment is aimed at removal of symptomatic warts, including those that cause obstructive symptoms of the urethral meatus or rectum. Although wart-free periods may be obtained, treatment has not been shown to affect the course of disease or to reduce infectivity. If left untreated, visible genital warts may resolve spontaneously, remain unchanged, or increase in number.

Many treatment options are available, although no specific treatment has been proved to be superior to another; all have significant failure and recurrence rates. For patient-applied regimens, the patient must be able to identify and reach the warts to be treated with these methods. Provider-administered regimens often require ongoing treatments on a weekly basis and usually are best administered by a primary care physician, who can monitor the patient's response to therapy. In general, warts located on moist surfaces respond better to topical treatments than do the keratinized warts found on drier surfaces. Patients should be instructed to watch for recurrences, which are most common in the first 3 months after treatment.

Patient preference, available resources, and physician experience should guide treatment. Most of these treatments are administered by the patient's primary care physician and not through the ED. Treatment regimens can be divided into patient-applied and provider-administered.

Patient-applied regimens include the following:

- Podofilox 0.5% solution or gel, applied twice a day for 3 days, followed by 4 days of no therapy—which may be repeated, as necessary, for up to four cycles.
- Imiquimod 5% cream, applied once daily at bedtime, three times a week for up to 16 weeks. The treatment area should be washed with soap and water 6 to 10 hours after application.

Provider-administered regimens include the following:

- Cryotherapy with liquid nitrogen or cryoprobe, which may need to be repeated every 1 to 2 weeks
- Podophyllin resin, 10 to 25%
- Trichloroacetic acid or dichloroacetic acid, 80 to 90%
- Surgical removal

Podophyllin and podophyllum resin should be avoided in pregnant patients because of possible teratogenic effects. Imiquimod also is not approved for use during pregnancy. Immunosuppressed patients are more likely to demonstrate a poor response to treatment, increased relapse rates, and dysplasia and need close follow-up. All patients need screening for other sexually transmitted infections. Treatment of partners is not necessary.[5]

In 2006, the U.S. Food and Drug Administration (FDA) licensed the human papillomavirus vaccine for use in girls and women aged 9 to 26 years. The vaccine covers the four virus types that are responsible for 70% of cases of cervical cancer and 90% of anogenital warts, and it is virtually 100% effective. Full vaccination involves a series of three injections over a 6-month period.

DISORDERS CHARACTERIZED BY GENITAL DISCHARGE

Patients with diseases that fall into the group of disorders characterized by genital discharge tend to present with ure-

thral or cervical discharge and do not have ulcerations or significant lymphadenopathy. These infections include chlamydial infection, gonorrhea, nongonococcal urethritis, trichomoniasis, bacterial vaginosis, candidiasis, and pelvic inflammatory disease (PID). Bacterial vaginosis and candidiasis are not sexually transmitted conditions but often are diagnosed in patients undergoing evaluation for STDs. Chlamydial infection and gonorrhea, the two most common nonulcerative STDs, also can cause vaginal discharge, especially in the setting of mucopurulent cervicitis, and both tend to cause urethral discharge in men. These two infections commonly occur concurrently, and clinical manifestations of these two infections are similar. It usually is not possible to distinguish between the two diseases on the basis of signs and symptoms alone, and patients often are appropriately treated presumptively for both infections (see Table 96-1).

CHLAMYDIAL INFECTION

In the United States, chlamydial infection is diagnosed in just over 1 million people annually, and estimates are for nearly 3 million cases each year, making it the most commonly reported STD.[5] The causative organism is *C. trachomatis*, an obligate intracellular organism that infects columnar and pseudostratified columnar epithelial surfaces.[14] Infection with *C. trachomatis* can cause a variety of symptoms, including urethritis, cervicitis, epididymitis, proctitis, prostatitis, PID, and perihepatitis, also known as *Fitz-Hugh–Curtis syndrome*.

Symptoms appear after an incubation period of 1 to 3 weeks. Although urethritis is the most common manifestation in men, men also can present with epididymitis or both in combination. When symptomatic, women may report symptoms and signs ranging from dysuria to systemic illness related to peritonitis. Often, however, the presenting manifestations in women are vague and nonspecific: vaginal discharge or bleeding or abdominal or pelvic pain, or some combination thereof. Unfortunately, infection commonly is asymptomatic; estimates show that up to 75% of infected women and 50% of infected men have no symptoms.[16,17] The highest rate of infection is in sexually active adolescent females, with infection rates as high as 10% in this group.[16,17] Of note, PID, with its increased risk of subsequent ectopic pregnancy and infertility, develops in up to 40% of women with untreated chlamydial infection.[16,17] Because of the high rate of asymptomatic infection and the increased risk for developing PID and its sequelae after chlamydial infection, screening of high-risk patients (those with multiple sexual partners) for disease may be appropriate in the ED so long as adequate follow-up is ensured. The CDC recommends *Chlamydia* testing for all women 25 years of age or younger and older women with risk factors (a new sexual partner or multiple sexual partners) and in all pregnant patients.[5]

Until recently, the "gold standard" modality for diagnosing chlamydial infection was cell culture. Unfortunately, this test is labor-intensive, is fraught with difficulties, and takes days for definitive results. Although other nonculture techniques (DNA probe and latex agglutination testing) have been used since the 1990s to make the diagnosis of chlamydial infection, the more recently available tests based on nucleic acid amplification techniques have better sensitivity and specificity than culture and are rapidly becoming the new diagnostic method of choice. These nucleic acid amplification tests (NAATs) include ligase chain reaction, polymerase chain reaction (PCR), strand displacement amplification, and transcript-mediated amplification techniques. All of these techniques amplify nucleic acid sequences specific to the organism being tested and do not require viable organisms. NAATs have sensitivity rates better than that for culture (greater than 90%, versus 60 to 80%), with specificity greater than 99%. These new NAATs are more sensitive than other nonculture tests (DNA probe testing, latex agglutination testing) by 17 to 35%.[18,19] NAATs can be performed on swabs (endocervical or urethral) and urine. Sensitivity of NAATs is lower when performed on urine than on endocervical swabs,[18] so endocervical swabs constitute the sample of choice in females. Urine screening using NAATs is adequate for symptomatic male patients, and urethral swabs generally are not necessary.[19] In sexual abuse cases, culture should still be performed in addition to the NAAT for medicolegal purposes.[5]

Treatment of chlamydial infection consists of azithromycin 1 g PO in a single dose or doxycycline 100 mg PO twice daily for 7 days; alternative regimens are shown in Table 96-3.[5] Coinfection with gonorrhea is common, so unless gonorrhea is definitively ruled out, patients should be treated for both infections. Patients should be instructed to abstain from sexual intercourse for 7 days after completion of treatment (either single-dose therapy or the 7-day regimen of doxycycline). Sexual partners need to be tested and treated, and the index patient also should be instructed to abstain from sexual intercourse until all partners are treated. Follow-up testing for cure is not required unless symptoms persist or reinfection is suspected.

NONGONOCOCCAL URETHRITIS

Nongonococcal urethritis is characterized by urethral discharge, dysuria, or urethral pruritus and, although most commonly diagnosed in men, also can be seen in women. Although *C. trachomatis* is implicated in many cases, other organisms such as *Mycoplasma* and *Ureaplasma* also may be etiologic agents.[20-22] All patients with suggestive presenting symptoms should be evaluated for both gonorrhea and chlamydial infection. The diagnosis is made by Gram's stain (more than 5 white blood cells [WBCs] per high-power field and no gram-negative diplococci), a positive result on the leukocyte esterase test on urinalysis, or more than 10 WBCs per high-power field on urinalysis.[5]

Treatment consists of azithromycin 1 g PO in a single dose or doxycycline 100 mg PO twice daily for 7 days. [5] In women, other causes of vaginal discharge must be ruled out, including chlamydial infection, trichomoniasis, and candidiasis. Patients with persistent symptoms despite adequate initial therapy (appropriate regimen and completion of treatment course) should be reevaluated for the accuracy of diagnosis. If the diagnosis was accurate, the patient should be treated with metronidazole 2 g in a single dose or tinadazole 2 g in a single dose; azithromycin 1 g as a single dose can be added if it was not used in the first treatment regimen.

GONORRHEA

Gonorrhea is the second most frequently reported STD after chlamydial infection, with an estimated 600,000 new *N. gonorrhoeae* infections in the United States each year.[5] Because infection involves columnar or transitional epithelium, this organism affects the urethra, rectum, cervical canal, pharynx, upper female genital tract, and conjunctival sac.

The most common clinical presentation in men is acute urethritis, characterized by dysuria and a penile discharge (Fig. 96-10), starting within 1 to 14 days of exposure. On examination, findings may include urethral meatal erythema and a purulent urethral discharge. Patients may present with epididymitis, although this is uncommon.

Figure 96-10. Purulent urethral discharge in a patient with gonorrhea.

In women, primary infections often are asymptomatic or produce only vague symptoms such as vaginal discharge, abnormal vaginal bleeding, abdominal or pelvic pain, dyspareunia or dysuria, and frequency. Patients may not present until after the emergence of complications such as PID, which develops in up to 20% of women with untreated gonorrhea. Like chlamydial infection, symptomatic and asymptomatic gonococcal infection can cause PID with consequent tubal scarring that may lead to infertility or ectopic pregnancy.

Gonorrhea also can involve the oropharynx and the anorectal area. Gonococcal infection of the pharynx often is asymptomatic, but in symptomatic cases, patients present with sore throat and exudative tonsillitis. Most cases are self-limited. Anorectal involvement is more common in persons who engage in receptive anal intercourse but can occur in women from contamination from cervicovaginal secretions. Like pharyngeal infection, it often is asymptomatic. When it is symptomatic, patients complain of rectal discomfort or pain, tenesmus, constipation, dyspareunia, pruritus ani, and purulent or mucoid anal discharge or bleeding. Anoscopy reveals friable mucosa and mucopurulent exudate.

Gonococcal conjunctivitis can be a sight-threatening infection, so recognition of this form of infection is crucial. This infection can occur in newborns, in whom it is acquired during passage through an infected birth canal, and in adults, who often acquire the infection by direct inoculation from organisms on the fingers and then rubbed onto the eye. Symptomatic conjunctivitis is characterized by beefy red conjunctiva, chemosis, and purulent eye discharge that often is copious. If untreated, it can progress to corneal ulceration or, in severe cases, gonococcal endophthalmitis and globe perforation.

Disseminated gonococcal infection (DGI) results from gonococcal bacteremia and occurs more frequently in women than in men. Typically, it manifests as the arthritis-dermatitis syndrome, characterized by a combination of any or all of the following: fevers, chills, monoarticular or oligoarticular arthritis or arthralgias, rash, and tenosynovitis. The rash of DGI consists of pustular acral skin lesions, usually found peripherally on the extremities. The lesions are described as necrotic pustules on an erythematous base and are tender to palpation. These lesions represent the consequence of septic emboli to small blood vessels during bacteremia. Joint involvement, the second most common manifestation of DGI, manifests with an acute monoarticular or oligoarticular septic arthritis. The knees are most commonly involved, followed by elbows, ankles, wrists, and small joints of the hands and feet. The involved joint is erythematous, is warm, often has an effusion, and is painful on range-of-motion testing. Other manifestations of DGI, although very rare, include hepatitis, myocarditis, endocarditis, and meningitis.

Definitive diagnosis of DGI is confirmed by isolating gonococci from the blood, synovial fluid, or infected skin; unfortunately, such isolation has relatively poor sensitivity. Presumptive diagnosis of DGI is based on the appropriate clinical presentation, plus isolation of gonococci from a source site.

Diagnosis

Diagnostic tests for gonorrhea include Gram's staining, culture, and NAATs. Gram's staining is most useful in symptomatic men with urethritis or in patients with gonococcal conjunctivitis. In these cases, it is an excellent diagnostic test, with a sensitivity and specificity approaching 100%,[23,24] and results are available rapidly. This test is much less useful in asymptomatic men and all women, owing to its decreased sensitivity in these groups.

Culture for *N. gonorrhoeae* is considered the "gold standard" method of diagnosis.[23] Because this test can be used to isolate the organism for antimicrobial testing and determination of antibiotic sensitivities, it is useful in areas of rapidly emerging resistance. However, the utility of this test may be limited by improper specimen collection and handling. To maximize the yield of gonococcal culture, inoculating the specimen immediately after collection directly onto the appropriate medium optimizes viability of the organisms. If the specimen is from a sterile site, such as cerebrospinal fluid or synovial fluid, a nonselective medium such as chocolate agar is best. Specimens from nonsterile sites such as the cervix, urethra, rectum, or oropharynx, where normal bacterial flora is present, should be inoculated on selective media such as Martin-Lewis agar. If not transported immediately to the laboratory, specimens should be incubated at 35° C to 36.5° C in a carbon dioxide–enriched atmosphere after collection and transported to the laboratory in a carbon dioxide–enriched atmosphere.[23,24]

The NAATs have good sensitivity and excellent specificity for detection of gonorrhea from endocervical, urethral, and urine samples. These tests are approved by the FDA for the detection of *C. trachomatis* and *N. gonorrhoeae* in endocervical swabs from women, urethral swabs from men, and urine from both men and women.[23] Although sensitivities of NAATs are comparable with culture (95 to 99%), selected NAATs may be less sensitive when performed on urine than when performed on endocervical specimens or male urethral swabs. Therefore, in symptomatic patients, NAATs of endocervical swabs from women or urethral swabs from men are good alternatives to gonococcal culture, particularly when appropriate techniques for maximizing organism viability and culture cannot be achieved.[23,24]

Although NAATs are useful for diagnosing cervical and urethral gonorrhea, culture is required for diagnosing organisms from sites such as the oropharynx, synovial fluid, anorectal area, and cerebrospinal fluid. In addition, culture is the diagnostic method of choice when the results will be used as evidence in legal investigations or to determine sensitivity to specific antibiotics.

Treatment

Currently, the CDC recommends only two cephalosporins for first-line single-dose treatment of cervical and urethral gonorrhea (see Table 96-3): ceftriaxone 125 mg IM and cefixime 400 mg PO.[5] Until recently, oral cefixime was in limited supply, but in April 2008, availability of this agent improved as a result of increased production. On account of increasing rates of quinolone resistance, this class of antibiotics is no longer recommended to treat gonorrhea diagnosed in the United States.[25] Because co-infection with *Chlamydia* is so common, treatment for presumptive chlamydial infection also should be provided unless co-infection can be ruled out. Sexual partners need referral for evaluation, testing, and treatment. Patients should be instructed to avoid sexual activity until therapy is completed and until they and their partners are no longer symptomatic. Referral for HIV testing should be offered.

TRICHOMONIASIS

Trichomoniasis is caused by *Trichomonas vaginalis*, a flagellated protozoan. It is the most common nonviral STD in the world. As with other vaginal infections, up to 50% of infected women are asymptomatic. The most common presenting signs and symptoms include dysuria, vulvar irritation or itching, and vaginal discharge, often described as thin, malodorous, and yellow-green (Table 96-4). Affected patients also may report lower abdominal pain or discomfort and dyspareunia. Males are frequently asymptomatic and most often present as partners of infected women. *Trichomonas* has been implicated as a cause of nongonococcal urethritis in men, possibly responsible for up to 20% of cases.[26] Rarely, men report purulent urethral discharge or symptoms consistent with prostatitis or epididymitis.

On physical examination, vaginal discharge is noted in up to 70% of patients, ranging in character from thin and scanty to the classic description of thick, frothy, and yellow. Vaginal pH is above 4.5. Punctate mucosal hemorrhages of the cervix ("strawberry cervix") has been described in 2 to 10% of patients. However, the history and physical examination findings are not sensitive or specific enough to make the diagnosis on clinical grounds alone, and testing is indicated.

The diagnosis most often is made by microscopic examination of a wet mount slide, but this method has a sensitivity of only 60 to 70%; sensitivity varies with the skill and thoroughness of the examiner and is optimized by examination of the slide soon after specimen collection. Culture is more sensitive than wet mount techniques but is not widely performed, and culture results are not available in a timely manner for ED diagnosis and treatment. In men, urine sediment can be examined for trichomonads and also can be sent for culture. PCR assay is an alternate method for diagnosis of trichomoniasis. Several PCR primers have been studied, and each has demonstrated higher sensitivity than wet mount or culture.[27,28] PCR assay also has been found to be highly specific, exceeding 95%. In addition, PCR analysis of specimens obtained from the distal vagina had a higher sensitivity and specificity for diagnosis of trichomoniasis than wet mount or culture of specimens obtained during a speculum examination, suggesting a role for less invasive diagnostic sampling such as use of vaginal introitus swabs.[27,29] PCR testing is now available for combined point-of-care testing for *Trichomonas* along with *Gardnerella vaginalis* and *C. albicans*.[28]

Either of two single-dose treatments is recommended: metronidazole 2 g PO or tinidazole 2 g PO. Alternative therapy is metronidazole 500 mg PO twice daily for 7 days (see Table 96-4). Because these nitroimidazoles can cause a disulfuram-type reaction in persons who subsequently consume alcohol, patients taking these agents should be advised to avoid imbibing for 24 or 72 hours after the last dose of metronidazole or tinidazole, respectively. Topical metronidazole is available but is less efficacious than oral preparations for treatment of trichomoniasis and is not recommended for this use.

Trichomoniasis has been associated with premature rupture of membranes, premature labor, low birth weight, and post-hysterectomy infection. Symptomatic pregnant women should be treated with metronidazole, 500 mg PO bid for 7 days. Metronidazole does not appear to be associated with an increased teratogenic risk during pregnancy.[30,31] Its role in treatment of asymptomatic pregnant women infected with *Trichomonas* is less clear, and routine screening and treatment of asymptomatic women are not recommended.[32]

Sexual partners of patients with *T. vaginalis* should be treated, and patients should be instructed to avoid sexual contact until they and their partners are clinically cured.

CANDIDIASIS

Vulvovaginal candidiasis most often is caused by *Candida albicans* but can be caused by other *Candida* species and other yeasts. It is estimated that 75% of women will have at least one episode of yeast vulvovaginitis in their lifetime, and 40 to 45% will have two or more episodes.

Common presenting signs and symptoms include vulvar itching or soreness, vaginal discharge, dyspareunia, and dysuria. Characteristic examination findings are vulvar erythema, vulvar edema or excoriation, and raised, white adherent vaginal plaques. Satellite lesions also may be seen. Vaginal pH is

Table 96-4 Characteristics of Vulvovaginitis by Cause

ETIOLOGIC DISORDER	PH	DISCHARGE APPEARANCE	WET MOUNT	TREATMENT
Bacterial vaginosis	>4.5	Gray, white, milky/creamy; amine odor present	Clue cells present	Metronidazole, 500 mg PO bid × 7 days *or* clindamycin cream 2% intravaginally qhs × 7 days *or* metronidazole gel 0.75% intravaginally bid × 5 days
Trichomonas infection	>4.5	Gray, yellow, greenish, or white; often frothy; homogeneous	Trichomonads present	Metronidazole 2 g PO × 1 *or* tinidazole 2 g PO × 1 or metronidazole 500 mg PO bid × 7 days
Candida infection	<4.5	White, often curdy	Mycelia present	Fluconazole 150 mg PO × 1 *or* intravaginal agents

normal (less than 4.5) (see Table 96-4). Because none of these symptoms or signs is specific for candidiasis and the history and examination findings are relatively unreliable,[33] diagnostic testing is indicated.

Diagnosis typically is based on wet-mount microscopy using potassium hydroxide (KOH) preparation or Gram's stain demonstrating yeast or pseudohyphae. The sensitivity of these tests ranges from 40 to 70%. Culture is considered the "gold standard" diagnostic modality but is rarely performed, and 10 to 20% of asymptomatic women harbor *Candida* organisms and other yeasts in the vagina. Latex agglutination tests also are available for point-of-care testing and may offer benefit over microscopy.

Multiple short-course topical preparations are available for treatment and effect an 80 to 95% cure rate in patients who complete therapy (see Table 96-4 for recommended regimens), and many are available over the counter. Self-medication with over-the-counter preparations should be advised only for women who have been diagnosed previously with vulvovaginal candidiasis and experience recurrence of the same symptoms. Unnecessary or inappropriate use of over-the-counter preparations is common, can lead to contact or irritant vulvar dermatitis, and may delay treatment for other causes of vulvovaginitis. In addition, patients should be counseled that vaginal preparations are oil-based, which may weaken latex condoms and diaphragms. Fluconazole, 150 mg in a single dose, is the only oral agent that is approved by the FDA for the treatment of candidiasis.

Candidal infections can be divided into complicated and uncomplicated types. *Uncomplicated* vaginitis is seen in 90% of patients. It is characterized by sporadic or infrequent episodes with mild to moderate symptoms due to *C. albicans* in a normal host. It responds readily to short-course treatments. *Complicated* infections, associated with severe or recurrent symptoms (four or more episodes of vulvovaginal candidiasis each year), tend to occur in patients with complicating medical problems (e.g., immunosuppression, poorly controlled diabetes mellitus) and require longer courses of treatment (e.g., 7 to 14 days of topical therapy or a 150-mg oral dose of fluconazole given in three doses on days 1, 4, and 7).[25,34] Vulvovaginal candidiasis in HIV-positive patients is not considered complicated and should be treated as for uncomplicated vulvovaginal candidiasis.

Vulvovaginal candidiasis occurs frequently during pregnancy and may be more difficult to cure. Only topical azole therapies, applied for 7 days, are recommended for use during pregnancy; fluconazole is contraindicated.

Evidence to support treatment of asymptomatic sexual partners is lacking. In addition, no direct association has been found between yeast infection and other STDs, and no difference in yeast isolation rates has been observed in patients who have an STD and in those who do not.

BACTERIAL VAGINOSIS

Bacterial vaginosis occurs owing to a shift in bacterial flora in the vagina, with replacement of the normal H_2O_2-producing *Lactobacillus* species with high concentrations of a polymicrobial group, including anaerobic bacteria (*Prevotella*, *Mobiluncus*, and *Bacteroides* species), *G. vaginalis*, and *Mycoplasma hominis*, and an attendant increase in the vaginal pH from 4.5 to as high as 7.0. Bacterial vaginosis is the most common cause of vaginal discharge and malodor (see Table 96-4). However, up to 50% of women with bacterial vaginosis are asymptomatic.

The most common manifestation is vaginal discharge, often with an offensive vaginal odor, which may be accentuated after coitus (the alkaline pH of semen induces a fishy odor, recognition of which constitutes a physiologic "whiff test"). Vaginal pruritus and irritation are not common complaints. On examination, a thin, white, homogeneous discharge is present.

Diagnosis can be made using the Amsel criteria (see Table 96-4).[35] Three of the four criteria must be present for diagnosis:

1. A thin, white homogeneous discharge.
2. Presence of clue cells in microscopic examination. True clue cells are epithelial cells that are so heavily stippled with bacteria that the cell borders are obscured. Epithelial cells with few bacteria do not classify as clue cells.
3. pH of vaginal fluid greater than 4.5.
4. A fishy odor to the vaginal discharge before or after the addition of 10% KOH ("whiff test").

Diagnosis also can be made with Gram's staining to determine the relative concentrations of bacterial morphotypes (Nugent criteria). Culture isolation of *G. vaginalis* is not useful, because this organism can be cultured from vaginal specimens in more than 50% of healthy women and is therefore not specific. Other diagnostic modalities include a DNA probe–based test (Affirm VP III) and card tests, which detect elevated pH as well as the presence of elevated amine concentration (FemExam test) or proline aminopeptidase (Pip Activity TestCard). The card tests indicate the presence of two of the four criteria recommended for diagnosis by the CDC, so correlation of results with microscopy or appropriate examination findings is necessary; such tests are not used in isolation to make the diagnosis.

All women who have symptomatic disease require treatment. Bacterial vaginosis is associated with an increased risk of acute upper genital tract infection by the various organisms recognized as likely pathogens in such infections.[36] It is not known whether treatment of bacterial vaginosis reduces the risk of ascending infection, so screening for and treatment of bacterial vaginosis in asymptomatic women are not recommended at this time. Bacterial vaginosis also has been associated with endometritis and PID and with vaginal cuff cellulitis after invasive procedures, including endometrial biopsy, hysterectomy, and placement of an intrauterine device. The latter association suggests some role for preprocedural prophylaxis in certain patients. Recommended treatment regimens for bacterial vaginosis include metronidazole 500 mg PO twice a day for 7 days, metronidazole gel 0.75% 5 g intravaginally every day for 5 days, and clindamycin cream 2%, 5 g intravaginally at bedtime for 7 days. The vaginal cream may be less efficacious than oral metronidazole. Alternative regimens include clindamycin 300 mg PO twice a day for 7 days and clindamycin ovules 100 mg administered intravaginally once at bedtime for 3 days. Of note, alternative regimens have lower efficacy for treatment of bacterial vaginosis. Patients should be advised to avoid alcohol for up to several days after treatment with metronidazole. Treatment of sexual partners does not affect response to therapy or recurrence rates in clinical trials and is therefore not recommended.[37]

Bacterial vaginosis during pregnancy is associated with premature rupture of membranes and preterm labor, preterm birth, and postpartum endometritis. Studies have not demonstrated a benefit of treatment for asymptomatic pregnant patients; however, in women with a previous preterm birth or those who are at high risk for preterm birth, treatment with metronidazole has been shown to reduce the risk of spontaneous preterm birth.[38,39] Treatment of asymptomatic bacterial vaginosis in pregnant women does not reduce the occurrence of preterm delivery. Recommended treatment regimens in

pregnancy include metronidazole 500 mg orally twice a day for 7 days, metronidazole 250 mg PO three times a day for 7 days, and clindamycin 300 mg PO twice a day for 7 days. Topical agents are not recommended for use during pregnancy.[5] Metronidazole use during pregnancy has no demonstrated association with teratogenic or mutagenic effects in newborns.

OTHER CAUSES OF GENITAL DISCOMFORT

Many other conditions manifest with vulvovaginal itching or discharge. Considerations in the differential diagnosis include the sexually transmitted and vaginal infections discussed previously, as well as allergic or chemical vaginitis, atrophic vaginitis, scabies, pediculosis pubis (genital lice), and vaginal foreign bodies.

Chemical vaginitis most commonly is associated with the use of douches, scented soaps, or feminine hygiene products. In addition, some women with a latex allergy may present with vaginal itching and discomfort after intercourse with a partner who uses latex condoms. Diagnosis is by history, and discontinuing use of the offending agent usually is sufficient treatment.

Atrophic vaginitis occurs when levels of circulating estrogens decrease after menopause. Patients may report increased vaginal itching, vulvar discomfort, and dyspareunia. Other sources of discomfort, such as *Candida* infection, must be ruled out, because relative lack of estrogen predisposes affected women to vaginal and vulvar infections. Treatment typically consists of topical estrogen creams.

The mite *Sarcoptes scabiei* causes scabies infestation, and any part of the body may be affected. Transmission is by skin contact. The main symptom is pruritus, which is caused by a hypersensitivity reaction to mite excrement. The diagnosis is made clinically by identification of characteristic silvery lines seen in the skin where the mites have burrowed. Papules or nodules also may be noted, especially in the genital area. Scrapings viewed under the light microscope contain mites, confirming the diagnosis. The CDC-recommended treatment is permethrin 5% cream, applied to the whole body from the neck down and washed off after 8 to 14 hours; or ivermectin, 200 μg/kg orally, repeated in 2 weeks. Treatment should be repeated in 1 week. An alternative regimen is lindane 1%, 1 ounce of lotion or 30 g of cream applied in a thin layer to all areas of the body from the neck down and washed off after 8 hours. Lindane should not be used on infants or during pregnancy. Antihistamines and topical creams may give symptomatic relief. Potentially contaminated clothes and bedding should be washed at high temperature or not used for 72 hours (mites die when separated from the human host for 72 hours). Sexual and household contacts should be treated.

Phthirus pubis is a crab louse transmitted by close body contact. Adult lice infest pubic hair, body hair, and occasionally the eyebrows and eyelashes. Eggs (nits) adhere to the hairs. The main symptom is pruritus due to hypersensitivity reaction to the feeding lice. Diagnosis is based on finding adult lice or eggs. A number of treatments are available. Lotions probably are more effective than shampoos and should be applied to all body hair. The primary CDC-recommended treatment is permethrin 1% cream rinse applied to affected areas and washed off after 10 minutes. Alternative regimens are malathion 0.5% lotion, applied for 8 to 12 hours and then washed off, and ivermectin 200 μg/kg orally, repeated in 2 weeks. Sexual partners should be treated, and patients should be screened for other STDs. Potentially contaminated clothes and bedding should be washed at high temperature.

PELVIC INFLAMMATORY DISEASE

Perspective

PID comprises a spectrum of disorders of the female upper genital tract, including any combination of endometritis, salpingitis, peritonitis, and tubo-ovarian abscess. Approximately 750,000 cases of PID are diagnosed annually in the United States.[40] The serious complications of PID (infertility, ectopic pregnancy, and chronic pelvic pain) account for a significant proportion of non-HIV STD-related morbidity in the United States and afflict approximately 25% of diagnosed patients.[40] PID is reported to be the most common serious infection in women of reproductive age and causes approximately 30% of infertility cases, 50% of ectopic pregnancies, and many cases of chronic pelvic pain.[41]

Principles of Disease

PID is an ascending infection, with the infecting microorganisms spreading from the cervix and vagina to the upper portions of the female genital tract. Although the most commonly implicated organisms are *C. trachomatis* and *N. gonorrhoeae*, the cause of PID often is polymicrobial, and various microorganisms have been recovered in patients with acute PID, including genital mycoplasmas and anaerobic and aerobic bacteria from endogenous vaginal flora such as *Prevotella* species, peptostreptococci, *G. vaginalis*, *E. coli*, *H. influenzae*, and aerobic streptococci. Although organisms that are associated with sexual transmission are those most commonly found with PID, this infection can be caused by nonsexually acquired organisms. Patients diagnosed with PID should be counseled that the infection can be acquired nonsexually and that the diagnosis does not imply that either sexual partner may have had sexual encounters outside the relationship.

Risk factors for the development of PID include young age, multiple sexual partners, cigarette smoking, and menses. Intrauterine contraceptive devices (IUDs) have previously been implicated as a major risk factor for PID; however, IUDs increase the risk of PID only in the first month after insertion. It should be noted that nearly half of patients with PID do not have identifiable risk factors; a lack of risk factors does not rule out the infection.

Clinical Features

Owing to the wide variety of presenting signs and symptoms, acute PID is challenging to diagnose. The most common presenting symptom is lower abdominal pain. Other common signs and symptoms include dyspareunia, abnormal bleeding, and abnormal cervical or vaginal discharge. Physical examination may reveal lower abdominal tenderness, cervical motion or adnexal tenderness (unilateral or bilateral) on bimanual palpation, and fever with temperatures higher than 38° C.[5]

Studies show that many women with PID demonstrate mild, vague, or subtle symptoms, often not recognized as manifestations of PID. Unrecognized PID probably is as common as, if not more common than, clinically apparent disease, and it is estimated that up to two thirds of cases go unrecognized. *Silent* or *atypical PID* is a term that has been used to describe the underlying disorder in women with documented tubal infertility who have no history of being diagnosed with PID despite confirmed chronic inflammatory residua. Unrecognized or atypical PID usually is characterized by abdominal pain, abnormal uterine bleeding, and mucopurulent endocervical discharge; fever may not be present in these patients.

Patients also can present with right upper quadrant pain and tenderness, which may be preceded or accompanied by the

signs and symptoms of PID. This syndrome, known as *perihepatitis* or Fitz-Hugh–Curtis syndrome, has been associated with both gonococcal and chlamydial salpingitis. Transaminases and gallbladder ultrasound findings will be normal. Fitz-Hugh–Curtis syndrome may develop in up to 10% of patients with PID, depending on the organisms implicated as the cause.[42]

Unfortunately, the clinical examination has low sensitivity for the diagnosis of PID. One study comparing clinical diagnosis with laparoscopic findings showed that the clinical diagnosis of PID is no more accurate than chance when compared with biopsy-confirmed diagnosis.[43,44] Laparoscopic studies support these findings, with sensitivity rates for clinical examination ranging from 50% to 75%.[41,44] No single historical, physical, or laboratory finding is adequately sensitive or specific to permit a definitive diagnosis of PID. Because of the difficulty in making the diagnosis and the serious long-term sequelae of PID, current recommendations call for increased readiness to consider this clinical entity and to institute appropriate treatment in patients with suspected PID.

The CDC recommends empirical treatment for PID in sexually active young women experiencing pelvic or lower abdominal pain if any one of the following minimum criteria is present without other identifiable causes:

- Cervical motion tenderness *or*
- Adnexal tenderness *or*
- Uterine tenderness

Controversy also surrounds what constitutes cervical motion tenderness. Although the traditional "chandelier sign" (pain so severe the patient ends up swinging from a chandelier) of severe tenderness has been taught as the criterion standard, studies indicate that the patient herself should be questioned about her degree of pain. If it is more than the usual discomfort experienced by the patient during a pelvic examination, this should be considered positive evidence for cervical motion tenderness.

Other criteria that support but are not necessary for the diagnosis of PID include the following:

- Oral temperature greater than 101° F (38.3° C)
- Abnormal cervical or vaginal mucopurulent discharge
- Presence of WBCs on wet mount preparations of vaginal secretions
- Elevated erythrocyte sedimentation rate
- Elevated C-reactive protein level
- Laboratory documentation of cervical infection with *N. gonorrhoeae* or *Chlamydia*

When more criteria for diagnosis are met, the specificity increases but the sensitivity decreases. The absence of WBCs on wet mount preparations makes the diagnosis of PID unlikely; in such cases, other causes of abdominal pain should be sought. Ultrasonography also may be useful in the diagnosis of PID, especially in identifying tubo-ovarian abscess or pyosalpinx. If the diagnosis is unclear, particularly in patients who present with fever and peritoneal signs, further testing is indicated. In these cases, computed tomography may rule out other causes of peritoneal clinical findings, such as appendicitis or diverticulitis, and in some cases, laparoscopy may be necessary to determine the cause of the patient's illness.

Differential Diagnosis

The differential diagnosis of lower abdominal pain in young women is broad in scope. Other common diagnostic considerations include ectopic pregnancy, acute appendicitis, endometriosis, ovarian cysts, and functional abdominal pain.

Management

The goal of treatment in PID is to prevent the chronic sequelae of infection. Treatment regimens must provide broad-spectrum coverage of likely pathogens, including *N. gonorrhoeae*, *Chlamydia*, anaerobes, gram-negative bacteria, and streptococci. Although endocervical testing is recommended in these patients, negative results do not preclude upper tract infection. Delaying treatment may increase the risk of developing long-term sequelae.

No studies have clearly demonstrated differences in efficacy of parenteral versus oral therapy, or of inpatient versus outpatient treatment. The decision to hospitalize a patient must be based on the clinical presentation and other comorbid or complicating factors. The CDC suggests that any of the following criteria constitutes grounds for hospitalization:

- Surgical emergencies such as appendicitis cannot be excluded.
- The patient is pregnant.
- The patient does not respond clinically to oral antimicrobial therapy.
- The patient is unable to follow or tolerate outpatient oral regimens.
- The patient has a severe illness, nausea and vomiting, or high fever.
- The patient has a tubo-ovarian abscess.

It also has been recommended that patients with an intrauterine device be treated on an inpatient basis, on account of the high rate of adnexal inflammatory masses in this group.

Parenteral and oral regimens are listed in Table 96-5. If outpatient treatment is chosen, patients must be reevaluated within 24 to 48 hours to assess response to oral therapy. If there

Table 96-5 Treatment for Pelvic Inflammatory Disease

REGIMEN A	REGIMEN B
Inpatient	
Cefoxitin 2 g IV q6h *or* Cefotetan 2 g IV q12h *plus* Doxycycline 100 mg PO or IV q12h	Clindamycin 900 mg IV q8h *plus* Gentamicin 2 mg/kg IV or IM load, *then* 1.5 mg/kg IV or IM q8h
Continue until at least 48 hours after improvement	Continue until at least 48 hours after improvement
Continue doxycycline 100 mg PO bid for 10–14 days total	Continue doxycycline 100 mg PO bid for 10–14 days total Continue clindamycin 450 mg PO q6h or change to doxycycline
Outpatient	
Ceftriaxone 250 mg IM once *plus* Doxycycline 100 mg PO bid × 14 days *with or without* Metronidazole 500 mg PO bid × 14 days	Cefoxitin 2 g IM *plus* Probenecid 1 g PO once *plus* Doxycycline 100 mg PO bid × 14 days *with or without* Metronidazole 500 mg PO bid × 14 days

is no response, the patient should be hospitalized for parenteral antibiotic therapy and confirmation of the diagnosis.

Patients should demonstrate significant clinical improvement, such as defervescence, decreased abdominal tenderness, and reduction in uterine, adnexal, and cervical motion tenderness, within 3 days of initiation of therapy. Sexual partners of patients diagnosed with PID should be evaluated and empirically treated for gonorrhea and chlamydial infection. Patients should be counseled to avoid sexual activity until both they and their partners have completed treatment. It is recommended by some specialists that patients with documented gonorrhea and chlamydial infection be reevaluated for test of cure in 4 to 6 weeks after completion of therapy, although this practice is not universal.

KEY CONCEPTS

- Patients with ulcerative genital lesions should be considered to have an STD and should be tested and treated accordingly.
- Patients with suspected gonorrheal infection also should be treated for chlamydial infection.
- Sexually active women with adnexal or cervical motion tenderness should be treated for PID.
- A single dose of azithromycin is inadequate to treat PID; patients require a 2-week course.
- Asymptomatic women with clue cells on wet mount preparations should not be treated for bacterial vaginosis.
- Pregnant women with bacterial vaginosis should not be treated if they are asymptomatic unless they are at risk for preterm labor or premature birth (i.e., if they have a history of preterm labor, miscarriage, or premature rupture of membranes).
- Patients with sexually transmitted infections are at risk for HIV infection and should be either tested in the ED or referred for HIV testing.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 97 Selected Urologic Problems

Kevin M. Ban and Joshua S. Easter

URINARY TRACT INFECTIONS

Perspective

Background. *Urinary tract infection* (UTI) describes an inflammatory response of urothelium to microorganisms in the urinary tract, resulting in clinical symptoms including dysuria, frequency, urgency, hematuria, and suprapubic or costovertebral angle discomfort self-reported by patient or later illicited on physical exam. This term does not differentiate between upper and lower tract infections. Traditionally, the emphasis has been on distinguishing lower tract from upper tract infections. Although this distinction may seem sensible from an anatomic perspective, it often does not provide additional information for making important management and disposition decisions. *Bacteriuria* is the presence of bacteria in the urine but is not considered to represent a UTI in the absence of clinical manifestations. Bacteriuria accompanied by symptoms should be treated, whereas bacteriuria in the absence of symptoms should be treated only in select patients (e.g., pregnant women).

It is more useful to designate UTIs as either being uncomplicated or complicated, rather than as lower or upper tract infections. An *uncomplicated* infection is one involving a structurally and functionally normal urinary tract. The causative pathogen generally can be eradicated with a short course of standard antibiotics.[1] This type of infection usually occurs in nonpregnant, sexually active, young women who have no evidence of an obstructive process. *Complicated* infection is that associated with underlying neurologic, structural, or medical problems, all of which may reduce the efficacy of standard antimicrobial therapy. These types of infections often require a prolonged course of antibiotic therapy and a more in-depth approach to testing and anatomic evaluation.

Urethritis refers to the inflammation of the urethra secondary to either an infection or trauma. Frequently, urethritis may be a manifestation of a sexually transmitted disease (STD), such as gonococcal urethritis in *Neisseria gonorrhoeae* infection, but may occur in other clinical scenarios as well. *Cystitis* generally refers to inflammation of the bladder resulting in increased urinary frequency, urgency, dysuria, and suprapubic pain. Cystitis can be separated into bacterial and nonbacterial (e.g., radiation, trauma) etiologic categories. *Acute pyelonephritis* is a UTI of the renal parenchyma and collecting system manifested by the clinical syndrome of fever, chills, and flank pain. Management and disposition of patients with acute pyelonephritis depend on whether the infection is simple or complicated.

Epidemiology. UTI is a problem that affects all age groups.[2-5] It is considered the most frequently occurring bacterial infection, accounting for 7 to 8 million annual outpatient visits, 1 million annual emergency department visits, 100,000 annual hospitalizations, and more than one third of all hospital-acquired infections.[1,6,7] These statistics notwithstanding, gauging the actual extent of the disorder is very difficult because it is not a reportable disease in the United States and the definition of a UTI is not exact.

Women have a 20% chance of experiencing a UTI during their lifetime. The prevalence of UTIs is 2 to 4% among young, sexually active women and gradually increases to 5 to 10% by the age of 70 years and to approximately 20% by the age of 80 years.

UTIs account for 5 to 14% of pediatric ED visits in the United States.[8] UTI is more common in boys during the neonatal period but becomes more common in girls during infancy and thereafter.[9,10] When a UTI is seen in preschool boys, it is almost always associated with congenital anomalies of the urinary tract.

UTIs in adult men are uncommon unless cystoscopy or catheterization has been performed. The prevalence is less than 1% from childhood through middle age but increases to 1 to 3% by the age of 65 years and to 10% by the age of 80 years. Among institutionalized men and women, prevalence rates for bacteriuria and UTI are increased to approximately 25% and 40%, respectively.[10] UTIs associated with presence of an indwelling catheter constitute the most common nosocomial infection in the United States, accounting for more than 1 million cases annually.[11]

Principles of Disease

Physiology. The urine is sterile along the entire urinary tract from the glomerulus to the external sphincter in men and to the bladder neck in women. The urinary tract maintains its sterility by means of various defenses.[6] A major mechanism is complete emptying. Free, unobstructed flow of urine within the kidney and down the ureter, coupled with complete evacuation of the bladder, is essential. Abnormal anatomy or physiology or the presence of a foreign body may compromise host defense mechanisms and predispose the patient to infection.[6]

In men, the distal end of the urethra is inhabited by staphylococci, streptococci, and diphtheroid organisms. Nevertheless, men generally do not become infected without an underlying obstruction of normal urinary flow.

In women, the urethra is short and opens close to the vulvar and perirectal areas. The organisms that cause UTI in women usually arise from the fecal reservoir and initially colonize the vaginal introitus and periurethral area. These factors contribute in part to the much higher incidence of UTI in women.

Pathophysiology. Bacteria most often enter the urinary tract by ascent through the urethra and into the collecting system. Infrequently, bacterial infection of the urinary tract arises from hematogenous or lymphatic sources. This is the usual pathomechanism in debilitated and chronically ill patients who are immunosuppressed. Organisms from distal foci of infection like endocarditis or soft tissue sources may make their way through lymphatic or hematogenous channels, resulting in a UTI. In these patients, it is important to identify and treat the primary source of infection.

Numerous abnormalities of the urinary tract interfere with its innate ability to resist infection. Obstruction from any cause, with resultant stasis of urine, is the major etiologic factor. Any obstruction or impediment to the free flow of urine or complete bladder emptying results in an increased incidence of infection. Urinary calculi may cause obstruction and increased susceptibility to the development of UTI. It is crucial that infection in the setting of obstruction be diagnosed and relieved promptly.

Vesicoureteral reflux in children plays an important role in the pathogenesis of UTIs, particularly upper tract infections. Reflux caused by congenital abnormalities or by bladder overdistention (as seen in advanced prostatic hypertrophy) also predisposes affected patients to infection. Subgroups of patients who are more susceptible than the normal population to UTIs include diabetic patients, pregnant women, the elderly, patients with spinal cord injury and indwelling urinary catheters, patients with multiple sclerosis, and those with acquired immunodeficiency syndrome (AIDS) or human immunodeficiency virus (HIV) infection.[6]

In young men, asymptomatic bacteriuria is rare and may signify urinary tract disease. UTIs in men generally begin to appear at 50 years of age (concomitant with the onset of prostatic hypertrophy) and slowly increase in incidence.[12] The occurrence of UTI in men of any age warrants referral to a urologist for further evaluation.

Bacteriology. The organisms that cause UTIs generally come from enteric flora colonizing the patient's perineum and urethra. *Escherichia coli* is the dominant pathogen in more than 80% of first infections in women, men, and children, as well as in 50% of nosocomial UTIs. *Staphylococcus saprophyticus*, a coagulase-negative gram-positive organism, is the second most common pathogen in UTI and accounts for approximately 11% of cases.[6,13] This species is present in normal skin flora, including the perineal area, but only in low numbers, and it does not appear to be of fecal origin. Occasionally it is falsely identified as *Staphylococcus albus* or *Staphylococcus epidermidis*. Other, less common bacteria that may be responsible for infection include *Proteus*, *Klebsiella*, and *Enterobacter*. Unusual microorganisms may be found in institutionalized or hospitalized populations and with complicated UTIs. Such settings and conditions predispose the patient to alterations in the normal gastrointestinal flora, leading to complex UTIs. The uropathogens in these patients include more resistant strains of *Escherichia*, *Klebsiella*, *Proteus*, and *Enterobacter*, as well as *Pseudomonas*, *Enterococcus*, *Staphylococcus*, *Providencia*, *Serratia*, *Morganella*, *Citrobacter*, *Salmonella*, *Shigella*, *Haemophilus*, *Mycobacterium tuberculosis*, and fungi. Although not necessary with uncomplicated UTIs, urine culture and sensitivity testing are recommended for all patients with complicated UTIs. Antibiotic therapy based on the most likely pathogen should be initiated immediately.

Uropathogenic organisms may elaborate various factors that affect their virulence, including aerobactin, hemolysins, and fimbriae (pili). Fimbriae, also called adhesions, are proteinaceous structures that can attach to specialized receptor sites on host cells. Attachment of bacteria to vaginal and uroepithelial cells ultimately leads to a higher incidence of UTI.[14]

Clinical Features

Signs and Symptoms. UTI is suspected in adolescents and adults on the basis of clinical findings including dysuria, frequency, urgency, and hematuria in the setting of suprapubic or CVA discomfort. Symptoms and signs will vary with age. In infants, initial manifestations may include irritability, fever, vomiting, diarrhea, and failure to thrive. Preschool children with UTI have vomiting, diarrhea, generalized abdominal pain, and febrile seizures. History of fever alone is not an adequate indicator of severity of infection in children because it may be historically absent in pediatric patients subsequently found to have significant renal scarring.[15]

In general, clinical signs and symptoms associated with *lower* UTIs are localized to the genitourinary system and include urgency, dysuria, frequency, and suprapubic pain. In addition to these problems, a patient with an *upper* UTI may have back and flank pain as well as constitutional symptoms and signs such as fever, nausea, vomiting, and malaise.

Clinical findings do not reliably differentiate between upper and lower tract infections. Stamm and coauthors report that 30 to 50% of women with signs and symptoms restricted to the lower urinary tract have silent (or subclinical) infection of the kidney.[16]

As discussed previously, it is more important to determine if the infection is simple or complex. Simple, uncomplicated infections do not require urine culture, may be treated on an outpatient basis, and may not always necessiate urinalysis when thought to represent isolated cystitis.[17] Complicated infections require urine culture with antibiotic sensitivity and also may necessitate inpatient therapy or further diagnostic evaluation, or both.[18] Distinction between upper and lower tract infections becomes important for understanding the differences in pathology and the pharmacokinetics of antibiotic delivery. Infection of the bladder generally involves only the superficial mucosa, and high urinary concentrations of antibiotics can easily be achieved with a short course of antibiotic therapy. The kidney, by contrast, tends to become infected in the medullary tissue, where achieving therapeutic concentrations of antimicrobial agents is far more difficult. As a result, parenteral antibiotics and longer courses of therapy are needed.

Men who complain of dysuria must be evaluated for the presence of urethral discharge before urinalysis is performed. In these patients, in whom the diagnosis of UTI is rare, the most likely etiologic disorder is an STD such as gonococcal or nongonococcal urethritis. If the patient has purulent urethral discharge, he should undergo testing for *Chlamydia trachomatis*, *N. gonorrhoeae*, and syphilis, as well as empirical treatment for STDs. If the patient does not have urethral discharge and complains predominantly of dysuria, frequency, urgency, and suprapubic or CVA discomfort, a urinalysis with culture should be performed. Male patients who have bacteriuria in the absence of clinical signs of urethritis or prostatitis should be considered to have a complicated UTI and should be treated with antibiotic therapy and receive urologic follow-up for further evaluation.

Diagnostic Strategies

Laboratory Tests

Urine Collection Methods. The diagnostic value of microscopic examination depends on the quality of the specimen obtained. In neonates, suprapubic aspiration is a safe procedure for obtaining a urine specimen, but it is invasive. In neonates and children younger than 6 months, urethral catheterization is more often successful and, like suprapubic aspiration, carries a very low complication rate. Before catheterization is attempted in these younger patients, the ultrasound or bladder scanner can be used to confirm the presence of urine in the bladder. Collection of urine in a perineal "bag" is the least invasive method but is useful only if culture results are negative, because of high associated contamination rates.

In older children, a sterile midstream urine sample can be collected from boys. In girls, if the voided specimen is free of cellular elements (epithelial cells), it is acceptable for analysis. Catheterization often is a traumatic experience for children and one that invades their sense of privacy. An alternative approach to catheterization in a young girl with classic symptoms of UTI who has epithelial cells in the urine suggesting contamination is to evaluate the urine for other signs of infection. If the urine contains bacteria and red and white blood cells and is either nitrite- or leukocyte esterase–positive, the most likely cause of the symptoms is an uncomplicated UTI, for which antibiotic therapy and referral for follow-up care with the child's pediatrician are indicated. If the clinical picture remains unclear and a definitive diagnosis is mandatory, straight catheterization is performed after examination of the child's bladder with an ED ultrasound machine has confirmed the presence of urine.

Recommendations regarding urine collection methods in women vary widely. Midstream-voided specimens rarely escape perineal contamination, because for most adult women, adequate preparatory self-cleansing of the perineal area is difficult to achieve. It has been shown that in up to 50% of women with sterile bladder urine, a midstream clean-catch specimen grows 1000 to 100,000 bacterial colony-forming units (CFUs) per milliliter. This finding assumes major significance in the ED evaluation, in which accurate, initial supportive evidence for the diagnosis of UTI is crucial.

Sterile catheterization is the quickest and most accurate method of obtaining a urine specimen from an adult woman and may be the best solution for achieving a reliable urinalysis if the patient is actively menstruating. It is safe and relatively atraumatic and carries a remarkably low risk of infection. This risk increases if the patient is pregnant, elderly, or debilitated. If the clinician decides against catheterization, a clean-catch, midstream urine specimen should be sought. A predominance of epithelial cells suggests that the specimen is contaminated. The lower the ratio of leukocytes to vaginal epithelial cells, the more likely it is that the leukocytes are vaginal contaminants.

In men, the specimen is not affected significantly by lack of cleansing or by the timing of specimen collection. Therefore, it is not appropriate to catheterize an adolescent or adult man simply for the purpose of collecting a urine specimen.

Urinalysis. Urine cultures constitute a majority of cultures performed by microbiology laboratories, and various screening tests have been developed for the purpose of reducing this burden and its attendant costs. The goal of urine screening tests is reliable selection of specimens that will provide negative cultures. This allows the laboratory to focus more appropriately on on higher-yield studies.

The most commonly used screening tests measure urinary leukocyte esterase and nitrite. Leukocyte esterase is an enzyme found in neutrophils, and nitrite is produced from urinary nitrate by nitrate reductase, which is present in gram-negative bacteria. Both can be detected by a color change on dipstick testing. The two tests often are combined to improve overall accuracy. Indirect urine dipstick tests for pyuria or bacteriuria are inexpensive and easy to perform and may aid in establishing the diagnosis of UTI. They should be used with caution, however, because they can be less sensitive than microscopic examination of urine (urinalysis). Urine dipstick testing for leukocyte esterase has shown a sensitivity of 75 to 96% in detecting pyuria associated with UTI. By contrast, a meta-analysis of screening tests for UTI in children has demonstrated that dipstick testing for leukocyte esterase and nitrite may be equivalent to microscopic urinalysis for detection of UTI.[19]

Symptomatic patients who have normal host defenses and demonstrate a positive result on leukocyte esterase testing (in the absence of other indications for urine culture) can be treated empirically without culture. In symptomatic patients, a negative result on tests for both leukocyte esterase and nitrite should be followed by urine microscopy. In adults, urine culture should be performed only if findings on the microscopic analysis also are negative or if the patient is at risk for bacteremia.

Urine Microscopy. Urine microscopy is another commonly used method of providing rapid results, thereby reducing the number of urine cultures performed. Up to 96% of infected urine specimens contain 10 or more white blood cells (WBCs) per cubic millimeter when counted by a hemocytometer. Various counting chamber methods detect pyuria with an accuracy approaching that of the hemocytometer. Unfortunately, these tests are not widely available, so direct microscopy commonly is used.

The accuracy of direct microscopy is compromised by a lack of standardization of the technique. Common sources of variability include specimen collection and transport, centrifugation speed and duration, decanting and resuspension techniques, staining, and the threshold used for significant numbers of WBCs or bacteria. One method, the slide centrifuge test, avoids many of these sources of error, and high sensitivity and specificity have been reported.

Although no accepted level of pyuria is diagnostic of UTI, on careful quantitation using a hemocytometer chamber, pyuria will be found in nearly all cases of acute UTI caused by coliforms. In patients with a low-count coliform infection, those with fewer than 8 WBCs/mm^3 of urine will have no demonstrable infection. In patients with more than 8 WBCs/mm^3, 85% will have documented infection (by the presence of coliforms, staphylococci, or chlamydiae). Despite these controversies and limitations, microscopic examination of urine to identify bacteria remains the most readily available and reliable test for a presumptive diagnosis of UTI in most patient populations. Any analysis of a urine sample must be performed immediately after collection. Urine specimens that are allowed to sit become alkaline, with subsequent dissolution of the cellular elements and multiplication of bacteria, thus providing the clinician with markedly unreliable results.

Urine Culture. Definitive diagnosis of UTI is based on isolation of significant numbers of bacteria on urine culture. Traditionally, growth of 10^5 CFUs/mL has been used as the statistically significant number for the presence of UTI. Of note, however, using an absolute number is fraught with limitations. The presence of 105 CFUs/mL of bacteria in cultures from urine is associated with a 95% likelihood of infection, whereas 10^4 CFUs/mL is associated with a 50% likelihood of infection.[20] It makes best clinical sense to put these results in clinical context regarding the presence of symptoms suggestive of a UTI. The

BOX 97-1 PATIENT GROUPS IN WHICH URINE CULTURE IS INDICATED

- Children
- Adult men
- Immunocompromised patients
- Patients with "treatment failure" (i.e., with persistent urinary symptoms despite recently completed course of antibiotics)
- Patients with duration of symptoms more than 4 to 6 days
- Elderly patients at risk for bacteremia
- Ill-appearing patients with signs and symptoms suggestive of pyelonephritis or bacteremia
- Pregnant women
- Patients with known chronic or recurrent renal infection
- Patients with known anatomic urologic abnormalities
- Patients in whom urinary tract obstruction is suspected (e.g., stones, benign prostatic hypertrophy)
- Patients with serious medical diseases, including diabetes mellitus, sickle cell anemia, cancer, and other debilitating diseases
- Patients with alcoholism or drug dependence
- Recently hospitalized patients
- Patients taking antibiotics
- Patients who recently have undergone urinary tract instrumentation (e.g., cystoscopy, catheterization)

symptom complex of dysuria, frequency, urgency, and suprapubic pain may be caused by a wide variety of infectious organisms in numbers far less than the traditional 10^5 CFUs/mL. In addition, these same symptoms may represent a significant upper tract infection or may be caused by urethritis.

The presence of bacteria on culture in the absence of clinical manifestations does not always indicate infection. Women often carry large numbers of pathogenic bacteria on the perineum, and uncircumcised men may harbor large quantities of uropathogenic bacteria on the foreskin. The presence of bacteria in these regions may contaminate otherwise sterile bladder urine during collection.

The decision to perform a urine culture should be assessed for its relevance to patient care. Patients with frequency, dysuria, urgency, and suprapubic pain should be treated on the basis of symptoms only if the infection is thought to be simple. For women who have host factors (e.g., structural abnormalities) or comorbid conditions (e.g., compromised immune status, pregnancy) necessitating definitive identification of the organism by culture, both urinalysis and culture are necessary. In general, the list of indications for urine culture (Box 97-1) define high-risk groups. In vitro sensitivity testing contributes little to the general management of patients with uncomplicated UTI. Correlation between the therapeutic response and in vitro testing results often is poor. Culture also represents an additional cost with minimal contribution to the therapeutic plan for most outpatients.

Imaging. A majority of patients with acute cystitis or pyelonephritis do not need emergency imaging of the urinary tract. In certain clinical settings, however, emergency imaging is indicated. Patients with either unusually severe signs and symptoms or an atypical clinical presentation are candidates for genitourinary imaging. For example, a patient with the classic signs and symptoms of pyelonephritis but unremarkable urinalysis findings may have an obstructive process that has prevented the leukocytes and bacteria from reaching the bladder. Another example is that of a patient with a known history of UTI, currently receiving antibiotic therapy, who has persistent fever, chills, and general toxicity. Perhaps one of the most sensitive predictors of a complicated infection (e.g., abscess) is the persistence of fever beyond 72 hours after the institution of antimicrobial therapy. Pyelonephritis with obstruction from any cause can rapidly lead to abscess formation with resultant deterioration of renal function and sepsis. Emergency imaging is indicated to rule out this condition or to identify a suspected renal stone serving as a nidus for infection.

First episodes of UTI in selected patients, such as boys and girls younger than 4 years of age, generally require evaluation after resolution of the UTI. These patients are more likely than those in the general pediatric population to have structural anomalies and, if untreated, are at increased risk for recurrent UTI or for the development of complications such as hydronephrosis, renal scarring, and ultimately renal failure. The female patient with multiple episodes of complex infection, the patient with diminishing renal function, and the patient with renal colic and suspicion of obstructing stone, which progresses to sepsis, all require imaging.

Several imaging studies may be useful in these patients. Historically, intravenous or excretory urography—typically, intravenous pyelography (IVP)—was used because such studies provide both structural and functional information about the upper urinary tract. Recent work has focused on obtaining this information through safer, less invasive, and less costly methods.[21] Ultrasonography compares favorably with IVP but is inferior to computed tomography (CT).[22] Radionuclide cystograms compare favorably with voiding cystourethrograms in the diagnosis of vesicoureteral reflux and give less ionizing radiation to the gonads by a factor of 50 to 100. Voiding cystourethrography is the traditional method for initial evaluation of the genitourinary tract. CT scan is exceptional for diagnosing upper tract complications such as various degrees of pyelonephritis, abscesses, pyonephrosis, granulomatous infections, and infected cysts. As with IVP, its disadvantages include higher cost, radiation exposure, and potential for contrast-induced reactions.

Ultrasonography. Ultrasonography is useful in the evaluation of patients with potential urinary obstruction. It is a sensitive tool for detecting intrarenal and perinephric abscess and the presence of hydroureter. It is less accurate in determining the presence of a partially obstructing ureteral stone. Ultrasound examination also can detect the presence of pyelonephritis and congenital anomalies.[23] Regardless of patient age group, this procedure is relatively inexpensive and avoids the hazards of contrast and radiation exposure.

Intravenous Pyelography. IVP, previously considered one of the mainstays in the evaluation of the genitourinary tract, has been nearly replaced by helical CT scanning and ultrasonography. IVP has higher sensitivity and specificity for determining the presence of obstruction than ultrasound examination but is inferior to CT scanning, and it is not sensitive for detecting the presence pf pyelonephritis and renal abscess.[24]

Radionuclide Scans. Radionuclide scans also are gaining popularity for the early evaluation of UTI. A dimercaptosuccinic acid scan is the most sensitive method of identifying pyelonephritis and is the imaging study of choice in infant girls with UTI and fever.

Computed Tomography of the Abdomen. A contrast-enhanced CT scan of the abdomen is perhaps the best test for assessing the kidneys, ureters, and bladder. It has the highest sensitivity for detecting abscess, obstruction, and acute inflammation.[22] Its disadvantages include cost, radiation exposure, and potential for contrast-induced reactions and radiocontrast agent–induced acute renal injury. CT without contrast can be performed in

patients with renal insufficiency and is the preferred study in patients with clinical concern for urolithiasis.

Complicated Urinary Tract Infection in High-Risk Populations

Pregnancy

UTI during pregnancy represents a special situation. The incidence of UTI in pregnancy is approximately 2 to 7%.[25] Maternal complications include acute pyelonephritis, increased incidence of postpartum chronic pyelonephritis, preterm delivery, and low newborn birth weight. The physiologic changes that occur within the urinary tract of pregnant women include ureteral and renal pelvis dilatation, as well as reduced peristalsis throughout the collecting system. During the last trimester, minimal ureteral contractions occur in many patients.

Unlike bacteriuria in nonpregnant females, bacteriuria in pregnant women, even if they are asymptomatic, must be treated. Complications that may result from untreated bacteriuria in pregnancy include premature labor, perinatal mortality, maternal anemia, and maternal pyelonephritis.

Reasonable antibiotic choices include amoxicillin, cephalexin, and nitrofurantoin. Trimethoprim-sulfamethoxazole (TMP-SMX) may be used before the third trimester. Single-dose therapy is not recommended, because these are not considered simple infections. Hospital admission should be considered in patients who are in their last trimester, who appear ill, or who have evidence of pyelonephritis and would benefit from treatment with parenteral antibiotics and intravenous fluids. Although pregnant patients with UTI are being treated on an outpatient basis more frequently than in the past, conservative treatment and close follow-up are warranted.

Diabetes and Sickle Cell Disease

Diabetic patients with bacteriuria also have an increased risk for the development of pyelonephritis, but treatment of asymptomatic bacteriuria has not been proved to be beneficial and should not be standard therapy at this time.[26] Papillary necrosis, perinephric and renal abscess formation, and emphysematous cystitis represent grave complications for this patient group. Manifestations of these complications may include altered vital signs, systemic signs and symptoms such as nausea and vomiting with dehydration, and a toxic appearance suggesting bacteremia and sepsis. These patients require aggressive fluid resuscitation, intravenous antibiotics, and a thorough diagnostic investigation including CT scanning.

Patients with sickle cell anemia also have shown a predilection for the development of papillary necrosis and generalized renal microvascular compromise. In these patients, compromised renal function is thought to be secondary to microvasculature damage from the chronic sickling of their erythrocytes. The renal damage from a UTI can compound the chronic renal insufficiency, leading to rapid worsening of their condition. These patients and all patients with underlying kidney disease or renal compromise should be approached conservatively, with hospitalization as deemed necessary for intravenous hydration and antibiotics.

Presence of an Indwelling Catheter

Treatment of asymptomatic bacteriuria in patients with indwelling catheters is not indicated. Antibiotic treatment results in the development of resistant microorganisms, whereas removal of the catheter leads to the spontaneous elimination of bacteria in many patients. Treatment of patients with a UTI in whom removal of the catheter is contraindicated includes urine culture and sensitivity, antibiotic therapy, replacement of the catheter, and strong consideration for hospitalization in those who exhibit altered vital signs, systemic symptoms, or a toxic appearance. These patients are at high risk for infection with an unusual pathogen and subsequent bacteremia. Urine culture with antibiotic sensitivity testing will help guide antibiotic therapy in this patient population.

Differential Considerations

Bacterial UTI is the most common cause of dysuria, with low-count infections. It is important, however, to consider the possibility of acute urethritis or acute vaginitis in these patients, as well as mechanical trauma or irritation (Tables 97-1 to 97-3; Fig. 97-1). Urethritis caused by *Chlamydia* may be seen in patients with acute dysuria; in fact, *C. trachomatis* may be present in up to 20% of women with dysuria. In general, if historical information includes contact with multiple sexual partners, a recent change in sexual partners, or a sexual partner with dysuria or discharge, *C. trachomatis* infection should be strongly considered. A pelvic examination should be performed, and culture specimens should be obtained to detect *C. trachomatis* and *N. gonorrhoeae*. Other causes of acute dysuria include infections with *Trichomonas vaginalis* and herpes simplex virus.

The dysuria of vaginitis most often is described as "external," the sensation being caused by the passage of urine over inflamed introital tissue. Elderly women may complain of dysuria secondary to atrophic vaginitis. In either case, a pelvic examination may be required. Urinary frequency and urgency are seldom if ever associated with a vaginal cause of dysuria.

Bacterial infection of the bladder is the most likely cause of dysuria in female patients. Most demonstrate positive results on urine cultures, with growth of more than 10^5 CFUs/mL of bacteria. This number is not absolute, because 30 to 50% of patients have low-count bacterial infections as a cause of their symptoms. It has been suggested that low bacterial counts may represent an early phase of UTI.

Management

Simple Urinary Tract Infection

Options for treating uncomplicated lower UTI include single-dose therapy, short-course therapy (3 to 5 days), and the more traditional 7- to 10-day course of therapy (Table 97-4). *E. coli* remains the most common urinary tract pathogen and is susceptible to many antibiotic regimens. Emerging resistance to TMP-SMX has been noted in 15 to 32% of organisms.[27] In some areas of Europe, resistance to TMP-SMX is approaching 50%.[28] Risk factors for UTI from TMP-SMX–resistant *E. coli* include recent use of antibiotics (especially TMP-SMX), recent travel to areas with a high prevalence of resistance, and age younger than 3 years with day care attendance.[29]

Three days of therapy is more effective than single-dose therapy. The longer-duration regimen shares the advantages of improved compliance, lower cost, and reduced side effects. It currently is the recommended regimen for treatment of uncomplicated lower UTI. Despite emerging resistance, TMP-SMX remains the best first-line agent for 3-day regimens when compared with other commonly used antibacterials, owing to its low cost and effectiveness.[28,30] Short-course 3-day therapy also is effective for asymptomatic bacteriuria in pregnancy. It is unclear whether this regimen can be used for symptomatic lower UTIs in pregnancy, so longer-course

Table 97-1 Differential Diagnosis of Dysuria Syndromes: Laboratory Findings

SYNDROME/DISORDER	MICROSCOPIC HEMATURIA OR PYURIA	BACTERIURIA	URINE CULTURE (>10^2 CFUS/ML)	POSITIVE FLUID OR CERVICAL SMEAR	POSITIVE CULTURE OF GENITAL LESIONS, CERVIX, OR URETHRA*
Acute pyelonephritis	+	+	+	–	–
Acute cystitis	+	±	+	–	–
Urethritis caused by sexually transmitted disease					
Herpes simplex virus	+	–	–	±	+
Neisseria gonorrhoeae	+	–	–	+	+
Chlamydia trachomatis	+	–	–	+	+
Vulvovaginitis (bacterial vaginosis, trichomoniasis, yeast, genital herpes simplex)	–	–	–	+	±
Noninflammatory dysuria (trauma, irritant, allergy)	–	–	–	–	–

*Positive for herpes simplex virus, *Neisseria gonorrhoeae*, or *Chlamydia trachomatis*.
From Stamm WE: Protocol for diagnosis of urinary tract: Reconsidering the criterion for significant bacteriuria. Urology 32(2 Suppl):6, 1988.

Table 97-2 Differential Diagnosis of Dysuria Syndromes: Physical Examination

SYNDROME/DISORDER	VAGINAL OR CERVICAL DISCHARGE, VULVAR LESIONS	SUPRAPUBIC TENDERNESS	FLANK TENDERNESS, FEVER
Acute pyelonephritis	–	±	–
Acute cystitis	–	±	–
Urethritis caused by sexually transmitted disease			
Herpes simplex virus	+	–	–
Neisseria gonorrhoeae	+	–	–
Chlamydia trachomatis	+	–	–
Vulvovaginitis (bacterial vaginosis, trichomoniasis, yeast, genital herpes simplex)	+	–	–
Noninflammatory dysuria (trauma, irritant, allergy)	–	–	–

From Stamm W: Protocol for diagnosis of urinary tract: Reconsidering the criterion for significant bacteriuria. Urology 32(2 Suppl):6, 1988.

Table 97-3 Clinical Differentiation among Major Causes of Dysuria

CAUSE	CLINICAL FEATURES
Urinary tract infection	Internal dysuria Frequency, urgency, voiding small volumes Abrupt onset Suprapubic pain Often associated with diaphragm use Presence of pyuria Presence of hematuria (50% of patients)
Sexually transmitted disease	Internal dysuria Occasional history of frequency, urgency, voiding small volumes Gradual onset History of new or multiple sexual partners Vaginal discharge
Vaginitis	External dysuria Gradual onset Vaginal discharge Vaginal odor Pruritus

From Stamm W: Protocol for diagnosis of urinary tract: Reconsidering the criterion for significant bacteriuria. Urology 32(2 Suppl):6, 1988.

therapy is recommended. Seven- to 10-day therapy generally offers no benefit over shorter courses in uncomplicated UTIs; however, it remains the standard of care in complicated infections (in patients with pregnancy, diabetes, or sickle cell anemia) for which cure rates are lower with shorter regimens.

The fluoroquinolones are considered first-line agents in regions in which the incidence of TMP-SMX resistance has approached 10 to 20%.[27] Ciprofloxacin is the most commonly used drug and requires twice-daily dosing. Although more expensive than ciprofloxacin, gatifloxacin and levofloxacin offer once-daily dosing, have the broadest activity, and have same-dose bioequivalence between oral and parenteral administration. Fluoroquinolones damage developing cartilage in animal studies and should be avoided in children.[31]

Nitrofurantoin and trimethoprim are excellent drugs for the treatment of acute bacterial cystitis. Nitrofurantoin is inexpensive and maintains low serum and high urine levels, with a bacterial resistance pattern that remains unchanged. Adverse reactions are primarily secondary to gastrointestinal disturbance, but they may be alleviated by using the macrocrystalline form (Macrodantin). Folate antagonists such as trimethoprim have a broader spectrum of activity than that of nitrofurantoin. The addition of sulfamethoxazole further broadens the spectrum to include coverage for *Proteus* and *Klebsiella*. Folate antagonists carry a higher incidence of adverse

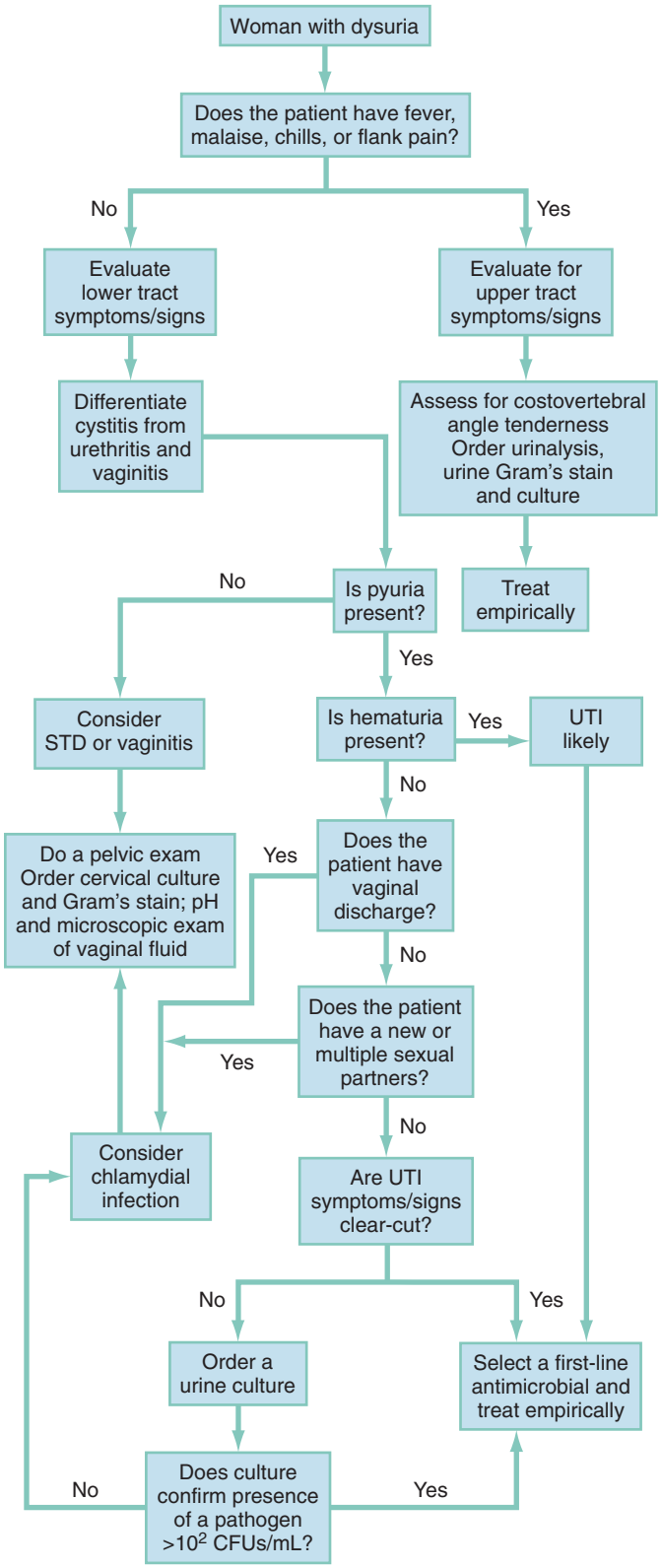

Figure 97-1. Diagnostic protocol for women with dysuria. CFUs, colony-forming units; STD, sexually transmitted disease; UTI, urinary tract infection. (From Stamm WE: Protocol for diagnosis of urinary tract: Reconsidering the criterion for significant bacteriuria. Urology 32[2 Suppl]:6, 1988.)

effects than nitrofurantoin, predominantly gastrointestinal upset, yeast vaginitis, and rash. Addition of the sulfa component further increases the likelihood of side effects.

Except in pregnancy, ampicillin and amoxicillin should not be used empirically as first-line drugs for the treatment of uncomplicated UTI. Recurrence rates with use against ampicillin-resistant strains are high, and neither agent effectively eradicates the vaginal reservoir of pathogenic bacteria.

A useful adjunctive therapy for UTIs is phenazopyridine (Pyridium). It produces topical analgesia in the urinary tract and helps relieve dysuria. Patients should be cautioned that body secretions and excretions (e.g., tears, urine) will turn orange. This side effect can stain contact lenses and alarm unknowing patients.

Complex Urinary Tract Infection

Mild to moderate pyelonephritis can be safely treated on an outpatient basis with a fluoroquinolone for 10 to 14 days (first-line agent) or TMP-SMX (second-line agent) so long as the patient is able to eat and drink, has achieved adequate pain control, and has approrpiate pychosocial support in the home. In many clinical centers, observation units have evolved to offer a short-stay (less than 24 hours) option for moderate cases in which immediate discharge for outpatient therapy may not be the optimal approach to management.

Severe upper tract UTI necessitating hospitalization initially should be treated with parenteral antibiotics, with transition to oral therapy after the patient has been afebrile for 24 to 48 hours. Oral therapy should be continued for 2 weeks. Because 20% of cultures are resistant to ampicillin, cephalothin, and sulfonamides, antibiotic therapy should be initiated with a fluoroquinolone.

Hospitalization is required in the presence of clinical toxicity (fever, tachycardia, hypotension, vomiting), inability to take oral medications, an immunocompromised state, third trimester pregnancy, inadequate social circumstances, failure of oral outpatient therapy, or urologic abnormalities or in patients with significant comorbid conditions including heart failure, renal insufficiency, and compromised immune status.

A subgroup of patients suffering from upper tract UTI do not require immediate hospital admission but may benefit from intravenous hydration and pain and fever control, along with a first dose of an intravenous fluoroquinolone. If these patients do not have any contraindications as previously discussed and they improve clinically and are able to tolerate food and drink, they can be safely discharged home on a 10- to 14-day course of an oral fluoroquinolone with close primary physician follow-up. Urine culture with sensitivity testing and further diagnostic evaluation are not necessary in this patient population.

URINARY TRACT INFECTION IN CHILDREN

Perspective

UTI is a major bacterial disease of childhood; it is estimated that 0.8 to 1.5% of children have bacteriuria. The risk for development of UTI before 11 years of age is 3% in girls and 1% in boys.[9] The incidence of UTI in the neonatal period is higher in boys, but the infection becomes more prominent in girls during infancy and thereafter. In children aged 1 to 3 months, UTI is associated with a high incidence of sepsis (30%).[10] After the age of 3 months, the incidence of sepsis associated with UTI decreases (to 5%).[10] Vesicoureteral reflux is a common risk factor for UTI and renal scarring in children.[19]

Table 97-4 Treatment Regimens for Bacterial Urinary Tract Infections (UTIs)

CONDITION	CHARACTERISTIC PATHOGENS	MITIGATING CIRCUMSTANCE(S)	RECOMMENDED EMPIRICAL TREATMENT*
Acute uncomplicated cystitis in women	*Escherichia coli*, *Staphylococcus saprophyticus*, *Proteus mirabilis*, *Klebsiella pneumoniae*	None	3-day regimens: oral TMP-SMX, trimethoprim, norfloxacin, ciprofloxacin, ofloxacin, lomefloxacin, or enoxacin[†]
		Diabetes, symptoms for >7 days, recent UTI, use of diaphragm, age >65 yr	Consider 7-day regimen: oral TMP-SMX, trimethoprim, norfloxacin, ciprofloxacin, ofloxacin, lomefloxacin, or enoxacin[†]
		Pregnancy	Consider 7-day regimen: amoxicillin, macrocrystalline nitrofurantoin, cefpodoxime proxetil, or TMP-SMX[†]
Acute uncomplicated pyelonephritis in women	*E. coli*, *P. mirabilis*, *K. pneumoniae*, *S. saprophyticus*	Mild to moderate illness, no nausea or vomiting—outpatient therapy	Oral[‡] TMP-SMX, norfloxacin, ciprofloxacin, ofloxacin, lomefloxacin, or enoxacin for 10–14 days
		Severe illness or possible urosepsis—hospitalization required	Parenteral[§] TMP-SMX, ceftriaxone, ciprofloxacin, ofloxacin, or gentamicin (with or without ampicillin) until fever gone; then oral[‡] TMP-SMX, norfloxacin, ciprofloxacin, ofloxacin, lomefloxacin, or enoxacin for 14 days
		Pregnancy—hospitalization recommended	Parenteral[§] ceftriaxone, gentamicin (with or without ampicillin), aztreonam, or TMP-SMX until fever gone; then oral[‡] amoxicillin, a cephalosporin, or TMP-SMX for 14 days
Complicated UTI	*E. coli*, *Proteus* species, *Klebsiella* species, *Pseudomonas* species, *Serratia* species, enterococci, staphylococci	Mild to moderate illness, no nausea or vomiting—outpatient therapy	Oral[‡] norfloxacin, ciprofloxacin, ofloxacin, lomefloxacin, or enoxacin for 10–14 days

*Treatments listed are those to be prescribed before the etiologic agent is known (Gram staining can be helpful); they can be modified once the agent has been identified. These recommendations are limited to drugs currently approved by the U.S. Food and Drug Administration, although not all of the regimens listed are approved for these indications. Fluoroquinolones should not be used in pregnancy. TMP-SMX, although not approved for use in pregnancy, has been widely used. Gentamicin should be used with caution in pregnancy because of its possible toxicity to eighth nerve development in the fetus.

[†]Multiday oral regimens for cystitis are as follows: TMP-SMX, 160 to 800 mg every 12 hours; trimethoprim, 100 mg every 12 hours; norfloxacin, 400 mg every 12 hours; ciprofloxacin, 250 mg every 12 hours; ofloxacin, 200 mg every 12 hours; lomefloxacin, 400 mg every day; enoxacin, 400 mg every 12 hours; macrocrystalline nitrofurantoin, 100 mg four times a day; amoxicillin, 250 mg every 8 hours; and cefpodoxime proxetil, 100 mg every 12 hours.

[‡]Oral regimens for pyelonephritis and complicated UTI are as follows: TMP-SMX, 160 to 800 mg every 12 hours; norfloxacin, 400 mg every 12 hours; ciprofloxacin, 500 mg every 12 hours; ofloxacin, 200 to 300 mg every 12 hours; lomefloxacin, 400 mg every day; enoxacin, 400 mg every 12 hours; amoxicillin, 500 mg every 8 hours; and cefpodoxime proxetil, 200 mg every 12 hours.

[§]Parenteral regimens are as follows: TMP-SMX, 160 to 800 mg every 12 hours; ciprofloxacin, 200 to 400 mg every 12 hours; ofloxacin, 200 to 400 mg every 12 hours; pentamicin, 1 mg/kg of body weight every 8 hours; ceftriaxone, 1 to 2 g every day; ampicillin, 1 g every 6 hours; imipenem-cilastatin, 250 to 500 mg every 6 to 8 hours; ticarcillin-clavulanate, 3.2 g every 8 hours; and aztreonam, 1 g every 8 to 12 hours.

TMP-SMX, trimethoprim-sulfamethaxozole.

Modified from Stamm W, Hooton TM: Management of urinary tract infections in adults. N Engl J Med 329:1328, 1993.

Data suggest that the incidence of scar formation after acute pyelonephritis may be as high as 37%.

Principles of Disease

As in adults, *E. coli* is the predominant pathogen. Age-related differences are recognized: In older boys, *Proteus* often is isolated during UTI, whereas in newborn children, *Klebsiella* often is the causative agent. The route of infection also is age-related. In the newborn period, it is thought that the bacteria are blood-borne (and often associated with generalized sepsis). In the older age group, as in adults, the ascending urethral route is primarily responsible for generating infection of the urinary tract.

Clinical Features

UTI often is overlooked in children because of inappropriate emphasis on classic signs and symptoms, with little regard to age variables. Nonspecific findings should be considered the rule and not the exception (Table 97-5). Pyelonephritis may be present without overt symptoms. A UTI in a febrile patient usually indicates pyelonephritis. An elevated BUN level or hypertension in a child older than 2 months strongly suggests bilateral hydronephrosis or advanced renal parenchymal disease.

Neonates

Generalized septicemia often is the major manifestation of neonatal UTI.[2] Classically, feeding difficulties, irritability, and sluggishness are seen in this age group. Bacteremia is present in nearly 50% of cases.[9]

Age 1 Month to 3 Years

This age group has the most deceptive clinical presentation of UTI. Nonspecific findings are typical: fever, irritability, abdominal pain, vomiting, and failure to thrive. Occasionally, gross hematuria may be present.

Table 97-5 Signs and Symptoms of Urinary Tract Infection by Age Group

NEWBORN	INFANT	PRESCHOOLER	SCHOOL-AGE CHILD
Poor feeding	Poor feeding	Abdominal pain	Fever
Vomiting	Vomiting	Vomiting	Enuresis
Jaundice	Diarrhea	Strong-smelling urine	Increased frequency of urination
Hypothermia	Fever	Fever	Dysuria
Fever	Strong-smelling urine	Enuresis	Urgency
Failure to thrive		Increased frequency of urination	Costovertebral angle tenderness (flank pain)
Sepsis		Dysuria	
		Urgency	

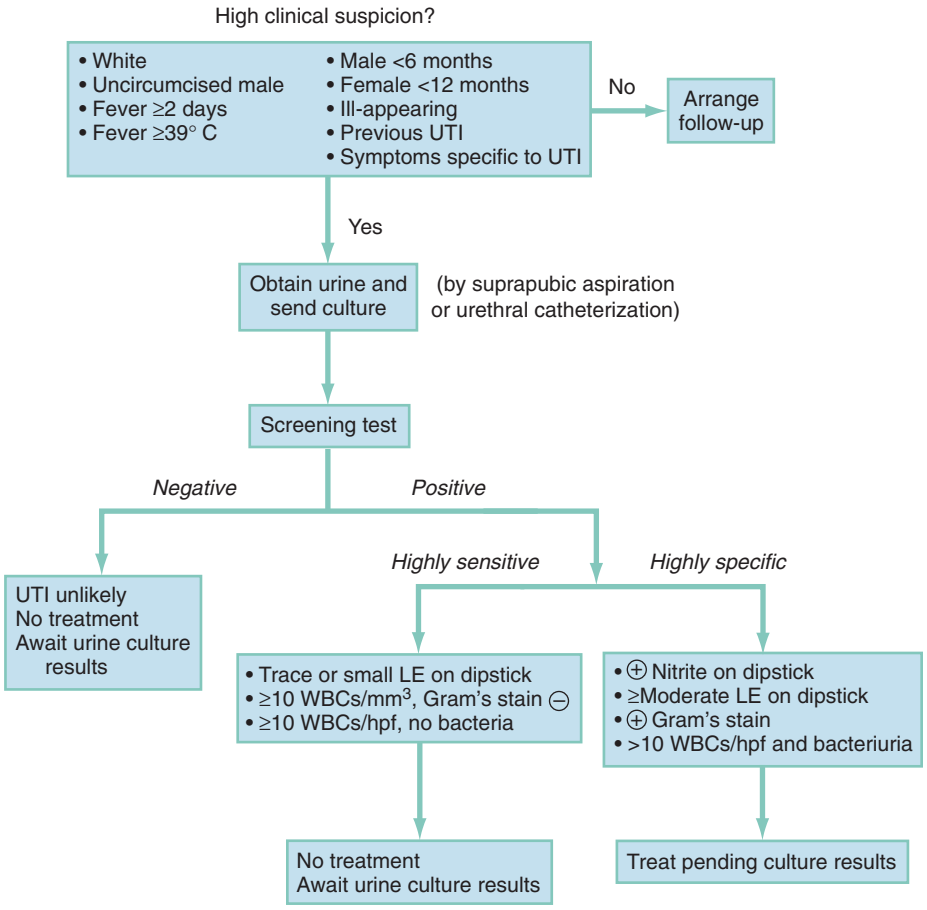

Figure 97-2. Screening for urinary tract infection (UTI) in febrile children (age 2 to 23 months) in the emergency department. hpf, high-power field; LE, leukocyte esterase; WBCs, white blood cells. (From Shaw KN, Gorelick MH: UTI in the pediatric patient. Pediatr Clin North Am 46:1111, 1999.)

Age 3 to 11 Years

In girls, abdominal pain, newly developed enuresis, and irritative voiding symptoms suggest the presence of UTI. In boys, fever is present in association with UTI in more than 50% of cases. Varying degrees of hematuria and irritative symptoms (urgency, dysuria) are present. *Proteus* is a common pathogen in this particular group. Most cases are simple, uncomplicated infections responsive to commonly used antimicrobial agents. The presence of certain signs and symptoms implies the possibility of serious underlying disease of the urinary tract. The most significant factors include a raised or palpable bladder, hypertension, abnormalities in electrolytes, acidosis, elevated BUN level, evidence of dribbling, poor urinary stream, and straining to void. If any of these factors is noted, prompt urologic referral or consultation is indicated. If the clinical picture is suggestive of an underlying obstructive process, emergency imaging is essential.

Diagnostic Strategies

Laboratory studies useful for diagnosing an infection of the urinary tract as previously described also apply to children. However, presumptive treatment may be indicated in high-risk patients based on clinical predictors and screening tests, as shown in Figure 97-2. Additional studies are dictated by the clinical setting and include renal function studies, a complete blood count, serum electrolyte panel, CT scan, voiding cystourethrography, and ultrasonography. Renal cortical scintigraphy has proved to be the most sensitive method of detecting pyelonephritis.

Urine collection often poses a challenge in a child with a suspected UTI. The following techniques represent acceptable methods of urine collection:

- *Urethral catheterization* is appropriate for all infants. Aseptic technique ensures a low risk of introducing bacteria. It is the preferred method of urine collection.

- *Suprapubic aspiration* is a superb reliable method if urine is available to be withdrawn, but it is seldom used these days. For patients 12 months or younger, it is a useful method and carries an incidence of adverse effects similar to that of urethral catheterization.
- *Plastic bag collection* is a reasonably reliable method, but the perineum (in girls) and the glans (in boys) should be properly cleansed before application of the bag. It is a less reliable form of collection and is associated with a high incidence of skin contamination.
- A *clean-catch urine specimen* is preferred in cooperative and continent male patients.

Management and Disposition

As in adults, many therapeutic options are available for children with UTI. Sulfonamides, nitrofurantoin, TMP-SMX, cephalosporins, and aminopenicillins all are effective.[32] Newborns and young infants should be treated with ampicillin and gentamicin on an inpatient basis, and sulfonamides should be avoided. Traditionally, inpatient treatment with parenteral antibiotics has been the standard of care for young children with suspected pyelonephritis. The literature suggests that oral therapy is acceptable in children with uncomplicated infections.[33] These patients should be managed conservatively, and hospital admission is advised for children who are dehydrated, severely ill, or not tolerating oral fluids or those with underlying structural abnormalities of the genitourinary system. In addition, family dynamics, which could affect compliance with medication, should be taken into account in decisions regarding the disposition of the case of a child with a UTI.

The appropriate duration of therapy currently is a subject of debate. Many experts believe that in children with uncomplicated lower UTI, short-course therapy can be used instead of the traditional 10-day regimen. Short-course (3-day) therapy is more widely accepted in adolescent girls. Once the decision to discharge a child has been made, the parents should be advised of signs of toxicity and the importance of compliance with medications. Parents should bring the child to the ED immediately if signs of toxicity develop and should arrange routine follow-up with the pediatrician if the child improves. The child should be seen for follow-up 2 to 3 days after the ED visit and again 2 to 3 weeks later (or 7 to 10 days after completion of the antibiotic course).

URINARY TRACT INFECTION IN MEN

Perspective

The incidence of UTI is much lower in men than in women. The route of infection in men generally is ascending, from the urethra to the prostate, bladder, and kidney. Pathogenic organisms responsible for UTI in men are similar in type, regardless of the site of infection in the genitourinary tract. *E. coli* causes 80% of infections in men. UTI in men should always be considered a complicated infection and mandates more extensive evaluation as well as a longer course of antibiotics.

Specific Disorders

Cystitis

Cystitis is rare in male patients in the absence of trauma, prostate pathology, or instrumentation. Chronic prostatitis, prostatic hyperplasia with obstruction, and previous instrumentation are the most common predisposing factors. Lack of circumcision and homosexuality are other recognized risk factors. Commonly, men with cystitis have symptoms of urinary urgency, frequency, dysuria, nocturia, suprapubic pain, and often low back pain. Gross hematuria occasionally occurs, but fever, chills, and flank pain generally are absent. On physical examination, suprapubic tenderness to palpation may be elicited. Pneumaturia may be present and is indicative of an infection with gas-forming bacteria. It also may indicate the presence of a vesicoenteric fistula, which often is caused by diverticulitis, although rectosigmoid carcinoma and regional enteritis are associated diseases as well. If fever and chills are present in association with irritative symptoms and difficulty voiding, acute bacterial prostatitis should be strongly considered. The most common pathogens found in men with cystitis are *E. coli*, *Proteus*, and *Providencia*.

A voided urine specimen should reveal pyuria, bacteriuria, and a variable degree of hematuria. Urine culture is essential. If there are no signs of toxicity, the patient generally can be treated on an outpatient basis with any of the urinary antibacterial agents (TMP-SMX, nitrofurantoins, sulfonamides, or fluoroquinolones).

Three qualifying factors must always be addressed in dealing with UTIs in men:

1. *Obstruction*. It is imperative that urinary obstruction be ruled out as a pathogenic mechanism. Infection and obstruction together can be catastrophic and lead to sepsis. Obstruction at the level of the prostate in older men is common and should be considered. Catheterization or bedside ultrasound examination may be indicated to rule out retention. Suggestion of obstruction of the upper tracts based on history necessitates performance of an abdominal CT scan without intravenous contrast or ultrasound.
2. *Genitourinary tract anomalies*. UTIs in men often are secondary to underlying, serious disease of the genitourinary tract. Therefore, all of these patients should be referred to a urologist for diagnostic studies.
3. *Catheterization*. Urethral catheterization should not be used to collect a urine specimen in men unless they are experiencing urinary retention. An inability to produce a specimen in the presence of infectious symptoms should be a major clue regarding the cause of the infection. If retention is suspected, catheterization for collection of residual urine is indicated. Referral for urologic consultation is mandatory and hospital admission is prudent for a majority of these patients.

Pyelonephritis

Clinical features in men with acute pyelonephritis include flank and costovertebral angle pain, chills and fever, urinary frequency, urgency, and dysuria. Generalized malaise, nausea, and vomiting are early signs of systemic toxicity, suggesting impending gram-negative sepsis. These patients require hospitalization for intravenous hydration and antibiotic therapys, as well as pain and fever control.

A voided urine specimen usually reveals leukocytes, occasional leukocyte casts, a variable number of red blood cells (RBCs), and bacteria. Urine culture is essential in this patient population. Blood cultures should be performed if the clinical picture suggests sepsis. A complete blood count, renal function studies, and electrolyte studies are recommended. Uncomplicated pyelonephritis should not produce detectable alterations in the BUN level. In males, imaging with ultrasonography or abdominal CT without contrast is required, because the etiology typically involves obstruction secondary to a stone, prostate pathology, stricture, or tumor. Catheteriza-

tion for collection of residual urine may be indicated if urinary retention is suspected.

Prostatitis

Bacterial prostatitis is an infection of the prostate caused primarily by gram-negative organisms. More than 80% of cases are caused by strains of *E. coli*; the remainder are caused by *Klebsiella*, *Enterobacter*, *Proteus*, and *Pseudomonas* species. Patients with prostatitis may complain of dysuria and perineal and low back pain associated with fever, chills, and malaise. A rectal exam must be part of the workup in all men who complain of symptoms suggestive of cystitis. Bacterial prostatitis is not a subtle disease, and patients will have an exquisitely tender and boggy prostate.

Acute bacterial prostatitis is an acute febrile illness characterized by chills, low back pain, and perineal pain. Irritative symptoms of voiding, including frequency, urgency, and dysuria, are present, along with various degrees of bladder outlet obstruction and retention. Patients often have constitutional symptoms of arthralgia, myalgia, and generalized malaise. Prostate examination reveals a tender, swollen gland that is firm and warm to touch. Palpation of an acutely inflamed prostate should be limited, to avoid the possibility of precipitating bacteremia or sepsis. Cystitis usually accompanies acute bacterial prostatitis. Thus, culture of voided bladder urine generally reveals the responsible pathogen.

Antimicrobial therapy has been shown to be beneficial and is recommended.[34] In patients without signs of systemic toxicity, a prolonged course of an antibiotic for 4 to 6 weeks is required. This may need to be repeated if only partial success is achieved. The following list represents an appropriate selection of drugs for *nontoxic* prostatitis:

1. Ciprofloxacin, 500 mg orally twice daily; norfloxacin, 400 mg orally twice daily; or ofloxacin, 400 mg by mouth twice daily for 30 days
2. Trimethoprim with sulfamethoxazole (Bactrim), one double-strength tablet by mouth twice daily for 30 days

If the patient is toxic-appearing with fever, chills, or urinary retention, hospitalization and parenteral antibiotics are warranted.[35] The following antibiotic choices are appropriate for *toxic* prostatitis:

1. Ciprofloxacin, 400 mg IV every 12 hours, or levofloxacin, 500 mg IV every 24 hours
2. Ceftriaxone, 2 g IV every 24 hours with or without gentamicin 3 to 5 mg/kg per day

If the patient is experiencing painful urinary retention, urethral catheterization should be avoided. Suprapubic needle aspiration or catheterization is much safer and more comfortable than urethral catheterization for initial management. A urologist should be consulted regarding management of all patients requiring suprapubic tube placement.

General support measures for outpatients should include bedrest, analgesics, antipyretics, hydration, and stool softeners.

Chronic Prostatitis

Patients with chronic prostatitis typically present to the ED when they experience an acute exacerbation of the disease. Clinical manifestations vary widely, but most patients complain of some degree of irritative voiding symptoms (frequency, urgency, dysuria), low back and perineal pain, and occasionally myalgias.[34] Fever and chills are uncommon except during an acute exacerbation of the chronic infection. A history of previous episodes of acute prostatitis may be absent. Findings on the physical examination, including examination of the prostate, often are unremarkable. The hallmark of chronic bacterial prostatitis is relapsing UTI caused by the same organism. Chronic bacterial prostatitis is the most common cause of recurrent UTI in men.

Antimicrobial therapy is recommended for the treatment of chronic prostatitis.[36] Unfortunately, most antimicrobials diffuse poorly from plasma into prostatic fluid. The fluoroquinolones achieve the highest concentrations in the prostate and are the drugs of choice, with cure rates of approximately 64%. The recommended dosages are as follows: ciprofloxacin, 500 mg twice daily for 30 days; norfloxacin, 400 mg twice daily for 30 days; enoxacin, 400 mg twice daily for 30 days; or ofloxacin, 300 mg twice daily for 6 weeks. TMP-SMX also is useful, with cure rates of 44 to 50%. The dosage is one double-strength tablet twice daily, but the optimal duration of therapy is unclear and may range from 4 to 16 weeks.

RENAL CALCULI

Perspective

Background. Renal calculi constitute a common clinical problem seen in the ED. From 1994 through 2000, presentations for urolithiasis nearly doubled, and all indicators point to a rise in the incidence of kidney stones in the general population.[37] Renal calculi are seen commonly in young adults and middle-aged men, with nearly 70% of all ureteral calculi occurring between the ages of 20 and 50 years. Most ureteral calculi originate in the kidney and then pass into the collecting system.

Epidemiology. Various clinical syndromes involve metabolic alterations and are therefore associated with an increased likelihood of stone formation[38] (Box 97-2). Risk factors include age, male gender, and family history. In the United States, prevalence rates for renal calculi are 7% in men and 3% in women.

Principles of Disease

Overview. Multiple pathogenic factors interact to cause the formation of renal calculi. Renal calculi can be stratified into the following types: calcium, struvite, uric acid, and cystine.

BOX 97-2 RISK FACTORS FOR UROLITHIASIS

- Metabolic disease/disturbance
  - Crohn's disease
  - Milk-alkali syndrome
  - Primary hyperparathyroidism
  - Hypernitraturia
  - Hyperuricosuria
  - Sarcoidosis
  - Recurrent UTI
  - Renal tubular acidosis (type I)
  - Gout
  - Laxative abuse
- Positive family history
- Hot arid climates (southeast United States)
- Male gender (white men affected more commonly than black men)
- Previous kidney stone
- Dehydration

UTI, urinary tract infection.

Most stones (75%) are composed of calcium oxalate, alone or in combination with calcium phosphate. Hyperexcretion of calcium is a major contributor to stone formation and occurs in various clinical settings. The major dietary sources of calcium are cheese and milk, and hypercalciuria may occur in adults who ingest more than 1 quart of milk daily. Many conditions are associated with the development of hypercalciuria with increased risk of stone formation. Perhaps the most common is hyperparathyroidism, in which calculi develop in 67% of patients. Peptic ulcer disease also may be a predisposing factor. These patients tend to ingest large amounts of calcium with food, in addition to absorbed alkali sources (sodium bicarbonate) and antacids. The other major component of calcium stones, oxalate, also is influenced by diet. Hyperoxaluria occurs in the presence of small bowel disease—Crohn's disease, ulcerative colitis, and radiation enteritis.

Magnesium-ammonium-phosphate (struvite) stones account for approximately 15% of all renal calculi. Struvite stones occur almost exclusively in patients with UTI and often are referred to as "infection stones." They form as a result of urea-splitting organisms such as *Proteus*, *Providencia*, *Klebsiella*, *Pseudomonas*, and *Staphylococcus*. Distinctive features of these stones include common occurrence as staghorn calculi and the formation of "coffin-lid" crystals, often in the presence of alkaline urine.

Uric acid stones account for 10% of all stones in the United States. The basic causative factor is excessive excretion of uric acid in urine. Approximately 25% of patients with symptomatic gout have uric acid calculi, and the incidence of uric acid stones increases with the use of uricosuric agents. A distinctive feature of uric acid stones is their radiolucency. These stones infrequently take the form of staghorn calculi.

Cystine stones are rare and account for only 1% of stones. They are caused by an inborn error of metabolism that results in increased secretion of cystine and often occur as staghorn calculi.

Pathophysiology. Impaction along the genitourinary tract is a serious complication of renal calculi and can cause several physiologic changes. Once obstruction occurs, a rapid redistribution of renal blood flow results in a decrease in the glomerular filtration rate. As glomerular and tubular function decreases, renal excretion shifts to the unaffected kidney. Obstruction also causes a rapid decrease in ureteral peristaltic activity. In the presence of infection, both renal and ureteral function may be impaired. Complete obstruction of the ureters may lead to loss of renal function, with an increased incidence of irreversible damage after 1 to 2 weeks, including rupture of the renal calyx. Partial obstruction is associated with a lower likelihood of renal injury, but it may still result in irreversible damage.

Although calculus size and location are important determinants of the degree of disease, the major cause of progressive renal damage is associated infection. The stone behaves as a foreign body and leads to stasis and obstruction, decreasing host resistance and increasing the incidence of infection. Subsequent infectious complications include pyelonephritis, perinephric abscess, and gram-negative bacterial sepsis.

The three primary predictors of stone passage without the need for surgical intervention are calculus size, location and the degree of patient pain at discharge.[39] The most important factor that relates to passage of a calculus though the genitourinary tract is its size. Approximately 90% of stones smaller than 5 mm pass spontaneously within 4 weeks. This number decreases to 15% for stones between 5 and 8 mm. Up to 95% of stones larger than 8 mm become impacted along the genitourinary tract, and lithotripsy or surgical removal often is required. Unless the stone is infected or renal damage is considerable, surgical intervention can be performed on an outpatient basis, provided that the patient is able to tolerate oral intake and adequate pain control can be obtained. Spontaneous passage is more frequent with stones located below the midureter than with those located above the midureter. Patients with well-controlled pain on discharge are less likely to require surgical intervention than those who do not have well-controlled pain.

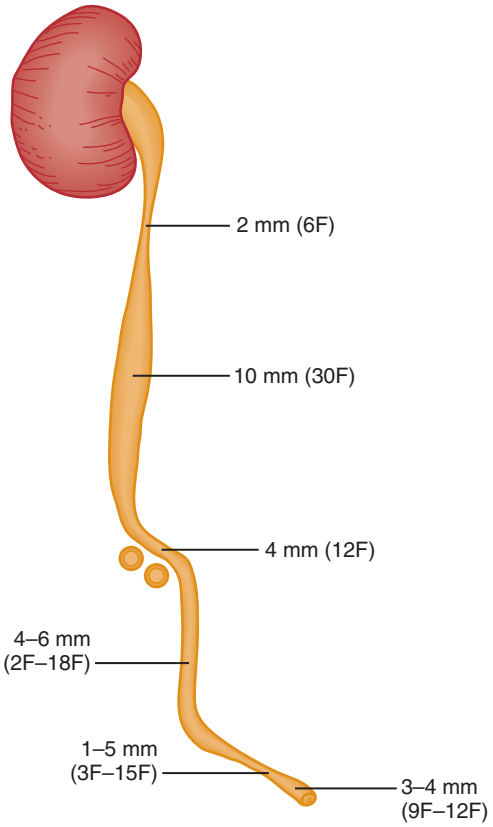

Figure 97-3. Variations in caliber of the ureter. F, French catheter size. (After Eisendrath, Rolnick. From Lich R Jr, et al: Childhood disorders and diseases. In Harrison JH, et al [eds]: Campbell's Urology, vol 1, 4th ed. Philadelphia, WB Saunders, 1978.)

Renal calculi seldom cause complete obstruction. There are five sites along the ureter at which calculi are likely to become impacted (Fig. 97-3). First, a stone may lodge in the calyx of the kidney or pass into the renal pelvis and become lodged at the ureteropelvic junction. The relatively large renal pelvis (1 cm) narrows abruptly at its distal portion, where it is equal in diameter to its adjoining ureter (2 to 3 mm). The third region is near the pelvic brim where the ureter arches over the iliac vessels posteriorly into the true pelvis. The most constricted area along the ureter, and a common location for impaction, is at the ureterovesicular junction. This location is the site at which the ureter enters the muscular coat of the bladder (intramural ureter). At the time of diagnosis, up to 75% of stones are located in the distal third of the ureter. Finally, calculi may become lodged in the vesical orifice.

Clinical Features

Signs and Symptoms. The onset of pain usually is abrupt, with a crescendo of extreme pain that begins in the flank, extends laterally around the abdomen, and radiates into the groin. Pain may radiate to the testicles in men and the labia majora in

women. A constant, underlying dull ache in the flank is common between episodes of colic. The cause of colicky, severe flank pain is hyperperistalsis of the smooth muscle of the calyces, pelvis, and ureter, whereas the cause of a dull ache can be acute obstruction and renal capsular tension.

Autonomic nerve fibers that serve the kidney, testicle, and ovary are involved in the transmission of pain with renal calculi, and the location of the stone may be suggested by the pattern of pain. A stone located high in the ureter may cause pain that radiates to the testicle (or ovary). As the stone approaches the bladder, the pain may shift to the scrotum or vulva. Symptoms of urinary urgency and frequency often develop as the stone nears the bladder.

Gastrointestinal symptoms of nausea and vomiting are common in patients with renal colic. A third of patients experience gross hematuria, with or without blood clots in the urine. A history of fever and chills strongly suggests superimposed infection; such cases should be regarded as a true urologic emergency.

Physical Examination. A patient with renal colic often is in severe pain and paces or writhes in pain on the stretcher, unable to find a comfortable position. The skin usually is pale, cool, and clammy. Fever generally is not noted but if present strongly suggests infection. The abdominal examination may reveal signs of an early ileus with hypoactive bowel sounds. A decrease in peristalsis often accompanies renal colic, but abdominal tenderness usually is absent and flank tenderness is more common. It is essential that the abdomen be auscultated and palpated in search of bruits and thrills over the abdominal aorta and iliac vessels, because the clinical manifestations of aortic abdominal aneurysms may mimic those of renal colic. Patients commonly have intermittent pain that may nearly resolve between episodes of severe discomfort. The clinical picture may be misleading, with the patient's repeated attempts to secure relief from the pain misinterpreted as drugseeking behavior, whereas actual pathology requiring medical attention is present.

Diagnostic Strategies

Laboratory Tests

Urinalysis. The initial diagnostic step in the management of suspected renal colic is urinalysis. This simple, noninvasive test provides helpful information on various aspects of the patient's condition. Generally, a dipstick test is performed first to evaluate for the presence of blood and infection. If results are abnormal, it is usually followed by microscopic analysis.

Sediment Analysis. RBCs generally are found in the urine of patients with urolithiasis. However, the absence of RBCs in urine does not exclude the diagnosis. From 10 to 20% of patients with documented urolithiasis have no microscopic hematuria.[40] Furthermore, there is no correlation between the degree of obstruction and the absence of hematuria. Although sterile pyuria can occur in the absence of infection as the result of ureteral inflammation, the presence of a UTI should be investigated if other clinical signs of infection are present, such as fever and chills. A urinalysis with culture should always be performed to look for pyuria and bacteriuria and to measure nitrites and leukocyte esterase when infection is suspected.

Urinary pH. The kidney will not produce urine with a pH greater than 7.5 under normal conditions, so urinary pH greater than 7.5 should raise suspicion for the presence of urea-splitting organisms such as *Proteus*. Renal tubular acidosis and ingestion of absorbable alkali also may increase urine pH and must be considered in the differential diagnosis. A pH less than 5 often is associated with the formation of uric acid calculi.

Crystalluria. Historically, examination of urine crystals present on microscopic evaluation has provided a clue to the type of stone present. As a result of consolidation of urine testing to a central laboratory in most hospitals, this test is no longer routinely performed in most EDs.

Other Laboratory Tests. Serum uric acid levels are elevated in 50% of all uric acid stone formers, but this determination is not mandatory in the ED evaluation of the patient. Measurement of BUN and serum creatinine levels is not routine but should be done in patients who have a renal calculus with a solitary kidney, a transplanted kidney, or a history of renal insufficiency. A complete blood count may reveal a slightly elevated WBC count in patients with renal calculi which may be due to demargination, but this is not a sensitive test and should only be performed in patients who are thought to be infected. A WBC count higher than 15,000/mm^3 or a significant left shift on the differential suggests active infection. Serum calcium and phosphorus levels can help screen for hyperparathyroidism, sarcoidosis, and other disorders of calcium metabolism, but this metabolic workup is not a necessary component of the ED evaluation of nephrolithiasis.

Imaging. Imaging is not needed in all patients with renal colic. If the signs and symptoms are atypical, the diagnosis is in question, the patient appears toxic, high-grade obstruction is suspected, or it is the patient's first episode of flank pain, imaging should be performed.

Computed Tomography. Non–contrast-enhanced helical (spiral) CT scan is the standard imaging modality in the United States. It is sensitive and specific (97% and 96%, respectively) in detecting both ureteral calculi and ureteral obstruction.[41,42] Other advantages include its ability to detect calculi as small as 1 mm in diameter and to provide direct visualization of complicating conditions such as hydroureter, hydronephrosis (Fig. 97-4), and ureteral edema.[43] The CT scan is superior to other imaging modalities in its ability to recognize other pathology (malignancy, renal abscess, abdominal aortic aneurysm). It also has the advantage of lack of contrast exposure, short duration of testing, and ease of interpretation.

Contraindications to CT imaging are few. Obese patients may be unable to undergo CT scanning if their girth or weight is beyond the capacity of the scanner. CT also is not the preferred modality in pregnant patients because of radiation exposure to the fetus. In recent reports, CT scans underestimated the actual size of the stone by as much as 12% compared with the scout film from an IVP or KUB study. This limitation may adversely affect the management of patients with 5-mm stones, for example, in whom conservative therapy would be chosen on the basis of CT findings, although specific intervention would be more appropriate.[44]

Intravenous Pyelography. IVP is an accurate imaging modality to detect renal stones, but it is seldom used since CT scanning and ultrasonography have become first-line imaging modalities. It is very sensitive, capable of establishing the diagnosis of calculous disease in 96% of cases, and it can quantify the presence and severity of obstruction. Contraindications to the use of urographic contrast media include renal insufficiency and previous reaction to radiocontrast material. The incidence of serious contrast reactions is extremely low and estimated to be 0.9 per 100,000. Its value also is limited by the complexity and length of time needed to perform the procedure, which can take as long as 2 hours.

Ultrasonography. Ultrasonography is safe and easily performed, but it is much less reliable than CT scanning for detecting small (less than 5 mm in diameter) ureteral and midureteral stones.[45] Although only 37 to 64% sensitive for detecting calculi, ultrasound examination shows hydronephrosis with a sensitivity of 85 to 94% and a specificity of 100% (Fig. 97-5).

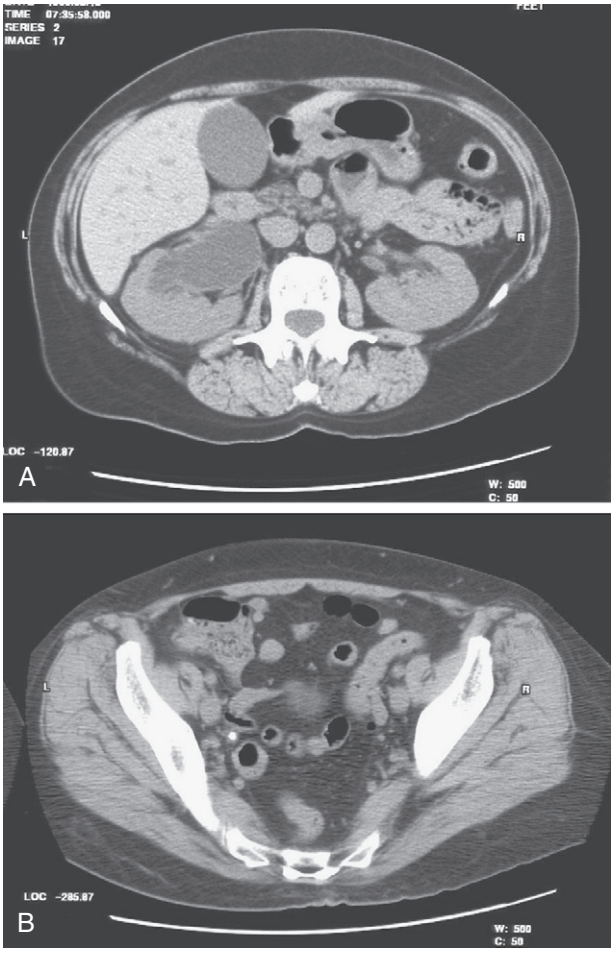

Figure 97-4. Computed tomography images obtained in a patient with renal colic. **A,** Right-sided hydronephrosis. **B,** Right ureteral calculi.

It is the study of choice for ruling out hydronephrosis in a pregnant patient with pyelonephritis, if obstructive urolithiasis is a concern, or in obese patients who cannot undergo CT scanning.[46]

Radiography of the Kidney, Ureter, and Bladder. A kidney-ureter-bladder (KUB) film is the standard initial radiographic study done before injection of contrast medium during IVP. It is of limited usefulness on its own except as a progress film after CT has already identified a radiopaque stone. A KUB film is not reliable for diagnosing urolithiasis because it provides only presumptive evidence of calculi (less than 70% specificity), so it should be followed by a more definitive study. The most common radiographic densities seen on KUB films are phleboliths in the pelvic veins, which are spherical with a hollow (lucent) center, whereas calculi usually are irregularly shaped and solid. Calcified mesenteric lymph nodes also may add confusion, although unlike phleboliths, these denisities commonly change position on subsequent films.

Most calculi (90%) are radiopaque, including calculi composed of calcium oxalate, cystine, calcium phosphate, or magnesium-ammonium-phosphate (Figs. 97-6 and 97-7). Uric acid stones, blood clots, and sloughed papillae are seen as "negative" shadow on radiographs. The most commonly overlooked calculi lie in the region over the sacrum, where small stones often are obscured by this bony density.

Differential Considerations

A number of significant clinical entities can produce flank pain (Box 97-3) and should be considered in patients with symptoms suggestive of renal colic. Such conditions include abdominal aortic aneurysm, pyelonephritis, carcinoma, renal tuberculosis, papillary necrosis, and vascular compromise.

Acute pyelonephritis can cause severe renal pain. Urinalysis will aid in the differential diagnosis by demonstrating pyuria and bacteriuria. However, infection also can occur concomitantly with an obstructive stone. This combination constitutes a true urologic emergency and requires imaging (renal CT, ultrasonography, IVP) to rule out hydronephrosis, which may warrant immediate urologic intervention (placement of ureteral stents).

Renal carcinoma also may produce flank pain, especially if hemorrhage has occurrred within the tumor. An abdominal flat-plate radiograph (a KUB film) may demonstrate calcifications overlying the renal shadow, which often are seen in renal neoplasms. IVP may suggest the diagnosis, but CT scan is the best imaging modality.

Papillary necrosis may cause renal colic as a result of passage of sloughed papillae down the ureter. It most is often seen in

BOX 97-3 DIFFERENTIAL DIAGNOSIS FOR PAIN ASSOCIATED WITH UROLITHIASIS

Urologic Disease

Upper Urinary Tract
Renal infarct
Renal parenchymal tumors
Urothelial tumors
Papillary necrosis
Pyelonephritis
Hemorrhage (blood clot)

Ureter
Urothelial tumors
Hemorrhage (blood clot)
Previous surgery (e.g., stricture)
Metastatic tumors

Lower Urinary Tract
Urothelial tumors
Urinary retention

Nonurologic Disease

Intra-abdominal
Peritonitis (especially appendicitis)
Biliary colic
Intestinal obstruction

Vascular
Abdominal aortic aneurysm
Superior mesenteric artery occlusion

Retroperitoneal
Retroperitoneal lymphadenopathy
Retroperitoneal fibrosis
Tumor

Gynecologic
Cervical cancer
Endometriosis
Ovarian vein syndrome

Musculoskeletal
Muscle strain or bony injury

From Lingeman J: Calculous disease of the kidney and bladder. In Harwood-Nuss A (ed): The Clinical Practice of Emergency Medicine, 2nd ed. Philadelphia, JB Lippincott, 1996.

diabetics and in patients with a history of acute or chronic UTI. Sloughed papillae may be visualized on renal imaging and can be mistaken for an obstructive stone.

Renal pain, either colicky or noncolicky, also is produced by acute vascular compromise of a kidney. The pain of renal infarction is severe and occasionally associated with microscopic or gross hematuria. The acute vascular changes may be secondary to renal artery embolism, renal vein thrombosis, dissection of the renal artery, rupture of a renal artery aneurysm, aortic dissection, or abdominal aortic aneurysm. If a vascular etiology is suspected, a contrast-enhanced CT scan or an angiogram should be performed. The most common of these relatively rare processes is renal artery embolism, which most often is of cardiac origin (as with atrial fibrillation, subacute bacterial endocarditis, or mural thrombus). An immediate angiogram is indicated because early diagnosis allows possible salvage of the ischemic kidney. Most renal artery aneurysms are small and seldom produce clinical manifestations. Dissection or rupture of a renal artery aneurysm is rare and causes shock and flank pain. Renal vein thrombosis often demonstrates microscopic hematuria and proteinuria. The KUB film may show an increased renal shadow, and in the early stages, contrast studies show decreased function of the affected kidney. Predisposing factors for renal vein thrombosis include nephrotic syndrome, malignancies, and pregnancy.

A renal or perinephric abscess may cause flank pain, fever, and a palpable mass. Ultrasonography or a CT scan should be performed. A chest radiograph may demonstrate a pleural effusion or elevation of the diaphragm. Both renal and perinephric abscesses require hospitalization for drainage, intravenous fluids, antibiotics, and determination of the underlying cause.

Management

General Approach. Patients with renal stones generally are in severe pain and are unable to find a comfortable position. Often, the history and physical examination, combined with the finding of hematuria, allow a presumptive diagnosis to be made and therapy to be initiated. The first priority is adequate pain control. Nonsteroidal anti-inflammatory drugs (NSAIDs) are first-line agents, but parenteral administration often is necessary because of vomiting. Intravenous ketorolac (Toradol) provides rapid effective analgesia with minimal side effects. In addition to their analgesic effects, NSAIDs decrease the pain of renal colic by decreasing ureterospasm and also reduce renal capsular pressure by diminishing the glomerular filtration rate in the obstructed kidney. Accordingly, caution is advised with use of these agents in patients with underlying renal insufficiency or peptic ulcer disease. An antiemetic may be useful if the patient complains of nausea, and intravenous fluids should be given to the vomiting patient who is unable to tolerate liquids and who is likely to undergo an imaging procedure.

Narcotics (morphine sulfate, meperidine, or hydromorphone) also are very effective in providing rapid analgesia, faster than NSAIDs. However, they carry a higher incidence of side effects than that noted with NSAIDs. The combination of NSAIDS and opiates is an acceptable approach that may

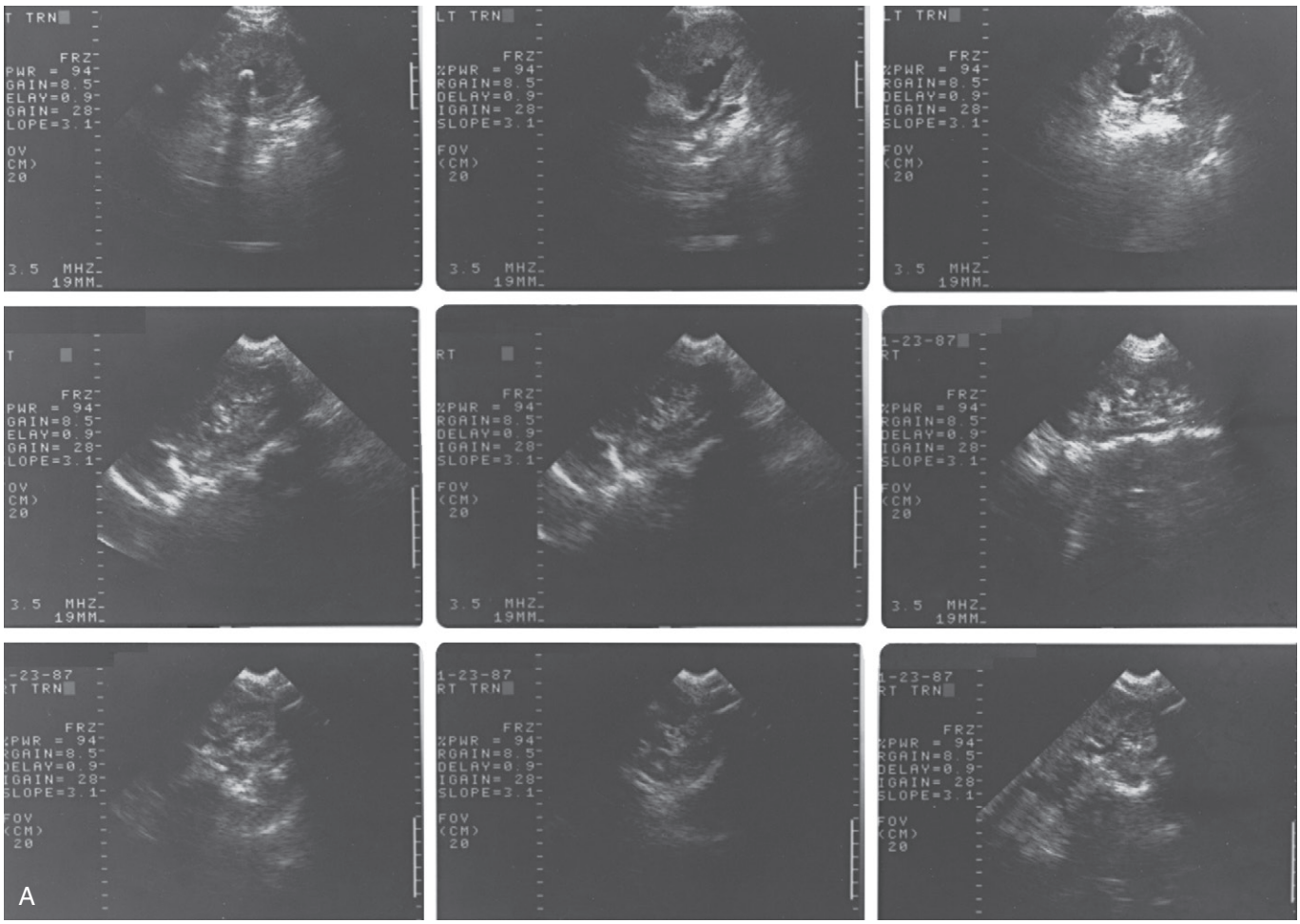

Figure 97-5. Ultrasound images of the kidney in a patient with renal colic. **A,** A long 1-1 axis view demonstrates hydronephrosis.

Continued

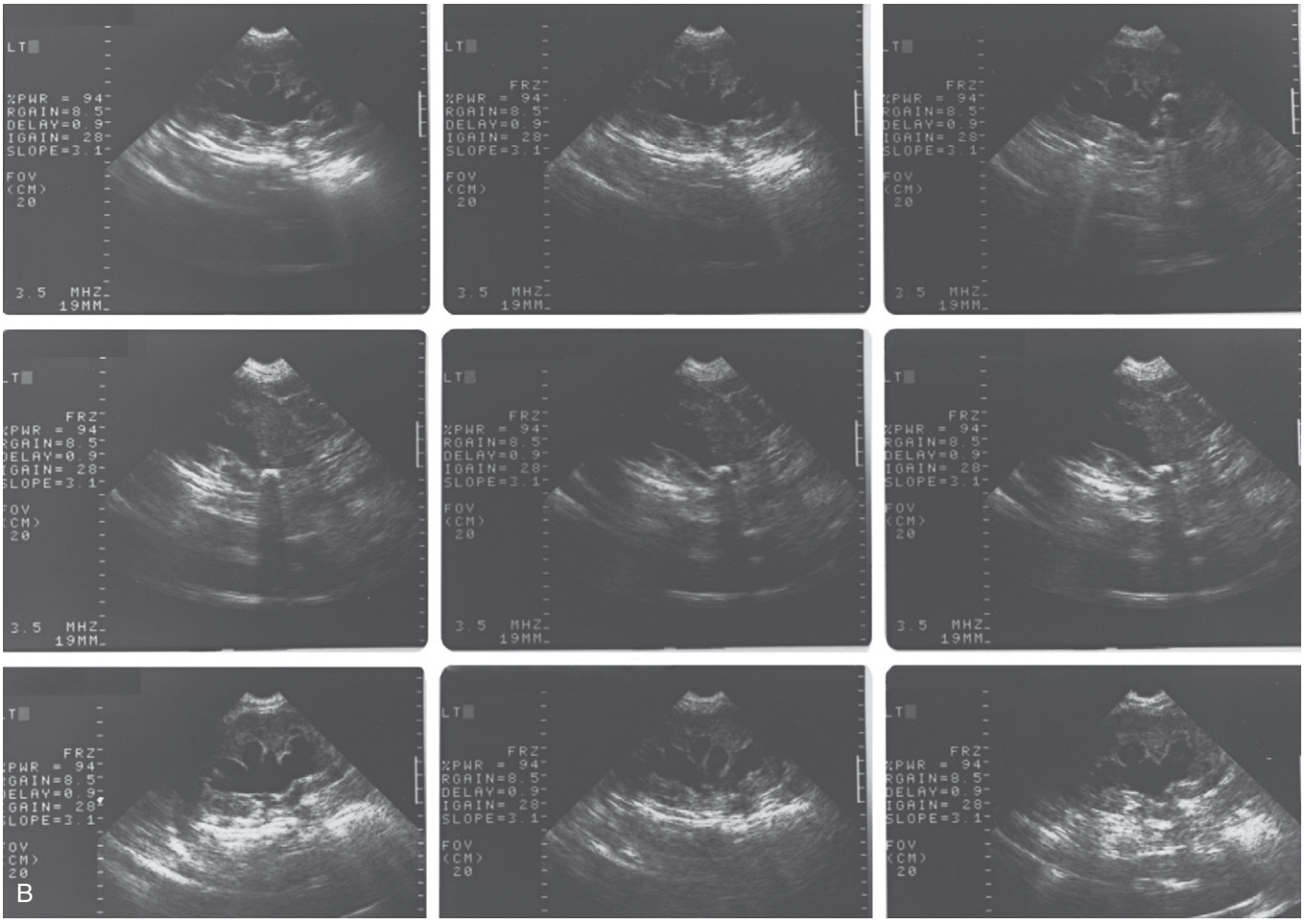

Figure 97-5, cont'd **B,** A transverse cut shows a calcification with an acoustic shadow in the renal calyx.

Figure 97-6. In a near-term pregnant woman with an obstructed left kidney, intravenous pyelography demonstrates a delayed nephrogram. The right kidney has physiologic hydronephrosis from ureteral compression by the fetal head.

Figure 97-7. In a near-term pregnant woman with an obstructed left kidney, intravenous pyelography demonstrates a delayed nephrogram. The right kidney has physiologic hydronephrosis from ureteral compression by the fetal head.

reduce length of stay in the ED.[47] Little evidence in the literature supports the use of anticholinergics or steroids for the treatment of acute colic.

Outpatient Management. Most patients with nephrolithiasis may be safely discharged to home from the ED. Current guidelines recommend urologic intervention in patients with symptoms persisting for longer than 2 months.[48] The patient should be instructed to drink a moderate amount of fluids, to take analgesics as needed for pain, and to engage in activity as tolerated.

Medical expulsive therapy is another important aspect in the management of ureteral stones. Because ureteral smooth muscle contraction is mediated by intracellular calcium and by the autonomic nervous system, α_1-antagonists and calcium channel blockers facilitate distal stone expulsion and decrease the time to spontaneous stone passage.[49,50] These agents work by blocking ureteral smooth muscle contraction and improving antegrade stone movement. Both types of medications have been shown to assist in stone passage. Such therapy tends to be most efficacious with stones less than 5 mm in diameter located in the distal ureter. No published studies have addressed the usefulness of medical expulsion therapy with stones larger than 6 mm in the absence of shockwave lithotripsy, and no studies have compared the efficacy of α_1-antagonists and calcium channel blockers.[51] The most common medication prescribed to facilitate stone passage is either tamsulosin or nifedipine, although other drugs in the same class seem to be equally effective.[52] Proper discharge instructions should include work and driving restrictions for patients taking narcotics. In addition, patients should be instructed to strain all urine with a strainer manufactured for this purpose. If such a device is not available, patients may simply void into a glass jar; the calculus should be visible at the bottom. The stone should be saved and submitted to the urologist for analysis. Patients should be instructed to return to the ED immediately for intractable or severe pain, persistent nausea and vomiting, fever or chills, or difficulty voiding. Finally, an outpatient urologic evaluation should be scheduled.

Indications for Hospital Admission. Hospital admission should be sought for patients who are severely dehydrated, are experiencing unrelenting pain or vomiting, or have an underlying urinary infection (Box 97-4). Sepsis and renal damage are risks in the presence of obstruction and infection, so admission to the hospital floor is inadequate. These patients require immediate urologic consultation to evaluate the need for drainage and for relief of the obstruction (usually ureteral stenting). If signs of sepsis (tachycardia, fever, hypotension, shock) are present, antibiotics and fluid resuscitation should be administered while awaiting urologic evaluation. Immediate operative intervention may be indicated to provide drainage and relieve the obstruction.

BOX 97-4 INDICATIONS FOR HOSPITAL ADMISSION OF PATIENTS WITH UROLOGIC SYMPTOMS

Absolute
Obstructing stone with signs of urinary infection
Intractable nausea/vomiting
Severe pain requiring parenteral analgesics
Urinary extravasation
Hypercalcemic crisis

Relative
Significant comorbid illness complicating outpatient management
High-grade obstruction
Leukocytosis
Size of stone
Solitary kidney/intrinsic renal disease
Psychosocial factors adversely affecting home management

A patient who returns to the ED with persistent colic may not need a second imaging study if the stone was identified previously. In such cases, a KUB film may localize the stone. An intervention by the urologist may be necessary if the stone has not progressed along the genitourinary tract. Several interventional strategies are available to the urologist for the management of stones that do not pass spontaneously. Optimal therapy depends on the size, location, and composition of the stone. Extracorporeal shock wave lithotripsy (ECSWL) has proved to be effective for stones located in the kidney, with a greater than 85% clearance rate. Upper ureteral stones also may be cleared with a high success rate when ECSWL is performed after ureteroscopic manipulation of the stone to a more proximal position. Percutaneous nephrolithotomy, which establishes a tract from the skin to the collecting system, is used for stones too large or hard for ECSWL by removing them directly from the renal pelvis. Stones unresponsive or unlikely to respond to other techniques may require surgical removal.

BLADDER (VESICAL) CALCULUS

Although calculi generally form in the kidneys, they also may originate in the bladder. Bladder stones constitute a different entity from that of renal stones. In the United States, bladder stones occur almost exclusively in elderly men, often as a complication of other urologic disease. The most common cause is infection of residual bladder urine with urea-splitting organisms. The other common cause of vesical stones is an indwelling catheter. Disorders predisposing to the formation of bladder stones include bladder neck obstruction (usually secondary to prostatic hyperplasia), neurogenic bladder, vesical diverticula, damage from irradiation, and schistosomiasis.

The presenting manifestations most often are pain on voiding and hematuria. The patient may complain of a sudden interruption of the urinary stream, which strongly suggests a vesical stone that intermittently obstructs the bladder outlet. Frequency, urgency, and dysuria are described by up to 50% of patients, and UTI is common. Physical examination is rarely rewarding because signs may be minimal. Rectal examination may reveal an enlarged prostate or a prostatic malignancy. Poor sphincter tone may suggest a neurogenic bladder. Urinalysis generally reveals pyuria, bacteriuria, and hematuria. Plain radiographs of the pelvis reveal a bladder stone in 50% of cases. Contrast scans may demonstrate obstructive changes in the upper tracts or bladder diverticula. Ultrasonography also is useful in the diagnosis of bladder stones.

ACUTE SCROTAL PAIN

Perspective

Several unique disorders encountered in the ED setting produce scrotal pain. It is crucial to determine the exact etiologic disorder in such cases because testicular torsion, a common cause of scrotal pain, represents a surgical emergency, mandating rapid recognition and treatment. Other causes of scrotal pain require less invasive and time-dependent therapies, such as antibiotics for epididymitis and observation for benign masses or torsion of the appendix of the testes.

Principles of Disease

Anatomy. Knowledge of testicular landmarks is essential for examination of the patient with an acute scrotal mass.

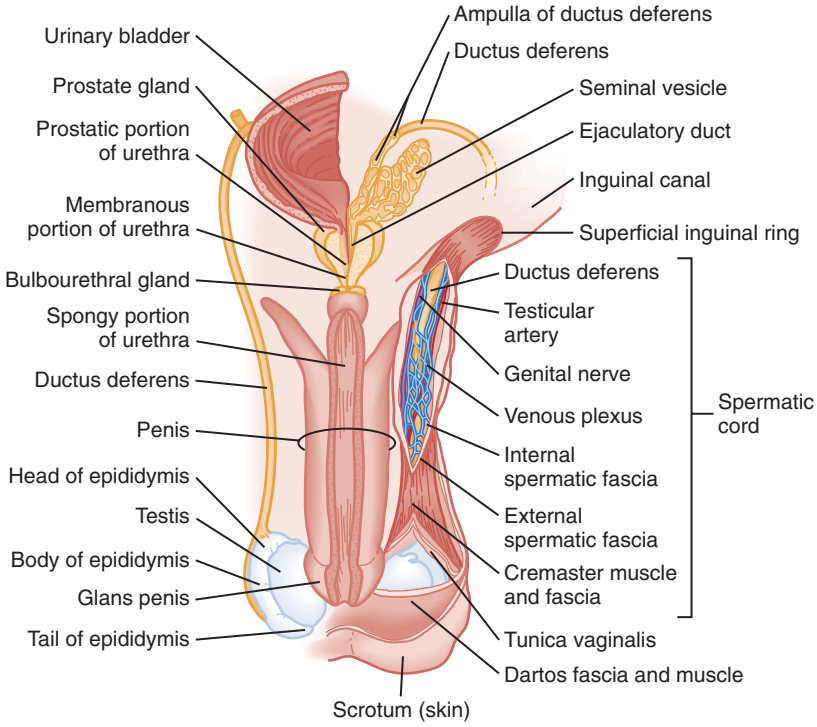

Figure 97-8. Testes, epididymis, ductus deferens, and glands of the male reproductive system. (From Seeley RR, et al [eds]: Anatomy and Physiology, 1st ed. New York, McGraw-Hill, 1989.)

Figure 97-8 demonstrates the normal anatomy of the scrotum and testis. A normal scrotum is relatively symmetrical, and both testicles are of equal mass and volume. The left testicle often is higher than the right, because its blood flow empties into the large, low-pressure vena cava, whereas the right drains into the relatively smaller, high-pressure renal vein. A normal testis is found in the vertical axis with a slight forward tilt, and the epididymis is above the superior pole in the posterolateral position.

Physical Examination. On examination of the testis, any tenderness to palpation, discrepancies in size, loss of testicular landmarks, or discoloration should be noted. The epididymis is located posterolateral to the testis and should be nontender and soft. The cremasteric reflex is elicited by stroking or pinching the inner aspect of the thigh; more than 0.5 cm of elevation of the ipsilateral testicle is considered evidence of a normal reflex. This reflex normally is absent in 50% of male infants younger than 30 months of age.[53]

Differential Considerations

Acute scrotal pain can arise with testicular torsion, epididymitis, torsion of the appendix of the testis, testicular tumor, or a hernia. Testicular torsion is the most important etiologic disorder to be excluded because any delay in treatment of this condition is associated with increased risk of testicular loss and infertility.

Specific Disorders

Testicular Torsion

Perspective. Testicular torsion is identified in approximately 16 to 42% of patients coming to the ED with scrotal pain.[54-56] It is the most common cause of the acute scrotum in prepubertal boys, with a peak incidence in the first year of life.[57] It also has a second peak incidence at puberty, when the rapid increase in testicular volume predisposes the testis to torsion. It also can occur in adulthood, as evidenced by a retrospective review of data for 44 patients with torsion, of which 17 were older than 21 years of age.[58] Factors that increase the likelihood of torsion include horizontal lie of the testis, increased length of the spermatic cord in the scrotum, and a history of cryptorchidism.[59]

Principles of Disease. With torsion, an extravaginal or intravaginal defect of the testis leads to twisting of the spermatic cord and decreased blood supply to the testicle. The cremasteric muscle surrounds the spermatic cord, and in the normal testicle, the testicle does not rotate when the cremasteric muscle contracts. In patients with torsion, however, the anatomic defect allows the tunica vaginalis to insert higher on the testicle, where it encircles the epididymis and distal spermatic cord. When the cremasteric muscle contracts in this abnormal scrotum, there is more room for the testicle to move, and it twists around the spermatic cord. Its movement resembles the ringing of the clapper in a bell—hence the description of a "bell clapper" deformity. By contrast, extravaginal defects occur almost exclusively in neonates and arise because the testicle lies outside of the tunica vaginalis, where it is prone to rotation. Torsion in neonates often is congenital and by the time the condition is noted at birth, the testicle is not salvageable.[60]

Testicular trauma also has been associated with torsion and has been noted in the literature to occur after motor vehicle collisions, straddle injuries, and athletic injuries. In these instances, the symptoms of torsion often are misattributed to the trauma itself, so the diagnosis is delayed. As a result, testicular salvage rates are only 40% after groin trauma.[61] In order to prevent loss of the testicle, scrotal pain persisting for an hour after any traumatic injury should raise suspicion for concomitant torsion of the testis.

As the testicle twists around the spermatic cord in torsion, it initially hinders venous return. Persistent torsion produces arterial obstruction, leading to ischemia and eventual necrosis of the testicle. With increasing degrees of rotation of the cord, ischemia increases, and infarction of the testicle occurs much more rapidly. Unfortunately, no clinical method has been devised for determining the extent of rotation of the testicle

Table 97-6 Differentiation among Causes of the Acute Scrotum

FEATURE	TESTICULAR TORSION	APPENDIX TORSION	EPIDIDYMITIS
Age	<1 yr, puberty	7–14 yr	Adult
Onset	Hours	1–2 days	Days to weeks
Location of pain	Entire testicle	Upper pole	Epididymis
Systemic symptoms	Nausea	None	Fever
Cremasteric reflex	No	Intact	Intact
Pyuria	No	No	Yes
Ultrasound findings	Diffusely hypoechoic Asymmetrical testicles Decreased flow	Focally hypoechoic Symmetrical testicles Normal flow	Hypoechoic epididymis Symmetrical testicles Increased flow
Treatment	Surgery	Supportive	Antibiotics

Note: No single finding in patients with an acute scrotum can reliably differentiate torsion from other causative disorders. When torsion is a diagnostic possibility, prompt urology consultation is mandatory.

and the resultant likelihood of rapid ischemia. The duration of vascular obstruction also affects the ability to salvage the testicle; torsion recognized within 6 hours is associated with testicular salvage rates of 80 to 100%, whereas persistence of symptoms for 24 hours or longer is associated with nearly universal loss of the testicle.[62]

Clinical Features. Patients typically complain of sudden onset of scrotal pain that awakens them from sleep or develops several hours after physical activity. The pain arises in the scrotum, lower abdomen, or inguinal area. Patients tend to seek medical attention at approximately 9.5 hours into their disease course, earlier than patients with alternate causes for an acute scrotum.[63] Up to 29% of patients describe similar pain in the past, due to previous intermittent torsion in a predisposed testicle.[64] Patients often complain of nausea and vomiting, although no historical factors, including nausea, vomiting, fever, urinary symptoms, and a history of trauma, have been found to differentiate torsion from other causative disorders (Table 97-6).

The physical exam is much more reliable than the history in determining the presence of testicular torsion. The most common finding is loss of the cremasteric reflex, observed in nearly 100% of patients older than 30 months of age with torsion.[57] In a retrospective review of 245 patients with acute scrotal swelling, none of the patients with a cremasteric reflex had torsion.[65] This sign also is relatively specific, because most patients with other causes of scrotal pain have an intact cremasteric reflex. In addition, patients with torsion frequently have a tender, firm testicle that can be higher than the contralateral testicle, owing to shortening of the spermatic cord as it twists. This twisting also can leave the testicle in the transverse position and displace the epididymis from its usual location along the posterior aspect of the scrotum. Often the patient's scrotum is so swollen and tender that a complete physical exam is impossible. After 24 hours, the physical exam is not particularly helpful, because many of the aforementioned findings are no longer present.[66] Despite the limitations of the physical exam, any patient presenting with acute onset of scrotal pain and any of the aforementioned physical findings should be considered to have torsion until proven otherwise.

Diagnostic Strategies. In patients in whom the history and physical findings strongly suggest torsion, urgent surgical consultation is warranted. If the diagnosis is equivocal, adjunctive tests can be performed to determine the cause of the pain. Although urinalysis results suggestive of infection are consistent with epididymitis, such findings also may be noted in patients with torsion and concomitant UTI. Similarly, a complete blood count does not adequately differentiate torsion from alternate causes of the acute scrotum.

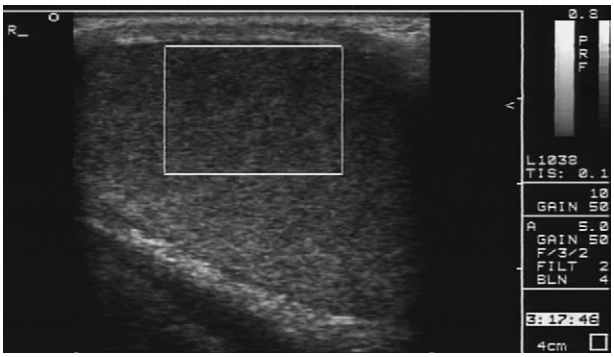

Figure 97-9. Doppler ultrasound image showing a testicle with no flow due to torsion. (From Blaivas M, Brannam L: Testicular ultrasound. In Rosen C, Wolfe R [eds]: Ultrasound in Emergency Medicine. Emerg Med Clin North Am 22:730, 2004 [Figure 7].)

Ultrasound imaging is a much better test, with a sensitivity of 88 to 100% and specificity approaching 90%.[67] Using a 7- to 10-mHz high-frequency probe on the supine patient, the asymptomatic testicle should be examined first, and the optimal settings for visualization and measurement of blood flow should be determined. In contrast with this testicle, the torsed testicle typically will be hypoechoic and enlarged (Fig. 97-9). False-negatives occur when the testicle is examined early in the course of the disease, when blood flow is still present, and with intermittent torsion. Examining the spermatic cord for twisting, instead of the testicle itself, has been shown to reduce the frequency of these false-negatives.[68] Color Doppler techniques can improve the specificity of ultrasound imaging to 100% by demonstrating reduced blood flow to the affected testicle. Doppler studies can be more difficult to interpret in younger children because blood flow is physiologically low in the testicles of prepubertal boys. However, there should still be symmetry between both testicles in a normal examination without torsion.

Color Doppler ultrasound imaging has the advantage of being an inexpensive, rapid test, readily performed in the ED setting.[69,70] It is helpful when it demonstrates torsion in cases with equivocal findings on the history and physical exam, but it does not have sufficient sensitivity to rule out a diagnosis of torsion. A urologist should evaluate any patient in whom ultrasound findings are negative but history and physical findings

are suggestive of torsion. Moreover, ultrasound examination should never delay evaluation by a urologist in any patient with probable torsion.

Radioisotope scanning has the advantage of improved sensitivity compared with ultrasonography, but it is a time-consuming test inappropriate for use in the ED.

Management. The first step in management of very strongly suspected testicular torsion is immediate consultation with a urologist. The longer the spermatic cord remains twisted, the lower the likelihood of testicular salvage. More than 90% of affected testicles can be saved within 6 hours of symptom onset, but by 24 hours, 100% are lost.[62] After consultation, intravenous access is established and analgesia is provided either systemically or with a block of the spermatic cord. Manual detorsion should then be attempted as follows: The operator stands at the supine patient's feet and then rotates the affected testicle away from the midline, as if turning the pages of a book. If this maneuver is successful, patients should report rapid reduction of symptoms. Most studies suggest this technique untwists approximately 26% of testicles under torsion; other studies, however, have achieved success rates as high as 80%.[71] Some torsions involve rotation through 720 degrees, so continuing the untwisting maneuver past 360 degrees is recommended if no improvement is obtained initially, especially in cases in which torsion is strongly suspected. Regardless of the outcome with manual detorsion, patients still require surgical evaluation. In addition, evaluation by a urologist should never be delayed in order to perform this or any other test or maneuver.

Disposition. Rapid diagnosis of testicular torsion is essential and should be followed by emergent surgical scrotal exploration and bilateral orchidopexy, if necessary. Loss of the testicle most commonly is due to delay in seeking medical attention. However, almost 30% of cases of failed testicular salvage have been attributed to misdiagnosis, and another 13% to a delay in treatment after the proper diagnosis was established.[64,72]

Torsion of Appendages

Perspective. A normal scrotum has several vestigial appendages that also can twist and become ischemic, with resultant scrotal pain. This process is most common between 7 and 14 years of age, with a mean age of 10 years. In retrospective analyses, torsion of an appendage rivals testicular torsion as the most common cause of the acute scrotum.[73]

Principles of Disease. The appendix testis, a remnant of the paramesonephric duct, is present in 92% of patients. It is located on the superior aspect of the testicle between the testis and the epididymis. The appendix epididymis, a remnant of the mesonephric duct, is the second most common testicular appendage, found in approximately 23% of patients. It typically is located on the tip of the epididymis (Fig. 97-10). These appendages are prone to torsion owing to their pedunculated shape. After several days of ischemia due to torsion, they will undergo necrosis with eventual reabsorption. Their loss does not permanently affect fertility or have any impact on surrounding structures.

Clinical Features. As with testicular torsion, patients with torsion of an appendage complain of scrotal pain but report milder symptoms with a more gradual onset. These patients usually seek medical attention in the ED after 48 hours of symptoms.[63] In contrast with testicular torsion, the pain often can be localized to one point on the testicle. These patients infrequently report nausea, vomiting, urinary symptoms, or previous episodes of similar pain.

On physical exam, twisting of the appendix testis leads to formation of a hard, tender, 2- to 3-mm nodule at the upper pole of the testicle. Unlike in testicular torsion, the entire testicle is not tender. The testicle also does not change in overall size, and the epididymis remains posterior. The cremasteric reflex typically is intact. On transillumination, the ischemic appendage may appear as a blue dot. Although highly specific for torsion of the appendix, this sign is found in as few as 10% of patients.[73] A reactive hydrocele can form during the course of disease, obscuring the physical findings with the twisted appendix.

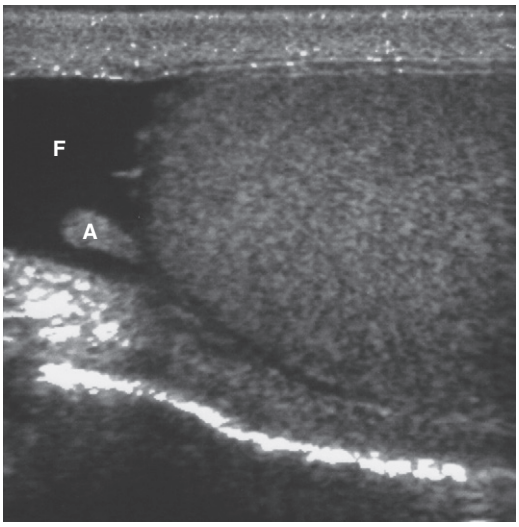

Figure 97-10. Ultrasound image showing the testicular appendage (A) surrounded by a hydrocele (F). (From Blaivas M, Brannam L: Testicular ultrasound. In Rosen C, Wolfe R [eds]: Ultrasound in Emergency Medicine. Emerg Med Clin North Am 22:729, 2004 [Figure 6].)

Diagnostic Strategies. Urinalysis does not show evidence of infection. On ultrasound imaging, the appendix under torsion will appear hypoechoic. When the appendix then enlarges, the "Mickey Mouse" sign may be apparent on the transverse view, as a result of juxtaposition of the testicle, enlarged appendix, and epididymis. Color Doppler ultrasound examination and nuclear scintigraphy are useful imaging studies that show normal to increased blood flow to the involved appendage and symmetrical testicles.

Differential Considerations. Other diagnostic entities such as testicular torsion, epididymitis, and testicular tumor must be considered and excluded before a firm diagnosis of torsion of an appendage can be made.

Management and Disposition. If testicular torsion is ruled out, surgical excision of the appendix is rarely necessary. Treatment consists of scrotal support, ice, and NSAIDs. Resolution of symptoms can be expected within 7 to 10 days. Surgical excision is reserved for uncontrollable pain.

Epididymitis

Perspective. Epididymitis is the most common intrascrotal inflammatory disease. Nearly one half of the cases arise in young men, between the ages of 20 and 29 years, but the disease also has affected patients from 4 months to 76 years of age.[74] If untreated, it can lead to orchitis, testicular abscess, and rarely sepsis.

Principles of Disease. The epididymis is a tightly coiled tubular area along the posterior aspect of the testes, where sperm mature before their transit to the vas deferens. It becomes infected when organisms travel retrograde from the vas deferens. With infection, the testis may become edematous secondary to passive congestion and inflammation. Resolution of

epididymitis typically concludes without sequelae, but peritubular fibrosis can occlude the ductules of the epididymis, leading to an increased risk of infertility.

Pathophysiology. The particular organisms involved in the infection depend on the sexual activity of the patient. Although the literature classically describes men younger than 35 years of age as prone to *C. trachomatis* and *N. gonorrhoeae* infections, all sexually active men, regardless of age, are at risk for epididymitis from these organisms. *C. trachomatis* is much more common, being identified in 47% of patients younger than 35 years, with *N. gonorrhoeae* seen in 20%.[75] *Ureaplasma* also has been identified in patients with epididymitis, although whether it was the actual causative agent is unclear.[76] In patients with syphilis, infection can spread to the epididymis during the secondary phase. In homosexual men who engage in anal intercourse, coliforms also can lead to sexually transmitted epididymitis.[75]

In men older than 35 years of age, urinary tract pathogens become the predominant cause of epididymitis. *E. coli* is the most common, occurring in 32 to 55% in this age group.[74,77] *Pseudomonas aeruginosa* and *Proteus mirabilis* also can infect the epididymis, and although much less common in the industrialized world, *M. tuberculosis* also has been implicated. In immunocompromised patients, fungal and other opportunistic infections have been reported.

Unlike younger patients, older men with epididymitis tend to have urinary tract abnormalities that predispose them to these infections of the epididymis. In one review, 56% of men older than 60 years of age with epididymitis had lower urinary tract obstruction.[78] Older men also are more likely to have undergone recent genitourinary instrumentation, another risk factor for epididymitis.[77] This includes hernia repair, which often can lead to iatrogenic infection of the nearby spermatic cord and epididymis. Acute or chronic prostatitis also may increase the risk of epididymitis. Finally, several authorities have suggested a possible association between indwelling catheters and epididymitis.[76] Each of these factors renders older men prone to epididymitis after they are no longer sexually active.

Children also can have epididymitis, although it is a much less common cause of scrotal pain in this age group than testicular torsion. Children with epididymitis tend to have congenital genitourinary anomalies that predispose them to recurrent infection.[79]

Amiodarone also has been implicated as a cause of epididymitis, with nearly 20 case reports in the literature. One study has suggested that amiodarone-induced epididymitis may be more common, arising in as many as 3 to 11% of patients receiving this agent.[80] The effect is dose-dependent, typically occurring after at least 4 months of treatment and with doses of 400 mg or more per day.[81] Amiodarone concentrates in the testicle, resulting in lymphocytic infiltration and epididymal fibrosis.[82] Unlike with infectious epididymitis, patients do not have fever, pyuria, or leukocytosis.[83]

Clinical Features. Patients with epididymitis experience scrotal pain of gradual onset, prompting them to come to the ED later in the clinical course than patients with torsion, whose symptoms tend to be more abrupt in onset. Initially, this pain may reside in the lower abdomen or flank, being due to inflammation of the vas deferens. In patients with STDs, urinary symptoms and urethral discharge are found in 10 to 30%. Nearly three fourths of patients report fever.[84] In the early stages of the disease, tenderness is localized to the epididymis, but it quickly spreads to the adjacent testicle. Also, later in the course, the scrotum can become edematous, erythematous, and extremely tender. Although Prehn's sign—decrease in pain with elevation of the scrotum—has been touted as indicative of epididymitis, it has low sensitivity and specificity. Similarly, only 10% of patients with epididymitis from sexually transmitted organisms have urethral discharge on exam.[76] None of these historical factors or physical findings have been shown to reliably differentiate torsion from epididymitis.

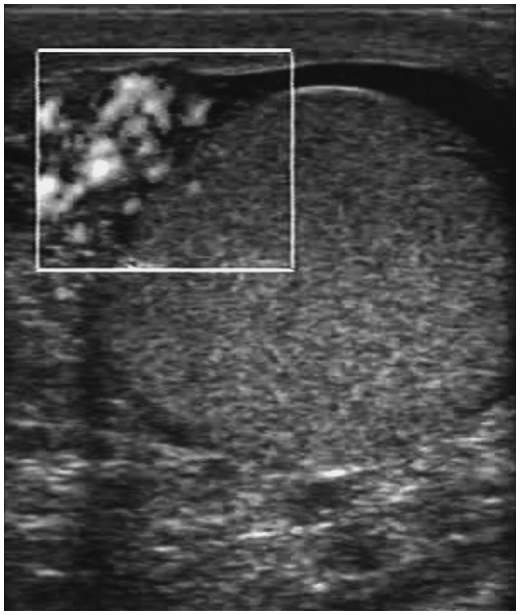

Figure 97-11. Ultrasound of the testicle showing an enlarged epididymis and increased blood flow on Doppler ultrasound imaging, outlined in a *white box*. (From Blaivas M, Brannam L: Testicular ultrasound. In Rosen C and Wolfe R [eds]: Ultrasound in Emergency Medicine. Emerg Med Clin North Am 22:741, 23, 2004 [Figure 23].)

Diagnostic Strategies. Urinalysis typically demonstrates evidence of infection, with the finding of pyuria in 50 to 93% of patients with epididymitis (defined as the presence of more than 4 leukocytes per high-power field).[85] If patients are at risk for STD, a urethral swab or urine sample should be obtained to test for *C. trachomatis* and *N. gonorrhoeae*; PCR and other nucleic acid amplification tests have the greatest sensitivity and should be used when available. The literature also describes epididymal aspiration, but this diagnostic modality has no role in the ED. Leukocytosis may be present but is a nonspecific finding and does not differentiate epididymitis from torsion.

In patients with a presentation equivocal for epididymitis and torsion, testicular ultrasound examination should be performed in the ED. With infection, the epididymis appears enlarged and hypoechoic (Fig. 97-11). On color Doppler ultrasound images, the affected testicle will show increased vascularity. These findings are 70% sensitive and 88% specific for epididymitis and can help differentiate the condition from torsion.[86]

Differential Considerations. Three intrascrotal processes are commonly confused with epididymitis: torsion, torsion of the testicular appendage, and tumor of the testicle. Epididymitis is the most common misdiagnosis in patients with torsion, and this error can lead to loss of the testicle.

Management. Empirical antibiotics should be selected in accordance with the patient's age, sexual history, and any previous genitourinary instrumentation (Table 97-7). In patients with a suspected sexually acquired infection, ceftriaxone 250 mg IM or ciprofloxacin 400 mg PO should be given to treat possible *N. gonorrhoeae* infection. In conjunction, doxycycline 100 mg PO twice daily for 14 days should be started to treat *C. trachomatis* infection. Although this regimen has never been

Table 97-7 Treatment of Epididymitis

DRUG OF CHOICE	DOSE/ROUTE	ALTERNATIVE REGIMEN(S)
Presumed Sexually Acquired Epididymitis		
Ceftriaxone	250 mg IM	Ciprofloxacin, 500 mg PO Ofloxacin, 400 mg PO
followed by		
Doxycycline	100 mg PO bid × 10 days	
or		
Tetracycline	500 mg qid × 10 days	
Presumed Nonsexually Acquired Epididymitis*		
Trimethoprim-sulfamethoxazole	One double-strength tablet PO bid × 14 days	Ciprofloxacin, 500 mg PO bid × 14 days Ofloxacin, 400 mg PO bid × 14 days

*Adjust antibacterial therapy with results of urine culture.

studied in patients with chlamydial epididymitis, it is presumed to be more successful than the single-dose azithromycin that is used for noncomplicated urethritis.[76] Treatment of sexual partners should be arranged even if the patient's urine culture demonstrates no growth, because in one study, 80% of female partners of men with epididymitis were found to harbor *C. trachomatis* infection, including partners of men with negative urine culture results.[87]

In patients with infection by urinary tract pathogens, ciprofloxacin 500 mg PO twice daily has been shown to be the most successful regimen, with 80% of patients improving after 14 days of treatment.[77] Ofloxacin 200 mg PO twice daily for 14 days is an alternative that also will cover sexually transmitted organisms and therefore is the ideal treatment when it is unclear if a patient has sexually acquired or urinary tract pathogens. Treatment can later be adjusted in accordance with the results of the patient's urine culture. In addition to appropriate antibiotics, bed rest, scrotal support, analgesics, sitz baths, and ice packs may be beneficial. A urologist can block the spermatic cord with bupivacaine to provide pain relief. This maneuver also appears to hasten the healing process, perhaps by increasing blood flow to the spermatic cord that was anesthetized. On discharge, the patient should be referred to a urologist for follow-up evaluation within 1 week.

Typically, symptoms resolve in 2 weeks in patients with sexually acquired disease and in 4 weeks in patients with urinary tract pathogens.[75] Complications are more common in older men, occurring in 39% of patients, and include intratesticular and epididymal abscess, testicular infarction, and late testicular atrophy. In younger patients, infection often reduces spermatogenesis, but the long-term effect on fertility is unclear.[76]

Disposition. Patients with systemic signs of toxicity (fever, chills, nausea, vomiting) or complications of acute epididymitis should be hospitalized and treated with parenteral antibiotics. Patients discharged from the ED should be reassessed within 1 week to ensure that their symptoms are resolving. Spread of infection, continued scrotal edema, ongoing testicular pain, and scrotal wall fixation are indications that outpatient management has failed, and hospitalization and emergent urologic evaluation are required to rule out an alternate diagnosis such as testicular torsion or scrotal abscess.

Testicular Tumors

Perspective. Tumor of the testis is the most common malignancy in young men but accounts for only 1% of all cancers in men.[88] These tumors are more common in infertile patients and whites. They also occur with increased frequency in the nondescended and descended testicles of patients with cryptorchidism. A number of simplified classification systems have been proposed for categorizing the different types of testicular tumors. Approximately 95% of tumors are germ cell tumors, with half of these being seminomas and the other half being mixed types, including teratomas, choriocarcinomas, and yolk sac tumors. The other 5% of testicular tumors are sex cord stromal tumors. The disease course will depend on the type of tumor present as well as the age of the patient.

Clinical Features. Unlike in torsion and epididymitis, patients with tumor typically present with a painless scrotal mass. When pain develops, it most often is due to acute hemorrhage within the tumor pushing against the nonpliable tunica albuginea. Presence of pain should be considered unusual with testicular tumor, and in such cases, torsion and epididymitis should be ruled out before a diagnosis of malignancy is considered. Patients with tumor also can present with symptoms related to metastases from a previously undiagnosed testicular cancer; 15% of patients have metastases to regional lymph nodes at the time of diagnosis and 5% have metastases to the abdomen or pelvis.

Diagnostic Strategies. All patients with a scrotal mass should undergo a scrotal ultrasound examination. This study can reveal a concomitant hydrocele or a homogeneous hypoechoic lesion. Although helpful for staging purposes, CT scans of the chest and abdomen are necessary in the ED only if the patient has complaints related to these parts of the body. Urinalysis findings typically are normal.

Management. Suspicion of a testicular tumor is an indication for urgent referral to a urologist, because radical orchiectomy with high ligation of the spermatic cord may be required. The radiosensitive nature of seminomas renders the combined treatment of orchiectomy and radiation therapy highly successful for early-stage disease. The ultimate treatment strategy, however, should be determined by a urologist. Any patient with systemic symptoms should be admitted to the hospital.

Orchitis

Perspective. Orchitis is a rare acute infection of the testis. It is most common in prepubertal boys, with viral infections such as mumps causing a majority of cases. Orchitis develops in approximately 20% of prepubertal boys with mumps but in almost no postpubertal males with mumps. It tends to arise several days after the onset of parotitis. Owing to the testes' relatively high threshold of resistance to infection, bacterial orchitis more commonly results from local bacterial spread from the epididymis. The most frequent bacterial pathogens are *N. gonorrhoeae*, *C. trachomatis*, *E. coli*, *Klebsiella*, and *P. aeruginosa*. These organisms tend to infect postpubertal males and men older than 50 years of age with benign prostatic hypertrophy (BPH).

Clinical Features. Patients with bacterial orchitis present with fever and scrotal pain. They often have constitutional signs and symptoms including nausea, vomiting, myalgias, and malaise. The affected testicle (the disease is unilateral in 70% of patients) and scrotum are swollen, tender, and erythema-

tous. A patient with viral orchitis has testicular pain and swelling that commonly begins 4 to 6 days after the onset of parotitis, although it can develop in the absence of parotitis. The clinical course varies, but resolution generally occurs in 4 to 5 days. More than 50% of testes involved with mumps orchitis suffer from atrophy; however, this seldom results in infertility.

Diagnostic Strategies. As with all causes of scrotal pain, the first priority is to exclude testicular torsion. If the patient clearly has mumps orchitis based on the clinical presentation and a history of preceding parotitis, then no other tests are necessary. For all other patients, urinalysis and urine culture should be performed. Patients in whom the diagnosis is unclear also should undergo color Doppler ultrasound examination to evaluate for torsion or concomitant epididymitis.

Management. In sexually active patients, ceftriaxone and doxycycline should be used as in epididymitis to cover *N. gonorrhoeae* and *C. trachomatis*. In older patients, fluoroquinolones provide the best coverage of gram-negative organisms. Treatment of viral orchitis is supportive only. All patients should receive local scrotal care, as described for epididymitis. Patients with marked pain, high fever, or constitutional symptoms merit hospitalization and parenteral antibiotics.

Inguinal Hernia and Acute Hydrocele

Both inguinal hernia and acute hydrocele are reasonable considerations in the differential diagnosis of an acute scrotal mass. However, both of these clinical entities should be readily identified by careful physical examination.

ACUTE URINARY RETENTION

Perspective

Acute urinary retention (AUR) is the sudden inability to pass urine voluntarily. In contrast with patients with anuria, in which the kidneys fail to produce urine, patients with AUR have normal renal function but cannot pass urine and typically have a distended bladder. The risk of AUR increases with age: 10% of men in their 70s and 33% of men in their 80s experience AUR at some point. The retention most commonly is secondary to an obstructive lesion but also can be the presenting manifestation of other pathologic processes (Box 97-5). For example, in women it often develops from infrequent voiding leading to an atonic bladder. In younger patients, it often is suggestive of a serious underlying neurologic disease.

The most common cause of AUR seen in the ED is obstruction of the urinary tract distal to the bladder. In men, BPH is the typical precipitant, causing AUR in 53% of patients.[89] Enlargement of the prostate coupled with constriction of the prostatic urethra from heightened α-adrenergic tone obstructs urinary output.[90] Prostate cancer also can block the urethra by means of similar mechanisms, and urinary retention develops in 70% of patients with this tumor. Approximately 25% of men presenting to the ED with AUR have prostate cancer, and often this cancer diagnosis was not known beforehand.[91] Strictures of the urethra can arise after trauma from manipulation with a Foley catheter, cystoscopy, previous infections, or radiation therapy. Such strictures may then lead to obstructed urinary outflow. Other, less common obstructive causes of AUR include phimosis (inability to retract the foreskin over the glans penis) and paraphimosis (inability to reduce the foreskin over an edematous glans).

In women, the most frequent causes of obstructive AUR are pelvic masses and prolapse of pelvic organs such as bladder, rectum, or uterus. These structures compress the urethra, thereby creating AUR. In both sexes, bladder neoplasms, fecal impaction, GI masses, foreign bodies, or stones can block urine outflow. Finally, congenital posterior urethral valves are the most common source of AUR in children.

Infection also can cause AUR and must be considered in the differential diagnosis, because treatment of the condition through placement of a catheter will correct the retention but not the underlying infection. The most common infectious etiologic disorder is acute prostatitis, which usually is due to infection of the prostate by *E. coli* or *P. mirabilis*. The resulting edema causes AUR, particularly in the setting of BPH or other underlying prostatic disease. Similarly, urethritis from a UTI or sexually transmitted infection can obstruct the urethra, and in women, vulvaginitis also can produce enough urethral edema to create AUR. In Elsberg syndrome, genital herpes involving the sacral nerves leads to AUR.[92] Finally, in pediatric

BOX 97-5 CAUSES OF ACUTE URINARY RETENTION IN ADULTS

Penis
Phimosis
Paraphimosis
Meatal stenosis
Foreign body constriction

Urethra
Tumor
Foreign body
Calculus
Urethritis (severe)
Stricture
Meatal stenosis (female)
Hematoma

Prostate Gland
Benign prostatic hypertrophy
Carcinoma
Prostatitis (severe)
Bladder neck contracture
Prostatic infarction

Neurologic Causes
Motor Paralytic
Spinal shock
Spinal cord syndromes

Sensory Paralytic
Tabes dorsalis
Diabetes
Multiple sclerosis
Syringomyelia
Spinal cord syndromes
Herpes zoster

Drugs
Antihistamines
Anticholinergic agents
Antispasmodic agents
Tricyclic antidepressants
α-Adrenergic stimulators
"Cold tablets"
Ephedrine derivatives
Amphetamines

Psychogenic Problems
Psychodynamic stressors such as lazy bladder syndrome

From Sacknoff EJ, Dretler SP: Urologic emergencies. In Wilkins E (ed): MCH Textbook of Emergency Medicine. Baltimore, Williams & Wilkins, 1978.

patients, UTIs can induce sufficient dysuria that the child refuses to void, with consequent urinary retention.

Pharmacologic agents have been associated with AUR. Anticholinergic agents inhibit detrusor muscle contraction, whereas sympathomimetic agents increase α-adrenergic tone in the prostate. In addition, NSAIDs may inhibit prostaglandin-mediated detrusor muscle contraction, leading to a twofold increase in risk of AUR in men taking these drugs.[93]

Although less common in older patients, neurogenic causes of AUR constitute an important etiologic category. Upper motor neuron lesions create bladder spasticity through a deficit above the micturition center in the sacral cord. They result from spinal cord and cortical lesions due to multiple sclerosis, trauma, Parkinson's disease, stroke, or neoplasms. Lower motor neuron deficits produce bladder flaccidity with lesions below S1. Such lesions typically are associated with spinal cord tumors, epidural abscesses, spinal trauma, Guillain-Barré syndrome, tabes dorsalis, and multiple sclerosis. Peripheral nerve lesions also can cause AUR. Diabetic peripheral neuropathy is the most commonly encountered peripheral lesion and occurs in 45% of patients with diabetes mellitus.[94]

Numerous alternate causes for AUR are recognized, as listed in Box 97-5. They include intervertebral disk herniation, recent surgery, and psychogenic causes. In the ED, these are encountered much less frequently than the aforementioned disorders. Psychogenic urinary retention also is rare and should be a diagnosis of exclusion made only after appropriate studies of bladder function have been performed by a urologist.

Clinical Features

Although the potential causes of AUR are many, the history and physical exam can considerably narrow the scope of the differential diagnosis (Table 97-8). Patients with AUR present in pain with a distended bladder that is tender to palpation (Box 97-6). With lesions proximal to the bladder, patients typically note pain in the flank, whereas lesions distal to the bladder can produce pain radiating to the scrotum or labia. By contrast, with slowly developing or chronic obstructions, patients typically are older, with multiple comorbid conditions, and they present with overflow incontinence and report little to no pain.

When obstruction is the cause of AUR, the patient often will recall multiple previous episodes of urinary retention. In addition to this history, patients with BPH will report frequency, urgency, hesitancy, nocturia, difficulty initiating the urinary stream, decreased force of the stream, a sensation of incomplete voiding, and terminal dribbling. The prostate is enlarged, firm, and non-nodular. Normal findings on the prostate exam do not exclude BPH. Patients with prostate cancer can have similar symptoms, but these often are accompanied by weight loss, bone pain, and other constitutional signs and symptoms. These patients generally will have an enlarged, nodular prostate. Examination of the penis also is crucial in men, because phimosis and paraphimosis will reveal edema of the penis with a nonretractable foreskin. In women with obstruction, pelvic pain and pressure are symptoms commonly associated with AUR. A prolapsed bladder, rectum, or uterus and enlarged ovaries or uterus can be identified on pelvic examination.

Patients with an infectious cause for their symptoms often complain of dysuria, frequency, urgency, hematuria, fever, chills, and low back pain. In acute prostatitis, these symptoms can be associated with penile discharge and a tender, warm, and boggy prostate. Despite the obstruction, the patient may nevertheless be able to void small amounts of urine. In vulvovaginitis and urethritis, presenting complaints also may include discharge and pruritus.

Patients with a neurogenic cause for their AUR may already have a history of neurologic disease. They require a thorough neurologic examination, focusing on strength, sensation, and reflexes in the lower extremities, for which innervation is similar to that of the bladder. The status of the bulbocavernosus reflex, anal reflex, sphincter tone, and perineal sensory also should be assessed.

BOX 97-6 SYMPTOMS OF URINARY RETENTION

Obstructive Symptoms
Urinary hesitancy
Straining to void
Decrease in size and force of urinary stream
Interruption of urinary stream
Sensation of incomplete emptying
Previous episode of urinary retention

Irritative Symptoms
Urinary frequency
Urinary urgency
Dysuria (usually secondary to infection)
Nocturia or nocturnal incontinence

Modified from Lapides J: Fundamentals of Urology. Philadelphia, WB Saunders, 1976.

Diagnostic Strategies

The only two mandatory tests in the ED for AUR are placement of a Foley catheter and a urinalysis. The urinalysis can reveal infection, whereas presence of hematuria suggests infection, tumor, or calculi. Patients with hematuria require follow-up, because the bleeding can arise from prostatic obstruction alone or may have other, more serious causes such as bladder cancer. A basic chemistry panel for assessment of renal function should be obtained only when renal damage or hydronephrosis is a concern.

Imaging studies are indicated when patients have evidence of concomitant infection or neurologic deficits. Renal and bladder ultrasound studies provide visualization of any obstruction, hydronephrosis, or other causes of upper urinary tract disease. Pelvic ultrasound examination and CT scan evaluate for masses or malignancy causing obstruction. Magnetic resonance imaging of the spine evaluates for disk herniation, cord compression, and cauda equine syndrome. Cystoscopy and retrograde cystourethrogram can depict problems in the lower urinary tract and usually are performed as outpatient procedures.

Several other tests described in the literature provide little benefit in the ED management of patients with AUR. Prostate-specific antigen (PSA) levels frequently are elevated in the setting of AUR, so a PSA assay will not help in differentiating cancer from other causes of retention. Similarly, alternate imaging modalities have rendered IVP unhelpful in the ED.

Management

Immediate placement of a 14F to 18F Foley catheter should provide decompression of the bladder. If this fails, placement of an elbowed catheter (Coude catheter) should

Table 97-8 Presentation and Diagnosis of Acute Urinary Retention

ETIOLOGY	HISTORY	PHYSICAL EXAM	DIAGNOSIS*
Benign prostatic hypertrophy	Frequency, urgency, hesitancy Prior retention	Enlarged, firm prostate	UA
Prostate cancer	Frequency, urgency, hesitancy Previous retention Constitutional symptoms	Enlarged, firm prostate Nodular prostate	UA
Phimosis/paraphimosis	Penile pain	Nonretractable foreskin Edematous penis	Clinical only
Prostatis	Dysuria, frequency, urgency Fever, chills	Warm, tender, boggy prostate Penile discharge	UA Urine culture
Urethritis/vulvovaginitis	Dysuria, frequency, urgency Itching	Discharge	UA Urine culture Urethral/cervical culture
Pelvic mass	Pelvic pain pressure	Prolapse of rectum, bladder, uterus	UA Ultrasound imaging/CT
Neurogenic bladder	Other neurologic complaints	Neurologic deficits	UA CT/MRI

*In the emergency department setting, each of these diagnoses is made primarily by the history and findings on the physical exam. Additional tests are needed as described.
CT, computed tomography; MRI, magnetic resonance imaging; UA, urinalysis.

be attempted; its curved tip allows it to pass more easily across any obstruction. If both of these techniques prove to be unsuccessful, a urologist should be consulted unless the ED personnel are well versed in the use of filiforms, followers, and metal sounds, because such instrumentation without the requisite degree of skill may result in serious tissue damage.

When immediate bladder decompression is required and a urologist is not available or major urethral trauma is present, suprapubic bladder drainage should be performed. Using ultrasound guidance and sterile technique, a 22-gauge spinal needle should be inserted two fingerbreadths above the symphysis pubis in the midline and directed toward the anus. The needle is advanced until urine is aspirated. Return of air suggests that the needle is in the bowel, and the needle should be retracted and moved more cephalad. Once the bladder is located, a 1-cm skin incision is made, and a suprapubic trocar is inserted into the bladder. The catheter is advanced over the trocar, which is then removed. If these devices are not available, a central venous set may be used, with the 12- to 18-inch tubing inserted into the bladder before the needle is withdrawn (Fig. 97-12).

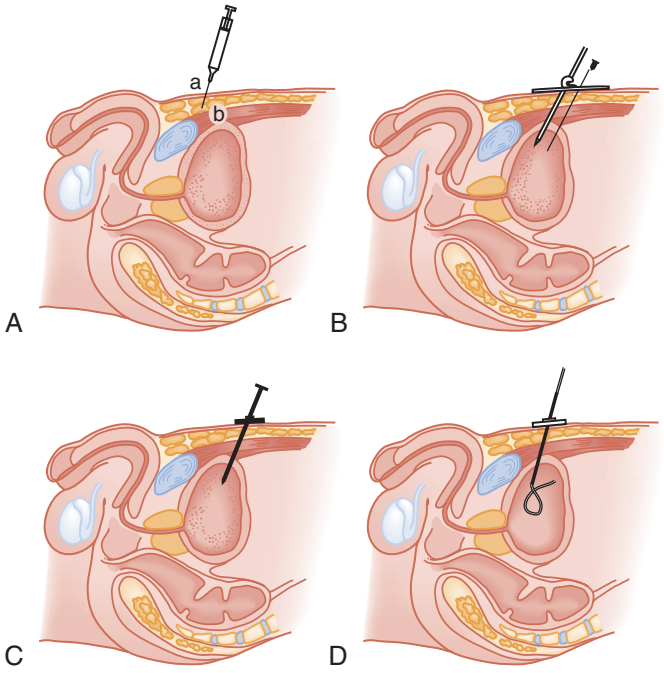

Figure 97-12. Cystostomy tube placement. **A**, Anesthetizing trocar tract. After a skin wheal (a) is raised, the suprapubic tract for the trocar is anesthetized, including the rectus fascia (b). Anesthetizing until the bladder is penetrated will ensure total comfort for the patient during insertion of the trocar. **B**, Needle localization of the bladder. A spinal needle may be used even during insertion of the trocar to locate the bladder. **C**, Trocar position. Advance the trocar until its sheath, as well as the point, is fully in the bladder. **D**, Tubing position. Insert enough tubing so that it will not pull out of the bladder when the bladder empties. (From Robert JR, Hedges JR: Clinical Procedures in Emergency Medicine. Philadelphia, WB Saunders, 1985.)

Complications

Catheterization has been associated with urethritis, cystitis, prostatitis, bacteremia, and sepsis. These infections are most common in patients with indwelling catheters and elderly debilitated female patients.[91] Placement of a catheter also has been reported to cause postobstructive diuresis and hematuria. Such problems are believed to be related to rapid bladder decompression, so historically, gradual decompression has been recommended to prevent complications such as hematuria, hypotension, and postobstructive diuresis. Although hematuria occurs in 2 to 16% of patients after rapid bladder emptying, no major consequences from this bleeding have been documented.[95] Similarly, postobstructive diuresis can cause transient hypotension, but it is responsive to fluid administration. The side effects of rapid bladder decompression are rare; therefore, all patients with AUR should undergo rapid, complete decompression of the bladder.

Rarely, chronic obstruction may lead to development of a salt-wasting nephropathy that requires treatment. The patient's urine output should be observed for 4 hours after catheterization. If output is greater than 200 mL/hour, the patient should be hospitalized for monitoring of blood pressure and sodium concentration.

Disposition

After bladder drainage, healthy and reliable patients can be safely discharged with an indwelling catheter. Follow-up with a urologist should be arranged before the patient leaves. Patients with concomitant infection, significant comorbid illnesses, impaired renal function, neurologic deficits, or complications from catheterization require emergent urology consultation and probably admission.

At hospital discharge, the catheter should remain in place and the patient educated about catheter management. Prophylactic antibiotic therapy should not be initiated, because although bacteriuria often develops in patients with indwelling catheters, it typically is asymptomatic. Antibiotics only promote resistance among these organisms. Although the catheter is an inconvenience for the patient and chronic use has been associated with UTI, trauma, stones, and urethral strictures, early removal of the catheter also is associated with heightened risk for recurrence of AUR.[96] In patients with suspected BPH, if the bladder was drained and a catheter was not left in place, recurrent AUR developed in 70%.[97] In patients in whom the catheter remained in place for 3 days, AUR developed in 49%, and when the catheter was in place for 7 days, AUR recurred in only 38% of patients.[98] As indicated by these results, the catheter should remain in place until the patient visits the urologist as an outpatient.

Studies also suggest that initiation of an α-adrenergic blocker, such as tamsulosin, at the time of catheter insertion improves the likelihood of spontaneous voiding after catheter removal.[99] These medications should be provided only after consultation with the urologist or primary care physician, because they increase the risk of orthostatic hypotension, particularly in the elderly.[91]

HEMATURIA

Perspective

Although hematuria is commonly encountered in the ED, the specific underlying disorder often is elusive. Most cases seen in the ED are asymptomatic microscopic hematuria, an incidental finding noted on routine examination through microscopic or dipstick analysis of the urine. The bleeding typically is transient and not indicative of serious underlying pathology. After an uneventful workup, patients often are referred for outpatient evaluation; however, the cause of the hematuria remains unknown in 61% of patients evaluated with lab and imaging studies.[100] Less commonly, patients come to the ED complaining of gross blood in their urine. Unlike microscopic hematuria, gross blood in the urine often is the presenting symptom of an underlying malignancy. The risk of malignancy is greater in older patients; in those older than 60 years, gross hematuria has a positive predictive value for malignancy of 22.1% in men and 8.3% in women.[101] Regardless of age or visibility of blood in the urine, patients with hematuria require evaluation in the ED to rule out life-threatening diagnoses such as malignancy and abdominal aortic aneurysm.

Principles of Disease

Blood in the urine can be gross or microscopic. As little as 1 mL of whole blood in 1 L of urine can produce *gross hematuria*, turning the urine red. Multiple other substances and reactions can turn the urine red, and centrifugation of the urine and microscopic analysis differentiate these false positives from true hematuria. After centrifugation, the red color persists only in the urine sediment with hematuria. By contrast, a red supernatant appears bloody but contains no RBCs on microscopic analysis, and the cause typically is a benign condition (Box 97-7). A red supernatant also may result from pathologic conditions such as myoglobinuria and hemoglobinuria. The supernatant will then contain heme in addition to a red coloring agent.

BOX 97-7 ETIOLOGY OF RED-COLORED URINE WITHOUT HEMATURIA

Phenazopyridine
Nitrofurantoin
Rifampin
Chloroquine
Hydroxychloroquine
Iodine
Bromide
Food coloring
Beets
Berries
Rhubarb

Microscopic hematuria is the presence of more than 3 to 4 RBCs per high-power field in clear urine. The particular cutoff for number of RBCs per high-power field used is arbitrary. Lower numbers of RBCs per high-power field decrease specificity but increase sensitivity, because significant disease can occur with as little as 1 RBC per high-power field. Urine dipstick increases sensitivity to 91 to 100% for the presence of blood, detecting 1 or 2 RBCs per high-power field. However, it is less specific, with false positives occurring when sperm are present and with alkaline or extremely concentrated urine).[102,103] Accordingly, a positive result on urine dipstick testing should be confirmed with microscopic analysis.

Bleeding from anywhere along the genitourinary tract can produce hematuria. In both the upper and lower portions of the urinary tract, infection, trauma, and renal calculi are the most common etiologic disorders. Patients also can have more serious causes of hematuria such as malignancy or vascular lesions (e.g., abdominal aortic aneurysm), and these diagnoses must be excluded. Age older than 40 years, cigarette smoking, occupational exposure to chemicals such as aniline dye and benzidine, and excess use of analgesics increase the risk of malignancy. When another cause for the hematuria, such as UTI or stone, is identified in the ED, close follow-up is still necessary, because patients with these risk factors often prove to have an underlying malignancy.[104] In the upper urinary tract, the glomerulus is the most frequent source of bleeding, which may result from glomerulonephritis, immunoglobulin A (IgA) nephropathy, or nephritis. The common causes of hematuria are further divided by patient age and gender in Box 97-8.

Occasionally, hematuria also has been attributed to warfarin usage, BPH, and exercise. Supratherapeutic anticoagulant therapy can lead to blood in the urine, but therapeutic anticoagulation does not produce hematuria. The incidence of hematuria was not significantly different between controls and 243 patients followed prospectively while receiving warfarin.[105] Similarly, BPH can lead to increased vascularity of the prostate but does not increase the risk of hematuria. High-intensity exercise also can produce hematuria. This bleeding typically is transient and clinically inconsequential. However, a concomitant genitourinary tract lesion can be present, particularly if the bleeding persists for more than 72 hours after exercise.[106] Because warfarin use, BPH, and exercise do not directly cause persistent hematuria, patients in

BOX 97-8 Most Frequent Causes of Hematuria by Age and Gender

Age 0–20 Years
Acute glomerulonephritis
Acute UTI
Congenital urinary tract anomalies with obstruction

Age 20–40 Years
Acute UTI
Bladder cancer
Urolithiasis

Age 40–60 Years
Women
Acute UTI
Bladder cancer
Urolithiasis

Men
Acute UTI
Bladder cancer
Urolithiasis

Age 60 Years and Older
Women
Acute UTI
Bladder cancer

Men
Acute UTI
Benign prostatic hyperplasia
Bladder cancer

UTI, urinary tract infection.
From Restrepo NC, Carey PO: Evaluating hematuria in adults. Am Fam Physician 40:149, 1989.
Modified from Gillenwater JY (ed): Adult and Pediatric Urology. St. Louis, Mosby, 1987.

whom these factors are present require evaluation identical to that for other patients.

Clinical Features

The timing and appearance of the blood in the urine can help narrow the scope of the differential diagnosis (Table 97-9). Repeated episodes of bleeding during and after menstruation in women suggests endometriosis of the urinary tract. Gross hematuria suggests lesions in the lower urinary tract. Passage of clots indicates a source below the kidney. Finally, passage of a large amount of congealed blood in the urine suggests malignancy of the kidney.

Several other historical factors also are associated with particular causes of hematuria (Box 97-9). A careful history will identify a benign cause for hematuria, such as menstruation, recent heavy exercise, or sexual activity, as well as the use of agents that can produce red urine without blood (see Box 97-7). Patients may report frequency, urgency, and dysuria in the setting of infection. They may complain of flank pain with urolithiasis or pyelonephritis. IgA nephropathy arises days after a viral respiratory infection, whereas poststreptococcal glomerulonephritis develops in children 1 to 2 weeks after skin or throat infections.

The physical exam is crucial in establishing the diagnosis. Hypertension occurs with glomerulosclerosis and, in the setting of peripheral edema, suggests nephrotic syndrome. Atrial fibrillation increases the likelihood of embolic disease and renal infarction. An abdominal bruit may be due to an arteriovenous fistula, whereas a palpable abdominal mass may represent an abdominal aortic aneurysm. Flank pain and tenderness can arise with pyelonephritis or nephrolithiasis. The external genital exam can show evidence of trauma or a tumor.

Table 97-9 Timing of Blood Appearance during Micturition and Disease Location

TIMING OF BLOOD APPEARANCE	LOCATION OF LESION
Beginning of micturition	Urethra
Between episodes of urination	Urethral meatus Distal urethra
End of micturition	Bladder Prostatic urethra
Throughout urination episode	Bladder Ureter Kidney

BOX 97-9 Medical History for Patients with Hematuria

- Exclude pseudohematuria—drugs, vegetable dyes, pigments
- Factitious—Munchausen syndrome, narcotic-seeking behavior
- Bleeding diathesis
- Clots—indicate nonglomerular bleeding; large, thick clots (bladder); small, stringy clots (upper tract)
- Gross hematuria—relationship to exercise, infection
- Relationship of gross hematuria to urinary stream—initial (urethra distal to the urogenital diaphragm), total (bladder proper or upper urinary tract), terminal (bladder neck or prostatic urethra)
- Painful hematuria—urinary tract infection or calculus, papillary necrosis, passage of clots, obstruction, loin pain–hematuria syndrome, glomerulonephritis
- Genitourinary history—flank trauma or pain frequency; nocturia; dysuria; previous stones, tissue passage, or infections; vaginal or penile discharge; sexual activity; presence of urinary catheter
- Relationship to menstruation—endometriosis
- Sickle cell disease or trait
- Medications
- Systemic symptoms—fever, rash, joint pain, weight loss
- Infectious etiology—night sweats, sore throat, impetigo, recent tooth extraction or other invasive procedure, diarrhea, travel to areas endemic for *Schistosoma haematobium*
- Risk factors for urologic cancer—age older than 40 years, tobacco use, analgesic abuse, pelvic irradiation, cyclophosphamide, *S. haematobium*, occupational exposure to dyestuffs and rubber compounds
- Family history—hematuria, renal disease, sickle cell disease, deafness, bleeding diathesis
- Previous testing—blood pressure, urinalysis, serum chemistries, intravenous pyelogram
- Pregnancies—proteinuria, hypertension (with month of onset)

Diagnostic Strategies

A clean-catch or catheterized urine specimen should be obtained in all patients with hematuria. Catheterization itself

BOX 97-10 RISK FACTORS MANDATING FURTHER EVALUATION OF HEMATURIA

Age older than 40 years
Cigarette smoking
Occupational exposure
Analgesic abuse
Persistent hematuria
Abdominal pain

induces hematuria in approximately 15% of patients, but the amount of bleeding is inconsequential, rarely exceeding 3 RBCs per high-power field.[107] Bedside urine dipstick testing and microscopic analysis of this urine should always be performed. This diagnostic approach will reveal WBCs in addition to RBCs in the presence of infection. Proteinuria and RBC casts are seen with glomerular disease. Patients with these disorders do not require further evaluation in the ED beyond the urinalysis and should be referred to a nephrologist.

By contrast, any patients with gross hematuria or risk factors for significant disease require thorough evaluation before discharge from the ED (Box 97-10). Their renal function should be assessed to rule out the development of renal insufficiency. They also should undergo appropriate imaging tests, although clear consensus is lacking on the appropriate radiographic study. If findings fail to suggest a particular etiologic disorder as a cause for the hematuria, a CT scan with contrast or a renal ultrasound study should be performed. If the possibility of an occult stone is a concern, the CT scan should be ordered without contrast. CT scanning is highly sensitive for stones, masses, and other diseases of the upper urinary tract. It should be avoided in pregnancy and renal insufficiency and with a history of anaphylaxis to contrast medium. In these patients, ultrasound imaging is the modality of choice. It is less sensitive than a CT scan for detecting stones and small masses. Although it is not as sensitive as IVP for identifying lesions of the bladder and ureters, it does provide adequate visualization of the kidney. IVP, angiography, and cystoscopy should be reserved for outpatient evaluations, when diagnostic imaging in the ED with ultrasonography or CT shows no evidence of disease.

Disposition

Patients younger than 40 years of age, with no risk factors for severe disease and an ED workup not revealing of a particular cause for their microscopic hematuria, can be discharged with outpatient follow-up to ensure resolution of the hematuria. By contrast, patients with known risk factors or gross hematuria require imaging in the ED. If findings on a subsequent workup are negative, urgent outpatient evaluation is essential, because within 3 to 4 years, a genitourinary malignancy will develop in 1% of older patients with initially negative findings on workup.[108]

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 98

Selected Gynecologic Disorders

Carrie D. Tibbles

PERSPECTIVE

Many women present to the emergency department (ED) complaining of either pelvic pain or vaginal bleeding. After the possibility of pregnancy has been eliminated, a primary goal of the ED evaluation is to recognize the presence of a few conditions, such as adnexal torsion, that warrant urgent intervention and others, such as new postmenopausal uterine bleeding, that require reliable outpatient follow-up. Most patients also benefit from relief of symptoms and reassurance.

This chapter specifically addresses the ED management of adnexal torsion, ovarian cysts, abnormal uterine bleeding and the provision of emergency contraception. Vaginal bleeding and pelvic pain in pregnant patients and gynecologic infections are discussed in other chapters.

ADNEXAL TORSION

Principles of Disease

Adnexal torsion accounts for roughly 3% of gynecologic emergencies.[1] Adnexal torsion can occur in young girls[2] and is increasingly recognized as a cause of pelvic pain in postmenopausal women but is still most common in the reproductive years because of the regular development of a corpus luteal cyst during the menstrual cycle.[3] Adnexal torsion is caused by a twisting typically of both the ovary and the fallopian tube on its vascular pedicle.[4] Many cases of torsion (50 to 80%) are associated with an ovarian tumor, typically a benign neoplasm, or with large, heavy cysts, as seen in ovarian hyperstimulation syndrome after in vitro fertilization, or polycystic ovaries.[1] Torsion may be a complication of pregnancy.[5,6] Torsion of a normal ovary only rarely occurs.[7] A slight predominance of ovarian torsion on the right side has been noted. The reason for this predilection is unclear but may relate to the stabilizing effect of the sigmoid colon on the left side.[4] In adnexal torsion, venous and lymphatic obstruction occurs initially, with subsequent congestion and edema of the ovary, progressing to ischemia and necrosis, and eventual infarction of the ovary[1] (Fig. 98-1). Thrombosis of the ovarian vein and artery can occur as well. The ovary often is salvageable if the diagnosis is made before thrombosis occurs.[4] Because of the dual blood supply of the ovary from both the uterine and ovarian arteries, complete arterial obstruction is rare[7] (Fig. 98-2).

Clinical Features

Adnexal torsion often can be a challenging diagnosis to make, because the classic symptoms of severe, sharp unilateral abdominal pain and nausea may not be present.[5,6,8] The presence of known risk factors for adnexal torsion such as an ovarian mass or infertility treatments may suggest the diagnosis.[1] Because the presentation can be variable and often subtle, the diagnosis can be difficult to make. In 87 patients with surgically confirmed torsion, the diagnosis was missed on the first visit in almost one half of the patients. Patients reported pain from several hours to weeks in duration, and almost all had some pain on abdominal palpation. Nausea also was a symptom in many of the patients. Other series report similar findings.[2-4,6,8]

Diagnostic Strategies

Laboratory Tests. No specific laboratory tests are helpful in the evaluation of a patient for suspected adnexal torsion, except for a pregnancy test to exclude ectopic pregnancy. A small percentage of patients may have an elevated white blood cell count above 15,000/μL,[5] but this is not a reliable indicator of adnexal torsion.[5,8]

Imaging

Ultrasonography. Ultrasound examination is usually the initial imaging test in the evaluation of patients with pelvic pain suggestive of adnexal torsion.[7] Enlargement of the ovary is the most common ultrasound finding.[4] The ovary also may have an abnormal position relative to the uterus. Enlargement of an ovary with a heterogeneous stroma and small, peripherally displaced follicles is the classic ultrasound appearance of torsion but often is not seen[4] (Fig. 98-3). The ultrasound study may reveal a mass in the ovary or evidence of hemorrhage[9] (Fig. 98-4). Free pelvic fluid also may be seen.[7] Hemorrhagic cysts and non-neoplastic masses frequently are associated with torsion. These may have a fluid-filled cystic component, exhibit a complex pattern with debris and septations, or be visualized as a solid mass.[9] The characteristic appearance of torsion may be difficult to appreciate if the ovary is obscured by an associated mass.[7]

Doppler Ultrasound Exam. Doppler ultrasound findings are inconsistent in adnexal torsion.[7,10,11] Many cases of surgically proven torsion will have documented blood flow on Doppler exam, because the ovary has a dual blood supply from both the

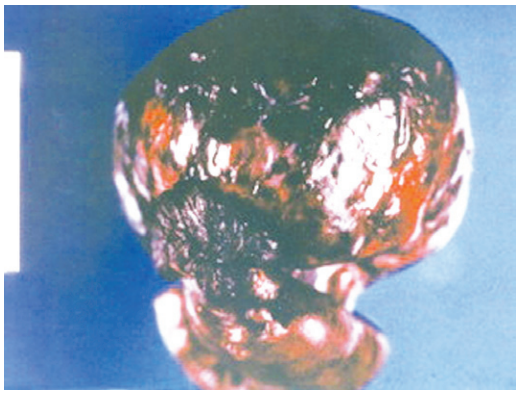

Figure 98-1. Pathology specimen demonstrating ovarian torsion. (From Andreotti RF, Shadinger L, Fleischer A: The sonographic diagnosis of ovarian torsion: Pearls and pitfalls. Ultrasound Clin 2:155, 2007.)

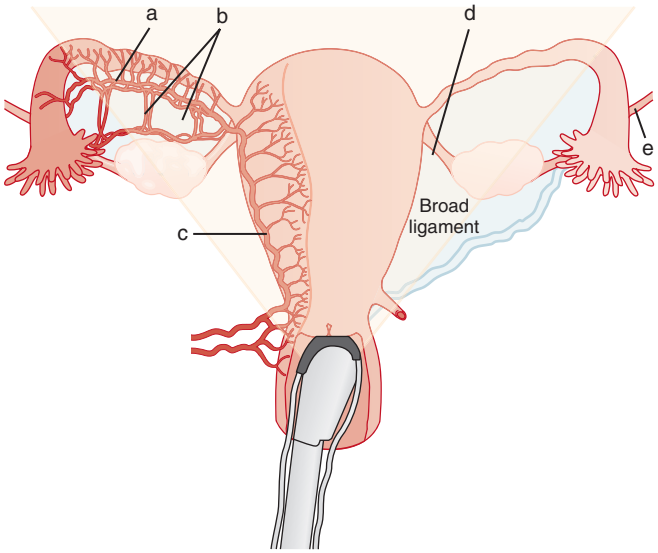

Figure 98-2. Ovarian blood supply: ovarian artery and vein (a), branching arterioles supplying ovary (b), utero-ovarian ligament (c), utero-ovarian ligament (d), infundibulo-pelvic ligament (e). (From Andreotti RF, Shadinger L, Fleischer A: The sonographic diagnosis of ovarian torsion: Pearls and pitfalls. Ultrasound Clin 2:155, 2007.)

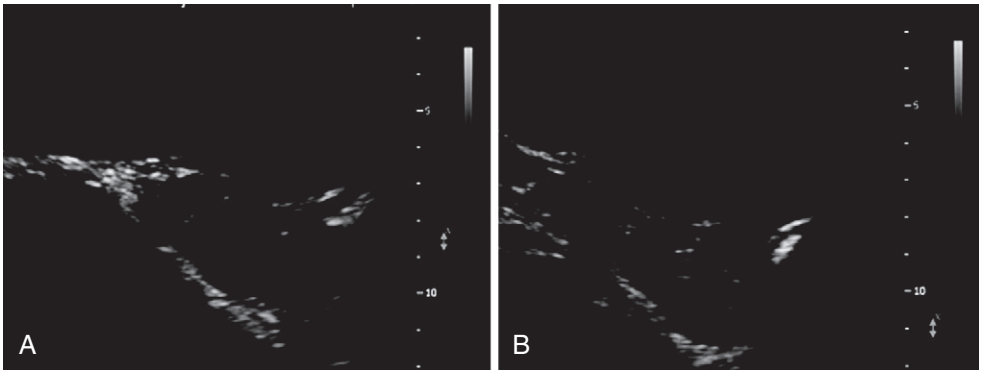

Figure 98-3. **A** and **B**, Ultrasound appearance of ovarian torsion in a prepubertal girl. (From Andreotti RF, Shadinger L, Fleischer A: The sonographic diagnosis of ovarian torsion: Pearls and pitfalls. Ultrasound Clin 2:155, 2007.)

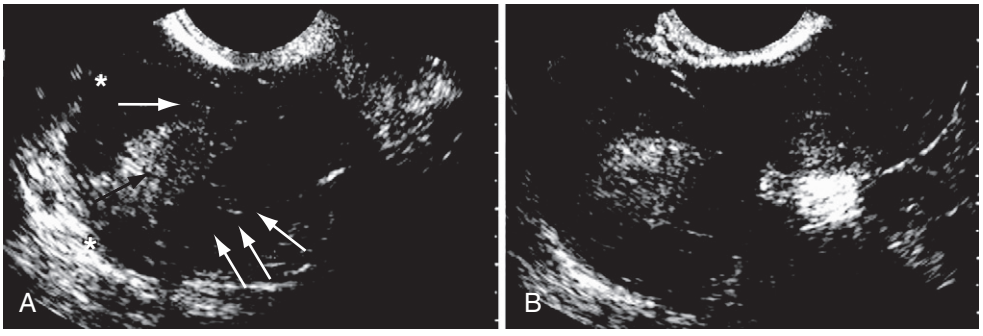

Figure 98-4. **A** and **B,** Intraovarian hemorrhage (*arrows* in **A**) in patient with ovarian torsion. (From Andreotti RF, Shadinger L, Fleischer A: The sonographic diagnosis of ovarian torsion: Pearls and pitfalls. Ultrasound Clin 2:155, 2007.)

ovarian and uterine arteries. Also, the torsion may be intermittent, so the findings may vary depending on the time of the exam.[7] If a large mass is present, the examination may be technically difficult to perform.[9] Despite these limitations, the Doppler exam may still be useful. Detection of abnormal venous flow is particularly important in early cases of torsion[10] (Fig. 98-5). Visualization of the twisting of the pedicle also is possible, and this image of the coiled vessels is referred to as a "whirlpool sign."[12] Lee and colleagues report an 88% accuracy for torsion when the twisted pedicle or whirlpool sign is visualized.[13]

Computed Tomography. When renal colic and appendicitis also are strong considerations in the differential diagnosis for acute pelvic pain, an abdominopelvic CT may be the best initial study, particularly in patients who have a presentation atypical for torsion. In ovarian torsion, CT findings include fallopian tube thickening, smooth wall thickening of the associated adnexal mass, ascites, and uterine deviation to the twisted side[14] (Fig. 98-6). Associated hemorrhage in patients with hemorrhagic infarction can be seen. A study of surgically confirmed ovarian torsion found that CT correctly diagnosed 5 of 13 cases (38%), as opposed to

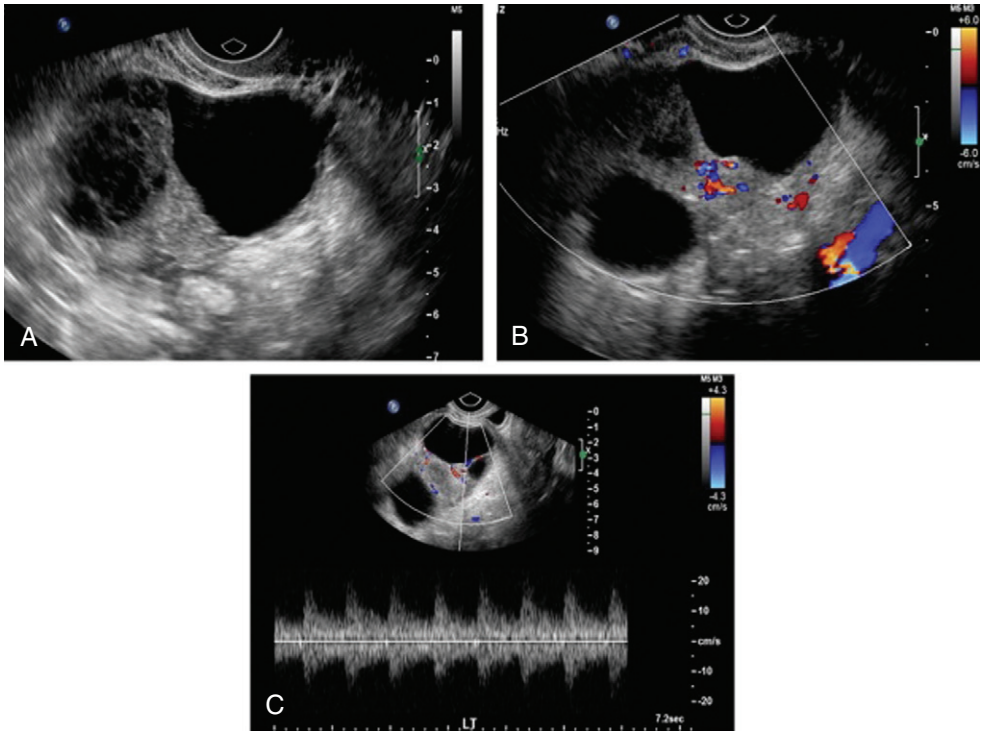

Figure 98-5. Arterial Doppler signal without venous signal in patient with surgically proven torsion. Ultrasound examination also demonstrated an associated hemorrhagic cyst. (From Andreotti RF, Shadinger L, Fleischer A: The sonographic diagnosis of ovarian torsion: Pearls and pitfalls. Ultrasound Clin 2:155, 2007.)

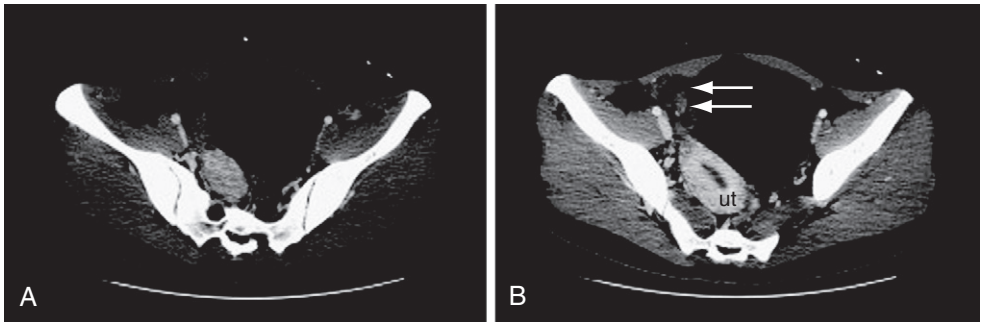

Figure 98-6. **A** and **B,** Computed tomography scans of the pelvis of a patient with ovarian torsion. Findings include a thickened fallopian tube, associated adnexal mass (*arrows* in **B**), and deviation of the uterus (ut) toward the twisted adnexa. (From Andreotti RF, Shadinger L, Fleischer A: The sonographic diagnosis of ovarian torsion: Pearls and pitfalls. Ultrasound Clin 2:155, 2007.)

ultrasonography, which correctly identified 15 of 21 cases (71%).[3] As illustrated by this and other studies, negative imaging findings should be interpreted with caution when clinical suspicion is high.

Magnetic Resonance Imaging. MRI is not typically ordered in the ED but also may demonstrate findings consistent with torsion. It is particularly helpful in cases in which the diagnosis is not clear, such as those characterized by intermittent pain over days.[15] Findings on MRI suggestive of torsion are similar to those on CT.[14] Table 98-1 lists the common imaging findings in ovarian torsion.

Laparascopy. A diagnostic laparoscopy is the gold standard investigative modality in patients in whom clinical suspicion is high despite negative imaging results. In 100 laparoscopies performed in nonpregnant patients with an acute abdomen, only 29 of the 66 cases of ovarian torsion were diagnosed preoperatively. Laparoscopy also diagnosed other unsuspected conditions including ovarian cysts, appendicitis, and pelvic inflammatory disease.[16]

Table 98-1 Imaging Characteristics of Ovarian Torsion

Ultrasonography
Enlargement of the ovary
Associated ovarian mass
Loss of enhancement
Edema
Free pelvic fluid
Loss of venous waveforms
Loss of arterial waveforms
Computed Tomography/Magnetic Resonance Imaging
Enlargement of the ovary
Associated ovarian mass
Thickening of the fallopian tube
Free pelvic fluid
Edema of the ovary
Deviation of the uterus to the affected side
Associated hemorrhage

Differential Considerations

Considerations in the differential diagnosis include other causes of acute lower abdominal pain such as appendicitis, ovarian cyst, urinary tract infection, renal calculi, pelvic inflammatory disease, diverticulitis, and ectopic pregnancy. A pregnancy test and pelvic imaging with either an ultrasound or a CT scan will usually allow distinction between these possibilities.

Management

Once the diagnosis of adnexal torsion is made, the patient should be taken to the operating room as soon as possible. Pediatric patients taken to surgery more than 24 hours later had a zero salvage rate, compared to patients who have the best chance for salvage, who were taken to the operating room within 8 hours.[17] The ovary often will recover even if black in appearance at the time of surgery because of its dual blood supply, so attempts at ovarian salvage are warranted even if the diagnosis is made late.[18] This is particularly true in adolescent patients. Return of ovarian function has been demonstrated in a majority of patients with surgery that saves the ovary.[17] Additional imaging studies, such as MRI, are an option if the diagnosis is not clear. Because torsion of a normal-appearing ovary is very rare, patients with a normal-appearing ovary on CT or ultrasound scan may be discharged from the ED.

■ OVARIAN CYSTS AND MASSES

Principles of Disease

Ovarian cysts are the most common gynecologic masses. They may manifest at any stage of life but are seen most frequently in the reproductive years because of the cyclic changes of the ovary associated with menstruation (Fig. 98-7). Most ovarian cysts are benign and resolve with no interventions; less commonly, however, they may either be malignant or associated with significant complications such as hemorrhage or torsion.

The most common type of cyst is a simple, follicular cyst. A follicular cyst develops normally during the first half of the menstrual cycle and is considered pathologic when it is greater than 2.5 cm in diameter. It is thin-walled and typically filled with clear fluid. A corpus luteum is considered to be a corpus luteal cyst when it attains a diameter greater than 3 cm. Several other types of cystic masses can occur in the ovary, including other types of cysts, non-neoplastic lesions such as benign cystic teratoma, and various types of ovarian malignancy.

Clinical Features

The most common presentation for patients with an ovarian cyst is pelvic pain. Rupture of a follicular cyst may produce transient pelvic pain or be associated with dyspareunia or may be asymptomatic. Because of its thin, fragile wall, a follicular cyst may rupture during sexual intercourse or during the pelvic exam.

Follicular cysts are rarely associated with hemorrhage. Presentation of a corpus luteal cyst may vary, ranging from an asymptomatic mass to dull, chronic pelvic pain to severe pain associated with rupture. Rupture of a corpus luteal cyst frequently is associated with a significant degree of hemorrhage. As with a follicular cyst, rupture may follow a pelvic exam, sexual intercourse, exercise, or trauma. Rupture of a large or complex cyst may result in severe pain and peritoneal signs, particularly if the associated bleeding is considerable. Occasionally, a large cyst may be discovered on a routine pelvic exam as an asymptomatic mass, but this is less common.

Diagnostic Strategies

Laboratory Tests. The initial step in the evaluation of pelvic pain or a pelvic mass is to exclude pregnancy with a urine or serum beta-human chorionic gonadotropin (β-hCG) test. A hematocrit may be valuable in the unstable patient as a marker of blood loss.

Imaging

Ultrasonography. Ultrasonography is the standard imaging modality to diagnose and characterize all ovarian pathologic processes and lesions including cysts and masses. Both transabdominal and endovaginal examinations provide useful information. The transabdominal approach permits an overall view of the pelvis and will visualize large masses and pelvic free fluid. Use of the endovaginal probe will provide a detailed picture of the ovary.[9] Figures 98-8 and 98-9 present endovaginal views of a normal ovary, and Figure 98-10 illustrates a simple cyst. Follicular cysts are part of the normal architecture of the ovary, but a cyst is considered to be pathologic if it is larger than 2.5 cm in diameter. Depending on the timing of the scan and the degree of clot formation and lysis, hemorrhage may be seen as well. Ultrasound findings suggestive of malignancy include internal septations, solid elements, internal echoes, daughter cysts, thickened wall, and large amounts of ascitic or free fluid.[9]

Computed Tomography. When considerations in the differential diagnosis of unilateral pelvic pain include renal colic, appendicitis, or other bowel pathology, a CT scan may be the best initial imaging study. CT scan also can demonstrate the

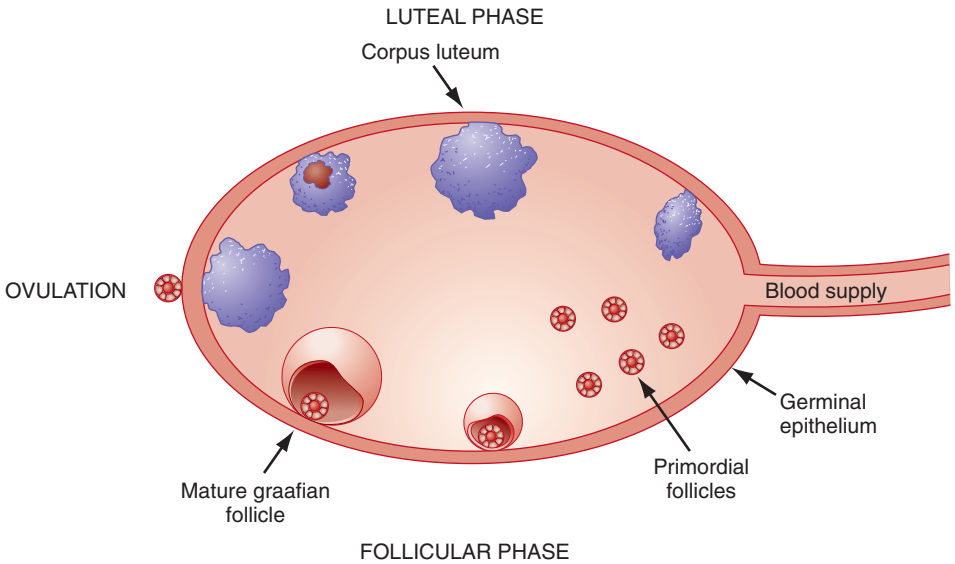

Figure 98-7. Ovarian function during the normal menstrual cycle. (From Lambert MJ, Villa M: Gynecologic ultrasound in emergency medicine. Emerg Med Clin North Am 22:683, 2004.)

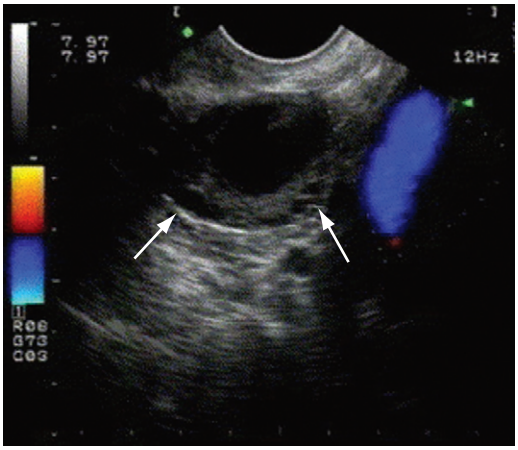

Figure 98-8. Endovaginal ultrasound image of a normal ovary with a dominant follicle *(arrows)*. (From Lambert MJ, Villa M: Gynecologic ultrasound in emergency medicine. Emerg Med Clin North Am 22:683, 2004.)

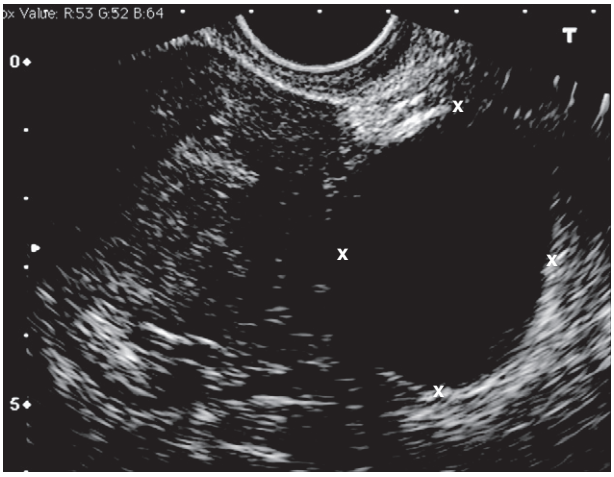

Figure 98-10. Simple ovarian cyst (within x's). (Courtesy of Robert Reardon, MD, Hennepin County Medical Center, Minneapolis, Minn; used with permission.)

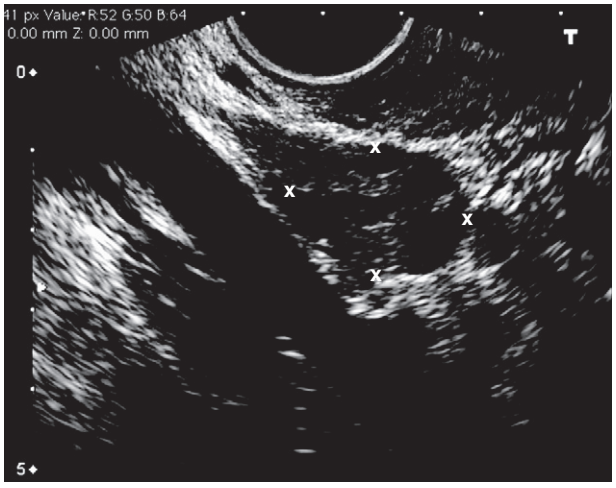

Figure 98-9. Endovaginal ultrasound image of a normal ovary (within x's). (Courtesy of Robert Reardon, MD, Hennepin County Medical Center, Minneapolis, Minn; used with permission.)

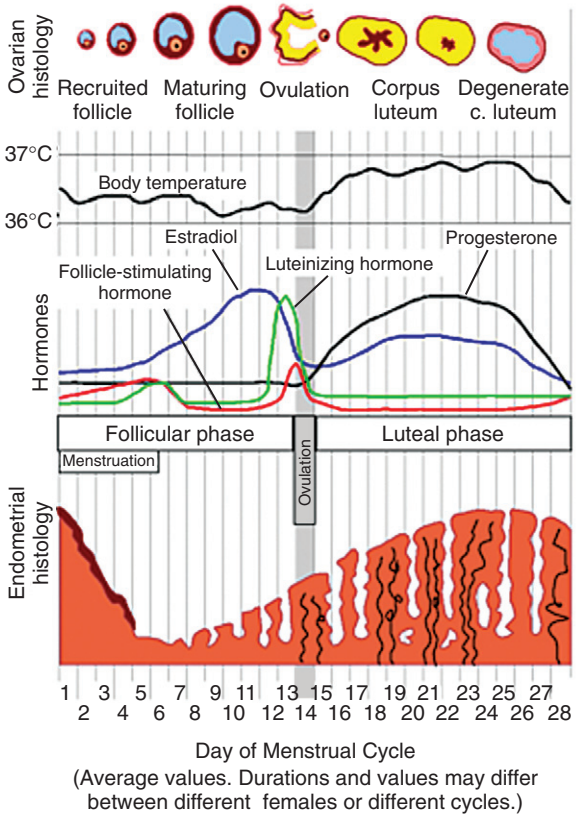

Figure 98-11. Normal menstrual cycle.

presence of a cyst and associated complications. A follow-up ultrasound exam may be useful in select cases after the CT scan is obtained, particularly if the cyst is complicated.

Differential Considerations

As with adnexal torsion, the differential diagnosis seeks to rule out other causes of pelvic pain such as ectopic pregnancy, pelvic inflammatory disease, urinary tract infections, renal colic, appendicitis, and diverticulitis. Cysts range from the benign to ovarian malignancies, so careful attention to the specific appearance of the cyst is important. Presence of large cysts or masses constitutes a risk factor for adnexal torsion.

Management

Patients with a simple cyst and reduction in their symptoms may be safely discharged with referral for outpatient gynecologic follow-up evaluation to ensure resolution of the cyst. Most uncomplicated, simple cysts will resolve within a month. More complex cysts may benefit from gynecology consultation in the ED, particularly if reliable follow-up is unlikely or if the patient is particularly symptomatic.

ABNORMAL UTERINE BLEEDING IN THE NONPREGNANT PATIENT

Principles of Disease

An understanding of the normal menstrual cycle is valuable in considering potential causes of abnormal uterine bleeding (Fig. 98-11). The menstrual cycle starts on the first day of

menses. During the first part of the menstrual cycle, the endometrium thickens under the influence of estrogen, and a dominant follicle develops in the ovary, releasing an ovum at the midpoint of the cycle. After ovulation, the luteal phase begins and is characterized by production of progesterone from the corpus luteum. Progesterone matures the lining of the uterus, and if implantation does not occur, the corpus luteum dies, accompanied by sharp drops in progesterone and estrogen. These changes typically are followed by menstruation. Menstrual bleeding typically is predictable and cyclic and results from withdrawal of the effects of hormones on the endometrium, which occurs approximately 14 days after ovulation.

Disruption of the hypothalamic-pituitary-ovarian axis from a variety of causes can result in abnormal uterine bleeding. Returning the balance of estrogen and progesterone closer to normal with oral contraceptives will help many patients regulate the cycle, with reduction in or cessation of abnormal uterine bleeding.[19-21]

Clinical Features

History. Abnormal uterine bleeding is a common presenting problem in the ED. Any of a large number of possible conditions can cause abnormal uterine bleeding, and a systematic history and physical exam can help narrow down the possibilities. Table 98-2 lists some terms frequently used to describe abnormal uterine bleeding.

Vaginal bleeding before the age of menarche is abnormal and is often the result of trauma, such as sexual abuse, or a structural lesion.[22] In a woman of reproductive age, abnormal uterine bleeding includes a change in the duration, frequency, or amount of bleeding, or bleeding between menstrual cycles. In the postmenopausal woman, any bleeding 12 months after the cessation of menses or unpredictable bleeding during hormone therapy should be considered abnormal. The amount and frequency of bleeding and the duration of symptoms, as well as the relationship to the menstrual cycle, should be established.[23] A menstrual cycle that is fewer than 21 days in duration or more than 35 days long or flow for less than 2 days or more than 7 days is classified as abnormal. The patient should be questioned about the possibility of pregnancy. A pattern of irregular bleeding between cycles or an abrupt change in the previous pattern of bleeding should be determined.[24] Systemic disease such as liver disease, diabetes, or thyroid disease may be associated with abnormal uterine bleeding.[25] Endometrial cancer is associated with underlying diabetes mellitus, anovulatory cycles, obesity, nulliparity, and age older than 35 years.[21] Cervical dysplasia or other genital tract pathology may cause postcoital or irregular bleeding.[26] Disruption along the hypothalamus-pituitary-ovarian pathway frequently is the cause of abnormal uterine bleeding. Causes of hypothalamic suppression include excessive exercise, stress, and weight loss.[27] Polycystic ovary syndrome (PCOS) results in excess estrogen production.

According to Dilley and colleagues, 10.7% of patients with heavy menstrual bleeding have an underlying coagulation disorder, the most common being von Willebrand's disease.[28] Although most patients with abnormal uterine bleeding do not require evaluation for coagulation disorder, the diagnosis is suggested by a family history of a bleeding disorder, prolonged history of heavy menses, excessive bleeding with surgery or dental procedures, or easy bruising.[29] Table 98-3 lists historical factors that can help suggest a potential cause for the bleeding.[21] *Dysfunctional uterine bleeding* is a diagnosis of exclusion in a woman of childbearing age after pregnancy, malignancy, and systemic disease have been ruled out.[21] Dysfunctional uterine bleeding typically is classified as anovulatory or ovulatory. Anovulatory bleeding is much more common, resulting from a disturbance of the normal hypothalamic-pituitary-ovarian axis, and is particularly common at the extremes of the reproductive years.[20]

Physical Exam. With prolonged, heavy bleeding, signs of chronic anemia may be noted on the physical exam. PCOS is a common cause of abnormal uterine bleeding. Physical findings suggestive of PCOS include obesity, acne, hirsutism, and acanthosis nigricans, which is hyperpigmentation typically

Table 98-2 Abnormal Uterine Bleeding

TERM	BLEEDING PATTERN
Menorrhagia	Bleeding occurring at regular intervals, but with heavy flow (≥80 ml) or duration (≥7 days)
Intermenstrual bleeding	Irregular bleeding between cycles
Amenorrhea	Bleeding absent for 6 months or more in a nonmenopausal woman
Midcycle spotting	Spotting occurring just before ovulation, typically from declining estrogen levels
Postmenopausal bleeding	Recurrence of bleeding in a menopausal woman at least 1 year after cessation of cycles
Acute emergent abnormal uterine bleeding	Bleeding characterized by significant blood loss that results in hypovolemic shock
Dysfunctional uterine bleeding	Ovulatory or anovulatory bleeding, diagnosed after the exclusion of pregnancy, medications, iatrogenic causes, genital tract pathology, and systemic disease

Table 98-3 Differential Diagnosis for Abnormal Uterine Bleeding

Pregnancy and pregnancy-related conditions
Miscarriage
Ectopic pregnancy
Placenta previa
Placental abruption
Trophoblastic disease
Medications/iatrogenic causes
Anticoagulants
Oral contraceptives
Steroids
Antipsychotics
Intrauterine devices
Thyroid hormone replacement
Systemic disease
Cushing's disease
Coagulopathies
Liver or renal disease
Hypothalamic suppression (excessive exercise, weight loss)
Polycystic ovary syndrome
Thyroid disease
Genital tract pathology
Cervicitis
Endometritis
Fibroids (leiomyomata)
Adenomyosis
Malignancy
Trauma
Foreign body
Dysfunctional uterine bleeding

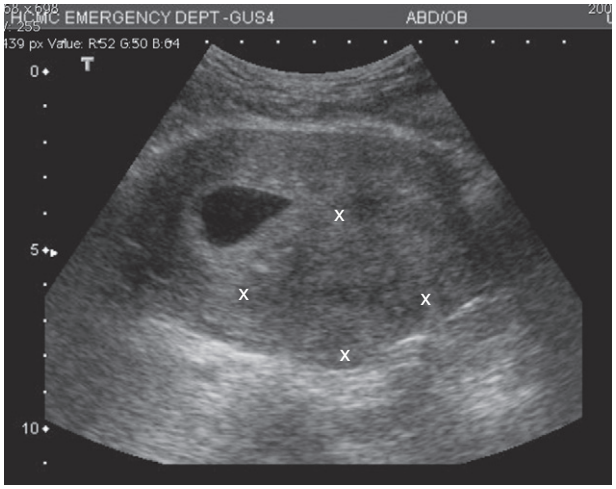

Figure 98-12. Longitudinal view of the uterus with thickened endometrium. (Courtesy of Robert Reardon, MD, Hennepin County Medical Center; used with permission.)

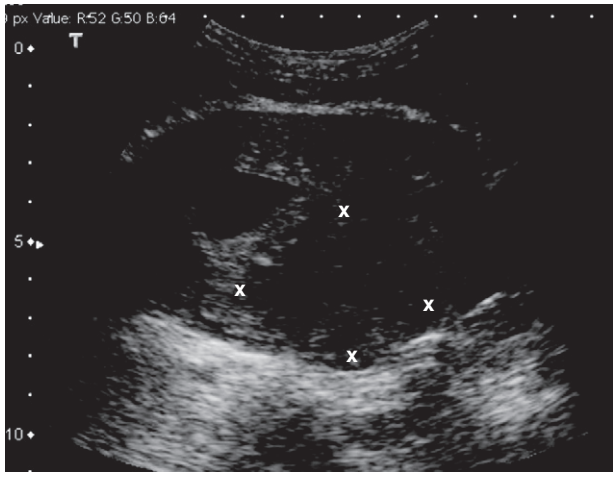

Figure 98-13. Ultrasound image of a uterine fibroid (within x's). (Courtesy of Robert Reardon, MD, Hennepin County Medical Center; used with permission.)

seen in the folds of skin in the neck, groin, or axilla.[30] Other causes of bleeding include vaginal or cervical lesions, which may be visible on the speculum exam. A leiomyoma or fibroid uterus may be palpable on the bimanual exam.[31] Patients with endometrial cancer frequently have an enlarged uterus as well.

Diagnostic Strategies

Laboratory Studies. In evaluating a woman of reproductive age with vaginal bleeding, a urine pregnancy test is the most essential laboratory test. If the patient is not pregnant, additional laboratory studies may be indicated depending on specific features of the history and physical exam. In a patient with excessive bleeding, any hemodynamic instability, or clinical evidence of anemia (e.g., excessive fatigue, pale conjunctiva), a hemoglobin and hematocrit may provide helpful information. Coagulation studies should be considered in patients with underlying liver disease or other coagulopathies.[29]

Imaging

Ultrasonography. Transvaginal ultrasonography may reveal a fibroid uterus, endometrial thickening, or a focal mass.[32] Endometrium measuring less than 4 mm thick is under the influence of low estrogen, either in the early follicular phase or in menopause, for example. Thickened endometrium may indicate an underlying lesion or excess estrogen[33] (Fig. 98-12). For a majority of nonpregnant patients with abnormal uterine bleeding, these ultrasound findings do not immediately affect ED decision-making. In patients who have access to adequate gynecologic services, imaging may be deferred until follow-up evaluation with the gynecologist. The decision to perform ultrasound imaging in the ED will depend on the urgency to determine the etiology of bleeding and on the reliability of outpatient follow-up.

With ED pelvic ultrasound imaging in nonpregnant patients, the etiology of the bleeding is determined in approximately 60% of cases. Uterine fibroids are by far the most common diagnosis (Fig. 98-13), but in one study, 9.6% of patients had endometrial changes suggestive of malignancy.[34] This finding illustrates the importance of arranging follow-up for any patient with new abnormal uterine bleeding, particularly if she has risk factors for endometrial cancer.

Differential Considerations

The etiology of abnormal uterine bleeding is extensive and includes systemic disease, structural lesions such as a fibroid uterus, hormonal abnormalities, and iatrogenic causes such as medication side effects. A careful physical exam will exclude vaginal or rectal sources of bleeding.

Management

The likely causative disorder, as well as the amount of bleeding, will guide the ED management. Nonsteroidal anti-inflammatory medications are generally effective for relief of associated cramping pelvic pain.[21] For anovulatory bleeding, combination oral contraceptive pills can help regulate the cycle and also counteract the effects of long-term effects of unopposed estrogen on the endometrium. In a patient who desires contraception and is not heavily bleeding on presentation to the ED, a combination oral contraceptive with 20 to 35 μg of ethinyl estradiol may be prescribed.[20] In the patient with heavy bleeding, an oral contraceptive with 35 μg of estrogen can be taken twice a day for 5 to 7 days until the bleeding stops, at which time the dose is decreased to once a day until the pack is completed.[21] Rarely, a patient will present with uncontrolled bleeding and signs of significant blood loss. These patients should have aggressive resuscitation with saline and blood as with other types of hemorrhagic shock. In these patients, surgical removal of the culprit lesion if one is present, or an urgent dilation and curettage (D&C) procedure may be necessary. Alternatively, intravenous conjugated estrogen (Premarin) may be used. The dose is 25 mg IV every 4 to 6 hours until the bleeding stops.[35]

EMERGENCY CONTRACEPTION

Emergency contraception, agents for which are known as the *morning-after pill*, consists of therapy to prevent pregnancy after unprotected sexual intercourse. It is estimated that more than 1 million unintended pregnancies could be avoided if emergency contraception were used.[36] The most common reasons cited by patients seeking emergency contraception include failure to use contraception and failure of the contraception method, such as from a broken condom or missed oral

contraceptive pill. Although, literature supports the efficacy and safety of emergency contraception, a recent survey of 800 women of reproductive age found that only 6% of the women had ever used emergency contraception.[37] Many patients are not aware of the availability of this technology, are not informed about its safety or use, or do not have access to the medications.[37,38]

Emergency contraception using high-dose estrogen was reported in the early 1960s and began to have widespread use after Yuzpe demonstrated the efficacy of a lower dose combination of estrogen and progestin to prevent pregnancy in 1974.[36,39,40] Until recently, the Yuzpe regimen—200 µg of estradiol plus 1.0 mg of levonorgestrel or 2.0 mg of norgestrel taken as two doses 12 hours apart—was the standard for postcoital contraception, but at present, levonorgestrel alone, marketed as Plan B in the United States, is more effective and has largely replaced the Yuzpe method.[41] Nausea occurs in 18% of patients using Plan B and in 43% of women taking combination pills.[42] Antiemetics given 1 hour before the combination pills are effective and should be considered with use of these pills. The incidence of nausea is much lower with Plan B, but antiemetics can be offered. The package insert of Plan B recommends taking the 0.75 mg pill as soon as possible and the subsequent dose 12 hours later; however, taking the doses simultaneously is equally effective. Emergency contraception should be administered before 24 hours if possible but can be given up to 120 hours after intercourse. The Yuzpe method is 87 to 90% effective if the regimen is given within 72 hours; this rate drops to 72 to 87% if the pills are given between 72 and 120 hours.[36]

Emergency contraception may be offered to any woman after inadequately protected intercourse who does not desire pregnancy. The typical contraindications to oral contraceptives do not apply to emergency contraception, because the duration of therapy is so brief.[43] Emergency contraception has no adverse effects on a developing fetus and does not pose a risk to an established pregnancy. A majority of nonpregnant women experience menses within a week of the expected time, but irregular bleeding may occur.[37] It is still possible for a patient who uses emergency contraception to get pregnant in the same menstrual cycle, so she should be advised to use an alternative form of contraception and to obtain a pregnancy test if menses is delayed more than 3 weeks. Advance provision of emergency contraception does not increase the number of unprotected sexual encounters.[44-47]

In 2007, after FDA approval, Plan B became available nationally over the counter without a prescription. Pregnancy rates as well as sexually transmitted diseases, and sexual activity remained unchanged even though the use of emergency contraception has increased, but the effect on these other outcomes was negligible.[48]

DISPOSITION

A majority of patients with pelvic pain from ovarian cysts or abnormal uterine bleeding without hemodynamic compromise may be managed with specific therapies to minimize symptoms and should be referred to a gynecologist for definitive management on an outpatient basis. Patients with confirmed or suspected adnexal torsion and those with severe, acute abnormal uterine bleeding and hemodynamic instability will require urgent gynecology consultation and hospitalization. Patients who receive emergency contraception could be counseled regarding birth control and have a follow-up pregnancy test should they miss their next period.

KEY POINTS

- Adnexal torsion is easily missed on initial presentation. This diagnosis should be a consideration in any patient with known risk factors, even if symptoms are subtle or atypical.
- Abnormal uterine bleeding has a myriad of structural or hormonal causes. A careful history and physical examination and selected imaging can help determine the likely cause.
- Ultrasound examination may distinguish among the various types of ovarian cysts and identify associated complications such as torsion and hemorrhage.
- Emergency contraception is a safe, effective option to prevent undesired pregnancy. Levonorgestrel (progestin) as Plan B is more effective and is associated with fewer side effects than the traditional Yuzpe method.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 99 Stroke

Todd J. Crocco, Allison Tadros, and Rashmi U. Kothari

PERSPECTIVE

Background

Stroke is the third leading cause of death in the United States and a leading cause of long-term disability.[1] It afflicts more than 700,000 patients per year,[1] with an in-hospital mortality rate of 5 to10% for ischemic stroke[2,3] and 46% for intracerebral hemorrhage (ICH).[4] Although 50 to 70% of stroke survivors will regain functional independence, 15 to 30% will be permanently disabled, and 20% will require institutional care at 3 months. The estimated cost of stroke for 2007 is $62.7 billion.[1] In terms of emergency care, almost 2% of all 911 calls and 4% of hospital admissions from the emergency department (ED) are for patients with potential strokes.[5,6]

Stroke can be defined as any vascular injury that reduces cerebral blood flow (CBF) to a specific region of the brain, causing neurologic impairment. The onset of symptoms may be sudden or stuttering, often with transient or permanent loss of neurologic function. Approximately 80% of all strokes are ischemic in origin, caused by the occlusion of a cerebral vessel.[3,4] The rest are hemorrhagic strokes due to the rupture of a blood vessel into the parenchyma of the brain (ICH) or into the subarachnoid space (subarachnoid hemorrhage [SAH]). Only ischemic stroke and ICH are discussed in this chapter.

In the past, treatment for stroke consisted of stabilization, observation, and rehabilitation. In recent years, a better understanding of the pathophysiology of neuronal injury and the introduction of new therapies have led to a shift to early evaluation and treatment. Current interventional treatment regimens include blood pressure management, anticoagulation, thrombolytic therapy, catheter-based interventions, and surgery. The key to success is early identification and treatment of patients with stroke before neurologic deficits become irreversible.

Epidemiology

Ischemic Stroke

An estimated 430,000 "first-ever" ischemic strokes occur each year in the United States, of which 10 to 15% are transient ischemic attacks (TIAs). These may result either from in situ thrombosis or embolic obstruction from a more proximal source, usually the heart. In more than one third of these first-ever strokes, no cause is found[7,8] (Table 99-1).

Approximately one third of all ischemic strokes are thrombotic in nature. These can be due to either large- or small-vessel occlusions. The incidence of large-vessel occlusions is higher among men than among women and among whites than black Americans.[7,8] Common areas for large-vessel occlusions are cerebral vessel branch points, especially in the distribution of the internal carotid artery. Thrombosis usually results from clot formation in the area of an ulcerated atherosclerotic plaque (which forms in the area of turbulent blood flow, such as a vessel bifurcation). A marked reduction in flow results when the stenosis occludes more than 90% of the blood vessel diameter. With further ulceration and thrombosis, platelets adhere to the region. A clot then either embolizes or occludes the artery.

Lacunae, or small-vessel strokes, involve small terminal sections of the vasculature and more commonly occur in black Americans and patients with diabetes and hypertension.[7] A history of hypertension is present in 80 to 90% of patients who experience lacunar strokes. The subcortical areas of the cerebrum and brainstem often are involved. The infarcts range in size from a few millimeters to 2 cm and are seen most commonly in the basal ganglia, thalamus, pons, and internal capsule. They may be caused by small emboli or by a process termed *lipohyalinosis*, which occurs in patients with hypertensive cerebral vasculopathy. Although nearly 20 lacunar syndromes have been described, the most common of these lacunar syndromes are pure motor strokes, pure sensory strokes, or ataxic hemiparesis. Because they are subcortical and well localized, lacunar strokes do not cause cognitive impairment, aphasia, or simultaneous sensorimotor findings.

One fourth of all ischemic strokes are cardioembolic in nature.[7,8] Embolization of a mural thrombus in patients with atrial fibrillation is the most common pathomechanism, and patients with atrial fibrillation have a four- to fivefold increased risk for development of a stroke.[9] Almost 20% of stroke patients will have atrial fibrillation on their admission electrocardiogram (ECG).[10] Strokes due to atrial fibrillation are more likely to involve large cerebral vessels, to be more severe, and to carry a higher mortality rate.[9,10] Noncardiac sources of emboli may include diseased portions of extracranial arteries, resulting in an artery-to-artery embolus. One common example is amaurosis fugax, in which emboli from a proximal carotid artery plaque embolizes to the ophthalmic artery, causing transient monocular blindness.

Approximately 12.2 ischemic strokes per 1000 nonfatal myocardial infarctions (MIs) occur within 1 month after the index event. Furthermore, 11.1 ischemic strokes per 1000 nonfatal MIs occur during the patient's hospitalization.[11] Independent predictors of stroke after acute MI are advanced age, diabetes,

Table 99-1 Estimated Number of First-Ever Strokes/TIAs in the United States

STROKE SUBTYPE	ESTIMATED NUMBER
Large-vessel	69,000 (16%)
Small-vessel/lacunae	76,000 (17.5%)
Cardioembolic	113,000 (26%)
Stroke of uncommon mechanisms	15,000 (3.5%)
Infarction of unknown etiology	157,000 (36.5%)
Total strokes/TIAs	430,000 (100%)

TIA, transient ischemic attack.
Data from Woo D, et al: Incidence rates of first-ever ischemic stroke subtypes among blacks: A population-based study. Stroke 30:2517, 1999; and Petty GW, et al: Ischemic stroke subtypes: A population-based study of incidence and risk factors. Stroke 30:2513, 1999.

hypertension, history of previous stroke, anterior location of index MI, previous MI, atrial fibrillation, heart failure, and nonwhite race.[11] The use of aspirin has been shown to reduce the incidence of post-MI stroke by 46%.[12]

Approximately 3 to 4% of all strokes occur in patients between the ages of 15 and 45 years. Although atherosclerosis is the most common cause in older patients, causative disorders and conditions in younger patients often are uncommon or are reversible. Pregnancy, the use of oral contraceptives, antiphospholipid antibodies (such as lupus anticoagulant and anticardiolipin antibodies), protein S and C deficiencies, and polycythemia all predispose patients to sludging or thrombosis, thereby increasing the risk of stroke. Fibromuscular dysplasia of the cerebral vasculature also may lead to stroke, and in rare instances, prolonged vasoconstriction from a migraine syndrome causes stroke. Recreational drugs such as cocaine, phenylpropanolamine, and amphetamines are potent vasoconstrictors that have been associated with both ischemic and hemorrhagic stroke.

Carotid and vertebral dissections often are associated with trauma but may follow such mild events as turning the head sharply. Carotid and vertebral dissections also are seen more frequently in people with underlying pathology of the vessel wall, such as in fibromuscular dysplasia and connective tissue disorders. Alteration in the vessel intima can lead to vessel stenosis, occlusion, or embolism. The patient may report a minor preceding event such as spinal manipulation, yoga, working overhead, coughing, or vomiting.[13] Presenting manifestations may include headache, facial pain, visual changes, cranial nerve palsies, pain over the affected vessel, Horner's syndrome, amaurosis fugax, subarachnoid hemorrhage, or an ischemic stroke. The headache frequently is unilateral and may occur days before onset of the other neurologic symptoms.[13] Although angiography has been the standard diagnostic study, dissections are increasingly being diagnosed by less invasive modalities such as ultrasonography, magnetic resonance imaging (MRI), and computed tomography angiography (CTA).[14] Medical therapy includes early anticoagulation if SAH is not suspected. If symptoms recur despite anticoagulation, the patient may be eligible for endovascular intervention. Carotid or vertebral dissection is not considered a contraindication to use of tissue plasminogen activator (t-PA) in the eligible patient.[15] This entity is considered a major cause of stroke in younger patients.[13,16,17]

A TIA was historically defined as a neurologic deficit that has complete clinical resolution within 24 hours. A newer definition of TIA proposed by Albers[18] is a "brief episode of neurologic dysfunction caused by a focal disturbance of brain or retinal ischemia, with clinical symptoms typically lasting less than 1 hour, and without evidence of infarction." This updated definition evolved as newer imaging techniques demonstrated infarction in up to 81% of patients with neurologic symptoms lasting less than 24 hours.[19,20] TIAs constitute an important warning sign for the future development of cerebral infarction. Approximately 10% of the patients who experience a TIA will experience a stroke within 3 months of the sentinel event, and one half of these occur within the first 2 days.[21] A majority of TIAs last less than 5 minutes, but the course can be variable.[22] Three or more TIAs occurring within 72 hours are termed crescendo TIAs. Almost one half of all patients 65 years of age and older with "first-ever" TIAs have MRI evidence of a previous, clinically silent, cerebral infarction.[20] These lesions usually are deep and less than 1 cm in diameter and often involve the nondominant right hemisphere.

BOX 99-1 Most Common Sites for Hypertensive Intracranial Hemorrhage

Affected Area	Frequency
Putamen	44%
Thalamus	13%
Cerebellum	9%
Pons	9%
Other cortical areas	25%

Hemorrhagic Stroke

Spontaneous ICH causes 8 to 11% of all acute strokes and is twice as common as SAH. It carries a 30-day mortality rate of up to 50%, with one half of patients dying in the first 2 days. Among survivors, only 1 in 5 are living independently at 6 months.[23] The incidence of ICH is higher in men than in women and in Asians than in whites, and it occurs more commonly in young and middle-aged black Americans than in whites of similar age.[24]

ICH may occur in association with long-standing hypertension (hypertensive hemorrhage), amyloid angiopathy in the elderly, or arteriovenous malformations (AVMs). Hypertensive hemorrhage results from degenerative changes in the small penetrating arteries and arterioles leading to the formation of microaneurysms, most commonly in penetrating vessels of the middle cerebral artery. Two thirds of these bleeding episodes occur within the region of the basal ganglia. The most common sites for hypertensive hemorrhage are listed in Box 99-1. The hematoma that forms usually enlarges, causing local tissue injury and a subsequent increase in intracranial pressure (ICP).

ICH due to amyloid angiopathy tends to be lobar in nature and to occur more commonly in the elderly, with a higher incidence in whites than in black Americans. Sudden increases in blood pressure that occur with such drugs as phenylpropanolamine and cocaine can cause ICH. Other causes include the use of anticoagulants, tumors, and AVMs (especially in the young).

Bleeding from an AVM may be subarachnoid or intraparenchymal, or both. In AVMs, the hemorrhage into the subarachnoid space generally is confined to the area of the AVM, and the major clinical presentation is due to the intraparenchymal involvement, with focal neurologic deficits. AVMs are more likely to bleed into the ventricles and subarachnoid space than are hypertensive ICHs and usually have a less disruptive impact on cerebral function. An AVM producing hemorrhage

is more common in younger patients than hypertensive ICH. Such patients may have no history of hypertension.

PRINCIPLES OF DISEASE

Pathophysiology

The cerebral vasculature supplies the brain with a rich flow of blood that contains the critical supply of oxygen and glucose necessary for normal brain function. When a stroke occurs, there are immediate alterations in CBF and extensive changes in cellular homeostasis. A complete interruption of CBF, which is rare, results in loss of consciousness within approximately 10 seconds and death of vulnerable pyramidal cells of the hippocampus within minutes. In stroke, collateral circulation helps maintain some blood flow to the ischemic region. The normal CBF is 40 to 60 mL/100 g of brain per minute. When CBF drops below 15 to 18 mL/100 g of brain per minute, several physiologic changes occur. The brain loses electrical activity, becoming electrically "silent," although neuronal membrane integrity and function remain intact. Clinically, the areas of the brain maintaining electrical silence manifest a neurologic deficit, even though the brain cells are viable. When CBF is below 10 mL/100 g of brain per minute, membrane failure occurs, with a subsequent increase in the extracellular potassium and intracellular calcium and eventual cell death. The ischemic penumbra is the area of the brain surrounding the primary injury, which is preserved by a tenuous supply of blood from collateral vessels. This border zone of neuronal tissue is the area of greatest interest to investigators for possible salvage in both ischemic and hemorrhagic stroke. As defined by CBF, the ischemic penumbra consists of brain tissue with blood flow of 10 to 18 mL/100 g of brain per minute in which electrical silence is present but irreversible damage has not yet occurred. In ischemic stroke, the duration of occlusion plays a critical role in neuronal survival.[25] Increasing the duration of occlusion increases both the irreversibility of deficits and the amount of cerebral infarction. In experimental animals, occlusion of cerebral vessels for longer than 6 hours leads to irreversible neurologic deficits. Thus, ischemic stroke trials using fibrinolytic or antiplatelet agents have attempted to recanalize occluded arteries and reperfuse ischemic areas of the brain within a 2- to 6-hour therapeutic window.[26-30] In patients with ICH, a complicated series of events including red blood cell lysis and increased blood-brain barrier permeability can lead to edema formation and secondary brain injury.[31,32] Using a protocol similar to that in ischemic stroke trials, investigators have begun looking at the feasibility of ultra-early hematoma evacuation in patients with ICH.[33-36]

Anatomy and Physiology

Blood is supplied to the brain by the anterior and posterior circulations. The anterior circulation originates from the carotid system and perfuses 80% of the brain including the optic nerve, retina, and frontoparietal and anterior-temporal lobes. The first branch off the internal carotid artery is the ophthalmic artery, which supplies the optic nerve and retina. As a result, the sudden onset of painless monocular blindness (amaurosis fugax) identifies the stroke as involving the anterior circulation (specifically the ipsilateral carotid artery) at or below the level of the ophthalmic artery. The internal carotid arteries terminate by branching into the anterior and middle cerebral arteries at the circle of Willis.

The anterior cerebral artery supplies the basal and medial aspects of the cerebral hemispheres and extends to the anterior two thirds of the parietal lobe (Fig. 99-1). The middle cerebral artery feeds the lenticulostriate branches that supply the putamen, part of the anterior limb of the internal capsule, the lentiform nucleus, and the external capsule. Main cortical branches of the middle cerebral artery supply the lateral surfaces of the cerebral cortex from the anterior portion of the frontal lobe to the posterolateral occipital lobe.

Figure 99-1. The CT slice with the largest area of hemorrhage is identified. The largest diameter of the hemorrhage on this slice is measured in centimeters (A). The largest diameter 90 degrees to A on the same slice is measured (B). C is the approximate number of 10-mm slices on which the intracerebral hemorrhage was seen. The volume of the hemorrhage equals A multiplied by C, divided by 2 (ABC/2).

Although the posterior circulation is smaller and supplies only 20% of the brain, it supplies the brainstem (which is critical for normal consciousness, movement, and sensation), cerebellum, thalamus, auditory and vestibular centers of the ear, medial temporal lobe, and the visual occipital cortex. The posterior circulation is derived from the two vertebral arteries that ascend through the transverse processes of the cervical vertebrae. The vertebral arteries enter the cranium through the foramen magnum and supply the cerebellum by the posterior inferior cerebellar arteries. They join to form the basilar artery, which branches to form the posterior cerebral arteries.

The extent of injury in either an anterior or a posterior stroke depends on both the vessel involved and the presence of collateral blood flow distal to the vessel occlusion. A patient with excellent collateral blood flow from the contralateral hemisphere may have minimal clinical deficits despite a complete carotid occlusion. By contrast, a patient with poor collateral flow may have hemiplegia with the same lesion.

CLINICAL FEATURES

Ischemic Stroke

The signs and symptoms of an ischemic stroke may appear suddenly and without warning or may have a stuttering, insidious onset. Disruption of the flow to one of the major vascular limbs of the cerebral circulation will result in physiologic disruption to the anatomic area of the brain supplied by that blood vessel. Ischemic strokes can be classified as anterior or posterior circulation strokes depending on the vasculature involved. The presence of neurologic deficits is highly dependent on collateral flow. In addition to the vascular supply involved, ischemic strokes can be further described by the

temporal presentation of their neurologic deficits. A "stroke in evolution" is one in which focal neurologic deficits worsen over the course of minutes or hours. Approximately 20% of anterior circulation strokes and 40% of posterior circulation strokes will show evidence of progression. Anterior circulation strokes may progress within the first 24 hours, whereas posterior strokes may progress for up to 3 days. Propagation of thrombus is postulated as a likely mechanism for progression. With anterior circulation strokes (involving variously and primarily the carotid, anterior, and middle cerebral arteries), the clinical presentation rarely includes complete loss of consciousness unless the lesion occurs in the previously unaffected hemisphere of a patient who has experienced a previous contralateral stroke. Occlusions in the anterior cerebral artery mainly affect frontal lobe function. The patient has altered mentation coupled with impaired judgment and insight, as well as the presence of primitive grasp and suck reflexes on physical exam. Bowel and bladder incontinence may be features. Paralysis and hypesthesia of the lower limb opposite the side of the lesion are characteristic. Leg weakness is more pronounced than arm weakness in anterior cerebral distribution stroke. Apraxia or clumsiness in the patient's gait also may be noted.

Marked motor and sensory disturbances are the hallmarks of occlusion of the middle cerebral artery. They occur on the side of the body contralateral to the side of the lesion and usually are worse in the arm and face than the leg. Such disturbances may involve only part of an extremity or the face but will almost always be accompanied by numbness in the same region as that of the motor loss. Hemianopsia, or blindness in one half of the visual field, occurs ipsilateral to the lesion. Agnosia, or the inability to recognize previously known subjects, is common, and aphasia may be present if the lesion occurs in the dominant hemisphere. Patients often have a gaze preference toward the affected hemisphere because of disruption of the cortical lateral gaze centers. The clinical aphorism is that a patient looks *at* a destructive lesion (stroke) but *away from* an irritative lesion (seizure focus).

Aphasia, a disorder of language in which the patient articulates clearly but uses language inappropriately or understands it poorly, also is common in dominant-hemisphere stroke. Aphasia may be expressive, receptive, or a combination of both. *Wernicke's aphasia* occurs when the patient is unable to process sensory input such as speech and thus fails to understand verbal communication (receptive aphasia). *Broca's aphasia* refers to the inability to communicate verbally in an effective way, even though understanding may be intact (expressive aphasia). Aphasia should be distinguished from dysarthria, which is a motor deficit of the mouth and speech muscles; the dysarthric patient articulates poorly but understands words and word choices. Aphasia is important to recognize because it usually localizes a lesion to the dominant (usually left) cerebral cortex in the middle cerebral artery distribution. *Aphasia* and *dysphasia* are terms that are used interchangeably but must be distinguished from *dysphagia*, which is difficulty in swallowing.

Pathology in the vertebrobasilar system (i.e., posterior circulation strokes) can cause the widest variety of symptoms and as a result may be the most difficult to diagnose. The symptoms reflect cranial nerve deficits, cerebellar involvement, and involvement of neurosensory tracts. The brainstem also contains the reticular activating system, which is responsible for mediating consciousness, and the emesis centers. Unlike those with anterior circulation strokes, patients with posterior circulation stroke can present with loss of consciousness and frequently have nausea and vomiting. The posterior cerebral artery supplies portions of the parietal and occipital lobes, so vision and thought processing are impaired. Visual agnosia, the inability to recognize seen objects, may be a feature, as may alexia, the inability to understand the written word. A third nerve palsy may occur, and the patient may experience homonymous hemianopsia. One of the more curious facets of this syndrome is that the patient may be unaware of any visual problem (visual neglect). Vertigo, diplopia, visual field defects, weakness, paralysis, dysarthria, dysphagia, syncope, spasticity, ataxia, or nystagmus may be associated with vertebrobasilar artery insufficiency. Posterior circulation strokes also demonstrate crossed deficits, such as motor deficits on one side of the body and sensory loss on the other. In anterior circulation strokes, by contrast, abnormalities are always limited to one side of the body.

A focused neurologic exam should assess level of consciousness, speech, cranial nerve function, motor and sensory function, and cerebellar function. Level of consciousness and fluency of speech can be rapidly assessed in a dialogue with the patient to determine the presence of dysarthria or aphasia. The head should be evaluated for signs of trauma. Pupillary size and reactivity and extraocular movements provide important information about brainstem function, particularly cranial nerves (CN) III through VI; an abnormal third nerve function may be the first sign of tentorial herniation. Gaze preference suggests brainstem or cortical involvement. Central facial nerve weakness from a stroke should be distinguished from the peripheral causes of CN VII weakness. With a peripheral lesion, the patient is unable to wrinkle the forehead. Assessment of facial sensation, eyebrow elevation and squinting, smiling symmetry, gross auditory acuity, gag reflex, shoulder elevation, sternocleidomastoid strength, and tongue protrusion complete the cranial nerve evaluation.

Motor and sensory testing is performed next. Muscle tone can be assessed by moving a relaxed limb. Proximal and distal muscle group strength should be assessed against resistance. Pronator drift of the arm is a sensitive sign of motor weakness and can be tested simultaneously by having the patient sit with eyes closed and arms outstretched, with palms toward the ceiling, for 10 seconds. Asymmetrical sensation to pain and light touch may be subtle and difficult to detect. Double simultaneous extinction evaluation tests for sensory neglect and can be easily performed by simultaneously touching the right and left limbs. The patient may feel both the right and left sides being touched individually but may not discern touch on one side when both are touched simultaneously. Similarly, the ability to discern a number gently scratched on a forearm, graphesthesia, is another easily tested cortical parietal lobe function. These tests can help differentiate a pure motor deficit of a lacunar stroke from a sensorimotor middle cerebral artery deficit.

Cerebellar testing and the assessment of reflexes and gait complete the examination. Finger-to-nose and heel-to-shin evaluations are important tests of cerebellar functions. Asymmetry of the deep tendon reflexes or a unilateral Babinski's sign may be an early finding of corticospinal tract dysfunction. Gait testing is commonly omitted yet is one of the most informative parts of the neurologic examination. Observing routine ambulation and heel-to-toe walking can assess for subtle ataxia, weakness, or focal cerebellar lesions.

The National Institutes of Health Stroke Scale (NIHSS) is a useful and rapid tool for quantifying neurologic deficit in patients with stroke and can be used in determining treatment options[37] (Box 99-2). NIHSS scores have been shown to be reproducible and valid and to correlate well with the amount of infarcted tissue on CT scan.[38,39] The baseline NIHSS can identify patients who are appropriate candidates for fibrinolytic therapy as well as those at increased risk for hemorrhage.

BOX 99-2 NIH Stroke Scale Scoring Form

Item	Scoring Definitions	Score
1a. *Level of consciousness (LOC)*	0 = alert and responsive 1 = arousable to minor stimulation 2 = arousable only to painful stimulation 3 = reflex reponses or unarousable	
1b. *LOC-related questions*: Ask patient's age and month. Must be exact.	0 = both correct 1 = one correct (or dysarthria, intubated, foreign language) 2 = neither correct	
1c. *Commands*: Open/close eyes, grip and release nonparetic hand. (Other one-step commands or mimic also acceptable.)	0 = both correct (acceptable if impaired by weakness) 1 = one correct 2 = neither correct	
2. *Best gaze*: Horizontal EOM by voluntary or doll's eye maneuver.	0 = normal 1 = partial gaze palsy; abnormal gaze in one or both eyes 2 = forced eye deviation or total paresis that cannot be overcome by doll's eye maneuver	
3. *Visual field*: Use visual threat if nec. If monocular, score field of good eye.	0 = no visual loss 1 = partial hemianopsia, quadrantanopia, extinction 2 = complete hemianopsia 3 = bilateral hemianopsia or blindness	
4. *Facial palsy*: If patient is stuporous, check symmetry of grimace to pain.	0 = normal 1 = minor paralysis, flat NLF, asymmetrical smile 2 = partial paralysis (lower face = UMN lesion) 3 = complete paralysis (upper and lower face)	
5. *Motor arm*: Arms outstretched 90 degrees (sitting) or 45 degrees (supine) for 10 seconds. Encourage best effort. Indicate paretic limb in score box.	0 = no drift for 10 seconds 1 = drift but doesn't hit bed 2 = some antigravity effort, but can't sustain 3 = no antigravity effort, but even miminal mvt counts 4 = no movement at all X = unable to assess due to amputation, fusion, fracture, etc.	L or R
6. *Motor leg*: Raise leg to 30 degrees (from supine) for 5 seconds. Indicate paretic limb in score box.	0 = no drift for 5 seconds 1 = drift but doesn't hit bed 2 = some antigravity effort, but can't sustain 3 = no antigravity effort, but even miminal mvt counts 4 = no movement at all X = unable to assess owing to amputation, fusion, fracture, etc.	L or R
7. *Limb ataxia*: Check finger-nose-finger, heel-shin position sense; and score only if out of proportion to paralysis.	0 = no ataxia (or aphasic, hemiplegic) 1 = ataxia in upper or lower extremity 2 = ataxia in upper *and* lower extremity X = unable to assess owing to amputation, fusion, fracture, etc.	L or R
8. *Sensory*: Use safety pin. Check grimace or withdrawal if patient is stuporous. Score only stroke-related losses.	0 = normal 1 = mild-moderate unilateral loss but patient aware of touch (or aphasic, confused) 2 = total loss, patient unaware of touch; coma, bilateral loss	
9. *Best language*: Describe cookie jar picture, name objects, read sentences. May use repeating, writing, stereognosis.	0 = normal 1 = mild-moderate aphasia (speech difficult to understand but partly comprehensible) 2 = severe aphasia (almost no information exchanged) 3 = mute, global aphasia, coma; no one-step commands	
10. *Dysarthria*: Read list of words.	0 = normal 1 = mild-moderate; slurred but intelligible 2 = severe; unintelligible or mute X = intubation or mech barrier	
11. *Extinction/neglect*: Simultaneously touch patient on both hands, show fingers in both visual fields, ask about deficit, left hand.	0 = normal, none detected (vis loss alone) 1 = neglects or extinguishes to double simultaneous stimulation in any modality (visual, auditory, sensation, spatial, body parts) 2 = profound neglect in more than one modality	

EOM, extraocular movement; NIH, National Institutes of Health; NLF, nasolabial fold; UMN, upper motor neuron.
Modified from online document. Massachusetts General Hospital Stroke Service. Available at: http://www2.massgeneral.org/stopstroke/pdfs/scoring_form.pdf

Table 99-2 Clinical Findings Associated with Ischemic Strokes, ICH, and SAH

FINDING	ISCHEMIC STROKE	ICH	SAH
Headache	11–17%	33–41%	78–87%
Vomiting	8–11%	29–46%	45–48%
Decreased LOC	13–15%	39–57%	48–68%
Seizure	0.3–3%	6–7%	7%

ICH, intracranial hemorrhage; LOC, level of consciousness; SAH, subarachnoid hemorrhage.

Data from Bogousslausky J, Van Melle G, Regli F: The Lausanne Stroke Registry: Analysis of 1000 consecutive patients with first stroke. Stroke 19:1083, 1988; Foulkes MA, et al: The Stroke Data Bank: Design, methods, and baseline characteristics. Stroke 19:547, 1988; and Mohr JP, et al: The Harvard Cooperative Stroke Registry: A prospective registry. Neurology 28:754, 1978.

In addition, it has been used as a prognostic tool to predict outcome and is currently being used by some stroke centers to stratify patients for entry into treatment trials.[37-40]

Hemorrhagic Stroke

The classic presentation of ICH is the sudden onset of headache, vomiting, severely elevated blood pressure, and focal neurologic deficits that progress over minutes. Similar to ischemic stroke, ICH often is associated with a motor and sensory deficit contralateral to the brain lesion. The patient may present with agitation and lethargy but may quickly deteriorate, with progression to stupor or coma. Almost 40% will demonstrate significant growth in hemorrhage volume within the first few hours.[41] Although headache, vomiting, and coma are common, a significant proportion of patients do not have these findings, and the clinical presentation may be similar to that of patients with ischemic stroke (Table 99-2).

Ongoing assessment of airway and mental status is of paramount importance in patients with ICH because precipitous deterioration is always a possibility. The respiratory pattern also may be affected in hemorrhagic stroke. Cheyne-Stokes respirations (increasing and decreasing depth of respirations with periods of apnea) may occur with a large ICH. Putaminal hemorrhages may cause deep, irregular respirations, whereas patients with cerebellar hemorrhage may have a normal respiratory pattern.

The pupillary examination can be extremely helpful in determining the location and extent of the insult. Pontine hemorrhage classically manifests with pinpoint pupils because of the interruption of the descending sympathetic tracts and unopposed parasympathetic stimulation. Dilated pupils may result from bleeding into the putamen, whereas bleeding into the thalamus may manifest with anisocoria, miosis, or a sluggish pupillary response. Cranial nerve abnormalities may result from cerebellar hemorrhages. The parasympathetic fibers course along the outside of CN III. As a result, compression of the nerve results in loss of pupillary reactivity before anisocoria. As noted previously, the physical exam may be insufficient to distinguish an ischemic stroke from an ICH, and radiographic confirmation is required.

As with ischemic stroke, a careful neurologic exam is important in localizing the region and extent of injury. Baseline NIHSS and Glasgow Coma Scale (GCS) scores can be used to assess stroke severity, although the GCS score may be more feasible to follow for neurologic deterioration (Box 99-3).

Poor prognostic indicators for patients with ICH include a decreased level of consciousness on arrival, intraventricular hemorrhage, and an ICH volume of greater than 40 cc, all of which can be assessed in the ED. The ABC/2 technique is a quick and accurate method of measuring ICH volume at the bedside[42] (see Fig. 99-1).

BOX 99-3 GLASGOW COMA SCALE

Eye Opening (E)	Verbal Response (V)	Motor Response (M)
4 = Spontaneous	5 = Normal conversation	6 = Normal
3 = To voice	4 = Disoriented conversation	5 = Localizes to pain
2 = To pain	3 = Words, but not coherent	4 = Withdraws to pain
1 = None	2 = No words; only sounds	3 = Decorticate posture
	1 = None	2 = Decerebrate posture
		1 = None

Scoring
Total score = E + V + M

Available at http://www.ssgfx.com/CP2020/medtech/glossary/glasgow.htm.

DIFFERENTIAL CONSIDERATIONS

Ischemic Stroke

Extra-axial collections of blood secondary to trauma can mimic stroke. An epidural or subdural hematoma can cause an altered mental status, focal neurologic signs, and rapid progression to coma. Elderly patients, who represent the age group at highest risk for stroke, can be victims of recurrent falls that lead to chronic subdural hematomas. Carotid dissection may occur after neck trauma or sudden hyperextension and may be associated with focal neurologic signs and symptoms, as with an aortic dissection that extends into the carotid arteries. The diagnosis is supported by a compatible history or relevant findings on contrast angiography or magnetic resonance angiography (MRA).

Other structural lesions that may cause focal neurologic signs include brain tumors and abscesses. Air embolism should be suspected in the setting of marked atmospheric pressure changes, such as in scuba diving or during medical procedures or injuries that may allow air into the vascular system. Seizures, altered mental status, and focal neurologic findings also may be manifestations of air embolism.

Metabolic abnormalities also can mimic stroke syndromes. Hypoglycemia often is responsible for an altered mental status and is a well-known cause of sustained focal neurologic symptoms that can persist for several days. Wernicke's encephalopathy causes ophthalmoplegia, ataxia, and confusion that can be mistaken for signs of cerebellar infarction.

Migraine may present with focal neurologic findings, with or without headache. A seizure followed by Todd's postictal paralysis may mimic stroke. Bell's palsy, labyrinthitis, peripheral nerve palsy, and demyelinating diseases may all mimic stroke. Meniere's disease may be difficult to distinguish from a posterior circulation stroke or TIA. Dizziness, vertigo, hearing loss, and tinnitus in Meniere's disease are common, whereas difficulties with vision, speech, or other focal symptoms are uncommon.

Like stroke, giant cell arteritis is a disease of the elderly. It may cause severe headache, visual disturbances, and, rarely, aphasia and hemiparesis. Other symptoms include intermittent fever, malaise, jaw claudication, morning stiffness, and

myalgias. The diagnosis should be suspected in patients with a very high erythrocyte sedimentation rate (ESR) and is confirmed by temporal artery biopsy. Collagen vascular diseases such as polyarteritis nodosa, lupus, and other types of vasculitis may cause stroke syndromes.

Venous sinus thrombosis is another cause of focal neurologic symptoms that most commonly affects the superior sagittal sinus and lateral sinuses. The cerebral venous sinuses receive blood from the cortical veins and deep veins. A venous sinus can become occluded through thrombus formation or compression (such as from a tumor or abscess). If collateral circulation is not sufficient, cerebrospinal fluid pressures can become elevated and venous congestion can develop, resulting in petechial or hemorrhagic infarction. Multiple risk factors predisposing affected patients to venous sinus thrombosis are recognized, including trauma, infectious processes, hypercoagulable states, low-flow states, compression of the venous sinus, dehydration, various drugs (such as androgens, "ecstasy," and oral contraceptives), and pregnancy or the postpartum state.[43] In many patients, no predisposing risk factor will be identified until further workup is completed.

The diagnosis of cerebral venous thrombosis can be difficult because of the nonspecific nature of symptoms, as well as the variable time frame of symptom onset (from hours to a few weeks). Patients may present with generalized headaches, nausea, vomiting, paresis, visual disturbances, depressed level of consciousness, seizures or even symptoms generally ascribed to psychiatric disorders (such as depression).[43,44] Depending on the location of the thrombus, physical examination of the patient may reveal papilledema, proptosis, or palsies of cranial nerves III, IV, and VI, as well as other focal neurologic signs and symptoms.[44]

The diagnosis of cerebral venous thrombosis sometimes can be made by CT. The so-called delta sign can be seen on a noncontrast CT scan as a dense triangle in the superior sagittal sinus. On a contrast-enhanced CT scan, this same area will lack demonstration of full contrast (the empty delta sign) owing to presence of thrombus in portions of the vessel's lumen. At many institutions, MRI and magnetic resonance venography (MRV) are the preferred modalities for the noninvasive detection of cerebral venous thrombosis. These studies can diagnose cerebral venous thrombosis by visualizing thrombosis within a vessel and provide evidence of hemorrhagic foci or of dilated venous collateral circulation.[43, 44]

The treatment of venous sinus thrombosis includes the use of heparin even in those patients with demonstrated hemorrhage. There is no evidence that low-molecular-weight heparin is superior to unfractionated heparin. In some cases, thrombolytic agents have been directly infused into the thrombus using endovascular techniques. Neurosurgical intervention has not been proved to be of benefit.[43]

The mortality rate from venous sinus thrombosis is approximately 10%.[45] In view of the nonspecific nature of the symptoms, it is important to keep this diagnosis in mind. In women who are pregnant or have recently given birth, the possibility of venous sinus thrombosis should be a primary consideration in the setting of new-onset neurologic disorders.

Hemorrhagic Stroke

The differential diagnosis for ICH is similar to that for ischemic stroke; considerations include migraine, seizure, tumor, abscess, hypertensive encephalopathy, and trauma. Hypertensive encephalopathy and migraine also can manifest with headache, nausea, and vomiting. Although focal neurologic signs are uncommon, they may occur with these entities. With hypertensive encephalopathy, patients usually exhibit marked elevation in blood pressure and other evidence of end-organ injury, including proteinuria, cardiomegaly, papilledema, and malignant hypertensive retinopathy. These patients usually improve significantly with treatment of their hypertension. Migraines frequently are associated with an aura, and the patient often has a history of similar headaches. The differentiation between ICH and labyrinthitis can be especially difficult in the elderly. The abrupt onset of vertigo, vomiting, and nystagmus can represent a peripheral process such as labyrinthitis or a central process such as cerebellar or brainstem infarct or hemorrhage. Age older than 40 years and a history of hypertension or other risk factors for ICH increase the possibility of a cerebellar hemorrhage. Pathologic features specifically referable to the brainstem must be sought. These include hiccups, diplopia, facial numbness, dysphagia, and ataxia. Vertiginous patients often have a strong desire to remain immobile with the eyes closed, but this must not preclude a thorough cranial nerve and cerebellar examination, including gait. Gross ataxia should be present with cerebellar stroke and absent with labyrinthine disease. A head CT scan should be strongly considered in patients older than 40, to assist in differentiating between labyrinthitis and cerebellar hemorrhage.

DIAGNOSTIC STRATEGIES

Ischemic Stroke

Although clinical data can help establish the diagnosis, cause, and location of the stroke, confirmatory diagnostic tests often are required to establish the final etiology or to eliminate other causes for the deficits. The immediate ED evaluation should include a blood glucose determination, cranial imaging (CT or MRI scan), and an ECG.

An emergent noncontrast cranial CT is the standard initial imaging technique for evaluating a patient with a potential stroke in the ED. It can quickly differentiate an ischemic stroke from ICH and other mass lesions. This information is crucial to subsequent therapeutic decisions. A CT scan can identify almost all parenchymal bleeds larger than 1 cm in diameter. Recent studies have yielded a sensitivity of 92 to 98% for the detection of SAH by CT scan; however, recent small studies suggest that sensitivity may be even higher with fifth-generation CT scanners.[46] More research is needed to confirm the sensitivity of these fifth-generation CT scanners, owing to small sample sizes in studies examining this issue to date. In a majority of ischemic strokes, gross signs of infarction will not appear on routine CT scans for at least 6 to 12 hours, depending on the size of the infarct. However, subtle, early ischemic changes have been noted in up to 60 to 80% of noncontrast CT scans within the first 3 hours in patients with middle cerebral artery occlusions.[47-49] These early ischemic changes include the hyperdense artery sign (acute thrombus in a vessel), sulcal effacement, loss of the insular ribbon, loss of gray-white interface, mass effect, and acute hypodensity (Fig. 99-2). Additionally, CTA can be used to identify the presence of intravascular thrombosis, vasculature dissection, or stenosis. In cases in which arterial dissection is suspected, imaging with MRA or CTA is indicated.[14]

The clinical importance of early ischemic CT findings in regard to fibrinolytic therapy within 3 hours of symptom onset is questionable because the ability of treating physicians to reproducibly identify these findings is poor and their clinical significance is questionable.[50,51] Only acute hypodensity and mass effect have been shown to be associated with an increased risk of ICH after fibrinolysis (over that in treated patients without these findings). However, these findings do not

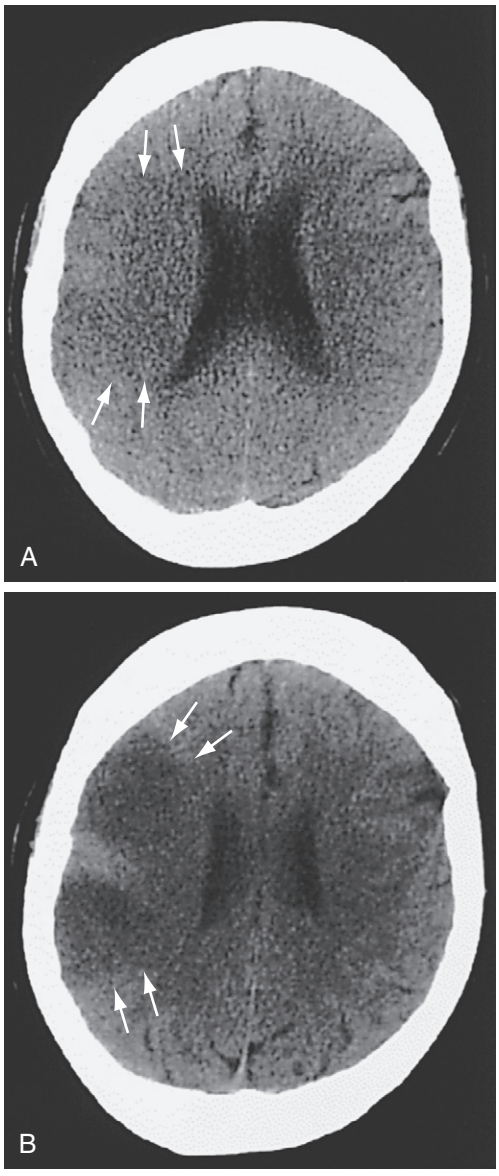

Figure 99-2. **A,** CT scan taken 2 hours and 50 minutes after a large right middle cerebral artery occlusion. There are subtle, ultra-early ischemic changes, including loss of the gray-white interface *(arrows)* and subtle evidence of sulcal effacement. **B,** CT scan of same patient approximately 8 hours after symptom onset shows acute hypodensity *(arrows)* and more prominent sulcal effacement.

exclude appropriate patients from fibrinolytic therapy, because the chance for excellent neurologic outcome at 3 months was better with such therapy than with placebo despite the presence of such abnormalities, and the risk of symptomatic ICH, severe disability, or death at 3 months was no different between treatment groups.[50] Patients with a hyperdense artery sign and acute hypodensity of one third of the middle cerebral artery distribution tend to have a poorer prognosis; however, their outcomes are still better with t-PA treatment than without such treatment.[50]

The role of MRI in the ED evaluation of stroke continues to evolve. MRI can visualize ischemic infarcts earlier and identify acute posterior circulation strokes more accurately than CT. In addition, recent studies suggest that it is as effective as CT in identifying ICH.[52,53] However, availability, difficulty in accessing critically ill patients, and scan time limit its general use. Advances in MRA technology have allowed a noninvasive method of demonstrating large-vessel occlusions of the anterior and posterior circulation, though small intracranial vascular occlusions may not be readily apparent. With the improvements in MRI and MRA speed and resolution, some stroke centers are replacing CT protocols with limited "stroke protocol" MRI or MRA as the initial imaging modality of choice. The choice of initial cranial imaging modality is highly dependent on the speed with which these scans can be done and interpreted at each individual center.

Diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI) are MRI techniques that take minutes to perform and may allow differentiation between reversible and irreversible neuronal injury. In one study of patients with DWI-PWI mismatch, 30-day clinical outcomes were better after early reperfusion than without such early reperfusion (56% and 19%, respectively).[54] Of importance, however, early reperfusion in patients without DWI-PWI mismatch did not result in a favorable outcome. Currently, further studies are being performed by clinicians and researchers to determine if t-PA administration in patients with DWI-PWI mismatch can increase reperfusion rates and limit expansion of the DWI lesion.[55]

Other potential imaging modalities include CTA and perfusion scans. In CTA, a computed tomography (CT) scan is enhanced by an intravenous contrast agent to better define the vasculature of the brain. Areas of vascular stenosis and occlusion can be visualized with this technique. This information can then be used by interventionalists to determine whether or not a lesion is amenable to intra-arterial t-PA therapy or mechanical retrieval. Also requiring intravenous contrast, perfusion CT scans can reveal perfusion deficits within different regions of the brain. Additionally, CTA and perfusion CT can differentiate reversible from irreversible ischemic insults.[56,57] Further studies using these newer imaging techniques to determine eligibility for thrombolytic therapy are ongoing.

An ECG should be obtained because atrial fibrillation and acute MI are associated with up to 60% of all cardioembolic strokes. The hematologic evaluation should include a complete blood count with platelet count and coagulation studies. A toxicologic screen and cardiac isoenzyme assay should be considered if appropriate. Elevated blood viscosity even when hematocrit levels are not frankly polycythemic can affect blood flow and prognosis. A platelet count can identify thrombocytosis or thrombocytopenia, which may precipitate a thrombosis or hemorrhage. Coagulation studies are especially helpful to guide management for patients in whom anticoagulation is being considered or for patients with a hemorrhagic stroke. Cocaine or amphetamine ingestion should be considered with either an ischemic or hemorrhagic stroke in patients younger than 40 years of age.

Other ancillary diagnostic tests to consider include an echocardiogram, carotid duplex scan, and angiogram. Some centers are performing these studies as part of an observation unit protocol in the ED. An echocardiogram can identify a mural thrombus, tumor, patent foramen ovale, or valvular vegetation in those patients in whom a cardioembolic stroke is suspected. An echocardiogram also should be considered in patients with no obvious cause for their stroke. Carotid duplex scanning may be helpful in patients with known or suspected high-grade carotid stenosis with worsening neurologic deficit or crescendo TIAs.[58,59] These patients may be candidates for heparinization or emergent carotid endarterectomy. Carotid duplex studies can accurately identify carotid artery stenosis with occlusion of more than 60% vessel diameter, but an angiogram is required to distinguish 95% stenosis from a complete occlusion.

Angiography is the definitive test to demonstrate stenosis or occlusion of both large and small blood vessels of the head

and neck. It can detect subtle abnormalities, such as with dissection, that may not be demonstrated with other imaging techniques.

Hemorrhagic Stroke

The hematologic evaluation for the patient with hemorrhagic stroke should be performed in the same manner as for the patient with ischemic stroke. Particular attention should be directed to uncovering the presence of a coagulopathy. A drug screen should be obtained to evaluate for use of sympathomimetics if substance abuse is suspected. Increased sympathetic outflow secondary to the hemorrhage may lead to an increase in dysrhythmias. Dysrhythmias also may signal impending brainstem compression from an expanding hemorrhage.

As in ischemic stroke, the cranial CT scan is the diagnostic test of choice to evaluate for an ICH.[23] The CT scan will reliably diagnose up to 95% of ICHs, although very small lesions may not be visible. Hemorrhages that are several days old may appear as isodense regions.

STROKE MANAGEMENT

Ischemic Stroke

With the recent focus on rapid recognition, evaluation, and treatment of stroke, EDs have attempted to streamline the care of these patients to meet recommended time goals (Table 99-3). This has led to the development of various stroke protocols, critical pathways, and acute interventional stroke teams that often are deployed in the field before the patient even arrives to the ED.

In the prehospital setting, the focus should be on maintenance of the "ABCs" (airway-breathing-circulation), rapid identification, early hospital notification, and rapid transport.[60] Although it is unusual for patients with ischemic stroke to be unresponsive on presentation, their ability to communicate may be altered secondary to dysphasia. After an ischemic stroke, patients usually can maintain their airway unless the brainstem is affected or unless significant cerebral edema is compressing the opposite hemisphere. Patients with intact protective airway reflexes should receive oxygen if they are hypoxic (oxygen saturation less than 95%),[61] and a monitor and intravenous line established.

Overhydration should be avoided to prevent cerebral edema. By contrast, dehydration may lead to decreased cerebral perfusion, and saline infusion should be given if dehydration is suspected. Dextrose-containing solutions should be avoided in normoglycemic patients suspected of having had a stroke, because elevated blood glucose levels may worsen an ischemic deficit.[60] Out-of-hospital personnel should attempt to rapidly ascertain the patient's blood sugar. If this is not possible, glucose should be given only to diabetic patients in whom hypoglycemia is strongly suspected. Electrocardiographic monitoring is necessary because of the frequency of cardiac causes of ischemic stroke.[60]

The circumstances surrounding the stroke as well as concomitant medical conditions should be ascertained. The initial out-of-hospital responders should document the exact time the patient was last seen to be neurologically normal and the level of neurologic functioning; reversible defects may completely resolve by the time the patient has arrived at the hospital. The level of consciousness, gross focal motor deficits, difficulty with speech, clumsiness, facial asymmetry, and any other focal deficits should be noted. Prehospital stroke scales have been developed to assist in differentiating patients who have had a stroke from those who have not and to identify potential candidates for fibrinolytic therapy.[62-65] Early recognition, notification, and transport by emergency medical service (EMS) and other out-of-hospital personnel have been shown to be valuable in enabling early treatment.[60]

In the ED setting, the ABCs should be reassessed on an ongoing basis, because patients may experience rapid deterioration, even with subacute stroke. They may be found at home 1 or 2 days after the event has occurred and may have concomitant illnesses, such as aspiration pneumonia, dehydration, hypothermia, rhabdomyolysis, or myocardial ischemia. Fever necessitates a thorough evaluation to identify the source of infection, followed by prompt institution of appropriate treatment. As supported by strong evidence, even minor degrees of hyperthermia will result in worsening of the neurologic injury.[66]

Blood Pressure Management. The management of blood pressure in patients with acute ischemic stroke and TIA is controversial because of limited data. Current guidelines for the management of hypertension in patients with acute ischemic stroke recommend that antihypertensive treatment be reserved for those with markedly elevated blood pressures, unless fibrinolytic therapy is planned or specific medical indications are present.[60,67] These medical indications include (1) acute myocardial infarction, (2) aortic dissection, (3) true hypertensive encephalopathy, and (4) severe left ventricular failure.

Oral or parenteral agents should be withheld unless the patient's systolic pressure is greater than 220 mm Hg or diastolic pressure is greater than 120 mm Hg or mean arterial pressure is greater than 130 mm Hg (Table 99-4). If parenteral agents are used, labetalol or enalapril is favored because of ease of titration and limited effect on cerebral blood vessels. Sublingual nifedipine or sublingual nitroglycerin is not recommended because either agent can produce a precipitous drop in blood pressure.

If fibrinolytic therapy is planned, stringent control of blood pressure is indicated to reduce the potential for bleeding after the thrombolytic is administered (see Table 99-4).[60,68] Thrombolytic therapy is not recommended for patients whose systolic pressure is consistently greater than 185 mm Hg or whose diastolic pressure is 110 mm Hg at the time of treatment. Simple measures can be used to try lowering blood pressure below this level. Recommended approaches include the use of nitroglycerin paste and one or two doses of labetalol, 10 to 20 mg given intravenously. If more aggressive measures are required to reduce blood pressure below 185/110 mm Hg, the use of t-PA is not recommended. Once thrombolytic therapy has been initiated, blood pressure must be monitored closely and hypertension treated aggressively.

Just as problematic as high blood pressure can be, low blood pressure can be quite detrimental to patients with ischemic

Table 99-3 NINDS-Recommended Stroke Evaluation Targets for Potential Thrombolytic Candidates

MANAGEMENT COMPONENT	TARGET TIME FRAME
Door to doctor	10 minutes
Door to CT completion	25 minutes
Door to CT scan reading	45 minutes
Door to treatment	60 minutes
Access to neurologic expertise*	15 minutes
Access to neurosurgical expertise*	2 hours

*By phone or in person.
CT, computed tomography; NINDS, National Institute of Neurological Disorders and Stroke.

Table 99-4 Emergency Antihypertensive Therapy for Acute Ischemic Stroke

BLOOD PRESSURE*	TREATMENT
Nonthrombolytic Candidates	
1. DBP >140 mm Hg	Sodium nitroprusside (0.5 µg/kg per minute). Aim for 10 to 20% reduction in DBP.
2. SBP >220, DBP >120, or MAP† >130 mm Hg	10–20 mg labetalol‡ IV push over 1–2 minutes. May repeat or double labetalol every 20 minutes to a maximum dose of 150 mg.
3. SBP <220, DBP <120, or MAP† <130 mm Hg	Emergency antihypertensive therapy is deferred in the absence of aortic dissection, acute myocardial infarction, severe congestive heart failure, or hypertensive encephalopathy.
Thrombolytic Candidates	
Pretreatment	
1. SBP >185 or DBP >110 mm Hg	1–2 inches of nitro paste or one to two doses of 10–20 mg labetalol‡ IV push. If BP is not reduced and maintained at <185/110 mm Hg, the patient should not be treated with TPA.
During and after treatment	
1. Monitor BP	BP is monitored every 15 minutes for 2 hours, then every 30 minutes for 6 hours, and then hourly for 16 hours.
2. DBP >140 mm Hg	Sodium nitroprusside (0.5 µg/kg per minute).
3. SBP >230 or DBP 121–140 mm Hg	*Step 1*: Give 10 mg labetalol‡ IV push over 1 to 2 minutes. May repeat or double labetalol every 10 minutes to a maximum dose of 150 mg, or give the initial labetalol bolus and then start a labetalol drip at 2–8 mg/minute. *Step 2*: If BP is not controlled by labetalol, consider sodium nitroprusside.
4. SBP 180–230 or DBP 105–120 mm Hg	10 mg labetalol‡ IVP. May repeat or double labetalol every 10–20 minutes to a maximum dose of 150 mg or give initial labetalol bolus and then start a labetalol drip at 2–8 mg/minute.

*All initial blood pressures should be verified before treatment by repeating reading in 5 minutes.
†As estimated by one-third the sum of systolic and double diastolic pressures.
‡Labetalol should be avoided in patients with asthma, cardiac failure, or severe abnormalities in cardiac conduction. For refractory hypertension, alternative therapy with sodium nitroprusside or enalapril may be considered.
BP, blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; SBP, systolic blood pressure; TPA, tissue plasminogen activator.

BOX 99-4 FIBRINOLYTIC THERAPY FOR ACUTE ISCHEMIC STROKE: INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria

1. Age 18 years or older
2. Clinical diagnosis of ischemic stroke causing a measurable neurologic deficit
3. Time of symptom onset well established to be less than 180 minutes before treatment would begin

Exclusion Criteria

1. Evidence of intracranial hemorrhage on noncontrast head CT
2. Only minor or rapidly resolving stroke symptoms
3. High clinical suspicion of subarachnoid hemorrhage even with normal CT findings
4. Active internal bleeding (e.g., gastrointestinal or urinary bleeding within last 21 days)
5. Known bleeding diathesis, including but not limited to:
   - Platelet count <100,000/µL
   - Patient has received heparin within 48 hours and had an elevated activated partial thromboplastin time (greater than upper limit of normal for laboratory)
   - Recent use of anticoagulant (e.g., warfarin sodium) and elevated prothrombin time >15 seconds
6. Within 3 months of intracranial surgery, serious head trauma, or previous stroke
7. Within 14 days of major surgery or serious trauma
8. Recent arterial puncture at noncompressible site
9. Lumbar puncture within 7 days
10. History of intracranial hemorrhage, arteriovenous malformation, or aneurysm
11. Witnessed seizure at stroke onset
12. Recent acute myocardial infarction
13. On repeated measurements, systolic pressure >185 mm Hg or diastolic pressure >110 mm Hg at time of treatment, requiring aggressive treatment to reduce blood pressure to within these limits

CT, computed tomography.

stroke.[69] Normally normotensive stroke patients with low blood pressure or normally hypertensive stroke patients with low or even low-normal blood pressure should be given a fluid bolus to try to increase cerebral perfusion. This is especially important in patients who present in a dehydrated state. If initial fluid challenge is ineffective, the patient may require vasopressor therapy (e.g., with dopamine) to gradually increase MAP and improve cerebral perfusion.[67]

Acute Drug Therapy. To date, only the use of intravenous t-PA has been approved by the U.S. Food and Drug Administration (FDA) for treatment of patients with acute ischemic stroke. These recommendations initially were based on the results of the National Institute of Neurological Disorders and Stroke (NINDS) trial, although subsequent analysis of other studies has supported its use.[70-73] Concern has emerged regarding the safety of the use of t-PA in community practice.[74] However, a meta-analysis of non–trial-related use of t-PA (n = 2639) in community practice demonstrated efficacy and safety for t-PA similar to those reported in the NINDS trial.[75] The current recommendation for recombinant t-PA (rt-PA) is that it be administered intravenously at a dose of 0.9 mg/kg to a maximum of 90 mg (10% of the dose given as a bolus followed by an infusion lasting 60 minutes). Treatment must be initiated within 3 hours of the onset of ischemic symptoms in patients who meet strict inclusion and exclusion criteria (Box 99-4). Intravenous t-PA is not recommended when the time of stroke onset cannot be ascertained reliably, including strokes recognized on awakening. In addition, caution is warranted in treating patients with large strokes (NIHSS score of 20 or higher) or early CT changes from a recent major infarction (e.g., acute hypodensity or mass effect), because they are at increased risk for symptomatic hemorrhage.[76] Earlier studies have demonstrated the importance of adhering to the inclusion-exclusion criteria established by the NINDS trial.[74,77] A recent study suggests that patients with mild or rapidly resolving symptoms may still benefit from the use of intravenous t-PA.[78] The use of intravenous t-PA beyond the 3-hour window

has not been demonstrated to be of clinical benefit, although a meta-analysis of these studies suggests a beneficial effect in a specific subset of patients.[27-29,70]

Intra-arterial thrombolysis is an alternative treatment for eligible patients presenting beyond the 3-hour time window but within 6 hours of symptom onset.[37,79,80] In the Prolyse in Acute Cerebral Thromboembolism II (PROACT II) study, patients with middle cerebral artery strokes were 58% more likely than those who received a placebo to have little or no neurologic disability at 90 days when treated with prourokinase up to 6 hours after stroke onset.[80] In addition, the use of intra-arterial thrombolysis in patients with posterior circulation strokes and those unresponsive to initial treatment with intravenous t-PA also is being evaluated and has shown favorable outcomes.[37,81-84]

A variety of mechanical clot retrieval devices are being investigated. The best studied is the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) retrieval device. This corkscrew-like device has been shown to be successful in recanalizing intracranial lesions of the internal carotid artery and has demonstrated improved clinical outcomes and survival compared with patients without successful recanalization of the artery.[85] Successful recanalization has been achieved when performed within an 8-hour window of symptom onset.[86,87] In 2004, the FDA cleared the MERCI retrieval device for use in the setting of acute ischemic stroke.

Previous studies have focused on the use of antiplatelet agents in acute ischemic stroke. Data from two large trials involving almost 40,000 patients indicate that early use of aspirin in patients with acute ischemic stroke who were not treated with a fibrinolytic agent was associated with a small but significant reduction in rates of stroke recurrence and mortality.[88] These studies in combination suggest a number needed to treat of 77 (i.e., 77 stroke patients would need to be treated with daily aspirin therapy to prevent a poor outcome, such as death, dependency at discharge or at 6 months after stroke, in 1 patient). The need for acute administration of aspirin in the ED is unclear, because patients were given aspirin up to 48 hours after stroke onset. Aspirin should not be given for the first 24 hours in patients who have received a fibrinolytic agent, because this has been associated with an increased risk of ICH and death.[89]

The use of low-molecular-weight or unfractionated heparin is common in patients with acute ischemic stroke or TIAs, but its value is unproved. Some studies suggest that heparin may reduce the risk of subsequent ischemic stroke but increase the risk of hemorrhagic stroke. To date, no studies have definitively established the efficacy of anticoagulants in the management of acute ischemic stroke.[90-92] However, heparin sometimes is considered in patients at high risk for stroke progression, including patients with crescendo TIAs or TIA due to a cardioembolic source, patients with a high-grade carotid artery stenosis, patients with posterior circulation TIA, and patients with evolving strokes. Heparin is recommended for the treatment of carotid and vertebral artery dissection unless a contraindication such as intracranial extension is present. If a dissection is diagnosed and the patient has no symptoms of ischemia, treatment with antiplatelet therapy alone may be an option.[13] Heparin therapy should not be initiated in patients with suspected endocarditis or in any patient until a CT scan has ruled out intracranial bleeding. Owing to the lack of consistent evidence of efficacy, the most prudent course in the ED setting is to determine the need for heparin therapy in conjunction with the patient's neurologist or the admitting physician.

Other innovative approaches to stroke care, including mild to moderate hypothermia and early hemicraniectomy, are currently being investigated.

Management of Intracranial Hemorrhage. The patient with a potential ICH requires rapid assessment and transport to a care center with CT scanning capability and intensive care management facilities. Out-of-hospital management is similar to that for ischemic stroke. The circumstances surrounding the event, as well as other concomitant medical conditions, also should be ascertained. The initial level of consciousness, GCS score, any gross focal deficits, difficulty with speech, clumsiness, gait disturbance, or facial asymmetry should be noted.

Supportive care involving attention to airway management and perfusion is of the highest priority. Patients with hemorrhagic stroke are more likely to have an altered level of consciousness that may rapidly progress to unresponsiveness requiring emergent endotracheal intubation. Intravenous access should be established and cardiac monitoring should be initiated. Evaluation of blood glucose and appropriate dextrose and naloxone administration should be considered in any patient with altered mental status.

Considerable disagreement exists regarding optimal blood pressure management in the patient with ICH. Hypertension may cause deterioration by increasing ICP and potentiating further bleeding from small arteries or arterioles. On the other hand, hypotension may decrease CBF, thereby worsening brain injury. In general, recommendations for treatment of hypertension in patients with ICH are more aggressive than those for patients with ischemic stroke. The current consensus regarding management of ICH is to recommend antihypertensive treatment with parenteral agents for systolic pressures higher than 160 to 180 mm Hg or diastolic pressures higher than 105 mm Hg. Treatment for lower pressures remains controversial.[23,60] Nitroprusside is the agent most commonly recommended because it can provide rapid and consistent lowering of the blood pressure to the desired level, and adjustments can be rapidly made. Nitroprusside provides a rapid onset, is titratable, and has no effect on mental status. Disadvantages include the need for careful monitoring (ideally with an indwelling arterial catheter) and the theoretical risk of worsening the hemorrhage due to the vasodilatory effects of nitroprusside on cerebral vessels. Labetalol is another therapeutic option. More recently, nicardipine has been proposed as an optimal antihypertensive agent in the setting of cerebrovascular emergencies, owing to both its good titration profile, which may create less need for adjunctive antihypertensive drugs, and its favorable cerebral hemodynamic effects.[93]

Hyperventilation and diuretics such as mannitol have been used when ICH is complicated by signs of progressively increasing ICP, clinical deterioration associated with mass effect, or impending uncal herniation.[23] These interventions should not be used prophylactically. Mannitol moves fluid from the intracranial compartment, thereby reducing cerebral edema. Although this effect may be temporarily helpful in the acute setting, the brain tissue will reequilibrate and rebound swelling can occur and worsen the patient's clinical status. The effectiveness of mannitol in the setting of ICH is questionable.[94-96] Hypertonic saline is being investigated as an alternative agent.[97] Use of steroids in cerebral hemorrhage, once a common practice, appears to be harmful and is not recommended. Other experimental modalities include barbiturate coma and hypothermia.

Seizure activity can cause neuronal injury, elevations in ICH, and destabilization of an already critically ill patient. In addition, nonconvulsive seizure may contribute to coma in up to 10% of patients in a neuro–intensive care unit.[23] Seizure prophylaxis (fosphenytoin 18 mg/kg) should be considered for patients with ICH, especially those with lobar hemorrhage.

Surgery is not beneficial in most cases of ICH. Selected patients with sizable lobar hemorrhage and progressive neuro-

logic deterioration may benefit from surgical drainage. Surgery is more efficacious in patients with cerebellar hemorrhage. The clinical course in cerebellar hemorrhage is notoriously unpredictable. Patients with minimal abnormalities may experience sudden deterioration, with progression to coma and death, with little warning. For this reason, most neurosurgeons will consider emergent surgery for patients with cerebellar hemorrhage within 48 hours of onset. In cases of severe intraventricular hemorrhage or hemorrhages in the posterior fossae, the normal circulation of cerebrospinal fluid (CSF) can become interrupted, leading to the development of hydrocephalus. This condition is characterized by an abnormal rise in CSF volume. In such cases a ventricular catheter should be inserted by a neurosurgeon.

DISPOSITION

Ischemic Stroke and Transient Ischemic Attacks

"Stroke center" definitions have been proposed, and a national certification process for primary stroke centers is now under way despite considerable political controversy. In broad terms, institutional certification as a primary stroke center requires the establishment of a stroke infrastructure (such as a stroke team, stroke unit, patient care protocols, and support services including CT scanning and laboratory testing availability), as well as institutional administrative support and strong leadership.[98] Additionally, recommendations also have been established for comprehensive stroke centers (CSCs). CSCs are expected to have the capability to provide the full spectrum of care to patients with stroke and other cerebrovascular diseases. More specifically, CSCs should offer advanced imaging modalities, perform surgical and endovascular interventions, and maintain a core infrastructure such as a stroke unit and stroke registry.[99] The establishment of PSCs and CSCs is intended to improve outcomes for stroke patients by providing them with a high level of coordinated care.

It has been recommended that patients with symptoms consistent with an acute stroke should be transported to emergency facilities capable of initiating fibrinolytic therapy within 1 hour of hospital arrival. At a minimum, this requires emergent CT capabilities, an institutional "acute stroke protocol," and availability of a physician versed in the use of thrombolytic therapy. Intensive care monitoring and neurosurgery capabilities should be available within 2 hours of drug initiation, either at the treating hospital or by helicopter or ground transport to an appropriate health care facility.[100]

In most cases, once the diagnosis of an acute stroke or stroke syndrome is established and the patient is stabilized, hospitalization will be necessary for further evaluation and treatment. Patients may deteriorate over the first 24 hours and require close in-hospital monitoring. Most patients can be managed on a general medical or telemetry unit. Patients with large acute hemispheric strokes (associated with increased risk for herniation) or with significant posterior circulation–related changes and those treated with a fibrinolytic agent should be monitored in a step-down or intensive care unit for at least 24 hours.

Some hospitals have specialized stroke units that provide organized, multidisciplinary care to stroke inpatients. A recent evidence-based medicine review amalgamated the results of 26 trials that compared the outcomes for more than 5500 stroke patients treated in either specialized stroke units or general wards. This review found a 14% reduction in the odds of post-stroke mortality for patients treated in a stroke unit compared with patients managed on a general ward (odds ratio [OR], 0.86; 95% confidence interval [CI]: 0.76 to 0.98). A similar reduction was found for the composite outcomes of death or institutionalized care (OR, 0.82; 95% CI: 0.73 to 0.92) and death or dependency (OR, 0.82; 95% CI: 0.73 to 0.92). All outcomes were independent of age, sex, or stroke severity, and evidence for increase in hospital length of stay by treatment in a stroke unit was lacking.[101]

In select cases, patients with multiple previous strokes who have been thoroughly evaluated or those who experience mild new episodes or have a completed stroke days to weeks after the event may be treated in the ED and discharged home after discussion with their primary care physician or neurologist. Close follow-up should be arranged.

Patients with new-onset TIAs should be hospitalized for evaluation and workup owing to the substantial short-term risk of stroke and other adverse events.[21] Exception can be made for patients with only minimal anterior circulation symptoms, for whom an extensive ED evaluation constitutes appropriate management. This evaluation must include a CT scan, a carotid Doppler study, MRA or CTA of the anterior circulation, and an echocardiogram (if indicated). A medically or surgically treatable cause for TIAs (e.g., high-grade carotid stenosis, mural thrombus) should be sought, which would require in-hospital treatment such as anticoagulation, stenting, or carotid endarterectomy. If the patient's symptoms have completely resolved, results of the workup are negative, and close neurologic follow-up can be arranged, outpatient therapy may be appropriate. The decision to start the patient on an antiplatelet agent should be made in conjunction with the neurologist.

The ABCD (*a*ge, *b*lood pressure, *c*linical features, *d*uration of TIA symptoms) score has been validated as a good predictor of future stroke risk in patients with TIA treated in the ED. ABCD scores range from 0 to 6, with a higher score indicating a higher future stroke risk; this scoring system is based on the following criteria: age 60 years or older = 1 point; systolic blood pressure greater than 140 mm Hg and/or diastolic greater than 90 mm Hg = 1 point; unilateral weakness = 2 points; speech disturbance without weakness = 1 point; symptom duration 10 to 59 minutes = 1 point; symptom duration 60 minutes or longer = 2 points. Patients with an ABCD score of 5 or 6 in the ED have a 30-day risk of stroke eight times that of patients with an ABCD score less than 5 (hazard ratio 8.01; 95% CI: 3.21 to 19.98).[102]

Hemorrhagic Stroke

All patients with an acute hemorrhagic stroke in whom surgical intervention is a consideration should be admitted to an intensive care unit under the care of a neurologist or a neurosurgeon. If this is unavailable at the evaluating institution, the patient should be transported to an appropriate institution.

Acknowledgment

The authors gratefully acknowledge the assistance of Stephen M. Davis, MPA, MSW, Co-Director of Clinical Research at the West Virginia University Department of Emergency Medicine, in the preparation of this chapter.

KEY CONCEPTS

- Patients presenting with the signs and symptoms of an acute ischemic stroke within 3 hours of symptom onset should be evaluated for thrombolytic therapy within the NINDS-recommended time frames (see Table 99-3).
- Carotid Doppler, MRA, or CTA studies are recommended before discharge of a patient with TIA from the ED.
- Overly aggressive blood pressure management should be avoided in patients with acute ischemic stroke.
- Accurate time of symptom onset should be documented in all patients with stroke.
- Assessment of gait is essential to rule out posterior circulation stroke in patients presenting with vertigo.
- The possibility of carotid or vertebral dissection should be considered in young patients with stroke and in patients with headaches and neck pain with acute stroke.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 100 Seizures

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PERSPECTIVE

A *seizure* is the clinical manifestation of excessive, abnormal cortical neuron activity. The physical manifestation depends on the area of brain cortex involved and, to a lesser extent, on the specific underlying abnormality. Patients who have recurring seizures without consistent provocation have *epilepsy*, although this term encompasses many disparate clinical syndromes. Seizures also may occur as a predictable response to certain toxic, pathophysiologic, or environmental stresses; these are *reactive* or *secondary seizures*, and patients who experience them do not have epilepsy. In the United States, 10% of people experience at least one seizure in their lifetime; the cumulative incidence of epilepsy is 3%.[1]

The evaluation of patients with seizures, whether ongoing or recent, in the emergency department (ED) may be complex and difficult. A careful history must be elicited to determine the presence of ictal events that represent epilepsy or exposure to ictogenic stimuli (e.g., alcohol, cocaine), significant underlying illness (e.g., meningitis, hypoxemia, hypoglycemia, intracranial mass), or contributing causes (e.g., sleep deprivation in an epileptic). The physical examination should focus on the identification of focal neurologic abnormalities, systemic illness, and signs of toxic exposure. If the patient continues to experience seizure activity, airway protection and abortive therapy must be provided. Laboratory and radiographic evaluation that is guided by historical and physical findings may be limited or unnecessary in some cases. Finally, the appropriate disposition of a patient presenting to the ED with a seizure or with a history of recent seizure requires an understanding of the underlying illness, likelihood of recurrence, indications for maintenance pharmacologic therapy, and state reporting regulations.

In addition to the distinction between primary (epileptic) and secondary (reactive) seizures, many other classifications of ictal events have been proposed.[2-7] Seizures are termed *generalized* or *focal* (*partial*) depending on their clinical manifestations. The former type of seizure results from the abnormal electrical event that simultaneously involves both cerebral hemispheres and is accompanied by loss of consciousness; in the latter, abnormal activity is limited to part of one cerebral hemisphere only. Generalized seizures usually are characterized by rhythmic, tonic-clonic muscle contractions, or *convulsions*, although *nonconvulsive generalized seizures* also occur. Partial seizures can be differentiated further into seizures during which cognition is maintained (*simple partial*) and seizures during which cognition is impaired (*complex partial*). The term *cognition* is defined as involving at least two of the five features—perception, attention, emotion, memory, and executive function[8,9]—and replaces the previously used term *consciousness*, which is both difficult to define and difficult to document. Finally, partial seizures may become generalized (*partial with secondary generalization*).

Inexperienced witnesses may provide histories that are insufficient for accurate categorization of seizures. However, when an accurate history is available, secondary (reactive) seizures typically are generalized, not partial, in nature. The definitive differentiation among these classifications may require electroencephalogram (EEG) recording *during* the seizure, sometimes in association with simultaneous video recording.

Seizures in children, as in adults, are classified as primary (idiopathic) and secondary (symptomatic or reactive). The term *cryptogenic* is used sometimes when seizures are thought to be secondary but no cause has been identified. The history is the most important diagnostic tool in evaluating seizures in children. The actual seizure activity usually is not observed, and the emergency physician must rely on a detailed and accurate history for diagnosis.

Other important terms to describe ictal events include *status epilepticus*, in which seizures occur serially without an intervening return to a normal neurologic condition; *spasm*, which is a specific, debilitating seizure syndrome that occurs in infants; and *myoclonus*, which refers to rhythmic, shock-like muscle contractions also typical for specific seizure syndromes. The *postictal period* is an interval after a seizure, of variable duration, usually characterized by impaired consciousness but sometimes also marked by self-limited focal paralysis or neurogenic pulmonary edema.

PRINCIPLES OF DISEASE

The pathophysiology of seizures at the neuronal level is incompletely understood, with most of what is known coming from animal studies in which either electrical or pharmacologic stimulation is applied directly to brain cortex. To produce generalized ictus, stimuli must be applied to both hemispheres simultaneously. Some studies show the concept of recruitment, which occurs when the initiating neurons' abnormal, increased electrical activity activates adjacent neurons and propagates until the thalamus and other subcortical structures are recruited. The clinical seizure activity typically, but not always, reflects the focus of initiation.[9-11]

What prompts such initiation is unclear. Proposed mechanisms include disruption of normal structure—whether congenital, maturational, or acquired (as with scar tissue)—and disruption of local metabolic or biochemical function. The latter mechanism is better elucidated because the roles of two neurotransmitters—acetylcholine, which is excitatory to cortical neurons, and γ-aminobutyric acid (GABA), which is inhibitory—have been more fully characterized. In sensitive neurons, such as those at an ictogenic focus, subtle changes in the local concentrations of these neurotransmitters can produce sustained membrane depolarization, ultimately followed by local hyperpolarization and recruitment. Recruitment may follow contiguous paths or extend along diverse integrated circuits that are deep and cross the midline.[9-11]

When the ictal discharge extends below the cortex to deeper structures, the reticular activating system in the brainstem may be affected, altering consciousness. In generalized seizures, the focus often is subcortical and midline, which explains the prompt loss of consciousness and bilateral involvement.[9,12] Seizures typically are self-limited; at some point, the hyperpolarization subsides, and the electrical discharges from the focus terminate. This termination may be related to reflex inhibition, loss of synchrony, neuronal exhaustion, or alteration of the local balance of acetylcholine and GABA in favor of inhibition.[9,12]

The systemic manifestations of convulsive ictal activity include hypertension, tachycardia, tachypnea, and hyperglycemia from sympathetic stimulation. With more prolonged convulsions, skeletal muscle damage, lactic acidosis, and, rarely, frank rhabdomyolysis may ensue.[9,10,13] Autonomic discharge and bulbar muscle involvement may result in urinary or fecal incontinence, vomiting (with significant aspiration risk), tongue biting, and airway impairment.

CLINICAL FEATURES

Primary Seizures in Adults

Primary ictal events in adults include events of genetic and of idiopathic origin. Onset is typically during childhood or adolescence, but occasionally idiopathic seizures may begin de novo in adulthood. Because idiopathic seizures are rare, a first-time seizure in an adult requires a thorough ED evaluation.

Focal seizures in adults may be classified as simple partial or complex partial. Simple partial seizures are limited in electrical focus to one cerebral hemisphere and do not cause loss of cognition. Although the specific function of the initiating neurons determines the clinical manifestation of the ictal event (i.e., motor, somatosensory, special sensory, autonomic, or psychic), such clinical manifestations are not sufficiently specific for anatomic localization without an EEG. Typical features of simple partial seizures include focal clonic movements; paresthesias; visual, auditory, olfactory, or gustatory experiences; sweating and flushing; dysphasia; a sense of déjà vu; or a sense of unwarranted fear.[9,11] Motor signs, which by definition remain ipsilateral in simple partial seizures, may spread contiguously in a stepwise fashion (*Jacksonian march*) as neuron recruitment occurs in the motor cortex. There is generally no postictal state after a simple partial seizure.

Complex partial seizures are ictal events that involve impairment of cognition, either at onset or evolving from focal activity. Amnesia for the ictal event is a consistent feature of complex partial seizures, although during the episode the patient may remain responsive to the surroundings. Complex partial seizures typically involve automatisms that are specific to the affected person, such as lip smacking, repeated swallowing or uttering verbal phrases, or picking at clothing. Complex partial seizures generally are associated with an aura, such as a specific smell, taste, visual hallucination, or intense emotional feeling. In contrast with those experiencing generalized seizures, these patients may continue with ongoing motor activity, such as driving an automobile, riding a bicycle, or playing a musical instrument (reactive automatisms), and they may react to their surroundings in a semiappropriate manner.[9] Partial seizures may progress rapidly to generalized seizures. A postictal state is common after complex partial seizures and may persist for hours.[9,11]

Generalized seizures in adults may be convulsive or nonconvulsive. By definition, patients lose consciousness in a generalized seizure, and no aura is present. Some patients may experience a brief, vague prodrome or dysphoric state just before the ictal event. Convulsive generalized seizures are typified by the tonic-clonic, or grand mal, seizure, in which the patient loses consciousness, stiffens with generalized muscular hypertonus, and then rhythmically and violently contracts multiple, bilateral, and usually symmetrical muscle groups. The muscular force may be sufficiently vigorous to result in posterior shoulder dislocation or fractures of thoracic spine vertebral bodies; significant tongue and buccal injuries also may be incurred from biting with repeated jaw muscle contractions. Dysautonomia, including transient apnea, is a potential manifestation of convulsive generalized seizures; urinary incontinence is more common than fecal incontinence. A generalized convulsive seizure generally lasts 1 to 2 minutes and is followed by a postictal state, headache, and drowsiness that may persist for hours. This state must be differentiated in the ED from altered consciousness attributable to other causes.

Nonconvulsive generalized seizures include absence, or petit mal, seizures; myoclonic seizures; tonic seizures; and atonic seizures. Absence seizures in adults are subclassified further as *typical* or *atypical*. Typical absence ictus is characterized by the sudden cessation of normal, conscious activity followed by a nonconvulsive, dissociative state that persists for a few seconds to several minutes before suddenly terminating. Eye movements, blinking, or automatisms may be present. There is no aura and no postictal state. If the seizure occurs midsentence, then the patient typically will resume speaking at precisely the point of interruption without awareness of the intervening event. Absence seizures typically begin in childhood but occasionally develop in adults. Atypical absence seizures are marked by more complicated motor signs, coexistence with other forms of generalized seizures, inconsistent postictal confusion, and irregular EEG abnormalities.[9,11]

Atonic seizures are characterized by focal diminution of muscle tone (limb or head) or generalized loss of postural tone in which the head falls forward and then the body slumps to the ground ("drop attack"), usually landing buttocks first (although this can vary depending on the axis of gravity at the time of the fall). Recovery occurs immediately, and there is either no loss or an extremely brief loss of consciousness. In *myoclonic-atonic seizures*, a brief (less than 100 msec) myoclonic jerk of muscle group of variable anatomy occurs before the episode of atonia.[9] Because typically no postictal state is associated with these episodes, an altered level of consciousness in a patient presenting to the ED after an atonic or myoclonic-atonic seizure should prompt an investigation for head trauma or a toxic or metabolic abnormality.

Status epilepticus is defined as serial seizure activity without interictal recovery or prolonged, continuous seizure activity. Traditionally, status epilepticus was defined as seizure activity lasting longer than 30 minutes, which is the estimated duration necessary for neuronal injury.[14,15] However, because an isolated tonic-clonic seizure rarely lasts more than a few minutes, an operational definition of status epilepticus has been

advocated as either a continuous seizure lasting more than 5 minutes, or more than two discrete seizures without intervening recovery of consciousness.[16] Although it is recognized that the underlying cause of status epilepticus is the predominant factor determining morbidity and mortality, prolonged seizure activity does cause neuronal injury and therefore warrants prompt abortive therapy. Furthermore, status epilepticus may become refractory to treatment over time.[14,17]

The most common cause of status epilepticus is discontinuation of anticonvulsant medication. This situation may be compounded by barbiturate withdrawal when phenobarbital therapy is abruptly withdrawn. Patients may present for the first time with a primary seizure disorder in status. Many other causes of status epilepticus have been documented[9,15,18,19] (Box 100-1). After prolonged status epilepticus or after incomplete treatment, the patient may exhibit very subtle manifestations of continued seizure activity, such as small-amplitude twitching of the extremities or jerking of the eyes, or any visible motor activity may cease while seizure activity detectable on the EEG continues.[9,20-22] Recognition of the latter scenario, termed *nonconvulsive status epilepticus*, requires a high index of clincial suspicion. Prompt treatment is essential; otherwise, neuronal damage can result.

All classes of primary seizures may recur sporadically, randomly, or predictably. Cyclic recurrence has been reported with awakening, sleep deprivation, emotional or physical stress, alcohol, and menses, among other factors. Seizures also may be triggered by specific senory stumuli, the most common of which is visual stimulation in the form of flashing lights, such as strobe lights, television, and video games.[9,23] Seizures also can be caused by auditory, gustatory, tactile or startle triggers that are specific to the affected person. The most common cause of recurrent primary seizures is medication noncompliance.[9,11]

Reactive Seizures in Adults

Reactive or secondary seizures do not result from genetic or idiopathic causes. The conditions that cause reactive seizures may be static (e.g., anatomic scarring), progressive (e.g., degenerative cortical disorders), or transient (e.g., acute electrolyte derangements).

Seizures Caused by Metabolic Derangements

Hypoglycemia is a common metabolic cause of reactive seizures. Ictal activity can occur when the plasma glucose level is less than 45 mg/dL, although some patients may manifest neurologic disturbances even at higher levels.[24] A rapid bedside glucose test should be an integral part of the ED evaluation of the patient exhibiting seizure activity. Convulsive and nonconvulsive seizures and generalized and partial seizures all may occur during hypoglycemia.[24] Patients at the extremes of age are particularly susceptible to glucose stress during acute illness. Hypoglycemia also may result from insulin reaction, a deliberate insulin or hypoglycemic agent overdose, alcoholism, poor nutrition, and sepsis. Hypoglycemic seizures respond to glucose therapy; anticonvulsants are unnecessary.

Cation derangements, notably hyper- and hyponatremia, hypomagnesemia, and hypocalcemia, are other common metabolic causes of ictal activity.[25,26] Hypo-osmolar and hyperosmolar states can precipitate seizures. Disorders of sodium—the primary cation in the extracellular fluid compartment and the primary determinant of serum osmolarity—are most common. Hyponatremia is the most frequently identified electrolyte disorder in hospitalized patients, and sodium levels less than 120 mEq/L often are associated with seizures.[27,28] The rate at which the sodium level decreases, and not the absolute magnitude of the decrease, determines the risk for neurologic manifestation.[27,29] Correcting hyponatremia should be undertaken slowly in the ED, to avoid osmotic demyelination. If seizures are persistent, administration of hypertonic (3%) saline may be indicated.[27] Hypernatremia will result in cerebral edema and seizures in the setting of rapid elevation of serum sodium to greater than 160 mEq/L or during aggressive correction of subacute hyponatremia.[25,29]

Hypercalcemia reduces neuronal excitability and rarely causes seizures; significant hypocalcemia (7.5 mEq/L) is associated, however, with ictal activity. Hypocalcemia may result

BOX 100-1 ETIOLOGY OF STATUS EPILEPTICUS: COMMON CAUSATIVE DISORDERS

Metabolic Disturbances
Hepatic encephalopathy
Hypocalcemia
Hypoglycemia or hyperglycemia
Hyponatremia
Uremia

Infectious Processes
CNS abscess
Encephalitis
Meningitis

Withdrawal Syndromes
Alcohol
Antiepileptic drugs
Baclofen
Barbiturates
Benzodiazepams

CNS Lesions
Acute hydrocephalus
Anoxic or hypoxic insult
Arteriovenous malformations
Brain metastases
Cerebrovascular accident
Chronic epilepsy
Eclampsia
Head trauma
Intracerebral hemorrhage
Neoplasm
Neurosurgery
Posterior reversible leukoencephalopathy
Remote structural injury

Intoxication
Bupropion
Camphor
Clozapine
Cyclosporine
Flumazenil
Fluoroquinolones
Imipenem
Isoniazid
Lead
Lidocaine
Lithium
Metronidazole
Theophylline
Tricyclic antidepressants

CNS, central nervous system.

from hypoparathyroidism, renal failure, or acute pancreatitis and typically is associated with hypomagnesemia, which also can precipitate seizures, particularly at serum levels less than 1 mEq/L. Hypomagnesemia is seen most often as a result of poor nutrition, especially in alcoholic patients. Patients with significant hypomagnesemia or hypocalcemia should be treated empirically for both disorders.[25,26]

Nonketotic hyperosmolar hyperglycemia also is associated with seizure activity. Partial seizures, including partial status, predominate. These seizures do not respond to anticonvulsants; rather, they are best managed with gradual correction of fluid deficits and glucose excess.[30-32]

Seizures may complicate the course and treatment of renal failure.[33] Ictal activity occasionally complicates uremic encephalopathy, is more common in conjunction with acute fluid and electrolyte shifts during dialysis (*dialysis disequilibrium syndrome*), and can occur as a complication of immunosuppressive therapy after renal transplantation.

Thyroid hormones lower seizure threshold, and consequently Graves' disease and thyrotoxicosis may occasionally manifest as seizures, including status epilepticus.[9,34,35] Seizures also occur with hypoparathyroidism as a direct result of secondary hypocalcemia.[36]

Seizures Caused by Infectious Diseases

Infectious diseases can cause seizures independent of a purely febrile mechanism. These seizures generally result from primary central nervous system (CNS) infections but occasionally arise from other septic sources. The most important ictogenic infections are meningitis, encephalitis, cerebral abscess, cerebral parasitosis, and human immunodeficiency virus (HIV) disease and associated opportunistic infections, with their protean CNS manifestations.

Seizures can occur as a result of the acute inflammatory response or as sequelae to bacterial or viral meningitis. During the acute course of their illness, up to 40% of patients with meningitis will have at least one seizure; this is more common at the extremes of age but is rarely associated with residual epilepsy.[9,37,38] By contrast, seizures occur in up to 50% of patients with a brain abscess, and epilepsy develops in 40% of the survivors.[9,39] After meningitic seizures are terminated with benzodiazepines, phenytoin should be initiated temporarily.[9]

Viral meningoencephalitides, the most common of which are caused by the herpes simplex virus, also are associated with seizures. These seizures may be generalized or partial, often recur during the acute phase of the illness, and may persist after the illness resolves.[9]

The parasitic CNS infection neurocysticercosis is relatively common in areas of the United States in which the population includes immigrants from Latin America. Seizures complicate 50 to 90% of neurocysticercosis cases.[40] Latent syphilis also may be a cause of adult-onset seizures. Primary HIV disease of the CNS, its attendant infectious and mass lesion complications, such as from toxoplasmosis and lymphoma, and the demyelinating infection progressive multifocal leukoencephalopathy constitute a significant cause of generalized and partial seizures.[41] Choosing an antiepileptic drug for an HIV-infected patient with seizures should be done in consultation with infectious disease and neurology specialists, because of the well-recognized increase in adverse effects of and interactions between antiepileptic drugs and antiviral medications.

Seizures Caused by Drugs and Toxins

The list of substances reported to cause seizures either as an idiosyncratic side effect of therapeutic use or as a manifestation of toxic overdose is extensive.[18,42] The recognition of this etiologic category is crucial in the ED setting. Seizure activity should be viewed as a dire sign of toxicity and may herald the onset of life-threatening instability.

Seizures may occur after therapeutic doses of antimicrobials, cardiovascular agents, neuroleptics, and sympathomimetics.[43] Seizures also may result from exposure to plant toxins, insecticides and rodenticides, and hydrocarbons. Certain over-the-counter supplements also have been associated with seizures, either alone or through adverse interactions with prescription medications.[44,45] The most common drug-associated and toxin-associated seizures occur, however, in conjunction with illicit drugs, such as cocaine, amphetamines, and phencyclidine; with overdoses of anticholinergic agents, such as cyclic antidepressants and antihistamines; as a manifestation of withdrawal from ethyl alcohol and sedative-hypnotics; and with toxic levels and deliberate overdoses of diverse medications including aspirin, theophylline, meperidine, isoniazid, lithium, and the anticonvulsants phenytoin and carbamazepine.[42,46] Standard ED therapeutic measures usually are effective for management of toxic seizures. In some cases, specific antidotal therapy is available, such as alkalinization for cyclic antidepressant and salicylate overdoses, pyridoxine (vitamin B_6) for isoniazid overdose, and hemodialysis for salicylate and lithium toxicity.

Because of its prevalence in urban ED patient populations, cocaine toxicity warrants special mention.[47] Seizures may occur after isolated recreational use or chronic abuse, after overdose, and in "body packers" and "body stuffers."[48] Cocaine-related seizures may be a manifestation of direct CNS toxicity or an indirect result of hypoxemia from cardiac toxicity.[49] Seizures in cocaine-intoxicated patients must be managed as part of the overall toxic reaction, which often includes high fever, rhabdomyolysis, and cardiac arrhythmias. A benzodiazepine is the appropriate initial therapeutic agent.

Ethyl alcohol is another common toxic cause of seizures. Ictal events may occur with acute inebriation but are more common during withdrawal from alcohol.[50] Withdrawal seizures typically are generalized, are recurrent, and may begin within 6 hours of cessation of or decrease in alcohol consumption. Through a phenomenon termed *kindling*, the risk and severity of seizures increase with each episode of withdrawal. Kindling implies that with each episode of alcohol withdrawal, the seizure threshold is lower. Alcoholic patients with seizures must be evaluated for other related, concomitant ictogenic problems (e.g., hypoglycemia, electrolyte derangements, head trauma, co-ingestion of other toxins, pregnancy). The preferred treatment for alcohol-associated seizures is with benzodiazepines; these drugs substitute for the GABA-enhancing effect of ethanol in the CNS.

Seizures Caused by Trauma

Post-traumatic seizures can occur acutely as a result of blunt or penetrating head trauma or as a post-traumatic sequela. Immediate post-traumatic seizures occur within 24 hours of injury. Epidural, subdural, and intracerebral hematomas and traumatic subarachnoid hemorrhages all can be acutely ictogenic, particularly as intracranial pressure rises. More often, however, the onset of seizure activity is delayed for at least several hours. Early post-traumatic seizures occur within 1 week of injury, whereas late post-traumatic seizures occur after 1 week. Immediate and early post-traumatic seizures are more common in children than in adults, and children also are more likely than adults to present in status epilepticus in the immediate or early post-traumatic phase.[51,52] Within the first year after significant head trauma, the incidence of seizures is at least 12 times that in the general population.[53]

The severity of head injury correlates with the likelihood of post-traumatic seizures. The incidence of seizures after injury with neurologic deficit without dural violation is 7 to 39%; when the dura is disrupted, the incidence is 20 to 57%.[53] Imaging studies should be performed urgently because the likelihood of identifying significant cerebral edema, cerebral contusions, hematomas, and depressed skull fractures is relatively high.[52,54] Antiepileptic drugs are recommended for prophylaxis against post-traumatic seizures occurring within the first 7 days after severe brain injury in adults; however, they have not been shown to be effective in preventing late post-traumatic seizures.[51,55,56]

Seizures Associated with Malignancy or Vasculitis

Seizures are a common manifestation of primary and metastatic CNS neoplasms. They also may complicate cancer treatment as a result of postsurgical scarring or chemotherapy-related electrolyte derangements, hematologic abnormalities, or immunosuppression. Although any CNS tumor can be ictogenic, low-grade and slow-growing primary neoplasms (e.g., well-differentiated gliomas and oligodendrogliomas) are implicated most commonly.[57] In such cases, seizures, which most often are partial with secondary generalization, may be the initial clinical manifestation. A new-onset seizure in a patient with a non-CNS primary malignancy, such as melanoma and tumors of the lung, breast, colon, germ cells, or renal cells, should prompt consideration of CNS metastasis and warrants neuroimaging.

Seizures also may be the presenting manifestation of CNS vasculitis in patients with systemic lupus erythematosus and polyarteritis nodosa. These commonly are complex partial seizures that give a general indication of the acute inflammatory focus. Sometimes secondary generalization follows.[58]

Seizures Caused by Strokes, Arteriovenous Malformations, and Migraines

Ischemic or hemorrhagic stroke is the cause of new-onset seizures in 40 to 54% of elderly patients.[59] The overall incidence of seizures with stroke ranges from 4 to 15%; more than one half occur within the first week after stroke. The incidence of epilepsy after stroke is 4 to 9%.[60,61] Seizures that occur acutely with stroke are thought to result from local metabolic alterations in the CNS; these events are transient, and the seizures often are focal and self-limited. Seizures that develop later are more likely to be generalized.

Seizures also occur in conjunction with unruptured cerebrovascular aneurysms and arteriovenous malformations.[9] Arteriography may be required to confirm the diagnosis; unruptured arteriovenous malformations are easier to detect on an enhanced cranial computed tomography (CT) scan than are smaller, unruptured aneurysms. Seizures also may arise in concert with vascular headaches, either coincidentally, by migrainous activation of an epileptic focus, or after vascular headache has induced cerebral infarction that becomes an epileptic focus.[62]

Seizures Caused by Degenerative Disease of the Central Nervous System

In approximately 5% of patients with multiple sclerosis, focal or generalized seizures develop during the course of their illness. These seizures must be differentiated from the tonic spasms that may occur in multiple sclerosis. Patients with demyelinating disease also should be evaluated for the other types of reactive seizures.[9]

CNS degeneration associated with aging, including dementia and Alzheimer's disease, increases the risk of reactive seizures and epilepsy.[59,63] The elderly also are more likely to have other ictogenic problems (e.g., stroke, brain neoplasm, toxic and metabolic disturbances, blunt head trauma from falls). Maintenance treatment of elderly patients with epilepsy often is complicated by drug-drug interactions, and breakthrough seizures may result even when patients are compliant. Although the incidence of unprovoked seizures increases after age 60 years, ED management of these patients must include a thorough evaluation for causes of secondary seizures.[59]

Gestational Seizures

Seizures associated with pregnancy are divided into two categories: *gestational epilepsy*, in which hormonal and metabolic changes exacerbate underlying epilepsy or adversely influence serum levels of anticonvulsants, and *eclampsia* or *toxemia*, which is a gestational hypertensive encephalopathy manifested by seizures, hypertension, coma, proteinuria, and edema. For the former, antiepileptic therapy should be tailored by the patient's neurologist and obstetrician to maximize seizure control and minimize the risk of teratogenic effects.[64] Convulsive generalized status epilepticus in pregnancy jeopardizes both mother and fetus. The definitive treatment for eclamptic seizures is magnesium sulfate. Simultaneous reduction in blood pressure using hydralazine, labetalol, or nifedipine is recommended.[65]

Psychogenic Nonepileptic Seizures

Psychogenic seizures, or pseudoseizures, are functional events that may be associated with alterations in consciousness, abnormal movements and behaviors, and autonomic changes. They are not the result of abnormal CNS electrical activiy. Psychogenic seizures may be primarily motor and mimic convulsive generalized seizures, including refractory status epilepticus, or they may be nonconvulsive and mimic either absence or complex partial seizures. Although certain features of convulsive psychogenic seizures may suggest the diagnosis, no clinical criteria are 100% specific; simultaneous video and EEG recordings may be required to confirm the diagnosis.[9]

The ED evaluation of these patients is difficult, because seizures and pseudoseizures can coexist. All but obviously functional abnormalities should be treated as for true ictus pending formal neurologic evaluation. Many patients with pseudoseizures are not deliberately attempting to mislead the examining physician. The long-term treatment of patients with confirmed pseudoseizures may include direct confrontation, intensive psychotherapy, and a placebo.

Postictal States

The postictal state that follows most generalized seizures typically is characterized by a decreased level of arousal and responsiveness, disorientation, amnesia, and headache. These conditions may persist for only a few minutes or for many hours and may not be consistent from seizure to seizure. The most important consideration in ED management of the postictal state is to monitor and investigate the altered mental status after a seizure; otherwise, dangerous underlying metabolic or toxic abnormalities may be overlooked. At the minimum, airway positioning maneuvers, pulse oximetry, rapid glucose determination, and cardiac rhythm monitoring are necessary.

Two unusual postictal manifestations may provoke particular consternation in the ED: postictal paralysis and neurogenic pulmonary edema. Postictal paralysis, or *Todd's paralysis*, may

follow generalized or complex partial seizures and is a focal motor deficit that may persist up to 24 hours. Weakness of one extremity or a complete hemiparesis may occur; in the latter case, the patient must be safely restrained to avoid falls caused by a combination of weakness and diminished responsiveness resulting from the postictal state. Todd's paralysis is associated with a high likelihood of an underlying structural cause for the seizure.

Neurogenic pulmonary edema is a relatively common, although often subclinical, complication of any structural CNS insult, including seizure, trauma, and hemorrhage.[66] Neurogenic pulmonary edema probably is caused by centrally mediated sympathetic discharge and generalized vasoconstriction, coupled with increased pulmonary capillary membrane permeability. After a seizure, neurogenic pulmonary edema can be confused clinically and radiographically with aspiration pneumonia. Neurogenic pulmonary edema is managed with ventilatory support, including positive end-expiratory pressure and other aggressive measures to reduce intracranial pressure. Hypoxia or other clinical evidence of pulmonary congestion after a seizure should prompt consideration of neurogenic pulmonary edema.[67]

DIAGNOSTIC STRATEGIES

First-Time Seizures

The essential components of the seizure evaluation in the ED setting are discussed in Chapter 16. An accurate and thorough history of the ictal event, any known or potential precipitants or exposures, and the patient's medical problems must be obtained. A thorough physical examination, including a complete neurologic examination, is essential. Any identified focal neurologic deficits must be monitored for progression or resolution. Appropriate ancillary studies may be comprehensive, but if precipitants (e.g., hypoglycemia, intoxication) are known, studies may be comparatively limited. Although the Academy of Neurology recommends neuroimaging, by either CT or magnetic resonance imaging (MRI), for all adults presenting with an apparent unprovoked first seizure,[68] the usefulness of emergent imaging depends on the clinical situation.

An emergent cranial CT scan is indicated when a serious structural lesion is suspected on clinical grounds, including presence of a new focal deficit, persistent altered mental status, fever, recent trauma, persistent headache, history of cancer, anticoagulant use, suspicion or known history of AIDS, age older than 40 years, and partial-complex seizure.[69] A reasonable approach may be to obtain scans on an outpatient, follow-up basis in patients who have recovered completely from the ictal event and in whom no apparent cause has been elucidated; if reliable follow-up care is unlikely or even questionable, the CT scan should be obtained in the ED to ensure its completion. In patients with known epilepsy and recurrent seizures, the same considerations apply, but in addition, epileptic patients with a change in seizure pattern, prolonged postictal state, or persistent abnormal mental status should be scanned in the ED.

The decision to initiate anticonvulsant therapy after a single seizure depends on the etiology of the seizure. Seizures due to structural lesions, such as stroke, tumor, or head injury, are likely to recur and may warrant antiepileptic medication. However, such patients also are likely to be admitted to the hospital if the lesion is newly discovered. For patients with a single unprovoked seizure, most authorities now agree that antiepileptic therapy should not be initiated; rather, the patient should be discharged with referral for neurologic consultation.[9,70] The rationale for this approach is threefold. First, the diagnosis may be incorrect, especially if the seizure-like activity was not witnessed by ED personnel. It is estimated that 20 to 25% of patients diagnosed as having seizures are found to have been misdiagnosed, with the most frequent alternative diagnoses being cardiovascular and psychopathologic.[71-74] Second, the patient may not have a recurrent seizure. It is estimated that less than 50% of patients who have had a single unprovoked seizure will experience a recurrent seizure within 2 years.[9,70,75,76] Furthermore, whereas treatment decreases the risk of early recurrent seizure, it does not affect long-term prognosis of epilepsy,[70,77,78] nor does it have an impact on patient quality of life,[79] with the exception of driving limitations, which are prolonged in a patient with a recurrent seizure. Third, antiepileptic medications have side effects that may outweigh the benefit of treatment, especially in women of childbearing age, owing to the teratogenic risk of antiepileptic drugs, and in patients with liver, kidney, or hematologic disorders and patients already receiving multiple medications.

Recurrent Seizures

The initial approach to stabilization of a patient with a known seizure disorder does not differ from that for a new-onset patient; this includes a rapid blood glucose determination. The most common cause of seizures in a patient with a diagnosed seizure disorder is noncompliance with medications.[9] However, supratherapeutic and toxic levels of some anticonvulsants, such as carbamazepine, phenytoin, and lamotrigine, whether attained chronically or after acute overdose, can also *cause* seizures.[80-83] Accordingly, it is prudent to check the serum drug level, if this test is available, before giving a full loading dose of anticonvulsants to patients on long-term therapy. Meanwhile, a thorough history and physical examination should focus on intercurrent illness or trauma, drug or alcohol use, potential adverse drug-drug interactions with anticonvulsants, a recent change in anticonvulsant dosing regimens, and any change in ictal pattern or characteristics. Clinical indications should dictate the selection of other laboratory or radiographic tests.

DIFFERENTIAL CONSIDERATIONS

Even when a "seizure" is witnessed in the ED, other abnormal movements and states of consciousness can be confused with ictal activity. The most common misdiagnoses are cardiovascular (syncope) and psychogenic, but other considerations in the differential diagnosis include hyperventilation and breath-holding, certain toxic and metabolic states, transient ischemic attacks, narcolepsy, and some movement disorders.[9,11,72,73,84]

Syncope—whether vasodepressive (e.g., "vagal" or micturition syncope), orthostatic, or arrhythmogenic (e.g., paroxysmal ventricular tachycardia or fibrillation, long Q-T syndrome)—may be confused with ictal events; differentiating among these may be particularly difficult when episodes are recurrent—hence the consideration "fit versus faint." Generally, ictal tonic-clonic movements are much more forceful and are more prolonged than the "twitches" sometimes associated with fainting. In addition, most seizures are characterized by a postictal state, which, with the important exception of atonic drop attack ictus, is not a feature of syncope. The cause of an unwitnessed, unprovoked loss of consciousness with a fall, after which the patient presents to the ED, may be difficult to classify. Retrograde amnesia suggests an ictal diagnosis. Hyperventilation syndrome can be associated with mood disturbances, paresthesias, and posturing movements of the distal extremities. Manifestations of toxic and metabolic disorders

that may mimic ictus include delirium tremens and alcoholic blackouts, the alteration in consciousness associated with hypoglycemia and acute intermittent porphyria, the buccolingual spasms of phencyclidine intoxication, and the tonic spasms caused by tetanus, strychnine, and camphor.[11] Nonictal CNS events, such as transient ischemic attacks, transient global amnesia, and atypical migraines, may manifest in a manner similar to that in absence seizures and postictal states such as Todd's paralysis. Carotid sinus hypersensitivity, which can even result from a too-tight necktie, may cause drop attacks.[85] Narcolepsy (recurrent irresistible daytime sleepiness), especially when it occurs with cataplexy (sudden falls), may be associated with hallucinations and abnormal movements. It can be differentiated from seizure activity by the history and response to stimulation. Movement disorders, such as hemiballismus and tics, usually are associated with other neurologic problems. Finally, dissociative states such as fugue and panic attacks can be confused with seizures. An EEG is an appropriate diagnostic option in unclear cases.

MANAGEMENT

Immediate Management

ED management of a patient experiencing a seizure begins with active, anticipatory airway management. In generalized ictus, the gag reflex is suppressed, and vomiting often is complicated by aspiration of gastric contents. The patient should be placed in a left lateral decubitus position, and any dentures should be removed. A bite-block should be placed to protect the tongue and allow access for suctioning.

If the patient is persistently apneic or if an unavoidable airway threat is present, endotracheal intubation is warranted for definitive protection. A benzodiazepine should be used as an induction agent in the hope that its action may terminate the seizure or obviate the need for tracheal intubation. Trismus may necessitate use of a short-acting neuromuscular blocking agent to facilitate intubation.

In general, the first-line pharmacologic agent for treatment of any active seizure is a parenteral benzodiazepine. Because benzodiazepines directly enhance GABA-mediated neuronal inhibition, they affect clinical and electrical manifestations of seizures. Benzodiazepines are effective in terminating ictal activity in a majority of patients and have been shown to be more effective than phenytoin in terminating status epilepticus.[86,87] Although phenobarbital appears to be as effective as the benzodiazepine lorazepam in terminating status epilepticus, the associated high risk of hypoventilation and hypotension limits its use as a first-line agent.[87]

Benzodiazepines available in the ED setting include diazepam (Valium), lorazepam (Ativan), and midazolam (Versed) (Table 100-1). All three may be used in patients of any age, and all share the following characteristics: rapid efficacy (seconds to minutes), relatively short duration of anticonvulsant action, a sedative effect, and the potential for hypotension and respiratory depression. Lorazepam has emerged as the drug of choice for the initial management of epilepsy, because it terminates seizure rapidly (within 2 minutes) and has a longer duration of action (4 to 6 hours, compared with 20 minutes for diazepam), thus necessitating fewer repeat doses.[88-91] For this reason, it also is the preferred agent for control of alcohol withdrawal seizures.[92,93] Lorazepam is available intramuscularly and as a sublingual preparation for out-of-hospital control of seizures in children.[9] An advantage of diazepam is that it is in liquid form at room temperature and is therefore available premixed in resuscitation kits, and it can be administered quickly and without a need for reconstitution by the intravenous, endotracheal, or intraosseous route. It also is available in a rectal gel formulation. Its onset of action with intravenous administration is within 10 to 20 seconds, but a 50% chance of recurrent seizure within 2 hours if diazepam is used alone has been noted.[87] Midazolam's onset of action is within 1 minute; it is available in both intranasal and buccal formulations,[94] and among the benzodiazepines it has the least cardiovascular effect.[91]

Second-line abortive anticonvulsant therapy consists of phenytoin (Dilantin) and phenobarbital. Phenytoin reduces the repetitive firing of action potentials through sodium channel blockade, thereby stabilizing neuronal membranes.[9] Phenytoin neither sedates patients nor causes respiratory depression, but rapid intravenous administration of phenytoin in its propylene glycol diluent may cause hypotension and cardiac bradydysrhythmias, as well as local vascular injury, including venous thrombosis and localized tissue necrosis (purple glove syndrome).[95-97] It should therefore be administered through a 20 gauge or larger line proximal to the forearm, at a rate no faster than 50 mg/minute, and the patient should have a cardiac monitor. Phenytoin's onset of action is within 10 to 30 minutes, and intravenous administration typically requires at least 20 minutes.[98] The duration of action is approximately 24 hours. Continued benzodiazepine dosing is appropriate until phenytoin achieves adequate brain levels.

Fosphenytoin is a water-soluble prodrug form of phenytoin, with a more physiologic pH. Its main advantages are that it is not likely to precipitate during intravenous infusion and that it also can be administered intramuscularly, although the volume required for full loading by the intramuscular route may be in the range of 20 mL or more.[99] Although fosphenytoin can be infused more rapidly, the time to therapeutic concentration of the active drug is the same as for intravenous phenytoin.[100] The hemodynamic advantages of fosphenytoin over intravenous phenytoin have not proved to be significant.[101,102] Its use is most appropriate when intravenous access is not obtainable or when the intravenous line is of small gauge, as is often the case in children or the elderly.[88] If levels of phenytoin or phenobarbital are subtherapeutic in a patient already being treated for seizures, loading doses can be given intravenously; alternatively, an adjusted oral dosing schedule can be prescribed to boost the serum level over 24 to 48 hours. Oral loading of phenytoin is associated with fewer adverse events than those noted with loading with either intravenous phenytoin or fosphenytoin,[101] but its use may be limited when therapeutic activity is required urgently.

Phenobarbital is similar to benzodiazepines in that it binds to and enhances the inhibitory neurotransmitter GABA, thereby acting as a CNS depressant that decreases ictal and physiologic cortical electrical activity. Sedation and depression of respiratory drive and blood pressure must be anticipated,[91] and, for this reason, nonsedating phenytoin is preferred. The onset of action of phenobarbital is within 15 to 30 minutes, and the duration of action is 48 hours.

Valproic acid administered intravenously has recently been recognized as a safe and effective treatment for seizures, especially in patients with allergies to phenytoin, the elderly, and patients with cardiorespiratory instability who might be at increased risk of adverse events from phenytoin.[103-105] Valproic acid administered intravenously has been shown to be as effective as phenytoin given intravenously in patients with benzodiazepine-refractory status epilepticus, with fewer cardiopulmonary side effects.[106] Hyperammonemic encephalopathy after valproic acid loading has been reported and should be evaluated by determination of serum ammonia level in a patient who does not regain consciousness after seizure resolution.[19,107] Appropriate ED dosing regimens for the

Table 100-1 Drugs Used in the Abortive Treatment of Status Epilepticus in the Emergency Department

GENERIC NAME	BRAND NAME	ADULT DOSE	COMMENTS
Diazepam	Valium	5–10 mg IV every 10 minutes, up to 30 mg per 8-hour period	May be given per rectum in pediatrics (0.3–0.5 mg/kg)
Lorazepam	Ativan	0.1 mg/kg IV (usually 4 mg in adult); may repeat in 10 minutes, then 0.01–0.1 mg/kg per hour infusion	Preferred benzodiazepine owing to its longer duration of action
Midazolam	Versed	0.2 mg/kg IV bolus, then 0.05–0.6 mg/kg per hour infusion	May be given intranasally (0.2 mg/kg)
Phenytoin	Dilantin	20 mg/kg IV at <50 mg/minute	Cardiac and blood pressure monitoring during infusion; large-bore intravenous line
Fosphenytoin	Cerebyx	20 PE/kg IV at 150 mg PE/minute	Cardiac monitoring Less risk of infusion site reaction; may be given IM
Phenobarbital	Luminal	20 mg/kg IV, then 5–10 mg/kg every 20 minutes, up to 2 g	May be given as IM loading dose
Valproate	Depakote	20–40 mg/kg at ≤6 mg/kg per minute	Unlabeled use
Propofol	Diprivan	1–2 mg/kg IV bolus, then 5–10 mg/kg per hour infusion	Intubation required; monitor hemodynamics
Pentobarbital	Numbutal	10–20 mg/kg IV load over 1–2 hours, then 0.5–1 mg/kg per hour infusion	Intubation required; monitor hemodynamics
Isoflurane	Forane, Terrell	Via general endotracheal anesthesia	Monitor with EEG

EEG, electroencephalogram; PE, phenytoin equivalent.
Data from Lowenstein DH: Treatment options for status epilepticus. Current Opin Pharmacol 5:334, 2005; Engel J Jr, Pedley TA (eds): Epilepsy: A Comprehensive Textbook, 2nd ed. Philadelphia, Lippincott Williams & Wilkins, 2008.

benzodiazepines, phenytoin, fosphenytoin, phenobarbital, and valproic acid are listed in Table 100-1.

Although such agents are being given to abort ongoing seizure activity, ED management must include a search for other underlying reversible causes. This search may prompt administration of dextrose for hypoglycemia, pyridoxine (vitamin B_6) for isoniazid overdose, sodium for hyponatremia, or magnesium for eclampsia.

Eclampsia complicates 1 in 1000 deliveries in the United States[108] and can occur ante partum (91% of cases occur after 28 weeks of gestation), in the peripartal period, or up to 4 weeks post partum.[109,110] Abortive treatment for eclamptic seizures is with magnesium sulfate, which is superior to either diazepam or phenytoin in limiting maternal mortality and preventing further seizures in eclampsia.[111,112] The loading dose of magnesium sulfate is 4 to 6 g, followed by an infusion of 2 g/hour for 24 hours.[65,111,113] Because hypermagnesemia may cause respiratory arrest, it is essential to monitor patients for hyporeflexia, which precedes respiratory compromise. In the uncommon event of excessive neuromuscular blockade secondary to respiratory compromise caused by magnesium sulfate, 1 g of 10% calcium gluconate is an effective reversal agent.[65] Simultaneous reduction in blood pressure in the eclamptic patient, using hydralazine, labetalol, or nicardipine, is recommended.[65]

Nonpregnant patients who continue having seizures in the ED despite management with benzodiazepines, phenytoin, or phenobarbital are likely to meet the clinical criteria for refractory status epilepticus. Additional therapeutic measures include use of valproate, midazolam infusion, propofol infusion, barbiturate coma, and general inhalational anesthesia. Valproate, which increases GABA concentration, may be given intravenously in status epilepticus (see Table 100-1).[22] Another alternative is the use of propofol, a nonbarbiturate anesthetic agent with hypnotic and anticonvulsant activity. Studies suggest that propofol acts at a location other than the benzodiazepine-binding site and modifies the chloride channel by a mechanism that is different from, and possibly synergistic with, those for benzodiazepines and barbiturates. Propofol usually is administered as an intravenous loading dose of 1 to 3 mg/kg; this is followed by an infusion of 1 to 15 mg/kg per hour,[114] with continuous EEG monitoring to ensure persistent burst suppression.[115]

Barbiturate coma is effective in terminating seizures by facilitating GABA, although it also suppresses all brainstem function. Neurologic consultation is advisable beforehand, however, because barbiturate coma may induce respiratory arrest, myocardial depression, and hypotension while decreasing intracranial pressure and increasing cerebral perfusion. The preferred agent for barbiturate coma is pentobarbital (see Table 100-1). Patients require intubation and ventilatory support, continuous cardiac monitoring, and invasive hemodynamic monitoring. Pressors may be required to support the blood pressure.[116]

Isoflurane anesthesia is one final alternative in the management of refractory ictus. Halothane is associated with more hemodynamic and hepatotoxic complications. Isoflurane suppresses electrical seizure foci and is easily titratable. Patients managed with barbiturate coma or inhalational anesthesia require intubation and mechanical ventilation. Intubation of a patient with ongoing seizure activity is best facilitated by using a benzodiazepine as an induction agent and lidocaine (1 mg/kg) as a pretreatment medication. Lidocaine reduces the increase in intracranial pressure that reflexively results from laryngoscopy and intubation.

The visible manifestations of convulsive ictus are extinguished by neuromuscular blockade. When a seizing patient is paralyzed and intubated, it cannot be assumed that pharmacologic therapy has terminated the seizure. Anticonvulsants should be administered, and EEG monitoring of the patient should be arranged. Without EEG, detection of seizure activity in a heavily sedated or paralyzed patient is difficult.

Long-Term Management

Identifying a new-onset seizure disorder in the ED should prompt consideration of the need for further management in the following three areas: pharmacologic, psychosocial, and legal. The primary dilemma concerns whether to initiate prophylactic anticonvulsant therapy after one seizure. The deci-

sion to treat should be based on (1) ensuring that the diagnosis of seizure is correct, (2) ascertaining the likelihood of seizure recurrence, (3) assessing the benefit versus risk of anticonvulsant therapy, and (4) discussing with the patient their approach to risk. Even when witnessed in the ED, apparent ictal activity may not be a seizure. Diagnosing a seizure is more difficult when the event resolved before the patient's arrival at the ED and is based on witness reports. In patients diagnosed with a seizure, 20 to 25% are subsequently found to have been misdiagnosed.[72,74,117]

The risk of seizure recurrence is difficult to estimate in the ED setting. In patients with an initial unprovoked seizure, the 2-year risk of recurrence without treatment generally is considered to be less than 50%.[70,75,76] The presence of EEG abnormalities suggests greater risk, but this information usually is unavailable in the ED setting. Other factors associated with an increased risk of recurrence are partial (versus generalized) ictus, status epilepticus, a history of intracranial surgery or trauma, and the presence of a persistent neurologic abnormality, such as Todd's paralysis.

The presence of specific underlying conditions may affect the decision to institute long-term therapy. For example, it would be reasonable to initiate antiepileptic therapy for an initial seizure in an HIV-positive patient when the seizure is thought not to be due to correctable factors such as drug toxicity or metabolic derangement.[41,70] Alcohol-related seizures are notoriously unresponsive to anticonvulsants. Prophylaxis against post-traumatic seizures beyond the first week after injury probably is unnecessary,[118] but the occurrence of early post-traumatic seizures should prompt at least short-term initiation of therapy.[119] Furthermore, if a patient not receiving antiepileptic therapy presents to the ED with a second seizure, then initiating treatment is warranted because of the estimated 70% risk of recurrent events.[120]

The side effects of anticonvulsants can be debilitating for the patient (Table 100-2). These effects must be considered before such therapy is initiated, particularly in women of reproductive age, because some anticonvulsants are teratogenic and furthermore may precipitate failure of oral contraceptives.

In the absence of specific underlying conditions that increase risk of recurrence, most authorities do not recommend initiation of anticonvulsant therapy from the ED after a single unprovoked seizure in adults.[11,78,79,121] If the seizure was provoked, the decision should be based on whether the provoking factor can be corrected; if it cannot, anticonvulsant therapy should be instituted. The anticonvulsant dosing regimen for a patient with known epilepsy should be modified only in consultation with the patient's physician (Table 100-3).

Drug monotherapy is always preferable in anticonvulsant regimens. The choice of drug to initiate antiepileptic therapy

Table 100-2 Important Adverse Effects and Drug-Drug Interactions of Anticonvulsants

GENERIC NAME	TRADE NAME	IMPORTANT ADVERSE EFFECTS	P-450 LIVER ENZYME METABOLIZERS*
Carbamazepine	Tegretol	Rash, leukopenia, hyponatremia, cardiac dysrhythmias (elderly), weight gain	Inducer
Clonazepam	Klonipin	Sedation, ataxia, irritability	No
Ethosuximide	Zarontin	Sedation, ataxia, nausea, anorexia	
Felbamate	Felbatol	Rare fatal aplastic anemia, hepatotoxicity, headache, anorexia, vomiting, insomnia	Inducer
Fosphenytoin	Cerebyx	Nystagmus, ataxia, sedation, headache	Inducer
Gabapentin	Neurontin	Sedation, ataxia, tremor	No
Lamotrigine	Lamictal	Hypersensitivity reaction (risk of renal failure, liver failure, DIC), rash (SJS, TEN), ataxia, headache, nausea	Inducer and inhibitor†
Levetiracetam	Keppra	Emotional lability, sedation, dizziness, infections (colds)	No
Oxcarbazepine	Trileptal	Hyponatremia, rash, dizziness, headache, fatigue	Inducer and inhibitor
Phenobarbital	Luminal	Sedation, depression, cognitive slowing, decline in libido, osteomalacia	Inducer
Phenytoin	Dilantin	Gingival hyperplasia, hirsutism, nystagmus, ataxia, sedation, nausea, osteoporosis, leukopenia, phenytoin hypersensitivity syndrome‡	Inducer
Pregabalin	Lyrica	Weight gain	No
Primidone§	Mysolline	Sedation, depression, cognitive slowing, decline in libido, acute toxicity after first dose	Inducer
Tiagabine	Gabitril	Dizziness, depression, tremor, poor concentration	No
Topiramate	Topamax	Cognitive slowing, anorexia, nephrolithiasis, paresthesias, metabolic acidosis, rare glaucoma	Inducer
Valproate	Depakote	Thrombocytopenia, tremor, weight gain, male-pattern hair loss, rare hepatotoxicity, osteoporosis	No
Zonisamide	Zonegran	Sedation, cognitive slowing, ataxia, anorexia, rash	No

*All inducers of liver enzymes reduce the efficacy of oral contraceptives.
†OCP also reduces Lamictal serum levels.
‡Phenytoin hypersensitivity syndrome includes rash, fever, hepatitis, lymphoid hyperplasia, and blood dyscrasias. Side effects of intravenous phenytoin include hypotension, arterioventricular block, and purple glove syndrome (edema, pain, and discoloration of the limb distal to the site of infusion).
§Primidone is a congener of phenobarbital.
DIC, disseminated intravascular coagulation; OCP, oral contraceptive pills; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.
Data from Engel J Jr, Pedley TA (eds): Epilepsy: A Comprehensive Textbook, 2nd ed. Philadelphia, Lippincott Williams & Wilkins, 2008; Harden CL, Leppik I: Optimizing therapy of seizures in women who use oral contraceptives. Neurology 67:S56, 2006; French JA, et al: Efficacy and tolerability of the new antiepileptic drugs I: Treatment of new onset epilepsy: Report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society [see comment]. Neurology 62:1252, 2004; and Mattson RH: Efficacy and adverse effects of established and new antiepileptic drugs. Epilepsia 36:S13, 1995.

Table 100-3 Drugs Used for Long-Term Anticonvulsant Therapy in Adults

DRUG	INDICATIONS	MAINTENANCE DOSE (MG/DAY)*	FORMULATION	THERAPEUTIC RANGE (mcg/mL)	DAILY DOSES
Carbamazepine	Partial, generalized	800–1600	PO	4–12	2–3
Clonazepam	Absence	1.5–8	PO	20–80	2–3
Ethosuximide	Absence	750–1250	PO	40–100	2
Felbamate	Refractory epilepsy only	2400–3600	PO	N/A	3–4
Fosphenytoin	Partial, generalized	4–6 PE/kg/day	IV, IM	10–20	
Gabapentin	Partial	900–3600	PO	N/A	3
Lamotrigine	Partial, generalized, absence	100–500	PO	N/A	2
Levetiracetam	Partial, generalized, absence	1000–3000	PO, IV	N/A	2
Oxcarbazepine	Partial, generalized	1200–2400	PO	N/A	2
Phenobarbital	Partial, generalized	90–150	PO, IV	20–40	2–3
Phenytoin	Partial, generalized	300–400	PO, IV, IM	10–20	1–3
Pregabalin	Partial	150–600	PO	N/A	2–3
Primidone‡	Partial, generalized	750–1250	PO	5–12	3–4
Tiagabine	Partial (adjunct)	32–56§	PO	N/A	2–4
Topiramate	Partial, generalized	200–400	PO	N/A	2
Valproate	Partial, generalized, absence	1000–3000	PO, IV	50–100	1–3
Zonisamide	Partial, generalized, absence	100–400	PO	20–30†	1–2

*Adjust dose for hepatic or renal disease and with use of other medications.
†Some studies indicate a range of 10–50 mg/L.
§If patient is not taking enzyme-reducing AED, then daily dose should be halved (16–28).
PE, phenytoin equivalents.
Data from Engel J Jr, Pedley TA (eds): Epilepsy: A Comprehensive Textbook, 2nd ed. Philadelphia, Lippincott Williams & Wilkins, 2008; Mattson RH: Efficacy and adverse effects of established and new antiepileptic drugs. Epilepsia 36:S13, 1995; Perucca E: Clinical pharmacology and therapeutic use of the new antiepileptic drugs. Fundam Clin Pharmacol 15:405, 2001; and Drugs for Epilepsy. Treatment Guidelines from the Medical Letter 6:37, 2008.

is complex and depends on numerous factors, including the type of seizure, any comorbid conditions, other medications the patient is taking, and the potential for pregnancy, and is best determined in consultation with a neurologist, ideally after MRI neuroimaging and an EEG.[68] However, if an antiepileptic drug is to be initiated in the ED, then the choice is among the three medications with the strongest evidence for efficacy in the treatment of a tonic-clonic seizure of either generalized-onset or partial onset with secondary generalization: carbamazepine, phenytoin, and valproate.[122] It is essential to inform women of childbearing age that carbamazepine and phenytoin decrease the efficacy of oral contraceptive pills, so a second form of contraception should be used until consultation with a neurologist. Valproate, although not altering the efficacy of oral contraceptives, carries a high risk of teratogenic effects and is therefore not an ideal first-line agent for women of childbearing years.[123,124]

The psychological and social implications of the new diagnosis of a seizure disorder should not be underestimated. Fear of seizures and stigmatization are common; employability and insurability may be adversely affected. Although the emergency physician is not usually in a suitable position to arrange for counseling, referral to local epilepsy support groups may be helpful.

The diagnosis of a new-onset seizure disorder has legal implications as well. Each state has regulations regarding driving privileges in patients with seizures, and some states require reporting by the physician. Accordingly, ED management should ensure compliance with such regulations, including informing patients about any restrictions. Patients also should be advised to refrain from hazardous or isolated activities until cleared to do so by their primary care physician. The need for a "medical alert" bracelet or other medical condition identifier should be stressed.

Finally, patients and their families should be counseled about seizure first aid, safety precautions such as avoiding swimming alone or operating dangerous machinery, and triggers for recurrence such as photic stimuli, sleep deprivation, and alcohol.

KEY CONCEPTS

- The possibility of reactive seizures should be considered in all patients who present to the ED with seizures or recent history of seizures, including patients with a history of epilepsy. The most common cause of reactive seizures is hypoglycemia. The most common cause of recurrent primary seizures is medication noncompliance.
- Nonconvulsive seizures may be confused with nonictal states, including psychiatric disorders. The presence of repetitive eye movements, blinking, or automatisms suggests the diagnosis.
- Neuroimaging is recommended for patients with seizures in whom head trauma, elevated intracranial pressure, intracranial mass, persistently abnormal mental status or focal neurologic abnormality, or HIV disease is suspected.
- Primary abortive therapy for seizures in the ED setting is with a benzodiazepine; second-line agents include phenytoin and phenobarbital.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 101 Headache

Thomas Kwiatkowski and Kumar Alagappan

Headache is a common complaint, more frequent than the common cold, and accounts for approximately 3 million visits to the emergency department (ED) per year in the United States.[1] In addition, many more patients present with headache as part of a constitutional illness, making the symptom of headache one of the most frequent complaints in the ED.[2]

Headache commonly is divided into *primary* and *secondary* disorders. The primary headache disorders include migraine, cluster, and tension-type headaches, which represent greater than 90% of headaches seen in clinical practice.[3] Secondary headache disorders include a variety of organic illnesses in which head pain is a symptom of an identifiable, distinct pathologic process. To facilitate a standardized approach to headache management, the International Headache Society (IHS) published classification and diagnostic criteria for "headache disorders, cranial neuralgias, and facial pain" in 2004.[4] This comprehensive and widely accepted system includes 14 categories of headache disorders and uses specific operational diagnostic criteria to define each headache type (Box 101-1). This revised classification system offers better separation of primary and secondary headaches and more standardized criteria for diagnosing secondary headaches.[5]

The vast majority of patients presenting with headache have a benign primary headache disorder requiring only symptomatic treatment and referral. The challenge for the emergency physician is to identify the very small subset of patients who have headache as a symptom of a serious or potentially life-threatening disease (see Chapter 16).

PRIMARY HEADACHE DISORDERS

Migraine Headache

Principles of Disease. Migraine is a common, chronic, sometimes incapacitating neurovascular disorder, characterized by attacks of severe headache, autonomic nervous system dysfunction, and, in some patients, an aura involving neurologic symptoms.[6] It is a primary headache disorder believed to have a genetic basis.[7]

Migraine headaches account for approximately 1 million visits to the ED per year.[8] They typically begin in the second decade of life, peaking in early to midadolescence, and are more prevalent among women (17%) than among men (6%).[7,9,10] During childhood, however, there is no gender difference in the prevalence of migraine.[3] After menarche a correlation between migraine headache and menses is found in approximately 15% of female migraine sufferers, possibly related to fluctuating estrogen and progesterone levels. After menopause, women also tend to experience fewer migraine headaches. The lifetime prevalence of migraine is at least 18%.[6] As many as 60% of women with migraines report an association between migraine and menstruation.[11]

Historically, migraine headaches have been considered to be vascular in origin. According to this hypothesis, an initial phase of cerebral vasoconstriction resulting in neurologic symptoms (migraine with aura) is followed by a vasodilatory phase, manifested by the typical pounding headache of migraine. Appropriate changes in blood flow have been demonstrated for the classic migraine attack, and pain relief provided by vasoconstriction has been cited as further support for this hypothesis.[12] However, this mechanism does not fully explain the entire spectrum of migraine attacks, and migraine is no longer thought to be caused by a primary vascular event.[6] It is now believed that the pathophysiologic cause of migraine may actually originate in the brainstem within its descending and ascending circuitry, including the ascending pain-modulating projections from the midbrain raphe nuclei.[13] Evidence suggests a perturbation of neural activity within this serotoninergic system as an important precursor to migraine.[14] Changes in serotoninergic activity can alter the cranial circulation, triggering a "vascular phase." In addition to constriction and dilatation of intracranial and extracranial arteries, this neurovascular reaction activates the nociceptive trigeminal vascular system.[15,16] Neural connections between cerebral blood vessels and the trigeminal nerve release neuropeptides that can induce a painful neurogenic or sterile inflammation.[17]

Agonists of the 5-hydroxytryptamine (5-HT) 1B/1D receptor, such as sumatriptan or dihydroergotamine, block the inflammatory process. Effective prophylactic agents are believed to act as antagonists of the 5-HT_2 receptor site.[18]

Migraine is further divided into two major categories. Migraine without aura, or "common migraine," is the most frequent form of migraine and accounts for approximately 80% of all cases (Box 101-2). "Classic migraine," or migraine with aura, has specific reversible neurologic symptoms that precede the actual headache (Box 101-3) and is seen less frequently.

Clinical Features. Migraine headaches tend to be chronic and recurrent. The headache often is unilateral, pulsating in quality, moderate to severe in intensity, and exacerbated by routine activities. The side of the headache can vary with individual attacks, and the headache may be bilateral in 40% of patients. The onset usually is gradual, and the attacks typi-

BOX 101-1 International Headache Society Classification of Headache

1. Migraine
2. Tension-type headache
3. Cluster headache and trigeminal autonomic cephalgias
4. Other primary headaches
5. Headache attributed to head and/or neck trauma
6. Headache attributed to nonvascular intracranial disorder
7. Headache associated with nonvascular intracranial disorder
8. Headache attributed to a substance or its withdrawal
9. Headache associated with noncephalic infection
10. Headache attributed to disorder of homeostasis
11. Headache or facial pain attributed to disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cranial structures
12. Headache attributed to psychiatric disorder
13. Cranial neuralgias and central causes of facial pain
14. Other headache, cranial neuralgia, central or primary facial pain

Available at http://ihs-classification.org/en/.

BOX 101-2 Migraine without Aura (Common Migraine): International Headache Society Criteria

A. At least five attacks fulfilling criteria in B, C, D, and E
B. Attack lasts 4 to 72 hours (untreated or unsuccessfully treated)
C. Headache has at least two of the following characteristics:
   1. Unilateral location
   2. Pulsating quality
   3. Moderate to severe pain intensity
   4. Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
D. During headache, at least one of the following:
   1. Nausea or vomiting (or both)
   2. Photophobia and phonophobia
E. Not attributable to another disorder

Available at http://ihs-classification.org/en/.

BOX 101-3 Migraine with Aura (Classic Migraine): International Headache Society Criteria

A. At least two attacks that fulfill criterion B
B. Presence of at least three of the following four characteristics for a diagnosis of classic migraine:
   1. One or more fully reversible aura symptoms indicating focal cerebral cortical or brainstem dysfunction (or both)
   2. At least one aura symptom developing gradually over more than 4 minutes, or two or more symptoms occurring in succession
   3. No single aura symptom lasting longer than 60 minutes
   4. Headache beginning *during* aura or *afterward*, with a symptom-free interval of less than 60 minutes (also may begin *before* aura)
C. Exclusion of related organic diseases by means of an appropriate history, physical examination, and neurologic examination with appropriate diagnostic tests

Available at http://ihs-classification.org/en/.

cally last from 4 to 72 hours. Headache frequency is quite variable, and some patients experience several episodes per month. Associated symptoms and signs include nausea, vomiting, anorexia, photophobia, phonophobia, osmophobia (aversion to odors), blurred vision, lightheadedness, and nasal congestion. Some patients experience cognitive impairment producing forgetfulness, irritability, and depression, whereas others may be manic, with outbursts of anger that can be disruptive in the ED setting. Many patients have dramatic light and sound sensitivity and seek a cool, dark, and quiet room.

The aura of classic migraine consists of focal neurologic symptoms that precede and herald the migraine attack. By definition, the aura is fully reversible and typically lasts 10 to 20 minutes, although it may continue for as long as 1 hour. The most common aura is visual; features may include scintillating scotomas (bright rim around an area of visual loss), teichopsias (subjective visual image perceived with eyes open or closed), fortification spectrums (zigzagged wall of fortress slowly drifting across visual field), photopsias (poorly formed brief flashes or sparks of light), and blurred vision. Less common auras include somatosensory phenomena such as tingling or numbness, motor disturbances, and cognitive or language disorders.[19]

Ophthalmoplegic migraine is a rare syndrome associated with paresis of one or more ocular nerves, most commonly the third cranial nerve. Patients typically present with ipsilateral headache associated with extraocular muscle paresis and occasionally pupillary changes. The ophthalmoplegia or pupillary changes may last for days to weeks and, rarely, may become permanent.[20] Because of the neurologic abnormalities, secondary causes including intracranial aneurysm and mass lesion must be ruled out.

Hemiplegic migraine is characterized by episodic hemiparesis or hemiplegia as an aura to the migraine attack. The progression of the motor deficit is slow or marching in quality and in most cases is accompanied by a sensory disturbance as well. The neurologic symptoms last 30 to 60 minutes, followed by a severe pulsating headache. Rarely, the motor deficit is persistent, resulting from a true migraine-induced stroke.

Basilar-type migraines arise with an aura referable to the brainstem and are associated with multiple neurologic findings, including visual symptoms (often total blindness), dysarthria, tinnitus, vertigo, bilateral paresthesias, paresis, and altered level of conciousness.[21] The symptoms are stereotypic and resolve spontaneously.

Status migranosus is a severe migraine headache that persists longer than 72 hours. Associated symptoms are debilitating, and patients often require hospitalization for pain management and supportive care.

Many factors can trigger migraine headaches in predisposed persons. Common precipitants include sleep deprivation, stress, hunger, hormonal changes including menstruation, and the use of certain drugs including oral contraceptives and nitroglycerin.[8] In addition, some patients report specific food sensitivities including chocolate, caffeine, and foods rich in tyramine, monosodium glutamate, and nitrates.[22,23] Alcohol, specifically red or port wine, has also been implicated. In others, certain sensory stimuli such as a strong glare or strong odors, loud noises, or weather changes can trigger an attack.[24]

Differential Diagnosis. Because of the complexity of the symptomatology, migraine headaches may be difficult to distinguish from other, secondary causes of headache. Other disorders that mimic migraine include ruptured berry aneurysm, arteriove-

nous malformation, intracranial mass lesions, giant cell arteritis, and cerebrovascular disease.

Diagnostic Evaluation. Routine neuroimaging is not necessary for patients with typical recurrent migraine headaches. However, neuroimaging must be considered for patients with new-onset headaches, headaches with a progressive course or change in pattern, headaches that never alternate sides, and headaches associated with any neurologic abnormalities or seizures. Such patients have a substantially higher likelihood of having a secondary cause such as tumor, arteriovenous malformation, or structural lesion.[25] In addition, patients who present with a severe headache or the "worst headache of [their] life" require a lumbar puncture to rule out subarachnoid hemorrhage if findings on a computed tomography (CT) scan are negative.

Treatment. The pharmacologic treatment of migraine is divided into *abortive* therapies, which attempt to limit the intensity and duration of a given episode, and *prophylactic* therapies, which are intended to decrease the frequency and intensity of attacks.[26] The goals of acute migraine therapy include treating attacks rapidly and consistently to avoid headache recurrence, restoring the patient's ability to function, and minimizing the use of backup and rescue medications.[24]

Patients who are unable to control their headaches at home often present to the ED for better pain control or supportive therapy. There are several approaches to treating the acute headache episode, depending on the severity of the attack (Table 101-1). In addition, patients with a history of migraine may relate specific interventions that have been successful. The choice of agents depends on several factors, including the patient's previous response to specific therapies, the existence of comorbid conditions, and the presence or absence of nausea or vomiting. Gastric stasis is common during acute migraine attacks and may limit the effectiveness of oral agents.

For mild to moderate attacks, the IHS recommends simple analgesics such as acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs). In the presence of nausea or vomiting, adding an agent such as metoclopramide enhances the absorption and effectiveness of these medications. Appropriate doses and possible side effects are listed in Table 101-1.

For moderate to severe attacks, several classes of medications are available to treat the pain in addition to the nausea and vomiting that frequently accompany the headache. Specific agents available for treating severe migraine include DHE and the triptans. DHE should be given intravenously (IV) in a dose of 1.0 mg over 2 minutes; this can be repeated in 1 hour if pain control has not been achieved. Because DHE can cause nausea and vomiting, patients should be pretreated with an antiemetic such as metoclopramide 10 mg IV or prochlorperazine 5 mg IV. Repeated administration of the intravenous form of DHE has been shown to be very effective in patients with intractable migraine and status migranosus (i.e., a migraine attack lasting more than 72 hours). Contraindications to using DHE include pregnancy, breast-feeding, poorly controlled hypertension, coronary artery disease, and peripheral vascular disease. DHE should not be used if the patient has already taken any drug in the triptan class.

Sumatriptan, the first-approved medication of the triptan class, is a selective 5-HT (1B/1D) receptor agonist. Other triptans that are available include zolmitriptan, naratriptan, and rizatriptan, but only sumatriptan is available for subcutaneous administration, and it is the most common preparation used in the ED setting. The initial dose is 6 mg given subcutaneously, which may be repeated once in 1 hour if the patient has a partial response to the first dose. Common side effects include tingling, flushing, warm or hot sensations, and heaviness in the

Table 101-1 Selected Medications for Acute Migraine Attacks

MEDICATION	DOSE AND ROUTE ADMINISTERED	COMMENTS
Mild to Moderate		
Acetaminophen	500–1000 mg PO	Gastrointestinal upset
Aspirin	650–1000 mg PO	Gastrointestinal upset
Ibuprofen	600–800 mg PO	Gastrointestinal upset
Naproxen sodium	275–550 mg PO	Gastrointestinal upset
Tolfenamic acid	200–600 mg PO	Gastrointestinal upset
Moderate to Severe		
Dihydroergotamine	1 mg IV or IM; may be repeated in 1 hour	Gastrointestinal upset (pretreat with antiemetic) Chest pain, throat tightness, flushing
Triptans		
Sumatriptan	6 mg SC; may be repeated once in 1 hr if partial response	Contraindicated with hypertension, coronary artery disease, peripheral vascular disease, and pregnancy
Sumatriptan	25–100 mg PO	Cannot be used within 24 hours of ergot usage
Rizatriptan	5–10 mg PO	
Zolmitriptan	2.5–5 mg PO	
Naratriptan	1–2.5 mg PO	
Prochlorperazine	10 mg IV or IM; may be repeated in 30 to 60 minutes	Sedation and dystonic reaction
Metoclopramide	10 mg IV	Dystonic reaction
Ketorolac	30 mg IV or 30–60 mg IM	Gastrointestinal upset; avoid this medication in elderly and in patients with renal insufficiency
Morphine	2–4 mg IM or IV	Opioids less efficacious than other treatment modalities
Refractory Attack, Status Migranosus		
Dihydroergotamine	1 mg IV q8h	Use in conjunction with antiemetic (e.g., metoclopramide, prochlorperazine)
Steroids	Various regimens	Gastrointestinal bleeding, infection, cataracts, aseptic necrosis, memory disturbances

chest. Sumatriptan has contraindications similar to those for DHE and should not be used within 24 hours of administration of an ergotamine-containing medication or DHE.[27] In addition to the subcutaneous preparation, sumatriptan and the other triptan agents are available in oral formulation for the treatment of acute migraine attacks.

Neuroleptics also have been shown to be effective in treating acute migraine attacks. Prochlorperazine can be administered as a slow 10-mg intravenous bolus, which can be repeated once in 30 to 60 minutes.[16,28] The most common side effects after parenteral administration include sedation, postural hypotension, and extrapyramidal symptoms including acute dystonic reactions.

Narcotic analgesics such as morphine should be reserved for patients who do not respond or have contraindications to standard migraine therapies. Although frequently used, narcotics have been shown to be less efficacious than other agents and are associated with a risk of addiction; however, some patients obtain relief with this class of medications.

The use of steroids for the treatment of migraine remains controversial. Anecdotal evidence suggests that they may be effective for prolonged migraine attacks that are refractory to standard therapies and for treating status migranosus.[13,29]

Occasionally, patients do not respond to initial therapy in the ED and require hospitalization for continued pain control and supportive therapy.

Prophylactic Therapy. Prophylactic therapy is indicated for patients who have frequent attacks (more than two or three episodes per month), prolonged attacks lasting more than 48 hours, or attacks that are severe and debilitating. Of note, prophylactic medications are seldom more than 55 to 65% effective.[30]

Several classes of medications are used for the prophylaxis of migraine. Many of these medications have significant side effects, especially among women of childbearing age; therefore, after headaches have decreased, attempts should be made to taper and discontinue treatment when possible.

Beta-adrenergic blocking agents reduce both the frequency and severity of migraine headache and are the drugs most widely used for prophylaxis in patients with recurrent migraine.[8] Propranolol has been the most extensively studied medication. Patients who do not respond to propranolol may respond to another drug in this class, which includes atenolol, metoprolol, timolol, and nadolol.[31] Contraindications to beta-blockers include pregnancy, asthma, heart failure, Raynaud's phenomenon, and diabetes mellitus.[13]

Other medications used for migraine prophylaxis include calcium channel blockers, tricyclic antidepressants, anticonvulsants including divalproex sodium and sodium valproate, and monoamine oxidase inhibitors.[13,31]

Methysergide, a semisynthetic ergot preparation, also has been widely used for prophylaxis. It is a potent peripheral serotonin antagonist with a presumed mechanism of action similar to that for other ergot drugs. Its use is contraindicated in patients with coronary artery or peripheral vascular disease. Prolonged use has been associated with retroperitoneal, pulmonary, and endocardial fibrosis.[32]

Cluster Headache

Perspective. Cluster headache is the only headache syndrome that is more common in men than in women. It typically occurs in young to middle-aged adults who smoke, with a peak incidence in the late 20s.[33] The headaches tend to occur repeatedly over a defined time interval—hence the term "cluster." Several attacks can occur in 1 day, and a typical cluster period may last 6 to 8 weeks. Several precipitating factors have been implicated, most notably the ingestion of alcohol. Stress and climatic changes may also play a role in susceptible persons.

Clinical Features. Cluster headaches occur suddenly with little warning, and several episodes can occur within a 24-hour period. Each headache lasts from a few minutes up to 2 hours. The headache typically begins with a unilateral sharp, stabbing pain in the eye, which may awaken the patient from sleep. The attacks tend to occur exclusively in the territory of the trigeminal nerve.[34] Unlike the migraineur, the patient with cluster headache presents in a predictable fashion (i.e., holding a hand to the affected eye, rocking, rubbing the head, and pacing). The attack subsides rapidly, often leaving the patient exhausted.

Up to 30% of patients have a partial Horner's syndrome with ptosis and miosis.[35] The eye often is injected and tearing, and many patients have unilateral nasal congestion.[12]

Differential Diagnosis. Other headache disorders that mimic cluster headache include migraine, trigeminal neuralgia, and chronic paroxysmal hemicrania (CPH). With migraine, the clinical presentation, gender, and age distribution usually are different. With trigeminal neuralgia, the pain peaks within seconds, lasts only a couple of minutes, and can be provoked by specific trigger points on the face or oral mucosa. CPH is manifested by a brief unilateral headache that recurs at least 15 times a day, often induced by rotation or turning of the head or by pressure on the cervical spine.[36]

Treatment. Because cluster headaches are abrupt in onset, treatment must be initiated rapidly to be effective. At present, subcutaneous sumatriptan 6 mg is the preferred abortive therapy in most cases if it can be given very early after the onset of the attack[37]; however, by the time the patient presents to the ED, a full-blown headache usually has developed, and symptomatic treatment is indicated. High-flow oxygen at a rate of 7 to 10 L/minute has been shown to abort the headache within several minutes.[38] DHE 1 mg given IV or intramuscularly (IM) also has been shown to be effective, but it is less practical than oxygen administration and has more side effects. For patients who do not respond to these measures, intranasal application of cocaine[30] or lidocaine to produce anesthesia of the sphenopalatine region has been advocated by some clinicians but has not gained widespread acceptance.[39]

In addition to acute therapies, several medications have been shown to be effective for the prophylactic treatment of cluster headaches. A short course of oral prednisone may effectively abort a cluster attack in some patients. A recommended regimen is 60 mg of prednisone daily for 10 days, followed by a 1-week taper.[39] To prevent breakthrough headaches after the steroid taper, patients may require the concurrent administration of another prophylactic agent (e.g., verapamil, lithium carbonate, methysergide).

Tension Headache

Perspective. Tension headache is the most common recurrent pain syndrome, affecting more than 78% of the population.[40,41] Women are affected more frequently (80% in all women) than men (66%), and most patients are middle-aged.[7] The headaches typically do not cause significant disability, and patients are able to continue with their normal daily activities.[42] The median frequency of headaches is six per month, and stress and lack of sleep are implicated as triggering factors.[43,44] The average duration of the headache is 4 to 13 hours, with a maximum of 72 hours.[44]

Little is known about the pathophysiology of tension headache.[40] There is no clear evidence that increased muscle activity is present, and the physical examination will reveal tender areas of the scalp and neck with both tension and

migraine headaches. Evidence suggests that tension and migraine headaches may be part of a continuum with similar pathophysiology.

Clinical Features. Patients typically complain of a tight, bandlike discomfort around the head that is nonpulsating and dull. They also may experience tightening of the neck muscles. A majority do not seek medical assistance because the headache usually is mild in intensity and of relatively short duration. Occasionally, the discomfort can build up slowly and fluctuate in severity over several days. Unlike in migraine, the headache does not worsen with physical activity, and accompanying symptoms such as nausea, vomiting, phonophobia, or photophobia are unusual. Anxiety and depression may coexist with chronic tension headache, which by definition occurs more than 15 days a month and can be daily and unremitting.[33]

Differential Diagnosis. Tension headache is the least distinct of all of the primary headache disorders, and its diagnosis is based mainly on the absence of features that would suggest another cause for the headaches. Because of this lack of specificity, the clinician often may hesitate to make this essentially benign diagnosis without other investigations to exclude organic disease.[45] The most common disorders mimicking tension headache include idiopathic intracranial hypertension, oromandibular dysfunction, cervical spondylosis, sinus or eye disease, and intracranial masses.

Treatment. For a majority of patients with tension headaches, simple analgesics such as acetaminophen or an NSAID are adequate for pain control. Because tension-type headache is more common in sedentary persons, a regular exercise program may help.[33] Patients with chronic symptoms may exhibit signs of depression or anxiety, and these patients often respond to medications and nonpharmacologic regimens that treat these conditions. Some nonpharmacologic regimens are meditation, massage, and biofeedback. For long-term management, psychotherapy may be of value in teaching patients to deal with tension effectively.

SECONDARY HEADACHE DISORDERS

Subarachnoid Hemorrhage

Principles of Disease. Subarachnoid hemorrhage (SAH) refers to extravasated blood in the subarachnoid space. Presence of the blood activates meningeal nociceptors, leading to diffuse occipital pain along with signs of meningismus. SAH accounts for up to 10% of all strokes and is the most common cause of sudden death from a stroke.[46]

Approximately 80% of patients with nontraumatic SAH have ruptured saccular aneurysms.[47] Other causes include arteriovenous malformations, cavernous angiomas, mycotic aneurysms, neoplasms, and blood dyscrasias. SAH may be caused secondarily by an intraparenchymal hematoma that dissects its way into the subarachnoid space.

The risk for aneurysmal SAH increases with age, with most cases occurring between the ages of 40 and 60 years.[48] In children and adolescents, aneurysms are uncommon, and when SAH occurs it usually is secondary to an arteriovenous malformation.[49] It is estimated that 5% of the general population harbor a berry aneurysm, and the risk of rupture may increase with aneurysmal size. Other risk factors associated with SAH include hypertension, smoking, excessive alcohol consumption, and sympathomimetic drugs.[50,51] Increased systolic blood pressure values and long-term hypertension before aneurysm rupture seem to predict fatal SAH independently of aneurysm size or the patient's age at the time of rupture; patient gender also does not influence mortality.[52] A familial association of cerebral aneurysms with several diseases, including autosomal dominant polycystic kidney disease, coarctation of the aorta, Marfan's syndrome, and Ehlers-Danlos syndrome type IV, has been described.

Of all patients presenting to the ED with headache, 1 to 4% have SAH. Many patients with SAH die before reaching the hospital, with preadmission mortality rates ranging from 3% to 26%.[47] Because of the significant morbidity and mortality associated with this condition (with reported rates of up to 50%) and the high likelihood of clinical deterioration in patients who initially are misdiagnosed, SAH should be a primary consideration in the initial ED evaluation. Accordingly, familiarity with its presentation is essential.[47]

Clinical Features. A majority of patients with SAH present with a sudden, cataclysmic "thunderclap" headache, which often is described as "the worst headache of [their] life." The onset of headache may be associated with exertional activities such as exercise, the Valsalva maneuver, or sexual intercourse in up to 20% of patients.[46] One study demonstrated that moderate to extreme physical exertion in the previous 2-hour period was associated with a tripling of the risk for SAH.[53] Associated signs and symptoms include nausea and vomiting in approximately 75% of patients, neck stiffness in 25%, and seizures in 17%.[48] Some patients experience a headache within the previous 6 to 8 weeks, indicating a warning leak or sentinel hemorrhage. Physical findings depend on the extent of the SAH. Meningismus is present in more than 50% of patients,[49] and up to 20% have focal abnormalities.[50] Funduscopic examination may reveal retinal or subhyaloid hemorrhages, and patients also may have an isolated third or sixth nerve palsy. Oculomotor (third) nerve compression secondary to an expanding aneurysm leads to pupillary dilation. Approximately 50% of patients with a ruptured aneurysm are restless or have an altered level of consciousness. Although a majority do not have focal neurologic signs, such signs when present may indicate the site of the aneurysm.[54]

The patient's prognosis is related to neurologic status at hospital admission. The Hunt and Hess scale stratifies patients according to their clinical signs and symptoms at the time of presentation and is predictive of outcome[46,55] (Table 101-2). Patients who present with a grade I or II hemorrhage tend to have a good prognosis, and patients in grades IV and V tend to do poorly. These latter patients have an altered mental status, ranging from stupor to deep coma, together with focal neurologic signs and symptoms. Patients with grade III hemorrhage present with drowsiness or confusion and are at risk for rapid clinical deterioration.

Diagnostic Studies. When the diagnosis of SAH is considered, a CT scan should be ordered emergently. Figure 101-1 shows an example of SAH on a CT scan. For acute hemorrhage less

Table 101-2 Hunt and Hess Clinical Grading Scale for Cerebral Aneurysms and Subarachnoid Hemorrhage

GRADE	CONDITION
0	Unruptured aneurysm
1	Asymptomatic or minimal headache and slight nuchal rigidity
2	Moderate or severe headache, nuchal rigidity, no neurologic deficit other than cranial nerve palsy
3	Drowsiness, confusion, or mild focal deficit
4	Stupor, moderate to severe hemiparesis
5	Deep coma, decerebrate posturing, moribund appearance

Figure 101-1. Cerebral aneurysm. Shown is a computed tomography scan of an aneurysmal subarachnoid hemorrhage in a 55-year-old woman. Subarachnoid blood can be seen within the interpeduncular and ambient cisterns and the right sylvian fissure, from a ruptured aneurysm at the junction of the right carotid artery and the posterior communicating artery. (From Soliman E, Kader A, Perez N: Cerebral aneurysm. Online article at eMedicine.com. Available at http://www.emedicine.com/med/topic3468.htm, picture 8.)

than 24 hours old, the sensitivity of CT in identifying hemorrhage is greater than 90%; however, it decreases to approximately 50% by the end of the first week.[47] When the CT scan is negative, a lumbar puncture should be performed. Using lumbar puncture as a first strategy, postulated to be cost-effective in carefully selected patients who have completely normal physical examinations, may be safe but has not been studied clinically.[56] To differentiate a traumatic lumbar puncture from SAH, the patient's cerebrospinal fluid (CSF) should be spun and the supernatant observed for xanthochromia. The yellowish pigmentation is secondary to the metabolism of hemoglobin to pigmented molecules of oxyhemoglobin and bilirubin, a process that takes approximately 12 hours to occur.[57,58] The method of comparing the red blood cell count in the first and the last tubes of CSF has been shown to be unreliable.[47] CSF xanthochromia in association with negative findings on the CT scan is diagnostic of SAH. After the diagnosis is established, angiography should be performed to study the vascular anatomy and identify the source of hemorrhage in patients who are candidates for surgical intervention.

Most authorities agree that the presence of xanthochromia as measured by spectrophotometry, which is much more sensitive than visual inspection,[47] is the primary criterion for a diagnosis of SAH. However, because xanthochromia may require up to 12 hours to be present after the initial bleeding, patients with persistently bloody CSF without xanthochromia should undergo vascular imaging when the level of clinical suspicion of SAH is high.[47]

Up to 90% of patients with SAH have cardiac arrhythmias or electrocardiographic abnormalities suggestive of acute cardiac ischemia, which may lead to an erroneous primary cardiac diagnosis.[47] Typical electrocardiographic findings include ST-T wave changes, U waves, and QT prolongation.[59]

Treatment. The management of SAH is complex and includes initial resuscitation, stabilization, and emergent neurosurgical consultation. The goals of management are to treat the acute medical and neurologic complications, prevent recurrent hemorrhage, and forestall the ischemic complications of vasospasm.[60] Because of an altered level of consciousness, patients with SAH of grade III or higher are at risk for respiratory depression and hypercapnia, which can lead to further increases in intracranial pressure (ICP); therefore, these patients may require early endotracheal intubation. Blood pressure also must be closely monitored because of the risk of continued bleeding or recurrent hemorrhage. Nimodipine, a calcium channel blocker, should be started soon after a diagnosis of aneurysmal SAH is made, to lessen the likelihood of ischemic stroke. Because nimodipine may cause transient hypotension in some patients, hemodynamic monitoring is required during its administration. The recommended dose is 60 mg by mouth or nasogastric tube every 4 hours. Calcium antagonists reduce the risk of poor outcome and secondary ischemia after aneurysmal SAH.[61] A Cochrane review concluded that treatment with antifibrinolytics (e.g., aminocaproic acid) does not improve overall outcome because the reduction in the rate of rebleeding is offset by an increase in poor outcome caused by cerebral ischemia.[62]

Blood pressure management should be determined by the patient's clinical status with involvement of the treating neurosurgeon. A typical goal would be a systolic blood pressure less than 160 mm Hg or a mean arterial pressure less than 130 mm Hg unless vasospasm is present.[63]

Analgesics, including opioids, should be used for persistent headache. In patients who are nauseated or at risk for vomiting, antiemetics also must be administered. Agitated patients require sedation, and all patients should be placed at bedrest in a quiet and dark environment. Clinically evident seizures should be treated with anticonvulsants, but the prophylactic use of these drugs is controversial.[59] A majority of these patients require hemodynamic and ICP monitoring in an intensive care setting. The role of surgery (e.g., aneurysmal clipping) versus endovascular coil embolization is not yet fully defined.[64]

Brain Tumor

Principles of Disease. Headache is the most common presenting complaint with brain tumor, being reported by approximately 50% of the patients.[65] A majority of these patients are elderly and have a cerebral metastasis as a cause of their headache.[66] The most common causes of metastasis are lung and breast carcinoma, followed by malignant melanoma and carcinomas of the kidney and gastrointestinal tract.[54] Primary brain tumors are much less common and typically occur in adults younger than 50 years.

The headache can be caused by several mechanisms, including direct involvement and traction on pain-sensitive structures such as meninges or larger cerebral vessels, or may be a symptom of increased ICP. The pain patterns produced are highly variable, depending on the location of the mass and the structures involved.[54] Headaches often but not always are on the same side as the tumor. With increased ICP, the pain often is bifrontal or bioccipital and may be accompanied by vomiting. Brain tumors also may disrupt sleep, awakening the patient during the night. This effect may be related to increases in cerebral pressure that occur with recumbency and sleep-related carbon dioxide retention.[9] Rapidly growing tumors are more likely to be associated with headache.[67]

Clinical Presentation. The typical patient presents with complaints of a worsening headache that has been present for weeks to months. The headache may have been present initially only on awakening, gradually becoming continuous. The classic triad of brain tumor headache—sleep disturbances,

severe pain, and nausea and vomiting—is seen in only one third of patients.[68] Vomiting, when present, may be projectile and not preceded by nausea. If increased ICP is present, the headache often is bilateral and worsened by coughing, sneezing, bending, defecation, and sexual intercourse.[69] Although patients may not complain of focal neurologic deficits, abnormal findings are often found with neurologic testing.[70] Other presentations include seizures, personality changes, and cognitive difficulties.

Diagnostic Evaluation. The diagnosis of brain tumor is often suspected from the history and neurologic examination. Neuroimaging with CT or magnetic resonance imaging (MRI) is the most efficient way to confirm the diagnosis. Contrast enhancement on CT often improves the identification of the underlying mass lesion and helps differentiate it from other causes, including abscess, hematoma, and vascular malformation.[70]

Treatment. Management consists of urgent referral to neurosurgery and treatment of any acute complications, including increased ICP and seizures. For patients who present with symptoms suggestive of increased ICP (e.g., headache, nausea, vomiting, confusion, weakness), treatment with steroids has been shown to be beneficial. Dexamethasone is the high-potency steroid used most often to treat edema associated with brain tumors. It has several advantages over other glucocorticoids, including a longer half-life, reduced mineralocorticoid effect, and a lower associated incidence of cognitive and behavioral complications.[70] The exact dose of steroids necessary for each patient varies in accordance with histology, size, and location of the tumor and the amount of edema present. In general, most patients require between 8 and 16 mg of dexamethasone per day. An appropriate starting dose in the ED is 10 mg IV, followed by 4 mg every 6 hours.

Patients with a seizure (generalized or partial) should receive anticonvulsant therapy. Appropriate first-line agents include phenytoin, carbamazepine, and valproic acid. Empirical or prophylactic treatment does not appear to delay or prevent the onset of seizure activity and may expose the patient to unnecessary complications and toxicity.[70]

Giant Cell Arteritis

Principles of Disease. Giant cell arteritis, or temporal arteritis, is a systemic inflammatory process of the small and medium-sized arteries. Extracranial branches of the aortic arch and the ophthalmic vessels most commonly are involved, but the process may affect any artery in the body.[71] The mean age at onset is 71 years, and it is rare before age 50. Females are affected more commonly than males.

Clinical Presentation. Headache is the most common initial manifestation of giant cell arteritis and occurs in more than 70% of patients with this disorder.[72] The headache often is of 2 to 3 months' duration and can be continuous or intermittent and often worsens at night or on exposure to cold. The pain may be described as sharp, throbbing, boring, or aching and usually is localized to the temporal region but may occur anywhere in the head. The physical examination may reveal tenderness over the scalp in the area of the temporal artery, with exacerbation of the pain by wearing a hat or resting the head on a pillow. Patients also may experience jaw claudication secondary to vascular insufficiency of the masseter and temporalis muscles. Systemic signs and symptoms including fever, anorexia, and weight loss often are present. Approximately 40% of patients complain of pain in their large proximal joints, with symptoms referable to the neck, torso, and lower back. Typically, pain and stiffness are worse in the morning and lessen as the day goes on.[72] This condition, known as *polymyalgia rheumatica*, can occur in the absence of giant cell arteritis.

The most serious complication of giant cell arteritis is permanent visual loss, which eventually occurs in 36% of untreated cases.[73] Amaurosis fugax also can occur before permanent visual loss. Other complications include peripheral neuropathies, transient ischemic attacks, and stroke.

Diagnostic Evaluation. The physical examination may reveal abnormalities of the temporal arteries, including tenderness, reduced or absent pulsations, erythema, and nodularity or swelling, best detected by light palpation just anterior and slightly superior to the tragus of the ear.[74] Visual acuity and visual field testing and a thorough funduscopic examination also should be performed.

A majority of patients have a significant elevation of the erythrocyte sedimentation rate (ESR), usually to more than 50 mm/hour and often more than 100 mm/hour, although an elevated ESR is not specific for the disorder and a normal value does not rule out the diagnosis. Other abnormalities on laboratory studies include mild to moderate anemia, elevated C-reactive protein level, and liver function abnormalities.[54] An elevated platelet count (greater than 400,000/μL) may be a risk factor for permanent visual loss.[75] The diagnosis is confirmed by temporal artery biopsy. Because this is a patchy disease, multiple biopsy specimens of a long segment of the artery may need to be examined.

Treatment. Because of the risk of visual loss, giant cell arteritis constitutes a medical emergency, and treatment should be initiated promptly when the diagnosis is suspected. Steroids are the mainstay of therapy; the recommended initial dose of prednisone ranges from 60 to 120 mg/day. Symptomatic response usually occurs rapidly over days, although therapy must be continued for months, with close ESR monitoring.

Carotid and Vertebral Dissection

Principles of Disease. Carotid and vertebral dissections are more common than previously realized. They are the most frequent cause of stroke in persons younger than 45 years, accounting for approximately 20% of all cases in this age group.[76] Although dissections may occur spontaneously, careful history taking frequently identifies an association with sudden neck movement or trauma preceding the event.[76,77] Reported mechanisms include neck torsion, chiropractic manipulation, coughing, minor falls, and motor vehicle accidents. Early symptoms and signs are often subtle, and in the absence of neurologic findings delays in diagnosis are common. The median delay from symptom onset to diagnosis was seven days in one report.[77]

The pathologic lesion is intramural hemorrhage within the media of the arterial wall. The hematoma can be localized or extend circumferentially along the length of the vessel, resulting in partial or complete occlusion. Platelet aggregation and thrombus formation also occur, further compromising vessel patency or causing distal embolization. The timing of these events is variable, and a patient may experience symptoms of cerebral ischemia days to years after dissection.[78,79]

Clinical Presentation. The typical presentation of the patient with carotid or vertebral dissection is the abrupt onset of pain in the neck or face. Neurologic findings usually occur within the first few hours, but autopsy studies have shown that strokes may occur months later.[76]

Carotid Dissection. The classic triad of symptoms for carotid dissection includes unilateral headache, ipsilateral Horner's syndrome, and contralateral hemispheric findings that may include aphasia, neglect, visual disturbances, or hemiparesis. The headache is often severe and throbbing but may be subacute and similar to previous headaches. Acute severe retro-orbital pain in a previously healthy person with no history of cluster headaches is particularly suggestive of carotid dissection.[12]

Figure 101-2. Axial T_1-weighted magnetic resonance image demonstrating a crescent sign *(arrow)* in a patient with a left internal carotid artery dissection. (From Kidwell C: Dissection syndromes. Online article at eMedicine.com. Available at http://www.emedicine.com/neuro/topic99.htm, picture 2.)

Most patients eventually develop signs of cerebral ischemia. Warning symptoms include transient ischemic attacks, amaurosis fugax, episodic light-headedness, and syncope. Spontaneous dissection of the carotid artery has a favorable prognosis and recurrence is uncommon.[79] Factors associated with a worse prognosis include old age, occlusive disease on angiography, or stroke as the initial presenting symptom.[80]

Vertebral Dissection. Vertebral artery dissections are less common than carotid dissections. The classic presentation is that of a relatively young person with severe, unilateral posterior headache and neurologic findings.[81] The majority of patients develop a rapidly progressive neurologic deficit with symptoms of brainstem and cerebellar ischemia. Common findings include vertigo, severe vomiting, ataxia, diplopia, hemiparesis, unilateral facial weakness, and tinnitus.[82] Spontaneous vertebral artery dissection appears to be relatively rare. Approximately 10% of patients who develop a vertebral dissection die during the acute phase, secondary to massive stroke. For patients who survive, the prognosis is usually good.[77]

Diagnosis and Treatment. The diagnosis of dissection may prove to be difficult. A CT scan should be obtained first but is often normal in uncomplicated dissection. Further imaging studies, including MRI, magnetic resonance angiography, or catheter angiography are required to confirm the diagnosis.[76] Figure 101-2 shows an example of carotid artery dissection on MRI. Duplex imaging is of limited value.[76] Treatment is aimed at stroke prevention and usually includes early anticoagulation followed by antiplatelet therapy.

Identifying patients with dissection is challenging. More than 50% of patients see their physician for symptoms before admission. The emergency physician must consider the diagnosis in any young patient who presents with head or neck pain with focal neurologic findings.

Cerebral Venous Sinus Thrombosis

Principles of Disease. Thrombosis of the intracranial veins and sinuses is an uncommon cause of stroke, in contrast with arterial causes. Because of the significant associated morbidity, however, cerebral venous sinus thrombosis (CVST) is an important consideration in the differential diagnosis for headache in patients with suggestive signs and symptoms.

Numerous factors have been associated with the development of CVST, including genetic and hypercoagulable disorders, pregnancy and the puerperium, inflammatory systemic disorders including vasculitis and connective tissue disorders, head trauma, CNS infections, medications (e.g., oral contraceptives, steroids), and neurosurgical procedures (e.g., dural puncture, internal jugular vein infusions).

Clinical Presentation. The clinical presentation can be quite variable, depending on the location of the thrombosis. Common symptoms and signs include headache, nausea and vomiting, seizures, decreased level of consciousness that may progress to coma, and focal neurologic deficits. Papilledema is frequent with chronic cases but is less common with acute presentations. With cavernous sinus thrombosis, the clinical picture is dominated by ocular findings including orbital pain, proptosis, and paralysis of extraocular movements.

Diagnostic Evaluation. An elevated D-dimer level is present in approximately 90% of cases of CVST and, along with the clinical findings, can be used to determine the need for further diagnostic testing in individual patients.[83,84] The diagnosis of CVST is based on neuroimaging of the area of thrombosis. CT by itself may reveal nonspecific lesions such as an infarct, hemorrhage, or edema. The key to diagnosis is to image the venous system itself, and this is best accomplished by a combination of MRI to visualize the thrombosed vessel and magnetic resonance venography (MRV) to detect nonvisualization of the same vessel.[85] CT angiography/venography has also been used to visualize the cerebral venous system.

Treatment. Specific treatment of CVST includes anticoagulation to prevent propagation of the thrombosis as well as complications (e.g., pulmonary embolism). In patients whose clinical condition worsens despite anticoagulation, thrombolysis or thrombectomy may be considered in centers with expertise in interventional procedures. Seizures should be treated with anticonvulsants.

The prognosis with CVST is based on the underlying etiology and the development of complications. During the acute phase, the overall death and dependency rate is approximately 15%. Approximately two thirds of patients will recover without sequelae, however—a rate far superior to that among patients who suffer an arterial stroke.

Idiopathic Intracranial Hypertension

Principles of Disease. Idiopathic intracranial hypertension (IIH) also is known as "pseudotumor cerebri" or "benign intracranial hypertension." The term *idiopathic intracranial hypertension*, however, is preferred, because this disorder is not always benign and may have significant neurologic sequelae in affected persons.

IIH is a relatively common neurologic disease seen primarily in young obese women of childbearing age. Several predisposing factors have been identified, including the use of oral contraceptives, anabolic steroids, tetracyclines, and vitamin A.[86,87]

Pathophysiology and Clinical Features. The pathophysiology of this disease remains controversial, with increased brain water content and decreased CSF outflow considered the two major causative factors.[88] The most prominent symptom is generalized headache, which often is gradual in onset and of moderate intensity. No specific localizing pattern has been documented, although in some patients the headache is worsened by eye movement. It may awaken the patient from sleep and is exacerbated by bending forward and the Valsalva maneuver, both of which impede cerebral venous return.

Visual complaints are common, and patients may experience transient visual obscuration several times a day secondary to

BOX 101-4 ICHD-II CRITERIA FOR DIAGNOSIS OF IDIOPATHIC INTRACRANIAL HYPERTENSION

1. Alert patient with neurologic examination that either yields normal findings or demonstrates any of the following abnormalities:
   A. Papilledema
   B. Enlarged blind spot
   C. Visual field defect (progressive if untreated)
2. Increased CSF pressure (>200 mm H_2O in nonobese patients, >250 mm H_2O in obese patients) measured by lumbar puncture in the recumbent position or by epidural or intraventricular pressure monitoring
3. Normal CSF chemistry (low CSF protein acceptable) and cellularity
4. Intracranial disease (including venous sinus thrombosis) ruled out by appropriate investigations
5. No metabolic, toxic, or hormonal cause of intracranial hypertension

CSF, cerebrospinal fluid; ICHD-II, International Classification of Headache Disorders, 2nd ed.
Available at http://ihs-classification.org/en/.

ischemia of the visual pathways. These episodes can be followed by prolonged periods of visual loss, which can become permanent in up to 10% of patients.[89] Patients also may complain of nausea, vomiting, and dizziness. The physical examination will reveal papilledema and visual field defects, including an enlarged blind spot initially, followed by loss of peripheral vision. Occasionally, a sixth nerve palsy is noted.

Diagnosis. The diagnosis of IIH should not be made without neuroimaging and measurement of ICP. The diagnostic criteria are listed in Box 101-4.

Treatment. Predisposing factors (e.g., discontinuation of implicated medications) should be corrected. Symptomatic treatment often includes lowering ICP and managing the headache. Acetazolamide (a carbonic anhydrase inhibitor) can be used to decrease CSF production alone or with a loop diuretic such as furosemide. Steroids also have been used, although their mechanism of action is unclear. Prolonged therapy is problematic, and rebound IIH often occurs when doses are tapered. Repeated lumbar punctures can be attempted, but most patients find this approach objectionable. In patients with impending visual loss or incapacitating symptoms, placement of a ventricular shunt or optic nerve sheath fenestration may be indicated.

Post-traumatic Headache

Headache is the most common symptom after minor head injury. It often is part of a complex syndrome that can include dizziness, fatigue, insomnia, irritability, memory loss, and difficulty with concentration. The prevalence of headache with post-traumatic syndrome is not known, because most patients are not admitted for this condition. There are approximately 2 million closed head injuries per year, and post-traumatic headache (PTHA) occurs in an estimated 30 to 50% of patients with these injuries.[90] Acute PTHA develops hours to days after the injury and resolves within 3 to 6 months.[91] Chronic PTHA may last from several months to years and may mimic other forms of headache, including tension and migraine headaches. The presence of headache, dizziness, or nausea on initial presentation is strongly associated with the development of chronic PTHA.[92]

Patients in whom PTHA develops after minor head injuries have normal findings on neurologic examination and neuroimaging studies. The pathophysiologic mechanism for their symptoms is unclear and may have both anatomic and functional components. Most patients are more concerned about the cause of the headache rather than the headache itself.

Treatment is symptomatic. For acute PTHA, analgesics such as acetaminophen or NSAIDs are adequate for pain control. For chronic PTHA, treatment must be individualized depending on the type of headache and associated symptoms the patient is experiencing. Novel therapies, such as antidepressants and beta-blockers, may be effective in selected patients.

Acute Glaucoma

Patients with acute angle closure glaucoma present with sudden onset of severe pain localized to the affected eye that may radiate to the ear, sinuses, teeth, or forehead.[69] Visual symptoms, including blurriness, halos around lights, and scotomas, typically are present, and many patients also experience nausea and vomiting. The underlying pathophysiologic mechanism is congenital narrowing of the anterior chamber angle that, under certain conditions, closes, resulting in a significant rise in intraocular pressure (IOP). Episodes can be precipitated by entering a low-light environment such as a movie theater, with resultant pupillary dilatation, or by the use of medications such as mydriatics (e.g., for dilated ocular examination), sympathomimetics (e.g., pseudoephedrine), or agents with anticholinergic properties (e.g., antiemetics, antihistamines, antipsychotics, antidepressants).[86,93]

Physical examination reveals a red eye with a fixed, mid-dilated pupil, corneal clouding, and shallow anterior chamber. The diagnosis is confirmed by demonstrating markedly elevated IOP in the range of 60 to 90 mm Hg (normal is less than 21 mm Hg).

Treatment includes topical miotics, topical beta-blockers, oral carbonic anhydrase inhibitors (e.g., acetazolamide, 250 mg four times daily), intravenous osmotic agents (e.g., mannitol), and prompt referral to an ophthalmologist. The potential for diagnostic confusion between acute glaucoma, iritis, and cluster headache must be recognized. Although cluster headache may arise with pain, nausea, and a red eye, vision is not affected and the pupil generally is small and the eyelid is ptotic (from an oculosympathetic paresis).[94] Acute iritis also arises with a painful red eye, but only acute angle closure glaucoma is associated with markedly elevated IOP.

Post–Dural Puncture Headache

Principles of Disease and Pathophysiology. Headache is the most common complication of lumbar puncture, occurring in up to 40% of patients.[95] The incidence is highest in the 18- to 30-year age group, but this complication is uncommon in young children and in adults older than 60. Although the onset often is immediate, patients may not report symptoms for several days. In a majority of affected persons, the duration of headache is less than 5 days.[95,96]

The cause of post–dural puncture headache (PDPH) is not entirely clear. The most likely explanation is a persistent CSF leak that exceeds CSF production, resulting in CSF hypotension. If sufficient CSF is lost, the brain descends in the cranial vault when the patient assumes the upright position, leading to increased traction on the pain fibers.[97] Thus, the headache is characteristically positional and increases with the upright position and decreases with recumbency. The amount of time a patient remains recumbent after lumbar puncture does not appear to affect the incidence of headache.[12]

Certain factors have been implicated as causes of PDPH, including the size or diameter of the spinal needle, the orientation of the bevel during the procedure, and the amount of fluid withdrawn. Smaller-diameter needles cause less leakage, and it is postulated that inserting the needle with the bevel up (i.e., bevel pointing up when the patient is in the lateral position) minimizes damage to the dural fibers. Using atraumatic needles or pencil-point needles (e.g., Whitaker[98] or Sprotte[99]) also has been shown to reduce significantly the incidence of PDPH.[100,101]

Clinical Features. PDPH typically is bilateral, throbbing, and exacerbated by the upright position. Associated signs and symptoms include neck stiffness; nausea; vomiting; auditory disturbances, including tinnitus and hearing loss (hypoacusis); and ocular symptoms, including blurred vision and diplopia.[97]

Treatment. Most PDPHs resolve spontaneously within a few days with bedrest, adequate hydration, and mild analgesics. For persistent headaches, methylxanthine agents have been found to help some patients. Oral caffeine (300 mg every 4 to 6 hours), caffeine sodium benzoate (500 mg in 1 L of fluid), or theophylline (300 mg PO every 8 hours) may be effective.[95] For severe headaches lasting longer than 24 hours, an epidural blood patch (autologous blood clot) relieves the headache in the majority of patients.[101]

Intracranial Infection

Headache is common among patients with intracranial infections, including meningitis, brain abscess, encephalitis, and acquired immunodeficiency syndrome. The severity and type of headache vary depending on the specific infection.

With acute bacterial meningitis, the patient often has a severe bursting headache that rapidly increases in severity over a short period.[102] These patients typically have significant meningismus, with both Kernig's and Brudzinski's signs. With viral meningitis, patients also may complain of severe headache and nuchal rigidity, but the course is more indolent than with bacterial meningitis.

The severity of headache associated with encephalitis depends on the type of virus involved. For example, the headache is usually mild with mumps encephalitis. With herpes simplex infection, however, the headache is abrupt and severe and frequently is associated with confusion, fever, altered level of consciousness, seizures, and focal neurologic signs.

Patients with brain abscess often have headache as their presenting complaint.[103] As the infection progresses, vomiting, focal neurologic signs, and depressed level of consciousness typically develop.

Headache is a frequent complaint in patients with human immunodeficiency virus infection and can be caused by a number of conditions, including aseptic meningitis, toxoplasmosis, cryptococcal or tuberculous meningitis, and cytomegalovirus encephalitis.

In a majority of cerebral infections, the mechanism of head pain includes meningeal irritation and increased ICP. In addition, headache may be a general reaction to fever or the toxic products of the infecting agent.[104]

Hypertensive Headache

Contrary to common belief, hypertension is not an important cause of headache, and the occurrence of headache and hypertension in the same patient is often coincidental.[105] Whether some patients with mild to moderate hypertension suffer from headache caused by elevated blood pressure is uncertain. The rate of blood pressure increase is more important as a cause of headache than the absolute blood pressure value. Diastolic pressures lower than 130 mm Hg are rarely the cause of headache.[72]

Nonetheless, the association of headache with severe hypertension is well documented. Acute, severe headache is a prominent symptom of hypertensive encephalopathy, and most patients have blood pressure readings in the range of 250/150 mm Hg. Other conditions include headache secondary to toxic agents (e.g., drug-induced hypertension), pheochromocytoma, and eclampsia.

The headache of severe hypertension typically is diffuse and is worse when the patient awakes in the morning and gradually subsides over the course of the day.[105] Treatment is directed at lowering the blood pressure; in most cases, the headache is relieved within 24 hours. In patients with hypertensive encephalopathy, the headache may persist for days until brain edema has resolved.

Cervicogenic Headache

Cervicogenic headache refers to headache originating from disorders of the neck. Diagnosis is based on the presence of one of the following three distinct sets of symptoms[106]:

1. Unilateral headache triggered by movements of the head or neck or certain head positions
2. Unilateral headache triggered by pressure on the neck
3. Unilateral headache spreading to the neck or possibly the ipsilateral shoulder or arm

Many of these headaches are reported after a whiplash injury. Even though neck structures play a primary role in the pathophysiology of some headaches, clinical patterns indicating a neck-headache relationship have not been adequately defined.

Medication-Induced Headache

Medication use, abuse, or withdrawal can be a cause of headache, and the term *medication-induced headache* is used to describe these conditions. Medication-induced headache is underdiagnosed and often difficult to manage.[107] Although not well understood, it tends to occur in patients with a primary headache disorder (e.g., migraine, tension-type) who use immediate-relief medications, often in excessive quantities.[108] Medications that have been implicated include NSAIDs, aspirin or acetylsalicylic acid (ASA), acetaminophen, barbiturate-analgesic combinations plus caffeine with or without codeine, opioids, caffeine, and ergotamine. A key factor in medication overuse headache is preemptive use of drugs, in anticipation of—rather than for—headache.[33] Women are affected more commonly than men, and the most frequently affected age group is that of persons between 30 and 40 years.[109] The headache itself is variable and may be accompanied by asthenia, nausea, anxiety, depression, and difficulty with concentration. Typically, it is worse on awakening in the morning and after physical exertion.

The symptomatic medication that leads to the development of this disorder initially provides some pain relief to the patient, but over time tolerance develops, and larger doses are required to obtain symptomatic improvement.[109]

Treatment typically requires complete withdrawal of the medication being overused, to achieve long-term results. In addition, these patients require a comprehensive education and follow-up program with pharmacologic, dietary, and behavioral components.[109]

Trigeminal Neuralgia

Trigeminal neuralgia is a painful unilateral affliction of the face, characterized by brief electric shock–like (lancinating) pains limited to the distribution of one or more divisions of the trigeminal nerve. Pain is commonly evoked by trivial stimuli (e.g., washing, shaving, smoking, talking, brushing the teeth) but also may occur spontaneously.[110] Individual attacks are brief, lasting a few seconds to less than 2 minutes, and are stereotypic in the individual patient. The lightning-like pains and unilateral grimaces characteristic of trigeminal neuralgia led to the designation of the term *tic douloureux*.[111] The diagnosis is straightforward in most patients on the basis of clinical criteria. However, because these symptoms also can be caused by an underlying mass lesion, CT or MRI is indicated in previously undiagnosed patients and when sensory loss or motor dysfunction is present.

Several drugs have been effective in treating trigeminal neuralgia, including carbamazepine, phenytoin, and baclofen; however, approximately 30% of patients fail to respond to medical therapy.[111] In these patients, surgical management, by alcohol or glycerol injection or microvascular decompression, may be indicated.[110,112]

Cough and Exertional Headache

In some patients, severe headache can be provoked by rapid increase in intra-abdominal pressure such as coughing, sneezing, laughing, heavy lifting or exertion, and the Valsalva maneuver. The pain starts within a few seconds of the precipitant and typically is brief when associated with cough but can last as long as 24 hours when associated with exertion. The headache is bilateral and throbbing in nature and in a majority of patients resolves spontaneously without persistent neurologic symptoms (e.g., neck stiffness or photophobia). In some patients, the headache may be secondary to structural lesions, especially in the posterior fossa[113]; therefore, all previously undiagnosed patients require CT, or preferably MRI, followed by lumbar puncture to rule out intracranial disease including SAH. For patients with recurrent benign exertional headache, treatment includes avoidance of the underlying triggering mechanism and use of analgesics as necessary. For patients with exertional headache, NSAIDs including indomethacin have been effective.[114]

Coital Headache

Coital cephalgia is a recurrent, benign headache associated with sexual activity and is more common in men than in women. Different types have been described, including headaches that occur before, during, or immediately after orgasm. They typically are occipital in location and may increase in severity with mounting sexual excitement. Their duration can be from minutes to hours. Occasionally, some patients experience a sudden, explosive headache that occurs during orgasm. In these patients, SAH should be ruled out.[113–115]

High-Altitude Headache

Headache is one of the cardinal manifestations of acute mountain sickness and can occur at altitudes higher than 5000 feet above sea level in unacclimatized persons. The headache is throbbing in nature, located in the temporal or occipital areas, and probably is caused by a mild increase in ICP secondary to brain swelling.[116] It is worse at night or in the early morning and exacerbated by the Valsalva maneuver or bending forward.[117] Other findings associated with high-altitude illness include fatigue, nausea, vomiting, dizziness, insomnia, and an altered mental status. Pulmonary edema and cerebral edema develop in severe cases. The treatment for these conditions includes supplemental oxygen and descent to a lower altitude.

KEY CONCEPTS

- Headache is a common presenting complaint in the ED. The goal of evaluation in this setting is to distinguish between benign primary headache disorders and the more serious and potentially life-threatening secondary causes of headache.
- A majority of patients do not have abnormal neurologic findings; therefore, the key to a successful diagnosis is a thorough and systematic history.
- Patients with the following headache presentations are at risk for serious underlying disease: sudden explosive headache; first or "worst-ever" headache; new-onset headache after age 50 years; headache associated with papilledema, alteration in or loss of consciousness, or focal neurologic symptoms; headache after head trauma; subacute headache with increasing frequency or severity; headache associated with fever, cancer, or immunosuppression; and headache triggered by exertion, sexual activity, or Valsalva maneuver.[118]
- The need for diagnostic studies is dictated by the suspected secondary cause of headache.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 103

Brain and Cranial Nerve Disorders

Brian A. Stettler

This chapter discusses cranial nerve problems, cerebral venous thrombosis, and multiple sclerosis—neurologic disorders that often provide significant diagnostic and therapeutic challenges in management in the emergency department (ED) setting (Table 103-1).

TRIGEMINAL NEURALGIA

Perspective

Trigeminal neuralgia, or *tic douloureux*, is a syndrome featuring painful paroxysms in one or more distributions of the trigeminal nerve. Trigeminal neuralgia is relatively uncommon, with an annual incidence of 4 to 13 cases per 100,000 population.[1,2] It is more common in women than in men, with a female-to-male ratio of 1.7:1. Affected persons typically are between 50 and 69 years of age, and symptoms occur more frequently on the right side of the face.[3]

Pathophysiology

Trigeminal neuralgia is an idiopathic disorder, although significant evidence points to vascular compression of the trigeminal nerve root in many cases. This compression commonly is caused by a tortuous arterial or venous loop in the posterior fossa, an arteriovenous malformation, or rarely a tumor. In surgical case series, vascular compression of the trigeminal nerve root is found in 80 to 90% of cases.[4,5] Of note, however, structural lesions are not found in all patients with trigeminal neuralgia.[6]

Clinical Features

Trigeminal neuralgia manifests with unilateral facial pain, typically characterized as lancinating paroxysms of pain in the lips, teeth, gums, or chin. The pain of trigeminal neuralgia commonly is associated with physical triggers such as chewing, brushing the teeth, shaving, washing or touching the affected area of the face, swallowing, or exposure to hot or cold temperature in the affected area. The maxillary and mandibular divisions of the trigeminal nerve are most commonly involved; rarely, the ophthalmic division alone is involved. Patients tend to experience the pain in clustered episodes that last a few seconds to several minutes. The attacks can occur during the day or night but rarely arise during sleep.[6,7]

Diagnostic Strategies

A careful history and physical examination should be performed to rule out other painful facial conditions including odontogenic infections, sinus disease, otitis media, acute glaucoma, temporomandibular joint disease, and herpes zoster. Patients who lack local pathologic findings to explain the painful syndrome require a very careful neurologic examination. The presence of a neurologic deficit should prompt suspicion of a structural lesion, such as aneurysm, tumor, or other intracranial lesion such as from multiple sclerosis (MS). Of note, 2 to 4% of patients with trigeminal neuralgia also have MS.[8] Patients with normal findings on the head and neck examination and no neurologic deficits who have episodic, unilateral facial pain associated with nonpainful triggers are likely to have trigeminal neuralgia.

Management

Since the 1960s the medical treatment of choice for trigeminal neuralgia has been use of the anticonvulsant carbamazepine. The purported effectiveness of this treatment is, however, based on uncontrolled studies, and the mechanism of action of anticonvulsant therapy for trigeminal neuralgia is unclear. The true efficacy of medical therapy is difficult to assess owing to a very high rate of spontaneous remission. Nonetheless, carbamazepine appears to be an effective and well-tolerated agent for treatment of trigeminal neuralgia. The initial dosage of carbamazepine is 100 mg twice daily; this dose is then increased to three times daily after one week. The dose may be increased by 100 mg per day, up to a maximum of 1200 mg per day. A complete blood count and liver function studies should be performed periodically in these patients to monitor for hematologic and hepatic side effects. Additional agents that have been used for treatment of trigeminal neuralgia include phenytoin, baclofen, valproate sodium, lamotrigine, and gabapentin. None of these drugs have been shown to be more effective than carbamazepine.[7]

Surgical management has been a theraputic option since the 1950s. Surgical procedures include both peripheral approaches and central procedures. Peripheral strategies include medication injection and cryotherapy techniques designed to temporarily block, or permanently ablate, branches of the peripheral trigeminal nerve. Although these procedures are relatively effective initially, recurrence is common. Repeated nerve

Table 103-1 The Cranial Nerves: Normal Function and Pathologic Considerations

CRANIAL NERVE	CLINICAL FUNCTION RELEVANT TO EMERGENCY MEDICINE	PATHOLOGIC FEATURES	POSSIBLE CAUSES
Cranial nerve I: Olfactory nerve	Sense of smell	Unilateral anosmia	*Trauma*: Skull fracture or shear injury interrupting olfactory fibers traversing the cribriform plate *Tumor*: Frontal lobe masses compressing the nerve
Cranial nerve II: Optic nerve	Vision	Unilateral vision loss	*Trauma*: Traumatic optic neuropathy *Tumor*: Orbital compressive lesion *Inflammatory*: Optic neuritis (MS) *Ischemic*: Ischemic optic neuropathy
Cranial nerve III: Oculomotor nerve	Extraoculomotor function via motor fibers to levator palpebrae, superior rectus, medial rectus, inferior rectus, inferior oblique muscles Pupillary constriction via parasympathetic fibers to constrictor pupillae and ciliary muscles	Ptosis caused by loss of levator palpebrae function Eye deviated laterally and down Diplopia Dilated, nonreactive pupil Loss of accommodation	*Trauma*: Herniation of the temporal lobe through the tentorial opening causing compression and stretch injury to the nerve *Ischemic*: Especially in diabetes Microvascular ischemic injury to nerve causes extraocular muscle paralysis but usually is papillary-sparing (often painful) *Vascular*: Intracranial aneurysms may press on the nerve, leading to dysfunction Myasthenia gravis can lead to atraumatic ocular muscle palsy
Cranial nerve IV: Trochlear nerve	Motor supply to the superior oblique muscle	Inability to move eye downward and laterally Diplopia Patients tilt head toward unaffected eye to overcome inward rotation of affected eye	Trauma is the most common cause of nerve dysfunction
Cranial nerve V: Trigeminal nerve	Motor supply to muscles of mastication and to tensor tympani Sensory to face, scalp, oral cavity (including tongue and teeth)	Partial facial anesthesia Episodic, lancinating facial pain associated with benign triggers such as chewing, brushing teeth, light touch	*Trauma*: Facial bone fracture may injure one section, leading to area of facial anesthesia Tic douloureux
Cranial nerve VI: Abducens nerve	Motor supply to the lateral rectus muscle	Inability to move affected eye laterally Diplopia on attempting lateral gaze	*Tumor*: Lesions in the cerebellopontine angle Any lesion, vascular or otherwise, in the cavernous sinus may compress nerve *Elevated intracranial pressure (ICP)*: Because of its position and long intracranial length, increased ICP from any cause may lead to injury and dysfunction of the nerve
Cranial nerve VII: Facial nerve	Motor supply to muscles of facial expression Parasympathetic stimulation of the lacrimal, submandibular, and sublingual glands Sensation to the ear canal and tympanic membrane	*Hemifacial paresis*: *Lower motor neuron lesion* leaves entire side of face paralyzed *Upper motor neuron lesion* leaves forehead musculature functioning Abnormal taste Sensory deficit around ear Intolerance to sudden loud noises	*Lower motor neuron*: *Infection* (viral): The likely cause of Bell's palsy *Lyme disease*: The most common cause of bilateral cranial nerve VII palsy in areas where Lyme disease is endemic Bacterial infection extending from otitis media *Upper motor neuron*: Stroke, tumor
Cranial nerve VIII: Vestibulocochlear nerve	Hearing and balance	Unilateral hearing loss Tinnitus Vertigo, unsteadiness	*Tumors*: Acoustic neuroma Mimics Ménière's disease, perilymphatic fistula

Table 103-1 The Cranial Nerves: Normal Function and Pathologic Considerations—cont'd

CRANIAL NERVE	CLINICAL FUNCTION RELEVANT TO EMERGENCY MEDICINE	PATHOLOGIC FEATURES	POSSIBLE CAUSES
Cranial nerve IX: Glossopharyngeal nerve	General sensation to posterior third of tongue Taste for posterior third of tongue Motor supply to the stylopharyngeus	Clinical pathology referable to the nerve in isolation is very rare Occasionally painful paroxysms beginning in the throat and radiating down the side of the neck in front of the ear but behind the mandible	Brainstem lesion Glossopharyngeal neuralgia
Cranial nerve X: Vagus nerve	Motor to striated muscles and muscles of the pharynx, larynx, and tensor (veli) palatini Motor to smooth muscles and glands of the pharynx, larynx, thoracic and abdominal viscera Sensory from larynx, trachea, esophagus, thoracic and abdominal viscera	*Unilateral loss of palatal elevation*: Patients complain that on drinking liquids, the fluid refluxes through the nose *Unilateral vocal cord paralysis*: Hoarse voice	Brainstem lesion Injury to the recurrent laryngeal nerve during surgery
Cranial nerve XI: Spinal accessory nerve	Motor supply to the sternocleidomastoid and trapezius muscles	Downward and lateral rotation of the scapula and shoulder drop	Trauma to the nerve
Cranial nerve XII: Hypoglossal nerve	Motor supply to the intrinsic and extrinsic muscles of the tongue	*Tongue deviations*: *Upper motor neuron lesion* causes the tongue to deviate toward the opposite side *Lower motor neuron lesion* causes the tongue to deviate toward the side of the lesion, and the affected side atrophies over time	Stroke or tumor can cause upper motor neuron lesion Amyotrophic lateral sclerosis (ALS) can cause bilateral lower motor neuron lesion with atrophy Metastatic disease to the skull base may involve the nerve

blocks are not recommended owing to a high risk of permanent facial anesthesia.

Central procedures can be divided into percutaneous approaches and open approaches. Percutaneous destruction of the trigeminal ganglion can be done by means of radiofrequency ablation, thermal ablation, glycerol injection, or balloon microcompression. These procedures carry the risk of corneal anesthesia, oculomotor paresis, or masticatory weakness.[9]

Open surgical management is the surgical option of choice in most treatment centers. Open surgical procedures include microvascular decompression of the nerve with or without partial ablation. Although the open microvascular decompression procedure has proved to be very effective, with pain relief achieved in 80 to 95% of patients, the surgery is associated with the risk of significant complications, including hearing loss, facial anesthesia, cerebrospinal fluid leak, brainstem or cerebellar injury, headaches, meningitis, and death.[10,11] Gamma knife radiosurgery, a minimally invasive, precision-directed stereotactic radiosurgery, also has been associated with good outcomes. This highly specialized technique requires extremely sophisticated stereotactic radiofrequency equipment and is available only in specialized centers.[12,13]

Disposition

Patients with suspected trigeminal neuralgia should be referred for specialty evaluation. Patients with a neurologic deficit require urgent imaging studies, typically magnetic resonance imaging (MRI), to rule out a mass or vascular abnormality.

KEY CONCEPTS

- Patients with unilateral, intermittent, lancinating facial pain without abnormalities on physical examination are likely to have trigeminal neuralgia.
- Carbamazepine is the first-line agent for medical treatment.
- Patients who do not tolerate or whose pain is refractory to medical management may be candidates for microvascular decompression or ablation.

FACIAL NERVE PARALYSIS

Perspective

The acute onset of facial nerve paralysis often will prompt an ED visit, when early diagnosis and therapy can improve the patient's chance for recovery of function of the facial nerve. Facial nerve paralysis of acute onset affects approximately 20 to 25 persons per 100,000 population per year, without geographic, gender, or race predilection.[14,15]

Principles of Disease

The facial nerve innervates the muscles of facial expression and the muscles of the scalp and external ear, in addition to the buccinator, platysma, stapedius, stylohyoid, and posterior belly of the digastric muscles. The sensory portion of the nerve supplies the anterior two thirds of the tongue with taste and

sensation to portions of the external auditory meatus, soft palate, and adjacent pharynx. The parasympathetic portion supplies secretomotor fibers for the submandibular, sublingual, lacrimal, nasal, and palatine glands.[16]

The nerve originates from the pontomedullary junction of the brainstem. The nerve enters the internal auditory meatus with cranial nerve VIII. Within the temporal bone the facial nerve has four major branches: the greater and lesser superficial petrosal nerves, the nerve to the stapedius muscle, and the chorda tympani. The facial nerve exits the temporal bone at the stylomastoid foramen. The nerve then enters the parotid gland, where it divides to supply the muscles of facial expression.[16,17]

Pathophysiology

Although a complete list of possibilities in the differential diagnosis for facial nerve paralysis would be a long one, the causes pertinent to emergency medicine can be grouped into three specific categories: infectious, traumatic, and neoplastic.

Infection

Bell's Palsy

Bell's palsy, also commonly called *idiopathic facial paralysis*, has long been postulated to have a viral cause. This disease entity is characterized by an abrupt onset of a lower motor neuron paresis that can progress over 1 to 7 days to complete paralysis. A prodromal illness is described by 60% of patients. Symptoms and signs frequently associated with the facial paresis include ear pain, a perception of sensory change on the involved side of the face, decreased tearing, an overflow of tears on the cheek (epiphora), abnormally acute hearing (hyperacusis), and an impairment or perversion of taste (dysgeusia).[18]

Treatment approaches can be medical or surgical. The primary medical therapies for Bell's palsy center on reducing inflammatory changes to the nerve with corticosteroids and treating the presumed viral cause. If these therapies are unsuccessful then surgical decompression may be considered.

The use of corticosteroids for Bell's palsy has been controversial. The rationale for this application of steroid therapy is that edema of the nerve, confined within the facial canal, is thought to cause or contribute to the nerve injury. On the basis of this theory, most experts currently recommend a course of prednisone with an initial dose of 1 mg/kg per day for 7 to 10 days, with or without a short taper.[14,17,19,20] The most definitive randomized, double-blind, placebo-controlled trial involving 496 patients showed an improvement in complete recovery of facial nerve function at 3 months from 64% with placebo to 83% with the use of prednisolone in a dose of 25 mg by mouth twice daily.[21] Therapy should be started as soon as possible, ideally within the first 24 hours, but is still recommended for patients without contraindications who seek treatment within 1 week of symptom onset.[19]

A number of publications have advanced the belief that Bell's palsy may be caused by herpesvirus infection. One study demonstrated herpes simplex virus type 1 DNA in the endoneural tissue of 11 of 14 patients with Bell's palsy but not in that of control subjects.[22] In a trial of prednisone and acyclovir in 99 patients, patients treated with prednisone and acyclovir had a more favorable recovery than that observed in patients receiving prednisone alone.[23] A study of 296 patients with Bell's palsy treated with valacyclovir or placebo in addition to a fixed dose of prednisolone found significant benefit to the addition of valacyclovir, particularly in the setting of severe palsy or in those treated within 24 hours of symptom onset.[24] Other studies have found conflicting results. Despite a lack of overwhelming evidence, the addition of an antiviral agent should be considered in the treatment of Bell's palsy, especially with severe loss of function. The most commonly recommended antiviral regimens include valacyclovir, 1000 mg orally two times daily for 10 days. Valacyclovir and famciclovir have better oral absorption, are better tolerated, and are dosed less frequently, resulting in higher compliance. Accordingly, they have been recommended as alternatives to acyclovir.[17,19,20,22,25] As with steroid therapy, although earlier treatment is preferred, treatment should be considered for patients presenting within 1 week of symptom onset.

Ramsay Hunt Syndrome

Ramsay Hunt syndrome (herpes zoster oticus) is characterized by unilateral facial paralysis, a herpetiform vesicular eruption, and vestibulocochlear dysfunction. The vesicular eruption may occur on the pinna, external auditory canal, tympanic membrane, soft palate, oral cavity, face, and neck as far down as the shoulder. The pain is considerably more severe than that associated with Bell's palsy, and it frequently is out of proportion to physical findings. In addition, outcomes are worse than with Bell's palsy, with a lower incidence of complete facial recovery and the possibility of sensorineural hearing loss. Therapy is similar to that for Bell's palsy. Both prednisone and antiviral therapy for 7 to 10 days are advocated.[17,26,27]

Lyme Disease

Lyme disease is the most frequent vector-borne infection in the United States. It is caused by the spirochete *Borrelia burgdorferi* and is spread by the bite of *Ixodes* genus ticks. Neurologic manifestations can arise in any phase of the disease, and the incidence of facial palsy in patients with neurologic involvement is 35 to 51%. In regions in which Lyme disease is endemic, it has been shown to be the leading cause of facial paralysis in children, responsible for one half of all pediatric cases of facial nerve paralysis.[28,29]

Bilateral facial nerve paralysis is rare but can occur with systemic infections. The two diseases most commonly associated with bilateral simultaneous onset of facial paralysis are Lyme disease and infectious mononucleosis. Bilateral facial paralysis should be considered to be a manifestation of Lyme disease until further testing excludes this diagnosis.[20,28-30] The evaluation and treatment of Lyme disease are discussed in Chapter 132.

Bacterial Infections

Facial paralysis can be caused by acute bacterial infections of the middle ear, mastoid, or external auditory canal. In the preantibiotic era, facial paralysis was associated with acute otitis media in approximately 2% of cases; today, however, it occurs in only 0.2% of cases. Treatment consists of intravenous antibiotics and myringotomy for decompression. Malignant otitis externa can be associated with facial paralysis. This disease entity is most commonly seen in immunocompromised patients and usually is caused by *Pseudomonas* infection. Treatment involves prolonged intravenous antipseudomonal antibiotic therapy and may require surgical débridement.[20,31]

Trauma

In patients with head trauma, the facial nerve is the most commonly injured cranial nerve. The cause generally is a temporal bone fracture with nerve transection. Surgical exploration is warranted if there is firm evidence that the nerve has been transected, indicated by a sudden onset of complete unilateral facial paralysis, loss of electrical activity, and evidence of a displaced fracture involving the facial canal.

Neoplasm

Tumors of the facial nerve itself, or tumors anywhere along the course of the facial nerve that invade or compress the nerve, may lead to facial paralysis. Typically the course is progressive over at least 3 weeks. A sudden onset of paralysis, however, does not rule out an underlying tumor, because facial paralysis secondary to a neoplasm is of sudden onset in approximately 25% of cases.[32] A neoplastic cause should be suspected in patients who suffer from recurrent ipsilateral facial paralysis, significant pain, prolonged symptoms, or any other concomitant cranial nerve abnormality.

Clinical Features and Differential Considerations

The medical history should focus on onset of the paralysis, concentrating on timing and rapidity of onset and looking for any associated signs and symptoms. A rapid onset of facial paralysis with dysgeusia and hyperacusis preceded by a viral prodrome is suggestive of Bell's palsy. A history of recurrent ipsilateral paralysis or slow progression of symptoms is more characteristic for a tumor. Associated cranial nerve abnormalities, although occasionally seen with Bell's palsy, also point to the possibility of a tumor or ischemic insult. The Ramsay Hunt syndrome causes significant pain and a vesicular rash, although the rash may follow the facial paresis by a few days. Significant anatomic abnormalities on visual or otoscopic inspection of the ipsilateral ear will be found with bacterial otitis media and otitis externa. Finally, systemic symptoms or bilateral facial paresis, especially in endemic areas, should raise the possibility of Lyme disease.

Diagnostic Strategies

The diagnostic workup of acute facial nerve paresis is based on whether the clinical picture is suggestive of a disease process other than Bell's palsy. If the clinical history is classic for Bell's palsy, then no imaging or laboratory studies are required. Of note, any history of possible exposure warrants serologic evaluation for Lyme disease. Although outpatient testing including electroneurography may ultimately be performed, this usually is not part of the initial evaluation.

The physical examination finding of a "central" seventh nerve paralysis (upper face–sparing) should prompt imaging with computed tomography (CT) or MRI, and consideration should be given to the possibility of an acute stroke or other hemispheric lesion. History or physical examination findings suggestive of a possible tumor require imaging to rule out a neoplasm. The study of choice will depend on the institution and preferences of the consultant.

Disposition

The vast majority of patients who have a seventh nerve paralysis will have a clinical diagnosis of Bell's palsy and may be discharged with referral for short-term follow-up. Patients with a possible hemispheric process such as stroke or tumor should be hospitalized for further evaluation. Patients suspected of having Lyme disease require immediate initiation of appropriate antibiotic therapy.

In patients with a peripheral facial nerve paralysis, the ipsilateral eye should be patched, and consideration should be given to ophthalmologic follow-up, because there is a high rate of corneal abrasions and corneal dryness associated with the inability to properly blink or completely close the eye.

KEY CONCEPTS

- Recent literature highlights significant potential benefit for patients with clinical evidence of Bell's palsy when they are treated early in the course with corticosteroids. The additional benefit of adding antiviral medication is controversial, but this treatment probably is warranted in patients with severe loss of function.
- Slowly progressive facial paralysis is suggestive of a neoplasm. Recurrent unilateral paralysis may occur with Bell's palsy but frequently (30%) is seen in patients with tumor.
- Simultaneous bilateral facial paralysis is suggestive of Lyme disease, which must be considered as a possible cause, especially in endemic regions.
- Patients who have facial muscle paresis with intact forehead movement should be considered to have an upper motor neuron lesion until the diagnostic investigation proves otherwise.

VESTIBULAR SCHWANNOMA

Perspective

Vestibular schwannoma, formally referred to as *acoustic neuroma*, is a rare but important cause of sensorineural hearing loss. The annual incidence of VS is 1 case per 100,000 population, with a mean age at the time of detection of 46 to 58 years.[33] The female-to-male ratio is 1.5:1. Vestibular schwannoma is very rarely bilateral, occurring in this form in approximately 5% of cases and generally associated with type II neurofibromatosis. Although histologically benign, vestibular schwannoma can cause neurologic damage by direct compression on the eighth cranial nerve and the other structures in the cerebellopontine angle.[34]

Principles of Disease

Vestibular schwannoma arises from the Schwann cells covering the vestibular branch of the eighth cranial nerve as it passes through the internal auditory canal. The tumor may compress the cochlear (acoustic) branch of the eighth cranial nerve, causing hearing loss, tinnitus, and dysequilibrium. Continued growth of the tumor may result in compression of structures in the cerebellopontine angle, where the facial and trigeminal nerves may be compressed and damaged. Larger tumors may further encroach upon the brainstem and if large enough may compress the fourth ventricle, ultimately resulting in signs of increased intracranial pressure (ICP).[35]

Clinical Features

Asymmetrical sensorineural hearing loss is the hallmark of vestibular schwannoma. Up to 15% of patients with this tumor, however, will have normal results on an audiogram. These patients typically have symptoms such as unilateral tinnitus, imbalance, headache, fullness in the ear, otalgia, or facial nerve weakness. Thus, patients with asymmetrical symptoms should be further evaluated for vestibular schwannoma even with normal findings on the audiogram.[36]

Vestibular schwannomas are extremely slow-growing tumors, averaging an approximately 1-mm increase per year, although many do not grow at all on serial examinations.[37] Symptom onset is therefore generally quite gradual. In one series of 126 cases, the average time from symptom onset to discovery of a vestibular schwannoma was approximately 4 years.[38]

Diagnostic Strategies

When vestibular schwannoma is suspected, the patient should be evaluated with an audiogram or a gadolinium-enhanced MRI. This imaging technique is extremely sensitive and has led to earlier diagnosis and a decrease in mean size at detection of vestibular schwannoma. CT lacks the necessary sensitivity in the posterior cranial fossa to reliably rule out the presence of vestibular schwannoma. The smaller the tumor at the time of diagnosis, the more options there are for therapy and the better the potential prognosis.[34]

Differential Considerations

A majority of disease entities included in the differential diagnosis for acoustic neuroma cause symmetrical sensorineural hearing loss. Asymmetrical sensorineural hearing loss has few causes other than vestibular schwannoma. Ménière's disease may present a diagnostic dilemma because it can be asymmetrical. Ménière's disease may be differentiated from vestibular schwannoma in that the tinnitus of Ménière's disease usually is intermittent, whereas the tinnitus of vestibular schwannoma typically is continuous. In addition, patients with Ménière's disease typically describe true vertigo, whereas patients with a vestibular schwannoma are more likely to describe imbalance or dysequilibrium.

Vestibular schwannomas account for 80% of all cerebellopontine angle tumors. Among all other lesions, meningioma is the most common. Meningiomas more frequently cause symptoms of facial palsy or trigeminal nerve abnormality. Of note, however, considerable similarity between the clinical picture of a meningioma and that of vestibular schwannoma in the cerebellopontine angle has been described.[39]

Management

Vestibular schwannoma may be removed surgically or ablated with stereotactic radiation. In general, tumors larger than 3 cm are recommended for microsurgery, because radiation treatments, such as with the Gamma Knife or linear accelerator, are less effective for local control and growth arrest in larger masses. Smaller tumors are amenable to use of stereotactic radiation, which may have greater salvage rates of facial nerve function and hearing. Stereotactic radiation therapy generally has good long-term outcomes of local growth arrest, with nerve salvage approaching 90% or greater. Injuries to the trigeminal, facial, and acoustic nerves, and to the cerebellum, are possible complications of both procedures. In patients who are minimally symptomatic with small tumors, serial monitoring with MRI is a viable nonsurgical option. All patients should be evaluated by a specialist in the evaluation and treatment of vestibular schwannoma, because smaller tumor size at detection is associated with a better long-term outcome.[33,37]

Disposition

Patients with suspected acoustic neuroma should be referred for an audiogram or MRI and evaluation by a specialist in either otolaryngology or neurosurgery.

■ DIABETIC CRANIAL MONONEUROPATHY

Perspective

Cranial mononeuropathies occur uncommonly, usually are a complication of diabetes, and most often affect the extraocular muscles. The oculomotor nerve is most commonly affected, followed in order by the trochlear and abducens nerves. In one large series in Japan, the incidence of cranial nerve palsies was 1.0% among diabetics and 0.1% among nondiabetics.[40,41] Whereas ophthalmoplegia appears to be closely related to diabetes, facial palsy is less strongly correlated with this disease.[40]

KEY CONCEPTS

- The onset of unilateral auditory symptoms, especially sensorineural hearing loss, requires evaluation and referral to an ear, nose, and throat specialist.
- Neurologic symptoms of lower cranial nerve dysfunction, ataxia, or raised ICP may be caused by a benign tumor of the cerebellopontine angle.
- The smaller the tumor at diagnosis, the better the long-term outcome with definitive treatment.

Principles of Disease

The pathologic basis of diabetic mononeuropathy appears to be ischemia of the affected cranial nerve caused by occlusion of an intraneural nutrient artery serving the nerve. This occlusion leads to injury located primarily in the center of the nerve, because the core fibers are more dependent on the supply from such nutrient arteries. The peripheral fibers are less affected because they also are supplied by collateral vessels. In the oculomotor nerve, the preservation of the circumferentially located parasympathetic fibers explains the pupillary sparing that usually is found in this syndrome. In two studies, the microvascular changes in the intraneural arteries that lead to occlusion were noted in diabetic patients but absent in nondiabetics.[42,43]

Clinical Features

Patients typically describe acute onset of unilateral retro-ocular and supraorbital pain, diplopia, and ptosis.[41] The physical manifestations of a third cranial nerve palsy include the inability to move the eye superiorly and medially, accompanied by ptosis. The pupillary light reflex usually is present. Although a less common finding, the fourth and sixth cranial nerves may be affected. Patients with a fourth cranial nerve palsy are unable to move the eye inferolaterally, and those with a sixth cranial nerve palsy are unable to move the eye laterally. Because of the long intracranial course of the sixth nerve, a patient with an isolated sixth nerve palsy should be evaluated for an intracranial lesion or increased ICP.[44]

Differential Considerations

Evaluating cranial nerve dysfunction requires a thorough history and physical examination and cranial imaging, usually with MRI. Diabetic mononeuropathy should be considered a diagnosis of exclusion, with considerations in the differential diagnosis including trauma, tumor, vertebrobasilar ischemia, aneurysm, and hemorrhage into the brainstem.[45]

Management

Treatment consists of patching the affected eye and administration of analgesics and antiplatelet therapy. The prognosis is good. If the neuropathy does not begin to resolve within 3 to 6 months, or if more than one nerve is affected, another cause should be sought. Complete resolution is expected within the first year. Antioxidant preparations, including α-lipoic acid, have been used therapeutically and have not shown harm, but

such agents have yet to be shown to have convincing clinical effect.[46]

KEY CONCEPTS

- Diabetic neuropathy is a diagnosis of exclusion because no definitive diagnostic testing is available.
- Both ischemic and hemorrhagic brainstem lesions must be ruled out in the case of an acute ophthalmoplegia.
- Extraocular mononeuropathy is sufficiently common in patients with diabetes mellitus that its occurrence in isolation warrants evaluation of the patient for previously undiagnosed diabetes.

CEREBRAL VENOUS THROMBOSIS

Perspective

No precise studies of the epidemiology of cerebral venous thrombosis (CVT) have been performed. In case series, the median patient age is approximately 37 years, with a female-to-male ratio of 3:1.[47]

Principles of Disease

Cerebral blood is drained by several major veins that lead into the dural sinuses. The major dural sinuses are the superior sagittal sinus, the inferior sagittal sinus, the straight sinus, the lateral sinuses, and the sigmoid sinuses. The variability in symptoms and signs in patients who present with CVT stems from differences in thrombus location and acuity of thrombus formation. Symptoms of intracranial hypertension are present in most patients with sinus thrombosis, whereas those with thrombosis of the cerebral veins are thought to be more prone to hemorrhagic infarction and localizing neurologic deficits.[48] As with venous thrombosis in other locations, multiple causes and predisposing factors for CVT are recognized. Underlying causes often are divided into infectious and noninfectious categories. Infectious causes include local infections, such as sinusitis, otitis media, cellulitis on the face, and systemic infections. Noninfectious causes include direct injury to the cerebral venous system from trauma, surgery, tumor, dehydration, or any other condition that may predispose the patient to development of a hypercoagulable state.[49]

Clinical Features

The symptoms and signs associated with CVT are quite varied. Headache is the primary feature of CVT in 74 to 92% of affected patients.[49,50] Papilledema is noted in 28 to 45% of cases.[47,50,51] Lethargy, decreased level of consciousness, or mental status changes may be noted. Seizures occur in 35 to 50% of patients in the acute phase.[47,49,51] In addition to the location and acuity of thrombosis formation, a patient's symptom onset will vary in accordance with the extent of collateral vessel growth in the venous territory. Early thrombotic changes may be well compensated for by the collateral venous drainage. Symptoms will appear only when the compensation for venous thrombosis is no longer sufficient. Variability in collateralization between patients also adds to the variability and time course of symptomatology. Two national and international observational studies document an average time from symptom onset to diagnosis of 7 days, reflecting the difficulty in diagnosing this rare disease entity.[47,51,52] The reported incidence of focal neurologic signs, including seizures, on clinical examination varies between series, ranging from 25 to 71%.[49,50] Because of the broad spectrum of possible clinical features, the diagnosis of CVT may be difficult but should be a consideration in any patient with unexplained headache, especially in combination with focal neurologic deficit, papilledema, or seizures.

Diagnostic Strategies

The gold standard modality for the diagnosis of CVT has shifted in recent years from cerebral angiography to magnetic resonance venography (MRV). CT scanning is useful in the initial workup of the patient with possible CVT, but noncontrast CT is neither sensitive nor specific enough to reliably confirm or exclude the diagnosis. Findings on CT that are consistent with CVT include hyperdensity of a thrombosed sinus, brain edema, and hemorrhage secondary to venous congestion. CT venography is both more sensitive and more specific in diagnosing CVT.

Similar to CT scanning, MRI also can demonstrate local changes secondary to venous congestion, such as brain edema or hemorrhage. In addition, MRI can demonstrate the possibility of CVT based on the lack of a "flow void." On conventional MRI, a flow void indicates the presence of blood flow within the sinus, whereas the absence of a flow void indicates a possible thrombus. Diagnostic accuracy, however, is greatly improved through use of MRV. This technique takes advantage of the MRI signal characteristics of flowing blood to create images of venous structures. Combining these imaging techniques further enhances diagnostic accuracy. For imaging a particular dural sinus, presence of the sinus on conventional MRI and lack of flow on MRV are diagnostic of a sinus thrombosis. This combined approach has diagnostic sensitivity similar to that of conventional angiography.[49,53]

Two small studies show similar sensitivity between MRV and CT venography for the diagnosis of CVT when the CT study is performed on a multidetector row CT scanner. Both studies, involving a total of 69 patients, showed 100% sensitivity of CT venography for CVT in comparison with MRV.[54,55] The sensitivity of CT venography performed by scanners that do not use multidetector row technology is unknown.

Several small studies have attempted to evaluate the usefulness of the D-dimer assay as a screening tool to exclude CVT, particularly when MRI or CT venography is not available. Although the reported sensitivity rates are fair at 83 to 100%, larger prospective studies need to be done to further define the role of D-dimer in the evaluation of CVT, because several case reports have noted normal D-dimer levels in the setting of documented CVT.[56-59] In general, although a normal D-dimer level does not exclude the diagnosis of CVT, it does appear to make this diagnosis much less likely, particularly in a patient with symptoms of less than 2 weeks in duration.

Differential Considerations

Considerations in the differential diagnosis of CVT include the conditions that cause patients to present with the new onset of neurologic deficits, alteration in consciousness, or severe headache. A diagnosis of CVT should be considered in a patient with such symptoms when the etiology is unclear, presence of having a hypercoagulable state is likely, and the head CT scan is normal in appearance or shows subtle signs of CVT.

Management

CVT is a relatively rare disease, and controlled studies evaluating its treatment are lacking. Current therapeutic consensus

strongly recommends systemic anticoagulation with low-molecular-weight or unfractionated heparin to prevent further clot formation and to promote recanalization, even in patients with intracranial hemorrhage on initial imaging.[49,50,60,61] In one placebo-controlled randomized trial comprising 20 patients, anticoagulation with heparin to a target partial thromboplastin time (PTT) of 80 to 100 seconds demonstrated benefit, even in patients in which evidence of intracranial hemorrhage was seen on the CT scan before anticoagulation.[62] In another study of 60 patients randomized to receive placebo or low-molecular-weight heparin, no statistical benefit was shown for treatment.[63] Two large observational trials showed improvement in modified Rankin scale at follow-up in the anticoagulated groups, although the trials were not randomized.[47,51] Despite a paucity of randomized controlled trials, expert opinion favors anticoagulation in all groups unless another contraindication is present.[64]

Catheter-based intervention with thrombolysis has been attempted in multiple case series using either urokinase or tissue plasminogen activator. Thrombolysis was shown to be relatively safe and relatively successful in very small case series.[61] In one nonrandomized study of 40 patients, 20 received systemic heparin and 20 received catheter-based infusion of urokinase followed by systemic heparin. Despite initially worse neurologic function in the thrombolysis group, a significant difference in neurologic function favoring thrombolysis was observed at discharge.[65] Although this therapy is promising, it should be considered only for patients with symptoms of decreased level of consciousness, elevated ICP, or rapid deterioration on neurologic examination.

Disposition

All patients with suspected CVT should be admitted to a unit capable of providing a high level of care with neurologic consultation. Patients should be anticoagulated if no contraindication exists, and catheter-based thrombolysis should be considered in patients with depressed mental status or focal findings on neurologic exam.

KEY CONCEPTS

- CVT is a relatively rare entity, and only awareness of and familiarity with the clinical presentation will lead to the correct diagnosis.
- The onset may be insidious with a considerable delay between onset and arrival in the treatment setting.
- The differential diagnosis for CVT should consider other conditions that cause patients to present with new-onset neurologic deficits, alteration in consciousness, or severe headache. CVT is more likely to be present in such patients when the etiology is unclear, the patient is suspected of having a hypercoagulable state, and the head CT is normal in appearance or shows subtle signs of CVT.
- Noncontrast CT scanning is not adequate to rule out CVT. An MRI with MRV is recommended, although multidetector row CT venography is an acceptable alternative.
- Treatment of most patients with CVT should include systemic anticoagulation, even in the setting of hemorrhagic cerebral infarcts, unless another contraindication exists.

MULTIPLE SCLEROSIS

Perspective

Multiple sclerosis (MS) is an inflammatory disease that affects the central nervous system (CNS). Although the exact etiology remains uncertain, the pathologic manifestation of this inflammatory disease is a demyelination of discrete regions (plaques) within the CNS with a relative sparing of axons. The clinical picture is highly variable but is classically characterized by episodes of neurologic dysfunction that evolve over days and resolve over weeks.

MS has an overall prevalence in the United States of 0.1%. The peak age at onset is 25 to 30 years, with women being slightly younger at onset than men. The incidence in women exceeds that of men by a ratio of 1.8 : 1. The worldwide prevalence is greatest in the United Kingdom, Scandinavia, and North America. Epidemiologic studies indicate that both genetic and environmental factors are associated with an increased incidence of this disease. MS has a 30% concordance rate between monozygotic twins, and 20% of patients with MS have at least one affected relative. MS is more common in temperate climates. It is rare between 23 degrees north and south latitudes but has a rising incidence above and below 50 degrees north and south latitudes, respectively. Although no exact environmental factor has been identified, if a person emigrates from an area of high prevalence to an area of low prevalence before the age of 20, the risk is diminished. MS is rare in Africans and Asians, but African Americans have a higher incidence than their relatives who remain in Africa.[66] In addition, reports of clusters or miniepidemics support environmental factors. Thus, an environmental cause superimposed on genetic susceptibility appears to be a likely etiologic scenario.[67,68]

Principles of Disease

MS is considered to be an organ-specific autoimmune disease. One theory proposes that genetic factors interact with an environmental trigger or infection to establish pathologically autoreactive T cells in the CNS. After a long and variable latency period (typically 10 to 20 years), a systemic trigger, such as a viral infection or superantigen, activates these T cells. The activated T cells, on reexposure to the autoantigen, initiate the inflammatory response. This sets off a complex immunologic cascade that leads to the demyelination characteristic of MS. This demyelination process releases CNS antigens that are hypothesized to initiate further episodes of autoimmune-induced inflammation. The mechanisms underlying this autoimmunity in MS are unknown.[69]

Clinical Features

The clinical picture in MS is one of marked heterogeneity. The classic clinical syndrome consists of recurring episodes of neurologic symptoms that rapidly evolve over days and slowly resolve. Variability occurs in age at onset, location of CNS lesions, frequency and severity of relapses, and the degree and time course of progression.

The clinical features of MS can be divided into areas of specific CNS impairment: cognition, cranial nerves, motor pathways, sensory pathways, cerebellar pathways, and bowel, bladder, and sexual dysfunction.[66]

Patients with MS have frequent complaints of poor memory, distractibility, and a decreased capacity for sustained mental effort. Formal neuropsychological testing suggests that cognitive involvement is common and underreported. Specifically,

neuropsychological testing has shown that 43 to 65% of patients with MS have some degree of cognitive impairment.[70,71] Of note, a correlation has been found between the MRI-based total lesion load and presence of cognitive impairment.[72]

Cranial nerve dysfunction is common in MS. The most common associated cranial nerve abnormality is *optic neuritis*, a unilateral syndrome characterized by pain in the eye and a variable degree of visual loss affecting primarily central vision. Within 2 years of an attack of optic neuritis, the risk of MS is approximately 20%, and within 15 years, it is approximately 45 to 80%.[73,74] Optic neuritis often is the first symptom of MS.[75,76]

As a result of lesions in the vestibulo-ocular connections, the oculomotor pathways also may be affected. The deficit may manifest as diplopia or nystagmus. The nystagmus may be severe enough that the patient may complain of oscillopsia (a subjective oscillation of objects in the visual field). Cranial nerve impairment also may include impairment of facial sensation, which is relatively common. Unilateral facial paresis also may occur. In addition, the occurrence of trigeminal neuralgia in a young person may be an early sign of MS.

Motor pathways also are commonly involved. Specifically, corticospinal tract dysfunction is common in patients with MS. Paraparesis or paraplegia is all too common and occurs with greater frequency than upper extremity lesions, owing to the common occurrence of lesions in the motor tracts of the spinal cord. In patients with significant motor weakness, spasms of the legs and trunk may occur on attempts to stand from a seated position. This dysfunction is manifested on physical examination as spasticity that typically is worse in the legs than in the arms. The deep tendon reflexes are markedly exaggerated, and sustained clonus may be demonstrated. Although these symptoms frequently are bilateral, they generally are asymmetrical.[66]

Sensory manifestations are a frequent initial feature of MS and will be present in nearly all patients at some point during the course of the disease. Sensory symptoms are commonly described as numbness, tingling, "pins and needles" paresthesias, coldness, or a sensation of swelling of the limbs or trunk.[66]

Impairment of the cerebellar pathway results in significant gait imbalance, difficulty with coordinated actions, and dysarthria. Physical examination reveals the typical features of cerebellar dysfunction, including dysmetria, dysdiadochokinesis (an impairment of rapid alternating movements), a breakdown in the ability to perform complex movements, an intention tremor in the limbs and head, truncal ataxia, and dysarthria.[66]

Impairment of bowel, bladder, and sexual function also is common. The extent of sphincter and sexual dysfunction usually parallels the motor impairment in the lower extremities. Urinary frequency may progress to urinary incontinence with progression of the disease. An atonic bladder may develop, which empties by simple overflow and often is associated with the loss of perception of bladder fullness and with anal and genital hypoesthesia. Constipation becomes common over time, and almost all patients with paraplegia require special measures to maintain effective bowel habits. Sexual dysfunction, although frequently overlooked, is very common in MS. Approximately 50% of patients become completely sexually inactive as a result of this disease.[66]

Diagnostic Strategies

Although no laboratory tests are diagnostic for MS, one clinical feature remains relatively unique to this disease: *Uhthoff's phenomenon*, temporary worsening of current or preexisting signs or symptoms of MS secondary to small increases in the patient's body temperature. Accordingly, exercise, a hot bath, exposure to a warm environment, or fever can bring about Uhthoff's phenomenon. This phenomenon reflects subclinical demyelination or preexisting injury to nerves without obvious significant clinical involvement before heat exposure or temperature elevation.[66]

The clinical diagnosis rests on occurrence of at least two clinical episodes with different neurologic symptoms at different times. Thus, MS commonly has been characterized as a disorder with lesions that differ in time and space. It also has been described as a relapsing-remitting disorder with symptoms that fluctuate over time.

Findings on cerebrospinal fluid (CSF) analysis are abnormal in 90% of the cases. Fifty percent of patients will have pleocytosis, with more than 5 lymphocytes per high-power field in the CSF. Approximately 70% of patients will have an elevated gamma globulin level, with immunoglobulin G (IgG) ranging from 10 to 30% of the CSF total protein. Electrophoresis of the CSF demonstrates oligoclonal bands of IgG in 85 to 95% of patients who carry a diagnosis of MS; however, oligoclonal bands of IgG also are seen with neurosyphilis, fungal meningitis, and other CNS infections. Lumbar puncture should be considered for all patients with suspected MS, but mass lesions and elevated ICP should be ruled out before lumbar puncture.[77]

The initial imaging test to aid in the diagnosis of multiple sclerosis is MRI. MRI is a sensitive test for the detection of lesions consistent with MS and also is useful to assess disease severity.[78] The lesions of MS typically appear hyperintense, or bright white, on T_2-weighted or fluid-attenuated inversion recovery (FLAIR) MRI studies. Lesions usually are multiple and commonly are found in the periventricular white matter.[79] In patients with an initial neurologic event consistent with CNS demyelination and an MRI cranial study showing multiple white matter lesions, the 5-year risk of developing MS is 60%. Patients with similar clinical syndromes and a normal MRI appearance have less than a 5% 5-year risk.[80]

Differential Considerations

Other diseases that affect the CNS white matter may be clinically and radiographically similar to MS. Considerable care must be taken to exclude these disease processes before making a diagnosis. These include CNS tumors (especially lymphomas and gliomas), spinal cord compression, vasculitides, Behçet's disease, neurosarcoidosis, postinfectious and postvaccinal encephalomyelitis, human immunodeficiency virus (HIV) encephalopathy, Lyme disease, and vitamin B_{12} deficiency.

Management

Management of patients with MS has essentially three aspects: (1) therapies aimed at halting the progression of the disease, (2) treatment for acute exacerbations, and (3) therapies designed to modify complications.

Therapies aimed at halting disease progress are based primarily on the use of either β-interferon or glatiramer acetate. The interferons are a group of natural compounds with antiviral and immunomodulatory actions, which are retained by the recombinant preparations used in therapy for MS, interferon beta-1a and interferon beta-1b. Side effects include flulike symptoms, depression, anxiety, and confusion. In one study, 560 patients with MS were randomly assigned to receive subcutaneous interferon beta-1a or placebo ($n = 187$) three times a week for 2 years. The relapse rate was significantly lower at 1 and 2 years with interferon beta-1a than with placebo. The time to first relapse was prolonged significantly and the accu-

mulation of brain lesions on MRI was lower in the treatment group than in the placebo group. The investigators concluded that subcutaneous interferon beta-1a is a well-tolerated and effective treatment for relapsing-remitting MS in terms of relapse rate, defined disability, and all MRI outcome measures.[81] β-Interferon also has been shown to retard progression to clinically definite MS and to decrease the total number of brain lesions seen on subsequent MRI studies in patients who have their first demyelinating episode with MRI abnormalities at initial presentation.[82-85] This finding highlights the importance of early evaluation and treatment.

Glatiramer acetate also has successfully been used in the treatment of MS. This agent is a mixture of synthetic polypeptides designed to mimic myelin basic protein. The mechanism of action by which glatiramer acetate exerts its effect is unknown, but it is thought to modify the immune processes responsible for the pathogenesis of MS. In one study, 251 patients with relapsing-remitting MS were randomized to receive daily subcutaneous injections of glatiramer acetate (previously called copolymer 1) or placebo for 24 months. Patients receiving glatiramer acetate experienced significantly fewer relapses and were more likely to demonstrate neurologic improvement, whereas those receiving placebo were more likely to worsen. This drug generally is quite well tolerated.[86]

Current recommendations for management of relapsing-remitting MS are to initiate treatment with β-interferon or glatiramer acetate. Such regimens have been demonstrated to decrease the volume of plaques seen on MRI and to diminish relapses.[69] Immunosuppressive agents, including mitoxantrone and azathioprine, also have been shown to be effective in reducing progression of disease but, in view of concerns over side effects, generally are used as second-line agents.[87,88]

Acute exacerbations of MS also should be targets for therapy. Although most such episodes will resolve without therapy, steroids have been demonstrated to diminish the duration of acute exacerbations. More than 85% of patients with relapsing-remitting MS show improvement with intravenous methylprednisolone. Intravenous steroids have been shown in controlled trials to speed the recovery from the visual loss of optic neuritis when compared with placebo. In addition, when patients with acute optic neuritis are treated with high-dose intravenous steroids, the 2-year rate of development of MS is reduced, although this effect diminishes over time.[74,89] Of interest, oral prednisone was not found to be helpful in the optic neuritis trials and was associated with a potential increase in the number of optic neuritis episodes.

The current standard therapy for an acute exacerbation in MS is intravenous methylprednisolone. A typical dose administered intravenously is 250 to 500 mg every 12 hours for 3 to 7 days. Whether this should be followed by an oral prednisolone taper remains controversial. Potential adverse effects of methylprednisolone therapy include fluid retention, gastrointestinal hemorrhage, anxiety, psychosis, infection, and osteoporosis.

Several therapies directed toward the complications of MS may be helpful. The associated spasticity generally is treated with baclofen. This is a highly effective therapy aimed at reducing the painful flexor and extensor spasms. A major side effect is drowsiness, which generally diminishes with continued use. Higher-dose therapy can cause confusion, especially in the setting of baseline cognitive impairment. For patients with intractable spasticity, baclofen is available for intrathecal administration by either bolus therapy or continuous implanted pump therapy. Additional therapeutic agents for control of spasticity include tizanidine, diazepam, and dantrolene.

The tremor and ataxia associated with MS occasionally are treated with propranolol, diazepam, or clonazepam. The results of these therapies, however, generally are unsatisfactory. Pain often is associated with MS and affects the shoulders, pelvic girdle, and face. The facial pain may be indistinguishable from that of trigeminal neuralgia. Treatment options include carbamazepine, baclofen, and tricyclic antidepressants. Fatigue, which is common, may be ameliorated with amantadine. This agent produces partial relief for a minority of patients. In controlled studies, the effect is only slightly better than placebo.[69]

Disposition

Patients with a history of MS who seek treatment for significant symptoms must first be evaluated to rule out other, non–MS-related pathology. Also, the presence of other systemic illnesses, especially infections, which can worsen the symptoms of MS, should be excluded. If the problem is thought to be an exacerbation of MS, most patients will require hospital admission for intravenous steroid therapy. An alternative to hospitalization may be to initiate intravenous steroids in the ED and to arrange for a next-day follow-up visit with the primary care physician or neurologist if outpatient intravenous steroid administration is an option.

Patients with the new onset of symptoms suggestive of MS should be admitted or referred to a neurologist, depending on the type and severity of symptoms.

KEY CONCEPTS

- Any patient with a long-term illness, such as MS, must be evaluated to rule out pathologic processes not related to that illness before an exacerbation of the illness can be assumed to be the cause of any problems experienced by the patient.
- Therapy for patients with MS will require consultation with the patient's primary care provider or neurologist to provide consistent disease management.
- Intravenous methylprednisolone effectively promotes earlier resolution of recurrences.
- Intravenous methylprednisolone has been shown to speed the recovery from vision loss from optic neuritis.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 103

Brain and Cranial Nerve Disorders

Brian A. Stettler

This chapter discusses cranial nerve problems, cerebral venous thrombosis, and multiple sclerosis—neurologic disorders that often provide significant diagnostic and therapeutic challenges in management in the emergency department (ED) setting (Table 103-1).

TRIGEMINAL NEURALGIA

Perspective

Trigeminal neuralgia, or *tic douloureux*, is a syndrome featuring painful paroxysms in one or more distributions of the trigeminal nerve. Trigeminal neuralgia is relatively uncommon, with an annual incidence of 4 to 13 cases per 100,000 population.[1,2] It is more common in women than in men, with a female-to-male ratio of 1.7:1. Affected persons typically are between 50 and 69 years of age, and symptoms occur more frequently on the right side of the face.[3]

Pathophysiology

Trigeminal neuralgia is an idiopathic disorder, although significant evidence points to vascular compression of the trigeminal nerve root in many cases. This compression commonly is caused by a tortuous arterial or venous loop in the posterior fossa, an arteriovenous malformation, or rarely a tumor. In surgical case series, vascular compression of the trigeminal nerve root is found in 80 to 90% of cases.[4,5] Of note, however, structural lesions are not found in all patients with trigeminal neuralgia.[6]

Clinical Features

Trigeminal neuralgia manifests with unilateral facial pain, typically characterized as lancinating paroxysms of pain in the lips, teeth, gums, or chin. The pain of trigeminal neuralgia commonly is associated with physical triggers such as chewing, brushing the teeth, shaving, washing or touching the affected area of the face, swallowing, or exposure to hot or cold temperature in the affected area. The maxillary and mandibular divisions of the trigeminal nerve are most commonly involved; rarely, the ophthalmic division alone is involved. Patients tend to experience the pain in clustered episodes that last a few seconds to several minutes. The attacks can occur during the day or night but rarely arise during sleep.[6,7]

Diagnostic Strategies

A careful history and physical examination should be performed to rule out other painful facial conditions including odontogenic infections, sinus disease, otitis media, acute glaucoma, temporomandibular joint disease, and herpes zoster. Patients who lack local pathologic findings to explain the painful syndrome require a very careful neurologic examination. The presence of a neurologic deficit should prompt suspicion of a structural lesion, such as aneurysm, tumor, or other intracranial lesion such as from multiple sclerosis (MS). Of note, 2 to 4% of patients with trigeminal neuralgia also have MS.[8] Patients with normal findings on the head and neck examination and no neurologic deficits who have episodic, unilateral facial pain associated with nonpainful triggers are likely to have trigeminal neuralgia.

Management

Since the 1960s the medical treatment of choice for trigeminal neuralgia has been use of the anticonvulsant carbamazepine. The purported effectiveness of this treatment is, however, based on uncontrolled studies, and the mechanism of action of anticonvulsant therapy for trigeminal neuralgia is unclear. The true efficacy of medical therapy is difficult to assess owing to a very high rate of spontaneous remission. Nonetheless, carbamazepine appears to be an effective and well-tolerated agent for treatment of trigeminal neuralgia. The initial dosage of carbamazepine is 100 mg twice daily; this dose is then increased to three times daily after one week. The dose may be increased by 100 mg per day, up to a maximum of 1200 mg per day. A complete blood count and liver function studies should be performed periodically in these patients to monitor for hematologic and hepatic side effects. Additional agents that have been used for treatment of trigeminal neuralgia include phenytoin, baclofen, valproate sodium, lamotrigine, and gabapentin. None of these drugs have been shown to be more effective than carbamazepine.[7]

Surgical management has been a theraputic option since the 1950s. Surgical procedures include both peripheral approaches and central procedures. Peripheral strategies include medication injection and cryotherapy techniques designed to temporarily block, or permanently ablate, branches of the peripheral trigeminal nerve. Although these procedures are relatively effective initially, recurrence is common. Repeated nerve

Table 103-1 The Cranial Nerves: Normal Function and Pathologic Considerations

CRANIAL NERVE	CLINICAL FUNCTION RELEVANT TO EMERGENCY MEDICINE	PATHOLOGIC FEATURES	POSSIBLE CAUSES
Cranial nerve I: Olfactory nerve	Sense of smell	Unilateral anosmia	*Trauma*: Skull fracture or shear injury interrupting olfactory fibers traversing the cribriform plate *Tumor*: Frontal lobe masses compressing the nerve
Cranial nerve II: Optic nerve	Vision	Unilateral vision loss	*Trauma*: Traumatic optic neuropathy *Tumor*: Orbital compressive lesion *Inflammatory*: Optic neuritis (MS) *Ischemic*: Ischemic optic neuropathy
Cranial nerve III: Oculomotor nerve	Extraoculomotor function via motor fibers to levator palpebrae, superior rectus, medial rectus, inferior rectus, inferior oblique muscles Pupillary constriction via parasympathetic fibers to constrictor pupillae and ciliary muscles	Ptosis caused by loss of levator palpebrae function Eye deviated laterally and down Diplopia Dilated, nonreactive pupil Loss of accommodation	*Trauma*: Herniation of the temporal lobe through the tentorial opening causing compression and stretch injury to the nerve *Ischemic*: Especially in diabetes Microvascular ischemic injury to nerve causes extraocular muscle paralysis but usually is papillary-sparing (often painful) *Vascular*: Intracranial aneurysms may press on the nerve, leading to dysfunction Myasthenia gravis can lead to atraumatic ocular muscle palsy
Cranial nerve IV: Trochlear nerve	Motor supply to the superior oblique muscle	Inability to move eye downward and laterally Diplopia Patients tilt head toward unaffected eye to overcome inward rotation of affected eye	Trauma is the most common cause of nerve dysfunction
Cranial nerve V: Trigeminal nerve	Motor supply to muscles of mastication and to tensor tympani Sensory to face, scalp, oral cavity (including tongue and teeth)	Partial facial anesthesia Episodic, lancinating facial pain associated with benign triggers such as chewing, brushing teeth, light touch	*Trauma*: Facial bone fracture may injure one section, leading to area of facial anesthesia Tic douloureux
Cranial nerve VI: Abducens nerve	Motor supply to the lateral rectus muscle	Inability to move affected eye laterally Diplopia on attempting lateral gaze	*Tumor*: Lesions in the cerebellopontine angle Any lesion, vascular or otherwise, in the cavernous sinus may compress nerve *Elevated intracranial pressure (ICP)*: Because of its position and long intracranial length, increased ICP from any cause may lead to injury and dysfunction of the nerve
Cranial nerve VII: Facial nerve	Motor supply to muscles of facial expression Parasympathetic stimulation of the lacrimal, submandibular, and sublingual glands Sensation to the ear canal and tympanic membrane	*Hemifacial paresis*: *Lower motor neuron lesion* leaves entire side of face paralyzed *Upper motor neuron lesion* leaves forehead musculature functioning Abnormal taste Sensory deficit around ear Intolerance to sudden loud noises	*Lower motor neuron*: *Infection* (viral): The likely cause of Bell's palsy *Lyme disease*: The most common cause of bilateral cranial nerve VII palsy in areas where Lyme disease is endemic Bacterial infection extending from otitis media *Upper motor neuron*: Stroke, tumor
Cranial nerve VIII: Vestibulocochlear nerve	Hearing and balance	Unilateral hearing loss Tinnitus Vertigo, unsteadiness	*Tumors*: Acoustic neuroma Mimics Ménière's disease, perilymphatic fistula

Table 103-1 The Cranial Nerves: Normal Function and Pathologic Considerations—cont'd

CRANIAL NERVE	CLINICAL FUNCTION RELEVANT TO EMERGENCY MEDICINE	PATHOLOGIC FEATURES	POSSIBLE CAUSES
Cranial nerve IX: Glossopharyngeal nerve	General sensation to posterior third of tongue Taste for posterior third of tongue Motor supply to the stylopharyngeus	Clinical pathology referable to the nerve in isolation is very rare Occasionally painful paroxysms beginning in the throat and radiating down the side of the neck in front of the ear but behind the mandible	Brainstem lesion Glossopharyngeal neuralgia
Cranial nerve X: Vagus nerve	Motor to striated muscles and muscles of the pharynx, larynx, and tensor (veli) palatini Motor to smooth muscles and glands of the pharynx, larynx, thoracic and abdominal viscera Sensory from larynx, trachea, esophagus, thoracic and abdominal viscera	*Unilateral loss of palatal elevation*: Patients complain that on drinking liquids, the fluid refluxes through the nose *Unilateral vocal cord paralysis*: Hoarse voice	Brainstem lesion Injury to the recurrent laryngeal nerve during surgery
Cranial nerve XI: Spinal accessory nerve	Motor supply to the sternocleidomastoid and trapezius muscles	Downward and lateral rotation of the scapula and shoulder drop	Trauma to the nerve
Cranial nerve XII: Hypoglossal nerve	Motor supply to the intrinsic and extrinsic muscles of the tongue	*Tongue deviations*: *Upper motor neuron lesion* causes the tongue to deviate toward the opposite side *Lower motor neuron lesion* causes the tongue to deviate toward the side of the lesion, and the affected side atrophies over time	Stroke or tumor can cause upper motor neuron lesion Amyotrophic lateral sclerosis (ALS) can cause bilateral lower motor neuron lesion with atrophy Metastatic disease to the skull base may involve the nerve

blocks are not recommended owing to a high risk of permanent facial anesthesia.

Central procedures can be divided into percutaneous approaches and open approaches. Percutaneous destruction of the trigeminal ganglion can be done by means of radiofrequency ablation, thermal ablation, glycerol injection, or balloon microcompression. These procedures carry the risk of corneal anesthesia, oculomotor paresis, or masticatory weakness.[9]

Open surgical management is the surgical option of choice in most treatment centers. Open surgical procedures include microvascular decompression of the nerve with or without partial ablation. Although the open microvascular decompression procedure has proved to be very effective, with pain relief achieved in 80 to 95% of patients, the surgery is associated with the risk of significant complications, including hearing loss, facial anesthesia, cerebrospinal fluid leak, brainstem or cerebellar injury, headaches, meningitis, and death.[10,11] Gamma knife radiosurgery, a minimally invasive, precision-directed stereotactic radiosurgery, also has been associated with good outcomes. This highly specialized technique requires extremely sophisticated stereotactic radiofrequency equipment and is available only in specialized centers.[12,13]

Disposition

Patients with suspected trigeminal neuralgia should be referred for specialty evaluation. Patients with a neurologic deficit require urgent imaging studies, typically magnetic resonance imaging (MRI), to rule out a mass or vascular abnormality.

KEY CONCEPTS

- Patients with unilateral, intermittent, lancinating facial pain without abnormalities on physical examination are likely to have trigeminal neuralgia.
- Carbamazepine is the first-line agent for medical treatment.
- Patients who do not tolerate or whose pain is refractory to medical management may be candidates for microvascular decompression or ablation.

FACIAL NERVE PARALYSIS

Perspective

The acute onset of facial nerve paralysis often will prompt an ED visit, when early diagnosis and therapy can improve the patient's chance for recovery of function of the facial nerve. Facial nerve paralysis of acute onset affects approximately 20 to 25 persons per 100,000 population per year, without geographic, gender, or race predilection.[14,15]

Principles of Disease

The facial nerve innervates the muscles of facial expression and the muscles of the scalp and external ear, in addition to the buccinator, platysma, stapedius, stylohyoid, and posterior belly of the digastric muscles. The sensory portion of the nerve supplies the anterior two thirds of the tongue with taste and

sensation to portions of the external auditory meatus, soft palate, and adjacent pharynx. The parasympathetic portion supplies secretomotor fibers for the submandibular, sublingual, lacrimal, nasal, and palatine glands.[16]

The nerve originates from the pontomedullary junction of the brainstem. The nerve enters the internal auditory meatus with cranial nerve VIII. Within the temporal bone the facial nerve has four major branches: the greater and lesser superficial petrosal nerves, the nerve to the stapedius muscle, and the chorda tympani. The facial nerve exits the temporal bone at the stylomastoid foramen. The nerve then enters the parotid gland, where it divides to supply the muscles of facial expression.[16,17]

Pathophysiology

Although a complete list of possibilities in the differential diagnosis for facial nerve paralysis would be a long one, the causes pertinent to emergency medicine can be grouped into three specific categories: infectious, traumatic, and neoplastic.

Infection

Bell's Palsy

Bell's palsy, also commonly called *idiopathic facial paralysis*, has long been postulated to have a viral cause. This disease entity is characterized by an abrupt onset of a lower motor neuron paresis that can progress over 1 to 7 days to complete paralysis. A prodromal illness is described by 60% of patients. Symptoms and signs frequently associated with the facial paresis include ear pain, a perception of sensory change on the involved side of the face, decreased tearing, an overflow of tears on the cheek (epiphora), abnormally acute hearing (hyperacusis), and an impairment or perversion of taste (dysgeusia).[18]

Treatment approaches can be medical or surgical. The primary medical therapies for Bell's palsy center on reducing inflammatory changes to the nerve with corticosteroids and treating the presumed viral cause. If these therapies are unsuccessful then surgical decompression may be considered.

The use of corticosteroids for Bell's palsy has been controversial. The rationale for this application of steroid therapy is that edema of the nerve, confined within the facial canal, is thought to cause or contribute to the nerve injury. On the basis of this theory, most experts currently recommend a course of prednisone with an initial dose of 1 mg/kg per day for 7 to 10 days, with or without a short taper.[14,17,19,20] The most definitive randomized, double-blind, placebo-controlled trial involving 496 patients showed an improvement in complete recovery of facial nerve function at 3 months from 64% with placebo to 83% with the use of prednisolone in a dose of 25 mg by mouth twice daily.[21] Therapy should be started as soon as possible, ideally within the first 24 hours, but is still recommended for patients without contraindications who seek treatment within 1 week of symptom onset.[19]

A number of publications have advanced the belief that Bell's palsy may be caused by herpesvirus infection. One study demonstrated herpes simplex virus type 1 DNA in the endoneural tissue of 11 of 14 patients with Bell's palsy but not in that of control subjects.[22] In a trial of prednisone and acyclovir in 99 patients, patients treated with prednisone and acyclovir had a more favorable recovery than that observed in patients receiving prednisone alone.[23] A study of 296 patients with Bell's palsy treated with valacyclovir or placebo in addition to a fixed dose of prednisolone found significant benefit to the addition of valacyclovir, particularly in the setting of severe palsy or in those treated within 24 hours of symptom onset.[24] Other studies have found conflicting results. Despite a lack of overwhelming evidence, the addition of an antiviral agent should be considered in the treatment of Bell's palsy, especially with severe loss of function. The most commonly recommended antiviral regimens include valacyclovir, 1000 mg orally two times daily for 10 days. Valacyclovir and famciclovir have better oral absorption, are better tolerated, and are dosed less frequently, resulting in higher compliance. Accordingly, they have been recommended as alternatives to acyclovir.[17,19,20,22,25] As with steroid therapy, although earlier treatment is preferred, treatment should be considered for patients presenting within 1 week of symptom onset.

Ramsay Hunt Syndrome

Ramsay Hunt syndrome (herpes zoster oticus) is characterized by unilateral facial paralysis, a herpetiform vesicular eruption, and vestibulocochlear dysfunction. The vesicular eruption may occur on the pinna, external auditory canal, tympanic membrane, soft palate, oral cavity, face, and neck as far down as the shoulder. The pain is considerably more severe than that associated with Bell's palsy, and it frequently is out of proportion to physical findings. In addition, outcomes are worse than with Bell's palsy, with a lower incidence of complete facial recovery and the possibility of sensorineural hearing loss. Therapy is similar to that for Bell's palsy. Both prednisone and antiviral therapy for 7 to 10 days are advocated.[17,26,27]

Lyme Disease

Lyme disease is the most frequent vector-borne infection in the United States. It is caused by the spirochete *Borrelia burgdorferi* and is spread by the bite of *Ixodes* genus ticks. Neurologic manifestations can arise in any phase of the disease, and the incidence of facial palsy in patients with neurologic involvement is 35 to 51%. In regions in which Lyme disease is endemic, it has been shown to be the leading cause of facial paralysis in children, responsible for one half of all pediatric cases of facial nerve paralysis.[28,29]

Bilateral facial nerve paralysis is rare but can occur with systemic infections. The two diseases most commonly associated with bilateral simultaneous onset of facial paralysis are Lyme disease and infectious mononucleosis. Bilateral facial paralysis should be considered to be a manifestation of Lyme disease until further testing excludes this diagnosis.[20,28-30] The evaluation and treatment of Lyme disease are discussed in Chapter 132.

Bacterial Infections

Facial paralysis can be caused by acute bacterial infections of the middle ear, mastoid, or external auditory canal. In the preantibiotic era, facial paralysis was associated with acute otitis media in approximately 2% of cases; today, however, it occurs in only 0.2% of cases. Treatment consists of intravenous antibiotics and myringotomy for decompression. Malignant otitis externa can be associated with facial paralysis. This disease entity is most commonly seen in immunocompromised patients and usually is caused by *Pseudomonas* infection. Treatment involves prolonged intravenous antipseudomonal antibiotic therapy and may require surgical débridement.[20,31]

Trauma

In patients with head trauma, the facial nerve is the most commonly injured cranial nerve. The cause generally is a temporal bone fracture with nerve transection. Surgical exploration is warranted if there is firm evidence that the nerve has been transected, indicated by a sudden onset of complete unilateral facial paralysis, loss of electrical activity, and evidence of a displaced fracture involving the facial canal.

Neoplasm

Tumors of the facial nerve itself, or tumors anywhere along the course of the facial nerve that invade or compress the nerve, may lead to facial paralysis. Typically the course is progressive over at least 3 weeks. A sudden onset of paralysis, however, does not rule out an underlying tumor, because facial paralysis secondary to a neoplasm is of sudden onset in approximately 25% of cases.[32] A neoplastic cause should be suspected in patients who suffer from recurrent ipsilateral facial paralysis, significant pain, prolonged symptoms, or any other concomitant cranial nerve abnormality.

Clinical Features and Differential Considerations

The medical history should focus on onset of the paralysis, concentrating on timing and rapidity of onset and looking for any associated signs and symptoms. A rapid onset of facial paralysis with dysgeusia and hyperacusis preceded by a viral prodrome is suggestive of Bell's palsy. A history of recurrent ipsilateral paralysis or slow progression of symptoms is more characteristic for a tumor. Associated cranial nerve abnormalities, although occasionally seen with Bell's palsy, also point to the possibility of a tumor or ischemic insult. The Ramsay Hunt syndrome causes significant pain and a vesicular rash, although the rash may follow the facial paresis by a few days. Significant anatomic abnormalities on visual or otoscopic inspection of the ipsilateral ear will be found with bacterial otitis media and otitis externa. Finally, systemic symptoms or bilateral facial paresis, especially in endemic areas, should raise the possibility of Lyme disease.

Diagnostic Strategies

The diagnostic workup of acute facial nerve paresis is based on whether the clinical picture is suggestive of a disease process other than Bell's palsy. If the clinical history is classic for Bell's palsy, then no imaging or laboratory studies are required. Of note, any history of possible exposure warrants serologic evaluation for Lyme disease. Although outpatient testing including electroneurography may ultimately be performed, this usually is not part of the initial evaluation.

The physical examination finding of a "central" seventh nerve paralysis (upper face–sparing) should prompt imaging with computed tomography (CT) or MRI, and consideration should be given to the possibility of an acute stroke or other hemispheric lesion. History or physical examination findings suggestive of a possible tumor require imaging to rule out a neoplasm. The study of choice will depend on the institution and preferences of the consultant.

Disposition

The vast majority of patients who have a seventh nerve paralysis will have a clinical diagnosis of Bell's palsy and may be discharged with referral for short-term follow-up. Patients with a possible hemispheric process such as stroke or tumor should be hospitalized for further evaluation. Patients suspected of having Lyme disease require immediate initiation of appropriate antibiotic therapy.

In patients with a peripheral facial nerve paralysis, the ipsilateral eye should be patched, and consideration should be given to ophthalmologic follow-up, because there is a high rate of corneal abrasions and corneal dryness associated with the inability to properly blink or completely close the eye.

KEY CONCEPTS

- Recent literature highlights significant potential benefit for patients with clinical evidence of Bell's palsy when they are treated early in the course with corticosteroids. The additional benefit of adding antiviral medication is controversial, but this treatment probably is warranted in patients with severe loss of function.
- Slowly progressive facial paralysis is suggestive of a neoplasm. Recurrent unilateral paralysis may occur with Bell's palsy but frequently (30%) is seen in patients with tumor.
- Simultaneous bilateral facial paralysis is suggestive of Lyme disease, which must be considered as a possible cause, especially in endemic regions.
- Patients who have facial muscle paresis with intact forehead movement should be considered to have an upper motor neuron lesion until the diagnostic investigation proves otherwise.

VESTIBULAR SCHWANNOMA

Perspective

Vestibular schwannoma, formally referred to as *acoustic neuroma*, is a rare but important cause of sensorineural hearing loss. The annual incidence of VS is 1 case per 100,000 population, with a mean age at the time of detection of 46 to 58 years.[33] The female-to-male ratio is 1.5:1. Vestibular schwannoma is very rarely bilateral, occurring in this form in approximately 5% of cases and generally associated with type II neurofibromatosis. Although histologically benign, vestibular schwannoma can cause neurologic damage by direct compression on the eighth cranial nerve and the other structures in the cerebellopontine angle.[34]

Principles of Disease

Vestibular schwannoma arises from the Schwann cells covering the vestibular branch of the eighth cranial nerve as it passes through the internal auditory canal. The tumor may compress the cochlear (acoustic) branch of the eighth cranial nerve, causing hearing loss, tinnitus, and dysequilibrium. Continued growth of the tumor may result in compression of structures in the cerebellopontine angle, where the facial and trigeminal nerves may be compressed and damaged. Larger tumors may further encroach upon the brainstem and if large enough may compress the fourth ventricle, ultimately resulting in signs of increased intracranial pressure (ICP).[35]

Clinical Features

Asymmetrical sensorineural hearing loss is the hallmark of vestibular schwannoma. Up to 15% of patients with this tumor, however, will have normal results on an audiogram. These patients typically have symptoms such as unilateral tinnitus, imbalance, headache, fullness in the ear, otalgia, or facial nerve weakness. Thus, patients with asymmetrical symptoms should be further evaluated for vestibular schwannoma even with normal findings on the audiogram.[36]

Vestibular schwannomas are extremely slow-growing tumors, averaging an approximately 1-mm increase per year, although many do not grow at all on serial examinations.[37] Symptom onset is therefore generally quite gradual. In one series of 126 cases, the average time from symptom onset to discovery of a vestibular schwannoma was approximately 4 years.[38]

Diagnostic Strategies

When vestibular schwannoma is suspected, the patient should be evaluated with an audiogram or a gadolinium-enhanced MRI. This imaging technique is extremely sensitive and has led to earlier diagnosis and a decrease in mean size at detection of vestibular schwannoma. CT lacks the necessary sensitivity in the posterior cranial fossa to reliably rule out the presence of vestibular schwannoma. The smaller the tumor at the time of diagnosis, the more options there are for therapy and the better the potential prognosis.[34]

Differential Considerations

A majority of disease entities included in the differential diagnosis for acoustic neuroma cause symmetrical sensorineural hearing loss. Asymmetrical sensorineural hearing loss has few causes other than vestibular schwannoma. Ménière's disease may present a diagnostic dilemma because it can be asymmetrical. Ménière's disease may be differentiated from vestibular schwannoma in that the tinnitus of Ménière's disease usually is intermittent, whereas the tinnitus of vestibular schwannoma typically is continuous. In addition, patients with Ménière's disease typically describe true vertigo, whereas patients with a vestibular schwannoma are more likely to describe imbalance or dysequilibrium.

Vestibular schwannomas account for 80% of all cerebellopontine angle tumors. Among all other lesions, meningioma is the most common. Meningiomas more frequently cause symptoms of facial palsy or trigeminal nerve abnormality. Of note, however, considerable similarity between the clinical picture of a meningioma and that of vestibular schwannoma in the cerebellopontine angle has been described.[39]

Management

Vestibular schwannoma may be removed surgically or ablated with stereotactic radiation. In general, tumors larger than 3 cm are recommended for microsurgery, because radiation treatments, such as with the Gamma Knife or linear accelerator, are less effective for local control and growth arrest in larger masses. Smaller tumors are amenable to use of stereotactic radiation, which may have greater salvage rates of facial nerve function and hearing. Stereotactic radiation therapy generally has good long-term outcomes of local growth arrest, with nerve salvage approaching 90% or greater. Injuries to the trigeminal, facial, and acoustic nerves, and to the cerebellum, are possible complications of both procedures. In patients who are minimally symptomatic with small tumors, serial monitoring with MRI is a viable nonsurgical option. All patients should be evaluated by a specialist in the evaluation and treatment of vestibular schwannoma, because smaller tumor size at detection is associated with a better long-term outcome.[33,37]

Disposition

Patients with suspected acoustic neuroma should be referred for an audiogram or MRI and evaluation by a specialist in either otolaryngology or neurosurgery.

■ DIABETIC CRANIAL MONONEUROPATHY

Perspective

Cranial mononeuropathies occur uncommonly, usually are a complication of diabetes, and most often affect the extraocular muscles. The oculomotor nerve is most commonly affected, followed in order by the trochlear and abducens nerves. In one large series in Japan, the incidence of cranial nerve palsies was 1.0% among diabetics and 0.1% among nondiabetics.[40,41] Whereas ophthalmoplegia appears to be closely related to diabetes, facial palsy is less strongly correlated with this disease.[40]

KEY CONCEPTS

- The onset of unilateral auditory symptoms, especially sensorineural hearing loss, requires evaluation and referral to an ear, nose, and throat specialist.
- Neurologic symptoms of lower cranial nerve dysfunction, ataxia, or raised ICP may be caused by a benign tumor of the cerebellopontine angle.
- The smaller the tumor at diagnosis, the better the long-term outcome with definitive treatment.

Principles of Disease

The pathologic basis of diabetic mononeuropathy appears to be ischemia of the affected cranial nerve caused by occlusion of an intraneural nutrient artery serving the nerve. This occlusion leads to injury located primarily in the center of the nerve, because the core fibers are more dependent on the supply from such nutrient arteries. The peripheral fibers are less affected because they also are supplied by collateral vessels. In the oculomotor nerve, the preservation of the circumferentially located parasympathetic fibers explains the pupillary sparing that usually is found in this syndrome. In two studies, the microvascular changes in the intraneural arteries that lead to occlusion were noted in diabetic patients but absent in nondiabetics.[42,43]

Clinical Features

Patients typically describe acute onset of unilateral retro-ocular and supraorbital pain, diplopia, and ptosis.[41] The physical manifestations of a third cranial nerve palsy include the inability to move the eye superiorly and medially, accompanied by ptosis. The pupillary light reflex usually is present. Although a less common finding, the fourth and sixth cranial nerves may be affected. Patients with a fourth cranial nerve palsy are unable to move the eye inferolaterally, and those with a sixth cranial nerve palsy are unable to move the eye laterally. Because of the long intracranial course of the sixth nerve, a patient with an isolated sixth nerve palsy should be evaluated for an intracranial lesion or increased ICP.[44]

Differential Considerations

Evaluating cranial nerve dysfunction requires a thorough history and physical examination and cranial imaging, usually with MRI. Diabetic mononeuropathy should be considered a diagnosis of exclusion, with considerations in the differential diagnosis including trauma, tumor, vertebrobasilar ischemia, aneurysm, and hemorrhage into the brainstem.[45]

Management

Treatment consists of patching the affected eye and administration of analgesics and antiplatelet therapy. The prognosis is good. If the neuropathy does not begin to resolve within 3 to 6 months, or if more than one nerve is affected, another cause should be sought. Complete resolution is expected within the first year. Antioxidant preparations, including α-lipoic acid, have been used therapeutically and have not shown harm, but

such agents have yet to be shown to have convincing clinical effect.[46]

KEY CONCEPTS

- Diabetic neuropathy is a diagnosis of exclusion because no definitive diagnostic testing is available.
- Both ischemic and hemorrhagic brainstem lesions must be ruled out in the case of an acute ophthalmoplegia.
- Extraocular mononeuropathy is sufficiently common in patients with diabetes mellitus that its occurrence in isolation warrants evaluation of the patient for previously undiagnosed diabetes.

CEREBRAL VENOUS THROMBOSIS

Perspective

No precise studies of the epidemiology of cerebral venous thrombosis (CVT) have been performed. In case series, the median patient age is approximately 37 years, with a female-to-male ratio of 3:1.[47]

Principles of Disease

Cerebral blood is drained by several major veins that lead into the dural sinuses. The major dural sinuses are the superior sagittal sinus, the inferior sagittal sinus, the straight sinus, the lateral sinuses, and the sigmoid sinuses. The variability in symptoms and signs in patients who present with CVT stems from differences in thrombus location and acuity of thrombus formation. Symptoms of intracranial hypertension are present in most patients with sinus thrombosis, whereas those with thrombosis of the cerebral veins are thought to be more prone to hemorrhagic infarction and localizing neurologic deficits.[48] As with venous thrombosis in other locations, multiple causes and predisposing factors for CVT are recognized. Underlying causes often are divided into infectious and noninfectious categories. Infectious causes include local infections, such as sinusitis, otitis media, cellulitis on the face, and systemic infections. Noninfectious causes include direct injury to the cerebral venous system from trauma, surgery, tumor, dehydration, or any other condition that may predispose the patient to development of a hypercoagulable state.[49]

Clinical Features

The symptoms and signs associated with CVT are quite varied. Headache is the primary feature of CVT in 74 to 92% of affected patients.[49,50] Papilledema is noted in 28 to 45% of cases.[47,50,51] Lethargy, decreased level of consciousness, or mental status changes may be noted. Seizures occur in 35 to 50% of patients in the acute phase.[47,49,51] In addition to the location and acuity of thrombosis formation, a patient's symptom onset will vary in accordance with the extent of collateral vessel growth in the venous territory. Early thrombotic changes may be well compensated for by the collateral venous drainage. Symptoms will appear only when the compensation for venous thrombosis is no longer sufficient. Variability in collateralization between patients also adds to the variability and time course of symptomatology. Two national and international observational studies document an average time from symptom onset to diagnosis of 7 days, reflecting the difficulty in diagnosing this rare disease entity.[47,51,52] The reported incidence of focal neurologic signs, including seizures, on clinical examination varies between series, ranging from 25 to 71%.[49,50] Because of the broad spectrum of possible clinical features, the diagnosis of CVT may be difficult but should be a consideration in any patient with unexplained headache, especially in combination with focal neurologic deficit, papilledema, or seizures.

Diagnostic Strategies

The gold standard modality for the diagnosis of CVT has shifted in recent years from cerebral angiography to magnetic resonance venography (MRV). CT scanning is useful in the initial workup of the patient with possible CVT, but noncontrast CT is neither sensitive nor specific enough to reliably confirm or exclude the diagnosis. Findings on CT that are consistent with CVT include hyperdensity of a thrombosed sinus, brain edema, and hemorrhage secondary to venous congestion. CT venography is both more sensitive and more specific in diagnosing CVT.

Similar to CT scanning, MRI also can demonstrate local changes secondary to venous congestion, such as brain edema or hemorrhage. In addition, MRI can demonstrate the possibility of CVT based on the lack of a "flow void." On conventional MRI, a flow void indicates the presence of blood flow within the sinus, whereas the absence of a flow void indicates a possible thrombus. Diagnostic accuracy, however, is greatly improved through use of MRV. This technique takes advantage of the MRI signal characteristics of flowing blood to create images of venous structures. Combining these imaging techniques further enhances diagnostic accuracy. For imaging a particular dural sinus, presence of the sinus on conventional MRI and lack of flow on MRV are diagnostic of a sinus thrombosis. This combined approach has diagnostic sensitivity similar to that of conventional angiography.[49,53]

Two small studies show similar sensitivity between MRV and CT venography for the diagnosis of CVT when the CT study is performed on a multidetector row CT scanner. Both studies, involving a total of 69 patients, showed 100% sensitivity of CT venography for CVT in comparison with MRV.[54,55] The sensitivity of CT venography performed by scanners that do not use multidetector row technology is unknown.

Several small studies have attempted to evaluate the usefulness of the D-dimer assay as a screening tool to exclude CVT, particularly when MRI or CT venography is not available. Although the reported sensitivity rates are fair at 83 to 100%, larger prospective studies need to be done to further define the role of D-dimer in the evaluation of CVT, because several case reports have noted normal D-dimer levels in the setting of documented CVT.[56-59] In general, although a normal D-dimer level does not exclude the diagnosis of CVT, it does appear to make this diagnosis much less likely, particularly in a patient with symptoms of less than 2 weeks in duration.

Differential Considerations

Considerations in the differential diagnosis of CVT include the conditions that cause patients to present with the new onset of neurologic deficits, alteration in consciousness, or severe headache. A diagnosis of CVT should be considered in a patient with such symptoms when the etiology is unclear, presence of having a hypercoagulable state is likely, and the head CT scan is normal in appearance or shows subtle signs of CVT.

Management

CVT is a relatively rare disease, and controlled studies evaluating its treatment are lacking. Current therapeutic consensus

strongly recommends systemic anticoagulation with low-molecular-weight or unfractionated heparin to prevent further clot formation and to promote recanalization, even in patients with intracranial hemorrhage on initial imaging.[49,50,60,61] In one placebo-controlled randomized trial comprising 20 patients, anticoagulation with heparin to a target partial thromboplastin time (PTT) of 80 to 100 seconds demonstrated benefit, even in patients in which evidence of intracranial hemorrhage was seen on the CT scan before anticoagulation.[62] In another study of 60 patients randomized to receive placebo or low-molecular-weight heparin, no statistical benefit was shown for treatment.[63] Two large observational trials showed improvement in modified Rankin scale at follow-up in the anticoagulated groups, although the trials were not randomized.[47,51] Despite a paucity of randomized controlled trials, expert opinion favors anticoagulation in all groups unless another contraindication is present.[64]

Catheter-based intervention with thrombolysis has been attempted in multiple case series using either urokinase or tissue plasminogen activator. Thrombolysis was shown to be relatively safe and relatively successful in very small case series.[61] In one nonrandomized study of 40 patients, 20 received systemic heparin and 20 received catheter-based infusion of urokinase followed by systemic heparin. Despite initially worse neurologic function in the thrombolysis group, a significant difference in neurologic function favoring thrombolysis was observed at discharge.[65] Although this therapy is promising, it should be considered only for patients with symptoms of decreased level of consciousness, elevated ICP, or rapid deterioration on neurologic examination.

Disposition

All patients with suspected CVT should be admitted to a unit capable of providing a high level of care with neurologic consultation. Patients should be anticoagulated if no contraindication exists, and catheter-based thrombolysis should be considered in patients with depressed mental status or focal findings on neurologic exam.

KEY CONCEPTS

- CVT is a relatively rare entity, and only awareness of and familiarity with the clinical presentation will lead to the correct diagnosis.
- The onset may be insidious with a considerable delay between onset and arrival in the treatment setting.
- The differential diagnosis for CVT should consider other conditions that cause patients to present with new-onset neurologic deficits, alteration in consciousness, or severe headache. CVT is more likely to be present in such patients when the etiology is unclear, the patient is suspected of having a hypercoagulable state, and the head CT is normal in appearance or shows subtle signs of CVT.
- Noncontrast CT scanning is not adequate to rule out CVT. An MRI with MRV is recommended, although multidetector row CT venography is an acceptable alternative.
- Treatment of most patients with CVT should include systemic anticoagulation, even in the setting of hemorrhagic cerebral infarcts, unless another contraindication exists.

MULTIPLE SCLEROSIS

Perspective

Multiple sclerosis (MS) is an inflammatory disease that affects the central nervous system (CNS). Although the exact etiology remains uncertain, the pathologic manifestation of this inflammatory disease is a demyelination of discrete regions (plaques) within the CNS with a relative sparing of axons. The clinical picture is highly variable but is classically characterized by episodes of neurologic dysfunction that evolve over days and resolve over weeks.

MS has an overall prevalence in the United States of 0.1%. The peak age at onset is 25 to 30 years, with women being slightly younger at onset than men. The incidence in women exceeds that of men by a ratio of 1.8 : 1. The worldwide prevalence is greatest in the United Kingdom, Scandinavia, and North America. Epidemiologic studies indicate that both genetic and environmental factors are associated with an increased incidence of this disease. MS has a 30% concordance rate between monozygotic twins, and 20% of patients with MS have at least one affected relative. MS is more common in temperate climates. It is rare between 23 degrees north and south latitudes but has a rising incidence above and below 50 degrees north and south latitudes, respectively. Although no exact environmental factor has been identified, if a person emigrates from an area of high prevalence to an area of low prevalence before the age of 20, the risk is diminished. MS is rare in Africans and Asians, but African Americans have a higher incidence than their relatives who remain in Africa.[66] In addition, reports of clusters or miniepidemics support environmental factors. Thus, an environmental cause superimposed on genetic susceptibility appears to be a likely etiologic scenario.[67,68]

Principles of Disease

MS is considered to be an organ-specific autoimmune disease. One theory proposes that genetic factors interact with an environmental trigger or infection to establish pathologically autoreactive T cells in the CNS. After a long and variable latency period (typically 10 to 20 years), a systemic trigger, such as a viral infection or superantigen, activates these T cells. The activated T cells, on reexposure to the autoantigen, initiate the inflammatory response. This sets off a complex immunologic cascade that leads to the demyelination characteristic of MS. This demyelination process releases CNS antigens that are hypothesized to initiate further episodes of autoimmune-induced inflammation. The mechanisms underlying this autoimmunity in MS are unknown.[69]

Clinical Features

The clinical picture in MS is one of marked heterogeneity. The classic clinical syndrome consists of recurring episodes of neurologic symptoms that rapidly evolve over days and slowly resolve. Variability occurs in age at onset, location of CNS lesions, frequency and severity of relapses, and the degree and time course of progression.

The clinical features of MS can be divided into areas of specific CNS impairment: cognition, cranial nerves, motor pathways, sensory pathways, cerebellar pathways, and bowel, bladder, and sexual dysfunction.[66]

Patients with MS have frequent complaints of poor memory, distractibility, and a decreased capacity for sustained mental effort. Formal neuropsychological testing suggests that cognitive involvement is common and underreported. Specifically,

neuropsychological testing has shown that 43 to 65% of patients with MS have some degree of cognitive impairment.[70,71] Of note, a correlation has been found between the MRI-based total lesion load and presence of cognitive impairment.[72]

Cranial nerve dysfunction is common in MS. The most common associated cranial nerve abnormality is *optic neuritis*, a unilateral syndrome characterized by pain in the eye and a variable degree of visual loss affecting primarily central vision. Within 2 years of an attack of optic neuritis, the risk of MS is approximately 20%, and within 15 years, it is approximately 45 to 80%.[73,74] Optic neuritis often is the first symptom of MS.[75,76]

As a result of lesions in the vestibulo-ocular connections, the oculomotor pathways also may be affected. The deficit may manifest as diplopia or nystagmus. The nystagmus may be severe enough that the patient may complain of oscillopsia (a subjective oscillation of objects in the visual field). Cranial nerve impairment also may include impairment of facial sensation, which is relatively common. Unilateral facial paresis also may occur. In addition, the occurrence of trigeminal neuralgia in a young person may be an early sign of MS.

Motor pathways also are commonly involved. Specifically, corticospinal tract dysfunction is common in patients with MS. Paraparesis or paraplegia is all too common and occurs with greater frequency than upper extremity lesions, owing to the common occurrence of lesions in the motor tracts of the spinal cord. In patients with significant motor weakness, spasms of the legs and trunk may occur on attempts to stand from a seated position. This dysfunction is manifested on physical examination as spasticity that typically is worse in the legs than in the arms. The deep tendon reflexes are markedly exaggerated, and sustained clonus may be demonstrated. Although these symptoms frequently are bilateral, they generally are asymmetrical.[66]

Sensory manifestations are a frequent initial feature of MS and will be present in nearly all patients at some point during the course of the disease. Sensory symptoms are commonly described as numbness, tingling, "pins and needles" paresthesias, coldness, or a sensation of swelling of the limbs or trunk.[66]

Impairment of the cerebellar pathway results in significant gait imbalance, difficulty with coordinated actions, and dysarthria. Physical examination reveals the typical features of cerebellar dysfunction, including dysmetria, dysdiadochokinesis (an impairment of rapid alternating movements), a breakdown in the ability to perform complex movements, an intention tremor in the limbs and head, truncal ataxia, and dysarthria.[66]

Impairment of bowel, bladder, and sexual function also is common. The extent of sphincter and sexual dysfunction usually parallels the motor impairment in the lower extremities. Urinary frequency may progress to urinary incontinence with progression of the disease. An atonic bladder may develop, which empties by simple overflow and often is associated with the loss of perception of bladder fullness and with anal and genital hypoesthesia. Constipation becomes common over time, and almost all patients with paraplegia require special measures to maintain effective bowel habits. Sexual dysfunction, although frequently overlooked, is very common in MS. Approximately 50% of patients become completely sexually inactive as a result of this disease.[66]

Diagnostic Strategies

Although no laboratory tests are diagnostic for MS, one clinical feature remains relatively unique to this disease: *Uhthoff's phenomenon*, temporary worsening of current or preexisting signs or symptoms of MS secondary to small increases in the patient's body temperature. Accordingly, exercise, a hot bath, exposure to a warm environment, or fever can bring about Uhthoff's phenomenon. This phenomenon reflects subclinical demyelination or preexisting injury to nerves without obvious significant clinical involvement before heat exposure or temperature elevation.[66]

The clinical diagnosis rests on occurrence of at least two clinical episodes with different neurologic symptoms at different times. Thus, MS commonly has been characterized as a disorder with lesions that differ in time and space. It also has been described as a relapsing-remitting disorder with symptoms that fluctuate over time.

Findings on cerebrospinal fluid (CSF) analysis are abnormal in 90% of the cases. Fifty percent of patients will have pleocytosis, with more than 5 lymphocytes per high-power field in the CSF. Approximately 70% of patients will have an elevated gamma globulin level, with immunoglobulin G (IgG) ranging from 10 to 30% of the CSF total protein. Electrophoresis of the CSF demonstrates oligoclonal bands of IgG in 85 to 95% of patients who carry a diagnosis of MS; however, oligoclonal bands of IgG also are seen with neurosyphilis, fungal meningitis, and other CNS infections. Lumbar puncture should be considered for all patients with suspected MS, but mass lesions and elevated ICP should be ruled out before lumbar puncture.[77]

The initial imaging test to aid in the diagnosis of multiple sclerosis is MRI. MRI is a sensitive test for the detection of lesions consistent with MS and also is useful to assess disease severity.[78] The lesions of MS typically appear hyperintense, or bright white, on T_2-weighted or fluid-attenuated inversion recovery (FLAIR) MRI studies. Lesions usually are multiple and commonly are found in the periventricular white matter.[79] In patients with an initial neurologic event consistent with CNS demyelination and an MRI cranial study showing multiple white matter lesions, the 5-year risk of developing MS is 60%. Patients with similar clinical syndromes and a normal MRI appearance have less than a 5% 5-year risk.[80]

Differential Considerations

Other diseases that affect the CNS white matter may be clinically and radiographically similar to MS. Considerable care must be taken to exclude these disease processes before making a diagnosis. These include CNS tumors (especially lymphomas and gliomas), spinal cord compression, vasculitides, Behçet's disease, neurosarcoidosis, postinfectious and postvaccinal encephalomyelitis, human immunodeficiency virus (HIV) encephalopathy, Lyme disease, and vitamin B_{12} deficiency.

Management

Management of patients with MS has essentially three aspects: (1) therapies aimed at halting the progression of the disease, (2) treatment for acute exacerbations, and (3) therapies designed to modify complications.

Therapies aimed at halting disease progress are based primarily on the use of either β-interferon or glatiramer acetate. The interferons are a group of natural compounds with antiviral and immunomodulatory actions, which are retained by the recombinant preparations used in therapy for MS, interferon beta-1a and interferon beta-1b. Side effects include flulike symptoms, depression, anxiety, and confusion. In one study, 560 patients with MS were randomly assigned to receive subcutaneous interferon beta-1a or placebo ($n = 187$) three times a week for 2 years. The relapse rate was significantly lower at 1 and 2 years with interferon beta-1a than with placebo. The time to first relapse was prolonged significantly and the accu-

mulation of brain lesions on MRI was lower in the treatment group than in the placebo group. The investigators concluded that subcutaneous interferon beta-1a is a well-tolerated and effective treatment for relapsing-remitting MS in terms of relapse rate, defined disability, and all MRI outcome measures.[81] β-Interferon also has been shown to retard progression to clinically definite MS and to decrease the total number of brain lesions seen on subsequent MRI studies in patients who have their first demyelinating episode with MRI abnormalities at initial presentation.[82-85] This finding highlights the importance of early evaluation and treatment.

Glatiramer acetate also has successfully been used in the treatment of MS. This agent is a mixture of synthetic polypeptides designed to mimic myelin basic protein. The mechanism of action by which glatiramer acetate exerts its effect is unknown, but it is thought to modify the immune processes responsible for the pathogenesis of MS. In one study, 251 patients with relapsing-remitting MS were randomized to receive daily subcutaneous injections of glatiramer acetate (previously called copolymer 1) or placebo for 24 months. Patients receiving glatiramer acetate experienced significantly fewer relapses and were more likely to demonstrate neurologic improvement, whereas those receiving placebo were more likely to worsen. This drug generally is quite well tolerated.[86]

Current recommendations for management of relapsing-remitting MS are to initiate treatment with β-interferon or glatiramer acetate. Such regimens have been demonstrated to decrease the volume of plaques seen on MRI and to diminish relapses.[69] Immunosuppressive agents, including mitoxantrone and azathioprine, also have been shown to be effective in reducing progression of disease but, in view of concerns over side effects, generally are used as second-line agents.[87,88]

Acute exacerbations of MS also should be targets for therapy. Although most such episodes will resolve without therapy, steroids have been demonstrated to diminish the duration of acute exacerbations. More than 85% of patients with relapsing-remitting MS show improvement with intravenous methylprednisolone. Intravenous steroids have been shown in controlled trials to speed the recovery from the visual loss of optic neuritis when compared with placebo. In addition, when patients with acute optic neuritis are treated with high-dose intravenous steroids, the 2-year rate of development of MS is reduced, although this effect diminishes over time.[74,89] Of interest, oral prednisone was not found to be helpful in the optic neuritis trials and was associated with a potential increase in the number of optic neuritis episodes.

The current standard therapy for an acute exacerbation in MS is intravenous methylprednisolone. A typical dose administered intravenously is 250 to 500 mg every 12 hours for 3 to 7 days. Whether this should be followed by an oral prednisolone taper remains controversial. Potential adverse effects of methylprednisolone therapy include fluid retention, gastrointestinal hemorrhage, anxiety, psychosis, infection, and osteoporosis.

Several therapies directed toward the complications of MS may be helpful. The associated spasticity generally is treated with baclofen. This is a highly effective therapy aimed at reducing the painful flexor and extensor spasms. A major side effect is drowsiness, which generally diminishes with continued use. Higher-dose therapy can cause confusion, especially in the setting of baseline cognitive impairment. For patients with intractable spasticity, baclofen is available for intrathecal administration by either bolus therapy or continuous implanted pump therapy. Additional therapeutic agents for control of spasticity include tizanidine, diazepam, and dantrolene.

The tremor and ataxia associated with MS occasionally are treated with propranolol, diazepam, or clonazepam. The results of these therapies, however, generally are unsatisfactory. Pain often is associated with MS and affects the shoulders, pelvic girdle, and face. The facial pain may be indistinguishable from that of trigeminal neuralgia. Treatment options include carbamazepine, baclofen, and tricyclic antidepressants. Fatigue, which is common, may be ameliorated with amantadine. This agent produces partial relief for a minority of patients. In controlled studies, the effect is only slightly better than placebo.[69]

Disposition

Patients with a history of MS who seek treatment for significant symptoms must first be evaluated to rule out other, non–MS-related pathology. Also, the presence of other systemic illnesses, especially infections, which can worsen the symptoms of MS, should be excluded. If the problem is thought to be an exacerbation of MS, most patients will require hospital admission for intravenous steroid therapy. An alternative to hospitalization may be to initiate intravenous steroids in the ED and to arrange for a next-day follow-up visit with the primary care physician or neurologist if outpatient intravenous steroid administration is an option.

Patients with the new onset of symptoms suggestive of MS should be admitted or referred to a neurologist, depending on the type and severity of symptoms.

KEY CONCEPTS

- Any patient with a long-term illness, such as MS, must be evaluated to rule out pathologic processes not related to that illness before an exacerbation of the illness can be assumed to be the cause of any problems experienced by the patient.
- Therapy for patients with MS will require consultation with the patient's primary care provider or neurologist to provide consistent disease management.
- Intravenous methylprednisolone effectively promotes earlier resolution of recurrences.
- Intravenous methylprednisolone has been shown to speed the recovery from vision loss from optic neuritis.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 104 Spinal Cord Disorders

Andrew D. Perron and J. Stephen Huff

PERSPECTIVE

Spinal cord disorders encompass a wide range of pathologic entities and affect all age groups. Some spinal cord disorders may have catastrophic outcomes if not recognized early in the clinical course. The ultimate neurologic outcome with many of these disorders may depend on expeditious recognition in the emergency department (ED), with appropriate initial investigations, neuroimaging, management, and consultation for definitive therapy. Diagnosis of these disorders may be extremely challenging, and certain disorders may mimic other disease processes until late in the clinical course, when there is clear neurologic impairment. As with many disease processes affecting the nervous system, correct diagnosis and appropriate management require knowledge of the anatomic organization of the spinal cord and skill in taking the history and in performing the neurologic examination.

This chapter generally is concerned with processes affecting the spinal cord and its vascular supply, as well as processes compressing the spinal cord. Direct trauma and mechanical instability of the spinal column are discussed in Chapter 40.

PRINCIPLES OF DISEASE

Anatomy

In adults, the spinal cord is approximately 40 cm long and extends from the foramen magnum, where it is continuous with the medulla oblongata, to the body of the first or second lumbar vertebra. Similar to the brain, the spinal cord is covered by three meningeal layers: the inner pial layer, the arachnoid, and the outer dural layer. At its lower end, the spinal cord tapers into the conus medullaris, where several segmental levels are represented in a small area. The lumbar and sacral nerve roots form the cauda equina as they descend caudally in the thecal sac before exiting the spinal canal at the respective foramina. The non-neural filum terminale runs from the tip of the conus and inserts into the dura at the level of the second sacral vertebra.

Two symmetrical enlargements of the spinal cord contain the segments that innervate the limbs. The *cervical enlargement* (cord level C5 to T1) gives rise to the brachial plexus and subsequently to the peripheral nerves of the upper extremity. The *lumbar enlargement* (L2 to S3) gives rise to the lumbosacral plexus and peripheral nerves of the lower extremity. The space surrounding the spinal cord within the spinal canal is reduced in the area of the enlargements, potentially leaving the cord more vulnerable to compression in these regions. At each segmental level, anterior (ventral) and posterior (dorsal) roots arise from rootlets along the anterolateral and posterolateral surfaces of the cord. At each level, the anterior root conveys the outflow of the motor neurons in the anterior horn of the spinal cord, and the posterior root contains sensory neurons and fibers that convey sensory inflow.

The arterial supply of the spinal cord is derived primarily from two sources. The single anterior spinal artery arises from the paired vertebral arteries. This anterior spinal artery runs the entire length of the cord in the midline anterior median sulcus and supplies roughly the anterior two thirds of the spinal cord. Blood supply to the posterior third of the spinal cord derives from the smaller paired posterior spinal arteries. The anterior and the posterior spinal arteries receive segmental contributions from radicular arteries, the largest being the radicular artery of Adamkiewicz, which typically originates from the aorta between T8 and L4. The venous drainage of the cord largely parallels the arterial supply.

The internal anatomy of the spinal cord is divided into central gray matter, which contains cell bodies and their processes, and surrounding white matter, where the ascending and descending myelinated fiber tracts are located. These fiber tracts are organized into discrete bundles, with the ascending tracts conveying sensory information and the descending tracts conveying the efferent motor impulses and visceral innervation.

For clinical purposes, neuroanatomy of the spinal cord may be greatly simplified, as depicted in Figure 104-1. Major ascending sensory tracts are represented on the right side of the figure, with motor tracts on the left side. The posterior columns carry afferent ascending proprioceptive and vibratory information on the ipsilateral side of the cord to the area stimulated; decussation of these fibers occurs in the medulla so that contralateral cortical representation ultimately occurs. In a portion of the lateral column of white matter, the lateral spinothalamic tract conveys afferent information about pain and temperature. (Tracts are named with their point of origin first—the spinothalamic tract, for example, arises in the spinal cord and travels to the thalamus.) The tract is laminated so that sacral fibers are represented most laterally. Crossing of fibers from this tract occurs near the level of entry of the spinal nerve; a cord lesion affecting one lateral spinothalamic tract results in decreased or absent pain and temperature perception below the level of injury on the contralateral side of the body.

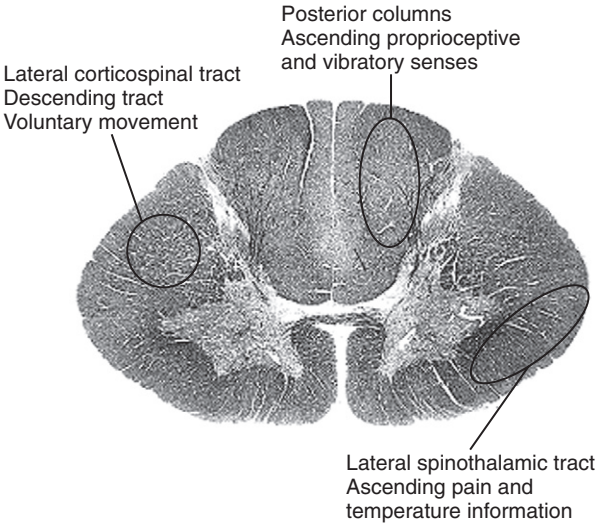


Figure 104-1. Simplified spinal cord anatomy showing clinically essential motor and sensory tracts. (Photomicrograph courtesy of John Sundsten, Digital Anatomist Project, University of Washington.)

For clinical purposes, the major descending motor tract is represented in the lateral corticospinal tract (which, as the name implies, originates in the cortex and flows toward the spinal cord). This tract also is anatomically organized, with efferent motor axons to the cervical area located medially and the sacral efferent axons located laterally. Decussation of this descending tract occurs in the medulla. The cell bodies of the lower motor neurons (anterior horn cells) are in the ventral portion of the gray matter of the spinal cord.

CLASSIFICATION OF SPINAL CORD SYNDROMES

The anatomic organization of the spinal cord lends itself to a corresponding anatomic-pathophysiologic classification of cord dysfunction. Any of the different anatomic syndromes may be the final clinical picture of a variety of clinical processes either intrinsic or extrinsic to the spinal cord. The syndromes frequently exist in partial or incomplete forms.

Complete (Transverse) Spinal Cord Syndrome

Complete spinal cord lesions may occur as either acute or subacute pathologic processes. A *complete* spinal cord lesion is defined as a total loss of sensory, autonomic, and voluntary motor innervation distal to the spinal cord level of injury. Reflex responses mediated at the spinal level, such as muscle stretch ("deep tendon") reflexes, may persist, although they also may be absent or abnormal. Autonomic dysfunction may manifest with hypotension (neurogenic shock) or priapism. The most common cause of the complete transverse cord syndrome is trauma, although this anatomic syndrome is nonspecific as to etiology.[1,2] Other causes of acute complete cord syndrome include infarction, hemorrhage, and entities causing extrinsic compression. Of patients in whom complete transverse syndromes develop and persist for more than 24 hours, functional recovery does not occur in 99%.[3,4] Any evidence of cord function below the level of injury denotes a partial rather than a complete lesion. Signs such as persistent perineal sensation ("sacral sparing"), reflex rectal sphincter tone or voluntary rectal sphincter contraction, or even slight voluntary toe movement suggest a partial cord lesion, which usually carries a better prognosis than a complete lesion.[1]

Spinal shock refers to the loss of muscle tone and reflexes with complete cord syndrome during the acute phase of injury. The intensity of the spinal shock increases with affected spinal cord level.[5] Spinal shock typically lasts less than 24 hours but has been reported occasionally to last days to weeks.[5,6] A marker of spinal shock is loss of the bulbocavernosus reflex, which is a normal cord-mediated reflex that also may be preserved in complete cord lesions. The bulbocavernosus reflex involves involuntary reflex contraction of the anal sphincter in response to a squeeze of the glans penis or a tug on the Foley catheter. The termination of the spinal shock phase of injury is heralded by the return of the bulbocavernosus reflex; increased muscle tone and hyper-reflexia follow later.[1,5,6]

Incomplete Spinal Cord Lesions

Incomplete spinal lesions are characterized by preservation of function of various portions of the spinal cord. Of all incomplete spinal lesions, most can be classified generally as one of three clinical syndromes: central cord syndrome, Brown-Séquard syndrome, or anterior cord syndrome (Table 104-1).

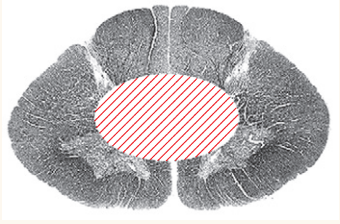
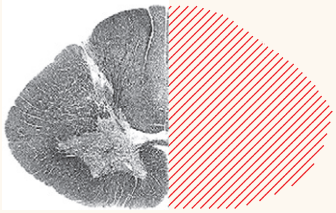
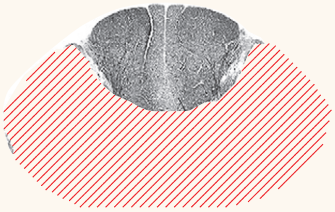
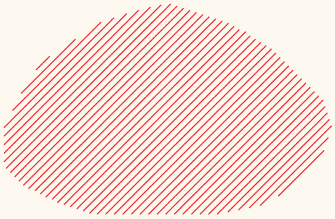
Central Cord Syndrome

Central cord syndrome, first described by Schneider and colleagues in 1954, is the most prevalent of the partial cord syndromes.[7,8] Because of the anatomic organization of the spinal cord, a central cord injury is characterized by bilateral motor paresis, with upper extremities affected to a greater degree than lower extremities, and distal muscle groups affected to a greater degree than proximal muscle groups. Sensory impairment and bladder dysfunction are variable features. At times, burning dysesthesias in the upper extremities may be the dominant feature.[9] Central cord injury affects the central gray matter and the central portions of the corticospinal and spinothalamic tracts. It is caused most often by a hyperextension injury, with the postulated pathomechanism being squeezing or pinching of the spinal cord anteriorly and posteriorly by inward bulging of the ligamentum flavum. The most common cause of such injuries is a fall, followed in frequency by a motor vehicle crash.[7,8] The result is contusion to the spinal cord, with the central portion being most affected. This injury classically occurs in elderly individuals with degenerative arthritis and spinal stenosis in the cervical area, but may affect any patient with cervical canal narrowing of any etiology (e.g., congenital narrow canal as seen in achondroplasia or canal narrowing from disk protrusion or tumor). The prognosis with central cord syndrome depends on the degree of injury at presentation and patient age.[10,11] In patients younger than 50 years of age, more than 80% regain bladder continence, and approximately 90% return to ambulatory status. In patients older than 50, only 30% regain bladder function, with approximately 50% regaining the ability to ambulate.[11]

Brown-Séquard Syndrome

Brown-Séquard syndrome, first described in 1846 by the one physician for whom it is named,[12] is the result of an anatomic or functional hemisection of the spinal cord. Usually associated with penetrating injuries,[13] Brown-Séquard syndrome also may be seen with compressive or intrinsic lesions. The syndrome has been reported in association with spinal cord tumors, spinal epidural hematoma, vascular malformations, cervical spondylosis, degenerative disk disease, and radiation injury and as a

Table 104-1 Spinal Cord Syndromes

SYNDROME	SENSORY	MOTOR	SPHINCTER INVOLVEMENT
Central cord syndrome 	Variable	Upper extremity weakness, distal > proximal	Variable
Brown-Séquard syndrome 	Ipsilateral position and vibration sense loss Contralateral pain and temperature sensation loss	Motor loss ipsilateral to cord lesion	Variable
Anterior cord syndrome 	Loss of pin and touch sensation Vibration, position sense preserved	Motor loss or weakness below cord level	Variable
Transverse cord syndrome—complete 	Loss of sensation below level of cord injury	Loss of voluntary motor function below cord level	Sphincter control lost
Conus medullaris syndrome	Saddle anesthesia may be present, or sensory loss may range from patchy to complete transverse pattern	Weakness may be of upper motor neuron type	Sphincter control impaired
Cauda equina syndrome	Saddle anesthesia may be present, or sensory loss may range from patchy to complete transverse pattern	Weakness may be of lower motor neuron type	Sphincter control impaired

complication of spinal instrumentation.[13] The syndrome in its pure form is characterized by ipsilateral loss of motor function and proprioception or vibration, with contralateral loss of pain and temperature sensation, below the spinal cord level of injury. Because fibers associated with the lateral spinothalamic tract ascend or descend one or two spinal cord segments before crossing to the contralateral side, ipsilateral anesthesia (pain and temperature modalities) may be noted one or two segments above the lesion, although this observation is variable. Most patients with Brown-Séquard syndrome incur only partial sensory and motor impairment, and the classic pattern is not seen.[11,13,14] Brown-Séquard syndrome carries the best prognosis of any of the incomplete spinal cord syndromes. Fully 80 to 90% of patients with Brown-Séquard syndrome regain bowel and bladder function, 75% regain ambulatory status, and 70% become independent in their activities of daily living.[11]

Anterior Cord Syndrome

Anterior cord syndrome is characterized by loss of motor function, pinprick, and light touch below the level of the lesion, with preservation of posterior column function, including some touch, position, and vibratory sensation. Although most reported cases of anterior spinal syndrome follow aortic surgery,[15] the syndrome also may occur after severe hypotension, infection, myocardial infarction, vasospasm from drug reaction, and aortic angiography.[16] The anatomic lesion may be the result of a cervical hyperflexion injury resulting in a

cord contusion or from protrusion of bony fragments or herniated cervical disk material into the spinal canal. Rarely, it is produced by laceration or thrombosis of the anterior spinal artery or a major radicular feeding vessel.[11] Patients present with the characteristic neurologic findings noted earlier. Functional recovery varies; most improvement occurs over the first 24 hours, but little improvement is expected thereafter.[4] Although anterior cord lesions from ischemia usually are incomplete, patients without motor function at 30 days have little or no likelihood of regaining any motor function by 1 year.[15,17] Overall, only 10 to 20% of patients with this entity regain some muscle function, and even in this group, there is little power or coordination.[11]

Conus Medullaris Syndrome and Cauda Equina Syndromes

The separation of conus medullaris and cauda equina lesions in clinical practice is difficult because the clinical features of the disorders overlap. Additionally, a combined lesion may occur that masks clear clinical symptoms or signs of either an upper or a lower motor neuron type of injury. The conus medullaris is the terminal end of the spinal cord, located at approximately the L1 level in adults. The conus medullaris syndrome may involve disturbances of urination (usually from a denervated, autonomic bladder that manifests clinically with overflow incontinence) and sphincter impairment or sexual dysfunction. Sensory involvement may affect the sacral and coccygeal segments, resulting in saddle anesthesia. Pure lesions of the conus medullaris are rare.[18] Upper motor neuron signs, such as increased motor tone and abnormal reflexes, may be present, but their absence does not exclude the syndrome. The conus medullaris syndrome can be caused by central disk herniation, neoplasm, trauma, or vascular insufficiency. Because the conus is such a small structure, with lumbar and sacral segments represented in a small area, a lesion usually causes bilateral symptoms. This finding may help distinguish lesions of the conus from lesions of the cauda equina, which often are unilateral.[18]

The *cauda equina* (Latin for "horse's tail") is the name given to the lumbar and sacral nerve roots that continue on within the dural sac caudal to the conus medullaris. Not a true "cord syndrome," cauda equina syndrome represents dysfunction at the level of nerve roots, but the anatomic clustering of nerve roots with the lumbar dural sac allows injury to several nerve roots to occur simultaneously. The etiologic lesion in the cauda equina syndrome usually is a midline rupture of an intervertebral disk, most commonly at the L4-5 level. Tumors and other compressive masses also may cause the syndrome. As in the conus medullaris syndrome, patients generally present with progressive symptoms of fecal or urinary incontinence, impotence, distal motor weakness, and sensory loss in a saddle distribution. Muscle stretch reflexes also may be reduced. The presence of urinary retention is the most consistent finding, with a sensitivity of 90%.[19] Low back pain may or may not be present.

■ CLINICAL FEATURES

History

Weakness, sensory abnormalities, and autonomic dysfunction are the cardinal manifestations of spinal cord dysfunction. The tempo and degree of impairment often reflect the disease process. Past medical history is vital because a history of coagulopathy or other systemic processes may be elicited. A history of cancer should suggest the possibility of metastatic disease. Recent trauma raises the possibility of vertebral fracture or disk protrusion.

Physical Examination

The physical examination pertinent to spinal cord dysfunction involves testing in three areas: (1) motor function, (2) sensory function, and (3) reflexes. Each component is best tested with the anatomic organization of the spinal cord in mind to help determine the level of the spinal cord dysfunction.

Motor Function

Testing of motor function encompasses examination of muscle bulk, tone, and strength. Muscle bulk is easily examined in large motor groups, such as the thigh or calf muscles, the biceps, or the triceps. Inspection of the intrinsic hand muscles also may be helpful for determining muscle bulk; wasting may be evident as hollowed or recessed regions of the hand. Decreased mass, asymmetry, or fasciculations should be noted. Tone is tested with repeated passive knee, elbow, or wrist flexion, with the examiner feeling for abnormally increased or decreased resistance. Rapid pronation-supination of the forearm is another useful method to assess tone. Increased tone may indicate spasticity or an upper motor neuron lesion, whereas decreased tone corresponds with lower motor neuron, motor endplate, or muscular problems. Finally, motor strength is graded in the upper and the lower extremities. Motor grading for the neurologic examination is relatively straightforward. Scored on a scale of 0 to 5, neuromuscular functioning is graded as follows:

0: No firing of the muscle is present.
1: The muscle fires but is unable to move the intended part.
2: The muscle is able to move the intended part with gravity eliminated.
3: The muscle is able to move the intended part against gravity.
4: The muscle is able to move the intended part, but not at full strength.
5: Full muscular strength is present.

A rectal examination is performed to assess voluntary sphincter contraction, resting tone, and, as described previously, the bulbocavernosus reflex.

Sensory Function

Sensory testing requires a cooperative patient and an attentive examiner. The spinal cord–related modalities that may be clinically useful in the ED setting include testing for pinprick, light touch (contralateral lateral spinothalamic tract), and proprioception (ipsilateral posterior column). Assessment of the patient's response to pinprick, light touch, and proprioception in all four extremities is necessary if a neurologic injury is suspected. Testing of sacral dermatomes may be an important part of the examination in some patients. As previously noted, sacral sparing is an important finding indicating that spinal cord dysfunction may be incomplete. The sensory fibers from sacral dermatomes are more peripherally located in the ascending fiber bundles; central or partial cord lesions may ablate sensation in the extremities yet allow some perception of sensation in the sacral area.

Reflexes

Muscle stretch ("deep tendon") reflexes may be tested rapidly at the bedside. Responses are graded on a scale of 0 to 4+, with

2 being normal. Hyperactive reflexes suggest upper motor neuron disease (affecting the neurons or their outflow from the brain or spinal cord), as do sustained clonus and a Babinski's sign. The absence of these reflex changes does not constitute evidence that a myelopathy is not present. In fact, one small series noted a low incidence of extensor planar responses, as well as a lack of hyper-reflexia, in patients presenting to the ED with acute or progressive cord compression or myelopathies.[20] Reflexes also may be diminished or absent when sensation is lost, or when spinal shock is present, or when lower motor neuron disease is present. Diseases of muscles or neuromuscular junctions also may decrease reflexes. In acute cord injury, reflexes may be diminished in the acute phase. The bulbocavernosus reflex may be helpful in this assessment.

DIAGNOSTIC STRATEGIES

Historical or physical examination findings that suggest spinal cord dysfunction prompt further investigations. The basic strategy is to detect or exclude extrinsic compressive lesions or other potentially treatable entities. Magnetic resonance imaging (MRI) has changed the diagnostic approach to patients with suspected spinal cord dysfunction. Plain radiographs and computed tomography (CT) scans may show bone and some soft tissue abnormalities. Conventional radiographs and CT scans are required in patients with trauma or suspected bone involvement by tumor or degenerative processes, but MRI shows many of these abnormalities and defines the spinal cord as well as the soft tissue structures associated with it. Tissue damage patterns within the cord, such as hemorrhage and edema, also may be detected with MRI. CT myelography may be able to answer some of these questions in patients in whom implanted metal precludes MRI but generally does not yield the same level of detail. After imaging studies exclude compressive lesions or other masses affecting the spinal cord, the possibility of inflammatory or demyelinating disorders remains, and lumbar puncture may be useful in diagnosis.

DIFFERENTIAL CONSIDERATIONS

The prime principle in management of spinal cord dysfunction is to consider and exclude potentially treatable problems. The clinical assessment of spinal cord dysfunction is limited to detecting weakness, sensory alterations, sphincter dysfunction, and perhaps reflex abnormalities. Pain in the back may be present depending on the pathologic process but generally is not helpful in formulating a list of considerations for the differential diagnosis. Because potential functional loss and impact on quality of life are great, the detection of a process for which some intervention is possible assumes great importance. A likely diagnosis of spinal cord infarction may be entertained, but the pursuit of a treatable process, such as spinal cord compression from an epidural hematoma, should be seriously considered.[21] This discovery process may involve specialty consultation or obtaining studies not readily available in many ED settings, such as MRI. As a general rule, liberal use of consultation and imaging is recommended when the possibility of spinal cord dysfunction is considered. The history may suggest a specific cause and will guide the tempo of investigation. The caveat is that spinal cord diseases may mimic many other disease processes, and neither the history nor physical examination may allow diagnosis until appreciable neurologic dysfunction has developed.

The picture of a *complete* transverse spinal cord syndrome with paraplegia, sensory loss at a clear anatomic level, and sphincter dysfunction cannot be fully simulated by other anatomic lesions. *Incomplete* or evolving spinal cord syndromes may be imitated by other disease processes. It is always prudent to focus the differential diagnosis on anatomic considerations—the classic "where is the lesion?" approach (Table 104-2). Progressive lower extremity weakness and sensory alteration may represent cord dysfunction but could reflect an intracranial vertex mass with bilateral cortical dysfunction. Ataxia may be a finding in cerebellar disease but also has rarely been reported as an isolated finding with spinal cord compression. Another example is rapidly progressive paralysis in a patient with areflexia and quadriplegia; ascending paralysis (Landry-Guillain-Barré syndrome) at times may mimic an acute cord lesion.

Generally, pathologic processes involving the spinal cord may be divided into processes affecting the cord or its blood supply primarily, such as demyelination, infection, or infarction, and processes that compress the cord, most often originating outside the dura (Box 104-1). *Myelitis* is a comprehensive term for spinal cord inflammation with dysfunction, and the potential causes are legion. The clinical presentation often is similar across the variety of entities that may cause cord compression. The tempo of the process may yield a different clinical picture. In chronic compression, muscle wasting and abnormal reflexes may be present, whereas both of these may be lacking in acute compression. A neurologic deficit in concert with back pain strongly suggests a spinal cord lesion, necessitating prompt investigation to identify a specific cause. Atypical presentations for these lesions are the rule, and additional diagnostic studies should be pursued as appropriate.

Table 104-2 Clinical Characteristics of Neuromuscular Diseases

	HISTORY	STRENGTH	DTR	SENSATION	WASTING
Myelopathy	Trauma, infection, cancer	Normal to decreased	Increased	Normal to decreased	No
Motor neuron disease (ALS)	Progressive difficulty with swallowing, speaking, walking	Decreased	Increased	Normal	Yes
Neuropathy	Recent infection Ascending weakness	Normal or decreased Distal > proximal	Decreased	Decreased	Yes
Neuromuscular junction disease	Food (canned goods) Tick exposure Easy fatigability	Normal to fatigue	Normal	Normal	No
Myopathy	Thyroid disease Previous similar episodes	Decreased Proximal > distal	Normal	Normal	Yes

ALS, amyotrophic lateral sclerosis; DTR, deep tendon reflex.

BOX 104-1 NONTRAUMATIC ETIOLOGIES OF SPINAL CORD DYSFUNCTION

Processes Affecting the Spinal Cord or Blood Supply Directly
- Multiple sclerosis
- Transverse myelitis
- Spinal arteriovenous malformation/subarachnoid hemorrhage
- Syringomyelia
- HIV myelopathy
- Other myelopathies
- Spinal cord infarction

Compressive Lesions Affecting the Spinal Cord
- Spinal epidural abscess
- Spinal epidural hematoma
- Diskitis
- Neoplasm
  - Metastatic
  - Primary CNS

HIV, human immunodeficiency virus; CNS, central nervous system.

MANAGEMENT

Just as the clinical manifestations of spinal cord dysfunction are nonspecific with respect to etiology, the treatment for many of the disease entities often is nonspecific. Steroid administration has been recommended as therapy in spinal cord trauma, although this use of steroids has been seriously questioned in the literature.[22-24] Steroids also have been used with many nontraumatic causes of cord compression, despite the lack of rigorous clinical studies supporting this use. Radiation treatment is recommended for cord compression by tumor. Surgical consultation for decompression may be considered, although the indications for surgery and timing of surgery are controversial.

A specific diagnosis is needed to guide therapy. Accordingly, involvement of appropriate consultants and discussion of what may be understudied therapies are suggested.

SPECIFIC DISEASE PROCESSES

As noted earlier, spinal cord disorders may be grouped into lesions resulting from processes intrinsic to the cord and vasculature and lesions causing extrinsic compression. The order of the following discussion roughly corresponds with the organization of Box 104-1.

Intrinsic Cord Lesions

Multiple Sclerosis

Principles of Disease. *Demyelination* denotes a disease process with the prominent feature of partial or complete loss of the myelin surrounding the axons of the central nervous system. Multiple sclerosis (MS) is the most common example of such a process; spinal cord involvement may dominate the clinical picture.

Clinical Features. Central nervous system lesions that are "scattered in time and space" are the hallmark of MS. The demyelinated segments do not transmit action potentials normally, resulting in a wide variety of spinal cord–related abnormalities, depending on the location and extent of the demyelination. In addition to patchy motor and sensory deficits, patients with MS may complain of bladder dysfunction or tremor or demonstrate evidence of a transverse partial or complete cord syndrome mimicking a compressive spinal lesion.[25,26] The history may include a previous episode of optic neuritis or transient visual problems. Spinal cord lesions in MS primarily involve the lateral corticospinal tracts, the posterior columns, and the lateral spinothalamic tracts. Motor system dysfunction is the most frequent manifestation of MS involvement of the spinal cord, usually as a result of lesions in the lateral corticospinal tracts.

The examination of patients with MS often reveals paresis, increased muscle tone, hyper-reflexia, clonus, and a Babinski's response. Spinal cord involvement also may result in dysautonomias.

Diagnostic Strategies. Spinal MRI is the diagnostic imaging modality of choice because it can exclude cord compression and show lesions suggesting MS.[26-28] Cranial MRI may be helpful in showing other central nervous system lesions. Cerebrospinal fluid (CSF) testing for myelin basic protein and oligoclonal bands also is a diagnostic option, but no CSF abnormalities are entirely specific for MS.[29,30] Oligoclonal bands in the CSF may aid in the diagnosis, but they are significant only if not present in the serum as well.[29]

Differential Considerations. Considerations in the differential diagnosis include systemic lupus erythematosus, Lyme disease, neurosyphilis, human immunodeficiency virus (HIV) myelopathy, and other disorders.

Management. MS exacerbations may be treated with high-dose methylprednisolone followed by a tapering dose of prednisone. Corticosteroids have been shown to be useful in shortening the time required for recovery from an exacerbation of MS.[26] Consultation and referral to a neurologist usually are indicated. Immunosuppressive therapy in patients with the chronic progressive form of the disease has met with variable success.[25,26] Because numerous disorders can mimic MS, the definitive diagnosis of this disease usually is not made in the ED.[31]

Transverse Myelitis

Principles of Disease. *Acute transverse myelitis* refers to acute or subacute spinal cord dysfunction characterized by paraplegia, a transverse level of sensory impairment, and sphincter disturbance. It is relatively rare, with a reported annual incidence of 1 case per 1.3 million population. The presentation may be mimicked by compressive lesions, trauma, infection, or malignant infiltration. The exact pathogenesis is unknown, although it is noted to follow viral infection in approximately 30% of patients and commonly is termed "postinfectious myelitis."[32] Other postulated etiologic categories include infectious, autoimmune, and idiopathic.[33,34] No apparent cause for acute transverse myelitis is identified in 30% of the patients.[32] Progression of symptoms usually is rapid, with 66% of the cases reaching maximal deficit by 24 hours.[35] Symptoms may progress, however, over days to weeks. The thoracic cord region is affected most often by this process (60 to 70%)[35]; the cervical spinal cord is rarely affected.[36]

Clinical Features. In addition to motor, sensory, and urinary disturbances, patients with acute transverse myelitis may complain of back pain and may have low-grade fever, raising concern for spinal epidural abscess. As with MS, the examination may reveal weakness progressing to paresis, hypertonia, hyper-reflexia, clonus, and a Babinski's response. Spinal cord involvement also can result in dysautonomias.

Diagnostic Strategies. Evaluation for acute transverse myelitis is done primarily with emergent MRI to exclude compressive

lesions. Results of CSF studies are normal in 40% of the cases, with only mildly elevated protein or pleocytosis in the remaining 60%.[37] The most essential aspect of the evaluation is to eliminate a potentially treatable cause, such as spinal epidural abscess, neoplasm, or hematoma.

Differential Considerations. Considerations in the differential diagnosis for transverse myelitis include MS, spinal epidural abscess, spinal neoplasm, and hematoma.

Management. Treatment with steroids is of unknown benefit. Anecdotal reports of improvement after steroid administration exist,[35,38] but some studies have found no benefit to their use.[37] Neurologic consultation is suggested, and hospitalization usually is required.

The clinical course of acute transverse myelitis varies widely, ranging from complete recovery to death from progressive neurologic compromise.[34] Maximal improvement usually is obtained within 3 to 6 months.[39,40] At 5-year follow-up evaluation of one series of patients with this disease, 30% had a good recovery, 25% had a fair recovery, 30% had a poor outcome, and 15% had died as a result of complications of the disease.[40]

Spinal Subarachnoid Hemorrhage

Principles of Disease. Intraspinal hemorrhage is rare and occurs in the same anatomic locations as intracranial hemorrhages: epidural, subdural, subarachnoid, and intramedullary hemorrhages are all possible.[5] Spinal subarachnoid hemorrhage usually is caused by an arteriovenous malformation.[41] Hemorrhage from tumors and cavernous angiomas and spontaneous hemorrhage secondary to anticoagulation therapy also have been reported.[42,43] Bleeding may occur exclusively in the subarachnoid space or within the substance of the spinal cord itself.

Clinical Features. Patients present with excruciating back pain, of paroxysmal onset, at the level of the hemorrhage. This pain also may be in a radicular distribution or extend into the flank. Patients may complain of headache and exhibit cervical rigidity if the blood migrates into the intracranial subarachnoid space, simulating an intracranial subarachnoid hemorrhage. Variable neurologic deficits are present, depending on the magnitude and anatomic location of the hemorrhage. These deficits typically include extremity numbness, weakness, and sphincter dysfunction.[42,44] Nuchal rigidity or signs of meningeal irritation also may be present.

Diagnostic Strategies. The diagnostic study of choice is MRI. Lumbar puncture also can confirm the presence of blood in the CSF.

Differential Considerations. Considerations in the differential diagnosis include epidural abscess, tumor, transverse myelitis, ischemia from an aortic catastrophe such as dissection, and anterior spinal artery thrombosis.

Management. Treatment depends on the etiology of the hemorrhage. Neurosurgical referral is obtained for further evaluation and for clot evacuation if compression is present. Angiography may be recommended if arteriovenous malformation is suspected.

Syringomyelia

Principles of Disease. *Syringomyelia* is the presence of a cavitary lesion within the substance of the spinal cord. A syrinx usually is a chronic progressive lesion, and its location within the cord determines the constellation of neurologic findings on examination.

Clinical Features. Headache and neck pain are the most common complaints, followed by sensory disturbance, gait disorder, and lower cranial nerve dysfunction.[45] The classic pattern of sensory deficit involves a loss of pain and temperature sensation in the upper extremities, with preservation of proprioception and light touch. This phenomenon is described as a "disassociative anesthesia" because of the discrepant loss of sensory modalities. The sensory deficit often is described as being in a "cape-like" distribution over the shoulders and arms. The anatomic basis for the neurologic features of a syrinx is its location near the central canal. Here it may compress the crossing fibers of the lateral spinothalamic tract that carries pain and temperature fibers. Crude touch, position, and vibratory sensation typically are unaffected. Sensory fibers from the lower limbs are similarly spared.

The symptoms of syringomyelia develop and progress in accordance with the intracavitary pressure and location of the syrinx. The most common features on physical examination are lower limb hyper-reflexia, weakness and wasting in the hands and arms, dissociated sensory loss, and gait disorder. Symptoms may be exacerbated by a sneeze, cough, or Valsalva maneuver.[46] Ninety percent of patients in whom this process develops have Arnold-Chiari I malformation (projection of cerebellar tonsils and medulla into the spinal canal).[47] Syringomyelia also may result from spinal cord trauma (often months to years later) or compressive tumors, or may be a sequela of meningitis.[48]

Diagnostic Strategies. Syrinx is best seen on MRI. No other study currently in widespread use is equal to MRI in diagnostic ability.

Differential Considerations. Considerations in the differential diagnosis for syrinx include intrinsic spinal tumor and demyelination.

Management. When the diagnosis of syringomyelia is considered, emergent imaging in the ED is not necessary if follow-up evaluation can be arranged, because this condition usually is a slowly progressive process. In patients for whom MRI studies are obtained and the diagnosis is made, referral to a neurosurgeon is indicated, because symptoms progress in approximately two thirds of patients.[49]

Idiopathic Spastic Paraparesis

Idiopathic spastic paraparesis is a progressive disorder characterized by progressive weakness and signs of spasticity of the lower extremities. This condition sometimes also is referred to as *primary lateral sclerosis*, which describes the demyelination pattern in the lateral column of the spinal cord. This disorder typically occurs in older men. Sometimes a heritable form may be discovered. It is a diagnosis of exclusion.[50-52]

Human Immunodeficiency Virus Myelopathy

HIV myelopathy typically occurs in patients with advanced HIV disease. Weakness, gait disturbance, sphincter dysfunction, sensory abnormalities, and signs of spasticity are features of this progressive process. This is a diagnosis of exclusion, because disorders such as toxoplasmosis, lymphoma, varicella zoster, and cytomegalovirus infection may produce a similar clinical picture in immunocompromised patients. Pathologically, vacuolization of myelin sheaths in the cord may be found. Treatment is directed at the retroviral infection, although there is no proven treatment.[53,54]

Spinal Cord Infarction

Spinal cord infarction is another diagnosis of exclusion. Aortic dissection, surgery, and global ischemia are the more common causes, although this disorder may occur as a complication of systemic lupus erythematosus or may be cryptogenic. An

anterior spinal cord syndrome is the most common clinical picture. Some recovery is possible, although it generally is less complete than in cerebral stroke. The site of clinical dysfunction may be distant from the site of vascular occlusion.[55]

Extrinsic Cord Lesions

Spinal Epidural Hematoma

Principles of Disease. Spinal epidural hematoma is a relatively rare condition resulting from a variety of etiologic disorders. Its incidence is 0.1 per 100,000 population.[56,57] The etiology may be traumatic, as after lumbar puncture or epidural anesthesia or associated with spinal surgery.[1,5,58] Spinal epidural hematoma is more likely to occur in anticoagulated or thrombocytopenic patients or in patients with liver disease or alcoholism.[59] Spontaneous bleeding is rare but may arise from spinal arteriovenous malformation or vertebral hemangioma. Approximately one fourth to one third of all cases are associated with anticoagulation therapy, including low-molecular-weight heparin.[60,61]

Clinical Features. The patient usually presents with sudden, severe, constant back pain with a radicular component. It may be noted to follow a straining episode. The pain may be worsened by percussion over the spine and maneuvers that increase intraspinal pressure, such as coughing, sneezing, or straining.[62] The pain often causes the patient to seek care before the development of neurologic signs, possibly leading to delays in diagnosis.[5] Neurologic deficits follow and may progress over hours to days.[57] Anticoagulant use or an intrinsic coagulation abnormality may be present.

The patient usually is in significant distress from the pain. Motor and sensory findings depend entirely on the level and size of the hematoma but can include weakness, paresis, loss of bowel or bladder function, and virtually any sensory deficit.

Diagnostic Strategies. MRI, as with virtually all suspected intrinsic spinal disorders, is the diagnostic study of choice.[62]

Differential Considerations. Considerations in the differential diagnosis include abscess, epidural neoplasm, acute disk herniation, and spinal subarachnoid hemorrhage.

Management. Recovery without surgery is rare, and surgical consultation for consideration of emergent decompressive laminectomy must be considered. The overall mortality rate is low (at approximately 8%).[57,62] Functional recovery is related primarily to the length of time the symptoms are present. Recovery after 72 hours of symptoms is rare[63] but has been reported even without surgery.[64]

Spinal Epidural Abscess

Principles of Disease. Spinal epidural abscess is an infectious process usually confined to the adipose tissue of the dorsal epidural space, where there is a rich venous plexus. It is an uncommon disease, with an overall frequency of 0.2 to 1.2 per 10,000 hospital admissions.[65,66] Major risk factors include diabetes, intravenous drug abuse, chronic renal failure, alcoholism, and immunosuppression.[66-68] Although the disease may manifest in subacute or chronic forms, the acute presentation is seen most frequently in the ED. Thoracic and lumbar sites of infection predominate, with cervical epidural abscess being much less common.[69,70] Infection typically extends over four to five spinal vertebral segments.[71] The dura mater limits the spread of an epidural infection, making subdural or intraspinal spread uncommon. Hematogenous spread of infection to the epidural space is the most common source (seen in 26 to 50% of cases),[5,65,71] either to the epidural space or to the vertebra with extension to the epidural space. Skin and soft tissue infections are the most frequently reported identified source (in 15%)[67,71]; *Staphylococcus aureus* is the most prevalent organism, being cultured in more than 50% of cases.[65,72] Other frequently identified pathogens include aerobic and anaerobic streptococci, *Escherichia coli*, and *Pseudomonas aeruginosa*. Multiple organisms are identified in approximately 10% of cases; no organism is identified in 40%.[65,72]

Clinical Features. The classic clinical presentation of spinal epidural abscess begins with a backache that progresses to localized back pain often associated with tenderness to percussion. Fever, sweats, and rigors are common, being reported in 30 to 75% of patients.[65,72] The classic triad of back pain, fever, and progressive neurologic deficits is present in only a few patients, however, and delayed clinical diagnosis is common.[65] Radicular symptoms may not be present initially but usually develop as the disease progresses.

Without treatment, myelopathic signs will develop, usually beginning with bowel and bladder disturbance. Weakness ensues, followed by paraplegia or quadriplegia. Approximately 10% of patients with spinal epidural abscess present with encephalopathy.[65,71]

Diagnostic Strategies. MRI is the imaging modality of choice and needs to be performed emergently if the diagnosis is entertained. Other diagnostic testing is nonspecific for spinal epidural abscess, but a complete blood count may support the diagnosis, because leukocytosis commonly is present, with an average white blood cell count of 13,000/μL to 16,000/μL.[71] The erythrocyte sedimentation rate, although not specific for epidural abscess, is virtually always elevated with this condition.[65,66,71] Plain films usually are normal in appearance, unless evidence of osteomyelitis of an adjacent vertebral body is seen. Lumbar puncture is relatively contraindicated with known epidural abscess but often is performed as part of the evaluation for meningitis. CSF findings are consistent with a parameningeal infection, showing elevation of protein and some cellular response.

Differential Considerations. Any compressive spinal lesion, including tumor or hematoma, can mimic spinal epidural abscess.

Management. Urgent surgical consultation for decompression usually is required. Antibiotics effective against the most common pathogens (particularly *S. aureus*) should be started empirically. One such regimen that covers gram-positive and gram-negative organisms consists of a third-generation cephalosporin plus vancomycin, both given intravenously, plus rifampin given orally.

Outcome is related to the speed of diagnosis before the development of myelopathic signs. The disease is fatal in 18 to 23% of cases, and patients with neurologic deficit rarely improve if surgical intervention is delayed more than 12 to 36 hours after onset of paralysis.[65,71] Patients operated on before development of neurologic symptoms have an almost universally good outcome.[66,67]

Diskitis

Principles of Disease. Diskitis is an uncommon primary infection of the nucleus pulposus, with secondary involvement of the cartilaginous endplate and vertebral body. It may occur after surgical procedures or spontaneously, the latter being more common in pediatric patients.[73,74] An increased incidence of diskitis has been noted in immunocompromised patients and in patients with systemic infections. Both an acute and a chronic disease course have been described, with the acute course being more common.[73]

Clinical Features. Patients present with moderate to severe pain, localized to the level of involvement and exacerbated by

almost any movement of the spine. Radicular symptoms are present in 50 to 90% of cases.[73,74] The lumbar spine is the most common site of disease. Elevated temperature is noted in more than 90% of patients.[73] Patients experience pain with range of motion. Neurologic deficits are the exception with diskitis.

Diagnostic Strategies. Plain radiographs usually are not helpful for early diagnosis, but destruction of the disk space is highly suggestive if present. The radiographic findings become positive after 2 to 4 weeks of disease. In addition to disk space narrowing, plain films may show irregular destruction of the vertebral body endplates. Often there is a latent period (2 to 8 weeks) between the onset of back pain and the development of other clinical symptoms or abnormalities on the physical examination. MRI is the radiographic study of choice because it not only can diagnose diskitis but also can rule out paravertebral or epidural abscess. Laboratory studies often show an elevated erythrocyte sedimentation rate, but the white blood cell count usually is normal.[73,74] *S. aureus* is the most common pathogen, but gram-negative, fungal, and tuberculous infections all have been recognized.

Differential Considerations. Considerations in the differential diagnosis include spinal epidural abscess, neoplasm, and hematoma.

Management. With timely diagnosis and treatment, outcome generally is good, and medical treatment with intravenous antibiotics usually is curative. Surgery often is not necessary.[73,74]

Neoplasm

Principles of Disease. Spinal cord tumors are classified according to their relationship to the dura and spinal cord (extradural, intradural or extramedullary, and intradural or intramedullary). Spinal cord tumors produce neurologic symptoms by compression, invasion, or destruction of myelinated tracts. The resulting neurologic symptoms are directly related to the growth rate and the location of the tumor. Spinal cord tumors account for 4 to 10% of central nervous system tumors but for only 1% of all cancers. Primary tumors occur with an incidence of 1 per 1 million population.[75] Most tumors of the spinal cord are metastatic in origin, however. Approximately 10% of patients with known cancer are diagnosed with a spinal metastasis at some point in the course of their disease, and 5 to 10% of patients ultimately diagnosed with cancer first present with a spinal metastasis.[2] Lung cancer, breast cancer, and lymphoma account for more than 50% of the primary malignancies that subsequently develop spinal metastasis, spreading by the hematogenous route and direct extension. Most metastases occur in the thoracic spine, and nearly 20% of patients with tumor spread to the spine will be found to have disease at multiple levels.[2,76,77]

Clinical Features. In 95% of patients with spinal neoplasm, the initial complaint is pain, either in the back at the level of the tumor or in a radicular distribution. Pain often is characterized as dull, constant, and aching and commonly is said to worsen with recumbency (in contrast with the pain of herniated disk).[5] Nighttime pain that is severe is characteristic of spinal neoplasm.[78] Any action that increases intraspinal pressure (Valsalva maneuver, sneeze, cough) may be associated with increased pain. Neurologic deficits vary, depending on the location of the lesion. Besides a thorough neurologic examination, a search for possible primary sites should be done on the physical examination.

Diagnostic Strategies. Plain radiographs are usually the initial diagnostic test, and 70 to 85% of patients with spinal column involvement show some abnormality on these films.[78] Patients with neurologic abnormalities and suspicious findings on plain films are candidates for emergent MRI or CT myelography. In patients with a known history of neoplasm and new back pain, some authorities recommend foregoing plain films and proceeding directly to MRI, because plain films can be misleading or nondiagnostic.[79]

Differential Considerations. Considerations in the differential diagnosis include any of the compressive lesions (blood, infection). Tumor also can mimic intrinsic lesions, such as transverse myelopathy and cord infarction.

Management. Acute compressive myelopathy from neoplasm constitutes an oncologic emergency. Immediate treatment is required to preserve function and prevent deterioration. With onset of paraplegia and incontinence, less than 5% of patients regain ambulatory status.[1,80] Of patients who are ambulatory at the time of diagnosis, 60% remain ambulatory.[5] High-dose steroids, radiotherapy, and surgery all may be necessary acute interventions, and consultation with neurosurgeons, neurologists, oncologists, and therapeutic radiologists may be required.

KEY CONCEPTS

- Spinal cord disorders may manifest in subtle fashion and with nonspecific clinical signs and symptoms. In the absence of neurologic abnormalities or complaints, diagnosis of these disorders can be extremely difficult.
- Patients with rapid onset and progression of spinal cord symptoms should receive specialized imaging and consultation in the ED.
- MRI frequently is required to make a definitive diagnosis for spinal syndromes.
- With compressive lesions of the spinal cord, duration of neurologic dysfunction is directly related to ultimate neurologic outcome. The diagnosis must be made expeditiously and definitive therapy begun as soon as possible.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 105 Peripheral Nerve Disorders

E. Bradshaw Bunney and E. John Gallagher

PERSPECTIVE

Background

The nervous system is traditionally divided into central nervous system (CNS) and peripheral nervous system (PNS) components. The PNS can be further subdivided into 12 cranial and 31 spinal nerves. Disorders of the cranial nerves are discussed in Chapter 103. Because diseases of the neuromuscular junction and the myopathies are located distal to the neuron itself, they are also considered separately in Chapter 104. Radiculopathies, which are disorders of the roots of the PNS, are so commonly associated with musculoskeletal neck and back pain that they are mentioned only briefly here and are discussed in detail in Chapter 51.

The simplest approach to diseases of the PNS parallels the CNS model of separating focal from nonfocal disease. In the PNS, the first broad category is the focal group, which can be divided into those with evidence of single versus multiple lesions of peripheral nerves, known respectively as *simple mononeuropathies* and *multiple mononeuropathies* (or *mononeuropathy multiplex*). The second broad category, which constitutes the nonfocal group of peripheral neuropathies, contains the polyneuropathies. These tend to produce bilaterally symmetrical symptoms and signs, reflecting the widespread nature of the underlying pathologic process.

The evaluation of PNS disease involves a goal-directed history and physical examination targeted at answering the following three questions, each of which corresponds to a stratum of the algorithm presented in Fig. 105-1:

1. Are the sensorimotor signs and symptoms symmetrical or asymmetrical?
2. Are the sensorimotor signs and symptoms distal or both proximal and distal?
3. Is the modality involved exclusively motor, sensory, or mixed sensorimotor?

By systematically combining responses to these questions, one can identify seven discrete categories of peripheral neuropathy, each of which contains a finite set of possible diagnoses. Because pure motor or sensory findings tend to occur mainly in an asymmetrical, distal distribution, this is the only category in Figure 105-1 subdivided into pure motor and pure sensory abnormalities.

Epidemiology

Although Guillain-Barré syndrome (GBS) is the most commonly encountered emergent peripheral neuropathy in developed countries, its annual incidence is just over 1 to 2 cases per 100,000 population.[1] In contrast to the low incidence of acute peripheral neuropathies, several of which are associated with short-term mortality, the vast majority of peripheral neuropathies seen in the emergency department (ED) are subacute or chronic and are associated not with mortality but with long-term morbidity.

Current estimates suggest that about 1.5% of the U.S. population suffers from peripheral neuropathy.[2] Over 7% of the population has diabetes mellitus, with a prevalence rate of 20% in individuals older than 60 years. Roughly 50% of these individuals have peripheral neuropathy.[3]

PRINCIPLES OF DISEASE

Anatomy

The spinal component of the PNS is shown schematically in Figure 105-2. The anterior and posterior nerve roots exit the spinal cord at each segmental level. Just distal to the dorsal root ganglion they converge to form a mixed (motor and sensory) spinal nerve, of which there are 31 pairs: 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, and 1 coccygeal. The spinal nerves immediately bifurcate into anterior (ventral) and posterior (dorsal) rami. The posterior ramus travels to the back. The anterior ramus innervates the anterolateral portion of the body and supplies all peripheral nerves for the upper and lower extremities through the brachial and lumbosacral plexus, respectively. Interweaving of fibers occurs within a plexus, producing a mixed sensorimotor innervation of peripheral nerves exiting the plexus.

In addition to the motor and sensory modalities of the PNS, the autonomic nervous system has a peripheral component. Anatomically and functionally, the autonomic nervous system is divided into two parts: a sympathetic (thoracolumbar) component and a parasympathetic (craniosacral) component. Autonomic dysfunction may cause systemic abnormalities, such as orthostasis, or local problems, such as atrophic, dry skin.

Pathophysiology

The PNS has only three basic responses to a wide array of pathologic stimuli. As shown in Figure 105-2, these are (1) the myelinopathies, where the primary site of involvement is limited to the myelin sheath surrounding the axon; (2) the axonopathies, where the primary site of involvement is the axon, with or without secondary demyelination; and (3)

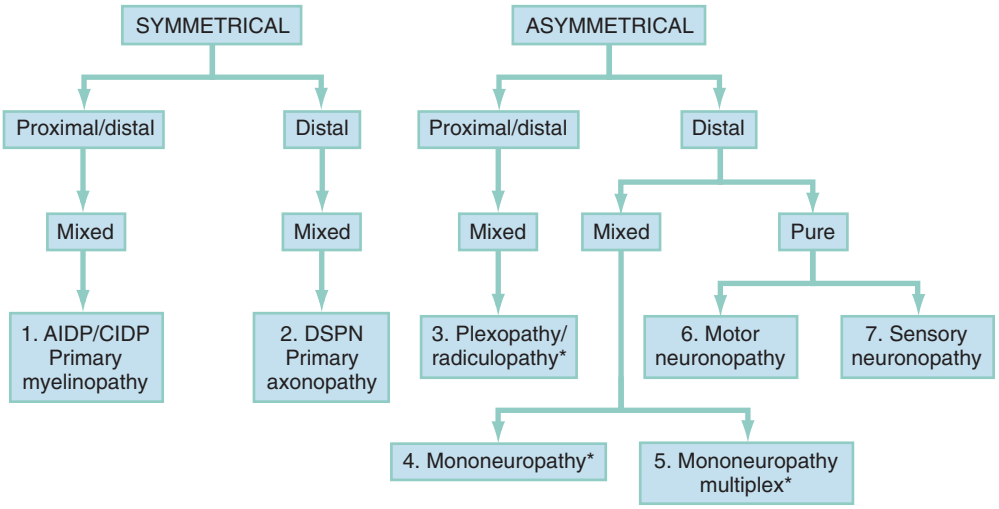


Figure 105-1. An approach to peripheral neuropathy in the emergency department. AIDP, acute inflammatory demyelinating polyneuropathy (Guillain-Barré); CIDP, chronic inflammatory demyelinating polyneuropathy; DSPN, distal symmetrical polyneuropathy. *A proximal distribution of sensorimotor findings may dominate the clinical picture in patterns 3, 4, and 5, depending on the location of the lesion(s).

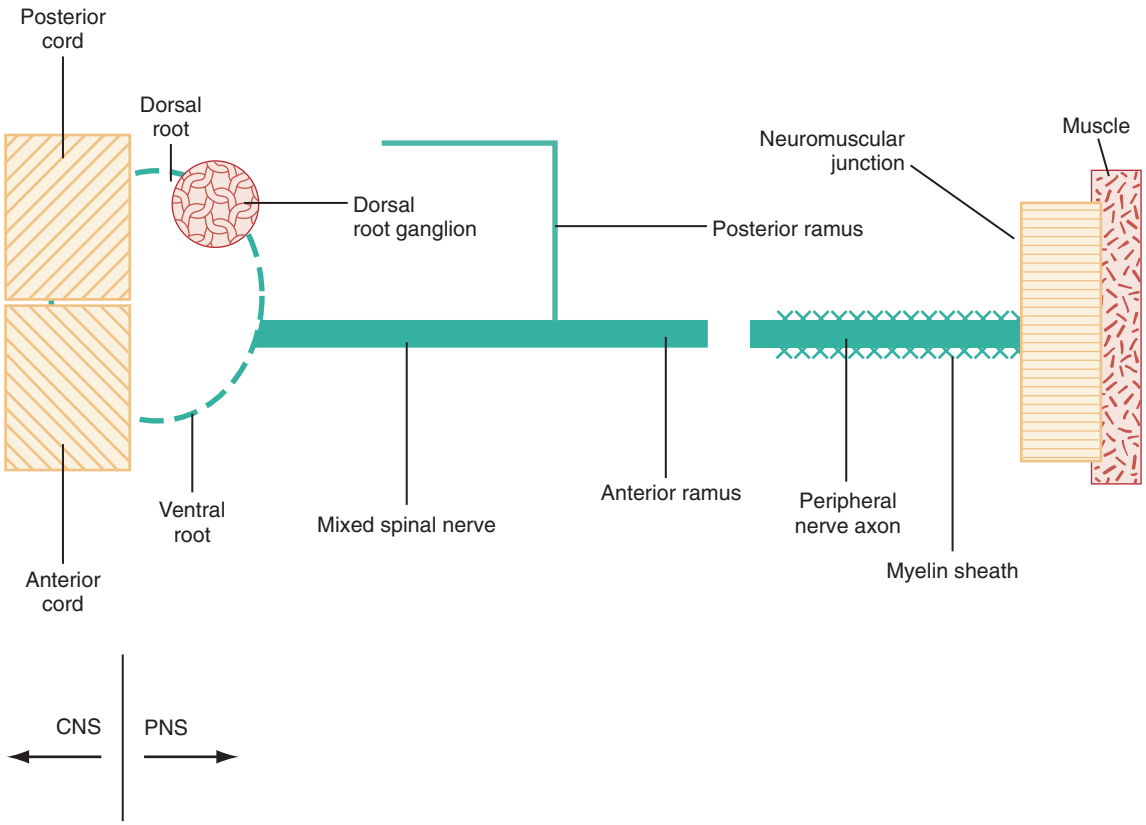


Figure 105-2. Schematic representation of macroscopic and microscopic anatomy of the peripheral nervous system and its interface with the central nervous system. See text for explanation.

the neuronopathies, where the cell body of the neuron itself is the primary site of involvement, ultimately affecting the entire peripheral nerve. Although overlap occurs, each of these prototypes has a distinctive clinical presentation, electrophysiologic profile, and microscopic appearance.

Electrophysiologic testing, that is, nerve conduction studies (NCSs) and needle electromyography (EMG), detects underlying pathologic abnormalities. Because neither test is readily available in the acute care setting, they are discussed only briefly here. Information gathered from NCSs and EMG can be used to obtain objective information on the anatomic distribution of involvement (symmetrical vs. asymmetrical and distal vs. proximal and distal) and the modalities involved (sensory, motor, or mixed). NCSs and EMG can also identify the level of the neuraxis affected by the disease process (i.e., root, plexus, or nerve); if the nerve is affected, electrophysiologic testing can help determine whether the lesion is mononeuropathic (either caused by an isolated mononeuropathy or mononeuropathy multiplex) or polyneuropathic. Finally, EMG and NCSs can distinguish axonal from myelinopathic disease, further narrowing the differential diagnosis. Prognosis is determined by the nature of pathologic involvement of the PNS. Primary demyelination spares the axon and thus carries the best prognosis. The prognosis is worse in axonopathies because reestablishing nerve function is dependent on the much slower process of axonal regeneration. Neuronopathies, which begin

BOX 105-1 CAUSES OF ACUTE, EMERGENT WEAKNESS AND POSSIBLE RESPIRATORY COMPROMISE

- Autoimmune
  - Demyelinating
    - Guillain-Barré syndrome
    - Chronic inflammatory demyelinating polyneuropathy (CIDP)
  - Myasthenia gravis
- Toxic
  - Botulism
  - Buckthorn
  - Seafood
    - Paralytic shellfish toxin
    - Tetrodotoxin (puffer fish, newts)
  - Tick paralysis
  - Metals
    - Arsenic
    - Thallium
- Metabolic
  - Dyskalemic syndromes
    - Acquired (especially with thyrotoxicosis)
    - Familial
  - Hypophosphatemia
  - Hypermagnesemia
  - Porphyria
- Infectious
  - Poliomyelitis
  - Diphtheria

with primary destruction of the nerve cell body, produce pure motor or pure sensory syndromes. Eventually the entire nerve is affected, resulting in the worst prognosis of the three.

CLINICAL FEATURES

The differential diagnosis for any patient presenting with sensory, motor, or sensorimotor complaints, particularly if localized to the extremities, should include a peripheral neuropathy. Within this group, patients with focal weakness are most concerning because they are at greatest risk for respiratory compromise. Box 105-1 lists the causes of acute, emergent weakness that may affect respiration. Although several of the disorders listed are myopathies (see Chapter 106) rather than peripheral neuropathies, they are lumped together because it is important to identify patients at risk for respiratory failure early in the course of evaluation.

As soon as the emergent causes of weakness have been excluded—which is possible in the majority of patients—the individuals with focal weakness should be assessed next to exclude CNS disease (e.g., stroke) (see Chapter 99). One can then proceed through the systematic approach to peripheral neuropathy outlined in Figure 105-1. Another way to look at the algorithm displayed in Figure 105-1 is shown in Table 105-1, with the distinguishing features of each of the seven peripheral neuropathic patterns described by distribution and modality and represented by a disease prototype.

Type 1: Demyelinating Polyneuropathies

The pattern of symmetrical weakness, usually worse distally, accompanied by variable sensory findings is characteristic of acute GBS. This pattern is discussed first because it is the most common cause of weakness associated with acute respiratory failure seen in emergency practice.

Table 105-1 Patterns and Prototypes of Peripheral Neuropathies

TYPE	PATTERN DISTRIBUTION	PROTOTYPICAL DISEASE MODALITIES
1	Proximal and distal, symmetrical, sensorimotor polyneuropathy	GBS
	Proximal and distal	Symmetrical
	Motor > sensory	
2	Distal, symmetrical, sensorimotor polyneuropathy	Diabetic DSPN
	Distal	Symmetrical
	Sensory > motor	
3	Proximal and distal, asymmetrical, sensorimotor neuropathy	Brachialplexopathy
	Proximal and distal	Asymmetrical
	Sensory and motor	
4	Distal, asymmetrical, sensorimotor mononeuropathy	CTS (median mononeuropathy)
	Distal	Asymmetrical
	Sensory and motor	
5	Distal, asymmetrical, sensorimotor mononeuropathy multiplex	Vasculitic mononeuropathy multiplex
	Distal	Asymmetrical
	Sensory and motor	
6	Distal, asymmetrical, pure motor neuronopathy	ALS
	Distal	Asymmetrical
	Motor	
7	Distal, asymmetrical, pure sensory neuronopathy	Pyridoxine toxicity
	Distal	Asymmetrical
	Sensory	

ALS, amyotrophic lateral sclerosis; CTS, carpal tunnel syndrome; DSPN, distal symmetrical polyneuropathy; GBS, Guillain-Barré syndrome.

Guillain-Barré Syndrome

GBS is a heterogeneous and unpredictable disorder, with marked variation in latency between antecedent infection and symptom onset. The clinical signs, cadence of disease progression, degree of respiratory compromise, laboratory findings, and time required for convalescence are also highly variable. The most common form of GBS is an acute inflammatory demyelinating polyneuropathy (AIDP), comprising 90% of the cases seen in the United States.[1] Less common variants include acute motor axonal neuropathy (AMAN), acute motor and sensory axonal neuropathy (AMSAN), and the Miller Fisher syndrome. AMAN accounts for most of the remaining cases seen in the United States afflicting those of Asian decent. Miller Fisher syndrome is a rare form of GBS characterized by the triad of ophthalmoplegia, ataxia, and areflexia (Box 105-2).[1,4]

The majority of patients seek treatment days to weeks after resolution of an upper respiratory or gastrointestinal illness, presenting with progressive, symmetrical distal (and usually to a lesser extent proximal) weakness. Signs and symptoms are usually worse in the lower extremities and are associated with diminution or loss of deep tendon reflexes (DTRs), variable sensory findings, and sparing of the anal sphincter. Up to 32% will have all four extremities affected at the time of presentation and 10% will have weakness that begins in the upper

BOX 105-2 DEMYELINATING POLYNEUROPATHIES

- Guillain-Barré syndrome
  - Acute inflammatory demyelinating polyradiculoneuropathy (AIDP)
  - Acute motor axonal neuropathy (AMAN)
  - Acute motor and sensory axonal neuropathy (AMSAN)
  - Miller Fisher syndrome
- Chronic inflammatory demyelinating polyradiculoplexo-neuropathy
- Malignancy
- HIV
- Hepatitis B
- Buckthorn
- Diphtheria

extremities.[1] However, the ocular muscles are usually spared. Urinary retention secondary to autonomic dysfunction may occur, contributing to a clinical picture easily mistaken for a spinal cord lesion or conus medullaris syndrome.

The most commonly infectious organisms associated with GBS are *Campylobacter jejuni* (in patients with a history of diarrhea), cytomegalovirus, Epstein-Barr virus, and *Mycoplasma pneumoniae*. AIDP is caused in part by macrophage invasion of the myelin sheath. The macrophage is believed to detect antigens in the myelin that are nearly identical to the antigens present on certain infectious organisms.[1,5,6]

In practice, patients with symmetrical weakness of relatively acute onset, decreased or absent DTRs, and variable degrees of sensory loss should be managed as if they have GBS or one of its variants, which places them at risk for respiratory compromise. Conversely, patients with predominantly sensory signs and symptoms are less likely to develop acute respiratory distress and have a more favorable prognosis.[7]

About half of patients with GBS have autonomic dysfunction, experience a peak of disease severity within a week of onset, have some form of cranial nerve involvement (usually VII), and suffer long-term sequelae of their illness. Nearly one third require ventilatory support. Both the mortality and the recurrence rate are about 3%.[8]

In addition to electrophysiologic testing, there are three ancillary tests that may be helpful in the diagnosis of GBS. Cerebrospinal fluid (CSF) analysis is useful when it demonstrates the characteristic picture of markedly elevated protein with only a mild pleocytosis. In the clinical setting of suspected GBS, this finding is highly specific. Early in the disease, however, patients may have normal CSF values. Consequently, a normal CSF cannot be used to exclude GBS because of the limited sensitivity of this test. Selective enhancement of the anterior spinal nerve roots on magnetic resonance imaging (MRI) is suggestive, but not diagnostic, of GBS.[9] The GBS disability score, which combines age, presence or absence of diarrhea, and a score of the patient's ability to ambulate independently at 2 weeks, has been shown to be predictive of prognosis at 6 months, particularly related to independent activity.[10]

Management. Individuals with suspected GBS must have their respiratory function tested. A decrease in forced vital capacity (FVC) has been shown to correlate with the need for intubation in patients with GBS. An FVC of less than 20 mL/kg was associated with pending respiratory failure and the need for intubation, whereas patients with an FVC of greater than 40 mL/kg did not require intubation.[11,12] Likewise, patients with a negative inspiratory force (NIF) of less than 30 cm water are more likely to require mechanical ventilation.[12] Other tests, such as the forced expiratory volume in 1 second (FEV_1) or peak flow rate (PFR) can also be used to assess respiratory function. Patients unable to perform these tests and those with less than 100% of predicted values should have an arterial blood gas obtained. Evidence of alveolar hypoventilation (elevated carbon dioxide [P_{CO_2}]) in a patient with an unsecured airway requires a level of intensive monitoring that is impractical in many emergency departments. Therefore, patients with weakness, CO_2 retention, or other evidence of early ventilatory failure should be considered for early, prophylactic intubation.[13]

Among patients with possible GBS who have normal pulmonary function, extensor neck strength can be monitored to predict impending ventilatory failure. Patients with probable GBS should receive neurologic consultation and be admitted to the hospital. Either plasma exchange or intravenous immunoglobulin (IVIG) should be administered. There is sound evidence that both are superior to placebo and that combination or sequential therapy confers no therapeutic advantage over either intervention alone. Plasma exchange is cumbersome and not available at many hospitals. IVIG is more readily available and is usually administered in a dose of 400 mg/kg/day for 5 days. However, IVIG is quite expensive, costing roughly $50 to $80 per gram.[14] Although not approved by the Food and Drug Administration, IVIG is supported in certain national guidelines.[15] Corticosteroids are no longer recommended for treatment of GBS.[16] Oral steroids have been shown to delay recovery. Intravenous steroids alone have been shown to impart no benefit, and though the combination of intravenous steroids and IVIG has hastened recovery, there was no affect on long-term outcome.[17–19] The marked elevation in blood pressure seen in some patients with GBS should not be treated because it is typically transient and may be followed by precipitous and unpredictable hypotension.

Type 2: Distal Symmetrical Polyneuropathies

Most polyneuropathies are characterized by a pattern of distal, symmetrical sensorimotor findings, worse in the lower than upper extremities, with a stocking-glove distribution of sensory abnormalities that gradually diminishes as one moves proximally. The motor findings and loss of DTRs, which lag behind the sensory features, follow a similar pattern of progression from distal to proximal. The diffuse, distal, symmetrical nature of this pattern is most consistent with a toxic-metabolic disease process, as yet unidentified, that causes a length-dependent axonopathy. Distal symmetrical polyneuropathy (DSPN) is the most common type of peripheral neuropathy seen in emergency practice. Only the most common causes of DSPN are discussed, with a more complete listing of causes shown in Box 105-3.

Diabetic Distal Symmetrical Polyneuropathy

The preponderance of cases of DSPN occur in diabetics, also termed diabetic polyneuropathy. Initial symptoms usually consist of "positive" sensory complaints (e.g., dysesthesias such as tingling or burning) beginning on the plantar surfaces of both feet. At the early stages of a typical DSPN, there may be some asymmetry.[20] At this juncture, it may be impossible to distinguish a focal neuropathic process such as a mononeuropathy from a polyneuropathy, although in this location, prior probability strongly favors a polyneuropathy. As the process advances, the plantar surfaces of both feet become dysesthetic before the dorsum of either foot is involved. Weakness of dorsiflexion of the big toe is usually the first motor sign, followed by weakness of foot dorsiflexion, footdrop, loss of Achilles' reflex, and later a "steppage gait."

BOX 105-3 DISTAL SENSORIMOTOR POLYNEUROPATHIES

- Diabetes mellitus
- Alcoholism
- Neoplastic or paraneoplastic
- Hereditary motor and sensory neuropathies (Charcot-Marie-Tooth)
- Cryptogenic sensorimotor polyneuropathies (CSPN)
- HIV
- Toxins
  - Organic or industrial agents
    - Acrylamide
    - Allyl chloride
    - Carbon disulfide
    - Ethylene oxide
    - Hexacarbons
    - Methyl bromide
    - Organophosphate-induced delayed polyneuropathy (OPIDP)
    - Polychlorinated biphenyls (PCBs)
    - Trichloroethylene
    - Vacor
  - Metals
    - Arsenic
    - Gold
    - Mercury (inorganic)
    - Thallium
  - Therapeutic agents
    - Amiodarone
    - Antiretrovirals
    - Dapsone
    - Disulfiram
    - Isoniazid
    - Metronidazole
    - Nitrofurantoin
    - Paclitaxel (Taxol)
    - Phenytoin
    - Statins (HMG-CoA reductase inhibitors)
    - Thalidomide
    - Vinca alkaloids (vincristine, vinblastin)
- Nutritional
  - Beriberi (thiamine or vitamin B_1)
  - Pellagra (niacin, B vitamins)
  - Pernicious anemia (vitamin B_{12})
  - Pyridoxine deficiency (vitamin B_6)
- End-organ dysfunction
  - Acromegaly
  - Chronic pulmonary disease
  - Hypothyroidism
  - Renal failure (uremic neuropathy)
- Paraproteinemias
  - Amyloidosis
  - Monoclonal gammopathy of unknown significance (MGUS)
  - Multiple myeloma
  - Waldenström's macroglobulinemia
- Porphyria

HMG-CoA, hydroxymethylglutaryl coenzyme A.

Sensory loss continues to move proximally, and before it reaches the knees, the fingertips are usually involved. DTRs are progressively lost, as is proprioception. If the latter becomes severe, patients may develop sensory ataxia. As the neuropathy continues to progress, sensory abnormalities ultimately involve all modalities and extend to a diamond-shaped periumbilical area. Far advanced disease may affect sensation over the skull vertex and facial midline structures. Atrophy and areflexia occur as weakness worsens. Severely impaired patients may be unable to ambulate or grasp objects. These symptoms have a significant impact on the patient's quality of life, affecting not only physical functioning but emotional, sleep, and social functioning. Many of these patients display signs of depression or anxiety.[21] Polyneuropathies can be difficult to diagnose and are best approached by performing electrodiagnostic studies on patients with a constellation of symptoms and signs suggesting a particular neuropathy.[22]

Management. As with virtually all peripheral neuropathies, referral is indicated for management of diabetic DSPNs. If discomfort is severe, the etiology of the neuropathy seems likely to be diabetic, and if referral is delayed, it may be necessary to provide the patient with some symptomatic relief. Because treatment of neuropathic pain has traditionally been linked to etiology rather than an underlying mechanism, the choice of pharmacologic agents is empirical, with substantial practice variation in the United States and worldwide.[23] In the United States the first choice is often a nonsteroidal anti-inflammatory drug, which has little proven efficacy and a high potential for renal impairment.[3] Based on placebo-controlled randomized clinical trials, tricyclic antidepressants and anticonvulsants appear to have the best NNTs (number of patients needed to treat in order to provide at least 50% relief of symptoms in one patient). These are generally in the range 3 to 5, with confidence intervals whose upper limits reach 10 in some instances.[24] Imipramine or amitriptyline may be started at a dose of 25 mg at bedtime (10 mg in elderly patients) and titrated slowly up to a dose of 300 mg. Carbamazepine at a dose of 200 to 400 mg every 8 hours or gabapentin at a dose of 900 to 3600 mg/day are also effective treatments.[25,26] Tramadol in two studies has shown an NNT below 5.[24] Although tramadol is a mixed opioid, development of dependence in long-term use appears to be uncommon. In a recently published guideline, the following medications were recommended for the treatment of neuropathic pain: gabapentin, opioids, tramadol, and tricyclic antidepressants.[3] Also being used is pregabalin at 150 to 600 mg/day, with a mechanism similar to that of gabapentin, and dulexetine at 60 mg/day, which is a selective serotonin and norepinephrine reuptake inhibitor.[3] Among the selective serotonin reuptake inhibitors (SSRIs), paroxetine and bupropion appear to be effective, but fluoxetine is not.[27] The summary NNT for the SSRIs has a confidence interval that reaches 50, suggesting that, pending further data, these agents should be considered second-line drugs.[24] Topical capsaicin provides relief in some patients, but the burning associated with its application has limited its usage. Improving glycemic control can prevent, diminish, or reverse early diabetic DSPNs. Patients will typically spend over $1,000 per year for pain relief from diabetic DSPN.[3]

Alcoholic Distal Symmetrical Polyneuropathy

Although the association between alcoholism and peripheral neuropathy has been well established for centuries, demonstration of a direct neurotoxic effect of alcohol remains elusive. The preponderance of evidence, from both observational studies in humans and experimental data from animal models,

suggests that the association between alcohol and peripheral neuropathy may be confounded by nutritional status (i.e., deficiency states might be the true underlying cause of alcoholic peripheral neuropathy).

The clinical and pathologic picture of alcoholic neuropathy is similar to that of the DSPN of diabetes. However, in alcoholism severe myopathy and cerebellar degeneration often complicate the clinical picture.[28] Autonomic skin changes with atrophy and hair loss accompany the sensorimotor abnormalities. Often other systemic effects of alcoholism are so severe that the patient may not notice the neuropathic symptoms. All patients with suspected alcoholic DSPN should receive dietary supplements and referral for outpatient management.

Human Immunodeficiency Virus Neuropathies

With the widespread use of highly active and effective antiretroviral treatment, peripheral neuropathies have become the most common neurologic complication of HIV infection. The typical HIV neuropathy is a DSPN, which appears to be triggered by a combination of dideoxynucleoside therapy and poorly characterized immune-mediated mechanisms associated with HIV.[29,30] These patients require referral for specialized care. In addition to standard therapies for DSPN, lamotrigine has been shown to be moderately effective in the treatment of HIV-associated painful neuropathies.[31]

Toxic and Metabolic Neuropathies

Many toxic agents and metabolic derangements produce a typical DSPN. Box 105-3 lists some of the most common toxic and metabolic causes of peripheral neuropathy. On the basis of preliminary results from a case-control study, the statins have been added to this list.[32]

BOX 105-4 Asymmetrical Proximal/Distal Peripheral Neuropathies

- Brachial plexopathy
  - Open
    - Direct plexus injury (knife or gunshot wound)
    - Neurovascular (plexus ischemia)
    - Iatrogenic (central line insertion)
  - Closed
    - Traction injuries
      - "Stingers"
      - Traction neurapraxia
      - Partial or complete nerve root avulsion
    - Radiation
    - Neoplastic
    - Idiopathic brachial plexitis
    - Thoracic outlet
- Lumbosacral plexopathies
  - Open
  - Closed
    - Traction injuries
      - Pelvic double vertical shearing fracture
      - Posterior hip dislocation
      - Retroperitoneal hemorrhage
    - Vasospastic (deep buttock injection)
    - Neoplastic
    - Radiation
    - Idiopathic lumbosacral plexitis
    - Infectious
      - Herpesvirus (sacrococcygeal)
      - Herpes simplex II
      - Herpes zoster
    - Cytomegalovirus (CMV) polyradiculopathy (HIV)

Type 3: Asymmetrical Proximal and Distal Peripheral Neuropathies (Radiculopathies and Plexopathies)

Radiculopathies are discussed in detail in Chapter 103. Plexopathies, which are discussed briefly in this chapter, are uncommon and often the result of trauma (Box 105-4). Generally, a plexopathy, whether brachial or lumbosacral, is identified by a process of elimination (i.e., a pattern of sensorimotor and reflex abnormalities that fit neither a radicular nor individual peripheral nerve distribution). Although this approach does not exclude a mononeuropathy multiplex on physical examination alone, a careful history should determine whether the patient is at risk for developing a mononeuropathy or plexopathy on the basis of underlying disease.

Most plexopathies are often the result of blunt trauma and are usually seen in young men following motor vehicle accidents. Most present for evaluation several months after injury because of the need to recover from concurrent injuries. Therapeutic intervention is often delayed in order to maximize the potential for spontaneous recovery. Several surgical repairs exist, including neurotization or nerve transfer.[33]

Radiation (actinic) plexopathy occurs after a variable period of latency following treatment, which may extend to 20 years or more. Almost all series include women who received radiation treatment for breast cancer. Among neoplastic causes, most originate from the lung or breast. Patients with probable neoplastic brachial plexopathy need imaging studies and may require immediate radiation therapy. Pain control is the focus of management.

Thoracic outlet syndrome remains a controversial disorder.[34] Although the pendulum has swung over the past 50 years from a postulated vascular cause to a neurogenic etiology, current evidence supporting the high prevalence of compression of the brachial plexus as a cause of thoracic outlet syndrome is in fact only slightly better[35] than earlier evidence favoring a vascular etiology.[36] Nevertheless, the disorder is currently felt to be most commonly due to compression of the medial or lower portion of the brachial plexus by a cervical rib or fibrous band.[37] The syndrome is characterized by gradually progressive weakness and wasting of median and ulnar hand muscles with ulnar forearm and hand sensory signs and symptoms. Patients with this clinical picture should be referred for NCSs and EMG, which are said to be diagnostic.[37] The treatment of true neurogenic thoracic outlet syndrome requires surgical removal of the rib or aberrant fibrous band to decompress the brachial plexus.[38] An excellent discussion of this entity from a different perspective can be found in Chapter 85.

Because of the complexity of plexopathies, there is no reason to expect that one can or should do more in the ED than localize the probable pathologic process to the brachial or lumbosacral plexus. Depending on severity and suspected etiology, one should either admit or refer the patient to a neurologist with experience in PNS disease.

Type 4: Isolated Mononeuropathies

The pattern of asymmetrical, sensorimotor, usually distal, peripheral neuropathy is characteristic of a mononeuropathy. Mononeuropathies are of two main types: isolated and multiple. The isolated mononeuropathies are discussed in this section, while the multiple mononeuropathies, also termed

BOX 105-5 ISOLATED MONONEUROPATHIES

- Upper extremity
  - Radial nerve
    - Axilla
    - Humerus
    - Elbow (posterior interosseous neuropathy)
    - Wrist (superficial cutaneous radial neuropathy)
  - Ulnar nerve
    - Axilla
    - Humerus
    - Elbow
    - Condylar groove
    - Cubital tunnel
  - Wrist (Guyon's canal)
  - Hand
    - Superficial terminal ulnar neuropathy
    - Deep terminal ulnar neuropathy
      - Proximal hypothenar
      - Distal hypothenar
  - Median nerve
  - Axilla
  - Humerus (musculocutaneous mononeuropathy)
  - Forearm
    - Anterior interosseus
    - Pronator syndrome (?)
  - Wrist (carpal tunnel)
  - Hand (recurrent motor branch)
  - Suprascapular mononeuropathy
    - Axillary mononeuropathy
- Lower extremity
  - Sciatic nerve
  - Femoral nerve
    - Iliacus compartment (proximal)
    - Saphenous mononeuropathy (distal)
  - Lateral femoral cutaneous (meralgia paresthetica)
  - Peroneal nerve
    - Common peroneal mononeuropathy (fibular head, popliteal fossa)
    - Deep peroneal mononeuropathy (anterior compartment)
  - Tibial nerve
    - Popliteal fossa (proximal)
    - Tarsal tunnel (distal)
  - Sural nerve
    - Popliteal fossa, calf (proximal)
    - Fifth metatarsal base (distal)
  - Plantar nerve
    - Distal to tarsal tunnel
    - Interdigital neuropathies (Morton's neuroma)
  - Obturator mononeuropathy

mononeuropathy multiplex, are discussed in the next section, as a type 5 peripheral neuropathy.

Isolated mononeuropathies are usually caused by trauma, either blunt or penetrating (Box 105-5). If the trauma is blunt, the injury may be secondary to compression from an internal or external source. Entrapment neuropathies are a subset of compression neuropathies occurring at anatomic locations where nerves traverse potentially constricting compartments or tunnels.[39] Isolated mononeuropathies may be acute, intermittent, or chronic and continuous. Antecedent peripheral neuropathy may be a risk factor for development of compression neuropathy (so-called double-crush syndrome), particularly in diabetics.[40]

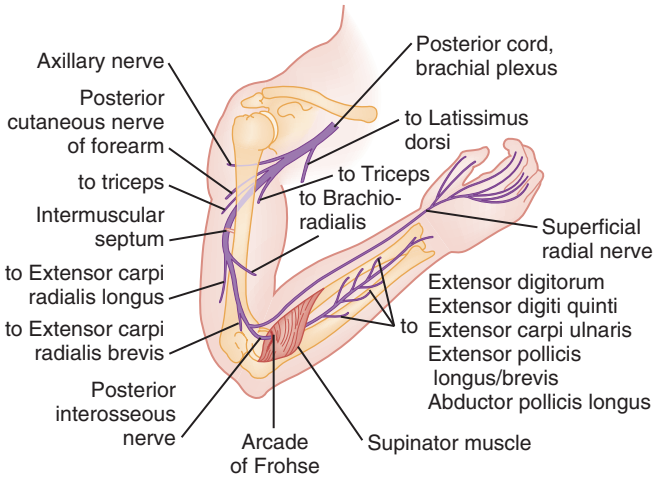


Figure 105-3. Radial nerve, major branches, right arm, lateral view. (From Stewart JD: Focal Peripheral Neuropathies, 3rd ed. Philadelphia, Lippincott Williams & Wilkins, 2000.)

Radial Mononeuropathy

The radial nerve arises from C5-T1 roots. After exiting the brachial plexus, it passes behind the proximal humerus in the spiral groove and takes a lateral (radial) course down the upper arm (Fig. 105-3). At about the level of the antecubital fossa, it bifurcates into the posterior interosseous (pure motor) and superficial radial (pure sensory) nerves.

The radial nerve controls extension of the fingers, thumb, wrist, and elbow (triceps). In contrast to the median and ulnar nerves, the radial nerve provides only *extrinsic* motor innervation to the hand (i.e., it does not supply motor fibers to any muscles that both originate and insert within the hand). In further contrast to the median and ulnar nerves, which supply most of the sensation to the hand, the radial nerve makes a contribution only to a cutaneous dorsal area overlying the first dorsal interosseus muscle, sometimes extending part of the way up the dorsa of the thumb, index, and long fingers.

Radial mononeuropathy caused by involvement at the level of the axilla is uncommon. When it occurs, it is usually associated with other upper extremity mononeuropathies or a brachial plexopathy. Although improper use of crutches may cause this syndrome, it usually occurs after an extended period of unconsciousness during which the arm is positioned in such a way that prolonged, deep compression is applied to the axilla. Axillary radial mononeuropathy is distinguished from the more common humeral form by the finding of triceps involvement in addition to typical wrist and finger drop. Triceps involvement occurs because the innervation to the triceps is proximal to the point where the nerve is most vulnerable as it winds around the humeral shaft (see Fig. 105-3).

Most radial mononeuropathies are due to so-called Saturday night palsies. The euphemism is derived from the association of radial mononeuropathy with improper positioning of the arm during deep, commonly inebriated sleep. Consequently, the radial nerve is trapped for a prolonged period between the humeral shaft and some firm surface, causing an external compression mononeuropathy. "Bridegroom's palsy" is another eponym for radial mononeuropathy, so named because the radial nerve may be compressed by the bride's head resting on the bridegroom's arm during sleep.

Because innervation of the wrist and finger extensors occurs distal to this area of the humeral shaft, findings are characterized by wrist and finger drop and mild numbness over the skin of the first dorsal interosseus muscle. Depending on the level,

degree, and duration of compression, some fascicles of the nerve may remain functional, resulting in a partial radial mononeuropathy. Thus, the superficial radial nerve may remain intact, resulting in no loss of sensation, or loss of wrist and finger extension may be incomplete.

Because the finger drop of radial mononeuropathy places the hand at a mechanical disadvantage, examination of ulnar function by testing interossei may produce false-positive findings of weakness. To adjust for this, the examiner should ask the patient to place the palm on a horizontal supporting surface such as a stretcher. With the fingers extended and no longer "dropped" at the metacarpophalangeal joints, interosseous strength can now be fairly tested. Failure to perform this maneuver may cause misdiagnosis of a simple radial mononeuropathy as a brachial plexopathy in an effort to explain what appears to be radial and partial ulnar nerve involvement.

About 90% of radial nerve palsies occurring during sleep, coma, or anesthesia recover fully, usually within 6 to 8 weeks. Evidence of denervation on EMG studies predicts a slower rate of recovery. Tourniquet injuries to the radial nerve usually recover spontaneously within 2 to 4 months. If axonal degeneration is seen on electrophysiologic testing, recovery may take longer, although virtually all radial mononeuropathies caused by tourniquets eventually resolve. About 75% of radial nerve injuries associated with a closed humeral shaft fracture recover spontaneously. In contrast, surgical intervention is needed to free the nerve from entrapment associated with complex fractures.

While patients are waiting for spontaneous recovery to occur, the hand should be maintained in about 60 degrees of dorsiflexion. Although a simple dorsal plaster or fiberglass splint treats the wristdrop, atrophy and contractures can be minimized, and function of the hand can be improved if wide rubber bands anchored to the splint at a point proximal to the wrist are attached to individual fingers to provide passive dorsiflexion.

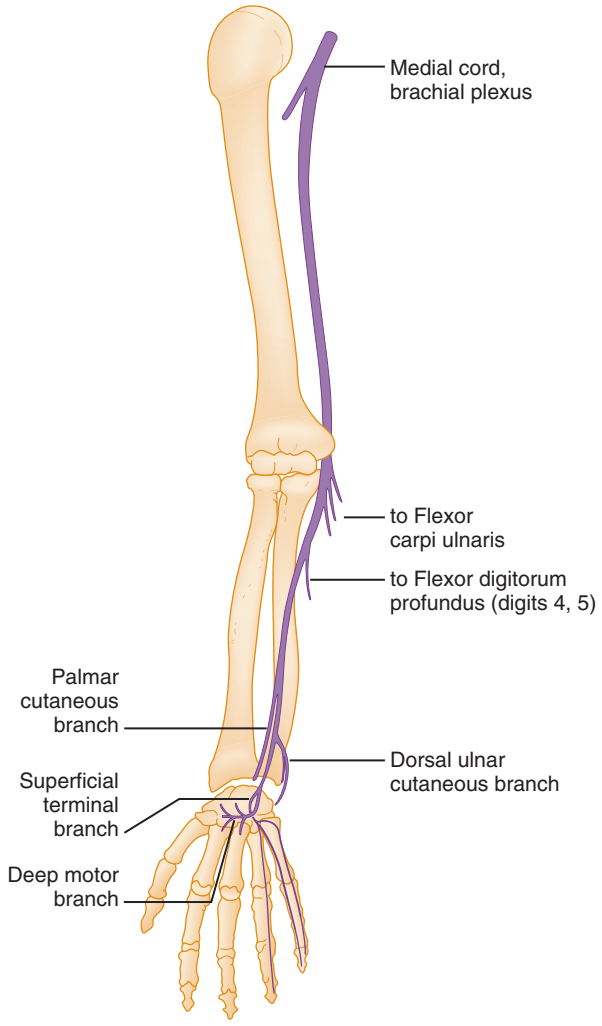


Figure 105-4. Ulnar nerve, major branches, right arm, anterior view. (From Stewart JD: Focal Peripheral Neuropathies, 3rd ed. Philadelphia, Lippincott Williams & Wilkins, 2000.)

Ulnar Mononeuropathy

The ulnar nerve includes C7-T1 roots and passes through the brachial plexus to descend medially, without branching, to the ulnar (medial) condylar groove at the elbow. It then enters the cubital canal, where it gives off branches to the ulnar wrist flexor and the deep flexors of the fourth and fifth digits.

Just proximal to the wrist, two important sensory branches leave the main trunk to supply cutaneous sensation to part of the hand (Fig. 105-4). These are the palmar and dorsal cutaneous branches, which do *not* pass through Guyon's canal. The palmar branch supplies sensation to the hypothenar eminence and the dorsal branch innervates the ulnar side of the dorsum of the hand, extending out nearly to the tip of the fifth and ulnar half of the fourth digit.

At the wrist, the nerve enters Guyon's canal (Fig. 105-5) between the pisiform and hook of the hamate, then bifurcates into the superficial terminal sensory branch and the deep motor branch.

The superficial sensory nerve supplies ulnar sensation to the palmar side of the fifth and half of the fourth digit (see Fig. 105-5). The deep motor nerve supplies the hypothenar muscles, then crosses to the radial side of the palm to innervate

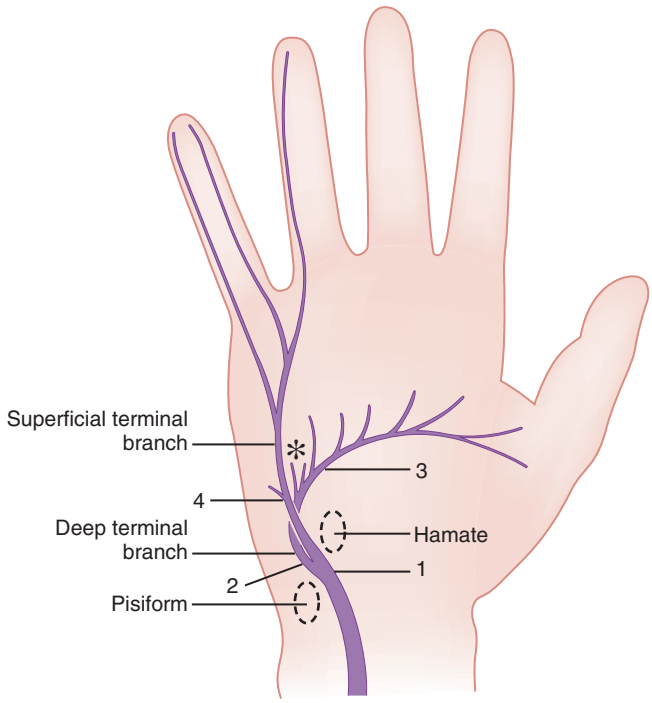


Figure 105-5. Distal ulnar nerve and branches, right hand, palmar view. Numbers indicate four main sites of distal ulnar mononeuropathy in the wrist and hand. *Denotes hypothenar branches. (From Stewart JD: Focal Peripheral Neuropathies, 3rd ed. Philadelphia, Lippincott Williams & Wilkins, 2000.)

the ulnar intrinsics (all interossei and the ulnar lumbricals of the fourth and fifth digits), terminating in the first dorsal interosseus. The interossei abduct and adduct the fingers and are all innervated by the ulnar nerve. The lumbrical muscles flex the metacarpal phalangeal joints and are evenly divided between the ulnar (fourth and fifth) and median (second and third) digits. The ulnar nerve can be thought of as the complement to the median nerve in the hand because it supplies all of the muscles and all palmar sensation not innervated by the median nerve.

The ulnar nerve may be injured at two locations near the elbow: in the ulnar condylar groove and distally in the cubital canal. Because the condylar groove is shallow, the ulnar nerve runs superficially in this location and is vulnerable to injury, usually from external pressure or from a fracture or dislocation. The ulnar nerve has a propensity to develop a "tardy ulnar palsy," occurring years after a traumatic event. Many of these delayed ulnar mononeuropathies can be localized to the elbow on electrophysiologic testing.

Some ulnar mononeuropathies occur secondary to compression just proximal to entry into the cubital canal or are entrapped within the canal itself. Transient symptoms may occur during prolonged flexion or with repeated flexion and extension at the elbow.

Although distinguishing a condylar from a cubital ulnar mononeuropathy is difficult, it is usually possible to localize the problem to the region of the elbow or the wrist. In addition to prior probability heavily favoring the elbow, the presence of sensory abnormalities in an ulnar distribution in the hand and fingers (i.e., usually including the fifth digit and "splitting" the fourth digit) strongly suggests that the lesion is at the level of the elbow rather than the wrist. The ulnar cutaneous innervation to the hand branches off from the main trunk proximal to the nerve entering Guyon's canal (see Figs. 105-4 and 105-5). Thus, a lesion at the wrist should not produce sensory abnormalities, whereas one at the elbow would be expected to do so.

Compression of the ulnar nerve within Guyon's canal is rare. When it does occur, it affects all of the ulnar intrinsics (i.e., the two ulnar [fourth and fifth] lumbricals) and all the interossei. However, the ulnar extrinsics (i.e., the deep flexors of the fourth and fifth digits) are not affected, nor is the ulnar flexor of the wrist. The only sensory abnormalities are those in the distribution of the superficial terminal sensory branch, sparing other areas of ulnar innervation (see Fig. 105-5).

There are three ulnar mononeuropathies that occur distal to Guyon's canal in the hand. The two most common ones involve the deep terminal branch, either proximal or distal to the separation of the hypothenar branches (see Fig. 105-5). If the lesion is proximal, it produces weakness of all the ulnar innervated muscles of the hand without sensory loss. If it is distal, the hypothenar ulnar intrinsics are spared but the picture is otherwise similar. Usually, this occurs secondary to a laceration or repeated compression in the hand from use of certain tools, a cane, or the handle of a crutch.

Involvement of the superficial terminal branch (see Fig. 105-5) arises as pure sensory loss of the palmar surface of the fifth digit and ulnar half of the fourth digit caused by direct compression of this branch just distal to Guyon's canal. The dorsal surface of these two digits should have normal sensation except for the distal tips. This configuration of findings is due to the intact innervation provided by the dorsal and palmar cutaneous branches that enter the hand without passing through Guyon's canal (see Fig. 105-4).

Most ulnar mononeuropathies will spontaneously resolve. However, if muscle atrophy, particularly in the hypothenar area, is detected, then surgery may be considered.[41,42]

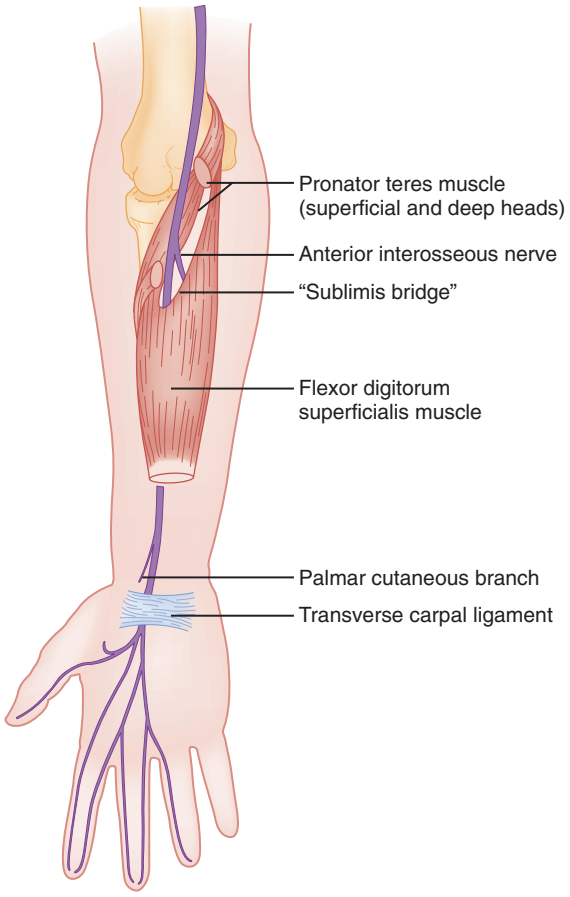


Figure 105-6. Median nerve, major branches, right arm, anterior view. (From Stewart JD: Focal Peripheral Neuropathies, 3rd ed. Philadelphia, Lippincott Williams & Wilkins, 2000.)

Median Mononeuropathy

The median nerve arises from C5-T1 spinal nerve roots and exits the brachial plexus through the lower trunk (Fig. 105-6). Median mononeuropathy is usually diagnosed as carpal tunnel syndrome (CTS), which is the most common of all entrapment neuropathies. CTS has a prevalence of 3 to 6% in the U.S. population.[43] Although the patient may complain of bilateral symptoms, a careful history usually reveals that symptoms in one hand preceded those in the other. Awakening at night and shaking the hand is a common symptom of CTS. Symptoms are often worsened by activity. For unclear reasons, the pain may spread as high as the arm or shoulder, although the paresthesias are generally confined to the fingers. Many patients on initial questioning state that their entire hand is involved, although this is not supported by careful sensory examination. Complaints that the hands are clumsy or weak, especially when holding a glass or opening a screw-top container, are frequent. The skin of the fingers innervated by the median nerve may be drier and rougher to the touch than the corresponding ulnar skin, depending on the duration of entrapment.[44]

When there is motor involvement in CTS it is confined to the median intrinsics, which innervate the *l*umbricals (flexion of the metacarpal phalangeal joints), and subserve thumb *o*pposition, *a*bduction, and *f*lexion, known as the LOAF muscles. However, the hallmark of CTS is sensory involvement, with motor abnormalities occurring later. The typical pattern of sensory innervation of the hand by the median, ulnar, and radial nerves shows marked individual variation.

BOX 105-6 CONDITIONS ASSOCIATED WITH CARPAL TUNNEL SYNDROME

Acromegaly
Amyloid
Diabetes mellitus
Hypothyroidism
Obesity
Pregnancy
Renal failure
Rheumatoid arthritis

The most specific finding for CTS is splitting of the fourth digit (i.e., normal sensation of the ring finger on the ulnar palmar side with abnormal sensation on the median [radial] palmar side of the same finger). The most sensitive finding is abnormal sensation of the distal palmar tip of the index finger. If sensory findings are absent in the presence of motor findings consistent with median nerve involvement, it is highly unlikely that the patient has CTS, and an alternative diagnosis should be sought. If neither sensory nor motor symptoms are evident, none of the provocative tests originally reported to reproduce the sensory symptoms of CTS—of which the most common are Tinel's sign (percussion of the median nerve at the wrist) and Phalen's sign (maximal palmar flexion at the wrist)—has shown adequate sensitivity or specificity to determine which patients should be referred for electrodiagnostic studies.[45–47] As suggested earlier, the best way to examine patients for sensory findings is to touch the distal palmar tips very lightly, asking the patient whether the sensation feels "abnormal."

CTS appears to be associated with the conditions listed in Box 105-6. Of these, the two most common are diabetes mellitus and pregnancy. CTS associated with systemic illness is commonly bilateral. Although CTS in pregnancy may be self-limiting, about half the women in one series were still symptomatic at 1-year follow-up.[48] All patients with suspected CTS should be referred for NCSs. However, because of the dissociation between clinical and electrodiagnostic indicators of CTS early in the disease, patients with normal electrodiagnostic findings in the presence of symptoms suggestive of CTS (with or without signs) should have an MRI[49] or sonogram.[50] At present, the sensitivity of MRI is good but its specificity is poor.[51] Ultrasound has been shown to be useful particularly in patients with symptoms and a negative NCS. This is done by measuring the cross-sectional area of the median nerve at the end of the pisiform.[52] Thus, if all diagnostic studies in a symptomatic patient are negative, or if only the MRI result is positive, they should be repeated within a few months if symptoms do not resolve.[44] This recommendation is based on the theory that the CTS will progress over time to the point that an objective indicator such as the NCS will become positive.

Because of the possibility of development of a disabling "median hand" after inadvertent direct injection of the median nerve, one should not inject the carpal tunnel with steroids in the ED. The physician to whom the patient is referred can decide after NCS whether to recommend splinting, injection, or surgical division of the transverse carpal ligament. Endoscopic repair appears to provide excellent results.[53]

Sciatic Mononeuropathy

The sciatic nerve includes L4-S3 spinal nerve roots that pass through the lumbosacral plexus and divide into two terminal branches: the common peroneal and tibial nerves. The nerve

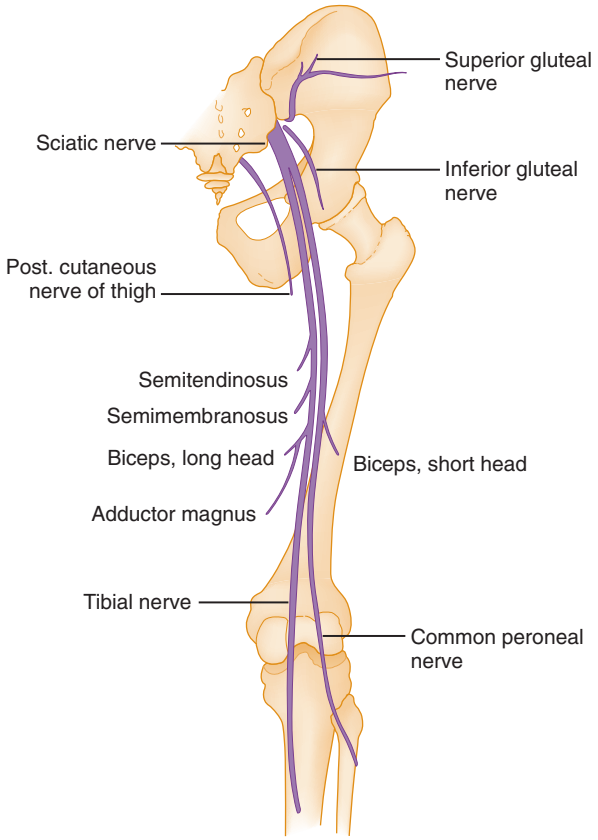


Figure 105-7. Sciatic nerve, major branches, right leg, posterior view. (From Stewart JD: Focal Peripheral Neuropathies, 3rd ed. Philadelphia, Lippincott Williams & Wilkins, 2000.)

exits the pelvis through the sciatic notch, passes behind the hip, and remains deep in the thigh until its terminal bifurcation in the proximal popliteal fossa (Fig. 105-7).

Lesions of the sciatic nerve occur with posterior hip dislocation or with virtually any form of penetrating or blunt trauma that causes formation of a buttock hematoma. Other causes include deep gluteal injection and prolonged supine immobilization on a firm surface. Because the sciatic nerve innervates the hamstrings and provides all sensorimotor function distal to the knee, a complete sciatic mononeuropathy is a devastating injury. Ambulation is extremely difficult because of inability to flex the knee and a flail foot (i.e., neither flexion nor extension is possible at the ankle). Fortunately, many sciatic mononeuropathies are incomplete. For unknown reasons, a partial lesion typically involves only the trunk of the sciatic nerve, which subsequently becomes the common peroneal nerve, sometimes making the two difficult to distinguish from one another clinically. On electrophysiologic studies, evidence of involvement of gluteal muscles or of any muscles innervated by the tibial nerve readily distinguishes a partial sciatic mononeuropathy from a lesion of the common peroneal nerve. Treatment of footdrop requires a posterior splint to maintain the ankle at 90 degrees until a brace can be obtained (see later section on "Common Peroneal Mononeuropathy").

Lateral Femoral Cutaneous Mononeuropathy

Lateral femoral cutaneous mononeuropathy (meralgia paresthetica) is a common syndrome believed to be caused by injury to this pure sensory nerve as it passes through or over the inguinal ligament, where it may become entrapped or kinked. Along with facial nerve neuropathy, meralgia paresthetica is

one of the most commonly reported mononeuropathies associated with HIV. External pressure and obesity may also contribute to nerve injury, causing numbness and dysesthesia over the skin of the upper lateral thigh. Regression usually occurs spontaneously, but recurrence is common and may require a release procedure for the inguinal ligament.

Common Peroneal Mononeuropathy

The common peroneal nerve is a continuation of one trunk of the sciatic nerve. It is most vulnerable to injury where it winds around the fibular neck (Fig. 105-8). It then passes through the fibular canal and bifurcates into its terminal branches, the superficial and deep peroneal nerves. The superficial peroneal nerve innervates the peroneal muscles (foot everters) and supplies sensation to the lateral, distal lower leg and dorsum of the foot. The deep peroneal nerve traverses the anterior compartment and supplies innervation to the dorsiflexors of the foot and toes, plus cutaneous sensation between the first and second toes.

Most common peroneal mononeuropathies are idiopathic and thought to be related to compression where the nerve is superficially located lateral to the fibular neck. Because this common neuropathy is often noted on awakening, it may be secondary to position during sleep. Leg crossing may also be a risk factor for development of this mononeuropathy. The most striking feature of a complete common peroneal mononeuropathy is footdrop caused by weakness of foot dorsiflexion. At testing, the everters of the foot are also weak, but the inverters, which are innervated by the tibial nerve, remain strong. This is the single most reliable clinical feature distinguishing sciatic from common peroneal mononeuropathy. Analogous to radial mononeuropathy in the upper extremity, sensory abnormalities in the leg and foot are inconstant and easily overlooked in peroneal mononeuropathy. Most patients with peroneal palsy recover. Those who do not should be studied electrophysiologically to ensure that the point of compression is not proximal to the fibular neck (i.e., in the popliteal fossa). If the point of peroneal injury appears to be in the region of, or distal to, the fibular neck on EMG, patients whose footdrop does not resolve should be considered candidates for exploration to determine whether the nerve is compressed within the fibular canal.

Treatment of common peroneal palsy may require a posterior splint to maintain the ankle at 90 degrees until the nerve regenerates. This splinting prevents the foot from falling into sustained equinus (plantar flexion), which in turn allows the intermalleolar distance to narrow, effectively locking the talus out of the ankle mortice.

The treatment of isolated mononeuropathies depends on their etiology, location, and natural history of spontaneous recovery. All penetrating neuropathies should have surgical exploration and repair performed. Blunt trauma may cause a mononeuropathy indirectly by entrapment of a nerve within a fracture, hematoma, or compartment, requiring surgical intervention. Alternatively, nerves may be injured at a point where they are superficial, either by a single direct blow or by sustained pressure caused by immobility (pressure palsies). Most of these resolve spontaneously over time, depending on the severity of injury and length of the nerve. If entrapment can be confirmed by imaging or electrophysiologic studies, a release procedure is indicated. In many instances, when there is disagreement between clinical and EMG findings, MRI may be helpful in selecting patients for exploration by visualizing entrapment or traction.[54] Characteristic sonographic findings have also been reported in several mononeuropathies.[55]

The mononeuropathies that do not require timely surgical exploration should be referred for further workup to confirm the location of the neuropathic lesion.

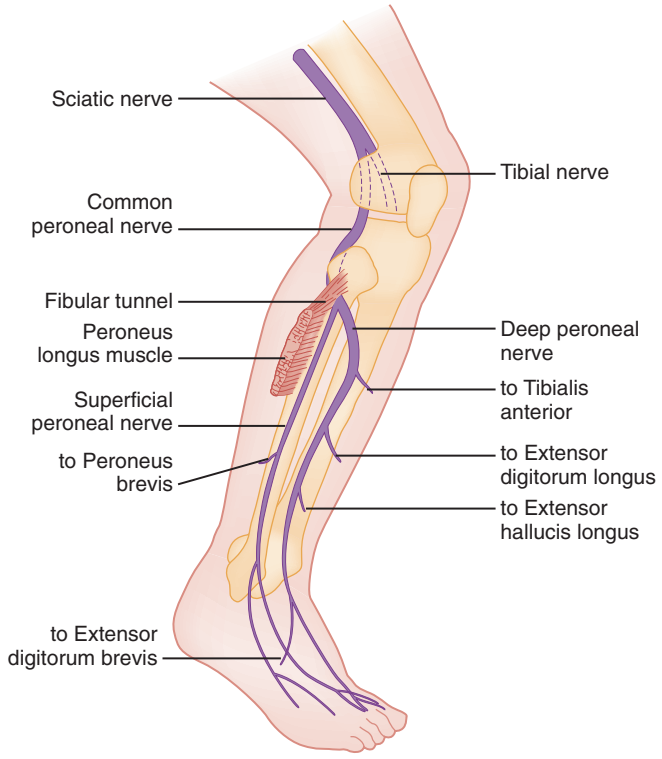


Figure 105-8. Common peroneal nerve, major branches, right leg, anterolateral view. (From Stewart JD: Focal Peripheral Neuropathies, 3rd ed. Philadelphia, Lippincott Williams & Wilkins, 2000.)

Type 5: Mononeuropathy Multiplex

Mononeuropathy multiplex is characterized by an asymmetrical, sensorimotor, usually distal pattern of peripheral neuropathy (Box 105-7). As with isolated mononeuropathies, sensory abnormalities tend to be located in the same general anatomic region as the accompanying motor findings. Whether DTRs are affected depends on which nerves are involved. For example, if the process includes the femoral nerve, the patellar reflex is likely to be diminished or absent.

BOX 105-7 MONONEUROPATHY MULTIPLEX

- Vasculitis
  - Systemic vasculitis
    - Polyarteritis nodosa
    - Rheumatoid arthritis
    - Systemic lupus erythematosus
    - Sjögren's syndrome (keratoconjunctivitis sicca)
  - Nonsystemic vasculitis
- Diabetes mellitus
- Neoplastic
  - Paraneoplastic
  - Direct infiltration
- Infectious
  - Lyme disease
  - HIV
- Sarcoid
- Toxic (lead)
- Transient (polycythemia vera)
- Cryoglobulinemia (hepatitis C)

Vasculitis

Mononeuropathy multiplex is strongly associated with vasculitis, which is the most common indication for sural nerve biopsy in most series. However, because diabetes mellitus is far more prevalent than vasculitis, the most common cause of mononeuropathy multiplex among ED patients is diabetes.

Diabetes Mellitus

Although the role of ischemia in diabetic neuropathies is controversial, evidence for a vascular cause is stronger in the asymmetrical diabetic multiple mononeuropathies than in the more common DSPNs seen in diabetes.

Lyme Disease

The PNS manifestations of Lyme disease can be divided into early and late. The early PNS syndromes commonly include facial nerve involvement (rarely other cranial nerve palsies) and radiculoneuritis. Late PNS involvement occurs as a DSPN, mononeuropathy multiplex, or radiculoneuropathy. The most common neurologic abnormality in Lyme disease is unilateral or bilateral facial nerve palsy, usually occurring within a month of exposure. Patients may also complain of headache and constitutional symptoms. Early in the course of Lyme disease, severe neuritic pain may develop in a radicular distribution, often in or near the dermatome where the tick bite occurred. There may also be associated sensory changes, motor weakness, and decreased reflexes consistent with nerve root involvement. Patients with chronic Lyme disease present with sensory symptoms, particularly distal paresthesias in the lower extremities. Less commonly, they develop a picture consistent with mononeuropathy multiplex or a radiculopathy. The latter is much less severe than the early radiculoneuritis of Lyme disease.

The most useful diagnostic tests for patients with suspected Lyme disease are a serum enzyme-linked immunosorbent assay, Western blot, and CSF examination. CSF abnormalities suggestive of Lyme disease are a lymphocytic pleocytosis, elevated protein, and normal glucose. The CSF is almost always abnormal in early radiculitis, sometimes abnormal with isolated facial palsy, and typically normal in chronic Lyme disease. Facial nerve palsy without CSF abnormalities may be treated with oral doxycycline 100 mg twice a day for 2 weeks. Intravenous ceftriaxone is the drug of choice for all other neurologic syndromes associated with Lyme disease. The adult dosage is 2 g/day, and the pediatric dosage is 75 to 100 mg/kg/day. Treatment with ceftriaxone should be continued for at least 2 weeks.

Type 6: Amyotrophic Lateral Sclerosis

Although *amyotrophic lateral sclerosis* (ALS) and *motor neuron disease* (MND) are often used synonymously, the latter represents a spectrum of diseases ranging from primary lateral sclerosis, in which degeneration is confined to upper motor neurons, to progressive muscle atrophy, in which only lower motor neurons are involved. ALS, which requires the presence of both upper and lower motor neuron findings, resides in the middle of this spectrum, representing the most common form of MND. The incidence of ALS is 1.5 to 2.5 per 100,000.[56]

In ALS, the primary pathologic process in the PNS component of the disease is a neuronopathy of the anterior horn cell. Because this structure is located proximal to the point where motor and sensory fibers merge to form mixed spinal nerve roots, the signs and symptoms of MND are purely motor (see Fig. 105-2). In the CNS, there is a loss of Betz cells from the motor cortex with secondary degeneration of the corticospinal tracts. Box 105-8 lists some representative upper, lower, and mixed motor signs. Patients typically demonstrate asymmetrical distal weakness without sensory findings. Positive motor phenomena in the form of fasciculations are found in almost all patients at diagnosis but are rarely an initial complaint. Although there is electrophysiologic evidence of autonomic involvement in ALS, this is generally subclinical.

BOX 105-8 Objective Clinical Findings Consistent with Amyotrophic Lateral Sclerosis

- Upper motor neuron signs
  - Hyperreflexia
    - Sustained clonus, especially at ankle
    - Finger flexors and jaw jerk
  - Spasticity, especially of gait
  - Positive Babinski sign
- Lower motor neuron signs
  - Positive motor phenomena
    - Fasciculations
    - Cramps
  - Negative motor phenomena
    - Asymmetrical distal weakness
    - Atrophy
- Combined upper and lower motor neuron signs
  - Dysarthria
  - Dysphagia
  - Respiratory compromise

Most patients with an asymmetrical, distal, pure motor neuropathy have ALS, for which only supportive treatment is currently available. However, there are some preliminary studies of recombinant human insulin–like growth factor 1 that have shown marginal improvement in this otherwise fatal disease.[57] All patients in whom this diagnosis is suspected should be referred for electrophysiologic confirmation against standardized criteria. Confirmation is particularly important because multifocal motor neuropathy, a rare disease that masquerades as ALS, responds dramatically to cyclophosphamide and immunoglobulin administration.[58]

Type 7: Sensory Neuronopathy (Ganglionopathy)

This category of peripheral neuropathy is characterized by a selective or predominant involvement of the dorsal root ganglion, producing a relatively pure sensory syndrome analogous to the pure motor syndrome of ALS. Although all sensory modalities are affected, proprioception is profoundly altered, leading to sensory ataxia and loss of DTRs without weakness. The distribution is typically asymmetrical and distal at the outset, but depending on severity and extent of progression, it may become functionally symmetrical. Sensory ganglionopathies can now be confirmed by MRI of the spinal cord and surrounding areas, showing degeneration of central sensory projections that localize the disease process to the dorsal root ganglion.[59] Some of the more common causes of this type of peripheral neuropathy are listed in Box 105-9.

BOX 105-9 SENSORY NEURONOPATHIES (GANGLIONOPATHIES)

- Herpes
  - Herpes simplex I and II
  - Varicella zoster (shingles)
- Inflammatory sensory polyganglionopathy (ISP)
- Paraneoplastic
- Primary biliary cirrhosis
- Sjögren's syndrome (keratoconjunctivitis sicca)
- Toxin induced
  - Pyridoxine (vitamin B_6) overdose
  - Metals
    - Platinum (cisplatin)
    - Methyl mercury
- Vitamin E deficiency

BOX 105-10 ANCILLARY DIAGNOSTIC TESTING IN SUSPECTED PERIPHERAL NEUROPATHY

- Obtained in most patients
  - Complete blood count (CBC)
  - Erythrocyte sedimentation rate (ESR)
  - Glucose
  - Creatine kinase (CK)
  - Creatinine
- Obtained only if indicated
  - Human chorionic gonadotropin (HCG)
  - Magnesium
  - Phosphate
  - Vitamin B_{12}
  - Hemoglobin A_{1c}
  - Serum protein electrophoresis (SPEP) with immune fixation electrophoresis (IFE)
  - Venereal Disease Research Laboratory (VDRL) or rapid plasma reagin (RPR) screen with fluorescent treponemal antibody-absorption (FTA-ABS) test, as appropriate
  - Thyroid function
  - HIV
  - Lyme enzyme-linked immunosorbent assay (ELISA) and Western blot
  - Rheumatoid factor and antinuclear antibody
  - Blood, urine, hair, or nails for metal, depending on suspected chronicity of exposure
  - Specific serum antibodies to components of peripheral nervous system
  - Cerebrospinal fluid for cells, protein, Lyme titer
  - Electrodiagnostic testing
    - Nerve conduction studies
    - Electromyography
  - Neurodiagnostic imaging
    - Magnetic resonance imaging
    - Computed tomography
    - Sonography
  - Quantitative sensory testing
  - Nerve biopsy
    - Sural
    - Intraepidermal nerve fiber density

ANCILLARY DIAGNOSTIC TESTING

Relatively few blood tests contribute to the diagnosis of peripheral neuropathy, and only a small number of these are available in the ED. CSF analysis may be helpful in GBS and Lyme disease. Additional tests that may be indicated in patients referred for evaluation are listed in Box 105-10, along with others that may be ordered selectively, depending on the clinical picture. Expensive batteries of tests purporting to measure a wide variety of antibodies to components of peripheral neuropathies are commercially available but have not been shown to be useful as screening tests.

KEY CONCEPTS

- In the emergency department, it is not usually possible to arrive at the diagnosis of a specific peripheral neuropathy because of the need for confirmatory ancillary testing that is beyond the scope of emergency practice. Rather, the focus should be on identifying one of seven categorical patterns of peripheral neuropathy, shown in Figure 105-1 and listed in Table 105-1, after other non-PNS causes have been eliminated.
- One of these seven patterns can usually be identified by combining three clinical features that are readily obtainable from a goal-directed history and physical: (1) right-left symmetry or asymmetry, (2) proximal-distal location, and (3) sensorimotor modalities affected. This approach is summarized as an algorithm in Figure 105-1.
- Identification of one of the seven types of peripheral neuropathy determines the need for ancillary diagnostic testing, therapeutic intervention, disposition, and the timing of neurologic referral.
- Respiratory compromise is the primary life-threatening event seen in some peripheral neuropathies; GBS is by far the most common peripheral neuropathic cause of respiratory arrest.
- Any patient with symmetrical weakness, distributed both proximally and distally, with loss or diminution of DTRs and variable sensory abnormalities should be treated as having GBS.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 106 Neuromuscular Disorders

Peter Shearer and Andy Jagoda

PERSPECTIVE

Disorders of the neuromuscular unit can result in clinical presentations that range from subtle symptoms to acute respiratory failure. Morbidity and mortality are often related to failure of the muscles that maintain airway integrity and drive respiration. In most cases, the pathophysiology of these disorders is well understood and permits an organization and understanding that is based on the level of the nervous system affected. This facilitates an approach that is based on signs and symptoms, the findings of which direct the urgency of diagnostic testing and treatment.

Processes involving the brainstem and brain can usually be differentiated from those in the spinal cord and in the peripheral nervous system on the basis of historical and physical findings. In general, lesions at the level of the brainstem or above produce unilateral weakness; bilateral weakness caused by lesions above the spinal cord is generally associated with a change in mental status or cranial nerve involvement. Lesions of the central nervous system result in upper motor neuron signs that include spasticity, hyperreflexia, and extensor plantar reflexes. As a corollary, when bilateral upper motor neuron signs are found in conjunction with normal mental status, diagnostic testing including neuroimaging should focus on looking for a lesion in the spinal cord.

PRINCIPLES OF DISEASE

The neuromuscular unit has four components: the anterior horn cells of the spinal cord, the peripheral nerve, the neuromuscular junction, and the muscle being innervated. The level of the pathology determines associated signs and symptoms (Table 106-1). *Myelopathies* involve the spinal cord; *radiculopathies* involve the nerve roots as they leave the spinal cord; *neuropathies* involve the peripheral nerves; and *myopathies* involve the muscle. The use of physical signs to differentiate these disorders is discussed in Chapter 11.

Neuropathies involve the axon itself or the myelin sheath (or the Schwann cells that make the myelin sheath) of the nerve. Nerve conduction studies can differentiate the locations of involvement. As the conduction along the axon is disrupted, the subsequent delay in transmission first causes symptoms in the muscles controlled by longer nerve axons, resulting in a history of weakness beginning in the distal extremities. As the myelin destruction or axonal degeneration progresses, patients usually note a slowly progressive course of symptoms.

The motor nerve branches into multiple terminals as it approaches the muscle. The neuromuscular junction is composed of the presynaptic membrane, the postsynaptic membrane, and the synaptic cleft. The neurotransmitter is acetylcholine (ACh). The motor synapse is a nicotinic receptor, whereas muscarinic synapses link the central nervous system with the autonomic nervous system. Disorders of the postsynaptic nicotinic receptors produce weakness. Postsynaptic ACh receptors are continually turned over at a rate that is related to the amount of stimulation. A disorder of transmission often leads to increased production of ACh receptors. Myasthenia gravis (MG) is the prototype of neuromuscular junction diseases.

CLINICAL FINDINGS

History

The history of patients with complaints of weakness focuses on the acuity and progression of onset and the potential for airway compromise. Any complaint of difficulty breathing or swallowing raises suspicion of bulbar involvement and concern for life-threatening deterioration. The history must elicit whether the weakness is muscular or nonspecific generalized fatigue. Weakness implies the inability to exert normal force, whereas fatigue implies a decrease in force with repetitive use. When muscular weakness exists, the clinician should determine whether it is focal or generalized, proximal or distal. The history of present illness must include the duration of symptoms, exacerbating and mitigating factors, and presence of associated symptoms such as fever, weight loss, and bowel or bladder changes.

Historical elements might explain the presenting complaint: a preexisting neuromuscular disorder that could lead to deterioration; prior episodes or a family history of weakness suggesting periodic paralysis; a recent respiratory or diarrhea illness suggesting a postinfectious, autoimmune process such as transverse myelitis or Guillain-Barré syndrome (GBS); a cancer history suggesting a metastatic tumor as the cause of a compressive myelopathy; a food or travel history suggesting botulism or tick exposure.

Physical Examination

The physical examination should first assess the patient's airway and ventilation and then proceed to localize the level

Table 106-1 Clinical Characteristics of Neuromuscular Diseases

DISEASE	HISTORY	STRENGTH	DEEP TENDON REFLEX	SENSATION	WASTING
Myelopathy	Trauma, infection, cancer	Normal to decreased	Increased	Normal to decreased	No
Motor neuron disease (ALS)	Progressive difficulty swallowing, speaking, walking	Decreased	Increased	Normal	Yes
Neuropathy	Recent infection Ascending weakness	Normal or decreased Distal > proximal	Decreased	Decreased	Yes
Neuromuscular junction disease	Food (canned goods) Tick exposure Easy fatigability	Normal to fatigue	Normal	Normal	No
Myopathy	Thyroid disease Previous similar episodes	Decreased Proximal > distal	Normal	Normal	Yes

ALS, amyotrophic lateral sclerosis.

BOX 106-1 GRADING SCORE FOR MOTOR STRENGTH

5 = Normal strength
4 = Weak but able to resist examiner
3 = Moves against gravity but unable to resist examiner
2 = Moves but unable to resist gravity
1 = Flicker but no movement
0 = No movement

of the lesion. The presence of swallowing and a strong cough suggests that the patient has sufficient protective and ventilatory reserve. The muscles used to lift the head off the bed may weaken before those of respiration and should be assessed. A patient who is not yet intubated but is complaining of shortness of breath or difficulty breathing should have frequent vital capacity measurements. Normally, these values range from 60 to 70 mL/kg. When the forced vital capacity reaches 15 mL/kg, intubation is necessary. If vital capacity cannot be measured, a maximal negative inspiratory force (NIF) is easily determined. An NIF less than 15 mm Hg suggests the need for endotracheal intubation. A bedside assessment used to follow ventilatory status is to have the patient count numbers with one breath.[1] With sequential performance of this test, a decline in respiratory function is detected as the patient fails to count as high as before. Arterial blood gas is not necessarily helpful because functional reserve can be severely diminished by the time a patient develops either hypercarbia or hypoxia.

The assessment of vital signs is important because some causes of weakness may result in dysregulation of the autonomic system. A systematic neurologic examination should assess the patient's mental status, cranial nerves, motor function, sensory function, deep tendon reflexes, and coordination, including cerebellar function. The motor examination begins by determining whether the weakness is unilateral or bilateral and which muscle groups are involved. Key components of the examination include motor strength, muscle bulk, and presence of fasciculations. Box 106-1 provides the grading system used in motor strength assessment. Table 106-2 provides the findings used to distinguish upper motor neuron from lower motor neuron processes.

Differential Considerations

Myelopathies

A patient with myelopathy shows signs of upper motor neuron dysfunction. Without upper motor neuron function, muscle weakness is present with increased spinal reflexes, including an extensor plantar reflex (Babinski's response). Muscle tone initially ranges from normal to slightly increased, eventually leading to spasticity as a late finding. The same reflex arcs eventually create spasticity in the affected muscles. The weakness is ascending in nature, and there is often bladder and bowel involvement. When sensory findings are present, they often define the level of the lesion. The presence of bowel or bladder dysfunction, or diminished sensation, localizes the lesion to the spinal cord. The presence of pain often connotes a compressive lesion such as a herniated intravertebral disk, epidural hematoma, abscess, or tumor. Acute, painless spinal cord lesions include transverse myelitis and spinal cord infarction.

Motor Neuron Disease

Amyotrophic lateral sclerosis is the prototypical disease process resulting from a degeneration of the motor neuron without sensory involvement. These patients may complain of dysarthria or dysphagia; however, the characteristic findings are those of combined upper and lower motor neuron dysfunction. Consequently, findings include hyperreflexia, muscle wasting, and fasciculation. Pain is not a component of the clinical picture.

Poliomyelitis affects the anterior horn cells and results in lower motor neuron disease without sensory involvement. The

Table 106-2 Distinguishing Upper Motor Neuron (UMN) from Lower Motor Neuron (LMN) Involvement

MOTOR NEURON	DEEP TENDON REFLEX	MUSCLE TONE	ATROPHY	FASCICULATIONS	BABINSKI
UMN	Increased	Increased	No*	No	Present
LMN	Decreased	Decreased	Yes	Yes	Absent

*Not significant but can occur.

weakness can be symmetrical or more often asymmetrical. Patients initially have a clinical picture similar to that of viral meningitis, with fever and neck stiffness. Currently, most cases follow exposure of an immunocompromised host to the oral polio vaccine, and this should be sought in the history. The cerebrospinal fluid analysis resembles that of viral meningitis.

Neuropathies

Weakness from a neuropathy is often noted first in distal muscles and then ascends. Decreased grip strength or footdrop may be noted first. Muscle tone ranges from slightly diminished to flaccid. As all outflow from the spinal cord is affected, deep tendon reflexes are diminished or absent. Patients exhibit varying degrees of altered sensation, muscle wasting, and fasciculation depending on the duration of the symptoms. Disorders that should be considered include GBS, toxic neuropathies, diabetic neuropathy, and tick paralysis (which is caused by inhibition of both nerve conduction and function of the neuromuscular junction).

Diseases of the Neuromuscular Junction

Disorders of the neuromuscular junction cause progressive motor fatigability. The initial depolarization of the muscle causes stimulation of a maximum number of receptors, producing a normal, or nearly normal, strength response. Repeated stimulation leads to diminishing motor strength, which is caused by the blockage of the receptors (as in MG) or by a decrease in the amount of ACh released (as in botulism) or by inactivating Ach by irreversibly binding with it (as in organophosphate poisoning). A decrease in the release of ACh may produce a combination of nicotinic and muscarinic effects leading to anticholinergic findings such as decreased visual acuity, confusion, urinary retention, tachycardia, low-grade fever, and dry, flushed skin. In the case of Lambert-Eaton myasthenic syndrome, weakness is more pronounced at the beginning of muscle use and improves with repeated use as more ACh builds up in the synaptic cleft with each stimulation. Diseases of the neuromuscular junction should be considered in patients who present with generalized weakness in association with an acute cranial nerve deficit. Muscle tone is generally diminished and sensation is preserved.

Myopathies

Myopathies produce generalized, symmetrical weakness. Reflexes are present but diminished, muscle tone is usually diminished, but sensation is preserved. Myopathies caused by inflammatory disorders (polymyositis, dermatomyositis, polymyalgia rheumatica, and viral myositis) cause muscle pain and tenderness. Metabolic disorders affecting muscle strength (e.g., electrolyte and endocrine disorders) are painless in nature.

DIAGNOSTIC STRATEGIES

Laboratory Studies

Serum potassium, calcium, and phosphorus should be assessed in patients with acute weakness. Thyroid function tests are recommended in cases of suspected myopathies. A creatine kinase (CK) level assesses for muscular inflammation; a urinalysis should be performed for the presence of myoglobinuria and possible rhabdomyolysis.

Special Studies

Magnetic resonance imaging (MRI) is the preferred test for suspected cases of acute myelopathy. Computed tomography of the spinal cord with myelography can help to differentiate compressive (herniation, abscess, tumor) from noncompressive causes when MRI is not available. Cerebrospinal fluid analysis is indicated when GBS or transverse myelitis is suspected.

SPECIFIC DISORDERS

Disorders of the Neuromuscular Junction

Myasthenia Gravis

Perspective. It is rare for the emergency physician to diagnose a new case of MG; more commonly, patients with established disease present with exacerbations of their disease that must be recognized and addressed. In addition, the emergency physician must be aware of medication interactions in patients with MG.

Principles of Disease. MG is a rare disorder that affects approximately 60,000 Americans.[2] Age of onset is bimodal, with the first peak among women 20 to 40 years of age and a second peak among men 50 to 70 years old.

MG results from autoantibodies directed against the nicotinic acetylcholine receptor (AChR) at the neuromuscular junction. This leads to complement-mediated destruction of AChRs with a decrease in the total number of available receptors. The autoantibodies further compete with ACh for binding at remaining receptors. Thus, with repeated stimulation of the same muscle, fewer and fewer sites are available and fatigue develops.

Fatigability and muscular weakness are the hallmarks of MG. Considering the slow clinical progression of MG and the low likelihood of short-term complications from its progression, the importance of suspecting the diagnosis is to facilitate proper referral for further evaluation.

Clinical Features. Ocular symptoms are often the first manifestation of MG. The typical symptoms are ptosis, diplopia, or blurred vision. Ocular muscle weakness is the first sign in up to 40% of patients, although 85% of patients with MG eventually have ocular involvement. When present, ptosis is often worse toward the end of the day. Respiratory failure is rarely the initial symptom of MG. Even so, up to 17% of patients may have weakness of the muscles of respiration.[3] Bulbar muscles may be involved, producing dysarthria or dysphagia.

Lambert-Eaton myasthenic syndrome is a rare disorder in which almost 50% of cases are associated with small cell carcinoma of the lung. Autoantibodies cause inadequate release of ACh from nerve terminals, affecting both nicotinic and muscarinic receptors. With repeated stimulation, the amount of ACh in the synaptic cleft increases, leading to an increase in strength, the opposite of that seen with MG. The classic syndrome includes weakness that improves with use of muscles, particularly proximal hip and shoulder muscles; hyporeflexia; and autonomic dysfunction, most commonly seen as dry mouth.[4] Management primarily focuses on treating the underlying neoplastic disorder, although IVIG has been reported to be useful.[5]

Diagnostic Strategies

New-Onset Myasthenia Gravis. The diagnosis of MG is based on clinical findings and a combination of serologic testing, electromyographic testing, and the bedside edrophonium or ice bag tests. Serum testing for AChR antibodies is positive in 80 to 90% of patients with MG, but not available in the emergency department setting.

The edrophonium test and ice bag tests are similar to perform and the results are based on their effect on the ptosis seen in patients with suspected MG. The production of edrophonium was discontinued in early 2008 and it will no longer be available once current stores are depleted. Edrophonium is a short-acting acetylcholinesterase (AChE)-blocking agent that produces an increase of ACh in the synaptic cleft and a reduction in ptosis after intravenous administration. With the ice bag test, cooling decreases symptoms in MG while heat exacerbates symptoms. In both tests, the change in the amount of ptosis is measured before and after the application of edrophonium or an ice bag. The distance from the upper to the lower eyelid in the most severely affected eye is measured first. If edrophonium is given, an intravenous test dose of 1 to 2 mg is given first as some patients have a severe reaction. If no adverse reaction is found and the patient does not dramatically improve in 30 to 90 seconds, a second dose of 3 mg is given. If there is still no response, a final dose of 5 mg is given for a total maximum dose of 10 mg.[6] Atropine should be available at the bedside during the test. Because of the potential for cholinergic-induced increased airway secretions, this test should be used with caution in asthmatics and patients with chronic obstructive pulmonary disease. If an ice pack is used, it is applied to the affected eye for approximately 2 minutes, and the distance between the lids is measured again. A prospective evaluation of the ice bag approach found the test result to be positive (an improvement in distance of at least 2 mm) in 80% of patients with MG and in no patients without MG.[7]

Myasthenic Crisis. Myasthenic crisis is defined as respiratory failure leading to mechanical ventilation. It occurs in 15 to 20% of patients with MG,[8] usually within the first 2 years of disease onset. Although it is potentially life-threatening, the mortality from this complication of MG has declined dramatically with better and more aggressive ICU care and the use of plasmapheresis (PE) and/or immunodulatory therapy with high-dose intravenous immunoglobulin (IVIG) and corticosteroids.

Underlying infection, aspiration, and medication changes—stopping anticholinergic medications or taking a new medication that precipitates weakness—most often set off crisis, but the precipitant may not be found in up to 30% of cases.[9] Other precipitants can be surgery and pregnancy (Box 106-2).

BOX 106-2 DRUGS THAT MAY EXACERBATE MYASTHENIA GRAVIS

Cardiovascular
- Beta-blockers
- Calcium channel blockers
- Quinidine
- Lidocaine
- Procainamide

Antibiotics
- Aminoglycosides
- Tetracyclines
- Clindamycin
- Lincomycin
- Polymyxin B
- Colistin

Other
- Phenytoin
- Neuromuscular blockers
- Corticosteroids
- Thyroid replacement

The initial step in managing the patient in crisis is stabilization of the airway. In less severe cases in which intubation is not imminent, it is imperative to monitor ventilatory status pending intensive care unit admission through forced vital capacity or NIF measurement. Noninvasive ventilation with biphasic positive airway pressure may be effective in managing patients who need ventilatory support.[10]

Signs of myasthenic crisis should be sought in all patients with MG, even when they do not complain of weakness. Many commonly used drugs can adversely affect patients with MG (see Box 106-2). A patient with stable MG who has an acute medical or surgical condition requires a full neurologic examination. The decision to admit or discharge a patient with MG from the emergency department should take into account the potential for neurologic deterioration.

Management

Cholinesterase Inhibitors. Pyridostigmine (60–120 mg every 4–6 hours) and neostigmine (15–30 mg every 4–6 hours) prolong the presence and activity of ACh in the synaptic cleft. They are the backbone of chronic outpatient therapy and provide symptomatic improvement. The most common side effects are those of excessive cholinergic stimulation, such as increased airway secretions and increased bowel motility. At extremes there may be bradycardia or even worsening of weakness, simulating a myasthenic crisis. These drugs are often used as adjunctive therapy to control symptoms while other therapy is being instituted, after which they are often discontinued.[11] The use of intravenous pyridostigmine in the setting of acute exacerbation is controversial and not recommended because PE or IVIG is recommended. Cholinergic drug therapy is not recommended for the treatment of MG in the emergency department.

Immunosuppressant Drugs. Immunosuppressant drugs are often used for the chronic control of MG. Although they have no role in the acute management of a myasthenic crisis, they may be started before extubation of a patient recovering from crisis. Cochrane Database reviews in 2005 and 2007 found support for the use of corticosteroids but only limited evidence that cyclosporine and cyclophosphamide and azathioprine improve MG.[12,13] Of note, the initiation of corticosteroids in patients with moderate to severe weakness may actually precipitate a worsening of weakness or even myasthenic crisis.

Thymectomy. While the association between thymoma and MG is not fully elaborated, it is well known that thymectomy for patients with thymoma can lead to remission of MG or enable a reduction in other medications. Thymectomy for patients with MG but without thymoma has been shown to have similar benefits and is recommended for patients younger than 60 with remission or improvement in up to 50% of cases and is supported by a clinical policy of the American Academy of Neurology.[14] The onset of improvement after thymectomy is often delayed for 2 to 5 years.

Immunomodulatory Therapy. PE and IVIG can be used for patients with exacerbations of MG or preoperatively in patients with stable MG.

PE removes the AChR antibodies and other immune complexes from the blood. The fall in AChR levels is associated with improvement in symptoms of MG. There is a risk of complications from hypotension or anticoagulation. Because of safety concerns, clinical trials have not been done in children. Although there are no randomized controlled studies, a review yielded many case series with short-term benefit, especially in myasthenic crisis, and it is recommended by the American Academy of Neurology.[15]

A review of IVIG trials found one randomized controlled trial of IVIG versus placebo that demonstrated the benefit from IVIG. Another trial failed to show a difference between

IVIG and PE.[16] The decision to institute either therapy is based on the input of the consulting neurologist and the resources available at the admitting hospital. If PE is not readily available for a patient with myasthenic crisis, IVIG should begin with 1 g/kg.

Botulism

Principles of Disease. Botulism is a toxin-mediated illness that can cause acute weakness leading to respiratory insufficiency. The Centers for Disease Control and Prevention (CDC) reports that an average of 145 cases are reported each year: 15% are foodborne, 65% are infant botulism, and 20% are wound related.[17] *Clostridium botulinum* is an anaerobic, spore-forming bacterium. Three of eight known toxins produced by *C. botulinum* (types A, B, and E) cause human disease. There has been an increase in the incidence of botulism from wound infections. In a 4-day period in 2003 in Washington State, four people contracted wound botulism from black tar heroin.[18] Botulism is also thought to be a potential agent for bioterrorism. The botulinum toxin works by binding irreversibly to the presynaptic membrane of peripheral and cranial nerves, inhibiting the release of ACh at the peripheral nerve synapse. As new receptors are generated, the patient improves.

Clinical Features. The toxin blocks both voluntary motor and autonomic functions. Because the disorder is at the neuromuscular junction, there is no sensory deficit and no sense of pain. The onset of symptoms is 6 to 48 hours after the ingestion of tainted food. There may or may not be accompanying signs and symptoms of gastroenteritis, with nausea, vomiting, abdominal cramps, diarrhea, or constipation. The classic feature of botulism is a descending, symmetrical, flaccid paralysis. The muscles often affected first are the cranial nerves and bulbar muscles, and the patient presents with diplopia, dysarthria, and dysphagia, followed later by generalized weakness. There may be associated blurring of vision. Because the toxin decreases cholinergic output, anticholinergic signs may be seen in the form of constipation, urinary retention, dry skin and eyes, and increased temperature. Pupils are often dilated and not reactive to light. This can be a point of differentiation from MG. Deep tendon reflexes are normal or diminished.

Infantile botulism results from the ingestion of *C. botulinum* spores that are able to germinate and produce toxin in the high pH of the gastrointestinal tract of infants. The same spores are not active in the gut of adults because of the lower pH. The CDC reports approximately 100 cases per year.[19] It occurs in infants between the ages of 1 week and 11 months and has been implicated as a cause of sudden infant death syndrome. Because spores can survive in honey, it is recommended that honey not be fed to infants. The clinical presentation includes constipation, poor feeding, lethargy, and weak cry; consequently, this diagnosis must be in the differential diagnosis of the floppy infant.

Diagnostic Strategies. The diagnosis is made by both clinical findings and exclusion of other processes. The toxin can be identified in serum and stool, but the assay is not commonly available in most hospitals and requires a prolonged turnaround time. If the suspected food source is available, it should also be tested for the toxin.

Management. The treatment is initially focused on stabilizing the airway and supportive measures. There is an equine antitoxin that can shorten the disease course, although it is not clear that the antitoxin decreases ventilator dependence and there is a risk of anaphylaxis and serum sickness. Nevertheless, the antitoxin should be administered as soon as possible. The toxin is available through the CDC by calling (404) 329-2888. An intravenous human botulism immune globulin (BIG-IV) has been developed for treatment of infantile botulism[20] and is available through the California Department of Health Services Infant Botulism Treatment and Prevention Program on-call physician at (510) 231-7600.

Tick Paralysis

Principles of Disease. The pathogenesis of tick paralysis, also known as *tick toxicosis*, is not fully understood. It is known that a toxin is injected while the tick feeds, and it is referred to as an *ixovotoxin*. The toxin appears to diminish the release of ACh at the neuromuscular junction and also reduces nerve conduction velocity. It may also have effects at autonomic ganglia, leading to pupillary signs. According to the CDC, the state of Colorado reports on average one case per year, though in 2006 four cases were reported during one week.[21]

Clinical Features. Tick paralysis is an acute, ascending, flaccid motor paralysis that can be confused with GBS, botulism, and MG. It typically begins with the development of an unsteady gait, followed by ascending, symmetrical, flaccid paralysis. Although symptoms usually begin 1 to 2 days after the female tick has attached and begun to feed, delays of up to 6 days have been reported.[22] There may be associated ocular signs, such as fixed and dilated pupils, that can help distinguish it from GBS.

Management. The management is supportive care and tick removal. A tick can be removed using forceps to grasp it as closely as possible to the point of attachment. Care must be taken not to leave mouth parts in the patient's tissue. Although symptoms may resolve rapidly after removal of the tick, supportive measures such as intubation should not be withheld pending resolution of symptoms.

Disorders of the Muscles

Perspective

Newly acquired weakness originating at the muscular level can be divided into two types: inflammatory and toxic-metabolic. Inflammatory disorders usually produce pain and tenderness, but metabolic disorders do not.

Inflammatory Disorders

Principles of Disease. The most common inflammatory myopathies are polymyositis (PM) and dermatomyositis (DM). PM may be idiopathic in nature, occur secondary to infections (viral or bacterial), or be seen in conjunction with other disorders such as sarcoidosis or hypereosinophilic syndromes. Inflammatory myopathies cause weakness, pain, and tenderness of the muscles involved. They must be distinguished from simple myalgias related to a fever or cramping that may suggest myotonia (inability to relax the muscle).

Clinical Features. DM and PM can occur at any adult age, although DM may also affect children. There is a slightly increased incidence in women. An associated increased risk of malignancy, especially breast, ovary, lung, gastrointestinal, and lymphoproliferative disorders, has been noted after the diagnosis of DM or PM, although the reported rate of malignancy varies widely. Proximal muscle weakness predominates and leads to complaints of difficulty rising from a seated position or climbing stairs and weakness in lifting the arms over the head. There is often pain and tenderness in these proximal muscles as well. There is a decrease in reflexes as the weakened muscles fail to contract. Thus, the decrease in reflexes is in proportion to the decrease in strength. Fasciculations are not seen, and atrophy is a very late finding.

DM is similar to PM, but it is also associated with classic skin findings. These are more prominent in childhood but are also found in adults. They include a periorbital heliotrope and erythema and swelling of the extensor surfaces of joints. The facial rash is usually photosensitive and may also involve the exposed areas of the chest and neck.

Diagnostic Strategies Electrolyte abnormalities must be ruled out and the serum CK checked. If possible, the skeletal muscle isoform (MM) should be distinguished from the cardiac muscle isoform (MB). The CK must be interpreted in light of the entire clinical picture. The presence of an elevated CK does not establish the cause of weakness as a myopathy because some neuropathies can also produce an elevated CK. Similarly, a normal CK does not rule out a myopathy as the cause of weakness. Electromyography and muscle biopsy are used to confirm the diagnosis.[23]

Management. PM and DM are usually managed with oral prednisone in a dose of 1 to 2 mg/kg/day. When steroids prove ineffective and during acute exacerbations, cytotoxic drugs such as azathioprine or methotrexate are added. Fortunately, the degree of rhabdomyolysis seen with the inflammatory myopathies is not sufficient to cause renal impairment.

Metabolic Disorders

Perspective. Acute, generalized muscle weakness can be seen with severe electrolyte abnormalities of any cause: hypokalemia, hyperkalemia, hypocalcemia, hypercalcemia, hypomagnesemia, and hypophosphatemia. Acute painless myopathies can also be seen with endocrine disorders involving the thyroid, parathyroid, or adrenal glands.

Of particular interest are several disorders referred to collectively as the *periodic paralyses*. This group of entities includes familial periodic paralysis (FPP) of the hyperkalemic and hypokalemic forms and thyrotoxic periodic paralysis (TPP), which is similar to hypokalemic FPP except that it is associated with hyperthyroidism.

Periodic Paralysis

Principles of Disease. These are autosomal-dominant disorders of ion channels resulting in intermittent attacks of flaccid extremity weakness associated with either hyperkalemia or hypokalemia, although the latter is more common. It is most often associated with an inherited genetic mutation. Patients usually report a personal and family history of similar episodes.[24]

Clinical Features and Diagnostic Strategies. Patients may suffer either isolated or recurrent episodes of flaccid paralysis. The lower limbs are involved more often than the upper, although both can be affected. Bulbar, ocular, and respiratory muscles are usually not involved. Onset is rapid; a prodrome of myalgias and muscle cramps may occur but is uncommon; mental status and sensory function are typically preserved, but reports of sensory nerve involvement have been documented.[25] Males are more often affected than females, and there is a higher incidence in Asians, particularly Japanese, although it occurs in other ethnic groups.

Attacks may be induced by the injection of insulin, epinephrine, or glucose. The onset of symptoms often follows a high carbohydrate intake (with subsequent insulin rise) and a period of rest. A typical complaint is the acute onset of weakness noted on waking in the morning after a large meal the preceding evening. An electrocardiogram, which should be done immediately in all patients suffering from acute paralysis, demonstrates signs of hyperkalemia or hypokalemia. An immediate potassium level should be ordered; in the hypokalemic form, the potassium level during an attack falls to values below 3.0 mEq/L.

Management. Many cases resolve spontaneously with supportive care alone. The mainstay of management is the treatment of the underlying electrolyte imbalance. In the hypokalemic state the total body potassium is not depleted but has shifted intracellularly. Thus, in the repletion of potassium, caution is necessary to prevent overtreatment. For this reason, intravenous potassium should be used sparingly; one or two 10-mEq doses of potassium chloride (KCl), each administered over 1 hour, should be the maximum given intravenously. This can be done in parallel with 40 mEq oral potassium repletion and retesting of serum potassium levels. Intravenous hydration helps to redistribute the body's potassium stores.

Thyrotoxic Periodic Paralysis. The clinical picture of TPP is almost identical to that of hypokalemic FPP, and indeed a small number of patients with hypokalemic FPP have hyperthyroidism. In TPP, symptoms related to hyperthyroidism are often present at the same time the patient develops weakness. The relation of the hyperthyroidism to hypokalemia is probably due to increased sodium-potassium adenosine triphosphatase activity, which causes a rapid shift of potassium from the extracellular into the intracellular compartment. Treatment of the hyperthyroid symptoms, such as tachycardia, may help the treatment of the paralysis as well. There are case reports of TPP in which the patient's weakness did not respond to potassium replacement until propranolol was given to treat tachycardia.[26,27] There is probably a genetic feature underlying this disorder because there is a higher incidence of repeated attacks of hypokalemic periodic paralysis among Japanese and Chinese patients with hyperthyroidism. It is important that all patients have thyroid function testing done after a first episode of hypokalemic paralysis.

KEY CONCEPTS

- The approach to evaluating patients with acute neuromuscular weakness is facilitated by first determining the location of the lesion (spinal cord, nerve, neuromuscular junction or muscle) and then considering the most common disorders that affect the area in question.
- In patients with bilateral upper motor neuron signs and a normal mental status, neuroimaging of the spinal cord should be strongly considered.
- In patients presenting with acute neuromuscular weakness, complaints of difficulty in breathing or swallowing should heighten suspicion of bulbar involvement with possible airway compromise. In such patients, a forced vital capacity less than 15 mL/kg or a maximal NIF less than 15 mm Hg are potential indications for mechanical ventilation.
- Botulism usually arises as a painless descending paralysis, often first affecting the cranial nerves and bulbar muscles, without sensory deficits or significant alteration of consciousness. The treatment is airway management and administration of antitoxin.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 107

Central Nervous System Infections

William J. Meurer and Frank W. Lavoie

PERSPECTIVE

Background

Central nervous system (CNS) infections have always been among the most perplexing and devastating illnesses. "Epidemic cerebrospinal fever," classically described by Viesseux in 1805, was associated with almost universal mortality.[1] The first American epidemic of meningococcal meningitis was recorded in 1806.[2] Since that time, epidemiologic changes have occurred in concert with advances in understanding of disease processes and evolution of effective treatment strategies.

The etiologic spectrum of CNS infection has changed considerably as a result of the development and aggressive use of antibiotics and the epidemic emergence of immune disorders such as infection with the human immunodeficiency virus (HIV). Some of the research on CNS infections has markedly increased in sophistication, which provides insights into pathogenesis, including the role of host mechanisms such as cytokines and other immune components. The pathophysiologic alterations are increasingly understood at the cellular and molecular levels.

Likewise, diagnostic tools have been developed that allow precise pathogen identification, most recently using molecular technologies such as polymerase chain reaction (PCR) tests for viral nucleic acids in cerebrospinal fluid (CSF). The initial treatment methodologies began by demonstrating the efficacy of antiserum treatment by Flexner in 1913 and of antibiotics by Colebrook and Kenny in 1936.[3,4] The mortality rates were decreased further with the use of high-dose penicillin by Dowling and colleagues in the 1940s.[5] Unfortunately, despite historical advances, the morbidity and mortality of these disorders remain considerable, although substantial progress has been made.[6] The use of pneumococcal *Haemophilus influenzae* type b (Hib) and meningococcal vaccines has led to dramatic changes in the incidence of meningitis caused by these bacteria.[7–14]

Definitions

CNS infections comprise a broad spectrum of disease entities. *Meningitis* is defined as inflammation of the membranes of the brain or spinal cord and is also called *arachnoiditis* or *leptomeningitis*. *Encephalitis* denotes inflammation of the brain itself, whereas *myelitis* refers to inflammation of the spinal cord. The terms *meningoencephalitis* and *encephalomyelitis* describe more diffuse inflammatory processes. Collections of infective and purulent materials may form within the CNS as abscesses. Brain abscesses may be intraparenchymal, epidural, or subdural, or may be found in intramedullary or epidural spinal locations.

This chapter focuses on the more common acute and subacute CNS infections. Infections of the nervous system with HIV or human T lymphotrophic virus, rabies virus, polio or hepatitis viruses, *Borrelia burgdorferi* (Lyme disease), *Treponema* organisms (syphilis), parasites, *Rickettsia,* and the chronic and slow infections of the CNS (subacute sclerosing panencephalitis, progressive multifocal leukoencephalopathy, and the prion-mediated spongiform encephalopathies, such as Creutzfeldt-Jakob disease, bovine spongiform encephalopathy, and kuru) are not addressed in detail. Of note, the incidence of neurocysticercosis is on the rise in the United States.[15]

Epidemiology

Bacterial meningitis is a common disease worldwide. Meningococcal meningitis is endemic in parts of Africa, and epidemics commonly occur in other countries, including the United States. A variety of other pathogens are also causative.[16–20] The overall incidence of bacterial meningitis in the United States is 5 to 10 cases per 100,000 people per year.[21] Men are affected more often than women.[21] In the United States, approximately 80% of cases are caused by either *Streptococcus pneumoniae* or *Neisseria meningitidis*.[22] In regions where vaccination is common, the epidemiology of bacterial meningitis has substantially changed.[9–11,14,23] The incidence of bacterial meningitis increases in late winter and early spring, but the disease may occur at any time of the year.

Because most cases are unreported, the actual incidence of viral meningitis is unknown. It is estimated to affect 11 to 27 individuals per 100,000 people.[24] A prominent increase of cases is seen in summer months, which is concurrent with seasonal predominance of the enterovirus group of the picornaviruses.

The same organisms responsible for viral meningitis may also be associated with encephalitis. Encephalitis is, however, far less common, and the ratio of cases of meningitis to encephalitis varies according to the specific pathogen. Arbovirus infection is transmitted by an insect vector, although clinical disease develops in only a small percentage of the people bitten. Before 1999, approximately 19,000 cases of encephalitis were hospitalized in the United States annually. Since then, there has been a rapid increase because of the emergence of

West Nile virus (WNV). In 2003, more than 8000 additional individuals were hospitalized because of WNV alone.[25,26]

Approximately 2000 cases of brain abscess occur in the United States annually.[27] Although CNS abscesses may occur at any age and any time of year, they are more commonly seen in men than women.[28,29] CNS abscesses are associated with local contiguous and remote systemic infections, intravenous (IV) drug use, neurologic surgery, and cranial trauma. Brain abscess secondary to otitis media most often occurs in pediatric or older adult populations. When associated with sinusitis, it most often arises among young adults. Increasingly, CNS abscesses are seen in the immunocompromised population, particularly those with HIV infection, and among bone marrow and solid organ transplant recipients. However, antimicrobial prophylaxis of immunosuppressed patients and more aggressive treatment of otitis and sinusitis have decreased the overall incidence to 0.9 per 100,000 person-years.[27]

PRINCIPLES OF DISEASE

Etiology

Meningitis

Meningeal inflammation may be caused by a variety of disease processes, but the infectious etiologies predominate. Among the bacterial etiologies, *Streptococcus pneumoniae* remains the predominant pathogen in adult patients, followed by *N. meningitidis* and *Listeria monocytogenes*.[30,31] *N. meningitidis* is the predominant organism in adults younger than 45 years. Five major serogroups cause most meningococcal disease worldwide (A, B, C, Y, and W-135). Serogroup A accounts for the majority of cases of meningococcal meningitis in developing nations.[32] Serogroup distribution for invasive disease has changed markedly in the United States, with B, C, and Y now most commonly responsible.[33–36] These pathogens account for the bulk of cases in nontraumatic meningitis, although virtually any organism can be encountered, particularly among patients who are elderly, alcoholic, and immunosuppressed and those who have cancer. Interestingly, higher case fatality has been observed in *N. meningitis* outbreaks versus sporadic cases, likely due to increased virulence of outbreak related strains.[37] Causes of aseptic meningitis, which simply defined is all cases with negative bacterial CSF cultures, are listed in Box 107-1.[38]

Meningeal infection may also occur in association with a dural leak secondary to neurosurgery or neurotrauma. *S. pneumoniae*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and coliform bacteria are seen most commonly in this population.

Viral meningitis may likewise be caused by a variety of etiologic agents.[39] Enteroviruses are statistically encountered most commonly.[40] Unfortunately, precise definition of the etiologic agent is often impossible. Fungal and parasitic meningitides are additional concerns, particularly among immunocompromised patients.[18,19]

Noninfectious meningitides include drug-induced meningitis, carcinomatous meningitis, CNS involvement in serum sickness, vasculitis, systemic lupus erythematosus, Behçet's disease, sarcoidosis, and others. The differentiation of noninfectious from infectious etiologies can often be perplexing.

Encephalitis

Arboviruses and herpes simplex virus (HSV), a human herpes virus (HHV), are the most common causes of epidemic and sporadic cases of encephalitis, respectively. Children are the most vulnerable to infection with these viruses, although adults are also commonly affected. Epidemics of viral encephalitis have been attributed to a wide variety of viral agents. WNV, a flavivirus, first infected humans in the New York City area and rapidly spread to 47 states by 2003.[19,41] Varicella, herpes zoster, HHV 6 and 7, and Epstein-Barr virus have been increasingly reported to be the cause of encephalitis in immunocompetent hosts.[42,43] Vaccinia encephalitis has been recognized in those receiving vaccination for smallpox.[44] Postinfectious encephalomyelitis is also induced by a variety of viral pathogens, most commonly by the measles virus.[45] However, *Mycoplasma pneumoniae* and idiopathic causes are becoming more common in developed countries.

Central Nervous System Abscess

The etiologies of CNS abscess are multiple and reflect the primary infective process and the immune state of the human host. A variety of mixed pathogens may be responsible for intracranial abscesses. Streptococci, particularly the *Streptococcus milleri* group, have been identified in nearly 50% of brain abscesses.[46] Anaerobic bacteria, predominantly *Bacteroides* species, are commonly seen when the primary infectious process is chronic otitis media or pulmonary disease. *S. aureus* and *Propionbacterium acnes* are often identified, particularly after cranial penetration from surgery or trauma.[47,48] The Enterobacteriaceae are an additional common isolate. Opportunistic fungal and parasitic etiologies are often seen in the immunosuppressed, including *Nocardia* species.[46,49] Culture of epidural and subdural abscesses more often yields a single organism, with streptococci most commonly seen when associated with contiguous spread and *S. aureus* and gram-negative rods most commonly encountered after neurologic trauma.[19] Etiologic agents in spinal abscess are similarly varied. *S. aureus* is most commonly encountered (Fig. 107-1).

Figure 107-1. Central nervous system abscess: computed tomography scan of an intraparenchymal abscess *(arrows)*.

BOX 107-1 CAUSES OF ASEPTIC MENINGITIS

I. Infectious causes
- 1. Viruses
  - Enteroviruses—polio, coxsackie, ECHO virus
  - Herpes group of viruses
  - Herpes simplex virus types 1 and 2
  - Varicella zoster virus
  - Cytomegalovirus
  - Epstein-Barr virus
  - Human herpes virus 6
  - Respiratory viruses
  - Adenovirus
  - Rhino virus
  - Influenza virus types A and B
  - Arboviruses
  - Mumps virus
  - Lymphocytic choreomeningitis
  - HIV
- 2. Bacteria
  - Partially treated meningitis
  - Parameningeal infection
  - Endocarditis
  - *Mycoplasma pneumoniae*
  - *Mycobacterium tuberculosis*
  - Ehrlichiosis
  - *Borrelia burgdorferi*
  - *Treponema pallidum*
  - *Brucella*
  - Leptospirosis
- 3. Fungi
  - *Cryptococcus neoformans*
  - *Histoplasma capsulatum*
  - *Coccidioides immitis*
  - *Blastomyces dermatitides*
  - *Candida*
- 4. Parasites
  - *Toxoplasma gondii*
  - Neurocysticercosis
  - Trichinosis
  - *Naegleria*
  - *Hartmannella*
  - *Bartonella henselae*
- 5. Rickettsiae
  - Rocky Mountain spotted fever
  - Typhus

II. Noninfectious causes
- 1. Postinfectious/postvaccinial
  - Rubella
  - Varicella
  - Variola
  - Rabies vaccine
  - Pertussis vaccine
  - Influenza vaccine
  - Vaccinia
  - Yellow fever vaccine
- 2. Drugs
  - Nonsteroidal anti-inflammatory drugs
  - Trimethoprim-sulfamethoxazole, amoxicillin
  - Muromunab CD3 (OKT3)
  - Azathioprine
  - Intravenous immunoglobulin
  - Isoniazid
  - Intrathecal methotrexate
  - Intrathecal cytosine arabinoside
  - Allopurinol
  - Carbamazepine
  - Sulfasalazine
- 3. Systemic disease
  - Collagen vascular disorders
  - Systemic lupus erythematosus
  - Wegener's granulomatosis
  - Central nervous system vasculitis
  - Rheumatoid arthritis
  - Kawasaki's disease
  - Sarcoidosis
  - Leptomeningeal cancer
  - Posttransplantation lymphoproliferative disorder
  - Behçet's disease
  - Vogt-Koyabagj syndrome
- 4. Neoplastic disorders
  - Leukemia
  - Carcinomatous meningitis secondary to primary or secondary tumors of the brain
- 5. Inflammation of neighboring structures
  - Brain abscess
  - Epidural abscess
- 6. Miscellaneous
  - Arachnoiditis
  - Migraine
  - Urinary tract infection

Reproduced from Kumar R: Aseptic meningitis: Diagnosis and management. Ind J Pediatr 72:57, 2005.

Pathophysiology

Bacterial Meningitis

The pathogenetic sequence in bacterial meningitis has been well characterized.[18,19,50,51] The first step is nasopharyngeal colonization and mucosal invasion. Although colonization rates vary, virulent microbes use secretion of immunoglobulin A proteases and induce cilio-stasis of mucosal cells. After penetration occurs by a variety of mechanisms, bacterial intravascular survival occurs because of evasion of the complement pathway. The varying capsular properties of each organism protect the bacteria. The third step occurs when the bacteria cross the blood-brain barrier to enter the CSF. The dural venous sinuses, cribriform plate area, and choroid plexus have all been implicated as potential sites of invasion. Although the mechanism of invasion is not completely understood, host defense mechanisms within the CSF are often ineffective; there are low levels of complement, immunoglobulin, and opsonic activity. Bacterial proliferation then occurs, which stimulates a convergence of leukocytes into the CSF.

Meningeal and subarachnoid space inflammation is also associated with the release of cytokines into the CSF, most notably tumor necrosis factor and interleukins 1 and 6.[50,52] This results in increased permeability of the blood-brain barrier, cerebral vasculitis, edema, and increased intracranial pressure (ICP). A subsequent decrease in cerebral blood flow leads to cerebral hypoxia. Glucose transport into the CSF is decreased concomitantly with an increased use of glucose by the brain,

bacteria, and leukocytes, which depresses CSF glucose concentrations. The increased permeability leads to increased CSF proteins.

Viral Meningitis and Encephalitis

Viruses enter the human host through the skin (i.e., insect vectors), through the respiratory, gastrointestinal, or urogenital tract, or by receipt of infected blood products or donor organs.[53,54] Viral replication subsequently occurs outside the CNS, most often followed by hematogenous spread to the CNS. Additional routes into the CNS include retrograde transmission along neuronal axons and direct invasion of the subarachnoid space after infection of the olfactory submucosa.[55,56]

Fortunately, most systemic viral infections do not result in meningitis or encephalitis. The development and subsequent magnitude of viral infection depend on the virulence of the specific virus, the viral inoculum level, and the state of immunity of the human host. The tropism of the virus for specific CNS cell types also influences the focality of disease and its manifestations.[55] Particular viruses may preferentially attack cortical, limbic, or spinal neurons, oligodendria, or ependymal cells. An example is the tropism of HSV for the temporal lobes and the development of temporal lobe seizures and behavioral changes in afflicted patients.

Fungal Meningitis

Fungal meningitis probably develops in much the same way as bacterial meningitis, although this has been incompletely studied. Pulmonary exposure followed by hematogenous spread is the primary pathogenetic mechanism in most cases. Immune system defects or immunosuppressive drugs compromise host defense mechanisms, with ensuing development of CNS infection.

Central Nervous System Abscess

Intraparenchymal brain abscesses, subdural empyema, or intracranial or spinal epidural abscesses form by inoculation of the CNS from contiguous spread of organisms from a sinus, middle ear, or dental infection or metastatic seeding from a distant site, usually from pulmonary infection, endocarditis, or osteomyelitis.[28,47] The primary infection can be identified in 75 to 85% of cases. These conditions may also follow surgery or penetrating cranial trauma, particularly when bone fragments are retained in brain tissue. Otogenic abscesses occur most commonly in the temporal lobe in adults and cerebellum in children, whereas sinogenic abscesses typically occur in frontal areas.[46] Multiple brain abscesses suggest hematogenous spread of organisms, although solitary lesions may also occur. The pulmonary system is the most common source of hematogenous spread.[19]

CLINICAL FEATURES

Symptoms and Signs

Numerous host factors have been implicated in the acquisition of meningitis (Box 107-2).[57] Although these factors alone and in combination increase the risk of meningitis, the disease often occurs in patients with none of these factors.

Many patients with meningitis present with advanced disease; in these patients, the diagnosis of acute meningitis is strongly suspected. The constellation of symptoms that may classically occur in an acute CNS infection consists of fever, headache, photophobia, nuchal rigidity, lethargy, malaise, altered sensorium, seizures, vomiting, and chills.[17,57]

BOX 107-2 HOST FACTORS PREDISPOSING TO MENINGITIS

- Age <5 yr
- Age >60 yr
- Male gender
- Low socioeconomic status
- Crowding (e.g., military recruits)
- Splenectomy
- Sickle cell disease
- Black race
- Alcoholism and cirrhosis
- Diabetes
- Immunologic defects
- Recent colonization
- Dural defect (e.g., traumatic, surgical, congenital)
- Continuous infection (e.g., sinusitis)
- Household contact with meningitis patient
- Thalassemia major
- Intravenous drug abuse
- Bacterial endocarditis
- Ventriculoperitoneal shunt
- Malignancy

Unfortunately, more subtle presentations are also common. Immunosuppressed and geriatric patients present a diagnostic challenge because the classical signs and symptoms of meningitis may not be present. Although some degree of fever is present in most patients, as are headache and neck stiffness, meningitis should be carefully considered in any immunosuppressed patient with symptoms or signs of infectious disease. Often, the only presenting sign of meningitis in the elderly patient is an alteration of mental status. However, a meta-analysis suggested that the absence of fever, stiff neck, and mental status change excludes meningitis in immunocompetent adults.[36]

The presentation of fungal meningitis can be obscure even in the healthy adult population. Headache, low-grade fever, lassitude, and weight loss may be present but often to such a mild degree that the correct diagnosis is not initially considered.[17] This is also true of tuberculous meningitis, which often has a protracted course and a vague nonspecific presentation consisting of fever, weight loss, night sweats, and malaise, with or without headache and meningismus.[16]

The physical findings in meningitis vary, depending on the host, causative organism, and severity of the illness. Nuchal rigidity or discomfort on flexion of the neck is common. Kernig's and Brudzinski's signs are present in approximately 50% of adults.[19] Described in 1882 by Vladimir Kernig, Kernig's sign is present in the patient if the examiner is unable, because of resistance and hamstring pain, to straighten the patient's leg passively to a position of full knee extension when the patient is lying supine with the hip flexed to a right angle. Jozef Brudzinski initially described five signs, two of which are currently utilized.[2] The contralateral sign is present if an attempt to flex the hip passively on one side is accompanied by a similar movement of the other leg. The neck sign is present if attempts to flex the neck passively are accompanied by flexion of the hips. The absence of jolt accentuation of headache with this maneuver may be useful in obviating the need for lumbar puncture (LP) in a patient with low suspicion for meningitis.[58] Deep tendon reflexes may be increased, and ophthalmoplegia may be present, especially of the lateral rectus muscles.

The systemic findings may include an obvious source of infection such as sinusitis, otitis media, mastoiditis, pneumonia, or urinary tract infection. Various manifestations of endocarditis may be present. Arthritis may be seen with *N. meningitidis* and occasionally with other bacteria.[57] Petechiae and cutaneous hemorrhages are widely reported with meningococcemia but also occur with Hib, pneumococcal organisms, *L. monocytogenes*, and echovirus infections, in addition to staphylococcal endocarditis.[57] Endotoxic shock with vascular collapse often develops in severe meningococcal disease, but shock may be present in the advanced stages of any bacterial meningitis. Any determination of a serious systemic infection should encourage rather than dissuade the clinician from considering the possibility of a concomitant CNS infection.

Patients with encephalitis may also have symptoms of meningeal irritation. An alteration of consciousness occurs in virtually all patients. Fever, headache, and a change of personality are also usually present.[56] Hallucinations and bizarre behavior may precede motor, reflex, and other neurologic manifestations by several days, occasionally prompting an initial diagnosis of a psychiatric disorder. Because focal neurologic deficits and seizures occur much more commonly with encephalitis than meningitis, there may also be diagnostic confusion with a brain abscess. Distinguishing the etiologic agent in encephalitis is clinically difficult, although HSV encephalitis results in a higher incidence of dysphasia and seizures.[59] In some patients, WNV produces a myelitis that affects the anterior horn cells of the spinal column, resulting in a flaccid paralysis with a clear sensorium, similar to findings in polio or Guillain-Barré syndrome.[41]

Patients with intracranial abscess may be indistinguishable from those with meningitis or encephalitis. Most patients with intraparenchymal abscess have a subacute course of illness, with symptoms progressing during the course of 2 or more weeks. However, nuchal rigidity and fever are present in fewer than 50% of cases. Focal neurologic deficits are present in most of these patients. A large number of patients exhibit papilledema, which is a rare finding in meningitis. An abrupt neurologic deterioration that results from uncal herniation or rupture into the ventricular system may occur.

Patients with a subdural or epidural abscess most often have headache, fever, and focal signs, although more subtle presentations are common. Most of the patients with spinal abscess typically present with spinal pain and other symptoms and signs of cord compression but not necessarily with fever.[60]

Complications

Bacterial Meningitis

The immediate complications of bacterial meningitis include coma (with loss of protective airway reflexes), seizures, cerebral edema, vasomotor collapse, disseminated intravascular coagulation, respiratory arrest, dehydration, syndrome of inappropriate secretion of antidiuretic hormone, pericardial effusion, and death (Box 107-3).[20] Various delayed complications include multiple seizures, focal paralysis, subdural effusions, hydrocephalus, intellectual deficits, sensorineural hearing loss, ataxia, blindness, bilateral adrenal hemorrhage (Waterhouse-Friderichsen syndrome), peripheral gangrene, and death.[57]

The case fatality rate for pneumococcal meningitis averages 20 to 25%, with higher fatality rates occurring in patients with serious underlying or concomitant disease or advanced age.[61,62] The prognosis is related to the degree of neurologic impairment on presentation. Overall, 20 to 30% of the survivors of pneumococcal meningitis have some residual neurologic deficit.[57] The case fatality rate for *Listeria* meningitis may be as high as 40%.[31]

BOX 107-3 Complications of Bacterial Meningitis

- Immediate
  - Coma
  - Loss of airway reflexes
  - Seizures
  - Cerebral edema
  - Vasomotor collapse
  - Disseminated intravascular coagulation (DIC)
  - Respiratory arrest
  - Dehydration
  - Pericardial effusion
  - Death
  - Others
- Delayed
  - Seizure disorder
  - Focal paralysis
  - Subdural effusion
  - Hydrocephalus
  - Intellectual deficits
  - Sensorineural hearing loss
  - Ataxia
  - Blindness
  - Bilateral adrenal hemorrhage
  - Death
  - Others

With the advent of antibiotic therapy, the mortality from meningococcal meningitis has markedly decreased to less than 20%, but it remains substantially higher in elderly patients or in those who also have meningococcemia.[62] Although most of the complications and sequelae are less common than with pneumococcal disease, the incidence of Waterhouse-Friderichsen syndrome is dramatically higher when meningococcemia is present.[57] The overall mortality rate in community-acquired gram-negative meningitis has been less than 20% since the introduction of the third-generation cephalosporins.[18]

Viral Meningitis

With rare exceptions, the overall prognosis for complete recovery from viral meningitis is excellent. Various complications related to the systemic effects of the particular virus include orchitis, parotitis, pancreatitis, and various dermatoses. Usually all of these complications resolve without sequelae.[39]

Viral Encephalitis

The outcomes in viral encephalitis are dependent on the infecting agent. Encephalitis caused by Japanese encephalitis virus, Eastern equine virus, and St. Louis encephalitis virus is severe, with high mortality rates and virtually universal neurologic sequelae among survivors.[63] WNV produces encephalitis in only 0.5% of those infected, yet it resulted in 120 deaths in 2003.[26] Western equine virus and California encephalitis virus cause milder infections, and death is rare. The incidence of neurologic sequelae is highly variable and appears to depend on both the host and the infecting agent.[63,64]

The mortality rate from HSV encephalitis before the use of acyclovir was 60 to 70%. Acyclovir treatment has reduced the mortality rate to approximately 30%.[45] Common sequelae observed among survivors include seizure disorders, motor deficits, and changes in mentation.

Tuberculous Meningitis

Death from tuberculous meningitis in the adult age group ranges from 10 to 50% of cases, with the incidence directly proportional to the patient's age and the duration of symptoms before presentation. Focal ischemic stroke may result from the associated cerebral vasculitis. In advanced disease, up to 25% of patients may require some neurosurgical procedure for obstruction (ventriculoperitoneal shunt or drainage).[65] In most patients some neurologic deficit develops, but severe long-term sequelae among survivors are unusual.[16,65]

Fungal Meningitis

Common CNS complications with fungal meningitis include abscesses, papilledema, neurologic deficits, seizures, bone invasion, and fluid collections. Direct invasion of the optic nerve results in ocular abnormalities in up to 40% of patients with cryptococcal meningitis.[17] The mortality rate is high but variable and is related to the timeliness of diagnosis, underlying illness, and therapeutic regimens.

Central Nervous System Abscess

With the early diagnosis afforded by the use of the cranial computed tomography (CT) scan; appropriate antimicrobial therapy; and combined management approaches with surgery, aspiration, and medical therapy, the mortality rate from brain abscess has declined dramatically from approximately 50% to less than 20%.[28,66] Seizure disorder is the most common sequela of intracranial abscess, occurring in 80% of patients.[18] Other neurologic sequelae of intracranial abscesses, including focal motor or sensory deficits or changes in mentation, are common. Complications of spinal abscess primarily result from cord compression, including paralysis, motor and sensory deficits, and bowel and bladder dysfunction. Generalized spread of CNS infection and death may also occur.[60]

DIAGNOSTIC STRATEGIES

Lumbar Puncture

General Considerations

Because the consequences of missing a CNS infection are devastating, CNS infection must be presumed to be present until excluded. The possibility of the diagnosis of meningitis mandates LP unless the procedure is contraindicated by the presence of infection in the skin or soft tissues at the puncture site or the likelihood of brain herniation.[45] Adherence to this principle prevents a delay in diagnosis, which substantially increases the morbidity and mortality of the disease. Some patients have clinically obvious bacterial meningitis, and CSF examination serves primarily to help identify the organism, thereby facilitating the appropriate treatment. Most patients, however, present more of a diagnostic problem, and analysis of the CSF fluid constitutes the critical step in the elucidation of the presence of CNS infection.

Increased Intracranial Pressure

In most patients with bacterial meningitis, LP may be safely performed without antecedent neuroimaging studies. As this may not be the case in other brain pathologies, in many circumstances it is advisable to obtain a CT scan of the head before performing an LP.[67,68] These indications must be carefully weighed against the patient's condition, the probability of meningitis, and the availability of the CT or magnetic resonance imaging (MRI) scan.[18]

It has been conventionally asserted that an LP in the presence of increased ICP may be harmful or fatal to the patient. Although data to address this concern are limited, the presence of focal neurologic signs does appear to be associated with a dramatic increase in complications from LP. These patients may deteriorate precipitously during or after the procedure.[69–72]

Patients with a markedly depressed sensorium that precludes careful neurologic examination or those with a focal neurologic deficit, papilledema, seizures, or evidence of head trauma must be considered to be at risk for a herniation syndrome that may be exacerbated by an LP. If the presentation is an acute, fulminating, febrile illness and bacterial meningitis is the concerning diagnosis, early initiation of antimicrobial therapy is mandatory because of the association of prognosis and time to treatment.[73] The algorithmic alternatives are therefore (1) immediate LP followed by initiation of antibiotic treatment before obtaining the results or (2) initiation of antibiotic treatment followed by a cranial CT scan and then an LP. The latter choice of empirical treatment with antibiotics is now the routine in many institutions, although in some cases a third option could be considered: antibiotics and no LP despite an unremarkable CT scan.[72] This reflects the efficacy of current methodologies of identification of causative organisms by means other than bacteriologic cultures. The controversy emerging regarding not performing LP despite a lack of CT scan findings is based on some reviews and case reports. These describe a fulminant herniation syndrome temporally related to LP in patients with normal CT scans.[70] Increased ICP may not be reliably detected using CT. Clinical signs of increased ICP, rapid change in consciousness, and recent seizures were identified as risk factors predicting deterioration despite a normal CT scan.[72] The risks of ongoing empirical treatment with antibiotics without additional information from CSF analysis appears to be low, as the yield from blood cultures and other diagnostic techniques such as PCR is relatively high. Therefore, this risk may be less than the risks of performing LP in certain very high-risk patients.

Cerebrospinal Fluid Analysis

Opening Pressure

The normal CSF pressure in an adult varies from 50 to 200 mm H_2O. This value applies only to patients in the lateral recumbent position and may increase substantially when the patient is in the sitting position. The pressure is often elevated in bacterial, tuberculous, and fungal meningitides and a variety of noninfectious processes.[56] Pressure may be falsely elevated when the patient is tense or obese or has marked muscle contraction.

Collection of Fluid

At least three sterile tubes each containing at least 1 to 1.5 mL of CSF should be obtained and numbered in sequence. A fourth tube may be desirable should later studies such as viral cultures or a Venereal Disease Research Laboratories (VDRL) test for syphilis become necessary. The fluid should be sent to the laboratory for immediate analysis of turbidity, xanthochromia, glucose, protein, cell count and differential, Gram's stain, bacterial culture, and antigen testing (Table 107-1). In certain cases, an India ink stain, bacteriologic stain for acid-fast bacilli, or VDRL test should be obtained. When only a small amount of fluid can be obtained, the most important studies

Table 107-1 Analysis of Cerebrospinal Fluid

TEST	NORMAL VALUE	SIGNIFICANCE OF ABNORMALITY
Cell count	≤5 WBC/mm^3 ≤1 PMN/mm^3 ≤1 eosinophil/mm^3	Increased WBC counts are seen in all types of meningitis and encephalitis; increased PMN count suggests bacterial pathogen
Gram's stain	No organism	Offending organism identified 80% of time in bacterial meningitis, 60% if patient pretreated
Turbidity	Clear	Increased turbidity with leukocytosis, blood, or high concentration of microorganisms
Xanthochromia	None	Presence of RBCs in spinal fluid for 4 hr before lumbar puncture; occasionally caused by traumatic tap (if protein ≥150 mg/dL) or hypercarotenemia
CSF-to-serum glucose ratio	0.6:1	Depressed in pyogenic meningitis or hyperglycemia; lag time if glucose given IV
Protein	15–45 mg/dL	Elevated with acute bacterial or fungal meningitis; also elevated with vasculitis, syphilis, encephalitis, neoplasms, and demyelination syndromes
India ink stain	Negative	Positive in one third of cases of cryptococcal meningitis
Cryptococcal antigen	Negative	90% accuracy for cryptococcal disease
Lactic acid	≤35 mg/dL	Elevated in bacterial and tubercular meningitis
Bacterial antigen tests	Negative	≥95% specific for organism tested; up to 50% false-negative rate
Acid-fast stain	Negative	Positive in 80% of cases of tuberculous meningitis if ≥10 mL of fluid

CSF, cerebrospinal fluid; PMN, polymorphonuclear; RBC, red blood cell; WBC, white blood cell.

are the cell count with differential, Gram's stain, and bacterial cultures. Ideally, the cell count should be performed on both the first and third or fourth tubes to help differentiate true CSF pleocytosis from contamination of the specimen by a traumatic LP.

Turbidity

The CSF should be assessed immediately for turbidity or cloudiness by the person performing the LP. Because normal CSF is completely clear and colorless and should be indistinguishable from water, any degree of turbidity is pathologic. Leukocytosis is the most common cause of CSF turbidity; counts greater than 200 cells/mm^3 usually cause clinically detectable changes in CSF clarity.[74]

Cell Count and Differential

Normal adult CSF contains no more than 5 leukocytes/mm^3 with at most one granulocyte (polymorphonuclear [PMN] leukocyte)[57,74,75]; therefore, the presence of more than one PMN or a total cell count of more than 5 cells/mm^3 should be considered evidence of CNS infection. In addition, the presence of any eosinophil in the CSF is abnormal, although occasionally basophils may be seen in the absence of disease.[74] Pretreatment with a few doses of antibiotics, although possibly diminishing the yield of Gram's staining and cultures, should not affect the CSF cell counts in meningitis.[18,30,76,77]

The cell counts in bacterial meningitis are usually markedly elevated, sometimes exceeding 10,000 cells/mm^3, and demonstrate a dramatic granulocytic shift.[57] In general, counts exceed 500 cells/mm^3, with a preponderance of PMN leukocytes. However, the initial CSF analysis exhibits lymphocytosis (lymphocyte count >50%) in 6 to 13% of all cases of bacterial meningitis. When only the patients with bacterial meningitis with fewer than 1000 cells/mm^3 are considered, 24 to 32% have a predominance of lymphocytes.[78,79] In addition, the same population of patients often has only a mild disturbance of CSF glucose and protein levels. In well-established viral meningitis and encephalitis, counts are usually less than 500 cells/mm^3, with nearly 100% of the cells being mononuclear.[40] Early (<48 hours) presentations may reveal significant PMN pleocytosis and hence be indistinguishable from presentations in early bacterial meningitis.[80]

Similarly, normal cell counts and differentials, although reassuring, do not absolutely exclude bacterial meningitis.[75] Any patient thought to have a clinical syndrome compatible with meningitis requires hospital admission with frequent reevaluation, repeated LP, and antimicrobial therapy. In some patients who have symptoms or signs of meningitis and have a normal initial CSF analysis, CSF pleocytosis may develop within 24 hours; the causative organism may be cultured from the original "normal" CSF.

Brain abscess and parameningeal infections, such as subdural empyema or epidural abscess, usually display CSF cell counts and differentials similar to those of viral meningitis and encephalitis, although the CSF may also be normal.

A traumatic LP is suggested by the presence of a clot in one of the tubes or the clearing of the CSF and a decreasing red blood cell (RBC) count from tubes one to three. In the presence of a traumatic LP, one may estimate the true degree of CSF white blood cell (WBC) pleocytosis with the formula given in Equation 107-1[74]:

$$\text{True CSF WBC} = \text{measured CSF WBC} - [(\text{CSF RBC} \times \text{blood WBC})/\text{blood RBC}] \quad \text{(Eq. 107-1)}$$

Alternatively, when peripheral cell counts are normal, the CSF from a traumatic LP should contain about 1 WBC per 700 RBCs.

Gram's Stain

A properly performed Gram's stain of a centrifuged specimen of CSF identifies the causative organism approximately 80% of the time in cases of bacterial meningitis.[76] Gram's stain characteristics of the most commonly encountered organisms are described in Table 107-2. The yield from this procedure is diminished by 20 to 30% when there has been prior treatment with antibiotics.[18] Misidentification of gram-positive organisms as gram-negative is also known to occur more commonly among pretreated patients because organisms with damaged walls stain unpredictably.

Table 107-2 Gram's Stain Characteristics of Selected Meningeal Pathogens

PATHOGEN	TYPICAL CHARACTERISTICS
Staphylococci	Gram-positive cocci: singles, doubles, tetrads, clusters
Streptococcus pneumoniae	Gram-positive cocci: paired diplococci
Other streptococci	Gram-positive cocci: pairs and chains
Listeria monocytogenes	Gram-positive rods: single or chains
Neisseria meningitidis	Gram-negative cocci: negative paired diplococci; kidney or coffee bean appearance
Haemophilus influenzae	Gram-negative coccobacilli: "pleomorphic" bacilli
Enterobacteriaceae (including *Escherichia coli*)	Gram-negative rods
Pseudomonas aeruginosa	Gram-negative rods

Xanthochromia

Xanthochromia refers to the yellowish discoloration of the supernatant of a centrifuged CSF specimen. Xanthochromia is abnormal and results from the lysis of RBCs and release of the breakdown pigments oxyhemoglobin, bilirubin, and methemoglobin into the CSF. This process normally begins within 2 hours, and pigments may persist up to 30 days; therefore, early analysis of the LP specimen is essential. If a traumatic tap has introduced enough plasma to raise the CSF protein level to 150 mg/dL or more, blood pigments may cause xanthochromia. If the CSF protein level is less than 150 mg/dL, however, and systemic hypercarotenemia does not exist, xanthochromia of a centrifuged CSF specimen should suggest that subarachnoid hemorrhage has occurred.[74]

Glucose

When the serum glucose is normal, the CSF glucose is usually between 50 and 80 mg/dL. The CSF glucose is normally in a ratio of 0.6:1 to the serum glucose, except with marked systemic hyperglycemia, when the ratio is closer to 0.4:1. Therefore, a CSF-to-serum glucose ratio of less than 0.5 in normoglycemic subjects or 0.3 in hyperglycemic subjects is abnormal and may represent the impaired glucose transport mechanisms and increased CNS glucose use associated with pyogenic meningitis.[57,74] Mild decreases in the CSF glucose level may occur with certain viral and parameningeal processes. However, bacterial or fungal meningitis should be presumed to be the cause of low CSF glucose, termed hypoglycorrhachia, until each is clearly excluded.[81] If the serum glucose level has increased rapidly—for example, after IV administration of 50% dextrose in water—equilibration in the CSF may take up to 4 hours, and therefore the interpretation of CSF-to-serum glucose ratios may be unreliable.

Protein

The normal CSF protein level in adults ranges from 15 to 45 mg/dL. An elevated CSF protein, usually higher than 150 mg/dL, commonly occurs with acute bacterial meningitis.[57] When a traumatic LP has occurred, the CSF protein can be corrected for the presence of blood by subtracting 1 mg/dL of protein for each 1000 RBCs.[74] Elevated CSF protein concentrations can result from any cause of meningitis, subarachnoid hemorrhage, CNS vasculitis, syphilis, viral encephalitis, neoplasms, and demyelination syndromes.[74] A greatly elevated CSF protein level (>1000 mg/dL) in the presence of a relatively benign clinical presentation should suggest fungal disease.[17]

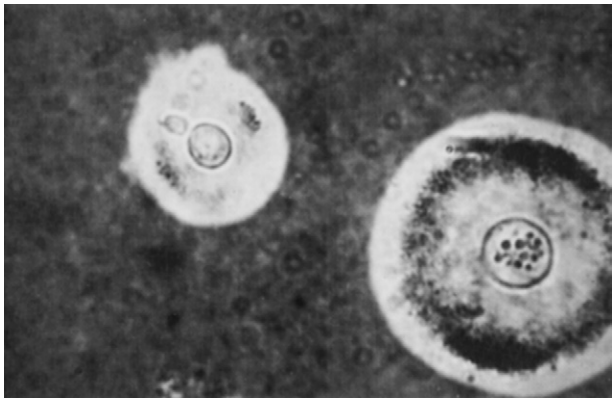


Figure 107-2. India ink staining of the cerebrospinal fluid.

India Ink Preparation

India ink staining of the CSF should be performed when a diagnosis of cryptococcal meningitis is being considered. The demonstration of budding organisms (Fig. 107-2) is virtually diagnostic for cryptococcal disease but occurs in only one third of the cases.[17] A more definitive diagnostic test is the cryptococcal antigen.

Lactic Acid

Although nonspecific, elevations in CSF lactic acid concentrations (>35 mg/dL) are potentially indicative of bacterial meningitis, and lactate may rise prior to the decline in glucose.[82,83] Normal lactate levels (<35 mg/dL) are usually seen in patients with viral meningitides.

Antigen Detection

Counterimmunoelectrophoresis (CIE), latex agglutination, and coagglutination are methods of detecting specific antigens. These tests are particularly useful in patients receiving antibiotic treatment before CSF sampling because the tests depend on the presence of only an antigen and not viable organisms.

The CIE techniques that are performed for the most common bacterial pathogens demonstrate high sensitivity and specificity for bacterial antigens, particularly when performed on CSF, blood, and urine simultaneously. Latex agglutination techniques are, however, more rapid and sensitive and are replacing the use of CIE in many facilities. Although reported results vary, the sensitivities of antigen tests are 50 to 90% for *Neisseria* organisms, 50 to 100% for *S. pneumoniae*, and approximately 80% for *H. influenzae*. A specific agglutination test for cryptococcal antigen is also highly sensitive (90%) and specific. Cultures are always indicated because a negative antigen test does not exclude the possibility of any particular bacterial or fungal etiology.

Antigen and antibody testing is also being used to identify viral and atypical pathogens. These have particular utility in HSV encephalitis. Enzyme-linked immunosorbent assays can detect HSV antibody production.[84] Unfortunately, the appearance of antibody in CSF occurs too late to aid in any therapeutic decision analysis. PCR amplification and the identification of HSV DNA have demonstrated a sensitivity of 95 to 100%

and a specificity of 100% early in the disease and have markedly decreased the need for diagnostic brain biopsy in this disorder.[85–87] PCR has improved the diagnosis of tuberculous meningitis, with a sensitivity of 80 to 85% and a specificity of 97 to 100% and is superior to standard techniques.[88–90] PCR has additionally been shown to be superior in identifying bacteria, enteroviruses, and other viral etiologies in both immunocompromised and immunocompetent patients.[91,92] Reported sensitivities of detection in CSF by PCR for *N. meningitidis*, *H. influenzae*, and *S. pneumoniae* are 88, 100, and 92%, respectively, with nearly 100% specificity.[93,94] The sensitivities of bacteriologic culture are much lower, especially for *N. meningitidis* at 37 to 55% and *H. influenzae* at 50%.[94–96]

In addition, PCR assays have nearly tripled the yield of viral culture in identifying the etiologic agent.[97] In studies of enteroviral meningitis, sensitivities and specificities for PCR ranged from 86 to 100% and 92 to 100%, respectively.[98] PCR has been shown to be at least as sensitive as culture technique in detecting cryptococcal meningitis. Quantitative PCR may be of benefit in monitoring response to therapy in some forms of severe disease.[42]

The growing availability of these molecular techniques does not, however, suggest that they should be routinely employed. Most cases of acute bacterial meningitis are readily diagnosed and treated on the basis of the standard Gram's stain and culture. PCR should be reserved for less clear presentations, patients pretreated with antibiotics, and cases in which concern exists for tuberculous, cryptococcal, and treatable viral CNS infections.[99]

Bacteriologic Cultures

Although results are not available for emergency management, bacteriologic cultures of CSF should be performed. Bacterial culture yields are significantly decreased in patients pretreated with antibiotics. Viral cultures may also be indicated.

Other Tests

A variety of additional, nonspecific tests of CSF have been advocated. These include measuring CSF lactate dehydrogenase, C-reactive protein, and the limulus lysate test; however, none of these have demonstrated a high degree of clinical usefulness. Likewise, the evaluation of CSF chloride as a diagnostic aid for tuberculous meningitis is no longer clinically relevant.

Neuroimaging Techniques

A cranial CT scan or MRI scan is indicated in the evaluation of any patient with presumed CNS infection in whom there is the possibility of an intracranial abscess, intracranial hemorrhage, or mass lesion. In the diagnostic evaluation of acute meningitis, however, a CT scan should not unnecessarily delay LP or antimicrobial therapy. The CT scan may also show hypodense lesions in the temporal lobes in patients with HSV encephalitis, although an MRI scan reveals this abnormality much earlier in the disease process. A contrast-enhanced cranial CT scan or MRI scan is invaluable in the diagnosis of a CNS abscess.[28] MRI scanning is also helpful in the evaluation of other infectious and noninfectious encephalitides.

Additional Investigations

As with other infectious diseases, the complete blood count with differential is a nonspecific adjunct in the diagnostic evaluation of a patient suspected to have a CNS infection. The peripheral cell counts are often normal in the presence of significant disease and may even be depressed, particularly in elderly or immunosuppressed persons. A "normal" leukocyte count and differential should not dissuade the emergency physician from performing a diagnostic LP, obtaining a CT scan, or otherwise pursuing the diagnosis of a CNS infection. Serum C-reactive protein is nonspecific, but a negative test result is potentially helpful.[100] Procalcitonin is emerging as a promising serum marker in infectious disease; however, there is not convincing evidence at this point to advocate its use to attempt to rule out bacterial meningitis.[101]

Even when antimicrobial therapy has already been administered, two or three blood cultures should be obtained for all patients who are being evaluated for a CNS infection. The blood cultures can improve the identification of the causative organisms, especially with pneumococcus and to a lesser degree meningococcus. Although blood cultures are not immediately useful in the acute diagnosis of meningitis in the emergency department, they may be of considerable clinical importance later in the management of the disease. The cultures are helpful in identifying a causative organism in only a small minority of cases of brain abscess.

As many as 50% of patients with pneumococcal meningitis also have evidence of pneumonia on an initial chest radiographic study. This association occurs in fewer than 10% of the cases of meningitis caused by Hib and *N. meningitidis* and in approximately 20% of cases of meningitis caused by other organisms. The identification of a pulmonary infection on chest radiography may assist in identification of causative organisms and appropriate antimicrobial therapy in approximately 10% of cases of brain abscess.[28]

Other ancillary investigations such as echocardiography, cultures of other body fluids, and bone scans may be undertaken as necessary to evaluate coexistent or complicated disease. Serum electrolytes, glucose, urea nitrogen, and creatinine levels should be measured to facilitate the interpretation of the CSF glucose level and to establish the level of renal function and the state of electrolyte balance. Although organism-specific abnormalities are uncommon, hyponatremia has been associated with tuberculous meningitis.

A number of characteristic but not pathognomonic electroencephalographic abnormalities have been associated with HSV type 1 encephalitis. The presence of focal or lateralized electroencephalographic abnormalities in the presence of an encephalitis syndrome should be considered strong evidence supporting a diagnosis of HSV encephalitis.[102]

DIFFERENTIAL CONSIDERATIONS

Patients with meningitis may have symptoms and signs ranging from mild headache with fever to frank coma and shock. To facilitate the discussion of diagnosis and treatment, meningitis may be divided into three clinical syndromes: acute meningitis, subacute meningitis, and chronic meningitis.

Acute meningitis encompasses patients with obvious signs and symptoms of meningitis who are evaluated in less than 24 hours after the onset of their symptoms and who rapidly deteriorate. In many of these patients the diagnosis of meningitis is not in doubt, and the crucial step is to initiate antimicrobial therapy immediately. The most likely pathogens in this syndrome are *S. pneumoniae* and *N. meningitidis*. Although *H. influenzae* has been reported in this context, it is not commonly implicated in the adult population.[20,30]

In the syndrome of subacute meningitis, the symptoms and signs causing the patient to seek care have developed during a period of 1 to 7 days. This syndrome includes virtually all cases of viral meningitis, along with most of the bacterial and

some of the fungal etiologies.[18,19] The differential diagnosis depends on the symptoms and signs at presentation. Among elderly and immunosuppressed individuals, a change in the patient's mental status may be the only presenting sign in meningitis. Even when a fever is present, the patient's change in mental status may be misattributed to another disease outside the CNS, such as pneumonia or urinary tract infection; neck stiffness may be misattributed to degenerative joint disease. The elderly patient is at high risk for meningitis and, rather than constituting a diagnostic endpoint, the identification of an infection outside the CNS in such a patient is a clear indication for LP because of the risk of bacteremic seeding by the involved organisms.

The differential diagnosis of encephalitis and brain abscess occurs in the context of the subacute meningitis syndrome. Brain abscess should be considered, especially if fever is minimal or absent or if there are focal neurologic findings. The presence of fever, altered sensorium, headache, seizures, and personality change is consistent with encephalitis. In addition, diagnoses such as subdural empyema, brain tumor, subarachnoid hemorrhage, subdural hematoma, and traumatic intracranial hemorrhage should be considered. In these circumstances a cranial CT scan should be obtained before performing an LP.

The spectrum of chronic meningitis includes some of the viral meningitides as well as meningitis caused by tubercle bacilli, syphilis, and fungi. Many of the patients in this group have had symptoms for at least 1 week before presentation and generally have a prolonged indolent course marked by difficult and changing diagnoses and multiple therapies.[16,17] Prediction rules have been both derived and validated and have not yet diffused into widespread practice, likely due to limitations in the models, shifts in the epidemiology of the causative organisms, and relatively small sample sizes.[103–105]

MANAGEMENT

Assessment and Stabilization

Septic shock, hypoxemia, seizures, cerebral edema, and hypotension resulting from dehydration require aggressive management. When possible, a thorough history should be obtained from the patient, family members, or ambulance personnel with particular emphasis on preexisting conditions that may complicate the patient's disease. Examples include recent neurosurgery, trauma, a history of leukopenia, immunocompromise, or diabetes mellitus.

Hypotension or shock should be treated as indicated with isotonic crystalloid infusion, high-flow oxygen, and pressors. IV dextrose may be required for hypoglycemia secondary to depletion of glycogen stores. Alcoholic or nutritionally compromised patients should also receive 50 to 100 mg of IV thiamine. In cases of moderate to severe hypotension, central venous pressure monitoring should be initiated and used as a guide for additional IV fluids or vasopressors. In children, after volume resuscitation there does not appear to be evidence to restrict fluids and appropriate maintenance fluids should be instituted.[106]

Active airway management with endotracheal intubation may be required, particularly in cases of coma, recurrent seizures, or severe accompanying pulmonary infection. Cardiac monitoring may also be necessary, particularly in elderly patients, those with known coronary disease, and those with an altered mental status. Seizures are a particularly prominent component of the clinical presentation in patients with a brain abscess but may also occur with any CNS infection, especially when an underlying seizure disorder is present.

If acute cerebral edema or an elevated ICP is present, it should be managed by immediate intubation and adequate ventilation. Osmotic agents such as mannitol or diuretics such as furosemide may be used, but caution should be exercised if shock or uncontrolled hypotension is present. If diuretics or osmotic agents are administered, the emergency physician must ensure that the patient does not become volume depleted and hypotensive.

Definitive Therapy

Bacterial Meningitis

Therapy for bacterial meningitis requires antibiotics that penetrate the blood-brain barrier and achieve adequate CSF concentrations, are bactericidal against the offending organism in vivo, and maintain adequate tissue levels to treat the infection effectively.

Until the pathogenetic organism is identified, broad-spectrum coverage of the most common pathogens is necessary (Table 107-3). Many authorities recommend cefotaxime or ceftriaxone, plus vancomycin to cover potentially resistant organisms.[107] High-dose ampicillin is also added if concern exists about *Listeria*.[107] In patients allergic to penicillin and cephalosporins, meropenem or chloramphenicol plus vancomycin may be effective while awaiting the outcome of desensitization techniques.[107]

After the pathogen is identified, more targeted therapy can be instituted. It is prudent to refer to a current antimicrobial reference to guide therapy in all instances, given rapid changes in etiologic spectrum, drug resistance, and available agents. Duration of treatment varies, and in certain situations (namely epidemics in sub-Saharan Africa), long-acting chloramphenicol or ceftriaxone is effective.[108]

Corticosteroid treatment is additionally recommended in adult acute bacterial meningitis. Animal studies demonstrate the salutary effects of the administration of corticosteroids in experimental pneumococcal meningitis, including reduced brain edema, CSF pressure, and CSF lactate levels.[109] Earlier resolution of the clinical and CSF stigmata of meningitis and a decrease in long-term hearing loss are observed in infants and children given dexamethasone with cefuroxime or ceftriaxone compared with those receiving the antibiotic alone, particularly when *H. influenzae* is the offending agent.[110,111] In adult bacterial meningitis, an absolute risk reduction of 10% for unfavorable outcome is seen when dexamethasone is given either 15 minutes before or concomitantly with antibiotics and continued for 4 days at 6-hour intervals.[112] This benefit was greatest in those with *S. pneumoniae*. Subgroup analyses for different causative organisms did not establish a benefit; however, the study was not designed with adequate power to detect improved outcomes. In addition, amoxicillin and penicillin were the most commonly used initial therapy, due to the process of health care delivery in Europe at the time of that study in which nearly all patients were seen initially in an office-based practice. A recent randomized controlled trial did not demonstrate a benefit of adjuvant dexamethasone in adult patients, even when only those with *S. pneumoniae* were included in a secondary analysis.[113] In the current era of initial empiric parenteral therapy, rising β-lactam resistance, the possibility of the decreased CSF penetration of vancomycin after dexamethasone treatment, and shifts in the likely causative organisms secondary to vaccination campaigns, the true effectiveness of dexamethasone is unclear. The most recent meta-analysis suggests a benefit, but the included studies suffer from one or more of the aforementioned limitations.[114]

Table 107-3 **Recommendations for Empirical Antimicrobial Therapy for Purulent Meningitis Based on Patient Age and Specific Predisposing Condition**

PREDISPOSING FACTOR	COMMON BACTERIAL PATHOGENS	ANTIMICROBIAL THERAPY
Age		
<1 mo	*Streptococcus agalactiae*, *Escherichia coli*, *Listeria monocytogenes*, *Klebsiella* species	Ampicillin plus cefotaxime or ampicillin plus an aminoglycoside
1–23 mo	*Streptococcus pneumoniae*, *Neisseria meningitides*, *S. agalactiae*, *Haemophilus influenzae*, *E. coli*	Vancomycin plus a third-generation cephalosporin[a,b]
2–50 yr	*N. meningitides*, *S. pneumoniae*	Vancomycin plus a third-generation cephalosporin[a,b]
>50 yr	*S. pneumoniae*, *N. meningitides*, *L. monocytogenes*, aerobic gram-negative bacilli	Vancomycin plus ampicillin plus a third-generation cephalosporin[a,b]
Basilar skull fracture	*S. pneumoniae*, *H. influenzae*, group A beta-hemolytic streptococci	Vancomycin plus a third-generation cephalosporin[a,b]
Penetrating trauma	*Staphylococcus aureus*, coagulase-negative staphylococci (especially *Staphylococcus epidermidis*), aerobic gram-negative bacilli (including *Pseudomonas aeruginosa*)	Vancomycin plus cefepime, vancomycin plus ceftazidime, or vancomycin plus meropenem
Post–neurosurgery	Aerobic gram-negative bacilli (including *P. aeruginosa*), *S. aureus*, coagulase-negative staphylococci (especially *S. epidermidis*)	Vancomycin plus cefepime, vancomycin plus ceftazidime, or vancomycin plus meropenem
Cerebrospinal fluid shunt	Coagulase-negative staphylococci (especially *S. epidermidis*), *S. aureus*, aerobic gram-negative bacilli (including *P. aeruginosa*), *Propionibacterium acnes*	Vancomycin plus cefepime,[c] vancomycin plus ceftazidime,[c] or vancomycin plus meropenem[c]

[a]Ceftriaxone or cefotaxime.
[b]Some experts would add rifampin if dexamethasone is also given.
[c]In infants and children, vancomycin alone is reasonable unless Gram's stains reveal the presence of gram-negative bacilli.
Reproduced from Tunkel AR: Practice guidelines for bacterial meningitis. Clin Infect Dis 39:1267, 2004.

In pediatric meningitis, the evidence that adjunctive dexamethasone is helpful is less compelling. Invasive Hib and pneumococcal infections have drastically been reduced by vaccination.[7,23] A randomized trial of dexamethasone in childhood meningitis in sub-Saharan Africa did not demonstrate a benefit.[115] Current recommendations are organism specific, which presents a major limitation as recommendations are to begin empiric therapy prior to laboratory results in suspicious cases. For Hib, "dexamethasone may be beneficial for treatment of infants and children with Hib meningitis to diminish the risk of neurologic sequelae, including hearing loss, if given before or concurrently with the first dose of antimicrobial agent(s). There probably is no benefit if dexamethasone is given more than 1 hour after antimicrobial agent(s)."[116] For *S. pneumoniae*, "for infants and children 6 weeks of age and older, adjunctive therapy with dexamethasone may be considered after weighing the potential benefits and possible risks. Experts do not agree on a recommendation to use corticosteroids in pneumococcal meningitis; data are not sufficient to demonstrate a clear benefit in children. If used, dexamethasone should be given before or concurrently with the first dose of the antimicrobial agent."[117] The implication for frontline physicians caring for children is that unless the causative organism is known prior to antibiotic treatment, there is probably little role for adjunctive dexamethasone in children.

Viral Meningitis

No specific agents are available for treating most types of viral meningitis. Investigational agents in development may reduce symptoms in enterovirus meningitis[118]; however, with the exception of HSV meningitis, the viral meningitides contracted in the United States are generally characterized by a short, benign, self-limited course followed by a complete recovery. The primary therapeutic consideration in cases of viral meningitis is therefore the validity of the diagnosis. Early cases of viral meningitis may be indistinguishable from bacterial meningitis, and this confusion may not be resolved by CSF analysis; therefore, when any doubt exists about the veracity of the diagnosis, appropriate cultures should be obtained and the patient admitted to the hospital. Antimicrobial therapy for presumed bacterial meningitis may be initiated on the basis of the clinical presentation or may be withheld pending the outcome of close clinical observation and repeated LP in 8 to 12 hours.

Viral Encephalitis

Specific therapy for meningoencephalitis from HHV is available. Acyclovir remains the current choice and is capable of substantially improving the patient's outcome. When the diagnosis of herpes meningoencephalitis is suspected or established, IV acyclovir should be administered in a dose of 10 mg/kg every 8 hours.[81] Ganciclovir, foscarnet, and cidofovir are also effective in HHV infections, and pleconaril has been effective in enteroviral disease. Additional antiviral treatments are in development.[41,42,118]

Tuberculous Meningitis

Early chemotherapeutic intervention in acute tuberculous meningitis improves the patient's prognosis. A strong clinical suggestion of this disease is an adequate indication to begin antituberculous therapy. A standard treatment regimen consists of isoniazid, rifampin, pyrazinamide, and ethambutol or streptomycin.[107] Corticosteroids have also been shown to decrease secondary complications.[107,119]

Fungal Meningitis

The treatment of fungal meningitis is complex.[17] Four agents are commonly used: amphotericin B, flucytosine, miconazole, and fluconazole. Of these, amphotericin B, either alone or in combination with flucytosine, is the most commonly recommended initial therapeutic regimen.[107] These diseases are rarely acutely life-threatening but rather are slowly progressive. Prolonged therapy, often with multiple agents, is necessary. The initiation of antifungal therapy is rarely indicated in the emergency department.

Central Nervous System Abscess

The treatment of cerebral abscess is complex, and neurosurgical consultation is indicated. The location, size, and number of abscesses influence the choice of medical management, surgical excision, aspiration, or a combination of these modalities.[46] In general, small multiple abscesses are more appropriately treated medically, whereas large, surgically accessible lesions should be excised. Empirical antimicrobial therapy before identification of specific organisms by aspiration or surgical excision should be guided by the principles of CSF penetration and the coverage of likely pathogens.

Otogenic and sinogenic abscesses are often treated with cefotaxime or ceftriaxone plus metronidazole.[107] Abscesses with traumatic or neurosurgical causes should have antimicrobial coverage for *S. aureus* or methicillin-resistant *S. aureus*. Patients at high risk for tuberculous, fungal, or parasitic abscess should also receive coverage for the suspected etiologic agent. Corticosteroids should be reserved specifically for managing any attendant cerebral edema; in other circumstances, steroid use is associated with increased mortality. In cases where the etiology is bacterial endocarditis, valve replacement is often required.[120]

Chemoprophylaxis

Among household contacts, the incidence of transmission of meningococcus is approximately 5%; therefore, it is recommended that household contacts of bacteriologically confirmed cases receive rifampin (adults, 600 mg; children older than 1 month, 10 mg/kg; children younger than 1 month, 5 mg/kg) orally every 12 hours for a total of four doses.[107] In addition, these contacts should be advised to watch for fever, sore throat, rash, or any symptoms of meningitis. They should be hospitalized with appropriate IV antimicrobial therapy if there are signs that active meningococcal disease is developing because rifampin is ineffective against invasive meningococcal disease. Intimate, nonhousehold contacts who have had mucosal exposure to the patient's oral secretions should also receive rifampin prophylaxis. Health care workers are not at increased risk for the disease and do not require prophylaxis unless they have had direct mucosal contact with the patient's secretions, as might occur during mouth-to-mouth resuscitation, endotracheal intubation, or nasotracheal suctioning. Ciprofloxacin 500 mg by mouth (adults only) and ceftriaxone 250 mg intramuscularly (125 mg intramuscularly for children younger than 15 years) provide single-dose alternatives.[107]

There is no indication for chemoprophylaxis in pneumococcal meningitis. Rifampin prophylaxis for the contacts of patients with Hib meningitis is recommended for nonpregnant household contacts when there are children younger than 4 years of age in the household[107] (adults, 600 mg by mouth; children, 20 mg/kg by mouth daily for 4 days).

Immunoprophylaxis

A quadrivalent vaccine based on the polysaccharide capsule and conferring protection against group A, C, Y, and W-135 meningococci has been in routine use by the U.S. military since the 1980s.[121] However, the capsular polysaccharide vaccines used to immunize adults are neither immunogenic nor protective in children younger than 2 years because of poor antibody response. In addition, no licensed vaccine is currently available against the serogroup B meningococcus.[36] The serogroup B capsular polysaccharide has proved to be poorly immunogenic in both adults and children.[122] The sequence variation of the surface proteins and cross-reactivity of the group B polysaccharide with human tissues have further impeded efforts to develop a successful vaccine. Efforts to enhance the immunogenicity and protective efficacy of meningococcal vaccines have focused on using conjugate methods that link polysaccharides and carrier proteins. Serogroup C and serogroup C + Y conjugate vaccines have been developed and utilized effectively.[123] Current recommendations for the quadrivalent vaccine are evolving. The vaccine is recommended in established meningococcal epidemics and for travelers to countries where meningococcal disease is currently epidemic. Elective vaccination of college freshmen has been recommended by the Advisory Committee on Immunization Practices (ACIP) in the United States and public health authorities in the United Kingdom.[124] The United Kingdom has also implemented universal childhood immunization with a group C conjugate vaccine.[123]

The development of effective pneumococcal vaccines has been hampered by the large number of serotypes of the organism. A small number of serotypes, however, is responsible for most clinical pneumococcal disease, and a 23-valent vaccine effective against many of these principal serotypes has been developed.[125] The recommendations for this polyvalent pneumococcal vaccine are targeted primarily at prevention of pneumonia, despite a potential beneficial effect for meningitis. A single dose of the vaccine should be considered for elderly or debilitated patients, especially those with pulmonary disease, and for patients with impaired splenic function, splenectomy, or sickle cell anemia.[22] A heptavalent conjugated pneumococcal vaccine has also been developed and is recommended for universal childhood immunization by the ACIP.[126] A conjugate vaccine effective against Hib has been developed for use in the pediatric, but not adult, population. It appears to be approximately 90% protective and has a very low incidence of adverse reactions.[7,8,127] Modern childhood immunization against Hib has raised the average age of patients afflicted with *Haemophilus* meningitis to 25 years and decreased the incidence of meningitis of any etiology by 55%.[99]

Vaccination is also available to confer immune protection against Japanese encephalitis virus, and it is recommended for people performing extensive outdoor activities or spending more than 30 days in endemic areas during transmission seasons.[128,129] The reported protective efficacy of the vaccine is approximately 90%. Although there is no current human vaccine for the WNV, vaccines for nonhuman mammals have been developed.[41]

■ DISPOSITION

With the exception of viral meningitis, all but the most chronic CNS infections require initial inpatient evaluation and treatment. Bed rest, analgesics, and the institution of appropriate IV antimicrobials are indicated.

Some patients with suspected viral meningitides merit hospitalization. These include patients with more severe disease, immunocompromise, suspicion of HSV meningitis, or potential nonviral causes. Some authorities manage patients with classical presentations of viral meningitis as outpatients and ensure close follow-up within 24 hours. Others admit all patients until the more serious causes, such as early bacterial meningitis or encephalitis, can be excluded with certainty.

KEY CONCEPTS

- CNS infection should be considered in all patients with headache, neck stiffness, fever, altered sensorium, or diffuse or focal neurologic findings.
- Lumbar puncture with sampling of CSF is the only reliable method of assessing the presence or absence of meningitis. In the absence of contraindications, any suspicion of meningitis mandates performance of LP.
- Early initiation of antimicrobial therapy is mandatory in any case of suspected acute CNS infection. Antibiotic administration must not be delayed for CSF analysis or performance of neuroimaging studies.
- Antibiotic chemoprophylaxis should be assured for close contacts of patients with meningitis resulting from *N. meningitidis* or *H. influenzae*. Single-dose and multiple-dose regimens are available.
- Vaccination against *N. meningitidis* is recommended for certain at-risk populations but does not afford protection against serogroup B infection.
- Concomitant CNS infection should be strongly considered in any patient with another severe systemic infection, such as urinary tract infection or pneumonia.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 108 Thought Disorders

Robert S. Hockberger and John R. Richards

PERSPECTIVE

In the 1800s, Morel introduced the term *dementia praecox* to describe a progressive deterioration of mental functioning and behavior with onset in adolescence to early adult life.[1] In 1911 Bleuler detailed the specifics of this disorder, which he termed *schizophrenia*, or "split-mindedness."[2] Early treatments for schizophrenia included ice water immersion, the use of barbiturates or insulin to induce prolonged narcosis or coma, seizure induction with pentylenetetrazol, electroconvulsive therapy, and frontal leukotomy.[3] The effectiveness of these treatments was marginal at best, and until more recent times most schizophrenic patients were relegated to lifelong institutionalization.

Modern-era pharmacotherapy of schizophrenia, principally with chlorpromazine and haloperidol, began in the early 1950s. This treatment proved so successful that, by the 1960s, most psychiatrists believed that schizophrenia could be successfully managed in the outpatient setting. In 1965, the Community Mental Health Centers Act initiated the release of medicated schizophrenic patients into the community.[4] Unfortunately, inadequate family support, the unavailability of jobs and low-cost housing, and the lack of funding for social services and outpatient psychiatric care left these individuals isolated without the tools needed for resocialization. This situation has improved little since that time, and currently 20 to 40% of homeless people in the United States have a major mental illness.[5] Emergency departments in the United States and worldwide frequently serve as the primary entry point into the mental health care system for many of these individuals.[6]

PRINCIPLES OF DISEASE

The etiology of schizophrenia is currently believed to be heterogeneous from interaction of biologic and environmental factors. Studies involving adopted twins whose biologic parents have schizophrenia demonstrate a strong genetic basis for the disorder. Although the overall incidence of schizophrenia in the general population is approximately 1%, it is approximately 10% in first-degree biologic relatives of individuals with the disorder.[7] With regard to the pathophysiology of schizophrenia, dopaminergic, serotonergic, cholinergic, and glutamatergic systems have been implicated.[8–11]

Schizophrenia is also postulated to be a neurodevelopmental disorder resulting from the influence of environmental factors on genetically predisposed individuals. Disruptions in fetal brain development, caused by perinatal hypoxia, poor nutrition, infection, and other insults, may set the stage for subsequent development of schizophrenia.[1,12] New imaging techniques have documented structural brain abnormalities, most of which appear to be developmental rather than degenerative in nature.[8] Evidence supports the existence of a progressive continuum of psychotic illness, beginning with unipolar depression, progressing to bipolar illness, schizoaffective psychoses, and finally to schizophrenia.[1,13,14]

CLINICAL FEATURES

Overt signs of schizophrenia usually become manifest during adolescence or early adult life. Many patients describe a childhood marked by few interpersonal relationships and a withdrawn, eccentric personality.

Phases of Schizophrenia

The development of schizophrenia involves three phases.[15] The *premorbid phase* is characterized by the development of "negative" symptoms with deterioration in personal, social, and intellectual functioning. Patients progressively withdraw from social interactions and neglect personal appearance and hygiene, which negatively impacts their work, school, and home life.

The *active phase* is usually precipitated by a stressful event with development of "positive" symptoms such as active delusions, hallucinations, and bizarre behavior. Patients may become agitated or exhibit a hypervigilant withdrawal state characterized by rocking or staring. It is during this phase that they are most likely to be brought to the emergency department by family, friends, coworkers, or the police.

In the *residual phase* patients are left with impaired social and cognitive ability, marked by bizarre ideation, delusions, peculiar behavior, poor personal hygiene, and social isolation. Most schizophrenic patients require a sheltered environment to function adequately. Despite a wide spectrum of severity, the general course for most patients is one of gradual deterioration with periodic episodes of psychotic decompensation.

Criteria for Schizophrenia

The diagnostic criteria for schizophrenia are outlined in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR) (Box 108-1).[15] (1) The patient must exhibit two or more of the following symptoms: delusions,

hallucinations, disorganized speech, grossly disorganized or catatonic behavior, and negative symptoms such as flattening of affect, poverty of speech, or inability to perform goal-directed activities. (2) There must be a sharp deterioration from the patient's prior level of functioning (work, school, self-care, or interpersonal relations), and there must be continuous signs of disturbance for at least 6 months. (3) The diagnoses of schizoaffective and mood disorders with psychotic features must be excluded. (4) In evaluating these patients, emergency physicians must exclude myriad medical conditions that can mimic or cause psychotic symptoms (Boxes 108-2 and 108-3).

BOX 108-1 SUMMARY OF DSM-IV-TR CRITERIA FOR SCHIZOPHRENIA

A. Presence of two (or more) characteristic symptoms for 1 month (or more) unless treated
   1. Delusions
   2. Hallucinations
   3. Disorganized speech (derailment or incoherence)
   4. Grossly disorganized or catatonic behavior
   5. Negative symptoms: affect flattening, alogia (poverty of speech), avolition (unable to perform goal-directed activities)

   Note: Only one symptom above is required if delusions are bizarre or hallucinations consist of a running commentary.
B. Sharp deterioration from prior level of functioning (i.e., work, self-care, interpersonal relations)
C. Continuous signs of disturbance for 6 months (or more)
D. Schizoaffective disorder and mood disorder with psychotic features have been ruled out
E. Not caused by substance abuse, medication, or a general medical condition

Modified from *Diagnostic and Statistical Manual of Mental Disorders*, ed 4-TR. Washington, DC, American Psychiatric Association, 2000.

Delusions

The DSM-IV defines *delusions* as "erroneous beliefs that usually involve a misinterpretation of perceptions or experiences."[15] The delusions seen with schizophrenia are most often persecutory, religious, or somatic.

Hallucinations

A *hallucination* is a sensory experience that exists only in the mind of the person experiencing it. Hallucinations associated with schizophrenia may be auditory, visual, olfactory, gustatory, or tactile. Auditory hallucinations (hearing voices) that are pejorative or threatening are especially common.

Disorganized Speech

Patients with schizophrenia experience loosening of associations, with thoughts shifting randomly from one topic to another without a logical connection. Their speech often shows lack of content. *Neologisms* (nonsense words invented by the patient) and *perseverations* (frequently repeated words or phrases) are common. Occasionally, the patient's speech may be so severely disorganized that it is totally incoherent, termed *word salad*.

Grossly Disorganized or Catatonic Behavior

Schizophrenic patients have difficulty formulating and producing goal-directed behavior. They are often found wandering about, disheveled, malnourished, talking to themselves, and exhibiting unpredictable agitation. It is this behavior that usually prompts family members, friends, or the police to bring them to the emergency department. Patients exhibiting catatonia appear to be completely unaware of their environment, maintain a rigid posture, and resist efforts to be moved.

BOX 108-2 PHARMACOLOGIC AGENTS THAT MAY CAUSE ACUTE PSYCHOSIS

Antianxiety agents
- Alprazolam
- Chlordiazepoxide
- Clonazepam
- Clorazepate
- Diazepam
- Ethchlorvynol

Antibiotics
- Isoniazid
- Rifampin

Anticonvulsants
- Ethosuximide
- Phenobarbital
- Phenytoin
- Primidone

Antidepressants
- Amitriptyline
- Doxepin
- Imipramine
- Protriptyline
- Trimipramine

Cardiovascular drugs
- Captopril
- Digitalis
- Disopyramide
- Methyldopa
- Procainamide
- Propranolol
- Reserpine

Drugs of abuse
- Alcohol
- Amphetamines
- Cannabis
- Cocaine
- Hallucinogens
- Opioids
- Phencyclidine
- Sedative-hypnotics

Miscellaneous drugs
- Antihistamines
- Antineoplastics
- Bromides
- Cimetidine
- Corticosteroids
- Disulfiram
- Heavy metals

BOX 108-3 MEDICAL DISORDERS THAT MAY CAUSE ACUTE PSYCHOSIS

- Metabolic disorders
  - Hypercalcemia
  - Hypercarbia
  - Hypoglycemia
  - Hyponatremia
  - Hypoxia
- Inflammatory disorders
  - Sarcoidosis
  - Systemic lupus erythematosus
  - Temporal (giant cell) arteritis
- Organ failure
  - Hepatic encephalopathy
  - Uremia
- Neurologic disorders
  - Alzheimer's disease
  - Cerebrovascular disease
  - Encephalitis (including HIV)
  - Encephalopathies
  - Epilepsy
  - Huntington's disease
  - Multiple sclerosis
  - Neoplasms
  - Normal-pressure hydrocephalus
  - Parkinson's disease
  - Pick's disease
  - Wilson's disease
- Endocrine disorders
  - Addison's disease
  - Cushing's disease
  - Panhypopituitarism
  - Parathyroid disease
  - Postpartum psychosis
  - Recurrent menstrual psychosis
  - Sydenham's chorea
  - Thyroid disease
- Deficiency states
  - Niacin
  - Thiamine
  - Vitamin B_{12} and folate

Negative Symptoms

Three negative symptoms—flattening of affect, alogia, and avolition—account for a significant degree of the morbidity associated with schizophrenia. Patients with a *flattened affect* exhibit little facial expressiveness, eye contact, or body language. *Alogia*, or poverty of speech, is manifested by brief, laconic, empty replies to questioning. *Avolition* is characterized by an inability to initiate and persist in goal-directed activities. Caution should be used in evoking negative symptoms to support a diagnosis of schizophrenia, because similar symptoms may be found in patients with severe depression, chronic environmental understimulation, and treatment with neuroleptic medications.

DIAGNOSTIC STRATEGIES

Patients with Known Psychiatric Disorders

Patients with previously diagnosed thought disorders who present with mild to moderate exacerbation of their symptoms do not require extensive laboratory evaluation.[16] Some of these patients may have coexisting substance abuse or undiagnosed medical disorders; thus, a complete history and physical examination, including routine toxicology studies, are indicated for most patients.[17–19] Patients exhibiting severe exacerbation of symptoms accompanied by marked agitation, violent behavior, or significantly abnormal vital signs should receive more extensive evaluation.

Patients without Known Psychiatric Disorders

Many toxicologic and medical disorders can mimic schizophrenia. Patients with the apparent new onset of psychosis should receive a medical evaluation to exclude toxicologic and medical disorders.[20–23] Both the DSM-IV and review articles on this topic make the point that most of the toxicologic and medical causes of altered mental status that simulate acute schizophrenia are best recognized by patterns of presentation combined with focused testing based upon one's index of suspicion for nonpsychiatric disease, rather than the broad use of screening tests.

DIFFERENTIAL CONSIDERATIONS

Medical Disorders

Certain medications and medical disorders may affect thought processes, causing patients to exhibit abnormal behavior (see Boxes 108-2 and 108-3). This behavior may range from mild personality changes to apparent acute psychosis, even in the absence of an underlying psychiatric disorder.[1] Factors that should alert one to a medical disorder include (1) history of substance abuse or a medical disorder requiring medication, (2) patient's age greater than 35 years without previous evidence of psychiatric disease, (3) recent fluctuation in behavioral symptoms, (4) hallucinations that are primarily visual in nature, (5) presence of lethargy, (6) abnormal vital signs, and (7) poor performance on cognitive function testing, particularly orientation to time, place, and person. These and other factors may be helpful in differentiating functional (psychiatric) from organic (medical) causes of abnormal behavior and can be organized for easy recall into the mnemonic MADFOCS (Table 108-1).[24]

Although the classic textbook differentiation between functional and organic causes of abnormal behavior is straightforward, the evaluation of individual patients may be difficult.[21] A patient with underlying psychiatric disease may develop a medical disorder, which may worsen the patient's behavioral symptoms and further cloud the distinction between functional and organic disease. This evaluation is particularly difficult in the emergency department when previous medical or psychiatric history is not available, the patient is uncooperative, and the time frame to make a disposition is brief. When the clinical differentiation between functional and organic disease is unclear on the basis of available information, a patient should be thoroughly evaluated to exclude a toxicologic or medical disorder.

Psychiatric Disorders

A previously undiagnosed patient who presents with an acute functional psychosis may ultimately be given one of several psychiatric diagnoses.[15] A *brief psychotic disorder* involves the sudden onset of psychotic symptoms in response to major stress and lasts from several days to 1 month. Patients with *schizophreniform disorder* have similar symptoms that last longer than 1 month but less than 6 months. While one third of

Table 108-1 Factors in Differentiating Organic and Functional Psychosis: MADFOCS

	ORGANIC	FUNCTIONAL
Memory deficits	Recent impairment	Remote impairment
Activity	Psychomotor retardation	Repetitive activity
	Tremor	Posturing
	Ataxia	Rocking
Distortions	Visual hallucinations	Auditory hallucinations
Feelings	Emotional lability	Flat affect
Orientation	Disoriented	Oriented
Cognition	Islands of lucidity	Continuous scattered thoughts
	Perceives occasionally	Unfiltered perceptions
	Attends occasionally	Unable to attend
	Focuses	Unable to focus
Some other findings	Age > 40 yr	Age < 40 yr
	Sudden onset	Gradual onset
	Physical examination often abnormal	Physical examination normal
	Vital signs may be abnormal	Vital signs usually normal
	Social immodesty	Social modesty
	Aphasia	Intelligible speech
	Consciousness impaired	Awake and alert

Modified from Frame DS, Kercher EE: Acute psychosis: Functional vs. organic. Emerg Med Clin North Am 9:123, 1991.

individuals initially given the diagnosis of schizophreniform disorder recover within 6 months, the other two thirds retain their symptoms and are diagnosed as having schizophrenia. Patients with mood disorders may develop psychotic symptoms. If these symptoms are present only during periods of mood disturbance, the diagnosis of *mood disorder with psychotic features* is applied; if they persist longer than 2 weeks in the absence of prominent mood symptoms, the diagnosis of *schizoaffective disorder* is made. Patients with *personality disorders* may occasionally develop brief psychotic episodes under stress.

Ganser's syndrome is a symptom complex considered to be emotional in origin in which the patient may appear to have amnesia, hallucinations, or alterations in consciousness, usually in association with physical complaints. An individual with Ganser's syndrome may have psychotic symptoms for no apparent gain except to assume the role of the psychiatric patient.

Persons with a *delusional disorder* experience nonbizarre delusions that may dominate their lives. They may believe that famous people are in love with them (erotomanic type), that they have extraordinary powers with a special relationship to a deity or a famous person (grandiose type), that their sexual partner is unfaithful (jealous type), that they are being malevolently treated in some way (persecutory type), or that they have some physical defect or general medical condition (somatic type). Although patients with somatic delusions may experience tactile or olfactory hallucinations related to the delusional theme (e.g., the sensation of being infested with insects), the other features associated with schizophrenia are not present.

MANAGEMENT

General Approach

Patients with thought disorders may be agitated and hyperactive, may be withdrawn but hypervigilant, or may complain of somatic delusions. In addition, they may have paranoid ideation, may be angry they have been brought to the emergency department against their will, or may be frightened because they have been confronted by the police, restrained, and isolated. The presence of such patients in the emergency department may be disconcerting to staff because these patients are often irrational, erratic, and unpredictable in their behavior. Although emergency personnel must remain calm, empathetic, and reassuring in their interactions with patients exhibiting a thought disorder, they must also take steps to ensure staff safety whenever dealing with patients at risk for sudden violence. Such patients include those who have manifested violent behavior before coming to the emergency department, those who physically or verbally threaten staff, and those who demonstrate an escalating level of agitation despite verbal attempts to calm them.

Each patient should have a complete history and physical examination performed, including a detailed mental status evaluation, to rule out an organic brain syndrome. Valuable information can be obtained from family members, friends, coworkers, neighbors, paramedical personnel, police, or previous medical records (see Table 108-1).[24]

The most important step in evaluating a patient with a suspected thought disorder is the assessment of the patient's thought processes through the initial interview. The goals are to establish a positive physician-patient relationship, to make a correct diagnosis, and to gather information necessary to render an optimal disposition. The interview should be conducted in a quiet, comfortable room with adequate privacy. The examiner should be sitting, and if possible the interview should proceed to completion without interruption. If the patient is believed to be potentially dangerous but is not in need of immediate restraint, the interview should take place in an open area with security personnel nearby.

The emergency physician should begin with an introduction and should express the desire to be "of help" to the patient. The interview should begin with open-ended questions designed to assess the patient's complaint and understanding of the current circumstances. Good opening questions include "Do you understand why you have been brought here

today?"; "You seem to be upset. Can you tell me why?"; and "Do you have any idea why you might be having these symptoms?" The patient's appearance, body language, affect, and speech should be observed during the responses to these questions.

A brief mental status examination should be performed. It may be initiated in a nonthreatening manner by stating, "I am now going to ask you a few questions to see how well you are concentrating." The patient should first be asked questions regarding orientation to time, place, and person, as this is the most sensitive test for differentiating organic from functional disease. Patients who are disoriented should have a detailed medical evaluation to exclude the presence of an organic brain syndrome. Patients who are oriented should be assessed for attention, memory, intellectual functioning, and judgment in an attempt to determine their specific diagnosis, their potential for danger to themselves or others, and their degree of dysfunction and ability to care for themselves in the outpatient setting.

Rapid Tranquilization

When psychotic patients exhibit behavior that is violent or so disorganized and uncooperative that clinical evaluation is impossible, the temporary use of physical restraints is indicated while rapid tranquilization is initiated (see Chapter 189). The technique of rapid tranquilization involves serial doses of a high-potency antipsychotic agent until target symptoms, such as agitation and excessive psychomotor activity, are improved. The goal is to facilitate cooperation of the patient without causing unnecessary sedation, which would inhibit further medical and psychiatric assessment. Oral, intramuscular (IM), or intravenous (IV) doses can be given every 30 to 60 minutes until the patient becomes calmer and more cooperative. If the patient is willing, an oral concentrate is preferred as it implies consent and can take effect almost as quickly as IM administration.

Haloperidol (Haldol), a butyrophenone, is widely used for rapid tranquilization in the United States.[25–27] The initial dose is 5 to 10 mg intramuscularly or intravenously for young to middle-aged patients and 0.5 to 2.0 mg intramuscularly or intravenously for elderly patients. Although rapid tranquilization with haloperidol quickly reduces tension, anxiety, and hyperactivity, delusions and hallucinations may not resolve for several weeks. In 2007, the U.S. Food and Drug Administration (FDA) released a non–black box warning about sudden death with the use of haloperidol in large doses or through the IV route. *Droperidol* (Inapsine), another butyrophenone, has also been extensively used for this indication in doses from 2.5 to 5.0 mg intramuscularly or intravenously.[28,29] Compared with haloperidol, droperidol has a faster onset and shorter duration of action and causes slightly more sedation. The FDA black box warning was published in 2001 because of reports of a potential association between droperidol and prolonged QT interval, torsades de pointes, and sudden death.[30] Despite subsequent studies supporting both the efficacy and safety of droperidol, the FDA warning has resulted in a significant decrease of its use in clinical practice.[31,32] Neuroleptics should not be used for pregnant or lactating females, phencyclidine overdose, or anticholinergic drug-induced psychosis. In addition, they should not be used as the sole agent to manage agitation in patients with drug or alcohol withdrawal.

Newer atypical antipsychotic agents appear to have a broader spectrum of response with fewer side effects than the typical agents. These medications are available in tablet form and should be considered for patients who consent to oral medication. However, oral administration of a pharmacologic agent during an acute episode of agitation and psychosis is usually impossible. *Ziprasidone* (Geodon), aripiprazole (Abilify), and olanzapine (Zyprexa) are newer atypical antipsychotics currently approved in the United States for IM injection.[33] For ziprasidone, the initial dose is 20 mg intramuscularly and can be repeated every 4 hours. It has been shown to be as or more effective than haloperidol for sedation and with fewer extrapyramidal side effects, but it has not yet been widely used in the emergency department setting.[34,35]

Benzodiazepines are effective in managing agitation in patients who have alcohol or sedative-hypnotic withdrawal, cocaine intoxication, or a contraindication to neuroleptic use. Benzodiazepines are helpful adjuncts to neuroleptic medication in providing rapid tranquilization, particularly in patients exhibiting combativeness or severe agitation. *Lorazepam* (Ativan), 1 to 2 mg, is frequently mixed with haloperidol, 5 mg, in the same syringe and administered intramuscularly or intravenously for this purpose.[27] Benzodiazepines have also been shown to mitigate catatonic signs in schizophrenic patients.[36] Disadvantages of benzodiazepines are the need for repeat dosing and close monitoring for potential respiratory depression with large doses.[37]

Outpatient Management

The outpatient treatment of schizophrenia involves maintenance therapy using neuroleptic agents, family counseling, and social rehabilitation. Emergency physicians rarely prescribe outpatient neuroleptic medications but should be familiar with complications associated with their long-term use.

Box 108-4 lists the most common neuroleptic medications currently used in the United States.[38–44] The mechanism of action is related to the blockade of dopamine receptors in the central nervous system, particularly dopamine D_2 receptors in the basal ganglia and limbic portions of the forebrain. The earlier, less potent drugs, of which chlorpromazine

BOX 108-4 COMMON NEUROLEPTIC AGENTS

Low potency
- Chlorpromazine (Thorazine)
- Chlorprothixene (Taractan)

Intermediate potency
- Acetophenazine (Tindal)
- Loxapine (Loxitane)
- Mesoridazine (Serentil)
- Molindone (Moban)
- Perphenazine (Trilafon)
- Thioridazine (Mellaril)
- Triflupromazine (Vesprin)

High potency
- Droperidol (Inapsine)
- Fluphenazine (Prolixin)
- Haloperidol (Haldol)
- Thiothixene (Navane)
- Trifluoperazine (Stelazine)

Atypical
- Aripiprazole (Abilify)
- Clozapine (Clozaril)
- Olanzapine (Zyprexa)
- Paliperidone (Invega)
- Quetiapine (Seroquel)
- Risperidone (Risperdal)
- Ziprasidone (Geodon)

is the prototype, cause more pronounced sedation, orthostatic hypotension, and cardiovascular toxicity. This is the result of a combination of anticholinergic, antihistaminic, and anti-alpha-adrenergic effects. More potent agents (e.g., haloperidol) are safer, especially in older patients, because of their relative lack of these adverse effects. However, these more potent drugs are associated with a higher incidence of extrapyramidal symptoms, such as dystonias, akathisia, akinesia, and rigidity.

The high frequency of severe adverse reactions, poor compliance by patients, and the large number of patients with symptoms refractory to traditional antipsychotic agents prompted the development of new alternative agents. These "atypical" neuroleptic agents block serotonin to a greater extent than dopamine, resulting in a low incidence of extrapyramidal side effects. *Clozapine* is particularly effective in patients who have not responded to other antipsychotic drugs.[41] However, clozapine is expensive, has a side effect profile similar to that of the low-potency antipsychotic agents, and causes agranulocytosis in approximately 1% of patients.[39] It is recommended only for the treatment of patients with refractory psychosis. *Olanzapine*, *quetiapine*, and the newest agent, *aripiprazole*, are similar to clozapine but have fewer side effects and less risk of agranulocytosis.[38] *Risperidone*, another newer neuroleptic agent with improved effects on negative symptoms, has been found to be superior to haloperidol in several short-term trials.[42–45] The most recent FDA-approved drug (2006), paliperidone (Invega), is the active metabolite of risperidone. Unfortunately, the expense and unavailability of these newer antipsychotic agents limits their utility for treating acute psychosis in the emergency department. Ziprasidone, risperidone, and quetiapine have been associated with QT interval prolongation similar to that seen with droperidol and haloperidol but have not yet been found to be associated with sudden cardiac death.[46]

Because of the high incidence of extrapyramidal symptoms in patients treated with high-potency neuroleptics, it is common practice to administer antiparkinsonian drugs (e.g., benztropine, procyclidine, trihexyphenidyl) at the same time, either to treat the adverse effects or to prevent them. Prophylactic treatment is most useful in patients with a history of extrapyramidal symptoms, those receiving high doses of high-potency antipsychotic agents, and those in whom the occurrence of these symptoms is likely to increase the risk of noncompliance.

Noncompliance with antipsychotic medication remains a leading cause of psychiatric hospitalization. Patients with recurrent psychotic relapses caused by noncompliance are candidates for treatment with long-acting injectable antipsychotic drugs, usually given every 2 weeks. Three such agents available in the United States are fluphenazine, risperidone, and haloperidol decanoate.[47]

Complications of Neuroleptic Drug Therapy

Dystonia

Acute dystonia, the most common adverse effect seen with neuroleptic agents, occurs in 1 to 5% of patients. This reaction is caused by a disruption of the dopaminergic-cholinergic balance in the nigrostriatal pathways of the basal ganglia, resulting in cholinergic dominance.[48] Dystonic reactions, which can occur at any point during long-term therapy and up to 48 hours after administration of neuroleptics in the emergency department, involve the sudden onset of involuntary contraction of the muscles of the face, neck, or back. The patient may have protrusion of the tongue (buccolingual crisis), deviation of the head to one side (acute torticollis), sustained upward deviation of the eyes (oculogyric crisis), extreme arching of the back (opisthotonos), and rarely laryngospasm. These symptoms tend to fluctuate, decreasing with voluntary activity and increasing under emotional stress, which occasionally misleads emergency physicians to believe they are factitious.

Dystonic reactions should be treated with IM or IV benztropine (Cogentin) 1 to 2 mg, or diphenhydramine (Benadryl), 25 to 50 mg, which usually results in immediate reversal of symptoms. Patients should receive oral therapy with the same medication for 48 to 72 hours to prevent recurrent symptoms.[48]

Akathisia

Akathisia is a state of motor restlessness characterized by a physical need to be moving constantly. It occurs most often in middle-aged patients during the first few months of therapy. Patients are usually pacing the room and expressing a sense of inner tension that is not relieved by activity. If asked, they do not want to be constantly moving but feel physically compelled to do so. This reaction can easily be mistaken for a decompensating psychosis, leading to a vicious circle in which more medication is given to treat a side effect caused by the same drug. This misdiagnosis can be avoided by carefully evaluating the patient for the exacerbation of positive psychotic symptoms, which are not increased by akathisia. Akathisia is treated with beta-blockers (e.g., propranolol, 30–60 mg/day) and anticholinergic drugs (e.g., benztropine, 1 mg twice to four times daily). A new potential agent for the treatment of akathisia is glycine, a nonessential amino acid that stimulates glutamatergic neurotransmission.[49] In addition, if possible, the dosage of the antipsychotic agent should be lowered or replaced with another drug.

Pseudoparkinsonism and Akinesia

A clinical picture can occur that may be indistinguishable from Parkinson's disease, particularly in elderly patients during the first month of therapy. Treatment with anticholinergic agents (e.g., benztropine) or antiparkinsonian drugs is usually effective. Akinesia, which is characterized by immobility, withdrawal, and lack of motivation, may be mistaken for a postpsychotic depression. It is responsive to antiparkinsonian drugs, but symptoms usually resolve gradually over time.

Tardive Dyskinesia

Tardive dyskinesia usually appears after several years of neuroleptic drug treatment and is characterized by involuntary movements, especially of the face and tongue, that are described as writhing, grimacing, and choreoathetoid in nature. The earliest manifestation is often a curling or twisting movement of the tongue. The onset of these symptoms can be falsely attributed to psychological factors because they intensify under emotional stress, fatigue, and voluntary activity, and disappear with sleep.

The reported prevalence of tardive dyskinesia ranges from 0.5 to 70%, with a mean value of 24%.[48] The incidence of the disorder appears to be directly related to the duration of treatment, total cumulative dosage, evidence of preexisting brain damage, and age of the patient. It is more common in elderly women and patients with associated mood disorders. For patients with mild symptoms, discontinuing or lowering the dosage of antipsychotic agents, switching to a newer atypical neuroleptic agent, and cotreatment with benzodiazepines may reverse the symptoms. Patients with moderate to severe symp-

toms are difficult to treat, but some have variable degrees of improvement when treated with reserpine or tetrabenazine along with discontinuation of neuroleptic treatment.[48]

Orthostatic Hypotension

All the antipsychotic agents can cause orthostatic hypotension, an effect related to alpha-adrenergic blockade. This complication is less common with the more potent agents (e.g., haloperidol). Typically, episodes are mild in severity and brief in duration. Symptomatic patients should be treated with oxygen, Trendelenburg's position, and IV crystalloid fluid administration. Pressor agents (e.g., dopamine) should be used only for severe, symptomatic episodes that fail to respond to the previous measures. Agents with beta-agonist activity (e.g., epinephrine, isoproterenol) are contraindicated in these patients.

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome (NMS) is a life-threatening complication of neuroleptic drug treatment that affects 0.5 to 1% of patients.[50] It is seen with both typical and atypical neuroleptic agents and usually occurs in the first few weeks after initiation of treatment, but can also be seen after a recent increase in drug dosage or after parenteral treatment with high doses of neuroleptic agents. Neuroleptic malignant syndrome is characterized by high fever, severe muscle rigidity, altered consciousness, autonomic instability, and elevated serum creatine kinase levels and can be confused with serotonin syndrome. Additional complications can include respiratory failure, gastrointestinal hemorrhage, hepatic and renal failure, coagulopathy, and cardiovascular collapse.

The pathophysiology of NMS is not well understood, but it is thought to be related to dopamine depletion in the central nervous system leading to defective thermoregulation in the hypothalamus. Predisposing factors include exhaustion, dehydration, and the use of long-acting depot neuroleptics. Treatment consists of recognition and discontinuation of the neuroleptic agent, fever reduction, rehydration with IV fluids, and general supportive measures. *Dantrolene*, a direct-acting muscle relaxant, should be used in severe cases. It can be administered by continuous rapid IV push at a minimum initial dose of 1 mg/kg, repeated until symptoms subside or up to a maximum cumulative dose of 10 mg/kg. For severe symptoms, dopamine agonists such as bromocriptine, levodopa, and amantadine have shown encouraging results. Because of earlier recognition and treatment, mortality rates with NMS have decreased from 30% to less than 10%.[51]

DISPOSITION

The ultimate disposition of the acutely psychotic patient depends on the underlying cause of the psychosis, whether the patient is a danger to self or others, and the presence of social support in the community. Hospitalization is indicated for patients experiencing their first psychotic episode, for patients deemed to be a danger to themselves (suicidal) or others (homicidal), for patients who are grossly debilitated, for patients who are moderately debilitated but have no social support system within the community, and for patients with either functional or organic psychosis that does not clear with a brief period of treatment and observation in the emergency department. The decision to hospitalize psychotic patients is complex and imprecise and often must be made in a short period with limited information.

A psychiatric short-procedure unit offers a cost-effective alternative to hospitalization.[52] After stabilization, patients are moved from the emergency department to a separate treatment area, where they are treated for a period of 12 to 24 hours by a small staff of consultants.

KEY CONCEPTS

- In patients exhibiting abnormal behavior, an organic etiology is suggested by (1) new onset of symptoms in a patient older than 35 years, (2) rapid onset of symptoms in a previously normal person, (3) visual hallucinations, (4) abnormal vital signs, and (5) lethargy or disorientation.
- Physical restraints should be considered for patients who have violent behavior, verbally threaten staff, or demonstrate escalating agitation despite verbal attempts to calm them. Restraints should be removed after sedation has been achieved.
- Rapid tranquilization is best accomplished with the use of high-potency neuroleptics (e.g., haloperidol, ziprasidone). Benzodiazepines (e.g., lorazepam) are a helpful adjunct for patients with severe agitation.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 109 Mood Disorders

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PERSPECTIVE

Happiness and sorrow are common emotions but usually cause no impairment in functioning or threat to life. Mood disorder, by contrast, can significantly impair physical, social, and family functioning and can cause psychological pain, physical pain, and a negative perception of physical health. The term *mood disorders* replaced the term *affective disorders* in the fourth edition (2000) of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR).[1] *Mood* usually refers to an individual's subjective emotional state, whereas *affect* normally refers to the individual's emotional state as it appears to an outside observer.[2] *Mood disorders* refers to a group of psychiatric disorders where pathological moods are the dominant feature. According to DSM-IV-TR, mood disorders are divided into four categories: (1) depressive disorders (unipolar depression), (2) bipolar disorders, (3) mood disorder due to a general medical condition, and (4) substance-induced mood disorder. DSM-IV-TR assigns psychiatric diagnoses to patients by assessing specific observable and measurable symptoms and signs and applying straightforward operational criteria. Research regarding the neurobiology of mood disorders and genetics may ultimately permit classification of mood disorders by specific, genetically predisposed pathophysiologic derangements.

EPIDEMIOLOGY

Psychiatric problems account for at least 5.4% of all emergency department (ED) visits, and the rate of psychiatric-related visits has increased 15% since 1992.[3] The World Health Organization ranks major depression as one of the most prevalent and disabling diseases in the world,[4] and the lifetime prevalence of major depressive disorders in the United States is 16.2%. Depressed patients also have associated anxiety disorders (almost 60%), substance use disorders (24%), and impulse control disorder (30%).[5] Depressed patients with substance abuse comorbidity have higher ED utilization than patients without such comorbidity.[6] Patients with chronic illness have a much higher prevalence of undiagnosed depression than the general population. The lifetime suicide risk for persons with major untreated depressive illness is 15%.[7] Mood disorders are becoming more common and have increased in every generation born after 1910.[8]

The prevalence of bipolar disorders (manic-depressive disorders) is substantially lower than that of major depression. The overall lifetime prevalence of a manic episode is 1.6%.

PRINCIPLES OF DISEASE

Current neurobiologic concepts provide the basis for various pharmacologic treatments. The psychosocial theories of depression consider the complex interaction of genetics, environment, and experience, providing the basis for understanding the various psychotherapeutic approaches to treatment.

Neurotransmitters

In the fourth century BCE, Hippocrates believed that the body contained four essential humors: blood, phlegm, yellow bile, and black bile. Harmony in the brain required a harmony of humors. "Disharmony" produced mental illness. In the second century, Galen believed that "melancholia" resulted from an excess of black bile acting on the brain. Such excesses were thought to be caused by noxious stomach vapors, grief, anxiety, excessive wine, and advancing age. Proposed treatments included bloodletting, surgery, special diets, and exercise.[9]

Modern theories regarding the pathophysiology of depression have focused on the three major monoamine systems—serotonin, norepinephrine, and dopamine. Of the three neurotransmitter systems, serotonin has received the most attention. There is very strong evidence of reduced activity of serotonergic neurons in depression as assessed by cerebrospinal fluid and neuroendocrine studies. There are also very strong data demonstrating the role that norepinephrine plays in the etiology of depression. Norepinephrine reuptake inhibitors, such as nortriptyline, have been found to be effective antidepressants. Research over the past several years has increasingly focused on the role of dopamine in the etiology of depression. A number of studies have found a reduction in the synaptic availability of dopamine in patients suffering from depression.[10]

Complex processes in the nervous system cause depression or mania. If the concentrations of neurotransmitters at synaptic sites were the only factors responsible for alleviation of depression, the therapeutic effect of an antidepressant agent would be almost immediate. However, clinical improvement with these agents takes several weeks and is highly individually variable. Emphasis has now shifted to the study of neurobehavioral systems, intricate regulatory mechanisms, development of preferred neural circuits, the effect of environment on phenotype expression, and gene transcriptors.[11]

Cerebral Anatomy

Certain areas of the brain are involved in processes that become abnormal during episodes of depression and mania.[12,13] Stress activates neurons in the locus ceruleus, resulting in increased alertness, decreased appetite, increased heart rate, increased cortisol production, and other features of a stress response. The response can be dampened by neurons in the cerebral cortex. Prolonged stress, from which escape appears hopeless, seems to decrease the activity of neurons in the locus ceruleus. Another noradrenergic system, the median forebrain bundle, elicits reward-seeking behavior when stimulated. Prolonged stress decreases levels of norepinephrine in this region and may explain the lack of energy and interest that accompany depression.[14,15]

Serotonergic neurons are located in the brainstem dorsal raphe and project diffusely throughout the brain. The serotonergic system seems to enhance sleep, appetite, libido, and circadian rhythms. Activation decreases aggressive behavior in animal models.[16,17]

Dopaminergic pathways include the tuberoinfundibular system, originating in the hypothalamus (prolactin secretion); the nigrostriatal system, originating in the substantia nigra (involuntary motor activity); the mesolimbic pathway, originating in the ventral tegmentum; and the mesocortical pathway, originating in the ventral tegmentum.[18] These pathways regulate emotion, pleasure, learning, and reinforcement. The mesocortical pathway extends to frontal cortical regions that regulate complex cognition concentration and motivation.[19]

Endocrine System

The cortical-hypothalamic-pituitary-adrenocortical system is affected in many patients with depression, causing increased levels of plasma cortisol, apparently from an impaired biofeedback loop regulating cortisol. The thyroid axis malfunctions in 5 to 10% of depressed patients. Thyroid-stimulating hormone levels are elevated, and thyroid replacement therapy facilitates treatment in certain patients.[20]

Genetics

Family studies have repeatedly demonstrated a relationship between genetic inheritance and mood disorders.[21] A review of twin studies in unipolar depression estimates that genetics accounts for 30 to 40% of the risk of developing depression, with the rest being attributed to environmental factors.[10] Monozygotic and dizygotic twins have a high concordance rate, 70 and 35%, respectively, for mood disorder.[22] The mechanisms of genetic transmission are still undetermined but may relate to the synthesis, transport, and action of serotonin and other transmitters.[23,24] The inherited susceptibility to depression may manifest only during severe stress or serious illness.[25]

Psychosocial Theories

The complex neural mechanism that regulates mood responds to and is modified by each person's experience, including events in early childhood, reward and punishment during growth and development, interpersonal relationships, and various kinds of loss. Psychosocial theories of mood disorder form the basis for psychotherapy. Freud noted that personal loss included grief and sadness, but that depression also involved guilt and lowered self-esteem.[26] Freud theorized that suicide in depressed patients is a manifestation of aggression that has been turned against the self in a person otherwise unable to express anger toward loved ones.

The interpersonal theory of depression emphasizes guilt, disputes between partners and family members, role transitions in families and relationships, and problems with social skills necessary to sustain a fulfilling relationship. The cognitive model of depression assumes that the "negative," distorted thoughts or cognitions (thinking one is helpless, hopeless, worthless) can cause depression in certain individuals. The concept of "learned helplessness" first developed when animals were blocked from escape and subjected to repeated noxious stimuli such as electric shock. They eventually stopped trying to escape and became apathetic, even when escape became available.[27] The concept was later applied to humans and adapted to construct a behavioral mode of therapy for depression.

CLINICAL FEATURES

Major Depressive Disorder

Major depressive disorder is characterized by one or more major depressive episodes, as defined by DSM-IV-TR criteria (Boxes 109-1 and 109-2), and the lifelong absence of manic episodes. A major depressive episode is characterized by disturbances in four major areas: mood, psychomotor activity,

BOX 109-1 SUMMARY OF DSM-IV-TR CRITERIA FOR A MAJOR DEPRESSIVE EPISODE

A. Five or more of the following symptoms present almost every day during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. Note: Do not include symptoms caused by a general medical condition, and do not include mood-incongruent delusions or hallucinations.
   1. Depressed mood (can be irritable mood in children and adolescents)
   2. Loss of interest or pleasure in activities
   3. Significant weight loss when not dieting, or weight gain or decrease, or increase in appetite
   4. Insomnia or hypersomnia
   5. Psychomotor agitation or retardation
   6. Fatigue or loss of energy
   7. Feelings of worthlessness, or excessive or inappropriate guilt
   8. Diminished ability to think or concentrate, or indecisiveness
   9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation, or a suicide plan or attempt
B. Symptoms do not meet criteria for a "mixed episode."
C. Symptoms cause clinically significant distress or impairment in social, occupational, or other functioning.
D. Symptoms are not caused by direct physiologic effects of a substance (e.g., drug of abuse, medication) or a general medical condition (e.g., hypothyroidism).
E. Symptoms are not better accounted for by bereavement; after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

Modified from American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th ed, Text Revision. Washington, DC, American Psychiatric Association, 2000.

BOX 109-2 FACTORS IN EVALUATING DEPRESSION: "IN SAD CAGES"

INterest
Sleep
Appetite
Depressed mood
Concentration
Activity
Guilt
Energy
Suicide

cognition, and vegetative function.[28] The patient must exhibit or experience at least five symptoms for a minimum of 2 weeks.

Mood Disturbances

Depressed mood is painful and referred to as being anguished, sad, gloomy, dejected, unhappy, discouraged, or in low spirits. The mood may also involve feelings of anxiety and irritability. The patient's feelings can be so intensely painful that suicide may be seen as the only way to terminate the agony.

Anhedonia refers to the inability to experience pleasure or interest in formerly pleasurable or satisfying activities. The patient must have actually stopped doing the formerly pleasurable activities, for example, an avid tennis or golf player who gives up playing entirely. Questions can help to elicit loss of interest or pleasure: "When were you last feeling well?"; "When you were feeling well, what kinds of things did you do for enjoyment?"; "Are you doing those things now?"; and "Are you enjoying them?"[29]

Disturbances in Psychomotor Activity

Psychomotor disturbances can take the form of retardation or agitation. *Psychomotor retardation* includes significant slowing of thought processes and physical activity. The patient is slow to answer questions and moves slowly or not at all. Questioning such patients in the ED may be frustrating when the answers come slowly, in short words or phrases, and are low in volume and lack inflection. The "body language" of depression includes sitting slumped over, arms folded, mouth turned down, and eyes closed or downcast. Such slowing clearly affects the patient's work, school, or family functioning. Symptoms may be erroneously attributed to worsening dementia in elders. An alternative presentation is *psychomotor agitation,* in which the patient fidgets, paces, rubs the skin, and is unable to sit still. Other common, almost stereotypical manifestations include hand wringing and tugging at the hair.

Vegetative Disturbances

Vegetative symptoms include disturbances in three major areas: sleep, appetite, and sexual function. Depressed patients typically report some form of sleep disorder, such as difficulty falling asleep, middle insomnia, or the classic symptoms of early-morning wakening and inability to fall back to sleep. Some depressed patients may report sleeping 12 to 14 hours a day and inability to arise in the morning. This may be a more common symptom in depressed teenagers. The depressed patient may lose appetite and weight or may gain weight in a short time. Loss of interest in sexual activity and impotence can be considered vegetative symptoms; they may accompany depression or may be part of the anhedonia associated with depressed mood.

Cognitive Disturbances

Depressed patients are unable to concentrate or think properly, which can cause significant dysfunction in a job or profession. Thought content is negative, such as recurrent thoughts of guilt, failure, worthlessness, and self-criticism. Suicide may preoccupy the patient's thinking and may reinforce feelings of helplessness, perpetuating self-reproach. The patient may formulate a definite plan for ending life. Depressed patients must be questioned about suicidal thoughts and plans, which allow them to describe their pain and may provide them with some relief.

Psychosis may accompany severe depression. Hallucinations and delusions are classified as mood congruent or mood incongruent. *Mood-congruent* delusions reflect the depressed mood. The patient may report, for example, being "already dead" or feeling like "my insides have rotted away." Hallucinations typically consist of voices saying extremely unpleasant things or punishing the patient for previous wrongs. *Mood-incongruent* delusions do not reflect the depressed mood as clearly and include the paranoid delusions of being followed and having one's thoughts controlled by external forces.

Special Considerations

Masked Depression

Mood disorders may not be clear at presentation. The depressed patient may have only vague physical symptoms, such as weakness, fatigue, headache, or complaints of pain. Patients may not be aware of their depression and are often heavy utilizers of medical care. Such symptoms may be the presenting features of a masked, or *hidden,* depression. Clues suggesting mood disturbance include the recent onset of a set of unusual behaviors, trouble at work or job loss, marital difficulties, or self-destructive behavior (e.g., substance abuse, sexual promiscuity).

Children and Adolescents

A common and overt presentation of depression in an older child or teenager is a suicide attempt. Such patients should be considered depressed and unstable until subsequent assessment differentiates depression from other conditions in these age groups, including transient psychoses, anxiety disorders, high levels of life stress, and substance abuse.

Symptoms of depression in children and adolescents generally follow the same criteria as for adults. Some children are misdiagnosed as having attention deficit disorder, especially if symptoms involve poor concentration, listlessness, agitation, and withdrawal from daily activities. Depression in these age groups is often misunderstood, masked in its presentation, or simply overlooked by friends, parents, teachers, and physicians. Adequate treatment maximizes the child's potential and minimizes the serious negative impact depression can have on multiple spheres of development.

Elders

Depression is common in elders; losses and grief, serious health issues, and loss of autonomy create a setting conducive to depression. The classic symptoms of moderate to severe depression, with or without psychosis, are typically seen. Depressed patients can present with symptoms involving

memory loss, inattention, withdrawal from daily activities, confusion, and lapses in personal and social hygiene that suggest dementia rather than depression. When such symptoms are from depression, the condition is called *pseudodementia*. Serious depression in elders is a highly treatable, reversible condition. Distinguishing it from dementia is essential for further diagnostic and therapeutic follow-up.

Other Depressive Disorders

Seasonal Affective Disorder

Seasonal affective disorder is not a separate mood disorder but a subclassification of major depressive disorder that is diagnosed when major depression occurs during seasons with less daylight (fall and winter), then either resolves or occasionally changes to manic episodes in seasons with more daylight, for at least 2 consecutive years. Melatonin, a hormone secreted in the brain and produced at high levels in the dark, has been implicated in the etiology of this disorder. Symptoms generally include hypersomnia, anergia, weight gain, and craving for carbohydrates. Phototherapy is an effective and safe treatment for this "winter depression,"[30] and light exposure to the eyes seems to be essential but the exact mechanism of action is still unknown.

Postpartum Depression

Symptoms of depression are common in the postnatal period. Up to 65% of mothers report some depressed mood after childbirth, often called "postpartum blues." Symptoms are generally mild and transient, although in some patients it may lead to an episode of major depression. Approximately 10% of mothers will experience a full-fledged episode of depression in the postpartum period. The signs and symptoms of postpartum depression are similar to those of a major depressive disorder, but the onset is within four weeks of delivery.[31]

Postpartum depression is more common in those who have a history of mood disorder, experience marital conflict, and have limited assistance with infant care. Severe postpartum depression may negatively influence development in the child.[32]

Dysthymic Disorder

Dysthymic disorder is a long-standing, fluctuating, low-grade depression. Some features of a major depressive episode may be present, but marked changes in appetite or psychomotor disturbances are not typically observed. Depressed mood typically begins early in life, and the individual may report having always been depressed. Affected individuals generally are able to carry out their work assignments, but they gain little pleasure from the leisure activities others find enjoyable, such as recreation, time with family, or sexual activity. They typically experience significant impairment in interpersonal functioning.

Bipolar Disorders

Bipolar disorder is lifelong, with episodic exacerbation of symptoms and deterioration of function characterized by extreme mood swings. Patients with bipolar disorder thus require different forms and intensities of treatment at different times. *Bipolar I disorder* includes at least one *manic* episode, and patients have typically had one or more major depressive episodes. *Bipolar II disorder* involves a *hypomanic* episode and at least one major depressive episode. A hypomanic episode includes the features of a manic episode without psychosis, marked impairment of function, or the need for hospitalization.

BOX 109-3 SUMMARY OF DSM-IV-TR CRITERIA FOR A MANIC EPISODE

A. Distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 2 weeks (or any duration if hospitalization is necessary).
B. During the period of mood disturbance, three or more of the following symptoms have persisted (four, if the mood is only irritable) and have been present to a significant degree:
   1. Inflated self-esteem or grandiosity
   2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep)
   3. More talkative than usual or pressure to keep talking
   4. Flight of ideas or subjective experience that thoughts are racing
   5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)
   6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation
   7. Excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., buying sprees, sexual indiscretions, foolish investments)
C. Symptoms do not meet criteria for a "mixed episode."
D. Mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or social activities or to necessitate hospitalization to prevent harm to self or others, or psychotic features are present.
E. Symptoms are not caused by direct physiologic effects of a substance (e.g., drug of abuse, medication) or a general medical condition (e.g., hyperthyroidism).

Modified from American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th ed, Text Revision. Washington, DC, American Psychiatric Association, 2000.

Manic Episode

To be considered manic (Box 109-3), the disturbance must be severe enough to cause psychosis, the need for hospitalization, or marked impairment in functioning. Bipolar disorders are much less common than major depressive disorder. The overall prevalence of a manic episode is 1.6% in both women and men.[33]

Patients who are experiencing a manic episode may be gregarious, humorous, and engaging. An alternative presentation is one of belligerence and irritability. Clues to mania include a history of the patient's behavior immediately before the evaluation and any prior history of bipolar disorder or a history of taking medications almost exclusively prescribed for bipolar disorder, such as lithium. In most cases, the manic patient will be brought to the ED by someone else (e.g., family, police, emergency medical services). They often try to leave as soon as possible, display impaired judgment and impulsivity, and may need to be restrained.

Pressured speech is one of the first clinical signs of mania. The patient keeps talking, with no interruption between thoughts or sentences. The speech may be loud and rapid, with creative, amusing, or trivial and irrelevant content. The patient may tell jokes, use puns, or play other word association games. A hallmark of mania is *grandiosity*, which involves feelings of inflated self-esteem and great personal importance. The patient may

describe a massive undertaking such as "uniting the world's churches" or "solving world poverty."

Manic patients have decreased or no need for sleep and typically report being awake for days during a manic episode. They may be involved in a massive project (e.g., writing a novel), may completely disregard consequences of actions, may have difficulty with spending (e.g., credit cards revoked), and may engage in risky behavior (e.g., sexual liaisons with strangers, risky driving). An accurate history must be obtained from family or others who know the patient's behavior.

Manic patients may present to the ED as trauma patients, injured by an action reflecting the patient's grandiosity (e.g., attempting to fly), impulsivity, or belligerence (e.g., fighting, resisting arrest). A manic episode may be punctuated by abrupt periods of tearfulness and profound depression, including suicidal ideation. When depressive and manic features occur concurrently in such a manner, the disorder is termed *mixed* or *bipolar, mixed phase*.

Cyclothymic Disorder

Cyclothymic disorder is characterized by a life of mood swings of insufficient severity to meet criteria for a bipolar disorder. Persons with this disorder may have a chaotic life, characterized by frequent mood swings, unstable relationships, and uneven school or work performance.

Mood Disorders Caused by a General Medical Condition

Certain medical illnesses have a well-known association with mood disorder (Box 109-4). In Parkinson's disease, electrical stimulation to a certain area of the substantia nigra alleviates symptoms of depression. Stimulation of an area only 2 mm away can cause acute reversible symptoms of depression, such as crying, not wanting to live, and hopelessness.[34] Parkinson's disease has a well-known association with depression, with up to 40% of patients demonstrating major depression.[35]

Certain malignancies have a well-known association with depression, including pancreatic carcinoma, brain neoplasm, and disseminated malignancy (e.g., lymphoma).[36] Coronary artery disease,[37] myocardial infarction, stroke, end-stage renal disease, acquired immunodeficiency syndrome, several endocrine diseases, and connective tissue disease are also associated with major depressive disorder.[38] After a myocardial infarction, patients with depression experience a 3.5-fold increase in cardiovascular mortality compared with nondepressed patients.[39] Patients with depression appear to be more likely to develop stroke, diabetes, and osteoporosis than those who are not depressed.[40,41]

Depression related to medical conditions may be different in some respects from primary depression. For instance, the former responds less favorably to antidepressant medication than primary depression.[42] Two significant issues arise in the assessment of patients with depression who have a serious medical illness. First, symptoms of depression must be distinguished from the symptoms and signs associated with serious medical illness (e.g., weight loss, loss of energy, slowing of activity, sleep disturbance, loss of ability to concentrate). Some experts have proposed that alternative criteria for depression caused by general medical condition be substituted for DSM-IV-TR neurovegetative symptoms in patients with serious medical illness such as *depressed appearance*, *social withdrawal*, *pessimism* or *self-pity*, *anhedonia*, and *nonreactive mood*. Second, it is important to determine whether the depression associated with terminal, rapidly progressive, or painful illness should be considered appropriate. Although patients with such diseases may understandably be sad, most do not have major depression. The treatment of major depression in such patients should always be attempted and can greatly improve their quality of life.

BOX 109-4 Medical Illnesses Associated with Onset of Depression

- Neurologic
  - Parkinson's disease
  - Stroke
  - Multiple sclerosis
  - Head trauma
  - Sleep apnea
- Neoplastic
  - Pancreatic carcinoma
  - Brain tumor
  - Disseminated carcinomatosis
- Endocrine
  - Hypothyroidism
  - Hyperthyroidism
  - Cushing's disease
  - Addison's disease
  - Diabetes mellitus
- Infectious
  - Human immunodeficiency virus
- Cardiac
  - Coronary artery disease
  - Myocardial infarction
- Renal
  - End-stage renal disease
  - Renal dialysis
- Connective tissue
  - Lupus erythematosus
  - Rheumatoid arthritis

Mood Disorders Caused by Medications or Other Substances

Certain medications are associated with symptoms of mood disorders (Box 109-5).

Intoxication or chronic heavy use of alcohol, sedatives, hypnotics, anxiolytics, narcotics, and other depressants can cause symptoms of a major depressive episode. Stimulants such as cocaine, phencyclidine, hallucinogens, and amphetamines can cause symptoms of a manic episode. Mood disorder symptoms can also develop during withdrawal. To qualify for this diagnosis, the symptoms must not occur exclusively during a course of delirium, must cause significant distress or impairment of functioning, and must develop within a month of either substance intoxication or withdrawal.

When the mood disorder predates the period of substance abuse or lasts longer than 1 month after the period of abuse, the diagnosis may be an underlying mood disorder, such as a major depressive disorder or bipolar disorder, with a comorbid substance abuse or dependence diagnosis.

Substance abuse is often seen in patients with underlying depressive or bipolar conditions.

DIAGNOSTIC STRATEGIES

The initial history and physical examination should focus on the presenting complaints and evaluate the possibility that drug abuse, medications, or a general medical condition may be responsible for the patient's condition. The diagnosis of a

BOX 109-5 MEDICATIONS THAT CAN CAUSE DEPRESSIVE OR MANIC SYMPTOMS

Depressive symptoms
- Antihypertensives
  - Beta-blockers
  - Captopril
  - Clonidine
  - Diltiazem
  - Enalapril
  - Nifedipine
  - Prazosin
  - Thiazide diuretics
- Anticonvulsants
  - Phenytoin
  - Topiramate
  - Valproic acid
- Hormones
  - Anabolic steroids
  - Contraceptives
  - Corticosteroids
  - Thyroid hormone
- Sedative-hypnotics
  - Barbiturates
  - Benzodiazepines

Manic symptoms
- Psychiatric agents
  - Antidepressants
- Antibiotics
  - Acyclovir
  - Chloroquine
  - Interferon
  - Isoniazid
  - Norfloxacin
  - Ofloxacin
  - Sulfonamides
- Other agents
  - Amantadine
  - Bromocriptine
  - Cyclobenzaprine
  - Cycloserine
  - Digitalis
  - Disopyramide
  - Levodopa
  - Metoclopramide
  - Nonsteroidal anti-inflammatory drugs
  - Phenylpropanolamine
  - Theophylline

mood disorder is based on history and observation of the patient's ability and style in relating to family and medical staff. The patient's body language may be helpful. Precipitating events (e.g., loss of job or relationship), accompanying symptoms (e.g., hallucinations, delusions, anxiety disorder, mania), and suicidal intent should be assessed. The patient's history should be confirmed through interviews with family, friends, or eyewitnesses to the events that precipitated the ED visit. A tentative diagnosis can be established using DSM-IV-TR criteria. Laboratory tests to investigate medical conditions may be necessary (see Box 109-4), but no tests can confirm or exclude mood disorders.

DIFFERENTIAL CONSIDERATIONS

Medical disorders, medications, and substance abuse or withdrawal not only can cause but also can mimic mood disorders. The patient who presents with agitation, for example, might have hypoxia, cocaine intoxication, or alcohol-sedative withdrawal. The patient with symptoms and signs of depression may have an unrecognized malignancy or sedative intoxication.

Antidepressant medications are used to treat a variety of disorders, such as anxiety, obsessive-compulsive disorder, post-traumatic stress disorder, pain syndromes, smoking cessation, and vasodepressor syncope. Patients taking antidepressant medication are often not being treated for depression.

Grief and *bereavement* are normal human reactions to the acute loss of another person, health, social position, or job. The period of mourning is characterized by sadness, diminished sense of well-being (somatic complaints), sleeplessness, and sadness triggered by thoughts of the loss. Normal grief, however, does not include guilt, loss of self-esteem, feelings of worthlessness, suicidal intent, psychomotor retardation, or occupational dysfunction.

Adjustment disorders are behavioral or emotional disorders that occur in response to an identifiable stress or stressors. The emotional component can involve sadness, low self-esteem, suicidal behavior, hopelessness, helplessness, or other self-threatening behavior. Acute adjustment disorder occurs within 3 months of the stressor and does not last longer than 6 months. The stressors are typically not as severe as those precipitating bereavement reaction, and the responses are often more maladaptive. The teenager who ends a romantic relationship, for instance, may attempt a drug overdose in response to the stress. In such cases, adjustment disorder is a more likely diagnosis than major depressive episode. The pattern of recurrent maladaptive behavioral responses to stress may be lifelong, but the acute episode should resolve within 6 months.

Borderline personality disorder is characterized by unstable personal relationships, unstable self-image, and inappropriate behaviors. The disorder may include chronic feelings of emptiness, which may be misdiagnosed as depression, or lability of mood, which may be mistaken for mania or hypomania. Borderline patients typically live lives of crisis and constant conflict.

Dementia can be confused with depression. Dementia is characterized by abnormal mental status, including abnormalities in tests of memory, calculation, and judgment. Delirium with waxing and waning sensorium, hallucinations, and delusions may involve disorganization, agitation, and restlessness, which might first be considered features of mania or agitated depression.

Differential considerations for manic symptoms include the manic phase of bipolar disorder, stimulant abuse (e.g., cocaine, amphetamines), hallucinogen abuse, alcohol or sedative withdrawal, delirium, hyperthyroidism, other medical conditions causing agitation, brief reactive psychosis, schizoaffective disorder, and schizophrenia.

MANAGEMENT

Emergency Department Stabilization

The creation of a safe and stable environment for the patient must be a first priority in management. The patient with an acute manic episode may be disruptive, refuse medical evaluation, and make repeated attempts to leave the ED. The initial step in treating such a disruptive patient is to offer assistance in reducing their agitation (placing the patient in a single room, recommending medication). At times this approach does not work and the patient may need to be placed in restraints for his or her safety and that of others.

Initiating treatment for a mood disorder is not typically done in the ED. An exception is the acute manic episode (or possibly a severe depressive episode with psychosis) with behavior so extreme that the patient or others are threatened. Such cases may well involve significant hallucinations, delusions, and other features of psychoses. In such cases an antipsychotic agent is often indicated. For years, clinicians have used intramuscular or oral haloperidol with or without lorazepam to calm such patients. A typical regimen for "rapid tranquilization" is an initial dose of 5 mg haloperidol with 2 mg lorazepam intramuscularly and reassessment in 30 to 45 minutes for resolution of "target" symptoms such as agitation. Another 5-mg dose is administered after 30 to 60 minutes as needed for improvement in hallucinations, delusions, agitation, or violent behavior.[43] Most patients respond after one or two doses. Benztropine (Cogentin), 1 to 2 mg, is often given initially to prevent extrapyramidal symptoms. Droperidol is a popular antipsychotic drug used effectively for agitation but has a black box Food and Drug Administration (FDA) warning about prolongation of QT intervals and torsades de pointes.[44]

The "atypical" antipsychotic medicines include ziprasidone, risperidone, olanzapine, aripiprazole, and quetiapine. The atypical agents are favored because they produce few of the side effects associated with conventional antipsychotic agents, such as acute dystonia, other extrapyramidal symptoms, and sedation. Oral doses should be offered first, and several agents, including risperidone, olanzapine, and aripiprazole, are available in rapidly dissolving tablet form. Three are available as an intramuscular injection: ziprasidone (Geodon), olanzapine (Zyprexa), and aripiprazole (Abilify). Ziprasidone 10 to 20 mg has been shown to be effective; however, its use is limited to 40 mg per 24 hours. Olanzapine 2.5 to 10 mg has also been shown to be effective, but has been associated with postural hypotension, and is not recommended in combination with benzodiazepines due to risk of hypoventilatory syndrome. Aripiprazole is the newest agent and at doses of 9.75 to 15 mg seems to be the least sedating of the atypicals, but more likely to cause nausea and vomiting.[45–50] Immediate psychiatric consultation should begin during the initiation of rapid tranquilization, since patients undergoing rapid tranquilization will generally require hospitalization (Box 109-6).

BOX 109-6 Criteria for Hospitalization of Emergency Department Patient with Acute Psychiatric Episode

- Patient demonstrates risk of suicide or homicide or of significant harm to self or others.
- Patient lacks the capacity to cooperate with treatment.
- Patient has inadequate psychosocial support for safe outpatient treatment and compliance.
- Patient has a comorbid condition or complication that makes outpatient treatment unsafe (e.g., acute psychosis, bizarre behavior, need for detoxification).

Long-Term Treatment

Depression

Effective treatment modalities for depression are grouped into three broad categories: (1) antidepressant medication, (2) psychotherapy, and (3) electroconvulsive therapy (ECT).

Antidepressant Therapy. Many effective antidepressants are available for first-episode uncomplicated major depression. After 4 to 6 weeks of therapy, the response rate is usually 60% or greater for all agents. However, 10 to 15% of patients quit medication trials,[51] and many patients in general medical practice are inadequately treated.[52]

Coexistent medical illness, psychotic or bipolar symptoms, substance use, and recurrent or refractory depressive symptoms must be considered in the choice of a medication for treatment of depression. The side effects of tricyclic antidepressants and monoamine oxidase inhibitors, along with strict dietary limitations, have led to the use of selective serotonin-reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors as first-line treatment for depression. Side effects of these agents may include dizziness, sedation, peripheral anticholinergic symptoms, weight gain, sexual dysfunction, neurologic symptoms, insomnia, and anxiety. Frequently another antidepressant, ECT, thyroid hormone, or other psychoactive medication may need to be added for patients with treatment-resistant depression.

Psychotherapy. Brief psychotherapy is often initially employed in patients with major depression. Interpersonal psychotherapy, psychodynamic psychotherapy, and group or family therapy are also used with some patients. Psychosocial therapeutic support typically includes community-based support groups that focus on specific individual, occupational, or family/marital issues that arise in depression and are amenable to group and supportive intervention.

Depressed patients benefit most from a combination of somatic therapy (medication and/or ECT) and psychotherapy. All patients with incomplete therapeutic response, recurrent depression, or comorbid conditions (e.g., anxiety/panic, substance abuse) should receive multimodal treatment.[53]

Electroconvulsive Therapy. ECT has a high therapeutic success rate and an excellent safety profile but is not a first-line treatment for uncomplicated major depression. In part, this is a result of an undeserved reputation among laypersons that ECT causes "permanent brain damage." Indications for ECT include severe depression with malnutrition, severe psychosis with agitation, continuing significant suicide risk with ongoing suicidal behaviors, prolonged catatonia, and recurrent depression previously with a positive response to ECT. ECT is more often used as a second-line treatment for patients with moderate to severe depression who have not responded to trials of medication or who cannot tolerate the medication because of side effects or concurrent medical conditions.

Bipolar Disorders

Bipolar disorder is treated primarily with mood-stabilizing drugs, including lithium, valproate, carbamazepine, and lamotrigine. Almost all bipolar patients require a mood stabilizer during exacerbation of depression or mania, and most patients benefit from a mood stabilizer for ongoing supportive maintenance treatment as well. Lithium was the first highly effective mood-stabilizing agent for the treatment of bipolar

patients.[54] Valproate is a very effective mood stabilizer with dose-related side effects, most of which clear after an initial period of treatment or with reduced dosage.[55] Valproate can be instituted rapidly in acutely manic bipolar patients.[56] Both lithium and valproate serum levels are routinely monitored during therapy. The therapeutic window is much wider for valproate than for lithium. Carbamazepine also has dose-related side effects but has rare potentially serious side effects.

Mood-stabilizing medications usually take 3 or more weeks to become effective.[57] Some bipolar patients require antipsychotic medications and benzodiazepines in the interim to control symptoms. Some patients with bipolar disorder have significant psychotic symptoms requiring use of a major neuroleptic, such as haloperidol, ziprasidone (Geodon), risperidone (Risperdal), olanzapine (Zyprexa), quetiapine (Seroquel),[58] or aripiprazole (Abilify). After 3 weeks, a second mood-stabilizing medication is often added for patients who have a partial response. Atypical antipsychotics have significant mood-stabilizing properties and studies have shown that they are effective in treating both bipolar mania and bipolar depression (although not all are FDA approved for this indication).[58] For bipolar patients with a depressive episode, adjunctive treatment with antidepressants should be done very cautiously because of associated risks of switching into mania or hypomania.[59] In addition, some recent studies found that antidepressants may not be effective for bipolar depression and may worsen the course of the illness.[60]

Bipolar patients are sensitive to psychosocial stressors, sleep loss, changes in medication dosage, substance abuse, and medical illness. This sensitivity can lead to a marked worsening in a patient's level of adaptation and functioning. It is helpful to understand these precipitating stressors when developing a therapeutic support plan for patients. Psychosocial therapeutic support, including individual psychotherapy, supportive community groups, family/marital treatment, and occupational support, are important in both the acute phase and the maintenance phase of treatment for bipolar patients.

KEY CONCEPTS

- Patients with apparent mood disorders should be evaluated for a medical disorder, medication effect, or drug use that can mimic both depression and mania.
- Mood disorders should be suspected in patients with multiple, vague, nonspecific complaints and in patients who are frequent, heavy utilizers of medical care.
- The differentiation of depression and dementia in elders can be difficult but is important, since depression often responds dramatically to treatment.
- Patients with mood disorders should be assessed for their potential for violence or self-harm before discharge.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 110 Anxiety Disorders

Eugene E. Kercher and Joshua L. Tobias

Anxiety is essential to the human condition. Confrontation with anxiety can relieve us from boredom, sharpen our sensitivity, and create the tension which is necessary to preserve human existence.

Rollo May

Acute anxiety and apprehension are common in emergency department (ED) patients. However, many medical entities mimic anxiety disorders, and up to 42% of patients thought to have anxiety disorders are later found to have organic disease. Emergency physicians must thoroughly assess the anxious patient and identify and appropriately treat any underlying medical conditions.[1]

PERSPECTIVE

Anxiety is a specific unpleasurable state of tension that forewarns the presence of danger. This uneasiness stems from the anticipation of some imminent danger, the source of which is unknown or unrecognized. Vigilance is a positive consequence of anxiety, helping people to recognize threats quickly, which produces more learning and more intelligence. The capacity to experience anxiety and the capacity to plan are therefore related, with anxiety accompanying intellectual activity as its "shadow."[1]

Anxiety facilitates performance up to a point with the well-described adrenergic responses to stress that contribute to survival. When responses go beyond this point, further increases in anxiety may lead to deterioration of performance and nonadaptive responses may add to the stress of the patient. The threshold for pain decreases and the person becomes more aware of bodily discomfort. Respiratory, cardiovascular, gastrointestinal, genitourinary, and neuromuscular complaints become prominent.[1] Once the normal reaction to a threat is surpassed and function is impaired, pathologic anxiety (anxiety disorders) is the result.

The emergency physician should not assume anxiety is purely functional because physical discomfort and illness often trigger an anxiety attack. The anxiety state makes significant metabolic demands that may actually cause a marginally compensated organ system to fail. It is the goal of the emergency physician to be able to distinguish between the anxiety and the illness and, if necessary, treat both entities.

EPIDEMIOLOGY

Approximately 40 million American over the age of 18 are affected by anxiety disorders each year. This is nearly 20% of the adult population of the United States.[2] Anxiety disorders are among the most prevalent psychiatric disorders, and are the most common psychiatric problem seen by primary care physicians, with 20% of these patients experiencing a type of anxiety disorder.[3] Most people who use primary care services have significant mood and anxiety symptoms, such as panic disorders, generalized anxiety disorders, and depression. Unfortunately, nearly half of these patients exhibit these symptoms but never receive appropriate treatment,[4] in part, because the patients would rather present with a physical complaint to the physician and try to disguise their anxiety, rather than undergo the perceived stigma that goes with psychiatric complaints.[5] Patients with chronic illness and those who make frequent medical visits have higher rates of anxiety and depression. The prevalence of anxiety disorders surpasses that of any other mental health disorder, including substance abuse. In view of the close relationship between alcohol abuse and anxiety disorders, those with anxiety disorders often turn to alcohol and substance abuse as a form of self-medication and the substance abuser frequently develops underlying anxiety in relation to the use of alcohol and drugs.[6]

PRINCIPLES OF DISEASE

The precise mechanism for the cause of anxiety has not been established. Noradrenergic, serotonergic, and other neurotransmitter systems all play a role in the body's response to a stressor. The serotonin system and the noradrenergic systems are common pathways implicated in anxiety. It is believed that low serotonin system activity and elevated noradrenergic system activity are involved. Gamma butyric acid (GABA) is the principal inhibitory neurotransmitter in the central nervous system. Benzodiazepines' principal mechanism of action is on the $GABA_A$ receptors. The well-established effectiveness of benzodiazepines in the treatment of anxiety has led to the study of the GABA system and its relationship to anxiety. Newer studies are focusing on the role that corticosteroids may play in fear and anxiety. Steroids are thought to induce chemical changes in select neurons that strengthen or weaken certain neural pathways which affect behavior under stress.[7]

Other investigators have found anxiety reactions are associated with aberrant metabolic changes induced by lactate infusion and hypersensitivity of the brainstem to carbon dioxide receptors. Newer research is focusing on the regulatory centers found in the cerebral hemispheres. The hippocampus and the amygdala regulate emotion and memory and are important areas in relation to an individual's response to fear.[8] Family studies suggest genetic factors are implicated in anxiety, but

the precise nature of the inherited vulnerability is unknown. Psychological and environmental factors, as outlined in psychodynamic, behavioral, and cognitive theories, also play a causative role in the generation of anxiety in biologically predisposed individuals.[8]

CLINICAL FEATURES

Many patients entering the unfamiliar environment of the ED are going to experience anxiety and stress, and for some this can be a significant clinical issue. The ED patient encounters a world of both internal and external dangers: assaults on bodily integrity in the form of uncomfortable procedures and forced intimacy with strangers; the atmosphere of illness, pain, and death; and separation from loved ones and familiar surroundings. The patient typically experiences uncertainty about his or her illness, the implications that the illness may have on personal relationships and employment, and the financial burden that may accompany the illness.

The anxious patient can be a diagnostic challenge. The presence of anxiety may represent the patient's reaction to medical illness or the medical setting or a manifestation of the physical disorder itself, or the anxiety may be an expression of an underlying psychiatric disorder. The distinction between anxiety as a symptom and anxiety as a syndrome may be difficult to make in the ED. There is an overlap between normal situational anxiety and fear, anxiety-like symptoms resulting from a variety of organic disease states and their treatments, and the characteristic presentation of anxiety itself.

The physical symptoms of autonomic arousal (e.g., tachypnea, tachycardia, diaphoresis, light-headedness) may be the only manifestation of anxiety (Box 110-1). Patients may only complain of overall poor health or vague subjective findings when they visit the physician. Classic panic disorder symptoms of chest pain, shortness of breath, and the sense of impending doom will often lead the patient to the ED, especially if it is the primary episode.[7] Anxiety associated with organic etiologies is more likely to present with physical symptoms and less likely to be associated with avoidance behavior.[9]

BOX 110-1 SOMATIC SYMPTOMS OF ANXIETY

Respiratory
- Hyperventilation
- Sense of dyspnea

Cardiovascular
- Palpitations
- Chest discomfort
- Awareness of missed beats

Gastrointestinal
- Dry mouth
- Difficulty in swallowing
- Epigastric discomfort
- Excessive flatulence
- Frequent or loose stools

Genitourinary
- Frequent or urgent micturition
- Failure of erection
- Amenorrhea
- Menstrual discomfort

Neuromuscular
- Tremor
- Aching muscles
- Prickling sensations
- Headache
- Dizziness, tinnitus

DIFFERENTIAL CONSIDERATIONS

Medical Illness Presenting as Anxiety

Patients with anxiety disorders may present with apparent physical disease, and many physical diseases may be strongly associated with symptoms of anxiety. Differentiating between these two scenarios is a daunting task for the emergency physician. Several factors help distinguish an organic anxiety syndrome from a primary anxiety disorder[10] (Box 110-2). With anxiety, the somatic symptoms can be so prominent that they occupy most of the patient's attention, making it difficult to differentiate between a primary anxiety disorder or reactive anxiety to a situation or disease. Anxiety disorder classifications, in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV), include anxiety caused by a general medical condition[11] (Box 110-3).

Anxious patients are frequently convinced that their problem is purely physical. The emergency physician must realize that the patient with anxiety is not in control of the symptoms and frequently cannot immediately identify the correct precipitant. Even though the patient may be uncomfortable, uncooperative, impatient, and unreasonable, triage medical personnel must recognize that the patient believes an illness truly exists and is not being consciously manipulative. Because anxiety may be the most obvious symptom of an underlying disease or condition, the patient should be evaluated for exacerbation of known preexisting disease as well as for onset of new illness. The emergency physician must keep in mind that anxiety is associated with increased medical risk in the acute exacerbation of chronic illness.[12]

The classic scenarios of pulmonary embolism and hyperthyroidism causing anxiety are well documented. Cardiac disease studies indicate poorer outcomes in post-myocardial infarction patients with anxiety than those without documented anxiety. Patients with respiratory diseases, such as asthma or chronic obstructive pulmonary disease, often develop anxiety with their long-standing illnesses. In addition, many of the medications used to treat the above illnesses may induce anxiety.[5] The most common organic cause of anxiety is alcohol and drug use, from either intoxication or, more typically, withdrawal states.

Cardiac Diseases

Various psychiatric conditions may present to the ED with complaints of chest pain. Approximately 25% of patients with chest pain that present to the ED have panic disorder. Their panic disorder often goes undiagnosed, resulting in multiple visits and expensive cardiac workups with each visit.[13] Some of the symptoms of *myocardial infarction* and *angina pectoris* may

BOX 110-2 PREDICTORS OF ORGANIC ANXIETY SYNDROME

1. Onset of anxiety symptoms after age 35 years
2. Lack of personal or family history of an anxiety disorder
3. Lack of childhood history of significant anxiety, phobias, or separation anxiety
4. Lack of avoidance behavior
5. Absence of significant life events generating or exacerbating the anxiety symptoms
6. Poor response to antipanic agents

BOX 110-3 DEFINITIONS OF ANXIETY DISORDERS

Panic attack is a discrete period in which there is a sudden onset of intense apprehension, fearfulness, or terror, often associated with feelings of impending doom.
Agoraphobia is an anxiety about, or avoidance of, places or situations from which escape might be difficult.
Panic disorder with agoraphobia is characterized by both recurrent, unexpected panic attacks and agoraphobia.
Agoraphobia without a history of panic disorder is characterized by the presence of agoraphobia and panic-like symptoms without a history of unexpected panic attacks.
Specific phobia is characterized by clinically significant anxiety provoked by exposure to a specific feared object or situation, often leading to avoidance behavior.
Social phobia is characterized by clinically significant anxiety provoked by exposure to certain types of social or performance situations, often leading to avoidance behavior. Blushing is the cardinal characteristic symptom.
Obsessive-compulsive disorder is characterized by obsessions that cause marked anxiety or distress and by compulsions that serve to neutralize anxiety.
Post-traumatic stress disorder is characterized by experiencing of an extremely traumatic event, accompanied by symptoms of increased arousal and by avoidance of stimuli associated with trauma.
Acute stress disorder is characterized by symptoms similar to those of post-traumatic stress disorder that occur immediately in the aftermath of an extremely traumatic event.
Generalized anxiety disorder is characterized by at least 6 months of persistent and excessive anxiety and worry.
Anxiety disorder caused by a general medical condition is characterized by prominent symptoms of anxiety that are judged to be a direct physiologic consequence of a general medical condition.
Substance-induced anxiety disorder is characterized by prominent symptoms of anxiety that are judged to be a direct physiologic consequence of a drug of abuse or medication or toxin exposure.
Anxiety disorder not otherwise specified is included for coding (1) disorders with prominent anxiety or phobic avoidance that do not meet criteria for specific anxiety disorders and (2) anxiety symptoms with inadequate or contradictory information.

From American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th ed, Text Revision. Washington, DC, American Psychiatric Association, 2000.

include crushing chest pain, shortness of breath, nausea, palpitations, heavy perspiration, and a feeling of impending death. These are also the primary symptoms of acute anxiety, but the pain is usually described as atypical, and patients are generally female and younger.[14] Because of the morbidity and mortality of cardiovascular disease, a patient warrants a full cardiac evaluation when the differentiation between myocardial infarction and acute anxiety is unclear.

Cardiac dysrhythmias can cause palpitations, discomfort, dizziness, respiratory distress, and fainting. An anxious patient with a panic disorder will frequently have similar symptoms. Fortunately, most dysrhythmias can be documented and characterized by an electrocardiogram. *Mitral valve prolapse* syndrome can be associated with palpitations and panic attacks indistinguishable from a panic disorder. Benzodiazepines can be used to provide symptomatic relief to patients who experience chest pain. Studies have shown that benzodiazepines reduce anxiety, pain, and cardiovascular activation. It is hypothesized that secondary to the reduction in circulating catecholamines, benzodiazepines may cause coronary vasodilatation, prevent dysrhythmias, and block platelet aggregation.[15]

Endocrine Diseases

The DSM-IV defines the most common endocrinologic conditions associated with anxiety states as hypoparathyroidism, hyper- and hypothyroidism, hypoglycemia, pheochromocytoma, and hyperadrenocorticism.[11] Anxiety is the predominant symptom in 20% of patients with *hypoparathyroidism*. Other symptoms include paresthesias, muscle cramps, muscle spasm, and tetany. Most cases are idiopathic or the result of surgical removal of the parathyroid glands during thyroidectomy, and studies indicate a higher incidence of anxiety in the surgically removed subset of patients.[16] The diagnosis of hypoparathyroidism is suggested by a low serum calcium level, a high phosphate level, and confirmed by a parathyroid hormone assay.

Approximately 14% of diabetic patients suffer from anxiety disorders, and elevated anxiety symptoms are seen in up to 40% of diabetics. There is evidence that diabetics who are treated with antianxiety medication not only experience a reduction in anxiety but also a decrease in glycosylated hemoglobin levels and high-density lipoprotein.[17] Many patients with anxiety, somatoform, or characterologic disorders are convinced that they have *reactive hypoglycemia*. A normal fingerstick blood glucose analysis done during an attack can exclude this diagnosis.

Pheochromocytomas are rare tumors that produce elevated levels of catecholamine in the body. Common symptoms include paroxysmal hypertension, headache, anxiety, sweating, flushing, abdominal and back pain, and vomiting and diarrhea. Pheochromocytoma attacks can present just like panic attacks and can be precipitated by emotional stress. While the sweating associated with pheochromocytoma attacks involves the whole body, the sweating in panic attacks is more likely to be confined to the hands, feet, and forehead. Elevated urinary catecholamine or plasma metanephrine can confirm a pheochromocytoma.[18]

Hyperthyroidism is one of the most frequently encountered endocrine diseases associated with anxiety. As with panic disorders, *hyperthyroidism* is associated with acute episodic anxiety. *Thyrotoxicosis* causes anxiety, palpitations, perspiration, hot skin, rapid pulse, active reflexes, diarrhea, weight loss, heat intolerance, proptosis, and lid lag.[19] Psychiatric presentations are often the first sign of *hypothyroidism*, occurring as the initial symptom in approximately 2 to 12% of reported cases along with organic mental deficits. Anxiety and progressive mental slowing associated with diminished recent memory and speech deficits with diminished learning ability are the characteristic initial progression of symptoms. The development of severe anxiety disorders in hypothyroid states are more related to the rapidity of change of thyroid hormone levels than the absolute levels encountered. In general, checking the serum thyroid-stimulating hormone and free thyroxine levels will suffice in the ED to make the diagnosis of thyroid emergencies.[20]

Respiratory Diseases

Most conditions causing airway compromise or impairing gas exchange would never be mistaken for a psychiatric disorder. However, certain conditions that cause hypoxemia or hypercarbia may present with significant anxiety, and up to a third

of the patients with chronic obstructive pulmonary disease meet the criteria for anxiety disorder.[21]

Asthma is characterized by episodic attacks of dyspnea and often anxiety. Anxiety can also precipitate and prolong asthma attacks. Patients who have severe asthma are twice as likely to have an anxiety disorder and almost five times as likely to have a phobia compared with nonasthmatics. Severe asthmatics are almost five times as likely to have a panic disorder and about four times as likely to have a panic attack. Acute dyspnea secondary to asthma is easily differentiated from pure panic in that there is good air movement with normal lung sounds in a patient experiencing a panic attack, but studies consistently show that anxiety disorders increase asthma morbidity and mortality.[22]

Shortness of breath is a common complaint in the ED. When accompanied by anxiety, panic attacks or anxiety disorders may be high on the differential diagnosis. The clinician must always fully evaluate these patients, as these are often the complaints of a patient presenting with a pulmonary embolism. Acute shortness of breath in any patient should never be dismissed lightly, especially since pulmonary embolus can present with only shortness of breath as the major symptom. These patients can be distinguished by close attention to history and examination, assessing risk factors for thromboembolic disease and use of basic investigations (e.g., pulse oximetry, electrocardiogram, chest radiography, arterial blood gas analysis, and D-dimer) and further tests as indicated.[23]

Neurologic Disorders

Many neurologic conditions are associated with anxiety symptoms.[24-26] *Temporal lobe* seizures, complex partial seizures, tumors, arteriovenous malformation and ischemia or infarction all have been reported to present with panic attacks. Anxiety often accompanies a *transient ischemic attack* and may be the major symptom on presentation if the transient ischemic attack has resolved by the time the patient reaches the ED. In *Huntington's disease*, anxiety has been reported as the most common prodromal symptom. Anxiety occurs in up to 40% of patients with Parkinson's disease and up to 37% of patients with multiple sclerosis. Similarly, anxiety symptoms have been noted to be common in moderate *Alzheimer's disease*. The coexistence of anxiety disorders plays an important role in the prognosis and impairment of patients who have had *cerebral vascular accidents* with neurologic sequelae. Anxiety and depression are associated with left-hemispheric strokes and anxiety alone with right-hemispheric strokes. And finally, anxiety disorders have also been reported in the aftermath of traumatic brain injury.[27]

Drug Intoxication and Withdrawal States

Amphetamines, *cocaine*, and *sympathomimetic drugs* are abused for their stimulant and mind-altering properties. Amphetamine use has exploded over the past decade, and cocaine use is still the drug of choice in many large cities. Patients often present to the ED agitated, anxious, or aggressive when these drugs are taken in large doses and with prolonged use. *Caffeine* is a common stimulant, and energy drinks and gourmet coffee represent a constantly growing market in the United States. These drinks are packed with caffeine and the herbal equivalent guarana as well as ginkgo biloba. Studies indicate that 240 to 300 mg of caffeine per day should be the upper limit of healthy consumption. Many of these energy drinks contain that amount in a single serving.[25] Lower doses of caffeine can be pleasantly stimulating, but higher doses cause hyperalertness, hypervigilance, motor tension, tremors, gastrointestinal distress, and anxiety. The acute symptoms of caffeine intoxication and generalized anxiety disorder are almost identical. Stimulants such as *Ephedra* and *ephedrine-based compounds* were found in many dietary supplements and listed by the herbal name of Ma Huang. Despite the Food and Drug Administration ban on Ephedra-containing compounds in 2004, access still exists over the Internet.

Many illicit drug users who use *marijuana* believe that the drug reduces their anxiety. But some experience a depersonalization that provokes severe anxiety, fearfulness, and agoraphobic symptoms. Lysergic acid diethylamide (*LSD*), phencyclidine (*PCP*), and *ecstasy* are hallucinogens that can produce anxiety and paranoia from chronic use or "bad trips." Flashbacks affect some users of LSD, where the person may experience the symptoms of anxiety and paranoia weeks or months after use.[26]

Sedative-hypnotic drugs (e.g., benzodiazepines, barbiturates, meprobamate, methaqualone, chloral hydrate, and paraldehyde) are taken to relieve anxiety or sleeplessness, but their discontinuation can cause *sedative withdrawal* and rebound anxiety. The severity of the withdrawal syndrome depends on the drug, dosage, duration of use, and speed of elimination. In general, the intermediate-acting sedative-hypnotics (4–6 hours) cause the worst withdrawal symptoms. These symptoms include hyperalertness, motor tension, muscle aches, agitation, anxiety, insomnia, hyperactive reflexes, postural hypotension, tremulousness, nausea, vomiting, convulsions, delirium, and even death.

Benzodiazepine withdrawal is rarely fatal but can be very unpleasant. In anxious patients, severe rebound anxiety can occur after a few weeks' use of recommended therapeutic doses. Lorazepam and alprazolam are short-acting agents and their abrupt discontinuation frequently causes panic attacks within 1 to 2 days. With longer-acting agents, withdrawal symptoms typically peak in about one week. Normal people may experience this rebound as stimulating. Although antidepressants are rarely abused, their abrupt withdrawal can also cause an abstinence syndrome of insomnia, vivid nightmares, and extreme anxiety.[27]

Alcohol withdrawal, in alcohol-dependent individuals or heavy binge drinkers, can appear 6 to 12 hours after the last drink or significant reduction in consumption of alcohol. Patients often have detectable alcohol still in their systems at this time. Anxiety is one of the first and most prominent symptoms and is seen within 24 to 48 hours of the withdrawal state.[28]

Anxiety in Primary Psychiatric Disorders

Even in patients with known mental illness, a panic disorder is a diagnosis of exclusion because several mental illnesses cause panic attacks as a secondary manifestation. The presence of panic often influences the treatment and outcome of the primary mental illness. Panic attacks can occur as part of a *bipolar* (*manic-depressive) disorder*, in either the manic or the depressed phase. In manic and hypomanic disorders the patient's predominant affect is usually cheerful and euphoric but may also be dysphoric with irritability and extreme anxiety of panic proportions.[29]

Early in the course of schizophrenia, a patient will often experience panic attacks. Fearfulness, tension, agitation, immobility, disorganized thinking, dilated pupils, extreme insecurity, suspiciousness, and delusions of reference and persecution may characterize schizophrenic panic attacks. The hallucinations often have derogatory accusative content. Social anxiety is a highly prevalent and disabling condition with schizophrenia that is unrelated to clinical psychotic symptoms.[30]

Patients with *somatoform disorders* report a variety of somatic symptoms, including panic attacks, and 68% report a history of anxiety. Patients claim to have most of the physical symptoms they are asked about, even when evidence excluding illness is presented to the patient. Fear and anxiety initiate, facilitate, and maintain many of the symptoms encountered in the somatoform patient. Patients with "pure" anxiety disorders tend to be hypochondriacal, while those with somatization are more likely to improve transiently on active medication or placebo but rarely respond so well that they stop seeking unnecessary medical attention. Patients with panic disorders, however, seek at least as much psychiatric attention as those with somatoform disorders.[31]

Approximately 50% of patients with a primary panic disorder develop *major depression* and many others are bothered by some degree of depression in mood. Twenty percent of patients with depression have panic attacks, and the remainder have considerable anxiety. Depression with panic attacks responds less well to treatment. Agitated depression with anxiety and psychosis, sometimes called "involutional melancholia," responds well to electroconvulsive therapy. Depression with anxiety and hostility responds well to antidepressants but benzodiazepines can exacerbate symptoms.[32]

Post-traumatic stress disorder is an anxiety disorder characterized by the reexperiencing of an extremely traumatic event. The symptoms are closely related to and worsened by reminders of the trauma. The "flashbacks," in which patients reexperience the original trauma, can have the same symptoms as panic attacks. These patients often avoid crowds or social situations.[33]

A panic disorder is one of the easier psychiatric diseases to feign because most of the symptoms can be duplicated by intentional hyperventilation. Functional hyperventilation can be distinguished from organic hyperventilation by its irregularity and interruptions by sighs. When in doubt, formal psychiatric evaluation is indicated, particularly before prescribing a potentially dangerous or addictive drug therapy.

A *phobia* is an irrational fear that results in avoidance and is considered normal in children. The objects of fear tend to be things that seem dangerous to a child (e.g., spiders, snakes, bats, cats, enclosed places, the dark, open spaces). Phobia becomes a disorder when it interferes with day-to-day function in an individual's life. A *social phobia* is characterized by clinically significant anxiety provoked by exposure to a specific feared object or situation, often leading to avoidance behavior. Social phobias prevent a patient from doing such activities as public speaking, performing, visiting, using public showers or restrooms, or eating in public places. *Agoraphobia* is a fear of being alone in public places. Nearly 75% of agoraphobic patients have panic attacks.[34] Those with panic attacks are more likely to seek treatment, whereas those with uncomplicated agoraphobia tend to stay at home. Agoraphobia without panic attacks may not differ fundamentally from other simple phobias. Most panic disorder patients have multiple phobias, including agoraphobia. The latter is believed to result from the panic patient's increasing attempts to avoid places or situations in which the panic attacks would be particularly inconvenient or difficult to control. Agoraphobic patients particularly avoid places from which escape would be difficult (e.g., bridges, crowded theaters). When they do attend theaters, they favor seats on the aisle and near the door. Panic attacks in agoraphobic patients are more likely to include fear of losing control, whereas those not associated with agoraphobia are more likely to include dyspnea and dizziness.[35]

An *obsessive-compulsive disorder* (OCD) is characterized by recurrent, obtrusive, unwanted thoughts (obsessions), such as fears of contamination, and compulsive behaviors or rituals (compulsions), such as handwashing or checking. OCD is classified as an anxiety disorder because (1) anxiety or tension is often associated with obsessions and resistance to compulsions, (2) anxiety or tension is often immediately relieved by yielding to compulsions, and (3) OCD often occurs in association with other anxiety disorders. In summary, the obsessions and intrusive thoughts increase anxiety and the compulsions and repetitive behaviors decrease anxiety but with significant disruption of one's life.[9]

MANAGEMENT

Initial Evaluation

The patient should first be placed in a quiet area for evaluation. Some patients calm down when removed from the ED environment. If the emergency physician encounters difficulty in calming the patient, supportive family members may help. Often a known and trusted face helps anxious patients make order out of their inner turmoil. Prior discussion and clarification with the family are essential to elicit their support.[1]

Once the patient is calmed, a more formal evaluation can begin. The emergency physician should ask open-ended questions and observe the patient's responses carefully. Questions regarding drug or alcohol use should be delayed until rapport has been established. Reassurance should not be premature, because this important interventional technique is more effective when it is delayed until after the patient's specific concerns are clarified.[1]

The extent of the medical workup for significant anxiety will vary depending on the age and health status of the patient, the nature of the anxiety, and the range and severity of associated symptoms. The emergency physician should consider the anxiogenic effects of medications, including beta-adrenergic agonists, theophylline, corticosteroids, thyroid hormones, and sympathomimetics. Potential contributory medical illness (e.g., thyroid dysfunction, hypoglycemic episodes in diabetes, hyperparathyroidism, dysrhythmias, chronic obstructive pulmonary disease, seizure disorders), substance use (e.g., caffeine, amphetamines, cocaine) and withdrawal states (e.g., alcohol, sedative-hypnotics) must also be considered.

If a somatic concern is the major component of the acute anxiety attack, a physical examination with particular attention to the area of complaint is important, even when there is overwhelming evidence of a functional etiology to the patient's complaints. Anxiety attacks are stressful experiences in themselves and can cause deterioration in marginally compensated organ systems. Careful evaluation reassures the patient and avoids the problem of a premature "medical clearance." Abnormal vital signs should immediately alert the emergency physician to an organic cause of the anxiety symptoms.[9]

Because of the physical nature of the symptoms, patients with anxiety and panic attacks often seek treatment in the ED rather than in a psychiatric setting. A calm manner and willingness to listen usually relieves some of the patient's initial anxiety. An anxiety or panic reaction may be precipitated by the loss of a significant relationship, a job, a living situation, or self-esteem, as well as by physical illness or injury. Once the patient describes a trigger event, the emergency physician should restate it, as if experiencing a similar situation. This gives the patient authoritative approval for expressing embarrassing feelings. A patient who has frequent anxiety reactions is usually suggestible and will respond to reassurance. Conversely, an anxious or unsympathetic physician will only compound the problem.[1]

Even an apparently calm patient may communicate anxiety through worried looks, nervousness, pressured speech, or

covert assaults on the physician's competence. In turn, the physician may empathetically respond to the patient's hidden anxiety by also becoming anxious. This is a strong clue that the patient's anxiety is real and significant. Without this self-awareness, physicians may focus on a patient's physical symptoms rather than on the irrational anxiety. The pressure to see patients quickly and to move them out of the ED expeditiously may result in limited interactions with patients, the misdiagnosis of anxiety disorders, and excessive and unnecessary medical workups. A careful medical evaluation is important, but excessive focus on unlikely illness suggests to the patient a reason to worry, avoids recognition of crucial psychological factors, and may increase anxiety and the severity of symptoms.

After organic illness, medications, and obvious psychiatric causes of the acute anxiety state have been ruled out, the physician should determine whether the anxiety is endogenous or exogenous. If the anxiety arises spontaneously without an identifiable stress, is unpredictable, and is accompanied by agoraphobia, an endogenous component is likely to be present. Such patients should be referred to a psychiatrist for evaluation and treatment. If the anxiety appears to be related to an identifiable external event or circumstance, the anxiety is exogenous and patients should be encouraged to discuss their feelings with a mental health worker. Talking about fears allows anxious patients some sense of mastery and control over events. These patients often require ongoing advice, support, and assistance in mobilizing necessary resources from family members, friends, and social agencies to achieve realistic expectations.

Anxiety is common in elders, with prevalence rates conservatively estimated at 10%, with higher rates in patients with chronic illness. Anxiety disorders may be the most common psychiatric ailments experienced by older adults, but that age group is the least studied of all patients.[36] Older patients with anxiety often have somatic complaints. These patients require a careful investigation for underlying medical illness, other psychiatric conditions, and the use of over-the-counter and prescription drugs.

Pharmacologic Treatment

Before medication is prescribed, education of the patient about their illness is a key component in the treatment of anxiety disorders. Patients are often worried and confused about their illness. Reassurance that they are not alone, education about what to expect and that therapy is available, and involvement of family are all critical pieces in the treatment of anxiety. Use of intravenous medication is rare but may be necessary when an anxiety state renders a patient so helpless and out of control that there is a significant threat of safety to self or others. Intravenous medication is also appropriate for the anxious patient experiencing a significant medical illness or undergoing a medical procedure. Lorazepam in small increments every 20 minutes can be helpful in alleviating the anxiety associated with substance withdrawal states. Midazolam is frequently used to reduce anxiety and increase amnesia for ED procedures.

Selective serotonin-reuptake inhibitors (SSRIs) have become the first-line treatment for most anxiety disorders because of their broad spectrum of efficacy and good tolerance by most patients. SSRIs have a lower potential for dependence and are safer than the previous classes of antidepressants and anxiolytics. This class of drugs includes fluoxetine, sertraline, fluvoxamine, paroxetine, citalopram, venlafaxine, and sertraline. Improvement is usually seen in 3 to 4 weeks, and the medication may have to be adjusted if no improvements in anxiety are seen. It is important to start the patient on low doses of SSRIs as an initial increase in anxiety may be seen.

In the past few years, emergency physicians and the public have become increasingly concerned about the growing use of benzodiazepines in the United States. Over 1 million Americans are physically dependent on tranquilizers. When tranquilizers are given in place of understanding, support, and intrapersonal therapies, patients are taught to rely on the external support of a pill rather than on inner resources.[8]

Benzodiazepines can be prescribed for motivated patients with acute exogenous anxiety for time-limited stress. Patients who are cooperative, employed, educated, married, and aware that their symptoms have a psychological basis are more likely to respond. Benzodiazepines are an attractive alternative to SSRIs when an immediate reduction of symptoms is desired because of the delayed response with SSRIs or a short-term treatment is needed. Benzodiazepines can be given in one or two daily doses to make use of their short half-lives; alternatively, a bedtime dose may minimize daytime sedation and still manifest a daytime anxiolytic effect. Benzodiazepines should not be prescribed for more than a week. Patients who do not improve within a week are unlikely to benefit from the drug. Patients with a history of alcoholism or drug abuse, who are excessively and emotionally dependent, or who become anxious in response to normal stress are at greater risk of drug dependency and are not good candidates for this treatment from an emergency physician. Dependence and abstinence syndromes have been reported to occur with low doses of tranquilizing drugs, especially if they are taken for more than 8 months. Short-acting benzodiazepines (e.g., lorazepam, oxazepam) should be prescribed at low dosages for patients with liver disease, organic brain syndrome, and those taking medications that either depress central nervous system function or inhibit benzodiazepine metabolism and clearance. Withdrawal rebound symptoms are more common with discontinuation of benzodiazepines than with other antianxiety treatments. Short-acting benzodiazepines produce a more severe abstinence syndrome when they are stopped abruptly, and thus many physicians prefer the longer-acting benzodiazepines.[7] For some patients, switching from a short-acting agent (e.g., alprazolam) to a long-acting agent (e.g., clonazepam) can be helpful before initiating a taper.

Buspirone is a nonbenzodiazepine tranquilizer used in the treatment of generalized anxiety disorder. Buspirone does not appear to cause dependency, is less sedating than benzodiazepines, and tolerance does not occur at therapeutic doses. It is the therapeutic lag in efficacy of 2 to 3 weeks that has limited the use of buspirone. It has had variable and sometimes disappointing results in clinical practice, particularly when used in patients with prior exposure to benzodiazepines.[36]

Monoamine oxidase inhibitors (MAOIs) demonstrate high effectiveness in the treatment of social phobia, panic, generalized anxiety disorders, OCD, and comorbid conditions (e.g., atypical depression). MAOIs (phenelzine and tranylcypromine) may be difficult to tolerate and require discipline and strict dietary restrictions and thus are rarely appropriate in the emergency setting.

Tricyclic antidepressants (TCAs) are effective for panic disorders and generalized anxiety disorders but are ineffective for social phobias and, with the exception of clomipramine, are largely ineffective for OCD as well. TCAs have been used effectively for depressive and anxiety symptoms associated with post-traumatic stress disorder. TCAs include imipramine, nortriptyline, desipramine, amitriptyline, and doxepin. The TCAs have been supplanted by the SSRIs as first-line interventions for the treatment of anxiety and depressive disorders.[37]

Patients with endogenous anxiety (panic attacks with or without agoraphobia) should be referred to a psychiatrist to

Table 110-1 Pharmacotherapy for Anxiety Disorders

	SSRIs	TCAs	MAOIs	BDZs	BUSPIRONE	CBT
Panic disorder	+	+	+	+	–	+
GAD	+	+	+	+	+	+
Social phobia	+	–	+	+	–	+
Specific phobia	–	–	–	+/–	–	+
PTSD	+	+/–	+	+/–	–	+
OCD	+	–*	+	+/–†	+/–†	+

*Clomipramine is effective.
†Used adjunctively with serotonergic antidepressant.
BDZs, benzodiazepines; CBT, cognitive-behavioral therapy; GAD, generalized anxiety disorder; MAOIs, monoamine oxidase inhibitors; OCD, obsessive-compulsive disorder; PTSD, post-traumatic stress disorder; SSRIs, selective serotonin-reuptake inhibitors; TCAs, tricyclic antidepressants.

establish a good therapeutic relationship before using anxiolytic medication. Benzodiazepines, tricyclics, SSRIs, and MAOIs are safe and effective in endogenously anxious patients who are under psychiatric care (Table 110-1). Recurrence rates of panic attacks are high when drug therapy is discontinued.[8]

Nonpharmacologic Therapy

Psychotherapies may be helpful for individuals whose psychological makeup, coping style, interpersonal dynamics, and situational stressors contribute to their pathologic anxiety. The use of supportive, insight-oriented family is helpful when these factors appear prominently in the patient's presentation.[8]

Cognitive-behavioral therapy is predicated on the theory that the distress and impairment associated with anxiety and panic are mediated by maladaptive cognitive responses that promote anxiety and avoidance. The core components of cognitive-behavioral therapy for panic disorder include correction of cognitive misperceptions and overreactions to anxiety symptoms, breathing retraining, muscle relaxation, as well as exposure and desensitization to phobic situations. Cognitive-behavioral therapy is very effective, but requires commitment from the patient.[8,9]

Meditation (e.g., Zen, yoga, transcendental) has been proposed by many authorities, but little clinical data support its efficacy in anxiety disorders. *Biofeedback* appears promising for the treatment of generalized anxiety disorder. *Hypnotic suggestion* may be effective because anxious patients tend to be cognitively scattered, unable to focus their attention, and highly suggestible. A hypnotic state can often be induced by certain stimuli.[38]

These nonpharmacologic techniques take anxious patients out of the future, about which they are frightened, and place them into the present. These techniques should be reinforced by the development of a physically and psychologically healthy lifestyle. A significant social support system not only protects against vulnerability to illness but also is highly anxiolytic. Regular exercise (e.g., dancing, swimming, bicycling, walking, jogging) also promotes tranquility. Encouraging activity that focuses on hand-eye-ear coordination (e.g., painting, playing keyboard, needlework) helps anxious patients regain and maintain control by bringing them into the present.[1]

DISPOSITION

Many patients with anxiety-related symptoms can be effectively treated in the ED. The emergency physician can proceed with the following general measures:

1. Rule out organic illnesses as cause of anxiety.
2. Evaluate for substance abuse and medications associated with anxiety.
3. Determine whether anxiety is endogenous or exogenous.
4. Clarify what is currently frightening the patient.
5. Evaluate the patient's capacity for self-awareness.
6. Assess techniques that have worked in the past.
7. Support coping skills.
8. Give the patient as much control over the care plan as feasible.
9. Select patients to start on a short course of benzodiazepines and educate patients about treatment.
10. Apply adjunctive techniques as appropriate for the patient's personality and the physician's preference (e.g., hypnotic suggestion, breathing exercises).

Patients with a panic disorder associated with suicidal or homicidal ideation or with severe depression require urgent psychiatric attention and admission to the hospital. Other patients with suspected endogenous or severe exogenous anxiety disorders should be referred for psychiatric evaluation. The Anxiety Disorders Association of America can be contacted (240-485-1001) for a national registry of clinicians and treatment programs specializing in anxiety disorders or can be found online at www.adaa.org.

KEY CONCEPTS

- Anxiety may accompany the onset of serious disease, may have significant metabolic demands, and may cause a marginally compensated organ system to fail.
- As many as 42% of patients thought to have anxiety disorders are later found to have organic disease.
- Anxiety caused by physical illness is usually suggested by the patient's physical findings but may require adjunctive testing.
- Anxiety affects at least 10% of elderly patients.
- Intravenous medication may be necessary for patients who are a significant threat to themselves or others and for anxious patients with significant medical illness.
- Limited benzodiazepine therapy may be helpful for select patients with exogenous anxiety.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 111 Somatoform Disorders

Adria O. Winter and Thomas B. Purcell

BACKGROUND

Occasionally patients present to the emergency department (ED) with a myriad of physical symptoms but no apparent physical disease. This presents a vexing conundrum for the physicians who are wary of missing subtle presentations of physical disease. Even when a somatoform disorder is strongly suspected, emergency physicians are reluctant to attribute physical complaints to functional etiologies.[1]

In one study, 20% of 1500 consecutive patient visits to primary care physicians involved somatization.[2] The prevalence of somatization has risen over the past 30 to 40 years, possibly because of a general decline of patients' tolerance for mild and self-limited ailments.[3,4]

It is not unusual for physicians to feel that patients with somatoform disorders have nonlegitimate disturbances, because their presentation and diagnosis are more generally felt to be the province of psychiatry and not emergency medicine. Nevertheless, proper diagnosis and treatment of patients' somatoform disorders is essential, as misidentification and mismanagement unnecessarily prolongs patients' distress and adds to the overall burden on the health care delivery system.

CLINICAL FEATURES

Somatization refers to a tendency to experience and communicate psychological distress as physical symptoms in the absence of identifiable pathology.[5,6] Patients with somatization disorders seek medical attention because they are convinced that their symptoms reflect real physical disease.[7–11] In direct contrast to malingering and factitious disorder, the symptoms are neither feigned nor under the voluntary control of the patient.[12,13] Somatization is most often associated with concurrent depressive and anxiety disorders.[14]

The term *somatoform disorders* embraces all disorders that have somatization as a common factor. In some cases, a demonstrable physical disorder does exist, often iatrogenic, but the complaints are out of proportion to the physical findings.[8] Almost any complaint involving any body system may occur, sometimes suggesting fashionable diseases recently popularized by the media.[11] For example, the environmental somatization syndrome refers to individuals convinced that their symptoms are caused by exposure to chemical or physical components of their environment, such as poisonous substances, electromagnetic fields, or ergonomic stress attributed to repetitive movements.[15] In general, it is the multiplicity of symptoms, rather than the specific symptom, that is most indicative of somatization.[16,17] In women with more than five and in men with more than three unexplained somatic complaints, the likelihood of a diagnosable psychiatric disorder doubles.[16,18,19] Certain categories of patients, such as women with chronic pelvic pain, have a high rate of sexual or physical abuse in childhood.[20] Somatizers have difficulty describing their feelings in words, a phenomenon termed alexithymia ("without words for mood"), resulting in alternative (somatic) forms of expression.[21] They steadfastly insist that their symptoms are caused by serious physical disorders even in the presence of conclusive evidence to the contrary.[8] Somatization may be unconsciously motivated by a desire to assume the "sick role" and seek the privileges afforded to a sick person by society, such as release from normal obligations and absolution from blame for their condition.[21,22]

Individual somatic complaints such as headache, low energy levels, and recurrent abdominal pain are common in children and adolescents in the general population and generally are not associated with significant social or emotional impairment. Pronounced polysymptomatic somatization, although uncommon in this age group, may occur in late childhood or early adolescence, and these patients are at increased risk for later development of major depression, anxiety disorders, panic attacks, and drug and alcohol abuse.[23,24] Interestingly, most physicians have experienced somatization, since up to 80% of all medical students become convinced they have a disease.[25]

The somatoform disorders were introduced in the *Diagnostic and Statistical Manual of Mental Disorders,* 3rd edition (DSM-III), and updated in DSM-IV as the initial classification of the "hysterical" and "hypochondriacal" neuroses and then their updated conceptualization. There is ongoing controversy whether the somatoform disorders require a reclassification since the diagnosis does not explain the etiology, nor does it predict treatment response.[26]

The somatoform disorders may be subdivided into four specific disorders, each different in terms of clinical presentation and management: (1) somatization disorder, (2) conversion disorder, (3) pain disorder, and (4) hypochondriasis.

Somatization Disorder

Historically referred to as hysteria and neurasthenia, somatization disorder was given the eponym Briquet's syndrome by Guze in 1975 to avoid the pejorative implications associated with the traditional terms.[27,28] The malady is chronic or

BOX 111-1 Criteria for the Diagnosis of Somatization Disorder

1. There must be a history of medically unexplained physical symptoms beginning before the age of 30 years.
2. A history of all of the following:
   a. Pain related to at least four different sites (e.g., head, abdomen, back, joints, chest) or functions (e.g., during menstruation, during urination)
   b. At least two gastrointestinal symptoms other than pain
   c. At least one sexual or reproductive symptom other than pain (e.g., sexual indifference, irregular menses)
   d. At least one symptom or deficit suggesting a neurologic condition not limited to pain (e.g., paralysis, lump in the throat, blindness)
3. Either the above symptoms must not be explainable by any known medical condition or, when there is a related general medical condition, the complaints or impairment must be out of proportion to what might be reasonably expected.
4. The symptoms must not be intentionally produced or feigned.

repetitive, dating from young adulthood, with numerous physical symptoms and complaints involving a variety of organ systems but few or no physical findings to explain those symptoms.[29–32]

The diagnosis of somatization disorder requires several criteria (Box 111-1).[12] This diagnosis is rarely made in the ED, even though it may be suspected, because the proper investigation of this disorder involves time-consuming interviews and may require four to six visits before the establishment of a definitive diagnosis. Many patients do not meet the criteria for a strict diagnosis of somatization disorder yet still have considerable functional impairment, psychological distress, and excess health care utilization.[1,33] A short list of symptoms provides a rapid screen for this disorder.[34] The seven symptoms that best discriminate between patients with and without somatization disorder are (1) dysmenorrhea, (2) the sensation of a "lump" in the throat, (3) vomiting, (4) shortness of breath, (5) burning in the sex organs, (6) painful extremities, and (7) amnesia lasting hours to days. Among patients displaying at least two of these symptoms, the diagnosis of somatization disorder is correctly predicted with a sensitivity of 93% and a specificity of 59%. When four or more of these seven symptoms are present, the specificity rises to 100%. Although this screening may identify patients at high risk for somatization disorder, such patients should still be evaluated thoroughly to confirm the diagnosis and exclude organic disease.

True somatization disorder is relatively uncommon, having a prevalence of 0.06 to 2% among the general population and up to 9% among hospitalized patients.[7,12,19,34] It tends to run in families and is rarely diagnosed in men,[9,10,12,35,36] although in some cultures the prevalence in men and women may be the same.[19] The typical patient is a woman in her 40s who has a 25- to 30-year history of multiple vague complaints, usually headache, dizziness, nausea and vomiting, syncope, abdominal pain, bowel trouble, fatigue, palpitations, dyspareunia, and dysmenorrhea.[20,32,36,37] Symptoms usually date back to the patient's teens and 20s, with menstrual complaints being common in these age groups.[7,12,32]

Only 33% of patients recover during 10- to 20-year follow-up,[38] and new symptoms requiring medical attention tend to surface at least every year.[7] Despite a "lifetime of suffering," the life span of these patients is normal.[39]

Somatization disorder is associated with lower socioeconomic groups, alcoholism and other addictions,[13,36,40] and poor education; fewer than 25% graduate from high school.[19,26] Many have occupational, interpersonal, and marital problems.[7,36]

The health care utilization and functional impairment of these patients are astounding. Expenditures for physician services are 14 times greater and overall health care expenditures nine times greater than for unaffected patients. The typical patient spends 7 days in the hospital each year and 7 days sick in bed each month (compared with less than a half-day for a control population). More than 82% stop work because of their health.[36] When the diagnosis is recognized, however, medical resource use among these patients tends to normalize.[41]

Patients with somatization disorder describe their symptoms in dramatic exaggerated fashion using colorful language, with great detail about how their lives have been disrupted. They usually admit to being sickly throughout life. Although extensive, their narrative suggests no clear diagnostic constellation. Patients offer detailed accounts of multiple prior medical encounters, termed "doctor shopping," and often display multiple abdominal scars because they undergo two to three times the number of surgeries of other patients.[1,36] Their medical records have numerous and exotic test results, and they faithfully consume an impressive array of medications acquired from multiple primary physicians and specialists. They report allergies to a comprehensive list of antibiotics and analgesics. These patients are often emotional and vain, exhibit limited interpersonal skills, and have few close personal relationships.[32] They are typically dependent and highly manipulative.

Of these patients, 68% fulfill the criteria for histrionic personality disorder.[42] Somatization disorder may be closely related to some anxiety and affective disorders; more than 80% of patients with somatization disorder report a lifetime history of major depression and 68% a history of anxiety.[36,43–45] These individuals may threaten or attempt suicide. Completed suicide is usually associated with psychoactive substance abuse.[7] Women with this disorder tend to marry men with antisocial personalities. The husband is often overly solicitous, demanding that his wife receive many clinical studies and quick, decisive action. Predictably, he usually shows some degree of dissatisfaction with physicians in general.[32]

Patients who do not meet the full criteria of somatization disorder but have suggestive symptoms for 6 months or longer are classified as having undifferentiated somatoform disorder, which is treated similarly to somatization disorder.[12]

Conversion Disorder

Also known as hysterical neurosis, conversion type, the rare conversion disorder is characterized by the sudden dramatic onset of a single symptom, typically simulating some nonpainful neurologic disorder for which there is no pathophysiologic or anatomic explanation.[7,46] In contrast to somatization disorder, conversion disorder typically revolves around a single physiologically impossible condition. The symptoms, generally conforming to the patient's own idiosyncratic ideas about illness, are not under the patient's voluntary control. Some symptoms provide gratification for unconscious dependency needs; other symptoms provide escape from painful external emotional stimuli (e.g., hysterical paralysis in battle).[40,41] Although the symptoms may have a symbolic relationship to the precipitating factors, this is often not the case.[31] The most common conversion symptoms are voluntary motor or

BOX 111-2 PRESENTATIONS OF CONVERSION DISORDER

1. Motor disturbances:
   a. Tremors (that worsen when attention is called to the movements)
   b. Seizures (wild, thrashing, writhing, often mimicking copulation)
   c. Paralysis or paresis (often a monoplegia, stocking-glove weakness, with normal reflexes and limb circumferences)
   d. Aphonia (wherein the patient can whisper and cough normally and vocal cords move normally with respiration)
   e. Coordination disturbances
2. Sensory disturbances:
   a. Anesthesia (the patient may not find this symptom disturbing)
   b. Blindness and tunnel vision[16,17]
3. An occasional patient may present with other nonneurologic symptoms such as vomiting or pseudocyesis.[13]

sensory functions and are therefore called pseudoneurologic (Box 111-2).[12] The most common ED presentations are pseudoseizures, syncope or coma, and paralysis or other movement disorders.[47]

Most patients are women, except for those in military service and industrial accidents.[12,41] Conversion disorder typically appears in adolescence and early adulthood and is more common among lower socioeconomic groups. Symptoms tend to be of sudden onset, waxing and waning in response to environmental stresses.[7,9,10,31,40] The history may show similar symptoms in the past, as well as anxiety, depression, phobias, and sexual disturbances.[31] Up to 29% of patients have a history of past psychiatric illness.[47] Patients describe their symptoms with a lack of appropriate concern about their profound bodily dysfunction, termed *la belle indifference*, although, this presentation is not necessary for diagnosis of conversion disorder, since it may be absent in over 50% of patients and is also seen in organic disease.[48]

Pain Disorder

Also termed somatoform pain disorder,[7] this condition is similar to conversion disorder in that stressful events are translated into somatic symptoms. The primary and often exclusive symptom is distressful pain that (1) is not intentionally feigned, (2) is persistent in nature, (3) limits daily function, (4) involves one or more organ systems, and (5) cannot be pathophysiologically explained.[12,13,31] The pain most frequently occurs in the face, low back, neck, or pelvic area and causes significant functional impairment, ultimately becoming a major focus in the patient's life.[4,9,10,12,20] One half of all patients have some precipitating traumatic event at the outset (e.g., motor vehicle accident, industrial injury).[7] Chronic pain behavior patterns are typically fixed within 3 months after the onset of symptoms, and patients who do not resume normal activities within 2 weeks deserve reevaluation and a careful psychosocial review.[4] Associated features include frequent visits to physicians despite medical reassurance, excessive use of analgesics, requests for surgery, and eventually the role of permanent invalid after the pain has forced the patient to discontinue gainful employment.[4,7]

Onset occurs most often in the 30- to 50-year-old age group but can occur at any age. Symptoms such as headaches or musculoskeletal pain are more likely in women.[7,9,12] The pain often approximates real pain from physical disease that the patient has experienced in the past (e.g., the patient with a history of pancreatitis may develop recurrent epigastric pain when stressed). Frequent surgical intervention may produce multiple and genuine iatrogenic pain symptoms.[20]

Hypochondriasis

The term *hypochondriasis* comes from *regio hypochondriaca*, a Latin term referring to the upper lateral regions of the abdomen inferior to the costal cartilages, especially the area of the spleen, which early physicians presumed to be the seat of this disorder. Hypochondriasis has four characteristics: (1) physical symptoms disproportionate to demonstrable organic disease; (2) a fear of disease and a conviction that one is sick, leading to "illness-claiming behavior" (a compulsive insistence on being considered a physical cripple); (3) a preoccupation with one's own body; and (4) persistent and unsatisfying pursuit of medical care (doctor shopping) with a history of numerous procedures and surgeries and eventual return of symptoms.[31]

These unfortunate patients manifest both a heightened awareness and an unrealistic interpretation of normal physical signs or sensations, such as bowel habits, heartbeat, sweating, or peristalsis. These sensations are perceived as abnormal, noxious, and alarming, a phenomenon known as amplification.[35] These aberrant perceptions result in a chronic morbid preoccupation with bodily functions and a lingering fear of having a disease despite medical reassurance.[7,12,13,31] A distinguishing feature of hypochondriasis is that the patient's symptoms do exist and often are confirmed by physical examination, but the patient exaggerates and misinterprets them.

Hypochondriasis is relatively common. Its prevalence in general medical practice ranges from 4 to 9%.[12] It has a peak incidence among men in their 30s and women in their 40s, affecting men and women equally.[9,10,21] Hypochondriacs have an increased sense of responsibility for, and place high value on, their personal health and physical appearance. They have an acute sense of body vulnerability and a heightened aversion to death and aging.[42] There is a strong correlation of hypochondriasis with major depression.[45] A milder form of this disorder may be an exaggerated interest in bodily function and health ("health nuts").[49]

The hypochondriac complains at length and in detail, using medical jargon. The complaints focus on the head, neck, and trunk, often in the form of pain. Hypochondriacs often believe they have lost control of their lives and have been described as "experts at defeating doctors in order to feel more powerful."[31] Consequently, physicians perceive hypochondriacal patients as more angry and hostile than other patients.[50] The diagnosis may be suggested when the physician feels "frustration, helplessness, or anger associated with a wish to be rid of the patient."[22,31]

Reactive hypochondriasis, or transient hypochondriasis, is an acute response to a psychosocial stress or life crisis, such as an acute myocardial infarction, terminal illness, or recent loss of a family member. In contrast to true hypochondriasis, this form is reversible and does respond to reassurance.[31,49]

DIAGNOSTIC STRATEGIES

Physicians are generally unwilling to consider somatoform disorders in their initial differential diagnosis. The often dramatic presentation of symptoms creates a sense of urgency to take action, a fear of undiscovered medical illness, and a subsequent exhaustive evaluation of every complaint. Repetitive or extensive diagnostic testing rarely excludes organic disease

with absolute certainty, however, and may yield false-positive results, prompting further testing. Somatizing patients are more likely to have morbidity from repeated or invasive evaluations than from undiagnosed organic disease.[1]

Yielding to the temptation to institute further diagnostic procedures or interventions typically leads to a temporary improvement, closely followed by renewal of symptoms and mutual physician-patient disappointment. This gives rise to inevitable dissatisfaction of the patient with the physician and vice versa, leading to an unsatisfactory parting of ways and a perpetuation of the doctor-shopping cycle.[51]

Managed care and capitated reimbursement have created an additional quandary by restricting the supply of care in a time of rising demand for care from patients whose symptoms are relatively minor.[3,16] The most effective diagnostic tool with somatizers is the interview. Evaluation starts with a thorough but focused history and, if available, a review of the patient's medical record. This is followed by a careful problem-oriented physical examination, with meticulous inspection of the area of complaint, and simple or routine diagnostic testing, when appropriate, until attaining a reasonable level of diagnostic certainty.[16] Further investigations or hospital admissions should be initiated solely on the basis of new objective signs of disease and only after confirming that the tests have not been performed. One rule of thumb in ordering laboratory tests is to do exactly what would be done if the patient were not a somatizer.[16,22] However, the clinician must resist the impassioned entreaties of the patient when it is clear that further complex or hazardous studies are unlikely to be productive.[9,10,16,52]

Multiple medical and surgical consultations generally prove counterproductive. Hypochondriacs perceive this as a test of their claim to illness and respond simply by propagating and demonstrating symptoms with redoubled zeal.[31]

DIFFERENTIAL CONSIDERATIONS

Distinguishing between the various somatoform disorders is less important than the diagnosis of treatable organic disease or the detection of anxiety and depression, which are both more common and more likely to respond to treatment. Coexistent depression or anxiety disorder should always be considered.[44,53] Patients who have a relatively recent onset of somatization are more likely than patients with long-standing complaints to be exhibiting subtle signs of acute psychosis, organic brain syndrome, grief reaction, depression, or anxiety.

Depression

Approximately 50 to 70% of depressed patients consult their physician for various somatic complaints.[54] Depressed patients may not be aware of a depressed mood or may feel their depression is secondary to the somatic symptoms.[53] As a result, depression is the psychiatric disorder most often mistaken for somatoform disorder.[13]

Although somatoform disorders often coexist with depression, the two conditions must be distinguished. Depression is worse in the morning, better at night, and often associated with a positive family history. The patient is reluctant to describe the symptoms and has vegetative signs of depression (e.g., sleep disturbances, decreased appetite with weight loss).[52,55] Pain is a common symptom, particularly headache and pain involving the back, chest, or pelvic area.[53,54] Somatoform disorders, on the other hand, are worse at the end of the day, and patients have a marked propensity to discuss their symptoms, usually do not have a family history, and show no vegetative signs.[31]

In general, elderly patients do not have more physical symptoms than younger patients. Multiple somatic complaints should not be dismissed as a normal consequence of aging but rather considered a symptom of another underlying problem, usually depression or medical disease. Older patients may communicate somatic complaints as a way of expressing anger and provoking guilt among family members.[21]

Anxiety

Patients with acute anxiety often hyperventilate and frequently exhibit physical signs of increased sympathetic activity. They may be hypervigilant and irritable and may show signs of muscular tension.[31] They may offer a history of excessive worrying about their health, feeling "on edge" or irritable, having difficulty relaxing, or sleeping poorly or having trouble falling asleep and report symptoms of headache, tingling, dizzy spells, and diarrhea.[55] Patients with somatoform disorders have a high prevalence of anxiety disorders, especially generalized anxiety disorder.[56]

Physical Illness

When patients with somatization disorder develop true organic disease, they present similar to other patients, with specific complaints, clear chronology, and objective findings that should be appropriately investigated.[32] Unfortunately, subjective reports of distress are often not dependable in these patients, and the physician must rely on more objective evidence, including the physical examination and routine laboratory tests.[22] Multiple physical symptoms starting late in life are frequently the result of physical disease.[7,12] In addition, patients who have a short duration of symptoms are more likely to have organic disease.

Although any organic disease may be mistaken for a somatoform disorder, the occasionally bizarre and atypical manifestations and presentations of the disorders listed in Box 111-3 merit special consideration.[13]

Factitious Disease and Malingering

Patients with somatoform disorders are not deliberately feigning illness; they are exhibiting the result of an unconscious behavior modification. For a subset of patients, they have unintentionally secured secondary gain from the sick role in the form of sympathy, encouragement, attention, support, and relief from responsibilities and challenges without significant loss of self-esteem.[49] In contrast, factitious disorder and malingering are both characterized by the intentional and conscious

BOX 111-3 ORGANIC DISEASES THAT MAY BE MISTAKEN FOR SOMATOFORM DISORDERS

Endocrine disorders: hyperparathyroidism, thyroid disorders, Addison's disease, insulinoma, panhypopituitarism
Poisonings: botulism, carbon monoxide, heavy metals
Porphyria
Multiple sclerosis
Systemic lupus erythematosus
Wilson's disease
Myasthenia gravis
Guillain-Barré syndrome
Uremia

simulation or production of disease (see Chapter 112). Because such deception is difficult to uncover in the ED, these patients are often mistaken for having a somatoform disorder.

MANAGEMENT

The symptoms of conversion disorder may provide a protective coping value for the patient, and the physician should be cautious about removing them without first providing adequate psychological support and treatment. Otherwise, new symptoms may arise to replace previous ones. The external precipitating stress or cause of anxiety should be removed if possible. These patients require psychiatric evaluation and management,[9,10] and psychiatric consultation in the ED can be beneficial.[47]

Recurrence is common, but the prognosis associated with an individual episode of conversion disorder is good and the likelihood of recovery from symptoms exceeds that of other somatoform disorders.[12,21,41] Factors associated with a good prognosis include (1) good premorbid health, (2) absence of organic illness or concomitant major psychiatric syndromes, (3) acute and recent onset, (4) definite precipitation by a stressful event, and (5) presenting symptoms of paralysis, aphonia, or blindness.[12]

Reassurance

Young patients with no underlying medical or psychiatric illnesses who present with somatization in response to a clear psychosocial stress can often be reassured successfully with an appropriate explanation of their symptoms. Patients with chronic somatization, however, perceive this as an official denial of their sick role and are almost invariably unwilling to accept reassurance. Because they desire the acknowledgment and recognition that come with the designation of illness, which they feel is rightfully theirs, they are disappointed when no pathologic condition is discovered. Conversely, they are elated when given a diagnosis, but they resist recovery because subconsciously the "specter of cure" poses a threat to their sick role.[49] Accordingly, attempts to cure the condition are countered with side effects, allergic reactions, and new symptoms. Such patients require another management strategy.

Legitimization of Symptoms

Most patients with chronic somatization interpret a psychological explanation for their symptoms as an accusation of lying or feeblemindedness. It is important to convince them that the physician believes in their symptoms and will not try to "talk them out of it." The priority is to listen and truly understand what the patient is feeling and trying to convey. Suffering is always a subjective phenomenon and, in that sense, is genuine in these patients.[22] The physician should convey empathy for the patient's physical discomfort. If the physician acknowledges the legitimacy of the claim to illness and assures the somatizer of ongoing care, limits may be set on the patient's illness behavior.[9,10,16,31]

Patients should be allowed to tell their story without interruption. They should be told that they have an illness that causes them to experience many symptoms but that these symptoms will not lead to medical deterioration.[1,57] The physician should offer only guarded projections regarding chances for complete "cure" of the condition. Ironically, this may be better received by these patients than overly optimistic assurances because the former serves to safeguard their sick role and shifts the physician away from an adversarial position.[16,52]

Diagnosis

Diagnostic labels are of critical importance for somatizers, but the precise meaning of the term should be clarified for the patient to avoid misinterpretation. Explanations for symptoms that incorporate somatic responses and descriptions such as hyperventilation, tension headache, muscle tension, muscle strain, chest wall muscle spasm, or stress may be better accepted than purely psychiatric diagnoses. This reassures the patient that the physician shares the belief that the symptoms result from socially acceptable ailments while allowing more in-depth explanations that incorporate the relationship of bodily function to psychological stress. This, in turn, serves as a preparation for future psychiatric consultation or psychotropic medication.[8–10,52]

At times, the best approach may be to share the diagnostic uncertainty with the patient, using such terms as "atypical pain" or "multiple complaints following injury." On a broader scale, managed care organizations must be encouraged to educate their enrollees about the process of somatization, the negative side effects of medications and other interventions, and the range of bodily symptoms in healthy people.[3]

Medications

Patients with somatoform disorder have a high affinity for medications and are reluctant to discontinue drugs, even those with no benefit.[31] Physicians should avoid drugs that produce an abstinence syndrome or dependence and those that cannot be safely continued indefinitely.[32] Pain medications, if given, should be prescribed for regular intervals, not "as needed."[31] Patients with somatoform pain disorder may benefit significantly from treatment with antidepressants, including tricyclic antidepressants.[58] Patients with somatization disorder with major depression may also improve with pharmacologic management of the depression.[45]

Therapy should be kept simple and limited to exercise, diet, physical therapy, and vitamins when possible.[52] Hospitalization and narcotics should be avoided. Benign remedies, such as lotions, nutritional supplements, elastic bandages, and heating pads, may be helpful.[16,22] Drug regimens should be simplified and only the most distressing symptoms addressed. Before starting any type of symptomatic drug treatment, specific target symptoms should be identified. The goal is to restore function and to make the target symptoms tolerable, not to remove them completely. If ED patients request an increase in dosage or a stronger medication, they should be told to review their medications with their regular physician before any changes are made. Insistent patients should be informed that long-term opioid use is associated with significant adverse effects, especially constipation, sedation, impaired cognition, and progressive development of tolerance and addiction.[22]

Mental Health Consultation

Patients with somatoform disorders have difficulty confronting their own emotions, view psychiatric evaluation as threatening to their sick role, and take offense at any suggestion that their fears or beliefs may be unwarranted.[7,11] They usually resist psychiatric consultation and interpret it as an attempt to be "dumped on the psychiatrist."[31] Nevertheless, psychiatric consultation may be appropriate (1) to confirm the diagnosis or discuss medications, (2) when the patient has coexistent manifestations of chronic depression or psychosis, (3) when symptoms suddenly change or become bizarre, (4) when the patient expresses suicidal ideation or severely disruptive behavior, (5)

when current management is not working, or (6) when the patient requests psychotherapy.[9,10,31] Favorable prognostic indicators include youth, acute onset, concurrent anxiety or depression, and limited medical comorbidity.[59]

Many patients accept psychological treatment under the rubric of "stress management" as long as it targets physical symptoms and somatic distress.[16] Group therapy techniques presented as education rather than psychotherapy have had some limited success.[60] Patients should be reassured that their relationship with the primary physician will continue to avoid the false interpretation that the referral is an abandonment.

Physician Attitudes

The key to diagnosing and treating patients with somatoform disorder is effective and appropriate communication skills on the part of the physician. Somatizing patients can present a challenge because it is tempting to point out to them that there is nothing "wrong" with them and that their symptoms need no treatment. Physicians caring for these patients predictably react with feelings of uncertainty, helplessness, anger, or guilt when they can find no physiologic pathology to explain the patient's distress. Patients with somatoform disorders can become as frustrated with their physician as the physician is with them. It is common for patients with a somatoform disorder to be quickly labeled as a "difficult patient" by the physician and staff.[61,62] Unfortunately, the frustration of working with these patients quickly overwhelms the physician's natural tendency towards compassion and can lead to a swift breakdown in communication. Despite the large number of distressing symptoms reported, physicians rarely demonstrate empathy with these patients.[63,64]

Treatment Goals

Somatizing patients, despite lack of objective physiologic pathology, are, in fact, patients who are in need of tangible and effective help. For some, attaining invalid status enables them to be cared for and nurtured. It offers them a sense of self-importance and respect not otherwise available to them, as well as an honorable release from noxious personal and vocational responsibilities and duties.[40] To attempt a cure poses a threat to this role, and unduly positive projections by physicians are therefore understandably met with disappointment, disbelief, and even thinly veiled reproaches regarding their professional competence.[4,16,52] Thus, the goal of therapy must be control of disability and appropriate referrals, rather than cure.[21,59] The course of management most likely to prove successful begins with performing a sympathetic and thorough problem-oriented history and physical examination, then offering the patient the paradoxical reassurance that he or she will probably always be ill. When pain is the dominant feature, the patient should not be promised complete relief; rather, a major task of the patient should be to "learn to live with some pain."[21]

Treatment goals should focus on modification of illness behavior and improvement of functional status.[40] Achievable endpoints include (1) decreased frequency and urgency of medical use, in particular a reduction in ED and unscheduled office visits; (2) avoidance of expensive and hazardous procedures; (3) improved work or school performance; (4) more social activities; and (5) better personal relationships.[9,13,22]

These principles apply equally to pediatric patients with somatoform disorders. Unnecessary tests and procedures, in addition to placing the patient at risk, may encourage somatization. Physician acknowledgment of the patient's suffering and family concerns, a "rehabilitative" approach emphasizing return to normal activities prior to definitive symptom relief, rewarding healthy behavior and discouraging the sick role, assumption by the patient of responsibility for coping with the symptoms, and treatment of coexistent anxiety or depression are the cornerstones of therapy.[24]

Patients with somatoform disorder have been described as the "least insightful, the least introspective and the least cognitively oriented patients one is likely to encounter."[32] Understanding the link between emotional and somatic distress need not be a treatment goal for these patients, and insight-oriented psychotherapy is neither productive nor cost effective.[16,21,22,32] On the other hand, both the physician and the patient must accept fundamental alterations in the traditional paternalistic physician-patient relationship. Increasing responsibility for health and disease management must be incrementally turned over to the somatizing patient.[21]

DISPOSITION

Appropriate psychiatric referrals should be provided for the patient. Outpatient tests or hospitalization should be avoided unless clear objective signs indicate a need for diagnostic investigation or therapeutic intervention.[21,32]

As a rule, management is best carried out by a single primary care physician who becomes the gatekeeper for all medical consultation and care.[8–10,13,16,31,52,59] The patient should be told that no alarming findings have come to light, that further testing and additional medications are not indicated at this time, and that ongoing care and periodic reassessment are indicated and will be arranged. Patients with chronic somatization should initially be seen every 2 to 4 weeks, preferably by their primary care physician, even if their symptoms are stable. The visits should be on a time-contingent, not a need-contingent, basis. For the patient, this severs the association between medical contact and the necessity for worsening or additional symptoms and complaints. It also decreases the patient's fear of abandonment by the physician and permits repeated evaluation for early detection of objective signs of organic disease.[13,21] The patient seems to value the visit to the physician more highly than any treatment.[32]

KEY CONCEPTS

- The behavior of patients with somatoform disorders is unconsciously driven. They are not "faking" the symptoms or their distress.
- Short-term management should include the legitimization of symptoms, communication of compassion, and assurance that ongoing vigilance of the patient's medical condition will be arranged and maintained.
- Long-term cure of somatization disorder is unlikely. However, a steady state of symptom coping with improved function is an achievable goal. This can be done only in the primary care setting, not in the ED.
- Laboratory tests, specialty consultations, initiation of medications, and hospitalization should be avoided (unless new objective clinical findings are found).
- Care decisions should be deferred to the patient's primary care physician when possible.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 112

Factitious Disorders and Malingering

Jag S. Heer and Thomas B. Purcell

PERSPECTIVE

Patients may present to the emergency department with symptoms that are intentionally produced or simulated. The inducements that generate this behavior define two distinct varieties: factitious disorders and malingering.

Factitious disorders are characterized by symptoms or signs that are intentionally produced or feigned by the patient in the absence of apparent external incentives.[1,2] Factitious disorders have been present throughout history. In the second century, Galen described Roman patients inducing and feigning vomiting and rectal bleeding.[3] Hector Gavin sought to categorize this behavior in 1834.[3] These patients constitute approximately 1% of general psychiatric referrals, but this percentage is somewhat lower than that seen in emergency medicine because these patients rarely accept psychiatric treatment.[1,4] Of patients referred to infectious disease specialists for fever of unknown origin, 9.3% of the disorders are factitious.[5] Between 5 and 20% of patients followed in epilepsy clinics have psychogenic seizures, and in some primary care settings the number reaches 44%.[6] Among patients submitting kidney stones for analysis, up to 3.5% have been found to be fraudulent.[7]

Munchausen syndrome, the most dramatic and exasperating of the factitious disorders, was originally described in 1951.[8] This fortunately rare syndrome takes its name from Baron Karl F. von Munchausen (1720–1797), a revered German military officer and noted raconteur who had his embellished life stories stolen and parodied in a 1785 pamphlet.[3] The diagnosis is appropriate for only 10 to 20% of patients with factitious disorders.[1,9] Other names applied include the "hospital hobo syndrome" (patients wander from hospital to hospital seeking admission), peregrinating (wandering) problem patients, hospital addict, polysurgical addiction, laparotomaphilia migrans, Kopenickades syndrome, Ahasuerus syndrome, and hospital vagrant.[4,10,11]

Munchausen syndrome by proxy (MSBP) is an especially pernicious variant that involves the simulation or production of factitious disease in children by a parent or caregiver, and was first described in 1977.[12] There are approximately 1200 estimated new cases of MSBP per year in the United States.[3] The condition excludes straightforward physical abuse or neglect and simple failure to thrive; mere lying to cover up physical abuse is not MSBP.[13,14] The key discriminator is motive: the mother is making the child ill so that she can vicariously assume the sick role with all its benefits. The mortality rate from MSBP is 9 to 31%.[14,15] Children who die are generally younger than 3 years, and the most frequent causes of death are suffocation and poisoning.[14] Permanent disfigurement or permanent impairment of function resulting directly from induced disease or indirectly from invasive procedures, multiple medications, or major surgery occurs in at least 8% of these children.[14,16] Other names applied include Polle's syndrome (Polle was a child of Baron Munchausen who died mysteriously),[3,10] factitious disorder by proxy,[17] pediatric condition falsification,[18] and Meadow's syndrome.[2]

Malingering is the simulation of disease by the intentional production of false or grossly exaggerated physical or psychological symptoms, motivated by external incentives such as avoiding military conscription or duty, avoiding work, obtaining financial compensation, evading criminal prosecution, obtaining drugs, gaining hospital admission (for the purpose of obtaining free room and board), or securing better living conditions.[2,19–21] The most common goal among such "patients" presenting to the emergency department is obtaining drugs, whereas in the office or clinic the gain is more commonly insurance payments or industrial injury settlements.[22] Because of underreporting, the true incidence of malingering is difficult to gauge, but estimates include a 1% incidence among mental health patients in civilian clinical practice, 5% in the military, and as high as 10 to 20% among patients presenting in a litigious context.[20] A survey by the American Board of Clinical Neuropsychology members revealed the most likely conditions to be feigned were mild head injury, fibromyalgia, chronic fatigue syndrome, and chronic pain.[23]

CLINICAL FEATURES

Factitious Disorders

With a factitious disorder, the production of symptoms and signs is compulsive in that the patient is unable to refrain from the behavior even when its risks are known. The behavior is voluntary only in the sense that it is deliberate and purposeful (intentional) but not in the sense that the acts can be fully controlled.[2] The underlying motivation for producing these deceptions, securing the sick role, is primarily unconscious.[9,24,25] Individuals who readily admit that they have produced their own injuries (e.g., self-mutilation) are not included in the category of factitious disorders.[17] Presentations may be acute, in response to an identifiable recent psychosocial stress (termination of romantic relationship, threats to self-esteem), or a chronic life pattern, reflective of the way the person deals with

life in general.[26] The symptoms involved may be either psychological or physical.

Psychological Symptoms

This disorder is the intentional production or feigning of psychological (often psychotic) symptoms suggestive of a mental disorder. Stimulants may be used to induce restlessness or insomnia, hallucinogens to create altered levels of consciousness, and hypnotics to produce lethargy. This psychological factitious condition is less common than factitious disorders with physical symptoms and is almost always superimposed on a severe personality disorder.[2,17]

Physical Symptoms

The intentional production of physical symptoms may take the form of fabricating symptoms without signs (e.g., feigning abdominal pain), simulation of signs suggesting illness (e.g., fraudulent pyuria, induced anemia), self-inflicted pathology (e.g., producing abscesses by injecting contaminated material under the skin), or genuine complications from the intentional misuse of medications (e.g., diuretics, hypoglycemic agents).[21] These patients are predominantly unmarried women younger than 40 years. They typically accept their illness with few complaints and are generally well-educated, responsible workers or students with moral attitudes and otherwise conscientious behavior.[21,27,28] Many are in health care occupations, including nurses, aides, and physicians.

These patients are willing to undergo incredible hardship, limb amputation, organ loss, and even death to perpetuate the masquerade.[21] Although multiple hospitalizations often lead to iatrogenic physical conditions, such as postoperative pain syndromes and drug addictions, patients continue to crave hospitalization for its own sake. They typically have a fragile and fragmented self-image and are susceptible to psychotic, and even suicidal, episodes.[27] Interactions with the health care system and relationships with caregivers provide the needed structure that stabilizes the patients' sense of self. The hospital may be perceived as a refuge, sanctuary, or womb-like environment.[4,21,24,29] Some patients are apparently driven by the conviction that they have a real, but as yet undiscovered, illness. Consequently, artificial symptoms are contrived to convince the physician to continue a search for the elusive disease process.[21] Factitious illness behavior has even emerged on the Internet. "Virtual support groups" offering person-to-person communications through chat rooms and bulletin boards have been perpetrated by individuals, under the pretense of illness or personal crisis, for the purpose of extracting attention or sympathy, acting out anger, or exercising control over others.[30]

There has been increasing recognition of factitious illness produced by children (distinct from the MSBP described later). These children, ranging in age from 8 to 18 years, are typically "bland, flat and indifferent during their extensive medical interventions … depressed, socially isolated and often obese."[31] Among the most common presentations are fever without clear etiology, diabetic ketoacidosis, purpura, and recurrent infections. The prognosis is good if identification and psychotherapeutic intervention can be carried out at a young age.[31]

Munchausen Syndrome

The uncommon patient with true Munchausen syndrome has a prolonged pattern of "medical imposture," usually years in duration. The behavior usually begins before age 20 years and is diagnosed between ages 35 and 39. Twice as many men are affected as women.[4,32] Patients' entire adult lives may consist of trying to gain admission to hospitals and then steadfastly resisting discharge. Their career of imposture usually lasts about 9 years but has continued unabated for as long as 50 years.[4] The quest for repeated hospitalizations often takes these patients to numerous and widespread cities, states, and countries.[2]

These individuals see themselves as important people, or at least related to such persons, and their life events are depicted as exceptional.[32] They possess extensive knowledge of medical terminology. Frequently there is a history of genuine disease, and the individual may exhibit objective physical findings.[27]

The symptoms presented are "limited only by the person's medical knowledge, sophistication, and imagination."[2] The alleged illnesses involved have been termed *dilemma diagnoses* in that investigators rarely can totally rule out the disorder, clarify the cause, or prove that it did not exist at one time.[4] Common presentations are those that most reliably result in admission to the hospital, such as abdominal pain, self-injection of a foreign substance,[10,11] feculent urine, bleeding disorders, hemoptysis, paroxysmal headaches, seizures, shortness of breath, asthma with respiratory failure,[4,33] chronic pain,[25] acute cardiovascular symptoms (e.g., chest pain, induced hypertension and syncope),[32] renal colic and spurious urolithiasis,[7] fever of unknown origin (hyperpyrexia figmentatica),[5,11] profound hypoglycemia, and coma with anisocoria.[34] Such self-induced conditions themselves may prove highly injurious or even lethal.[10]

The patient usually presents to the emergency department during evenings or on weekends so as to minimize accessibility to psychiatric consultants, personal physicians, and past medical records.[11,27] In teaching institutions these patients typically present in July, shortly after the change in resident house officers.[4] They relate their history in a precise, dramatic, even intriguing fashion, embellished with flourishes of pathologic lying and self-aggrandizement. Pseudologica fantastica, or pathologic lying, is a distinctive peculiarity of these patients. In a chronic, often lifelong behavior pattern, the patient typically takes a central and heroic role in these tales, which may function as a way to act out fantasy.[35] The history quickly becomes vague and inconsistent, however, when the patient is questioned in detail about medical contacts.[2,29] Attempts to manage the complaint on an outpatient basis are adamantly resisted.[25] Once admitted, the patient initially appeals to the physician's qualities of nurturance and omnipotence, lavishing praise on the caregivers. Behavior rapidly evolves, however, as the patient creates havoc on the ward by insisting on excessive attention while ignoring both hospital rules and the prescribed therapeutic regimen.[2] When the hoax is uncovered and the patient confronted, fear of rejection abruptly changes into rage against the treating physician, closely followed by departure from the hospital against medical advice.[10,11,25]

Munchausen Syndrome by Proxy

The diagnosis of MSBP depends on specific criteria (Box 112-1).[14] The presenting complaints typically evade definitive diagnosis and are refractory to conventional therapy for no apparent reason.[14] The symptoms are usually more than five in number, presented in a confused picture, are unusual or serious, and, by design, are unverifiable. They invariably occur when the mother is alone with the child or otherwise unobserved.[36] In 72 to 95% of cases, simulation or production of illness occurs while the victim is hospitalized.[14]

Simulated illness, faked by the mother without producing direct harm to the child (e.g., adding blood to a urine specimen), is present in 25% of cases. *Produced illness*, which the

BOX 112-1 CRITERIA FOR THE DIAGNOSIS OF MUNCHAUSEN SYNDROME BY PROXY

1. Apparent illness or health-related abnormality that the parent or someone who is in loco parentis has concocted or produced
2. Presentation of the child for medical treatment, usually persistently
3. Failure by the perpetrator to acknowledge the true etiology or the deception
4. Cessation of the acute symptoms and signs of illness when the child is separated from the perpetrator

mother actually inflicts on the child (e.g., injection of feces into an intravenous line), is found in 50% of cases. Both simulated and produced illnesses are found in 25% of cases.[14]

MSBP most commonly arises with factitious bleeding, seizures, central nervous system (CNS) depression, apnea, diarrhea, vomiting, fever, and rash.[14] Reported techniques of simulation or production of disease include administration of drugs or toxins (e.g., chronic arsenic poisoning, ipecac, warfarin, phenolphthalein, hydrocarbons, salt, imipramine, laxatives, CNS depressants), caustics applied to the skin, and nasal aspiration of cooking oil.[12,14–16,27,37] Techniques of asphyxiation include (1) covering the mouth or nose with one or both hands, a cloth, or plastic film and (2) inserting the fingers into the back of the mouth. In such instances, even struggling infants may sustain no cutaneous markings.[38] Cases involving seizures are common and may involve third-party witnesses. On personal questioning, however, these witnesses frequently deny the occurrence of seizure activity.[14]

In a variant of MSBP termed *serial Munchausen syndrome by proxy*, there may be a history of similar strange presentations in multiple siblings, although typically only one child is involved at a time.[15,16,38] In 9% of such cases there is a history of siblings who died under mysterious circumstances.[14]

Perpetrator Characteristics. Ninety-eight percent of perpetrators are biologic mothers from all socioeconomic groups.[14] Many have a background in health professions or social work, features of Munchausen syndrome themselves, or a past history of psychiatric treatment, marital problems, or suicide attempts.[14,15] Depression, anxiety, and somatization are common, but frankly psychotic behavior by the mother is atypical.[14,16] Perpetrators of MSBP have an inherent skill in manipulating health workers and child protection services.[39] They are pleasant, socially adept, cooperative, and appreciative of good medical care. They often display a peculiar eagerness to have invasive procedures performed on their child.[3] They often choose to stay in the hospital with their child, cultivate unusually close relationships with hospital staff, and thrive on the staff's attention.[12–14,16,37] This affable relationship with the medical team rapidly changes to excessive anger and denial when confronted with suspicions.[19]

Most of these mothers have had an abusive experience early in life, and they use the health care system as a means to satisfy personal nurturing demands.[36,40] They often cannot distinguish their needs from the child's and satisfy their own needs first. They derive a sense of purpose from the medical and nursing attention gained when their children are in the hospital.[13,14,16,40] Alternatively, the behavior may enable the mothers to escape from their own physical or psychological illnesses, marital difficulties, or social problems.[36]

Victim Characteristics. Victims of MSBP are equally male and female children. The mean age at diagnosis is 40 months, and the mean duration from the onset of signs and symptoms to diagnosis is 15 months.[14] A known physical illness that explains part of the symptoms is common among these children.[40] Most have a history of significant failure to thrive and have been hospitalized in more than one institution. Delays in many areas of performance and learning, difficulty with family relationships, attention deficit disorder, or clinical depression may coexist.[16] Some of these victims may develop factitious disorder later in life.[3] Victims of MSBP are also found among the elderly population, although this is uncommon.[41]

Malingering

Malingering is frequently found in association with *antisocial personality disorder*. On questioning, malingerers are vague about prior hospitalizations or treatments. The physicians who previously treated them are usually unavailable. At times, malingerers may be careless about their symptoms and abandon them when they believe no one is watching.[27] In some "patients," such as those seeking drugs, homeless persons seeking hospital admission on a cold night, or prisoners wanting a holiday from incarceration, the secondary gain may be clear. In other persons the external incentive may be obscure.

In contrast to the person with factitious disorders, the malingerer prefers *counterfeit mental illness* because it is objectively difficult to verify or disprove. Amnesia is the most common psychological presentation, followed by paranoia, morbid depression, suicidal ideation, and psychosis.[20]

DIAGNOSTIC STRATEGIES

Factitious Disorders

Initial diagnosis is often delayed because the possibility of factitious disease is not considered, physicians may be unfamiliar with this problem, or the patient does not exhibit the type of personality expected with this behavior.[7] Diagnosis may be confounded by genuine medical illnesses predating and coexisting with a factitious disorder. For example, patients with factitious hypoglycemia may have a history of insulin-dependent diabetes mellitus, or factitious skin disorders may be preceded by true dermatologic diseases.[1] Identification of a factitious disorder is usually made in one of four ways: (1) the patient is accidentally discovered in the act, (2) incriminating items are found, (3) laboratory values suggest nonorganic etiology, or (4) the diagnosis is made by exclusion.[17] Wallach provides a useful review of the laboratory diagnosis of factitious disorders including feigned endocrine, hematologic, genitourinary, gastrointestinal, and infectious disorders.[42]

Suspected MSBP requires a detailed description of the event or illness and a search for caregiver witnesses, who should be interviewed personally. Although it is essential to see the child when the symptoms are present, the parents show great ingenuity at frustrating this effort.[40] Additional history of unusual illness in siblings and parents should be sought. Child victims who are verbal should be interviewed in private regarding foods, medicines, and their recollection of the symptoms or events. Prior medical records of the victim and, if possible, the siblings should be examined, although parents may impede such data gathering.

The major obstacle to early discovery of MSBP is its omission from the differential diagnosis. When it is considered, the diagnosis is generally made easily and quickly.[14] A suspected diagnosis may be confirmed through separation of the parent from the child (with consequent cessation of symptoms), covert video surveillance during hospitalization, or toxin screens.[16,36,38] In the majority of cases, the caregiver attempts

BOX 112-2 CHARACTERISTICS OF MALINGERING

1. Medicolegal context of the presentation (e.g., the patient was referred by his or her attorney).
2. Marked discrepancy between the person's claimed stress or disability and objective findings.
3. Poor cooperation during the diagnostic evaluation or poor compliance with previously prescribed treatment regimens.
4. The person exhibits, or has a history of, antisocial behavior.

to induce episodes surreptitiously while in the hospital, often during the first day of admission.[14,36]

Malingering

Malingering should be strongly suspected with any combination of certain factors (Box 112-2).[2,43] A definitive diagnosis of malingering can be established only by securing the patient's confession, a rare circumstance.[44] Because malingering constitutes criminal behavior, documentation of this diagnosis must be made with care.[20] In the absence of proof of wrongdoing, it is best to assume that the patient is not a malingerer but rather a common somatizer.[44] Malingerers who pursue drugs may report an unusually large number of drug allergies to persuade the physician toward prescribing their drug of choice or simply insist on a specific drug (e.g., Demerol or Dilaudid).[45] One unfortunate circumstance of the Internet is the wide availability of quality medical advice on how to convincingly feign pain and disability.[45]

DIFFERENTIAL CONSIDERATIONS

Patients with factitious disorders are distinguished from malingerers because their desired hospitalization or surgery seems to offer no secondary gain other than to play the sick role.[2,10,22] The clinical presentation of the majority of patients with factitious disorders, unlike those with Munchausen syndrome, is relatively subtle and convincing. The complaints are generally chronic in nature rather than emergent and precipitous, and there are no obvious associated behavioral aberrations.[21] The most important diagnosis to exclude when faced with a likely factitous disorder is a genuine medical condition that might account for the illness. Malingering is usually associated with less chronicity than factitious disorder, and malingerers are more reluctant to accept expensive, possibly painful, or dangerous tests or surgery.[22]

MANAGEMENT

Treatment options for factitious disorders depend on the patient's characteristics. Although it is challenging, managing common forms of factitious disorder can be more rewarding, especially with adolescents, than managing Munchausen syndrome.[1,9,24,29] Cases stemming from an underlying depression have a more favorable prognosis than those associated with borderline personalities.[27]

The best approach to patients with factitious disorder, other than Munchausen syndrome and MSBP, remains an area of controversy. Direct nonaccusatory confrontation has been advocated as "the foundation of effective management" when coupled with the assurance that an ongoing relationship with a physician will be provided.[4,21,22,27] This may be the first step in the acceptance of outpatient therapy.[4]

Others point out that confrontation is ineffective in most patients and may even be counterproductive in that it threatens to undermine a needed psychological defense. Enforced recognition of external objective reality, while simultaneously disallowing the patient's subjective experience, may generate even more dysfunction directed at legitimizing and maintaining symptoms and may even place the patient at risk for suicide.[9,17,29,46,47] Some patients may relinquish this defense if they feel safe in doing so and may abandon a claim to disease if some face-saving option is offered. This approach, termed the *therapeutic double bind* or *contingency management*, involves informing the patient that a factitious disorder may exist. The patient is further told that failure to respond fully to medical care would constitute conclusive evidence that the patient's problem is not organic but rather psychiatric. The problem is therefore reframed or redefined in such a way that (1) symptoms and their resolution are both legitimized and (2) the patient has little choice but to accept and respond to a proposed course of action or seek care elsewhere.[9,47]

Individuals with Munchausen syndrome typically demonstrate overt sociopathic traits or a borderline personality disorder and are demanding and manipulative, especially regarding analgesics.[5,9] They have been described as "essentially untreatable," and successful management of this condition is, in fact, considered reportable. Early confrontation or limit setting, especially regarding drug use, is advocated.[9,11,21,25,27] Although Munchausen patients typically do not want to be examined extensively, a thorough physical examination should be performed to rule out physical pathology.

MSBP constitutes a form of child (or elder) abuse, and appropriate action to protect the victim, including notification of welfare services, should take immediate priority.[38,41] When the diagnosis has been established and the parents confronted, psychiatric care should be made immediately available to the parents because maternal suicide is a significant risk.[14]

Malingerers do not want to be treated. Because they are "gaming the system" for personal advantage, the last thing they want is an accurate identification of their behavior and appropriate intervention. The emergency physician should maintain clinical neutrality, offering the reassurance that the symptoms and examination are not consistent with any serious disease.

Some authors have characterized patients' use of medical resources under false pretenses as criminal behavior, and several states have enacted legislation against the fraudulent acquisition of medical services. Successful prosecution of such behavior has been reported.[48] Conversely, patients with factitious disorders can and do sue. In dealing with such patients, it is advisable to involve hospital administration and risk management. Clandestine searches are inadvisable, and respect for the patient's confidentiality should be maintained.[17]

DISPOSITION

Patients with factitious disorder should receive primary care follow-up and ongoing care. If acceptable, psychiatric referral should be arranged. Referral to other medical specialists or hospitalization should be avoided when possible.

The manner of presentation and the unavailability of past medical history often allow patients with Munchausen syndrome to achieve hospital admission. If the patient is discharged from the emergency department, outpatient primary care follow-up and psychiatric referral should be offered, although both are likely to be refused.[25]

Because perpetrators of MSBP typically induce symptomatic episodes soon after hospitalization, admission of the victims (children or elderly persons) without taking appropri-

ate precautions may actually place them at increased risk.[14] Visits by the suspected perpetrator should be closely supervised, and no food, drink, or medicines should be brought in by the family. Protective services should be notified. Out-of-home placement of children in established cases of MSBP is advisable, and best outcomes are seen among children taken into long-term care at an early age without access to their mother. Children allowed to return home have a high rate of repeated abuse.[39] In 20% of reported deaths, the parents had been confronted and the child sent home to them, subsequently to die.[14]

After courteous but assertive reassurance, suspected malingerers should be offered primary care follow-up if the symptoms do not resolve. These individuals may become threatening when they are either denied treatment or overtly confronted.[19]

KEY CONCEPTS

- Emergency department patients who have consciously synthesized symptoms and signs may be divided into two broad diagnostic categories: (1) those with obvious secondary gain (malingering), who control their actions, and (2) those with a motivation of achieving the sick role (factitious disorders), who cannot control their actions.
- Emergency department management of patients suspected of fabricating disease includes a caring attitude and a search for objective clinical evidence of treatable medical or psychiatric illness.
- Unnecessary tests, medications, and hospitalizations should be avoided in the absence of objective evidence of a medical or psychiatric disease, and patients should be referred for ongoing primary care.
- In cases of suspected MSBP involving children or elderly persons, protection of the victim takes first priority.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 113 Suicide

Stephen A. Colucciello

PERSPECTIVE

Although suicide has occurred in all societies since the beginning of recorded history, attitudes toward suicide have differed dramatically among various eras and cultures. Seneca viewed suicide as the ultimate expression of personal freedom, but later Judeo-Christian religions have routinely condemned it. Shakespeare portrayed suicide sympathetically and expressed either pity or admiration for the victim.[1]

In the United States, suicide is illegal in 49 states, and only since 1994 has assisted suicide of terminally ill patients been sanctioned in Oregon. On the Internet, suicide help groups provide active advice on methods, and numerous bulletin boards condemn them. More than 100,000 sites about suicide now appear on the Internet.[2]

Suicidal patients comprise almost 2% of emergency department (ED) visits.[3] Two facts are especially important to remember when approaching potentially suicidal patients in the ED. First, many suicide attempts occur during an acute crisis, such as a personal loss or the exacerbation of an underlying psychiatric disorder. This acute crisis is usually time limited and may be resolvable or treatable. Second, except for the acutely psychotic patient, suicidal patients are usually ambivalent about dying. The attitude and approach of the emergency physician can help a patient choose crisis resolution rather than death.

Definitions

The term *suicide*, from the Latin *suicidum* (to kill the self), refers to a continuum of thought and action that runs from ideation to completion of the act.[4] *Parasuicide* is used by the British to describe an attempted suicide that is more of a gesture than a serious act. Statistically, there are 10 to 40 suicide attempts for every completed act.[5] *Chronic suicidal behavior* consists of recurrent self-destructive acts, such as heavy drinking in the presence of alcoholic liver disease. *Occult suicide* refers to self-destructive acts disguised as accidents, such as the intoxicated, depressed driver in an apparently accidental car crash. *Silent suicide* describes the act of slowly killing oneself by nonviolent means, such as starvation or noncompliance with essential medical treatment. Silent suicide is most common in elders and frequently goes unrecognized.

A *suicide pact* involves an agreement between two people who are intimately involved and accounts for 0.6% of all suicides.[6] *Mass suicide* or *group suicide* involves a number of willing and sometimes not-so-willing persons, such as members of an apocalyptic cult.

Epidemiology

Suicidal ideation is common, with as many as one in three people considering suicide during their lifetime.[7] Suicide is the eleventh leading cause of death in the United States, claiming more than 32,000 lives annually, with an overall rate of 11.05 per 100,000 population in 2004.[8] This is the equivalent of 89 suicides per day or one suicide every 16 minutes. Over a 5-year period, there were approximately 412,000 annual ED visits for attempted suicide and self-inflicted injury. The most common method of injury was poisoning (68%), followed by cutting or piercing (20%). One third were admitted to the hospital, with 31% going to the intensive care unit. A psychiatric diagnosis was assigned for 55% of visits, with depressive disorder accounting for 34% and alcohol abuse for 16%.[9]

Suicide rates vary with age, gender, race, and marital status. Suicides are highest among older individuals, particularly elderly white men. The case fatality rate also increases tremendously with advancing age, from 5% in youths aged 5 to 14 years, to 34% in adults older than 64 years.[10] White men commit 73% of all suicides in the United States. Whites and Native Americans are much more likely to commit suicide than African Americans, Hispanics, or Asians. Marriage decreases the likelihood of suicide, but separated or divorced people have a higher rate of suicide than those who never had a close relationship.

Women attempt suicide three to four times more often than men, whereas men are three to four times more likely to succeed. In one U.S. study, only 5% of suicide attempts by females were fatal, compared to 23% of those by males.[10] In general, men tend to use more lethal methods, such as firearms. Worldwide, Chinese and Indian women have higher rates of suicide than women of other nationalities.[11] Pregnant women are at a significantly lower risk than women of childbearing age who are not pregnant. Motherhood seems to protect against suicide, except that postpartum depression is associated with a higher than normal suicide rate.

Most people who attempt suicide have one or more known risk factors (Box 113-1). Individuals with the highest risk include those with psychiatric disorders, alcohol or substance abusers, adolescents, elders, and patients with certain chronic illnesses. In patients hospitalized for psychiatric disorders, the first month after discharge carries a high risk of suicide,[12] and

BOX 113-1 RISK FACTORS FOR SUICIDE

- Demographics
  - White men older than 65 years
  - Women older than 60 years
  - Males 15 to 24 years old
  - American Indian or Native Alaskan 15 to 34 years old
- Psychiatric disorders
  - Major depression
  - Bipolar disorder
  - Schizophrenia
  - Borderline personality disorder
  - Panic disorder
- Substance abuse
  - Alcoholism
  - Drug abuse (especially cocaine)
- Medical history
  - Prior suicide attempts
  - Chronic pain or illness
  - Physical or sexual abuse
  - Recent psychiatric hospital discharge
  - Terminal illness (especially cancer and AIDS)
  - Low intelligence scores (in men)
  - Lower body mass index
  - Short stature (in men)
  - Cosmetic breast augmentation (in women)
- Family history
  - Family violence
  - Suicide in family
- Social factors
  - Firearm in home
  - Living alone
  - Separated, widowed, or divorced
  - Unemployed
  - Homeless
  - Recent personal loss
  - Veterans
  - Recent incarceration
  - Lack of religious affiliation
- Emotional factors
  - Hopelessness
  - Chronic loneliness
  - Fixation on death

that risk is especially great for patients who are in the first week after discharge from a psychiatric facility.[13] Any prior history of suicide, even in the remote past, is an important risk factor.[14]

A strong association may exist between suicide risk and bisexuality or homosexuality in men.[15] This association is also seen in lesbian, gay, and bisexual adolescents.[16] Unemployment appears to be a risk factor for suicide among 18- to 24-year-old men.[17] Homeless people with mental illness are at particularly high risk for suicidal behavior, in part because of the high prevalence of traditional risk factors. Recent incarceration is also a risk factor for suicide. During the first 2 weeks after release, the risk of death among former inmates is more than 12 times that of the general population. The leading causes of death among former inmates include drug overdose, cardiovascular disease, homicide, and suicide.[18] In general, the risk of suicide in recently released prisoners is approaching that seen in recently discharged psychiatric patients.[19]

Suicide completers and suicide attempters represent separate but overlapping populations.[20] Although 10 to 15% of suicide attempters ultimately complete suicide, 60 to 70% of suicide completers have no prior history of attempts and commit suicide on the first known attempt.[21] In individuals who committed suicide while not in contact with mental health services, nearly one third of cases (32%) had no concurrent mental disorder.[22]

PATHOPHYSIOLOGY AND ETIOLOGY

Societal, Psychiatric, and Biologic Factors

There are many motivations for attempting suicide. It may be seen as the only escape from a terminal disease or intense chronic pain. It may be an act of revenge or political protest. Most suicide attempts occur in individuals with intense feelings of hopelessness, guilt, or self-hatred, often compounded by the exacerbation of an underlying psychiatric disorder or by the occurrence or perception of a great personal loss. The underlying causes for suicide are similar for adults and adolescents; however, adolescents tend to romanticize suicide, and "copycat" suicides are frequent after the suicide of celebrities or friends. Regardless of the motivation, most suicide attempters are ambivalent, and their attraction to death is usually counterbalanced by a desire to live. This internal conflict is reflected in the high ratio of attempted to completed suicides, and the fact that most people consult a physician shortly before their death.

Psychoanalysts explain suicide in terms of psychic forces. Freud believed that suicide stems from aggression, initially directed toward another person, which ultimately turns against the self. Depression and suicide in the Freudian model represent internalized anger. Many authorities have recognized this association between aggression and suicide. In the United States, more than 1000 deaths each year result from murder-suicides. The perpetrators are usually depressed mothers, despairing elderly men or young men with intense sexual jealousy. Their victims are usually young children, blood relatives, or female sexual partners. The dual risk for suicide and violence is greatest in alcoholics.[23]

The impulses that lead to suicide differ between violent and nonviolent people. "Suicidality" is correlated with anger, fear, and suspiciousness in violent individuals and with feelings of sadness and despair in nonviolent persons. The psychic roots of suicide may arise from childhood trauma. Chronic loneliness during childhood is associated with subsequent suicide attempts during adolescence, and a history of sexual molestation is linked to suicide attempts in women and adolescents.

Current research suggests a biologic basis for depression and suicide involving the serotonergic and dopaminergic systems. People who attempt suicide have altered serotonin receptor function and low serotonin levels.[24,25] These abnormalities may be regulated through serotonergic-related genes in persons with major depression.[26] The genetic basis of suicide is not clearly understood. The STin2 genetic locus might, at least in part, account for the observed familial aggregation of suicidal behavior.[27] Polymorphisms in the tryptophan hydroxylase gene may affect the synthesis of serotonin. Recent data also indicate that certain genetic markers may be linked to suicidal ideation associated with medications used to treat depression.[28] The genetic susceptibility to suicide, however, may affect individuals only when associated with psychiatric illness or stress.[29] The rate of suicide is twice as high in families of suicide victims, and a family history of suicide predicts suicide independent of severe mental disorder.[30] Relatives of suicide completers are over 10 times more likely than relatives of comparison subjects to attempt or complete suicide.[31]

Depressed patients who attempt suicide excrete less homovanillic acid in their urine and produce less dopamine

than depressed patients who have not attempted suicide. Low concentrations of dopamine and serotonin metabolites in the cerebrospinal fluid also correlate with suicidal behavior. Suicide attempts in women vary with estrogen levels, with 42% of attempts occurring during the first week of the menstrual cycle.[32]

Neuroanatomy may also influence suicidality; suicide victims have smaller right-sided parahippocampi than control subjects.[33] Although there are no currently available laboratory tests that can identify individuals at increased risk for suicide, research holds promise for biologic markers in the future.

Some drugs, including reserpine, benzodiazepines, and barbiturates, are associated with depression and suicidal behavior. The Food and Drug Administration recently linked suicidal ideation among children and adolescents to selective serotonin-reuptake inhibitors (SSRIs) and added a black box warning regarding SSRI use for all age groups.[34] It is ironic that in both the United States and the Netherlands, SSRI prescriptions for children and adolescents decreased after these regulatory warnings, and that these decreases were associated with *increases* in suicide rates in both children and adolescents.[35] Patients who commit suicide shortly after the initiation of antidepressant medications are explained by the "mobilization of energy" theory.[36,37] According to this theory, patients who are profoundly depressed may develop the energy to attempt suicide only as their condition improves with treatment. Such patients must be monitored very closely during their initial phase of treatment.

Methods of Attempting Suicide

Most completed suicides involve firearms (70%), whereas most attempted suicides involve the ingestion of drugs or poisons (72%).[38] In one large study, poisoning with drugs accounted for 74% of acts but only 14% of fatalities; firearms and hanging accounted for only 10% of acts but 67% of fatalities. Firearms were the most lethal means (91% resulted in death), followed by drowning (84%) and hanging (82%).[10] Episodes involving firearms are 2.6 times more lethal than the second most lethal suicide method, suffocation.[39] In 2005, 17,002 suicides involved firearms in the United States.[40] Guns represent the most common method of suicide in all victim subgroups, especially among older persons and adolescents, and the use of guns has increased dramatically in the past decade, recently replacing ingestion as the major cause of suicide among women.[41] The simple presence of a gun in the home represents an independent risk factor for firearm-related suicide, but not by nonfirearm means.[42] This is particularly true for adolescents, whose risk for suicide increases 5 to 10 times when there is a gun in the household.[43,44] In general, firearm prevalence is positively related to the suicide rate, even after controlling for rates of attempted suicide.[45] Suicide by handgun is often associated with drug or alcohol use.[46] The rate of gun-related suicide is 57 times higher in the first week after purchasing a handgun.[47]

After gun-related deaths, lethal methods chosen by men tend to include hanging, suffocation, or jumping from a height, whereas women are more likely to commit suicide by poisoning. Antidepressant overdose is the most common cause of suicide by ingestion.[48] Cyclic antidepressants are associated with more deaths because of their widespread use and high potential for lethality. Most patients hospitalized for self-poisoning have ingested drugs prescribed by their physicians for depression.[49] SSRIs, including fluoxetine (Prozac), sertraline (Zoloft), and paroxetine (Paxil), are less lethal when taken in overdose and have replaced cyclic antidepressants as the first therapy in depression.

The method of suicide depends on many factors, including psychic issues of self-hate, the desire for a peaceful versus violent death, and the availability of fatal means. Those who jump to their death are more likely single, unemployed, or psychotic. Those who use firearms are more likely to be male, alcoholic, to have been arrested, or to have an antisocial or borderline personality disorder.[50] Communities with tall buildings and bridges have higher rates of suicide from falls, whereas suicide by gunfire occurs more often in areas where firearms are prevalent.

"Suicide by cop" occurs when a suicidal individual intentionally provokes a police officer by orchestrating a lethal situation where the officer is forced to shoot in self-defense or to protect other civilians. This may account for as many as 11% of officer-involved shootings in Los Angeles.[51] Certain individuals carry a suicide note; some offer an eerie postmortem apology to the police officer who ultimately kills them.

CLINICAL FEATURES

Psychiatric Illness

Although most psychiatric patients never attempt suicide, most people who commit suicide have either a diagnosable psychiatric illness or alcoholism. Exceptions include those with mental retardation, dementia, and agoraphobia.[52] Patients with an affective disorder, especially major depression, are at highest risk.[53,54] Approximately 15 to 20% of people with major depression commit suicide, usually while under psychiatric care.[55] Individuals who experience hopelessness, anhedonia (loss of ability to experience pleasure), and mood cycling are at highest risk. Impulsive-aggressive personality disorders and alcohol abuse/dependence are independent predictors of suicide in major depression.[56]

Approximately 10% of schizophrenic patients will kill themselves. Psychotic patients who commit suicide are most often unmarried whites with high intelligence quotient scores.[57] Patients with borderline personality disorders are also predisposed to commit suicide. Women with borderline personality disorder who attempt suicide often have a history of childhood sexual abuse and impulsive behavior. The risk is especially high when patients require hospitalization for psychiatric illness and is greatest the first month after discharge.[58,59]

Approximately 40% of patients with panic disorder attempt suicide at some point in their lives. These patients usually have an additional comorbid psychiatric diagnosis (e.g., borderline personality disorder, substance abuse, emotional instability). However, any preexisting anxiety disorder (including social phobia, simple phobia, generalized anxiety disorder, panic disorder, agoraphobia, obsessive-compulsive disorder) is an independent risk factor for subsequent suicidal ideation and attempts.[60] Post-traumatic stress disorder, sustained by military combat personnel and disaster survivors, is also associated with suicide. Post-traumatic stress disorder frequently coexists with a major depressive episode, and this combined psychopathology enhances the risk for suicidal behavior.[61] In 2005, there were at least 6256 suicides among those who served in the U.S. armed forces; a rate double that of nonveterans. Veterans between the ages of 20 and 24 years who served in Iraq or Afghanistan had the highest suicide rate among all veterans.[62]

Alcoholism and Substance Abuse

Of successful suicides reported by the National Violent Death Reporting System, 33.3% tested positive for alcohol, 16.4% for

opiates, 9.4% for cocaine, 7.7% for marijuana, and 3.9% for amphetamines.[63] Other studies show that approximately 25% of all suicides involve alcoholics, and estimates of the lifetime risk of suicide from chronic alcoholism range from 3 to 25%.[64] Alcoholics who commit suicide usually have multiple risk factors, including major depressive episodes, unemployment, medical illness, and interpersonal loss. In psychiatric patients, the use of alcohol increases depression and suicidal behavior.

Substance abuse among mentally ill patients is increasingly common. Psychoactive substance abuse is associated with a greater frequency, repetitiveness, and lethality in suicide attempts than are most other medications.

Nearly one half of all adolescents who attempt suicide use drugs shortly before the attempt, and alcohol intoxication is strongly associated with suicide by firearms.[65] Cocaine use is particularly dangerous; in New York City, 20% of all suicide victims younger than 61 years used cocaine within days of their death. Among young Hispanic men, nearly one half of the suicide victims have toxicologic screens positive for cocaine.[66] In general, cocaine abusers choose violent means of self-destruction, especially firearms.

Adolescents

Suicide among adolescents has quadrupled during the past 40 years and is now the third leading cause of death (after accidents and homicides) in people between 5 and 24 years of age.[67] Approximately 2 million U.S. adolescents attempt suicide each year, and 19% report serious consideration of suicide in the past year.[68] Although some authorities believe that the rise in adolescent suicide simply corresponds to changing demographics in the United States, others believe that the increase is related to a growing sense of hopelessness, increased economic pressures, and access to firearms. In a survey of high school students in North Carolina, 24% had seriously considered suicide, 19% had planned suicide, and 9% had actually attempted suicide during a 1-year period.[69]

Adolescent girls are more likely to attempt suicide, whereas adolescent boys are more likely to complete suicide; the ratio of attempted to completed suicides is 25:1 for adolescent girls and 3:1 for boys.[70] Most adolescents who complete suicide have made previous suicide threats.

The majority of youths who kill themselves meet criteria for diagnosable psychiatric disorders, and both alcohol and substance abuse play a significant role in teenage suicide attempts. Adolescents with panic attacks are twice as likely to make suicide attempts as adolescents without panic attacks.[71] Gay, lesbian, bisexual, or "not sure" youths may also be more prone to self-harm.[72] Belonging to the "Goth" subculture is a predictor of self-harm and attempted suicide.[73]

Nearly 40% of youths in runaway programs report prior suicide attempts.[74] Young people may also be influenced by movies or television shows that feature suicide. Teenage suicides typically increase after television broadcasts on the subject.

From 1989 to 1995, suicide by firearm in young people increased dramatically.[75] The firearm-related suicide rate in U.S. adolescents is 11 times higher than the combined rates of 25 other industrialized countries.[76] Having a gun in the home places the troubled adolescent in great danger, and storing the gun in a locked cabinet or separating it from the ammunition does not deter suicide attempts.[77] Surprisingly, up to 23% of adolescents who have attempted suicide report that their families continue to keep firearms and ammunition in the home despite their suicide attempt.

Older Adults

The highest rates of completed suicide occur in elders. Suicide by firearm is the fourth leading cause of injury-related deaths among older U.S. residents.[78] Older Americans use highly lethal methods when attempting suicide and, unlike adolescents, rarely stage an attempt that permits rescue. Self-inflicted gunshot wounds account for 88% of elder suicides.

White men older than 65 years account for approximately 80% of suicide deaths, whereas suicide is rare among elderly people belonging to minority groups.[79] Suicide among older adults is especially common in those with prior suicide attempts or major depression. Severity of depression is the strongest predictor of suicide in elders.[80] Physicians often overlook signs of depression in older patients, even though most who commit suicide see their primary care physician during the month before their death. In one study, almost half of all elders who committed suicide visited a physician in the preceding week.[81] Elders also have more chronic illnesses that predispose to suicide. Perceived poor health, poor sleep quality, and limited presence of a relative or friend to confide in are also associated with suicide among elders.[82]

Chronic Illness

Patients with terminal illnesses may commit suicide to end their suffering and to reduce the emotional and financial burden on their families. Diseases more highly associated with suicide include cancer, stroke, renal failure, congestive heart failure, and chronic lung disease. In the elderly, congestive heart failure, chronic obstructive lung disease, seizure disorder, urinary incontinence, anxiety disorders, depression, bipolar disorder, and moderate to severe pain are specific illnesses associated with suicide.[81] A history of cancer is an especially strong risk factor in elders.

The acquired immunodeficiency syndrome (AIDS) epidemic has also increased suicide rates, and the relative risk of suicide in men with AIDS is nearly 37 times higher than in uninfected men. Patients who are positive for human immunodeficiency virus but do not have AIDS-defining conditions are more likely to be suicidal than those with active disease.[83]

History

Recognition of Depression and Suicide Potential

Recognition of suicide potential is relatively straightforward in patients who present shortly after a suicide attempt, as well as in individuals who complain of depression or express suicidal ideation during their evaluation. The potential for suicide should also be considered in patients with any acute problem related to chronic alcoholism, substance abuse, or any psychiatric disorder. Silent suicide is possible with patients who present to the ED repeatedly because of noncompliance with treatment of their medical disorders. Occult suicide should be suspected in patients who "unintentionally" overdose or have had "accidental" gunshot wounds, lacerated wrists, automobile crashes, or falls from heights.

Patients Who Present after a Suicide Attempt or Have Suicidal Ideation

Following a suicide attempt, patients with a normal mental status should be queried regarding the specifics of the act after medical evaluation and treatment are initiated. Suicidal patients may give inaccurate histories or may refuse to speak

to the physician. Because most people who attempt suicide communicate their intent to others at some point, an attempt should be made to interview family, friends, police, and paramedics regarding the patient's recent actions and possible motivations. They may also provide information regarding the specifics of the current suicide attempt. Although some physicians worry that current federal laws regarding patient privacy conflict with the need to obtain information with the family, an emergency exception to the Health Insurance Portability and Privacy Act rule exists. Section 164.512(j), "Uses and Disclosures to Avert a Serious Threat to Health or Safety," allows physicians to disclose protected health information without individual authorization "based on a reasonable belief that use or disclosure of the protected health information was necessary to prevent or lessen a serious and imminent threat to health or safety of an individual or of the public."[84]

Once the patient is medically stable, the presence of risk factors for suicide should be determined. Such factors may include a history of previous suicide attempts or psychiatric care; a history of excessive alcohol or drug use, both acute and long term; family history of suicide; and signs of depression, including a sense of hopelessness. Patients who have a history of deliberate self-harm (self-poisoning, cutting, burning, or hitting oneself) have a higher risk of suicide, especially male patients.[85] Over 5% of people seen at a hospital after self-harm commit suicide within 9 years.[86]

The patient's marital status and social support are important factors, and the motivation for and the seriousness of the suicide attempt are assessed. Some physicians ask patients to provide their own lists of "reasons why they want to live"—a sort of reverse score for suicidality. If discharge is being considered, patients should be asked whether they would harm themselves if they were released from the ED. Additional demographic information may be helpful (see Box 113-1). The SAD PERSONS mnemonic can be used to document salient points and facilitate subsequent communications with primary care providers and psychiatrists (Table 113-1).

Patients Suspected of Occult or Silent Suicide Attempts

Patients who are not overtly depressed or suicidal but who exhibit one or more of the high-risk presentations previously described should be assessed in a sympathetic but direct manner using a "graduated" approach. First, rapport should be established during an assessment of the presenting complaint. This should include a general medical and psychiatric history, as well as an evaluation of the patient's home, work, and social situation, followed by specific questions regarding the signs and symptoms of depression. The emergency physician should ask direct questions regarding suicide, such as, "Have you ever had the thought that life is not worth living?"; "Do you have thoughts of killing yourself now?"; and "What plans, if any, have you made to do this?" Patients who are not depressed or suicidal are generally not offended by this approach, and it does not place the concept of suicide into the mind of someone who has not been considering it. Patients who are depressed or suicidal are often thankful and relieved for the intervention.

Physical Examination

Patients should be examined closely for evidence of drug ingestion, trauma, or an associated medical illness. Look at the wrists for evidence of prior cutting attempts. The patient's mental status, vital signs, pupils, skin, and nervous system are helpful in detecting organic conditions, particularly the toxidromes associated with common ingestions (see Chapter 145). Altered mental status should be assessed to determine whether the condition is caused by an organic (medical) or functional (psychiatric) cause (Table 113-2). Physical findings associated with chronic disease, alcoholism, and substance abuse should be sought. The physical examination is often overlooked or performed in a cursory manner in patients with psychiatric complaints. Up to 50% of patients with an acute psychiatric presentation harbor unrecognized medical illnesses.[87]

DIAGNOSTIC STRATEGIES

Routine toxicologic screening tests are unnecessary in the evaluation of suicidal patients. Nearly all patients with dangerous overdoses and poisonings demonstrate clinical signs within several hours of ingestion. An electrolyte panel, while it need not be routine, may be useful in certain ingestions, particularly if an acid-base abnormality is suspected as in salicylate or methanol toxicity. Although the likelihood of potentially lethal acetaminophen ingestion is small in patients who deny taking acetaminophen, the emergency physician should consider measuring the acetaminophen level in patients with intentional overdose.[88] An electrocardiogram should be obtained if cyclic antidepressant overdose is suspected. Patients with acute depression, particularly if newly diagnosed, may need screening tests for underlying medical disorders; however, a

Table 113-1 Modified SAD PERSONS Scale

FACTOR	POINTS ASSIGNED
Sex (male)	1
Age (≤19 or ≥45 years)	1
Depression or hopelessness	2
Previous attempts or psychiatric care	1
Excessive alcohol or drug use	1
Rational thinking loss	2
Separated, divorced, or widowed	1
Organized or serious attempt	2
No social supports	1
Stated future intent	2

Five points or fewer, questionable outpatient treatment; 6 or more points, emergency psychiatric treatment/evaluation; more than 9 points, psychiatric hospitalization.

From Hockberger RS, Rothstein RJ: Assessment of suicide potential by nonpsychiatrists using the SAD PERSONS score. J Emerg Med 6:99, 1988.

Table 113-2 Factors in Differentiating Organic from Functional Psychosis

	ONSET	AGE OF ONSET	HALLUCINATIONS	ORIENTATION	VITAL SIGNS
Organic	May be acute	Any age	Often visual	Often disoriented	Abnormal
Functional	Subacute to chronic	14–40 yr	Usually auditory	Normal	Normal

primary care physician or psychiatrist can safely perform this evaluation during follow-up.

MANAGEMENT

Out-of-Hospital Care

Out-of-hospital management must focus on the patient's injuries and potential harm from poisoning or overdose. If the patient refuses to be transported to the hospital or becomes aggressive, emergency medical personnel should involve law enforcement officers. All states give police the right to place individuals into protective custody if they are suspected of being a danger to self or others. The presence of law enforcement officers, or even the threat of calling the police for assistance, usually ensures patient cooperation during transport. Hospitalized psychiatric patients who are transported to the medical facility by police have an independent risk factor for an imminent suicide attempt.[89]

Emergency Department

The clinical assessment of suicide potential requires an empathetic approach. Patients feel more comfortable discussing personal issues when health care personnel are friendly, nonjudgmental, and supportive. Unfortunately, ED staff may be unsympathetic toward patients who attempt suicide because of religious or philosophic beliefs, lack of formal psychiatric training, or inadequate time and personnel to provide appropriate psychiatric evaluation. They may perceive the patient's behavior as abusive or manipulative and may become frustrated regarding ineffective disposition and follow-up options. Failure to anticipate and overcome these factors can result in inadequate patient assessment and reinforce these patients' already low self-esteem.

Medical Clearance

The first priority in managing patients is medical stabilization and treatment of injuries, poisoning, or overdose. The second priority is the identification and treatment of associated medical conditions that may underlie a patient's altered mental status or violent behavior. Patients with significant injury, poisoning, or other medical problems should be hospitalized, sometimes in an intensive care setting, where their medical problems can be treated as they remain under constant observation. Five to 40 inpatients commit suicide for every 100,000 hospitalizations.[90,91]

Suicide Precautions

Most suicide attempts involve minor injury or overdose that can be definitively treated in the ED. Suicidal patients who are calm and cooperative should be placed in an area where they can be safely observed by staff. Having a dedicated "sitter" to watch the patient is helpful and decreases the need for restraints. The sitter should accompany the patient when leaving the area to use the restroom or smoke. No potentially suicidal patient should be allowed to leave the ED before an evaluation is completed. The use of family members as "sitters" is discouraged because they may collude with the suicidal patient to leave or may not intervene if the patient attempts to leave. The use of "wander alert" bracelets, which set off an alarm if a patient wearing one crosses an established threshold may help in monitoring.

Security personnel should search all potentially suicidal patients early in the ED stay. Having the patient change into a hospital gown facilitates removal of weapons, medications, and other possessions that might be used to inflict injury, such as belts, neckties, and long shoelaces. The patient's room should be cleared of all potentially harmful objects, including medications, instruments, and glass objects. Suture carts, which may contain scissors, scalpels, or other dangerous objects, must also be kept out of reach. Some rooms designed for psychiatric patients may contain a lockable "pull-down" wall, like those used on storefronts at night, that cover medical equipment and cabinets when a psychiatric patient is in the room.

Use of Restraints

Mechanical and chemical restraint use is based primarily on the physician's impression regarding the immediate risk of elopement or subsequent suicide attempt as well as personnel available to contain the patient. Some authorities believe that placing a depressed patient in mechanical restraints can impair rapport and contribute to the patient's diminished self-esteem. Chemical restraints may calm a violent patient but may make subsequent psychiatric evaluation more difficult in the short term.

Nevertheless, restraints may be essential and even lifesaving for uncooperative, violent, or psychotic patients and for those at high risk for elopement or self-harm. The Joint Commission, as well as state and federal government, have stringent requirements regarding the use of restraints. A hospital policy that conforms to these guidelines and an approved and consistently employed restraint flow sheet are important to comply with these regulations. A timed and dated physician order, as well as frequent rechecks of distal neurovascular function, are required for all patients placed in restraints.

Determination of Risk

Once a patient has demonstrated suicidal behavior or ideation, the physician must determine whether the risk is imminent (i.e., within 48 hours), short term (i.e., within days to weeks), or long term.[7] The likelihood of an impending repeat attempt will drive disposition: whether psychiatric hospitalization, emergency psychiatric consultation, or discharge and referral for follow-up. One must consider the potential lethality of the method chosen; for example, ingesting a handful of birth control pills is less worrisome than shooting oneself or setting oneself on fire. It is also important to consider if the patient believed the attempt would result in death. Even if the method chosen was nonlethal from a medical standpoint (such as ingestion of antibiotics), but the patient believed it was lethal, the patient may be at risk for a future, more lethal attempt. Patients who plan and hide their suicide attempt may be more desperate to die than someone who makes the attempt in front of a family member who rescues them. In depressed patients, an intense sense of desperation is an important predictor of suicide.[92] Another important consideration in the evaluation of the suicidal patient involves the wish to live versus the wish to die. Not surprisingly, those patients with a wish to live are six times less likely to commit suicide than those who wish to die.[93]

Although one should determine an individual patient's likelihood for committing suicide if discharged, this assessment is far from exact. No single psychological test can accurately predict suicidal attempts.[94] In a group of 4800 psychiatric patients who were followed prospectively over 5 years, 44% of all suicides were not foreseen by the psychiatrist.[95] In another group of individuals who completed suicides after evaluation by an emergency psychiatric service, no specific factors could be identified that predicted imminent suicide.[96]

There are at least 31 different English-language scales devised to predict the risk of suicide, but the vast majority are not designed for or suitable for use in the ED.[97] Some researchers are even using "fuzzy logic" and neural networks to achieve computerized prediction models for suicidality.[98] One study evaluated six clinical suicide assessment scales to identify high-risk patients: the Modified SAD PERSONS scale, revised Beck Depression Inventory, Beck Anxiety Inventory, Beck Hopelessness Scale, Beck Scale for Suicidal Ideation, and the High-Risk Construct Scale.[99] The outcome measured was psychiatric hospitalization admission for suicide risk, not completed suicide or future suicide attempts. All of the scales showed 100% sensitivity and negative predictive value, but lower specificity (38–90%) and positive predictive value (28–71%). Although scoring systems might help in determining the need for hospitalization, they cannot predict future attempts at self-harm.[100,101] Nevertheless, an attempt to determine a patient's immediate risk of self-harm should occur and, when indicated, be communicated to other health care providers.

The SAD PERSONS mnemonic provides a "suicide score" (see Table 113-1) and is well suited for use in the ED. Two points are given for each of four high-risk factors: (1) complaints of depression or hopelessness, (2) existence of an organic brain syndrome or acute psychosis, (3) presence of a well-conceived plan or life-threatening presentation, and (4) expression of determination or ambivalence regarding future suicidal behavior. One point is assigned for other important but less significant factors: male gender; age younger than 19 or older than 45 years; a history of previous suicide attempts or psychiatric care; stigmata of chronic alcoholism or substance abuse or the history of recent increased use of these substances; a patient who is separated, divorced, or widowed; and the absence of social support systems, such as close family, friends, job, or active religious affiliation.

A SAD PERSONS score of 6 or more has a sensitivity of 94% and a specificity of 71% compared with formal psychiatric evaluation in identifying the need for hospitalization in patients who present immediately after a suicide attempt.[102] A score of less than 6 has a negative predictive value of 95%. No deaths at 6 to 12 months occurred in patients with low scores.

Another risk assessment tool used for adolescents is the Risk of Suicide Questionnaire.[103] The four most useful questions on the Risk of Suicide Questionnaire were the following:

1. Are you here because you tried to hurt yourself?
2. In the past week, have you been having thoughts about killing yourself?
3. Have you ever tried to hurt yourself in the past?
4. Has something very stressful happened to you in the past few weeks?

Any positive answer on this rapid screen correlated with potential risk for self-harm when compared to a longer Suicidal Ideation Questionnaire, but correlation with suicidal outcomes is unknown.

Another simple scoring system is the British Manchester Self-Harm Rule. It uses the following four clinical correlates to determine future risk of suicide attempts[104]:

1. Any history of self-harm
2. Previous psychiatric treatment
3. Benzodiazepine use in this attempt
4. Any current psychiatric treatment

For 9086 patients, any positive answer on the four-question Manchester Self-Harm Rule had a sensitivity of 94% and specificity of 25% for a repeat attempt. Whether this rule would perform as well in a U.S. population with a far greater access to handguns remains unclear.

Suicide assessment should be performed after the patient metabolizes any drugs or alcohol. Intoxicated patients who complain of depression or state ambivalence regarding their future intentions to commit suicide may disavow these feelings once they are sober (but may still be at risk despite the disavowal). In addition, the information obtained from a potentially suicidal patient is best confirmed with a family member or friend as patients who are determined to commit suicide may give false or misleading information.

The crises that precipitate suicide attempts are often time limited, usually lasting from a few hours to a few days. If a crisis has passed or can be adequately addressed, the risk of subsequent suicide is substantially diminished. Hospitalization or emergency psychiatric evaluation should be strongly considered when a patient cannot or will not participate in an evaluation of the current crisis or when the problem is unlikely to be resolved.

Ultimately, the assessment of suicide risk remains a highly individualized process. The crisis that precipitated the suicide event, the patient's current emotional state, and the presence or absence of a supportive home environment must also be considered. When emergency physicians are uncertain regarding the need for hospitalization, they should err on the side of caution and either admit the patient for psychiatric care or request emergency psychiatric evaluation. A psychiatric social worker or other paraprofessional may assist in gathering information and in making decisions about the need for hospitalization; however, the physician still must make an independent judgment about the patient's suicide risk.[105] Despite the medical-legal threats involved, nearly a quarter of emergency physicians occasionally send patients with suicidal ideation home without any evaluation by a mental health professional.[3]

Some investigators recommend hospitalization for adolescents who have attempted suicide and cannot be adequately monitored at home. However, discharge to home is an option for those with suicidal thoughts if urgent psychiatric follow-up is arranged and the caregivers can adequately supervise and protect the youth. Discharged adolescents should not be actively suicidal, should not have access to lethal methods, should have a supervising adult to closely monitor them, and should have a mental health evaluation before ED discharge whenever feasible.[68]

Involuntary Commitment

Many patients who are severely depressed or suicidal will agree to be hospitalized for further evaluation and care; however, others may resist hospitalization. Patients who refuse recommended medical treatment usually do so because of anger or fear. Patients may be angry for being brought to the ED against their wishes or for having to wait for evaluation. Alternatively, they may fear the loss of control associated with hospitalization or the perceived negative stigma associated with a psychiatric disorder. When a patient is reluctant to be hospitalized, the physician should attempt to identify and address the specific concerns. The patient's family and friends may help convince the patient to accept voluntary hospitalization. Involuntary admission may be necessary if the physician believes the patient may inflict self-harm. Depression alone is not a criterion for involuntary commitment; the accepted legal standard requires the imminent risk of harm to self or others. In some states, even patients who voluntarily agree to hospitalization may need involuntary commitment papers filled out if they are an acute danger to self or others. This is to provide

the legal basis for holding them against their will during transport if they change their mind about hospitalization during the trip between the ED and the receiving psychiatric facility.

Civil commitment statutes differ among the 50 states and the District of Columbia. Nearly 85% of the jurisdictions require dangerousness to self to be the result of a mental illness, and only two jurisdictions mandate attempts at involuntary commitment if a person is deemed to be an imminent harm to self.[106]

The efficacy of commitment as a long-term preventive measure is controversial.[93] Involuntary commitment is not proven to prevent future suicide and may even precipitate adverse psychiatric consequences (e.g., increased feelings of hopelessness and dependency) or cause rebellion in some patients. Many authorities believe that people who are determined to kill themselves will probably prevail despite the best efforts of family members and health care professionals.[7] Still, despite the lack of hard data, involuntary commitment remains a primary intervention when patients are deemed acutely suicidal.

DISPOSITION

Most patients at high risk for suicide will need psychiatric evaluation or hospitalization in a psychiatric facility. If patients require transfer to such a facility, they must be protected from self-harm during transport. Deaths from jumping from an ambulance during such transports have been reported.[107]

Many patients who attempt suicide or have symptoms of depression can be safely managed as outpatients, if the risk of subsequent suicide is judged to be acceptably low (Box 113-2). Before discharging a patient, one should address the crisis that precipitated the suicide attempt. The patient should also be considered low risk for subsequent suicide (e.g., low SAD PERSONS score). Evaluation by a mental health professional is useful, especially if the safety of outpatient management is in doubt. Some physicians ask the patient to form a verbal or written "contract" with them. This "no harm" agreement usually involves patients vowing not to hurt themselves and agreeing to return to the ED to seek help if the situation worsens before follow-up. Although the "no harm" agreement has not been validated, some believe this is a reasonable approach, whereas others believe that it provides only a false sense of security for the physician. On its own, it will certainly not absolve the clinician from malpractice liability if the patient commits suicide.[108]

BOX 113-2 FACTORS FOR PATIENTS AT LOW RISK FOR SUICIDE

1. Few significant risk factors (e.g., low SAD PERSONS score)
2. Stable and supportive home environment
3. Patient agrees to "no harm" contract and will return to emergency department if situation worsens
4. Family member or friend staying with or available to patient
5. Phone contact with health care provider responsible for follow-up
6. Specific appointment made for follow-up within 24 to 48 hours
7. No gun in home
8. Young female who took a nonlethal ingestion or made "hesitation cuts" to wrists
9. Patient expresses a strong desire to live

If the patient is to be discharged, a family member or friend should agree to stay with the patient or to be immediately available to the patient until follow-up is provided. The patient should be discharged to a stable and supportive home environment that is free of guns and lethal medications.

Adequate disposition may include a conversation with the ongoing provider. If possible, the follow-up appointment should be scheduled within a few days of discharge and should be specific regarding the location and time. This approach maximizes patient compliance with follow-up. Providing a card that indicates how to contact an available physician may be helpful.[109]

DOCUMENTATION

Documentation is important when patients are committed or discharged, as well as when restraints are used. If a patient requires involuntary commitment, one should document why the patient is a danger to self or others. If the patient is to be discharged, the record should reflect that the patient is low risk and does not intend self-harm after leaving the ED. Documenting that there is no gun in the home is also useful. Preformatted charts may improve documentation.[110]

PREVENTION

The incidence of suicide parallels the incidence of alcoholism, drug abuse, and psychiatric disease in society. Although most suicide prevention programs are of mixed value, legislation to control access to lethal drugs and handguns is effective. Laws requiring prescriptions for all sedative and hypnotic drugs in Japan led to a decrease in their use for suicide, with no increase in the use of other methods.[111] In Canada, suicide decreased after gun control laws were tightened.[112] Keeping a gun locked and unloaded and storing ammunition locked in a separate location are each associated with a protective effect against suicide by firearms in children and teens.[113]

Screening for suicidal ideation or depression may be a useful strategy. Physician education in depression recognition and treatment may reduce suicide rates.[114] Programs that screen for depression in the elderly,[115] and school-based programs that screen for suicide risk in teens,[116] may decrease suicidal ideation and suicide attempts. Occult suicidality is common in ambulatory ED patients who present for nonpsychiatric problems. In one study, waiting room patients were screened for suicidality with a computerized mental health assessment tool. Eleven percent had passive thoughts of suicide while another 8% had active thoughts about killing themselves.[117] While screening for occult suicide in all ED patients is an intriguing notion, the implications of referring 20% of all ED patients for psychiatric evaluation are staggering.

Contacting patients by telephone 1 month after being discharged from an ED for deliberate self-poisoning may reduce the number of reattempted suicides over 1 year.[118]

Despite great interest in the prevention of suicide, it is unclear which, if any, interventions are effective to prevent future attempts at self-harm.[119] No strong evidence suggests that antidepressants prevent self-harm in patients with prior suicide attempts; however, one small study did show an advantage to using depot flupenthixol in multiple repeaters.[120] In another small study, dialectic behavior therapy was more effective than standard aftercare in preventing further episodes of self-harm.[121]

Suicide attempts correlate with future suicide. In one study on survivors of self-poisoning, the 5-year mortality rate from suicide was 65.5 times greater than expected in the female group (compared to a control group who did not attempt self-harm) and 41.5 times greater among males.[122]

KEY CONCEPTS

- Suicide is often provoked by a treatable or reversible short-term crisis.
- Suicidal patients frequently see a physician shortly before their death.
- The most complete information can be elicited with an empathetic approach to the patient and communication with family members, friends, health care providers, and others.
- Suicide precautions in the ED include appropriate use of "sitters" and, when necessary, physical and chemical restraints and involuntary commitment.
- The emergency physician should identify risk factors for suicide, even though determination of suicide risk is not a hard science. The SAD PERSONS score can be of help in documenting this assessment.
- Older men and those who attempt suicide using a firearm are at highest risk for a future completed suicide. Young females, especially those who cut themselves or take a nonlethal ingestion, are generally at lower risk.
- If patients are sent home because their risk of suicide is low, ensure a safe and supportive gun-free environment and early psychiatric follow-up.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 114 Arthritis

Bruce D. Adams and Douglas W. Lowery III

PERSPECTIVE

Socioeconomics

Arthritis and the over 100 related rheumatic diseases represent the leading cause of disability in the Western World.[1,2] Many of the arthritides, including rheumatoid arthritis (RA), are associated with premature mortality and their treatments often manifest with major toxicity.[3] Because of the tremendous pain and disability associated with joint inflammation, patients with the gamut of arthritic maladies present frequently for emergency evaluation.[2]

Up to 25% of all patients with rheumatologic disorders visiting the emergency department (ED) require admission, one third of these to an intensive care unit.[4] There are three reasons to develop a comprehensive approach to patients with arthritis symptoms: to utilize the symptoms as a diagnostic clue to a serious systemic illness (e.g., acute rheumatic fever [ARF], scleroderma, and renal crisis), to evaluate for acute emergencies related to or masked by the disease, and to alleviate acute and chronic pain.[4,5]

History

Rheumatic diseases (derived from the Greek *rheuma*, "a substance which flows") were among the first diseases recognized. Egyptian physicians more than three millennia ago recognized gout, as did Hippocrates in the 5th century BCE (who described other joint ailments, including scleroderma).[6,7] Podagra, the foot-torturess and offspring of Aphrodite (Venus) and Dionysus (Bacchus), was a bad-tempered virgin who attacked victims after they overindulged to dietary or sexual excess.[8] Roman surgeons under Nero first applied colchicine alkaloids from the meadow saffron (*Colchicum autumnale*) over 2000 years ago.[8,9] Sir Thomas Sydenham in the 17th century advanced more scientifically modern descriptions of gout (from which he suffered), but it was his keen observations of ARF, to include his eponymous chorea, that are probably better remembered from the man that first advised modern physicians "*primum non nocere*."[10,11] Dundas proposed the term *acute rheumatic fever* in 1808 and Trousseau linked the rash of Scarlatina with it in 1873.[12,13] Its causal relationship with streptococcal infection was finally confirmed in 1900.[14] Similarly, Swediaur noted a relationship between urethritis and arthritis in 1784, but the discovery of gonococcal arthritis waited until 1883.[15]

Garrod in 1858 coined the term *rheumatoid arthritis*, although Landre-Beauvais in 1800 and Brodie in 1819 are credited with its early scientific descriptions.[16] Heberden described his "nodes" as early as 1802, and Bouchard described his in 1884, but the entity of osteoarthritis was not clearly defined until 1907.[15] The other connective tissue diseases—systemic lupus erythematosus, systemic sclerosis, and polymyositis—were all described in the middle to late 1880s.[15] Ankylosing spondylitis was first mentioned in 1831 but was not accurately described until the 1930s.[15] The generic term *reactive arthritis* is now preferred over the eponym of the discredited Nazi war criminal Hans Reiter, who was probably not the first to describe the syndrome.[17–19]

Did the course of history shift because of this group of rheumatic maladies? Gout, long known as the "disease of kings" because of its predilection for diets of rich foods and alcohol, afflicted emperors throughout the ages.[20–22] Despite the untreated pain of RA, Presidents Jefferson, Madison, and Franklin Roosevelt succeeded to the extent of being honored on U.S. currency and the artists Renoir and Rubens both painted masterpieces for many years.[16,23] Some have even theorized that gout led to the fall of the Roman Empire (via its association with lead poisoning) and the rise of the American one (by afflicting its gluttonous European colonizers).[24–26]

PRINCIPLES OF DISEASE

Anatomy and Physiology

Joints are designed to bear weight and allow motion with as little wear as possible.[27] Three classes of joints are identified: synarthroses (suture lines of the skull), amphiarthroses (fibrocartilaginous unions of the pubic symphysis and the lower third of the sacroiliac joint), and diarthroses (moving joints). The most common type is the diarthrosis or synovial joint, which consists of two ends of subchondral bone (one convex, one concave) almost completely covered by articular cartilage.[27] The cartilage consists of a matrix of collagen fibers and proteoglycans, which are synthesized by the chondrocytes within it. The cartilaginous surfaces are well lubricated and slide against each other.[28] The joint is surrounded by a capsule that is supported by ligaments, tendons, and muscle and is lined with a synovial membrane (Fig. 114-1).

Cartilage is deformable, compressible, and lubricated by synovial fluid secreted by cells of the synovial membrane lining the joint space. The synovium is up to three cells thick and consists of two cell types: type A cells, which contain lysosomes, and type B cells, which synthesize the fluid. Both types multiply in synovitis and interact with the vasculature to produce arthritis.[28] Joint fluid has a high viscosity because

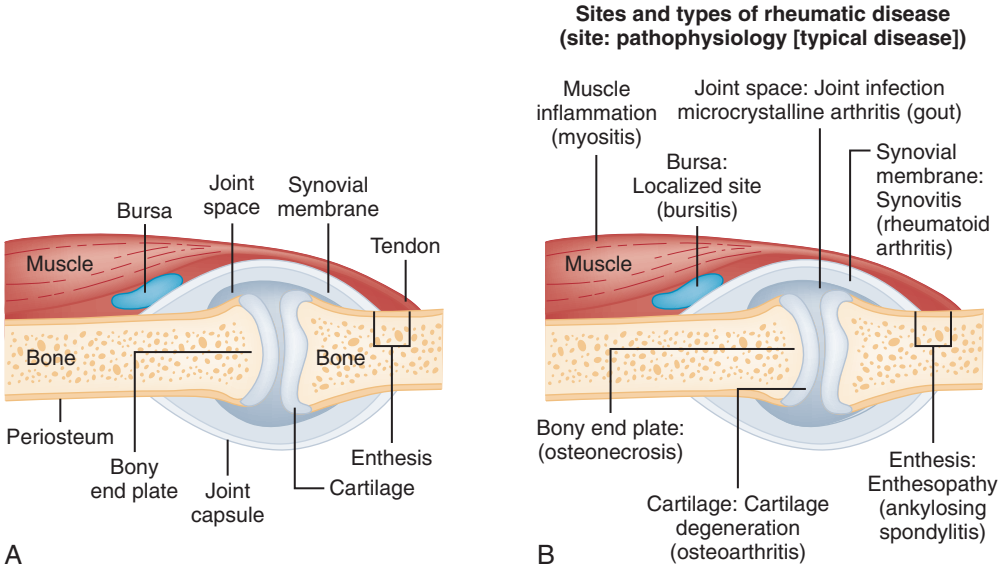


Figure 114-1. Anatomic structures of the joint with location of selected arthritis diseases. (Redrawn from Goldman: Cecil Medicine, 23rd ed. Copyright © 2007 Saunders, An Imprint of Elsevier.)

of its major component, a polysaccharide, hyaluronic acid. The fluid also contains water, glucose, electrolytes, and proteins of low molecular weight.

Pathophysiology

The disease-specific pathologies are further detailed in the following sections, but the final common pathways of arthritis are initially triggered by trauma, infection, or endogenous cell and humoral inflammatory components.[29] The joint's metabolic balance then shifts towards catabolic mediators and tissue destruction.[30] The trigger for this inflammatory reaction is different with different diseases. In nongonococcal bacterial arthritis, the cells of the synovial lining phagocytize bacteria. In gout and pseudogout, crystals are released from cells lining the synovium by conditions that precipitate an acute attack.[31] Joint inflammation of the traditional rheumatic diseases has a complex immunologic basis.[32,33]

CLINICAL FINDINGS

Symptoms and Signs

Pain is the hallmark complaint of patients with joint problems who come to the ED (Table 114-1). The pain may be acute or chronic (with the typical duration cutoff being 6 weeks), or an acute episode in a person with chronic disease. The patient may have had similar pain before, so it is important to know whether a diagnosis was previously made and what treatment, if any, was instituted. One must first determine whether the source of the inflammation or pain is articular or periarticular (outside the joint capsule). True arthritis produces generalized joint pain, warmth, swelling, and tenderness. Discomfort increases with both passive and active motion of the joint because the inflamed synovium is exquisitely sensitive to stretching and because all parts of the joint are involved in the inflammatory process. By contrast, periarticular inflammation (bursitis, tendinitis, or localized cellulitis) tends to be more focal. Tenderness and swelling do not occur uniformly across the joint, and pain is produced only with certain movements, with the most common being resisted active contraction or passive stretching of the affected muscles or tendons.

Table 114-1 Causes of Joint Pain

MONARTICULAR	POLYARTICULAR	PERIARTICULAR
Acute (<6 wk)		
Acute rheumatic fever	Gout	Bursitis
Lyme disease	Gonococcal arthritis	Tendinitis
Reactive arthritis (Reiter's)	Pseudogout	Cellulitis
Viral arthritis	Septic arthritis	Enthesitis
	Trauma and hemarthrosis	
Chronic (>6 wk)		
Adult-onset Still's disease	Osteoarthritis	
Relapsing polychondritis		
Rheumatoid arthritis		
Seronegative spondyloarthropathies		

Patterns

If the site of the patient's pain is articular, one must next determine whether the arthritis is monarticular or polyarticular. The arthritis may be symmetrical (e.g., rheumatoid or drug induced) or asymmetrical (e.g., rubella, ARF, or gonococcal). In addition, it may also be migratory (e.g., gonococcal or rubella), subsiding in one area before presenting in another, or additive, remaining in the first joint and progressing to additional joints (Box 114-1).

Distribution

The distribution of joint involvement may give some clues to the disease: the first metatarsophalangeal (MTP) joint is classically affected in gout; the metacarpophalangeal (MP) joints and proximal interphalangeal (PIP) joints in RA; and the distal interphalangeal (DIP) joints and the first carpometacarpal joint in osteoarthritis.[34] Patients with inflammatory arthritis may have low-grade fever, but high fever with chills is more likely

BOX 114-1 Differential Diagnosis of Arthritis in the Emergency Department

- Monarticular
  - Septic arthritis
  - Gout
  - Pseudogout
  - Osteoarthritis
  - Trauma/hemarthrosis
  - Charcot's joint
- Polyarticular
  - Symmetrical
    - Gonococcal arthritis
    - Viral arthritis
    - Lyme disease
    - Drug-induced arthritis
    - Reiter's syndrome
    - Rheumatic fever
    - Seronegative spondyloarthropathies
  - Asymmetrical
    - Gonococcal
    - Acute rheumatic fever
    - Lyme disease
    - Systemic lupus erythematosus
    - Immune complex diseases (viral)
    - Reactive arthritis

to be caused by septic arthritis. Morning stiffness (gel phenomenon) and improvement of symptoms with activity suggest inflammatory arthritis, while improvement with rest suggests mechanical disorders.[34] Concomitant renal stones suggest gout, genital ulcerations occur in Behçet disease and reactive arthritis, and a purulent urethral discharge suggests gonococcal arthritis or reactive arthritis. The use of isoniazid, procainamide, and hydralazine can precipitate lupus, and thiazides can increase the serum uric acid level, leading to gouty arthritis. Many of the newer RA medicines convey serious potential toxicity.[35,36]

Physical Examination

General Examination

A thorough physical examination should be performed that specifically searches for evidence of particular rheumatic diseases. The skin, eyes, and cardiac, pulmonary, and neurologic systems should be examined carefully, searching for systemic manifestations of rheumatic disorders (Table 114-2).

Joint Examination

The most important diagnostic tool for evaluating acute arthritis is the examiner's own hands. Each joint in question should be specifically examined for the following attributes: warmth (the dorsum of the hand can detect a 0.5°C difference); effusion; synovial thickening; deformity; range of motion; pain on actively loaded motion; and tenderness (generalized or localized, articular or periarticular).[34,37]

Spine. When evaluating the spine, the patient should stand, and the vertebral column should be assessed for abnormal curvature or asymmetry. One should perform the Schober maneuver to assess for the limitation of the lumbar spine motion that occurs in ankylosing spondylitis while examining the sacrum and anterior iliac crests to elicit pain in the sacroiliac joints (Fig. 114-2).[37]

Table 114-2 Clinical Signs of Arthritis Diseases

ORGAN SYSTEM	FINDINGS	DISEASES
Airway	Airway obstruction	RA, RP
Cardiac	Pericarditis	RA, ARF
	Murmurs	ARF, RP, AS
Eyes	Iritis, uveitis	Spondyloarthropathies
	Conjunctivitis	Reactive arthritis
Gastrointestinal	IBD	Spondyloarthropathies
	Dysentery	Reactive arthritis
Genitalia	Lesions, urethral discharge	Reactive arthritis, gonococcemia
Hematologic	Aplastic anemia	Parvovirus
	Anemia of chronic disease	Any chronic arthritis disease
Neurologic	Cauda equina syndrome	AS
	Cervical spine instability	AS, RA, OA
Oral mucosa	Ulcerations	Reactive arthritis
Pulmonary	Pleuritis, nodules	RA
Renal	Renal crisis, ARF	Scleroderma
Skin	Plaques on elbows, knees	Psoriasis
	Sclerodactyly, calcinosis	Scleroderma
	Erythema chronicum migrans	Lyme disease
	Tophi	Gout
	Erythema marginatum	Rheumatic fever
	Subcutaneous nodules	Rheumatoid arthritis

Excludes rheumatic vasculitis diseases.
ARF, acute rheumatic fever; AS, ankylosing spondylitis; IBD, inflammatory bowel disease; OA, osteoarthritis; RA, rheumatoid arthritis; RP, relapsing polychondritis.

Upper Extremities. Localized tenderness and pain associated with active movement are more likely to be periarticular in origin. A shoulder affected by chronic arthritis or bursitis will have atrophy of the deltoid muscle. Generalized tenderness and pain, both at rest and with active and passive motion, suggest joint involvement. With the patient's hands placed behind the head, one may then perform the back tests for external and internal rotation, respectively. Early signs of joint inflammation in the elbow are limitation of extension and an increase in the normal angle at which the patient holds the elbow at the side. The hand and wrist provide many clues to the presence of long-standing rheumatic diseases: MP and PIP joints are affected in RA; and the first carpometacarpal, PIP, and DIP joints are affected in osteoarthritis. The fingers may be swollen or sausage-like in appearance, an indication of psoriasis or reactive arthritis. Subluxation at the MP joints, ulnar deviation, and swan neck deformities occur in RA. The nails may have pitting characteristic of psoriatic arthritis. Although the wrist may not be obviously swollen, discomfort and decreased range of motion, particularly on extension, may indicate synovial involvement.

Hip. Inflammation affecting the hip joint can be reported by the patient as pain in the anterior thigh, knee, or groin. A hip joint effusion will cause the patient to hold the hip partially flexed. An externally rotated and abducted leg in a neonate strongly suggests infection.[38] Range of motion of the hip is most easily tested by flexing the hip, bending the knee at a

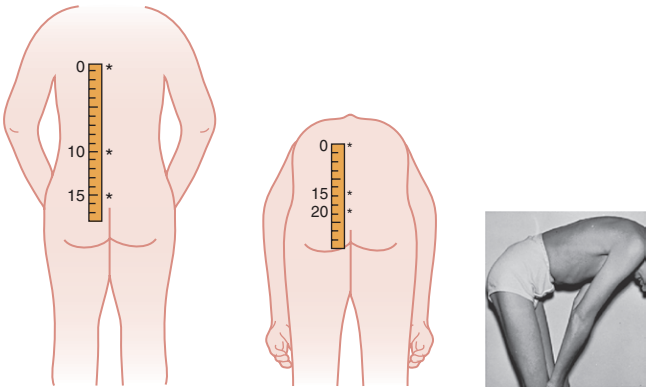


Figure 114-2. **A,** Schober's maneuver. Limited lumbar mobility secondary to spondylitis is documented with an abnormal Schober's maneuver. To perform this maneuver, the clinician makes a mark at the level of the posterior superior iliac spines (dimples of the pelvis) and another mark 10 cm above the first mark with the patient standing. The patient is then asked to bend forward, attempting to touch his or her toes. The distance between the two marks is remeasured. With normal lumbar motion, the distance between the two points increases by at least 5 cm. (Redrawn from Frontera: Essentials of Physical Medicine and Rehabilitation, 1st ed. Copyright © 2002 Hanley and Belfus.) **B,** Loss of lumbodorsal spine mobility in ankylosing spondylitis. The lower spine remains straight when the patient bends forward. (From Behrman: Nelson Textbook of Pediatrics, 17th ed. Copyright © 2004 Saunders, An Imprint of Elsevier.)

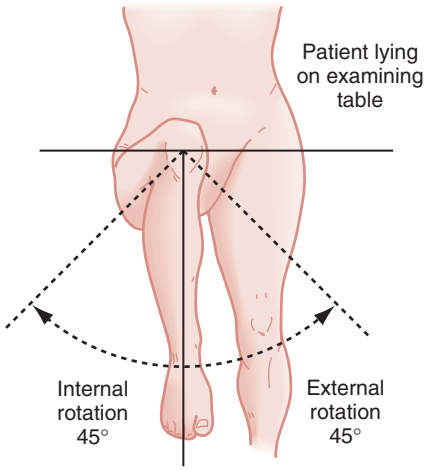


Figure 114-3. Testing for intrinsic disease of the hip joint. (From Branch WT: Office Practice of Medicine, 2nd ed. Saunders, 1987.)

right angle, and rotating the heel medially and laterally to test for external and internal rotation, respectively (Fig. 114-3).[39]

Knee. An effusion of the knee joint is relatively easy to detect when it appears as a ballotable fullness medially and laterally. Small effusions can be detected by examining for a transmitted fluid wave. Fullness of the popliteal fossa may indicate a Baker cyst. Passive range of motion may elicit crepitus or clicking. Tibiotalar joint effusions produce swelling under the medial malleolus and make it difficult to palpate the extensor hallucis longus tendon. Tenderness, warmth, and swelling of the great toe MTP joint occur in cases of gout but can also occur with osteoarthritis and RA. Sausage-like swellings of the toes are seen in reactive arthritis.

DIAGNOSTIC STRATEGIES

Laboratory Tests

Laboratory tests other than synovial fluid analysis generally convey only modest diagnostic value in evaluating acute arthritis in the ED.[38–40] Three widely used screening tests are a white blood cell (WBC) count, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). These values are modestly sensitive but quite nonspecific.[39,41] An elevated ESR can be used to screen for inflammatory arthritis when taken into careful clinical context.[40] Likewise for CRP with the notable exceptions of scleroderma, polymyositis, and dermatomyositis.[40] The ESR is particularly useful when suspecting polymyalgia rheumatica or giant cell arteritis.[40] Antistreptolysin O titers or a throat culture provides evidence of antecedent streptococcal infection in ARF. Rheumatoid factor, antinuclear antibody, HLA B27, and other disease specific serologies are generally best deferred to the follow-up physician.[41] The serum uric acid level is not helpful in diagnosing acute gouty arthritis because it can actually normalize during the acute phase.[42]

BOX 114-2 THE RADIOGRAPH OF A JOINT CAN BE SURVEYED USING THIS SYSTEMATIC APPROACH[38]

A—Alignment: Rheumatoid arthritis manifests with ulnar deviation.
B—Bone mineralization: Osteoporosis is more typical of the inflammatory arthritides, while periostitis (reactive bone formation) indicates seronegative spondylarthropathies or osteoarthritis.
C—Calcification: Gouty tophi and typical linear cartilage calcification of CPPD.
D—Distribution: RA is typically symmetrical. Specific target sites suggest diagnoses.
E—Erosions: Overhanging edges and sclerosis characteristic of gout.
S—Soft tissue: Assess for soft tissue swelling, nail hypertrophy (psoriatic arthritis), and sclerodactyly (scleroderma).

Radiology

Plain Radiographs

Plain radiographs are more helpful in patients with chronic disease than in those with acute arthritis (Box 114-2).[43–45] Common findings that help distinguish the different forms of arthritis are set out in Table 114-3.[43]

Computed Tomography, Magnetic Resonance Imaging, and Sonography

Other radiologic modalities are occasionally performed as part of the workup in an emergency setting. Ultrasonography is useful in evaluating joint effusions and synovitis.[46] Computed tomography (CT) detects early sacroiliac joint disease in difficult cases and is the preferred method for evaluating the sternoclavicular joint.[47] Sonography, CT, and magnetic resonance imaging (MRI) have been used to evaluate acute hip pain in children to distinguish septic arthritis and transient synovitis.[44] MRI is excellent for (1) imaging cruciate ligaments of the knee, (2) detecting early edema in periarticular structures and fluid collection in tendon sheaths, and (3) determining the extent of cartilage destruction.[44]

Arthrocentesis

Arthrocentesis is the most important diagnostic modality for evaluating the acutely inflamed joint, especially when considering septic arthritis.[45,48]

Indications and Contraindications

The emergency indications for arthrocentesis in evaluating joint pain include obtaining joint fluid for analysis, draining tense hemarthroses in patients with hemophilia (of the elbows, knees, or ankles and after the appropriate clotting factor replacement), and instilling analgesics and anti-inflammatory agents for the treatment of acute and chronic arthritis.[49–51] Emergency arthrocentesis is relatively contraindicated with an overlying cellulitis unless the infected area can be avoided during the puncture. Coagulopathy is the other major relative contraindication, but arthrocentesis can be safely performed in the presence of therapeutic levels of warfarin, ideally with a smaller needle.[52,53] Arthrocentesis of prosthetic joints should only be performed to rule out infection and are best done in consultation with an orthopedic surgeon.[54]

Table 114-3 Common Radiologic Findings in Arthritis

ARTHRITIS	FINDINGS
Acute arthritis (gout, pseudogout, septic arthritis)	Soft tissue swelling
Late septic arthritis (need at least 8–10 days to see changes)	Subchondral bone destruction Periosteal new bone Loss of joint space Osteoporosis Late joint space narrowing
Late pseudogout (knee, hip, radiocarpal, midcarpal, all MP)	Linear calcification in cartilage Asymmetrical joint space narrowing MP "hook spurs" in HHC Osteophyte formation Subchondral cyst formation Lack of osteoporosis
Degenerative arthritis (acromioclavicular, first carpometacarpal, first MTP, DIP, knee, hip, cervical spine, lumbosacral spine)	Asymmetrical joint space narrowing Sclerosis of juxta-articular bone Bone spurs and cysts—adjacent to severe cartilage degeneration No osteoporosis
Tuberculous arthritis (knee, hip, shoulder)	Soft tissue swelling Marked demineralization Bony rarefaction Little reactive sclerosis Late bony destruction Joint space preserved
Late rheumatoid arthritis (wrist, MP, PIP, MTP, first IP, foot, atlantoaxial, glenohumeral)	Symmetrical joint space narrowing Osteoporosis of periarticular bone Marginal erosions (no overhanging margins as in gout) Little reactive bone formation

DIP, distal interphalangeal; HHC, hereditary hemochromatosis; IP, interphalangeal; MP, metacarpophalangeal; MTP, metatarsophalangeal; PIP, proximal interphalangeal.

Complications

The primary complications of arthrocentesis are bleeding or infection in the joint space, allergic reaction to anesthetic agents, and long-term corticosteroid-related complications. Dry taps (when no fluid is aspirated after joint puncture) are more common in patients with chronic arthritis owing to obstructing tophi or anatomic abnormalities in the synovium and periarticular tissues.[55,56] Using a smaller syringe or a larger needle may help in such cases.[49] Even if no synovial fluid is apparent in the syringe barrel after multiple attempts, the capped syringe can be sent for culture analysis and just a single drop from the needle bevel can be used for crystal analysis on a slide mount.[49] An average on the slide of fewer than two WBCs per high-power field predicts a noninflammatory effusion.[50]

Technique

The patient should be positioned comfortably, with adequate exposure and cushioned support for the joint. Muscle tension during the procedure can reduce the joint volume, making the procedure more difficult; thus, every opportunity to provide for the patient's comfort should be employed. Bony landmarks should be carefully palpated. Under aseptic technique, the skin should be prepared with an appropriate surgical scrub. Adequate local anesthesia can be achieved either by use of a vapor coolant or by local infiltration with anesthetic solution such as 1 or 2% lidocaine.[51] Using an 18- to 22-gauge needle attached to a syringe, the joint space is punctured and aspirated while carefully avoiding abrasion of the articular cartilage. After aspiration, a long-acting anesthetic can be instilled to alleviate pain, but only if septic arthritis has been excluded can therapeutic steroids be injected.[49]

Synovial Fluid Examination

Analysis of synovial fluid is essential for identifying crystalline and suppurative causes of acute arthritis (Table 114-4).

Table 114-4 Synovial Fluid Interpretation

PROPERTY	CLASS I (NONINFLAMMATORY)	CLASS II (INFLAMMATORY)	CLASS III (SEPTIC)	CLASS IV (HEMORRHAGIC)
Color	Clear/yellow	Yellow/white	Translucent/opaque	Opaque, may contain fat droplets (lipohemarthrosis)
Viscosity	High	Variable	Low	
WBC count (/mm^3)	<2000	2000–100,000	>100,000	
Differential	<25% PMNs	>50% PMNs	>95% PMNs	
Culture	Negative	Negative	Positive	Variable
Leading diagnosis	Osteoarthritis	Inflammatory arthritis	Bacterial arthritis	Trauma, coagulopathy

PMNs, polymorphonuclear neutrophils.
From Fye KH, Morehead K: Joint aspiration & injection. In Imboden J, Hellman D, Stone J (eds): Current Rheumatology Diagnosis & Treatment. New York, McGraw-Hill, 2007, p 12.

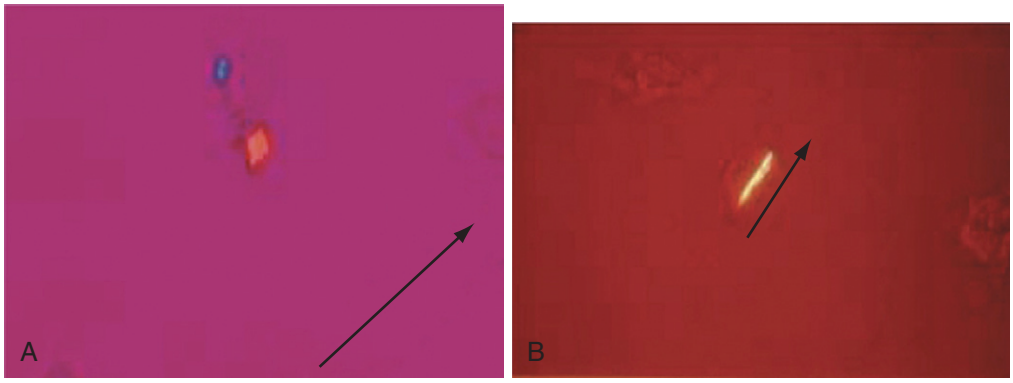


Figure 114-4. Pseudogout (**A**, blue crystal with a more plump structure) and gout (**B**, yellow crystal in parallel refraction with a longer, more needle-like structure) crystals under polarizing light. (From Goldman L: Cecil Textbook of Medicine, 23rd ed. Copyright © 2007 Saunders. An Imprint of Elsevier.)

General Appearance

Bedside inspection of synovial fluid for color, clarity, and viscosity can provide diagnostic clues. Viscosity is judged using the "string test"; normal viscosity allows stretching of a "string" of fluid between the thumb and forefinger, whereas inflamed fluid acts more like water.[57,58] Hemarthrosis presents after acute trauma or in the presence of coagulopathy, particularly with hemophilia.[55] Lipohemarthrosis indicates ligamentous injury or an intra-articular fracture.[49,56] Brownish synovial fluid may suggest the rare diagnosis of pigmented villonodular synovitis.[59]

Synovial Fluid Studies

Routine laboratory analysis should be sent for cell count, differential, Gram's stain, and crystal analysis. A positive Gram's stain is diagnostic, but a negative result for bacteria does not rule out septic arthritis; cultures should also be obtained.[48] Synovial glucose or protein is of little assistance.[48,57]

White Blood Cell Count. The WBC count dictates the inflammatory class of the fluid, but there is unfortunately significant overlap between inflammatory and septic causes of acute arthritis.[48,58,60,61] This test can be analogously compared to that of cerebrospinal fluid and meningitis. A very high fluid WBC or polymorphonuclear cell (PMN) pleocytosis indicates infection, but a more modest WBC or differential does not exclude it.[48,58] The likelihood ratio (LR) for septic arthritis increases as the joint WBC count rises: a WBC count of less than 25,000/mm^3 = LR of 0.32; a WBC count of greater than 25,000/mm^3 = LR of 2.9; a WBC count of greater than 50,000/mm^3 = LR of 7.7; and a WBC count of greater than 100,000/mm^3 = LR of 28.0.[48] However, low WBC counts do occur early in infectious arthritis and in partially treated infections; high WBC counts (>50,000/mm^3) can occur in RA, gout, and pseudogout. Most of the cells in both septic and severe inflammatory arthritis are PMNs. Cell counts should not be used to absolutely rule out a septic cause; rather, bacterial cultures (in blood culture bottles) should be obtained if there is any suspicion of infection.[58,62]

Crystal Analysis. Crystal analysis is best performed using polarizing microscopy of a drop of synovial fluid or postcentrifugation sediment placed on a slide with cover slip (Fig. 114-4).[45,49,63] Monosodium urate crystals are needle shaped and negatively birefringent (yellow when parallel to the compensator and blue when perpendicular), ranging in size from 2 to 10 µm. Calcium pyrophosphate crystals, in contrast, are polymorphic, rhomboid, and positively birefringent (yellow when perpendicular to the compensator, blue when parallel).[49,64] Crystal and septic arthritis can coexist because the infection could actually represent the precipitant of the former.[65]

Electrocardiography

Electrocardiography is indicated for evaluating a patient with acute arthritis for whom a diagnosis of ARF is being considered.[66] Prolongation of the P-R interval is a nonspecific minor Jones criterion, but any number of electrocardiographic findings can manifest.[66,67]

DIFFERENTIAL CONSIDERATIONS

Although certain disease entities (i.e., RA, gonococcal arthritis, Lyme arthritis [LA]) can be placed in several anatomic or temporal categories, the most useful classification of arthritis to guide the differential diagnosis is by chronicity and number of joints involved (see Table 114-1).[32,56,68–70] Some rheumatology textbooks include an intermediate category of pauciarthritis or oligoarthritis, but the simpler category system appears to better facilitate care and decision making in the ED.[70,71]

MANAGEMENT

Descriptive guidelines are provided for the diagnostic strategies for patients with monarticular (Fig. 114-5) and polyarticular (Fig. 114-6) presentations. After a specific diagnosis is made, treatment varies by underlying pathology.

MONARTICULAR ARTHRITIS—ACUTE

Inflammatory conditions of the periarticular soft tissues such as olecranon bursitis, rotator cuff shoulder tendonitis, and prepatellar bursitis can mimic monarticular arthritis, and classically polyarticular conditions such as RA and the seronegative spondyloarthropathies may present initially in only one joint. The emergency patient with monarticular arthritis should be considered to have septic arthritis until proven otherwise.[72,73]

Septic Arthritis—Nongonococcal Bacterial

Epidemiology

The incidence of septic arthritis is approximately 2 to 10 cases per 100,000 per year, with an age distribution curve for septic arthritis revealing bimodal peaks for young children and adults over age 55.[73–75] Additional risk factors include low socioeconomic status, intravenous drug abuse, alcoholism, diabetes, skin infections, HIV and other immunocompromised states, chronic arthritis (particularly rheumatoid, crystalline, and degenerative osteoarthritis), and following intra-articular corticosteroid injections or prosthetic implants.[39,64,66,76–78] Importantly, septic arthritis can occur simultaneously with other forms of arthritis, especially RA and gout.[65,79] The diagnosis of

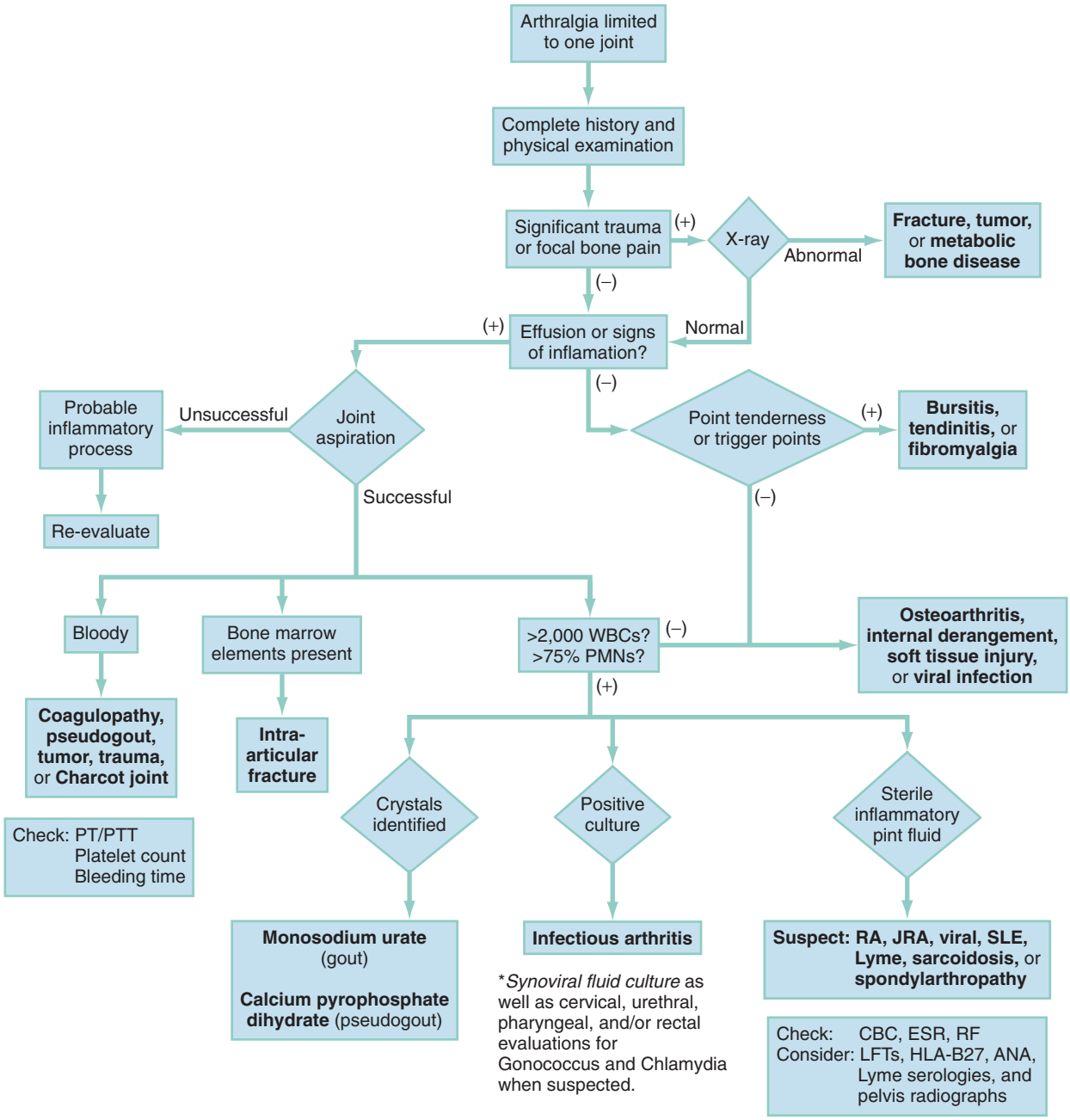


Figure 114-5. An initial approach to the patient with monarticular arthritis. The majority of diagnoses will be determined by the history and physical examination findings. ANA, antinuclear antibodies; CBC, complete blood cell count; ESR, erythrocyte sedimentation rate; JRA, juvenile rheumatoid arthritis; LFTs, liver function tests; PMNs, polymorphonuclear neutrophils; PT, prothrombin time; PTT, partial thromboplastin time; RA, rheumatoid arthritis; RF, rheumatoid factor; SLE, systemic lupus erythematosus; WBCs, white blood cells. (Adapted from American College of Rheumatology Ad Hoc Committee on Clinical Guidelines: Arthritis Rheum 39:1, 1996.)

infectious arthritis in a patient with known crystal arthritis can be thorny because acute flare-ups of pseudogout or gout can cause fever, while crystals can emerge from an infected joint.[42,80] Gram's stain and culture must always be done on joint fluid, even when a diagnosis of crystal arthritis is evident by microscopy.[54] Joint infection in injection drug users usually involves the axial skeleton but can involve the extremities.[54]

Pathophysiology

Any joint, whether native, chronically diseased, or prosthetic, can develop septic arthritis.[68] Bacterial pathogens infect the joint space most commonly by hematogenous spread, but direct inoculation and contiguous spread from bony or soft tissue infections occurs also.[73,74] Once in the joint, bacteria proliferate essentially unchecked in the highly vascular synovium, which has no limiting basement membrane.[68] This induces an inflammatory cascade, synovial proliferation with neovascularization, and subsequent enzymatic, cellular, and cytokine degradation of articular cartilage.[61,69] Septic arthritis, unless rapidly recognized and treated, results in serious disabling morbidity with mortality ranging from 5 to 15% or higher.[48,68]

Microbiology

The microbiology of nongonococcal arthritis has remained fairly constant over time, except for the notable decline of *Haemophilus* and pneumococcal species in the postimmuniza-

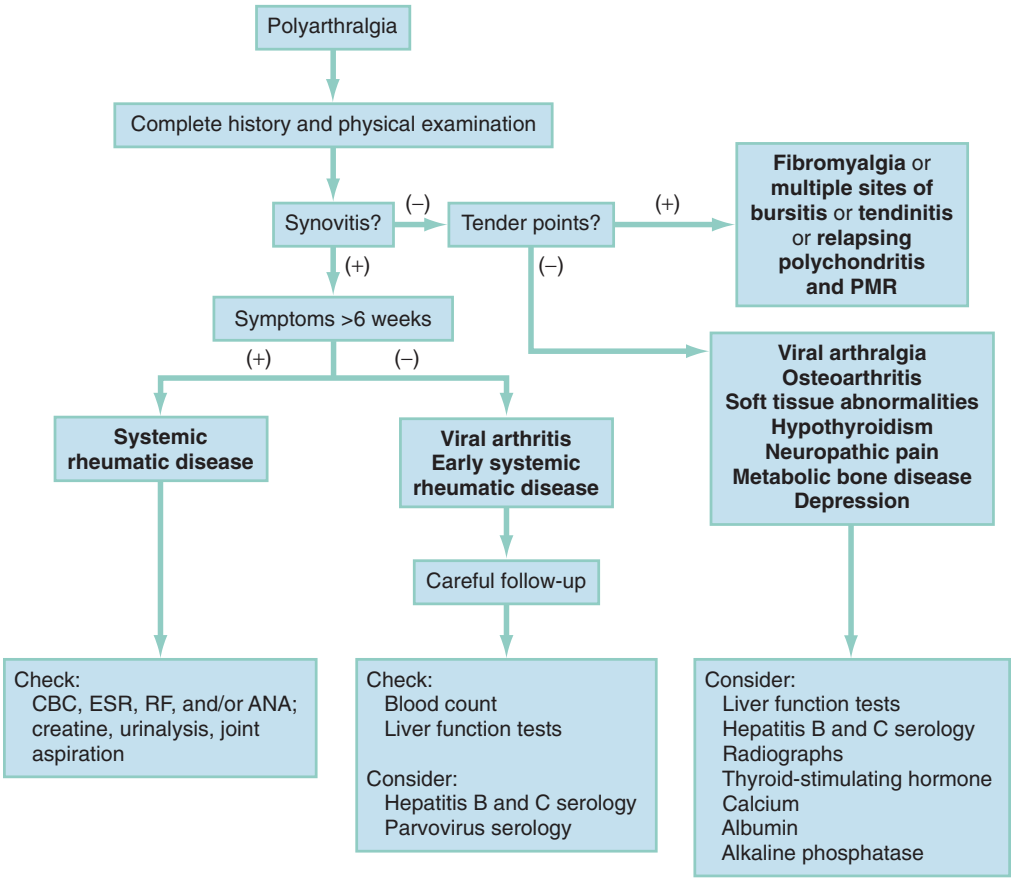


Figure 114-6. An initial approach to the patient with polyarticular joint symptoms. ANA, antinuclear antibodies; CBC, complete blood cell count; ESR, erythrocyte sedimentation rate; RF, rheumatic factor. (Adapted from American College of Rheumatology Ad Hoc Committee on Clinical Guidelines: Arthritis Rheum 39:1, 1996.)

tion era.[68,73] Acute nongonococcal septic arthritis in adults is caused most often by gram-positive organisms (75–90%) followed by gram-negative bacilli (10–20%) and then anaerobes, mycobacterium, fungal and other unusual organisms.[63,74,75,81] Overall, *Staphylococcus aureus* is still the most common cause of septic arthritis, with the rapid emergence of methicillin-resistant strains.[82,83] *Neisseria gonorrhoeae* accounts for only 20% of cases of all monarticular septic arthritis and more commonly presents with polyarthritis; it is discussed separately. Select populations have higher propensities for specific infecting organisms (Table 114-5).

Table 114-5 Microbiology of Bacterial Septic Arthritis Related to Patient

PATIENTS	ORGANISMS
Neonates and infants	*Staphylococcus aureus*, group B streptococcus, GNR
Children	*Haemophilus influenzae*, *S. aureus*
Adolescents/young adults	*Neisseria gonorrhoeae*, *Chlamydia trachomatis*
Older adults	*S. aureus*, *Streptococcus*, GNR
Sickle cell anemia	*Salmonella*
IVDA	*Pseudomonas*, *S. aureus*, GNR

GNR, gram-negative rod bacteria; IVDA, intravenous drug abusers.
From Levine and Noble: Textbook of Primary Care Medicine, 3rd ed. Copyright © 2001 Mosby, Inc.

Prosthetic Joint Infection

Prosthetic joint infections are classified as early (<1 month after surgery) or late. The latter can be caused by hematogenous spread or by indolent organisms introduced at surgery that may not surface for up to 1 year.[69] Because the joint is literally replaced, antibiotic bioavailability and host immune response are both impaired in the prosthetic environment. A wide range of culprit organisms have been identified; methicillin-resistant *Staphylococcus aureus* (MRSA) is increasingly prevalent.[74,75] Arthrocentesis diagnosis of a suspected prosthetic joint infection is best done in consultation with the operating surgeon.[72] A fluid WBC count of greater than 1700/mm^3 or a pleocytosis of greater than 65% PMNs is sensitive and specific for infection in this setting.[84]

Clinical Features

Signs and Symptoms. Classically, septic arthritis presents with fever, joint pain, and effusion, typically in the large joints.[61,69] Moderate fever occurs in most cases but is typically absent in the presence of immunosuppressive states.[63,75] Rigors and chills only occur in about 20% of patients.[69] Polyarticular presentation occurs in about 20% of cases, particularly in patients with chronic joint disease and in meningococcal infections.[58] Even in cases of septic polyarthritis, however, the knees are the most common sites of infection.[58]

Tests. Laboratory evaluation typically includes complete blood cell count, ESR, and CRP, although they are of marginal discriminatory value.[48] Blood cultures yield the causative organism approximately 50% of the time.[39,74] Radiographs demonstrate only soft tissue swelling if present; the bony changes of septic arthritis are long-term findings and are not usually present on the initial examination.

The only definitive diagnostic test for septic arthritis is arthrocentesis with examination of the synovial fluid.[58] The fluid

WBC count is directly proportional to the probability of a septic joint, but a low WBC count alone should not be used to rule out septic arthritis.[39,58] Gram's stain will show bacteria in 50 to 70% of infected joints.[61] Synovial fluid cultures for both aerobic and anaerobic organisms should be obtained, ideally by inoculation of pediatric blood culture bottles.[68,76,77]

Management

The key to successful treatment of septic arthritis is early diagnosis. Substantial delays in diagnosis directly worsen prognosis. Empirical antibiotic therapy should be based on Gram's stain or the presumptive consideration of likely organisms. Once the diagnosis is made, hospital admission is indicated for administration of intravenous antibiotics and either needle, arthroscopic, or open drainage of the affected joint.[78,85] In the hospital, daily aspiration to dryness of the joint should be performed, along with irrigation of the joint using a large-bore needle or arthroscopy.[72] Failure to respond to therapy within a few days, the presence of osteomyelitis, involvement of the hips or shoulders, or involvement of any prostheses usually mandates open arthrotomy for drainage. Parenteral narcotic analgesics and immobilization will control pain and discomfort. The antibiotic regimen should initially be based on the Gram's stain results and then adjusted based on final culture results and sensitivities. For gram-positive organisms, the initial drugs of choice are cefazolin with addition of vancomycin if MRSA is suspected.[58,68,81] For gram-negative bacilli, therapy should begin with a third-generation cephalosporin, such as ceftriaxone, cefotaxime, or ceftazidime (especially if *Pseudomonas* infection is suspected).[58,68,81] Antibiotic therapy should continue parenterally for 2 to 4 weeks, depending on the response to therapy, and should be followed with 2 to 6 weeks of oral antibiotic therapy at a high dose.[61,81]

Gonococcal Arthritis

Epidemiology

Gonococcal arthritis remains the most common form of joint infection in the sexually active population, although it has declined somewhat over the past decade because of the general decline of *N. gonorrhoeae* prevalence, particularly with the more virulent strains.[82,83] Host risk factors for gonococcal arthritis include pregnancy, menses, and complement deficiency. The 4:1 female predominance may also be explained by mucosal infections more often being asymptomatic in women.[82]

Pathophysiology

Gonococcal arthritis represents a clinical and pathologic course distinctly different from other bacterial infections and is less likely to create long-term joint pathology.[69]

Clinical Features

Systemic gonococcal infection complicates 0.5 to 3% of mucosal infections and presents with two somewhat overlapping musculoskeletal syndromes. The first is a localized septic arthritis, more commonly oligoarthritis than monarthritis, predominantly in the knee, ankle, or wrist. The effusions may be modest. True disseminated gonococcal infection (sometimes termed arthritis-dermatitis syndrome) manifests with bacteremia, diffuse migratory arthralgias, characteristic skin lesions, and tenosynovitis (Fig. 114-7).[82] A similar syndrome has recently been recognized as a result of *Neisseria meningitidis* infection.[86]

Figure 114-7. Pustular lesion with disseminated gonococcal infection. (From Mandell, Bennett, Dolin: Principles and Practice of Infectious Diseases, 6th ed. © 2005 Churchill Livingstone, An Imprint of Elsevier.)

Management

Microbiologic diagnosis is problematic because both synovial and blood cultures are positive for gonococcus in no more than 10 to 50% of cases.[61] The diagnostic yield is higher when specimens are plated on Thayer-Martin medium and even greater with the use of polymerase chain reaction.[87] Synovial fluid often yields a positive Gram's stain and the synovial WBC count tends to be lower than in nongonococcal arthritis (40,000–60,000 cells/mm^3).[81,83] Cervical, urethral, rectal, and pharyngeal cultures are positive in up to 75% of cases, so all mucosal orifices of the patient (and partner, if possible) should be cultured appropriately.[82,83] In disseminated gonococcal infection, the skin lesions often contain the gram-negative diplococcus. Treatment should be initiated with parenteral third-generation cephalosporins, such as ceftriaxone, ceftizoxime, or cefotaxime, with transition to oral regimens 24 to 48 hours after clinical improvement.[82,83] Therapeutic arthrocentesis need not be as aggressive in this form of septic arthritis.[84]

Gouty Arthritis

Epidemiology

Acute intercritical gout typically presents in middle-aged men or postmenopausal women, often in the setting of alcohol and dietary binging or acute physiologic stressors such as illness, trauma, or surgery.[88] Gout risk factors include chronic obesity, hypertension, diabetes, thiazide diuretic or cyclosporine use, radiocontrast and lead exposure, and alcohol or fructose consumption.[88–90] Purine-rich diets predispose one to gout; such diets include meat, seafood (especially anchovies and shellfish), beer, and legumes.[91,92] The prevalence of gout appears to be increasing.[93] Not all patients with elevated uric acid levels, or even joint crystals, have acute attacks, and many patients with an acute gouty arthritis have a normal uric acid level.[88]

Pathophysiology

Gout results from inflammation caused by the acute precipitation of uric acid crystals from supersaturated extracellular fluid.[94,95] Uric acid is a normal metabolic end product of purine metabolism.[80,96] Hyperuricema results from its underexcretion in the kidney or, less commonly, from systemic

overproduction (to include inborn errors of metabolism and myeloproliferative diseases).[89,94] Asymptomatic hyperuricemia typically exists for decades, and less than a quarter of these patients ever develop acute manifestations.[88,89] During an attack of gouty arthritis, the crystals are ingested by PMNs, resulting in cytokine release and an inflammatory synovial reaction.[93–95]

Clinical Presentation

Gouty attacks most commonly occur in the great toe MTP joint (*podagra*, up to 75%), the knee (*gonagra*), the ankle, and the tarsal joints. Usually only one joint is involved initially, but some patients can experience polyarticular involvement, bursitis, tenosynovitis, or even skin inflammation.[80] The pain is so excruciating at onset that some patients cannot even tolerate the weight of a sheet on the joint.[80,89] Systemic symptoms range from absent to dramatically mimicking a picture of septic arthritis.[63] Without treatment, the attack is self-limiting, peaking over 24 to 48 hours and lasting about a week.[80] Subsequent attacks tend to get closer together, involve more joints, and last longer, eventually morphing into the final stage of chronic gouty arthritis within a decade.[9,88,89,96] Long-term sequelae include renal stones and tophi in the musculotendinous units such as the olecranon bursa, Achilles tendon, ulnar surface of the forearm, hands and fingers, knees, feet and toes, and even the helix of the ear.[80,92,96] The ED patient may present with a first attack or have a known history of gout with a recurrent episode. Cellulitis and septic arthritis need to be excluded, particularly if the knee is involved.

Diagnostic Tests

Serum uric acid is not helpful in the acute setting because it can be transiently normal, but renal function should be checked. During an acute attack, radiographs of the affected joint will only show soft-tissue swelling, but long-standing disease produces typical asymmetrical bone erosions as a result of crystal deposits, with overhanging margins.[97] The definitive diagnosis of gouty arthritis is made by observing intracellular negative birefringent joint fluid crystals with a polarizing microscope (see Fig. 114-4).[91]

Management

The therapy for gout can be separated into acute treatment and chronic prophylaxis.[88,89,96–98] The latter strategy is not generally an ED consideration except to note that chronic prophylactic agents such as allopurinol, febuxostat, or probenecid should not be stopped, nor should they be initiated during an acute attack.[91] The goal of therapy is to rapidly resolve the pain and inflammation while avoiding toxicity.[9,80,91,96,98] Physical modalities such as rest, elevation, and ice are simple and demonstrate modest benefit.[9,42,98,99] Narcotic analgesics and either local or regional anesthetic blocks are potential adjunctive therapy.[42] The key ED pharmacologic mainstays for acute gout are nonsteroidal anti-inflammatory drugs (NSAIDs; including COX-2-selective agents), corticosteroids (including adrenocorticotropic hormone [ACTH]), and colchicine.[9,80,89,91,98,100] Caution should be exercised in using these agents because hypertension, diabetes, and renal and vascular disease are prevalent in this cohort of patients.[101]

NSAIDs. Indomethacin is the most commonly used NSAID for gout at dosages of 75 to 200 mg/day.[100] However, other short half-life NSAIDs at full anti-inflammatory dose are probably as effective.[91,99] The COX-2 inhibitors such as celecoxib are also alternatives.[42,102] Relief occurs rapidly over the first 24 hours of NSAID therapy, and duration should continue for another 24 hours after the symptoms abate.[9]

Colchicine. Colchicine inhibits microtubule formation and impedes the inflammatory response to crystals in the joint.[9] Dose recommendations vary, but a reasonable regimen is 0.5 to 0.6 mg orally every 1 to 2 hours until one of three events occurs: the pain is controlled, side effects supervene, or a maximum threshold of three tablets in three hours (or 10 tablets in 24 hours) is reached.[9,42,89,91] All patients will eventually develop gas, nausea, vomiting, or diarrhea from oral colchicine at the higher doses, so many experts recommend lower doses, especially for elders.[80,92,100,103] Colchicine's effectiveness wanes after about 24 hours, and once a full course of colchicine is given, no more should be used for at least a week.[9,92] Because it is effective for pseudogout and other crystal arthritides, it cannot be used for diagnostic purposes, although a gratifying therapeutic response does help distinguish crystal arthritis from septic arthritis.[9] Colchicine is contraindicated in patients with hematologic, renal, and hepatic insufficiency.[9,42,89] Of note, intravenous colchicine is no longer recommended because of its extremely narrow therapeutic window; more than 20 iatrogenic deaths have now been reported.[42,92,104,105]

Steroids. In resistant cases, oral prednisone (40 mg/day for 3–5 days, then tapering by 5 mg/day) can be used. Once septic arthritis has been excluded, the intra-articular injection of steroids may be effective for individuals with only one or two joints involved, thereby avoiding the systemic side effects of the other medications.[42,106] Triamcinolone acetonide in a dose of 20–40 mg for the knee and 5–10 mg for smaller joints is recommended.[107,108]

Adrenocorticotropic Hormone (Corticotropin). Corticotropin is an excellent alternative to the above agents because it acts faster and generally avoids their toxicity in older patients.[96,109,110] The dose of ACTH is 40 to 80 IU given intramuscularly.[9,96,110] With only a single administration, hypothalamic-pituitary-adrenomedullary axis suppression should not occur.[111]

Pseudogout

Pathophysiology

Calcium pyrophosphate dihydrate deposition disease (CPPD) results when calcium complex crystals form across articular surfaces, manifesting on radiographs as chondrocalcinosis.[112,113] The pathologic mechanisms are incompletely understood but involve overproduction of chondrocyte pyrophosphate, increased calcium, and histologic changes in the cartilage's extracellular matrix.[114,115] CPPD is associated with hemochromatosis, hypothyroidism, hyperparathyroidism, amyloidosis, hypomagnesemia, Wilson's disease, inflammatory osteoarthritis, and especially aging.[113] The condition is most often asymptomatic, but when precipitating crystals create an inflammatory synovitis, in about 25% of the cases, it is properly termed pseudogout.[114]

Clinical Presentation

The clinical presentation is very similar to gout and indeed the two conditions may overlap, so synovial diagnosis is important.[116,117] Pseudogout patients tend to be older and the knee is more commonly involved.[113,117] Radiographs of the affected joint show the pathognomic linear chondrocalcinosis (Fig. 114-8), but other radiologic variants are described.[112,118]

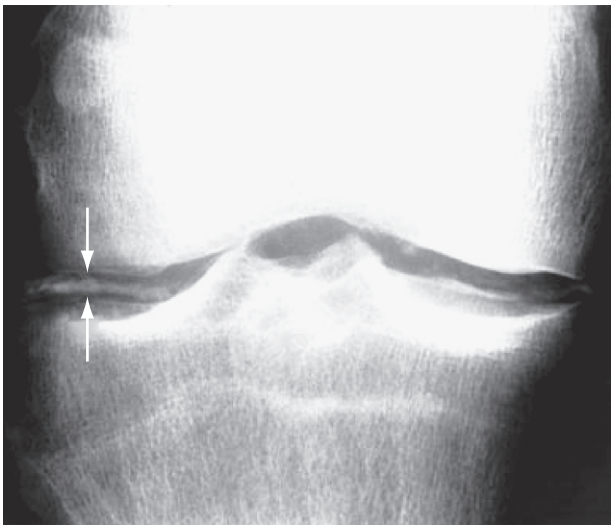


Figure 114-8. Chondrocalcinosis *(arrows)* in calcium pyrophosphate deposition disease. (From Mettler: Essentials of Radiology, 2nd ed. © 2005 Saunders, An Imprint of Elsevier.)

Diagnostic Tests

Joint fluid examination shows the rhomboidal, weakly positive birefringent crystals of CPPD (see Fig. 114-4). As with gout, the patient's symptoms may mimic septic arthritis, so joint fluid should be Gram stained and cultured.[119]

Treatment

Treatment for an acute attack is identical to the above therapy for acute gout: NSAIDs, steroids, corticotropin, or oral colchicine (although the latter is not as effective as with gout).[113,117,119] Prophylaxis unfortunately is generally less effective because the calcium pyrophosphate crystals cannot be removed.[110,114] Treatment of secondary metabolic causes of CPPD, while important, also does not influence the course of the pseudogout.[113,116,117]

Basic Calcium Phosphate Hydroxyapatite Crystal Disease

A variant form of crystalline disease results from basic calcium phosphate hydroxyapatite (BCP) deposits.[116] BCP deposition in synovial fluid is more difficult to detect with light microscopy and is more rapidly progressive and destructive than pseudogout.[115] BCP arthropathy also presents with calcific tendinitis, calcific bursitis, and a "pseudopodagra" of the first MTP in young females.[116,120,121] The Milwaukee shoulder syndrome is characterized by severe bilateral osteoarthritis of the glenohumeral joint, rapid destruction of the rotator cuff, and BCP crystals.[116,122] Treatment is often ineffective, but steroid injections and physical therapy provide some benefit.[116,121]

Acute Calcific Periarthritis

A recently recognized form, acute calcific periarthritis results when amorphous calcium hydroxyapatite deposits extravasate into periarticular soft tissue, causing a self-limited, crystal-induced inflammatory reaction.[123,124] Usually occurring in women, the symptoms last less than a week and the radiographic findings resolve after about 3 weeks.[123]

Trauma and Hemarthrosis

Trauma is a common cause of acute monarticular effusion.[53,72]

■ MONARTICULAR ARTHRITIS—CHRONIC

Osteoarthritis (Degenerative Joint Disease)

Epidemiology

Osteoarthritis (degenerative joint disease) is the most common form of arthritis in the adult population, especially in elders.[125]

Pathophysiology

The basic science of osteoarthritis pathophysiology has evolved from a simple hypothesis of mechanical wear and tear to a more complex interaction of multiple molecular pathways that involve mechanical, biochemical, and genetic factors.[126] Chondrocytes react to injury by promoting degradative enzymes, growth factors, and cytokines, which can lead to inappropriate repair responses of cartilage, synovial membrane, and subchondral bone.[125,127]

Clinical Features

The chief complaint in osteoarthritis is pain that worsens with activity and improves with rest.[128,129] The absence of systemic symptoms helps distinguish these patients from those with RA. The hands are predominantly affected in some patients with osteoarthritis. Bouchard's and Heberden's nodes (osteophyte spurs) are visible and palpable at the PIP and DIP joints, respectively.[130] The knee has crepitus on active and passive motion.[120] Radiographs of an osteoarthritic joint show asymmetrical joint space narrowing, osteophyte formation at the joint margins, and subchondral cyst formation without osteoporosis.[128] The synovial fluid is generally noninflammatory, with fewer than 2000 cells/mm and few PMNs.[35]

Management

Treatment includes judicious exercise for muscle strengthening, weight loss, relief of muscle spasm, and support for the joint.[129,130] Acetaminophen is generally the first-line drug for mild osteoarthritis.[112] For more advanced disease, there is a modest efficacy advantage toward NSAIDs and cyclooxygenase-2 inhibitors.[129,131] Alternative therapies including glucosamine and chondroitin sulfate have gained popularity, enjoy good safety profiles, and may show symptomatic benefit; however, their effectiveness is still controversial.[129,132–134] Capsaicin is a low-toxicity topical agent that may help following a few weeks of therapy.[130,134] Intra-articular hyaluronic acid injections for osteoarthritis of the knees provides a modest benefit for some patients.[132,135] Intra-articular glucocorticoid injections are reserved for exacerbations of painful osteoarthritis knee effusions and should be given no more than three times annually.[129,130,134] Those patients with completely denuded cartilage in the hip and knee may need joint replacement.[129,134]

■ POLYARTHRITIS

The differential diagnosis of polyarticular arthritis is much broader than monarticular arthritis. It is helpful to divide polyarticular presentations into two groups. Acute presentations

(<6 weeks) include gonococcal arthritis, viral arthritis (e.g., rubella, hepatitis), Lyme disease, reactive arthritis, and rheumatic fever. Chronic polyarticular presentations are caused by RA, systemic lupus erythematosus, scleroderma, psoriatic arthritis, dermatomyositis, and other autoimmune diseases. The diseases may also be distinguished on the basis of symmetrical or asymmetrical presentations. RA and lupus tend to be symmetrical, the others asymmetrical. The spondyloarthropathies (ankylosing spondylitis, reactive arthritis, psoriatic arthritis, and the arthropathy of inflammatory bowel disease) involve predominantly larger joints, but psoriatic arthritis affects the small joints of the hands.

POLYARTHRITIS—ACUTE

Viral Arthritis

Viral arthritis typically manifests with acute, self-limited, nondestructive polyarticular arthritis.[136,137]

Parvovirus

Acute parvovirus B19, the causative agent of pediatric erythema infectiosum, accounts for over 10% of adult acute polyarthritis.[136] This symmetrical polyarthritis resembles acute RA on physical examination, but precipitously follows about a week after a flulike illness with parvovirus.[137] Laboratory diagnosis is supported by a negative or low titer rheumatoid factor and positive B19 antibodies.[136] Concurrent B19-induced aplastic anemia should be excluded, especially in HIV, sickle cell, and other hematology patients.[136,137]

Rubella

Rubella, once a relatively common form of epidemic arthritis, has declined dramatically since introduction of an effective vaccine. The classic presentation is acute symmetrical polyarthritis, malaise, fever, lymphadenopathy, and maculopapular rash that spreads from the face to the body.[136,137] A postvaccination syndrome of arthralgia and arthritis occurs commonly, especially in women, from 10 days to several months after immunization.[137–139]

Hepatitis B and Hepatitis C Viruses

A self-limited acute symmetrical polyarthritis often occurs 2 to 3 weeks before the jaundice phase of hepatitis B virus infection.[136,137] Musculoskeletal pain frequently accompanies hepatitis C virus infection, ranging from arthralgias, myalgias, and fibromyalgia to cryoglobinemia and a chronic inflammatory polyarthritis.[136,140]

Alphaviruses

Several related arboviruses discretely manifest with acute arthritis, fever, rash, and sometimes hemorrhage.[136,137] Management is generally supportive with NSAIDs, but aspirin should be avoided because of potential hemorrhage. Epidemic febrile polyarthritis occurs throughout the world from viral outbreaks in Sindbis (Scandinavia), Chikungunya (India, Pacific, and South America), O'nyong-nyong (Uganda), and Ross River/Barmah Forest (South Pacific).[141–143]

Lyme Disease

Epidemiology

Borrelia burgdorferi infection causes the multisystem disorder Lyme disease, the most common vector-borne illness in the Western World.[144–146] Highly endemic areas in the United States for *B. burgdorferi* and its vector tick *Ixodes* include the Northeast Seaboard, the upper Midwest, and the far West from Northern California to Oregon.[147] Lyme disease follows a proscribed pattern of early disseminated disease (weeks to months after a tick bite) and late disease (from several months to years later).[146,148–150] Musculoskeletal manifestations of the early stage primarily consist of migratory myalgias and arthralgias without objective evidence of actual arthritis or effusions.[146,147] Lyme disease is further described in Chapter 132.

Natural History

When Lyme disease is not treated, 50 to 60% of patients will develop frank arthritis within 6 months, most commonly in large joints, particularly the knees.[149,151] The natural history of LA is for intermittent episodes gradually abating in intensity and frequency over several years even if untreated. Associated tendinitis or bursitis can occur.[147,150,152] LA appears to be autoimmune mediated, rather than a direct result of the spirochetal infection, but early antibiotic therapy clearly reduces its incidence.[149,151,153] LA seems to be more prevalent in U.S. infections because its endemic *B. burgdorferi* displays stronger arthritogenic properties than other strains.[147]

Diagnosis

The history of a previous tick bite from an endemic area or the classic erythema migrans rash (although often not remembered by the patient) may aid the clinician in suspecting the diagnosis.[146,147,152] Patients have minimal joint pain and usually are afebrile despite large joint effusions.[149,150] The joint fluid is inflammatory with PMN predominance, but *Borrelia* cannot be cultured from it.[146–148] The differential diagnosis includes gonococcal arthritis, septic arthritis, ARF, RA, and reactive arthritis.[146,148] Routine blood testing is nonspecific and unhelpful.[146,152] Confirmatory diagnosis is by immunoglobulin M and immunoglobulin G serologies, which should be strongly positive at the onset of LA.[146,147,152] Immunoglobulin G status will remain positive for an indefinite period despite adequate therapy and resolution of symptoms.[148,149] Unproven and unreliable urinary antigens are marketed but not recommended.[154]

Treatment

Prophylactic therapy after a tick bite is not generally recommended except for an *Ixodes* attachment of longer than 36 hours in an endemic region; a single doxycycline dose of 200 mg is then sufficient.[155] LA can generally be treated with a 4-week oral course of doxycycline, 100 mg twice daily. Amoxicillin 500 mg three times daily or cefuroxime axetil 500 mg twice daily are acceptable alternatives.[146,155] Amoxicillin is used instead of doxycycline for pregnant and lactating women and for children under 8 years of age.[155] If Lyme disease is diagnosed at the early stage of erythema migrans, only 2 weeks of treatment is required.[155] More expensive intravenous regimens should be reserved for neurologic or cardiac Lyme disease or refractory LA.[145,146,149,155] Antibiotic refractory LA can be treated with either an intravenous regimen or retreated with an oral regimen of antibiotics, but these prob-

lematic cases should generally be referred to an infectious disease expert.[145,149,155,156]

Acute Rheumatic Fever

Epidemiology

ARF is a systemic disease triggered by a complex hyperimmune response to group A streptococcal (GAS) pharyngitis.[66,157–159] Host cellular and humoral response to GAS attacks joint, cardiac, and other tissue via molecular mimicry mechanisms.[66,160,161] The incidence of ARF has dramatically declined in recent decades. This success is only partly due to the widespread use of antibiotics; improvements in social hygiene and transformation of GAS strains are probably more important factors.[66,158,159] However, ARF remains the leading cause of cardiac death among the young in developing countries, and reports of both endemicity and outbreaks in the United States still occur.[158,162,163] The highest incidences of ARF (50–500 cases/100,000) occur within indigenous populations of the South Pacific.[159,164] The vast majority of cases strike children 5 to 15 years of age.[157,159,165]

Clinical Diagnosis

The clinical diagnosis of ARF is based on the Jones criteria, which have been updated and revised several times.[157,159,166,168] The presence of two major criteria, or one major and two minor criteria, in the presence of laboratory evidence of prior GAS infection is required (Box 114-3). This stratagem is probably moderately insensitive for developing countries where alternate World Health Organization criteria are recommended.[158,159,168]

Arthritis. Symptoms of ARF generally occur 2 to 3 weeks after an oropharyngeal GAS infection, of which only half are symptomatic.[158] Arthritis, typically migratory, occurs in 75% of patients and mostly affects the large joints.[157,158] The arthritis last 2 to 3 days in each joint and 2 to 3 weeks overall; the axial skeleton is spared.[149] Joints appear modestly inflamed, but the pain is disproportionately excruciating to the patient.[157] ARF arthritis responds so dramatically to salicylate or steroid therapy that the diagnosis can become clouded. Lack of response should promote an alternate diagnosis.[157] Poststreptococcal reactive arthritis (PSRA) is another sterile GAS-related arthritis recently proposed for patients not fulfilling the Jones criteria for ARF.[169,170] The arthritis of PSRA tends to be more additive than migratory, with a lower extremity predominance.[131] It typically responds less robustly to salicylates and persists longer than ARF.[171]

Skin. Erythema marginatum and subcutaneous nodules occur in 1 to 2% of cases.[157] Erythema marginatum is manifested by the appearance of well-demarcated, pinkish areas of nonpruritic rash, usually on the trunk, but sometimes spreading to the proximal limbs (Fig. 114-9).

Carditis. Carditis occurs in 50% of patients with ARF and is the most important complication accounting for excess mortality.[157–159] The most severe form is a pancarditis that simultaneously attacks the pericardium, myocardium, and endocardium. Endocarditis can be overt, subclinical (detectable only by echocardiography), or transient, with many murmurs regressing after a few weeks of therapy.[172] Pericarditis by itself is rare and tamponade even rarer.[157] Myocarditis manifests with a host of electrocardiographic abnormalities from prolonged PR interval to atrioventricular blocks.[164]

Chorea. Sydenham's chorea occurs in about 10 to 15% of patients with ARF and presents with characteristic facial tics, tremor, weakness, and psychological disturbances.[173,174]

Laboratory Tests. The laboratory workup for suspected ARF consists of pharyngeal cultures and surveys of antibodies to streptolysin O or anti-DNase B to demonstrate antecedent GAS infection.[157,158] The synovial fluid is inflammatory in nature, with an average WBC count of 16,000/mm^3, no crystals, and a negative culture.

Management of ARF

Successful management of ARF requires three things: rapid eradication of the GAS infection, prophylaxis against recurrent infection, and the acute treatment of arthritis, carditis, and chorea.[157,158,175]

Antibiotics. The current recommended treatment of suspected acute GAS infection is benzathine penicillin, 0.6 to 1.2 million U IM or 10 days of oral penicillin (or erythromycin if the patient is penicillin-allergic).[157–159,164] Long-term prophylactic treatment to prevent recurrences of ARF is provided with

BOX 114-3 Jones Criteria for Diagnosis of Acute Rheumatic Fever

Major Manifestations	Minor Manifestations
Polyarthritis	Clinical findings
Carditis	Arthralgia
Chorea	Fever
Erythema marginatum	Laboratory findings
Subcutaneous nodules	Elevated acute phase reactants
	Erythrocyte sedimentation rate
	C-reactive protein
	Prolonged PR interval on electrocardiography

Plus:
Supporting evidence of prior group A streptococcal infection (elevated or increasing streptococcal antibody titer, positive rapid streptococcal test or bacterial throat culture results, recent scarlet fever)

From Anonymous: Guidelines for the diagnosis of rheumatic fever. Jones Criteria, 1992 update. Special Writing Group of the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young of the American Heart Association. JAMA 268:2069, 1992.

Figure 114-9. Erythema marginatum in acute rheumatic fever. The pen mark shows the location of the rash approximately 60 minutes previously. (From Cohen, Powderly: Infectious Diseases, 2nd ed. © 2004 Mosby, An Imprint of Elsevier.)

either oral or parenteral penicillin or erythromycin.[68,175] The duration of prophylaxis depends on patient age, the presence of cardiac involvement, the number of previous attacks, and other factors.

General Measures. Other than antibiotics, ARF treatments were developed well before the era of randomized controlled trials, so their evidentiary basis is suboptimal.[68,176] Nevertheless, the historic clinical experience with ARF is compelling. Bed rest with gradual mobilization once the initial carditis symptoms have abated has long been a mainstay of therapy.[68,159,177,178]

Medications. High-dose aspirin rapidly improves the arthritis and fever, but not the symptoms of carditis.[158,159,179] Naprosyn may be a more tolerable alternative to aspirin.[180,181] Prednisone 1 to 2 mg/kg/day slowly tapered after 2 to 4 weeks is generally recommended for patients with acute carditis, and it also alleviates the arthritis and the chorea.[158,159,174,182] Sydenham's chorea is often self-limited but can be controlled with haloperidol, valproic acid, or carbamazepine.[157–159]

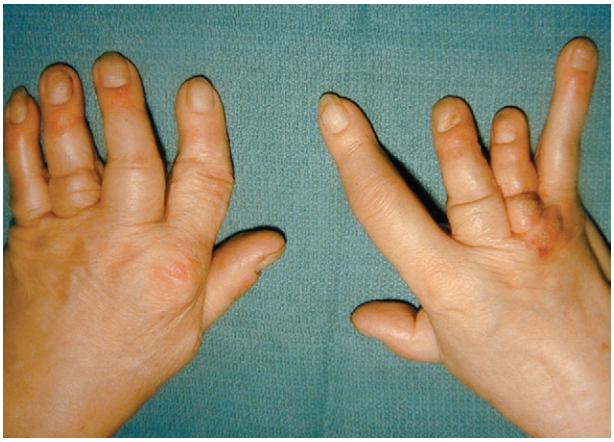


Figure 114-10. Arthritis mutilans (destructive arthritis) involving all digits. This condition may occur in either long-standing rheumatoid arthritis or psoriatic arthritis. (From Harris: Kelley's Textbook of Rheumatology, 7th ed. © 2005 Saunders, An Imprint of Elsevier).

POLYARTHRITIS—CHRONIC

Rheumatoid Arthritis

Epidemiology and Pathophysiology

Although RA is a chronic disease, at least 20% of patients have an acute presentation. RA develops in women two to three times more often than in men, with a peak incidence between the fourth and sixth decades of life. There appears to be a genetic predisposition related to the HLA-DR4 haplotype. Immune complexes are formed that stimulate PMNs to release the enzymes that ultimately cause joint destruction. The synovial cells increase dramatically in number and produce even more inflammatory substances. A pannus of granulation tissue is formed that ultimately destroys the joint.[183]

Clinical Presentation

Patients commonly see a physician after a prodromal period of fatigue, weakness, and musculoskeletal pain that may last weeks to months. The patient's joints begin to swell in a symmetrical and additive pattern, particularly the hands (MP and PIP joints), wrists, and elbows. The foot, however, may be the initial site of involvement and is affected in more than 90% of patients with RA, particularly the great and little toe MTP joints. The DIP joints of the fingers are not involved, which helps distinguish RA from osteoarthritis, reactive arthritis, and psoriatic arthritis.[184]

Acute presentations may have only warm, tender, swollen joints that may be difficult to distinguish from a viral arthropathy. Tenosynovitis can occur. Acute pericarditis is not related to the duration of disease and also may be an early presentation. In the patient with long-standing RA, long-term changes may be observed. These include MP and PIP swelling, ulnar deviation, swan neck and boutonnière deformities of the hands, and limitation of dorsiflexion of the wrist (Fig. 114-10). The knee is often affected, in the short term with effusion and in the long term with muscle atrophy and Baker cysts.[184] Bursae in the retrocalcaneal region are common complications. Extra-articular complications include subcutaneous nodules (associated with more severe disease), vasculitis of the skin, pulmonary fibrosis, mononeuritis multiplex, and Sjögren's and Felty's syndromes. Patients with long-standing RA may have degeneration of the transverse ligaments of the C1-C2 junction, and this requires that precautions be taken during endotracheal intubation.[106,109]

Diagnosis

The workup of the patient in whom RA is suspected should be directed at excluding other causes of arthritis, particularly septic arthritis. Rheumatoid factor, which is an antibody against gamma globulin, is positive in approximately 85% of patients with RA.[184] ESR and C-reactive protein levels may be elevated but are nonspecific and elevated in other rheumatologic diseases.

Early radiographic features of RA are soft tissue swelling and juxta-articular osteoporosis leading to uniform joint space narrowing. Arthrocentesis reveals inflammatory fluid with WBC counts between 4,000 and 50,000/mm^3 and more PMNs (75%) than usually seen with crystal disease.

Management

Excessive movement increases inflammation, so the initial treatment is rest in combination with anti-inflammatory medication.[185] For early mild disease, many clinicians often still use the salicylates or other NSAIDs, which have gastrointestinal and renal toxicities related to their inhibition of cyclooxygenase. Oral prednisone, 5 to 7.5 mg daily, can effectively control mild inflammation as a bridge to more advanced therapy in early disease. Because the first 12 to 18 months are critical in preventing major joint damage, particularly in aggressive disease, the era of disease-modifying antirheumatic drugs (DMARDs) has emerged.[110–112] Recent clinical studies support the efficacy of a combination of methotrexate and a tumor necrosis factor blocker in reducing early disease activity.[186] DMARDs are typically prescribed by the consulting rheumatologist, but emergency physicians should be familiar with their potentially life-threatening complications (Table 114-6).[34]

Adult-Onset Still's Disease

Adult-onset Still's disease (AOSD) is a rare multisystem inflammatory disorder characterized by acute arthritis, characteristic rash, and quotidian or double-quotidian fevers (with the highest temperatures seen in the late afternoon or early evening).[187] The rash is a salmon-colored macular evanescent rash that occurs only with the fever.[188] AOSD's protean manifestations include sore throat, myalgias, splenomegaly, hepatitis, and pericarditis.[187,188] The differential diagnosis includes

Table 114-6 Toxicity of Rheumatoid Arthritis Drugs

DRUG	CLASS	MAJOR TOXICITY	PEARL
Methotrexate	Conventional DMARD	Hepatic, bone marrow, lung	Pulse therapy less toxic than daily
Hydroxychloroquine	Antimalarial	Retinal	
Gold salts	Conventional DMARD	Bone marrow	Uncommonly used now
Anakinra	Anti-IL-1	Pneumonia, serious infections, leukopenia	Higher risk in patients with asthma
Abatacept	T cell modulator		Avoid in COPD
Leflunomide	Pyrimidine antagonist	Diarrhea	Very long half-life
Etanercept	Anti-TNF	Sepsis, pneumonia, tuberculosis	
Infliximab	Anti-TNF	Sepsis, pneumonia, tuberculosis	
Adalimumab	Anti-TNF	Sepsis, pneumonia, tuberculosis	
Rituximab	Anti-CD20 of B cell lymphocytes	Fatal infusion reactions	Multiple organ collapse typically with first infusion

COPD, chronic obstructive pulmonary disease; DMARD, disease-modifying antirheumatic drug; IL-1, interleukin-1; TNF, tumor necrosis factor.

other acute arthritides (especially rheumatic fever) and other causes of "fever of unknown origin."[189] Acute treatment options for AOSD include aspirin, NSAIDs, low-dose corticosteroids, and intravenous gamma globulin.[187,190]

Relapsing Polychondritis

Relapsing polychondritis, a rare multisystem disorder of unknown etiology, presents with recurrent severe inflammation of joints, sclera, ears, nose, and cardiac and tracheobronchial cartilage.[191] Airway compromise, which can be precipitous, is treated with high-dose steroids and sometimes stenting.[192,193]

Seronegative Spondyloarthropathies

The seronegative spondyloarthropathies share the characteristics of sacroiliac involvement, peripheral inflammatory arthropathy, absence of rheumatoid factor, pathologic changes around the enthesis (ligamentous and tendinous insertion into bone), and a genetic component related to the HLA-B27 marker. The most important of these chronic polyarthritic inflammatory diseases are ankylosing spondylitis, reactive arthritis, psoriatic arthritis, and the arthropathy of inflammatory bowel disease. While some clinical overlap exists, each has its own distinctive features.[194]

Ankylosing Spondylitis

Clinical Presentation. Patients with ankylosing spondylitis generally have back discomfort with radiologic evidence of sacroiliitis (see Fig. 114-2). There is a male predominance. The classic presentation is chronic, insidious back discomfort of more than 3 months' duration, with morning stiffness that improves with exercise, in someone under 40 years of age.[195] Uveitis is the most common extra-articular manifestation, but life-threatening aortic root disease can rarely occur.[195] The peripheral joints are involved in up to 30% of patients with enthesopathic involvement, such as plantar fasciitis and Achilles tendinitis. Radiologically, there is a symmetrical squaring of the margins of the vertebral bodies, and later the development of a "bamboo spine." MRI changes occur even earlier at the sacroiliac joint.[196]

Management. The goal of therapy is to control pain, decrease inflammation with NSAIDs, and begin physiotherapy and strengthening exercises.[195,197] The new anti-tumor necrosis factor agents also seem to be effective.[195,198]

Reactive Arthritis (Reiter's)

Clinical Presentation. Reactive arthritis occurs in genetically susceptible hosts after infection with *Chlamydia trachomatis* in the genitourinary tract or *Salmonella*, *Shigella*, *Yersinia*, or *Campylobacter* organisms in the gastrointestinal tract.[199] A number of other microorganisms have also been postulated as causative agents.[199] Reactive arthritis is generally a disease of young men 15 to 35 years of age in whom arthritis develops 2 to 6 weeks after an episode of urethritis or dysentery. Because cervicitis is often asymptomatic, the diagnosis is more problematic in women. The syndrome is predominantly polyarticular and asymmetrical. The weight-bearing joints of the lower extremities are commonly involved: knees, ankles, and feet, particularly the heels ("lover's heel").[200] Other physical signs appear early and may be gone when the musculoskeletal complaints persist. Patients may have conjunctivitis early in the disease, which may progress to uveitis.[199] Up to 10% of patients have initially painless lesions of the oral mucosa and tongue that later develop into shallow painful ulcers.[199] Similar lesions are seen on the glans penis (balanitis circinata), particularly in uncircumcised men (20% of patients). The penile lesions in circumcised men are more psoriatic in appearance. Fingers and toes may swell and appear sausage-like, a phenomenon that also occurs in psoriatic arthritis. In 10% of patients, hyperkeratotic lesions of keratoderma blennorrhagia (waxy plaques) develop on the palms and soles and look like pustular psoriasis. Patients may have inflammation at the insertion of the Achilles tendon, and up to one third of patients have low back pain with limitation of vertebral movement on range of motion.[200] Synovial fluid is inflammatory in nature with a predominance of PMNs. *Chlamydia*, *Salmonella*, and *Yersinia* antigens have been found in the synovial membrane and even in the joint fluid, but cultures are sterile. Early x-ray films show an enthesitis where ligaments attach to bone and occurs at the sacroiliac joints, ischial tuberosities, greater trochanter, and Achilles insertion.[200] Patients may have a single episode (the mean length of an episode is 4–7 months) or recurrent episodes of arthritis, or a continuous spectrum of disease generally involving the ankles and calcaneus.[200]

Management. Patients with reactive arthritis respond well to NSAIDs, particularly indomethacin, up to 200 mg/day. Antibiotics improve recovery time for patients with *Chlamydia-*

triggered reactive arthritis, but not thus far for arthritis with a gastrointestinal cause.[199]

Enteropathic Arthritis

Roughly 10 to 20% of patients with inflammatory bowel disease develop acute migratory, inflammatory polyarthritis of the peripheral joints, especially the knees.[200,201] Associated inflammatory sacroiliitis and spondylitis are more common with males.[200] The peripheral arthritis generally correlates with flare-ups of the bowel disease, but the spinal manifestations do not.[200,201]

Psoriatic Arthritis

Psoriatic arthropathy occurs in up to 20% of patients with psoriasis. Several forms exist: asymmetrical oligoarthropathy (with sausage digits), symmetrical polyarthropathy, spondylitis (asymmetrical as in reactive arthritis), DIP involvement, and arthritis mutilans (see Fig. 114-10).[202] Anti-tumor necrosis factor agents show promise for its treatment. [203]

Fibromyalgia

Emergency Department Considerations

Patients with fibromyalgia commonly present to the ED with diffuse musculoskeletal pain.[204] The encounter is typically unpleasant for both the patient and the physician because the disease is ill-defined, there may be suspicion of analgesic abuse, and psychiatric comorbidity is common.[204] Current thinking regarding the pathophysiology of this disorder hypothesizes that the patients process normal pain stimuli aberrantly.[205] Patients with fibromyalgia have a history of idiopathic widespread pain (bilateral, upper and lower body, and spine) and an examination showing excessive tenderness of 11 of 18 specific muscle-tendon sites. The differential diagnosis includes the other rheumatic diseases, hypothyroidism, and depression.[205]

Management. Treatment of fibromyalgia in the ED includes ruling out associated disease, relieving acute pain with anti-inflammatory medications, providing empathy and education, and referring the patient to a provider experienced in chronic pain management.[206] For patients in significant distress, the combination of tramadol 75 mg four times daily in combination with acetaminophen may give relief.[207] Selective serotonin reuptake inhibitors or low-dose tricyclic antidepressants improve both sleep and pain measures in patients with fibromyalgia.[205,208,209]

Polymyalgia Rheumatica

Polymyalgia rheumatica presents with musculoskeletal aching and morning stiffness, especially of the shoulder and pelvic girdle, generally in persons over age 50 years.[210,211] The ESR should exceed 50 mm/hr, but physical examination signs are modest.[210] Patients usually respond to low-dose prednisone (10 mg/day) and should be referred for evaluation for giant cell arteritis, a closely associated disorder.[210]

Scleroderma (Systemic Sclerosis)

Musculoskeletal manifestations of scleroderma include morning stiffness, generalized arthralgia, sclerodactyly, and Raynaud's phenomenon.[212] Scleroderma renal crisis is the most feared emergent complication.[213]

DISPOSITION

The major challenge in the emergency management of acute arthritis is ruling out septic causes. If a patient is diagnosed with nongonococcal septic arthritis based on a positive Gram's stain or culture, or based on strong clinical suspicion even in the face of a negative Gram's stain, the patient should be admitted with emergency orthopedic consultation for parenteral antibiotics and evaluation for possible arthroscopy or arthrotomy. Patients in whom a disseminated gonococcal infection is suspected should be admitted for parenteral antibiotics and orthopedic consultation, except in cases in which the patient is well-appearing, the symptomatology is mild, and the patient is able to comply with the daily follow-up plans. Patients with noninfectious causes of arthritis can be discharged, assuming their pain is controlled and appropriate follow-up is arranged.

KEY CONCEPTS

- The most likely cause of acute arthritis can usually be identified by considering the time course (greater or less than 6 weeks' duration), the number of joints involved (monarticular vs. polyarticular), and the distribution of joint involvement (large vs. small joints and symmetrical vs. asymmetrical joint involvement).
- The possibility of septic arthritis should be considered in all patients who present with monarticular arthritis.
- The most definitive test for evaluating an inflamed joint for the possibility of bacterial infection is synovial fluid analysis. Delays in the diagnosis and treatment of septic arthritis worsen outcomes.
- A negative Gram's stain of synovial fluid does not rule out bacterial arthritis.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 115

Tendinopathy and Bursitis

Michael J. Schmidt and Stephen L. Adams

TENDINOPATHY

Perspective

Diseases of rheumatism have long been of concern to physicians, with evidence that many of Hippocrates' aphorisms made reference to such ailments. In the mid-1600s, Sydenham, a physician who had gout, described gout, acute rheumatism, and Sydenham's chorea and hence began to identify distinctions among various processes of musculoskeletal complaints and joint inflammations.[1] Today, given the increased participation of people in athletics and fitness, the emergency physician may see a wide variety of patients with tendinopathies due to overuse and injury.[2] Approximately half of all sports participants will be injured at some time, and of these injuries, up to one half will involve a tendinopathy. Among athletes, studies have indicated that tendinopathies have been involved in approximately 30% of running-related injuries and in nearly 40% of tennis injuries.[3,4] In the workplace, the incidence of work-related musculoskeletal disorders is higher in occupations that involve repetitive motion, localized contact stress, awkward positions, vibrations, and forceful exertion. Studies have demonstrated that improvements in ergonomic design can reduce the incidence of tendinopathies.[5]

Complicating the acute pain and functional limitations, tendinopathies often become chronic and can be disabling. Patients may have symptoms for extended periods of time despite appropriate therapy.[6] The management of tendinopathy focuses on identification of the cause of discomfort; elimination of sources of primary tendinopathy; institution of treatment modalities such as analgesic medication, protection, relative rest, application of ice, compression, and elevation as necessary; modification of behavior to minimize or eliminate sources of continuing irritation; and, importantly, referral for appropriate follow-up care.[7,8]

Principles of Disease

Tendons are collagenous structures that connect muscle to bone. They transmit the forces originating in the muscle to the bone, which enables joint motion.[7] The diagnosis of *tendinitis*, a commonly used term implying an "inflammation of the tendon," has long been attached to many overuse injuries.[2] Many practitioners now advocate use of the term *tendinosis* as a more accurate reflection of the pathologic process, given that histologic findings consistent with inflammation are not clearly evident in pathoanatomic studies.[2,9] Although it has been noted that reliable, well-conducted epidemiologic studies have not been performed for most tendinopathies, the histopathologic substratum, in many cases, is degenerative.[2] The term *tendinopathy* is used throughout this chapter to refer to the impaired tendon, as it encompasses the variety of pathologies.[2]

Mechanical overload and repetitive microtrauma to the musculotendinous unit are thought to be the major precipitating causes of most tendinopathies. This is a result of extrinsic and intrinsic factors that modify the pathophysiologic state.[10] Intrinsic factors, such as malalignment, poor muscle flexibility, muscle weakness, or imbalance, can result in excessively high or frequent mechanical loads during normal activity. Extrinsic factors, such as poor ergonomic design or excessive duration, frequency, or intensity of activity, can also contribute to the development of a tendinopathy. Many injuries have a multifactorial origin. Individual factors can contribute as well. For example, a young athlete may develop a tendinopathy as a result of mechanical overload on the basis of repetitive exercise and poor technique, whereas an older athlete with previously occult underlying tendon degeneration and decreased vascularity may see the symptoms of a tendinopathy develop with minimal exercise.[10] An increased incidence of tendinopathy and tendon rupture, particularly of the Achilles tendon, is reported in patients taking fluoroquinolone antibiotics, particularly in individuals older than 60 years who are receiving steroid treatment.[11-13]

Under optimal conditions, such as appropriate athletic training, the musculotendinous units are able to adapt to tension overload because of the ability of bone to increase its load-bearing capacity and due to an increase in size and strength by hypertrophy of existing muscle fibers. An enhancement of tendon and ligament strength occurs by an increase in collagen content, collagen cross-linking, and mucopolysaccharide content.[8] Unfortunately, many athletes may not allot sufficient time for this adaptive process to occur. For instance, a runner may increase mileage, intensity, or both with excessive alacrity, not allowing time for the cellular changes that are required to adapt to the increased stresses. Poor technique and improper equipment may also contribute to the development of an overuse syndrome.[8]

As the damaged tendon goes through several stages in the healing process, it may take 6 to 12 weeks for structural organization and collagen cross-linking to return the tendon to its preinjured strength.[8]

As the healing process ensues, unrestricted activity is generally avoided. However, atrophy associated with immobilization should also be avoided because the strength in healing tendons

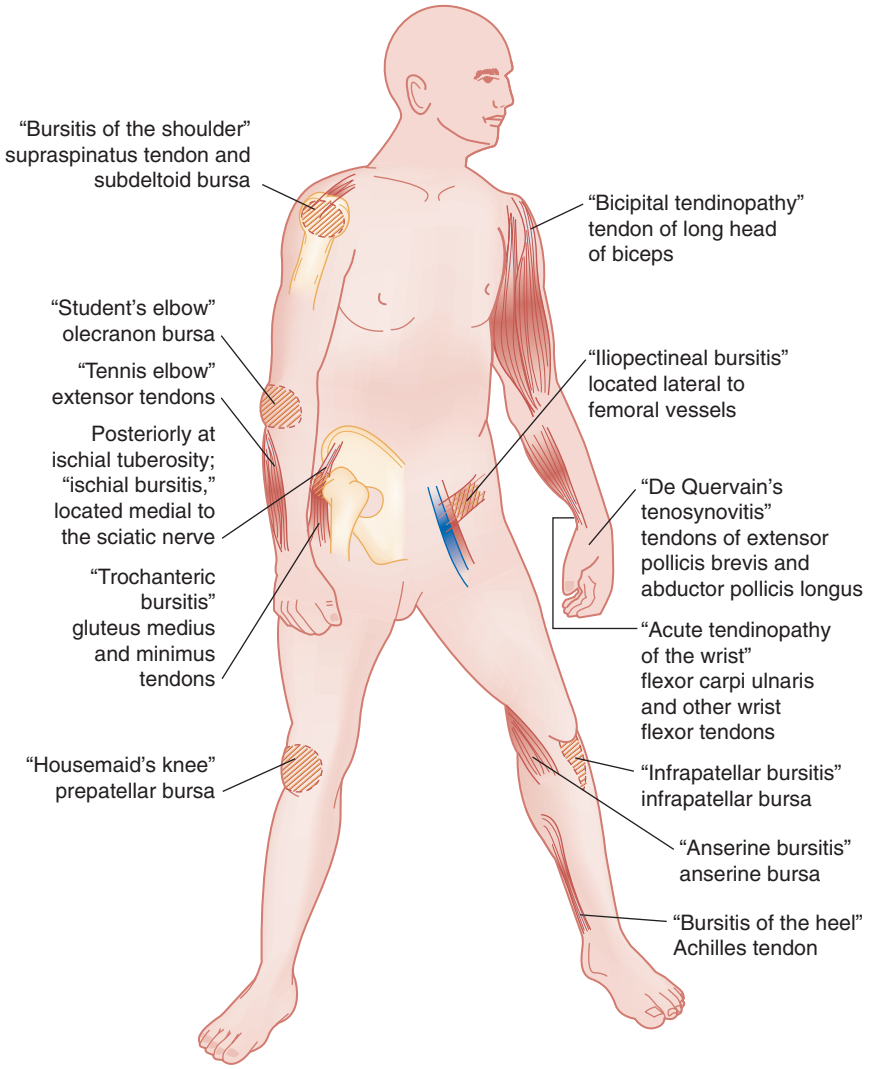


Figure 115-1. Location of common sites for tendinopathy or bursitis. (Modified from Branch WT: Office Practice of Medicine, 2nd ed. Philadelphia, WB Saunders, 1987.)

and ligaments increases faster when controlled forces are applied. Consequently, flexibility forces, isometric contractions, and a measured return to resistive exercises have been suggested as long as pain is not produced.[8] In summary, a prescription for good follow-up with proper rehabilitation is important in caring for the patient with tendinopathy.

Some areas with common presentations of tendinopathies are diagrammed in Figure 115-1.

Clinical Features

History

The history of the patient presenting with a tendinopathy can be quite variable, although certain clinical aspects are characteristic. A recent history of repetitive stress may be obtained by inquiring about changes in sports or other recreational activities, work activities, or changes in the workplace. Many patients initially report no such changes, but when prompted to consider activities over several weeks or months (including sports equipment utilized, workplace ergonomic features, protective boots, or other features), a potential inciting change or activity may be elicited. Occasionally, no cause is identified for an inciting mechanical overload. A history of infectious disease, fluoroquinolone therapy, or other systemic illness should also be obtained.[11-16]

Pain is the most common symptom of the patient who presents with tendinopathy. Increasing discomfort, nonradiating, at the site of the affected tendon is a general symptom.[7] The discomfort is frequently described as more severe subsequent to periods of rest. Unlike the discomfort of morning stiffness associated with arthritis, the pain of tendinopathy may resolve after initial movement, only to manifest itself as a throbbing pain after completion of exercise. The patient may have had prior similar epsiodes.[7] Continued episodes may be accompanied by an increased severity in pain. Consequently, it may be helpful to know whether a diagnosis was made (and how) and which treatment rendered (if any) was successful.

Physical Examination

In the evaluation of the patient with a tendinopathy, a thorough, directed musculoskeletal examination yields important information. Inspection searching for signs of edema, effusion, erythema, atrophy, deformity, symmetry, or trauma can be helpful. Palpation of the tendon, noting warmth or evidence of crepitation on movement, is important. Evidence of tenderness over the tendon, especially localized, reproducing the patient's pain should be elicited.[7] Underlying bony tenderness (and consideration of other differential diagnoses, including avulsion fracture and osteomyelitis) should be assessed as well. Motor evaluation, particularly passive and active range of

motion (and symptoms elicited during the examination), strength (and evidence of weakness or pain), and joint involvement and stability should be noted.

In narrowing the diagnosis, it is important to determine whether the source of pain is articular (within the joint capsule) or periarticular (around the joint capsule). In general, arthritis produces generalized joint pain, warmth, swelling, and tenderness. The discomfort of arthritis increases with both passive and active motion of the joint. In contrast, the pain of a tendinopathy tends to be more localized.[7] Tenderness and swelling do not occur uniformly across the joint, and pain may be produced only with certain movements, most commonly with resisted active contraction or passive stretching of the affected muscles or tendons.

Specific Tendinopathies

Shoulder

Tendinopathies of the shoulder joint include impingement syndrome, which includes subacromial bursitis or rotator cuff tendinopathy, bicipital tendinopathy, calcific tendinopathy, and adhesive capsulitis.[17]

Impingement Syndrome and Rotator Cuff Tendinopathies. The shoulder joint is predisposed to soft tissue injury because of its extensive range of motion and unique anatomic structure. Although inherently unstable, the muscles of the rotator cuff (supraspinatus, infraspinatus, teres minor, and subscapularis) and the glenohumeral ligaments serve to stabilize the joint. The muscles of the rotator cuff originate from the scapula (hence their nomenclature), and their tendinous insertion is found on the fibrous capsule of the glenohumeral joint after traversing through the subacromial space. The presence of the subacromial bursa, as for all bursae, serves to ensure fluidity of movement but it may become inflamed as a part of an impingement syndrome.[17] Impingement of the tendons occurs because of their unique position interposed between the humeral head and the acromion, which may predispose to a chronic tendinopathy. The functional arc of the elevated shoulder is forward and in the anterior plane.[18] As a result of this position, the greater tuberosity of the humerus may compress (impinge) the tendons of the rotator cuff (usually the supraspinatus) against the undersurface of the anterior third of the acromion. Because of the insertion of the tendon of the long head of the biceps, it too may be involved as part of the impingement syndrome.[19] Development of this tendinopathy may be a result of overuse of the extremity that leads to microtrauma of the tendinous fibers or due to individual anatomic differences (congenital or from the process of aging, such as osteophytic changes) that predispose to tendinopathy, or both. Other entities that may coexist and complicate an impingement syndrome include subacromial bursitis, bicipital tendinopathy, and calcific tendinopathy.[17]

More than 30 years ago, Neer noted that 95% of rotator cuff tears are associated with impingement (excluding tears due to a one-time traumatic event).[18,20] He described three progressive stages of the impingement syndrome as a result of overuse.[18,20] The first stage is frequently seen in athletes younger than 25 years who participate in sports that require repetitive overhead motions of the shoulder (e.g., swimming and baseball).[20,21] It is characterized by edema and hemorrhage within and around the tendon. The pain is usually described as a dull ache over the anterolateral shoulder, extending from the shoulder to the middle upper arm, often occurring after an activity involving flexion and abduction of the arm. Point tenderness may be elicited over the greater tuberosity. No weakness or loss of motion is generally present. This condition is generally believed to be reversible with appropriate treatment. In the second stage, as mechanical trauma continues, fibrosis and thickening of the tendon and subacromial bursa can occur. This generally affects patients between 25 and 40 years of age. The pain becomes constant and may worsen at night. Active motion may be limited by pain, and any activity involving overhead movement exacerbates the symptoms. Passive range of motion should be preserved, and on physical examination, pain is more diffuse and intense. The third stage has symptoms similar to those of the second stage but may involve a prolonged history of shoulder problems. The range of motion of the shoulder is usually decreased due to either disuse or a partial rotator cuff tear.[20] Pathologically, tendon degeneration and attrition may be present. Partial-thickness tears may occur or extend with minor trauma or stress. Complete tears of the rotator cuff, biceps tendon rupture, and osteophytic bony changes are sometimes seen.[17,18,20]

Physical examination in the evaluation of a rotator cuff tendinopathy includes maneuvers that can exacerbate the symptoms of impingement. Because the supraspinatus tendon is most often involved, a physical examination sign (sometimes referred to as *Jobe's sign*, after Dr. Frank Jobe, team physician of the Los Angeles Dodgers, or the *empty can test*, describing the position of emptying aluminum cans) is helpful in assessing the supraspinatus tendon with resistance testing. With the arms abducted at 90 degrees in the scapular plane (30 degrees anterior to the coronal plane), the arms are internally rotated with the thumbs pointed downward. The examiner places a downward force on the arms, and the patient is instructed to resist the examiner and keep the arms parallel to the floor. Weakness or pain would be considered a positive finding. If the patient is unable to resist the force of the examiner, supraspinatus weakness should be suspected.[18,22]

Another sign of rotator cuff tendinopathy is the Neer test, which suggests mechanical impingement with decrease of the subacromial space. The examiner forward-flexes the arm, which causes impingement of the greater tuberosity of the humerus with the anterior and inferior edge of the acromium. The patient's shoulder should then be fully flexed to 180 degrees. A positive result occurs if there is pain produced at the end range of the arc.[18,22]

The Hawkins test, also indicative of mechanical impingement, is performed by forcibly internally rotating the proximal humerus while the shoulder is forward-flexed to 90 degrees and the elbow flexed to 90 degrees. Pain with this maneuver indicates a positive finding.[17,18,22]

A sign of complete rotator cuff tear is the drop arm test, in which the arm is passively abducted at 90 degrees and the patient is asked to maintain the abduction. If the arm drops to the side, a large rotator cuff tear must be considered.[20,22]

The shrug sign is exhibited when a patient with acute macrotrauma to the rotator cuff is asked to abduct the arm at 90 degrees and appears to be giving a shrug with that side. This movement results from the scapula attempting to abduct the arm without the assistance of the rotator cuff.[23] Patients with adhesive capsulitis (frozen shoulder) have limitation of active and passive range of motion.[24]

Bicipital Tendinopathy. The tendon of the long head of the biceps, given its insertion into the humerus in proximity to the rotator cuff, can be associated with the impingement syndrome. The patient with bicipital tendinopathy may report pain in the anterior shoulder that radiates down to the radius. Discomfort occurs when rolling on the shoulder at night or when attempting to reach a hip pocket or a back zipper. Focal tenderness can be obtained by palpation in the groove between the greater and lesser tuberosities of the humerus while testing for Yergason's sign, which is elicited by having the patient flex

the elbow to 90 degrees with the arm against the body and resisting supination of the forearm. Pain in the area of the proximal tendon is considered to be a positive finding and indicative of bicipital tendinopathy.[19,22]

Another physical examination tool in the diagnosis of bicipital tendinopathy is the Speed test. With the elbow extended and the forearm supinated, the patient is instructed to resist forward flexion of the adducted shoulder at 60 degrees. Pain in the area of the proximal biceps tendon (bicipital groove) is indicative of a positive finding. (This may also be suggestive, however, of labral pathology.[19])

Calcific Tendinopathy. Calcific tendinopathy is an aptly named condition in which the deposition of calcium hydroxyapatite crystals occurs in or around the tendons of the rotator cuff. The cause is unknown but has been postulated to be related to continuous microtrauma.[17] It can manifest as either an acute or a chronically painful condition. Although it can affect any of the rotator cuff tendons, it seems to have a predilection for the supraspinatus. The symptoms are similar to those of an impingement syndrome, and the condition generally affects people older than 40 years. Calcium deposition occurs over time and then undergoes spontaneous resorption. This resorptive phase is thought to be the painful aspect, but the severity of the symptoms is not related to the size of the deposit.[17] Some practitioners have suggested that acute attacks of calcific tendinopathy also occur secondary to crystal release from the tendon, often after trauma.[25]

On physical examination, there may be specific tenderness over the greater tuberosity as well as symptoms consistent with impingement. Radiographic evaluation will confirm evidence of calcification in or around the rotator cuff tendons. The presence of calcium in the tendon does not necessarily affirm the origin of the pain because asymptomatic patients may have evidence of calcification on a routine radiograph.[26]

Elbow

Increasingly, athletes of all ages and skill levels are participating in sports involving overhead arm motions; consequently, elbow injuries are increasingly seen.[27] From an anatomic and functional perspective, the extensors and supinators of the wrist attach to the lateral elbow, and the flexors and pronators attach medially.

Lateral Epicondylitis. Lateral epicondylitis ("tennis elbow") is a painful elbow condition that occurs at the insertion of the common extensor tendon (extensor carpi radialis brevis) onto the lateral epicondyle of the humerus. Although it occurs in many tennis players, epidemiologic studies suggest that fewer than 5% of patients with such a syndrome actually play tennis. Activities such as driving in screws, use of a wrench, and repetitive work on an assembly line have also been implicated. Symptoms often begin as a dull ache on the outer (lateral) aspect of the elbow.[21,25,28] The discomfort can be exacerbated by activities that involve extension or supination of the wrist, such as grasping and twisting. The Cozen test is performed by having the patient keep the fist clenched while extending the wrist. The examiner grasps the forearm with the left hand while the right hand pulls the patient's hand toward flexion against the patient's resistance. A positive finding is pain at the lateral epicondyle, reproducing the patient's symptoms.[29]

Active extension of the long finger against resistance with the elbow in extension can also reproduce the pain over the lateral epicondyle at the insertion of the extensor carpi radialis brevis. A similar sign, referred to as "the finger-snapping test," is characteristic for an enthesopathy of the extensor carpi radialis brevis. If the test is negative, it is assumed that the pain is caused by spondylogenic, arthrogenic, or neurogenic phenomena.[30]

Radiographs can be helpful in cases with atypical or prolonged symptoms and to rule out other pathologic conditions. Approximately 20% of patients demonstrate tendon calcification or a reactive exostosis at the tip of the epicondyle.[28]

The differential diagnosis of lateral epicondylitis includes posterior interosseus nerve entrapment (motor aspect of radial nerve in forearm). Other associated lesions include plica, synovitis, chondromalacia, and adolescent osteochondral defect.[28]

Medial Epicondylitis. The pain of the less common medial epicondylitis ("pitcher's elbow" or "golfer's elbow") can result from microtrauma at the site of the insertion of the flexor carpi radialis on the medial epicondyle. It is important to differentiate medial epicondylitis from other causes of medial elbow pain, including medial ulnar collateral ligament injury. As a result of repetitive valgus stress placed on the joint, microtraumatic injury and valgus instability at the ligament can occur. With disruption of the medial ulnar collateral ligament, abnormal stress is placed on the articular surfaces, which may lead to degenerative changes and the formation of osteophytes.[27,31] In the case of medial epicondylitis, patients will generally have tenderness over the flexor-pronator origin slightly distal and anterior to the medial epicondyle. Pain can be reproduced by having the patient attempt wrist flexion and forearm pronation against resistance.[32]

Wrist

De Quervain's Tenosynovitis. The wrist and hand comprise several tendons that pass through thick, fibrous retinacular tunnels. These help prevent subluxation of the tendons and act as a pulley system. Overuse syndromes are thought to result from changes of the synovial lining between these tendons and retinaculum. De Quervain's tenosynovitis involves the synovial lining of the abductor pollicis longus and extensor pollicis brevis. Although the term *tenosynovitis* indicates an inflammation of the tendon sheath, it has been noted that there are many potential forms of tenosynovitis. Classic acute inflammatory changes that are characteristic of tenosynovitis may be related to systemic manifestations of disease (e.g., rheumatoid arthritis and gout); tenosynovitis related to de Quervain's syndrome is referred to by some practitioners as *stenosing tenosynovitis*. The pathology of de Quervain's tenosynovitis does not generally involve inflammation because the primary pathologic change seen is thickening of the extensor retinaculum covering the first dorsal compartment of the wrist. It has been suggested that de Quervain's disease is a result of intrinsic degenerative mechanisms rather than extrinsic inflammatory ones.[33]

The history may consist of chronic, repetitive trauma or unaccustomed repetitive efforts such as firm grasping and movement of the hand in a radial direction. Direct trauma, such as a direct blow or fall, has occasionally been implicated.[34] The discomfort of de Quervain's tenosynovitis can be localized over the radial styloid process. Radiation of pain proximally to the forearm or distally down the thumb has been noted. The pain is generally constant but may be exacerbated by maneuvers that include grasping, abduction of the thumb, and ulnar deviation of the wrist. In many cases of De Quervain's tenosynovitis, the onset is gradual and not associated with a history of acute trauma.[34]

On physical examination, slight swelling may be seen over the radial styloid. Crepitation may be palpable over the tendons with flexion and extension of the thumb. An increase in the tensile load (passive stretching or active contraction) in the abductor pollicis longus or extensor pollicis brevis increases

pain.[34] The Finkelstein test, which exacerbates the discomfort of de Quervain's tenosynovitis, is the most pathognomonic physical sign. The patient is instructed to hold the affected thumb in the palm by the fingers and then to ulnar-deviate the wrist. Pain will occur near the radial styloid, which is also the point of tenderness. Pain with this maneuver is considered to be a positive finding. Routine laboratory study findings and radiographs are characteristically normal.[34]

The differential diagnosis includes scaphoid fracture and osteoarthritis of the carpometacarpal joint, which has pain caused by longitudinal traction and compression. Tuberculous tenosynovitis can manifest with a tenosynovitis of the extensor tendon of the thumb, and gonococcal tenosynovitis has been reported as an extensor tenosynovitis as well.[34]

Knee

Patellar Tendinopathy. Patellar tendinopathy or "jumper's knee" occurs in sports that have jumping as a part of the activity, although it can also occur as a result of other sporting activities.[35] Patients complain of pain at the inferior pole of the patella. The discomfort may abate with activity early in the tendinopathy but later progresses to the point of discomfort during exercise and at rest. With the knee flexed at 30 degrees, which relaxes the quadriceps, tenderness may be localized to the deep surface of the proximal attachment of the patellar tendon at the inferior pole of the patella. However, healthy active athletes sometimes have tenderness on examination as well.[35,36]

The differential diagnosis includes patellofemoral syndrome, which arises from imbalances in the forces controlling tracking during knee flexion and extension. The patient usually complains of anterior knee pain, described as "behind" or "around" the patella, which is classically worse when ascending or descending stairs or on rising from a seated position. Occasionally, there is tenderness of the medial or lateral retinacula or facets.[37]

Imaging with ultrasonography and magnetic resonance imaging (MRI) may reflect collagen degeneration but is generally adjunctive to the distinctive history and physical examination findings. It is noted that some asymptomatic jumping athletes have similar appearances to those affected, and that prognosis and outcome are not predicted by such imaging.[35]

Ankle

Achilles Tendinopathy. Achilles tendinopathy is a common overuse syndrome that typically affects male athletes. The Achilles tendon, named for the mythological Achilles, whose heel was not immersed in the River Styx as his mother dipped him in the river for its protective powers, arises from the medial and lateral heads of the gastrocnemius muscle and the deep layers of the soleus muscle and inserts on the calcaneal tuberosity. A major function is plantar flexion of the foot. It is the strongest and largest tendon in the body and can withstand tensile loads over 12 times the body's weight during running.[38]

The Achilles tendon is vulnerable to injury from either trauma or overuse. A tendinopathy can also develop as a result of systemic disease (e.g., ankylosing spondylitis, Reiter's syndrome, gout, and pseudogout). The use of fluoroquinolones has also been related to Achilles tendinopathy.[13]

The occurrence of Achilles tendinopathy is highest among individuals who participate in middle- and long-distance running, orienteering, track and field, tennis, badminton, volleyball, and soccer.[38] Some studies have noted an almost 10% annual incidence of Achilles disorders in elite runners.[38] The most common Achilles disorders are tendinopathy (55–66%) and insertional problems such as retrocalcaneal bursitis and insertional tendinopathy (20–25%).[38] Many cases of Achilles tendinopathy are thought to be multifactorial in origin. Body mechanics and environmental factors (e.g., uneven terrain) may apply valgus or varus stress to the tendon. Technique, equipment, and body mechanics can also contribute to the development of this tendinopathy. Anatomically, the vascular supply to the tendon creates a watershed area approximately 2 to 6 cm above the calcaneal insertion. This is thought to be responsible for clinical symptoms and the pathologic disruption commonly seen at this site.

The patient's history should provide the majority of the information to make the diagnosis of Achilles tendinopathy.[38] Pain, a cardinal symptom of Achilles tendinopathy, may lead the patient to seek medical help. Some practitioners have noted that the patient's symptoms reflect the degree of the tendon abnormality. As with many tendinopathies, pain following strenuous activities is reported in the early phase, whereas pain in the later phase occurs during activity and even at rest. At this point, the patient is often unable to perform sporting activities.[38]

On physical examination, inspection of the contour of the muscle-tendon unit and areas of swelling and erythema should be evaluated. Acutely in Achilles tendinopathy, the tendon may be diffusely swollen and exhibit tenderness on palpation, usually greatest in the middle third. Typically, in the patient who has acute symptoms of tendinopathy, the area of swelling and tenderness does not move with dorsiflexion of the ankle joint.[38] On palpation, local heat, crepitation, and palpable tendon nodules or defects should be noted. Examination for ankle instability and biomechanical faults may be considered as well.[38]

Achilles Tendon Rupture. Although rupture of the Achilles tendon most often occurs when preceded by tendon damage,[39] it is possible for untrained athletes to apply excessive force and rupture the tendon, even in the absence of prior changes of tendinopathy. Partial and complete rupture may occur, most commonly in 30- to 40-year-old men. Complete rupture is more common in the middle-aged recreational athlete. Historically, the patient may note a "popping" sensation followed by acute weakness and inability to continue the exercise or sport. The patient may report that it felt as though someone kicked him or her in the back of the ankle or, if playing a racket sport, as if he or she were struck on the calf by a ball.

On physical examination, a defect in the tendon can sometimes be palpated. If enough time has elapsed to allow hematoma formation, bogginess may be noted over the injured area of the tendon. It is important to note that the ability to plantarflex the foot is not incompatible with a complete rupture of the Achilles tendon. There are multiple plantar flexors of the foot and toes. Muscles such as the tibialis posterior, flexor digitorum longus, flexor hallucis longus, peroneus brevis, and peroneus longus can remain functional and therefore disguise a complete rupture with the ability to plantar-flex the foot.[40,41] The Simmonds (Thompson) test can be performed to evaluate for complete rupture. With the patient prone and feet hanging over the edge of the bed, the examiner squeezes the calf muscles at their widest point and looks for passive plantar flexion. The absence of plantar flexion is considered a positive finding, indicative of a complete tear of the Achilles tendon. The presence of plantar flexion does not, however, negate the possibility of a partial tear of the Achilles tendon.[41]

Diagnostic Strategies

The diagnosis of tendinopathy is generally made on clinical grounds. Although plain radiographs may be helpful in

excluding bony abnormalities, ultrasonography has been recommended by some practitioners as the modality of choice for evaluating pathologic tendon conditions.[42] Ultrasonography can be especially useful when other conditions (e.g., gouty arthritis) obscure the findings of concomitant tendinopathy. Although ultrasound imaging is employed in the emergency department, the use of this imaging technique for soft tissue evaluation in this setting is relatively unstudied and, thus, it is not frequently used.[43,44] In cases of acute or chronic tendinopathy, one or more of the following features can be seen: loss of the fibrillar echotexture, focal tendon thickening, diffuse thickening, focal hypoechoic areas, extended hypoechogenicity, irregular and ill-defined borders, microruptures, and peritendinous inflammatory edema.[45] Hypoechoic areas surrounding tendons provide evidence for surrounding soft tissue inflammation. In addition to tendinopathy, tendon tears, both partial and complete, can be delineated by ultrasonography.[45]

Magnetic resonance imaging has been used to visualize pathologic conditions of the tendon. It is able to provide high intrinsic tissue contrast, which permits the distinction between normal tendons and abnormal tendons, as well as providing the high spatial resolution that permits detailed anatomic structures to be identified. The resolution of the tendon by MRI can aid in the diagnosis of Achilles tendon disorders, which include rupture (complete or partial), postoperative assessment of tendinous healing, tendinopathy, tenosynovitis, and various tumors of the Achilles tendon.[46]

Differential Diagnosis

The differential diagnosis for tendinopathy includes tendon ruptures, bursitis, ligamentous injuries, septic and inflammatory arthritis, nerve entrapment syndromes, and bony abnormalities such as fracture, foreign body, tumor, and osteomyelitis.

Management

The management of tendinopathy focuses on identification of the cause of discomfort; elimination of sources of primary tendinopathy; institution of treatment modalities such as analgesic medication, protection, relative rest, application of ice, compression, and elevation as necessary; modification of behavior to minimize or eliminate sources of continuing irritation; and, importantly, referral for appropriate follow-up care.[7,8]

Cryotherapy (cold treatments, 20 minutes at a time every several hours, for the first 24 to 48 hours) may be beneficial. Nonsteroidal anti-inflammatory drugs (NSAIDs) are also sometimes indicated to provide pain relief, although there is little evidence to support a beneficial effect with their use because tendinopathies tend to represent a degenerative, rather than inflammatory, process.[47] Graduated range-of-motion exercises may be useful after the period of immobilization. Although often used, the role of corticosteroid injection for most tendinopathies is unclear.[48,49] The use of corticosteroid injection in the emergency department is controversial. Steroids should not be injected into such major tendons as the Achilles tendon and patellar tendon, which may be at risk for spontaneous rupture if already weakened.

Impingement Syndrome and Rotator Cuff Tendinopathies. The treatment for rotator cuff tendinopathies and the impingement syndrome follows the treatment of tendinopathy in general. Emphasis is placed on physical rehabilitation and strengthening exercises. A significant proportion of patients will improve with conservative management. In those who do not, surgical intervention, such as acromioplasty or repair, may be indicated.[50,51]

Calcific Tendinopathy. The treatment of calcific tendinopathy is mainly conservative and consists of analgesia and brief sling immobilization because prolonged immobilization may result in adhesive capsulitis.[17] The use of corticosteroids is controversial. Ultrasonography and extracorporeal shock wave therapy have been utilized with some success.[26] A small percentage of patients who do not respond to the previously discussed interventions may need surgery. Localized disruption in the resorptive phase by needle lavage under fluoroscopy or in the operating room has been noted to be an efficacious therapy.[26] Follow-up care is important because calcific tendinopathy has been described as the best known cause of reactive cuff failure.[17]

Lateral and Medial Epicondylitis. In up to 95% of patients, epicondylitis will improve with conservative therapy.[27] Initial efforts include making the patient more comfortable with the standard principles of protection, relative rest, cryotherapy, compression, elevation, medication (NSAIDs), and modalities of physical therapy. The term *relative rest* implies the avoidance of abuse and not the absence of activity. Activities that aggravate the pain should be eliminated, and an attempt to protect the tendon through such strategies as a reduction in playing time or intensity should be considered. Control of force loads by bracing, improved performance technique, and use of appropriate equipment should also be considered. Follow-up evaluation should be ensured.[28]

De Quervain's Tenosynovitis. The initial treatment of de Quervain's tenosynovitis consists of immobilization with a thumb spica splint, anti-inflammatory medications, and prompt, appropriate referral. Corticosteroid injection has been shown to be an effective treatment for de Quervain's disease, and failure to respond may be due to anatomic variation or poor technique. Surgical decompression of the first dorsal compartment may be indicated if these treatments fail.[33]

Achilles Tendinopathy and Rupture. In addition to routine conservative treatment, patients with Achilles tendinopathy should be referred for orthopedic evaluation and correction of limb malalignment with the use of orthotics or heel lifts. Eccentric loading exercise and low-energy shock wave therapy have been shown to be effective therapies for Achilles tendinopathy. [52-54]

The management of Achilles tendon rupture may be either operative or nonoperative, depending on the patient involved. Appropriate consultation with an orthopedist is essential. A conservative approach, including immobilization in a short or long leg cast in the equinus position, may be indicated.[55] Some authors note that complete ruptures in active athletes should be treated surgically in most cases.[56] Although other risks and benefits must be taken into consideration, some studies indicate that early surgery may be indicated because the risk for Achilles tendon re-rupture is less.[55,56]

Disposition

Most patients with tendinopathy are safely discharged home with proper discharge instructions, relative rest of the tendon, analgesia, and appropriate follow-up. The exception is elderly or disabled patients for whom the tendinopathy renders them unable to perform the activities of daily living. Although appropriate rest and analgesia provide symptomatic relief, underlying causes should be sought and modified.

BURSITIS

Perspective

Bursae are closed, round, flat sacs lined by synovium.[57,58] They occur at areas of friction between skin and underlying

ligaments and bone. The bursa permits the lubricated movement of soft tissues over areas of potential impingement (e.g., subacromial bursa) and friction (e.g., olecranon bursa and prepatellar bursa). Many bursae are nameless, and new bursae can form as a result of frequent irritation.[57,59] The two most common identifiably inflamed bursae are the olecranon and the prepatellar. When these bursae are inflamed, they are generally recognizable over the extensor surface of the elbow or the knee, respectively.

Principles of Disease

Many cases of bursitis are idiopathic in nature, but common identifiable causes of inflammation include infection (most often due to *Staphylococcus aureus*), trauma (which may predispose to infection), rheumatologic disorders (e.g., gout, pseudogout, ankylosing spondylitis, and rheumatoid and psoriatic arthritis), and other systemic diseases.

Clinical Features

Olecranon and Prepatellar Bursitis

Less than half of patients who present to the emergency department with olecranon or prepatellar bursitis show signs of an infectious origin.[59-61] Distinguishing septic from nonseptic bursitis is not always straightforward, either on clinical grounds or as a result of diagnostic testing.[60] Patients with septic bursitis generally present earlier in the clinical course and have more pain, tenderness, erythema, and warmth compared with those who have an inflammatory process.[58] The most important predisposing factor in septic bursitis is trauma, which precedes septic bursitis in up to 70% of cases.[58] Other predisposing factors for septic bursitis include chronic illness such as diabetes mellitus or alcohol abuse, chronic skin conditions such as atopic dermatitis, and previous noninfectious inflammation of the bursae such as rheumatoid arthritis or gout.[58,62] It may also be seen more commonly in people in occupations in which repetitive knee (e.g., carpet layer) or elbow (e.g., miner) trauma is common.[59]

The olecranon bursa, on the extensor surface of the elbow, is the only bursa of the elbow joint and is easily traumatized, resulting in inflammation, pain, and swelling. Septic bursitis involves the olecranon more commonly than the prepatellar bursa.[60] Infection can occur from local trauma (e.g., puncture wound and laceration) but may also be present in the absence of visible trauma. Hematogenous bacterial seeding has been described as rare, probably due to the limited vascular supply of the bursal tissue; however, some series have noted up to an 8% incidence of an associated bacteremia.[56,57]

On physical examination, localized swelling and fluctuance are usually present.[59] In the septic bursa, tenderness is present in more than 90% of patients, and there is evidence of a traumatic wound (e.g., abrasion and laceration) in half of patients.[59] A nontender bursal effusion is usually present in nonseptic (e.g., traumatic and idiopathic) types of bursitis, although up to 45% of patients have mild tenderness, and one fourth have mild peribursal edema, warmth, and erythema.[59] Fever is more commonly seen in patients with septic than in those with nonseptic bursitis.[57] Most patients with septic bursitis present with swelling and peribursal cellulitis, and there may be peribursal soft tissue inflammation.[59] Crystal-induced bursitis may reflect an acute inflammatory process, and the concomitant existence of septic bursitis in a patient with gouty bursitis has been described.[59]

Passive range of motion should not produce much pain, with the exception of full flexion, at which point there may be discomfort as the inflamed bursa is compressed. Evidence of significantly diminished range of motion, generalized joint swelling, or other signs and symptoms of joint involvement (e.g., joint pain, warmth, and joint effusion) should raise a concern for septic arthritis. Although the olecranon and prepatellar bursae generally do not communicate with the joint space, one must consider this possibility in the differential diagnosis, especially if trauma is involved and the integrity of the underlying joint is disrupted.[49,53] Arthrocentesis (to rule out septic arthritis) may then be indicated.[49]

Diagnostic Strategies

When signs of acute inflammation are present, aspiration of the bursa is indicated to exclude the presence of infection or crystal-induced disease.[58-60] Although a discussion of the technique of bursal aspiration is beyond the scope of this chapter, it should be performed observing sterile technique. A lateral approach utilizing an 18- to 20-gauge needle has been recommended.[59] Other authors have described a distal approach when aspirating the olecranon bursa.[60] Reports of sinus drainage from the center of the bursa have been described, but the relation to aspiration is unclear. In a prospective study of 47 patients with bursitis who underwent aspiration, only 3 developed a draining sinus, all around the center of the bursa and not at the site of aspiration. In this study, aspiration was performed at the distal aspect in olecranon bursitis and from the lateral aspect in prepatellar bursitis, but the three cases of sinus drainage occurred only in patients with olecranon bursitis.[60] In cases of septic bursitis, the aspirate usually appears purulent but can occasionally appear serosanguineous or straw-colored.[59] In the case of nonseptic bursitis, the aspirate may vary from bloody aspirate to straw-colored.[59] The aspirate of an inflamed bursa should be sent for evaluation of white blood cell (WBC) count with differential, microscopy for crystals (if crystalline disease is suspected), Gram's stain, and appropriate cultures and sensitivities.[60,61] Some practitioners have suggested the use of a glucose level in the aspirate as an indicator of bacterial infection, but this has been shown to be neither very sensitive nor specific.[57]

Organisms found on either Gram's stain or culture are diagnostic for septic bursitis.[57] If organisms are not seen on Gram's stain, the WBC count may give an indication as to whether the cause is infectious. The noninfected bursa usually has a WBC count of less than 1500/μL (predominantly mononuclear cells) and uncommonly greater than 10,000/μL. The septic bursa has been reported to have WBC counts that range from fewer than 1000/μL to 300,000/μL (predominantly polymorphonuclear cells).[57] A bursal fluid WBC count greater than 5000/μL^3 suggests bursal fluid infection, even in the presence of a negative Gram's stain.[25] *Staphylococcus aureus* is the most common organism in bursal infection.[59]

Since most cases of septic bursitis occur in the olecranon or prepatellar bursae, the diagnosis is made clinically in conjunction with aspiration. MRI can be used to aid in the diagnosis of inflammation or infection of deep bursae.[63,64] Ultrasound has also been used as a modality for aspiration of deep bursae.[65]

Differential Diagnosis

Conditions that mimic bursitis include underlying fracture and osteomyelitis. Radiographs and bone scan or MRI may be necessary to exclude these conditions. Other causes of the nontraumatic, nonseptic bursitis include rheumatoid arthritis, gout, pseudogout, scleroderma, ankylosing spondylitis, systemic lupus erythematous, hypertrophic pulmonary

osteoarthropathy, Whipple's disease, oxalosis, and idiopathic hypereosinophilic syndrome.[57]

Management

The optimal treatment for septic bursitis is uncertain because large-scale clinical prospective trials in this area are lacking. Debate remains regarding the use of outpatient (oral) versus inpatient (intravenous) administration of antibiotics, duration of therapy, use of needle aspiration and incision and drainage, and use of operative intervention.[66]

Patients who have bursal inflammation with suspicion (clinical or laboratory) of infection should be treated with appropriate antibiotics. Empirical therapy (including coverage for *S. aureus* and *Streptococcus* species) may be indicated until definitive culture results are available.[59] Oral antibiotic therapy (some recommend 14 days) and treatment on an outpatient basis in the patient with uncomplicated bursitis and no underlying disease has been recommended as initial therapy.[59] It must be kept in mind, however, that high failure rates (32–67%) for outpatient treatment of septic bursitis have been described.[66] One of the largest observational studies on the successful outpatient treatment of septic bursitis showed an admission rate of only 1 of 118 patients, but all patients in this study received sequential intravenous antibiotics at an outpatient clinic followed by oral antibiotic therapy. The median number of total days of intravenous therapy was four.[67] Treatment in an observation unit or inpatient setting with intravenous antibiotics therefore should be considered for patients with significant symptoms, significant overlying cellulitis, or for patients unlikely to receive close follow-up.

Needle aspiration is a commonly used technique for the management of septic bursae. Stell showed a high success rate in the treatment of septic bursitis in patients receiving outpatient oral antibiotics following initial needle aspiration.[60] Laupland and Davies showed no difference between patients who received aspiration (51% of total patients) and those who did not, but the authors conceded that patients who had more severe disease were likely selected for drainage.[67] Also, the diagnosis of septic bursitis was confirmed by culture in only 26% of these patients, potentially underestimating the importance of bursal drainage in patients with true septic bursitis.[58] Because needle aspiration is used for the diagnosis of septic bursitis, initial drainage at the same time seems warranted. Those with a purulent aspirate may require repeat aspiration at 1- to 3-day intervals if the effusion persists.[59] In all cases, appropriate follow-up to assess response to therapy should be arranged. Warm soaks and wound care are also indicated. Surgical incision and drainage or bursectomy may also be necessary in severe, recurrent, or refractory cases.[66]

The optimal treatment of nonseptic bursitis has not been clarified. Most cases improve with conservative therapy, although complete recovery can take many months.[68] Similar times to recovery have been described for both septic and nonseptic bursitis.[60] Aspiration can be considered in the initial treatment of acute nonseptic bursitis. Further conservative therapy includes the administration of NSAIDs and application of a compression dressing with an elastic bandage to prevent recurrent swelling. Systemic causes of bursitis (e.g., crystalline disease) should be treated appropriately. Avoiding local trauma is important to treat and successfully prevent bursitis.[59] Recurrent olecranon bursitis may be caused by an underlying bone spur that needs resection.[59] Steroid injection into a nonseptic bursa has been utilized as a treatment modality, but significant complications have been noted, such as skin atrophy over the bursa (20%), chronic pain (30%), and the development of septic bursitis (10%).[68] Other complications of intrabursal injection include bleeding, postinjection flare as a result of release of microcrystals, and tendon rupture.[25] It should be noted that the bursal sac, with recent injection of a long-acting steroid, may reveal evidence of birefringent crystals under microscopy.[57]

Disposition

Patients without underlying medical problems who present with uncomplicated septic bursitis can usually be discharged on appropriate oral antibiotics. Those with underlying diseases (e.g., immunocompromise, leukopenia, and diabetes) and those with systemic toxicity or severe bursal infection (e.g., purulent drainage) should be considered for intravenous antibiotics and inpatient therapy. Patients with a purulent aspirate may need repeat aspiration. Close follow-up is necessary to ensure response to therapy. Patients with presumed nonseptic bursitis should have close follow-up as well.[59]

Other Types of Bursitis

Subacromial Bursitis

The subacromial bursa lies between the supraspinatus tendon and the acromion. Subacromial bursitis is thought to be nearly synonymous with supraspinatus tendinopathy and may be involved in the stages of rotator cuff impingement. Pain and tenderness, localized to the lateral aspect of the shoulder, and signs of impingement may be noted on physical examination.[17] Although uncommon, there have been reports of septic subacromial bursitis.[65,69]

Trochanteric Bursitis

The trochanteric bursa has both deep and superficial components. The deep bursa is located between the greater trochanter and the tensor fascia lata; the superficial bursa is located between the greater trochanter and the skin. Generally, middle-aged or older women report acute or chronic pain over the bursal area as well as the lateral thigh. Lying on the hip and walking may exacerbate the pain. Trochanteric bursitis can occur as a complication of rheumatoid arthritis. On examination, the pain of superficial bursitis may be reproduced by hip adduction and the pain of deep trochanteric bursitis reproduced with hip abduction. The hip joint should have normal examination findings.[70] There has been a report of a trochanteric bursitis associated with bacterial endocarditis.[69]

Ischiogluteal Bursitis

The ischiogluteal bursa is located adjacent to the ischial tuberosity and overlies the sciatic and posterior femoral cutaneous nerves. Inflammation, known as *weaver's bottom*, is described as pain over the center of the buttocks with radiation down the back of the leg. Sitting on a hard surface exacerbates the pain, and palpation over the ischial tuberosity causes discomfort.[71]

Iliopsoas Bursitis

The iliopsoas bursa is the largest bursa around the hip. It lies between the iliopsoas tendon and the lesser trochanter. The pain of iliopsoas bursitis usually presents as anterior hip pain that can radiate down the medial thigh to the knee and is increased on hip extension.[25,72]

Anserine Bursitis

The anserine bursa lies deep to the three tendons (sartorius, gracilis, and semitendinosus) that form the pes anserina ("foot of the goose") and superficial to the medial collateral ligament.[29,61] The patient with anserine bursitis usually complains of medial knee pain approximately 2 or 3 cm distal to the joint line. There is usually tenderness to palpation in this area and occasionally swelling.[29] Diabetes mellitus and possibly obesity and osteoarthritis of the knee are risk factors for development of this condition.[73]

KEY CONCEPTS

Tendinopathy

- Mechanical overload and repetitive microtrauma are key underlying mechanisms in the development of tendinopathy. Patients most often present with a history of progressively worsening localized pain after work or sport-related activities that are repetitive in nature.
- Tendinopathy may also be associated with nonmechanical causes, including systemic manifestations of diseases and the use of fluoroquinolones.
- Most patients with tendinopathy can initially be treated with conservative measures such as protection, relative rest, application of ice, medication, and elevation. Overuse syndromes can take at least 6 to 12 weeks to heal. Patients should be informed of this and have appropriate referral for follow-up.
- Operative treatment may be indicated for selected cases of tendon injury that require primary repair (e.g., rupture of the Achilles tendon) or that have failed conservative treatment (e.g., impingement syndrome) and are amenable to surgical amelioration.

Bursitis

- The possibility of an infectious cause should be considered in all cases of acute bursitis.
- The definitive diagnosis of bursitis is made by aspiration of the bursa and evaluation of the fluid.
- Septic bursitis is most commonly caused by *Staphylococcus aureus*.
- Nonseptic bursitis may be traumatic, rheumatologic (e.g., gout and pseudogout), or idiopathic in nature. Other conditions, such as septic arthritis, osteomyelitis, or underlying fracture, should be considered in the differential diagnosis of bursitis.
- The management of bursitis includes treatment with appropriate medication, rest, application of ice, compression, and elevation as well as prompt referral for appropriate follow-up. Hospitalization should be considered for severe local infections, for patients who are immunosuppressed, and in the presence of high fever or systemic toxicity.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 116

Systemic Lupus Erythematosus and the Vasculitides

Jill F. Lehrmann and Clare T. Sercombe

SYSTEMIC LUPUS ERYTHEMATOSUS

Perspective

Systemic lupus erythematosus (SLE) is a multisystem autoimmune connective tissue disorder with a broad range of clinical presentations, including renal failure and neurologic compromise. Symptoms and clinical courses vary widely, but patients with a known diagnosis of SLE are at risk for many different complications. Use of corticosteroids and immunosuppressive agents for therapy may cause further complications.

Background

The disease was originally described by Biett in 1822. The term *lupus erythematosus* was used by Cazanave to describe the cutaneous manifestations in 1851. Sir William Osler coined the term *systemic lupus erythematosus* in 1904 to describe many of the visceral manifestations.[1] The term *lupus*, which means "wolf" in Latin, was used to describe the skin lesion, differentiating it from lupus vulgaris. It was not until 1949 that the lupus erythematosus cell was identified, allowing Haserick to describe the autoimmune nature of the disease.[2,3]

Epidemiology

The incidence of SLE varies significantly among ethnic groups and populations, with an annual incidence in adults ranging from 1.9 to 5.6 per 100,000. The highest incidence, for women in their childbearing years, is 1 per 1000 in white women and 1 per 250 in black women.[4] Seven women present with the disease for every man, with an 11 : 1 ratio during the childbearing years.[5] Pediatric data suggest the incidence of SLE with onset before age 19 years is probably between 6 and 18.9 cases per 100,000 in white females and higher in black females (20–30 per 100,000).[6] The incidence of SLE may have tripled since the 1970s. Factors thought to increase the prevalence include familial cases and a lupus-like syndrome caused by certain medications, including hydralazine, isoniazid, minocycline, procainamide, and quinidine.

Principles of Disease

The underlying mechanism is an autoimmune response with production of autoantibodies and a failure of the body to suppress them.[7] There is a polyclonal activation of B cells with exaggerated production of autoantibodies. The abnormal cellular and humoral response to the formation of these autoantibodies is modified by genetic, environmental, and hormonal factors. Genetic factors include familial association and relationship to certain human leukocyte antigen (HLA) genotypes. Environmental factors play a role not only in the onset of SLE but also in triggering the "flares" (relapses). The most recognized environmental trigger is ultraviolet light exposure. Autoantibodies are also found in laboratory workers who handle SLE sera. An antecedent viral-like illness may occur at the outset of lupus or immediately before a flare. Exposure to certain drugs can also produce an SLE-like syndrome. Because 90% of patients with lupus are female, an important role for female hormones seems likely, although a protective role of male hormones is also possible.[8] There may also be a link to Klinefelter's syndrome.[7] The different manifestations in different patients may reflect the varied autoantibodies produced, the varied organs targeted, and the individual patients' responses to the autoantibodies. These autoantibodies may induce immune complex formation or interact directly at the site, binding to tissue, resulting in different disease manifestations. Pathologic findings are manifestations of the inflammation, inflammatory vasculitis, noninflammatory blood vessel damage, and immune complex deposition.

Clinical Features

The triad of fever, joint pain, and rash in a woman of childbearing age should suggest the diagnosis of SLE. However, the disease ranges from mild illness with cutaneous abnormalities to severe life-threatening complications such as renal failure and lupus cerebritis.

The American Rheumatism Association Revised Criteria for the Classification of Lupus were published in 1982 and updated in 1997.[9,10] These criteria consist of 11 conditions that are associated with SLE. Patients must have four criteria present, serially or simultaneously, to be given the diagnosis of SLE (Box 116-1).

Rheumatologic

The vast majority of patients with SLE will experience arthritis. Polyarthralgias and myalgias occur at some time during the course of the disease in 90% of patients. As in rheumatoid arthritis, the inflammation of the hands, specifically the proximal interphalangeal and the metacarpophalangeal joints, is symmetrical and nonerosive. Although the initial presentation can mimic that of rheumatoid arthritis, joint deformities are less common. Thirty percent of patients develop hitchhiker's

BOX 116-1 American College of Rheumatology Revised Criteria for the Classification of Systemic Lupus Erythematosus

- Malar rash
- Discoid rash
- Photosensitivity
- Oral ulcers
- Arthritis
- Serositis
  - Pleuritis
  - Pericarditis
- Renal disorders
  - Persistent proteinuria >0.5 g/24hr or 3+ persistently
  - Cellular casts
- Neurologic disorders
  - Seizures
  - Psychosis
- Hematologic disorders
  - Hemolytic anemia
  - Leukopenia
  - Lymphopenia
  - Thrombocytopenia
- Immunologic disorders
  - Raised anti–native DNA antibody binding
  - Anti-Sm antibody
  - Positive finding of antiphospholipid antibody, based on
    - Abnormal serum level of IgG or IgM anticardiolipin antibody
    - Positive test result for lupus anticoagulant
    - False-positive serologic test for syphilis for 6 months and confirmed by treponema pallidum fluorescent treponemal antibody absorption test
  - Positive antinucleaur antibody

Classification based on 11 criteria. Patient is diagnosed with SLE if any four or more criteria are present, serially or simultaneously, during any interval of observation.

Modified from Hochberg M: Updating the American College of Rheumatology revised criteria for classification of systemic lupus erythematosus. *Arthritis Rheum* 40:1725, 1997.

thumb, a hyperextension of the interphalangeal joint of the thumb. Tenosynovitis and tendon rupture may also occur, especially in patients taking corticosteroids. Avascular necrosis of the large joints, especially the femoral heads, can also be seen with ischemia caused by the vasculitis or as a complication of the large doses of corticosteroids used to treat SLE. As many as 30% of SLE patients have coexisting fibromyalgia, which is a noninflammatory chronic pain syndrome presenting with symmetrical tender points above and below the waist.[11]

Dermatologic

The malar or butterfly rash is the hallmark of SLE (Fig. 116-1). This facial eruption, seen in up to 50% of patients with SLE,[12] may be the first sign of SLE or may accompany flares of the disease. It is a maculopapular rash over the cheeks extending over the bridge of the nose. It can be exacerbated by exposure to ultraviolet light. Discoid lupus consists of an erythematous raised plaque with scales usually on the face, head, or neck. This can be associated with alopecia. Only 10% of patients with discoid lupus have SLE, whereas up to 25% of patients with SLE develop skin lesions consistent with discoid lupus.[13] Mucous membrane lesions can be seen with small, shallow ulcerations and are present in up to 19% of patients.[12] Vasculitic lesions such as ulcerations, purpura, and digital infarcts may occur.

Figure 116-1. The malar or butterfly rash is the hallmark of SLE. (From Habif TP: Clinical Dermatology, 4th ed. New York, Mosby, 2004, pp 592–606.)

Renal

Clinical nephritis, defined as persistent proteinuria, is seen in approximately 50% of patients, although mesangial and glomerular immunoglobulin deposition is seen in almost all patients with SLE. Most patients have no symptoms from their lupus nephritis until it progresses to nephrotic syndrome or frank renal failure. Serum creatinine is an insensitive indicator of early renal disease because many nephrons must be involved before any elevation is seen. In patients with renal disease, the urinalysis shows hematuria, proteinuria, and red blood cell casts. Active urine sediment with excretion of red blood cell casts and increasing proteinuria is worrisome.

These patients may benefit from aggressive therapy with steroids or other immunosuppressive therapy. With aggressive treatment, survival has increased to 95% at 5 years and 75 to 80% at 10 years in Western Europe and the United States.[14] Indications for treatment include worsening renal failure, decreasing serum complement levels, increasing anti-double-stranded DNA (dsDNA) levels, and nephritic urinary sediment, especially when accompanied by increasing or nephrotic-range proteinuria. Renal biopsy can be useful in making treatment decisions. The use of high-dose corticosteroids and immunosuppressive agents for renal disease is controversial. Patients who have end-stage SLE renal disease have survival rates similar to those of other patients receiving dialysis, approaching 85% at 5 years.[15] Although patients receiving dialysis experience an improvement of their nonrenal SLE manifestations, they run a high risk of dying from severe SLE or infection in their first year of dialysis. Renal transplantation has been successful in these patients, and recurrent nephritis in the allograft is rare.[16,17]

Neurologic

Nervous system manifestations are varied and include seizures, stroke, psychosis, migraines, and peripheral neuropathies.[18] These symptoms may appear early in the course of the disease but are rarely the initial sign of SLE. Central nervous system (CNS) involvement occurs in approximately 50% of patients with SLE.[19] The most common form of neurologic

involvement is cognitive impairment, occurring in 80% of SLE patients 10 years after diagnosis. Seizures are also a common manifestation in up to 70% of patients with CNS involvement.[20] Strokes are common as well, especially in association with antiphospholipid syndrome (APS). Frank psychosis can be seen, either as a manifestation of SLE or as a result of corticosteroid use. Lupus cerebritis should be considered in any patient with SLE who exhibits a change in behavior or mental status. The presence of infection should also be considered, especially in patients receiving immunosuppressive agents. These patients are at risk for bacterial, fungal, and tuberculous infections in addition to abscesses. Other causes include uremia and hypertensive encephalopathy. Mononeuritis multiplex and peripheral neuropathy have also been described.

A computed tomography (CT) scan is useful in patients with gross focal neurologic deficit to assess for bleeding or edema associated with an embolic stroke. A magnetic resonance imaging (MRI) scan is much more sensitive for small infarcts, edema, or evidence of vasculitis. Full recovery from neuropsychiatric manifestations is approximately 70 to 85%; however, the mortality from such events is 10 to 15%.[19]

Cardiac

Pericarditis is the most common cardiac manifestation of SLE, reported in 30% of patients.[21,22] The diagnosis may be determined on the basis of electrocardiographic (ECG) findings alone, or patients may have signs and symptoms of fever, tachycardia, chest pain, and transient cardiac rubs. Pericarditis is associated with effusion in 20% of patients; however, this rarely progresses to tamponade.[21] Purulent pericarditis related to *Staphylococcus aureus* and tuberculosis has been reported in patients taking steroids. Purulent pericarditis, which is exudative with a high protein and white blood cell count,[22] may mimic the effusion seen with SLE, which causes a transudative, serous fluid. Pericarditis in SLE is generally benign and responds well to corticosteroids.

Myocarditis resembling cardiomyopathy is clinically diagnosed in fewer than 10% of patients with SLE but is found in 40% of patients at autopsy.[23] Some degree of left ventricular dysfunction may be found in a large number of patients with SLE.[24] It may be accompanied by congestive heart failure, ventricular dysrhythmia, tachycardia, or nonspecific ECG changes. Severe myocarditis should be treated with large doses of systemic corticosteroids, control of hypertension, and correction of volume overload.

A noninfectious endocarditis, as described by Libman and Sachs, produces vegetative growths on the valves that are usually clinically silent; however, these may be complicated by infection, valvular dysfunction, and, rarely, thromboembolism.[25] Libman-Sachs vegetations are seen in up to 10% of patients with SLE.[26] The mitral valve is most commonly involved, although all four valves may have vegetations. Valvular dysfunction may occur independent of vegetations secondary to valvulitis, mucoid degeneration, or aortic dissection. The aortic valve has the highest incidence of hemodynamically significant regurgitation, followed by the mitral valve.

Vasculitis of the coronary arteries or accelerated atherosclerosis related to corticosteroid use may cause coronary ischemia. Mortality from coronary artery disease (CAD) is seen in up to 30% of patients with SLE despite improved survival in renal and cerebral SLE.[22] Coronary vasculitis, although rare, is best treated with steroids, whereas the atherosclerosis is best treated with conventional methods including aspirin, nitrates, beta-blockers, angioplasty, or bypass surgery. Treatment differences make the distinction between the two entities important. The diagnosis can be made by coronary angiography, with evidence of aneurysmal dilatation of the coronary arteries seen in patients with vasculitis.[21] Patients with SLE, hypertension, smoking, and hypercholesterolemia are at significantly increased risk for CAD and should be treated aggressively for these problems as well as screened regularly for CAD.[21,22]

Patients with SLE tend to have systemic hypertension secondary to lupus nephritis and steroid use, with all of the resultant complications of hypertension. The incidence has been reported as 25 to 50% of patients with SLE. Hypertension is noted in patients who take high, long-term doses of corticosteroids.

Pulmonary

Pleural effusions and pleurisy are common. Pleural effusions, seen in 12% of SLE patients, are usually exudative in nature. Pleural fluid glucose levels are usually similar to serum glucose levels, in contrast to those of rheumatoid arthritis, in which the pleural fluid glucose level is very low. Other manifestations include pulmonary infarcts and hemorrhage. Lupus pneumonitis causes diffuse interstitial infiltrates, although patients have usually had the disease for several years before they suffer from pneumonitis. Bacterial, fungal, and opportunistic infections must be considered, especially in patients taking immunosuppressive agents, before a diagnosis of lupus pneumonitis is given. Patients with SLE are particularly at risk for pneumococcal disease, in part because of autosplenectomy or splenic dysfunction. Patients with SLE may also develop chronic interstitial infiltrates leading to pulmonary fibrosis. These patients need inpatient treatment, and their conditions may progress to chronic hypoxia, pulmonary hypertension, and right-sided heart failure.[27]

Gastrointestinal

Gastrointestinal complaints in SLE are common, ranging from oral ulcerations to the much more serious intestinal vasculitis. Oral ulcerations usually accompany disease flares. Esophageal dysmotility is occasionally seen, but it is much less common than in patients with scleroderma. Patients with intestinal pseudo-obstruction may have crampy abdominal pain and a clinical and radiographic picture consistent with obstruction. They should be observed for resolution. Pancreatitis can result from either an SLE flare or corticosteroid therapy. Spontaneous bacterial peritonitis is also described. Elevated liver function tests are common, usually the result of the medications given to treat SLE, such as azathioprine. However, infection with cytomegalovirus while taking immunosuppressive agents may also occur. Portal hypertension caused by scarring and fibrosis is seen in 4% of patients.[27] The most serious complication is intestinal vasculitis, a syndrome of abdominal pain, bloody diarrhea, and evidence of vasculitis elsewhere. This vasculitis may progress to perforation or gangrene, resulting in peritonitis.

Hematologic

Hematologic and vasculitic problems are complex. A normochromic, normocytic anemia is found in approximately 50% of patients with SLE, with anemia of chronic disease being the most common form.[28] Thrombocytopenia occurs in 25% of patients. Treatment for severe thrombocytopenia is controversial, with some authors advocating use of vinca alkaloids and intravenous gamma globulin.[29] Splenectomy is controversial. Some believe that splenectomy exacerbates the disease. Thrombotic thrombocytopenic purpura and immune idiopathic thrombocytopenic purpura have also been reported

in patients with SLE.[30] Leukopenia is common with disease flares as well.

Diagnostic Strategies

The diagnosis of SLE can be difficult. The fundamental rule is that a patient must have 4 or more of the 11 criteria to qualify for the classification category of SLE. Rarely can the diagnosis of SLE be made with absolute certainty at the first onset of symptoms. As such, it has been common for rheumatologists to refer to cases as probable, definite, or classic.[31] The diagnosis of SLE is often confirmed with antinuclear antibodies (ANAs). Positive ANAs occur in more than 95% of patients with SLE.[12] The degree of positivity of the test is important, with higher titers having a positive predictive value. ANAs may also be positive in elders taking certain medications, such as hydralazine and procainamide, as well as with subacute bacterial endocarditis, infectious hepatitis, and other immune diseases such as primary biliary cirrhosis. Five percent to 7% of healthy people may also have a positive ANA.[32] Antibodies to dsDNA and anti-Smith (anti-Sm) antibodies are most specific for SLE.[33] Patients with disease flares may show an increase in their ANA or dsDNA titers. Decreases in complement levels for C3 and C4 also correlate with disease flares in certain patients. The erythrocyte sedimentation rate (ESR) is a very poor index of disease activity. Patients who have an ESR of 50 to 100 mm/hour often show minimal disease activity. C-reactive protein levels often remain low except in the presence of concurrent infection. Patients with SLE may have a false-positive Venereal Disease Research Laboratory or Rapid Plasma Reagin result, and this is also one of the diagnostic criteria.

Management

The treatment of SLE is controversial because the manifestations and severity vary widely among patients. After many years, new biotherapies are yielding improvements in the management of SLE. General treatments that continue to be recommended include avoidance of stress and fatigue, which can exacerbate symptoms. Approximately one third of patients are photosensitive and should avoid sunlight and use sunscreen. Not smoking is also recommended because smoking increases the already higher risk of accelerated atheroma and studies show that smoking increases the likelihood of developing or worsening lupus.[34] Oral contraceptives may also exacerbate symptoms, and only low-estrogen oral contraceptives should be used. However, studies indicate that oral contraceptives and hormone replacement may be less hazardous than once thought.[35]

Acetaminophen may be useful for mild to moderate pain control. Drug therapy starts with anti-inflammatory agents. Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) have been used to treat minor inflammatory complaints such as arthralgias, pleurisy, and pericarditis. The maximum recommended doses of these agents are usually needed. These agents should be avoided in patients with severe gastrointestinal complications or thrombocytopenia. Patients with lupus nephritis should also avoid NSAIDs because the inhibitory effect on prostaglandins may reduce renal function, confusing the clinical picture of worsening renal failure. Some NSAIDs, including ibuprofen, have also been associated with aseptic meningitis, with headache, fever, and meningismus.[36] Cerebrospinal fluid studies in these patients show lymphocytosis, elevated protein levels, and sterile culture.

Corticosteroids are usually the next agent of choice. Topical application controls most cutaneous manifestations. Oral corticosteroids are prescribed in dosages that control disease activity. Minor disease activity (e.g., arthralgias, fatigue, and pleurisy) is usually controlled with 0.5 mg/kg or less in a single daily dose. With minor symptoms, however, anti-inflammatory and antimalarial drugs such as hydroxychloroquine have been advocated to avoid the long-term complications of corticosteroids. Major disease activity (e.g., hemolytic anemia and severe thrombocytopenia) is usually controlled with prednisone 1.0 mg/kg/day. With lupus cerebritis and acute worsening of lupus nephritis, methylprednisolone 1.0 g intravenously (IV) once daily may be given for several days. Treatment of glomerulonephritis with long-term steroids has not been proved to alter the outcome or course in patients with SLE, and their long-term use remains controversial.[30,37] When tapering, corticosteroids may be changed to an alternate-day dosing regimen; however, some patients may experience disease flares at these dosages.

Antimalarial drugs are also effective for the cutaneous and musculoskeletal manifestations of SLE. Hydroxychloroquine and chloroquine are given on an outpatient basis in a loading dose for 4 weeks, followed by maintenance dosing when these symptoms are under control. The underlying mechanism by which these medications work is unclear. Withdrawal of these medications may result in a disease flare. The antimalarial agents can result in two major ophthalmologic side effects. Corneal deposits, easily seen on slit-lamp examination in patients who complain of floaters in the visual field, are reversible with drug withdrawal or decreased dosage. The second complication, an irreversible retinopathy, is unrelated to the corneal deposits. All patients with SLE who take antimalarial medications should be observed biannually by an ophthalmologist to detect evidence of retinopathy that may lead to blindness. If evidence of retinopathy appears, patients should stop taking the antimalarial medication under a rheumatologist's supervision.

Immunosuppressive agents (e.g., azathioprine, methotrexate, and cyclophosphamide) are reserved for patients with severe renal or cerebral disease in whom other therapies have failed or for patients who have not tolerated corticosteroids.[37] Cyclophosphamide is now one of the standards for treating SLE, most notably with renal involvement, and studies support its effectiveness.[35] Studies examining the use of immunosuppressants have shown decreased chronic renal scarring and reduced likelihood of end-stage renal disease without an increase in mortality.[38] The toxicities of such drugs are numerous and include infections, myelosuppression, and future risk of neoplasms.[37]

Newer treatments include autologous marrow stem cell transplantation, intravenous immunoglobulins, and mycophenolate mofetil, an inhibitor of purine synthesis.[14,39] Rituximab and new anti-B-cell drugs hold promise for the treatment of severe SLE.[35] All of the trials involving patients are small, of short duration, or anecdotal. A controlled clinical trial with significant power is needed to prove the efficacy of these therapies in patients with SLE.[35,39]

Special Considerations

Drug-Induced Lupus. Drug-induced lupus was first described in 1954 by Dustan and colleagues and Perry and Schroeder.[40,41] Procainamide was first implicated in 1962 by Ladd.[42] Since then, a large number of agents have been implicated, with hydralazine, quinidine, and procainamide being the most common (Table 116-1). Patients with drug-induced lupus usually present with skin and joint manifestation; renal and neurologic features are very rare.[8] The full manifestations are present in less than 1% of patients taking high-risk drugs,

Table 116-1 Drugs Implicated in Lupus-Like Syndromes

SYSTEM	DRUG	RISK
Cardiovascular	Procainamide	High
	Amiodarone	
	Quinidine	
	Practolol*	High
Antihypertensive	Hydralazine	High
	Methyldopa	
	Reserpine	
Antimicrobial	Isoniazid	Moderate
	Penicillin	
	Sulfonamides	
	Streptomycin	
	Tetracycline	
	Nitrofurantoin	
Anticonvulsant	Phenytoin	Moderate
	Mephenytoin	Moderate
	Ethosuximide	Moderate
	Primidone	
Antithyroid	Propylthiouracil	Low
	Methylthiouracil	Low
Psychotropic	Chlorpromazine	Low
	Lithium carbonate	
Miscellaneous	D-Penicillamine	High
	Methysergide	Low
	Phenylbutazone	
	Allopurinol	
	Gold salts	
	Aminoglutethimide	

*Removed from market because of lupus-like syndrome.

BOX 116-2 Clinical Manifestations of Antiphospholipid Syndrome

- Arterial occlusion
  - Extremity gangrene
  - Stroke
  - Myocardial infarct
  - Other visceral infarct
  - Aortic occlusion
- Venous occlusion
  - Peripheral venous occlusion
  - Visceral venous occlusion
    - Budd-Chiari syndrome
    - Portal vein occlusion
- Recurrent fetal loss
- Thrombocytopenia
- Coombs' positive hemolytic anemia
- Livedo reticularis
- Neurologic abnormalities
  - Chorea
  - Multiple sclerosis–like syndrome
  - Transient ischemic attacks
- Valvular heart disease
- Sudden multisystem arterial occlusion

Modified from Sammaritano LR, et al: Commonly agreed clinical manifestations of antiphospholipid antibody syndrome, *Semin Arthritis Rheum* 20:81, 1990.

although a positive ANA titer can be found in more than 50% of patients taking high-risk drugs.[43] The patients are usually women, middle-aged or older, and rarely black, but these findings may be representative of the group of patients taking these drugs. The condition is usually reversible when the agents are stopped, with resolution within days or weeks; however, manifestations lasting for years have been reported. In patients with significant pleuropericardial disease, a short course of tapered steroids has been used successfully when the implicated medication has been discontinued.

Antiphospholipid Antibody Syndrome. Synonyms for the antiphospholipid antibody syndrome (APS) are anticardiolipin antibody, lupus anticoagulant, and Hughes' syndrome. Diagnosis requires that a patient have both a clinical event (thrombosis or pregnancy loss) and an antiphospholipid antibody (aPL) documented by a solid-phase serum assay (anticardiolipin), an inhibitor of phospholipid-dependent clotting (lupus anticoagulant), or both. The lupus anticoagulant and anticardiolipin antibody are antiphospholipid antibodies that bind to the prothrombin activator complex. This binding results in a prolongation of the partial thromboplastin time (PTT) but is clinically associated with clotting. Antiphospholipid antibodies are found in young healthy controls at a prevalence of 1 to 5% for both anticardiolipin antibodies and lupus anticoagulant antibodies. Among patients with SLE, the prevalence is much higher, ranging from 12 to 30% for anticardiolipin antibodies and 15 to 34% for lupus anticoagulant antibodies.[44] This disorder can also be seen in patients with human immunodeficiency virus (HIV), in some malignancies, and with drug-induced lupus. Patients without evidence of SLE have a much lower incidence of complications. A prolonged PTT that is not corrected when the patient's sample is mixed 50:50 with normal serum suggests the presence of an inhibitor; the lupus anticoagulant and anticardiolipin antibody can then be found with further testing.

The spectrum of the clinical manifestations of APS is wide. Some patients may have repeated episodes of arterial or venous clotting, including recurrent strokes and pulmonary emboli. Elevated serum creatinine values may be a result of renal vein thrombosis, seen on CT with contrast, mimicking worsening nephritis. Multiple spontaneous abortions have been reported (Box 116-2).

This syndrome may also be associated with thrombocytopenia, with clinically significant bleeding, and with neuropsychiatric disorders believed to be secondary to cerebral ischemia and infarcts.[45] Patients who have evidence of APS may still undergo surgery, with routine precautions for deep vein thrombosis. Despite the prolonged PTT, there is minimal risk for prolonged bleeding unless thrombocytopenia is also present. Any patient with APS and a documented thrombosis should receive anticoagulants, with a goal of maintaining an international normalized ratio (INR) of 2.5 to 3.0.

Pregnancy. Recurrent spontaneous abortions occur in some patients with APS. Subcutaneous lovostatin with low-dose aspirin throughout pregnancy is currently the treatment of choice. As the pregnancy progresses, there is a risk of worsening manifestations of SLE and nephritis. These patients are also at risk for pregnancy-induced hypertension. In patients who do not respond to subcutaneous lovostatin, monthly doses of intravenous gamma globulin may be effective, although this increases the risk of preeclampsia and preterm delivery.[14] Patients with evidence of thrombosis and APS should receive anticoagulation and be admitted for further workup. Corticosteroids in combination with aspirin have shown some benefit in maintaining the pregnancy. Although they cross the placenta and show little evidence of fetal harm, corticosteroids are a second-line agent because of complications of long-term, high-dose therapy. Other medications, including NSAIDs, immunosuppressive agents, and antimalarials, should be stopped, although evidence shows that hydroxychloroquine is

effective and safe in pregnancy.[35] These patients should be referred to a high-risk obstetrician early in the pregnancy.

Neonatal lupus syndrome is usually diagnosed by dermatologic manifestations of lupus and is associated with transient anemia and thrombocytopenia. Neonates can also experience congenital complete heart block that may require permanent pacing.[30] The congenital heart block has been associated with transmission of a maternal antibody to anti-SSA (Ro).

Complications of Therapy

The complications of SLE are many and varied because of the systemic nature of the illness. Treatment of the disease causes further complications. Treatment with NSAIDs can worsen lupus nephritis, either by causing interstitial nephritis or by inhibiting prostaglandins.

Corticosteroids are associated with well-known, long-term complications, including steroid-induced diabetes, osteoporosis and resultant fractures, weight gain, pancreatitis, osteonecrosis, accelerated atherosclerosis, and, most important, immunosuppression. Patients receiving steroid therapy should be monitored for evidence of infection and should be evaluated for any episode of fever. Patients taking corticosteroids should also be given stress-dose steroids with hydrocortisone 100 mg IV every 8 hours for any systemic infection, surgery, delivery, or obvious stressor.

Patients using antimalarial agents are at risk for dose-related corneal deposits, which can be managed by outpatient drug discontinuation and rheumatology follow-up. The retinopathy associated with antimalarial agents is irreversible and may progress to blindness. Prompt attention by an ophthalmologist is important.

Patients taking immunosuppressive agents are also at risk for infection, especially with gram-negative organisms, encapsulated gram-positive organisms, herpes zoster, and opportunistic organisms. Febrile patients who are receiving azathioprine, methotrexate, or cyclophosphamide should be admitted, whether a source is evident or not, because gram-negative or streptococcal sepsis occurs in this population. Patients with localized herpes zoster should be admitted for intravenous acyclovir administration to prevent viral dissemination.

Disposition

Because of the systemic and varied nature of the disease, there are no hard and fast rules about admission for complications of SLE. Patients without a previous diagnosis of lupus may be admitted for workup and treatment of possible connective tissue disease if they have symptoms that warrant immediate diagnosis (e.g., pericarditis, myocarditis, pleural effusion or infiltrates, evidence of vasculitis, or renal insufficiency). In the patient who has monoarticular or polyarticular arthritis, the joint can be aspirated in the emergency department if fluid is present. Further workup can be done on an outpatient basis by a primary care physician or rheumatologist. NSAIDs may alleviate the symptoms.

Patients with known SLE may come to the emergency department for a flare of their disease or for new systemic complaints, including fevers. Patients with known disease can usually tell if the symptoms are consistent with a previous flare or different. Patients with worsening disease who take large doses of steroids or immunosuppressive agents should be admitted for consideration of other diagnoses or more aggressive therapy. Patients with known disease and increasing arthritic pain, or mild flares without fever, may be effectively treated with an increase in their NSAID or corticosteroid dosages and prompt follow-up with their rheumatologists.

Patients with evidence of lupus nephritis and worsening renal failure should be admitted for aggressive therapy with steroids or immunosuppressive agents. The serum creatinine level may be elevated, but it is a poor indicator of disease. Urinalysis is more sensitive than serum creatinine for the diagnosis of nephritis. Proteinuria and red blood cell casts may indicate nephritis. Treatment for lupus nephritis should be done in conjunction with a rheumatologist or nephrologist. Consideration of renal vein thrombosis is also warranted in patients with evidence of APS or nephrotic syndrome.

Mental status changes in the patient with SLE should be evaluated thoroughly because lupus cerebritis is a diagnosis of exclusion. Infections, including meningitis, pneumonia and urinary tract infections, electrolyte imbalances, hypoxia or hypoglycemia, and medications all can cause altered mental status. A CT scan to assess for hemorrhage, especially in the hypertensive, thrombocytopenic, or anticoagulated patient, should be considered. Lumbar puncture to evaluate for infection may be indicated if the patient is febrile or immunocompromised. MRI may reveal abnormalities with increased signal intensity in the area of involvement. Cerebral ischemia may cause acute mental status changes as a result of a lupus vasculitis or thrombosis associated with APS. Consultation with a rheumatologist is prudent before giving high-dose steroids for lupus cerebritis. Patients with seizures should be treated in the routine manner, with ongoing care supported by a neurologist.

Patients with cardiac or pulmonary complaints should be admitted for observation or therapy. Those who take corticosteroids are at high risk for coronary artery disease. Patients with chest pain should be aggressively evaluated for myocardial infarction. If pericarditis is suspected, evaluation of pericardial effusion may be necessary, although tamponade is rare. Patients with myocarditis should be observed for evidence of congestive heart failure and dysrhythmias. Patients taking immunosuppressive agents should be given antibiotic prophylaxis for invasive dental and genitourinary procedures.

Pulmonary complaints may indicate either common or atypical disease. Patients with fever and infiltrates may have community-acquired pneumonia, especially pneumococcal disease, but opportunistic infection, atypical tuberculosis, and lupus pneumonitis need to be considered. Sputum culture and pulmonary consultation may be appropriate, especially in the hypoxic patient. Hypoxic patients may have pulmonary embolism as a complication of antiphospholipid antibody with thrombosis. Patients with pleural effusions should be admitted for diagnostic thoracentesis and treatment. Pleural effusions may be complicated by infection, tuberculosis, or malignancy.

Patients with abdominal pain are typically young women of childbearing age. Workup should therefore include a pelvic examination and pregnancy test. Laboratory examination may not be helpful without baseline values because many patients are chronically anemic and the white blood cell count may be elevated in those taking corticosteroids. Evidence of an increased anion gap or metabolic acidosis may be indicative of lactic acidosis. Abdominal films may be helpful to show bowel wall thickening or free air. Consultation with a surgeon, overnight observation for serial examinations, or a CT scan may be necessary to diagnose vasculitic problems, abscess in immunocompromised patients, or routine causes of abdominal pain. Even if the patient has a common cause of abdominal pain (e.g., pelvic inflammatory disease, pancreatitis, peptic ulcer disease, or biliary colic), admission may be necessary for administration of stress-dose steroids and workup of fever.

SLE predisposes patients to anemia and thrombocytopenia. Patients should be admitted if there is evidence of active hemolysis with decreased hematocrit or if hemolysis is evident

on the blood smear. Patients with thrombocytopenia should be admitted if there is evidence of bleeding or if platelet counts are severely decreased (<50,000/mm^3). If the patient is actively bleeding, platelet transfusion is appropriate; however, rapid destruction of the platelets may occur. Simultaneous administration of intravenous corticosteroids and intravenous gamma globulin aids in increasing the platelet count and decreasing the amount of platelet destruction.

Patients with evidence of arterial or venous thrombosis should be admitted for anticoagulation and possible embolectomy. Anticoagulation can be achieved acutely with heparin, although large doses are occasionally needed to overcome the antibody effect. The PTT, if not elevated, can be followed to assess for evidence of adequate anticoagulation, with careful observation for bleeding in patients who are also thrombocytopenic. Otherwise, patients with prolonged PTT and evidence of the lupus anticoagulant can be monitored with thrombin times if necessary. Patients with an INR less than 2.5 should still be considered to have a possible thrombus if they have a history of APS.

Pregnant patients with SLE should have early follow-up with a high-risk obstetrician. Emergency delivery for the pregnant patient with SLE should include stress-dose steroid administration and close observation of the neonate for congenital complete heart block. Emergent cardiac pacing may be necessary.

Patients experiencing overwhelming sepsis or shock should be given stress-dose steroids in the emergency department with hydrocortisone 100 mg IV. Broad-spectrum antibiotics may also be given empirically after appropriate cultures are obtained. Adrenal insufficiency from abrupt discontinuation of steroids is another possible cause of shock. If the patient is unstable, admission to the intensive care unit is warranted.

THE VASCULITIDES

Perspective

The vasculitic syndromes are a heterogeneous group of disorders of unknown etiology characterized by inflammation and necrosis of different-sized blood vessels. Depending on the size, distribution, and severity of inflammation in the effected vessels, vasculitis can result in clinical syndromes that vary in severity from a minor self-limited rash to a life-threatening multisystem disorder.

Background

The first classical description of a vasculitic syndrome was in 1866 by Kussmaul and Maier. This syndrome is now known as *polyarteritis nodosa*.[46] By the 1950s, many investigators realized that there were a number of distinct forms of vasculitis. In 1952, Zeek presented the first classification system.[47] Since then, a number of well-described disease states have been attributed to vasculitic syndromes. Because the etiologies of most forms of vasculitis remain unknown, the most commonly used method for classifying the vasculitides is the size of the predominant blood vessels involved (Box 116-3). Current classification schemes recognize approximately 20 primary forms of vasculitis, as well as several categories of secondary vasculitis (e.g., other rheumatologic diseases, malignancies, and infection).[48]

Epidemiology

In general, the vasculitides are relatively uncommon, although not rare, in Western countries. Approximately 1 of 2000 adults has some form of vasculitis, and each year vasculitis develops in approximately 1 of 7000 adults.[49] In the United States, the most common forms of primary systemic vasculitis are giant cell arteritis, Wegener's granulomatosis, and microscopic polyangiitis.[50]

BOX 116-3 CLASSIFICATION OF VASCULITIDES

Predominantly Large Vessel Disease
Temporal (giant cell) arteritis
Takayasu's arteritis

Predominantly Medium Vessel Disease
Polyarteritis nodosa
Buerger's disease (thrombophlebitis obliterans)
Kawasaki's disease (mucocutaneous lymph node syndrome)
Primary angiitis of the central nervous system
Associated with viruses
- Hepatitis B or C
- Cytomegalovirus
- Herpes zoster
- HIV

Associated with malignancy
- Hairy cell leukemia

Other
- Familial Mediterranean fever

Predominantly Small Vessel Disease
Behçet's disease

Vasculitis Associated with Antineutrophil Cytoplasmic Antibodies
Wegener's granulomatosis
Churg-Strauss syndrome
Microscopic polyangiitis

Immune Complex–Mediated
Goodpasture's syndrome (antiglomerular basement membrane disease)
Henoch-Schönlein purpura
Cutaneous leukocytoclastic angiitis (hypersensitivity vasculitis)
Essential cryoglobulinemia
Hypocomplementemic urticarial vasculitis
Erythema elevatum diutinum

Vasculitis Associated with Connective Tissue Diseases
SLE
Sjögren's syndrome

Vasculitis Associated with Specific Syndromes
Primary biliary cirrhosis
Lyme disease
Chronic active hepatitis
Drug-induced vasculitis

Erythema Nodosum

Serum Sickness

HIV, human immunodeficiency virus; SLE, systemic lupus erythematosus.

Principles of Disease

Vasculitic syndromes are thought to arise because immune complexes are deposited in vessel walls and the complement system is activated. The complement system then stimulates accumulation of polymorphonuclear cells at the site and release of lysosomal enzymes, resulting in vessel wall damage and

necrosis. The clinical manifestations of this process depend on the size of the immune complexes, the mechanics of blood flow through the vessel, the vessel permeability, and the site of deposition.

The relationship between immune complexes and the subsequent development of vasculitis is best studied in the infectious causes of vasculitis. Infectious agents known to be associated with vasculitis include hepatitis A, hepatitis B, hepatitis C, cytomegalovirus, herpes zoster, parvovirus, and HIV.[48,51-53] Environmental factors are also implicated. Malignancies such as hairy cell leukemia, some lymphomas, and the myeloproliferative disorders are also associated. Immune complexes are rarely found in some other vasculitic syndromes, such as polyarteritis nodosa and Wegener's granulomatosis, because of rapid clearing of the complexes.

It is important to differentiate thrombosis and vasculitis because treatments are dramatically different. APS can mimic vasculitis, especially when present in patients without SLE. Yet in SLE, both vasculitis and thrombosis from APS may be present.

Large Vessel Vasculitides

Temporal Arteritis

Temporal or giant cell arteritis, the most common vasculitis, is a chronic disease affecting predominantly large to medium vessels.[54] It is characterized by granulomatous inflammation with multinucleated giant cells, and the distribution is most common in branches of the carotid artery but may involve any large or medium artery. The disease is most commonly seen in women in the sixth and seventh decades of life.

The onset of temporal arteritis tends to be gradual but can be abrupt, and systemic manifestations including fever, anorexia, and weight loss are present in up to half of patients.[55] The classical symptoms are consistent with ischemia to the organs fed by branches of the internal and external carotid artery: visual loss in one eye, temporal artery tenderness, and jaw claudication. A headache is probably the most frequent initial symptom and occurs in two thirds of patients. Some patients experience central retinal occlusion or transient diplopia. Approximately 30 to 40% of patients also have polymyalgia rheumatica,[56] with patients complaining of severe myalgias and early morning stiffness of the muscles of the shoulder and pelvic girdle. On physical exam, the frontal or parietal branches of the superficial temporal arteries may be thickened or occasionally erythematous, and the pulses may be decreased or absent.

The diagnosis is relatively straightforward in the presence of the typical cranial manifestations. Helpful laboratory findings include elevated ESR (usually >100 mm/hr on a Westergren blot test), elevated C-reactive protein, and anemia. Although the role of ultrasonography and high-resolution magnetic resonance imaging in diagnosis is being studied,[55] temporal artery biopsy remains the standard for diagnosis. Criteria for classification of temporal arteritis have been formulated by the American College of Rheumatology (Box 116-4).

Permanent partial or complete loss of vision in one or both eyes occurs in up to 20% of patients, so early diagnostic and therapeutic efforts are targeted to minimize this complication. Affected patients may report partially obscured vision, which may progress to total blindness. If untreated, the other eye is likely to become affected within 1 or 2 weeks. Amaurosis fugax is an important visual complaint that precedes permanent vision loss in 44% of patients.[57]

Corticosteroids are the treatment of choice for temporal arteritis and the response is rapid. Treatment should be started for any patient with a high clinical suspicion of temporal arteritis. Steroids do not significantly change the results of the biopsy and may prevent progression to visual loss.[58] Prednisone should be started at a dosage of 1 mg/kg/day until biopsy can be performed. Patients with severe disease or impending visual loss should be hospitalized and given high-dose steroids until the diagnosis is obtained. The likelihood of visual symptom resolution correlates with the time of corticosteroid initiation: More than 50% of patients treated in the first 24 hours can expect to recover compared to only 6% of patients treated after the first 24 hours.[59] Although there is no consensus regarding treatment duration or tapering schedules, most patients are given the initial dose of steroids for 2 to 4 weeks and then a slow tapering of the steroid dosage over several weeks, although relapse rates are lower in those who use them longer (1 or 2 years).[60,61]

BOX 116-4 American College of Rheumatology Criteria for the Classification of Temporal Arteritis

Onset of disease at the age of 50 years or older
New headache
Temporal arteries abnormalities (tenderness to palpation or decreases in pulsation)
Erythrocyte sedimentation rate >50 mm/hr
Abnormal findings on temporal artery biopsy

From Hunder GG, et al: The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum 33:1122, 1990.

Takayasu's Arteritis

Takayasu's arteritis (pulseless disease), named for the Japanese ophthalmologist who first described the ocular manifestations in 1908, is a chronic, recurrent, inflammatory vascular disease that primarily affects the aorta and its major branches.[62] It is characterized by lymphocytic infiltration and fibrosis of the vessels, resulting in marked thickening of the intima and adventitia, eventually leading to obstruction of the arteries and ischemic complications. Adolescent girls and women in their second and third decades are predominantly affected, and women are affected eight times more frequently than men. The syndrome is most commonly seen in Japan, Southeast Asia, India, and Mexico.[63] In the United States, the annual incidence is approximately 1 to 3 cases per 1 million people.[56]

The cause of Takayasu's arteritis is unknown. The clinical features can be broadly categorized into two groups: those caused by systemic inflammation and those caused by vascular damage. In the prepulseless or early phase, the diagnosis is difficult. Almost half of patients experience constitutional symptoms including fatigue, weight loss, and low-grade fever caused by systemic inflammation. Hypertension is frequently seen secondary to aortic or renal artery involvement. With progression of the disease, ischemic symptoms caused by the vascular manifestations appear, including diminished or unequal pulses, claudication, retinopathy, lightheadedness (associated with vertebral or carotid artery dissection), and visual loss. Strokes, syncope, subclavian steal syndrome, abdominal pain, and coronary ischemia are also reported.

Early diagnosis is difficult because symptoms are nonspecific and there is no specific laboratory test. Disease activity may be subclinical and not recognized by laboratory markers in up to half of cases.[64] Later, pulses may be unequal, bruits may be auscultated, and there may be blood pressure differ-

ences in the extremities. Definitive diagnosis is made with arteriography demonstrating stenotic lesions, poststenotic dilation, aneurysms, and increased collateral circulation.

Treatment with prednisone 1 mg/kg/day for 1 to 3 months induces remission in up to 60% of patients.[65] Other cytotoxic agents, such as methotrexate, cyclophosphamide, or azathioprine, or tumor necrosis factor modulatory therapy may be added to achieve remission if relapses occur. Infections may complicate therapy. Complications of Takayasu's arteritis, such as hypertension, congestive heart failure, angina, or aortic regurgitation, may benefit from other forms of medical therapy. Hypertension may be treated with calcium channel blockers and angiotensin-converting enzyme inhibitors, although this may be especially difficult in patients with extensive disease who may have two or more arterial beds with substantially different blood pressures. Antiplatelet agents may be of benefit. Bypass grafting and endarterectomy are useful in patients with significant disease. Mortality has resulted mainly from renal failure, cardiac failure, or infectious complications of immunosuppressive treatment.[64]

Medium Vessel Vasculitides

Polyarteritis Nodosa

Polyareteritis nodosa (PAN) is a necrotizing vasculitis of predominantly medium-sized arteries. Immune deposits are minimal or absent, and test results for anti-neutrophil cytoplasmic antibodies (ANCAs) are typically negative. A distinction has been made between PAN and microscopic polyangiitis (MPA). PAN includes vasculitis associated with nervous system and gastrointestinal tract involvement, whereas MPA is positive for ANCAs directed at myeloperoxidase and is associated with nerve, glomerular, and lung tissue. The etiology of PAN is unknown. Viral hepatitis B or C is associated with a vasculitis identical to PAN but is treated differently, and PAN is excluded if chronic hepatitis B or C is found.[66] PAN is also linked with drug reactions, serum sickness, and HIV. Patients with classic PAN can be any age, including children, but the peak age at onset is in the fifth or sixth decade, and there is an approximately 2:1 male-to-female ratio. Reported annual incidence rate of PAN ranges from 2 to 9 cases per 1 million people.[67]

The early clinical picture consists of constitutional symptoms including fever, malaise, arthralgias, and myalgias. Cutaneous manifestations occur in up to one third of patients, usually seen as areas of palpable purpura, sometimes with ulceration. Frequent sites include the fingers, the ankles around the malleoli, and the pretibial areas. In severe cases, there may be widespread digital cyanosis secondary to ischemia. Splinter hemorrhages and livedo reticularis are also commonly observed. PAN can progress to peripheral neuropathy and bowel ischemia, and it can cause hypertension related to renal artery inflammation.

The diagnosis is made by the clinical pattern and histopathology seen on biopsy. After endocarditis and concomitant infections are ruled out as a cause of the vasculitis, biopsy of the involved segment may reveal the diagnosis, although the irregular distribution of the disease can make obtaining a diagnostic biopsy difficult. Probably the most common biopsy site is the sural nerve. In patients with a neuropathy, especially if the sural nerve conduction is abnormal, the biopsy finding is positive in more than 80% of cases.[68] Mesenteric angiography may be useful to demonstrate widespread aneurysms, but these may not be present early in the course of the illness.

PAN is treated with corticosteroids, especially in cases without organ involvement. Patients with organ involvement may need additional therapy with immunosuppressive agents such as cyclophosphamide.[69] Active viral hepatitis, if present, should be treated with antiviral therapy.

Buerger's Disease

Buerger's disease, also known as thromboangiitis obliterans, is an inflammatory vaso-occlusive disease that primarily affects the lower extremities in young adult male cigarette smokers, although women may also be affected. The role of tobacco, especially cigarette smoking, is clear, but the pathogenesis is unknown.

In most cases, Buerger's disease is limited to medium to small arteries and veins of the distal extremities. The disease typically begins with bilateral pain and ischemia of both lower extremities. At onset, the symptoms may be mild, such as paresthesias or pain only with exposure to cold, but most cases rapidly progress to a painful condition with digital cyanosis and severe claudication. Digital ulcers often occur with minor trauma.[70] Characteristic angiographic changes include multiple bilateral areas of narrowing or occlusion in the digital, palmer, planter, ulnar, radial, tibial, and peroneal arteries. The disease must be differentiated from premature atherosclerosis and other rheumatic diseases.

Treatment consists of abstinence from all forms of tobacco. Affected limbs must be protected from trauma and cold. Calcium channel blockers and pentoxyfylline have reportedly been beneficial in some patients. Therapy using transfer of the gene for vascular endothelial growth factor is under investigation.[71] Approximately half of individuals who continue to smoke will require amputation, often multiple times as more proximal vessels become involved.

Small Vessel Vasculitides

Behçet's Disease

Behçet's disease is a chronic relapsing vasculitis characterized by oral and genital ulceration; cutaneous lesions; and ophthalmologic, neurologic, or gastrointestinal manifestations. The prevalence of Behçet's disease ranges from 1 in 1000 in Japan to 1 in 150,000 in the United States and Europe.[72,73] It affects men more often than women, mainly young adults, with age of onset of 25 to 35 years. In Japan, it has been linked to histocompatibility antigen HLA-B5. Behçet's disease is one of the rare forms of vasculitis also capable of affecting large vessels.

Oral ulceration is the hallmark of the disease, tends to be the earliest manifestation, and is required for the diagnosis of Behçet's disease. Genital aphthae occur slightly less often than oral ulceration. The frequency of eye involvement is approximately 70% and includes bilateral or unilateral iritis, uveitis, and optic neuritis, all of which can lead to blindness.[74] An additional hallmark of Behçet's disease, a hypopyon uveitis, is seen rarely. CNS vasculitis, resulting in meningoencephalitis, intracranial hypertension, or a multiple sclerosis–like syndrome, may develop in 10 to 20% of patients. Gastrointestinal ulceration, including ileocecal perforation, has been reported in Japanese patients. Skin lesions, including erythema nodosum and cutaneous vasculitis, may occur. Cardiac and renal involvement is rare.[72,75] Nondeforming arthritis involving the knees and ankles has been described. Laboratory examination is nonspecific.

The diagnosis of Behçet's disease is made when a consistent clinical syndrome is associated with a nonnecrotizing perivascular infiltrate of lymphocytes and monocytes on biopsy of affected tissue. Therapeutic options should be based on the

degree of involvement.[76] Patients with mucocutaneous lesions only may be treated with intralesional topical or aerosolized (not inhaled) corticosteroids. Topical tacrolimus can also be used, often in combination with topical corticosteroids. Patients with more severe mucocutaneous involvement may be treated with thalidomide. Systemic involvement is generally well controlled with glucocorticoids at 1 mg/kg/day. Gastrointestinal disease can be controlled with sulfasalazine 2 to 6 g/day. Patients with eye involvement should be referred to an ophthalmologist because the most common cause of morbidity is ocular involvement, which can cause blindness. Serious manifestations of uveitis and CNS involvement warrant use of azathioprine or cyclophosphamide, and patients should be admitted to the hospital. Deep vein thrombosis associated with Behçet's disease rarely results in pulmonary emboli but should be treated with systemic anticoagulation.

Wegener's Granulomatosis

Wegener's granulomatosis (WG) is a necrotizing granulomatous vasculitis involving the respiratory tract, kidneys, and, to varying degrees, the medium to small vessels in other organs. Based on the National Hospital Discharge Survey, the 1986 to 1990 period prevalence of WG was estimated to be approximately 3 per 100,000 people. Both sexes were equally represented. The mean age at onset was 45 years, and most patients were white (80.9%).[77]

Patients first complain of upper respiratory tract symptoms with sinusitis, otitis, and nasal ulceration. Destruction of the sinus walls may also occur. Lower respiratory tract symptoms include cough, dyspnea, hemoptysis, and asymptomatic pulmonary infiltrates, occasionally with cavitation. Tracheal stenosis occurs in 13% of patients.[78] Renal involvement is a later finding with glomerulonephritis, which may be aggressive in 85% of patients.[79,80] Eye involvement includes conjunctivitis and scleritis caused by granulomatous deposition in the sclera. Skin lesions include ulcers, nodules, and granuloma formation. Neurologic involvement is rarely a presenting feature of WG, but it may develop during the course of disease in 22% to more than 50% of cases[81,82] and includes cerebral vasculitis, granulomatous deposition in cranial nerves, and peripheral nerve vasculitis resulting in neuropathies. Coronary vasculitis, pericarditis, and conduction defects are rare.[78,83]

Laboratory examination includes findings of a markedly elevated ESR, normochromic normocytic anemia, and, occasionally, thrombocytopenia. Urinalysis may show hematuria, active sediment excretion, proteinuria, and red blood cell casts. Antibodies against cytoplasmic components of polymorphonuclear cells (c-ANCA) have been found to be sensitive and specific for a diagnosis of WG.[79] ANAs are usually absent. The chest x-ray study shows multiple sharply demarcated nodular densities, predominantly in the lower lung fields, with pleural effusions in 25% of patients.[78] Lymphadenopathy is rarely seen on radiography.

Diagnosis of WG is confirmed by lung biopsy. Transbronchial biopsies are rarely diagnostic (<7%), whereas open lung biopsies reveal various combinations of vasculitis, granulomas, and necrosis in approximately 90% of cases.[78,84]

Treatment with corticosteroids alone does little to alter the prognosis. Until 20 years ago, WG had a mortality rate of 80% at 1 year.[85] The use of cyclophosphamide and corticosteroids in combination induced remissions in up to 90% of patients.[78] Complications of this therapy include increased risk of infection, especially disseminated herpes zoster and *Pneumocystis carinii* pneumonia. Patients with known WG with flares of renal disease should be admitted for intravenous corticosteroid administration. Patients suspected to have WG should be admitted for diagnosis and possible therapy. Renal transplantation has been successful in patients who progress to end-stage renal disease.

Lymphomatoid granulomatosis, often confused with WG, is characterized by destructive infiltration of lymphocytoid and plasmacytoid cells. The lower respiratory tract disease is the most prevalent, and upper respiratory tract involvement is rarely seen. Involvement of the kidney with deposition of granulomata is rare; however, in contrast to findings in WG, no vasculitis or glomerulonephritis is present. The spleen, lymph nodes, and bone marrow are usually spared. Malignant lymphoma develops in 50% of patients.[80] There are no specific laboratory findings, although in contrast to that in WG, the ESR is usually normal or only mildly elevated and the c-ANCA is negative. The chest x-ray study shows multiple nodules similar to those seen in metastatic cancer. Diagnosis is made by biopsy, usually of lung tissue. Treatment is the same as for WG. Remissions with corticosteroids and cyclophosphamide are seen in 50% of patients, except in those who are also diagnosed with malignant lymphoma, in whom mortality is 90%.[80]

Churg-Strauss Syndrome

Churg-Strauss syndrome (allergic granulomatosis and angiitis), first described in 1951 by Churg and Strauss, is characterized by granulomatous vasculitis of multiple organs, with hypereosinophilia in patients with asthma and allergic rhinitis. The etiology of Churg-Strauss syndrome is not known, but there is a definite association with allergy and atopic disorders. Nearly 70% of patients have a history of allergic rhinitis, often associated with nasal polyposis, and the association with asthma, usually adult onset, is part of most case definitions.[80] The vasculitis usually involves the veins and venules of the lower respiratory tract. The annual incidence of Churg-Strauss syndrome is approximately 2.4 cases per 1 million individuals.[86] The mean age is 44 years, with men affected more often than women.

Patients have systemic symptoms of fever, weight loss, and malaise. Pulmonary symptoms are predominant, with a history of asthma for at least 2 years before diagnosis.[87] Skin lesions occur in 60 to 70% of patients, with subcutaneous nodules or palpable purpura present. Pericarditis can lead to constrictive pericarditis. The Churg-Strauss syndrome is the ANCA-associated vasculitis most likely to involve the heart, usually in the form of heart failure.[88] Gastrointestinal symptoms caused by infiltration of the small bowel or stomach walls are associated with infarction, perforation, or bloody diarrhea. Renal disease is much less prominent. The neurologic manifestation is mainly mononeuritis multiplex, found in up to 80% of patients.[86]

Laboratory examination reveals a persistent eosinophilia greater than 1500/mm^3, often up to an absolute count of 5000 to 20,000/mm^3.[80] There is no definite correlation between eosinophilia and disease activity. Patients may have antineutrophil cytoplasmic antibodies directed against myeloperoxidase (p-ANCA). The chest x-ray study can show patchy, fleeting infiltrates known as Löffler's syndrome, consolidation, or cavitation.

The diagnosis of Churg-Strauss syndrome is made by biopsy, usually of skin or lung tissue. The patient may also have an elevated immunoglobulin E. Churg-Strauss syndrome is extremely responsive to corticosteroids, with usual dosing of prednisone at 60 mg/day orally. The prognosis is much improved with treatment, with 5-year survival greater than 50% in contrast to 25% in untreated patients. Nevertheless, certain disease complications, particularly the presence of

vasculitic neuropathy, cardiac involvement, or glomerulonephritis, should trigger the use of cyclophosphamide as part of the remission induction strategy.[89]

Microscopic Polyangiitis

Microscopic polyangiitis is a systemic neutrophilic small vessel vasculitis most often associated with rapidly progressive renal disease. MPA is the most common cause of the pulmonary-renal syndrome of alveolar hemorrhage and glomerulonephritis. There has been increasing recognition of this disorder in the United States since the 1994 Chapel Hill Consensus Conference on the nomenclature of systemic vasculitides because many cases before then were considered to be forms of polyarteritis nodosa. MPA has an estimated annual incidence of 4 cases per 1 million. MPA occurs in people of all ethnic backgrounds, but epidemiologic studies in the United States demonstrate a predilection for whites. The male-to-female ratio is approximately 1:1. The typical patient is middle-aged, but the disease may affect people of all ages.[90]

The term "polyangiitis" is preferred to "polyarteritis" for MPA because of the tendency of the disease to involve veins as well as arteries. Several studies have attempted to elucidate environmental factors associated with the onset of MPA. Seventy percent of patients with MPA have ANCAs, and anti-MPO antibodies are also detected. The five most common clinical manifestations of MPA are glomerulonephritis (nearly 80% of patients), weight loss (>70%), mononeuritis multiplex (60%), fevers (55%), and a variety of cutaneous findings (>60%). In contrast, alveolar hemorrhage occurs in a comparative minority (12%).[90]

MPA usually requires both glucocorticoids and a cytotoxic agent to control disease. The usual regimen to induce remission in patients with severe organ involvement includes high doses of prednisone (often preceded by a 3-day "pulse" of methylprednisolone, 1 g/day) plus cyclophosphamide. Following the induction of remission, patients may be switched to either azathioprine (up to 2 mg/kg/day) or methotrexate (up to 25 mg/week, assuming that residual renal dysfunction does not preclude this medication). Plasma exchange has also been shown to be useful. If MPA is diagnosed early and treated promptly, patients have a high likelihood (>90%) of achieving disease remission, although approximately one third of patients suffer disease flares after the achievement of remission.[91]

Goodpasture's Syndrome

Goodpasture's syndrome, or anti-glomerular basement membrane disease (anti-GBM), is characterized by the linear deposition of anti-glomerular basement membrane antibodies in the glomerular and alveolar basement membrane resulting in alveolar hemorrhage and progressive glomerulonephritis. Environmental factors and genetic susceptibility are thought to play a role, but no clear etiology has been identified. All age groups are affected. In adults, the mean age of onset is 20 to 30 years, with a peak incidence in young men age 20 to 30 years. A second peak occurs in those age 50 to 70 years, with men and women equally affected. The annual incidence is estimated to be 1 case per 2 million people among people of white European descent.[92]

General malaise, weight loss, fever, or arthralgia may be the initial features of anti-GBM disease. Patients may also have cough, dyspnea, and hemoptysis. The principal clinical features of the disease are development of renal failure due to progressive glomerulonephritis or pulmonary hemorrhage. Historically, hemoptysis has been the most common presenting feature, occurring in approximately 70% of reported cases.[92] Initially, the pulmonary hemorrhage may be mild, or it may be severe and life threatening. Hypoxia is common. The renal manifestations are varied; some patients have normal renal function, whereas others have a rapidly progressing glomerulonephritis. Patients may also have skin involvement with palpable purpura. Laboratory examination is notable for elevated ESR and urinalysis with red blood cell casts. On blood testing, anti-GBM antibodies can be measured, but the level of circulating antibodies does not correlate with the severity of the disease. Complement levels are normal, and in contrast to findings in Wegener's granulomatosis, c-ANCA tests are negative. A chest radiograph shows hilar pulmonary infiltrates.

The differential diagnosis includes SLE and Wegener's granulomatosis. Diagnosis is made by renal biopsy. Lung tissue shows pulmonary alveolar hemorrhage, with similar linear deposition of antibodies along the alveolar basement membrane.

Management of the airway is the first priority in patients with severe pulmonary hemorrhage. Treatment with methylprednisolone 10 to 15 mg/kg IV is necessary if rapidly progressive glomerulonephritis or severe pulmonary hemorrhage complicates the patient's course. The use of cytotoxic agents such as cyclophosphamide, as well as plasmapheresis (2–4 L/day of plasma), has been associated with improvement in pulmonary hemorrhage and glomerular lesions if extensive renal damage has not already occurred. Patients who progress to end-stage renal disease are candidates for transplantation if anti-GBM antibodies return to undetectable levels with treatment; otherwise, the disease may recur in the transplanted kidney.[93] Some patients present with the occasional flare of pulmonary hemorrhage. These patients should be admitted to the hospital to be observed for airway complications and for development of renal disease. The prognosis is varied but has greatly improved in the past 15 years because plasma exchange has been used more aggressively.

Henoch-Schönlein Purpura

Henoch-Schönlein purpura (HSP) is a small vessel vasculitis involving the skin, gut, and kidney and is characterized by immunoglobulin A (IgA)-dominant immune deposits in target organs. This vasculitis is particularly common in children, although patients of any age can be affected. The annual incidence in children is approximately 15 cases per 100,000 children.[94] The male-to-female ratio is 2:1. The syndrome occurs most often in the winter and early spring; two thirds of the cases follow an upper respiratory tract infection, with onset an average of 10 days after the start of respiratory symptoms.[95] Other inciting agents associated with HSP include insect stings and drugs.

The classic full presentation includes the acute onset of fever, palpable purpura on the lower extremities and buttocks, abdominal pain, arthritis, and hematuria. The rash is accompanied by arthralgias of the lower extremities, most commonly the ankles, with swollen, tender joints. The rash can be urticarial or purpuric and is usually in the lower extremities (Fig. 116-2). Frank arthritis is usually absent. Gastrointestinal complaints, seen in 70% of patients, include abdominal pain, nausea, vomiting, and diarrhea with blood and mucus per rectum.[79] Renal involvement occurs in 50% of patients with hematuria and red blood cell casts; however, it rarely progresses to renal failure.[73] Nervous system involvement is rare, especially in children. The syndrome is relapsing and remitting over several weeks.

Antigens to drugs, infectious agents, food, insect bites, and immunizations have been implicated in the pathogenesis of the IgA-dominant immune deposition. Treatment of the

Figure 116-2. Henoch-Schönlein purpura is a small vessel vasculitis involving the skin, gut, and kidney. (From Habif TP: Clinical Dermatology, 4th ed. New York, Mosby, 2004.)

BOX 116-5 Drugs Associated with Hypersensitivity Vasculitis

Nonsteroidal anti-inflammatory drugs
Ibuprofen, diclofenac, etodolac, piroxicam, naproxen
Antibiotics
β-Lactams, macrolides, sulfonamides, quinolones, antivirals
Growth factors
G-CSF, GM-CSF
Selective serotonin reuptake inhibitors
Paroxetine, fluoxetine
Antithyroid drugs
Propylthiouracil
Antihypertensive medications
Thiazides, beta-blockers
Anticonvulsants
Phenytoin
Vaccinations
Allopurinol
Aspirin
Acetaminophen
Insulin
Methotrexate
Anti–tumor necrosis factor agents
Etanercept, infliximab

G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor.
Adapted from Harris E, et al (eds): Kelley's Textbook of Rheumatology, 7th ed. Philadelphia, Saunders, 2005.

precipitating infection or discontinuation of the inciting drug is necessary. The treatment of HSP is an area with little evidence but much ongoing investigation.[96] NSAIDs may alleviate arthralgias but can aggravate gastrointestinal symptoms and should be avoided in any patient with renal disease. Dapsone may be effective in cases of HSP, possibly through interference with the interactions of IgA and neutrophils. Children with more severe arthralgias and abdominal pain benefit from prednisone at 1 mg/kg/day orally. Adults who have symptoms may be given prednisone 60 mg/day. Glucocorticoids do not appear to improve the rash, and their effectiveness in renal disease is controversial. Uncontrolled trials suggest that high-dose methylprednisolone followed by oral prednisone or high-dose prednisone combined with azathioprine or cyclophosphamide may help patients with severe nephritis.[94] Most patients do well with supportive care because HSP follows a self-limited course, resolving without substantial morbidity. The vast majority of cases resolve within 6 to 8 weeks. The disease may recur in up to 33% of patients. A small percentage of patients have prolonged renal impairment.[95]

Hypersensitivity Vasculitis

Hypersensitivity vasculitis, also known as cutaneous leukocytoclastic angiitis, is a small-vessel vasculitis that is restricted to the skin and not associated with any other form of primary or secondary vasculitis. It can be seen at any age and has no gender predominance. The etiology is often unknown, although drugs seem the most commonly identifiable offender.[97] Vaccinations have more rarely been associated with hypersensitivity vasculitis. Onset can be abrupt after exposure to the etiologic agent, but it usually ranges from 7 to 21 days after initial exposure. Although almost any medication can be associated with a hypersensitivity vasculitis, certain classes of drugs are more commonly associated with a hypersensitivity vasculitis (Box 116-5).[98] In up to 40% of cases, however, no specific cause is identified.[99]

The skin lesions of hypersensitivity vasculitis include purpura (either palpable or nonpalpable), papules, urticaria/angioedema, erythema multiforme, vesicles, pustules, ulcers, and necrosis. The lesions typically occur first and most prominently in dependent regions (i.e., the lower extremities or buttocks). The lesions tend to occur in cohorts or "crops" that are the same age. The occurrence of the lesions may be asymptomatic but is usually accompanied by a burning or tingling sensation. Arthralgias and even frank arthritis, with a predominance for large joints, are sometimes present. Laboratory examination is nonspecific, with a mildly elevated ESR and mild leukocytosis. The pathologic finding in the vessels, primarily the postcapillary venules, is immune complex deposition with infiltration by polymorphonuclear leukocytes with or without destruction of vessel walls. Hypersensitivity vasculitis must be distinguished primarily from other small vessel vasculitides, from autoimmune inflammatory conditions associated with joint disease and rashes, and from other cutaneous reactions to medications.

Treatment includes discontinuation of the offending agent. In mild cases, symptomatic treatment may be needed. For more severe involvement, corticosteroids (40–60 mg of prednisone per day gradually tapering the dose) are indicated.[100]

Mixed Cryoglobulinemia

Cryoglobulins are immunoglobulins and immune complexes that precipitate in the cold (4° C) and dissolve on rewarming. Mixed cryoglobulinemia syndrome is a consequence of immune complex-mediated vasculitis and is characterized by a typical clinical triad of purpura, weakness, and arthralgias. Middle-aged women are most commonly affected. Precipitat-

ing antigens include hepatitis A, B, and C; cytomegalovirus; or Epstein-Barr virus.[101]

The clinical features of mixed cryoglobulinemia include leukocytoclastic vasculitis (manifested as palpable purpura), polyarthralgias and arthritis, lymphadenopathy, hepatosplenomegaly, peripheral neuropathy, and hypocomplementemia, especially decreased C_4 serum levels. Recurrent palpable purpura occurs in virtually all patients. The most serious involvement is renal deposition of the cryoglobulins, resulting in glomerulonephritis, and it occurs in 20 to 60% of patients.[102] Patients may have fulminant or slowly progressive chronic renal disease. Laboratory examination demonstrates an elevated ESR, decreased serum complement levels, and the presence of cryoglobulins.

Diagnosis is made clinically in the presence of cryoglobulins; however, it may be difficult to distinguish from SLE or HSP. Treatment depends on the extent of involvement. Patients with disease limited to the skin may try low-dose steroids, and patients with systemic manifestations are usually started on prednisone 60 mg/day orally, although low-dose steroids should be avoided during initial antiviral therapy. Cyclophosphamide has been helpful in controlling systemic disease and allows decreases in steroid dosages. Approximately 75% of patients with mild to moderate hepatitis C-associated cryoglobulinemic vasculitis respond to antiviral therapy initially, but sustained responses are low.[103] Plasmapheresis has also been used in life-threatening cases but often requires concomitant immunosuppressive treatment. Rituximab, an anti-CD20 monoclonal antibody that depletes B cells, is also being explored as a therapeutic agent.

Serum Sickness

Serum sickness is a type III hypersensitivity reaction that results from injection of foreign proteins or serum. Reactions secondary to the administration of nonprotein drugs are clinically similar to serum sickness reactions. Not all substances that are recognized as foreign will elicit an immune response. The antigen must be of characteristic size or have specific antigenic determinants and physiological properties to be an effective stimulator of the immune system. After an appropriate antigen is introduced, an individual's immune system responds by synthesizing antibodies. The antibody reacts with the antigen, forming soluble circulating immune complexes that may diffuse into the vascular walls, where they may initiate fixation and activation of complement. Complement-containing immune complexes generate an influx of polymorphonuclear leukocytes into the vessel wall, where proteolytic enzymes that can mediate tissue damage are released. Immune complex deposition and the subsequent inflammatory response are responsible for the widespread vasculitic lesions seen in serum sickness.

Serum sickness has distinctive skin findings. Typically, erythema first occurs on the sides of the fingers, toes, and hands, before a more widespread eruption that is most often morbilliform (in two thirds of patients), sometimes with urticaria. Urticaria is seldom seen alone. Approximately half the cases of serum sickness have visceral involvement. Rash, fever, constitutional symptoms, arthralgia, and arthritis are the most frequent clinical findings.[104] Usually, symptoms start 12 to 36 hours after ingestion if there is a previously immunizing exposure, but they may occur up to 7 to 21 days after antigen exposure. The manifestations seen in serum sickness are due to immune complex deposition but not to systemic vasculitis as described in this chapter. In serum sickness, serum C3 and C4 complement levels are markedly decreased.[105] Withdrawing the drug usually leads to rapid resolution. Treatment is supportive with antihistamines and antipyretics. Systemic corticosteroids may benefit some patients. Symptoms usually last 1 or 2 weeks before spontaneously subsiding. Long-lasting sequelae generally do not occur.

Erythema Nodosum

Erythema nodosum is a vasculitis of the venules in the subcutaneous layers of the skin. The cause is unclear, but it is usually the result of a hypersensitivity vasculitis from infections, drugs, or a systemic disease. The disease is seen most commonly in spring and fall. The incidence of erythema nodosum is approximately 1 to 5 per 100,000 people. Women are more commonly affected than men, with a male-to-female ratio of 1:6. The peak incidence is in the third decade of life.[106,107] Erythema nodosum is thought to be caused by a circulating immune complex-mediated process, although the exact pathogenic process is not clear.

The hallmark lesions of erythema nodosum are tender erythematous subcutaneous nodules that have a blue hue as they resolve (Fig. 116-3). Symmetrical pretibial involvement is most common, although the extensor surfaces of the forearm, thigh, and trunk may also be affected. Patients may have just the nodules or may have systemic symptoms, including fever and malaise. Arthralgias are seen in 90% of patients at some time during the disease course and have been known to persist for up to 2 years after resolution.[107]

Erythema nodosum is usually idiopathic, although patients who have erythema nodosum should be considered for underlying diseases such as viral upper respiratory tract infection, streptococcal infection, sarcoidosis, tuberculosis, and drug exposure. Much rarer causes include inflammatory bowel diseases, histoplasmosis, *Yersinia*, *Salmonella*, *Chlamydia*,

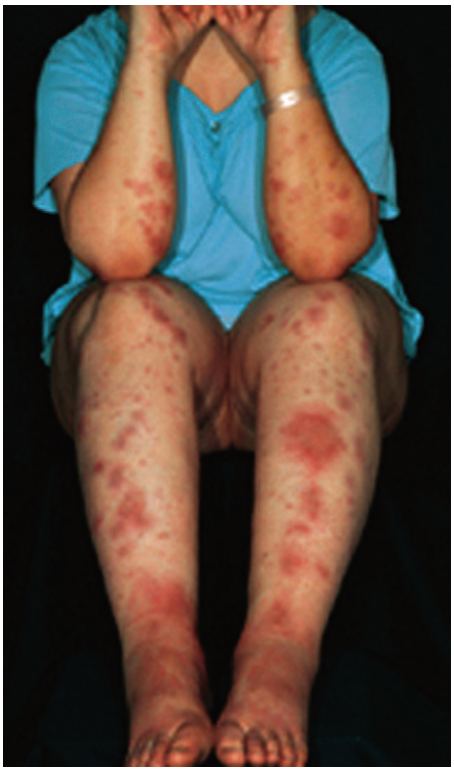


Figure 116-3. The hallmark lesions of erythema nodosum are tender erythematous subcutaneous nodules that have a blue hue as they resolve. (From Habif TP: Clinical Dermatology, 4th ed. New York, Mosby, 2004.)

coccidioidomycosis, psittacosis, and autoimmune diseases such as SLE. Drugs implicated include penicillins, sulfa drugs, aspartame, phenytoin (Dilantin), and oral contraceptives. The eruption can last up to 6 weeks. Although the lesions are exquisitely tender, erythema nodosum tends to be self-limited. The most common approach is treatment of any underlying disorder and supportive therapy. NSAIDs may be useful in controlling the arthralgias. Disposition depends on suspicion of underlying disease but is usually outpatient follow-up.

Panniculitis

The panniculitides are a group of heterogeneous inflammatory diseases involving the subcutaneous fat. Biopsy of the involved subcutaneous tissue shows fat cell necrosis, infiltration of inflammatory cells with macrophages, and vasculitis. Several forms of panniculitis exist. The inflammatory infiltrate can involve the septa or the lobule, and vasculitis may or may not be present. Diseases associated with panniculitis are erythema nodosum, erythema induratum, lupus profundus, pancreatitis, superficial thrombophlebitis, α_1-antitrypsin deficiency, light-chain paraproteinemia, and C_1 inhibitor deficiency.[108]

Erythema nodosum can exist as a manifestation of systemic disease or as a hypersensitivity to drugs (as discussed previously). Erythema induratum (Bazin's disease) and nodular vasculitis are synonymous terms used to describe a vasculitis of the skin of the calf associated with tuberculosis. Typical erythema induratum is a disease of middle-aged women in whom erythematous subcutaneous nodules and plaques appear on the posterior aspects of the lower leg. The bilateral lesions are usually tender and begin as nodules but then ulcerate and scar. The course is protracted and recurrent episodes over years or decades are common. Mycobacteria are rarely found in the lesions. Therapy is supportive with dressing changes and elevation, unless evidence of active tuberculosis is found elsewhere.[109]

Lupus profundus is a chronic recurrent panniculitis that appears in approximately 1 to 3% of patients with cutaneous lupus erythematous. Patients have subcutaneous nodules in the scalp, face, breasts, thighs, and buttocks. The lesions ulcerate and then heal. The differential includes erythema nodosum, but in lupus profundus the lesions are usually more chronic and nontender.[109]

Superficial thrombophlebitis presents with erythematous, tender subcutaneous nodules with a linear arrangement along a tender cordlike thickening of the involved vein. Usually, these cords are located on the lower limbs and are associated with venous insufficiency. Although a primary or secondary hypercoagulable state should be investigated, most of the time venous insufficiency of the lower extremities is usually the only precipitating factor. Treatment of thrombophlebitis is conservative, with application of a support stocking on the involved leg. In chronic and recurrent cases, especially those associated with malignancy, heparin, and fibrinolytic drugs may be used.[110]

KEY CONCEPTS

Systemic Lupus Erythematosus

- Patients with SLE can have multiple and varied symptom complexes. The diagnosis should be considered in patients with fever, rash, or unexplained systemic complaints.
- Patients with deep vein thrombosis without risk factors should be considered for APS. Patients with evidence of thrombosis should receive anticoagulation and be admitted for further workup.
- Febrile patients with SLE receiving immunosuppressive therapy should be hospitalized and treated aggressively because they have a high risk for gram-negative or streptococcal sepsis.
- Patients with worsening renal function or with involvement of the heart, lungs, or CNS should be hospitalized for aggressive treatment to prevent progression of the disease and symptoms.
- Patients with symptoms of coronary ischemia should be aggressively treated. Even young patients with risk factors for CAD should be evaluated for coronary ischemia.

The Vasculitides

- The diagnosis of systemic vasculitis is difficult and should be considered in patients with rash and pulmonary or renal complaints.
- Consultation with a rheumatologist is helpful for determining management when patients have flares of a known vasculitis.
- Febrile patients receiving immunosuppressive therapy or corticosteroids have a high risk for sepsis or disseminated viral infections and should be treated aggressively.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 117

Allergy, Hypersensitivity, and Anaphylaxis

T. Paul Tran and Robert L. Muelleman

PERSPECTIVE

Over millions of years, the human immune system has evolved to become a highly complex, elegant, and efficient organ whose chief function is to protect the human host (*self*) from harmful offenders (*nonself*). *Antigens* are foreign (or self) molecules that will elicit an immune response. Immunologic responses to antigens in humans are coordinated by two immune systems: the ancient *innate* immune system, which humans inherited from invertebrates, and the recently evolved *adaptive* immune system, which is present in humans and vertebrates. The innate system is considered the first line of defense. Its effector components include mast cells, macrophages, dendritic cells, natural killer cells, granulocytes, antimicrobial peptides, complements, and cytokines. Encoded in the germline, receptors in the innate immune system can recognize foreign molecular patterns that are highly conserved in microbes but not in humans, and they immediately begin the process of clearing the antigens. The adaptive system, on the other hand, must allow time for the antigen-specific cells (B and T cells) to amplify through a process known as *clonal expansion* to mount an effective immune response. Its effector components include B and T lymphocytes and cytokines. The adaptive immune system is characterized by having an immune memory and enormous diversity, capable of recognizing the myriad antigens through a vast library of antibodies and receptors (up to 10^{15}).[1] This diversity of antigen receptors is achieved by somatic rearrangement of fewer than 400 genes. Despite the complexity, the two immune systems work in concert and with great fidelity to provide the human host immunity. However, they can overreact, causing allergic disease.

For practical purposes, the term *allergy* is used herein to refer to an IgE-mediated (also known as type I or immediate) hypersensitivity reaction. Antigens that elicit an allergic reaction are referred to as *allergens*. Cases of allergy and anaphylaxis have historically been documented to the days of antiquity. Pharaoh Menes died of anaphylaxis in 2641 BCE. In 1902, Portier and Richet discovered that although a dog tolerated an injection of sea anemone toxin the first time, it died within minutes when injected again several weeks later.[2] They coined the term *anaphylaxis* from Greek (*ana*, against; *phylax*, guard or protect), meaning "against protection." For this and subsequent work in anaphylaxis, Richet was awarded the Nobel Prize in Medicine and Physiology in 1913. Today, anaphylaxis refers to a life-threatening allergic syndrome (i.e., IgE mediated) characterized by multiorgan involvement and rapid onset. Patients having an anaphylactic reaction would prototypically present in distress with prominent pruritic urticaria, orolaryngeal edema, bronchospasm, hypotension, and central nervous system and gastrointestinal (GI) symptoms. Common allergens that can induce an anaphylactic reaction include drugs, foods, insect stings, and latex. Deaths from anaphylaxis usually result from acute respiratory failure or cardiovascular collapse. Prompt recognition and aggressive treatment in the emergency department (ED) can usually stave off this potentially life-threatening allergic reaction. The term *anaphylactoid reaction* refers to a syndrome clinically similar to anaphylaxis that is not mediated by IgE. Its clinical presentation and treatment are identical to those of anaphylaxis. Anaphylactoid reactions seem to result from direct degranulation of mast cells (and basophils) and may follow a single, first-time exposure to certain inciting agents. In this chapter, the term anaphylaxis is used to refer to both IgE- and non-IgE-mediated reactions, obviating the need for the term anaphylactoid reaction.

Definition, Epidemiology, and Risk Factors for Anaphylaxis

Although anaphylaxis has traditionally been considered a clinical syndrome, there has been no universal agreement on a clinical definition of an anaphylactic reaction; anaphylaxis is usually defined in mechanistic terms as an IgE-mediated event. In an attempt to provide a working definition that clinicians can apply in the clinical setting, the National Institute of Allergy and Infectious Disease, in collaboration with the Food Allergy and Anaphylaxis Network, advanced a set of clinical criteria for identifying and diagnosing anaphylaxis (Box 117-1).[3] In the most common scenario encountered in the ED, the diagnosis of anaphylaxis is considered "highly likely" if a patient presents with acute onset (within minutes after an exposure) of rash or mucosal swelling and respiratory insufficiency or hypotension.

The epidemiology of anaphylaxis is not known with certainty, and estimates in medical literature vary widely. As a measure of risk, the annual incidence rate for all-cause anaphylaxis is generally believed to be 21 per 100,000 person-years[4]; the case mortality in this series is 0.65%. As a measure of burden of disease, the prevalence rate of anaphylaxis ranges from 1.21 to 15.04% for the U.S. population.[5] Given the U.S. population of 272 million in 1999, these prevalence figures imply that between 3.3 million and 43 million Americans are at risk for an anaphylactic reaction. It is commonly believed that there are probably 100,000 cases of anaphylaxis per year

BOX 117-1 Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
   AND AT LEAST ONE OF THE FOLLOWING:
   a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. Two or more of the following occurring rapidly (minutes to several hours) after exposure to a likely allergen for that patient:
   a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than 70 mm Hg + 2 × age from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

BP, blood pressure; PEF, peak expiratory flow.

From Sampson HA, Munoz-Furlong A, Campbell RA, et al: Second symposium on the definition and management of anaphylaxis: Summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 117:391, 1996.

in the United States; of these, approximately two thirds are new cases and 1% are fatal.[6]

The cause of anaphylaxis remains unidentified in more than one third of cases.[7,8] When a cause can be determined, food, drugs, insect stings, and latex are the most common etiologic agents. Food is the cause in one third of known cases, most commonly peanuts and crustaceans.[7] Insect stings, particularly bee and wasp stings, are an important cause of anaphylaxis, occurring in 0.5 to 5% of the population and accounting for 50 to 100 deaths per year in the United States.[5] Penicillin allergy occurs at a frequency of one to five reactions per 10,000 treatments, with 1 per 50,000 to 100,000 treatments resulting in a fatality.[9] Radiocontrast medium (RCM) reactions occur in 0.22% of patients given the hyperosmolar contrast agents but in only 0.04% of patients given the newer nonionic agents.[10] Latex, the natural rubber widely used in the manufacture of medical products (latex gloves and latex medical devices), is a common source of allergy but an uncommon cause of anaphylactic reactions.[5]

Although race, geographic location, and occupation do not seem to predispose individuals to the risk of anaphylaxis, other risk factors tend to show a multifactorial pattern. For example, atopy is a risk factor for anaphylaxis in an all-cause anaphylactic series.[11] This is particularly true when the allergen is administered by the mucosal route (e.g., food). Atopy does not, however, seem to be a risk factor when the allergen is administered parenterally (e.g., penicillin). Limited data tend to suggest that economic status, age, sex, and season of the year seem to affect the risks of having an anaphylactic reaction. Anaphylactic reactions seem to be more common in summer and early fall (the outdoor season), in people of higher socioeconomic status, in women older than 30 years, and in adults. The dose, frequency, duration, and route of administration of a drug also affect the tendency to develop an anaphylactic reaction, with the parenteral and topical routes more likely to lead to an anaphylactic reaction. One interesting aspect of drug-related anaphylaxis is the constancy of administration. An anaphylactic reaction may not occur in a susceptible patient as long as a drug is administered at regular intervals. The same patient may, however, experience an anaphylactic reaction if the drug is resumed after an interruption of therapy. Lastly, the more distant the last exposure, the lower the risks of anaphylaxis upon reexposure, presumably because of some forgetfulness of the immune memory.

PRINCIPLES OF DISEASE

Development of the Immune System and Mechanism of Immune-Mediated Injury

The adaptive and innate immune systems originate from the common pluripotential hematopoietic stem cells, which are derived from the yolk sac and later reside in the bone marrow. These stem cells differentiate and develop into the lymphoid precursor cells and the colony-forming unit for granulocyte, erythroid, myeloid, and megakaryocyte (CFU-GEMM) stem cells. The lymphoid precursor cells in turn differentiate into bursa-equivalent lymphocytes (B cells), thymus-derived lymphocytes (T cells), and natural killer (NK) cells; the CFU-GEMM cells, in the meantime, develop into mast cells, basophils, and others (Fig. 117-1). When the body encounters an allergen, the cellular components of the adaptive immune system interact with the cellular and protein components of the innate immune system to mount a concerted defense aimed at neutralizing and removing the harmful allergen.

T Cell Development

Lymphoid precursor cells migrate from the bone marrow into the thymus, where they progress through ontogeny. Under regulation by cytokines and cell-cell interaction, these precursors undergo gene rearrangement and positive and negative selection. In the process, T cells acquire the T cell antigen receptors and various surface markers and eventuate into two main T cell lineages. Using the cluster of differentiation (CD) classification, there are principally two types of mature T cells that eventuate out of the thymus: $CD4^+$, also called helper T cells, and $CD8^+$, also called suppressor T cells. Depending on the type of cytokine produced, T helper cells are subdivided into type 1 helper cells (Th1) and type 2 helper cells (Th2), with opposing activities. Whereas Th1 cells inhibit IgE production and IgE isotype switching, Th2 cells stimulate IgE production and IgE isotype switching. The balance of these stimulatory and inhibitory activities of the Th1 and Th2 cells is believed to determine an individual's propensity to develop allergic disease or atopy and may help explain the increased prevalence of allergy in urbanized and Western societies in the past three decades. Early in utero and soon after birth, naive T lymphocytes in the infant's immune system are dominated by the allergy-prone Th2 cells and their associated cytokines (interleukins [ILs] 4, 5, and 13). These cytokines are

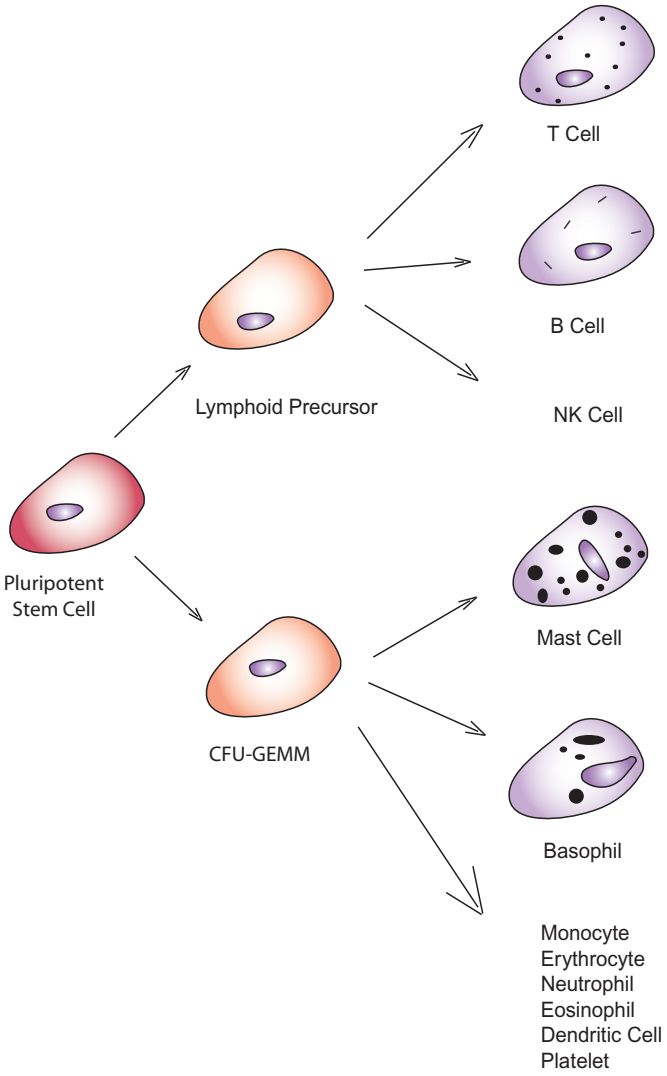


Figure 117-1. Developmental pathways of the immune and hematopoietic systems. CFU-GEMM, colony-forming unit for granulocyte, erythroid, myeloid, and megakaryocyte; NK, natural killer. (Redrawn from Shearer WT, Fleisher TA: The immune system. In Middleton E, et al [eds]: Allergy: Clinical and Practice. St. Louis, Mosby, 1998, pp 1–13.)

important inducers for production of IgE antibodies. Later, during infancy through early childhood and adolescence, the nonatopic infant's immune system gradually shifts from this allergy-prone Th2 environment to an allergy-protective Th1 environment. The cytokines associated with this Th1 environment include IL-2 and interferon-γ. This shift is thought to be caused by the continual exposure of the young individual's immune system to allergenic stimuli from the surrounding environment, mainly microbes. Features of Western lifestyles ("hygiene hypothesis") such as changes in infant diets, widespread use of antibiotics, smaller family size, and cleaner childcare are believed to reduce this stimulatory antigenic exposure in an individual's early years, leading to an environment in which the immune system is dominated by a persistent allergy-prone Th2 system. This lack of balance between the two immune systems supposedly leads to atopy and thus an allergy-prone population.[12,13]

B Cell Development and Immunoglobulins

B cell ontogeny can be divided into antigen-independent and antigen-dependent stages. During the antigen-independent stage, B cells mature in primary lymphoid organs (bone marrow and fetal liver), where they undergo gene rearrangement in a stochastic manner and acquire various surface markers. Later during the antigen-dependent stage in the secondary lymphoid organs (lymph nodes and spleen), B cells differentiate into memory B cells and plasma cells and are ready to secrete immunoglobulins. Throughout B cell ontogeny, B cell maturation, isotype switching, and immunoglobulin production are driven by activated T cells, cytokines, and interaction with antigen and bone marrow stromal cells.

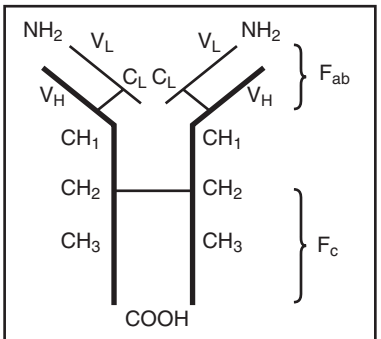
Immunoglobulins are protein molecules composed of two identical polypeptide heavy chains and two identical polypeptide light chains, covalently linked by disulfide bonds (Fig. 117-2). The heavy (H) chains have one variable domain, V_H, and three or four constant domains, C_H. The light (L) chains have one variable domain, V_L, and one constant domain, C_L. The variable domains of the heavy and light chains together form a pair of identical antigen binding sites and, together with the adjacent constant heavy domain pair, make up the Fab (antibody-binding fragment) region of the immunoglobulin molecule. The remaining constant domains of the heavy chains together form the Fc (crystallizable fragment) region of the immunoglobulin molecule. The Fc binds to the surface receptors of effector cells such as mast cells, B cells, or macrophages. There are five isotypes or classes of immunoglobulins, IgG, IgA, IgM, IgD, and IgE, with isotype IgG having four subclasses (IgG1, IgG2, IgG3, and IgG4) and IgA two subclasses (IgA1 and IgA2). The body usually produces IgM antibodies when it first encounters an antigen. Repeated antigenic exposure, however, may cause the constant region of the IgM to switch to another class (IgA, IgG, or IgE), a process also known as isotype switching. Isotype IgE (and IgG4) is the most important antibody in the pathogenesis of allergic disease and anaphylaxis.

Classification of Reactions

There are four types of hypersensitivity reactions in the Coombs and Gell classification system. Type I (immediate hypersensitivity) is IgE (and IgG4) mediated and accounts for most allergic and anaphylactic reactions observed in humans. Type II (cytotoxic) denotes antibody-mediated cytotoxic reaction. In this scheme, complement-fixing IgG (or IgM) engages cell-bound antigen, activating the classic complement pathway, leading to the fixation of membrane attack complexes and cell lysis. In the process, anaphylatoxins C3a and C5a may also cause mast cell mediators to be released, producing the same action as the classic mediators of anaphylaxis. Type III (immune complex) is IgG or IgM complex mediated. Circulating soluble antigen-antibody immune complexes migrate from the circulation to deposit in the perivascular interstitial space, thereby activating the complement system. Anaphylactic reactions to blood transfusions or blood component therapy, including serotherapy (immunoglobulin administration), are clinical examples of the overlap of type II and type III reactivity; thus, they have been classified as complement-mediated or immune complex-mediated anaphylaxis. Type IV (delayed hypersensitivity) is T cell mediated and has no documented relationship to the pathogenesis of anaphylaxis.

PATHOPHYSIOLOGY

Mast cells (and basophils) and their contents are the central effector cells and mediators in allergy and anaphylaxis. Exposure of a genetically predisposed individual to a novel allergen leads to the synthesis and release of allergen-specific IgE by plasma cells into the circulation. Fixation of this allergen-specific IgE to surface receptors on mast cells (FcεRI) com-



Immunoglobulin molecule Ig is composed of a pair of heavy chains and a pair of light chains with variable (V) and constant (C) domains.

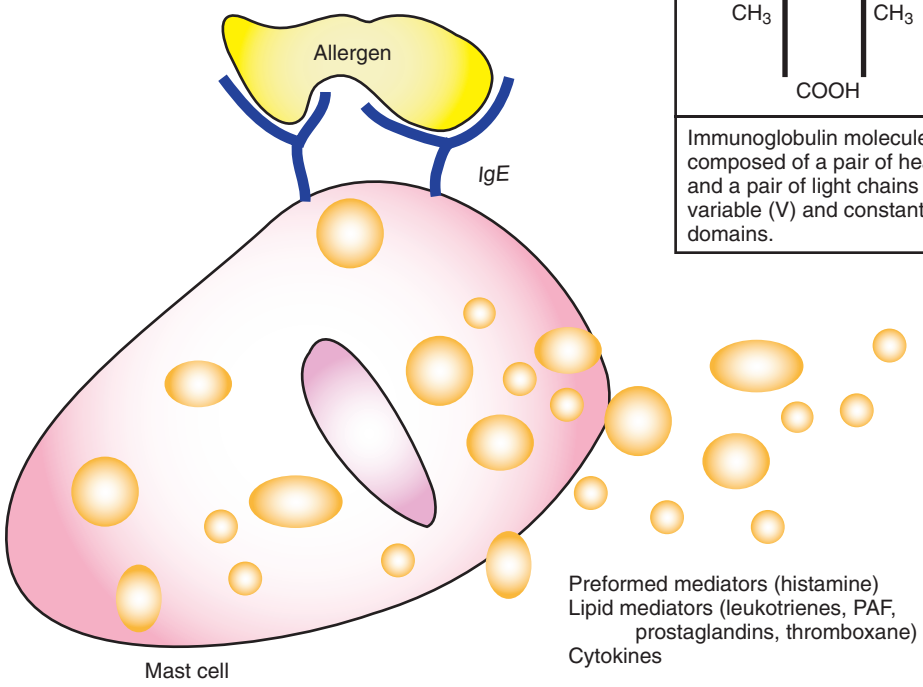


Figure 117-2. Activation of mast cells with degranulation of mast cell mediators by antigen (Ag) cross-linking adjacent immunoglobulin E (IgE) on cell surface. PAF, platelet-activating factor.

pletes the process known as *sensitization*. These IgE-bearing mast cells usually reside in the mucosal surfaces, submucosal tissue (around venules), and cutaneous surfaces, and they are capable of becoming activated upon reexposure to a specific allergen. Cross-linking of the FcεRI on the mast cells by a specific multivalent allergen sets off a cascade of conformational and biochemical events, leading eventually to the degranulation of preformed mediators and the generation and release of arachidonic acid metabolites and cytokines from mast cells (and basophils). At the target tissue level, these mediators cause enhanced capillary permeability, vasodilation, smooth muscle contraction, sensory nerve stimulation, myocardial depression, and activation of secondary inflammatory pathways. These pathologic events result in clinical manifestations that include flushing syndrome, urticaria and angioedema, pruritus, nausea, vomiting, diarrhea, abdominal pain, chest pain, dyspnea, wheezing, respiratory insufficiency and failure, dizziness, syncope, hypotension, and shock.

Immunoglobulin E–Mediated Signal Transduction System

Following cross-linking of FcεRI, signal transduction is initiated by a tyrosine kinase, termed Lyn, which is constitutively associated with the FcεRI receptor (Fig. 117-3).[14,15] Subsequently, Lyn phosphorylates the immunoreceptor tyrosine-based activation motif (ITAM) of the subunits of the FcεRI, leading to the activation and binding of protein tyrosine kinases (PTK) with SRc homology domain 2 (SH2). One such PTK is spleen tyrosine kinase (Syk). An activated Syk subsequently leads to further tyrosine phosphorylations of several "adapter" proteins. Principally among these are (1) the phosphorylation of linker for activation of T cells (LAT), which serves as the attachment site for several proteins including leukocyte-specific phosphoprotein of 76 kd (SLP-76), and (2) the phosphorylation of phospholipase C γ (PLC-γ). Phosphorylated PLC-γ generates diacylglycerol (DAG) and inositol-1,4,5-triphosphate (IP_3) from membrane phospholipids. DAG in turn activates protein kinase C, which promotes exocytosis of preformed granules and cytokine transcription factors. IP_3 binds to receptors in the endoplasmic reticulum, causing a rise in intracellular Ca^{2+} and resulting in a depletion of Ca^{2+} store, which leads to more influx of calcium from extracellular space via the activation of the Ca^{2+} release-activated Ca^{2+} channel (I_{CRAC}). Spikes in intracellular calcium activate a number of calcium-gated kinases, including phospholipases, which cleave membrane phospholipids to generate lysophospholipids, which in turn facilitate the fusion of secretory granules with the cell membrane, leading to the exocytosis of the secretory granules. Through the LAT/SLP-76 multimolecular complex, tyrosine phosphorylation and activation of a number of enzymes and adapters lead to the activation of JNK and ERK (among others) and ultimately the synthesis and release of cytokines and arachidonic acid (AA) metabolism. The end result is the secretion of preformed mediators, AA metabolites, and cytokines (Box 117-2) into the circulation, which act on target organs to cause the clinical syndrome of anaphylaxis.

Mediators of Anaphylaxis

The mediators released by the mast cells and basophils can be categorized into three main groups: preformed mediators, lipid-derived metabolites (AA metabolism), and cytokines (see Box 117-2). Of the preformed mediators, histamine is the most

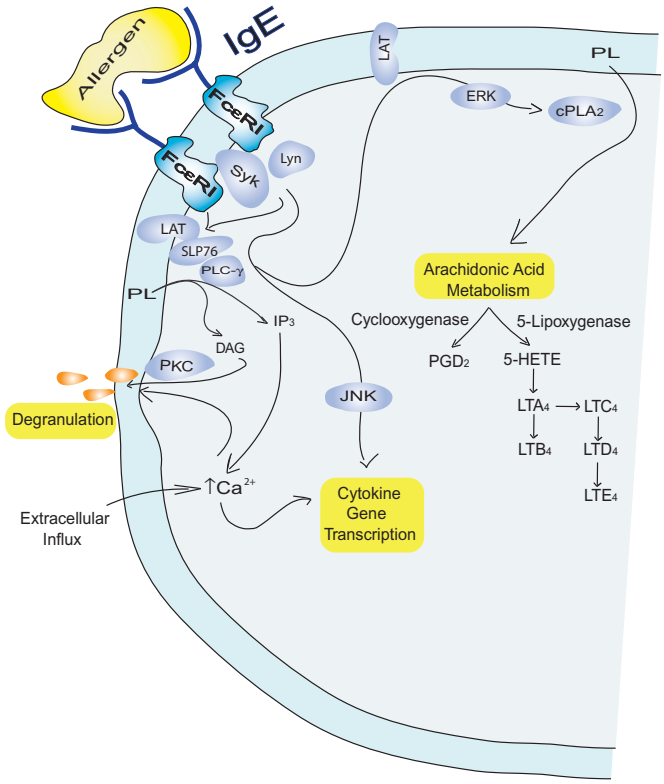


Figure 117-3. Signal transduction sequence following the cross-linking of adjacent immunoglobulin E (IgE) on the surface of mast cell. $cPLA_2$, cytoplasmic phospholipase A_2; DAG, diacylglycerol; ERK, extracellular signal-regulated kinase; HETE, hydroxyeicosatetraenoic (acid); IP_3, inositol triphosphate; JNK, S-Jun N-terminal kinase; LAT, linker for activation of T cell; LTA_4, leukotriene A_4; Lyn, Src-like protein-tyrosine kinase; PGD_2, prostaglandin D_2; PKC, protein kinase C; PTK, protein tyrosine kinase; SLP-76, leukocyte-specific phosphoprotein of 76 kd; Syk, spleen tyrosine kinase.

BOX 117-2 MEDIATORS OF ACTIVATED MAST CELLS AND BASOPHILS

Preformed Mediators (Granule)
Histamine
Tryptase
Carboxypeptides
Chymase
Cathepsin G
Heparin
Proteoglycans

Arachidonic Acid Metabolism Products (Membrane)
LTB_4
LTC_4
PGD_2
Platelet-activating factor

Cytokines (Nucleus)
TNF
CCL2, CCL3, CCL5
GM-CSF
IL-3, -4, -5, -6, -8, -10, -13

CCL, CC chemokine ligand; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; LTB_4, leukotriene B_4; PGD_2, prostaglandin D_2.

clinically apparent and is responsible for the immediate symptoms. Histamine is an essential mediator in immediate hypersensitivity and inflammation, and infusion of histamine has been shown to produce the majority of the clinical features of anaphylaxis syndrome.[16] Histamine is produced and stored in preformed granules (pg) in mast cells and basophils, at approximately 1 or 2 pg/cell. There are three classes of histamine receptors—H_1, H_2, and H_3—that mediate the activity of histamine in the body. H_1 receptor stimulation produces bronchial, intestinal, and uterine smooth muscle contraction; increased vascular permeability; nasal mucus production; coronary artery spasm; and increased eosinophil and neutrophil chemokinesis and chemotaxis. H_2 receptor stimulation increases the rate and force of ventricular and atrial contraction, gastric acid secretion, airway mucus production, and vascular permeability while also causing bronchodilation and inhibition of basophil histamine release. H_3 receptors, found in neurons (in the central nervous system) and peripheral tissues, control the synthesis and release of histamine. The roles of the other preformed mediators in mast cell and basophil degranulation syndrome are not well delineated.

In contrast to the preformed mediators, cytokines and lipid metabolites are elaborated following the activation of mast cells and basophils (see Fig. 117-3). Prostaglandin D_2 (PGD_2) is the main AA metabolite released by activated mast cells (but not basophils). PGD_2 (and thromboxanes) is synthesized from AA by the cyclooxygenase pathway (via both COX-1 and COX-2). PGD_2 is responsible for causing hypotension, inhibition of platelet aggregation, and bronchospasm; PGD_2 is approximately 30 times more potent than histamine in causing bronchoconstriction. The leukotrienes—LTB_4, LTC_4, LTD_4, and LTE_4—also referred to as cysteinyl leukotrienes or slow-reacting substances of anaphylaxis, are synthesized from AA via the lipoxygenase pathway. LTB_4 and LTC_4 are first synthesized intracellularly in mast cells and basophils and then secreted; LTC_4 is subsequently converted to LTD_4, and LTE_4 in the extracellular space (by gamma-glutamyl transpeptidase and dipeptidase). They are involved in cholinergic-independent bronchospasm, increased vascular permeability, and increased mucous gland production. These cysteinyl leukotrienes have a slow onset but are 10 to 1000 times more potent than histamine in causing bronchoconstriction when administered by aerosol.[17] They also have a longer duration of action and potentiate the effects of other bronchoconstrictors such as histamine.

Platelet-activating factor (PAF) is an unstored phospholipid and the most potent compound known to cause aggregation of human platelets with subsequent release of platelet-derived vasoactive mediators. Its other actions include neutrophil activation and chemotaxis and ileal and parenchymal lung strip smooth muscle contraction. PAF has been demonstrated to produce many of the important clinical manifestations of anaphylaxis, including decreased myocardial contractile force, coronary vasoconstriction, pulmonary edema, and a prolonged increase in total pulmonary resistance with a decrease in dynamic compliance. Indeed, blockage of PAF with experimental antagonists leads to improved cardiac function, suggesting that PAF may be involved in the late cardiac dysfunction and lethality associated with anaphylaxis.[18]

Physiologic Effects

The chemical mediators released from mast cells exert their effect on various target organs to produce the clinical syndrome of anaphylaxis. Increased vascular permeability can lead to urticaria, angioedema, laryngeal edema, nasal congestion, or gastrointestinal swelling with abdominal cramping and

vomiting. Vasodilation can lead to flushing, headaches, reduced peripheral vascular resistance, hypotension, and syncope. Contraction of smooth muscle can lead to bronchospasm, abdominal cramping, or diarrhea. Pulmonary vessel vasoconstriction can lead to pulmonary hypertension, pulmonary edema, and decreased cardiac filling pressures. Coronary vasoconstriction can lead to myocardial ischemia and decreased myocardial contractile force. Changes in atrial chronotropy and ventricular and atrial isotropy can lead to cardiac dysrhythmias. In addition to the direct actions on the target tissues, these preformed mediators, lipid-derived mediators, and cytokines activate a number of inflammatory pathways, including the complement system, clotting and clot lysis systems, and the kallikrein-kinin (contact) system, to contribute to the clinical manifestations of allergy and anaphylaxis.

Cardiovascular collapse in anaphylaxis has classically been described as a result of peripheral vasodilation, enhanced vascular permeability, leakage of plasma, and intravascular volume depletion (the "empty ventricle" syndrome). However, hemodynamic reports for humans experiencing anaphylactic shock indicate that the explanation may be more complicated. In a variety of clinical settings, hypotension in anaphylaxis has been associated with an initial increase in cardiac index, which may become depressed, and altered peripheral and pulmonary vascular resistance (increased/decreased). In the setting of decreased cardiac index and elevated peripheral vascular resistance, organ perfusion is compromised, resulting in metabolic acidosis. The use of pressors alone in this situation may not improve hemodynamics as peripheral blood vessels are already maximally vasoconstricted. Aggressive volume expansion with crystalloid (or colloid) is needed in this scenario.

Pathologic features identified at autopsy in fatal cases of anaphylaxis are most commonly observed in the respiratory and cardiac systems. These include orolaryngeal edema, pulmonary hyperinflation, peribronchial vascular congestion, intra-alveolar hemorrhage, pulmonary edema, increased tracheobronchial secretions, and eosinophilic infiltration of the bronchial walls. Death from asphyxia is usually caused by angioedema of the epiglottis, larynx, hypopharynx, and, to some extent, the trachea. Patients who die of vascular collapse show varying degrees of myocardial damage, visceral congestion, and other findings suggestive of a loss of intravascular blood volume. Other autopsy findings include urticarial eruptions, angioedema, visceral congestion, submucosal edema, and hemorrhagic gastritis. Notably, autopsy findings may also be normal after an anaphylactic death.[19] A summary of the physiologic effects and clinical signs and symptoms is given in Table 117-1.

ETIOLOGY

Numerous agents are known to cause anaphylaxis in humans. They are organized by immunopathogenetic mechanism: IgE mediated, immune complex mediated, nonimmunologic activators, or AA modulators (Box 117-3). Reactions without identifiable causative agents are classified as physically induced or iatrogenic anaphylaxis (IA).

Immunoglobulin E–Mediated Agents

This diverse group of agents includes foods, antibiotics, latex, drugs, and Hymenoptera stings.

Foods

Foods are the major identifiable causative agents, accounting for approximately one third of the cases of anaphylaxis.[7] A variety of foods ranging from the well-known, such as nuts, shellfish, and eggs, to the obscure, such as chamomile tea (which may have cross-reactivity with ragweed), have been identified. Cow's milk, egg, peanut, soy, wheat, fish, shellfish, and tree nuts are foods that most commonly cause anaphylaxis. Even for a person with a known history of food allergy, it may be difficult to avoid foods that may cause allergic reactions because their identity may be obscured in processing (e.g., wine contaminated with Hymenoptera venom).[20] Because allergenic foods are first absorbed transmucosally, symptoms of food anaphylaxis may first appear localized to the upper airway of the respiratory tract. When anaphylactic allergens are administered parenterally, symptoms of anaphylaxis tend to be more cardiovascular and systemic. Allergic reactions to foodstuffs are more common in children, ranging from 0.3 to 7.5%.[21]

Therapeutic and prophylactic use of large quantities of antibiotics is common in the production of beef cattle, swine, fish, poultry, and sometimes vegetables and fruits. Along with antibiotics, sodium and potassium bisulfites and metabisulfites are used as preservatives in foods. Sulfites have been used as antioxidants in the food and restaurant industry to prevent discoloration of vegetables (e.g., salad bars and avocado dips), fruits, and potatoes and to preserve fruit and vegetable juices. They are also used to prevent bacterial contamination and oxidation of wines, beers, and distilled beverages. Sensitivity to ingested sulfites has been well documented, especially among the asthmatic population.[22] Establishing a particular foodstuff or preservative as the causative agent of anaphylaxis can be difficult.

Antibiotics

Benzylpenicillin, semisynthetic penicillin, and cephalosporins are the most commonly used antibiotics, with penicillin perhaps the most commonly reported medication allergy. The first penicillin-induced anaphylactic fatality was reported in 1949.[23] Because of their low molecular weights, these antimicrobials do not themselves possess antigenic properties. Immunologically, they are haptens, simple chemicals that are not antigenic in themselves but become antigenic after the chemicals or their metabolites form a stable bond with the host proteins. Certain binding properties of particular drugs make them more likely to induce sensitization. Although patients often report a history of penicillin allergy, this usually does not stand up to close scrutiny.[24] Studies have shown that up to 9 of 10 individuals with a reported history of penicillin allergy can safely use penicillin; these individuals usually are either mislabeled as penicillin allergic or lose their allergy after years of avoidance.[25] Depending on the studies, the frequency of allergic reactions to penicillin varies from 0.01 to 0.05% of administrations of penicillin (1 to 5 reactions per 10,000), with an anaphylactic reaction rate less than 0.01% and a fatality rate less than 0.002% (less than 1 fatality per 50,000 penicillin administrations).[9,26] Parenterally administered penicillin is responsible for most of the anaphylactic reactions. The extensive use of this drug in unsuspected sources such as foods, in which it is used as a bacteriostatic agent, may make it difficult to ascertain historically that penicillin is not the causative agent.

Cephalosporins share the β-lactam ring structure and side chains of the penicillins and have been incriminated for allergic cross-sensitivity in 1 to 8% of patients.[27] It is unclear which epitope is responsible for the cross-reactivity. Patients who have urticaria or anaphylactic reactions after taking penicillin are approximately four times more likely to have an adverse reaction to cephalosporins. Even in this setting, the risk of an anaphylactic reaction to cephalosporins is still less than 0.1%.

Table 117-1 Clinical Manifestations of Anaphylaxis and Related Pathophysiology

ORGAN SYSTEM	REACTION	SYMPTOMS	SIGNS	PATHOPHYSIOLOGY
Respiratory tract				
Upper	Rhinitis	Nasal congestion Nasal itching Sneezing	Nasal mucosal edema Rhinorrhea	Increased vascular permeability Vasodilation Stimulation of nerve endings
	Laryngeal edema	Dyspnea Hoarseness Throat tightness Hypersalivation	Laryngeal stridor Supraglottic and glottic edema	As above, plus increased exocrine gland secretions
Lower	Bronchospasm	Cough Wheezing Retrosternal tightness Dyspnea	Cough Wheeze, rhonchi Tachypnea Respiratory distress Cyanosis	As above, plus bronchiole smooth muscle contraction
Cardiovascular system	Circulatory collapse	Light-headedness Generalized weakness Syncope Ischemic chest pain	Tachycardia Hypotension Shock	Increased vascular permeability Vasodilation Loss of vasomotor tone Increased venous capacitance
	Dysrhythmias	As above, plus palpitations	ECG changes: Tachycardia Nonspecific and ischemic ST-T wave changes Right ventricular strain Premature atrial and ventricular contractions Nodal rhythm Atrial fibrillation	Decreased cardiac output Decreased mediator-induced myocardial suppression Decreased effective plasma volume Decreased preload Decreased afterload Hypoxia and ischemia Dysrhythmias Iatrogenic effects of drugs used in treatment Preexisting heart disease
	Cardiac arrest		Pulseless ECG changes: Ventricular fibrillation Asystole	
Skin	Urticaria	Pruritus Tingling and warmth Flushing Hives	Urticaria Diffuse erythema	Increased vascular permeability Vasodilation
	Angioedema	Nonpruritic extremity, periorbital and perioral swelling	Nonpitting edema, frequently asymmetric	Increased vascular permeability
Eye	Conjunctivitis	Ocular itching Increased larcrimation Red eye	Conjunctival inflammation	Stimulation of nerve endings
Gastrointestinal tract		Dysphagia Cramping, abdominal pain Nausea and vomiting Diarrhea (rarely bloody) Tenesmus	Nonspecific	Increased mucus secretions Gastrointestinal smooth muscle contraction
Miscellaneous central nervous system		Apprehension Sense of impending doom Headache Confusion	Anxiety Seizures (rarely) Coma (late)	Secondary to cerebral hypoxia and hypoperfusion Vasodilation
Hematologic	Fibrinolysis and disseminated intravascular coagulation	Abnormal bleeding and bruising	Mucous membrane bleeding, disseminated intravascular coagulation Increased uterine tone Vaginal bleeding	Mediator recruitment and activation Uterine smooth muscle contraction Bladder smooth muscle contraction
Genitourinary		Pelvic pain Vaginal bleeding Urinary incontinence	Urinary incontinence	

ECG, electrocardiographic.

BOX 117-3 Etiologic Agents and Pathogenetic Mechanisms of Anaphylaxis

IgE-Mediated Agents
Foods (eggs, peanuts, tree nuts, cow's milk, fruits, shellfish, shrimp, other crustaceans, many others)
Antibiotics (penicillins, cephalosporins, sulfonamides, nitrofurantoin, tetracycline, streptomycin)
Other therapeutics (methylparaben, human diploid cell rabies vaccine, egg-based vaccines: measles, mumps, rubella, vasopressin, antilymphocyte globulin)
Insect stings (Hymenoptera venoms, fire ant stings)
Latex
Allergens used in immunotherapy
Heterologous and human sera
Hormones (insulin, methylprednisolone, parathormone, estradiol, progesterone, corticotropin)
Enzymes (trypsin, streptokinase, chymotrypsin, chymopapain, L-asparaginase)
Polysaccharides (dextran, iron dextran)
Local anesthetics (mostly ester family, procaine, tetracaine, benzocaine)

Direct Mast Cell Degranulation
Radiocontrast media
Opiates
Curare, *d*-tubocurarine
Protamine
Polysaccharides (some are IgE mediated)
ACE inhibitor used during hemodialysis with certain HD membranes
Ethylene oxide gas on dialysis tubing

Immune Complex Mediated
Whole blood (transfusion reaction to formed elements)
Immunoglobulin administration

Arachidonic Acid Metabolism
Aspirin and NSAIDs (presumed)
Benzoates (presumed)
Food colorants (tartrazine [possibly])

Physical Factors
Exercise
Temperature (heat or cold)

Idiopathic
Factitious
Undifferentiated somatoform idiopathic anaphylaxis
Idiopathic

ACE, angiotensin-converting enzyme; HD, hemodialysis; IgE, immunoglobulin E; NSAID, nonsteroidal anti-inflammatory drug.
Modified from Kemp SF, Lockey RF: Anaphylaxis: A review of causes and mechanisms. *J Allergy Clin Immunol* 110:341, 2002.

Although it may be prudent to administer a class of antibiotics other than the cephalosporins when a well-documented significant history of penicillin allergy is obtained, if no other antibiotic choices are available, the first dose of cephalosporin can be administered orally under medical supervision and observation.[28]

Latex

Allergy to natural rubber latex in gloves and other medical products has become a health issue for health care providers, patients, and rubber industry workers.[29] Latex is derived from the commercial rubber tree *Hevea brasiliensis*, which is native to the southern Amazon and harvested commercially from plantations in Southeast Asia and Africa. The functional unit is a rubber particle coated with a layer of proteins, lipids, and phospholipids to provide structural integrity. Latex allergy refers to sensitivity to either the proteins or the chemical products contained in the latex products. The sensitivity reaction can be delayed (type IV) contact dermatitis or an immediate hypersensitivity (type I) reaction (asthma, urticaria, and anaphylaxis). Although latex allergy is common, affecting 0.7 to 1.1% of the population,[30] in the United States, only 220 people per year are estimated to be at risk for an anaphylactic reaction from latex.[5]

The most common symptoms of latex allergy include allergic urticaria, rhinitis, conjunctivitis, and occupational asthma. There is evidence that patients with specific food allergies are predisposed to latex allergy.[31] The true risks of latex-induced anaphylaxis are not known, but in a review of anaphylactic incidents in 50 children, 27% were due to latex allergy.[32] Diagnostic tools include serologic assays and skin prick testing. There is no effective prophylaxis for latex allergy. In fact, routine use of the H_2 blocker ranitidine for gastroesophageal reflux was reported to increase the risk of a heart conduction block in a case of anaphylaxis caused by latex.[33] Avoidance of latex-containing products is the recommended approach.

Insect Stings

Hymenoptera venoms and fire ant stings are responsible for significant anaphylactic morbidity and mortality.[34] The first recorded fatality from anaphylaxis was probably the hieroglyphic-documented death of King Menes of Egypt in 2641 BCE, when he succumbed to the sting of a wasp or hornet. Stinging Hymenoptera insects affect up to 13.6 million Americans annually (circa 1999), accounting for approximately 50 to 100 deaths annually.[5] Allergic sensitization to Hymenoptera has been reported in 0.4 to 4% of the general population. The principal offenders (in decreasing order of frequency) are yellow jackets, honeybees, wasps, and yellow and bald-faced hornets. The imported fire ant has become a significant pest responsible for anaphylaxis, spreading from the Atlantic and Gulf coasts inland.[35] The introduction of killer (Africanized) bees in Brazil and their subsequent northern migration make them a significant cause of sting-induced anaphylaxis in areas of Texas, Arizona, and the southwestern United States.[36]

The Hymenoptera venoms are complex mixtures of pharmacologically and biochemically active substances. Honeybee venom has been subjected to the greatest amount of research and contains two major enzymes—hyaluronidase and phospholipase A (PLA)—and other peptides, including a mast cell-degranulating peptide. Yellow jacket venom contains not only phospholipases A and B and hyaluronidase but also kinins. Hornet venom has, in addition, acetylcholine. Wasp venom has not been extensively studied. Fire ant venom is mostly a nonproteinaceous alkaloid suspension containing PLA and hyaluronidase.

Other Therapeutic Agents

Heterologous sera that were used in diphtheria and tetanus equine antitoxins in the past can act as whole antigenic markers. In fact, until the advent of penicillin, these two therapeutic agents were the most common iatrogenic causes of

anaphylaxis in humans. The use of human antisera was associated with a marked reduction in the incidence of serum-induced anaphylactic reactions. In fact, no adverse reactions were noted on repeated immunization using human tetanus antisera in approximately 250 patients who had previous anaphylactic reactions to equine tetanus antisera.[37] Equine antisera are still used in the administration of antilymphocyte serum and in the management of venomous snake bites. Although anaphylactic reactions are rare (1:500,000), the equine antiserum should still be diluted and pretested.

Since the development of heterologous insulin hormone therapy for the management of diabetes mellitus, local and systemic allergic complications have been recognized. A large percentage of local reactions were eliminated with the introduction of purified, single-peak pork insulin. With the introduction of Humulin, an insulin preparation prepared from recombinant DNA, the incidence of anaphylaxis and insulin resistance has declined dramatically.

Allergen extracts are used diagnostically in skin testing and therapeutically in immunotherapy (also known as hyposensitization or desensitization).[38] Exposure to therapeutic pollens, by injection or inhalation, can result in local allergic or systemic anaphylactic reactions. High-dose therapy, too frequent administration, or inadvertent intravascular injection increases the risk of anaphylaxis with immunotherapy.

Although corticosteroids are used in the management of acute allergic syndromes and anaphylaxis, adverse reactions to these medications have been observed after parenteral administration.[39] Skin testing may demonstrate the specific class of steroids responsible for hypersensitivity, and substitution of a different class should be considered.

Local anesthetics occasionally produce adverse reactions.[40] Most of these reactions are not allergic in nature but are related to a direct effect of the medication. True allergic reactions are rare and are most commonly seen with local anesthetics from the ester family (e.g., procaine, tetracaine, and benzocaine). Allergic reactions to local anesthetics belonging to the amide family (e.g., lidocaine, bupivacaine, mepivacaine, and dibucaine) are extremely rare if they occur at all. Multidose vials of lidocaine contain the preservative methylparaben, which belongs structurally to the ester family. This preservative has been implicated in allergic reactions in patients with a history of previous lidocaine hypersensitivity.[41] Pure lidocaine (without the methylparaben preservative) should be used intravenously (as in Bier's block).

Anaphylactic reactions have occurred after the administration of egg embryo-grown vaccines, including the combined measles, mumps, and rubella (MMR), yellow fever, and influenza vaccines. A patient who is able to tolerate eggs orally, even if he or she has previously experienced anaphylaxis and shows a positive skin test to eggs, is likely to tolerate the vaccines. Anaphylactic reactions have also occurred against ethylene oxide (ETO), which is used to sterilize hemodialyzers. ETO can bind with human proteins such as human serum albumin (HSA), thus rendering the ETO-HSA complex allergenic.

Immune Complex–Mediated Agents

Anaphylactic-type reactions are uncommon complications after the administration of whole blood and immunoglobulins. The fixation of antibodies to formed elements such as red blood cells, platelets, and leukocytes and soluble components activates the complement system. This is particularly relevant in IgA-deficient patients exposed to multiple transfusions, who may have produced antibodies to IgA present in previous transfusions. With subsequent transfusions, an antigen (IgA)–anti-IgA antibody (IgG) immune complex forms, and subsequent activation of the complement cascade may occur.

Nonimmunologic Activators

Many of the opioid analgesics can cause anaphylactic reaction through a direct histamine release mechanism, although there is evidence that, rarely, some reactions are true IgE-mediated reactions. It is unclear how much cross-sensitivity is present among these agents.[42]

Radiocontrast media (RCM) represents one important class of drugs that can cause an anaphylactic reaction.[10,11] RCM is available as high-osmolar RCM (HRCM, >1400 mOsm/kg), iso-osmolar RCM (same as serum, 290 mOsm/kg), and low-osmolar RCM (LRCM, 500–900 mOsm/kg). In addition, depending on the charge of the iodine molecule used, RCM is classified as ionic or nonionic. The majority of RCM is ionic HRCM or nonionic LRCM.

Approximately 10 million radiologic studies using RCM are performed in the United States annually, most of which use nonionic LRCM. Of these studies, approximately 35 per 100,000 exposed patients have a serious reaction, with an estimated fatality rate of 1 to 3.9 per 1 million injections.[9] The older hyperosmolar agents can cause a reaction in up to 5.6% of patients and fatalities in up to 0.01%.[43] Subsequent studies put the risk of a serious reaction to high-osmolar contrast media at 0.22%, with 11.7 fatalities per 1 million injections.[44] Protocols have been developed to minimize risks of a serious allergic reaction in patients who have had a previous adverse reaction to RCM but who still require additional radiographic studies with contrast. One common protocol is shown in Box 117-4.

Anaphylactic reactions to RCM are largely idiosyncratic, occur within minutes of infusion, and are independent of the dose. Risk factors for an anaphylactic reaction include a previous adverse reaction to RCM, a history of atopy or allergic disease, asthma, and certain medications. Of note, it is a misconception that a history of allergy to fish or shellfish is a contraindication to the use of RCM or increases the risk of an adverse reaction to RCM.[45]

The pathophysiology of anaphylactic reactions to RCM is unknown, but it is believed to be nonimmunologic. Suggested mechanisms include direct histamine release, alternative complement pathway activation, and activation of the contact system.

Modulators of Arachidonic Acid Metabolism

Interruption of AA metabolism by aspirin (ASA) and other nonsteroidal anti-inflammatory drugs (NSAIDs) has been

BOX 117-4 A Standard Treatment Protocol for Patients with a History of Radiocontrast-Induced Anaphylaxis

Prednisone, 50 mg by mouth given 13, 7, and 1 hour before the procedure.
Diphenhydramine, 50 mg intramuscularly given 1 hour before the procedure.
Consider ephedrine, 25 mg by mouth given 1 hour before the procedure.
Consider an H_2 antagonist, such as ranitidine, 300 mg by mouth given 3 hours before the procedure.

From Lieberman P: Anaphylaxis. Med Clin North Am 90:77, 2006

postulated as the mechanism responsible for anaphylactoid reactions resulting from these agents, although AA modulation, anaphylatoxin generation, and direct histamine release may all be partially responsible.[46] The incidence of anaphylactoid reactions to aspirin and NSAIDs varies widely, depending on the population (healthy, atopic, or those with nasal polyps). One study estimates the incidence as 2.1 anaphylactoid reactions per 100,000 exposed patients.[9] Aspirin allergy refers to a clinical spectrum ranging from ASA GI intolerance to ASA-induced asthma exacerbation, which is a true ASA-anaphylactoid reaction. Desensitization protocols have been suggested for cardiovascular patients with a history of aspirin allergy.[47] For ASA-induced cutaneous disease, an ASA desensitization protocol that can be used for cardiovascular patients in the ED is to administer ASA every 15 minutes, starting with 0.1 mg, up to 325 mg at 135 minutes.[48] ASA should be avoided in patients with true anaphylactic reaction to ASA. For noncardiovascular applications, most aspirin-sensitive patients can tolerate sodium salicylate or acetaminophen as an aspirin substitute. Of note, one of many food additives, tartrazine (foods, drugs, and cosmetics [FD&C] yellow dye number 5), is a stable azo coloring agent present in thousands of foods and drugs in the United States.[49] The exact mechanism of tartrazine sensitivity is unknown, although modulation of AA metabolism and several other theories have been proposed.

Physically Induced Anaphylaxis

Thermomechanical and physical factors (heat and cold), especially exercise, have increasingly been recognized as etiologic agents in certain anaphylactic-like incidents.[50] The mechanism is unclear, but release of mast cell and basophil mediators has been implicated. Patients with exercise-induced anaphylaxis are generally dedicated athletes who may have a personal or family atopic history. Exercise-induced anaphylaxis has been demonstrated in some cases to depend on previous ingestion of food to which the patient may be subclinically sensitive. Provocative foods, if identified, should be avoided. Patients should discontinue the exercise when they experience pruritus. When exercise is continued beyond this point, clinical deterioration is likely in susceptible individuals. Prophylactic treatment with an antihistamine as a single agent or in combination with other agents may be helpful. Avoidance of precipitating factors, modification of exercise, and use of a self-injectable epinephrine kit have been recommended for patients with exercise-induced anaphylaxis.

Idiopathic Anaphylaxis

Prednisone-responsive IA refers to an anaphylactic condition in which no eliciting factors can be detected.[11,51] In the United States, it is estimated that 20,000 to 47,000 patients annually see allergists for signs and symptoms of IA. A specific causative agent cannot be found historically. Laboratory studies including a complete blood count with differential leukocyte count, erythrocyte sedimentation rate, blood chemistries, complement levels, C1 esterase inhibitor levels, serum and urinary histamine levels, urinalysis, skin testing, and occasionally more specialized tests when clinically indicated are all nondiagnostic. Food diaries and efforts to find systemic disease are often fruitless. Although IA may be life-threatening, it is usually responsive to conventional therapies, including antihistamines, sympathomimetics, and especially prednisone.[51] Some cases of IA may be caused by kissing or conversion disorders.[52] The overall prognosis for IA is good, but certain patients may experience recurrent IA despite intensive prophylactic administration of antihistamines, sympathomimetics, or steroids. Sometimes, IA can represent "progesterone" anaphylaxis. Women suffering from this disorder may present with recurrent episodes of anaphylaxis that are temporally related to the menstrual cycle. Other patients may have anaphylactic reactions to injection of medroxyprogesterone or luteinizing hormone-releasing hormone.

CLINICAL FEATURES

Anaphylaxis in humans primarily affects organs that are rich in mast cells—the cutaneous, upper and lower respiratory, cardiovascular, neurologic, and gastrointestinal systems. Anaphylactic reactions range from mild to fatal with variable durations of attack. The clinical expression depends on the degree of hypersensitivity; the quantity, route, and rate of antigen exposure; the pattern of mediator release; and the target organ sensitivity and responsiveness. One cardinal feature of a serious anaphylactic reaction is its rapid onset. Most anaphylactic reactions become clinically evident within minutes (average 5 to 30 minutes) after a parenteral exposure; onset can be slower (average 2 hours) after ingestion. Most fatalities occur within the first 30 minutes after antigenic exposure. Symptoms can sometimes resolve and recur hours later in what has been termed *biphasic anaphylaxis*.[53] In general, the sooner the clinical syndrome is manifest after antigenic exposure, the more severe the reaction. Anaphylactic reactions after parenteral antigenic exposure are usually more immediate in onset, progress more rapidly, and are more severe in quality than those occurring after topical or oral exposures. Fatal cases of anaphylaxis are usually caused by cardiovascular collapse or respiratory failure. Although urticaria and angioedema are the most common presenting symptoms in anaphylaxis (88%), fatal anaphylaxis syndromes with laryngeal edema and circulatory collapse can occur even in the absence of any premonitory warning symptoms or signs or cutaneous manifestations.

The first clinical manifestation of anaphylaxis usually involves the skin; the patient experiences generalized warmth and tingling of the face, mouth, upper chest, palms, soles, or the site of antigenic exposure. Pruritus is a nearly universal feature and may be accompanied by generalized flushing and urticaria. Patients presenting with angioedema may complain of swelling and a sensation of burning under the skin but no itchy rash. This may be followed by mild to severe respiratory distress. The patient may describe a cough; a sense of chest tightness, dyspnea, and wheeze from bronchospasm; or throat tightness, dyspnea, odynophagia, or hoarseness associated with laryngeal edema or oropharyngeal angioedema. Hypotension or dysrhythmias may manifest as light-headedness or syncope. Seizure activity caused by decreased cerebral perfusion may rarely be observed. Any of these clinical patterns may occur independently or in association with nasal congestion and sneezing; ocular itching and tearing; cramping abdominal pain with nausea, vomiting, diarrhea, and tenesmus; incontinence; pelvic pain and uterine cramping; headache; or a sense of impending doom.

The physical examination may reveal tachypnea, tachycardia, and hypotension. Laryngeal stridor, hypersalivation, hoarseness, and angioedema indicate upper airway obstruction, whereas coughing, wheezing, rhonchi, and diminished air flow suggest lower respiratory tract bronchoconstriction. Tachycardia and hypotension suggest cardiac insufficiency. Commonly observed dysrhythmias include sinus tachycardia, premature atrial and ventricular contractions, nodal rhythm, and atrial fibrillation. Other electrocardiographic changes include nonspecific and ischemic ST-T wave changes, right ventricular strain, and intraventricular conduction defects. The patient may have a depressed level of consciousness due

to hypotension; rarely, this may be caused by a postictal state due to seizure activity. Urticaria, angioedema, rhinitis, and conjunctivitis may be evident. A summary of the observed clinical manifestations of anaphylaxis along with their related pathophysiology is presented in Table 117-1.

DIAGNOSTIC STRATEGIES

A good history and physical examination, coupled with a high index of suspicion, are the best diagnostic tools in approaching patients with possible anaphylaxis. A new set of clinical parameters has been advanced to aid in the clinical diagnosis of an anaphylactic reaction. The diagnosis of anaphylaxis is considered to be "highly likely" when patients present with cutaneous symptoms (itchy urticaria, flushing, and swollen lips, tongue, and throat) and either respiratory difficulty (dyspnea, wheezing, and stridor) or reduced blood pressure or symptoms of end-organ dysfunction (see Box 117-1). Anaphylaxis can be confirmed by testing for allergen-specific IgE and serum tryptase—tests that are not normally available in the ED. As clinically indicated, other diagnostic modalities may be employed concurrently to rule out other emergencies. The initial screening studies can include a complete blood count, complete metabolic panel (hypoglycemia), coagulation panel (prothrombin time, partial thromboplastin time, and international normalized ratio), cardiac enzymes, an electrocardiogram to rule out an acute coronary syndrome, urine analysis, erythrocyte sedimentation rate, and a portable chest radiograph. Serum level of serotonin and urinary 5-hydroxyindole acetic acid, catecholamines, and vanillylmandelic acid are useful to rule out carcinoid syndrome. Serum and urinary histamine and serum tryptase levels are helpful to confirm the diagnosis of anaphylaxis after the fact. The optimal time to obtain the serum histamine level is within 1 hour and serum tryptase within 1 or 2 hours (but no longer than 6 hours) of the onset of symptoms. Samples of vomitus may be collected for the allergist to create a custom radioallergosorbent test panel for later desensitization therapy. Serial arterial blood gases may help monitor clinical response. Blood culture, urine culture, computed tomography of the head and lateral soft tissue of the neck, and indirect and direct laryngoscopy can be considered depending on clinical suspicion.

DIFFERENTIAL CONSIDERATIONS

The diagnosis of an anaphylactic reaction depends largely on recognizing the key symptoms and signs (see Box 117-1) that occur abruptly after an exposure to a suspected inciting agent. Considerations for other diseases with overlapping presentations should include those shown in Table 117-2.

Flush Syndromes and Rash

Flushing disorders range from the benign, such as alcohol-induced flushing, to the more pathologic, such as mastocytosis or carcinoid syndrome. Scombroidosis refers to histamine poisoning from the ingestion of fish improperly stored at an elevated temperature. Histamine and *cis*-urocanic acid are produced by various bacteria that multiply in the spoiled fish. Patients usually present with a frightening flush but no urticaria, palpitations, syncope, nausea, vomiting, or diarrhea.

Stridor

In the absence of oropharyngeal angioedema or other clinical manifestations of anaphylaxis, the diagnosis of laryngeal edema should be confirmed by direct or indirect laryngoscopy to exclude epiglottitis and supraglottitis, retropharyngeal or peritonsillar abscess, laryngeal spasm, foreign body aspiration, or tumor.

Bronchospasm

Obstructive lung diseases such as acute asthma and status asthmaticus are usually not associated with other symptoms and signs of anaphylaxis. Patients with acute pulmonary embolism may present with shock, respiratory distress, and bronchospasm. Exercise-induced anaphylaxis should be differentiated from exercise-induced asthma because the former is usually accompanied by pruritus and other systemic manifestations.

Syncope

Vasovagal syncope is the most common differential diagnosis in the patient arriving with collapse as a result of parenteral administration of an antigen. Classically, the patient has bradycardia, hypotension, and pallor as opposed to the tachycardia, hypotension, and diaphoresis usually associated with anaphylaxis. The absence of any other clinical manifestations of anaphylaxis, along with history of stress, pain, and previous episodes of simple faints, helps point toward the diagnosis of vasovagal syncope. Other causes of syncope, such as seizure, stroke, hypoglycemia, acute coronary syndrome, or cardiac dysrhythmia, also need to be considered. Ordinary allergic reactions and especially anaphylaxis can precipitate an acute coronary syndrome.[54]

Shock

Clinically, anaphylactic, septic, and spinal shock may appear similarly with signs and symptoms of shock including end-organ hypoperfusion and vasodilation. Skin is usually moist and warm, suggesting a state of decreased peripheral vascular resistance. Cardiogenic, restrictive, hypovolemic, or hemorrhagic shock would more likely be seen with cold, clammy skin, suggesting a state of heightened peripheral vascular resistance. Because anaphylactic shock can progress to cardiogenic shock, measurement of central venous pressures (CVPs) may be necessary.

MANAGEMENT

Out-of-Hospital

When a susceptible patient is reexposed to an antigen to which there has been a previous reaction, 50 mg of oral diphenhydramine should be taken if available. At the first signs of any clinical manifestations of anaphylaxis, the patient should self-administer epinephrine if available (adult dose, 0.3 mL of 1:1000 intramuscular; pediatric dose, 0.01 mL/kg of 1:1000 intramuscular). Susceptible patients may even use aerosolized epinephrine from a metered-dose inhaler to counteract the effects of laryngeal edema, bronchoconstriction, and other manifestations of anaphylaxis.[55] Multiple inhalations (e.g., 10–20 doses, resulting in the inhalation of 1.5–3 mg of epinephrine) produce therapeutic plasma levels, with the advantages of ease of administration, rapid absorption, and locally high epinephrine levels in the upper and lower airways. Epinephrine must be used with caution in elderly people and in those with a history of cardiac or hypertensive problems.

Out-of-hospital personnel may be required to resuscitate a moribund patient using basic life support. Their first priority should be to establish and maintain ventilation, intravenous access, cardiac monitoring, and administration of supplemental

Table 117-2 Differential Diagnosis of Anaphylactic Reaction and Anaphylactic Shock

FINDING	DISORDERS	COMMENTS
Flush syndromes/rash	Carcinoid syndrome Medullary carcinoma of the thyroid Vasointestinal peptide secreting tumor (VIPoma) Systemic mastocytosis Urticaria pigmentosa Pheochromocytoma Scombroidosis Occult infections Alcohol flush syndrome Sulfite and monosodium glutamate toxicity Leukemia (basophilic/acute promyelocytic) Hydatid cyst	Urticaria and hypotension not typical in carcinoid syndrome. Serum serotonin and urinary 5-hydroxyindole acetic acid are elevated. There is episodic hypertension in pheochromocytoma. Check levels of metanephrine and urinary vanillylmandelic acid. Mastocytosis is a risk factor for anaphylaxis, and anaphylaxis may be the presenting manifestation of systemic mastocytosis. Scombroidosis is caused by histamine poisoning, which in turn is caused by ingestion of spoiled fish. The flushing is prominent and prolonged but no urticaria; tryptase level is low. Flush syndrome induced by alcohol is more common in Asian populations.
Syncope/altered mental status	Vasovagal reaction Seizure/epilepsy Stroke Neuroleptic malignant syndrome (NMS) Serotonin syndrome Hypoglycemia Acute coronary syndrome Cardiac dysrhythmia	Bradycardia, hypotension, nausea, diaphoresis, and pallor favor the diagnosis of a vasovagal reaction, whereas tachycardia, hypotension, and diaphoresis favor the diagnosis of anaphylaxis. Anaphylaxis can occur concurrently with or precipitate an acute coronary syndrome. Fever, encephalopathy, muscle rigidity, and hemodynamic instability characterize NMS. Fever, encephalopathy, hypertension, clonus, hyperreflexia, and other autonomic instability characterize serotonin syndrome.
Stridor	Epiglottitis Supraglottitis Retropharyngeal Peritonsillar abscess Laryngeal spasm Foreign body aspiration Tumor	After stabilization and arrangement for good backup for airway support, investigations can be started to locate source of stridor.
Acute respiratory insufficiency	Asthma/status asthmaticus Obstructive airway diseases Pulmonary embolism Spontaneous pneumothorax	Exercise-induced asthma does not have the stigmata of exercise-induced anaphylaxis.
Shock	Cardiogenic Hemorrhagic/hypovolemic Septic Pulmonary embolism	Moist and warm skin suggests decreased peripheral vascular resistance; cold, clammy skin suggests increased peripheral vascular resistance.
Miscellaneous	Urticarial vasculitis Hereditary angioedema Progesterone Redman's syndrome Progesterone anaphylaxis Capillary leak syndrome Postmenopausal state	Pruritic urticaria is usually absent in hereditary and acquired angioedema. Rapid infusion of vancomycin occurs in Redman's syndrome.

oxygen to keep the oxygen saturation level greater than 90%.

Local measures to decrease antigen absorption from an extremity include dependent positioning of the extremity, ice to vasoconstrict locally, and application of a loose tourniquet to obstruct the venous and lymphatic circulation. The tourniquet should be released for 1 of every 10 minutes. If an insect stinger remains, the wound should not be squeezed because it may inject more venom into the patient. The stinger should be removed gently with instruments, avoiding disturbance of the venom apparatus.

Emergency Department

Since most of the morbidity and mortality associated with anaphylaxis originates from acute respiratory failure or cardiovascular collapse, the immediate goal in the ED is to stabilize any cardiorespiratory insufficiencies while confirming the diagnosis of anaphylaxis and anaphylactic shock along with other diagnostic alternatives. Box 117-5 summarizes the treatment options for acute anaphylaxis.

Epinephrine and antihistamines (H_1 and H_2) should be administered early in most cases. Patients should have supplemental oxygen administered, large-bore (e.g., 16-gauge) intravenous lines inserted to infuse crystalloid or colloid solutions, and continuous cardiac monitoring. A large volume of crystalloid fluid may be required to reverse the hypotension associated with anaphylaxis.

Upper airway obstruction from laryngeal edema or angioedema can progress rapidly. While preparing for more definitive airway management, a chin lift or jaw thrust may help obtain a patent airway. Suctioning the oropharynx of excess

BOX 117-5 TREATMENT OPTIONS FOR ANAPHYLAXIS

1. **Immediate general interventions**
   - (a) Remove any triggering agent
   - (b) Place patient in the Trendelenburg position if hypotensive
   - (c) Assessment of airway patency, breathing, and circulation
     - (i) Hyperextension of neck, jaw thrust, chin lift
     - (ii) Administer supplemental oxygen by nasal cannula or non-rebreather mask
     - (iii) Racemic epinephrine 0.5 mL of 2.25% in 2.5 mL of NS by nebulizer while awaiting definitive airway management
     - (iv) Establish airway
       - (1) Endotracheal intubation with or without RSI (rapid sequence intubation)
       - (2) Adjunct airway technique (jet ventilation, LMA, surgical airway) as per local institution
     - (v) Establish large-bore IVs
       - (1) Administer colloid/crystalloid, titrate to blood pressure
     - (vi) Pulse oxymetry
     - (vii) Cardiac monitoring/ECG
     - (viii) Portable CXR
     - (ix) Blood draw
     - (x) Place a loose tourniquet proximal to the reaction site; if reaction site on extremity, place extremity in dependent position
     - (xi) Inject 0.1–0.2 mL 1:1000 epinephrine locally to the reaction site
2. **Specific measures**
   - (a) Epinephrine
     - (i) Intramuscular (subcutaneous route acceptable) 1:1000
       - (1) Adult: 0.3–0.5 mL every 5 min as necessary, titrated to effects
       - (2) Pediatric: 0.01 mL/kg, every 5 min as necessary, titrated to effects
       - (3) Alternatively, epinephrine (EpiPen) (0.3 mL) or EpiPen Jr (0.15 mL) can be administered into anterolateral thigh. Removal of clothing is unnecessary
     - (ii) Intravenous 1:100,000 (0.1 mL of 1:1000 in 10 mL of NS)
       - (1) Continuous hemodynamic monitoring required
       - (2) 10 mL of 1:100,000 over 10 min, titrated to effects, repeat as necessary
   - (b) Antihistamines
     - (i) Diphenhydramine: intravenous (or oral)
       - (1) Adult: 50 mg, up to 400 mg/24 hr, titrated to effects
       - (2) Pediatric: 1 mg/kg, up to 300 mg/24 hr, titrated to effects
     - (ii) Ranitidine: intravenous (or oral)
       - (1) Adult: 50 mg IV (150 mg oral)
       - (2) Pediatric: 1 mg/kg IV or oral
   - (c) Aerosolized beta-agonists and others
     - (i) Adult
       - (1) Albuterol: 2.5 mg, diluted to 3 mL of NS, may be given continuously
       - (2) Levalbuterol: 0.625–1.25 mg, diluted to 3 mL of NS, may be given continuously
       - (3) Ipratropium: 0.5 mg in 3 mL of NS, repeat as necessary
     - (ii) Pediatric
       - (1) Albuterol: 2.5 mg, diluted to 3 mL of NS, may be given continuously
       - (2) Levalbuterol: 0.31–0.625 mg, diluted to 3 mL of NS, may be given continuously
       - (3) Ipratropium: 0.25 mg in 3 mL of NS, repeat as necessary
   - (d) Methylprednisolone
     - (i) Adult: 125–250 mg IV
     - (ii) Pediatric: 1–2 mg/kg/IV
3. **Special situations**
   - (a) Refractory hypotension
     - (i) Glucagon: 1–5 mg IV over 5 min, followed by 5–15 µg/min continuous infusion
     - (ii) Consider:
       - (1) Discontinue epinephrine
       - (2) Dopamine, 5–20 µg/kg/min continuous infusion and/or dobutamine 5–20 µg/kg/min continuous infusion
       - (3) Norepinephrine: 8–12 µg/min (2–3 mL/min; 4 mg added to 1000 mL of D5W provides a concentration of 4 µg/mL)
   - (b) Patients on beta-blockade
     - (i) Glucagon: 1–5 mg IV over 5 min, followed by 5–15 µg/min continuous infusion
     - (ii) Transcutaneous pacing for bradycardia
     - (iii) Atropine for bradycardia
       - (1) Adult: 0.3–0.5 mg IV/subcutaneous, to a maximum of 3 mg
       - (2) Pediatric: 0.02 mg/kg IV/subcutaneous, to a maximum of 2 mg
     - (iv) Isoproterenol: 0.05–0.2 µg/kg/min (1–2 mg in 500 mL of D5W, infused at a rate of 0.5–2 mL/min)
   - (c) Refractory bronchospasm
     - (i) Aminophylline: 5.6 mg/kg loading dose IV over 20 min, followed by 0.1–1.1 mg/kg/hr continuous infusion
   - (d) Hypertensive crisis due to unopposed alpha-blockade
     - (i) Nitroprusside: 0.3–10 µg/kg/min (6 µg/kg/min, neonates) continuous infusion
     - (ii) Phentolamine: 5–20 mg IV
   - (e) Dysrhythmia
     - (i) Lidocaine 1–2 mg/kg IV bolus, followed by 2 mg/min continuous infusion

CXR, chest x-ray; D5W, 5% dextrose in water; ECG, electrocardiogram; LMA, laryngeal mask airway; NS, normal saline.

secretions may be necessary. A nasopharyngeal or oropharyngeal airway may aid in maintaining a patent airway at this stage. Racemic epinephrine, delivered as a 2.25% solution (0.5 mL placed in a nebulizer in 2.5 mL of normal saline), may be used as a temporizing measure. A laryngeal airway mask, jet ventilation, or surgical airway may be needed for difficult airways.

The success rate of intubation is improved when it is performed early and before soft tissue swelling progresses. Oral endotracheal intubation is the route of choice because

significant anatomic distortion may be present as a result of edema. Sedation and paralysis should be used with caution because a distorted airway may preclude intubation after paralysis. Patients in acute respiratory distress should be given definitive airway treatment without waiting for results of an arterial blood gas. Once a patent airway has been obtained and supplemental oxygen delivered, therapy should focus on relieving the patient's bronchospasm.

Epinephrine

Drugs used in the treatment of anaphylaxis either inhibit the release of chemical mediators or reverse the effects of mediators on target tissues. Epinephrine, with its combined alpha- and beta-adrenergic agonist actions, is the first drug of choice in the treatment of anaphylaxis.[56] The alpha-agonist effects of epinephrine increase peripheral vascular resistance and reverse peripheral vasodilation, vascular permeability, and systemic hypotension. The beta-agonist effects of epinephrine produce bronchodilation, cause positive inotropic and chronotropic cardiac activity, and result in increased production of intracellular cyclic adenosine monophosphate (cAMP). Epinephrine therefore reverses bronchospasm, stimulates increased cardiac output, and inhibits further mediator release. The alpha- and beta-agonist actions of epinephrine can also be potentially dangerous. Excessive alpha-agonist activity can result in a hypertensive crisis. Excessive beta-agonist activity can increase myocardial oxygen consumption through increased wall tension, contractility, and chronotropism and can result in myocardial ischemia or infarction. Increased automaticity and chronotropism can produce hemodynamically significant supraventricular and ventricular tachydysrhythmia. Epinephrine should be used with caution in elders and those with known coronary artery disease and should be avoided in patients with life-threatening tachydysrhythmias.

The route of epinephrine administration depends on the severity of the clinical presentation. Subcutaneous epinephrine is usually effective in situations in which the clinical manifestations are mild and the patient is normotensive. In the patient with diffuse, generalized urticaria, subcutaneous absorption of epinephrine may be slow and unpredictable and the intramuscular route may be more efficacious.

For subcutaneous and intramuscular injections, the initial dose of epinephrine is 0.01 mL/kg of a 1:1000 solution to a maximum of 0.5 mL of 1:1000 solution (0.5 mg). A fraction of the total dose (0.1 or 0.2 mL) should be administered at the site of antigenic exposure if accessible (e.g., a bee sting or antigen injection in an extremity).

If the patient demonstrates severe upper airway obstruction, acute respiratory failure, or shock (systolic blood pressure <80 mm Hg, not associated with a ventricular tachydysrhythmia), intravenous epinephrine should be administered. Use of the intravenous route with epinephrine increases the risk of supraventricular, accelerated idioventricular, and ventricular tachydysrhythmia; accelerated hypertension; and myocardial ischemia, including the stunned heart syndrome. Because of these risks, dilution and slow administration are recommended. The initial intravenous dose should be 10 mL of a 1:100,000 dilution of aqueous epinephrine over 10 minutes. This is equivalent to a 100-µg bolus administered at 10 µg/min for 10 minutes. If no improvement is seen, a continuous infusion should be set up. Mixing 1 mL of a 1:1000 dilution of epinephrine in 250 mL of 5% dextrose in water (D5W) results in a concentration of 4 µg/mL. This can be started at 1 µg/min and increased to 4 µg/min if needed. In children and infants, an infusion rate of 0.1 µg/kg/min is advised, increasing in increments of 0.1 µg/kg/min to a maximum of 1.5 µg/kg/min. Continuous cardiac monitoring should be done at all times. If a percutaneous intravenous line cannot be established, alternative routes are available. In addition to the subcutaneous and intramuscular routes of administration, intraosseous or sublingual injection or endotracheal nebulization should be considered. The dosage and concentration guidelines for these routes of administration of epinephrine are the same as those for intravenous administration.

Antihistamines

In addition to epinephrine, antihistamines should be used in all cases of anaphylaxis, although their role in severe or persistent cases is limited. The antihistamines competitively block the action of circulating histamines at target tissue cell receptors but have no role in decreasing mediator release and have no effect on the leukotrienes. There are seven classes of H_1 antihistamines, and members of the ethanolamine family, such as diphenhydramine hydrochloride, and the alkylamine family, such as chlorpheniramine maleate, are potent H_1 antagonists. Diphenhydramine hydrochloride is the most commonly used H_1 antihistamine. The typical dose is 50 mg every 4 to 6 hours in adults or 5 mg/kg/day in divided doses for the pediatric population. Diphenhydramine hydrochloride orally or by intramuscular injection may be the only medication required for mild to moderate reactions. A loading dose of 1 to 2 mg/kg intravenously (IV) to a maximum of 100 mg is recommended for severe reactions, although too large a dose or too rapid administration can result in marked sedation and hypotension. Chlorpheniramine can be administered to children by the same routes at a standard dose of 10 to 20 mg or 0.35 mg/kg/day in divided doses.

Blockade of H_2 receptors may be beneficial with simultaneous H_1 antihistamine therapy. H_2 antagonists may inhibit the effect of histamine on myocardial and peripheral vascular tissue. Ranitidine (50 mg IV) or other H_2 blockers should be considered, followed by an oral course as an outpatient.

Aerosolized Beta-Agonists

Bronchospasm refractory to epinephrine may respond to a nebulized beta-agonist such as albuterol sulfate (Ventolin and Proventil), levalbuterol (Xopenex), terbutaline (Brethaire and Brethine), bitolterol (Tornalate), pirbuterol (Maxair), and/or metaproterenol (Alupent 5%). Continuous nebulization of the beta-agonists may be necessary for persistent bronchospasm. The use of anticholinergic therapy with ipratropium bromide (Atrovent) is an additional option in the management of acute bronchospasm. Anticholinergic medications decrease cyclic guanosine monophosphate levels, thereby decreasing mediator release and reversing the action of mediators on target tissue cells. Nebulized ipratropium bromide is used in a dose of 0.5 mg (2.5 mL of a 0.02% solution).

As a second-line therapy for refractory bronchospasm, an aminophylline bolus (5.6 mg/kg loading dose IV over 20 minutes), followed by a maintenance infusion (0.1–1.1 mg/kg/hr), can also be added. Aminophylline is an old drug with a narrow therapeutic window. Its main purported action is bronchodilation, although it may also act to potentiate the action of catecholamines. Side effects include atrial fibrillation, nausea, vomiting, and abdominal pain.

Corticosteroids

Systemic corticosteroids have an onset of action of approximately 4 to 6 hours after administration and therefore are of limited benefit in the acute treatment of the anaphylactic

patient.[11,57] They are most useful in persistent bronchospasm or hypotension and have some theoretical benefits in the prevention of the biphasic reaction. Rare cases of deterioration after corticosteroid administration may be the result of anaphylactic sensitivity to this medication. An initial intravenous loading dose of hydrocortisone (Solu-Cortef), 250 mg to 1 g, or methylprednisolone (Solu-Medrol), 125 to 250 mg, followed by oral prednisone over 7 to 10 days is an acceptable regimen after the anaphylactic episode.

Vasopressors

In patients with persistent hypotension despite administration of epinephrine and large volumes of intravenous crystalloid, the use of colloid solutions (e.g., 5% albumin) should be considered in addition to crystalloid because of increased vascular permeability in anaphylaxis. If the CVP is less than 12 mm Hg, crystalloid and colloid fluids should be administered first. If the CVP is greater than 12 mm Hg, dopamine (5 µg/kg/min) should be started and titrated to effect. Dobutamine can be added if myocardial depression is judged to be an important cause of the hypotension. Other causes of elevated filling pressures other than vascular volume or myocardial dysfunction should be considered (e.g., vasopressor administration, increased intraperitoneal and intrathoracic pressures, vasoconstriction, or pulmonary artery hypertension). If the cause of hemodynamic instability is uncertain, a pulmonary artery catheter to monitor wedge pressure and cardiac output may be required to guide the administration of fluid and vasopressor. If pulmonary hypertension exists, hyperventilation, hyperoxygenation, and large doses of steroids should be considered. The use of true pressors with primarily alpha-adrenergic activity, such as norepinephrine, could be considered if all of these measures fail to restore the inadequate hemodynamics.

In the rare case in which the anaphylactic patient develops a hypertensive crisis secondary to unopposed alpha- or beta-adrenergic activity from the treatment, nitroprusside drips or phentolamine should be considered. Dysrhythmias from elevated circulating catecholamines can be treated with lidocaine.

Patients Receiving Beta-Blockade

Glucagon, with positive inotropic and chronotropic cardiac effects mediated independently of alpha- and beta-receptors, may be helpful in patients who are receiving beta-blockers and who do not respond to epinephrine and antihistamines.[58] Glucagon is thought to effect positive inotropism by augmenting cAMP synthesis through a nonadrenergic pathway. The initial dose is 1 mg for adults and 0.5 mg for children subcutaneously, intramuscularly, or intravenously, and the patient may require a glucagon infusion of 1 to 5 mg/hr to sustain its therapeutic effect. Side effects include nausea, vomiting, hypokalemia, and hyperglycemia. Atropine (0.3–0.5 mg IV) and isoproterenol (0.05–0.2 µg/kg/min; 1–2 mg in 500 mL of D5W, infused at a rate of 0.5–2 mL/min) can be tried as second-line therapy. Atropine is probably more useful for bradycardia. Isoproterenol should be used as the last resort for the rare patient who is in refractory shock after all the preceding therapy.

DISPOSITION

Most patients with anaphylaxis respond to early aggressive management and can be safely discharged home. Patients with mild to moderate anaphylaxis who respond completely to initial treatment are appropriate for discharge after an observation period of 2 to 6 hours. An oral antihistamine, such as diphenhydramine hydrochloride 25 to 50 mg every 6 hours for 48 hours, may prevent possible relapse. These patients should be instructed to return to the ED if their symptoms recur. They should be warned about the sedating side effects of the antihistamines. Oral H_2 blockers for 48 hours may be useful, and patients with initially persistent bronchospasm or hypotension who required initial steroid therapy should continue oral prednisone for 7 to 10 days. Patients with initially persistent bronchospasm should continue a metered-dose beta-adrenergic bronchodilator inhalant (e.g., albuterol [Ventolin] and metaproterenol [Alupent]). Hospital admission should be considered for patients who have experienced hypotension, upper airway involvement, prolonged bronchospasm, or other indications of a severe reaction. Although the risk of clinical deterioration after apparently complete resolution of a severe anaphylactic reaction is minimal, symptoms redevelop in a small proportion of patients 24 to 48 hours after the initial systemic reaction.[59] This may be related to the high-molecular-weight neutrophil chemotactic factor-mediated late-phase reaction of the biphasic allergic response, which peaks in 4 to 12 hours and lasts up to 48 hours. Patients taking chronic beta-blocker medications may be susceptible to a similar rebound after the initial therapeutic interventions resolve. These patients may be candidates for an extended observation.

Prevention

Spending a few additional minutes with the patient before discharge, obtaining an allergy history, offering environmental modifications, and educating the patient on initiating treatment for recurrence may decrease morbidity and mortality associated with subsequent episodes of anaphylaxis (Box 117-6). Avoid prescribing medications with marginal benefits

BOX 117-6 PREVENTION OF ANAPHYLAXIS AND ANAPHYLACTIC DEATH

1. Get thorough drug allergy and atopic history.
2. Check all drugs for proper labeling.
3. Give drug orally rather than parenterally when possible.
4. Give drug in distal extremity if possible when parenteral route necessary.
5. Always have resuscitation equipment available when administering antigenic compounds.
6. Ensure that patients wait in emergency department 30 minutes after drug administration.
7. Use unrelated drugs when feasible in susceptible population.
8. When antiserum is essential, use human if available.
9. If heterologous serum is essential, always perform pretest.
10. Predisposed patients should carry warning identification (Medic-Alert, wallet identification).
11. Predisposed patients are taught self-injection of epinephrine, and patients are instructed to carry treatment kit at all times.
12. Patients should avoid known antigens (stinging insects, foods, antibiotics).
13. Perform skin test and consider hyposensitization immunotherapy when appropriate (see section on stinging insect anaphylaxis).
14. Pretreat with antihistamines, steroids if appropriate (see section on radiocontrast media reactions).

for patients at high risk of significant allergy and allergic reaction. A thorough personal and family drug allergy and atopic history can be useful before starting a new drug therapy. All drugs should be correctly identified before being administered. Whenever possible, the oral route of administration is preferred to the parental route to decrease the severity of a systemic anaphylactic reaction.

Physicians who administer antigenic compounds in their medical practice must be prepared to manage an anaphylactic reaction, and resuscitation equipment should be readily available. Because most anaphylactic reactions that follow parenteral administration begin within 30 minutes, patients should be observed during this period, discharged only if completely asymptomatic, and given a warning to return if there are subsequent symptoms.

Human antiserum is now available for rabies, tetanus, and diphtheria; however, heterologous equine antisera is still used (e.g., for snake bites). Intradermal pretesting should be performed before treatment if time permits, as outlined in the product monographs. However, even pretesting solution can precipitate an anaphylactic reaction. Furthermore, unnecessary pretesting sensitizes predisposed patients to future hypersensitivity reactions to antiserum.

Predisposed patients who have experienced a moderate or severe anaphylactic reaction should be taught self-administration of an oral antihistamine (e.g., diphenhydramine) on known exposure and self-injection of epinephrine (e.g., EpiPen and Ana-Kit) at the first indication of allergic symptoms or signs. Epinephrine injection kits have a limited shelf life, which is prolonged by refrigeration. Although the true effectiveness of these kits is unknown, they should be readily available at all times, with one kit available at home, one at work or school, one in the patient's purse or briefcase, and one in the patient's automobile. Predisposed patients should be strongly encouraged to carry warning identification stating their hypersensitivity (Medic-Alert bracelet or wallet card).

Pretreatment with antihistamines and steroids significantly decreases the frequency and severity of anaphylactoid reactions in patients who have had prior adverse reactions to RCM. Skin testing and hyposensitization immunotherapy by an allergist are an appropriate way to minimize the frequency and severity of subsequent anaphylactic reactions from bee stings in an appropriately sensitive population. Patients with an uncertain history of penicillin allergy should be referred for additional testing to confirm the allergy.

URTICARIA AND ANGIOEDEMA

Urticaria and angioedema are physical findings with a multitude of causes. Urticaria (hives) is a reaction that consists of papules or wheals that are nonpitting, edematous, pruritic, slightly erythematous, raised circular or annular, and range in size from millimeters to several centimeters (Fig. 117-4). The centers of the wheals are usually clear and the borders can be serpiginous. The erythema is due to dilation of blood vessels in the dermal layer of the skin, and the edematous wheals are due to transudation from these blood vessels. Urticaria favors the extremities and trunk and is usually transient, with crops of hives appearing and resolving spontaneously in a matter of hours.

Angioedema is pathogenetically similar to urticaria but involves the deeper dermal and subcutaneous tissue.[60] The presence of urticaria usually indicates a mast cell component to the reaction. Conversely, the absence of urticaria or pruritis suggests that the reaction is kinin related. Angioedema commonly involves the face, mouth, lips, tongue, extremities, and genitalia. Recurrent episodes of angioedema and urticaria that last less than 6 weeks are considered *acute* (90%), and those that persist longer than 6 weeks are classified as *chronic* (10%). Acute urticaria tends to be associated with angioedema in approximately half of cases. In approximately 40% of cases, urticaria is present alone, without angioedema. In the remaining 10%, angioedema is present exclusively without urticaria. Angioedema without urticaria could be the presenting physical finding of C1 inhibitor deficiency, or these cases may be angiotensin-converting enzyme (ACE) inhibitor induced.

Figure 117-4. Acute urticaria. (Copyright © 2001–2003, Johns Hopkins University School of Medicine. http://dermatlas.med.jhmi.edu/derm.)

It should be remembered that urticaria and angioedema are merely presenting symptoms and signs of potentially distinct underlying disease entities. Most mast cell-related attacks of acute urticaria and angioedema are hypersensitivity and IgE-mediated allergic reactions (similar to anaphylaxis). A variety of chemical allergens (e.g., foods, drugs, RCM, and Hymenoptera venoms) and physical stimuli (e.g., dermatographism, heat, wet, cold, vibratory, exercise, and solar) may also present with angioedema and associated urticaria and pruritis.

Angioedema without urticaria and pruritis is usually kinin related and causes include hereditary angioedema (HAE), acquired C1 inhibitor deficiency (ACID), and ACE inhibitors. All three result in elevated bradykinin levels.[61] In the case of HAE and ACID, the deficiency of C1 inhibitor causes activation of the kallikrein-kinin system, with consumption of kininogen, and results in increased production of bradykinin. In the case of ACE inhibitor drugs, the inhibition of ACE, one of the main inactivators of bradykinin, results in increased bradykinin levels.[62] Substance P is also thought to play a role in ACE inhibitor-associated angioedema.

HAE affects less than 200,000 people in the United States and may account for 15,000 to 30,000 ED visits annually. It is an autosomal dominant condition caused by C1 esterase inhibitor deficiency or functional deficiency, which is biochemically confirmed by low levels of C4 and C1 esterase inhibitor activity. This ultimately results in intermittent elevated bradykinin levels, resulting in angioedema. The cardinal symptoms and signs of HAE include edema of the airway, face, genitalia, or extremities and abdominal pain associated with nausea, vomiting, and diarrhea. These clinical manifestations may occur singly or in combination. Trauma and stress are common precipitating factors. There is usually a family history.

ACID is clinically indistinguishable from HAE attacks and is often associated with underlying lymphoproliferative diseases. The underlying disease results in consumption of C1 inhibitor or the development of anti-C1 inhibitor autoantibodies. It is less common than HAE, typically involves older patients, and there is an absence of family history.

ACE inhibitor-induced angioedema has an incidence of 0.1% to 0.7% and has a predilection for the tongue, lips, and laryngeal soft tissue.[63] The highest incidence occurs in the first month of therapy, but it can occur as many as 10 years after therapy is started. Increased risk factors include African American race, smoking, older age, and female gender. Diabetes decreases the risk. The pathophysiology is thought to be prevention of the metabolism of bradykinin and substance P, both of which are potent mediators of tissue inflammation. Most patients who develop angioedema on ACE inhibitors should be able to tolerate angiotensin receptor blocker drugs.

The clinical evaluation of angioedema starts with a focused search for emergency conditions, followed by a detailed history aimed at identifying the underlying cause.[64] Life-threatening airway compromise can occur if the angioedema involves the upper airway. HAE, ACID, ACE inhibitors, thermal burn, or local allergic reaction to inhaled drugs (e.g., Quincke's disease)[65] tend to cause glossopharyngeal angioedema, resulting in upper airway obstruction, dysphagia, or both. The detailed history is aimed at eliciting exposures to foods, drugs, physical stimuli, infection (especially viral hepatitis), occupational elements, and insect stings. The differential diagnosis includes evolving anaphylaxis syndrome, erythema multiforme minor, bullous pemphigoid and dermatitis herpetiformis, urticarial vasculitis, mastocytosis, HAE (C1 esterase deficiency), ACID, ACE inhibitor-associated angioedema, and serum sickness, among others. The constellation of pruritus, urticarial rash or angioedema, hypotension, and wheezing after exercise should raise the possibility of exercise-induced anaphylaxis. Angioedema of the upper extremity raises the possibility of superior vena cava syndrome. Brawny edema and shock raise the possibility of capillary leak syndrome.

Management of acute urticaria and angioedema (mast cell related) in the ED is first focused on stabilizing respiratory insufficiency and hemodynamic instability. Antihistamines (both H_1 and H_2) are the first-line therapeutic drugs. Epinephrine can be considered for moderate to severe cases but should be used with caution in patients older than 35 years to minimize the risk of precipitating an acute coronary syndrome. Steroids may help in preventing recurrence. In the longer term, the most effective treatment of urticaria and angioedema involves removal of the etiologic factors. H_1 antihistamines such as diphenhydramine (12.5–100 mg per dose every 4 hours) or the nonsedating agents such as cetirizine, loratadine, or fexofenadine are the first-line drugs. Hydroxyzine (10–100 mg daily at bedtime) can be tried when other H_1 antihistamines are inadequate. Because 85% of histamine receptors in the skin are H_1 and 15% H_2, adding an H_2 blocker (e.g., ranitidine or cimetidine) theoretically would benefit a histamine-induced urticarial reaction. Doxepin (25–100 mg/day) is an excellent alternative because it has both H_1 and H_2 activity. Topical steroids are of no value, and systemic steroids should be reserved for pressure urticaria, vasculitis urticaria, and intractable chronic urticaria.

Management of angioedema without urticaria (kinin related) is somewhat more problematic with fewer therapeutic options. Life-threatening acute attacks of kinin-related angioedema do not usually respond satisfactorily to treatment with epinephrine, antihistamines, or steroids. Active airway management is the mainstay of treatment. Aerosolized racemic epinephrine may help stabilize the airway edema. For HAE, fresh frozen plasma (FFP), which contains C1 inhibitor, has been reported to be effective in abolishing acute attacks; however, there are rare reports of FFP exacerbating the angioedema. Steroids should be avoided if the patient is known to have HAE.

Although not approved by the Food and Drug Administration, four agents are either being used in other countries or under investigation for the treatment of HAE. The use of C1 inhibitor replacement protein (C1-INHRP), a product of pooled human plasma, has become the standard of care for the treatment of HAE in Europe, Canada, Japan, and Argentina. A recombinant C1-INHRP has been developed and is in phase II/III trials in the United States for the treatment of HAE. Both products have been shown to shorten time to relief of symptoms, but the recombinant product has a shorter half-life.

Another investigational agent in phase II/III trials is ecallantide-DX88. It is a kallikrein inhibitor and prevents the generation of bradykinin. The fourth investigational agent with two completed phase III studies is Icatibant.[66] It is a bradykinin receptor-2 antagonist. Both of these agents have been shown to shorten time to relief of symptoms for HAE. At the time of this writing, recombinant C1-INHRP still is not approved by the FDA for the treatment of HAE. Pooled C1-INHRP was approved by the FDA in October 2008 for the prevention of HAE but not for the treatment of acute attacks. Ecallanide-DX 88 has completed phase II/II trials. It currently carries the *orphan* drug designation for the treatment of angioedema and *fast track* designation for the treatment of acute HAE. Icatibant currently carries the *orphan* drug status designation for the treatment of HAE.

For ACE inhibitor-induced angioedema, the treatment is mainly supportive. There is a report of FFP being used with success in a severe case of ACE inhibitor-induced angioedema.[67] It is thought that the benefit may have been due to the effect of kininase II in breaking down accumulated bradykinin. Theoretically, since there is impaired breakdown of bradykinin in ACE inhibitor-induced angioedema, perhaps the bradykinin receptor blocker class of drug may ultimately also be found to be effective in shortening time to relief of symptoms.

MASTOCYTOSIS

Mastocytosis refers to disorders caused by too many mast cells in the body. There are two forms of mastocytosis. *Cutaneous mastocytosis*, also called urticaria pigmentosa, occurs when the mast cell hyperplasia is in the skin. Cutaneous mastocytosis is more common and affects mostly children. *Systemic mastocytosis* refers to the clinical syndrome caused by mast cell hyperplasia in bone marrow, gut mucosa, liver, or spleen. Pathologic fractures, osteoblastic lesions on skeletal radiographs, cutaneous pigmented lesions, abdominal pain, diarrhea, hepatosplenomegaly, lymphadenopathy, headache, flushing, anemia, and, rarely, vascular collapse (from released vasoactive substances) are some of the clinical findings in this form of mastocytosis. The diagnosis is made by a 24-hour urine collection for histamine or its metabolites, PGD_2, or serum tryptase level. Adjunct diagnostic measures include bone scans, skeletal surveys, or upper gastrointestinal workup (upper gastrointestinal series, small bowel radiograph, computed tomography scan, and endoscopy). A skin or bone marrow biopsy helps confirm the diagnosis. Treatment options include steroids, interferon-α, H_1 antihistamines for pruritus and flushing (aspirin can be added if flushing is severe), H_{12} blockers for dyspepsia, and tricyclics for headache.

KEY CONCEPTS

- Allergy and allergic diseases are caused by overreactions of the immune system. Anaphylaxis is a systemic, life-threatening allergic reaction, precipitated within minutes of an exposure to an allergen in a previously sensitized individual. Diagnostic features include a history of recent exposure, urticaria, angioedema, flush, respiratory difficulty, dizziness, syncope, hypotension, and GI symptoms. Foods, drugs, insect stings, and latex are the main identifiable etiologic agents.
- Priority should be given to airway management and stabilizing any hemodynamic instability. Epinephrine is the first drug of choice for the management of anaphylaxis. Prolonged treatment with epinephrine or glucagon may be required for patients receiving beta-adrenergic blockade. Both H_1 and H_2 antihistamines should be used in all cases of anaphylaxis. Fluid, vasopressors, and inotropic agents should be instituted for refractory hypotension, guided by CVP or pulmonary catheter. Corticosteroids should be given in severe anaphylactic reactions or to prevent the biphasic anaphylaxis.
- Hospitalization or prolonged observation should be considered for patients who have experienced hypotension, upper airway involvement, prolonged bronchospasm, or other indications of a severe reaction.
- Identifying and avoiding the causative agent, prescribing abortive medications (EpiPen kits), and referral to an allergist are most important in long-term management and prevention of anaphylaxis and should be discussed by the emergency physician with the patient and family before the patient's discharge.
- The clinical evaluation of urticaria and angioedema starts with airway assessment, followed by a detailed history aimed at identifying the underlying cause. Life-threatening airway compromise can occur if the angioedema involves the upper airway.
- Angioedema is clinically a single disease entity, but the underlying causes can be distinctly different, requiring different treatment plans. If the angioedema is IgE mediated (usually urticaria is present), antihistamines (both H_1 and H_2) are the first-line therapeutic drugs. Epinephrine can be considered for moderate to severe cases. If the angioedema is kinin mediated (usually urticaria is absent), treatment is mostly supportive. FFP has been used with varying success in HAE, ACID, and ACE-induced angioedema. New drugs are being evaluated for this form of angioedema.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 118 Dermatologic Presentations

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PERSPECTIVE

Skin conditions and related complaints account for an estimated 4 to 12% of all emergency department (ED) visits.[1,2] In addition to medical and family history, three factors are particularly important: onset and evolution of the skin problem, associated symptoms, and prior treatment. Cutaneous eruptions can be manifestations of primary dermatologic disease or can signal underlying systemic illness.

For physical examination, the patient must be undressed and adequate lighting must be present. The scalp, mouth, and nails should be thoroughly examined. Although the examination depends largely on inspection of the skin, palpation helps assess the texture, consistency, and tenderness of the lesions.

Skin lesions may be divided into growths and rashes. Growths are subdivided into epidermal, pigmented, and dermal or subcutaneous proliferative processes. Rashes may be divided into two groups depending on whether the epidermis is involved. Lesions and rashes with epidermal involvement include eczematous rashes; scaling; and vesicular, papular, pustular, and hypopigmented rashes. Rashes without epidermal involvement include erythema, purpura, and induration.

The diagnosis is aided by the configuration of the lesions and distribution on the body's surface. Occasionally, a configuration is specific for a disease; however, the morphology of the primary lesion is usually given more diagnostic weight (Table 118-1). Finally, many skin diseases have preferential areas of involvement, so the location of the eruption may aid in diagnosis.

SCALES, PLAQUES, AND PATCHES

Fungal Infection

Principles of Disease

The dermatophytoses are superficial fungal infections that are limited to the skin. A variety of lesions may occur, but the most common are scaling, erythematous papules, plaques, and patches, which often have a serpiginous or wormlike border.[3] Dermatophytes generally grow best in excessive heat and moisture and grow only in the keratin or outer layer of the skin, nails, and hair. Keratin tends to accumulate in body folds, such as between toes and in the inguinal area, the axilla, and the inframammary areas. With the exception of tinea capitis, dermatophyte infections are not markedly contagious.[3]

Any eruption thought to be a dermatophyte infection can be examined under the microscope in a potassium hydroxide (KOH) preparation. The specimen is examined for the characteristic branching hyphae of the dermatophytes or the short, thick hyphae and clustered spores of tinea versicolor.[4] Affected hair, nail, or scales may be cultured using Sabouraud agar incubated at room temperature for 2 or 3 weeks.[5]

Tinea Capitis

Clinical Features. Tinea capitis is a fungal infection of the scalp. Although primarily regarded as a disease of preschool children, tinea capitis is becoming increasingly recognized in adults, infants, and neonates. It is more common among African Americans, although the reasons for this are unknown.[6] The current epidemic in the United States caused by *Trichophyton tonsurans* differs from the epidemic of the 1940s and 1950s caused by *Microsporum audouinii* in that many patients have seborrheic-like scaling in the absence of alopecia.[6] Clinically, "black dots," representing hair broken off near the scalp, may be noted.[7,8] Hair loss occurs because hyphae grow within the shaft, rendering it fragile, so that the hair strands break off 1 to 2 mm above the scalp. Circular patches of partial baldness may result. The disease may be transmitted by close child-to-child contact and contact with household pets, hats, combs, barber's shears, and similar items. Complications include lymphadenitis, bacterial pyoderma, tinea corporis, pigmenting pityriasis alba, "id" reaction after treatment, secondary bacterial infection, and scarring alopecia.[6]

Differential Considerations. The differential diagnosis of tinea capitis includes alopecia areata, atopic dermatitis, nummular eczema, bacterial infection, psoriasis, seborrheic dermatitis, "tinea" amiantacea, trichotillomania (hair pulling), and Langerhans cell histiocytosis.

Diagnostic Strategies. A KOH preparation is not helpful in the presence of a kerion or the absence of alopecia, in which case a fungal culture should be obtained.[9] A bacterial culture should be considered in the case of kerion to exclude superinfection.[5,9] A toothbrush, Papanicolaou smear cytology brush,[10] or moistened cotton swab[11] is helpful for obtaining quick, painless sampling of large areas of the scalp.[10-12]

Management. Systemic therapy is required for tinea capitis. Treatment usually begins with griseofulvin 20 mg/kg/day taken as a single dose with a fat-containing food for a minimum of 6 weeks, or 2 weeks after clinical resolution of inflammation.[5,9] Patients should be referred for monthly follow-up

Table 118-1 Definitions of Skin Lesions

LESION	APPEARANCE
Macule	Flat; color differs from surrounding skin
Patch	A macule with surface changes (i.e., scale or wrinkling)
Papule	Elevated skin lesion <0.5 cm in diameter
Plaque	Elevated skin lesion >0.5 cm in diameter; without substantial depth
Nodule	Elevated skin lesion >0.5 cm in diameter and depth
Cyst	Nodule filled with expressible material
Vesicle	Blisters <0.5 cm in diameter filled with clear fluid
Bullae	Blisters >0.5 cm in diameter filled with clear fluid
Pustule	Vesicle filled with cloudy or purulent fluid
Crust	Liquid debris that has dried on the skin surface; usually moist and yellowish brown
Scale	Visibly thickened stratum corneum; usually white
Lichenification	Epidermal thickening characterized by visible and palpable skin thickening and accentuated skin markings
Induration	Dermal thickening that *feels* thick and firm
Wheal	Papule or plaque of dermal edema; often with central pallor and irregular borders
Erythema	Red appearance of skin caused by vasodilation of dermal blood vessels; blanchable
Purpura	Red appearance of skin caused by blood extravasated from disrupted dermal blood vessels; nonblanchable
Macular purpura	Flat, nonpalpable
Papular purpura	Elevated, palpable

Modified from Lookingbill DP, Marks JG: *Principles of Dermatology*, 3rd ed. Philadelphia, Saunders, 1993.

Figure 118-1. Tinea corporis. (Courtesy of David Effron, MD.)

evaluation. Higher dosages may be needed. Alternative therapy includes fluconazole 200 mg/day (adults) or 3 to 5 mg/kg/day (children), itraconazole 200 mg daily (adults) and 3 to 5 mg/kg/day (children) for 4 to 6 weeks, oral terbinafine at 3 to 6 mg/kg/day for 4 to 6 weeks, or terbinafine cream once a day for 8 weeks.[5,9,13,14] Selenium sulfide shampoo 250 mg twice weekly decreases shedding of spores.[9] Family members should be evaluated.

Kerion

A kerion is a dermatophytic infection, usually of the scalp, that appears as an indurated, boggy inflammatory plaque studded with pustules.[3] It is commonly confused with bacterial infections. Kerions should be treated as tinea capitis, with the addition of prednisone 1 mg/kg/day for 1 or 2 weeks to help decrease the inflammatory reaction and subsequent scarring.[6,15,16] If bacterial superinfection exists, oral cephalexin or dicloxacillin can be added for the first week of treatment.[9]

Tinea Corporis

Clinical Features. Tinea corporis is the classic "ringworm" infection. It affects the arms, legs, and trunk and is classically a sharply marginated, annular lesion with raised or vesicular margins and central clearing (Fig. 118-1). Lesions may be single or multiple, the latter occasionally being concentric. Tinea cruris, which involves the groin, is similar in appearance and may also include the perineum, thighs, and buttocks, but the scrotum is characteristically spared.

Differential Considerations. The differential diagnosis of tinea cruris includes granuloma annular psoriasis, intertrigo with secondary candidiasis, and erythrasma.[17]

Management. Infections of the body, groin, and extremities usually respond to topical measures alone.[17] A number of effective topical antifungal agents are available, including clotrimazole (Lotrimin), haloprogin (Halotex), miconazole (Micatin), tolnaftate (Tinactin), terbinafine, naftifine, and griseofulvin 1%. Two or three daily applications of the cream form of any of these preparations result in healing of most superficial lesions in 1 to 3 weeks.[5,9,18-20] Acute inflammatory lesions displaying oozing or blisters should be treated additionally (four times a day) with open, wet compresses of Burow's solution—an aluminum acetate solution that is useful as a soothing wet dressing for inflammatory skin conditions. There is often involvement of the feet and toenails.[5]

Tinea Pedis

Tinea pedis, or athlete's foot, appears with scaling, maceration, vesiculation, and fissuring between the toes and on the plantar surface of the foot. In extensive cases, the entire sole may be involved. A secondary bacterial infection may occur. The vesicular pustular form of tinea pedis should be considered when vesicles and pustules on the instep are noted. The differential diagnosis includes contact dermatitis and dyshidrotic eczema. A KOH preparation should help differentiate between these processes. Treatment is similar to that of tinea corporis.[21]

Figure 118-2. Tinea versicolor. (Courtesy of David Effron, MD.)

Tinea Versicolor

Clinical Features. Tinea versicolor is a superficial yeast infection caused by *Pityrosporum ovale*.[22] Superficial scaling patches occur mainly on the chest and trunk but may extend to the head and limbs. As the name implies, lesions can be a variety of colors, including pink, tan, or white.[3] The disease may be associated with pruritus, but medical care is often sought because the spots do not tan. On physical examination, a fine subtle scale is noted that may appear hypopigmented (Fig. 118-2). Pale yellow or orange fluorescence under Wood's light is sometimes present. The differential diagnosis includes vitiligo and seborrheic dermatitis. A KOH preparation reveals short hyphae mixed with spores ("chopped spaghetti and meatballs").

Management. Tinea versicolor is treated with 2.5% selenium sulfide shampoo, imidazole creams, or oral ketoconazole as a single 400-mg dose or 200 mg daily for 3 to 5 days.[5,22-24] Recurrence rates vary from 15 to 50%, and recurrence is considered the rule rather than the exception.[22] Monthly prophylaxis with propylene glycol and water, selenium shampoo, or azole creams can help prevent recurrences.[9,22] Pigmentation may not return to normal for months.

Tinea Unguium

Clinical Features. Tinea unguium results in nails that are opaque, thickened, cracked, and crumbled. Subungual debris is present, and the nail may contain yellowish longitudinal streaks. The nail of the great toe is most commonly involved. Involvement of all of the nails of the hands and feet is rare.

Management. Topical therapy of the nails alone rarely results in a cure because penetration into the nail keratin is poor. Fingernails typically respond more rapidly to therapy than toenails. Oral griseofulvin and ketoconazole require prolonged courses with high relapse rates and numerous side effects.[24] Newer agents such as itraconazole, fluconazole, and terbinafine are safer and more effective. They also offer shorter treatment periods, thus improving compliance.[24] The infection may be resistant to this regimen as well, however, and surgical removal of the nail is occasionally required.[17] Recurrence is common.

Candidiasis

Perspective

Infection by *Candida albicans* can occur in infancy and old age; in people with acquired immunodeficiency syndrome (AIDS), pregnancy, obesity, malnutrition, diabetes and other endocrine imbalances, and malignancy; and those with other debilitating illnesses. Patients treated with corticosteroids, immunosuppressive agents, and antibiotics are also prone to cutaneous fungal infections.

Oral Thrush

Clinical Features. Oral thrush is the most common clinical expression of *Candida* infection.[25] Thrush is most common in newborns, with one third being affected by the first week of life. It appears as patches of white or gray friable material covering an erythematous base on the buccal mucosa, gingiva, tongue, palate, or tonsils. Fissures or crust at the corners of the mouth may be present. The differential diagnosis of oral thrush includes lichen planus, which is not easily scraped off like *C. albicans*. Oral mucous membrane infection with *C. albicans* is an AIDS-defining illness.[9] If the patient does not use dentures and has not taken antibiotics, underlying immunosuppression should be considered.

Management. Treatment of oral thrush involves painting the mouth with 1 mL of oral nystatin suspension (100,000 U/mL) four times a day for infants or 4 to 6 mL four times a day swish and swallow for older children and adults. Treatment should be continued for 5 to 7 days after the lesions disappear. Clotrimazole troches dissolved in the mouth two to five times daily is a preferable treatment option for adults.[3] If topical therapy is not effective or in cases of chronic candidosis, oral ketoconazole, itraconazole, or fluconazole may be prescribed.[25]

Patients with oral candidiasis because of dentures should soak their dentures overnight in dilute (1:10) sodium hypochlorite solution.[3]

Cutaneous Candidiasis

Clinical Features. Cutaneous candidiasis favors the moisture and maceration of the intertriginous areas—the interdigital web spaces, groin, axilla, and intergluteal and inframammary folds. Lesions appear as moist, bright red macules rimmed with a collarette of scale, which represents the pustule roof with scalloped borders. Small satellite papules or pustules are just peripheral to the main body of the rash. These satellite lesions are the most typical indicators of a *Candida* infection. Intertriginous lesions are prone to bacterial superinfection.

Candidal onychia and paronychia are occupational conditions in those whose hands are frequently immersed in hot water. These infections also occur with thumb sucking by children who have thrush. The paronychial area becomes red and swollen and the nails thick and brittle, with transverse ridging. Destruction of the nail plate may occur.

Differential Considerations and Diagnostic Strategies. The differential diagnosis of cutaneous candidiasis includes contact dermatitis,

tinea cruris, intertrigo, malaria, or folliculitis. Candidiasis, however, is less sharply demarcated than tinea cruris and brighter red than intertrigo. A KOH preparation taken from a pustule and roof of the lesion will reveal hyphae and pseudohyphae.

Management. Treatment of intertriginous lesions requires the removal of excessive moisture and maceration. Lesions should be exposed to circulating air from a fan several times a day. Inflammatory lesions should be soaked in or covered with compresses of cool water or Burow's solution. Topical imidazole creams, such as clotrimazole and miconazole, should be applied sparingly to affected areas. Prescription creams, such as econazole, ketoconazole, or sulconazole, are also effective.

Protecting the hands from water is an integral part of the treatment of candidal paronychia. Prolonged immersion should be avoided and contact with water prevented by gloves with cotton liners. Nystatin or clotrimazole cream should be applied frequently to the nail folds for 6 to 8 weeks. A search for underlying immunocompromise should begin in patients with chronic, recurrent candidiasis.

Diaper Dermatitis

Clinical Features

Diaper dermatitis is a common disorder that is exacerbated by heat, moisture, friction, and the presence of urine and fecal material. Occlusive clothing in infants tends to foster all of these. Lesions begin as erythematous plaques in the genital, perianal, gluteal, and inguinal areas. More severe involvement results in moist, eroded lesions that may extend beyond the primary areas of appearance.

Infection with *C. albicans* and fecal bacterial flora is an important contributory factor to the development of diaper dermatitis. Lesions infected with *Candida* are moist, red patches with well-demarcated borders. Papular or pustular satellite lesions are also present.

Diaper dermatitis may reflect the presence of atopic or seborrheic dermatitis in the infant. The presence of lesions elsewhere on the body—particularly on the face in cases of atopic dermatitis or the scalp in cases of seborrhea—alerts the physician to these possibilities. Ammonia and bacterially produced putrefactive enzymes produce dermatitis as contact irritants. Such rashes are accompanied by characteristic odors. The existence of diaper dermatitis as a true allergic contact dermatitis is rare.

Management

Treatment consists primarily of altering the physical environment in which diaper dermatitis thrives. Excess clothing should be removed, and occlusive plastic or rubber diaper covers should not be used. Diapers should be changed frequently and left off for prolonged periods if possible. Sterilized cloth diapers are preferred.

If exudative lesions are present, treatment with topical cool wet compresses of saline or Burow's solution is indicated for 2 or 3 days. Continuous air exposure of the area should be attempted.[26] Zinc oxide (Desitin) may dry the area. Severe contact or seborrheic dermatitis may require short-term treatment with topical corticosteroids, such as 1% hydrocortisone in a cream base.[26] Ointment-based topical medications for treatment of diaper dermatitis should be avoided because their occlusive nature enhances moisture retention. Nystatin cream or powder should be applied to lesions infected with *Candida*.

SCALY PAPULES

Fungal lesions are typically scaly, as are lesions of secondary syphilis. Additional scaly diseases are discussed next.

Pityriasis Rosea

Pityriasis rosea is a mild skin eruption predominantly found in children and young adults. The lesions are multiple pink or pigmented oval papules or plaques 1 to 2 cm in diameter on the trunk and proximal extremities. Mild scaling may be present. The lesions are parallel to the ribs, forming a Christmas tree–like distribution on the trunk. Oral lesions are rare. In children, papular or vesicular variants of the disease may occur.[3]

In half the cases, the generalized eruption is preceded by 1 week by the appearance of a "herald patch." This is a larger lesion, 2 to 6 cm in diameter, that resembles the smaller lesions in other respects. The eruption is usually asymptomatic, although pruritus may be present.

Pityriasis rosea is self-limited, resolving in 8 to 12 weeks. Its cause is unknown, although a virus is suspected. The differential diagnosis includes tinea corporis, guttate psoriasis, lichen planus, drug eruption, and secondary syphilis. Recurrences are rare. Treatment is usually unnecessary, except for symptomatic alleviation of bothersome pruritus.

Atopic Dermatitis

Principles of Disease

Atopic dermatitis (AD) is a common dermatologic condition encountered in the ED and commonly referred to as "eczema" or "chronic dermatitis." AD is the cutaneous manifestation of an atopic state, and although it is not an allergic disorder, it is associated with allergic diseases such as asthma and allergic rhinitis. Patients with AD are known to have abnormalities of both humoral and cell-mediated immunity.[25] The exact mechanism is unclear, but eosinophil, mast cell, and lymphocyte activation triggered by increased production of interleukin-4 by specific T helper cells seems to be involved. Increased IgE levels are found in most but not all patients with AD, but there is a poor correlation between the severity of the dermatitis and the serum IgE level.[25] The course of AD involves remissions and exacerbations. More than 90% of patients have the onset of AD before 5 years of age. New-onset AD in older children or adults should raise suspicion for other diagnoses.

Clinical Features

Atopic dermatitis has no pathognomonic skin lesions or unique laboratory parameters. The United Kingdom's Working Party revised diagnostic criteria include itchy skin plus three or more of the following: history of flexural involvement, generalized dry skin, history of asthma or hay fever, onset of rash before 2 years of age, and flexural dermatitis.[27] These criteria are quite sensitive (85%) and specific (96%).

Skin lesions generally appear as inflammatory thickened, papular, or papulovesicular lichenification and hyperpigmentation.[28] The skin is typically dry and may be scaly, but in the acute phase, it may also be vesicular, weeping, or oozing. The distribution of lesions varies with the age of the patient. In infants, inflammatory exudative plaques are seen on the cheeks, extensor surfaces, and in the diaper area. Older children and adults have lesions in the antecubital and popliteal flexion areas, neck, face, and upper chest. Infantile AD usually

begins in the fourth to sixth month of life and improves by the third to fifth year of life. The childhood form occurs between 3 and 6 years of age and resolves spontaneously or continues into the adult form.[28]

Intense pruritus is a hallmark of AD. During flares, patients may present with complaints of intense itching and failure of routine treatments to control their symptoms. Patients may also present with secondary infections. The itching may be focal or generalized, is worse during the winter, and is triggered by increased body temperature and emotional stress. It may be particularly annoying at night. Excoriations may be prominent, and secondary bacterial infection of excoriated lesions is common. Repeated scratching and rubbing produce lichenification, a condition of hyperpigmentation, thickening of the skin, and accentuation of skin furrows. Lichenification is a common feature of chronic AD.

Differential Considerations

The differential diagnosis of infantile AD includes histiocytosis X, Wiskott-Aldrich syndrome, chronic seborrheic dermatitis, phenylketonuria, Bruton's X-linked agammaglobulinemia, psoriasis, and scabies. Fixed-drug eruptions and contact dermatitis round out the differential diagnosis regardless of age.[25,27] Complications of AD include pyogenic skin infections, otitis externa, cataracts, keratoconus, retinal detachment, and cutaneous viral infections.

Management

The optimal protocol for management in children has not been established. Treatment should be aimed at controlling inflammation, dryness, and itching. The use of sedating antihistamines at bedtime can be beneficial in patients with AD who have comorbid allergic conditions and sleep disturbances.

Daily skin care should be reviewed with patients or caregivers. General recommendations for all patients include avoidance of nonspecific skin irritants, wool, nonessential toiletries and detergents, and using cotton clothing as much as possible. Patients should take daily warm baths or showers for approximately 10 to 15 minutes to hydrate the skin. Baths are followed by gentle pat drying and immediate application of a topical anti-inflammatory medication on the affected areas and a moisturizer such as Cetaphil cream on the asymptomatic areas. Medium-potency topical corticosteroids may be sufficient to treat moderate flares. Ointment-based medications are usually better tolerated by most patients during an acute flare.

Skin dryness may be treated by the application of lubricating ointments such as Vaseline or 10% urea in Eucerin cream (not lotion). Treatment of exudative areas includes the application of wet dressings. Such dressings are useful for their moisturizing, anti-inflammatory, and antipruritic actions. Two or three layers of gauze soaked in Burow's solution should be applied for 15 to 20 minutes four times a day. Antihistamines may be helpful in reducing the pruritus and are also useful for their sedative and soporific effects, although there is no convincing evidence that H_1 antihistamines decrease itching in patients with atopic eczema.[2]

Topical corticosteroids are the cornerstone of therapy and should be prescribed in ointment form. When the dermatitis is severe, a fluorinated corticosteroid ointment such as half-strength betamethasone valerate should be applied to affected areas of the body three times a day. Fluorinated corticosteroids should not be used on the face because they can produce permanent cutaneous atrophy. Milder corticosteroid preparations such as 0.025% triamcinolone ointment may be used on the face and intertriginous areas. Patients with extremely severe disease may require systemic steroids. Ultraviolet B treatment is moderately effective, although its mechanism of action is not well understood.[28]

Cyclosporine and other immunosuppressant agents are being used with some promising benefit. Further studies are needed to determine ideal dosing and safety profiles for these agents.[28]

Topical calcineurin inhibitors, including tacrolimus ointment and pimecrolimus cream, are nonsteroidal topical immunosuppressants approved in the United States for use on children 2 years or older and are useful for treating lesions on the thinner skin areas (face, groin, and axillae) where repeated applications of topical corticosteroids may result in skin atrophy or striae.[29] A burning sensation at the site of application may occur. Note that the Food and Drug Administration has issued a "black box" warning concerning long-term continuous treatment with topical calcineurin inhibitors and cancer, although there is currently no evidence for a causal link.[30,31]

Inpatient admission should be strongly considered for patients with generalized erythema and exfoliation (erythroderma), and intractable itching as skin breakdown and severe secondary bacterial or viral skin infections may occur.

Skin Infections in Patients with Atopic Dermatitis

Patients with AD are susceptible to infection and colonization by a variety of organisms because of their defective skin barrier functions and local skin immunodeficiency. Widespread disseminated viral infections, such as eczema molluscatum, eczema vaccinatum, or eczema herpeticum, and recurrent staphylococcal pustulosis are especially concerning.[29]

Eczema molluscatum is self-limited. Eczema vaccinatum results from exposure of patients to vaccinia virus either via intentional inoculation or via contact with someone recently immunized against smallpox. Therapy of eczema vaccinatum requires prompt administration of intravenous immunoglobulin, which can be obtained from the Centers for Disease Control and Prevention.[32] Eczema herpeticum constitutes a medical emergency. Patients present with disseminated eruptions of dome-shaped vesicles that may or may not be superimposed on areas of eczematous rashes, with the head, neck, and trunk commonly affected. Fever, malaise, and local lymphadenopathy are variable depending on the timing of presentation and host characteristics. Complications include keratoconjunctivitis, viremia, multiorgan involvement with meningitis, and encephalitis.[32] Clinical suspicion of eczema herpeticum mandates initiation of intravenous acyclovir in conjunction with antistaphylococcal antibiotics for possible bacterial superinfection. Lumbar puncture should not be attempted if infected lesions are present over the lumbar area. Ophthalmology consultation is needed for patients with periocular or suspected eye involvement.

PUSTULES

Impetigo

Principles of Disease

Impetigo is a slowly evolving pustular eruption, most common in preschool children. Currently, *Staphylococcus aureus* is the most common pathogen, with group A streptococcus a distant second.[33] Poor health and hygiene, malnutrition, and various antecedent dermatoses, especially atopic dermatitis, predispose individuals to impetigo.

Clinical Features

Streptococcal impetigo is found most often on the face and other exposed areas. The eruption often begins as a single pustule but develops into multiple lesions. It begins as 1- to 2-mm vesicles with erythematous margins. When these break, they leave red erosions covered with a golden yellow crust. Lesions may be pruritic but usually are not painful. Regional lymphadenopathy is commonly present. Lesions are contagious among infants and young children and less so in older children and adults. Postpyodermal acute glomerulonephritis is a recognized complication of streptococcal impetigo.

Staphylococcal impetigo may be differentiated from streptococcal impetigo (ecthyma) by little surrounding erythema in the staphylococcal infection that is more superficial.[3] Other diagnostic considerations are herpes simplex virus (HSV) and inflammatory fungal infections. A Gram's stain obtained from the weepy erosion after removing the crust will reveal gram-positive cocci.

Bullous impetigo is caused by staphylococci infected by phage group 2. This form is seen primarily in infants and young children. The initial skin lesions are thin-walled, 1- to 2-cm bullae. When these rupture, they leave a thin serous crust and collarette-like remnant of the blister roof at the rim of the crust. The face, neck, and extremities are most often affected. The differential diagnosis is contact dermatitis, HSV infection, superficial fungal infections, and pemphigus vulgaris. A Gram's stain of the fluid from a bulla reveals gram-positive cocci. Cultures are positive in 95% of cases.

Management

Systemic and topical therapies are equally successful in treating impetigo.[33-35] For more extensive lesions, systemic treatment should be used. There is no evidence, however, that systemic antibiotics prevent the development of acute glomerulonephritis.[31,36] The efficacy of topical mupirocin 2% ointment three times a day and oral erythromycin, 250 mg four times a day for 10 days in adults or 30 mg/kg/day in children, or cephalexin, 30 to 40 mg/kg/day three times for 7 to 10 days, is similar.[9,33-35,37] Mupiricin should be avoided if there is concern about methicillin-resistant strains.

Therapy for bullous impetigo consists of an oral penicillinase-resistant semisynthetic penicillin such as dicloxacillin, 250 mg four times a day for 5 to 7 days for adults, or erythromycin, 250 mg four times a day in adults or 30 to 50 mg/kg/day in children. If the infection is limited to a small area, mupirocin 2% ointment three times a day may be applied. Without treatment, impetigo heals within 3 to 6 weeks.[33-35,37]

Folliculitis

Clinical Features

Folliculitis is an inflammation in the hair follicle, usually caused by *S. aureus*. It appears as a pustule with a central hair. The lesions are usually on the buttocks and thighs, occasionally in the beard or scalp, and may cause mild discomfort. Differential diagnosis includes acne, keratosis pilaris, and fungal infection. Gram-negative folliculitis with *Pseudomonas aeruginosa* occurs with infected hot tubs and swimming pools or in individuals taking antibiotics for acne, and it can be differentiated from staphylococcal folliculitis by a Gram's stain of the lesion.

Management

Treatment with an antiseptic cleanser such as povidone-iodine or chlorhexidine every day or every other day for several weeks is usually adequate. For patients with extensive involvement, a 10-day course of erythromycin, 250 mg four times a day, or dicloxacillin, 250 mg four times a day, may be added.[3,35,37]

Hidradenitis Suppurativa

Hidradenitis suppurativa affects the apocrine sweat glands. Recurrent abscess formation in the axillae and groin resembles localized furunculosis. The condition tends to be recurrent and may be extremely resistant to therapy. Hidradenitis suppurativa may be treated with drainage of abscesses. Antistaphylococcal antibiotics are useful if administered early and for a prolonged period.[9] Many cases do not respond, however, and eventually require local excision and skin grafting of the involved area. Antiandrogen therapy may be considered if antibiotics do not produce improvement.[9]

Carbuncle

A carbuncle is a large abscess that develops in the thick, inelastic skin of the back of the neck, back, or thighs. Carbuncles produce severe pain and fever. Septicemia may accompany the lesions. The diagnosis of skin abscess, furuncle, or carbuncle is usually made clinically.

Local heat should be applied to furuncles and carbuncles, which should be incised and drained when fluctuant. Antibiotics are unnecessary with incision and drainage unless cellulitis or septicemia is present.

Community-Associated Methicillin-Resistant *Staphylococcus Aureus*

The incidence of community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) has soared since the first report in 1993.[38] In many major U.S. cities, CA-MRSA is now the most common pathogen cultured from ED patients presenting with skin and soft tissue infections.[39]

Concern exists that CA-MRSA may be more virulent than methicillin-sensitive strains and colonization with CA-MRSA may produce more overt infections.[39]

Epidemiology

Hospital-acquired MRSA isolates can survive on a variety of inanimate surfaces, sometimes for weeks. It is unclear whether this is also true for CA-MRSA isolates; if it is true, their presence on such items as clothing, towels, and athletic equipment might contribute to outbreaks. Pets (including dogs and cats), livestock, and birds have been identified as MRSA carriers[40]; their role in MRSA transmission to humans requires further evaluation.

Clinical Features

CA-MRSA infections most often present as skin and soft tissue suppuration such as an abscess, furuncle, or cellulites. Lesions frequently exhibit central necrosis and are often confused with spider bites by patients. No clinical features distinguish with certainty skin and soft tissue infections caused by MRSA from those caused by methicillin-susceptible *S. aureus*.[41] Although rare, CA-MRSA infection can also present as necrotizing fasciitis.[42] Recurrences of CA-MRSA cellulitis are common. Contagion among the close household contacts of patients, as well

as correctional facility, school, and sports-team contacts, is well recognized.

Management

Several studies have demonstrated excellent outcomes for abscesses caused by CA-MRSA that are treated with incision and drainage alone.[43] If antibiotics are needed, information on local antibiotic-resistance patterns can help clinicians assess the likelihood of CA-MRSA infection and guide decisions regarding empirical treatment. Obtaining a specimen for culture and susceptibility testing, which was considered to be unnecessary in the pre-CA-MRSA era, may be useful in guiding therapy. Specimens are obtained at the time of incision and drainage of purulent lesions.

In patients with larger abscesses, systemic signs of infection, or both, antimicrobial therapy is needed in addition to incision and drainage. The optimal oral antimicrobial regimen for the treatment of skin and soft tissue infections is not known. The type and route of therapy should be guided by the severity of the clinical syndrome.

Clindamycin combines MRSA activity with effectiveness against the majority of other gram-positive organisms. Side effects include diarrhea, *Clostridium difficile* colitis, and increasing rates of clindamycin resistance.[44] Rifamycin has anti-MRSA activity, but resistance readily develops, so it should not be used alone. Its long half-life allows once-a-day administration. It penetrates well into all tissues and body fluids. It has a high potential for drug-drug interactions.[45] Linezolid, a newer antimicrobial agent, is active against almost all CA-MRSA isolates and group A streptococci. Disadvantages of its use include high cost, lack of routine availability, hematologic side effects, and potential for resistance among *S. aureus* strains. Prolonged linezolid administration increases the likelihood of resistance.[46]

Trimethoprim-sulfamethoxazole or tetracycline is not recommended as sole empirical therapy for a nonpurulent cellulitis of unknown cause because of group A streptococci resistance to these agents.[44] A β-lactam antibiotic may augment treatment. Cephalosporins and macrolides, including newer ones, are ineffective against CA-MRSA.[10] Fluoroquinolones should be avoided because *S. aureus* resistance develops readily and is already widely prevalent.[39]

Patients with large abscesses, abscesses in high-risk locations, fever, signs of systemic infection, young age, or immunodeficiency should prompt consideration of hospitalization. The detailed management of invasive disease due to CA-MRSA is discussed elsewhere. Vancomycin is still considered the parenteral drug of choice for patients with invasive *S. aureus* infection, although clinical failures have been reported. It seems reasonable to combine vancomycin with another effective antistaphylococcal agent because many antibiotics have better bactericidal activity. In severely ill patients, carbapenems such as meropenem, panipenem, and ertapenem, which are active against CA-MRSA and synergistic with vancomycin, should be used. [47] Use of parenteral clindamycin (not recommended as monotherapy), bactrim, and linezolid has been described. In addition, daptomycin and tigecycline are now approved for the treatment of skin and soft tissue infections caused by MRSA.[48,49] A fixed combination of the streptogramins quinupristin and dalfopristin (Synercid) can be used to treat CA-MRSA skin and soft tissue infections. Its use has been limited by the potential for drug-drug interactions and by side effects.[50]

Recurrent infections are generally treated like initial episodes. Some providers recommend "decolonization" strategies, although neither the indications for their use nor their effectiveness in reducing the risk of recurrences is established. Decolonization strategies include the use of intranasal mupirocin to reduce nasal carriage of MRSA; however, eradication of nasal colonization appears to be transient. The efficacy of attempts to eradicate CA-MRSA among household members has not been studied.

Prevention

Common antiseptics appear to retain reasonable activity against CA-MRSA, although the results of recent studies are somewhat conflicting. Good personal hygiene including appropriate hand-washing techniques, separation of infected patients from other types of patients, and routine cleaning of shared equipment are essential to limiting CA-MRSA spread.[50,51]

Gonococcal Dermatitis

Clinical Features

The arthritis-dermatitis syndrome is the most common presentation of disseminated gonococcal disease.[52,53] It occurs in 1 or 2% of patients with gonorrhea, affecting women primarily.[52] Fever and migratory polyarthralgias commonly accompany the skin lesions. The lesions are often multiple and have a predilection for periarticular regions of the distal extremities.[52]

The lesions begin as erythematous or hemorrhagic papules that evolve into pustules and vesicles with an erythematous halo (Fig. 118-3). They closely resemble the lesions of meningococcemia at this stage. They are tender and may have a gray necrotic or hemorrhagic center. Healing with crust formation usually occurs within 4 or 5 days, although recurrent crops of lesions may appear even after antibiotics have been started.[52]

Diagnostic Strategies

The lesions usually have a negative culture for gonococci, and the Gram's stain only occasionally reveals the organisms. A more reliable diagnostic technique is immunofluorescent antibody staining of direct smears from pustules.[52] This method indicates that the lesions may be the result of hematogenous dissemination of nonviable gonococci.[52]

Management

Current treatment of disseminated gonococcal infection is ceftriaxone, 1 g intramuscularly (IM) or intravenously (IV) every 24 hours, or ceftizoxime or cefotaxime, 1 g IV every

Figure 118-3. Typical skin lesions of disseminated gonococcal disease. (Courtesy of David Effron, MD.)

Figure 118-4. Facial cellulitis. (Courtesy of David Effron, MD.)

8 hours. Patients allergic to β-lactam antibiotics may be treated with spectinomycin 2 g IM every 12 hours. A total of 7 days of antibiotic therapy is required, with the remaining course of cefixime, 400 mg twice a day, cefuroxime or ciprofloxacin, 500 mg twice a day, or ofloxacin, 400 mg twice a day. Ciprofloxacin and ofloxacin are not recommended due to increasing resistance patterns or for pregnant women or children younger than 17 years.[52,53] Hospitalization is recommended for patients in whom the diagnosis is uncertain and for those who have septic arthritis, meningitis, or endocarditis.

■ ERYTHEMA

Cellulitis is an infection of the skin tissue denoted by erythema, swelling, and local tenderness (Fig. 118-4).[54-58] Erysipelas is a streptococcal infection of the skin and subcutaneous tissue. The involved area is red, indurated, and edematous.[59] These disorders are discussed in Chapter 135.

■ RED MACULES

Drug Eruption

Principles of Disease

A given drug can produce a skin eruption of a different appearance in different patients or a different appearance in the same patient on different occasions. The most common eruptions are urticaria (hives) (Fig. 118-5) and, more commonly, morbilliform rashes (Fig. 118-6).

Drug reactions tend to appear within a week after the drug is taken, with the exception of reactions to semisynthetic penicillins, which commonly occur later. Skin lesions may appear after a drug has been discontinued and may worsen if the drug or its metabolites persist in the system. Special note should be made of penicillin because it is the most common cause of drug reaction. Serum sickness and urticaria are the most common manifestations of penicillin allergy. Atopic patients and those with a history of hay fever, asthma, or eczema are at special risk.

On the other hand, a number of drugs in common use rarely produce eruptions. Among these are acetaminophen, aluminum hydroxide (Maalox), codeine, digoxin, erythromycin, ferrous sulfate, meperidine (Demerol), morphine, and prednisone.

Clinical Features

Some of the more common skin reactions produced by commonly used drugs are listed in Table 118-2. *Exanthematous drug eruptions* resemble the skin manifestations of various viral or bacterial infections and are usually widespread symmetric maculopapular eruptions. Severe cases may progress to exfoliative dermatitis.

Eczematous drug rashes resemble those of contact dermatitis but are generally more extensive. They begin as erythematous or papular eruptions that may become vesicular. Prior sensitization to a topical medication is common in cases of this type of eruption.

Vasculitic lesions begin as erythematous papules or nodules but may ulcerate and become gangrenous. Urticarial vasculitis is characterized by persistent urticarial lesions with histologic evidence of leukocytoclastic vasculitis. Wheel-and-flare–like lesions that hurt or burn more than itch, lesions lasting more than 24 hours, and urticarial lesions that leave prolonged pigmentary changes or inflammatory lesions should prompt suspicion for urticarial vasculitis.[60] Purpuric drug eruptions

Figure 118-5. Urticaria (hives). (Courtesy of David Effron, MD.)

Figure 118-6. Morbilliform drug eruption. (Courtesy of David Effron, MD.)

Table 118-2 Types of Lesions Characteristically Caused by Commonly Used Drugs

THERAPEUTIC AGENTS	TYPE OF ERUPTION									
	EXANTHEMATOUS	URTICARIAL*	ERYTHEMA MULTIFORME†	TOXIC EPIDERMAL NECROLYSIS	ECZEMATOUS	ERYTHEMA NODOSUM	VASCULITIS	PURPURA	PHOTOSENSITIVE	FIXED
Aminophylline					×					
Anovulatory drugs		×				×			×	×
Barbiturates	×	×	×	×				×		×
Bromides		×	×			×				
Chloramphenicol		×					×			
Insulin	×	×								
Iodides		×	×			×	×	×		
Isoniazid	×	×								
Meprobamate	×	×			×			×		×
Penicillin	×	×	×	×	×	×	×	×		
Phenacetin										×
Phenolphthalein		×	×	×						×
Phenothiazines	×	×	×		×			×		×
Phenylbutazone	×	×		×			×	×		×
Quinidine	×	×	×				×		×	×
Quinine	×	×								
Salicylates	×	×	×			×				×
Sulfonamides	×	×	×	×	×	×	×		×	×
Tetracycline	×	×		×			×		×	×
Thiazides	×		×		×				×	
Others	Chloral hydrate	Opiates	Tolbutamide, phenytoin	Tolbutamide	Diphenhydramine ephedrine, thiamine, methyldopa		Antimalarial drugs, guanethidine		Antimalarial drugs, chlordiazepoxide, reserpine	Diazepam, indomethacin

*The most common causes of drug-induced urticaria are aspirin and penicillins.
†The long-acting sulfonamides have been linked to Stevens-Johnson syndrome.

Figure 118-7. Purpuric lesions. (Courtesy of David Effron, MD.)

may be the result of bone marrow suppression, platelet destruction, or vasculitis (Fig. 118-7). Ultimately, a skin biopsy is needed to confirm the diagnosis of vasculitis.

Photosensitive drug reactions require the presence of sunlight and are seen most commonly on sun-exposed areas of skin. This class of reactions is commonly divided into phototoxic and photoallergic. Phototoxic reactions are more common. Sulfonamides, sulfonylureas, thiazide diuretics, and tetracyclines are common causes (see Fig. 118-7). This type of reaction does not primarily involve immunologic mechanisms and occurs in any person taking an adequate quantity of the drug and exposed to sunlight. The lesions usually have the appearance of a severe sunburn but may be bullous or papular. Pruritus is typically minimal or absent.[61]

Photoallergic reactions are the result of antigen formation that results in the formation of sensitized lymphocytes. These reactions therefore represent a delayed immunologic response. A photoallergic reaction occurs only in sensitized individuals, usually 2 weeks or longer after exposure to the drug and sunlight. Its occurrence is not dose related, and the eruption usually appears eczematous and intensely pruritic. Chlorpromazine, promethazine, and chlordiazepoxide are common sensitizers of photoallergic reactions.[61]

Patients who develop photoallergic reactions should be withdrawn from inciting drugs. Patients who are subject to photosensitive drug eruptions may be required to avoid prolonged sunlight exposure. Sunscreen containing 5% aminobenzoic acid should be used during any such exposure.

Fixed-drug eruptions appear and recur at the same anatomic site after repeated exposure to the same drug. The lesions are usually sharply marginated and round or oval. They may be pigmented, erythematous, or violaceous. Pruritus may be prominent.

Differential Considerations

The differential diagnosis of drug eruptions includes viral exanthem, chronic exfoliative erythroderma caused by psoriasis or atopic dermatitis, malignancy, scarlet fever, staphylococcal scarlatiniform eruptions, and Kawasaki disease.[9,61]

Management

Treatment of drug eruptions should begin with discontinuation of the inciting agent. Patients should be warned that drug eruptions clear *slowly* after discontinuation of the offending agent. Itching may be treated with the application of a drying antipruritic lotion such as calamine. Cool compresses, tepid water baths with colloidal oatmeal (Aveeno) emollient or cornstarch, and diphenhydramine (Benadryl), 50 mg (5 mg/kg/24 hr in children) every 6 hours, are likely to be beneficial.

Staphylococcal Scalded Skin

Clinical Features

Staphylococcal scalded skin syndrome generally occurs in children 6 years of age or younger. It is caused by an infection with phage group 2 exotoxin-producing staphylococci. The illness begins with erythema and crusting around the mouth. The erythema then spreads down the body, followed by bulla formation and desquamation. Mucous membranes are usually not involved, but minimal involvement is occasionally seen. After desquamation occurs, the lesions dry up quickly, with clinical resolution in 3 to 7 days.

Management

Most group 2 toxin-producing organisms are penicillin resistant. Although most patients will recover without antibiotic treatment, IV therapy with 50 to 100 mg/kg of nafcillin daily or oral cloxacillin 50 mg/kg/day or dicloxacillin is recommended.[9,62,63]

Toxic Epidermal Necrolysis

Principles of Disease

Many consider Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) as a continuous spectrum of the same disease. Both are true dermatologic emergencies. The main feature of non–staphylococcal-induced TEN, or Lyell's disease, is the separation of large sheets of epidermis from underlying dermis. Drugs, including the long-acting sulfa drugs, penicillin, aspirin, barbiturates, phenytoin, carbamazepine, allopurinol, and nonsteroidal anti-inflammatory drugs, are an important cause of TEN. TEN has occurred after vaccination and immunization against poliomyelitis, measles, smallpox, diphtheria, and tetanus. It has also been found in association with lymphoma.

Clinical Features

Toxic epidermal necrolysis commonly begins with prodromal symptoms, such as malaise, rhinitis, sore throat, body aches, and fever. These are followed by the abrupt development of a macular rash that may or may not appear as target lesions.[64] Mucous membrane involvement commonly precedes the rash in TEN. The macular exanthem usually starts centrally and then spreads to the extremities. The exanthem becomes confluent and dermal-epidermal dissociation ensues, resulting in a positive Nikolsky's sign, denudation with shear stress, and the skin is commonly painful to the touch.

Mucous membrane involvement becomes more apparent during the progression phase.[64] Involvement of the conjunctivae and cornea may lead to permanent scarring and blindness. The full thickness of epidermis is involved. The two conditions are easily histologically distinguishable with a skin biopsy (Fig. 118-8). A mortality rate of 15 to 20% is expected with this condition.[61]

Management

The treatment of TEN includes discontinuation of the offending agent, fluid replacement, and aggressive infection control.[9,61]

Figure 118-8. Toxic epidermal necrolysis. (Courtesy of David Effron, MD.)

Administration of systemic corticosteroids is controversial.[61] They have little effect on the disease and may mask signs of impending sepsis. Plasmapheresis is considered experimental.[45] The mainstay of treatment is excellent supportive care, prevention of secondary infection, and expert wound management. This is usually best accomplished in a center with burn expertise.

Toxic Shock Syndrome

Principles of Disease

Toxic shock syndrome (TSS) is an acute febrile illness characterized by a diffuse desquamating erythroderma. Classically composed of high fever, hypotension, constitutional symptoms, multiorgan involvement, and rash, the syndrome gained notoriety in the early 1980s because of association with tampon use. However, it is also well-known in men and children. Its appearance has often been linked to exotoxin-producing *S. aureus*. Most cases of nonmenstrual TSS occur in the postoperative setting. TSS has also been associated with various staphylococcal and streptococcal infections, including empyema, osteomyelitis, fasciitis, septic abortion, peritonsillar abscess, sinusitis, burns, and subcutaneous abscess.[63]

TSS is associated with severe group A beta-hemolytic streptococcal infections. It has been reported in previously healthy patients, immunocompromised patients, and elderly patients. Fatigue, localized pain, and nonspecific symptoms herald the onset of this disease, followed by septic shock and multisystem organ failure.[63,65]

Clinical Features

Diagnosis of TSS requires the presence of (1) fever of at least 38.9° C; (2) hypotension, with a systolic blood pressure of 90 mm Hg or less; (3) skin rash; and (4) involvement of at least three organ systems.[9,63] Systemic involvement may include the gastrointestinal (GI) tract, muscular system, or central nervous system (CNS) and laboratory evidence of renal, hepatic, or hematologic dysfunction. Headache, myalgias, arthralgia, alteration of consciousness, nausea, vomiting, and diarrhea may be present.

The rash is typically a diffuse, blanching, macular erythroderma. Accompanying nonexudative mucous membrane inflammation is common. Pharyngitis, sometimes accompanied by a "strawberry tongue," conjunctivitis, or vaginitis may be seen. As a rule, the rash fades within 3 days of its appearance. This is followed by a full-thickness desquamation, most commonly involving the hands and feet.

Management

Initial treatment of TSS consists of IV fluid replacement, ventilatory support, pressor agents, penicillinase-resistant antibiotics, and drainage of infected sites.[63,66]

Urticaria

Principles of Disease

Urticaria may occur in isolation or as part of a systemic anaphylactic reaction. The following discussion pertains to urticaria occurring in the absence of systemic symptoms. Anaphylactic reactions are discussed in Chapter 117. Approximately 15 to 20% of the population experience urticaria during their lifetime. Acute urticaria is seen in both sexes and is more likely to have an allergic cause. Chronic urticaria is more common in women in their 40s and 50s. Half of all patients with chronic urticaria have the disease for 5 years and one fourth for 20 years.[67]

Various mediators, including histamine, bradykinin, kallikrein, and acetylcholine, are thought to play a role in urticaria production. Urticaria may be initiated by immunologic or nonimmunologic mechanisms. Hives found in anaphylaxis and serum sickness represent an immunologic reaction. Nonimmunologic urticaria may be produced by degranulation of mast cells, which may be caused by a number of foods and drugs, including aspirin and narcotics.

Substances that can cause urticaria by contact with the skin include foods, textiles, animal dander and saliva, plants, topical medications, chemicals, and cosmetics.[68] The role of drugs in the production of urticaria is discussed in the section on drug eruption. Almost any drug may produce urticaria, although penicillin and aspirin are the most common. Traces of penicillin may be present in dairy products as well as in medications. The mechanism of production of urticaria by aspirin is unknown but is probably nonimmunologic, and the effects of aspirin may persist for a number of weeks after ingestion.[68]

A variety of food allergies, such as fish, eggs, or nuts, may result in urticaria. In addition, foods such as lobster and strawberries can release histamine through a nonimmunologic mechanism. Hereditary forms of urticaria include familial cold urticaria and hereditary angioneurotic edema.

Infections are an uncommon cause of urticaria, except in children in whom viral infections often cause hives. Occult infections with *Candida*, the dermatophytes, bacteria, viruses, and parasites may trigger hives. Viral infections that produce urticaria include hepatitis, mononucleosis, and coxsackievirus infections.

The inhalation of pollens, mold, animal dander, dust, plant products, and aerosols may produce urticaria. Respiratory symptoms may accompany the dermatosis, and a seasonal pattern of occurrence may be present. Stings and bites of insects, arthropods, and various marine animals may also produce an urticarial eruption.

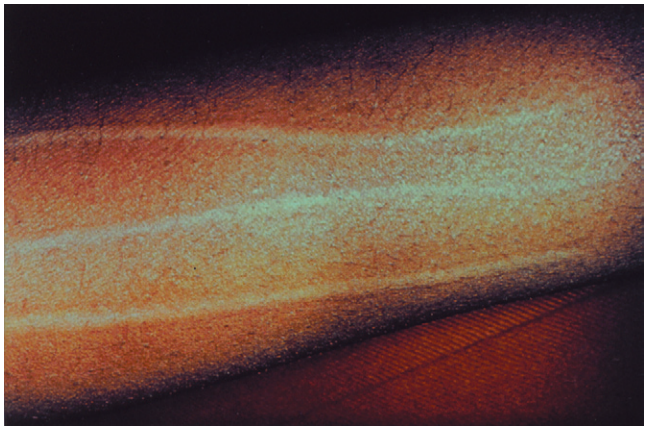

Figure 118-9. Dermatographism. (Courtesy of David Effron, MD.)

Occasionally, patients with systemic lupus erythematosus, lymphoma, carcinoma, hyperthyroidism, rheumatic fever, and juvenile rheumatoid arthritis develop an urticarial eruption. The association is uncommon enough that it is not necessary for a urticaria workup to include a search for malignancy in most cases.

A number of physical agents produce urticaria. Dermatographism is present when firm stroking of the skin produces an urticarial wheal within 30 minutes (Fig. 118-9) and is the most common form of physical urticaria. Pressure urticaria is distinct from dermatographism in that the onset of urticaria is delayed by 4 to 8 hours after the application of physical pressure. There is no other particular significance to this form of urticaria.

Cold urticaria may be either familial or, more commonly, acquired. Cold urticaria may also be associated with underlying illness, such as cryoglobulinemia, cryofibrinogenemia, syphilis, and connective tissue disease.[67,68] Cyproheptadine, 2 to 4 mg two or three times a day, is useful in the suppression of primary cold urticaria.[67] Side effects of this drug include drowsiness and an increased appetite.[67] Antihistamines taken 30 to 60 minutes before cold exposure may be helpful. Doxepin is also useful; begin at 10 mg at bedtime and gradually increase to 10 to 25 mg three times a day.[67]

Cholinergic urticaria is induced by exercise, heat, or emotional stress. It may be associated with pruritus, nausea, abdominal pain, and headache.[67]The lesions of cholinergic urticaria are wheals 1 to 3 mm in diameter surrounded by extensive erythematous flares and, occasionally, satellite wheals. Cholinergic urticaria responds better to hydroxyzine than do other physical urticarias.[67]

Heat is a rare cause of hives. Solar urticaria, also uncommon, is confined to sun-exposed areas of skin and clears rapidly when the light stimulus is removed. Extensive sun exposure may cause wheezing, dizziness, and syncope in a susceptible individual.[67] Sunscreens have not been proven to be effective for the prevention of solar urticaria.[67]

The cause of chronic urticaria in adults is often not determined, although the etiologic factors responsible for urticaria in children are more readily identifiable.[69]

Clinical Features

Urticaria appears as edematous plaques with pale centers and red borders and is easily recognizable (see Fig. 118-5). Individual hives are transient, lasting less than 24 hours, although new hives may continuously develop, which represent localized dermal edema produced by transvascular fluid extravasation.

Differential Considerations

The differential diagnosis of urticaria includes erythema multiforme, erythema marginatum, and juvenile rheumatoid arthritis.

Management

Treatment of urticaria involves the removal of the inciting factor, when applicable, and the administration of antihistamines or other antipruritics. Hydroxyzine (Atarax and Vistaril) in a dose of 10 to 25 mg (2 mg/kg/24 hr in children) is usually effective in providing symptomatic relief. Alternatives are nonsedating antihistamines, such as terfenadine 60 mg twice a day, astemizole 10 mg daily, or fexofenadine 60 mg twice a day.[70] Prednisone is also effective, but the urticaria can rebound, making cessation of prednisone sometimes difficult. For chronic urticaria, long-term therapy with antihistamines may be needed.

Serum Sickness

Serum sickness is a clinical syndrome most commonly caused by drugs and characterized by fever, lymphadenopathy, arthralgias, cutaneous eruptions, gastrointestinal disturbances, and malaise. It is often associated with proteinuria, without evidence of glomerulonephritis.[71] A widespread morbilliform or urticarial rash or erythema multiforme–like eruption develops, sometimes involving the palms and soles. [72] The most common cause of serum sickness and serum sickness–like reactions is a hypersensitivity reaction to drugs.[73] Cefaclor is a common culprit in causing serum sickness–like reactions.

Serum sickness usually begins 1 to 3 weeks after the start of administration of the medication, although it can occur within 12 to 36 hours in individuals who have been sensitized during a previous exposure. Serum sickness is mediated by the tissue deposition of circulating immune complexes, the activation of complement, and the ensuing inflammatory response. This is a type III (immune complex) reaction, or Arthus reaction.

Management

Discontinuation of the culprit drug and symptomatic treatment with antihistamines and topical corticosteroids are recommended. A short course of oral corticosteroids may be required in patients with more severe symptoms.[73] The drug causing the reaction should be avoided in the future. For cefaclor and cefprozil, the risk of cross-reaction with other β-lactam antibiotics is small, and the further administration of another cephalosporin is usually well tolerated.[73] However, some clinicians recommend that patients who experience serum sickness–like reactions from cefaclor avoid all β-lactam drugs.

■ EXANTHEMS

Principles of Disease

An exanthem is defined as a skin eruption that occurs as a symptom of a general disease. Approximately 30 enteroviruses, predominantly the coxsackievirus and echovirus groups, and four types of adenoviruses are known to produce exanthems. Other viruses may do so as well. The exanthems of the coxsackievirus and echovirus are most thoroughly documented. Most viral exanthems are maculopapular, although scarlatiniform, erythematous, vesicular, and petechial rashes

are occasionally seen. The eruptions are variable in their extent, nonpruritic, and do not desquamate. Oropharyngeal lesions may be present.

Infection with echovirus type 9 may be accompanied by meningitis and a petechial exanthem resembling meningococcemia, although the exanthem also occurs without meningeal involvement. Infections caused by echovirus type 16 (Boston exanthem) and coxsackievirus group B, type 5, may resemble roseola infantum but are more likely to occur in adults.

Infections caused by coxsackievirus group A, type 16, cause a distinctive syndrome of vesicular stomatitis and 1- to 4-mm oral vesicles involving the dorsa of the hands and lateral borders of the feet. Disease caused by coxsackievirus group A, type 9, has been the most extensively studied. It may be associated with meningoencephalitis or interstitial pneumonia. The rash is usually maculopapular, begins on the face or trunk, and spreads to the extremities. A vesicular eruption resembling varicella may occur.

The classic viral exanthems are rubeola (measles), rubella (German measles), herpesvirus 6 (roseola), parvovirus B19 (erythema infectiosum, or fifth disease), and the enteroviruses (echovirus and coxsackievirus).[3,9] Widespread immunization programs have reduced the incidence of rubeola and rubella.

Measles

Clinical Features

Measles is a highly contagious viral illness spread by contact with infectious droplets, with an incubation period of 10 to 14 days. Patients are contagious from 1 or 2 days before onset of symptoms up to 4 days after the appearance of the rash.[74] Symptoms begin with fever and malaise. The fever usually increases daily in a stepwise manner until it reaches approximately 40.5° C on the fifth or sixth day of the illness. Cough, coryza, and conjunctivitis begin within 24 hours of the onset of symptoms.

On the second day of the illness, Koplik's spots, which are pathognomonic of the disease, appear on the buccal mucosa as small, irregular, bright red spots with bluish-white centers. Beginning opposite the molars, Koplik's spots spread to involve a variable extent of the oropharynx.

The cutaneous eruption of measles begins on the third to fifth day of the illness. Maculopapular erythematous lesions involve the forehead and upper neck and spread to involve the face, trunk, arms, and finally the legs and feet. Koplik's spots begin to disappear coincident with the appearance of the rash. By the third day of its presence, the rash begins to fade, doing so in the order of its appearance, and the fever subsides.

Complications include otitis media, encephalitis, and pneumonitis. Otitis media is the most common complication. Encephalitis occurs in approximately 1 in 1000 cases of measles and carries a 15% mortality. Measles pneumonia may also be life threatening.

Management

If bacterial invasion occurs with otitis or pneumonia, the use of antibiotics is indicated. Otherwise, treatment is supportive. Isolation of infected children is of limited value because exposure usually occurs before the appearance of the rash and the presence of Koplik's spots renders the disease diagnosable. Measles is not contagious after the fifth day of the presence of the rash. Infection confers lifelong immunity.

The illness can be modified or prevented by the administration of human immune serum globulin (ISG) in a susceptible person within 6 days of exposure. The recommended dose of ISG is 0.25 mL/kg IM in children. Live measles virus vaccine given within 72 hours of exposure may be effective in preventing measles.[74] Some authors suggest vitamin A soon after exposure. The incidence of measles has decreased since the resurgence seen in 1989 to 1991.[74] The patterns observed during outbreaks include a shift from preschool-aged children to older adults and among groups who do not routinely obtain vaccination, such as immigrants.

Rocky Mountain Spotted Fever

Principles of Disease

Rocky Mountain spotted fever is caused by *Rickettsia rickettsii*, an organism harbored by a variety of ticks. The organism is transmitted to humans through tick saliva at the time of a tick bite or when the tick is crushed while in contact with the host. Although originally described in the Rocky Mountain region, this disease occurs in other areas of North, South, and Central America. Most reported cases are from the southeastern United States.

Clinical Features

The onset of the illness is usually abrupt, with headache, nausea and vomiting, myalgias, chills, and a fever spiking to 40° C. Occasionally, the onset is more gradual, with progressive anorexia, malaise, and fever. The disease may last 3 weeks and may be severe with prominent CNS, cardiac, pulmonary, GI, renal, and other organ involvement; disseminated intravascular coagulation; or shock.

The rash develops on the second to fourth day or, occasionally, as late as the sixth day of the illness. It begins with erythematous macules that blanch on pressure, appearing first on the wrists and ankles. These macules spread up the extremities and to the trunk and face in a matter of hours. They may become petechial or hemorrhagic. Lesions on the palms and soles are particularly characteristic. Increased capillary fragility and splenomegaly may be present.

Diagnostic Strategies

The Weil-Felix reaction is the best known serologic diagnostic test, but the development of Weil-Felix agglutinins in cases of Rocky Mountain spotted fever is not constant, and more specific immunofluorescent procedures have been developed.[75] Treatment should not await the result of such tests, however, but should begin as soon as the disease is suspected on clinical grounds.

Management

Tetracycline (25–30 mg/kg/day in divided doses) is the antibiotic of choice. If the patient is unable to take oral medications, tetracycline may be administered IV, with a 15 mg/kg loading dose followed by a maintenance dosage of 15 mg/kg/day. Doxycycline may be used as well in a dosage of 4.4 mg/kg/day divided every 6 hours followed by 1.1 mg/kg twice a day, up to 30 mg/day. Chloramphenicol may be used for patients allergic to tetracycline and in children younger than 9 years. A usual course is 6 to 10 days and should continue for 72 hours after defervescence.[75] Sulfa drugs should be avoided because they can exacerbate the illness. Rickettsiae are routinely resistant to penicillins, cephalosporins, aminoglycosides, and erythromycin.[75]

Roseola Infantum

Roseola infantum, otherwise known as *exanthem subitum* or sixth disease, is a benign illness caused by human herpesvirus 6 and characterized by fever and a skin eruption. A roseola-like illness has occasionally been associated with other illnesses.[74] Ninety-five percent of cases are seen in children 6 months to 3 years of age, and most of these are in infants younger than 2 years. A febrile seizure may occur. The fever typically has an abrupt onset, rising rapidly to 39° C to 41° C, and is present consistently or intermittently for 3 or 4 days, at which time the temperature drops precipitously to normal.

The rash appears with defervescence. The lesions are discrete pink or rose-colored macules or maculopapules 2 or 3 mm in diameter, which blanch on pressure and rarely coalesce. The trunk is involved initially, with the eruption typically spreading to the neck and extremities. Occasionally, the eruptions are limited to the trunk. The rash clears over 1 or 2 days without desquamation.

Despite the presence of a high fever, the infant usually appears well. Encephalitis is a very rare complication.[74] The prognosis is excellent, and no treatment is necessary.

Rubella

Rubella, or German measles, is a viral illness characterized by fever, skin eruption, and generalized lymphadenopathy. It is spread by droplet contact, and peak incidence is in the winter and early spring. The incubation period is typically 14 to 21 days, and the rash heralds the onset of the illness in children. The maximum time of communicability is in the few days before and 5 to 7 days after the onset of the rash.[74] Infants with congenital rubella can shed virus for more than 1 year.[74] In adults, a 1- to 6-day prodrome of headache, malaise, sore throat, coryza, and low-grade fever precedes the rash. These symptoms generally disappear within 24 hours after the appearance of the skin eruption.

The rash of pink to red maculopapules appears first on the face and spreads rapidly to the neck, trunk, and extremities. Those on the trunk may coalesce, but lesions on the extremities do not. The rash remains for 1 to 5 days, classically disappearing at the end of 3 days. Although clearing may be accompanied by fine desquamation, this sign is usually absent.

Lymphadenopathy may begin as early as 1 week before the rash. Although this is generalized, the nodes most apparent are the suboccipital, postauricular, and posterior cervical groups. Palpable adenopathy may be apparent several weeks after other signs and symptoms have subsided.

The major complications of rubella include encephalitis, arthritis, and thrombocytopenia. The most severe complication is fetal damage. A total of 24% of infected fetuses have a congenital defect. A maternal infection may be determined by obtaining serum for hemagglutination inhibition antibody determinations, acutely and in 2 weeks. A fourfold rise in the titer is diagnostic of rubella infection. The routine use of postexposure prophylaxis of rubella in an unvaccinated woman in early pregnancy is *not* recommended.

No treatment is required in many cases of rubella. Antipyretics are usually adequate for the treatment of headache, arthralgias, and painful lymphadenopathy.

Erythema Infectiosum

Erythema infectiosum, or fifth disease, is caused by parvovirus B19 infection. It is characterized by mild systemic symptoms, fever in 10 to 15% of patients, and a characteristic rash. Arthralgia and arthritis occur commonly in adults but rarely in children. The rash is intensely red on the face and gives a "slapped-cheek" appearance with circumoral pallor. A maculopapular lacelike rash, which may be noted on the arms, moves caudally to the trunk, buttocks, and thighs. The rash may recur with changes in temperature and exposure to sunlight. The incubation period is usually between 4 and 14 days.[74]

Parvovirus B19 infection may also result in asymptomatic infection, upper respiratory infection, atypical rash, and arthritis without rash.

Rarely, it has been reported to cause hepatitis.[74] Infected immunodeficient patients may experience chronic anemia as a result of this disease. Patients with sickle cell disease or other hemolytic anemias may develop an aplastic crisis lasting 7 to 10 days.[74] Parvovirus B19 infection during pregnancy can cause fetal hydrops and death.[74] No congenital anomalies have been reported. No treatment is required.

Scarlet Fever

Clinical Features

The incidence of scarlet fever has declined in recent years. The illness has an abrupt onset with fever, chills, malaise, and sore throat followed within 12 to 48 hours by a distinctive rash that begins on the chest and spreads rapidly, usually within 24 hours. Circumoral pallor may be noted. The skin has a rough sandpaper-like texture because of the multitude of pinhead-sized lesions. The pharynx is injected, and there may be erythematous lesions or petechiae on the palate. After the resolution of symptoms, desquamation of the involved areas occurs and is characteristic of the disease.

Complications include the development of a streptococcal infection of lymph nodes, tonsils, the middle ear, and the respiratory tract. Late complications include rheumatic fever and acute glomerulonephritis (Fig. 118-10).

Management

Treatment is aimed at providing adequate antistreptococcal blood antibiotic levels for at least 10 days. Oral penicillin VK 50 mg/kg/day (40,000–80,000 units) in four divided doses in children or 250 mg four times a day in adults is administered. Benzathine penicillin (given as Bicillin CR) is administered IM. In patients weighing less than 30 pounds, 300,000 units of benzathine penicillin is used; in patients weighing 31 to 60

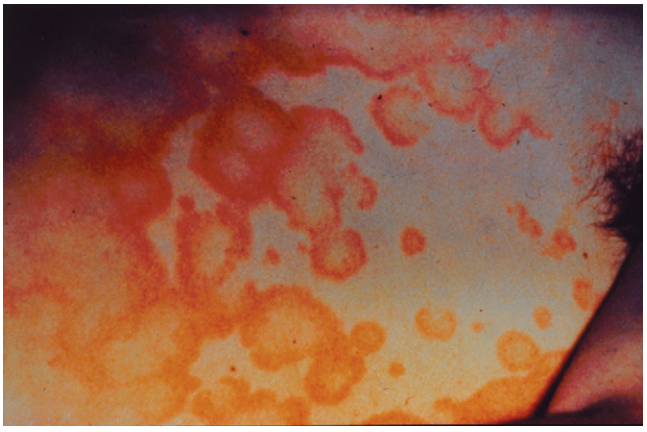

Figure 118-10. Erythema marginatum associated with rheumatic fever. (Courtesy of David Effron, MD.)

pounds, 600,000 units of benzathine is used; in patients weighing 61 to 90 pounds, 900,000 units of benzathine is used; and in those weighing more than 90 pounds, 1.2 million units of benzathine is used. In patients allergic to penicillin, 250 mg of erythromycin four times a day or 40 mg/kg/day should be given orally for 10 days. Other macrolides and certain other cephalosporins may also be used.

PAPULAR LESIONS

Contact Dermatitis

Principles of Disease

Contact dermatitis is an inflammatory reaction of the skin to a chemical, physical, or biologic agent. The inducing agent acts as an irritant or allergic sensitizer. Allergic contact dermatitis is a form of delayed hypersensitivity mediated by lymphocytes sensitized by the contact of the allergen to the skin. It is less common than irritant contact dermatitis.[26] Caustics, industrial solvents, and detergents are common causes of irritant dermatitis. Dermatitis may result from brief contact with a potent caustic or from repeated or prolonged contact with milder irritants.

Clothing, jewelry, soaps, cosmetics, plants, and medications contain allergens that commonly cause allergic contact dermatitis. The most common allergens include rubber compounds, plants of the *Rhus* genus (poison ivy, oak, and sumac), nickel (often used in jewelry alloys), paraphenyldenediamine (an ingredient in hair dyes and industrial chemicals), and ethylenediamine (a stabilizer in topical medications).[26] Sensitization to poison ivy results in sensitization to other plants in this family, such as cashew, mango, lacquer, and ginkgo trees.[76]

Clinical Features

The primary lesions of contact dermatitis are papules, vesicles, or bullae on an erythematous bed. Of the allergens, *Rhus* species are the most likely to cause bullous eruptions. Oozing, crusting, scaling, and fissuring may be found, along with lichenification in chronic lesions. The distribution of the eruption depends on the specific contactant and may be localized, asymmetric linear, or unilateral (Figs. 118-11 and 118-12). Mucous membranes are usually spared unless directly exposed to the inciting agent. A history of exposure is the most significant factor favoring the diagnosis. If doubt exists about the diagnosis, the patient should be referred for allergic patch testing.

Management

Treatment of contact dermatitis includes avoidance of the irritant or allergen and treatment of secondary bacterial infection. Oozing or vesiculated lesions should be treated with cool wet compresses of Burow's solution applied for 15 minutes three or four times a day. Topical baths, available over the counter, may also be comforting. A course of systemic corticosteroids is often necessary.[26] Prednisone in a dosage of 30 to 80 mg/day (depending on the severity of involvement) should be prescribed initially. This should be tapered over at least 10 to 14 days, and 21 days for poison ivy. The long, slow taper is needed to prevent rebound of the disease. The treatment may be discontinued when a daily dose of 10 mg is reached. Systemic antihistamines, such as hydroxyzine or diphenhydramine, may help control pruritus.[9,26,76]

The patient should also be counseled to wash all clothes that might have contacted the plant because the irritant plant oil can persist. Once the offending agent is reliably removed from the skin and clothes, ongoing outbreak is attributable to the initial contact, not spread from the serous fluid from the bullae. The patient is not contagious to others unless there is direct contact with the plant oil in people who are sensitized.

Erythema Multiforme

Principles of Disease

The most common precipitating factors in erythema multiforme are exposure to drugs and HSV infection. Other causes include other viral infections, especially hepatitis and influenza A. Less common causes include fungal diseases, such as dermatophytosis, histoplasmosis, and coccidioidomycosis, and bacterial infections, especially streptococcal infections and tuberculosis. Various collagen vascular disorders have been known to precipitate erythema multiforme, particularly rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, and periarteritis nodosa. Pregnancy and various malignancies have also been associated with erythema multiforme. No provocative factor can be identified in approximately half of all cases. Differential diagnosis includes urticaria, scalded skin syndrome, pemphigus, and pemphigoid and viral exanthems.

Clinical Features

Erythema multiforme is an acute, usually self-limited disease precipitated by a variety of factors. It is characterized by the

Figure 118-11. Contact dermatitis secondary to nickel. (Courtesy of David Effron, MD.)

Figure 118-12. Typical linear lesions of contact dermatitis secondary to poison ivy. (Courtesy of David Effron, MD.)

sudden appearance of skin lesions that are erythematous or violaceous macules, papules, vesicles, or bullae. Their distribution is often symmetrical, most commonly involving the soles and palms, the backs of the hands or feet, and the extensor surfaces of the extremities. The presence of lesions of the palms and soles is particularly characteristic.[61]

The target lesion with three zones of color is the hallmark of erythema multiforme. It is a central, dark papule or vesicle that is surrounded by a pale zone, a halo of erythema (Fig. 118-13), and is commonly found on the hands or wrist.

Stevens-Johnson syndrome, a severe form of erythema multiforme, is occasionally fatal. It is characterized by bullae, mucous membrane lesions, and multisystem involvement (Fig. 118-14). The patient may be toxic; complaining of chills, headache, and malaise; and displaying fever, tachycardia, and tachypnea. Systemic involvement may occur, with renal, GI, or respiratory tract lesions, resulting in hematuria, diarrhea, bronchitis, or pneumonia. Purulent conjunctivitis may be severe enough to cause the eyes to swell shut. Death results from infection and dehydration.

Management

Treatment should begin with a search for the underlying cause. Mild forms resolve spontaneously in 2 or 3 weeks. Severe cases may last up to 6 weeks and may require hospital admission for IV hydration, local skin care, systemic analgesia, and systemic corticosteroid therapy, which should consist of 80 to 120 mg of prednisone daily in divided doses. Bullous lesions should be treated with the application of wet compresses soaked in a 1:16,000 solution of potassium permanganate or a 0.05% silver nitrate solution several times a day. The major complications of Stevens-Johnson syndrome are infection and fluid loss. Renal involvement and pneumonia are rare. Severe conjunctivitis may result in corneal scarring and blindness. Reported mortality rates for Stevens-Johnson syndrome range from 0 to 15%.[3,15]

Figure 118-13. Erythema multiforme. (Courtesy of David Effron, MD.)

Figure 118-14. Stevens-Johnson syndrome. (Courtesy of David Effron, MD.)

Pediculosis

Clinical Features

The diagnosis is made by identification of nits or adult lice on microscopic examination of plucked hairs from the symptomatic area. Nits are relatively more common than the adult louse form. Nits attach to the bases of hair shafts and appear as white dots (Fig. 118-15). Adult forms look like blue or black grains. The patient complains of intense itching and scratching. A secondary infection may result from the latter.

The organisms causing pediculosis corporis reside in the seams of clothing and bedding materials while they feed on the human host. Except for heavily infested individuals, the parasites are absent from the body. Erythematous macules or wheals may be present, along with intense pruritus. The treatment consists of laundering or boiling clothing and bed linen. If nits are found in the body hair, a treatment with lindane lotion may be instituted, but this is not necessary is most cases (Figs. 118-16 and 118-17).

Pediculosis capitis is seen more commonly in small children than in adults. Pruritus is the major symptom and may be confined to the occipital or postauricular scalp. Excoriations commonly result in secondary bacterial infections and regional lymphadenopathy.

Diagnostic Strategies

The diagnosis is made by the identification of nits cemented to hairs at the hair-scalp junction (see Fig. 118-15).

Management

Lindane (Kwell) lotion or cream is no longer the preferred prescription topical treatment.[77] Permethrin (Nix) is the recommended treatment. It remains active for 2 weeks. Creme rinses and conditioning shampoos should not be used during this period because they coat the hairs and protect the lice from the insecticide. Permethrin is applied to the scalp after

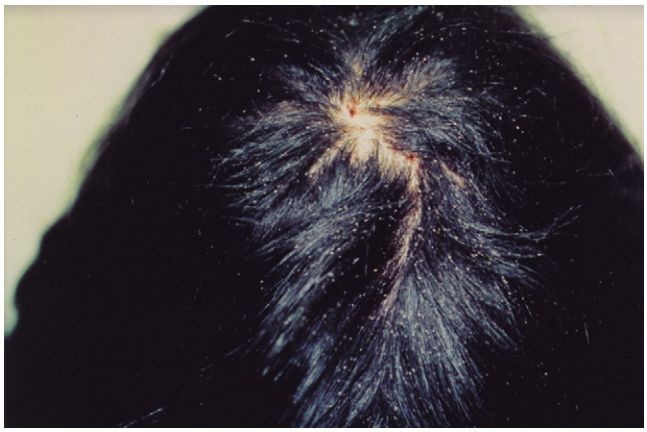

Figure 118-15. Nits as seen in head lice. (Courtesy of David Effron, MD.)

Figure 118-16. Body lice. (Courtesy of David Effron, MD.)

Figure 118-17. Body lice. (Courtesy of David Effron, MD.)

the hair is shampooed and dried. It is rinsed out with water after 10 minutes. It must be applied when the hair is dry because lice can close down their respiratory airways for up to 30 minutes when immersed in water.[77] Higher cure rates are achieved if the dose is repeated 1 week after the initial usage.

Because the condition may be spread by sexual contact, sexual partners should also be treated. Other uninfested household members need not undergo a course of therapy. Underclothing, pajamas, and sheets and pillowcases should be machine washed (hot water) and dried, laundered and ironed, or boiled. Pruritus that persists after the course of therapy may result from an irritation of the skin by the pediculicide, sensitization, or patient anxiety.

Permethrin is used to treat pediculosis capitis. A single dose of oral ivermectin, 200 μg/kg repeated in 10 days, has been shown to eradicate head lice.[77] Lindane should be reserved for treatment failures. Household contacts should be examined for involvement, but uninfected persons need not be treated.

Figure 118-18. Scabies. (Courtesy of David Effron, MD.)

Scabies

Clinical Features

Scabies is a mite infestation characterized by severe itching, which usually worsens at night. The areas of the body most commonly involved are the interdigital web spaces, flexion areas of the wrists, axillae, buttocks, lower back, penis, scrotum, and breasts (Fig. 118-18). The infestation tends to be more generalized in infants and children than in adults. The typical lesions are reddish papules or vesicles surrounded by an erythematous border and scratch marks. Scabies in infants and young children often have generalized skin involvement, including the face, scalp, palms, and soles. In infants, the most common presenting lesions are papules and vesiculopustules.[78]

Nodular scabies is a clinical variant in which extremely pruritic nodules are present on the male genitalia, buttocks, groin, and axillary regions. The nodules are reddish to brown, do not contain mites, and are thought to represent hypersensitivity reactions. They can persist for weeks despite adequate scabicidal treatment.

Immunosuppressed patients may develop Norwegian scabies, which is manifested by extensive hyperkeratosis and crusting of the hands, feet, and scalp. It is highly contagious because of excessive mite proliferation.[79,80] Secondary infections of these lesions are common.

Close personal contact is involved in transmission of scabies. Multiple family members are likely to become infested. The infestation is also transmitted with sexual contact.

Management

Treatment options include crotamiton (Eurax) lotion and cream or permethrin 5% cream (Elimite) and ivermectin. Lindane is no longer the preferred treatment. Patients in

whom the former treatment fails may respond to the latter. Permethrin 5% cream (Elimite) applied overnight once weekly for 2 weeks over the entire body is the treatment of choice for infants and small children. It is more effective than crotamiton (Eurax) in eliminating the mite, in reducing secondary bacterial infection, and in reducing pruritus. Postscabietic nodules and pruritus may persist for months, even after successful treatment.[62,63,66,67] Treatment of Norwegian scabies may require repeated treatment with scabicides and sometimes sequential use of several agents.

A single dose of oral ivermectin, 200 µg/kg, may also be used.[81] A second dose given 1 week later has been demonstrated to substantially improve the cure rate. Patients with crusted scabies may require repeat doses of ivermectin (200 µg/kg) along with topical scabicides (full-body application, repeated initially every few days) and keratolytics.

The full benefit of ivermectin becomes evident when eradication of scabies in epidemic or endemic situations is needed since ivermectin leads to reliable disease control.[82] The safety of ivermectin has been documented in millions of people with microfilarial diseases. Although ivermectin does not normally penetrate the blood-brain barrier and there should be no risk of seizures, neurotoxicity has been reported in the elderly.[83] Because of limited safety data, ivermectin should not be used in children younger than 5 years or during pregnancy or lactation.

The essential oil of the tea tree (*Melaleuca alternifolia*) and the essential oil of the *Lippia multiflora* Moldenke have also been noted to have scabicidal and antibacterial activity, although the dosing schedule of tea tree oil has not been established.[84]

All family members and sexual contacts should also be treated. Intimate articles of clothing and sheets and pillowcases should be washed and dried by machine (hot water), laundered and ironed, or boiled.

It may take several weeks after therapy for the signs and symptoms to abate. A hypersensitivity state or anxiety may prolong symptoms long after the mites have been destroyed.

Syphilis

Clinical Features

Syphilis is transmitted only by direct contact with an infectious lesion. The causative organism is the spirochete *Treponema pallidum*. After an incubation period of 10 to 90 days, the primary lesion appears, which lasts from 3 to 12 weeks and heals spontaneously. In 6 weeks to 6 months after exposure, the disease enters the secondary stage, which involves a variety of mucocutaneous lesions. These lesions also heal spontaneously in 2 to 6 weeks as the disease enters the latent phase. Either a prolonged latent phase or tertiary syphilis follows. Of untreated patients, 25% display at least one relapse of mucocutaneous lesions of the oral cavity or anogenital region.

The chancre is the dermatologic manifestation of primary syphilis. Chancres usually appear as single lesions but may be multiple. They appear at the site of spirochete inoculation, usually the mucous membranes of the mouth or genitalia. The chancre begins as a papule and characteristically develops into an ulcer approximately 1 cm in diameter with a clean base and raised borders. The chancre is painless unless secondarily infected, and it may be accompanied by painless lymphadenopathy.

The secondary stage usually follows the primary stage by 6 weeks or more but rarely overlaps primary syphilis. There are a number of cutaneous manifestations of secondary syphilis. Lesions may be erythematous or pink macules or papules, usually with a generalized symmetrical distribution (Fig. 118-19). Pigmented macules and papules classically appear on the palms and soles (Figs. 118-20 and 118-21). The lesions may be scaly but are rarely pruritic.

Papular, annular, and circinate lesions are more common in people of color. Generalized lymphadenopathy and malaise accompany the skin lesions. Irregular, patchy alopecia may be seen. Moist, flat, verrucous condyloma latum may appear in the genital area. These lesions are highly contagious.

Figure 118-19. Secondary syphilis. (Courtesy of David Effron, MD.)

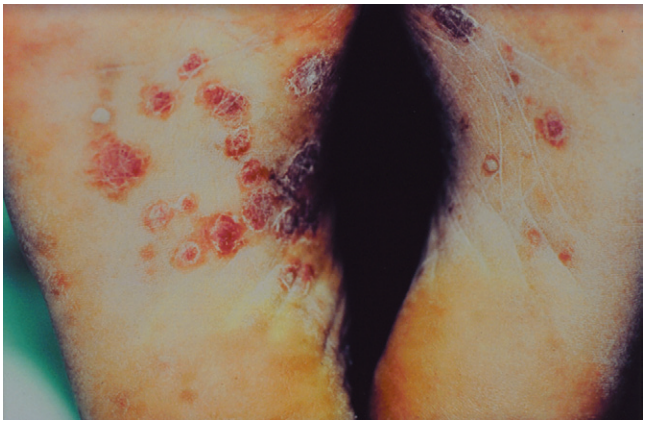

Figure 118-20. Cutaneous manifestation of secondary syphilis on the soles of the feet. (Courtesy of David Effron, MD.)

Figure 118-21. Cutaneous manifestation of secondary syphilis on the palms of the hands. (Courtesy of David Effron, MD.)

Diagnostic Strategies

The diagnosis of primary syphilis is made primarily by the identification of spirochetes with darkfield microscopy. Because a darkfield microscope is often not available to the emergency physician, the diagnosis of primary syphilis must be suspected on clinical grounds and the patient referred to a dermatologist or appropriate public agency for diagnosis and treatment. The Venereal Disease Research Laboratory (VDRL) test, the most commonly used diagnostic serologic test, is positive in approximately three fourths of patients with primary syphilis, but the test tends to be negative early in the course of the disease.[53]

The VDRL test is invariably positive in cases of secondary syphilis, usually in titers of 1:16 or greater. The darkfield examination of moist lesions may also be positive, but the diagnosis in this stage is based on a positive serologic test. The most specific and sensitive serologic test is the fluorescent treponemal antibody absorption (FTA-ABS) test.[53]

A biologic false-positive serologic test for syphilis is defined as a positive VDRL test with a negative FTA-ABS test. This situation is seen acutely after vaccination or infections, especially mycoplasmal pneumonia, mononucleosis, hepatitis, measles, varicella, and malaria, and in pregnancy. Chronic biologic false-positive reactions (i.e., those lasting longer than 6 months) may occur with systemic lupus erythematosus, thyroiditis, lymphoma, narcotic addiction, or in elderly patients. Most false-positive reactions are in low titer ranges of 1:1 to 1:4.

Management

Incubating syphilis, the stage before the appearance of primary lesions, may be treated with 4.8 million units of procaine penicillin IM after 1 g of probenecid orally. Primary and secondary syphilis is treated with benzathine penicillin G in a dose of 2.4 million units IM. Patients allergic to penicillin should be treated for 14 days with doxycycline, 100 mg twice a day, tetracycline, 500 mg four times a day, or erythromycin, 500 mg four times a day.[52] HIV-infected patients require more intensive therapy.

Treatment may be administered in the ED if the diagnosis can be made on clinical, microscopic, or serologic grounds. If this cannot be done, a serologic sample should be drawn and the patient referred for treatment. The VDRL test may be expected to return to nonreactive 6 to 12 months after the treatment of primary disease or 1 to 1½ years after the treatment of secondary disease. Patients with tertiary syphilis who are adequately treated may nevertheless retain a positive serologic result. Within 12 hours of receiving therapy, patients may experience a febrile reaction and diffuse rash called the Jarisch-Herxheimer reaction. The reaction resolves spontaneously, usually within 24 hours.

NODULAR LESIONS

Erythema Nodosum

Clinical Features

Erythema nodosum is an inflammatory reaction of the dermis and adipose tissue that is seen with painful red to violet nodules. Nodules are elevated lesions located deep in the skin, and the skin over the nodules can be moved by palpation. These painful nodules occur most commonly over the anterior tibia but may also be seen on the arms or body. Fever and arthralgia of the ankles and knees may precede the rash.[3,9] As the lesions evolve, they may turn yellow-purple and resemble bruises (Fig. 118-22). Women are affected three times more often than men, with the highest incidence in the third to fifth decades of life.[68]

Figure 118-22. Erythema nodosum. (Courtesy of David Effron, MD.)

A number of underlying conditions produce erythema nodosum: tuberculosis, sarcoidosis, coccidioidomycosis, histoplasmosis, ulcerative colitis, regional enteritis, pregnancy, infections with streptococci, *Yersinia enterocolitica*, and *Chlamydia*. As with erythema multiforme, many cases of erythema nodosum are idiopathic. The relationship of drugs to erythema nodosum was noted in the section on drug eruption. Oral contraceptive agents are a leading cause of drug-induced cases. The differential diagnosis includes traumatic bruises and subcutaneous fat necrosis.

Management

When an underlying condition can be determined, this should be treated as indicated. Chest radiograph may be considered to rule out sarcoidosis, tuberculosis, or deep fungal infection. Bed rest, elevating the legs, and wearing elastic stockings reduce pain and edema. Aspirin in a dosage of 600 mg every 4 hours or nonsteroidal anti-inflammatory agents may also afford some relief.[9,85] Erythema nodosum is a self-limited process that usually resolves in 3 to 8 weeks.[9] Patients with severe pain may be treated with 360 to 900 mg of potassium iodide daily for 3 or 4 weeks. Stopping therapy before this time may result in a relapse. Potassium iodide may act through an immunosuppressive mechanism mediated via heparin release from mast cells.[9,85]

VESICULAR LESIONS

Perspective

Vesicles are elevated lesions that contain clear fluid. Vesicles greater than 1 cm are known as bullae. Vesicles may sometimes be associated with red papular lesions, as in contact dermatitis or erythema multiforme.

Pemphigus Vulgaris

Clinical Features

Pemphigus vulgaris is an uncommon, but important, dermatologic disorder. The mortality rate before the use of steroids was approximately 95%. The current mortality rate is 10 to

15%, related more to steroid-induced complications than to the disease. Pemphigus is a bullous disease, affecting both sexes equally, and is most common in patients 40 to 60 years old.[86] The disease is mostly prevalent in people of Jewish, Mediterranean, or south Asian descent.[86]

The typical skin lesions are small, flaccid bullae that break easily, forming superficial erosions and crusted ulcerations. Any area of the body may be involved. Nikolsky's sign is present and characteristic of the disease. Blisters may be extended or new bullae may be formed by firm tangential pressure of a finger on the intact epidermis.

Before the appearance of the skin involvement, mucous membrane lesions occur; 50 to 60% of patients have oral lesions. The oral lesions typically antedate the cutaneous lesions by several months.[9,86] The most common site is in the mouth, especially the gums and vermilion borders of the lips. Oral lesions are bullous but commonly break, leaving painful, denuded areas of superficial ulceration.

The cause of pemphigus is unknown, although studies suggest an autoimmune mechanism. The development of pemphigus has been associated in a few instances with the use of medications, most notably penicillamine and captopril.[9] A positive Tzanck cytologic test suggests the diagnosis (i.e., finding acantholytic cells or degenerated, rounded epithelial cells with amorphous nuclei). Acantholytic cells are not specific for pemphigus, however, and the diagnosis must be confirmed by serum immunofluorescence. The differential diagnosis includes bullous pemphigoid, epidermolysis, dermatitis herpetiformis, toxic epidermal necrolysis, bullous scabies, and bullous systemic lupus erythematosus (Fig. 118-23).[9,86]

Management

Pain control and local wound care are essential components of therapy. Once the diagnosis is made, treatment with oral glucocorticoids in initial doses of 100 to 300 mg of prednisone, or an equivalent drug, should be instituted in conjunction with a dermatologist. Other immunosuppressant drugs may also be used. Despite the condition's localization to the skin and mucous membranes, death was the rule before treatment with steroids, and the mortality rate continues to be substantial.[9] Deaths are related to an uncontrolled spread of the disease, secondary infection, dehydration, and thromboembolism. Other medical illnesses, as well as the side effects of high-dosage corticosteroids, also contribute to mortality.

Figure 118-23. Bullous pemphigus. (Courtesy of David Effron, MD.)

Herpes Simplex

Perspective

Two known variants of HSV cause human infection: HSV-1 and HSV-2. The former primarily affects nongenital sites, whereas lesions caused by the latter are found predominantly in the genital area and are transmitted primarily by venereal contact.

Clinical Features

The hallmark of skin infection with HSV is painful, grouped vesicles on an erythematous base. Those above the waist are usually caused by HSV-1, whereas those below the waist generally result from HSV-2 (Figs. 118-24 and 118-25). The lesions are usually localized in a nondermatomal distribution. The skin distribution may become more generalized in patients with atopic eczema and other dermatoses. Adults with HSV infection should avoid contact with children with atopic dermatitis, especially in the first 3 to 5 days of infection.

Figure 118-24. RSV-1 infection. (Courtesy of David Effron, MD.)

Figure 118-25. Herpetic whitlow. (Courtesy of David Effron, MD.)

The mouth is the most common site of HSV-1 infections. Children are affected more commonly than adults.[9] Small clusters of vesicles appear but are soon broken, leaving irregularly shaped, crusted erosions. The severity of gingivostomatitis varies from the presence of small ulcers to extensive ulceration of the mouth, tongue, and gums accompanied by fever and cervical lymphadenopathy. The infection may be so severe that oral fluid intake is difficult, and dehydration may result. Healing typically occurs in 7 to 14 days, unless a secondary infection with streptococci or staphylococci occurs.

HSV-2 infections in men are seen with either single or multiple vesicles on the shaft or glans penis. Fever, malaise, and regional adenopathy may be present.[53] A prodrome of local pain and hyperesthesia may precede the appearance of the cutaneous lesions. The vesicles erode after several days, become crusted, and heal in 10 to 14 days. Infections in women involve the introitus, cervix, or vagina. Vesicles may be grouped or confluent. Herpetic cervicitis or vaginitis may be the cause of severe pelvic pain, dysuria, or vaginal discharge.[9,53] Recurrence is common, but recurrent episodes tend to be less severe. A correlation based on serologic and epidemiologic data has been discovered between HSV-2 reproductive tract infections and carcinoma of the cervix.[9,53]

Management

Recommended treatment for a first clinical episode of genital herpes is with acyclovir (Zovirax), 200 mg orally five times a day for 7 to 10 days, famciclovir, 125 mg twice a day, or valacyclovir, 500 mg three times a day or until clinical resolution occurs. These agents reduce the duration of viral shedding, accelerate healing, and shorten the duration of symptoms, but they have not succeeded in preventing recurrent episodes.[9] Prophylactic administration of acyclovir may be effective in ameliorating the severity of recurrent genital herpes, but the effects of long-term administration are unknown.[9] Although many episodes of recurrent herpes infection do not benefit from acyclovir therapy, 200 mg five times a day may be given orally for recurrences at the beginning of the prodrome. Famciclovir, 125 mg twice a day for 5 days, and valacyclovir, 500 mg three times a day for the same duration, are equally effective.[9]

Severe initial attacks of genital herpes have been successfully treated with the IV infusion of acyclovir. Admission to the hospital is required, however, because such treatment is necessary for several days, especially for the immunocompromised patient. A mucocutaneous herpes infection in such patients is potentially fatal because it has a propensity for generalization and dissemination to the internal organs.

Supportive care is important and pain control is a major concern. Systemic analgesics and topical anesthetic agents may be useful. Patient education regarding the prevention or spread of the disease during sexual contact and the birth process is imperative.

Varicella

Clinical Features

Varicella, or chickenpox, is an infection caused by the varicella-zoster virus. After an incubation period of 14 to 21 days, the illness begins with a low-grade fever, headache, and malaise. The exanthem coincides with these symptoms in children and follows them by 1 or 2 days in adults.

The skin lesions rapidly progress from macules to papules to vesicles to crusting, sometimes within 6 to 8 hours. The vesicle of varicella is 2 or 3 mm in diameter and surrounded by an erythematous border (Fig. 118-26). An unusual form of varicella presents with larger bullae (Fig. 118-27). The drying of the vesicle begins centrally, producing umbilication. The dried scabs fall off in 5 to 20 days.

Figure 118-26. Chickenpox. (Courtesy of David Effron, MD.)

Figure 118-27. Bullous chickenpox. (Courtesy of David Effron, MD.)

Lesions appear in crops on the trunk, where they are seen in the highest concentration, and on the scalp, face, and extremities. The hallmark of varicella is the appearance of lesions in all stages of development in one region of the body. Extensive eruptions are often associated with a high and prolonged fever.

Complications of chickenpox include encephalitis or meningitis, pneumonia, staphylococcal or streptococcal cellulitis, thrombocytopenia, arthritis, hepatitis, and glomerulonephritis.[73] Varicella pneumonia occurs more commonly in adults than in children.

Management

The illness is self-limited, and treatment is symptomatic only. Salicylates should be avoided in patients with chickenpox to minimize the risk of subsequent Reye's syndrome. Oral acyclovir may be effective if it can be started within 24 hours of development of rash for patients with chronic respiratory or skin disease. Some studies report a diminution in duration and magnitude of fever and number and duration of lesions with the early use of acyclovir.[74]

Isolation of infected patients is often futile because the disease may be transmitted before the diagnosis is clinically evident. Because the disease has the potential to be contagious until all vesicles are crusted and dried, infected persons should be kept at home until this stage is reached.

Varicella-zoster and varicella titers should be checked in pregnant women and immunocompromised patients who are exposed to chickenpox, and if negative, varicella-zoster immune globulin should be administered within 96 hours of exposure.[87] Fetal infection after maternal varicella in the first or early second trimester of pregnancy may result in varicella embryopathy, a condition characterized by limb atrophy, scarring on extremities, and CNS and ocular manifestations.[34] Maternal varicella that occurs between 5 days before delivery and 2 days after delivery may result in disseminated herpes in the newborn.[34]

The varicella vaccine is a live attenuated virus; it is highly efficacious and very safe.[88] A single dose is effective in children between the ages of 1 and 13 years. For older children, two doses separated by 4 to 8 weeks is recommended.[88] In addition, the incidence of zoster occurring after vaccination appears to be lower than after naturally acquired disease.[88]

Herpes Zoster

Clinical Features

Herpes zoster, or shingles, is an infection caused by the varicella zoster virus. It occurs exclusively in individuals who have previously had chickenpox. Before the rash appears, the patient typically develops pain in a dermatomal distribution. This pain precedes the eruption by 1 to 10 days; is of variable intensity; and is described as sharp, dull, or burning in quality. The rash consists of grouped vesicles on an erythematous base involving one or several dermatomes. The thorax is involved in most cases, and the trigeminal distribution is the next most commonly involved region.[89]

The vesicles initially appear clear and then become cloudy and progress to scab and crust formation. This process takes 10 to 12 days, and the crusts fall off in 2 or 3 weeks (Figs. 118-28 and 118-29). Herpes zoster has a peak incidence in patients 50 to 70 years old and is unusual in children. Although the association with leukemia, Hodgkin's lymphoma, and other malignancies is well known, rarely does the appearance antedate the diagnosis of such diseases. Most cases of herpes zoster occur in healthy individuals.[89]

Herpes zoster may be transmitted from patients with chickenpox to susceptible individuals. Chickenpox may also be acquired by contact with shingles, although this is less common.[89] It is generally believed, however, that herpes zoster is caused by a reactivation of latent varicella-zoster virus present since the initial infection with chickenpox. During the latent period between the two illnesses, the virus is thought to reside in dorsal root ganglion cells.[9,89]

Herpes zoster has a very low mortality rate and is rarely life threatening, even when dissemination to the visceral organs occurs. Complications include CNS involvement, ocular infection, and neuralgia. Meningoencephalitis, myelitis, and peripheral neuropathy have been reported.

Ocular complications occur in 20 to 70% of cases involving the ophthalmic division of the trigeminal nerve. The severity varies from mild conjunctivitis to panophthalmitis, which threatens the eye.[89] Eye involvement produces anterior uveitis, secondary glaucoma, and corneal scarring. There is a close correlation between eye involvement and vesicles located at the tip of the nose.

Postherpetic neuralgia, pain that persists after the lesions have healed, occurs more commonly in elderly and immunosuppressed patients.[89] It may last a number of months and is often resistant to treatment with standard analgesic medications.

Herpes zoster generally tends to be more severe in immunosuppressed patients, especially those with AIDS, Hodgkin's disease, or other lymphomas.[89] Cutaneous dissemination occurs more commonly in these patients than in the general population. Visceral and CNS dissemination is also more likely to occur in these patients; therefore, they should be considered for hospitalization.

Management

Treatment other than analgesia is rarely necessary. Burow's solution compresses diluted 1:20 to 1:40 in water may be applied to hasten drying. Early systemic corticosteroid therapy may shorten the duration of postherpetic neuralgia but does not lessen the severity of pain or the rate of the healing of the lesions.[90] Antiviral chemotherapy, with acyclovir, famciclovir, vidarabine, foscarnet, valacyclovir, and interferon-α, has been shown to be effective for immunocompromised patients.[89] Postherpetic neuralgia is a complicated problem with few satisfactory solutions. Some success has been achieved using capsaicin cream, but this cannot be applied to inflamed or eroded skin.[9]

Intravenous acyclovir may be of some benefit in the treatment of severe ocular herpes zoster. Treatment includes mydriasis and the application of topical corticosteroids. Unlike the situation with herpes simplex conjunctivitis, eye involvement caused by herpes zoster does not appear to be exacerbated by corticosteroids.

Figure 118-28. Herpes zoster. (Courtesy of David Effron, MD.)

Figure 118-29. Herpes zoster infection. (Courtesy of David Effron, MD.)

Table 118-3 Differentiation of Chickenpox from Smallpox

	CHICKENPOX	SMALLPOX
Prodromal signs/symptoms	Prodromal signs/symptoms absent or mild	1–4 days of systemic signs/symptoms before onset of rash
Illness severity	Illness usually not severe unless complications/immunosuppressed	Very ill from onset, may be toxic
Lesion development	Superficial vesicles developing rapidly (1 day) and in multiple stages in each affected area	Hard, circumscribed pustules developing slowly (over days); lesions in same stage in every affected area
Lesion locations	Commonly on face and trunk, *not* palms and soles	Commonly on face and extremities, including palms and soles
Contagiousness	Contagious until all lesions crusted over	Contagious until *all* scabs have fallen off

Figure 118-30. Smallpox. (From the Centers for Disease Control and Prevention Public Health Image Library [http://phil.cdc.gov].)

Smallpox

The last naturally occurring case of smallpox was in Somalia in 1977. Subsequently, the routine vaccination of the general public was stopped. Except for laboratory stockpiles, the variola virus had been eliminated.[82] Due to recent concerns regarding biological agents as weapons, it is important that smallpox be differentiated from chickenpox (Table 118-3; Fig. 118-30).[91]

Cutaneous Anthrax

Cutaneous anthrax begins as a pruritic pustule or vesicle that enlarges and erodes over 1 or 2 days. Subsequently, a necrotic ulcer with central black eschar is formed.[92] The lesion may be painless and may be surrounded by significant edema (Fig. 118-31).

Figure 118-31. Cutaneous anthrax. (From the Centers for Disease Control and Prevention Public Health Image Library [http://phil.cdc.gov].)

SKIN LESIONS ASSOCIATED WITH SYSTEMIC DISEASE

Numerous systemic illnesses have cutaneous manifestations (Table 118-4; Figs. 118-32 to 118-39). Some of the most common illnesses include AIDS, diabetes mellitus, connective tissue diseases, and endocrine disorders.

CLINICAL FEATURES OF LESIONS ASSOCIATED WITH INTERNAL MALIGNANCY

Cutaneous lesions most directly indicative of an internal malignancy arise from the extension of the tumor to the skin or by hematogenous or lymphatic metastasis. The neoplasms that most commonly produce such a cutaneous extension are lymphomas, leukemias, and carcinomas of the breast, GI tract, lung, ovary, prostate, uterus, and bladder. Skin metastases generally signify a poor prognosis.[93]

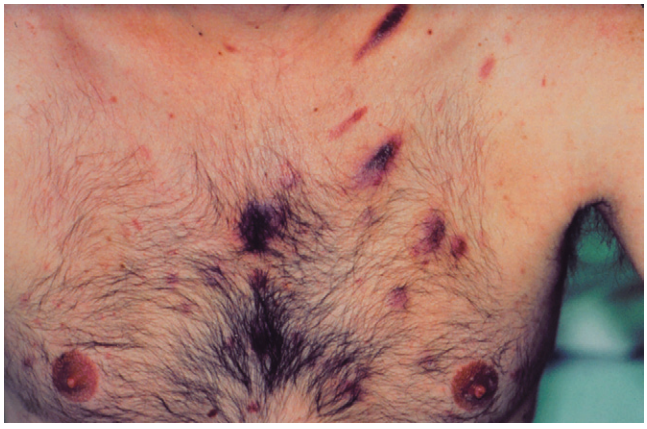

Figure 118-32. Kaposi's sarcoma associated with AIDS. (Courtesy of David Effron, MD.)

Table 118-4 Skin Lesions Associated with Systemic Disease

DISEASE	LESIONS	COMMENTS
AIDS[3,9,87]	Chronic ulcerative herpes simplex	
	Kaposi's sarcoma (Figs. 118-32 and 118-33)	Diagnostic for AIDS
	Severe herpes zoster	
	Oral hairy leukoplakia	
	Genital warts	
	Molluscum contagiosum (Fig. 118-34)	
	Seborrheic dermatitis 2 *Pityrosporum*	
	Recurrent staphylococcal abscesses	
	Mycobacterial papules, nodules, abscesses	
	Oral and rectal squamous cell carcinoma	
	Lymphoma	
	Severe psoriasis	
	Acquired ichthyosis	
	Folliculitis	
	Human papillomavirus infection	
	Lichenoid photoeruptions	
Diabetes mellitus[85]	Diabetic dermopathy	Most common
	Necrobiosis lipoidica diabeticorum	Most characteristic
	Cellulitis (Fig. 118-35)	Control of diabetes does not affect presence
	Vascular ulceration (Fig. 118-36)	
	Acanthosis nigricans	
	Bullosis diabeticorum	
	Diabetic thick skin	
	Scleroderma	
Dermatomyositis	Heliotrope discoloration and edema of eyelids	Skin lesions may precede muscle disease
	Scaly erythema of malar prominences	Symmetrical proximal weakness, remissions, exacerbations
	Erythematous dermatitis over joint extensor surfaces, especially hands (Fig. 118-37)	Increased creatine phosphokinase aldolase with active disease
	Raynaud's phenomenon	
Systemic lupus erythematosus	Discoid lesions	Patients with cutaneous discoid lupus generally have benign diseases
	Malar erythema (Fig. 118-38)	
	Hypertrophic or verrucous palm and sole lesions	
	Lupus panniculitis	
	Oral ulcers	
	Raynaud's phenomenon	
Rheumatoid arthritis	Rheumatoid nodules and necrobiosis	
	Vasculitic lesions	
	Pyoderma gangrenosum	
	Urticaria	Still's disease
Hyperthyroidism[85]	Fine, velvety, smooth skin	
	Increased sweating	
	Hyperpigmentation or hypopigmentation	
	Pretibial edema	
	Alopecia	
	Onychosis	
	Urticaria	
Hypothyroidism[85]	Dry, coarse skin	
	Myxedema (Fig. 118-39)	
	Carotene color	
	Pruritus	
	Atopic dermatitis	
	Ichthyosis	
	Erythema nodosum	
	Easy bruising	
	Alopecia (lateral third of eyebrows)	
Ulcerative colitis[93]	Pyoderma gangrenosum	Associated with state of disease
	Erythema nodosum	
	Aphthous stomatitis	

Figure 118-33. Kaposi's sarcoma in an AIDS patient. (Courtesy of David Effron, MD.)

Figure 118-36. Vascular ulceration secondary to diabetes. (Courtesy of David Effron, MD.)

Figure 118-34. Molluscum contagiosum caused by a virus is more prevalent with AIDS. (Courtesy of David Effron, MD.)

Figure 118-37. Erythematous dermatitis over the joint extensor surfaces, dermatomyositis. (Courtesy of David Effron, MD.)

Figure 118-35. Gangrene of the toe with cellulitis in a diabetic patient. (Courtesy of David Effron, MD.)

Figure 118-38. Malar erythema in a patient with systemic lupus erythematosus. (Courtesy of David Effron, MD.)

Acanthosis Nigricans

Acanthosis nigricans is associated with internal malignancy, despite the fact that most patients do not have tumors.[93] Benign cases may be familial or related to endocrine disease or obesity. The term *malignant acanthosis nigricans* is used to designate the form associated with neoplastic disease. This phrasing is misleading because acanthosis nigricans is only a marker of the underlying disease and is never infiltrated with malignant cells.

The lesion appears as a hyperpigmented verrucous, velvet-like hyperplasia and hypertrophy of the skin accompanied with accentuation of the skin markings. The chief sites of involvement are the body folds, especially the axillae, antecubital fossae, neck, and groin.

More than 90% of cases of "malignant" acanthosis nigricans are associated with intra-abdominal malignancies, of which two thirds are adenocarcinomas of the stomach.[93] Carcinomas of the colon, ovary, pancreas, rectum, and uterus make up the majority of the rest.[93] Regardless of the tumor type, acanthosis

Figure 118-39. Severe myxedema in a hypothyroid patient. (Courtesy of David Effron, MD.)

nigricans is associated with tumors that are usually highly malignant and metastasize early.[93] The mechanism of this dermatosis in cases of internal malignant disease is postulated to be a result of tumor products that bind to and stimulate insulin-like growth factors in the skin.[77]

Dermatomyositis

The incidence of dermatomyositis with malignant disease ranges from 6 to 55% and is generally higher in older patients. In younger individuals, the appearance of dermatomyositis does not necessarily call for a tumor workup. Tumors commonly associated with dermatomyositis are carcinomas of the breast, ovary, and GI and female genital tracts. Polymyositis occurring alone without the accompanying skin findings is rarely associated with malignancies.[85]

Erythema Multiforme

Erythema multiforme may be associated with acute forms of leukemia. It is seen with acute monocytic, lymphocytic, and granulocytic forms and is also found in chronic leukemias and Hodgkin's disease.[9,94]

Erythema Nodosum

Erythema nodosum is another reaction found in association with leukemia and Hodgkin's lymphoma, as well as with metastatic carcinoma and inflammatory bowel disease.[94]

Erythroderma

Generalized erythroderma is almost pathognomonic for Hodgkin's disease; however, it is also a common skin manifestation of lymphocytic leukemia. Although less common, it is also seen with other forms of leukemia, carcinoma, and mycosis fungoides. The appearance of erythroderma may precede the diagnosis of internal malignant disease by many years. The skin eruption is invariably accompanied by intractable pruritus.[94]

Acquired Ichthyosis

Acquired ichthyosis is a skin condition manifested as generalized dryness of the skin, scaling, and superficial cracking or as hyperkeratosis of the palms and soles. Hodgkin's disease is the most common malignant disease associated with the nonfamilial form of ichthyosis. Non-Hodgkin's lymphoma and carcinomas of the breast, lung, colon, and cervix have also been associated with acquired ichthyosis.[85]

BOX 118-1 CAUSES OF PURPURA

Thrombocytopenic
Aplastic anemia
Drug induced
Idiopathic
Malignant disease
Sarcoidosis
Splenomegaly
Systemic lupus erythematosus
Thrombotic
Tuberculosis

Nonthrombocytopenic
Drugs
Infection (meningococcemia, Rocky Mountain spotted fever)
Qualitative platelet defect
Vasculitis

Pruritus

Itching may be an important indicator of Hodgkin's disease, leukemia, adenocarcinoma or squamous cell carcinoma of various organs, carcinoid syndrome, multiple myeloma, and polycythemia vera. It may appear years before the underlying malignancy is identified.[85] In cases of Hodgkin's disease, the itching is usually continuous and may be accompanied by a severe burning sensation. Although usually generalized, pruritus commonly begins in the feet and may be limited to the lower extremities. It may be intractable and associated with urticaria, erythroderma, excoriation, or lichenification.

The pruritus of leukemia and systemic carcinoma is generally less severe than that found with Hodgkin's disease. Nevertheless, itching associated with internal malignant disease may be difficult to control. Conventional anti-H_1 antihistamines, cimetidine, cholestyramine, and cyproheptadine have each been used with variable results.[94] Occasionally, only the suppression of the tumor is beneficial.

Purpura

Purpura is the most common manifestation of acute granulocytic and monocytic leukemia. It may also be associated with myeloma, lymphoma, and polycythemia vera. Although the most common cause of purpura in these conditions is thrombocytopenia secondary to bone marrow infiltration, in some instances the platelet count is normal and the causative mechanism obscure.[9] Purpura is caused by vascular abnormalities, thrombocytopenia, or other coagulation defects. A variety of diseases and conditions may be the underlying cause, and the treatment should be directed toward this cause whenever possible (Boxes 118-1 and 118-2).[94,95] Thrombocytopenic and nonthrombocytopenic forms are differentiated by the results of the patient's platelet count. Serious bleeding seldom occurs if the platelet count is greater than 50,000/mm^3. If the platelet count is less than 10,000/mm^3 or serious bleeding is encountered, platelet transfusion should be initiated. Because of the short circulating half-life of infused platelets, transfusion should be used as a short-term measure only.

BOX 118-2 COMMONLY USED DRUGS ASSOCIATED WITH PURPURA

Amitriptyline
Aspirin
Cephalothin
Chloramphenicol
Chlorpromazine
Chlorpropamide
Diazoxide
Digitoxin
Furosemide
Hydrochlorothiazide
Indomethacin
Isoniazid
Meprobamate
Methyldopa
Penicillin
Phenacetin
Phenobarbital
Phenylbutazone
Quinidine
Rifampin
Sulfonamides
Tolbutamide

Figure 118-40. Tracks secondary to intravenous heroin abuse. (Courtesy of David Effron, MD.)

Urticaria

Urticaria is occasionally found in Hodgkin's disease and more rarely in leukemia and internal carcinoma. Cold urticaria may occur with multiple myeloma (Table 118-5).

CLINICAL FEATURES OF LESIONS ASSOCIATED WITH NARCOTIC ADDICTION

Individuals who inject opiates and other drugs parenterally develop characteristic skin lesions secondary to such use. Skin lesions have been most extensively described in heroin addicts. Skin tracks, or indurated linear hyperpigmented streaks, are produced by repeated IV injection (Fig. 118-40). They follow the course of the superficial veins used in the injection, most commonly in the antecubital fossae and the dorsa of the hands.

Subcutaneous injection results in round or oval hyperpigmented atrophic depressed scars 1 to 3 cm in diameter (Fig. 118-41). Abscesses, which often require drainage, commonly precede the development of such scars. Hypertrophic scarring

Table 118-5 Common Causes of Urticaria

CAUSE	COMMON RESPONSIBLE FACTORS
Bacterial infection	*Streptococcus* *Staphylococcus* *Yersinia* *Mycobacterium*
Viral infection	Herpes simplex virus Epstein-Barr virus Cytomegalovirus Hepatitis viruses (especially B) Many acute viral syndromes (adenovirus, enterovirus)
Other infections	Parasites Coccidioidomycosis Histoplasmosis *Rickettsia* Spirochete (Lyme disease)
Envenomation	Bees Wasps Scorpions Spiders Jellyfish Fleas Mites
Drugs	Penicillin Sulfa Cephalosporins Salicylates Morphine, codeine, other opioids Nonsteroidal anti-inflammatory drugs Barbiturates Amphetamines Blood and blood products
Foods	Nuts Shellfish Eggs Strawberries Tomatoes Milk, cheese Chocolate
Contacts	Chemicals Cosmetics Topical medications Plants Textiles Foods
Inhalants	Dust Pollen Animal dander Chemicals/aerosols Mold spores
Physical agents	Heat Cold Light Pressure (dermatographism) Water
Diseases	Collagen vascular disease Lupus, juvenile rheumatoid arthritis, polyarteritis nodosa, dermatomyositis, Sjögren's syndrome, rheumatic fever Inflammatory bowel disease Crohn's disease, ulcerative colitis Malignancy Carcinoma, leukemia, lymphoma Miscellaneous Serum sickness, thyroiditis, aphthous stomatitis, Behçet's disease

Data from Edwards L: Dermatology in Emergency Medicine. New York, Churchill Livingstone, 1997; and Westo WL, Badgett JT: Urticaria. Pediatr Rev 19:240, 1998.

Figure 118-41. Scars from subcutaneous illicit drug injection. (Courtesy of David Effron, MD.)

and keloid formation may also occur. Increased pigmentation may occur in sun-exposed areas and at the site of tourniquet applications.

In addition to the characteristic skin lesions associated with drug injection, people who inject intravenous drugs are prone to sharp foreign body retention, pseudoaneurysm, gram-negative local and systemic infections, wound botulism (associated with the use of black tar heroin), and numerous other illnesses.

KEY CONCEPTS

- Infection with *C. albicans* can occur normally in infancy, in obese people, during pregnancy, and in old age. In other patients, the following underlying problems should be considered: AIDS and other immunodeficiency states, diabetes and other endocrine imbalances, malignancy, malnutrition, and other debilitating illnesses.
- Rashes that are associated with mucosal lesions, blisters, or desquamating skin are often caused by significant soft tissue infections, drug eruptions, or immune disorders.
- Purpura result from blood leaking from vessels into the skin and do not blanch when pressure is applied. Purpura less than 3 mm in diameter are called petechiae. Nonpalpable purpura are often caused by coagulation defects (usually platelet abnormalities), whereas palpable purpura are usually a sign of vasculitis.
- Diffuse pruritus in the absence of a skin rash may be a sign of underlying malignancy.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 119 Anemia, Polycythemia, and White Blood Cell Disorders

Timothy G. Janz and Glenn C. Hamilton

ANEMIA

Definition

Anemia is an absolute decrease in the number of circulating red blood cells (RBCs). The diagnosis is made when laboratory measurements fall below accepted normal values (Table 119-1).

In emergency medicine, anemia may be divided into two broad categories: emergent, having immediate life-threatening complications, and nonemergent, with less imminent patient danger. Factors other than the absolute number of circulating RBCs may place the patient in one category or another (e.g., rate of onset and underlying hemodynamic reserve of the patient).[1,2] Both groups necessitate a sound diagnostic approach, but emergent anemia may require supportive therapy concomitant with or in advance of the definitive diagnosis. Although patients with nonemergent anemia are usually referred to a specialist, they are seen in the hospital often enough to make an understanding of anemia necessary for emergency physicians. The urgency of consultation depends predominantly on the patient's hemodynamic tolerance of the anemia.[1,3]

Pathophysiology

The major function of the RBC is oxygen transport from the lung to the tissue and carbon dioxide transport in the reverse direction. Oxygen transport is influenced by the amount of hemoglobin, its oxygen affinity, and blood flow. An alteration in any of the major components usually results in compensatory changes in the other two. For example, a decrease in hemoglobin from anemia is compensated by both inotropic and chronotropic cardiac changes that result in increased blood flow and decreased hemoglobin affinity at the tissue level, thereby allowing more oxygen release. These compensatory responses may collapse because of disease severity or underlying pathologic conditions. The result is tissue hypoxia and eventual cell death.[1,4]

Anemia often stimulates the compensatory mechanism of erythropoiesis controlled by the hormone erythropoietin. Erythropoietin is a glycoprotein produced in the kidney (90%) and the liver (10%). It regulates the production of RBCs by controlling differentiation of the committed erythroid stem cell. It is stimulated by tissue hypoxia and products of RBC destruction during hemolysis. Erythropoietin levels are elevated in many types of anemia.[5,6]

Bone marrow contains pluripotent stem cells that can differentiate into erythroid, myeloid, megakaryocytic, and lymphoid progenitors. Erythropoietin enhances the growth and differentiation of erythroid progenitors. When the late normoblast extrudes its nucleus, it still contains a ribosomal network, which identifies the reticulocyte (Fig. 119-1). The reticulocyte retains its ribosomal network for approximately 4 days, 3 of which are spent in bone marrow and 1 in the peripheral circulation. The RBC matures as the reticulocyte loses its ribosomal network and circulates for 110 to 120 days. The erythrocyte is then removed by macrophages that detect senescent signals.

Under steady-state conditions, the rate of RBC production equals the rate of destruction. RBC mass remains constant because an equal number of reticulocytes replace the destroyed, senescent erythrocytes during the same period.[5]

Common sites of blood loss in trauma include the pleural, peritoneal, pelvic, and retroperitoneal spaces. In nontraumatic circumstances, especially in patients on anticoagulants, the gastrointestinal tract, retroperitoneal space, uterus, and adnexa must be considered.

Causes other than blood loss may be responsible for severe anemia of rapid onset. Certain rare hemolytic conditions can cause rapid intravascular destruction of RBCs (Box 119-1). More common are patients with chronic compensated hemolytic anemia (e.g., sickle cell disease), who decompensate with an acute-onset anemia as a result of decreased erythrocyte production triggered by a viral infection.

Beyond red cell destruction, the status of hemoglobin function must be considered. Impaired hemoglobin transport of oxygen is seen in cases of carbon monoxide poisoning. Methemoglobinemia from nitrates, cyanhemoglobin from cyanide, and sulfhemoglobinemia resulting from hydrogen sulfide may severely decrease functional hemoglobin. These patients often have fatigue, altered mental status, shortness of breath, and other manifestations of hypoxia without signs of RBC loss or volume depletion.[7,8]

Diagnostic Findings in Emergent Anemia

Clinical Features

The most common cause of clinically severe anemia is blood loss. The clinical manifestation of anemia depends on how rapidly the hematocrit falls and also on the patient's ability to compensate.

Table 119-1 Hemogram Normal Values

AGE	HEMOGLOBIN (G/DL)	HEMATOCRIT (ML/DL)	RED BLOOD CELL COUNT ($\times 10^6$)
3 mo	10.4–12.2	30–36	3.4–4.0
3–7 yr	11.7–13.5	34–40	4.4–5.0
Adult man	14.0–18.0	40–52	4.4–5.9
Adult woman	12.0–16.0	35–47	3.8–5.2

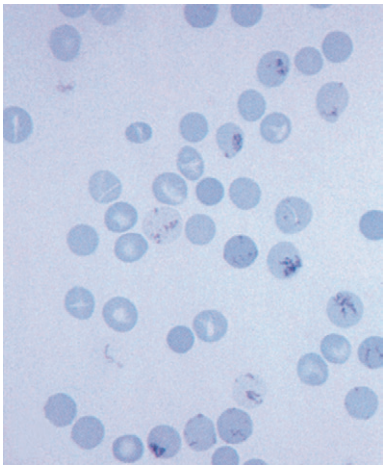

Figure 119-1. Reticulocytes with reticular material after methylene blue staining. (From Hoffbrand AV, Pettite JE: Color Atlas of Clinical Hematology, 3rd ed. London, Mosby, 2000, p 18.)

BOX 119-1 CAUSES OF RAPID INTRAVASCULAR RED BLOOD CELL DESTRUCTION

Mechanical hemolysis associated with disseminated intravascular coagulation
Massive burns
Toxins (e.g., some poisonous venoms—brown recluse spider, cobra)
Infections such as malaria or *Clostridium* sepsis
Severe glucose-6-phosphate dehydrogenase deficiency with exposure to oxidant stress
ABO incompatibility transfusion reaction
Cold agglutinin hemolysis (e.g., *Mycoplasma* organisms, infectious mononucleosis)
Paroxysmal nocturnal hemoglobinuria exacerbated by transfusion
Immune complex hemolysis (e.g., quinidine)

Clinical signs and symptoms include tachycardia, decreased blood pressure, postural hypotension, light-headedness, increased heart rate, and increased respiratory rate. Complaints of thirst, altered mental status, and decreased urine output may also be present. The patient's age, concomitant illness, and underlying hematologic, cerebral, and cardiovascular status tremendously influence the clinical findings. Children and young adults may tolerate significant blood loss with unaltered vital signs until a precipitant hypotensive episode occurs. Pediatric patients may become markedly tachycardic, physiologically attempting to maintain cardiac output, since their ability to increase stroke volume is limited. Elderly patients commonly have underlying disease states that compromise their ability to compensate for blood loss.[9]

BOX 119-2 HISTORY AND PHYSICAL EXAMINATION FOR CLINICALLY SEVERE ANEMIA

History

General
Out-of-hospital status, therapy, response to therapy
Bleeding diathesis
Previous blood transfusion
Underlying diseases, including allergies
Current medications, especially those causing platelet inhibition

Trauma
Nature and time of injury
Blood loss at scene

Nontrauma
Skin: petechiae, ecchymoses
Gastrointestinal: hematemesis, hematochezia, melena, peptic ulcer
Genitourinary: last menstruation, menorrhagia, metrorrhagia, hematuria

Physical Examination

Vital Signs Measured Serially
Blood pressure, pulse, respiratory rate, oxygen saturation
Orthostatic blood pressure and pulse (contraindicated with severe hypotension)
Level and content of consciousness

Skin
Pallor
Diaphoresis
Jaundice
Cyanosis
Purpura, ecchymoses, petechiae
Evidence of penetrating wounds

Cardiovascular
Murmurs, S_3, S_4
Quality of femoral and carotid pulses

Abdomen
Hepatosplenomegaly
Pain, guarding, rebound on palpation
Rectal and pelvic examination
Masses
Stool hemoglobin testing

Pertinent elements of the history and physical examination of patients with acute anemia are listed in Box 119-2.[10]

Ancillary Evaluation

Stabilization of emergent anemia commonly runs parallel to assessment. If the signs and symptoms suggest potential life-threatening conditions, intravenous lines are placed and samples for the following initial laboratory tests are drawn:

1. Complete blood count and peripheral smear
2. Blood sample for type and crossmatch
3. Prothrombin time
4. Partial thromboplastin time
5. Electrolyte levels
6. Glucose level (especially if the patient has altered consciousness)
7. Creatinine level

BOX 119-3 HISTORY AND PHYSICAL EXAMINATION FOR NONEMERGENT ANEMIA

History

Symptoms of anemia
- Chest pain, decreased exercise tolerance, dyspnea
- Weakness, fatigue, dizziness, syncope

Bleeding diathesis
- Bleeding after trauma, injections, tooth extractions
- Spontaneous bleeding, such as epistaxis, menorrhagia
- Spontaneous purpura and petechiae

Sites of blood loss
- Respiratory: epistaxis, hemoptysis
- Gastrointestinal: hematemesis, hematochezia, melena
- Genitourinary: abnormal menses, pregnancies, hematuria
- Skin: petechiae, ecchymoses

Intermittent jaundice, dark urine

Dietary history
- Vegetarianism
- Poor nutrition

Drug use and toxin exposure, including alcohol

Racial background, family history

Underlying disease
- Uremia, liver disease, hypothyroidism
- Chronic disease states such as cancer, rheumatic or renal disease
- Previous surgery
- Miscellaneous

Previous treatment of anemia

Weight loss

Back pain

Physical Examination

Skin
- Pallor
- Purpura, petechiae, angiomas
- Ulcerations

Eye
- Conjunctival jaundice, pallor
- Funduscopic hemorrhage, petechiae

Oral
- Tongue atrophy, papillary soreness

Cardiopulmonary
- Heart size, murmurs, extra cardiac sounds
- Rales, other signs of pulmonary edema

Abdomen
- Hepatomegaly, splenomegaly
- Ascites
- Masses

Lymph nodes

Neurologic
- Altered positions or vibratory sense
- Peripheral neuritis

Rectal and pelvic

8. Urinalysis for free hemoglobin
9. Clotting and unclotted blood samples for later testing

If possible, a blood sample is obtained for measurement of hematocrit in the emergency department. Although it may take hours before the hematocrit correctly reflects the degree of blood loss, the initial value is useful in determining an initial baseline. Occasionally, this value reveals an underlying anemia with the acute blood loss superimposed. Depending on severity, a blood sample is sent for type and crossmatch. Peripheral smear interpretation is done on pretreatment blood samples.

Measurements of coagulation status, electrolytes, glucose, blood urea nitrogen, and creatinine are useful in the diagnosis of underlying disease processes that may relate to the patient's anemia. Values of folate, vitamin B_{12}, iron, total iron-binding capacity, reticulocytes, and direct antiglobulin (Coombs' test) are altered by transfusion. Therefore, pretreatment samples are best saved.[11,12]

Diagnostic Findings in Nonemergent Anemia

Clinical Features

Nonemergent anemias are usually seen in ambulatory patients complaining of fatigue and feeling "washed out." Other voiced complaints include irritability, headache, postural dizziness, angina, decreased exercise tolerance, shortness of breath, and decreased libido. When the anemia is of slow onset, the patient may adapt until the hemoglobin is very low. Alternatively, patients with rapid blood loss may experience lightheadedness or syncope even when the measured hemoglobin is not critically low. For patients without evidence of acute bleeding or emergent condition, elements of history and physical examination may help identify the cause (Box 119-3). Most of these patients do not need immediate stabilization and can be further evaluated as outpatients.

Ancillary Evaluation

The initial laboratory evaluation includes a complete blood count with leukocyte differential, reticulocyte count, peripheral smear (Fig. 119-2), and RBC indices, including mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC).

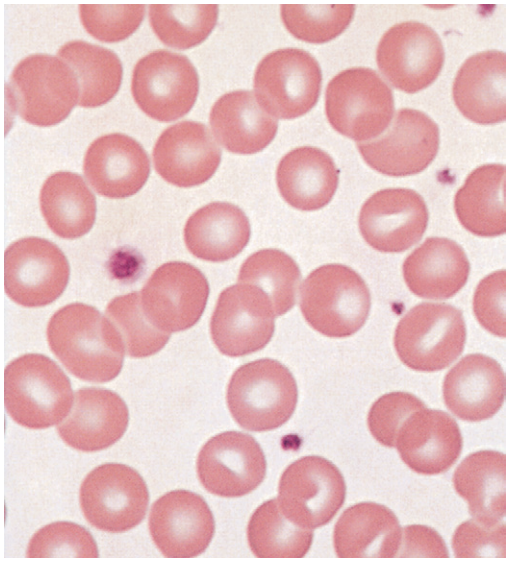

Figure 119-2. Normal smear. (From Hoffbrand AV, Pettite JE: Color Atlas of Clinical Hematology, 3rd ed. London, Mosby, 2000, p 22.)

BOX 119-4 ADMISSION CRITERIA FOR NONEMERGENT ANEMIA

Developing cardiac symptoms, such as shortness of breath or chest pain, or neurologic symptoms
Initial unexplained hemoglobin value less than 8–10 g/dL or hematocrit less than 25–30%
Major difficulty in obtaining outpatient care for patients whose hemoglobin levels are significantly low or when comorbidity is present

BOX 119-5 DIFFERENTIAL DIAGNOSIS OF ANEMIAS CAUSED BY DECREASED RED BLOOD CELL PRODUCTION: SUBCLASSIFICATION BY RED BLOOD CELL INDICES

Hypochromic Microcytic Anemias (Decreased MCV and Hemoglobin Concentration)
Iron deficiency
Thalassemia
Sideroblastic anemia or lead poisoning
Chronic disease (e.g., cancer, renal or inflammatory disease); normochromic and normocytic indices often found

Macrocytic (Elevated MCV)
Vitamin B_{12} deficiency
Folate deficiency
Liver disease
Hypothyroidism

Normocytic (Normal MCV and Hemoglobin Concentration)
Primary bone marrow involvement: aplastic anemia, myeloid metaplasia with myelofibrosis, myelophthisic anemia
Resulting from underlying disease: hypoendocrine state (thyroid, adrenal, pituitary), uremia, chronic inflammation, liver disease

MCV, mean corpuscular volume.

Disposition

Reasonable criteria for the admission of patients with nonemergent anemia are shown in Box 119-4.[12]

Differential Diagnosis

The differential diagnosis of anemia is facilitated by classifying the anemia into one of three groups: decreased RBC production, increased RBC destruction, and blood loss.[12] A complementary approach uses RBC morphology and indices.[13]

Decreased Red Blood Cell Production

Anemias caused by decreased RBC production have a natural history of insidious onset and an associated decreased reticulocyte count. A subclassification by indices of anemias caused by decreased RBC production is listed in Box 119-5. The RBC indices and morphology manifested in a peripheral smear are useful in securing the diagnosis. The definitive diagnosis is usually made outside the emergency department and may require bone marrow examination. The emergency physician rarely initiates replacement therapy, except in circumstances that require transfusion. Appropriate diagnostic tests may be initiated, but replacement of iron, vitamin B_{12}, or folate without proof of cause is unnecessary and unwise.

Table 119-2 Calculation of Red Blood Cell Indices and Normal Values

INDEX	FORMULA FOR CALCULATION	NORMAL RANGE
Mean corpuscular volume	Hematocrit (%) divided by red blood cell count (10^6/μL)	81–100 fL
Mean corpuscular hemoglobin	Hemoglobin (g/dL) divided by red blood cell count (10^6/μL)	26–34 pg
Mean corpuscular hemoglobin concentration	Hemoglobin (g/dL) divided by hematocrit (%)	31–36%

fL, femtoliter.

RBC indices are useful in classifying anemias caused by a production deficit. Their calculation and normal ranges are provided in Table 119-2. MCV is a measure of RBC size. Decreases and increases reflect microcytosis and macrocytosis, respectively. MCH incorporates both RBC size and hemoglobin concentration. It is influenced by both and is the least helpful of the indices. The MCHC index is a measure of the concentration of hemoglobin. Low values represent hypochromia, whereas high values are noted only in patients with decreased cell membrane relative to cell volume, such as in the case of spherocytosis. An additional index is the RBC distribution width (RDW), which is a measure of the homogenicity of the RBCs measured. RDW is automatically calculated as the standard deviation of MCV divided by MCV multiplied by 100. A normal RDW is 13.5 ± 1.5%. It is useful in differentiating iron deficiency from thalassemia.[14]

Microcytic Anemias. Hypochromic microcytic anemias can be subdivided into deficiencies of the three building blocks of hemoglobin: iron (iron-deficiency anemia [Fig. 119-3]), globin (thalassemia), and porphyrin (sideroblastic anemia and lead poisoning). Anemia of chronic disease, a secondary iron abnormality, rounds out the differential diagnosis. Not all microcytic anemias are the result of iron deficiency, and routine iron therapy for a patient with a low MCV and MCHC is inappropriate.

Iron-Deficiency Anemia. Iron deficiency is a frequent cause of chronic anemia seen in the emergency department. It is the most common anemia in women of childbearing age. In older patients, occult blood loss, especially gastrointestinal, may initially appear as iron-deficiency anemia. Because changes in RBC size and hemoglobin content occur only after bone marrow and cytochrome iron stores are depleted, a patient may have early symptoms of iron deficiency (e.g., fatigue) without manifesting changes in RBC structure. Actually, a low MCV is relatively rare in iron-deficiency anemia.

The diagnosis is made by laboratory evaluation of the fasting level of serum iron, serum ferritin, and total iron-binding capacity. The laboratory interpretation and pitfalls are outlined in Table 119-3. A concentrated search for occult blood loss is vital.

Therapy consists of oral iron replacement. A cost-effective form is ferrous sulfate. The dosage is 300 mg for adults (60 mg of elemental iron) or 3 mg/kg/day for children. This medication is generally well tolerated, although it may cause nausea, vomiting, or constipation. Patients should be warned that their stools will be blackened. In rare patients with poor oral tolerance or absorption, parenteral iron therapy may be necessary.

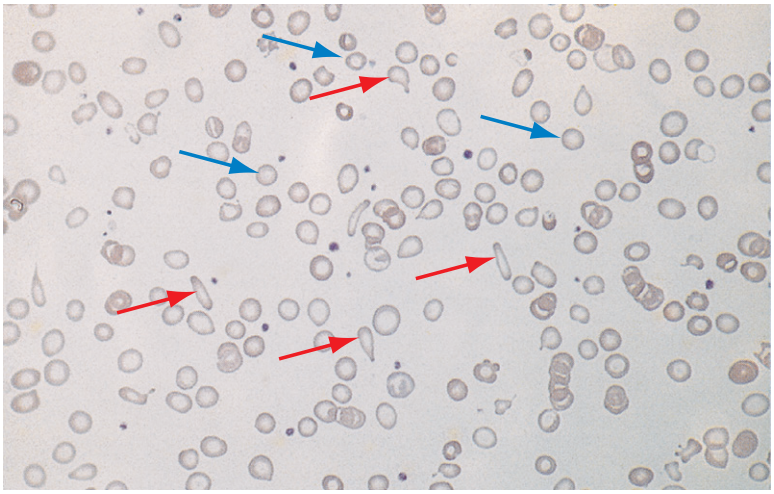

Figure 119-3. Iron-deficiency anemia with hypochromic, microcytic cells and poikilocytes (abnormally shaped cells). (From Hoffbrand AV, Pettite JE: Color Atlas of Clinical Hematology, 3rd ed. London, Mosby, 2000, p 44.)

Table 119-3 Diagnostic Tests for Iron-Deficiency Anemia

TEST	NORMAL RESULT	IRON-DEFICIENCY LEVEL	INTERPRETATION
Fasting serum iron	60–180 µg/dL	<60 µg/dL	Diurnal variation (draw in morning); increased by hepatitis, hemochromatosis, hemolytic anemia, and aplastic anemia; decreased in infection
Total iron-binding capacity	250–400 µg/dL	>400 µg/dL	Increased in late pregnancy or hepatitis; decreased in infection
Percentage of saturation (serum iron) of total iron-binding capacity	15–45%	<15%	
Serum ferritin	10–10,000 mg/mL	<10 mg/mL	Reflects iron stores; may increase as an acute-phase reactant in infection
Bone marrow stainable iron	Hemosiderin granules in reticuloendothelial cells	Absent	Standard for assessment of iron stores

The patient may experience a sense of improvement in as few as 24 hours. Reticulocytosis appears over a 3- or 4-day period in children but may take more than 1 week in adults. The hemoglobin concentration rises on a similar schedule. If such a response does not occur, the patient is noncompliant with the iron supplementation, the blood loss may exceed the replacement, the diagnosis is incorrect, or the diagnosis is partially correct with an additional process complicating the iron deficiency.[15,16]

Thalassemia. Thalassemia is a genetic autosomal defect reflected by the decreased synthesis of globin chains.[17] The globin in hemoglobin is present as two paired chains. Each type of hemoglobin is made up of different globins. For example, normal adult hemoglobin (HbA) is made up of two α chains and two β chains ($\alpha_2\beta_2$). HbA_2 is $\alpha_2\delta_2$, and fetal hemoglobin (HbF) is $\alpha_2\gamma_2$. A separate autosomal gene controls each globin chain. Deletions in this globin gene result in an absence or decreased function of the messenger RNA that codes for the creation of that globin. The various globins (α, β, δ, and γ) may be affected by a number of genetic combinations. The decrease in globin production in thalassemia results in decreased hemoglobin synthesis and ineffective erythropoiesis. The latter is attributable to increased intramarrow hemolysis with destruction of RBCs before they are released. Normal erythropoiesis has a 10 to 20% incidence of ineffective release, with associated intramarrow RBC destruction. This ineffective release of erythropoiesis may double or triple in patients with thalassemia. The cause is believed to be excess chains of the uninhibited globin precipitating in RBCs.[17,18]

Although many variations in thalassemia are possible, only three are commonly considered. Homozygous β-chain thalassemia (thalassemia major) occurs predominantly in Mediterranean populations. It represents one of the most common single-gene disorders. The disease is characterized by severe anemia, hepatosplenomegaly, jaundice, abnormal development, and premature death. Patients are transfusion dependent and die from iron deposition in tissues, particularly the myocardium, or infection. Treatment is supportive and consists of transfusion and iron-chelating therapy.[19,20]

Heterozygous β-chain thalassemia (thalassemia minor) is manifested as a mild microcytic hypochromic anemia with target cells seen on the peripheral smear (Fig. 119-4), an MCV commonly more severely lowered than with iron-deficiency anemia, a normal level of serum iron, and an elevated level of HbA_2 ($\alpha_2\delta_2$) on hemoglobin electrophoresis (2–5%). Usually, no treatment is necessary.

α-Thalassemia varies in spectrum from an asymptomatic carrier state to prenatal death. Four gene loci control this range. In the tolerated forms, it is more commonly seen in Asians and African Americans. Microcytosis, hypochromia,

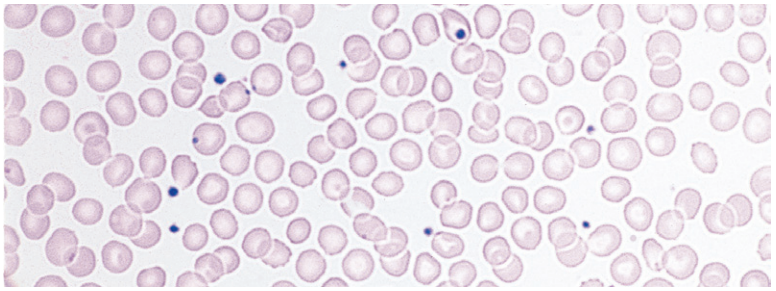

Figure 119-4. β-Thalassemia with microcytic hemochromic red cells and target cells. (From Hoffbrand AV, Pettite JE: Color Atlas of Clinical Hematology, 3rd ed. London, Mosby, 2000, p 96.)

target cells, and basophilic stippling are noted on the peripheral smear. The diagnosis is made with hemoglobin electrophoresis and genetic testing.

Screening for carriers is performed by measurement of RBC indices and estimation of the hemoglobin A_2 concentration. Prenatal diagnosis can be made by analysis of fetal blood and, more recently, by fetal DNA obtained by chorionic villus sampling.

Therapy consists of blood transfusions, which are based on the clinical severity of the anemia. The goals of transfusion therapy include correction of anemia, suppression of erythropoiesis, and inhibition of increased gastrointestinal iron absorption. Iron-chelating therapy, most commonly deferoxamine, is often required to control excess iron stores. Bone marrow transplantation from HLA-identical donors has resulted in disease-free survival in 60 to 90% of recipients, but its role in thalassemia has yet to be determined. Although much interest centers on permanent correction of genetic deficits in thalassemia, gene therapy does not yet exist.[18,21]

Sideroblastic Anemia. Sideroblastic anemia involves a defect in porphyrin synthesis. The resultant impaired hemoglobin production causes excess iron to be deposited in the mitochondria of the RBC precursor, but some also circulates. The result is increased serum iron and ferritin levels, with transferrin saturation. The defective heme synthesis results in ineffective erythropoiesis, mild to moderate anemia, and a dimorphic peripheral smear with hypochromic microcytes along with normal and macrocytic cells.[22]

Sideroblastic anemia, although found in a rare sex-linked hereditary form, is typically a disease of the elderly. Indeed, the idiopathic form is a common type of refractory anemia in elderly patients. Pallor and splenomegaly may be noted, and iron staining of the peripheral smear may demonstrate iron-containing Pappenheimer inclusion bodies in RBCs. Some of these patients are deficient in pyridoxine (vitamin B_6) and respond to treatment with 100 mg of pyridoxine three times a day. Most remain anemic, but a 1- or 2-month pyridoxine trial is acceptable treatment. These patients may be susceptible to iron overload, particularly if long-term transfusion therapy is necessary, but they may respond to iron chelation therapy. Idiopathic sideroblastic anemia is considered a preleukemic state, and acute myelogenous leukemia develops in approximately 20% of these patients.

Secondary causes of sideroblastic anemia include toxins such as chloramphenicol, isoniazid, and cycloserine, as well as diseases such as hemolytic and megaloblastic anemia, infection, carcinoma, leukemia, and rheumatoid arthritis. The exact mechanisms of these causative agents and diseases are unknown. Lead poisoning is one reversible cause of sideroblastic anemia. It may be suggested by the appearance of RBC basophilic stippling on the peripheral smear. Elevated blood lead levels are diagnostic. Alcohol abuse may also result in disordered heme synthesis, which can be corrected by alcohol cessation or by parenteral pyridoxal phosphate in cases of continued abuse. Oral pyridoxine may be ineffective because of impaired conversion to the active form in alcoholic patients.[22]

Anemia of Chronic Disease. Anemia of chronic disease is common and typically normochromic, normocytic. It is characterized by low serum iron levels, low total iron-binding capacity, and normal or elevated ferritin levels. Bone marrow is normal, but staining reveals an abnormality in the mobilization of iron from reticuloendothelial cells. This anemia can be differentiated from iron deficiency by the total iron-binding capacity, the serum ferritin level, bone marrow examination, and nonresponsiveness to a trial of iron therapy. Because the hematocrit is seldom less than 25 to 30%, therapy is not usually required. A complete search for occult blood loss is necessary during the evaluation of this diagnosis because iron deficiency may be superimposed. Disseminated cancer, chronic inflammation, uremia, and infection are common causes.[23-25]

Macrocytic and Megaloblastic Anemia. In terms of the potential for a therapeutic response, the most important cause of macrocytosis is megaloblastic anemia. Megaloblastic anemia is the hematologic manifestation of a total-body alteration in DNA synthesis. The defective DNA synthesis is caused by a lack of the coenzyme forms of vitamin B_{12} and folic acid. The deficiency appears clinically in tissues with rapid cell turnover, including hematopoietic cells and those of mucosal surfaces, particularly in the gastrointestinal tract. Hematopoietically, this deficiency is characterized by ineffective erythropoiesis and pancytopenia. Vitamin B_{12} and folate deficiencies have different developmental histories, but the clinical result may be similar. Differentiation of folate and vitamin B_{12} deficiencies usually depends on measured levels in the laboratory.

Folic acid, absorbed in the duodenum and jejunum, is commonly found in green vegetables, cereals, and fruit. It may be destroyed completely by cooking. The body requires approximately 100 μg/day and usually stores 6 to 20 mg. Therefore, a 2- to 4-month supply is available before megaloblastic changes occur. Causes of folate deficiency are listed in Box 119-6. Most patients with folate deficiency have either an inadequate dietary intake, such as alcoholic patients, or increased use, as in pregnancy.

Vitamin B_{12} is found in foods of animal origin only and is not destroyed by cooking. It is absorbed in the ileum after binding to intrinsic factor. This glycoprotein factor is secreted by the parietal cells of the gastric mucosa and allows low levels of B_{12} to be actively absorbed. The adult requirement is 1 or 2 μg/day, with a body store of 5 mg. Therefore, megaloblastic changes may take up to 4 years to develop after cessation of vitamin B_{12} uptake. The various causes of vitamin B_{12} deficiency are listed in Box 119-7. The most common cause is chronic malabsorption.

Megaloblastic anemia that is not responsive to folate or vitamin B_{12} is commonly related to antimetabolites used in chemotherapy or rare inherited disorders of DNA synthesis.

Table 119-4 lists a number of the problems associated with megaloblastic anemia and their underlying pathologic states.

BOX 119-6 CAUSES OF FOLATE DEFICIENCY

Inadequate Dietary Intake
Poor diet or overcooked or processed food diet
Alcoholism

Inadequate Uptake
Malabsorption with sprue and other chronic upper intestinal tract disorders, drugs such as phenytoin and barbiturates, or blind loop syndrome

Inadequate Use
Metabolic block caused by drugs such as methotrexate or trimethoprim
Enzymatic deficiency, congenital or acquired

Increased Requirement
Pregnancy
Increased RBC turnover: ineffective erythropoiesis, hemolytic anemia, chronic blood loss
Malignancy: lymphoproliferative disorders

Increased Excretion or Destruction or Dialysis

BOX 119-7 CAUSES OF VITAMIN B_{12} DEFICIENCY

Inadequate Dietary Intake
Total vegetarianism: no eggs, milk, or cheese
Chronic alcoholism (rare)

Inadequate Absorption
Absent, inadequate, or abnormal intrinsic factor, as seen in patients with pernicious gastrectomy and anemia. In the latter, autoimmune antibodies act against gastric parietal cells and intrinsic factor. Abnormal ileum, as can occur in sprue and inflammatory bowel disease

Inadequate Use
Enzyme deficiency
Abnormal vitamin B_{12}–binding protein

Increased Requirement by Increased Body Metabolism

Increased Excretion or Destruction

Table 119-4 Clinicopathologic Correlation of Manifestations of Megaloblastic Anemia

CLINICAL FEATURES	PATHOLOGIC CONDITION
Lemon yellow skin	Combination of pallor with low-grade icterus from ineffective erythropoiesis
Petechiae, mucosal bleeding	Thrombocytopenia
Infection	Leukopenia
Fatigue, dyspnea on exertion, postural hypotension	Anemia
Sore mouth or tongue	Megaloblastosis of mucosal surfaces
Diarrhea and weight loss	Malabsorption from mucosal surface change
Paresthesias and ataxia	Related to myelin abnormality in vitamin B_{12} deficiency only

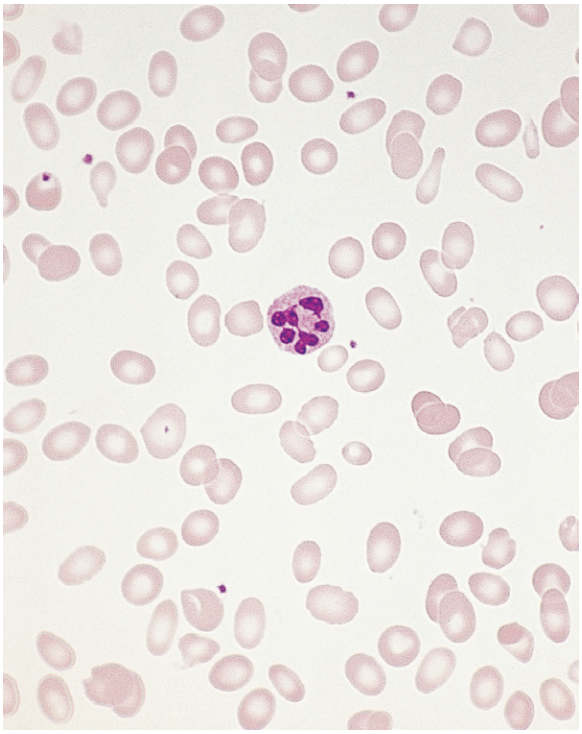

Figure 119-5. Megaloblastic anemia with macrocytic red cells and hypersegmented polymorphonuclear neutrophils. (From Hoffbrand AV, Pettite JE: Color Atlas of Clinical Hematology, 3rd ed. London, Mosby, 2000, p 61.)

A unique feature of vitamin B_{12} deficiency is its neurologic involvement. Patients may have paresthesias in their hands and feet, decreased proprioception, or decreased vibratory sense. The insidiously developing classic neurologic complex includes loss of proprioception, weakness and spasticity of the lower extremities with altered reflexes, and variable mental changes such as depression, paranoid ideation, irritability, and forgetfulness. The latter two complaints have also been noted with folic acid deficiency. Vitamin B_{12}–deficient patients have some of the lowest hemoglobin levels seen in any disease state.[26]

Macrocytic anemia is suggested when the MCV is greater than 100 fL^3, but other criteria must be met for megaloblastosis to be considered the cause of the macrocytic anemia. On the peripheral smear, large oval red cells (macro-ovalocytes) and hypersegmented polymorphonuclear neutrophils are believed to be diagnostic (Fig. 119-5). A bone marrow aspirate may reveal morphologic changes consistent with megaloblastic erythropoiesis. Other potentially useful laboratory tests include vitamin B_{12} and folate levels, red cell folate, and lactate dehydrogenase (LDH). Laboratory techniques, values, and interpretations are listed in Table 119-5. Once megaloblastic anemia is diagnosed and folate or vitamin B_{12} deficiency determined, standard diagnostic regimens are followed to determine the precise origin of the deficiency.

Because one deficiency may cause gastrointestinal absorption changes that beget other deficiencies, the emergency physician may be forced to initiate therapy before the final diagnosis is made. However, a caution is given to obtain necessary laboratory specimens before pursuing this course. The usual dosage for patients with megaloblastic anemia secondary to folate deficiency is 1 mg of oral folic acid per day. Parenteral administration is generally unnecessary because most cases are due to dietary deficiency. In contrast, malabsorption is the most common cause of vitamin B_{12} deficiency, and parenteral

Table 119-5 Serum Tests for Diagnosis and Differentiation of Megaloblastic Anemia

TEST	TECHNIQUE	VALUE	INTERPRETATION
Vitamin B_{12}	Microbiologic or radioisotope	Normal: 300–900 µg/L Deficient: <200 µg/L	Although they may overlap clinically, vitamin B_{12} is usually normal in folate deficiency.
Folate	Microbiologic or radioisotope	Deficient: <3 µg/L	Vitamin B_{12} deficiency may elevate folate levels by blocking transfer of serum folate to RBCs; hemolysis may elevate folate levels.
Red cell folate	Calculated	Normal: 200–700 µg/L Folate deficiency: <140 µg/L	Index of tissue folate is less influenced by diet and is increased in vitamin B_{12} deficiency because of block.
Lactate dehydrogenase	Spectrophotometric	Normal: 95–200 IU Megaloblastic anemia: 4–50 times normal	Normal in other macrocytic anemias; elevated two to four times normal in hemolytic anemias; isoenzymes may be helpful.

therapy is initiated at 100 µg/day intramuscularly for the first 7 to 10 days. Thereafter, only monthly 100-µg doses are necessary. The response is often dramatic, with reticulocyte counts rising up to 30 to 50% and normalization of RBC, white blood cell (WBC), and platelet counts in 6 to 8 weeks. The use of vitamin B_{12} or folate supplements in patients with undiagnosed anemia is to be discouraged. The use of routine vitamin B_{12} injections in the elderly has decreased but is still a too common practice.[26,27]

Macrocytic anemias unrelated to megaloblastic changes are seen frequently. Liver disease, often associated with alcoholism, is the most common cause.[29] Macrocytic target cells may be seen on the peripheral smear in conjunction with this disorder. Hypothyroidism and hemolysis may also be manifested as macrocytic anemia. Screening tests to differentiate between megaloblastic anemia and macrocytic anemia of other causes include a peripheral smear for macro-ovalocytes, hypersegmented polymorphonuclear neutrophils, and the LDH level.[26,28]

Normochromic and Normocytic Anemias. The origin of normochromic and normocytic anemia secondary to decreased production is not as obvious as that of macrocytic and microcytic anemia because the latter give clues to their origin by alterations in RBC indices. One hematologic parameter that can aid in the diagnosis of normocytic anemia associated with hypoproduction is the corrected reticulocyte count. Reticulocytes reflect RBC production in bone marrow. They are RBCs released from bone marrow every 1 to 3 days and contain residual RNA that can be detected by supravital staining. Reticulocytes have an average MCV of 160 fL and in sufficient numbers can increase the MCV of the total erythrocyte count. The reticulocyte count is expressed as a percentage of the total RBC population and must be related ("corrected") to the RBC count of the patient. Thus, the corrected reticulocyte count is equal to the measured percentage of reticulocytes times the patient's hematocrit (%) divided by 45% (taken as the normal hematocrit). The normal range is 1 to 3%.

Normocytic anemia may be classified as being due to primary bone marrow involvement or a secondary marrow response to underlying disease.

Aplastic anemia is rare but may have severe manifestations. It is suspected in anemic patients with normal indices, a low reticulocyte count, and a history of exposure to certain drugs or chemicals (Table 119-6). It is related to drug or chemical exposure in 50% of cases. Viral hepatitis, radiation, and pregnancy have been associated with aplastic anemia. Another group of patients is considered to have an "autoimmune" origin.

Table 119-6 Aplastic Anemia Caused by Drugs or Chemicals

CAUSE	RELATIVE INCIDENCE (%)
Chloramphenicol	61
Phenylbutazone	19
Anticonvulsants	4
Insecticides	4
Solvents	4
Sulfonamides	3
Gold	3
Benzene	2

From Silver BJ, Zuckerman KS: Aplastic anemia: Recent advances in pathogenesis and treatment. *Med Clin North Am* 64:607, 1980.

The aplastic state may extend to all cell lines and results from destruction by immune-stimulated lymphocytes or failure of the marrow stem cell. Occasionally, only one cell line fails, as in RBC aplasia. This condition represents injury occurring at a later stage of cellular differentiation. The precise diagnosis necessitates bone marrow examination, but the causative factor may be difficult to determine.

General treatment of aplastic anemia includes removal of suspected marrow toxins from the environment, avoidance of aspirin, oral hygiene, and suppression of menses. Transfusions are given in life-threatening circumstances only. Bone marrow or peripheral blood stem cell transplantation from a histocompatible sibling can cure the bone marrow failure, with survival rates of 77 to 90% reported. However, because just 30% of patients have suitably matched sibling donors, only a small number undergo allogeneic transplantation. Immunosuppression with antithymocyte globulin, antilymphocyte globulin, and other cytotoxic chemotherapy is used in the majority of patients who are not stem cell transplantation candidates. Unrelated donors are preferred to avoid sensitization of the patient against the non-HLA antigens that are present in bone marrow from a family donor. The disease has a wide range of severity, and the overall 5-year survival rate is 30 to 40%. Given supportive therapy, up to 80% of patients with severe aplastic anemia still die. Bone marrow transplantation before blood product sensitization has resulted in an 80% 5-year survival rate. This is usually combined with immunosuppressive

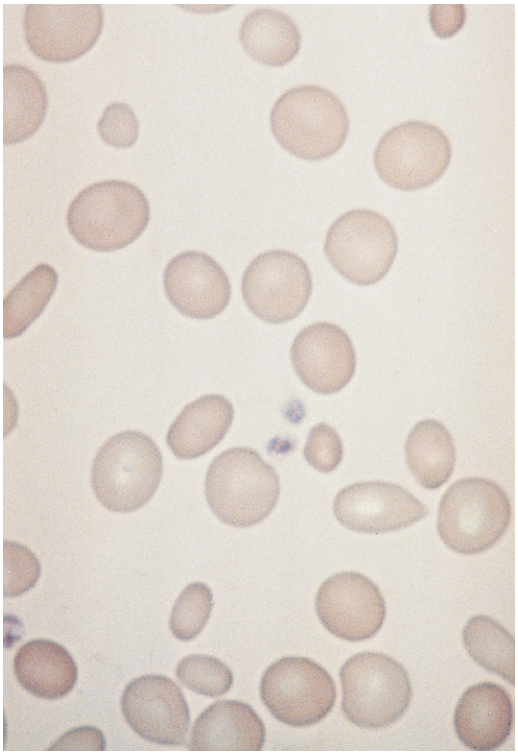

Figure 119-6. Anisocytosis and poikilocytosis. (From Hoffbrand AV, Pettite JE: Color Atlas of Clinical Hematology, 3rd ed. London, Mosby, 2000, p 113.)

therapy consisting of antilymphocyte globulin. Difficulty is still encountered in finding the correct immunologic match.[29,30]

Myelophthisic anemia is bone marrow failure resulting from replacement by an invading tumor, leukemia, lymphoma, or, rarely, a granuloma. A more basic defect or inhibitor may complicate the problem because the degree of anemia cannot always be correlated with the extent of bone marrow invasion. Any patient with oncologic disease may be subject to the development of this type of anemia. Useful clues are signs of extramedullary hematopoiesis, such as hepatosplenomegaly and a leukoerythroblastic peripheral smear that demonstrates immature WBCs, nucleated RBCs, and poikilocytosis (teardrop-shaped red cells) (Fig. 119-6). The final diagnosis is made by bone marrow examination. Therapy is directed at the underlying disorder.[29,30]

Myelofibrosis of unknown origin is the usual cause of primary bone marrow failure associated with extramedullary hematopoiesis. This myeloid metaplasia occurs in the liver and spleen and imparts a blood picture similar to that of myelophthisic anemia. The diagnosis may be made by bone marrow examination. Treatment is supportive, although splenectomy or the use of alkylating agents may be necessary to treat complications of extramedullary blood cell production, such as hepatosplenomegaly.

The hypoplastic anemias of secondary origin are commonly seen as mild chronic anemias with low reticulocyte counts. They have a normal MCV and RDW. Their diagnosis is made by exclusion. Anemia of chronic disease may have microcytic or normocytic indices. It is associated with chronic inflammation (e.g., rheumatoid arthritis, chronic infections such as tuberculosis and osteomyelitis, and malignancy). Hypoendocrinism caused by hypothyroidism, hypoadrenalism, or hypopituitarism results in a hypometabolic state in which the bone marrow responds poorly to erythropoietin. Erythropoietin levels may be low. The anemia of chronic renal failure is thought to be caused by a number of factors. Decreased erythropoietin production, hemolysis, suppression by dialyzable factors, and increased blood loss caused by platelet abnormalities combine to cause mild to moderate anemia. If necessary, it may be corrected by erythropoietin replacement therapy.[31]

Increased Red Blood Cell Destruction

The hemolytic anemias are defined by a shortened life span of the erythrocyte. In their acute form, hemolytic anemias can be devastating and require rapid diagnosis and intervention (see Box 119-1). Fortunately, they are relatively rare in comparison to the chronic hemolytic conditions. Chronic disorders may be related to primary blood disorders (e.g., sickle cell anemia) or may be a result of other disease states (e.g., chronic renal failure). These disorders may be manifested as acute hemolytic anemia if the tenuous balance between red cell production and destruction is upset. If the patient can be demonstrated to have a normal hematocrit and reticulocyte count at the same time, differentiation between acquired and inherited hemolytic anemia is possible.[32]

Clinical Features. The clinical signs and symptoms of hemolytic anemia are, in general, caused by either intravascular or extravascular processes. Although not a precise representation of the underlying pathophysiologic condition, this division assists in the differential approach in the emergency department.

Intravascular hemolysis is usually associated with an acute process and has a dramatic appearance. Large numbers of RBCs may be lysed within the circulation. Pathologically, it primarily involves the handling of released hemoglobin and a compensatory response to an acute decrease in oxygen-carrying capability. Free hemoglobin initially binds to haptoglobin and hemopexin. This complex is transported to the liver, converted to bilirubin, conjugated, and excreted. When this binding and transport system is overwhelmed, free hemoglobin may appear in the blood. Hemoglobin is a large molecule that remains in serum and may tint it pink.

In contrast, myoglobin is a small molecule that is rapidly cleared from serum. Examination of spun whole blood demonstrates clear serum in myoglobinemia, pink serum with free hemoglobin from intravascular hemolysis, and yellow serum from extravascular hemolysis with increased bilirubin production. In severe cases, the latter mechanism may also result in free hemoglobin.

The clinical appearance of intravascular hemolysis may vary from mild chronic anemia, as seen in cases of mechanical hemolysis, to prostration, fever, abdominal and back pain, and mental changes, as seen with transfusion reactions. Jaundice, brown to red urine, and oliguria associated with acute renal failure induced by the hemoglobin complex can also occur.

Extravascular hemolysis is more common and usually better tolerated. Splenic blood flow slows as RBCs travel in the sinusoids close to the reticuloendothelial system, the latter being uniquely designed for removing older or damaged cells. Primary splenic overactivity, antibody-mediated changes, or RBC membrane abnormalities may cause this normal splenic function to increase to a pathologic degree. Hemolysis may also occur within the bone marrow. As stated previously, normal erythropoiesis is ineffective 10 to 20% of the time. This percentage increases when abnormal RBCs are produced, as in thalassemia, megaloblastic anemia, or some hemolytic anemias.[32,33]

After hemoglobin is disassembled in the reticuloendothelial cell, globin returns to the amino acid pool, iron is transported via transferrin to the bone marrow or iron stores, and the pyrrole ring is converted to bilirubin. The unconjugated bili-

BOX 119-8 PERTINENT FACTORS IN THE HISTORY AND PHYSICAL EXAMINATION FOR HEMOLYTIC ANEMIA

History

Alteration of color in urine or feces
Association with drugs, cold, sleep
Early or recent-onset anemia history with symptoms
Ethnic background
Family history of anemia or jaundice
Drug or toxic exposure
Disease states associated with hemolysis, such as systemic lupus erythematosus, renal failure, lymphoma, infectious mononucleosis, prosthetic heart valve

Physical Examination

Jaundice
Hepatosplenomegaly
Ulcerations, particularly in the lower extremities
Enlarged lymph nodes

BOX 119-9 DIAGNOSTIC TESTS FOR HEMOLYSIS

Peripheral blood smear
Corrected reticulocyte index or reticulocyte production index
Haptoglobin levels
Plasma free and urinary hemoglobin
Lactate dehydrogenase level
Fractionated bilirubin level
Direct and indirect Coombs' test
RBC membrane stability (osmotic fragility)

rubin circulates to the liver and is transformed. It is excreted in urine as conjugated bilirubin. The clinical picture of extravascular hemolysis is usually mild to moderate anemia, mild and intermittent jaundice, and enlargement of the spleen. The signs and symptoms vary with the severity and chronicity of the hemolysis.

Ancillary Evaluation. Once hemolysis is suspected, the history and laboratory tests have diagnostic precedence over physical examination. Important historical and physical examination points are listed in Box 119-8.[32,33]

Laboratory Assessment. Important diagnostic tests for hemolysis are provided in Box 119-9.

The blood smear is often more diagnostic than bone marrow examination. The typical cell seen in intravascular hemolysis is the schizocyte (Fig. 119-7). The classic cell of extravascular hemolysis is the spherocyte (Fig. 119-8). It may be seen in congenital spherocytosis but more commonly indicates splenic activity against an antibody-coated RBC membrane. An increase in macrocytes reflects the presence of younger cells associated with reticulocytosis. The specific diagnosis may be made by a blood smear, as with sickled cells or Heinz bodies in glucose-6-phosphate dehydrogenase (G6PD) deficiency.[33,34]

Haptoglobin binds hemoglobin on a molecule-for-molecule basis. Its absence implies saturation and degradation after binding with hemoglobin and is an early finding in hemolysis. It has a normal range of 40 to 180 mg/mL, is decreased in hepatic failure, and increases as an acute-phase reactant. After haptoglobin is bound, hemoglobin binds with hemopexin, transferrin, and albumin before circulating in its free form. Plasma free hemoglobin levels are determined in suspected cases of intravascular hemolysis. The result is considered positive if the level is greater than 40 to 50 mg/dL. Hemoglobin is excreted by the kidney and may be found as a smoky red pigment that is orthotoluidine positive with no associated

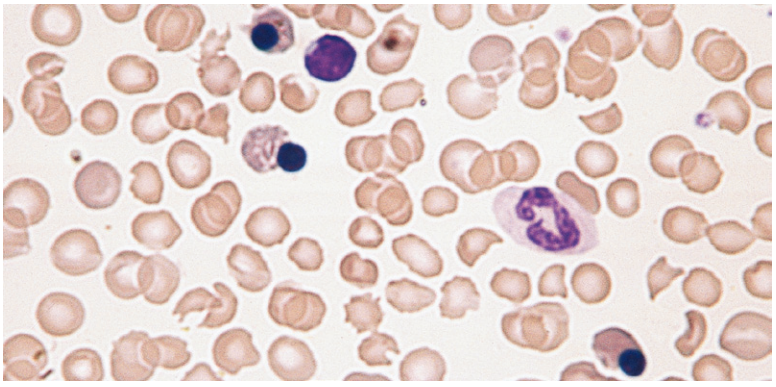

Figure 119-7. Schizocytes (fragmented cell and nucleated red cells). (From Hoffbrand AV, Pettite JE: Color Atlas of Clinical Hematology, 3rd ed. London, Mosby, 2000, p 115.)

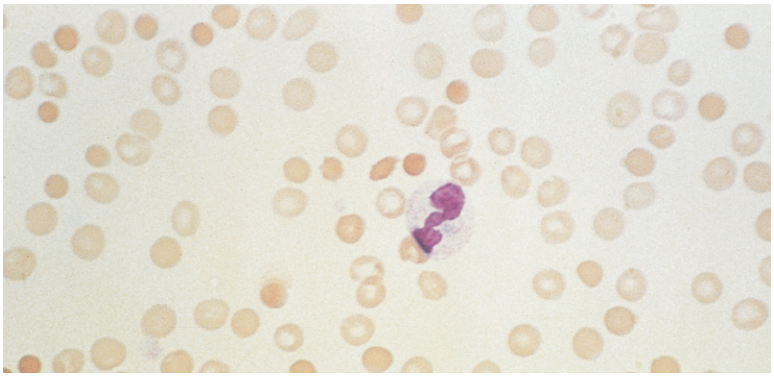

Figure 119-8. Spherocytosis. (From Hoffbrand AV, Pettite JE: Color Atlas of Clinical Hematology, 3rd ed. London, Mosby, 2000, p 115.)

RBCs. Prussian blue–staining granules of hemosiderin may be found intracellularly in renal tubule cells excreted in urine during chronic hemolytic states.[34]

LDH is released when the RBC is broken down peripherally or in the marrow. It is elevated in hemolytic, thalassemic, sideroblastic, and megaloblastic anemia. It may also be seen in cases of uremia, polycythemia vera, and erythroleukemia. Normal levels of LDH range from 95 to 200 IU and may be fractionated.[33,34]

In extravascular hemolysis, bilirubin is often delivered to the liver faster than the conjugating mechanism can handle it. Normal total levels are less than 1.5 mg/dL, and the indirect component amounts to less than 0.5 mg/dL. Conjugated or indirect bilirubin may rise as high as 4 or 5 mg/dL even with normal liver function. Higher levels connote some degree of underlying hepatic insufficiency.[33,34]

The direct antiglobulin (Coombs') test detects antibody or complement on human RBC membranes. It is an essential test in the evaluation of hemolysis. Approximately 90% of patients with autoimmune hemolytic anemia have a positive direct Coombs' test. The indirect test measures antibody titers in serum. The key to the direct antiglobulin test is the reagent. It contains an antihuman IgG that is produced in rabbits. This antihuman IgG in its broad-spectrum form reacts with the IgG, IgM, or C3 proteins that may coat RBCs. The reaction causes an agglutination of RBCs that is graded from 0 to 4. Agglutinating properties depend on the size of the immunoglobulin. IgM is a large antibody form that can bridge the distance between cells, cause agglutination, and fix complement. The direct antiglobulin test is limited in diagnosing IgM-mediated hemolysis. It is best in determining IgG or complement on the RBC surface. IgG is not large enough to cause agglutination, and the antihuman globulin attaches to RBC-bound IgG, which allows agglutination. C3 is detected in a similar manner. Both represent possible immunologic causes of hemolysis. This form of hemolysis is usually mediated extravascularly through the spleen because IgG is a poor initiator of the complement system. The direct antiglobulin test evaluates the RBC surface for immunologic markers. The indirect test assumes that IgG or C3 is in the serum and tests for serum antibody activity against RBCs. Positive tests for immunologic markers do not correlate agglutination activity with the severity of hemolysis.[35]

Differential Diagnosis. Hemolytic anemias may be classified as congenital or acquired, Coombs' positive or Coombs' negative, or caused by processes intrinsic or extrinsic to the cell membrane. The last method gives a useful differential classification of hemolysis (Box 119-10).

Intrinsic Enzyme Defects. Eighty-five to 90% of the membrane-sustaining energy production of the erythrocyte is through the anaerobic glycolytic pathway. At least eight known enzyme deficiencies are associated with this pathway. The most common is pyruvate kinase, deficiency of which is seen as hemolytic jaundice and is usually diagnosed in infancy.[36]

The remaining 10 to 15% of RBC glycolysis occurs by way of the hexose monophosphate shunt. This bypass mechanism occurs in the early stages of the glycolytic pathway and generates reduced nicotinamide adenine dinucleotide phosphate (NADPH), which is important in maintaining reduced glutathione. Glutathione is essential in the protection of hemoglobin from oxidant injury. A deficiency of the first enzyme in this pathway, G6PD, occurs in 11% of African American men. In this form, the enzyme deteriorates with age, and older RBCs are subject to hemolysis by oxidant stress. G6PD deficiency is sex linked and has a wide range of severity. The most common form in African Americans is self-limited because as the bone marrow responds, younger cells with more normal levels of G6PD predominate and can handle the oxidant stress. The variants in Sicilians, Greeks, and Arabs can be particularly devastating. The clinical manifestation is usually an acute hemolytic episode that may be both intravascular and extravascular in appearance. It occurs 24 to 48 hours after the ingestion of an oxidant drug (Box 119-11) or after acute infections such as viral hepatitis. The anemia induced by oxidant drugs is dose related. The older cells lyse at certain drug levels. The oxidant creates forms of activated oxygen, such as peroxide, that either denature the hemoglobin or destroy cell membranes. The former process produces Heinz bodies, which are clumps of denatured hemoglobin found in RBCs early during an episode. These cells are removed by the spleen. The diagnosis is made by enzymatic screening for G6PD, but this test cannot be performed immediately after the hemolytic episode. A 3-week delay avoids a false-negative result caused by a predominance of young cells. Treatment includes volume and RBC support as necessary. Avoidance of oxidant drugs is the only prevention.[37,38]

Intrinsic Membrane Abnormality. These abnormalities are manifested in a number of ways. An altered shape is the main feature of autosomal dominant hereditary spherocytosis or elliptocytosis.

BOX 119-10 CLASSIFICATION OF HEMOLYTIC ANEMIA

Intrinsic

A. Enzyme defect
   1. Pyruvate kinase deficiency
   2. Glucose-6-phosphate dehydrogenase deficiency
B. Membrane abnormality
   1. Spherocytosis
   2. Elliptostomatocytosis
   3. Paroxysmal nocturnal hemoglobinuria
   4. Spur cell anemia
C. Hemoglobin abnormality
   1. Hemoglobinopathies
   2. Thalassemias (anemias)
   3. Unstable hemoglobin
   4. Hemoglobin M

Extrinsic

A. Immunologic
   1. Alloantibodies
   2. Autoantibodies
B. Mechanical
   1. Microangiopathic hemolytic anemia
   2. Cardiovascular, such as prosthetic heart valve disease
C. Environmental
   1. Drugs
   2. Toxins
   3. Infections
   4. Thermal
D. Abnormal sequestrations, as in hypersplenism

BOX 119-11 DRUGS ASSOCIATED WITH HEMOLYSIS IN G6PD DEFICIENCY

Analgesics and antipyretics: acetanilid, aspirin, phenacetin
Antimalarials: primaquine, quinacrine, quinine
Nitrofurans
Sulfa drugs: sulfamethoxazole, sulfacetamide, sulfones
Miscellaneous: naphthalene, fava beans, methylene blue, phenylhydrazine, nalidixic acid

G6PD, glucose-6-phosphate dehydrogenase.

The spleen sequesters these abnormal cells. Clinical sequelae range from compensated asymptomatic anemia to severe life-threatening acquired aplastic crises. The diagnosis is made by reviewing the family history, blood smear, and osmotic fragility testing. Splenectomy is the treatment of choice for patients requiring therapeutic intervention.[36,39]

Paroxysmal nocturnal hemoglobinemia is a stem cell defect causing abnormal erythrocyte, neutrophil, and platelet sensitivity to complement. It is most often seen as chronic hemolysis, hemosiderinuria, leukopenia, and thrombocytopenia. The peripheral smear is normal and the direct Coombs' test is negative. Its major complication is thrombosis, with a predilection for the hepatic vein. Normal activation of complement with the use of sucrose or acid hemolysis (the Ham test) is diagnostic. Transfusion can be a life-threatening hazard in patients with this disease because RBC lysis is caused by donor complement. Because of this danger, only washed packed cells should be used.[39]

Intrinsic Hemoglobin Abnormality. More than 350 types of abnormal hemoglobin have been documented. Problems that may be seen include unstable hemoglobins that appear as Heinz body positive anemia, M hemoglobins that fix iron in its ferric or methemoglobin state, and hemoglobins with increased oxygen affinity that result in tissue hypoxia and erythrocytosis.

Sickle Cell Disease. Sickle cell disease is the most important hemoglobinopathy for the emergency physician. In hospitals serving a large African American population, it is seen on an almost daily basis. Even experienced physicians may overlook major complications, perhaps due to complacency with regard to the patients. Clinicians with less experience may fail to recognize the complexity of the disease and the many potential complications.

Pathophysiology. Sickle cell disease is genetically determined. An abnormal allele at the gene loci for hemoglobin β chains produces altered messenger RNA, which in turn results in replacement of glutamic acid by valine at the sixth position from the N-terminal end of the β chain. On the molecular level, this change causes an interlocking of the affected chain with adjacent hemoglobin in the deoxygenated state. This connection causes the formation of bundles of parallel rods called tactoids. These polymers grow to form a *p*-crystalline gel and then a crystal. This gel formation is facilitated by low pH and reduced by the presence of other hemoglobins, such as HbF. The result is a sickled cell that is less deformable, causes an increase in the viscosity and sludging tendency of blood, and is sequestered in and destroyed by the spleen and liver. These changes may occur when smaller amounts of polymer do not result in a sickled cell and are associated with a RBC membrane leak. The clinical complex of vaso-occlusive events, chronic hemolysis, thrombosis, and organ injury is derived from this pathologic process.[40-44]

The globin in hemoglobin is made up of two pairs of identical polypeptide chains. In normal hemoglobin variants and most clinically significant hemoglobinopathies, the β chains are constant. The gene loci for β chains result in HbA (α_2,β_2). They may have a normal allelic substitution, such as δ chains, and result in HbA_2 (α_2,δ_2) or an abnormal substitution as noted in HbS. Each person has two non–sex-linked gene foci for β chains, one from each parent. The alleles appearing at these loci are both expressed in the formation of RBC hemoglobin. This fact explains the basis for the various HbS syndromes. In sickle cell trait (HbAS), the patient is heterozygous and only one parent contributes the abnormal S allele. In each cell, 50% of the hemoglobin is normal HbA. Sickle disease (HbSS) is homozygous, and all hemoglobin is HbS. Because a parent may contribute alleles other than S, a wide number of variants can exist. Two clinically important S variants are sickle cell-thalassemia and sickle cell-hemoglobin C disease. Therefore, all hemoglobinopathies that cause sickling are not HbS.[40,41]

In addition, HbSS is not limited to the African American population. Up to 10% of patients with various sickling disorders are not ethnically African American.[40-42]

The sickle cell trait is found in 8 to 10% of African Americans. It is usually asymptomatic, although it may also be manifested as decreased urine-concentrating ability, spontaneous hematuria, and rare vaso-occlusive crises with an increased incidence of splenic infarction at high altitudes. No added risk occurs during general anesthesia. The diagnosis is usually made after sickle cell screening (Sickledex) and a characteristic result on hemoglobin electrophoresis. Genetic counseling is a useful service for these patients.[40,41]

Clinical Features. Sickle cell disease can be a recurrent, painful, and frustrating problem for both patients and physicians. It is estimated that less than 10% of a sickle cell population are recurrent emergency department users. The patients are seen in what is considered a vaso-occlusive crisis. Preceding infection, cold exposure, and stress such as trauma are all potential precipitating factors. Many episodes are thought to be spontaneous. The painful crisis is believed to have its origin in tissue ischemia caused by increased viscosity, sludging, and microvascular obstruction as a result of irreversibly sickled cells. Sludging and vascular blockage cause stasis, deoxygenation, and local acidosis, which promote the vicious circle of continued sickling. The pain is commonly deep and aching and is most often found in the abdomen, chest, back, and extremities. The disease may mimic an acute abdomen (e.g., cholecystitis), pulmonary embolus, renal colic, or other painful problems. Neurologic complications are not uncommon and include transient ischemic attacks, cerebral infarction, spinal cord infarction, vestibular hearing problems, and hearing loss.[45] Unfortunately, HbSS may also contribute to these same problems. A directed history that relates this pain pattern to previous sickling episodes, a careful repeated physical examination, and specific organ-related laboratory tests are all the physician has to differentiate "uncomplicated" crises from a more serious pathologic condition. Children may be seen more often with skeletal crises leading to bone deformities. In these cases, osteomyelitis and bone infarct must be differentiated.[41-45]

Acute chest syndrome is a leading cause of death and accounts for 25% of premature deaths associated with sickle cell disease. It is a common cause of hospitalization in sickle cell disease, second only to vaso-occlusive crisis. Patients with acute chest syndrome have fever, cough, chest pain, dyspnea, and new infiltrates on the chest radiograph. The pathophysiology of the syndrome is not well understood but suggests that it may be a specific form of acute lung injury. The injury is postulated to be related to pulmonary microvascular sludging, infarction of pulmonary parenchyma, and bone marrow fat embolization from infarcted bone. Macrovascular pulmonary embolism and infection may also have a pathogenetic role. The differential diagnosis includes pneumonia, pulmonary embolism, congestive heart failure, and adult respiratory distress syndrome. No definitive diagnosis or therapy is currently available for acute chest syndrome. Management is supportive and consists of hydration, analgesia, maintenance of adequate oxygenation and ventilation, and empirical antibiotics.[46,47]

Although most of the diagnostic and therapeutic problems of sickle cell disease are related to vaso-occlusive crises, other serious complications must be anticipated. Sickle cell disease is a chronic hemolytic state with reasonably compensated hematocrit values in the 20 to 30% range and elevated reticulocyte counts. This compensated balance may be disrupted by a rare iron deficiency or, more commonly, by folate deficiency. A potentially life-threatening aplastic crisis may be seen as a

result of suppression of erythropoiesis by an acute postinfectious condition or folate deficiency. This aplastic condition is suspected when the hemoglobin level falls 2 g/dL or more from previous stable levels and the reticulocyte count remains low (<2%). Finally, children may have an acute splenic sequestration syndrome. This syndrome involves acute splenic enlargement from increased intrasplenic sickling and obstruction. The child may demonstrate lassitude and be in shock. Each of these conditions may result in a rapidly falling RBC count and progressive symptoms of anemia. Patients with HbSS are also subject to all other causes of anemia, such as hemolysis from G6PD deficiency.[47] An increased susceptibility to infection is well documented with HbSS. In infancy, an increased incidence of sudden death may be related to pneumococcal sepsis and meningitis. A WBC count and blood cultures should be performed on all febrile children with sickle cell anemia. Those younger than 2 years with temperatures of 39.5° C or higher and WBC counts greater than 20,000/mm^3 should be given intravenous antibiotics immediately. Adults with fever require careful evaluation and laboratory assessment, including appropriate cultures. Early institution of appropriate antibiotics is necessary in patients with a discernible source of infection. In children and adults, infection with *Staphylococcus* and *Pneumococcus* species and *Haemophilus influenzae* is particularly common. An increased incidence of *Salmonella* osteomyelitis also occurs. The origin of this related immunologic deficiency is believed to be multifactorial, with functional asplenia, poorly migrating neutrophils, and decreased opsonin production being contributors.[48]

Major, chronic organ damage in patients with sickle cell anemia is common. A cross section of these problems is listed in Table 119-7. These associated conditions should be quickly reviewed every time a patient with sickle cell anemia enters the emergency department. The leading causes of death in HbSS patients are cardiopulmonary disease, chronic renal failure, stroke, and infection.[42,43]

Diagnostically, most patients with HbSS seen in the emergency department are well-known with defined pain patterns. Because of a slow but longer growth period caused by the delayed onset of puberty, adult patients with HbSS have a youthful appearance and long, thin extremities. In a patient with suspected sickle cell disease, inquiry should be made into the family history, previous pain episodes, and symptoms relative to chronic anemia, susceptibility to infection, and ischemic organ damage. Table 119-7 suggests an outline to follow for the physical examination.

All patients should have a complete blood count performed, and current blood levels should be compared with those of previous visits. A reticulocyte count should be obtained whenever the patient's hemoglobin level has decreased by 2 g/dL from baseline. In sickle cell disease, the typical absolute reticulocyte count is three or four times the upper limit of normal. A reticulocyte count 3% or lower than the patient's usual value may suggest an aplastic crisis. A reticulocyte count greater than 12%, particularly if accompanied by numerous nucleated red blood cells, may indicate rapid hemolysis. Other laboratory tests are selected on the basis of potential organ complications. Unfortunately, no test is available that detects whether a patient is in a crisis. Currently, this difficult task is based on inadequate clinical grounds. In new cases, the peripheral smear may show sickled cells (Fig. 119-9), and a sickle cell screening test with Sickledex may help, particularly if drug-motivated malingering is suspected. Definitive diagnosis of sickle cell disease is aided by hemoglobin electrophoresis.[41]

Management. The antisickling agent hydroxyurea reduces the frequency of painful crises in adults with a history of three or more crises annually. The beneficial effects of hydroxyurea in sickle cell disease are assumed to be due to induction of hemoglobin F, but additional mechanisms may be operative.[49-52] Other agents, including clotrimazole, magnesium 5-azacitidine, erythropoietin, and butyric acid, may have a future role in therapy.[53-57] Bone marrow transplantation offers the only current cure for sickle cell disease. Despite survival rates greater than 90% and disease-free survival rates of 80 to 90%, the role of bone marrow transplantation in sickle cell disease remains uncertain.[58,59]

Current therapies, including rest, adequate nutrition, hydration, oxygenation, analgesia, transfusion, and therapy for infection, are directed toward symptomatic relief and attempts to stop the cycle of deoxygenated sickling and intravascular sludging. Most patients with sickle cell anemia are mildly dehydrated because of urine-concentrating difficulty. Fluid replacement can be oral or intravenous, and the emergency physician should be aware of the potential for congestive heart

Table 119-7 Organ Damage Seen in Sickle Cell Disease

ORGAN OR SYSTEM	INJURY
Skin	Stasis ulcer
Central nervous system	Cerebrovascular accident
Eye	Retinal hemorrhage, retinopathy
Cardiac	Congestive heart failure
Pulmonary	Intrapulmonary shunting, embolism, infarct, infection
Vascular	Occlusive phenomenon at any site
Liver	Hepatic infarct, hepatitis resulting from transfusion
Gallbladder	Increased incidence of gallstones caused by bilirubin
Spleen	Acute sequestration
Urinary	Hyposthenuria, hematuria
Genital	Decreased fertility, impotence, priapism
Skeletal	Bone infarcts, osteomyelitis, aseptic necrosis
Placenta	Insufficiency with fetal wastage
Leukocytes	Relative immunodeficiency
Erythrocytes	Chronic hemolysis

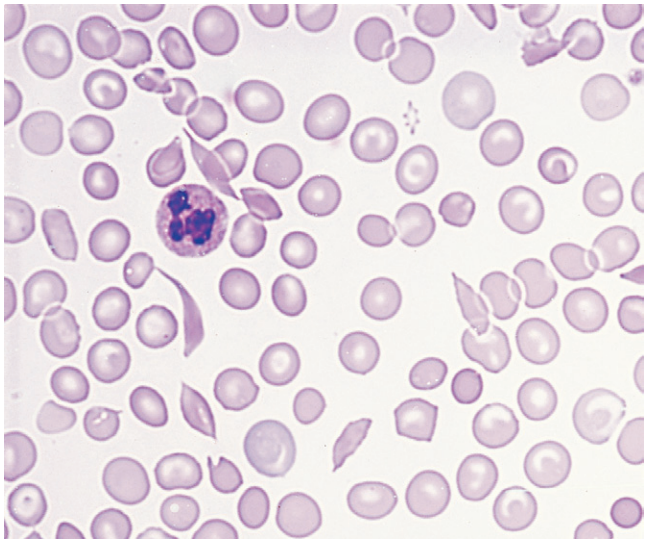

Figure 119-9. Sickle cells. (From Hoffbrand AV, Pettite JE: Color Atlas of Clinical Hematology, 3rd ed. London, Mosby, 2000, p 103.)

failure in patients past their second decade. A satisfactory starting solution is 5% dextrose in half-normal saline begun at a rate of 150 to 200 mL/hr.[60]

Oxygen through a nasal cannula at 2 to 4 L/min may help hypoxic patients and may be given to any patient with HbSS as a low-risk treatment modality with potential benefit. Oxygenation has been shown to decrease erythropoietin levels and the number of irreversibly sickled cells.

Analgesia is a major benefit and essential early therapy for acute sickle cell crisis. Most patients with sickle cell disease will rarely require emergency department care and only present during a severe crisis or complex illness. Because a small subgroup of patients repeatedly and frequently seek care in the emergency department, emergency department caregivers may become understandably suspicious of needs and motivations. Care protocols are advised in order to ensure rapid appropriate treatment. Many emergency physicians caring for large sickle cell patient populations have developed protocols for establishing better physician-patient rapport and lessening the chance of narcotic addiction and manipulation. The following is one protocol for severe pain: Patients are evaluated, treated with oxygen and hydration, and given intravenous morphine sulfate, 5 mg, then a constant infusion at 5 mg/hr. Another approach consists of intravenous bolus doses of morphine sulfate (0.15 mg/kg per dose up to 10 mg per dose). At 4 to 6 hours, the patient is allowed to decide whether inpatient or outpatient therapy is desired. Outpatient therapy includes 4 to 6 days of an effective oral analgesic. A 60-mg dose of oral morphine sulfate or equivalent is given 1 or 2 hours before stopping the infusion. Such a protocol may bring uniformity to the patient's expectations for care and the physician's decisions regarding therapy and admission. Its major disadvantage has been a tendency to treat patients automatically rather than closely considering the potential acute complications of sickle cell disease. No standard pain management exists for sickle cell disease. A variety of analgesics (nonsteroidal anti-inflammatory drugs, mixed opioid agonist-antagonists, and opiates), dosages, and timing intervals may be chosen. The most important aspect of pain management in these patients is a consistent, thorough, and attentive approach that offers true pain relief.

Blood transfusion has a well-accepted role in sickle cell anemia. Very selected use can decrease the chronic transfusion problems of antigen sensitization, iron overload, and hepatitis. Aplastic or splenic sequestration crises may necessitate transfusion. Serial hemoglobin values and reticulocyte counts must be obtained during hospitalization. Priapism may improve with transfusion, although urologic drainage procedures should be considered. Pharmacologic agents such as alpha- or beta-agonists have been used in priapism with mixed success. Exchange transfusions are recommended for patients, particularly children, with cerebrovascular accidents. Acute symptoms may be reversed and the frequency of recurrence decreased with a regulated 3- or 4-week transfusion program. The goal is to suppress reticulocytosis and decrease the HbS level to less than 25%. Rarely, transfusions are given for control of bony or visceral crises. This is not an emergency department procedure and is considered only after hematologic consultation. Prophylactic transfusions to dilute HbS levels are also recommended in pregnancy and before major surgery.[61]

A number of other therapies are being tested for both prophylaxis and crisis management, including supplemental zinc, induced hyponatremia, gelation inhibitors, membrane-active agents, and gene manipulation. Poloxamer 188 is an artificial surfactant with hemorheologic and antithrombotic properties. Although the mechanism of action of this agent is not fully understood, it improves microvascular blood flow by reducing blood viscosity and adhesive frictional forces. In clinical trials of sickle cell patients with acute painful crisis, poloxamer reduced the total narcotic requirement, the duration of pain, and pain intensity.[62,63] Careful examination, an analgesic protocol, and compassion remain the basis for management. A reason for a painful crisis should always be sought.

The general prognosis of sickle cell patients has improved because of an improvement in their care and the rapid use of antibiotics for potential infections.

Sickle Cell–β-Thalassemia. Sickle cell–β-thalassemia disease is seen most commonly in people of Mediterranean descent. The severity of the disease is related to the concentration of HbS in RBCs and the decrease in MCHC. It should be considered in a patient with a low MCV and a positive sickle preparation. It is generally a milder form than homozygous sickle cell disease. HbSC disease falls between HbSS and HbS-thalassemia in terms of severity. In addition to many of the complications of HbSS, HbSC disease has an increased incidence of eye hemorrhage and pregnancy complications and may cause splenomegaly. The peripheral smear demonstrates a combination of sickled cells and normocytic target cells.[41]

Extrinsic Alloantibodies. Alloantibodies are formed in response to foreign RBC antigens. In the case of the ABO system, these antibodies are preformed. The ABO system is one of the most important RBC wall antigens. ABO incompatibility resulting in donor cell destruction by the recipient's alloantibodies can be a life-threatening reaction. These antibodies are IgM in nature and can act as a hemolysin, both agglutinating RBCs and fixing complement and consequently causing intravascular hemolysis.

The Rh system is another set of antigens on the RBC. This system is unique in that individuals do not have antibodies that correspond to antigens in the Rh system unless they have been sensitized by previous exposure to antigens that they lack. The antibodies produced are IgG in nature, and they accelerate extravascular destruction of RBCs by the spleen and liver. Most autoimmune antibodies are directed toward antigens in the Rh system.[64]

Extrinsic Autoantibodies. Evaluation of autoimmune hemolysis is as complex as its origin. The major feature of autoimmune hemolysis is the production of an IgG or IgM antibody to an antigen present on the RBC membrane. Why the body responds in this manner is unknown. IgM antibodies can agglutinate, fix complement, and act as intravascular hemolysins. IgG antibodies may fix complement to the cell but do not usually complete the hemolysis process. These IgG- or C3-labeled cells undergo accelerated extravascular destruction. The direct antiglobulin test is useful in revealing these labeled cells.[65]

Autoimmune hemolytic anemias are acquired disorders, with 40 to 50% being idiopathic. The remainder are associated with a number of diseases (Box 119-12). Classification of autoimmune hemolytic anemias is based on the optimal temperature at which the antibody reacts with the RBC membrane. Therefore, there are warm-reacting (>37° C) and cold-reacting (<37° C) antibodies.[65]

Warm-reacting antibodies are characterized by a higher incidence in younger patients (30–60 years of age), predominance in women, variable complement fixation, and a positive direct antiglobulin test for IgG. Cold-reacting antibodies, or cold agglutinins, are seen predominantly in men and older patients (50–80 years of age) and with IgM complement fixation. They may also be found in patients with infectious mononucleosis and *Mycoplasma* infection, as well as lymphoma. Hemolysis may be intravascular and extravascular, and the direct antiglobulin test is positive for complement.[65]

BOX 119-12 Diseases Associated with Autoimmune Hemolytic Anemia

Neoplasms
Malignant: chronic lymphocytic leukemia, lymphoma, myeloma, thymoma, chronic myeloid leukemia
Benign: ovarian teratoma, dermoid cyst

Collagen Vascular Disease
Systemic lupus erythematosus
Periarteritis nodosa
Rheumatoid arthritis

Infections
Mycoplasma
Syphilis
Malaria
Bartonella
Virus: mononucleosis, hepatitis, influenza, coxsackievirus, cytomegalovirus

Miscellaneous
Thyroid disorders, ulcerative colitis
Drug immune reactions

BOX 119-13 Drugs Associated with Immune Hemolytic Anemia

Hapton type with antibodies to the drug

1. Complement-fixing antibody: quinidine, quinine, phenacetin, ethacrynic acid, *p*-aminosalicylate, sulfa drugs, oral hypoglycemic agents
2. Non-complement-fixing antibody: penicillin dosages >20 million U/day

Autoimmune type with antibodies to the RBC membrane: D-methyldopa, L-dopa, mefenamic acid, chlordiazepoxide
Cephalosporins at dosages >4 g/day may cause hemolysis by direct membrane injury

Clinically, a patient with immune hemolytic anemia has the signs and symptoms of anemia and, often, splenomegaly. Spherocytosis and reticulocytosis are noted in the blood smear. The direct antiglobulin test is positive in 90% of cases. The strength of the direct antiglobulin test does not correlate with the severity of the hemolysis because the Coombs' reaction is a different antibody function than hemolysis or stimulation of reticuloendothelial sequestration. In patients with newly diagnosed, reticulocytopenic or severe hemolytic anemia, the emergency physician may need to institute transfusion therapy. Compatible blood may be almost impossible to find because the antibody can react with almost all donors. The most compatible donor cells in terms of the ABO and Rh systems should be transfused with the knowledge that they will be no more compatible than the patient's own blood cells. Prednisone or its equivalent in a dose of 60 to 100 mg should be given orally or intravenously. It is believed to produce an improvement in 60% of patients with warm antibody reactions. Splenectomy and immunosuppressive therapy are also effective in treating these reactions. Cold agglutinin hemolytic anemia may be self-limited, as after infectious mononucleosis. Other forms respond well to cold avoidance, variably to immunosuppressive agents, but poorly to steroids and splenectomy. Death commonly results from uncontrolled hemolysis, the underlying primary disorder, and pulmonary embolism.[65]

Drug-induced hemolytic anemia may be difficult to diagnose. The emergency physician should know the drugs most often associated with this Coombs'-positive phenomenon and realize that this test is sometimes positive only in the drug's presence. Common drugs and mechanisms of action are listed in Box 119-13.[66]

Extrinsic Mechanical Causes. Hemolysis may be caused by trauma to RBCs. The peripheral smear may demonstrate schizocytes or fragmented cells, which should immediately raise the suspicion of traumatic injury (see Fig. 119-7). Microangiopathic hemolytic anemia, cardiac trauma, and "march" hemoglobinemia are the most commonly encountered forms of traumatic hemolysis.

Microangiopathic hemolytic anemia is a form of microcirculatory fragmentation by threads of fibrin deposited in the arterioles. An underlying disease is inevitably present. It may be found in renal lesions such as malignant hypertension and preeclampsia, vasculitis, thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, and vascular anomalies. The signs and symptoms are those of intravascular hemolysis. Treatment is directed at the causative disease.

Cardiac trauma to RBCs results from increased turbulence. It may be found in patients with prosthetic valves, traumatic arteriovenous fistula, aortic stenosis, and other left-sided heart lesions. Surgical correction may be necessary. Supportive therapy with an iron supplement is usually required.

March hemoglobinemia is a form of trauma caused by breaking of intravascular RBCs by repetitive pounding. Soldiers, marathon runners, and anyone with repetitive striking against a hard surface may incur this problem. Reassurance and a change in the patient's pattern of activity are the recommended therapy.[34,67]

Environmental Causes. Hemolysis may be seen in cases of severe burns, freshwater drowning, and hyperthermia. Toxic causes of hemolysis have been documented to be of animal origin, such as brown recluse spider and some snake bites; vegetable origin, such as castor beans and certain mushrooms; and mineral origin, such as copper. Certain infections are associated with hemolytic states. Malaria, *Bartonella*, and *Clostridium* sepsis are well-known causes.

Abnormal Sequestration. Hypersplenism may be caused by any disease that enlarges the spleen or stimulates the reticuloendothelial system. An unfortunate cycle can be set up in which the enlarged spleen traps more blood components and grows larger. It is usually seen as splenomegaly with pancytopenia and marrow hyperactivity. Chromium-labeled RBCs may demonstrate increased trapping in the spleen. Therapy for symptomatic or severe disease is splenectomy. Adults usually tolerate splenectomy well, but children should be approached conservatively because the risk of postsplenectomy life-threatening sepsis is increased significantly.[68]

POLYCYTHEMIA

Definition

Polycythemia is a term commonly used for erythrocytosis (i.e., increased number of RBCs). This disorder is seen occasionally in emergency medicine but rarely in a life-threatening manner that requires emergency intervention.

Pathophysiology

Erythropoiesis is controlled by the kidney-produced glycoprotein hormone erythropoietin. It is activated in the liver and regulates the committed erythropoietic stem cell.

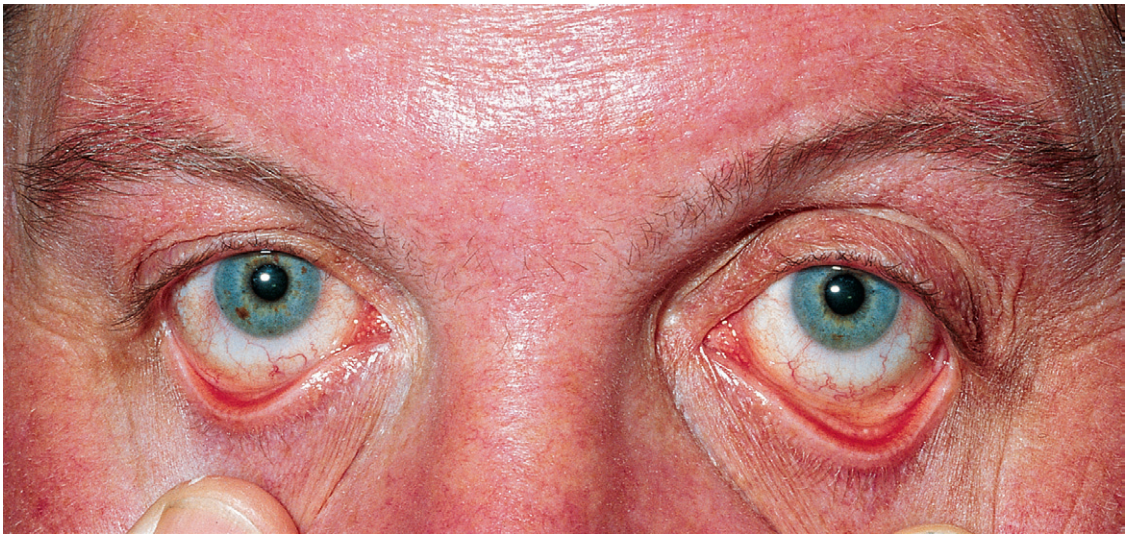

Figure 119-10. Polycythemia vera. Facial plethora and conjunctival suffusion in a 40-year-old woman (Hb, 19.5 g/dL). (From Hoffbrand AV, Pettite JE: Color Atlas of Clinical Hematology, 3rd ed. London, Mosby, 2000, p 248.)

Its major stimulant is tissue hypoxia. Neoplastic dysfunction of bone marrow may also result in an elevated absolute RBC count.

The major complication of polycythemia is related to the increase in blood viscosity associated with increased RBC numbers. As the hematocrit rises past 60%, viscosity increases in an almost exponential manner. This condition increases the possibility of reduced tissue flow, thrombosis, and hemorrhage. This hazard is usually blunted to a degree by an associated increase in blood volume and some viscosity-reducing vascular dilatation.[69,70]

Clinical Features

The history may range from only mild headaches to a full-blown syndrome of hypervolemia (vertigo, dizziness, blurred vision, and headache), hyperviscosity (venous thrombosis), and platelet dysfunction (epistaxis, spontaneous bruising, and gastrointestinal bleeding).

On physical examination, the skin and mucous membrane manifestations of the elevated RBC count are often readily observed. Plethora, engorgement, and venous congestion are commonly noted (Fig. 119-10). Other systems to be examined include the fundus for venous congestion, the abdomen for evidence of splenomegaly, and the cardiopulmonary system for signs of congestive heart failure. Uterine, central nervous system, renal, and hepatic tumors should be sought. All are associated with secondary polycythemia. An elevated RBC count, usually greater than the hematocrit, defines the disorder. It results in a low MCV, usually related to low serum iron and iron stores. Specific laboratory testing is discussed in the section on differential diagnosis.[71]

Differential Diagnosis

Polycythemia is classified as apparent, primary, or secondary (Box 119-14). Apparent polycythemia is a decrease in plasma volume such as found with dehydration. The RBC volume does not exceed the upper limit of normal. Although a questionable diagnostic entity, "stress" polycythemia is the tendency for an elevated hematocrit and is found in overweight, hypertensive, and overstressed middle-aged men. Increased cigarette smoking with its associated increased carboxyhemoglobin level is considered to be partially responsible. The symptoms are minimal, and treatment is confined to moderation, weight loss, and blood pressure control. The risk of vascular occlusive complications is minimal. The hematocrit is usually less than 60% and RBC mass measurements are normal.[70,71]

BOX 119-14 CAUSES OF APPARENT AND SECONDARY POLYCYTHEMIA

1. Appropriately increased erythropoietin caused by tissue hypoxia
   a. Congenital heart disease with a right-to-left shunt
   b. Pulmonary disease (e.g., bronchial-type chronic obstructive pulmonary disease)
   c. Carboxyhemoglobinemia
   d. High-altitude acclimatization
   e. Decreased tissue oxygen release from hemoglobinopathies with high oxygen affinity
2. Inappropriate autonomous erythropoietin production
   a. Renal origin: carcinoma, hydronephrosis, cyst
   b. Other lesions: uterine fibroids, hepatoma of adrenal origin, cerebellar hemangioma
   c. Congenital overproduction
3. Pure or essential erythrocytosis
4. AIDS and zidovudine treatment

Primary polycythemia vera is a myeloproliferative disorder found predominantly in middle-aged or older patients. It may have all the clinical components of polycythemia. Initial symptoms are reported in up to 30% of patients. The most common problems are thrombotic episodes (cerebrovascular accident, myocardial infarction, and deep vein thrombosis), bleeding, and bruising. Primary polycythemia vera is a disease that involves all cell lines—hematopoietic stem, erythroid, granulocytic, and megakaryocytic. The diagnostic criteria used by the Polycythemia Vera Study Group are listed in Box 119-15.

Polycythemia vera may be satisfactorily treated by phlebotomy as necessary. The reduced hematocrit improves some symptoms, but neither the leukocyte nor the platelet count is decreased. Maintaining the hematocrit at less than 55% is

BOX 119-15 DIAGNOSTIC CRITERIA FOR POLYCYTHEMIA VERA*

Category A
Increased RBC mass
In men: Hgb > 18.5 g/dL
In women: Hgb > 16.5 g/dL
Normal arterial oxygen saturation (>92%)
Splenomegaly

Category B
Thrombocytosis: platelets >400,000/mm^3
Leukocytosis: WBC count >12,000/mm^3 (with no fever or infection)
Leukocyte alkaline phosphatase score >100
Vitamin B_{12} >900 pg/mL, unbound vitamin B_{12}–binding capacity <2200 pg/mL

*For polycythemia vera to be diagnosed, either all three criteria in category A or the first two criteria in category A along with any two criteria in category B must be present.

recommended to decrease hypervolemia and hyperviscosity. Complications necessitating additional therapy include hyperuricemia, refractory increased RBC mass, severe pruritus, excessive splenomegaly, and thrombocytosis. Additional therapy may consist of hydroxyurea, busulfan, chlorambucil, interferon-α, anagrelide, or radioactive phosphorus (^{32}P). Studies suggest no improvement in long-term survival with the addition of these treatments. The natural history of the disease is that it burns out over a period of 15 to 20 years. However, myelofibrosis with myeloid metaplasia may develop. In 10% of cases, acute leukemia develops with a rapid and poorly responsive downhill course. Median survival beginning from treatment to death ranges from 9 to 14 years.[71,72] The most common causes of death are thrombosis (29%), hematologic malignancies (23%), nonhematologic malignancies (16%), hemorrhage, and myelofibrosis with myeloid metaplasia.[73]

Secondary polycythemia is classified first according to the appropriate erythropoietin response to abnormal tissue oxygen levels. This group of disorders may be ruled out by normal measured arterial oxygen saturation. Second, inappropriate autonomous erythropoietin production is considered. This condition can be assessed with an erythropoietin assay. Because of a strong association with renal pathologic conditions, computed tomography should be used to evaluate a patient with a suspected inappropriate erythropoietin response. Most patients with secondary polycythemia have no central nervous system symptoms or splenomegaly. Because erythropoietin stimulates only the red cell pathway, these patients have normal WBC and platelet counts.[71]

Management

The emergency treatment of any form of symptomatic polycythemia is phlebotomy. Usually, not more than 500 mL of blood is slowly removed as the volume is replaced with a comparable amount of saline. No hemodynamic compromise should occur if this procedure is performed slowly. In true emergencies, up to 1 to 1.5 L of blood may be removed over a 24-hour period. The initial goal is to lower the hematocrit toward 60%. The final goal is a level less than 55%. Low-dose aspirin, 80 to 100 mg/day, has been shown to prevent thrombotic complications in patients with polycythemia vera and can be used in the acute and chronic treatment of this disorder.[71,73,74]

Disposition

A number of patients with known polycythemia may be managed by outpatient phlebotomies. Any newly diagnosed or symptomatic patient should be admitted to the hospital for full evaluation.

WHITE BLOOD CELL DISORDERS

The WBC count and accompanying differential are the most common laboratory tests ordered in the emergency department. It is essential that the basic physiology, pathophysiology, and clinical evaluation of WBCs be understood.

Physiology and Pathophysiology

The series has three morphologically indistinguishable cell types: B cells (humoral immunity), T cells (cellular immunity), and null cells. Because lymphocytes can freely leave and return to the circulation, the storage pools are less well defined. Only 5% of the total lymphocytes in the body are in the circulation. No marginal pool exists.[75]

Leukocytes primarily function extravascularly. The primary function of each series is closely integrated with the other. WBCs reach their site of action through the circulation. The rate that new cells enter the circulation is usually in equilibrium with the rate of loss in tissues.

Abnormal cell counts are due to changes in production, the marginal pool, or the rate of tissue destruction. Just as in anemia or platelet count abnormalities, the differential diagnosis of increased (leukocytosis) or decreased (leukopenia) WBC counts can be organized by processes altering production, destruction, loss, and sequestration. This chapter focuses primarily on quantitative rather than qualitative disorders.[75]

The granulocytic and lymphocytic series are the two cell lines of WBCs. The granulocytic series is primarily involved in phagocytic activity. Its origin is the pluripotential stem cells located in the bone marrow. A subset of these cells differentiates and matures into the phagocytic cell lines, which include neutrophils, monocytes, basophils, and eosinophils. Granulocytes are maintained in a series of developmental and storage pools. The most important is the postmitotic storage pool for neutrophils, which represents 15 to 20 times the circulating population. This pool contains metamyelocytes, band neutrophils, and mature neutrophils (polymorphonuclear neutrophils). The pool can be drawn on as a ready reserve during rapid consumption of granulocytes. Circulating neutrophils are subdivided equally into the circulating neutrophil pool and the marginal pool. The latter consists of mature cells adherent to the blood vessel walls. These cells can rapidly enter the circulating pool and cause a substantial increase, even doubling, of the WBC count. This involvement does not alter the maturity pattern of the differential count.[75] The lymphocytic series matures in lymphoid tissues located in the bone marrow, thymus, spleen, lymph nodes, and elsewhere. They are involved in the immune response against foreign substances.

Normal Values and Influences

One unique problem in WBC disorders is the wide variability in normal values and the multiple factors influencing them. WBC counts are generally performed automatically by using electrical impedance or optical diffraction techniques. Differential counts are commonly performed by direct examination of 100 to 500 cells with the oil immersion lens of the microscope. Automated techniques for all differential counts are

becoming more popular, however. Normal values for the WBC count are listed in Table 119-8. The "normal" count is age dependent until childhood and may be shifted upward by exercise, gender (women), smoking, and pregnancy. Decreases in the total WBC count range of 1000 to 1200 cells/mm^3 have been noted in the African American population. Laboratory errors may be due to improper sample preparation, nucleated RBCs, or platelet clumping. The blood smear differential count may also be influenced by small sample size, improper cell identification, and age group (children). Differential ranges are listed in Table 119-9. One common but easily corrected error in laboratory reporting is giving the results in terms of the percentage of cell types. Absolute counts for each cell type are more accurate and useful in assessing the risk for infection.[75,76]

Abnormal Values

Because of the wide range of normal values, all abnormal WBC counts should be interpreted in the context of the patient's condition. A careful history and physical examination, absolute cell counts, and review of the peripheral smear differential count are the starting points for determining the origins of quantitative WBC disorders.

Leukocytosis

Most cases of leukocytosis are caused by increases in the neutrophil or lymphocyte cell lines. Neutrophil leukocytosis (neutrophilia) is an absolute neutrophil count greater than 7500 cells/mm^3 and is commonly associated with infection or inflammation (Box 119-16). Because increased neutrophil destruction is associated with both these pathologic processes, bone marrow stores are drawn on, and the usual ratio of 1 band to 10 neutrophils increases. This increase is manifested as a "left shift" in the differential count and represents immature neutrophils from the postmitotic pool moving into the circulation.

WBC counts can increase without a left shift or an increase in band forms by demarginating neutrophils from the vessel walls. It is often seen as a response to stress, exercise, or epinephrine. Severe stress can raise the WBC count to 18,000 to 20,000 cells/mm^3.[75,76]

Chronic Myeloid Leukemia

One of the myeloproliferative causes of neutrophilic leukocytosis is chronic myeloid leukemia (CML). Although it is the least common of the major leukemias (60% acute, 31% chronic lymphocytic leukemia, and 15% CML), it must be considered in neutrophilia. Patients with CML are usually older than 40 years and have WBC counts greater than 50,000 cells/mm^3. The differential count shows elevated polymorphonuclear neutrophils and metamyelocytes. Less often, the basophil and eosinophil counts are increased. CML is a stem cell disorder in which the WBC count is elevated and the differential is normal. Mature and intermediate granulocytes are overproduced. Platelets may also be increased, but RBC production is down, thereby resulting in anemia. The patient often complains of fatigue, anorexia, sweating, and weight loss. Physical findings include pallor, sternal tenderness, and splenomegaly (90% of patients; Fig. 119-11). In the laboratory, decreased leukocyte alkaline phosphatase and increased vitamin B_{12} levels are found, which helps differentiate CML from other causes of neutrophilia. The Philadelphia chromosome (Ph^1) is almost constantly associated with the disease. The chronic phase of CML is treated with an alkylating agent (e.g., busulfan) or an antimetabolite (e.g., hydroxyurea). Selected patients may benefit from bone marrow transplantation.[77,78]

The need for urgent therapy in CML is usually related to hyperuricemia and renal injury or severe anemia and subsequent angina or heart failure. Rarely, hyperleukocytosis occurs, but the more mature, "less sticky" cells in CML do not usually cause problems unless the count exceeds 500,000 cells/mm^3. A higher cell count may cause leukostasis and result in deafness, visual impairment, pulmonary ventilation-perfusion abnormalities, and priapism. Treatment involves hydration, leukapheresis, transfusion as necessary, allopurinol to prevent severe hyperuricemia, and specific chemotherapy (hydroxyurea). Late problems in the natural history of CML involve progressive loss of cell differentiation and response to therapy. The term *blastic crisis* represents the sudden appearance of an acute form of leukemia, which is a rare substage of the evolving deterioration.[77,78] The condition may occur in lymphoid or myeloid forms. Blast counts greater than 50,000 cells/mm^3 may predispose the patient to the complications of leukostasis.

Table 119-8 Normal Ranges for the Blood Leukocyte Count (Cells/mm^3)

AGE	AVERAGE	95% RANGE (AVERAGE VALUE ± 2 SD)
1 wk	12,200	5,000–21,000
6 mo	11,900	6,000–17,500
12 mo	11,400	6,000–17,500
4 yr	9,100	5,500–15,500
8 yr	8,300	4,500–13,500
Adults	7,400	4,500–11,000

Modified from Miale JB: *Laboratory Medicine: Hematology*, 6th ed. St. Louis, Mosby, 1982.

Table 119-9 Normal Percentage Ranges for the Leukocyte Differential Count in Blood*

AGE	SEGMENTED NEUTROPHILS	BAND NEUTROPHILS	LYMPHOCYTES	MONOCYTES	EOSINOPHILS	BASOPHILS
1 wk	34 ± 15 (4100)	11.8 ± 4 (1420)	41 ± 5 (5000)	9.1 (1100)	4.1 (500)	0–4 (50)
6 mo	23 ± 10 (2710)	8.8 ± 3 (1000)	61 ± 15 (7300)	4.8 (480)	2.5 (300)	0–4 (50)
12 mo	23 ± 10 (2680)	8.1 ± 3 (990)	61 ± 15 (7000)	4.8 (550)	2.6 (300)	0–4 (50)
4 yr	34 ± 11 (3040)	8.0 ± 3 (730)	50 ± 15 (4500)	5.0 (450)	2.8 (250)	0–6 (50)
8 yr	45 ± 11 (3700)	8.0 ± 3 (660)	39 ± 15 (3300)	4.2 (350)	2.4 (200)	0–6 (50)
Adult	51 ± 15 (3800)	8.0 ± 3 (620)	34 ± 10 (2500)	4.0 (300)	2.7 (200)	0–5 (40)

*Numbers in parentheses indicate the average number of cells per cubic millimeter.
Modified from Miale JB: *Laboratory Medicine: Hematology*, 6th ed. St. Louis, Mosby, 1982.

BOX 119-16 CAUSES OF LEUKOCYTOSIS

Neutrophils (Absolute Count >7500 Cells/mm^3)
Inflammation: rheumatoid arthritis, gout
Infection: bacterial most common
Tissue necrosis: cancer, burns, infarctions
Metabolic disorders: diabetic ketoacidosis, thyrotoxicosis, uremia
Rapid RBC turnover: hemorrhage, hemolysis
Myeloproliferative disorders: chronic myeloid leukemia, polycythemia vera
Malignancy (e.g., gastrointestinal cancers)
Stress: exercise, pain, surgery, hypoxia, seizures, trauma
Drugs: epinephrine, corticosteroids, lithium, cocaine
Pregnancy
Heredity or idiopathic disease
Laboratory error: automated counters, platelet clumping, precipitated cryoglobulin

Lymphocytosis (Absolute Count >9000/mm^3, Ages 1–6; 7000/mm^3, Ages 7–16; 4000/mm^3, Adults)
Viral infection (primary cause): mononucleosis, rubeola, rubella, varicella, toxoplasmosis
Bacterial infection: pertussis, tuberculosis, hepatitis, cytomegalovirus
Lymphoproliferative: acute or chronic lymphocytic leukemia
Immunologic response: immunization, autoimmune diseases, graft rejection
Endocrine: hypothyroidism
Relative lymphocytosis associated with granulocytopenia

Modified from Miale JB: *Laboratory Medicine: Hematology,* 6th ed. St. Louis, Mosby, 1982.

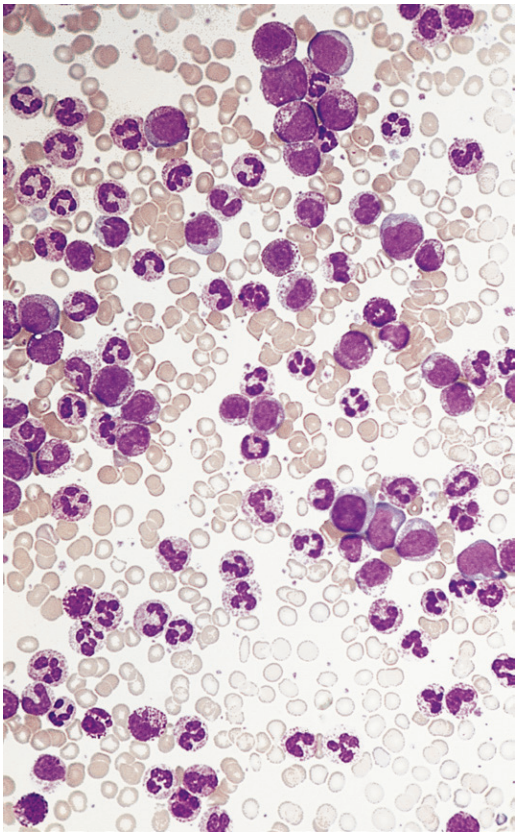

Figure 119-11. Chronic myeloid leukemia. (From Hoffbrand AV, Pettite JE: Color Atlas of Clinical Hematology, 3rd ed. London, Mosby, 2000, p 169.)

Leukemoid Reaction

A leukemoid reaction is a nonleukemic reactive granulocytic leukocytosis that resembles CML but has no associated Ph[1] chromosome, no absolute increase in basophils and eosinophils, and an increase in leukocyte alkaline phosphatase. It is difficult to distinguish from CML in the emergency department, and both must be considered as a potential diagnosis in granulocytic leukocytosis. WBC counts are usually greater than 50,000 cells/mm^3. A leukemoid reaction may be seen in tuberculosis, Hodgkin's disease, sepsis, and metastatic tumor, particularly bronchogenic, gastric, and renal carcinoma.[76]

Lymphocytic Leukocytosis

Lymphocytic leukocytosis (lymphocytosis) is an age-dependent definition: 9000 cells/mm^3, ages 1 to 6 years; 7000 cells/mm^3, ages 6 to 16 years; and 4000 cells/mm^3, adults. It is seen in a variety of disorders, primarily infections and lymphoproliferative disease.[79]

In the past, *acute* and *chronic* were descriptive terms applied to lymphocytic neoplasms with respect to patient survival time before present therapy was available. The terms *acute* and *chronic* are currently used to describe the cell maturity, rapidity of onset, and aggressiveness of therapy.

Chronic Lymphocytic Leukemia. Chronic lymphocytic leukemia is primarily a B cell disorder and is the most common type of leukemia in the population 50 years or older. Patients initially complain of fatigue, weight loss, increased susceptibility to infection, rashes, and easy bruising. The lymph nodes are nontender and smooth, and they may appear in only one or two areas. Splenic and hepatic enlargement occurs in more than 50% of patients. Laboratory support of the diagnosis is an absolute lymphocyte count greater than 5000 cells/mm^3 in adults. Anemia, thrombocytopenia, and neutropenia are often found. Autoimmune hemolytic anemia, a positive direct antiglobulin test, and other altered immune system problems are seen. Early therapy may be directed toward complications of anemia, thrombocytopenia, an impaired or accentuated immune response, or enlarged lymph nodes or spleen. Leukostasis is seldom seen in chronic lymphocytic leukemia, but therapy is considered when the total count rises to higher than 200,000/mm^3.[79]

Acute Lymphocytic Leukemia. Acute lymphocytic leukemia is most commonly diagnosed in children younger than 10 years. It is the most frequent malignancy in children younger than 15 years. The potential for leukostasis increases in acute lymphocytic leukemia when the blast count rises above 50,000 cells/mm^3. Oncologic therapy is based on clinical staging and includes chemotherapy or radiation therapy. Aggressive therapy has improved childhood survival from 1 to 15 years or more. This response to treatment has not been found to the same degree in adults.[80-82]

Leukopenia

In adults, leukopenia is defined as an absolute blood cell count less than 4000 cells/mm^3. Leukopenia is commonly associated with a reduction in one cell type, the neutrophil, and this decrease has the greatest clinical significance. The absolute neutrophil count is calculated by multiplying the WBC count by the combined percentage of band and segmented neutrophils. The absolute neutrophil count can be classified as mild (1000–1500 cells/mm^3), moderate (500–1000 cells/mm^3), or severe (<500 cells/mm^3) according to the risk for infection. The latter is a potentially life-threatening state because the patient is markedly susceptible to overwhelming infection.

Table 119-10 Linkage of Leukopenia to Phases of Neutrophil Maturation

MECHANISM	EXAMPLE
Proliferation in bone marrow	Aplastic anemia, leukemia, cancer chemotherapy (cyclophosphamide, azathioprine, methotrexate, chlorambucil) Drugs: phenothiazines, phenylbutazone, indomethacin, propylthiouracil, phenytoin, cimetidine, semisynthetic penicillins, sulfonamides Infection: viral, tuberculosis, sepsis
Maturation in bone marrow	Folate or vitamin B_{12} deficiency, chronic idiopathic neutropenia Starvation
Distribution	Hypersplenism: sarcoidosis, portal hypertension, malaria
Increased use	Infection: viral most common (mononucleosis, rubella, rubeola), *Rickettsia* organisms, overwhelming bacterial infection Autoimmune disease: systemic lupus erythematosus, AIDS, Felty's syndrome
Laboratory error	Leukocyte clumping, long delay in performing test

BOX 119-17 AGENTS AND CONDITIONS THAT ELEVATE THE WBC COUNT

Acetylcholine
Acidosis
Adrenergic drugs
Alcohol
Allergic reactions
Bacterial infection
Blood donation
Burns
Competitive running
Crying in infants
Fever
Gout
Hemolysis
Heparin
Histamine
Hypoxia
Iron overdose
Juvenile rheumatoid arthritis
Lead and other toxins
Lithium
Menstruation
Myocardial infarction
Neonatal asphyxia
Neoplasm
Normal pregnancy
Pain
Polyarteritis nodosa
Prednisone
Pulmonary infarction
Seizures
Snake bite
Supraventricular tachycardia
Surgery
Trauma
Uremia
Viral infection
Vomiting

The physical signs of infection may be minimal in severe neutropenia because there are too few cells to generate a substantial inflammatory or purulent response. Neutropenia may be caused by decreased production, increased destruction, or movement of circulating neutrophils into marginal or tissue pools. Until recently, it was most often caused by a decrease in bone marrow production (Table 119-10). Autoimmune neutropenia is also becoming more commonly diagnosed because it is thought to have a role in acquired immunodeficiency syndrome.[76,83]

A thorough medication history must be taken in all patients found to have neutropenia. A previous history of neutropenia, a review of recent infection, and a family history are obtained. The review of systems focuses on bleeding problems, fatigue, sweats, weight loss, and autoimmune symptoms. The physical examination is directed toward sites of infection, lymphadenopathy, hepatosplenomegaly, and underlying disease. In patients with severe neutropenia and fever, a full radiologic and direct examination of commonly involved areas, such as the chest and urine, should be performed and sputum, urine, and blood cultures obtained. Basic isolation techniques, early admission, and consultation with another specialist are recommended. Specific therapies may be started after cultures and consultation are completed. A number of empirical antibiotic regimens are recommended for febrile patients with neutropenia.[84,85] Human granulocyte colony-stimulating factor is often used in the setting of neutropenia, but it is best done in consultation with a hematologist.[86,87] Patients with a clear reversible source or without significant clinical findings and mild to moderate levels of neutropenia may have outpatient follow-up arranged, preferably after discussion with their physician.

RATIONALE FOR SELECTION OF WHITE BLOOD CELL AND DIFFERENTIAL COUNTS

The WBC count has not proved to be a highly sensitive or specific test for the diagnosis of a variety of disease entities. However, in certain clinical situations, the WBC count may have utility. For example, studies evaluating the WBC count for the diagnosis of abdominal pain have found it to be a useful confirming test or helpful in selecting patients for observation. In evaluating the bacterial versus viral infectious potential in febrile children, the WBC and differential counts have demonstrated limited usefulness, except in children younger than 2 years, in whom counts greater than 15,000 cells/mm^3 have an increased correlation with bacteremia.[88-90]

In addition to the nonspecificity of the WBC count, the differential count provides additional helpful information in less than 1% of cases. The absolute leukocyte count or the differential cannot reliably distinguish between viral and bacterial infection. The test should be viewed as having limited screening value in the acute care setting. Multiple agents and conditions increase the WBC count (Box 119-17), thus making the test less specific for infection than previously assumed.[88-90]

KEY CONCEPTS

- Anemia in the elderly often occurs as an exacerbation of preexisting comorbid diseases.
- Anemia of uncertain etiology should be thoroughly evaluated. If the patient has no adverse hemodynamic consequences, the evaluation can proceed on an outpatient basis.
- One of the most important but often overlooked studies in the evaluation of suspected hemolytic anemia is the peripheral blood smear.
- Patients with sickle cell disease who come to the emergency department are most commonly having a true crisis and are not simply exhibiting drug-seeking behavior.
- The white blood cell determination in the emergency department has poor sensitivity and specificity for disease.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 120

Disorders of Hemostasis

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PERSPECTIVE

Hemostasis is the process of blood clot formation and represents a coordinated response to vessel injury. It requires an orchestrated response from platelets, the clotting cascade, blood vessel endothelium, and fibrinolysis. Thrombin-stimulated clot formation and plasmin-induced clot lysis are closely related and regulated. This dynamic process is often viewed in phases: formation of a platelet plug, propagation of the coagulation cascade, formation of a clot, and fibrinolysis of the clot.

Most hemostatic abnormalities are acquired and result from drugs (e.g., aspirin or warfarin [Coumadin]), from associated disease (e.g., hepatic insufficiency), or from iatrogenic causes (e.g., multiple transfusions).

PATHOPHYSIOLOGY

Hemostasis depends on normal function and integration of the vasculature, platelets, and the coagulation pathway.

Vasculature

Vascular integrity is maintained by a lining of nonreactive overlapping endothelial cells supported by a basement membrane, connective tissue, and smooth muscle. These cells are important in maintaining a barrier to macromolecules and, when injured, in contributing to the metabolic response and local vasoconstriction. The vascular wall is an important contributor to hemostasis.[1]

The endothelium contributes to both clot formation and regulation by producing substances such as von Willebrand's factor (vWF), antithrombin III, heparin sulfate, prostacyclin, nitric oxide, and tissue factor pathway inhibitor.

Platelets

Platelets have multiple and ever-expanding roles in our understanding of hemostasis. They are complex cytoplasmic fragments released from bone marrow megakaryocytes under the control of thrombopoietin. Platelets contain lysosomes, granules, a trilaminar plasma membrane, microtubules, and a canalicular system. Granules are an important component of hemostasis and contain platelet factor 4, adhesive and aggregation glycoproteins, coagulation factors, and fibrinolytic inhibitors. Each participates in the process of coagulation. The platelet's role is termed *primary hemostasis*, and it serves as the initial defense against blood loss. A fibrin clot that incorporates coagulation factors usually reinforces a platelet clot. Platelet activity is summarized in Box 120-1. Any of the steps listed may be absent, altered, or inhibited by inherited or acquired disorders.[2-6]

Coagulation Pathway

The coagulation pathway is a complex system of checks and balances that results in controlled formation of a fibrin clot. Coagulation factors have been given standard Roman numerals matching their order of discovery (Box 120-2).[7]

A simplified version of the coagulation pathway is presented in Figure 120-1. The clotting cascade is traditionally depicted as consisting of intrinsic and extrinsic pathways. The intrinsic pathway is initiated by exposure of blood to a negatively charged surface, such as a glass surface in the activated partial thromboplastin clotting time. The extrinsic pathway is activated by tissue factor exposed at the site of vessel injury or thromboplastin. Both pathways converge to activate factor X, which then activates prothrombin to thrombin. The primary physiologic event that initiates clotting is exposure of tissue factor at the injured vessel site. Tissue factor is a critical cofactor that is required for activation of factor VII. Activated factor VII activates factor X directly, as well as indirectly by activating factor IX.

Because of limited amounts of tissue factor and rapid inactivation by tissue factor pathway inhibitor, the extrinsic pathway initiates the clot process. Sustained generation of thrombin and clot formation depend on the intrinsic pathway through activation of factor IX by activated factor VII, which helps explain the bleeding problems associated with hemophilia.[7,8] Intrinsic, extrinsic, and common pathways must function normally for hemostasis to occur, and each may be evaluated with laboratory tests.[1,7] The clinically important groups of coagulation factors are as follows:

1. Thrombin-sensitive factors contributing to the metabolic response and local vasoconstriction: I, V, VIII, XIII
2. Vitamin K–sensitive factors: II, VII, IX, X
3. Sites of heparin activity: IIa, IXa, Xa (major site), XIa, platelet factor 3

Thrombin-sensitive factors are activated by thrombin and may give rise to a bleeding disorder if defective synthesis occurs. Vitamin K–sensitive factors may also cause bleeding from defective synthesis, as occurs with liver disease and warfarin anticoagulants. Heparin in combination with antithrombin III affects the coagulation pathway at multiple sites.[9-12]

BOX 120-1 Role of Platelets in Hemostasis

Adhesion to subendothelial connective tissue: collagen, basement membrane, and noncollagenous microfibrils; serum factor VIII (von Willebrand's) permits this function; adhesion creates the initial bleeding arrest plug
Release of adenosine diphosphate, the primary mediator and amplifier of aggregation; release of thromboxane A, another aggregator and potent vasoconstrictor; release of calcium, serotonin, epinephrine, and trace thrombin
Platelet aggregation over the area of endothelial injury
Stabilization of the hemostatic plug by interaction with the coagulation system:
- Platelet factor 3, a phospholipid that helps accelerate certain steps in the coagulation system
- Platelet factor 4, a protein that neutralizes heparin
- Pathway initiation and acceleration by thrombin production
- Possible secretion of active forms of coagulation proteins

Stimulation of limiting reactions of platelet activity

Coagulation Control

All the components of the coagulation reaction are necessary to prevent excessive bleeding. Hemostasis is a balance between the excessive bleeding state and thrombosis. Once coagulation is initiated, controls are necessary to prevent local or generalized thrombosis. These controls include the following:[11,13-18]

1. Removal and dilution of activated clotting factors via blood flow, which also mechanically opposes growth of the hemostatic plug

BOX 120-2 Coagulation Factors

I. Fibrinogens
II. Prothrombin
III. Tissue thromboplastin
IV. Calcium
V. Labile factor (proaccelerin)
VI. Not assigned
VII. Proconvertin
VIII. Antihemophilic A factor
IX. Antihemophilic B factor (plasma thromboplastin component, Christmas factor)
X. Stuart-Prower factor
XI. Plasma thromboplastin antecedent
XII. Hageman factor (contact factor)
XIII. Fibrin-stabilizing factor

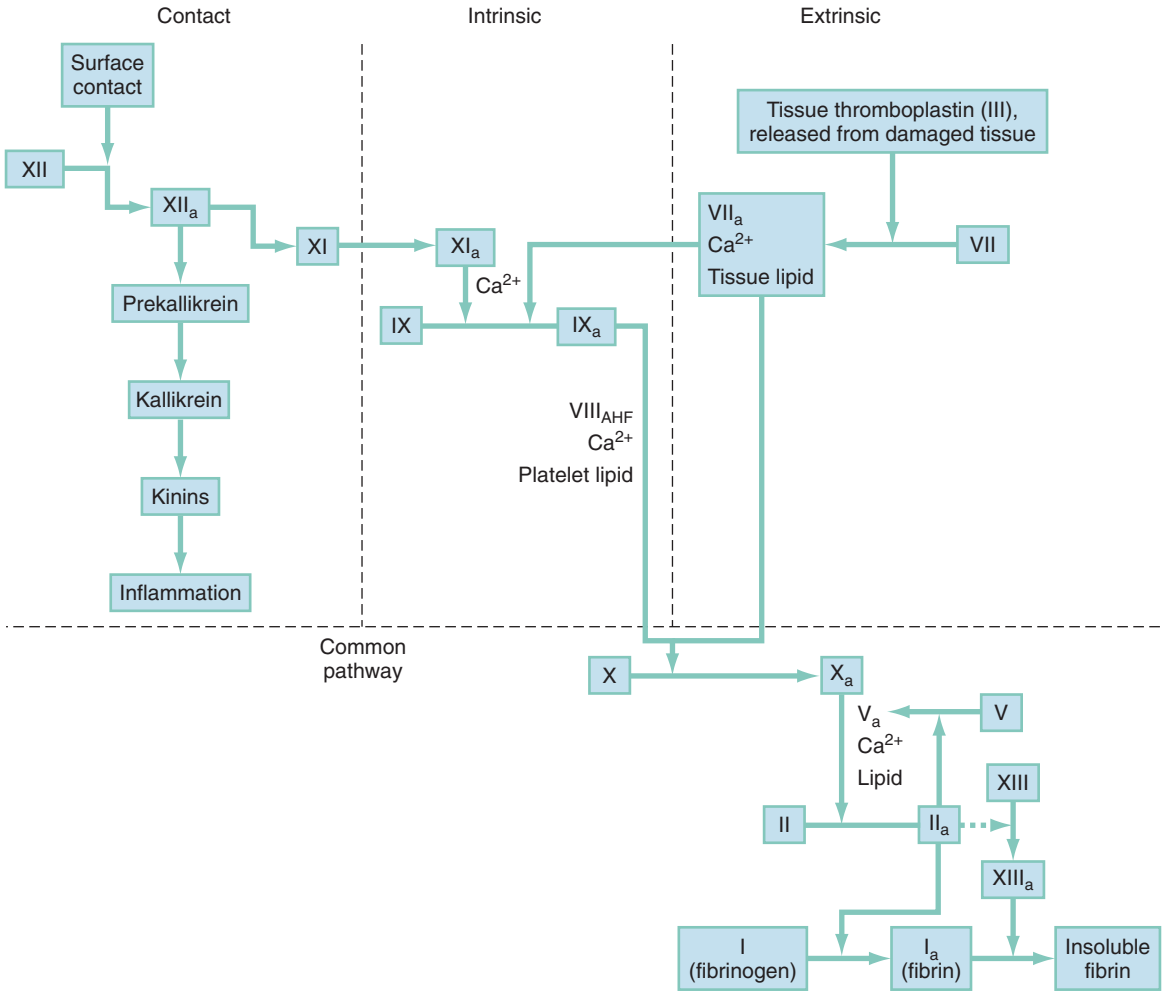

Figure 120-1. Coagulation pathway.

2. Modulation of platelet activity by endothelial-generated nitric oxide and prostacyclin
3. Removal of activated coagulation components by the reticuloendothelial system
4. Regulation of the clotting cascade by antithrombin III, protein C, protein S, and tissue factor pathway inhibitor
5. Activation of the fibrinolytic system

CLINICAL FEATURES

Out-of-Hospital Treatment

The out-of-hospital treatment of bleeding problems presents no special concerns. Local pressure and volume repletion are the mainstays of therapy for blood loss. The out-of-hospital team must be aware that inherited coagulopathies may complicate any medical or traumatic problems and that coagulopathy can rapidly develop in critically ill patients. Patients who do not respond quickly to the usual measures of hemostasis either in the field or in the emergency department (ED) should be considered to have a potential bleeding disorder.

History and Physical Examination

An outline of the history and physical examination is presented in Box 120-3. The history alone may be useful in differentiating between platelet and coagulation factor abnormalities. Platelet disorders are usually manifested as acquired petechiae, purpura, or mucosal bleeding and are more common in women. Coagulation problems are commonly congenital, are characterized by delayed deep muscle or joint bleeding, and are seen more often in men.

Ancillary Evaluation

A definitive diagnosis depends on laboratory evaluation. Tests pertinent to the ED are discussed in the following sections and listed in Box 120-4.

Complete Blood Count and Blood Smear

The complete blood count (CBC) assesses the degree of anemia associated with the bleeding episode. Reductions in hemoglobin and hematocrit often lag behind the actual loss of red blood cells (RBCs) in acute hemorrhage because of a slow equilibration time. The peripheral blood smear may demonstrate schistocytes or fragmented RBCs in disseminated intravascular coagulation (DIC). Teardrop-shaped or nucleated RBCs may reflect myelophthisic disease. A characteristic white blood cell morphologic condition is seen with thrombocytopenia associated with infectious mononucleosis, folate or vitamin B_{12} deficiency, or leukemia.[19]

Platelet Count

The platelet count may be estimated from the smear. Normally, one platelet is present per 10 to 20 RBCs. Often, the count is automated, the normal range being 150,000 to 400,000/mm^3. Platelet counts less than 100,000/mm^3 define thrombocytopenia. With normal platelet function, the bleeding time increases in direct relation to a decrease in the platelet count below 100,000/mm^3. Levels below 20,000/mm^3 may be associated with serious spontaneous hemorrhage. However, the count gives no information about the functional capability of platelets.[20]

BOX 120-3 CLINICAL EVALUATION OF A BLEEDING PATIENT

History
- Nature of bleeding
  - Petechiae
  - Purpura
  - Ecchymosis
  - Significant bleeding episodes
- Sites of bleeding
  - Skin
  - Mucosa: oral or nasal
  - Muscle
  - Gastrointestinal
  - Genitourinary
  - Joints
- Patterns of bleeding
  - Recent onset or lifelong
  - Frequency and severity
  - Spontaneous or after injury
- Challenges to hemostasis
  - Tooth extraction
  - Operative procedures
  - Association with medication, particularly aspirin
- Medications
- Associated diseases
  - Uremia
  - Liver disease
  - Infection
  - Malignancy
- Previous transfusion
- Family history

Physical Examination
- Vital signs
- Skin: nature of bleeding, signs of liver disease
- Mucosa: oral or nasal
- Lymphadenopathy
- Abdomen: liver size and shape, splenomegaly
- Joints: signs of previous bleeding
- Other sites of blood loss: pelvic, rectal, urinary tract

BOX 120-4 COAGULATION STUDIES

- CBC and smear (EDTA—purple top)
- Platelet count (EDTA—purple top)
- Bleeding time
- Prothrombin time (citrate—blue top)
- Partial thromboplastin time (citrate—blue top)
- Other coagulation studies: fibrinogen level, thrombin time, clot solubility, factor levels, inhibitor screens
- As necessary: electrolytes, glucose, BUN, creatinine, type and crossmatch

BUN, blood urea nitrogen; CBC, complete blood count; EDTA, ethylenediaminetetraacetic acid.

Bleeding Time

Bleeding time is the best test for determining both vascular integrity and platelet function that can be performed in the ED. The test is performed after making two standard incisions 1 mm deep and 1 cm long on the volar aspect of the forearm under 40 mm Hg pressure via a blood pressure cuff utilizing a template to ensure appropriate incisions. The time is mea-

sured from the incision to the moment when the blood oozing from the wound is no longer absorbed by filter paper. Some institutions have replaced the traditional bleeding time with a platelet function analyzer instrument, which is just as accurate and more convenient. A normal time is 8 minutes, a time of 8 to 10 minutes is borderline, and a time longer than 10 minutes is typically abnormal. Because of the high incidence of drug-induced platelet dysfunction, it is important to ask the patient about medications, particularly aspirin and other antiplatelet medications (e.g., clopidogrel). The test is independent of the coagulation pathways.[20-22] As mentioned previously, the bleeding time is prolonged with platelet counts below 100,000/mm^3, but such prolongation does not represent platelet dysfunction. However, a prolonged bleeding time associated with platelet counts greater than 100,000/mm^3 suggests impaired function.

Prothrombin Time

The prothrombin time (PT) tests the factors of the extrinsic and common pathways. The patient's anticoagulated plasma is combined with calcium and tissue factor prepared from rabbit or human brain tissue. Sensitivity to factor deficiencies depends on the source of the tissue factor. The PT detects deficiencies in fibrinogen, prothrombin, factor V, factor VII, and factor X. It is used to test the extrinsic pathway. A normal control sample is simultaneously run, and the clotting times of both are recorded. The time in seconds is usually given over the normal control time, for example, 12.5/11.5. A PT 2 seconds or more over the control time can be considered significant. Results are usually reported as the international normalized ratio (INR), which compensates for differences in sensitivity of various thromboplastin reagents to the effects of warfarin. The test is helpful in monitoring the use of coumarin anticoagulants, and the time may be prolonged in patients with liver disease and other abnormalities of vitamin K–sensitive factors.[20]

Partial Thromboplastin Time

The partial thromboplastin time (PTT) tests the components of the intrinsic and common pathways, that is, essentially all factors but VII and XIII in the entire clotting cascade. In this test a phospholipid source and a contact-activating agent (kaolin) are added to anticoagulated citrate plasma. After an incubation period that allows factor XII to become activated, calcium is added and the clotting time is recorded. A normal control sample is run simultaneously. Normal ranges may vary, and each hospital laboratory should be checked. The average time is 25 to 29 seconds. The sensitivity of the test varies from factor to factor, but factor levels must usually be less than 40% before the PTT is prolonged. The test may be altered by clotting factor inhibitors of external origin (e.g., heparin) or internal origin (e.g., anti-VIII antibody). Inappropriately high values may occur if the plasma is too turbid or icteric. The activated PTT is most sensitive to abnormalities in the sequence of the coagulation cascade that precedes activation of factor X.[20,23,24]

Fibrinogen

Fibrinogen is present in sufficient concentration to be measured directly. Because it is the final coagulation substrate, its level reflects the balance between production and consumption. It may be decreased by hypoproduction, as in severe liver disease, or by overconsumption, as in DIC. Low levels or altered function increase the PT, PTT, and thrombin clotting time. Because fibrinogen is an acute phase reactant, certain conditions, including malignancy, sepsis, inflammation, and pregnancy, may alter the test result.

Thrombin Time

Measurement of the thrombin clotting time bypasses the intrinsic and extrinsic pathways by directly converting fibrinogen to fibrin. It is a useful screening test for both qualitative and quantitative abnormalities of fibrinogen and inhibitors such as heparin and fibrin split products.[20]

Clot Solubility

The result of clot solubility testing may be the only abnormality in disorders involving factor XIII deficiency and some abnormal fibrinogen. A washed clot is incubated in acetic acid or urea. If the clot is not properly cross-linked, it dissolves.[12]

Factor Level Assays

Factor levels are determined either by bioassay, in which the ability of the sample of plasma to normalize controlled substrate-deficient plasma is evaluated, or by immunologic assay. Inhibitor screening tests reveal antibodies in plasma that prolong the normal plasma clotting time when mixed.[9,18,24]

DIFFERENTIAL DIAGNOSIS AND MANAGEMENT

When a bleeding disorder is diagnosed or suggested, the assessment initially includes stabilization, which may necessitate volume, RBC, and coagulation factor replacement. If the disorder is known, clinical complications associated with its underlying pathophysiologic condition must be considered. If the disorder is unknown, a rapid differential diagnosis must be made. A clinically useful scheme approaches bleeding disorders in terms of three constituents: vascular integrity, platelets, and coagulation factors. This differential diagnostic approach can be further divided into inherited and acquired disorders.

Vascular Disorders

Vascular disorders have signs and symptoms similar to those of thrombocytopenic states. The inherited forms are rare. Acquired forms are usually associated with connective tissue changes or endothelial damage. The differential diagnosis of vascular disorders is listed in Box 120-5.[25]

Platelet Disorders

General Approach

Most platelet abnormalities occur in women and are acquired. The bleeding source is usually capillary, with resultant cutaneous and mucosal petechiae or ecchymosis. Epistaxis, menorrhagia, and gastrointestinal bleeding are common initial symptoms. The bleeding is generally mild and occurs immediately after surgery or dental extractions. Petechiae and purpura may be noted on physical examination, and superficial ecchymoses may be found around a venipuncture site. Deep muscle hematomas and hemarthroses are not aspects of the clinical picture. The bleeding time is prolonged, and the platelet count may be low, normal, or high. The differential diagnosis of platelet disorders is listed in Box 120-6.

BOX 120-5 DIFFERENTIAL DIAGNOSIS OF VASCULAR DISORDERS

Inherited
Disorders of connective tissue
- Pseudoxanthoma elasticum
- Ehlers-Danlos syndrome
- Osteogenesis imperfecta

Disorders of blood vessels
- Hemorrhagic telangiectasia

Acquired
Scurvy (vitamin C deficiency)
Simple or senile purpura
Purpura secondary to steroid use
Vascular damage
- Infection (meningococcemia)
- Hemolytic-uremic syndrome
- Hypoxemia
- Thrombotic thrombocytopenic purpura
- Snakebite
- Dysproteinemic purpura

BOX 120-6 DIFFERENTIAL DIAGNOSIS OF PLATELET DISORDERS

Thrombocytopenia
Decreased production
- Decreased megakaryocytes secondary to drugs, toxins, or infection
- Normal megakaryocytes with megaloblastic hematopoiesis or hereditary origin

Platelet pooling and splenic sequestration
Increased destruction
- Immunologic
  - Related to collagen vascular disease, lymphoma, leukemia
  - Drug related
  - Infection
  - Post-transfusion
  - Idiopathic (autoimmune) thrombocytopenic purpura
- Mechanical
  - Disseminated intravascular coagulation
  - Thrombotic thrombocytopenic purpura
  - Hemolytic-uremic syndrome
- Vasculitis

Dilutional secondary to massive blood transfusion

Thrombocytopathy
Adhesion defects such as von Willebrand's disease
Release defects: acquired and drug related
Aggregation defects such as in thrombasthenia

Thrombocytosis
Autonomous (primary thrombocythemia)
Reactive (secondary thrombocythemia)
Iron deficiency
Infection/inflammatory
Trauma
Nonhematologic malignancy
Postsplenectomy
Rebound from alcohol, cytotoxic drug therapy, folate/vitamin B_{12} deficiency

Thrombocytopenia

Decreased Production. Thrombocytopenia from decreased bone marrow production is usually caused by the effects of chemotherapeutic drugs, myelophthisic disease, or direct bone marrow effects of alcohol or thiazides.

Splenic Sequestration. Splenic sequestration is rare and seen primarily with hypersplenism resulting from hematologic malignancy, portal hypertension, or disorders involving increased splenic RBC destruction, such as hereditary spherocytosis or autoimmune hemolytic anemia.[26]

Increased Destruction

Immune Thrombocytopenia. Thrombocytopenia associated with increased peripheral destruction of platelets and shortened platelet survival caused by an antiplatelet antibody is seen in a number of diseases. In most cases a cause is identifiable.

Collagen vascular diseases, particularly systemic lupus erythematosus, may cause an antiplatelet antibody–related platelet decrease. Similar associations have been noted with leukemia and lymphoma, particularly lymphocytic lymphoma. All evaluations of suggested immune thrombocytopenia should include a CBC, peripheral smear, antinuclear antibody test, and bone marrow examination.[27] A number of drugs have been associated with thrombocytopenia of immunologic origin. Quinine and quinidine are common offenders that affect platelets through an "innocent bystander" mechanism. The platelet is coated with a drug-antibody complex, complement is fixed, and intravascular platelet lysis occurs. Because of its relatively high frequency, heparin is an important cause of drug-induced thrombocytopenia in hospitalized patients. Platelets are activated by the formation of an IgG-heparin complex.

Low-molecular-weight heparin may be associated with less thrombocytopenia than standard, unfractionated heparin; however, both forms of heparin demonstrate cross-reactivity.[28] Heparin-induced thrombocytopenia (HIT) is a serious immune-mediated side effect associated with heparin. HIT occurs in 0.76 to 2.6% of patients receiving unfractionated heparin and in less than 1% of those receiving low-molecular-weight heparin. It usually occurs within 5 to 7 days of heparin treatment. Thrombus develops in approximately half the patients with HIT. The thrombotic complications can lead to loss of a limb in up to 20% and death in as many as 30%. The diagnosis should be suggested in the presence of absolute thrombocytopenia or a greater than 50% reduction in platelets after the initiation of heparin. The most specific diagnostic tests for HIT are serotonin release assays, heparin-induced platelet aggregation assays, and solid-phase immunoassays. Platelet-associated IgG levels are commonly elevated, but this finding is less specific or sensitive than the other diagnostic tests. More concerning to the emergency physician is delayed-onset HIT. This form of HIT occurs a median of 14 days after the initiation of heparin, but it has been reported to occur up to 40 days after starting heparin. Arterial or venous thrombosis typically develops in patients with HIT after receiving heparin. Treatment of thrombotic complications in these patients involves the use of direct thrombin inhibitors (lepirudin, argatroban), factor Xa inhibitors (fondaparinux), or heparinoids (danaproid).[29-32]

Digitoxin, sulfonamides, phenytoin, and aspirin are other problem drugs. The patient has usually ingested the medication within 24 hours. An idiopathic thrombocytopenic purpura (ITP) type of syndrome has been reported in intravenous cocaine users.[33] Clinical trials with platelet glycoprotein IIb-IIIa antagonists suggest that intravenous glycoprotein IIb-IIIa inhibitors may confer an increased risk for associated thrombocytopenia, independent of heparin therapy.[34] The platelet count may fall below 10,000/mm^3 and be complicated by serious bleeding. Laboratory testing may confirm the presence of antibody, especially with the use of quinine and quinidine. After stopping administration of the drug, the platelet count improves slowly over a period of 3 to 7 days. A short course of

corticosteroid therapy such as prednisone in a dose of 1 mg/kg with rapid tapering may facilitate recovery.[35,36]

Postinfectious immune thrombocytopenia is usually associated with viral diseases such as rubella, rubeola, and varicella. Although many cases associated with sepsis have a mechanical origin, some immune mechanisms have been demonstrated.[35]

Post-transfusion thrombocytopenia is a rare disorder that causes a precipitous fall in platelets approximately 1 week after the transfusion. In 90% of cases, its origin is linked to the 98% of the population carrying a PLA1 antigen on platelets. Despite the fact that 2% of blood recipients are mismatched with respect to this antigen, it is fortunately a rare occurrence. When transfused into a PLA1 antigen-negative patient, the platelets with attached PLA1 antibodies provoke an anamnestic response, but the actual mechanism of platelet destruction remains unknown. The platelet count often falls precipitously below 10,000/mm^3, with a significant risk for major bleeding. Intracranial hemorrhage occurs in approximately 10% of such cases. Patients are usually middle-aged women with a history of pregnancy who may have been previously sensitized to the PLA1 antigen during pregnancy. Plasma exchange therapy is an effective antidote.[35,37]

Idiopathic Thrombocytopenic Purpura. Autoimmune idiopathic thrombocytopenic purpura (ITP) should be considered after other causes have been excluded. ITP is associated with an IgG antiplatelet antibody that has proved difficult to detect. The two clinically important forms are acute and chronic.[27,38,39]

The acute form of ITP is seen most often in children 2 to 6 years of age. A viral prodrome commonly occurs within 3 weeks of its onset. The platelet count falls, usually to less than 20,000/mm^3. The course is self-limited, with a greater than 90% rate of spontaneous remission. Morbidity and mortality rates are low, although full recovery may take several weeks. Treatment is supportive, and steroid therapy does not alter the disease course.[35,39]

The more chronic form of ITP is primarily an adult disease found three times more often in women than men. The onset of chronic ITP is insidious, without a prodrome, and it is manifested as easy bruising, prolonged menses, and mucosal bleeding. The patient may have petechiae or purpura, and platelet counts between 30,000/mm^3 and 100,000/mm^3 are common. Bleeding complications are of unpredictable frequency and severity, although the long-term mortality rate is approximately 1%.[38,39] Splenomegaly is unusual in either acute or chronic ITP.

Recently a thrombopoietin-receptor agonist, eltrombopag, has been shown to increase platelet counts in patient with relapsed or refractory ITP.[40] Eltrombopag has also been used to increase platelet counts in patients with cirrhosis secondary to hepatitis C virus.[41] The role that this and other thrombopoietic agents have in the standard treatment of thrombocytopenia remains to be defined. The course is one of waxing and waning severity, and spontaneous remission is rare.

Associated diseases, such as lymphoma and systemic lupus erythematosus, must be ruled out before the diagnosis can be made. Quantitative laboratory tests of antiplatelet antibody may differentiate between patients who will favorably respond to therapy and those who will not. Hospitalization is recommended during the initial evaluation because the differential diagnosis is complex and the risk of bleeding is significant. Treatment usually includes corticosteroids, splenectomy, and in refractory cases, immunosuppressive therapy such as with cyclophosphamide, azathioprine, or vincristine. Plasmapheresis, androgens, immune globulin, anti-Rh(D), danazol, and colchicine have all met with varied success. Platelet transfusions are used only to control life-threatening bleeding because of increased antiplatelet antibody titers and short-lived hemostatic effect. Though rare, life-threatening bleeding should be treated with platelet transfusions, intravenous immune globulin (1 g/kg), and methylprednisolone (30 mg/kg IV). Otherwise, care is supportive. The use of all nonessential drugs should be stopped, particularly those that might inhibit platelet function, such as aspirin.[35,38,39,42,43]

A similar pattern of thrombocytopenic purpura has been reported in sexually active homosexual men. Although the clinical findings and response to therapy mimic ITP, the mechanism is believed to be nonspecific deposition of immune complexes and complement rather than antiplatelet IgG.[44]

Nonimmune Thrombocytopenia. Nonimmune platelet destruction is usually consumptive or mechanical. Consumption occurs as part of the process of intravascular coagulation, although it may be seen at sites of significant endothelial loss. Thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome, and vasculitis all initiate platelet destruction through endothelial damage.[45,46] The most striking difference between the first two is the age at onset and the prognosis.

Thrombotic Thrombocytopenic Purpura. The pathologic state of TTP is the result of subendothelial and intraluminal deposits of fibrin and platelet aggregates in capillaries and arterioles. Hemolytic uremic syndrome is considered to be very similar to TTP; however, the former is associated with less central nervous system and more renal involvement than TTP is. Although the initiating event is unclear, prostacyclin and abnormal platelet aggregation are believed to play a central role in pathogenesis of the disease. The disease may affect patients of any age or sex, but the majority are 10 to 40 years of age and 60% of cases occur in women. Most cases of TTP are idiopathic. However, TTP can be associated with medications. Quinine is the most common drug associated with the disease. The antiplatelet drugs ticlopidine and clopidogrel, which are used to treat a variety of cardiovascular and cerebrovascular disorders, have also been associated with TTP. It is classically seen as the constellation of thrombocytopenic purpura, microangiopathic hemolytic anemia, fluctuating neurologic symptoms, renal disease, and fever, but only 40% of cases have the classic pentad.

The platelet count ranges from 10,000/mm^3 to 50,000/mm^3, and generalized purpura and bleeding complaints are common. Anemia is universal, with hematocrit levels commonly less than 20%. The hemolysis may cause jaundice or pallor, and the blood smear characteristically contains numerous schistocytes and fragmented RBCs. Neurologic symptoms include stroke, seizures, paresthesias, altered levels of consciousness, and coma, all of which characteristically fluctuate in severity. The renal component varies from hematuria and proteinuria to acute renal failure. Fever is present in 90% of patients.

Untreated, the disease follows a progressive and fatal course, with 80% mortality rate 1 to 3 months after diagnosis. Therapy has included corticosteroids, splenectomy, anticoagulation, exchange transfusion, and dextran. However, plasma exchange with fresh frozen plasma (plasmapheresis) is the current treatment of choice. Over the last several years, the aggressive use of plasma exchange has reduced the mortality rate from 90 to 17%. In addition to plasma exchange, initial therapy may also include steroids such as prednisone and antiplatelet agents such as aspirin and dipyridamole (Persantine). Splenectomy, immune globulin, vincristine, and other therapies may have a role in resistant cases. With the exception of life-threatening bleeding, platelet transfusion should be avoided because platelets may cause additional thrombi in the microcirculation.[45-50]

Dilutional Thrombocytopenia. Dilutional thrombocytopenia occurs in cases of massive transfusion, exchange transfusion, or extracorporeal circulation. Volume replacement with stored bank blood is platelet-poor because platelets have a life span

of only 9 days. The number of transfusions directly correlates with the degree of thrombocytopenia. Current transfusion practice is to monitor platelet counts for every 10 U of RBCs and transfuse once the platelet count approaches 50,000/mm^3.[46]

Thrombocytopathy

Knowledge of abnormal platelet function as a clinical disorder has grown rapidly in recent years. The drug-induced form may be one of the most commonly seen causes of abnormal bleeding.[36] Defects may occur at any level of platelet function, including adhesion, release, and aggregation.

Adhesion Defects. The representative adhesion disorder is von Willebrand's disease, which is more a factor VIII problem than a platelet deficiency. Platelets are normal in terms of their morphologic condition, number, release, and aggregation. The abnormal adhesion results not from the platelet but from an endothelium-based plasma deficiency of a factor VIII component (vWF) that permits platelet adhesion.[51,52]

Release Defects. Release defects include "storage pool" syndromes in which release is normal but amounts of adenosine diphosphate, calcium, and serotonin are decreased. Release defects may be congenital or acquired, as in systemic lupus erythematosus, alcoholism, or lymphoma. Drugs induce the most common release problem. Aspirin and related drugs block the enzyme cyclooxygenase, which participates in thromboxane A_2 formation. Decreased release of thromboxane A_2 results in decreased aggregation and less local vasoconstriction. Both may contribute to an increased risk of bleeding. Testing for this risk has been suggested by development of the postaspirin bleeding time as a screening test for hemostatic disorders. Aspirin is unique in that it permanently poisons this reaction for the life of the platelet in dosages of only 300 to 600 mg. Phenylbutazone and indomethacin affect function only while measurably circulating. A similar problem may occur in patients with uremia or dysproteinemia and as a rare inherited form.[5,6,53]

Aggregation Defects. Primary aggregation defects are associated with the rare recessive trait thrombasthenia. This platelet membrane abnormality may be detected by the lack of clot retraction during a 2-hour clot retraction test.[20]

Platelet Transfusions. Most platelet function disorders are not treated by platelet transfusion because its efficacy is questionable and alloimmunization may occur. Platelet transfusions are commonly indicated for primary bone marrow disorders (e.g., aplastic anemia or acute leukemia). Assessing the risk for spontaneous bleeding by using platelet counts is an imprecise science. Less mature platelets associated with peripheral consumption or sequestration are less likely to allow spontaneous hemorrhage than are those associated with primary bone marrow involvement. An estimate of functionality is combined with the platelet count for a better predictor of primary hemostasis potential. At counts below 50,000/mm^3, a variable degree of risk exists, especially that associated with trauma, ulcers, or invasive procedures. At counts higher than 50,000/mm^3, hemorrhage caused by platelet deficiency is unlikely. The transfusion threshold for platelets in trauma is not well defined and may be as high as 75,000/mm^3 to 80,000/mm^3. Spontaneous bleeding in the absence of surgery, trauma, or other risk factors may occur in patients with platelet counts less than 10,000/mm^3.[54]

Thrombocytosis

Thrombocytosis may be discovered in the ED. The reactive form is considered benign. The differential diagnosis (see Box 120-6) should be considered when confronted with a platelet count higher than 600,000 to 1,000,000/mm^3. The primary or autonomous state may be associated with bleeding or thrombosis. It is often an associated finding in patients with polycythemia vera, myelofibrosis, or chronic myelogenous leukemia. Suggested autonomous thrombocytosis requires a full hematologic evaluation.[1,55]

Disorders of the Coagulation Pathway

The coagulation system accomplishes secondary hemostasis through a complex enzymatic cascade. The clinically significant disorders have a number of characteristic features that help differentiate them from platelet disorders, including the following:[18]

1. The bleeding source is often an intramuscular or deep soft tissue hematoma from small arterioles.
2. The congenital form of the disease occurs predominantly in men, often as a sex-linked inheritance.
3. Bleeding may occur after surgery or trauma but is delayed in onset up to 72 hours.
4. Epistaxis, menorrhagia, and gastrointestinal sources of bleeding are rare, whereas hematuria and hemarthrosis are common in severe cases.
5. The bleeding time is normal except in patients with von Willebrand's disease.

The PT and PTT are the basic laboratory diagnostic tools for the evaluation of coagulation disorders and can be used to organize the approach to their diagnosis.[18]

Abnormal Prothrombin Time and Other Tests Normal

An elevated PT reflects an extrinsic pathway abnormality mediated through deficiency of factor VII. The hereditary form is caused by a rare autosomal recessive gene. The acquired form is commonly seen and may be a result of vitamin K deficiency, coumarin use, or liver disease. Because factor VII has the shortest half-life (3–5 hours) of the coagulation factors, it is the first to manifest a deficiency when its active form is underproduced. The PT is a sensitive gauge of hepatic function and the efficacy of warfarin administration. INRs calculate the prothrombin ratio raised to the power of an international sensitivity index for specific thromboplastin reagents. It is recommended with most warfarin therapy that the INR be maintained between 2.0 and 3.0.[56-58]

Abnormal Partial Thromboplastin Time and Other Tests Normal

Two groups of inherited disorders manifest an isolated elevation in the PTT. The first group consists of the contact factors (e.g., XII [Hageman factor]), prekallikrein (Fletcher factor), and high-molecular-weight kinogen. They cause a benign disorder in which the PTT is elevated but the patient has no bleeding diathesis. These deficiencies exist as isolated laboratory abnormalities, and thus they should not be invoked as a cause of the patient's bleeding problem. They may be specifically assayed when a precise diagnosis is necessary.[11,17]

The second group causes significant bleeding problems resulting from deficiencies of factors within the intrinsic coagulation system. They are the most common inherited abnormalities of the entire clotting system. Deficiencies of factors VIII, IX, and XI account for 99% of inherited bleeding disorders. Patients with active life-threatening bleeding who are thought to have a congenital bleeding disorder can be sup-

ported with fresh frozen plasma, 15 mL/kg, while diagnostic studies are being performed. The risk of viral transmission of hepatitis B or C or human immunodeficiency virus must be considered.

In a patient with a prolonged PTT and a lifelong history of bleeding, the most important tests in initiating the differential diagnosis are factor VIII and factor IX assays. This test measures the ability of the patient's plasma to correct the prolonged PTT of plasma deficient in factor VIII. This ability is compared with that of normal plasma and the result is given as a percentage of normal. The test measures the procoagulant activity of factor VIII but does not discriminate between abnormal activity resulting from abnormal factor VIII or low levels of normal factor VIII. The two forms of this deficiency are hemophilia A and von Willebrand's disease.[9]

Hemophilia A. Hemophilia A is caused by a variant form of factor VIII that is present in normal levels but lacks a clot-promoting property. The incidence is 60 to 80 persons per million population. Of known cases, 70% have been found to have a sex-linked recessive nature; that is, the disease is carried on the X chromosome at location Xq28. Factor VIII circulates in plasma in very low concentration and is normally bound to vWF. The source of factor VIII production is uncertain, but the liver is thought to be a significant source because hemophilia A can be corrected by liver transplantation. A female carrier mating with a normal man would be predicted to pass the disease to half her sons. Likewise, a male hemophiliac would have all normal sons and all carrier daughters. The remaining 25 to 30% of cases of the disease are believed to result from a spontaneous genetic abnormality. The familial form has a remarkable consistency of severity from generation to generation, although the degree of severity has considerable variation. This severity may be directly related to the level of factor VIII coagulant (factor VIII:C) activity. Cases with less than 1% activity are severe, with a tendency toward spontaneous bleeding. Cases with 1 to 5% activity are moderate, with rare spontaneous bleeding but increased problems with surgery or trauma. Cases with 5 to 10% activity and above are considered mild, with little risk of spontaneous bleeding but still with hazards after trauma and surgery. A number of hemophiliacs may have activity above 10% but have few problems under normal conditions. The PTT may lack sensitivity for this group because it is significantly prolonged only at factor VIII:C levels less than 35 to 40%.[9,59-62]

The disease is seen as a disorder of secondary hemostasis with a characteristic pattern of bleeding. Bleeding can occur anywhere, but deep muscles, joints, the urinary tract, and intracranial sites are the most common. Recurrent hemarthrosis and progressive joint destruction are major causes of morbidity in hemophilia. Intracranial bleeding is the major cause of death in all age groups of hemophiliacs. Mucosal bleeding such as epistaxis and oral bleeding or menorrhagia is rare unless the disease is associated with von Willebrand's disease or platelet inhibition, such as with aspirin use. Gastrointestinal bleeding is rare unless peptic ulcer disease is also present. Trauma is a common initiator of bleeding in all stages of severity. This potential hazard must be viewed expectantly in all hemophiliacs because late bleeding may occur, usually by 8 hours but potentially up to 1 to 5 days, and, rarely, even longer after traumatic injury.[60-62]

Management of Hemophilia A. Comprehensive management of hemophilia involves a team effort of physicians, specialized nurses, physical therapists, social workers, the patient, and the patient's family. The therapeutic responsibility of the emergency physician consists of three areas: preparation for and identification of the problem, initial evaluation, and admission of new bleeders; replacement therapy for bleeding episodes; and anticipation of potential life threats and admission of known bleeders for observation in selected circumstances. At one time, treatment of hemophilia-associated bleeding was a relatively common emergency medicine activity, but since 1975, hemophilia home therapy has increasingly been instituted. Therefore, many hemophiliacs now come to the ED only with complicated problems or trauma-related difficulties, and most are knowledgeable about their disease.[60-63]

Preparation. In preparing for the problem, the emergency physician should have updated information covering disease processes and current therapy. A cooperative effort should be made between the ED and the hematology service to generate a file of known hemophiliacs in the area who are monitored at the hospital. The file should include the primary physician, diagnosis, factor VIII activity level, blood type, presence of antihemophilic factor antibodies, and time of last hospitalization. A protocol should be developed for ordering and administering factor VIII.

Replacement Therapy. The accepted therapy for hemophilia A is factor VIII replacement with cryoprecipitate or factor VIII:C concentrates. These concentrates are exposed to heat treatment or solvent-detergent mixtures to decrease transmission of hepatitis B, hepatitis C, and human immunodeficiency virus. In the past, the concentrate was made from fractionated freeze-dried antihemophilic factor and contained 250 to 1500 IU of factor VIII:C in a reconstituted volume. Factor VIII is also produced by recombinant DNA techniques and is considered to be the replacement product of choice. Recombinant-derived factor VIII is comparable to plasma-derived factor VIII in terms of characteristics and control of bleeding, but it has no discernible side effects. Factor VIII:C concentrates are commonly used in severe hemophilia and for home use. Cryoprecipitate is the cold precipitable protein fraction derived from fresh frozen plasma thawed at 1°C to 6°C. It was once the mainstay of hemophilia A therapy and may be used when noninfectious factor VIII concentrates are not available.[63-67]

Plasma-derived replacement therapies pose some risk for hepatitis C and hepatitis B. Persistent hepatitis B surface antigen occurs in the blood of 5% of hemophiliacs, whereas the anti-B surface antigen is found in 80%. This problem has been overshadowed by the association of acquired immunodeficiency syndrome with hemophilia. The association is related to blood product use, and although the total number is low, the incidence is high—3.6 per 1000 hemophilia A patients.[64,65]

Therapy for a bleeding episode includes a number of considerations: the circumstances in which factor VIII is given, the dosage, the timing of maintenance, the duration of the dosage, the presence of antibodies, and the means of gauging effectiveness. Tables 120-1 and 120-2 include guidelines for the recommended treatment in a variety of circumstances. Most importantly, the emergency physician should believe patients who say that they are bleeding and institute early therapy.[61,63]

The response to therapy can be monitored by clinical improvement, a decreasing PTT, and, optimally, serial factor VIII:C activity levels. The infusion of 1 U of factor VIII per kilogram increases factor VIII levels by 2%. The lack of a response to factor VIII administration should raise the possibility of circulating antibodies. All hemophiliacs should be screened for the development of these antihemophilic factor antibodies when they are given in-hospital therapy or if their condition becomes refractory to home therapy. The 7 to 20% of patients in whom these IgG antibodies develop usually have a severe deficiency necessitating multiple factor VIII transfusions. The treatment may be complex, and hospitalization is

Table 120-1 Recommended Factor VIII Therapy for Specific Problems in Hemophilia

TYPE OF BLEEDING	INITIAL DOSAGE	DURATION	COMMENT
Skin			
Abrasion	None	None	Treat with local pressure and topical thrombin
Laceration	Usually none; if necessary, treat as minor	None	Local pressure and anesthetic with epinephrine may benefit; watch 4 hours after suturing; reexamine in 24 hours
Superficial			
Deep	Minor bleeding (12.5 mg/kg)	Single-dose coverage	May need hospitalization for observation; repeat may be necessary for suture removal
Nasal epistaxis			
Spontaneous	Usually none; may need to be treated as mild bleeding	None	Uncommon; consider platelet inhibition; treat in usual manner
Traumatic	Moderate bleeding (25 mg/kg)	Up to 5–7 days	Trauma-related bleeding can be significant
Oral			
Mucosa or tongue bites	Usually none; treat as minor if persists	Single dose	Commonly seen
Traumatic (laceration) or dental extraction	Moderate (25 U/kg) to severe (50 U/kg)	Single dose; may need more	Saliva rich in fibrin lytic activity; oral ε-aminocaproic acid (Amicar) may be given at 100 mg every 6 hr for 7 days to block fibrinolysis; check contraindications; hospitalize patients with severe bleeding
Soft tissue/muscle hematomas	Moderate (25 U/kg) to severe (50 U/kg)	2–5 days	May be complicated by local pressure on nerves or vessels (e.g., iliopsoas, forearm, calf)
Hemarthrosis			
Early	Mild (12.5 U/kg)	Single dose	Treat as earliest symptom (pain); knee, elbow, ankle more common
Late or unresponsive cases of early hemarthrosis	Mild to moderate (25 U/kg)	3–4 days	Arthrocentesis rarely necessary and only with 50% level coverage; immobilization is critical point of therapy
Hematuria	Mild (12.5 U/kg)	2–3 days	Urokinase, the fibrinolytic enzyme, is in urine; with persistent hematuria an organic cause should be ruled out
Major bleeding	Major bleeding (50 U/kg)	7–10 days or 3–5 days after bleeding ceases	In head trauma, therapy should be given prophylactically; early CT scan of head recommended for all
Gastrointestinal severe bleeding			
Neck/sublingual			
Retroperitoneal			
Intra-abdominal			
Major trauma			
Head injury (see text)			
Central nervous system bleeding (see text)			
Surgical procedure			

CT, computed tomography

necessary. A variety of therapies have been considered, including "overwhelming" factor VIII doses, exchange plasmapheresis, immunosuppressive therapy, and the infusion of prothrombin complexes containing activated clotting factors. Other recommended therapies include porcine factor VIII, which has less cross-reactivity with the human product, and probably in the future, recombinant activated factor VIIa. Recombinant factor VIIa has been used in the treatment of some nonhemophiliac patients with serious or intractable bleeding but has not proved more effective than placebo. Until more data are available, the efficacy of recombinant factor VIIa in settings outside of congenital coagulation disorders remains to be determined.[63,68-71] Acquired IgG antihemophilic factor antibodies may exist in nonhemophiliac patients. They can occur in the postpartum period, as immunologic reactions to penicillin or phenytoin, and in association with systemic lupus erythematosus, rheumatoid arthritis, or inflammatory bowel disease. The diagnosis is made by the occurrence of an acquired hemophilia-like syndrome with positive antibody titers in the appropriate setting.

The "lupus anticoagulant" is unique in that it may be associated with an increased risk for thrombosis, as well as a hemorrhagic diathesis.[61,72]

Desmopressin acetate has been shown to increase levels of factors VIII:C and VIII:Ag in patients with hemophilia A and in some with von Willebrand's disease. It is given intrave-

Table 120-2 Dosage of Factor VIII (Antihemophilic Factor)

BLEEDING RISK	DESIRED FACTOR VIII LEVEL (%)	INITIAL DOSE (U/KG)
Mild	5–10	12.5
Moderate	20–30	25
Severe	50 or greater	50

Standard Calculation

1. Patient's plasma volume (50 mL/kg × weight in kg) × (Desired level of factor VIII [percent]) – (Present level of factor VIII [percent]) = Number of units for initial dose.
2. In emergency therapy, the present level of factor VIII is assumed to be zero.
3. One unit is the activity of the coagulation factor present in 1 mL of normal human plasma.
4. Because the half-life of factor VIII is 8–12 hr, the desired level is maintained by giving half the initial dose every 8–12 hr.
5. Cryoprecipitate is assumed to have 80–100 U of factor VIII:C per bag; factor VIII:C concentrates list the units per bottle on the label.

nously at 0.3 μg/kg per dose. Benefits are primarily noted in patients with mild to moderate disease and last for 4 to 6 hours.[73,74]

Prophylaxis. The anticipation of delayed bleeding in patients with hemophilia may necessitate admission and observation for a variety of trauma-related injuries. Candidates for prophylactic admission are patients with deep lacerations; those with soft tissue injuries in areas where the pressure from a developing hematoma could be destructive, such as in the eye, mouth, neck, back, and spinal column; and patients with a history of major trauma forces without injury. Head trauma is potentially life-threatening to hemophiliacs, and central nervous system bleeding is the major cause of death for patients in all age groups. Studies find a 3 to 13% risk of intracranial hemorrhage, yet no patient given replacement therapy within 6 hours had intracranial bleeding. It is recommended that patients who sustain head trauma but who have normal CT scans have factor VIII therapy initiated to greater than 50% activity level.[75,76] All hemophiliacs with head trauma should be considered for admission and their primary physician and hematologist consulted early.

Gene therapy represents a potential development in the treatment of hemophilia. With cloning of the genes encoding factor VIII, the possibility exists for either a partial or complete cure of hemophilia. The goal of gene therapy is not to restore factor levels to normal but rather to convert from a severe to a mild phenotype and dramatically improve clinical outcomes. Early studies are encouraging. Although genetic testing and counseling are currently available, no genetic therapies for hemophilia A are available at present.[61,77-80]

von Willebrand's Disease. To understand von Willebrand's disease, it is helpful to review the nomenclature used to refer to factor VIII in some centers. Factor VIII has at least three activities. First is its antihemophilic, or coagulant, activity, VIII:C. All references to factor VIII in this chapter thus far have been to this activity. A second activity supports platelet adhesion and in vitro aggregation with the antibiotic ristocetin; it is called von Willebrand's factor activity, or VIII/vWF. A third component reacts with rabbit antibodies to factor VIII. It is termed the factor VIII antigen, or VIII:Ag, and relates to the measured plasma level rather than the activity of factor VIII. The antigen and cofactor activity for platelet function are structurally related.[52,81] von Willebrand's disease has both decreased factor VIII:Ag levels and decreased VIII:C activity secondary to underproduction. The patient's platelets are normal in number, morphologic condition, and other functions, but in the absence of circulating factor VIII/vWF, their adhering properties are diminished. Von Willebrand's disease is the most common hereditary bleeding disorder, with an estimated prevalence of 1%. The disease occurs in 5 to 10 persons per million population as an autosomal dominant trait with a variable penetrance pattern. A rare X-linked inheritance has been described.[52,81,82]

Manifestations of von Willebrand's disease are usually milder and less crippling than those of hemophilia. The factor VIII:C level is in the 6 to 50% range. Bleeding sites are predominantly mucosal (e.g., epistaxis) and cutaneous. Hemarthroses are rare, but menorrhagia and gastrointestinal bleeding are common. Laboratory differentiation from hemophilia A includes an abnormal bleeding time, a decreased level of factor VIII:Ag, and abnormal platelet aggregation with ristocetin.[83] In patients with severe disease, replacement therapy with factor VIII in the form of intermediate purity factor VIII concentrate is the method of choice. The initial dose is 20 to 30 IU/kg every 12 hours to keep vWF levels at 50% or to control bleeding. A unique response to the transfusion of plasma components in patients with von Willebrand's disease is the stimulation of a progressive increase in VIII:C activity that lasts 12 to 40 hours. After the initial dose, fewer units are necessary, and longer dosage schedules may be followed by a clinical response and a combination of factor VIII:C activity and serial bleeding times.

In extreme circumstances without alternatives, fresh frozen plasma may be used. A factor VIII concentrate (Humate-P) has also demonstrated sufficient VIII/vWF to treat the disease.[54,84] Drug therapy with desmopressin is of benefit in patients with mild to moderately severe von Willebrand's disease. It is most useful in the common form of the disease and ideally would be given in consultation with a hematologist.[35,85,86]

Hemophilia B (Christmas Disease). Hemophilia B is a deficiency of factor IX activity. Its genetic pattern and clinical findings are indistinguishable from those of hemophilia A, but its incidence is only a fifth that of hemophilia A. Factor IX is a vitamin K–dependent glycoprotein. Its deficiency is diagnosed by a factor IX assay, usually after the factor VIII:C assay is found to be normal. The replacement schedule for factor IX is similar to that for hemophilia A, but a purified factor IX concentrate or recombinant factor IX preparation is used. The plasma prothrombin complex (factors II, VII, IX, and X) and fresh frozen plasma are also useful, but they pose a higher risk of viral transmission and venous or arterial thrombosis. The maintenance dosage schedule is increased to every 24 hours because of the longer half-life of factor IX. Clinical concerns and treatment strategies associated with hemophilia A also apply to hemophilia B.[63,87,88]

Similar to hemophilia A, gene testing and counseling are available. Gene therapy in animals has demonstrated promising results, and preliminary results from a human study suggest that the severity of hemophilia B can be altered and improved by gene manipulation.[77,79,89,90]

Miscellaneous Coagulation Disorders

A number of other disorders may be caused by a deficiency in the common coagulation pathway. An altered fibrinogen level or abnormal function is a relatively common cause. Patients with this deficiency also have an abnormal thrombin time. The inherited forms are rare. The acquired forms have been related to fibrin-blocking substances and hypofibrinogenemia, which are found most often in cases of DIC and dysfibrinogenemia associated with macroglobulinemia, multiple myeloma, and hepatoma. In the context of emergency medicine, fibrinogen's most important role relates to its activity in DIC.

The other components of the common pathway (factors II, V, and X) have rare inherited deficiencies. The acquired forms are far more common and relate to vitamin K deficiency (decreased factor II, VII, IX, and X activity), warfarin use (same factors as with vitamin K deficiency), hepatic insufficiency (potentially all factors except VIII), and massive transfusion of stored blood (low in factors V and VIII and platelets).

Disseminated Intravascular Coagulation. DIC is a relatively common acquired coagulopathy. Its ubiquitous nature, multiple origins, and potentially devastating sequelae, balanced by an effective mode of therapy, make early diagnosis of this hematologic process critical. It is most often encountered in the critical care setting. Hemostasis is achieved by a fine balance between procoagulants and inhibitors and thrombus formation and lysis. The balance may be disturbed by pathologic processes that result in an out-of-control coagulation and fibrinolytic cascade within the systemic circulation. The following occurs in this abnormal clotting sequence:

1. Platelets and coagulation factors are consumed, especially fibrinogen and factors V, VIII, and XIII.
2. Thrombin is formed, and it overwhelms its inhibitor system and acts to accelerate the coagulation process and directly activate fibrinogen.
3. Fibrin is deposited in small vessels in multiple organs.
4. The fibrinolytic system by means of plasmin may lyse fibrin and impair thrombin formation.
5. Fibrin degradation products are released and affect platelet function and inhibit fibrin polymerization.
6. Coagulation inhibition levels (e.g., antithrombin III, protein C, and tissue factor pathway inhibitor) are decreased.

The clinical consequence of these processes is the life-threatening combination of a bleeding diathesis from loss of platelets and clotting factors, fibrinolysis, and fibrin degradation product interference; small vessel obstruction and tissue ischemia from fibrin deposition; and RBC injury and anemia from fibrin deposition. The condition must be considered in any patient in whom purpura, a bleeding tendency, and signs of organ injury, particularly the central nervous system and kidney, develop. This broad description is further confused clinically by the variable acuteness and intensity of intravascular clotting, the effectiveness of fibrinolysis, and other systemic manifestations of the initiating disease.[91-93]

The clinical diagnosis is necessarily supported by laboratory tests. The tests recommended in Table 120-3 usually confirm the presence of DIC. Other tests (e.g., specific degradation products of fibrin, particularly D-dimer, and fibrinogen) can confirm the diagnosis. These tests are rarely available in the ED.

Two conditions that may simulate DIC are severe liver disease and primary fibrinolysis. Liver disease of this severity is usually manifested by clinical jaundice and splenomegaly. Primary fibrinolysis is a rare disorder that affects fibrinogen and fibrin but generally leaves the coagulation components (platelets, factor V, and factor VIII) in the low normal range. The paracoagulation test is negative, and the euglobulin lysis time is rapid.[92,93]

When planning therapy, the emergency physician must remember that defibrination is always secondary to a serious underlying pathologic process. Once the diagnosis is confirmed, the initial treatment is focused on reversing the triggering mechanism. Many episodes of DIC are self-limited, such as in a transfusion reaction, or compensated, such as associated with a tumor mass, and do not require intervention other than support.[91,92]

Table 120-3 Laboratory Diagnosis of Disseminated Intravascular Coagulation

TEST	FINDING	PATHOPHYSIOLOGY
Peripheral smear	Low platelets, schistocytes, RBC fragments	RBC fragmentation on fibrin strands; schistocytes not always seen
Platelet count	Low (usually <100,000/mm^3)	Consumed in clotting; lower numbers are reflected in the bleeding time
PT	Prolonged	Factors II and IV consumed
PTT	Prolonged	Factors II, V, and VIII consumed
Thrombin time	Prolonged	Decrease in factor II and fibrin degradation products
Fibrinogen level	Low	Factor II consumed; may be difficult to interpret because it is an acute-phase reactant
Fibrin degradation products (D-dimer)	Zero to large	Dependent on the amount of secondary fibrinolysis
Serum creatinine or urinalysis	May be abnormal	Functional assessment of the organ most commonly injured by fibrin deposition

PT, prothrombin time; PTT, partial thromboplastin time; RBC, red blood cell.

Replacement therapy is usually instituted simultaneously with attempts to control the primary process. The goal is to avoid depletion of clotting factors. Treatment is partially based on which of the two major pathologic components of DIC dominates the clinical picture. If active bleeding is present, replacement therapy with platelets, coagulation factors found in fresh frozen plasma or cryoprecipitate (I, V, VIII), and blood is recommended. Selective replacement therapy can be based on the laboratory and clinical response. Retardation of bleeding, a decrease in fibrin degradation products, and a rise in platelet counts and fibrinogen levels are useful monitors. Normalization of clotting times occurs too late to be of value in monitoring.[91-93]

Heparin has selective use in the treatment of DIC when fibrin deposition and thrombosis dominate the pathologic picture. Certain disease states are associated more with fibrin deposition, in which case heparin therapy should be considered. Examples include purpura fulminans, retained dead fetus before delivery, giant hemangioma, and acute promyelocytic leukemia. Heparin therapy is of little benefit in cases of meningococcemia, abruptio placentae, severe liver disease, and trauma. Low doses of heparin (300–500 U/hr) as a continuous infusion are currently recommended. Low-molecular-weight heparin may also be used instead of unfractionated heparin. Continuous monitoring of the clinical response, heparin levels, and bleeding status is necessary.

Other therapeutic agents such as antithrombin III and activated protein C have been evaluated. However, none has demonstrated an improved outcome in DIC, and only recombinant activated protein C (drotrecogin alfa) has been associated with improved outcomes in septic shock, regardless of whether DIC was present.[94-97]

The goals of emergency care of patients with DIC include initial suggestion, aggressive pursuit of the diagnosis, understanding of potential life-threatening complications, and only rarely, initiation of therapy.

DISPOSITION

All patients with bleeding disorders of unknown cause or of a significant degree should be admitted to the hospital for further evaluation. The circumstances in which a patient with a known bleeding disorder may be discharged for home care are discussed in earlier sections on individual disease states. Transferring these patients may be necessary, particularly if hematologic consultation is not readily available. The standard criteria of hemodynamic stability, appropriate monitoring, and full knowledge and understanding on the part of the family and accepting physician should be met before transfer. Because of the delayed bleeding pattern in hemophiliacs, it may be especially hazardous to transfer them long distances. Therefore, the importance of advance knowledge and preparation is reemphasized. Outpatients are usually treated under the auspices of the hematologic consultant. Early notification and appropriate follow-up arrangements should be made with these specialists.

KEY CONCEPTS

- Although hemostatic disorders are confirmed by specific patterns of laboratory tests, a careful history and focused physical examination are often the key to the diagnosis of hematologic diseases.
- The frequency of hemostatic disorders seen in the ED is unknown; however, they are likely to be more common than thought. Although classic diseases such as hemophilia and DIC are uncommon, the use of antiplatelet and anticoagulation agents is common in other disease states such as cardiovascular diseases.
- Hemophilia patients are often highly informed about their disease. Patient input should be solicited and respected, and early consultation with the patient's hematologist is encouraged. Early treatment with replacement factor while diagnostic testing proceeds is encouraged.
- Platelet dysfunction is often equated with low platelet counts. Even though critical thrombocytopenia increases the risk of bleeding, particularly with trauma and surgery, dysfunction can occur at normal platelet counts. For example, antiplatelet therapy and renal disease can alter platelet function without reducing blood counts.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 121

Selected Oncologic Emergencies

Sandra Ugras-Rey and Mark Watson

PERSPECTIVE

Cancer remains the second leading cause of death in the United States. In 2007 alone, more than 1.4 million cases were diagnosed and 559,000 people died of cancer.[1] The most commonly diagnosed new cancer in men is prostate cancer and in women, breast cancer. The most common cause of cancer death for both sexes is lung and bronchial cancer.[2] Worldwide, the most commonly diagnosed new cancer in men is lung and bronchial cancer and in women breast cancer. Similarly, the most common cause of cancer death worldwide in men is lung and bronchial cancer and in women, breast cancer.[3]

Oncologic emergencies include fever and neutropenia, superior vena cava syndrome (SVCS), acute tumor lysis syndrome, hyperviscosity syndrome (HVS), hyperuricemia, hypercalcemia, neoplastic cardiac tamponade, spinal cord compression, and raised intracranial pressure (ICP). The accurate diagnosis and appropriate treatment of oncologic emergencies can improve the quality of life dramatically in patients with cancer. In addition, a reversible life-threatening emergency can occur in a patient with an underlying malignancy that is otherwise highly treatable or even curable, making identification and management of the oncologic emergency a potentially lifesaving action.

In 2003, it was estimated that the lifetime risk of developing cancer was 1:2 for men and 1:3 for women.[4] Therefore, the emergency department (ED) physician should be well-versed in oncologic emergencies. Many factors can hinder the identification and management of oncologic emergencies in the ED (Box 121-1):

Changing trends in cancer that have produced an increased number of ED visits secondary to cancer and its complications include:

- More aggressive and broader use of chemotherapy regimens
- Increasing use of bone marrow transplantation
- More effective treatment options, increasing cure and survival rates
- Increased number of elderly patients receiving chemotherapy
- Increased survival for all cancers combined[5]

FEVER

Fever in the cancer patient can be caused by inflammation, transfusions, antineoplastics, antimicrobials, and tumor necrosis. Although fever can be secondary to malignancy with a significant tumor burden, most fevers (55–70%) occurring in cancer patients have an infectious origin. Neutropenia is defined as an absolute neutrophil count (ANC) fewer than 500 cells/mm^3 or less than 1000 cells/mm^3 with predicted decrease to less than 500 cells/mm^3. ANC can be calculated as follows:

$$(\text{Total white blood cell [WBC] count}) \times (\text{Percentage of neutrophils and bands})$$ [6]

The risk of infection and morbidity are increased with an ANC less than 1000/mm^3, and substantially higher when counts are less than 100/mm^3. In addition to the ANC, the risk of infection is related to the rate of development and the duration of neutropenia.

Fever in the neutropenic cancer patient should be considered a medical emergency. Prior to the era of empirical antibiotic therapy, infection accounted for almost 75% of mortality related to chemotherapy.[6] Cancer patients with significant fever (defined by the Infectious Disease Society of America as a single oral temperature ≥ 38.3° C [101° F] or an elevation of 38° C [100.4° F] for at least 1 hour) and a polymorphonuclear (PMN) leukocyte count less than 500/mm^3 should be presumed to have an infectious origin. Antimicrobial therapy should be started immediately after appropriate cultures have been obtained.[7]

Clinical Features

Because fever is often the first and occasionally the only sign of infection in the neutropenic cancer patient, the emergency physician must take a careful and thorough history and perform a meticulous physical examination. In the absence of PMNs, traditional markers of inflammation such as erythema, warmth, and pyuria may be absent or minimal, making it essential to search for subtle signs of inflammation. On occasion, a neutropenic patient may not present with fever despite infection. This occurs more commonly in elderly patients and patients on corticosteroids.[6]

Many factors predispose the neutropenic patient to infection and sepsis, including prolonged bedrest, clinical deterioration, nutritional compromise, disruption of mucous membranes and skin barriers, and indwelling catheters. An undetected and untreated infection can be rapidly fatal in this population of patients. Therefore, broad-spectrum empirical antibiotic

BOX 121-1 Factors That Can Hinder Identification and Management of Oncologic Emergencies

- Patient or physician discomfort with the diagnosis of cancer
- A voluminous and frequently changing database of chemotherapeutic agents and complex classification systems
- Time constraints
- Lack of privacy
- Lack of an established physician-patient relationship
- Inappropriate or premature labeling of the cancer patient as "terminal"
- Failure to appreciate that effective treatments are available for oncologic emergencies and many of the cancers that cause them

BOX 121-2 Factors Predisposing to Infection and Sepsis

- Clinical debilitation, prolonged bedrest
- Nutritional compromise
- Disruption of mucous membranes and skin barriers
- Indwelling catheters
- Central nervous system dysfunction secondary to cancer, sedatives, opiates, or psychotropic medications

BOX 121-3 Current Recommendations for Antimicrobial Therapy of Fever in Neutropenic Cancer Patients[2,5,10]

- An antipseudomonal penicillin + an aminoglycoside ± vancomycin
- Ceftazidime ± an aminoglycoside
- Ceftazidime ± vancomycin
- Cefepime ± an aminoglycoside
- Cefepime ± vancomycin
- Imipenem/cilastatin
- Meropenem

therapy should be initiated promptly in all febrile, granulocytopenic patients (Box 121-2). Consulting with the oncologist will help categorize the risk for patients and aid selection of antibiotics based on local resistance patterns (Box 121-3).

Diagnostic Strategies

While antibiotics are being started, the patient should have a complete blood count (CBC) with differential cell count, platelet count, prothrombin time, partial thromboplastin time, blood chemistries, urinalysis, and analysis of any accessible sites suggestive of infection. Two sets of blood culture specimens should be obtained for aerobic, anaerobic, and fungal growth. If an indwelling catheter is present, at least one set of blood culture specimens should be obtained from the device lumen as well as from a peripheral vein.[7] Obtaining a routine chest radiograph is currently the standard of care at most institutions. However, studies show that a chest radiograph is not necessary in patients with no respiratory symptoms and a normal physical examination.[7,8] Urine should be sent for culture even in the absence of pyuria. However, the use of sputum culture and Gram's stain, although still recommended, has become controversial because of inconsistencies in collection and preparation that have led to false-negative and false-positive results.

Some oncologists discourage rectal temperature readings for patients with neutropenia because of the risk of tearing the rectal mucosa and establishing a potential nidus for disseminated infection. However, this has not yet become the standard of care and may vary among institutions. An indwelling nasogastric tube predisposes the neutropenic patient to sinusitis. When imaging for suggested sinusitis is required, computed tomography (CT) rather than sinus films is preferred. A lumbar puncture, preceded by head CT, is indicated when symptoms point to the central nervous system (CNS). Some authorities have recommended surveillance cultures of the stool, nose, and throat. This recommendation is not universally accepted and is generally not indicated in patients with solid tumors. Despite an intensive and comprehensive evaluation, an infectious cause is initially substantiated in only 30% of febrile, granulocytopenic patients.[9] Nuclear scans, gallium citrate, and indium III scans do not have a place in the emergency diagnosis and treatment of these patients but may be useful in the definitive evaluation.

Differential Considerations

Overall, approximately 85% of the initial pathogens are bacterial, and of these, 60 to 70% are gram-positive pathogens. Gram-negative bacilli, particularly *Psuedomonas aeruginosa*, were the most common pathogens until the 1980s. However, the administrations of prophylactic antibiotics primarily active against gram-negative pathogens during chemotherapy, the widespread use of indwelling venous catheters and newer chemotherapy regimens have lead to an increase in gram-positive pathogens.[7,10]

Staphylococcus aureus, *Staphylococcus epidermis*, and *Streptococcus epidermidis* are the predominant gram-positive organisms. Once believed to be a contaminant, *S. epidermidis* has arisen as a major pathogen and may be resistant to antistaphylococcal penicillins and cephalosporins. *Escherichia coli*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae* remain the most common gram-negative pathogens.

Fungal, viral, and parasitic infections are also important primary and secondary complications. Fungal infections, especially with *Candida albicans*, can be a major problem in granulocytopenic febrile patients treated with broad-spectrum antibiotics for protracted periods. Although significant institutional variation has been noted, *Histoplasma*, *Cryptococcus*, *Aspergillus*, and *Phycomycetes* are additional fungal pathogens encountered in the compromised host. In contrast to patients with acquired immunodeficiency syndrome (AIDS), parasitic infections are not a common source of infection in patients with solid tumors. *Pneumocystis jiroveci* (formerly carinii), however, may be seen when corticosteroid use or hematologic malignancy has resulted in lymphocyte dysfunction. Herpes simplex, herpes varicella zoster, and cytomegalovirus are common viral pathogens. The compromised host is at risk for infection from a large number of individual pathogenic agents, thus further complicating the diagnosis and treatment of these patients.[6,11]

In an attempt to prevent these infections, oncologists may initiate antimicrobial prophylaxis with trimethoprim sulfamethoxazole (Bactrim) or quinolones for immunosuppressed patients prior to development of fever.[9] Additionally, recombinant human granulocyte-stimulating colony-stimulating factor (G-CSF) and granulocyte macrophage CSF (GM-CSF) are used to stimulate rapid increase in granulocytes in neutropenic patients in an effort to decrease the duration and degree of neutropenia and immunosupression.[12]

Occasionally fever is without a source and is believed to arise from the underlying disease. However, it is impossible to differentiate using clinical and demographic factors those patients with bacteremia-induced fever from those with unexplained fever. In addition, the absence of physical findings indicative of infection does not exclude a potentially life-threatening septic event because at least 50% of septic patients lack any distinct physical findings. Despite the potential for few physical findings, a meticulous physical examination should be conducted, including the fundi (looking for *Candida* endophthalmitis), rectum, perineum and groin (for perirectal abscess), skin and mucous membranes (for any lesions suggesting malignancy or cellulitis), axillae, and catheters.[6,11]

Management

In the initial evaluation and management of the febrile cancer patient, one must take into account the particular underlying malignancy, prior use of antimicrobial therapy, and how the degree of treatment has affected the host's immunologic compromise. For example, in acute leukemia normal circulating neutrophils and monocytes are largely replaced by blast cells, which do not function well in the phagocytizing and killing of bacterial and fungal agents. Chemotherapeutic agents and irradiation exacerbate or potentiate the underlying defect in already compromised host defenses. Corticosteroids impair granulocyte and mononuclear cell mobilization in leukemic patients. Patients with severely compromised host defenses and those in whom fever is accompanied by an increase in respiratory rate; change in mental status, agitation, or apprehensiveness; and hemodynamic instability should be urgently treated.

The optimal antimicrobial regimen should be synergistic, broad-spectrum, and bactericidal with a low potential for toxicity and chosen for efficacy against the most likely causes of systemic and rapidly progressing infection: *S. areus, S. epidermidis, E. coli, P. aeruginosa,* and *Klebsiella* species. Traditionally, a two-drug regimen was selected because historical studies from the 1980s found that patients with gram-negative bacteremia had a higher survival rate when the isolate was sensitive to and treated with two antibiotics, compared with when the isolate was sensitive to only one of two antibiotics in the combined regimen.

In the past 10 years there has been significant advances in the antimicrobial armamentarium with development of broad-spectrum single agents such as the carbapenems (imipenem/cilastin, meropenem) and the third- to fourth-generation cephalosporins (ceftazidime, cefipime). These agents when investigated as monotherapy for granulocytopenic, febrile patients have been found to be as effective as a dual-drug combination of an antipseudomonal penicillin (ticarcillin, carbenicillin, or pipericillin) plus an aminoglycoside (gentamycin or tobramycin) in clinical trials. Amikacin is generally reserved as a second-line aminoglycoside for isolates that demonstrate aminoglycoside resistance.[7,10,11]

Local resistance patterns should be used to guide treatment. Patients are risk-stratified and then treated accordingly. Patients with fever who appear in good condition are considered low risk. Patients with fever who have severe neutropenia, appear ill, and who are expected to have a protracted course, are high risk.[13]

Use of initial empirical vancomycin is included as first-line therapy at institutions where the incidence of methicillin-resistant *S. aureus* has been significant. Vancomycin should be included empirically in selected patients with:

- Clinically suspected catheter infections
- Known colonization with penicillin- and cephalosporin-resistant pneumococci or methicillin-resistant *S. aureus*
- Positive blood cultures for gram-positive bacteria before final identification and susceptibility testing
- Hypotension or other evidence of cardiovascular impairment

Patients should be admitted to an isolation room if possible, but rapid movement out of a congested waiting room into a private space is the higher priority. Hand washing and reverse isolation techniques should be used.

Current recommendations for antimicrobial therapy of fever in neutropenic cancer patients include the following:[2,5,8-10]

- An antipseudomonal penicillin + an aminoglycoside ± vancomycin
- Ceftazidime ± an aminoglycoside
- Ceftazidime ± vancomycin
- Cefipime ± vancomycin
- Imipenem/cilastin
- Meropenem

SUPERIOR VENA CAVA SYNDROME

Epidemiology

SVCS is an acute or subacute process caused by the obstruction of blood flow through the superior vena cava (SVC) secondary to compression, infiltration, or thrombosis. Malignancy, most commonly lung cancer, is the most common cause of SVCS and currently accounts for 60 to 85 % of cases of SVCS.[14] In fact, SVCS is often the initial presenting sign of the tumor.[15]

In recent years, benign causes for SVCS have gradually increased due to increasing use of intravascular devices.[14] Other common nonmalignant causes include goiter, pericardial constriction, primary thrombosis, idiopathic sclerosing aortitis, tuberculous mediastinitis, fibrosing mediastinitis (histoplasmosis and methysergide treatment), arteriosclerotic or (rarely) luetic aneurysm, nephritic syndrome, and indwelling central venous catheters.[16,17] In contrast to the adult population SVCS in pediatric patients is most often iatrogenic secondary to indwelling catheters, ventriculoperitoneal shunts, and complications of cardiovascular surgical procedures.

Clinical Features

Knowledge of the unique anatomic relationship of the SVC in the anterior superior mediastinum is crucial to understanding the clinical presentation of SVC obstruction. The SVC is easily compressed by any of its bounding contiguous structures (trachea, heart, aorta, azygos vein, and paratracheal and bronchial lymph nodes). This compression can produce a constellation of symptoms that reveal the exact site of the pathophysiologic process (Fig. 121-1). The SVC arises from the innominate veins, which in turn arise from the internal jugular and subclavian veins. The azygos vein, the last main auxiliary vessel of the SVC, drains blood from the chest wall. As a consequence of this anatomic relationship, if the SVC is blocked above or at the entrance of the azygos, blood may bypass and decompress the obstruction through the chest wall collateral vessels and rejoin the SVC via the azygos. If the obstruction falls below or at the entrance of the azygos, blood must traverse in a retrograde manner down the azygos and other chest wall veins to reach the drainage area of the inferior vena cava and subsequently cause more prominent symptoms.[18] The severity of the syndrome is also related to the rate at which complete obstruction occurs. The more gradual the onset of obstruction, the longer the time for development of collateralization with less severe symptomatology.[2]

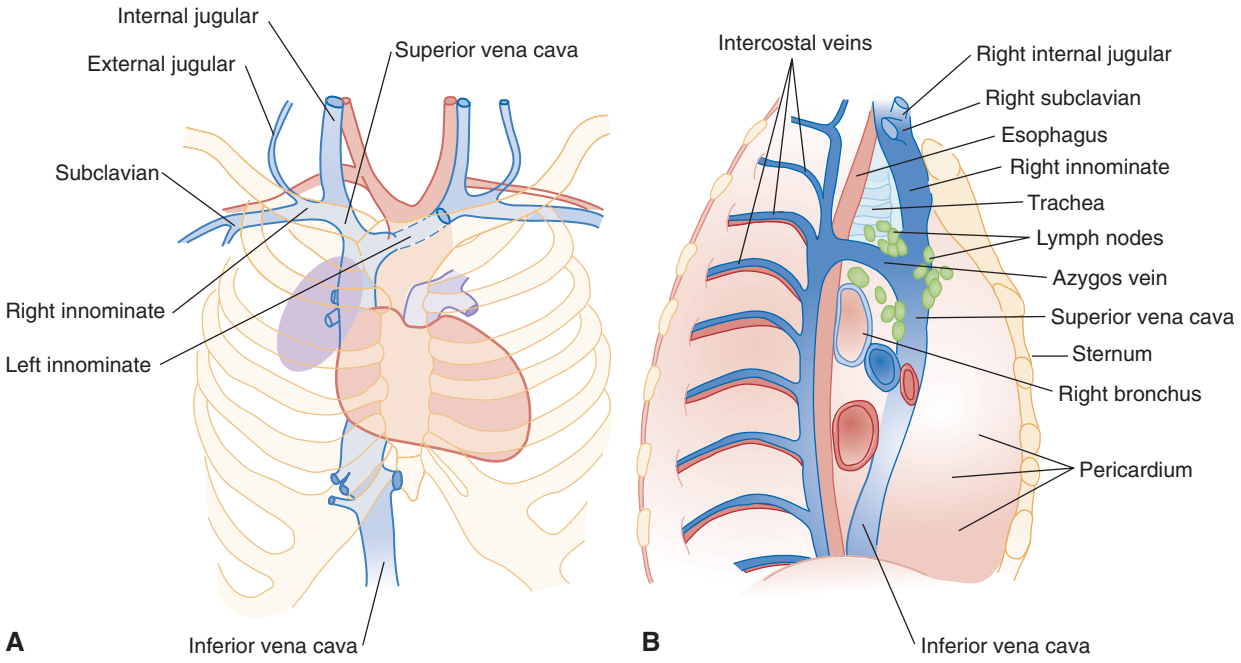

Figure 121-1. Frontal (**A**) and sagittal (**B**) sections of the thorax showing the relationship of the azygos vein to the superior vena cava (SVC), coalescence of innominates to form the SVC at the right second rib, and encasement of the SVC by nodal structures. Shaded area indicates classical site of obstruction. (From Lokich JL, Goodman R: Superior vena cava syndrome. JAMA 231:58, 1975.)

Because the clinical features of the SVCs are characterized by venous hypertension within the area ordinarily drained by the SVC, many of the findings are more noticeably evident in the recumbent or stooped-over position.

Early signs may include periorbital edema, conjunctival suffusion, and facial swelling, which will be most evident in the early morning hours and subside by midmorning. The most common symptom associated with SVCS is dyspnea with swelling of the face, trunk, and upper extremities observed in approximately 40% of patients. Cough, dysphagia, and chest pain are less commonly reported, each occurring in approximately 20% of patients. With increasing impedance to blood flow, the full-blown syndrome begins to manifest itself with thoracic and neck vein distention (67% and 59%, respectively), facial edema (56%), tachypnea (40%), tightness of the shirt collar (the Stoke sign), plethora of the face, edema of the upper extremities, and cyanosis.[18,19]

Early reports of severe SVCS or prolonged and severe SVCS were believed to lead to irreversible thrombosis and death.[20,21] Important concepts have changed since these early reports. Little evidence in the current literature substantiates the notion of untreated SVC obstruction as life-threatening except when it occurs with tracheal compression. Survival in patients with SVCS depends mainly on the course of the underlying disease.[16,18]

SVCS can occur in conjunction with spinal cord compression (Rubin's syndrome). Venous obstruction usually develops before the spinal cord compression, which is localized in most instances to the low cervical or upper thoracic spinal cord. This syndrome is most commonly found with malignancies of lymphoma and lung cancer. Patients with venous obstruction and back pain should be evaluated with magnetic resonance imaging (MRI) of the vertebral spine.

Ancillary Evaluation

The clinical diagnosis of SVC obstruction is mimicked by a few other clinical entities—most noteworthy of which are pericardial tamponade and heart failure, which can usually be excluded by physical examination, and pericardial effusion, which can be excluded by two-dimensional echocardiography. Because SVCS does not usually represent an immediately life-threatening oncologic emergency, once the clinical diagnosis is entertained, a tissue biopsy specimen should be obtained promptly. Although supportive therapy may be instituted to alleviate symptoms, definitive therapy should await the determination of histologic diagnosis because malignancy is known to be the cause of 60 to 85 % of reported cases. The chest film reveals a mass in nearly 10% of patients. When superior mediastinal mass is present, 75% are on the right side, and in approximately 50% of patients the masses are combined with pulmonary lesions or hilar adenopathy.

Pleural effusion is an associated finding in approximately 20 to 25% of patients and is customarily found in the right hemithorax.[14] Morbidity secondary to excessive bleeding from puncture sites has been reported rarely with venous access procedures. IV injections may be less reliable because of slowing of drug distribution. Low flow rates may result in local irritation with thrombosis or phlebitis. Venous access is preferable on the contralateral side to the obstruction.

Venography is relatively contraindicated because of its concomitant bleeding complications. Invasive diagnostic procedures, including bronchcoscopy, mediastinoscopy, scalene node biopsy, and limited thoracotomy are commonly used to establish the diagnosis and extent of the disease. Once SVC obstruction is suggested, the appropriate consulting services should be contacted and plans for prompt diagnosis undertaken.[19,21]

Management

Historically, emergent radiation therapy was the treatment for SVCS. Currently, this is only recommended emergently for patients who present with stridor due to central airway obstruction or severe laryngeal edema. Current management uses chemotherapy because of the increased incidence of tumor

sensitivity to newer antineoplastic agents in an attempt to relieve the obstruction.[15] However, temporizing measures that would alleviate symptoms related to vascular compression should be rapidly instituted.

Elevation of the head of the bed has been shown to be an effective immediate measure. Diuretics have been used with transient symptomatic relief, although they must be used judiciously because they can result in hypovolemia and further slowing of blood flow. Steroids have been shown to be of limited effectiveness but may be useful in the presence of respiratory compromise in reversing symptomatology.[15] Current management approaches include percutaneous transluminal stent placement or bypass surgery.[15,17]

The prognosis for patients treated for SVCS depends on the tumor type, with better survival rates in patients with lymphoma than with bronchogenic carcinoma. The overall survival is approximately 25% at 1 year and 10% at 30 months after treatment.

ACUTE TUMOR LYSIS SYNDROME

Acute tumor lysis syndrome (TLS) refers to the constellation of metabolic disturbances that occur as a result of ongoing cell death in a rapidly growing tumor. It also occurs frequently within a few hours to a few days after the initiation of chemotherapy or radiation therapy to treat bulky and treatment-responsive tumors.

This syndrome is most commonly seen after chemotherapy of hematologic malignancies, including acute leukemias and high-grade non-Hodgkin's lymphomas, particularly Burkitt's lymphoma, in which the growth fraction often exceeds 90%.[22-24] With advances in the effectiveness of chemotherapy it has also been described following treatment of solid tumors such as small-cell lung carcinoma and germ cell tumors.

The risk of acute TLS increases with the bulk of the tumor, with the presence of hyperuricemia or with renal impairment before antineoplastic therapy (Box 121-4). Large numbers of neoplastic cells are killed rapidly, leading to release of intracellular ions and metabolic by-products into the systemic circulation. A correlation between a very high level of blood lactate dehydrogenase and the development of TLS has been observed.[22,24]

Biochemical hallmarks of this syndrome include hyperuricemia (DNA [nucleic acids-purine] breakdown), hyperkalemia (cytosol breakdown), and hyperphosphatemia (protein breakdown). Hypocalcemia develops secondary to hyperphosphatemia. Acute renal failure; cardiac dysrhythmias, neuromuscular symptoms, and sudden death from hyperkalemia or hypocalcemia; and lactic acidosis and metabolic acidosis from acute renal failure may ensue. Early aggressive treatment is crucial.

Clinical Features

Symptoms are related to the underlying malignancy and hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. Hyperuricemia with resultant urate nephropathy is the most commonly recognized metabolic cause of renal insufficiency.[24]

BOX 121-4 RISK FACTORS FOR ACUTE TUMOR LYSIS SYNDROME

Increased lactate dehydrogenase levels (>1500 U/L)
Advanced disease with abdominal involvement
Preexisting renal dysfunction
Post-treatment renal failure
Acidic urine
Concentrated urine
Preexisting volume depletion
Young age

The kidney provides the primary mechanism for excretion of uric acid, potassium, and phosphate. Rapid proliferation of tumor cells may exceed the removal rate of the respective substances, resulting in increased levels. In fact, increased quantities of these substances have been observed in patients undergoing rapid lysis of chemosensitive tumors.

The integrity of renal function is a critical factor in determining the degree of metabolic derangements. In patients with preexisting renal insufficiency, the metabolic derangements of acute tumor lysis are more likely to be severe. However, even when renal function appears normal at the start of treatment, the rapid lysis of certain tumors may overwhelm the excretory capacity of the kidney. Similar to hyperuricemia, hyperphosphatemia may also cause renal failure. A possible mechanism is precipitation of calcium phosphate within the kidney.[24]

Hyperkalemia, along with a contributing hypocalcemia, may result in life-threatening ventricular dysrhythmias.[22] Hypocalcemia may also cause neuromuscular instability with muscle cramps and occasionally tetany. Confusion and convulsions also have been described in case reports.[24]

Management

In approaching a patient with potential TLS, it is "easier to stay out of trouble than get out of trouble."[24] The main principles of TLS management are (1) identification of high-risk patients with initiation of preventive therapy and (2) early recognition of metabolic and renal complications with prompt supportive care, including hemodialysis. Most of the complications can be readily managed when they are recognized early; however, delay in recognition and initiation of treatment of TLS can be life-threatening.[25]

Chemotherapy should be delayed, if possible, until metabolic disturbances, especially prerenal azotemia and hyperuricemia are corrected. Initial management is aimed at the control of preexisting hyperuricemia with hydration, allopurinol, and alkalinization of the urine to a pH greater than 7. Diuretics are added if necessary, and frequent monitoring of electrolytes, calcium, and phosphorus is essential.

Hydration

Volume depletion is a major risk factor for TLS and must be corrected vigorously. Rapid intravenous (IV) hydration is the single most important intervention. Hydration not only helps correct electrolyte disturbances by diluting extracellular fluid, but it also increases intravascular volume. Increased volume enhances renal blood flow, glomerular filtration rate, and urine volume, which consequently decreases the concentration of solutes in the distal nephron and medullary microcirculation. Continuous infusion rates as high as 4 to 5 L/day yielding urine volumes of at least 2 to 3 L/day should be given unless the patient's cardiovascular status indicates impending volume overload. Ideally, IV hydration in high risk patients should begin 24 to 48 hours prior to initiation of cancer therapy and continue for 48 to 72 hours after completion of chemotherapy.[25]

Hyperuricemia

Allopurinol is a xanthine oxidase inhibitor and is given to reduce the conversion of nucleic acid by-products to uric acid in order to prevent urate nephropathy and subsequent oliguric

BOX 121-5 CRITERIA FOR INSTITUTING HEMODIALYSIS

Serum potassium 6 mEq (6 mmol/L)
Serum uric acid 10 mg/dL (590 mol/L)
Serum creatinine 10 mg/dL (880 mol/L)
Serum phosphorus 10 mg/dL (phosphate 3.2 mmol/L) or rapidly rising
To reduce volume overload
Symptomatic hypocalcemia

renal failure. Because allopurinol inhibits the synthesis of uric acid but has no effect on preexisting uric acid, uric acid levels usually do not fall until after 48 to 72 hours of treatment. Allopurinol usually is given orally between 300 and 600 mg/day for prophylaxis and 600 to 900 mg/day for treatment of TLS.[25]

Rasburicase (recombinant urate oxidase) is a newer therapy that can be used when the uric acid levels cannot be lowered sufficiently by standard approaches. This modality of treatment is rarely initiated by emergency physicians. Rasburicase is useful in cases of hyperuricemia. Humans don't express urate oxidase; urate oxidase catalyses the conversion of poorly soluble uric acid to soluble allantoin. By converting uric acid to water-soluble metabolites, it effectively and rapidly decreases plasma and urinary uric acid levels. Unlike allopurinol, rasburicase does not increase the excretion of xanthine and other purine metabolites; therefore, it does not increase tubule crystallization of these compounds, thereby decreasing the risk of urate nephropathy.[25]

Most articles agree that it is wise to alkalinize the urine as a prophylactic measure against hyperuricemia, but caution is advised should hyperphosphatemia and hypocalcemia develop. In patients with concomitant hyperphosphatemia, alkalinization favors precipitation of calcium/phosphate complexes in the renal tubules. Furthermore, alkali therapy may aggravate manifestations of hypocalcemia such as tetany.[22,26] Although alkalinization increases the solubility of uric acid, the primary means of uric acid control is hydration and diuresis to maintain adequate urinary flow.[24,26]

The use of furosemide or mannitol for osmotic diuresis has not proven to be beneficial as front-line therapy. In fact, these modalities may contribute to uric acid or calcium phosphate precipitation in renal tubules in a volume-contracted patient. Instead, diuretics should be reserved for well-hydrated patients with insufficient diuresis, and furosemide alone should be considered for the normovolemic patient with hyperkalemia or for the patient with evidence of fluid overload.

If TLS develops and it is refractory to the previously mentioned treatments, hemodialysis should be considered as a potentially lifesaving measure. This therapy is effective in lowering uric acid, potassium, and phosphate levels, as well as in controlling uremic symptoms. See the suggested criteria for instituting hemodialysis in Box 121-5.

The prognosis is good in the absence of renal failure. If renal failure exists and hemodialysis of 5 to 7 days is necessary, the prognosis is grave. With aggressive management, the incidence of renal and metabolic complications of cytoreductive therapy may be decreased.

HYPERVISCOSITY SYNDROME

Hyperviscosity syndrome (HVS) refers to the clinical sequelae of increased blood viscosity. Viscosity is the resistance that a liquid exhibits to the flow of one layer over another. Excessive elevations in certain paraproteins (circulating immunoglobulins) or cellular blood components (leukocytosis, erythrocytosis, and thrombocytosis) can result in elevated serum viscosity and the development of significant sludging, decreased perfusion of the microcirculation, and vascular stasis.

The outcome of these pathophysiologic events leads to the development of HVS, which requires urgent medical therapy to forestall or reverse the effects of sludging in the microcirculation of the CNS, visual system, and cardiopulmonary system.[27]

Pathophysiology

HVS is most commonly associated with plasma cell dyscrasias (the paraproteinemias) and is due to the large size of the excess immunoglobulin M (IgM) paraproteins in these disorders. Waldenström's macroglobulinemia is the most common cause and accounts for about 85 to 90% of cases of HVS. Less frequently, the disease can occur in multiple myeloma (especially with myeloma proteins of the IgA and IgG_3 types). Other causes include cryoglobulinemia, a benign hyperglobulinemia of the IgM-IgG type, and leukemias.[27-29]

The blastic phase of chronic myelogenous leukemia, chronic granulocytic leukemia, and the blast cell crisis of acute lymphoblastic and nonlymphoblastic leukemias also commonly cause HVS.[27,28] Other more benign causes include leukemoid reaction, polycythemia vera, and the accumulation of abnormal hemoglobins in sickle cell disease. The incidence of HVS in Waldenström's macroglobulinemia is found to be approximately 20%, in IgG myeloma approximately 4.2%, and in IgA myeloma as high as 25%.[28]

The inherent physiochemical properties of the dysproteinemias along with extremely high concentrations of these proteins seem to predispose to the development of hyperviscosity. Paradoxically, HSV also has been reported in κ-light-chain disease owing to a greater tendency to form unstable, highly polymerized circulating aggregates. The etiologic factor most responsible for HVS in the leukemias appears to be leukocytosis with WBC counts in excess of 100,000, usually accompanied by blast forms exceeding 100,000 in the peripheral smear. The clinical manifestations of HVS become most apparent when the serum viscosity relative to water is greater than 4 to 5, normal serum viscosity relative to water being 1.4 to 1.8.[27-29]

Clinical Features

A symptomatic triad of mucosal bleeding, visual disturbances, and neurologic manifestations is a classic presentation of HSV. Visual disturbances and, on occasion, visual loss may occur with retinopathy characterized by venous engorgement (e.g., "sausage-link" or "boxcar" segmentation), which is also seen in the bulbar conjunctiva, microaneurysms, hemorrhages, exudates, and occasionally papilledema. Persistent bleeding diatheses from mucosal surfaces, especially nasal mucosa, the gastrointestinal (GI) tract, and sites of minor surgery or trauma, even in the face of a normal platelet count, are common. Other clinical findings encompass myriad neurologic disturbances, including headache, dizziness, jacksonian and generalized seizures, somnolence, lethargy, coma, auditory disturbances (including hearing loss), and hypotension. Constitutional symptoms of fatigue, anorexia, and weight loss that are nonspecific early on are commonly associated with the underlying malignancy or with numerous electrolyte disturbances related to the underlying malignant process. Cardiopulmonary findings, including acute respiratory failure and hypoxemia, congestive heart failure, myocardial infarction, and valvular abnormalities have all been reported. Renal insufficiency and

failure may be a complication of the syndrome and will exacerbate existing clinical findings secondary to the expanded plasma volume.[27,28]

The laboratory evaluation of the patient with suggested HVS should include a coagulation study and renal, electrolyte, and differential white count profiles. Serum and urine protein electrophoresis should be done in all cases of suggested dysproteinemias; the diagnosis is supported by a large spike on the serum electrophoresis. A clue to the presence of hyperviscosity may be the inability of the laboratory to perform chemical tests on the blood because of the serum stasis and increased viscosity that jams analyzers. In multiple myeloma significant hypercalcemia may also occur, and with high M-protein fractions a factitious hyponatremia may be present. The diagnosis may be also entertained when a patient is brought to the emergency room in a stupor or coma and anemia and rouleaux formation are found on the peripheral smear.[30]

Because HVS is often a presenting characteristic of dysproteinemias and leukemias with blastic transformation and because a history of previously documented disease is often absent, this syndrome should be considered in patients with unexplained somnolence and coma.

Management

Emergency leukapheresis or plasmapheresis is the definitive treatment. Temporizing measures provided by the emergency physician should focus on adequate rehydration and diuresis. An immediate temporizing measure in a patient with frank coma and an established paraproteinemia is a two-unit phlebotomy with replacement of the patient's RBCs with physiologic saline.[27-30] After plasmapheresis or leukapheresis has adequately alleviated the clinical findings, chemotherapeutic modalities can be used.

HYPERURICEMIA

Hyperuricemia is a serious and well-known consequence of certain malignant disorders, which, if recognized early, can result in a significant decrease in morbidity for the cancer patient. The major source is cell breakdown, and its major excretory pathway is via the kidneys.

Pathophysiology

The pathogenesis of hyperuricemia results from either the increased production or decreased excretion of uric acid, or both. Increased production of uric acid commonly results from accelerated generation of uric acid through purine metabolism as a result of rapid dissolution of neoplastic tissues (cell death) following chemotherapy or radiation therapy of undifferentiated lymphomas or lymphoblastic lymphomas and rapid cell proliferation and turnover with acute lymphoblastic leukemias.

In addition, hyperuricemia may be seen with multiple myeloma and occasionally with disseminated metastatic carcinoma. With massive release of precursors, uric acid levels rise precipitously and may reach levels as high as 15 to 20 mg/dL. As a result, uric acid crystals form in the highly concentrated and acidified urine of the distal tubules, intrarenal obstruction follows, and acute renal failure ensues.[24,31]

Chronic, moderately elevated levels of the serum uric acid may result in renal colic, obstructive uropathy, or chronic renal failure. Either uric acid renal calculi or interstitial deposits of sodium urate may develop. This situation is associated with neoplastic overproduction of uric acid precursors. Polycythemia vera, myeloid metaplasia, mast cell disease, and chronic granulocytic leukemia are often associated with this type of hyperuricemia.

Decreased excretion may be a result of underlying renal insufficiency or as a consequence of precipitation of urates in the renal tubules, parenchyma, or ureters with subsequent development of renal insufficiency and further reduction in excretion of uric acid. Three types of renal diseases are attributable to hyperuricemia: acute hyperuricemic nephropathy, uric acid nephrolithiasis, and gouty nephropathy.

Clinical Features

Hyperuricemia can occur with or without symptoms. Symptoms may be associated with the underlying malignancy. Hyperuricemia precipitated or aggravated by therapy of these diseases may occur as an isolated metabolic disturbance or may be accompanied by other manifestations of the TLS (see previous discussion on TLS). If an underlying neoplastic disease has been diagnosed, the possibility of hyperuricemia should be investigated before, during, and after treatment with chemotherapy or radiation. The hyperuricemia should be treated to prevent renal damage. In patients with urate stones and hyperuricemia, examination of the peripheral blood may provide evidence of an underlying myeloproliferative disorder. Acute oliguria following chemotherapy or radiation therapy suggests the diagnosis of hyperuricemia, and the uric acid level in the blood often far exceeds that associated with acute renal failure.

A number of benign diseases are associated with hyperuricemia that may coexist with neoplasia. These include hereditary gout, hyperparathyroidism, psoriasis, sarcoidosis, and renal failure of any cause. The long-term administration of certain drugs may lead to elevation of the serum uric acid level. Various diuretics, including thiazides and furosemide, are important examples.[24,32] From a therapeutic standpoint, however, the finding of hyperuricemia obviates the importance of the primary cause; the therapy is the same.

Management

When possible, hyperuricemia should be treated before chemotherapy or radiation therapy, especially with bulky tumors or if the serum uric acid level is borderline or increased. If a uric acid elevation of more than 9 mg/dL is found, allopurinol, fluids, and alkalinization of the urine should be initiated. If possible, this regimen should be started a day or two before the initiation of chemotherapy or radiation treatment.

Patients with histories of gouty arthritis should also receive colchicine (0.6 mg orally twice a day) to avoid the acute attacks that can be associated with allopurinol administration. Patients should be kept well hydrated. In patients with acute distal tubular uric acid obstruction, treatment includes the administration of allopurinol, together with the fluid and electrolyte management used in other forms of acute renal failure.

If hyperuricemia is secondary to malignancy, cytolytic therapy should be stopped. Allopurinol in dosages of 300 to 600 mg/day usually causes a decrease in the serum uric acid level in approximately 3 days, so its administration should be started 2 or 3 days before cytolytic therapy, if time permits. Hydration is vital in maintaining a urine output above 2 L/day. Again, rasburicase (recombinant urate oxidase) is a newer therapy that can be used when the uric acid levels cannot be lowered sufficiently by standard approaches (see previous discussion on TLS).

Alkalinization to keep the urine pH above 7 can be accomplished by administering sodium bicarbonate (9–12 g/day). Diuretics are to be used as needed. Acetazolamide (Diamox)

in doses of 1 g/day usually alkalinizes the urine temporarily until allopurinol becomes effective. If oliguria occurs, IV mannitol may be started with 12.5 g of a 20% solution given over 3 minutes to keep urine output more than 250 mL/hr. The dose of mannitol is limited to 100 g/24 hours to avoid clinical features resembling water intoxication. If these measures fail, peritoneal dialysis or hemodialysis or flushing the ureters via retrograde catheters may be considered. Clearly, prevention of this complication is far better than treatment.

The cancer patient who comes to the ED with renal colic warrants careful evaluation for hyperuricemia. The prognosis depends on the underlying malignancy and degree of renal failure.[24,31]

HYPERCALCEMIA

Hypercalcemia occurs in approximately 20 to 40% of cancer patients and is the most common life-threatening metabolic disorder associated with cancer.[33] It affects multiple organ systems and induces a variety of pathophysiologic events that may be more immediate threats to life than the cancer itself. For the purpose of this discussion, we discuss nonparathyroid hormone-mediated hypercalcemia, which is associated with malignancy.[34]

Pathophysiology

Two mechanisms have been proposed to explain the development of hypercalcemia associated with malignancy. The first mechanism involves patients with metastatic bone involvement. This hypercalcemia is most likely associated with the release of calcium and phosphate caused by associated increased osteoclastic activity within the bone. The second mechanism involves those patients with no bone disease. A variety of tumor-produced hormone-like substances have been associated with the development of hypercalcemia, including parathyroid hormone, prostaglandins, and peptides, all of which affect bone turnover.

Hypercalcemia is a common feature of many malignancies but most often complicates cancer of the breast, lung, head, and neck, as well as multiple myeloma and leukemia. Bony metastases are not a prerequisite for hypercalcemia and when present do not necessarily cause hypercalcemia. In patients who are hypercalcemic from squamous cell lung cancer, only one in six has bone metastases. In small-cell lung carcinoma; hypercalcemia is almost never seen, despite the presence of bone marrow metastases in 20 to 50% of cases. A complex interaction of various substances (parathyroid hormone, prostaglandins, peptides, steroids, osteoclastic factors) appears to result in both increased bone synthesis and degradation. The exception is multiple myeloma, in which bone destruction is accompanied by minimal bone synthesis. Other entities that cause hypercalcemia are listed in Box 121-6.[35,36]

Rarer still are factitious hypercalcemia, idiopathic hypercalcemia of infancy (with elfin facies), familial hypocalciuric hypocalcemia, and hypercalcemia from pheochromocytoma or periostitis

Clinical Features

The development of symptoms of hypercalcemia is nonspecific. There is little correlation between serum calcium levels and the presence and severity of symptoms. Acute hypercalcemia results in marked CNS effects ranging from personality changes (depression, paranoia, lethargy, somnolence) to coma. With chronic hypercalcemia, symptoms include a history of anorexia, nausea, vomiting, constipation, polyuria, polydipsia, and memory loss. The signs, symptoms, and complications of hypercalcemia are summarized in Box 121-7.

BOX 121-6 NON-NEOPLASTIC CAUSES OF HYPERCALCEMIA

Hyperparathyroidism
Hyperthyroidism
Renal insufficiency (diuretic phase of acute renal failure, after transplantation, secondary hyperparathyroidism)
Drugs (thiazide diuretics, lithium, and calcium carbonate)
Hypervitaminosis (A and D)
Acute adrenal insufficiency
Immobilization (Paget's disease, fracture, paraplegia)
Acromegaly
Myxedema
Milk-alkali syndrome
Sarcoidosis
Benign monoclonal gammopathy
Rarer still are factitious hypercalcemia, idiopathic hypercalcemia of infancy (with elfin facies), familial hypocalciuric hypercalcemia, and hypercalcemia from pheochromocytoma or periostitis

BOX 121-7 COMMON SIGNS AND SYMPTOMS OF HYPERCALCEMIA IN MALIGNANCY

General
Itching

Neurologic
Fatigue, muscle weakness, hyporeflexia, lethargy, apathy, disturbances of perception and behavior, stupor, coma

Renal
Polyuria, polydipsia, renal insufficiency

Gastrointestinal
Anorexia, nausea, vomiting, constipation, abdominal pain

Cardiovascular
Hypertension, dysrhythmias, digitalis sensitivity

In patients with carcinoma, any of these symptoms should suggest the diagnosis of hypercalcemia, but the emergency physician should be particularly alert to the possibility of hypercalcemia in any cancer patient with lethargy or a change in mental status. Many may also have electrolyte abnormalities such as hypokalemia and dehydration. Thus evaluation of serum electrolytes should accompany the measurement of serum calcium, phosphorus, albumin, and alkaline phosphate. In general, a serum calcium level above 14 mg/dL constitutes a medical emergency. In chronic hypercalcemia, one may see patients with blood calcium levels as high as 15 mg/dL with only mild symptoms. With an acute onset, one can see patients comatose at a level of only 12 to 13 mg/dL.[24,31-34]

Many benign conditions can result in hypercalcemia. The most common are hyperparathyroidism and Paget's disease of bone. Clinical features include a long history of hypercalcemia symptoms, particularly renal stones. Chronic changes on bone films, such as subperiosteal reaction and cysts or a "ground-glass" appearance of the skull, suggest hyperparathyroidism. Diagnosis of Paget's disease rests in biopsy results. Vitamin D excess, milk-alkali syndrome, and adrenal insufficiency are other common causes in the differential diagnosis of hypercalcemia.[24,31]

The acute onset of severe hypercalcemia or chronic exposure of the renal tubules to elevated calcium levels may reduce

the glomerular filtration rate and renal blood flow, resulting in acute renal failure.[24]

Management

The therapeutic modalities used in the treatment of hypercalcemia are numerous, but they should always be used in conjunction with therapy of the underlying malignant disease. The exception to this is breast cancer, when hormone therapy should be stopped until hypercalcemia is regulated.

The treatment depends on the clinical status of the patient and on the calcium level in the blood, but the general principles of treatment include treating the cancer when possible, encouraging ambulation, correcting dehydration, increasing urinary calcium excretion; inhibiting osteoclastic activity (calcium removal from bone) and reducing calcium intake.

If serum calcium levels are below 14 mg/dL, oral rehydration and ambulation may suffice. Normal saline solution can be administered if the oral intake is not sufficient. If the serum phosphate level is not elevated, oral phosphates may be used cautiously. Phosphosoda (5 mL by mouth, two or three times daily) is usually tolerated with mild to no diarrhea. IV phosphates are able to effectively lower the serum calcium level through precipitation of inorganic calcium phosphate salts in bone. This modality of treatment is usually not recommended, however, and if needed, it should only be done in consultation with a nephrologist or oncologist in view of their serious complications, which include widespread visceral calcifications, shock, and renal failure. This agent is usually reserved for hypercaecemia unresponsive to other agents.

Mithramycin (given as 25 μg/kg IM once every 4 to 5 days) is not generally part of the initial emergency management of hypercalcemia and has been supplanted in most cases by the bisphosphonates.

Prednisone (60–80 mg) or other corticosteroids may be effective within a few days to a week. This drug is more useful for long-term treatment than for acute control. Corticosteroids are particularly valuable in breast carcinoma, myeloma, and lymphoma. They should not be initiated without oncologic consultation because they are chemotherapeutic agents for these malignancies.

If the serum calcium level is greater than 14 mg/dL or significant symptoms are present, a more vigorous management should be undertaken. Continuous cardiac monitoring in the ED is necessary and central venous or pulmonary artery pressure monitoring may be required.

Saline rehydration and diuresis stimulates renal tubular excretion of calcium and is the most important initial component of the emergency management of hypercalcemia. Dehydration should be corrected within 1 to 2 hours with normal saline solution. When urine flow is adequate, furosemide (40–60 mg IV) may be given to increase excretion of calcium. Although the calciuric effect of furosemide is modest, it is also useful in preventing fluid overload in patients predisposed to cardiac failure. Careful attention to fluid input and output to ensure that the patient remains euvolemic is necessary.

Calcitonin is a naturally occurring hormone that inhibits bone resorption and increased excretion of calcium. Calcitonin may be effective in doses of 4 to 8 IU/kg IM/SC. This treatment, although relatively safe when renal function is normal, is not generally part of the initial emergency management of hypercalcemia.

Fifty percent of hypercalcemic cancer patients also have hypokalemia. Serum potassium levels should be monitored every 4 hours and potassium chloride (20–40 mEq, IV or PO) supplemented as necessary to prevent severe hypokalemia.[24,31,33,35]

In the past 5 years following approval by the Food and Drug Administration, bisphosphonates have become the treatment of choice for management of cancer-induced hypercalcemia supplanting all other pharmacologic approaches except corticosteroids. Bisphosphonates act by binding to hydroxyapatite in bone and thereby inhibiting the dissolution of crystals. These agents prevent osteoclast attachment to bone matrix and interfere with osteoclast recruitment without inhibiting bone formation and mineralization.

Several agents are now available, including clodronate, pamidronate, and ibandronate, with other more potent bisphosphonates in development. Pamidronate (90 mg, given as an infusion over 4–24 hr) effectively and safely achieves normocalcemia within a few days (mean 4 days) in over 90 to 95% of patients.[32-35]

NEOPLASTIC CARDIAC TAMPONADE

Although cardiac tamponade resulting from neoplasm is uncommon, it can occur abruptly and result in death if not treated quickly. In most cases neoplastic cardiac tamponade is observed in patients with a previous diagnosis of cancer, typically at late stages of the disease. It is rarely seen as the initial manifestation of an extracardiac malignancy.

The decompensated state of cardiac function comes from a marked rise in intrapericardial pressure caused by accumulation of fluid within the pericardial sac resulting from malignancy or from pericardial thickening with scar formation, which results in a thick constrictive neoplastic encasement. This condition, if not recognized and decompressed promptly, can lead to circulatory compromise and death. Signs and symptoms are partially affected by the rapidity of development. In the era prior to diagnostic ultrasound this medical/oncologic emergency was often unrecognized. In one early series prior to the advent of ultrasound, the diagnosis was missed by the first physician in 11 of 17 patients and a number of times was missed by more than a single examiner.[37]

In most instances, pericardial effusion is accompanied by signs and symptoms that presage the development of the clinical picture of tamponade, including dyspnea, apprehension, anxiety, and chest pain. In rare instances, tamponade may be the first manifestation of the malignancy, solid tumor, or leukemia. Any patient in the ED with a history of cancer, shortness of breath, and hypotension should be suspected of having pericardial tamponade. The diagnoses of pulmonary embolism, congestive heart failure, and anxiety can be mistakenly made in this setting.

Etiology

The most common cause of neoplastic pericardial tamponade is malignant pericardial effusion, often associated with postirradiation pericarditis, fibrosis, and effusion. Only rarely does a tumor or radiation fibrosis cause a neoplastic constrictive pericarditis with resultant tamponade. In most reported cases, cardiac tamponade represents a clinical progression of neoplastic or postirradiation pericarditis.

Neoplastic pericarditis can result from any number of benign, malignant, primary, or secondary tumors of the pericardium or mediastinum.[38-40] The most common benign tumors of the pericardium or mediastinum are fibromas, angiomas, and teratomas. Pericardial mesothelioma can have a clinical course characterized by rapid accumulation of massive quantities of bloody pericardial fluid, eventually leading to tamponade. Secondary involvement of the pericardium may result from either direct invasion from structures or metastases from a distant primary tumor. These metastases are usually multiple rather

than solitary lesions. The tumors most commonly associated with pericardial involvement include those of the lung and breast, leukemia, Hodgkin's and non-Hodgkin's lymphomas, melanomas, GI primary tumors, and sarcomas.[40,41] Clinically recognizable symptoms or signs of pericardial disease are difficult to appreciate before death. Less than 30% of patients with autopsy-proven malignant pericardial disease were diagnosed antemortem.[40,41]

Radiation pericarditis has been a well-known complication of radiotherapy since the introduction of modern megavoltage techniques. The cardiac effects of radiotherapy may manifest themselves immediately with acute pericarditis or be delayed for months to years, although the majority develop effusion within the first year. The acute forms are inflammatory or effusive, usually self-limited, and subside without residual constriction; the chronic effusive and constrictive types may lead to tamponade and death.[42]

Neoplastic constrictive pericarditis, although rare, may be caused by the invasion of the pericardium by metastatic lesions or indirectly from the complication of radiation therapy with resultant fibrous thickening of the pericardium. Each of these entities can progress to cardiac tamponade because of thickening by tumor or radiation fibrosis, resulting in a decrease in the distensibility of the pericardium, thus reaching the critical point of cardiopulmonary decompensation earlier, despite smaller volumes of slowly accumulating effusion.

The symptoms and signs of neoplastic and radiation pericarditis mimic pericarditis from other causes, and because of the usual insidious onset of the effusion of fibrous pericardial thickening, the condition might be attributed to the underlying malignancy and not considered until the full-blown picture of cardiac tamponade develops.

Pathophysiology

The severity of cardiac tamponade and eventual cardiopulmonary decompensation depend on the rate of pericardial fluid accumulation, the fluid volume, and the underlying cardiac function. Clinically the progressive elevation of intracardial pressure interferes with ventricular expansion and results in a decrease in the cardiac volume. Intracardial chamber pressures rise rapidly with subsequent transmission of this pressure peripherally in pulmonary and vena caval beds. In an effort to maintain cardiac output, various compensatory mechanisms come into play (tachycardia, peripheral vasoconstriction, decrease in renal flow with resultant increase in blood volume by sodium and water retention), all to maintain arterial pressure and venous return. When these compensatory mechanisms fail to maintain cardiac output, ventricular end-diastolic pressure increases and subsequent circulatory collapse is impending. The signs and symptoms parallel these pathophysiologic changes. The most common symptoms include extreme anxiety and apprehension, a precordial oppressive feeling, or actual retrosternal chest pain with dyspnea of varying degrees. True orthopnea and paroxysmal nocturnal dyspnea are uncommon, but when they occur the patient assumes a variety of positions to get relief from the chest pain and the dyspnea. Other prominent symptoms include cough, hoarseness, hiccups, and occasional GI manifestations such as dysphagia, nausea, vomiting, and epigastric or right upper quadrant abdominal pain that is probably the result of visceral congestion.[12,40-43]

Clinical Features

Patients with severe tamponade are acutely ill and may appear ashen, pale, or markedly diaphoretic with an impaired consciousness ranging from mildly confused to unresponsive.

Table 121-1 Physical Evaluation of Neoplastic Cardiac Tamponade

Beck Triad or Acute Compression Triad

Described in 1935, this complex of physical findings refers to increased jugular venous pressure, hypotension, and diminished heart sounds.

These findings result from a rapid accumulation of pericardial fluid. However, this classic triad is usually observed in patients with acute cardiac tamponade.

Pulsus Paradoxus or Paradoxical Pulse

This is an exaggeration (>12 mm Hg, or 9%) of the normal inspiratory decrease in systemic blood pressure.

To measure the pulsus paradoxus, patients are often placed in a semirecumbent position; respirations should be normal. The blood pressure cuff is inflated to at least 20 mm Hg above the systolic pressure and slowly deflated until the first Korotkoff sounds are heard only during expiration. At this pressure reading, if the cuff is not further deflated and a pulsus paradoxus is present, the first Korotkoff sound is not audible during inspiration. As the cuff is further deflated, the point at which the first Korotkoff sound is audible during both inspiration and expiration is recorded. If the difference between the first and second measurement is greater than 12 mm Hg, an abnormal pulsus paradoxus is present.

The paradox is that while listening to the heart sounds during inspiration, the pulse weakens or may not be palpated with certain heartbeats, while S_1 is heard with all heartbeats.

A pulsus paradoxus can be observed in patients with other conditions, such as constrictive pericarditis, severe obstructive pulmonary disease, restrictive cardiomyopathy, pulmonary embolism, rapid and labored breathing, and right ventricular infarction with shock.

A pulsus paradoxus may be absent in patients with markedly elevated left ventricular diastolic pressures, atrial septal defect, pulmonary hypertension, and aortic regurgitation.

Kussmaul's Sign

This was described by Adolph Kussmaul as a paradoxical increase in venous distention and pressure during inspiration.

This sign is usually observed in patients with constrictive pericarditis but occasionally is observed in patients with effusive-constrictive pericarditis and cardiac tamponade.

Rapid, shallow, and occasionally labored breathing may be present along with peripheral cyanosis and distended jugular veins. Seizures have been reported. Striking facial plethora and a full neck secondary to edema (Stoke's collar) can also be seen in SVCS. Pulses are soft and easily compressible. The systolic blood pressure is usually low, with a decreased pulse pressure, although normal systolic, diastolic, and pulse pressures have been reported with moderate degrees of tamponade. Kussmaul's signs (muffled heart sounds, an enlarged cardiomediastinal silhouette, tachycardia, and, most notably, pulsus paradoxus) are extremely useful findings in the physical evaluation of tamponade (Table 121-1).[44] Ascites, hepatomegaly, peripheral edema, and mottling are other findings that reflect the elevation in venous pressure and decrease in cardiac output.[12,40,41,45]

Ancillary Evaluation

Low-voltage and the nonspecific findings of pericardial effusion, sinus tachycardia, ST elevation, and nonspecific ST-T wave changes may occur. Electrical alternans with 1:1 total atrial-ventricular complexes has been considered almost pathognomonic of cardiac tamponade. Electrical alternans is the alternation of electrocardiographic QRS complexes, usually

in a 2:1 ratio. This is due to movement of the heart in the pericardial space. Electrical alternans is also observed in patients with myocardial ischemia, acute pulmonary embolism, and tachyarrhythmias.[44]

Approximately two thirds of the reported cases of pulsus alternans occur in patients with tamponade caused by massive pericardial effusion in neoplastic pericarditis. The alternation customarily disappears soon after removal of a small volume of fluid, but it can also disappear spontaneously or be observed in attendance with a fluid increase.[41]

Radiographic signs of tamponade suggestive of pericardial effusion include an enlarged cardiac silhouette with clear lung fields and normal vascular pattern, although a normal chest radiograph does not exclude tamponade. The typical "water-bottle" appearance of the heart on a plain radiograph is often present.

Echocardiography is the simplest and most sensitive of diagnostic tests and can be done at the bedside for confirmation of pericardial effusion. Thoracic CT has also become an important diagnostic tool in diagnosing pericardial effusions.[41,46]

Cardiac tamponade should be considered in any cancer patient with dyspnea. Highly suggestive symptoms include clouded sensorium, thready pulse, pulsus paradoxus exceeding 50% of the pulse pressure, low systolic pressure, engorged neck veins with a rising peripheral venous pressure above 130 mm H_2O, a falling pulse pressure below 20 mm Hg, and electrical alternans. This is an uncommon yet pathognomonic sinusoidal variation in QRS size secondary to the pendular effect of the heart swinging in the fluid medium of the pericardial sac.[45] In this setting, sudden death may occur and pericardiocentesis should be performed as soon as possible.

Management

In the ED, the only lifesaving treatment for tamponade that is effective is immediate removal of the pericardial effusion via pericardiocentesis. The procedure carries some risk, including induction of cardiac dysrhythmias and hemorrhage from an injured coronary vessel. Aspiration of as little as 50 to 100 mL of fluid has been shown to temporarily alleviate the pathologic process.[12,40,41]

Emergency subxiphoid percutaneous drainage is a lifesaving bedside procedure. The subxiphoid approach is extrapleural; hence, it is the safest for blind pericardiocentesis. A 16- or 18-gauge needle is inserted at an angle of 30 to 45 degrees to the skin, near the left xiphocostal angle, aiming toward the left shoulder. When performed emergently, this procedure is associated with a reported mortality rate of approximately 4% and a complication rate of 17%.[44]

Echocardiographically guided pericardiocentesis can also be performed in the ED, but the cardiac catheterization laboratory is a more controlled setting and is preferable: this is usually performed from the left intercostal space. First, mark the site of entry based on the area of maximal fluid accumulation closest to the transducer. Then, measure the distance from the skin to the pericardial space. The angle of the transducer should be the trajectory of the needle during the procedure. Avoid the inferior rib margin while advancing the needle to prevent neurovascular injury. Leave a 16-gauge catheter in place for continuous drainage.[44]

Removal of the maximal amount of fluid is advisable, along with inserting of an indwelling catheter, during the first pericardiocentesis since fluid may reaccumulate during the first 24 hours. Once the pericardial fluid has been obtained, it must be sent for biochemical and cytologic analysis. Neoplastic cardiac tamponade accounts for at least 50% of all reported cases of pericardial fluid collection. Other types of supportive therapy may be needed during the evaluation process while preparing for pericardiocentesis, such as IV hydration with normal saline and oxygen therapy.

Once the patient has been stabilized, additional therapeutic interventions should be planned and initiated by the appropriate admitting services because reaccumulation of effusion in neoplastic tamponade is not easily managed on a short-term basis. Pericardial windows, radiotherapy, intrapericardial chemotherapy, and pericardiectomy may be justified.[12,40,41]

The prognosis after neoplastic cardiac tamponade depends on the underlying type and extent of cancer. The presence of total electrical alternans is an adverse prognostic sign, even when the alternans disappears with pericardiocentesis. Despite a poor prognosis for patients with cancers such as melanoma or non-small-cell lung cancer, some patients with treatment-responsive lymphomas have survived long-term after neoplastic cardiac tamponade.

NEUROLOGIC EMERGENCIES

Of all patients with cancer, 15 to 20% have neurologic complications.[47] Neurologic symptoms are occasionally the presenting complaint in patients with systemic cancer, but more often symptoms develop in patients known to have cancer. Neurologic emergencies in cancer patients include cerebral herniation, seizures, epidural spinal cord compression, CNS infections, and reversible toxic or metabolic encephalopathies. Treatment is needed urgently after the patient arrives at the ED to prevent permanent neurologic dysfunction or death.

CEREBRAL HERNIATION

Pathophysiology

Cerebral herniation occurs when the ICP increases locally within the skull from an expanding mass lesion. The increase produces a shift of brain substance in the direction of least resistance caudally through the tentorial opening and the foramen magnum. Causes of cerebral herniation in cancer patients commonly include primary or metastatic brain tumors and intracerebral hemorrhage. Less common causes include subdural hematoma, brain abscess, acute hydrocephalus, and radiation-induced brain necrosis.[46] Primary brain tumors account for approximately one half of intracranial tumors. Metastatic brain tumors are seen most commonly in lung, breast, colon, kidney, and testicular cancer and in patients with choriocarcinoma and malignant melanoma.[47,48]

Clinical Features

Three distinct herniation syndromes have been described: uncal, central, and tonsillar herniation. In *uncal* herniation a lateral mass displaces the temporal lobe, which compresses the upper brainstem. A rapid loss of consciousness is seen in conjunction with unilateral pupillary dilatation and ipsilateral hemiparesis. *Central* herniation usually results from slowly expanding, multifocal lesions that cause a downward and lateral shift of the diencephalon and upper pons. A slowly decreasing level of consciousness, small reactive pupils, and Cheyne-Stokes respirations, without focal signs, are seen clinically. Central herniation is sometimes mistaken for toxic or metabolic encephalopathy because of the lack of focal signs. A history of headache or focal neurologic complaints or any lateralizing findings indicates the need for prompt CT of the head to rule out a herniating mass lesion before lumbar puncture. *Tonsillar* herniation is produced by a large posterior fossa mass that pushes the cerebellar tonsils through the foramen magnum, compressing the medulla and resulting in a rapidly decreasing level of consciousness, occipital headache, vomit-

ing, hiccups, hypertension, meningismus, and abrupt changes in the respiratory pattern.[47-50]

Management

When the clinical diagnosis of cerebral herniation is made, emergency management is necessary before the cause can be established. Intubation with hyperventilation to a carbon dioxide partial pressure (P_{CO_2}) of 25 to 30 mm Hg temporarily lowers the ICP by producing cerebral vasoconstriction. This should be avoided if possible but may be necessary for brief periods in response to reversible, acute neurologic deterioration. Excessive or prolonged hyperventilation may cause paradoxical vasodilation and should be avoided. Mannitol (1 g/kg IV) should be given and may be repeated in 4 to 6 hours. Dexamethasone (12–24 mg IV) has not been shown to improve outcome or reduce ICP acutely in severe head injury,[51,52] but is often administered in patients with raised ICP or impending herniation caused by CNS malignancy because of the effect of corticosteroids on reducing cerebral edema associated with the neoplastic process. CT of the brain should be obtained as soon as emergency stabilization is accomplished. Epidural or subdural hematoma and hydrocephalus usually require surgery, whereas abscess and metastases are usually managed with antibiotics and antineoplastics or radiation, or both, respectively. When stabilization and an initial diagnosis have been made, neurologic or neurosurgical consultation and prompt admission to an intensive care unit are mandatory.[47,49]

SEIZURES

Seizures are common in patients with cancer. Their immediate management is necessary to prevent physical injury, increased ICP, and risk of aspiration. Seizures increase the brain's metabolic requirements and lead to increased cerebral blood flow. This may precipitate increased ICP in susceptible patients. Seizures may be due to brain metastases, toxic or metabolic disturbances (usually hyponatremia or uremia), vascular problems (especially intracerebral hemorrhage or subdural hematomas), and infections. Diagnostic laboratory studies should include a CBC, electrolytes, glucose level, blood urea nitrogen (BUN), measurement of calcium and magnesium levels, liver function tests, coagulation studies, and appropriate cultures. CT of the head should be done and followed by a lumbar puncture, when indicated.[47,49]

The therapy for seizures depends on the specific cause and the patient's clinical status. For example, a single hypoglycemic or hypoxic seizure usually requires only correction of the underlying metabolic defect. Patients with a single seizure whose workup reveals a chronic problem (e.g., a cerebral metastasis) require anticonvulsants and therapy specific for the malignancy. A loading dose of phenytoin (15–18 mg/kg IV) may be given followed by oral maintenance. Prolonged single seizures or repetitive seizures require more vigorous treatment, including diazepam (5–10 mg IV) or lorazepam (1–2 mg IV) followed by IV phenytoin. Active airway and ventilatory management is essential. A bedside fingerstick glucose level should be obtained promptly. Thiamine and naloxone are not routinely indicated. In addition, when repetitive seizures have occurred, management of the underlying cause should be initiated rapidly and the patient admitted to an intensive care unit.[47,49]

EPIDURAL SPINAL CORD COMPRESSION

Principles of Disease

Epidural spinal cord compression from metastatic cancer is common, serious, and potentially treatable. It is most often caused by lymphoma or lung, breast, or prostate carcinoma. With the exception of lymphoma, which extends through the intervertebral foramina from paravertebral lymph nodes, these tumors metastasize to the vertebral body and extend into the spinal canal to compress the spinal cord. Less common causes of spinal cord compression in patients with cancer include melanoma, myeloma, renal cell carcinoma, vertebral subluxation, spinal epidural hematomas, and intramedullary metastasis. Acute myelopathy in patients with cancer may also be caused by radiation, paraneoplastic necrotizing myelitis, a ruptured intervertebral disk, and meningeal carcinomatosis with spinal cord involvement. Most cases (68%) of epidural cord compression occur in the thoracic spine, 15% occur in the cervical spine, and 19% in the lumbosacral spine.[53]

Clinical Features

Back pain, either local or radicular, is the initial symptom in 95% of patients with epidural metastasis. It may be acute in onset or develop insidiously over weeks to months and usually predates other symptoms. The pain may increase during physical examination with spinal percussion, neck flexion, Valsalva maneuver, or straight leg raising and is usually located at the level of the tumor.[50,54,55] Other symptoms are usually present at the time of diagnosis and may include weakness (75% of patients) and autonomic or sensory symptoms (50% of patients). Fifty percent of patients are not ambulatory at the time of diagnosis. The neurologic examination usually reveals symmetrical weakness with either flaccidity and hyporeflexia (if the diagnosis is made very early) or spasticity and hyperreflexia (if the diagnosis is made later).

Diagnostic Strategies

Plain films show evidence of tumor in the vertebral body in 70 to 90% of patients with vertebral metastases.[47,51] Immediate myelography or MRI is indicated if the plain films are abnormal, regardless of whether the neurologic examination is abnormal or is consistent with spinal cord compression or the plain film findings. In cases with questionable findings on plain films of the spine, tomograms, coned-down views, or CT may reveal bone metastases not otherwise appreciated. Myelography can demonstrate a complete or near-complete obstruction of contrast dye flow at the level of vertebral body involvement. MRI has emerged as the procedure of choice for intramedullary metastases and has also replaced myelography, which is associated with significant morbidity related to lumbar puncture and dye insertion at multiple levels (including cisternal puncture), to demonstrate the length of the compression or skip lesions along the spinal cord.[50,55]

Management

Because minimal weakness at the time of presentation may progress to profound, irreversible weakness over several hours, treatment should be started rapidly. In the ED, a loading dose of dexamethasone (10–100 mg IV), followed by 4 to 24 mg every 6 hours for 3 days to reduce cord edema, is initiated at the time of diagnosis. Immediate oncology and radiation oncology consultations should be obtained. Although corticosteroids are routinely administered to patients with suggested spinal cord compression, high-dose corticosteroids, such as dexamethasone (100 mg), have been associated with complications and their use is controversial.[55] Radiation treatment is the usual therapy and can be initiated after steroid treatment. The prognosis depends on the radiosensitivity of the tumor, the location of the compression, the pretreatment performance status, and the rate of decompensation. Surgery is indicated

only if the diagnosis is in doubt, if a tissue diagnosis is required, if the spine is unstable, or when maximal doses of radiation have already been given to the involved area.[47,48,56]

Intramedullary metastases are similar in presentation and treatment to epidural cord compression but are associated with a very poor prognosis. Epidural hematomas have been described in patients with thrombocytopenia or a coagulopathy as a complication of lumbar puncture. A rapidly progressive paraparesis and back pain are seen. MRI or myelography can establish the diagnosis; the treatment is surgical decompression. Platelet transfusions may limit progression in the ED.[47,56]

CENTRAL NERVOUS SYSTEM INFECTIONS

Principles of Disease

Patients with cancer are susceptible to a variety of CNS infections. These patients may have impaired immune responses secondary to their underlying disease or treatment with steroids, chemotherapy, splenectomy, or irradiation. Most CNS infections occur in patients with leukemia, lymphoma, or head and neck cancer. Patients with head and neck cancer are susceptible (in addition to the reasons discussed) because of fistula formation and tumor invasion, which allows organisms access to the CNS. Important CNS infections include meningitis, brain abscess, and encephalitis. These often have similar presentations, making their differentiation in the ED difficult.

Clinical Features

Meningitis is characterized by fever, headache, and altered mental status. Meningismus is often absent. The diagnosis of meningitis in patients with cancer is often delayed because the manifestations of the disease are attributed to other processes: fever to systemic infection, headache to cerebral metastases, and altered mental status to a toxic or metabolic encephalopathy.

Diagnostic Strategies

All cancer patients with fever and an altered mental status require a lumbar puncture, which should be preceded by head CT if cerebral metastases are suggested.[49,52] In addition, thrombocytopenia and coagulopathy should be considered and either ruled out or treated appropriately with platelet transfusions or fresh frozen plasma, respectively, before a lumbar puncture is done. Platelet transfusion is usually reserved for patients with platelet count less than 10,000/μL. The fluid obtained should be sent for a cell count and differential cell count, Gram's stain, India ink stain, protein and glucose levels, bacterial and fungal cultures, cryptococcal antigen level, and cytologic examination. The absence of WBCs in the cerebrospinal fluid does not rule out meningitis, especially in neutropenic patients. The likely organisms responsible for meningitis vary with the underlying disease and the peripheral WBC count.

Differential Considerations

Brain abscess is usually seen in patients with leukemia or head and neck tumors and accounts for 30% of CNS infections in cancer patients.[49] Patients have symptoms of elevated ICP (headache, vomiting, and papilledema), lateralizing findings, and a source of infection.[48,52] Fever is usually present. Head CT characteristically demonstrates an ill-defined mass early in the course of an abscess, with the classic well-defined mass with a low-density center and a contrast-enhancing ring seen later. Edema and mass effect are common. A lumbar puncture is not helpful in making the diagnosis and may precipitate cerebral herniation. Organisms that cause abscess include gram-negative rods, *Aspergillus* and *Phycomycetes* species, and *Toxoplasma gondii*. Emergency management includes high-dosage antibiotics. If herniation develops, immediate steps to reduce the ICP, followed by emergency surgery, are indicated.

Encephalitis is rare in patients with cancer and is most often caused by herpes zoster or *T. gondii*. The presenting complaints are usually headache, fever, and altered mental status. The CT scan is commonly normal but may show diffuse edema, whereas the lumbar puncture may show pleocytosis with an elevated protein level but no demonstrable organism. It is difficult to distinguish encephalitis from meningitis in the ED, but the overall clinical picture in both diseases mandates hospital admission for further evaluation.

Management

Until further evaluation is able to distinguish between meningitis and encephalitis, empirical broad-spectrum antibiotic coverage with a third-generation cephalosporin (ceftriaxone or ceftazidime) and vancomycin should be initiated for all patients. Ampicillin may be added when there is suggestion of *Listeria*. Ceftazidime with or without an aminoglycoside is generally selected when the likelihood of infection with *Pseudomonas* is high. Neutropenic patients (polymorphonuclear WBC count < 1000/mm^3) with either leukemia or lymphoma usually have a gram-negative infection (often with *P. aeruginosa*). Patients with lymphoma and a normal WBC count are commonly infected with *Listeria monocytogenes*, *Streptococcus pneumoniae*, or *Cryptococcus neoformans*. Infections with *Haemophilus influenzae* and *Neisseria meningitidis* are uncommon. Patients with head and neck tumors may develop staphylococcal infection.[47-50]

Encephalopathy

Toxic and metabolic encephalopathy should be actively considered when patients with cancer have an acute or subacute altered mental status in the absence of fever or headache. Toxic and metabolic causes should be routinely excluded even when infection or a metastatic complication is suggested. Signs of encephalopathy include confusion, aberrant behavior, and a decreased level of consciousness. These may develop acutely or insidiously over days to weeks. Patients with cancer are particularly susceptible to toxic and metabolic encephalopathy because their disease can have multiple organ system involvement, can cause electrolyte and nutritional abnormalities, and the drugs used to treat the disease (especially chemotherapeutic agents and narcotics) can cause encephalopathy even when used in therapeutic doses.[47,48] In the ED, encephalopathic patients should first be evaluated carefully for a possible infection or mass lesion. The metabolic workup should include electrolytes; BUN, creatinine, glucose, and calcium levels; arterial blood gases; and liver function tests. Toxicology screens should be considered in possible ingestions and in patients who are unable to give a history. Naloxone and 50% dextrose should be given while the workup is proceeding. Specific treatment is indicated for any abnormalities found during the workup. Hospital admission is usually required unless the cause is easily and rapidly reversible and is unlikely to recur.

KEY CONCEPTS

- Hypercalcemia due to malignancy is unrelated to bone metastases in 20% of patients and is associated with a poor prognosis independent of therapeutic response. Hydration and use of bisphosphonates (e.g., pamidronate) have become the mainstays of initial treatment.
- Spinal cord compression arises as back pain in more than 95% of patients. If ambulatory at the time of diagnosis, 80% of patients maintain the ability to ambulate. MRI has become the diagnostic modality of choice, and high-dose dexamethasone is given to all patients, followed by radiation therapy in most cases.
- Superior vena cava obstruction is rarely life-threatening and requires tissue diagnosis. Although caused by malignancy in 70 to 80% of cases, thrombosis secondary to indwelling central lines is increasing as a cause. Stenting of the SVC has become the approach to SVC obstruction unresponsive to chemotherapy or radiation therapy, or both.
- Fever and neutropenia in the cancer patient are a true medical emergency requiring rapid diagnosis, cultures, and treatment with broad-spectrum, bactericidal, synergistic antimicrobials. An aminoglycoside plus an extended-spectrum penicillin and third-generation cephalosporin with or without vancomycin remain the standard combinations in patients without penicillin allergy.
- Neoplastic pericardial effusion can arise insidiously with symptoms such as apprehension, anxiety, dyspnea, and weakness. Bedside ultrasonography has become a rapid, safe imaging modality for establishing the diagnosis prior to the development of clinically apparent tamponade in a critically ill patient.
- Acute TLS, previously limited to hematologic malignancies, is now being described in patients receiving chemotherapy for solid tumors. It can arise with dyspnea, mental status changes, cardiac dysrhythmia, or seizures. Treatment includes urinary alkalinization and emergency hemodialysis in cases complicated by acute renal failure.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 122 Acid-Base Disorders

Jamie L. Collings

The human body must be maintained in a precise acid-base balance to maintain healthy cellular function. This balance is controlled by the lungs, kidneys, and serum buffers, interacting and responding to physiologic changes. Physiologic insults such as vomiting, diarrhea, respiratory failure, kidney dysfunction, diabetes, toxic ingestions, among others can result in life-threatening acid-base crises. Identifying and optimally treating the underlying condition is often achieved only through the diagnostic insights gained from acid-base measurements and calculations. This chapter presents essential acid-base physiology, beginning with an overview of the principles of acid-base function. This is followed by a discussion of primary respiratory acidosis and alkalosis and then metabolic causes of acidosis and alkalosis. Finally, mixed acid-base disorders are analyzed. Clinical implications are included along with the mathematical knowledge that the emergency physician requires to expertly manage these complex and potentially life-threatening conditions.

PRINCIPLES OF DISEASE

The kidneys, lungs, and physiologic buffers normally maintain the serum pH within a narrow spectrum, between 7.36 and 7.44. Each of these three systems dynamically responds to small changes in acid-base balance. Such precise physiologic control is required for normal cellular function. Consequently, disorders of kidneys, lungs, and physiologic buffers result in acid-base abnormalities.

Blood pH is determined by the ratio of the serum bicarbonate concentration and $Paco_2$ (partial pressure of CO_2 in arterial blood). Primary metabolic acid-base disorders and the secondary metabolic compensation for primary respiratory disturbances alter the serum bicarbonate concentration [HCO_3^-]. Primary respiratory acid-base disorders and the secondary respiratory compensation for primary metabolic disturbances alter the $Paco_2$.

The Henderson-Hasselbalch equation relates the concentrations of the acid-base pair to the pH. As the pH changes, so does the concentration. Because the equation produces a logarithmic result, subtle changes in the serum pH can cause large and often significant alterations in the concentration of the acid-base pair. Clinically, this equation dictates how drugs disperse, enzymes react, and medications bind at a given serum pH. In humans, hydrogen ion concentration [H^+] is extremely low (approximately 4×10^{-12} mEq/L) and strictly regulated. Normally, blood is slightly alkalemic relative to water (pH 7.0). Blood pH must be maintained within relatively narrow limits because protein and enzyme systems function properly only within a narrow pH spectrum. A pH outside the range of 6.8 to 7.8 is generally associated with serious disease processes and the potential for considerable morbidity or mortality.

Acidemia is defined as a serum pH of less than 7.36. Conversely, *alkalemia* is defined as a pH of greater than 7.44. *Acidosis* is defined as a pathologic process that lowers the [HCO_3^-] (metabolic acidosis) or raises the $Paco_2$ (respiratory acidosis); *alkalosis* is defined as a pathologic process that raises the [HCO_3^-] (metabolic alkalosis) or lowers the $Paco_2$ (respiratory alkalosis). A simple acid-base disorder is a single acid-base disturbance with its accompanying compensatory response. Mixed acid-base disorders are the result of two or more primary disturbances.

Physiologic Buffers

Physiologic buffers, defined as a weak acid and its salt, oppose marked changes in pH after the addition of an organic acid or a base, as follows:

$$H^+ + \text{buffer}^-Na^+ \rightleftarrows \text{buffer}^-H^+ + Na^+$$

The human body uses three important physiologic buffers to minimize surges in pH: (1) the bicarbonate/carbonic acid system (primarily located in red blood cells), (2) intracellular protein buffers, and (3) phosphate buffers located within bone. Patients with malnutrition or chronic disease, and thus low albumin and bone density, and anemic patients have an ineffective buffering capability.

Bicarbonate/Carbonic Acid Buffer System

The bicarbonate/carbonic acid buffer system is unique among physiologic buffering systems. The system is open-ended; continuous removal of organic acid is made possible by the exhalation of carbon dioxide (CO_2). In equilibrium, the equation is as follows:

$$H^+ + HCO_3^- \rightleftarrows H_2CO_3 \rightleftarrows H_2O + CO_2$$

Bicarbonate is present in large quantities and can be controlled by the lungs and kidneys; thus, it serves as the major contributor to the maintenance of acid-base balance. Clinically, its importance is in the transient buffering of serum and interstitial fluid.

Intracellular Protein Buffers

Many protein buffers in blood are effective in maintaining acid-base homeostasis. Plasma proteins, particularly albumin and hemoglobin, can buffer large amounts of H^+, preventing significant changes in the pH. If hemoglobin did not exist, venous blood would be 800 times more acidic than arterial blood, circulating at a pH of 4.5 instead of the normal venous pH of 7.37.

Bone as Buffer

Bone contains a large reservoir of bicarbonate and phosphate and can buffer a significant acute acid load. Bone is probably involved in providing some buffering (mostly ionic exchange) in most acute acid-base disorders, but there is very little research in this area. In terms of duration, only two types of metabolic acidosis are long-lasting enough to be associated with the loss of bone mineral (through release of calcium carbonate): renal tubular acidosis and uremic acidosis. In uremic acidosis, loss of bone crystal is multifactorial (changes in vitamin D metabolism, phosphate metabolism and secondary hyperparathyroidism) and acidosis is only a minor factor.

Pulmonary Compensation

The second compensatory system for pH changes involves a relationship between the peripheral chemoreceptors, located in the carotid bodies, and central chemoreceptors, located in the medulla oblongata. Both these receptors influence respiratory drive and can initiate changes in minute ventilation. A drop in pH stimulates the respiratory center, resulting in increased minute ventilation. This in turn lowers the $Paco_2$, driving the pH toward the normal range. Conversely, an increase in pH decreases ventilatory effort, which increases $Paco_2$ and lowers the pH back toward normal. A diabetic patient in ketoacidosis hyperventilates to compensate for the organic acidemia and would be expected to have a low $Paco_2$. This compensatory response is the expected reaction to a fall in serum pH. In general, compensatory processes return the pH toward normal over a period of 4 to 12 hours, but do not fully normalize it. Respiratory alkalosis is the only primary acid-base disorder in which the pH does often normalize with time.

Renal Compensation

The kidneys play little role in the acute compensation of acid-base disorders because they do not immediately respond to changes in pH. More than 6 to 12 hours of sustained acidosis results in active excretion of H^+ (predominantly in the form of ammonium, NH_4^+, with retention of bicarbonate, HCO_3^-). Conversely, more than 6 hours of alkalemia stimulates renal excretion of bicarbonate with retention of H^+ in the form of organic acids, resulting in near-normalization of pH.

In metabolic acidosis, there is either an excess production or an infusion of H^+ (e.g., lactic acid production, ketoacid production) or an excessive loss of anion (HCO_3^-) and accompanying sodium and potassium cations (Na^+, K^+; e.g., diarrhea). In general, the kidneys attempt to preserve Na^+ by exchanging it for excreted H^+ or K^+. The quantity of potassium excreted depends on the level of acidosis and the serum K^+ level. In the presence of an H^+ load, hydrogen ions move from the extracellular fluid (ECF) into the intracellular fluid. For this to occur, K^+ moves outside the cell into the ECF to maintain electroneutrality. In cases of severe acidosis, significant overall depletion of total body K^+ stores can occur despite serum hyperkalemia. Clinically, this is the rationale for initiating intravenous administration of K^+ in the patient with diabetic ketoacidosis (DKA) and good renal function, despite an often elevated serum K^+ level.

In metabolic alkalosis, there is a shift of H^+ extracellularly, accompanied by an electroneutral shift of serum Na^+ and K^+ intracellularly. Renal excretion of K^+ also occurs in an attempt to preserve H^+. If the alkalosis continues, the renal compensation may be unable to keep pace, especially if hypokalemia ensues. With excessive total body depletion of K^+ (usually as the result of nasogastric suction or some other inciting event), the kidney paradoxically begins to excrete H^+ in an attempt to retain K^+; thus, an aciduria can coexist with a serum alkalosis. This paradoxical aciduria is a clinical clue to the magnitude of hypokalemia and explains why renal compensation is unable to correct for alkalosis until K^+ levels are restored.

Conditions that change serum K^+ also alter serum pH. Excessive diuresis, occurring without potassium supplementation, generate a mild alkalemia, as H^+ is shifted intracellularly to support the extracellular osmotic movement of K^+. Conversely, excessive administration of potassium can cause H^+ to shift extracellularly, which may produce a mild acidosis.

DIAGNOSTIC STRATEGIES

A stepwise clinical approach to acid-base disorders starts with a well-conducted history and physical examination. Particular attention should be paid to the patient's past medical history, current medications, chance of toxic ingestion, occurrence of vomiting or diarrhea, level of consciousness on admission, respiratory rate, skin turgor, and urine output.

Evaluation progresses with analysis of serum electrolytes and pH, and calculation of any anion gap, and calculation of the delta gap. These calculations assist in determining the type of acidosis or alkalosis present and whether it is part of a mixed condition. The anion gap (AG) can be calculated as follows:

$$AG = Na^+ - (Cl^- + HCO_3^-)$$

Traditionally, a normal AG has been considered 12 ± 3 mEq/L. This number can vary from one laboratory to another (mostly based on whether potassium is included in the calculation) and the clinician should take this possibility into consideration. The "gap" provides an estimate of unmeasured anions in plasma, primarily albumin plus small amounts of sulfate, phosphate, and organic anions (e.g., citrate). If there are excess organic acids in the circulation, the organic acids dissociate and the resulting H^+ is titrated by HCO_3^-, which increases the AG. If the AG is increased, especially when it is more than 10 mEq/L above the upper limit of the reference range, the clinician should consider an excess in organic acids or acidic substances. With smaller gaps up to one third of patients will not have a metabolic acidosis. The concept of a "low" AG (<3 mEq/L) may be useful in the diagnosis of lithium toxicity, immunoglobulin G myelomas, and hypoalbuminemia of chronic disease.

Calculating the delta gap (ΔG = deviation of AG from normal – deviation of HCO_3^- from normal) may help resolve the possibility of a mixed acid-base disorder or further differentiate an elevated AG metabolic acidosis. Mathematically refined and with normal values substituted, the equation is as follows:

$$\Delta G = (\text{calculated AG} - 12) - (24 - \text{measured } HCO_3^-)$$

Values greater than +6 equate with metabolic alkalosis or respiratory acidosis. Values less than –6 imply a greater loss of HCO_3^-, suggesting a mixed disorder.

No significant differences were found for pH, $Paco_2$, or [HCO_3^-] when values obtained from intraosseous sites were compared with central venous specimens during steady and low-flow cardiac states.[1] Venous blood gas measurements, when compared with arterial specimens, accurately demonstrate the degree of acidemia in adult emergency department patients presenting with organic acidemia.[2] In infants, capillary tube blood gases are as reliable as formal arterial blood gases in determining hypercarbia or acidosis.[3]

It is also possible to utilize the acid-base calculations to predict the magnitude of shock and need for blood products. The base deficit or base excess can be a valuable indicator of shock and the efficacy of resuscitation. The base excess is a calculated figure that estimates the metabolic component of the acid-base balance. The base excess is defined as the amount of H^+ that would be required to return the pH of blood to 7.35 if the $Paco_2$ were adjusted to 40. A large base deficit (typically more than 6) indicates that even if the patient's respiratory problems were resolved, a significant metabolic acidosis is present. The clinician should keep in mind, however, that given the dynamic condition of pH balance, the base deficit and base excess numbers could be out of sync with the real-time condition of the patient. Therefore, circumspection is required when deciding what these numbers mean for treatment.

RESPIRATORY ACIDOSIS

Respiratory acidosis is defined as decreased pH that results from pulmonary CO_2 retention. In other words, hypoventilation leads to hypercapnia. CO_2 retention results in excess H_2CO_3 production, which leads to acidemia. In the acute state, the serum [HCO_3^-] is normal. The transition from acute to chronic respiratory acidosis is defined as the point at which renal compensation manifests as HCO_3^- retention (Fig. 122-1).[4]

Clinical Features

Respiratory acidosis is caused by any disorder that results in a decrease in minute ventilation and thus CO_2 retention. Common causes include pulmonary pathologic conditions, airway obstruction, and conditions that influence respiratory drive (Box 122-1). The clinical picture depends on the severity and chronicity of the process as well as on the underlying disease. Patients with acute respiratory acidosis may have CO_2 narcosis, characterized by symptoms and signs such as headache, asterixis, weakness, tremors, blurred vision, confusion, or somnolence. If prolonged, signs of intracranial pressure elevation with papilledema become manifest.

Physiologic Compensation

In acute respiratory acidosis, the only effective buffers are the intracellular proteins. The HCO_3^- formed by intracellular buffering diffuses out of the cell into the ECF, increasing about 1 mEq/L for every 10-mm Hg rise in the $Paco_2$. In acute situations, this HCO_3^- compensation is insignificant and has only minimal effect on the prevailing pH. Profound acidemia develops quickly if ventilation is not improved.

In chronic respiratory acidosis, such as chronic obstructive pulmonary disease, renal retention of HCO_3^- plays a significant role in acid buffering. The initial response occurs beyond the first 6 to 12 hours and takes several days to reach maximal contribution. Chloride (Cl^-) is excreted to maintain electrical neutrality and results in the characteristic hypochloremia of a chronic respiratory acidosis. Plasma [HCO_3^-] increases approx-

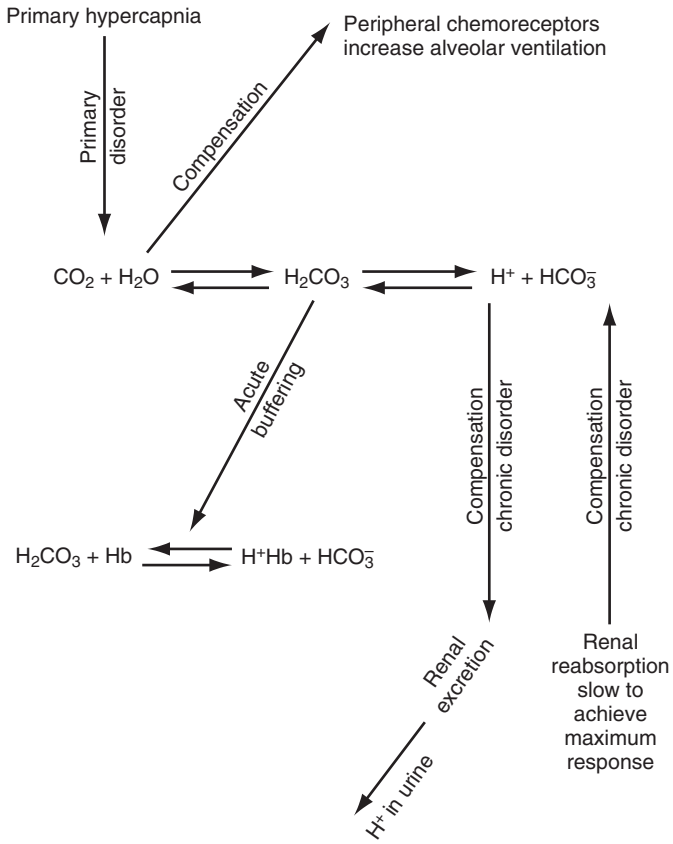

Figure 122-1. Respiratory acidosis and regulation.

BOX 122-1 CAUSES OF RESPIRATORY ACIDOSIS

Acute

- Airway disturbances
  - Obstruction (foreign body, bronchospasm, laryngospasm)
  - Aspiration
- Drug-induced CNS depression
  - Alcohol
  - GHB/GABA toxicity
  - Narcotics
  - IV sedation
- Hypoventilation of muscular or CNS origin
  - Myasthenia gravis
  - CNS injury
  - Guillain-Barré syndrome
- Pulmonary disease
  - Pneumonia
  - Edema
- Thoracic cage disorders
  - Pneumothorax
  - Flail chest

Chronic

- Lung disease
  - Chronic bronchitis
  - Chronic obstructive pulmonary disease
  - Interstitial fibrosis
- Neuromuscular disorders
  - Myasthenia gravis
  - Muscular dystrophy
- Obesity with decreased alveolar ventilation

CNS, central nervous system; GHB/GABA, γ-hydroxybutyrate/γ-aminobutyric acid; IV, intravenous.

imately 3.5 mEq/L for every 10-mm Hg increase in the $Paco_2$. This response provides excellent compensation and nearly normalizes the pH.

Management

Therapy of acute respiratory acidosis is directed toward correction of minute ventilation, thus returning the $Paco_2$ to normal. This may entail establishment of a definitive airway, initiation of artificial respiration, or treatment of an underlying toxic or neurologic condition.

Likewise, improving ventilation treats chronic respiratory acidosis. Bronchodilators, postural drainage, and antibiotics for infection are used to manage the underlying cause. In patients with chronic respiratory acidosis, sensitivity of the respiratory center progressively decreases with prolonged exposure to acidosis and hypercapnia, resulting in a ventilatory drive that depends on relative hypoxemia. Administration of oxygen to these patients reduces their hypoxic drive and minute ventilation, potentially creating CO_2 narcosis. Therefore, oxygen must be given with caution to patients with chronic respiratory acidosis. If the patient has severe hypoxemia, however, sufficient oxygen must be administered and the physician should be prepared to actively manage airway and ventilation. If assisted ventilation is required, the $Paco_2$ should be lowered slowly to avoid posthypercapnic metabolic alkalosis.

In patients with known coronary artery disease, research suggests that acute respiratory acidosis leads to direct vasodilation of coronary vasculature. This is believed to be an instinctive attempt to maintain myocardial blood flow.[5]

RESPIRATORY ALKALOSIS

Increased minute ventilation is the primary cause of respiratory alkalosis, characterized by decreased $Paco_2$ and increased pH. Patients with uncompensated acute respiratory alkalosis have normal plasma [HCO_3^-]. In chronic respiratory alkalosis, eventual renal compensation results in decreased plasma [HCO_3^-].

Etiology

Conditions that lead to respiratory alkalosis are central nervous system (CNS) diseases, hypoxemia, anxiety, hysteria, hypermetabolic states, toxic states, hepatic insufficiency, and assisted ventilation (Box 122-2).

BOX 122-2 CAUSES OF RESPIRATORY ALKALOSIS

- Hypoxia-mediated hyperventilation
  - High altitude
  - Severe anemia
  - Ventilation-perfusion inequality
- CNS-mediated hyperventilation
  - Voluntary, psychogenic
  - Cerebrovascular accident
  - Increased intracranial pressure, tumor
  - Trauma
- Pharmacologic
  - Salicylate, caffeine, or nicotine toxicity
  - Progesterone
  - Pressors, epinephrine
  - Thyroxine
- Septicemia
- Pulmonary
  - Pneumonia
  - Pulmonary embolism
  - Edema
  - Mechanical hyperventilation
  - Atelectasis
- Hepatic
  - Encephalopathy
- Hyponatremia

CNS, central nervous system.

Clinical Features

Symptoms vary according to the degree and chronicity of the alkalosis and the associated symptoms caused by the underlying disorder. The symptoms of alkalosis result from irritability of the central and peripheral nervous systems and from increased resistance in the cerebral vasculature. Symptoms include paresthesias of the lips and extremities, lightheadedness, dizziness, muscle cramps, and carpopedal spasms; symptoms are identical to those seen with hypocalcemia.

Physiologic Compensation

Acute Alkalosis

After the onset of respiratory alkalosis, H^+ is secreted from within the cell to the ECF. H^+ reduces the plasma [HCO_3^-], attempting to offset the acute alkalosis. During the acute state, the plasma [HCO_3^-] is lowered approximately 2 mEq/L for each 10-mm Hg decrease in the $Paco_2$.

Chronic Alkalosis

With persistently low $Paco_2$, renal H^+ secretion is decreased. Mild hypokalemia often occurs as K^+ shifts into the cells while H^+ enters the ECF. Renal secretion of HCO_3^- occurs, and Cl^- is retained to maintain electroneutrality. This creates the hypokalemia and hyperchloremia characteristic of a chronic respiratory alkalosis. During the first 7 to 9 days, compensation is insufficient to normalize the pH, and alkalemia prevails. Beyond 2 weeks, patients with a chronic respiratory alkalosis have a normal or near-normal pH, making this the only primary acid-base disorder in which the pH does often normalize.

Alkalemia of pregnancy (pH 7.46–7.50) is primarily respiratory in origin, occurs early, and is sustained throughout the gestation. A $Paco_2$ of 31 to 35 mm Hg is considered normal in the antepartum period. Therefore, a $Paco_2$ of 40 mm Hg in the pregnant woman represents hypercapnia. In these patients, renal compensation leads to an excretion of HCO_3^-, and a serum HCO_3^- level between 18 and 22 mEq/L in these women is normal.[6]

Management

Respiratory alkalosis itself is rarely life-threatening, and treatment should be directed toward the underlying cause. Treatment should be aimed at removing the stimulus, and when that is not possible, at treating the symptoms. For example, benzodiazepines and pain control may benefit the patient who is overbreathing the ventilator, the anxious patient, or the cocaine or methamphetamine toxic patient. In the patient with tetany or syncope caused by psychogenic hyperventilating, a rebreathing mask allows for CO_2 retention and acid-base normalization. This should be used cautiously and only when other serious conditions have been eliminated from the differential diagnosis.

METABOLIC ACIDOSIS

Metabolic acidosis is defined as acidemia created by a primary increase in [H^+] or a reduction in [HCO_3^-]. The acute state is compensated for by hyperventilation, resulting in reduction of $Paco_2$. Chronically, renal reabsorption of HCO_3^- takes place (Fig. 122-2).

Etiology

Metabolic acidosis can be caused by one of three mechanisms: (1) increased production of acids, (2) decreased renal excretion of acids, or (3) loss of alkali. The causes of metabolic acidosis can be clinically divided into those that create an elevation in AG (Box 122-3) and those that do not (Box 122-4). Dehydration from prolonged diarrhea is the most common cause of normal gap metabolic acidosis.

Elevated Anion Gap

Metabolic acidosis with an elevated AG implies either the addition of exogenous acids or the creation of endogenous acids that cannot be fully neutralized by buffers. The causes can be broadly broken into ketoacidosis, lactic acidosis (either physiologic or from toxins), renal failure, toxins that are metabolized to acids, and, rarely, rhabdomyolysis.

Carbon Monoxide and Cyanide Poisoning. Elevated serum levels of carbon monoxide and cyanide have increasingly been found together in patients exposed to smoke from fires. Victims of smoke inhalation found unconscious and with metabolic acidosis should be considered to have been exposed to both agents. Known as *cellular poisons*, both toxins interfere with cellular respiration at the cytochrome/electron transfer stage, resulting in anaerobic metabolism and the generation of organic acidemia.

Alcoholic Ketoacidosis. Alcoholic ketoacidosis (AKA) results from an abrupt termination of ethyl alcohol intake after a significant and usually lengthy exposure to it. AKA also has a component of malnutrition and dehydration. Clinically, AKA manifests similarly to DKA; however, hyperglycemia and glycosuria are traditionally absent. Patients may present with AGs in the range of 30 to 35 mEq/L and hypocapnia secondary to compensatory hyperventilation. They may also have double and triple acid-base disorders due to alcohol withdrawal (respiratory alkalosis) and vomiting (metabolic alkalosis), which results in a pH that may be alkalemic. The ratio of β-hydroxybutyrate to acetoacetate is at least twice as high in AKA (6–10:1) as it is in DKA (3–4:1).[7] This is important because there is a greater chance of missed diagnosis and inappropriate therapy in cases of AKA, since the β-hydroxybutyrate is not detected by the usual means and because during recovery, as β-hydroxybutyrate is converted to acetoacetate and acetone, a paradoxi-

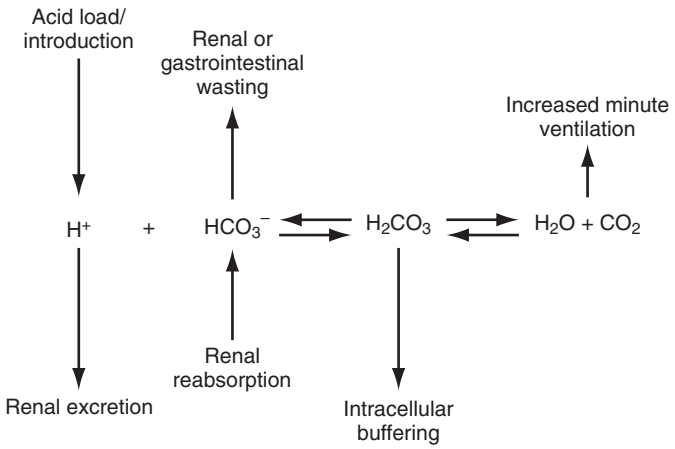

Figure 122-2. Metabolic acidosis and regulation.

BOX 122-3 CAUSES OF ANION GAP METABOLIC ACIDOSIS

Ketoacidosis
Diabetes
Alcohol intoxication/alcoholic ketoacidosis
Malnutrition/fasting

Lactic Acidosis (from physiologic processes)
Shock
Primary hypoxia due to lung disorders
Seizures

Lactic Acidosis (from exogenous toxins)
Carbon monoxide
Cyanide
Iron
Isoniazid
Toluene (initially high gap; subsequent excretion of metabolites normalizes gap)

Renal Failure

Toxins Metabolized to Acids
Alcohol
Methanol (formate)
Ethylene glycol (oxalate)
Paraldehyde (acetate, chloracetate)
Salicylates

Rhabdomyolysis (rare)

BOX 122-4 CAUSES OF NORMAL ANION GAP METABOLIC ACIDOSIS

GI HCO_3^- Loss
Colostomy
Diarrhea
Enteric fistulas
Ileostomy
Use of ion-exchange resins

Urologic Procedures
Ureterosigmoidostomy
Ureteroileal conduit

Renal HCO_3^- Loss
Tubulointerstitial renal disease
Renal tubular acidosis, types 1, 2, and 4
Hyperparathyroidism

Ingestions
Acetazolamide
Calcium chloride ($CaCl_2$)
Magnesium sulfate ($MgSO_4$)

Parenteral Infusion
Arginine
Lysine
Ammonium chloride (NH_4Cl)
Rapid sodium chloride infusion

Other
Hypoaldosteronism
Hyperkalemia
Toluene (late)

cal worsening of the ketoacidosis results. (The usual dipstick tests have 0% sensitivity for β-hydroxybutyrate, 100% for acetoacetate, and 5% for acetone.) The main treatment for AKA is hydration with 5% dextrose in normal saline (D_5NS). Carbohydrate and fluid replacement reverse the pathophysiologic derangements that lead to AKA by increasing serum insulin levels and suppressing the release of glucagon and other counter-regulatory hormones. Fluids alone do not correct AKA as quickly as fluids and carbohydrates together, and in general, insulin is contraindicated.

Toluene Inhalation. Traditionally used as a solvent, toluene has become an inhalational agent abused for its euphoric effect. Toluene produces AG acidosis that is further complicated by distal renal tubular damage. The end result is a mix of non-AG and AG metabolic acidosis due to the renal tubular acidosis and HCO_3^- loss. Treatment is supportive and is aimed at fluid and electrolyte replacement when needed.

Methanol, Ethylene Glycol, and Paraldehyde. The toxic effects of methanol (methyl or wood alcohol) ingestion result from the formation of its metabolite, formaldehyde, which is converted to formic acid, which causes metabolic acidosis. Ethylene glycol's toxic metabolites are oxalates, aldehydes, and lactic acid; oxalates result in significantly elevated AGs and increased mortality. Paraldehyde poisoning is rare; its use is now restricted to hospitalized patients and patients under close medical supervision. Ingestion leads to the creation of acetic and chloracetic acids. Treatment of methanol or ethylene glycol poisoning is aimed at preventing their metabolism into toxins with fomepizole or ethanol or elimination through hemodialysis.

Uremia. The acidosis in uremic patients results from a failure by the kidneys to excrete acids. H^+ elimination is a direct secretory function of the renal tubules. The ability to excrete NH_4^+, HSO_4^-, and HPO_4^{-2}, however, varies directly with the glomerular filtration rate (GFR). Any pathologic process affecting the GFR increases HSO_4^- and HPO_4^{-2}, resulting in an increased AG. In cases of pure uremia, the AG rarely exceeds 25 mEq/L. In the patient with chronic renal failure, increased AG metabolic acidosis is common. In cases of acute renal failure, however, hyperchloremic, non-AG metabolic acidosis is more common.

In pyelonephritis or obstructive uropathy, the acidosis is not related to an increased AG because tubular function is affected more than GFR. Increased AG metabolic acidosis in the patient with elevated serum blood urea nitrogen and creatinine levels suggests renocortical disease.

Diabetic Ketoacidosis. DKA manifests clinically as a triad: hyperglycemia (usually >200 mg/dL), ketonemia (>1:2 dilutions), and acidemia (pH < 7.3). DKA can be caused by any condition that reduces insulin availability or activity or that increases glucagon. DKA occurs most often in type 1 diabetic patients with little or no endogenous insulin; however, its occurrence in patients with type 2 diabetes, particularly obese African Americans, is not as rare as once thought. DKA in these patients results from increased lipolysis, and the breakdown of free fatty acids leads to production of ketoacids. Precipitating events usually include infections, surgery, and emotional or physical stressors. Treatment is aimed at fluid replacement over the first 24 to 48 hours, insulin replacement, and potassium replacement.

Isoniazid and Iron Toxicity. Isoniazid is a common, important, but potentially lethal medication used for the treatment of tuberculosis. Clinicians must be aware that ingestions of greater than 40 to 60 mg/kg pose a danger of not only recurrent seizures but also life-threatening metabolic acidosis (as a result of the lactate-producing seizure activity). Treatment involves pyridoxine administration to control seizures and hemodialysis to reduce both intravascular drug concentration and acidemia.

Elevated AG metabolic acidosis from iron ingestion is a direct result of mitochondrial poisoning and uncoupled oxidative phosphorylation. Metabolic acidosis is typically appreciated in phase I of toxicity, usually within 6 hours of ingestion. It becomes quite apparent in phase III, signaling impending hepatic failure and shock. Effective treatment depends on early recognition and administration of deferoxamine.

Lactic Acidosis. There are two forms of lactic acid, the levorotary, or "L," form and the dextrorotary, or "D," form. The L form is most common and is the traditional form measured when obtaining serum lactate levels. A product of anaerobic metabolism, lactic acidosis develops when an imbalance exists between lactic acid production and subsequent conversion by the liver and kidney. Thus, lactic acidosis is a marker of hypoperfusion and ongoing shock, as hypoperfusion, hypoxemia, hypermetabolic states, or some combination of these results in an increase in serum lactate.

The D form has recently gained attention because of an increasing number of patients with small-bowel resection or gastric bypass surgery.[8] D-Lactic acidosis is characterized by episodes of encephalopathy and acidemia. Development of short-gut syndrome requires ingestion of a large carbohydrate load, carbohydrate malabsorption with increased delivery of carbohydrates to the large bowel, prominent lactobacilli, diminished colonic motility, and impaired D-lactic acid metabolism.

Nucleoside analogue reverse transcriptase inhibitors (e.g., zidovudine and stavudine) for human immunodeficiency virus have also been shown to induce lactic acidosis. The syndrome that results from the mitochondrial toxicity of these agents can manifest with severe lactic acidosis, hepatic steatosis, and a high rate of mortality.[9]

Initial measurement of metabolic acidosis (serum lactate levels), compared with the traditional carboxyhemoglobin levels, might better indicate the severity of carboxyhemoglobin toxicity and better predict hyperbaric treatment requirements.[10]

Metformin, currently considered the initial drug of choice for overweight patients with type 2 diabetes mellitus, is a biguanide derivative that is pharmacologically related to phenformin hydrochloride, which was withdrawn from the U.S. market in 1976 (owing to a high incidence of lactic acidosis). Studies support the clinical experience of metformin-induced lactic acidosis as well.[11] Metformin is believed to induce lactic acidosis, especially in the patient with renal insufficiency, by reducing pyruvate dehydrogenase activity and enhancing anaerobic metabolism. A serum creatinine concentration greater than 1.5 mg/dL, congestive heart failure requiring medications, acute or chronic metabolic acidosis, or exposure to iodinated contrast agents within 48 hours are considered absolute contraindications to the drug.

Salicylates. Salicylates' first toxic effect on acid-base balance results from direct stimulation of the respiratory center, increasing minute ventilation and inducing hypocapnia. This is known as the first phase and may last as long as 12 hours. In the early presentation of salicylate toxicity, respiratory alkalosis is often the only acid-base disturbance appreciated. Salicylates can also cause metabolic acidosis by uncoupling oxidative phosphorylation and inhibiting the dehydrogenase enzymes of the Krebs cycle. The second phase of salicylate poisoning is marked by paradoxical aciduria in the presence of continued respiratory alkalosis. This phase may begin within hours and may last 12 to24 hours. The third phase is marked by dehydration, hypokalemia, and progressive metabolic acidosis. This phase may begin within 4 to 6 hours in infants or more than 24 hours later in adolescents and adults. Treatment

is supportive, and gastrointestinal decontamination with charcoal may be indicated. Fluid and electrolyte replacement will likely be necessary, and both urinary and serum alkalinization may be of benefit in enhancing elimination and minimizing toxicity.

Normal Anion Gap Metabolic Acidosis

Metabolic acidosis with a normal AG is caused by either an excessive loss of HCO_3^- or an inability to excrete H^+ (see Box 122-4). Any condition that causes excessive loss of intestinal fluid distal to the stomach can cause a normal AG metabolic acidosis. Normal AG metabolic acidosis is primarily a HCO_3^--wasting condition and in 95% of cases results from diarrhea. Other possible, although less common, causes include tube drainage and skin fistulae, with loss of HCO_3^--rich intestinal, biliary, or pancreatic fluids. Ureterosigmoidostomy (surgical insertion of ureters into the sigmoid colon) produces a hyperchloremic acidosis because of loss of HCO_3^- in exchange for the reabsorption of Cl^-.

Patients with renal failure develop an inability to excrete their dietary H^+ load; the severity is proportional to the degree of reduction in the GFR. Patients with renal tubular acidosis type 1 are unable to secrete H^+ at the distal tubule, whereas impairment of HCO_3^- reabsorption at the proximal tubule is the defect in renal tubular acidosis type 2. Calculation of the urinary anion gap (UAG = $[Na^+ + K^+] - Cl^-$) may be helpful; a negative urinary AG suggests GI loss of HCO_3^-, whereas a positive urinary AG suggests altered urinary acidification, indicating a renal tubule abnormality.

Other causes of normal AG metabolic acidosis include hyperparathyroidism, medications such as carbonic anhydrase inhibitors (e.g., acetazolamide [Diamox], mafenide acetate [Sulfamylon]), spironolactone and cholestyramine, chloride-containing acids ingestion (e.g., NH_4Cl, arginine HCl, lycine), renal tubular acidosis, sulfur, $CaCl_2$ and $MgCl_2$ ingestions, and hyperalimentation with excess arginine, lysine, or Cl^-.

Physiologic Compensation

The body responds to acidemia by utilizing four buffering systems: (1) extracellular bicarbonate/carbonic acid (HCO_3^-/H_2CO_3) system, (2) intracellular blood protein system, and (3) renal and (4) respiratory compensation systems (see Fig. 122-2).

The first two processes minimize the initial $[H^+]$, while the kidneys eliminate excessive H^+ in the urine, reabsorb HCO_3^-, and restore acid-base homeostasis. The CNS responds to increased $[H^+]$, through direct stimulation of the chemoreceptors in the medulla oblongata, by stimulating the respiratory center. This results in an increase in alveolar ventilation, producing a compensatory elimination of $Paco_2$ and elimination of excess H^+. It may take 12 to 24 hours to achieve a maximal respiratory response to a sustained metabolic acidosis. When the arterial pH is 7.1 or less, the minute ventilation can reach 30 L/min, and at this level of pH, Kussmaul's respiration and its prominent hyperventilation can be seen.

In response to metabolic acidosis, H^+ is excreted by the kidney while HCO_3^- is reabsorbed. The rate-limiting reaction (the synthesis of H_2CO_3 from CO_2 and H_2O) is catalyzed by carbonic anhydrase. Therefore, inhibitors of this enzyme can create a metabolic acidosis by preventing the renal excretion of H^+. The excretion of H^+ requires buffering with HPO_4^- or NH_3, with NH_4^+ playing the largest role. This buffering is called *titratable acidity*. The kidney responds to an increased H^+ load by the augmentation of cellular NH_3 production and consequently NH_4^+ excretion.

In summary, H^+ is acutely buffered by extracellular and intracellular mechanisms. However, these mechanisms are not potent enough to correct acidosis sufficiently. Acidemia stimulates the CNS ventilatory center, and the $Paco_2$ is reduced secondary to Kussmaul's respiration. With continued and chronic acidemia, the kidneys secrete H^+ (as NH_4^+ and $H_2PO_4^-$) and reabsorb HCO_3^- in an attempt to neutralize the acidosis.

Management

In treating patients with metabolic acidosis, primary efforts should be directed at restoring their homeostatic mechanisms. The clinician must treat the patient, using laboratory markers only as a guide. Individual therapies are directed toward the particular cause of the acidosis.

Active correction of the pH depends on the severity of the acid-base imbalance, the cause, the patient's compensatory capabilities, and the potential harm caused by therapy. Most patients with metabolic acidosis do not require aggressive attempts at pH manipulation. For many, the causality is easily discernible, and treatment involves stabilization of homeostatic mechanisms. For example, metabolic acidosis (average pH 7.1) after a seizure resolves within approximately 15 minutes, and the bicarbonate normalizes within 45 to 60 minutes. Rather than administration of sodium bicarbonate ($NaHCO_3$), immediate treatment would involve termination of the seizure activity, maintenance of the airway, and provision for acid-base normalization by ventilatory loss of CO_2.

Therapy with $NaHCO_3$ has some inherent complications, and rapid $NaHCO_3$ replacement can result in paradoxical CNS intracellular acidosis, impaired oxygen delivery, hypokalemia, hypocalcemia, "overshoot" alkalosis, hypernatremia, volume overload, and hyperosmolality. Bicarbonate penetration into the CNS across the blood-brain barrier is very slow; consequently, intravenous HCO_3^- therapy alkalinizes the plasma much faster than the CNS. As the serum pH increases, the peripheral chemoreceptors decrease minute ventilation, raising $Paco_2$ in an attempt to normalize the serum pH. CO_2, which rapidly diffuses across the blood-brain barrier, rises intracerebrally, and the CNS becomes more acidemic despite alkalinization of the plasma. This inverse reaction is referred to as *paradoxical CNS acidosis*. Much discussion surrounds this phenomenon and intravenous HCO_3^- use. Buffer therapy during out-of-hospital cardiac arrest had little to no benefit in one study, regardless of the arterial pH.[12] The only prospective, randomized, controlled study was done on hypovolemic rats and failed to demonstrate any difference between the HCO_3^- and control groups.[13] Furthermore, alkali therapy can lead to ECF volume overload (especially in patients with congestive heart failure) and hypokalemia, which may lead to respiratory muscle weakness and inability to hyperventilate if it is severe. Administration of loop diuretics may prevent or treat this complication, but if adequate diuresis cannot be established, emergent dialysis may be necessary.

Because $NaHCO_3$ imparts a significant sodium load on the patient, several low-sodium buffers have been developed. Unfortunately, none has proven to be clinically more efficacious than $NaHCO_3$.[14]

Because of the inherent complications associated with HCO_3^- replacement, the rule of thumb is to consider treatment in patients who have pH less than 7.1 with $NaHCO_3$ 1 mEq/kg unless the condition of acidemia is expected to be self-limited. For example, many experts do not recommend administration of HCO_3^- in patients with DKA and pHs as low

as 6.9. Another formula available to assist in determining the adequate dose is the following:

$$NaHCO_3(mEq) = 25 - (\text{measured } HCO_3^-) \times (\text{weight [kg]}/2)$$

Half should be replaced initially, and further $NaHCO_3$ therapy should be determined by patient response and laboratory parameters. Patients with normal AG metabolic acidosis have a greater loss of HCO_3^- than those with an increased AG, and therefore the clinician may have a lower threshold for replacement (i.e., treat serum HCO_3^- less than 8 mEq/L and correct to 12–15 mEq/L versus AG acidosis where it should be corrected to 10 mEq/L).

METABOLIC ALKALOSIS

Metabolic alkalosis is produced by conditions that increase HCO_3^- or reduce H^+. This usually requires either the loss of H^+ or the retention of HCO_3^-. The diagnosis requires knowledge of the $Paco_2$, because elevation of the plasma HCO_3^- may be secondary to renal compensation of a chronic respiratory acidosis.

Etiology

Metabolic alkalosis is usually caused by an increase in HCO_3^- reabsorption secondary to volume, potassium, or Cl^- loss (Box 122-5). Loss of H^+ and Cl^- from protracted vomiting and nasogastric suctioning can also lead to HCO_3^- retention. Renal impairment of HCO_3^- excretion, especially in the setting of alkali therapy, can lead to a significant metabolic alkalosis.

An ECF volume reduction can increase the plasma HCO_3^- concentration when combined salt and water losses occur, typically in patients using diuretics. This state forces a contraction of the ECF around a constant plasma HCO_3^-, creating a relative excess in HCO_3^- concentration; this is known as *contraction alkalosis*.

Metabolic alkalosis can be caused by hypokalemia as H^+ is shifted intracellularly in exchange for the osmotic movement of K^+ extracellularly. There is also an increase in renal H^+ secretion and HCO_3^- reabsorption. The net effect is ECF alkalosis with paradoxical intracellular acidosis, which is easily reversed with K^+ therapy.

Primary hyperaldosteronism, hyper-reninism, licorice ingestion, Cushing's syndrome, and congenital adrenal hyperplasia are associated with mineralocorticoid excess. This leads to an increased Na^+ reabsorption in the distal tubule with its accompanying H^+ and K^+ secretion to maintain electroneutrality.

BOX 122-5 CAUSES OF METABOLIC ALKALOSIS

Volume-Contracted (Saline-Responsive)
Vomiting/gastric suction
Diuretics
Ion-deficient baby formula
Colonic adenomas
Postrespiratory acidosis

Normal Volume/Volume-Expanded (Saline-Resistant)
Hyperaldosteronism (primary, secondary, or exogenous mineralic corticoids, e.g., licorice, tobacco)
Cushing's syndrome
Severe potassium depletion
Adenocarcinoma
Bartter's syndrome
Ectopic adrenocorticotropic hormone

Unclassified
Milk-alkali syndrome
Carbenicillin therapy
Metabolism of organic acid anion (bicarbonate, lactate, citrate)
Massive transfusion with citrate anticoagulant or plasmanate (acetate) if renal impairment
Nonparathyroid hypercalcemia

Physiologic Compensation

Although somewhat less predictable, acute compensation of metabolic alkalosis involves the respiratory center, and chronic compensation involves the renal system. During acute compensation, chemoreceptors controlling ventilation respond to an increased pH by inducing hypoventilation, thus increasing $Paco_2$ and forming H^+, which lowers the pH back to normal. A $Paco_2$ of greater than 55 mm Hg is unlikely to be caused by simple respiratory compensation of metabolic alkalosis, and this value should alert the clinician to a ventilation disorder complicating the picture. Chronic compensation for metabolic acidosis results from the kidneys excreting excess HCO_3^- in the urine. In patients with renal failure, impairment in renal HCO_3^- excretion results in sustained metabolic alkalosis.

Management

Clinicians can easily treat the simple loss of H^+ from protracted vomiting or nasogastric suction. For more complicated causes, however, management can be directed by measurement of the urinary Cl^-, which helps classify metabolic alkalosis into saline-responsive or saline-resistant.

Saline-Responsive Alkalosis

Patients with saline-responsive alkalosis have a urinary Cl^- level less than 10 mEq/L. Treatment is directed toward correcting the urinary excretion of HCO_3^-. Administration of NaCl and KCl suppresses both renal acid excretion and renal HCO_3^- excretion. Administration of NaCl and KCl should be considered for patients with mild to moderate saline-responsive alkalosis. In patients who are severely volume-depleted, consultation for admission and administration of intravenous mineral acids (e.g., arginine monohydrochloride) may be necessary. In edematous states for which saline therapy may be contraindicated, acetazolamide increases the excretion of $NaHCO_3$, treating both the alkalosis and the edema. In renal failure patients, severe metabolic alkalosis should be treated with dialysis.

Saline-Resistant Alkalosis

Patients with saline-resistant alkalosis have a urinary Cl^- level greater than 10 mEq/L. In mineralocorticoid excess, hypokalemia and increased secretion of aldosterone lead to excessive renal excretion of H^+ and a reabsorption of HCO_3^-. Treatment can be successful with K^+ replacement by reversing the intracellular shift of H^+. This reduction of cellular H^+ also enhances HCO_3^- excretion. Additional therapy can be directed toward reducing mineralocorticoid activity (e.g., administering spironolactone, an aldosterone antagonist).

MIXED ACID-BASE DISORDERS

Double and triple primary acid-base disturbances are common. Traditionally, mixed disorders have been difficult to evaluate in the emergency department. However, recent literature pro-

vides some guidelines for ascertaining the mixed disorder and its causes. Clues to the presence of a mixed acid-base disturbance can either be historical (e.g., polydrug ingestion) or clinical, with varied chemistry and arterial blood gas findings that differ from those anticipated. We can use a six-step approach to analyzing acid-base disturbances as outline below and in Figure 122-3.

Step 1 involves measuring the pH. It is necessary to first assess whether the patient has an acidemia (pH < 7.36) or alkalemia (pH > 7.44). The human body almost never fully compensates for any primary acid-base disturbance except for chronic respiratory alkalosis.

Step 2: Is the primary disturbance respiratory or metabolic?

Step 3 requires the clinician to calculate the AG. Box 122-3 lists possible causes of an AG greater than 15 mEq/L, and Box 122-4 lists possible causes for a case in which the AG is normal but the patient has a metabolic acidosis.

Step 4 involves calculating the delta gap (ΔG = deviation of AG from normal – deviation of HCO_3^- from normal) to help resolve the possibility of a mixed acid-base disorder or further differentiate an elevated AG metabolic acidosis.

Values for the ΔG are all gaussian, and therefore the mean value should be near zero.[15] An expected normal range for the ΔG would be 0 ± 6. A positive ΔG (+6 or greater) is almost always caused by high AG acidosis and a primary metabolic alkalosis. DKA or AKA with severe vomiting, lactic acidosis in the setting of chronic diuretic use, and renal disease with vomiting are clinical examples.

A negative ΔG (–6 or less), on the other hand, can be of varied clinical representation. Most often there is either a mixed high AG and normal AG acidosis, or a high AG acidosis with chronic respiratory alkalosis and a compensating hyperchloremic acidosis. Clinically, these patients often have severe underlying metabolic disease with ongoing toxic ingestion (e.g., profound hypermagnesemia, hyponatremia, or hypercalcemia in patients with lithium toxicity) or chronic lung disease, acute lactic acidosis, and furosemide use. Other relationships in these disorders can also assist in rapid interpretation of mixed acid-base disturbances (Box 122-6).

Step 5 asks whether the respiratory disturbance (if there is one) is acute or chronic. If acute, for each change in P_{CO_2} of 10 mm Hg, the pH changes by 0.08 in the opposite direction. If chronic, for each change in P_{CO_2} of 10, the pH changes by 0.03 in the opposite direction.

Step 6 involves determining if the respiratory system has compensated fully when the primary disturbance is a metabolic acidosis. Using Winter's formula (P_{CO_2} = 1.5 ($HCO3^-$) + 8 ± 2), you can calculate the degree of compensation.

Mixed acid-base disturbances typically result from compensation failure, excessive compensation, or more than one disease process. Examples of compensation failures resulting in metabolic acidosis and respiratory acidosis include: cardiac arrest patients, chronic obstructive pulmonary disease patients with respiratory failure and hypoxemia, and hypoventilation and acidosis-causing toxins. Metabolic alkalosis and respiratory alkalosis may result from compensation failure in patients who are pregnant with hyperemesis and in patients with postoperative pain and vomiting. Patients with salicylate overdose, pulmonary edema, sepsis, and hepatic failure may exhibit excessive compensation and a combined metabolic acidosis and respiratory alkalosis that results in a near normal pH. Superimposed metabolic acidosis and alkalosis may also be present in patients with excessive compensation due to vomiting in association with DKA or AKA. In the alcoholic patient with AKA you may find a triple acid-base disturbance as a result of vomiting (metabolic alkalosis), withdrawal (respiratory alkalosis), and the AKA (metabolic acidosis). A thorough history and physical examination can be especially important in prompting the clinician to consider a complicated acid-base disturbance.

BOX 122-6 RELATIONSHIPS IN ACID-BASE DISTURBANCES

Respiratory Acidosis

Acute

HCO_3^- increases 1 mEq/L (range, 0.25–1.75) for every 10-mm Hg increase in P_{CO_2}.

pH drops 0.08 for every 10-mEq/L rise in HCO_3^-.

Chronic (>5 days of hypercapnia)

HCO_3^- increases 4 mEq/L for every 10-mm Hg increase in P_{CO_2} (±4).

Limit of compensation: bicarbonate will rarely exceed 38–45 mEq/L.

Metabolic Acidosis

Note: It may take 12–24 hours for maximal respiratory response to develop.

$P_{aCO_2} = (1.5 \times HCO_3) + 8 \pm 2$.

P_{aCO_2} is equivalent to last two digits of pH (e.g., if P_{CO_2} is 20, pH should be 7.20).

$\Delta P_{CO_2} - 1\ [1.3 \times (\Delta HCO_3^-)]$

For pure AG acidosis, the rise in anion gap should be equal to the fall in $[HCO_3^-]$ (i.e., ΔG should equal 0).

For pure non-AG (hyperchloremic) acidosis, the fall in HCO_3^- should be equal to the rise in $[Cl^-]$ (i.e., $\Delta HCO_3^- = -\Delta Cl^-$).

Limit of compensation: P_{aCO_2} will not fall below 10–15 mm Hg.

Respiratory Alkalosis

Acute

HCO_3^- drops 1 to 3.5 mEq/L for every 10-mm Hg drop in P_{CO_2}.

Limit of compensation: bicarbonate is rarely below 18 mEq/L.

Chronic (renal compensation starts within 6 hours and is usually at a steady state by 1½–2 days)

HCO_3^- drops 2–5 mEq/L for every 10-mm Hg drop in P_{CO_2}.

Limit of compensation: bicarbonate is rarely below 12–14 mEq/L.

Metabolic Alkalosis

$P_{CO_2} = 0.9\ (HCO_3^-) + 9$.

P_{CO_2} increases 0.6 mm Hg for each 1-mEq/L increase in HCO_3^-.

Limit of compensation: P_{CO_2} rarely exceeds 55 mm Hg but has been reported as high as 75.

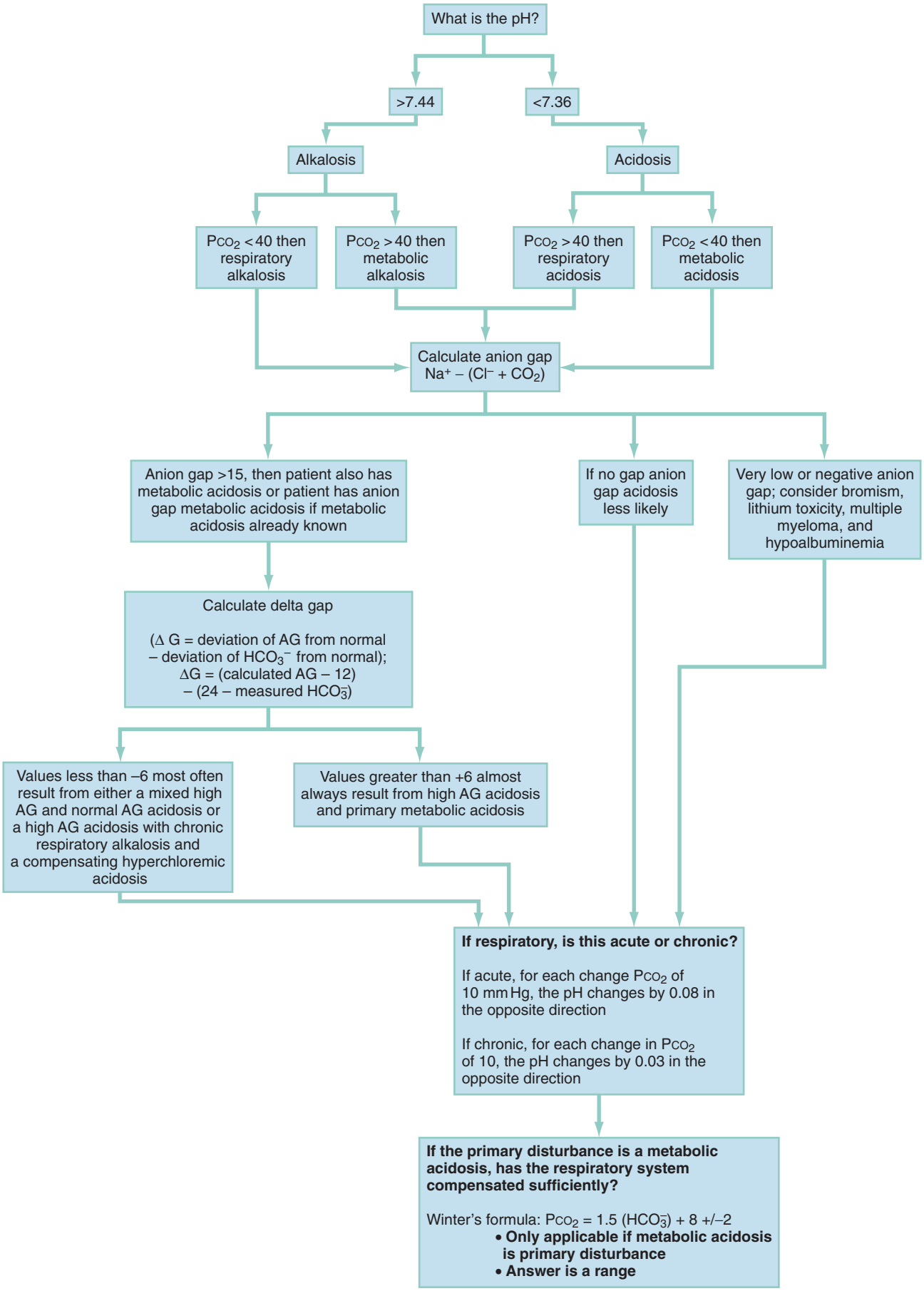

Figure 122-3. Algorithm for acid-base calculation.

KEY CONCEPTS

- Changes in serum pH are dealt with by three compensatory systems: (1) the physiologic buffers, (2) the lungs, and (3) the kidneys.
- HCO_3^- is present in large quantities and can be controlled by the lungs and kidneys, making it the major contributor to the maintenance of acid-base balance and the primary system to handle the acute load of organic acidemia.
- Respiratory acidosis is defined as decreased pH that results from pulmonary CO_2 retention. This CO_2 retention leads to excess H_2CO_3 production and acidemia.
- Increased minute ventilation is the primary cause of respiratory alkalosis, characterized by decreased $Paco_2$ and increased pH.
- Metabolic acidosis can be caused by one of three mechanisms: (1) increased production of acids, (2) decreased renal excretion of acids, or (3) loss of alkali. The causes of metabolic acidosis can be divided into those that create an elevation in the AG and those that do not.
- Metabolic alkalosis is usually caused by an increase in HCO_3^- reabsorption secondary to volume, potassium, or Cl^- loss.
- Contraction alkalosis can result from extracellular volume reduction, with a consequent increase in the plasma HCO_3^- concentration, when combined salt and water losses occur. This typically occurs in patients using diuretics.
- Determination of a mixed acid-base disorder requires knowledge of the pH, calculation of the AG, and calculation of the ΔG.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 123 Electrolyte Disturbances

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PERSPECTIVE

An electrolyte is any substance that has free ions and therefore can conduct an electrical charge when in solution. The principle electrolytes in human physiology are sodium (Na^+), potassium (K^+), calcium (Ca^{2+}), magnesium (Mg^{2+}), chloride (Cl^-), and hydrogen phosphate (HPO_4^{2-}). Gradients of electrolytes between the intracellular and extracellular spaces are carefully maintained and are responsible for the electrical conduction required for muscles and nerves to function. The electrolyte concentrations of the body are maintained principally through kidney function, but also through action of hormones such as antidiuretic hormone, aldosterone, and parathyroid hormone. Dysfunction of any of these mechanisms or even severe physiologic stress, can disrupt electrolyte balance and result in a life-threatening emergency.

SODIUM

Normal Physiology

Since electrolytes exist in solution in the human body, fluid balance and electrolyte balance are linked, and under hormonal control. Water makes up approximately 60% of body weight and is distributed in three compartments: the intracellular space, the interstitial space, and the intravascular space. The intracellular space makes up approximately two thirds of total body water, with the remaining one third in the interstitial and intravascular spaces. The concentration of sodium [Na^+], the predominant extracellular cation, governs the movement of water among these three compartments. When the extracellular [Na^+] decreases, water shifts to the intracellular space to restore osmotic equilibrium. When the extracellular [Na^+] rises, water shifts out of the intracellular space. Under normal conditions, Na^+ leaks passively into cells down a concentration gradient and is transported back out of the cell by the sodium-potassium adenosine triphosphatase (Na^+-K^+ ATPase) pump.

Na^+ homeostasis and water balance are under the hormonal regulation of the renin-angiotensin system and antidiuretic hormone, respectively. Renin, an enzyme produced by the kidney, is released in response to decreases in circulating intravascular volume. Renin catalyzes the production of angiotensin I, which is then converted to angiotensin II in the lung. Angiotensin II stimulates the production of aldosterone, a mineralocorticoid hormone produced by the zona glomerulosa of the adrenal glands. Aldosterone enhances Na^+ reabsorption and K^+ excretion in the distal nephron.

Antidiuretic hormone (ADH, vasopressin, arginine vasopressin) is synthesized in the hypothalamus and secreted from the posterior pituitary. ADH is released primarily in response to rises in serum osmolality but also to decreases in intravascular volume or arterial pressure. Volume depletion is the most potent stimulus for ADH production, and with decreases in plasma volume, ADH may be secreted even in the face of hypotonicity. ADH enhances renal water reabsorption by increasing tubular water permeability. Other factors that may stimulate ADH release include angiotensin, catecholamines, opiates, caffeine, hypoglycemia, hypoxia, and stress.

Hyponatremia

Principles of Disease

Hyponatremia is defined as a serum [Na^+] of less than 135 mEq/L. Hyponatremia can be classified into three categories based on the patient's clinical volume status: (1) hypovolemic hyponatremia, (2) euvolemic hyponatremia, and (3) hypervolemic hyponatremia (Box 123-1). When assessing the patient with a low serum Na^+ level, it is also important to consider the possibility of sampling errors (e.g., phlebotomy from a venous site proximal to an infusion of hypotonic solution), as well as pseudohyponatremia and redistributive hyponatremia.

Pseudohyponatremia. *Pseudohyponatremia* refers to a falsely low serum Na^+ measurement in patients whose plasma contains excessive protein or lipid. The relative percentage of water in plasma is reduced. Flame photometry, which determines Na^+ content per unit of plasma, shows an artifactually low Na^+ level, although both the total Na^+ content and the serum osmolarity remain within the normal range. Measurement of the serum Na^+ by direct potentiometry avoids this problem.[1]

Redistributive Hyponatremia. Redistributive hyponatremia is caused by osmotically active solutes in the extracellular space that draw water from the cell, diluting the serum [Na^+]. Common situations causing such hyperosmolar states include hyperglycemia (e.g., diabetic ketoacidosis [DKA]) and parenteral administration of mannitol or glycerol for the management of intracranial hypertension or glaucoma. The measured serum Na^+ in patients with hyperglycemia can be corrected by adding approximately 1.6 mEq/L for every 100-mg/dL rise in the serum glucose over 100 mg/dL.

Hypovolemic Hyponatremia. Hypovolemic hyponatremia results from the loss of water and Na^+ with a greater relative loss of Na^+. Typical causes include vomiting, diarrhea, gastrointesti-

BOX 123-1 CAUSES OF HYPONATREMIA

- Sampling error
- Pseudohyponatremia
  - Hyperlipidemia
  - Hyperproteinemia
- Redistributive type
  - Hyperglycemia
  - Mannitol
- Hypovolemic type
  - Renal losses
  - Gastrointestinal
  - Third-space losses
  - Excessive sweating
  - Addison's disease
- Euvolemic type
  - SIADH
  - Psychogenic polydipsia
- Hypervolemic type
  - Congestive heart failure
  - Hepatic cirrhosis
  - Nephrotic syndrome

SIADH, syndrome of inappropriate secretion of antidiuretic hormone.

nal suction or drainage tubes, fistulas, and "third spacing" of fluids (e.g., burns, intra-abdominal sepsis, bowel obstruction, pancreatitis). Causes specifically attributable to renal losses include diuretic use, mineralocorticoid deficiency, renal tubular acidosis, and salt-wasting nephropathy. When Na^+ losses are sufficient to decrease the glomerular filtration rate (GFR) significantly, the amount of filtrate delivered to the loop of Henle (where free water is generated) is decreased, and little free water appears in the urine. Also, because ADH is released in response to intravascular volume deficits despite hypotonicity, hyponatremia may be maintained even in patients whose GFR would otherwise be adequate to excrete excess free water. Hypovolemic hyponatremia can also be worsened when fluid losses are replaced with hypotonic fluids.

Euvolemic Hyponatremia. The many causes of euvolemic hyponatremia include the syndrome of inappropriate secretion of ADH (SIADH), defined as the secretion of ADH in the absence of an appropriate physiologic stimulus. Its hallmark is an inappropriately concentrated urine despite the presence of a low serum osmolality and a normal circulating blood volume. Causes of SIADH include central nervous system (CNS) disorders, pulmonary disease, drugs, stress, pain, and surgery (Box 123-2). Before the diagnosis of SIADH can be confirmed, other potential causes of euvolemic hyponatremia (e.g., hypoadrenalism, hypothyroidism, renal failure) should be ruled out. Psychogenic polydipsia is a rare cause of euvolemic hyponatremia. This is most often seen in patients with psychiatric disorders who consume large volumes of water, usually in excess of 1 L/hr, overwhelming the capacity of the kidneys to excrete free water in the urine.[2] In contrast to SIADH, the urine in patients with psychogenic polydipsia is maximally dilute.

Hypervolemic Hyponatremia. Hypervolemic hyponatremia results when Na^+ is retained but retention of water exceeds that of Na^+. This is seen in edematous states such as congestive heart failure, hepatic cirrhosis, and renal failure. In these conditions, decreased effective renal perfusion causes the secretion of both ADH and aldosterone. This leads to increased tubular reabsorption of both Na^+ and water, decreased delivery of water to the distal nephron, and inability to produce hypotonic urine.

BOX 123-2 CAUSES OF SYNDROME OF INAPPROPRIATE SECRETION OF ANTIDIURETIC HORMONE

CNS Disease
- Brain tumor, infarction, injury, or abscess
- Meningitis
- Encephalitis

Pulmonary Disease
- Pneumonia
- Tuberculosis
- Lung abscess
- Pulmonary aspergillosis

Drugs
- Exogenous vasopressin
- Diuretics
- Chlorpropamide
- Vincristine
- Thioridazine
- Cyclophosphamide

CNS, central nervous system.

Clinical Features

The primary symptoms of hyponatremia are CNS symptoms, including lethargy, apathy, confusion, disorientation, agitation, depression, and psychosis. Focal neurologic deficits, ataxia, and seizures have been reported.[3] Other nonspecific signs and symptoms include muscle cramps, anorexia, nausea, and weakness.

The signs and symptoms of hyponatremia depend on the rapidity with which the serum $[Na^+]$ declines, as well as on its absolute level. The acutely hyponatremic patient is almost always symptomatic when the serum Na^+ level falls below 120 mEq/L, whereas patients with chronic hyponatremia may tolerate much lower levels. Very young and very old patients typically develop symptoms with lesser decreases in the serum Na^+ level.

Diagnostic Strategies

The urinary $[Na^+]$ can be a useful tool in the assessment of the patient with hyponatremia. Patients with hypovolemic hyponatremia caused by renal Na^+ wasting typically have an inappropriately high urinary $[Na^+]$ (>20 mEq/L); those with extrarenal Na^+ wasting and intact renal Na^+-conserving mechanisms have a low urinary $[Na^+]$ (<10 mEq/L). Patients with euvolemic hyponatremia generally have a urinary Na^+ concentration greater than 20 mEq/L. Patients with hypervolemic hyponatremia caused by congestive heart failure or cirrhosis typically have a $[Na^+]$ below 10 mEq/L, and those with renal failure have a concentration above 20 mEq/L.[4]

Management

Because tolerance for hyponatremia is highly variable, treatment should be guided by the severity of symptoms, the estimated duration of illness, and the patient's volume status rather than by the serum Na^+ level alone. Severe neurologic dysfunction and seizures are an indication for immediate treatment. Patients with signs of shock or symptomatic fluid overload also require rapid intervention. Because individuals with acute hyponatremia typically develop more prominent symptoms than those with chronic hyponatremia and are more tolerant of rapid correction of Na^+ deficits, vigorous treatment is a

reasonable goal in these patients. In contrast, patients with chronic hyponatremia are usually less symptomatic and are more susceptible to complications when the serum Na^+ level is corrected rapidly, making vigorous treatment both less necessary and less desirable.

Hypovolemic Hyponatremia. Patients with hypovolemic hyponatremia should have volume deficits corrected with an isotonic saline solution (NaCl, 0.9%). Isotonic saline is hypertonic compared with the hyponatremic patient's serum and will therefore cause a modest elevation of the serum $[Na^+]$.

Euvolemic Hyponatremia. Patients with hyponatremia and a normal total circulating volume can usually have free water intake restricted while the cause of the hyponatremia is determined and specific treatment for the underlying disorder is begun. Significantly, patients with SIADH who are given normal saline may actually experience a further decrease in the serum Na^+ as free water is retained and a hypertonic urine is excreted. Lithium and demeclocycline, which inhibits the action of ADH, can also be used in the treatment of SIADH.

Hypervolemic Hyponatremia. The cornerstone of therapy for patients with hypervolemic hyponatremia is fluid restriction, which is effective in most patients. The addition of diuretics may accelerate water excretion, although this approach should be used with caution because Na^+ excretion is also enhanced. Dialysis may be required to remove large amounts of water in patients with advanced renal failure.

Symptomatic Hyponatremia. Patients with severely symptomatic hyponatremia (e.g., seizures) may require administration of 3% saline (513 mEq of Na^+/L). In general, the serum Na^+ level should not be corrected to above 120 mEq/L or increased by more than 10 mEq/L in a 24-hour period. The rate of correction of hyponatremia should be dictated by the rapidity of its onset. Acute hyponatremia can be corrected at rates of up to 1 to 2 mEq/L/hr, and chronic hyponatremia should be corrected at a rate not greater than 0.5 mEq/L/hr. Hypertonic saline should be administered through a controlled intravenous (IV) infusion, paying careful attention to fluid input and output and frequently assessing serum electrolytes. The approximate required dose of hypertonic saline can be calculated with the following formula:

$$(\text{Desired } [Na^+] - \text{measured } [Na^+]) \times (0.6)\ (\text{weight in kg}) = \text{mEq } [Na^+] \text{ administered}$$

Overly aggressive correction of the serum Na^+ level can have serious consequences. Central pontine myelinolysis, also known as cerebral demyelination, involves the destruction of myelin in the pons and is thought to result from rapid elevation of the serum Na^+. Patients may develop cranial nerve palsies, quadriplegia, or coma. Central pontine myelinolysis is more likely to occur in patients with chronic hyponatremia than in those with acute hyponatremia. Most cases have been associated with rapid correction of serum Na^+ in alcoholic, malnourished, and elderly patients, although it has also been described in otherwise healthy patients.

Hypernatremia

Principles of Disease

Hypernatremia is defined as a serum $[Na^+]$ above 145 mEq/L. Patients at the extremes of age and those with chronic disorders are particularly vulnerable.[5] Hypernatremia is most often the result of a decrease in free water because of either reduced water intake or increased water loss. Less often, hypernatremia is caused by an increase in total Na^+ (Box 123-3). This classification scheme helps in identifying the underlying cause and guiding therapy.

BOX 123-3 CAUSES OF HYPERNATREMIA

- Reduced water intake
  - Disorders of thirst perception
  - Inability to obtain water
    - Depressed mentation
    - Intubated patient
- Increased water loss
  - Gastrointestinal
    - Vomiting, diarrhea
    - Nasogastric suctioning
    - Third spacing
  - Renal
    - Tubular concentrating defects
    - Osmotic diuresis (e.g., hyperglycemia, mannitol)
    - Diabetes insipidus
    - Relief of urinary obstruction
  - Dermal
    - Excessive sweating
    - Severe burns
  - Hyperventilation
- Gain of sodium
  - Exogenous sodium intake
    - Salt tablets
    - Sodium bicarbonate
    - Hypertonic saline solutions
    - Improper formula preparation
    - Salt water drowning
    - Hypertonic renal dialysate
  - Increased sodium reabsorption
    - Hyperaldosteronism
    - Cushing's disease
    - Exogenous corticosteroids
    - Congenital adrenal hyperplasia

Reduced water intake may be the result of limited access, inability to tolerate oral fluids, defective thirst mechanisms, or depressed mentation.

Increased water loss can occur through several different organ systems, including the gastrointestinal tract, skin, respiratory tract, or kidney. Gastrointestinal losses can occur from protracted diarrhea, vomiting, nasogastric tube suction, or third spacing. Renal causes of water loss include osmotic diuresis (e.g., hyperglycemia, mannitol administration) and renal tubular concentrating defects. Diabetes insipidus (DI) results in the loss of large amounts of dilute urine from the loss of concentrating ability in the distal nephron. DI may be central (lack of ADH secretion from the pituitary) or nephrogenic (lack of responsiveness to circulating ADH) (Box 123-4). Central DI is seen with CNS disease or surgery involving the hypothalamus and pituitary. Common mechanisms include stroke, infection, tumor, trauma, and systemic diseases. Nephrogenic DI can be caused by congenital disease, renal failure, sickle cell anemia, hypercalcemia, hypokalemia, and certain drugs, including lithium, cisplatin, amphotericin B, aminoglycosides, and demeclocycline. With a normal thirst mechanism and access to water, DI patients are generally able to maintain near-normal serum levels.[6,7] However, they quickly become hypernatremic when removed from a water source, and any sodium-containing IV fluids will exacerbate the problem.

Excessive Na^+ intake, accidentally, intentionally, or iatrogenically, can cause hypernatremia in the absence of corresponding intake of water. Because the kidney can usually

BOX 123-4 CAUSES OF DIABETES INSIPIDUS

Central
Idiopathic
Head trauma
Suprasellar/infrasellar tumors (e.g., craniopharyngioma)
Cerebral hemorrhage
CNS infections (e.g., meningitis, encephalitis)
Granulomatous disorders (e.g., tuberculosis, sarcoid, Wegener's, histiocytosis)

Nephrogenic
Congenital renal disorders
Obstructive uropathy
Renal dysplasia
Polycystic disease

Systemic Disease with Renal Involvement
Sickle cell disease
Sarcoidosis
Amyloidosis

Drugs
Amphotericin B
Phenytoin
Lithium
Aminoglycosides
Methoxyflurane

CNS, central nervous system.

excrete an increased Na^+ load effectively, most cases are seen in patients with renal insufficiency. Examples include hypertonic enteral or parenteral nutritional fluids, saline absorption, administration of large amounts of sodium bicarbonate, seawater drowning, and salt ingestion.[6] The administration of ticarcillin and carbenicillin, which contain large amounts of NaCl, is another potential cause.

Clinical Features

In cases of hypernatremia, free water is lost in excess of Na^+, so patients may be significantly dehydrated before signs of volume depletion are evident. Total free water deficits are often underestimated in this setting. Common symptoms include anorexia, nausea, vomiting, fatigue, and irritability.[3] Physical findings include lethargy, confusion, stupor, coma, muscle twitching, hyper-reflexia, spasticity, tremor, ataxia, or focal findings such as hemiparesis or extensor-plantar reflexes.

Management

Hypovolemic Hypernatremia. The primary goals in the emergency management of hypovolemic hypernatremia are to restore volume deficits and to maintain organ perfusion. Treatment should be initiated with an infusion of isotonic saline solution (0.9%). Once the patient is hemodynamically stable, the remaining free water deficits can be replaced.

Euvolemic Hypernatremia. Euvolemic hypernatremic patients may have had either hypotonic fluid losses (e.g., with DI) or hypertonic fluid losses from increased insensible fluid loss. Patients with DI generally have a low urine specific gravity (<1.005) and low urine osmolality. The DI is usually the result of a previously recognized disorder, and patients can usually maintain their serum osmolality if they have access to water. Treatment is with oral fluids or 0.45% saline. Patients with central DI require parenteral or intranasal vasopressin. The response to vasopressin can be monitored by checking urine osmolality, urine specific gravity, and serum electrolytes.[7]

Hypervolemic Hypernatremia. The treatment of hypervolemic hypernatremia should focus on increasing renal Na^+ excretion while maintaining free water intake. A strategy of diuretic administration (e.g., furosemide) followed by infusion of hypotonic fluids gradually restores the serum Na^+ to the normal range. Dialysis may be needed for patients with renal failure.

Symptomatic Hypernatremia. Patients with acute hypernatremia usually tolerate rapid correction of free water deficits. On the other hand, aggressive treatment of chronic hypernatremia with hypotonic fluids may result in life-threatening complications. It is recommended that in this setting free water deficits be corrected over at least a 48-hour period. When hypernatremia develops over days, brain cells produce osmotic substances (*idiogenic osmoles*) that hold water in the cell and help maintain cellular volume and tonicity.[6] Overzealous administration of hypotonic fluids may cause rapid shifts of water into brain cells, cellular swelling, and cerebral edema.

Assuming only loss of free water, the free water deficit can be calculated as follows:

$$\text{FW deficit} = 0.6 \times \text{weight (kg)} \times \left(\frac{\text{current } Na^+}{4} - 1 \right)$$

POTASSIUM

Normal Physiology

The relative concentrations of potassium [K^+] in the intracellular fluid and extracellular fluid are the major determinants of the normal osmotic and electrochemical gradients of all living cells. Precisely controlled transcellular movement of K^+ in excitable tissues is required for neuronal transmission, cardiac conduction, and excitation-contraction coupling. K^+ is also important for acid-base balance; the exchange of K^+ and hydrogen ions H^+ across the cell membrane serves as a first-line buffering system during acute acidosis and alkalosis. K^+ is also required for intracellular glucose metabolism, oxidative phosphorylation, and protein synthesis.[8]

The adult human body contains between 2500 and 3500 mmol of K^+, 98% of which is found in the intracellular compartment. For this reason, the serum K^+ level is not an accurate indicator of total K^+ stores. The normal range of the serum [K^+] is 3.5 to 5.0 mEq/L.[9]

Ingested potassium is absorbed in the small intestine through passive transport mechanisms. Renal excretion is the major route of K^+ elimination; less than 8% of losses occur in the feces and sweat. In the kidneys, 90% of the filtered load of K^+ is reabsorbed in the proximal tubule, and K^+ balance is determined by the handling of the cation in the distal nephron. The Na^+-K^+ ATPase pump transports K^+ from the serum into distal tubular cells against a concentration gradient. K^+ then moves passively into the tubular lumen in exchange for Na^+ and is excreted in the urine. When the serum K^+ level increases, pump activity increases and renal K^+ excretion increases. When the serum K^+ level falls, the pump is less active and excretion decreases. Aldosterone also controls K^+ homeostasis. Increased aldosterone release causes retention of Na^+ and excretion of K^+ at the distal tubule. Decreased aldosterone release or inhibition of aldosterone (by drugs such as angiotensin-converting enzyme inhibitors or spironolactone) promotes K^+ retention. Acidosis and alkalosis also affect renal K^+ handling. Acidosis promotes secretion of H^+ into the distal tubule, with retention of K^+, and alkalosis tends to favor renal K^+ excretion.[10]

The serum K^+ level depends on the distribution of K^+ between the serum and cells, as well as the balance between

K^+ intake and excretion. Acute decreases in the plasma pH cause K^+ to shift out of the cell in exchange for H^+. Conversely, alkalosis promotes movement of extracellular K^+ into the cell in exchange for intracellular H^+. In general, a change of 0.1 pH unit causes an inverse change of approximately 0.6 mEq in the serum K^+. Respiratory acid-base disturbances affect serum K^+ in the same manner as metabolic changes, but not as predictably. K^+ levels are also influenced by hormones and hormone receptor stimulation. Insulin increases cellular K^+ uptake by means of the Na^+-K^+ ATPase pump. Insulin release is stimulated by hyperkalemia, and hypokalemia inhibits insulin release. Alpha-adrenergic stimulation promotes hyperkalemia, and beta-stimulation causes uptake of K^+ into cells.[9]

Hypokalemia

Principles of Disease

Hypokalemia is relatively common, although life-threatening hypokalemia is much less common.[10] Hypokalemia may be the result of decreased K^+ intake, increased K^+ excretion, or transcellular K^+ shifts (Box 123-5).

Hypokalemia resulting from decreased dietary intake is rare. However, when poor intake is combined with other factors (e.g., vomiting or diarrhea, high insulin or aldosterone levels), severe hypokalemia can result. Patients suffering from prolonged starvation may become hypokalemic when they are fed because insulin secretion and increased cellular uptake cause K^+ to move into cells.

Pronounced renal or gastrointestinal K^+ losses can result in hypokalemia. Diuretic therapy, the most common cause of hypokalemia in clinical practice, increases Na^+ delivery to the distal tubule, promoting K^+ excretion. Associated volume depletion and high levels of aldosterone cause K^+ and H^+ excretion and may worsen hypokalemia. In addition, alkalosis from H^+ excretion promotes cellular K^+ uptake, further lowering the serum K^+ level.[10]

Other disorders can cause significant renal K^+ loss. These include osmotic diuresis, high mineralocorticoid states, Mg^{2+} depletion, and high urinary concentrations of anions such as penicillin. Intrinsic renal causes of K^+ loss include renal tubular acidosis (RTA), chronic interstitial disease, and drugs that affect tubular potassium reabsorption. RTA type 1 is caused by a defect in H^+ secretion in the distal tubule, and RTA type 2 is associated with a similar defect in the proximal tubule. In both cases, increased K^+ excretion at the distal tubule is the result. Other causes of increased renal K^+ loss include hypercalcemia, toxins (e.g., cisplatin, amphotericin B, aminoglycosides), leukemia, interstitial nephritis, and postobstructive diuresis.

Primary hyperaldosteronism (Conn's syndrome), which is typically caused by adrenal adenoma, is characterized by hypertension and hypokalemia.[11] Secondary hyperaldosteronism, due to increased renin release, causes hypokalemia in the face of volume depletion as K^+ is exchanged for Na^+ at the distal tubule. In Bartter's syndrome, a disorder causing hyperplasia of the juxtaglomerular apparatus and hyper-reninism, patients typically have weakness and hypokalemia.

Gastrointestinal losses of K^+ occur in patients with protracted vomiting and diarrhea. Vomiting itself does not cause K^+ loss; rather, hypokalemia results from hypovolemia, secondary hyperaldosteronism, and alkalosis. Diarrhea can cause

BOX 123-5 CAUSES OF HYPOKALEMIA

- Decreased intake
  - Decreased dietary potassium
  - Impaired absorption of potassium
  - Clay ingestion
  - Kayexalate
- Increased loss
  - Renal
    - Hyperaldosteronism
      - Primary
        - Conn's syndrome
        - Adrenal hyperplasia
      - Secondary
        - Congestive heart failure
        - Cirrhosis
        - Nephrotic syndrome
        - Dehydration
      - Bartter's syndrome
    - Glycyrrhizic acid (licorice, chewing tobacco)
    - Excessive adrenocorticosteroids
      - Cushing's syndrome
      - Steroid therapy
      - Adrenogenital syndrome
    - Renal tubular defects
      - Renal tubular acidosis
      - Obstructive uropathy
      - Salt-wasting nephropathy
    - Drugs
      - Diuretics
      - Aminoglycosides
      - Mannitol
      - Amphotericin B
      - Cisplatin
      - Carbenicillin
  - Gastrointestinal
    - Vomiting
    - Nasogastric suction
    - Diarrhea
    - Malabsorption
    - Ileostomy
    - Villous adenoma
    - Laxative abuse
  - Increased losses from skin
    - Excessive sweating
    - Burns
- Transcellular shifts
  - Alkalosis
    - Vomiting
    - Diuretics
    - Hyperventilation
    - Bicarbonate therapy
  - Insulin
    - Exogenous
    - Endogenous response to glucose
  - $Beta_2$-agonists (albuterol, terbutaline, epinephrine)
  - Hypokalemic periodic paralysis
    - Familial
    - Thyrotoxic
- Miscellaneous
  - Anabolic state
  - Intravenous hyperalimentation
  - Treatment of megaloblastic anemia
  - Acute mountain sickness

hypokalemia from losses in the stool and secondary hyperaldosteronism. Patients with villous adenomas classically have tremendous losses of K^+ from diarrheal fluid.

Loss of K^+ from the skin in sufficient quantities to cause hypokalemia is unusual unless the patient has experienced extreme sweating or is a victim of extensive burns or toxic epidermal necrolysis.[10]

Hypokalemia may result from transcellular K^+ shifts, most often because of alterations in acid-base balance. Acidosis causes K^+ to move out of the cell in exchange for H^+, and the reverse is true for alkalosis. Although acidosis is typically associated with hyperkalemia, acidosis may also be associated with hypokalemia in the presence of increased urinary K^+ losses (e.g., DKA). Beta-receptor stimulation is another common cause of hypokalemia resulting from transcellular shifts. In the emergency department, this is most likely to occur in the patient receiving large doses of beta-agonists for the treatment of asthma or chronic obstructive pulmonary disease.[12,13]

The periodic paralyses are associated with varying serum K^+ levels, including hypokalemia. They often are associated with thyroid disease and are distinguished by symmetrical proximal weakness.[14]

Clinical Features

Hypokalemia can affect the neuromuscular, cardiovascular, gastrointestinal, and renal systems, as well as acid-base balance. Signs and symptoms of neuromuscular dysfunction usually occur when the serum K^+ level is less than 2.5 mEq/L.[15] CNS signs include lethargy, depression, irritability, and confusion. Peripheral manifestations include paresthesias, depressed deep tendon reflexes, fasciculations, myalgias, and prominent muscle weakness. Muscular paralysis can occur with serum levels below 2.0 mEq/L.

Patients with severe hypokalemia may develop rhabdomyolysis because of impaired energy metabolism, membrane pump dysfunction, and local muscle ischemia.[16] K^+ is released from injured muscle, so the responsible hypokalemia may not be clinically evident, with serum levels normal or even elevated.

Cardiovascular manifestations of hypokalemia include palpitations, postural hypotension, ectopy, and dysrhythmias. First- and second-degree heart block, atrial fibrillation, paroxysmal ventricular contractions, ventricular fibrillation, and asystole have all been reported. The electrocardiogram (ECG) shows flattening of T waves, ST segment depression, and the appearance of U waves.[16]

Hypokalemia impairs intestinal smooth muscle activity and may cause nausea, vomiting, and abdominal distention. Severe hypokalemia may produce paralytic ileus.[10] The renal manifestations of hypokalemia include polyuria, polydipsia, and impaired ability to concentrate urine or excrete an acid load.

The effect of hypokalemia on acid-base balance is to promote metabolic alkalosis. In response to a low serum K^+ level, K^+ moves out of the cell in exchange for H^+, causing an extracellular alkalosis and an intracellular acidosis. In response to the drop in intracellular pH, renal tubular cells excrete H^+, leading to paradoxical aciduria and exacerbating the extracellular alkalosis.

Management

Because K^+ is an intracellular cation, a low serum K^+ level reflects a much greater total K^+ deficit. In the absence of acute shifts caused by acid-base disturbances, a decrease of the serum K^+ by 1.0 mEq/L may reflect a 370-mEq deficit of total K^+. Because up to 50% of administered K^+ is excreted in the urine, correction of large deficits may require several days.

Whenever possible, oral therapy is preferable to IV therapy because the risk of hyperkalemia is significantly less. However, patients with prominent symptoms (e.g., dysrhythmias) and those who are unable to tolerate oral supplements should receive IV K^+ replacement. IV K^+ is usually given at a rate of 10 to 20 mEq/hr, but larger doses can be given to patients with severe depletion or severely symptomatic hypokalemia (e.g., respiratory muscle weakness). Doses greater than 20 mEq/hr should be given in a monitored setting through a large-bore peripheral venous catheter or a central venous access site.[17]

Burning at the infusion site is the most common side effect of IV K^+ administration. Slowing the rate of infusion usually decreases venous irritation. The most important potential risk of IV K^+ administration is acute hyperkalemia, which is most likely in patients with renal insufficiency. If dysrhythmias (e.g., frequent premature ventricular contractions, heart block, tachycardia, widening of the QRS complex) develop, the K^+ infusion should be discontinued immediately.

Oral potassium is preferred for mild hypokalemia. Several oral preparations are available in liquid or tablet form. Although liquid preparations are typically better absorbed, matrix tablets are often better tolerated. Hypokalemia can be effectively corrected with oral supplements, and large amounts of oral potassium can be given to increase serum levels rapidly.

Potassium can be given as the chloride salt in most patients. Potassium phosphate, rather than potassium chloride, can be given if there is associated hypophosphatemia (e.g., in DKA). Patients with distal RTA should be treated with potassium bicarbonate, potassium citrate, or potassium gluconate, which provide both K^+ and base equivalents. The hypokalemia of proximal RTA may be better treated with potassium chloride because the administered base cannot be reabsorbed well proximally and can obligate K^+ loss when it reaches the distal tubule.

Hyperkalemia

Principles of Disease

Hyperkalemia may be the result of increased K^+ intake, enhanced K^+ absorption, impaired K^+ excretion, or shifts of K^+ out of cells into the serum (Box 123-6).

When faced with a report of a high serum K^+ level, the emergency physician should first consider the possibility of laboratory error. Hemolysis during phlebotomy, as can occur when blood is obtained with a small needle or sampled in a high-vacuum tube, releases K^+ into the sample and causes a spuriously high K^+ measurement. Laboratory technicians usually note the presence of pink serum, indicating hemolysis. Pseudohyperkalemia can also occur when K^+ is released from platelets in patients with severe thrombocytosis or from leukocytes in patients with extreme leukocytosis.[18]

Hyperkalemia rarely results from increased K^+ intake. This is more common when K^+ supplements are inadvertently taken by patients with renal insufficiency or in those taking a K^+-sparing diuretic or an angiotensin-converting enzyme inhibitor.[18] Parenteral medications such as penicillin and carbenicillin, as well as transfused blood, also contain significant amounts of K^+ and can precipitate hyperkalemia.

Renal insufficiency (i.e., decreased GFR), defects in tubular K^+ secretion, or hypoaldosteronism can cause hyperkalemia. As GFR decreases to approximately 5 to 15 mL/min, excretion of the normal daily K^+ load is impaired. Defects in tubular K^+ excretion are associated with a number of conditions. Hypoaldosteronism may be the result of causes as varied as RTA type

BOX 123-6 CAUSES OF HYPERKALEMIA

- Pseudohyperkalemia
  - Hemolysis of sample
  - Thrombocytosis
  - Leukocytosis
  - Laboratory error
- Increased potassium intake and absorption
  - Potassium supplements (oral and parenteral)
  - Dietary (salt substitutes)
  - Stored blood
  - Potassium-containing medications
- Impaired renal excretion
  - Acute renal failure
  - Chronic renal failure
  - Tubular defect in potassium secretion
    - Renal allograft
    - Analgesic nephropathy
    - Sickle cell disease
    - Obstructive uropathy
    - Interstitial nephritis
    - Chronic pyelonephritis
    - Potassium-sparing diuretics
    - Miscellaneous (lead, systemic lupus erythematosus, pseudohypoaldosteronism)
  - Hypoaldosteronism
    - Primary (Addison's disease)
    - Secondary
      - Hyporeninemic hypoaldosteronism (renal tubular acidosis type 4)
      - Congenital adrenal hyperplasia
      - Drug-induced
        - Nonsteroidal anti-inflammatory drugs
        - Angiotensin-converting enzyme
        - Heparin
        - Cyclosporine
- Transcellular shifts
  - Acidosis
  - Hypertonicity
  - Insulin deficiency
  - Drugs
    - Beta-blockers
    - Digitalis toxicity
    - Succinylcholine
  - Exercise
  - Hyperkalemic periodic paralysis
- Cellular injury
  - Rhabdomyolysis
  - Severe intravascular hemolysis
  - Acute tumor lysis syndrome
  - Burns and crush injuries

4, Addison's disease, nonsteroidal anti-inflammatory drugs, and angiotensin-converting enzyme inhibitors.

Transcellular K^+ shifts (e.g., acute acidosis, beta-receptor antagonism) are another major cause of hyperkalemia. Periodic paralysis is an inherited disorder characterized by hyperkalemia caused by cellular efflux of K^+ associated with stressors such as exercise, infection, and diet. Drugs may also be the cause of transcellular K^+ shifts. Digitalis poisons the Na^+-K^+ ATPase pump, with resultant hyperkalemia in severe cases. Succinylcholine causes transient K^+ efflux because of depolarization of the muscle cell membrane. High-dose trimethoprim-sulfamethoxazole has also been implicated in hyperkalemia, especially with concomitant renal insufficiency.[19,20]

Life-threatening hyperkalemia may result when large amounts of K^+ are released from damaged cells. Rhabdomyolysis, tumor cell necrosis, and hemolysis are important causes.[15] Acute renal failure that may be associated with these conditions impairs K^+ excretion, further exacerbating endogenous hyperkalemia.

Clinical Features

Cardiovascular and neurologic dysfunction is the primary manifestation of hyperkalemia.[18] Patients may have a variety of dysrhythmias, including second- and third-degree heart block, wide-complex tachycardia, ventricular fibrillation, and even asystole. The ECG can provide valuable clues to the presence of hyperkalemia. As K^+ levels rise, peaked T waves are the first characteristic manifestation. Further rises are associated with progressive ECG changes, including loss of P waves and widening and slurring of the QRS complex. Eventually, the tracing assumes a sine wave appearance, followed by ventricular fibrillation or asystole. Concomitant alkalosis, hypernatremia, or hypercalcemia antagonizes the membrane effects of hyperkalemia and may delay or diminish the characteristic ECG findings.

Neuromuscular signs and symptoms of hyperkalemia include muscle cramps, weakness, paralysis, paresthesias, tetany, and focal neurologic deficits, but these are rarely specific enough to suggest the diagnosis in themselves.[15,16]

Management

The treatment of hyperkalemia includes cardiovascular monitoring, administration of calcium chloride or gluconate to treat hemodynamic instability, initiation of measures to lower serum [K^+], and correction of the underlying cause.

All patients with suggested hyperkalemia should be on a cardiac monitor, and attention should be paid to the morphology of the T waves and QRS complex. Peaked T waves, loss of P waves, slurring of the QRS, and second- or third-degree heart block all suggest hyperkalemia and are indications for prompt therapy. Treatment of the hyperkalemia is directed toward antagonism of the membrane effects of hyperkalemia, promotion of transcellular K^+ shifts, and removal of K^+ from the body.

Calcium Chloride or Gluconate. Immediate antagonism of K^+ at the cardiac membrane is achieved with IV administration of calcium chloride or gluconate. This is indicated in patients with unstable dysrhythmia or hypotension. Several ampules of calcium (10 mL of 10% solution) may be required.[16,18] Because of the brief duration of action (approximately 20–40 minutes), other measures should also be instituted promptly.[18]

Sodium Bicarbonate. Sodium bicarbonate infusion promotes a shift of K^+ into cells. One ampule (44 mEq) should be given by slow IV push over 5 to 15 minutes. The duration of action is approximately 2 hours. Sodium bicarbonate should be used with caution when hypertonicity, volume overload, or alkalosis poses a risk to the patient. Bicarbonate therapy is less efficacious than insulin or albuterol.[21,22]

Glucose and Insulin. Cellular uptake of K^+ can also be induced with a regimen of IV glucose and insulin. Regular insulin (10–20 U) can be given by bolus infusion. Dextrose should be administered to euglycemic and diabetic patients with a blood glucose level below 250 mg/dL to prevent hypoglycemia. This combination lasts 4 to 6 hours.[18] Rapid infusion of hypertonic glucose solution may transiently exacerbate hyperkalemia by its osmotic effect on cells.

Beta$_2$-agonists. The known effect of beta$_2$-agonists to cause movement of K^+ into cells can be harnessed to lower the

serum K^+ level acutely. Treatment with nebulized albuterol (5–20 mg) lowers the serum K^+ level for at least 2 hours.[22,23]

Exchange Resins. Definitive treatment for hyperkalemia remains the removal of K^+ from the body. Exchange resins (e.g., sodium polystyrene sulfonate [Kayexalate]) and hemodialysis are two such options. Given orally or rectally, each gram of Kayexalate can remove approximately 1.0 mEq of K^+. An oral dose of 20 g of Kayexalate in a sorbitol produces effects in 1 to 2 hours. Rectal enemas of 50 g of Kayexalate, retained for 30 minutes, work in approximately 30 minutes. Kayexalate should be used with caution in patients with poor cardiovascular reserve because of the potential to exacerbate volume overload.

Dialysis. Hemodialysis corrects hyperkalemia rapidly, and consultation with a nephrologist is indicated in the unstable hyperkalemic patient with newly diagnosed or chronic renal failure. Hyperkalemia resulting from severe rhabdomyolysis is difficult to treat with the usual measures and also mandates consultation for emergency dialysis. Dialysis removes K^+ from the blood only, and subsequent shifts of intracellular K^+ may cause rebound hyperkalemia. Dialysis can be effective in treating hyperkalemia-induced cardiac arrest.[24]

Underlying Cause. Treatment of any underlying causative disorder should be initiated at the same time as therapy for hyperkalemia. This may include the treatment of rhabdomyolysis with fluids and bicarbonate; treatment of Addison's disease with corticosteroids, IV fluids, and glucose; treatment of digitalis toxicity with digoxin-binding antibodies; or discontinuation of drugs that may have precipitated the hyperkalemia.

Patients with hyperkalemia should be admitted to a monitored bed with care provided by a clinician skilled in the treatment of electrolyte disorders.

CALCIUM

Normal Physiology

Hundreds of enzymatic reactions are mediated by changes in intracellular calcium. Cellular growth and reproduction, membrane integrity, receptor activation, neurotransmission, glandular secretion, enzyme activation, muscle contraction, cardiac contractility, platelet aggregation, and immune function all depend on the precise regulation of free calcium. Evidence also indicates that cellular injury and ultimately cell death are mediated by changes in free intracellular calcium.[25]

The adult human body contains approximately 1200 g of calcium, with more than 99% in the mineral component of bone. The remaining 1% is distributed in three different plasma fractions: (1) approximately 50% is bound to serum proteins, primarily albumin; (2) 10% is complexed with serum anions (phosphate, bicarbonate, citrate, lactate); and (3) 40% is in the free ionized state (Ca^{2+}). Ca^{2+} is the physiologically active form, and concentrations are tightly regulated by the endocrine system.

Dietary calcium is absorbed in the proximal intestine through both active and passive processes. Absorption is enhanced by the action of vitamin D. In the kidneys, 99% of the filtered load of calcium is reabsorbed. Approximately 90% of calcium reabsorption occurs passively in the proximal tubule and loop of Henle. The remaining 10% occurs in the distal tubule under the control of *parathyroid hormone* (PTH, parathormone). A fall in free serum calcium stimulates the release of PTH, which in turn increases reabsorption. PTH also mediates the hydroxylation of vitamin D to its active form, 1,25-dihydroxycholecalciferol (1,25-DHCC).

The skeleton acts as a calcium pool that buffers acute changes in serum concentration. When the serum calcium level falls, PTH stimulates an increase in bone turnover and the release of calcium into the serum. A rise in serum calcium suppresses PTH production and causes the release of calcitonin. *Calcitonin* decreases osteoclastic activity and enhances skeletal deposition of calcium.

The serum calcium level reflects the net outcome of several processes. On one hand, intestinal absorption and bone resorption add calcium to the blood; on the other, calcium is lost from the blood by renal excretion, skeletal uptake, or abnormal deposition in soft tissues. A decrease in the serum Ca^{2+} activates the PTH–vitamin D system to increase the entry of calcium into the blood from the bone and gastrointestinal tract. A rise in the serum calcium level suppresses the PTH–vitamin D system and increases the release of calcitonin, which decreases calcium entry into the blood.

Many hospital laboratories measure total serum calcium concentrations, which is a combination of both Ca^{2+} and calcium that is bound to proteins. Normal value of total serum calcium ranges from 8.5 to 10.5 mg/dL. However, the total serum calcium is often a poor indicator of the Ca^{2+} status, since abnormalities of serum protein concentrations (primarily albumin) affect the total calcium. A decrease in albumin concentration lowers the measured serum calcium, and an increase raises it, even as the Ca^{2+} level remains unchanged. A corrected serum calcium level that accounts for changes in serum albumin concentrations can be calculated as follows:

$$\begin{aligned}\text{Corrected calcium} &= \text{serum calcium (mg/dL)} \\ &\cong +0.8[4 - \text{serum albumin (g/dL)}]\end{aligned}$$

This formula is only an estimate, and the Ca^{2+} should be measured whenever hypocalcemia is suggested. Blood gas analyzers can measure Ca^{2+} from a sample of blood or serum. The normal range is 1.00 to 1.15 mmol/L.

Changes in acid-base status influence the ratio of bound to ionized calcium without altering the total measured calcium. Acidosis decreases calcium binding to albumin, and alkalosis increases binding. Thus, acute changes in blood pH may have important physiologic effects by changing the Ca^{2+} level even when the total serum calcium level remains unchanged.[25]

Hypocalcemia

Principles of Disease

The causes of ionized hypocalcemia are numerous (Box 123-7) and can be divided into disorders causing PTH insufficiency, vitamin D insufficiency, PTH resistance states, and calcium chelation.

Parathyroid Hormone Insufficiency. PTH insufficiency can be caused by either primary or secondary hypoparathyroidism. Primary hypoparathyroidism is rare and is usually congenital. Maternal hyperparathyroidism may result in fetal parathyroid hypoplasia and transient hypoparathyroidism.

Secondary hypoparathyroidism is more common and is most often iatrogenic, resulting from inadvertent removal of the parathyroid glands or disruption of the vascular supply during parathyroid, thyroid, or carotid surgery. Permanent hypocalcemia is the usual consequence. Excision of a functional parathyroid adenoma, leaving only the chronically suppressed but otherwise unaffected parathyroid tissue, causes hypocalcemia that usually resolves over several days. Metastatic carcinoma or infiltrative disorders (e.g., hemochromatosis, sarcoidosis, Wilson's disease) may destroy parathyroid tissue and cause hypocalcemia. Both severe hypomagnesemia and severe hypermagnesemia can impair PTH release. Drugs that may suppress parathyroid function include chemotherapeutic agents, cimetidine, and ethanol.

BOX 123-7 CAUSES OF HYPOCALCEMIA

- Parathyroid hormone insufficiency
  - Primary hypoparathyroidism
    - Congenital syndromes
    - Maternal hyperparathyroidism
  - Secondary hypoparathyroidism
    - Neck surgery
    - Metastatic carcinoma
    - Infiltrative disorders
    - Hypomagnesemia, hypermagnesemia
    - Sepsis
    - Pancreatitis
    - Burns
    - Drugs (chemotherapeutics, ethanol, cimetidine)
- Vitamin D insufficiency
  - Congenital rickets
  - Malnutrition
  - Malabsorption
  - Liver disease
  - Renal disease
    - Acute and chronic renal failure
    - Nephrotic syndrome
  - Hypomagnesemia
  - Sepsis
  - Anticonvulsants (phenytoin, primidone)
- Parathyroid hormone resistance states (pseudohypoparathyroidism)
- Calcium chelation
  - Hyperphosphatemia
  - Citrate
  - Free fatty acids
  - Alkalosis
  - Fluoride poisoning

Vitamin D. Vitamin D deficiency can result in hypocalcemia because of decreased gastrointestinal calcium absorption. Nutritional vitamin D deficiency is rare in the United States because of the fortification of milk but can occur when exposure to sunlight is limited, especially in elderly, chronically ill, and debilitated patients. Children of mothers with vitamin D deficiency may be born with congenital rickets. Characteristic findings include hypocalcemia, hypophosphatemia, and specific radiographic findings (widening of the distal radius and ulna, craniotabes). Vitamin D insufficiency resulting from intestinal malabsorption can occur in patients with small-bowel or biliary disease or pancreatic exocrine failure. Cholestyramine can also prevent adequate vitamin D absorption. Once absorbed, vitamin D is hydroxylated in the liver and kidney to its active form, 1,25-DHCC. Hepatic disease and renal disease may lead to inadequate activation of the vitamin. Hypercatabolism of vitamin D may occur in association with agents that stimulate the hepatic microsomal oxidase system, such as the anticonvulsants phenytoin and primidone.

Parathyroid Hormone Resistance States. PTH resistance states are termed *pseudohypoparathyroidism*. These rare familial syndromes are characterized by renal unresponsiveness to PTH and resultant parathyroid hyperplasia.[26] Differentiation from hypoparathyroidism is based on elevated PTH levels and a lack of increase in urinary cyclic adenosine monophosphate after PTH administration.

Hypocalcemia is common in patients with chronic renal failure. This results from vitamin D deficiency, impaired responsiveness to PTH, and phosphate retention. Generally, these patients are asymptomatic, possibly because of a protective effect of systemic acidosis. However, rapid correction of metabolic acidosis with exogenous sodium bicarbonate can precipitate severe hypocalcemia, often causing tetany and seizures.

Calcium Chelation. Calcium complexes with several different substances in serum, including proteins, fatty acids, and anions. Increases in the concentration of these substances may thus result in ionized hypocalcemia. Citrate is used as a blood preservative and anticoagulant. The citrate load associated with massive blood transfusion (>6 U) causes hypocalcemia in up to 94% of patients.[27] Hypocalcemia is usually short-lived, and Ca^{2+} levels return to normal shortly after transfusion. Because citrate is metabolized by temperature-dependent enzymes in tissues and excreted by the liver, hypothermia and hepatic failure are important risk factors for protracted hypocalcemia after blood transfusion. Citrate is also a constituent of radiocontrast material, and hypocalcemia has been associated with the administration of these agents.

Exogenous administration of phosphate and endogenous hyperphosphatemia (e.g., with acute renal failure, rhabdomyolysis, or tumor lysis syndrome) are well-known causes of hypocalcemia.[28] Exogenous bicarbonate also complexes with calcium and may cause symptomatic hypocalcemia. Alkalosis, either metabolic or respiratory, enhances the binding of calcium to serum proteins, resulting in ionized hypocalcemia. Free fatty acids liberated in various conditions (e.g., acute pancreatitis, hyperadrenergic states, acute ethanol ingestion) can chelate free Ca^{2+} to form calcium soaps. Fluoride poisoning can also cause hypocalcemia. This may occur after exposure to hydrofluoric acid or ammonium bifluoride, components of many household cleaners and rust removers. These compounds release free fluoride ion, a direct cellular toxin that binds Ca^{2+}, forming calcium fluoride. Numerous cases of severe hypocalcemia, cardiac dysrhythmias, and death have been reported after ingestion, inhalation, or cutaneous exposure to these products.

Clinical Features

The clinical manifestations of hypocalcemia depend not only on the serum level but also on the rapidity with which it declines. Although the signs and symptoms of hypocalcemia are numerous (Box 123-8), the effects on neuromuscular function predominate.

A declining serum calcium level is associated with progressive neuromuscular hyperexcitability. CNS manifestations include depression, irritability, confusion, and focal or generalized seizures. Peripheral nervous system manifestations include perioral paresthesias, muscle weakness and cramps, fasciculations, and tetany.[25] Latent tetany can often be demonstrated by eliciting Chvostek's or Trousseau's sign. *Chvostek's sign* is elicited by tapping over the facial nerve and causing twitching of the ipsilateral facial muscles. *Trousseau's sign* describes carpal spasm in response to inflation of an arm blood pressure cuff to 20 mm Hg above systolic blood pressure for 3 minutes.

Severe hypocalcemia causes a decrease in myocardial contractility and, rarely, bradycardia, hypotension, and symptomatic congestive heart failure. Patients with preexisting cardiac dysfunction and those taking digoxin or diuretics are especially at risk. The ECG may demonstrate QT prolongation, and an inverse relationship exists between the serum calcium level and the QT interval. However, the ECG is a poor predictor of hypocalcemia and should not be used to rule in or rule out this disorder.

Bronchospasm and laryngeal spasm occur rarely. Symptoms and signs ranging from anxiety and depression to psychosis and dementia can be seen.

BOX 123-8 CLINICAL FEATURES OF HYPOCALCEMIA

Neuromuscular
Paresthesias
Muscle weakness
Muscle spasm
Tetany
Chvostek's and Trousseau's signs
Hyper-reflexia
Seizures

Cardiovascular
Bradycardia
Hypotension
Cardiac arrest
Digitalis insensitivity
QT prolongation

Pulmonary
Bronchospasm
Laryngeal spasm

Psychiatric
Anxiety
Depression
Irritability
Confusion
Psychosis
Dementia

Management

In patients with suggested hypocalcemia or a documented low total serum calcium level, the first step in management should be verification of true ionized hypocalcemia. When hypocalcemia is the presumed cause of tetany, seizures, hypotension, or dysrhythmias, it may be appropriate to initiate treatment before the Ca^{2+} level is available. All patients with symptomatic hypocalcemia should be treated with parenteral calcium. Two different formulations are readily available in most emergency departments: (1) 10-mL ampules of 10% calcium chloride, which contain 360 mg of elemental calcium, and (2) 10-mL ampules of 10% calcium gluconate, which contain 93 mg of elemental calcium. For the adult patient, the recommended initial dose is 100 to 300 mg of elemental calcium given as calcium chloride or calcium gluconate. This dose of calcium increases the serum Ca^{2+} level for only a short time (1–2 hours) and should be followed by repeated doses or an infusion at a rate of 0.5 to 2 mg/kg/hr.[25] For neonates, infants, and children, the recommended initial dose is 0.5 to 1.0 mL/kg of 10% calcium gluconate over 5 minutes.[26]

The most common side effects of IV calcium administration are hypertension, nausea, vomiting, and flushing. Bradycardia and heart block occur in rare cases. Patients receiving IV calcium should be placed on a cardiac monitor, and administration should be discontinued if bradycardia ensues. Calcium should be administered with extra caution in patients taking digoxin because it may precipitate (or exacerbate) digoxin-induced cardiotoxicity. Because calcium can cause severe tissue irritation and necrosis if it extravasates, it should always be given through a well-functioning catheter. Whenever possible, calcium chloride should be diluted in 5% dextrose in water (D_5W).[25,26]

Symptoms refractory to appropriate doses of calcium may be caused by coexisting hypomagnesemia. In patients with normal renal function, administration of 2 to 4 g of 10% magnesium sulfate should be considered.

Patients with asymptomatic hypocalcemia can be treated with oral calcium supplements. Available preparations include calcium ascorbate, calcium gluconate, and calcium lactate. Most patients require 1 to 4 g of elemental calcium daily in divided doses.

Hypercalcemia

Principles of Disease

Hypercalcemia is a relatively common medical disorder. Routine laboratory screening can be expected to detect hypercalcemia in 0.1 to 1.0% of patients, depending on the population being screened.[29-31] Hypercalcemia is usually mild (<12 mg/dL) and asymptomatic and rarely requires emergency treatment. Nevertheless, hypercalcemia may be an important clue to a serious underlying medical disorder. *Hypercalcemic crisis* occurs in a subset of patients who have severe hypercalcemia (usually >14 mg/dL) and is generally associated with prominent signs and symptoms. In this situation, immediate measures to lower the serum calcium level are indicated.

Although hypercalcemia has many causes, more than 90% of cases result from primary hyperparathyroidism or malignancy (Box 123-9).[32]

Primary hyperparathyroidism is the most common cause of hypercalcemia in outpatients, accounting for 25 to 50% of cases.[33] This can result from parathyroid adenoma (80%), parathyroid hyperplasia (15%), or parathyroid carcinoma (5%).[34] Hyperparathyroidism can also occur in association with other endocrine tumors as part of one of the familial syndromes of

BOX 123-9 CAUSES OF HYPERCALCEMIA

Primary hyperparathyroidism
Malignant disease
  Parathyroid hormone–related protein
  Ectopic production of 1,25-dihydroxyvitamin D
  Other bone-resorbing substances
  Osteolytic bone metastasis
Medications
  Thiazide diuretics
  Lithium
  Estrogens
  Vitamin D toxicity
  Vitamin A toxicity
  Calcium ingestion
Granulomatous disorders
  Sarcoidosis
  Tuberculosis
  Coccidioidomycosis
  Berylliosis
  Histoplasmosis
  Leprosy
Nonparathyroid endocrine disorders
  Hyperthyroidism
  Adrenal insufficiency
  Pheochromocytoma
  Acromegaly
  Vasoactive intestinal polypeptide–producing tumor
Miscellaneous
  Milk-alkali syndrome
  Immobilization
  Idiopathic hypocalcemia of infancy
  Physiologic (in the newborn)

multiple endocrine adenomatosis. In primary hyperparathyroidism, the PTH level is elevated in more than 90% of cases; the remainder of patients have high-normal PTH levels that are inappropriate for the degree of hypercalcemia. An elevated PTH level leads to increased bone resorption, a relative decrease in renal calcium excretion, and increased intestinal calcium absorption. Patients typically develop hypercalcemia, phosphaturia, hypophosphatemia, and a hyperchloremic metabolic acidosis.

Malignancy is the most common cause of hypercalcemia in hospitalized patients, and hypercalcemia is the most common paraneoplastic complication of cancer. The reported prevalence of hypercalcemia in patients with cancer ranges from 15 to 60%.[35,36] A multitude of solid tumors can cause hypercalcemia, including cancers of breast, lung, colon, stomach, cervix, uterus, ovary, kidney, bladder, and head and neck. Hypercalcemia is also seen with hematologic malignancies such as multiple myeloma and lymphoma. Hypercalcemia in patients with cancer can result from several different mechanisms, including production of PTH-related protein by the tumor.[37,38] This polypeptide is homologous to PTH in its first 13 N-terminal amino acids and binds to the PTH receptor, mimicking all the actions of the hormone. PTH-related protein is secreted by solid malignancies and their metastases and is not subject to normal feedback control mechanisms.[39] Assays for PTH-related protein are available to confirm this cause of cancer-related hypercalcemia.[40] Less often, hypercalcemia results from the production of other bone-resorbing substances by the tumor (e.g., transforming growth factor-α) or the local effects of osteolytic skeletal metastasis. Virtually all patients with cancer-associated hypercalcemia have low concentrations of PTH, readily distinguishing this cause of hypercalcemia from primary hyperparathyroidism.

Thiazide diuretics are associated with up to 20% of cases of hypercalcemia. These agents can increase the reabsorption of calcium in the distal convoluted tubule by as much as 70%. Hypercalcemia is typically mild, although it may be exaggerated in patients with dehydration.

Granulomatous disorders (e.g., sarcoidosis, tuberculosis, coccidioidomycosis, histoplasmosis, leprosy) can cause hypercalcemia. In these conditions, activated macrophages convert 1,25-hydroxyvitamin D to its active form (1,25-DHCC), resulting in enhanced intestinal calcium absorption, hypercalcemia, and hypercalciuria.[41] Certain lymphomas cause severe hypercalcemia by a similar mechanism. Interestingly, hypercalcemia in patients with sarcoidosis occurs as a seasonal event in patients who live in the Northern Hemisphere, presumably because of increased production of vitamin D in the skin during longer exposure to the summer sun.[42]

Acute vitamin A intoxication is an uncommon but well-recognized cause of hypercalcemia, resulting from an increase in osteoclastic activity. This usually occurs after an accidental massive ingestion of a preparation containing vitamin A. Chronic hypervitaminosis A can occur in patients using large doses of the vitamin for a variety of dermatologic conditions (e.g., acne vulgaris). Because vitamin A is highly lipophilic, toxicity may take several weeks to resolve after discontinuation of the vitamin. Increased exogenous vitamin D intake may also result in hypercalcemia.

Milk-alkali syndrome is caused by excessive ingestion of calcium and absorbable antacids such as milk or calcium carbonate and is characterized by hypercalcemia, alkalosis, and renal failure. The disorder is less common since nonabsorbable antacids and H_2-receptor antagonists became available for the treatment of peptic ulcer disease.

Lithium therapy for bipolar (manic-depressive) disorders can put patients at increased risk for developing hypercalcemia. Clinical and in vitro studies suggest that lithium alters the release of PTH by shifting the set point for inhibition of hormone secretion by circulating calcium.

Thyroid hormone causes hypercalcemia by increasing bone turnover through direct stimulation of osteoclastic bone resorption. In most cases, the symptoms of hyperthyroidism predominate, and hypercalcemia does not become apparent until hyperthyroidism is managed. Hypercalcemia can also be seen in patients after renal transplantation or in the early phase of acute tubular necrosis.

Clinical Features

The clinical manifestations of hypercalcemia are nonspecific and vary widely from patient to patient (Box 123-10). Severity of symptoms depends on both the level of serum calcium and the rapidity of its rise.

Hypercalcemia decreases neuronal conduction and in general causes CNS depression. Symptoms range from fatigue, weakness, and difficulty concentrating to confusion, lethargy, stupor, and even coma.

Hypercalcemia has several effects on the cardiovascular system. The volume depletion with which hypercalcemia is typically associated can result in hypotension. Because hypercalcemia causes an increase in vascular tone, however, the blood pressure may be misleadingly normal. Characteristic ECG changes include shortening of the QT interval and, to a lesser degree, prolongation of the PR interval and QRS widening. Rarely, severe hypercalcemia causes sinus bradycardia, bundle branch block, high-degree atrioventricular block, and even cardiac arrest. Calcium potentiates the action of digoxin, and the side effects of digoxin are accentuated when hypercalcemia is present.[34]

BOX 123-10 Clinical Features of Hypercalcemia

Neurologic
Fatigue, weakness
Confusion, lethargy
Ataxia
Coma
Hypotonia, diminished deep tendon reflexes

Cardiovascular
Hypertension
Sinus bradycardia, atrioventricular block
ECG abnormalities (short QT, bundle branch block)
Ventricular dysrhythmias
Potentiation of digoxin toxicity

Renal
Polyuria, polydipsia
Dehydration
Loss of electrolyte
Prerenal azotemia
Nephrolithiasis
Nephrocalcinosis

Gastrointestinal
Nausea, vomiting
Anorexia
Peptic ulcer disease
Pancreatitis
Constipation, ileus

ECG, electrocardiographic.

An acute rise in the serum calcium level impairs the reabsorption of fluid and electrolytes in the renal tubule, promoting the development of dehydration, which is worsened by vomiting and poor fluid intake. This may lead to a vicious cycle of volume depletion, reduced GFR and calcium excretion, intensified hypercalcemia, and further dehydration, culminating in oliguric renal failure, coma, and death. Chronically, hypercalcemia and associated volume depletion predispose the patient to renal calculi, nephrocalcinosis, and calcium-induced interstitial nephritis.

Anorexia, nausea, vomiting, and abdominal pain are common but nonspecific symptoms of hypercalcemia. Hypercalcemia decreases smooth muscle tone and may lead to constipation or intestinal ileus. An increased serum calcium level enhances the release of hydrochloric acid, gastrin, and pancreatic enzymes. Chronic hypercalcemia has been associated with an increased risk of peptic ulcer disease and pancreatitis.

Management

Treatment should be initiated at once in patients with evidence of significant dehydration, alteration of consciousness, or symptomatic dysrhythmias. Patients with severe hypercalcemia (>14 mg/dL) require rapid treatment regardless of symptoms. The four basic goals of therapy are (1) restoration of intravascular volume, (2) enhancement of renal calcium elimination, (3) reduction of osteoclastic activity, and (4) treatment of the primary disorder (Box 123-11). Although it may not be realistic to expect to achieve these goals in the emergency department, it is important for the emergency physician to initiate therapy and involve the appropriate consultants as early as possible.

Fluid Administration. The administration of isotonic saline is the first step in the management of severe hypercalcemia. Once the intravascular volume has been restored to normal, the serum calcium level will usually have decreased by 1.6 to 2.4 mg/dL, although hydration alone rarely leads to complete normalization. The expansion of intravascular volume increases renal calcium clearance by increasing GFR and Na^+ delivery to the distal tubules. The rate of fluid administration should be based on the severity of hypercalcemia, the degree of dehydration, and the patient's cardiovascular tolerance of acute volume expansion. In elderly patients and those with poor left ventricular function, central venous pressure monitoring can be used to adjust fluid administration rates. Two to 5 L per day is often required. Coexisting electrolyte deficiencies should also be corrected.

Furosemide. Loop diuretics such as furosemide inhibit the resorption of calcium in the thick ascending loop of Henle, increasing the calciuric effect of hydration. Volume expansion must precede the administration of furosemide, however, because the drug's effect depends on the delivery of calcium to the distal nephron. IV doses of 10 to 40 mg every 6 to 8 hours are usually sufficient. Thiazide diuretics should not be used because they enhance distal absorption of calcium and may worsen hypercalcemia.

Osteoclast Inhibitors. Therapy for severe hypercalcemia should also include agents that reduce the mobilization of calcium from bone. Drugs that inhibit osteoclast-mediated bone resorption include the bisphosphonates, calcitonin, glucocorticoids, and gallium nitrate. Because these drugs are used very infrequently in the emergency department, consultation with a specialist and/or pharmacist to select the best agent and dosing strategy is advised.

The bisphosphonates act by inhibiting osteoclastic bone resorption and decreasing the viability of osteoclasts.[43] Etidronate, palmidronate, and zoledronic acid have similar efficacy and a reasonable adverse effect profile.[44-47]

Calcitonin is a naturally occurring hormone that lowers serum calcium by inhibiting osteoclastic activity. Among the anticalcemic agents available, calcitonin has the most rapid onset of action, although it causes only a modest reduction in the serum calcium level.[48] When hypercalcemia is severe and the need to lower the serum calcium is urgent, it is reasonable to administer a dose of calcitonin in combination with a more potent agent such as a bisphosphonate.

The glucocorticoids act by inhibiting the action of vitamin D. They may be effective calcium-lowering agents in patients with hypercalcemia caused by hematologic malignancies, granulomatous disorders, or vitamin D intoxication.

Underlying Cause. Pharmacologic therapy does not permanently normalize the serum calcium concentration. The underlying cause of the hypercalcemia needs to be treated as well. Primary hyperparathyroidism is definitively managed by parathyroidectomy. In the hands of experienced surgeons, more than 90% of patients are cured. When hypercalcemia is caused by malignancy, treatment must be directed at the underlying tumor because normocalcemia is difficult to sustain without successful treatment of the underlying cause. Hypercalcemia caused by medication responds to discontinuation of the offending agent. Hypercalcemia caused by nonparathyroid endocrine disease responds to treatment of the underlying disorder.

BOX 123-11 MANAGEMENT OF HYPERCALCEMIA

- Restoration of intravascular volume
  - Correct dehydration with isotonic solution
  - Correct associated electrolyte abnormalities
- Enhancement of renal calcium elimination
  - Saline diuresis
  - Loop diuretics (e.g., furosemide)
  - *Avoid* thiazide diuretics
- Reduction of osteoclastic activity
  - (Consult specialist for agent selection dosing.)
  - Bisphosphonates
    - Etidronate
    - Pamidronate
  - Zoledronic acid
  - Calcitonin
  - Hydrocortisone
- Treatment of primary disorder
  - Parathyroidectomy for hyperparathyroidism
  - Withdrawal of causative medications
  - Treatment of nonparathyroid endocrine disorders

MAGNESIUM

Normal Physiology

Magnesium (Mg^{2+}) is the second most abundant intracellular cation. It is a cofactor in hundreds of enzymatic reactions, including all those involving adenosine triphosphate (ATP). Magnesium is essential for the production and use of energy, DNA, and protein synthesis, ion channel gating, hormone receptor binding, neurotransmission, cardiac excitability, and muscle contraction.[49]

The adult human body contains approximately 2000 mEq of magnesium. One half of total magnesium is in the mineral

component of bone, and 40 to 50% is found in the intracellular compartment. Only 1 to 2% of the body's magnesium is present in the extracellular fluid, so the serum magnesium level is often a poor reflection of the total magnesium content. One third of the serum magnesium is bound to albumin, with the rest in the biologically active ionized form. The normal range for serum magnesium is 1.8 to 3.0 mg/dL. A balance between gastrointestinal absorption and renal excretion maintains magnesium homeostasis.

Dietary sources of magnesium include green vegetables, meats, fish, beans, nuts, and grains. Absorption of ingested magnesium occurs in the small intestine through both active and passive transport mechanisms. In the kidney, 95% of the filtered load of magnesium is reabsorbed in the proximal tubule and loop of Henle.[50] In deficiency states, magnesium resorption is enhanced in the distal convoluted tubule under the influence of PTH. In hypermagnesemic states, renal excretion of magnesium increases.

Hypomagnesemia

Principles of Disease

Hypomagnesemia is one of the most common electrolyte deficiencies in clinical practice.[49] Approximately 10 to 20% of hospitalized patients and 50 to 60% of patients admitted to the intensive care unit are hypomagnesemic.[51] Despite the high prevalence of hypomagnesemia, several factors can make the diagnosis a challenge. First, the clinical manifestations of hypomagnesemia are nonspecific, so the disorder is often overlooked. Second, the serum magnesium level is not measured as part of the "routine" electrolyte panel.[52] Third, the serum magnesium level is an insensitive indicator of magnesium deficiency. Although a low serum magnesium level is indicative of a magnesium deficit, patients with a normal magnesium level may still have a severe deficiency. Fourth, hypomagnesemia often coexists with and may be masked by other electrolyte deficiency states.

Numerous studies have demonstrated the high prevalence of hypomagnesemia in patients with hypokalemia.[53] Because magnesium is required for the normal functioning of the Na^+-K^+ ATPase pump, hypomagnesemia can result in refractory hypokalemia that is not correctable by the administration of potassium alone. Magnesium replacement enhances potassium retention and decreases the amount of supplemental potassium required to achieve a net positive balance.[54] Magnesium is also required for the normal synthesis and release of PTH. Patients with hypomagnesemic hypocalcemia typically have inappropriately low levels of PTH and target organ resistance to the hormone, which are corrected by magnesium administration. A high prevalence of hypophosphatemia in patients who are hypomagnesemic has also been described.

Because the kidneys normally conserve magnesium efficiently, significant hypomagnesemia usually occurs only when there is renal magnesium wasting or when intestinal losses exceed dietary intake and absorption (Box 123-12). In the emergency department, hypomagnesemia is most often associated with the use of diuretics and with alcohol abuse.

Diuretics. Patients taking diuretics for the treatment of hypertension, congestive heart failure, or both are at significant risk for hypomagnesemia. Both the thiazide and the loop diuretics promote renal magnesium loss and may cause severe magnesium deficiency.[55] In one study, typical diuretic doses increased urinary magnesium excretion by 25 to 50%. Some authors recommend that all patients receiving diuretics be considered candidates for magnesium supplementation. The use of a potassium-sparing diuretic in conjunction with a conventional diuretic is less likely to cause hypomagnesemia because these agents also have a magnesium-sparing effect.

Alcoholism. The reported prevalence of hypomagnesemia in alcoholic patients varies widely, from 30 to 80%.[56,57] Hypomagnesemia in the alcoholic patient is multifactorial; potential causes include poor nutrition, increased urinary excretion, gastrointestinal losses from vomiting and diarrhea, and pancreatic insufficiency.

Renal, Gastrointestinal, and Endocrine Disorders. Hypomagnesemia can also result from renal magnesium wasting or from decreased production of (or end-organ responsiveness to) PTH.[58] Magnesium wasting may be seen in some patients with postobstructive diuresis, acute tubular necrosis, chronic glomerulonephritis, chronic pyelonephritis, or interstitial nephropathy, as well as after renal transplantation. The decreased magnesium excretion typically found with acute and chronic renal failure, however, generally results in these patients tending to be hypermagnesemic.

BOX 123-12 CAUSES OF HYPOMAGNESEMIA

- Alcohol abuse
- Diuretic use
- Renal losses
  - Acute and chronic renal failure
  - Postobstructive diuresis
  - Acute tubular necrosis
  - Chronic glomerulonephritis
  - Chronic pyelonephritis
  - Interstitial nephropathy
  - Renal transplantation
- Gastrointestinal losses
  - Chronic diarrhea
  - Nasogastric suctioning
  - Short-bowel syndrome
  - Protein-calorie malnutrition
  - Bowel fistula
  - Total parenteral nutrition
  - Acute pancreatitis
- Endocrine disorders
  - Diabetes mellitus
  - Hyperaldosteronism
  - Hyperthyroidism
  - Hyperparathyroidism
  - Acute intermittent porphyria
- Pregnancy
- Drugs
  - Aminoglycosides
  - Amphotericin
  - Beta-agonists
  - Cisplatin
  - Cyclosporine
  - Diuretics
  - Foscarnet
  - Pentamidine
  - Theophylline
- Congenital disorders
  - Familial hypomagnesemia
  - Maternal diabetes
  - Maternal hypothyroidism
  - Maternal hyperparathyroidism

Gastrointestinal causes of hypomagnesemia include short-bowel syndrome, protein-calorie malnutrition, bowel fistula, continuous nasogastric suctioning, chronic diarrhea, and administration of total parenteral nutrition.[58] Patients with acute pancreatitis typically have an intracellular magnesium deficiency despite normal serum concentrations. This is most likely in patients who are also hypocalcemic.

Hypomagnesemia is the most common electrolyte abnormality in ambulatory diabetic patients and is also a common finding in patients with DKA. Excessive urinary loss associated with glycosuria and transcellular shifts of the cation are the proposed mechanisms. The clinical consequences of magnesium deficiency include impairment of insulin secretion and peripheral insulin resistance. Hypomagnesemia also may play a role in the development of retinopathy, hypertension, and the abnormal platelet function often observed in diabetic patients. Other endocrine and metabolic causes of hypomagnesemia include primary and secondary aldosteronism, hyperthyroidism, primary hyperparathyroidism, and acute intermittent porphyria.

Pregnancy. Pregnancy is marked by a state of hypomagnesemia. Serum levels usually decline in the third trimester. Patients with preterm labor are more likely to have a significantly depressed serum magnesium level.[59]

Drugs. Hypomagnesemia has also been associated with a number of drugs.[60] It can result from renal magnesium wasting (e.g., aminoglycosides, amphotericin B, cisplatin, diuretics, foscarnet, pentamidine) or from transcellular magnesium shifts (e.g., beta-agonists, cyclosporine, theophylline).[61]

Congenital Disorders. Congenital disorders causing hypomagnesemia include primary infantile hypomagnesemia and familial hypomagnesemia. Maternal diabetes, maternal hyperparathyroidism, and maternal hypothyroidism are also associated with hypomagnesemia in the newborn.

Clinical Features

The clinical manifestations of hypomagnesemia are nonspecific and can easily be confused with those caused by other metabolic abnormalities. Symptoms are inconsistent, variable in severity, and not well correlated with a specific serum magnesium level. However, patients are usually symptomatic at serum levels of 1.2 mg/dL or less. The clinical manifestations of hypomagnesemia most likely to be prominent in the emergency setting involve the neuromuscular and cardiovascular systems.

Neuromuscular manifestations include muscle weakness, tremor, hyper-reflexia, tetany, and a positive Chvostek's or Trousseau's sign. CNS findings range from apathy, irritability, and dizziness to seizures, papilledema, and coma. Focal neurologic findings have also been described.

Dysrhythmia is the most common cardiovascular manifestation of hypomagnesemia. A number of studies demonstrate an increased incidence of supraventricular dysrhythmias (atrial fibrillation, multifocal atrial tachycardia, paroxysmal supraventricular tachycardia) and ventricular dysrhythmias (premature ventricular contractions, ventricular tachycardia, torsades de pointes, ventricular fibrillation) in patients who are magnesium deficient.[62] Patients taking diuretics for the treatment of congestive heart failure are particularly vulnerable. Digitalis-induced dysrhythmias are also more likely in the presence of hypomagnesemia. Because magnesium is an essential cofactor for the Na^+-K^+ ATPase pump that is inhibited by digitalis, hypomagnesemia typically worsens the manifestations of digitalis toxicity.

Hypomagnesemia has been associated with a wide range of ECG findings, including prolongation of the PR, QRS, and QT intervals; ST-T segment abnormalities; flattening and widening of the T wave; and presence of U waves. These findings, however, are nonspecific and may be at least partly caused by associated hypokalemia. Thus, the ECG should not be used to rule out magnesium disturbances.

The relationship between hypomagnesemia and ischemic heart disease is controversial. Hypomagnesemia is common in emergency department patients with chest pain and in those admitted to the coronary care unit.[62] Patients who have a myocardial infarction are more likely to be hypomagnesemic than those who do not. This finding has been shown to be independent of concomitant diuretic use. Serum magnesium levels decline transiently after acute myocardial infarction, increasing the risk of dysrhythmia.[63,64] Proposed mechanisms include transcellular shifts of the cation and chelation with free fatty acids released after acute myocardial infarction. Although several studies demonstrate a benefit of empiric magnesium administration after acute myocardial infarction, the largest trial to date, the International Study of Infarct Survival, failed to confirm a significant benefit.[65]

Management

Because it is often an inaccurate reflection of total magnesium stores, the serum magnesium level should not be used alone to guide therapy. However, magnesium administration is appropriate in patients with a low serum level (<1.2 mg/dL), as well as in those with a normal serum magnesium level and symptoms suggestive of hypomagnesemia. For life-threatening conditions (dysrhythmias, seizures) in which hypomagnesemia is the possible cause, parenteral magnesium should be given. In patients with normal renal function, 2 to 4 g of 50% magnesium sulfate (16.6333 mEq) is a reasonable initial dose. This should be diluted in saline or dextrose and given over 30 to 60 minutes. More rapid administration may result in venous irritation and phlebitis. Bolus administration should be avoided because this may cause bradycardia and varying degrees of heart block, as well as hypotension. Magnesium should be administered with caution, if at all, in patients with atrioventricular block or renal insufficiency. Most administered magnesium is promptly excreted in the urine. Total magnesium repletion therefore requires administration of more than a single dose, generally over days.

Several different oral magnesium formulations are available. Preparations of magnesium gluconate, magnesium carbonate, magnesium oxide, and magnesium chloride each provide different doses of elemental magnesium. Large doses of magnesium salts can cause diarrhea. Magnesium as the chloride salt or as enteric-coated tablets (e.g., Slow-Mag) is usually better tolerated.

Hypermagnesemia

Principles of Disease

Hypermagnesemia is a fairly rare disorder. Under normal circumstances, the kidneys increase magnesium excretion as the magnesium load increases. A healthy adult can excrete more than 6 g of magnesium daily. For this reason, clinically significant hypermagnesemia is encountered almost exclusively in the setting of renal insufficiency (Box 123-13). Serum magnesium levels rise as the creatinine clearance falls below 30 mL/min and typically reach approximately 2.5 mEq/L as renal function nears zero. Although severe renal failure alone can cause symptomatic hypermagnesemia, this is more likely when a patient with preexisting renal failure is challenged with an exogenous magnesium load. Clinically significant

BOX 123-13 CAUSES OF HYPERMAGNESEMIA

- Impaired renal magnesium excretion
- Exogenous magnesium administration
  - Antacids
  - Laxatives
  - Cathartics
  - Dialysate
  - Parenteral
- Impaired magnesium elimination
  - Anticholinergics
  - Narcotics
  - Chronic constipation
  - Bowel obstruction
  - Gastric dilation
  - Colitis
- Miscellaneous
  - Rhabdomyolysis
  - Tumor lysis syndrome
  - Adrenal insufficiency
  - Hyperparathyroidism
  - Hypothyroidism
  - Lithium therapy

hypermagnesemia can be produced even by usual therapeutic doses of magnesium-containing preparations in patients with renal insufficiency. Elderly patients misusing over-the-counter medications are particularly at risk.

Iatrogenic hypermagnesemia can result from parenteral magnesium administration, excessive magnesium in dialysate solutions, or ingestion of magnesium-containing antacids or laxatives.[66] Severe hypermagnesemia occurs rarely in the patient with normal renal function, but only when such massive magnesium loads are administered that magnesium absorption exceeds the normal renal excretory capacity. IV magnesium infusion for the treatment of preeclampsia and eclampsia is a common cause of hypermagnesemia but leads to problems only when excessive doses are given or when renal function is compromised. Another situation particularly relevant to the emergency physician is multidose administration of magnesium-containing cathartics during overdose management. Although several case reports document severe hypermagnesemia in this setting, clinically significant hypermagnesemia is rare in the absence of preexisting renal insufficiency.[67] A review of 102 patients receiving multiple doses of magnesium citrate during overdose management (mean dose, 9.22 g) reported only modest rises in serum magnesium, with no clinically significant side effects.[68]

Decreased gastrointestinal motility may cause an increase in the absorption of magnesium-containing substances and result in toxicity. This may occur after the ingestion of certain drugs (e.g., anticholinergics, narcotics) or in patients with hypomotility disorders (e.g., chronic constipation, colitis, bowel obstruction, gastric dilation). Although symptomatic hypermagnesemia is more likely in patients with preexisting renal insufficiency, it has been reported in patients with normal renal function.[69]

Other, less common causes of hypermagnesemia include rhabdomyolysis, tumor lysis syndrome, adrenal insufficiency, hyperparathyroidism, hypothyroidism, and lithium therapy.

Clinical Features

The clinical manifestations of hypermagnesemia generally correlate well with the serum level. Early signs of hypermagnesemia, including nausea, vomiting, weakness, and cutaneous flushing, usually appear at serum levels of approximately 3 mg/dL. As levels rise above 4 mg/dL, hyporeflexia is seen, and deep tendon reflexes are eventually lost. Hypotension and ECG changes (e.g., QRS widening, QT and PR prolongation, conduction abnormalities) are seen at serum levels of 5 to 6 mg/dL. Levels greater than 9 mg/dL are associated with respiratory depression, coma, and complete heart block.[70] Asystole, cardiac arrest, and death have been reported in patients with serum magnesium levels of 10 to 15 mg/dL.[71,72] Although hypermagnesemia may decrease the anion gap, numerous cases of hypermagnesemia with a normal anion gap have been reported.

Management

The first step in the management of hypermagnesemia is to discontinue all exogenous magnesium. Further treatment depends on the clinical presentation, the degree of hypermagnesemia, and the patient's underlying renal function. Patients with mild symptoms and normal renal function may require only observation. If more prominent symptoms are present, hydration with isotonic fluids and administration of IV furosemide can be used to accelerate magnesium elimination. If these measures are used, the serum potassium level should be closely monitored.

Patients with severe hypermagnesemia should receive IV calcium. Calcium directly antagonizes the membrane effects of hypermagnesemia and reverses respiratory depression, hypotension, and cardiac dysrhythmias. For life-threatening manifestations of hypermagnesemia, 100 to 200 mg of calcium, as either 10% calcium gluconate (93 mg calcium per ampule) or 10% calcium chloride (360 mg calcium per ampule), is a reasonable dose. Repeat boluses or a continuous infusion (2–4 mg/kg/hr) may be required to sustain the effect while measures to increase magnesium elimination are instituted. Dialysis should be considered in patients with coma, respiratory failure, or hemodynamic instability and in those with severe hypermagnesemia associated with renal failure.

PHOSPHORUS

Normal Physiology

Phosphorus is located primarily in the cell complexed with oxygen and hydrogen as phosphate. In this form, phosphate is an important component of nucleic acids (RNA and DNA) and of the phospholipid cell membrane. Phosphate is an essential component of ATP, the energy currency of all living cells, and of erythrocyte 2,3-diphosphoglycerate (2,3-DPG), which promotes the release of circulating oxygen at the tissue level. Phosphate also binds with calcium to form hydroxyapatite, the major salt of bone matrix.[73]

In the serum, phosphate is an important acid-base buffer. In the presence of acidosis, divalent phosphate (HPO_4^{2-}) binds excess hydrogen ions, shifting to the monovalent form ($H_2PO_4^-$). The reverse occurs when the extracellular fluid becomes alkalotic.

The normal adult human body contains approximately 700 g of phosphate, 80% of which is contained in the mineral component of bone. Phosphate balance is maintained by three different organs: intestine, kidney, and bone. PTH and vitamin D are the major hormonal regulators of plasma phosphate concentration, although these hormones are released in response to changes in Ca^{2+} rather than phosphate. Normal serum phosphate levels range from 3 to 4.5 mg/dL.

Dietary sources of phosphate include fruits, vegetables, meats, and dairy products. Absorption of ingested phosphate occurs through active and passive transport in the small intestine. Vitamin D enhances the absorption of both phosphate and calcium.

In the kidneys, 90% of the filtered load of phosphate is reabsorbed in the proximal tubule. Renal reabsorption increases in deficiency states. When serum phosphate levels increase, renal reabsorption decreases. PTH acts at the proximal and distal tubules to inhibit phosphate resorption. In the absence of normal renal function, PTH cannot increase phosphate excretion and may actually increase serum phosphate levels because of its effect on intestine and bone.[74] Thyroid hormone and growth hormone both increase renal phosphate resorption.

The release and uptake of phosphate by bone are primarily determined by the mechanisms governing calcium metabolism. When the serum calcium level falls, both calcium and phosphate are released into the extracellular space by the action of PTH. When serum calcium levels rise, bone formation increases, and phosphate and calcium shift from the serum into bone.[73]

Hypophosphatemia

Principles of Disease

Hypophosphatemia has traditionally been classified as mild (2.5–2.8 mg/dL), moderate (1.0–2.5 mg/dL), or severe (<1.0 mg/dL). The incidence of hypophosphatemia in hospitalized patients is 2 to 3% and as high as 30% in those admitted to the intensive care unit. Severe hypophosphatemia is seen in up to 0.5% of hospitalized patients. Important risk factors include DKA, malnutrition, diuretic or antacid therapy, sepsis, and alcoholism. The many causes include (1) disorders that result in increased renal excretion, (2) disorders that are associated with decreased gastrointestinal absorption, and (3) disorders in which phosphate shifts from the serum into cells (Box 123-14).[75]

Renal phosphate loss is most often the result of diuretic therapy. The thiazides, loop diuretics, and acetazolamide promote renal phosphate wasting.[74-76] Hypophosphatemia can also be seen in patients with acute renal failure, renal transplantation, and long-term peritoneal dialysis, although renal insufficiency is typically associated with hyperphosphatemia rather than hypophosphatemia.[77] In hyperparathyroidism, high levels of circulating PTH increase renal phosphate excretion and may cause hypophosphatemia.

DKA is an important cause of hypophosphatemia. Metabolic acidosis and insulin deficiency mobilize intracellular phosphate stores, and in the setting of an ongoing osmotic diuresis, urinary losses increase. Because of a shift of phosphate from cells to the blood, serum levels may be normal in the face of a profound total deficit. Treatment of DKA with insulin causes phosphate to move back into cells and may result in a sharp decline in the serum level.[78] The benefit of routine phosphate replacement in DKA is unproven, although patients with low serum phosphate levels in the face of acidosis should be presumed to have a severe deficiency. Because these patients are often hypokalemic, replacement with potassium phosphate salts is a reasonable approach.

Decreased phosphate intake and impaired intestinal phosphate absorption are other causes of hypophosphatemia. Up to 50% of alcoholics are hypophosphatemic. Increased renal excretion and decreased intake are the proposed mechanisms. Hypophosphatemia may be exacerbated when glucose-containing solutions are administered, because these cause phosphate to shift from the serum into cells.

BOX 123-14 CAUSES OF HYPOPHOSPHATEMIA

- Renal loss
  - Diuretic therapy
  - Renal tubular dysfunction
  - Hyperosmolar states
    - Diabetic ketoacidosis
    - Hyperosmolar hyperglycemic nonketotic coma
  - Hyperparathyroidism
  - Aldosteronism
  - Glucocorticoid administration
- Insufficient intestinal absorption
  - Decreased dietary intake
  - Starvation/malnutrition
  - Phosphate-binding antacids
  - Vitamin D deficiency
  - Chronic diarrhea
  - Nasogastric suctioning
- Transcellular shift
  - Respiratory alkalosis
    - Sepsis
    - Heatstroke
    - Salicylate poisoning
    - Neuroleptic malignant syndrome
    - Hepatic encephalopathy
    - Alcohol withdrawal
  - Hyperglycemia
  - Insulin administration

Because phosphate is ubiquitous in most food sources, starvation and chronic malnutrition are relatively uncommon causes in the developed world, although low-birth-weight infants are particularly vulnerable. Decreased intestinal phosphate absorption occurs in malabsorptive syndromes, chronic diarrhea, and vitamin D deficiency. Phosphate-binding antacids (calcium carbonate, aluminum hydroxide, aluminum carbonate) prevent the absorption of dietary phosphate, and long-term therapy can lead to hypophosphatemia.

Transcellular shifts of phosphate from the extracellular space into cells is the third mechanism of hypophosphatemia. Respiratory alkalosis is a common cause of hypophosphatemia. Reduction of intracellular carbon dioxide tension increases the activity of phosphofructokinase, the rate-limiting enzyme of glycolysis, and phosphorylation of glucose precursors increases cellular uptake of serum phosphate, causing hypophosphatemia. Hyperventilation-induced hypophosphatemia may occur in the setting of sepsis, heatstroke, salicylate poisoning, neuroleptic malignant syndrome, hepatic encephalopathy, alcohol withdrawal, and acute panic disorders.

The administration of glucose-containing solutions to chronically malnourished patients can precipitate the so-called *refeeding syndrome*, in which insulin release increases cellular phosphate uptake, decreasing the serum concentration. This can be prevented by adding supplemental phosphate to the diet. Beta-receptor agonists used in the management of acute asthma stimulate cellular uptake of phosphate and can precipitate hypophosphatemia.[79,80] Administration of catecholamines and sodium bicarbonate also shifts phosphate into the cell. Increased metabolic demands in postoperative patients increase cellular phosphate uptake and can cause a deficiency state. Certain rapidly growing malignancies (e.g., leukemia, Burkitt's lymphoma, histiocytic lymphoma) also take up enough phosphate to cause hypophosphatemia.

BOX 123-15 Clinical Features of Hypophosphatemia

Cardiovascular
Decreased contractility
Hypotension
Dysrhythmias
Cardiomyopathy

Pulmonary
Respiratory failure
Ventilator dependence

Skeletal Muscle
Weakness
Myalgias
Rhabdomyolysis

Hematologic
Decreased tissue oxygen delivery
Hemolysis
Leukocyte dysfunction
Platelet dysfunction

Neurologic
Paresthesias
Seizures
Coma

Clinical Features

The signs and symptoms of hypophosphatemia result from impaired production of ATP and inadequate energy metabolism. Virtually every organ system can be affected (Box 123-15). Mild or moderate hypophosphatemia is usually asymptomatic, and major clinical sequelae are usually seen only in severe hypophosphatemia.

With severe phosphate depletion, myocardial depression is seen, and hypotension, impaired pressor responsiveness, and left ventricular dysfunction have been reported.[81] Hypophosphatemia also reduces the threshold for ventricular dysrhythmias.

Respiratory insufficiency is common among severely hypophosphatemic patients. Decreased energy substrate leads to respiratory muscle weakness, depressed diaphragmatic contractility, hypoxia, and respiratory acidosis. Rapid correction of chronic respiratory acidosis with assisted ventilation may decrease the serum phosphate level further by shifting the anion into the cell. Inability to wean a ventilated patient may be an important consequence of hypophosphatemia.

The effects of hypophosphatemia on skeletal muscle are also related to depletion of intracellular ATP. Symptoms include muscle weakness, myalgias, and fatigue.[82] Hypophosphatemia can cause rhabdomyolysis. This may be asymptomatic, manifested only by increased serum muscle enzyme levels, or may cause severe muscle pain and weakness and acute renal failure. Rhabdomyolysis may be precipitated by acute alcohol withdrawal, by the treatment of DKA, and in hypophosphatemic patients by hyperalimentation. Significant rhabdomyolysis results in the release of phosphate from muscle cells, and serum phosphate levels can be normal or even high despite intracellular hypophosphatemia.

Hypophosphatemia results in impaired production of 2,3-DPG in the erythrocyte, causing a leftward shift of the oxyhemoglobin dissociation curve and decreased tissue oxygen delivery. In the absence of adequate ATP stores, the erythrocyte is unable to maintain membrane integrity and the ability to deform and alter its shape as it passes through capillaries. This may result in hemolysis and increased destruction in the spleen. Hypophosphatemia is also associated with leukocyte dysfunction with impaired chemotaxis, phagocytosis, and opsonization, increasing the susceptibility to infection.

Neurologic manifestations of severe hypophosphatemia include weakness, confusion, seizures, and coma. Peripheral neuropathy and an ascending motor paralysis resembling Guillain-Barré syndrome have been reported.

BOX 123-16 Causes of Hyperphosphatemia

Pseudohyperphosphatemia
  Paraproteinemia
  Hyperlipidemia
  Hemolysis
  Hyperbilirubinemia
Renal
  Acute and chronic renal failure
  Increased renal tubular reabsorption
    Hypoparathyroidism
    Thyrotoxicosis
    Excess vitamin D administration
Cellular injury
  Rhabdomyolysis
  Tumor lysis syndrome
  Hemolysis
Increased intake
  Phosphate enemas or laxatives
  Intravenous or oral phosphate administration

Management

The treatment of hypophosphatemia depends both on the serum level and on the severity of symptoms. Mild or moderate hypophosphatemia can usually be treated with oral supplements such as potassium phosphate. Severe hyperphosphatemia should be treated with IV phosphate. Two preparations are available: potassium phosphate and sodium phosphate. Because hypophosphatemia and hypokalemia can coexist in some disorders (e.g., DKA, alcoholism), replacement with the potassium salt is most appropriate.[83,84]

Complications of IV phosphate administration include acute hypocalcemia and hyperphosphatemia. Patients should be monitored for signs of hypocalcemia, such as tetany. Phosphate should be administered with particular caution in patients with renal dysfunction.[73,74]

Hyperphosphatemia

Principles of Disease

Hyperphosphatemia (>5.0 mg/dL) is rare in patients with normal renal function because the kidneys readily excrete an excess phosphate load. True hyperphosphatemia can result from decreased phosphate clearance, an increased endogenous phosphate load, or an increased exogenous load (Box 123-16).

Pseudohyperphosphatemia represents a spurious elevation of inorganic phosphate measurements caused by interference with analytic methods. Causes include paraproteinemia (e.g., multiple myeloma), hyperlipidemia, hemolysis, and hyperbilirubinemia.

Renal failure is the most common cause of hyperphosphatemia.[74] The serum phosphate level typically remains normal until the creatinine clearance falls below 30 mL/min.[85] Hyper-

phosphatemia is usually mild unless an exogenous phosphate load is given. Hyperphosphatemia may also occur in patients with normal renal function when renal phosphate resorption is increased, as occurs with PTH deficiency, and in the setting of thyrotoxicosis or excessive vitamin D administration.

Hyperphosphatemia can also occur with large endogenous phosphate loads, as with extensive cell damage, which causes phosphate to be released into the extracellular space. This may occur in the setting of rhabdomyolysis, tumor lysis syndrome, or hemolysis.[86] Patients with these disorders often develop renal failure, impairing phosphate excretion and further increasing serum levels.

Hypophosphatemia may also result from exogenous loads, as with IV, oral, or rectal phosphate administration. Infants, elderly persons, and patients with preexisting renal insufficiency are particularly vulnerable.[87-90]

Clinical Features

The clinical signs of hyperphosphatemia reflect the associated hypocalcemia that results when excess serum phosphate binds with calcium and precipitates in tissues. Signs of neuromuscular hyperexcitability (e.g., paresthesias, hyper-reflexia, tetany, seizures) and myocardial depression (e.g., hypotension, bradycardia, left ventricular dysfunction) predominate. Tissue deposition of calcium phosphate may result in acute heart block and death.

Management

The emergency treatment of hyperphosphatemia involves supportive care and treatment of symptomatic hypocalcemia. In patients with normal renal function, infusion of isotonic saline increases phosphate clearance. The administration of dextrose and insulin drives phosphate into cells, temporarily lowering the serum level.

Aluminum-containing antacids are the mainstay of the prevention of hyperphosphatemia in patients with chronic renal failure.[91] Although these are usually not administered in the emergency department, their use is reasonable in the management of hyperphosphatemia after a large overdose of exogenous phosphate. When hyperphosphatemia poses a threat to life, hemodialysis or peritoneal dialysis should be considered, especially in patients with renal failure.

KEY CONCEPTS

- Hyponatremia affects the central nervous system, causing lethargy, apathy, confusion, disorientation, agitation, depression, and psychosis.
- Treatment of hyponatremia is based on severity of symptoms, estimated duration of illness, and patient's volume status. Patients with acute hyponatremia are usually symptomatic (e.g., severe weakness, diminished consciousness, seizures) when the serum Na^+ level falls below 120 mEq/L, whereas patients with chronic hyponatremia can tolerate much lower levels.
- Acute hyponatremia may be corrected at rates of up to 1 to 2 mEq/L/hr, and chronic hyponatremia should be corrected at a rate not greater than 0.5 mEq/L/hr. In general, the serum Na^+ level should not be increased by more than 10 mEq/L in a 24-hour period.
- Oral therapy for hypokalemia is preferable to IV therapy because of the risk of inducing hyperkalemia through the IV route. However, patients with prominent symptoms (e.g., dysrhythmias) and those who are unable to tolerate oral supplements should receive IV potassium replacement.
- The ECG can provide valuable clues to the presence of hyperkalemia (e.g., peaked T waves, loss of P waves, QRS widening).
- Treatment of hyperkalemia includes cardiovascular monitoring, administration of calcium for hemodynamic instability, lowering of serum K^+, and correction of the underlying disorder.
- Treatment of hypercalcemia (IV fluids, furosemide, osteoclastic inhibitors, e.g., bisphosphonates [etidronate, pamidronate], plicamycin, calcitonin, glucocorticoids, and gallium nitrate) should be initiated in patients with significant symptoms (e.g., severe dehydration, alteration of consciousness, dysrhythmias) or when the calcium level is above 14 mg/dL. The goals of therapy are normalization of volume status, enhancement of renal calcium elimination, diminution of osteoclastic activity, and treatment of the underlying disorder.
- In hypomagnesemia, although the serum magnesium level often inaccurately reflects total body stores, magnesium supplementation should be considered when the level is less than 1.2 mg/dL. IV magnesium therapy should be instituted for patients with significant symptoms (e.g., seizures, dysrhythmias).

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 124

Diabetes Mellitus and Disorders of Glucose Homeostasis

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PERSPECTIVE

Diabetes mellitus is the most common endocrine disease. It comprises a heterogeneous group of hyperglycemic disorders characterized by high serum glucose and disturbances of carbohydrate and lipid metabolism. Acute complications include hypoglycemia, diabetic ketoacidosis (DKA), and hyperglycemic hyperosmolar nonketotic coma (HHNC). Long-term complications include disorders of blood vessels, especially the microvasculature. The cardiovascular system, eyes, kidneys, and nerves are particularly susceptible to complications. Despite the discovery of insulin more than 75 years ago by Banting and Best,[1] the incidence of severe debilitating complications, including arteriosclerosis, renal failure, retinopathy, and neuropathy, remains high. The Diabetes Control and Complications Trial proved that tight blood glucose control reduces the risk of these late sequelae for type 1 diabetics.[2] The United Kingdom Prospective Diabetes Study (UKPDS) trials have also shown benefit to tight glycemic control in type 2 diabetics.[3] Patients with diabetes mellitus incur emergency department (ED) costs three times higher and are admitted to the hospital four times more often than nondiabetic patients.

PRINCIPLES OF DISEASE

Normal Physiology

Maintenance of the plasma glucose concentration is critical to survival because plasma glucose is the predominant metabolic fuel used by the central nervous system (CNS). The CNS cannot synthesize glucose, store more than a few minutes' supply, or concentrate glucose from the circulation. Brief hypoglycemia can cause profound CNS dysfunction, and prolonged severe hypoglycemia may cause cellular death. Glucose regulatory systems have evolved to prevent or correct hypoglycemia.[4]

The plasma glucose concentration is normally maintained within a relatively narrow range, between 60 and 150 mg/dL, despite wide variations in glucose levels after meals and exercise. Glucose is derived from three sources: intestinal absorption from the diet; *glycogenolysis*, the breakdown of glycogen; and *gluconeogenesis*, the formation of glucose from precursors, including lactate, pyruvate, amino acids, and glycerol. After glucose ingestion, the plasma glucose concentration increases as a result of glucose absorption. Endogenous glucose production is suppressed. Plasma glucose then rapidly declines to a level below the baseline.

Insulin

Insulin receptors on the beta cells of the pancreas sense elevations in blood glucose and trigger insulin release into the blood. For incompletely understood reasons, glucose taken by mouth evokes more insulin release than parenteral glucose. Certain amino acids induce insulin release and even cause hypoglycemia in some patients. Sulfonylurea oral hypoglycemic agents work, in part, by stimulating the release of insulin from the pancreas.

The number of receptor sites helps determine the sensitivity of the particular tissue to circulating insulin. The number and sensitivity of receptor sites are also the primary factors in the long-term efficacy of the sulfonylurea oral hypoglycemic agents. Receptor sites are increased in glucocorticoid deficiency and may be relatively decreased in obese patients.

Under normal circumstances, insulin is rapidly degraded through the liver and kidneys. The half-life of insulin is 3 to 10 minutes in the circulation. Whereas insulin is the major anabolic hormone pertinent to the diabetic disorder, glucagon plays the role of the major catabolic hormone in disordered glucose homeostasis.

Although most tissues have the enzyme systems required to synthesize and hydrolyze glycogen, only the liver and kidneys contain glucose-6-phosphatase, the enzyme necessary for the release of glucose into the circulation. The liver is essentially the sole source of endogenous glucose production. Renal gluconeogenesis and glucose release contribute substantially to the systemic glucose pool only during prolonged starvation.

The hepatocyte does not require insulin for glucose to cross the cell membrane. However, insulin augments both the hepatic glucose uptake and storage needed for the process of energy generation and glycogen and fat synthesis. Insulin inhibits hepatic gluconeogenesis and glycogenolysis.[5]

Muscle can store and use glucose, primarily through glycolysis to pyruvate, which is reduced to lactate or transaminated to form alanine. Lactate released from muscle is transported to the liver, where it serves as a gluconeogenic precursor. Alanine may also flow from muscle to liver. During fasting, muscle can reduce its glucose uptake, oxidize fatty acids for its energy needs, and, through proteolysis, mobilize amino acids for transport to the liver as gluconeogenic precursors. Adipose tissue can also use glucose for fatty acid synthesis for oxidation to form triglycerides. During fasting, adipocytes can also decrease their glucose use and satisfy energy needs through the beta-oxidation of fatty acids. Other tissues do not

have the capacity to decrease glucose use on fasting and therefore produce lactate at relatively fixed rates.

Glucose transport across the fat cell membrane also requires insulin. A large percentage of the adipocyte glucose is metabolized to form α-glycerophosphate, required for the esterification of fatty acids to form triglycerides. Although most insulin-mediated fatty acid synthesis occurs in the liver, a very small percentage occurs in fat cells, using the acetyl coenzyme A generated by glucose metabolism. Very low levels of insulin are required to inhibit intracellular lipolysis while stimulating the extracellular lipolysis required for circulating lipids to enter the fat cell.

Glucose Regulatory Mechanisms

Maintenance of the normal plasma glucose concentration requires precise matching of glucose use and endogenous glucose production or dietary glucose delivery. The regulatory mechanisms that maintain systemic glucose balance involve hormonal, neurohumoral, and autoregulatory factors. Glucoregulatory hormones include insulin, glucagon, epinephrine, cortisol, and growth hormone. Insulin is the main glucose-lowering hormone. Insulin suppresses endogenous glucose production and stimulates glucose use. Insulin is secreted from the beta cells of the pancreatic islets into the hepatic portal circulation and has important actions on the liver and the peripheral tissues. Insulin stimulates glucose uptake, storage, and use by other insulin-sensitive tissues such as fat and muscle.[4]

Counter-regulatory hormones include glucagon, epinephrine, norepinephrine, growth hormone, and cortisol. When glucose is not transported into the cells because of either a lack of food intake or lack of insulin, the body perceives a "fasting state" and releases *glucagon*, attempting to provide the glucose necessary for brain function. In contrast to the fed state, in the fasting state the body metabolizes protein and fat. Glucagon is secreted from the alpha cells of the pancreatic islets into the hepatic portal circulation. Glucagon lowers hepatic levels of fructose 2,6-biphosphate, resulting in decreased glycolysis and increased gluconeogenesis, an effect that may be enhanced by ketosis.[6] Glucagon increases the activity of adenyl cyclase in the liver, thereby increasing glycogen breakdown to glucose and further increasing hepatic gluconeogenesis. Glucagon acts to increase ketone production in the liver. Thus, whereas insulin is an anabolic agent that reduces blood glucose, glucagon is a catabolic agent that increases blood glucose. Glucagon is released in response to hypoglycemia as well as to stress, trauma, infection, exercise, and starvation. It increases hepatic glucose production within minutes, although transiently.

Epinephrine both stimulates hepatic glucose production and limits glucose use through both direct and indirect actions mediated through both alpha- and beta-adrenergic mechanisms. Epinephrine also acts directly to increase hepatic glycogenolysis and gluconeogenesis. It acts within minutes and produces a transient increase in glucose production but continues to support glucose production at approximately basal levels thereafter. Norepinephrine exerts hyperglycemic actions by mechanisms similar to those of epinephrine, except that norepinephrine is released from axon terminals of sympathetic postganglionic neurons.

Growth hormone initially has a plasma glucose-lowering effect. Its hypoglycemic effect does not appear for several hours. Thus, growth hormone release is not critical for rapid glucose counter-regulation; this is also true for *cortisol*. Over the long term, both growth hormone and cortisol may also increase glucose production.

BOX 124-1 CLASSIFICATION OF DIABETES MELLITUS AND OTHER CATEGORIES OF GLUCOSE INTOLERANCE

Diabetes Mellitus
Type 1 (or type I, formerly "insulin-dependent")
- Immune-mediated
- Idiopathic

Type 2 (or type II, formerly "non-insulin-dependent")
Other specific types
- Genetic defects of beta-cell function
- Genetic defects in insulin action
- Diseases of exocrine pancreas
- Endocrinopathies
- Drug- or chemical-induced
- Infections
- Uncommon forms of immune-mediated diabetes
- Other genetic syndromes sometimes associated with diabetes

Gestational Diabetes Mellitus

Impaired Glucose Tolerance
Impaired fasting glucose

From American Diabetes Association: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 20:1183, 1997.

Types of Diabetes

The National Diabetes Data Group (NDDG) defines four major types of diabetes mellitus: type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, and IGT/IFG (Box 124-1).[7] The 1997 NDDG report discontinued the use of the terms "insulin-dependent diabetes mellitus" and "non-insulin-dependent diabetes mellitus" because they are confusing and clinically inaccurate. The group also recommended that Arabic numerals 1 and 2 be used to replace roman numerals I and II in the designation of types "one" and "two."[7]

Type 1 Diabetes Mellitus

Type 1 (or I) diabetes is characterized by abrupt failure of production of insulin with a tendency to ketosis even in the basal state. Parenteral insulin is required to sustain life. From 85 to 90% of patients with type 1 diabetes demonstrate evidence of one or more autoantibodies implicated in the cell-mediated autoimmune destruction of the beta cells of the pancreas. Strong human leukocyte antigen (HLA) associations are also found in type 1 diabetes. The autoimmune destruction has multiple genetic predispositions and may be related to undefined environmental insults.[7]

Type 2 Diabetes Mellitus

Patients with type 2 (or II) diabetes may remain asymptomatic for long periods and show low, normal, or elevated levels of insulin because of insulin resistance. Ketosis is rare in type 2 disease. Patients have a high incidence of obesity. No association exists with viral infections, islet cell autoantibodies, or HLA expression. Hyperinsulinemia may be related to peripheral tissue resistance to insulin because of defects in the insulin receptor.[8] Defects in muscle glycogen synthesis have an important role in the insulin resistance that occurs in type 2. A subgroup of patients who develop type 2 disease before 25 years of age have a mutation in the glucokinase gene and on chromosome 7.[9]

Gestational Diabetes

Gestational diabetes "mellitus" is characterized by an abnormal oral glucose tolerance test (OGTT) that occurs during pregnancy and either reverts to normal during the postpartum period or remains abnormal. The clinical pathogenesis is thought to be similar to that of type 2. The clinical presentation is usually nonketotic hyperglycemia during pregnancy.

Impaired Glucose Tolerance

A fourth category is impaired glucose tolerance (IGT) and its analogue, *impaired fasting glucose* (IFG). This group is composed of persons whose plasma glucose levels are between normal and diabetic and who are at increased risk for the development of diabetes and cardiovascular disease. The pathogenesis is thought to be related to insulin resistance.[6] Presentations of IGT/IFG include nonketotic hyperglycemia, insulin resistance, hyperinsulinism, and often obesity.

IGT/IFG differs from the other classes in that it is not associated with the same degree of complications of diabetes mellitus. Many of these patients even spontaneously develop normal glucose tolerance. The emergency physician, however, should not be complacent about the patient with IGT because the decompensation of this group into the category of diabetes mellitus is 1 to 5% per year.[10,11]

Epidemiology

The prevalence of diabetes is difficult to determine because many standards have been used. The NDDG, using the 75-g OGTT as the diagnostic criterion, estimates the prevalence as 6.6%, with 11.2% of the population having IGT.[4] These figures are probably too high because most subjects diagnosed with IGT or diabetes by OGTT never develop the disease.[4] The true prevalence of the disease is probably 6.3% of the population.[12] Approximately 5 to 10% of these patients have type 1, and 90 to 95% have type 2.[3] Some groups have a much higher rate of diabetes, such as the Pima Native Americans, who have a 40% rate of type 2 disease; however, diabetes mellitus is significantly more prevalent in whites than in nonwhites.[13]

The peak age of onset of type 1 diabetes is 10 to 14 years. Approximately 1 of every 600 schoolchildren has this disease. In the United States the prevalence of type 1 is approximately 0.26% by age 20 years, and the lifetime prevalence approaches 0.4%. The annual incidence among persons from birth to 16 years of age in the United States is 12 to 14 per 1 million population. The incidence is age-dependent, increasing from near-absence during infancy to a peak occurrence at puberty and another small peak at midlife.[14]

The morbidity in diabetes is related mostly to its vascular complications. A mortality rate of 36.8% has been related to cardiovascular causes, 17.5% to cerebrovascular causes, 15.5% to diabetic comas, and 12.5% to renal failure.

Pathophysiology and Etiology

Type 1 diabetes results from a chronic autoimmune process that usually exists in a preclinical state for years.[5] The classical manifestations of type 1—hyperglycemia and ketosis—occur late in the course of the disease, an overt sign of beta-cell destruction.

The most striking feature of long-standing type 1 diabetes is the near-total lack of insulin-secreting beta cells and insulin, with the preservation of glucagon-secreting alpha cells, somatostatin-secreting delta cells, and pancreatic polypeptide-secreting cells.

Although the exact cause of diabetes remains unclear, research has provided many clues. Studies of the pathogenesis of diabetes mellitus have demonstrated that the cause of the disordered glucose homeostasis varies from individual to individual.[15,16] This cause may determine the presentation in each patient. Individual patients are currently not studied for the source of their disease except on an experimental basis. The goals of the work in progress, however, are to identify who is susceptible to the development of diabetes and to prevent diabetic emergencies and sequelae or to prevent expression of the disease.

A genetic basis for diabetes is suggested by the association of type 1 disease with certain HLA markers and by the findings of numerous twin and family studies.[5,17] Families who move from areas with a low frequency of type 1 diabetes to areas with a high frequency have an incidence of disease similar to that in the areas where they reside; this suggests an environmental basis for diabetes. An autoimmune cause has been clearly demonstrated in many type 1 diabetic patients. Islet cell amyloid has also been associated with diabetes. In both types, a variety of viruses have been implicated, most notably congenital rubella, coxsackievirus B, and cytomegalovirus.

Research has identified two groups of cellular carbohydrate transporters in cell membranes. Sodium-linked glucose transporters are found primarily in the intestine and kidney. The glucose transporter (GLUT) proteins are found throughout the body and transport glucose by facilitated diffusion down concentration gradients. The GLUT-4 transporter, found primarily in muscle, is insulin-responsive, and a signaling defect in the protein may be responsible for insulin resistance in some diabetic patients.[18]

CLINICAL FEATURES

Type 1

The patient with type 1 diabetes is usually lean, younger than 40 years of age, and ketosis-prone. Plasma insulin levels are absent to low; plasma glucagon levels are high but suppressible with insulin, and patients require insulin therapy when symptoms appear. Onset of symptoms may be abrupt, with polydipsia, polyuria, polyphagia, and weight loss developing rapidly. In some cases the disease is heralded by ketoacidosis.[4] A myriad of problems related to type 1 diabetes may prompt an ED visit, including acute metabolic complications such as DKA and late complications such as cardiovascular or circulatory abnormalities, retinopathy, nephropathy, neuropathy, foot ulcers, severe infections, and various skin lesions.

Type 2

The patient with type 2 diabetes is usually middle-aged or older, overweight, with normal to high insulin levels. Insulin levels are lower than would be predicted for glucose levels, however, leading to a relative insulin deficiency, probably because of an insulin secretory defect.[4] All type 2 patients demonstrate impaired insulin function related to poor insulin production, failure of insulin to reach the site of action, or failure of end-organ response to insulin.

As with type 1 diabetes, research suggests distinct subgroups of patients fall within the classification of type 2 diabetes. Although most adult patients are obese, 20% are not. Nonobese patients form a subgroup with a different disease, more similar to type 1. Another subgroup comprises young persons with maturity-onset diabetes.[9] They have an autosomal dominant inheritance of their disease, are usually not obese, and have a relatively mild course of disease.

Symptoms tend to begin more gradually in type 2 diabetes than in type 1. The diagnosis of type 2 is often made because of an elevated blood glucose found on routine laboratory examination. Glucose may be controlled by dietary therapy, oral hypoglycemic agents, or insulin administration, depending on the individual. Decompensation of disease usually leads to hyperosmolar nonketotic coma rather than ketosis.

Type 2 diabetes is increasingly being diagnosed in children and adolescents.[19]

DIAGNOSTIC STRATEGIES

Serum Glucose

As a rule, any random plasma glucose level greater than 200 mg/dL, a fasting plasma glucose concentration greater than 126 mg/dL, or a 2-hour postload OGTT is sufficient to establish the diagnosis of diabetes. In the absence of hyperglycemia with metabolic decompensation, these criteria should be confirmed by repeat testing on a different day.[7] A value of 150 mg/dL is likely to distinguish diabetic from nondiabetic patients more accurately. Formal OGTTs are unnecessary except during pregnancy or in patients who are thought to have diabetes but who do not meet the criteria for a particular classification. The World Health Organization and NDDG provide protocols for performance of the OGTT.

Glycosylated Hemoglobin

Measurement of glycosylated hemoglobin (HbA_{1c}) is one of the most important ways to assess the level of glucose control. Elevated serum glucose binds progressively and irreversibly to the amino-terminal valine of the hemoglobin beta-chain. The HbA_{1c} measurement provides insight into the quality of glycemic control over time. Given the long half-life of red blood cells, the percentage of HbA_{1c} is an index of glucose concentration of the preceding 6 to 8 weeks, with normal values approximately 4 to 6% of total hemoglobin, depending on the assay used.[20] Levels in patients with poorly controlled disease may reach 10 to 12%. Measurement of glycated albumin can be used to monitor diabetic control over 1 to 2 weeks because of its short half-life but is rarely used clinically. The American Diabetes Association (ADA) recommends at least biannual measurements of HbA_{1c} for the follow-up of all types of diabetes.[20] The ADA currently sets an HbA_{1c} of less than 7% as a treatment goal.[21]

Urine Glucose

Urine glucose measurement methods are basically of two types: reagent tests and dipstick tests. The reagent tests (e.g., Clinitest) are copper reduction tests. They are somewhat more cumbersome and expensive than dipstick methods, use tablets that are very caustic and dangerous if accidentally ingested, and may be affected by many substances (Box 124-2).

Dipstick tests generally use glucose oxidase, which may also be affected by different substances (Box 124-3). Dipsticks are inexpensive and convenient but may vary in their sensitivity and strength of reaction to a given concentration of glucose. Dipstick interpretation can vary significantly, depending on the observer and the type of lighting. Both falsely high and falsely low urine glucose readings can also occur.[22] With the "plus" system, one-plus, two-plus, three-plus, and four-plus have different implications about urine glucose concentrations, depending on the brand of dipstick. Using reflectance colorimeters to read dipsticks increases accuracy. Urine glucose tests must be interpreted loosely because many factors can affect their results.

BOX 124-2 SUBSTANCES INTERFERING WITH COPPER REDUCTION TESTS (FALSE-POSITIVE RESULTS)

Ascorbic acid
Cephaloridine
Cephalothin
Dilute urine
Gentisic acid (aspirin)
Glucuronic acid conjugates
Homogentisic acid
Isoniazid
Lactose in pregnant women
Levodopa
Metaxalone (Skelaxin)
Methyldopa
Penicillin
Probenecid
Reducing sugars
Salicylates
Streptomycin

From Contemp Pharm Pract 3:224, 1980.

BOX 124-3 SUBSTANCES INTERFERING WITH GLUCOSE OXIDASE TESTS

False-Positive Results
Chloride glucose hypochlorite
Glutathione
Homogentisic acid
Hydrogen peroxide

False-Negative Results
Ascorbic acid
Aspirin
Bilirubin
Catalase
Catechol
Cysteine
3,4-Dihydroxyphenylacetic acid
L-Dopamine
Epinephrine
Ferrous sulfate (Feosol)
Gentisic acid
5-Hydroxyindoleacetic acid
5-Hydroxytryptamine
5-Hydroxytryptophan
Levodopa
Meralluride injection
Methyldopa (Aldomet)
Sodium bisulfate
Tetracycline (with vitamin C)
Uric acid

From Contemp Pharm Pract 3:224, 1980.

Urine Ketones

Urine ketone dipsticks use the nitroprusside reaction, which is a good test for acetoacetate but does not measure β-hydroxybutyrate. Although the usual acetoacetate/β-hydroxybutyrate ratio in diabetic ketoacidosis is 1:2.8, it may be as high as 1:30, in which case the urine dipstick does not reflect the true level of ketosis. When ketones are in the form of β-hydroxybutyrate, the urine ketone dipsticks may infrequently yield negative reactions in patients with significant ketosis.

Dipstick Blood Glucose

Dipsticks for testing blood glucose are clearly a more accurate means of monitoring blood glucose than urine dipsticks but also may be inaccurate. Hematocrits below 30% or above 55% cause unduly high or low readings, respectively, and a number of the strips specifically disclaim accuracy when used for neonates. Sensitivity of dipsticks to a variety of factors varies with the particular brand. The largest errors are in the hyperglycemic range. Dipstick readings rarely err more than 30 mg/dL when actual concentrations are below 90 mg/dL. Although specific glucose concentrations may not be accurately represented, blood glucose dipsticks are useful in estimating the general range of the glucose value. Reflectance meters increase the accuracy of the dipstick blood glucose determination. If maximum accuracy is desired, a laboratory blood glucose level should be obtained.

HYPOGLYCEMIA

Hypoglycemia is a common problem in patients with type 1 diabetes, especially if tight glycemic control is practiced, and may be the most dangerous acute complication of diabetes. The estimated incidence of hypoglycemia in diabetic patients is 9 to 120 episodes per 100 patient-years.[23-25] As significant efforts continue to keep both fasting and postprandial glucose within the normal range, the incidence of hypoglycemia may increase. The most common cause of coma associated with diabetes is an excess of administered insulin with respect to glucose intake. Hypoglycemia may be associated with significant morbidity and mortality. Severe hypoglycemia is usually associated with a blood sugar level below 40 to 50 mg/dL and impaired cognitive function.[26]

Principles of Disease

Protection against hypoglycemia is normally provided by cessation of insulin release and mobilization of counter-regulatory hormones, which increase hepatic glucose production and decrease glucose use. Diabetic patients using insulin are vulnerable to hypoglycemia because of insulin excess and failure of the counter-regulatory system.[4]

Hypoglycemia may be caused by missing a meal, increasing energy output, or increasing insulin dosage. It can also occur in the absence of any precipitant (Box 124-4). Oral hypoglycemic agents have also been implicated in causing hypoglycemia, both in the course of therapy and as an agent of overdose.

Hypoglycemia without warning, or *hypoglycemia unawareness*, is a dangerous complication of type 1 diabetes probably caused by previous exposure to low blood glucose concentrations.[26] Even a single hypoglycemic episode can reduce neurohumoral counter-regulatory responses to subsequent episodes.[27,28] Other factors associated with recurrent hypoglycemic attacks include overaggressive or intensified insulin therapy, longer history of diabetes, autonomic neuropathy, and decreased epinephrine secretion or sensitivity.[26]

The *Somogyi phenomenon* is a common problem associated with iatrogenic hypoglycemia in the type 1 diabetic patient. The phenomenon is initiated by an excessive insulin dosage that results in an unrecognized hypoglycemic episode that usually occurs in the early morning while the patient is sleeping. The counter-regulatory hormone response produces rebound hyperglycemia, evident when the patient awakens. Often, both the patient and the physician interpret this hyperglycemia as an indication to increase the insulin dosage, which exacerbates the problem.[29] Instead, the insulin dosage should be lowered or the timing changed.

BOX 124-4 PRECIPITANTS OF HYPOGLYCEMIA IN DIABETIC PATIENTS

Addison's disease
Akee fruit
Anorexia nervosa
Antimalarials
Decrease in usual food intake
Ethanol
Factitious hypoglycemia
Hepatic impairment
Hyperthyroidism
Hypothyroidism
Increase in usual exercise
Insulin
Islet cell tumors
Malfunctioning, improperly adjusted, or incorrectly used insulin pump
Malnutrition
Old age
Oral hypoglycemics
Overaggressive treatment of diabetic ketoacidosis and hyperglycemic hyperosmolar nonketotic coma
Pentamidine
Phenylbutazone
Propranolol
Recent change of dose or type of insulin or oral hypoglycemic
Salicylates
Sepsis
Some antibacterial sulfonylureas
Worsening renal insufficiency

Clinical Features

Symptomatic hypoglycemia occurs in most adults at a blood glucose level of 40 to 50 mg/dL. The rate at which glucose decreases, however, as well as the patient's age, gender, size, overall health, and previous hypoglycemic reactions all contribute to symptom development. Signs and symptoms of hypoglycemia are caused by excessive secretion of epinephrine and CNS dysfunction and include sweating, nervousness, tremor, tachycardia, hunger, and neurologic symptoms ranging from bizarre behavior and confusion to seizures and coma.[23] In patients with hypoglycemia unawareness, the prodrome to marked hypoglycemia may be minimal or absent. These individuals may rapidly become unarousable without warning. They may have a seizure or show focal neurologic signs, which resolve with glucose administration.

Diagnostic Strategies

The cardinal laboratory test for hypoglycemia is blood glucose. It should be obtained, if possible, before therapy is begun. As noted, dipstick readings are very helpful in permitting rapid, reasonably accurate blood glucose estimates before therapy.

Laboratory testing should address any suggested cause of the hypoglycemia, such as ethanol or other drug ingestion. If factitious hypoglycemia is suggested, testing for insulin antibodies or low levels of C peptide may be helpful. A patient who is surreptitiously administering exogenous insulin will have normal to low levels of C peptide and markedly elevated insulin levels.

BOX 124-5 SUMMARY OF TREATMENT FOR HYPOGLYCEMIA

1. Consider hypoglycemia.
   Check serum glucose; obtain sample before treatment.
   If clinical suggestion of hypoglycemia is strong, proceed before laboratory results are available.
2. Correct serum glucose.
   If patient is awake and cooperative, administer sugar-containing food or beverage PO.
   If patient is unable to take PO:
   25–75 g glucose as $D_{50}W$ (1–3 ampules) IV
   Children: 0.5–1 g/kg glucose as $D_{25}W$ IV (2–4 mL/kg)
   Neonates: 0.5–1 g/kg glucose (1–2 mL/kg) as $D_{10}W$
   If unable to obtain IV access:
   1–2 mg glucagon IM or SC; may repeat q20min
   Children: 0.025–0.1 mg/kg SC or IM; may repeat q20min

$D_{10}W$, 10% dextrose in water; $D_{25}W$, 25% dextrose in water; $D_{50}W$, 50% dextrose in water; IM, intramuscular; IV, intravenous; PO, by mouth; SC, subcutaneous.

Management

In alert patients with mild symptoms, oral consumption of sugar-containing foods or beverages is often adequate (Box 124-5). In other patients, after blood is drawn for glucose determination, one to three ampules of 50% dextrose in water ($D_{50}W$) should be administered intravenously while the patient's airway, breathing, and circulation are assessed and maintained. Augmentation of the blood glucose level by administering an ampule of $D_{50}W$ may range from less than 40 to more than 350 mg/dL.[30] These therapeutic steps are appropriately performed in the field if out-of-hospital care is available. If alcohol abuse is suggested, thiamine should also be administered. $D_{50}W$ should not be used in infants or young children because venous sclerosis can lead to rebound hypoglycemia. In a child younger than 8 years it is advisable to use 25% ($D_{25}W$) or even 10% dextrose ($D_{10}W$). $D_{25}W$ may be prepared by diluting $D_{50}W$ 1:1 with sterile water. The dose is 0.5 to 1 g/kg body weight or, using $D_{25}W$, 2 to 4 mL/kg.

If intravenous (IV) access cannot be rapidly obtained, 1 to 2 mg of glucagon may be given intramuscularly or subcutaneously.[31] The onset of action is 10 to 20 minutes, and peak response occurs in 30 to 60 minutes. It may be repeated as needed. Glucagon may also be administered intravenously; 1 mg has an effect very similar to that of one ampule of $D_{50}W$. Glucagon is ineffective in causes of hypoglycemia in which glycogen is absent, notably alcohol-induced hypoglycemia.

Families of type 1 diabetic patients are often taught to administer intramuscular glucagon at home. Of the families so instructed, only 9 to 42% actually inject the glucagon when indicated.[32] Intranasal glucagon may become more widely accepted.[33] Out-of-hospital care providers and emergency physicians should seek a history of glucagon administration because it alters initial blood glucose readings.

All patients with severe hypoglycemic reactions require aspiration and seizure precautions. Although the response to IV glucose is generally rapid, older patients may require several days for complete recovery.

Oral hypoglycemic agents pose special problems because the hypoglycemia they induce tends to be prolonged and severe. There are isolated case reports in which hypoglycemia was delayed in onset by as much as 24 hours and recurred more than 72 hours later. Chlorpropamide is particularly troublesome in this respect. Thus, patients with overdose of oral hypoglycemic agents should have a minimum observation period of 24 hours and longer if hypoglycemia is recurrent.

Patients at risk for hypoglycemia from oral sulfonylureas include patients with impaired renal function; pediatric patients; and patients who are naive to hypoglycemic agents. Although symptoms may occur after an overdose, in patients with renal failure and pediatric patients, refractory hypoglycemia has been reported with a single pill.

Treatment of hypoglycemia secondary to oral hypoglycemic agents depends on the agent. Metformin and the thiazolidinedione agents rarely cause significant or prolonged hypoglycemia, whereas sulfonylureas, which are insulin secretagogues, do cause hypoglycemia. A patient with hypoglycemia from sulfonylureas, in addition to standard glucose replacement, frequently requires treatment with an agent to inhibit further insulin release, such as octreotide, a somatostatin analogue. Several case series reporting the use of octreotide in both adult and pediatric patients suffering from sulfonylurea-induced hypoglycemia have been described, frequently reporting successful results with a significant decrease in the number of episodes of recurrent hypoglycemia.[34,35] No single set protocol for their use has been described; however, typical adult doses have ranged from 50 to 100 µg IV or SQ every 12 hours and pediatric dosages of 25 to 50 µg IV or SQ. Data on the use of octreotide is promising though it does not obviate the need for prolonged observation and serial glucose measurements.

When therapy for hypoglycemia has been given, a careful history must be taken to determine the cause.

Disposition

Type 1 diabetic patients with brief episodes of hypoglycemia uncomplicated by other disease may be discharged from the ED if a cause of the hypoglycemia can be identified and corrected by instruction or medication. All patients should be given a meal before discharge to ensure their ability to tolerate oral feedings and to begin to replenish glycogen stores in glycogen-deficient patients. Patients who are discharged should receive short-term follow-up for ongoing evaluation. Patients with hypoglycemia caused by oral agents should be observed in the hospital because of the high likelihood of recurrent hypoglycemia.

Nondiabetic Patients

Hypoglycemia in the nondiabetic patient may be classified as postprandial or fasting (Box 124-6). The most common cause of *postprandial hypoglycemia* is alimentary hyperinsulinism, such as that seen in patients who have undergone gastrectomy, gastrojejunostomy, pyloroplasty, or vagotomy. *Fasting hypoglycemia* is caused when there is an imbalance between glucose production and use. The causes of inadequate glucose production include hormone deficiencies, enzyme defects, substrate deficiencies, severe liver disease, and drugs. Causes of overuse of glucose include the presence of an insulinoma, exogenous insulin, sulfonylureas, drugs, endotoxic shock, extrapancreatic tumors, and a variety of enzyme deficiencies.

Emergency treatment is similar to that of hypoglycemia in the diabetic patient. The determination of inpatient versus outpatient evaluation of hypoglycemia in a nondiabetic patient should be based on the suggested cause and the nature of the episode (i.e., factors such as severity, persistence, and recurrence).

BOX 124-6 CAUSES OF HYPOGLYCEMIA

Postprandial
Alimentary hyperinsulinism
Fructose intolerance
Galactemia
Leucine sensitivity

Fasting
Underproduction of Glucose
Hormone deficiencies
- Hypopituitarism
- Adrenal insufficiency
- Catecholamine deficiency
- Glucagon deficiency

Enzyme defects
Substrate deficiency
- Malnutrition
- Late pregnancy

Liver disease
Drugs

Overuse of Glucose
Hyperinsulinism
- Insulinoma
- Exogenous insulin
- Sulfonylureas
- Drugs
- Shock

Tumors

DIABETIC KETOACIDOSIS

Principles of Disease

Pathophysiology

DKA is a syndrome in which insulin deficiency and glucagon excess combine to produce a hyperglycemic, dehydrated, acidotic patient with profound electrolyte imbalance (Fig. 124-1).[36] All derangements producing DKA are interrelated and are based on insulin deficiency. DKA may be caused by cessation of insulin intake or by physical or emotional stress despite continued insulin therapy.

The effects of insulin deficiency may be mimicked in peripheral tissues by a lack of either insulin receptors or insulin sensitivity at receptor or postreceptor sites. When the hyperglycemia becomes sufficiently marked, the renal threshold is surpassed and glucose is excreted in the urine. The hyperosmolarity produced by hyperglycemia and dehydration is the most important determinant of the patient's mental status.[37]

Glucose in the renal tubules draws water, sodium, potassium, magnesium, calcium, phosphorus, and other ions from the circulation into the urine. This osmotic diuresis combined with poor intake and vomiting produces the profound dehydration and electrolyte imbalance associated with DKA (Table 124-1). Exocrine pancreatic dysfunction closely parallels endocrine beta-cell dysfunction, producing malabsorption that further limits the body's intake of fluid and exacerbates electrolyte loss.

In 95% of patients with DKA, the total sodium level is normal or low. Potassium, magnesium, and phosphorus deficits

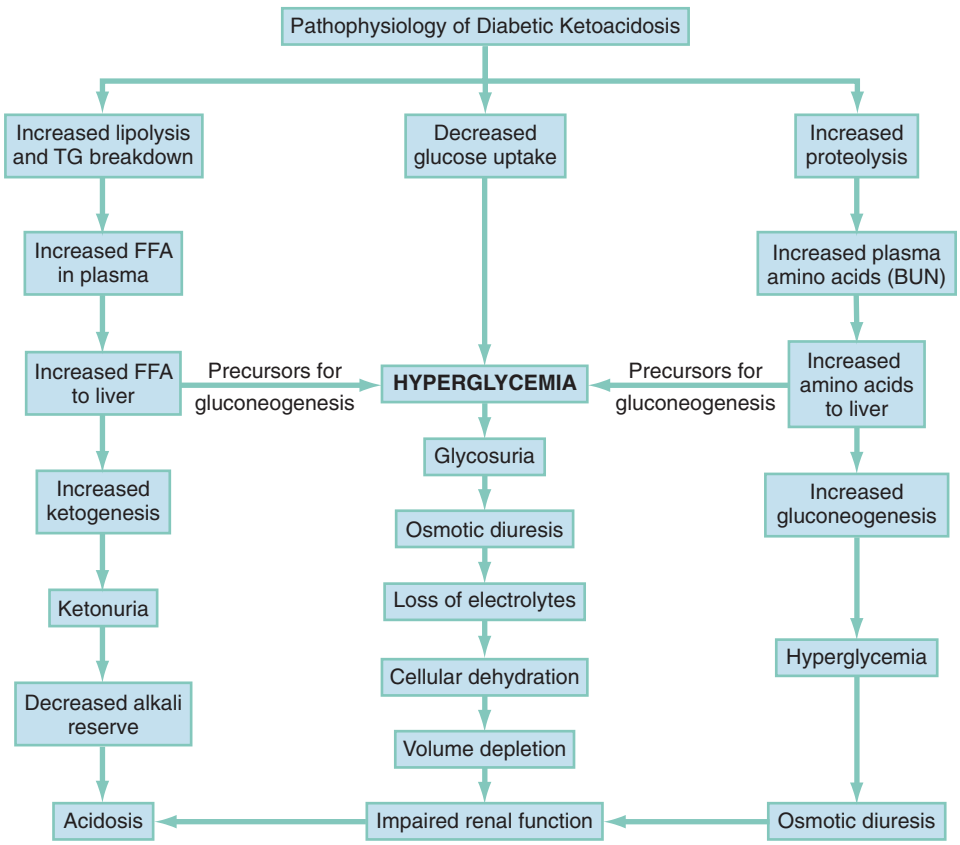

Figure 124-1. Syndrome of diabetic ketoacidosis. BUN, blood urea nitrogen; FFA, free fatty acids; TG, total glucose concentration.

Table 124-1 Average Fluid and Electrolyte Deficits in Severe Diabetic Ketoacidosis (per Kilogram Body Weight)

WEIGHT	WATER (ML/KG)	SODIUM (MEQ/L)	POTASSIUM (MEQ/L)	CHLORIDE (MEQ/L)	PHOSPHORUS (MEQ/L)
<10 kg	100–120	8–10	5–7	6–8	3
10–20 kg	80–100	8–10	5–7	6–8	3
>20 kg	70–80	8–10	5–7	6–8	3

are usually marked. As a result of acidosis and dehydration, however, the initial reported values for these electrolytes may be higher than actual body stores. Hypokalemia may further inhibit insulin release.

The cells, unable to receive fuel substances from the circulation, act as they do in starvation from other causes. They decrease amino acid uptake and accelerate proteolysis such that large amounts of amino acids are released to the liver and converted to two-carbon fragments.

Adipose tissue in the patient with DKA fails to clear the circulation of lipids. Insulin deficiency results in activation of a hormone-sensitive lipase that increases circulating free fatty acid (FFA) levels. Long-chain FFAs, now circulating in abundance as a result of insulin deficiency, are partially oxidized and converted in the liver to acetoacetate and β-hydroxybutyrate. This alteration of liver metabolism to oxidize FFAs to ketones rather than the normal process of re-esterification to triglycerides appears to correlate directly with the altered glucagon/insulin ratio in the portal blood. Despite the increased pathologic glucagon-mediated production of ketones, the body acts as it does in any form of starvation, to decrease the peripheral tissue's use of ketones as fuel. The combination of increased ketone production with decreased ketone use leads to ketoacidosis.

The degree of ketosis has been related to the magnitude of release of the counter-regulatory hormones epinephrine, glucagon, cortisol, and somatostatin. Glucagon is elevated fourfold to fivefold in DKA and is the most influential ketogenic hormone. It is believed to affect ketogenesis by reducing the concentration of malonyl coenzyme A and by inhibiting glycolysis. Epinephrine, norepinephrine, cortisol, growth hormone, dopamine, and thyroxin have all been shown to enhance ketogenesis indirectly by stimulating lipolysis. Because propranolol and metyrapone can block the effect of counter-regulatory hormones, they have been successfully used to inhibit the development of DKA in patients with frequent episodes not otherwise treatable.

Acidosis plays a prominent role in the clinical presentation of DKA. The acidotic patient attempts to increase lung ventilation and rid the body of excess acid with Kussmaul's respiration. Bicarbonate is used up in the process. Current evidence suggests that acidosis compounds the effects of ketosis and hyperosmolality to depress mental status directly.

Acidemia is not invariably present, even with significant ketoacidosis. *Ketoalkalosis* has been reported in diabetic patients vomiting for several days and in some with severe dehydration and hyperventilation. The finding of alkalemia, however, should prompt the consideration of alcoholic ketoacidosis, in which this finding is much more common.

Etiology

Most often, DKA occurs in patients with type 1 diabetes and is associated with inadequate administration of insulin, infection, or myocardial infarction (MI). DKA can also occur in type 2 patients and may be associated with any type of stress, such as sepsis or gastrointestinal (GI) bleeding. Approximately 25% of all episodes of DKA occur in patients whose diabetes was previously undiagnosed.[6,38]

Table 124-2 Typical Laboratory Values in Diabetic Ketoacidosis (DKA) and Hyperglycemic Hyperosmolar Nonketotic Coma (HHNC)

	DKA	HHNC
Glucose (mg/dL)	>350	>700
Sodium (mEq)	low 130s	140s
Potassium (mEq)	≈ 4.5–6.0	≈ 5
Bicarbonate (mEq)	<10	>15
BUN (mg/dL)	25–50	>50
Serum ketones	Present	Absent

BUN, blood urea nitrogen.

Diagnostic Strategies

History

Clinically, most patients with DKA complain of a recent history of polydipsia, polyuria, polyphagia, visual blurring, weakness, weight loss, nausea, vomiting, and abdominal pain. Approximately one half of these patients, especially children, report abdominal pain. In children this pain is usually idiopathic and probably caused by gastric distention or stretching of the liver capsule; it resolves as the metabolic abnormalities are corrected. In adults, however, abdominal pain more often signifies true abdominal disease.

Physical Examination

Physical examination may or may not demonstrate a depressed sensorium. Typical findings include tachypnea with Kussmaul's respiration, tachycardia, frank hypotension or orthostatic blood pressure changes, the odor of acetone on the breath, and signs of dehydration.[39] An elevated temperature is rarely caused by DKA itself and suggests the presence of infection.

Laboratory Tests

Initial tests allow preliminary confirmation of the diagnosis and immediate initiation of therapy (Table 124-2). Subsequent tests are made to determine more specifically the degree of dehydration, acidosis, and electrolyte imbalance and to reveal the precipitant of DKA.

On the patient's arrival to the ED, serum and urine glucose and ketones, electrolytes, and arterial blood gases (ABGs) should be checked. Glucose is usually elevated above 350 mg/dL; however, euglycemic DKA (blood glucose < 300 mg/dL) has been reported in up to 18% of patients.[4] ABGs demonstrate a low pH. Venous pH is not significantly different from arterial pH in patients with DKA, and some researchers con-

sider the use of venous blood superior to repeated arterial puncture. Metabolic acidosis with an anion gap is primarily the result of elevated plasma levels of acetoacetate and β-hydroxybutyrate, although lactate, FFAs, phosphates, volume depletion, and several medications also contribute to this condition.[4] Rarely, a well-hydrated patient with DKA may have a pure hyperchloremic acidosis with no anion gap. If an immediate potassium level is not available through ABG, an electrocardiogram may indicate potassium levels. Despite initial potassium levels that are normal to high, a total potassium deficit of several hundred milliequivalents results from potassium and hydrogen shifts.

Other tests may include complete blood count with differential, magnesium, calcium, amylase, blood urea nitrogen (BUN), creatinine, phosphorus, ketone, and lactate level determinations. A complete urinalysis helps in the determination of possible infection or renal disease. Elevations of urine specific gravity, BUN, and hematocrit suggest dehydration. Appropriate cultures should be dictated by clinical findings.

The serum sodium value is often misleading in DKA. Sodium is often low in the presence of significant dehydration because it is strongly affected by hyperglycemia; hypertriglyceridemia; salt-poor fluid intake; and increased GI, renal, and insensible losses. When hyperglycemia is marked, water flows from the cells into the vessels to decrease the osmolar gradient, thereby creating dilutional hyponatremia. Lipids also dilute the blood, thereby further lowering the value of sodium. Newer autoanalyzers remove triglycerides before assay, thus eliminating this artifact.

Hypertriglyceridemia is common in DKA because of impaired lipoprotein lipase activity and hepatic overproduction of very-low-density lipoproteins.[4] In the absence of marked lipidemia, the true value of sodium may be approximated by adding 1.3 to 1.6 mEq/L to the sodium value on the laboratory report for every 100 mg/dL glucose over the norm. Thus, if the laboratory reports a serum sodium value of 130 mEq/L and a blood glucose value of 700 mEq/L, the total serum sodium value is more accurately assessed to be between 137.8 and 139.6 mEq/L.

Acidosis and the hyperosmolarity induced by hyperglycemia shift potassium, magnesium, and phosphorus from the intracellular to the extracellular space. Dehydration produces hemoconcentration, which contributes to normal or high initial serum potassium, magnesium, and phosphorus readings in DKA, even with profound total body deficits. The effect of acidosis on the serum potassium determination can be corrected by subtracting 0.6 mEq/L from the laboratory potassium value for every 0.1 decrease in pH noted in the ABG analysis.[40] Thus, if the potassium is reported as 5 mEq/L and the pH is 6.94, the corrected potassium value would be only 2 mEq/L, representing severe hypokalemia. While insulin is administered and the hydrogen ion concentration decreases, the patient needs considerable potassium replacement. Finally, hyperglycemia and the anion gap have significant effects on the plasma potassium concentration, independent of acidosis.[37] No conversion factor has been developed for estimating true magnesium levels, although initial values may be high.

All laboratory determinations must be interpreted with caution. Serum creatinine determinations made by autoanalyzer may be falsely elevated.[36] Leukocytosis more closely reflects the degree of ketosis than the presence of infection. Only the elevation of band neutrophils has been demonstrated to indicate the presence of infection, with a sensitivity of 100% and a specificity of 80%. The diagnosis of pancreatitis is confounded by the usually elevated urine and serum amylase levels in DKA. Typically, this is salivary amylase, but most laboratories are not equipped to make this distinction. A serum lipase determination helps to distinguish pancreatitis from elevated salivary amylase levels.

Differential Considerations

Alcoholics, especially those who have recently abstained from drinking, with Kussmaul's respiration, a fruity odor to the breath, and acidemic ABG values may have alcoholic ketoacidosis. These patients may be euglycemic or hypoglycemic, and a large part of their acidosis is often caused by the unmeasured β-hydroxybutyric acid. Alcoholic ketoacidosis accounts for approximately 20% of all cases of ketoacidosis.

Ketoacidosis can also develop with fasting in the third trimester of pregnancy and in nursing mothers who do not eat.[41]

Other entities that may manifest with various combinations of altered mental status, acidosis, and abdominal pain include hypoglycemia, cerebrovascular accident (stroke), trauma, sepsis, hyperglycemic hyperosmolar nonketotic coma, postictal states, lactic acidosis, uremic acidosis, and abdominal emergencies. Intoxications by ethanol, salicylates, methanol, isopropyl alcohol, chloral hydrate, paraldehyde, ethylene glycol, and cyanide all share some features of DKA.

Management

General Measures

The approach to the patient with severe DKA is the same as that to any patient in extremis. The comatose patient, especially if vomiting, requires intubation. Once the patient is intubated, hyperventilation should be maintained to prevent worsening acidosis. The patient in hypovolemic shock requires aggressive fluid resuscitation with 0.9% saline solution rather than pressors. Other possible causes of shock (e.g., sepsis or myocardial dysfunction secondary to MI) should be considered. Close monitoring of vital signs is essential. In the patient whose therapy may precipitate fluid overload caused by cardiac compromise or renal failure, a central venous pressure line or Swan-Ganz catheter should be inserted.

The diagnosis of DKA is generally simple. When hyperglycemia, ketosis, and acidosis have been established, fluid, electrolyte, and insulin therapy should begin (Box 124-7).

Insulin

DKA cannot be reversed without insulin, and insulin therapy should be initiated as soon as the diagnosis is certain. In the past, very high dosages of insulin were administered to diabetic patients in DKA because they were thought to be extremely insulin-resistant. However, low-dosage insulin therapy has proved as effective as high-dosage therapy.[6] The rate of decrease in blood sugar is equal or only slightly more gradual. The overall potassium requirement is less. High dosages of insulin have potentially harmful effects, including a greater incidence of iatrogenic hypoglycemia and hypokalemia.[36]

The exact amount of insulin administered varies. Many start therapy with a bolus of 10 U of regular insulin intravenously. This initial bolus may produce certain problems, however, and makes no significant difference in therapy.[42] The current therapy of choice is regular insulin infused at 0.1 U/kg/hr up to 5 to 10 U/kg/hr, mixed with the IV fluids. Regular insulin, 10 to 20 U/hr, administered intramuscularly accomplishes similar effects but subjects the patient to repeated painful injections. In theory, intramuscular insulin may accumulate at a poorly perfused administration site, failing to enter the systemic circulation in a timely manner.

BOX 124-7 SUMMARY OF TREATMENT FOR DIABETIC KETOACIDOSIS

Identify DKA: serum glucose, electrolytes, ketones, and ABG; also draw CBC with differential; urinalysis; chest radiograph film and ECG, if indicated.

1. Supplement insulin.
   ± Bolus: 0.1 U/kg regular insulin IV
   Maintenance: 0.1 U/kg regular insulin IV
   Change IV solution to D_5W 0.45% NS when glucose ≤ 300 mg/dL.
2. Rehydrate.
   1–2 L NS IV over 1–3 hours
   Children: 20 mL/kg NS over first hour
   Follow with 0.45% NS
3. Correct electrolyte abnormalities.
   Sodium
   Correct with administration of NS and 0.45% NS.
   Potassium
   Ensure adequate renal function.
   Add 20–40 mEq KCl to each liter of fluid.
   Phosphorus
   Usually unnecessary to replenish
   Magnesium
   Correct with 1–2 g $MgSO_4$ (in first 2 L if magnesium is low).
4. Correct acidosis.
   Add 44–88 mEq/L to first liter of IV fluids only if pH ≤ 7.0.
   Correct to pH 7.1.
5. Search for and correct underlying precipitant.
6. Monitor progress and keep meticulous flow sheets.
   Vital signs
   Fluid intake and urine output
   Serum glucose, K^+, Cl^-, HCO_3^-, CO_2, pH
   Amount of insulin administered
7. Admit to hospital or intensive care unit.
   Consider outpatient therapy in children with reliable caretaker *and*
   Initial pH > 7.35
   Initial $HCO_3^- \geq 20$ mEq/L
   Can tolerate PO fluids
   Resolution of symptoms after treatment in emergency department
   No underlying precipitant requiring hospitalization

ABG, arterial blood gas; CBC, complete blood count; DKA, diabetic ketoacidosis; ECG, electrocardiogram; NS, normal saline; PO, by mouth.

In children, the IV dosage of regular insulin may be calculated at 0.1 U/kg. Children are more likely than adults to develop cerebral edema in response to a rapid lowering of plasma osmolarity. Thus, reduction of glucose levels in children should be gradual.

Because the half-life of regular insulin is 3 to 10 minutes, IV insulin should be administered by constant infusion rather than by repeated bolus. When the blood glucose has dropped to 250 to 300 mg/dL, dextrose should be added to the IV fluids to prevent iatrogenic hypoglycemia and cerebral edema. In patients with euglycemic DKA, dextrose should be added to the IV fluids at the start of insulin therapy.

Insulin adheres to the walls of glass and polyvinyl bottles and tubing, making the exact amount of insulin being administered uncertain.[43] Running approximately 10 U of the insulin infusion through the tubing accomplishes adherence without altering the delivered concentration of the remainder of the infusate.

Insulin resistance occurs rarely in diabetic patients and requires an increase in dosage to obtain a satisfactory response. Resistance may be caused by obesity or accelerated insulin degradation.[4]

Two general categories of insulin resistance are described.[44] Postreceptor-binding resistance is the more common type. It is a mild to moderate resistance probably caused by defects in intracellular metabolism. It takes only a small amount of insulin to fill the receptors. When they are filled, administration of additional insulin produces no further effect. The second type, prereceptor-receptor resistance, is rare. This severe resistance may be caused by insulin antibodies, high concentrations of stress hormones, antireceptor antibodies, or any combination of these.[45]

Dehydration

The severely dehydrated patient is likely to have a fluid deficit of 3 to 5 L. No uniformly accepted formula exists for the administration of fluid in this disorder.

If the patient is in hypovolemic shock, normal saline (NS) should be administered as rapidly as possible in the adult, or in 20 mL/kg boluses in the child, until a systolic pressure of 80 mm Hg is obtained. In the adult who has marked dehydration in the absence of clinical shock or heart failure, 1 L of NS may be administered in the first hour. In general, 2 L of NS over the first 1 to 3 hours is followed by a slower infusion of half-NS solution. Patients with DKA without extreme volume depletion may be successfully treated with a lower volume of IV fluid replacement.[38] NS solution at 20 mL/kg over the first hour is the usual fluid resuscitation therapy for a child. Thereafter, fluid rate should be adjusted according to age, cardiac status, and degree of dehydration to achieve a urine output of 1 to 2 mL/kg/hr. Whereas some authors advocate half-NS or colloid solution, most evidence and practice favor initial resuscitation with 0.9% NS solution.

Fluid resuscitation alone may help to lower hyperglycemia. Because even in DKA a low level of circulating insulin may be present, increased perfusion may transport insulin to previously unreached receptor sites. In addition, a large volume of glucose may be cleared by the kidneys in response to improved renal perfusion. The mean plasma glucose concentration has been noted to drop 18% after administration of saline solution without insulin.[6]

Acidosis also decreases after fluid infusion alone. Increased perfusion improves tissue oxygenation, thus diminishing the formation of lactate. Increased renal perfusion promotes renal hydrogen ion loss, and the improved action of insulin in the better-hydrated patient inhibits ketogenesis.

Some authors believe that the rapid decrease of the hyperosmolarity of DKA caused by the administration of 0.45% NS solution may precipitate cerebral edema, one of the most dangerous complications associated with the patient in DKA, especially children.[46-48]

Potassium

Potassium replacement is invariably needed in DKA. The initial potassium level is often normal or high despite a large deficit because of severe acidosis. Potassium levels often plummet with correction of acidosis and administration of insulin. Potassium should be administered with the fluids while the laboratory value is in the upper half of the normal range. Renal function should be monitored. In patients with low serum potassium at presentation, hypokalemia may become life-threatening when insulin therapy is administered.

IV potassium should be vigorously administered in concentrations of 20 to 40 mEq/L as required.

Some clinicians administer a portion of the potassium as the phosphate salt. In DKA, phosphate falls from a mean value of 9.2 to 2.8 mg/dL within 12 hours of therapy, reflecting an average total deficit of 0.5 to 1.5 mmol/kg.[44] This may result in a decreased level of 2,3-diphosphoglycerate (2,3-DPG) and subsequent poor oxygen delivery to red blood cells. Other problems associated with the hypophosphatemia are depressed myocardial and respiratory muscle performance, hemolysis, impaired phagocytosis, thrombocytopenia, platelet dysfunction, confusion, and disorientation.[6] The only caveat with phosphorus administration is that its magnesium- and calcium-lowering properties may induce symptomatic hypomagnesemia and hypocalcemia. Despite theoretical benefits, no clinical benefit has been shown from the routine administration of phosphorus in DKA.[6]

Magnesium

Magnesium deficiency is a common problem in patients with DKA without renal disease. Both the initial pathophysiology and the therapy for DKA induce profound magnesium diuresis. Magnesium deficiency may exacerbate vomiting and mental changes, promote hypokalemia and hypocalcemia, or induce fatal cardiac dysrhythmia. The normal person requires 0.30 to 0.35 mEq/kg/day. Thus, it is reasonable to include 0.35 mEq/kg of magnesium in the fluids of the first 3 to 4 hours, with further replacement dependent on blood levels and the clinical picture. This amounts to 1.0 to 3 g of magnesium sulfate in the 70-kg patient.

Acidosis

Bicarbonate therapy may be indicated in severely acidemic patients (pH ≤ 7.0).[6] The use of bicarbonate is not warranted in less ill patients for several reasons.[49,50]

1. Bicarbonate worsens the inhibition of oxygen release from red blood cells caused by the 2,3-DPG deficiency seen in phosphorus-depleted patients with DKA.
2. Overly rapid correction of acidosis is contraindicated because the blood-brain barrier (BBB) is much more permeable to carbon dioxide than to bicarbonate. Thus, the correction of intravascular acidosis terminates Kussmaul's respiration, further augmenting the blood carbon dioxide available to cross the BBB. Slowly, sufficient bicarbonate crosses the BBB to provide adequate buffering. In the short term, however, as the blood acidosis is corrected, the acidity of the fluid surrounding the brain increases, causing paradoxical cerebrospinal fluid acidosis. The clinical significance of an acid cerebrospinal fluid pH is controversial.
3. The administration of bicarbonate increases the potassium requirement, both immediately by driving potassium into the cell and more gradually by affecting the kidney, making iatrogenic hypokalemia more likely. When bicarbonate is used, serum potassium levels need to be followed even more closely.
4. The overaggressive use of bicarbonate may produce alkalosis, which induces dysrhythmias largely through its effect on the distribution of electrolytes. Alkalemia occurring late in the course of therapy is more common in patients who have received bicarbonate because ketones are metabolized to carbon dioxide, water, and bicarbonate.
5. Evidence suggests that lowered pH produces a feedback mechanism that directly inhibits ketogenesis. Bicarbonate can increase ketonuria and delay the fall in serum ketones compared with saline infusion alone.
6. Patients treated with bicarbonate fare no better and possibly fare worse than patients treated without bicarbonate. Studies indicate that bicarbonate worsens the prognosis even in patients with severe acidosis and pH values in the range 6.9 to 7.1. It is possible to manage severe DKA with fluids and insulin alone. When this is done, pH normalization is similar to that in a bicarbonate control group.

When bicarbonate therapy is deemed necessary, the pH should not be corrected above 7.1. Response to therapy should be followed initially with hourly vital signs; fluids should be administered and urine output measured; insulin should be given; and glucose, pH, and anion gap measurements taken. Plasma bicarbonate may remain low even while pH increases and anion gap narrows because of the hyperchloremia that develops from rapid saline infusion, loss of bicarbonate in the urine as ketones, and exchanges with intracellular buffers.

Complications

The precipitating causes of DKA may have associated morbidity and mortality rates equal to or worse than those for DKA itself. These include iatrogenic causes as well as infection and MI. Morbidity in DKA is largely iatrogenic: (1) hypokalemia from inadequate potassium replacement, (2) hypoglycemia from inadequate glucose monitoring and failure to replenish glucose in IV solutions when serum glucose drops below 250 to 300 mg/dL, (3) alkalosis from overaggressive bicarbonate replacement, (4) congestive heart failure from overaggressive hydration, and (5) cerebral edema probably caused by too rapid osmolal shifts. DKA is responsible for 70% of diabetes-related deaths in children. Poor prognostic signs include hypotension, azotemia, coma, and underlying illness.[51]

The mortality rate in treated DKA decreased from approximately 38% between 1930 and 1959 to about 5 to 7% in the 1980s. The primary causes of death remain infection (especially pneumonia), arterial thromboses, and shock. The decrease in mortality rate demonstrates that appropriate therapy can make a difference.

Cerebral edema should be considered when the patient remains comatose or lapses into coma after the reversal of acidosis. It generally occurs 6 to 10 hours after the initiation of therapy. There are no warning signs, and the associated mortality rate is currently 90%. Cerebral edema has been associated with low partial pressures of arterial carbon dioxide, high BUN concentration, and the use of bicarbonate. Subclinical cerebral edema in children is probably very common. Furthermore, subclinical cerebral edema may either precede or follow the onset of therapy, raising the question of whether this entity is caused by therapy or is simply a manifestation of the basic pathophysiology of DKA.

Because clinically evident cerebral edema does not usually occur unless the blood sugar level is below 250 mg/dL and insulin is being used, insulin may directly antagonize the brain's defenses against fluid shifts while the plasma glucose level approaches normal values. Other theories attribute the formation of cerebral edema to (1) "idiogenic osmols" developed in the brain as a result of insulin therapy, (2) the rate of fluid administration, and (3) the rate of correction of the acidosis. Other less common causes have been suggested. Several authors recommend the administration of mannitol, 0.25 to 2 mg/kg, at the first sign of altered mental status in children being treated for DKA.[47] Steroids are ineffective treatment for cerebral edema secondary to DKA and may worsen DKA.

Disposition

Most patients with DKA require hospital admission, often to the intensive care unit. All pregnant diabetic patients in DKA require admission and consultation with an endocrinologist and obstetrician specializing in the care of high-risk pregnancies. Some children (initial pH > 7.35, bicarbonate ≥ 20 mEq/L) with resolution of findings who can tolerate oral fluids after 3 or 4 hours of treatment may be discharged home with a reliable caregiver.[52] Patients who have mild DKA may be treated on an outpatient basis if (1) the patient or parent is reliable, (2) the underlying causes do not require inpatient therapy, and (3) close follow-up is pursued.

HYPERGLYCEMIC HYPEROSMOLAR NONKETOTIC COMA

Hyperglycemic hyperosmolar nonketotic coma (HHNC) represents a syndrome of acute diabetic decompensation characterized by marked hyperglycemia, hyperosmolarity and dehydration, and decreased mental functioning that may progress to frank coma. Ketosis and acidosis are generally minimal or absent. Focal neurologic signs are common. DKA and HHNC may occur together; some even consider HHNC and DKA to be at two ends of a spectrum, with many patients in the middle.[6,53]

Principles of Disease

Pathophysiology

As with DKA, the pathophysiology of HHNC varies with the particular patient. Because most patients with HHNC are elderly, decreased renal clearance of glucose produced by the decline of renal function with age often contributes to the illness. As with DKA, decreased insulin action results in glycogenolysis, gluconeogenesis, and decreased peripheral uptake of glucose. The hyperglycemia pulls fluid from the intracellular space into the extracellular space, transiently maintaining adequate perfusion. Soon, however, this fluid is lost in a profound osmotic diuresis, limited finally by hypotension and a subsequent drop in the glomerular filtration rate (GFR). The urine is extremely hypotonic, with a urine sodium concentration between 50 and 70 mEq/L, compared with 140 mEq/L in extracellular fluid. This hypotonic diuresis produces profound dehydration, leading to hyperglycemia, hypernatremia, and associated hypertonicity. Often the patient is prevented from taking in adequate fluids by stroke, Alzheimer's disease, or other diseases, greatly exacerbating the dehydration of renal origin.

The reason for the absence of ketoacidosis in HHNC is unknown. FFA levels are lower than in DKA, thus limiting substrates needed to form ketones. The most likely reason for the blunted counter-regulatory hormone release and lack of ketosis seems to be that these patients continue to secrete the tiny amount of insulin required to block ketogenesis.[54]

Etiology

HHNC is a syndrome of severe dehydration that results from a sustained hyperglycemic diuresis under circumstances in which the patient is unable to drink sufficient fluids to offset the urinary losses. The full-blown syndrome does not usually occur until volume depletion has progressed to the point of decreased urine output.

HHNC is most common in elders with type 2 diabetes but has been reported in children with type 1 diabetes.[55]

BOX 124-8 PRECIPITANTS OF HYPERGLYCEMIC HYPEROSMOLAR NONKETOTIC COMA

External Insult
Trauma
Burns
Dialysis
Hyperalimentation

Disease Process
Cushing's syndrome and other endocrinopathies
Hemorrhage
Myocardial infarction
Renal disease
Subdural hematoma
Cerebrovascular accident
Infection
Down syndrome

Drugs
Antimetabolites
L-Asparaginase
Chlorpromazine
Chlorpropamide
Cimetidine
Diazoxide
Didanosine
Ethacrynic acid
Furosemide
Glucocorticoids
Immunosuppressants
Olanzapine and other atypical antipsychotics
Phenytoin
Propranolol
Thiazides

Box 124-8 lists the broad range of predisposing factors.[5] HHNC may occur in patients who are not diabetic, especially after burns, parenteral hyperalimentation, peritoneal dialysis, or hemodialysis.[56]

Clinical Features

The prodrome of HHNC is significantly longer than that of DKA. Clinically, extreme dehydration, hyperosmolarity, volume depletion, and CNS findings predominate.[54] If awake, patients may complain of fever, thirst, polyuria, or oliguria. Approximately 20% of patients have no known history of type 2 diabetes. The most common associated diseases are chronic renal insufficiency, gram-negative pneumonia, GI bleeding, and gram-negative sepsis. Of these patients, 85% have underlying renal or cardiac impairment as a predisposing factor. Arterial and venous thromboses often complicate the picture.

The patient often exhibits orthostatic hypotension or frank hypotension, tachycardia, and fever with signs of marked dehydration. On average, the HHNC patient has a 24% fluid deficit, or 9 L in the 70-kg patient. The depression of the sensorium correlates directly with the degree and rate of development of hyperosmolarity. Some patients have normal mental status. Seizures are usually associated with neurologic findings, especially epilepsia partialis continua (continuous focal seizures) and intermittent focal motor seizures. Stroke and hemiplegia are also common. Less common neurologic findings include choreoathetosis, ballismus, dysphagia,

segmental myoclonus, hemiparesis, hemianopsia, central hyperpyrexia, nystagmus, visual hallucinations, and acute quadriplegia.

Diagnostic Strategies

Laboratory findings usually reveal a blood glucose level greater than 600 mg/dL and serum osmolarity greater than 350 mOsm/L. The BUN concentration is invariably elevated (see Table 124-2). Although patients with HHNC do not have a ketoacidosis caused by diabetes, they may have a metabolic acidosis secondary to some combination of lactic acidosis, starvation ketosis, and retention of inorganic acids attributable to renal hypoperfusion.

The patient with HHNC typically manifests more profound electrolyte imbalance than the patient with DKA. Levels of potassium, magnesium, and phosphorus may seem initially high, even in the presence of marked total deficit. In the absence of acidemia, however, the discrepancy between the initial electrolyte reading and body stores is less than that of DKA. Initial serum sodium readings are inaccurate because of hyperglycemia.

Differential Considerations

The differential diagnosis of HHNC is identical to that for DKA. In addition, diabetic patients receiving chlorpropamide are subject to water intoxication with dilutional hyponatremia, which may manifest as coma without acidosis that is clinically indistinguishable from HHNC. The patient with HHNC who has a sharply depressed sensorium may not be initially distinguishable from the patient with profound hypoglycemia. When blood glucose cannot be rapidly checked, the immediate administration of one ampule of $D_{50}W$ minimally worsens HHNC and may be lifesaving for patients with hypoglycemia.

Management

The fluid, electrolyte, and insulin regimens for the initial resuscitation in HHNC are subject to the same controversies as the therapies for DKA (Box 124-9). Whereas some physicians use half-NS solution rapidly infused, most use NS solution, switching to half-NS later in the resuscitation. Just as in DKA, overly rapid correction of serum osmolarity may predispose to the development of cerebral edema in children. There are few reports of cerebral edema complicating HHNC in adults.

Dehydration

Under central venous or pulmonary artery pressure monitoring, rapid administration of NS in a similar fashion to initial therapy for DKA is generally safe. For patients in coma or hypovolemic shock, initial IV fluid infusion should be given as rapidly as possible. If the patient does not have central monitoring and is not in coma or shock, vigorous IV fluid administration, such as 1 L/hr, is prudent and provides sufficient rehydration. In any circumstance, after 2 to 3 L of NS, 0.45% NS solution should be substituted. As the fluid deficits and hyperosmolarity are corrected, the infusion rate must be slowed and electrolytes managed. In patients with concomitant congestive heart failure, sterile water has been successfully administered by central venous line at a rate of 500 mL/hr, with no detectable hemolysis or other complications. Glucose should be added to resuscitation fluids when the blood glucose level drops below 300 mg/dL.

BOX 124-9 Summary of Treatment for Hyperglycemic Hyperosmolar Nonketotic Coma

Identify HHNC, then treatment is the same as initial DKA treatment.

1. Supplement insulin.
   ± Bolus: 0.05–0.1 U/kg regular insulin IV
   Maintenance: 0.05–0.1 U/kg regular insulin IV
   Caution: Serum glucose rapidly corrects with fluid administration alone; monitor glucose to avoid hypoglycemia.
   Change IV solution to D_5W 0.45% NS when glucose ≤ 300 mg/dL.
2. Rehydrate.
   Rapid administration of 2–3 L NS over first several hours
   CVP monitoring may be necessary in patients with history of heart disease.
   Correct one half of fluid deficit in first 8 hours, remainder over 24 hours.
3. Correct electrolyte abnormalities.
   Sodium
   Correct with administration of NS and 0.45% NS.
   Potassium
   First ensure adequate renal function.
   Add 20–40 mEq KCl to each liter of fluid.
   Phosphorus
   Usually unnecessary to replenish
   Magnesium
   Correct with 1–2 g $MgSO_4$ (in first 2 L if magnesium is low).
4. Correct acidosis.
   Add 44–88 mEq/L to first liter of IV fluids *only* if pH ≤ 7.0.
   Correct to pH 7.1.
5. Search for and correct underlying precipitant.
6. Monitor progress and keep meticulous flow sheets.
   Vital signs
   Fluid intake and urine output
   Serum glucose, K^+, Cl^-, HCO_3^-, CO_2, pH, ketones
   Amount of insulin administered
7. Admit to hospital or intensive care unit.

CVP, central venous pressure; DKA, diabetic ketoacidosis; HHNC, hyperglycemic hyperosmolar nonketotic coma; NS, normal saline.

Electrolytes

The guidelines for the administration of potassium, magnesium, and phosphorus are similar to those for DKA.

Insulin

Low-dosage insulin, such as that administered in the patient with DKA, is generally effective and safe when the restoration of volume has been instituted.

Other Considerations

A vigorous search for the underlying precipitant for HHNC must be pursued. Response to therapy should be followed in the manner described for patients in DKA. Phenytoin (Dilantin) is contraindicated for the seizures of HHNC because it is often ineffective and may impair endogenous insulin release. Phenytoin-induced HHNC even occurs in nondiabetic patients. Low-dosage subcutaneous heparin may be

indicated to lessen the risk of thrombosis, which is increased by the volume depletion, hyperviscosity, hypotension, and inactivity associated with HHNC.

Complications

Reasons for high morbidity and mortality rates are not always clear, but many patients with HHNC are elders who have underlying cardiac and renal disease. Pediatric HHNC differs from adult HHNC in that children have a much higher incidence of fatal cerebral edema.[57] Other causes for morbidity and mortality are similar to those described for DKA. The mortality rate of treated HHNC patients has been 40 to 70% in the past, but now ranges from 8 to 25%.[58]

Disposition

Patients with HHNC should be hospitalized for IV hydration, glucose control, and evaluation of precipitating and complicating conditions.

■ LATE COMPLICATIONS OF DIABETES

Late complications of diabetes cause significant morbidity and mortality. They develop approximately 15 to 20 years after the onset of overt hyperglycemia. The Diabetes Control and Complications Trial showed that tight glycemic control significantly reduces the risk of microvascular disease, such as microalbuminuria (the earliest sign of nephropathy), neuropathy, and retinopathy, but at the expense of greatly increasing the risk of recurrent hypoglycemia.[59-61]

Vascular Complications

Diabetes is associated with an increased risk for atherosclerosis and thromboembolic complications, which are a major cause of morbidity and premature death.[62] The cause of accelerated atherosclerosis is unknown, although it is probably related to oxidated low-density lipoprotein and increased platelet activity. Atherosclerotic lesions are widespread, causing symptoms in many organ systems. Coronary artery disease and stroke are common. Diabetic patients have an increased incidence of "silent" MI, complicated MIs, and congestive heart failure.[7,63,64] Peripheral vascular disease is noted clinically by claudication, nonhealing ulcers, gangrene, and impotence.

Diabetic Nephropathy

Renal disease is a leading cause of death and disability in diabetic patients. Approximately one half of end-stage renal disease in the United States is caused by diabetic nephropathy.[65] Diabetic nephropathy involves two pathologic patterns: diffuse and nodular. Clinical renal dysfunction does not correlate well with the histologic abnormalities. Disease usually progresses from enlarged kidneys with elevated GFR to the appearance of microalbuminuria, to macroproteinuria with hypertension, reduced GFR, and renal failure.[66] The appearance of microalbuminuria correlates with the presence of coronary artery disease and retinopathy.[67]

Azotemia generally does not begin until 10 to 15 years after the diagnosis of diabetes. Progression of renal disease is accelerated by hypertension. Meticulous control of diabetes can reverse microalbuminuria and may slow the progression of nephropathy.[2,18,59-61] Hypertension should be aggressively managed. Angiotensin-converting enzyme inhibitors are effective in controlling hypertension and lowering microalbuminuria.[67,68] Chronic hemodialysis and renal transplantation are unfortunate endpoints for many diabetic patients with renal disease.

Retinopathy

Diabetes is a leading cause of adult blindness in the United States. Approximately 11 to 18% of all diabetic patients have treatable diabetic retinopathy ranging from mild to severe and manifesting in many forms. The severity of diabetic retinopathy is clearly related to the quality of glycemic control.[64]

Background (simple) retinopathy is found in most diabetic patients who have prolonged disease. Background retinopathy is characterized by microaneurysms, small vessel obstruction, cotton-wool spots or soft exudates (microinfarcts), hard exudates, and macular ischemia.[66] The characteristics of proliferative retinopathy are new vessel formation and scarring. Complications of proliferative retinopathy are vitreal hemorrhage and retinal detachment, which may ultimately cause unilateral vision loss. Treatment for diabetic retinopathy is photocoagulation.

Maculopathy is background retinopathy with macular involvement. It results primarily in a deficit of central vision. As with proliferative retinopathy, it is vital that the patient be under the care of an ophthalmologist. Laser therapy in the early stages can dramatically alter the course of this disabling disease.

The diabetic patient may present with complaints ranging from acute blurring of vision to sudden unilateral or even bilateral blindness. Less often, diabetic patients have more gradual vision loss caused by the common senile cataract or the "snowflake" cataract, which may disappear as hyperglycemia is corrected. The associated hyperlipidemia of diabetes may lighten the color of retinal vessels, producing lipidemia retinalis. Anterior ischemic optic neuropathy has been reported.

Diabetic patients with retinopathy should be referred to an ophthalmologist. Even in those with normal vision, ophthalmologic procedures may limit visual loss or prevent crises such as neovascular glaucoma.

Neuropathy

Both autonomic and peripheral neuropathies are well-known complications of diabetes. The prevalence of peripheral neuropathy ranges from 15 to 60%.[4] The cause of the neuropathy is not clearly understood, but evidence suggests several factors in its development. Neuropathy may result from the effects of diabetic vascular disease on the vasa nervorum. Myoinositol, the polyol pathway, and nonenzymatic glycosylation of protein may have roles. All these factors are related to an elevated blood glucose level. Neurologic manifestations of diabetes may regress with improved glycemic control. Pathologically, segmental demyelinization occurs with loss of both myelinated and unmyelinated axons, particularly those affecting the distal part of the peripheral nerve.

Several distinct types of neuropathy have been recognized in diabetes. Peripheral symmetrical neuropathy is a slowly progressive, primary sensory disorder manifesting bilaterally with anesthesia, hyperesthesia, or pain. The pain is often severe and worse at night. It affects upper and lower extremities, although lower extremities and the most distal sections of the involved nerves are most often affected. There may be a motor deficiency as well. Pain is very difficult to control. Simple pain medications, amitriptyline, and fluphenazine are effective for some patients.[66]

Mononeuropathy, or mononeuropathy multiplex, affects both motor and sensory nerves, generally one nerve at a time.

The onset is rapid, with wasting and tenderness of the involved muscles. Clinically, sudden onset of wristdrop, footdrop, or paralysis of cranial nerves III, IV, and VI is noted.

Diabetic truncal mononeuropathy occurs rapidly in a radicular distribution. In contrast to other mononeuropathies, it is primarily, if not exclusively, sensory. If it causes pain, it may mimic that of an MI or acute abdominal inflammation. Like diabetic mononeuropathy, it may be most bothersome at night and generally resolves in a few months. Whereas diabetic mononeuropathy is often the first clue of diabetes, truncal mononeuropathy is more often found in known diabetic patients.

Autonomic neuropathy occurs in many forms. Neuropathy of the GI tract is manifested by difficulty swallowing, delayed gastric emptying, constipation, or nocturnal diarrhea. Impotence and bladder dysfunction or paralysis may occur. Orthostatic hypotension, syncope, and even cardiac arrest have resulted from autonomic neuropathy. Diabetic diarrhea responds to diphenoxylate and atropine, loperamide, or clonidine. Orthostatic hypotension is treated by sleeping with the head of the bed elevated, avoidance of sudden standing or sitting, and the use of full-length elastic stockings.

The Diabetic Foot. Approximately 20% of hospitalizations in diabetic patients are related to foot problems. Sensory neuropathy, ischemia, and infection are the principal contributors to diabetic foot disease. Loss of sensation leads to pressure necrosis from poorly fitting footwear and small wounds going unnoticed. The most common cause of injury is pressure on plantar bony prominences. All neuropathic foot ulcers should be assessed for infection and débrided of devitalized tissue, and radiographs should be obtained to examine for the presence of foreign bodies, soft tissue gas, or bone abnormalities. Weightbearing must be eliminated by total-contact casting.[69]

Not all ulcers are infected. Infection is suggested by local inflammation or crepitation. Conversely, some uninflamed ulcers are associated with underlying osteomyelitis. Most mild infections are caused by gram-positive cocci, such as *Staphylococcus aureus* or streptococci, and may be treated with oral antibiotics, a strict non-weight-bearing regimen, meticulous wound care, and daily follow-up. This approach may not be possible when patients are deemed unreliable, do not have good home support, or do not have ready access to follow-up care.

Deeper, limb-threatening infections—as evidenced by full-thickness ulceration, cellulitis greater than 2 cm in diameter with or without lymphangitis, bone or joint involvement, or systemic toxicity—are usually polymicrobial in origin and caused by aerobic gram-positive cocci, gram-negative bacilli, and anaerobes. These patients require hospitalization and, after culture, IV empirical antimicrobial therapy with ampicillin-sulbactam, ticarcillin-sulbactam, cefoxitin, imipenem, or a fluoroquinolone and clindamycin; strict non-weight-bearing status; tight glycemic control; early surgical intervention for débridement; drainage; and meticulous wound care.[69,70] Occult osteomyelitis should be considered in all cases of neuropathic ulceration. Up to one third of patients must undergo amputation.

Infections

Diabetic patients are more susceptible to complications of infections because of their inability to limit microbial invasion with effective polymorphonuclear leukocytes and lymphocytes.[4] They have an increased incidence of extremity infections and pyelonephritis compared with the general population. In addition, they are particularly susceptible to certain other infections such as tuberculosis, mucocutaneous candidiasis, intertrigo, mucormycosis, soft tissue infections, nonclostridial gas gangrene, osteomyelitis, and malignant *Pseudomonas* otitis externa.[4] Treatment for diabetic patients with infection includes rapid culture and antibiotics, glycemic control, and generally hospitalization.

Cutaneous Manifestations

Dermal hypersensitivity is manifested by pruritic, erythematous indurations that occur at insulin injection sites. The declining prevalence of this condition has paralleled the improved purification of insulin. Insulin lipoatrophy likewise seems to be a result of insulin impurities and is manifested as subcutaneous depressions at injection sites. Although lipoatrophy is now more common than dermal hypersensitivity, its prevalence has also declined sharply because insulin preparations have improved. Insulin lipohypertrophy is manifested by raised areas of subcutaneous fat deposits at insulin injection sites. These lesions generally reflect the failure of the patient to rotate injections sites adequately. They resolve spontaneously over months if insulin injection is avoided in the affected areas and sites are properly rotated.

Insulin pumps are often associated with localized skin problems, usually a reaction to the tape securing the tubing and needles. Occasionally, sensitivity to the catheters is seen. Skin infections at the site of injection are the most common complication of insulin pumps. Changing the patient to buffered pure-pork from unbuffered beef-pork insulin is the only intervention that seems to reduce the rate of infection. A few patients have been noted to develop hard nodules at the injection site. The cause of these nodules is uncertain.

Diabetic patients who use oral hypoglycemic agents may develop rashes associated with these medications. After consuming ethanol, approximately 38% of type 2 patients taking chlorpropamide exhibit a "flush" consisting of redness of the face and neck and a sense of warmness or burning. Patients may demonstrate urticaria in response to both insulin and oral hypoglycemics.

Diabetic skin conditions include fungal infections, acanthosis nigricans, necrobiosis lipoidica diabeticorum, xanthoma diabeticorum, bullosis diabeticorum, and diabetic dermopathy. *Acanthosis nigricans* is characterized by a velvety brown-black thickening of the keratin layer, most often in the flexor surfaces. It is the cutaneous marker for a group of endocrine disorders with insulin resistance.[8] *Necrobiosis lipoidica diabeticorum* begins as erythematous papular or nodular lesions, usually in the pretibial area, but in other areas as well. The early lesions may contain telangiectasias. These lesions spread and frequently form a single pigmented area of atrophic skin, often with a yellow and sometimes ulcerated center and an erythematous margin. A history of previous trauma is sometimes found.

The three forms of diabetic thick skin are (1) scleroderma-like skin changes of the fingers and dorsum of the hand associated with stiff joints and limited mobility, (2) clinically inapparent but measurable thick skin, and (3) "scleroderma adultorum," or increased dermal thickness on the back and posterior upper neck in middle-aged, overweight patients with type 2 diabetes.

Xanthoma diabeticorum is evidence of the hyperlipidemia associated with diabetes. It is similar to the xanthoma found in nondiabetic hyperlipidemic patients. Xanthomas have an erythematous base and a yellowish hue.

Bullosis diabeticorum is a rare occurrence. Bullae are usually filled with a clear fluid and are most often found on the extremities, especially the feet. The fluid is occasionally

slightly hemorrhagic. The bullae usually heal spontaneously without scarring.

Diabetic dermopathy, or "skin spots," is the most common finding in diabetes. It arises as discrete, depressed, and brownish lesions generally less than 15 mm in diameter and found in the pretibial area.

Resistant, aggressive *impetigo* or *intertrigo* should suggest diabetes.

Insulin Allergy

Insulin allergy is mediated by immunoglobulin E and is manifested by local itching or pain and delayed brawny edema, urticaria, or anaphylaxis. Systemic reactions are usually seen in patients who have previously discontinued insulin and then resumed therapy. Mild reactions may be treated with antihistamines, whereas anaphylaxis must be treated with epinephrine. Patients with significant reactions must be admitted for desensitization.[4]

DIABETES IN PREGNANCY

Before the discovery of insulin in 1922, diabetes in pregnancy was associated with a fetal death rate of 60 to 72% and maternal morbidity of approximately 30%. In 1977, a linear relationship between glycemic control and perinatal mortality was discovered. Strict metabolic control is now a goal in all diabetic pregnancies.[41,57]

Pregnant patients should be watched extremely closely and aggressively treated for impending or actual DKA. For a variety of reasons, pregnant women have a special predisposition to both glucose intolerance and excess ketone production. Although uncommon, DKA may cause perinatal asphyxia and reduce fetal oxygen delivery.[41,57] Intellectual deficits in offspring have been associated with maternal ketonuria from any cause.

Pregnancy is associated with progression of retinopathy for unknown reasons.[71] Whether pregnancy worsens diabetic nephropathy or hastens the progression to end-stage renal disease is controversial.[72] Although nephrotic syndrome develops in 71% of pregnancies, blood pressure and proteinuria eventually return to first-trimester values. Diabetic nephropathy is associated with an increased risk of preterm labor, stillbirth, neonatal death, fetal distress, and intrauterine growth retardation; otherwise, the literature is sparse on the effect of pregnancy on diabetic neuropathy. Autonomic neuropathy, particularly gastroparesis, makes adequate nutrition difficult for both mother and fetus. Pregnant women should be referred for parenteral feedings if conservative therapy fails to control vomiting.[41]

Hypoglycemia is common in pregnancy in part because of intensive insulin treatment to maintain euglycemia.[73] Hypoglycemic unawareness is not uncommon. The effects of hypoglycemia on the fetus are unclear. Ketoacidosis is associated with a 50 to 90% fetal mortality rate.[41,74]

NEW-ONSET HYPERGLYCEMIA

Patients often present to the ED with typical diabetic symptoms such as polyuria, polydipsia, and polyphagia. Many have serum glucose greater than 200 mg/dL but are not ketotic. These patients with normal electrolytes may be treated with IV hydration alone or with insulin, often reducing the glucose to 150 mg/dL. In reliable patients whose initial glucose is greater than 400 mg/dL, initiation of oral hypoglycemic therapy may be appropriate, with lifestyle modification. An HbA_{1c} value should be obtained before initiation of therapy to help evaluate treatment. Initial therapy with sulfonylureas is appropriate; glyburide (2.5–5 mg once daily) or glipizide (5 mg once daily) is recommended. In obese patients or those in whom sulfonylureas are contraindicated, metformin may be an alternative. Follow-up should be stressed and warning signs of hypoglycemia discussed.

ORAL HYPOGLYCEMIC AGENTS

The widespread availability of a variety of oral medications for hyperglycemia, some with serious side effects, requires the emergency physician to be familiar with these drugs. *Sulfonylureas*, developed in the 1940s, continue to be the mainstay of oral diabetes treatment. These drugs increase insulin secretion by binding to specific beta-cell receptors.[75] This class of drugs works best in patients with early onset of type 2 diabetes and fasting glucose levels less than 300 mg/dL.[76] This class of drugs is contraindicated in patients with a known allergy to sulfa agents. Patients with renal failure may be predisposed to hypoglycemia.

Metformin is an agent in the biguanide class. It works by decreasing hepatic glucose output and increasing peripheral uptake of glucose, leading to decreased insulin resistance and lower blood glucose. Used alone, metformin does not cause hypoglycemia, but it is contraindicated in patients with renal insufficiency and metabolic acidosis. Metformin is renally excreted. Metformin should be withheld for 48 hours before or after administration of iodinated contrast media because of the risk of acidosis from transient decrease in renal function. Metformin must be used with caution in patients with hypoxemia, liver compromise, and alcohol abuse. These patients are at increased risk for developing lactic acidosis, which has a 50% mortality rate.[76,77]

The *thiazolidinediones* reduce insulin resistance and are especially useful in patients who require large amounts of insulin and still lack adequate glucose control. Because of hepatotoxicity, troglitazone has been removed from the market.[77] Pioglitazone and rosiglitazone are approved for monotherapy. Liver function should be monitored for at least 1 year after the initiation of therapy with thiazolidinediones.

α-Glucosidase inhibitors delay intestinal monosaccharide absorption and prevent complex carbohydrate breakdown.[76] They must be titrated to minimize GI side effects and should not be used in patients with certain GI disorders. Liver function monitoring is required because of dose-dependent hepatotoxicity.

Repaglinide is similar to the sulfonylureas in action and mechanism. It has a more rapid onset of action, involves less risk of hypoglycemia, and is suitable for patients allergic to sulfa.[77] Care should be used in patients with renal or hepatic dysfunction.[76]

Exanatide is a GLP (glucagon-like peptide) agonist. GLP stimulates release of insulin from pancreatic cells. GLP itself has a half-life of only a few minutes, but the GLP agonists bind to the GLP receptor on the pancreas and have a much longer half-life.

Vildagliptin and *sitagliptin* are classified as DPP-4 (dipeptidyl peptidase-4) inhibitors. DPP-4 degrades endogenous GLP; the DPP-4 inhibitors, by preventing this degradation, prolong the half-life of GLP and increases insulin secretion.[78]

NEW TRENDS

Changes in the therapy of diabetes include greater use of human insulin, which has prevented some of the adverse reactions to beef and pork products. Unfortunately, some patients demonstrate sensitivity reactions even to subcutaneously

injected human insulin.[79] More physicians are teaching their type 1 patients and families how to administer glucagon to treat severe hypoglycemia. Initiation of immunosuppressive therapy at the initial diagnosis of type 1 diabetes can prolong the patient's ability to secrete insulin. However, this beneficial effect, whether achieved by azathioprine or cyclosporine, is not usually sustainable.[80] The potential side effects of immunosuppressive agents have precluded large trials in patients early in their disease.[81] Prophylactic insulin therapy, nicotinamide, oral insulin, or glutamate decarboxylase and avoidance of cow's milk may prevent or delay the onset of type 1 diabetes in patients at risk.[5]

Glycemic control now involves improved technology and more widespread individual monitoring. More patients alter their insulin dosages daily in response to their findings. Diabetic patients with tight glycemic control benefit by limiting the progression of microvascular disease: neuropathy, renal disease, and certain types of retinopathy. However, they are more likely than other diabetic patients to experience hypoglycemic episodes.

Emergency physicians and out-of-hospital care providers are encountering patients with insulin pumps. Many insulin pumps are available, each having a pump mechanism, a reservoir for insulin, tubing, and indwelling subcutaneous needles. They are attached, usually with tapes, to the patient's body and administer insulin at a regular adjustable rate. Most pumps also allow the patient to administer additional boluses of insulin as necessary. These pumps support tight glycemic control and are acceptable to some patients. However, motivated patients can achieve equivalent control by adjusting daily injections. Insulin pumps are associated with a variety of complications (e.g., iatrogenic hypoglycemia).

Because glucose rotates the polarization of light waves, new fiberoptic technology has been developed to determine blood glucose noninvasively. This technology may be applied to the insulin pumps in the future.

Inhaled insulins have been studied, and one was even marketed briefly; further research into this area is likely. A variety of available insulins, including ultra-short-acting (Humalog) and long acting (Lantus) have come out in recent years, which have provided a wider array of possibilities in diabetes management.

The basic concepts of the diabetic diet remain unchanged, although many studies emphasize foods and medications that alter glucose absorption. Various high-fiber diets have improved glycemic control. The mostly beneficial but occasionally deleterious effects of exercise have also been elaborated.[75]

Newer therapies include pancreatic and pancreatic beta-cell transplants. Solid-organ pancreatic transplantation remains controversial among both diabetologists and transplant surgeons. Transplantation ameliorates many secondary complications of diabetes, such as nephropathy, neuropathy, gastroparesis, retinopathy, and microvascular changes. The percentage of grafts functioning after 1 year and the 1-year survival rate of patients are greater than 75% in selected medical centers. Rejection, post-transplantation pancreatitis, and graft thrombosis, as well as other vascular and immunosuppression problems, continue to plague transplant recipients.

Pramlintide is part of a new class of drugs called amylin analogues. These decrease gastric emptying and decrease glucagon secretion. Currently, pramlintide must be administered by subcutaneous injection after a meal.[78]

Other new areas for research have included agents that increase urinary excretion of glucose or increase hepatic gluconeogenesis.

KEY CONCEPTS

- Hypoglycemia may be associated with significant morbidity and mortality. When the diagnosis is suggested and, if possible, confirmed by laboratory evaluation, treatment should be initiated immediately.
- Hypoglycemia caused by oral hypoglycemic agents may be prolonged. Patients should be observed for an extended period or hospitalized.
- The essential treatment of DKA includes restoration of insulin, correction of dehydration, correction of potassium level, correction of acidosis, and treatment of the underlying cause.
- Hyperglycemic hyperosmolar nonketotic coma is often associated with focal neurologic signs that resolve with treatment. The essentials of treatment are correction of profound dehydration, correction of electrolytes, and treatment of the underlying cause.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 125

Rhabdomyolysis

Laura J. Bontempo and Amy H. Kaji

PERSPECTIVE

Rhabdomyolysis, defined as the dissolution or disintegration of striated muscle,[1] describes a clinical and biochemical syndrome resulting from the release of intracellular contents into the extracellular fluid and circulation. The diagnosis of rhabdomyolysis rests on measurement of these released substances in either plasma or urine. The classic presentation includes symptoms of myalgias, weakness, red to brown urine due to myoglobinuria, and elevated serum muscle enzymes, such as creatine kinase (CK).[2] Approximately 26,000 incident cases of rhabdomyolysis are reported annually.[3] The spectrum of disease severity ranges from an asymptomatic elevation of muscle enzymes to life-threatening electrolyte imbalances, acute renal failure, multiorgan failure syndrome, and death.

Historically, the earliest reference to rhabdomyolysis occurs in the Old Testament, from the Book of Numbers.[4] During the Exodus, the Israelites consumed large amounts of quail, which fed on hemlock seeds, and many became ill and died from an illness described by intense muscle pain and weakness. In the late 19th century a clinical syndrome of muscle pain, weakness, and brown urine was called "Meyer-Betz disease" in the German literature.[5] In 1941, Bywaters and Beall[6] described the clinical course of four victims with crush injuries to the limbs after air raids during World War II. They noted the link between muscle injury and renal dysfunction in their classic monograph, as follows:

"The patient has been buried for several hours with pressure on a limb. On admission he looks in good condition except for swelling of the limb, some local anesthesia and whealing. The hemoglobin, however, is raised and a few hours later despite vasoconstriction made manifest by pallor, coldness and sweating, the blood pressure falls. This is restored to the preshock level by (often multiple) transfusions of serum, plasma, or occasionally, blood. Anxiety may now arise concerning the circulation in the injured limb, which may show diminution of arterial pulsation distally, accompanied by all the changes of incipient gangrene. Signs of renal damage soon appear and progress, even though the crushed limb be amputated. The urinary output, initially small, owing perhaps to the severity of the shock, diminishes further. The urine contains albumin and many dark brown or black granular casts, which later decrease in number. The patient is alternately drowsy and anxiously aware of the severity of his illness. Slight generalized edema, thirst, and incessant vomiting develop, and the blood pressure often remains slightly raised. The blood urea and potassium, raised at an early stage, become progressively higher, and death occurs comparatively suddenly, frequently within a week. Necropsy reveals necrosis of muscle and in the renal tubules, degenerative changes and casts containing brown pigment."

Acute renal failure (ARF) is one of the most serious complications of rhabdomyolysis, and the presence of ARF is associated with multisystem organ failure and a higher mortality rate.[7] Well-designed prospective studies of rhabdomyolysis and its complications are lacking, so the true incidence of ARF in this setting is unknown but is estimated at 4 to 33%.[8] Approximately 5 to 15% of patients hospitalized with ARF in the United States have rhabdomyolysis as the cause.[9]

PRINCIPLES OF DISEASE

Anatomy and Physiology

Skeletal muscle is the largest organ in the human body. The functioning of muscle cells is critically dependent on a healthy cell membrane, the sarcolemma, which maintains ionic gradients and ensures proper metabolic functioning. The sarcolemma contains sodium-potassium pumps, calcium protein-carrier pumps, and other channels and structures.[10] The sodium-potassium pump moves sodium out and potassium into the sarcoplasm. More sodium is transported out than potassium is transported in, creating a net negative intracellular charge. A sodium concentration gradient is thus created. Normally, the concentration of intracellular sodium ions is very low, approximately 10 mEq/L, when compared with the extracellular fluid.[10]

Located in the sarcolemma, the calcium pumps work to maintain a low intracellular fluid calcium concentration by moving calcium out of the sarcoplasm to the extracellular space. Additional pumps help move calcium into the muscle cell's internal structures, the sarcoplasmic reticulum and the mitochondria. As sodium ions move down the electrochemical gradient (i.e., return into the cell), calcium ions are able to move out of the cell into the extracellular fluid (Fig. 125-1). With the exception of the sodium-calcium exchange, all of these pumps depend on active transport, with adenosine triphosphate (ATP) as the energy source.[10]

Also found within a cell's sarcoplasm, myoglobin is the major heme protein supplying oxygen to skeletal and cardiac

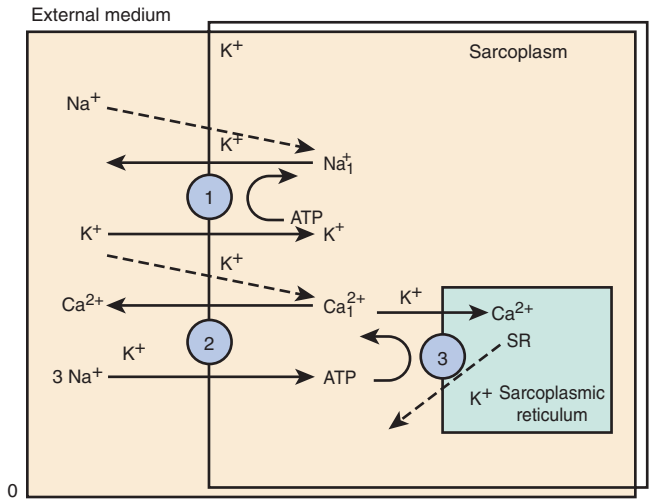

Figure 125-1. Normal membrane ionic pump function of skeletal muscle cell. When this function is ineffective, calcium stores will increase in the cell, which may initiate a series of outputs leading to cellular injury. SR, sarcoplasmic reticulum. (Redrawn from Blaustein MP: Sodium ions, calcium ions, blood pressure regulation, and hypertension: A reassessment and a hypothesis. Am J Physiol 232:C165, 1977.)

muscle. Myoglobin has a higher affinity than hemoglobin for oxygen and thus facilitates an influx of oxygen into muscle cells.[11] Under normal circumstances, plasma myoglobin is bound to haptoglobin and the concentration is low. However, if greater than 100 g of skeletal muscle is damaged, serum haptoglobin-binding capacity is exceeded, and "free" myoglobin is filtered by the glomerulus, producing the classic dark-colored urine of rhabdomyolysis.[12] When myoglobin precipitates in the glomerular filtrate, it causes renal tubular obstruction and ARF.

Skeletal muscle cytoplasm contains proteases and other proteolytic enzymes, which decompose myofibrillar proteins for recycling. The activity level of these enzymes depends on intracellular calcium levels. In the cell's normal physiologic state, these enzymes have low activity; however, with significant elevations of intracellular calcium, these proteolytic enzymes are maximally disinhibited and become destructive to the cell.[13]

Pathophysiology

Despite the large number of diverse diseases leading to rhabdomyolysis, the final common pathway of injury involves damage to the sarcolemma, resulting in a rise in the intracellular calcium and the liberation of intracellular contents, such as myoglobin, aldolase, aspartate transaminase, lactate dehydrogenase, CK, potassium, uric acid, and phosphorus.[14] Excess intracellular calcium causes a pathologic interaction between myosin and actin, and activates intracellular proteases, phospholipases, and other proteolytic enzymes, resulting in further cell damage and destruction[11,15]

Direct cellular membrane damage (e.g., crush injury) or ATP depletion results in loss of the ionic gradients created by the sodium-potassium pumps and the sodium-calcium channels. Membrane damage from direct trauma makes the sarcolemma more permeable to calcium, which follows the electrochemical gradient and travels into the cell.[13,16] This causes extracellular hypocalcemia and intracellular hypercalcemia.[17] In atraumatic rhabdomyolysis, lack of adequate ATP causes membrane ion pump dysfunction, which also results in excess intracellular calcium accumulation.[11,13] ATP depletion may result from a mismatch between energy supply and demand (e.g., vigorous or prolonged exercise) or a defect in energy use (e.g., McArdle's syndrome or absence of muscle phosphorylase).[11]

Once destruction of the myocyte begins, myoglobin is released. As the levels of free plasma myoglobin increase, excess myoglobin is filtered by the kidneys and enters the urine.[18] Excess myoglobin, when coupled with hypovolemia and acidosis, can precipitate and block renal tubular flow.[6,19,20] Although universally present, tubular obstruction may not be the primary event in the development of acute intrinsic renal failure (AIRF) associated with rhabdomyolysis. Interestingly, myoglobin infusions in normovolemic rabbits with a urine pH above 6 have no deleterious effect on kidney function.[20] Other studies have demonstrated that myoglobin dissociates into its two components—globin and ferrihemate—at pH values of 5.6 or less.[20] Since infusions of the globin component have no effect on renal function even in the presence of hypovolemia and acidic urine, ferrihemate may be the toxic subunit of myoglobin.[21] Myoglobin may also be directly toxic to the renal tubular cells.[9,20,22] The most common cause of rhabdomyolysis-induced ARF is AIRF, which is defined as a decrease in the glomerular filtration rate caused by a toxic or ischemic event that is not reversed on discontinuation of the insult. AIRF is invariably associated with some degree of tubular injury and has a characteristic urine profile of low specific gravity (≈ 1.010), brown casts, and a fractional excretion of sodium greater than 1% (Box 125-1).

Compartment syndrome may be a cause or a complication of rhabdomyolysis. A compartment syndrome exists when the circulation to tissues within a closed space is compromised by increased pressure within that space.[23,24] The excessive pressure may occur as a result of a decrease in the size of the compartment, an increase in the size of the contents of the compartment, or a combination of both. Once established, compartment syndrome tends to be self-sustaining because (1) capillaries become occluded as a result of the increased pressure; (2) venous pressure increases, further decreasing perfusion pressure; and (3) arteriolar vasospasm leads to tissue ischemia, swelling, and edema. The swelling and edema cause an increase in the compartmental pressure and the cycle continues. In 2 to 4 hours, ischemic skeletal muscle may develop functional deficits, which may become irreversible after 10 hours.[23] Within 30 minutes of ischemia, nerve tissue exhibits reversible deficits that may become permanent after 12 to 24 hours of ischemia.[24]

BOX 125-1 Diagnostic Parameters in Acute Renal Failure and Acute Intrinsic Renal Failure

Odorless urine
Specific gravity <1.015
Urine sediment: "dirty" brown, granular casts
Urine osmolarity <350 mOsm/L
U/P osmolarity ratio <1.1
Urine sodium >20–40 mEq/L
U/P urea <4
U/P creatinine <20
Renal failure index: U_{Na} > 1–2
Fractional excretion of filtered sodium >1–20%
Free water clearance: rising to >15 mL/hr

U/P, urinary to plasma.
Modified from McGoldrick MD: Diagnosis and management of acute renal failure: Part I. Cardiovasc Rev Rep 5:1031, 1984.

BOX 125-2 GENERAL CAUSES OF RHABDOMYOLYSIS

Metabolic myopathies
Drugs and toxins
Trauma and compression
Infections
Exertion
Electrolyte abnormalities
Electrical current
Hypoxia
Hyperthermia
Idiopathic

Etiology

The relationship between traumatic muscle injury and kidney failure has been reviewed extensively over the past 60 years. In the mid-1970s the first references were made to nontraumatic rhabdomyolysis.[25,26] Since then, the number of known causes for this syndrome has greatly increased. In addition to trauma and compression, exercise, alcohol, drugs, infections, and seizures are the leading causes of rhabdomyolysis.[13] In many cases, the etiology is multifactorial (Box 125-2).

Metabolic Myopathies

Certain genetic defects do not allow appropriate use of carbohydrates or lipids as energy substrates, resulting in ATP depletion. These disorders include defects in glycolysis or glycogenolysis, defects of fatty acid oxidation, and dysfunction of cellular mitochondria. Each entity can cause recurrent attacks of reversible rhabdomyolysis or progressive weakness.[11] These enzyme defects are found in 23 to 47% of adult patients with rhabdomyolysis.[27,28] A genetic defect should be considered, particularly in a child who has no other apparent risk factors but has recurrent episodes of rhabdomyolysis, exercise intolerance, and muscle cramps. A genetic myopathy may be confirmed by a muscle biopsy.

Trauma and Compression

Most information regarding rhabdomyolysis from trauma and compression has been obtained from mass-casualty incidents,[29-31] such as traffic accidents and building collapses following earthquakes. In fact, crush-induced rhabdomyolysis is the most frequent cause of death after earthquakes, apart from trauma.[32] Thus, rhabdomyolysis should be expected in victims of crush injury. Direct mechanical injury to the sarcolemma disrupts its homeostatic functions.[16] Sodium and calcium travel down their concentration gradients into the intracellular fluid, resulting in an abrupt rise in the intracellular calcium and an influx of water.[11] The elevated calcium then activates enzymes destructive to the cell and sarcolemma, and the water influx contributes to intravascular volume depletion.[13,16,33]

In addition to overt trauma, immobilization in one position due to coma or altered mental status may lead to compression-induced traumatic rhabdomyolysis. It can be seen in surgical patients due to improper operative positioning (e.g., lithotomy) during a long procedure, as well.[11,34] Recently, there has been a rise in documented cases of rhabdomyolysis following bariatric surgery.[35] Identified risk factors include prolonged surgery (>4 hours), presence of diabetes, and body mass index (BMI) greater than 40.[36]

Exertion

Rhabdomyolysis can result from prolonged or strenuous exercise and is seen in both trained and untrained athletes.[37-39] Eccentric exercise (work done by a muscle during lengthening) is more damaging to muscle fibers, as evidenced by higher CK levels, than concentric exercise (work done by a muscle during shortening).[14] Hot conditions contribute to the incidence of exertional rhabdomyolysis because of increased dehydration and increased activity of heat-sensitive degradative enzymes.[39,40] Hypokalemia increases the risk of exertional rhabdomyolysis, since hypokalemia limits vasodilation and perfusion of the muscle microvasculature.[41] With prolonged exercise, the sarcolemmic ion pumps may also fail because of a depletion of cellular energy sources, specifically ATP.[11] The failure of these pumps leads to elevated intracellular calcium and subsequently rhabdomyolysis, which, coupled with dehydration and acidosis from lactic acid production, can cause ARF.[13,39,42] Exertional rhabdomyolysis is not always the result of voluntary muscle exertion, since the same pathophysiology is seen in patients with status epilepticus, myoclonus, dystonia, chorea, tetanus, psychotic agitation, and mania.[11,43-45]

Electrical Current

Rhabdomyolysis occurs in approximately 10% of patients who initially survive a high-voltage electrical injury or lightning strike.[18] Note that the severity of rhabdomyolysis is not related to the size of the wound or the site of entry.[18] Rhabdomyolysis from electrical current appears to be a result of both the heat generated by the electrical current and the direct effects of the current on the sarcolemma (electroporation).[46]

Heat and Cold Injury

Multiple disorders can raise the core body temperature and result in sarcolemma disruption. Neuroleptic malignant syndrome (fever in patients treated with phenothiazines or haloperidol), malignant hyperthermia (rapid rise in body temperature after anesthesia with halogenated hydrocarbons or succinylcholine), and both classic and exertional heatstroke[47] are some of the most common causes.[19,48,49] In hyperpyrexic syndromes, cellular energy demands outstrip available energy supplies, causing membrane dysfunction and cellular injury.[50]

Hypothermia may also cause rhabdomyolysis, most likely through cold-induced ischemia and direct injury to components of the sarcolemma, which cannot maintain structural integrity below certain temperature levels.[51]

Drugs and Toxins

Drugs in almost every class of medication have been implicated as a cause of rhabdomyolysis.[11] Common offenders include ethanol, cocaine and other licit and illicit drugs, lipid-lowering agents, carbon monoxide, and biologic toxins.

Ethanol. Ethanol is directly toxic to the skeletal muscle cell membrane, and this toxicity appears to be potentiated by starvation.[13] For this reason, ethanol-induced rhabdomyolysis is often seen in patients who are "binge drinkers." Electrolyte abnormalities also play a role, since chronic alcohol abusers often have hypokalemia, hypophosphatemia, and hypomagnesemia.[19] These deficiencies, coupled with ethanol's direct sarcolemmic toxic effects, make the ethanol abuser more susceptible to rhabdomyolysis.[13]

Ethanol is also a sedative-hypnotic, which can induce obtundation and lead to immobilization of a body part with

external compression of its blood supply. In addition, excessive motor activity from seizures or delirium tremens can induce rhabdomyolysis.

Cocaine. The incidence of rhabdomyolysis in patients who use cocaine varies from 5 to 30% in published reports.[48] Cocaine may produce rhabdomyolysis by several mechanisms; hypotheses include cocaine-induced vasospasm with resultant muscle ischemia, excessive energy demands placed on the sarcolemma, and direct toxic effects on myocytes.[52-54] Seizures, agitation, trauma, and hyperpyrexia may also play a role.[11] In general, the severity of rhabdomyolysis parallels the severity of intoxication.[52,55] Intravenous cocaine may be associated with a higher incidence of rhabdomyolysis-induced ARF than for smoking cocaine.[52]

Other Illicit Drugs. Agents such as D-lysergic acid diethylamide (LSD); phencyclidine hydrochloride (PCP); sympathomimetics, such as amphetamines; and "ecstasy" (MDMA; 3,4-methylenedioxymethamphetamine)[56] may also cause rhabdomyolysis.[11,57] Delirium and agitation, resulting in involuntary and voluntary muscle contraction, may raise energy demands of muscle cells. The increased demand may outstrip the supply of normally available ATP.[58]

Lipid-Lowering Agents and Other Licit Drugs. The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor lipid-lowering agents (e.g., lovastatin, simvastatin) have been associated with rhabdomyolysis,[59] as have the branched-chain fatty esters that inhibit liver triglyceride synthesis (e.g., clofibrate, gemfibrozil).[11,60,61] The mechanism of action is unclear, although statins are considered to be direct myotoxins that may interfere with ATP production through the electron transport chain. Statins may cause rhabdomyolysis when used alone or with other drugs, particularly gemfibrozil.[60,62,63] Patients with preexisting renal dysfunction, hypothyroidism, and inflammatory myopathies may be at greater risk.[64] Other direct myotoxins include colchicine and immunosuppressants such as cyclosporine. Overuse of diuretics or cathartics, leading to severe hypokalemia and dehydration, may also result in rhabdomyolysis.

Carbon Monoxide. Rhabdomyolysis is a known complication of carbon monoxide poisoning.[65,66] The pathophysiology is unknown, but hypoxia, muscle compression from coma, and direct myocyte toxic effects may play a role.[65]

Biologic Toxins. Some snake envenomations cause rhabdomyolysis through direct myocyte injury resulting in the release of intracellular contents to the extracellular circulation. Species known to do this include the European adder, Australian tiger snake, Australian king brown snake, sea snakes, North and South American rattlesnakes, and the death adder. Multiple myocyte toxins may be present in a single venom.[11] Stings from Africanized bees ("killer bees") and honeybees can also cause rhabdomyolysis. This is also mediated through direct myotoxins.[11,67,68] Mushroom poisoning has also been associated with rhabdomyolysis.[69]

Infections

Bacterial, viral, and parasitic infections have been associated with rhabdomyolysis.[70] Many viruses have been implicated, including influenza, coxsackievirus, parainfluenza, adenovirus, herpes simplex, Epstein-Barr, cytomegalovirus, and human immunodeficiency virus (HIV).[71] Patients classically report a history of a viral illness 1 to 2 weeks prior to the onset of myalgias and myoglobinuria. Influenza viruses A and B[72] are the most frequently cited viral causes.[73,74] Although viruses may be directly toxic to myocytes, this has not been proven.[13,75] Whereas rhabdomyolysis has been reported in many patients with HIV, the independent role of this virus is unclear because many of the patients in these studies were taking multiple medications or had concurrent infections.[76,77]

Bacterial infections may cause muscle damage through multiple mechanisms, including direct muscle infection in pyomyositis, as well as the release of exotoxins and cytokines, and the induction of fevers and rigors. *Legionella* is the most common known bacterial cause of rhabdomyolysis. Its myotoxic effects are mediated through an endotoxin.[13,78,79] *Salmonella* and *Streptococcus* also can induce rhabdomyolysis through both direct myocyte invasion and inhibition of glycolytic enzymes.[13,78,80]

Of parasitic infections, falciparum malaria (*Plasmodium falciparum*) is the most notorious for causing rhabdomyolysis, as patients have high fevers, rigors, vomiting, and ARF.[81]

Electrolyte Abnormalities

A variety of electrolyte disorders, particularly hypophosphatemia and hypokalemia, have been associated with rhabdomyolysis. Hypophosphatemia is believed to cause membrane injury by severe depletion of ATP, and most cases have been described in alcoholic patients[82] or those receiving treatment for diabetic ketoacidosis.[83] Since potassium is a vasodilator of the microcirculation for metabolically active muscle cells, hypokalemia may prevent local vasodilation and lead to focal muscle ischemia.[9,13] Hypocalcemia has also been associated with rhabdomyolysis in the setting of hypoparathyroidism.[84] Both hyponatremia and hypernatremia have also been associated with rhabdomyolysis,[11] with case reports of the former primarily involving hyponatremia induced by psychogenic polydipsia.[85]

Hypoxia and Ischemia

Intrinsic vascular injury or obstruction, hypotension, and external compression of the blood supply to a muscle group may all cause tissue hypoxia and rhabdomyolysis. For example, it may follow orthopedic or vascular reconstruction procedures in which a tourniquet is used. When circulation is reestablished, the damaged cell is reperfused and the extruded intracellular contents, including myoglobin, are brought into the general circulation.[13,86] Reperfusion is associated with an influx of neutrophils, which release proteolytic enzymes that can directly occlude the microcirculation and cause further muscle ischemia.[11,13] Certain blood disorders (e.g., sickle cell anemia)[87] may cause vascular thrombosis, resulting in tissue hypoxia and subsequent muscle injury, as well.[17,88]

Miscellaneous Causes

Endocrine disorders, such as diabetic ketoacidosis and nonketotic hyperglycemia, have been associated with rhabdomyolysis, possibly due to hypophosphatemia and hypokalemia and the hyperosmolar state.[89] Rhabdomyolysis has also been infrequently described in association with hypothyroidism, hyperthyroidism,[90] and pheochromocytoma.[91] Case reports have also been documented in the literature of rhabdomyolysis occurring in patients with inflammatory myopathies, such as dermatomyositis and polymyositis.[92]

CLINICAL FEATURES

Patients with rhabdomyolysis classically present with the complaints of muscle weakness, pain, and tea-colored urine. The myalgias may be focal or diffuse, depending on the underlying cause of the disease. However, a high clinical suggestion for rhabdomyolysis must be maintained in patients at risk, because

up to 50% of those with serologically proven rhabdomyolysis do not complain of myalgias or muscle weakness.[93] In fact, in the United States, rhabdomyolysis is most often due to prolonged muscle compression in the intoxicated patient who lays motionless or in the elderly patient with dementia following a fall.[93]

History

The history can be extremely helpful in making the diagnosis. The history should include any recent trauma or compression, excessive exertion, envenomations, infections, electrical shock, or temperature extremes. Other areas of interest are the use of prescription medications, over-the-counter drugs, alcohol or illicit drugs, known medical conditions, and a family history of muscle dysfunction or disease. Unfortunately, many patients with rhabdomyolysis are unable to provide an adequate history because of an altered sensorium.

Physical Examination

Physical examination may reveal weakness with tenderness to palpation of the affected muscle groups. Skin may be discolored, and there may be evidence of pressure necrosis. With trauma or compression, the affected area may have sensory and motor deficits that do not follow a single nerve distribution.[16] Some patients with severe rhabdomyolysis show bradypnea, presumably caused by diaphragmatic muscle involvement. Patients may also appear clinically dehydrated from the reduced extracellular fluid volume. Compartment syndrome is a relatively common complication of rhabdomyolysis, and thus, the exam may reveal firm muscle compartments, pain with passive extension, or neurovascular compromise of the affected extremity. Characteristic physical signs are present in only 4 to 15% of patients, however.[93] Therefore the absence of these exam findings does not rule out the diagnosis.

DIAGNOSTIC STRATEGIES

Myoglobin

In the past, the diagnosis of rhabdomyolysis rested on the demonstration of myoglobin in the serum. Serum myoglobin, however, is an insensitive marker for rhabdomyolysis. The half-life of myoglobin in plasma is 1 to 3 hours and can be cleared completely from plasma within 6 hours after injury.[93] Similarly, urine myoglobin, which is rapidly excreted, may also be an inaccurate measure. Myoglobinuria may be absent in patients who present late in the course of their illness, and the amount of myoglobinuria depends on the plasma concentration of myoglobin, renal function, the glomerular filtration rate, the extent of myoglobin binding in plasma, and urine flow rate.[93]

Methods used to measure urine myoglobin include immunodiffusion, radioimmunoassay, and specific dipstick tests. The dipstick tests involve use of reagents (e.g., guaiac, or *o*-toluidine) and are only slightly less sensitive than radioimmunoassay, which is the best method available.[94] Urinalysis typically shows brown urine with a large amount of blood on dipstick evaluation but few, if any, red blood cells (RBCs) on microscopic evaluation. This occurs because most dipstick tests cannot distinguish myoglobinuria from hematuria or hemoglobinuria.[94] Protein, brown casts, and renal tubular epithelial cells may also be found.[11]

Creatine Kinase

Measurement of CK levels (formerly CPK, creatine/creatinine phosphokinase) is a more sensitive method than myoglobin testing. CK is an excellent marker for rhabdomyolysis because it is easily measured, is present in the serum immediately after muscle injury, and is not rapidly cleared from serum (half-life is 1.5 days).[95] In general, peak CK levels occur within 24 to 36 hours of muscle injury and diminish approximately 39% per day (Fig. 125-2).[49] Failure of levels to decrease in this manner suggests ongoing muscle injury, possibly from an undetected compartment syndrome.

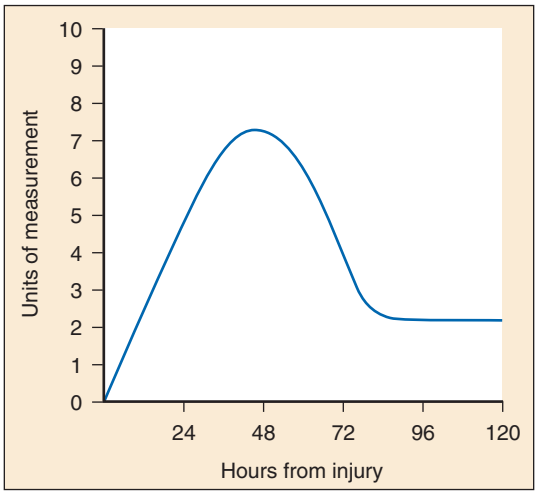

Figure 125-2. Typical creatine kinase elimination curve.

Rhabdomyolysis is not defined by a specific CK level. In general, however, in the absence of cerebral or myocardial infarction, a CK above 5000 indicates serious muscle injury, and a CK level greater than five times normal is thought to be diagnostic, although levels as high as several hundred thousand have been reported.[14,42,53,76] Higher CK levels, especially levels greater than 16,000, are correlated with the development of ARF.[96] However, since patients may have significant morbidity with only moderately elevated CK levels,[53,96,97] even modest elevations of CK must be taken seriously. The CK subtype present in skeletal muscle is MM, but when considerable skeletal muscle injury occurs, a small amount of CK-MB is also released. The CK-MB fraction rarely exceeds 3 to 5% and is indicative of the CK-MB released from skeletal muscle rather than from concomitant myocardial damage.

Other Tests

Other laboratory evaluation may show hyperkalemia, hyperphosphatemia, hypocalcemia, hyperuricemia, and hypoalbuminemia. An elevated anion gap is characteristically present.[98] Hyperkalemia (>5.5 mEq/L) has been reported on initial laboratory studies in 20 to 40% of patients.[93] It is caused by a combination of intracellular potassium release from muscle necrosis and decreased renal excretion. Hyperphosphatemia results from a leakage of phosphorus from injured muscle. Levels usually do not exceed 7 mg/dL, but a normal serum phosphate level in the setting of significant rhabdomyolysis raises the possibility that hypophosphatemia was the underlying cause of the rhabdomyolysis. The most common electrolyte abnormality—hypocalcemia—occurs early, and it can be exacerbated by hyperphosphatemia. Hypocalcemia results from the deposition of calcium into damaged muscle and decreased bone responsiveness to parathyroid hormone.[99] In one series of 76 patients, hypocalcemia was present in 63%.[100] Hypercalcemia often develops later. Although the exact cause of hypercalcemia is unknown, it is hypothesized that calcium is mobilized from damaged muscle, and parathyroid hormone

and 1,25-dihydroxycholecalciferol levels are increased during the recovery period.[13] The combination of elevated serum phosphate and calcium may result in precipitation of calcium phosphate in soft tissue, blood vessels, and eyes.[11]

Hyperuricemia results from the release of purines from damaged muscles. Hyperuricemia is more likely to occur in well-trained athletes with exertional rhabdomyolysis due to their increased muscle mass. Hypoalbuminemia may result from leakage of protein from injured vessels coupled with proteinuria.

Many patients with acute rhabdomyolysis demonstrate evidence of disseminated intravascular coagulopathy as a late complication. Thrombocytopenia, hypofibrinogenemia, and an elevated D-dimer with prolongation of prothrombin time may be seen. The coagulopathy is a result of muscle necrosis and liberation of activating substances (e.g., thromboplastin) from injured cells.

Some patients may have elevated levels of aspartate transaminase, alanine transaminase, and lactate dehydrogenase due primarily to muscle necrosis and less to hepatic injury from proteases released from injured muscle.[101]

DIFFERENTIAL CONSIDERATIONS

Pigmenturia has a variety of causes (Box 125-3). Hematuria can be distinguished from myoglobinuria through microscopic identification of RBCs in the urine with hematuria. Note that hematuria can be present with rhabdomyolysis if there is concomitant renal trauma. Similar to myoglobinura, hemoglobinuria demonstrates a positive dipstick test for blood but no, or few, RBCs on microscopic analysis. With hemoglobinuria, however, the plasma appears discolored as brown or red.[19] Pigmenturia can be associated with acute intermittent porphyria, as well, although these patients generally have a very different clinical presentation, and their urine contains porphobilinogen.[11] Bilirubin, a degradation product of heme, also causes pigmenturia when present in the urine. In this case, the urine tests positive for urobilinogen. Pigmenturia can also be a direct effect from certain drugs or foods, though the urine should test negative for blood, and the microscopic evaluation should demonstrate no RBCs.

In crush injury, the motor weakness and possible paralysis may mimic spinal injury.[102] All trauma patients must be treated with spinal precautions, and laboratory-proven rhabdomyolysis does not rule out concurrent spinal injury. With rhabdomyolysis, however, motor function often improves as the disease is treated.

BOX 125-3 DIFFERENTIAL DIAGNOSIS OF PIGMENTURIA

Hemoglobinuria
Hemolysis
Hematuria
Renal causes
Trauma
Acute Intermittent Porphyria
Bilirubinuria
Food
Beets
Drugs
Vitamin B_{12}
Rifampin
Phenytoin
Laxatives

Myocardial infarction must be considered in patients with an elevated CK level and pain, especially if the pain is localized to the chest. Measuring serum troponin, obtaining an electrocardiogram, and eliciting a history of ischemic chest pain help discern a cardiac cause of the CK elevation.

COMPLICATIONS

Complications of rhabdomyolysis may be categorized as early, if they occur within the first 24 hours after injury. Such early complications of rhabdomyolysis include electrolyte abnormalities, such as hyperkalemia, hypocalcemia or hypercalcemia, hyperphosphatemia, and hyperuricemia. The hyperkalemia may lead to cardiac arrhythmia and death. Hepatic dysfunction, another early complication, manifests as elevation in liver enzymes and occurs in 25% of patients. Proteases released from injured muscle are implicated in the hepatic inflammation.[101] Renal failure and disseminated intravascular coagulopathy are later complications, more commonly developing after 24 to 48 hours. In contrast, compartment syndrome, usually developing in muscles whose expansion is restricted by tight fascia, such as the tibialis anterior, may be an early or late complication of fluid resuscitation with worsening edema.

MANAGEMENT

After initial stabilization and resuscitation, the primary objective in managing rhabdomyolysis should be to identify and treat the underlying cause and to mitigate the associated complications: electrolyte derangements, renal failure, coagulopathy, and compartment syndrome.

Saline Infusion

The mainstay of therapy for rhabdomyolysis is the administration of large volumes of saline very early in the course of the disease. Fluid is sequestered in necrotic muscle and contributes to intravascular hypovolemia and prerenal renal failure. In patients with trauma or compression, saline resuscitation should begin in the field.[103] Delays in initiating rehydration increase the risk of oliguric and anuric renal failure.[104] In one study, no patients who underwent aggressive saline rehydration within the first 6 hours of admission developed ARF.[13,105]

Initial resuscitation should be undertaken with normal saline. Potassium-containing fluids should be avoided due to the risk of rhabdomyolysis-associated hyperkalemia. High-volume infusions should be started as soon as possible and infusion rates titrated for a urine output of 200 to 300 mL/hr.[18] Patients may require up to 20 L of fluid in the first 24 hours to achieve adequate urine flow rates. Ideally, the amount of fluid to be administered should be determined on the basis of the clinical course or central venous pressure measurements.[106]

Mannitol

Mannitol use is somewhat controversial in the treatment of rhabdomyolysis, since its use is mostly supported by animal studies and retrospective clinical studies.[107,108] In one study, mannitol did not confer any benefit compared with normal saline alone.[109] Mannitol is an osmotic diuretic, an intravascular volume expander, a renal vasodilator, and possibly a free radical scavenger. As a diuretic, mannitol increases urine flow, which may help prevent obstruction from myoglobin casts. Renal vasodilation increases renal blood flow and GFR, and

may also decrease tubular obstruction. As a volume expander, mannitol draws fluid from the interstitial space, decreasing intravascular dehydration and potentially reducing muscular swelling.[11,19,104] In cases of early ARF, mannitol may convert oliguric renal failure to nonoliguric renal failure, which has a somewhat better prognosis. Since mannitol is a diuretic, however, adequate volume resuscitation and urine flow should be established prior to its administration. Loop diuretics (e.g., furosemide) can acidify the urine and should not be used.[18]

Urine Alkalinization

Myoglobin precipitation is enhanced in acidic conditions, and myoglobin alone may not be nephrotoxic unless accompanied by intravascular volume depletion and acidosis.[20] Thus, urine alkalinization theoretically facilitates renal myoglobin clearance by increasing its solubility. The goal is to keep the urine pH greater than 6.5, which can be accomplished by adding bicarbonate to intravenous fluids. Two ampules of bicarbonate in 1 L of half normal saline produce a slightly hypertonic solution. Thus, it may be prudent to add 1.5 ampules of bicarbonate to 1 L of half normal saline or 2 ampules of bicarbonate in 5% dextrose in water, especially when mannitol, a hyperosmolar agent, is also administered. Potential adverse effects of sodium bicarbonate therapy include hypernatremia, aggravation of fluid overload in patients with congestive heart failure, and the exacerbation of hypocalcemia.

Similar to mannitol administration, alkalinization as a therapeutic modality for rhabdomyolysis is being questioned, since no randomized studies have demonstrated a benefit. In fact, Hosmi and colleagues[109] found no benefit of bicarbonate therapy over vigorous fluid hydration. More recently, Brown and associates reviewed the case records of 1771 critically ill trauma patients with increased CK levels and demonstrated no difference in the incidence of renal failure (22% vs. 18%), dialysis (7% vs. 6%), or mortality (15% vs. 18%) between the group that received mannitol and bicarbonate versus the group that only received saline hydration.[110] Thus, further studies are needed to demonstrate if any treatment regimen is truly superior to early, vigorous saline hydration.[111]

Experimental Therapies

A potential role for iron chelators, such as desferrioxamine, is under investigation. Chelation therapy reduces renal injury in animal models.[112] The theory is that iron chelation diminishes exposure to free iron, thereby decreasing lipid peroxidation and myocyte breakdown.

One case report demonstrated that hyperbaric oxygen was beneficial when used as adjunctive therapy for a patient with compartment syndrome, rhabdomyolysis, and ARF after a heroin overdose.[113]

Other experimental models demonstrate a reduction in muscle necrosis due to ischemia-reperfusion injury with the administration of free-radical scavengers and antioxidants, such as vitamin E and vitamin C, and minerals, such as zinc, manganese, and selenium. These, therefore, are potential therapeutic agents in the management of rhabdomyolysis.[114]

General Measures

Electrolyte Abnormalities

Hyperkalemia is a potentially life-threatening complication of rhabdomyolysis and must be treated. However, intravenous calcium may be ineffective as a treatment for hyperkalemia if given to a patient with hyperphosphatemia, since the calcium and phosphate may precipitate.[11] Moreover, correction of initial hypocalcemia with intravenous calcium can exacerbate the normal hypercalcemia that occurs in the recovery phase of rhabdomyolysis when calcium deposited in the injured muscle cells is mobilized back into the extracellular space. Thus, the use of calcium for asymptomatic hypocalcemic patients should be avoided because it may raise intracellular calcium levels, promoting further muscle injury.[84] In addition to administering potassium resin binders, as well as insulin, glucose, and bicarbonate, dialysis may be required to treat hyperkalemia. Symptomatic hypercalcemia generally requires only volume expansion and diuretic therapy. For patients with a rising or elevated potassium level, persistent acidosis, uremia, or oliguric or anuric renal failure with fluid overload, dialysis may be necessary.[11,13] Dialysis with supportive care should effectively limit the morbidity and mortality from ARF associated with rhabdomyolysis.

Coagulopathy/Disseminated Intravascular Coagulopathy

Therapy for coagulopathy is directed at treatment of the underlying disease process. However, if hemorrhagic complications occur, therapy with platelets, vitamin K, and fresh frozen plasma may be necessary.

Compartment Syndrome

Clinicians should monitor compartment pressures in the patient with suggested or existing compartment syndrome. When compartmental pressure exceeds 30 to 35 mm Hg, fasciotomy should be strongly considered, although the decision to perform a fasciotomy must be decided on a case-by-case basis.[115] The failure of CK levels to decline appropriately suggests ongoing muscle injury from a compartment syndrome (Fig. 125-3).

DISPOSITION

No good prospective studies support a standardized approach to disposition of the patient with rhabdomyolysis. The high

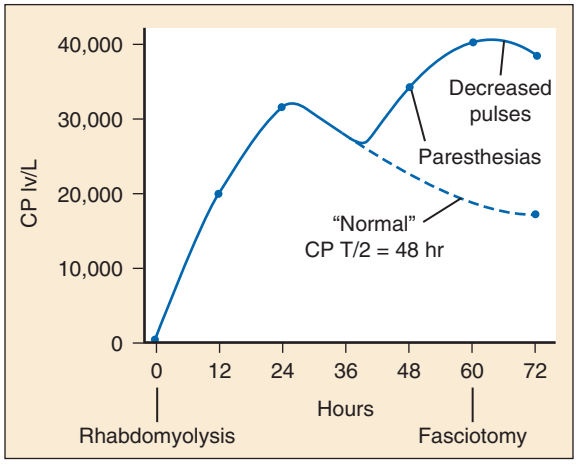

Figure 125-3. Rhabdomyolysis: second-wave phenomenon. Serum creatine kinase (CK) activity resulting from a single bout of muscle injury usually peaks at about 24 hours. Its half-life (T/2) is about 48 hours. A second rise may occur if necrosis has involved a muscle in a tight fascial compartment in which sufficient edema accumulates to produce ischemia and a second wave of necrosis. (Redrawn from McGoldrick MD: Diagnosis and management of acute renal failure: Part I. Cardiovasc Rev Rep 5:1031, 1984.)

risk for renal failure, however, mandates close monitoring of renal function, electrolytes, and hydration status, which usually requires admission to the hospital. Also, if the patient is a victim of trauma, serial CK levels should be followed to assess for ongoing muscle injury. If the patient is not a victim of trauma or compression injury, the underlying etiology of the rhabdomyolysis requires investigation to prevent recurrences.

KEY CONCEPTS

- Classic clinical manifestations of rhabdomyolysis include myalgias, weakness, and tea-colored urine. Because only half of patients present classically, the emergency physician should consider rhabdomyolysis in patients at risk, particularly when they present with an altered sensorium.
- Alcohol abuse, illicit drug use, certain medications, muscle overexertion, and traumatic muscle compression are the most common causes of rhabdomyolysis.
- In rhabdomyolysis, urine dipstick testing is strongly positive for blood, with few, or no, RBCs on microscopic examination. The diagnosis is confirmed by an elevated serum CK level.
- Early fluid resuscitation resulting in a urine output of 200 to 300 mL/hr reduces the risk of rhabdomyolysis-induced renal failure. Intravenous fluids are the primary treatment, with mannitol and urine alkalinization as adjuncts of unproven benefit. Loop diuretics should not be used since they can acidify the urine.
- Hyperkalemia can precipitate malignant cardiac dysrhythmias and must be treated promptly.
- To avoid exacerbating the hypercalcemia, which normally occurs during the recovery period when excess intracellular calcium shifts into the extracellular space, initial asymptomatic hypocalcemia should not be corrected.
- CK levels that do not decrease or continue to rise beyond 48 hours may indicate continued muscle injury and warrant a careful evaluation for compartment syndrome.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 126

Thyroid and Adrenal Disorders

David Zull

Hyperthyroidism, hypothyroidism, and adrenal insufficiency are endocrine disorders that often manifest with chronic, nonspecific symptoms such as fatigue, weakness, and depression, and as a result are difficult to recognize in a typical medical encounter. With increased severity, each disorder has classic clinical manifestations that are more easily recognizable. Most importantly for the emergency physician, acute stresses can precipitate life-threatening illnesses in these patients, requiring vigorous medical management based on clinical judgment and suggestive laboratory data alone.

HYPERTHYROIDISM

Perspective

Background and Epidemiology

Although the terms *hyperthyroidism* and *thyrotoxicosis* are often used interchangeably, hyperthyroidism refers to conditions in which the production of thyroid hormone is increased, whereas thyrotoxicosis is defined as any state in which thyroid hormone levels are increased in the blood, whether it be from overproduction (Graves' disease, toxic multinodular goiter [TMG]), thyroid hormone release from an injured gland (thyroiditis), or exogenous thyroid hormone. The clinical spectrum of hyperthyroidism is a continuum from asymptomatic or subclinical disease to life-threatening thyroid storm.

On large random population screenings, the prevalence of hyperthyroidism is 0.5 to 2.2%, with more than half of these patients considered subclinical (prehyperthyroid state with depressed thyroid-stimulating hormone [TSH] and normal tetraiodothyronine, thyroxine [T_4]).[1-3] The prevalence of hyperthyroidism in women is tenfold greater than in men.

Graves' disease is the predominant cause of thyrotoxicosis, with TMG becoming more common with increasing age, exceeding Graves' disease by 2 to 1 in patients older than 55 years.[4,5] Hyperthyroidism is rare in childhood, but when seen is related to Graves' disease. It is estimated that 1 to 2% of patients with thyrotoxicosis will progress on to thyroid storm when an acute intercurrent stress supervenes.[6]

Principles of Disease

The follicular cells of the thyroid gland produce T_4 and triiodothyronine (T_3), which are regulated by a feedback loop with the anterior pituitary gland, which produces TSH. If levels of T_4 drop, TSH production is stimulated, whereas if the T_4 level is high, TSH is suppressed. TSH is in turn regulated by the hypothalamus's production of thyrotropin-releasing hormone (TRH).

Thyroid hormone synthesis by the follicular cells starts with the production of thyroglobulin, a large hormonal precursor protein with numerous tyrosines in its structure. Iodine is then actively transported into follicular cells where it is oxidized and then bound to tyrosine residues. Linking of iodotyrosines within thyroglobulin produces T_4 and T_3, which are released into the circulation by proteolyisis. All of T_4 is produced in the thyroid gland, whereas only 15 to 20% of T_3 is synthesized directly; the remainder is formed by deiodonation of T_4 in peripheral tissues. During systemic illness, deiodonation occurs, but at an inner ring of T_4, rather than the outer ring, and reverse T_3 is produced. T_4 is a prohormone with only mild intrinsic activity, whereas T_3 is the biologically active hormone, and reverse T_3 is inactive. Over 99.5% of thyroid hormones are protein-bound in the serum to thyronine-binding globulin (TBG) and other proteins, rendering them metabolically inactive. As a result, only free T_4 and free T_3 are clinically relevant.[4,6,7]

Although iodide is a substrate for thyroid hormone production, excess iodide inhibits iodide trapping and thyroglobulin iodination (the Wolff-Chaikoff effect) and most importantly blocks the release of thyroid hormone from the gland. Iodide's inhibition of thyroid hormone production and release is transient, with the gland escaping inhibition after 10 to 14 days. In contrast, an iodide load can induce hyperthyroidism (Jod-Basedow effect) in some patients with multinodular goiter and latent Graves' disease, especially if the patient is iodine-deficient to begin with.[4,6,7]

Thyroid hormone has effects on the metabolism of all tissues, exerting these at several levels. Thyroid hormone regulates gene activity by interaction at nuclear receptors. It has direct effects on metabolism by interaction with cellular enzymes, like adenosine triphosphatase. Most importantly, T_3 and T_4 increase the number and sensitivity of beta-adrenergic receptors, dramatically increasing response to endogenous catecholamines.[4,6]

Graves' disease is the most common cause of thyrotoxicosis and consists of the syndrome of hyperthyroidism, a diffuse symmetrical goiter, ophthalmopathy, and dermopathy. Graves' disease primarily affects females between the ages of 20 and 40 years, often those with a family history of thyroid disease. It is an autoimmune disorder in which B lymphocytes produce

immunoglobulins that stimulate the TSH receptor (thyroid-stimulating immunoglobulin [TSI]). The eye disease that accompanies the disease is thought to result from thyroid antibodies sensitized to common antigens in orbital fibroblasts and muscle.[4,6]

TMG is the second leading cause of hyperthyroidism, characterized by multiple autonomously functioning nodules typically developing in women older than 50 years of age. It is unusual in youth unless the patient has a preexisting nontoxic multinodular goiter or lives in a region of iodine deficiency. The population of the United States is generally iodine-sufficient, but areas of the world with populations that are deficient include Central America, South America, the Himalayas, Eastern Europe, and Central Africa. The hyperthyroidism in TMG is milder than Graves' disease and is gradual in onset, but acute presentations can occur when iodine replacement is given to an iodine-deficient individual. Because of the age of the patients, cardiovascular manifestations like atrial fibrillation and heart failure predominate,[8] whereas tremors and hypermetabolic features are less pronounced than Graves' disease. Muscle wasting and weakness is common, and the patient is often described as apathetic.[5] As multinodular goiters often extend retrosternally, obstructive symptoms may occur.[9,10]

A single hyperfunctioning (hot) nodule referred to as a toxic adenoma may occur in this same population, but it is less common than the multinodular form.

In thyroiditis, acute thyrotoxicosis can result from thyroid gland inflammation and cell breakdown with release of preformed thyroid hormone. Thyroiditis may be autoimmune in origin, infectious, or drug-induced. Hashimoto's thyrioditis is the most common type of thyroiditis. It is an autoimmune disorder characterized by thyroid antibodies and lymphocytic infiltration of the thyroid gland. Patients present with painless goiter and hypothyroidism, but thyrotoxicosis is rarely evident early in the disease (hashitoxicosis).[11]

Related autoimmune disorders of the thyroid include postpartum thyroiditis and sporadic thyroiditis. They are also referred to as painless, or silent, thyroiditis due to their small nontender goiter and mild symptoms. Five to 10% of pregnant women develop transient thyrotoxicosis 1 to 6 months postpartum, followed by a hypothyroid state for up to 6 months, then a return to baseline. There is a 70% chance of recurrence in subsequent pregnancies, and some women develop permanent hypothyroidism. Sporadic thyroiditis, which may account for up to 1% of thyrotoxicosis, is a similar entity, except for its lack of association with pregnancy.[12]

Subacute thyroiditis (de Quervain's thyroiditis) appears to be a viral or postviral disease that presents with a prodrome of fatigue, myalgias, and pharyngitis, followed by fever and severe anterior neck pain. Pain often radiates to the jaw and ears, and the gland is exquisitely tender. Symptoms of hyperthyroidism with sweats, palpitations, and tremor develop during this acute painful phase and may last several weeks, transitioning to a hypothyroid state for several months, then a return to a euthyroid state. Subacute thyroiditis may account for 2% of thyrotoxic patients and as is the case for other thyroid diseases, women predominate.[13]

Suppurative thyroiditis is a rare disorder that also presents with fever and anterior neck pain, but is marked by neck swelling, induration, and erythema and the presence of dysphonia and dysphagia. The cause is usually bacterial infection with abscess formation, but parasites, mycobacteria, and fungi may be responsible. Most patients have preexisting thyroid disease and are immunocompromised (AIDS).[14]

In North America, about 2% of patients treated with amiodarone develop thyrotoxicosis (higher in areas of iodine deficiency). Most of these cases result from a destructive thyroiditis, but a minority are due to amiodarone's iodine load (400 times the daily requirement), which may unmask hyperthyroidism in patients with multinodular goiter and subclinical Graves' disease. An exacerbation of the tachyarrhythmia that the patient is being treated for or heart failure is the typical presentation of a patient with thyrotoxicosis related to amiodarone. Other drugs that may induce thyroiditis include interferon, interleukin-2, granulocyte-macrophage colony-stimulating factor, and lithium.[12,15,16]

Chronic excess ingestion of thyroid hormone can result in thyrotoxicosis, referred to as thyrotoxicosis factitia. Although iatrogenic or patient errors may be responsible, medical personnel with psychiatric disease account for the majority of reported cases. Inadvertent ingestion of thyroid hormone in herbal products for weight reduction or in contaminated ground beef has been reported as well. Surprisingly, acute ingestions of thyroid hormone usually manifest only minor toxicity. The reasons for this are multiple: the 7-day half-life of T_4, the suppression of T_4-to-T_3 conversion and inhibition of endogenous hormone production by negative feedback loops, and the down-regulation of thyroid hormone receptors.[17,18]

A variety of rare forms of thyrotoxicosis have been described, including struma ovarii, thyroid carcinoma, hydatidiform mole, choriocarcinoma, and TSH-secreting pituitary adenomas[4,6,19] (Box 126-1).

Clinical Features

The symptoms and signs of thyrotoxicosis are caused by a hypermetabolic state and increased beta-adrenergic activity. Clinical manifestations vary from minimal (apathetic hyperthyroidism) to life-threatening (thyroid storm) and depend on the patient's age, duration of disease, the level and rate of rise of hormone levels, drug interactions, and the stress of intercurrent illness. Hyperadrenergic manifestations are often masked in the elderly. Thyrotoxicosis of long duration and gradual course may go unnoticed by many patients, or symptoms may be attributed to other causes like emotional stress, dieting, or physical deconditioning.[4,6]

BOX 126-1 CAUSES OF THYROTOXICOSIS

- Graves' disease (toxic diffuse goiter)
- Toxic multinodular goiter
- Toxic adenoma (single hot nodule)
- Factitious thyrotoxicosis
- Thyrotoxicosis associated with thyroiditis
  - Hashimoto's thyroiditis
  - Subacute (de Quervain's) thyroiditis
  - Postpartum thyroiditis
  - Sporadic thyroiditis
  - Amiodarone thyroiditis
- Iodine-induced hyperthyroidism (areas of iodine deficiency)
  - Amiodarone
  - Radiocontrast media
- Metastatic follicular thyroid carcinoma
- hCG-mediated thyrotoxicosis
  - Hydatidiform mole
  - Metastatic choriocarcinoma
  - Hyperemesis gravidarum
- TSH-producing pituitary tumors
- Struma ovarii

hCG, human chorionic gonadotropin; TSH, thyroid-stimulating hormone.

Constitutional symptoms such as fatigue and generalized weakness are very common in thyrotoxicosis. Despite increased calorie intake, weight loss is seen in most patients, averaging about a 15% drop from baseline. To confound things, elderly patients often have a decreased appetite, leading to a suggestion of occult cancer. Hypermetabolic symptoms like heat intolerance, excessive sweating, and preference for the cold are most pronounced in younger patients.[20]

Neuropsychiatric complaints include anxiety, restlessness, tremor, feeling jittery or unable to sit still, insomnia, memory loss, and poor attention span. Family members often report emotional lability and agitation, which may progress to altered mental status and coma in thyroid storm. Weakness and fatigue of proximal muscle groups may result from thyroid myopathy, with patients often complaining of difficulty combing their hair, climbing stairs, or rising from a chair.[21] A sudden and profound muscle weakness progressing to flaccid paralysis is described in a thyrotoxic variant of hypokalemic periodic paralysis.[22]

Cardiopulmonary symptoms are very common and include palpitations, dyspnea on exertion, and reduced exercise tolerance. Older patients may present with new-onset angina, atrial fibrillation, or congestive heart failure as the presenting and only symptoms of thyroid disease.[8,16,23]

Gastrointestinal complaints often include more frequent bowel movements, but not diarrhea. Dysphagia may result from enlargement of the thyroid gland in Graves' disease or retrosternal extension of the gland in TMG. Nausea and vomiting may be seen with severe thyrotoxicosis.[4,6,9]

Reproductive endocrine function can be affected. Women often complain of a change in their menses, anywhere from amenorrhea to menometrorrhagia, and infertility is very common. Men may complain of a decrease in libido and breast swelling.[4,6]

Ocular complaints may result from ophthalmopathy in Graves' disease, but not in other causes of thyrotoxicosis. A sense of irritation and excessive tearing are early symptoms, with diplopia, retrobulbar discomfort, blurring of vision, and foreign body sensation occurring late in the disease[24] (Box 126-2).

Physical examination of the thyrotoxic patient may reveal distinctive findings, especially in younger individuals. The patient often appears anxious and fidgety, with a fine tremor of the hands and tongue and lightly closed eyelids. The skin feels warm, smooth, and velvety, likened to a baby's skin, especially over the elbows. The face is rosy and blushes readily. The hands may reveal palmar erythema and the distal part of the nails may separate from the nail bed (onycholysis, or Plummer's nails). Scalp hair is fine and brittle, and diffuse alopecia may occur.[4,6] Specifically in Graves' disease, about 5% of patients develop marked thickening of the pretibial skin by mucopolysaccharide infiltration of the dermis (pretibial myxedema). These lesions are painless, raised nodules and plaques that become confluent over the pretibial area and dorsum of the feet. Hyperpigmentation and induration are present, but pitting is absent, and pretibial myxedema is always associated with Graves' eye disease.[25]

Tachycardia is seen in virtually all patients, and there is widening of the pulse pressure with bounding pulses. The apical impulse is prominent and the heart sounds are enhanced. A systolic flow murmur is usually present, and rarely a friction rublike sound along the left sternal border (Means-Lerman scratch) may also be heard. Atrial fibrillation can be seen at any age in hyperthyroidism, with an overall prevalence of 2%, but the frequency is age-dependant, rising to 15% in patients older than 70 years.[26] Even subclinical hyperthyroidism appears to increase the prevalence of atrial fibrillation threefold over that in the average population.[27]

The ventricular response in thyrotoxic atrial fibrillation may be unusually fast, and the patient may be resistant to attempts to slow the rate as well as to convert to sinus rhythm. The chronic tachycardia and high cardiac output state in hyperthyroidism may lead to dilated cardiomyopathy, especially in elders and those with atrial fibrillation, resulting in an S_3 gallop and basilar crackles.[8,16,23,28] Primary pulmonary hypertension, sometimes associated with tricuspid regurgitation and right heart failure, may also be seen.[16,29,30]

The characteristic stare of thyrotoxicosis results from retraction of the upper and lower eyelids revealing a rim of sclera beyond the limbus. As the eyelids are sympathetically innervated, the increased sensitivity to adrenergic stimuli in thyrotoxicosis leads to the widening of the palpebral fissures. Other hyperadrenergic eye findings in thyrotoxic patients include lid lag and globe lag. In lid lag, the upper lid lags behind the globe when the patient is asked to look slowly downward. In globe lag, the globe lags behind the upper lid with slow upward gaze.[4,24]

Although stare is frequent in any form of thyrotoxicosis, proptosis of the globe is unique to Graves' disease, resulting from mucopolysaccharide infiltration and inflammation of the ocular muscles and soft tissue leading to exophthalmos. Imaging with ultrasound, computed tomography, or magnetic resonance imaging reveals orbital swelling in virtually all patients with Graves' disease, but only about 50% have clinical findings. Conjunctival injection, periorbital edema, and chemosis are early findings. Proptosis is defined by the anteroposterior distance from the lateral orbital ridge to the anterior cornea as greater than 20 mm. Progressive orbital involvement may lead to infiltration of the inferior rectus muscle with limitation of upward gaze. Very late findings can include keratitis from inability to close the eyes completely, and visual loss from optic nerve compression.[24] Treatment of hyperthyroidism, especially with radioactive iodine, may paradoxically aggravate Graves' eye disease.[31]

Chronic proximal muscle wasting and weakness may result from thyrotoxic myopathy.[21] More acute weakness with flaccidity may occur in Asian and Latino males from the thyrotoxic form of hypokalemic periodic paralysis.[22]

Most thyrotoxic patients have a palpable abnormality on examination of the thyroid gland. In Graves' disease, the gland is often two to three times normal size, but may be massively enlarged. A normal-size gland is unusual in younger patients, but more than 20% of older patients lack a goiter.[4] The thyroid

BOX 126-2 PATIENT COMPLAINTS IN THYROTOXICOSIS

Constitutional: Weight loss despite hyperphagia, fatigue, generalized weakness
Hypermetabolic: Heat intolerance, cold preference, excessive perspiration
Cardiorespiratory: Heart pounding and racing, dyspnea on exertion, chest pains
Psychiatric: Anxiety, restlessness, hyperkinesis, emotional lability, confusion
Muscular: Tremor, difficulty getting out of a chair or combing hair
Ophthalmologic: Tearing, irritation, wind sensitivity, diplopia, foreign body sensation
Thyroid Gland: Neck fullness, dysphagia, dysphonia
Dermatologic: Flushed feeling, hair loss, pretibial swelling
Reproductive: Oligomenorrhea, decreased libido, gynecomastia

gland in Graves' disease is symmetrical, smooth, soft to rubbery consistency, and has no evident nodules. In severe disease a palpable thrill and audible bruit are present and are usually continuous, rather than the systolic bruit seen with vascular disease. In TMG, the gland is variably enlarged and although multiple irregular nodules are often palpable, a single dominant nodule is not unusual, making distinguishing TMG from toxic adenoma difficult. The multinodular goiter may extend retrosternally, hiding it on examination unless the supraclavicular area is palpated on swallowing. By mass effect, a multinodular goiter may cause tracheal deviation and hoarseness as well as facial and neck vein engorgement, the latter becoming evident when the arms are elevated above the head (Pemberton's sign)[9,10] (Box 126-3).

In subacute thyroiditis, the thyroid gland is exquisitely tender, but redness or warmth of the overlying skin is only seen in suppurative thyroiditis. In the more typical entities of sporadic, postpartum, and Hashimoto's thyroiditis, the gland is nontender with modest to no enlargement.[11-14] In factitious thyrotoxicosis, the gland may be atrophic but this may be difficult to appreciate.

Thyroid Storm

Thyroid storm is a life-threatening decompensation of poorly controlled, untreated, or unrecognized thyrotoxicosis. It occurs in 1 to 2% of thyrotoxic patients and in about 10% of patients hospitalized for hyperthyroidism. Thyroid storm occurs predominately in Graves' disease, but occasionally is seen in TMG and toxic adenoma.[32,33] Occurrences in thyroiditis,[34] factitious thyrotoxicosis,[35] struma ovarii, hydatidiform mole,[19] and other causes of thyrotoxicosis are limited to rare case reports.

Thyroid storm is an exaggeration of the clinical manifestations of thyrotoxicosis, further distinguished by the presence of fever, marked tachycardia, central nervous system dysfunction, and gastrointestinal symptoms. Decompensation of one or more organ systems, such as shock or heart failure, also defines thyroid storm. If untreated, thyroid storm is uniformly fatal, and even with aggressive management it still carries a 20% mortality rate.[6,32,36,37]

BOX 126-3 Physical Findings in Thyrotoxicosis

Vital Signs: Tachycardia, widened pulse pressure, bounding pulses, fever
Cardiac: Hyperdynamic precordium, systolic flow murmur, prominent heart sounds, systolic rub (Means-Lerman scratch), tricuspid regurgitation, atrial fibrillation, evidence of heart failure
Ophthalmologic: Widened palpebral fissures (stare), lid lag, globe lag, conjunctival injection, periorbital edema, proptosis, limitation of superior gaze
Neurologic: Fine tremor, hyper-reflexia, proximal muscle weakness
Psychiatric: Fidgety, emotionally labile, poor concentration
Dermatologic: Warm, moist, smooth skin; fine, brittle hair; alopecia, flushed facies; palmer erythema; hyperpigmented pretibial plaques, nodules, or induration that is nonpitting; onycholysis
Neck: Diffuse symmetrical thyroid enlargement, sometimes with a bruit and palpable thrill; thyroid with multiple irregular nodules or a prominent single nodule; tracheal deviation, venous prominence with arm elevation (Pemberton's sign)

Central to the pathophysiology of thyroid storm is an increase in catecholamine-binding sites and hence a heightened response to adrenergic stimuli. Superimposed on this vulnerable state is an acute stress that causes an outpouring of catecholamines that in conjunction with high levels of free T_4 and T_3 precipitates the exaggerated response we call thyroid storm.[4,6,37] It was once thought that thyroid storm resulted from a sudden dumping of thyroid hormone into the circulation, but except for sudden cessation of antithyroid therapy in a hyperthyroid patient and blunt or penetrating trauma to the thyroid gland (in both hyperthyroid and euthyroid patients) in which hormone leaks from injured acini, rapid rises in T_4 and T_3 are not responsible for storm.[38-41] In fact, hormone levels in thyroid storm are not generally distinguishable from poorly controlled thyrotoxicosis.[7]

Infection and sepsis are the most common precipitants of thyroid storm, but as fever is a prominent feature of storm, the thyrotoxic state may be overlooked. Historically, thyroid and nonthyroid surgery have been the leading triggers of thyroid storm, but identification and treatment of thyrotoxicosis preoperatively has dramatically decreased this as a precipitant. Other common precipitating events include myocardial infarction, stroke, pulmonary embolism, diabetic ketoacidosis, parturition, trauma, and administration of iodinated contrast media and amiodarone (Box 126-4).

The clinical presentation of thyroid storm is often dramatic. Although many of the findings of thyrotoxicosis are evident on

BOX 126-4 Precipitants of Thyroid Storm

Medical
Infection/sepsis
Cerebral vascular accident
Myocardial infarction
Congestive heart failure
Pulmonary embolism
Visceral infarction
Emotional stress
Acute manic crisis

Trauma
Thyroid surgery
Nonthyroid surgery
Blunt and penetrating trauma to the thyroid gland
Vigorous palpation of the thyroid gland
Burns

Endocrine
Hypoglycemia
Diabetic ketoacidosis
Hyperosmolar nonketotic coma

Drug-Related
Iodine-131 therapy
Premature withdrawal of antithyroid therapy
Ingestion of thyroid hormone
Iodinated contrast agents
Amiodarone therapy
Iodine ingestion
Anesthesia induction
Miscellaneous drugs (chemotherapy, pseudoephedrine, organophosphates, aspirin)

Pregnancy-Related
Toxemia of pregnancy
Hyperemesis gravidarum
Parturition and the immediate postpartum period

exam, certain features distinguish thyroid storm. Fever out of proportion to the physician's expectations is characteristic of storm, sometimes mimicking heatstroke with temperatures exceeding 106° F. Inappropriately excessive diaphoresis is frequently observed, and sinus tachycardia over 140 beats per minute is common.[4,6,36,37] Heart rates exceeding 150 beats per minute may be indicative of atrial fibrillation or other supraventricular tachycardias. In addition, symptoms and signs of congestive heart failure often accompany such rapid rates.[8,16]

Altered mental status from metabolic encephalopathy is a hallmark of thyroid storm, ranging from restlessness and agitation to delirium, seizures, and coma.[21,42]

Gastrointestinal symptoms are often pronounced, with nausea, vomiting, and diarrhea leading to volume depletion and hypotension. Abdominal pain mimicking bowel obstruction may be present. An unusual complication of severe thyrotoxicosis is cholestatic jaundice, which carries a bad prognosis if hepatic failure ensues.[43]

Although hyperthermia, exaggerated tachycardia, and altered mental status can quickly identify possible thyroid storm, the clinical presentation can be difficult to differentiate from uncomplicated thyrotoxicosis. Taking into account the severity of fever, tachycardia, central nervous system dysfunction, congestive heart failure, and gastrointestinal symptoms, Burch and Wartofsky developed a scoring system to help distinguish uncomplicated thyrotoxicosis from impending thyroid storm and true thyroid storm (Table 126-1). Although this scoring system has not been rigorously tested, it may prove useful in decisions to treat in borderline cases.[44]

Table 126-1 Diagnostic Criteria for Thyroid Storm

	SCORE
Fever (°F)	
99–99.9	5
100–100.9	10
101–101.9	15
102–102.9	20
103–103.9	25
≥104	30
Tachycardia (beats/min)	
90–109	5
110–119	10
120–129	15
130–139	20
≥140	25
Mental Status	
Normal	0
Mild agitation	10
Delirium, psychosis	
Extreme lethargy	20
Coma/seizures	30
Congestive Heart Failure	
Absent	0
Mild (edema)	5
Moderate (rales)	10
Pulmonary edema	15
Atrial fibrillation	10
Gastrointestinal and Hepatic Symptoms	
None	0
Nausea, vomiting	10
Diarrhea, abdominal pain	
Unexplained jaundice	20
Precipitating Event	
None	0
Present	10

Adapted from Burch HB, Wartofsky L: Life-threatening thyrotoxicosis: Thyroid storm. Endocrinol Metab Clin North Am 1993; 22: 263–277.

Tally the maximum score from each category. A score of 45 or greater suggests thyroid storm; a score of 25–44 suggests impending storm, and a score below 25 is unlikely to represent thyroid storm.

Diagnostic Strategies

The best screening tool for the diagnosis of thyrotoxicosis is the ultrasensitive TSH, which is depressed or undetectable in thyrotoxicosis. A normal TSH excludes hyperthyroidism and an elevated TSH is diagnostic for hypothyroidism, except in the rare circumstance of secondary hyperthyroidism from overproduction of TSH by a pituitary adenoma. Although a nondetectable TSH is specific for thyrotoxicosis, a modest depression of the TSH measurement is not always the result of mild or subclinical hyperthyroidism. Severe systemic illness may depress TSH production, leading to low levels of TSH, free T_3, and free T_4. This nonthyroidal illness pattern is often referred to as the euthyroid sick syndrome, and it appears to be a transient form of central hypothyroidism, an adaptive response to slow metabolism during systemic stress. Chronic conditions in which TSH may be suppressed include anorexia nervosa, depression, and renal failure. Medications, including dopamine, glucocorticoids, somatostatin, and octreotide, may also depress TSH levels.[6,7]

Although screening for thyroid disease with TSH is a reasonable strategy, measurement of thyroid hormone levels is required for a definitive diagnosis. Total T_3 and total T_4 assays may be misleading as they are influenced by changes in TBG. Increases in TBG with resultant false elevations in total T_3 and T_4 are seen in pregnancy, infectious hepatitis, and drug therapy with estrogens, tamoxifen, methadone, or heroin. In contrast, decreases in TBG with subsequent low total T_3 and T_4 are seen in cirrhosis, malnutrition, and nephrotic syndrome, as well as treatment with androgens or glucocorticoids. Lastly, many drugs inhibit the binding of T_3 and T_4 to TBG, thus resulting in higher levels of free T_3 and free T_4 levels, which will not be reflected in the total hormone measurements. Such drugs include salicylates, nonsteroidal anti-inflammatories, heparin, furosemide, diphenylhydantoin, carbamazepine, and sulfonylureas. Because of the many limitations in the measurement of total hormone levels, only free T_3 and free T_4 assays should be relied on.[6,7]

The combination of both free T_4 and free T_3 elevation with TSH suppression is diagnostic of thyrotoxicosis. If TSH is suppressed and free T_4 is normal, subclinical hyperthyroidism is likely; however, about 5% of patients with thyrotoxicosis have an elevated free T_3 and normal free T_4—referred to as T_3 toxicosis, an entity more common in TMG. The reverse situation, in which free T_3 is normal and free T_4 is elevated may be seen in thyroiditis, exogenous levothyroxine ingestion, and hyperthyroidism in the elderly, often with suppressed T_4 to T_3 conversion due to comorbid illness[4,7] (Table 126-2).

Differentiating Graves' disease from other forms of thyrotoxicosis is usually straightforward clinically, but the measurement of thyroid antibodies to thyroglobulin and thyroid peroxidase may be helpful in questionable cases.

In addition to thyroid function tests, multiple laboratory abnormalities may be seen in thyrotoxicosis and thyroid storm. Hyperglycemia is the most common abnormality, seen in up to half the patients, likely related to glycogenolysis and catecholamine-mediated antagonism of insulin. Mild hypercalcemia is seen in 10% of patients and is related to hormone-mediated bone resorption, osteoporosis, and increased fracture risk.

Table 126-2 Thyroid Function Test Interpretation

TSH	FREE T_4	FREE T_3	DISEASE
Normal	Normal	Normal	None
Low	High	High	Hyperthyroidism
Low	Normal	Normal	Subclinical hyperthyroidism
Low	Normal	High	T_3 toxicosis
Low	High	Normal	Thyroiditis, T_4 ingestion, hyperthyroidism in the elderly or with comorbid illness
Low	Low	Low	Euthyroid sick syndrome; central hypothyroidism
High	Normal	Normal	Subclinical hypothyroidism; recovery from euthyroid sick syndrome
High	Low	Low	Primary hypothyroidism
High	High	High	TSH producing pituitary adenoma

T_3, triiodothyronine; T_4, thyroxine; TSH, thyroid-stimulating hormone.

Abnormal liver function tests are frequent in hyperthyroidism. The abnormalities observed include mild increases in serum aspartate transaminase, alanine transaminase, lactate dehydrogenase, bilirubin, and, most commonly, alkaline phosphatase. Although elevated serum bilirubin occurs in hyperthyroidism, clinical jaundice develops infrequently. Other abnormalities may include a leukocytosis with a left shift, a mild normocytic normochromic anemia, and low serum cholesterol levels.[7]

The diagnostic evaluation for thyroiditis is more difficult. If there is exquisite gland tenderness and a sedimentation rate greater than 100, the diagnosis of subacute thyroiditis is likely. Other forms of thyroiditis, however, lack these findings.[12,13] Doppler ultrasound of the thyroid may be helpful in differentiating among the hypervascular enlarged gland of Graves' disease, the nodules of TMG, and thyroiditis or factitious thyrotoxicosis (decreased Doppler flow).[45] Another option is a radioactive iodine uptake, which is depressed in thyroiditis and factitious thyrotoxicosis but increased in hyperthyroidism. If exogenous thyroid hormone abuse is suggested, measurement of thyroglobulin levels may confirm the diagnosis, being very low in factitious thyrotoxicosis but elevated in all other forms of thyrotoxicosis.[35]

Differential Considerations

The overtly thyrotoxic patient is often thought to be very anxious, manic, or in the midst of a panic attack. In addition, hyperadreneric signs may suggest sympathomimetic (cocaine, amphetamine) or anticholinergic intoxication or a withdrawal syndrome (alcohol, narcotics, sedative-hypnotics). The high fever and altered mental status seen in thyroid storm may mimic heatstroke, neuroleptic malignant syndrome, serotonin syndrome, bacterial meningitis, and sepsis.

In elders, the hyperadrenergic features of thyrotoxicosis may be masked, facial muscles may lack expression, and mental status may be depressed leading to the syndrome of apathetic hyperthyroidism. Patients with multinodular goiters and those older than 70 are most likely to present in this manner. New-onset atrial fibrillation and congestive heart failure exacerbations are often the presenting symptoms of apathetic hyperthyroidism. In addition, elders with thyrotoxicosis may have significant weight loss without increased appetite, suggestive of occult cancer.

Management

Patients with mild thyrotoxicosis with minor symptoms can often await outpatient follow-up for initiation of treatment. Of more importance to the emergency physician is the avoidance of interventions that may increase thyroid hormone levels or accentuate adrenergic stimuli. Thyrotoxic patients should not receive iodinated contrast media or amiodarone, both of which present an iodine load that may enhance thyroid hormone production.[46] Caution is advised with the use of aspirin and nonsteroidal anti-inflammatories as they may interfere with protein binding of thyroid hormone, leading to increases in free T_4 and T_3.[47] Drugs such as pseudoephedrine, ketamine, and albuterol that increase sympathomimetic tone should also be used with caution.[48] Patients with thyrotoxicosis who are symptomatic may require initiation of beta-blocker therapy in the emergency department, but the initiation of thionamides like propylthiouracil (PTU) and methimazole are rarely indicated.

The prompt recognition and treatment of thyroid storm is crucial for patient survival. Therapeutic interventions have several aims: (1) reducing production of thyroid hormone, (2) inhibiting thyroid hormone release, (3) blocking peripheral conversion of T_4 to T_3, (4) initiating beta-adrenergic blockade, (5) instituting general supportive measures, and (6) identifying and treating the precipitating event.

Reducing Production of Thyroid Hormone

The first-line treatment of thyroid storm is the use of thionamides, which inhibit oxidation and organic binding of iodine to thyroglobulin, thus blocking synthesis of thyroid hormone. PTU and methimazole are available, but PTU is preferred due to its additional effect of impairing conversion of T_4 to T_3. PTU is given as an initial loading dose of 600 to 1000 mg by mouth, followed by 200 to 250 mg every 4 hours. The recommended dose for methimazole is 20 to 25 mg initially with the same dose repeated every 4 hours.[4,6,32,36,37] If a patient cannot take medication orally, the same dose can be given by nasogastric tube or by retention enema. Such solutions require pharmacy preparation on a case-by-case basis.[49] Due to solubility limitations, there is no IV form of PTU or methimazole, yet methimazole has been tried intravenously. Such solutions also require pharmacy preparation, and can be administered 30 mg every 6 hours.[50] The intravenous (IV) route should be considered only in a dire situation where oral or rectal administration is not feasible or ineffective (Box 126-5).

Inhibiting Thyroid Hormone Release

Although thyroid hormone synthesis can be stopped by thionamides, preformed hormone in the gland is still available for release. Inorganic iodine blocks the release of thyroid hormone stored in the gland, but administration should be delayed at least 1 hour after PTU or methimazole is started. The reason for this delay is that an iodine load presented to an actively synthesizing gland provides further substrate for hormone production and release. Iodine is given as saturated solution of potassium iodide (SSKI) 5 gtt every 6 hours or Lugol's solution 8 gtt every 6 hours. Published dosage recommendations range from one-half to double these doses, yet the effective iodine dose appears to be just a fraction of these numbers. As there is no apparent harm in administering larger iodine doses, this middle figure is most commonly recommended.[4,6,32,36,37] Because no IV form of iodide is available, the rectal route can be used if the oral or nasogastric route cannot be used.[49] If allergy to iodine is encountered, lithium is an alternative agent

BOX 126-5 MANAGEMENT OF THYROID STORM

Inhibition of Thyroid Hormone Synthesis

Propylthiouracil 600–1000 mg loading dose, then 200–250 mg every 4 hr
OR
Methimazole 20–25 mg initially, then 20–25 mg every 4 hr
(*Preferred route:* PO or NG. *Alternative route:* PR. Enema prepared by pharmacy. Same dose for all routes. No IV preparation is available, but IV methimazole can be prepared with the use of a Millipore filter and given 30 mg every 6 hr)

Inhibition of Thyroid Hormone Release

Saturated solution of potassium iodide (SSKI) 5 gtt by mouth, NG, or PR every 6 hr
OR
Lugol's solution 8 gtt by mouth, NG, or PR every 6 hr
OR
Sodium Iodide 500 mg in solution prepared by pharmacy IV every 12 hr
OR
If allergic to iodine, lithium carbonate 300 mg by mouth or NG every 6 hr

Beta-adrenergic Blockade

Propanolol 60–80 mg PO every 6 hr
OR
Metoprolol 50 mg PO every 6 to 12 hr
If IV route required, propanolol 0.5–1.0 mg IV slow push test dose, then repeat every 15 min to desired effect, then 2–3 mg every 3 hr
OR
Esmolol 250–500 µg/kg bolus, then 50–100 µg/kg/min infusion
Strict contraindication to beta-blocker: reserpine 0.5 mg PO every 6 hr

Administration of Corticosteroids (inhibit T_4 to T_3 conversion, treat relative adrenal insufficiency)

Hydrocortisone 300 mg IV, followed by 100 mg every 6 hr
OR
Dexamethasone 2–4 mg IV every 6 hr

Diagnosis and Treatment of Underlying Precipitant

Consider empirical antibiotics if critical

Supportive Measures

Volume resuscitation and replacement of glycogen stores
D_5/0.9NS 125–1000 mL/hr depending on volume status and CHF
Tylenol with caution
Cooling blanket, fans, ice packs, ice lavage

Miscellaneous

Lorazepam or diazepam as anxiolytic and to decrease central sympathetic outflow
L-Carnitine (block entry of thyroid hormone into cells), 1 g PO every 12 hr
Cholestyramine (block enterohepatic recirculation of thyroid hormone), 4 g PO every 6 hr

CHF, congestive heart failure; D_5/0.9NS, 5% dextrose in 0.9% normal saline; IV, intravenous; NG, nasogastric; PO, by mouth; PR, in rectum; T_3, triiodothyronine; T_4, thyroxine.

that impairs thyroid hormone release. The lithium dose is 300 mg every 6 hours by mouth or nasogastric tube, but lithium levels should be monitored to maintain a level of about 1 mg/L. Iodine should not be used in amiodarone-induced thyrotoxicosis as iodine overload may contribute to amiodarone's toxicity. In hyperthyroidism unmasked by iodine excess (iodinated contrast agents), lithium should be used to inhibit hormone release and further iodine administration avoided. Iodine's effects cease after 2 to 3 weeks of therapy, thus a delayed exacerbation of hyperthyroidism may ensue unless adequate thionamide therapy has been maintained.[51]

Blocking Peripheral Conversion of T_4 to T_3 and Initiating Beta-adrenergic Blockade

Blockade of peripheral hyperadrenergic activity by beta-blockers is a cornerstone of therapy in thyroid storm and symptomatic thyrotoxicosis. Propanolol has traditionally been the beta-blocker of choice because it blocks conversion of T_4 to T_3 and its nonselective effects also improve tremor, hyperpyrexia, and restlessness. Dosage recommendations vary from 20 to 120 mg by mouth at 6-hour intervals, with most authors suggesting 60 to 80 mg per dose.[4,6,32,36,37] If the patient cannot take anything by mouth or rapid beta-blockade is desired while waiting for the oral dose to be effective, IV propanolol can be administered as a test dose of 0.5 to 1 mg over 10 minutes. A cautious start is recommended if there is evidence of severe heart failure or hypotension as there are rare case reports of cardiovascular collapse after propanolol administration in thyroid storm.[52] If the patient tolerates the initial dose of propanolol, it can be repeated every 15 minutes until the desired effect is achieved, then transitioning to 3-hour intervals with 1 to 3 mg boluses. If there are contraindications or concerns about beta-blocker therapy, a short-acting agent such as esmolol may be prudent. Esmolol is usually started as a loading dose of 250 to 500 µg/kg, then continued as an infusion of 50 to 100 µg/kg/min.[53] $Beta_1$-selective drugs like esmolol or metoprolol (50 mg every 6–12 hours) may be preferable in asthma patients, but if not tolerated, reserpine 0.5 mg orally every 6 hours could be considered, while monitoring for hypotension.[54]

Corticosteroids are recommended in thyroid storm, because they inhibit peripheral conversion of T_4 to T_3, as well as block the release of hormone from the gland. The synergistic effect of PTU, iodide, and steroids in thyrotoxicosis can restore the concentration of T_3 to normal within 24 to 48 hours.[36] Corticosteroids are also suggested due to an absolute or relative adrenal insufficiency that can occur in thyroid storm. Addison's disease can occur concomitantly with Graves' disease in polyglandular autoimmune syndrome type 2, but more importantly, the increased clearance of cortisol in thyrotoxicosis coupled with the high demand for cortisol in such critically ill patients leads to a relative adrenal insufficiency in most. Hydrocortisone can be given as an initial bolus of 100 to 300 mg IV, followed by 100 mg every 8 hours for several days. Dexamethasone has also been used in this setting as well, in doses of 2 to 4 mg every 6 hours or 8 mg every 24 hours.[55]

Instituting General Supportive Measures

Supportive measures are equally important in the management of thyroid storm. Fluid resuscitation should be vigorous

BOX 126-6 THYROTOXICOSIS AND THYROID STORM: SPECIAL SITUATIONS

Congestive Heart Failure
If rate-related, high-output failure
- Beta-blockade is first-line therapy (dose as in Box 126-5)
- ACEI, digoxin, diuretics as needed

If depressed EF
- Avoid beta-blocker or ¼ dose
- ACEI if BP adequate
- Digoxin and furosemide as needed

If pulmonary hypertension
- Oxygen
- Sildenifil

Atrial Fibrillation
Beta-blocker preferred for rate control (doses as in Box 126-5)
Calcium channel blockers prone to hypotension; diltiazem
- 10-mg test dose. Avoid verapamil

Digoxin less effective but may be tried
Amiodarone should be avoided due to iodine load
Refractory to conversion to sinus unless euthyroid first

Thyroiditis (Subacute)
NSAIDs for inflammation and pain control
Prednisone 40 mg/day if refractory to NSAIDs
Beta-blockade to control thyrotoxic symptoms
No role for PTU, methimazole, or iodides

Factitious Thyrotoxicosis
Beta-blockade for thyrotoxic symptoms
Cholestyramine to block absorption of ingested thyroid hormone
No role for PTU, methimazole, or iodides

ACEI, angiotensin-converting enzyme inhibitor; BP, blood pressure; EF, ejection fraction; NSAIDs, nonsteroidal anti-inflammatory drugs; PTU, propylthiouracil.

unless clear signs of congestive heart failure are evident. Due to the depletion of glycogen stores in thyrotoxicosis, a 5% dextrose solution is recommended; hence for volume replacement, D5/0.9NS is a rational choice. As high fever to the point of heatstroke is not unusual in thyroid storm, therapy to dissipate heat is a priority, typically by means of cool mists, fans, ice packs, cooling blankets, and ice water lavage. Acetaminophen could be used for moderate fever, but as hepatic dysfunction may occur in storm, it should be used with caution. Aspirin is contraindicated in thyroid storm because it increases levels of free thyroid hormone.[4,6,32,36,37]

Treatment to hasten elimination of thyroid hormone has been described. Cholestyramine, an anion exchange resin, binds thyroid hormone in the bowel lumen, thus interrupting enterohepatic recirculation. Cholestyramine in a dose of 4 g every 6 hours has been shown to result in a more rapid decline in hormone levels than thionamides alone.[56] Colestipol has been shown to have a similar effect, but not ezetimibe.[57] Progressive deterioration in a patient with thyroid storm, despite aggressive multidrug therapy, may lead to the consideration of plasmapharesis, plasma exchange, or dialysis to attempt rapid reduction in thyroid hormone levels.[58]

Benzodiazepines for agitation and hypomania of thyrotoxicosis may be considered as the hyperadrenergic state resembles cocaine intoxication. L-Carnitine has been described in thyroid storm, its suggested mechanism being the inhibition of thyroid hormone entry into cell nuclei. The dose used is 1 g every 12 hours by mouth[59] (Box 126-5).

Radioactive iodine or surgery has no role in the management of thyroid storm or thyrotoxicosis until a sustained euthyroid state has been achieved, as these interventions can precipitate storm themselves.[60]

Beta-blockers are a mainstay in the treatment of high-output heart failure as defined by a normal or exaggerated ejection fraction on echocardiography.[8,16] Preexisting heart disease aggravated by thyrotoxicosis may be associated with low-output congestive heart failure (low ejection fraction on echocardiography), in which circumstance caution should be exercised with the use of beta-blockers, because cases of cardiovascular collapse have been described with their use in this setting.[52] Routine management with angiotensin-converting enzyme inhibitors, diuretics, and digoxin are appropriate in both groups.[8,16]

The management of atrial fibrillation in thyrotoxicosis also has unique features. The rapid ventricular response generally requires high doses of beta-blocker for control. If thyroid storm is present, calcium channel blockers should be avoided as hypotension is a potential complication. Digoxin tends to be ineffective in this setting, but could be tried. Amiodarone should not be used due to its iodine load and potential to induce thyroiditis. Attempts to convert to sinus rhythm are usually fruitless while the patient remains thyrotoxic and thus should be postponed until the patient is euthyroid.[16,26]

Pain and tenderness as seen in subacute thyroiditis is treated with nonsteroidal anti-inflammatories. If refractory or recurrent, prednisone may be required.[12,13] Thyrotoxicosis in thyroiditis is usually mild, and beta-blockers alone are recommended. In fact, thionamides and iodine have no effect in thyroiditis. If drug-related, the offending agent (amiodarone, interferon) should be stopped immediately. Thyrotoxicosis from exogenous thyroid hormone ingestion should be treated with beta-blockade alone because the thyroid gland is shut down, thereby rendering thionamides and iodine ineffective. Cholestyramine could be used to bind hormone in the gut in both the acute and chronic intoxication, but evidence to its efficacy is limited[17,35] (Box 126-6).

Special mention should be made regarding potential toxicity of thionamide therapy, as it may be a presenting manifestation of a thyrotoxic patient. The minor adverse reactions that occur in up to 5% of patients include drug fever, alteration in sense of taste, skin eruptions, arthralgias, and sialoadentitis. Such reactions should not lead to discontinuation of therapy in the patient with thyroid storm, but should be reason to stop in the mildly thyrotoxic individual. The most feared and life-threatening adverse reaction to PTU and methimazole is agranulocytosis, which is often heralded by onset of fever and severe sore throat. Any patient who develops fever while on thionamide therapy should have his or her white blood cell count determined and if at all depressed, therapy should be stopped immediately. Fortunately, such reactions occur only in 3 or 4 patients per 1000. Other infrequent yet serious reactions to thionamides include hepatitis, vasculitis, and polyarthritis.[61]

Simultaneous with the previously detailed treatment measures, an aggressive search for an underlying precipitant of thyroid storm should be undertaken. As infection is the most common culprit, a chest radiograph, urinalysis, and blood cultures are routine. Silent myocardial ischemia should be assessed by an electrocardiogram and troponin, and the possibility of stroke or pulmonary embolism considered. Empirical use of antibiotics are tempting in the setting of thyroid storm, but restraint is prudent unless there is strong clinical evidence.

Aggressive management of thyroid storm with PTU followed by iodine, beta-blockers, corticosteroids, fluid resuscitation, rapid cooling, and treatment of the precipitating illness can resolve fever, tachycardia, and altered mental status within a 24-hour period. All patients with storm should be admitted to an intensive care setting, and any interruption in therapy should be avoided as it can lead to a sudden recrudescence of symptoms and death.

HYPOTHYROIDISM

Perspective

The clinical presentation of the hypothyroid patient can vary from asymptomatic or subclinical cases to life-threatening myxedema coma. In random population sampling, the prevalence of TSH elevation has ranged from 3.7 to 9.5%, with the majority of these having a normal free T_4, which by definition is subclinical hypothyroidism. Overt hypothyroidism (elevated TSH and depressed free T_4) is seen in a minority of these patients, about 0.3% of the population overall, with the prevalence rising with age, such that patients older than 80 years have a fivefold greater likelihood of developing hypothyroidism than do 12- to 49-year-olds.[1-3] Some surveys estimate the incidence of hypothyroidism as high as 20% in elders.[5] The female to male ratio is about 4:3 in hypothyroidism, in contrast to 8:1 for hyperthyroidism. Race differences are notable in that hypothyroidism is seen in 5.1% of whites, 4.1% of Hispanic-Americans, and 1.7% of African-Americans.[1-3]

Principles of Disease

The etiology of hypothyroidism includes primary thyroid failure, thyroiditis, pituitary/hypothalamic causes, drug-related and iatrogenic. The vast majority of hypothyroidism encountered in the United States is due to thyroid gland failure, and the majority of these are caused by autoimmune destruction of the gland in Hashimoto's thyroiditis. In younger patients, the disease is associated with a goiter and elevated titers of antithyroid antibodies, specifically to thyroid peroxidase, thyroglobulin, and TSH. The TSH receptor antibody in Hashimoto's disease blocks the receptor, in contrast to the stimulating antibody in Graves' disease. In older patients, the thyroid gland is typically atrophic, and evidence of autoimmunity is often lacking.[62-64]

End-stage Graves' disease can also result in autoimmune destruction of the thyroid gland, occurring spontaneously following several exacerbations of hyperthyroidism. More commonly, hypothyroidism follows treatment of Graves' disease with radioactive iodine or thyroidectomy.

Drug-induced hypothyroidism is often encountered with lithium carbonate because it inhibits hormone release. Iodine excess, as seen with amiodarone, iodinated contrast media, kelp supplements, and iodine-containing cough medicines, can impair thyroid hormone release and synthesis (Wolff-Chaikoff effect), thereby converting subclinical hypothyroidism to overt hypothyroidism and sometimes precipitating hypothyroidism de novo. In contrast, iodine-deficient patients administered an iodine load increase production of thyroid hormone and may develop hyperthyroidism. Interferon-alfa can result in hypothyroidism by precipitating Hashimoto's thyroiditis. Overtreatment with PTU or methimazole may lead to hypothyroidism due to their inhibition of hormone synthesis. Phenytoin, carbamazepine, phenobarbital, and rifampin may aggravate hypothyroidism by enhancing metabolism of thyroid hormone.[62-64]

Patients on thyroid replacement therapy can develop hypothyroidism when drugs are introduced that interfere with hormone absorption, including iron, calcium, phosphate binders, sucralfate, aluminum hydroxide, cholestyramine, colestipol, and even coffee.[65]

Iatrogenic causes of hypothyroidism include neck irradiation for cancer or lymphoma and thyroidectomy for nodular goiter or thyroid cancer.

Hypothyroidism may be seen as a late phase of thyroiditis.[12] In Hashimoto's disease the initial hyperthyroid phase is rarely identified, and hypothyroidism predominates.[11] In subacute, silent, and postpartum thyroiditis the hyperthyroid phase is usually clinically evident, and the hypothyroidism is often very mild and transient, but can become chronic.[13]

Rare causes of hypothyroidism include inherited disorders of hormone biosynthesis and central hypothyroidism. Central causes are usually due to pituitary destruction by an adenoma, hemorrhage (Sheehan's syndrome), or infiltration (sarcoid, amyloid), but can also result from hypothalamic dysfunction.[66]

A form of central hypothyroidism that appears to be an adaptive response to significant nonthyroidal illness is the euthyroid sick syndrome. Mild suppression of TSH release leads to a decrease in free T_4 and T_3. Impairment of T_4 to T_3 conversion also develops leading to elevation of reverse T_3 levels. Euthyroid sick syndrome remits spontaneously with resolution of the acute illness, and treatment with thyroid replacement is not indicated. Drugs that may contribute to TSH suppression in nonthyroidal illness include glucocorticoids, dopamine, and octreotide[62,64,67] (Box 126-7).

Clinical Features

Symptoms and signs of hypothyroidism are often very subtle and difficult to recognize in their milder presentation. Patients often ignore or tolerate symptoms when their development is very gradual, as is the case in Hashimoto's thyroiditis, where the delay from symptom appearance and diagnosis may be several years. Acute hypothyroidism presenting over weeks to months may be seen in thyroiditis or withdrawal of exogenous thyroid hormone. Chronic disease may present acutely due to drug toxicity or when an intercurrent illness is superimposed.[62-64]

The clinical manifestations of hypothyroidism result from changes induced by lack of thyroid hormone, most notably a generalized slowing of metabolic processes (due to altered gene expression and decreased catecholamine sensitivity) and an accumulation of glycosaminoglycans (decreased metabolism) in interstitial fluids.

Patients with hypothyroidism typically have pale, cool skin from decreased blood flow and fluid accumulation. Epidermal and sweat gland changes result in dry, scaly, rough skin. The skin is firm to the touch and appears swollen, but does not pit. In severe, chronic disease, the patient has a typical facies characterized by puffy eyelids, broad nose, swollen lips, and macroglossia. The hair in hypothyroidism becomes coarse and brittle, and alopecia is common. Thinning of the lateral third

BOX 126-7 CAUSES OF HYPOTHYROIDISM

Primary Hypothyroidism

Autoimmune hypothyroidism
- Hashimoto's thyroiditis (chronic—atrophic thyroid, acute with goiter)
- Graves' disease (end stage)

Iatrogenic
- Radioactive iodine therapy for Graves' disease
- Thyroidectomy for Graves' disease, nodular goiter, or thyroid cancer
- External neck irradiation for lymphoma or head and neck cancer

Iodine-related
- Iodine deficiency (common worldwide, but rare in North America)
- Iodine excess (inhibition of hormone release can unmask autoimmune thyroid disease) (see under Drug-related)

Drug-related
- Lithium (inhibit hormone release)
- Amiodarone (destructive thyroiditis or iodine excess)
- Interferon-alfa (precipitate Hashimoto's thyroiditis)
- Iodine excess (iodinated contrast media, kelp, amiodarone)
- Propylthiouracil, methimazole
- Interference with thyroid hormone absorption in patients on replacement therapy (iron, calcium, chromium, phosphate binders, cholestyramine, colestipol)

Thyroiditis
- Subacute
- Silent (sporadic)
- Postpartum
- Amiodarone

Congenital defect in thyroid hormone synthesis

Central Hypothyroidism

Euthyroid sick syndrome

Pituitary disease
- Pituitary adenoma
- Hemorrhage
- Infiltrative (amyloid, sarcoid)

Hypothalamic disease

of the eyebrows may occur. The nails also become brittle and thin. The skin may take on a yellowish tinge from carotene, which accumulates because of impaired conversion to vitamin A. Carotenemia is distinguished from jaundice by the sparing of the conjunctiva. Vitiligo may occur in association with polyglandular syndrome, whereas hyperpigmentation may be seen if the patient has concomitant Addison's disease (Schmidt's syndrome).[62,68]

Generalized edema of the face and extremities may develop—nonpitting from accumulation of glycosaminoglycans and pitting from a capillary leak phenomenon seen in hypothyroidism. A localized pretibial myxedema and exophthalmos may still be seen in patients with Graves' disease rendered hypothyroid by surgery or radioactive iodine.[68]

The hypothyroid patient is usually normothermic, but complaints of cold intolerance and cool extremities are common. Blood pressure is usually normal, but 20 to 40% of patients have diastolic hypertension and narrowing of the pulse pressure. Bradycardia is common, but asymptomatic.[62,63] In contrast to hyperthyroidism, in which atrial arrhythmias are frequently seen, hypothyroidism may be associated with QT prolongation and ventricular irritability.[69,70] Patients with hypothyroidism often complain of dyspnea on exertion and decreased exercise capacity, and although decreased cardiac contractility and diastolic dysfunction is present in chronic hypothyroidism, signs of congestive heart failure are usually absent. Angina and coronary artery disease may be masked by slowed metabolism and decreased ischemic stress, but coronary disease is accelerated by elevations in cholesterol and blood pressure.[62,71]

Pericardial effusions may be seen in chronic hypothyroidism, but are usually small and asymptomatic. Larger effusions may result in diminished heart sounds and decreased apical impulse, but cardiac tamponade is rarely seen due to slow chronic build up.[72,73]

Complaints of fatigue, dyspnea, and decreased exercise capacity are most likely to be from a respiratory origin, rather than cardiac. Hypothyroidism is characterized by impaired ventilator responses to hypercapnea and hypoxia, as well as myopathy of respiratory musculature, with resultant slow, shallow respirations. Macroglossia may contribute to the respiratory distress and lead to obstructive sleep apnea. Mucopolysaccharide infiltration or edema of the vocal cords leads to a deep, husky voice in the hypothyroid patient. Primary pulmonary hypertension is reported with increased prevalence in hypothyroidism and may contribute to complaints of dyspnea or chest pain.[74,75]

A modest weight gain is characteristic of hypothyroidism, but massive obesity is unusual. Limiting the anticipated weight gain in this hypometabolic state is a concomitant decrease in appetite.[62]

Neurocognitive impairment may be a presenting feature of hypothyroidism, especially in elders. Slowness of comprehension, lethargy, decreased attention span, poor short-term memory, and impaired abstract thinking may all be present. The patient generally appears placid or depressed, moves slowly and deliberately, and speaks hesitantly.[76,77] Although unusual in hypothyroidism, extreme agitation, psychosis, and even seizures have been described—the last is referred to as myxedema madness or Hashimoto's encephalopathy.[42,78]

Paresthesias are common in hypothyroidism and although peripheral polyneuropathy may occur, mononeuropathies are much more prevalent. Edema of perineural and synovial tissue within the carpal tunnel leads to carpal tunnel syndrome, which is reported in about 25% of hypothyroid patients. Another common mononeuropathy in hypothyroidism involves the eighth cranial nerve, resulting in sensorineural hearing loss and tinnitus.[77]

Muscle-related symptoms are frequent in hypothyroid patients, often manifesting with proximal muscle weakness, myalgias, stiffness, and fatigue. Hypothyroid myopathy leads to slowing of the relaxation phase of deep tendon reflexes, referred to as hung-up or pseudomyotonic reflexes. This reflex phenomenon is best demonstrated with the Achilles tendon reflex performed while the patient is kneeling on a chair. Hung-up reflexes are not unique to hypothyroidism, as they can be seen with aging, diabetes, and pregnancy. Muscle palpation in most patients is normal, but some with hypothyroid myopathy develop firm, enlarged muscles referred to as pseudohypertrophy. Prolonged mounding of muscle mass may sometimes be evident when reflexes are elicited (myoedema). Ataxia and dysmetria reversible with thyroid replacement have been described, which may by myopathic or cerebellar in origin.[77,79]

Elevation of the serum creatine kinase (CK) concentration is seen in 70 to 90% of patients with hypothyroidism; however, the magnitude of the CK elevation does not correlate well with the severity of the patient's myopathy or hypothyroidism. Rare cases of acute rhabdomyolysis have been reported in severe

hypothyroidism, precipitated by exercise, statin therapy, or renal failure.[80]

One of the most common complaints of the hypothyroid patient is constipation, which results from decreased bowel motility. Rarely, ileus or megacolon may occur and be confused with intestinal obstruction.

Although oligo- or amenorrhea may suggest a pituitary/hypothalamic origin, primary hypothyroidism can result in menstrual abnormalities due to altered metabolism of estrogen. Menorrhagia is also described. Decreased fertility and early abortions are commonly associated complaints. Hypothyroid men often report decreased libido, erectile dysfunction, and delayed ejaculation.[62,63]

Initial symptoms of hypothyroidism may be rheumatic in character. Arthralgias and stiffness, sometimes associated with noninflammatory joint effusions, may be seen. Acute monoarthritis may be seen due to an increased prevalence of hyperuricemia and gout in hypothyroid patients, and perhaps as a result of a minor link with pseudogout and chondrocalcinosis as well[81,82] (Box 126-8).

Myxedema coma is a life-threatening decompensation of severe long-standing hypothyroidism, often precipitated by an acute illness or stress. The hallmarks of myxedema coma are altered mental status and hypothermia, but hypotension, bradycardia, and hypoventilation are often present as well. The typical patient is an elderly woman with chronic hypothyroidism that is untreated or unrecognized. Hashimoto's thyroiditis is the most common underlying thyroid pathology due to its insidious nature, but any cause of hypothyroidism is possible. The history is one of progressive weakness, lethargy, and immobility that may progress to shock and death.

Virtually any acute illness may precipitate myxedema coma, but the most common factors include infection, cold exposure, trauma, cerebrovascular accident, congestive heart failure, gastrointestinal bleeding, and drug effects. Sedatives and narcotics are commonly implicated drug classes, but general anesthesia, thyroid hormone noncompliance, amiodarone, lithium, iodides, phenytoin, and rifampin may be factors[33,63,75,83-85] (Box 126-9).

BOX 126-8 SYMPTOMS AND SIGNS OF HYPOTHYROIDISM

Vital Signs
Systolic BP—normal or low
Diastolic BP—normal or elevated
Slow pulse to sinus bradycardia
Respirations—normal or slow, shallow
Temperature—normal, but prone to hypothermia with stress

Hypometabolic Complaints
Cold intolerance
Fatigue
Weight gain, but decreased appetite

Cutaneous
Coarse, brittle hair
Alopecia
Dry skin, decreased perspiration
Pallor, cool hands and feet
Coarse, rough skin
Yellow tinge from carotenemia
Thin, brittle nails
Lateral thinning of the eyebrows

Neurologic
Slow mentation and speech
Impaired concentrating ability and attention span
Lethargy
Decreased short-term memory
Agitation, psychosis
Seizures
Ataxia, dysmetria
Mononeuropathy
  Carpal tunnel syndrome
  Sensorineural hearing loss
Peripheral neuropathy

Muscular
Proximal myopathy
Pseudohypertrophy
Delayed relaxation of reflexes (hung-up or pseudomyotonic)

Cardiac
Decreased exercise capacity
Dyspnea on exertion
Sinus bradycardia
Long QT with increased ventricular arrhythmia
Chest pain—accelerated coronary disease
Diastolic heart failure (delayed ventricular relaxation)
Pericardial effusion (asymptomatic)
Peripheral edema

Respiratory
Dyspnea on exertion
Obstructive sleep apnea
Primary pulmonary hypertension

Gastrointestinal
Constipation
Ileus
Gastric atrophy

Reproductive
Oligo- and amenorrhea
Menorrhagia
Decreased fertility
Early abortions
Decreased libido
Erectile dysfunction

Rheumatic
Polyarthralgias
Joint effusions
Acute gout or pseudogout

HEENT
Hoarseness
Deep, husky voice
Macroglossia
Hearing loss
Periorbital swelling
Broad nose
Swollen lips
Goiter

BP, blood pressure; HEENT, head, ear, eyes, nose, and throat.

BOX 126-9 Myxedema Coma: Aggravating or Precipitating Factors

Infection/sepsis (especially pneumonia)
Exposure to cold
Cerebrovascular accident
Drug effect
- *Altered sensorium:* Sedative-hypnotics, narcotics, anesthesia, neuroleptics
- Decrease T_4 and T_3 release: amiodarone, lithium, iodides
- Enhance elimination of T_4 and T_3: phenytion, rifampin
- *Inadequate thyroid hormone replacement:* Noncompliance; interference with absorption (iron, calcium, cholestyramine)

Myocardial infarction
Gastrointestinal bleeding
Trauma/burns
Congestive heart failure
Hypoxia
Hypercapnia
Hyponatremia
Hypoglycemia
Hypercalcemia
Diabetic ketoacidosis

T_3, triiodothyronine; T_4, thyroxine.

BOX 126-10 Recognition of Myxedema Coma

Patient profile: Elderly female in the winter
Known hypothyroidism; thyroidectomy scar
Hypothermia: Usually below 95.9°F; below 90°F is bad prognostic sign; as low as 75°F reported. Near normal in presence of infection
Altered mental status: Lethargy and confusion to stupor and coma, agitation, psychosis and seizures (myxedema madness)
Hypotension: Refractory to volume resuscitation and pressors unless thyroid hormone administered
Slow, shallow respirations with hypercapnea and hypoxia; high risk of respiratory failure
Bradycardia (sinus)/long QT and ventricular arrhythmias
Myxedema facies: Puffy eyelids and lips, large tongue, broad nose
Evidence of severe chronic hypothyroidism: Skin, hair, reflexes, bradykinesis, voice
Acute precipitating illness (e.g., pneumonia)
Drug toxicity (e.g., sedative, narcotic, neuroleptic)
Hyponatremia

It is important to appreciate that although infection is the most common precipitant of myxedema coma, the patient does not usually mount a febrile response due to the profound hypometabolic state. Peripheral vasoconstriction helps maintain core temperature in severe hypothyroidism, but this compensation may be tenuous. Hypothermia is characteristic of myxedema coma and it is usually marked, with body temperatures as low as 24°C (75°F) described. Temperatures below 90°F are common and carry a grave prognosis. In contrast to environmental hypothermia, shivering is often absent.[63,75,85]

Whereas diastolic hypertension is common in hypothyroidism, the blood pressure in myxedema coma is usually low and may be refractory to fluid resuscitation and pressors unless thyroid hormone is administered.[75] Sinus bradycardia is routinely seen and may be unresponsive to atropine, but heart block is unusual. Prolongation of the QT interval with cases of torsades de pointes is described.[70] Despite cardiac enlargement and decreased myocardial contractility seen in most patients, evidence of congestive heart failure is not common.[62]

Signs of severe hypothyroidism are usually evident in the myxedema coma patient. Dry, coarse skin; sparse, brittle hair; cool extremities; puffy eyelids and face; large tongue; hoarse voice; and slow, delayed speech and movement are typical. Pitting and nonpitting edema are prominent in the extremities.[68] Pleural and pericaridial effusions are common, and ascites may be present.[86]

Despite the name myxedema coma, most patients present with confusion, lethargy, or stupor and are not comatose, but progression to coma is inexorable if therapy is not instituted. The cause of altered mental status is multifactorial, including thyroid hormone deficiency, hypothermia, hypercapnea, hyponatremia, hypotension, and hypoglycemia.[75,83] Paradoxically, a more agitated, psychotic state may sometimes occur, referred to as myxedema madness.[77] Focal or generalized seizures may occur in up to 25% of patients, and status epilepticus has been reported.[78]

Respiratory depression with carbon dioxide retention is common in myxedema coma, contributing further to the altered mental status. An enlarged tongue, supraglottic edema, and obesity further aggravate hypercapnea and hypoxia. Pneumonia, a common precipitant of myxedema coma, accelerates the downward spiral toward respiratory failure. Mechanically assisted ventilation is required in most patients, often leading to extended hospitalization[74,85] (Box 126-10).

Diagnostic Strategies

The diagnosis of primary hypothyroidism requires the measurement of an elevated serum TSH and a depressed free T_4 level. If the index of suspicion is low, the serum TSH alone can be used as a screening test, and the free T_4 test only performed if the TSH is abnormal. The total T_4 level is not recommended in evaluating thyroid disease because of numerous confounding factors on protein binding that alter its measurement, thus the free T_4 is preferred. The serum T_3, whether total or free, should not be relied on in the diagnosis hypothyroidism due to its great variability. Almost any acute or chronic illness or physiologic stress can lead to depression of T_4 5′-deiodinase activity, thereby leading to decreased peripheral conversion of T_4 to T_3 and an increase in reverse T_3 levels.[7]

The elevation of TSH accompanied by a normal free T_4 is referred to as subclinical hypothyroidism (SCH). The prevalence of SCH is 4 to 9% in large general population screening surveys and in 7 to 26% in geriatric series.[1,2,62,87] Although by definition SCH is asymptomatic, this laboratory abnormality is associated with the development of depression, cognitive impairment, subtle systolic and diastolic dysfunction, and hyperlipidemia.[88]

The distinction of myxedema coma from moderate to severe hypothyroidism cannot be made by thyroid functions tests alone. Elevation of the serum TSH may be blunted by any concomitant systemic illness (hypothyroid sick syndrome), resulting in a misleadingly minor elevation in TSH in a severely hypothyroid patient. Central hypothyroidism is characterized by a low serum TSH together with a low free T_4 level. The euthyroid sick syndrome can have very similar results but the TSH is only mildly suppressed and the free T_4 is normal or slightly low. Because central hypothyroidism is usually not a chronic condition, many of the clinical findings of hypothyroidism are absent.[67,75,88]

Hyponatremia is a common electrolyte abnormality in severe hypothyroidism and myxedema coma, but it is not seen in milder forms of the disease. Hyponatremia results from decreased free water clearance due to diminished renal blood flow from volume depletion and depressed cardiac output as well as excess excretion of anti-diuretic hormone. A reversible elevation in serum creatinine is also seen in this setting.[62,75,84]

Hypoglycemia may also occur in severe hypothyroidism and myxedema coma. Decreased gluconeogenesis and reduced insulin clearance are the likely mechanisms, but it is important to recognize that a low blood sugar may be a clue of concomitant adrenal insufficiency, which is present in up to 10% of myxedema coma patients.

CK from a muscular origin is often elevated in severe hypothyroidism, but acute rhabdomyolysis is uncommon.[80] Serum transaminases and lactate dehydrogenase are frequently elevated as well.

Lipid clearance is decreased in hypothyroidism, resulting in elevations of total cholesterol, low density lipoprotein, and triglyceride. In the Colorado Thyroid Disease Prevalence Study of 25,862 patients, euthyroid patients averaged a total cholesterol of 214 mg/dL, whereas subclinical and overt hypothyroid subjects averaged 224 and 251 mg/dL, respectively.[1-3]

Severe hypothyroidism may be associated with a normocytic, normochromic anemia from decreased red cell production and a depressed white blood count that does not rise appropriately in response to infection.[75] Increased bleeding times may result from an acquired von Willebrand's syndrome.

A chest radiograph may reveal an enlarged cardiac silhouette, but evidence of heart failure is unusual. Although myocardial hypertrophy may be present in hypothyroidism, cardiomegaly usually represents the presence of pericardial effusion, seen in 30 to 78% of severe, chronic disease, but less than 5% of mild hypothyroidism. Pleural effusions may be seen as well.[62,72,73,75]

Electrocardiographic findings include sinus bradycardia, nonspecific ST and T wave abnormalities, and decreased voltage or electrical alternans if a pericardial effusion is present. Prolongation of the QT interval and ventricular arrhythmias may be seen as well.[69,70,75]

If a lumbar puncture is performed to evaluate altered mental status, findings of increased opening pressure and an elevated cerebrospinal fluid protein level may be seen in myxedema coma.

Differential Considerations

The overtly hypothyroid patient is often thought to be severely depressed, and the diagnosis of hypothyroidism may be overlooked. In fact, about 10 to 15% of patients hospitalized for depression are found to be hypothyroid. Roughly 25% of bipolar patients with a rapid cycling pattern are found to be hypothyroid. Even subclinical hypothyroid patients have more than twice the incidence of depression than euthyroid patients.[76] The profound fatigue and weakness that may occur in hypothyroidism may be diagnosed as depression, chronic fatigue syndrome, Addison's disease, or anemia.

Respiratory failure in patients with substrates of obstructive sleep apnea such as obesity, hypoventilation, and macroglossia, should be evaluated for hypothyroidism. In addition, any patient with decreasing exercise capacity and dyspnea without any clear cardiopulmonary cause should be evaluated for hypothyroidism.

The hypothermia of myxedema coma may be attributed to environmental stress, sepsis, or hypoglycemia. The altered mental status, as well, may be attributed to concomitant conditions in myxedema coma, such as drug toxicity, hypothermia, hypercapnea, hypoxia, hypoglycemia, or hyponatremia, and the hypothyroidism overlooked.

Management

The patient with a new diagnosis of overt or subclinical hypothyroidism generally does not require the initiation of treatment from the emergency department, yet it is important to be familiar with the principles of diagnosis and treatment. Before commitment to lifelong therapy, the serum TSH and free T_4 should be repeated for confirmation. About 5% of patients with subclinical hypothyroidism normalize within 1 year and, of the remainder, approximately 5% per year develop overt hypothyroidism. Treatment with thyroid hormone replacement may be considered in SCH if symptomatic or the TSH is greater than 10.[62,64,88]

Levothyroxine (T_4) is the mainstay of treatment of hypothyroidism. Treatment is generally started at a dose of 1.6 µg/kg/day in younger patients, whereas elders and patients with underlying coronary artery disease are often started at less than half that dosage due to their susceptibility to angina and arrhythmias. The long half-life of T_4 (7 days) and its gradual conversion to T_3, leads to dosage adjustments of 12.5- to 25-µg increments at no less than 6-week intervals.[62,63]

The management of myxedema coma requires immediate attention to airway management, fluid resuscitation, thyroid hormone replacement, general supportive measures, and treatment of the precipitating illness (Box 126-11).

BOX 126-11 TREATMENT OF MYXEDEMA COMA

- Protect the airway/ventilatory support; monitor for alkalosis
- Fluid resuscitation:
  - 0.9NS or D_5/0.9NS if hypoglycemia
  - Watch for unmasking of CHF
- Thyroid hormone replacement:
  - T_4 alone (elderly and patients with cardiac comorbidity):
    - T_4 300–500 µg IV as initial bolus
    - Or split bolus 200–300 µg IV day 1 and 2
    - Then 50–100 µg IV daily until able to take PO
  - T_3 alone (younger patient, no cardiac risks; rapid correction desired):
    - T_3 10–20 µg IV initially, then 10 µg IV every 4 hr for 1 day, then 10 µg IV every 6 hr for 1–2 days
  - Combination T_4 and T_3 therapy (intermediate approach):
    - T_4 200–250 µg IV as initial bolus
    - T_3 10 µg IV initial dose, then 10 µg IV every 8–12 hr
    - T_4 100 µg IV in 24 hr, followed by 50 µg/day
- Hydrocortisone
  - 50–100 mg IV every 6–8 hr
- Hyponatremia
  - Avoid hypotonic fluids, use only 0.9NS or D_5/0.9NS
  - If less than 120 mEq/L, consider 3% saline, 50–100 mL boluses
- Passive rewarming
  - Regular blankets, prevent heat loss
  - If heating blankets considered, pretreat with IV fluids and monitor BP closely
  - Avoid mechanical stimulation
- Treatment of any precipitating illness, with special attention to infectious causes

BP, blood pressure; CHF, congestive heart failure; D_5/0.9NS, 5% dextrose in 0.9% normal saline; IV, intravenous; T_3, triiodothyronine; T_4, thyroxine.

Airway Management

Prompt attention to the airway is critical, as there may be partial obstruction from macroglossia and supraglottic edema, myopathy of respiratory muscles, and central hypoventilation. Most myxedema coma patients require endotracheal intubation and prolonged ventilatory support. Blood gases should be monitored closely as life-threatening alkalosis can occur during the initial phase of full ventilator support.[74]

Fluid Resuscitation

Intravascular volume depletion is prominent in myxedema coma, even in the presence of normal vital signs. Fluid resuscitation should be started immediately, but the aggressiveness of administration should be tempered by the risk of unmasking congestive heart failure. The initial fluid of choice is D_5/0.9NS because the myxedema coma patient is at high risk for both hyponatremia and hypoglycemia.[75,83-85]

Thyroid Hormone Replacement

Prompt thyroid hormone replacement is critical for patient survival from myxedema coma, although the most effective regimen is unclear. Determination of the form of thyroid hormone (T_4 or T_3 or both) and the dosage must balance the high mortality of untreated myxedema coma against the risk of myocardial infarction or cardiac arrhythmias induced by therapy. T_4 has lower risk of toxicity as its action depends on peripheral conversion to T_3, which is a slow, delayed process. Proponents of T_3 administration suggest that the quicker onset of action and the increased biologic activity of T_3, as well as the impaired conversion of T_4 to T_3 in the critically ill, make T_3 the logical choice. High doses of T_4 or T_3 appear to increase mortality, hence there is a limit on how fast hormone replacement can be given.[33,63,75,83-85]

The most widely published approach to myxedema coma involves the IV administration of T_4 in a dose of 300 to 500 µg that depends on patient weight and cardiac risks. It is suggested that this dose replaces total body stores of T_4, and the pool can be maintained by 50 to 100 µg/day. Some authors suggest splitting the loading dose over 2 days.[75,83,84]

For critically ill younger patients without cardiac disease, where a more rapid correction of hormone levels is desired, the use of T_3 alone should be considered. An IV loading dose of 10 to 20 µg, followed by 10 µg IV every 4 hours for 24 hours, followed by 10 µg every 6 hours for 1 to 2 days is suggested.[75]

An intermediate approach using both T_4 and T_3 is suggested by some authors to speed clinical response while minimizing cardiac toxicity. T_4 is administered IV in half the loading dose (200–250 µg) with 10 µg of T_3, followed by T_3, 10 µg every 8 to 12 hours, and maintenance T_4, 50 µg every 24 hours. Due to impaired oral absorption and transit of medications in myxedema coma, the IV route is recommended until the patient is alert and able to tolerate oral intake, and then maintenance T_4 alone is continued.[75,83]

General Supportive Measures

The management of hyponatremia in myxedema coma requires water restriction, but in the face of the volume depletion and hypotension seen in myxedema coma, normal saline solutions should be used. If hyponatremia is severe (<120 mEq/L), hypertonic saline in 50- to 100-mL boluses should be considered.[75,83,84]

Hydrocortisone should be administered to all patients in myxedema coma. A small proportion of these patients may have central hypothyroidism where concomitant adrenocorticotropic hormone (ACTH) deficiency may be present. Another subset may have autoimmune destruction of both the thyroid and adrenal glands (Schmidt syndrome). Most patients are presumed to suffer from relative adrenal insufficiency unmasked by stress and the enhanced clearance of cortisol. Hydrocortisone is given IV, 50 to 100 mg, every 6 to 8 hours for several days.[75]

Hypothermia is treated with passive rewarming, using regular blankets and prevention of further heat loss. Heating blankets could be employed, but there is risk that the resulting vasodilation will lead to a fall in peripheral vascular resistance and hypotension. As in accidental hypothermia, excessive mechanical stimulation should be avoided due to risk of precipitating arrhythmias.

Identification and Treatment of Precipitating Illness

Concomitant with the previous treatment measures, a precipitating illness for myxedema coma should be sought and treated aggressively with special attention paid to a potential infectious cause, which accounts for about one third of cases.[89,90]

Without thyroid hormone replacement and a vigorous approach, the mortality rate from myxedema coma exceeds 80%; but with the comprehensive approach described and monitoring in the intensive care unit, the mortality rate falls to 20% or less. Factors that predict a poor outcome in myxedema coma include advanced age, a body temperature of less than 90° F or hypothermia refractory to treatment, hypotension, pulse less than 44 beats per minute, and sepsis.[91-93]

ADRENAL INSUFFICIENCY

Perspective

Adrenal insufficiency in its chronic form is an uncommon disease with nonspecific symptoms that include fatigue, weakness, weight loss, depression, and nonspecific gastrointestinal symptoms. This presentation is difficult to diagnose on a single encounter, yet recognition is critical as an acute superimposed stress can lead to vascular collapse and death. The acute development of severe adrenal insufficiency de novo can also occur and be life-threatening. Both the acute and chronic forms of adrenal insufficiency can be primary, due to adrenal gland destruction, or secondary, caused by pituitary gland failure to produce ACTH. Recognition of acute adrenal insufficiency and prompt administration of hydrocortisone is critical to patient survival.[94-97]

Principles of Disease

The adrenal cortex produces cortisol, aldosterone, and androgens, and the adrenal medulla produces catecholamines. Primary adrenal failure leads to a deficit of cortisol and aldosterone only, but catecholamine and androgen production continues from other sites. Secondary adrenal failure is related to decreased production of ACTH from the pituitary gland and as a result, only cortisol deficiency develops, as aldosterone is regulated by the rennin-angiotensin system. Cortisol has numerous actions that include facilitating gluconeogenesis and lipolysis, inhibiting insulin secretion, anti-inflammatory actions, immune-modulating effects, augmenting vascular reactivity to vasoconstrictors, promoting catecholamine synthesis, and retarding bone growth.[94,96,97] Aldosterone acts primarily at the distal nephron where it promotes the reabsorption of sodium and the excretion of potassium and hydrogen. A deficiency of cortisol alone may lead to blood pressure lower-

ing, but the loss of both cortisol and aldosterone causes a greater hypotensive effect.[96]

Etiology

Primary failure of the adrenal gland is referred to as Addison's disease, and the majority of such cases in the Western world are due to autoimmune adrenalitis, with about half of these being isolated deficiencies and the other half associated with a polyglandular autoimmune syndrome (PGA). There are two variants of the PGA: PGA type I is a rare autosomal recessive condition consisting of Addison's disease, hypoparathyroidism, chronic mucocutaneous candidiasis, and vitiligo. PGA type II (Schmidt's syndrome), the predominant form, includes primarily Addison's disease and hypothyroidism, as well as diabetes and hypogonadism[94-97] (Box 126-12).

Destruction of the adrenal glands by tuberculosis is the most common cause of Addison's disease worldwide, but is rare now in the United States except when associated with AIDS. Other disseminated infections such as cryptococcosis, histoplasmosis, blastomycosis, CMV, toxoplasmosis, and lung disease from *Mycobacterium avium-intercellulare*, and *Pneumocystis* may result in adrenalitis and Addison's disease, but these too are seen almost exclusively in the setting of HIV infection. Infiltration with Kaposi's sarcoma and direct involvement by HIV alone may lead to adrenal insufficiency, and overall, about 20% of HIV patients who are critically ill have laboratory evidence of cortisol deficiency.[98]

Adrenal metastases, most commonly from lung and breast cancer, are often found at autopsy, but symptomatic adrenal insufficiency is seen in only about 4% of these patients, probably because over 90% of both adrenals must be destroyed before function is affected. Infiltration of the adrenals by nonmalignant processes, such as sarcoid, amyloid, and hemochromatosis may also lead to Addison's disease.[96,97]

Drug therapy may precipitate or unmask adrenal insufficiency. The most noteworthy cause is etomidate, an imidazole agent used in the induction and maintenance of anesthesia. Etomidate blocks cortisol synthesis by inhibiting the 11β-hydroxylase enzyme. Etomidate infusions in an intensive care setting have been associated with acute adrenal insufficiency and are not recommended, but bolus administration for rapid sequence intubation appears safe, yet rare cases of crisis have been described.[99,100] Adrenal inhibition subsequent to a single etomidate bolus can be demonstrated in 80% of patients in the first 12 hours, and about one half at the 24-hour mark, followed by rapid resolution by 48 hours.[101] Trends toward hypotension and pressor use have been demonstrated in trauma patients admitted to an intensive care unit who have received rapid sequence intubation with etomidate, but a cause-and-effect relationship is difficult to assess. Other drugs that may aggravate adrenal insufficiency include ketoconazole (inhibits cortisol synthesis), rifampicin (increases cortisol catabolism), and megastrol acetate (stimulates the glucocorticoid receptor and suppresses ACTH).[102]

The presentation of hypoadrenalism in childhood often suggests an inherited disorder such as PGA syndromes, adrenoleukodystrophy, adrenal hypoplasia, or ACTH unresponsiveness.[96,97]

The development of bilateral hemorrhagic infarction of previously normal adrenal glands can result in acute adrenal insufficiency, carrying a very high mortality rate. Meningococcal sepsis (Waterhouse-Friderichsen syndrome) is classically described, but infections with *Pseudomonas*, *Escherichia coli*, group A *Streptococcus*, *Pneumococcus*, and *Staphylococcus* can result in a similar syndrome.[103]

Adrenal hemorrhage or infarction from coagulopathies can also result in acute adrenal insufficiency if 90% of both glands are involved. Warfarin or heparin anticoagulation in excess or during severe stress can result in hemorrhage that leads to acute crisis.[104] Venous infarction of the adrenals resulting in addisonian crisis has been described in the antiphospholipid antibody syndrome, and in one series it was the presenting manifestation of the disease in 36% of patients.[105] Adrenal hemorrhage has also been described in blunt thoracoabdominal trauma, but although associated liver, spleen, and kidney injuries are common, adrenal insufficiency is rare.[106]

Acute and chronic hypoadrenalism may also result from ACTH deficiency, in which exogenous glucocorticoid therapy is the most common cause. Reduced responsiveness and possible atrophy of the adrenal gland can be anticipated whenever supraphysiologic doses of a glucocorticoid (hydrocortisone 30 mg, prednisone 7.5 mg, or dexamethasone 0.75 mg daily) are taken for more than 3 weeks, but as little as 5 days is required if the daily dose exceeds the equivalent of 20 mg of prednisone.[94,96,97] Inhibition of ACTH secretion depends not only on the dose and duration of therapy but also on the frequency and timing of the dose, such that more than once per day and any evening dose have a much greater suppressive

BOX 126-12 CAUSES OF ADRENAL INSUFFICIENCY

Primary Adrenal Insufficiency

Chronic

Autoimmune adrenalitis (Addison's disease)—isolated or polyglandular deficiency, HIV infection (direct involvement or disseminated CMV, MAI, TB, cryptococcosis, histoplasmosis, blastomycosis, toxoplasmosis, *Pneumocystis* pneumonia)
TB and disseminated infections as seen with HIV
Metastatic cancer (breast, lung)
Infiltrative (sarcoid, hemochromatosis, amyloid)
Congenital (adrenal hypoplasia, adrenoleukodystrophy, ACTH resistance)
Bilateral adrenalectomy
Drug toxicity (etomidate, ketoconazole, rifampicin)

Acute

Adrenal hemorrhage
  Meningicoccemia and other sepsis
  Anticoagulation (heparins and warfarin)
  Anticardiolipin antibody syndrome
  Trauma

Secondary Adrenal Failure

Chronic

Pituitary tumor (primary or metastatic)
Pituitary surgery or irradiation
Chronic steroid use with functional deficiency
Infiltrative (sarcoid, eosinophilic granuloma, TB)
Traumatic brain injury
Postpartum pituitary necrosis (Sheehan's syndrome)
Empty sella syndrome

Acute

Pituitary apoplexy (hemorrhage into a pituitary tumor)
Postpartum pituitary necrosis (Sheehan's syndrome)
Traumatic brain injury
Relative adrenal insufficiency (sepsis, hepatic failure, severe acute pancreatitis, trauma)

ACTH, adrenocorticotropic hormone; CMV, cytomegalovirus; HIV, human immunodeficiency virus; MAI, *Mycobacterium avium-intracellulare*; TB, tuberculosis.

effect on pituitary ACTH, even if by the inhalational route.[107]

Other causes of secondary adrenal insufficiency result from direct destruction of the pituitary gland. Chronic hypopituitarism can result from pituitary adenomas or metastatic involvement, surgical hypophysectomy or pituitary irradiation, and granulomatous disease of the pituitary (sarcoid, tuberculosis, eosinophilic granuloma).[66]

Acute onset of secondary adrenal insufficiency can result from hemorrhage into a pituitary adenoma, referred to as pituitary apoplexy. Ischemic necrosis of the pituitary associated with hypotension, most commonly in the postpartum period (Sheehan's syndrome), can result in either acute or chronic hypoadrenalism and hypopituitarism.[108]

Traumatic brain injury is an increasingly recognized cause of central hypoadrenalism. In a compilation of 710 patients, the majority of whom presented with a Glasgow Coma Score of 3 to 13, 13% developed ACTH deficiency, many were evident in the initial hospitalization, but some presented up to 6 months after injury. Similar percentages were seen for growth hormone and gonadotropin deficiencies.[109,110]

Functional adrenal insufficiency, another central cause of hypoadrenalism, occurs in critically ill patients who have an inability to mount an adequate ACTH and cortisol response to sepsis or overwhelming stress, leading to increased mortality during the acute illness. Looking specifically at septic shock, more than 50% of patients have evidence of this relative adrenal insufficiency.[111-114]

Symptoms and Signs

The presentation of Addison's disease and other causes of chronic primary adrenal gland failure is often vague and nonspecific, with the insidious onset of fatigue, generalized weakness, and weight loss. Gastrointestinal symptoms are common with nausea, intermittent vomiting, abdominal pain, and diarrhea or constipation.[115] Low-grade fever, arthralgias, and muscle cramps suggest a persistent flulike syndrome. Salt craving, sometimes with massive salt ingestion, and postural dizziness or syncope result from concomitant mineralocorticoid deficiency. Psychiatric symptoms occur early in the disease and may predate other symptoms. The most common presentations include depression, manifested by apathy and lack of initiative, memory impairment that can progress to confusion and delirium, a dementia-like picture, and psychosis[94-97] (Box 126-13).

Adrenal insufficiency due to ACTH deficiency may present with similar symptoms, but salt craving and postural hypotension are absent because the renin-aldosterone axis remains intact. Symptoms often relate more to deficiency of pituitary hormones other than ACTH, specifically follicle-stimulating hormone/luteinizing hormone, resulting in loss of libido, infertility, amenorrhea, and TSH with cold intolerance and weight gain.[66,94,96]

In most cases Addison's disease is not recognized until an acute intercurrent illness precipitates a crisis, but some clinical clues may alert the clinician to the diagnosis. The systolic blood pressure is usually below 110 mm Hg, and postural changes may be found. Hyperpigmentation of sun-exposed areas, palmar creases, nipples, axillae, recent scars, and all mucous membranes is typically seen in Addison's disease, due to compensatory elevation of ACTH, which in turn stimulates melanocyte receptors to produce melanin. In women, loss of adrenal androgen can lead to thinning of pubic and axillary hair. Patients with secondary adrenal insufficiency lack hyperpigmentation and hypotension, and thus the condition is more difficult to identify. Vitiligo may be seen in 10 to 20% of patients with Addison's disease associated with polyglandular autoimmune syndrome I. Auricular cartilage calcification is an unexplained phenomenon seen in men with either chronic primary or secondary adrenal insufficiency.[116,117]

BOX 126-13 Clinical Features of Adrenal Insufficiency

General	
Weakness, fatigue	100%
Anorexia	100%
Gastrointestinal symptoms	92%
Weight loss	100%
Hyponatremia	90%
Blood pressure ≤110/70 mm Hg	88–94%
Fevers (mild)	Common
Depression, apathy	20–40%
Myalgia, arthralgias	6–13%
Auricular calcifications	5%
Primary	
Hyperpigmentation	94–97%
Salt craving	16–22%
Orthostasis, syncope	12–16%
Vitiligo	10%
Hyperkalemia	65%
Hyperchloremia and acidosis	65%
Hypoglycemia	Mild, occasional
Secondary	
Hyperkalemia	Not present
Hyperpigmentation	Not present
Hypoglycemia	More severe, common
Orthostasis, hypotension	Uncommon
Amenorrhea	Common
Axillary and pubic hair loss	Occasional
Decreased libido	Occasional
Crisis	
Refractory hypotension	100%

Most adrenal crises occur in the setting of chronic adrenal insufficiency in which almost any acute intercurrrent illness or stress overwhelms the patients limited cortisol reserve. Less common, but a more fulminant presentation, is acute adrenal or pituitary hemorrhage or infarction.[104,105,108]

The presentation of acute adrenal insufficiency can vary from a picture suggesting acute gastroenteritis with nausea, vomiting, fever, and dehydration to sudden vascular collapse and death. The cardinal feature of adrenal crisis is hypotension or shock out of proportion to the severity of the current illness. Despite aggressive fluid resuscitation, the blood pressure typically shows little response and is often refractory to pressors.[94-96]

Abdominal pain may be a presenting symptom, mimicking an acute abdomen, this picture being particularly dramatic with acute adrenal hemorrhage or infarction. Hypotension accompanying sudden severe headache and visual field cuts suggests acute pituitary apoplexy.

Diagnostic Strategies

The diagnostic approach to adrenal insufficiency depends on whether you are screening for a chronic condition or evaluating an acutely ill or critical patient, but in all circumstances the serum cortisol measurement is the mainstay. Serum cortisol has a diurnal variation, peaking between 6 and 8 AM, and reaching a nadir in the late evening and during early sleep. Screening the patient who is not acutely ill starts with an AM cortisol

measurement, which is normally between 10 and 20 µg/dL. An AM cortisol level above 20 µg/dL excludes hypoadrenalism, while a level below 3 µg/dL is diagnostic. Measurements between 3 and 10 µg/dL are strongly suggestive, but require confirmation with an ACTH (cosyntropin) stimulation test, and if the clinical suspicion is high, any patient with a level less than 20 µg/dL should have a stimulation test. This test can be performed any time of the day and involves obtaining a baseline cortisol, then administering 250 µg of ACTH as an IV bolus, followed by repeat serum cortisol levels at 30 or 60 minutes. The post-ACTH cortisol should exceed 20 µg/dL to exclude the diagnosis. If hypoadrenalism is confirmed, an AM ACTH level can be used to distinguish primary from central, a high ACTH being consistent with primary causes and a low or normal ACTH seen in secondary ones.[95,96] An ACTH stimulation test is the gold standard for diagnosing adrenal insufficiency, but it may be normal in the unusual circumstance of partial pituitary insufficiency. If such a possibility exists, measurement of ACTH in response to metapyrone or hypoglycemia could be performed by the endocrinologist. Another option is the measurement of plasma renin and aldosterone. Their values should be normal in secondary hypoadrenalism, whereas primary adrenal failure results in a decreased plasma aldosterone and an elevated plasma renin (Table 126-3).

If the patient is acutely ill, the physiologic stress should result in an elevation of serum cortisol regardless of the time of the day, such that a random level is adequate. If a patient is acutely ill, a cortisol level below 15 µg/dL is presumptive evidence of hypoadrenalism. Consensus opinion suggests that a random level greater than 33 µg/dL excludes the diagnosis in the acutely stressed patient. For serum cortisol measurements between 15 and 33 µg/dL, the patient should be treated presumptively with IV hydrocortisone. If an ACTH stimulation test can be performed, a rise in serum cortisol less than 9 µg/dL from the prestimulation level is diagnostic of adrenal insufficiency. The relative adrenal insufficiency of sepsis and other critical illness should be suggested if a random cortisol level is less than 25 µg/dL, and treatment should not be delayed awaiting confirmation by a stimulation test.[111-114]

Hyponatremia is seen in about 90% of patients with chronic primary adrenal insufficiency.[116,117] It is usually of mild to moderate severity, seldom below 120 mEq/L. Adrenal gland failure leads to aldosterone deficiency, which results in sodium loss. In addition, cortisol deficiency leads to increased antidiuretic hormone secretion and excess water reabsorption. Although aldosterone is not deficient in secondary adrenal insufficiency, increased antidiuretic hormone secretion alone results in hyponatremia in about 50% of patients and it may be severe. In hypoadrenalism of either cause, the administration of hydrocortisone suppresses antidiuretic hormone production and can correct hyponatremia.[96,97]

Due to aldosterone deficiency, hyperkalemia is seen in about two thirds of patients with primary adrenal insufficiency, but it is absent in secondary causes where aldosterone production is not affected. Serum potassium elevation is usually mild in Addison's disease and rarely exceeds 7 mEq/L. A mild hyperchloremic metabolic acidosis usually accompanies the elevated potassium due to impaired exchange of sodium with hydrogen and potassium when aldosterone is deficient.[96,97,116,117]

Older reviews describe fasting hypoglycemia in more than two thirds of patients with Addison's disease, whereas more recent literature suggests that hypoglycemia is more pronounced in secondary adrenal insufficiency and is often the presenting manifestation. Inhibition of gluconeogenesis resulting from cortisol deficiency, as well as reduced calorie intake and depletion of glycogen stores, makes adrenal insufficiency a set-up for hypoglycemia.[96,116] Deficiency of growth hormone and ACTH in hypopituitarism further increases the propensity to and severity of hypoglycemia.[66] Patients with type I diabetes and adrenal insufficiency often present with unexplained recurrent hypoglycemic reactions.[118]

Other laboratory abnormalities seen in adrenal insufficiency include hypercalcemia in about 6%, elevated BUN and creatinine in 55%, anemia in 40%, and eosinophilia in 17%.[96,97,116,117] Evaluation of the etiology of hypoadrenalism is usually beyond the scope of the emergency physician, but abdominal computed tomography may reveal adrenal hemorrhage, infarction, or metastatic disease, while computed tomography of the brain may demonstrate pituitary hemorrhage, tumor, or empty sella.[119]

Table 126-3 Diagnosis of Hypoadrenal States

	LEVEL (µg/dL)	DIAGNOSTIC CONCLUSION
Chronic, Nonstressed		
Serum cortisol (6–8 AM)	<3	Diagnostic
	<10	Suggestive
	10–20	Normal
	>20	Excludes
ACTH stimulation test (peak)	<20	Diagnostic
	>20	Excludes
Acute Crisis		
Serum cortisol (random)	<15	Diagnostic
	15–33	Indeterminant
	>33	Excludes
ACTH stimulation test (delta)	<9	Diagnostic
Relative Hypoadrenalism of Sepsis and Critical Illness		
Serum cortisol (random)	<25	Likely
ACTH stimulation test (delta)	<9	Diagnostic

Differential Diagnosis

Chronic adrenal insufficiency may be marked by wasting suggestive of anorexia nervosa or occult carcinoma. Generalized weakness, fatigue, and myalgias resemble chronic fatigue syndrome, polymyalgia rheumatic, myopathy, hypothyroidism, or flu syndromes.

Acute adrenal crisis with refractory hypotension often leads to a search for sepsis, gastrointestinal bleeding, myocardial ischemia, or anaphylaxis. Abdominal pain in crisis may mimic an acute abdomen especially if precipitated by adrenal hemorrhage. The headache and visual field cuts in pituitary apoplexy may resemble a hemorrhagic stroke.

Steroid withdrawal syndrome should be distinguished from adrenal insufficiency as both can occur with the cessation of chronic glucocorticoid therapy. Steroid withdrawal syndrome is characterized by symptoms that resemble chronic adrenal insufficiency, including weakness, malaise, fatigue, nausea, dizziness, and arthralgias. Patients with steroid withdrawal syndrome, however, are not predisposed to adrenal crisis as their hypothalamic-pituitary-adrenal axis is intact by ACTH stimulation testing.[96]

Management

Acute adrenal insufficiency and relative adrenal insufficiency of sepsis and critical illness are life-threatening conditions in which aggressive fluid resuscitation, hydrocortisone replacement, and treatment of any precipitating illness are the main-

BOX 126-14 TREATMENT OF HYPOADRENALISM

Maintenance
Hydrocortisone 20 mg AM, 10 mg PM
Fludrocortisone 100 µg/day

Maintenance during Minor Illness
Hydrocortisone 40 mg AM, 20 mg PM
Fludrocortisone 100 µg daily

Coverage during Procedural Stress
Hydrocortisone 100 mg IV (one time only)

Adrenal Crisis or Relative Adrenal Insufficiency of Critical Illness
Hydrocortisone 50–100 mg IV every 6 hr
OR
Hydrocortisone 50–100 mg IV followed by an infusion,
20 mg/hr
0.9 NS 2–3 L over the first few hours
Switch to D_5 NS if hypoglycemia
Treat precipitating illness

D_5 NS, 5% dextrose in normal saline.

stays of treatment. IV access should be established with two large-bore IVs and 2 to 3 L of 0.9% saline should be infused over the first few hours, monitoring for signs of fluid overload and blood pressure response. A bedside glucose should be determined due to the frequent incidence of hypoglycemia and 5% dextrose in normal saline substituted if indicated. Hypotonic fluids should be avoided as the frequency of hyponatremia is high. Bicarbonate is not required for the correction of acidosis and hyperkalemia, as rapid correction is generally seen with saline and hydrocortisone administration[95,96,120-122] (Box 126-14).

Blood should be drawn for random serum cortisol and ACTH, as well as electrolytes, but hydrocortisone treatment should not be withheld awaiting laboratory confirmation. Hydrocortisone is the glucocorticoid of choice as it has intrinsic mineralocorticoid properties, which obviates the need to administer a mineralocorticoid separately. Dexamethasone should not be used in this acute setting, as it has no mineralocorticoid effects. In a nonacute setting, dexamethasone is often suggested for glucocorticoid replacement while an ACTH stimulation test is being performed since it does not interfere with cortisol measurements. In a critical patient with possible adrenal insufficiency, an ACTH stimulation test is not recommended due to inherent delays.[95,112,113]

Approximately 200 to 300 mg per day of hydrocortisone is considered a physiologic stress dosage, such that dosage recommendations range from 50 to 100 mg IV every 6 to 8 hours. Another option is to administer a 50- to 100-mg bolus of hydrocortisone, followed by an infusion of 20 mg per hour.[95,96,112,113]

If the diagnosis of adrenal insufficiency is correct, these measures will improve the blood pressure and clinical picture over 4 to 6 hours. A careful search for a precipitating cause, especially infections, should have been completed by now and empirical antibiotic therapy often started. The rate of saline infusion and the dose of IV steroids can often be tapered after 24 hours. By the third or fourth day, conversion to oral hydrocortisone is feasible, usually at twice the maintenance dose (40 mg AM, 20 mg PM) initially, then to the standard replacement dose (20 mg AM, 10 mg PM). Hydrocortisone can be discontinued altogether if the random cortisol exceeds 25 µg/dL (preferably greater than 33 µg/dL) and the patient is much improved clinically. If there is any doubt, IV steroids should be continued until an ACTH stimulation test can be completed. Fludrocortisone, a mineralocorticoid, should be administered in a dose of 100 µg by mouth before cessation of the saline infusion, and it should be continued every 12 to 24 hours as maintenance.[95,96,112,113]

Chronic replacement therapy in patients with established adrenal insufficiency consists of hydrocortisone, 20 mg on arising and 10 mg at 6 PM, as well as fludrocortisones, 100 µg per day. During minor to moderate febrile illness or stress, the patient should be advised to increase the glucocorticoid dose two- or threefold for the few days of illness, but the fludrocortisone dose is not changed. For moderately stressful procedures like endoscopy or angiography, a single 100-mg IV dose of hydrocortisone is given prior to the procedure.[96]

KEY CONCEPTS

- Thyroid storm is a life-threatening decompensation of severe hyperthyroidism precipitated by an intercurrent illness, typically sepsis. The hallmarks of thyroid storm include hyperthermia, exaggerated tachycardia, altered mental status, and gastrointestinal symptoms. Therapy of thyroid storm includes actions to reduce production of thyroid hormone, to inhibit thyroid hormone release, to block peripheral conversion of T_4 to T_3, to initiate beta-adrenergic blockade, to institute general supportive measures, and to identify and treat the precipitating event.
- Myxedema coma is a life-threatening deterioration of severe chronic hypothyroidism precipitated by an acute intercurrent illness. The prototypical case is an elderly woman in the winter who presents with marked hypothermia, altered mental status, respiratory failure, and hypotension. The management of myxedema coma requires immediate attention to airway management, fluid resuscitation, thyroid hormone replacement, general supportive measures, and treatment of the precipitating illness.
- Hallmarks of chronic adrenal insufficiency include generalized weakness, malaise, fatigue, gastrointestinal symptoms, weight loss, blood pressure less than 110/70 mm Hg, and hyponatremia. Primary autoimmune adrenal failure is the more common cause and is distinguished by the presence of hyperpigmentation, hyperkalemia, and more severe orthostasis. Hypopituitarism resulting in secondary adrenal insufficiency is distinguished by more severe hypoglycemia and the lack of the classic features seen in primary disease.
- Hypotension refractory to fluid resuscitation may be the only clue to the diagnosis of adrenal crisis or relative adrenal insufficiency of critical illness. In this setting, a random serum cortisol level should be obtained and IV hydrocortisone administered before confirmation is obtained.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 127 Bacteria

Madonna Fernández-Frackelton

DIPHTHERIA

Perspective

Background

References to the disease now known as diphtheria date back to ancient Syria and Egypt. In the fifth century BC, Hippocrates provided the first clinical description of this disease characterized by sore throat, membrane formation, and death through suffocation. Epidemics of "throat distemper" were described throughout the 16th, 18th, and 19th centuries. In 1821 French physician Pierre Bretonneau named the condition "diphtherite," from the Greek word for "leather," to describe the characteristic pharyngeal membrane.[1] Klebs observed the *Corynebacterium diphtheriae* microorganism on smears obtained from pharyngeal membranes in 1883, and 1 year later Löffler isolated *Corynebacterium* organisms in pure cultures. Löffler subsequently demonstrated that diphtheria was a localized infection and postulated that its systemic effects were caused by an elaborated toxin. In 1888 Roux and Yersin demonstrated that bacteria-free filtrates of diphtheria culture were able to kill guinea pigs.[1]

In 1890 von Behring and Kitasato first demonstrated diphtheria immunization using a heat- and formalin-treated toxin to make toxoid. One year later they administered the first dose of antitoxin to a human with diphtheria. Schick developed the skin test for diphtheria immunity in 1913. During the 1930s and 1940s, toxoid immunization was routinely used. In the 1950s Freeman found that only bacteria infected with the B phage produced toxin. Subsequent studies elucidated the toxin genome and the mechanism of toxin activity at the cellular level.[1,2]

Epidemiology

Humans are the only known reservoir for *C. diphtheriae*. Spread is primarily by person-to-person contact through respiratory droplets or by direct contact with skin lesion exudates. Transmission is associated with crowded living conditions. Individuals may spread the disease when they are actively ill, in the convalescent stage after acute illness, or as asymptomatic carriers. Fomites and foods have occasionally been implicated but do not represent a major route of transmission.[1]

Between 1991 and 1996 the first large-scale epidemic of diphtheria in an industrialized country in three decades occurred in the newly independent states of the former Soviet Union. During the peak of the epidemic more than 98,000 cases and 3400 deaths were reported. Several factors contributed to this outbreak, including (1) decreased childhood immunity due to vaccine supply interruption and administration of adult-formulation tetanus-diphtheria toxoids (Td) to children, (2) increased adult susceptibility due to waning immunity, (3) poor socioeconomic conditions and increased population movement, and (4) resurgence of more toxigenic strains of diphtheria.[3]

Immunization against diphtheria is highly effective. Before widespread immunization programs in the United States, the incidence of diphtheria was in excess of 100 cases per 100,000 population, and the disease predominantly affected children. During this time, 80% of people acquired natural immunity to diphtheria by age 15, and recurrent exposure to toxigenic strains of the bacteria acted as boosters. Because childhood immunization nearly eliminates these toxigenic strains in a population, adult immunity wanes. Thus, more adults in industrialized nations are susceptible to diphtheria.[4] By 1980 the Centers for Disease Control and Prevention (CDC) reported 0 to 5 cases per year nationwide. Currently, sporadic cases occur primarily in adults, many of whom are not adequately immunized.[3] Three urban outbreaks of predominantly cutaneous diphtheria occurred in Seattle between 1972 and 1982 among a population of urban alcohol abusers. Outbreaks are associated with poor hygiene, crowding, underlying skin disease, contaminated fomites, pyoderma, and the appearance of new *C. diphtheriae* strains.[1] Even in industrialized nations in which childhood vaccination rates are high, more than 50% of adults older than 40 lack protective antibodies.[4] The ease of international travel and the epidemic in eastern Europe in the 1990s underscore the importance of aggressively continuing childhood immunizations and reimmunization of adults.

Principles of Disease

Etiology

Diphtheria is caused by *C. diphtheriae*, an unencapsulated, gram-positive bacillus named for its shape ("korynee" for club) and for its characteristic clinical presentation ("diphtheria" for "leather hide," referring to the appearance of the pharyngeal membrane). When viewed on stained smears, the bacteria look like Chinese characters.[1]

Infection by *C. diphtheriae* occurs at various sites of the respiratory tract or the skin. Respiratory diphtheria includes faucial (pharyngeal or tonsillar), nasal, and laryngeal (tracheobronchial) types, named for the primary location of infection.

Cutaneous diphtheria may occur as a primary skin infection or as a secondary infection of a preexisting wound.

Pathophysiology

The *C. diphtheriae* bacterium produces an exotoxin that contributes to formation of the diphtheritic membrane and is responsible for the systemic effects of infection.[5] The exotoxin is a 62,000-dalton polypeptide produced by bacterial strains lysogenized by the corynephage B tox$^+$.[1,5] The exotoxin inhibits cellular protein synthesis. Circulating exotoxin most profoundly affects the nervous system, heart, and kidneys.[1] The degree of local and systemic toxicity depends on the location and extent of membrane formation. Pharyngeal diphtheria generally has the greatest toxicity and cutaneous diphtheria the least.

The diphtheritic membrane forms as a result of necrosis caused by the local effects of the exotoxin. The membrane is composed of leukocytes, erythrocytes, fibrin, epithelial cells, and bacteria. Initially, the pharynx appears erythematous, but as necrosis occurs, grayish-white patches appear and eventually coalesce. The membrane is accompanied by surrounding edema and cervical adenitis. The initial grayish-white, filmy appearance changes to a thick, grayish-black membrane with sharply defined borders. This membrane adheres to the underlying tissue, and bleeding occurs if removal is attempted.[1]

Systemic effects of diphtheria infection are caused by the circulating exotoxin's action primarily on the cardiovascular and nervous systems. The exotoxin's disruption of cellular protein synthesis produces a peripheral neuropathy manifested by muscle weakness. About 20% of all patients with symptomatic respiratory infection have polyneuritis, but 75% of patients with severe disease develop some form of neuropathy.[5] The muscles of the palate are usually the first to become paralyzed. Less commonly, other cranial nerves, peripheral nerves, and the spinal cord may be affected. Degenerative lesions develop in the dorsal root and ventral horn ganglia of the spinal cord and in cranial nerve nuclei. Cortical cells are spared. Proximal muscle groups are affected first. In severe cases, paralysis may develop in the first few days of illness. Generally the paralysis does not last more than 10 days, and complete recovery over a longer period of time is the rule.[1]

The extent of cardiac complications correlates with the degree of local infection and membrane formation. Signs of myocardial dysfunction usually appear 1 to 2 weeks after the onset of illness. In more severe cases, cardiac symptoms arise earlier in the course of the illness. The exotoxin directly damages myocardial cells, producing myocarditis. Electrocardiographic (ECG) changes suggestive of myocarditis occur in up to two thirds of patients, but clinical manifestations of myocarditis are less common (10–25%).[1]

Clinical Features

Symptoms and Signs

The average incubation period of respiratory tract diphtheria is 2 to 4 days but may range from 1 to 8 days. Signs and symptoms are often indistinguishable from those of other upper respiratory tract infections. In a series of 676 patients, fever and sore throat were the most frequent presenting complaints (79% and 69%, respectively). Weakness (42%), dysphagia (35%), headache (20%), change of voice (15%), and loss of appetite (10%) were also common. Cough, shortness of breath, nasal discharge, and neck edema occurred in less than 10% of patients. Fever, although common, is usually low grade. Cervical adenopathy is present in approximately one third of patients, and a diphtheritic membrane is observed in more than half of all patients. Of note, however, one report indicated that shortness of breath and neck edema were present in approximately 40% of patients who died of the disease.[6]

In patients with faucial diphtheria, the extent of the membrane usually parallels the clinical toxicity. If the membrane is limited to the tonsils, the disease may be mild; if the membrane covers the entire pharynx, the onset of illness is usually abrupt and the disease severe. Swelling of the cervical lymph nodes and infiltration of tissues of the neck may be so extensive that the patient has a "bull-neck" appearance. Patients with this form of "malignant diphtheria" usually have high fever, severe muscle weakness, vomiting, diarrhea, restlessness, and delirium.[1,6,7] Death occurs from respiratory tract obstruction or cardiac failure from myocarditis. Nasal diphtheria arises with a unilateral or bilateral serous or serosanguineous discharge from the nose. A diphtheritic membrane may be visible. These patients do not usually develop constitutional symptoms. Treatment is important to prevent a persistent carrier state. Laryngeal (tracheobronchial) diphtheria may begin in the larynx or spread downward from a more cephalad primary site. Respiratory tract edema with subsequent upper airway obstruction may develop.

Patients with cutaneous diphtheria generally do not display systemic toxicity. The skin characteristically has an ulcer with a grayish membrane. Wounds from which *C. diphtheriae* is cultured are clinically indistinguishable from other chronic skin conditions.[1]

Complications

The most serious complications of diphtheria are airway obstruction (resulting from membrane formation and edema), congestive heart failure, cardiac conduction disturbances, and muscle paralysis. Mortality in two large series ranged from 2.3 to 3% overall but was up to 7% in patients with myocarditis and 25.7% in patients with the malignant form of the disease (with neck swelling).[7] Unimmunized and underimmunized children requiring intensive care may have higher mortality rates (78.1%) from myocarditis and often develop renal failure.[8] Although systemic infection is rare, endocarditis, mycotic aneurysms, osteomyelitis, and septic arthritis have all been described in immunocompromised hosts.[1]

Diagnostic Strategies

When *C. diphtheriae* is suggested, the laboratory should be notified because routine cultures do not identify the organism. Throat or nasopharyngeal swabs should be obtained for respiratory diphtheria, and, if present, membranous material should be examined. For cutaneous infections, samples should be obtained from skin lesions. Specimens should be collected before antibiotic therapy is initiated and should be transported to the laboratory immediately for rapid inoculation onto tellurite (Tinsdale's) or Löffler's selective culture medium.[1,9] Immunofluorescent staining of a 4-hour culture may provide a rapid diagnosis, but direct staining is frequently unreliable. Definitive identification is made by using a combination of colony morphology, microscopic appearance, and fermentation reactions.[1] *C. diphtheriae* isolates should be tested for the production of toxin. The Elek immunoprecipitation test for toxin A is technically demanding and subject to misinterpretation by inexperienced users. Polymerase chain reaction (PCR), which is more reliable but not as readily available, can be used to detect the diphtheria toxin structural gene.[9] A positive culture for group A beta-hemolytic streptococcus does not exclude diphtheria as a pathogen, as up to 30% of patients with

BOX 127-1 DIFFERENTIAL DIAGNOSIS OF RESPIRATORY DIPHTHERIA

Streptococcal or viral pharyngitis
Tonsillitis
Vincent's angina
Acute epiglottitis
Mononucleosis
Laryngitis
Bronchitis
Tracheitis
Monilial infection (thrush)
Rhinitis

diphtheria test positive for streptococcal coinfection or carrier state.

Several laboratory abnormalities such as leukocytosis, mild thrombocytopenia, and proteinuria are common but are neither sensitive nor specific for diphtheria. ECG changes are nonspecific and include ST-T wave changes, varying degrees of atrioventricular block, and dysrhythmias. An ECG may be normal even in the presence of myocarditis. Cardiac enzymes may detect myocarditis, and serum troponin levels correlate with the severity of myocarditis.[10]

Differential Considerations

In the absence of a diphtheritic membrane, it may be difficult to differentiate respiratory diphtheria from many other respiratory conditions, especially in the early phase of infection (Box 127-1). Generally, the diphtheritic membrane is darker, grayer, more fibrous, and more firmly attached to the underlying tissues than in other conditions that have a membrane-like appearance. Vincent's angina frequently involves the gingivae, which are unaffected in diphtheria. Acute bacterial epiglottitis generally has a much more rapid onset than diphtheria, and indirect laryngoscopy reveals an erythematous, edematous epiglottis without membrane formation.[1]

Cutaneous diphtheria is difficult to differentiate from other acute and chronic ulcerative skin lesions. *C. diphtheriae* can secondarily infect any of these lesions, especially in high-risk patients such as alcoholic, socioeconomically disadvantaged, and unimmunized or underimmunized people.

Management

Patients with clinical evidence of diphtheria should be placed in respiratory isolation and treated presumptively for *C. diphtheriae*. The goals of therapy are to protect the airway, limit the effects of already produced toxin, and eliminate future toxin production by terminating the growth of *C. diphtheriae*. Although the likelihood of a patient in the United States developing airway obstruction from diphtheria is remote, the management is identical to that for other forms of airway obstruction. Bronchodilators may be useful in symptomatic patients.[10] Patients may be dehydrated from fever and decreased oral intake related to dysphagia or neurologic impairment. Fluid resuscitation should be undertaken cautiously as the toxin's effect on the myocardium may result in congestive heart failure.

Equine serum diphtheria antitoxin (DAT) should be administered promptly after the clinical diagnosis of respiratory diphtheria is made. DAT is not licensed by the Food and Drug Administration (FDA) for use in the United States. The CDC is authorized to distribute DAT to physicians as an investigational new drug. DAT can be obtained by contacting the CDC Emergency Operations Center at 770-488-7100. The diphtheria duty officer can also be contacted at 404-639-3158 during duty hours.[11] The size and location of the membrane, duration of illness, and the patient's overall degree of toxicity determine the dosage of antitoxin. The Committee on Infectious Diseases of the American Academy of Pediatrics (AAP) recommends 20,000 to 40,000 units for pharyngeal or laryngeal involvement of 48 hours' duration, 40,000 to 60,000 units for nasopharyngeal lesions, and 80,000 to 120,000 units for extensive disease of 3 or more days' duration or for diffuse swelling of the neck.[10,11] After conjunctival or intradermal sensitivity skin testing, the antitoxin is administered intravenously (IV). If the patient exhibits sensitivity to the antitoxin, desensitization should be performed. Active immunization against diphtheria should also be initiated because clinical infection does not necessarily confer immunity.[10]

Antibiotics are beneficial in preventing growth and spread of the organism but are no substitute for antitoxin. Erythromycin, 40 to 50 mg/kg/day (up to 2 g) IV or orally in divided doses, intramuscular (IM) aqueous crystalline penicillin (100,000–150,000 units/kg/day in four divided doses), and procaine penicillin (25,000–50,000 units/kg/day in two divided doses) for 14 days given IM are acceptable alternatives.[10,12] Treatment failures are more common with penicillin than with erythromycin. The newer generation macrolides (azithromycin and clarithromycin) have activity similar to that of erythromycin in vitro and may result in better compliance. These agents have not yet been adequately tested in clinical disease. An equivalent daily oral therapy may be substituted when the patient is able to swallow. Three negative cultures should be documented after treatment.[12]

Myocarditis and neuritis are treated with supportive care and careful monitoring. Patients with ECG changes of myocarditis have three to four times the mortality rate of those with normal ECGs. The mortality rate for patients with left bundle branch block and atrioventricular block is 60 to 90%, and serial tracings are recommended. No data support the use of steroids.[1,10]

Cutaneous lesions should be débrided of necrotic tissue and cleansed vigorously. A course of antibiotics is recommended, but the administration of antitoxin for cutaneous lesions is of questionable value. Some experts recommend 20,000 to 40,000 units of antitoxin, but few data support its use in this setting.[1,12]

Carriers of *C. diphtheriae* should receive oral penicillin G or erythromycin for 7 days or IM benzathine penicillin (600,000 units for those less than 30 kg and 1,200,000 units for those over 30 kg). Active immunization should also be provided to unimmunized and partially immunized carriers. After 2 weeks of therapy is completed, cultures should be obtained; if cultures are positive, erythromycin therapy should be given for 10 additional days.[12]

Individuals who have been in close contact with infected patients should have culture specimens taken, and the patient should be kept under surveillance for 7 days. Previously immunized close contacts should receive a booster of diphtheria toxoid if the last booster was more than 5 years earlier. The vaccine should be diphtheria, tetanus, and pertussis (DTP), diphtheria-tetanus (DT), or tetanus-diphtheria with a lower dose of diphtheria toxoid (Td) as appropriate for age according to the recommended immunization schedule. Close contacts who are not immunized or whose immunization status is unknown should receive the same antimicrobial therapy as carriers (as previously described), have culture specimens taken before and after therapy, and have active immunization initiated. Close contacts who cannot be kept under surveillance should receive benzathine penicillin IM to ensure com-

pliance and a Td booster (appropriate for age and immunization history). Some practitioners treat this group with 5000 to 10,000 units of antitoxin IM (at a site separate from the toxoid booster) after sensitivity testing. This is generally not recommended, however, because of the risk of horse serum allergy.[12]

A universal program of primary immunization along with regular diphtheria boosters every 10 years is the most effective method for controlling diphtheria. For this reason, emergency physicians should routinely administer DT toxoids as part of wound management.

Disposition

All patients with possible pharyngeal diphtheria should be isolated and admitted. A monitored setting is recommended for the early detection of arrhythmias. A cardiologist should be consulted for patients with evidence of myocarditis. The CDC should be contacted for all suggested or proven cases of diphtheria.

PERTUSSIS

Perspective

Background

Pertussis is an acute respiratory disease that was first described in 1578 when an epidemic swept through Paris. The name "pertussis" was first used by Sydenham in 1670 when he described the illness in infants. Pertussis literally means "violent cough," which is the hallmark of the disease. In China it is known as "the cough of 100 days." It is also called *whooping cough* because the severe episodes of coughing are followed by forceful inspiration, which creates the characteristic whooping sound. The causative organism was identified in 1906 by Bordet and Gengou.[13] In the prevaccination era, pertussis was a major cause of mortality among infants and children in the United States. A vaccine was developed in the 1940s, but pertussis still remains a significant cause of morbidity and mortality in the United States and worldwide.

Epidemiology

Pertussis is a localized respiratory illness transmitted by aerosolized droplets. It is highly contagious, with attack rates greater than 50% in adults exposed more than 12 years after completion of a vaccination series, and up to 100% in susceptible individuals with a household exposure.[13] The average incubation period is 7 to 10 days but may range from less than 1 week to 3 weeks. Neither vaccination nor prior infection confers lifelong immunity.

Pertussis remains prevalent worldwide. In the United States, annual pertussis rates declined sharply after the introduction of the vaccine and reached a nadir of 1010 cases in 1976. Since then, there has been a steady increase in the incidence of pertussis, with 11,647 cases reported in 2003 (Fig. 127-1A and B).[14] Waning immunity in the adult population and increased reporting of adult cases may be contributing factors. A 1991 report found evidence of a causal relationship between the

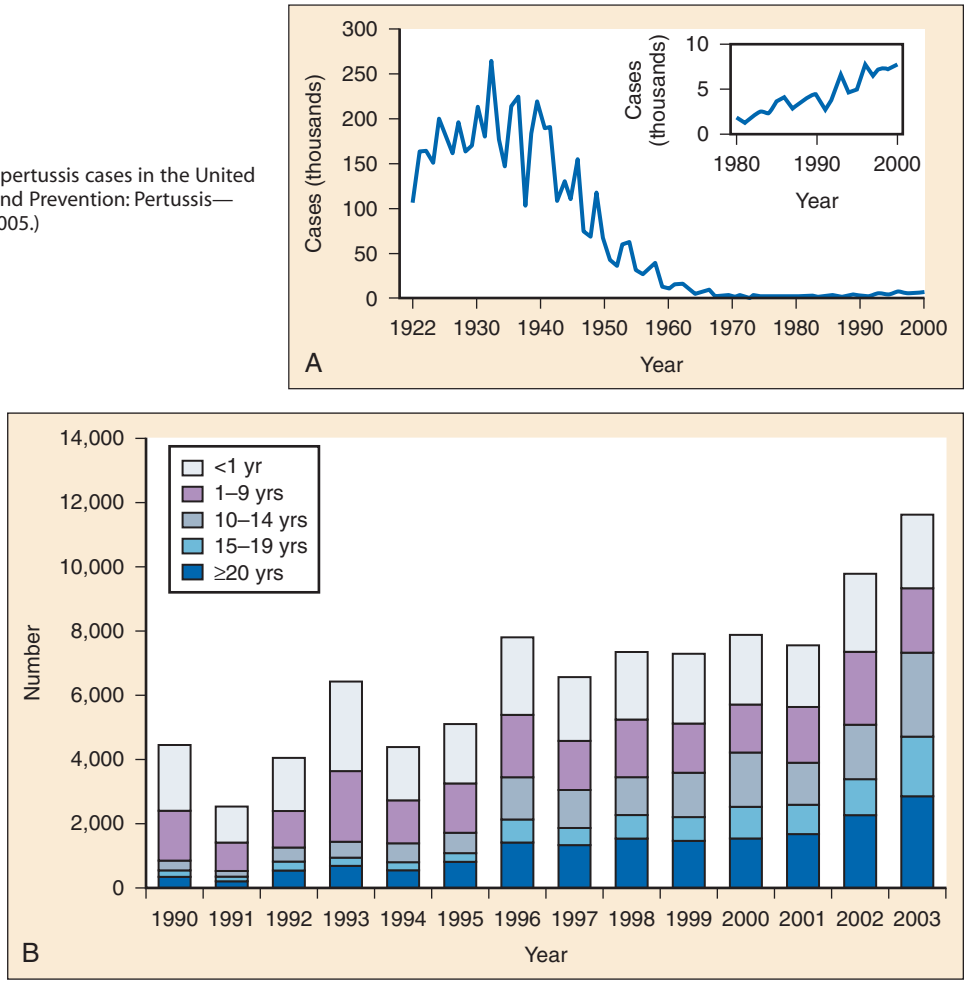

Figure 127-1. **A** and **B,** Number of reported pertussis cases in the United States by year. (Centers for Disease Control and Prevention: Pertussis—United States, 2001–2003. MMWR 54:1283, 2005.)

vaccine and acute encephalopathy. Although there appears to be no causal relationship between the vaccine and long-term neurologic complication, the report resulted in a decline in the use of the whole-cell pertussis vaccine. The acellular pertussis vaccine has been approved in the United States since 1991 for persons older than 15 months and since 1996 for infants.

Although pertussis can occur at any age, it is predominantly a pediatric and adolescent illness. The age-specific attack rates are highest in children younger than 1 year who have not yet received the entire vaccine series. There appears to be a seasonal variation; 50% of cases in the United States occur from June through September.

Principles of Disease

Etiology

Pertussis is caused by organisms of the *Bordetella* genus, which are small, nonmotile, gram-negative coccobacilli that occur singly or in pairs. *Bordetella pertussis* and *Bordetella parapertussis* are responsible for disease in humans. The organisms are fastidious and require nicotinamide and an optimal temperature of 35° C to 37° C to grow. *Bordetella bronchiseptica*, a flagellated, motile organism, causes illness in animals, including kennel cough, and may rarely cause respiratory infection in immunocompromised humans.[13]

Pathophysiology

The *Bordetella* organism adheres preferentially to ciliated respiratory epithelial cells. *B. pertussis* does not invade beyond the submucosal layer in the respiratory tract and is almost never recovered in the bloodstream. The organism elaborates several toxins that act locally and systemically. These toxins include pertussis toxin, dermonecrotic toxin, adenylate cyclase toxin, and tracheal cytotoxin.[13]

Local tissue damage consists of inflammatory changes in the mucosal lining of the respiratory tract, primarily congestion and cellular infiltration with lymphocytes and granulocytes. As the infection progresses, secondary pneumonia or otitis media may occur. Systemic effects of pertussis toxin include sensitization to the lethal effects of histamine and increased secretion of insulin.[13]

Clinical Features

Symptoms and Signs

Pertussis arises in three distinct sequential clinical stages: the *catarrhal phase*, the *paroxysmal phase*, and the *convalescent phase*. The catarrhal phase begins after an incubation period of approximately 1 to 3 weeks and lasts approximately 1 to 2 weeks. Infectivity is greatest during the catarrhal phase, when the disease is clinically indistinguishable from other upper respiratory tract infections. Signs and symptoms include rhinorrhea, low-grade fever, malaise, and conjunctival injection. A dry cough usually begins at the end of the catarrhal phase.[13]

The paroxysmal phase begins as fever subsides and cough increases and lasts from 2 to 4 weeks. Paroxysms of staccato coughing occur 40 to 50 times per day. The patient coughs repeatedly in short exhalations followed by a single, sudden, forceful inhalation that produces the characteristic "whoop." Only one third of adults (range 8–82%) with pertussis develop this whoop, and it is rare in young infants, who may present with apneic episodes and no other symptoms. Paroxysms may be spontaneous, occur more frequently at night, or be precipitated by noise or cold. During the paroxysm, the patient may exhibit cyanosis, diaphoresis, protrusion of the tongue, salivation, and lacrimation. Post-tussive vomiting, syncope, and brief episodes of apnea may occur. Infants may be physically exhausted after a typical paroxysm. Between episodes of coughing, patients do not appear acutely ill.[13]

The convalescent phase is characterized by a residual cough that lasts for several weeks to months. Paroxysms of coughing may be triggered by an unrelated upper respiratory infection or by exposure to a respiratory irritant. This recurrence of coughing does not represent recurrence of pertussis infection.

Atypical presentations may occur in young and preterm infants. Fever is usually not present in uncomplicated neonatal pertussis. Tachypnea, apnea, and cyanotic and bradycardic episodes may be the predominant symptoms.[15] Older children and adults who have partial protection from vaccination or previous illness may have a long-lasting intractable dry cough that is frequently misdiagnosed as bronchitis.

Physical examination findings are nonspecific. Tachypnea is variably present and may be related to the degree of pulmonary involvement. Low-grade fever is common during the catarrhal phase, as are conjunctival injection and rhinorrhea. The presence of fever during other stages of illness suggests secondary infection. Petechiae above the nipple line, subconjunctival hemorrhages, and epistaxis may occur because of increased intrathoracic pressure during coughing paroxysms.[13,15] Chest examination may reveal rhonchi or clear lung fields; the presence of rales suggests pneumonia.

Complications

The major complications of pertussis are pneumonia superinfection, central nervous system (CNS) sequelae, otitis media, and complications related to the paroxysm of coughing.[13-16] Pneumonia complicating pertussis is a leading cause of death, especially in infants and young children.[13,16] Aspiration of gastric contents and respiratory secretions may occur during the paroxysm of coughing, whooping, and vomiting. Secondary pulmonary infection may also be a consequence of decreased respiratory tract clearance related to the actions of the *Bordetella* organism and its toxins on bronchial and lung mucosa. Bacterial (*Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Haemophilus influenzae*, and *Staphylococcus aureus*) and viral (respiratory syncytial virus, cytomegalovirus, and adenovirus) superinfections can complicate pertussis infections. A fever during the paroxysmal phase should alert the physician to a possible superinfection.

CNS complications include seizures (0.2–2%) and encephalopathy (0.3%).[14] The causes are unclear but may include hypoxia, hypoglycemia, cerebral petechia, effects of a toxin, or secondary infection by neurotropic viruses or bacteria. CNS hemorrhages may occur as a consequence of the increased cerebrovascular pressures generated during the paroxysm of coughing. Sudden increases in intrathoracic and intra-abdominal pressures can result in several other complications (Box 127-2).[13,16]

Bradycardia, hypotension, and cardiac arrest can occur in neonates and young infants with pertussis. Severe pulmonary hypertension has increasingly been recognized in this age group and can lead to systemic hypotension, worsening hypoxia, and increased mortality.[15,16] Intensive care monitoring is recommended for these patients, regardless of how well they may appear on admission.

Diagnostic Strategies

The diagnosis of pertussis should be entertained in any patient with prolonged cough with paroxysms, whoops, or post-tussive

BOX 127-2 PERTUSSIS COMPLICATIONS

Periorbital edema
Subconjunctival hemorrhage
Petechiae
Epistaxis
Hemoptysis
Subcutaneous emphysema
Pneumothorax
Pneumomediastinum
Diaphragmatic rupture
Umbilical and inguinal hernias
Rectal prolapse

emesis regardless of previous vaccination status. Up to 25% of adults in the United States who have a prolonged cough have serologic evidence of pertussis.[13]

Ancillary studies are of limited value in the emergency department. During the late catarrhal and early paroxysmal phases, a marked leukocytosis and a characteristic lymphocytosis are often present. The white blood cell (WBC) count of 25,000 to 50,000/mL is not uncommon and may exceed 60,000/mL in infants.[13,16] Adults with pertussis frequently do not have the characteristic leukocytosis and lymphocytosis, and some infants and immunocompromised hosts may not be able to mount this response. The chest radiograph may show peribronchial thickening, atelectasis, or pulmonary consolidation.[17]

Laboratory confirmation of the diagnosis is made by nasopharyngeal culture and PCR, if both are available; sputum and throat swabs are inadequate.[18] The *Bordetella* organism is fastidious, and isolation requires a nicotinamide or Bordet-Gengou medium impregnated with antibiotics to reduce overgrowth of competing bacteria. The slow-growing hemolytic colonies of *B. pertussis* take 3 to 7 days to appear. A synthetic culture medium is also available. The sensitivity of pertussis cultures is only 20 to 40%. Direct fluorescent antibody techniques are no longer recommended to identify *B. pertussis*.[14] Adults generally come to medical attention late in the disease, at which time cultures are rarely positive (3.6%). PCR is much more likely to identify the organism.

Differential Considerations

The differential diagnosis includes acute viral upper respiratory tract infection, pneumonia, bronchiolitis, cystic fibrosis, tuberculosis, exacerbation of chronic obstructive pulmonary disease, and foreign body aspiration. The marked leukocytosis may suggest the diagnosis of leukemia.

Management

Acute Treatment

Treatment of pertussis is primarily supportive and includes oxygen, frequent suctioning, maintenance of hydration, parenteral nutrition if necessary, and avoidance of respiratory irritants. Patients with suggested pertussis and associated pneumonia, hypoxia, or CNS complications or those experiencing severe paroxysms should also be hospitalized. Children younger than 1 year old should also be admitted because they are not yet fully immunized and have the greatest risk for morbidity and mortality.[13] Neonates with pertussis should be admitted to an intensive care unit (ICU), as apnea and significant cardiac complications can occur without warning.[17]

Antibiotic treatment does not appear to significantly reduce the severity or duration of illness when started in the paroxysmal phase and may have only a minimal effect in the catarrhal phase. The primary goal of antibiotic therapy is to decrease infectivity and carriage. Erythromycin estolate ester is the antibiotic of choice at 40 to 50 mg/kg/day (maximum 2 g/day) in two or three divided doses for 14 days.[13,17] Azithromycin (10 mg/kg on day 1 followed by 5 mg/kg on days 2–5), clarithromycin (15 mg/kg/day in two divided doses), and a 7-day course of erythromycin estolate ester are effective alternatives for patients who do not tolerate 14 days of erythromycin well.[13,17,19] Trimethoprim-sulfamethoxazole (8 mg/kg/day of trimethoprim) is an alternative for macrolide-allergic patients but efficacy is unproven. Patients should be considered infectious for 3 weeks after the onset of the paroxysmal phase or until at least 5 days after antibiotics are started.[11] Strict isolation is recommended during this period.

Corticosteroids, especially in young critically ill infants, may reduce the severity and course of illness, but effectiveness is not well established. Beta$_2$-adrenergic agonists do not reduce the frequency or severity of paroxysmal coughing episodes[15,20] but may be helpful in patients with reactive airway disease. Trials with pertussis immune globulin are limited and to date show no proven benefit.[21] Standard cough suppressants and antihistamines are ineffective.[20]

Postexposure prophylaxis, with erythromycin as described previously, is recommended for household contacts of patients with pertussis regardless of previous vaccination status.[13] Erythromycin should also be prescribed for any unimmunized person or partially immunized infant with a history of significant exposure to the index case.[13]

Vaccination

Whole-cell and acellular pertussis vaccines are distributed in combination with diphtheria and tetanus toxoids as DPT and DTaP, respectively. The acellular pertussis vaccines contain inactivated pertussis toxin and one or more other bacterial components. The acellular vaccine is as effective as the whole-cell vaccine with fewer adverse reactions reported.[22,23] Most recipients develop fever, irritability, behavioral changes, and local discomfort at the site of inoculation. Moderately severe reactions are uncommon but include fever with temperature over 40° C, persistent crying, high-pitched crying, and seizures. Severe neurologic complications (prolonged seizures and encephalopathy) occur rarely but led to decreased use of the whole-cell form of the vaccine and the development of DTaP.[23] DTaP has replaced DPT for childhood immunizations, and the whole-cell pertussis vaccine is recommended for use in the United States only when the acellular vaccine is not available.[23]

Pertussis immunity wanes significantly 6 to 8 years after immunization and 15 years after natural infection,[24] causing an increasing incidence of the disease in people older than 15 years. The acellular pertussis vaccine is safe and effective in adolescents and adults, and routine booster immunization is currently recommended by the CDC Advisory Committee on Immunization Practices for persons aged 11 to 18 years.[14]

TETANUS

Perspective

Background

Tetanus is a toxin-mediated disease characterized by severe uncontrolled skeletal muscle spasms. Involvement of the

muscles of respiration leads to hypoventilation, hypoxia, and death. Dramatic descriptions of this disease date back to ancient Egypt when physicians recognized a frequent relationship between tissue injury and subsequent fatal spasm.[25,26]

In 1884 Carle and Rattone produced tetanus in rabbits by injecting material from an acne pustule that came from an infected human. In the same year, Nicolaier isolated the strychnine-like toxin from anaerobic soil bacteria. In 1889 Kitasato obtained pure cultures of spore-forming bacteria that caused tetanus when introduced into animals.[25] One year later, Faber proved that tetanus was a toxin-mediated disease when he induced the illness by injecting animals with bacteria-free filtrates of *Clostridium tetani* cultures. In the 1890s von Behring and Kitasato discovered tetanus antitoxin in the serum of immune animals and demonstrated its efficacy in preventing disease. Prophylactic injection of this antitoxin provided passive immunity to wounded soldiers during World War I. It was not until the 1930s that an effective vaccine was developed. Large-scale testing during World War II indicated that the tetanus toxoid conferred a high degree of protection against disease.

Epidemiology

Despite the availability of an effective vaccine, tetanus remains endemic worldwide. It is more common in warm, damp climates and relatively rare in cold regions. The global incidence of tetanus is estimated to be between 800,000 and 1 million cases a year, with half occurring in neonates. Eighty percent of these cases occur in Africa and Southeast Asia because of low immunization rates and poor hygiene.[26]

Since the introduction of vaccination programs in the United States, the incidence of tetanus has steadily declined from 4 cases per million population in the 1940s to 0.095 cases per million population in 2005 (Fig. 127-2).[27,28] The highest incidences occurs in people older than 60 years (0.35 cases per million population), Hispanic Americans (0.37 cases per million population), and diabetics (0.70 cases per million population). Fifteen percent of cases occur in injection drug users. The overall case fatality rate is 18% but approaches 50% in patients older than 70 years (Fig. 127-3). Cases have been reported in patients who had been fully vaccinated, but in the eight patients from 1998 to 2000, no deaths occurred.[29]

Tetanus typically occurs as a result of a deep penetrating wound. A history of injury is present in more than 70% of patients, but the injury may be trivial in 50% of patients and unapparent in up to 30% of patients.[25,26,29] The most common portals of entry for the organism are puncture wounds, lacerations, and abrasions. Tetanus has also been reported in association with chronic skin ulcers, abscesses, and otitis media, as well as with foreign bodies, corneal abrasions, abortions, childbirth, and dental procedures.[26,30] Postoperative tetanus has been reported in patients who have undergone intestinal operations and abortions. In these cases the source of bacteria is probably endogenous, as up to 10% of humans harbor *C. tetani* in the colon.

Inadequate primary immunization and waning immunity continue to be the primary risk factors for tetanus in the United States. As tetanus vaccination of children has improved, older people have accounted for an increasing percentage of reported cases.

Etiology

C. tetani is a spore-forming, motile, slender, rod-shaped, obligate anaerobic bacillus. It stains gram positive in fresh culture but has a variable staining pattern in old cultures and tissue

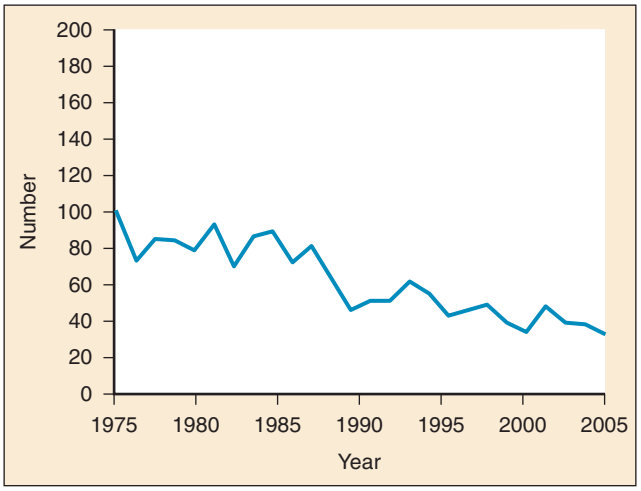

Figure 127-2. Incidence of tetanus in the United States from 1975 to 2005. (From McNabb SJN, et al: Summary of notifiable diseases—United States 2005. MMWR 54:2, 2007.)

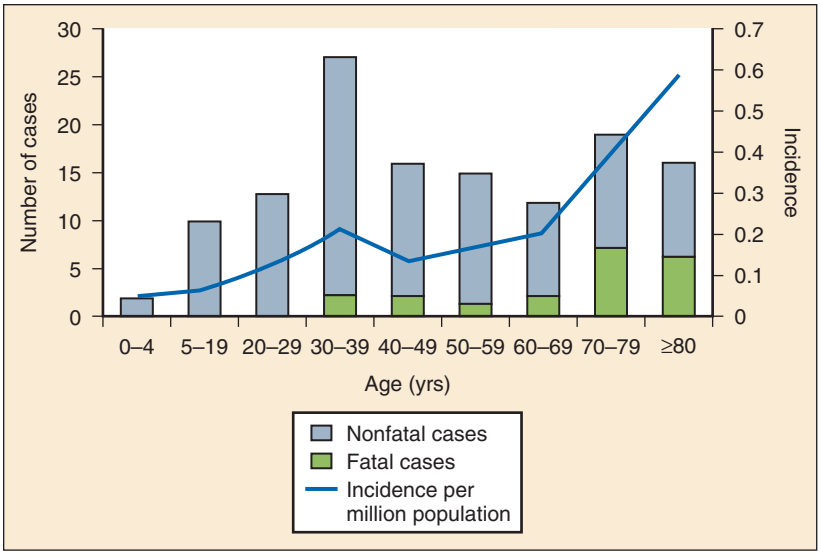

Figure 127-3. Incidence and mortality from tetanus by age group in the United States, 1998–2000. (From Pascual FB, et al: Tetanus surveillance—United States, 1998–2000. MMWR Surveill Summ 52[SS-3]:1, 2003.)

samples. The bacillus can form a single spherical terminal endospore that swells the end of the organism to produce a characteristic drumstick appearance. *C. tetani* is ubiquitous in soil and dust and is also found in the feces of animals and humans.[25] Mature bacilli are highly susceptible to heat and other adverse environmental conditions. Spores are resistant to heating and chemical disinfectants and can survive in soil for months to years. When introduced into a wound, spores may not germinate for weeks because of unfavorable tissue conditions. When injury favors anaerobic growth, the spores germinate into mature bacilli. Only these mature bacilli produce the tetanus toxin that causes clinical disease.[30]

Principles of Disease

C. tetani is a noninvasive organism. The development of clinical tetanus requires a portal of entry for the infecting spores as well as tissue conditions that promote germination and growth in an immunologically susceptible host. Tetanus-prone wounds are those with damaged or devitalized tissue, foreign bodies, or other bacteria. Under these conditions, *C. tetani* produces the neurotoxin that causes clinical illness. Germination and replication of *C. tetani* can occur without clinical signs of a local wound infection.

C. tetani produces the neurotoxin tetanospasmin (TS) at the site of tissue injury. TS first binds the motor nerve ending and then moves by retrograde axonal transport and trans-synaptic spread to the CNS.[31] It binds preferentially to inhibitory (γ-aminobutyric acid [GABA]ergic and glycinergic) neurons and blocks the presynaptic release of these neurotransmitters. Interneurons afferent to alpha motor neurons are affected first.[32] Without inhibitory control, the motor neurons undergo sustained excitatory discharge, resulting in the muscle spasm characteristic of tetanus.[26]

TS may also affect preganglionic sympathetic neurons and parasympathetic centers, resulting in autonomic nervous system dysfunction.[32] The clinical manifestations include dysrhythmias and wide fluctuations in blood pressure. The binding of TS at the synapse is irreversible; recovery occurs only when a new axonal terminal is produced.[30]

Clinical Features

Symptoms and Signs

The incubation period for tetanus ranges from 1 day to several months. A shorter incubation period portends a worse prognosis.[26] The duration of the incubation period is not useful in making the diagnosis of tetanus because many patients have no history of an antecedent wound.

Four types of clinical tetanus have been described.

1. *Generalized tetanus* is the most common form of the disease and results in spasms of agonist and antagonist muscle groups throughout the body. The classic initial presenting symptom of trismus ("lockjaw") caused by masseter spasm is present in 50 to 75% of patients. As the other facial muscles become involved, a characteristic sardonic smile (risus sardonicus) appears. Other early symptoms include irritability, weakness, myalgias, muscle cramps, dysphagia, hydrophobia, and drooling. As the disease progresses, generalized uncontrollable muscle spasms can occur spontaneously or as a result of minor stimuli such as touch or noise. Spasms may result in vertebral and long bone fractures and tendon rupture. Opisthotonus is a prolonged tonic contraction that closely resembles decorticate posturing. Spasms of laryngeal and respiratory muscles can lead to ventilatory failure and death. Autonomic dysfunction is the major cause of death in patients who survive the acute phase and manifests by tachycardia, hypertension, temperature elevation, cardiac dysrhythmias, and diaphoresis. The illness is progressive, with an increase in symptoms over the first 3 days, persistence of symptoms for 5 to 7 days, and reduction of spasms after 10 days. If the patient survives, recovery is complete after 4 or more weeks. Throughout the course of this horrific illness, patients remain completely lucid unless chemically sedated.[25,27,30,32]
2. *Localized tetanus* is a form of the disease characterized by persistent muscle spasms close to the site of injury. Symptoms may be mild or severe, but mortality is much less frequent than with generalized tetanus. Local tetanus may progress to generalized disease. This form of illness may probably reflect partial immunity to tetanospasmin and may be present for weeks to months before resolution.[25]
3. *Cephalic tetanus* is a rare variant of local tetanus that results in cranial nerve palsies as well as muscle spasms. The palsies precede the spasm in 42% of cases, resulting in frequent misdiagnosis. The most commonly involved cranial nerve is the facial nerve (VII), mimicking Bell's palsy. Most of these cases occur after facial trauma or otitis media. Patients develop trismus and palsies of cranial nerve III, IV, VII, IX, X, or XII, ipsilateral to the site of local infection. The clinical course is variable. In one third of cases, resolution of symptoms is complete. The remainder progress to generalized tetanus with an overall mortality rate of 15 to 30%.[30,32]
4. *Neonatal tetanus* is generalized tetanus of the newborn and occurs almost exclusively in developing countries, where maternal immunization is inadequate and contaminated material is used to cut and dress umbilical cords. Symptoms begin during the first week of life and include irritability and poor feeding. Mortality approaches 100% because of the high toxin load for body weight and inadequate medical support in developing countries. Even with limited resources, mortality can be reduced to less than 50% with basic medication and experienced medical and nursing personnel.[30,33] The CDC reported one case of neonatal tetanus in the United States between 1998 and 2000. The infant was born at home to an unimmunized mother. The umbilical cord had been treated with bentonite clay. The child was treated and recovered after 19 days of hospitalization.[28]

Complications

Acute respiratory failure, the main cause of morbidity and mortality in tetanus, results from respiratory muscle spasms or laryngospasms and airway obstruction. If the patient survives the acute onset of illness and has adequate ventilatory support, autonomic dysfunction becomes the leading cause of death. Autonomic instability occurs several days after the onset of generalized spasms. Disinhibition of the sympathetic nervous system predominates and causes dysrhythmias, hypertension, myocarditis, and pulmonary edema.[34] Dysrhythmias and myocardial infarction are the most common fatal events during this phase.

Forceful tetanic muscle spasms can cause vertebral subluxations and fractures, long bone fractures, and shoulder and temporomandibular joint dislocations. Rhabdomyolysis occasionally occurs and can cause acute renal failure. Renal failure may also result from dehydration and sympathetic nervous system hyperactivity. Renal vein thrombosis may cause renal failure in neonatal tetanus.

Secondary infection may occur in the initial inoculating wound or as a complication arising from invasive treatment

modalities such as mechanical ventilation.[32] Hyperthermia may also result from muscle spasms and sympathetic hyperactivity. Prolonged immobility can lead to deep venous thrombosis and pulmonary embolism. Gastrointestinal complications include peptic ulcers, ileus, intestinal perforation, and constipation. The syndrome of inappropriate secretion of antidiuretic hormone occurs in a small number of patients. Hemolysis has also been reported.

Mortality is a function of the previous immunization status, incubation period, severity and rapidity of onset of symptoms, comorbid disease, age, and the sophistication of medical treatment available.[35] With appropriate intensive care treatment, elder patients may fare as well as their middle-aged counterparts.[36] Long-term physical complications in survivors are rare. The most common persistent problem may be psychological trauma related to the disease and its treatment.[25]

Diagnostic Strategies

The diagnosis of tetanus should be made on clinical grounds alone. Wound cultures for *C. tetani* are of little value as they are positive in only one third of cases. Even if a positive culture is obtained, it does not indicate whether the bacterium is a toxin-producing strain. There are no laboratory tests to confirm or exclude the diagnosis of tetanus.[25] In 1990 the CDC adopted a clinical case definition for the public health surveillance of generalized tetanus: "acute onset of hypertonia or painful muscular contractions (usually of the muscles of the jaw and neck) and generalized muscle spasms without other apparent medical cause (as reported by a health care professional)."[29]

Lumbar puncture may be indicated to exclude meningitis in the neonate when the diagnosis of tetanus is uncertain. A computed tomography scan is helpful in assessing for intracranial pathology. A serum calcium level is helpful to exclude hypocalcemia. Electromyography (EMG) may be useful if the diagnosis of cephalic or localized tetanus is in doubt.[25]

Differential Considerations

Strychnine poisoning is the only clinical condition that truly mimics generalized tetanus. Strychnine, like TS, antagonizes glycine release, but unlike TS, it has no effect on GABA release. Patients develop opisthotonus while remaining alert. The annual incidences of tetanus and strychnine poisoning are similar in the United States, and serum and urine tests for strychnine should be performed when tetanus is considered.[30]

In patients who present with diffuse generalized spasm, the diagnosis of tetanus is less likely to be missed, but ideally the disease should be considered and diagnosed in the early stages to minimize complications and decrease mortality. Some conditions with clinical similarities to tetanus are listed in Box 127-3. Trismus is most commonly caused by intraoral infections. These can be excluded with careful history and physical examination of the oral cavity and teeth. Mandibular dislocation can be ruled out with appropriate radiographs of the mandible and temporomandibular joints. Dystonic reactions can be differentiated from tetanus by medication history and symptoms that are alleviated by benztropine or diphenhydramine. Patients with encephalitis usually exhibit an altered mental status. Meningitis can be excluded by examining the cerebrospinal fluid (CSF). Rabies must be considered when there are symptoms of brainstem dysfunction, including dysphagia and respiratory muscle dysfunction. A history of exposure to secretions of an infected animal is the most helpful historical point. In addition, rabies does not cause trismus.

BOX 127-3 DIFFERENTIAL DIAGNOSIS OF TETANUS

Acute abdomen
Black widow spider bite
Dental abscess
Dislocated mandible
Dystonic reaction
Encephalitis
Head trauma
Hyperventilation syndrome
Hypocalcemia
Meningitis
Peritonsillar abscess
Progressive fluctuating muscular rigidity (stiff-man syndrome)
Psychogenic
Rabies
Sepsis
Status epilepticus
Strychnine poisoning
Subarachnoid hemorrhage
Temporomandibular joint syndrome

Cephalic tetanus is especially difficult to diagnose when the cranial nerve palsy precedes trismus. The differential diagnosis of cephalic tetanus also includes Bell's palsy, botulism, cranial nerve palsies, and facial cellulitis with facial nerve compression and ophthalmoplegia.

Management

Acute Treatment

The four treatment strategies for patients with tetanus should be undertaken simultaneously: (1) aggressive supportive care, (2) elimination of unbound TS, (3) active immunization, and (4) prevention of further toxin production.[25,29,30]

Supportive Care. Supportive care begins with control of the muscle spasms. Reflex spasms can result from stimulation of the patient, such as that caused by any movement of the patient or loud noises. Avoidance of unnecessary stimulation is recommended.[30,32] Benzodiazepines are the mainstay of symptomatic therapy for tetanus. These drugs are GABA agonists and indirectly antagonize many of the effects of TS. They have no effect on the inhibition of glycine release by TS. Diazepam is the most extensively studied of these agents, but lorazepam and midazolam are equally effective. Diazepam has a rapid onset of action, a wide margin of safety, and can be given orally, rectally, or IV. It is inexpensive and thus available in most parts of the world. It has a long cumulative half-life and active metabolites that can cause prolonged sedation and respiratory depression. The IV formulations of diazepam and lorazepam contain propylene glycol, which, at high doses, can produce lactic acidosis.[25] Gastrointestinal delivery of these agents is limited by motility problems associated with tetanus. Midazolam has a short half-life and does not contain propylene glycol, but it must be given by continuous infusion and is cost-prohibitive in most areas of the world. Propofol infusion is effective, but it is also expensive and patients may not tolerate the lipid vehicle. Neuroleptics, barbiturates, and intrathecal baclofen have no advantage over benzodiazepines. Dantrolene is a direct muscle relaxant without CNS activity. It has been reported as an adjunctive agent for muscle spasms and may decrease the need for mechanical ventilation.[37] Magnesium sulfate infusion has been advocated as both adjuvant

and first-line therapy for tetanus. Alone or in combination with other agents, it improves spasm control and may alleviate some of the autonomic instability associated with tetanus toxicity.[38]

If spasm cannot be controlled with these regimens or if any signs of airway compromise develop, the patient should receive neuromuscular blockade and mechanical ventilation. Although succinylcholine can be used in the *initial* phase of the disease, the clinician must be aware of the risk of severe hyperkalemia resulting from its use in any neuromuscular disease. This effect does not begin until about 4 days after the onset of disease.[30] Long-acting nondepolarizing agents are preferred, even in the initial phase. Pancuronium has traditionally been used, but it is an inhibitor of catecholamine reuptake and may worsen autonomic instability.[26] Vecuronium and rocuronium are shorter acting and are without significant cardiovascular side effects but require continuous infusion. Whichever agent is used, adequate sedation should be provided and neuromuscular blockade should be withheld at least once a day to assess the patient's status. All intubated patients should be considered for early tracheostomy to decrease reflex spasms caused by the endotracheal tube.[26,32]

Autonomic instability requires monitoring and aggressive treatment. Sympathetic hyperactivity can be treated with combined alpha- and beta-adrenergic antagonists such as labetalol or propranolol. The use of beta-antagonists alone can lead to unopposed alpha-activity resulting in severe hypertension.[34] If beta-antagonists are necessary, a short-acting agent such as esmolol should be used.[26] Clonidine has shown variable success at modulating sympathetic outflow.[30] Morphine and magnesium sulfate infusions as well as spinal anesthesia and intrathecal baclofen have all been shown to improve autonomic dysfunction.[25,26] Diuretics should be avoided for blood pressure control as volume depletion can worsen autonomic instability. Bradydysrhythmia should be treated with temporary pacing. Atropine and sympathomimetic drugs should be used with caution as the autonomic instability is essentially due to catecholamine eccess.[32,34]

Elimination of Unbound Tetanospasmin and Active Immunization. Human tetanus immunoglobulin (HTIG) and Td should be administered as soon as possible to all patients with possible tetanus. Tetanus immunoglobulin (TIG) does not neutralize toxin already present in the nervous system, nor does it treat any existing symptoms. HTIG neutralizes any circulating toxin as well as toxin at the site of production and reduces mortality. TIG should be administered at a site separate from the toxoid. Dosage recommendations vary (500–10,000 units of TIG), but multiple injections are stimuli for spasm and most authorities note that 500 units is as effective as higher doses. Adult and pediatric doses are the same.[25,30] If the larger doses are used, they should be given in divided doses. Administration of a portion of the TIG proximal to the site of inoculation is often recommended but has not been studied.[25-27] Protective antibody levels are achieved 48 to 72 hours after administration of TIG. Because the half-life of TIG is 25 days, repeated doses are not needed. The preparation of TIG available in the United States is not licensed for intrathecal administration, which is of no proven benefit.[25,27,32]

Prevention of Further Toxin Production. Toxin production is eliminated by treating the *C. tetani* infection. Wound débridement and antibiotic administration can cause a transient release of TS, and the emergency physician should consider delaying these measures until after the HTIG is administered. The wound should be débrided and irrigated and any foreign bodies removed. Metronidazole (500 mg orally or IV every 6 hours) is the antibiotic of choice for *C. tetani*. Pediatric doses of metronidazole depend on age and weight. (Neonates < 2000 g and 0–7 days: 7.5 mg/kg IV/PO every 24 hours; Neonates < 2000 g and 8–28 days: 7.5 mg/kg IV/PO every 12 hours; Neonates > 2000 g and 0–7 days: 7.5 mg/kg IV/PO every 12 hours; Neonates > 2000 g and 8–28 days: 15 g IV/PO every 12 hours; Infants and children: 15–30 mg/kg/day IV divided every 6 hours, maximum 4 g/day.)[27] Penicillin has traditionally been used to treat tetanus and has good in vitro and in vivo activity against *C. tetani* but also has GABA antagonistic activity and may potentiate the effects of TS. Metronidazole has better penetration into devitalized tissue and abscesses than penicillin and is superior in terms of recovery time and effect on mortality. Macrolides, doxycycline, chloramphenicol, and tetracycline are effective alternatives in metronidazole-allergic patients.[27,30,32]

Vaccination

Tetanus toxoid is an inactivated form of TS, and vaccination confers protective antibody levels in nearly 100% of people who receive three doses. Immunity wanes between 5 and 10 years after completion of the series. In high risk patients such as elders, IV drug users, and patients with human immunodeficiency virus and other causes of immunocompromise, immunity wanes more quickly and the response to vaccine is less brisk.

Adults with an uncertain history of a complete primary immunization series should receive a primary series. The standard vaccination program consists of a primary series of three tetanus toxoid doses, followed by booster doses every 10 years. Age-specific guidelines for tetanus prophylaxis have been developed by the Immunization Practices Advisory Committee and published by the CDC (Tables 127-1 to 127-3).[38]

Tetanus vaccination should be updated for all patients who come to the emergency department for management of a wound, even if the presenting complaint is not wound-related. Patients with unknown or uncertain immunization status should be considered to have no previous tetanus immunization. Those younger than 7 years should receive diphtheria-tetanus or DTaP. Patients 7 years of age or older should receive Td instead of DT because adverse reactions from the larger doses of diphtheria toxoid in DT are more common in older individuals.

HTIG prophylaxis (250 units IM) is recommended for unimmunized and underimmunized patients with wounds at high risk for tetanus (>6 hours old, greater than 1 cm deep, contaminated, stellate, denervated, ischemic, infected).[30] When tetanus toxoid and HTIG are given concurrently, separate injection sites should be used. The only contraindication to tetanus and diphtheria toxoids is a history of a neurologic or severe hypersensitivity reaction to a previous dose. Adverse reactions to tetanus toxoid and tetanus-diphtheria toxoids occur commonly and may be the result of the preservative thiomersal. The most common side effects are minor: local swelling, pain, erythema, pruritus, fever, nausea, vomiting, malaise, and nonspecific rash. Local reactions do not preclude future use of toxoid. Serious anaphylactic reactions are rare. If a patient who requires immunoprophylaxis gives a history suggestive of a neurologic or severe anaphylactic reaction, HTIG should be administered alone to protect the patient from developing tetanus as a result of the present injury. HTIG does not confer active immunity, and such patients should be referred to an allergist for measurement of antibody levels, antitoxin desensitization, and immunization. No evidence exists that tetanus or diphtheria toxoids are teratogenic. HTIG is not contraindicated in pregnancy. For inadequately immunized patients of any age, referral should be made to ensure that the patient receives the remainder of the immunizations required.[38]

Table 127-1 Routine Diphtheria, Tetanus, and Pertussis Vaccination Schedule for Children Younger than 7 Years—United States, 1997

DOSE	CUSTOMARY AGE	AGE/INTERVAL	PRODUCT
Primary 1	2 mo	6 wk or older	DTaP or DTP*
Primary 2	4 mo	4–8 wk after first dose†	DTaP or DTP*
Primary 3	6 mo	4–8 wk after second dose†	DTaP or DTP*
Primary 4	15 mo	6–12 mo after third dose†	DTaP or DTP*
Booster	4–6 yr, not needed if fourth vaccination administered after birthday		DTaP or DTP*
Additional booster	Every 10 yr after last dose		Td

*DTaP is preferred; DTP is an acceptable alternative.
†Prolonging the interval does not require restarting the series.
DTaP, diphtheria, tetanus, and acellular pertussis; DTP, diphtheria, tetanus, and pertussis; Td, tetanus and diphtheria.
Modified from Recommended childhood immunization schedule—United States, 1997. MMWR 46:35, 1997.

Table 127-2 Routine Diphtheria and Tetanus Vaccination Schedule Summary for Persons 7 Years and Older—United States, 1991

DOSE	AGE/INTERVAL	PRODUCT
Primary 1	First dose	Td
Primary 2	4–8 wk after first dose*	Td
Primary 3	6–12 mo after second dose*	Td
Booster	Every 10 yr after last dose	Td

*Prolonging the interval does not require restraint series.
Td, tetanus and diphtheria.
Modified from Diphtheria, tetanus, and pertussis: Recommendations for vaccine use and other preventive measures. Recommendations of the Immunization Practices Advisory Committee (ACIP). MMWR Recomm Rep 40(RR-10):1, 1991.

Table 127-3 Summary Guide to Tetanus Prophylaxis in Routine Wound Management, 1991

	CLEAN MINOR WOUNDS		ALL OTHER WOUNDS*	
HISTORY OF ABSORBED TETANUS TOXOID (DOSES)	*Td*†	*TIG*	*Td*†	*TIG*
Unknown or less than three	Yes	No	Yes	Yes
Three or more‡	No§	No	No‖	No

*Such as, but not limited to, wounds contaminated with dirt, feces, soil, and saliva; puncture wounds; avulsions; and wounds resulting from missiles, crushing, burns, and frostbite.
†For children <7 years old, DPT (DT, if pertussis vaccine is contraindicated) is preferred to tetanus toxoid alone. For persons ≥7 years of age, Td is preferred to tetanus toxoid alone.
‡If only three doses of fluid toxoid have been received, a fourth dose of toxoid, preferably an adsorbed toxoid, should be given.
§Yes, if >10 years since last dose.
‖Yes, if >5 years since last dose. (More frequent boosters are not needed and can accentuate side effects.)
DPT, diphtheria, pertussis, and tetanus; DT, diphtheria and tetanus; Td, tetanus and diphtheria; TIG, tetanus immune globulin.
Modified from Diphtheria, tetanus, and pertussis: Recommendations for vaccine use and other preventive measures. Recommendations of the Immunization Practices Advisory Committee (ACIP). MMWR Recomm Rep 40(RR-10):1, 1991.

■ BOTULISM

Perspective

Background

Botulism is a rare life-threatening paralytic illness caused by neurotoxins produced by *Clostridium botulinum*. The disease usually occurs in one of five forms: food-borne botulism, infant botulism, wound botulism, unclassified botulism, and inadvertent botulism.

In 1820, Kerner, a health officer in Germany, noted an association between sausage ingestion and a paralytic illness. The term *botulism* comes from the Latin *botulus*, meaning "sausage," because of these early descriptions of the disease. Van Ermengem investigated an epidemic of botulism in a group of musicians at a funeral in Belgium in 1897. He isolated the organism from ham and demonstrated that an elaborated toxin produced illness when injected into animals. This toxin was later identified as type A toxin.[39]

Botulism first received attention in the United States during World War I, when housewives were encouraged to preserve fruits and vegetables. The recommended methods for home canning did not destroy the spores of *C. botulinum*. Because these foods were often not adequately heated, epidemics of botulism occurred. Meyer described the circumstances favoring toxin production and the conditions necessary to destroy spores during food processing. Wound botulism was first described in 1943. In 1950 the CDC began surveillance of this form of the disease. Infant botulism, which is now the most common form of the illness, was first described in 1976.[39]

Epidemiology

Seven types of toxin (A through G) are produced by *C. botulinum*, but only types A, B, E, and F cause illness in humans, and types C and D cause disease in animals. Type G has been found in soil but has not been definitively linked to human or animal outbreaks. *C. botulinum* spores are found throughout the United States. Type A is found more commonly in the west and type B in the east. Type E is frequently associated with fish products. An average of 110 cases a year are reported to the CDC; 25% are food-borne botulism, 72% are infant botulism, and the rest are wound-related.[39,40,41] Despite the ubiquitous nature of botulinum spores and the variety of possible routes of toxin entry, the incidence of disease is low.

Typical food-borne botulism results from the ingestion of preformed heat-labile toxin rather than ingestion of spores or live bacteria. Food-borne botulism usually results from expo-

sure to home-canned foods that are inadequately preserved and undercooked, but occasionally large outbreaks occur after the ingestion of contaminated food at restaurants or from commercial sources. A variety of preserved foods have been implicated, and botulism has also been reported to result from ingestion of improperly prepared and stored fresh foods.[42]

Infant botulism is the most common form of the illness in the United States. It occurs in children younger than 1 year with a peak incidence between the ages of 2 and 6 months. In contrast to food-borne botulism in adults, infant botulism is caused by the ingestion of spores with in vivo production of toxin. Honey and, to a lesser extent, corn syrup have been implicated as sources of *C. botulinum* spores in infant botulism. Soil and vacuum cleaner dust have also been implicated, but the source of ingestion remains unknown in most cases. Types A and B botulinum toxins have been responsible for all infant cases.[43]

Some investigators have explored a possible relationship between infant botulism and the sudden infant death syndrome, but a 10-year prospective study of 248 infants diagnosed with sudden infant death syndrome revealed no cases attributable to *C. botulinum*.[44]

Wound botulism once accounted for approximately one botulism case per year, but the increased use of black tar heroin has resulted in a dramatic increase in cases. In 1994, 11 of the 53 adult botulism cases reported to the CDC were wound botulism. All occurred among injection drug users in California. Toxin types A and B are the causative agents.[45]

Unclassified, hidden, or adult infectious botulism is a rare illness that is analogous to infant botulism. The *Clostridium* bacterium produces its toxin in vivo. Patients with compromised gastric acidity, disturbances of gastrointestinal motility, or abnormal gastrointestinal bacterial flora may be susceptible to in vivo production of botulinum toxin. Between 1976 and 1996, 39 cases were reported to the CDC. Toxin types A, B, and F were identified in these patients.[46]

Inadvertent botulism is an iatrogenic form of the disease that occurs in patients who have been treated with injections of botulinum toxin for dystonia and other movement disorders and for cosmetic purposes. Inadvertent generalized weakness as well as unintentional focal weakness may be seen.[40]

The potential exists for botulinum toxin to be used as an offensive biologic weapon. It is highly potent and easy to produce. The Aum Shinrikyo, responsible for the 1995 sarin gas attack on the Tokyo subway, have produced and dispersed aerosols of botulinum toxin in Japan on at least three occasions between 1990 and 1995. In 1995, Iraq admitted to the United Nations that it had produced 19,000 L of concentrated botulinum toxin and loaded approximately 10,000 L into warheads. These 19,000 L are not fully accounted for and constitute three times the amount needed to kill the entire human population by inhalation.[47]

Principles of Disease

Etiology

C. botulinum is a strictly anaerobic, large gram-positive, rod-shaped organism. It forms spores that germinate under certain environmental conditions. The bacteria may then produce a potent exotoxin that is responsible for the disease. Each strain of *C. botulinum* produces a specific toxin type—A, B, C, D, E, F, or G. Only types A, B, E, and rarely F produce disease in humans.[39] Botulinum toxins are the most potent known biologic compounds.[46] Doses as small as 0.09 to 0.15 μg IV or 0.7 to 0.9 μg inhaled can cause death in a 70-kg human.[47] The toxins are heat-labile. Heating at 85° C for 5 minutes destroys any botulism toxin. Consequently, heating toxin-contaminated food just before ingestion prevents food-borne botulism. Spores are highly heat-resistant, however, and can survive at a temperature of 100° C for several hours.[42]

Pathophysiology

Food-borne botulism results from ingesting food that contains preformed toxin. Toxin-contaminated food may have a normal appearance and taste or exhibit signs of food spoilage caused by proteolytic enzymes produced by the type A and B strains. Because of the tremendous potency, one taste can expose a person to enough toxin to cause clinical illness. Digestive enzymes do not destroy preformed toxin. Infant and adult infectious botulism results from in vivo bacterial elaboration of toxin in the gastrointestinal tract. Achlorhydria and recent antibiotic use predispose the gastrointestinal tract to colonization with *C. botulinum*. Wound botulism results from in vivo bacterial elaboration of toxin in a wound. Inadvertent botulism results from injection of preformed toxin for medical purposes. Primate studies indicate that aerosolized botulinum toxin can also be absorbed systemically through the respiratory tract.[40,46]

The neurotoxin produced by *C. botulinum* is similar in structure and function to the TS toxin produced by *C. tetani*, but the clinical effects differ dramatically. TS targets inhibitory interneurons in the CNS, causing generalized muscle spasm, whereas botulinum toxin targets peripheral neuromuscular junctions and autonomic synapses, thereby causing a flaccid paralysis.[45] When botulinum toxin is absorbed from the entry site, it circulates until it reaches the neurons. The toxin binds to the presynaptic nerve membrane, becomes internalized, and then inhibits the release of acetylcholine, resulting in neuromuscular blockade. This interference with neurotransmission occurs predominantly at the cholinergic synapses of the cranial nerves, autonomic nerves, and neuromuscular junction. Clinically, this is manifested by cranial nerve palsies, parasympathetic blockade, and a descending, flaccid paralysis. Once affected with type A toxin, the nerve is permanently damaged, and recovery requires axonal regeneration and the formation of new synapses, which may take several months. Recovery after type F toxin is substantially faster.[39-41]

Clinical Features

Symptoms and Signs

Food-borne botulism is the prototype for understanding the clinical signs and symptoms of all forms of botulism. Symptoms begin approximately 18 to 36 hours (range, 6 hours to 8 days) after the ingestion of toxin-containing food. A shorter incubation period is associated with a more severe form of illness. Early symptoms include weakness, malaise, lightheadedness, nausea, vomiting, and constipation. These symptoms are generally not severe and occur in fewer than half of the patients.[46]

Neurologic symptoms may begin at the same time or be delayed in onset for several days. The cranial nerves are first affected. Patients experience diplopia, blurred vision, dysphonia, dysphagia, and dysarthria. Vertigo is also a common symptom. Next, a symmetrical descending muscular weakness occurs, involving the upper and lower extremities and the muscles of respiration. Blockade of the cholinergic fibers of the autonomic nervous system leads to a variety of symptoms. Decreased salivation causes a dry mouth, which may be so severe that the patient complains of a painful tongue and sore

throat. Ileus and urinary retention may also occur. In one emergency department series of patients with food-borne botulism, all had at least three of the following four symptoms: weakness, dry mouth, double vision, and difficulty speaking. This constellation of symptoms should prompt the emergency physician to inquire about the ingestion of home-canned or improperly prepared food, as well as the presence of similar symptoms in family members or friends.[39,40,46]

The patient with botulism is usually alert and afebrile unless secondary infection is present. Postural hypotension may be present. Ocular signs are prominent and include ptosis, extraocular palsies, and markedly dilated and fixed pupils; the absence of ocular abnormalities does not exclude the diagnosis. The oropharynx may be erythematous, with dry mucous membranes.[39] The gag reflex is depressed or absent.

Muscle weakness is usually present and varies from mild to severe. Neck muscles are often weak. Upper extremity muscles are more affected than those of the lower extremity. Proximal muscles are weaker than distal muscles. Deep tendon reflexes may be normal, symmetrically decreased, or absent. The sensory examination is normal. The abdomen may be distended with hypoactive or absent bowel sounds. Bladder distention may be apparent on examination. Respirations may be tachypneic and shallow or normal. In advanced illness, signs of respiratory failure may be present.[39]

Atypical presentations of food-borne botulism have been reported, and certain serotypes produce distinct variations in the pattern of symptoms. Type A disease may be more severe and is more commonly associated with bulbar findings and upper extremity weakness. Types A and B disease may rarely cause a decreased level of consciousness. Type E is associated with a greater incidence of gastrointestinal symptoms.[39]

The presentation of *infant botulism* is different from that of food-borne botulism. Constipation is a common presenting complaint, followed by several days to weeks of poor feeding, weak cry, loss of head control, and hypotonia. On physical examination, patients have decreased muscle tone and depressed deep tendon reflexes. Cranial nerve involvement causes alterations in facial expression, ptosis, and extraocular palsies. Respiratory failure occurs in 50% of patients. Fever is absent unless secondary infection is present.[40,43]

Wound botulism has some notable differences from food-borne botulism. The incubation period is longer, from 4 to 14 days, because the toxin must be produced within the wound after the spores have germinated. If the wound is infected, the patient may be febrile. Gastrointestinal symptoms are notably absent in wound botulism.

The clinical presentation of *unclassified (adult infectious) botulism* is similar to that of food-borne botulism, although the mortality rate in the former is significantly greater. Recovery from botulism is slow, and survivors are hospitalized for several weeks to months.[39-40]

Complications

Complications from botulism are related to respiratory failure and problems associated with prolonged intensive care management. The major cause of death from botulism is respiratory failure resulting from weakness of the respiratory muscles. Aspiration of oral secretions and gastric contents because of loss of protective airway reflexes can occur. In the past 50 years, the overall mortality rate has decreased from 50% to less than 8% with modern intensive care. In patients who recover, muscle strength and endurance may not return to normal for up to 1 year, and persistent psychological problems are common.[39-41]

Diagnostic Strategies

The initial diagnosis of botulism is clinical and should be considered in any patient who presents with the constellation of gastrointestinal, autonomic, and cranial nerve dysfunction. Bilateral cranial nerve involvement and the progression of neurologic findings should increase clinical suggestion. Routine laboratory studies are of no value in the diagnosis. If a lumbar puncture is performed, the CSF in patients with botulism is normal or may show a slight elevation of protein.[39]

The diagnosis is confirmed by detecting (1) botulinum toxin in the patient's blood; (2) botulinum toxin or *C. botulinum* in the gastric contents, stool, or wound of the patient; or (3) toxin or organisms in the suspected food source. Because most hospital laboratories are unable to process such specimens, the local health department and CDC should be notified for specific instruction on the handling of specimens. Ideally the specimens should be obtained prior to administration of antitoxin. Serial measurements of the patient's vital capacity are helpful in recognizing deteriorating ventilatory function.[39,40,48]

EMG can detect electrophysiologic abnormalities consistent with the diagnosis of botulism. EMG may also be useful in differentiating botulism from other paralytic illnesses. The EMG signature of botulism is decreased amplitude of the compound muscle action potential in response to a supramaximal stimulus and facilitation of the muscle action potential with repetitive nerve stimulation. Not all motor units are affected, and normal test results do not exclude the diagnosis.[39]

Differential Considerations

The differential diagnosis of *adult botulism* includes a wide variety of illnesses. Commonly, the first presenting case is misdiagnosed because early symptoms suggest pharyngitis or gastroenteritis, both of which can affect several members of a single household. Only after one or more cases progress to classical botulism is the diagnosis usually suggested.

Botulism must be differentiated from other illnesses that cause paralysis. In Guillain-Barré syndrome, weakness usually starts distally and ascends, paresthesias may be present, and the CSF protein may be elevated. Tick paralysis is an ascending paralysis, notable for a lack of bulbar involvement and the presence of a tick. In myasthenia gravis, eye signs are also prominent, but pupillary response is preserved, no autonomic symptoms are present, and weakness responds to the administration of edrophonium. Of note, minimal improvement in weakness after the administration of edrophonium has been reported in botulism.[39] Poliomyelitis causes fever, asymmetrical neurologic signs, and CSF abnormalities. Diphtheria can be distinguished by the prolonged interval between pharyngitis and neurologic symptoms. Eaton-Lambert syndrome does not usually involve bulbar muscles. Cerebrovascular accidents of the brainstem have an acute onset and asymmetrical, neuroanatomically localizing signs and symptoms.[39,40]

Certain toxins must also be considered in the differential diagnosis of botulism. Anticholinergics (atropine, belladonna, jimson weed) cause pupillary dilation and dry, red mucous membranes but also cause delirium with alterations in mental status. Organophosphate insecticides have a characteristic odor, and poisoning causes fever and altered mental status. Dystonic reactions are self-limited and respond to diphenhydramine or benztropine. Neuromuscular blockade from the administration of aminoglycosides is distinguished by the medication history. Heavy-metal poisoning produces changes in mental status. Magnesium toxicity may mimic botulism, but the history and serum magnesium levels distinguish these

entities.[39,40,46] In paralytic shellfish poisoning, paresthesias are prominent, a history of shellfish ingestion is present, and recovery occurs within 24 hours.[46]

Infant botulism has a broader differential diagnosis. Common illnesses that mimic the presentation of infant botulism include sepsis, various viral illnesses, dehydration, encephalitis, meningitis, and failure to thrive. Neurologic illnesses such as Guillain-Barré syndrome, myasthenia gravis, and poliomyelitis should also be considered.[43] Hypothyroidism, hypoglycemia, diphtheria, and toxin exposures are all part of the differential consideration, as are less common conditions such as inborn errors of metabolism, congenital muscular dystrophy, and cerebral degenerative diseases.

Management

The treatment of botulism consists of supportive care and specific treatment with antitoxin and other medications to block the effects of the toxin. All patients with suggested botulism should be admitted to the hospital and placed in an ICU as respiratory failure may develop rapidly and insidiously. When signs of ventilatory failure develop, early endotracheal intubation should be performed. A decrease in vital capacity to less than 12 mL/kg is an appropriate criterion for intubating a patient. Ileus should be treated with nasogastric suction and urinary retention with an indwelling urinary catheter. Fortunately, the autonomic dysfunction of botulism is much less severe than that of tetanus and rarely requires any intervention.[39,40]

Saline enemas and cathartics have been recommended by some authors to cleanse the gastrointestinal tract of residual toxin. Cathartics should not be given in the presence of ileus. Magnesium-containing cathartics should be avoided because elevated serum magnesium levels can exacerbate muscle weakness. Special care must be taken when using gastrointestinal clearance in infants with botulism. Because the source of toxin is outside the gastrointestinal tract in wound botulism, bowel decontamination is not indicated.[39,46]

Equine trivalent antitoxin contains antibodies to toxin types A, B, and E. It should be administered intravenously as soon as possible after appropriate laboratory specimens have been obtained. It neutralizes only circulating toxin and has no effect on bound toxin. Early administration prevents the progression of illness, decreases hospital length of stay, prevents respiratory failure, and shortens the duration of respiratory failure in patients with severe disease.[46] Antitoxin can be obtained from the CDC or state health department. After skin testing for hypersensitivity, one 10-mL vial should be given IV. This dose results in circulating antitoxin levels capable of binding circulating toxin concentrations many times in excess of those reported in botulism patients. The serum half-life is 5 to 8 days. For these reasons, and contrary to the information in the package insert, only one vial of antitoxin is required. Repeated doses are unnecessary and may increase the risk of hypersensitivity reactions, which occur in approximately 9% of patients.[39,40]

Antitoxin is generally not recommended in infant botulism because efficacy has not been demonstrated and because of the risk of anaphylaxis to horse serum. A human botulism immunoglobulin (BabyBIG) is pooled plasma from immunized adults with high titers of antibodies to toxins A and B. It was approved by the FDA for the treatment of infant botulism in October 2003. BabyBIG shortens hospital length of stay by a mean of 3.1 weeks and mechanical ventilation by a mean of 1.7 weeks. It can be obtained by calling the California Department of Health Services' Infant Botulism Treatment and Prevention Program at 510-231-7600.[43]

Antibiotics are not currently recommended for food-borne botulism and may increase cell lysis and promote toxin release. Because the source of toxin is in vivo production within an infected wound, débridement and antibiotic administration should be considered only after antitoxin has been administered. Otherwise, the use of antibiotics should be limited to treating secondary infections (e.g., aspiration pneumonia) that may develop. Antibiotic treatment of both infant and wound botulism has no proven benefit. If an antibiotic is used for any reason in a botulism patient, all attempts should be made to avoid the aminoglycosides and tetracyclines because they can impair neuron calcium entry and worsen the effects of botulinum toxin.[39]

Guanidine hydrochloride may enhance the release of acetylcholine from terminal nerve fibers. For this reason, it has been recommended as an experimental component of botulism therapy.[39]

Disposition

All patients with possible botulism should be admitted to the hospital and placed in an ICU as respiratory failure may develop rapidly and insidiously. An infectious disease specialist should be consulted for management issues.[40] The CDC should be called for assistance in any case of suggested botulism. The CDC can be reached by calling 404-639-3311 (days) and 404-639-2540 (nights, weekends, and holidays). State and local health departments may also be helpful in investigating and preventing major epidemics. Area emergency departments should be alerted so that subsequent cases can be looked for and diagnosed.

PNEUMOCOCCEMIA

Perspective

Background

More than a century after the identification of *Streptococcus pneumoniae* as a pathogen in human disease and more than 80 years after the discovery of antibiotics, pneumococcus remains a significant cause of morbidity and mortality worldwide. *Pneumococcemia* is defined as the presence of *S. pneumoniae* in the blood. The clinical presentation ranges from a mild illness to a fulminant, life-threatening, systemic syndrome. *S. pneumoniae* also causes a myriad of localized infections, including otitis media, pneumonia, meningitis, and, less commonly, endocarditis, septic arthritis, and peritonitis.[49]

S. pneumoniae was discovered in 1881 by Sternberg in the United States and simultaneously by Pasteur in France. By the late 1880s it was referred to as "pneumococcus" because it was the most common cause of lobar pneumonia. In 1884 Friedländer described pneumococcemia. In 1902 Cole published the first case reports of pneumococcemia, including a patient who had meningitis and arthritis without pneumonia. In the early 20th century, Maynard, Lister, Wright, and others demonstrated a decreased incidence of pneumonia after inoculating miners with killed pneumococci. In the 1920s, Heidelberg and Avery showed that antibodies to the surface capsular polysaccharide conferred immunity to pneumococcal disease.[49] Two routes to bacteremia were described. Wandel described the migration of *S. pneumoniae* from the lung to the bloodstream by way of the lymphatic system. In 1964, Robert Austrian described bacteria passing directly from the upper respiratory tract (middle ear or sinus) to the subarachnoid space, then through the arachnoid villa and into the venous sinus.[49,50]

An *S. pneumoniae* vaccine was initially developed in the 1940s but was not produced commercially because of the availability of penicillin. The first vaccine was not licensed for use in the United States until 1977. This 14-valent pneumococcal vaccine was replaced in 1983 by a 23-valent vaccine for use in people older than 2 years. The heptavalent conjugate vaccine (Prevnar) is now available and licensed for use in infants younger than 2 years and for other high-risk patients.[51]

Epidemiology

S. pneumoniae remains a substantial cause of serious illness despite the availability of antibiotics and vaccines. Pneumococcal infection appears sporadically in normal individuals and in patients with impaired host defenses. Epidemics of pneumococcal infection occur rarely, although bacterial serotypes may cluster by geographic area. Most cases of pneumococcal infections are community-acquired, and the peak incidence is in winter.[49]

Invasive pneumococcal disease (IPD) is defined as isolation of *S. pneumoniae* from a normally sterile site such as blood, pleural fluid, or CSF.[49] In 1997, the CDC estimated 15 to 30 cases per 100,000 population annually in the United States for all people, 50 to 83 cases per 100,000 population annually for those older than 65 years, and 160 cases per 100,000 population annually for children younger than 2 years. Rates were three- to fivefold higher in black adults (49–58 cases per 100,000 population) than whites. Rates were even higher among Alaskan natives at 74 and 624 cases per 100,000 population for adults and children younger than 2 years, respectively. The highest incidence in the United States occurred among Apache Native Americans, with an overall annual incidence of 156 and 2396 cases per 100,000 population for adults and children younger than 2 years, respectively.[51] The introduction of the heptavalent vaccine for infants has decreased the incidence of IPD by 65 to 84% in children younger than 2 years in all populations studied.[52-56] This decline is almost entirely attributable to the fact that the vaccine is 97% effective at providing immunity to the seven serotypes included.[57] The IPD in these studies in almost entirely due to nonvaccine serotypes, with particular concern recently attributed to multidrug-resistant serotype 19A. Ongoing surveillance will determine the need to change the serotypes included in the vaccine.[54,58]

Pneumococcemia occurs in 10 to 25% of patients with pneumococcal pneumonia, and the lungs are the most common source, accounting for about 71% of pneumococcemia in adults. Other sources include the meninges (8%) and the sinuses or middle ear (4%). Bacteriemia is primary in 18% of adults, but a much higher percentage of children. People at higher risk for pneumococcemia include those with chronic respiratory or cardiovascular disease; chronic alcohol abusers; patients with cirrhosis, diabetes mellitus, or an absent or functionally impaired spleen (i.e., those with splenectomy or sickle cell disease); those receiving immunosuppressive therapy; and those with chronic renal failure, nephrotic syndrome, organ transplantation, lymphoma, Hodgkin's disease, multiple myeloma, and acquired immunodeficiency syndrome (AIDS).[51] Pneumococcus is spread from person to person by close contact, and crowded living conditions are associated with epidemics.[49]

The mortality rate from pneumococcemia is approximately 15 to 20% for young adults and 30 to 40% for elders, those with underlying disease, and those with localized infections such as meningitis.[51] The case fatality rate is significantly lower for children (1–11%).[53] The overall mortality rate from pneumococcemia may increase in the future because of the increasing number of elders and AIDS patients and the emergence of antibiotic-resistant strains.

Principles of Disease

Etiology

Pneumococcemia is caused by *S. pneumoniae*, an encapsulated, gram-positive facultative anaerobic coccus that occurs in pairs and chains. Antigenic differences in the polysaccharide capsule separate *S. pneumoniae* into 90 serotypes.[49] In the United States, the seven serotypes present in Prevnar account for 80% of invasive disease in children younger than 6 years and 50% of invasive disease in people older than 6 years. Worldwide, 10 capsular types account for 62% of invasive disease.[57,59]

Pathophysiology

S. pneumoniae enters the blood by one of two routes: (1) It begins as a pulmonary infection and spreads to the mediastinal lymph nodes, into the thoracic duct, and then into the circulation. (2) It colonizes or causes infection in the upper respiratory tract and spreads to the subarachnoid space through the arachnoid villi to the venous sinus and into the blood (with or without meningeal involvement).

S. pneumoniae bacteremia causes a clinical picture that ranges from a minor febrile illness to life-threatening septic shock. Different capsules of *S. pneumoniae* confer varying levels of resistance to phagocytosis, resulting in a spectrum of virulence among these serotypes. Multiple virulence factors contribute to adherence to tissues, inhibition of phagocytosis, activation of compliment, and stimulation of cytokines.[49]

The diversity of individual clinical reactions to pneumococcemia is not well understood. Host defenses rely heavily on antibody and complement production, and people who have impaired humoral immunity are more susceptible to invasive pneumococcal disease. In patients with pneumococcal infections, antibodies specific to the capsule serotype develop within several days of onset of infection. This response occurs approximately 30 days after a patient receives the pneumococcal vaccine.[49] Patients who demonstrate substantial host resistance are able to develop active immunity, and it is clear that some children can spontaneously clear culture-proven pneumococcemia.[60]

Clinical Features

Symptoms and Signs

The clinical presentation of pneumococcemia ranges from mild illness to fulminant disease, progressing to death within several hours. Occult bacteremia arises as a febrile illness in which the only direct indication of pneumococcemia is a positive blood culture (most often at 24–48 hours). Sepsis is the systemic response to infection, manifested by two or more of the following: (1) temperature greater than 38°C or less than 36°C, (2) heart rate greater than 90 beats per minute, (3) respiratory rate greater than 20 breaths per minute or partial pressure of carbon dioxide in arterial gas less than 32 mm Hg, and (4) WBC count greater than 12,000/mm^3, less than 4000/mm^3, or greater than 10% immature (band) forms.[59] Patients may present with lethargy, signs of poor tissue perfusion, cyanosis, and hypoventilation or hyperventilation. Either occult bacteremia or sepsis can occur in conjunction with a localized infection.

The history should include a description of symptoms, including fever, chills, cough, shortness of breath, headache, and rash; a review of systems; and any recent use of antibiotics. The shaking chills and fever that occur with pneumococcemia are believed to be caused by a toxin. There should be an assessment of the patient's social situation, including avail-

ability of caregivers, transportation to medical care, and the ability to comply with discharge instructions.

In children, the clinical presentation of pneumococcemia is similar to that of other common febrile illnesses. Although signs of focal infection such as pneumonia may be present, often the only indication of pneumococcemia is fever or other signs of bacterial toxicity.

Most adult patients have fever or hypothermia. Cough, rigors, pleuritic pain, and gastrointestinal symptoms occur in approximately one third of adult patients. Many patients complain of vague, nonspecific constitutional symptoms similar to those of common viral illnesses. Fever (temperature >38.5° C) occurs in 90% of younger patients but in fewer than 60% of those older than 65 years. Patients with signs of sepsis have an increased risk for a fulminant course with rapid deterioration.[61,62]

Findings on physical examination vary with the site, if any, of primary infection. Pneumonia is the primary source of infection in 71% of adults and 37% of children. The physician should also evaluate for signs of otitis media, sinusitis, and meningitis. Pneumococcemia is considered primary in 18% of adults and 30% of children, so lack of localized infection as a source does not rule out IPD.[49,63]

Complications

Cardiovascular collapse can occur with fulminant pneumococcal sepsis. Patients who develop severe illness from pneumococcemia may have end-organ damage from inadequate perfusion, disseminated intravascular coagulopathy (DIC), septic emboli, and other complications. These include respiratory failure, meningitis, hypothermia, gastrointestinal bleeding, hepatic coma, renal failure, and myocardial infarction.[62]

Pneumococcemia occasionally results in hematogenous seeding, which causes peritonitis, arthritis, endocarditis, meningitis, and cellulitis.[62,63] Adults and children with functional or anatomic asplenia may develop fulminant pneumococcemia termed *overwhelming postsplenectomy infection (OPSI)*. This is characterized by septic shock, adrenal hemorrhage, and DIC. Although the true incidence of OPSI is unknown, studies demonstrate that it is substantial and that the risk for it does not decrease over time after splenectomy. Most invasive pneumococcal infections occur in the first 2 years after splenectomy, and about two thirds occur between 5 and 20 years. OPSI may initially arise with symptoms indistinguishable from those of common viral illnesses.[63,64] The 100-fold increased incidence of pneumococcal bacteremia and meningitis in children with sickle cell disease is probably primarily due to splenic dysfunction, but complement abnormalities may also play a role.[49]

Diagnostic Strategies

The only test specific for pneumococcemia is a blood culture that grows *S. pneumoniae*. Ancillary testing of adults with suggested bacteremia should include a complete blood count with differential, blood cultures, urine culture and sensitivity, electrolytes, glucose, serum creatinine, and blood urea nitrogen. A chest radiograph may demonstrate pneumonia as the source of infection. Sputum Gram's stain, culture, and sensitivity testing, if pneumonia is suggested, are of questionable value in the emergency department but may be useful for continued inpatient care. For sputum specimens to be of value, they should be collected before instituting antimicrobial therapy; however, therapy should not be significantly delayed for the sole purpose of obtaining sputum.[49] Antigen testing of urine for pneumococcal polysaccharide is up to 100% sensitive in IPD.[65]

If the patient appears to be toxic or has signs of respiratory compromise, an arterial blood gas and a coagulation profile should be obtained. If signs of meningitis or alterations in mental status are present, a lumbar puncture should be performed. A Gram's stain of the buffy coat may be positive in cases of overwhelming pneumococcal sepsis.[63] The WBC count is usually elevated. A normal or low WBC count is suggestive of more serious disease, as are hypoxemia and hypercarbia. Musher and colleagues demonstrated an increased mortality rate in patients with serum creatinine levels higher than 2.0 mg/dL, bilirubin levels higher than 1.5 mg/dL, and albumin levels less than 2.5 g/dL.[62]

Differential Considerations

Pneumococcemia in its more benign presentation must be differentiated from other febrile illnesses, such as viral infections. The combination of clinical findings and culture results enables the emergency physician to distinguish between bacteremia and sepsis of other origins. The presence of fever and shock, with or without a distinct rash, suggests the possibility of sepsis caused by *Haemophilus influenzae*, *Neisseria meningitidis*, and other streptococcus types. The presence of confirmed pneumococcemia does not exclude other diagnoses, such as influenza and lung cancer.[49]

Management

Acute Treatment

Managing pneumococcemia consists of stabilizing life-threatening conditions, eradicating the infection, and treating predisposing or coexisting conditions. The decision to initiate antibiotic therapy for pneumococcemia is often made with limited objective data, which include the clinical findings, the patient's age, underlying conditions, and possible preliminary laboratory studies.

Elimination of the *S. pneumoniae* organism by prompt initiation of antibiotics is essential for reducing the morbidity and mortality of pneumococcal infection. Antibiotic administration should begin in the emergency department. To simplify selection of a treatment strategy, patients can be divided into three groups:

1. *Bacteremia or sepsis is suggested on the basis of clinical findings; however, the organism has not been identified*. The patient in this group is given broad-spectrum antibiotics initially, with the selection based on factors that include the most likely organism or organisms, the patient's age (neonate, child, adult, or elder) and immune status, the presence of coexisting disorders, and local patterns of antibiotic resistance. The antibiotic regimen is changed to a narrower spectrum drug after positive identification of the organism and its sensitivities.
2. *S. pneumoniae growth is reported from cultures of blood drawn (usually 1–2 days) previously*. The treatment regimen for "occult bacteremia" is guided by the patient's age, history, physical examination, general appearance, and ancillary tests. Often, the antibiotic selected on the initial visit for a localized infection (e.g., amoxicillin) is sufficient to treat the pneumococcal bacteremia subsequently identified by the laboratory. The patient should be reevaluated promptly. Repeated blood cultures should be obtained if the patient has not been taking an antibiotic. For well-appearing children a 7- to 10-day course on an appropriate oral antibiotic is reasonable. The decision to admit a child for inpatient care is based on the findings at the time of reevaluation.[60]

3. *Bacteremia or sepsis is suggested, and S. pneumoniae is identified from a site of local infection, such as a Gram's stain of sputum.* The antibiotic regimen is focused narrowly.

The adult patient with laboratory-proven pneumococcemia may be treated with penicillin G if susceptibility has been documented: 2 to 4 million units every 4 hours IV if local penicillin resistance patterns are still low. Meningitis is treated with 4 million units of penicillin G every 4 hours.[63] In children, the dosage for meningitis is 250,000 units/kg per 24 hours in divided doses every 4 hours IV up to a maximum of 20 million units.

As of 2006, the *S. pneumoniae* susceptible to penicillin in the United States ranged from 50.9% in the Southeast to 73.8% in the Northwest.[66] Unless penicillin susceptibility has been documented in a patient's isolate, treatment should begin with either ceftriaxone (1–2 g IV every 12–24 hr; 50–100 mg/kg/day in children) or cefepime (1–2 g IV every 12 hr; 50 mg/kg every 8 hr in children). When meningitis is present, the higher doses should be given. In areas where ceftriaxone resistance has emerged, the addition of vancomycin (1 g IV every 12 hr; 40 mg/kg/day divided every 6–8 hr in children) should be considered. An infectious disease consultant may be able to assist with antibiotic selection based on local resistance patterns.

IM ceftriaxone is commonly administered to children with suggested occult bacteremia who are treated as outpatients while blood culture results are pending. Ceftriaxone (initial dose of 50–100 mg/kg IM or IV, followed by daily dosage of 100 mg/kg in divided doses every 12 hr, up to a maximum of 4 g) and cefotaxime (200 mg/kg/day in divided doses every 6 hr IV, up to a maximum of 12 g) offer the advantage of being excellent antibiotics for *N. meningitidis* and *H. influenzae*. Alternative initial treatment of pneumococcemia in penicillin- or cephalosporin-allergic patients includes vancomycin, imipenem, and chloramphenicol. Chloramphenicol has the associated risk of toxicity and interaction with anticonvulsant medications.

The patient with pneumococcemia may not have an obvious response to treatment for the first 24 to 48 hours of therapy. This may be attributed to the normal course of the disease, an incorrect diagnosis, underlying illness, or an antibiotic regimen that does not treat the infection sufficiently.

Disposition

Disposition of the patient depends on three factors: the patient's age, overall clinical condition, and the presence of coexisting illnesses. Toxic-appearing patients of any age should be promptly treated with antibiotics and admitted to the hospital. Patients with underlying or coexisting conditions and those with an unclear course of illness should also be admitted.

Children who are afebrile and appear well at the time of the initial examination are unlikely to have serious sequelae develop.[56] A large randomized, controlled trial involving 37,868 infants showed that invasive pneumococcal disease is rare in children who have received the heptavalent pneumococcal vaccine. Children were observed for 3 years. There was only one case of bacteremic pneumonia in a patient who had received all four doses of vaccine and two cases in children who had received one dose; one of these children had developed acute myelogenous leukemia after entering the study and was receiving immunosuppressive chemotherapy.[67] It is important to note that the heptavalent vaccine contains serotypes responsible for only approximately 85% of pneumococcal disease in infants and children. The decision to treat a febrile child with antibiotics and discharge should be based on clinical findings, medical history, ability of the parents to follow the discharge instructions, and availability of timely follow-up.

Vaccination

The pneumococcal vaccine is effective in preventing infection; the currently available 23-valent vaccine contains the purified polysaccharide antigens of the serotypes that cause 85 to 90% of pneumococcemia infections in the United States. Although the overall protective efficacy of the vaccine is only 56 to 57%, it is safe, inexpensive, and of substantial value for well-defined groups at risk.[52] Unfortunately, the 23-valent pneumococcal vaccine has limited immunogenicity in children younger than 2 years. The heptavalent conjugate vaccine links the polysaccharide to proteins, resulting in an improved immunogenic response in children younger than 2 years.[59]

The CDC recommendations for the use of the 23-valent vaccine are given in Box 127-4.[59]

The CDC and AAP recommendations for the use of the heptavalent vaccine are listed in Box 127-5.[59]

The Immunization Practices Advisory Committee on pneumococcal vaccine and the AAP recommend that revaccination be strongly considered at 2 to 6 years of age or older for people who are most likely to have a rapid decline of pneumococcal antibodies (e.g., patients with renal failure, transplant recipients, and patients with nephrotic syndrome) and for those at risk for fatal infection (e.g., asplenic patients). Children 10 years of age or younger with nephrotic syndrome, sickle cell anemia, or asplenia should be considered for revaccination after 3 to 5 years. Other preventive measures for pneumococcemia include passive immunization with immunoglobulins for patients with congenital or acquired immunodeficiency

BOX 127-4 CDC RECOMMENDATIONS FOR THE USE OF THE 23-VALENT PNEUMOCOCCAL VACCINE

- Immunocompetent adults with chronic illnesses
  - Cardiovascular or pulmonary disease
  - Diabetes mellitus
  - Alcoholism or cirrhosis
  - CSF leaks
  - Those 65 years of age or older
- Immunocompromised adults including those with:
  - Splenic dysfunction or asplenia
  - Hodgkin's disease, lymphoma, or leukemia
  - Multiple myeloma
  - Chronic renal failure or nephrotic syndrome
  - Alcoholism
  - Organ transplantation associated with immunosuppression
- Adults and children older than 2 years with asymptomatic HIV infections
- Children older than 2 years with chronic illness
  - Anatomic or functional asplenia (including sickle cell disease)
  - Nephrotic syndrome
  - CSF leak
- Other conditions associated with immunosuppression
- Persons living in special environments or social settings with an identified increased risk (e.g., certain Native American populations)
- The vaccine is not indicated for children having only recurrent upper respiratory tract disease, such as otitis media and sinusitis

CDC, Centers for Disease Control and Prevention; CSF, cerebrospinal fluid; HIV, human immunodeficiency virus.

BOX 127-5 CDC AND AAP RECOMMENDATIONS FOR THE USE OF THE 7-VALENT VACCINE

All children ages 2–23 months at 2, 4, 6, and 12–15 months
Children ages 24–59 months who are at high risk of pneumococcal disease, including those with:
- Sickle cell disease
- HIV infection
- Other immunocompromising medical conditions

This should be followed by the 23-valent vaccine 2 months after the heptavalent vaccine is given
Consider for all children ages 24–59 months with priority given to the following:
- Those ages 24–35 months
- Alaskan natives, Native Americans, and African Americans
- Children who attend daycare

AAP, American Academy of Pediatrics; CDC, Centers for Disease Control and Prevention; HIV, human immunodeficiency virus.

diseases and daily antibiotic prophylaxis for children with functional or anatomic asplenia.[49]

MENINGOCOCCEMIA

Perspective

Background

Few clinical situations in emergency medicine produce greater anxiety in the physician than meningococcal infection. Virtually all experienced emergency physicians have had a patient who appeared relatively well on initial presentation, only to be moribund and in critical condition with fulminant infection several hours later.

"Epidemic cerebrospinal fever" was initially described in 1805 by Vieusseaux in Geneva. Weichselbaum identified the causative bacterial agent in 1887. Throughout the 19th and first half of the 20th centuries, epidemics occurred periodically in most regions of the world. "Serum therapy" was introduced in France in 1907 and in the United States in 1913 as the first specific treatment of meningococcal disease. The introduction of sulfonamide therapy in 1937 replaced serotherapy and dramatically improved the outcome of meningococcal infection. Sulfonamide prophylaxis was also effective at eradicating the carrier state and was used to prevent the epidemics that occurred in military barracks. Not surprisingly, in the 1940s sulfonamide resistance began to emerge. In 1963, an outbreak of resistant meningococcal disease occurred in the United States, which spurred efforts to develop a vaccine for this devastating infection. Subsequent worldwide resistance has resulted in continued efforts to develop safe and effective vaccines.[68]

Epidemiology

As of 2004, 1400 to 2800 cases of meningococcal infection are reported to the CDC annually (Fig. 127-4). Of the more than 13 serogroups, groups A, B, C, Y, and W-135 cause most of the infections. More than 95% of cases occur sporadically, with occasional outbreaks, most notably on college campuses in dormitories, or in other crowded living situations. Most outbreaks in the United States are caused by serogroups B (25%), C (63%), and Y (12%). More than half of the cases in infants are caused by serogroup B, for which there is no effective vaccine.[69] Although grouping is important for tracking the disease, all groups are capable of causing the same spectrum of clinical disease.

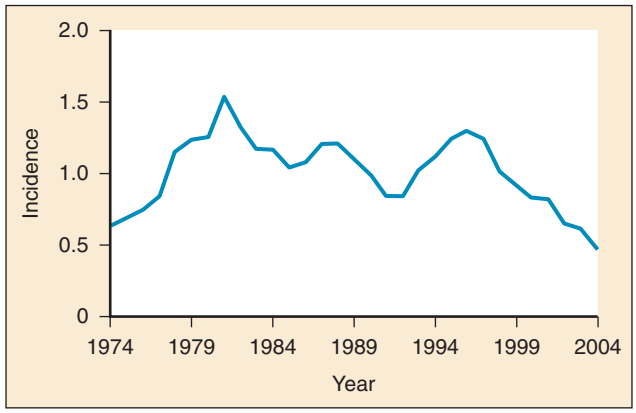

Figure 127-4. Incidence of meningococcal disease in the United States 1974–2004.

The incidence of meningococcal disease peaks in the winter and falls in the summer. Superimposed on this annual variation are cyclical peaks of disease every 5 to 15 years. Approximately every 10 years massive outbreaks of serogroup A occur in sub-Saharan Africa (the "meningitis belt"). The last outbreak was in 2007. During nonepidemic periods, children younger than 5 years have the highest incidence of infection. During epidemics, the incidence increases among children ages 5 to 9, an observation that may be of value in predicting the beginning of an epidemic. Crowded living conditions increase the risk of spread of meningococcal disease. The incidence of disease and the carrier state are several times higher among military recruits in the first few weeks of service than in the general public. This is also true of college freshmen, particularly those living in dormitories or residence halls. Other risk factors for developing invasive meningococcal disease include close contact with an infected patient, complement deficiency, properdin deficiency, asplenia, chronic alcohol abuse, active and passive smoking, corticosteroid use, and recent respiratory illness.[69]

The overall mortality rate of meningococcal disease is 10% in the United States. Septicemia without meningitis carries a much higher mortality rate (up to 70%) than meningitis alone (2–10%).[68,69]

Principles of Disease

Etiology

Meningococcal disease is caused by *N. meningitidis*, a fastidious, aerobic, gram-negative diplococcus. *N. meningitidis* is an encapsulated organism classified into at least 13 serogroups on the basis of the capsular polysaccharides.[68]

Pathophysiology

N. meningitidis attaches to nonciliated epithelial cells in the nasopharynx using a number of adhesion factors. Once attached, it may either remain on the epithelial surface, causing an asymptomatic carrier state, or produce mild symptoms of an upper respiratory tract infection. In certain patients the bacteria enter the bloodstream and cause symptoms and signs of localized infection, bacteremia, sepsis, or fulminant infection. The precise host and microorganism characteristics that determine whether clinical disease develops are not fully understood, but the presence of bacteriocidal antibodies is

protective. Complement deficiency may play a role in a host's inability to fight this infection. The capsule is required for *N. meningitidis* to adhere to epithelium, but only unencapsulated meningococci enter epithelial cells; capsular biosynthesis has been shown to stop as the bacteria enters the epithelial cell.[68] The release of lipooligosaccharide and endotoxin by autolysis of the *N. meningitidis* cell is the initial event in the development of meningococcal sepsis. The exogenous mediators appear to stimulate the release of endogenous mediators, including tumor necrosis factor, interleukin-1, and the host's complement system. All of the major pathophysiologic events of meningococcal sepsis are caused by the host's inflammatory response to the organism. The complement-activating products and other chemical mediators cause functional and histologic damage to the microvasculature, resulting in increased vascular permeability, pathologic vasoconstriction and vasodilation, loss of thromboresistance, DIC, and profound myocardial dysfunction.[70-72]

After exposure to *N. meningitidis*, protective antibodies develop. Immunity in children is conferred initially by maternal antibodies that pass through the placenta and later by the development of antibodies after exposure to the bacteria. In children, the incidence of meningococcal disease is inversely proportional to the levels of antibodies against *N. meningitidis*.[71]

Clinical Features

Symptoms and Signs

The clinical presentation of meningococcemia ranges from a mild febrile illness to fulminant disease progressing to death within hours. Most patients have fever on presentation. Other initial complaints include headache, irritability, lethargy, myalgias, emesis, diarrhea, cough, and rhinorrhea. Only 60% of patients have the classic signs of meningococcemia: fever and petechiae or purpura. These patients can rapidly progress to purpura fulminans, with hypotension, adrenal hemorrhage, and multiorgan failure.[70] The following categories detail the five patterns of presentation:

1. *Occult Bacteremia:* This condition arises as a febrile illness in which the only direct indication of meningococcemia is a positive blood culture with results available most often 24 to 48 hours after the clinical evaluation. In its mildest form, meningococcal bacteremia cannot clinically be distinguished from more benign febrile illnesses. Initial diagnoses in these patients include common childhood infections such as otitis media, acute viral upper respiratory infections, and gastroenteritis. For some patients the illness resolves after treatment with an oral regimen of antibiotics; others experience spontaneous resolution without antibiotic treatment.[68] *N. meningitidis* accounts for 1 to 5% of occult bacteremia cases, but these patients are much more likely to develop meningitis (up to 58%) than those with *S. pneumoniae*. Also, despite the total absence of clinical clues to meningococcal infection at initial presentation, some untreated patients subsequently deteriorate rapidly.[73]
2. *Meningococcal Meningitis:* Patients with meningococcal meningitis may present similarly to patients with meningitis of other origins with headache, photophobia, vomiting, fever, and signs of meningeal inflammation. This classic constellation of symptoms and signs is present in less than half of the patients. Infants and small children may present with fever, irritability, and vomiting as the only complaints. More than half of patients with meningococcal meningitis have rash on presentation, and 20% present with seizures.[73] Patients with meningococcal meningitis have a less abrupt onset of symptoms (usually over 24 hours) and a better prognosis than those with meningococcemia without clinical signs of meningitis.
3. *Meningococcal Septicemia:* Patients with meningococcal septicemia present with lethargy, poor tissue perfusion, cyanosis, and hypoventilation or hyperventilation. Hemorrhagic skin lesions are present in 28 to 77% of patients, but a macular or maculopapular rash may also occur and be mistaken for a variety of viral exanthems. Petechiae generally appear on the extremities and may appear under pressure points such as the elastic bands of socks and underwear. They may progress to involve almost any body surface, including the mucosa and sclera, but typically spare the palms, soles, and head. Macular lesions may progress to purpura and ecchymoses in fulminant meningococcemia. The purpurae are not a coalescence of petechiae but a distinct entity that more specifically characterizes meningococcemia. *Purpura fulminans*, the most dreaded and advanced form of meningococcal septicemia, occurs most often in children and is usually associated with DIC. This condition is characterized by rapidly spreading ecchymoses and gangrene of the extremities. Evidence of mucosal and gastrointestinal bleeding as well as oozing from IV sites may be noted on examination. Clinical signs of meningitis and CSF pleocytosis may not be present, even when diplococci are isolated from the CSF. This is probably because the systemic progression of the disease is so rapid that it precludes a host meningeal inflammatory response to the organism in the CSF. Shock results from both intravascular volume loss and congestive heart failure, probably related to myocarditis. Renal failure, coma, and bilateral adrenal hemorrhage often occur.[68,73,74]
4. *Fever and a Nonblanching Rash:* Up to 30% of patients present without signs of meningitis or septicemia. They are typically admitted for fever and a nonblanching rash and no other specific findings. If untreated, they can develop meningitis or fulminant septicemia and shock.[68]
5. *Chronic Meningococcemia:* This syndrome is characterized by fever, rash, and arthritis in conjunction with a positive blood culture for *N. meningitidis*. Headache and upper respiratory symptoms are often present. This is the rarest form of meningococcal disease, accounting for 1 to 2% of cases. It may progress to meningitis, endocarditis, or fulminant meningococcemia regardless of treatment.[68]

Complications

The most common complication of meningococcemia is myocarditis with congestive heart failure or conduction abnormalities. Many of the inflammatory mediators released during sepsis cause myocardial dysfunction, and the severity of sepsis is related to the degree of impairment of myocardial contractility. The acidosis, hypoglycemia, hypokalemia, hypocalcemia, hypophosphatemia, and hypoxia that accompany meningococcemia also contribute to the myocardial dysfunction. Patients may become unresponsive to positive inotropic medications.[71]

Acute respiratory failure occurs due to capillary leak in the patient who requires volume resuscitation. It is also likely that intrapulmonary DIC contributes to the pulmonary edema, and patients frequently require mechanical ventilation. Renal failure is common secondary to impaired renal perfusion; acute tubular necrosis may develop. If meningitis accompanies meningococcemia, focal neurologic signs as well as seizures may occur but are less common than with pneumococcal meningitis. Vasculitis in severe cases of meningococcal septicemia

may result in skin lesions that necessitate plastic surgery and loss of digits or limbs resulting from gangrene. Purulent or immune complex arthritis and pericarditis with tamponade may also occur.[69,71,74]

Poor prognostic indicators in meningococcemia include seizures on presentation, hypothermia, hyperpyrexia, a total peripheral WBC count of less than 500/mm^3, a platelet count of less than 100,000/mm^3, metabolic acidosis (pH < 7.30), the development of purpura fulminans, the onset of petechiae within 12 hours of admission, absence of meningitis, the presence of shock, a low sedimentation rate, and extremes of age. In one study, all patients who developed organ system failure had one or more of the following at the time of initial presentation: circulatory insufficiency (hypotension or shock), peripheral WBC count less than 10,000 cells/mm^3, or a coagulopathy. Herpes labialis occurs in 5 to 20% of patients with meningococcal disease.[73,75]

Diagnostic Strategies

The tentative diagnosis of meningococcemia is based on clinical findings and confirmed by the isolation of *N. meningitidis* from blood cultures or any other usually sterile site such as CSF or synovial, pleural, or pericardial fluid. Ideally, blood cultures should be obtained before the administration of antibiotics unless this unduly delays the patient's treatment. Blood cultures are positive in approximately 50 to 80% of cases. A lumbar puncture should only be performed in stable patients without evidence of DIC. The CSF shows either gram-negative diplococci on Gram's stain or a positive culture in about 80 to 90% of cases. Even patients without clinical signs of meningitis frequently have the organism grown from the CSF. Gram's stain of petechial scrapings may show gram-negative diplococci in up to 70% of cases, and, rarely, the organism can be seen in the peripheral blood buffy coat. Highly specific antigen tests for CSF are available but have a high false-negative rate. PCR of the buffy coat or CSF is more sensitive and specific than any of the preceding tests and is not affected by prior antibiotic therapy.[68,74-76]

Ancillary laboratory tests are of little value in establishing a specific diagnosis of meningococcal sepsis but may be useful in ruling out other disease, determining prognosis, and monitoring complications. The WBC count may be high, low, or normal, but a bandemia is typically present. The symptoms and signs of CNS infection may be nonspecific in the infant and child younger than 2 years. If meningitis is present, the CSF opening pressure is usually elevated, the protein level is increased, and glucose is decreased. Pleocytosis is usually present, with a predominance of polymorphonuclear leukocytes. Gram-negative diplococci may be seen on microscopy. Early in the disease or with fulminant disease, the CSF may be free of inflammatory cells. Serologic evidence of DIC is frequently present.[68,74-76]

A chest radiograph is useful in evaluating for pneumonia and acute respiratory distress syndrome. An echocardiogram helps assess for myocardial dysfunction and pericardial effusion.[75]

Differential Considerations

It is difficult to distinguish the clinical signs of meningococcemia from those of bacteremia caused by *S. pneumoniae*, other streptococcal groups, *H. influenzae*, and *Neisseria gonorrhoeae*. The differential diagnosis of meningococcemia also includes viral exanthems, Rocky Mountain spotted fever, typhus, typhoid fever, endocarditis, vasculitis syndromes (polyarteritis nodosa and Henoch-Schönlein purpura), toxic shock syndrome, acute rheumatic fever, drug reactions, idiopathic thrombocytopenic purpura, and thrombotic thrombocytopenic purpura.[75]

In one study of 184 children hospitalized with fever and petechiae, 24 (11%) had proven *N. meningitidis*. The remainder showed evidence of viral or other organisms. These data were acquired prior to the initiation of a vaccination program.[77]

Management

Acute Treatment

Morbidity and mortality in meningococcemia are reduced with prompt recognition and immediate initiation of antibiotic therapy. Delays in initiating therapy for the completion of diagnostic studies or admission to an inpatient unit should be avoided. To simplify selection of a treatment strategy, patients can be divided into three general groups:

1. *Bacteremia or sepsis is suggested on the basis of clinical findings; however, the organism has not been identified.* These patients should receive broad-spectrum antibiotics, with selection based on factors that include the most likely organism or organisms, the patient's age and immune status, the presence of coexisting disorders, and local patterns of antibiotic resistance. A narrower spectrum agent is selected after positive identification of the organism and its sensitivities.
2. *N. meningitidis growth is reported from prior blood cultures.* The treatment regimen for occult bacteremia is guided by the patient's age, history, physical examination, general appearance, and ancillary tests. The antibiotic selected at the time of the initial visit may be sufficient to treat the meningococcal bacteremia subsequently identified by the laboratory. The decision to hospitalize the patient is based on the findings at the time of reevaluation and the risk of sequelae. Regardless of the patient's clinical appearance, most physicians would redraw blood for cultures, consider lumbar puncture, and admit the patient to the hospital until results of repeated cultures are obtained.
3. *Bacteremia or sepsis is suggested and N. meningitidis is identified.* The antibiotic regimen is focused narrowly.

The standard antibiotic regimen for laboratory-proven meningococcemia is penicillin G, 4 million units every 4 hours IV for adults, and penicillin, 250,000 to 300,000 units/kg/day in divided doses every 4 hours IV for children, up to a maximum of 20 million units. Penicillin resistance in *N. meningitidis* remains low in the United States but has been reported in Spain and the United Kingdom.[68,77] The emergency physician should keep informed of any emerging resistance patterns in the practice area.[78]

Although it is appropriate first-line therapy, penicillin is rarely given as the initial agent in patients with suggested meningocoocal sepsis or meningitis. Ceftriaxone (initial dose of 100 mg/kg IV, followed by daily dosage of 100 mg/kg in divided doses every 12 hours up to a maximum of 4 g) or cefotaxime (100 mg/kg/day IV in divided doses every 6 hours up to a maximum of 12 g) are appropriate initial antibiotics as well. The cephalosporins offer the advantages of safety, rapid onset of action, and excellent coverage for *S. pneumoniae* and *H. influenzae*. Chloramphenicol (50–100 mg/kg/day divided every 6 hours to a maximum of 4 g/day) should be considered in penicillin- and cephalosporin-allergic patients.[68] Ceftriaxone IM is commonly administered to children with suspected bacteremia who are treated as outpatients while culture results are pending. Several reports have demonstrated the efficacy of ceftriaxone (80–100 mg/kg IV) in a single daily dose; however,

twice-daily dosing remains the standard recommendation at this time. In addition to the obvious advantage of extended dosing intervals, ceftriaxone-treated patients have a more rapid sterilization of the CSF and a lower incidence of hearing loss than conventionally treated patients.

Patients with fulminant meningococcemia require prompt airway management, IV fluid resuscitation, and vasopressor support. Fluid requirements may be high because of third spacing of fluid, and in the setting of frequent myocardial dysfunction, intensive cardiovascular monitoring is required. Electrolyte and acid-base abnormalities should be corrected. If the patient is oliguric or anuric, hemodialysis may be necessary to correct these abnormalities. Fresh frozen plasma should be considered for patients with bleeding complications.[68,79]

The role of steroids for the treatment of meningococcemia without meningitis remains controversial. Although corticosteroids were once widely recommended for the treatment of the adrenal insufficiency associated with fulminant meningococcemia, more recent studies demonstrate that adrenal function is not impaired in all patients. If a patient has persistent shock despite vigorous fluid resuscitation and vasopressor therapy, glucocorticoid therapy may be considered and adrenal function tested.[80]

The use of corticosteroids in patients with bacterial meningitis is currently recommended for adults and children, but not neonates. The most recent clinical data show that corticosteroid administration prior to antibiotic administration decreases mortality rates in adults and long-term neurologic sequelae in adults and children. Dexamethasone (0.4–0.6 mg/kg/day every 6 hours for 4 days) should be given to patients with bacterial meningitis. The first dose should be given prior to the first dose of antibiotics if possible.[81]

Plasmapheresis, blood exchange, and extracorporeal membrane oxygenation have all been described with favorable outcome, but data are limited.[74]

Disposition

All patients with possible or confirmed meningococcemia should be admitted to the hospital, preferrably to an ICU because these patients can decompensate rapidly and without warning.[76] A possible exception is the child who has culture-proven *N. meningitidis* and has been taking appropriate antibiotics as an outpatient. This child should have a lumbar puncture to determine CSF involvement if one was not performed at the initial evaluation. Antibiotics should be continued as an inpatient, but an ICU may not be necessary if the child appears well.

Antibiotic Prophylaxis and Vaccination

Patients with meningococcemia should be placed in respiratory isolation for at least 24 hours. Close contacts should receive antibiotic prophylaxis. Household, nursery school, and daycare center contacts should receive prophylaxis promptly. Intimate contacts and health care workers with intimate exposure (e.g., mouth-to-mouth resuscitation, intubation, or suctioning) should receive rifampin, 10 mg/kg (up to 600 mg) orally every 12 hours for four doses. The dose for infants younger than 1 month is 5 mg/kg. Patients should be warned that rifampin discolors the urine and secretions; contact lenses should be removed to avoid permanent staining. Ceftriaxone IM (125 mg for children younger than 15 years and 250 mg for those older than 12) is effective against group A strains. This is an alternative for pregnant women and for people in whom compliance with an oral regimen cannot be ensured. Ciprofloxacin (500 mg orally) is another alternative for adults.[68,70]

Meningococcal vaccine should be considered as an adjunct to prophylaxis in epidemics and for close contacts in sporadic cases if one of the serotypes contained in the vaccine is identified as the causative agent. The currently available vaccine is a quadrivalent vaccine containing purified capsular polysaccharides for groups A, C, Y, and W-135. Unfortunately, the polysaccharides other than A are poorly immunogenic for children younger than 2 years. In addition, no vaccine exists for group B, a serogroup that causes a significant portion of meningococcal infection in the United States. The quadrivalent vaccine is not recommended for routine use but should be administered to children 2 years of age and older in high-risk groups, such as those with functional or anatomic asplenia, and those with terminal complement deficiency. In 2000, the CDC Advisory Committee on Immunization Practice (ACIP) recommended that college students, especially those living in dormitories, and their parents be advised of the risks of meningococcal disease and be offered vaccination. In August 2007, the ACIP recommended that all persons aged 11 to 18 years receive the vaccine. The vaccine is currently administered to U.S. military recruits. Consideration should be given to vaccinating people traveling to endemic areas of the world such as sub-Saharan Africa.[69,70,82]

TOXIC SHOCK SYNDROME

Perspective

Background

Toxic shock syndrome (TSS) is a toxin-mediated systemic inflammatory response syndrome that was first described by Todd and colleagues in 1978. They reported a series of seven children from ages 8 to 17 years who had high fever, rash, headache, confusion, conjunctival injection, edema, vomiting, diarrhea, renal failure, hepatic dysfunction, DIC, and shock. *S. aureus* was cultured from various body sites but not the blood in five of the seven cases.[83,84]

The disease gained notoriety in the early 1980s when many cases were reported in association with tampon use in young, healthy menstruating women. The term *toxic shock syndrome* was coined to describe the constellation of signs and symptoms. Investigators noted positive vaginal cultures for *S. aureus*, recurrence of illness during subsequent menses, and the value of antistaphylococcal antibiotics in preventing recurrences. In response to the growing concern about TSS, changes were made to reduce the absorbency and composition of tampons. Nonmenstrual cases were also recognized in both men and women as a result of a variety of predisposing conditions, and a case definition was published in 1982 (Box 127-6).[83–88]

In the late 1980s, several reports described group A *Streptococcus* (GAS) infection associated with shock and multisystem organ failure. This has been called *streptococcal toxic shock syndrome (strep TSS)* because it shares so many features with staphylococcal TSS.[85,86] Box 127-7 shows the case definition for strep TSS.[89]

Epidemiology

The peak incidence of TSS occurred in 1980, when 890 cases were reported, 91% of which were associated with tampon use. Since then, the reduction in cases of the menstrual form of TSS has followed an active effort to decrease tampon absorbency and change their composition.[90] Menstruation remains the most common setting for TSS, but nonmenstrual TSS accounts for just under half of the reported cases. TSS has also been reported in association with barrier contraceptives and

BOX 127-6 Case Definition of Toxic Shock Syndrome (Revised)

Fever: Temperature ≥ 38.9° C (102° F)
Rash: Diffuse macular erythroderma
Desquamation 1–2 weeks after onset of illness, particularly of palms and soles
Hypotension: Systolic blood pressure ≤90 mm Hg for adults or below fifth percentile by age for children less than 16 years of age, orthostatic drop in diastolic blood pressure ≥15 mm Hg from lying to sitting, orthostatic syncope, or orthostatic dizziness
Multisystem involvement—*three* or more of the following:
- **Gastrointestinal:** Vomiting or diarrhea at onset of illness
- **Muscular:** Severe myalgia or creatine phosphokinase level at least twice the upper limit of normal for laboratory
- **Mucous membrane:** Vaginal, oropharyngeal, or conjunctival hyperemia
- **Renal:** BUN or creatinine at least twice the upper limit of normal for laboratory or urinary sediment with pyuria (≥5 leukocytes/hpf) in the absence of urinary tract infection
- **Hepatic:** Total bilirubin, AST, and ALT at least twice the upper limit of normal for laboratory
- **Hematologic:** Platelets ≤ 100,000/mm^3
- **CNS:** Disorientation or alterations in consciousness without focal neurologic signs when fever and hypotension are absent

Negative results on the following tests, if obtained:
- Blood, throat, or CSF cultures (blood culture may be positive for *Staphylococcus aureus*)
- Rise in titer to Rocky Mountain spotted fever, leptospirosis, or rubeola

ALT, serum alanine aminotransferase; AST, serum aspartate aminotransferase; BUN, blood urea nitrogen; CNS, central nervous system; CSF, cerebrospinal fluid.

BOX 127-7 Case Definition for Streptococcal Toxic Shock Syndrome

Hypotension: Systolic blood pressure ≤90 mm Hg for adults or below fifth percentile by age for children younger than 16 years
Multisystem involvement—*two* or more of the following:
- **Renal:** Creatinine > 2 mg/dL (177 µmol/L) for adults or more than twice the upper limit of normal for age or more than twofold elevation over baseline for patients with preexisting renal disease
- **Hematologic:** Platelets ≤ 100,000/mm^3 or DIC defined as prolonged clotting times, low fibrinogen level, and the presence of FDPs
- **Hepatic:** Total bilirubin, AST, and ALT at least twice the upper limit of normal for laboratory, or a twofold increase in patients with preexisting liver disease
- **Acute respiratory distress syndrome:** Acute onset of pulmonary infiltrates and hypoxemia in the absence of cardiac failure or by evidence of diffuse capillary leak manifested by acute onset of generalized edema, or pleural or peritoneal effusions with hypoalbuminemia

Generalized erythematous maculopapular rash that may desquamate
Soft tissue necrosis, including necrotizing fasciitis, myositis, or gangrene
Laboratory criteria for diagnosis:
- Isolation of GAS

Case Classification
- **Probable:** A case meets the clinical case definition in the absence of another identified cause for the illness and with isolation of GAS from a nonsterile site.
- **Confirmed:** A case meets the clinical case definition with isolation of GAS from a normally sterile site (e.g., CSF or joint, pleural, or pericardial fluid).

ALT, serum alanine aminotransferase; AST, serum aspartate aminotransferase; CSF, cerebrospinal fluid; DIC, disseminated intravascular coagulation; GAS, group A *Streptococcus*.

childbirth. Nonmenstrual TSS occurs in people of all ages and in both sexes. The CDC reported an average of about 200 cases a year (≈ 1 case per 100,000 population) from 1994 to 2001 with a steady increase in the incidence of streptococcal TSS and a slight decrease in the incidence of staphylococcal TSS.[91] The age and sex distribution reflects the association with menses. In 2003, 294 cases were reported, but a steady decline continues to occur, with 182 cases reported in 2007. Streptococcal TSS accounts for a little more than half of the cases.[92]

Nonmenstrual staphylococcal TSS is associated with superinfection of various skin lesions, including burns, surgical sites, dialysis catheters, and lung (influenza associated). It may also occur in association with staphylococcal respiratory infections or even with colonization by a toxigenic strain of the organism, without an obvious infectious source. Streptococcal TSS is classically associated with more severe soft tissue infections such as necrotizing fasciitis and myositis as well as pneumonia, peritonitis, myometritis, and osteomyelitis.[84–87]

The mortality rate from staphylococcal TSS has declined since the disease was first described. The case fatality rate in 1980 was 10%, and it was less than 3% in the past several years. Streptococcal TSS remains a highly fatal disease, with a mortality rate of 30 to 70%.[84–87]

Principles of Disease

Etiology

Staphylococcal TSS is caused by colonization or infection with toxigenic strains of *Staphylococcus aureus*. This strain produces toxic shock syndrome toxin-1 (TSST-1). *S. aureus* has been detected in virtually all cases of both forms of the illness. *S. aureus* has been isolated from the vagina or cervix in 98% of women with menstrual TSS, compared with a colonization rate of less than 10% of unaffected women. Because the organism is often not invasive, the blood cultures are often negative. Streptococcal TSS is caused by invasive infection with toxigenic strains of GAS.[84–87]

Pathophysiology

The shock and multiorgan dysfunction associated with TSS are caused by the effects of various exotoxins produced by *S. aureus* and GAS. *S. aureus* produces TSST-1 and enterotoxin B. TSST-1 is identified in more than 90% of menstrual cases and 60% of nonmenstrual cases. Other toxins may play a role in nonmenstrual TSS. Antibodies to these toxins are protective against disease. GAS produces streptococcal pyrogenic exotoxins A (SPEA) and B (SPEB). These exotoxins are

absorbed into the bloodstream through inflamed or traumatized mucous membranes or from areas of focal infection. Absorbed toxins act as superantigens, inducing mononuclear cells to synthesize and release cytokines, tumor necrosis factor α, and interleukins, which begin the cascade of systemic vasculitis and the multisystem manifestations of the disease. Host immune factors are important in the pathogenesis of TSS. GAS is an invasive organism, and circulating GAS organisms induce the production of tumor necrosis factor α and other cytokines by mononuclear cells.[84–87,93]

Clinical Features

Symptoms and Sings

The clinical presentations of streptococcal TSS and staphylococcal TSS are similar. The primary difference is that an identifiable infectious source is virtually always present with streptococcal TSS, and colonization alone may be the source in staphylococcal TSS.

Patients may have fever, chills, nausea, vomiting, watery diarrhea, headache, myalgias, and pharyngitis. This prodromal illness may last for 2 to 3 days before progression to frank sepsis and organ dysfunction. Others patients may become abruptly symptomatic within hours. Rapid progression is more typical of streptococcal TSS. Patients may complain of pain at a site of infection more often with streptococcal TSS. Risk factors for TSS are listed in Box 127-8.

The fever is usually high and abrupt in onset, although septic patients may have hypothermia on presentation. The classic rash is a nonpruritic, diffuse, blanching, macular erythroderma. It develops over the first few days of the illness and initially may be faint, evanescent, and mistaken for the flush associated with a fever. The rash is usually diffuse but may be localized to the trunk, extremities, or perineum. After about a week, a fine flaking desquamation occurs on the face, trunk, and extremities, followed by full-thickness peeling of the palms, soles, and fingers. This classic rash progression is much more common in staphylococcal TSS and is present in less than 10% of patients with streptococcal TSS.[93]

The patient's mental status is frequently abnormal, out of proportion to the degree of hypotension. Confusion, somnolence, agitation, and combativeness are present in 55% of patients with streptococcal TSS and in even more patients with staphylococcal TSS.[84,85,93]

Other findings on physical examination may include pharyngeal and conjunctival erythema, strawberry tongue, and peripheral edema. Vaginal mucosal erythema and purulent vaginal discharge may be present in menstrual TSS but are not required to make the diagnosis. As multiple organ systems become involved, a wide constellation of signs and symptoms may be seen. Gastrointestinal involvement is manifested by vomiting, diarrhea, and severe abdominal pain. Hepatomegaly may be present. Patients may become hypoxic and develop rales on pulmonary examination. Comparisons between staphylococcal and streptococcal TSS are presented in Table 127-4.

BOX 127-8 RISK FACTORS FOR TOXIC SHOCK SYNDROME

- Use of superabsorbent tampons
- Postoperative wound infections
- Postpartum period
- Nasal packing
- Cancer
- Common bacterial infections
- Ethanol abuse
- Infection with influenza A
- Infection with varicella
- Diabetes mellitus
- Human immunodeficiency virus infection
- Chronic cardiac disease
- Chronic pulmonary disease
- Nonsteroidal anti-inflammatory use (may mask symptoms rather than be a risk factor)

Complications

Complications of TSS include acute respiratory distress syndrome, shock, gangrene, DIC, renal failure, and a constellation of neuropsychiatric symptoms. Less common findings in staphylococcal TSS include rhabdomyolysis, seizures, pancreatitis, pericarditis, and cardiomyopathy. Women with the menstrual form of TSS may experience one or more recurrent episodes; recurrences of the nonmenstrual form are rare. Complication rates are higher with streptococcal TSS. Rhabdomyolysis occurs in up to 63% of patients with streptococcal TSS and is usually related to the underlying soft tissue infections.[84–87,93]

Diagnostic Strategies

The case definition for TSS does not require a positive culture for *S. aureus* but does for *Streptococcus* organisms. These case definitions (see Boxes 127-6 and 127-7) are useful to the clinician, but they are neither specific nor foolproof. Specific tests are not required to exclude other diseases, but if such tests are obtained, the results of these studies must be negative.

No specific laboratory changes are associated with TSS, but many abnormalities are common. Either leukocytosis or leukopenia can occur, but a marked bandemia is very common. Elevated creatinine levels and hemoglobinuria occur in most patients. Laboratory evidence of renal dysfunction occurs prior to hypotension in half of the patients. Hypoalbuminemia and life-threatening hypocalcemia are prominent initially and persist throughout the course of the disease. Other abnormalities include anemia, thrombocytopenia, hyperbilirubinemia, elevated transaminase levels, and sterile pyuria.[84–87]

Chest radiography may reveal evidence of acute respiratory distress syndrome or a pulmonary source of the organism. Plain radiographs of any infected skin or soft tissue site typically

Table 127-4 Comparison of Staphylococcal and Streptococcal Toxic Shock Syndrome

FEATURE	STAPHYLOCOCCAL	STREPTOCOCCAL
Age	Primarily 15–35 yr	Primarily 20–50 yr
Sex	Greatest in women	Either
Severe pain	Rare	Common
Hypotension	100%	100%
Erythroderma rash	Very common	Less common
Renal failure	Common	Common
Bacteremia	Low	60%
Tissue necrosis	Rare	Common
Predisposing factors	Tampons, packing, NSAID use?	Cuts, burns, bruises, varicella, NSAID use?
Thrombocytopenia	Common	Common
Mortality rate	<3%	30–70%

NSAID, nonsteroidal anti-inflammatory drug.

show only soft tissue swelling but may reveal evidence of a retained foreign body or air in the soft tissue. It is important to note that a lack of air in the soft tissue does not rule out a necrotizing soft tissue infection.

An ECG may reveal evidence of ischemia, arrhythmias, and varying degrees of atrioventricular block in association with sepsis.[85] A blood gas analysis may indicate metabolic acidosis secondary to hypotension or hypoxia. A lumbar puncture should be performed in febrile patients with altered mental status to evaluate for meningitis. It is prudent to wait for the results of a coagulation profile in these patients before performing the lumbar puncture as DIC may be present at presentation. The CSF is normal in patients with TSS. Serologic tests for Rocky Mountain spotted fever and leptospirosis should be considered in endemic areas.[85]

Differential Considerations

The differential diagnosis includes any severe febrile illness with exanthema, associated with hypotension. Other diseases to consider include heat stroke, cellulitis, Kawasaki disease, staphylococcal scalded-skin syndrome, scarlet fever, drug reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), Rocky Mountain spotted fever, Clostridial gas gangrene, leptospirosis, meningococcemia, gram-negative sepsis, atypical measles, and viral illnesses.

Kawasaki disease occurs almost exclusively in children, usually does not progress to shock, lacks multisystem involvement, exhibits a protracted fever, and is associated with thrombocytosis later in its course. Staphylococcal scalded-skin syndrome arises with a desquamating rash acutely, whereas the desquamation of TSS occurs in the convalescent phase. Staphylococcal scalded-skin syndrome does not progress to shock, is not associated with multisystem illness, and lacks mucous membrane involvement. Scarlet fever differs in its clinical course by lack of shock and multisystem involvement, positive cultures for GAS, and a rise in the convalescent titer. Stevens-Johnson syndrome usually occurs after drug administration, has characteristic mucous membrane lesions, and lacks desquamation. TEN may be difficult to distinguish from TSS, as TEN patients are typically febrile, in shock, and can progress to multisystem failure. The desquamation of TEN occurs early in the course of the disease, and it usually occurs after administration of a drug. Rocky Mountain spotted fever occurs after a tick bite, has a distinctive rash, and is associated with a severe headache without an altered mental status or hypotension. Leptospirosis occurs in endemic areas and may be distinguished by positive serologic studies and cultures. The rash of meningococcemia is characterized by petechiae and purpura occurring anywhere on the skin.[84,85]

Management

Patients with TSS should receive aggressive fluid resuscitation with crystalloids and may require up to 10 to 20 L/day. Supplemental oxygen should be provided to all septic patients regardless of initial pulse oxymetry. This allows maximum tissue oxygenation and reduces acidosis. Patients should be placed in a monitored setting. Assisted ventilation may be necessary in patients with acute respiratory distress syndrome. Hyperbaric oxygen therapy has been studied as a potential treatment for TSS but without proven benefit.[84,85]

The source of bacteria, such as tampons, nasal packs, and other foreign bodies, must be removed. Prompt surgical consultation should be obtained to débride wounds. If specimens are sent for culture, the laboratory should be informed of the suggested diagnosis.

Patients who do not respond to fluid resuscitation require vasopressors such as dopamine, phenylephrine, norepinephrine, and epinephrine.

Antibiotics should be initiated early in the treatment of TSS, as the clinical presentation of the disease is similar whether the source is staphylococcal or streptococcal. For septic patients without an identified organism, broad-spectrum antibiotics should be administered. Although the penicillinase-resistant penicillins (nafcillin, oxacillin) have been widely used in the treatment of TSS, most clinicians recommend clindamycin as a first-line agent. Clindamycin is a potent suppresser of bacterial toxin synthesis; it also facilitates phagocytosis of streptococci and has a longer postantibiotic effect than the β-lactams. The dose is 600 to 900 mg IV every 8 hours. (The pediatric dose is 20–40 mg/kg/day divided every 6–8 hr.) Clindamycin and azithromycin have also been shown to decrease monocyte synthesis of cytokines.[84–87]

Patients who do not respond to massive fluid resuscitation, antibiotics, and vasopressors should be considered for IV immunoglobulin treatment, especially if pulmonary edema develops and mechanical ventilation is required. Pooled immune globulin has high titers for antibodies to TSS-1 and other exotoxins, and significant improvement has been reported with its use. If used, the recommended dose is 2 g/kg on day 1 administered IV over several hours followed by 400 mg/kg/d for up to 5 days.[84–87,94]

The value of corticosteroids in TSS is still unresolved. They are not currently recommended for treating staphylococcal or streptococcal TSS but should be given to patients thought to have adrenal insufficiency related to underlying disease or chronic steroid use.[84]

Disposition

All patients thought to have TSS should be admitted to an ICU. Prompt surgical consultation should be obtained for patients with a wound source.[85]

KEY CONCEPTS

- All patients appearing septic should be treated with broad-spectrum antibiotics as soon as possible, even before a definitive diagnosis is made.
- A surgeon should be consulted as soon as possible for patients with sepsis and a débridable source of infection.
- Immunity to diphtheria, tetanus, and pertussis wanes significantly in adults. Pertussis should always be considered as a cause of persistent cough in adults. A tetanus vaccination history should always be obtained from patients with trauma or infection. When there is doubt about the history, the age-appropriate vaccine according to CDC guidelines is administered.
- Neonates with suggested pertussis should be admitted to an intensive care setting.
- Botulism should be kept in the differential for the infant with failure to thrive, constipation, or decreased muscle tone and for the IV drug user with neurologic symptoms.
- IV gamma globulin should be administered as soon as a diagnosis of Kawasaki disease is made.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 128 Viral Illnesses

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PERSPECTIVE

Most viral infections manifest as benign, self-limited upper respiratory tract or gastrointestinal infections, and therapy most often is directed at control of symptoms. Exact identification of the causative virus usually is not required. With some viral diseases for which specific therapy or postexposure prophylaxis (PEP) is available, however, recognizing the disease and promptly instituting therapy or prevention can prevent permanent sequelae or death. Examples of how prompt recognition and therapy can change the outcome of potentially fatal viral illness are the early institution of acyclovir treatment for herpes simplex virus (HSV) encephalitis and the appropriate use of rabies vaccine and immunoglobulin for patients exposed to rabies.

CLASSIFICATION

Viruses were first distinguished from other microorganisms by their ability to pass through filters of small pore size. Initial classifications of viruses were based on their pathologic properties (e.g., enteroviruses) or epidemiologic features (e.g., arthropod-borne). More recently, classification has been based on the genetic relationships of the viruses. The components of the current classification are the type and structure of the viral nucleic acid, the type of symmetry of the virus capsid, and the presence or absence of an envelope (Table 128-1).

The genetic information of viruses is encoded in either DNA or RNA, which can be either single- or double-stranded and circular (closed-ended) or linear (open-ended). The genomes of the smallest viruses may code for only three or four proteins, whereas those of the largest viruses encode several hundred. A protein coat, called the *capsid*, is composed of a repeating series of protein subunits, called *capsomeres*. The viral nucleic acid and the surrounding protein coat are jointly referred to as the *nucleocapsid*. The use of repeating protein structures limits the shape of the capsid. All but the most complex viruses are either helically symmetrical or icosahedral. Finally, some virus nucleocapsids are surrounded by a lipid envelope acquired by the virus as it buds from the cell cytoplasm, nuclear membranes, or endoplasmic reticulum.

VIRAL IMMUNIZATIONS

Whereas treatment strategies against most bacterial diseases have focused on treating and eradicating bacteria from the host after disease has developed, the most successful strategies against viral diseases have concentrated on immunization. The history of immunization against viral diseases began in 1796, when Jenner injected pustular material from the lesions of cowpox into a child to prevent smallpox.[1] The word *vaccination* is derived from *vaccinia*, referring to the skin reaction at the site of injection of such material for smallpox immunization, and originally meant "inoculation to render a person immune to smallpox." Currently, the terms *vaccination* and *immunization* are used interchangeably to mean the administration of any vaccine. *Immunization* is a broader term that includes administering immunobiologics such as immunoglobulins.

Viral vaccines are suspensions of live, attenuated, or inactivated whole viruses or parts of viruses that are administered to induce immunity. Some vaccines, such as the surface antigen of hepatitis B, are highly defined; others, such as live, attenuated viruses, are complex. Immunoglobulin is an antibody preparation obtained from large pools of human blood plasma. It is given intramuscularly for passive immunization against measles and hepatitis A, and intravenously as replacement therapy for antibody-deficiency disorders. Specific immunoglobulins are preparations of monoclonal antibodies or are prepared from special donor plasma pools preselected for high antibody titers against specific antigens, such as those presented by the hepatitis B, varicella-zoster, or rabies viruses. None of the immunoglobulin preparations, when properly prepared, can transmit infectious viruses.

The modern era of immunization began in 1885, when Louis Pasteur and colleagues injected the first of 14 daily doses of rabbit spinal cord suspensions containing progressively inactivated rabies virus into 9-year-old Joseph Meister, who had been bitten by a rabid dog 2 days earlier.[2] The introduction of the inactivated poliomyelitis vaccine (IPV) in 1955 and the attenuated live oral polio vaccine (OPV) in 1962 has virtually eliminated the threat of paralytic poliomyelitis in the United States and other developed countries.[3,4] Currently, a massive World Health Organization (WHO) campaign to eradicate polio worldwide is under way. As of 2007, in four countries (Pakistan, India, Afghanistan, and Nigeria), polio transmission has never been interrupted, and in several more countries in Asia and Africa, polio has re-emerged. [5] Vaccines against measles, mumps, rubella, influenza, and hepatitis B have greatly reduced morbidity and mortality associated with these diseases. The worldwide eradication of smallpox in 1977 is a testament to the advances made against viral diseases.[6]

Administration of an immunobiologic agent does not automatically confer adequate immunity. Some preparations require more than one dose to produce an adequate antibody response, or periodic boosters may be needed to maintain

Chapter 128 is in the Public Domain

Table 128-1 Classification of Viruses

FAMILY	EXAMPLE(S)	REPRESENTATIVE DISEASE(S), COMMENTS
DNA Viruses		
Poxviridae	Variola	Smallpox
	Orf	Contagious pustular dermatitis
Herpesviridae	HSV-1, HSV-2	Mucocutaneous ulcers, herpes encephalitis
	Cytomegalovirus	Pneumonitis in immunocompromised patients
	VZV	Chickenpox, shingles
	HHV-6	Roseola infantum
	EBV	Mononucleosis
	Kaposi's sarcoma herpesvirus	Kaposi's sarcoma
Adenoviridae	Adenovirus (50+ species)	Upper respiratory tract infections, diarrhea
Papillomaviridae	Papillomavirus (80+ species)	Warts (e.g., plantar, genital)
Polyomaviridae	JC virus	PML
Hepadnaviridae	Hepatitis B	Hepatitis
Parvoviridae	Parvovirus B-19	Aplastic anemia
RNA Viruses		
Reoviridae	Colorado tick fever	Fever and rash
	Rotavirus	Gastroenteritis
Togaviridae	Eastern equine encephalitis	Epidemic encephalitis
	Rubella	German measles
Flaviviridae	Yellow fever	Hemorrhagic fever
	Dengue	Dengue hemorrhagic fever
	West Nile virus	West Nile encephalitis
Hepacivirus	Hepatitis C	Chronic hepatitis
Coronaviridae	Coronavirus	Upper respiratory tract infections
	SARS-CoV	Severe acute respiratory syndrome
Paramyxoviridae	Respiratory syncytial virus	Bronchiolitis
	Measles	Measles (rubeola), SSPE
	Parainfluenza	Croup
Rhabdoviridae	Rabies	Rabies
Filoviridae	Ebola	Hemorrhagic fever
Orthomyxoviridae	Influenza A, B	Influenza
Bunyaviridae	La Crosse	Encephalitis
	Hantaan	Hemorrhagic fevers, ARDS
Arenaviridae	Lassa	Hemorrhagic fever
	Lymphocytic choriomeningitis virus	Meningoencephalitis
Retroviridae	HIV	AIDS
Picornaviridae	Poliovirus	Polio
	Coxsackie B	Myocarditis
	Hepatitis A	Enteric hepatitis
	Rhinovirus (115+ species)	Upper respiratory infections
Caliciviridae	Norwalk virus	Gastroenteritis
Unclassified viruses	Hepatitis E	Enteric hepatitis
Subviral Agents		
Satellites	Delta virus	Hepatitis
Prions		Kuru, Creutzfeldt-Jakob disease

AIDS, acquired immunodeficiency syndrome; ARDS, acute respiratory distress syndrome; CoV, coronavirus; EBV, Epstein-Barr virus; HHV, human herpesvirus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; PML, progressive multifocal leukoencephalopathy; SARS, severe acute respiratory syndrome; SSPE, subacute sclerosing panencephalitis; VZV, varicella-zoster virus.

protection. The simultaneous administration of immunoglobulin with a live virus vaccine may result in diminished antibody response to the vaccine. Deviation from the recommended volume or number of doses of any vaccine is strongly discouraged. Significant problems also remain in developing countries that cannot afford vaccines or have problems delivering vaccines to their at-risk populations. Table 128-2 summarizes currently available viral vaccines, their indications, and recommended uses.[7-11] Over the past several years, new vaccines have been developed against rotavirus,[9] a major cause of diarrheal disease in young children worldwide; human papillomaviruses (HPVs), which are associated with urogenital cancers[10]; and herpes zoster (shingles), which is a major cause of morbidity in mostly elderly patients.[11]

ANTIVIRAL CHEMOTHERAPY

Because most viral illnesses are self-limited, treatment generally is targeted at ameliorating symptoms. The revolution in molecular biology has unlocked pathophysiologic mechanisms

Table 128-2 Viral Vaccines

VIRUS	VACCINE	TYPE	INDICATION	RECOMMENDED SCHEDULE
Smallpox	Vaccinia	Live	For persons at risk or for emergency responders	Once, before anticipated risk of exposure
Polio	Oral polio vaccine (Sabin)	Live	During outbreaks Unvaccinated travelers	Inactivated polio vaccine preferred in almost all cases
	Inactivated polio vaccine (Salk)	Inactivated	All children	At 2, 4, and 12 to 18 months, and at 4 to 6 years
Measles	Measles, mumps, rubella (MMR)	Live	All normal children	At 12–15 months and 4–6 years
Mumps	MMR	Live	All normal children	Same as for measles
Rubella	MMR	Live	All normal children	Same as for measles
Hepatitis A	HAV vaccine	Inactivated	Persons at risk (e.g., travelers, persons living in areas of high prevalence)	Two doses, 6 months apart Immunoglobulin should be given if travel is imminent
Hepatitis B	HBV vaccine	Inactivated or recombinant	All children Persons at risk of exposure (e.g., health care workers)	At birth, 1–4 months, and 6–18 months HBIG should be given in addition in case of high-risk exposure
Influenza A and B	Influenza vaccine	Inactivated	Persons at high risk for complications (e.g., elderly) or persons capable of transmitting influenza to high-risk patients (e.g., health care workers)	One dose yearly in the fall or winter
	Intranasal vaccine	Live, cold adapted	As above, for persons 5–49 years of age	As above
Rabies	Human diploid cell vaccine (HDCV)	Inactivated	Postexposure prophylaxis	HDCV, RVA, or PCEC 1.0 mL IM in the deltoid region on days 0, 3, 7, 14, and 28
	Rabies vaccine absorbed (RVA)	Inactivated	Preexposure prophylaxis in high-risk groups (e.g., veterinarians)	Rabies immune globulin (RIG), 20 IU/kg should be administered around the wound site, as possible, with the remainder given IM at an anatomically distant site
	Purified chick embryo cell (PCEC)	Inactivated		
Yellow fever	17D virus strain	Live	Persons older than 6 months traveling to endemic areas	Boosters every 10 years
Varicella	Varicella	Live	All healthy children	Persons 1–12 years old should receive one dose
			At-risk adults	Persons older than 13 should receive two doses 4–8 weeks apart

of viral diseases and opened up the field of viral chemotherapy. The initial therapeutic armamentarium for viral diseases has been aimed at illnesses associated with significant mortality (e.g., ribavirin for Lassa fever, acyclovir for herpes simplex encephalitis) or those associated with significant end-organ damage (e.g., ganciclovir for cytomegalovirus [CMV] retinitis, acyclovir for ophthalmic zoster) (Table 128-3).

Amantadine and Rimantadine

Amantadine (Symmetrel) and rimantadine (Flumadine) are effective in preventing and treating influenza A but have no activity against influenza B. They prevent or greatly reduce the uncoating of the viral RNA of influenza A after attachment and endocytosis by host cells. When initiated before exposure to influenza A, amantadine, 200 mg/day orally, is effective in preventing illness in 50 to 90% of subjects. When begun within 2 days after the onset of symptoms of influenza A, amantadine has reduced the duration of fever and systemic symptoms by 1 to 2 days. The drug generally is well tolerated, with the most common therapy-limiting toxicities being central nervous system (CNS) effects, such as nervousness, lightheadedness, difficulty concentrating, insomnia, and decreased psychomotor performance. These reactions occur particularly in elderly patients who have impaired renal function; they should receive no more than 100 mg of amantadine daily. Rimantadine is mostly metabolized before renal excretion and is associated with a lower incidence of CNS toxicity than amantadine. Other side effects include nausea and loss of appetite. Overdose is associated with an anticholinergic syndrome.[12]

Prophylaxis with daily amantadine or rimantadine is indicated for the duration of the influenza season in persons at high risk for contracting influenza in whom the influenza vaccine is contraindicated. When influenza A is reported in a community, appropriate management is to administer the influenza vaccine and give amantadine for 2 weeks while antibody production is induced. Adults with acute onset of fever, cough, headache, and myalgias may be treated with 200 mg of amantadine, followed by 100 mg for 5 to 7 days.

Table 128-3 Drugs for the Treatment of Viral Illnesses

VIRUS	DISEASE	DRUG OF CHOICE	ALTERNATE TREATMENT	PROPHYLAXIS OR SUPPRESSIVE	COMMENTS
Cytomegalovirus	Retinitis	Ganciclovir, 5 mg/kg IV bid for 14–21 days, then 5 mg/kg IV qd Valganciclovir, 900 mg PO bid for 14–21 days, then 900 mg PO qd	Foscarnet, 90 mg/kg IV bid for 14–21 days, then 90–120 mg/kg IV qd Cidofovir, 5 mg/kg weekly IV for 2 weeks, then 5 mg/kg q2wk Ganciclovir implant Ganciclovir, foscarnet, or cidofovir intraocular injections		
	Colitis, esophagitis Pneumonitis	Same as for retinitis, but need for maintenance not established Ganciclovir, as above, with or without IV immunoglobulin Need for maintenance not established	Foscarnet, as above		
Hepatitis B	Chronic hepatitis	Interferon alfa, 5 million units SC or IM qd or 10 million units SC or IM 3 times/week for 16–24 weeks	Lamivudine, 100 mg PO qd for 1–3 years Adefovir, 10 mg PO qd	Hepatitis B immunoglobulin (HBIG)	See Chapter 89 for treatment guidelines
Hepatitis C	Chronic hepatitis	Peginterferon alfa-2b, 1–1.5 µg/kg SC weekly for 24–48 weeks *or* Peginterferon alfa-2a, 180 µg SC weekly for 24–48 weeks *Either with* Ribavirin, 1000–1200 mg PO daily in divided doses	Interferon alfa, 3 million units SC or IM 3 times/wk *with* Ribavirin, 1000–1200 mg PO daily in divided doses		See Chapter 89 for treatment guidelines
Herpes simplex virus (HSV)	Genital	Acyclovir 200 mg PO, 5 times/day, or 400 mg PO tid for 7–10 days If severe or complicated by asceptic meningitis, can give acyclovir, 5 mg/kg q8h for 5 days	Foscarnet 40–60 mg IV q8h (for acyclovir-resistant HSV)	Acyclovir 200–400 mg PO bid *or* valacyclovir 500–1000 mg PO qd *or* famcyclovir 250 mg PO bid	
	Mucocutaneous disease in immunocompromised host	Acyclovir 400 mg qid, famicyclovir 500 mg tid, or valacyclovir 500 mg bid for 7–14 days	Acyclovir 5 mg/kg q8h for 7–14 days	Variable regimen depending on length of immunocompromised state	
	Neonatal keratoconjunctivitis	Trifluridine 1% ophthalmic solution, 1 drop topically q2h, up to 9 drops daily for 10 days			
	Primary encephalitis	Acyclovir 10 mg/kg q8h for 14–21 days	Foscarnet 40–60 mg IV q8h (for acyclovir-resistant HSV)		

Continued

Table 128-3 Drugs for the Treatment of Viral Illnesses—cont'd

VIRUS	DISEASE	DRUG OF CHOICE	ALTERNATE TREATMENT	PROPHYLAXIS OR SUPPRESSIVE	COMMENTS
Human immunodeficiency virus (HIV)		Combination therapy with: Zidovudine Didanosine Zalcitabine Lamivudine Stavudine Abacavir Tenofovir Emtricitabine Saquinavir Ritonavir Indinavir Nelfinavir Amprenavir Atazanavir Fosamprenavir Nevirapine Delavirdine Efavirenz Enfuvirtide, T-20	See Chapter 130 for dosing and therapeutic combination therapy		See Chapter 130 for dosing and therapeutic combination therapy
Influenzavirus A	Influenza A	Oseltamivir, 75 mg PO bid for 5 days Rimantadine, 100 mg PO bid for 5 days	Zanamivir, 2 inhalations bid for 5 days Amantadine, 100 mg PO bid for 5 days		
Influenzavirus B	Influenza B	Oseltamivir, 75 mg PO bid for 5 days	Zanamivir, 2 inhalations bid for 5 days		
Lassa fever virus	Lassa fever	Ribavirin, 1 g IV q6h for 4 days, then 500 mg IV q8h for 6 days			Treatment for Lassa fever is investigational
Papillomavirus	Condyloma accuminatum	Interferon alfa-2b, 1 million units/0.1 mL intralesional injection in up to 5 warts three times/week for 3 weeks Imiquimod 5%, topical application to warts 3 times/week			
Respiratory syncytial virus (RSV)	Severe bronchiolitis or pneumonia in infants and children	Ribavirin aerosol, 12–18 hours daily for 3–7 days with a 20 mg/mL concentration reservoir		RSV immunoglobulin can be used for prophylaxis in young children Palivizumab, a monoclonal antibody, can be given monthly to premature infants	
Varicella-zoster virus (VZV)	Varicella (chickenpox) Herpes zoster (shingles) Varicella or zoster in an immunocompromised host	Acyclovir, 20 mg/kg, up to 800 mg, PO qid for 5 days Valacyclovir, 1 g PO tid for 7 days Famciclovir, 500 mg PO tid for 7 days Acyclovir, 10 mg/kg IV q8h for 7 days	Acyclovir, 800 mg PO 5 times/day for 7–10 days Foscarnet, 40 mg/kg IV q8h for 10 days (for acyclovir-resistant VZV)		

Zanamivir and Oseltamivir

Zanamivir (Relenza) and oseltamivir (Flumadine) were approved in 1999 for the treatment of influenza A and B. Both medications act by inhibiting the activity of neuraminidase, an enzyme involved in the release of viral progeny from infected cells. They have been shown to decrease the duration of moderate or severe symptoms of influenza by approximately 1 day. Either medication should be started within 2 days of onset of symptoms if efficacy is to be expected. Zanamivir is administered by inhalation through a novel device (Diskhaler) and is approved for use in patients older than 12 years. The dose is 2 inhalations twice a day for 5 days. Most of the inhaled dose is deposited in the respiratory tract and cleared unchanged in the urine or stool. The most common side effect is bronchospasm in predisposed patients. Such patients should be given a fast-acting inhaled bronchodilator before receiving zanamivir.[12,13]

Oseltamivir is an oral medication approved for patients older than 18 years of age. The dose is 75 mg twice daily for 5 days. It is cleared by renal secretion, and reduction of the dose to 75 mg once daily is recommended for patients with a creatinine clearance of less than 30 mL/minute. Initial reports of influenza virus resistance to oseltamivir were followed by a rapid rise in such resistance in H1N1 strains in the United States during the 2008-2009 influenza season.[13,14] This resistance was not seen in the H3N2 strain that was also circulating during the same season. This resulted in the CDC issuing interim treatment recommendations in December 2008. If treatment was based on the identification of the infecting virus, zanamivir was recommended as first-line treatment for H1N1 and oseltamivir for H3N2. If such data were not available to the treating physician, the CDC recommended that clinicians review local disease surveillance data to determine which subtype was more likely to be the offending agent and choose treatment accordingly.[13] It is unclear if these new recommendations will change during subsequent influenza seasons.

Acyclovir

Acyclovir (Zovirax) is one of the drugs of choice for serious infections caused by HSV or varicella-zoster virus (VZV). Only 15 to 30% of the oral formulation is absorbed, so the intravenous form is required to treat HSV encephalitis, disseminated or ophthalmic zoster, or extensive HSV or VZV infection in the immunocompromised patient. Oral acyclovir has some use in treating primary HSV infections and in suppressing frequent recurrences of these infections.[15] In general, the more immunocompromised the patient, the greater the likelihood that he or she will require intravenous acyclovir therapy. Acyclovir rarely is associated with gastrointestinal upset, reversible renal dysfunction, or encephalopathy. Acyclovir-resistant isolates have been found in immunocompromised patients receiving multiple courses of therapy for HSV and VZV infections. These isolates may be less virulent and may remain sensitive and respond to treatment with foscarnet.[16,17]

Famciclovir and Valacyclovir

Famciclovir (Famvir) and valacyclovir (Valtrex) are analogs of acyclovir that inhibit herpesvirus DNA synthesis.[18,19] They are much more bioavailable than acyclovir and can be given less frequently. Both are available only as oral formulations.

Ganciclovir

Ganciclovir (Cytovene) is used to treat life- or sight-threatening CMV infections in immunocompromised patients.[20] Patients with acquired immunodeficiency syndrome (AIDS) and CMV colitis or esophagitis may also improve with ganciclovir. Some CMV isolates in immunocompromised patients have been found to be or may become resistant to ganciclovir.[21] Ganciclovir also is effective against HSV, but isolates resistant to acyclovir also are resistant to ganciclovir.[16,17] The most common therapy-limiting toxic effects of ganciclovir are granulocytopenia and thrombocytopenia, which usually are reversible when therapy ceases.

Cidofovir

Cidofovir (Vistide) is a nucleotide agent used to treat CMV retinitis in patients with human immunodeficiency virus (HIV) infection and for acyclovir-resistant HSV infections. It is available only for parenteral administration but has a long half-life, allowing a once-weekly dosing schedule of once per week or less frequent administration.[22] The most common form of toxicity is renal insufficiency, which usually is reversible on discontinuation of the drug.

Foscarnet

Foscarnet (Foscavir, trisodium phosphonoformate hexahydrate, phosphonoformic acid) is an antiviral agent with activity against the human herpesviruses and HIV-1. It has been shown to be effective against CMV retinitis in AIDS patients and in acyclovir-resistant HSV and VZV infections.[16,21] The main limiting form of toxicity with foscarnet is renal insufficiency, which usually is reversible after the drug is discontinued. Other side effects include malaise, headache, fatigue, nausea, vomiting, anemia, hypomagnesemia, hypophosphatemia, hyperphosphatemia, and hypocalcemia.

Vidarabine

Intravenous vidarabine (Vira-A, Adenine Arabinoside, Ara-A) can be effective for life-threatening HSV and VZV infections, but because of its potential for toxicity, acyclovir and foscarnet have largely replaced it.[17]

Trifluridine

Trifluridine 1% ophthalmic solution (Viroptic, Trifluorothymidine) is effective for treating primary keratoconjunctivitis and recurrent epithelial keratitis caused by HSV. Treatment of ocular infections should be undertaken in consultation with an ophthalmologist. Duration of treatment depends on the lesions' response to the medication.

Interferon Alfa, Recombinant

Interferons are naturally occurring proteins with both antiviral and immunomodulating properties that are produced by host cells in response to an inducer. Injected intralesionally, recombinant preparations of interferon-alpha (interferon alfa-2a [Roferon-A], interferon alfa-2b [Intron A], peginterferon-alfa-2b [PEG-Intron]) are effective in treating refractory condyloma acuminatum.[23] High-dosage interferon therapy with subcutaneous injection of these agents has induced remission in cases of Kaposi's sarcoma associated with HIV-1 infection.[24] Patients with chronic hepatitis B who have lost hepatitis B e antigen with interferon therapy have better long-term outcome with

lower rates of end-stage liver disease and its complications.[25] Newer agents for treatment of hepatitis B infection include lamivudine, adefovir, entecavir, and telbivudine.[26] Interferon alfa-2b combined with ribavirin has been shown to induce virologic and histologic response in patients with chronic hepatitis C infection.[27] Therapy is discontinued because of side effects in approximately 20% of patients. The side effects of interferon therapy include fever, malaise, headache, fatigue, alopecia, and bone marrow suppression. Use of newer pegylated interferons is now standard therapy for hepatitis C.[28,29]

Therapy for HIV Infection

More than 30 antiretroviral drugs are currently available for the treatment of HIV infection (see Table 130-3). Treatment regimens usually include at least three of the recommended antiretroviral agents. Treatment of HIV infection is covered in Chapter 130.

Therapy for Hepatitis B Infection

At present, four antiviral agents are licensed for the treatment of chronic hepatitis B: lamivudine, adefovir, entecavir, and telbivudine. Additionally, emtricitabine, tenofovir, and their combined tablet, licensed for HIV infection, are off-label options. The treatment of hepatitis B infection is highly specialized. Treatment of hepatitis B infection is covered in Chapter 88.

■ SPECIFIC VIRAL DISEASES

Infections Caused by DNA Viruses

Poxviridae

The elimination from the natural environment of variola virus, the virus that causes smallpox, at one time the most devastating worldwide pestilence, is one of the great medical and public health accomplishments of the past century.[6] The elimination of smallpox from the natural environment was possible because of the lack of nonhuman reservoirs or human carriers of variola and the availability of rapid diagnostic techniques and an effective vaccine. Global eradication was certified by the WHO in 1980. Other human poxvirus diseases include monkeypox, vaccinia virus infection, molluscum contagiosum, orf, and paravaccinia virus infection. The poxviruses are the largest pathogenic viruses, consisting of complex, brick-shaped capsids and double-stranded DNA.

Variola (Smallpox), Monkeypox, Vaccinia, and Cowpox Viruses

Within the Poxviridae family, the orthopoxvirus genus contains at least nine homogeneous viruses, including variola, vaccinia, cowpox, and monkeypox viruses. The last naturally acquired case of smallpox occurred in Somalia in October 1977.[6] Two cases occurred in 1978 in Birmingham, England, related to a research laboratory accident.

Principles of Disease. Recently, the possibility that military and research stores of virus could become weaponized and used as tools of terrorism or war has mandated that health care professionals familiarize themselves with the manifestations of smallpox, the clinical manifestations of vaccine-related illness, and the risks and benefits of the vaccine. The Centers for Disease Control and Prevention (CDC) has established extensive web-based information and training materials in preparation for the possibility of an outbreak.

Clinical Features. Smallpox is transmitted by infected droplets or close contact with a patient in any stage of illness. The most common manifestation in the unvaccinated host is variola major, which has a fatality rate of approximately 30%. The illness is characterized by a short prodrome of headache, backache, and fever. An ensuing enanthem progresses from small macules to papules and then vesicles over a few days. Lesions begin on the face and limbs and spread in a centrifugal pattern. These develop into 4- to 6-mm firm, deep-seated vesicles or pustules that umbilicate, crust, and then desquamate over the next several weeks (Fig. 128-1). All lesions are at the same stage of development. Modified, milder forms of smallpox can appear in previously vaccinated patients and, more rarely, in nonimmune hosts. There are also two more rare, but almost uniformly fatal, forms of smallpox: a fulminant, "hemorrhagic" form and "flat type" smallpox, characterized by plaquelike lesions.[30]

Figure 128-1. Smallpox.

Major criteria for diagnosis include a prodrome of 1 to 4 days with fever (temperature higher than 38.3° C) with symptoms and signs such as headache and vomiting. Minor criteria include a centrifugal distribution of the rash, lesions on the palms and soles, a toxic appearance, and a rash that develops over several days. Routine laboratory tests are not helpful in the diagnosis. In the prodromal phase, there may be a relative granulocytopenia, but the white blood cell count usually is elevated in the eruptive phase. Laboratory diagnosis can be established by antibody testing, cell culture, or electron microscopy.

Differential Considerations. Smallpox has been confused with other papulovesicular eruptions, including varicella (chickenpox), measles, erythema multiforme, molluscum contagiosum, generalized vaccinia virus infection, and monkeypox. The lesions of chickenpox generally are at different stages of development and healing and often spare the palms and soles.

Management and Disposition. The CDC guidelines classify suspected cases of smallpox into categories of high, moderate, or low risk. Cases with high or moderate risk should prompt appropriate isolation and consultation with an infectious disease specialist or local health care authority. Quarantine, contact tracing, and immunization efforts are a priority for public health officials, and prompt involvement of the appropriate agencies will be crucial to containment efforts in the event of an outbreak.

Immunization with vaccinia virus was the cornerstone of smallpox containment and eradication efforts. Vaccinia virus immunization has been associated with morbidity and death in vaccinated persons and their close contacts. The decision to vaccinate must balance the risk of smallpox infection against the risk of vaccine-related injury. Pre-event vaccination is contraindicated in several groups of patients, including those who are pregnant, are breast-feeding, have significant immunosup-

pression, or have eczema. Close household contacts of persons at risk for serious side effects from vaccine should not be vaccinated. Recent mass vaccination campaigns have found a relatively low level of complications.[31] There are no absolute contraindications to vaccination for persons who have been exposed to smallpox.

Vaccinia Virus

The origin of the vaccinia virus is not well established. Edward Jenner, in his "An Inquiry into the Causes and Effects of the Variolae Vaccinae" in 1798, observed that the pustular material from the lesions of cowpox, when inoculated into humans, protected them from infection with smallpox.[1]

Cowpox Virus

Cowpox causes vesicular lesions on the udders and teats of cows. Human disease is manifested as vesicular lesions on the hands. Generalized infection is rare.

Monkeypox Virus

The disease of monkeypox is clinically similar to that of smallpox. Most cases have occurred in west and central Africa, with a case-fatality rate of 1 to 10% and higher death rates among children. An outbreak of 72 cases in the midwestern United States in spring 2003 was traced to contact with prairie dogs housed with Gambian giant rats that were imported from Ghana.[32] No deaths were associated with this outbreak.

Parapoxviruses, Molluscum Contagiosum, and Tanapox Viruses

Other viruses within the Poxviridae family that cause disease in humans include the parapoxviruses (paravaccinia virus and bovine pustular stomatitis virus) and the molluscum contagiosum and tanapox viruses. The milker's node virus, or paravaccinia virus, produces vesicular lesions on the udders or teats in cattle and is transmitted to humans by direct contact. Milker's nodules, which develop on the fingers or hands, are small, watery, painless nodules occasionally associated with lymphadenopathy. The lesions generally resolve completely within 3 to 8 weeks.

Bovine pustular stomatitis, ecthyma contagiosum, and orf viruses all cause papillomatous lesions on the mucous membranes and corneas of sheep. Single lesions generally develop in infected persons at the site of an abrasion.

Molluscum contagiosum is a generally benign human disease characterized by multiple small, painless, pearly, umbilicated nodules. They appear on epithelial surfaces, commonly in anogenital regions, and may be spread through close contact or autoinoculation. In immunocompetent persons, the lesions may clear rapidly or persist for up to 18 months. The infection often is seen in patients with HIV infection, in whom the lesions often are not restricted to the genital area and may increase in size and number.[33] Curettage or other forms of local ablation may be helpful in such recalcitrant cases.

Herpesviridae

At least eight human herpesviruses are known. Herpes simplex virus types 1 and 2 (HSV-1 and HSV-2) are the agents of herpes genitalis, labialis, and encephalitis. VZV is the agent of chickenpox and herpes zoster. Epstein-Barr virus (EBV) is the agent of infectious mononucleosis and also is associated with nasopharyngeal carcinoma, Burkitt's lymphoma, and other lymphoproliferative syndromes. Cytomegalovirus (CMV) is associated with heterophile-negative infectious mononucleosis and invasive disease in immunocompromised patients. Human herpesvirus-6 (HHV-6) is associated with roseola infantum.[34] The role of HHV-7 has not been completely elucidated. HHV-8 is associated with Kaposi's sarcoma,[35] body cavity–based lymphomas, and multicentric Castleman's disease. In addition, a closely related monkey virus, herpesvirus simiae or herpes B virus, has been shown to cause fatal encephalitis in humans.

Herpes Simplex Virus

Principles of Disease. A localized primary lesion, latency, and a tendency for local recurrence characterize infections with HSV-1 and HSV-2 (*Herpesvirus hominis*). The primary lesion with HSV-1 may be mild and inapparent; the first outbreak may occur during childhood. Reactivation of latent HSV-1 infection usually results in herpes labialis (cold sores, fever blisters). Neurologic involvement is not uncommon with HSV-1. Although such involvement usually occurs in association with a primary infection, neurologic signs may appear after a recrudescence and may manifest as encephalitis. Although uncommon, HSV-1 encephalitis is one of the most common causes of encephalitis in the United States, with estimates of several hundred to several thousand cases occurring yearly. HSV-2 most commonly is associated with genital herpes, although either HSV-1 or HSV-2 may infect any mucous membrane, depending on the route of inoculation. HSV-2 is commonly associated with aseptic meningitis rather than meningoencephalitis. The incubation period for primary herpes infection is 2 to 12 days.[36]

On contact with abraded skin or mucous membranes, HSV replicates locally in epithelial cells, which lyse and cause a local inflammatory response. Thin-walled vesicles on an erythematous base are the characteristic lesions of superficial HSV infection. Multinucleated giant cells with ballooning degeneration and intranuclear inclusions may be seen on a Tzanck preparation of a smear of material obtained from the base of these vesicles. After primary infection, HSV can become latent within sensory nerve ganglia. Emotional stress, sunlight, fever, or local trauma can trigger reactivation of the virus. HSV encephalitis usually involves the temporal lobes, resulting in a necrotizing, hemorrhagic encephalitis.

Clinical Features. Primary HSV-1 often is asymptomatic but may appear as pharyngitis and gingivostomatitis in children younger than 5 years. Associated with fever, pharyngeal edema, erythema, cervical adenopathy, and multiple small vesicles that ulcerate and multiply, the disease generally lasts 10 to 14 days. Recurrences occur in 60 to 90% of people after primary infection but generally are milder than the primary infection. Vesicles generally recur on the vermilion border, usually are small, and crust within 48 hours.

Herpes simplex infections of the eye most often are caused by HSV-1. Primary infections manifest as follicular conjunctivitis, blepharitis, or corneal epithelial opacities, which usually heal completely within 2 to 3 weeks. Recurrences may result in keratitis. Branching dendritic ulcers, detectable with fluorescein staining, are diagnostic and may result in diminished visual acuity. Deep stromal involvement may result in corneal scarring.

Primary herpetic finger infections (i.e., herpetic whitlow) generally are caused by HSV-1 among medical or dental personnel and by HSV-2 among the general population. The lesions are associated with intense pain and itching but generally resolve in 2 to 3 weeks. Recurrent whitlow with severe local neuralgia may occur.

Primary genital herpes generally is seen in the sexually active population and is caused by HSV-2 in 70 to 95% of cases. The lesions usually involve the shaft or glans of the penis in men and the vulva, perineum, buttocks, cervix, and vagina in women. Primary infection may be associated with

fever, malaise, anorexia, and inguinal adenopathy. Vaginal discharge is common. Urethral involvement resulting in urinary retention is not uncommon in women. Herpetic sacral radiculomyelitis is uncommon but also can lead to urinary retention, myalgias, and obstipation. The lesions can last for several weeks before completely clearing. Recurrences of genital herpes generally are shorter and milder than the primary episodes and may be preceded by a prodrome of tenderness, itching, or tingling. Healing of recurrent lesions generally is complete in 6 to 10 days.

Primary perianal and anal herpes is common among persons who practice anal intercourse and may be especially prolonged and severe among HIV-1–infected patients.

Neonatal herpes infection occurs in 7 in 100,000 births and is caused by the transmission of the virus at the time of delivery. The rate of infection is estimated to be 40 to 50% after a primary maternal infection and less than 10% after a recurrence.[37] The use of invasive monitoring and premature delivery also are associated with an increased risk of infection. [38] Infection may manifest after several days to weeks with vesicles or conjunctivitis; neurologic involvement, with seizures, cranial nerve palsies, lethargy, and coma, is common. Untreated disseminated or CNS disease is fatal in more than 70% of patients.

Encephalitis caused by HSV is uncommon, but it is the most common acute, nonepidemic encephalitis in the United States. Cases do not have a seasonal distribution. Other than in the neonate, HSV-1 is the usual pathogen. The clinical disease begins acutely, with fever and focal neurologic signs, often localized to the temporal lobe. The patient may complain of a bad odor not perceived by anyone else (temporal lobe hallucination). Common clinical manifestations include headache, meningeal signs, lethargy, confusion, stupor, and coma. Cerebrospinal fluid (CSF) findings are nonspecific, with a moderate mononuclear pleocytosis. Results of culture of the CSF generally are negative for HSV. Localization of the encephalitis within the temporal lobes by electroencephalogram, magnetic resonance imaging (MRI), or computed tomography (CT) scan increases the likelihood of a diagnosis of HSV encephalitis. The diagnosis of HSV encephalitis can be made reliably only with a biopsy of the lesion and subsequent isolation or detection of the virus by culture, direct fluorescent antibody tests, or polymerase chain reaction (PCR) assay.[39] The mortality rate among untreated patients approaches 80%, and less than 10% of patients are left with no neurologic sequelae. Treatment with acyclovir appears to reduce mortality and decrease the neurologic sequelae more effectively than treatment with vidarabine.[40]

Differential Considerations. The superficial lesions of HSV infection are indistinguishable from those of VZV infection. Pharyngitis and gingivostomatitis in children can mimic streptococcal or diphtheritic pharyngitis, herpangina, aphthous stomatitis, Stevens-Johnson syndrome, Vincent's angina, or infectious mononucleosis. Primary genital herpes can mimic the appearance of chancroid, syphilis, candidiasis, or Behçet's syndrome. In the neonate, in the absence of vesicles, congenital HSV infection can mimic disease caused by rubella, cytomegalovirus, or *Toxoplasma* organisms. Encephalitis caused by HSV may be clinically indistinguishable from other viral encephalitides, tuberculous and fungal meningitis, brain abscesses, brain tumors, and cerebrovascular accidents.

Management. Oral acyclovir (400 mg three times daily), oral valacyclovir (1 g twice daily), or intravenous acyclovir (5 mg/kg three times daily) is recommended for treating primary genital herpes or mucocutaneous herpes in the immunocompromised host, although some authorities use higher dosages in these patients.[41] Because of the safety and efficacy of oral acyclovir, there is little indication for using acyclovir ointment. In people with severe or frequent recurrences, acyclovir, ranging in doses from 200 mg five times daily to 800 mg once daily, can be used as an effective suppressive regimen. Both famciclovir and valacyclovir also are approved for suppressive therapy.

In the immunocompromised host, acyclovir is effective for both treatment and prophylaxis of recurrent mucocutaneous herpes. Foscarnet has been shown to be effective for the treatment of mucocutaneous herpes that is resistant to acyclovir.[16,17] Intravenous acyclovir, 10 mg/kg every 8 hours, is the treatment of choice for HSV encephalitis in adults and children. Vidarabine, 30 mg/kg/day IV, also is effective in neonatal encephalitis but is rarely used.[40]

Disposition. Patients with cutaneous HSV infections generally can be managed easily. The diagnosis often carries with it a great deal of stigma that must be addressed.[36] Assurance of the generally benign nature of the infection is helpful. Counseling should include cautions about the transmissibility of the virus, even during asymptomatic periods. Women of childbearing age should discuss management of HSV infection during pregnancy and delivery with their obstetricians.

Encephalitis caused by HSV constitutes a treatable medical emergency. Prompt recognition and institution of appropriate therapy in the ED before a definitive diagnosis has been made may decrease the high mortality rate and neurologic sequelae associated with this disease. When HSV encephalitis is suspected, empirical initiation of intravenous acyclovir is indicated in the ED. This approach has minimal toxicity and demonstrable efficacy.

Varicella-Zoster Virus

Varicella-zoster virus (VZV), or human (alpha) herpesvirus-3, is the agent of both chickenpox and herpes zoster, or shingles.

Clinical Features. Chickenpox is an acute, generalized viral disease characterized by sudden onset of fever, malaise, and a skin eruption that initially is maculopapular and then becomes vesiculated for several days before a granular scab is left (Fig. 128-2). Lesions occur in crops, with several stages present at the same time. Lesions can appear anywhere on the skin and mucous membranes. There may be few lesions and mild, inapparent infections. Most cases occur in children younger than 9 years; adults with the disease may have high fevers and severe constitutional symptoms. Children with acute leukemia are at increased risk for disseminated disease, which carries a case-fatality rate of greater than 5%. Neonates in whom varicella develops before 10 days of age and mothers who contract

Figure 128-2. Chickenpox.

Figure 128-3. Herpes zoster.

the disease in the perinatal period are at increased risk for generalized infection. Fatal disease in adults, although uncommon, usually is associated with pneumonic involvement. In children, fatal disease usually is associated with septic complications and encephalitis.

Herpes zoster is due to reactivation of VZV that has been latent in a dorsal root ganglion. Often preceded by tingling or hypesthesia, multiple vesicles on an erythematous base appear in crops along nerve pathways supplied by sensory nerves of a single or associated group of dorsal root ganglia. The distribution usually is unilateral and dermatomal (Fig. 128-3). Zoster occurs predominantly in older adults but has been seen in younger people when associated with HIV infection.[42] The lesions often are extremely painful. Postherpetic neuralgia is common in the elderly, can last for months or years, and is refractory to treatment. Involvement of the ophthalmic branch of the trigeminal nerve may lead to corneal ulceration.

Differential Considerations. With chickenpox and herpes zoster, the diagnosis is clinical. Laboratory tests generally are not required. Multinucleated giant cells may be seen on Tzanck preparations of material from the base of a lesion, but these also can occur in herpes simplex lesions. Scrapings also can be submitted for antibody-linked fluorescent microscopy testing, which will yield rapid results and differentiate between HSV and VZV infection.

Management. Using acyclovir for uncomplicated chickenpox in children is safe but only modestly effective. Parents of children with chickenpox should be cautioned not to give their children aspirin or aspirin-containing compounds because of the strong association between this practice and the development of Reye's syndrome.[43] Acetaminophen can be used as an antipyretic. Adults experience increased morbidity and mortality from chickenpox, so treatment of otherwise healthy adults with acyclovir, famciclovir, or valacyclovir frequently is indicated. Patients with pneumonitis or other severe illness should be treated with intravenous acyclovir. In immunocompromised patients, varicella-zoster immunoglobulin and intravenous acyclovir have been shown to decrease morbidity.

A live, attenuated vaccine that shows a high degree of protection for both normal children and children with leukemia was licensed in the United States in 1995. It is recommended for immunocompetent people older than 12 months. In those older than 12 years, two doses of vaccine are to be administered 4 to 8 weeks apart. It also is recommended for use as PEP in the nonimmune host. The vaccine is most effective in preventing or attenuating illness in these circumstances if it is administered within the first 3 to 5 days after exposure.[44] The vaccine is a live attenuated virus and not recommended for use in immunocompromised patients.

Uncomplicated herpes zoster generally is treated with supportive measures, especially pain control, and antivirals (acyclovir, famciclovir, or valacyclovir). Treatment with intravenous acyclovir should be considered for patients with disseminated disease and complicated zoster (involving more than one dermatome). Foscarnet is useful for treating infections due to acyclovir-resistant VZV in immunocompromised patients.[16] Famciclovir may decrease the duration of postherpetic neuralgia. Susceptible immunocompromised patients exposed to infected persons should receive varicella-zoster immunoglobulin within 72 hours to prevent or modify clinical illness.[44] Using corticosteroids to decrease the incidence of postherpetic neuralgia is controversial.

Herpes zoster is estimated to eventually occur in approximately 30% of the population, with the chance of an outbreak increasing with age. In persons older than 60 years, the possibility of developing postherpetic neuralgia is greater than 40%. Thus, it is currently recommended that immunocompetent persons older than 60 years be vaccinated with one dose of varicella zoster vaccine. [11]

Disposition. Chickenpox and herpes zoster are highly contagious. Although these diseases generally are benign, patients should avoid situations that put them in contact with steroid-treated or immunocompromised persons. The incubation period most commonly is 13 to 17 days, and the period of communicability may range from 5 days before to 5 days after the appearance of the vesicles. Susceptible persons should be considered potentially infectious from 10 to 21 days after exposure. Susceptible health care workers should not care for people with varicella or zoster. Health care workers without a well-documented history of chickenpox or herpes zoster should have antibody levels checked before they begin their employment to determine susceptibility to VZV, and they should strongly consider vaccination if they prove to be nonimmune.

Cytomegalovirus

Principles of Disease. CMV, or human herpesvirus-5, commonly is associated with heterophile-negative infectious mononucleosis syndrome and is clinically and hematologically similar to EBV-associated mononucleosis. More severe infections with CMV occur in the perinatal period and among immunocompromised patients. Severe CMV infections also are found in transplant recipients when organs from CMV-seropositive donors are transplanted into CMV-seronegative recipients.

Primary infection with CMV often is associated with a vigorous T lymphocyte response. CMV persists indefinitely, probably within multiple cell types in various organs. Reactivation leading to CMV-associated disease may occur in response to a variety of external stimulants.

Clinical Features. CMV infection in immunocompetent older children and adults generally is subclinical. It is characterized by fever, lymphadenopathy, exudative pharyngitis, and peripheral lymphocytosis, with atypical lymphocytes present on peripheral blood smears. The acute infection resolves in 2 to 4 weeks, but malaise and viral excretion can persist for months. In the perinatal period, severe, generalized infection can occur and may be associated with lethargy, convulsions, jaundice, petechiae, hepatosplenomegaly, chorioretinitis, and pulmonary infiltrates. Survivors may exhibit various degrees of neurologic impairment. Fetal infection can occur after primary or reactivated maternal infections, with primary infections carrying a much higher risk. Severe, generalized disease can occur in immunocompromised patients and often is associated with severe end-organ disease, such as colitis, esophagitis, pneumonitis, retinitis, and adrenalitis. Retinitis caused by CMV was the most common cause of blindness among people with AIDS in the pre-HAART era, but its incidence has fallen precipi-

tously. CMV can cause a polyradiculopathy and other, less common neurologic manifestations in patients with AIDS or other conditions of immunocompromise. Therapy with ganciclovir and foscarnet is indicated, but treatment results may be disappointing.[45]

Differential Considerations. Mononucleosis caused by CMV may be clinically indistinguishable from syndromes caused by EBV or *Toxoplasma*. In the perinatal period, infants with generalized infections require evaluation for other common perinatal infections, such as toxoplasmosis, rubella, syphilis, and HSV infection. Recipients of organ transplants and other immunocompromised patients with fever and other signs and symptoms of generalized infection require intensive evaluation for bacterial and viral causes of infection. Diagnosis of CMV infection depends on viral isolation, detection of CMV pp65 antigen, or the demonstration of a fourfold rise in antibody to viral antigens.

Management. Only supportive care is indicated for infected immunocompetent adults and children, and they generally can be managed at home. CMV infection in the perinatal period or complicated by impairment of immune function can be life-threatening, and patients in whom such infections are suspected generally require hospitalization for aggressive evaluation, monitoring, and specialized care. Valganciclovir, ganciclovir, foscarnet, and cidofovir all are useful in treating CMV infections in immunocompromised patients.

Epstein-Barr Virus (Infectious Mononucleosis)

Principles of Disease. EBV, or human herpesvirus-4, most commonly is associated with infectious mononucleosis, an acute viral syndrome characterized by fever, exudative pharyngotonsillitis, lymphadenopathy, and peripheral lymphocytosis with atypical lymphocytes. EBV also has been strongly implicated in the pathogenesis of African Burkitt's lymphoma and nasopharyngeal carcinoma. Acute immunoblastic sarcoma, involving a polyclonal expansion of EBV-infected B lymphocytes, may occur in people with an X-linked immunoproliferative disorder. Hodgkin's disease and other lymphomas in immunocompromised patients, such as renal transplant recipients or persons with AIDS, also have been associated with EBV infection. A chronic form of the disease has been suggested as the cause of chronic fatigue syndrome, but data supporting this association are limited.[46]

EBV infects and transforms B lymphocytes. Infection is common and widespread in early childhood in developing countries, where it usually is mild or asymptomatic. In developed countries, infectious mononucleosis usually manifests in older children and young adults, commonly among high school and college students. It is transmitted by way of the oropharyngeal route, often by kissing. The incubation period may be as long as 4 to 6 weeks, and pharyngeal excretion can persist for 1 year or more.

Clinical Features. The syndrome usually is mild in children, but 95% of young adults have abnormal transaminases and 4% have jaundice. Hepatosplenomegaly is common. Severe exudative pharyngitis, fevers, lymphadenopathy, and fatigue are characteristic of infectious mononucleosis. The disease generally resolves in 1 to 3 weeks, but malaise and fatigue rarely can persist for several months. Occasionally, tonsillar swelling causes respiratory compromise. Splenic rupture is rare but must be considered in patients with left upper quadrant pain and a falling hematocrit. Neurologic complications, including encephalitis, aseptic meningitis, transverse myelitis, Guillain-Barré syndrome, optic neuritis, and peripheral neuropathies, occur in less than 1% of patients.

Diagnostic Strategies and Differential Considerations. Laboratory diagnosis is based on the finding of lymphocytosis (greater than 50% of the total white cell count) or an elevation in heterophile antibodies (Monospot test). Heterophile antibodies are sensitive and specific antibodies that usually appear early in the illness. Other assays for virus-specific antibodies are available but rarely are needed to diagnose mononucleosis, because in 90% of cases the patient is heterophile-seropositive.

A presumptive diagnosis can be made on the basis of the finding of significant cervical lymphadenopathy, particularly posterior cervical, and exudative pharyngitis coupled with a lymphocytosis and the presence of atypical lymphocytes on a blood smear. HHV-6, cytomegalovirus, and toxoplasmosis can cause syndromes that are clinically and hematologically similar to infectious mononucleosis.

Management. Treatment is supportive only, except when rare complications of organ compromise are present. The use of corticosteroids in uncomplicated illness is controversial. These agents generally are used for impending airway obstruction, hemolytic anemia, or severe thrombocytopenia. Infection confers a high degree of resistance to reinfection. Patients should be cautioned about potential communicability to previously uninfected people.

Human Herpesvirus-6

Principles of Disease. HHV-6 has been implicated as an agent of roseola infantum (exanthem subitum).[34]

Clinical Features. Roseola infantum is the most common exanthem of children younger than 2 years of age and occurs most often at approximately 1 year of age. The illness begins abruptly with the acute onset of fever, often as high as 41° C, lasting 3 to 5 days. A fine, evanescent, rose-colored maculopapular rash appears on the trunk after lysis of the fever and lasts for 1 to 2 days. The rash may spread to the face and extremities. Most cases are self-limited, and despite the fever, the child usually remains active and alert. HHV-6–associated febrile seizures are thought to account for a significant percentage of ED visits for pediatric fever and febrile seizures.[47] Although secondary cases occur after an incubation period of approximately 10 days, most cases of roseola occur without known exposure.

Differential Considerations. The disease appears similar to other childhood exanthems. The child generally looks well despite the high fever.

Management. Acetaminophen may reduce the fever. Routine supportive measures should be used if febrile seizures occur.

Human Herpesvirus-7

HHV-7 has been associated with a clinical presentation similar to that for HHV-6, but its role in disease has not yet been fully elucidated.[48]

Human Herpesvirus-8 (Kaposi's Sarcoma–Associated Herpesvirus)

HHV-8 has been implicated as the cause of Kaposi's sarcoma regardless of the HIV serostatus of the affected patient.[49] Mechanisms of disease pathogenesis as well as epidemiology of transmission for this virus remain unclear and continue to be actively investigated.

Herpes B Virus

Principles of Disease. Herpes B virus, or herpesvirus simiae, a close relative of human herpes simplex virus, is enzootic in macaques and most commonly is associated with Rhesus, cynomolgus, or African green monkeys. Like human herpes simplex virus, herpes B virus produces mild disease in monkeys that is characterized by intermittent reactivation and shedding, particularly during times of stress, such as during handling. Among monkey handlers and those exposed to the animals' saliva or tissues, monkey B virus is a serious occupational hazard. Of 23 symptomatic human infections, 18 resulted in a progressive

mucocutaneous disease and fatal encephalitis.[50] The first known case of fatal herpesvirus B infection, from a mucosal splash exposure, occurred in 1998.[51]

Postexposure Management. The most important step that can be taken to prevent B virus disease is thorough cleansing of exposed tissues. Current recommendations are that mucous membranes be flushed with sterile saline or water for 15 minutes and that areas of exposed skin be washed for 15 minutes with a detergent or a solution containing disinfectants (such as chlorhexidine or povidone-iodine). Affected tissue (except ocular or mucous membranes) can be initially washed with 0.25% hypochlorite (Dakin's) solution before being washed with a detergent solution.

The decision to initiate PEP is based on the severity of the exposure and the appropriateness of first aid measures. PEP does not need to be initiated if the exposed skin is intact or the exposure is to a nonmacaque species of monkey. Valacyclovir, 1 g PO every 8 hours for 14 days, is recommended for PEP.[51]

Clinical Features. After a penetrating bite or scratch from an infected monkey, herpetiform vesicles may form at the site of the injury. Giant cells can be seen on a Tzanck preparation. An acute febrile illness with headache and lymphocytosis may follow as late as 3 weeks after the injury. An ascending myelitis ensues, leading to death from respiratory paralysis or encephalomyelitis within 3 weeks of onset of symptoms. The incidence of asymptomatic infection is unknown.

Differential Considerations. The initial skin lesions appear similar to those of herpes simplex. In the context of any exposure to monkey tissues and the appearance of a herpetiform lesion, the diagnosis of herpes B virus infection must be considered because of its associated high mortality rate.

Treatment. Suspected B virus infection constitutes a medical emergency. Anecdotal reports have described successful prevention of disease progression with intravenous acyclovir. The apparent response of the infection to appropriate regimens emphasizes the need for early recognition and treatment. If CNS symptoms are present, ganciclovir is the drug of choice.[51]

Adenoviridae

Adenovirus

Principles of Disease. Adenoviruses are the most clinically important viruses because of their capacity to cause upper respiratory tract infections, conjunctivitis, and gastroenteritis. Nevertheless, no drugs or therapeutic measures specifically effective for adenoviral infections are available.

Clinical Features. Adenoviruses cause respiratory diseases ranging from pharyngitis and tracheitis to fulminant bronchiolitis and pneumonia. Cough, fever, sore throat, and rhinorrhea are the most common symptoms and generally last only a few days. Pneumonitis with interstitial infiltrates are occasionally seen with some strains. Upper respiratory findings may be associated with conjunctivitis (pharyngoconjunctival fever). Adenoviruses may cause an epidemic keratoconjunctivitis, which in severe cases may be associated with conjunctival scarring. Other syndromes associated with adenoviruses include hemorrhagic cystitis, infantile diarrhea, intussusception, encephalitis, and meningoencephalitis.

Differential Considerations. Other pathogens causing similar atypical pneumonia syndromes include influenza and parainfluenza viruses and *Mycoplasma pneumoniae*. Diarrheal syndromes may be similar to those caused by rotaviruses.

Management. Treatment for adenovirus infections is supportive.

Papillomaviridae

Principles of Disease. HPVs cause a variety of cutaneous and mucous membrane lesions, including common warts, anogenital or venereal warts (condyloma acuminatum), and respiratory or laryngeal papillomas.

More than 70 types of HPVs have been identified. Laryngeal papillomas (most commonly caused by HPV types 6 and 11) and genital warts (most commonly caused by HPV types 16 and 18) can undergo malignant transformation.[52]

The association between HIV infection and more aggressive forms of HPV infection, including a greater likelihood for malignant transformation of lesions, has been shown.[53]

Clinical Features. Common warts generally are well-circumscribed, hyperkeratotic, painless papules occurring most commonly on the extremities and transmitted by close personal contact. Plantar warts, found on the soles of the feet, may be very painful. Venereal warts, found on the internal or external genitalia or perianal region, are hyperkeratotic, exophytic papules, either sessile or pedunculated, and are sexually transmitted. Laryngeal papillomas in children presumably are acquired during passage through the birth canal. Malignant transformation can occur, particularly in patients receiving radiation therapy.

Differential Considerations. The diagnosis of warts usually is made clinically. Condyloma acuminatum must be distinguished from the condyloma latum of syphilis. Diagnosis of cervical HPV infections can be made during colposcopy with previous application of a 3 to 5% acetic acid solution to the internal genital tract. Flat condylomata appear as shiny white patches with ill-defined borders and irregular surfaces. Acetowhitening also can reveal subclinical vulvar or penile warts.

Management. Genital warts generally regress spontaneously within months or years, and it is unclear whether their removal decreases infectivity or decreases the chance of malignant transformation. Therapy is at the discretion of the patient and the caregiver. Patient-applied therapies use podofilox 0.5% gel or imiquimod 5% cream. Freezing with liquid nitrogen, surgical removal, and intralesional interferons also are effective for most accessible lesions. Combination therapies also can be used.[54] Salicylic acid plasters and curettage are useful for plantar warts. Laryngeal warts require surgery or laser therapy.

Polyomaviridae

Principles of Disease. JC virus and BK virus are human polyomaviruses that cause ubiquitous but asymptomatic infection in populations worldwide. Progressive multifocal leukoencephalopathy (PML) is a rare, slowly progressive, demyelinating CNS disease associated with JC virus. The demyelinated lesions of PML slowly enlarge to become large plaques, associated with progressive neurologic deterioration, dementia, and eventually death. The disease occurs mostly in severely immunocompromised patients.[55] Similarly, BK virus viruria is relatively common in immunosuppressed patients or pregnant women. Rare, symptomatic infection can manifest as urethral stenosis in renal transplant recipients and as hemorrhagic cystitis in bone marrow transplant recipients.

Clinical Features. Initial presentations of PML in immunocompromised patients include paresis, personality changes, and impaired higher cortical functioning. The disease generally is rapidly progressive, usually progressing to death within 2 to 4 months of the initial neurologic symptoms. PML commonly is seen in people with advanced AIDS.[55]

Differential Considerations. Considerations in the differential diagnosis include other causes of progressive neurologic

disease in immunocompromised patients—toxoplasmic encephalitis, primary CNS lymphoma, HIV encephalopathy, tuberculous meningitis, vascular disease, and others. A lack of enhancement on contrast CT and MRI scans is helpful in making the diagnosis. PCR assay identification of JC virus in the appropriate clinical setting with consistent radiographic findings establishes the diagnosis.[56]

Management. No specific treatment for PML is available; the disease generally is rapidly progressive, and ultimate transfer to appropriate nursing care facilities often is necessary. Recently, there have been reports of significant improvements in persons with AIDS who have been placed on potent antiretroviral (anti-HIV) therapy.[57]

Hepadnaviridae

Hepatitis B Virus and Hepatitis Delta Virus

A description of hepatitis B and delta hepatitis can be found in Chapter 88.

Parvoviridae

Parvoviruses (Erythema Infectiosum, Aplastic Crisis)

Principles of Disease. Parvovirus B19 has been implicated as the causal agent in several epidemics of erythema infectiosum, or "fifth disease." It also is associated with transient aplastic crisis in patients with chronic hemolytic disease, particularly those with sickle cell disease. Infections during pregnancy have been associated with hydrops fetalis and spontaneous abortion.[58] Humans constitute the only reservoir for parvovirus B19. Transmission usually occurs through contact with aerosol or respiratory secretions. Transmission by contaminated blood products has been documented.

Clinical Features. *Erythema infectiosum* is a mild, usually nonfebrile disease of children between 4 and 10 years of age, characterized by a striking erythema of the cheeks—a "slapped-cheek" appearance (Fig. 128-4). The rash usually appears after an incubation period of 4 to 14 days without a prodrome. One to 4 days later, an erythematous rash on the extremities may be seen spreading to the trunk in a lacelike pattern. The rash generally fades within a week but can persist for several weeks and recrudescence can be precipitated by skin trauma or sunlight exposure. Constitutional symptoms generally are mild in children, but adults with the disease commonly have associated arthralgias and arthritis. Rare cases of encephalitis and pneumonia have been reported.

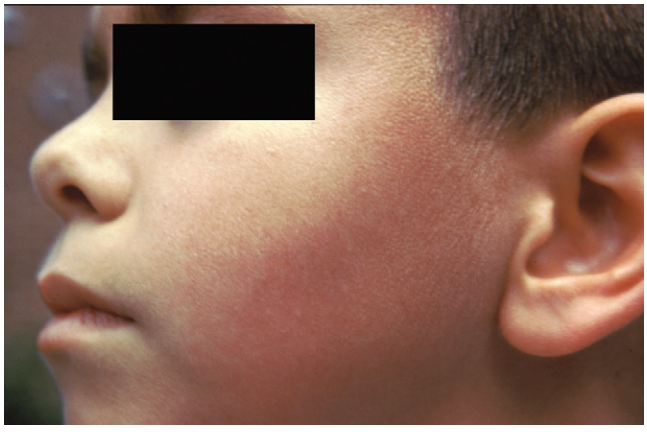

Figure 128-4. Erythema infectiosum.

Parvovirus B19 infects and causes a marked reduction in erythroid cell precursors and is a cause of transient *aplastic crisis* in patients with chronic hemolytic anemia. Recovery is associated with reappearance of reticulocytes in the peripheral smear 7 to 10 days after their disappearance. In patients with AIDS and other immunosuppressive illnesses, parvovirus B19 infection can manifest as chronic anemia. These patients often have persistent parvovirus infection without an appropriate immunoglobulin response.[59]

Differential Considerations. In children, erythema infectiosum resembles other viral exanthems. The "slapped-cheek" appearance of the rash is characteristic.

Management. Erythema infectiosum generally is a mild disease, and no treatment is required. Patients with parvovirus B19–associated aplastic crisis may require blood transfusions. Therapy with immunoglobulin can lessen the need for transfusions in immunosuppressed patients with chronic anemia.[60] Women in whom parvovirus infection develops during pregnancy should be followed closely for the development of nonimmune fetal hydrops. The role of intrauterine blood transfusions in the treatment of this disorder remains controversial.[58]

Infections Caused by RNA Viruses

Reoviridae

The family Reoviridae (*r*espiratory *e*nteric *o*rphan viruses) includes four viruses causing human disease: orthoreovirus, orbivirus, coltivirus, and rotavirus. The reoviruses commonly infect humans but infrequently cause human disease. Upper respiratory infections, exanthems, pneumonia, hepatitis, encephalitis, gastroenteritis, and biliary atresia have on occasion been associated with these viruses.

Colorado Tick Fever

Principles of Disease. Colorado tick fever, or mountain fever, is caused by a coltivirus similar to the orbiviruses that are transmitted to humans through the bite of the hard-shelled wood tick *Dermacentor andersoni*. It occurs primarily in the western United States, but a serotype has been isolated from the *Ixodes ricinus* tick in Germany and from the dog tick, *Dermacentor variabilis*, in Long Island, New York. Illness generally occurs in late spring through summer (see also Chapter 132).

Clinical Findings and Features. The incubation period for Colorado tick fever is 3 to 6 days, and a history of tick exposure is elicited in 90% of patients. The disease generally occurs in people engaged in activities that bring them into contact with ticks. The fever is biphasic, as indicated by a "saddle-back" curve plotting temperatures over time, with the patient initially acutely experiencing chills, lethargy, prostration, headache, ocular pain, photophobia, abdominal pain, and severe myalgias. The initial fever lasts 2 to 3 days, recedes for a similar period, and then is followed by a second fever lasting approximately 3 days. Rash, occasionally petechial, is uncommon, occurring in 5 to 10% of patients. Meningoencephalitis is a rare but serious complication in children. Convalescence lasts 1 to 3 weeks; one half of infected persons are viremic 4 weeks after the onset of illness.[61]

Differential Considerations. Colorado tick fever commonly is misdiagnosed as Rocky Mountain spotted fever. Patients with fever and rash after tick bites in endemic areas should be treated for Rocky Mountain spotted fever. Confirmation of the diagnosis of Colorado tick fever is by mouse inoculation or fluorescent staining of erythrocytes.

Management. Treatment is supportive and symptomatic.

Orbivirus

Six orbiviruses have been implicated in human disease. Changuinola virus is transmitted from *Phlebotomus* flies; Lebombo and Orungo viruses from mosquitoes; and Kemerovo, Lipovnik, and Tribec viruses from ticks. All six have been associated with febrile illnesses and, rarely, encephalitis.

Rotavirus

Principles of Disease. Rotaviruses derive their name from their wheel-like appearance on transmission electron microscopy. These organisms cause severe gastroenteritis in infants and young children, particularly between the ages of 6 months and 2 years; the gastroenteritis is manifested by severe diarrhea and vomiting, which often lead to dehydration and occasionally death.[62] In temperate climates, illness occurs mainly in the winter, commonly is associated with nosocomial infection, and is spread primarily from person to person by the fecal-oral route. The incubation period is approximately 2 days.

Clinical Features. Mucosal epithelial cells of the small intestine appear to be infected selectively, leading to shortening of villi and decreased absorption of salt and water. A secretory diarrhea is produced with impaired D-xylose absorption. Clinical disease ranges from asymptomatic to severe, fatal diarrhea and dehydration. The illness is abrupt in onset with nausea, vomiting, watery diarrhea, low-grade fever, headache, and myalgias. The course of the disease generally is 3 to 5 days in duration. Fatalities are common in developing countries but rare in developed regions of the world.[63] In newborns, rotavirus has been associated with neonatal necrotizing enterocolitis. Infections in adults usually are asymptomatic.

Differential Considerations. Rotavirus enteritis should be suspected in any child with watery diarrhea occurring during the cooler months of the year. Fecal leukocytes and erythrocytes generally are not seen in rotaviral diarrhea. Other enteric viruses can produce a clinical syndrome similar to that due to rotavirus. Radioimmunoassays, enzyme immunoassays, and latex agglutination methods for detecting antigen are highly reliable and available at most hospital laboratories.

Vaccination. An attenuated human rotavirus vaccine and a human-bovine reassortant rotavirus vaccine have been shown to be both efficacious and safe in trials conducted in both developed and developing countries.[64,65] Currently, the human bovine reassortant vaccine is approved in the United States as a three-dose (at 2, 4, and 6 months of age) orally administered live vaccine.

Management. Specific treatment for rotaviral infections is not currently available. Intravenous fluids provide effective therapy for dehydration, but if the patient tolerates oral fluids, oral rehydration using packaged oral rehydration salts can be used in the outpatient setting for mild to moderate dehydration.

Togaviridae

Alphavirus (Group A Arbovirus)

Principles of Disease. Arboviruses (*ar*thropod-*bo*rne viruses) are transmitted to humans by an arthropod vector; humans usually are an unimportant host in the reproductive cycle of the virus. Most arboviruses are mosquito-borne, but ticks, sandflies, gnats, and midges serve as important vectors for some diseases. The alphaviruses and flaviviruses are the most common arboviruses causing disease in humans, but some bunyaviruses, reoviruses, rhabdoviruses, filoviruses, arenaviruses, and orthomyxoviruses also are transmitted by arboviral vectors.

The alphaviruses are transmitted by the bite of a mosquito. The three alphaviruses that cause human disease in the United States are the agents of eastern equine encephalitis, western equine encephalitis, and Venezuelan equine encephalitis. Other important alphaviruses include the Chikungunya (Africa, Southeast Asia, Philippines), Mayaro (South America), O'nyongnyong (Africa), Ross River (Australia, South Pacific), and Sindbis (Africa, Asia, Soviet Union, Australia, and Scandinavia) viruses.

Clinical Features. These arboviruses can cause outbreaks of encephalitis in various parts of the United States.[66] The few annual cases of eastern equine encephalitis in the United States occur predominantly near freshwater swamps of the Eastern seaboard. Although more than 95% of cases are subclinical, the mortality rate among patients presenting with clinical encephalitis approaches 50%. Infections occur most commonly in children younger than 10 years of age or in the elderly. The onset of symptoms often is fulminant, with headache, fever, and convulsions progressing rapidly to decreasing level of consciousness and death. Focal neurologic deficits also may develop. Western equine encephalitis is present throughout the United States but occurs mostly in the western and central parts of the nation. Children younger than 1 year and elderly persons are most often affected. More than 99% of cases are inapparent, and the encephalitis usually is mild, with an associated mortality rate of approximately 3%. Venezuelan equine encephalitis is found predominantly in Central and South America, but the disease has been seen in Texas and Florida. Venezuelan equine encephalitis usually manifests as an influenza-like illness. One third of patients have encephalitis, with a mortality rate of less than 1%, predominantly in children.

Differential Considerations. Other viral causes of encephalitis in the United States include HSV, HIV, St. Louis encephalitis (a flavivirus), California (La Crosse) encephalitis (a bunyavirus), and the recently encountered West Nile–like encephalitis (a flavivirus).[67,68] Other viruses, such as mumps, rabies, polio, and other enteroviruses, can also manifest as encephalitides. The WBC count in the CSF of persons with eastern equine encephalitis may be very high, and the diagnosis of meningoencephalitis must be considered. Diagnoses can be confirmed by a rise in antibody titers.

Management. Management is supportive only. For people with expected intensive exposure to these viruses, an investigational vaccine may be available from the U.S. Army Medical Research Institute for Infectious Diseases in Fort Detrick, Maryland.

Rubella Virus (German Measles)

Clinical Features. Rubella is a mild febrile illness associated with a diffuse maculopapular rash, fever, malaise, headache, and postauricular, occipital, and posterior cervical lymphadenopathy (Fig. 128-5).

Transmission of rubella is through contact with respiratory secretions. The incubation period of rubella ranges from 12 to 23 days. Accompanied by viremia, the rash usually lasts 3 to 5 days. The disease is highly communicable from approximately 1 week before to 4 days after the onset of the rash. The most common complications of rubella are arthropathies, or frank arthritis, predominantly affecting the fingers, wrists, and knees; the arthropathies may persist for several months. Encephalitis and thrombocytopenia are rare complications.

Although the disease generally is a mild, febrile illness in children and adults, the consequences of rubella occurring during pregnancy (congenital rubella syndrome) may be tragic. Severe consequences include fetal death, premature delivery, and a variety of congenital defects, including hearing loss,

Figure 128-5. Rubella.

cataracts, retinopathy, mental retardation, and a variety of cardiac abnormalities. The younger the fetus is at the time of a maternal infection, the more likely it is that the fetus will be affected. During the first 2 months of pregnancy, the fetus has an approximately 90% chance of being affected. The risk decreases to approximately 80% during the third month and to 66% during the fourth month. No congenital defects were found in 106 children born to mothers after laboratory-proven maternal infection contracted after the 17th week of pregnancy.[69]

Differential Considerations. The rash associated with rubella ("third disease") is one of the classic common exanthems of childhood. It may be similar to the rash of measles (rubeola, or "first disease"), scarlet fever ("second disease"), a variant of scarlet fever or toxin-producing staphylococcal disease ("fourth disease"), erythema infectiosum ("fifth disease"), and roseola (exanthem subitum, or "sixth disease").[70]

Management. Rubella control is required to prevent birth defects in the offspring of women who develop the disease during pregnancy. In the United States, vaccination to prevent rubella is recommended for all children at the age of 15 months. Vaccination results in a greater than 95% seroconversion rate. Because of the production of a transient viremia, pregnancy should be delayed for 3 months after a susceptible woman has been vaccinated. No cases of the congenital rubella syndrome attributable to rubella vaccine occurred in more than 300 women inadvertently vaccinated during pregnancy who carried their infants to term.[71] There is no evidence of decreasing immunity with age. Persons with rubella should be cautioned to avoid contact with susceptible women. Because of an increasing failure to vaccinate susceptible persons, a moderate resurgence of rubella and a major increase in the congenital rubella syndrome in the United States occurred in 1990.[72] Since then, a general decline in rubella incidence has been observed, but outbreaks continue to occur, especially among foreign-born adults.[73]

Flaviviridae

Flavivirus (Group B Arbovirus)

More than 60 flaviviruses have been identified, with more than 20 causing human disease. Four of the most common, all transmitted to humans by a mosquito vector, are the agents of yellow fever, dengue, St. Louis encephalitis, and West Nile virus.

Clinical Features. *Yellow fever* is present in tropical South America and Africa. Fever, chills, headache, nausea, and vomiting follow a 3- to 6-day incubation period.[74] The disease may be biphasic, with fever, jaundice, hemorrhage, and characteristic "black vomit" (from the coagulopathy secondary to an affected liver) occurring after a brief period of remission. The case-fatality rate is 5%.

Dengue occurs in tropical areas worldwide. Classic dengue fever (breakbone fever) is a nonfatal disease characterized by fever, headache, arthralgias, weakness, nausea, and anorexia after an incubation period of 5 to 10 days. Patients may experience severe bone pain. A generalized macular rash that occasionally desquamates may be seen. The fever lasts 5 to 7 days, but the recovery period may be prolonged. Dengue hemorrhagic fever, characterized by increased vascular permeability and bleeding associated with thrombocytopenia, carries a mortality rate of less than 5% in people who receive good medical care but up to 50% in those left untreated. The number of reports of dengue transmission within the United States on the U.S.-Mexico border in Texas and in Hawaii has been increasing.[75,76] With a population that shows evidence of previous exposure to dengue fever and the continued presence of the *Aedes aegypti* mosquito, the potential for cases of dengue hemorrhagic fever in persons without a recent history of foreign travel certainly exists. The possibility of dengue fever and its hemorrhagic form should be considered in all persons presenting with suggestive symptoms, even if they have not traveled outside the United States.

St. Louis encephalitis occurs in the summer in most areas of the Western Hemisphere. After an incubation period of 4 to 21 days, infection with the St. Louis encephalitis virus can produce fever and headache, aseptic meningitis, or encephalitis. The mortality rate associated with the encephalitis approaches 10%. The disease commonly affects the elderly.

West Nile virus causes a febrile illness, with potential for meningoencephalitis. It was first described in the United States in 1999 but also has caused illness in many areas of Africa, Asia, and Europe.[77] In 2003, the CDC confirmed 9858 cases and 262 deaths attributable to West Nile virus, qualifying this epidemic as the largest outbreak of arboviral meningoencephalitis recorded in the Western hemisphere.[78] The primary cycle of infection is maintained by vector mosquitoes in bird populations. Humans are infected by cross-feeding mosquitoes. The virus has disproportionately affected certain bird populations in the United States, resulting in bird deaths. Recognition of this phenomenon led to early elucidation of the life cycle and has helped in characterization of the zoonotic activity of the virus.[68]

Non–arthropod-borne human cases from laboratory transmission and person-to-person transmission by blood transfusion, organ transplantation, maternal-fetal transmission, or breast-feeding have been documented. These modes of transmission account for a small number of cases.[77] It is now very clear that the virus has established itself in North America, and yearly outbreaks are to be expected. The peak incidence of disease is during the months of July through October; however, as the disease has moved into the southern states, transmission is being reported as early as April and as late as December.[77]

The incubation period for West Nile virus appears to be 3 to 14 days. West Nile fever will develop in 20% of infected persons, and meningitis or encephalitis will develop in 1 in 150.[68,79] West Nile fever usually is characterized by fever, headache, myalgia, anorexia, and lymphadenopathy; half of infected patients develop a maculopapular central rash. West Nile virus meningoencephalitis is characterized by fever, headache, mental status changes, and motor disturbances that range from generalized weakness to myoclonus, tremor, and parkinsonian movement disorders. A poliomyelitis-like syndrome has been described.[80] Cranial nerve and bulbar abnormalities can be seen.[81]

Laboratory testing is nonspecific. CSF findings in patients with meningoencephalitis are similar to those with other viral infections: elevated protein level, normal glucose level, and a mild to moderate pleocytosis with a lymphocytic predominance.[78] Viremia usually clears by the onset of meningoencephalitis, but IgM can be detected in the CSF. IgM levels in the serum can remain elevated long after clinical illness has resolved. Imaging studies are nondiagnostic, but the MRI scan can show nonspecific leptomeningeal inflammation.[78]

Disease outcome is related to patient age; elderly persons are at significantly higher risk for the development of encephalitis and death from West Nile virus infection.[78] Patients with disease severe enough to necessitate hospitalization often have long-term sequelae.

Differential Considerations. The differential diagnosis for yellow fever is broad in scope; considerations include hepatitis, malaria, typhoid, dengue, and other viral hemorrhagic fevers in endemic areas. Viral antigen detected in the blood by enzyme-linked immunoadsorbent assay provides for a rapid diagnosis. The differential diagnosis for dengue is similar to that for yellow fever. Diagnosis is made by viral isolation or serology. St. Louis encephalitis can manifest like other causes of meningoencephalitis. In the elderly, it may be misdiagnosed as stroke. Diagnosis is made by serology. West Nile virus infection occurs most often in the summer and fall and may be clinically indistinguishable from other arboviral illnesses. CSF IgM antibody testing is the best means of establishing the diagnosis, but results may be falsely positive after other flaviviral infections such as St. Louis encephalitis, or after immunization against yellow fever.[68]

Management. Treatment for these viral diseases is supportive. The diseases are not contagious through person-to-person contact, but the virus generally is transmissible to the mosquito vector during the period of clinical illness. Control of epidemics is achieved by reducing the mosquito vector populations and limiting access of mosquitoes to infected hosts. Persons traveling to endemic areas should be vaccinated for yellow fever.[82]

No recommended therapies are currently available for West Nile virus infection. Treatment is supportive. Suspected disease should be reported to public health authorities. Control of West Nile virus infection will rest in control of vector mosquito populations. Physicians should join public health officials in aggressive efforts to educate the public on mosquito control and bite protection measures, such as the use of repellents and protective clothing.

Hepatitis C

Hepatitis C, now classified in its own genus, *Hepacivirus*, within the Flaviviridae, is an important contributor to morbidity and mortality throughout the world. In the United States, hepatitis C formerly was associated with most cases of post-transfusion (non-A, non-B) disease. As a result of testing the blood supply, the incidence of transfusion-related hepatitis C has decreased. However, the prevalence of infection remains high in certain populations, such as injection drug users. In the United States, it is estimated that 3.9 million people have hepatitis C infection.[83]

Chronic hepatitis C infection has been associated with cirrhosis and hepatocellular carcinoma. Estimates of the rate of long-term morbidity and mortality resulting from chronic hepatitis C vary. The likelihood of developing cirrhosis ranges from 5 to 25% in different studies.[84] Hepatitis C is discussed further in Chapter 88.

Coronaviridae

Coronavirus

Principles of Disease. The severe acute respiratory syndrome (SARS) was first documented in China's Guangdong province in November 2002. By the time the epidemic was contained in July 2003, it had affected approximately 8000 persons in 29 countries, with a case-fatality rate of approximately 10%.[85] The causative agent was identified as a novel coronavirus (SARS-CoV).[86,87] Early in the epidemic, astute researchers noted that the illness was more prevalent among restaurant workers and focused attention on live animals that were being sold for human consumption. Their efforts revealed that the virus was transmitted to humans by handling and consumption of wild mammals, such as the civet.[88]

By 2003, 161 cases of SARS had been reported in the United States. Of these, 8 were confirmed and 153 are still under investigation, but no U.S. deaths were reported that were attributable to SARS.[85] Most patients had traveled to an area of documented or suspected SARS transmission.

The SARS epidemic has posed a challenge to national and international agency-based medical personnel and public health authorities. Public health measures have been implemented to contain the infection and establish sentinel systems to warn of recurrent outbreaks. Health care practitioners, especially ED personnel, should notify local public health authorities of suspected or confirmed cases of SARS.

Clinical Features. The current CDC case definition for SARS-CoV disease includes the presence of laboratory-confirmed infection or severe respiratory illness in the setting of epidemiologic criteria for likely exposure to SARS-CoV.[85] *Early disease* is defined by the presence of two or more of the following features: fever (which may be subjective), chills, rigors, myalgia, headache, diarrhea, sore throat, and rhinorrhea. *Mild to moderate disease* requires presence of fever with temperature greater than 38°C and evidence of lower respiratory tract illness. *Severe respiratory illness* is defined as noted previously but also includes radiographic evidence of pneumonia or acute respiratory distress syndrome. Laboratory diagnosis of the disease relies on SARS-CoV antibody testing, cell culture, or reverse transcription–PCR techniques. Epidemiologic criteria for *possible exposure* include travel within the past 10 days to an area with documented or suspected recent transmission of SARS-CoV or close contact with a symptomatic person who recently engaged in such travel. Epidemiologic criteria for *likely exposure* requires that transmission be somehow linked to a person with confirmed disease. [85]

Retrospective analyses of the SARS-CoV infection outbreak suggest an incubation period of 3 to 10 days with an ensuing viral prodrome characterized by headache, malaise, and myalgias. Fever, clinical evidence of upper and lower respiratory infection, dyspnea, and gastrointestinal disturbances also may be features. Chest radiographs are normal in appearance in up to 25% of patients with early infection, despite the presence of fever and respiratory complaints.[89,90] CT scans may be more useful in identifying early pulmonary involvement. Hypoxemia, with clinical and radiographic evidence of pneumonitis,

develops as the disease progresses. In a minority of patients, progressive respiratory failure and acute respiratory distress syndrome may follow. Patients older than 60 years and those with comorbid illness such as diabetes mellitus have worse outcomes.[89-91]

Laboratory findings are nonspecific but include lymphopenia, thrombocytopenia, elevated lactate dehydrogenase, and prolonged activated partial thromboplastin time. Hemolytic anemia and electrolyte disturbances, such as severe hypomagnesemia with associated tetany, have been reported.[92]

Differential Considerations. The clinical features of SARS-CoV mimic those of many community and nosocomial respiratory infections, so the differential diagnosis is quite broad in scope. The initial workup should include routine laboratory and radiographic evaluations similar to those for workup of other, more common respiratory infections. A greater level of suspicion for SARS-CoV infection should be entertained based on travel or exposure history. Specific testing for coronavirus can be conducted through the health department.

Several outbreaks of SARS-CoV infection have occurred after exposure of patients or medical staff to a sentinel case or to a clinical specimen.[93] Therefore, effective evaluation and management of suspected or proven cases of SARS-CoV disease must begin with a travel and occupational history, astute clinical observation, appropriate triaging, and patient isolation measures. Quarantine of persons who may be in the incubation period has proved useful in containing outbreaks.[93] Contact and airborne precautions should be instituted and protective eyewear should be considered. Detailed guidelines for the diagnosis, isolation, treatment, and disposition of patients with suspected or proven SARS-CoV infection are continuously being updated by the WHO and the CDC. These guidelines are available at www.cdc.gov and www.who.int; local health officials also can be contacted for guidance.

Management. No therapeutic measures beyond supportive care have been shown to be clearly effective for the treatment of SARS-CoV infection.[89,92,94] Patients manifesting signs and symptoms of lower respiratory tract infection should be treated with conventional antibiotic and supportive therapy, even if they are suspected of having SARS-CoV infection.

Disposition. It is not necessary to hospitalize all patients who are suspected to have been exposed to or have a respiratory syndrome that could be attributed to SARS-CoV infection. Persons well enough to be cared for at home should be placed in home quarantine with contact and air-borne precautions. Termination of quarantine precautions for suspected SARS-CoV infection should be done in consultation with public health officials.

Other Coronaviruses

Principles of Disease. Coronaviruses are agents of the common cold in adults and of lower respiratory tract disease in children. More recently, they have been implicated in diarrheal disease in children.

Clinical Features. Coronaviruses primarily cause upper respiratory tract disease in adults. Lower respiratory tract infections caused by coronaviruses occur uncommonly in adults and more commonly in children. They appear to cause diarrheal disease in children younger than 1 year of age.

Differential Considerations. Coronaviruses probably account for 15% of adult colds. Rhinoviruses account for most of the rest, with parainfluenza viruses, influenza viruses, respiratory syncytial viruses, adenoviruses, and enteroviruses also causing upper respiratory infections and colds. Rotaviruses, Norwalk viruses, and enteroviruses cause most viral cases of gastroenteritis in children.

Management and Disposition. Treatment of most coronaviruses is supportive only.

Paramyxoviridae

Parainfluenza Viruses

Clinical Features. The parainfluenza viruses are the most common causes of croup in children and, along with the respiratory syncytial virus (RSV), are the most common causes of lower respiratory tract infections that require hospitalization in infants.[95]

The virus is passed by way of the respiratory route, and hand–to–mucous membrane transmission is the likely mode of spread. The incubation period most often is 1 to 4 days, and the clinical picture is that of a febrile illness lasting approximately 4 days.

Infection with the parainfluenza viruses does not confer lasting immunity. Parainfluenza virus type 1 is the predominant cause of croup, or laryngotracheobronchitis, occurring during the autumn months in children younger than 3 years. Parainfluenza virus type 2 also is associated with croup, causes less morbidity than type 1, and often occurs in alternate years with type 1. Parainfluenza type 3 infections occur in the spring and are associated with bronchiolitis and pneumonia in infants younger than 1 year, similar to RSV. Parainfluenza type 3 also is associated with croup in children younger than 3, and with tracheobronchitis in older children. Parainfluenza type 4 is recovered less often but appears to be associated with mild respiratory illness. Severe croup or bacterial superinfection of laryngotracheitis may lead to respiratory compromise.

Differential Considerations. Viruses causing upper respiratory tract infection similar to that caused by the parainfluenza viruses include adenoviruses, rhinoviruses, influenza virus, RSV, echoviruses, coxsackieviruses, and coronaviruses. Identification of parainfluenza viral infection can be made by demonstrating a fourfold rise in antibody titer between acute and convalescent serum.

Management. Croup may be worse at night; mist inhalation often is helpful. Treatment with nebulized racemic epinephrine can be used to treat severe croup, but the relief it affords can be short-lived, and return to pretreatment state can be seen within 2 hours of therapy. Intramuscular steroids have been shown to be helpful, and their use has been associated with a decreased requirement for hospitalization of children with croup.[95] A single dose of oral dexamethasone at 0.6 mg/kg has been shown to reduce return visits to a health care practitioner.[96] The parainfluenza viruses can cause reinfection within months of the primary infection, so prevention of infection is unlikely to be feasible. More aggressive tracheal diseases, such as larygotracheobronchitis and laryngotracheobronchopneumonitis, may be caused by viruses but most are often a result of superinfection with bacteria, including *Staphylococcus aureus* and group A streptococci.[97]

Respiratory Syncytial Virus

Principles of Disease. Infections with RSV occur worldwide, mostly in midwinter to late spring. Infants with pneumonia show marked inflammation in the interstitial tissue and alveoli of the lungs, whereas infants with bronchiolitis show less alveolar involvement but may exhibit marked changes in the bronchioles. Severe disease may result in obstruction of bronchioles with evidence of peripheral airway obstruction or emphysema. Transmission is through contact with respiratory secretions and probably also by hand-to-nose or eye droplet inoculation.

Infections caused by RSV account for the largest number of hospitalizations for respiratory infections in infants. Bronchiolitis and pneumonia, the most severe manifestations of RSV infection, commonly occur in children younger than 6 months. Children older than 1 year are less likely to have lower respiratory tract infection.[98] Older children and adults commonly

have colds and cough, but older patients may have severe disease.

Clinical Features. The average incubation time for RSV infections is 2 to 8 days. The most common manifestations are bronchiolitis and pneumonia in infants; tracheobronchitis, croup, and otitis media in young children; and upper respiratory infections in older children and adults. Bronchiolitis in infancy may lead to an increased risk of asthma and the development of chronic obstructive airway disease in later life. Fatal disease can occur in immunocompromised infants.

The diagnosis of RSV infection can be made definitively by culturing the virus or detecting RSV antigens from respiratory secretions, nasal wash specimens, or nasopharyngeal or throat swabs.

Differential Considerations. The syndromes associated with RSV infections overlap those due to other upper and lower respiratory tract pathogens, including rhinovirus, parainfluenza and influenza viruses, echoviruses, coxsackieviruses, and coronaviruses. RSV infection can be presumptively diagnosed in an infant with pneumonia or bronchiolitis when no bacterial pathogens are noted. Noninfectious causes for hypoxemia in infants, such as foreign-body aspiration and asthma, also must be considered.

Management. Therapy of RSV infection is largely supportive. For infants sick enough to be hospitalized, aerosolized ribavirin has been shown to shorten the duration of illness and ameliorate hypoxemia in normal infants.[99] Corticosteroids have not been shown to be beneficial. During the winter, high-risk infants can be protected against RSV infection with monthly infusions of human RSV immunoglobulin or with monthly intramuscular injections of a monoclonal anti-RSV antibody preparation.[99] Severe disease may occur in immunocompromised infants, and respiratory precautions are required to prevent transmission from patient to patient and staff to patient.

Mumps Virus

Principles of Disease. Mumps, or infectious parotitis, is an acute viral illness characterized by fever, swelling, and tenderness of the salivary glands, with the parotid gland most commonly involved. Mumps occurs most commonly in the winter and spring and, since the advent of widespread pediatric immunization, mostly in older children. The virus is spread by way of the respiratory tract and through direct contact with the saliva of infected people. The incubation period is 2 to 4 weeks, and the disease is communicable from 1 week before to 9 days after the onset of parotitis, with a period of maximal infectiousness approximately 2 days before the onset of illness. One third of cases are asymptomatic.

Clinical Features. Nonsuppurative parotid swelling is the hallmark of mumps; the swelling may be unilateral. Trismus sometimes is a feature. In the first 3 days, the patient's temperature may range between normal and 40°C. The most important but less common manifestations are epididymo-orchitis and meningitis. Orchitis occurs in 15 to 25% of postpubertal male patients and usually is unilateral. Although some degree of testicular atrophy is usual, the incidence of sterility is very low, especially when the orchitis is unilateral.[100] More than 50% of patients with mumps have a lymphocytic pleocytosis in the CSF, and hypoglycorrhachia is common; symptomatic meningitis occurs in less than 10% of cases. Encephalitis is uncommon, occurring in 1 in 6000 cases, and is the major determinant of mortality. Congenital infection is rare but may result in fetal loss if it occurs in the first trimester.[101] Rare complications of mumps include hydrocephalus, deafness, transverse myelitis, Guillain-Barré syndrome, pancreatitis, mastitis, oophoritis, myocarditis, and arthritis.

Differential Considerations. In children, the diagnosis of mumps is made by a history of infectious exposure and the presence of parotid swelling and tenderness in association with constitutional symptoms. Laboratory confirmation generally is not required. Considerations in the differential diagnosis include other viral infections and other causes of parotid swelling and tenderness, such as bacterial parotitis or sarcoidosis.

A multistate outbreak of mumps was reported in the United States in 2006, with almost 6000 reported cases.[102] Because the likelihood of infection was five times higher in persons who had received only one dose of mumps vaccine as opposed to those who had received two doses of the vaccine, updated recommendations that all persons receive two doses of mumps vaccine were introduced by the CDC's Advisory Committee on Immunization Practices.[103]

Management. Treatment is supportive and should include an analgesic and an antipyretic agent. No data support the use of steroids to prevent complications of or ameliorate the symptoms of orchitis in postpubertal men.

Contacts who have had no history of mumps or of previous vaccination should be immunized. Because there is no risk in vaccinating those who are already immune, serologic screening to identify susceptible people is unnecessary. Long-lasting immunity develops in more than 95% of recipients of the vaccine. Among previously infected people, including those who had asymptomatic disease, long-lasting and possibly lifelong immunity is possible.

Measles Virus (Rubeola)

Principles of Disease. Measles is a highly communicable viral illness acquired as an infection of the respiratory tract. Generally, all susceptible people exposed to an active case will acquire infection. After multiplication in the respiratory mucosa, the virus spreads to regional lymphoid cells and then travels in the bloodstream to leukocytes in the reticuloendothelial system. The clinical manifestations appear after a second viremic phase.

Before the availability of an effective vaccine in 1963, measles was a ubiquitous disease. In 2006, measles accounted for approximately 240,000 deaths globally; in view of higher death rates in previous years, it is clear that great strides have been made to decrease measles deaths in many areas of the world. Measles continues to be a leading cause of death in young children, especially those living in developing countries.[104] Endemic measles in the United States has been eradicated, although the disease continues to occur among inadequately vaccinated persons who, in most instances, have been exposed to the disease by someone who has been infected abroad.[105] Measles is a reportable disease, and the local health authority should be contacted. Children should be kept out of school for at least 4 days after the appearance of the rash.

Clinical Features. The incubation period of measles is 10 to 14 days. Cough, coryza, conjunctivitis, and fever precede development of the characteristic rash by 2 to 4 days (Fig. 128-6A). Pinpoint grayish spots surrounded by bright red inflammation (Koplik's spots) typically are found on the lateral buccal mucosa before the appearance of the rash and are considered pathognomonic for measles (see Fig. 128-6B). Discrete red macular and papular lesions begin on the head and progress downward over a period of 3 days to cover the entire body. Laryngitis, tracheobronchitis, bronchiolitis, and pneumonitis may accompany the disease. Bacterial superinfections occasionally delay recovery. A rare acute encephalomyelitis, associated with a mortality rate of 25%, can complicate recovery. Unlike rubella, measles acquired during pregnancy is not teratogenic but may result in stillbirth or premature delivery.

Figure 128-6. **A,** Measles. **B,** Koplik's spots due to measles.

Among infants and malnourished children, more severe illness is usual. Deaths from pneumonia and diarrhea occur in up to 10% of cases. Measles can exacerbate vitamin A deficiency and lead to blindness.

Measles may manifest with atypical findings in people who were vaccinated with the inactivated vaccine before its removal from the market in the United States in 1968. An atypical rash, predominantly on the extremities, can accompany pneumonitis, pleural effusion, and peripheral edema. The current vaccine is a live, attenuated strain available as a single antigen or in combination with rubella vaccine or with mumps and rubella vaccines.

Differential Considerations. The diagnosis is made primarily on the basis of clinical characteristics. Other viral exanthems may at times manifest with a similar rash.

Management. Treatment of the primary disease is supportive. Immunocompromised children and infants younger than 1 year who are susceptible and have been exposed to measles can be given passive immunization within 6 days of exposure. Healthy infants should receive 0.25 mL/kg of immunoglobulin intramuscularly, and immunocompromised children should be given 0.5 mL/kg intramuscularly, up to 15 mL.

Subacute Sclerosing Panencephalitis

Principles of Disease. Subacute sclerosing panencephalitis (SSPE) is a degenerative disease of the brain caused by measles virus or a defective variant that persists in the CNS after primary measles. SSP has virtually disappeared in the United States since the 1970s, approximately 10 years after measles vaccination began.

Clinical Features. SSP is a subacute encephalitis involving both the white and the gray matter of the cerebral hemispheres and brainstem and follows 1 in 100,000 cases of measles. It generally occurs in patients with a history of an uncomplicated case of primary measles that occurred at a younger-than-average age. Five to 10 years later, subacute SSP manifests with myoclonus and variable focal neurologic deficits. Progressive neurologic degeneration ensues, and death usually occurs within months to years of diagnosis.

Differential Considerations. The disease can resemble other degenerative neurologic disorders, but characteristic electroencephalographic changes and the detection of measles antibodies in the CSF and markedly elevated serum antibodies to measles will confirm the diagnosis.

Management. Treatment is supportive only.

Rhabdoviridae

Within the Rhabdoviridae family of viruses are two genera, *Lyssavirus*, containing the rabies and rabies-like viruses, and *Vesiculovirus*, containing the vesicular stomatitis and related viruses. Six lyssaviruses are known, but only the rabies, Duvenhage, and Mokola viruses are known to cause disease in humans. Rabies is discussed further in Chapter 129.

Vesicular Stomatitis Virus and Related Viruses

Vesicular stomatitis virus commonly infects wild and domestic animals and occasionally infects humans. Transmission is believed to be through insect bites. Vesicular stomatitis virus New Jersey type and vesicular stomatitis virus Indiana type produce an influenza-like febrile illness 1 to 2 days after exposure that lasts 4 to 7 days. Oral vesicular lesions occasionally have been noted.[106] Accompanying disease manifestation can be nonspecific. Diagnosis can be made serologically. Treatment is supportive.

Filoviridae

Marburg and Ebola Viruses

Principles of Disease. Marburg and Ebola viruses cause a systemic febrile illnesses associated with multiorgan failure. Although the viruses have infected African green monkeys and cynomolgus monkeys, respectively, the infection is fatal to the monkeys, and the natural reservoir is unknown. Recent reports indicate a possible reservoir in certain bat species, but definitive proof is pending.[107] Monkey-to-human and human-to-human transmission through contact with contaminated tissues or materials has been documented. Aerosol transmission has not been reported.

Clinical Features. The illness is of sudden onset 2 to 10 days after exposure to infected tissue or contact with contaminated materials. Headache, fever, myalgias, arthralgias, and lethargy are early signs. The cardinal sign is diffuse coagulopathy. With both Marburg and Ebola infections, documented mortality rates are greater than 90%. Human infection with Marburg virus was documented in Germany and the former Yugoslavia as a result of contact with imported green monkeys. Human outbreaks also have been documented in the Democratic

Republic of the Congo and Angola.[108] To date, approximately 1850 cases of Ebola have been documented worldwide, with more than 1200 deaths.[107]

Differential Considerations. Marburg and Ebola virus diseases may appear clinically similar to other African hemorrhagic fevers, particularly Rift Valley fever, Lassa fever, and yellow fever. Diagnosis is made by isolation of the virus from blood or demonstration of rising antibody titers.

Management. No vaccine exists; treatment is supportive.[109]

Orthomyxoviridae

Influenza Virus

Principles of Disease. Influenza generally is a self-limited infection of the upper respiratory tract associated with fever, cough, coryza, sore throat, and malaise.[13] Three types of influenza are recognized. Type A has been associated with most widespread epidemics and pandemics and is associated with most of the deaths caused by influenza. Influenza B causes regional or widespread epidemics every 2 to 3 years. Influenza C is associated with sporadic cases.

Clinical Features. The usual clinical disease caused by influenza begins 1 to 4 days after exposure to aerosol respiratory secretions. Clinical manifestations include fever accompanied by myalgias, coryza, conjunctivitis, headache, and a nonproductive cough. Patchy infiltrates can be seen on the chest radiograph. Signs and symptoms generally last only a few days, but fatigue and malaise may persist for weeks. The most common serious complications of influenza, particularly among the elderly and persons with chronic diseases, are pneumonia caused by influenza itself and pneumonia attributable to secondary bacterial infections. Rare complications of influenza infection include aseptic meningitis, pericarditis, and a postinfectious neuritis that resembles the Guillain-Barré syndrome.

Viral culture remains the "gold standard" modality for the laboratory diagnosis of influenza, but results often are not timely enough to aid in clinical decisions regarding therapy. Several rapid assays using nasal specimens for the diagnosis of influenza A and/or B are commercially available. Positive bedside test results are associated with increased use of antivirals and decreased use of antibiotics in both pediatric and adult patients.[110,111]

Differential Considerations. The syndromes produced by the influenza viruses overlap with those produced by other viruses such as the parainfluenza viruses, RSV, adenoviruses, coronaviruses, and echoviruses.

Management. General supportive measures will ameliorate the symptoms of influenza. The neuraminidase inhibitors zanamivir and oseltamivir have been approved for treating both influenza A and B. The dose of oseltamivir should be decreased to 75 mg once daily in patients with creatinine clearance less than 30 mL/min. Zanamivir or oseltamivir should be administered within 2 days of onset of symptoms if efficacy is to be expected.[14] Vaccination is recommended yearly for all children 6 months to 4 years of age, adults older than 50 years, and persons at high risk for significant morbidity or death from influenza; these include immunosuppressed patients, those with chronic illnesses, and pregnant women. Vaccination is also recommended for health care workers and persons who are household contacts of infected persons younger than 5 or older than 50 years. In addition, the CDC recommends annual vaccination for all persons "who want to reduce the risk of becoming ill with influenza or of transmitting influenza to others."[13] Aspirin and aspirin-containing products should be avoided, especially among children and adolescents, particularly during influenza epidemics, because of the association between the use of aspirin during a bout of influenza and the subsequent development of Reye's syndrome.[42]

A highly pathogenic strain of avian influenza virus, H5N1, was first reported in a farmed goose in China in 1996.[112] Since then, the virus has spread among wild birds and poultry across the Asian continent into large parts of Europe and some areas in Africa. H5N1 has yet to be reported among fowl in the Americas or Australia. Human disease attributable to highly pathogenic avian influenza virus has been reported in several countries of Asia, the Middle East, and Africa. Although direct human contact with affected birds appears to be the major mode of transmission, human-to-human spread has been documented, and cases of unexplained transmission indicate that environment-to-human transmission may be possible.[113] The incubation period is less than a week. Clinical disease can range in severity from an asymptomatic or mildly symptomatic viral syndrome to a highly fulminant and deadly illness.[114]

Highly pathogenic avian influenza virus infection should be suspected in a person who is at risk for contracting the illness because of exposure to a known disease reservoir and who has a progressive respiratory illness.[115] Public health officials should be contacted if the disease is suspected, and full infection control measures should be instituted. Early antiviral therapy with oseltamivir at high doses (150 mg twice a day) and possibly with amantadine or rimantadine is recommended, along with appropriate supportive care.[116] Oseltamivir-resistant H5N1 has been described.[3] PEP and the use of antiviral medication for asymptomatic persons during an outbreak should be prescribed in consultation with disease experts.

To date, there have been 385 laboratory-confirmed cases with 243 deaths reported by the WHO; actual morbidity and mortality figures probably are higher.[117] Despite aggressive public health measures, such as culling of affected fowl populations, many experts feel that avian influenza can become a serious global pandemic.

Bunyaviridae

California Encephalitis and Bunyavirus Hemorrhagic Fevers

Pathophysiology and Clinical Findings. California encephalitis viruses, including the La Crosse and Johnson Canyon viruses, are transmitted by mosquito bites, predominantly in the northern United States in the summer and fall. Approximately 100 cases are reported yearly. Infection is mostly asymptomatic, but the mortality rate associated with the encephalitis is approximately 1%.[118]

The Bunyaviridae family of viruses includes the Crimean-Congo hemorrhagic fever virus, the Rift Valley fever virus, and the hantaviruses, a genus of viruses that cause a hemorrhagic fever with renal syndrome.[119]

Rodents carry hantaviruses; the disease is transmitted by way of aerosols from infected rodent excretions. Hantaviruses can be divided into Old World and New World varieties. Old World hantaviruses, which predominate in Europe and Asia, tend to cause milder disease and have been associated with hemorrhagic fever with renal syndrome. More than 100,000 cases occur in Asia and Europe yearly, and the mortality rate is approximately 6%.[120] New World hantaviruses occur mainly in the Americas. In 1994, a previously unknown New World hantavirus was found to cause a pulmonary syndrome associated with tachypnea, hemoconcentration, thrombocytopenia, and leukocytosis.[121] Cases occurred predominantly in the southwestern United States and were associated with a mortality rate higher than 50%. The disease was transmitted from the deer mouse, *Peromyscus maniculatus*. The virus has been designated the sin nombre virus.

Several other hantavirus species have been identified in central and south America that also have been associated with *hantavirus pulmonary syndrome* or *hantavirus cardiopulmonary syndrome*.[122] Rift Valley fever virus is carried by a mosquito and generally produces a nonspecific febrile disease. Up to 100,000 cases occur yearly in Africa. In some patients, a severe retinitis develops that may lead to blindness. Congo-Crimean hemorrhagic fever is a severe, rare, tick-transmitted disease that occurs in Africa and Asia, with a mortality rate approaching 50%.[119]

Management. Treatment of all of these diseases is supportive. The CDC provides intravenous ribavirin for investigational use.

Arenaviridae

Lymphocytic Choriomeningitis, Lassa, and Arenaviral (Hemorrhagic Fever) Viruses

Principles of Disease. The arenaviruses are carried by parasites of rodents and probably are passed to humans from contact with infected rodent urine. Four arenaviruses are known to cause human disease: Lymphocytic choriomeningitis (LCM) virus causes a meningoencephalitis that may be severe but is rarely fatal. Junin and Machupo viruses, from Argentina and Bolivia, respectively, and the Lassa virus, from Africa, cause severe and often fatal hemorrhagic fevers.

Clinical Features. *LCM virus infection* commonly is transmitted from person to person. LCM occurs in the Americas, Europe, and Asia and usually is passed from house mice, pet hamsters, or laboratory animals.[123] Influenza-like symptoms follow a 1- to 3-week incubation period and generally are followed by complete recovery. Meningitis may ensue, but even severe cases are associated with good recovery. Orchitis and parotitis may accompany the disease. LCM still poses a hazard in research settings in the United States.[124]

Lassa fever is a highly contagious disease occurring in West Africa, with a case-fatality rate of up to 25% in hospitalized patients.[125] The vector is a common rat species. Transmission is thought to occur by contact with the rats or their droppings or by contact with infected persons. In certain areas of Africa, the rate of seropositivity in the general population can be as high as 55%. A gradual onset of fever and malaise after an incubation period of 6 to 21 days is characteristic. The disease is mild or asymptomatic in up to 80% of infected persons, but in approximately 20%, it causes high fever, exudative pharyngitis, and diffuse pain (headache, chest pain, abdominal pain) and often is accompanied by vomiting and diarrhea. Worsening disease is characterized by multiorgan failure, mucosal bleeding, coma, and death. Pneumonitis and respiratory distress may develop. Early lymphopenia followed by neutrophilia and elevated transaminases is associated with a poor prognosis.[125] *Argentine hemorrhagic fever*, caused by the Junin virus, causes a skin rash and petechiae and is more likely to be hemorrhagic than Lassa fever. The disease manifests after a 7- to 10-day incubation period with fever, malaise, anorexia, and myalgias. Petechiae and gastrointestinal bleeding occur between days 4 and 6, and shock may follow. Case-fatality rates range up to 30%. Bolivian hemorrhagic fever, caused by Machupo virus, is similar to Argentine hemorrhagic fever but occurs much less commonly.[126]

Differential Considerations. LCM virus infection can resemble other viral causes of meningitis or encephalitis. The diagnosis of arenavirus infections requires a fourfold rise in antibody titer.

Management. Only supportive care is required for LCM. Ribavirin has been used effectively to treat Lassa fever and can result in a fivefold decrease in mortality.[127] Argentine hemorrhagic fever and possibly Bolivian hemorrhagic fever can be successfully treated with convalescent plasma from a recovered patient. Prevention of arenavirus infections is best accomplished by controlling the infected vectors. Special care must be taken to prevent person-to-person spread of Lassa fever.

Retroviridae

Three subfamilies are described in family Retroviridae: the type C oncoviruses (human T-cell leukemia virus types I and II [HTLV-I, HTLV-II]), the lentiviruses (e.g., human immunodeficiency viruses types 1 and 2 [HIV-1, HIV-2]), and the spumaviruses. Only the oncoviruses and lentiviruses have been shown to cause disease in humans.

Type C Oncoviruses

The demonstration that RNA could be transcribed into DNA by the reverse transcriptase in RNA tumor viruses laid the groundwork for the discovery of human retroviruses.[128] HTLV-I was isolated in 1980.[129] In approximately 1% of people infected in childhood with HTLV-I, adult T-cell leukemia-lymphoma develops later in life. HTLV-I also has been associated with *tropical spastic paraparesis*, also known as *HTLV-I–associated myelopathy*. HTLV-II was isolated in 1982 and found to be associated with a T-cell variant of hairy cell leukemia.[130]

Human Immunodeficiency Virus

HIV is a slow virus, or lentivirus, related to animal viruses such as the visna virus and feline leukemia virus. A full description of HIV and AIDS is presented in Chapter 130.

Picornaviridae

The designation for family Picornaviridae is derived from *pico*, meaning "very small," and *RNA*, their nucleic acid type. Picornaviridae includes two viruses that infect humans: the *enterovirus*, containing 67 recognized species (including the polioviruses, coxsackieviruses, echoviruses, and hepatitis A virus), and the *rhinovirus*, with more than 100 human species that cause illness in humans.

Poliovirus

Principles of Disease. Poliomyelitis is an acute viral infection that ranges in severity from an inapparent infection to a nonspecific febrile illness to aseptic meningitis to severe paralysis and death. Since the introduction of polio vaccination in the United States, only a handful of cases of paralytic poliomyelitis have been diagnosed each year, and most of these cases are either imported or vaccine-associated.[131] Since oral polio vaccine (OPV) was replaced by inactivated polio vaccine (IPV) in 2000, there have been no reports of vaccine-associated paralytic polio in the United States, although rare cases of imported paralytic polio have been reported.[132]

Poliovirus is transmitted during close contact; transmission both by the fecal-oral route and through contact with respiratory secretions has been documented. Susceptibility to poliovirus is universal, but paralytic infections are rare, increasing in incidence with age at the time of infection. At least 95% of infections are inapparent or asymptomatic.

Clinical Features. With paralytic poliomyelitis, the usual incubation period is 7 to 14 days. The disease in children usually is biphasic, with a brief viremic phase lasting 1 to 3 days. After recovery for 2 to 5 days, an abrupt onset of headache, fever, malaise, vomiting, and CSF pleocytosis ensues. This meningitic phase lasts for 1 to 2 days before the beginning of

weakness and flaccid paralysis. Bulbar paralytic poliomyelitis involves paralysis of the muscle groups innervated by the cranial nerves. The most important complications of paralytic poliomyelitis are respiratory, especially respiratory failure caused by paralysis of the respiratory muscles, aspiration pneumonia, and pulmonary embolism. Myocarditis may rarely occur. Muscular paralysis usually lasts for only 1 to 3 days after its onset. A postparalytic paralysis syndrome has been described in which neuromuscular weakness recurs several decades after resolution of the acute poliovirus infection.[133]

Differential Considerations. Paralytic poliomyelitis usually can be recognized on clinical presentation. Other enteroviruses can cause a similar syndrome. Guillain-Barré syndrome and postencephalitic syndromes may resemble paralytic poliomyelitis. Considerations in the differential diagnosis for nonparalytic poliomyelitis include any of the causes of bacterial and viral meningitis and encephalitis. The definitive diagnosis is made by isolation of the virus from fecal material or respiratory secretions.

Management. Specific antiviral treatment for poliomyelitis is not available. Management is supportive, and reporting to local health authorities is mandatory. In the acute phase of paralytic poliomyelitis, patients require hospitalization.

Routine vaccination in the United States has dramatically reduced the number of cases of paralytic poliomyelitis. The Salk IPV is recommended for most indications in the United States. IPV has the advantage of preventing paralytic disease, but it does not protect susceptible contacts by secondary spread. The Sabin OPV protects susceptible contacts, but it is associated with vaccine-associated cases of paralytic disease.[134] In 2000, the CDC recommended that all U.S. children receive four doses of IPV at ages 2, 4, and 6 to 18 months and 4 to 6 years.[7]

Coxsackieviruses, Echoviruses, and Other Enteroviruses

Principles of Disease. The enteroviruses are spread from person to person by the fecal-oral route. As with poliovirus, inapparent infections greatly outnumber symptomatic cases.

All enteroviruses enter the body through the oropharynx and multiply in the tissues around the oropharynx. The viruses are stable in acid conditions and are capable of passing through the stomach to the intestines.

Clinical Features. Most enteroviral infections are inapparent. The most common clinical presentation is that of a nonspecific febrile illness. Young children may be hospitalized with enteroviral fevers that simulate bacterial sepsis. Coxsackievirus B and some of the echoviruses may cause severe perinatal infection associated with fever, meningitis, myocarditis, and hepatitis.

Febrile diseases with rashes often are associated with enteroviruses. Exanthems resembling that of rubella occurring during the summer months have been seen with the echoviruses and coxsackie A viruses. Vesicular lesions are seen, such as with the hand-foot-and-mouth syndrome caused by some coxsackieviruses A and B. Herpangina, a specific disease characterized by a vesicular rash on the cheeks and soft palate and associated with fever, sore throat, and severe pain on swallowing, is caused by the coxsackievirus A. Roseola-like exanthems and petechial exanthems also are associated with coxsackievirus and echovirus infections.

The enteroviruses are the most common causes of viral meningitis. The course generally is benign, but enteroviral infections often can be confused with a bacterial process, particularly in the acute phase, when CSF analysis may show a neutrophil predominance.

Coxsackie B viruses are strongly associated with myocarditis, although echoviruses and coxsackie A viruses also can cause the disease. Severe cases may lead to dysrhythmias, heart failure, or death.

Enteroviruses cause upper respiratory tract infections similar to other causes of the common cold. Interstitial pneumonias also can occur. Pleurodynia (Bornholm's disease—the "devil's grippe") generally is associated with the coxsackie B viruses. This disease involves the intercostal muscles and can last for several weeks.

Other proven or suggested associations with the enteroviruses and disease include enterovirus 70 and acute hemorrhagic conjunctivitis; coxsackieviruses and echoviruses with diarrhea and gastroenteritis; coxsackieviruses and echoviruses with hemolytic-uremic syndrome; and enteroviruses with acute myositis. Other possible associations include chronic cardiomyopathy, aortitis, hepatitis, pancreatitis, orchitis, diabetes mellitus, lymphadenopathy, a mononucleosis-like syndrome, and infectious lymphocytosis. A progressive, dementing, chronic meningitis associated with enteroviruses has been reported in persons with common variable immunodeficiency syndrome.

Management. No specific treatments are available for infections caused by the enteroviruses. Care is supportive. Vaccination against poliovirus and hepatitis A is recommended, and immune serum globulin also can prevent the acquisition of hepatitis A infection.

Hepatitis A Virus

The hepatitis A virus is now classified among the picornaviruses. Hepatitis A is discussed in Chapter 88.

Rhinovirus

Principles of Disease. Rhinoviruses are the most common cause of the common cold. More than 100 strains exist. Rhinovirus transmission generally occurs primarily by hand contact and through inoculation of the eye or nasal mucosa and less commonly by aerosolization of respiratory secretions. Viral replication probably occurs on the epithelial surface of the nasal mucosa.

Clinical Features. After a 1- to 4-day incubation period, the usual signs and symptoms of rhinoviral infection occur, including nasal obstruction, sneezing, sore throat, cough, and malaise. Severe tracheobronchitis and pneumonia occur rarely. Fever and lower respiratory tract infections are more common in children than in adults with rhinovirus infections.

Differential Considerations. Other respiratory pathogens such as coronaviruses, RSV, parainfluenza viruses, influenza viruses, adenoviruses, and enteroviruses can produce clinical syndromes similar to those produced by the rhinoviruses. The rhinoviruses in general cause less morbidity than that typical for the parainfluenza viruses and RSV. Definitive diagnosis is made by the demonstration of a rise in antibody titer.

Management. Treatment is aimed at relieving symptoms. Routine vaccination appears to be an unlikely prospect because of the number of serotypes. Because hand-to-face inoculation appears to be the predominant means of transmission, frequent hand washing during epidemic periods may decrease the spread of rhinovirus infections.

Caliciviridae

Caliciviruses and Astroviruses

Principles of Disease. Caliciviruses and astroviruses are small RNA viruses that have been implicated in outbreaks of gastroenteritis, predominantly in children. The noroviruses (which include the Norwalk virus) and the sapoviruses are caliciviruses. The sapoviruses cause gastroenteritis in children, whereas the noro-

viruses affect people of all ages. Norwalk virus may peak in the winter months and often is associated with outbreaks in populations living in close quarters (such as cruise ships).[135]

Clinical Features. The incubation period probably is 1 to 4 days, and the disease lasts from 1 to 3 days. The disease is generally mild and accompanied by low-grade fever. Vomiting appears to be less common with astroviral disease than with calicivirus infections. One third of outbreaks of gastroenteritis can be attributed to a Norwalk virus–like agent. Diarrhea induced by these agents is associated with transient fat malabsorption. Outbreaks have occurred in schools and other institutions and through the ingestion of inadequately cooked shellfish. The mode of transmission is unknown but probably is by the fecal-oral route. Vomiting and diarrhea occur along with myalgias, malaise, headache, and low-grade fever. Severe diarrhea is rare and stools are not bloody.

Differential Considerations. Other causes of gastroenteritis associated with a similar syndrome include adenoviruses, enteroviruses, and coronaviruses. Electron microscopy can make the definitive diagnosis.

Management. Treatment is supportive. The gastroenteritis generally is self-limited and resolves without specific therapy. Oral rehydration solutions generally are adequate; rarely, intravenous therapy is required.

Unclassified Viruses

Hepatitis E Virus

Hepatitis E virus is an RNA virus that has been identified as a cause of enterically transmitted hepatitis. It has been implicated as a cause of fulminant hepatitis in pregnant women.

Prions

Principles of Disease. The coined term *prion* (*pr*oteinaceous *i*nfectious particle [-*on*]) refers to the transmissible agent putatively responsible for a group of chronic neurodegenerative disorders sharing certain pathologic features. Prions have not been found to contain nucleic acid.[136,137] Other terms for these agents have included *unconventional virus* and *virino*. The group of diseases caused by these agents, also referred to as *slow virus infections* or simply *slow infections*, includes Creutzfeldt-Jakob disease (CJD), kuru, and the Gerstmann-Straussler syndrome. Bovine spongiform encephalopathy in cattle, or new-variant CJD in humans, occurred primarily in the United Kingdom in the early 1990s, probably as a result of a change in the practice of offal rendering.[138] By 2001, a few cases had been found elsewhere in Europe but not in the United States. Fortunately, owing to changes in handling meat byproducts and cattle feed, the incidence of bovine spongiform encephalopathy appears to be decreasing.

A characteristic feature of these diseases is the lack of any inflammatory response. A reactive astrocytosis to the presence of the virus occurs in the CNS, accompanied by neuronal vacuolation resulting in spongiform encephalopathy.

Clinical Findings. CJD is a rare disease, usually manifesting in late middle age with a progressive dementia combined with ataxia and myoclonic jerking. Distribution is worldwide and sporadic. CJD has been transmitted from person to person by direct inoculation (e.g., in corneal transplants and dura mater grafts). Kuru and the Gerstmann-Straussler syndrome manifest as cerebellar syndromes, with dementia occurring late in the course of the disease. Kuru has been associated with cannibalism confined to a few tribes in the highlands of New Guinea.[139] With both CJD and kuru, progression is rapid, with death usually occurring in less than 1 year. The Gerstmann-Straussler syndrome follows a more slowly progressive course of up to 10 years.

Differential Considerations. CJD can be confused with Alzheimer's disease or other slowly progressive dementing diseases. Other diseases to consider in the differential diagnosis include multi-infarct dementia, nutritional deficiency syndromes, and primary brain tumors. CT and magnetic resonance imaging scans usually are nondiagnostic, but the electroencephalogram often shows changes characteristic of CJD.

KEY CONCEPTS

- New vaccines have been introduced against rotavirus, HPV, and herpes zoster virus.
- Cases of highly pathogenic avian influenza (due to the H5N1 strain of the virus) have been documented.
- Patients who have primary genital herpes or severe or frequent recurrences of infection and patients who are immunosuppressed and have continuous infections should receive acyclovir, famciclovir, or valacyclovir. Herpes simplex encephalitis constitutes a medical emergency requiring rapid diagnosis and treatment with intravenous acyclovir.
- Patients with herpes zoster that is disseminated or that involves more than one dermatome should be treated with intravenous acyclovir.
- West Nile virus infection most severely affects the elderly. Treatment is supportive; management of the disease requires reporting to public health authorities and control of vector mosquito populations.
- The presentation of SARS-CoV infection mimics that of other community-acquired or nosocomial respiratory infections. Its recognition depends on obtaining a good possible contact history; its control requires prompt initiation of isolation procedures.
- Young children should be routinely vaccinated against influenza A. People at higher risk of becoming infected, those in whom considerable morbidity can be expected, or those who are likely to transmit influenza A to at-risk groups should receive an influenza vaccine annually. In patients with symptoms of influenza, the duration of illness may be shortened by 1 to 2 days if treatment with neuraminidase inhibitors is initiated within 48 hours after symptom onset.

The references and suggested reading list for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 129 Rabies

Ellen J. Weber and Prasanthi Ramanujam

PERSPECTIVE

Rabies is arguably the oldest infection known to humans. The term *rabies* comes from the Sanskrit *rabhas*, which means "to do violence." The Eshmuna Code of Babylon, from the 23rd century BCE, contains one of the earliest regulations regarding rabies: A fine of 40 shekels was levied on the owner of a dog that killed another man through a rabid bite.[1,2]

Today, rabies is a huge public health problem in Third World countries; according to the World Health Organization (WHO), an estimated 55,000 deaths from rabies occur annually worldwide, 31,000 of these in Asia and 24,000 in Africa[3] (Fig. 129-1). In the United States and Puerto Rico, however, human rabies is extremely rare as a result of a successful vaccination program for domestic animals that began in 1947. In the pre-vaccination era, approximately 40 human cases were reported each year. By contrast, during 2006 only three cases of human rabies were reported to the Centers for Disease Control and Prevention (CDC).[4-7]

EPIDEMIOLOGY

Although it is believed that any mammal can contract rabies, species within the orders Carnivora and Chiroptera (bats) are considered to be the most important reservoirs for maintenance and transmission of the disease.[8-10] Worldwide, dogs are the most commonly infected animal and the most common source of rabies in humans. Dogs are the primary reservoir of rabies in Asia and in many developing countries of Africa, although since 2003, South America has reported more human deaths from wildlife bites than from dog bites.[11] In Europe, Canada, and the Arctic and sub-Arctic regions, the principal carrier is the fox, and in Puerto Rico, it is the mongoose. Jackals are the main wildlife reservoir of rabies in Africa. Bats are an important source of rabies in North and South America and Mexico. Bats carrying rabies-related lyssaviruses also are found in Africa, Europe, and Australia.

In the United States, more than 90% of all cases of rabies occur in wild animals; the principal reservoirs are raccoons, bats, skunks, and foxes.[7] In Mexico, the primary reservoirs are dogs and bats, while other reservoirs include the coyote (likely a spillover from dog rabies), the gray fox (overlapping with the same species in the United States), and the skunk.[12]

Rabies in terrestrial animals occurs in discrete geographic regions where the virus is transmitted primarily among members of a single species (Fig. 129-2). Each species and location are associated with a unique variant of the rabies virus. In the United States, for example, rabies is endemic in raccoons along the Eastern seaboard. A different strain of virus is carried by skunks in the north central states; two additional distinctive strains are carried by the skunks in the south central states and rabid skunks endemic to California. Arctic and red foxes in Alaska carry another rabies variant. As a result of their migration across Canada, the red foxes of New England have the same rabies virus variant. Two gray fox reservoirs with a unique rabies virus variant are found in Arizona and in Texas. For many years, a distinct variant was found in the dog-coyote mix along the Texas-Mexico border, although no transmission of dog-coyote rabies variant has been documented since 2004, supporting the contention that no canine rabies variant has been in circulation in the United States for the past 2 years.[5]

Wherever rabies is endemic, other wild carnivores or domestic animals may become infected by contact with the endemic species and will carry the viral variant of the endemic species (spillover). The increase in skunk rabies in New England is largely attributable to the raccoon epizootic that has occurred there, although some of the skunk rabies has resulted from spillover from foxes. Although rabies has never been transmitted from a rodent or lagomorph (rabbit or hare) to humans, these animals do contract rabies, usually from the terrestrial reservoir in their region. Most rodent cases are found in larger rodents, such as groundhogs or beavers. In the United States, infected groundhogs generally are found in the areas in which raccoon rabies is endemic.[5] Rabid bats are ubiquitous throughout the United States and North America and account for 24% of all cases of rabies in U.S. animals, making them the second most common source of rabies in the United States; 6% of all bats submitted to state health departments tested positive for rabies in 2006. The only U.S. state that remains rabies-free is Hawaii, where there are no rabid bats or rabid terrestrial animals.[5] As with terrestrial reservoirs, bats carry viral variants unique to that species, but the geographic associations are less distinct, relating only to where a particular species of bats makes its home (Fig. 129-3). Rabid bats are capable of infecting terrestrial animals, as well as humans, in any area of the mainland United States. However, spillover (in which these animals carry and transmit the bat virus variant) appears to be extremely rare.[13]

The association of a unique rabies virus variant with a particular species and locale makes it possible to determine the

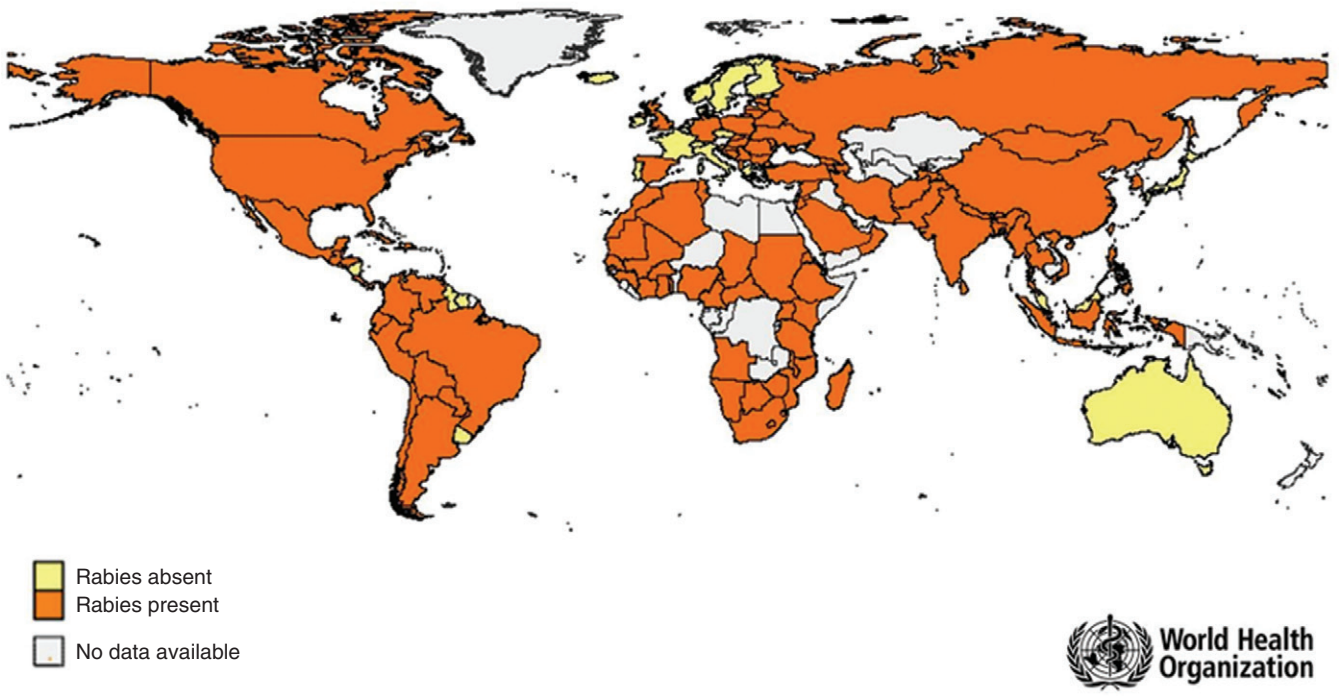

Figure 129-1. Presence/absence of rabies worldwide, 2005. The World Health Organization has been collecting rabies data through the World Survey of Rabies every year. According to the rabies database, 43 countries reported no rabies in 2004 and 2005. (From Rabnet/World Survey of Rabies/OIE/FAO.)

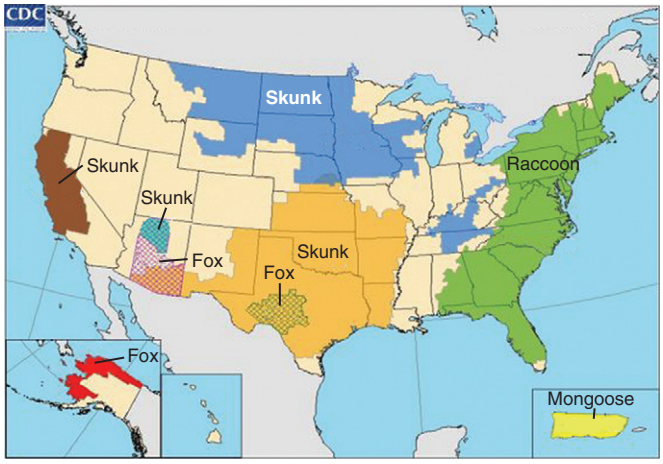

Figure 129-2. Distribution of terrestrial rabies virus variants in the United States and Puerto Rico, 2006. In 2006, wild animals accounted for 92% of reported cases of rabies. Raccoons were the most frequently reported rabid wildlife species, followed by bats, skunks, and foxes in 2006. (From Blanton JD, Hanlon CA, Rupprecht CE: Rabies surveillance in the United States during 2006. J Am Vet Med Assoc 231:540, 2007.)

source of rabies in areas or species that previously were rabies-free. Additionally, antigenic typing permits identification of the source of human infections when the animal contact is unknown.[14,15]

Wild and Domestic Animal Rabies

Since the 1950s, rabies in U.S. domestic animals has significantly decreased, but the population of rabid wild animals has actually increased (Fig. 129-4). In 2006, rabies was reported in 6940 wild animals, compared with 4742 cases in 1988.[5,16] The primary reservoirs are raccoons, bats, skunks, and foxes (Fig. 129-5). In the 1960s and 1970s, a majority of cases of wildlife rabies were found in skunks in the United States. However, in the late 1970s, an epizootic among raccoons began in the mid-Atlantic states and spread north and south to cover the entire eastern seaboard; in 2006, more cases of wildlife rabies in the United States were attributable to raccoons than to any other wild animal (n = 2615, or 37.7%), with skunks now representing the second most populous (22%) of the rabid animal population. The source of this epizootic appears to be the inadvertent translocation of rabid raccoons from the southeastern states to the mid-Atlantic region by humans to stock the area for hunting, as evidenced by the fact that rabid raccoons seen first in the mid-Atlantic states, and now along the entire East Coast, carry the same viral variant as those in the southeastern states. The population has spread geographically north and westward. Raccoon rabies is now enzootic in all of the eastern coastal states as well as in Alabama, Ohio, Tennessee, Pennsylvania, Vermont, and West Virginia. The first rabid raccoon in Canada was found in Ontario in 1999; 89 rabid raccoons were reported in 2001, but the population declined to 26 cases in 2002 after wildlife control measures were instituted: In 2006, only five cases in raccoons were reported.[5,17,18] A smaller epizootic of coyotes began in the early 1990s in southern Texas; three rabid coyotes were reported in 1990 and 71 in 1993, but the population has since returned to low levels. No instances of dog-coyote rabies have been reported since 2004 in the United States.[5,19,20]

The number of rabid domestic animals has remained relatively constant for the last decade and accounted for approximately 8% (547 cases) of all rabies in the United States.[5] In 2006, Pennsylvania reported the largest number of domestic rabid animals (72 cases), followed by Virginia (62 cases). Cats are the domestic animal most frequently reported as rabid, accounting for approximately 58% of all cases of domestic animal rabies. There were 318 cases of rabies in cats in 2006, compared with 192 in 1988.[21] Approximately 80% of rabid cats were reported from states in which raccoon rabies is present, whereas cases in the central plains states were a result of spill-

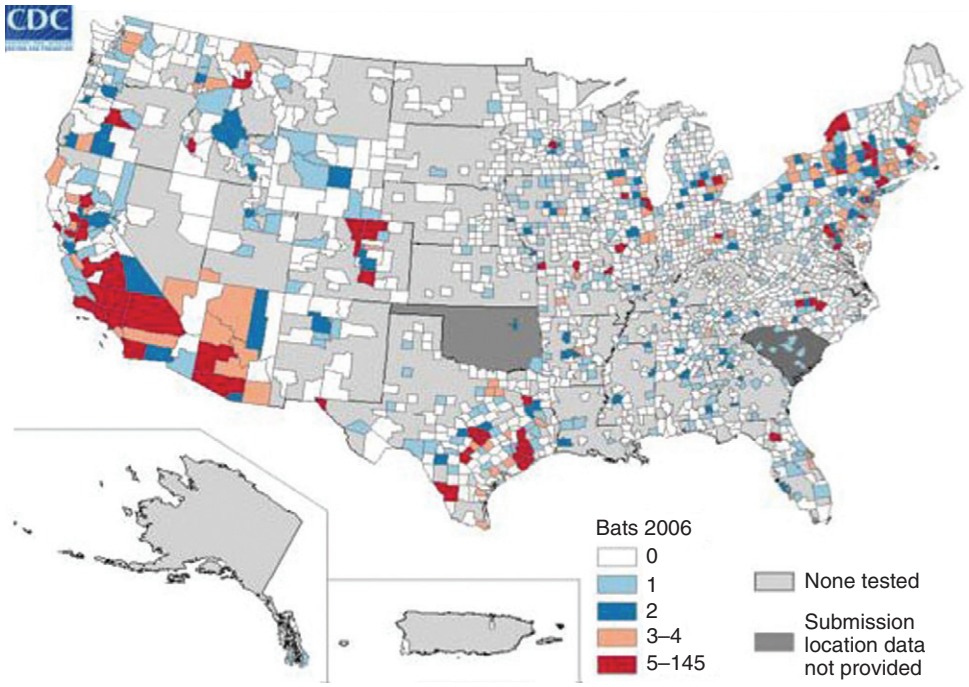

Figure 129-3. Reported U.S. cases of rabies in bats by county, 2006. Rabies in bats accounted for 24% of all cases of animal rabies. Texas reported the largest number of cases in bats, followed by California and New York. (From Blanton JD, Hanlon CA, Rupprecht CE: Rabies surveillance in the United States during 2006. J Am Vet Med Assoc 231:540, 2007.)

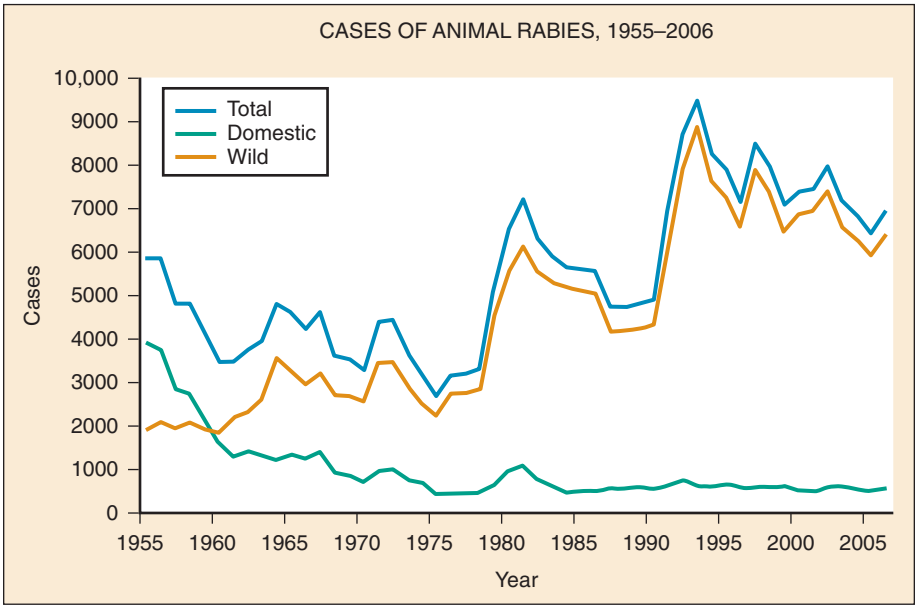

Figure 129-4. Cases of animal rabies, 1955 to 2006. Rabies vaccination campaigns in the 1940s and 1950s resulted in a substantial decrease in rabies in domestic animals. Similarly, elimination of the dog-coyote rabies virus variant and reduction in the gray fox virus variant also have been documented. (From Blanton JD, Hanlon CA, Rupprecht CE: Rabies surveillance in the United States during 2006. J Am Vet Med Assoc 231:540, 2007.)

over from rabid skunks.[5] In 2006, there were 79 rabid dogs in the United States; in 1988, there were 128. Texas, Georgia, and North Carolina reported the largest number of cases of dog rabies in 2006. Dog rabies also appears to parallel the distribution of rabid skunk rabies in the south central states and of gray fox rabies in Texas. The number of rabid cattle decreased by 11.8% (82 total cases) in 2006; distribution closely follows that of skunks in the central and midwestern United States and raccoons in the Northeast and mid-Atlantic regions.[5]

The median age of rabid cats and dogs is 1 year; most have not been vaccinated or have received only one vaccination.[21] Dogs and cats generally are infected with a strain of rabies virus that is endemic in the terrestrial reservoir in their geographic area. Puerto Rico reported a total of five cases of cat rabies in 2005 and 2006, which is a presumed spillover from mongoose variant.[5,22] Most owners are unaware of their pets' exposure to wild animals that may carry rabies.

Rabies in Humans

Human cases of rabies in the United States remain low owing to effective animal vaccination programs and availability of human vaccines and immunoglobulins.[5] Between 1996 and 2006, 33 cases of human rabies were reported to the CDC, 21 of which were acquired from animal sources in the United States. One case was associated with the raccoon variant from the eastern United States, one case was due to a dog-mongoose variant in Puerto Rico, and the rest were associated with bats.[5,23-34] Four cases were in transplant recipients, from a donor who died of an unknown encephalopathy, only later identified as rabies.[32] For most bat-associated cases, a history

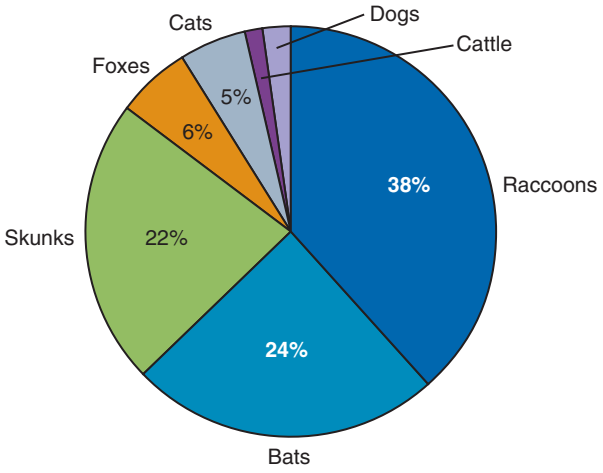

Figure 129-5. Relative proportion of cases of rabies in animals in the United States, 2006. Data for other domestic and wild animals are not shown in the pie chart. Numbers may not add up to 100% because of rounding. A total of 2615 cases of rabies in raccoons were reported in 2006, representing an increase after 3 years of decline. Increases also were reported among bats, skunks, and foxes in 2006 compared with 2005. (From Blanton JD, Hanlon CA, Rupprecht CE: Rabies surveillance in the United States during 2006. J Am Vet Med Assoc 231:540, 2007.)

of bat contact was discovered only during hospitalization or determined after the patient's death, when antigenic analysis of the rabies virus infecting the victim revealed a bat variant. In more than one half of the cases, the victim was known to have had contact with a bat, although no rabies prophylaxis was sought.[23,26,27,29,30,32-34] In most other cases, a history of bat exposure was lacking.[24,25,28,31] Although rabies has been found in most of the bat species in the United States, the species most frequently identified with "cryptic" bat rabies in humans is the silver-haired, eastern pipistrelle bat, a solitary, reclusive, tree-dwelling species that is seldom found in buildings and is thought to be rarely encountered by humans. The viral strain associated with this species appears to replicate better and at lower temperatures than a canine rabies variant, suggesting that even a small, superficially administered quantity of virus is sufficient to transmit infection.[9,13]

PRINCIPLES OF DISEASE

Rabies is caused by a neurotropic rhabdovirus of the genus *Lyssavirus* (from the Greek word *lyssa*, which means frenzy). Animals are the natural reservoir for the virus; animals that are infected with the virus become sick and die, usually within 3 to 9 days of the time they first begin secreting virus in the saliva.[35] Insectivorous bats may live 10 days; vampire bats, possibly longer.[36,37] Some evidence suggests that dogs can become asymptomatic carriers, but transmission of disease from such an animal to humans has never been documented.[38] A survey of rabid dogs in the United States in 1988 found that all died within 8 days of becoming ill; the median time until death was 3 days.[21]

Animals are capable of transmitting rabies once they start secreting virus in saliva. Most animals with rabies will be sick before excretion of virus, but some may not become ill for several days after virus can be found in their saliva.[37] The classic picture of a mangy dog foaming at the mouth and wildly running through town is not often seen; clinical signs are invariably present but frequently are more subtle. Indeed, less than one half of cases of rabies in domestic animals are initially recognized by veterinarians.[21] The animal may display aggressive behavior, ataxia, irritability, anorexia, lethargy, or excessive salivation; cats are more likely than dogs to demonstrate aggressive or irritable behavior. In a wild animal, however, what may be most apparent is a change in instinctive behavior—for instance, a nocturnal animal may be observed boldly walking through downtown in broad daylight.[39] An unprovoked bite from a domestic animal may be a sign of rabies; however, humans, especially children, often inadvertently provoke a pet by cornering it or competing with it for its natural prey.

Rabies is transmitted when the virus is introduced into bite wounds or open cuts in skin or onto mucous membranes.[40] Almost all documented cases of human rabies have been transmitted by a bite. The risk of transmission by a bite is approximately 50 times that with a scratch[41]; rabies also has been contracted by recipients of corneal and organ transplants from infected donors.[32,40] In animals, rabies is known to be transmitted transplacentally and has been shown to be transmissible experimentally by aerosol under artificial and extreme conditions and by ingestion.[8,42] Other than through transplants, human-to-human transmission has never been confirmed, although two possible cases in family members of rabies victims in Ethiopia that were not laboratory-confirmed have been described.[43] Rabies virus has never been isolated from blood.

The virus replicates in muscle cells near the site of the bite, remaining at the site of inoculation for most of the incubation period before entering the peripheral nerve by way of the neuromuscular junction, and then rapidly ascending by retrograde conduction along peripheral nerves to the central nervous system. It is estimated that the virus travels along motor and sensory axons at a rate of approximately 8 to 20 mm/day and has a predilection for the thalamus, basal ganglia, and brainstem.[44] Once in the CNS, the virus creates the well-known Negri bodies in the nuclei of neurons, where it manufactures copies of itself that then bud out to infect other neurons. Virus then is transported through the peripheral nerves by antegrade conduction to the salivary glands, where it can be excreted and transmit the disease to a new victim through a bite.[45]

Of interest, the virus does not destroy the neurons; in fact, it prevents cell apoptosis. How rabies actually kills humans, therefore, has been something of a mystery. Recent theories suggest that in the presence of the rabies virus, there is an outpouring of cytokines and proinflammatory molecules that modify electrical activity in the brain and affect the hypothalamic-pituitary axis and serotonin metabolism, causing the clinical symptoms. The immune reaction recruits T and B cells and results in more cytokine and nitric oxide production. Eventually, cells are depleted of all metabolic pools and cell death then occurs. Thus, the body's own immune reaction may be the actual cause of death. Clinical support for this theory is that persons who have intact T cell immunity are more likely to have encephalitic rabies and die quickly, whereas those with impaired immunity are more likely to have paralytic rabies and live longer.[46]

The risk of developing rabies after a bite ranges from 5 to 80% and depends on the type of biting animal, the severity of the exposure, and the location of the bite. All of these factors contribute to the ultimate mortality rate in unvaccinated victims.[41,47]

CLINICAL FEATURES

Clinical rabies progresses through five stages: incubation, prodrome, acute neurologic illness, coma, and death. The incubation period (bite to first symptom) typically is 20 to 90 days but has been documented to be as short as 10 days and as long as 7 years.[41,47] Bites on the head and neck result in disease with

a shorter incubation period (as short as 15 days) than that for bites on the trunk or lower extremity, most likely because of the rich peripheral nerve supply in the head and neck area.[35] The mortality rate is lower among victims with lower-extremity bites.[48]

The prodromal phase can last a day to a week. The clinical manifestations usually are nonspecific and range from numbness or pain at the bite site to generalized flulike signs and symptoms, such as low-grade fever, nausea, vomiting, headache, myalgias, sore throat, runny nose, and malaise.

The acute neurologic syndrome occurs after the prodromal phase and will vary according to the type of rabies that is being manifested. Full-blown rabies has two classic forms: the "furious" or encephalitic form and the paralytic or "dumb" form; another, more recently identified form, "nonclassic," also has been described.[46] Encephalitic rabies is the far more common of the classic forms and is manifested by agitation, hydrophobia, fluctuating consciousness, and extreme irritability; periods of hyperexcitability fluctuate with lucidity or lethargy. Vital signs often are abnormal, with tachycardia, tachypnea, and fever. Hyperactivity is aggravated by light, noise, thirst, and fear. Hydrophobia, so named because of patients' inability to swallow, appears to result from an exaggerated respiratory tract protective reflex that results in a violent, jerky contraction of the diaphragm and accessory muscles of inspiration when the patient attempts to swallow liquids.[44] Overwhelming terror accompanies the phenomenon and may generalize to the sight of water or having water touch the face.[49] Aerophobia, an extreme fear of air in motion, can be elicited in some patients by blowing air across the face. This results in muscle spasms in the neck and pharyngeal regions.[50,51] Signs of autonomic dysfunction, such as excessive salivation and priapism, may be noted. Hyperactive deep tendon reflexes with Babinski's signs and nuchal rigidity often are present. Seizures and focal weakness are rare.

Approximately 20% of cases manifest as paralytic or "dumb" rabies, with limb weakness and fever; consciousness initially is spared. Rabies may be very difficult to diagnose because of the lack of the typical irritability and hydrophobia, and may be confused with Guillain-Barré syndrome. It also may be difficult to make a distinction between the paralytic form of rabies and Guillain-Barré syndrome on the basis of clinical, pathologic, or electrophysiologic criteria. Features that may suggest paralytic rabies instead of Guillain-Barré include persistent fever from the onset of limb weakness; intact sensory function except at the bite site; bladder dysfunction; and percussion myodema (a mounding of the muscle at the percussion site that lasts a few seconds, most easily elicited on the chest, deltoid, and thigh).[46] Neuropathologic findings of motor axon neuropathy in the absence of motor neuron degeneration and inflammation also may help with the recognition of paralytic rabies, although these findings are not unique to rabies.[52] The two forms of classic rabies can overlap or progress from one to the other.

The nonclassic form of rabies is seen with rabies contracted from bats or from dogs in Thailand. This form is associated with more pronounced motor and sensory deficits than those typical for classic rabies of either form, brainstem signs such as cranial nerve abnormalities (dysarthria, dysphagia), choreiform movements, ataxia, nystagmus, and vertigo. Seizures are more common in this form, whereas phobic spasms are rare.

Eventually, in all forms of rabies, coma occurs, generally 7 to 10 days after onset of the acute neurologic phase. Hydrophobia persists, accompanied by prolonged apnea, and generalized flaccid paralysis. Seizures may ensue, and ultimately the disease culminates in respiratory and vascular collapse. Unless the patient is supported by intensive care, death ensues in 2 to 3 days.[53]

DIAGNOSIS AND MANAGEMENT

In most clinical situations, rabies is not considered until late in the course of the disease. Antemortem diagnosis may involve isolation of virus and detection of viral RNA, antigen, or antibody. Brain biopsy is the definitive method for isolating virus, but the risks associated with this procedure prohibit its use in most cases. Detection of antigen from the peripheral nerves of a nuchal skin biopsy specimen frequently has been successful and is superior to detection of antigen in corneal epithelium.

Cerebrospinal fluid (CSF) analysis will show a pleocytosis, and in some cases, virus can be isolated or viral antibody detected in the fluid. Saliva also may yield virus. Antibody to rabies virus is variably detected in serum and generally is not seen until the second week of illness. Results of direct fluorescent antibody testing for viral antigen in saliva, corneal impressions, and nuchal skin biopsy specimens are variably positive, and such tests should be repeated if the diagnosis remains in doubt. Rabies virus RNA is present in saliva, urine, and CSF, and detection in saliva and urine using reverse transcriptase–polymerase chain reaction (RT-PCR) amplification is a promising advance.[3,54,55] Magnetic resonance imaging (MRI) of the brain may be useful in distinguishing rabies from other forms of encephalitis.[56] Because evidence of infection may not be present for many days after the onset of illness, negative findings on antemortem studies do not rule out the disease. Also, antemortem diagnosis is important in limiting contacts with the victim and ascertaining that no others were exposed to the rabies source.

Once manifested clinically, rabies usually is fatal within 3 to 10 days; with intensive care unit (ICU) support, survival times are as long as 4 months, but the outcome remains dismal. No clearly effective rabies treatment currently exists; pooled human rabies immune globulin given intrathecally, cytarabine, adenine arabinoside, ribavirin, acyclovir, and interferon all have been administered after onset of symptoms, without success.[6,7,36,49,57,58] In vitro, high concentrations of ketamine inhibit replication of rabies virus and have been shown experimentally to reduce brain infection. Corticosteroids have been shown to increase the mortality rate in mouse models.[53] There is only one well-documented case of survival from rabies in a patient who had not received any postexposure prophylaxis (PEP).[59] This 11-year-old girl from Minnesota was treated with ketamine for sedation, beta-blockade, antiseizure medications, and neuromuscular blockade. She was not given immune globulin or vaccine, to avoid stimulating an immune response. After 4 months in an ICU, she survived with intact sensorium but significant neurologic sequelae. Unfortunately, two other rabies victims who subsequently were treated with the same regimen did not survive.[34] Only five other patients have been reported to have survived clinical rabies, with a satisfactory neurologic status in only one. All five had received some form of preexposure or postexposure prophylactic treatment, and none had rabies virus isolated or antigen detected, raising the question of whether the survivors in fact had the disease.[52]

POSTEXPOSURE PROPHYLAXIS ASSESSMENT

Despite the fact that human rabies is extremely rare in the United States, from 20,000 to 39,000 people a year receive PEP; direct costs of delivering prophylaxis are estimated at approximately $2500 per case, with an additional $1100 cost

to the patient in the form of lost wages, child care, and transportation.[60,61] From 30 to 60% of treatments probably are avoidable because the exposure was in the low-risk category, no exposure occurred, or animals were not tested or observed appropriately.[62-64] Accordingly, it is imperative that practitioners understand the regional risk of rabies, animal handling procedures, indications for prophylaxis, and recommended treatment measures. The clinical scenario should be discussed with public health officials to reduce unnecessary treatments. Local or state agencies should be contacted first because they are most familiar with the animals in the area. If immediate consultation is required and local agencies are unavailable, emergency physicians can call the CDC's clinician information line, 877-554-4625, which is available 24 hours a day, 7 days a week.

The decision about whether to begin PEP after a bite depends on a number of factors: the type of exposure, the location of the incident, and availability of the biting animal (Table 129-1). Treatment decisions may be modified if the animal is available for testing or observation.

Exposure

Bites are considered significant exposures; nonbite exposures that involve contamination of either a mucous membrane or an open wound (one that has bled within 24 hours) with saliva also may necessitate prophylaxis. Petting a rabid animal and contact with its blood, urine, or feces are not considered exposures.[40] Skunk spray exposure does not require prophylaxis. Dry virus is not infectious.

Biting Animal

In the United States, high-risk animals are raccoons, skunks, foxes, bats, and coyotes. Dogs found along the U.S.-Mexico border and in developing countries also are high-risk animals. Wild carnivores in areas in which rabies is endemic may be infected with rabies; the risk of transmission of rabies to humans from the bites of these animals is approximately 10 times lower than the risk from the predominant reservoir but high enough to warrant prophylaxis.[65] Therefore, bites from most wildlife require immediate prophylaxis; exceptions, as noted later on, are lagomorphs and rodents. Significant nonbite exposures to these animals also constitute grounds for initiation of treatment. PEP for the victim may be discontinued if the animal is proved not to be rabid after testing.

Transmission of rabies from bats appears to have occurred from seemingly unimportant or unrecognized bites. Accordingly, the threshold for providing treatment after bat exposures is exceedingly low. The CDC recommends that "postexposure prophylaxis should be considered when direct contact between a human and a bat has occurred, unless the exposed person can be certain bite, scratch or mucous membrane exposure did not occur."[40] PEP is recommended when a bat is found indoors in the same room with a person who might be unaware that a bite or direct contact had occurred (such as someone sleeping, an unattended child, or a mentally disabled person) and rabies cannot be ruled out by testing the bat. Prophylaxis would not be recommended for other household members unless contact with the bat had occurred.

Small rodents (squirrels, gophers, rats, chipmunks, and guinea pigs) and lagomorphs (rabbits and hares) are very unlikely to carry rabies and thus are low risk. However, in areas in which raccoon rabies is endemic, groundhogs (woodchucks) have been found to be rabid in significant numbers. Woodchucks accounted for 93% of the 371 cases of rabies in rodents reported to the CDC between 1990 and 1996 and for 43 of the 44 cases among rodents and lagomorphs in 2006.[5] Current recommendations are to consult state or local health departments before initiation of PEP for cases involving rodents. Bites from rodents outside the United States should receive prophylaxis.

Bites from livestock should be considered individually, and public health officials should be consulted.[40] No human cases of rabies from livestock have ever been reported in the United States.[8]

Domestic animals, particularly urban cats and dogs, in the United States are generally at low risk, with the exception of dogs at the U.S.-Mexico border. However, domestic animals in endemic areas may be at somewhat higher risk. Healthy-appearing domestic animals (dogs, cats, and ferrets) should be observed for 10 days, and PEP for the victim should be withheld unless the animal becomes ill. In nonendemic areas, PEP usually is withheld even if the animal is not available. Rabies has rarely been diagnosed in vaccinated domestic animals and appears to have occurred only in animals that had received

Table 129-1 Guidelines for Determining Need for Rabies Prophylaxis

ANIMAL TYPE	EVALUATION AND DISPOSITION OF ANIMAL	POSTEXPOSURE PROPHYLAXIS RECOMMENDATIONS
Dogs, cats, and ferrets	Healthy and available for 10-day observation period*	Persons should not begin vaccination unless animal develops clinical signs of rabies.
	Rabid or suspected rabid	Immediately vaccinate.
	Unknown (escaped)	Consult public health officials.
Raccoons, skunks, foxes, and most other carnivores; bats	Regarded as rabid unless animal is proved to be seronegative for rabies by laboratory test†	Consider immediate vaccination.
Livestock, horses, rodents, rabbits and hares, and other mammals	Consider individually	Consult public health officials. Bites of squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats, mice, other small rodents, and rabbits and hares almost never require rabies postexposure prophylaxis.

*During the 10-day observation period, begin postexposure prophylaxis at the first sign of rabies in a dog, cat, or ferret that has bitten someone. If the animal exhibits clinical signs of rabies, it should be euthanized immediately and tested.

†The animal should be euthanized and tested as soon as possible. Holding for observation is not recommended. Discontinue vaccine if immunofluorescence test results for the animal are negative.

For consultation, contact local health officials; if these are unavailable, call the CDC at 877-554-4625.

Adapted from Human rabies prevention—United States, 1999. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 48:1, 1999. Available at http://www.cdc.gov/rabies/exposure/types.html; accessed February 20, 2008.

only one vaccination in their lifetime.[21,66] Bites from dogs in developing countries should always be considered high risk, and prophylaxis should be given without waiting for test results.

Biting Incident

Animals that are behaving oddly, or that bite without provocation, have a higher risk of carrying rabies. However, the circumstances of the bite should be taken into consideration only in evaluating a bite from an otherwise low-risk animal, such as a dog or cat.

Animal in Captivity

Wild animals that have been caught should be sacrificed immediately and the head sent, under refrigeration, to an appropriate laboratory for rabies fluorescent antibody testing. Unless the risk of transmission is low, the victim should begin prophylaxis, which may be discontinued when the results of the test are known. Domestic animals (dogs, cats, ferrets) in the United States that are apparently healthy should be observed for 10 days; if the animal does not become ill, the victim does not require treatment. If the animal appears sick or is stray or unwanted, it should be sacrificed and tested immediately and the victim treated accordingly.

POSTEXPOSURE PROPHYLAXIS

Prophylaxis consists of three steps: wound care, passive immunization, and active immunization. No step in this treatment should be omitted. When prophylaxis appears to be indicated, treatment should be begun immediately. Discussions with local public health officials will decrease unnecessary treatment, and advice is available from either state health officials or the CDC 24 hours a day. It is not known whether, or for how long, it is safe to delay treatment, nor is such delay recommended.[67] On the other hand, if prophylaxis is indicated, it should be administered regardless of the duration of the delay because evidence exists that the incubation period of rabies can be more than a year.

Wound Care

Although wound care should never be relied on as the only preventive measure, it is an essential part of postexposure rabies prevention, especially because in rare cases, rabies subsequently developed in persons who received what was thought to be appropriate immunoprophylaxis. Furthermore, wound treatment may be the only prevention available for a victim in the wild who is days or weeks away from medical care. Rabies virus is easily killed by sunlight, soap, or drying. Experimental studies have shown that the combination of scrubbing and flushing the wound with benzalkonium chloride, 20% soap solution, or Ivory soap was nearly 100% protective when performed within 3 hours of inoculation of virus.[68] For wounds in which rabies transmission is of concern, the CDC recommends immediate and thorough washing with soap and water and also application of a virucidal agent such as povidone-iodine[40] (Box 129-1). Wounds should be scrubbed or swabbed, not simply flushed.[69] After cleansing the wound as described above, rinse with water or saline.

Immunoprophylaxis

Rabies immunoprophylaxis requires both passive immunization with antibody (immune globulin) and active immunization with vaccine (Box 129-2). It is essential that both parts of this regimen be given, even when treatment is delayed. Human rabies immune globulin (HRIG), 20 IU/kg, should be administered as soon after the bite as possible, but not longer than 7 days after tissue culture vaccine has been given. If anatomically feasible, the entire dose of HRIG should be infiltrated into and around the wound(s); any remaining volume should be injected intramuscularly at a site distant from the vaccine.[6]

Human diploid cell vaccine (HDCV) is the vaccine most widely available in the United States. The first dose should be administered on the day of the bite; four subsequent injections are required. The vaccine should be administered in the deltoid rather than the gluteal region, to avoid accidental injection into fat, which will prevent antibody formation.[55,70] HRIG and HDCV should be given in different anatomic sites and

BOX 129-1 RABIES WOUND TREATMENT

- Early treatment is essential (less than 3 hours after the bite/injury occurred).
- Scrub the wound and its edges with soap and water.
- If the wound is a puncture, swab deeply in the wound and around its edges.
- Follow with application of a virucidal agent:
  1% or 2% benzalkonium chloride
  or
  povidone-iodine*
- Rinse.

*Povidone-iodine has never been tested but is recommended by the Centers for Disease Control and Prevention. Tetanus prophylaxis should be given as indicated by patient's current immunization status.

BOX 129-2 RABIES POSTEXPOSURE IMMUNOPROPHYLAXIS

Wound cleansing	All postexposure prophylaxis should begin with immediate thorough cleansing of all wounds with soap and water. If available, a virucidal agent such as povidone-iodine solution should be used to irrigate the wounds.
Nonimmunized Persons	
Human rabies immune globulin (HRIG)	If possible, the full dose should be infiltrated around any wound(s), and any remaining volume should be administered IM at an anatomic site distant from vaccine administration. Also, HRIG should not be administered in the same syringe as for vaccine. Because HRIG may partially suppress active production of antibody, no more than the recommended dose should be given.
Vaccine	Human diploid cell vaccine (HDCV) or purified chick embryo culture vaccine (PCECV) 1.0 mL, IM (deltoid area), one each on days 0, 3, 7, 14, and 28.
Previously Immunized Persons	
HRIG	HRIG should not be administered.
Vaccine	HDCV or PCECV 1.0 mL, IM (deltoid area), on days 0 and 3.

From Centers for Disease Control and Prevention: Rabies post-exposure. Available at http://www.cdc.gov/rabies/exposure/postexposure.html; accessed February 20, 2008.

never mixed in the same syringe. All known treatment failures since 1980 have occurred after a deviation from the recommended regimen. Patients either did not have their wounds cleansed with soap and water, did not receive rabies vaccine in the deltoid region, or did not receive HRIG at the wound site.[40,57,70-72]

Local reactions (itching, erythema, pain, or swelling) occur in 30 to 74% of PEP recipients; systemic reactions including headache, myalgia, and nausea occur in 5 to 40% of recipients, usually those who receive frequent vaccine boosters.[40] Anaphylaxis has occurred in 0.1% of cases; three cases of Guillain-Barré syndrome have occurred after millions of doses given.[40,73] An immune complex type of reaction involving urticaria, arthralgia, arthritis, angioedema, nausea, and vomiting occurs in approximately 6% of patients who receive boosters of HDCV; it is uncommon in those receiving primary vaccination.[40] Two alternative vaccines, rabies vaccine adsorbed (RVA) and purified chick embryo culture (PCEC) vaccine, also are available in the United States. Both appear to be associated with fewer hypersensitivity reactions in patients receiving boosters.[74] Although HDCV may be administered intradermally for preexposure prophylaxis, neither RVA nor PCEC vaccine is approved for intradermal use.

Patients requiring rabies immunoprophylaxis when outside the United States may receive a different regimen and different vaccines from those used within the United States. Some countries still use vaccines derived from nerve tissue, rather than cell cultures, which are poorly immunogenic and carry a greater risk of side effects. In many areas, rabies immune globulin may not be available. The WHO has approved several treatment regimens that reduce cost by giving fewer vaccine injections, or using the intradermal route, which requires less vaccine. Additionally, the WHO recommends immune globulin only for severe bites.[74] These regimens are not approved in the United States for PEP. The WHO cautions that intradermal injections should be administered only by medical personnel who have been trained in this technique.[74,75] Additionally, because chloroquine has been shown to interfere with the antibody response to vaccine given intradermally, victims of bites who are currently receiving malaria prophylaxis (with any medication) should undergo postexposure rabies prophylaxis only by the intramuscular route.[40,74] Accordingly, bite victims traveling abroad may require additional treatment when they return to the United States. Public health officials should be contacted for advice.

Prophylaxis, including both passive and active immunization, given during pregnancy does not result in an increase in fetal wastage, congenital defects, or side effects and should not be withheld when indicated.[76] Corticosteroids, antimalarials, and other immunosuppressives can interfere with the development of active immunity and should be withheld during the course of treatment if possible. Patients who must receive these drugs, or those who are immunosuppressed, should receive prophylaxis by the intramuscular route and have antibody titers checked at 2 to 4 weeks after completion of the injection series.[40,70] Patients with a history of hypersensitivity should nevertheless be cautiously given immunoprophylaxis in a controlled setting, with antihistamines and epinephrine available.[40] Rabies has been reported in a patient who was sensitive to equine antirabies immune globulin and was not given passive immunization.[50,77]

PREEXPOSURE PROPHYLAXIS

For people with frequent exposures to rabies, preexposure prophylaxis may be indicated.[40] Such persons include laboratory personnel working with live rabies virus, veterinarians, animal handlers, and those spending long periods in countries in which rabies is endemic and medical care is difficult to obtain (Table 129-2). Preexposure prophylaxis guarantees protection for persons who incur continuous and unapparent exposures (e.g., lab workers); it also allows protection when postexposure therapy may be delayed (e.g., in remote areas). After an exposure, patients who have had preexposure

Table 129-2 Rabies Preexposure Prophylaxis Guide

RISK CATEGORY	NATURE OF RISK	TYPICAL POPULATION	PREEXPOSURE RECOMMENDATIONS
Continuous	Virus present continuously, often in high concentrations Specific exposures likely to go unrecognized Bite, nonbite, or aerosol exposure	Rabies research laboratory workers; rabies biologics production workers	Primary course Serologic testing every 6 months; booster vaccination if antibody titer is below acceptable level
Frequent	Exposure usually episodic, with source recognized, but exposure also might be unrecognized Bite, nonbite, or aerosol exposure	Rabies diagnostic lab workers, spelunkers, veterinarians and staff, and animal-control and wildlife workers in rabies-enzootic areas. All persons who frequently handle bats	Primary course Serologic testing every 2 years; booster vaccination if antibody titer is below acceptable level
Infrequent	Exposure nearly always episodic with source recognized Bite or nonbite exposure	Veterinarians and terrestrial animal-control workers in areas where rabies is uncommon to rare Veterinary students Travelers visiting areas where rabies is enzootic and immediate access to appropriate medical care, including biologics, is limited	Primary course No serologic testing or booster vaccination
Rare	Exposure always episodic with source recognized Bite or nonbite exposure	U.S. population at large, including persons in rabies-epizootic areas	No vaccination necessary

Adapted from Human rabies prevention—United States, 1999. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 48:1, 1999. Available at http://www.cdc.gov/rabies/exposure/postexposure.html; accessed February 20, 2008.

prophylaxis do not require HRIG; vaccine is given only on days 0 and 3 (see Box 129-2). However, travelers should be aware that chloroquine prophylaxis for malaria can interfere with antibody response to preexposure vaccination given intradermally; therefore, the vaccination regimen should be completed at least 1 month before initiation of malaria prophylaxis, or the preexposure regimen should be given intramuscularly.[7,40]

KEY CONCEPTS

- The epidemiology of rabies in the United States has undergone a major evolution, with the primary source of this disease now in wild animals rather than in domestic animals.
- Despite an increase in the numbers of terrestrial wild animals with rabies, particularly raccoons, the predominant threat to humans in the United States appears to be contact with bats.
- PEP is indicated for victims of bites or significant nonbite exposures from wild carnivores in endemic areas and bat contact when a bite cannot be ruled out and the bat cannot be tested. In most cases in the United States, healthy domestic animals should be observed before initiation of PEP.
- Discussion with public health officials is highly recommended to guide decisions about PEP and reduce the number of unnecessary treatments.
- PEP involves three important components: local wound care with soap and water and a virucidal agent, passive immunization with rabies immune globulin, and active immunization with vaccine. The regimen should be adhered to precisely because treatment failures have occurred when it was not followed.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 130

AIDS and HIV Infection

Richard E. Rothman, Catherine A. Marco, and Samuel Yang

PERSPECTIVE

History

The first cases of AIDS came to light in 1981, when reports of Kaposi's sarcoma (KS) and *Pneumocystis* pneumonia (PCP) in previously healthy homosexual men appeared in the literature. Shortly thereafter, it was recognized that these patients shared the common characteristic of a defect in cell-mediated immunity; accordingly, the clinical disease was designated the *acquired immunodeficiency syndrome* (AIDS). In 1983, a ribonucleic acid (RNA)–type retrovirus, the *human immunodeficiency virus* (HIV), was identified as the causative agent for the syndrome. The development of an antibody assay in 1985 permitted serologic diagnosis, allowing researchers to track the HIV epidemic and identify the principal modes of and risk factors for disease transmission. Significant therapeutic advances have occurred over the past 2 decades with institution of prophylaxis for opportunistic infections and introduction of highly active antiretroviral therapy (HAART) for slowing progression of disease. Despite these advances, HIV continues to be a major public health threat and is responsible for a large number of emergency department (ED) visits, for both acute and subacute conditions, each year.

Epidemiology

Most epidemiologic data regarding HIV infection are derived from studies in patients with illness that meets the definition of AIDS. The most up-to-date definition of AIDS, published in 1997 by the Centers for Disease Control and Prevention (CDC), is shown in Box 130-1.[1] Case definitions include either the presence of one or more AIDS-indicator conditions or laboratory evidence of severe immunosuppression as evidenced by a $CD4^+$ T lymphocyte count of less than 200 cells/μL.

Worldwide estimates indicate that approximately 39.5 million adults and 2.3 million children were living with HIV/AIDS at the end of 2006.[2] Cumulative HIV-related deaths totaled 25 million. Approximately 95% of HIV-infected persons live in the developing world. Sub-Saharan Africa has the highest levels of infection, with more than 25 million persons living with disease and more than 3 million newly reported cases in 2003 (representing approximately 60% of all incident cases). The medical and economic impacts of HIV and AIDS continue to devastate these areas, because these populations have the least access to the medical, social, and economic resources that might prevent new disease or delay the progression of HIV-related illnesses.

In developed countries significant progress has been made in controlling the HIV epidemic. In 1996, for the first time since HIV was recognized, there was a decline in the incidence of AIDS and the number of AIDS-related deaths,[3] attributed primarily to availability of new antiretroviral therapies. Unfortunately, the rates of decline in AIDS cases and AIDS deaths have slowed over the past several years.[4] In the United States an estimated 56,000 new cases of HIV were reported in 2007 and an estimated 1 million persons were living with HIV or AIDS.[4]

Within the United States, HIV-positive persons are concentrated primarily in large urban settings. Until 1987, New York City, Newark, Miami, San Francisco, and Los Angeles accounted for nearly 50% of AIDS cases. Although these cities still represent high-intensity pockets of infection, significant increases also have been seen in smaller metropolitan areas. The percentage distribution of AIDS cases by area of residence in 2001 was 81% from large metropolitan areas and 7% from nonmetropolitan areas. As of 2007 the ten states reporting the highest number of cumulative AIDS cases were New York, California, Florida, Texas, New Jersey, Pennsylvania, Illinois, Maryland, Georgia, and Massachusetts.

The incidence of HIV infection has remained relatively stable, at 40,000 new cases per year, although new methods of estimating HIV incidence currently under investigation suggest that this may be an underestimate. Approximately 80% of AIDS cases have occurred in adult men, 18% in adult women, and just over 1% in children. The proportion of adult women among those infected with HIV has increased over the past several years, with adult women now representing 26% of those living with HIV/AIDS.[2,4] Nearly one half of all people who are infected with HIV in the United States become infected before they turn 30, and the vast majority will die before reaching the age of 45 years. There is a disproportionate rate of infection among minority groups, with African Americans and Hispanics accounting for an ever-increasing proportion of new HIV cases and persons living with AIDS. In 2005, more than 70% of all AIDS cases diagnosed occurred in minority racial or ethnic groups.[4]

The primary risk factors associated with an increased likelihood of acquiring HIV infection include homosexual or bisexual orientation, intravenous drug use, heterosexual exposure to a partner at risk, blood transfusion before 1985, and vertical and horizontal maternal-neonatal transmission. A greater

BOX 130-1 AIDS-DEFINING ILLNESSES*

Laboratory-confirmed evidence of HIV infection *and*

Bacterial infections, multiple or recurrent
Candidiasis of bronchi, trachea, or lungs
Candidiasis of esophagus
CD4+ lymphocyte count of <200 cells/μL
Cervical cancer, invasive
Coccidioidomycosis, disseminated or extrapulmonary
Cryptococcosis, extrapulmonary
Cryptosporidiosis, chronic intestinal (>1 month's duration)
Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 month
Cytomegalovirus retinitis (with loss of vision)
Encephalopathy, HIV related
Herpes simplex: chronic ulcers (>1 month's duration or bronchitis, pneumonitis, or esophagitis (onset at age >1 month)
Histoplasmosis, disseminated or extrapulmonary
Isosporiasis, chronic intestinal (>1 month's duration)
Kaposi's sarcoma
Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia complex
Lymphoma, Burkitt (or equivalent term)
Lymphoma, primary, of brain
Mycobacterium avium complex or *Mycobacterium kansasii*, disseminated or extrapulmonary
Mycobacterium tuberculosis of any site, pulmonary, disseminated, or extrapulmonary
Mycobacterium, other species of unidentified species, disseminated or extrapulmonary
Pneumocystis jiroveci pneumonia
Pneumonia, recurrent
Progressive multifocal leukoencephalopathy
Salmonella septicemia, recurrent
Toxoplasmosis of brain, onset at age >1 month

*From the Centers for Disease Control: Revised surveillance case definitions for HIV infection among adults, adolescents, and children ages <18 months and for HIV infection and AIDS among children ages 18 months to <13 years—United States, 2008. MMWR: Recommendations and Reports 2008 (RR10), pp 1–8. Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5710al.htm?s_cid=rr5710al_e. Accessed April 4, 2009.

number of risk factors is associated with a greater likelihood of infection. CDC HIV surveillance data demonstrate significant changes in the distribution of newly acquired HIV cases over the past several years. A relative decrease in newly acquired HIV infection has been documented among homosexual and bisexual men, and a relative increase in incidence of infection has been noted among intravenous drug users and heterosexual contacts. The change in the distribution of AIDS cases in adults and adolescents by mechanism of transmission since the start of the HIV epidemic is shown in Figure 130-1.

During the past several years, the greatest percentage increase in reported AIDS cases has occurred among women (attributed principally to heterosexual exposure from an infected partner), in minority populations, and among children. Because these populations often lack access to primary health services and frequently are underinsured, an emerging trend has been toward increasing use of ED services by patients with HIV infection and AIDS. Surveillance data from centers in Baltimore, Chicago, Atlanta, and New York City indicate HIV seroprevalence rates ranging from 2 to 15%.[5]

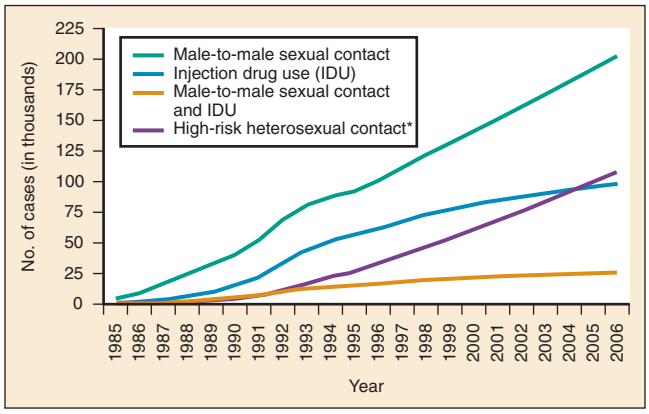

Figure 130-1. Proportions of AIDS cases among adults and adolescents by exposure category and year of diagnosis, 1985 to 2001, United States. (From Centers for Disease Control and Prevention: AIDS Surveillance—Trends [1985–2006]. Available at: http://www.cdc.gov/hiv/graphics/trends.htm.)

PRINCIPLES OF DISEASE

Pathophysiology

HIV is a cytopathic human retrovirus that belongs to the lentivirus subfamily. The two major subtypes of HIV are HIV-1 and HIV-2. HIV-1 is the predominant subtype worldwide and is the cause of AIDS. HIV-2 causes a similar immune syndrome but is rarely seen in the United States being restricted primarily to western Africa.

The HIV virion is composed of a central single-stranded RNA molecule and the enzyme reverse transcriptase. These are surrounded by a core protein and a lipid bilayer envelope that contain virally encoded transmembrane proteins critical for recognition and attachment to target host lymphocytes (predominantly $CD4^+$ cells). HIV-1 has been isolated from a variety of body fluids including blood, serum, semen, vaginal secretions, urine, cerebrospinal fluid (CSF), tears, breast milk, bone marrow, alveolar fluid, synovial fluid, amniotic fluid, and saliva. Only a few modes of transmission have been proved: in semen, vaginal secretions, blood or blood products, and breast milk and transplacental transmission in utero. There have been no instances of transmission by casual contact, although one case report described possible salivary transmission. The HIV virion is extremely labile and easily neutralized by heat and common disinfecting agents such as 50% ethanol, 35% isopropyl alcohol, 0.3% hydrogen peroxide, disinfectant (Lysol), or a 1:10 solution of household bleach (sodium hypochlorite).

HIV selectively attacks cells within the immune system (primarily T_H4 helper cells, but macrophages and monocytes also may be involved), a characteristic that accounts for much of the immunodeficiency it produces in affected persons. HIV-1 transmembrane proteins gp41 and gp120 play a critical role in recognition and attachment of HIV virions to receptors on host lymphocytes. After infection, viral RNA is reverse-transcribed into deoxyribonucleic acid (DNA) by reverse transcriptase, one of the critical enzymes required for HIV replication. The viral genome thus becomes permanently integrated into the host's genome. Once integrated, retroviral DNA may lie dormant, or it may be actively transcribed and translated to produce virally encoded proteins and new HIV virions. HIV protease is another critical retroviral enzyme in the life cycle of the virus, responsible for activation of viral protein precursors into the functional enzymes required for virion infectivity.

Primary HIV exposure is characterized by a transient viremia and a decrease in $CD4^+$ cell counts, followed by establishment of equilibrium between virus and host immunity. A persistent latent period, during which the virus lies dormant in the host genome, can last for years. The "set point" or steady-state viral load level in the blood of the patient allows prediction of long-term clinical outcomes. Lower levels of viremia correlate with longer clinical latency periods. In the later stages of HIV infection, a sudden increase of viremia correlates with a dramatic decrease in $CD4^+$ T lymphocytes. These hematologic changes are followed by the appearance of opportunistic infections or malignancies and ultimately death.

HIV-1 is highly heterogeneous. Multiple genetic subtypes exist in a variety of geographic and sociologic settings. Further genetic diversity exists within individual hosts owing to the highly mutable character of the virus. High error rates, which are associated with reverse transcription, ensure extensive viral diversity, a critical factor in the pathogenesis of infection and ongoing emergence of drug-resistant phenotypes.[6]

Tests for Human Immunodeficiency Virus Infection

General Approach

HIV infection most commonly is established by HIV serologic studies or by detection of antibodies to the virus. Testing involves sequential use of an enzyme immunoassay (EIA) and a Western blot assay. Criteria for positive results are positive results on EIA followed by Western blot assay. EIA detects the binding of specific serum antibodies to HIV antigens that are adherent to a microtiter plate. Western blot assay detects electrophoretically separated viral antigens in the patient's serum. A positive Western blot result requires detection of two of the following: p24, gp41, or gp120/160. Final HIV serology results are reported as positive, negative, or indeterminate. Overall sensitivity and specificity rates for HIV serologic testing are greater than 99.9%.

False-negative HIV test results are accounted for primarily by testing too early, during the "window period" (usually the first several months) of acute infection, after viral transmission but before the appearance of antibodies. Rates of false-negative testing range from 0.3% in high-prevalence populations to less than 0.001% in low-prevalence populations. Ninety-five percent of false-negative test results become positive by 3 months and 98% by 6 months. A less common explanation for false-negative results is seroreversion, which may occur in late-stage disease or in patients on HAART regimens, or in those harboring atypical strains of HIV-1 or with HIV-2 infection. False-positive test results are exceedingly rare (with a frequency of less than 0.0004%); they may occur in several clinical populations, including (1) recipients of transfused blood containing the HIV antibody; (2) children younger than 6 months of age, in whom a positive test result may be caused by transplacentally acquired antibodies; (3) patients with cross-reacting antibodies (e.g., antihepatitis A immunoglobulin M [IgM], antihepatitis B core IgM, antinuclear, anti-smooth muscle, anti-parietal cell, and antimitochondrial antibodies); and (4) patients with cross-reactive human lymphocyte antigens (HLAs) from the H9 cell line or other human retroviruses. In populations with a low prevalence of true-positive results (e.g., heterosexual men or women in low-seroprevalence areas), the frequency of false-positive results (on both EIA and Western blot assay) is increased. This finding has been cited as one of the reasons for not offering indiscriminate HIV screening in the ED.

Indeterminate results are most common with a positive EIA result and a single band (rather than two or three) on Western blot assay. In evaluating an indeterminate result on the latter, the patient's risk profile should be assessed. Low-risk patients with indeterminate results are rarely infected with HIV-1 or HIV-2, and repeat testing usually shows persistence of one band, with the cause rarely established. Referral to an infectious disease specialist and follow-up serologic testing at 3 months are indicated. Patients in higher-risk groups with indeterminate results usually are found to have definitively positive results on Western blot assay 3 or 6 months later and therefore should be counseled to follow appropriate risk-reduction behavior until follow-up definitive testing is completed.

Other methods for detection of HIV infection include detection of virus-specific antigens and assays for HIV nucleic acid. Neither of these techniques is considered superior to routine serologic tests in terms of accuracy, and they should be used only in patients with confusing serologic results requiring clarification; in the ED, the most common situation in which viral detection testing may be considered is in cases of suspected acute retroviral infection. Quantitative plasma HIV RNA assay is most commonly employed and is routinely used for HIV staging and monitoring of response to retroviral therapy. Test results are reported as copies per milliliter, with survival time directly correlated with viral burden. Sensitivity of the various viral detection methods varies with stages of diseases but generally is greater than 99% for DNA polymerase chain reaction (PCR) assay, 90 to 95% for quantitative HIV RNA assay, and 95 to 100% for viral culture of peripheral blood mononuclear cells.

The U.S. Food and Drug Administration (FDA) has approved a number of rapid HIV tests. These tests are easy to use and can be performed at the bedside or in a nearby satellite laboratory using saliva or fingerstick or whole blood specimens. Delivery of results is possible in as little as 10 to 20 minutes. Sensitivity and specificity is approximately 99%. Negative test results can be reported immediately as negative; reactive test results require confirmatory follow-up testing with a Western blot assay and should be reported as reactive. The first test to receive FDA approval is the OraQuick Rapid HIV-1 Antibody Test (OraSure Technologies, Inc., Bethlehem, Pennsylvania). Advantages of rapid test technologies include ease of specimen collection, reduced costs, rapid availability of results, and improved compliance with testing.

Human Immunodeficiency Virus Testing in the Emergency Department

Traditionally it has been thought that serologic testing of patients for HIV infection in the ED is not indicated. With the advent of rapid testing methodologies, the concept of ED testing for HIV infection is being reexamined. This is being driven by a number of factors, including the ease of the testing process, the recognized value of knowing a patient's HIV status if the acute clinical presentation raises suspicion for disease, and the now-widespread recognition that early detection of HIV infection (and early therapeutic intervention) provides a significant health benefit both for individual patients and for the community. Benefits to the infected patient include delaying progression of disease and reducing the risk of opportunistic infections; an important advantage for the community includes decreased disease transmission associated with reduction in high-risk behavior in persons who are aware of their HIV serostatus.

The most recent CDC guidelines for HIV testing, released in 2007, recommend that such testing be performed in health care settings.[7] These guidelines give special emphasis to the

role of the ED, driven largely by multiple studies showing that the ED is the most frequent site of encounter with the health care system for persons with unrecognized HIV infection (representing approximately 30% of all patients infected). Shortly after the CDC guidelines were published, the American College of Emergency Physicians (ACEP) released a corresponding policy statement supporting the availability of HIV testing for evaluation of related acute care conditions, indicating that testing and results should be available in an expeditious and efficient fashion, as with the management of other conditions. With regard to HIV *screening*, the policy suggests that individual institutions need to consider the appropriateness and feasibility of screening based on the particular characteristics of their ED and available resources. A list of important considerations that must be attended to before initiation of such a program is provided in the ACEP statement.[8] For institutions considering establishing ED-based HIV testing and screening programs, the American Hospital Association provides an online guide.[9]

A number of EDs around the country have implemented HIV testing using both rapid and traditional testing approaches.[10-12] Such HIV testing programs have included both routine, broad-based screening and focused testing based on clinical suspicion. Funding for implementation has been supported in part by the CDC as well as by state and local health departments. In spite of some success, barriers to implementing screening (more so than clinically based testing) remain. Most important among these barriers are time constraints, financial burdens, impact of testing on ED crowding, and concerns regarding the responsibility for ensuring follow-up care.[11,13,14]

Emergency physicians need to be aware of state laws and local regulations governing testing. Although separate informed consent or formal pretest counseling is no longer considered mandatory by the CDC,[15] many states have laws requiring informed consent before testing.[16] AIDS is a reportable disease in all 50 states, and HIV infection is reportable in most states. As of 2007, 47 states are conducting confidential name-based HIV infection reporting, based on the 2005 CDC recommendations.[17]

CLINICAL FEATURES

The broad spectrum of disease presentation for HIV-related disorders ranges widely from asymptomatic seropositive status to severe, life-threatening complications of AIDS. Included are a wide variety of opportunistic infections, malignancies, and other HIV-related diseases. Nearly every organ system may be affected by HIV infection and related conditions. Because the differential diagnosis is so broad in scope for many ED presentations, this chapter addresses clinical symptoms, signs, and focused information on some of the more common disorders.

Initial Evaluation of the Human Immunodeficiency Virus–Infected Patient

The initial evaluation and management of the HIV-infected patient consist of rapid and early assessment of stability. Any problems with airway, breathing, and circulation must be promptly identified and appropriate interventions performed. For unstable patients, intravenous access, cardiac monitoring, and administration of oxygen typically are indicated. After initial stabilization, the remainder of the history and physical examination may be conducted.

Relevant elements of the history include information pertinent to the chief complaint, including duration, location, qualities, characteristics, level of distress, and relieving or inciting factors. The past medical history should identify a previous history of similar problems, the time of diagnosis of HIV infection, previous AIDS-defining conditions, recent hospitalizations, past surgical history, current medications, and allergies. The existence of an advance directive may be important historical information, because many HIV-infected patients have expressed opinions about the level of intervention desired in various clinical settings, particularly in critical care settings and at the end of life.

Information regarding potential risk factors for HIV infection may be appropriate to gather in the ED evaluation in patients not known to be HIV-seropositive, particularly in endemic areas. The infection rate may be surprisingly high, even for those patients with presenting complaints not associated with HIV infection. Furthermore, inquiries about risk factors help direct the medical evaluation, remind ED personnel of the potential for occupational exposure to the virus, and afford the opportunity to offer referral for testing and counseling to persons who engage in high-risk behavior. Many cases of early HIV infection may not be detected during ED evaluation because of a low clinical suspicion for the disease, particularly in areas with a low prevalence of AIDS. Although inquiries regarding risk factors may be offensive to some patients, any difficulty usually can be averted by beginning with tactful inquiries about previous HIV testing or risk factors and indicating that these questions are routinely asked in the ED.

After initial stabilization and gathering of historical information, a focused physical examination should be conducted. In elements of the examination relevant to the chief complaint, special attention should be paid to the identification of potentially treatable disorders.

The universal goals of ED management are to rapidly and effectively assess the patient, identify potentially life-threatening disorders, administer urgent interventions, generate an appropriate differential diagnosis, and provide or arrange for appropriate initial therapy, consultation, and disposition.

Stages of Human Immunodeficiency Virus Infection

Several methods of classification and staging of HIV infection have been developed. The Walter Reed classification system is based on clinical and immunologic features. Other classifications are based on $CD4^+$ counts.[18] In 1993, the CDC case definition of AIDS incorporated $CD4^+$ counts of less than 200 cells/μL as an AIDS-defining condition. The median survival time for *untreated* patients with AIDS is 3.7 years for those with $CD4^+$ cell counts less than 200 cells/μL and 1.3 years for those with their first AIDS-defining complication (see Box 130-1).

Primary Human Immunodeficiency Virus Infection

Acute HIV syndrome (acute seroconversion syndrome) commonly follows primary exposure by 2 to 4 weeks and may be associated with nonspecific flulike symptoms and signs such as fever, adenopathy, fatigue, pharyngitis, diarrhea, weight loss, and rash. Additional signs and symptoms such as myopathy, peripheral neuropathy, or other neurologic or immunologic manifestations are less common.[19] These relatively nonspecific problems are seen in approximately 40 to 90% of patients and usually last 1 to 3 weeks. The differential diagnosis of acute HIV infection is broad in scope; considerations mainly include a wide variety of viral illnesses, such as Epstein-Barr virus (EBV) infection and viral hepatitis. Pres-

ence of a rash or mucocutaneous ulcers should raise suspicion for acute HIV seroconversion.

During the acute phase of HIV infection, results of standard HIV testing (enzyme-linked immunosorbent assay [ELISA] antibody testing) usually are negative, because the median time for seroconversion is approximately 2 months. If acute HIV infection is strongly suspected (on the basis of presentation and history of recent exposure), RNA viral load testing can be performed, either in the ED or by referral. Identification of acute HIV is important because HIV viral load is significantly higher during this phase of the illness and the risk of transmission is elevated. No current consensus has emerged among HIV experts, however, regarding the optimal timing and treatment regimen for acute HIV infection. Accordingly, any patient identified as having acute infection should be referred for urgent evaluation by an HIV specialist.

Predictors of Disease Progression

Although the rate of disease progression from initial HIV infection to development of AIDS-defining illnesses varies widely, the average time is 10 to 12 years. Some long-term nonprogressors have remained free of AIDS-defining conditions for more than 20 years. Clinical predictors of more rapid development of clinically significant immunodeficiency include oral candidiasis, oral hairy leukoplakia, dermatomal varicella, lymphadenopathy, and constitutional symptoms.[20,21] The best predictor of immunologic susceptibility to opportunistic infection is the $CD4^+$ cell count.[22] Other laboratory markers of disease progression include neutropenia and plasma HIV-1 RNA determinations.

Complications

Systemic Symptoms and Signs of Human Immunodeficiency Virus Infection

Systemic symptoms and signs such as fever, weight loss, and malaise are common among patients presenting to the ED. The differential diagnosis is lengthy and includes a variety of infectious causes, malignancy, and drug reactions (Box 130-2). Fever is a common presenting complaint in patients with AIDS. Evidence of an infectious cause or other reason for fever should be sought by careful history and physical examination. Initial workup for the cause of fever in an immunocompromised patient may include a complete blood count, electrolytes, comprehensive metabolic panel (CMP), chest radiograph, urinalysis and culture, and blood cultures (aerobic, anaerobic, mycobacterial, and fungal). Additional testing, based on current and past medical history and physical exam, may include stool (for culture, examination for ova and parasites, and Gram's stain), urine (for histoplasmosis and fungal and mycobacterial culture), and induced sputum (for smear fungal and mycobacterial culture) studies; erythrocyte sedimentation rate determination; liver function tests; serum cryptococcal antigen assay; and serologic tests for syphilis, *Toxoplasma*, and *Coccidioides*. In the absence of neurologic signs or symptoms or if no other source of fever is identified, lumbar puncture should be considered after a cranial computed tomography (CT) scan. Two of the most common causes of febrile illness in patients with later-stage HIV are disseminated atypical mycobacterial infections and cytomegalovirus (CMV) infection.

Atypical mycobacteral infections, caused by *Mycobacterium avium* complex or *M. kansasii*, cause disseminated disease in up to 50% of patients with AIDS and usually are associated with $CD4^+$ counts less than 100 cells/μL. Presentation typically includes severe weight loss, diarrhea, and various constitutional symptoms, such as fever, malaise, and anorexia. Anemia is common. Ziehl-Neelsen (acid-fast) stain of stool or other body fluids commonly yields positive findings, and the organism also can be cultured from blood. Treatment for *M. avium* complex infection consists of clarithromyin, 500 mg twice a day, and ethambutol, 15 mg/kg daily. Such regimens often reduce the degree of bacteremia and symptomatology but typically do not eradicate the organism. Clarithromycin or azithromycin should be used for prophylaxis in patients with $CD4^+$ counts below 50 cells/μL.

Disseminated CMV infections typically occur in patients with $CD4^+$ counts below 50 cells/μL. In addition to fever, patients often present with odonophagia, abdominal pain, and diarrhea secondary to esophagitis and colitis. Diagnosis usually requires endoscopy or colonoscopy for biopsy, because culture has poor sensitivity. Complications include gastrointestinal bleeding and perforation. Treatment includes immune restoration with antiretrovirals and a regimen of ganciclovir or foscarnet. Oral ganciclovir is used for prophylaxis.

Some patients with HIV infection and fever or other systemic symptoms may be managed on an outpatient basis if they are not severely immunosuppressed and not systemically ill. Requirements for discharge from the ED include ability to take oral fluids, assurance of timely follow-up including obtaining results of ED-initiated cultures, and capability of providing adequate self-care. Indications for hospital admission include

BOX 130-2 ETIOLOGY FOR SYSTEMIC SYMPTOMS IN HUMAN IMMUNODEFICIENCY VIRUS (HIV)–INFECTED PATIENTS

Infections
Primary HIV infection (e.g., acute retroviral syndrome, HIV wasting syndrome)

Protozoal Infections
Pneumocystis jiroveci pneumonia
Toxoplasmosis
Cryptosporidiosis

Bacterial Infections
Streptococcus pneumoniae infection
Haemophilus influenzae infection
Pseudomonas aeruginosa infection
Salmonellosis
Bacteremia (any organism)

Atypical Bacterial Infections
Mycobacterium avium-intracellulare (MAI) infection
Mycobacterium tuberculosis (MTB) infection

Fungal Infections
Histoplasmosis
Cryptococcosis
Coccidioidomycosis

Viral Infections
Herpes simplex virus infection
Herpes zoster virus infection
Cytomegalovirus infection
Hepatitis virus infections

Noninfectious Processes
Adverse drug reactions

Neoplasms
Kaposi's sarcoma
Lymphoma
Hodgkin's disease

toxic appearance, neutropenia with fever, active bleeding, or other need for urgent diagnosis and treatment. For patients with persistent fevers, in whom one or more of the discharge criteria are not met, hospitalization is warranted.

Pulmonary Involvement

Pulmonary manifestations of HIV infection are among the most common reasons for ED visits among patients with AIDS. Careful consideration is mandated to establish the diagnosis and initiate early treatment. The differential diagnosis of respiratory involvement is broad in scope; considerations include bacterial infections (e.g., *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Chlamydia pneumoniae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Mycobacterium tuberculosis* [MTB], *Mycobacterium avium-intracellulare* [MAI] complex), fungal infections (e.g., *Pneumocystis jiroveci* [formerly *Pneumocystis carinii*], *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Aspergillus fumigatus*, *Blastomyces dermatitides*), viral infections (e.g., cytomegalovirus, adenoviruses), protozoal infections (e.g., *Toxoplasma gondii*), malignancies (e.g., Kaposi's sarcoma, carcinoma, lymphoma), and others (e.g., lymphocytic interstitial pneumonitis, pulmonary hypertension, pulmonary embolism).

Occurrence of specific pulmonary infections often is related to $CD4^+$ counts. In patients with pulmonary involvement and $CD4^+$ counts greater than 500 cells/μL, encapsulated bacteria, tuberculosis, and malignancies are common. With lower $CD4^+$ counts, PCP, infections due to atypical mycobacteria, fungal infections, cytomegalovirus infection, lymphoma, lymphoproliferative disorders, and Kaposi's sarcoma are seen with increasing frequency.

Patients with fever and a productive cough are likely to have a bacterial pneumonia, whereas a nonproductive cough is more likely to accompany PCP, other fungal infections, or neoplasm. Hemoptysis often is associated with pneumococcal pneumonia and tuberculosis. Fulminant respiratory failure is most likely to be caused by *Pneumocystis jiroveci* (the agent of PCP) or CMV.

Diagnostic evaluation of patients with HIV infection and suspected pneumonia should routinely include pulse oximetry, chest radiography, and complete blood count. Additional testing based on the stage of disease and clinical presentation may include arterial blood gas (ABG) analysis, serum lactate dehydrogenase determination, assays for serum cryptococcal antigen and urine *Histoplasma* antigen, and induced sputum specimen studies including Gram stain, acid-fast bacillus (AFB) smear, and Gomori, Giemsa, or immunofluorescent antibody (IFA) staining for *Pneumocystis jiroveci*. Blood culture specimens should be obtained in the ED from all HIV-infected patients with suspected pneumonia; this component of the evaluation becomes increasingly important in patients with later-stage disease. Blood culture collection, however, should not delay the initiation of antimicrobial therapy.

Although radiographic findings in many pulmonary complications may be nondiagnostic, certain patterns may be suggestive of specific disorders. A focal infiltrate on the plain chest film often suggests bacterial pneumonia, whereas a diffuse interstitial or perihilar, granular pattern is associated with PCP. PCP is suggested by increased serum lactate dehydrogenase and hypoxia (especially exercise-induced), which may be more severe than expected from radiographic findings. Hilar adenopathy with diffuse pulmonary infiltrates suggests cryptococcosis, histoplasmosis, mycobacterial infection, or neoplasm. Kaposi's sarcoma (KS) can manifest with cough, fever, and dyspnea and may mimic PCP on the chest radiograph. Table 130-1 lists common radiographic findings and associated conditions in the HIV-infected patient.

Table 130-1 Chest Radiographic Abnormalities: Differential Diagnosis in the AIDS Patient

FINDING	POTENTIAL ETIOLOGIES
Diffuse interstitial infiltration	*Pneumocystis jiroveci* Cytomegalovirus *Mycobacterium tuberculosis* *Mycobacterium avium* complex Histoplasmosis Coccidioidomycosis Lymphoid interstitial pneumonitis *Mycoplasma pneumoniae*
Focal consolidation	Bacterial pneumonia *Mycoplasma pneumoniae* *Pneumocystis jiroveci* *Mycobacterium tuberculosis* *Mycobacterium avium* complex
Nodular lesions	Kaposi's sarcoma *Mycobacterium tuberculosis* *Mycobacterium avium* complex Fungal lesions Toxoplasmosis
Cavitary lesions	*Pneumocystis jiroveci* *Mycobacterium tuberculosis* Bacterial infection Fungal infection
Pleural effusion	Kaposi's sarcoma (small effusion may be associated with any infection)
Adenopathy	Kaposi's sarcoma Lymphoma *Mycobacterium tuberculosis* *Cryptococcus*
Pneumothorax	Kaposi's sarcoma
Normal radiograph	Histoplasmosis (40%) *Pneumocystis jiroveci* (20%) *Mycobacterium tuberculosis* Cryptococcosis Many other disease entities

As with all disease processes, ED management of pulmonary complications must first include stabilization with appropriate support of airway, breathing, and circulation. Definitive airway management may be indicated in severe cases. Volume repletion or pressors, or both, may be indicated for hypotension. Other treatment measures should include administration of supplemental oxygen and volume repletion if indicated. If the diagnosis can be ascertained or is strongly suspected, specific treatment should be instituted while the patient is in the ED, particularly if PCP is suspected. If the symptoms are of new onset or there has been a change from previous status, hospitalization should be considered. Decisions regarding patients with known pulmonary involvement are based on comparison with baseline status, the effectiveness of ongoing or previous treatment, and the individual's ability to obtain outpatient follow-up observation (see "Disposition"). The Pneumonia Outcomes Research Team (PORT) study did not include HIV-infected patients, and most experts suggest that hospital admission should be more readily considered for patients with HIV infection and pneumonia. Staging systems for predicting death from HIV-associated pneumonia found that clinical factors associated with increased mortality include the presence of neurologic symptoms, respiratory rate of 25 breaths per minute or less, and creatinine level greater than 1.2 mg/dL.[22]

Bacterial infections are the most frequent type of pulmonary infection among patients with AIDS and commonly are caused

by *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, and numerous other organisms.[23] Infections with *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella* are relatively less common. *P. aeruginosa* is a more common pathogen in later stages of AIDS. Presentations of bacterial pneumonia may be typical or atypical in symptoms, duration, and severity. Severely ill patients with pneumonia being managed in an ICU should be treated with linezolid or vancomycin, an antipseudomonal agent, in addition to a macrolide or respiratory fluoroquinolone.

Pneumocystis Pneumonia

PCP is one of the most common opportunistic infections in AIDS. More than 80% of patients with AIDS acquire PCP at some time during their illness, and it is the initial opportunistic infection in many cases. As noted earlier, PCP is caused by the organism *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*[24]—the original basis for the "PC" in *PCP*, which remains in use to refer to *Pneumocystis* pneumonia). Although *P. jiroveci* traditionally is classified as a protozoan, its morphology has been suggested to closely resemble that of a fungus.[25] The incidence of PCP has declined since the widespread use of HAART.[26]

Patients typically present with an insidious cough (often nonproductive), dyspnea, unexplained fever for longer than 2 weeks, chest pain, and fatigue. The chest radiograph commonly shows a diffuse interstitial infiltrate but also may be normal in appearance or reveals asymmetry, nodules, cavitation, or bullae.[27] Considerations in the differential diagnosis include viral, bacterial, mycobacterial, fungal, and protozoal pneumonias, as well as malignancies. The more common causes to be considered in the differential diagnosis are shown in Box 130-2. Negative findings on the chest radiograph are reported in up to 20% of patients ultimately found to have PCP.[28] In situations in which a high clinical suspicion exists for PCP, chest CT should be performed; CT findings frequently are suggestive of PCP. Gallium scanning of the chest also offers improved sensitivity over that of chest radiography, but this modality generally is not available in the ED and is associated with a high false-positive rate. Serum LDH often is elevated in patients with PCP (sensitivity of approximately 90%) but, again, has poor specificity so it cannot be used for definitive diagnosis.

In the ED, a presumptive diagnosis of PCP can be made in a patient with later-stage HIV ($CD4^+$ count less than or in the range of 200 cells/μL) with unexplained hypoxia when other causes (e.g., pulmonary embolism) have been eliminated. The organism cannot be grown in the laboratory, so diagnosis relies on indirect IFA staining using monoclonal antibodies. Studies using induced sputum (often not practical to obtain in the ED) have a relatively low sensitivity. Accordingly, bronchoscopy (bronchoalveolar lavage, brush biopsy, or transbronchial biopsy) often is required for establishing the diagnosis. Establishment of a definitive diagnosis is not necessary before the initiation of treatment. Treatment should begin as early as possible with 15 to 20 mg/kg per day of trimethoprim and 75 mg/kg per day of sulfamethoxazole (TMP-SMX), given either orally or intravenously in two or three daily divided doses for a total of 21 days (e.g., two Bactrim DS tablets every 8 hours). Indications for intravenous therapy include tenuous respiratory status, an alveolar-arterial gradient above 45 mm Hg, and Pao_2 below 60 mm Hg. Other therapeutic agents that can be used with PCP include pentamidine isethionate, dapsone, clindamycin plus primaquine, atovaquone, and trimetrexate. Steroid treatment (prednisone 40 mg PO, twice daily for five days with a 3-week taper) is recommended for patients with a Pao_2 less than 70 mm Hg, or an alveolar-arterial gradient greater than 35 mm Hg.[29] Most patients (60 to 80%) respond to therapy, although *Pneumocystis* persists in the lungs of two thirds of patients. All patients requiring steroids should be hospitalized because clinical status in those with PCP typically will worsen a few days after the initiation of therapy.

Adverse effects of TMP-SMX occur in up to 65% of patients with AIDS and are 20 times more common than in the general population (Table 130-2); such effects generally become apparent after 7 to 14 days of therapy. The most common adverse effects are nausea, vomiting, rash, fever, neutropenia, thrombocytopenia, hyponatremia, and hepatitis. Pentamidine can cause nausea, vomiting, diarrhea, neutropenia, hypoglycemia, hyperglycemia, renal impairment, hepatic toxicity, and orthostatic hypotension.[30] Because sterile abscesses may develop at the injection site, intravenous infusion is preferred. Prophylaxis (with Bactrim DS, one tablet by mouth once daily) against PCP may be an important step in preventing reinfection and is recommended for patients with $CD4^+$ cell counts below 200 cells/μL.[31]

The mortality rate for PCP-associated respiratory failure is close to 60%. Patients requiring ventilatory support should be maintained on low tidal volumes and plateau pressures, because PCP is associated with an increased risk of pneumothorax. The presence of a pneumothorax in a patient with a low $CD4^+$ count should be presumed to be caused by PCP, although KS, intravenous drug use, toxoplasmosis, and viral, fungal, and mycobacterial infections also can cause pneumothoraces. Asymptomatic patients with a small pneumothorax (involving less than 20% of lung volume) may be treated with observation or insertion of a Heimlich valve.

Mycobacterium Tuberculosis Infection

The incidence of MTB infection in HIV-infected patients has increased dramatically, and it is estimated that over 10 million patients worldwide are co-infected with HIV and tuberculosis.[32] HIV-infected patients have an estimated 50- to 200-fold increased risk of acquiring tuberculosis over the general population.[33] The increase in tuberculosis among the HIV-infected population is thought to be due to a number of factors, including increased risk of reactivation of latent infection, high rates of infection after exposure, overlap in at-risk groups, and rapid progression to clinically significant disease. Tuberculosis may be a very early manifestation of AIDS.

Common presenting signs and symptoms include fever, cough, and hemoptysis, but in patients with immunosuppression, clinical manifestations are more atypical and extrapulmonary findings more common. Classic radiographic abnormalities are upper lobe alveolar lesions with cavitation accompanied by pleural effusions and mediastinal adenopathy.[34] Findings may vary considerably, however, and atypical features and absence of radiographic abnormalities are more common among patients with lower $CD4^+$ cell counts.[35] Central nervous system (CNS), bone, visceral, skin, pericardial, eye, pharynx, and lymph node involvement also may occur.

The diagnosis of tuberculosis is based on a number of factors, including risk of infection, clinical presentation, direct examination of patient specimens, and identification of mycobacteria from cultures.[36] Because a definitive diagnosis cannot be made in the ED, and the disease is transmitted by the aerosol route, isolation and hospital admission are indicated for any patient with suggestive clinical factors. Definitive laboratory diagnosis can be made by a nucleic acid amplification test (NAAT), an AFB smear, or culture evaluation of induced sputum specimens or samples obtained on bronchoscopy. NAAT has a higher sensitivity than AFB smear, and bronchoscopy or tissue biopsy a higher yield than induced sputum.

Table 130-2 Common Drug Reactions in HIV-Infected Persons*

	FEVER	RASH	N/V	DIARRHEA	H/A	ΔMS	NEUROPATHY	↑ LFT	↓ WBC	↓ HCT	↓ PLT	OTHER
Acyclovir		X	X	X								Vertigo
Amphotericin	X		X		X				X	X	X	Nephrotoxicity
Atovaquone	X	X	X	X	X				X	X		
Azithromycin		X	X	X	X							
Clarithromycin			X	X	X							
Clindamycin		X										
Clotrimazole			X	X								
Dapsone	X	X	X		X				X	X		Hepatitis
Didanosine		X	X	X	X	X	X					Pancreatitis
Fluconazole		X	X	X	X			X				
Foscarnet	X		X	X						X		Nephrotoxicity, seizures
Ganciclovir	X		X	X					X	X		
Ibuprofen		X	X	X				X	X	X		
Indinavir		X	X		X							Nephrolithiasis
Isoniazid	X	X	X				X	X	X	X	X	Hepatitis
Itraconazole		X	X	X	X			X				
Ketoconazole			X	X				X				
Lamivudine	X		X	X	X		X					Cough
Narcotics			X			X						
Pentamidine		X							X	X		Metallic taste
Pyrimethamine									X	X		
Rifabutin		X	X					X	X		X	Skin discoloration
Ritonavir			X	X	X							Paresthesias
Saquinivir		X	X	X								
TMP-SMX	X	X	X					X	X		X	Hepatotoxicity, ↓K
Zalcitabine	X	X	X	X	X		X					
Zidovudine	X	X	X	X	X	X			X	X		

*This table represents only a partial list of adverse drug reactions. An authoritative source should be consulted whenever adverse drug reactions are suspected.

Purified protein derivative (PPD) skin testing generally is not helpful, particularly in patients with more advanced immunosuppression, because negative PPD test results are common among those infected. Dissemination of pulmonary infection results in miliary tuberculosis, which can affect nearly every organ system.

Treatment of patients with suspected tuberculosis should be determined in conjunction with an infectious disease specialist, taking into consideration local resistance as well as individual susceptibility tests. Patients with AIDS found to have tuberculosis should receive a four-drug regimen consisting of isoniazid, rifampin, pyrazinamide, and ethambutol, for 6 months.[37,38] Second-line agents include ciprofloxacin, ofloxacin, kanamycin, amikacin, capreomycin, ethionamide, cycloserine, and para-aminosalicylic acid (PAS). Multidrug-resistant tuberculosis strains, resistant to multiple pharmacologic agents including isoniazid and rifampin, remain a concern.[39] Empirical treatment for tuberculosis should be provided for HIV-infected persons with close contact with a patient with active tuberculosis.[40] All HIV-infected patients with a positive result on PPD testing should receive tuberculosis prophylaxis with a regimen of isoniazid plus pyridoxine or rifampin plus pyrazinamide. Steps toward prevention of tuberculosis and its spread include the use of HAART, early identification of tuberculosis, early initiation of multidrug therapy, the use of respiratory isolation, and the use of personal respiratory protection devices.

Other Pulmonary Complications

Fungal pulmonary infections other than PCP may be seen in patients with AIDS. Such infections may include cryptococcosis, histoplasmosis, coccidioidomycosis, aspergillosis, nocardiosis, and blastomycosis.[41] *Cryptococcus neoformans* is the most common fungal pathogen in patients with AIDS after *Pneumocystis jiroveci*, typically causing infection in patients with $CD4^+$ counts less than 100 cells/μL. Radiographic findings often are nonspecific and may include consolidation, reticulonodular infiltrates, and nodules. Diagnosis is with serum cryptococcal antigen assay. Geographic regions with identified predilections for infection with specific pathogens include the eastern and central United States for *Histoplasma*, the south central and central United States for *Blastomyces*, and the southwestern United States for *Coccidioides*. Each of these pathogens is seen more commonly in late-stage HIV disease. In patients with cavitary lesions on chest radiographs, aspergillosis as well as tuberculosis and methicillin-resistant *Staphylococcus aureus* infection should be suspected.

Viral respiratory infections are common among HIV-infected patients. CMV infection is the most frequent, typically occurring with advanced immunosuppression. Radiographic findings may include alveolar consolidation or ground-glass opacities.

Pulmonary malignancies include Kaposi's sarcoma, non-Hodgkin's lymphoma, Hodgkin's disease, and bronchogenic carcinoma. Kaposi's sarcoma typically is associated with hilar

peribronchovascular thickening, lower lobe reticulonodular opacities, adenopathy, pleural effusion, or focal consolidation.[42] Pulmonary Kaposi's sarcoma is treated with cytotoxic agents and HAART. Lymphoproliferative disorders also may have a pulmonary presentation among HIV-infected patients. Such disorders include lymphocytic interstitial pneumonia, nonspecific interstitial pneumonia, and bronchiolitis obliterans.

Patients hospitalized with pulmonary involvement in whom the diagnosis cannot be determined may require bronchoscopy, bronchial lavage, and possibly biopsy. If the clinical probability of PCP is high, treatment should begin before diagnostic bronchoscopy.

Neurologic Involvement

Neurologic diseases are the initial manifestation of AIDS in 10 to 20% of patients. The frequency of neurologic complications increases over the course of HIV infection, with cross-sectional studies showing a 75 to 90% prevalence of neurologic disorders in patients with AIDS.[43] The overall incidence rates of HIV-associated neurologic diseases and CNS opportunistic infections have been decreasing since the introduction of HAART, although this trend is expected to change as resistance to antiretroviral drugs emerges.[44]

Neurologic complications in the HIV-infected patient may be caused by both direct effects of HIV infection on the CNS and opportunistic infections and neoplasms occurring as a result of immunosuppression. In the early stages of HIV infection, aseptic meningitis, herpes zoster radiculitis, and inflammatory demyelinating polyneuropathy are common. Later stages of HIV infection are associated with cognitive dysfunction, dementia, opportunistic infections, cancers, and sensory neuropathies. The most common AIDS-defining neurologic complications are HIV encephalopathy (dementia), *C. neoformans* infection, toxoplasmosis, and primary CNS lymphoma. Less common CNS complications include bacterial meningitis, histoplasmosis (usually disseminated), CMV infection, progressive multifocal leukoencephalopathy, herpes simplex virus (HSV) infection, neurosyphilis, and tuberculosis. Noninfectious CNS processes include CNS lymphoma, cerebrovascular accidents, and metabolic encephalopathies.

Clinical presentations in patients with serious neurologic complications can be nonspecific, making the diagnosis and disposition challenging. The most common clinical manifestations of CNS pathology are seizures, meningismus, focal neurologic deficits, altered mental status, and headache (new or persistent). Infection accounts for a majority of neurologic disorders and most often is accompanied by fever.

Patients with $CD4^+$ cell counts greater than 200 cells/μL who present with fever and meningismus in the absence of focal neurologic deficits should have an immediate lumbar puncture performed. For those with focal deficits or new seizures, neuroimaging is recommended first, followed by lumbar puncture if neuroimaging is unrevealing. For patients with altered mental status or headache, diagnostic evaluation should proceed as in the non-HIV-infected population, with neuroimaging and lumbar puncture reserved for those cases in which another cause for the symptoms is not identified or with a clear indication for workup (e.g., patient complaint of "the worst headache of my life").[44] For patients with $CD4^+$ cell counts less than 200 cells/μL, a more aggressive approach is advocated, with any of the aforementioned findings demanding emergent imaging, usually followed by lumbar puncture[45,46] (Fig. 130-2).

Generally speaking, for those CNS processes that require immediate identification, CT without contrast is considered adequate.[47,48] If the entire ED evaluation is unrevealing, more advanced diagnostic imaging should be pursued immediately, usually in an inpatient setting, if the patient's symptoms are severe or if new neurologic findings are present. For all other cases, close follow-up is indicated with the patient's primary provider, because it has been demonstrated that more subtle lesions may be identified by contrast CT scan or magnetic resonance imaging (MRI). Cerebrospinal fluid (CSF) analysis should include determination of opening and closing pressures, cell count, measurement of glucose and protein, Gram's stain, and bacterial, viral, and fungal cultures. Testing for toxoplasmosis and cryptococcal antigens and coccidioidomycosis titer also are appropriate, particularly in patients with later-stage disease. A prudent measure is to direct the laboratory to hold excess CSF for further testing if the preliminary workup is unrevealing.

HIV Encephalopathy

HIV encephalopathy, or *AIDS dementia complex*, occurs in up to one third of patients with HIV, and is the initial manifestation of AIDS in 3% of affected adults.[43] It is a progressive process caused by direct HIV infection and commonly is heralded by impairment of recent memory or subtle cognitive deficits, such as difficulty concentrating. Traditionally, symptoms are expected to occur in patients with $CD4^+$ counts less than 200 cells/μL, although since 1996, increasing numbers of cases are being seen in patients with $CD4^+$ counts greater than 200 cells/μL.[3,49] Early stages of dementia may be easily confused with depression, the effects of psychoactive substances, or anxiety disorders. Deficits become more debilitating in later stages of disease and can include more obvious changes in mental status, seizures, frontal release signs, and hyperactive deep tendon reflexes; in such cases, physical examination usually reveals the hallmarks of advanced AIDS, including wasting, alopecia, generalized dermatitis, and lymphadenopathy. AIDS dementia is a diagnosis of exclusion: Even among patients with AIDS presenting to the ED with an established diagnosis of AIDS dementia, the appearance of progressive signs or symptoms requires immediate further evaluation to rule out other CNS processes. Neuroimaging findings in patients with HIV encephalopathy typically show atrophy and diffuse deep matter hyperintensities; MRI may reveal patchy punctate lesions in the white matter. Lumbar puncture findings typically are normal. Controlled trials in adults and children with HIV dementia have demonstrated benefit of high-dose zidovudine.[49]

Cryptococcus Neoformans Infection

C. neoformans is the agent of a fungal CNS infection that causes either focal cerebral lesions or diffuse meningoencephalitis. It occurs in up to 10% of patients with HIV infection but most commonly in those with $CD4^+$ counts less than 100 cells/μL. The most frequent initial symptoms are fever and headache, often accompanied by nausea and vomiting. Less frequent manifestations are visual changes, dizziness, seizures, and cranial nerve deficits.[50] The brainstem and basal ganglia are typical locations; high intracranial pressure and sudden clinical deterioration from herniation are relatively common. The mortality rate approaches 30%.

Patients with *C. neoformans* infection usually have no significant changes on CT. Definitive diagnosis relies on finding cryptococcal antigen in the CSF, which is nearly 100% sensitive and specific; other diagnostic tests include India ink staining (60 to 80% sensitive), fungal culture (95% sensitive), and serum cryptococcal antigen (95% sensitive). All patients with a positive result on serum cryptococcal antigen assay should undergo lumbar puncture to rule out neurologic involvement.

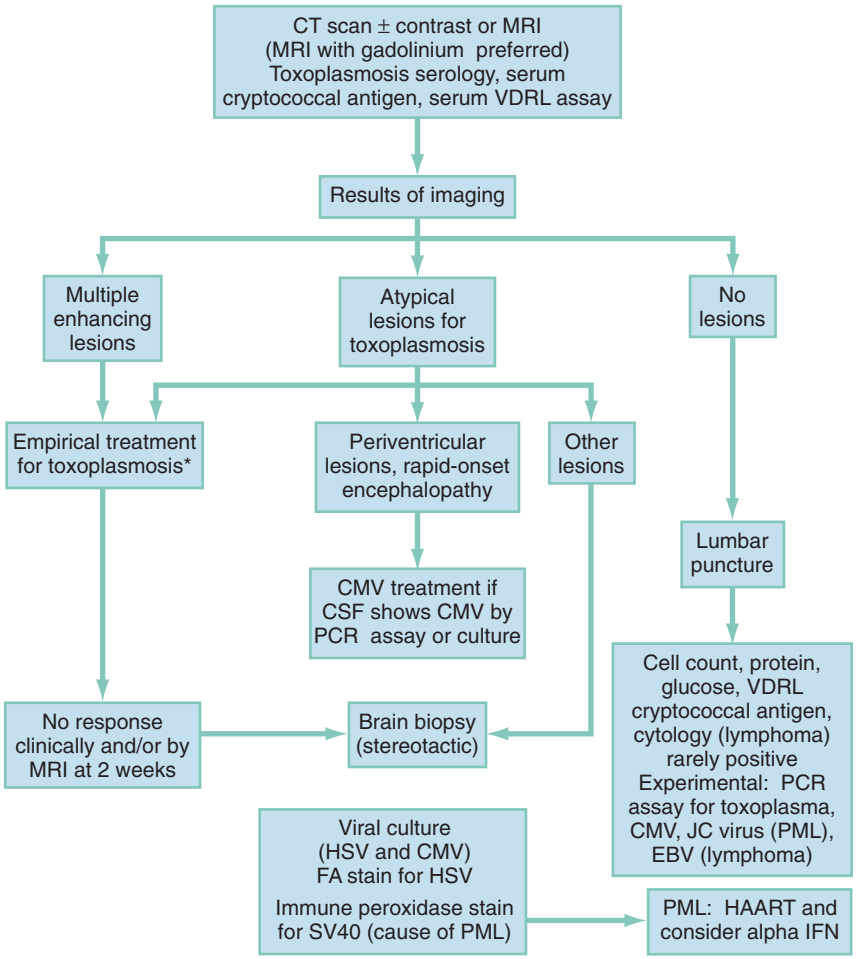

Figure 130-2. Approach to the evaluation of patients presenting to the emergency department with advanced HIV disease plus altered mental status, new-onset seizures, headache (severe or persistent), or focal neurologic deficits. CMV, cytomegalovirus; CSF, cerebrospinal fluid; CT, computed tomography; EBV, Epstein-Barr virus; FA, fluorescent antibody; HAART, highly active antiretroviral therapy; HSV, herpes simplex virus; IFN, interferon; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; PML, progressive multifocal leukoencephalopathy; SV40, simian virus 40; VDRL, Venereal Disease Research Laboratory. (Modified from McArthur J, Bartlett JG: Headache in patients with AIDS. In Bartlett JG [ed]: 1999 Medical Management of HIV Infection. Baltimore, Port City Press, 1999, p 333.)

*Serology for *Toxoplasma gondii* is positive 85–90% with toxoplasmic encephalitis. Clinical response to empirical treatment is anticipated within 1 week. Negative serology, atypical presentation, and/or delayed clinical response should prompt early biopsy.

Additional findings associated with cryptococcal infection include elevated CSF opening pressure and a mononuclear pleocytosis. Treatment requires hospital admission for administration of intravenous amphotericin B (0.7 mg/kg per day) plus 5-flucytosine (100 mg/kg per day) for 2 weeks, followed by oral fluconazole (400 mg per day) for 8 weeks or until the CSF is sterile. The most clinically significant adverse effect of treatment for cryptococcal meningitis is bone marrow suppression due to flucytosine; amphotericin B also may cause fever and renal dysfunction. After successful treatment, chronic suppressive therapy with lower doses of oral fluconazole is indicated because of the high relapse rate (approximately 50%). This therapy can be discontinued in patients with immune reconstitution.

Toxoplasma Gondii Infection

T. gondii is the most common cause of focal intracranial mass lesions in patients with HIV infection, with an incidence of 3 to 4%.[43,49] In most cases, symptomatic disease is a result of reactivation of latent infection. Common signs and symptoms include headache, fever, altered mental status, and seizures. Focal neurologic deficits are found in up to 80% of cases. Serologic testing is not useful, because up to 30% of the U.S. population has antibodies to *T. gondii*. Diagnosis most often is made by the presence of multiple subcortical lesions on CT. Noncontrast CT often is used as the initial study in the ED, because addition of contrast has been shown to be of marginal value in patients with completely normal findings on noncontrast CT scans.[48] In those patients with suspicious lesions, or those with clinical findings strongly suggestive of a pathologic process but equivocal or negative findings on noncontrast scans, a contrast CT or MRI study may be helpful. In the presence of contrast, toxoplasmosis lesions are ring-enhancing with surrounding edema. MRI is considered even more sensitive than contrast CT in delineating the extent of lesions but usually is not indicated in the ED setting.[51]

Clinical and radiologic features often cannot reliably distinguish CNS toxoplasmosis from a wide variety of other potential causative disorders (e.g., lymphoma, cerebral tuberculosis, fungal infections, progressive multifocal leukoencephalopathy, CMV infection, KS, hemorrhage). Toxoplasmosis more typically is characterized by a greater number of lesions with a predilection for the basal ganglia and corticomedullary area, whereas lymphomas more often are singular lesions located in the periventricular matter or corpus callosum. Tuberculosis is characterized by an inflammatory appearance on the CT scan, with a thick isodense exudate filling the basal cisterns.

Patients with suspected toxoplasmosis should be hospitalized and treated with pyrimethamine (200 mg loading dose, then 50 to 75 mg/day) plus sulfadiazine (4 to 6 g/day). Folinic acid (leucovorin, 10 mg/day) should be added to reduce the incidence of pancytopenia. Alternative agents to sufadiazine include sulfisoxazole, clindamycin, azithromycin, atovaquone,

or doxycycline and often are required due to the relatively high frequency of side effects associated with sulfadiazine. Dexamethasone (4 mg IV) may be used in cases with the radiographic finding of midline shift, critically elevated intracranial pressure (ICP), or clinical deterioration. Seizure prophylaxis is not recommended. Bactrim is indicated for chronic suppressive therapy after initial treatment as well as for prophylaxis in patients with a positive result on serologic testing and a $CD4^+$ cell count less than 100 cells/μL. Failure to respond to treatment suggests an alternate diagnosis, which may necessitate biopsy.

Primary Central Nervous System Lymphoma

A previously rare disorder, primary CNS lymphoma occurs in up to 3% of patients with HIV infection, typically in those with $CD4^+$ cell counts less than 50 cells/μL. Incidence has decreased slightly since 1996 with the introduction of HAART.[49] Primary CNS lymphomas originate from B cells that express Epstein-Barr virus (EBV). Patients present with headache, aphasia, memory loss, hemiparesis, or seizure. Diagnosis usually is based on CT findings, which show hyperdense or isodense round or multiple lesions that enhance with contrast, and have a predilection for the periventricular region. Differentiation from toxoplasmosis can be challenging and often is made after failure to respond to therapy for that infection. PCR assay for EBV is a helpful diagnostic adjunct, but definitive diagnosis often necessitates biopsy. Prognosis for lymphoma is poor, with median survival time of less than 1 month. Life expectancy may be extended to several months with whole-brain irradiation along with corticosteroids and chemotherapy.[49]

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy occurs in approximately 1 to 3% of patients with AIDS and is caused by reactivation of the polyomavirus (JC virus). The most common presenting features are weakness, speech disturbances, cognitive dysfunction, and headaches. CT or MRI scans show hypodense white matter disease. JC virus PCR assay is approximately 80% sensitive. Progressive multifocal leukoencephalopathy carries a poor prognosis unless immune reconstitution can occur.

Tuberculosis Meningitis

Mycobacterium avium-intracellulare (MAI) infection is the most common cause of tuberculosis meningitis; it occurs in less than 1% of patients with AIDS and may be associated with intracranial abscesses or spinal cord absesses. CT findings in MAI infection may suggest toxoplasmosis. Because findings on CSF analysis may be negative, definitive diagnosis often requires brain biopsy. Four-drug therapy for at least 9 months is required for cure.[49]

Human Immunodeficiency Virus Neuropathy

HIV infection also is associated with a variety of disorders of the peripheral nervous system. These disorders rarely are emergent but necessitate appropriate referral. The most common peripheral nervous system disorder is HIV neuropathy, which occurs in up to 50% of HIV-infected patients and is characterized by painful sensory symptoms in the feet. Treatment in the ED should be directed toward analgesia. Ibuprofen may be used for first-line therapy, although narcotics may be required in more severe cases. Amitriptyline and phenytoin have been shown to be helpful but should be used judiciously because of their potential for causing delirium in patients with concurrent HIV dementia.

Gastrointestinal Involvement

Most patients with AIDS have gastrointestinal signs or symptoms at some time during the course of their illness. The most common clinical manifestations are diarrhea, weight loss, malabsorption, abdominal pain, bleeding, esophageal symptoms, and hepatobiliary symptoms.[52] Nonspecific findings may include nausea, vomiting, and abdominal pain as common adverse effects of antiretroviral therapy.[53] Evaluation for a specific causative disorder often is difficult until objective studies are performed. More than one source of infection often is present, which may further complicate the diagnosis. Treatment in the ED focuses on supportive care, fluid and electrolyte repletion, and obtaining appropriate studies for further investigation.

Oropharynx

Oral involvement is common in AIDS and may manifest as a variety of problems, including fungal infections (oral candidiasis, histoplasmosis, cryptococcosis, penicillinosis), viral lesions (herpes simplex, herpes zoster, cytomegalovirus, hairy leukoplakia, papillomavirus infection), bacterial lesions (periodontal disease, necrotizing stomatitis, tuberculosis, *Mycobacterium avium* complex [MAC], bacillary angiomatosis), neoplasms (Kaposi's sarcoma, lymphoma, Hodgkin's lymphoma), and autoimmune or idiopathic lesions (salivary gland disease, aphthous ulcers). Presence of oral lesions may be an indicator of disease progression.[54]

Oral candidiasis affects more than 80% of patients with AIDS. *Candida albicans* infection, the most common fungal infection in HIV-infected patients, typically involves the tongue and buccal mucosa and may be asymptomatic. Symptoms may include soreness, burning, and dysphagia. Candidiasis can be distinguished from hairy leukoplakia by its characteristic whitish, lacy plaques, which are easily scraped away from an erythematous base. Any of three forms of candidiasis may be seen: pseudomembranous candidiasis (thrush), erythematous candidiasis, and angular cheilitis. Microscopic examination with a potassium hydroxide smear can confirm the diagnosis in the ED. Most oral lesions can be managed symptomatically on an outpatient basis. Preferred treatment is with clotrimazole troches, 10 mg, PO, five times daily for 14 days. Other treatment options include nystatin vaginal tablets, one tablet dissolved slowly in the mouth four times daily, and nystatin pastilles, two dissolved in the mouth five times daily. Systemic therapy with fluconazole, ketoconazole, or itraconazole may be used for resistant lesions.

Hairy leukoplakia also is commonly seen, typically manifesting as white, corrugated or filiform, thickened lesions on the lateral aspects of the tongue. Because it often is asymptomatic, therapy is not necessary, but when indicated, treatment is with acyclovir, 800 mg PO five times a day for 2 to 3 weeks.

Painful oral and perioral ulcerations may be caused by HSV. HSV infection can be diagnosed in the ED by the identification of multinucleated giant cells in scrapings of the lesions. Definitive diagnosis is by culture. Therapy is with acyclovir, 400 mg PO three times daily for 7 to 10 days. MAC also may cause painful oral ulcerative lesions. Diagnosis is by acid-fast stain. Oral Kaposi's sarcoma may appear as nontender, well-circumscribed, slightly raised, violaceous or erythematous lesions anywhere in the oropharynx. Definitive diagnosis requires biopsy. Treatment may include surgical excision, localized chemotherapy, sclerosing agents, or radiation therapy.

Periodontal disease, including gingival erythema and necrotizing periodontal disease, may be seen in up to 10% of

patients. Outpatient treatment, including local irrigation and mouth rinses and oral antibiotics such as amoxicillin-clavulanate or clindamycin, may be instituted. Dental follow-up care is essential.

Aphthous ulcerations, often painful and recurrent, are small crateriform ulcers with white to yellow membranes surrounded by an erythematous ulcer. The etiology is unknown but is thought to involve immune deficiency. Other potential causes of ulcerations, such as fungal or mycobacterial infection, HSV or CMV infection, and lymphoma, should be excluded. Aphthous ulcers usually respond to topical steroids, such as 0.05% flucinomide ointment mixed 50-50 with an oral topical anesthetic such as benzocaine preparations (e.g., Orabase).

Esophagus

In HIV infected patients with dysphagia or odynophagia and a $CD4^+$ count greater than 200 cells/μL, non-HIV-related causes of esophagitis, such as gastroesophageal reflux disease or medications, must be considered. In patients with a $CD4^+$ count below 200 cells/μL, *Candida* is responsible for 50 to 70% of esophagitis cases. Other etiologic disorders include HSV and CMV infection, Kaposi's sarcoma, *Mycobacterium avium* complex disease, and reflux esophagitis, as well as idiopathic esophagitis.

The most cost-effective approach to the evaluation of patients with esophageal complaints is to initiate empirical therapy with fluconazole (100 to 200 mg PO daily for 2 to 3 weeks). Alternative agents include clotrimazole, ketoconazole, and itraconazole. Endoscopy, fungal stains, viral cultures, and occasionally biopsy may be required to definitively establish diagnosis in nonresponders. On endoscopy, *Candida* infection is associated with an ulcerative pattern with plaques separated by normal mucosa compared with herpes, which typically produces "punched-out" ulcerations without plaques.

Relapses are common after cessation of treatment, and intravenous amphotericin B is recommended in these cases. Disseminated candidiasis is managed with intravenous amphotericin B and flucytosine. Fluconazole has been shown to be effective for prophylaxis against fungal infections in patients with a $CD4^+$ count less than 100/μL, although survival is unaffected by prophylactic therapy.[55]

Diarrhea

Diarrhea is the most common gastrointestinal complaint in AIDS, occurring in 50 to 90% of patients. Diarrhea can vary in severity, ranging from a few loose stools per day to massive fluid loss with prostration, fever, chills, and weight loss. Medication side effects should be considered, because use of antiretroviral agents is associated with a high incidence of gastrointestinal adverse effects. Potential pathogens include parasites (*Cryptosporidium parvum*, *Enterocytozoon bieneusi*, *Isospora belli*, *Giardia lamblia*, *Entamoeba histolytica*, *Microsporidia*, *Cyclospora*, and others), bacteria (*Salmonella*, *Shigella*, *Campylobacter*, *Helicobacter pylori*, MTB, *Mycobacterium avium* complex, *Clostridium difficile*, and others), viruses (CMV, herpes simplex virus, HIV, and others), and fungi (*Histoplasma capsulatum*, *Cryptococcus neoformans*, *Coccidioides immitis*, and others). Opportunistic infections are more commonly seen among patients with $CD4^+$ cell counts less than 100 cells/μL. Significant gastrointestinal bleeding and dehydration have been associated with many pathogens, particularly CMV. *Salmonella* infection can be of particular concern in HIV-infected patients because it often produces recurrent bacteremia. Neoplastic gastrointestinal tract involvement with Kaposi's sarcoma or lymphoma may produce dysphagia, obstruction, intussusception, or diarrhea.

ED management of diarrhea should be directed toward stabilization, hydration, and obtaining appropriate diagnostic studies. Initial studies should include blood cultures (for MAC and salmonellae), stool cultures, microscopic examination of stool for ova and parasites, trichrome stain for microsporidia, *Giardia* EIA, and *C. difficile* assay for toxins A and B. If indicated, colonoscopy or sigmoidoscopy (with or without biopsy) may be arranged for patients who require further evaluation.[56] Often, no definitive diagnosis of the cause of diarrhea can be made in patients with AIDS. Management of severe diarrhea not necessitating specific therapy may include attapulgite (Kaopectate), psyllium (Metamucil), diet modification, or diphenoxylate hydrochloride with atropine (Lomotil).

Cryptosporidium and *Isospora* infections commonly are associated with HIV infection, and both organisms may produce prolonged watery diarrhea.[57] Diagnosis may be sought using acid-fast staining of stool samples, monoclonal antibody assay, or ELISA. Treatment of these disorders is variably successful. Symptoms may be managed with diet modification or loperamide. *Cryptosporidium* infections may be treated with some success using paromomycin or azithromycin. *Isospora* infections often are successfully treated with TMP-SMX. Pyrimethamine or metronidazole may be used as alternative agents. HAART also may reduce duration and severity of symptomatology.

Viruses causing diarrhea include CMV, adenovirus, astrovirus, rotavirus, and others.[58] CMV colitis most commonly is seen in patients with $CD4^+$ cell counts below 50 cells/μL. Diarrhea is associated with weight loss and abdominal pain; CT shows colonic thickening. Complications include hemorrhage and perforation. Treatment is with intravenous ganciclovir, valganciclovir, or foscarnet.

C. difficile is responsible for approximately 50% of cases of diarrhea in HIV-infected patients. The typical history is one of watery diarrhea and recent antibiotic use. *C. difficile* testing should be performed. Treatment is with oral metronidazole (Flagyl) or vancomycin.

MAC consists of *M. avium* and *M. intracellulare*, acquired by ingestion or inhalation. The typical presentation is that of fever, night sweats, and diarrhea in patients with $CD4^+$ counts less than 100 cells/μL. Diagnosis can be made by stool or blood cultures, results of which may take up to weeks to turn positive. Treatment is with oral clarithromycin, 500 mg twice a day, plus ethambutol, 15 mg/kg per day. Prophylaxis is indicated in patients with $CD4^+$ cell counts less than 50 cells/μL.

Malabsorption syndromes are relatively common with HIV infection. Delayed gastric emptying and intestinal infections may contribute and lead to significant weight loss. Treatment includes nutritional counseling, parenteral nutrition, and adjunctive agents such as dronabinol, megestrol acetate, and human growth hormone.[59]

Liver Involvement

Hepatomegaly is seen in up to 50% of patients with AIDS. Jaundice is less common. Hepatitis B and hepatitis C are common among these patients, especially among intravenous drug users. Previous hepatitis B virus infection may become reactivated after HIV infection or may be acquired with increased frequency after HIV infection. Several opportunistic organisms, including CMV, MAI, *M. tuberculosis*, *Histoplasma capsulatum*, and *Cryptosporidium*, also can produce hepatitis-like disease in patients with HIV infection. Typically, an elevation in the alkaline phosphatase level occurs that is disproportionate to levels of other liver enzymes. Hepatotoxicity also may result from a variety of medications, including indinavir.

Complete examination of the anus and rectum is important in diagnosing such disorders. Fissures, masses, infection, and inflammation will be detected by inspection, palpation, digital examination, anoscopy, and, when indicated, sigmoidoscopy. Proctocolitis is common in patients with AIDS and may be caused by any of several organisms, including *Campylobacter jejuni*, *Shigella* species, *Salmonella* species, *Giardia*, HSV, *Entamoeba histolytica*, *Chlamydia*, and *Neisseria gonorrhoeae*. Diagnostic tests include anoscopy with evaluation of stool for blood, leukocytes, ova, and parasites. Additionally, bacterial cultures, an HSV culture or Tzanck preparation, a rapid plasma reagin (RPR) test, and appropriate assays for detection of *N. gonorrhoeae* and *Chlamydia* may be useful. The diagnosis of anal gonorrhea can be confirmed on a Gram's stain of stool showing leukocytes and intracellular organisms. HSV infection can be diagnosed by viral cultures or by identification of multinucleated giant cells on scrapings of anal lesions.

Cutaneous Involvement

Several common cutaneous manifestations of AIDS are likely to be seen in the ED. Preexisting dermatologic conditions may be exacerbated by HIV infection. Common infections and conditions may manifest in an atypical fashion. Generalized cutaneous complaints such as xerosis (dry skin) and pruritus are common and may be manifested before an AIDS-defining illness. Treatment for these conditions is identical to that in patients who do not have AIDS. Xerosis may be treated with emollients. Pruritus may be treated with oatmeal baths and, if necessary, antihistamines.

Kaposi's sarcoma is the second most common manifestation of AIDS. It is found commonly among homosexual or bisexual men and is caused by human herpesvirus-8 (HHV-8). The disease usually is widely disseminated with mucous membrane involvement. Kaposi's sarcoma typically manifests in HIV-infected patients with any variation of mucocutaneous involvement, lymph node involvement, or involvement of the gastrointestinal tract or other organs. The typical appearance includes pink, red, or purple papules, plaques, nodules, and tumors. Treatment is based on site and extent of involvement. Kaposi's sarcoma is incurable but rarely is fatal. Palliative therapies include cryotherapy, radiotherapy, infrared coagulation, sclerosing agents, intralesional vinblastine, and systemic chemotherapy with doxorubicin (Adriamycin), bleomycin, and vincristine.[60]

Varicella-zoster (VZ) eruptions are nearly 27 times more likely in HIV-infected patients than the general population, and multidermatomal involvement is more frequent in those with AIDS.[61] In the HIV-infected patient with simple dermatomal zoster infection, outpatient management options include oral famciclovir (500 mg three times a day), acyclovir (800 mg fives times daily), and valacyclovir (1000 mg three times daily).[62] Hospital admission to an isolation bed for administration of intravenous acyclovir (10 mg/kg every 8 hours) is warranted for any patient with systemic involvement, ophthalmic zoster, or severe dermatomal zoster.[63] Varicella immune globulin may be useful in patients with primary infection and visceral involvement.

HSV infections are highly prevalent among HIV-infected patients. Both HSV-1 and HSV-2 infections may occur as localized infection or systemic disease. HSV infections commonly manifest with fever, adenopathy, malaise, and ulcerative lesions of mucosal and cutaneous sites. Common sites of involvement include oral mucosa, genital areas, and rectum. HSV and HZV infections may be difficult to distinguish clinically, and cultures may be required for differentiation of the two conditions. Reactivation is common. Mucocutaneous HSV infection responds well to oral famciclovir (750 mg three times daily) or acyclovir (200 mg five times daily for 10 days). For disseminated infection or neurologic involvement, intravenous acyclovir is recommended (5 to 10 mg/kg every 8 hours for 7 to 21 days). Famciclovir, penciclovir, foscarnet, or valacyclovir also may be used. Suppressive therapy is effective in decreasing rates of recurrence. Patients with these viral infections should be assigned to isolation beds in the hospital.

Molluscum contagiosum manifests with small flesh-colored papules with a whitish core (see Fig. 151-4). The condition is difficult to cure; cryotherapy or curettage is reserved for symptomatic lesions. Intertriginous infections with either *Candida* or *Trichophyton* are common and may be diagnosed by microscopic examination of scrapings in potassium hydroxide. Treatment may include topical imidazole creams (e.g., clotrimazole, miconazole, ketoconazole).

Scabies should be considered in all HIV-infected patients, particularly those with dermatitis complicated by excoriations or pruritus. Microscopic identification of mites is diagnostic. Preferred treatment is with single application 5% permethrin. Sexual and household contacts also should be treated. Norwegian scabies is particularly resistant to treatment and should be considered if lesions consistent with scabies fail to respond to traditional therapy. Treatment should be undertaken in consultation with an infectious disease specialist.

Seborrheic dermatitis is common, particularly among patients with AIDS-associated dementia. Lesions are erythematous, hyperkeratotic scaling plaques involving the scalp, face (especially the nasolabial folds), ears, chest, and genitalia. Treatment with topical steroids often is effective, although less so than in the general population. Alternative therapy includes topical or oral ketoconazole.

Human papillomavirus infections occur with increased frequency in immunocompromised patients. Treatment is cosmetic or symptomatic and may include cryotherapy, topical agents, or, in extreme cases, laser therapy.

Other dermatologic disorders, including psoriasis, atopic dermatitis, and alopecia, occur with increased frequency in patients with AIDS. Any preexisting dermatologic disorder may be exacerbated by HIV infection.

Ophthalmologic Manifestations

Ocular findings are common in the HIV-infected patient. Cotton-wool spots in the retina are the most common eye finding and do not require intervention. Other common ophthalmologic manifestations of HIV include CMV retinitis, herpes zoster ophthalmicus, and Kaposi's sarcoma of eyelids or conjunctiva.

CMV retinitis occurs in 10 to 30% of HIV-infected patients and is the most common cause of blindness in patients with AIDS. With advances in HAART, reduced incidences of CMV retinitis have been observed, but discontinuation of HAART may result in intraocular inflammation.[64] CMV retinitis typically produces severe necrotic vasculitis and retinitis. This may be asymptomatic or may manifest as blurred vision, a change in visual acuity, "floaters," flashes of light, photophobia, scotoma, redness, or pain.[65] Funduscopic examination typically shows fluffy white perivascular lesions with areas of hemorrhage that may be confused with retinal cotton-wool spots, a benign condition with no prognostic implications for those with AIDS. Considerations in the differential diagnosis also include toxoplasmosis, syphilis, HSV infection, VZV infection, and tuberculosis. Because of the risk of rapid progression and blindness, any patient in whom ophthalmic CMV

infection is a possibility requires immediate evaluation by an ophthalmologist. Treatment is with intravenous ganciclovir (5 mg/kg every 12 hours for 2 weeks, followed by 6 mg/kg/day maintenance therapy) or foscarnet (90 mg/kg every 12 hours). Intravitreal injections of fomivirsen also may be used for patients unresponsive to traditional therapy.[66] Similar rates of efficacy are achieved with ganciclovir and foscarnet. Ganciclovir-containing intravitreal implants constitute another therapeutic option that provides higher intravitreal concentrations and is associated with reduced risk for CMV-related retinal detachment. Immune recovery uveitis may occur as a complication of treatment during the recovery phase.[67] Chronic suppressive therapy with ganciclovir or foscarnet may be indicated.

Patients with serum anti-*Toxoplasma* antibodies and $CD4^+$ cell counts below 100 cells/μL should receive prophylaxis with TMP-SMX.[68] Herpes zoster ophthalmicus is another common cause of ocular damage in patients with HIV infection. The typical presentation is pain or paresthesia in the distribution of cranial nerve V_1, followed by the emergence of the vesicular zoster skin rash. Complications include conjunctivitis, episcleritis, iritis, keratitis, secondary glaucoma, and, rarely, retinitis. As with CMV infection, early recognition and treatment can prevent morbidity. All patients with suspected zoster ophthalmicus require immediate ophthalmologic consultation and may need hospital admission. Treatment should be initiated with oral or intravenous acyclovir, famciclovir, or valcyclovir.

Cardiovascular Manifestations

Cardiac manifestations of AIDS may include pericardial effusion, cardiomyopathy, increased left ventricular mass, myocarditis, endocarditis, malignancy, and cardiotoxicity of medications.[69] The pericardium is the most common site of cardiac involvement, although many patients have clinically insignificant effusions. Pericardial effusions may be secondary to malignancies, uremia, lymphatic obstruction, or infections such as with *Mycobacterium tuberculosis*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, or a host of other bacterial, viral, fungal, or protozoal pathogens. Infective endocarditis occurs commonly in HIV-infected patients with a history of intravenous drug use and should be considered in all injection drug users presenting with febrile illnesses. Cardiac neoplasms also may occur, typically as either Kaposi's sarcoma or lymphoma. Such neoplasms may be clinically silent or may manifest congestive heart failure, tamponade, or arrhythmias or other clinical syndromes. Some antiretroviral agents are associated with a fat redistribution syndrome and diabetes, which may increase the risk of coronary artery disease. Patients with HIV infection also have higher rates of dilated cardiomyopathy. Etiologic categories include primary HIV infection; viral, mycobacterial, fungal, or protozoal infection; drug-induced; immunologic; and ischemic. Patients present with typical signs and symptoms of congestive heart failure; echocardiography shows left ventricular diastolic dysfunction with decreased ejection fraction. These patients are at an increased risk for arrhythmias.

Renal Manifestations

Renal insufficiency in the patient with AIDS may be associated with a variety of underlying disorders, but initial ED presentation may include general malaise, edema, or oliguria. Prerenal azotemia is the most common renal abnormality, especially in conjunction with volume loss related to systemic or gastrointestinal infection. It is diagnosed and treated by evaluation and therapy of fluid status. Acute renal failure also may occur and often is secondary to drug nephrotoxicity (e.g., from pentamidine, aminoglycosides, sulfa drugs, foscarnet, rifampin, dapsone, or amphotericin B). HIV-associated nephropathy (HIVAN) typically is a cause of chronic renal insufficiency in the late stages of immunosuppression, but may occur earlier in disease progression.[70] Vasculitis, tuberculosis, or other systemic infections also may contribute to renal insufficiency. Postrenal azotemia may result from tubular, ureteral, or pelvis obstruction or from lymphoma, stones, fungus ball, blood clot, or sloughed papillae. ED evaluation should include urinalysis, assessment of fluid status, and determination of blood urea nitrogen and serum creatinine. If indicated, ultrasonography or intravenous pyelography may demonstrate the site and degree of obstruction. Renal biopsy may be indicated for patients with proteinuria and undiagnosed renal disease. Treatment depends on the causative agent. Therapies that have demonstrated limited benefit in HIVAN include corticosteroids, angiotensin-converting enzyme inhibitors, and dialysis and should be initiated in consultation with a nephrologist.

Psychiatric Considerations

HIV-infected patients may present with a variety of social and emotional issues complicated by neuropsychiatric and cognitive impairments. The diagnosis of AIDS may dramatically alter interactions with family and friends, and patients may be devastated by the prospect of confronting chronic illness and death. Although psychiatric issues are common among HIV-infected patients, many do not receive optimal care.[71]

Depression is common among AIDS patients and often is responsive to hospitalization and psychosocial intervention. It has been estimated that 60% of HIV-infected patients experience depression during their illness.[71] Patients with depression generally have lower $CD4^+$ counts and may report more AIDS-related symptoms.[72] Referral for antidepressant therapy should be considered if symptoms have lasted for longer than 2 weeks. Depression may result in suicidal ideation and may bring the patient to the attention of the ED for medical treatment after a suicide attempt. Other psychiatric disorders may be seen, including personality disorders, addiction disorders, and adjustment disorders.

Delirium suggests the presence of a primary physiologic disease state. Considerations in the differential diagnosis include CNS, toxic, and metabolic derangements. AIDS psychosis commonly manifests with psychiatric symptoms such as hallucinations, delusions, or other abnormal behavioral changes. Treatment should be undertaken with traditional antipsychotic agents.

Sexually Transmitted Diseases

Sexually transmitted diseases (STDs) are common among HIV-infected patients, and the prevalence of STDs, including syphilis, is increasing.[73] Syphilis is associated with increased susceptibility to HIV seroconversion by an unknown mechanism.[74] For EDs that are able to institute screening for HIV, combined testing for both HIV and other STDs may be most cost-effective.[75]

Common STDs include gonorrhea, chlamydial infection, herpes, and syphilis. Serologic testing for syphilis should be performed for all HIV-infected patients with a suspected STD. Empirical therapy for syphilis may be instituted even without laboratory proof of infection. Recommended treatment for primary or secondary syphilis of less than 12 months' duration is with a single intramuscular dose of benzathine penicillin (2.4 million units). For latent syphilis or unknown

duration of secondary syphilis, three weekly injections are recommended. Patients with known or suspected syphilis should be evaluated for the presence of neurosyphilis, which has an increasing incidence among HIV-infected persons. Patients with neurosyphilis should be treated with penicillin G, 12 to 24 million units IV daily for 10 to 14 days.

Hematologic Complications

Hematopoiesis may be adversely affected by HIV infection, tumor, infection, or HIV medications. Anemia in AIDS is independently associated with an increased risk of death. Chronic anemia in AIDS characteristically is of the normocytic, normochromic type, with a low reticulocyte count and low erythropoietin level. HAART usually results in improvement.

Pediatric Considerations

HIV/AIDS in pediatric patients may have a variety of ED presentations, including recurrent or severe bacterial infections, chronic diarrhea, candidiasis, opportunistic infections, and numerous other clinical syndromes. In addition to stabilization, diagnostic tests, and definitive management, close follow-up and communication with family members and primary physicians are imperative in this population.

Drug Reactions

Drug reactions are extremely common among HIV-infected patients; these patients commonly are treated with a variety of drugs known to produce adverse effects in some people. In addition, for unclear reasons, HIV-infected persons often experience more frequent or more severe reactions to commonly used medications than noninfected patients. Dermatologic reactions are particularly common. Antimicrobial drugs frequently are implicated. Drug reactions must *always* be considered as a possible cause of new symptoms in HIV-infected patients. Table 130-2 presents a brief summary of common drug reactions in the HIV-infected patient.

Table 130-3 Antiretroviral Drugs Approved by FDA for Treatment of HIV Disease

DRUG CLASS	GENERIC NAME	TRADE NAME
NRTIs[a]	Zidovudine (AZT, ZDV)	Retrovir
		Combivir (AZT + 3TC)
		Trizivir (AZT+3TC + ABC)
	Didanosine (ddI)	Videx and Videx EC
	Zalcitabine (ddC)	Hivid
	Stavudine (d4T)	Zerit
	Lamivudine (3TC)	Epivir
		Epzicom (3TC + ABC)
	Abacavir (ABC)	Ziagen
	Emtricitabine (FTC)	Emtriva
		Atripla (FTC + EFV + TDF)
		Truvada (FTC + TDF)
	Tenofovir (TDF)	Viread
NNRTIs[b]	Nevirapine (NVP)	Viramune
	Delavirdine (DLV)	Rescriptor
	Efavirenz (EFV)	Susitiva
PIs[c]	Indinavir	Crixivan
	Tipranavir (TPV)	Aptivus
	Darunavir (DRV)	Prezista
	Fosamprenavir (FPV)	Lexiva
	Ritonavir (RTV)	Norvir
	Saquinavir (SQV)	Invirase
	Nelfinavir (NFV)	Viracept
	Atazanavir (ATV)	Reyataz
	Lopinavir/ritonavir	Kaletra
EIs[d]	Enfuvirtide (T20)	Fuzeon
	Maraviroc (MVC)	Selzentry
II[e]	Raltegravir (RAL)	Isentress

[a]Nucleoside analog reverse transcriptase inhibitors
[b]Nonnucleoside reverse transcriptase inhibitors
[c]Protease inhibitors
[d]Entry inhibitors
[e]Integrase inhibitor

■ MANAGEMENT

Antiretroviral Therapy and Chemoprophylaxis

The introduction of HAART in 1996 has had dramatic effects on the clinical consequences of HIV infection in the developed world. The incidence of AIDS-defining illnesses and death rate declined rapidly through 1998.[3] Reports of high levels of treatment failure due to serious adverse effects, emergence of drug resistance, and difficulties in maintaining long-term adherence have raised concerns regarding the continued success of HAART; however, recent studies suggest that the reduction in morbidity and mortality associated with HAART has been sustained.[76] The U.S. Department of Health and Human Services (DHHS) has published guidelines for use of antiretroviral agents in HIV-infected adults and adolescents.[77]

Antiretroviral therapy for HIV infection is constantly evolving, and optimal decisions regarding such therapy will require a basic understanding of the classes of drugs available, the rationale for initiating treatment, and the common adverse drug reactions. The five classes of antiretroviral drugs currently in use are listed in Table 130-3. Each class of drugs independently interrupts the normal life cycle of the HIV. When used with appropriate timing and in combination, these agents have been shown to significantly delay progression of disease and prolong life.

The first drug demonstrated to have antiretroviral activity was an nucleoside analogue reverse transcriptase inhibitor (NRTI), a competitive inhibitor of the viral enzyme reverse transcriptase. Several controlled trials showed that zidovudine (azidothymidine [AZT], Retrovir) decreases the number and severity of opportunistic infections.[78,79] Although zidovudine also was found to decrease the rate of AIDS progression in patients with early symptomatic HIV infection, no significant change in survival was found.[80] This finding, coupled with the recognition of the emergence of drug resistance and the appearance of significant side effects, led to the development of other NRTIs. Combination therapy, with zidovudine and another NRTI, resulted in not only prevention of disease progression but also decreased mortality.[81] The FDA has since approved multiple agents in this class, each with its own unique adverse effect profile. The most common side effects are bone marrow suppression with zidovudine; distal sensory peripheral neuropathy with didanosine (Videx), stavudine (Zerit), and zalcitabine (Hivid); and pancreatitis with didanosine.[81]

The non-nucleoside reverse transcriptase inhibitors (NNRTIs) are noncompetitive inhibitors of reverse transcriptase and block RNA-dependent and deoxyribonucleic acid (DNA)–dependent DNA polymerase activity. Three NNRTIs are currently available; the most commonly used agents are nevirapine (Viramune) and efavirenz (Sustiva). Target organ-

isms have a high propensity for developing resistance to these agents, which are recommended for use only as part of a three-drug (or more) regimen. Rash is the most common side effect associated with use of the NNRTIs, with the development of Stevens-Johnson syndrome seen in a small minority of patients (less than 5%).[82] Symptomatic hepatitis, including fatal hepatic necrosis, has been reported with use of nevirapine.[83]

The enzyme HIV protease activates the HIV proteins that are required for infectivity by cleaving the inactive viral polypeptide precursors. Protease-inhibiting agents block this step, thereby preventing HIV particles from becoming infectious. Ten protease inhibitors currently are approved for clinical use in the United States. Introduction of this class of drugs is believed to be responsible in large part for the marked decline in mortality rates for HIV infection, which was first realized in 1996. Protease inhibitors are expensive, however, and they also have been associated with a high frequency of side effects. Short-term effects are principally gastrointestinal (including nausea, diarrhea, and bloating); long-term effects are metabolic, the most common of which are hyperglycemia, hyperlipidemia, and fat redistribution.

Additional newer classes of drugs include entry inhibitors and integrase inhibitors. Entry inhibitors prevent HIV entry into cells by targeting specific viral surface proteins or their corresponding receptors.[84] Enfuvirtide and maraviroc are two entry inhibitors currently approved for use in combination with other antiviral agents only in treatment-experienced patients. Major side effects include local injection site reactions and increased rate of bacterial pneumonia (with enfuvirtide). Integrase inhibitors work by blocking integrase, a protein required by HIV to allow it to insert its viral genetic material into the genetic material of an infected cell.[85] Raltegravir is the only integrase inhibitor currently approved for use, restricted to patients who have limited or no treatment options. Common side effects include diarrhea, nausea, headache, and fever.

The DHHS recently published updated guidelines for use of antiretroviral agents in HIV-infected adults and adolescents.[77] In general, the goals of antiretroviral therapy are virologic, immunologic, clinical, and therapeutic. Because virologic (HIV RNA levels) and immunologic ($CD4^+$ cell count) parameters are independent predictors of clinical outcomes, therapeutic recommendations are based on both of these factors. The *virologic* goal is to reduce viral load as much as possible, halt disease progression, and prevent development of resistant HIV variants. *Immunologic* goals are to achieve both quantitative ($CD4^+$ cell count) and qualitative (pathogen-specific immune response) immune reconstitution. The principal *clinical* goals are to prolong and improve the quality of life. The *therapeutic* goal is to achieve the other three goals by choosing a sequence of drugs that maintains therapeutic options, minimizes side effects, and optimizes the likelihood of patient compliance with the chosen regimen.

Expert consensus on the timing of initiation of HAART continues to evolve. The current consensus recommends mandatory treatment for HIV-infected patients with $CD4^+$ counts below 350 cells/μL or with history of AIDS-defining illness. Other patient populations in whom initiation of antiretroviral therapy is indicated regardless of $CD4^+$ count include pregnant women, patients with HIVAN, and patients with HBV co-infection requiring treatment. Similarly, in patients with recognized primary HIV infection, antiretroviral therapy is recommended, because early treatment is believed to decrease the number of infected cells, maintain or restore immune response, and perhaps lower the viral "set point," resulting in improved course of the disease.[81] Therapy may be considered in some patients with $CD4^+$ greater than 350 cells/μL, given some evidence suggesting that higher $CD4^+$ counts can be achieved with early therapy; however, initiation of treatment in these patients should be individualized in accordance with the willingness and readiness of the person to begin therapy, the potential benefits and risks of initiating therapy in an asymptomatic person, and the likelihood of compliance with the prescribed treatment regimen.

Selection of an appropriate combination of drugs also is a complex issue for which no definitive recommendations exist. Twenty-eight antiretroviral drugs are currently approved by the FDA. A complete list and up-to-date guide for their use can be found on the NIH website (AIDSinfo.nih.gov). The current DHHS recommended first-line HAART regimens include NNRTI-based regimens (one NNRTI and two NRTIs), or protease inhibitor–based regimens (one or two protease inhibitors and two NRTIs).[77] Triple-NRTI regimens are recommended as second-line regimens. Therapy should be individualized with consideration of tolerability, comorbid conditions, adverse effect profile, likely drug-drug interactions, convenience, and likelihood of adherence.

Pregnancy should not preclude women from receiving optimal treatment regimens; however, issues relating to prevention of mother-to-child transmission as well as maternal and fetal safety deserve special considerations. Previous studies have shown that HAART reduces perinatal transmission to 1 to 2%, and the rate is strongly correlated with viral load at the time of delivery.[86,87] On the basis of these observations, HAART should be recommended for any pregnant woman. Selection of antiretroviral combinations should take into account known safety efficacy and pharmacokinetic data for each agent during pregnancy. Efavirenz-containing regimens should be avoided in pregnancy or in women of reproductive age owing to potential teratogenic effects. Elective cesarean section has established merit in reducing prenatal transmission if done at 38 weeks of gestation with a maternal viral load greater than 1000 copies/mL.[88]

The goal of the antiretroviral therapy is to produce long-term viral suppression. Clinical situations that should prompt consideration for changing therapy include drug toxicity or intolerance, difficulty with adherence, and failure to suppress viral infection. Decisions regarding alternative treatment regimens should be made in consultation with infectious disease experts to assess potential cross resistance from previously used drugs. With advances in genotypic and phenotypic analysis of HIV strains, selection of a drug regimen based on drug resistance patterns will soon become an essential part of therapeutic decision-making.

Chemoprophylaxis is directed toward preventing initial and subsequent episodes of certain opportunistic infections (i.e., primary and secondary prophylaxis). Emphasis on measures to prevent opportunistic infections is critical because of the inherent limitations of HAART and the recognition that these infections constitute a cause of significant morbidity and mortality in the HIV-positive population. The $CD4^+$ cell count is the best predictor of the risk for opportunistic infections and is used most often in making decisions about initiating or maintaining antimicrobial prophylaxis. The most serious and common infections for which antimicrobial prophylaxis has been shown to be effective include PCP, toxoplasmosis, tuberculosis, and MAC infection. Specific timing and choice of agents are described in earlier clinical sections of this chapter; a more comprehensive review can be found in the Public Health Service and Infectious Disease Society Revised Guidelines for the Prevention of Opportunistic Infections.[89] The emergency physician can play a critical role in recognizing those patients requiring initiation of chemoprophylaxis and then should work closely with the patient's

primary care doctors or an infectious disease consultant to begin therapy.

Immunizations for Human Immunodeficiency Virus–Infected Patients

Response to immunizations may be variable among HIV-infected patients. Many such patients mount an adequate antibody response to immunizations, but the immune response is not predictable.[90] Most routine immunizations recommendations are the same as for the non-HIV-infected patients.[91] However, HIV-infected patients should not receive live virus or live bacterial vaccines. Pneumococcal vaccine is recommended for all patients older than 2 years of age[92]; however, immunization is recommended early in the disease course to optimize antibody development.[93] Hepatitis B vaccine is indicated for patients at risk of exposure, although owing to variable immune response, follow-up serologic testing is indicated. Hepatitis A vaccination also should be considered because of increased risk of severe liver damage among patients previously infected with hepatitis B or C.[94] Influenza vaccination is considered safe and is routinely recommended.[95] Measles-mumps-rubella (MMR) vaccine may be considered because studies have not documented an increased incidence of adverse effects. If polio vaccine is indicated, enhanced inactivated polio vaccine may be administered. Although evidence suggests that the expression of HIV may be transiently increased by administration of tetanus toxoid,[96] the clinical significance of this observation is unknown; current recommendations include providing a booster every 10 years for patients who have completed their primary series. Because the smallpox vaccine has not been rigorously studied in the HIV-infected population, the adverse effects and immune response are unknown, and some experts currently advise against its use.[97] The potential risks and benefits of immunization in the HIV-infected patient should be considered in decisions regarding immunization.

DISPOSITION

When questions remain about specific diagnostic or management options, consultation with specialists is appropriate. Consultations with an infectious disease specialist, neurologist, psychiatrist, AIDS specialist, and others may be indicated. Although symptomatic patients are cared for predominantly by AIDS specialists, the increasing numbers of symptomatic patients are shifting the focus of primary care to nonspecialists.

Disposition decisions for HIV-infected patients are based, as for any patient, on clinical condition, availability of outpatient resources, and ability to arrange adequate follow-up observation. Any patient to be discharged must demonstrate capability for self-care or have sufficient in-home assistance available. In the AIDS population, particular attention should be given to ability to ambulate and to tolerate oral intake, as well as availability of timely and appropriate medical follow-up care.

Although the AIDS epidemic has raised concerns regarding the economic impact of the disease, financial considerations should not be a factor in determining management or disposition. Guidelines for hospital admission and discharge are presented in Box 130-3.

BOX 130-3 GENERAL EMERGENCY DEPARTMENT (ED) DISCHARGE REQUIREMENTS

- Stable medical condition
- Normal or baseline vital signs
- Appropriate follow-up arrangements have been made
- Appropriate consultations and referrals have been made
- Patient understands discharge instructions
- Patient or caregiver is able to comply with discharge instructions
- Patient or caregiver understands warning signs indicating the need for repeat ED evaluation

ETHICAL CONSIDERATIONS

Numerous ethical issues arise in the management of HIV-infected patients. General issues relevant to many patients may include issues of confidentiality, discrimination, access to health care, justice, informed consent, respect for autonomy, and advance directives. Additionally, concerns specific to HIV infection may arise, such as questions related to prenatal testing, abortion, euthanasia, suicide, access to experimental therapies, and role in clinical trials. In general, commonly accepted principles of medical ethics may be applied, which include principles of beneficence, nonmaleficence, respect for autonomy, and justice. Additionally, codes of ethical conduct developed by the define and the Society for Academic Emergency Medicine (SAEM) may provide general guidance.[98,99]

Testing of patients to detect HIV infection has some controversial aspects. Routine HIV testing initiated in the ED often is not appropriate because of difficulties in ensuring appropriate pre- and post-test counseling and confidentiality issues. However, recommendations and referral for testing often are indicated for patients with risk factors or with clinical evidence of HIV infection. Each institution should have appropriate mechanisms arranged for these referrals.

Occupational exposures to blood and body fluids may necessitate testing of patients and health care workers in the ED to expedite initiation of antiretroviral therapy. In such cases, institutions not only must comply with state guidelines but should implement uniform policies and procedures for testing that ensure pretest and post-test counseling and confidentiality of results.

Confidentiality of the patient's identity and medical data are of paramount importance in the ED, particularly for HIV-infected patients, for whom breached confidentiality may have numerous clinical, social, psychological, career, and insurability effects.

Public health responsibilities may at times override the duty of the physician to maintain strict confidentiality. AIDS is a reportable disease in most states, and state guidelines for reporting should be followed as a public health measure, even if this breaches confidentiality, as in cases of child abuse, gunshot wounds, or other infectious diseases. Moreover, the physician who is aware of potentially contagious practices of an infected patient has an obligation to provide appropriate counseling for that person. Additionally, infected patients should be encouraged to divulge their disease state with sexual or needle-sharing partners. In many states, the physician has the discretion to inform public health officials about the culpable practices, to allow partners potentially at risk to be informed.[100]

The potential value of aggressive interventions in critical care settings must be determined on an individual case basis. Some clinicians believe that in the advanced stages of AIDS, resuscitative measures are not appropriate because of the uniformly poor prognosis. Many patients may agree as they approach the terminal stages of their disease. Appropriate advance directives should be completed before the patient

enters the resuscitation setting. However, many patients fail to provide such documentation. Decisions regarding the withholding of extraordinary resuscitation efforts may be difficult to make in the ED because of insufficient information about an individual patient, his or her wishes, the specific disease state, prognosis, and the judgment and intentions of the primary care and consultant physicians. Although some ethicists argue against the excessive use of extensive resources for this class of patients, decisions in the ED should be largely unbiased and based on the appropriate factors relevant to the individual case. As with all patients with clinical indications for invasive monitoring or interventions, decisions should be based on factors including the patient's wishes (if known) or a surrogate's assessment of the patient's wishes, expected outcome of the intervention, and potential risks of the intervention. Interventions should not be withheld or discontinued merely because of the presence of AIDS.

If certain diagnostic and therapeutic interventions are withheld, particular attention should be made to ensure adequate control of pain and other symptoms. Psychosocial, religious, and cultural needs also should be addressed.

The courts have addressed increasing numbers and varieties of cases regarding the treatment of AIDS and HIV-related illness. The AIDS Litigation Project (a review of cases) has shown increasing cases of litigation involving areas of AIDS education, blood supply, epidemiologic surveillance, criminal law, public places, products and fraud, torts, court system, family law, confidentiality, prisons, military, fear of exposure, homelessness, and discrimination.[101]

In general, the same ethical principles of respect for autonomy, beneficence, nonmaleficence, justice, confidentiality, communication, informed consent, and research ethics should be honored in the treatment of HIV-infected patients as for all ED patients.

PRECAUTIONS AND POSTEXPOSURE PROPHYLAXIS FOR HEALTH CARE WORKERS

Precautions and Exposures

Health care workers often are exposed to the blood and body secretions of HIV-infected patients or of other persons who are at high risk of harboring HIV and other infectious pathogens. The overall risk of having any occupational blood exposure is not insignificant, with more than one half of emergency physicians reporting at least one occupational exposure during a 2-year period.[102]

The overall risk of contracting HIV infection remains small. As of December 2006, the CDC had received reports of 57 documented cases of HIV seroconversion that were temporally associated with occupational exposure to HIV among U.S. health care workers.[103] An additional 140 infections among health care workers were considered to represent possible cases of occupational transmission. No new documented cases of occupationally acquired HIV/AIDS have been reported since December 2001. Global surveillance data is less reliable, so the overall rates of occupational transmission are not known. A majority of cases occurred in nurses; less frequently affected were laboratory technicians and physicians.[102] Of all transmissions, a majority were percutaneous, followed by mucocutaneous or both. There have been no confirmed seroconversions to date with exposures to a suture needle. Efficacy of transmission is estimated at 0.3% for percutaneous exposure and 0.09% for mucocutaneous exposure.[104]

The proportion of patients infected with a pathogen varies by geographic setting and practice locale. A survey conducted at a Baltimore inner city hospital found that up to 11% of patients were infected with HIV and nearly 24% were infected with HIV or hepatitis B or C.[105] Numerous studies have demonstrated that a substantial number of patients in the ED have previously undiagnosed HIV infection, and HIV seroreactivity cannot be accurately predicted even with the aid of risk factor assessment. Because asymptomatic persons who are HIV antibody–positive can transmit the disease, *all* contacts with patients' blood or body secretions must be considered to be potentially infectious by ED personnel.

HIV transmission by health care workers to patients appears to be extremely rare. Only seven cases have been reported to date, six of which occurred from a single dentist's practice, and one from a patient who apparently acquired HIV during orthopedic surgery. At present, routine screening of health care personnel is not indicated.

Numerous studies have demonstrated that health care workers can significantly reduce their risk of exposure to blood-borne pathogens by following universal precautions. CDC guidelines for universal precautions include the use of protective equipment (including gloves, gown, mask, and eye protection) for any situation in which the potential for exposure exists. Protective equipment is indicated for most ED procedures, including examination of the bleeding patient, chest tube placement, lumbar puncture, and other commonly performed procedures in which contact with blood or body fluids is likely. Although significant improvement has been made in observance of universal precautions in the ED setting, studies have indicated that continued education and improvements in work environments are required to ensure consistent compliance.[106,107]

Postexposure Prophylaxis

Occupational Exposures

Postexposure prophylaxis (PEP) reduces the risk of HIV transmission and seroconversion.[108] The CDC provides explicit guidelines for institution of PEP for occupational exposure to HIV.[104] Current guidelines advise case-by-case determination of exposure risk to resolve whether PEP should be recommended. Recommendations are based on two primary factors: (1) type of exposure and (2) HIV status of the source (or, if the source status is unknown, evaluation of risk status of the source). Separate recommendations are provided by the CDC for percutaneous and mucus membrane or nonintact skin exposures. Exposures involving contact between intact skin and blood or other body fluids contaminated by HIV are not indications for therapy. Higher-risk percutaneous exposures associated with an increased likelihood of transmission include those involving deep injuries, visible blood on a device, and injuries sustained during placement of a catheter in a vein or artery; lower-risk percutaneous exposures are superficial or involve solid needles. High-risk sources are patients with symptomatic HIV infection, AIDS, acute seroconversion, or high viral load; low-risk sources are patients with asymptomatic HIV infection or viral load of less than 1500 copies/mL.[109] When the serostatus of the source is not known (i.e., no recent positive or negative results on serologic tests), rapid testing should be performed. A negative result on EIA (using either SUDS or OraQuick) is adequate for a decision to withhold or discontinue therapy if initiated. Some states allow testing the source patient without informed consent. Confidentiality should be rigorously protected while still ensuring that the appropriate information is provided to all exposed persons. In unusual circumstances in which the source patient has an illness consistent with acute

HIV infection, testing should include assay of HIV RNA levels.

Current public health guidelines recommend a 4-week regimen of two drugs for most HIV exposures given by percutaneous or mucous membrane routes.[104] Two-drug therapy options include zidovudine plus lamivudine (available as Combivir), lamivudine plus stavudine, and didanosine plus stavudine. For highest-risk exposures, an expanded PEP regimen with the addition of a protease inhibitor (preferably lopinavir plus ritonavir) is advised. When the source is known to be infected with a resistant HIV strain, the selection of PEP drugs to which the source's virus is unlikely to be resistant is recommended.

PEP should be initiated as soon as possible, preferably within hours rather than days of exposure; in general, antiretroviral therapy is not indicated in patients presenting more than 36 hours after exposure. The optimal duration of PEP is 4 weeks, if tolerated. Constitutional and gastrointestinal side effects may be significant and often lead to early termination of treatment. Initial treatment should never be delayed during the wait for information regarding final determination of overall risk of exposure, because therapy subsequently can be altered or stopped after the first dose. If the source person's HIV infection status is unknown at the time of exposure, use of PEP should be decided on a case-by-case basis, with type of exposure and likelihood of HIV infection in the source taken into consideration. If the findings suggest a possibility for HIV transmission and the result of HIV testing of the source person is pending, a two-drug PEP regimen should be initiated until laboratory results become available. PEP should be discontinued if the source patient is determined to be HIV-seronegative. In addition to the evaluation and management of HIV exposure risk, all patients should be tested and treated for other highly infectious diseases, such as hepatitis.

Patients often present to the ED seeking PEP because services are available at any time and early initiation of PEP is critical for efficacy. Many EDs are developing protocols and starter treatment packets for PEP. If possible, however, the choice of intervention and regimen usually is best accomplished in consultation with an infectious disease specialist and the patient's primary physician, to allow arrangement for appropriate medical follow-up and counseling.

Nonoccupational Exposure

Recent interest in the use of PEP for nonoccupational exposure has emerged, because the probability of HIV transmission by certain sexual or injection drug exposures is of the same order of magnitude as for percutaneous exposures, for which the CDC recommends PEP. The current DHHS recommendations regarding nonoccupational postexposure prophylaxis (nPEP) are as follows[110]: (1) For persons seeking care at 72 hours or earlier after nonoccupational exposure to blood, genital secretions, or other potentially infectious body fluids of a person known to be HIV-infected, when that exposure represents a substantial risk for transmission, a 28-day course of a HAART regimen is recommended, and antiretroviral medications should be initiated as soon as possible after exposure. (2) For persons seeking care at 72 hours or earlier after nonoccupational exposure to blood, genital secretions, or other potentially infectious body fluids of a person of unknown HIV status, when such exposure would represent a substantial risk for transmission if the source were HIV-infected, no recommendations are made for the use of nPEP. (3) For persons with an exposure history that represents no substantial risk for HIV transmission or who seek care later than 72 hours after exposure, DHHS does not recommend the use of nPEP. (4) Clinicians may consider prescribing nPEP for exposures conferring a serious risk for transmission, even if the person seeks care later than 72 hours after exposure if, in their judgment, the diminished potential benefit of nPEP outweighs the risks for transmission and adverse events. All patients seeking care after HIV exposure should be tested for the presence of HIV antibodies at baseline and at 4 to 6 weeks, 3 months, and 6 months after exposure to determine whether HIV infection has occurred. In addition, testing for STDs, hepatitis B and C, and pregnancy should be offered. Early experience with implementation of these guidelines indicates that challenges exist in ensuring routine implementation.[111]

For most cases in which a patient with recent exposure is likely to have continuing risk for exposure, the CDC recommends providing basic risk reduction counseling and referral to risk reduction programs rather than offering PEP. Additional resources should be used whenever possible to assist with decision making and follow-up services; in-house infectious disease consultation should be sought. Other useful resources for information on both occupational and nonoccupational exposure include the CDC/University of California–San Francisco (UCSF) National Clinicians PEP Hotline (1-888-448-4911), providing 24-hour assistance, and the University of California at Los Angeles (UCLA)'s online decision-making support (http://www.needlestick.mednet.ucla.edu).

KEY CONCEPTS

- The seroprevalence of HIV infection and AIDS among patients presenting to EDs serving large metropolitan areas is 2 to 15%. Many of these are undiagnosed cases, so compliance of ED personnel with universal precautions is extremely important.
- Acute HIV seroconversion syndrome commonly follows exposure by 2 to 6 weeks and manifests with common nonspecific signs and symptoms such as fever, fatigue, diarrhea, weight loss, adenopathy, and rash. Patients fitting this profile should be screened for HIV risk factors and appropriately referred for HIV testing.
- PCP is the most common opportunistic infection in patients with AIDS. It often manifests as progressive dyspnea on exertion associated with a nonproductive cough. The chest radiograph commonly shows a diffuse interstitial infiltrate but may be normal in appearance. Blood gas analysis usually reveals hypoxemia that often is more pronounced after exercise.
- CNS disease is common in HIV-infected patients and may be caused by the disease itself, opportunistic infections, or malignancy. An algorithm for the evaluation of HIV-infected patients with severe or prolonged headache, altered mentation, new-onset seizures, or focal neurologic deficits is presented in Figure 130-2.
- The evaluation and management of HIV-infected patients with acute symptoms often are complex and best accomplished either in the hospital or in the outpatient setting with close follow-up.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 131 Parasitic Infections

Bruce M. Becker and John D. Cahill

PERSPECTIVE

Challenge

Parasitology has become increasingly important in the practice of emergency medicine. Recent years have seen a dramatic increase in immigration from South East Asia, Central and South America, and Africa into the United States. Many of the people in transit have left their countries of origin under dire circumstances, fleeing civil unrest, war, famine, economic hardship, political persecution, and environmental devastation; they often lived in regions where parasitic infections were endemic. Business and adventure travel, including ecotourism, frequently transports immunologically naive and vulnerable hosts to sites rich in parasitic disease (Fig. 131-1). Patients with human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS) who travel to countries where parasitic illnesses are endemic are at higher risk of contracting these illnesses. Patients with AIDS who emigrate or travel to the United States or Europe may harbor a number of devastating parasitic illnesses. There is a significant prevalence of endemic parasitic disease in many rural areas of the southeastern and southwestern United States and in some parts of Europe. Often, patients with parasitic illness initially seek treatment in the emergency department (ED).

Correct diagnosis and chemotherapy given early in the course of parasitic illness often result in rapid recovery (Table 131-1); mismanagement can be disastrous. Osler wrote, "Early in the course of disease, diagnosis is difficult and treatment easy; late in the course, diagnosis is easy and treatment difficult." Parasitic illness often begins insidiously and, without appropriate treatment, commonly pursues a chronic course, eventuating in end-organ damage and severe morbidity and even death. To diagnose parasitic infection, the emergency physician will need to play detective, obtaining a thorough travel history, performing a detailed physical examination, ordering appropriate laboratory studies, and integrating these findings with a strong understanding of the basic life cycles of parasites, usual and unusual presentations of infection, and the intersecting geography of the organism and the host.

An important point is that the incubation period for the development of symptoms for parasitic diseases ranges from days (falciparum malaria) to months (vivax malaria) to years (filariasis). Uncovering parasitic illness depends heavily on Osler's principle—to *make* the diagnosis, one must first *think* of the diagnosis.

A detailed account of individual parasites can be found in Bell's *Tropical Medicine*[1] and Guerrant and colleagues' *Tropical Infectious Diseases*.[2]

Travel History

Parasitic illness should be considered in the differential diagnosis for almost every sign or symptom imaginable, particularly in patients who recently have spent time in areas of the world with endemic parasitic illnesses (Table 131-2). Accordingly, a travel history should be included in the evaluation of most if not all patients presenting to the ED. Important questions are summarized in Box 131-1. For patients who recently emigrated to the United States, the history should elicit additional information specific to the country of origin, also summarized in Box 131-1.

PRINCIPLES OF THERAPY

New and more effective antiparasitic agents are continually being developed. The list of drugs used to treat parasitic infestations is large and varied (Table 131-3; see also Table 131-1). Table 131-3 includes some of the newest pharmaceutical agents, in addition to many medications that, although still recommended, have become almost obsolete because of toxicity or mediocre efficacy.

The newer antiparasitic drugs are less toxic to the patient and more effective. Parasite biochemical pathways are sufficiently different from those in the human host to permit selective interference by relatively small doses of chemotherapeutic agents. In many instances, single-dose treatment can eradicate an entire parasite burden, and this approach has led to implementation of mass treatment programs in infected populations in endemic areas. Treatment and disposition in the ED focus on the individual patient and particular disease entity. The evolutionary goal of the successful parasite is to live with and at the expense of the living host; a parasite that kills its host has no survival advantage. Most parasitic infections (with certain important exceptions, such as falciparum malaria) pursue a chronic course and are not acutely life-threatening. Alterations in host immune function can change the virulence and morbid course of more benign infections (e.g., strongyloidiasis can become fulminantly disseminated in patients receiving immunosuppressive medication after organ transplantation or after the initiation of long-term steroid therapy). Despite the subacute or chronic nature of most parasitic infections,

when a diagnosis (or a diagnostic plan) has been made and chemotherapy instituted, arrangements for careful follow-up and repeat laboratory examinations will be needed to ensure a cure. When the parasites are not eliminated promptly, repeat doses or alternative drugs should be considered, because drug resistance is becoming increasingly common. In such cases, referral to a geographic medicine clinic or an infectious disease clinic is indicated. Any patient who appears clinically ill or has presumptive falciparum malaria (by symptoms or travel history) should be admitted to the hospital for initial diagnosis, treatment, and observation.

FEVER

Malaria

Principles of Disease. The febrile patient with shaking chills and a time-appropriate history of travel to an endemic region should be evaluated for malaria. *Plasmodium falciparum*, *Plasmodium ovale*, *Plasmodium vivax*, and *Plasmodium malariae* are the species responsible for human malaria. More than 41% of the world's population lives in malaria-endemic areas (e.g., parts of Africa, Asia, Oceania, Central America, and South America). Approximately 300 million to 500 million clinical infections occur annually, resulting in 1.5 million to 2.7 million deaths.[3] Approximately 1500 cases of malaria are diagnosed yearly in the United States. The female *Anopheles* mosquito is the arthropod vector that can transmit malaria after ingesting gametocytes from infected persons. After sexual reproduction in the gut of the mosquito, sporozoites are released from the salivary glands of the arthropod into the human host during a blood meal. Sporozoites rapidly penetrate the liver parenchymal cells of their host. The protozoans, now termed *cryptozoites* or *exoerythrocytic schizonts*, rapidly multiply. Eventual lysis of the hepatic cells results in the release of merozoites into the bloodstream, where they invade erythrocytes. In *P. vivax* and *P. ovale* infection, dormant hypnozoites can reside in hepatocytes; recrudescence of infections can occur many months to years later.

After invading red blood cells (RBCs), the merozoites transform into trophozoites, which feed on the cells' hemoglobin.

Text continued on p. 1758

Table 131-1 Drug Classes and Modes of Action for Agents Used for Treatment of Parasitic Disease

TYPE OF DRUG	EXAMPLE(S)	USEFUL IN THE TREATMENT OF	LIKELY TARGET(S) IN THE PARASITE	PROPOSED EFFECTS ON TARGETS
Anthelmintics	Thiabendazole Mebendazole Albendazole	*Ascaris*, *Enterobius*, hookworm, *Strongyloides*, *Trichuris*, hydatid disease (long-term therapy)	Tubulin polymerization	Blocks cellular structural integrity and egg production; secondary effects on mitochondrial fumarate reductase and on glucose uptake
	Ivermectin* (Stromectol)	Many nematodes of humans (except hookworms) Filariasis Onchocerciasis	GABA-sensitive neuromuscular interface	Flaccidity or contraction (a tight-binding drug effective at low dose)
Trematodicides	Praziquantel (Biltricide)	Schistosomes Most other flukes, such as *Clonorchis*, *Paragonimus*, *Fasciolopsis* (many tapeworms of humans)	Surface structure Carbohydrate metabolism	Vacuolization and surface disruption followed by immune attacks by the host; contraction of the muscles due to flooding of calcium through a permeable tegument; initial increase of glucose metabolism followed by shutdown
Antiprotozoals	Metronidazole (Flagyl) Tinidazole Niridazole	Amebiasis Balantidiasis Giardiasis *S. haematobium*	Molecular electron transport systems Acetylcholine recycling systems	Failure to sustain energy-producing systems Binds to acetylcholinesterase, inactivating normal neuromuscular function
Antimalarials	Chloroquine phosphate (Aralen)	Many species of susceptible malaria	Parasite digestive vacuole hemoglobinase	Local pH is changed so that enzyme becomes inoperative
	Chloroguanide Pyrimethamine Trimethoprim and combinations of antifolate and sulfa drug (e.g., sulfadoxine/pyrimethamine [Fansidar])	Many species of susceptible malaria Various malaria species partially or totally refractory to chloroquine	Dihydrofolate reductase step in folate synthesis or incorporation of PABA in folic acid	Blocks normal folate synthesis and eventually one-carbon metabolism

*Available at present from CDC Drug Service, Centers for Disease Control and Prevention, Atlanta, Georgia 30333, telephone: 404-639-3670 (evenings, weekends, and holidays: 404-639-2888).

GABA, γ-aminobutyric acid; PABA, para-aminobenzoic acid.

Table 131-2 Parasites Causing Human Disease: Geographic Location and Portal of Entry

PARASITE	GEOGRAPHIC DISTRIBUTION	COMMON INFECTIVE STAGE AND PORTAL OF ENTRY
Protozoa		
Entamoeba histolytica	Cosmopolitan, especially prevalent in warm climates	Cyst via mouth
Balantidium coli	Warm climates	Cyst via mouth
Giardia lamblia	Cosmopolitan, especially prevalent in warm climates	Cyst via mouth
Trichomonas vaginalis	Cosmopolitan, United States	Trophozoite via vulva or urethra
Leishmania tropica	Mediterranean area to western India	Leptomonad via skin
Leishmania braziliensis	Mexico to northern Argentina	Leptomonad via skin
Leishmania donovani	China, India, Africa, Mediterranean area, continental Latin America	Leptomonad via skin
Trypanosoma gambiense	West and Central Africa	Trypanosome via skin
Trypanosoma rhodesiense	Central and East Africa	Trypanosome via skin
Trypanosoma cruzi	Continental Latin America	Trypanosome via skin
Plasmodium vivax	Warm and cooler climates	Sporozoite via skin
Plasmodium malariae	Warm climates	Sporozoite via skin
Plasmodium falciparum	Warm climates	Sporozoite via skin
Nematodes		
Trichinella spiralis	Cosmopolitan, common in the United States	Encysted larva in pork via mouth
Trichuris trichiura	Warm, moist climates	Embryonated egg via mouth
Strongyloides stercoralis	Warm, moist climates	Filariform larva via skin
Necator americanus	Common in warm climates	Filariform larva via skin
Ancylostoma duodenale	Western South America	Filariform larva via skin
Enterobius vermicularis	Cosmopolitan, common in the United States	Embryonated egg via mouth
Ascaris lumbricoides	Cosmopolitan, common in the United States	Embryonated egg via mouth
Wuchereria bancrofti	Prevalent in warm climates	Filariform larva via skin
Brugia malayi	Asia	Filariform larva via skin
Onchocerca volvulus	Tropical Africa, Mexico, Central America, and northern South America	Filariform larva via skin
Loa loa	Tropical West Africa	Filariform larva via skin
Dracunculus medinensis	Tropical Eastern Hemisphere	Ingestion of larva via copepod via mouth
Cestodes		
Taenia saginata	Cosmopolitan, United States	Cysticercus in beef via mouth
Taenia solium		
1. Adult worm	Cosmopolitan, United States	1. Cysticercus in pork via mouth
2. Cysticercus stage	Cosmopolitan, United States	2. Eggs in human infections via mouth
Echinococcus granulosus	Cosmopolitan, United States	Eggs from canines via mouth
Echinococcus multilocularis	Central Europe, Asia, Alaska	Eggs from foxes via mouth
Hymenolepis nana	Warm climates	Eggs in human infections via mouth
Hymenolepis diminuta	Warm climates	Larva in arthropod host via mouth
Diphyllobothrium latum	North Temperate Zone, Argentina, Chile, Australia	Sparganum larva in fish flesh via mouth
Trematodes		
Fasciola hepatica	Sheep-raising countries	Larva on vegetation via mouth
Fasciolopsis buski	Asia	Larva on water nuts
Clonorchis sinensis	Asia	Larva encysted in freshwater fish
Opisthorchis felineus	Europe, Asia	Larva encysted in freshwater fish
Opisthorchis viverrini	Thailand	Larva encysted in freshwater fish
Paragonimus westermani	Primarily Asia, also South America and Africa	Larva encysted in crabs or crayfish via mouth
Schistosoma japonicum	Asia	Cercarial larva in water via skin
Schistosoma mansoni	Africa, Latin America	Cercarial larva in water via skin
Schistosoma haematobium	Africa to India, southern Portugal	Cercarial larva in water via skin

Modified from Beaver PC, et al: Clinical Parasitology, 9th ed. Philadelphia, Lea & Febiger, 1984.

BOX 131-1 COMPREHENSIVE TRAVEL HISTORY FOR EVALUATION FOR PARASITIC DISEASE IN THE EMERGENCY DEPARTMENT

Questions for All Patients

- What were the exact dates of travel?
- What countries did the patient visit?
- How much time was spent in each country?
- What was the patient doing in the country, and where was he or she living?
- Was the patient a tourist, an adventure traveler, or a worker?
- Did the patient stay in cities or rural villages?
- Was the patient sleeping in hotels or tents?
- Did the patient engage in protected or unprotected sexual intercourse?
- What did the patient eat and drink?
- What were the patient's activities (e.g., swimming in freshwater leads to schistosomiasis)?
- Did the patient receive prophylactic immunizations before travel?
- Did the patient take malaria chemoprophylaxis and comply with the regimen?
- Did the patient use mosquito repellent and netting?
- Does the patient have underlying chronic medical problems?
- What medications does the patient take?
- When did symptoms start, and what has been the chronology of symptoms, particularly fever and diarrhea?

Questions for Patients Who Are Recent Immigrants to the United States

- When did the patient arrive and from where?
- What acute and chronic illnesses did the patient have previously while living in the country of origin?
- What treatment did the patient receive there?
- If a refugee, what countries did the patient pass through, and what were the living conditions (especially relevant for persons who have lived in numerous refugee camps)?
- What was the season during the patient's stay or travel in the countries (e.g., monsoon versus dry)?
- What animal exposures and bites has the patient experienced?
- Has the patient had exposure to fresh water, in either work or recreational activities?

Table 131-3 Drug Regimens for Treatment of Parasitic Infections

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Amebiasis (*Entamoeba histolytica*)			
Asymptomatic			
DRUG OF CHOICE:	Iodoquinol	650 mg tid × 20 days	30 mg/kg/day in 3 doses × 20 days
ALTERNATIVES:	Diloxanide furoate	500 mg tid × 10 days	20 mg/kg/day in 3 doses × 7 days
	or Paromomycin	25–30 mg/kg/day in 3 doses × 7 days	25–30 mg/kg/day in 3 doses × 7 days
Mild to moderate intestinal disease			
DRUG OF CHOICE:	Metronidazole	750 mg tid × 10 days	35–50 mg/kg/day in 3 doses × 10 days
ALTERNATIVE:	Tinidazole	2 g/day × 3 days	50 mg/kg (maximum 2 g) qd × 3 days
Severe intestinal disease, hepatic abscess			
DRUG OF CHOICE:	Metronidazole	750 mg tid × 10 days	35–50 mg/kg/day in 3 doses × 10 days
ALTERNATIVE:	Tinidazole	600 mg bid or 800 mg tid × 5 days	50 mg/kg or 60 mg/kg (maximum 2 g) qd × 3 days
Amebic meningoencephalitis, primary (*Naegleria* spp.)			
DRUG OF CHOICE:	Amphotericin B	1 mg/kg/day IV, uncertain duration	1 mg/kg/day IV, uncertain duration
Anisakiasis (*Anisakis*)			
TREATMENT OF CHOICE:	Surgical or endoscopic removal		
Ascariasis (*Ascaris lumbricoides*): roundworm			
DRUGS OF CHOICE:	Mebendazole	100 mg bid × 3 days	100 mg bid × 3 days
	or Pyrantel pamoate	11 mg/kg once (maximum 1 g)	11 mg/kg once (maximum 1 g)
Balantidiasis (*Balantidium coli*)			
DRUG OF CHOICE:	Tetracycline	500 mg qid × 10 days	40 mg/kg/day in 4 doses × 10 days (maximum 2 g/day)
ALTERNATIVES:	Iodoquinol	650 mg tid × 20 days	40 mg/kg/day in 3 doses × 20 days
	Metronidazole	750 mg tid × 5 days	35–50 mg/kg/day in 3 doses × 5 days

Table 131-3 Drug Regimens for Treatment of Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Cutaneous larva migrans (creeping eruption)			
DRUG OF CHOICE:	Ivermectin	200 µg/per kg once daily × 1 or 2 days	
Dracunculus medinensis (Guinea worm)			
DRUG OF CHOICE:	Metronidazole	750 mg tid × 5–10 days	25 mg/kg/day (maximum 750 mg/day) in 2 doses × 10 days
ALTERNATIVE:	Thiabendazole	50–75 mg/day in 2 doses × 3 days	50–75 mg/kg/day in 2 doses × 3 days
Enterobius vermicularis (pinworm)			
DRUGS OF CHOICE:	Albendazole	A single dose of 400 mg; repeat after 2 wk	11 mg/kg once (maximum 1 g); repeat after 2 wk
	Mebendazole	A single dose of 100 mg; repeat after 2 wk	A single dose of 100 mg; repeat after 2 wk
Filariasis			
Wuchereria bancrofti, *Brugia malayi*			
DRUG OF CHOICE:	Diethylcarbamazine	Day 1: 50 mg PO Day 2: 50 mg tid Day 3: 100 mg tid Days 4–21: 6 mg/kg/day in 3 doses	Day 1: 1 mg/kg PO Day 2: 1 mg/kg tid Day 3: 1–2 mg/kg tid Days 4–21: 6 mg/kg/day in 3 doses
Loa loa			
DRUG OF CHOICE:	Diethylcarbamazine	Day 1: 50 mg PO Day 2: 50 mg tid Day 3: 100 mg tid Days 4–21: 9 mg/kg/day in 3 doses	Day 1: 1 mg/kg PO Day 2: 1 mg/kg tid Day 3: 1–2 mg/kg tid Days 4–21: 6 mg/kg/day in 3 doses
Onchocerca volvulus			
DRUG OF CHOICE:	Ivermectin*	150 µm/kg PO once, repeated every 3–12 mo	150 µm/kg PO once, repeated every 3–12 mo
Fluke, hermaphroditic			
Clonorchis sinensis (Chinese liver fluke)			
DRUG OF CHOICE:	Praziquantel	75 mg/kg/day in 3 doses × 1 day	75 mg/kg/day in 3 doses × 1 day
Fasciola hepatica (sheep liver fluke)			
DRUG OF CHOICE:	Bithionol	30–50 mg/kg on alternate days × 10–15 doses	30–50 mg/kg on alternate days × 10–15 doses
Fasciolopsis buski (intestinal fluke)			
DRUG OF CHOICE:	Praziquantel	75 mg/kg/day in 3 doses × 1 day	75 mg/kg/day in 3 doses × 1 day
Opisthorchis felineus			
DRUG OF CHOICE:	Praziquantel	75 mg/kg/day in 3 doses × 1 day	75 mg/kg/day in 3 doses × 1 day
Paragonimus westermani (lung fluke)			
DRUG OF CHOICE:	Praziquantel	75 mg/kg/day in 3 doses × 2 days	75 mg/kg/day in 3 doses × 2 days
ALTERNATIVE:	Bithionol	30–50 mg/kg on alternate days × 10–15 doses	30–50 mg/kg on alternate days × 10–15 doses
Giardiasis (*Giardia lamblia*)			
DRUG OF CHOICE:	Metronidazole	250 mg tid × 5 days	15 mg/kg/day in 3 doses × 5 days
ALTERNATIVES:	Furazolidone	100 mg qid × 7–10 days	6 mg/kg/day in 4 doses × 7–10 days
	Tinidazole	2 g as a single daily dose for 1–3 days	50 mg/kg as a single daily dose for 1–3 days
Hookworm infection (*Ancylostoma duodenale*, *Necator americanus*)			
DRUGS OF CHOICE:	Albendazole	400 mg × one dose	
	Mebendazole	500 mg × one dose	500 mg × one dose
	or Pyrantel pamoate	11 mg/kg (maximum 1 g) × 3 days	11 mg/kg (maximum 1 g) × 3 days

Table 131-3 Drug Regimens for Treatment of Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Leishmaniasis (*Leishmania braziliensis*, *Leishmania mexicana*, *Leishmania tropica*, *Leishmania donovani* [kala-azar])			
DRUG OF CHOICE:	Miltefosine	Not indicated in those 12 years or younger	2.5 mg/kg/day PO × 28 days
	or Stibogluconate sodium	20 mg/kg/day IV or IM × 20–28 days	20 mg/kg/day IV or IM × 20–28 days
ALTERNATIVE:	Amphotericin B	0.25–1 mg/kg by slow infusion daily or every 2 days for 8 wk	0.25–1 mg/kg by slow infusion daily or every 2 days for 8 wk
Malaria, treatment of (*Plasmodium falciparum*, *P. ovale*, *P. vivax*, and *P. malariae*)			
All *Plasmodium* species except chloroquine-resistant *P. falciparum*			
Oral			
DRUG OF CHOICE:	Chloroquine phosphate	600 mg base (1 g), then 300 mg base (500 mg) 6 hr later, then 300 mg base (500 mg) at 24 and 48 hr	10 mg base/kg (maximum 600 mg base), then 5 mg base/kg 6 hr later, then 5 mg base/kg at 24 and 48 hr
Parenteral			
DRUGS OF CHOICE:	Quinine dihydrochloride	20 mg/kg loading dose in 10 mg/kg 5% dextrose over 4 hr followed by 10 mg/kg over 2–4 hr q8h (maximum 1800 mg/day) until oral therapy can be started	Same as adult dose
	or Quinidine gluconate	10 mg/kg loading dose (maximum 600 mg) in normal saline slowly over 1–2 hr, followed by continuous infusion of 0.02 mg/kg/min for 3 days maximum	Same as adult dose
	or Artesunate for treatment failure or adverse reactions from quinidine/quinine, available from the CDC		
ALTERNATIVE:	Chloroquine hydrochloride	200 mg base (250 mg) IM q6h if oral therapy cannot be started	0.83 mg base/kg/hr × 30 hr continuous infusion or 3.5 mg base/kg q6h IM or SC
Chloroquine-resistant *P. falciparum*			
Oral			
DRUGS OF CHOICE:	Quinine sulfate	650 mg tid × 3 days	25 mg/kg/day in 3 doses × 3–7 days
	plus Doxycycline	100 mg bid × 7 days	
	or Clindamycin	900 mg tid × 3–5 days	20–40 mg/kg/day in 3 doses × 3–5 days
ALTERNATIVE:	Mefloquine	1250 mg once	25 mg/kg once (<45 kg)
	Atovaquone/proguanil	1000/400 mg qd × 3 days	
Parenteral			
DRUGS OF CHOICE:	Quinine dihydrochloride	Same as above	Same as above
	or Quinidine gluconate	Same as above	Same as above
	or Artesunate	Same as above	Same as above
Prevention of relapses: *P. vivax* and *P. ovale* only			
DRUG OF CHOICE:	Primaquine phosphate	15 mg base (26.3 mg)/day × 14 days or 45 mg base (79 mg)/wk × 8 wk	0.3 mg base/kg/day × 14 days
Malaria, prevention of			
DRUG OF CHOICE:	Chloroquine phosphate	300 mg base (500 mg salt) PO, once a week beginning 1 wk before and continuing for 4 wk after last exposure	5 mg/kg base (8.3 mg/kg salt) once a week, up to adult dose of 300 mg base, same schedule as for adult

Table 131-3 Drug Regimens for Treatment of Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Chloroquine-resistant areas			
DRUGS OF CHOICE:	Mefloquine	250 mg tablet PO once a week × 4 wk, then every other week, continuing for 4 wk after last exposure	Same schedule as for adults using the following dosing guidelines: *15–19 kg*: ¼ tablet *20–30 kg*: ½ tablet *31–45 kg*: ¾ tablet *>45 kg*: 1 tablet
	or Atovaquone/ proguanil	250/100 mg qd 1 day before travel, each day in endemic region, and for 1 week afterward	
	or Doxycycline	100 mg daily during exposure and for 4 weeks afterward	*>8 yr*: 2 mg/kg/day PO, up to 100 mg/day
Schistosomiasis			
Schistosoma haematobium			
DRUG OF CHOICE:	Praziquantel	40 mg/kg/day in 2 doses × 1 day	40 mg/kg/day in 2 doses × 1 day
Schistosoma japonicum			
DRUG OF CHOICE:	Praziquantel	60 mg/kg/day in 3 doses × 1 day	60 mg/kg/day in 3 doses × 1 day
Schistosoma mansoni			
DRUG OF CHOICE:	Praziquantel	40 mg/kg/day in 2 doses × 1 day	40 mg/kg/day in 2 doses × 1 day
ALTERNATIVE:	Oxamniquine	15 mg/kg once	20 mg/kg/day in 2 doses × 1 day
Schistosoma mekongi			
DRUG OF CHOICE:	Praziquantel	60 mg/kg/day in 3 doses × 1 day	60 mg/kg/day in 3 doses × 1 day
Strongyloidiasis (*Strongyloides stercoralis*)			
DRUGS OF CHOICE:	Thiabendazole	50 mg/kg/day in 2 doses (maximum 3 g/day) × 2 days	50 mg/kg/day in 2 doses (maximum 3 g/day) × 2 days
	or Ivermectin	200 µg/kg/day × 1–2 days	200 µg/kg/day × 1–2 days
Tapeworm infection—adult (intestinal stage)			
Diphyllobothrium latum (fish), *Taenia saginata* (beef), *Taenia solium* (pork), *Dipylidium caninum* (dog)			
DRUG OF CHOICE:	Praziquantel	5–10 mg/kg once	5–10 mg/kg once
Hymenolepis nana (dwarf tapeworm)			
DRUG OF CHOICE:	Praziquantel	25 mg/kg once	25 mg/kg once
Tapeworm infection—larval (tissue) stage			
Echinococcus granulosus (hydatid cysts)			
DRUG OF CHOICE:	Albendazole	400 mg bid × 28 days, repeated as necessary	15 mg/kg/day × 28 days, repeated as necessary
Echinococcus multilocularis			
TREATMENT OF CHOICE:	Surgical excision		
Cysticercus cellulosae (cysticercosis)			
DRUG OF CHOICE:	Praziquantel	50 mg/kg/day in 3 doses × 15 days	50 mg/kg/day in 3 doses × 15 days
ALTERNATIVE:	Surgery		
Trichinosis (*Trichinella spiralis*)			
DRUGS OF CHOICE:	Steroids for severe symptoms		
	plus Mebendazole	200–400 mg tid × 3 days, then 400–500 mg tid × 10 days	Same as adult
Trichomoniasis (*Trichomonas vaginalis*)			
DRUG OF CHOICE:	Metronidazole	2 g once *or* 250 mg tid *or* 375 mg bid PO × 7 days	15 mg/kg/day PO in 3 doses × 7 days
Trichuriasis (*Trichuris trichiura*, whipworm)			
DRUGS OF CHOICE:	Mebendazole	100 mg bid × 3 days	100 mg bid × 3 days
	or Albendazole	400 mg once	400 mg once

Table 131-3 Drug Regimens for Treatment of Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Trypanosomiasis			
Trypanosoma cruzi (South American trypanosomiasis, Chagas' disease)			
DRUG OF CHOICE:	Nifurtimox	8–10 mg/kg/day PO in 4 doses × 120 days	*1–10 yr*: 15–20 mg/kg/day in 4 doses × 90 days *11–16 yr*: 12.5–15 mg/kg/day in 4 doses × 90 days
ALTERNATIVE:	Benznidazole	5–7 mg/kg/day × 30–120 days	Same as adult
Trypanosoma brucei gambiense, *Trypanosoma brucei rhodesiense* (African trypanosomiasis, sleeping sickness) hemolymphatic stage			
DRUG OF CHOICE:	Suramin	100–200 mg (test done) IV, then 1 g IV on days 1, 3, 7, 14, and 21	20 mg/kg on days 1, 3, 7, 14, and 21
ALTERNATIVE:	Pentamidine isethionate	4 mg/kg/day IM × 10 days	4 mg/kg/day IM × 10 days
Late disease with central nervous system involvement			
DRUG OF CHOICE:	Melarsoprol	2–3.6 mg/kg/day IV × 3 days; after 1 wk 3.6 mg/kg/day IV × 3 days; repeat again after 10–21 days	18–25 mg/kg total over 1 mo; initial dose of 0.36 mg/kg IV, increasing gradually to maximum 3.6 mg/kg at intervals of 1–5 days for total of 9–10 doses
ALTERNATIVES: (*T. b. gambiense* only)	Tryparsamide	One injection of 30 mg/kg (maximum 2 g) IV every 5 days to total of 12 injections; course may be repeated after 1 mo	Unknown
	plus Suramin	One injection of 10 mg/kg IV every 5 days to total of 12 injections; course may be repeated after 1 mo	Unknown
Visceral larva migrans (toxocariasis)			
DRUG OF CHOICE:	Diethylcarbamazine	6 mg/kg/day in 3 doses × 7–10 days	6 mg/kg/day in 3 doses × 7–10 days
ALTERNATIVES:	Mebendazole *or* Albendazole	100–200 mg bid × 5 days 400 mg bid × 3–5 days	Same as adult 400 mg bid × 3–5 days

*Some drugs available from CDC Drug Service, Centers for Disease Control and Prevention, Atlanta, 30333, telephone: 404-639-3670 (nights, weekends, and holidays: 404-639-2888).

Modified from Drugs for parasite infections. Med Lett Drug Ther 37:99, 1995.

Trophozoites mature into schizonts, which may divide asexually into additional merozoites. The RBCs undergo lysis, releasing merozoites into the blood. Although some merozoites are destroyed by the host's immune apparatus, many enter new erythrocytes. After several repetitions of this erythrocytic cycle, the cyclic process changes, and male microgametocytes or female macrogametocytes may develop instead of merozoites. These gametes subsequently complete the reproductive cycle by fusion, accomplished sexually, within the gut of a new female *Anopheles* mosquito after she has taken a blood meal from an infected host. Most people contract malaria after being bitten by an infected vector mosquito in an endemic region. Other means of transmission have been reported, including blood transfusions, injection drug use with contaminated syringes, perinatal transmission, organ transplantation, and so-called airport malaria. *Airport malaria* has been reported in people who have never been in an endemic area but live near or work in an international airport. The infected mosquito is transported from the endemic region and released when the plane arrives at its destination.[4,5]

Clinical Features. Most patients with malaria present with irregular fevers. Other signs and symptoms include anemia, headache, nausea, chills, lethargy, abdominal pain, and upper respiratory complaints.[6] The important difference between *P. falciparum* and the other malaria species is the capacity of *P. falciparum* to cause severe organ system damage and death. *Acute* falciparum infection may have any of the following manifestations: cerebral malaria with cerebral edema and encephalopathy (Fig. 131-2), hypoglycemia (especially in children), metabolic acidosis, severe anemia, renal failure, pulmonary edema, disseminated intravascular coagulation, and death.

In *chronic* malaria, hepatosplenomegaly may develop because of increased cellularity from the host's immune response. Within the liver, parasites and malarial pigment distend the Kupffer cells. Parasitized RBCs also adhere to the sinusoidal system of the spleen, reducing its immunologic effectiveness. Anemia results from acute and chronic hemolysis. So-called blackwater fever—hemoglobinuria caused by severe hemolysis—may occur in patients with either chronic or acute falciparum malaria.

Diagnostic Strategies. Light microscopic examination of thick and thin blood films is the "gold standard" modality for the diagnosis of malaria. The clinician may have to view several slides to make the diagnosis if the parasite burden is small. Peripheral blood smears are stained with Giemsa or Wright stains and examined with ordinary light microscopy. The diag-

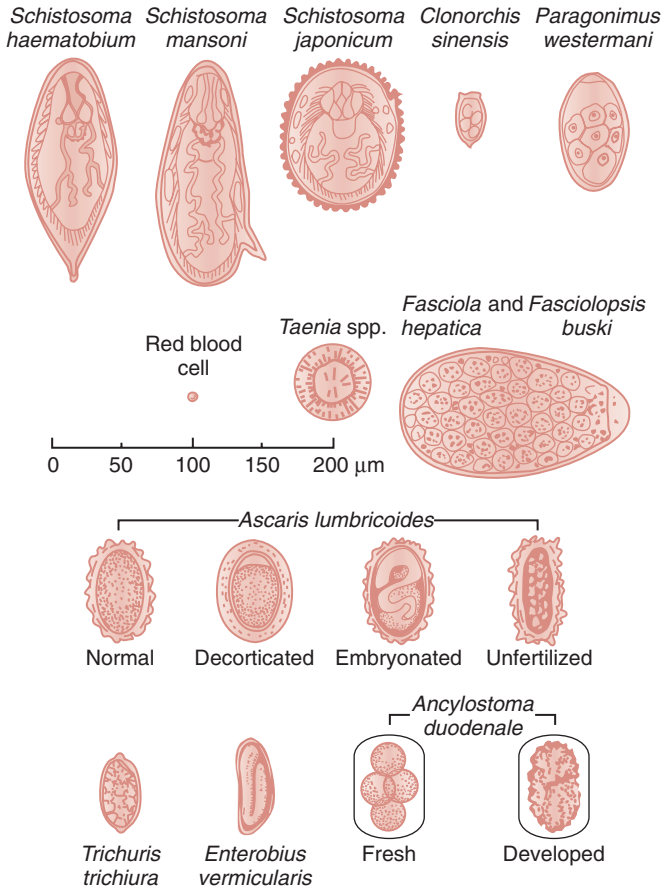

Figure 131-1. Eggs of major parasitic worms causing disease in humans.

nosis can be made in a simply equipped laboratory. Even if the parasite is not visualized in the smear, treatment for malaria is nevertheless indicated if the disease is suspected on clinical grounds. The U.S. Food and Drug Administration (FDA) has approved the use of an antigen-based rapid diagnostic test for screening patients. Microscopy must still be performed in all patients with positive results on such tests, to determine species and the severity of parasitemia.

Management. In the past, chloroquine phosphate was the treatment of choice for acute, uncomplicated attacks of malaria. Resistance to chloroquine has been steadily increasing, and now the drug should be used only in regions of known chloroquine sensitivity: Haiti, Dominican Republic, Central America, and limited regions of the Middle East. For uncomplicated malarial infections in patients from chloroquine-resistant regions, oral quinine and doxycycline given together may be used. Another suitable alternative combination is proguanil-atovaquone. For complicated *P. falciparum* infection (e.g., cerebral malaria, involvement of multiple organ systems, unability to tolerate oral medication), intravenous quinine (not available in intravenous form in the United States) or quinidine is used. Rapid infusion of intravenous quinine can cause profound hypoglycemia. Patients should not receive intravenous quinine without cardiac monitoring.

The artemisinin agents are excellent antimalarials and are available in enteral and parenteral preparations. They have a rapid onset of action and are well tolerated. Most are not available in the United States; however, artesunate (which is an artemisinin agent) is now available as an investigational new drug for patients who have complicated malaria not responding to quinidine. To obtain this drug, physicians can contact the Centers for Disease Control and Prevention (CDC) Malaria Hotline at 770-488-7788 or, during off hours, at 770-448-7100.[7]

Figure 131-2. Patient in coma from falciparum cerebral malaria.

Primaquine is used to expunge the hepatic phases of *P. ovale* and *P. vivax*, to prevent recrudescent disease. Before starting primaquine therapy, the patient must be tested for glucose-6-phosphate dehydrogenase enzyme deficiency, to avoid precipitating severe hemolysis. Prompt diagnosis and appropriate therapeutic intervention are essential for patients infected with falciparum malaria, to prevent coma and death.[8,9]

Babesiosis

Babesiosis is a malaria-like illness that is becoming increasingly prevalent in the northeastern United States (*Babesia microti*), the northwestern United States (*Babesia gibsoni*), and Europe (*Babesia divergens*). Babesiosis is endemic on Martha's Vineyard and Nantucket. The organism is a protozoan similar in structure and life cycle to the plasmodia. It is transmitted by the deer tick, *Ixodes dammini*, the vector of Lyme disease. Several cases have been attributed to transfusions with infected blood.[10] Patients with babesiosis experience fatigue, anorexia, malaise, and emotional lability, with myalgia, chills, high spiking fevers, sweats, headache, and dark urine. Other manifestations include hepatosplenomegaly, anemia, thrombocytopenia, leukopenia, elevated liver enzyme levels, and signs of hemolysis with hyperbilirubinemia and decreased haptoglobin. In an otherwise healthy person, the disease may remit spontaneously. In asplenic, elderly, and immunocompromised patients (especially patients with AIDS and patients taking corticosteroids), 85% of RBCs may contain organisms. Clinical syndromes include massive hemolysis, jaundice, renal failure, disseminated intravascular coagulation, hypotension, and adult respiratory distress syndrome.[11] Diagnosis is based on clinical suspicion, multiple thin and thick blood smears, and serologic testing (results of which may not turn positive for several weeks after the infection). The treatment of choice consists of quinine plus clindamycin. Patients infected with *B. divergens* tend to be sicker and require more supportive care. Co-infection with *Borrelia burgdorferi*, the agent of Lyme disease, results in more severe and prolonged illness.[12] *Babesia* organisms resemble plasmodia in blood smears.

Other Parasites Causing Fever

Other parasitic illnesses that commonly cause significant fever include schistosomiasis, fascioliasis, African and American trypanosomiasis, leishmaniasis, toxoplasmosis, and amebic liver abscess. Katayama fever may be the initial phase of schistosomiasis. Infected patients report brief exposures to fresh water in endemic areas. Clinical manifestations include spiking fevers, diaphoresis, and cough. Eosinophilia is common.[13] Fascioliasis, caused by the liver fluke, *Fasciola hepatica*, is endemic throughout Asia, the former Soviet Union, southern Europe, and South America. Infection begins with ingestion of the metacercariae often found in watercress. Within 6 weeks, patients exhibit right upper quadrant abdominal pain, fever, and eosinophilia.[14]

American trypanosomiasis (Chagas' disease) is endemic to Central and South America. The vector, the reduviid bug, sheds trypomastigotes in its feces proximal to the bite site, leading to local infection and subsequent systemic spread in the host. Acute Chagas' disease begins with the *chagoma*, the infected and swollen bite site often periorbital in location, and quickly progresses to fever, malaise, facial swelling, and pedal edema. Parasitization of cardiac muscle leads to the dysrhythmias and ventricular dysfunction that are classically found in late disease (chronic Chagas' cardiopathy).[15] Leishmaniasis is spread to humans by the sandfly and is found in the Middle East, India, and East Africa; along the Mediterranean coast; and in Brazil. Although leishmaniasis can involve the skin (cutaneous) and the mucosa (mucosal), fever is seen only in visceral leishmaniasis in immunocompetent persons. Signs and symptoms also include massive hepatosplenomegaly, neutropenia, and weight loss.[16] Amebic liver abscesses frequently manifest with high fevers, right upper quadrant pain, and an elevated white blood cell count.[17]

NEUROLOGIC SYMPTOMS

Cerebral Malaria

Principles of Disease and Clinical Features. Cerebral malaria is a common, life-threatening complication of *P. falciparum* infection. Parasitized RBCs express malarial cell surface glycoproteins called *knobs* that are sticky. They adhere to capillary walls, causing sludging in the cerebral microvasculature, localized ischemia, capillary leak, and petechial hemorrhages. Clinical manifestations include fever, altered mentation including obtundation and coma (see Fig. 131-2), and occasionally seizures. A careful history and early diagnosis and therapy are essential to prevent severe morbidity and death.

Management. Treatment of cerebral malaria consists of intravenous quinine, quinidine, or artemisinin (if available); supportive care, including mechanical ventilation for comatose patients and patients with noncardiogenic pulmonary edema; antiepileptics; and correction of acidosis and hypoglycemia (associated with quinine use and cerebral malaria). The mortality rate is high, especially in children (30%), but if the patient recovers, neurologic sequelae are rare (seen in less than 10%).[18,19] Corticosteroids, including dexamethasone, are not beneficial and are potentially harmful in cerebral malaria.

Cysticercosis

Principles of Disease. Cysticercosis is caused by the larval form of *Taenia solium*, a common central nervous system (CNS) pathogen in many tropical areas. It is acquired by humans who eat pork containing the larval cysts. The adult worm matures in the small intestine; the larval forms may penetrate through the gut wall and end up anywhere in the body. The most common sites include the CNS, muscle, and soft tissue.[20,21]

Clinical Features. In the brain, the cluster of larvae of *T. solium* form an expanding cyst that induces an intense immunologic reaction from the host, including inflammation, fibrosis, and ultimately calcification. Neurologic abnormalities develop when the involved neural tissue cannot accommodate the enlarging cyst. Seizure activity often is the first indication of cysticercosis, which should be considered in any adult patient with undiagnosed seizures. The diagnosis of *T. solium* infection is established by finding characteristic proglottids (gravid segments) or scolices (worm heads) in stool preparations.

Diagnostic Strategies and Management. Cranial computed tomography (CT) scan with contrast or magnetic resonance imaging (MRI) may reveal an enhancing ring lesion. These lesions can mimic a CNS abscess, metastasis, or a primary tumor such as glioblastoma multiforme. Albendazole is the therapeutic agent of choice, and corticosteroids may be necessary during therapy, particularly if CNS cysts are present.[22] Neurosurgical consultation should be sought in treating neurocysticercosis because acute obstructive hydrocephalus can occur.

Echinococcosis

Principles of Disease and Clinical Features. *Echinococcus granulosus* is another tapeworm capable of causing CNS disease. Cerebral hydatid cysts are loculated structures containing *E. granulosus* scolices (heads) and remains of germinal epithelium, termed *hydatid sand*. Common types of exposure include ingestion of food or water contaminated by the ova from feces of sheep or cattle infected by the adult worm or close contact with a sheep-herding dog. Infection results in the liberation of the embryo oncosphere into the small intestine. After penetrating the intestinal wall, the larvae travel through the bloodstream to multiple sites for encystment. The liver is the target organ in nearly two thirds of cases, but 7% of patients have brain involvement; infected patients may present with seizures or focal neurologic signs.

Diagnostic Strategies and Management. The diagnosis of hydatid cyst disease is suggested by the appearance and localization of the cyst on ultrasound or CT scan. Serologic evaluation of serum or cerebrospinal fluid (CSF) may help confirm the diagnosis. Aspiration of the cyst should not be attempted because of the risk of seeding the host's body with metastatic cysts. Treatment options include albendazole and surgical resection. Resection of the cyst may cause an anaphylactoid reaction if there is spillage of hydatid sand[23] (Figs. 131-3 and 131-4).

Figure 131-3. Hydatid cysts removed surgically.

Figure 131-4. Additional hydatid cysts removed surgically.

African Trypanosomiasis

Principles of Disease. African sleeping sickness is caused by *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense*. This infection is endemic in limited areas of West and East Africa.[24] Several recent cases have been reported in returned travelers who were on safari in East Africa. The motile organisms are transmitted by the bite of the *Glossina* (tsetse) fly, which introduces the infective form of the trypanosome into the host's blood. A small lesion or boil may develop and persist for several days. The flagellated organism travels throughout the bloodstream, invading the lymph nodes and spleen.

Clinical Features. Winterbottom's sign, which is posterior cervical lymphadenopathy, usually is apparent at the time treatment is sought. The patient often is febrile, and trypanosomes are visible in a thick peripheral blood smear. A maculopapular rash may be noted in fair-skinned persons. After invasion of the CNS, severe headache may result from cerebral inflammation. Patients may display psychiatric symptoms, progressing eventually to extreme sleepiness and lethargy. Coma and death from starvation and trypanotoxins are inevitable in untreated patients.[25,26]

Diagnostic Strategies and Management. Diagnostic suspicion is aroused by an appropriate exposure history and characteristic symptoms. Trypanosomes in peripheral blood, CSF, or lymph node and bone marrow aspirates establish the diagnosis. The presence of parasites in the CSF indicates advanced progression of the disease. Suramin sodium is the treatment of choice for early infection with *T. b. rhodesiense*. Pentamidine isethionate is the preferred treatment for early *T. b. gambiense*. Trivalent arsenicals, such as melarsoprol, which can penetrate the blood-brain barrier, are used in advanced disease with neurologic sequelae.[2]

Other Parasites Causing Neurologic Symptoms

CNS involvement with *Trichinella spiralis* has been reported in severe cases, after larval migration of this parasite into the brain and meninges. Serious consequences are meningitis, encephalitis, seizures, paresis, coma, and death. The pathophysiology may reflect obstruction of small arterioles by migrating larvae, with subsequent vasculitis or cerebral edema from immunologic reaction to the larvae or larval fragments. Therapy for trichinosis with severe muscle or CNS involvement includes mebendazole or thiabendazole coupled with steroids, which depress the host immune response to infection.[27,28]

Amebic abscess of the brain or meningoencephalitis caused by *Entamoeba histolytica* is a rare complication of infection with this intestinal parasite. Infestation occurs with ingestion of food or drink contaminated with cysts of this protozoan. Spread of amebae to the brain or meninges from the colonized large bowel wall is rare but should be considered in any patient with amebiasis and subsequent neurologic impairment. The diagnosis may be made by microscopic identification of trophozoites (motile amebae) in CSF; however, biopsy of affected tissue is more specific. CNS amebiasis is treated with intravenous metronidazole but may require neurosurgical intervention.

Naegleria and *Acanthamoeba* are free-living amebae in fresh water that can be acquired while swimming and diving in ponds and lakes. The amebae invade the CNS through the olfactory neuroepithelium or cornea (violated by abrasion or associated with contact lens wear), causing an amebic meningoencephalitis. The combination of amphotericin B and miconazole is the pharmacologic regimen of choice when these motile amebae are identified in CSF.[29] *Strongyloides stercoralis* infection is a common disease in the tropics. The worm enters through the skin and migrates to the small bowel. Infection with *Strongyloides* is more clinically significant in an immunosuppressed patient, who may suffer larval dissemination throughout the body with subsequent encephalitis and pyogenic meningitis in the CNS. *Strongyloides* infection is treated with thiabendazole or albendazole.[30]

Granulomas may occur in the brain from egg deposition by *Schistosoma*. Generally, they do not cause major symptoms; however, several cases of transverse myelitis with paraplegia have been reported.

Figure 131-5. Five-year-old child with severe life-threatening anemia (hematocrit of 9) in association with chronic malaria.

ANEMIA

Malaria

Malaria infection often is associated with anemia, especially in children younger than 5 years of age (Fig. 131-5). Anemia may develop quickly, from massive hemolysis in acute infection, or it may have a more insidious onset, developing over months. Mature merozoites lyse parasitized RBCs. Uninfected RBCs

undergo immune destruction from cell surface antibodies produced in response to parasite-associated changes in RBC surface proteins. This process of destruction is abetted by increased reticuloendothelial activity. The reticulocyte response in infected persons is blunted by inhibition of erythropoietin secretion.[31,32] The antimalarial drug primaquine can precipitate hemolysis in patients who have glucose-6-phosphate dehydrogenase deficiency, which is common in black Africans and some Asians.

Whipworm and Hookworm

Infestation by the whipworm *Trichuris trichiura* and, especially, the two human hookworms *Necator americanus* and *Ancylostoma duodenale* is a major cause of iron deficiency anemia worldwide. Adult worms penetrate into intestinal mucosa and feed, causing significant ongoing luminal blood loss. The host defecates eggs that mature in the soil through a rhabditiform larval form to the infective filariform larva. These larvae penetrate the human skin, usually through the feet. In trichuriasis, anemia is seen only with massive parasite infestation. Ova from the whipworm are ingested through stool-contaminated food and water. Diagnosis of these infections requires identification of characteristic ova in the stool. As with most helminthic infections, peripheral eosinophilia is common. Mebendazole or albendazole effectively controls trichuriasis and hookworm infections in adults and children. Anemic patients should receive iron supplementation.

Tapeworm

Infection with the fish tapeworm *Diphyllobothrium latum* is associated with pernicious anemia. This tapeworm competes with the human host for absorption of vitamin B_{12}. When the host ingests raw freshwater fish that contains the embryo plerocercoid larvae in its muscle fibers, the large adult tapeworm develops within the human small intestine. The diagnosis is made by identifying the ova in the feces. Praziquantel is the drug of choice in adults and children.

PERIPHERAL EDEMA

Elephantiasis

Principles of Disease. Elephantiasis, or filariasis, is manifested in the host by the development of massive peripheral edema with distention and thickening of the overlying skin, which acquires the appearance and texture of elephant skin. It is caused by infection with the filarial worm *Wuchereria bancrofti* or *Brugia malayi*. The infection is confined to humans and is widely distributed in the equatorial regions of the world, including Africa, Asia, South America, and Oceania. More than 90% of all infections are found in Asia, where the disease has reached epidemic proportions. Even in endemic regions in which most residents are infected, the disease is rare among travelers. Infected mosquitoes introduce microfilariae into the bloodstream of the human host during a blood meal. After infecting the host, the worms migrate into the lymphatic system and mature into coiled, gravid adults. The adult worm triggers a robust inflammatory reaction in the lymphatic vessels, particularly in the lower extremities and genitalia. The macrophages, lymphocytes, plasma cells, giant cells, and eosinophils migrate to the inflamed and fibrotic lymphatic vessel, which becomes erythematous, edematous, and tender, suggesting the diagnosis of filariasis.

Clinical Features. Chronic manifestations of filariasis include fibrosis of a lymphatic vessel containing a dead or calcified worm. Subsequent mechanical blockage of the lymphatic system leads inevitably to severe lower extremity and genital edema accompanied by thickening of the skin. Recurrent cellulitis is common in these patients; prevention requires meticulous skin care.[33]

Diagnostic Strategies and Management. The adult female worm produces microfilariae, which reach the peripheral blood through the lymphatics, whereupon the patient experiences shaking chills and fever. Thick peripheral blood smears may show infection, particularly at night, when the release of microfilariae is most likely. Diethylcarbamazine rapidly clears the microfilariae from the peripheral blood and slowly sterilizes the gravid female nematode. Established elephantiasis of the scrotum can be successfully treated surgically. Chronic lymphatic obstruction of the limbs rarely responds to operative intervention.[34]

DERMATOLOGIC SYMPTOMS

Cutaneous Leishmaniasis

Principles of Disease. Cutaneous leishmaniasis is one of the most important causes of painless chronic ulcerating skin lesions in the world. *Leishmania braziliensis* and *Leishmania mexicana* responsible for New World leishmaniasis, whereas *Leishmania tropica* and *Leishmania major* commonly cause Old World leishmaniasis. The female *Phlebotomus* sandfly transmits the promastigotes during a blood meal, which are ingested by host macrophages and survive in their leishmanial form in the skin.

Clinical Features. Skin papules and nodules are seen early in the course of infection at the site of the insect bite. A raised macule also can appear, which subsequently develops painless central ulceration and a raised border. Lymphocyte and macrophage invasions of the epidermis and dermis cause the induration that occurs at the ulcer border. Secondary bacterial infections of these ulcers increase the associated scarring. *L. braziliensis braziliensis* (subspecies of *L. braziliensis*) attacks the mucocutaneous skin borders (i.e., in tissues of the nose and mouth). Mutilation of the face occurs after massive tissue and nasal cartilage destruction. The larynx and trachea also can be involved, compromising the airway. Disseminated cutaneous leishmaniasis (*L. mexicana amazonensis* in South America and *L. tropica aethiopica* in Ethiopia) is characterized by diffuse nodules and papules resembling those of lepromatous leprosy (Fig. 131-6). Persons with this manifestation of leishmaniasis are thought to have a defect in their cell-mediated immunity response.[35,36]

Figure 131-6. Cutaneous leishmaniasis.

Diagnostic Strategies and Management. Definitive diagnosis of leishmaniasis is made by direct visualization of the parasite with light microscopy. Diagnosis also can be made by an indirect fluorescent antibody test. Results of intradermal skin testing often are negative during the acute stages of the disease. Many forms of cutaneous leishmaniasis, especially *L. tropica* and *L. mexicana* infection, are self-limited and require no treatment, unless the wounds become secondarily infected. Treatment options for advanced disease include sodium stibogluconate, meglumine antimonate, and amphotericin B. An oral drug, miltefosine, has been used with success for treating both the visceral and the cutaneous forms of leishmaniasis.[37] These treatments rarely are initiated in the ED setting.

Dracunculiasis

Principles of Disease and Clinical Features. *Dracunculus medinensis*, the "fiery serpent," appears in the host as the adult worm migrates through the subcutaneous tissues of the leg. The head of the gravid adult female erodes through the skin of the leg and releases larvae into the water when the host wades in a pond or open well. The larvae promptly infect the *Cyclops* water flea. Humans who drink water containing the infected crustacean complete the cycle of infection. The patient may complain of rash, intense pruritus, nausea, vomiting, dyspnea, and diarrhea before the female worm erupts through the skin.

Management. The "classic" treatment in developing countries has been to wind the worm around a stick and slowly extract the parasite from the skin over the course of 1 or 2 days. If the worm breaks while being extracted, the patient experiences an intense inflammatory reaction with cellulitis along the worm tract. The diagnosis is confirmed when microscopic larvae are found in the fluid of the cutaneous ulcer or when the adult female worm is identified extruding from the skin. The use of metronidazole to shorten the time of extraction is controversial. The World Health Organization set a goal to eradicate this disease through public health awareness: encouraging covering wells, filtering well water to remove the fleas, and keeping infected persons with active skin lesions out of potable water. These efforts have had a tremendous impact on the eradication of dracunculiasis from Africa.

Other Parasites Causing Dermatologic Symptoms

Cutaneous larva migrans, the "creeping eruption," occurs in the host's epidermis when the skin is penetrated by *Ancylostoma braziliense* (dog or cat hookworm) larvae. Exposure usually occurs after walking barefoot or lying on beaches or other warm soil contaminated by animal feces. The diagnosis is suggested by the presence of a characteristic meandering erythematous track on the skin surface caused by larval migration. Visceral larva migrans occurs in young children after ingestion of soil containing ova from the dog ascarid *Toxocara canis*. Thiabendazole, ivermectin, or albendazole may be used for treatment of cutaneous larva migrans, and antipruritics give symptomatic relief. Diethylcarbamazine treats visceral larva migrans. An alternative is thiabendazole.[38]

"Swimmer's itch" is a dermatitis that occurs when skin is penetrated by the nonhuman schistosome of avians and mammals, usually from swimming in northern U.S. freshwater lakes. The infection spontaneously resolves when the nonhuman schistosome is destroyed by the human host's immune system. A similar dermatitis also can occur after infection with schistosome species that are trophic for humans. Treatment is symptomatic.

Strongyloides can cause a transient, pruritic rash that may appear and then disappear within hours. *Taenia solium* can cause cysts in the soft tissues and muscles. These cysts often are an incidental finding. Onchocerciasis (from *Onchocerca volvulus*), which is commonplace in West Africa and parts of South America, can cause severe pruritus and the development of nodules on bony protuberances.

VISUAL SYMPTOMS

Onchocerciasis

Principles of Disease. Onchocerciasis is a major cause of blindness in the world. Ninety-five percent of all cases occur in Africa.[39] The parasite is found only in humans and is transmitted by the bite of the *Simulium* fly. These flies live near rivers—hence the common name of the disease, "river blindness." Microfilariae of *O. volvulus* are released by adult nematodes, which coil in subcutaneous nodules in the infected host; the microfilariae then migrate through the dermis and epidermis. The presence of adult worms stimulates a brisk immune response, including the infiltration of lymphocytes, macrophages, plasma cells, and eosinophils.

Clinical Features. The skin becomes chronically edematous and pruritic; it then atrophies, resulting in loose, thin folds of skin. River blindness is more likely to develop in patients with nodules in proximity to the eyes. When the microfilaria dies during its migration in the eye, the foreign tissue that is deposited in the iris musculature incites an immune sclerosing keratitis, which is a major cause of the ocular destruction with subsequent blindness (Fig. 131-7).

Diagnostic Strategies and Management. The diagnosis of onchocerciasis requires identification of characteristic microfilariae in skin snipped from the patient. Ivermectin is the therapeutic drug of choice. In many countries in which the disease is endemic, the manufacturers of ivermectin have donated the drug in an attempt to eradicate the disease. Surgical excision of the subcutaneous nodules is recommended when they are located on the head.

Loiasis

Principles of Disease and Clinical Features. Another filarial infection that causes ocular problems is loiasis. Loiasis is confined to forest areas in West and Central Africa. Transmission of *Loa loa* occurs through the bite of flies of the genus *Chrysops*. The edema initially associated with migration of the worm is called a *Calabar swelling*. The disease is caused by a migrating adult worm in the subcutaneous tissue. The adult worm occasionally

Figure 131-7. Patient with onchocerciasis, or "river blindness."

migrates through the subconjunctival tissues of the eye and can be surgically excised from the conjunctiva. Although upsetting to the patient, the disease often is fairly benign. The adult worm releases sheathed microfilariae into the peripheral bloodstream during the daytime.

Diagnostic Strategies and Management. Microfilariae can be detected within a thick blood smear, securing the diagnosis of loiasis. The treatment of choice for *L. loa* infection is diethylcarbamazine. Corticosteroids or antihistamines often must supplement specific chemotherapy because of the intense allergic reaction that occurs when the killed adult worms and microfilariae disintegrate.[40,41]

Other Parasites Causing Ocular Symptoms

T. canis has a trophism for the host's eyes. Toxocariasis is a roundworm infection found in urban dogs. Humans ingest eggs by the fecal-oral route. The larvae migrate and often enter the retina, where they become trapped. They stimulate an immune response that culminates in granuloma formation. These granulomas can impair vision and sometimes are mistaken for retinal tumors. There is no means of direct diagnosis except tissue biopsy. Although serologic tests are available, results need to be interpreted with caution. Infection is treated with albendazole and steroids; larvae visible in the retina can be destroyed with a laser.

Toxoplasma gondii infection can precipitate a vitreal inflammation with retinal hemorrhages. Immunocompromised patients may develop chorioretinitis and optic neuritis with visual field defects and ocular palsies. Erythrocytes with sticky "knobs" from *P. falciparum* infection can cause retinal vascular congestion and ischemia with hemorrhage, exudate, infarction, and macular destruction. Cerebral malaria can produce cortical blindness. Mucocutaneous leishmaniasis can involve the eyelids, tear glands, retina, or iris and may result in total ocular destruction. *Acanthamoeba* can cause a dangerous keratitis in contact lens wearers. The patient complains of severe pain, tearing, and photophobia. Early infection may be misdiagnosed as herpetic keratitis. The infection may become chronic and necessitate keratoplasty for preservation of vision. Numerous worms migrate to or through the eye, causing inflammation, tissue destruction, and blindness. *Echinococcus* and *Cysticercus* can initiate destructive cystic lesions in the eye.

■ PULMONARY SYMPTOMS

Patients with *P. falciparum* malaria initially may seek treatment for fever and cough. Early in the course of treatment for severe malaria, noncardiogenic pulmonary edema or acute respiratory distress syndrome may develop that necessitates mechanical ventilation with positive end-expiratory pressure.[42,43]

E. histolytica can cause sympathetic pleural effusions, pulmonary or pleural involvement by direct extension or rupture of an amebic liver abscess, or direct hematogenous seeding of the lungs, leading to considerable additional morbidity and mortality among patients with underlying amebic infection.[44] *Pneumocystis* pneumonia, caused by *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*), is one of the most common respiratory opportunistic infections in patients with human immunodeficiency virus (HIV) infection in the United States and Europe; however, it is responsible for less than 10% of pulmonary opportunistic infections in Africa and the developing world. The reason for this discrepancy is unclear. Many patients with AIDS in these countries die with $CD4^+$ cell counts that are higher than those associated with *P. jiroveci* pneumonia in the United States.[45]

Löffler's syndrome, characterized by persistent and nonproductive cough, substernal chest pain, wheezing, rales, pulmonary infiltrates on the chest radiograph, and marked eosinophilia,[46] often is seen when larvae from the roundworm *Ascaris lumbricoides*, the hookworms *N. americanus* and *A. duodenale*, and the threadworm *S. stercoralis* transit the lungs as part of their developmental cycles. *Ascaris* larvae penetrate the small intestinal wall to gain entry into the small venules of the gastrointestinal tract and then migrate to the lungs. *Strongyloides* and the hookworm filariform larvae penetrate through the skin of the feet, entering small cutaneous venules before migration to the lungs. The pulmonary infiltrates and symptoms are transient, resolving within 2 weeks. Diagnosis depends on discovering larvae in sputum or gastric aspirates. Negative stool examinations initially are nondiagnostic, because eggs do not appear in the stool for at least 1 month after initial infection.

The patient's immune response to the microfilariae of *W. bancrofti* and *B. malayi* is the cause of tropical eosinophilic pneumonia.[47] Affected persons present with malaise, weight loss, new-onset nocturnal wheezing and asthma, shortness of breath, and chest discomfort. Chest radiographs may show nodular or interstitial infiltrates, consolidations, or cavitation. Microfilariae can be seen in lung biopsy material. Untreated infection may result in obstructive or restrictive lung disease. Patients have marked eosinophilia and elevations of serum IgE.[48]

Paragonimus westermani and echinococcal species are trophic for the lungs in their human hosts. *P. westermani* eggs are shed in stool, hatch in fresh water, and, as miracidia, infect a snail intermediary. After further development, cercariae are released from the snail, penetrating and encysting in freshwater crab or crayfish. After consumption by the human host, metacercariae from the crab or crayfish excyst within the duodenum, penetrating the duodenal wall into the abdominal cavity. The larvae migrate from the peritoneal cavity through the diaphragm into the pleural cavity, finally migrating to the lungs, where they cause hemorrhage, necrosis, and a granulomatous response. Early in the process, patients may have infiltrates and eosinophilia; later disease is marked by bronchiectasis, chronic bronchitis, fever, hemoptysis, and cachexia. Pulmonary nodules and cysts may cavitate.[49] Many of these patients may have a positive result on purified protein derivative (PPD) testing, and their symptoms and chest radiographic findings may mimic those in tuberculosis. Sputum often is blood-streaked and flecked with dark brown particles containing diagnostic ova. Radiography, stool examination, and immune testing of sputum and blood can help make the diagnosis.[50] Praziquantel is the therapeutic agent of choice.

E. granulosus causes pulmonary hydatid cyst disease that remains asymptomatic until a cyst grows large enough to cause a mass effect, becomes superinfected, or leaks cyst material, which is highly immunogenic, causing a severe anaphylactoid reaction. Pulmonary hydatid cysts also can be associated with cough, expectoration of sandlike material, chest pain, and hemoptysis.[51] Primary hydatid disease in the liver can metastasize to the lungs or brain. A thoracic CT scan shows a unilocular lung cyst; on a plain radiograph, a ruptured cyst is said to resemble a water lily—a pathognomonic finding. Cysts can be treated with careful surgical excision and pharmacotherapy.

Early schistosomal disease, or Katayama fever, can manifest with fever, cough, eosinophilia, and diffuse pulmonary nodules as the schistosomula pass through the lungs. In long-standing disease, ova shed from worm pairs can lodge in the vasculature of the lungs, causing pseudotubercles, granulomatous lung disease, pulmonary hypertension, and cor pulmonale. In

patients with long-standing, latent, and asymptomatic *S. stercoralis* infections who are started on corticosteroids or immunosuppressive therapy, the helminth disseminates widely. Fatal, massive pulmonary infections with radiographic whiteouts and unsupportable respiratory failure have been reported in patients who have received organ transplants; this clinical disaster occurs more commonly in patients who originally came from developing countries and were never evaluated for *Strongyloides* infection before transplantation.[52,53] *Strongyloides* infection can be misdiagnosed as bronchospasm and asthma, prompting the clinician to prescribe steroids, which precipitate dissemination.[54]

CARDIOVASCULAR SYMPTOMS

Chagas' Disease

Principles of Disease. *T. cruzi* infection causes acute and chronic myocarditis. *T. cruzi* is endemic in South and Central America and causes Chagas' disease. The vector is the reduviid or "kissing bug" that inhabits the walls and roofs of thatched dwellings built adjacent to forest. Previously a disease of rural populations, urban transmigration has expanded the epidemiologic scope of Chagas' disease. The disease is not seen commonly in travelers. The reduviid's bite is no longer the only source of *T. cruzi* infection; transfusion with blood containing live trypanosomes from infected hosts is a growing source of infection.[55] Oral transmission also has recently been noted as well.[56]

The reduviid bites the patient, often around the eye, and excretes feces containing the trypomastigote of *T. cruzi*. The trypanosome enters the inflamed bite wound or other mucosal or conjunctival surfaces, causing a local swelling, called a *chagoma*. Romaña's sign (painless unilateral periorbital edema) is pathognomonic but rarely seen. The trypomastigote migrates to trophic tissues, including smooth muscle, cardiac muscle, and autonomic ganglia in the heart, esophagus, and colon, causing local inflammation and tissue destruction.

Clinical Features. Acute infection is heralded by fever, facial and dependent extremity edema, hepatosplenomegaly, lymphadenopathy, malaise, lymphocytosis on peripheral blood smear, and elevated liver transaminases. At this stage, fatal left ventricular dysfunction and dysrhythmias are uncommon. Early illness lasts 1 to 2 months and resolves spontaneously, resulting in a latency known as the *indeterminate phase*, which can persist throughout the patient's lifetime. In approximately 25% of the cases, the infection progresses to chronic Chagas' disease, principally with cardiopathy and gastrointestinal disease. Amastigotes invade cardiac muscle and the cardiac conduction system. Chronic inflammation, mononuclear cell infiltration, and fibrosis are other findings. Additional features may include atrial bradydysrhythmias, right and left bundle branch blocks, complete heart block, and ventricular dysrhythmias including ventricular fibrillation. With development of right and left ventricular dysfunction with dilated cardiomyopathy, cardiac muscle is replaced by fibrosis and scarring. Mural thrombi are common; thromboembolic disease manifesting as pulmonary embolism, stroke, or peripheral arterial embolism can be the first indication of long-standing asymptomatic infection. Congestive heart failure is rapidly progressive and fatal within months unless aggressively treated with pharmacologic intervention and transplantation.[57]

Diagnostic Strategies. Acute Chagas' disease can be diagnosed by the presence of motile trypomastigotes in anticoagulated blood specimens. The organism also can be cultured in special liquid media. Chronic Chagas' disease can be diagnosed using several serologic tests, including complement fixation, enzyme-linked immunosorbent assay (ELISA), and indirect immunofluorescence testing. The assays are nonspecific, cross-reacting with malaria, syphilis, leishmaniasis, and some collagen vascular diseases. Polymerase chain reaction technology is improving and soon will provide the "gold standard" modality for diagnosis.[58]

Management. Nifurtimox and benznidazole are used for treating *T. cruzi* infection. Cure rates rarely exceed 50%. The duration of treatment with nifurtimox is prolonged, and the drug has many serious side effects. Its production has been discontinued; however, it is the only antitrypanosomal medication available in the United States today (it can be obtained from the CDC by calling 404-639-2888). Benznidazole has fewer side effects. It is now recommended for indeterminate-phase treatment. Late complications of chronic diseases are modulated by autoimmune activity and do not respond to antiparasitic pharmacotherapy. Use of nifurtimox and benznidazole has been associated with lymphoma in an animal model.[59,60] Chronic Chagas' disease of the heart, esophagus, or colon is treated symptomatically. Automated implantable cardioverter-defibrillators have been demonstrated to decrease the incidence of sudden death in this patient population.[61] Patients receiving immunosuppressive therapy to prevent rejection after cardiac transplantation have shown recurrent disease in the transplanted myocardium.

Other Causes

Aberrant migration of *Ascaris* to the myocardium is well described, causing myocarditis and pericardial effusions. *E. histolytica* abscesses of the liver also may cause pericardial effusions if they erode through the diaphragm.

GASTROINTESTINAL SYMPTOMS

Diarrhea

Diarrhea is one of the most common symptoms for which travelers seek medical attention. Gorbach[62] wrote, "Travel expands the mind and loosens the bowels." Diarrhea also is the leading cause of death in children younger than 5 years of age in developing countries and a major source of morbidity for older children and adults (Fig. 131-8). Most diarrheal disease is viral or bacterial; however, some clinically significant diarrheal disease is caused by parasites.

Cryptosporidium parvum and *Cyclospora cayetanensis* are foodborne and water-borne coccidians that cause watery diarrhea.

Figure 131-8. Fecal-oral transmission of diarrheal agents occurring in a developing country.

Both are particularly significant causes of morbidity in malnourished children and patients with AIDS. In these populations in the developing world, the prevalence may approach 50%.[63,64] Cryptosporidial oocysts can be seen in stool when an acid fast–based stain is used. ELISA and immunofluorescent assays of stool also are available. Paromomycin decreases diarrheal frequency in patients with AIDS, who often have prolonged illness. Treatment is symptomatic for immunocompetent hosts.[65] *Cyclospora* oocysts can be detected in stool samples using a Ziehl-Neelsen stain. Trimethoprim-sulfamethoxazole treats the infection.[66]

E. histolytica causes an invasive or inflammatory diarrhea. Patients complain of fever, tenesmus, abdominal pain, and watery stool containing blood and mucus. Untreated disease can progress to widespread colitis and perforation of the bowel wall with peritonitis and death.[67] Stool examination reveals mobile trophozoites containing ingested RBCs. Cysts noted on stool studies do not necessarily reflect active infection. Immune assays of stool can now differentiate between *E. histolytica* and nonpathogenic ameba species. Serologic tests may be useful in an infected patient from a nonendemic region but take a month for results to turn positive. Metronidazole is the drug of choice for treatment of amebiasis. *Balantidium coli* is the other protozoan that can cause invasive diarrhea. It has trophism for the terminal ileum, sometimes resulting in a clinical picture suggestive of appendicitis. Tetracycline and metronidazole are active against *B. coli*.

Giardia lamblia can cause persistent diarrhea, abdominal bloating, cramps, flatulence, and weight loss. The organism is ingested and reproduces exponentially in the small bowel. In severe infection, the entire jejunum becomes covered with organisms, and the patient has malabsorption with steatorrhea. The organisms are rarely seen in fresh stool preparations because they quickly break down and become indiscernible. Accordingly, an antigen test often is used to confirm the diagnosis. *Giardia* has many animal reservoirs, including the beaver. Campers who drink unfiltered, pure mountain spring water in the United States commonly contract *Giardia* infection. Metronidazole and tinidazole treat the disease.

S. stercoralis, *Capillaria philippinensis*, *T. trichiura*, and *Schistosoma* all have been associated with diarrhea. Hyperinfection or dissemination of *Strongyloides* can cause persistent diarrhea, weight loss, and abdominal pain. *Trichuris* causes diarrhea when the parasite load in the intestine is high. Schistosomiasis can cause a chronic granulomatous colitis, which may resemble inflammatory bowel disease, or an acute, bloody, febrile colitis associated with Katayama fever in the immunologically naive patient.

In chronic schistosomiasis, worm pairs in patients' mesenteric and portal venous systems lay eggs that become ensnared in the liver, causing intense local inflammation and scarring and the classic "pipestem" cirrhosis with periportal fibrosis. Clinical manifestations in these patients include portal hypertension, ascites, and esophageal varices (Figs. 131-9 and 131-10). Upper gastrointestinal bleeding is not as common as in patients with alcoholic cirrhosis; however, a high number of patients are infected with schistosomiasis in endemic regions, so variceal bleeding is an important cause of gastrointestinal hemorrhage in these populations.[68,69]

Abdominal Pain

In an extensive review of a number of cases of appendicitis, parasitic infection was found to be the cause in 3%. Pathologic examination revealed enterobiasis, amebiasis, ascariasis, trichuriasis, and taeniasis.[70]

A. lumbricoides can cause significant persistent or recurrent abdominal pain in adults and partial intestinal obstruction in children with significant worm loads. Antihelminthics and conservative, supportive therapy usually eliminate the problem, thereby avoiding surgical intervention.[71,72] The diagnosis of ascariasis is made by identifying eggs in the stool. Patients with large worm loads may excrete adult worms, especially after therapy is started. Severe intestinal amebiasis can be complicated by colonic perforation and peritonitis.

Angiostrongylus costaricensis, a nematode known as the rat lung worm, is common in Central America. Infected children may appear clinically to have Meckel's diverticulum or acute appendicitis. Manifestations of the infection include nausea, vomiting, fever, abdominal pain localized to the right lower quadrant, and a tender mass. Surgical exploration may uncover abscesses, obstruction, or intestinal infarction.[73]

Anisakiasis is characterized by severe abdominal pain after ingestion of raw fish (sushi and sashimi primarily). *Anisakis*

Figure 131-9. Pipestem cirrhosis with extensive ascites in a patient with chronic schistosomiasis.

Figure 131-10. Extensive ascites in a child, which may be from schistosomiasis or kala-azar (leishmaniasis).

marina, a nematode that burrows into the intestine, is the pathogen.[74]

The liver fluke, *F. hepatica*, causes a syndrome that mimics viral hepatitis: right upper quadrant pain, fever, nausea and vomiting, jaundice, a tender enlarged liver, and elevated transaminases. Patients also have eosinophilia and urticaria. Imaging studies, including CT, show the tracts of burrowing flukes. Serologic testing establishes the diagnosis; the patient's stool may not contain eggs for several months after ingestion.[75] The eggs of schistosomes become trapped in the portal venules, where they trigger an inflammatory response, leading to granulomatous liver disease, fibrosis, and cirrhosis. Hepatic granulomas also are seen in disseminated strongyloidiasis and aberrant biliary ascariasis.

E. histolytica can cause hepatic abscesses. Affected patients typically do not have amebic dysentery and do not shed *Entamoeba* in their stool, but results of serologic studies almost always are positive. Patients have fever, weight loss, anorexia, and right-sided abdominal pain, but no jaundice. Treatment is with metronidazole or tinidazole and a luminal amebicide, such as iodoquinol.[76] *E. granulosus* produces hydatid cysts of the liver that, on CT, contain septations and so-called daughter cysts. Pharmacotherapy with albendazole and careful excision remain the treatments of choice. Leaking cyst material can initiate a severe anaphylactoid reaction in the host.

Jaundice may result from hemolysis secondary to direct infection of RBCs with *Plasmodium* or *Babesia* or from biliary obstruction with pigmented stones. *Ascaris* can cause biliary colic, pyogenic cholangitis, pancreatitis, or liver abscess. Dead worms can be the nidus for gallstone formation. Biliary imaging and endoscopic retrograde cholangiopancreatography will show worms in the biliary tree. Mechanical removal by endoscopy combined with anthelminthic therapy is curative.[77] *Clonorchis sinensis* and *F. hepatica* are trophic for the biliary tree. These worms can be present without producing symptoms for years before eventually precipitating cholecystitis, cholangitis, or cholangiocarcinoma.[78]

Pruritus Ani

Enterobius vermicularis, or pinworm, causes pruritus ani, a syndrome of intense perianal itch occurring primarily in children. Autoinfection is common because children (and adults) scratch the pruritic anal area and then bite their nails or put their fingers in their mouth. The worm has a worldwide distribution. Diagnosis is clinical and is confirmed by finding the small adult worms wiggling about on the anal verge. Eggs are rarely seen in the stool but can be visualized using the tape test: Transparent tape touched to the perianal region collects eggs, which can be seen with light microscopy. Albendazole or mebendazole is the drug of choice.

PARASITIC CO-INFECTIONS IN PATIENTS WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION AND AIDS

Perspective

HIV infection and AIDS are prevalent in developing countries. Heterosexual and perinatal transmission are common; young children and young adults of both sexes are primarily infected. Patients presenting to the ED may be co-infected with HIV or any other infectious agent, including all of the parasites discussed in this chapter. HIV co-infection may worsen the symptoms and outcome, alter the presentation, increase the virulence, or assist the infective process.

AIDS causes abnormalities in almost every aspect of a host's immune response to infection; cell-mediated immunity (which is important in combating parasitic infection) is most affected.[79] The diagnosis and response to therapy of many parasitic infections are monitored serologically. HIV infection interferes with this response, rendering many of these tests unreliable. Therapies that are extremely effective in the normal host may be ineffective in a patient with HIV infection. Pharmacologic agents may have to be given for long periods or for the patient's entire life.

Specific Parasitic Infections

Malaria is not an opportunistic infection in patients with AIDS; however, many patients, especially children, with recurrent malaria and anemia from hemolysis have required transfusions from blood supplies not screened for HIV and have become infected.[80] Treating febrile patients for malaria in areas in which it is endemic is a common practice. Patients with AIDS have more severe allergic reactions to drugs, especially sulfonamides, that are antimalarials. In patients with AIDS, fever alone is not predictive of malaria; diagnosis should precede therapy. Patients with HIV infection are at greater risk for severe clinical manifestations of babesiosis.[81]

Visceral leishmaniasis is more commonly disseminated and fatal in patients with AIDS. Latent leishmanial infections may reactivate, and a prolonged febrile illness in an HIV-positive patient with a lifetime history of travel in leishmaniasis-endemic areas of the world should prompt consideration of this co-infection.[82] Cutaneous infection also may become disseminated in these patients. Several clinical trials are currently examining the role of chemoprophylaxis for leishmaniasis in HIV-positive persons who live in endemic regions of the world. Chagas' disease in the indeterminate phase can be reactivated in patients infected with HIV. These patients frequently have CNS involvement with meningoencephalitis and severe myocarditis.[83] Single-drug therapy may be insufficient, because benznidazole penetration into the CSF is minimal. *T. gondii* infection is well recognized throughout the world as a common opportunistic infection of patients with AIDS, with a particular trophism for the CNS.

The coccidial organisms *Isospora belli*, *C. parvum*, and *C. cayetanensis* all have been associated with prolonged diarrhea in patients with AIDS. These organisms cause infections that are difficult to treat and are almost impossible to eradicate in these patients. The diarrhea is extremely debilitating and can be as profuse as that seen in cholera. *E. histolytica* has a high prevalence among homosexual men who practice unprotected anal intercourse; however, invasive amebiasis is not an opportunistic infection associated with HIV infection. Schistosomiasis enhances the pathogenesis of HIV infection and is more difficult to treat and eradicate in patients who are HIV-positive.[84] *S. stercoralis* infection is more likely to manifest as hyperinfection and disseminated disease in patients who are HIV-positive.[85] In patients who are at risk for HIV infection and parasitic illness, it is essential to consider co-infection in the differential diagnosis.

KEY CONCEPTS

- Parasitic diseases may manifest with almost any symptom or constellation of symptoms. Accordingly, a travel history should be obtained in all patients with clinically significant signs and symptoms of unclear etiology. The combination of presenting symptoms and signs and a history of recent travel to specific geographic regions can lead to early diagnosis of most parasitic infections.
- Parasitic co-infections are particularly common in patients with HIV infection and AIDS.
- Acute malaria should be suspected in patients with irregular high fevers associated with headache, abdominal pain, or respiratory symptoms. Patients who are clinically ill or who are suspected of having falciparum malaria should be hospitalized for evaluation and treatment.
- Cysticercosis should be considered in the differential diagnosis for new-onset seizures.
- Giardiasis should be suspected in patients with diarrhea who recently have been camping or drinking unfiltered mountain spring water.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 132

Tick-Borne Illnesses

Edward B. Bolgiano and Joseph Sexton

PERSPECTIVE

Ticks are hematophagous parasites of humans and animals, distributed worldwide. They transmit rickettsial, bacterial, spirochetal, viral, and protozoal diseases and cause disease by means of their own toxins (Table 132-1). As vectors of human disease, ticks rank second in importance only to mosquitoes. People who travel during the summer months may return from endemic areas with tick-borne disease. In addition, reports of infection acquired within urban areas emphasize the need to consider tick-borne illness even in the absence of a history of travel to high-risk areas.[1] Tularemia (category A) and Q fever (category B) are now considered by the Centers for Disease Control and Prevention (CDC) to be significant threats during biologic warfare. For this reason, research involving ticks and their diseases has become increasingly important.

Reports on ticks, their feeding habits, and their possible relation to disease can be found from early history.[2] Pliny (CE 77), in *Historia naturalis*, referred to "an animal living on blood with its head always fixed and swelling, being one of the animals which has no exit [anus] for its food, it bursts with over-repletion and dies from actual nourishment." Tick-borne illness was first recognized on the North American continent by Native Americans. According to legend, Shoshone men avoided the "evil spirits" that caused illness by sending only women into certain areas of the Rocky Mountain region known to be especially hazardous. The etiologic association of the tick vector with Rocky Mountain spotted fever (RMSF) was noted by missionaries and by early settlers, who named the affliction "tick fever." Physicians in Idaho and Montana recorded the classic clinical descriptions of the disease in 1899.

PRINCIPLES OF DISEASE

Identification of Ticks

Ticks are arthropods but not insects. They have eight legs instead of six and generally two fusing body parts—a capitulum (head) and an opisthosoma (abdomen)—instead of three. Identification of an arthropod as a tick and subsequent categorization into family and some genera are not difficult (Figs. 132-1 and 132-2). Speciation requires a trained acarologist. However, tick identification has limited importance in clinical decision-making. Color, which varies seasonally, and size, which varies by amount of blood ingested at the time of presentation, are unreliable criteria for identification purposes.

Physiology of Tick Feeding

An understanding of the physiology of feeding in arthropods is more essential than species identification in assessing the risks of transmission of diseases. Blood-sucking arthropods are divided into two groups according to their method of acquiring blood. The solenophagic feeders insert their mouthparts directly into capillaries to obtain blood. Telmophagic feeders insert their mouthparts indiscriminately, lyse tissue along with capillaries, and feed on the resultant pool of blood, extracellular fluid, and tissue. Ticks and deer flies, for example, are telmophagic feeders, whereas mosquitoes are mostly solenophagic.

Argasid ticks (soft-bodied), are short, rapid feeders with preformed distensible endocuticles. They therefore need to feed for only minutes to hours to acquire a full meal. As a result, they tend to be found in nests and burrows where their hosts visit frequently. The genus *Ornithodoros* is the vector for relapsing fever. Ixodid ticks (hard-bodied) include the genera *Ixodes*, *Dermacentor*, *Amblyomma*, and *Rhipicephalus*, which are those responsible for the remainder of human tick-borne diseases discussed in this chapter. These ticks need to form a new exocuticle (phase I of feeding) and thus feed slowly during the first 12 to 24 hours. Once fully formed, the new endocuticle allows rapid feeding (phase II) and significant engorgement.

In the capitulum of ticks, the sucking structure, consisting of the chelicerae, is surrounded by a sheath from which it protrudes during feeding. Sense organs on the capitulum, or podomeres, help locate a host by means of chemoreceptors. Hair, or setae, on the legs act as tactile and temperature receptors. A special sensory structure, Haller's organ, is located on the first set of legs and is a humidity and olfactory receptor.[3]

When a suitable location is found, adjacent cheliceral digits incise the skin, and the chelicerae and barbed hypostome are inserted. Two mechanisms prevent the tick from being removed from the skin: the barbed hypostome and a cement-like salivary secretion from the base of the hypostome, composed of lipoproteins and glycoproteins. This allows ixodid ticks to attach for as long as 2 weeks. Because argasids are much faster feeders, they secrete no cement substance.

During a bite, trauma and salivary gland products can cause local inflammation, hyperemia, edema, hemorrhage, and skin thickening. The saliva injected during feeding contains many different substances. Both hard and soft ticks produce a histolytic secretion that liquifies tissue, which is then sucked into the gut. Eventually, the secretion breaks down the walls of the

Table 132-1 Tick-Borne Illnesses

TYPE	DISEASE	PATHOGEN	ARTHROPOD VECTOR	GEOGRAPHIC DISTRIBUTION
Bacterial (including spirochetal)	Lyme disease	*Borrelia burgdorferi*	*Ixodes scapularis* *I. pacificus* *I. ricinus*	Northeastern U.S. Upper midwestern U.S. Pacific coast Europe
	Tularemia	*Francisella tularensis*	*I. scapularis* *Amblyomma americanum* *Dermacentor variabilis*	Southwest central U.S.
Rickettsial	Rocky Mountain spotted fever	*Rickettsia rickettsii*	*D. andersoni* *D. variabilis* *Rhipicephalus sanguineus*	Predominantly southeastern U.S. Arizona
	Q fever	*Coxiella burnetii*	*D. andersoni*	Worldwide
	Human monocytic ehrlichiosis	*Ehrlichia chaffeensis*	*A. americanum*	South central and southeastern U.S.
	Human granulocytic anaplasmosis	*Anaplasma phagocytophilum*	*I. scapularis*	New England and north central U.S.
			I. pacificus	Northern California
Parasitic (protozoal)	Babesiosis	*Babesia microti*	*I. scapularis*	Coastal New England
Viral*	Colorado tick fever	Orbivirus	*D. andersoni*	Mountain areas of western U.S. and Canada
Miscellaneous	Tick paralysis	Ixobotoxin	*D. andersoni* *D. variabilis* *A. americanum* *I. scapularis* *I. pacificus* *I. holocyclus*	Worldwide

*Many other viruses are transmitted to humans by ticks. In the United States, only Colorado tick fever occurs with any significant frequency.

dermal blood vessels and the released blood is ingested. To prevent hemostasis, the saliva contains a thrombokinase inhibitor, apyrase, which prevents platelet aggregation by depleting adenosine diphosphate, prostaglandin E_2, and prostacyclin (prostaglandin I_2) to prevent vasoconstriction, and cytolysins. *Ixodes scapularis* also secretes a carboxypeptidase that destroys other inflammatory mediators such as anaphylatoxins and bradykinin, as well as anti–complement C3 factor. These other mediators normally would cause further inflammation, which would enhance hemostasis. All infectious agents, as well as excretory liquids from some argasids, are transmitted through this saliva. Transmission of a disease from *Ixodes* ticks is unlikely if the tick is not yet engorged with blood at the time of removal. Likewise, a tick removed within a few hours after attachment is unlikely to transmit disease. The neurotoxins responsible for tick paralysis also are found in tick saliva.

The local physiologic changes associated with tick feeding produce the characteristic 1- to 4-mm erythematous mark typically seen on the skin after a tick bite. This is a common finding from most blood-sucking arthropods. The mark should not be confused with certain rashes associated with disease progression—for example, erythema migrans. Informing patients of this difference may be reassuring.

LYME DISEASE

Perspective

Lyme disease, the most common vector-borne disease in the United States, is a tick-borne illness caused by the spirochete *Borrelia burgdorferi*. The story of Lyme disease begins in 1975, when health officials at Connecticut's State Department of Health and physicians at Yale University were alerted by two skeptical mothers to an unusually large number of cases of apparent juvenile rheumatoid arthritis (JRA) occurring in their small coastal community of Old Lyme, Connecticut. Investigation led to the description of a "new" entity called *Lyme arthritis*.[4]

Lyme disease occurs worldwide and has been reported on every continent except Antarctica.[5] It now accounts for more than 95% of all reported cases of vector-borne illness in the United States.[6] The actual overall incidence of Lyme disease is unknown, because many cases go unreported. Lyme disease occurs in people of all ages but is more common in children younger than 15 years and in adults 30 to 60 years of age.[7]

Persons at greatest risk live or vacation in endemic areas. In the United States, three distinct endemic foci are recognized: the northeastern coastal, mid-Atlantic, and north central states. During 2000, a total of 17,730 cases of Lyme disease were reported from 44 states and the District of Columbia. Twelve states—Connecticut, Rhode Island, New Jersey, New York, Delaware, Pennsylvania, Massachusetts, Maryland, Wisconsin, Minnesota, New Hampshire, and Vermont—accounted for 95% of cases reported in the nation (Fig. 132-3).[7]

The principal tick vectors are *I. scapularis* in the Northeast and Midwest and *Ixodes pacificus* in the West. Nymphal *Ixodes* ticks satisfy all known epidemiologic requirements for the zoonosis as it exists in nature. There is no compelling evidence for alternate arthropod vectors of infection.

The *I. scapularis* population density depends on that of its preferred hosts: the white-footed field mouse, *Peromyscus leucopus*, for the larval and nymphal forms and the white-tailed deer, *Odocoileus virginianus*, for the adult form. The white-footed mouse readily becomes infected after being bitten by infected ticks and remains highly infectious for periods of time that approach its life span in nature, thereby providing an important reservoir for *B. burgdorferi*.[8] Adult *I. scapularis* ticks feed primarily on deer, which are key hosts in the tick life cycle and in whose fur the adult tick may survive the winter. The relatively recent repopulation of several areas in the

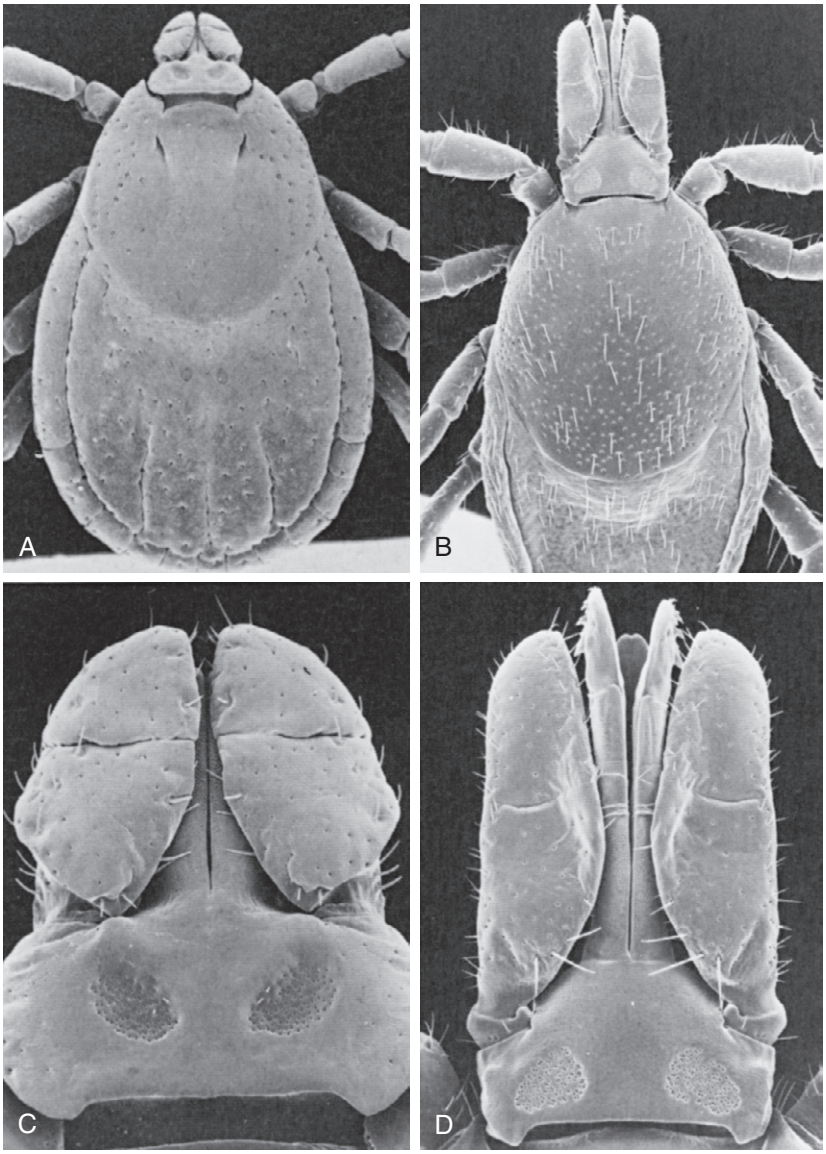

Figure 132-1. Scanning electron micrographs of two tick species. **A,** Dorsal view of adult female *Dermacentor variabilis*. **B,** Dorsal view of adult female *Ixodes scapularis*. **C,** Dorsal close-up view of *D. variabilis* head. **D,** Dorsal close-up view of *I. scapularis* head. (Courtesy of Dr. J.E. Keirans, Georgia Southern University, Statesboro, Georgia.)

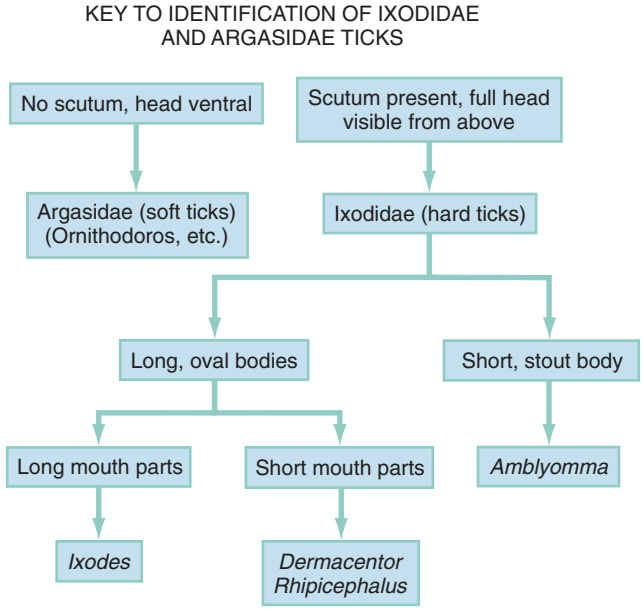

Figure 132-2. Identification scheme for genera within Ixodidae and Argasidae, the two primary disease-transmitting families of ticks.

United States by white-tailed deer preceded the recent emergence of Lyme disease in those regions.[9]

Although all stages of the tick may feed on humans, the nymph is primarily responsible for the transmission of Lyme disease. It is not surprising that more than two thirds of patients with Lyme disease do not recall a tick bite, in view of the small size (1 to 2 mm) of nymphs (Fig. 132-4). The nymph feeds in the spring and summer, which correlates with a peak incidence of early Lyme disease occurring between May and August. In addition, recreational and occupational exposure is greatest during this time. Later manifestations of Lyme disease may appear throughout the year.

Principles of Disease

The spirochete *B. burgdorferi* persists and multiplies in the midgut of its tick vector, *I. scapularis*. Transmission of the spirochete to humans occurs during feeding, generally 2 days after attachment.[10] The mechanism of transmission probably is inoculation with infectious saliva or, alternatively, with tick gut fluids periodically regurgitated during the feeding process.[11]

After an incubation period that lasts several days to several weeks, spirochetemia develops, and *Borrelia* organisms may

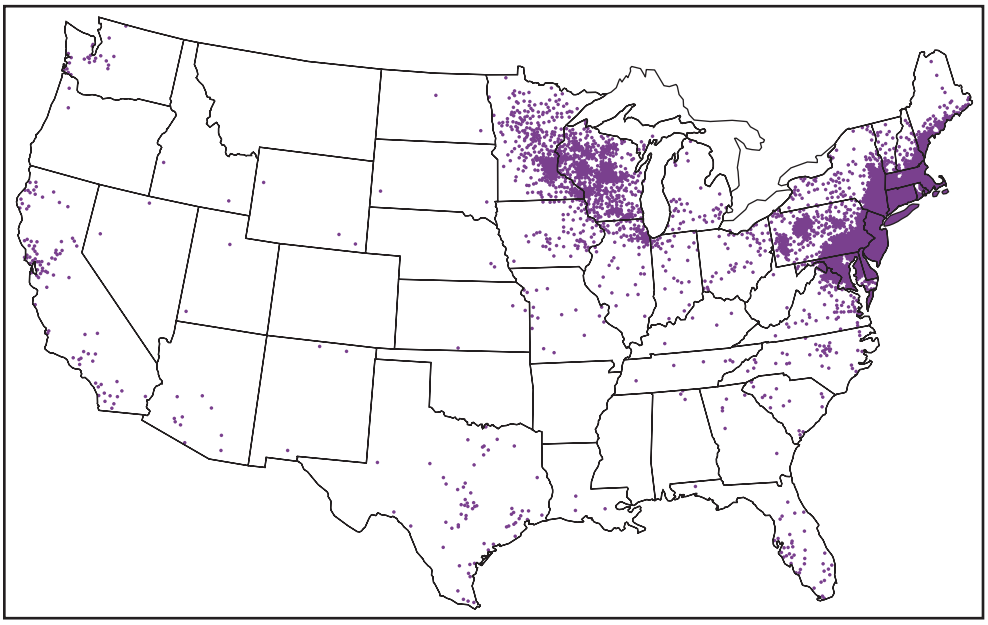

Figure 132-3. Number of newly reported Lyme disease cases, by county in the United States in 2005. *N* = 23,174; the county was unknown for 131 other cases. One *dot* was placed randomly within the county of patient residence for each reported case. (From Lyme disease—United States, 2003–2005. MMWR Morb Mortal Wky Rep 56:573, 2007.)

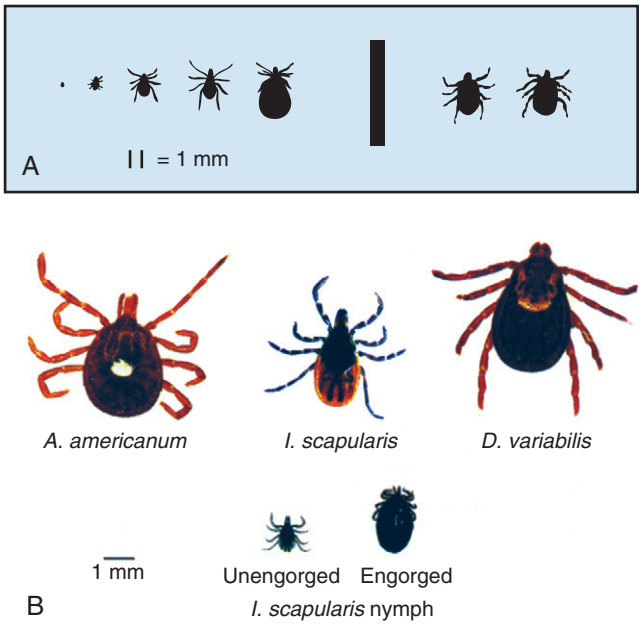

Figure 132-4. **A** *(Left to right),* Larva, nymph, adult male, adult female, and engorged adult female *Ixodes* ticks and adult male and female *Dermacentor* ticks. Actual size. **B,** Adult female *Amblyomma americanum* (Lone Star tick), adult female and nymphal *Ixodes scapularis* (deer tick), and adult female *Dermacentor variabilis* (dog tick). (From Hayes EB, Piesman J: How can we prevent Lyme disease? N Engl J Med 348:2424, 2003.)

migrate outward in blood or lymph to virtually any site in the body. The spirochete appears to be tropic for synovial tissue, skin, and cells of the nervous system, but the mechanism of this tropism is not yet understood. Infection by the spirochete itself accounts for early clinical manifestations. It remains unclear whether late disease manifestations require the continued presence of viable spirochetes or whether an ongoing host immune response to initial infection is sufficient to cause some late disease manifestations. Although the exact roles of infecting spirochetes, spirochetal antigens, and host immune responses are unknown, it is likely that persistent live spirochetes are responsible for most later manifestations of the disease. The variable severity of Lyme disease may in part result from genetic variations in the human immune system. Patients with chronic Lyme arthritis have an increased frequency of human leukocyte antigen (HLA) specificity—in particular, for HLA-DR4 and, less often, HLA-DR2.

Clinical Features

Lyme disease, a multisystem disorder, can be classified into three stages: early localized, early disseminated, and late disease. Virtually any clinical feature may occur alone or recur at intervals, and some patients who had no early symptoms may have late symptoms. The disorder usually begins with a rash and associated constitutional signs and symptoms, suggesting a "viral syndrome" (early Lyme disease). Neurologic, joint, or cardiac manifestations may emerge weeks to months later (early disseminated Lyme disease), and chronic arthritic and neurologic abnormalities may appear weeks to years later (late Lyme disease). The time course for the clinical features of untreated Lyme disease is illustrated in Figure 132-5.

Early Lyme Disease

Ticks may attach to human hosts at the initial point of contact (generally around ankle level) or may move about until they encounter an obstruction. The groin, popliteal fossae, gluteal folds, axillary folds, and ear lobes are common sites of attachment. After transmission of *B. burgdorferi* through a tick bite, the initial site of infection is the skin at the site of the bite. After an incubation period of approximately 1 week (range, 1 to 36 days), the spirochetes cause a gradually spreading localized infection in skin and a resultant skin lesion, erythema migrans. Erythema migrans is the most characteristic clinical manifestation of Lyme disease and is recognized in 90% or more of patients. Erythema migrans may go unnoticed if the entire skin surface is not examined.[12] The characteristic rash begins at the site of the tick bite with an erythematous papule or macule. The lesion expands gradually (1 to 2 cm/day, a rate of expansion slower than that of cellulitis). The patch of erythema may be confluent or may have bands of normal-appearing skin. Central clearing may occur but is not an invariable feature. The lesion borders usually are flat but may be raised. The lesions generally are sharply demarcated and blanch with

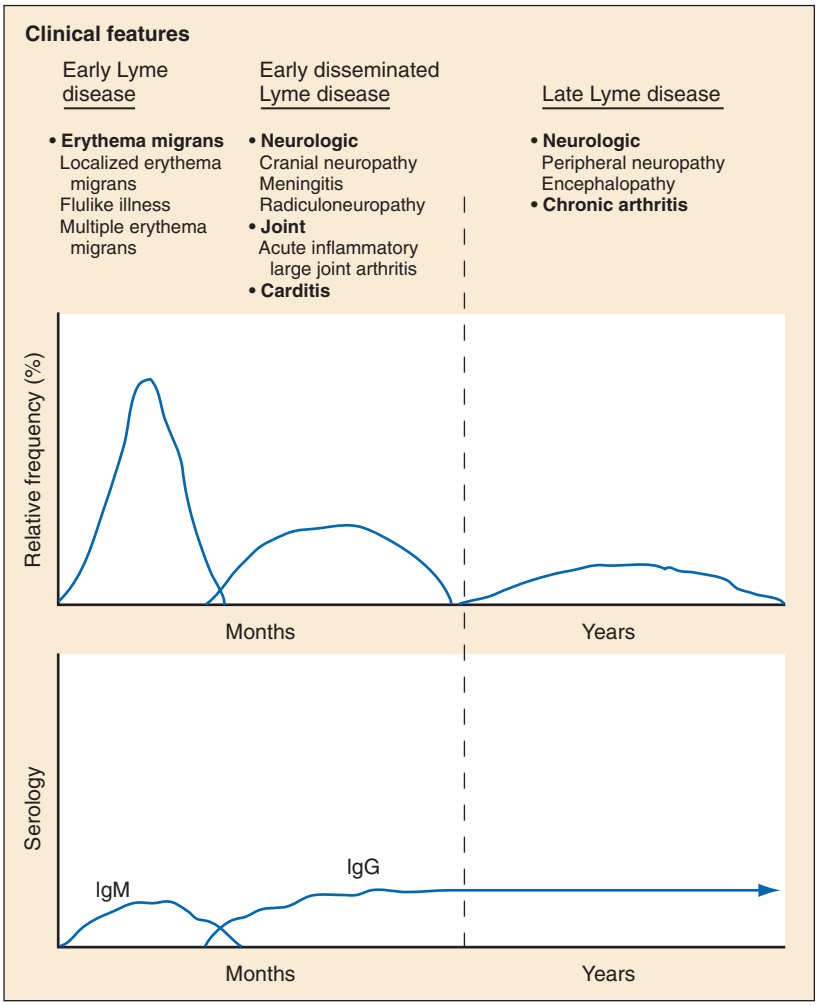

Figure 132-5. Natural history of serologic response, with clinical features, in untreated Lyme disease. IgG, immunoglobulin G; IgM, immunoglobulin M. (From Rahn DW: Natural history of Lyme disease. In Rahn DW, Evans J [eds]: Lyme Disease. Philadelphia, American College of Physicians, 1998, pp 35–48.)

pressure. Most lesions are oval or round, but triangular and elongated patches may occur. In patients presenting 1 to 7 days after the appearance of lesions, the average lesion size is approximately 8 by 10 cm (range, 2 by 3 cm to 25 by 25 cm). In some cases, the center of some early lesions becomes red and indurated or vesicular and necrotic. The lesion is warm to the touch and may be described by the patient as nontender to minimally tender (Fig. 132-6).

Hematogenous spread of viable spirochetes (not additional tick bites) may result in one or more secondary lesions. These secondary lesions are smaller, migrate less, and typically spare the palms and soles. In all, 10 to 15% of patients have more than 20 such lesions; on rare occasions they may number more than 100. Blistering and mucosal involvement do not occur. The primary and secondary skin lesions generally fade after approximately 28 days (range, 1 week to 14 months) without treatment and within several days of antibiotic therapy. Recurrent lesions may develop in patients who do not receive antibiotic therapy, but apparently not in those who receive appropriate antibiotics.

Constitutional signs and symptoms commonly appear in early Lyme disease. Malaise, fatigue, and lethargy are most common (seen in approximately 80% of patients) (Table 132-2) and may be severe. Fever typically is low grade and intermittent. Lymphadenopathy usually is regional in the distribution of erythema migrans or may be generalized; splenomegaly may occur. Musculoskeletal complaints, such as arthralgias and myalgias, are common, and the discomfort typically is short-lived and migratory, sometimes lasting only hours in one location. Frank arthritis may occur at this stage but is rare.

Clinical manifestations of meningeal irritation are frequently seen. Headache, the most common symptom, usually is intermittent and localized. Nausea, vomiting, and photophobia occasionally accompany the headache. Kernig's and Brudzinski's signs typically are absent, and neck stiffness usually is noted only on extreme forward flexion. At this stage, the neurologic examination and cerebrospinal fluid (CSF) assessment (usually) both yield normal findings.

Signs and symptoms of hepatitis, including anorexia, abdominal pain, right upper quadrant tenderness, nausea, and vomiting, may be present. Mild pharyngitis also may be present, but other upper respiratory symptoms such as rhinorrhea do not occur. Although the systemic symptoms of early Lyme disease often are described as "flulike," this term can be misleading because clinically significant cough usually does not occur. Conjunctivitis develops in approximately 10% of patients.

The incidence of Lyme disease without erythema migrans appears to be approximately 10%.[12] Because of the variety of nonspecific signs and symptoms at this stage, in the absence of the characteristic rash or history of tick bite, early Lyme disease may be easily confused with a viral or collagen-vascular disease. The intermittent and rapidly changing nature of the early signs and symptoms of Lyme disease may be a helpful distinguishing feature, especially in a patient from an endemic area. In untreated disease, early symptoms usually last for several weeks but may persist for months.

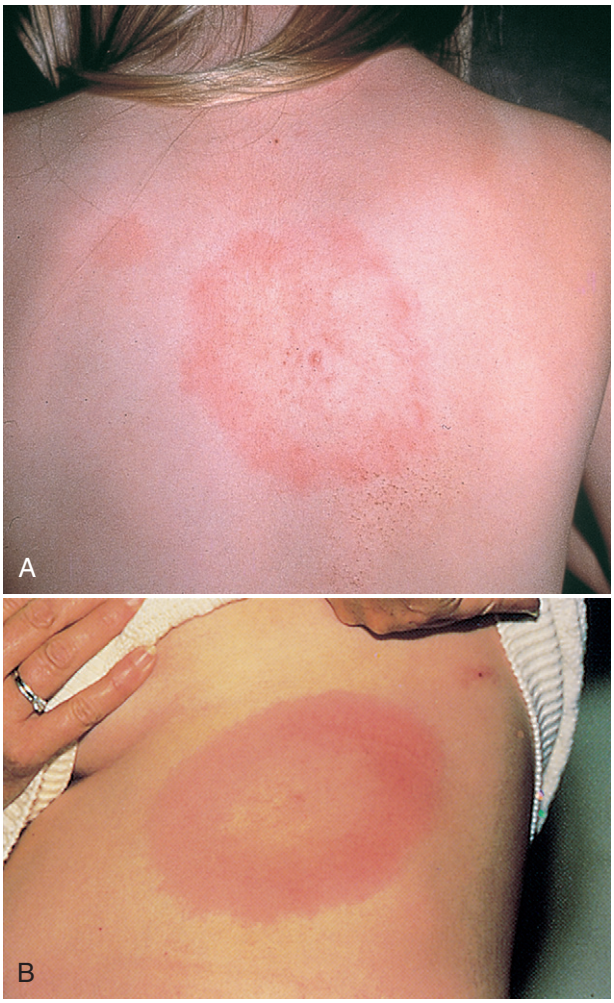

Figure 132-6. Lyme disease usually begins with a slowly expanding skin lesion, erythema migrans, which occurs at the site of the tick bite. **A,** A classic "bull's-eye" or target lesion with partial central clearing, a bright red outer border, and a "target" center. **B,** Expanding erythematous lesion, with central clearing, on trunk. (**A,** Courtesy of Michael O. Murphy, MD. From Malawista SE, Bockenstedt LK: Lyme disease. In Goldman L, et al [eds]: Cecil Medicine: Expert Consult, 23rd ed. Philadelphia, Saunders, 2008, pp 2289–2294; **B,** courtesy of John Cook, MD. From Goldstein BG, Goldstein AE [eds]: Practical Dermatology, 2nd ed. St. Louis, Mosby, 1997, p 63.)

Table 132-2 Early Clinical Manifestations of Lyme Disease

MANIFESTATION	NO. OF PATIENTS (%)
Signs	
Erythema chronicum migrans*	314 (100)
Multiple annular lesions	150 (48)
Lymphadenopathy	
Regional	128 (41)
Generalized	63 (20)
Pain on neck flexion	52 (17)
Malar rash	41 (13)
Erythematous throat	38 (12)
Conjunctivitis	35 (11)
Symptoms	
Malaise, fatigue, lethargy	251 (80)
Headache	200 (64)
Fever and chills	185 (59)
Stiff neck	151 (48)
Arthralgias	150 (48)
Myalgias	135 (43)
Backache	81 (26)
Anorexia	73 (23)
Sore throat	53 (17)
Nausea	53 (17)
Dysesthesia	35 (11)
Vomiting	32 (10)

*Required for inclusion in this study.
From Steere AC, et al: The early clinical manifestations of Lyme disease. Ann Intern Med 99:76, 1983.

Acute Disseminated Infection

Shortly after disease onset, hematogenous spread can cause a variety of systemic signs and symptoms and result in secondary sites of infection. Organ systems commonly affected are the nervous system, heart, and joints. Less commonly, the eyes, liver, skeletal muscle, subcutaneous tissue, and spleen are infected.

Neurologic Manifestations

A relatively symptom-free interval usually occurs between early and disseminated infection; however, neurologic signs and symptoms may be the presenting manifestations of Lyme disease or may overlap with early or late manifestations. Beginning at an average of 4 weeks (range, 0 to 10 weeks) after the onset of erythema migrans, neurologic involvement occurs in approximately 15% of untreated patients.

The most common neurologic manifestation of Lyme disease is a fluctuating meningoencephalitis with superimposed symptoms of cranial neuropathy, peripheral neuropathy, or radiculopathy. A triad of meningitis, cranial neuropathies (usually Bell's palsy), and radiculopathy has been described, but each entity may occur alone. Headache of variable intensity usually is present; other signs and symptoms of a mild meningoencephalitis may be noted, including lethargy or irritability, sleep disturbances, poor concentration, and memory loss. At this point, the disease often is misdiagnosed as viral meningitis. As in early disease, Kernig's and Brudzinski's signs are absent and computed tomography (CT) findings are normal. Unlike in early disease, however, findings on CSF examination often are abnormal, with a lymphocytic pleocytosis and elevated protein level. CSF glucose concentration usually is normal. Intrathecal *B. burgdorferi* antibody (usually immunoglobulin G [IgG] or IgA) is present in 80 to 90% of patients. CSF polymerase chain reaction (PCR) assay results are positive in less than one half of patients.[13]

Cranial neuropathies are common, occurring in approximately 50% of patients with Lyme meningitis; usually the seventh nerve is involved. Other cranial nerves are affected less often. Bell's palsy is bilateral in approximately one third of patients. Its duration usually is from weeks to months, and the condition generally resolves spontaneously without treatment.

Peripheral nervous system manifestations also may occur in early disseminated Lyme disease. The spinal root and plexus and the peripheral nerves may be involved in the form of thoracic sensory radiculitis, brachial plexitis, mononeuritis, and motor radiculoneuritis in the extremities. Patients may complain of weakness, pain, or dysesthesia. Examination may reveal loss of reflexes. Involvement of the extremities usually is asymmetrical, but cervical and thoracic dermatomes may be affected. Other rare neurologic abnormalities described in association with Lyme disease include chorea, transverse myelitis, ataxia, and pseudotumor cerebri.

Cerebral vasculitis associated with Lyme disease also has been reported.

Cardiac Manifestations

Cardiac involvement in Lyme disease is uncommon. Estimates of the incidence of carditis in untreated patients who have Lyme disease range from 4 to 10%.[14] The average time from initial illness to the development of carditis typically is 3 to 5 weeks (range, 4 days to 7 months). Direct myocardial invasion has been demonstrated with endomyocardial biopsy.[15] Electrophysiologic testing has demonstrated widespread involvement of the conduction system.[16]

The most common cardiac manifestation of Lyme disease is atrioventricular (AV) block, although conduction defects may involve any level of the conducting system. Myopericarditis, tachydysrhythmias, and ventricular impairment occur less often. In a review of 105 reported cases of Lyme carditis, 49% of cases were third-degree AV block, 16% were second-degree, and 12% were first-degree.[16] The degree of AV block seen in a specific patient may fluctuate rapidly.[14]

A commonly observed feature of AV block in patients with Lyme carditis is its gradual resolution, resembling that occurring after an acute inferior wall myocardial infarction and presumably related to the resolution of inflammation. Assessment of the level of the AV block is important to determine the prognosis of a patient with Lyme carditis. In most cases, block appears to be at or above the level of the AV node; therefore, the prognosis is favorable.[17] However, infranodal AV block does occur and may be characterized by slow escape rhythms of wide QRS pattern, asystole, or fluctuating left and right bundle branch block. Other electrocardiographic findings include nonspecific ST- and T-wave abnormalities and intraventricular conduction delay.[17]

Patients with high-degree AV block usually are symptomatic. Symptoms include light-headedness, palpitations, syncope, chest pain, and dyspnea on exertion. Physical examination may reveal flow murmurs and murmurs of mild mitral regurgitation, pericardial friction rub, or evidence of congestive heart failure. Associated left ventricular dysfunction may be present and has been documented by two-dimensional echocardiography and radionuclide studies; in most reported cases, it has been mild and transient.

Arthritis

Although classically considered a sign of late Lyme disease, acute arthritis may begin during the acute disseminated stage. Monarticular or oligoarticular arthritis, primarily affecting large joints, especially the knee, may develop weeks to months after the onset of initial illness. In an early study of the natural history of Lyme arthritis, approximately 50% of untreated patients experienced one episode or multiple intermittent attacks of arthritis. Acute arthritis typically is monoarticular, with involvement of only one knee. The shoulder, elbow, temporomandibular joint, ankle, wrist, hip, and small joints of the hands and feet are involved less commonly. Episodes of arthritis typically are brief (lasting weeks to months) and separated by variable periods of remission.

Arthrocentesis generally is nondiagnostic, yielding an inflammatory synovial fluid with a mean white blood cell (WBC) count of approximately 25,000 cells/μL (75% polymorphonuclear leukocytes). Higher WBC counts have been reported, simulating septic arthritis.[18] The synovial glucose concentration usually is normal, and protein levels are variable, ranging from 3 to 8 g/dL. Cultures of the fluid rarely identify the causative spirochete.[19] Complement level generally is greater than one third that of serum. Synovial biopsy reveals hypertrophy, vascular proliferation, and a mononuclear cell infiltrate. Findings therefore are similar to those in rheumatoid arthritis, except that rheumatoid factor and antinuclear antibody assays yield a negative result in Lyme arthritis. Radiography may reveal nonspecific abnormalities such as juxta-articular osteoporosis, cartilage loss, cortical or marginal bone erosions, and joint effusions.

Ophthalmic Manifestations

Ocular involvement also may be seen in early disseminated disease, with manifestations including conjunctivitis, keratitis, choroiditis, retinal detachment, optic neuritis, and blindness.[20] These findings also may be seen in late disease.

Late Lyme Disease

The chronic phase of Lyme disease is characterized by arthritic and, less commonly, neurologic symptoms. Transition from a pattern of episodic inflammation in early disease to a more indolent persistent inflammation is observed over time. The term *chronic* (or *late*) *Lyme disease* is used to describe continuous inflammation in an organ system for more than 1 year.[21]

A pattern of exacerbation and remission of arthritis may extend over several years, with a gradual tendency toward less frequent and less severe occurrences. The spontaneous long-term remission rate approximates 10 to 20% annually in untreated patients. However, patients commonly have episodes of periarticular involvement, arthralgias, or fatigue interspersed between attacks of frank arthritis. During the second or third year of illness, attacks of joint swelling sometimes become longer in duration, lasting months rather than weeks. Chronic arthritis eventually develops in approximately 10% of patients.[22]

Late neurologic complications include a wide variety of abnormalities of the central and peripheral nervous systems, as well as fatigue syndromes. Diagnosis may be difficult because of the large number of other neurologic conditions that Lyme disease may imitate and because late neurologic symptoms may be the first symptoms of the disease. The manifestations of chronic neuroborreliosis usually appear months to years after the onset of infection.

The most common late neurologic manifestation of Lyme disease is a chronic encephalopathy that manifests as a mild to moderately severe impairment of memory and learning. Hypersomnolence and mild psychiatric disturbances (depression, irritability, or paranoia) also may develop.[13]

Peripheral nervous system manifestations often are seen in late disease, with involvement of cranial nerves, spinal roots, spinal plexuses, and peripheral nerves. A predominantly sensory polyradiculoneuropathy that manifests as either radicular pain or distal paresthesia is common. Significant overlap occurs with early symptoms. Less commonly, a demyelinating condition resembling multiple sclerosis may appear in late disease. Symptoms are variable and, as in multiple sclerosis, may undergo exacerbations and remissions. CT and magnetic resonance imaging (MRI) may reveal multiple white matter lesions.[23]

Chronic inflammation also may occur in the skin, causing a seldom-recognized late cutaneous manifestation of Lyme disease, acrodermatitis chronica atrophicans.[24] This condition usually involves the skin of distal extremities at the site of a tick bite. It is characterized in its initial stages by an edematous infiltration, which progresses to an atrophic lesion resembling localized scleroderma in its more established form. *B. burgdorferi* has been demonstrated in the skin of patients with acrodermatitis chronica atrophicans as well as positive findings on serologic studies.

Diagnostic Strategies

The diagnosis of Lyme disease is based primarily on clinical and epidemiologic features, and identification of the disorder often is difficult, especially in the early stage. A history of tick bite is elicited in only approximately one third of cases. Erythema migrans is present in most patients and, in endemic areas, is considered diagnostic. Isolated late symptoms may emerge months after the initial infection, however, and the patient may not recall the rash. The disease should be considered in patients who live in or have visited an endemic area and who present during the summer months with nonspecific symptoms suggesting a viral illness or meningitis. In addition, the development of monarticular arthritis, multiple neurologic abnormalities, or heart block in previously healthy patients should raise the suspicion of Lyme disease.

Results of routine laboratory studies are nonspecific and such studies generally are not helpful in diagnosing Lyme disease. Abnormalities may include an elevated erythrocyte sedimentation rate, mild anemia, total WBC count in the normal range with a decreased absolute lymphocyte count, microhematuria, proteinuria, and increased alanine transferase level.[25] Cultures of blood, tissue, and body fluids (including CSF and synovial fluid) for *B. burgdorferi* and direct visualization techniques are difficult to perform properly and have such a low yield that they are not clinically useful.[26,27]

Serologic testing is the most practical and useful means of confirming a clinical diagnosis of Lyme disease, but it is not without limitations. Results of serologic tests must be interpreted cautiously within the clinical context, and such tests should be regarded as only adjuncts in the diagnostic process. Current serologic tests measure host antibody response (for both IgG and IgM) to *B. burgdorferi*. Problems with the performance of these tests and interpretation of findings often result in diagnostic confusion. False-negative and especially false-positive results are common. The antibody response to *B. burgdorferi* develops slowly. The peak of IgM titers appears between 3 and 6 weeks after the onset of illness. Earlier in the course of the illness, IgM titers may be negative. IgM usually returns to nondiagnostic levels 4 to 6 weeks after their peak, but elevations may persist. IgG antibody may be detectable 2 months after exposure and peaks at approximately 12 months. Early antibiotic therapy may blunt or even abolish the antibody response. During the first month of illness, both IgM and IgG titers should be determined, preferably in acute and convalescent serum samples. In approximately 20 to 30% of patients, a positive response occurs with acute samples, whereas even after antibiotic treatment, a positive response occurs with convalescent samples obtained 2 to 4 weeks later in approximately 70 to 80% of patients. After that time, most patients demonstrate a positive IgG antibody response, and a single test usually is sufficient.

In patients with illness lasting longer than 1 month, a positive IgM test result alone is likely to be false positive. Therefore, a positive IgM response should not be used to support the diagnosis after the first month of infection.

Testing with the enzyme-linked immunosorbent assay (ELISA) is the cornerstone of laboratory diagnosis of Lyme disease. Although ELISA alone has a sensitivity of 89% and a specificity of 72%, a positive test result in patients with a low pretest probability (i.e., less than 0.20) of Lyme disease is more likely to be a false positive than a true positive.[28] In patients with a positive or equivocal ELISA result, a confirmatory Western blot assay should be ordered.[29] Specimens that yield a negative result on ELISA are not tested further. Criteria for positive Western immunoblotting (requiring the presence of bands at particular locations) have been adopted by the CDC.[29]

IgG (and occasionally IgM) antibody may persist for several years after adequate treatment and symptom resolution. Persistent seropositivity is not diagnostic of ongoing infection. Even an IgM response cannot be interpreted as a demonstration of recent infection or reinfection unless the appropriate clinical characteristics are present. IgG antibody developed after natural infection does not always confer immunity against future infection by *B. burgdorferi*. Patients who are treated for erythema migrans may become reinfected; patients with Lyme arthritis, however, usually have high antibody titers to many spirochetal proteins and seem not to become reinfected.[30]

False-positive ELISA results are common. Serologic cross-reactivity can occur between *B. burgdorferi* and other spirochetes, most notably *Treponema pallidum*. False-positive results for Lyme disease also can occur with relapsing fever, gingivitis, leptospirosis, enteroviral and other viral illnesses, rickettsial diseases, autoimmune diseases, malaria, and subacute bacterial endocarditis.[31] In addition, it is estimated that up to 5% of the normal population will "test positive" for Lyme disease by ELISA. Bayes' theorem states that if the pretest likelihood of the disease is low, then the positive predictive value is low: A positive test result is more likely to be a false-positive result. For this reason, screening serologic tests are not indicated in the absence of objective clinical evidence of Lyme disease.[31]

Patients suspected of having acute Lyme neuroborreliosis should be evaluated with serologic tests and routine CSF examination. Paired serum and CSF samples should be obtained to evaluate for intrathecal production of antibody, although most patients with neuroborreliosis have positive results on serum serologic testing, thereby making additional laboratory confirmation with CSF serology unnecessary.[32]

Polymerase chain reaction (PCR) assay is superior to culture for the detection of *B. burgdorferi* in synovial fluid[33] and has a sensitivity of 73% and specificity of 99% in untreated Lyme arthritis.[34]

Differential Considerations

Although Lyme disease manifests in many ways, each stage has characteristic clinical findings that are helpful in narrowing the scope of a differential diagnosis that at first may seem overwhelmingly broad. Early Lyme disease (erythema migrans and associated constitutional symptoms) may be easily confused with a variety of other diseases, especially if the characteristic rash of erythema migrans is absent. A common clinical presentation is a flulike illness with headache, nausea, fever, chills, myalgias, arthralgias, stiff neck, and anorexia, occurring during the summer months. Even in endemic areas during the summer months, most patients with such symptoms do not have Lyme disease. When headache and stiff neck are the predominant symptoms, the principal diagnostic distinction to be made is between Lyme disease and the enteroviral diseases (and other causes of aseptic meningitis). The enteroviral diseases also have their peak incidence during the summer months; however, diarrhea, commonly associated with enteroviral infection, is not a feature of Lyme disease. Abdominal pain, anorexia, and nausea suggest hepatitis; sore throat, adenopathy, and fatigue suggest mononucleosis; and myalgias and arthralgias suggest connective tissue diseases.

The rash of erythema migrans is characteristic of but not pathognomonic for Lyme disease. Some patients are not aware of having had such a rash, and in others, its appearance is atypical. Secondary lesions may be confused with the target lesions of erythema multiforme, which generally are smaller and nonexpanding. Erythema multiforme also may involve the mucous membranes, palms, and soles; erythema migrans does not. The presence of a malar rash in association with Lyme

disease suggests systemic lupus erythematosus. Erythema nodosum generally causes more painful induration than erythema migrans and has a predilection for the extensor surfaces of the legs. Erythema marginatum of acute rheumatic fever also is in the differential diagnosis for erythema migrans; the Lyme disease rash differs in comprising generally fewer, larger, less evanescent lesions that migrate more slowly.[35] Atypical erythema migrans manifesting as an urticarial rash may suggest hepatitis B infection or serum sickness. Other cutaneous entities in the differential diagnosis for erythema migrans include cellulitis, fungal infection, fixed drug-related eruptions, plant dermatitis, and insect or spider bites. Lyme disease must be considered in a patient with any atypical rash accompanied by a "viral syndrome" or meningitis-like illness, especially during the months of peak incidence.

Acute rheumatic fever, coronary artery disease, or viral myocarditis may be suggested by the cardiac manifestations of Lyme disease. The carditis of Lyme disease, like the carditis of rheumatic fever, may follow pharyngitis and migratory polyarthritis. Erythema marginatum usually occurs with the onset of arthritis, in contrast with erythema migrans, which usually precedes the carditis. Although some patients with Lyme disease may satisfy the clinical aspects of the Jones criteria for acute rheumatic fever, they lack evidence of a preceding streptococcal infection; in addition, valvular involvement is not a prominent feature of Lyme carditis.

The differential diagnosis of the neurologic manifestations caused by Lyme disease is extensive. Considerations include aseptic meningitis, herpes simplex encephalitis, Bell's palsy of other causes, multiple sclerosis, Guillain-Barré syndrome, dementia, primary psychosis, cerebral vasculitis, and brain tumor. Neurologic symptoms often occur in the absence of any epidemiologic clues or preceding clinical symptoms suggestive of Lyme disease, making the diagnosis particularly challenging.

Lyme arthritis may mimic other immune-mediated disorders. The arthritis of Lyme disease generally is asymmetric, oligoarticular, and episodic. In contrast to patients with rheumatoid arthritis, those with Lyme arthritis rarely have symmetric polyarthritis, morning stiffness, a positive result on rheumatoid factor assay, or subcutaneous nodules. Lyme arthritis commonly is mistaken for seronegative rheumatoid arthritis; however, Lyme arthritis is most similar to the spondyloarthropathies, particularly reactive arthritis.[36] Lyme disease and Reiter's syndrome both commonly cause huge knee effusions, but in Lyme disease, absence of the extra-articular features of Reiter's syndrome (conjunctivitis, urethritis or cervicitis, balanitis, keratosis blennorrhagica) at the time of the arthritis helps distinguish it from Reiter's syndrome. In children, Lyme arthritis may mimic juvenile rheumatoid arthritis, but joint involvement in Lyme disease usually occurs in short, intermittent attacks, and iridocyclitis typically is absent. Rheumatoid factor titers will be negative in both juvenile rheumatoid arthritis and Lyme disease. The diseases resemble one another closely enough to have been confused at the time of the initial description of Lyme disease. Other diseases in the differential diagnosis for Lyme arthritis include acute gouty arthritis, septic arthritis, gonococcal arthritis, rheumatic fever, polymyalgia rheumatica, and the temporomandibular joint syndrome.

Management

Prompt treatment of early disease can shorten the duration of symptoms and prevent progression to later stages of disease. Most of the various manifestations of Lyme disease can be treated successfully with oral antibiotic therapy, with the exception of neurologic abnormalities, which usually require intravenous therapy. Treatment of Lyme disease is summarized in Table 132-3.

Vaccination

No vaccine against Lyme disease is currently available in the United States. The LYMErix vaccine (SmithKline Pharmaceuticals, Philadelphia), initially licensed in 1999, was withdrawn from the market in 2002. The vaccine, directed against the outer surface protein A of *B. burgdorferi* (OspA), was apparently safe and efficacious but required multiple and repeated doses for optimal protection. Ongoing questions about its safety and cost-effectiveness dampened demand for the vaccine.[37]

A history of vaccination with the previously licensed vaccine should not change the approach to ED management. Because protective immunity produced by the vaccine is short-lived, it is unlikely that previous vaccination will provide any residual protective effect. Vaccination may cause a persistently positive ELISA result but a negative Western blot result.

Prophylaxis and Asymptomatic Tick Bites

Although previous expert consensus has recommended that persons bitten by deer ticks (*I. scapularis*) should not routinely receive antimicrobial chemoprophylaxis,[5] this recommendation should be modified in accordance with the findings of a well-designed trial in which a single 200-mg dose of doxycycline effectively prevented Lyme disease when given within 72 hours after tick bite.[37] A single 200-mg dose of doxycycline should be considered for adult patients and children 8 years of age and older (4 mg/kg, up to a maximum dose of 200 mg) when all of the following criteria are met: (1) the tick is an adult or nymphal *I. scapularis*, (2) the tick has been attached for 36 hours or more as indicated by certainty of the time of exposure or the degree of engorgement, (3) proplylaxis can be started within 72 hours after tick removal, (4) the local rate of infection of these ticks with *B. burgdorferi* is 20% or greater, and (5) doxycycline is not contraindicated. Infection rates of 20% or greater of ticks with *B. burgdorferi* generally are reported from highly endemic areas such as New England, parts of the mid-Atlantic region, and parts of Minnesota and Wisconsin. Most other areas of the United States do not have infection rates high enough to warrant prophylaxis.[5]

The efficacy of single-dose doxycycline in patients who present more than 72 hours after removing a tick is unknown. In children, dosing and efficacy of prophylactic treatment have not been evaluated. The effectiveness of doxycycline for the prevention of other infections transmitted by *I. scapularis* ticks (e.g., babesiosis, human granulocytic ehrlichiosis) is unknown and should not be assumed.[37] Other antimicrobial agents that are effective for the treatment of Lyme disease (e.g., amoxicillin) and even other regimens of doxycycline (e.g., 100 mg twice daily) have unknown efficacy for Lyme disease prophylaxis.

Bites from *Dermacentor variabilis* and *Amblyomma americanum* do not require prophylactic treatment. Any patient who has been bitten by a tick should be instructed to seek medical evaluation if symptoms of tick-borne illness develop.

Early Disease

Prompt antibiotic therapy is essential in early Lyme disease because it generally shortens the duration of the rash and associated symptoms and, more important, prevents later illness in most patients. Some patients with severe early

Table 132-3 Treatment of Lyme Disease

SYNDROME/MANIFESTATION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE*
Early Lyme disease	Doxycycline†	100 mg PO bid for 21 days	
	or		
	Amoxicillin	250–500 mg PO tid for 21 days	25–40 mg/kg/day divided tid
	Alternative:		
	Cefuroxime axetil	500 mg PO bid for 21 days	250 mg bid
	or		
	Erythromycin (less effective than doxycycline or amoxicillin)	500 mg PO qid for 14–21 days	
Neurologic disease			
Facial nerve paralysis	With an isolated deficit, oral regimens for early disease, used for at least 30 days, may suffice. For a deficit associated with other neurologic manifestations, intravenous therapy is warranted (see below).		
Lyme meningitis‡	Ceftriaxone	2 g IV by single dose for 14–28 days	75–100 mg/kg/day IV
	Penicillin G	20 million units daily in divided doses for 10–14 days	300,000 U/kg/day IV
	Alternative:		
	Chloramphenicol	1 g IV every 6 hr for 10–21 days	
Cardiac disease			
Mild§	Doxycycline†	100 mg PO bid	
	or		
	Amoxicillin	250–500 mg PO tid	25–50 mg/kg/day divided tid
More severe	Ceftriaxone	2 g IV daily by single dose for 14–21 days	75–100 mg/kg/day IV
	or		
	Penicillin G	20 million units daily in divided doses for 14–21 days	300,000 U/kg/day IV
Arthritis	*Oral*:		
	Doxycycline†	100 mg PO bid for 30 days	
	or		
	Amoxicillin	500 mg PO tid for 30 days	50 mg/kg/day divided tid
	Parenteral:		
	Ceftriaxone	2 g IV by single dose for 14–21 days	75–100 mg/kg/day IV
	or		
	Penicillin G	20 million units daily in divided doses for 14–21 days	300,000 U/kg/day IV

*Pediatric dosage should not exceed adult dosage.
†Tetracycline, 250 to 500 mg PO qid, may be substituted for doxycycline. Neither doxycycline nor any other tetracycline should be used for children younger than 8 years of age or for pregnant or lactating women.
‡Regimens for radiculoneuropathy, peripheral neuropathy, and encephalitis are the same as those for meningitis.
§Oral regimens are reserved for mild cardiac involvement (see text).
Modified from Abramowitz M (ed): Med Lett 42:37, 2000; and Wormser GP, et al: The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: Clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis 43:1089, 2006.

disease, however, progress to later stages despite appropriate antibiotic regimens.

The drug of choice for men, nonpregnant and nonlactating women, and children older than 8 years of age is doxycycline, 100 mg twice daily for 3 weeks.[5] An advantage of doxycycline is that it also is effective for treatment of human granulocytic ehrlichiosis, which is transmitted by the same tick that transmits Lyme disease. Pregnant or lactating women and children younger than 8 years of age should receive amoxicillin, 500 mg PO (20 to 40 mg/kg per day in three doses for children). Cefuroxime axetil has been shown to be as effective as doxycycline[38] and may be used in children of any age, but cephalexin is ineffective in Lyme disease.

Macrolide antibiotics are not recommended as first-line agents for therapy for early Lyme disease.[38] They should be reserved for patients who cannot tolerate doxycycline, amoxicillin, and cefuroxime axetil. Macrolide regimens[5] for adults include azithromycin, 500 mg PO daily for 7 to 10 days; erythromycin, 500 mg PO four times daily for 14 to 21 days; and clarithromycin, 500 mg PO twice daily for 14 to 21 days.

A Jarisch-Herxheimer–type reaction may occur in the first 24 hours of antibiotic treatment, consisting of fever, chills, myalgias, headache, tachycardia, increased respiratory rate, and mild leukocytosis.[39] Defervescence usually takes place within 12 to 24 hours, and the patient's symptoms can be managed with bedrest and aspirin. The pathogenesis of this reaction is controversial, but it probably is caused by the killing of spirochetes with release of pyrogens. The Jarisch-Herxheimer reaction occurs more commonly with penicillin and doxycycline than with erythromycin, probably because of their superior spirocheticidal activity.

Early Disseminated Infection

Neurologic Disease

For patients with relatively mild symptoms (e.g., solitary facial nerve palsy with normal findings on CSF examination), doxycycline or amoxicillin can be used in the same dosage as for early disease, but the duration of therapy should be extended to 30 days. The use of prednisone for facial nerve palsy from Lyme disease has been suggested but is not currently recommended.

For patients with other objective neurologic abnormalities (e.g., meningitis or encephalitis, peripheral neuropathies, cranial neuritis other than facial nerve palsy) or evidence of the spirochete in the CSF, parenteral antibiotic therapy is required. Ceftriaxone, 2 g/day IV for 14 days (75 to 100 mg/kg/day for pediatric patients), or penicillin G, 18 to 24 million

units daily IV for 10 to 14 days, may be used.[38] Ceftriaxone may be more effective than penicillin, and many experts recommend longer courses (e.g., up to 4 weeks).[40] In cases of penicillin or cephalosporin allergy, oral doxycycline for 30 days may be used.

Cardiac Disease

Patients with mild cardiac conduction system involvement (first-degree AV block with a PR interval less than 0.30 second) and no other significant symptoms usually can be treated safely on an outpatient basis with oral doxycycline or amoxicillin for 21 to 30 days.[38] Patients with higher degrees of AV block, including first-degree block with a PR interval greater than 0.30 second or evidence of global ventricular impairment, should be hospitalized for cardiac monitoring and treatment with parenteral antibiotics. Either penicillin G, 18 to 24 million units IV, or ceftriaxone, 2 g daily for 21 days (50 to 80 mg/kg/day for children), may be used.

The benefit of adjuvant use of aspirin or prednisone in treating Lyme carditis is uncertain. Temporary cardiac pacing may be necessary in patients who have severe heart block with hemodynamic instability. The block generally resolves completely with antibiotic treatment, so the recognition of Lyme carditis in young patients with unexplained heart block is critical to avoid unnecessary permanent pacemaker implantation.

Late Infection

Arthritis

In established Lyme arthritis, the response to antibiotic therapy may be delayed for several weeks or months.[5] Thirty-day oral regimens such as doxycycline, 100 mg PO twice daily, or amoxicillin, 500 mg three times daily, usually are effective and, for reasons of cost and convenience, may be selected as first-line therapy given on an outpatient basis before use of parenteral antibiotic therapy is considered.[38] Persistent or recurrent joint swelling after recommended courses of antibiotic therapy can be treated with another 4-week course of oral antibiotics or with a 2- to 4-week course of intravenous ceftriaxone.[5] A small percentage of patients with Lyme arthritis, particularly those with HLA-DR4 specificity or antibody reactivity with OspA, may have persistent joint inflammation despite treatment with either oral or intravenous antibiotics.[22] Such patients often do not respond to any antibiotic therapy and may require arthroscopic synovectomy.

Neurologic Disease

Patients with late neurologic disease affecting the central or peripheral nervous system should be treated with ceftriaxone (2 g once a day intravenously for 2 to 4 weeks). Alternative parenteral therapy may include cefotaxime (2 g IV every 8 hours) or penicillin G (18 million to 24 million units daily, given in divided doses every 4 hours). Response to treatment is usually slow and may be incomplete.

Lyme Disease and Pregnancy

Similar to the spirochetal agents of syphilis and relapsing fever, *B. burgdorferi* can be passed transplacentally. In rare cases, Lyme disease acquired during pregnancy may lead to infection of the fetus and possibly to stillbirth, but adverse effects on the fetus have not been documented conclusively. Counseling the termination of a pregnancy because of maternal Lyme disease is unwarranted.

Lyme disease contracted during pregnancy can be treated and cured. Treatment for pregnant patients can be identical to that for nonpregnant patients with the same disease manifestations, except that doxycycline should be avoided.[5] Most women give birth to normal infants despite documented Lyme borreliosis during their pregnancies.[41]

RELAPSING FEVER

Perspective

Relapsing fever is caused by bacteria of the *Borrelia* species, order Spirochaetales. Human *Borrelia* infections occur worldwide and all are associated with arthropod vectors. The epidemic (louse-borne) form of relapsing fever is caused solely by *Borrelia recurrentis* and is found mostly in Africa, where mortality rates can reach 70% with outbreaks. The endemic form, tick-borne relapsing fever, is caused by a group of closely related *Borrelia* species, their names derived from the species names of *Ornithodoros* tick vectors that carry them. The more common ones in North America are *Borrelia hermsii*, *Borrelia turicatae*, and *Borrelia parkeri*.[42] *B. burgdorferi* has been recognized as the etiologic agent of the third and most recently described borrelial disease, Lyme disease.

Principles of Disease

Tick-borne relapsing fever is maintained in an animal reservoir consisting primarily of wild rodents, including squirrels, mice, rats, chipmunks, and rabbits. It is found predominantly at altitudes of 2000 to 7000 feet in coniferous forest habitats.[43] The tick vectors are argasids belonging to several species of the genus *Ornithodoros*, which routinely reside in the nests and burrows of their mammalian hosts. Ticks acquire the infection by feeding on a spirochetemic rodent. The borreliae remain viable in the ticks for several years and can be passed transovarially to the next generation; thus, the tick is a major reservoir and vector. These soft ticks feed for brief periods (15 to 30 minutes), usually at night, and their painless bite generally is unnoticed by the sleeping victim. Transmission occurs by injection of infected saliva through the bite site or intact skin. Less common modes of transmission (e.g., by way of venipuncture equipment in intravenous drug users) have been reported.

In the United States, relapsing fever occurs primarily in the western Mountain and Pacific states, including Montana, Wyoming, Nevada, Colorado, California, and Washington. Persons who come in contact with infected ticks from wild rodents are at greatest risk. Outbreaks have been reported among groups of persons sleeping overnight in hunting cabins inhabited by wild rodents.[42-44]

In tick-borne relapsing fever, the initial febrile episode lasts 3 days. This is followed by an asymptomatic period of variable duration but usually approximately 7 days, during which patients generally feel better and may return to their usual daily activity levels under the assumption that they have recovered from another viral illness. Relapse then occurs, with symptoms that mimic those of the original illness. With tick-borne relapsing fever, this cycle repeats itself three to five times. Each successive relapse usually is less severe. Relapse is caused by the spirochete's unique ability to undergo antigenic variation within the body of the infected host. Each successive antigenic variation is cleared from the bloodstream by specific host antibodies, and a characteristic relapsing febrile course results.[42]

Clinical illness manifests in two classic stages as each fever episode resolves. The first stage is called the "chill" phase (high fevers with reported temperatures of to 106.7° F, mental status changes, tachycardia, and tachypnea) lasting approximately 30 minutes, followed by a "flush" phase (rapid tem-

perature decrease, sweats, and hypotension), which can be confused with a Jarisch-Herxheimer reaction.[45]

Clinical Features

After a postbite incubation period of 4 to 18 days, during which time the host concentration of spirochetes increases, fever of abrupt onset occurs, often accompanied by shaking chills, headache, arthralgias, myalgias, nausea, and vomiting. Occasionally a pruritic eschar may be noted at the site of the tick bite, but this usually is absent by the onset of clinical symptoms. Consequently, the nonspecific nature of the clinical presentation often leads to misdiagnosis of the disease as a viral illness. The patient's temperature is high, and generalized muscle weakness and lethargy are common. Hepatomegaly, splenomegaly, and jaundice are sometimes seen. Neurologic involvement is less common but can manifest as delirium, nuchal rigidity, peripheral neuropathy, or pupillary abnormalities. Uveitis has been described.[46] A macular or petechial skin rash, more apparent on the trunk than on the extremities, may be present.

Recent severe cases of tick-borne relapsing fever resulting in ARDS in California and Nevada near the Lake Tahoe area and in the state of Washington prompted a comprehensive epidemiologic investigation of cases in those areas over a 10-year period. This study showed that ARDS may be more common than was previously suspected. Reported occurrence rates for Jarisch-Herxheimer reaction were between 6% and 21%; for hypoxia, 16%; for elevated liver function test values, 8%; and for ARDS, 6%. Forty-six percent of the patients required hospitalization.[43]

Diagnostic Strategies

The definitive diagnosis of relapsing fever depends on the demonstration of spirochetes in the peripheral blood during a febrile episode. This is not a typical finding with other spirochetal diseases.[47] In most cases, spirochetes are readily visible on a routine blood smear prepared with Wright or Giemsa stain. Thick or thin blood smears, such as those prepared for malaria evaluation, also are satisfactory. The organisms are seen within the plasma spaces between blood cells or may overlie the blood cells. Several organisms per high-power field typically are visible in smears from febrile patients with relapsing fever.[42] Blood specimens for the smears should be obtained as the temperature curve swings up, and repeated samples may be required before a positive result is observed, because sensitivity approaches only 70%. Spirochetes also may be visible in wet mounts with the use of phase contrast microscopy. Cultures, although the most sensitive diagnostic method available, require a special medium and do not yield rapid results and so are not commonly performed. Genus-specific PCR testing has now been successfully used and may be higher in sensitivity than either serology or blood smear, especially in the acute phase of disease.[48] Serologic testing offered by the CDC can be accessed through local and state health departments. Nonspecific laboratory findings may include mildly increased bilirubin and liver function levels, thrombocytopenia, and elevated erythrocyte sedimentation rate.[45]

Differential Considerations

On initial presentation, the differential diagnosis is extensive; however, it narrows with the occurrence of relapse. A history of possible soft tick exposure together with recurrent fever should suggest the diagnosis. Other conditions that initially may be considered include malaria, typhus, dengue, yellow fever, Colorado tick fever, and tularemia. Careful examination of blood smears, together with clinical data and other laboratory tests, will aid in making the correct diagnosis.

Management

Relapsing fever is effectively treated with tetracycline or erythromycin. Tetracycline should be avoided in children younger than 8 years and in pregnant women. Tetracycline or erythromycin should be given in an oral dose of 500 mg for 7 days; single-dose therapy is also effective.[42] Other treatment regimens, including doxycycline and chloramphenicol, have been recommended. Treatment with penicillin G has been associated with an increased rate of relapse. Success with ceftriaxone has been reported in a patient with relapsing fever that did not respond to penicillin. Prophylaxis with doxycycline for tick-borne relapsing fever in exposed subjects in high-risk infested areas has been shown to be effective.[49]

As many as one third of patients will experience a Jarisch-Herxheimer–type reaction during treatment with antibiotics. The reaction can be severe, especially with louse-borne relapsing fever. This phenomenon may be related to release of high levels of cytokine intermediaries or endogenous opioids. Approximately 4 hours after antibiotic treatment and coinciding with the clearance of spirochetes from the blood, the patient usually experiences an increase in temperature and severe rigors, accompanied by a drop in leukocyte and platelet counts and onset of hypotension. Anticipation of this reaction is crucial because intravenous volume expansion with saline solution may be required to maintain the blood pressure; the reaction can be more threatening than the disease itself. Meptazinol, an opioid antagonist with agonist properties, has been proposed for use in treatment of this reaction.

Prognosis is good in treated patients with relapsing fever, with approximately 95% achieving complete recovery. Bad prognostic signs include the presence of jaundice, high spirochete counts in the blood, and hypotension.[42] Transplacental transmission can occur in infected pregnant women. Perinatal death of the fetus or infant and spontaneous abortions occur in nearly 50% of the cases in pregnant women.[50] Death is rare in tick-borne relapsing fever and is limited to infants and the elderly.

■ TULAREMIA

Perspective

Tularemia was first characterized in 1837 by Soken, who described a febrile illness with generalized lymphadenopathy in people who had eaten infected rabbit meat.[51] In 1912, McCoy first isolated *Bacterium tularense*, now known as *Francisella tularensis*, from rodents in Tulare County, California, giving rise to the name of the disease. Edward Francis, for whom the genus *Francisella* was later named, contributed much to the understanding of the bacteriology and epidemiology.[52]

Tularemia occurs worldwide and is endemic between 30 and 71 degrees north latitude. The incidence of tularemia is low. There were 247 reported cases of tularemia in the United States between 2004 and 2005, although it is not a notifiable disease in all states.[53] Tularemia has been seen in every state but is most common in the southwest central region (Arkansas, Louisiana, Oklahoma, Texas, and Mississippi). Fifty-six percent of reported cases have come collectively from Missouri, Oklahoma, South Dakota, and Arkansas. It is more common in men than in women. Persons at increased risk for infection include hunters, trappers, butchers, agricultural

workers, campers, sheepherders, mink farmers, and laboratory workers.[54,55]

Ticks, lagomorphs (hares, rabbits), and rodents (mice, rats) are believed to be the most important sources of transmission to humans; however, the organism has been recovered from animals of more than 100 different species with significant epidemics linked to contact with a variety of them, including domestic cats.[52,56] A large number of commercially distributed prairie dogs from Texas died from tularemia in 2002.[57] The ticks most commonly involved in transmission in the United States are the deer tick (*I. scapularis*), the Lone Star tick (*A. americanum*), and the dog tick (*D. variabilis*), all of which have been associated with other tick-borne illnesses. Whereas mosquitoes are major vectors in many European countries,[58,59] horse fly and deer fly bites have been implicated in endemic situations in the United States.[60]

Transmission to humans most commonly occurs through tick bites or handling infected animals. It also can occur with ingestion of infected food or water, with inhalation of dust or water aerosol, and through insect bites.[58,60] Nonimmune laboratory workers who work with *F. tularensis* can acquire the disease. Person-to-person transmission is rare. Tularemia has a bimodal prevalence in the United States, with an increased incidence in May to August associated with tick-borne transmission and a December to January peak associated with hunting and skinning of infected mammals (primarily rabbits). *Francisella tularensis* has been found to coexist in reservoir populations harboring the agent responsible for Lyme disease.[61] Eleven cases of pneumonic tularemia, found to be from aerosolization of contaminated vegetation clippings, were discovered in Martha's Vineyard.[62] Outside of the United States, tularemia has been confirmed in hundreds of cases in Kosovo, through rodent contamination of food. In addition, Sweden has reported a high number of cases, usually associated with aquatic environments and mosquitoes.[52,59,63]

Principles of Disease

Francisella tularensis is a small pleiomorphic gram-negative coccobacillus and is a facultative pathogen of macrophages, neutrophils, and nonphagocytic cells such as hepatocytes and alveolar epithelial cells.[64] Two serologically identical types of *F. tularensis* organisms are responsible for human disease and can be distinguished from each other on the basis of geographic distribution, fermentation reactions, and virulence. Jellison type A (*F. tularensis* biovar *tularensis*), the predominant biovar in North America, is associated with ticks and rabbits and causes severe disease in humans. Strain B (*F. tularensis* biovar *holarctica*) occurs in Asia, Europe, and, to a minor extent, North America; it is associated with rodents and causes milder disease in humans.[64]

Tularemia manifests in different ways, depending on the portal of entry of the organism. The primary route of infection by *F. tularensis* is through the skin. Entry can occur through hair follicles or through small cuts and abrasions that may be contaminated by exposure to an infected animal; tick exposure can also introduce the bacteria.[54] Because the bacterium has not been isolated from the salivary glands of ticks, it is thought that they transmit the organism through their feces.[51] Scratching after a tick bite introduces the infected feces into the skin. Inhalation or ingestion of the organism or transmission through the conjunctivae also can cause infection. The incubation period is approximately 2 to 6 days, depending on the size of the inoculum.

After penetration of the skin or epithelial membrane, the organism usually spreads to the regional lymph nodes. An erythematous tender papule develops at the primary infection site, followed by inflammation and skin ulceration. The regional nodes enlarge, necrose, and may rupture. The necrotic, purulent, painful lymph node is termed a *bubo*. In the ulceroglandular form of the infection, the organism may not spread further than the regional lymph nodes. If the inoculum is sufficiently large or the host defenses are inadequate, bacteremia ensues, with dissemination to phagocytic cells of the reticuloendothelial system.

Pulmonary tularemia may result from inhalation of small-particle aerosols containing *F. tularensis* or may be secondary to hematogenous dissemination. Small areas of localized pneumonitis most commonly are seen, although chest radiographic findings are nonspecific; lobar consolidation or abscess formation is rare. Oculoglandular tularemia occurs when the conjunctiva becomes infected from contact with material from an ulcer or a contaminated finger. Typhoidal tularemia follows systemic spread of *F. tularensis* from the oropharynx and probably the gastrointestinal tract when a large inoculum is swallowed.

Clinical Features

Tularemia has six clinical presentations, depending on whether disease is localized to an entry site and its regional lymph nodes—ulceroglandular, glandular, oculoglandular, and oropharyngeal forms—or is more invasive and generalized—typhoidal and pulmonary forms.

Ulceroglandular tularemia is the most common form of the disease (accounting for approximately 80% of the cases). Typically, a skin lesion on an extremity at the site of primary inoculation begins as an erythematous papule, which then ulcerates 2 to 3 days later.[54] The ulcer is slow to heal and often is still present when the subsequent regional lymphadenopathy and fever develop. The distribution of the regional adenopathy reflects the primary entry site; patients with tick-borne tularemia usually have inguinal or femoral adenopathy, whereas those who acquire rabbit-associated tularemia have axillary or epitrochlear nodal involvement. Generalized lymphadenopathy also may be seen. Occasionally, nodes suppurate and drain.[54]

Glandular tularemia, the second most common form, is characterized by the development of lymphadenopathy (usually cervical) without an associated skin ulcer. *Oculoglandular* tularemia is seen in 1 to 2% of cases and is characterized by unilateral conjunctivitis with regional adenopathy involving preauricular lymph nodes. *Oropharyngeal* tularemia *manifests* as severe exudative pharyngitis with associated cervical lymphadenitis. It has been known to cause acute glaucoma.[52,65]

Typhoidal tularemia is a systemic form of the disease in which no obvious entry site can be found; it occurs in approximately 10% of cases. Only 10 to 50 organisms are required to induce disease; incubation time is 2 to 10 days.[58] Symptoms and signs may include fever, chills, constipation or diarrhea, abdominal pain, and weight loss. A 30 to 60% case-fatality rate is associated with untreated typhoidal tularemia.[60]

Pulmonary tularemia is common and has symptoms similar to those of other bacterial pneumonias: fever and chills, cough (usually nonproductive), substernal burning, dyspnea, malaise, and prostration. It may result from either direct inhalation of aerosolized organisms or bacteremic spread from another site.

Uncommon complications of tularemia include pericarditis, meningitis, endocarditis, peritonitis, appendicitis, perisplenitis, and osteomyelitis.[54] Guillain-Barré syndrome associated with tularemia also has been reported.[66]

Tularemia is one of the most widely studied diseases with respect to potential biologic warfare. The United States devel-

oped an aerosolized form in the 1950s, and the Japanese allegedly contaminated prisoners with the disease in the 1930s.[67] It was removed from the national list of notifiable diseases in 1995 but then was reinstated in view of the heightened biologic weapons threat.[55] It is now classified by the CDC as one of the six category A critical biologic diseases.[68] An aerosolized form of the bacterium would be the most likely delivery mechanism used in biologic warfare.[69] With release of aerosolized particles, disease would manifest clinically as acute fever, progressive pneumonia, pleuritis, and hilar lymphadenopathy, beginning as early as 3 to 5 days after delivery.[70] Only approximately 55% of emergency departments have been adequately educated on the recognition of and preparedness for tularemia.[71]

Diagnostic Strategies

Diagnosis of tularemia is based on clinical findings and serologic testing. Antibody titers begin to rise approximately 7 to 10 days after exposure and peak in 3 to 4 weeks. In a patient with a clinical presentation suggesting tularemia, an antibody titer of 1:160 or greater in a single specimen is diagnostic. Confirmatory evidence is provided by a fourfold or greater rise in titer in a second sample obtained 2 weeks later. Unfortunately, titers of IgG and IgM can continue to be high for up to 10 years, and cell-mediated immunity can be maintained for up to 25 years.[72,73] Rapid testing with PCR assay is available.[74,75] A rapid point-of-care test using an immunochromatographic approach is currently being evaluated.[76]

Aspiration of affected lymph nodes for culture is not routinely recommended because of the associated risk to laboratory personnel. If tularemia is suspected, the laboratory should be alerted so that appropriate precautions can be taken in specimen handling and so that enriched culture medium can be used.

Management

Isolation of patients with tularemia is not required. Streptomycin is the drug of choice for treatment of all forms of tularemia. When given intramuscularly in a dose of 30 to 40 mg/kg per day in two divided doses every 12 hours, streptomycin usually produces symptomatic improvement and resolution of fever in 1 to 2 days.[54] After the third treatment day, one half of the dose is given for a total course of 7 to 14 days.[54,58] With this regimen, relapses are unusual.

Ulcers and tender lymph nodes usually heal within 7 to 10 days; however, enlarged nodes occasionally develop into fluctuant sterile buboes, requiring incision and drainage after completion of the course of antibiotics. Gentamicin also is effective for treatment (3 to 5 mg/kg/day for 10 to 14 days).[58] Tetracycline and chloramphenicol are effective; however, the risk of relapse is greater than that associated with the aminoglycosides. Imipenem-cilastatin, an antibiotic without nephrotoxicity, has been used successfully to treat pulmonary tularemia in a patient with acute renal failure. Ceftriaxone is not effective against *F. tularensis* infections.[77] Prophylaxis for possible exposure requires doxycycline, 100 mg twice a day for 14 days. Doxycycline or ciprofloxacin prophylaxis is recommended for a large biologic attack.[70] An effective live vaccine strain has been available for vaccination against tularemia for nearly 50 years, but licensure approval has been delayed owing to a lack of understanding of the vaccine's mechanism of action and attenuation.[64] Because of recent interest in biologic warfare, research on tularemia vaccines has resurged.

The overall mortality rate in untreated tularemia ranges from approximately 5 to 30%; the higher figure is associated with severe disease or significant pulmonic involvement. With appropriate antibiotic treatment, death is rare (mortality rate of less than 1%).

ROCKY MOUNTAIN SPOTTED FEVER

Perspective

RMSF is an acute, febrile, systemic tick-borne illness caused by *Rickettsia rickettsii*. There are 11 other rickettsial species that cause human disease in other parts of the world. RMSF is found in North, South, and Central America. The number of reported cases in the United States more than tripled between 2001 and 2005, especially in suburban areas.[78,79] RMSF ranges in clinical severity from mild or even subclinical illness to a fulminant disease with vascular collapse and death within several days of onset. It is the only rickettsiosis still associated with significant mortality, causing approximately 40 deaths in the United States each year,[80] with a mortality rate ranging from 3 to 5% despite appropriate treatment. Before tetracycline and chloramphenicol were available, death occurred in as many as 30% of cases in the 1930s.[79] The age-specific incidence is highest in children younger than 10 years, and case-fatality rates are highest in persons older than 60 years.[81] RMSF is a nationally reportable disease, with all cases to be registered with the respective state department.

The recorded history of RMSF suggests that the disease was present at least before the white settlement of western North America, in afflicted Native American inhabitants of wooded Rocky Mountain regions. Early terms used to name the disease included "tick fever" and "black measles." In 1899, RMSF was described as "an acute, endemic, noncontagious but probably infectious, febrile disease, characterized by a continuous moderately high fever, severe arthritic and muscle pains, and a profuse petechial or purpuric eruption in the skin, appearing first on the ankles, wrists, and forehead, but rapidly spreading to all parts of the body." In 1906, the causative organism, *Rickettsia rickettsii*, was identified by Howard T. Ricketts, who also described the importance of the tick vector in transmission to humans.

Although RMSF was first described in Montana and Idaho, it is now relatively rare in the Rocky Mountain states. Endemic in all 48 contiguous states except Maine, the disease continues to be most prevalent in the southeastern United States. RMSF has been reported in Canada, Central America, Mexico, and South America but never outside the Western Hemisphere. In 1987, four cases of RMSF were reported among residents of the Bronx in New York City; none of the affected persons had recently traveled to an area known for endemic disease—raising the possibility that other urban foci of RMSF may exist.

RMSF also tends to be focally endemic, with clustering of cases within a larger endemic area that may correspond to "islands" of infected ticks. These areas, ecologically distinct from surrounding areas, may be ideally suited to ticks; they usually consist of wild open fields, deciduous forests with thick ground cover and poor water drainage, or uncultivated areas. In areas with frequent occurrence of RMSF (Oklahoma, North and South Carolina, Tennessee, and Pennsylvania), an infectivity rate of 2 to 15% of the tick population has been reported. North Carolina and Oklahoma carry the highest incidence rates (35% of all cases) for RMSF.[79]

Rickettsia rickettsii organisms are obligate intracellular bacteria that often occur in pairs and possess a cell wall similar in structure and chemical composition to that of gram-negative bacteria.[82] *R. rickettsii* contain both RNA and DNA and, in contrast with other rickettsial organisms, can invade the nucleus as well as the cytoplasm.

The American dog tick, *Dermacentor variabilis*, and the Rocky Mountain wood tick, *Dermacentor andersoni*, have been the responsible vectors of human RMSF cases in the United States to date[79]; however, the common brown dog tick, *Rhipicephalus sanguineus*, has recently emerged as a third vector.[83] *R. sanguineus* has been the main RMSF vector in Mexico and Central America. The ticks feed on virtually any available warm-blooded animals and humans; the occurrence of *R. rickettsii* in the United States does not depend on the presence of any given order of mammal. Domestic dogs infected with *R. rickettsii* can demonstrate clinical illness similar to that seen in humans. Although dogs do not play an important role in the amplification cycle of RMSF, they can serve as a conduit for infected ticks, carrying them into close contact with pet owners. Dogs may serve as sentinels for RMSF in humans. Communication between physicians and veterinarians is important when cases of zoonotic diseases are detected.[84] Humans serve only as accidental participants in the cycle of infection. A retrospective study revealed that none of 10 recipients of blood products found to be from donors with either confirmed or probable RMSF contracted the disease.[85]

Principles of Disease

After introduction of *R. rickettsii* into the host by the tick vector, the organisms invade and multiply in the vascular endothelial cells. They then enter deeper areas of the vessel walls and infect vascular smooth muscle. Rickettsial organisms move from cell to cell by actin-based motility.[86] Damage to endothelial cells not only exposes subendothelium but also releases tissue plasminogen activator and von Willebrand factor, thereby causing microhemorrhage, microthrombus formation, and increased vascular permeability. In addition, antibody forms, with antigen activating the complement system (type III immune response), and a cellular response is recruited.

These widespread vascular lesions form the basis for most of the clinical features associated with RMSF. Hypotension, edema, and increased extravascular fluid space result from the increased small-vessel permeability. The early rash results from the vasculitis and the associated changes in permeability; later petechial and hemorrhagic lesions are secondary to the vasculitis and thrombocytopenia. Microinfarcts and focal lesions develop in various organs, including the brain, heart, lungs, kidneys, adrenal glands, liver, and spleen. Rickettsial encephalitis and diffuse microinfarcts are usual features of central nervous system involvement. An interstitial pneumonitis caused by direct lung invasion by the organism may occur, and acute respiratory distress syndrome (ARDS) can ensue. Acute renal failure and hypovolemic shock, the primary causes of death, can occur as early as the second week of illness.

Clinical Features

Children from 5 to 9 years of age are the most common victims of RMSF. Two thirds of all cases are in children younger than 15 years. More than 90% present with a fever and rash. A history of tick bite or presence in possible tick-infested areas is elicited in 60 to 70% of all patients with RMSF, although only 49% of the pediatric population reports a tick bite.[87] The incubation period ranges from 2 to 14 days, with a mean of 7 days.[79] A short incubation period may indicate a more serious infection.

Onset of symptoms usually is abrupt but is gradual in approximately one third of patients. Early symptoms are nonspecific and similar to those of many acute infectious diseases, making early diagnosis very difficult. "Typical" patients experience sudden onset of fever, severe headache, myalgias, prostration, nausea, and vomiting. Tenderness may be noted in large muscle groups (Table 132-4). As many as 80% of patients may have gastrointestinal symptoms, secondary to myositis of the abdominal wall. Fever (temperature usually higher than 102° F) is nearly always present during the first 2 to 3 days of illness and may precede other signs by 1 week or more.[79] Occasionally, the onset of illness is mild, with lethargy, headache, anorexia, and low-grade fever; these patients may remain ambulatory. Although the triad of fever, rash, and tick exposure traditionally has been seen in only approximately 3 to 18% of cases, newer data show that it is found in up to 45% of children with the disease.[87] An extreme complication of RMSF is gangrene, which probably is induced by small-vessel occlusion.[88]

Table 132-4 Symptoms and Signs in 262 Persons with Rocky Mountain Spotted Fever

SYMPTOM OR SIGN	FREQUENCY DURING ILLNESS (%)	
	ANY TIME	FIRST 3 DAYS
Fever (temperature of 37.8° C–38.9° C [100° F–102° F])	99	73
Headache, mild to moderate	91	71
Fever (≥102° F)	90	63
Any rash	88	49
Myalgia, mild to moderate	83	57
Rash, maculopapular	82	46
Rash, palms/soles	74	28
Triad of fever, rash, history of tick exposure	67	3
Nausea/vomiting	60	38
Headache, severe	57	40
Abdominal pain	52	30
Rash, petechial and hemorrhagic	49	13
Myalgia, severe	47	25
Conjunctivitis	30	13
Lymphadenopathy	27	13
Stupor	26	6
Diarrhea	19	9
Edema	18	3
Ataxia	18	7
Meningismus	18	5

From Helmick CG, Bernard KW, D'Angelo LJ: Rocky Mountain spotted fever: Clinical, laboratory, and epidemiological features of 262 cases. J Infect Dis 150:480, 1984.

Cutaneous Manifestations

Vasculitis secondary to rickettsial invasion of vascular endothelial cells causes the rash commonly associated with RMSF; however, the rash reportedly is absent in 4 to 16% of laboratory-confirmed cases, referred to as "Rocky Mountain spotless fever." In addition, the rash may go unnoticed in dark-skinned patients. It usually appears on the third to fifth febrile day but can emerge as early as the second and as late as the sixth day. The initial lesions generally are restricted to the ankles and wrists, spreading to the palms and soles. The rash then spreads centripetally to the forearms, arms, legs, thighs, and trunk. Although usually spared, the face can be involved. Despite the common belief that the palms and soles are critical for diagnosis, they are not consistently involved (rash on the palms and soles is reported in approximately 50% of cases). Involvement of the scrotum or vulva can be an evasive clue for RMSF.[89]

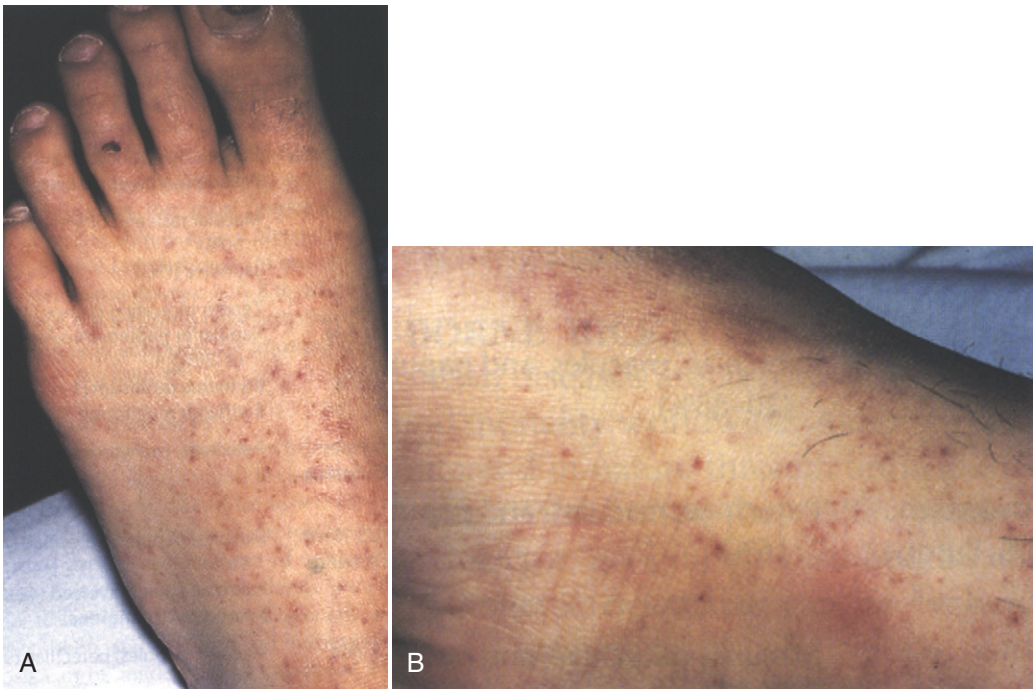

Figure 132-7. **A,** Exanthem of Rocky Mountain spotted fever. **B,** Exanthem of Rocky Mountain spotted fever, close-up view. (From McGinley-Smith DE, Tsao SS: Dermatoses from ticks. J Am Acad Dermatol 49:363, 2003.)

The rash of RMSF typically begins as 1- to 5-mm blanchable pink to bright red discrete macules that may be pruritic (Fig. 132-7). At this initial stage, the lesions fade when pressure is applied and are not palpable. A warm compress applied to the area enhances the rash. After 6 to 12 hours, the rash spreads centripetally. After 2 to 3 days, the rash becomes maculopapular and changes to a deeper red; at this stage, skin changes can be appreciated on light palpation. By approximately the fourth day, the rash becomes petechial and no longer fades with applied pressure. Applying tourniquets for several minutes or taking the blood pressure may cause additional petechiae to form distal to the site of occlusion (Rumpel-Leede phenomenon). Occasionally, the lesions coalesce to form large ecchymotic areas that may slough and form indolent ulcers (Fig. 132-8).

Prompt institution of specific therapy can cause the initial nonfixed lesions to disappear rapidly, unlike the later fixed lesions. Patients who have had the typical rash may exhibit brownish discolorations at the site during the convalescent period.

Cardiopulmonary Manifestations

Echocardiographic evidence of decreased left ventricular contractility secondary to myocarditis commonly is seen and often is detectable even before clinical signs of RMSF appear. Clinical manifestations of left ventricular dysfunction are uncommon, however, and hypotension and pulmonary edema, when present, usually have noncardiogenic causes. Chest radiographs may demonstrate cardiac enlargement. Electrocardiographic changes include low-voltage, nonspecific ST-T changes, first-degree AV block, dysrhythmias (sinus and nodal tachycardia, paroxysmal atrial tachycardia, atrial fibrillation), and left ventricular hypertrophy. Most cardiac abnormalities are transient, but persistent echocardiographic changes have been described. Decreased systolic function, elevated serum cardiac markers, no finding of vascular lesions, and a fourfold rise in antibody titers are consistent with myocarditis from RMSF.[90]

Figure 132-8. Late appearance of rash: Rocky Mountain spotted fever manifesting on lower extremity. (Courtesy of Theodore Woodward, MD.)

Interstitial pneumonitis and increased pulmonary capillary permeability may result from infection of the pulmonary capillaries with rickettsiae. Nonproductive cough and dyspnea secondary to pneumonitis are sometimes seen on presentation.[91] Chest radiographic abnormalities are identified in approximately 25% of patients. These abnormalities include interstitial infiltrates, patchy alveolar infiltrates, pleural effusions, and

cardiomegaly with pulmonary edema. Pulmonary consolidation is rare. In severe cases, progression to noncardiogenic pulmonary edema and ARDS may occur.

Neurologic Manifestations

Neurologic manifestations of RMSF range from mild headache and lethargy to seizures and coma. Acute disseminated encephalomyelitis has been described.[92] Headache, generally severe, is common, occurring in 50 to 90% of cases. Meningismus is present in 16 to 29% of patients. The CSF may be normal or show slight protein elevation and pleocytosis of both lymphocytes and polymorphonuclear cells (usually 8 to 35 cells/mL). CSF glucose level and opening pressure usually are normal. Resolution of eosinophilic meningitis during RMSF after appropriate antibiotic treatment has been reported. Fewer than 40% of patients have a positive CSF finding.

Cerebral thrombovasculitis may cause focal neurologic deficits, which usually are transient. Seizures can occur, especially during the acute phase of the illness. Generalized cerebral dysfunction ranging from lethargy to coma can occur secondary to systemic toxicity (fever, hypotension, hyponatremia) or to vasculitic lesions involving the central nervous system. Coma is a late finding in patients with severe disease and is seen in less than 10% of cases. Some reports have described patients who remain alert but are amnesic for their illness after recovery.

Other reported neurologic manifestations include transient deafness, tremor, rigidity, athetoid movements, paralysis, ataxia, opisthotonos, aphasia, and blindness.[79,82] Generally, neurologic signs abate without residua; permanent neurologic deficits are rare. Behavioral disturbances and learning disabilities have been reported after recovery from RMSF-associated coma in children.

Diagnostic Strategies

Most immediately available laboratory tests provide little help in diagnosing RMSF. Early in the course of the illness, the diagnosis is based primarily on clinical evidence, so epidemiologic features must be correlated with clinical signs and symptoms. The initial presentation of RMSF is similar to that of many acute febrile infectious diseases, and almost invariably a therapeutic decision must be made on clinical grounds alone, without the luxury of confirmatory laboratory evidence.[93] Abnormalities such as thrombocytopenia and hyponatremia may be detected by routine laboratory tests, but they are nonspecific and unhelpful diagnostically. Up to 30% of patients present with anemia.[94] A definitive diagnosis of RMSF requires positive results on one or more of several tests: serologic study, skin biopsy, or direct isolation and identification of the organism (Box 132-1).

Serology

Rickettsial infection can be confirmed by demonstrating antibody rise in paired sera. Even with the most sensitive serologic tests, however, elevations in antibody titers do not occur until approximately 5 to 7 days after the onset of initial symptoms. Accordingly, serodiagnosis is retrospective. It is achieved by comparing acute serum, which typically yields negative findings, with convalescent serum, which yields positive results for antibodies. The indirect immunofluorescence assay (IFA) generally is considered the reference standard for diagnosis of RMSF and is the test currently used by the CDC and most state public health laboratories. It has a high specificity and sensitivity (94%).[89] IFA can be used to detect either IgG or IgM antibodies. A RMSF latex agglutination test that reportedly gives a turnaround result in less than 24 hours is available in selected laboratories.[95] A recent study showed a 12% seroprevalence, with antibody titers of 1:64 or greater, in the pediatric population in the southeastern and south central regions of the United States.[87] Accordingly, clinical correlation with titers in these regions is critical.

Convalescent-stage blood samples are best obtained 2 to 3 weeks after the onset of clinical illness. Antibiotic therapy does not affect the time of appearance of antibodies or their ultimate titer if such treatment is begun several days after the onset of illness. However, if antibiotic therapy is initiated earlier in the course of the illness, the rise in titers can be delayed for 4 weeks or more. Under these circumstances, antibody titers should be tested again at 4 to 6 weeks after the onset of illness.

Skin Biopsy

Identification by immunofluorescent assay and immunoperoxidase staining of *R. rickettsii* in biopsy specimens of the skin rash from patients with suspected RMSF are the best rapid diagnostic tests currently available.[79] In experienced laboratories, the diagnosis of RMSF can be confirmed as soon as 4 hours after the specimen is obtained. The organisms can be detected as early as day 3 of clinical illness and as late as day 10. Unfortunately, this technique can be used only when a rash is visible for accurate localization of the biopsy site. Biopsy specimens generally are obtained with a 3-mm punch in the

BOX 132-1 Diagnostic Criteria for Rocky Mountain Spotted Fever

Laboratory Criteria

- Serologic evidence of a significant change in serum antibody titer reactive with *Rickettsia rickettsii* antigens between paired serum specimens, as measured by a standardized assay conducted in a commercial, state, or reference laboratory
- Demonstration of *R. rickettsii* antigen in a clinical specimen by immunohistochemical methods
- Detection of *R. rickettsii* DNA in a clinical specimen by the polymerase chain reaction (PCR) assay
- Isolation of *R. rickettsii* from a clinical specimen in cell culture

For confirmed cases, a significant change in titer must be determined by the testing laboratory; examples of commonly used measures of significant change include, but are not limited to, a fourfold or greater change in antibody titer as determined by indirect immunofluorescent antibody (IFA) assay or an equivalent change in optical density measured by enzyme-linked immunosorbent assay (EIA or ELISA).

Case Classification (CDC Case Definition, 2004)

Confirmed: The patient has a clinically compatible illness that is laboratory confirmed.

Probable: The patient has a clinically compatible illness and serologic evidence of antibody reactive with *R. rickettsii* in a single serum sample at a titer considered indicative of current or past infection (cutoff titers are determined by individual laboratories).

CDC, Centers for Disease Control and Prevention.

From Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever, ehrlichioses, and anaplasmosis—United States. MMWR Recomm Rep 55(RR-4):18, 2006.

center of the skin lesion. Immunofluorescent demonstration of rickettsiae in frozen sections of skin biopsies has a sensitivity of 70%. Results of immunohistochemical staining of tissues at autopsy were positive in all fatal cases in one study, whereas IFA results were negative in the majority of cases.[96] Failure to obtain a biopsy specimen of a rickettsial cutaneous lesion or failure to obtain sections through its center is associated with false-negative results. Treatment with antirickettsial drugs for 24 hours does not appreciably alter the sensitivity of the test; however, after 48 hours, rickettsiae are substantially reduced in numbers.

Isolation of Organism

For most pathogenic infections, the standard diagnostic criterion is isolation and identification of the etiologic organism from the patient's blood or tissues. This is seldom attempted in rickettsioses, however, because the isolation procedures are time-consuming, expensive, and hazardous to laboratory personnel. In addition, primary isolation of rickettsiae by inoculation in the yolk sac of a chick embryo usually fails because of the small number of organisms in the patient's blood.

Differential Considerations

Delayed diagnosis or misdiagnosis is the principal reason for the significant mortality associated with RMSF. Clinical diagnosis is difficult, especially early in the course of the illness, because of the nonspecific presentation. To prevent avoidable deaths, a diagnosis of RMSF must be considered in any patient with an unexplained febrile illness (with or without a rash and headache), even in the absence of a history of tick bite or travel to an area known to be endemic for the disease.[97] An atypical presentation or manifestation of RMSF also must be considered during the differential diagnosis, including (1) absence of a rash ("Rocky Mountain spotless fever") or late appearance of a rash, (2) predominant gastrointestinal features or abdominal pain suggestive of an acute condition in the abdomen, (3) cough and pulmonary congestion suggestive of pneumonitis, and (4) meningismus suggestive of viral meningitis.[81] A presumptive diagnosis must be made and specific therapy initiated well before specific confirmatory laboratory values are available.

A wide variety of other infections with similar exanthems can be confused with RMSF.[89] The most common include meningococcal infection, measles (rubeola) and atypical measles, gonococcemia, infectious mononucleosis, toxic shock syndrome, and enteroviral infections. Less common diseases include dengue, leptospirosis, murine typhus, and epidemic typhus.

Management

Treatment of RMSF consists of antibiotic therapy, supportive care, and possibly administration of steroids. An understanding of the underlying pathophysiologic changes and an appreciation of the systemic complications that can occur in the patient afflicted with RMSF are necessary for the formulation of a balanced therapeutic regimen. The course of the disease can be complicated by circulatory collapse, coma, renal failure, and electrolyte imbalances. Although often absent in the mildly ill patient, in whom antibiotic therapy alone usually suffices, these complications should be anticipated in the seriously ill patient, especially if first seen late in the disease course.[93]

The most important factor contributing to the persistent case-fatality rate of 5% is delayed administration of specific antibiotic therapy. Without appropriate treatment, the fatality rate rises to 25%.[89] For a select group of early-stage, mildly ill patients, outpatient therapy with oral antibiotics can be successful if the patient is reliable and close follow-up observation is arranged. More severely ill patients in whom the diagnosis is uncertain should be hospitalized for administration of intravenous antibiotics.

Antibiotics

Antibiotic therapy is most effective when initiated during the early stages of disease, coincident with the initial appearance of the rash. Although data from randomized clinical trials regarding antibiotic selection for RMSF are lacking, doxycycline is still widely regarded as the therapeutic agent of choice for most patients.[98] Chloramphenicol should be considered only for patients in whom the tetracyclines have caused significant adverse events and for pregnant women (except those who are near term). The recommended doses of doxycycline and chloramphenicol are summarized in Table 132-5.

Although previous treatment guidelines recommended avoiding doxycycline in children younger than 8 years of age, the American Academy of Pediatrics and the CDC currently recommend doxycycline therapy as the agent of choice for treatment of RMSF in children of all ages.[79,97,99] The risk of cosmetically perceptible tooth staining appears to be small for a single course of treatment and is subordinate to the potential lethality of this illness.[93]

The effectiveness of therapy depends on both the duration of therapy and the interval between the onset of illness and the initiation of therapy. Treatment should begin as early as possible and continue for 7 to 10 days or until the patient is afebrile for 2 to 5 days. Patients who are clinically ill should be hospitalized for parenteral antibiotic treatment. Response to treatment, as manifested by decreasing fever and subsiding rash, generally occurs 36 to 48 hours after beginning antibiotic therapy. Resistance to chloramphenicol or the tetracyclines has not been reported.[81] Penicillin, erythromycin, cephalosporins, aminoglycosides, clindamycin, and sulfonamides are ineffective against RMSF. In fact, empirical use of these agents for presumed bacterial infections may potentially permit progression of the illness.

Occasionally, secondary bacterial infection from the RMSF rash may occur. Although sulfonamides have recently become a mainstay for empirical treatment of MRSA for skin infections, the use of these agents should be avoided in RMSF patients, since their mechanism of inhibiting para-aminobenzoic acid may worsen the primary RMSF infection. The role

Table 132-5 Antibiotic Therapy for Rocky Mountain Spotted Fever*

PATIENT	DOXYCYCLINE† (ORAL/INTRAVENOUS)	CHLORAMPHENICOL‡ (ORAL/INTRAVENOUS)
Adult	100 mg bid	50–75 mg/kg/day, divided, q6h
Child (<45 kg)	2.2 mg/kg PO q12h	50–75 mg/kg/day, divided, q6h

*Continue treatment at least 3 days after fever subsides or until unequivocal clinical improvement is seen; minimum course, 5 to 7 days.
†Doxycycline should not be given to pregnant women.
‡Chloramphenicol should not be given to patients with thrombocytopenia; maximum of 1 g/day for children.
Data from Dantas-Torres F: Rocky Mountain spotted fever. Lancet Infect Dis 7:724, 2007; and Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever, ehrlichioses, and anaplasmosis—United States. MMWR Recomm Rep 55(RR-4):18, 2006.

of the new quinolones as potential replacements for doxycycline and chloramphenicol in the treatment of RMSF is as yet unproved. At present, no vaccine is available for RMSF.

Supportive Care

Major complications of RMSF, such as shock, congestive heart failure, disseminated intravascular coagulation, and ARDS, should be anticipated and standard supportive measures instituted when appropriate. Circulatory collapse is common in patients with severe illness and is a major contributor to morbidity and mortality in RMSF. Hypotension unresponsive to fluid administration may require the use of vasopressors such as dopamine. In the critically ill patient with widespread vasculitis, however, a delicate balance exists between maintenance of effective circulating volume and excessive leakage of fluids into the tissues, including the lungs and brain. Under these circumstances, the excessive administration of intravenous fluids can be catastrophic.[81] Isolation of the patient is unnecessary unless the diagnosis is still uncertain and other highly communicable illnesses such as meningococcemia or measles have not been excluded.

Corticosteroids

The use of steroids in RMSF is controversial and is not routinely recommended. However, these agents should be considered for severe cases of RMSF complicated by extensive vasculitis, encephalitis, and cerebral edema.[81] In these critically ill patients, short-term, high-dosage steroid therapy is recommended, along with concomitant specific antibiotic therapy.

Q FEVER

Perspective

Q fever was first described in 1937 in Australia as an occupational disease of abattoir workers and dairy farmers. Cattle, sheep, goats, and ticks are the primary reservoirs of the causative rickettsia, *Coxiella burnetii*, but many other species may be infected. The disease is endemic worldwide, although it is rare in Scandinavian countries. The Q fever rickettsiae are extremely resistant to desiccation and to physical and chemical agents and can survive for long periods in an inanimate environment.

Principles of Disease

Coxiella burnetii is extremely infectious for humans and animals; a single inhaled organism is sufficient to initiate infection in guinea pigs and probably in humans as well. Consequently, it is classified as a category B biologic warfare agent by the CDC and has been a nationally notifiable disease since 1999.[100] This organism's infectivity and estimated casualty rate have been judged to be comparable with those of anthrax. Humans most commonly are infected by inhalation of aerosolized particles from contaminated environments. Patients with Q fever rarely can recall a history of tick bite. The Rocky Mountain wood tick, *Dermacentor andersoni*, is the only currently known tick vector.

Clinical Features

The incubation period of Q fever ranges from 14 to 39 days, with an average of 20 days. Up to 60% of initial infections are asymptomatic.[101] The acute form of the disease includes clinical manifestations such as severe retrobulbar headache, a fever with temperatures to 40° C or higher, shaking chills, general malaise, myalgia, and chest pain. Although Q fever is widely regarded as primarily a respiratory disease, the reported incidence of pulmonary involvement varies, ranging from zero to 90%. The reasons for this reported variation are unclear, but explanations include geographic strain variation, plasmids that may regulate virulence, and the source, route, and dose of the agent. Hepatic involvement may be common, but liver dysfunction is usually minimal. Osteomyelitis in children, acute renal failure, and lymphocytic meningitis secondary to *C. burnetii* have been described.[102-104]

Q fever also may be a chronic infection, with or without an antecedent acute episode. Clinical syndromes with the chronic form of the disease include granulomatous hepatitis and culture-negative endocarditis. Endocarditis has been documented in up to 68% of patients with chronic Q fever, and the mortality rate for this group approaches 25%.[105] Q fever accounts for 3 to 5% of all cases of endocarditis.[106] Most patients with Q fever in whom endocarditis develops have a history of valvular heart disease, particularly affecting the aortic valve. These patients should be especially cognizant of the potential hazards of Q fever infection and should be restricted from certain at-risk occupational settings. Patients with aneurysms and vascular grafts also are at risk.

Human fetal demise and deaths have been attributed to *C. burnetii* infection.[107] Persons infected with human immunodeficiency virus (HIV) are at increased risk for contracting Q fever.[108]

Diagnostic Strategies

The diagnosis of Q fever should be suspected in any patient with a severe febrile illness without obvious cause, especially someone who has had recent contact with sheep, cattle, goats, or animal by-products. Because of the laboratory hazards associated with cultivation of Q fever rickettsiae, isolation of *C. burnetii* is not recommended for routine diagnosis. Rather, serologic studies such as IFA and ELISA are the preferred diagnostic tests, but the results are not identifiable until 2 to 3 weeks after the onset of illness.

Coxiella burnetii displays an antigenic phase variation: In patients with acute Q fever, phase II antibodies dominate the humoral immune response and are detectable by the second week of illness, whereas phase I antibodies are prominent only in patients with chronic Q fever. Confirmation of a Q fever case requires (1) a fourfold increase in IgG titers between acute and convalescent samples or the presence of IgM phase II antibodies, (2) a positive PCR test result, (3) culture of *C. burnetii* from a clinical specimen, or (4) positive immunostaining of the organism in tissue.[100] Measurement of IgA and IgG together has been useful in diagnosing endocarditis. The finding of granulomatous changes on bone marrow biopsy can be characteristic of Q fever in patients with osteomyelitis.[104]

Management

Treatment of uncomplicated acute Q fever is accomplished with doxycycline (200 mg once daily for 2 to 3 weeks). Acute disease with concomitant valvular heart disease is treated with doxycycline (200 mg once daily) plus hydroxychloroquine (600 mg once daily) for 1 year. Chronic sufferers should receive the same regimen for 1.5 to 3 years.[100,109] Combination therapy with both doxycycline and hydroxychloroquine has been shown to be effective for treatment of endocarditis in HIV-infected patients.[108] In mass casualty situations, prophylaxis is accomplished with 5 to 7 days of doxycycline.[110] Most acute Q fever infections resolve without treatment, but the risk of

chronic infection makes treatment advisable. The mortality rate is less than 1% in untreated patients and lower still in those treated with antibiotics. The prognosis is worse in those patients with protracted illness and hepatic involvement or endocarditis. Inactivated whole-cell vaccines for Q fever have proved effective for as long as 5 years.[111] Vaccination can afford considerable protection to slaughterhouse and dairy workers and others at risk.

THE EHRLICHIOSES

Perspective

There are currently two major forms of human ehrlichiosis in the United States: human monocytic ehrlichiosis (HME) and human granulocytic anaplasmosis (HGA), caused by the bacteria *Ehrlichia chaffeensis* and *Anaplasma phagocytophilum*, respectively. In 2001, restructuring of the *Ehrlichia* phylogenetic branches placed the previously known bacteria of human granulocytic ehrlichiosis (HGE) into the genus *Anaplasma*—hence the revised name. Both genera, *Ehrlichia* and *Anaplasma*, are now considered to be in the tribe Ehrlichiae, family Anaplasmataceae, but are still collectively referred to as being in the group of diseases called ehrlichioses.[112,113] Before 1986, *Ehrlichia sennetsu* was the only member of the genus of these organisms thought to infect humans, having been isolated in Japan in 1954 as the causative agent of sennetsu fever, a mononucleosis-like illness. A third species, *Ehrlichia ewingii*, has been shown to cause human disease in the United States.[114] HME was discovered in 1986 and HGA (previously HGE) in 1994. Both are identified as emerging diseases by the CDC and are nationally notifiable diseases, reportable through the appropriate state departments.

More than 1220 U.S. ehrlichiosis cases were reported between 1986 and 1997. From 1999 through 2001, the CDC collected a mean number of 81 and 190 cases, respectively, for HME and HGA. Seroprevalence rates up to 13% for *E. chaffeensis* in children in the southeast and south central states and 3 to 15% for *A. phagocytophilum* in adults in New York and Wisconsin[115] strongly suggest that these diseases are highly underdiagnosed or underreported (or both). Both diseases peak around June through August. High-risk populations are similar to those at high risk for Lyme disease, including those living in endemic areas or with frequent contact with wildlife or rural, wooded areas. A unique case series of ehrlichiosis in a group of golfers showed that those who spent more time in the rough and wooded areas searching for lost balls were at higher risk.[116] HME has been reported predominantly in the south central and southeastern United States; HGA mostly is found in the upper Midwest, New England, parts of the mid-Atlantic states, northern California, and many parts of Europe.[113,115,117]

Principles of Disease

The causative agents in the ehrlichioses are gram-negative, obligate intracellular rickettsia-like coccobacilli. Transmitted from the midgut and salivary glands of their tick vectors,[118] these organisms reside in specific circulating leukocytes in human and other mammalian hosts. Reservoirs include the white-tailed deer and the white-footed mouse. *E. canis* is the common pathogenic species in dogs.[119] The species *E. equina* has been isolated in California elk. HME, transmitted by the Lone Star tick, *Amblyomma americanum*, is caused by the organism *E. chaffeensis* (named for Fort Chaffee, Arkansas), which invades monocytes. *E. chaffeensis* has been isolated from *I. pacificus* ticks in California. *A. phagocytophilum* invades neutrophils (granulocytes), causing HGA, and in the United States is transmitted by the black-legged tick, *I. scapularis*, and its West Coast counterpart, the western black-legged tick, *I. pacificus*.[120] Deer, elk, and wild rodents are the main reservoirs for *Anaplasma*. Both ticks also are the vectors for Lyme disease. *A. phagocytophilum* has now been detected in significant numbers in various *Ixodes* human tick species in mainland Portugal, Italy, and Japan.[121-123] Two cases of HGA in Italy have been reported.[124]

Clinical Features

The clinical presentations of HME and HGA are similar, and for case management, it is not necessary to differentiate between the two illnesses. The average time to onset of symptoms (for HME) from tick discovery is 9 days but ranges from 0 to 34 days. More than 90% of patients with HME report a history of tick bite or tick exposure. Ehrlichiosis characteristically manifests with abrupt onset of fever, headache, myalgia, and shaking chills. Other, less frequent manifestations include nausea, vomiting, diarrhea, abdominal pain, cough, and confusion. Leukopenia, thrombocytopenia, and elevated liver function test values can be seen in 50 to 90% of patients.[125]

Rashes occur in approximately one third of patients with HME but in only 2 to 11% of those with HGA. In a small series of pediatric patients (average age, 7.4 years) with HME, a rash rate of 67% was found. A majority of these patients suffered permanent cognitive or other neurologic damage.[126]

Ehrlichiosis (HME) also has been associated with optic neuritis.[127] ARDS, meningitis, pancarditis, renal failure, and disseminated intravascular coagulation have been associated with the ehrlichioses. Case-fatality rates vary between studies, but range between 0.5% and 3% for both diseases, with HGA usually reported as the lower of the two. Approximately 45% of patients with HGA require hospitalization, although almost all recover without residual problems.

Diagnostic Strategies

For both HME and HGA, the initial diagnosis is based largely on clinical presentation. With most tests, the diagnosis will be retrospective, or results rarely are available immediately. The most common mode of diagnosis is confirmation of acute and convalescent antibodies with IFA. Enzyme immunoassay and confirmatory tests with Western blot have been developed. PCR testing for DNA fragments, although not readily available in most hospitals, probably is most reliable in the acute phase of illness (at 1 week after onset of symptoms). Diagnostic serologic testing is available at the CDC through state health departments.[128]

Laboratory criteria required in the CDC's 2000 case definition to establish the presence of either HME or HGA include detection of either *E. chaffeensis* or *A. phagocytophilum*, respectively, through the use of the following diagnostic tests: (1) fourfold change in antibody titer to the organism antigen by IFA in paired serum samples, (2) positive result on PCR assay and confirmation of organism-specific DNA, (3) identification of morulae in leukocytes and a positive titer to the organism antigen, (4) immunostaining of organism antigen in a biopsy or autopsy specimen, or (5) culture of the organism from a clinical specimen. A designation of "probable disease" requires a single positive IFA titer, based on cutoff values from the performing laboratory, or the presence of morulae within infected cells. All tests require compatible clinical findings.[128,129] Most patients with clinical manifestations have IFA titers between 1:160 and 1:1280 at presentation.[130]

Cytopenia and abnormal liver function usually resolve after the acute phase of illness by 14 to 28 days. Microscopic identification of mulberry-like clusters, called morulae, inside leukocytes on peripheral blood smears is helpful, but this finding usually has disappeared after the first week of illness with HGA, especially if the patient has been treated with doxycycline. Cultures take up to 2 weeks to grow the organisms.

Management

Tetracycline, which has been shown to be effective in cases of canine ehrlichiosis, is also effective in cases of human ehrlichiosis. Doxycycline (100 mg twice a day) and tetracycline regimens for 7 to 14 days are curative. Most patients respond rapidly after treatment is begun, and fever subsides within 24 to 48 hours. For pediatric patients, the concern for tooth staining is obvious, although it has been argued that most of this effect is seen only with multiple dosing periods. Rifampin as an alternative has been shown to be effective in children with human ehrlichiosis.[126] Data supporting the use of chloramphenicol are still inconclusive. The same ticks that transmit HGA (*Ixodes* species) also are responsible for Lyme disease and babesiosis. Each disease entity requires a full diagnostic workup, because amoxicillin treats Lyme disease but not HGA or babesiosis, and doxycycline alone does not treat babesiosis. Failure of fever to resolve beyond 6 or 7 days of treatment of a suspected tick-borne disease should heighten suspicion of an alternative disease organism.[5]

BABESIOSIS

Perspective

Babesiosis is a tick-borne, malaria-like, acute febrile illness caused by intraerythrocytic protozoal parasites of the genus *Babesia*. Babesiosis has long been recognized as an important veterinary disease and probably was known in ancient times; in fact, it has been proposed that the fifth plague described in the Book of Exodus was actually babesiosis.

The first human cases of babesiosis were reported in Montana in 1904; investigators seeking the cause of RMSF examined blood smears from local inhabitants and described parasitic forms now known to be characteristic of *Babesia*. Since the late 1950s, several widely scattered cases (mostly in Europe) of human babesiosis have been reported in splenectomized persons. *Babesia divergens*, a species primarily infecting cattle, is the most common agent reported in Europe, but other species have been implicated as well, including *Babesia bovis*, *Babesia equi*, and a single case of *Babesia caucasia* infection. Two strains, WA-1, related to a canine pathogen *B. gibsoni*, and MO1, related to *B. divergens*, also have been found to cause disease in humans.[131] In all of the reported cases, the course was fulminant and the disease usually fatal.

Since the late 1960s, more than 350 cases have been documented in the United States. Almost all of these cases were caused by *Babesia microti*, a rodent parasite, and occurred in the coastal regions of southern New England, where *B. microti* is endemic. New Jersey and the eastern part of Long Island recently have been found to be endemic with babesiosis as well.[132,133] Babesiosis also has been reported in Maryland, Virginia, Georgia, Wisconsin, Minnesota, California, and Washington. These cases differ from the European cases in that most (approximately 80%) have occurred in persons with intact spleens. Up to now, significant morbidity has been low in the United States despite lack of specific therapy. However, the status of the disease in Long Island may cause more significant morbidity rates in U.S. endemic areas than was previously thought.[133] Asplenic persons, the elderly, and otherwise immunosuppressed patients usually have more severe disease.

Principles of Disease

B. microti is associated with deer and mice, rather than cattle. The ecology of *B. microti* is similar to that of *B. burgdorferi*, the etiologic agent of Lyme disease, with the same major vector, *I. scapularis*, and the same mammalian reservoirs: white-footed mice, which host the larval and nymphal stages of the tick, and white-tailed deer, which host the adult ticks.

Human babesiosis results from accidental human intrusion on the natural cycle of infection. The nymphal form of the *Ixodes* tick most commonly transmits the disease to humans, although babesiosis also can be transmitted by the adult tick. *I. scapularis* nymphs measure only 1 to 2 mm long and thus are easily overlooked by the patient (see Fig. 132-4). In more than one half of all cases of babesiosis, patients cannot recall tick exposure. As is true for other tick-borne illnesses, the peak incidence of babesiosis is between May and August, coinciding with the nymphal feeding period and also the time of maximal human exposure in endemic areas. Babesiosis acquired through blood transfusion is well documented.

Clinical Features

Babesiosis has an incubation period of 1 to 4 weeks after tick exposure. A nonspecific flulike illness, with fever, chills, headache, fatigue, and anorexia, is characteristic. Less common manifestations are nausea, diaphoresis, depression, photophobia, myalgias, arthralgias, dark urine, emotional lability, and hyperesthesias. Unlike in Lyme disease, rash is not a feature of this illness; however, erythema figuratum, a widespread exanthema with well-established annular lesions, has been associated with septic babesiosis.[134] Physical examination usually reveals normal findings, except for fever, which typically is present, and splenomegaly, which occurs in some patients. Meningeal signs are absent. More severe disease occurs in splenectomized patients[135]; severe hemolytic anemia, hemoglobinuria, jaundice, renal insufficiency, ARDS, and disseminated intravascular coagulation can be seen in these cases.[133] In a review of data for 139 patients from New York State, the mortality rate approached 6.5%.[136] Some patients with babesiosis are only mildly ill, and asymptomatic infection also may occur, as demonstrated by serologic surveys in endemic areas. The diagnosis of babesiosis should be considered in any febrile patient from an endemic area during the tick season and should be part of the differential diagnosis for post-transfusion infections.

Diagnostic Strategies

The diagnosis may be established through microscopy, antibody detection through IFA staining, or PCR assay. Microscopic examination is done with thick and thin Giemsa-stained blood smears. Characteristic intraerythrocytic forms (pyriform, ring, tetrad) may be present. Babesiosis has been known to be misdiagnosed as malaria. The latter may be excluded by the absence of intracellular pigment granules, schizonts, and gametocytes. The presence of parasites in budding tetrad formation, resembling a Maltese cross, is more suggestive of babesiosis, although this finding is uncommon. Because parasitemia may vary, in suspected cases, serial smears over the course of several days may be necessary. An immunohistochemical assay has been developed that further allows for easier microscopic differentiation between babesiosis and malarial organisms.[137]

The diagnosis can be confirmed by serologic studies. IFA antibody to *B. microti* is available through the CDC, and titers usually rise to 1:1024 or greater within the first few weeks of illness. IgM-indirect IFA is 91% sensitive and 99% specific in acute babesiosis.[138] Serologic tests for Lyme disease, which shares a common tick vector with babesiosis, also should be performed; concurrent Lyme disease has been reported in up to 50% of cases of babesiosis.[132] PCR testing also is now available and is thought to be highly sensitive and specific.[139]

Parasitemia observed at 1 to 4 weeks after inoculation of blood from infected patients into gerbils or hamsters supports the diagnosis. Other nonspecific laboratory findings include mild to moderate hemolytic anemia, which is present in most patients, and resultant mild elevations in bilirubin and serum lactate dehydrogenase.

Management

Patients who have not undergone splenectomy generally recover without specific therapy, although prolonged malaise and fatigue are common. In patients with severe disease and in those who have had splenectomies, the combination of clindamycin (1.2 g twice daily IV or 600 mg three times a day PO) plus quinine (650 mg three times a day PO) has been shown to be effective and is currently the treatment of choice. An alternative regimen that may be better tolerated, especially by children and infants, consists of atovaquone (750 mg twice daily PO) plus azithromycin (600 mg once followed by 250 mg once a day PO), because up to 25% of patients may have an adverse effect from quinine. Pediatric doses need to be adjusted accordingly. Therapy should be continued for a minimum of 7 to 10 days.[140-142] Other antimalarial drugs such as chloroquine and quinacrine are not effective. Fulminantly ill patients with marked degrees of parasitemia and hemolysis have benefited from exchange transfusion.[133] Effective live vaccines have been developed for bovine babesiosis but not yet for human disease.[143]

COLORADO TICK FEVER

Perspective

Endemic to the Rocky Mountain area, Colorado tick fever is an acute tick-borne viral infection characterized by headache, back pain, biphasic febrile course, and leukopenia. The etiologic agent of Colorado tick fever is a small RNA virus of the genus *Orbivirus*, family Reoviridae. It is one of more than 500 viruses in the heterogeneous group of arthropod-borne viruses (arboviruses).[144] Colorado tick fever has a sharply defined endemic zone encompassing mountainous and highland areas, from an altitude of approximately 4000 to more than 10,000 feet, in the Canadian provinces of British Columbia and Alberta and in at least 11 western states (California, Colorado, Idaho, Montana, Nevada, New Mexico, Oregon, South Dakota, Utah, Washington, and Wyoming).[145] The largest number of cases has been reported in Colorado. The distribution of the virus coincides with that of its principal tick vector, *Dermacentor andersoni*, the Rocky Mountain wood tick. Although RMSF is transmitted by the same vector, that disease is far less common in Colorado. The cases of RMSF are outnumbered at least 20-fold by cases of Colorado tick fever.

Principles of Disease

The Colorado tick fever virus has been isolated from at least eight species of ticks, but *D. andersoni* is the only proven vector for humans. The tick is a significant reservoir for the virus because trans-stadial transmission (from larva to nymph to adult) of virus occurs, and the tick remains infected and infectious for life (up to 3 years). The primary vertebrate host species for Colorado tick fever virus maintenance are the chipmunk, *Tamias minimus*, and the golden-mantled ground squirrel, *Spermophilus lateralis*; many other vertebrate hosts have been identified as well, including a species of porcupine in Colorado in Rocky Mountain National Park. Larval and nymphal stages of *D. andersoni* ticks are responsible for transmission of Colorado tick fever virus among rodents, and overwintering of the virus is accomplished by nymphal and adult *D. andersoni*. Only adult ticks transmit Colorado tick fever virus to humans.

Several hundred cases per year are reported in the United States.[145] The actual incidence undoubtedly is much higher, because many cases are diagnosed as nonspecific "viral illness," and other cases may be very mild or entirely subclinical. Human susceptibility to Colorado tick fever is universal, but it occurs most commonly in young men, reflecting greater occupational and recreational tick exposure.

Clinical Features

After an incubation period of approximately 3 to 5 days (range, 0 to 14 days), a moderate to severe flulike illness occurs abruptly, with signs and symptoms similar to those in the early stage of RMSF. Fever, chills, headache, myalgia, lethargy, anorexia, and nausea are common; vomiting and abdominal pain occasionally are reported. Early physical findings are nonspecific. A macular or maculopapular rash has been reported in 5 to 12% of patients, but unlike the rash of RMSF, the rash of Colorado tick fever is not a prominent feature of the illness.

A distinct feature of the illness is a biphasic course that occurs in approximately 50% of patients, causing a characteristic "saddleback" fever curve. Initial symptoms resolve after 2 to 3 days, and the patient feels relatively well for 1 or 2 days, after which the fever, headache, and myalgias return. The second phase may be more intense than the first phase and generally lasts 2 to 4 days. There may even be a third febrile period. Alternatively, a single prolonged febrile illness may occur. Recovery from Colorado tick fever usually occurs within 2 weeks, but convalescence can be prolonged, especially in patients older than 30 years of age.

Colorado tick fever is a self-limited disease, and virtually all patients recover without sequelae. Reports of severe complications such as meningoencephalitis and hemorrhagic diathesis have been limited to children. Only a few fatal cases have been recorded.[144]

Diagnostic Strategies

The peripheral leukocyte count often is depressed during the acute phase of illness to as low as 1000/μL, with a relative lymphocytosis. Transient thrombocytopenia can accompany the leukopenia and, less often, a mild anemia can occur. These hematologic abnormalities normalize during convalescence, but persistence of the virus in red blood cells causes a prolonged viremia even when clinical recovery is complete. Transfusion-acquired infection has been reported and is caused by this persistent viremia in asymptomatic blood donors. No one should donate blood for at least 6 months after recovery from Colorado tick fever.[144]

The diagnosis of Colorado tick fever can be confirmed by serologic testing (IFA, neutralizing antibody, complement fixation, enzyme immunoassay) of acute and convalescent samples, but serologic study is of little help early on because of the slow rise of titers.[146] The most rapid confirmation of Colorado tick

fever, with corresponding elimination of concern about possible RMSF, is provided by direct immunofluorescent staining of virus in red blood cells in peripheral blood smears. PCR testing is now available for more rapid diagnosis.[147]

Management

Treatment for Colorado tick fever is supportive only. Most patients do not require hospitalization, but if RMSF remains a diagnostic possibility, initial treatment with tetracycline or chloramphenicol and a period of observation are necessary until the diagnosis of RMSF can be ruled out. Ribavirin has been suggested as a possible therapeutic agent but has not yet been tested.[147]

TICK PARALYSIS

Perspective

Tick paralysis occurs when an adult female tick attaches to a host and releases a neurotoxin that can produce cerebellar dysfunction or an ascending paralysis. Tick paralysis was recognized as early as the beginning of the 19th century. Hovell, while traveling through Australia, wrote in 1824 of "the small insect called the tick, which buries itself in the flesh, and would in the end destroy either human or beast if not removed in time."[148]

Tick paralysis has been reported worldwide, but most cases occur in the southeastern and northwestern regions of the United States, western Canada, and Australia. Cases have been reported to occur in clusters.[149] Forty-three species of ticks have been found to cause tick paralysis in humans, other mammals, or birds. Most cases in North America and Canada are caused by *Dermacentor andersoni* (Rocky Mountain wood tick) and *D. variabilis* (American dog tick); species responsible for paralysis cases that also are associated with other tick-borne diseases include *Amblyomma americanum* (Lone Star tick), *Ixodes scapularis* (black-legged tick), and *I. pacificus* (western black-legged tick)[149-151]; in Australia, *Ixodes holocyclus* is primarily associated with this disorder. Family Argasidae ticks (soft ticks) also have been implicated. Tick paralysis usually occurs in the spring and summer months, and most reported cases are in children, primarily girls, probably because ticks are more easily concealed in longer hair. Among adults, however, more men than women acquire the disease.[152]

Principles of Disease

Tick paralysis is thought to be caused by a toxin secreted from the salivary glands of the tick during a blood meal.[151] The toxin, ixobotoxin, affects sodium flux across axonal membranes without affecting the neuromuscular junction itself.[153] The mechanism of action of the toxin is poorly understood, but it appears to produce a conduction block in the peripheral branches of motor fibers, resulting in a failure of release of acetylcholine at the neuromuscular junction. Electrophysiologic studies have confirmed a rapid reversal of significant impairment of motor nerve terminal function after tick removal, indicating that the disturbance is not a result of a neuromuscular junction defect.[154] Possible central sites of action of the toxin have been postulated to explain cases in which the clinical picture is dominated by cerebellar dysfunction.

Clinical Features

Onset of symptoms usually occurs from 4 to 7 days after the tick attaches. Initial manifestations include restlessness and irritability, followed by ascending flaccid paralysis, acute ataxia, or a combination of the two. Deep tendon reflexes are almost invariably lost. These signs and symptoms can progress rapidly over a few days to bulbar involvement, respiratory paralysis, and ultimately death if the tick is not detected and removed.

The ascending nature of tick paralysis has been noted in most descriptions; however, ataxia and associated cerebellar abnormalities in the absence of muscle weakness may be seen. Thus, tick paralysis may sometimes manifest as "tick ataxia." Isolated facial paralysis has been reported in patients with ticks embedded behind the ear. Fever, other systemic symptoms, and sensory deficits are unusual. Concomitant infection with Colorado tick fever has been reported.[155]

Diagnostic Strategies

No diagnostic tests to confirm tick paralysis are available other than the combination of the clinical scenario, the presence of a tick, and improvement after its removal. The Tensilon test yields a negative result in patients with this condition, and CSF is normal.[154]

Differential Considerations

Tick paralysis should be considered in the differential diagnosis for any patient thought to have Guillain-Barré syndrome, Eaton-Lambert syndrome, myasthenia gravis, poliomyelitis, botulism, diphtheritic polyneuropathy, or any disease with an acute onset of ascending flaccid paralysis or acute ataxia.

Management

Treatment in the United States consists simply of removing the tick; improvement generally is seen within a few hours and complete recovery within 48 hours. Supportive care, including mechanical ventilation, may be necessary. The mortality rate is approximately 10%; nearly all patients who die are children. The recommended procedure for the removal of any tick (including ticks causing tick paralysis) is summarized in Box 132-2. Traditional methods such as burning, forceful removal, or application of petroleum, viscous lidocaine, or gasoline are not consistently successful and do not guarantee removal of mouthparts, where the salivary glands and toxin may remain. Retained mouthparts also may cause infection.

BOX 132-2 RECOMMENDED METHOD FOR TICK REMOVAL

1. Remove an embedded tick by grasping it with blunt forceps or tweezers as close to the point of attachment as possible.
2. Do not use bare fingers to remove ticks from animals or humans; when tweezers are unavailable, fingers should be shielded with a tissue, paper towel, or rubber glove.
3. Apply gentle, steady, upward traction with the forceps; do not twist or jerk the tick. Avoid squeezing or crushing the tick.
4. Do not handle the tick with bare hands. After removing the tick, thoroughly disinfect the bite site and wash hands with soap and water.
5. Dispose of ticks by placing them in a container of alcohol or flushing them down the toilet.

Modified from Needham GR: Evaluation of five popular methods for tick removal. Pediatrics 75:997, 1985.

Tick paralysis in Australia often is more devastating than in the United States. Symptoms and signs of illness caused by the Australian tick, *I. holocyclus*, do not resolve and often worsen after tick removal. Hyperimmune serum is available in Australia and often is needed because symptoms may worsen up to 48 hours after removal.

Prophylaxis with Insect Repellents

Insect repellents have long been used to prevent mosquito bites. With recent increased public awareness of and concern about tick-borne illness, especially Lyme disease, skin and clothing repellents are now also being marketed for tick protection.

The most effective topical insect repellent known is *N*,*N*-diethyl-*m*-toluamide, commonly called DEET. A long-acting DEET formulation (U.S. Army Extended Duration Topical Insect and Arthropod Repellent [EDTIAR]), available in the United States as Ultrathon (3M), provides protection for 6 to 12 hours. Despite some earlier concerns, toxic and allergic reactions to DEET have been uncommon, and serious adverse effects are rare. Used as directed, concentrations up to 50% appear to be safe even in young children, although toxic encephalopathy can occur.[156]

Permethrin, actually a contact insecticide rather than a repellent, can be used as a clothing spray for protection against ticks. Applied to the clothing as an aerosol, it is nonstaining, nearly odorless, and resistant to degradation by light, heat, or immersion in water. Permethrin is toxic to the nervous system of insects, but in mammals it is poorly absorbed and rapidly inactivated. Reported adverse effects have been limited to the skin and are uncommon.

Both topical DEET and clothing impregnated with permethrin have been shown to be effective in field trials when used alone. Wearing protective clothing treated with permethrin, in addition to using DEET on exposed skin, provides the greatest degree of protection against tick bites.[156]

KEY CONCEPTS

- Tick-borne illnesses frequently are misdiagnosed as viral or bacterial infections. Early diagnosis can be facilitated by considering these diagnoses in patients who live in or recently have traveled to endemic areas and by routinely asking for a history of recent tick or insect bites in patients who present with febrile illnesses.
- Lyme disease should be suspected in patients who present with signs of a viral illness, monoarticular arthritis, meningitis, multiple neurologic abnormalities, or heart block. Diagnosis can be confirmed with serologic testing of acute and convalescent serum samples. Normal physiologic changes from bites should not be confused with erythema migrans. A significant amount of time of attachment is required for transmission of disease.
- Relapsing fever should be suspected in patients who present with recurrent viral-like illness associated with high fever. The diagnosis can be confirmed by identifying spirochetes on a blood smear obtained during a period of rising temperature.
- Ulceroglandular tularemia should be suspected in patients with slow-healing extremity ulcers associated with large lesions of regional adenopathy (buboes). The diagnosis can be confirmed with serologic testing.
- RMSF should be considered in patients who present with an unexplained febrile illness, even in the absence of a rash or known tick exposure. Delayed diagnosis and late initiation of specific antirickettsial therapy may lead to a fatal outcome. Treatment never should be delayed pending laboratory diagnosis.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 133 Tuberculosis

Peter E. Sokolove and Robert W. Derlet

PERSPECTIVE

History and Epidemiology

Tuberculosis (TB) has plagued humankind throughout recorded history. Clear evidence of tuberculous lesions of bone has been found in Egyptian mummified human remains that date to 3400 BCE.[1] The presence of TB also has been microscopically confirmed in the mummies of small children, one from the dynastic period of Egyptian history and one from pre-Columbian southern Peru around 700 CE.[1-3]

Hippocrates (460 to 370 BCE) is credited for providing the first accurate clinical description of TB. He coined the term *phthisis* ("a melting or wasting away") to describe the wasting character of the disease, which he noted also was associated with fever and incurable lung ulcerations.[4] TB became a major public health problem during the Industrial Revolution. The corresponding urbanization of European cities led to overcrowding, widespread poverty, and poor hygienic conditions that were ideal for the epidemic spread of the disease throughout western Europe from the early 1600s through the 1800s.[5] Approximately 25% of all adult deaths in Europe were caused by TB during this period, and in 1861 Oliver Wendell Holmes named it the "white plague."[1] TB gradually became a global epidemic as Europeans colonized North America and explored and colonized other parts of the world.[5,6] The TB epidemic peaked in western Europe in the early 1800s and by 1900 had peaked in the Americas. Globally, the disease still has not reached a peak in some developing countries in Africa and Asia.[7]

Laënnec, who invented the stethoscope in 1816, accurately described the evolution of TB, from the small initial tubercle through all of its pathologic manifestations, in 1819.[4] Twenty years later, Schönlein also recognized the tubercle as the fundamental anatomic lesion and named the disease *tuberculosis*.[8] Koch identified the tubercle bacillus in 1882, and Roentgen's discovery of x-rays in 1895 greatly improved the ability to diagnose TB early in the disease course.[1,4]

In 1892, Biggs instituted a comprehensive program of TB control in New York City that included public education, systemic surveillance, isolation of patients, nursing follow-up, improved sanitation, and free sputum testing.[8,9] These types of programs and the subsequent introduction of the antituberculosis drugs led to an impressive decline in the incidence of TB throughout the 20th century. Between 1953 and 1985, TB cases decreased by an average of 5.8% per year.[10] As recently as the 1970s, U.S. health officials believed that TB was well under control and could soon be eradicated.[11] Unfortunately, as the incidence and perceived importance of the disease decreased, so did the public health programs to control it.[12] The premature decline in government support for TB control programs made it impossible to manage the disease appropriately. The decline of the infrastructure dedicated to TB control during the late 1980s and early 1990s was compounded by new problems including the human immunodeficiency virus (HIV)–acquired immunodeficiency syndrome (AIDS) epidemic, increasing immigration from countries with high TB prevalence, increasing occurrence of TB in institutional living settings, escalating poverty, substance abuse, homelessness, and urban overcrowding. These factors contributed to a resurgence of TB in the United States from 1986 through 1992 and to the emergence of drug-resistant strains of *Mycobacterium tuberculosis* (MTB).[12]

Worldwide, the disease had become so widespread that in 1993 the World Health Organization declared TB a global emergency. TB is currently the world's second leading infectious cause of death, and one third of the world's population has been infected by TB.[13] Each year more than 8 million people acquire active TB infection and nearly 2 million die from the disease.[14]

Elderly persons who harbor dormant infection that is reactivated constitute an important reservoir of MTB in the United States.[15] Debilitating disease or immunosenescence may predispose the affected person to reactivation. Nursing homes are particularly vulnerable to TB outbreaks because reactivation of disease in remotely infected persons may be followed by epidemic spread among the many susceptible hosts living in close quarters.

Immigration from endemic countries is another major factor.[6,13] As reported in 2002, a majority of U.S. TB cases occur among foreign-born persons.[16] The largest numbers of people with TB originate from Mexico, the Philippines, Vietnam, India, and China, accounting for more than one half of all TB cases among foreign-born persons.[17] Homelessness also has contributed to the spread of TB in major urban centers. Homelessness often is associated with conditions that decrease resistance to TB, such as malnutrition, alcoholism, or substance abuse. MTB infection in the homeless population may quickly progress to active TB infection.[18]

The HIV/AIDS epidemic has had the greatest impact on the reemergence of TB in the United States.[19] The pandemic of HIV-related TB has led to an increase in TB cases among non–HIV-infected people owing to the higher numbers of

source cases in the community.[20] The rate of TB among patients who are HIV-infected and TB skin test–positive is approximately 200 to 800 times higher than that estimated for the U.S. population overall.[21]

The reemergence of TB also has affected children. Between 1962 and the mid-1980s, the rates of childhood TB in the United States decreased an average of 6% a year.[22,23] This trend has reversed along with the young urban adult trend, and the number of cases reported in children 4 years of age or younger increased 36% from 1985 through 1992.[10] This increase reflected ongoing transmission of TB in the community, because TB in young children must result from recent infection.[10]

After a 32-year decline, the number of TB cases in the United States increased 20% between 1986 and 1992. By 1992, roughly 14% more cases (26,673) were reported over the 1985 nadir. This trend, however, reversed in 1993, largely owing to the mobilization of new federal resources provided to the states for TB control and prevention.[12] The number of reported cases during 1996 decreased in each age group, as well as in all ethnic groups.[24] The number of reported cases in the United States during 2006 (13,767) represents a 48% decrease from 1992 and reflects the 14th consecutive year of decline.[17] Although the rapid resurgence of TB appears to be subsiding in the United States, there is no justification for complacency. Rates of newly diagnosed TB are still significant in different regions of the country and among certain demographic groups.[17] The populations most likely to acquire and transmit TB infection commonly are seen by emergency physicians, who then necessarily play a key role in identification, prevention, and treatment.

Etiology

One microorganism, *M. tuberculosis*, causes human TB in nearly all cases. Humans constitute the sole known reservoir for MTB. Two other pathogenic mycobacteria, *Mycobacterium bovis* and *Mycobacterium africanum*, have on rare occasions been implicated as causing TB. *M. bovis* is transmitted by drinking milk from diseased cows, but because pasteurization of milk is now common, it has become a relatively unusual cause of TB. *M. africanum* also is a rare cause of human TB. This mycobacterium is thought to be intermediate in pathogenicity between *M. tuberculosis* and *M. bovis* and has been documented to cause human TB, predominantly in Africa.[25] Worldwide, MTB remains the major causative agent.

MTB is an intracellular, aerobic, nonmotile, non–spore-forming bacillus with a waxy lipid coat.[25] This coating makes MTB resistant to decolorization with acid alcohol after staining—hence the term *acid-fast bacillus* (AFB). MTB grows slowly: Its generation time is 15 to 20 hours, compared with less than 1 hour for some common bacteria; cultures take 4 to 6 weeks to grow on standard solid media.[25]

MTB produces neither endotoxins nor exotoxins. Its cell components are immunoreactive; some are immunosuppressive, and others are the agents of granuloma formation, macrophage activation, host toxicity, and modification of the immune response.[26]

■ PRINCIPLES OF DISEASE

Transmission

TB is transmitted primarily by the respiratory route; transmission by other routes, such as direct inoculation, occurs primarily among health care workers. Patients with active disease expel MTB in liquid droplets during coughing, sneezing, and vocalizing. A single cough or 5 minutes of talking can produce 3000 infectious droplets, and sneezing can produce an even higher number.[6] The droplets rapidly evaporate, and the desiccated bacilli circulate air-borne for prolonged periods. These infective particles, or droplet nuclei, measure 1 to 5 μm in diameter, contain one to three tubercle bacilli, and when inhaled can travel to the distal alveoli.

The susceptible host may become infected when only a few of the droplet nuclei are inhaled. Fomites are not important in the transmission of the disease, and patients' rooms, eating utensils, and bed clothes do not require special decontamination procedures.[25] Because the infectious droplet nuclei are airborne, exchanging contaminated air is the most important environmental control. In addition, MTB is susceptible to ultraviolet radiation, and transmission rarely occurs outdoors because of the dilution of infectious particles and exposure to ultraviolet radiation.[27]

The risk for TB transmission increases when source patients have airway and cavitary disease. Infectivity correlates with the number of organisms seen on sputum smear, the extent of pulmonary disease, and the frequency of cough. After institution of proper chemotherapy (with regimens comprising three or four drugs) for 2 weeks, patients with initially AFB-negative sputum smears can be considered noncontagious. However, after 2 weeks of treatment, patients who initially were smear-positive may still have viable MTB detectable in their post-treatment sputum cultures, and patients with extensive disease may still have AFB detectable on their post-treatment sputum smears. The latter two groups generally should still be considered contagious.[28] There is currently no clear epidemiologic evidence to define better the contagiousness of patients after they are started with effective therapy.[28] The Centers for Disease Control and Prevention (CDC) has published guidelines requiring presence of three negative smears on different days as the criterion for removing a patient from respiratory isolation, but debate is ongoing regarding this recommendation.[29,30]

Extrapulmonary TB also may be infectious but only if in the oral cavity or an open skin lesion.[29] Transmission of MTB to health care workers caring for patients with skin ulcers and draining tuberculous abscesses has been reported.[31] Irrigation of the abscess may aerosolize the bacilli, forming infectious droplet nuclei.[32]

Pathogenesis

When infectious droplet nuclei are inhaled, the airflow through the bronchial tree tends to deposit them in the midlung zone on the respiratory surface of the alveoli.[25] The deposition launches a complex series of immunologic events. Dannenberg has organized the complex pathogenesis of TB into four stages.[33]

Stage 1

The first stage begins when an alveolar macrophage phagocytoses the recently inhaled bacillus. A macrophage from a resistant host can immediately destroy a less virulent bacillus. In these cases, no tuberculous infection develops and the process ends. If a virulent bacillus can overcome a macrophage's microbicidal capability, the infection may progress to the next stage.

Stage 2

When the alveolar macrophage is unable to destroy the inhaled tubercle bacilli, the bacilli replicate until the macrophage

lyses. Circulating monocytes are attracted to the site of infection by the released bacilli, cellular debris, and various chemotactic factors. The monocytes differentiate into macrophages and ingest the free bacilli. Initially, these new macrophages are not activated and cannot destroy or inhibit the mycobacteria. The bacilli multiply logarithmically within macrophages and accumulate at the primary focus of infection, now called a tubercle.[34] The infected macrophages also may be transported through lymphatics to regional lymph nodes, from which they can reach the bloodstream, with subsequent spread.

During this lymphohematogenous dissemination, the pathogens tend to distribute preferentially to lymph nodes, kidney, epiphyses of long bones, vertebral bodies, meningeal areas, and the apical posterior areas of the lungs.[25] These sites may be favored because of a high oxygen tension. Some investigators, however, believe that the lung apices are favored because of impaired clearance mechanisms from poor lymph flow.[25]

Stage 3

The third stage of TB begins 2 to 3 weeks after the initial infection, with development of the immune response that terminates the unimpeded growth of MTB.[33] Cell-mediated immunity occurs through $CD4^+$ helper T cells.[35] When the T cell encounters mycobacterial antigens, it is activated and produces an expanded population of specific T cells. These T cells secrete cytokines (e.g., interferon-γ [IFN-γ], tumor necrosis factor) that attract and activate monocyte-macrophages. Once activated, the macrophages, containing previously ingested mycobacteria and their progeny, kill the bacilli. The destruction of the mycobacteria is associated with the formation of epithelioid cell granulomas and clearance of the organisms.[34]

Delayed-type hypersensitivity is mediated by cytotoxic $CD8^+$ suppressor T cells.[35] The cytotoxic cells kill nonactivated macrophages laden with mycobacteria and thus cause local tissue destruction as well. Delayed-type hypersensitivity results in the formation of caseating necrotic granulomas. This stops bacillary growth; mycobacteria, now extracellular, cannot multiply in this acidic, anoxic, extracellular environment.[34] Tubercle bacilli can survive dormant in this solid caseous material for years.[34] The host's resistance determines whether the disease remains dormant or immediately progresses to active disease.

In the immunocompetent host with strong cell-mediated immunity, the primary lesion is effectively walled off by epithelioid cells. Eventually, the caseous center inspissates, and the disease is arrested, often for a lifetime.[33] Similarly, at sites of lymphohematogenous spread, the mycobacteria are quickly destroyed, with little caseous necrosis, by a rapid immunologic response.[33] The rapid destruction of the mycobacteria by cell-mediated immunity terminates the infectious process, and the only evidence of the infection is conversion to a positive tuberculin (purified protein derivative [PPD]) skin test result.[25]

This sequence of events from stage 1 to stage 3 represents the pathogenesis of primary TB in the immunocompetent patient.[35] In most cases, primary TB is subclinical and self-limited. In the immunocompromised host, however, clinically active primary disease may develop rapidly after the initial MTB infection.

The less-resistant host with weak cell-mediated immunity relies more on delayed-type hypersensitivity to control the infection. The primary lesion is surrounded by nonactivated macrophages so it is not effectively walled off, and the caseous center expands, compromising more lung tissue. If the infection eventually can be contained by the host, any initial manifestations may go unnoticed, and the infection may be evident only radiographically as healed parenchymal calcifications of the primary or Ghon focus and of the regional lymph nodes.[25] If host defenses are unable to contain the primary infection, however, as can occur in infants and immunosuppressed adults, the primary focus may become an area of advancing pneumonia.[25] This process is called *primary progressive TB*. In addition, this host may be unable to control the infection at the sites of lymphohematogenous spread, resulting in formation of multiple uncontrolled caseous tubercles and development of disseminated TB.[34] HIV-infected patients are particularly susceptible to primary progressive TB because HIV specifically targets $CD4^+$ cells and macrophages.

Stage 4

The final stage usually occurs months to decades after an apparent recovery from the initial infection. TB may progress to stage 4 even in immunocompetent persons. Usually, host factors lead to decreased resistance and reactivation of dormant foci of MTB. The progression is due to liquefaction and cavity formation.

The liquefied tubercle serves as an excellent growth medium for the mycobacteria. The large numbers of extracellular bacilli stimulate delayed-type hypersensitivity, which secondarily causes local damage. The tubercle eventually erodes through the bronchial wall and drains its contents, forming a cavity. The liquified caseous material, teeming with mycobacteria, enters other parts of the lung and the outside environment. The spilling of this liquified material within the lung may produce a caseous bronchopneumonia.[34]

The cavity formed at the site of the initial focus remains a significant lesion. Cavities provide optimal conditions for mycobacterial growth. The oxygen tension is increased, and the host's defenses are ineffective at interrupting multiplication of the mycobacteria within a cavity.[34]

CLINICAL FEATURES

The initial infection with MTB most often is asymptomatic in otherwise healthy persons. Mild fever and malaise may develop in association with the immune response at 4 to 6 weeks, but generally the primary infection is clinically insignificant.[36] Conversion to a positive PPD skin test result may be the only means of diagnosing the infection. Clinically active TB develops in 8 to 10% of otherwise healthy PPD converters who do not take prophylactic agents—3 to 5% in the first 2 years (acute primary TB) and another 5% during the remainder of life (reactivation TB).[19] By contrast, in persons also infected with HIV, progression to acute primary TB occurs at a rate of 37% within 6 months and then to active TB at a rate of 7 to 10% per year.[19]

Reactivation of dormant foci is responsible for the major clinical manifestations of TB.[36] Exogenous reinfection of patients with well-documented previous TB infection causes clinical disease indistinguishable from reactivation TB.[37] Because it may be incorrect to label all late-onset cases as reactivation disease, *postprimary TB* is the preferred term. Postprimary TB is active or chronic disease in a patient previously infected. In the United States and other developed countries, reactivation is thought to be the primary mechanism of postprimary TB. Exogenous reinfection has played a role in circumstances in which contagion levels are high, as in outbreaks of TB, in developing countries, or in immunocompromised hosts.[37-39]

Patient's History

History of Present Illness

Clinically significant pulmonary TB often is indolent, and signs and symptoms are absent or minimal until the disease advances. The patient also may experience a systemic reaction to the infection. The systemic reaction, thought to be mediated by cytokines, especially tumor necrosis factor α, causes the constitutional symptoms of anorexia, weight loss, fatigue, irritability, malaise, weakness, headache, chills, and, most commonly, fever.[36,40] The fever usually develops in the afternoon; defervescence occurs during sleep, leading to the classic night sweats of TB.[36]

Cough is the most common symptom of pulmonary TB. Initially it may be nonproductive, but as caseation necrosis and liquifaction develop, mucopurulent and nonspecific sputum typically is produced.[25,36,40] Hemoptysis, caused by caseous sloughing or endobronchial erosion, usually is minor but often indicates extensive lung involvement.[25] Many asymptomatic patients present for medical attention because they are alarmed by the hemoptysis.

Patients also may complain of pleuritic chest pain, which is caused by parenchymal inflammation adjacent to the pleural surface. Dyspnea with chest pain may indicate a spontaneous pneumothorax.[41] Shortness of breath from parenchymal lung involvement is unusual, however, and if present indicates extensive parenchymal disease or tracheobronchial obstruction.[36] Table 133-1 shows the frequency of symptoms found in one study of patients with culture-proven pulmonary TB.[42] The clinical manifestation of TB in patients presenting to the emergency department (ED) may be especially confusing. In one study, only one third of ED patients with active pulmonary TB had pulmonary chief complaints, only 64% ever reported a cough, and only 8% had hemoptysis.[43]

Any vague systemic disorder or fever of unknown etiology may represent TB.[19] Atypical presentations are particularly common in infants, the elderly, and immunocompromised persons. In infants and young children, the development of large hilar lymph nodes is common; such nodes may compress a bronchus, leading to atelectasis and possibly obstructive pneumonia; the child may have a "brassy cough." A node also may erode through the bronchial wall, causing symptomatic endobronchial disease and allowing endobronchial spread of tuberculous pneumonia to other areas of the lungs.[25] By contrast, fewer elderly persons present with respiratory symptoms. The diagnosis may be masked by coexistent disease and nonspecific presenting symptoms.[44] Pulmonary TB should be considered in elderly patients with chronic cough and failure to thrive.[16]

Clinical manifestations of TB in patients co-infected with HIV are even more subtle and nonspecific, especially because these patients are vulnerable to opportunistic infections and neoplasms that can cause the same constitutional symptoms as in TB. A synergy between the two infections (MTB and HIV) leads to a greatly increased viral load.[20] Active TB with HIV co-infection has been associated with an increased risk for opportunistic infections and death.[21] Patients with advanced HIV infection also commonly have extrapulmonary involvement (seen in 30%), as well as combined pulmonary and extrapulmonary TB (in 32%).[40]

Risk Factors

All patients in the ED who have been coughing should be screened for the presence of TB risk factors[45] (Box 133-1). Risks for acquiring TB may also be stratified by age. Because infants and toddlers have poorly developed cell-mediated immunity, they have a much higher incidence of TB than adults. Children 5 to 10 years of age are relatively resistant to TB. Infants and toddlers commonly have extrapulmonary disease and acute lower and midlung bronchopneumonia that rarely progresses to cavitary disease. Young adults show the adult pattern of apical pulmonary disease, including cavity formation, suggesting reactivation. Because of decreased immunocompetence, elderly persons typically have disease manifestations similar to those in young children.[25] Patients with a history of PPD conversion should be asked about the presence of medical conditions associated with increased risk for the development of active postprimary disease through reactivation[45] (Box 133-2).

Patients with a history of active TB should be asked about all antituberculosis medications previously or currently being taken and about compliance. Failure to improve after 2 months on an appropriate regimen may signal nonadherence to therapy or the presence of a resistant strain.[46]

Table 133-1 Frequency of Symptoms and Signs in Pulmonary Tuberculosis

SYMPTOM/SIGN	NUMBER AFFECTED	NUMBER EVALUATED	PERCENTAGE AFFECTED
Cough	144	185	78
Weight loss	134	181	74
Fatigue	112	165	68
Tactile fever	109	183	60
Night sweats	98	177	55
Chills	92	180	51
Anorexia	76	167	46
Chest pain	71	179	40
Dyspnea	64	173	37
Hemoptysis	51	181	28
No respiratory symptoms	13	186	7
None of above symptoms	9	187	5

From Barnes PF, et al: Chest roentgenogram in pulmonary tuberculosis: New data on an old test. Chest 94:316, 1988.

BOX 133-1 POPULATION GROUPS WITH INCREASED RISK FOR TUBERCULOSIS

- Close contacts of known case
- Persons with HIV infection
- Foreign-born from Asia, Africa, Latin America
- Medically underserved, low-income populations
- Elderly persons
- Residents of long-term care facilities (e.g., nursing homes, correctional facilities)
- Injection drug users
- Groups identified locally (e.g., homeless, migrant farmworkers)
- Persons who have occupational exposure

HIV, human immunodeficiency virus.
From CDC: TB Care Guide: Highlights from Core Curriculum on Tuberculosis. Atlanta, U.S. Department of Health and Human Services, 1994.

BOX 133-2 Risk Factors for Development of Active Tuberculosis in Previously Infected Persons

HIV infection
Recent tuberculosis infection (within past 2 years)
Chest radiographic findings suggestive of previous untreated tuberculosis
Injection drug use
Diabetes mellitus
Silicosis
Prolonged corticosteroid therapy
Immunosuppressive therapy
Head or neck cancer
Hematologic and reticuloendothelial diseases
End-stage renal disease
Intestinal bypass or gastrectomy
Chronic malabsorption syndromes
Low body weight (10% or more below the ideal)

HIV, human immunodeficiency virus.
Modified from CDC: TB Care Guide: Highlights from Core Curriculum on Tuberculosis. Atlanta, U.S. Department of Health and Human Services, 1994.

Figure 133-1. Chest radiograph demonstrating cavitary tuberculosis with left-sided pneumothorax. The underlying cause of the pneumothorax was later determined to be a bronchopleural fistula. (Courtesy of John Pearce, MD.)

Physical Findings

Examination of the chest is unlikely to establish the extent of disease. Over areas of infiltration, rales may be heard when the patient breathes in after a short cough (post-tussive rales), and bronchial breath sounds may be present over areas of lung consolidation. Distant, hollow breath sounds that can be heard over cavities are called *amphoric* breath sounds.[25] One ED study reported abnormal physical examination findings in 80% of patients with active pulmonary TB.[43]

Erythema nodosum or phlyctenular keratoconjunctivitis (severe unilateral inflammation of an eye) may appear with the onset of tuberculin hypersensitivity. These self-limited, allergic manifestations are not common in the United States.[25] The patient's overall appearance and state of health may be the most useful indicators in evaluating for the potential presence of TB. General signs include pallor secondary to anemia, fever, and cachexia with weight loss.

Complications

Pneumothorax

Spontaneous pneumothorax is not common (affecting less than 5% of patients with severe cavitary disease) but may occur when a tuberculous cavity ruptures and creates a bronchopleural fistula or when a bleb ruptures into the pleural space[47] (Fig. 133-1). Delayed tube thoracostomy and suction result in progressive infection and fibrosis of the pleura that leads to air trapping within affected lung.

Empyema

An empyema may develop in patients with TB characterized by extensive, progressive parenchymal disease and cavitation. Although rare (with a frequency of 1 to 4%), empyema is more common late in the course of the disease in debilitated patients. Rupture of a cavity into the pleural space usually is catastrophic and often is associated with bronchopleural fistula formation. An untreated empyema can result in spontaneous pleurocutaneous fistula formation, presence of a chest wall mass on the radiograph, or rib and vertebra destruction.[47]

Endobronchial Spread

Endobronchial spread is the most common complication of cavitary disease. It is manifested radiographically as 5- to 10-mm, poorly defined nodules clustered in dependent portions of the lungs. These nodules may rapidly coalesce into parenchymal consolidation—so-called galloping consumption.[47]

Airway Tuberculosis

When a cavity drains its highly infectious material into the bronchial tree, the airways not only spread the infection but also develop endobronchial TB. Bronchiectasis commonly complicates endobronchial TB. Bronchial stenosis may result from extensive damage caused by endobronchial TB or from direct extension of infection from tuberculous adenitis or from lymphatic dissemination to the airway.[25,47] Tuberculous bronchostenosis may appear radiographically as persistent segmental or lobar collapse, lobar hyperinflation, and obstructive pneumonia.[47]

Tracheal TB and laryngeal TB are less common than endobronchial TB. Laryngeal disease is the most infectious form of TB; it results from the proximal extension of lower airway disease, pooling of infected secretions in the posterior larynx, or hematogenous dissemination to the anterior larynx. Patients with laryngeal TB also usually have active pulmonary disease.[47]

Superinfection

Extensive TB infection often heals with open cavities and areas of bronchiectasis.[36] Superinfection may occur with a wide variety of organisms, including *Aspergillus fumigatus*.[48] The characteristic finding on chest radiographs is the aspergilloma or "fungus ball" (Fig. 133-2). Aspergillomas are of particular clinical significance because they may cause massive and fatal hemoptysis.[36]

Hemoptysis

Mild hemoptysis is a common complication of acute infection. TB also causes massive hemoptysis. The destruction of lung parenchyma leads to rupture of blood vessels. A tuberculous lesion or cavity may erode into a pulmonary artery, leading to

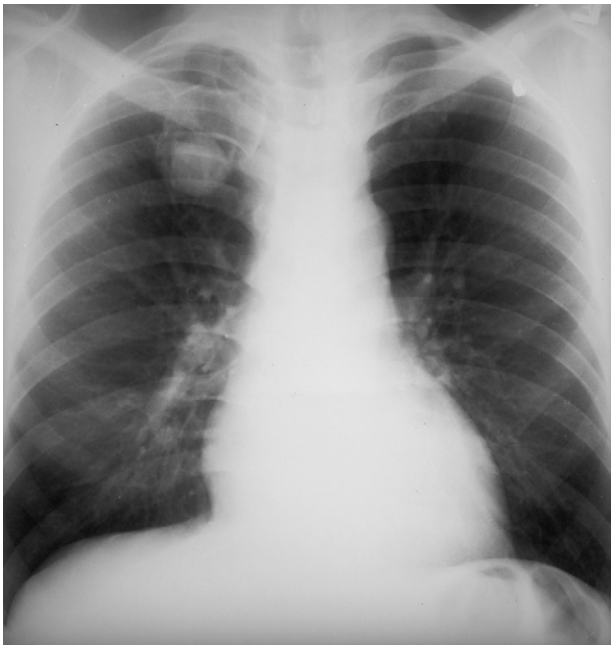

Figure 133-2. Chest radiograph showing superinfection of healed tuberculous cavity. An aspergilloma can be seen in the right upper lung. (Courtesy of John Pearce, MD.)

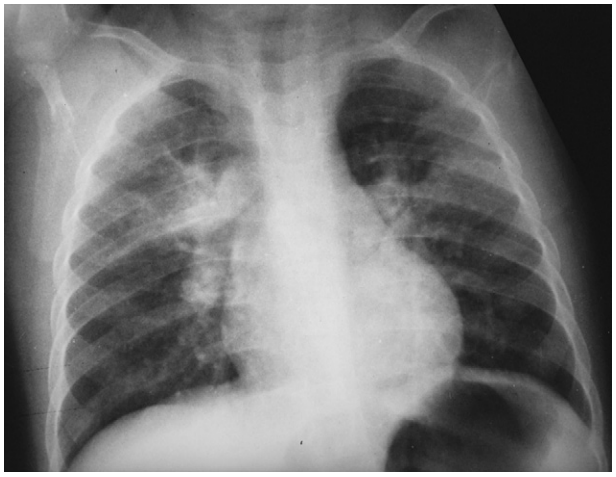

Figure 133-3. Chest radiographic findings in a child with primary tuberculosis. Note the active Ghon focus with associated hilar adenopathy and presence of bilateral infiltrates. (Courtesy of John Pearce, MD.)

pseudoaneurysm formation (Rasmussen's aneurysm) with potentially fatal hemoptysis.[47] This complication has become uncommon since the development of antituberculosis medications.[25] Alternatively, superinfection of cavities by invasive organisms or tumor development in scarred lung may cause erosion of bronchial or pulmonary vessels, with resultant major hemorrhage. Affected patients often require emergency surgical resection or selective embolization.[49]

Primary Tuberculous Pericarditis

Primary tuberculous pericarditis usually results from direct extension of infection from the tracheobronchial tree, mediastinal or hilar lymph nodes, sternum, or spine. Pericardial involvement also may result from hematogenous spread secondary to acute miliary TB or from another focus elsewhere in the body.[25,50] In the United States, TB is the leading cause of pericarditis among HIV-infected patients, with a prevalence of up to 15%.[51] The predominant symptoms are cough, chest pain, and dyspnea, and the most common signs are cardiomegaly, an audible rub, fever, and tachycardia.[52] Complications of pericardial TB include pericardial effusion, constrictive pericarditis, myocarditis, and cardiac tamponade.[50] Cardiac tamponade may result from accumulation of pericardial fluid but also may occur if enlarging lymph nodes rupture into the pericardium. Emergency echocardiography reliably confirms the presence of pericardial fluid.[53]

DIAGNOSTIC STRATEGIES

Laboratory Tests

Routine laboratory studies generally are not useful in suggesting or establishing the diagnosis.[36] Normochromic normocytic anemia, elevated erythrocyte sedimentation rate and serum globulin level, hyponatremia, and hypercalcemia all can occur in active pulmonary TB, but these findings are nonspecific.[36,48,54] Tuberculin skin testing is important epidemiologically as a modality for diagnosing MTB infection but is of limited value for detecting active clinical disease. At least 20% of patients with active TB have false-negative results on tuberculin skin testing.[25]

Diagnostic Imaging

Plain radiography of the chest is the most useful study for making a presumptive diagnosis of pulmonary TB. Chest radiographic abnormalities are not limited to the classic upper lobe cavitary infiltrates. Primary TB infection and postprimary disease each have distinctive radiographic features. A normal appearance on the chest radiograph has a high negative predictive value and is therefore useful in screening ED patients for active pulmonary TB. However, the false-negative rate is approximately 1% among immunocompetent adults and increases to 7 to 15% among HIV-positive patients.[24] Therefore, depending on the clinical circumstances, absence of specific abnormalities on the chest radiograph does not always exclude active TB, especially in patients with concomitant endobronchial disease and HIV infection.

Primary Tuberculosis

Chest radiographic manifestations of primary disease in adults often are not recognized as TB.[55,56] Primary tuberculous infiltrates can occur in any lobe.[47,57,58] With any age group, a pneumonic infiltrate with enlarged hilar or mediastinal nodes should strongly suggest the diagnosis.[57] The infiltrate usually is homogeneous and most commonly involves a single lobe. Thus, primary TB may appear radiographically identical to a bacterial pneumonia, with associated lymphadenopathy, if present, being the only distinguishing feature.

Lymphadenopathy is considered the radiologic hallmark of primary TB in children but is seen less commonly in adults.[24,58] When present, adenopathy usually is unilateral and associated with parenchymal infiltrate (Fig. 133-3). It may occur bilaterally or, more rarely, may be an isolated finding on chest radiography.[36] Massive hilar adenopathy is more common in young children. As a result, atelectasis, resulting from airway compression by adjacent enlarged nodes, is a likely finding in children younger than 2 years but is less common among older children and adults.[47]

Other primary TB chest radiographic findings include a moderate to large pleural effusion, which often is an isolated finding whose prevalence increases with age; miliary TB (characterized by the presence of innumerable, 1- to 3-mm noncalcified nodules dispersed throughout both lungs with mild basilar predominance), which is mainly a threat to children younger than 2 years, immunocompromised patients, and the elderly; and tuberculomas, well-circumscribed nodular lesions of the parenchyma thought to be a result of healed primary TB.[24,47] When the healed primary focus is visible on the chest radiograph as a calcified scar, it is known as the *Ghon focus*. Calcified secondary foci of infection are known as *Simon's foci*. A Ghon focus associated with calcified hilar nodes is called a *Ranke complex*.[25,47] A right-sided predominance in the distribution of Ghon's foci and Ranke's complexes is well recognized and probably reflects the higher statistical probability that an air-borne infection will affect the right lung.[24] Calcification seen on the chest radiograph indicates healing, but viable bacilli may still exist in a partially calcified lesion.[57]

When resolution does not occur, the result is progressive primary TB, which appears radiographically as progressive parenchymal consolidation often including secondary foci in the upper lobes.[47] In some patients, the primary tuberculous pneumonia breaks down into multiple cavitary lesions or a single large abscess.[57] These chest radiographic findings may easily be confused with the findings in postprimary TB.

Postprimary Tuberculosis

Postprimary TB typically appears as an upper lung infiltrate or consolidation, with or without cavitation. The lesion may be small or extensive and usually is located in the apical or posterior segment of the upper lobe but may appear in the superior segment of the lower lobe.[59] Postprimary disease also occurs in the lower lung. In addition, bronchogenic spread can occur, leading to involvement of multiple lobes[59] (Fig. 133-4). The patient with bilateral upper lobe disease is extremely likely to have TB.[57] The other important, recognizable characteristics of postprimary disease are fibrosis and cavitation.

The initial lesion of postprimary TB is a poorly defined, heterogeneous alveolar opacity called an *exudative* lesion.[47] These lesions are not purely exudative in that they are associated with a fibrotic pattern of nodules and a few fine, linear densities. Unchecked, the infection may rapidly progress to lobar or complete lung opacification and destruction.[47] Postprimary TB, however, usually runs a chronic course characterized by reactive fibrosis, and in most cases the initial exudative lesions gradually are replaced by more well-defined reticular and nodular opacities or "fibroproductive" lesions.[47,57]

Fibroproductive lesions often are irregular and angular in contour, have strands extending toward the hilum, and demonstrate calcification of one or more nodules. This pattern is characteristic of granulomatous disease and rarely is found in other bacterial infections.[31] As fibrosis continues, distortion of normal vascular and mediastinal structures secondary to contraction and shrinkage of the scar may be apparent. Severe fibrosis with upper lobe volume loss may eventually lead to retraction of the interlobar fissure and upward displacement of the hilum.[57] The chest radiographic appearance at this stage has been variably referred to as "old scarring," "no active disease," or "fibrotic, apparently well-healed TB." Many of the patients have positive sputum culture results, and infectivity cannot be accurately assessed by chest radiography.[47,57] Only serial radiographs can reliably differentiate active from inactive disease. Lack of radiographic changes over a 4- to 6-month interval generally indicates "inactive" or, more precisely, "radiographically stable" disease.[24]

Cavitation should alert ED personnel to the high infectivity of the patient and the potential for associated complications such as bronchogenic spread of TB when an area of caseous necrosis liquefies, with consequent communication with the bronchial tree (see Fig. 133-4). Cavities usually are multiple and range in diameter from a few millimeters to several centimeters.[47] The walls of the cavities initially are thick and rough and become thinner and smoother with healing (Fig. 133-5). A hazy, parenchymal reaction around a cavity with an ill-defined wall strongly suggests an active lesion. Most cavities heal by obliteration, often leaving a small linear or stellate scar; others remain patent and become thin-walled bullae.[57]

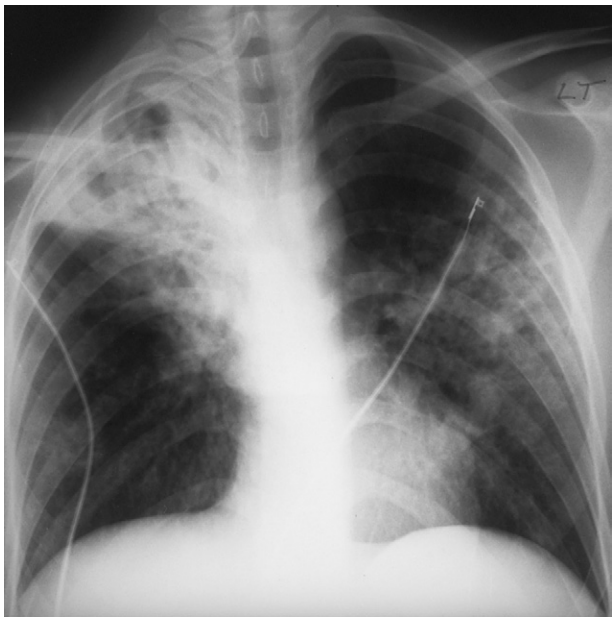

Figure 133-4. Chest radiograph showing evidence of right upper lobe cavitary disease. Also note the left-sided infiltrate, secondary to endobronchial spread.

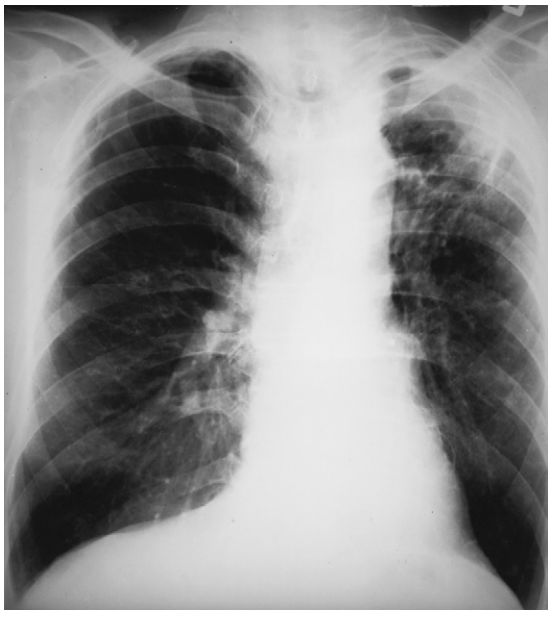

Figure 133-5. A healed, thin-walled cavity can be seen in the left upper lobe on this chest film. (Courtesy of John Pearce, MD.)

Although pulmonary TB usually induces chest radiographic changes, patients with sputum cultures positive for MTB may nevertheless demonstrate normal radiographic findings. In a series of 103 patients, 10 people (9.7%) with confirmed pulmonary TB had normal findings on their chest radiographs.[56] Chest radiographs also may be normal in appearance in patients with endobronchial TB.[41,60]

Chest radiographs of patients with pulmonary TB and HIV infection may be atypical in approximately one third of cases.[61] However, the radiographic appearance of disease is heavily influenced by the degree of immunocompromise. Patients with late HIV infection more often demonstrate mediastinal adenopathy or atypical infiltrates and less often have cavitation.[62,63] Severe immunosuppression has been reported to be associated with a miliary pattern of disease on chest radiographs.[24] Conversely, chest radiographs of patients with early HIV infection are more similar to those of patients without HIV infection, with upper lobe infiltrates, more cavitation, and less adenopathy.[64] A normal chest radiographic appearance also is common in patients with HIV infection. In one study, chest radiographic findings were normal in 14% of HIV-infected patients, including 21% of those with $CD4^+$ counts below 200/μL and 5% of those with $CD4^+$ counts greater than 200/μL.[61]

Microbiology

Sputum Studies

If the clinical or chest radiographic findings suggest the diagnosis of pulmonary TB, mycobacteriologic studies of the patient's sputum should be ordered. Spontaneously produced sputum collected under direct supervision is preferred, and early-morning samples are the best diagnostic specimens.[25] Classically, three initial sputum specimens should be obtained on different days. A positive smear supports a presumptive diagnosis, and the number of bacilli seen correlates with infectivity. For patients who are not producing sputum, nebulized induction of sputum and gastric aspiration of swallowed respiratory secretions are the methods of choice for collecting samples.[65] The diagnostic yield is higher for nebulizer-induced sputum samples than for gastric aspirates in adult patients with TB, but in some patients, especially children, gastric aspirates may be the only obtainable specimens. Induction of sputum with nebulization may increase the risk of TB transmission to health care workers and should be performed only in specially ventilated rooms, preferably not in the ED.

When sputum is not diagnostic in adults, fiberoptic bronchoscopy with bronchial washings, brushings, and bronchoalveolar lavage or transbronchial biopsy may be necessary for laboratory diagnosis of TB.[65] In children, sputum obtained by bronchoscopy has a lower culture yield, so this technique is used less often to obtain sputum from pediatric patients.[66]

Direct Microscopy

Direct microscopic examination of a stained sputum specimen for AFB (i.e., an AFB smear) is the most rapid laboratory test widely available to support a presumptive diagnosis of TB (Fig. 133-6), and results usually are available within 24 hours.[67] Although nontuberculous mycobacteria can cause pulmonary disease, they are less common than MTB and vary by geographic location and population of patients. Fluorochrome stains are more sensitive than the traditional Ziehl-Neelsen or Kinyoun methods for the detection of AFB from clinical specimens.[66,67] Negative findings on an AFB smear, however, do not rule out active pulmonary TB, because microscopy is relatively insensitive when performed on samples with small numbers of bacilli. At least 5000 bacilli/mL of sputum must be present for a positive result by microscopy.[67] Because cavitary disease is associated with great numbers of bacilli, the diagnostic yield of microscopy increases with cavitation. Concentrated smears are prepared by decontamination, liquefaction, and centrifugation of sputum, and such smears may be more sensitive than unconcentrated samples.[14] Overall, AFB smears have a sensitivity of 20 to 80% and a specificity of 90 to 100%.[67] Despite its limitations, microscopy remains an essential diagnostic test because of its ease of performance, low cost, rapid turnaround time, and reasonable diagnostic yield.

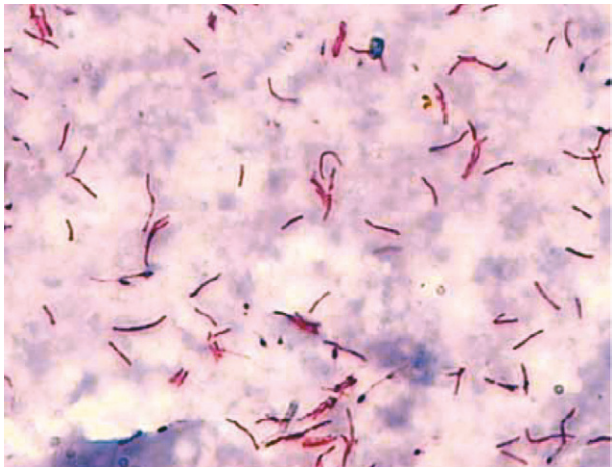

Figure 133-6. Photomicrograph of an acid-fast bacillus smear of *Mycobacterium tuberculosis*. (Courtesy of Alfredo Ponce de Leon, MD.)

Culture

A presumptive diagnosis of TB based on a positive sputum smear usually is confirmed by isolating MTB by culture. Traditional culture methods using solid media require 3 to 8 weeks for colony formation. The development of liquid culture systems has shortened the detection time to 7 to 14 days. A number of liquid culture systems are available for detection of MTB. For example, the BACTEC (Becton Dickinson, Franklin Lakes, NJ) method measures $^{14}CO_2$ produced by growing mycobacteria when they metabolize the ^{14}C-labeled palmitic acid contained in the system, and the mycobacteria growth indicator tube (MGIT) method measures mycobacterial oxygen consumption with a fluorescence assay.[67]

Sputum culture is more sensitive than microscopy for detecting MTB and is still considered the "gold standard" diagnostic modality. Liquid culture can detect 10 to 100 bacilli/mL, compared with 5000 to 10,000 bacilli/mL for AFB smear. When the presence of mycobacteria is established, the specific identification of MTB may be accomplished by subjecting the initial mycobacteria to various isolation techniques. These include the detection of pigmentation on solid culture media, various biochemical tests, high-performance liquid chromatography, and nucleic acid probes.[67]

Drug Susceptibility Testing

Because of the emergence of multidrug-resistant MTB, all initial isolates of MTB should be tested for susceptibility to isoniazid (INH), rifampin (RIF), and ethambutol (ETH).[68] Further susceptibility testing should be performed when resistance to one of the three agents is detected or if the patient has had previous TB treatment, has been exposed to a drug-

resistant contact or source, or has demonstrated a positive result on sputum cultures beyond 3 months of therapy.[68] Conventional susceptibility testing detects selective growth of drug-resistant TB on media containing antituberculosis drugs. For first-line agents, this requires waiting until 4 to 7 days after a positive culture result is obtained; testing for susceptibility to other drugs may require 2 to 3 months. The BACTEC and MGIT systems also can be used for rapid drug susceptibility testing, with resluts obtained in fewer than 12 days.[67] Other new approaches to susceptibility testing include flow cytometry, genotypic sequence–based methods, and bacteriophage viability testing.[67,69]

Nucleic Acid Amplification Tests

A number of nucleic acid amplification assays are available to assist in the rapid diagnosis of MTB infection, including polymerase chain reaction (PCR) tests, the *Mycobacterium tuberculosis* direct test (MTDT), and the ligase chain reaction.[67] These tests can be used directly on clinical specimens but at present are of limited utility in the diagnosis of MTB. They are undergoing refinement, however, and may become valuable tools in the future. Problems include high cost and potential for suboptimal performance in clinical settings because of factors such as variability in laboratory methodology, potential for specimen contamination, and lower-than-expected sensitivity.[14,66] Sputum smears are still needed to evaluate for infectiousness, because these tests are unable to differentiate active from treated infection. Sputum cultures also are still needed, because these tests do not assess drug susceptibility.[14] Nucleic acid amplification tests may be useful, however, when findings on standard clinical and microbiologic tests are negative or inconclusive. The PCR assay may provide a method for confirming the diagnosis of TB within a few hours. PCR testing is based on a DNA amplification technique that bypasses the delays inherent with mycobacterial cultures. It allows the in vitro synthesis of millions of copies of a specific MTB DNA segment.[70] Diagnostic techniques based on PCR allow direct testing of routine clinical specimens to confirm the diagnosis of TB in hours. Test performance varies greatly, depending on whether the sputum sample is AFB smear–positive or –negative. For example, for AFB smear–positive specimens, the Roche (Roche, Nutley, NJ) Amplicor system has a sensitivity of 95 to 96% and specificity of 100%. When it is applied to AFB smear–negative specimens, the sensitivity drops to 48 to 53%, with a specificity of 96 to 99%.[67,71] The MTDT enzymatically amplifies a 16S ribosomal RNA (rRNA) segment that is specific for MTB complex species. Preliminary studies suggest that the MTDT has excellent sensitivity (86 to 98%) and specificity (97 to 100%) for the rapid identification of MTB and can be performed in approximately 5 hours. As with PCR assays, specimen quality and the degree of AFB smear positivity affect test performance.[67,72]

The Ligase Chain Reaction

The ligase chain reaction amplification assay involves repetitive cycles of high-temperature DNA denaturation, oligonucleotide annealing, and ligation. The Abbott Laboratories (Abbott Park, IL) LCx assay has a sensitivity of 98% for AFB smear–positive specimens and 27% for AFB smear–negative specimens and a specificity of 100% (equal to that of culture).[67] When LCx was compared with PCR assay and MTDT in a clinical trial, no significant difference in sensitivity or specificity was found among these three tests.[73] Tuberculostearic acid (TSA) is a fatty acid found only in mycobacteria. It can be detected with gas chromatography–mass spectrometry in clinical specimens containing small numbers of bacilli. TSA testing is not frequently used, because the equipment and expertise needed to run this test are not widely available outside specialized research laboratories.[74]

Interferon-γ Levels

IFN-γ is a cytokine associated with cell-mediated immunity. Determination of IFN-γ levels also can be used as a diagnostic test for tuberculous pleural effusions, ascites, and pericardial effusions. Clinical studies have reported sensitivity and specificity of 100% and 100%, respectively, for assay of IFN-γ in pericardial fluid and 78% and 97% in pleural fluid.[75,76] IFN-γ assay can be used independently, as a confirmatory test, or in combination with other tests, such as PCR assay.[76]

Serology

Serodiagnosis of TB, if such testing were readily available, would be a minimally invasive approach to rapid diagnosis. Using an enzyme-linked immunosorbent assay (ELISA) to diagnose TB from serum would be especially useful in patients who cannot produce sputum. Although ELISAs have been developed for several MTB antigens, in practice, no serodiagnostic approach to the diagnosis of TB currently is in widespread clinical use in the United States. Limitations of the ELISA include inadequate accuracy and reproducibility, inability to distinguish active from latent infection, poor discrimination between MTB and other mycobacteria, and relative cost.[66,67]

Tuberculin Skin Test

While newer diagnostic tests undergo development, the tuberculin skin test remains the best tool available for detecting latent MTB infection. The tuberculin test is based on the principle that MTB infection induces sensitivity to certain antigens of the bacillus. These antigens are contained in the tuberculin preparation called PPD. In a person infected with TB, the PPD test result usually turns positive 3 to 8 weeks after the infection, when the immune response is developed.[25]

The standard 0.1-mL dose used in skin testing contains 5 tuberculin units (TU). This dose is administered intradermally with the needle bevel up, using the Mantoux technique. A properly placed needle should leave a blanched, distinct wheal 6 to 10 mm in diameter.[45] If the tuberculin dose is incorrectly administered, the test may be repeated immediately at a site several centimeters away. Various types of test kits and applicators are available (Heaf and tine tests), but for diagnostic purposes the Mantoux test with PPD (5 TU) is preferred.[29,66,77]

Tests are "read" 48 to 72 hours after administration of PPD. The largest diameter of palpable induration is measured and recorded in millimeters; erythema by itself is not measured. The precise measurement that denotes a positive test result depends on the patient's other clinical factors. The current CDC guidelines use 15 mm of induration as a positive test for people without TB risk factors[78] (Table 133-2).

Some persons with previous TB infection gradually lose their hypersensitivity reaction to PPD and may react weakly or not at all. The PPD test, however, can restimulate or enhance their hypersensitivity, so that a subsequent test does elicit a positive reaction. This phenomenon is called the booster effect. This boosted reaction may be mistaken for a new infection. To eliminate the booster effect as a confounding factor, a two-step testing method is recommended for

Table 133-2 Criteria for a Positive Tuberculin Skin Test Result

SIZE OF REACTION	PERSONS IN WHOM REACTION IS CONSIDERED POSITIVE
≥5 mm	HIV-infected persons Close contacts of persons with infectious tuberculosis Persons with abnormalities on chest radiograph consistent with previous tuberculosis* Immunosuppressed patients receiving the equivalent of ≥15 mg of prednisone per day for ≥1 month
≥10 mm	Foreign-born persons recently arrived (≤5 years earlier) from a country with a high prevalence of tuberculosis Persons with a medical condition that increases the risk of tuberculosis† Injection drug users Members of medically underserved, low-income populations (e.g., homeless persons) Residents and staff members of long-term care facilities (e.g., nursing homes, correctional institutions, homeless shelters) Health care workers Children <4 years of age Persons with conversion on a tuberculin skin test (increase in induration of ≥10 mm within a 2-year period)
≥15 mm	All others‡

*Chest radiographic abnormalities consistent with previous tuberculosis consist of fibrotic opacities occupying more than 2 cm^2 of the upper lobe; presence of pleural thickening or isolated calcified granulomas is not considered to be suggestive of previous tuberculosis.
†Medical conditions that increase the risk of development of tuberculosis in the presence of latent tuberculosis infection include silicosis, end-stage renal disease, malnutrition, diabetes mellitus, carcinoma of the head and neck or lung, immunosuppressive therapy, lymphoma, leukemia, loss of more than 10% of ideal body weight, gastrectomy, and jejunoileal bypass.
‡These persons should not be screened in the absence of an indication.
HIV, human immunodeficiency virus.
From Jasmer RM, Nahid P, Hopewell PC: Latent tuberculosis infection. N Engl J Med 347:1860, 2002.

BOX 133-3 FACTORS CAUSING DECREASED ABILITY TO RESPOND TO TUBERCULIN

Factors Related to Person Being Tested
- Infections
  - Viral (e.g., measles, mumps, chickenpox)
  - Bacterial (e.g., typhoid fever, brucellosis, typhus, leprosy, pertussis, overwhelming tuberculosis, tuberculosis pleurisy)
  - Fungal (e.g., South American blastomycosis)
- Live virus vaccinations (e.g., measles, mumps, polio)
- Metabolic derangements (e.g., chronic renal failure)
- Nutritional factors (e.g., severe protein depletion)
- Diseases affecting lymphoid organs (e.g., Hodgkin's disease, lymphoma, chronic lymphocytic leukemia, sarcoidosis)
- Drugs (corticosteroids and many other immunosuppressive agents)
- Extremes of age (newborns, elderly with "waning" sensitivity)
- Recent or overwhelming infection with *Mycobacterium tuberculosis*
- Systemic stress (surgery, burn injury, mental illness, graft-versus-host reactions)

Factors Related to Tuberculin Used
- Improper storage (exposure to light and heat)
- Improper dilutions
- Chemical denaturation
- Contamination
- Adsorption (partially controlled by addition of Tween 80)

Factors Related to Method of Administration
- Injection of too little antigen
- Delayed administration after antigen has been drawn into syringe
- Injection site too close to control

Factors Related to Reading and Interpreting Test Results
- Inexperience of reader
- Conscious or unconscious bias
- Error in recording

persons who undergo serial PPD screening (health care workers). If the result of the first test is negative and the person does not have a documented negative PPD test result during the previous 12 months, a second test is done 1 week later using the same dose. If the second test is positive, it is most likely to represent a boosted reaction and the person should be considered previously infected. If the second test result remains negative, the person is considered uninfected and a positive reaction to a subsequent test indicates new infection.[29]

Infection with nontuberculous mycobacteria may cause a false-positive PPD result. These reactions tend to be smaller than the true-positive reaction to MTB infection. Similarly, bacille Calmette-Guérin (BCG) vaccination may produce a PPD reaction that generally is mild and deteriorates with time. A large reaction to PPD and a long time interval between BCG vaccination and the current skin test make it more likely that the reaction is due to MTB infection.[29] Because the BCG vaccine is imperfect in protecting against MTB infection and because most vaccinated persons come from areas of high TB prevalence, the CDC recommends that tuberculin skin test results be interpreted without regard to BCG vaccination status.[79]

Many conditions can lead to false-negative reactions to PPD testing (Box 133-3). The incidence of false-negative results in one study was 25% among the 200 patients with active TB.[25] Therefore, the clinical significance of a negative PPD result is best determined by considering other clinical factors. Despite some limitations, PPD skin testing remains useful to diagnose individual patients, to screen populations, and to evaluate infected persons for prophylactic treatment[78] (Table 133-3).

DIFFERENTIAL CONSIDERATIONS

Pulmonary Tuberculosis

Bacterial Pneumonia

Segmental or lobar infiltrates on chest radiographs in bacterial pneumonia may easily be confused with those seen in TB, especially primary disease. Compared with TB, however, bacterial pneumonias usually arise with more profound symptoms of systemic toxicity, a more acute onset, and an elevated white blood cell count.[48] In pulmonary TB, there is no prompt response to antibiotics, as seen in bacterial pneumonia.[25]

Table 133-3 Persons at Increased Risk Who Should Be Tested for Latent Tuberculosis Infection

RISK COMPONENT	EXAMPLES OF PERSONS WITH RISK
Increased risk of exposure to infectious cases	Persons with recent close contact with persons known to have active tuberculosis* Health care workers who work at facilities where patients with tuberculosis are treated
Increased risk of tuberculosis infection	Foreign-born persons from countries with a high prevalence of tuberculosis Homeless persons Persons living or working in facilities providing long-term care
Increased risk of active tuberculosis once infection has occurred	HIV-infected persons Persons with recent tuberculosis infection† Injection drug users Patients with end-stage renal disease Patients with silicosis Patients with diabetes mellitus Patients receiving immunosuppressive therapy Patients with hematologic cancers Malnourished persons or those with a recent weight loss of more than 10% of their ideal body weight Persons who have undergone gastrectomy or jejunoileal bypass

*We define close contact as at least 12 hours of contact with a person with infectious tuberculosis, but well-established criteria for such contact are lacking.

†Persons with recent infection include children younger than 4 years and persons found to have tuberculin conversion, defined as an increase in induration of at least 10 mm on a tuberculin skin test within a 2-year period.

HIV, human immunodeficiency virus.

From Jasmer RM, Nahid, P, Hopewell PC: Latent tuberculosis infection. N Engl J Med 347:1860, 2002.

Fungal and Nontuberculous Mycobacterial Infections

Histoplasmosis, coccidioidomycosis, and blastomycosis, as well as nontuberculous mycobacterial infections (mainly with *Mycobacterium avium* complex and *Mycobacterium kansasii*), may be radiologically indistinguishable from TB.[80] The incidence of these infections is influenced by geographic location.[48,81] Nontuberculous mycobacterial infection most commonly involves chronic pulmonary infection in HIV-infected patients.[82] Immunocompetent persons also may become infected with MTB, especially patients with chronic lung disease such as cystic fibrosis. Other important risk factors include work in the mining industry, warm climate, advancing age, and male gender.[83]

Pneumonias in Patients with Human Immunodeficiency Virus

Bacterial pneumonias including upper lobe *Pneumocystis* pneumonia (due to *Pneumocystis jiroveci*) and, rarely, *Nocardia* and *Rhodococcus* infections may mimic TB in patients with HIV infection.[54]

Cavitary Lesions

Lung abscess or cavitating pneumonia caused by *Klebsiella pneumoniae*, *Staphylococcus pyogenes*, or aspiration may appear similar to cavitary TB on chest radiographs.[48] In older patients, especially smokers, bronchogenic carcinoma may mimic TB; this is particularly true of squamous cell carcinoma, which tends to cavitate.[48] Because cancer may cause a focus of TB to spread, the two diseases may be present simultaneously.[36] Other causes of nontuberculous cavitary lesions include *M. avium* complex infection in HIV-negative patients, pulmonary infarction secondary to pulmonary embolus, Wegener's granulomatosis, and upper lobe bullous disease secondary to emphysema or neurofibromatosis.[48,54,82]

Upper Lobe Infiltrate with and without Fibrosis

A radiographic pattern characterized by presence of an upper lobe infiltrate with or without fibrosis may be seen with atypical mycobacteria, ankylosing spondylitis, silicosis, collagen vascular diseases, lymphomas, and actinomycosis.[54] Upper zone fibrosis and volume loss can occur in the later stages of extrinsic alveolitis, allergic bronchopulmonary aspergillosis, and sarcoidosis. The presence of calcification suggests TB.[48]

Mediastinal Lymphadenopathy

The main considerations in the differential diagnosis for adenopathy include lymphoma and sarcoidosis. In sarcoidosis, lymphadenopathy usually is bilateral, symmetrical, and asymptomatic. Lymphadenopathy in TB tends to be unilateral or, if bilateral, is asymmetrical and associated with parenchymal lung disease. Lymphoma tends to involve very bulky mediastinal lymphadenopathy.[48]

Extrapulmonary Tuberculosis

Tuberculous infection involving multiple sites most commonly is seen in patient populations less capable of containing MTB infection such as infants, the elderly, and immunocompromised persons.[40] Extrapulmonary TB accounted for roughly 15% of newly diagnosed TB cases in the United States before the HIV epidemic. As reported in 2002, approximately 21% of TB patients in the United States had extrapulmonary disease, and another 7.5% had both pulmonary and extrapulmonary infection.[17] In children younger than 4 years, approximately 25% of TB infections are extrapulmonary.[66] Among HIV-infected persons, extrapulmonary TB infection becomes progressively more common as $CD4^+$ counts fall below 350 cells/μL.[63] One study of patients with TB concurrent with advanced HIV infection reported that 38% had only pulmonary disease, 30% had extrapulmonary TB alone, and 32% had both pulmonary and extrapulmonary TB.[40]

Extrapulmonary TB may occur in multiple sites, with relative frequencies of 42% for lymphatic, 18% for pleural, 12% for bone or joint, 6% for genitourinary, 6% for meningeal, 5% for peritoneal, and 11% for other sites.[17] The lymph nodes are the most common site of extrapulmonary TB for both otherwise normal and HIV-infected patients. Involvement of the meninges is more common in young children than in other age groups (present in approximately 4% of children with TB), and the incidence of TB in the remainder of the extrapulmonary sites increases with age.[40,66] Less commonly involved locations for extrapulmonary TB include the skin, heart, pericardium, thyroid gland, mastoid cells, sclerae, and adrenal glands.

Lymphadenitis

Tuberculous lymphadenitis (scrofula) is the most common form of extrapulmonary TB. Scrofula is common in children but most commonly is seen in young adult women, usually of minority races.[25] The patient usually has an enlarging, painless, red, firm mass in the region of one or more lymph nodes, most commonly in the anterior or posterior cervical chain or the supraclavicular fossa. Early on, the nodes are discrete, rubbery masses that are freely mobile, and the overlying skin is normal. Eventually, the nodes may become matted and

harder and the overlying skin inflamed. Fluctuance may be present, as well as an abscess or sinus tract if a node erodes through the skin.[84] Systemic signs and symptoms are uncommon, except in HIV-positive patients, in whom lymphadenitis usually is generalized.[40] Pulmonary infection is present in only 10 to 20% of cases.[84] Considerations in the differential diagnosis include lymphoma, metastatic cancer, fungal disease, cat-scratch disease, sarcoid, toxoplasmosis, reactive adenitis, and bacterial adenitis.

The diagnosis of scrofula usually is made by fine needle aspiration of an affected lymph node. Although AFB smears are positive in only approximately 20% of cases, granulomatous inflammation may be obvious. Overall, fine needle aspiration has a sensitivity of 77% and specificity of 93% for TB infection. First-line treatment of scrofula consists of antituberculosis drugs, but surgical excision may be performed when medical therapy has failed or if the diagnosis is unclear. Incision and drainage should not be done because permanent sinuses and prolonged drainage can result.[84]

Pleural Effusion

Pleural extrapulmonary TB may occur early after primary infection with MTB and manifest as pleurisy with effusion, or more rarely, it may occur late in postprimary cavitary disease and arise as an empyema.

Tuberculous pleural involvement often causes no symptoms and resolves spontaneously; however, in untreated patients, a 65% relapse rate has been reported, with development of active pulmonary or extrapulmonary TB within 5 years. Dyspnea may occur if the effusion is large, but the effusions usually are small and unilateral. Often the presentation is acute, severe, and indistinguishable from that of a bacterial pneumonia. In the elderly, however, the onset may be more insidious and likely to be confused with congestive heart failure, cancer, or a pulmonary embolus.[25]

The diagnosis usually is confirmed by microscopic and chemical examination of pleural fluid or pleural biopsy. White blood cell counts usually range from 500 to 2500 cells/mL. The fluid is an exudate with protein usually exceeding 50% of the serum protein, and the glucose may be normal to low. Because there are few bacilli, AFB smears rarely are positive, and cultures grow MTB for only 25 to 30% of patients known to have the disease. Pleural biopsy can confirm the diagnosis in approximately 75% of patients.[25]

Bone and Joint Infection

Bone and joint TB remains a disease of older children and young adults in developing countries, and it is increasingly a disease of adults in developed countries.[25] Skeletal TB presumably develops from reactivation of dormant tubercles originally seeded during stage 2 of the primary infection or, in the case of spinal TB, from contiguous spread from paravertebral lymph nodes to the vertebrae. Generally, spinal TB (Pott's disease) accounts for 50 to 70% of the reported cases; the hip or knee is involved in 15 to 20% of cases, and the ankle, elbow, wrists, shoulders, and other bones and joints account for 15 to 20% of cases.[40] Approximately 50% of patients have a previous history or concurrent case of pulmonary TB, and the chest radiograph is normal in appearance in up to one half of the cases.

Patients with Pott's disease may simply complain of back pain or stiffness. Examination may show fever, point tenderness, and decreased range of motion. If the initial radiograph is normal in appearance, the diagnosis may be delayed, allowing the disease to progress. The initial lesion usually spreads to the intervertebral disk and then to the adjacent vertebrae, producing the classic radiographic appearance of anterior wedging of two involved vertebral bodies with destruction of the disk. Early changes of spinal TB can be difficult to detect on plain radiographs and include loss of the "white stripe" of the vertebral end plate subsequent to destruction of subchondral bone. Unfortunately, plain films usually are unable to reveal TB infection until roughly 50% of the vertebra has been destroyed.[85] Thus, computed tomography (CT) and magnetic resonance imaging (MRI) scanning should be used when the disease is suspected.[25,40]

Paraspinal "cold" abscesses develop in 50% or more of cases, with occasional formation of sinus tracts. The abscess can spread the infection up and down the spine, sometimes sparing vertebral bodies along its course, forming the so-called skip lesions.[25,85] These skip lesions can easily be missed in imaging the spine for Pott's disease. The main complication of Pott's disease is spinal cord compression.[40]

Medical management includes chemotherapy, modified bedrest, and early ambulation and results in improvement in approximately 90% of patients without neurologic involvement.[25] Surgical treatment usually is reserved for patients with neurologic complications.

Renal Disease

The kidney is well vascularized, and hematogenous dissemination to that organ is fairly common. After the typical tuberculous lesions develop within the parenchyma, infection can spread into the calyces, renal pelvis, ureters, and bladder. As a result, tuberculous granulomas, scarring, and obstruction can occur anywhere along the urinary tract.[86]

The initial presenting signs and symptoms of urinary involvement are nonspecific. Advanced renal disease and destruction may occur before the diagnosis is made. The urinalysis often reveals pyuria, hematuria, and albuminuria. Sterile pyuria is a classic finding in renal TB, but in many cases with this finding, cultures will be positive for other urinary pathogens. The finding of pyuria in an acid urine with no organisms isolated should increase clinical suspicion for TB.[40] In one study of the diagnosis of renal TB, AFB stains were found to be 52% sensitive and PCR testing was 96% sensitive.[87] Both tests had excellent specificity (97 to 98%). Mycobacterial cultures should be ordered when genitourinary TB infection is suspected.

Complications of renal TB include nephrolithiasis, ureteral obstruction or reflux, recurrent bacterial infections, hypertension, papillary necrosis, renal insufficiency, autonephrectomy, and, rarely, development of transitional cell cancer.[86,87]

Male Genital Disease

Male genital TB usually is associated with coexistent renal TB. Spread of infection from the kidney may involve the prostate, seminal vesicles, epididymides, and testes.[25] A painless or slightly painful scrotal mass is a typical finding, and the patient may have symptoms of prostatitis, epididymitis, or orchitis.[40] Epididymal or prostatic calcifications may be clues to the diagnosis. TB involvement of the seminal vesicles may lead to infertility.[87]

Female Genital Disease

In women, the disease usually begins with a hematogenous focus in the fallopian tubes. The infection then spreads to the endometrium (in 50%), ovaries (in 30%), cervix (in 5 to 15%), and vagina (in 1%).[25] Clinical manifestations may include abdominal or pelvic pain, ascites, infertility, menstrual irregularities, and, rarely, vaginal discharge. An ulcerating mass may be present on the cervix. Genital TB may be confused with ovarian or endometrial cancer, Meigs' syndrome, vulvar or vaginal ulcer, pelvic abscess, cervicitis, or cervical carcinoma.[88]

Sexual transmission of TB by persons with active genital TB has been described.[89] Women with genital TB who become pregnant are at increased risk for ectopic pregnancy.[25]

Multisystem Disease

Acute disseminated TB refers to active hematogenous spread of MTB to several organs in the body. The term *miliary tuberculosis* was first used to describe the pathologic lesions, which resemble small millet seeds. This term is now used as a clinical term referring to the massive dissemination that leads to generalized systemic illness. Miliary TB occurs when the host is unable to contain either a recently acquired or a dormant TB infection. In the past, miliary TB occurred mainly in young children after primary infection; today, it is more common in the elderly and in persons infected with HIV.[40]

In infants and young children, the illness generally is acute and severe. In young adults, the acute illness runs a slower course and usually is less severe. Miliary TB often is a subtle disease associated with alcoholism, cirrhosis, neoplasm, pregnancy, collagen vascular disease, or use of corticosteroids or immunosuppressive medications.[25]

The clinical presentations are varied because of the multisystem nature of miliary TB. Systemic symptoms of fever, weight loss, anorexia, and weakness generally are present.[40] The choroidal tubercle (a granuloma in the choroid of the retina) may represent the only physical finding specific for disseminated TB.[40]

A presumptive diagnosis can be made rapidly if chest radiographs show a miliary infiltrate (Fig. 133-7). Unfortunately, the classic miliary pattern is absent on radiographs in approximately 50% of cases. Routine laboratory tests generally are not helpful. Hyponatremia from the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is common and often is associated with meningitis. Panculturing usually has a high yield, and HIV-infected patients may have positive results on blood cultures. Transbronchial biopsy can be performed to obtain tissue rapidly for analysis. Other potential biopsy sites include liver, lymph nodes, and bone marrow.[25]

Mortality rates for miliary TB are higher than for the other forms of TB, with one case series reporting a rate of 21%.[90] The high mortality rate often is caused by delay in treatment, which should always be initiated immediately on the basis of clinical suspicion and not delayed until confirmation of the diagnosis.

A fulminant form of miliary TB may cause the acute respiratory distress syndrome and disseminated intravascular coagulation. In these cases, the addition of corticosteroids (prednisone, 60 to 80 mg/day) is indicated.[25]

Central Nervous System Disease

Approximately 6% of all cases of extrapulmonary TB involve the central nervous system (CNS),[17] and CNS involvement remains a grave consequence of tuberculous infection. The peak incidence of CNS TB is in newborn to 4-year-old children.[40]

Tuberculous Meningitis

Tuberculous meningitis usually results from the rupture of a subependymal tubercle into the subarachnoid space, rather than from direct hematogenous seeding of the CNS.[25] When it is a complication of miliary TB, meningitis usually develops within several weeks. In children, it is an early postprimary TB event, usually appearing within 6 months. Tuberculous cerebral involvement is most marked at the base of the brain, and vasculitis of local arteries and veins may lead to aneurysm formation, thrombosis, and focal hemorrhagic infarction. The vessels to the basal ganglia most commonly are involved, leading to formation of lacunar infarcts or deficits associated with movement disorders. Involvement of other vessels, such as the middle cerebral artery, may lead to hemiparesis or hemiplegia.[25]

Tuberculous meningitis begins with a prodrome of malaise, intermittent headache, and low-grade fever. In 2 to 3 weeks, a protracted headache develops. Vomiting, confusion, meningismus and focal neurologic signs, and coma may follow. Nuchal rigidity may be absent. Diplopia resulting from basilar exudate is present in up to 70% of patients. Hyponatremia may be present because SIADH is common. The CSF cell count usually ranges from 0 to 1500 white blood cells per mL, with a predominance of lymphocytes; however, polymorphonuclear cells may predominate early in the course. CSF protein usually is elevated and CSF glucose typically is low. A single lumbar puncture CSF specimen yields a positive AFB culture result in only 37% of cases, but pooled samples from multiple lumbar punctures[4] yield a positive result in 90% of cases.[25]

The classic triad of neuroradiologic findings in patients with TB meningitis consists of basal meningeal enhancement, hydrocephalus, and cerebral or brainstem infarction. CT or MRI also may reveal rounded lesions typical of evolving parenchymal tuberculomas.[91]

Prognosis is influenced by age, duration of symptoms, and the presence of neurologic deficits. In children, the overall mortality is 13%, and permanent neurologic deficits develop in approximately one half of the survivors.[66] Outcome also is closely linked to the clinical stage at which the disease arises. Complete recovery is the rule in stage 1, wherein the alert patient has no focal neurologic signs and no hydrocephalus. Stage 2 is characterized by confusion and focal neurologic changes, and patients in stage 3 present with stupor or with dense hemiplegia or paraplegia. In contrast with the excellent prognosis for stage 1 disease, approximately one half of patients with stage 3 disease either die or are left with severe neurologic disability.[25]

Treatment starts with a four-drug regimen. INH and pyrazinamide (PZA) reach increased concentrations in the CSF in the presence of inflamed meninges. RIF also crosses the

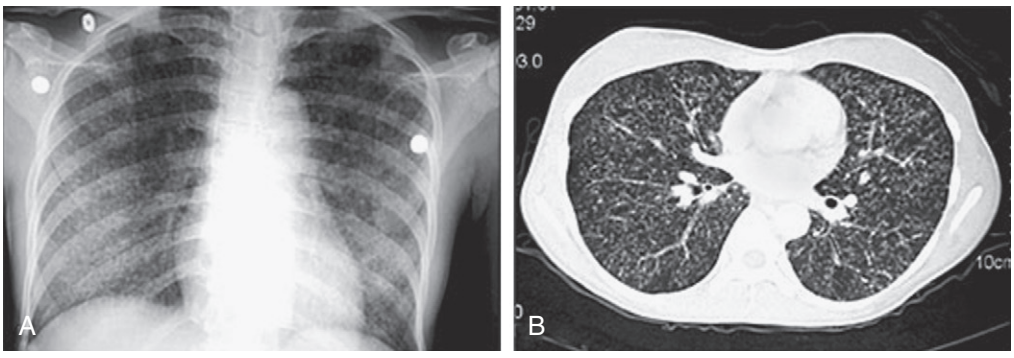

Figure 133-7. Chest radiograph (**A**) and CT image (**B**) demonstrate a miliary pattern. (Images reprinted with permission from "Extrapulmonary tuberculosis: An overview," November 1, 2005, American Family Physician. Copyright 2005 American Academy of Family Physicians. All rights reserved.)

blood-brain barrier. Whereas for most other forms of extrapulmonary TB, 6-month regimens are used, the CDC recommends 9 to 12 months of therapy for TB meningitis.[68] Corticosteroids also are recommended by the CDC. Prednisone, 60 to 80 mg, should be given in a daily dose and tapered over 4 to 6 weeks.[25] Ventricular shunting may be needed if hydrocephalus develops.

Spinal Meningitis

Tuberculous spinal meningitis is a complication of CNS infection that usually originates through hematogenous dissemination from an outside source, although tuberculous meningitis may extend caudally and involve the spine. Local extension of bone or disk TB also has been described. Presenting symptoms and signs result from nerve root or cord compression and may include pain, sensory changes, paralysis, or weakness of bladder or rectal sphincters.[25]

Intracranial Tuberculoma

A tuberculoma usually begins in an area of TB cerebritis as a cluster of microgranulomas, which coalesce into a mature noncaseating granuloma.[91] These space-occupying lesions may cause focal or generalized signs or symptoms, such as tonic-clonic seizures. Involvement of the CNS parenchyma also may be accompanied by meningitis. Imaging reveals either solitary or multiple tuberculomas (Fig. 133-8), usually involving the frontal or parietal lobes.[91] Treatment includes chemotherapy before surgical removal. Corticosteroids may reduce edema and decrease the symptoms. If MTB is discovered at the time of surgery, postoperative chemotherapy may prevent the further spread of the disease.[25]

Gastrointestinal Disease

Gastrointestinal TB infection usually is secondary to hematogenous or lymphatic spread but also may result from swallowed bronchial secretions or direct spread from local sites, such as lymph nodes or fallopian tubes.[92] TB may occur in any gastrointestinal location from the mouth to the anus, but lesions proximal to the terminal ileum are rare. The ileocecal area is the most common site of involvement, producing signs and symptoms of pain, anorexia, diarrhea, obstruction, hemorrhage, and often a palpable mass.

Figure 133-8. Head computed tomography scan demonstrating tuberculomas in a patient with acquired immunodeficiency syndrome.

The most common clinical manifestations of gastrointestinal TB are abdominal pain, fever, weight loss, anorexia, nausea, vomiting, and diarrhea.[92] The nonspecificity of these findings as well as those on the physical examination may lead to the misdiagnosis of gastrointestinal TB as appendicitis, intestinal obstruction, or cancer. Approximately 12 to 16% of cases present as an acute abdomen.[92] The signs and symptoms can be so similar to those of other diseases that the diagnosis often is made at surgery. The clinical manifestations of anal TB include fissures, fistulas, and perirectal abscesses.[40] Antimicrobial treatment of gastrointestinal TB is the same as that of pulmonary disease.[68,92]

Peritonitis

Tuberculous peritonitis may develop from local spread of MTB infection from a tuberculous lymph node, intestinal focus, or infected fallopian tube. In addition, peritonitis can develop from seeding of the peritoneum in miliary TB or from the reactivation of a latent focus.[25]

The patient with tuberculous peritonitis commonly has pain and abdominal swelling associated with fever, anorexia, and weight loss. Diagnosis may be confounded by the similarity of this disease to alcoholic hepatitis and by the fact that this disease often coexists with other disorders, especially cirrhosis with ascites.[40] Paracentesis is thus essential. The peritoneal fluid is exudative, with a cell count of 500 to 2000 cells per mL. Lymphocytes usually predominate, with rare exceptions early in the process, when polymorphonuclear leukocytes may predominate.[25] AFB smears of the fluid have a low diagnostic yield, with a reported sensitivity of no more than 7%, and the culture result is positive in only 25% of the cases. Peritoneal biopsy often is necessary to confirm the diagnosis. Treatment is the same as for pulmonary TB, with a 6-month regimen.[25,68]

■ MANAGEMENT

Initial Emergency Department Management

The most emergent presentation of pulmonary TB is massive hemoptysis, defined as loss of at least 600 mL of blood in 24 hours. Exsanguination rarely occurs, and the major morbidity is due to asphyxiation from aspirated blood. The airway should be secured with a large-diameter (8-mm) endotracheal tube that can accommodate a fiberoptic bronchoscope. The patient should be positioned with the bleeding lung in a dependent position. Selective main bronchus intubation should be considered to allow ventilation of the unaffected lung and to minimize the spread of blood from the affected lung. Emergent consultation for bronchoscopy, surgical resection, or angiography with selective embolization is required.[49] Patients suspected of having active pulmonary TB should be immediately placed in respiratory isolation.

Medical Therapy

Patients suspected of having pulmonary TB whose sputum smears return positive for AFB can be presumptively diagnosed and treated with antituberculosis agents. In patients with negative findings on a sputum smear but clinical and radiographic findings consistent with pulmonary TB, it also may be appropriate to initiate treatment for presumptive TB.[68] A few days of therapy with antituberculosis agents does not interfere with bacteriologic diagnosis, so severely ill patients with presumed TB should be treated immediately. Local factors, including the prevalence of TB and available resources, help determine the appropriateness of presumptive therapy.

Antituberculosis Medications

Three basic therapeutic principles govern the treatment of TB: (1) any treatment regimen must contain multiple drugs to which the MTB organism is susceptible, (2) the therapeutic agents must be taken regularly, and (3) the therapy must continue for a sufficient period.[46] In clinical practice, the last is the most problematic.

It is estimated that approximately 33 to 50% of patients with TB fail to follow medical recommendations. Patients at higher risk for noncompliance are those with previous treatment failures; substance abusers; patients with mental, emotional, or physical impairment; and those in whom preventive treatment has failed.[93] The most effective strategy to ensure compliance is directly observed therapy (DOT), which is now the preferred practice in the United States.

The medications used to treat MTB generally are divided into first-line and second-line agents[68] (Tables 133-4 and 133-5). Of these agents, 10 have been approved by the U.S. Food and Drug Administration (FDA) for treating MTB. The most

Table 133-4 Doses of Antituberculosis Drugs for Adults and Children

DRUG	PREPARATION	ADULTS/ CHILDREN	DOSES*† DAILY	1×/WK	2×/WK	3×/WK
First-Line Drugs						
Isoniazid	Tablets (50, 100, 300 mg); elixir (50 mg/5 mL); aqueous solution (100 mg/mL) for intravenous or intramuscular injection	Adults (max)	5 mg/kg (300 mg)	15 mg/kg (900 mg)	15 mg/kg (900 mg)	15 mg/kg (900 mg)
		Children (max)	10–15 mg/kg (300 mg)	—	20–30 mg/kg (900 mg)	—
Rifampin	Capsule (150, 300 mg); powder may be suspended for oral administration; aqueous solution for intravenous injection	Adults‡ (max)	10 mg/kg (600 mg)	—	10 mg/kg (600 mg)	10 mg/kg (600 mg)
		Children	10–20 mg/kg (600 mg)	—	10–20 mg/kg (600 mg)	—
Rifabutin	Capsule (150 mg)	Adults‡ (max)	5 mg/kg (300 mg)	—	5 mg/kg (300 mg)	5 mg/kg (300 mg)
		Children	Appropriate dosing for children is unknown	Appropriate dosing for children is unknown	Appropriate dosing for children is unknown	Appropriate dosing for children is unknown
Rifapentine	Tablet (150 mg, film-coated)	Adults	—	10 mg/kg (continuation phase) (600 mg)	—	—
		Children	Not approved for use in children	Not approved for use in children	Not approved for use in children	Not approved for use in children
Pyrazinamide	Tablet (500 mg, scored)	Adults	See Table 133-5	—	See Table 133-5	See Table 133-5
		Children (max)	15–30 mg/kg (2.0 g)	—	50 mg/kg (2 g)	
Ethambutol	Tablet (100 mg, 400 mg)	Adults	See Table 133-5	—	See Table 133-5	See Table 133-5
		Children§ (max)	15–20 mg/kg (1.0 g)	—	50 mg/kg (2.5 g)	
Second-Line Drugs						
Cycloserine	Capsule (250 mg)	Adults (max)	10–15 mg/kg/day (1.0 g in two doses), usually 500–750 mg/day in two doses‖	No data to support intermittent administration	No data to support intermittent administration	No data to support intermittent administration
		Children (max)	10–15 mg/kg/day (1.0 g/day)	—	—	—
Ethionamide	Tablet (250 mg)	Adults¶ (max)	15–20 mg/kg/day (1.0 g/day), usually 500–750 mg/day in a single daily dose or two divided doses¶	No data to support intermittent administration	No data to support intermittent administration	No data to support intermittent administration
		Children (max)	15–20 mg/kg/day (1.0 g/day)	No data to support intermittent administration	No data to support intermittent administration	No data to support intermittent administration

Table 133-4 Doses of Antituberculosis Drugs for Adults and Children—cont'd

DRUG	PREPARATION	ADULTS/ CHILDREN	DOSES*†			
			DAILY	1×/WK	2×/WK	3×/WK
Streptomycin	Aqueous solution (1-g vials) for intravenous or intramuscular administration	Adults (max) Children (max)	** 20–40 mg/kg/day (1 g)	— —	— 20 mg/kg	— —
Amikacin/ kanamycin	Aqueous solution (500-mg and 1-g vials) for intravenous or intramuscular administration	Adults (max) Children (max)	** 15–30 mg/kg/day (1 g) intravenous or intramuscular as a single daily dose	— —	— 15–30 mg/kg	— —
Capreomycin	Aqueous solution (1-g vials) for intravenous or intramuscular administration	Adults (max) Children (max)	** 15–30 mg/kg/day (1 g) as a single daily dose	— —	— 15–30 mg/kg	— —
Para-aminosalicylic acid (PAS)	Granules (4-g packets) can be mixed with food; tablets (500 mg) are still available in some countries but not in United States; a solution for intravenous administration is available in Europe	Adults Children	8–12 g/day in two or three doses 200–300 mg/kg/day in two to four divided doses (10 g)	No data to support intermittent administration No data to support intermittent administration	No data to support intermittent administration No data to support intermittent administration	No data to support intermittent administration No data to support intermittent administration
Levofloxacin	Tablets (250, 500, 750 mg); aqueous solution (500-mg vials) for intravenous injection	Adults Children	500–1000 mg daily No long-term use††	No data to support intermittent administration No long-term use††	No data to support intermittent administration No long-term use††	No data to support intermittent administration No long-term use††
Moxifloxacin	Tablets (400 mg); aqueous solution (400 mg/250 mL) for intravenous injection	Adults Children	400 mg daily No long-term use‡‡	No data to support intermittent administration No long-term use‡‡	No data to support intermittent administration No long-term use‡‡	No data to support intermittent administration No long-term use‡‡
Gatifloxacin	Tablets (400 mg); aqueous solution (200 mg/20 mL, 400 mg/40 mL) for intravenous injection	Adults Children	400 mg daily No long-term use§§	No data to support intermittent administration No long-term use§§	No data to support intermittent administration No long-term use§§	No data to support intermittent administration No long-term use§§

*Dose per weight is based on ideal body weight. Children weighing more than 40 kg should be dosed as for adults.
†In regimens given in this table, adult dosing begins at age 15 years.
‡Dose may need to be adjusted for patients who also are taking protease inhibitors or non-nucleoside reverse transcription inhibitors.
§The drug probably can be used safely in older children but should be used with caution in children younger than 5 years, in whom visual acuity cannot be monitored. In younger children, EMB at the dose of 15 mg/kg per day can be used if there is suspected or proven resistance to INH or RIF.
‖Of note, although this is the dose recommended generally, most clinicians with experience using cycloserine indicate that it is unusual for patients to be able to tolerate this amount. Serum concentration measurements often are useful in determining the optimal dose for a given patient.
¶The single daily dose can be given at bedtime or with the main meal.
**Dose: 15 mg/kg per day (1 g) and 10 mg/kg in persons older than 59 years (750 mg). Usual dose: 750–1000 mg administered intramuscularly or intravenously, given as a single dose 5–7 days per week and reduced to two or three times per week after the first 2–4 months or after culture conversion, depending on the efficacy of the other drugs in the regimen.
††The long-term use (for more than several weeks) of levofloxacin in children and adolescents has not been approved because of concerns about effects on bone and cartilage growth. However, most experts agree that the drug should be considered for children with tuberculosis caused by organisms resistant to both INH and RIF. The optimal dose is not known.
‡‡The long-term use (for more than several weeks) of moxifloxacin in children and adolescents has not been approved because of concerns about effects on bone and cartilage growth. The optimal dose is not known.
§§The long-term use (for more than several weeks) of gatifloxacin in children and adolescents has not been approved because of concerns about effects on bone and cartilage growth. The optimal dose is not known.
EMB, ethambutol; INH, isoniazid; RIF, rifampin.
From American Thoracic Society; CDC; Infectious Diseases Society of America: Treatment of tuberculosis. CDC MMWR Recomm Rep 52(RR-11):1, 2003.

Table 133-5 Suggested Pyrazinamide and Ethambutol Doses, Using Whole Tablets, for Adults Weighing 40 to 90 kg

	DOSE BY WEIGHT*		
DOSING SCHEDULE, UNITS	**40–55 KG**	**56–75 KG**	**76–90 KG**
Pyrazinamide			
Daily, mg (mg/kg)	1000 (18.2–25.0)	1500 (20.0–26.8)	2000† (22.2–26.3)
Thrice weekly, mg (mg/kg)	1500 (27.3–37.5)	2500 (33.3–44.6)	3000† (33.3–39.5)
Twice weekly, mg (mg/kg)	2000 (36.4–50.0)	3000 (40.0–53.6)	4000† (44.4–52.6)
Ethambutol			
Daily, mg (mg/kg)	800 (14.5–20.0)	1200 (16.0–21.4)	1600† (17.8–21.1)
Thrice weekly, mg (mg/kg)	1200 (21.8–30.0)	2000 (26.7–35.7)	2400† (26.7–31.6)
Twice weekly, mg (mg/kg)	2000 (36.4–50.0)	2800 (37.3–50.0)	4000† (44.4–52.6)

*Based on estimated lean body weight.
†Maximum dose regardless of weight.
Adapted from American Thoracic Society; CDC; Infectious Diseases Society of America: Treatment of tuberculosis. MMWR Recomm Rep 52(RR-11):1, 2003.

commonly used first-line agents include INH, RIF, PZA, and ETH.[68] Agents that are used in special circumstances but are not FDA approved for this purpose include rifabutin, levofloxacin, moxifloxacin, amikacin, and kanamycin.

First-Line Agents

INH demonstrates extremely potent early bactericidal activity and can rapidly decrease the patient's infectiousness. The incidence of INH-induced hepatitis is estimated to be 0.6% when INH is given alone, 1.6% when given with other antituberculosis agents (excluding RIF), and 2.7% when given with RIF. The risk increases with age and also with underlying liver disease, alcohol use, and administration during the postpartum period. Another adverse effect is peripheral neuropathy. This is uncommon (less than 0.2%) at standard doses and may be avoided by the co-administration of pyridoxine (25 mg/day). Patients who have conditions associated with neuropathy (e.g., diabetes, HIV infection, alcoholism) and pregnant or breast-feeding women are at increased risk. Supplemental pyridoxine is recommended for such patients.[68]

RIF also demonstrates strong early bactericidal activity. This agent causes orange discoloration of body fluids, including urine, tears, sweat, and sputum. Patients should be warned of this effect before administration of the medication. It is especially important to warn soft contact lens wearers, in whom permanent lens staining may occur. Rifapentine is a rifamycin derivative with excellent activity against MTB. Its long half-life makes it a good candidate for intermittent therapy regimens (given once weekly). Rifabutin is another rifamycin-like antibiotic that most often is used for treatment or prophylaxis of infections with *M. avium* complex; however, it also is effective against MTB. This medication generally is used for treatment in patients who do not tolerate RIF or who are taking medications with known adverse interactions with RIF (e.g., antiretrovirals, oral contraceptives, methadone, warfarin).

PZA works against organisms contained in the acid environment of the macrophage. The chief side effect is hepatotoxicity, but this risk is very low at daily doses of 25 mg/kg or less. Polyarthralgias occur commonly (up to 40% of patients) but usually respond to nonsteroidal anti-inflammatory drugs or aspirin.

ETH is a first-line agent that helps prevent the emergence of RIF resistance during TB treatment. Retrobulbar neuritis can occur, resulting in decreased visual acuity or red-green color blindness. Thus, monitoring of visual symptoms is key to prevention of adverse effects in patients using ETH. Because of the difficulty in visual testing in small children and infants, ETH should be avoided in these populations, except in the cases of adult-type TB or with INH or RIF resistance.[68]

Fixed-Dose Combination Drugs

Fixed-dose combinations are multiple antituberculosis agents packaged into single tablets. They are useful to prevent monotherapy (e.g., when the patient selectively takes only one of the prescribed drugs) and the emergence of drug resistance. Rifater contains INH, RIF, and PZA. Rifamate contains INH and RIF. These preparations are indicated when DOT is not possible.[68]

Second-Line Agents

Streptomycin was once a first-line anti-TB agent, but increasing resistance rates now limit its usefulness. Streptomycin must be given parenterally and has a peak of action 1 hour after the intramuscular dose. The chief side effects of this potentially teratogenic agent are ototoxicity and nephrotoxicity. Amikacin, kanamycin, and capreomycin also are injectable agents used for drug-resistant TB. As with streptomycin, ototoxicity and neurotoxicity are their major adverse effects. TB strains resistant to streptomycin usually are sensitive to both amikacin and kanamycin, and resistance to these two latter drugs usually is linked.

Cycloserine, ethionamide, and para-aminosalicylic acid (PAS) are oral agents used for treatment in patients with drug-resistant TB when the strain is presumed or known to be sensitive to these agents. Cycloserine also sometimes is used temporarily for patients with acute hepatitis. The main adverse effect of cycloserine is psychosis or seizures (occurring in 3 to 16% of patients). Ethionamide is similar to INH in both structure and toxicity. Major adverse effects of PAS include gastrointestinal distress (most common), hypothyroidism, and hepatitis.

Fluoroquinolones have played a more recent but limited role in the treatment of TB. They are less effective than the first-line agents and are used mainly in the treatment of drug-resistant disease. They also may be used when first-line agents are not tolerated. If they are used singly, resistance may develop quickly. The agents most active against MTB are levofloxacin, moxifloxacin, and gatifloxacin. Because the long-term experience regarding safety and tolerability is greatest with levofloxacin, this fluoroquinolone is preferred. The main side effects are gastrointestinal upset, minor CNS symptoms, and photosensitivity or rash.[68]

Initial Therapy

Adults

In 2003, the American Thoracic Society, the CDC, and the Infectious Diseases Society of America published a joint statement providing updated evidence-based recommendations for the treatment of TB.[68] The goals of therapy are to rapidly kill large numbers of bacilli (bactericidal activity), prevent emergence of drug resistance, and prevent relapse by eliminating dormant or slowly dividing bacilli (sterilizing activity). There are four basic recommended regimens[68] (Table 133-6). These are used when the organism is known or presumed to be susceptible to INH, RIF, PZA, and ETH. All begin with a 2-month initial phase, followed by a continuation phase lasting 4 to 7 months (total treatment duration of 6 to 9 months). Therapeutic regimens less than 6 months in duration usually are associated with an unacceptably high relapse rate. Dosing frequency varies, ranging from 1 to 7 days per week. There is also variation in the strength of evidence supporting each regimen, depending on the patient's HIV serostatus. The regimen that is rated as preferred and supported by the strongest evidence (randomized clinical trials) consists of INH, RIF, PZA, and EMB for 8 weeks (5 to 7 days per week), followed by INH and RIF for 18 weeks (2, 5, or 7 days per week). DOT must be used whenever medications are given less often than 7 days per week.[68]

HIV-Seropositive Patients

Adequate treatment of active TB in patients co-infected with HIV is critical. It has been observed that immune activation from TB enhances both systemic and local HIV replication and may accelerate the natural progression of HIV infection. Active TB in HIV-infected patients has been associated with increased risk for opportunistic infections and death. TB treatment alone leads to reduction in viral load in these patients.[21] Untreated or inadequately treated TB may result in increased morbidity and mortality, not only from MTB but also from accelerated AIDS. Furthermore, TB can spread rapidly through immunocompromised populations when a source case remains contagious for a prolonged period.[94]

Table 133-6 Drug Regimens for Culture-Positive Pulmonary Tuberculosis Caused by Drug-Susceptible Organisms

INITIAL PHASE			CONTINUATION PHASE			RANGE OF TOTAL DOSES (MINIMAL DURATION)	RATING† (EVIDENCE)‡	
REGIMEN	DRUGS	INTERVAL/NO. OF DOSES* (MINIMAL DURATION)	REGIMEN	DRUGS	INTERVAL/NO. OF DOSES*,§ (MINIMAL DURATION)		HIV⁻	HIV⁺
1	INH RIF PZA EMB	7 days/wk for 56 doses (8 wk) or 5 days/wk for 40 doses (8 wk)‖	1a	INH/RIF	7 days/wk for 126 doses (18 wk) or 5 days/wk for 90 doses (18 wk)‖	182–130 (26 wk)	A (I)	A (II)
			1b	INH/RIF	Twice weekly for 36 doses (18 wk)	92–76 (26 wk)	A (I)	A (II)‖
			1c¶	INH/RPT	Once weekly for 18 doses (18 wk)	74–58 (26 wk)	B (I)	E (I)
2	INH RIF PZA EMB	7 days/wk for 14 doses (2 wk), then twice weekly for 12 doses (6 wk); or 5 days/wk for 10 doses (2 wk),‖ then twice weekly for 12 doses (6 wk)	2a	INH/RIF	Twice weekly for 36 doses (18 wk)	62–58 (26 wk)	A (II)	B (II)‖
			2b¶	INH/RPT	Once weekly for 18 doses (18 wk)	44–40 (26 wk)	B (I)	E (I)
3	INH RIF PZA EMB	Three times weekly for 24 doses (8 wk)	3a	INH/RIF	Three times weekly for 54 doses (18 wk)	78 (26 wk)	B (I)	B (II)
4	INH RIF EMB	7 days/wk for 56 doses (8 wk) or 5 days/wk for 40 doses (8 wk)**	4a	INH/RIF	7 days/wk for 217 doses (31 wk) or 5 days/wk for 155 doses (31 wk)**	273–195 (39 wk)	C (I)	C (II)
			4b	INH/RIF	Twice weekly for 62 doses (31 wk)	118–102 (39 wk)	C (I)	C (II)

*When DOT is used, drugs may be given 5 days/week and the necessary number of doses adjusted accordingly. Although no studies have compared 5 with 7 daily doses, extensive experience indicates this would be an effective practice.

†A = preferred; B = acceptable alternative; C = offer when A and B cannot be given; E = should never be given.

‡I = randomized clinical trial; II = data from clinical trials that were not randomized or were conducted in other populations; III = expert opinion.

§Patients with cavitation on initial chest radiograph and positive culture results at completion of 2 months of therapy should receive a 7-month (31 weeks: either 217 doses [daily] or 62 doses [twice weekly]) continuation phase.

‖Not recommended for human immunodeficiency virus–infected patients with $CD4^+$ cell counts <100/μL.

¶Options 1c and 2b should be used only in HIV-seronegative patients who have negative sputum smears at the time of completion of 2 months of therapy and who do not have cavitation on initial radiograph. For patients started on this regimen and found to have a positive culture from the 2-month specimen, treatment should be extended an extra 3 months.

**Five-day-a-week administration is always given by DOT. Rating for these regimens is A(III).

DOT, directly observed therapy; EMB, ethambutol; INH, isoniazid; PZA, pyrazinamide; RIF, rifampin; RPT, rifapentine.

From American Thoracic Society; CDC; Infectious Diseases Society of America: Treatment of tuberculosis. MMWR Recomm Rep 52(RR-11):1, 2003.

Current recommendations for treating MTB in HIV-infected patients are the same as those for patients who are not HIV-infected, with a few important exceptions. The once-weekly INH-RIF dosing for the continuation phase should not be used because of a high relapse rate (17%). The twice-weekly INH-RIF dosing should also not be used in patients with $CD4^+$ counts below 100 cells/μL because of emergence of RIF monoresistance. Treatment duration should be a minimum of 6 months. The duration should be extended to 9 months if sputum cultures remain positive after the 2-month initial phase of treatment.[68]

Significant drug interactions between rifamycins used for TB and antiretroviral drugs (protease inhibitors and non-nucleoside reverse transcriptase inhibitors [NNRTIs]) used for HIV infection complicate the treatment of patients with active TB who are co-infected with HIV. These drug interactions are due primarily to changes in the metabolism of the antiretrovirals and the rifamycins secondary to induction or inhibition of the hepatic cytochrome CYP450 enzyme system. The currently available rifamycins are inducers of CYP450, with RIF being the most potent, rifapentine intermediate, and rifabutin the least potent.[95] Because all of the protease inhibitors are metabolized by CYP450, coadministration of RIF and the protease inhibitors would cause a marked decrease in the blood concentration of the protease inhibitors, probably reducing their antiretroviral activity as well. For treating MTB in patients who are taking protease inhibitors, rifabutin can be used instead of the other rifamycins. Rifabutin provides good activity against MTB without substantially affecting the effectiveness of protease inhibitors.[68]

There are major differences in the actions of NNRTIs on CYP450 and the degree to which they are substrates of CYP450; therefore, their interactions with rifamycins cannot be fully summarized as a class.[95] However, RIF reduces serum concentrations of all three NNRTIs (delavirdine, nevirapine, and efavirenz). Serum concentrations of NNRTIs must be maintained at an optimal steady state to prevent resistant mutations of HIV. When RIF is used in patients taking nevirapine or efavirenz, the NNRTI dose must be increased. Alternatively, rifabutin can be substituted for RIF without NNRTI dose adjustment. Because of the dramatic reduction in serum concentration, none of the rifamycin preparations are acceptable for patients taking delavirdine.[68]

When TB treatment is initiated in HIV-positive patients, a paradoxical reaction to medical therapy may develop in some instances. The reaction manifests with development of fever, new or enlarging lymph nodes, or worsening of radiographic disease. It is more common in HIV-infected patients, occurring in 7 to 36% of cases after beginning treatment. Other causes of deterioration, such as treatment failure, must be considered when this reaction is suspected. Severe paradoxical reactions may be managed with a 2-week tapering course of prednisone or methylprednisolone.[68]

Children and Adolescents

The treatment of adolescents, children, and infants who are culture-positive for MTB is in principle the same as that of adults. Some important differences are recognized, however. In children, active pulmonary TB usually is part of the initial infection. The chest radiograph demonstrates hilar adenopathy and middle or lower lobe infiltrates. Less commonly, the development of "adult-type" infection, which resembles postprimary infection in adults (upper lobe infiltrates, cavitary lesions, sputum production), is seen in this age group. Because the bacillary load of primary infection is lower than with adult-type disease, the recommended regimen for children with primary TB is a three-drug regimen (INH, RIF, PZA) for the 2-month initial phase, followed by INH and RIF for a 4-month continuation phase (for a total of 6 months). For adult-type infection in children, EMB is added to the initial phase. EMB also is added if INH or RIF resistance is suspected. Because it can be difficult to isolate MTB from children, available resistance patterns of the source should be taken into consideration. Visual acuity and color discrimination should be monitored monthly for older children who are treated with EMB. Inability to monitor vision because of young age is not a contraindication to EMB use in adult-type infection or in the case of INH or RIF resistance. Some important points in treating children are presented in Box 133-4.[68]

BOX 133-4 TREATMENT OF TUBERCULOSIS IN CHILDREN

- Infection with tuberculosis in children younger than 4 years is more likely to disseminate and therefore demands prompt recognition and aggressive management.
- Sputum smears are a less reliable diagnostic tool. It may be more appropriate to confirm the diagnosis in a child using culture results or results from the adult source. If neither is available, early-morning gastric aspirates, bronchoalveolar lavage, or tissue may be used.
- Because of its ocular toxicity, ethambutol should be avoided in this age group. Streptomycin, kanamycin, and amikacin are alternatives.
- The primary cause of treatment failure in this population is noncompliance. Therefore, directly observed therapy is preferable, and twice-a-week regimens are an option.
- Treat extrapulmonary tuberculosis as described above for pulmonary variety except for infections involving bones or joints, meningitis, and miliary disease, for which therapy may be required for 9 to 12 months.
- Hilar adenopathy on chest radiographs may take 2 to 3 years to resolve after treatment.

Drug-Resistant Tuberculosis

Two types of drug-resistant MTB have emerged as a result of spontaneous mutations. *Multidrug-resistant TB* (MDR-TB) is defined as TB in which the mycobacteria are resistant to two or more first-line antituberculosis agents. Multidrug resistance may develop when a single drug is added to a failing regimen, an intervention equivalent to giving monotherapy.[96] *Extensively drug-resistant TB* (XDR-TB) is TB characterized by resistance to both first-line and at least three second-line drugs. Patients with TB who are improperly treated (especially with monotherapy) or who are nonadherent to their treatment regimen present a microbiologic milieu likely to offer the drug-resistant strains a selective advantage. When these strains predominate, "acquired resistance" has occurred. Patients with acquired resistance can transmit drug-resistant organisms to previously uninfected (never treated) persons, a process resulting in primary drug resistance.[97]

Multidrug-Resistant Tuberculosis

Although MDR-TB ultimately can be traced back to suboptimal treatment, it is the transmission of primary drug resistance from person to person that allows rapid dissemination of drug-resistant strains.[97] The spread of primary drug resistance is faster when HIV infection is highly prevalent in a population.[39,98,99] Because initial TB infection in HIV-infected patients progresses rapidly to active disease, newly infected persons

BOX 133-5 RISK FACTORS FOR DRUG-RESISTANT *MYCOBACTERIUM TUBERCULOSIS* INFECTION

- Previous unsuccessful antituberculosis treatment
- Failure to respond or adhere to a good treatment regimen
- Human immunodeficiency virus infection
- Intravenous drug abuse
- Close contact with source cases
- Recent immigration from area with a high prevalence of drug resistance
- Cavitary lung disease
- Homelessness
- Imprisonment
- Drug malabsorption due to gastrectomy or ileal bypass surgery

Data from O'Brien RJ: Drug-resistant tuberculosis: Etiology, management and prevention. Semin Respir Infect 9:104, 1994; and Ellner JJ: Multidrug-resistant tuberculosis. Adv Intern Med 40:155, 1995.

can quickly become source cases for further transmission of the resistant bacilli.[100,101] In reports on hospital outbreaks of MDR-TB, more than 90% of patients had co-infection with HIV, and case-fatality rates were as high as 70 to 90%.[102] However, patients without HIV infection demonstrate excellent clinical responses when treated for MDR-TB.

Health care workers should know the prevalence of drug resistance in their community and the risk factors (Box 133-5) for drug resistance in order to identify potential cases. Rapid identification and prompt isolation of these patients, along with other control measures, can reduce nosocomial transmission of MDR-TB to patients and health care workers. Failure to control drug resistance may lead to wide dissemination of MDR-TB and to a public health crisis that physicians must confront without effective medications.

Treatment of drug-resistant TB can be challenging and requires familiarity with second-line agents. For MDR-TB, specialist consultation is essential. A general principle that applies in such cases is to use at least three drugs to which the organism is susceptible and that have not been used previously. In general, one of these medications should be an injectable agent. TB infections with strains that are resistant only to INH can be managed with a 6-month course of RIF, PZA, and EMB. Recommended regimens for some other resistance patterns are listed in Table 133-7.[68]

Extensively Drug-Resistant Tuberculosis

XDR-TB was first recognized in patients co-infected with AIDS in South Africa in 2005.[103] A retrospective analysis of several thousand banked specimens from sources worldwide found that the strain was present in samples every year since year 2000 and that it presented a major threat in Africa, Asia, and areas of the former Soviet Union.[104] In that study, up to 17% of patients in the MDR-TB group actually had XDR-TB. The strain has virulence similar to MTB, and disease does not progress faster in the absence of antibiotics.[105,106] As resistance to so many antibiotics has developed, however, this strain has become a major threat, especially in patients with AIDS. Most alarming is a recent study that reported as many as 33% of patients with TB co-infected with HIV and MDR-TB had the XDR-TB strain.[107] Mortality rates for this patient population are high, because few alternative drugs exist. The CDC is extremely concerned and has reported a handful of cases in several states.[105] EDs could become a major focus for spread of this disease, because some U.S. EDs are overcrowded and lack procedures, personnel, and space to recognize and isolate potentially infected persons. Reports from Africa have shown that XDR-TB can be transmitted directly to health care workers.[108] Of great concern is the potential for transmission of the disease within the ED by a previously undiagnosed patient with XDR-TB, recently arrived from an endemic country, who presents for treatment for TB-related symptoms or an unrelated condition.

Table 133-7 Potential Regimens for the Management of Patients with Drug-Resistant Pulmonary Tuberculosis

PATTERN OF DRUG RESISTANCE	SUGGESTED REGIMEN	DURATION OF TREATMENT (MO)
INH (± SM)	RIF, PZA, EMB (an FQN* may strengthen the regimen for patients with extensive disease)	6
INH and RIF (± SM)	FQN, PZA, EMB, IA,† ± alternative agent‡	18–24
INH, RIF (± SM), and EMB or PZA	FQN (EMB or PZA if active), IA, and two alternative agents	24
RIF	INH, EMB, FQN, supplemented with PZA for the first 2 mo (an IA may be included for the first 2–3 mo for patients with extensive disease)	12–18

*Most experience involves ofloxacin, levofloxacin, or ciprofloxacin.
†May include aminoglycosides (streptomycin, amikacin, or kanamycin) or the polypeptide capreomycin.
‡Alternative agents include ethionamide, cycloserine, para-aminosalicylic acid, clarithromycin, amoxicillin-clavulanate, and linezolid.
EMB, ethambutol; FQN, fluoroquinolone; IA, injectable agent; INH, isoniazid; PZA, pyrazinamide; RIF, rifampin; SM, streptomycin.
From American Thoracic Society; CDC; Infectious Diseases Society of America: Treatment of tuberculosis. MMWR Recomm Rep 52(RR-11):1, 2003.

Extrapulmonary Tuberculosis

Evidence from clinical trials, including some randomized controlled trials, indicates that 6- to 9-month regimens provide effective treatment for extrapulmonary TB. An exceptions is tuberculous meningitis: The CDC recommends 6 to 9 months for bone or joint infection, 9 to 12 months for meningitis, and 6 months for all other forms of extrapulmonary TB.[68]

Corticosteroids

The use of corticosteroids in the treatment of extrapulmonary TB is more common than in pulmonary disease. Corticosteroids may prevent constriction in tuberculous pericarditis and decrease the neurologic sequelae in all stages of tuberculous meningitis, especially if given early in the disease.[46] The CDC strongly recommends corticosteroids for MTB pericardial or CNS infections.[68] Corticosteroids may provide some benefit to children with bronchial obstruction caused by enlarged lymph nodes.[66] In addition, in patients with pulmonary TB, prednisone, 20 to 60 mg/day, may benefit those who continue to experience temperature spiking and to lose weight despite a

good bacteriologic response to appropriate antituberculosis therapy.[109]

Pregnancy

Treatment of TB during pregnancy poses little risk to the fetus, especially in comparison with untreated disease. INH, RIF, and ETH cross the placenta but have no known teratogenic effects. These three drugs should be used for the initial regimen, followed by a continuation phase of INH plus RIF for an additional 7 months (9 months total). Pyridoxine is recommended for pregnant women receiving INH. The use of PZA in the initial regimen is controversial, mainly because of insufficient data regarding its safety during pregnancy. When PZA is used, the total treatment duration can be reduced to 6 months. Streptomycin may cause congenital deafness and is contraindicated. Kanamycin, amikacin, and capreomycin should therefore be avoided as well. Fluoroquinolones should be avoided because of the potential for arthropathies (as demonstrated in animal models).[68] Although these chemotherapeutic agents are present in breast milk, they are not harmful to the infant and are not present in high enough concentrations (approximately 20% of the daily dose) to be therapeutic or preventive.[46,68]

Surgical Management

The most common indication for surgery is MDR-TB with severe localized disease.[107] When optimal medical therapy based on drug susceptibility testing is given preoperatively and postoperatively, the outcome appears to improve.[110] In one study of 172 patients who underwent pulmonary resection for MDR-TB, 96% of those with MTB-positive preoperative sputum samples became sputum-negative for MTB after surgery.[111] The CDC recommends that surgery be performed after several months of an intensive medication regimen.[68] Other indications for surgery may include bronchopleural fistula, massive uncontrolled hemoptysis, extensive bronchostenosis, destroyed lung, solitary nodule, trapped lung, complicated cavity, and empyema.[110]

Treatment of Latent *Mycobacterium tuberculosis* Infection

After primary infection with MTB, host defenses usually are able to contain the infection within 2 to 10 weeks. This begins the latent period for MTB infection, when affected persons are not contagious and do not have active disease. Preventive therapy is directed at treating MTB infection during this latent phase to prevent reactivation and development of active disease. Tuberculin skin testing for the presence of latent MTB infection should be performed in persons who are at increased risk for either MTB infection, exposure to infectious cases, or development of active disease (see Table 133-3).[78]

Treatment of latent MTB infection is indicated for persons in whom the risk for development of active TB outweighs the risks associated with the therapy itself. The risk of INH-induced hepatitis increases with age, but age older than 35 years is *not* a contraindication to INH administration. In fact, if a patient belongs to a risk group listed in Table 133-3, age is no longer a factor, and treatment for latent MTB infection is warranted.[78,79] Persons with impaired cell-mediated immunity, such as young children or immunocompromised patients, may not have positive tuberculin skin test results after initial infection with MTB. Thus, treatment of latent MTB infection should still be considered for such patients if they have experienced a recent (within 3 months) high-risk exposure to MTB.[78] Continuation of therapy in such cases should be based on tuberculin skin test results at 3 months after the exposure. Excluding active TB with chest radiographs and clinical evaluation is a critical step before initiation of therapy for latent MTB infection.

Table 133-8 Ratings for Regimens for Treatment of Latent Tuberculosis Infection

DRUGS	DURATION (MO)	INTERVAL	RATING* (EVIDENCE)† HIV⁻	RATING* (EVIDENCE)† HIV⁺
Isoniazid	9	Daily Twice weekly	A (II) B (II)	A (II) B (II)
Isoniazid	6	Daily Twice weekly	B (I) B (II)	C (I) C (I)
Rifampin-pyrazinamide	2 2–3	Daily Twice weekly	B (II) C (II)	A (I) C (I)
Rifampin	4	Daily	B (II)	B (II)

*A = preferred; B = acceptable alternative; C = offer when A and B cannot be given.
†I = randomized clinical trial data; II = data from clinical trials that are not randomized or that were conducted in other populations.
From Targeted tuberculin testing and treatment of latent tuberculosis infection. American Thoracic Society. MMWR Recomm Rep 49(RR-6):1, 2000.

Any of four regimens may be used to treat latent MTB infection[79] (Table 133-8). The preferred regimen is daily INH for 9 months. The dose is 5 mg/kg in adults and 10 to 20 mg/kg for children, with a maximum of 300 mg/day for both populations. INH also may be given twice weekly by DOT. For HIV-positive patients, the recommended regimen is daily INH for 9 months or daily RIF plus PZA for 2 months.[79] DOT is recommended for all intermittent-therapy regimens and for persons at high risk for development of the disease, to decrease possible MDR-TB emergence.

DISPOSITION

Most patients with TB can be managed on an outpatient basis. The ideal situation for the patient with newly diagnosed or suspected TB is to be at home, receiving antituberculosis therapy, with the patient's contacts receiving preventive treatment. The CDC strongly recommends DOT in order to maximize compliance and completion of therapy.[68] The ED discharge instructions should clearly emphasize the importance of adhering to the prescribed treatment regimen and home isolation procedures (avoidance of meeting new contacts). The case must be immediately reported to the health department to ensure that the patient has an adequate source of TB care, that support systems and resources are available to complete the care, and that the patient's contacts are investigated and screened. Two weeks of treatment is widely accepted as the minimum time to be rendered noninfectious, so long as the patient has been treated with appropriate medications (see also earlier section, "Transmission").[25]

Acutely ill or elderly patients may require hospitalization during the first few days of treatment because adverse reactions are common and may occasionally be life-threatening.[112] In addition, severely ill patients may require parenteral drug administration. Patients with TB have a high rate of HIV coinfection, and the comorbid illnesses associated with HIV infection, the complex synergy between MTB and HIV disease, and the potentially harmful drug interactions between the antiretroviral agents and the rifamycins may favor inpatient treatment for initial management of these complicated cases.

Hospital admission also is indicated for patients with active MDR-TB. These patients commonly require observation during initiation of therapy because of the complexity of the treatment regimens, the toxicity of the drugs, and the need for close monitoring to ensure adherence to treatment and isolation measures.[99] Finally, social issues such as homelessness, presence of infants or immunocompromised persons in the household, substance abuse, and incapacity for self-care may necessitate hospitalization. The recalcitrant patient constitutes a potential threat to public health, and legal measures for involuntary hospitalization may be required.[113]

PREVENTION OF TRANSMISSION IN THE EMERGENCY DEPARTMENT

EDs often care for patients at increased risk for active pulmonary TB, such as those who are homeless, foreign born, recently incarcerated, or chronically ill. Accordingly, ED workers can be at high risk for occupational TB infection. In one county hospital in Los Angeles, 31% of emergency department workers became tuberculin skin test–positive at some time during employment, including 20% of attending physicians, 32% of nurses, and 33% of residents.[114] Tuberculin skin test conversion risk was found to be 6% after 1 year of ED employment, 14% after 2 years, and 27% after 4 years. In addition, increased hospital occupancy and ED overcrowding can lead to extended waiting periods for both ED beds and hospital beds.[115,116] Some EDs may lack an adequate number of TB isolation rooms.[117] Nosocomial transmission risk in the ED setting also is increased, because patients with TB often receive care before the diagnosis is suspected; this risk is particularly high with critically ill patients, who by definition require close, intensive contact with multiple emergency care providers.

Early Identification

For the most effective minimization of infectious exposures among health care workers and other patients, all patients with active pulmonary TB would ideally be placed in respiratory isolation when initially presenting for care. Not surprisingly, this is difficult to accomplish, and delays in identification and respiratory isolation of such patients are frequent. In one ED study of patients with TB, the mean time from ED registration to respiratory isolation was 6.5 hours, and 46% of patients were first isolated on the hospital ward.[118] In order to improve the early identification of patients who may have TB, the CDC has recommended screening for TB at triage.[29] Triage screening protocols can detect patients with more classic presentations of TB, but reported protocols are only moderately sensitive and somewhat cumbersome.[119] Immediate respiratory isolation should be considered for patients with high-risk chief complaints, such as the HIV-positive patient with cough, the person with hemoptysis, or the patient with a history of TB presenting with cough or fever. The best guideline is to initiate respiratory isolation as soon as TB is considered as a possible diagnosis. Masks should be placed on such patients *before* chest radiographs are obtained. In addition, the development of policies providing for expedited admission to hospital isolation beds and for improved access to local public health facilities may help decrease TB transmission at virtually no cost.[117]

Isolation and Environmental Control

In addition to triage screening, the use of proper isolation facilities and environmental control measures can help prevent TB exposures. Airflow in the ED plays a central role, and inadequate ventilation has been a contributing factor in many nosocomial outbreaks of TB. Ideally, there should be single-pass airflow from waiting rooms to outside the facility. Within the ED, air should flow from clean areas to less clean areas, rather than vice versa. For EDs that frequently see patients with TB, at least one true respiratory isolation room should be available. The CDC recommends that respiratory isolation rooms have at least 12 air changes per hour and have "negative pressure" (air flows *into* the room from other ED areas). Other engineering approaches to TB infection control include the use of high-efficiency particulate air (HEPA) filters and upper room ultraviolet light irradiation.[29]

Personal Respiratory Protection

ED personnel should be familiar with the appropriate use of respiratory protection against TB. Surgical masks (e.g., string-tie masks) should be placed on potentially contagious patients to decrease the release of infectious droplets into the air.[29] Air can leak around such masks, however, so they may not adequately prevent health care workers from inhaling infectious droplet nuclei.[120] Thus, surgical masks should be used only for source control, not for health care worker protection. More advanced personal respiratory protection devices include N-95 particulate respirators.[121] These masks can filter 1-μm particles with at least 95% efficiency and are the preferred masks for health care workers in the ED. They are available in a variety of shapes and sizes and from various manufacturers. HEPA-filtered masks can also be used for health care worker respiratory protection, and these masks were used more extensively before the development of the N-95 masks. Although HEPA-filtered masks are very effective, they are more costly and can make breathing uncomfortable.[120]

Preventive Therapy after Inadvertent Exposure

Health care workers who are exposed to patients with active pulmonary TB should be referred to their primary care physicians or employee health services for follow-up testing and treatment. Tuberculin skin testing usually is performed within days after exposure to establish whether the health care worker has previously been infected with MTB. If the baseline test result is negative, a follow-up skin test is performed 3 months later to determine whether tuberculin skin test conversion has occurred. Health care workers whose tuberculin skin test result converts to positive (5-mm induration) after an exposure should undergo chest radiography and clinical evaluation to rule out active disease. When active TB infection is excluded, preventive therapy is recommended. The recommendations in Box 133-6 can assist physicians in deciding who should be treated after an exposure.[122] For exposures to MDR-TB, expert consultation is advised for selecting an individualized regimen.

Tuberculin Skin Testing

Because all ED personnel are potentially exposed to MTB, a skin test program is essential.[29] Skin testing at regular intervals monitors TB transmission among ED personnel and targets staff members who need prophylactic therapy or treatment. Although recommendations for various health care settings depend on the number of TB patients encountered, most ED health care workers should be skin tested every 6 months.[29]

BOX 133-6 GUIDELINES FOR MANAGEMENT AFTER ACCIDENTAL EXPOSURE TO TUBERCULOSIS

- Healthy persons who remain PPD-negative after a heavy exposure do not require chemotherapy.
- If exposure is discovered immediately, preventive therapy should be started in particularly heavily exposed people who are known to be PPD-negative. If the skin test remains negative after 3 months, therapy can be discontinued.
- Persons who seroconvert to a positive PPD test result after the exposure should take preventive therapy regardless of age.
- Persons without preexposure PPD results who react positively after the exposure should be treated as convertors (see item 3 above).
- Persons known to be PPD-positive before exposure have too slight a risk to warrant preventive therapy.
- Persons who are younger than 35 years of age, have HIV infection, are receiving cancer chemotherapy or long-term corticosteroid therapy, or are otherwise immunocompromised should be considered for preventive therapy, regardless of the exposure.

HIV, human immunodeficiency virus; PPD, purified protein derivative.
Modified from Stead WW: Management of health care workers after inadvertent exposure to tuberculosis: A guide for the use of preventive therapy. Ann Intern Med 122:906, 1995.

Bacille Calmette-Guérin Vaccine

Although the BCG vaccine has been used since 1921, its overall efficacy, the duration of protective immunity, and the optimal age for administration remain unclear. In the United States, BCG is rarely recommended because of the belief that it may undermine the epidemiologic and diagnostic value of PPD skin testing. However, tuberculin skin tests in patients given previous BCG vaccination usually demonstrate less than 10 mm of induration. Thus, previous BCG vaccination status should be ignored in interpreting skin test results.[79]

Institutional outbreaks of TB and the emergence of MDR-TB are sparking reassessment of the BCG issue in the United States. Reports of BCG vaccine efficacy range from zero to 80%. One meta-analysis reported the efficacy of BCG vaccine to be approximately 50%.[123] Variation in efficacy of the vaccine reported from many studies may be a result of numerous factors. These include differences in strains of BCG associated with the many worldwide production laboratories, study design, and patient age and immunocompetence. A 60-year study in a Native American population showed a 50% reduction in the development of TB in persons receiving BCG vaccine.[124] BCG vaccine is currently recommended in the United States only for tuberculin-negative infants and children who cannot take INH and have ongoing exposure to a persistently untreated or inadequately treated patient with active TB, who are continuously exposed to persons with INH- and RIF-resistant TB, or who belong to groups with rates of new MTB infection exceeding 1% per year.[123] The World Health Organization recommends that all infants in developing countries receive the vaccine.

One decision analysis suggested that BCG vaccination would be more effective than the current annual testing strategy for health care workers.[125] In some European hospitals, health care workers are required to have received BCG. However, the routine use of BCG vaccine in U.S. heath care workers is still controversial. What is not controversial is that the vaccine is strongly contraindicated in persons with HIV infection or other immunosuppressive disease. New vaccines against MTB are being researched, including those using attenuated strains of the MTB complex, recombinant mycobacteria, and subunit proteins and DNA vaccines.[126]

KEY CONCEPTS

- In the mid-1980s, there was a resurgence of TB cases in the United States. Immigration and the HIV epidemic were important contributing factors. The reemergence of TB has affected both adults and children.
- TB infection starts with primary infection, followed by a latent period in immunocompetent patients. Approximately 10% of infected patients eventually develop reactivation of disease.
- Beyond pulmonary manifestations, a variety of extrapulmonary manifestations may occur including involvement of lymph nodes, pleura, bones or joints, CNS, and genitourinary and gastrointestinal systems.
- TB infection may be more difficult to diagnose in HIV-infected or elderly patients, in whom the clinical presentation often is variable.
- Therapy must be individualized to reflect acuity, sensitivity, system involvement, and underlying conditions. The most commonly used agents are INH, RIF, PZA, and ETH.
- Prevention and screening are fundamental components of any TB control strategy. Patients suspected of having active pulmonary TB should be placed into respiratory isolation as soon as possible.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 134

Bone and Joint Infections

Brian J. Zink and Neha P. Raukar

PERSPECTIVE

Historically, bone and joint infections have been described in grim terms. *Aids to Surgery,* written in 1919, notes that "acute infective osteomyelitis … is a very fatal disease." With septic arthritis "the patient becomes exhausted from toxaemia or pyemia," and "ankylosis is the usual most favorable termination."[1] Advances in diagnostic methods, antibiotic therapy, and surgical techniques have resulted in much better outcomes. In the case of bone infections, the mortality rate has decreased from 15 to 25% in the preantibiotic era to less than 5% today.[2] However, new challenges are being unveiled. The types of infections that are encountered today are evolving, host immunity is decreased in many populations, and management of bone and joint infections is becoming more complex. Emergency physicians must consider many subsets of patients who are at increased risk for infection, including intravenous drug users (IVDUs), patients with acquired immunodeficiency syndrome (AIDS), postsurgical patients, and patients with iatrogenic immune suppression.[3–6] The emphasis of modern management of bone and joint infections has shifted from preventing sepsis and death to making a prompt diagnosis, initiating treatment, and avoiding the complications and morbidity associated with chronic bone or joint infections. [7,8]

The overall occurrence of bone and joint infections has remained constant over the past 3 decades.[4,9] The incidence of bone infections in hospitalized patients is approximately 1%. In the United States, the incidence of osteomyelitis in children under the age of 13 years is 1 in 5000, while septic arthritis ranges from 5.5 to 12 per 100,000 individuals.[10] Global epidemiologic data regarding community-acquired bone and joint infections in adults vary significantly, with an overall higher incidence in patients of a lower socioeconomic class in developing countries. In the United States, there is no correlation between socioeconomic factors or race and the incidence of bone and joint infections. Bone infections show a bimodal age distribution, occurring most commonly in people under 20 or over 50 years of age. Joint infections have a similar distribution.[8,9] In children, bone and joint infections usually occur in previously healthy individuals, and boys have an increased susceptibility to bone infections, with a male/female ratio of 2 to 3:1.[9] In adults, risk factors can usually be identified in patients who present with either bone or joint infection.

Infectious processes are generally designated as acute, subacute, or chronic. Orthopedic infections are also classified according to the site of involvement and include osseous (osteomyelitis), articular (septic or suppurative arthritis), bursal (septic bursitis), subcutaneous (cellulitis or abscess), muscular (infectious myositis or abscess), and tendinous (infectious tendinitis or tenosynovitis) varieties. The word *osteomyelitis* literally means inflammation of the marrow of the bone, but the term is loosely used to refer to infection in any part of the bone. A specific definition of chronic osteomyelitis is difficult to find.

From a histologic standpoint, *chronic* osteomyelitis is diagnosed when areas of necrotic bone are identified. Chronic osteomyelitis may also be defined as a bone infection lasting for more than 10 days or infection that fails a normal course of antibiotic therapy.

Septic arthritis is defined as an infection of a joint by bacterial or fungal organisms. Bacterial arthritis is sometimes called pyogenic or suppurative arthritis. Several common infectious processes can result in a sterile, secondary inflammation of joints, termed reactive arthritis. Reactive arthritis is not classified as septic arthritis because there are no infecting microorganisms within the joint. This type of arthritis is far more common than septic arthritis. Commonly, a reactive arthritis occurs after infection with human parvovirus, rubella, chickenpox, and other viruses,[11,12] although reactive arthritis can also develop after group A streptococcal infection.

There are many classification systems for osteomyelitis based on the condition of the host, functional impairment caused by the disease, site of involvement, and extent of bony necrosis. For the emergency physician, the most practical way to classify osteomyelitis is based on etiology as described by Waldvogel. Waldvogel divides osteomyelitis into two broad categories: hematogenous osteomyelitis and osteomyelitis secondary to a contiguous focus of infection.[7,13] Osteomyelitis from a contiguous focus is further subdivided based on the presence or absence of vascular insufficiency. The latter is often secondary to trauma, surgery, or insertion of a prosthetic joint or other hardware into bone. Recognition of the etiologic mechanism of osteomyelitis assists in the interpretation of diagnostic imaging examinations and helps to guide management.

Septic arthritis usually results from hematogenous migration of bacteria into the joint. Less commonly it is caused by direct inoculation of bacteria from trauma or joint aspiration, or from infected foreign material such as a prosthesis. It is important to consider that septic arthritis may occur concomitantly with osteomyelitis, with infection spreading from bone to joint, and vice versa.

PRINCIPLES OF DISEASE

Bones are composed of an outer shell, or cortex, of compact bone and an inner framework of trabeculae, called cancellous, spongy, or medullary bone. On a microscopic level, compact bone is composed of structural units called haversian systems that are made up of concentric rings of osteocytes. Osteocytes synthesize and maintain the bony matrix. The central haversian canals run parallel to the long axis of the bone and contain the blood supply and reticular connective tissue for the haversian system. Cancellous bone consists of irregular branching trabeculae that enclose marrow cavities.

Long bones consist of a diaphysis, or shaft, and two ends, called epiphyses, which articulate with other bones. The metaphysis is the region between the diaphysis and epiphysis (Fig. 134-1).

Joints are enclosed within a two-layered capsule. The outer layer is dense fibrous tissue, interwoven with ligaments and the periosteum of articulating bones. The inner layer is the synovial membrane, consisting of secretory cells sitting on a loose fibrous stroma. In some joints, such as the shoulder, hip, and knee, the synovial membrane extends beyond the epiphysis and attaches to the metaphysis. This anatomic relationship allows bacteria to spread from the metaphysis into the joint.[13–16]

Osteomyelitis begins when bacteria invade the medullary space of bone. The metaphysis is the first to be infected due to the slow flow of blood in the sinusoidal blood vessels. Acute inflammatory cells migrate to the area, causing edema, vascular congestion, and small vessel thrombosis. Acutely, pus spreads into the haversian and vascular channels, raising the intraosseous pressure and compromising blood flow to the bone. Infection may proceed laterally through Volkmann's canals, which are small channels that run perpendicularly to the haversian system, and reach the subperiosteal space. Eventually, blood supply to both the medullary canal and the periosteum are compromised, leading to areas of necrotic bone called sequestra. The presence of necrotic bone is the hallmark of chronic osteomyelitis. Since there is significantly reduced blood supply to this necrotic bone and ischemic tissue, bacterial infection is very difficult to eradicate with medication alone and chronic osteomyelitis often requires both surgery and antibiotic therapy.

The variation of the blood flow at the metaphyseal/epiphyseal junction results in the variety of pathologic features of hematogenous osteomyelitis among the different age groups. This is partly due to the differences in vascular anatomy as the skeleton ages.

In neonates and infants, arterial vessels from the metaphysis perforate the epiphyseal growth plate and terminate in the epiphysis in venous sinusoids. This communication allows osteomyelitis to advance readily from the metaphysis to the epiphysis and adjacent joint space, leading to septic arthritis.

Cortical bone in neonates and infants is thin and loosely attached to the underlying bone. It is composed primarily of woven bone, which allows for the release of pressure caused by the infection and also allows the infection to rapidly spread in the subperiosteal region. Because of these structural char-

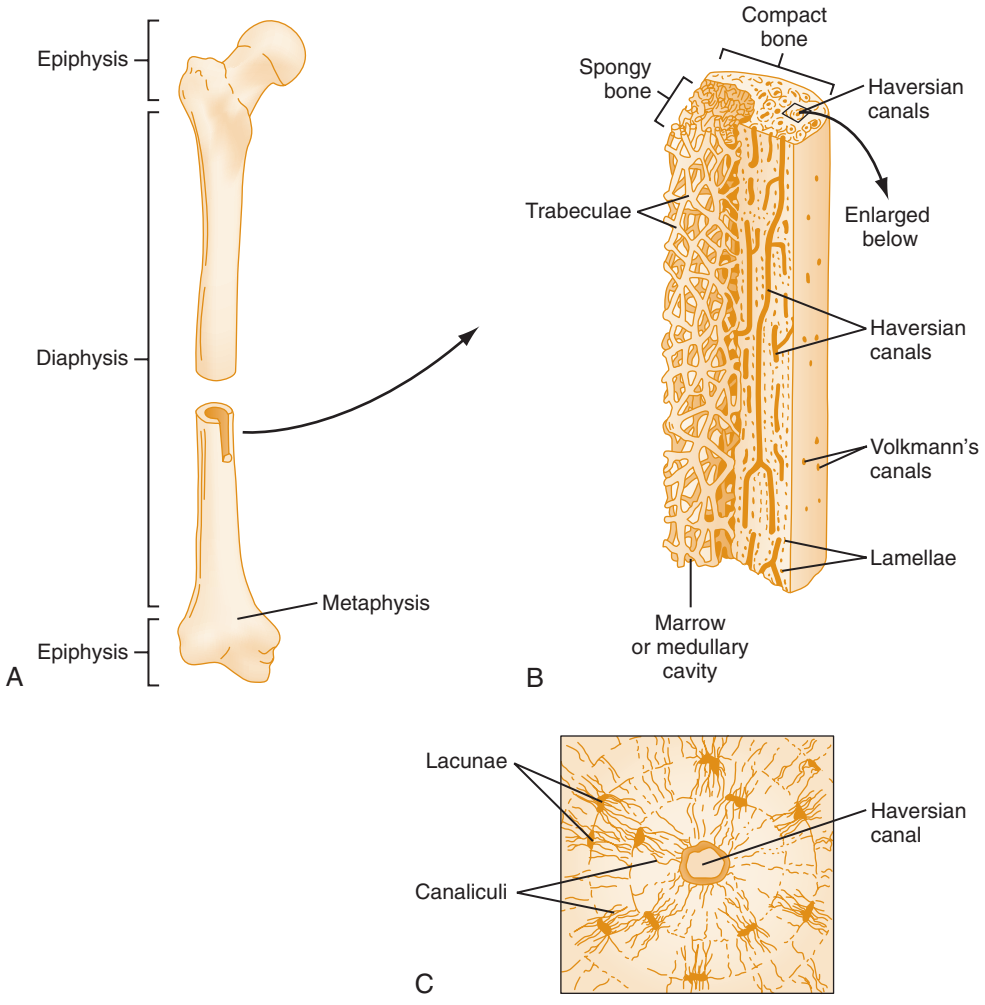

Figure 134-1. Schematic drawing of long bone. **A,** Regions of long bone. **B,** Cross-structure of long bone. **C,** Microscopic structure.

acteristics of bone in neonates and infants, pressure-related cortical infarction does not usually occur and sequestra are not created. Infection remains trapped in the subperiosteal region and eventually leads to subperiosteal abscess formation. The periosteum is stimulated and vigorous formation of new periosteum occurs. This new growth of the periosteum is called an involucrum.

After the first year of life there is no longer a vascular connection between the metaphysis and epiphysis. The metaphyseal arteries end in loops that abut the growth plate. The epiphyseal growth plate is avascular and inhibits the spread of infection to the epiphysis and joint. The infection spreads laterally via Volkmann's canals, breaks through the cortex, and lifts the loose periosteum to form a subperiosteal abscess.[17]

In the adult, after the closure of the epiphyseal plate and resorption of the growth plate, anastomoses form between the metaphyseal and epiphyseal blood vessels, and infection can once again spread from metaphysis to epiphysis and eventually into the synovium and joint space.[14,18] In addition, the periosteum is firmly attached to the underlying bone, limiting subperiosteal abscess formation. Decreased osteoblastic activity in adults limits involucrum formation. However, infection can erode through the periosteum, forming a draining sinus tract[13] with more extensive longitudinal diaphyseal spread. The devascularized weakened bone is prone to fractures.[7,13,19] If osteomyelitis proceeds unchecked, ischemic segments of bone may detach from surrounding bone. These separated sections are called *sequestra* and occur only in advanced or chronic osteomyelitis. Bone infection may progress into the adjacent soft tissues with abscess formation. The sequestrum can migrate outward from the medullary space through a cortical opening (cloaca) and then to the skin surface through a fistula.

Hematogenous osteomyelitis develops when blood-borne bacteria are deposited in bone. This is most common in children and in adults with vertebral osteomyelitis. A number of local and humoral factors play a role in determining whether bacteremia progresses to significant skeletal infection. Normal bone is highly resistant to infection. Three main factors contribute to the pathogenesis of osteomyelitis: the virulence of the infecting organism, the underlying immune status of the host, and the type, location, and vascularity of the bone. Some sites in the skeletal system are more likely to become colonized by bacteria. Bones containing slow-moving venous systems or venous sinusoids, such as the metaphyses of long bones and the vertebral bodies, have increased susceptibility to hematogenous osteomyelitis. In the metaphysis, a relative lack of phagocytic cells in the venous capillaries and sinusoids may further predispose to infection. In the synovial membrane, the existence of a deep venous plexus that also has sluggish blood flow may invite deposition of bacteria.

Staphylococcus aureus, the most common cause of both hematogenous and contiguous osteomyelitis, has developed mechanisms to increase bone adherence, increase proteolytic activity, and increase resistance to host defense mechanisms. A number of extracellular and cell-associated factors contribute to the enhanced virulence. In the early stages of osteomyelitis or septic arthritis, *S. aureus* expresses microbial surface proteins that promote adherence to many components of the extracellular matrix proteins. In joints, the synovium lacks a basement membrane, allowing bacteria to penetrate and bind to the exposed surfaces of articular cartilage, bone, and even prosthetic devices. The adherence of bacteria such as *S. aureus* is facilitated by expression of adhesins, which link to a glycoprotein called fibronectin. Fibronectin is found in bone and synovium and can coat artificial surfaces such as prostheses. *S. aureus* has been shown to produce fibronectin-binding adhesins that encourage the attachment of the bacteria. A biofilm is rapidly formed, and this promotes adherence of other bacteria and colony formation. [7,13,20] Biomaterials, including the metal and plastic components of prosthetic joints, acrylic bone cement, devascularized bone graft, and synthetic bone substitutes, cause local immune impairment and allow nonpathogenic skin flora such as coagulase negative staphylococci to become significant pathogens. Proteolytic enzymes that are present in noninfected joints are normally inhibited; however, this inhibition is lost in the face of infection, enabling the invading bacteria to persist. Finally, *S. aureus* can surmount host defense mechanisms at both the cellular and matrix levels. For example, *S. aureus* can increase expression of protein A. This is covalently bound to the bacterial cell wall and binds to the Fc portion of immunoglobulin G on neutrophils that interfere with the opsonization and phagocytosis of *S. aureus,* leading to an increase in virulence.[21,22]

The humoral immune response to bone or joint infection is usually well developed by the time the infection is clinically apparent. B lymphocytes sense bacterial antigens and release antibodies, and an antigen-antibody complex is formed at the site of infection. Via the complement cascade, bacteria are destroyed by neutrophils or macrophages. Bacterial toxins may be destroyed directly by bound antibody.[8,13,20,23]

Tissue injury in bone or joint infections can occur by several different mechanisms. Direct tissue destruction by invasive bacteria is the initial insult. After this, microabscesses and edema in infected tissues may lead to vascular occlusion and ischemic necrosis, which is most damaging in the venous capillaries of the metaphysis, where no collateral blood vessels exist to compensate for ischemic injury. If immune complexes become embedded in the bone or cartilage matrix, a prolonged inflammatory response can occur even after the primary infection has been cleared. This is particularly a problem in joints, where articular cartilage can be destroyed. A final type of tissue injury caused by infection is abnormal synthesis of bone or joint matrix and cells. Abnormally synthesized bone or cartilage may be structurally unsound and function poorly.[13,23]

Hematogenous spread causes almost all cases of osteomyelitis in children and in the subset of adults who have vertebral osteomyelitis. In the appendicular skeleton of adults, osteomyelitis occurs more commonly by either spread of the pathogens from a contiguous source of infection or direct implantation. The direction of contamination for contiguous focus osteomyelitis is from the soft tissues inward into the bone, and the pathogen is disseminated via haversian and Volkmann's canals to the bone marrow. This is the opposite of hematogenous osteomyelitis, where infection starts in the medullary bone and progresses outward to involve the surrounding structures. The most common sites of contiguous focus osteomyelitis are in the foot and hand. Other common sites affected by this mechanism include the skull, maxilla, and mandible. Head and neck osteomyelitis is usually caused by sinus disease and odontogenic infections.

Most infections caused by direct implantation of bacteria into bones are caused by deep puncture wounds and tend to occur in the hands and feet. Animal bites are another cause of infections that can result in osteomyelitis. Although cats account for only 10% of animal bites, significant infection results from 20 to 50% of cat bites versus only 5% of dog bites. Most human bite injuries are related to fist fights, with contamination of the metacarpophalangeal joints and metacarpals with secondary infection. Osteomyelitis from direct implantation of pathogens is seen commonly with open fractures, and can occur during surgical instrumentation. Artificial joints and other implanted surgical materials can serve as sites for colonization of bacteria.[24,25]

In septic arthritis, unless there is direct injection of bacteria into the joint, infection occurs first in the synovium and then extends into joint fluid, and finally to articular cartilage. The synovial membrane responds to infection by increasing synovial fluid production, resulting in a large joint effusion. Septic arthritis is a closed space infection, and increasing pressure in the joint contributes to a decreased rate of exchange of solutes across the synovial lining. The resultant slow diffusion of nutrients across the synovial membrane may limit the growth of bacteria and may cause bacteria to enter a dormant state. Dormant bacteria has increased resistance to levels of antibiotics that would normally be bactericidal.[8,14,26] Even small numbers of bacteria in the joint space can elicit a profound and persistent inflammatory and immune response. Bacteria can be cleared from the joint, resulting in a sterile-appearing inflammatory response. In animal models, the injection of isolated bacterial DNA into joints can produce a marked inflammatory arthritis.[27] These types of observations have led to the hypothesis that some forms of arthritis, previously believed to be sterile or reactive, may in fact be due to an initial infection of the joint with small numbers of microorganisms followed by clearance of these microorganisms with a prolonged inflammatory response.[28]

The most important factor that determines morbidity from septic arthritis is the degree of articular cartilage destruction. Once destroyed, hyaline (articular) cartilage cannot be replaced. As part of the response to infection, synovial cells and polymorphonuclear leukocytes release lysosomal enzymes into joint fluid. These enzymes contain collagenase and elastase, both of which degrade cartilage. Cytokines also seem to play a key role in the release of metalloproteinases and other harmful enzymes. Other structures that are enclosed within or adjacent to the synovium, such as bursae, tendons, and bone, may become damaged in septic arthritis.[8,14,26]

ETIOLOGY AND MICROBIOLOGY OF BONE AND JOINT INFECTIONS

The pathogenic organisms in osteomyelitis are numerous. The organism responsible for most types of osteomyelitis is *S. aureus*,[29] which has a number of mechanisms to resist host response, as discussed above.

Certain types of trauma may predispose patients to osteomyelitis by particular bacteria. Patients who are wounded or sustain open fractures in fresh water are susceptible to infection with the gram-negative bacillus *Aeromonas hydrophila*.[30,31] People who are bitten by animals, particularly dogs and cats, are at risk for developing osteomyelitis from *Pasteurella multocida*.[25,32] In the IVDU population, *S. aureus* is the most likely cause of infection, followed by *Pseudomonas* species. *Pseudomonas aeruginosa* is also an important cause of osteomyelitis in puncture wounds, postsurgical wounds, and in patients with sickle cell anemia. Osteomyelitis caused from human bites is most common in the hand and involves human oral flora such as *Streptococcus anginosus*, *Fusobacterium nucleatum*, and *Eikenella* species.[33]

Certain underlying disease states predispose a patient to acquiring bone and joint infections. These conditions include diabetes mellitus, sickle cell disease, AIDS, alcoholism and IVDU, chronic corticosteroid use, preexisting joint disease, and other immunosuppressed states. Common to most of the diseases that predispose to bone and joint infections are a decreased ability to mount an inflammatory and immune response, impaired bacterial killing, and poor vasculature. Another subset of patients who are susceptible to bone and joint infections are postsurgical patients, especially those who have had prosthetic devices implanted. In children, an association may exist between prior respiratory illness or minor extremity trauma and the development of bone and joint infections.[4,15,23]

Although most serious bone and joint infections are bacterial, on rare occasions, viruses, fungi, and parasites may be the responsible pathogens. The microbiology of osteomyelitis and septic arthritis is a function of several host and environmental factors. As has been described, age is an important variable in determining the type of bacteria that cause bone and joint infections. A patient's living environment also has some role in determining the incidence of bone and joint infections. For example, people living in crowded conditions where tuberculosis is prevalent are at increased risk for tubercular bone and joint infections. Elderly patients in hospitals and institutions may be more susceptible to infections with gram-negative bacteria.[2,34–36] A summary of the organisms that cause osteomyelitis and septic arthritis is given in Table 134-1. The following points deserve special mention:

1. In all age groups except neonates, *S. aureus* is the leading cause of osteomyelitis. It also accounts for more cases of septic arthritis than any other bacterium. In neonates, group B streptococci, *Escherichia coli* and other gram-negative coliforms, and *Staphylococcus epidermidis* are the most common pathogens in bone and joint infections.[37]
2. Before the introduction of the vaccine, *Haemophilus influenzae* type B caused up to 34% of septic arthritis and 13% of osteomyelitis in children under 2 years of age. However, since the introduction of the vaccine, *H. influenzae* type B has essentially disappeared as a pathogen in hematogenous osteomyelitis and septic arthritis among vaccinated children.[38] Another gram-negative coccobacillus within the Neisseriaceae family, *Kingella kingae*, has become more common than *Haemophilus* in causing bone and joint infections in children.[39] *K. kingae* can be part of the normal flora of the nasopharynx, which, like *H. influenzae*, can be spread hematogenously to bones and joints. It is a fastidious organism and may be mistaken for *Haemophilus* or *Neisseria* species.[2,39]
3. Gonococcal arthritis is the most common type of monoarticular septic arthritis in individuals under 30 years of age.
4. In elders, gram-negative bacteria account for a higher percentage of cases of bone and joint infections than in younger people.[2]
5. Methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *S. epidermidis*, and vancomycin-resistant enterococci have emerged as a significant microbiologic problem in the past decade. Multiresistant enterococci pose the greatest potential danger in that no currently available regimen is reliably bactericidal against such organisms.[34]

A typical case of hematogenous osteomyelitis or septic arthritis is caused by a single strain of bacterium. Polymicrobial infection is more likely to occur in diabetic foot osteomyelitis, post-traumatic osteomyelitis, and chronic septic arthritis. Overall, polymicrobial osteomyelitis occurs in 36 to 50% of reported cases. Anaerobic bacteria can complicate polymicrobial infection and may be present in bone and joint infections more often than is commonly recognized. In chronic osteomyelitis, anaerobic bacteria may be present in up to 40% of cases. Culture techniques that are inadequate for isolating anaerobic bacteria may lead to underreporting of infections caused by these agents.[2,15,16,34,40]

Pseudomonas aeruginosa has been reported as a cause of cervical spine osteomyelitis in injection drug users and lumbar spine osteomyelitis in patients with urinary catheters in place for long periods of time. *Pseudomonas* colonizes the rubber and

Table 134-1 Microbiology and Initial (Empirical) Antibiotic Treatment of Bone and Joint Infection

	SEPTIC ARTHRITIS		OSTEOMYELITIS	
AGE GROUP	**COMMON ORGANISMS**	**ANTIBIOTIC REGIMEN**	**COMMON ORGANISMS**	**ANTIBIOTIC REGIMEN**
Neonate to <3 mo	*Staphylococcus aureus* Group B *Streptococcus* Enterobacteriaceae	PRP + Ceph 3 Alt: PRP + APAG If MRSA is prevalent, use vancomycin in place of PRP	*S. aureus* Group B *Streptococcus* Enterobacteriaceae	PRP + Ceph 3 Alt: PRP + APAG If MRSA is prevalent, use vancomycin in place of PRP
3 mo to 14 yr	*S. aureus* Group A *Streptococcus* *Streptococcus pneumoniae* *Haemophilus influenzae*	PRP + Ceph 3 Alt: vancomycin + Ceph 3	*S. aureus* Group A *Streptococcus* *H. influenzae*	PRP + Ceph 3 Alt: vancomycin + Ceph 3, chloramphenicol
14 yr to adult	*S. aureus* Streptococcal sp. Enterobacteriaceae	PRP or Ceph 3 Alt: vancomycin + Ceph 3 or PCN + aminoglycoside or Ceph 3	*S. aureus*	PRP Alt: vancomycin
Infection Subsets				
Sexually active adolescents or adults with acute arthritis	*Neisseria gonorrhoeae*	Ceph 3 3rd or 4th generation FLQ, if sensitive		
Chronic osteomyelitis and diabetic foot infections			*S. aureus* Enterobacteriaceae Anaerobic bacteria	PRP + FLQ + metronidazole Alt: PRP + Ceph 3 + Clind
Infected orthopedic joint prosthesis	*S. aureus* *Staphylococcus epidermidis* *Pseudomonas aeruginosa*	Vancomycin + FLQ Alt: PRP + APAG	*S. aureus* *S. epidermidis* *P. aeruginosa*	Vancomycin + FLQ Alt: PRP + APAG
Sickle cell disease	*S. aureus* *Salmonella* sp.	PRP + Ceph 3 Alt: FLQ	*S. aureus* *Salmonella* sp.	PRP + Ceph 3 Alt: FLQ
Intravenous drug abuse	*P. aeruginosa* *S. aureus* Enterobacteriaceae	PRP + APAG or FLQ Alt: vancomycin + FLQ	*S. aureus* *P. aeruginosa* Enterobacteriaceae	PRP + APAG or FLQ Alt: vancomycin + FLQ
Plantar puncture wound	*P. aeruginosa*	AP Ceph Alt: FLQ	*P. aeruginosa*	AP Ceph Alt: FLQ
Human or animal bites	*Eikenella corrodens* *Pasteurella multocida*	Penicillin +/– AC Alt: Ceph 3, TS	*E. corrodens* *P. multocida*	Penicillin +/– AC Alt: Ceph 3, TS

Concurrent treatment for *Chlamydia trachomatis* should be given in patients with suspected *N. gonorrhoeae* septic arthritis. Bone and joint infections with *H. influenzae* are now rare in vaccinated children; however, if the Gram's stain is suggestive of *H. influenzae*, empirical treatment should be started. Fluoroquinolones are not recommended for use in children.

AC, amoxicillin-clavulanate; Alt, alternative antibiotics; APAG, antipseudomonal aminoglycoside; AP Ceph, antipseudomonal cephalosporin (ceftazidime or cefipime); Ceph 3, third-generation cephalosporin (ceftriaxone, cefotaxime, cefamandole, ceftizoxime, ceftazidime, moxalactam, etc.); Clind, clindamycin; FLQ, fluoroquinolone; MRSA, methicillin-resistant *Staphylococcus aureus*; PRP, penicillinase-resistant penicillin (oxacillin, nafcillin, methicillin, amoxicillin-clavulanate); TS, trimethoprim-sulfamethoxazole.

plastic inserts in footwear and is therefore seen in soft tissue infections and osteomyelitis of the foot after a puncture wound. Patients in whom prosthetic devices are implanted during orthopedic surgery are also at risk for *Pseudomonas* bone and joint infection.[2,6,15,34,41]

Tuberculosis may occur in bones and joints. The two most common forms of skeletal infection are vertebral osteomyelitis (Pott's disease) and tubercular arthritis. The spine is affected in half of cases of tubercular skeletal infection. The arthritis of tuberculosis is a chronic, low-grade inflammatory process that resembles rheumatoid arthritis more than acute septic arthritis.[36,37,42,43]

Fungal infection is a complication of catheter-related fungemia, the use of injection drugs contaminated by *Candida* species, and prolonged neutropenia. Fungal organisms are responsible for less than 1% of cases of osteomyelitis, but the number of reported cases is increasing. *Candida* osteomyelitis occurs through hematogenous spread or as a postoperative wound infection. Fungal bone infection is indolent and may go through periods of activity and remission.[44,45] *Aspergillus* has been reported to cause osteomyelitis in vertebrae, hip prostheses, and ribs. In adults the infection is hematogenous. In children *Aspergillus* osteomyelitis is most common in those with prior granulomatous disease and spreads from a primary pulmonary infection. *Blastomyces* and *Cryptococcus* are two other fungi that may become disseminated and infect the skeleton.[34,46] Treatment of these infections is difficult, and therapy needs to be individualized against the specific organism.

Patients with human immunodeficiency virus (HIV) are predisposed to a variety of common and opportunistic pathogens. Although *S. aureus* is still the most likely cause of bone and joint infections in patients with AIDS, fungal and other atypical organisms should be considered. One unusual, but particularly characteristic, form of osteomyelitis in HIV-positive patients is bacillary angiomatosis. This infection is caused by a gram-negative rickettsia-like organism that frequently causes osteolytic bone lesions.[3,5]

CLINICAL FEATURES OF OSTEOMYELITIS

Diagnosis

History and Physical Examination

The symptoms and signs of osteomyelitis in adults are predictable, although not always present. The predominant symptom of osteomyelitis is pain over the affected bone. Patients with osteomyelitis often present with fever and rigors and may appear toxic. Fever appears to be present more commonly in children. Systemic complaints of headache, fatigue, malaise, and anorexia are often reported.[13,46] However, these findings are inconsistently present and are less likely with chronic osteomyelitis. In children with lower extremity osteomyelitis, a sudden limp or inability to weight bear may be reported. Localized warmth, swelling, and erythema may be reported. A careful review of the patient's past medical history is especially important in order to identify risk factors that may predispose to bone infection.

The physical examination findings of osteomyelitis are fairly specific. Palpation of the involved bone usually elicits point tenderness over the infected segment. Palpable warmth and soft tissue swelling with erythema may be present, but these findings are variable. Because osteomyelitis has a propensity to occur in the metaphyses of long bones, it is often difficult to distinguish infection in bone from infection in the neighboring joint. A "sympathetic" effusion in the adjacent joint may develop in some patients with osteomyelitis even when the joint is not infected. In chronic advanced osteomyelitis, the involucrum or sequestrum may be palpated, and sinus tracts that drain through the skin may be noted.

Diagnostic Strategies

Laboratory Data and Diagnostic Imaging. Bone biopsy and culture are the gold standard and definitive test used to confirm the diagnosis and guide treatment of osteomyelitis. Biopsy may be performed with an open procedure or by fine-needle aspiration.

Laboratory data in patients with osteomyelitis are not diagnostic and can only suggest osteomyelitis. The white blood cell (WBC) count is often, although not always, elevated, with typical values ranging from normal to 15,000 cells/mm^3. The erythrocyte sedimentation rate (ESR), a nonspecific measure of inflammation, is more helpful than the WBC count. The ESR represents the rate at which red blood cells fall when anticoagulated blood is placed in an upright tube. When an inflammatory process is present, the high proportion of fibrinogen in the blood causes the red blood cells to form stacks, called rouleaux, which settle faster. This is a sensitive marker for bone infection; many series report elevated ESRs in more than 90% of patients who have confirmed osteomyelitis.[47] The mean ESR in one large pediatric review was 70 mm/hr. Fewer than 8% of patients with osteomyelitis will have an ESR less than 15 mm/hr. An elevated ESR in the presence of appropriate physical findings should alert the emergency physician to pursue the diagnosis of osteomyelitis, but a normal or slightly elevated ESR does not eliminate the diagnosis. Other inflammatory conditions such as cellulitis can cause an elevated ESR, although the degree of elevation of ESR is often higher with osteomyelitis. C-reactive protein (CRP), another nonspecific marker of inflammation, is produced by the liver and by adipocytes in response to interleukin-6 and may have some use in evaluating patients with bone infections. CRP increases within the first 24 hours of infection, peaks within approximately 48 hours, and is usually normal within 1 week of therapy.[48–50] In children presenting with osteomyelitis, it has been shown that ESR was elevated in 92%, CRP was elevated in 98%, and the WBC count was elevated in 35%.[48] These tests have a high positive predictive value, and elevated values should increase suspicion of this diagnosis. However, normal values of these nonspecific inflammatory markers cannot be used to rule out the diagnosis of osteomyelitis. The CRP may be a better early indicator of disease, but the ESR is most valuable in following response to treatment.[51] Typically, the ESR falls steadily as osteomyelitis resolves, and increases should it recur.[48,50]

The diagnosis of osteomyelitis in the emergency department (ED) is almost always made by skeletal imaging. Since conventional radiography is readily available, relatively inexpensive, and useful in differentiating infection from trauma and tumors, it remains the initial imaging test of choice for suspected osteomyelitis. In addition, plain radiography is often a helpful adjunct to secondary imaging studies. Unfortunately, radiographic evidence of osteomyelitis lags behind the clinical picture, and less than one third of patients have abnormalities on plain radiographs in the first 7 to 10 days after the onset of symptoms. The characteristic early findings on the plain radiograph in osteomyelitis are lucent lytic areas of cortical bone destruction (Fig. 134-2). However, lucency is not detected on radiographs until approximately 50% of bone mineral is lost, and this often takes up to 2 weeks from the onset of infection. Soft tissue edema, deep soft tissue swelling, distorted fascial planes, and altered fat interfaces may be present within 3 to 5 days from the onset of infection and can serve as a clue to osteomyelitis in the underlying bone. Periosteal reaction is another early sign. It may appear on radiographs as hypertrophy or elevation of the periosteum (involucrum) (Fig. 134-3). These early periosteal changes are more commonly seen in children than in adults. In advanced disease, the lytic lesions are surrounded by dense, sclerotic bone, and sequestra may be noted. Because radiographic resolution may lag behind clinical resolution, radiographs are also not helpful in tracking the course of osteomyelitis.[52] Radiographs have more utility in the diagnosis of chronic osteomyelitis. By 28 days from the onset of disease, 90% of the plain radiographs are positive.[53–55] (See Figs. 134-2 and 134-9.)

Radionuclide skeletal scintigraphy (bone scanning) is more sensitive than plain radiographs in the early diagnosis of osteomyelitis, especially in the presence of prosthetics or other hardware. Radionuclide scans can detect osteomyelitis within 48 to 72 hours after the onset of infection. A radioactive tracer is injected into the bloodstream and given time to bind or accumulate in body tissues. A gamma camera or collimator is used to sense released radioactivity, and an image is created that is evaluated for increase or decrease in expected uptake of the radionuclide.

For nuclear imaging, the radiopharmaceutical of choice for skeletal scintigraphy, both in the ED and as an inpatient, is technetium methylene diphosphonate (^{99m}Tc MDP). Technetium-labeled diphosphonates bind to the hydroxyapatite crystals in the bone matrix and therefore identify areas of increased osteoblastic activity. Consequently, this technique is highly sensitive for the early detection of acute osteomyelitis. The standard ^{99m}Tc MDP scan is a three-phase process. After injection of the ^{99m}Tc MDP, images are obtained within 60 seconds. This "radionuclide angiogram" illustrates the relative blood flow to the area of concern. The second phase involves imaging of the "blood pool" of ^{99m}Tc MDP at 5 to 15 minutes after injection. The third phase is the delayed or static image that is obtained 2 to 4 hours after injection. Areas of osteomyelitis show increased uptake on all three phases of ^{99m}Tc MDP scintigraphy.[7,55–57] Figure 134-4 shows diagnostic categories

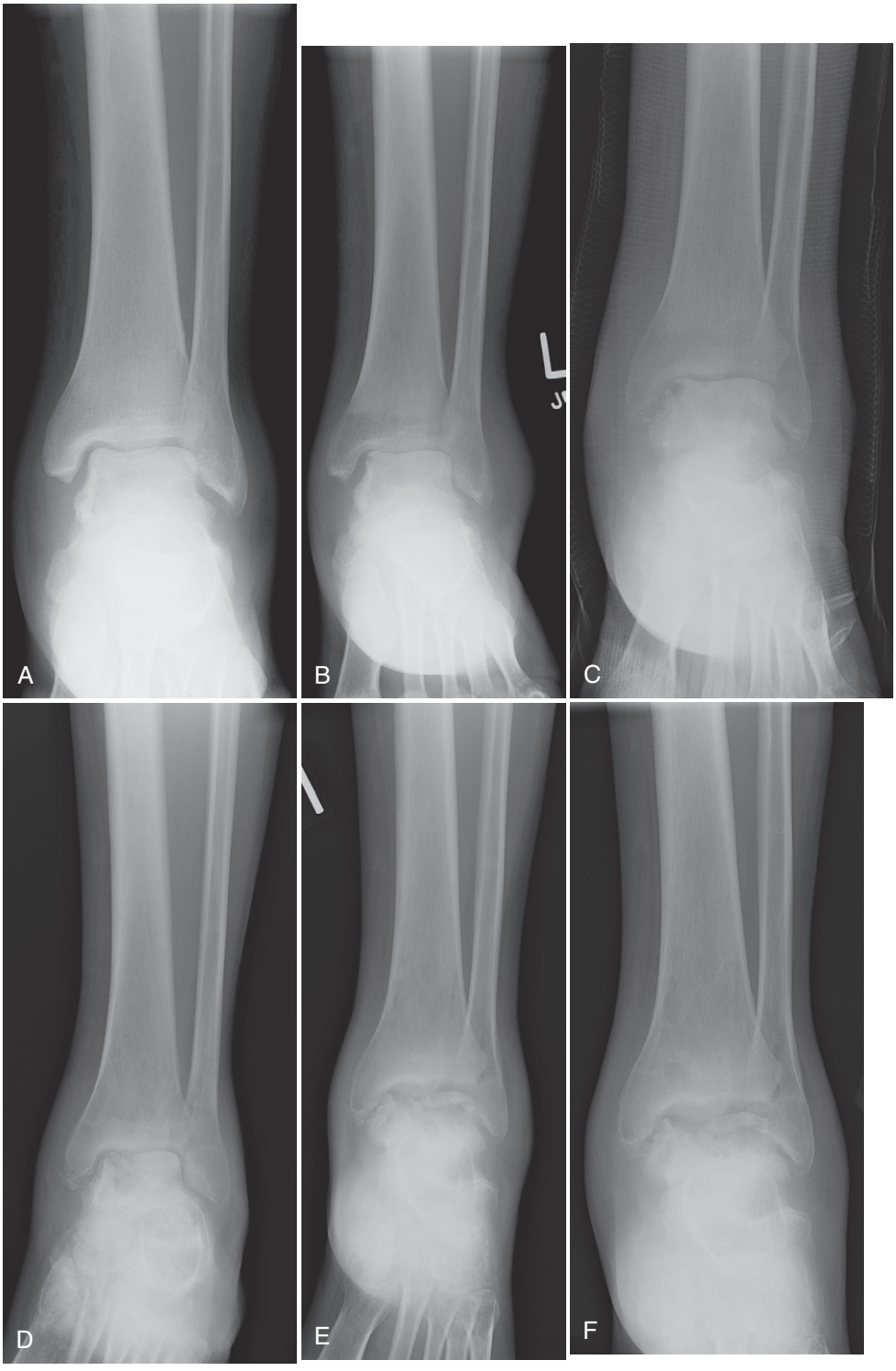

Figure 134-2. Radiographic progression of acute osteomyelitis. **A,** Soft tissue swelling at both the medial and lateral aspects of the ankle with a moderate-sized effusion (August 2, 2006). **B,** Large ankle effusion with extensive soft tissue swelling. There is complete loss of the tibiotalar joint space as well as widening of the medial joint space, suggesting chondrolysis. There are lucent areas in the distal tibia and fibula, suggestive of hyperemia, and the talus is diffusely sclerotic (September 11, 2006). **C,** Increased erosion of the medial aspect of the talar dome with increased joint effusion (October 12, 2006). **D,** Talar bony destruction with demineralization involving all of the osseous structures. There is also a small joint effusion (January 2, 2007). **E,** Avascular necrosis of the talus is present, as is destruction of the articular surfaces of the tibia and talus consistent with chronic osteomyelitis. There is diffuse osteopenia as well as loose bodies within the joint (April 19, 2007). **F,** There is continued irregularity of the articular surface of the tibia as well as collapse of the talus. Loose bodies are still present within the joint, and there is a persistent joint effusion and soft tissue swelling (June 14, 2007). (Courtesy of Thomas Egglin, MD, Department of Diagnostic Imaging, Rhode Island Hospital, Brown University.)

based on ^{99m}Tc MDP three-phase scanning. Figure 134-5 shows a positive ^{99m}Tc MDP scan.

The ^{99m}Tc MDP scan is a sensitive test for osteomyelitis in patients who have no existing bone abnormalities. Most series report a sensitivity of greater than 90% with the three-phase scan. Lower sensitivities are found in cases of neonatal osteomyelitis. False-negative scans are possible if pressure and edema in an area of active osteomyelitis prevent vascular delivery of the radionuclide. The resulting "cold spot" may actually signify an area of aggressive active osteomyelitis. False-negative scans may also occur if the patient has been receiving antibiotic treatment before presentation. The specificity of a ^{99m}Tc MDP bone scan is not as high as its sensitivity. False-positive scans may result from trauma, surgery, tumors, or chronic soft-tissue infections. Simple cellulitis does not usually produce a false-positive bone scan, since the radionuclide is cleared from soft tissues prior to acquisition of the delayed (third phase) images. Any process that encourages inflammation and new bone formation can result in increased uptake of radionuclide. The false-positive rate for bone scans is as high as 64% in various case series.[53,56,58] A four-phase ^{99m}Tc MDP study with an additional image at 24 hours may further improve specificity, because the amount of activity within the lesion theoretically continues to increase with time.[58]

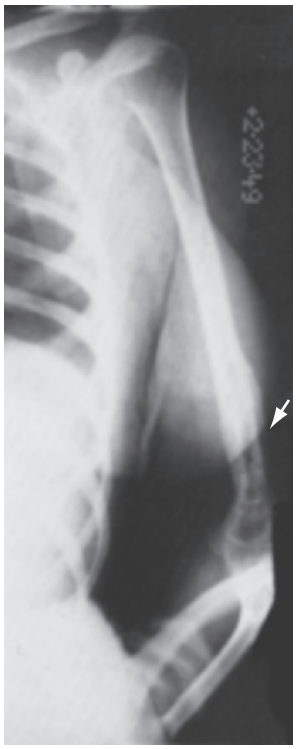

Figure 134-3. Plain radiograph of the humerus. Distal portion of the humerus has involucrum formation *(arrow)*, representing an advanced case of osteomyelitis. (Courtesy of Department of Radiology, University of Cincinnati Medical Center.)

Other radioisotopes, such as gallium citrate, indium oxine, and hexamethyl-propyleneamine oxime, may be used in skeletal scintigraphy as adjuncts to ^{99m}Tc scans, and various combinations of these tests are done to improve specificity. These scans are more expensive, take longer to complete, and entail more radiation exposure than technetium scans. These disadvantages greatly limit the use of other bone scan radioisotopes in the ED diagnosis of osteomyelitis.

In the past decade there has been a movement away from skeletal scintigraphy in the diagnosis of osteomyelitis. There is a significant radiation burden associated with scintigraphy, and recent recommendations are that children suspected of having acute osteomyelitis should have magnetic resonance imaging (MRI) rather than a bone scan.[58]

Computed tomography (CT) may be useful in the diagnosis of osteomyelitis. CT is most commonly used to detect and define areas of possible infection in bones with complex anatomy that is difficult to visualize on plain radiographs and bone scans. The bony cortex is particularly well seen on CT, and involucrum and sequestrum formation is easily identified. The sternum, vertebrae, pelvic bones, and calcaneus are far better imaged with a CT scan than with plain radiographs. Osteomyelitis appears as rarefaction, or lucent areas, on the CT scan images. Gas may be seen in bony abscess cavities. The limitation of CT scans for early diagnosis of osteomyelitis is the same as that for plain radiographs in that the disease must be present for more than a week for changes to be apparent. An important role of a CT scan in osteomyelitis is to help localize bony lesions that have been found with other imaging modalities. The CT scan can guide the surgeon in débridement and resection of infected bone and in choosing a site for diagnostic bone biopsy.[56,58]

The use of bone scans and CT for detection of osteomyelitis in the ED is decreasing as the availability and image quality of MRI improves while its cost decreases. The anatomic resolution of both CT and MRI is far superior to that of bone scans and plain radiographs. Both can reveal edema and the destruction of the medulla, as well as any periosteal reaction, cortical destruction, articular damage, and soft-tissue involvement, even when conventional radiographs are still normal. While the presence of ferromagnetic material is a contraindication to MRI, most materials used in orthopedics, such as titanium and chrome cobalt, do not interfere with this imaging modality.

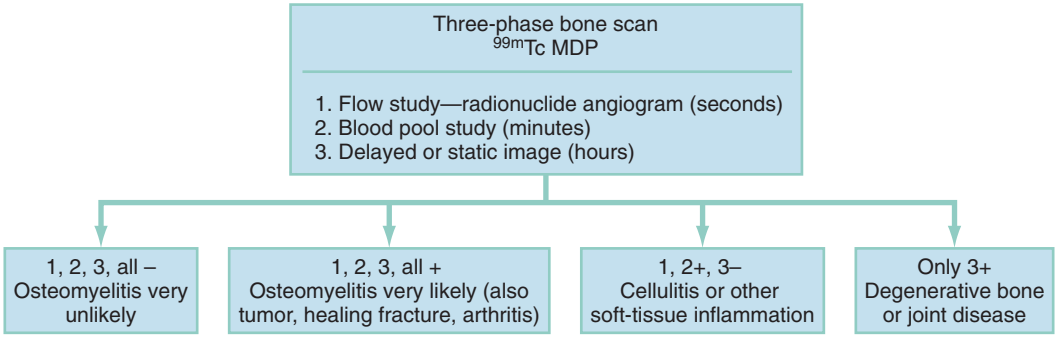

Figure 134-4. Diagnostic use of the three-phase ^{99m}Tc methylene diphosphonate (MDP) bone scan. (Modified from Demopulos GA, Bleck EE, McDougall IR: Role of radionuclide imaging in the diagnosis of acute osteomyelitis. J Pediatr Orthop 8:558, 1988.)

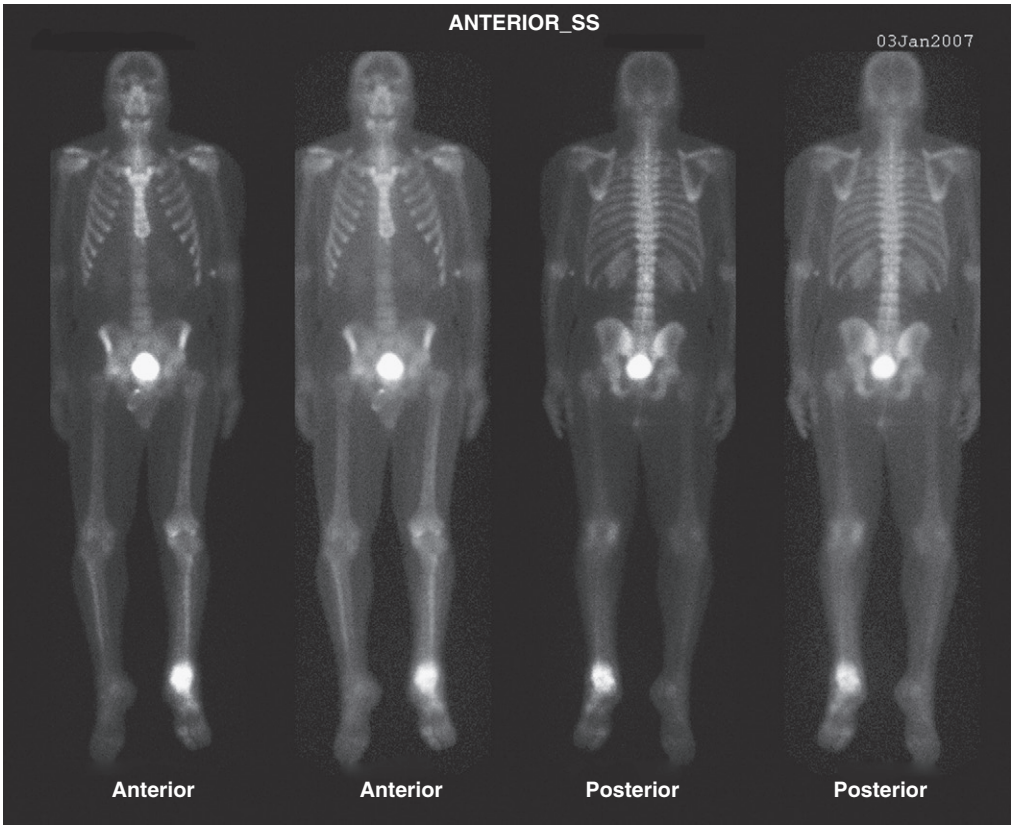

Figure 134-5. Bone scan of osteomyelitis. There is an abnormal increase in uptake in the left ankle in the region of the tibiotalar joint. There is also diffusely increased uptake of both lower extremities and in the medial and lateral compartments of the left knee likely secondary to altered biomechanics. (Courtesy of Thomas Egglin, MD, Department of Diagnostic Imaging, Rhode Island Hospital, Brown University.)

MRI uses a combination of spin-echo T_1-weighted and T_2-weighted images, short tau inversion recovery (STIR) images, and fat-suppressed T_2-weighted images. Osteomyelitis produces a diminished intensity of the normal marrow signal on MRI T_1-weighted images and a normal or increased signal on T_2-weighted images (Fig. 134-6). The images obtained by MRI in acute osteomyelitis are the result of the medullary space edema and exudate formation. MRI findings are often evident before a positive result is seen with skeletal scintigraphy because of the earlier detection of bone marrow involvement. While the interface between normal and abnormal marrow is indistinct, administration of gadolinium leads to enhancement of the involved viable marrow and helps to distinguish devitalized from normally perfused bone. Gadolinium becomes localized in areas of increased vascularity and blood flow and helps to distinguish soft tissue infections such as abscesses and cellulitis from osteomyelitis. Most radiologists recommend gadolinium contrast MRI when osteomyelitis is the leading suspected diagnosis. Soft tissue swelling and edema are best detected with fat-suppressed images, where the resolution is much greater with MRI than with plain radiographs or the CT scan. Bony cortical changes, periosteal reaction, soft tissue edema, abscesses, and sinus tracts are clearly shown on MRI.

It is likely that in the next decade MRI will supplant bone scans as the preferred imaging modality for evaluating osteomyelitis. When done with STIR images, MRI has a 100% negative predictive value and osteomyelitis can be essentially excluded in the presence of a normal MRI.[59] The sensitivity of MRI is reported to be between 88 and 100%, with a specificity of 75 to 100%.[60] MRI with gadolinium contrast also has a higher sensitivity and specificity than radionuclide bone scans in the diagnosis of vertebral osteomyelitis[61–63] (Fig. 134-7). The differential diagnosis for the MRI findings in acute osteomyelitis are trauma, noninfectious inflammatory and metabolic lesions, histiocytosis, tumors, and cancer. In cases where a surgical procedure will be done to obtain a microbiologic diagnosis or is needed to treat osteomyelitis, MRI has obvious advantages over a radionuclide bone scan in detailing the anatomy for the surgeon. One drawback to MRI is the presence of metal in bone, especially prosthetic joints. Metal may cause distortion of the signal in the area adjacent to a joint prosthesis, but this does not exclude MRI scan in this group of patients.[7,62,64,65]

Microbiologic Diagnosis. The most direct and often most effective way to diagnose osteomyelitis is to obtain infected bone by needle aspiration or surgical resection. Culture results from infected bone allow for specific antimicrobial therapy. Cultures of draining fistulas or sinus tracts are not an acceptable substitute because the organisms cultured from these sites are often different from those in the underlying infected bone.[7,34] Because osteomyelitis may be polymicrobial or due to unusual microorganisms, especially in immunocompromised patients, cultures for fungal and anaerobic organisms should be obtained.

Particularly in cases of hematogenous osteomyelitis, cultures of blood, urine, cerebrospinal fluid, and pus from other sites of infection can help uncover the infecting bacteria. Blood cultures in patients with acute untreated osteomyelitis are positive for the offending bacteria approximately 50% of the time.[46] In children with hemotogenous osteomyelitis, it is not unusual to identify the infecting organism in other bodily fluid cultures in addition to blood cultures. Blood cultures are almost always negative in patients with chronic forms of osteomyelitis.[34]

The likelihood of establishing a bacteriologic diagnosis in acute osteomyelitis is 80 to 90%, but in some cases, even culturing of resected bone yields no organism. Possible reasons for this are poor culture techniques and inadequate preparation of recovered tissue for culture, previous antibiotic

Figure 134-6. Magnetic resonance image of osteomyelitis. **A,** Sagittal T_1 image shows decreased signal within the talus, suggesting osteomyelitis. **B,** Axial T_2 image demonstrating increased signal throughout the talus and distal fibula consistent with osteomyelitis (fat-suppressed image). **C,** Sagittal T_1 image postgadolinium demonstrates a small focus of nonenhancing fluid just anterior to the distal fibula, suggestive of an abscess. (Courtesy of Thomas Egglin, MD, Department of Diagnostic Imaging, Rhode Island Hospital, Brown University.)

treatment, and culturing from necrotic ischemic regions that may be devoid of bacteria.[34,51]

When the emergency physician is confronted with a patient with possible osteomyelitis, the diagnostic options can seem confusing. The algorithm in Fig. 134-8 provides a simplified approach to the management of the patient with suspected osteomyelitis. A few key points should be considered when using this algorithm:

1. Radiographs lag behind the clinical picture.
2. When there is little clinical support for a diagnosis of osteomyelitis and the initial bone scan or MRI is negative, it is extremely unlikely that the patient has osteomyelitis.
3. In infants and children the amount of radiation exposure with imaging techniques must be considered.[64]
4. In easily accessible bones, aspiration is a low-risk procedure that will often help to establish a microbiologic diagnosis.
5. If the clinical presentation strongly suggests osteomyelitis, a lengthy diagnostic workup should not delay empirical treatment. Cultures of blood, urine, and other appropriate sites should be obtained and antibiotic treatment started.
6. The cost of imaging tests for osteomyelitis must be considered in deciding how to pursue the diagnosis. Expense must be weighed against the benefit of early diagnosis of osteomyelitis, the prevention of chronic osteomyelitis, and the numerous surgeries and increased length of treatment associated with this diagnosis.

Clinical Subsets of Osteomyelitis

Acute hematogenous osteomyelitis (AHO) is the most common form of osteomyelitis, but it has different presentations, diagnosis, and treatment in adults compared with children. The other main type of osteomyelitis, arising from a contiguous focus of infection, has special diagnostic and management features. This section reviews the common clinical subsets of osteomyelitis.

Figure 134-7. Magnetic resonance image, T_1-weighted with gadolinium contrast, demonstrating increased signal in the eighth and ninth thoracic vertebrae and intervertebral disk, consistent with osteomyelitis and diskitis. The patient was a 71-year-old man with back pain. Computed tomography–guided biopsy of the lesion was culture positive for *Staphylococcus aureus*. (Courtesy of Department of Radiology, University of Michigan Health System.)

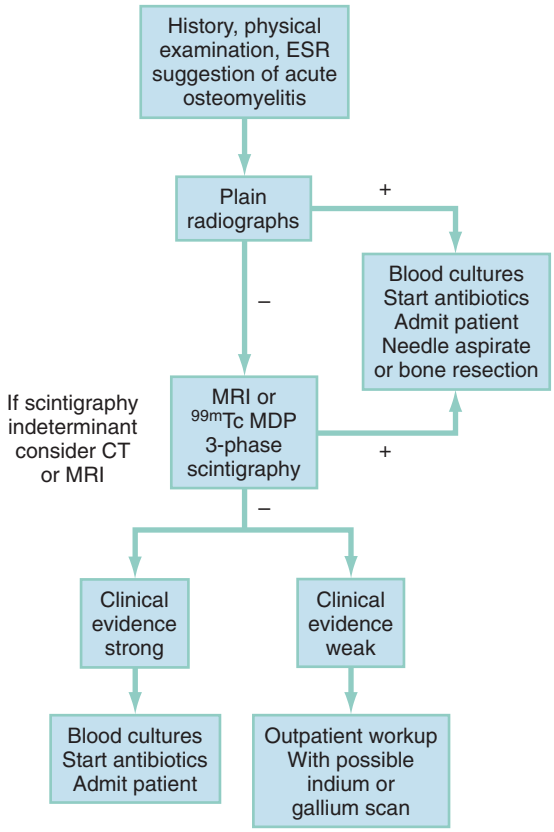

Figure 134-8. An algorithm for use of imaging studies in emergency department diagnosis of osteomyelitis.

Osteomyelitis in Children

Osteomyelitis in children tends to be acute, almost always arises from hematogenous seeding of bone, and can often be treated with antibiotics alone. AHO is seen in children as young as 3 months and as old as 16 years. Bacteremia is the presumed cause of bone infection. *S. aureus* is the most common infecting organism in children of all ages except neonates (see Table 134-1). As noted above, *H. influenzae* is no longer a common cause of AHO.

AHO has a well-established male preponderance (male/female ratio of 2 to 3 : 1) and involves long bones approximately 80% of the time. The site of infection is usually the distal metaphysis, but up to 30% of AHO occurs in other parts of the bone. The epiphysis may be involved in a "subacute" type of osteomyelitis. Children with AHO may have fever, chills, vomiting, dehydration, and malaise; but they usually do not appear toxic. Most children have characteristic pain, limited use, and point tenderness in the involved limb. The diagnostic evaluation for AHO is listed in Fig. 134-8. Blood cultures are positive for the bacterial cause of osteomyelitis in 60% of patients with AHO. A positive blood culture and a physical examination consistent with osteomyelitis may be sufficient to make a diagnosis of AHO. Figures 134-2 and 134-5 show a typical radiograph and bone scan of AHO, respectively.[10,46,48,55,65-68]

Neonatal osteomyelitis is increasingly reported and may be difficult to diagnose because of minimal systemic findings. Neonatal osteomyelitis is more commonly seen after abnormal pregnancies or deliveries and often accompanies other acute illnesses. Multiple sites of bony involvement are found in approximately half the reported cases. Because of the special vascular anatomy of the neonate, septic arthritis often accompanies osteomyelitis. Osteomyelitis in the neonate is more common in flat bones, such as the facial bones. Group B streptococci are becoming the leading causative bacterium in neonatal osteomyelitis, but staphylococcal species are still common. Skeletal scintigraphy is of limited value in diagnosing neonatal osteomyelitis. The reasons are an inadequate inflammatory response in the neonate, the small size of bones and joints, and the ability of the epiphyses to concentrate the radiolabeled isotope, making it difficult to distinguish between infection and normal activity in this area. Plain radiographs show abnormalities within days of development of neonatal osteomyelitis and are usually positive by the time the disease is suspected.[65–67]

Two less common forms of osteomyelitis can occur in children: subacute osteomyelitis and chronic recurrent multifocal osteomyelitis (CRMO). Subacute osteomyelitis refers to a form of the disease in which clinical symptoms and signs are slow to appear and radiographs show small areas of osteomyelitis, usually in the metaphysis of long bones. Cultures of blood and bone are negative more than 50% of the time and, when positive, usually implicate staphylococcal species. Like subacute osteomyelitis, CRMO usually affects older children (6–10 years) and adolescents. CRMO is characterized by small foci of infection at various sites in the skeleton. The disease is defined by multiple episodes of indolent infection. Diagnosis is made by radiographs; culture of the bony sites is almost always negative. This disease may be associated with a type of psoriasis.[68,69]

Another form of subacute osteomyelitis is Brodie's abscess. This is a localized form of subacute osteomyelitis that also

occurs mostly in children. Metaphyseal locations are most common before closure of the growth plates, and after closure, a metaphyseal abscess is most frequent. The wall of the abscess contains large amounts of dense fibrous tissue. This is demonstrated by pronounced rim enhancement on contrast-enhanced MRI or CT scans. The central portions are pus filled. *S. aureus* is cultured in half of the cases. *Proteus* and *Pseudomonas* species are also isolated. Symptoms are usually minimal and include localized pain that is often nocturnal, suggesting a tumor. On plain radiographs the lesion is lytic, with a well-defined sclerotic margin.[53,68]

Vertebral Osteomyelitis

Vertebral osteomyelitis usually afflicts older adults in a manner analogous to AHO in children and appears to be increasing in frequency as the population ages. The spine is susceptible to bacterial infection because the venous system surrounding vertebral bodies is valveless (permitting two-way flow of blood) and has transverse and longitudinal anastomoses. Bacteria that reach the spine and enter the venous plexus are more likely to aggregate and cause infection in this slow-moving system. Infection can readily spread to adjacent vertebral bodies. A clear source of bacterial hematogenous seeding with positive blood cultures occurs in approximately 40% of cases of vertebral osteomyelitis. *S aureus* (including MRSA) is the most common offending agent in vertebral osteomyelitis, followed by aerobic, gram-negative rods from urinary or gastrointestinal sources.

Only 10% of patients with vertebral osteomyelitis appear septic or toxic; the rest have a subacute presentation. In most patients, physical examination will reveal back pain and tenderness over the spinous process. Neurologic deficits are reported in less than 20% of patients with vertebral osteomyelitis and are often an indication of an epidural abscess. Up to 50% of patients with these abscesses present without fever or leukocytosis. On laboratory testing, the ESR is commonly elevated greater than 50 mm/hr and the CBC may demonstrate an anemia of chronic disease.[70–74] While many patients with vertebral osteomyelitis present with nonspecific complaints and findings, the constellation of severe acute back pain and fever with neurologic symptoms is suggestive of spinal epidural abscess. Rapid diagnosis and treatment of this medical emergency starts with initiation of empirical antibiotics, immediate imaging, and early surgical involvement.

The areas most prone to vertebral infections include the lumbar, thoracic, and cervical spine, in that order. Vertebral osteomyelitis typically involves two adjacent vertebrae and the disk space between them. Cervical spine osteomyelitis can cause a retropharyngeal abscess, while lumbar spine osteomyelitis may be complicated by a psoas muscle abscess. When osteomyelitis affects the thoracic spine, infection can spread to the chest. Paraspinal abscesses, reactive pleural effusions, and empyema have been reported and may mislead the clinician to suspect that the primary problem is not in the spine.[72,75,76] The most dreaded complications of vertebral osteomyelitis are the spread of infection into the spinal canal, the development of an epidural abscess, and progression of the infection to cause spinal cord injury and permanent paralysis. Fortunately, this occurs in less than 15% of cases of vertebral osteomyelitis. The spinal cord may suffer ischemic injury if the vertebral infection causes septic thrombosis or compression of local blood vessels.[75,76]

The imaging strategy for the diagnosis of vertebral osteomyelitis starts with plain radiographs, which may show disk space narrowing or destruction of the vertebral endplates or the vertebral body. Similar to osteomyelitis in other parts of the body, findings on plain radiographs are not seen until at least the second week of vertebral infection. Bone scintigraphy has been largely replaced by MRI in further imaging of suspected vertebral osteomyelitis. CT is good for defining bony destruction and is often used to assist needle aspiration of the lesion, but MRI can detect vertebral osteomyelitis at an earlier stage than CT and provides better detail and assessment of the spinal cord and adjacent structures, especially when gadolinium contrast is used[62,64,76] (see Fig. 134-6).

The diagnostic procedure of choice for vertebral osteomyelitis is needle biopsy which can provide multiple specimens for microbiologic and pathologic examination. In order to avert the potentially catastrophic progression to spinal cord compression, ED patients who present with a clinical picture consistent with vertebral osteomyelitis should have the diagnosis rapidly confirmed either through imaging or by direct needle biopsy performed by a surgeon, with or without CT guidance. Patients who are at increased risk for paralysis include elders, those with cervical spine osteomyelitis, and those with serious underlying diseases, such as rheumatoid arthritis or diabetes mellitus.

Most patients with vertebral osteomyelitis require prolonged antibiotic therapy. Surgical therapy may also be necessary, especially when there is spinal cord compression, abscess formation, persistent pain, progressive deformity, and recurrence after adequate treatment.[76]

A variant of vertebral osteomyelitis seen in children that must be distinguished is diskitis. This subacute disease is thought to be a low-grade infection (usually *Staphylococcus* species) within the disk, sometimes extending to the adjacent vertebral plates. The child complains of back pain and may refuse to walk. Bone scintigraphy may show increased uptake in the disk space. Single-photon emission computed tomography imaging and pinhole collimation can accurately identify the site and extent of involvement. As in adults, MRI will demonstrate the anatomy of diskitis better than bone scintigraphy. CT is used to guide aspiration. Cultures of the disk from needle aspiration are reported to be positive for bacteria 30 to 60% of the time. The disease resolves with nonoperative treatment.[72,75]

Post-traumatic Osteomyelitis

Post-traumatic osteomyelitis is a form of contiguous-focus osteomyelitis that results from open fractures, surgery and invasive procedures, burns, bites, and puncture wounds.

At least 10% of open fractures later develop osteomyelitis, and the tibia is the most commonly affected bone. The fracture site may be directly contaminated from the environment or iatrogenically contaminated from emergency procedures or surgery. The intraoperative implantation of prosthetic devices further increases the chance of infection. Extreme damage to adjacent soft tissues may result in a necrotic nidus of infection that can spread to bone. Polymicrobial infection is more common with this type of osteomyelitis. The imaging of post-traumatic osteomyelitis is complicated by changes induced by surgery and new bone formation in the fracture. Imaging modalities that are best in this situation are MRI, CT, and ^{18}F-FDG PET.[77,78]

Infection that is due to direct inoculation associated with joint arthroplasty may become evident within 12 weeks after the surgery. These patients generally do not report relief of their pain after the surgery. Patients who develop symptoms of infection more than 12 weeks after surgery and who have postoperative improvement of their pain are considered to have a hematogenous source of their infection. If either of these presentations are recognized within the first 2 weeks of

onset of infectious symptoms, the prosthesis is considered salvageable. After 2 weeks, the chances of eradicating the infection without removing the prosthesis decreases substantially.[79–83]

Postsurgical osteomyelitis is difficult to diagnose. Fever is often absent and the patient often presents with a painful, unstable joint on physical examination. *S. aureus* and *S. epidermidis* account for 75% of postsurgical and prosthesis-related osteomyelitis. Radiographs are often negative but may show subtle signs of bone resorption about the prosthetic components. It is difficult to distinguish mechanical from infectious loosening, so joint aspiration and synovial fluid analysis is necessary. However, this should only be attempted in the sterile operating room to avoid introducing infection. Other imaging techniques such as CT, MRI, and ^{18}F-FDG PET are used but are also difficult to interpret due to scatter from the metallic components and postsurgical changes. The most common form of postsurgical osteomyelitis is infection of a hip prosthesis, which occurs in 1 to 5% of hip replacement surgeries. It has been shown experimentally that bacteria can become immersed in an extremely adherent material called the glycocalyx, which binds to the inert substance of the prosthesis. Systemic antibiotics cannot penetrate this glycocalyx, and surgical removal of the prosthesis is usually the only way to cure the infection.[84] Puncture wounds to the feet have approximately a 2% incidence of developing osteomyelitis. The causative organism is usually *P. aeruginosa* or *S. aureus*. Other puncture wounds are nosocomial—in the form of subclavian venipuncture, fetal scalp monitors, and other invasive procedures. Osteomyelitis can result from inoculation of bone with bacteria during these punctures.

Diabetic Foot Osteomyelitis

The pathologic changes induced by long-standing diabetes mellitus encourage the development of osteomyelitis. Foot infections are common in diabetics because of compromised vascularity. Peripheral neuropathy is present in a majority of diabetic patients, and this leads to repetitive trauma and loss of the protective barrier of the skin and foot ulcers. Once the skin has been violated and infected, the altered host defense of diabetic patients allows infection to occur and spread. The small bones and phalanges are most often affected. Infection spreads first to the periosteum and then to the cortex and may finally disrupt medullary bone. The initial phase of foot infection in diabetic patients may exacerbate preexisting hyperglycemia. This allows bacteria to replicate at an increased rate and impairs leukocyte function, with defective chemotaxis, abnormal phagocytosis, and decreased bactericidal function.[85] Defective antibody synthesis and decreased complement levels also exacerbate osteomyelitis in diabetics. The typical patient with diabetic foot osteomyelitis is more than 50 years old and has advanced insulin-dependent diabetes. More than 60% of such patients have polyneuropathy, more than 50% have retinopathy, and at least 30% have concurrent cardiovascular disease.[86,87]

Local findings in diabetic foot infections consist of swelling, erythema, and sometimes pain. Indolent ulcers and frank cellulitis are seen in more than 50% of cases. Because the process is often chronic, radiographic changes may have sufficient time to develop. Mottled lytic lesions are typical, and air may be present in the soft tissues. The bone scan is of limited value because of generalized poor perfusion in the area and the frequency of concurrent soft tissue infection. The only reliable way to make the bacteriologic diagnosis is by surgical culture of the bone; however, if a wound can be probed all the way to the bone, wound cultures have an 89% positive predictive value for osteomyelitis.[87,88] Bone biopsy for diabetic foot osteomyelitis has a reported sensitivity of 94%.[89] Diabetic foot osteomyelitis is usually polymicrobial. The most common organism is *S. aureus*. Other common organisms include streptococci, Enterobacteriaceae, and anaerobes. Surgical treatment is often required, and severe cases commonly lead to amputation of toes or portions of the foot. However, treatment with intravenous (IV) followed by oral antibiotics can be successful in some patients. In general, patients are treated with a longer treatment course of about 8 to 10 weeks.[90]

Osteomyelitis in Sickle Cell Disease

Patients with sickle cell disease are at increased risk for hematogenous infection, including osteomyelitis. Macrophage function is impaired in sickle cell patients, rendering them susceptible to infections with encapsulated organisms. AHO in children with sickle cell disease has two major differences from AHO in other children. First, infection in sickle cell disease is usually located in the diaphysis of long bones as opposed to the metaphysis as is seen in other AHO patients. Second, although *S. aureus* is still the most common bacterium in children with sickle cell disease who develop osteomyelitis, *Salmonella* species are the next most common infecting organism. The reason patients with sickle cell disease are predisposed to bone infection with *Salmonella* is not completely understood, although it is postulated that microinfarcts in the bowel allow *Salmonella* bacteremia to seed the bloodstream and become hematogenous osteomyelitis.[91]

The differentiation of bone infection from bone infarction in sickle cell patients is a challenge. Fever, a toxic appearance, and an elevated ESR are all more commonly associated with osteomyelitis than with bone infarction. Plain radiographs are not helpful in distinguishing between the two entities. Skeletal scintigraphy may help make the diagnosis. The best method appears to be ^{99m}Tc MDP followed by gallium or indium scanning. Although both infection and infarction may show increased uptake on the technetium scan, the gallium or indium scan should be "hot" with osteomyelitis but "cold" with sickle cell infarction. Another approach is to note the response to conservative therapy: Bone infarctions usually improve within 24 to 48 hours, whereas bone infection worsens.[53,92,93] Antibiotic treatment of osteomyelitis in the sickle cell patient should include coverage against *Salmonella*, for example, with a third-generation cephalosporin.

Chronic Osteomyelitis

Historically, chronic osteomyelitis usually resulted from inappropriate or inadequate treatment of AHO. However, most chronic bone infections now occur as a complication of posttraumatic infection, surgical procedures, or diabetic foot infections. The inflammatory response to infection triggers bone resorption, cartilage destruction, and ultimately leads to bone death. The necrotic bone acts like a foreign material, providing an inanimate surface to which microorganisms adhere.[94] Clinical signs that the infection has become chronic include the formation of sequestra and the presence of draining tracts or fistulas (Fig. 134-9). This infection is almost always polymicrobial and commonly involves anaerobes. Bone scans are of limited use in chronic osteomyelitis, as it is difficult to differentiate active foci of infection and identify improvement of infection. Cultures of sinus tracts are not a reliable method for predicting which bacteria are active in the underlying bone infection. Therefore, direct biopsy of bone is the only option for accurately diagnosing most cases of chronic osteomyelitis.[20,86,95] Chronically established orthopedic infection can be

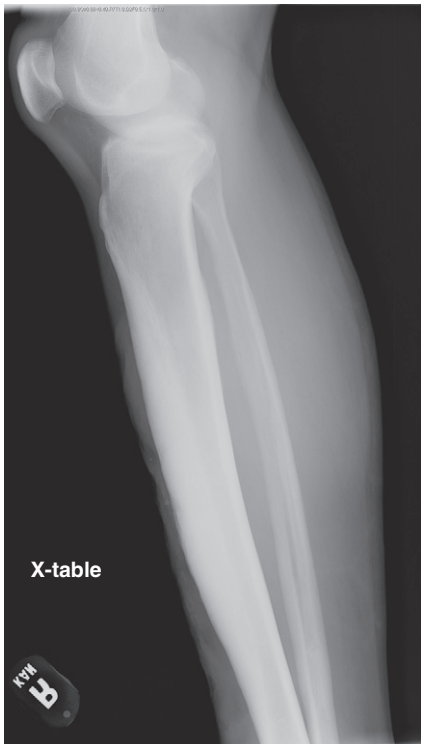

Figure 134-9. Chronic osteomyelitis. Endosteal new bone formation and the thickening of the anterior cortex of the tibia with cortical irregularity in the mid-portion of the shaft. Periosteal reaction, sequestrum, and fracture are absent. (Courtesy of Thomas Egglin, MD, Department of Diagnostic Imaging, Rhode Island Hospital, Brown University.)

remarkably persistent or evolve even in the face of prolonged antibiotic therapy; therefore, treatment commonly involves surgery.

Complications of Osteomyelitis

In addition to the development of chronic osteomyelitis, several other complications can arise from the acute infection. The blood may also become seeded with bacteria or bacterial toxins, resulting in sepsis. In fact, toxic shock syndrome has been reported with osteomyelitis caused by *S. aureus*.[96] Depending on the location of osteomyelitis, local extension of an invasive, suppurative process can lead to septic arthritis, brain abscess, meningitis, spinal cord compression, pneumonia, and empyema. In children, osteomyelitis damages the developing skeleton. If infection involves the epiphysis, permanent growth alteration can occur, resulting in a shorter or deformed extremity on the affected side. Pathologic fractures may occur through sites of osteomyelitis.

Differential Considerations of Osteomyelitis

Many different processes involving bone may masquerade as osteomyelitis. Bone tumors may produce local pain, radiographic changes, and even bone scan abnormalities consistent with osteomyelitis. Tumors most likely to mimic osteomyelitis are osteoid osteomas and chondroblastomas. These produce small round radiolucent lesions on radiographs. Ewing's sarcoma is a tumor of bone marrow in children that can be mistaken for osteomyelitis. Metastatic bone tumors and lymphomas should also be considered in the differential diagnosis of osteomyelitis. Trauma can produce a clinical picture similar to osteomyelitis. In children, when trauma is common and may be occult, the evaluation for osteomyelitis may reveal a buckle fracture.

Other inflammatory and infectious diseases that may be initially confused with osteomyelitis are myositis ossificans, erythema nodosum, cellulitis, and eosinophilic granuloma. This enlarging collection of histiocytes occurs in the marrow cavity and causes lytic destructive lesions.

Management of Osteomyelitis

Once the diagnosis of osteomyelitis is considered, it is important to obtain cultures and commence treatment. The goal of therapy is to contain the infection before bone death occurs. Cure rates fall dramatically once necrotic bone is present. Treatment of most patients with osteomyelitis is best guided by culture results from specimens taken from infected bone. Since culture results are usually not available to the ED physician, the standard of care is to promptly begin empirical treatment in suspected acute infections of native joint and bone. In chronic or implant-related infection, early antibiotic therapy is less crucial unless the presentation suggests bacteremia or necrotizing soft tissue infection. The ideal antibiotic for treating osteomyelitis should be bactericidal against the offending bacteria, have low toxicity, be chemically stable at the site of infection, and be relatively inexpensive. The low pH of infected bone may limit the bactericidal action of some antibiotics, particularly the aminoglycosides. Cephalosporins and penicillins are more stable in this environment. The emergency physician will usually have to empirically initiate broad-spectrum treatment of suspected osteomyelitis and should be aware of regional resistant patterns.[7,20,97]

The antibiotic of choice for osteomyelitis should be active against beta-hemolytic streptococci and staphylococci, including MRSA. Although gram-negative organisms are uncommon pathogens, the serious consequences of inadequate treatment justify the inclusion of anti-gram-negative coverage in the initial drug regimen. Once culture results are obtained, the antibiotic regimen can be tailored.[98–102]

ED care of most types of osteomyelitis involves treatment of an infection that has been present for days or weeks. In the case of post-traumatic osteomyelitis, emergency care may help to prevent the disease. The proper management of open fractures in the field is to cut away surrounding clothing, pour sterile saline or water over the exposed bone, and cover the wound with moist sterile gauze bandages or a sterile sheet. Only in the case of severe vascular compromise to the distal limb should an open fracture site be manipulated or realigned because of the danger of further contaminating the wound. Since wound surface cultures in the emergency setting are not reliable in predicting future pathogens in bone infections, they need not be done as part of emergency care.[44]

Treatment of osteomyelitis often requires a combined medical and surgical approach. This is usually true when osteomyelitis is caused by direct inoculation into bone or spreads from a contiguous focus of infection. If the area of osteomyelitis is small, aspiration or resection of the bone abscess may be both a diagnostic and therapeutic procedure.[103] Acutely, indications for surgery include the presence of an abscess, necrosis, wound dehiscence, or failure to respond to appropriate therapy. In chronic infections, surgery is invariably required for radical cure of infection, and a team with orthopedic and infectious disease expertise may provide the best results.[104]

AHO in children can be treated with antibiotics alone. In other situations, such as diabetic foot osteomyelitis and chronic osteomyelitis, the use of antibiotics with surgical débridement is necessary to eradicate the infection.[2,20,88,99,105]

The first priority remains adequately treating *Staphylococcus* species with a penicillinase-resistant penicillin such as oxacillin or nafcillin or a first-generation cephalosporin. In patients with a severe penicillin allergy, clindamycin is an acceptable alternative. MRSA is usually sensitive to clindamycin, linezolid, or combination therapy of vancomycin with rifampin. Nonenterococcal streptococci are usually sensitive to antibiotics used to combat staphylococci. Gram-negative bacteria, including Enterobacteriaceae, *Escherichia coli*, *Proteus mirabilis*, and *Serratia marcescens*, are rare causes of osteomyelitis. Third-generation cephalosporins, aminoglycosides, imipenem-cilastatin, and ampicillin are the usual choices for broad gram-negative coverage. Beyond this initial broad-spectrum therapy, prophylactic treatment for anaerobic bacteria, *Pseudomonas*, and fungal organisms must be based on clinical suspicion. Due to emerging resistance patterns, fungal bone and joint infections are best treated with the azole antibiotics such as fluconazole and itraconazole.[106]

The incidence of antibiotic resistance is increasing. Resistance to both penicillinase-resistant penicillins (oxacillin and methicillin) and fluoroquinolones by staphylococci, vancomycin by enterococci, and imipenem by pseudomonads have all been reported. Therefore, if the bacterium is identified in the emergency setting, it is important to select the most specific antimicrobial agent based on regional resistant patterns.[97,99,107] The increase in antimicrobial resistance highlights the need for new antibiotics to expand therapeutic options. Second-generation fluoroquinolones, such as ciprofloxacin and lomefloxacin, and third-generation agents, such as levofloxacin, offer excellent bone and joint penetration and are active against a broad spectrum of gram-positive and gram-negative organisms. Since blood concentrations are similar between oral and parenteral administration of these drugs, development of oral treatment protocols for osteomyelitis is being studied.[2,97,99,107] Successful treatment of osteomyelitis correlates best with serum levels of antibiotics, not the route of administration. The standard recommendation is that the antibiotic used should achieve serum levels *eight* times greater than its minimum inhibitory concentration. If the serum concentration of an antibiotic is bactericidal, bactericidal levels in bone will almost always be present.[107] Table 134-1 lists common treatment regimens for the variety of bacteria that cause osteomyelitis. The standard recommendation is parenteral antibiotics for 4 to 6 weeks and then an oral course of antibiotics.

Treatment of chronic osteomyelitis is a difficult surgical problem. Instillation of antibiotic-containing beads into infected bone can help eradicate the infection so that bone grafts can be successfully used in chronic osteomyelitis.[108,109] Hyperbaric oxygen therapy is reported to be effective in treating chronic osteomyelitis in noncontrolled clinical case series, and may work best in diabetic foot osteomyelitis. Further randomized clinical trials are necessary to confirm the favorable results seen in case series.[110]

Disposition of the Patient with Osteomyelitis

Patients with osteomyelitis are admitted for IV antibiotic treatment. A subset of these patients will also need operative débridement. Oral antibiotics that have the same bioavailability as their IV forms can be used; however, an initial IV course of antibiotics is still recommended. Some recent studies have demonstrated good results with outpatient treatment of osteomyelitis. After steady-state serum antibiotic levels have been achieved, patients can be treated with outpatient IV antibiotic therapy.[111,112]

CLINICAL FEATURES OF SEPTIC ARTHRITIS

Diagnosis of Septic Arthritis

It is estimated that 20,000 cases of septic arthritis are diagnosed per year. Septic arthritis most commonly results from hematogenous migration of bacteria into a joint. Like osteomyelitis, septic arthritis may also result from spread from a contiguous focus of infection or by direct inoculation of bacteria. Direct inoculation can result from penetrating trauma or iatrogenically, as a consequence of any procedure that invades the synovium, such as joint aspiration or injection. Septic arthritis may occur concomitantly with osteomyelitis, with infection spreading from bone to joint, and osteomyelitis may also be the result of septic arthritis. Septic arthritis occurs in all age groups but is most common in children. It is almost always a monoarticular process; polyarticular involvement is present in fewer than 10% of pediatric cases and fewer than 20% of adult cases.[8,14,26,113]

Septic arthritis is most likely to occur in the joints of a lower extremity. In infants and children, the knee and hip are most often infected. In adults the knee is the site of septic arthritis 50% of the time, followed by the hip (20%), shoulder (8%), ankle (7%), and wrist (7%). As noted previously, since the synovial membrane extends beyond the epiphysis and attaches to the metaphysis in the knee, hip, and shoulder joints, infection can easily spread from the metaphysis of the femur or humerus into the joint.[14,16,114-116]

History and Physical Examination

The onset of septic arthritis is usually more acute than osteomyelitis. The predominant symptom of septic arthritis is joint pain, exacerbated with range of motion. Many children who have septic arthritis will not use the involved limb at all. If the hip is infected, the child may present with referred pain to the thigh or knee. Immune-suppressed patients, especially those on corticosteroids, may develop septic arthritis with minimal joint pain. It is important to ascertain the presence of underlying joint disease such as osteoarthritis, gout, rheumatoid arthritis, joint surgery, and the presence of other conditions, such as IV drug use, that predispose patients to septic arthritis. In these patients, a careful history may help differentiate chronic joint pain from the acute pain associated with septic arthritis. Greater than 80% of children and 40% of adults have a fever on presentation; however, constitutional symptoms such as weakness, malaise, anorexia, nausea, and diffuse myalgias are inconsistently reported.[4,8,15,16,116]

Tachycardia and hypotension may indicate a generalized septic process. Examination of the skin, nose, ears, and pharynx may reveal a focus of infection. In the neonate or infant, there may be "pseudoparalysis" of the affected limb. This can be mistaken for a neurologic problem; however, an isolated true paralysis is far less common than septic arthritis. The inability of a child to bear weight on a lower extremity or to spontaneously move any joint must be considered a sign of septic arthritis until proven otherwise.

In the older child and adult, signs may be more localized. The extremity will usually be held motionless in the position of greatest comfort, which is slight flexion. Palpation of the septic joint causes exquisite pain, and any maneuver that stretches the synovium, such as flexion and extension, will cause severe pain. The cardinal signs of inflammation, swelling, erythema, and warmth, are commonly found in the affected joint. The hip joint, with its deeper location, may not produce obvious external findings when infected; however, passive range of motion will be painful. Periarticular processes such as

bursitis, tendonitis, and cellulitis may produce erythema, warmth, and tenderness, but these processes can be differentiated from septic arthritis since palpation of the joint line and maneuvers that stress the synovium and joint are not usually painful. Periarticular processes also do not commonly produce an effusion. In general, the triad of fever (seen in 45–60% of cases), pain (seen in 75% of cases), and impaired range of motion suggests septic arthritis. One caveat with the physical examination is that an increasing number of adult patients are on chronic immunosuppressive drugs, and in these patients the classic history and examination findings may be significantly less dramatic than in their immunocompetent counterparts.[4,14,15,116]

Diagnostic Strategies of Septic Arthritis

Joint Aspiration and Joint Fluid Analysis. The diagnosis of septic arthritis requires joint fluid for culture and analysis. It is fortunate that the knee joint is both the most likely to be infected and the easiest to aspirate. Other joints such as the hip are more difficult to aspirate and may require orthopedic surgical consultation. Ultrasound and fluoroscopy-guided aspiration are adjunct modalities used to obtain fluid from the joint and may be useful in detecting early, less obvious intra-articular fluid collections.[114] However, the absence of sonographic fluid does not rule out septic arthritis as the cause for joint pain. When attempting to obtain synovial fluid from the hip under fluoroscopy, a small amount of contrast material should be injected into the joint during aspiration to confirm that the needle has entered the intra-articular space.[115,117] Sterile technique should always be practiced; however, the risk of introducing infection into a joint during intra-articular aspiration or injection has been reported to be only 0.4% or approximately 1 in 10,000 joint injections or aspirations.[15,26]

Because joint fluid analysis is not done as often as other diagnostic tests in the ED, a joint fluid protocol form is useful to ensure that all necessary tests are prepared and ordered properly. Joint fluid cultures must be inoculated as soon as possible after the fluid is obtained. The laboratory should include special media to test for fastidious organisms such as *Neisseria gonorrhoeae* and *H. influenzae*.[4,26] Anaerobic and fungal organisms should also be cultured.

One method that may increase the yield in isolating bacteria from joint fluid is to inoculate blood culture bottles with joint fluid immediately after joint aspiration. This allows some bacteria, which would normally die before being inoculated on culture media in the laboratory, to survive and grow in the blood culture bottle (brain-heart infusion broth).[4,16] Joint fluid culture results in clinically suspected septic arthritis are negative in 20 to 25% of cases. This may be due to an inadequate joint fluid sample, poor culturing techniques, the presence of fastidious organisms, or misdiagnosis of the joint inflammation. In addition, leukocytes may have cleared bacteria from the joint space; however, the bacteria may still persist in the synovial membrane and may be detected by a synovial biopsy.[4,16,26]

The definitive test to determine bacterial arthritis is joint fluid culture. Other tests of the synovial fluid are commonly obtained, but the efficacy of these additional tests is debated. The Gram's stain, WBC count and differential, and the ratio of the joint fluid glucose to serum glucose have traditionally been used to differentiate bacterial arthritis from other joint diseases and can be included as adjunct studies in the evaluation of the patient with joint pain. The primary reason for the decreasing utility of the traditional joint fluid tests is the number of patients who have a chronically activated or suppressed immune response in the infected joint. The synovial fluid leukocyte count in a septic joint is often greater than 50,000 cells/mm^3 with a predominance of polymorphonuclear leukocytes, but other processes can give similar cell counts, and up to 30% of patients with septic arthritis have been documented to have counts less than 50,000 cells/mm^3. The fasting joint fluid glucose level is often lowered in patients with septic arthritis, and the joint fluid/serum glucose ratio is less than 1 : 2, but this test is also not reliable. The joint fluid lactate level is often higher in infected joints than in inflamed joints, but this test does not appear to be more helpful than the glucose ratio, particularly in partially treated septic arthritis. Joint fluid WBC counts and glucose may be most helpful to rule out septic arthritis when the WBC count is low (<10,000 cells/mm^3) and the glucose is normal.[4,8,26,116] The examination under polarizing microscopy for the presence of crystals may be of some use in differentiating inflammatory from noninflammatory joint disease but is not helpful in separating infectious from noninfectious inflammatory joint disease.

When only a drop or two of synovial fluid can be recovered from a joint aspiration, the emergency physician must establish priorities for diagnostic tests. The single most important test is a bacterial culture. Culture of the synovial fluid or of synovial tissue itself (obtained by arthrotomy) is the only definitive method of diagnosing infective arthritis. If extra fluid is available after obtaining a culture, it can be used to obtain a Gram's stain and smear, and then a cell count and crystal analysis.[4,14,16] Since therapeutic decisions should not be delayed until results of the culture are available, the Gram's stain is used to guide antibiotic treatment; however, empirical treatment should not be delayed if the Gram's stain is negative. The Gram's stain is less than 60% sensitive for detection of bacteria in synovial fluid.

Blood tests are not consistently helpful in making a diagnosis of septic arthritis. Two sets of blood cultures should be obtained; however, it should be noted that blood cultures reveal the infecting organism in only 25 to 50% of cases. The ESR is elevated in approximately 90% of cases of septic arthritis and, along with the CRP, is used to track resolution of the infection. A WBC count greater than 10,000 cells/mm^3 may suggest a systemic illness, but is present in only 50% of patients with septic arthritis, and many sterile inflammatory processes create a similar leukocytosis. Cultures of infectious foci, such as the throat, cervix, and urine, may demonstrate the bacteria responsible for septic arthritis.[4,14,16,116]

Plain radiography is not an effective tool for the early evaluation of septic arthritis but may detect surrounding osteomyelitis. Radiographs may reveal a joint effusion that displaces capsular fat planes. Clinically, this is most helpful in the hip joint, where it is difficult to detect an effusion on physical examination. In most joints the small areas of attachment of the synovial membrane to bone are devoid of cartilage. These "bare areas" at the margins of the joint appear as lucencies or erosions early in the course of septic arthritis. Bone beneath the articular cartilage may start to erode 1 to 3 weeks into the disease. Air density in the joint may be a sign of infection with gas-forming organisms or may be the result of a previous joint aspiration.[53,62] In patients with existing joint disease, radiographs provide minimal assistance in diagnosing septic arthritis.

Skeletal scintigraphy has been used in the diagnosis of septic arthritis. Its main advantage is in detecting septic arthritis earlier than other imaging techniques. In septic arthritis, scintigraphy shows symmetrical areas of increased uptake on both sides of the joint. In a three-phase ^{99m}Tc scan, all three phases will be "hot" with septic arthritis; however, it may be difficult to distinguish osteomyelitis in the metaphysis of a long bone from septic arthritis in the adjacent joint. In general,

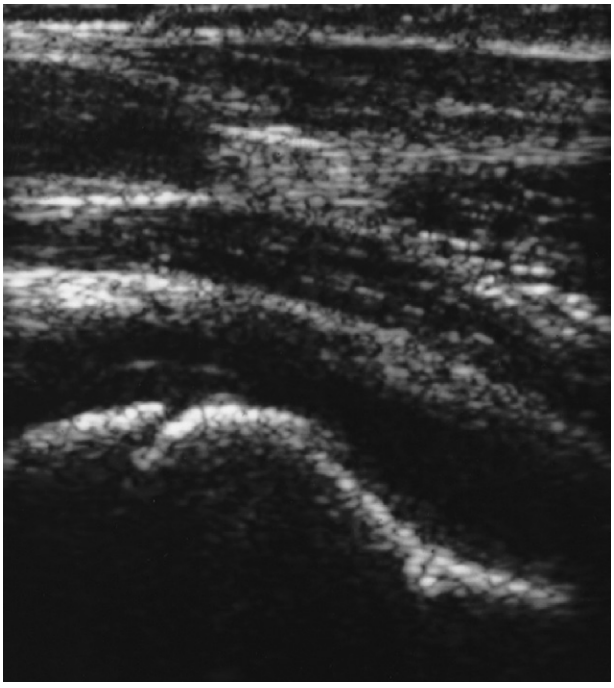

Figure 134-10. Ultrasound of the right hip in an 8-year-old girl with septic arthritis. A significant joint effusion can be seen just superior to the round contour of the femoral head. Joint aspiration revealed purulent fluid with a WBC count of 71,000 cells/mm^3.

skeletal scintigraphy is used only when there is enough uncertainty about the diagnosis to warrant further investigation before proceeding with joint aspiration. This is most common in evaluating a hip for septic arthritis. In joints where aspiration is easier, skeletal scintigraphy has little role in diagnosing septic arthritis. There is some risk that the time delay associated with obtaining skeletal scintigraphy may lead to further joint destruction before definitive treatment is rendered.

Ultrasound is a useful modality for detecting a joint effusion in suspected septic arthritis and in assisting joint aspiration, particularly in the hip. Ultrasound of suspected septic arthritis of the hip in children both permits the evaluation for the presence of an effusion and helps to guide the diagnostic aspiration of the joint[116,118] (Fig. 134-10). CT provides better anatomic images of the joint and can help to assess the size of effusions. MRI is most useful in visualizing the detailed anatomy of joints, will determine if septic arthritis is complicated by concurrent osteomyelitis, and can detect even small effusions.[26,62,117,118]

Complications of Septic Arthritis

Septic arthritis leads to two types of serious complications, those involving the joint itself and those that are systemic. Children are at great risk for epiphyseal damage if the infection extends through subchondral bone. This can result in impaired growth and limb length discrepancy. Other tissues adjacent to the joint can be invaded. Bursae, tendons, ligaments, and muscles can be destroyed by the suppurative process. Sinus tracts may lead the infection out through the skin. In the hip, the pressure and edema of a septic synovial effusion can occlude blood supply, resulting in avascular necrosis of the femoral head. Septic hip arthritis in both children and adults needs to be promptly diagnosed and treated with drainage to prevent destruction of the hip joint. In other joints the sequela of uncontrolled septic arthritis is ankylosis. The joint becomes stiff, fused, and devoid of articular cartilage. Septic arthritis can result in systemic sepsis, especially in elderly and immunocompromised patients.

Clinical Subsets of Septic Arthritis

Septic Arthritis in Infants and Children

Septic arthritis is more common in children than in adults, and the incidence of septic arthritis is twice that of osteomyelitis in children.[116] Of pediatric cases, two thirds occur in children less than 2 years old, and boys are affected twice as often as girls.[116] The bacterial etiologic agent of septic arthritis varies with age. Overall, *S. aureus* is the most common infecting organism in all pediatric age groups, followed by group A streptococci and *Streptococcus pneumoniae*.[10,116,118] In neonates, group B streptococci, *S. aureus*, and gram-negative enteric bacilli are usual pathogens. *Candida albicans* must also be considered in neonates and premature infants.[36,119] Since the widespread introduction of the *H. influenzae* type B vaccine, *S. aureus* has become the most common cause of septic arthritis in children 3 months to 5 years of age. In this age range, concomitant respiratory infection or otitis media is often present. Prior trauma or skin infection may be more common with staphylococcal septic arthritis. Even with full culturing of joint fluid and blood, a causative organism is not discovered in up to 30% of cases of septic arthritis in children, and prior antibiotic treatment in children decreases the yield on synovial fluid cultures from 80 to 38%.[10,15,26] If the hip joint is infected, the complication rate is higher, and permanent joint damage is more likely. This is especially true in infants, particularly those who have coexisting septic arthritis and osteomyelitis.

Gonococcal Septic Arthritis

N. gonorrhoeae is the most common cause of septic arthritis in teenagers and young adults. In the United States it is most common in those with lower socioeconomic status in urban areas. A person with gonorrhea of the urethra, cervix, rectum, or pharynx has a 1 to 3% chance of developing disseminated gonococcal infection (DGI).[120] Even though gonorrhea is more common in men, women are more commonly afflicted with DGI. In fact, more than 75% of the cases of DGI occur in women, especially during pregnancy or after menstruation when the alkaline vaginal environment makes the organisms more resistant to host defenses in the bloodstream and therefore more likely to disseminate.

The strains of *N. gonorrhoeae* that cause disseminated infection and septic arthritis have different characteristics than those that cause local infection. Those strains that cause disseminated infection contain outer membrane proteins, which make them resistant to serum bactericidal activity. These strains are not more resistant to antibiotics than other types of *N. gonorrhoeae*; however, penicillin-resistant and fluoroquinolone-resistant gonococcal infections appear to be increasing in some parts of the world, including the United States. The common finding of sterile joint fluid in DGI, even when mucosal cultures are positive, suggests that the host immune response plays a significant role in the development of purulent arthritis.[14,121]

Most, but not all, patients with DGI are symptomatic with a local genital or oral infection. Symptoms may be less noticeable in women, and this is likely the reason for delays in treatment and a higher incidence of the disease. The time for local infection to disseminate can vary from 1 day to several weeks. Symptoms begin soon after gonococcal bacteria enter the bloodstream. On presentation, fever and chills are often present. The classic triad of gonococcal bacteremia is migra-

tory polyarthritis, tenosynovitis, and dermatitis. Asymmetrical polyarthralgia, which may be migratory, is the most common presenting complaint, occurring in two thirds of cases, with 25% of patients having monoarthralgia. The arthralgia is usually asymmetrical and most frequently involves the knee, elbow, wrist, metacarpophalangeal, and ankle joints. The sacroiliac and sternoclavicular joints may be involved, although these sites are far less common.[122-124] Tenosynovitis occurs in two thirds of patients with bacteremia, usually occurring in the hands and fingers. Dermatitis also occurs in two thirds of patients and presents in a variety of forms. Most commonly, there are scattered painless, nonpruritic, small (0.5- to 0.75-cm) papules distributed below the neck that can involve the palms and the soles. These papules can turn into pustules on a broad erythematous base with either a necrotic or hemorrhagic center.[14,124] Usually, there are fewer than 50 lesions, distinguishing DGI from the rash of meningococcus.

Septic arthritis develops in approximately 40% of patients with DGI. This is usually a monoarticular process, although polyarticular arthritis has been reported. The patient will present with classic signs of a septic joint, including a joint effusion, warmth, tenderness, decreased range of motion, and marked erythema. There is usually no clear progression of the disease from polyarthralgias to purulent monoarticular arthritis and many patients are afflicted with dermatitis and tenosynovitis without developing true arthritis.[14,124] Some of the strains of *N. gonorrhoeae* that produce disseminated gonococcal infection favor the development of tenosynovitis and dermatitis, whereas others favor the development of purulent arthritis.[122,123]

The diagnosis of gonococcal arthritis is made by synovial fluid culture results. Joint fluid analysis in gonococcal arthritis reveals some differences in comparison with other types of bacterial arthritis. The synovial fluid WBC count in gonococcal arthritis is often less than 50,000 cells/mm^3. Gram's stains of aspirated joint fluid are positive for bacteria only 25% of the time in gonococcal arthritis, and cultures of the joint fluid are negative in approximately 50% of cases. This may be due to poor culturing techniques, or because a suppurative reactive process can occur in the joint in DGI even when bacteria are no longer present. When gonococcal arthritis is suspected, cultures of the synovial fluid have to be done on prewarmed chocolate agar for the highest yield. Also, it is important to culture the mucosal surfaces for *N. gonorrhoeae* when clinical suspicion for gonococcal arthritis is high because these may be the only places where bacteria are readily recovered. In 80% of cases, cultures of the genital tract, pharynx, or rectum will be positive.[125,126] Gonococcal septic arthritis responds rapidly to antibiotic treatment and, unlike other types of bacterial arthritis, rarely causes permanent damage to the joint.[14,124]

Patients with septic arthritis will require hospital admission with antibiotic coverage against the likely pathogens until laboratory results are available. With the rise in fluoroquinolone-resistant gonorrhea, the recommended treatment of gonococcal arthritis is a third-generation cephalosporin, such as ceftriaxone, ceftizoxime, or cefotaxime. Patients should be given the first dose intravenously or intramuscularly in the ED and admitted until culture results are available. In some cases, patients with reliable follow-up can be sent home with an oral regimen that should be continued for 1 week.[125]

Lyme Arthritis

Lyme disease is caused by infection with a spirochete, *Borrelia burgdorferi,* that is transmitted by the *Ixodes* tick and is an important cause of arthritis in endemic areas, including states between Maryland and Maine, Wisconsin, Minnesota, California, and Oregon. The spirochete induces an immune response that leads to a reactive arthritis. While a history of a tick bite is important to ascertain, up to 30% of people do not remember being bitten. Patients with Lyme arthritis present with migratory polyarthralgia involving not only joints but also bursae and tendons. This usually rapidly evolves into a monoarticular process, although polyarticular processes are reported, involving the knee, ankle, or wrist. Patients usually present during the monoarticular phase. The arthritis is similar to other inflammatory processes of the joint and produces warmth, erythema, swelling and pain upon motion of the joints; however, it is usually not as severe as in a suppurative joint. Effusions may be large and generally recur following aspiration. The history of a rash is often overlooked by patients, and the arthritis usually presents within 6 months of the erythema migrans lesion. If the arthritis is untreated, the arthralgia lasts approximately 1 week. In the following 3 months, two thirds of the patients will have recurrences and approximately 10% of these patients will develop a chronic arthritis, usually involving the knee. This may last several years; however, this is usually not a destructive process. Confirming a septic arthritis is often best done by cultures; however, cultures of synovial fluid in Lyme arthritis are usually ineffective. The most widely used test to diagnose Lyme disease is serum antibody titers. Synovial fluid analysis usually reveals an inflammatory process, with WBC counts ranging from 500 to 98,000 cells/mm^3. Lyme arthritis can be treated with oral doxycycline for 30 days. If this is unsuccessful, patients can be retreated with the same oral regimen for another 30 days or the antibiotic can be changed to IV ceftriaxone for 14 to 30 days.[124–128]

Septic Arthritis in Patients with Existing Joint Disease

Patients with underlying joint disease are more likely to develop septic arthritis than patients with normal joints. This is especially true for patients with rheumatoid arthritis and crystalline arthritis. In patients with rheumatoid arthritis, septic arthritis is more likely to be polyarticular and more likely to result in complications.[15,26] In patients with the crystalline arthropathies, neutrophil invasion secondary to septic arthritis also leads to increased precipitation and release of crystals. Therefore, the clinician who discovers crystals on joint fluid aspiration should not abandon the search for an infectious agent.

Surgical implantation of a joint prosthesis is followed by joint infection in 1 to 5% of cases. The infection is most likely to occur in the first 3 months (50% of cases) after surgery and may be due to bacterial contamination during surgery, spread from a contiguous wound infection, or spread from hematogenous seeding. The prosthesis and cement are foreign bodies and are ideal sites for bacterial colonization. The most common infectious agents are *S. epidermidis* (40% of cases), *S. aureus* (20%), and streptococcal species (20%). The predominant symptom is pain in the joint, and unlike the pain from a loose prosthesis, it is constant and present at rest.[15,26,41,129] The clinical course is variable. With *S. epidermidis* infections, the course is usually indolent. With *S. aureus,* a more aggressive infection occurs, with more pronounced inflammation, effusion, and systemic symptoms. Radiographic changes that may signify a prosthetic joint infection include widening and lucency of the bone-cement interface to greater than 2 mm, movement of the prosthesis, periosteal reaction, and fractures through the cement. Aspiration may be more difficult in this situation because of scarring and alteration of the joint space. Joint aspiration reveals infection in a prosthetic joint in more than 85% of patients. Patients with prosthetic joints who are undergoing invasive oropharyngeal or genitourinary procedures require antibiotic prophylaxis.[15,41,130-132]

Septic arthritis can be particularly difficult to diagnose and treat if it occurs in fibrocartilaginous joints such as the sternoclavicular, acromioclavicular, and sacroiliac joints and the symphysis pubis. Septic arthritis of the axial skeleton, especially of the sternoclavicular joint, is commonly seen in IVDUs, with *Pseudomonas* as a common infecting agent. In patients who do not have other predisposing factors, the most common bacterial causes are *S. aureus* and *S. epidermidis*. The presentation is usually pain and point tenderness over the involved joint. Fever and an elevated ESR are commonly reported, although they are not always present due to the suppressed immune status of the patient. Bone scans may be able to detect the infected joint but are less useful in establishing a diagnosis in the ED setting due to the time required to complete the scan.[15,130,131] CT and MRI are more timely in making the diagnosis and are very helpful in diagnosing septic arthritis in the fibrocartilaginous joints.

Differential Diagnosis Considerations of Septic Arthritis

Many disease processes can be confused with septic arthritis. Metaphyseal osteomyelitis may mimic septic arthritis because the adjacent joint may develop an effusion. The two infections can be concurrent. Juvenile rheumatoid arthritis is usually more gradual in onset and produces polyarticular arthritis in children less than 16 years old but may present as a monoarticular process that mimics septic arthritis. Toxic or transient synovitis is another inflammatory process in children that can be confused with septic arthritis. It occurs in the 3-month to 6-year age range, usually affects the hip, and is a self-limited disease with no long-term morbidity. It may be more common after upper respiratory infections. Children with transient synovitis have less pain with passive joint motion than patients with septic arthritis, do not usually have a fever or appear ill, but tend to favor the unaffected leg as in septic arthritis. Diagnostic evaluation typically reveals a normal WBC count and ESR and no radiographic abnormalities. However, the only way to reliably differentiate between toxic synovitis and septic arthritis in the hip joint is to obtain synovial fluid for analysis, and this is usually done under ultrasound guidance.

Other diseases of the hip in children that are included in the differential diagnosis are Legg-Calvé-Perthes disease (avascular necrosis of the femoral head) and slipped capital femoral epiphysis; however, these processes are not as acutely disabling as septic arthritis. Rheumatic fever commonly presents with a migrating polyarthritis and may mimic gonococcal bacteremia. Patients with Lyme arthritis are not as debilitated as those with septic arthritis, but in endemic areas, antibody titers should be obtained.

In the adult, osteoarthritis, gout, and pseudogout may yield joint examination findings that are similar to those of septic arthritis. Other arthropathies in the differential diagnosis of septic arthritis are Reiter's syndrome, psoriatic arthritis, arthritis associated with inflammatory bowel disease, and ankylosing spondylitis. Collectively, these are known as the seronegative spondyloarthropathies. Trauma to the joint can produce synovitis and hemarthrosis, which may be mistaken for septic arthritis. In a patient with hemophilia, hemarthrosis causes joint inflammation and destruction, and there may be superimposed infection.[8,10,14,116]

Reactive arthritis has been traditionally considered a sterile inflammatory response to a distant infection. However, recent data suggest that antigens from the infectious trigger are often present in the joint. Several viral and bacterial microorganisms can produce reactive arthritis. The most recognized syndrome is post-streptococcal reactive arthritis. Some other common organisms to cause reactive arthritis are *Chlamydia*, *Salmonella*, *Shigella*, *Borrelia burgdorferi* (Lyme disease), *Yersinia*, human T-cell lymphotropic virus type 1, rubella virus, hepatitis B virus, adenoviruses, parvovirus, and Epstein-Barr virus. In reactive arthritis, host factors rather than microbial aggression account for most of the inflammatory process. The pathogenesis of reactive arthritis involves deposition of immune complexes in the joint, persistence of organisms in the joint, and stimulation of the immune system. Strong evidence exists to support a link between the susceptibility to reactive arthritis and the HLA-B27 human leukocyte histocompatibility antigen. Reactive arthritis can usually be distinguished from septic arthritis because it tends to involve multiple joints in a migratory pattern. The inflammatory process is also less severe with reactive arthritis. There is less effusion, the joint is not as hot or tender as it is with septic arthritis, and joint fluid cell counts are usually below 50,000/mm^3.[3,4,11,12,28]

Management of Septic Arthritis

Septic arthritis is an orthopedic emergency, and empirical antibiotics should be promptly administered if the diagnosis is strongly suspected. Considerable disagreement exists regarding medical versus surgical joint decompression, and a number of patient factors need to be evaluated before a decision is made. Medical management includes needle aspiration of the joint. If pus reaccumulates, repeat aspiration is performed. The only situation in which antibiotics alone can adequately treat a septic joint is in gonococcal septic arthritis. After the diagnostic joint aspiration, almost all cases of gonococcal septic arthritis will quickly resolve with antibiotics alone.[14,124] Surgical drainage is accomplished by arthrotomy or arthroscopy. Surgical drainage may involve the placement of tubes in the joint that can be used for irrigation and drainage.

Although needle aspiration may be adequate treatment for most septic joints, surgical drainage is usually necessary in at least two settings. Septic arthritis of the hip, especially in infants and children, is accompanied by rapid destruction of the joint if drainage is not quickly performed. Needle aspiration is often ineffective in this situation, and arthrotomy is the treatment of choice for infected hips.[116] Some experts recommend a similar approach with a septic shoulder. Patients with joint prosthetics represent another population where the surgeon must be involved early. Once a joint prosthesis is infected, the implants are removed, and the infection needs to be treated and cleared. After this is accomplished, a new prosthetic can be installed.[132] Patients with a surgical implant in whom septic arthritis is suspected should not undergo aspiration in the ED. Aspiration is best done in the sterile environment of the operating room in order to avoid introducing infection.

The selection of antibiotics for the treatment of septic arthritis is outlined in Table 134-1. In most cases the emergency physician does not know the identity of the causative organism, but treatment must be tailored to the most likely causative agents based on the patient's age and immune status. *S. aureus* remains the predominant pathogen for all age groups, and unless gonococcal arthritis is confirmed, antibiotic selection should always include an antibiotic that has excellent bactericidal activity against *S. aureus*. Gonococcal septic arthritis is the most common cause of arthritis in young adults. Penicillin- and fluoroquinolone-resistant strains are becoming more prevalent, and a third-generation cephalosporin is the best choice for gonococcal arthritis. In elders, gram-negative septic arthritis is more common, and agents such as the

third-generation cephalosporins and aminoglycosides are added to the antistaphylococcal regimen. Establishing good bactericidal serum levels of antibiotics will ensure that the levels in joint fluid are also bactericidal.[4,8,14,26,124]

Disposition of the Patient with Septic Arthritis

Any patient suspected of having septic arthritis requires joint aspiration. In some cases the initial culture results, Gram's stain, and cell counts make the diagnosis of septic arthritis extremely likely. The patient should be given an initial parenteral dose of antibiotics in the ED and admitted for continued management. Consultants will then determine the need for further drainage procedures. If cultures of the synovial fluid are negative but the clinical appearance strongly suggests septic arthritis, the patient should be treated with appropriate antibiotics and admitted to the hospital. If the joint fluid aspirate is not consistent with septic arthritis and clinical findings are equivocal, the patient can be discharged from the ED and reevaluated in 24 hours. In immunosuppressed patients, patients with preexisting joint disease, and patients with joint replacements, septic arthritis can be difficult to detect. A conservative approach with in-hospital observation and treatment is indicated if there is any possibility of septic arthritis in these patients.

In most cases the prognosis for the patient with septic arthritis is favorable. Two thirds of afflicted patients can expect to recover completely and achieve full, painless range of motion of the afflicted joint. In approximately one third of cases there is decreased mobility or ankylosis, pain on joint movement, chronic infection, or overwhelming sepsis and death. Those patients most likely to do poorly include those who have a delay in diagnosis and treatment, patients with underlying joint disease, especially rheumatoid arthritis, those with polyarticular septic arthritis, and those who have positive blood cultures.[4] Despite many advances in diagnosis and treatment, the overall morbidity for patients with septic arthritis has not decreased in the past 2 decades. A general rule is that if the diagnosis of septic arthritis is made and treatment is initiated within 1 week of the onset of symptoms, the outcome is almost always favorable. Delays beyond 1 week are associated with worse outcomes. Diagnosis and rapid treatment of septic arthritis prove to be most elusive in two groups of patients: infants and people with existing joint disease. In infants and children, early symptoms can be nonspecific and difficult to assess; consequently, children with septic arthritis, especially of the hip, who experience a delay in diagnosis and treatment have a disappointingly high rate of complications. In patients with existing joint disease, septic arthritis may be mistaken for an acute exacerbation of their underlying disease process and ED physicians must remain vigilant in their pursuit of the correct diagnosis.[4,8,14,116]

KEY CONCEPTS

- The emergency physician should consider skeletal infection in the differential diagnosis of all patients who present with bone or joint pain. In those cases in which a bone or joint infection exists, early diagnosis and treatment can have a potent impact on the long-term morbidity.
- The vascular anatomy of long bones changes throughout life. In infants and adults, vascular connections exist between the metaphysis and epiphysis, which allow for extension of bone infection into the joint. In children the epiphyseal plate prevents this from happening.
- The diagnostic evaluation for septic arthritis is relatively simple. Joint aspiration is the definitive diagnostic procedure, and synovial culture is the only reliable joint fluid test in establishing a diagnosis. The diagnosis of osteomyelitis is more complex and increasingly involves MRI. Operative culture of infected bone is the most direct way to arrive at a diagnosis.
- Hematologic evaluation is of little value in diagnosing bone and joint infections, with the exception of the ESR and CRP, which are elevated in approximately 90% of cases of bone and joint infections.
- When clinical findings suggest the presence of a bone or joint infection, antibiotic treatment should not be delayed. With suspected septic arthritis, joint fluid and blood cultures are obtained as IV antibiotics are administered. With suspected osteomyelitis, blood cultures are obtained, and IV antibiotics are administered while plans are made for further imaging studies or surgical aspiration or resection of bone.
- The most important aspect of antibiotic treatment of suspected osteomyelitis is providing potent bactericidal activity against *S. aureus.* In suspected septic arthritis, initial antibiotic treatment must be tailored to the age and clinical characteristics of the patient.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 135 Soft Tissue Infections

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OVERVIEW

Soft tissue infections run the gamut from mild superficial infections that require only "tincture of time" to infections that will quickly result in death without immediate diagnosis and resuscitation. Unfortunately, the literature on soft tissue infections is often confusing with respect to definition and therapy, in part because the nomenclature has been based on individual names, anatomic areas, or events (e.g., postsurgical gangrene). The clinical characteristics of soft tissue infections often overlap (Table 135-1) as they evolve from superficial to deep. In addition, the bacteriologic spectrum can change with time, and thus the clinical manifestations, including systemic symptoms, may be altered. A patient does not strictly have to have an abscess, a cellulitis, or a fasciitis, but can have all of them at any time. A good rule of thumb is that the deeper the soft tissue infection is, the more normal the skin surface appears.

CELLULITIS

Perspective

Cellulitis is a soft tissue infection of the skin and subcutaneous tissue usually characterized by erythema, swelling, and tenderness. Cellulitis can be acute, subacute, or, on rare occasions, chronic. Trauma, or breaks in the protective cutaneous skin layer, may be a predisposing cause, but hematogenous and lymphatic dissemination can account for its sudden appearance in previously normal skin.

Principles of Disease and Clinical Features

The signs and symptoms of cellulitis are generally pain or tenderness, erythema that blanches on palpation, swelling of the involved area, and local warmth. Without therapy, it will spread in a radial fashion both distally and proximally with associated swelling. Cellulitis occurs most often in the lower extremities, then upper extremities, and the face. *Staphylococcus aureus* and *Streptococcus pyogenes* are by far the most commonly isolated organisms.[1] In children, *Haemophilus influenzae* may cause facial cellulitis, although anaerobic and oral mucosa flora play a role in facial and orbital cellulitis. Risk factors for cellulitis include lymphedema, a portal of entry, venous insufficiency, and obesity. Interestingly, diabetes mellitus, alcohol misuse, and smoking are not associated with increased risk.[2]

In general, the bacterial cause of cellulitis is a reflection of the bacteria found on the skin or mucous membranes of the anatomic site involved. Ludwig's angina is a cellulitis of the submandibular spaces bilaterally. This deep soft tissue infection caused by oral flora may quickly result in respiratory distress by causing swelling and subsequent elevation of the floor of the mouth and the tongue. Odontogenic infection, especially of the second and third lower molars, is the most common origin of Ludwig's angina. Approximately 80% of patients offer a history of recent dental work or tooth pain.[3–5] Cellulitis around the perineum is often due to anaerobes or fecal flora and may spread rapidly through the soft tissues, producing a necrotizing fasciitis.

Differential Considerations

Other conditions simulate the appearance of bacterial cellulitis, including arthropod and marine envenomation, the inflammatory response to foreign bodies, healing or postsurgical wounds, chemical or thermal burns, septic or inflammatory joints, osteomyelitis, dermatitis, and the arthritides. Differentiation, especially if the process is early and localized, may be difficult. In nonbacterial cellulitis, the inflammation tends to stay localized and is often less tender to palpation.

In bacterial cellulitis, lymphangitis and local lymphadenopathy may be seen. Fluctuance, if present, signifies abscess formation; however, the absence of fluctuance does not rule out abscess.[6] Fever is uncommon and should prompt the physician to consider secondary bacteremia or systemic involvement. With local involvement, vital signs, other than a slight tachycardia, are usually normal. Unless there is systemic involvement, white blood cell counts are usually normal or mildly elevated with little or no shift to the left. One exception is *H. influenzae* type B in children. This cellulitis is usually associated with high fever and white blood cell counts greater than 15,000/mm^3, with a left shift.[7] Fortunately, the incidence of such infections in children has decreased with the advent of an effective vaccine.

Diagnostic Strategies

Bacterial cultures of material obtained by direct needle aspiration of the area of cellulitis, either in the area of greatest erythema intensity or at the leading edge, are not helpful when no purulence is present. A recent study of needle aspiration of cellulitis indicated that only about 10% of the time is the

Table 135-1 Clinical Characteristics of Soft Tissue Infections

	CELLULITIS	NECROTIZING FASCIITIS	MYONECROSIS
Depth	Skin, subcutaneous tissue	Skin, subcutaneous tissue, fascia	Fascia, muscle
Predisposing factors	Trauma, superficial infection	Trauma, surgery, diabetes, deep soft tissue infection	Trauma, surgery, contaminated wounds
Skin	Erythema, lymphatic streaking, mildly swollen	Erythema; may have blebs, bullae, or patches of gangrene; severe swelling	Blanched with massive swelling; hemorrhagic bullae to frank necrosis to gangrene
Gas	No	Variable	Often
Pain	Mild	Moderate	Severe
System toxicity	Mild	Moderate to severe	Severe
Bacteriology	Skin flora, one or more agents	Mixed anaerobic and aerobic	Clostridia, anaerobes, aerobes
Therapy	None to local incision	Wide débridement	Radical excision
Mortality	Low	20–50%	>25%

causative bacteria identified.[8] Blood cultures of patients with cellulitis are also not helpful, except in cases of *H. influenzae* type B cellulitis, which are associated with bacteremia in children more than two thirds of the time.[1,9]

Soft tissue radiographs and ultrasonograms may be useful to detect radiopaque foreign bodies, including glass. Computed tomography or magnetic resonance imaging scans are reserved for instances in which deep space infections or abscesses are suspected. For most localized infections, no radiographic procedures are indicated.

Ultrasound can also be valuable in guiding the management of patients presenting with cellulitis. Recent prospective studies in both adult and pediatric emergency patients demonstrate that sonographic evaluation of cellulitis can alter patient management by detecting abscesses not apparent on physical examination. Ultrasound-guided needle aspiration of abscesses decreased hospitalizations and treatment durations in at least one pediatric emergency department study. Given increasing availability of ultrasound and the safety of this modality, sonographic evaluation of patients presenting with cellulitis should be considered in their evaluation.[6,10,11]

Management

The time-honored treatment for cellulitis includes immobilization, elevation, heat or warm moist packs, analgesics, and antibiotics. Studies do not document any difference in morbidity or resolution with this regimen versus the use of antibiotics alone.

When managing a patient with cellulitis, the emergency physician must attempt to identify the cause. Trauma, puncture wounds, breaks in the skin, lymphatic or venous stasis, immunodeficiency, and foreign bodies are all predisposing factors. Hematogenous or contiguous spread from nearby infected tissue is an uncommon cause. Most patients will respond to appropriate oral antimicrobial agents. Cellulitis in the area of edema from venous or lymphatic stasis is often difficult to manage and may need aggressive parenteral antibiotic therapy. Secondary bacterial overgrowth occurs commonly in these circumstances.

Disposition

Localized cellulitis of an extremity in an immunologically intact, afebrile patient can be treated on an outpatient basis with oral antibiotics. Follow-up is indicated within 24 to 48 hours if the erythematous area is not diminishing in size or if fever or systemic symptoms develop. Methicillin-resistant *Staphylococcus aureus* (MRSA) as a causative organism in cellulitis is increasingly a concern, even in community acquired infections. For outpatient management of cellulitis, the suggested agents are shown in Table 135-2. When community-acquired MRSA is considered, trimethoprim-sulfamethoxazole, clindamycin, or tetracyclines can be used as first-line treatment, holding agents like linezolid and vancomycin in reserve for refractory cases.[12] Patients whose cellulitis continues to worsen after 48 to 72 hours of appropriate outpatient therapy should be treated with parenteral antibiotics. This can sometimes be achieved on an outpatient basis with home health agency assistance, reducing costs and risk of nosocomial infection.[13] Inpatient management with parenteral antibiotics and closer observation are indicated in patients with systemic toxicity, and with severe infections involving significant portions of an extremity (particularly the hands and feet), the head and neck, or the perineum. All patients with cellulitis should be monitored closely to ensure that the process is resolving. Patients who are immunocompromised, including those who are diabetic, alcoholic, on chemotherapy or steroid therapy, asplenic, or at extremes of age, require aggressive monitoring and treatment.

Patients do not have a simple cellulitis if they have a fever, hypotension, confusion, crepitus, or bullae formation of the involved soft tissues. These patients may be septic, with infectious seeding to other sites such as blood, bone, lung, solid organs, or brain. They may have deep soft tissue infections necessitating aggressive surgical débridement. If an infection spreads to deeper tissues, either directly or through lymph or blood with distal seeding, the initially localized superficial infection can quickly evolve into a severe systemic illness. Patients with these symptoms should be hospitalized and evaluated for deep soft tissue infections and systemic bacteremia.[14]

SPECIAL TYPES OF CELLULITIS

Periorbital (Preseptal) and Orbital Cellulitis

Perspective

Cellulitis of the central face involving the area of the orbits must be treated aggressively. The venous drainage of that area is through communicating vessels into the brain via the cavernous sinus. Streptococcal species are currently the most common infecting organisms. The incidence of cellulitis and other infections from *H. influenzae* has decreased from

Table 135-2 Oral Therapy of Superficial Soft Tissue Infections

AGENT	DOSE
Group A *Streptococcus*	
Penicillin V (phenoxymethyl penicillin)	250–500 mg qid
First-generation cephalosporin	250–500 mg qid
Erythromycin	250–500 mg qid
Azithromycin	500 mg × 1 dose, then 250 mg qd × 4
Clarithromycin	500 mg bid
Staphylococcus aureus* (not MRSA)	
Dicloxacillin	125–500 mg qid
Cloxacillin	250–500 mg qid
First-generation cephalosporin	250–500 mg qid
Erythromycin (variable effectiveness)	250–500 mg qid
Azithromycin	500 mg × 1 dose, then 250 mg qd × 4
Clarithromycin	500 mg bid
Clindamycin	150–450 mg qid
Amoxicillin/clavulanate	875/125 mg bid or 500/125 mg tid
Ciprofloxacin	500 mg bid
Haemophilus influenzae	
Amoxicillin/clavulanate	250–500 mg tid
Cefaclor	250–500 mg tid
Trimethoprim (TMP)/ sulfamethoxazole (SMX)	160 mg TMP/800 mg SMX bid
Azithromycin	500 mg × 1 dose, then 250 mg qd × 4
Clarithromycin	500 mg bid

*Methicillin-resistant strains require treatment with alternate antibiotics such as vancomycin, linezolid, daptomycin, and others. Combination therapies may be necessary. Trimethoprim-sulfamethoxazole may be effective against some strains. There is no clearly accepted therapy for vancomycin-resistant strains; combinations of the above drugs with other antimicrobials may be effective. Single-drug therapy should be avoided to decrease the development of resistance.

MRSA, methicillin-resistant *Staphylococcus aureus*.

previous prominence due to the advent of an effective vaccine.[15–17]

Principles of Disease and Clinical Features

Periorbital (preseptal) cellulitis is an infection lying anterior to the orbital septum. It is usually associated with swelling of the eyelid, discoloration of the orbital skin, redness, and warmth. Conjunctival ecchymosis and infection with occasional discharge, fever, and leukocytosis are present. Vision, extraocular movements, pupillary findings, and optometric examination findings are normal.

Orbital cellulitis tends to have similar but more severe symptoms than preseptal cellulitis. Patients with orbital cellulitis may have proptosis, decreased ocular mobility, ocular pain, and tenderness on eye movement. Retro-orbital gas or abscess formation increases the severity of these findings and results in decreased visual acuity; it can be detected with computed tomography or magnetic resonance imaging.

Both orbital and periorbital cellulitis tend to be associated with young age and to be unilateral. There is a strong association of both orbital and periorbital cellulitis with preexisting sinus infections.[16,18] Other causes include penetrating or abrading skin trauma and preexisting vascular or pustular periocular skin infections. Facial fractures are rarely associated with periorbital or orbital cellulitis, unless preexisting paranasal sinusitis is present or develops within several weeks of the injury.[19] Less common causes are chemical agents and dental infections.

Diagnostic Strategies

Differentiation of periorbital (preseptal) from orbital cellulitis is an important clinical decision that affects management and prognosis. If orbital cellulitis is suspected, a computed tomography scan of the orbit is the most useful aid to determine retro-orbital involvement.[20] Sinus and orbital radiographs tend to be less specific.[21] Causative organisms now are predominantly *Streptococcus* species, but *S. aureus*, *H. influenzae*, and anaerobes are also occasionally identified.[16,17] Blood cultures and lumbar punctures are indicated in those patients with high fevers or those showing signs of meningismus or sepsis.

Management

Early periorbital (preseptal) cellulitis may be followed on an outpatient basis for the first 24 to 48 hours of antibiotic therapy, with daily follow-up to determine whether resolution is occurring. A broad-spectrum antistaphylococcal agent will provide appropriate coverage. Treatment for orbital cellulitis includes hospitalization, intravenous antibiotics, and, in some cases, incision and drainage. Indications for operative intervention include clinical deterioration on antibiotics, the presence of a foreign body as the cause of the infection, and the presence of an abscess.[18,19,21,22] Broad-spectrum antibiotic coverage of *H. influenzae*, *S. aureus*, *S. pyogenes*, and anaerobes is indicated.[4,20]

Streptococcal Cellulitis

Principles of Disease and Clinical Features

Streptococcal cellulitis, often termed *ascending cellulitis*, is usually seen after surgery or trauma but can occur with no predisposing event. The cause may be as subtle as a break in the skin around the webs of the fingers or toes. Ascending cellulitis usually progresses rapidly with prominent lymphangitic streaking and a swollen extremity. Untreated patients can quickly become toxic.

Management

Treatment includes the use of an antistreptococcal agent along with elevation of the involved extremity and warm soaks.

Erysipelas

Principles of Disease and Clinical Features

Erysipelas is an acute superficial cellulitis characterized by a sharply demarcated border surrounding skin that is raised, deeply erythematous, indurated, and painful. It usually involves the dermis, lymphatics, and most of the superficial subcutaneous tissue. Erysipelas most often occurs in the very young and in 50- to 60-year-olds and is associated with small breaks in the skin, nephrotic syndrome, and postoperative wounds. Patients usually appear toxic, with a prodrome of fever, chills, and malaise preceding the eruption of a bright red cellulitis predominantly on the lower extremities or on the

face. Streptococci are the predominant pathogenic organism in erysipelas, including *S. pyogenes* (58–67%), *Streptococcus agalactiae* (3–9%), and *Streptococcus dysgalactiae* (14–25%). Other bacteria are also found in some patients, such as *S. aureus*, *Pseudomonas*, and enterobacteria. The leg is involved in erysipelas 90% of the time, but the arm (5%), the face (2.5%), and the thigh can also be involved.[23]

Management

Treatment of erysipelas includes elevation of the infected part, treatment of the portal of entry, if any, and antibiotic therapy. Penicillin G continues to be a standard treatment, but amoxicillin can also be used for 10 to 20 days. Macrolides, cephalosporins, and fluoroquinolones have been shown to be more effective but should be reserved for complicated cases.[23]

Staphylococcal Cellulitis

Principles of Disease and Clinical Features

Staphylococcus aureus produces various toxins that result in local and systemic effects. Tissue invasion, blister formation, and inflammation are caused by toxins such as alpha toxin, hyaluronidase, fibrinolysin, various proteases, and pyrogenic toxin superantigens. Staphylococcal cellulitis is usually an indolent infection. The patient often appears less toxic than with streptococcal cellulitis, and the lesions usually appear more localized and are more likely to result in the formation of an abscess.[24]

Management

Antistaphylococcal agents are indicated, along with heat, immobilization, elevation, and incision and drainage, if an abscess is present. With increasing prevalence of community-acquired MRSA, coverage for this organism should be considered in antibiotic selection. Trimethoprim-sulfamethoxazole and clindamycin can be effective agents.[12] Where available, local antibiotic resistance patterns may be helpful.

Staphylococcal Scalded Skin Syndrome

Principles of Disease and Clinical Features

Staphylococcal scalded skin syndrome, also called staphylococcal epidermal necrolysis, is caused by an exfoliative toxin produced by phage group II, type 71 staphylococci. This toxin is a serine protease that acts specifically on the Desmoglein 1 (Dsg1) protein in the zona granulosa of the superficial epidermis to produce a separation that results in widespread painful erythema and blistering of the skin.[25,26] The syndrome usually occurs in children between the ages of 6 months and 6 years. The mortality rate is approximately 3% in children but reaches 50% in adults and up to 100% in adults with underlying systemic disease.[27,28] Mucous membranes are usually not involved. Nikolsky's sign, the easy separation of the outer portion of the epidermis from the basal layer when pressure is exerted, is often present. The skin lesion is characterized by the formation of bullae and vesicles leading to the loss of large sheets of superficial epidermis. The resultant appearance is that of scalded skin.

Differential Considerations

The primary differential diagnosis is toxic epidermal necrolysis. Toxic epidermal necrolysis is a full-thickness epidermal necrosis that starts on acral sites and involves mucous membranes. There is also usually a history of drug ingestion with toxic epidermal necrolysis, and Nikolsky's sign is positive only on the lesions. In staphylococcal scalded skin syndrome, unaffected skin also has a positive Nikolsky's sign. Staphylococcal scalded skin syndrome usually responds to antibiotics. Toxic epidermal necrolysis has no curative treatment and is associated with up to a 50% rate of mortality.[29]

Diagnostic Strategies

The diagnosis is based on clinical, histologic, and microbiologic findings, including (1) a clinical pattern of tenderness, erythema, desquamation, or bullae formation; (2) histopathologic evidence of intraepidermal cleavage through the stratum granulosum; (3) isolation of an exfoliative exotoxin producing *S. aureus*; and (4) the absence of pemphigus foliaceus by immunofluorescence.[29] Blister fluid and the skin are usually sterile because this syndrome is toxin generated. *S. aureus* may be cultured from mucous membrane sites such as the oral and nasal cavity.

Management

Treatment of staphylococcal scalded skin syndrome includes adequate hydration, management of fluid and electrolyte balance, and treatment with systemic antibiotics such as a penicillinase-resistant penicillin.[24]

Haemophilus influenzae Cellulitis

Principles of Disease and Clinical Features

Haemophilus influenzae cellulitis is usually seen in children younger than 5 years and occurs primarily on the face or the extremities. The skin often appears red with a violaceous tinge.[20] The patient appears acutely ill, often with a high fever, a white blood cell count greater than 15,000/mm^3, and a high incidence (75-90%) of positive blood cultures. With widespread *H. influenzae* type B immunization, there has been a dramatic decrease in the incidence of *H. influenzae* skin infections.

Management

Treatment is parenteral antibiotics with a second- or third-generation cephalosporin followed by ampicillin/clavulanic acid for a total of 10 to 14 days.[30]

Gram-Negative and Anaerobic Cellulitis

Gram-negative and anaerobic cellulitis usually occur in the immunocompromised patient. Cellulitis is seen most often around mucous membranes, primarily the perineum and in chronic wounds that are not kept clean and thus become superinfected. The diagnosis requires culturing the causative organism. Aggressive débridement and broad-spectrum antimicrobial coverage are indicated.

TOXIC SHOCK SYNDROME

Staphylococcal Toxic Shock Syndrome

Perspective

Toxic shock syndrome often occurs in menstruating women who use vaginal tampons. Although prevalent in the early 1980s, the incidence of toxic shock syndrome has decreased

BOX 135-1 TOXIC SHOCK SYNDROME: CRITERIA FOR DIAGNOSIS

Fever of 38.9°C (102°F) or higher
Rash (diffuse macular erythema) that resembles the rash of scarlet fever
Desquamation of skin 1 to 2 weeks after onset of disease
Hypotension (systolic blood pressure <90 mm Hg, orthostatic drop of 15 mm Hg or more, or orthostatic dizziness of syncope)
Clinical or laboratory abnormalities in at least three organ systems:
- Gastrointestinal: nausea and vomiting, diarrhea
- Muscular: myalgia or creatine phosphokinase at least two times normal level
- Mucous membrane: vaginal, oropharyngeal, or conjunctival hyperemia
- Renal: blood urea nitrogen or creatinine level at least twice normal or pyuria greater than five cells per high-power field
- Hepatic: bilirubin, serum transaminases at least twice normal level
- Hematologic: thrombocytopenia, less than 100,000/mm^3
- Neurologic: disorientation or altered consciousness without focal findings

Reasonable evidence for the absence of other cause of illness

remarkably since highly absorbent tampons were withdrawn from the market. Today, toxic shock syndrome occurs in patients of both sexes who have focal soft tissue staphylococcal infections; nonmenstrual causes are more prevalent.

Principles of Disease and Clinical Features

In menstruating women with toxic shock syndrome, *S. aureus* is isolated more than 90% of the time. The clinical manifestations are mainly due to the exfoliative exotoxin produced by *S. aureus*. This is the same exotoxin produced in bullous impetigo, but toxic shock syndrome results from systemic circulating exotoxin, whereas the localized blistering in bullous impetigo is caused by a direct *S. aureus* inoculum. The exotoxin in both cases has exquisite specificity in causing loss of desmosome-mediated cell adhesion within the superficial epidermis only.[25,26,29] Other clinical features include fever, a "sunburn/sandpaper" rash, hypotension, and abnormalities in at least three organ systems. Mucosal inflammation, myalgia, profuse watery diarrhea, and changes in mental status are common (Box 135-1). Differential diagnosis includes Rocky Mountain spotted fever, streptococcal scarlet fever, Kawasaki syndrome, and leptospirosis.[24]

Management

Treatment includes early goal-directed therapy for sepsis (i.e., restoration and maintenance of adequate central venous pressure and mean arterial pressure, maintaining central venous oxygenation, and achieving adequate urine output).[31–33] This may consist of central venous pressure monitoring to direct aggressive fluid resuscitation and the use of alpha- and beta-adrenergic vasoactive agents. Intravenous antibiotics that cover for penicillinase-producing staphylococci, such as nafcillin or oxacillin, can be used when there is low probability for MRSA. Clindamycin and vancomycin are acceptable for patients who are allergic to penicillin and to provide adequate MRSA coverage. Source control is a key component of management: tampons and foreign bodies must be removed, focal areas of infection drained, and mucous membranes and other sources cultured for the offending pathogen.[34]

Streptococcal Toxic Shock Syndrome

Perspective

Streptococcus has long been known to cause invasive infections. Previously, these infections occurred most commonly in patients with compromised immune systems. Since the mid-1980s, however, a streptococcal toxic shock–like syndrome has been described worldwide in younger otherwise healthy patients with serious soft tissue infections.[35] Streptococcal toxic shock syndrome was first described by Cone in 1987 when he reported two cases of shock due to isolated *S. pyogenes* soft tissue infections and postulated a toxin responsible for the shock state.[36] Stevens further characterized the syndrome in 1989 as involving otherwise healthy young patients who presented in shock or progressed to a shock state within 4 hours of admission.[37] These facts seem to indicate an increased virulence of group A alpha-hemolytic *Streptococcus*. Also, although these cases are predominantly caused by Lancefield group A strains, other groups have also been shown to cause streptococcal toxic shock syndrome.[38]

Principles of Disease and Clinical Features

The route of pathogen entry is unknown in up to 50% of cases, with others related to surgery, minor nonpenetrating trauma resulting in hematoma or muscle strain, skin superinfection, or viral infections.[39] In children, streptococcal toxic shock syndrome most commonly follows chickenpox.[38] There is also an association with the use of nonsteroidal anti-inflammatory drugs, which may mask presenting symptoms, resulting in delayed presentation and increased severity of disease.

Patients commonly present with pain, which is severe, abrupt in onset, and may be present prior to the onset of tenderness or other physical findings. Though usually in an extremity, the pain may mimic pelvic inflammatory disease, pneumonia, acute myocardial infarction, peritonitis, or pericarditis. A minority of patients will present with influenza-like symptoms of fever, chills, myalgias, and diarrhea.

Fever is the most common presenting physical sign. However, if shock is present, the patient may be hypothermic. Tachycardia and hypotension are also frequent signs. Most patients also have evidence of soft tissue infection: swelling, erythema, bullae, or tenderness. A scarlet fever–like rash is commonly seen (Box 135-2).[39]

These patients often have renal and respiratory failure. The hemodynamic compromise seen in affected patients suggests a cardiotoxic effect of the streptococcal toxins, resulting in normal to low cardiac output, normal systemic vascular resistance, and a reduced left ventricular stroke work index.[40] Mortality ranges from 33 to 81%.[41]

The virulence of these infections is attributed to surface proteins, toxin production, and host factors. Streptococcal strains that produce M protein seem to be associated with overwhelming infection. M protein binds to complement control factors and other host proteins to prevent activation of the alternate complement pathway and thus evade phagocytosis and killing by polymorphonuclear neutrophil leukocytes. Extracellular toxins, including superantigenic streptococcal pyrogenic exotoxins, contribute to tissue invasion and initiate the cytokine storm believed to be responsible for illnesses such as necrotizing fasciitis and the highly lethal streptococcal toxic shock syndrome.[42] The toxins act as superantigens to

BOX 135-2 DEFINITION OF STREPTOCOCCAL TOXIC SHOCK SYNDROME

Must meet criteria from both 1 and 2 below:

1. Isolation of group A *Streptococcus* from:
   a. A normally sterile site such as blood or cerebrospinal fluid is a definite case.
   b. A normally nonsterile site such as sputum or skin lesion is a probable case.
2. Hypotension and at least two of the following:
   a. Renal impairment
   b. Coagulopathy
   c. Liver involvement
   d. Adult respiratory distress syndrome
   e. Generalized erythematous macular rash that may desquamate
   f. Soft tissue necrosis

activate a large population of T cells, bypassing the antigen presentation phase and liberating massive amounts of cytokines, tumor necrosis factor alpha, interleukin-1, and interleukin-6. These cytokines induce the clinical signs of fever, hypotension, shock, rash, and ultimately multiorgan failure.[43] Lack of host antibodies to the surface proteins and toxins will predispose to infection and increased virulence.

Differential Considerations

Differential diagnosis includes staphylococcal toxic shock syndrome and gram-negative sepsis. Patients with *Staphylococcus* infection are unlikely to show cutaneous involvement or extremity pain, may demonstrate a "strawberry tongue," rarely have soft tissue destruction, and have a lower incidence of bacteremia. Endotoxic shock is differentiated by high cardiac output with lowered systemic vascular resistance and a left ventricular stroke work index that is not reduced.

Diagnostic Strategies

A creatinine level greater than 2.5 mg/dL indicates renal involvement, which may precede hypotension. Serum creatine kinase correlates well with deep soft tissue involvement, and increasing values may indicate necrotizing fasciitis or myositis ("flesh-eating bacteria").

Other laboratory test abnormalities include hypoalbuminemia, hypocalcemia, and a sometimes mild leukocytosis with prominent "left shift." Platelets and hematocrit may be initially normal but drop within 48 hours and may be associated with disseminated intravascular coagulation. Blood cultures are positive 60% of the time, and wound cultures are positive in 95% of cases.[44]

Management

Patients with streptococcal toxic shock syndrome require hospitalization for care, usually initially into an intensive care setting. Early goal-directed therapy for sepsis as described above for staphylococcal toxic shock syndrome is a mainstay of treatment.[31–33] Even with appropriate antibiotic therapy and intensive supportive care, the mortality rate for this disease is 30 to 70%.

It is often difficult to determine initially whether *Streptococcus* or *Staphylococcus* is the offending bacterium, so coverage for both is necessary. Suggested regimens include penicillin plus clindamycin, erythromycin, or ceftriaxone plus clindamycin. Penicillin is only moderately effective against the large inoculum of slow-growing *Streptococcus* seen in necrotizing fasciitis or myositis. A recent retrospective study confirms that clindamycin may work better than β-lactams for streptococcal toxic shock syndrome.[45] Drugs like clindamycin seem to work by two mechanisms: (1) by more effective killing of *S. pyogenes* organisms and (2) by decreasing production of extracellular products that play a role in the pathogenesis of systemic toxicity and/or tissue destruction. Because clindamycin-resistant strains of *S. pyogenes* have been reported in some localities, the presumptive selection of a combination of clindamycin and a β-lactam antibiotic would be prudent in the initial treatment of invasive streptococcal disease.[45] Early surgical débridement may be life-saving, and consultation is appropriate as soon as the possible need for surgical intervention is considered.

Intravenous gamma globulin remains experimental despite some reports of success. Gamma globulin preparations contain antibodies to staphylococcal toxins with some cross-reactivity to streptococcal toxins. A recent comparative observational study showed a benefit for intravenous immunoglobulin in the treatment of streptococcal toxic shock syndrome. Dosing was 2 g/kg, repeated 48 hours later if the patient was unstable.[46] A randomized, controlled trial showed a trend toward decreased mortality for the arm treated with intravenous immunoglobulin, but the study had to be stopped before significance was reached owing to slow enrollment. Dosing in that study was 1 g/kg on day 1, and 0.5 g/kg on days 2 and 3.[47]

Currently, antibiotic prophylaxis is not recommended for household contacts of patients with this disease, although contact with an infected person increases carrier rates in the young.[38,48] Elders are at increased risk for invasive disease after an infectious contact.[49]

IMPETIGO

Perspective

Impetigo is a superficial infection of the skin caused by group A beta-hemolytic *Streptococcus* and occasionally coagulase-positive *S. aureus*. There are two distinct subtypes: impetigo contagiosa and bullous impetigo.[50,51] Impetigo is communicable and is the most common cutaneous childhood infection.[52] Most cases occur in late summer and early fall, and the incidence is higher in tropical climates.

Principles of Disease and Clinical Features

Insect bites, flies, and infected abrasions play a role in the nonbullous form of impetigo.[50] The pathogenesis and epidemiology of this infection are a mystery in that inoculation of normal skin does not produce clinical disease. During outbreaks of impetigo, streptococci usually appear on normal skin several days before spreading to the nose or throat. In contrast, *Staphylococcus* colonization of the nose and throat takes place before the development of skin lesions. Streptococci found on the skin are not the same subtype as those that infect the pharynx.[51]

The lesions of impetigo contagiosa begin as tiny papules that rapidly develop into vesicles, which quickly progress to pustules that rupture and crust over within 24 hours. The lesions are usually painless but often are pruritic and may coalesce.[50,51] The crusts are usually thick, amber colored, and crumbly. Cultures of early vesicles, pustules, or crusts usually yield beta-hemolytic streptococci and occasionally *S. aureus*. After the fifth or sixth day, the crusts become thicker and reddish brown. The lesions tend to extend in size, clearing

centrally. Lesions are most commonly seen on the legs, with the arms, face, and trunk less commonly affected. Regional lymphadenopathy is common, lymphadenitis is rare, and fever is not usually present.[52]

Bullous impetigo is most commonly seen in neonates. It starts as a small vesicle that quickly enlarges into a bulla, often 2 to 5 cm in diameter. When a bulla ruptures, it leaves a red base with a varnish-like thin crust and scales. Satellite lesions are frequently seen. Nikolsky's sign is not present, and the patient is not toxic.[53] Bullous impetigo occurs most commonly on the face and trunk. Regional lymphadenitis is rare. These lesions generally heal faster than those of impetigo contagiosa.

Differential Considerations

Impetigo of Bockhart is a superficial staphylococcal folliculitis consisting of clusters of small pustules surrounding hair follicles.[54] Ecthyma is closely related to impetigo, except that the infection is usually deeper and heals with scarring. The lesions of ecthyma are usually on the legs and begin as a vesicle that ruptures to form a shallow ulcer. Causative organisms are group A beta-hemolytic *Streptococcus* and rarely *S. aureus*. Treatment is 10 to 14 days of penicillin or topical mupirocin.

Diagnostic Strategies

The diagnosis is made clinically, since bacteria are usually not seen in the Gram's stain of vesicular fluid. Certain strains of streptococci are nephritogenic. Post-streptococcal glomerulonephritis is more likely to follow streptococcal pharyngitis than impetigo. In contrast, acute rheumatic fever is not a consequence of impetigo.[51] Although serologic findings in streptococcal pyoderma may show increases in antibodies to various streptococcal antigens, primarily anti-DNAase B and antihyaluronidase, the serologic response as measured by antistreptolysin O is usually poor.[51] The streptozyme test, which measures several streptococcal antibodies, often gives false-negative results.[51]

Management

Soaks and wet dressings have not proven useful in treating impetigo. Topical antimicrobial agents such as hexachlorophene or povidone-iodine scrubs or washes are of limited usefulness and may result in the development of satellite lesions.[52,55,56] First-line treatment of limited impetigo is with topical mupirocin or fusidic acid. Recent systematic reviews state that these topical antibiotics are superior to systemic treatment with erythromycin, are as effective as other systemic antibiotics, and are better tolerated than systemic treatment. Systemic treatment of widespread disease with penicillinase-resistant antibiotics is recommended despite a lack of randomized prospective clinical trials for this subset of patients.[55,56] Local resistance patterns should be taken into account when selecting a systemic antibiotic. First-generation cephalosporins or clindamycin may be effective (see also Table 135-2). In some studies, intramuscular benzathine penicillin G is more effective than oral phenoxymethyl penicillin or erythromycin. The addition of topical steroids to topical antibiotic agents does not improve outcome.

Although cultures of early lesions often grow only *Streptococcus*, older lesions may yield *Staphylococcus*. *Streptococcus* seems to be the prime infecting agent, with *Staphylococcus* as a secondary invader. Treatment of impetigo with systemic and topical antibiotics does not prevent post-streptococcal glomerulonephritis, although it clears lesions quickly, reduces local extension and complications such as adenitis, and prevents spread to other individuals.[50]

In cases of bullous impetigo, some topical antibiotic preparations, such as gentamicin and a mixture of polymyxin, neomycin, and bacitracin, are as effective as a combination of oral and intramuscular benzathine penicillin G. Antistaphylococcal agents such as oral cephalosporins and semisynthetic penicillins are usually very effective. In most cases, for a solitary lesion or just a few lesions, a topical antibiotic alone is reasonable therapy.[51]

ABSCESSES

Simple Cutaneous Abscesses

Perspective

A cutaneous abscess is a localized collection of pus resulting in a painful fluctuant soft tissue mass surrounded by firm granulation tissue and erythema. Abscesses occur in all areas of the body. Approximately 20% occur in the head and neck region, 25% in the axillae, 18% in the extremities, 25% in the perirectal area, and 15% in the inguinal area. Most patients complain of pain and the presence of a tender fluctuant mass. Although abscesses may be associated with localized erythema and lymphangitis, the presence of fever or systemic toxicity suggests the possibility of deeper tissue involvement or systemic bacteremia.[57]

Principles of Disease and Clinical Features

The cause of localized abscesses depends on the anatomic region involved.[58] Abscesses on the extremities tend to be associated with interruptions of the integrity of the protective epithelial layer of the skin caused by minor trauma, such as cuts, abrasions, or needle punctures. Abscesses of the head, neck, and perineal regions tend to be associated with obstruction of the apocrine sweat glands.[59,60] The incidence of these abscesses increases in adults because the apocrine and sebaceous glands become active after puberty. Perirectal abscesses arise from bacterial spread from the anal crypts. Vulvovaginal abscesses usually result from obstruction of the Bartholin gland duct. Pilonidal abscesses are caused by plugging of small tears in the skin, usually by hairs around the buttock crease.[61]

Although most abscesses contain bacteria, approximately 5% of abscesses, especially those associated with parenteral drug abuse, are sterile.[57] Clinically, sterile abscesses cannot be differentiated from bacterial abscesses. The bacteria in cutaneous abscesses generally reflect the skin flora of the anatomic area of the body that is involved (Table 135-3). The most common bacterium cultured from abscesses in parenteral drug abusers is *S. aureus*, with streptococcal and mixed flora including anaerobes also occurring.[62,63] *Eikenella corrodens* is also sometimes seen with head and neck abscesses associated with intravenous drug abuse.[64] Anaerobic bacteria, which are known to be part of the normal flora of the skin and mucous membranes, outnumber aerobes 10 to 1 in the oral cavity and 1000 to 1 in the distal colon.[65,66] Most abscesses that originate from mucous membranes (e.g., perioral, perirectal) tend to be predominately anaerobic. Bacteria from abscesses in areas more remote from the rectum are primarily constituents of the microflora of the skin. *S. aureus* is the most prevalent aerobe found in abscesses that originate from the skin, yet it is isolated in less than one third of cutaneous abscesses and one half of axillary abscesses.[67] *S. aureus* is not commonly associated with abscesses that originate from mucous membranes (e.g., perirectal, vulvovaginal).[57,67] *Bacteroides fragilis* is one of the

Table 135-3 Bacterial Characterization of 135 Outpatient Abscesses

ANATOMIC AREAS	ABSCESSES (NUMBER)	PERCENT OF TOTAL CULTURES	TYPES OF BACTERIAL GROWTH (% FROM EACH AREA)				BACTERIAL SPECIES PER ABSCESS*	
			NO GROWTH	AEROBES ONLY	ANAEROBES ONLY	AEROBES AND ANAEROBES	AEROBES (AVERAGE NO.)	ANAEROBES (AVERAGE NO.)
Head and neck	25	19	4	28	20	48	1	2
Trunk	11	8	0	45	18	36	1	2
Axilla	22	16	0	55	5	41	1	1
Extremity	16	12	19	44	13	25	1	1
Hand	8	6	25	63	0	13	2	0
Inguinal	7	5	0	29	57	14	0	3
Vulvovaginal	13	10	0	15	46	38	1	3
Buttock	12	9	0	33	33	33	1	3
Perirectal	21	16	0	0	33	67	1	5

*Cultures with no growth were excluded.
From Meislin HW, et al: Cutaneous abscesses: Anaerobic and aerobic bacteriology and outpatient management. Ann Intern Med 87:145, 1997.

few anaerobes resistant to penicillin.[68] *Bacteroides* resistance to other antibiotics has been reported, including cefoxitin, metronidazole, clindamycin, carbapenems, and fluoroquinolones.[69,70] This pathogen, which produces β-lactamase, has been associated with more than 50% of intra-abdominal infections. Although it is the most common gram-negative anaerobic species in human feces, it is found in fewer than 50% of perineal abscesses.[57] *Escherichia coli* and *Neisseria gonorrheae* are rarely found in cutaneous abscesses from any location.

Differential Considerations

Although the development of an abscess is usually an isolated event, recurrent abscesses in the perineal and lower abdominal area may signify the presence of inflammatory bowel disease. Recurring abscesses in the axillae and inguinal areas may represent hidradenitis suppurativa. Finally, recurring abscesses may be associated with immunocompromise such as occurs with neoplasm, corticosteroid therapy, chemotherapy, diabetes mellitus, acquired immunodeficiency syndrome, leukemia, vascular insufficiency, trauma, or thermal injury.

Diagnostic Strategies

Ultrasonography is a useful technique to localize subcutaneous and intramuscular abscesses, differentiate abscess from cellulites, and identify foreign bodies that are not radiopaque.[6,11,71]

The examination of Gram's stain of material from cutaneous abscesses allows a quick identification of the morphotype of the offending pathogen. In general, the Gram's stain shows one of three patterns: (1) white blood cells without bacteria, which indicates a sterile abscess; (2) a mixed pattern of gram-positive and gram-negative rods and cocci of varied morphotypes, which indicates mixed aerobic and anaerobic infection; and (3) gram-positive cocci in grapelike clusters, diagnostic of *S. aureus* infection.[57]

Management

The treatment of cutaneous abscesses is incision and drainage. Several studies confirm that antibiotics are not indicated in patients with normal host defenses.[1,57,72,73] Thus, a Gram's stain and culture are also unnecessary in these patients. In the immunosuppressed patient, Gram's stain, culture, and antibiotics are indicated. The selection of antibiotics is guided by (1) the flora anticipated at the location of the abscess, (2) the Gram's stain results, (3) the presence of a feculent odor that is indicative of anaerobes, and (4) culture and sensitivity findings (see Table 135-2).[57,67] Incision and drainage are generally painful because local anesthetics are less effective in inflamed acidic locations. The use of parenteral or regional analgesia may be indicated in addition to a local anesthetic agent. Nitrous oxide is an option, especially in a self-administered 50% concentration. The incision should be deep enough into the abscess cavity to ensure adequate drainage. Elliptical incisions are preferred by some to prevent premature closure of the cutaneous surface. The cavity should be gently curetted to free all loculated areas of pus, and the cavity should be irrigated. A loose packing should be removed within 48 hours or within 24 hours in cosmetically important areas such as the face. Once the packing is removed, warm soaks are recommended three or four times a day for 10 to 15 minutes for 2 to 3 days.[57]

Furuncle

A furuncle usually evolves from a superficial folliculitis. It is a deep inflammatory nodule surrounded by an intense local tissue reaction. The abscess tends to be very thin walled, and purulence is present. Skin flora (*S. aureus*, streptococci) are usually isolated.

Carbuncle

A carbuncle is an extensive process of interconnecting deep abscesses that extend into subcutaneous tissues. The microbes are usually aerobic; however, *Pseudomonas aeruginosa* may be present in chronic cases. Predisposing factors include folliculitis, blood dyscrasias, steroids, heavy perspiration, obesity, diabetes, and skin location, such as areas of friction (e.g., the back of the neck).

Hidradenitis Suppurativa

Perspective

Hidradenitis suppurativa is a disease consisting of chronic suppurative abscesses in the apocrine sweat glands. One in

300 adults is affected, usually after puberty and before the age of 40 years. It may be more common in females and blacks, and perianal occurrence is twice as common in males.[59,60] Inflammation begins deep within the acinus or convoluted tubules of the sweat glands as a result of obstruction to apocrine glandular secretions. Additional predisposing factors include obesity, poor hygiene, excessive perspiration, shaving, and irritating deodorants.[74] The axillary location is more common than inguinal and perianal. This condition may be premalignant in extra-axillary sites, and surgical resection should be considered for treatment of such cases.[75,76]

Principles of Disease and Clinical Features

In most cases, the disease manifests as episodic occurrences of one or more painful subcutaneous nodules, associated with burning, itching, local cellulitis, swelling, and a malodorous discharge. These nodules drain spontaneously or are surgically incised with drainage of scant pus. Resolution usually occurs within a few days. In some patients, however, the disease tends to be chronic and extensive, with multiple abscesses, sinus tracts, and fistulas. These often heal with hypertropic scars and may result in a tender, unsightly area.

Staphylococcus aureus, *Staphylococcus viridans*, and common skin anaerobes are commonly isolated. Chronic disease often results in overgrowth with fecal flora in the perineum and *Proteus* with other mixed aerobes and anaerobes in the axillae.

The pathogenesis of this disease is more complex than a simple infection model. Success in treating hidradenitis with immunosuppressive drugs indicates that the disease may be primarily or at least in part an inflammatory process.[77,78]

Differential Considerations

Hidradenitis suppurativa must be differentiated from a simple cutaneous abscess of the axillary region or perianal and perirectal abscesses. This differentiation is usually accomplished by noting the chronicity of the process, the multiplicity of abscesses, and the lack of involvement with the rectal mucosa.

Management

Although clindamycin alone or in combination with rifampin may provide temporary recession of the disease, the almost inevitable recurrence makes surgery the definitive therapy.[74,79] Severe cases may improve with immunosuppressive therapy.[77,78] Incision and drainage usually suffice in an acute situation. Sinus tracts and fistulas should be unroofed, all loculations excised, and all purulence and necrotic tissue evacuated. Subsequent antibiotic coverage is usually unnecessary in patients with normal host defenses and without additional soft tissue involvement. Chronic or extensive disease often requires extensive surgical removal of all hair-bearing skin in the apocrine gland areas. Coverage requires either primary closure, rotated skin flaps, or grafting.[74] Although rare, the most serious complication of hidradenitis suppurativa is squamous cell carcinoma, so pathologic examination of surgical specimens is recommended.[76] Routine colostomy in patients undergoing surgical treatment of perineal disease is usually not necessary, as long as aggressive wound care is instituted. Patients who might benefit from fecal diversion are those in whom proper wound care is not feasible, and those patients suffering from concomitant Crohn's disease and hidradenitis suppurativa.[59,60]

Hidradenitis suppurativa has been associated with social, personal, and vocational difficulties because of the chronic, uncomfortable, malodorous, and unsightly nature of the disease. Early referral for surgical obliteration of the apocrine glands should be considered in these patients.

Bartholin's Cyst Abscess

Principles of Disease and Clinical Features

A Bartholin's cyst abscess is caused by an obstructed Bartholin duct. The flora is usually a mixture of aerobic and anaerobic flora from the vagina, with *Chlamydia trachomatis* and *N. gonorrheae* cultured approximately 10% of the time.[57,80] The patient usually has a painful cystic mass on the inferior lateral margin of the vaginal introitus. Signs and symptoms are usually localized, but septic shock can occur in rare cases.[81]

Management

Abscesses should be drained from the mucosal rather than the cutaneous surface. Simple incision and drainage carries a high risk of recurrence, so the cavity should be packed open. The Word catheter is a 10-Fr balloon catheter designed specifically for this purpose and is both convenient to use and highly successful. After incision and drainage, the catheter is inserted and inflated with 2 to 5 mL of water or saline (Fig. 135-1). The catheter should be left in place for 4 to 6 weeks so that a sinus

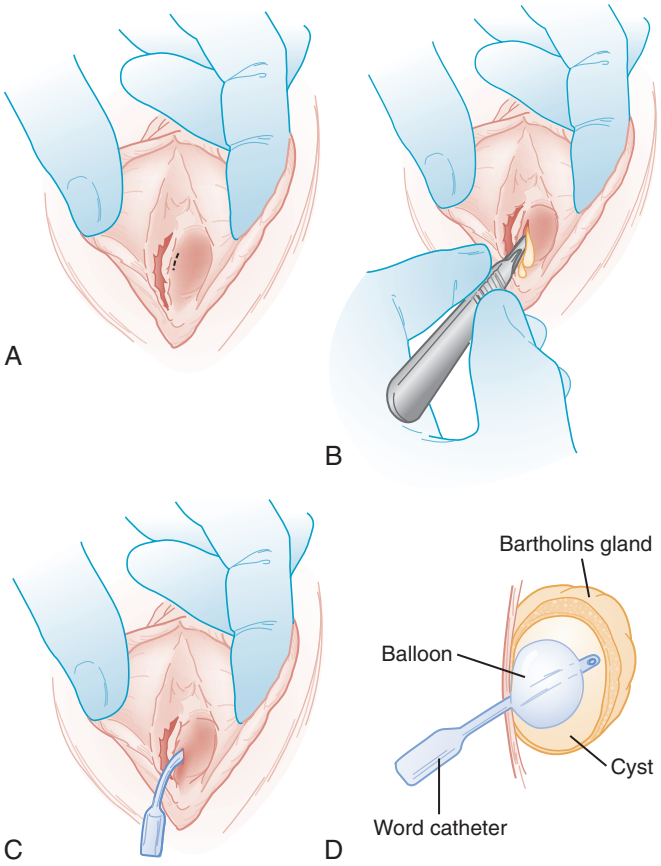


Figure 135-1. Incision and drainage of Bartholin's abscess. **A,** Local anesthetic is injected into the mucosal surface of the abscess and the mucocutaneous junction of the labia minora. **B,** A 1-cm incision is made on the mucosal surface. **C** and **D,** The Word catheter is inserted and the balloon inflated with 5 mL normal saline solution. (From Campbell CJ: Incision and drainage of Bartholin's cyst. In Rosen P, et al. [eds]: Atlas of Emergency Procedures. St. Louis, Mosby, 2001.)

will have time to form. Sitz baths will help keep the area clean and draining. Marsupialization is a more complex treatment option, involving incision and drainage of the cavity followed by suturing of the walls of the cyst to the skin.

Fasciitis

Principles of Disease and Clinical Features

Fasciitis is an infection of the fascia, subcutaneous tissue, and skin. Erythema, marked edema, and, sometimes, areas of gangrene occur (see Table 135-1). Much confusion has surrounded the nomenclature of these necrotizing infections because they have been named for specific bacteria (e.g., hemolytic streptococcal gangrene), after individuals (e.g., Meleney's synergistic gangrene), by anatomic appearance (e.g., necrotizing fasciitis), and for specific circumstances (e.g., postoperative progressive bacterial gangrene). By definition, fasciitis does not involve muscle, but it can spread to invade underlying muscle, causing myonecrosis. Patients with fasciitis manifest moderate to severe systemic toxicity, often out of proportion to the cutaneous findings, with high fever, tachycardia, anxiety, disorientation, and often frank shock. Tissue invasion is rapid, often spreading from a cellulitis to a necrotizing fasciitis within 1 to 2 days. Massive subcutaneous edema and necrosis are common. Early on, the skin may be relatively spared, but as the disease progresses, the cutaneous tissues often demonstrate blebs, crepitus, or frank necrosis.[82] Diabetes, peripheral vascular disease, trauma, and recent surgery are predisposing factors. Pain varies because cutaneous nerve endings are quickly destroyed. Thus, the absence or cessation of pain may indicate worsening rather than improvement.[83]

Management

The initial treatment of all of these infections involves fluid resuscitation, parenteral antibiotics, and early surgical consultation for incision, drainage, and débridement. Large quantities of crystalloids are often necessary to replace fluid sequestered in the wound. Hemolysis occurs and may require the use of blood replacement products. Disseminated intravascular coagulopathy occurs in severe cases. Intravenous calcium may be necessary to reverse the hypocalcemia that results from necrosis of subcutaneous fat. The usual anaerobic infection has a foul discharge, occurs in locations near mucosal openings (perineum, oral pharynx), may manifest with tissue gas, and often has a Gram's stain that shows a polymorphic array of organisms with negative aerobic cultures. The initial choice of antibiotics for necrotizing fasciitis should be guided by the Gram's stain, culture, and anatomic area involved. Use of high-dose penicillin, clindamycin, and an aminoglycoside, third-generation cephalosporin, or fluoroquinolone is recommended for a broad spectrum of coverage of aerobes, gram-negative enteric organisms, and anaerobes.[84,85] If gram-positive organisms are expected or are seen on stain, a penicillinase-resistant penicillin should be added.[84,86]

NECROTIZING FASCIITIS

Principles of Disease

Necrotizing fasciitis is the preferred term for describing certain uncommon but potentially lethal infections. The condition usually occurs in men in the lower extremities and may evolve after only minimal local trauma. There are two types of necrotizing fasciitis. Type 1 is polymicrobial and involves non-group A streptococci plus anaerobes. These are typically found on the abdomen and perineum. In type 2, the pathogen is group A beta-hemolytic streptococci and the infection is typically found on the extremities.[86] A substance in the cell wall of streptococci causes a separation of the dermal connective tissue, resulting in continued inflammation and necrosis. Streptococcal necrotizing fasciitis is frequently associated with streptococcal toxic shock syndrome.[87,88]

Early clinical findings are similar to those of most infected wounds, but the involved site quickly becomes erythematous, tender, and edematous; fever is usually present. Numbness or deep pain is often out of proportion to the physical findings. Early on, the skin may appear relatively benign, but necrotic patches and bullae appear between days 2 and 4, as a serosanguinous watery fluid begins to ooze.[89] Deep structures and muscles are not involved. Hypotension, tachycardia, leukocytosis, and hypocalcemia ensue with systemic toxicity out of proportion to the clinical findings. Radiographs may reveal gas in the tissues, but tissue gas is not a universal finding.[86] The absence of gas does not exclude the diagnosis of necrotizing fasciitis. Frozen-section biopsy can be useful in diagnosis. Magnetic resonance imaging helps differentiate acute cellulitis from necrotizing fasciitis. Magnetic resonance imaging can overestimate the extent of disease due to adjacent noninfectious edema. Because of the rapidly progressive and frequently fatal outcome of this condition, delaying treatment to wait for imaging is not justified.[90,91]

Management

Treatment is surgical débridement, fluid and critical care resuscitation, and parenteral antibiotics against *S. aureus*, *Streptococcus*, gram-negative organisms, and anaerobes as directed by Gram's stain and culture findings. Débridement should be aggressive and may have to be repeated. The mortality rate associated with this condition has ranged from 6 to 76%, with a cumulative mortality rate of 34%. Diabetes mellitus is the most important predictor of mortality. Advanced age, two or more associated comorbidities, and a delay before surgery of greater than 24 hours also contribute to mortality, as does the presence of streptococcal toxic shock syndrome.[92]

SPECIFIC FASCIITIS SYNDROMES

Meleney's synergistic gangrene (progressive bacterial synergistic gangrene) involves superficial and deep fascial planes with thrombosis of the subcutaneous vessels and gangrene of tissues. It is usually seen at the site of a laceration or surgical wound, but sometimes no portal of entry can be found. The skin appears erythematous and may eventually take on a bluish, gangrenous appearance. The patient is toxic, with fever and leukocytosis. Group A *Streptococcus* is found on the skin and in the blood, although *S. aureus* and gram-negative enteric organisms can also be found. Treatment is wide incision and débridement and appropriate antibiotics.[37,93,94]

Clostridial cellulitis (anaerobic cellulitis, local gas gangrene) is a gas-forming infection of the skin and subcutaneous tissue that spreads through intrafascial planes. Other bacterial flora can be seen. Healthy muscle is not involved. It results from superinfection of previously traumatized or necrotic tissue. Gas distributes in large bubbles in the fascial plane but not the muscle. Patients show signs of systemic toxicity: fever, tachycardia, edema of the affected part, and pain. Incision and débridement of involved tissue and blebs are necessary. Antibiotic treatment is penicillin or clindamycin. These patients must be hospitalized.

Nonclostridial crepitant cellulitis is similar to clostridial cellulitis except that the flora are usually polymicrobial, with aerobic

and anaerobic coliforms such as *E. coli*, *Klebsiella*, *Enterobacter*, *Peptostreptococcus*, *Peptococcus*, and *B. fragilis*. These infections tend to progress from a fasciitis to a myositis. The treatment is broad-spectrum intravenous antibiotics and close observation and débridement.[95]

Fournier's syndrome is an insidious necrotizing subcutaneous infection of the perineum that occurs primarily in men, usually between 20 and 50 years of age, and usually involves the penis or scrotum. The disease occasionally occurs in women, especially in patients who are immunocompromised. Pain or itching in the genitalia is followed by fever, chills, and impressive perineal swelling, which may simulate a strangulated hernia. The inflammation may involve the entire abdomen, back, and thighs. There is frequently crepitance on palpation, indicating subcutaneous gas. Systemic symptoms include nausea and vomiting, changes in sensorium, and lethargy. Eventually, gangrenous areas demarcate and become less painful as destruction and sloughing of sensory nerves occur. The tissue breaks open, sloughs, and gives off an overwhelming feculent odor.

The most common causal factors are infection or trauma to the perianal area, including anal intercourse, scratches, chemical or thermal injury, and diabetes. Local trauma and perianal disease precede approximately one third of all cases. Cultures demonstrate bacteria of the distal colon, with a complex picture of aerobic and anaerobic bacteria. *B. fragilis* tends to be the predominant anaerobe and *E. coli* the predominant aerobe.

This bacterial invasion of the subcutaneous tissues of the perineum causes obliteration of the small branches of the pudendal arteries that supply the perineal or scrotal skin, resulting in acute dermal gangrene. This combination of erythema, edema, inflammation, and infection in a closed space stimulates anaerobic growth. Identification of the offending organism can be done with Gram's stain and wound cultures. Emergency management includes antibiotic therapy against anaerobes and gram-negative enterics and wide incision and drainage of the area to remove all the necrotic tissue.[96] The mortality rate is approximately 3 to 38%.[97]

■ MYOSITIS

Principles of Disease and Clinical Features

Myositis, or myonecrosis, is a deep soft tissue infection with death of muscle and a variable degree of inflammation of the overlying tissues (see Table 135-1). The skin may show minimal erythema to frank gangrene, but usually the infection is associated with massive edema. Myositis includes gas gangrene (clostridial myonecrosis), nonclostridial myonecrosis, and synergistic necrotizing cellulitis.[98]

Clostridial myonecrosis, or gas gangrene, is a rapidly progressive muscle-necrosing infection, often with little inflammatory skin reaction but with gas formation. It is usually a result of trauma or recent surgical wounds.[99] Pathogenesis includes the elaboration of exotoxins by clostridial bacilli. Clostridia are spore-forming anaerobic gram-positive bacilli usually found in the soil and in the intestinal tracts of humans and animals. Clostridia produce a toxin that damages and kills muscle, setting up the anaerobic environment that promotes further growth of the bacilli. The incubation period is 1 to 4 days. The onset of disease can occur in 6 to 24 hours. Pain is the earliest and most important symptom. Tachycardia out of proportion to fever is noted. Temperature is not a reliable index of infection. Mentally, patients are apathetic, with varying levels of stupor and delirium. The wound appearance is striking in the later stages but does not show the usual erythema of a pyogenic cellulitis. Early on, the skin may be white, shiny, and tense, or essentially normal. Progressive swelling can produce a dusky bronze appearance of the skin, with further progression leading to formation of vesicles filled with dark red or purplish fluid. A brown watery discharge with a peculiar, foul "mousy" odor is noted. Crepitus is not a reliable finding, owing to overlying edema. Gas alone in the tissues cannot make the diagnosis of gas gangrene.[99] The muscle appears to be cooked or dead and does not bleed when cut or retract when pinched.

Nonclostridial myonecrosis is similar to gas gangrene, except that the flora include anaerobes such as *B. fragilis* and *Peptostreptococcus* along with gram-positive aerobes such as *Staphylococcus*. The prognosis is better than that for patients with gas gangrene. Treatment is appropriate débridement and antibiotic coverage. Gas may be present.[86,99]

Synergistic necrotizing cellulitis is a rapidly progressive infection usually of the lower extremities and perineum, commonly seen in patients with diabetes or peripheral vascular disease. Systemic manifestations are variable, from minimal to frank shock. The overlying skin often has a "dishwater" discharge and may show blebs, crepitus, or necrosis. The infection often extends from skin through the muscle. Pain is usually present. The causative pathogens include aerobes, *Streptococcus*, *Staphylococcus*, *Klebsiella*, *Proteus*, *E. coli*, and anaerobes, often *Bacteroides* and *Peptostreptococcus*. Hemolysis is common and the mortality rate is high. Treatment includes aggressive fluid and blood product resuscitation, appropriate antibiotics, and rapid surgical débridement.[83,94]

Diagnostic Strategies

Gram's stain smears of the area show large gram-positive rods. Radiographs may reveal gas. Where available, magnetic resonance imaging may be helpful if the initial presentation is unclear or nonspecific, to speed diagnosis and reveal the extent of tissue involvement.[100]

Management

Treatment is wide débridement and excision of the wound. Parenteral antibiotics should be given to cover anaerobes and enterics; penicillin in large doses, a cephalosporin, or clindamycin is indicated.[98] The mortality rate is high.[99] Hyperbaric oxygen therapy may be effective very early in this disease. Hyperbaric oxygen therapy has been advocated for deep anaerobic infections that result in necrotizing fasciitis and myonecrosis, especially by clostridial species. Hyperbaric oxygen therapy is also a consideration in cases of nonclostridial involvement and Fournier's syndrome.[101] The definitive benefit of hyperbaric oxygen therapy in necrotizing infections remains unproven.[83,86] Hyperbaric oxygen therapy may provide an environment less appropriate for anaerobic growth by reducing the oxygen-reduction potential, decreasing edema via hyperoxic vasoconstriction, enhancing the ability of phagocytes to destroy bacteria, and promoting angiogenesis and subsequent granulation tissue.[101]

Acknowledgment

Drs. Meislin and Guisto would like to acknowledge and thank Drs. Brooke Rosonke and Gregory Gardner for their help and assistance with the writing of this chapter.

KEY CONCEPTS

- Soft tissue infections encountered in the emergency department vary widely in location, severity, and causative organisms.
- A working knowledge of the usual presentation of specific infections, based on the anatomic area involved and origin (mucosal or skin) of the infection, will allow selection of appropriate empirical antibiotic therapy.
- Identification of the infecting organism by culture or other laboratory technique is often unnecessary in common mild to moderate infections and can usually be reserved for severe or unusual cases.
- Severe or potentially life-threatening bacterial infections mandate immediate administration of the best empirical choice of antibiotics; attempts to identify the exact organism should not delay therapy.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 136 Sepsis Syndromes

Nathan I. Shapiro, Gary D. Zimmer, and Adam Z. Barkin

PERSPECTIVE

Background

Sepsis syndrome represents the body's host response to an infection. The causative agent and the host's activated inflammatory cascade cause the body's defenses and regulatory systems to become overwhelmed, leading to a disruption in homeostasis. Tachycardia, tachypnea, fever, and immune system activation are manifestations. If the body is unable to overcome this insult, cellular injury, tissue damage, shock, multiorgan failure, or death may ensue.

In 1992, the American College of Chest Physicians/Society for Critical Care Medicine issued a consensus statement to establish uniform criteria defining the sepsis syndromes.[1] For the first time, this allowed a common nomenclature for disease classification and systematic comparisons across studies of septic patients. The definitions vary. *Systemic inflammatory response syndrome (SIRS)* is defined as two or more of the following: tachycardia, tachypnea, hyperthermia or hypothermia, high or low white blood cell count, or a bandemia; *sepsis* is the combination of infection plus SIRS; *severe sepsis* is sepsis plus organ dysfunction; and *septic shock* is severe sepsis plus hypotension, defined as a systolic blood pressure less than 90 mm Hg, not responsive to a fluid challenge (Box 136-1). The importance of the sepsis syndromes is to provide a common nomenclature for disease classification and research purposes. Efforts to validate this classification scheme in the emergency department (ED) population have demonstrated the term *sepsis* when characterized by fulfilling the SIRS criteria alone is perhaps overly sensitive and nonspecific and does not convey an increased mortality risk, though it should prompt further evaluation. However, the presence of organ dysfunction and shock were shown to be significant predictors of adverse outcome. Newer efforts have proposed the "PIRO" approach to better understand and prognosticate illness.[2] Assessing *p*redisposing conditions, *i*nfection source, *r*esponse of the host, and *o*rgan dysfunction will lead to improved classification.[2] Approaching the patient to determine *who* they are (e.g., underlying comorbidities), *what* infection they have, *how* they are responding, and *where/if* organ dysfunction is occurring is a clinically useful and pragmatic way to approach the septic patient.

Bacteremia is often present, but positive cultures are not obligatory in the diagnosis of sepsis. In recent prospective studies, only 17 to 27% of patients with sepsis, 25 to 53% of patients with severe sepsis, and 69% of patients with septic shock actually had positive blood cultures.[3–5] Culture-negative and culture-positive septic populations have similar outcomes in patients with similar severity of illness.[3,5,6] Pneumonia, abdominal abscess with viscus perforation, and pyelonephritis are common primary causes of sepsis.[3,5,7,8] Gram-positive organisms account for 25 to 50%, gram-negative for 30 to 60%, and fungi for 2 to 10% of cases. The distribution varies with the study and, more importantly, with host factors such as the status of the host immune system, patient age, recent hospitalizations, and presence of indwelling vascular catheters.

The health status of the host is a crucial risk factor in the development and progression of sepsis. Elders and those with multiple comorbidities are overwhelmed more easily by systemic infection. Chemotherapy-induced neutropenia, acquired immunodeficiency syndrome, and steroid dependency increase susceptibility to sepsis. Increased use of indwelling devices such as intravascular catheters, prosthetic devices, and endotracheal tubes contribute to the risk of systemic infection and sepsis.

Epidemiology

Sepsis is now the 10th most common cause of death in the United States.[9] It is estimated that 571,000 cases of severe sepsis present to U.S. EDs each year.[10] Mortality rates from sepsis are estimated between 20 and 50%.[3,7,8,11–16] Sepsis accounts for 4 out of 1000 ED visits in the United States.[17] The incidence of sepsis as a reason for hospitalization is rising at a disproportionately high rate among elders, compared to the young (Fig. 136-1). The incidence of sepsis in patients under age 65 years is less than 5 in 100,000, while it is 26 in 100,000 in those 65 or older.[18] The cost of caring for septic patients is estimated to be $17 billion per year in the United States.[11] Hospital discharge data have shown that the incidence of sepsis is increasing as identification improves and the population ages. Estimates have suggested that the incidence will rise 1.5% per annum or more.[11,12] The number of ED visits for sepsis has risen proportionally with the rise in ED volume over the past 15 years.[17] Recent research has confirmed the long-held belief that respiratory and genitourinary infections are the most common causes of sepsis.[10]

PRINCIPLES OF DISEASE

Pathophysiology

Sepsis is the endpoint of a complex process that begins with an infection. The initial host response is to mobilize inflammatory cells, particularly neutrophils and macrophages, to the site of infection. These inflammatory cells then release circu-

BOX 136-1 DEFINITIONS OF SEPSIS

Bacteremia (fungemia): presence of viable bacteria (fungi) in the blood, as evidenced by positive blood cultures
Systemic inflammatory response syndrome (SIRS): at least two of the following conditions: (1) oral temperature of >38° C or <35° C, (2) respiratory rate of >20 breaths/min or partial pressure of arterial carbon dioxide ($PaCO_2$) of <32 mm Hg, (3) heart rate of >90 beats/min, (4) leukocyte count of >12,000/dL or <4000/dL or >10% bands
Sepsis: SIRS that has a proven or suspected microbial source
Severe sepsis: sepsis with one or more signs of organ dysfunction, hypoperfusion, or hypotension, such as metabolic acidosis, acute alteration in mental status, oliguria, or adult respiratory distress syndrome
Septic shock: sepsis with hypotension that is unresponsive to fluid resuscitation plus organ dysfunction or perfusion abnormalities as listed for severe sepsis
Multiple organ dysfunction syndrome (MODS): dysfunction of more than one organ, requiring intervention homeostasis

Data from Bone R, Balk R, Cerra F: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The APP/SCCM Consensus Conference Committee. Chest 101:1644, 1992.

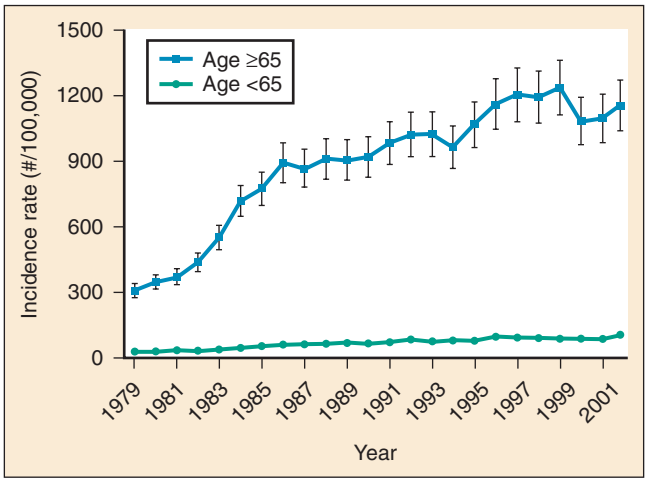


Figure 136-1. Incidence of disease in young and old over time.

lating molecules, including cytokines, which trigger a cascade of other inflammatory mediators that result in a coordinated host response. Synthesis of the components of the cascade is increased at many steps along the pathway. If these mediators are not appropriately regulated, sepsis will occur. In the setting of ongoing toxin release, a persistent inflammatory response occurs with ongoing mediator activation, cellular hypoxia, tissue injury, shock, multiorgan failure, and potentially death. This interaction is complex and multifactorial, and our understanding of it continues to evolve.

Mediators of Sepsis

The nature of the body's inflammatory response to a pathogenic insult is central to the pathophysiology of sepsis. The response is perhaps more important than the pathogen and is mostly responsible for determining patient outcome.[1,19,20] A pathogen is sensed by pattern recognition receptors, most notably toll-like receptors, located on the surface of the white blood cell.[21] The resulting host-pathogen interaction results in activation of the inflammatory and coagulation cascades.[21–28] The subsequent inflammatory signaling occurs via cytokines, chemokines, and other soluble mediators, including increased circulating levels of interleukin-1 (IL-1), IL-6, IL-8, and tumor necrosis factor alpha (TNF-α).[29–31] Activation of the clotting cascade results in increased D-dimer levels (~100% patients) and decreased circulating levels of protein C (>90% patients).[32–34] In benign conditions, a self-limited response helps to clear the pathogen. However, in more severe disease, unchecked proinflammatory and procoagulant activity leads to disruption of homeostasis as organs are damaged and the oxygen supply to vital organs is reduced. If uncorrected, the process leads to cellular hypoxia, organ dysfunction, shock, and death.

The primary mediators are cytokines that are primarily proinflammatory, anti-inflammatory, or growth promoting. The molecular mechanisms by which they are regulated are not well understood. The initial cytokine, TNF-α, is found in serum approximately 90 minutes after the administration of endotoxin to healthy volunteers.[35] IL-6 and IL-8 reach peak levels at approximately 120 minutes. The main proinflammatory cytokines are IL-1, TNF, and IL-8. The primary anti-inflammatory cytokines are IL-10, IL-6, transforming growth factor beta, soluble receptors to TNF, and IL-1 receptor antagonist (IL-1ra).[36–38] If the resultant inflammatory response is adequate, the infection is controlled and cleared. If the response is deficient or excessive, however, a persistent and worsening cascade is produced, ultimately leading to shock, organ failure, and potentially death.

IL-1 and TNF have both been implicated as key mediators in the development of sepsis. Increasing levels of circulating IL-1 and TNF correlate with worsening clinical status.[39] At high doses, both IL-1 and TNF are lethal. They act by stimulating granulocyte-colony stimulatory factors and activating leukocytes.[40] TNF is present first in the bloodstream, and it induces the formation of IL-1.[41] Infusing either cytokine into an animal model creates a sepsis syndrome.[42] Selective blockade of either cytokine protects against sepsis in animal models.[43–46] Anti-inflammatory regulators are released in response to rising proinflammatory mediators. IL-1ra is found in increased levels in healthy volunteers injected with endotoxin and many patients with infection.[47] IL-10 has a purely anti-inflammatory role.[48] In experimental models, it has been shown to decrease mortality in the presence of endotoxemia.

Other noncytokine molecules have been implicated in sepsis. Metabolites of the arachidonic acid pathway are involved in peripheral vasodilation, vasoconstriction, and leukocyte and platelet aggregation.[49] Prostaglandins are responsible for fever.[50] Elevated thromboxane A_2 levels are found in sepsis.[51] Little is known about the actual mechanisms by which eicosanoids participate in sepsis.

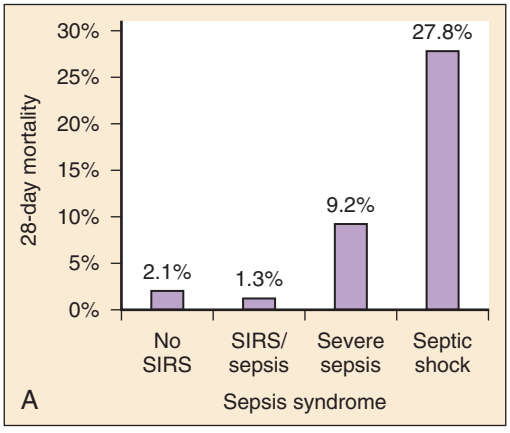
Instability in vascular tone is becoming increasingly important in our understanding of the pathophysiology of sepsis. Vasopressin, also known as antidiuretic hormone, is a naturally occurring hormone that is essential for cardiovascular stability. It is produced as a prohormone in the hypothalamus. The hormone is stored in the pituitary gland and released in response to stressors such as pain, hypoxia, hypovolemia, and hyperosmolality.[52] In severe sepsis, there is a brief rise in circulating vasopressin levels followed by a prolonged and severe suppression. This pattern of secretion is different from other forms of shock in which vasopressin levels remain elevated.[53] Vasopressin has numerous physiologic effects, including vasoconstriction of the systemic vasculature, osmoregulation, and maintenance of normovolemia.

Nitric oxide (NO) is a gas that has an important role in septic shock, regulating vascular tone[54] by an indirect effect on smooth muscle cells.[55] NO also contributes to platelet adhesion, insulin secretion, neurotransmission, tissue injury, and inflammation and cytotoxicity.[56–58] Its half-life is quite short (6–10 seconds) and it easily diffuses into cells.[55] Although its mechanisms of action are not well understood, it seems to be a key mediator of sepsis. Animal data show that nitric oxide synthase, the enzyme that produces NO, is up-regulated in cases of sepsis.[59] Enhanced NO production is thought to contribute to the profound vasodilation found in patients in septic shock.

In the setting of ongoing inflammatory activation, the mediators of sepsis continue to be produced and the cascade perpetuates. Unless appropriately and rapidly controlled, the ultimate effect is a sequence of events starting with cellular dysfunction and ultimately leading to tissue damage, organ dysfunction, and death.

Organ System Dysfunction

The organ dysfunction that results from sepsis is central to the pathogenesis of the disease. A 3000-patient ED-based study demonstrated that organ dysfunction with septic shock portends increasingly worse outcomes.[60] Patients with suspected infection alone had a mortality rate of 2.1%, while the presence of SIRS criteria and suspected infection had a mortality rate of only 1.3% (Fig. 136-2A). However, the mortality rate was 9% for those patients with severe sepsis (sepsis plus organ dysfunction) and 28% for those with septic shock. The risk of death from sepsis approximately doubles for each organ that fails. The mortality rate for patients with no organ dysfunctions was 1.0%, while rates for single organ dysfunction, two organ dysfunction, three organ dysfunction, and four or more organ dysfunctions were 6%, 13%, 26% and 53%, respectively (Fig. 136-2B).



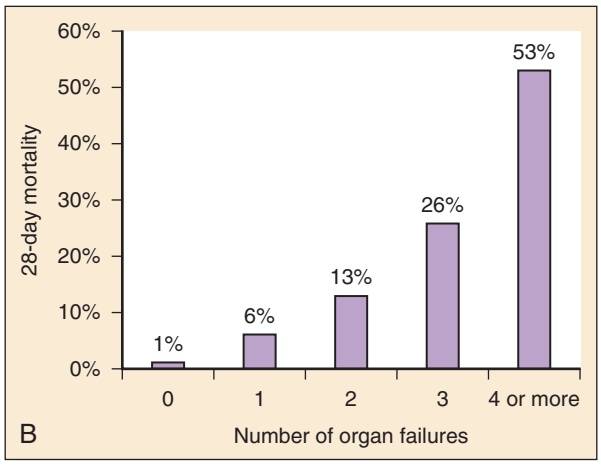


Figure 136-2. Mortality rates by sepsis syndrome **(A)** and number of organ dysfunctions **(B)**.

Neurologic

Patients with sepsis often display neurologic impairment manifested by altered mental status and lethargy, commonly referred to as *septic encephalopathy*. The incidence has been reported between 10 and 70%.[61,62] The mortality rate in patients with septic encephalopathy is higher than in septic patients without significant neurologic involvement.[63] One prospective case series showed that a Glasgow Coma Scale score of less than 13 correlated with an increase in mortality rate from 20 to 50%.[64] Although the pathophysiology has not been clearly defined, contributing factors include direct bacterial invasion, endotoxemia, altered cerebral perfusion or metabolism, metabolic derangements, multiorgan system failure, and iatrogenic injury. In addition, impaired renal or hepatic function in the absence of overt organ failure has been shown to correlate with encephalopathy.[64,65]

Cardiovascular

Profound cardiovascular dysfunction is common with sepsis. The etiology of cardiovascular dysfunction and failure arise from both direct myocardial depression and distributive shock. Gram-negative, gram-positive, and killed organisms can cause myocardial depression.[66,67] The direct insults of the toxic mediators as well as the mobilization of host mediators of sepsis produce a distributive shock. Early in sepsis, a hyperdynamic state develops, characterized by increased cardiac output and decreased systemic vascular resistance.[68,69] Although the cardiac output is increased, it is at the expense of ventricular dilation and decreased ejection fraction. Aggressive fluid resuscitation usually increases preload and, secondarily, ejection fraction, thereby improving the cardiac index, even late in shock.[70] Much of the cardiovascular compromise from septic shock is reversible, and normal cardiovascular function usually returns within 10 days.[71]

Pulmonary

The lung is an early victim to the inflammatory response to sepsis. These effects are apparent irrespective of the primary infection that caused sepsis. Early infiltration with neutrophils, surfactant dysfunction, and edema later give way to monocyte infiltration and fibrosis. Significant right-to-left shunting, arterial hypoxemia, and intractable hypoxemia occur. The resulting morbidity is high and is a common endpoint to sepsis-related deaths.

Sepsis produces a highly catabolic state and places significant demands on the respiratory system. At the same time, airway resistance is increased and muscle function is impaired.[72] Irrespective of whether pneumonia is the cause of sepsis, the common pulmonary endpoint is acute respiratory distress syndrome (ARDS).[73] ARDS is defined clinically (Box 136-2) and correlates with the pathologic finding of diffuse alveolar damage. The development of ARDS occurs 4 to 24 hours after radiographic abnormalities develop.[74] Because of alveolar-capillary membrane damage, fluid accumulates in the alveoli. Rather than being a diffuse disease, ARDS is a heterogeneous process that results in interspersed damaged and normal alveoli.

BOX 136-2 DEFINITION OF ACUTE RESPIRATORY DISTRESS SYNDROME

Impaired oxygenation, defined as a ratio of partial pressure of arterial oxygen to fractional inspired oxygen <200, irrespective of how much positive end-expiratory pressure is used
Bilateral pulmonary infiltrates on frontal chest radiograph
Pulmonary artery occlusion pressure ≤18 mm Hg or no clinical evidence of elevated left atrial pressures

Data from Bernard G, et al: The American-European Consensus Conference on ARDS: Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 149:818, 1994.

Gastrointestinal

The hollow viscus is significantly affected by the shock state. A prolonged ileus accompanies hypoperfusion and persists beyond the malperfused state. Splanchnic blood flow is dependent on mean arterial pressure because there is relatively little autoregulation. Therefore, hemodynamic dysfunction may have a profound effect on viscus metabolism.

Solid organ involvement is also common. Even in the previously normal host, elevations in aminotransferases and bilirubin are common early in sepsis, although frank hepatic failure is quite rare. The liver has also been implicated in the pathogenesis of sepsis; some of the mediators of sepsis are produced by the liver.[75]

Endocrine

The presence of an absolute or relative adrenal insufficiency is common in sepsis. Depending on the balance of circulating cytokines, augmentation or suppression of the hypothalamic-pituitary axis is possible. IL-1 and IL-6 both activate the hypothalamic-pituitary-adrenal axis. TNF-α and corticostatin depress pituitary function. Other factors that may contribute to adrenal insufficiency in sepsis include decreased blood flow to the adrenal cortex, decreased pituitary function, and decreased pituitary secretion of adrenocorticotropic hormone due to severe stress. As a result of these interactions, the hypothalamic thermoregulatory mechanism may be reset, and temperature lability may develop.

Hematologic

Sepsis causes abnormalities in many parts of the coagulation system. Endotoxin, TNF-α, and IL-1 are the key mediators. Pathologic activation of the extrinsic (tissue factor–dependent) pathway, protein C–protein S, and fibrinolysis lead to consumption of essential factors, causing disseminated intravascular coagulation (DIC). The activation of the coagulation cascade produces fibrin deposition and microvascular thrombi. If not corrected, these depositions can compromise organ perfusion and contribute to organ failure. Tissue factor expression on monocytes is increased. This results in fibrin deposition and perhaps contributes to an increased incidence of multiorgan failure due to microvascular thrombi. In one study, the degree of tissue factor expression was found to portend a poorer prognosis.[76]

Protein C has been identified as an important modulator of both inflammation and coagulation in patients with sepsis. Impairment of the protein C–dependent anticoagulation pathway is critical to the development of the thrombotic complications of sepsis.[77] In healthy humans, protein C is activated by a combination of thrombin and thrombomodulin. The activation of protein C results in down-regulation of many portions of the coagulation cascade, including release of tissue factor, inactivation of factor VIIIa and factor Va, and stimulation of fibrinolysis.[78] It is possible that protein C activation in early sepsis is impaired because of an inflammatory cytokine-mediated down-regulation of thrombomodulin. As a result, a consumptive coagulopathy ensues. This leads to increased fibrin deposition and a resulting up-regulation of the fibrinolytic pathway as identified by low plasma levels of the fibrinolytic proteins and increased fibrin-split products.[79] This sequence of events leads to consumption of coagulation factors and DIC. In late sepsis, the fibrinolytic system is suppressed.[80]

CLINICAL FEATURES

Symptoms and Signs

The approach to a patient with sepsis relies on identifying the presence of a systemic infection, as well as localizing the source of the initial infection. This allows for appropriate and aggressive directed treatment to the source of infection. Often, the source is not readily apparent, but early identification of the septic state allows implementation of broad-spectrum antibiotics that may be potentially lifesaving.

Patients with altered consciousness who are unable to protect their airway require intubation. Septic patients with severe tachypnea or hypoxia with impending respiratory failure also require intubation to allow positive pressure ventilation. Patients needing hemodynamic blood pressure support must be identified and rapidly and aggressively treated with fluids and vasopressor and inotropic support as needed.

The septic patient manifests signs of systemic infection through tachycardia, tachypnea, hyperthermia or hypothermia, and, if severe, hypotension. A septic patient will often have flushed skin with warm, well-perfused extremities secondary to the early vasodilation and hyperdynamic state. Alternatively, the severely hypoperfused patient with an advanced shock state may appear mottled and cyanotic. Very early in the patient's presentation, vital sign changes such as tachycardia and tachypnea may be the only early indicators of sepsis.

If the patient is in shock, a rapid assessment that excludes other causes, such as hypovolemic or cardiogenic shock, is essential to the proper initial treatment. A complete detailed clinical examination will help the physician determine the cause of the shock state (see Chapter 4). The aforementioned are "classic" signs; a septic patient may not manifest these findings, and signs and symptoms may be subtle. In evaluating the patient with septic shock, the cause must be considered: sepsis is a pathogenic insult resulting in a dysregulated inflammatory cascade with release of proinflammatory and anti-inflammatory mediators.

Both underlying comorbidities and the etiology of sepsis should be considered. In the evaluation of the septic patient. Risk factors, such as immunocompromised states (acquired immunodeficiency syndrome, malignancy, diabetes, splenectomy, and concurrent chemotherapy), older age, debilitation or high-risk environments for iatrogenic infections (such as long-term care facilities), and multiple comorbidities should be considered.

The respiratory system is the most common source of infection in the septic patient. A history of a productive cough, fevers, chills, upper respiratory symptoms, and throat and ear pain should be sought. Both the presence of pneumonia and the findings of tachypnea or hypoxia have been found to be predictors of death in patients with sepsis.[81] Physical examination should also include detailed evaluation for focal infection,

such as exudative tonsillitis, sinus tenderness, tympanic membrane injection, and crackles or dullness on lung auscultation. Also, pharyngeal thrush should be noticed as a potential marker of an immunocompromised state.

The gastrointestinal system is the second most common source of sepsis. A history of abdominal pain, including its description, location, timing, and modifying factors should be sought. Further history, including the time of the last bowel movement and the presence of nausea, vomiting, and diarrhea, should be noted. A careful physical examination, looking for signs of peritoneal irritation, abdominal tenderness, and hyperactive or hypoactive bowel sounds, is critical in identifying the source of abdominal sepsis. Particular attention must be paid to physical findings suggestive of common sources of infection or disease: Murphy's sign indicating cholecystitis, pain at McBurney's point indicating appendicitis, left lower quadrant pain suggesting diverticulitis, or rectal examination revealing a rectal abscess or prostatitis.

The neurologic system is examined by looking for signs of meningitis, including nuchal rigidity, fevers, and change in consciousness. A detailed neurologic examination is important. Lethargy or altered mentation may indicate primary neurologic disease or may be the result of decreased brain perfusion from a shock state.

The genitourinary history includes queries regarding the presence of flank pain, dysuria, polyuria, discharge, Foley catheter placement, and genitourinary instrumentation. A sexual history should assess for the risk of sexually transmitted diseases. Genitalia should be evaluated for ulcers, discharge, and penile or vulvar lesions, looking specifically for the woody induration of Fournier's gangrene. A rectal examination should be performed, looking for a tender, boggy prostate, consistent with prostatitis. A red and friable cervix, cervical discharge, or cervical motion tenderness is consistent with a sexually transmitted disease. Adnexal tenderness in a toxic-appearing female potentially represents a tubo-ovarian abscess.

Musculoskeletal history includes the presence of any localizing symptoms to a particular joint. Redness, swelling, and warmth over a joint, especially if there is a decreased range of motion in that joint, may be signs of septic arthritis and may mandate arthrocentesis. A patient should be completely exposed and the skin examined for evidence of cellulitis, abscess, wound infection, or traumatic injury. Deep injuries, foreign bodies, and fasciitis may be difficult to identify clinically. The physician should look for crepitus representing the presence of an aggressive, gas-forming organism. Local lymphadenopathy, swelling, and streaking should also be noted as signs of an advancing infection. Petechiae and purpura may represent a *Neisseria meningitidis* infection or DIC. Generalized erythroderma and rash may represent an exotoxin from pathogens such as *Staphylococcus aureus* or *Streptococcus pyogenes*.

A history of fevers or chills in the setting of intravenous drug abuse, an artificial heart valve, or mitral valve prolapse should increase the suspicion of endocarditis. The clinician should suspect endocarditis in the presence of a murmur or other stigmata of endocarditis (e.g., splinter hemorrhages, Roth's spots, Janeway lesions).

Clinicians must identify the severity of illness in patients with infection and initiate aggressive resuscitation for those patients with the potential of becoming critically ill. Although a patient may meet SIRS criteria, this alone has little predictive value in determining the severity of illness and mortality.[60] The Mortality in Emergency Department Sepsis (MEDS) score is a method to risk stratify ED patients with sepsis.[82] The MEDS prediction rule assigns point values to specific clinical characteristics (Table 136-1). The total score can be used to assess risk of death. Thus, the greater the number of risk factors, the more likely a patient is to die during the hospitalization.

Table 136-1 Mortality in Emergency Department Sepsis (MEDS) Prediction Rule

RISK FACTOR	ODDS RATIO FOR DEATH	MEDS SCORE
Terminal illness (death within 30 days)	6.1	6 points
Tachypnea or hypoxia	2.7	3 points
Septic shock	2.7	3 points
Platelet count < 150,000/min^3	2.5	3 points
Bands > 5%	2.3	3 points
Age > 65 years	2.2	3 points
Pneumonia	1.9	2 points
Nursing home resident	1.9	2 points
Altered mental status	1.6	2 points

RISK OF DEATH	TOTAL MEDS SCORE (% OF SEPSIS DEATHS)
Very low	0–4 (1.1%)
Low	5–7 (4.4%)
Moderate	8–12 (9.3%)
High	13–15 (16.1%)
Very high	>15 (39%)

DIAGNOSTIC STRATEGIES

The use of diagnostic testing in patients with sepsis syndromes or suspected syndromes serves two purposes. Diagnostic studies are used both to identify the type and location of the infecting organisms and to define the extent and severity of the infection to assist in focusing therapy. As a result, the diagnostic approach must be tailored to the particular patient.

Hematology

The white blood cell count is a marker of inflammation and activation of the inflammatory cascade. Leukocytosis is associated with infection and is incorporated in the consensus definition of sepsis; however, it is often insensitive and nonspecific, limiting its absolute utility in the ED. The febrile neutropenic patient has been shown to be at increased risk for severe infection. Thus, a white blood cell count of less than 500 cells/mm^3 should prompt admission, isolation, and empirical intravenous antibiotics in most chemotherapy patients. A bandemia (>10% bands on a peripheral smear) represents the release of immature cells from the bone marrow and is considered to be a sign of infection and inflammation. Like the white blood cell count, it is an imperfect indicator of infection. The absence of leukocytosis or bandemia does not preclude the possibility of severe sepsis, nor does their absence have any proven predictive value in determining mortality risk. The hemoglobin and hematocrit should be obtained to ensure adequate oxygen delivery in shock. Patients should be maintained with a hematocrit greater than 30% and hemoglobin greater than 10 g/dL. Platelets are an acute-phase reactant and may be elevated in the presence of infections. Conversely, a low platelet count has been found to be a significant predictor of bacteremia in patients with shock.[81,83,84] Thrombocytopenia, elevated pro-

thrombin time, an elevated activated partial thromboplastin time, decreased fibrinogen, and increased fibrin split products are associated with DIC and severe sepsis syndrome.

Chemistry

Electrolyte abnormalities should be identified and corrected. Low bicarbonate level suggests acidosis and inadequate perfusion. An elevated anion gap acidosis in the setting of sepsis syndrome commonly represents lactic acidosis or diabetic ketoacidosis, but other causes need to be ruled out. Elevated serum creatinine or decreased glomerular filtration rate is indicative of renal dysfunction or failure, which, if due primarily to sepsis, indicates organ failure and a worse prognosis. Calcium, magnesium, and phosphorus levels should be checked.

The presence of an elevated lactate level is associated with inadequate perfusion, shock, and a poorer prognosis.[85] One ED-based study showed a progression in mortality rate with increasing venous lactate level: a lactate level of 0 to 2.5 mg/dL was associated with a 5% mortality rate; a lactate level of 2.5 to 4.0 mg/dL, 9% mortality; and greater than 4 mg/dL, 28% mortality.[85] An arterial blood gas assessment may be helpful in identifying and classifying acid-base disturbances. Metabolic acidosis suggests inadequate tissue perfusion. Liver function tests can be used to identify liver failure or dysfunction. An elevated bilirubin level may suggest the gallbladder as a cause of sepsis. An elevated amylase and lipase level may represent pancreatitis as the cause of noninfectious SIRS.

Microbiology

Obtaining proper blood, sputum, urine, cerebrospinal fluid, and other tissue culture samples is important in guiding therapy. Although not helpful in the initial management, culture samples should be obtained before or soon after the administration of antibiotics in the patient with sepsis syndrome. The initiation of antibiotic therapy should not be delayed while waiting for culture samples to be obtained. One well-designed prospective study suggests the following factors as predictive of a positive blood culture: fever greater than 38.3 °C, the presence of a rapidly (<1 month) or ultimately (<5 years) fatal disease, shaking chills, intravenous drug abuse, acute abdomen, or major comorbidity.[4] These factors have not been validated in independent populations. The literature suggests that the yield of initial blood cultures is low (5–10%), but this is likely an artifact of the lack of reliable discriminatory guidelines for obtaining blood culture samples in the ED.[4,83,86,87] Among patients with clinical sepsis, only 30 to 60% of patients will have positive cultures.[5,8,15]

The results of initial microbiologic tests, including Gram's stains whenever possible, will help guide subsequent antibiotic treatment, but initial empirical therapy should be broad spectrum to allow for early treatment of all likely organisms.

Special Procedures

The comprehensive protocol of early goal-directed therapy published by Rivers and associates[88] showed that a resuscitation strategy guided by central venous pressure (CVP), an arterial line, and a central venous catheter with continuous central venous oxygen saturation ($ScvO_2$) monitoring capability can reduce mortality in patients with sepsis. However, whether each of these components is mandatory is unclear. A CVP line may guide fluid resuscitation, with a low CVP indicating the need for continued fluid repletion. The goal CVP is 8 to 12 mm Hg in patients not on mechanical ventilation, and 12 to 16 mm Hg in patients who are ventilated. The $ScvO_2$ monitor measures venous blood saturation, which is a marker of tissue metabolism and extraction. It has been suggested that intermittent monitoring of $ScvO_2$ may suffice, although there are no firm data to support this. The goal is to ensure proper tissue oxygenation, which is routinely achieved by adjusting oxygen delivery, keeping the $ScvO_2$ greater than 70%. An arterial line can be useful for close monitoring of hypotensive patients, especially when one or more vasopressors are being titrated to maintain an adequate blood pressure; however, it is not necessarily mandatory. Finally, the Swan-Ganz catheter is not a mandatory part of the ED management, although the physiologic measurements may be useful in identifying the cause of shock and guiding fluid and inotropic therapy. Low systemic vascular resistance and high cardiac output are most commonly associated with sepsis, although this may vary with the stage of shock and the individual patient. There is literature that indicates that the use of Swan-Ganz catheters does not substantially impact mortality.[89]

Radiology

A chest radiograph should be obtained in all patients with suspected sepsis syndrome, looking not only for a focal infiltrate representing pneumonia but also for the fluffy, bilateral infiltrates indicative of ARDS. The pathophysiology of ARDS is often delayed as much as 24 hours after radiographic identification. An upright chest radiograph should be obtained for suspected bowel perforation to detect free air under the diaphragm. The presence of pneumomediastinum is suggestive of esophageal perforation and current or impending mediastinitis.

Soft tissue plain radiographs of infected areas should be obtained, looking for air in the soft tissues associated with necrotizing or gas-forming infection. Periosteal thickening or bone erosion may be seen on plain radiographs of patients with osteomyelitis; a bone scan may be diagnostic. Computed tomography (CT) of superficial infections may be helpful to further quantify the extent of infection and to identify abscesses that are not readily evident on physical examination. A CT scan of the abdomen and pelvis may identify abdominal or pelvic pathologic lesions, provided there is no clear clinical indication for immediate operative intervention. Suspected diseases such as diverticulitis, appendicitis, necrotizing pancreatitis, microperforation of the stomach or bowel, or formation of an intra-abdominal abscess may be best diagnosed by CT scan. A head CT scan can identify septic emboli from endocarditis or increased intracranial pressure from a mass and should be considered before a lumbar puncture is performed. An abdominal ultrasonogram may be indicated for suspected cholecystitis, and a pelvic ultrasonogram for tubo-ovarian abscess or endometritis. A transesophageal echogram should be obtained if endocarditis is suspected to detect the presence of any valvular vegetations. A magnetic resonance imaging scan can be useful to identify soft tissue infections such as necrotizing fasciitis or epidural abscess.

DIFFERENTIAL CONSIDERATIONS

The sepsis syndromes represent a spectrum of disease and clinical presentation. SIRS is defined by hemodynamic and laboratory parameters alone, whereas sepsis must include a suspected infectious cause. Often, noninfectious sources can cause a syndrome that mimics sepsis; thus, one must keep in mind a broad differential diagnosis when approaching these patients (Box 136-3). A detailed history and physical examination are always the first step in narrowing the differential diagnosis to identify the true source.

BOX 136-3 DIFFERENTIAL CONSIDERATIONS FOR SEPSIS AND SEPTIC SHOCK

Sepsis	Septic Shock
Dehydration	Hypovolemic shock
Acute respiratory distress syndrome	Acute blood loss
Anemia	Severe dehydration
Ischemia	Cardiogenic shock
Hypoxia	Pulmonary embolus
Congestive heart failure	Myocardial infarction
Vasculitis	Pericardial tamponade
Toxicologic	Tension pneumothorax
Poisonings	Vasogenic shock
Overdose	Anaphylaxis
Drug-induced	Paralysis
Pancreatitis	
Hypothalamic injury	
Disseminated intravascular coagulation	
Anaphylaxis	
Metabolic	
Hyperthyroidism	
Diabetic ketoacidosis	
Adrenal dysfunction	
Environmental	
Burn	
Heat exhaustion/stroke	
Trauma	
Blood loss	
Cardiac contusion	
Neuroleptic malignant syndrome	

MANAGEMENT

Early detection and aggressive management can significantly reduce the chance of mortality from sepsis. Antimicrobial therapy and maintenance of adequate tissue oxygenation and perfusion remains the primary goal, but the means by which this is achieved has changed substantially in the past years. With the advent of early goal-directed therapy[88] and therapies such as drotrecogin alfa targeting the cascade leading to septic shock,[90] there is increasing evidence that the natural history of sepsis can be altered. Initial resuscitation, including appropriate airway management, intravenous access, oxygen, early and appropriate antibiotics, and fluid resuscitation remain the foundation on which new efforts may be applied.

In the study by Rivers and associates,[88] a protocol for early and aggressive care was used to guide resuscitation in the ED. This randomized, double-blind, placebo-controlled study showed a 16% mortality reduction in patients with severe sepsis and septic shock. The protocol measures targeted "goals" and uses a resuscitation algorithm to facilitate an aggressive and early resuscitation. The use of this strategy has been endorsed by the Surviving Sepsis Campaign, an 11-organization international consensus panel.[91] The recommendation is for the use of goal-directed therapy on all patients who have: (1) suspected infection, (2) two or more SIRS criteria, and (3) evidence of hypoperfusion signified by either a systolic blood pressure of less than 90 mm Hg after 20 to 30 mL/kg fluid challenge or a lactic acid level greater than 4 mmol/dL (Fig. 136-3). The theory behind the protocol is to normalize preload and pressure and to prevent tissue hypoxia by matching oxygen delivery with consumption.

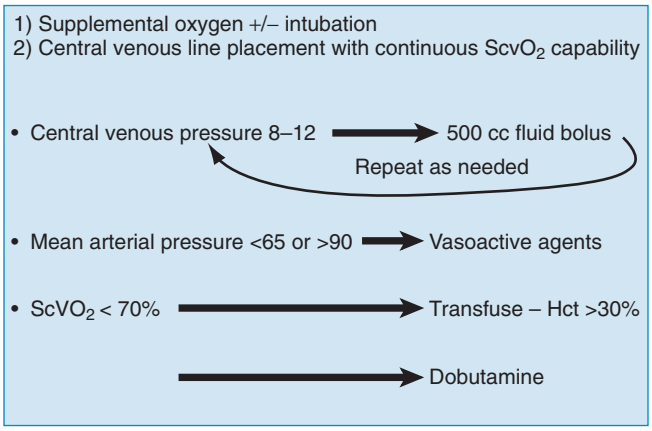


Figure 136-3. Summary of goal-directed therapy protocol.

Preload

The first step in goal-directed therapy is to provide a proper filling pressure to ensure adequate cardiac preload. Patients in sepsis and septic shock are often in a state of substantial fluid deficit. Rivers and colleagues showed that patients required an average of 5 L of fluids in the first 6 hours of their resuscitation. A CVP measurement should be obtained, and the patients should receive crystalloid or colloid resuscitation to keep the CVP at a level of 8 to 12 mm Hg. In intubated patients with positive pressure ventilation, pathophysiologic principles support raising the target level to 12 to 16 mm Hg.

Perfusion Pressure

The next step in goal-directed therapy is to maintain an adequate blood pressure. A mean arterial blood pressure (⅔ diastolic + ⅓ systolic) should be kept between 60 and 90 mm Hg. If the mean arterial blood pressure is below 65 mm Hg in the presence of adequate preload, treatment with a vasopressor agent should be started, with norepinephrine or dopamine being considered first-line agents.

Oxygen Delivery

The initial management of all critically ill patients should include adequate supplemental oxygen to provide adequate peripheral oxygen saturation. In the adult patient, continuous peripheral oxygen saturation monitoring should be implemented and supplemental oxygen should be provided to maintain a saturation of 95% or the patient's baseline in the case of underlying lung disease. Once preload and pressure are normalized, the next focus is on oxygen delivery. A mixed venous saturation assessment can be used to guide this part of the resuscitation. Organ hypoperfusion is a result of global and distributive changes in both systemic blood flow and the microvasculature. As a result of marrow suppression and dilution with crystalloid fluids, many patients with sepsis have a hemoglobin between 8 and 10 g/dL after initial resuscitation. A hematocrit between 27 and 30% has been reported to be most effective,[92] although other studies challenge this dogma.[93–96]

The goal is to maintain a mixed venous saturation ($ScvO_2$) greater than 70%. As oxygen demand due to sepsis increases, the $ScvO_2$ starts to fall below 70%. This must be corrected by first ensuring that preload and pressure are adequate. Next, the arterial oxygen saturation should be optimized with nonrebreather oxygen delivery or intubation, as needed. Once these are optimized, one should ensure that the patient has

adequate oxygen-carrying capacity by transfusing the patient to a hematocrit greater than 30%. If this is normalized, and the patient is not tachycardic, dobutamine can be added to increase cardiac contractility and increase cardiac output, resulting in an overall improved oxygen delivery. The protocol should be run continuously with an effort toward normalizing the parameters during the entire resuscitation (Table 136-2).

Respiratory Support

Altered mental status is common in patients in septic shock, and they may require rapid airway protection. Patients with a respiratory rate greater than 30 breaths per minute are likely to develop respiratory collapse, irrespective of arterial oxygenation. Wheeler and coworkers[97] reported that 85% of patients with "severe sepsis" require mechanical ventilation during their hospital course. Because patients with impending respiratory failure use a disproportionately large amount of energy for the muscles of respiration, improved oxygen delivery to other organs is achieved by mechanical ventilation, sedation, and paralysis. Although there are no clear intubation guidelines, hypercapnia, persistent hypoxemia, airway compromise, and profound acidosis are valid indicators.

In addition to airway protection, intubation and mechanical ventilatory support provide positive pressure ventilation. The pattern of injury is such that normal lung parenchyma is adjacent to affected tissue. Therefore, increased airway pressures are required to maintain normal oxygen delivery. Current recommendations are to maintain transalveolar pressures (measured as plateau pressures) below 35 cm H_2O, because increased pressures are associated with ventilator-induced lung injury.[98,99] Maintaining relatively low transalveolar pressure with increasing end-expiratory pressure is an effective way to increase arterial oxygen delivery.[100,101] The ArdsNet trial established the benefit of low tidal volumes in acute lung injury (6 mL/kg), which has translated to a recommended approach of lower tidal volumes in the routine mechanically intubated patients in order to prevent subsequent iatrogenic lung damage.[101]

Table 136-2 Management Recommendations for Hemodynamic Support

Basic Principles

Admission to intensive care unit

Arterial cannulation in patients with shock, although insertion may not be practical in the emergency department

Resuscitation to target tissue perfusion

Central venous or pulmonary arterial catheter placement to assess cardiac filling pressures

Fluid Resuscitation

Fluids are the primary modality to resuscitation*

Colloids and crystalloids are equally effective*

Invasive monitoring for patients not responding to initial resuscitation with target pulmonary capillary wedge pressure of 12 to 15 mm Hg†

Hemoglobin concentrations should be maintained above 8 to 10 g/dL†

Vasopressor Therapy

Dopamine is the first-line agent in shock unresponsive to aggressive fluid resuscitation‡

Dopamine and norepinephrine are equally effective and can be used together†

Phenylephrine is an alternative, but decreased stroke volume may be associated with worse outcome*

Epinephrine is reserved for refractory hypotension†

Routine low-dose (≤5 μg/kg/min) dopamine is not recommended§

Vasopressin may be considered in refractory shock not responsive to aggressive fluid resuscitation and high-dose conventional vasopressors‡

Inotropic Therapy

Dobutamine is the first choice for patients with refractory low cardiac index‡

Dobutamine may improve cardiac index and organ perfusion, but empiric use is not recommended†

Vasopressors and inotropes can be titrated separately to maintain mean arterial pressure and cardiac output†

Epinephrine and dopamine can be used as inotropes, but splanchnic perfusion may be compromised*

*Supported by small randomized trials with uncertain results.
†Supported by at least one contemporaneous nonrandomized trial.
‡Supported by nonrandomized trials with historical controls and expert opinion or case series.[75,86]
§Supported by one randomized, controlled trial with clear results.
Data from Hollenberg S, et al: Practice parameters for hemodynamic support of sepsis in adult patients with sepsis. Crit Care Med 27:639, 1999.

Cardiovascular Support

Fluid Resuscitation

Patients with sepsis often require large volumes of intravenous fluid to maintain adequate perfusion.[102] The primary reasons for this intravascular hypovolemia are venodilation and diffuse capillary leak.[103] Initial therapy for adults with septic shock should generally be 2 L of isotonic crystalloid. As much as 6 to 10 L of crystalloid may be required in the first 24 hours.[102] Early goal-directed therapy has been shown to be an effective way to guide fluid resuscitation and should be considered in all cases of septic shock. In less critically ill patients, fluid replacement should be titrated to clinical parameters such as heart rate, blood pressure, change in mental status, capillary refill, cool skin, and adequate urine output (0.5–1 mL/kg/hr). Normal (0.9%) saline and Ringer's lactate solution are equally effective and neither worsens lactic acidosis. Colloids are as effective as crystalloids, but they are far more expensive. Experience with hypertonic saline is limited, and no recommendation on its use can be made based on current literature.[104] There have been recent efforts to identify ways to measure regional perfusion more directly. In particular, direct measurement of splanchnic blood flow has been proposed. Even in the absence of global hypoxia and impaired tissue perfusion, there is evidence that regional hypoperfusion and ischemia exist.[105] Although further study is necessary, there is early evidence that therapy guided toward maintaining splanchnic perfusion can decrease the rate of mortality.[106]

Vasopressors

If appropriate fluid resuscitation has failed, vasopressor support may be required (Table 136-3). Only in cases of profound hypotension should vasopressors be started before adequate fluid resuscitation. Using mean arterial pressure alone as an

Table 136-3 Dosing of Vasoactive Therapy

DRUG	DOSAGE
Dobutamine	5–15 μg/kg/min
Dopamine	2–20 μg/kg/min
Epinephrine	5–20 μg/min
Norepinephrine	5–20 μg/min
Phenylephrine	2–20 μg/min

indicator of overall efficacy of therapeutic intervention is not helpful.[107] A mean arterial pressure of 65 mm Hg has been recommended in otherwise healthy, normovolemic adult patients but must be correlated with other indicators of adequate perfusion, such as mental status and urine output.[108] Patients with previously uncontrolled hypertension may require mean arterial pressures of 75 mm Hg or even higher.

The 2008 Surviving Sepsis Campaign guidelines provide consensus recommendations for treatment of septic shock.[91] Fluid resuscitation remains the fundamental treatment option and should not be foregone. Dopamine or norepinephrine should be used as the initial vasopressor with the addition of vasopressin to norepinephrine as a reasonable adjunct. Vasopressin alone has been shown to be ineffective compared to norepinephrine in the initial treatment of refractory septic shock.[109] Epinephrine should be considered as a supplemental agent if dopamine or norepinephrine are ineffective. Dobutamine should be used as the primary inotropic agent if myocardial dysfunction is evident.[91]

Norepinephrine

Norepinephrine is a mixed alpha- and beta-agonist with minimal $beta_2$ activity. Its primary function is to increase cardiac output and systemic vascular resistance. Along with dopamine, it is considered a first-line agent. Although there are no definitive outcomes studies, it is gaining popularity as a vasopressor of choice for the treatment of septic shock. Its physiologic properties, along with some small studies using hemodynamic outcomes, make it a sensible choice. At least one controlled trial showed norepinephrine to be more effective than dopamine at reversing hypotension for at least 6 hours.[110] There was no difference between norepinephrine and dopamine in terms of adverse events. When compared with dopamine in septic patients, norepinephrine increases glomerular filtration and urine output equally well.[111–113] Norepinephrine has been studied as a rescue drug to dopamine and has produced consistent, replicated improvement in hemodynamics, although reduced mortality has not been shown. It is an important component of the therapy for septic shock, either as a sole vasopressor or in conjunction with dopamine.[104] Recommended doses are from 0.5 to 3 μg/min.

Dopamine

Dopamine is also a first-line agent used for septic shock that is unresponsive to adequate volume expansion. Dopamine is the immediate precursor of norepinephrine and epinephrine. It is primarily an alpha, $beta_1$, and dopaminergic agonist. Although low doses alone are not effective, they may be effective in combination with other agents. "Renal-dose" dopamine has not been shown to reduce mortality or decrease dialysis dependence and should not be used.[114,115] Dosages greater than 20 μg/kg/min may produce significant vasoconstriction. Persistent tachycardia, decreased partial pressure of arterial oxygen (Pao_2), and increased pulmonary artery occlusion pressure are common side effects of dopamine use. Dopamine has been shown to increase oxygen delivery better than other catecholamines.[116,117] Based on its mechanism of action, it is most useful in patients who have depressed cardiac output.

Phenylephrine

Phenylephrine is a selective $alpha_1$-agonist, increasing systemic vascular resistance without significant changes in cardiac output. It can produce a reflexive bradycardia or suppression in cardiac output. A single small study has shown that phenylephrine is effective in restoring perfusion in patients with septic shock refractory to dopamine or dobutamine.[118] Phenylephrine does not impair cardiac and renal function and may be a good choice when significant tachyarrhythmia limits the use of other agents.[104]

Epinephrine

Epinephrine a very potent mixed alpha and beta agonist. Epinephrine infusion is also associated with increased oxygen consumption, increased systemic lactate concentrations, and decreased splanchnic blood flow. Studies have shown that the rise in lactate is short-term and there is no evidence regarding the long-term effects.[119,120] As a result of all of the possible adverse effects of epinephrine, it is currently recommended only for those patients who are unresponsive to other vasopressors.

Vasopressin

Vasopressin is a naturally occurring nonapeptide that is synthesized as a large prohormone in the hypothalamus. In states of septic shock, there is an early surge of vasopressin followed by a profound drop in circulating vasopressin levels.[52] This is the foundation for using vasopressin as an adjunct therapy for patients with severe sepsis. Vasopressin should not be used as the sole initial therapy for refractory septic shock.[109] In a well-designed randomized trial, investigators demonstrated no change in mortality for patients with severe sepsis when vasopressin was added to catecholamine vasopressors.

Inotropic Agents

Dobutamine

Dobutamine is a mixed alpha- and beta-agonist. In dosage ranges from 2 to 28 μg/kg/min, cardiac index is increased at the expense of heart rate. In addition, decreased splanchnic blood flow is common.[121] Its use should be reserved for patients with depressed cardiac index and persistent hypoperfusion in spite of adequate volume expansion and other vasopressor agents. In patients undergoing formal early goal-directed therapy, when preload, perfusion pressure, and oxygen-carrying capacity have been normalized, and a low $ScvO_2$ persists, dobutamine is used to increase cardiac output and oxygen delivery.

Bicarbonate

Bicarbonate supplementation was previously the standard of care for patients with presumed lactic acidosis. Current consensus is that it should be reserved for severe acidemia (pH < 7.0–7.2), as there may be a paradoxical decrease in intracellular pH as a result of diffusion of soluble CO_2 across the cell membrane. Alternatively, hyperventilation has been suggested to help increase systemic pH.[107]

Antibiotics

Early and appropriate antibiotic therapy should target the nidus of infection; this reduces mortality, perhaps by as much as 30 to 50%.[122–124] If the patient's condition permits, appropriate cultures should be drawn before the administration of broad-spectrum antibiotics (Table 136-4). Surgically correctable conditions, such as intra-abdominal abscesses, perforated viscus, retained products of conception, or retained foreign body (such as a tampon), should be treated concurrently.

Table 136-4 Suggested Initial Antibiotic Management Pending Microbiologic Identification of Organism and Sensitivity

INFECTION	MODIFYING FACTORS	ANTIBIOTIC
Sepsis, unknown source	Immunocompetent	Antipseudomonal cephalosporin *plus* aminoglycoside or fluoroquinolone; *or* antipseudomonal penicillin *plus* aminoglycoside or fluoroquinolone; *or* carbapenem *plus* aminoglycoside or fluoroquinolone
	Anaerobic infection	Add metronidazole or clindamycin to above regimen
	Methicillin-resistant *Staphylococcus aureus* (MRSA)	Add vancomycin to above regimen
	Neutropenia	Antipseudomonal penicillin *plus* aminoglycoside or fluoroquinolone; *or* carbapenem *plus* aminoglycoside or fluoroquinolone
	Splenectomy	Cefotaxime *or* ceftriaxone
	HIV infection	Ticarcillin-clavulanate *plus* tobramycin
Pneumonia	Immunocompetent	Second- or third-generation cephalosporin *plus* second-generation macrolide *or* fluoroquinolone
	Legionella suspected	Azithromycin or fluoroquinolone or high-dose erythromycin
Abdominal infection	Immunocompetent	Ampicillin *plus* aminoglycoside *plus* metronidazole
	Multidrug-resistant organism suspected	Ticarcillin/clavulanate carbapenem; *or* piperacillin/tazobactam *plus* aminoglycoside
	Urinary tract source	Fluoroquinolone; *or* third-generation cephalosporin; *or* ampicillin *plus* aminoglycoside
Cellulitis	Non-necrotizing fasciitis	Cefazolin *or* nafcillin
	MRSA possible	Vancomycin
	Necrotizing fasciitis (surgical drainage)	Ampicillin/sulbactam; *or* ticarcillin/clavulanate; *or* piperacillin *plus* aminoglycoside *plus* clindamycin; *or* carbapenem
IV catheter infection (remove catheter)	Outpatient acquired	Third-generation cephalosporin
	MRSA suspected	Add vancomycin
	Fungal infection	Amphotericin B
Cerebrospinal infection	Immunocompetent	Ceftriaxone *plus* vancomycin
	Elders or immunocompromised	Add ampicillin
Intravenous drug abuse	MRSA not suspected	Nafcillin *plus* aminoglycoside
	MRSA suspected	Vancomycin *plus* aminoglycoside

In the absence of an obvious source of infection, the use of broad-spectrum antibiotics is recommended. The specific agent depends on many variables, including institutional preference and local resistance patterns. As results from cultures become available, therapy should be modified. There is no consensus about the need for double or triple antibiotic coverage for particular organisms, although it is common practice to double-cover virulent organisms, such as *P. aeruginosa*, as well as areas that are commonly infected with multiple organisms such as the peritoneum. And, with increasing rates of methicillin-resistant organisms, combinations that include nonpenicillin choices may be warranted.

Novel Therapies

Activated Protein C

After years of unsuccessful, large-scale, multicenter trials of novel therapeutic agents for sepsis, recombinant activated protein C (APC) became the first therapy to be approved by the Food and Drug Administration (FDA) for the treatment of sepsis. APC was shown to improve survival by 6.1% in patients with severe sepsis.[90] This benefit is realized most in patients who are more severely ill, as characterized by an APACHE II score greater than 25. The FDA has approved APC for use in this group only. A recent cost-benefit analysis estimated the cost per life-year saved by APC to be $27,936 in all patients.[125] When stratified by severity of illness, the cost-benefit in patients with an APACHE II score less than 25 is $24,484 per life-year saved; for those with an APACHE II score greater than 25, it is $575,054 per life-year saved. Although its use primarily occurs in the intensive care unit, patient selection can begin in the ED. Additionally, an emphasis continues to be placed on early intervention in the appropriate patient to enhance its benefit. However, recent negative trials in a lower-risk adult population and a pediatric population both raise some doubts about the efficacy of the medication and emphasize the need to optimize the risk : benefit ratio by targeting more critically ill patients who are likely to receive the most benefit from therapy.

Steroid Therapy

It has been nearly 30 years since the first treatment attempts to block inflammation in sepsis. Because sepsis involves a systemic inflammatory response, corticosteroids are a logical treatment modality as anti-inflammatory agents. Physicians have been working for decades to prove or disprove their value. A large study in the mid-1980s conducted by the Veterans Administration Systemic Sepsis Cooperative Study Group found no reduction in mortality among patients receiving early methylprednisolone therapy.[126] Bone and associates[127] also studied the use of methylprednisolone in patients with sepsis and found increased mortality in those patients who were randomized to the steroid arm. Briegel and associates showed decreased time of vasopressor therapy with stress doses of hydrocortisone but no reduction in mortality.[128]

Annane and associates[129] performed a randomized, double-blind, placebo-controlled study of 300 patients with septic shock that demonstrated benefit when steroids (hydrocortisone, 50 mg IV every 6 hours, plus fludrocortisone, 50 µg each

day) were given to nonresponders in a corticotropin stimulation test. Among nonresponders, those treated with steroids had a 53% mortality rate, compared to 63% in the placebo group, for a 10% absolute benefit. Steroid therapy was not beneficial to those who responded to the corticotropin stimulation test. Marik and Zaloga[130] asserted that an initial random cortisol level of less than 25 µg/dL should be used to determine adrenal insufficiency. However, a recent large-scale multicenter validation failed to show a statistically significant improvement in mortality in both all-comers with septic shock as well as those with adrenal suppression.[131] Steroids were more effective in reducing the amount of time patients spent hypotensive, but the rates of secondary infection increased, contributing to a null effect overall. At this time, with somewhat conflicting data, the utility of steroids in sepsis remains controversial and should be reserved for cases where the risk of cardiovascular collapse from refractory hypotension due to adrenal suppression outweighs the risk of increased morbidity and mortality from secondary infection.

Disposition

Once the ED management is complete, antibiotics are given, and the need for emergency operative intervention or procedure has been excluded, patients who are deemed at increased risk should be admitted to the hospital. Patients with septic shock should be admitted to an intensive care unit, and those with one of the other sepsis syndromes can be admitted to a monitored floor with close supervision or an intensive care unit, as needed.

KEY CONCEPTS

- Sepsis is a progression of disease due to a dysregulated inflammatory cascade, leading to organ dysfunction and circulatory compromise in severe cases.
- Elders, immunocompromised and neutropenic patients, and patients with multiple comorbidities are at increased risk for development of sepsis syndromes.
- Early goal-directed therapy can improve the outcome of patients with sepsis. Treatment should focus on (1) improving tissue perfusion (through administration of fluids and vasopressor medications), (2) improving tissue oxygenation (through administration of oxygen and positive pressure ventilation), (3) administration of appropriate antibiotics, and (4) early identification of infections requiring surgical management.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

PART IV

Environment and Toxicology

CHAPTER 137 Frostbite

Daniel F. Danzl

PERSPECTIVE

Peripheral cold injuries occur primarily in humans. The highest homeostatic priority is to maintain the body's core temperature. This is accomplished through vasoconstriction and shunting, which prevents adequate heat distribution to the extremities. As a result, failure to achieve adequate protection from the environment results in injuries that are usually preventable.[1–4]

Peripheral cold injuries include both freezing and nonfreezing syndromes, which may occur independently or in conjunction with systemic hypothermia.[5] Frostbite is the most common freezing injury.[6] Trench foot and immersion foot are nonfreezing injuries that result from exposure to wet cold.[7] Nonfreezing injury that usually occurs after exposure to dry cold is termed *chilblains* (pernio).

The incidence and severity of frostbite correlate with the predisposing factors associated with the cold stress. Most cases of civilian frostbite result from routine exposure to cold by individuals who have not given due consideration to risk factors for cold injury.[8–10] Well-equipped treks up the world's highest peaks have been completed without cold injury when appropriate steps are taken to address these factors.[11] Current trends show an increase in outdoor recreational activities that produce exposure to unanticipated drastic climatic changes.[12,13] Unsheltered and homeless people are no longer the most likely group at risk.

Military history is replete with accounts of the effects of cold injury on combat troops.[14,15] Amputations and time lost to local cold injuries in both World Wars and the Korean conflict were extensive. Trench foot was particularly common among the Royal Marines in the Falkland Islands and United States troops in the Vietnam War.

Napoleon's Surgeon General, Baron de Larrey, first recorded the disastrous effects of the freeze-thaw-refreeze cycle.[16] During the 1812 to 1813 Russian invasion and retreat, soldiers would acutely thaw frozen extremities directly over open fires. The subsequent refreeze further increased tissue destruction. Unfortunately, the resultant gangrene was misattributed to this rapid thawing of frostbite and trench foot injuries. Therefore, gradual thawing, often including friction massage with snow, remained the standard treatment regimen until the 1950s.[17,18] In addition to dry radiant heat rewarming and massage, another misdirected rewarming modality was immersion thawing in icy water. In 1961, Mills ultimately popularized rapid warm immersion rewarming after extensive experience with severe Alaskan frostbite cases.[18,19]

PRINCIPLES OF DISEASE

Physiology

Human cold stress should induce adaptive behavioral reactions such as an attempt to find heat or shelter. In addition, complex endocrinologic and cardiovascular physiologic responses are engaged. Peripheral cooling of the blood activates the preoptic anterior hypothalamus. This central thermostat orchestrates temperature regulation. This dynamic process encompasses catecholamine release, thyroid stimulation, shivering thermogenesis, and peripheral vasoconstriction.

Cutaneous circulation is one of the keys to maintaining thermoneutrality. Baseline cutaneous circulation greatly exceeds the nutritional requirements. This reflects the skin's "radiator" function to maintain thermostability. Cutaneous blood flow in the euthermic 70-kg human averages 200 to 250 mL/min. Heat stress causes vasodilation that can increase this amount to 7000 mL/min. In contrast, extreme cold-induced vasoconstriction reduces flow 10-fold to less than 50 mL/min.

During cold stress, peripheral vasoconstriction limits radiant heat loss. Acral skin structures (fingers, toes, ears, nose) contain a plethora of arteriovenous anastomoses. These facilitate shunting and subsequent drastic reductions in blood flow to these areas. This "life-versus-limb" mechanism reflects the homeostatic attempt to prevent systemic hypothermia.

In contrast to heat exposure, humans do not appear to display significant physiologic adaptation to the cold. Exposing extremities to temperatures down to 15° C results in maximal peripheral vasoconstriction with minimal blood flow. Continued exposure to progressively colder temperatures down to 10° C produces the "hunting response," which is termed *cold-induced vasodilation*.[20] These periods of vasodilation, recurring in 5- to 10-minute cycles, interrupt vasoconstriction and serve to protect the extremity. Eskimos, as well as Lapps and others of Nordic extraction, are capable of stronger cold-induced vasodilation than individuals from tropical regions. Measuring the speed of cold-induced vasodilation may help predict an individual's risk for cold injury.[21]

Pathophysiology

The pathologic phases that occur with local cold injury often overlap and vary with the extent and rapidity of the cold response (Box 137-1). Frostbite occurs when the tissue temperature drops to less than 0° C. There are two putative

BOX 137-1 FREEZING INJURY CASCADE

Prefreeze phase
- Superficial tissue "cooling"
- Increased viscosity of vascular contents
- Microvascular constriction
- Endothelial plasma leakage

Freeze-thaw phase
- *Extra*cellular fluid ice crystal formation*
- Water diapedesis across cell membrane
- *Intra*cellular dehydration and hyperosmolality
- Cell membrane denaturation or disruption
- Cell shrinkage and collapse

Vascular stasis and progressive ischemia
- Vasospasticity and stasis coagulation
- Arteriovenous shunting
- Vascular endothelial cell damage or prostanoid release
- Interstitial leakage or tissue hypertension
- Necrosis, demarcation, mummification, or slough

*Extremely rapid cooling produces more initial intracellular than extracellular ice crystallization.

mechanisms of tissue injury: architectural cellular damage from ice crystal formation and microvascular thrombosis and stasis.

In the *prefreeze* phase, tissue temperatures drop below 10° C and cutaneous sensation is lost. Before ice crystal formation, microvascular vasoconstriction occurs along with endothelial leakage of plasma into the interstitium. Radiation and conduction of heat from deeper tissues prevent crystallization until the skin temperature drops well below 0° C.

In the *freeze-thaw* phase, the timing, location, and rate of ice crystal formation depend on the exposure circumstances. In addition to ambient temperatures, wind and moisture increase the freezing rate. Skin must cool below 0° C to freeze because of the underlying radiation of heat.

During usual exposure conditions, ice crystal formation initially occurs extracellularly. This results in diapedesis of water exiting the cell to maintain osmotic equilibrium. Cellular dehydration increases the intracellular osmolarity and electrolyte concentrations. When approximately one third of the cellular volume is lost, cellular collapse and death result. This may occur with or without direct architectural damage from the crystals. Extracellular crystallization also increases the tissue pressure on cell membranes and surrounding vascular structures. Sludging, stasis, and cessation of flow are initiated at the capillary level.

The third phase, progressive microvascular collapse, first affects venules and then arterioles. Red blood cells sludge and form microthrombi during the first few hours after the tissues are thawed. Factors adversely affecting flow include hypoxic vasospasm, hyperviscosity, and direct endothelial cell damage. Anaerobic metabolism subsequently extends the surrounding injury. Tissues are deprived of nutrients and oxygen. Ultimately, plasma leakage and arteriovenous shunting result in thrombosis, increased tissue pressure, ischemia, and necrosis.

Some direct skin injury is reversible. For example, frozen skin grafted to a normal site can survive. Zones immediately surrounding injured areas are potentially salvageable. The histopathology of frostbite suggests that some changes in the epidermis are primary and some reflect damage to the endothelial cells. During initiation of rewarming, these tissues are revitalized.

An additional insult, progressive dermal ischemia, is partially mediated by thromboxane.[22] Fluid analysis of clear vesicles identifies prostaglandins. When subdermal vascular plexi are injured, hemorrhagic blisters develop that also contain these prostanoids. The arachidonic acid breakdown products released from underlying damaged tissue into the blister fluid include both prostaglandins and thromboxane. These mediators produce platelet aggregation, vasoconstriction, and leukocyte immobilization.[23]

The ultimate determinant of progressive tissue damage appears to be injury to the microvasculature. Endothelial cells are the tissue most susceptible to freezing injury. After thawing, the vasculature is patent only temporarily. Platelet and erythrocyte aggregates promptly clog and distort the vasculature. Intense vasoconstriction coupled with arteriovenous shunting occurs at the interface between normal and damaged tissue. The injured viable vasculature remains distorted. Local arteritis, medial degeneration, and intimal proliferative thickening are seen. Nerve and muscle tissues are also more susceptible to cold injury than connective tissue. For example, nonviable hands and feet can be moved after thawing if the tendons are intact.

Edema progresses for 48 to 72 hours after tissue has been thawed. Leukocyte infiltration, thrombosis, and early necrosis become apparent as this edema resolves. The dry gangrene carapace of frostbite is superficial in comparison to arteriosclerotic-induced, full-thickness gangrene. Final clinical demarcation between viable and nonviable tissue can require more than 60 to 90 days, hence the historical surgical aphorism, "Frostbite in January, amputate in July."[19] Advances in imaging modalities can accelerate the identification of demarcation.

Predisposing Factors

The extent of peripheral cold injury is determined by the type and duration of cold contact with the skin[24,25] (Box 137-2).

Any conditions affecting judgment can jeopardize the physiologically tropical human. In urban settings, cold injuries are often attributed to overt or covert risk taking or psychiatric impairment or ingestion of intoxicants. Ethanol also produces peripheral vasodilation, which increases heat loss. Whenever self-protective instincts are blunted, appropriate adaptive maneuvers may not be undertaken.

Direct skin contact with good thermal conductors such as metal, water, and volatile liquids affects the extent and rapidity of tissue destruction. Commercial aerosol spray propellants such as propane and butane are potentially hazardous. One passenger on a commercial airline flight suffered a full-thickness lumbar injury from a "cold pack" provided by the stewardess that contained dry ice.[24–26] Overenthusiastic application of standard ice packs while treating soft tissue injuries can also result in tissue loss.[27] Although air alone is a poor thermal conductor, associated cold and wind (wind chill index) markedly increase heat loss.

■ CLINICAL FEATURES

Symptoms and Signs

"Frostnip" is a superficial cold insult manifested by transient numbness and tingling that resolves after rewarming. This does not represent true frostbite, because no tissue destruction occurs.

The symptoms of frostbite usually reflect the severity of the exposure. The most common presenting symptom is numbness, present in more than 75% of patients. All patients

BOX 137-2 PREDISPOSING FACTORS

Physiologic
Genetic
Core temperature
Previous cold injury
Acclimatization
Dehydration
Overexertion
Trauma: multisystem, extremity
Dermatologic diseases
Physical conditioning
Diaphoresis, hyperhidrosis
Hypoxia

Mechanical
Constricting or wet clothing
Tight boots
Vapor barrier, alveolite liners
Inadequate insulation
Immobility or cramped positioning

Psychological
Mental status
Fear, panic
Attitude
Peer pressure
Fatigue
Intense concentration on tasks
Hunger, malnutrition
Intoxicants

Environmental
Ambient temperature
Humidity
Duration of exposure
Wind chill factor
Altitude and associated conditions
Quantity of exposed surface area
Heat loss; conductive, evaporative
Aerosol propellants

Cardiovascular
Hypotension
Artherosclerosis
Arteritis
Raynaud's syndrome
Cold-induced vasodilation
Anemia
Sickle cell disease
Diabetes
Vasoconstrictors, vasodilators

have some initial sensory deficiency in light touch, pain, or temperature. Anesthesia is produced by intense vasoconstrictive ischemia and neurapraxia. Acral areas and distal extremities are the usual insensate sites. The distal extremities—the fingers, toes, nose, ears, and penis—are specific locations at risk. Patients often complain of clumsiness and report a "chunk of wood" sensation in the extremity. The history of complete acute anesthesia in a painful cold digit suggests a severe injury.

Significant pain usually accompanies reestablishment of perfusion. With partial tissue destruction, intermittent pain may be noticed during ongoing exposure. The dull continuous ache evolves into a throbbing sensation in 48 to 72 hours. This often persists until tissue demarcation several weeks to months later.

Chilblains (pernio) is a mild form of cold injury that often follows repetitive exposure. These "cold sores" appear less than 24 hours after exposure and usually affect facial areas, the dorsa of the hands and feet, and the pretibial areas. Young women with a history of Raynaud's phenomenon or systemic lupus erythematosis or with antiphospholipid antibodies are especially at risk. Persistent vasospasm and vasculitis result in burning, pruritus, erythema, and mild edema. Plaques, blue nodules, and ulcerations can develop and last 1 to 2 weeks.

The other common nonfreezing cold injury is trench foot (immersion foot). This remains a significant threat during recreational activities and expeditions in cold, wet climates. Trench foot is produced by prolonged exposure to wet cold at temperatures above freezing.[7] It usually develops slowly over several days and results in neurovascular damage in the absence of ice crystal formation. Immersion foot commonly develops while a person is wearing sweat-dampened or neoprene socks, vapor-barrier boots, or constrictive gaiters. Patients who soak their feet for hours each night in cool water for pain relief are also at risk.

The clinical presentation varies. Most patients' symptoms include cool, pale feet that are numb or tingle. Later the feet appear cyanotic, cold, and edematous. Often, numbness and leg cramping are present. The clinical hallmark is that after rewarming, the skin remains erythematous, dry, and very painful to touch. Rubor on dependency and pallor on elevation are caused by vasomotor paralysis.

Bullae that are indistinguishable from those seen with frostbite commonly develop. Vesiculation proceeds to ulceration and liquefaction gangrene in severe cases. Protracted symptoms of pain during weightbearing, cold sensitivity, and hyperhidrosis often last for years. Prevention of trench foot often simply requires continual drying of socks.

Classically, the initial presentation of frostbite is deceptively benign. Most patients do not arrive in the emergency department with frozen, insensate tissue. Frozen tissues often appear mottled or violaceous-white, waxy, or pale yellow. In severe cases, the examiner will not be able to roll the dermis over bony prominences. Rapid rewarming results in an initial hyperemia, even in severe cases. After thawing, partial return of sensation should be expected until blebs form.[19]

Favorable initial symptoms include normal sensation, warmth, and color. Soft, pliable subcutaneous tissue suggests a superficial injury. A residual violaceous hue after rewarming is ominous. Early formation of clear large blebs that extend to the tips of the digits are more favorable than delayed appearance of smaller hemorrhagic blebs. These dark vesicles are produced by damage to the subdermal vascular plexi. Vesicles and large bullae eventually form in 6 to 24 hours.

Lack of edema formation suggests significant tissue damage. Post-thaw edema usually develops in less than 3 hours. In severe cases, frostbitten skin forms an early black, dry eschar until mummification and apparent demarcation.

Historically, frostbite, like burns, has been classified into degrees of injury. Anesthesia and erythema are characteristic of first-degree frostbite. Superficial vesiculation surrounded by edema and erythema is considered second-degree. Third-degree frostbite produces deeper hemorrhagic vesicles. Fourth-degree injuries extend into subcuticular, osseous, and muscle tissues.

Classification by degrees is often incorrect in relation to the actual severity of the frostbite and thus therapeutically misleading. Mills suggests two simple retrospective classifications.[18,19] Superficial or mild frostbite does not entail eventual tissue loss, whereas deep or severe frostbite does result in tissue loss. As a result, it is not feasible to predict, on presentation, the eventual tissue loss. Another classification attempts to establish severity based on clinical features coupled with early bone scan results.[28]

DIAGNOSTIC STRATEGIES

Many ancillary diagnostic imaging techniques attempt to diagnose the severity of injury. Unfortunately, none consis-

tently and accurately predict tissue loss at the time of initial examination.

Routine baseline radiographs should be obtained, and at follow-up radiographs will begin to demonstrate specific frostbite abnormalities 4 to 10 weeks after injury. Intravenous isotope studies have mixed success experimentally and clinically.[29,30] In one study, triple-phase bone scans performed 2 days after cold injury demonstrate ischemic tissue at risk.[31,32] Delayed bone scans in 7 to 10 days can image deep tissue and bone infarction. The absence of radionuclide uptake even after 10 days, however, does not reliably predict the eventual need for amputation. The patient should be advised that accurate prediction of eventual tissue loss is difficult. As an ancillary tool, scintigraphy predicts the eventual demarcation line better than thermography.[33,34] Scintigraphy as early as day 2 may predict tissue loss and monitor the efficacy of treatment.[35]

Large vessel angiography does not assess the microvasculature at presentation because of vasospasm. Papaverine may help distinguish vasospasm from frostbite sludging and vascular injury. Transitory vascular instability often lasts 2 to 3 weeks. Angiography does facilitate evaluation of associated traumatic or chronic vascular abnormalities. Doppler ultrasonography and digital plethysmography are insensitive but may help determine the need for sympathetic blockade.

In clinical practice, magnetic resonance imaging and magnetic resonance angiography may be superior to technetium bone scanning. In one study, the clear-cut line of demarcation was noted before clinical demarcation.[36]

MANAGEMENT

Field rewarming of frozen tissue is rarely practical. If possible, constricting or wet clothing should be removed and affected areas insulated and immobilized. Friction massage is not efficacious and increases tissue loss. Frozen parts should be kept away from dry heat sources in the transport vehicle to prevent a gradual partial thaw.

A direct relationship exists between the length of time that tissue is frozen and the ultimate extent of cellular damage. Rewarming should not be initiated in the field, however, if there is any potential for interrupted or incomplete thawing. Tissue refreezing is disastrous, and it is preferable to ambulate to safety on frozen extremities if rescue will be delayed.

When evacuation is not possible, rapid field rewarming, preferably in water at 40° to 42° C, may be the only option. Logistic considerations include risks to the party, the availability of shelter and necessary equipment, and the anticipated mode of eventual transportation.

Emergency Department

Prethaw

Pertinent history regarding the ambient temperature, wind velocity, and duration of exposure should be obtained. The type of apparel worn, the circumstances surrounding rescue, and the presence of preexisting cardiovascular or neurologic diseases that could affect tissue loss should be noted.[37]

After stabilizing the core temperature and addressing associated conditions, rapid thawing should be initiated. Treatment should not be delayed while awaiting the results of laboratory and radiographic studies. Most patients have some degree of dehydration and benefit from crystalloid administration. Poor oral intake and hypothermia-induced cold diuresis further increase blood viscosity and sludging.

Thaw

Frozen or partially thawed tissue should be rapidly and actively rewarmed by immersion in gently circulating water that is carefully maintained at a temperature of 40° to 42° C by thermometer measurement.[18] Marginal tissue can be thermally injured when the water temperature exceeds 42° C. Although a circulating tank is ideal for the extremities, a large container suffices for the hands or feet. In some cases, 35° to 40° C water is better tolerated and less painful.

Incomplete thawing and increased tissue loss are hazards when lower water temperatures are used. Rewarming should be continued until the part feels pliable and distal erythema is noted. This usually requires 10 to 30 minutes of submersion. Active gentle motion of the part by the patient during rewarming should be encouraged, but avoid direct tissue massage.

Parenteral analgesia is often indicated during rewarming of deep frostbite. Reperfusion is intensely painful. It produces throbbing, burning pain, and tenderness. A common error is premature termination of rewarming, which results in a partial thaw. Sensation is often diminished after thawing until it disappears with bleb formation.

Patients with completely frozen extremities are invariably hypothermic and at risk for significant fluid and electrolyte fluxes during rewarming. The acute thawing of large amounts of distal musculature extinguishes peripheral vasoconstriction. This results in the sudden return of cold, hyperkalemic, acidotic blood to the central circulation. This produces "core temperature after-drop," which is dysrhythmogenic. In the most severe cases, extracorporeal rewarming should be considered to manage these massive metabolic and electrolyte derangements (Box 137-3).

Post-thaw

The injured extremities must be kept elevated to minimize edema formation. Sterile dressings should be applied and

BOX 137-3 EMERGENCY DEPARTMENT REWARMING PROTOCOL

Prethaw
- Assess Doppler pulses and appearance
- Protect part—no friction massage
- Stabilize core temperature
- Address medical and surgical conditions
- Rehydrate patient
- Prevent partial thaw and refreeze

Thaw
- Provide parenteral ketorolac and analgesia
- Administer ibuprofen 400–600 mg q 6 hours PO
- Immerse part in circulating water that is thermometer-monitored at 37° to 40° C
- Encourage gentle motion of part

Post-thaw
- Dry and elevate part
- Aspirate or débride clear vesicles
- Débride broken vesicles and apply topical antibiotic or sterile aloe vera ointment every 6 hours
- Leave hemorrhagic vesicles intact
- Consider tetanus and streptococcal prophylaxis
- Provide hydrotherapy at 37° C tid
- Consider phenoxybenzamine in severe cases
- Consider imaging, angiography, and thrombolysis
- Obtain admission and serial photographs

involved areas handled gently. Persistent cyanosis in the extremities after a complete thaw may reflect increased fascial compartment pressure. Because of the cold-induced anesthesia, other occult soft tissue injuries are often not appreciated by the patient or physician. Tissue pressures should be monitored carefully, although decompressing escharotomies are usually not necessary during the initial treatment rendered in the emergency department.

The clinical role of thromboxane inhibition in frostbite is limited. Thromboxane inhibition does not appear to result in additional clinically significant tissue salvage. In one experimental model, methimazole did not improve tissue survival even when therapy was initiated immediately.[38] Progressive secondary dermal ischemia is addressed by attempts to limit the accumulation of the products of arachidonic acid breakdown. Topical aloe vera (Dermaide) every 6 hours is a specific thromboxane inhibitor when applied directly to frostbitten areas[23] but has not definitively been proven to salvage tissue. Other alternatives include topical antibiotic ointment. Systemically, ibuprofen appears preferable to salicylates. Although both agents inhibit this cascade, ibuprofen also produces fibrinolysis. Parenteral ketorolac should also be considered.

Frostbite blister management varies widely. Earlier recommended options for large clear blisters included leaving them intact, débridement, or aspiration (Fig. 137-1). Although all clinicians débride broken blisters, many prefer to aspirate intact clear blisters rather than leaving them intact. In contrast, if hemorrhagic blisters are débrided, secondary desiccation of deep dermal layers appears to extend the injury (Fig. 137-2). In this case, aspiration is preferable to débridement.

In severe cases, parenteral penicillin is indicated for streptococcal prophylaxis. Cultures and Gram stains of areas adjacent to the damaged tissue should be performed. Common organisms include staphylococci, streptococci, and *Pseudomonas* species. Broad-spectrum prophylaxis should be considered if excessive heat was used to thaw tissue, since liquefaction and infection are inevitable. Tetanus can also occur after frostbite.

Management of the chilblains syndrome is usually supportive. Nifedipine (20–60 mg daily) is an effective treatment for refractory perniosis.[39–41] Topical or systemic corticosteroids have also been useful. Other options include oral pentoxifylline or limaprost, a prostaglandin E_1 analogue.

Adjunctive Treatment

Numerous ancillary modalities have been suggested for frostbite.[42] The only treatment consensus is removal from the cold and rapid complete thawing in a 40° to 42° C bath.

Capillary flow ceases early after cold injury, whereas thrombosis proceeds.[11,32] This observation has led to multiple experimental antithrombotic and vasodilation treatment regimens, although most lack adequate controls. Most of these studies were conducted before the elucidation of some of the pathophysiologic consequences of frostbite. As demonstrated in a pilot study on triple-phase bone scans, thrombolytic agents may restore some flow to severely frostbitten limbs. The fibrinolytic agent urokinase can also conserve slowly thawed tissue.

In one study, intravenous tissue plasminogen activator and heparin reduced predicted digit amputations in severe frostbite.[35] Nonresponders had over 24 hours of exposure, over 6 hours of warm ischemia, or multiple freeze-thaw cycles. In another study, intra-arterial tissue plasminogen activator decreased the incidence of amputations when administered within 24 hours.[43]

Low-molecular-weight dextran may inhibit intravascular cellular aggregation. Animal models suggest that low-molecular-weight dextran is not harmful. Pentoxifylline, a phosphodiesterase inhibitor, may decrease blood viscosity and increase tissue oxygenation.[44] Its ability to increase red blood cell flexibility facilitates revascularization and may enhance tissue survival. The suggested dosage is 400 mg three times daily for 2 to 6 weeks.[45]

Various anti-inflammatory drugs and other agents have not been conclusively evaluated. These include steroids, nonsteroidal anti-inflammatory drugs, dipyridamole, dimethyl sulfoxide, nonionic detergents, and calcium channel blockers.[46,47] A long-acting alpha-blocker, phenoxybenzamine, may decrease vasospasm while increasing peripheral blood flow. The dosage starts with 10 mg/day to a maximum of 60 mg/day. With this agent, adequate hydration is necessary to prevent orthostatic hypotension.

Hyperbaric oxygen produces vasoconstriction and subsequently reduces cutaneous blood flow. A small number of patients report a temporary flush and increased limb motion, but this appears to depend on the elapsed time interval after injury. Hyperbaric oxygen could accelerate demarcation. Insufficient data on severe frostbite exist to assess the potential value of hyperbaric oxygen therapy for tissue salvage.[48,49]

Figure 137-1. Frostbite with clear vesiculations. (Courtesy of Bill Mills, MD.)

Figure 137-2. Severe frostbite with early hemorrhagic vesicles. (Courtesy of Bill Mills, MD.)

The theoretical benefits of sympathectomy include relief of painful vasospasm, decreased edema, and tissue salvage. Long-term vasodilation could protect against repeated cold injury and some of the degenerative sequelae of frostbite. The value of these benefits is speculative. Epidural spinal cord stimulation combined with conventional treatment may reduce pain and conserve tissue.

A "medical" sympathectomy results from direct injection of an agent such as reserpine into an artery. Common injection sites include the radial, brachial, and femoral arteries. This injection produces local depletion of arterial wall norepinephrine for 2 to 4 weeks. No significant systemic effects are appreciated with the recommended dose of 0.5 mg. This can be repeated in 2 to 3 days. Parenteral reserpine is not commercially available in the United States. Guanethidine is an alternative.

There is angiographic documentation of temporary improvement in perfusion and vasospasm after medical sympathectomy. When tissue is rapidly thawed, experimental attempts to demonstrate further enhancement of tissue salvage have failed. Intra-arterial reserpine may prove most useful in patients with residual pain after gradual thawing.

Early results with surgical sympathectomy were encouraging. Decreased pain, edema, and residual autonomic dysfunction were reported. Tissue demarcation also appeared to accelerate. Bouwman and colleagues[50] performed unilateral surgical sympathectomy on 10 patients with bilateral matched frostbite injuries. Delayed protection against reinjury was one direct benefit. Ultimately, however, there was no increased tissue salvage. Mills observes that surgical sympathectomy produces a smoother initial clinical course but no long-term benefits, with the possible exception of decreased causalgia.[18,19]

DISPOSITION

Except in minor cases, all patients should be hospitalized to determine the extent of injury. Superficial injuries to facial structures may be followed on an outpatient basis. Damaged tissues are best protected with loose sterile sheets and towels rather than compressive dressings. Feet must be kept elevated under a protective cradle. Sterile cotton pledgets should be placed between the toes, and the hands may rest elevated on the chest.

Whirlpool hydrotherapy with an antiseptic should be performed two to three times daily for 20 to 30 minutes. Range-of-motion exercises should be encouraged during immersion. Severe cases may require position-of-function splinting. Hydrotherapy is continued as the eschar sloughs. At this point, sterile precautions may be discontinued. During hospitalization, all vasoconstrictive agents, including nicotine, should be avoided.

SEQUELAE

Direct neuronal damage and residual abnormalities in sympathetic tone are responsible for most of the common symptomatic sequelae of frostbite. In a series of military patients with documented frostbite, 65% had long-term residual symptoms. Vasospasm with secondary cold intolerance is the other major sequela.[51]

Intermittent paresthesias resulting from ischemic neuritis are reported after the first week. The severity of this symptom often reflects the extent of tissue damage. Symptoms may persist for many months. Burning electric shock sensations are worse at night, after heat exposure, and on first returning to ambulation. Thermal perception is also altered. Hyperhidrosis suggests an abnormal sympathetic nervous system response and often serves as both a cause and an effect of frostbite.

Delayed cutaneous findings include nail deformities and pigmentation changes. Squamous and epidermoid cell carcinoma can occur. Osseous reabsorption and subchondral lytic defects develop months after the cold insult. In pediatric patients, concerns include premature fusion, destruction, and fragmentation of epiphyses. Shortening of the distal phalanges is common.[51] Frostbite arthritis also occurs, commonly 3 to 10 years later. Thumb sparing is a characteristic idiosyncrasy. Clenching of the fists can spare both thumbs and metacarpophalangeal joints. Identification of subchondral cysts following bone infarction differentiates frostbite arthritis from osteoarthritis.[52] In severe cases involving extremity muscle compartments, rhabdomyolysis and subsequent renal failure are a concern. Continuous monitoring of serum muscle enzymes and urinalyses is warranted.

BOX 137-4 SEQUELAE OF FROSTBITE

- Neuropathic
  - Pain
    - Phantom
    - Causalgia
    - "Tabes" burning
    - Chronic
  - Sensation
    - Hypesthesia
    - Dysesthesia
    - Paresthesia
    - Anesthesia
  - Thermal sensitivity
    - Heat
    - Cold
  - Autonomic dysfunction
    - Hyperhidrosis
    - Raynaud's syndrome
- Musculoskeletal
  - Atrophy
  - Compartment syndrome
  - Rhabdomyolysis
  - Tenosynovitis
  - Stricture
  - Epiphyseal fusion
  - Osteoarthritis
  - Osteolytic lesions
  - Subchondral cysts
  - Necrosis
  - Amputation
- Dermatologic
  - Edema
  - Lymphedema
  - Chronic or recurrent ulcers
  - Epidermoid or squamous cell carcinoma
  - Hair or nail deformities
- Miscellaneous
  - Core temperature after-drop
  - Acute tubular necrosis
  - Electrolyte fluxes
  - Psychological stress
  - Gangrene
  - Sepsis

Surgical decisions regarding amputation are complex.[51,53] The amount of tissue eventually salvaged often exceeds even optimistic initial estimates. Historically, the natural progression of demarcation, mummification, and eventual sloughing was allowed to occur. Necrotic tissue was classically débrided at least 1 to 2 months after injury when the line of demarcation was clear. Exceptions include refractory pain, sepsis, and supervening gangrene. Advances in radiologic assessment of tissue viability are facilitating earlier surgical intervention. Most grafts and amputations now occur at 3 to 4 weeks after injury. Free flap tissue transfer to salvage function after earlier débridement of soft tissues should be a consideration.[53,54]

Various neuropathic, musculoskeletal, and dermatologic sequelae of frostbite are listed in Box 137-4.[55]

KEY CONCEPTS

- Premature termination of thawing in 40° to 42° C water is a common error. Reperfusion of completely frozen tissue is very painful and will require parenteral analgesia.
- The early formation of clear blebs is more favorable than delayed hemorrhagic blebs, since the latter reflect damage to the subdermal vascular plexi.
- The patient should be advised that accurate prediction of eventual tissue loss is not always possible at presentation, despite imaging.
- Thrombolytic agents may restore some flow to severely frostbitten limbs.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 138

Accidental Hypothermia

Daniel F. Danzl

PERSPECTIVE

The "reanimations" of profoundly cold victims in prolonged cardiac arrest help explain the contemporary allure of hypothermia. A physician was successfully resuscitated from accidental hypothermia at 13.7° C after a 9-hour resuscitation.[1] This included cardiopulmonary resuscitation (CPR) initiated at the scene and 179 minutes of cardiopulmonary bypass.[2]

Although used for medical purposes for millennia, cold modalities were not scientifically evaluated until the 18th century. The hemostatic, analgesic, and therapeutic effects of cold were well known. Accidental hypothermia was also common and its treatment controversial. Biblical references cite truncal rewarming of King David by a damsel, and various remedies, including rubbing the extremities with hot oil, were mentioned by Hippocrates, Aristotle, and Galen.

Cold weather has had a major impact on military history.[3,4] Hannibal lost nearly half of his army of 46,000 while traversing the Pyrenees Alps in 218 BCE. Baron Larrey, Napoleon's chief surgeon, reported that only 350 of the 12,000 men in the 12th division survived the cold during their retreat from Russia in 1812. Those soldiers who were rapidly rewarmed closest to the campfire died.

The winter of 1777 took its toll on Washington's troops at Valley Forge. The French subsequently suffered heavy losses to the cold in the Crimean War (1845–1855). These lessons were relearned during both world wars. Many pilots and U-boat crews perished from the cold water in the North Atlantic. Approximately 10% of the U.S. casualties in Korea were cold related.

Innumerable cold-related tragedies affect both military personnel and civilians, in particular hunters, sailors, skiers, climbers, boaters, and swimmers. Widespread participation in outdoor winter sports increases the number of patients who develop hypothermia.[5]

Hypothermia is geographically and seasonally pervasive.[6–8] Most cases occur in urban settings. "Primary" hypothermia fatalities are classified as accidental, homicidal, or suicidal. Death certificate data, however, under-report secondary hypothermia deaths, in which cold complicates many systemic diseases. The effect of cold on mortality from cardiovascular and neurologic disorders is greatly underestimated.[9]

Hypothermia is defined as a core temperature less than 35° C. Many variables contribute to the development of accidental hypothermia. Exposure, age, health, nutrition, medication, and intoxicants can decrease heat production, increase heat loss, or interfere with thermostability. The healthy individual's compensatory responses to heat loss through conduction, convection, radiation, and evaporation are often overwhelmed by exposure. Medications can also interfere with thermoregulation, and central nervous system (CNS) processes commonly decrease the efficiency of thermoregulation.[10]

PRINCIPLES OF DISEASE

Physiology of Temperature Regulation

Human basal heat production generates approximately 40 to 60 kcal/m^2 of body surface area per hour. This increases with food ingestion, muscular activity, fever, and acute cold exposure. Cold stress increases preshivering muscle tone, and heat production can double. Maximal heat production lasts only a few hours because of fatigue and glycogen depletion.[11]

Shivering thermogenesis increases the basal metabolic rate two to five times. This shivering, which markedly increases oxygen consumption, is modulated by the posterior hypothalamus and the spinal cord.

The preoptic anterior hypothalamus orchestrates nonshivering heat conservation and dissipation. Serotonergic and dopaminergic neurons are pivotal. They exert immediate control through the autonomic nervous system and delayed control through the endocrine system. Thermal suppression or activation of the sympathetic nervous system with cold-induced release of norepinephrine also occurs. Cold also stimulates the hypothalamus to release thyrotropin-releasing hormone. This activates the anterior pituitary gland, which releases thyroid-stimulating hormone, and results in the release of thyroxine from the thyroid gland.[12]

The discomfort of cold can be reduced after long periods of exposure. No evidence exists, however, that there is any significant physiologic adaptation to the cold (Fig. 138-1).

Normal heat loss occurs through five mechanisms. Assuming an average basal metabolic rate, 55 to 65% of this loss is through radiation. Heat loss by radiation is greatest when one is spread nude and least when curled and insulated. Radiative heat loss depends on the temperature gradient between the environment and the exposed body surface area. Conduction normally accounts for only approximately 2 to 3% of the heat loss, but this may increase up to five times in wet clothing and up to 25 times in cold water.

Close correlation exists between subcutaneous fat thickness and cooling rates. Individuals with greater insulation lose heat more slowly. Conduction and convection normally account for

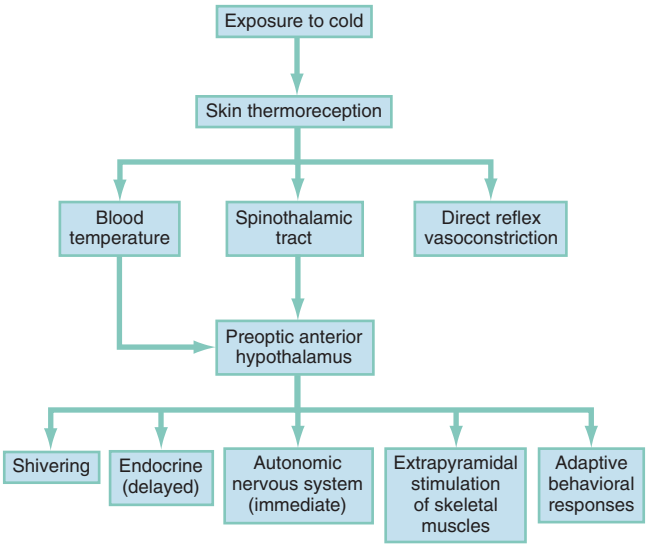


Figure 138-1. Physiology of cold exposure.

about 15% of the body's heat loss, but convective losses increase with shivering. Respiration and evaporation account for the remainder of the loss, with 2 to 9% lost in heating inspired air and 20 to 27% lost to insensible evaporation from the skin and lungs.

Cutaneous and respiratory heat loss is markedly influenced by the ambient temperature, air motion, and relative humidity. Greater losses occur in a cool, dry, windy environment (wind-chill index). When the body is not perspiring, most heat loss is through radiation and convection. Conductive losses become significant in immersion-induced hypothermia. Children cool faster than adults because of the elevated ratios of surface area to mass.

When the temperature is between 37° and 32° C, vasoconstriction, shivering, and nonshivering basal and endocrinologic thermogenesis generate heat. From 32° to 24° C, a progressive depression of the basal metabolic rate occurs without shivering thermogenesis. At temperatures less than 24° C, autonomic and endocrinologic mechanisms for heat conservation become inactive.

Pathophysiology

Cardiovascular

After an initial tachycardia, a progressive bradycardia develops. The pulse usually decreases by 50% at 28° C. If an observed tachycardia is inconsistent with a patient's temperature, associated conditions such as hypoglycemia, drug ingestion, or hypovolemia should be considered.

The bradycardia of hypothermia results from decreased spontaneous depolarization of the pacemaker cells. As a result, the bradydysrhythmia is refractory to atropine. Hypothermia also decreases the mean arterial pressure and the cardiac index.

The electrocardiographic features of hypothermia are unique.[13,14] Initially described by Tomaszewski in 1938, the Osborn (J) wave is seen at the junction of the QRS complex and ST segment (Fig. 138-2). J waves are potentially diagnostic but not prognostic. They may appear at any temperature under 32° C. The size of the J wave is not related to arterial pH but does increase with temperature depression.

J waves are normally upright in the aVL, aVF, and left precordial leads.[15] The J deflection may be a result of hypothermic ion flux alterations, with delayed depolarization or early repolarization of the left ventricular wall. It can also be seen during local cardiac ischemia and with sepsis or CNS lesions, hypercalcemia, and the Brugada syndrome.

Some J waveform abnormalities simulate a myocardial injury current. Hypothermic electrocardiographic changes are not easily computer programmable. Reliance on computer interpretations can result in mistaken thrombolysis, which would be expected to exacerbate preexistent coagulopathies.[16]

All atrial and ventricular dysrhythmias are common in moderate or severe hypothermia. Reentrant dysrhythmias result from decreased conduction velocity with increased myocardial conduction time and a decreased absolute refractory period. Independent electrical foci also precipitate dysrhythmias.

Because the conduction system is more sensitive to the cold than the myocardium, cardiac cycle prolongation occurs. Fluctuations of available oxygen, pH, electrolytes, and nutrients also alter conduction. As hypothermia worsens, the PR interval, then the QRS interval, and finally (and most characteristically) the QT interval become prolonged. In the absence of obvious shivering, thermal muscular tone may obscure P waves or produce artifacts.

Atrial fibrillation is common when the core temperature is less than 32° C. Other rhythms are sinus, atrial, or junctional. Atrial fibrillation usually converts spontaneously during rewarming, and mesenteric embolization is a hazard.

The development of ventricular fibrillation (VF) or asystole in hypothermia is multifactorial. Putative explanations include tissue hypoxia, physical jostling, electrophysiologic or acid-base disturbances, and autonomic dysfunction. Asystole and VF can occur spontaneously when the core temperature falls below 25° C.[17,18] Hypothermia causes a decrease in transmembrane resting potential, which, in turn, decreases the threshold for ventricular dysrhythmias. VF can also result from an independent focus or a reentrant phenomenon. When the heart is cold, a large dispersion of repolarization exists, which facilitates the development of a conduction delay. The action potential is also prolonged, and this increases the temporal dispersion of the recovery of excitability.

The term *core temperature afterdrop* refers to a further decline in an individual's core temperature after removal from the cold. The two processes that contribute to afterdrop are simple temperature equilibration across a gradient and circulatory changes. Countercurrent cooling of the blood, which is perfusing cold tissues, results in a temperature decline until the gradient is eliminated.[19]

Active external rewarming of the extremities obliterates peripheral vasoconstriction and reverses arteriovenous shunting. This is most vividly demonstrated by Hayward, who measured his own esophageal, rectal, tympanic, and cardiac temperatures (using a flotation tip catheter) after cooling in 10° C water on three different days.[20] Warm bath immersion rewarming caused a 30% fall in mean arterial pressure, coupled with a 50% decline in peripheral vascular resistance.

Core temperature afterdrop is a clinically relevant consideration when treating patients with a large temperature gradient between the core and the periphery. This is common in patients who are dehydrated after chronic exposure. Major afterdrops also occur in severely hypothermic patients if frostbitten extremities are thawed before thermal stabilization of the core.

Central Nervous System

Hypothermia progressively depresses the CNS.[21] Significant alteration of the brain's electrical activity begins below 33.5° C, and the electroencephalogram silences at 19° to 20° C.

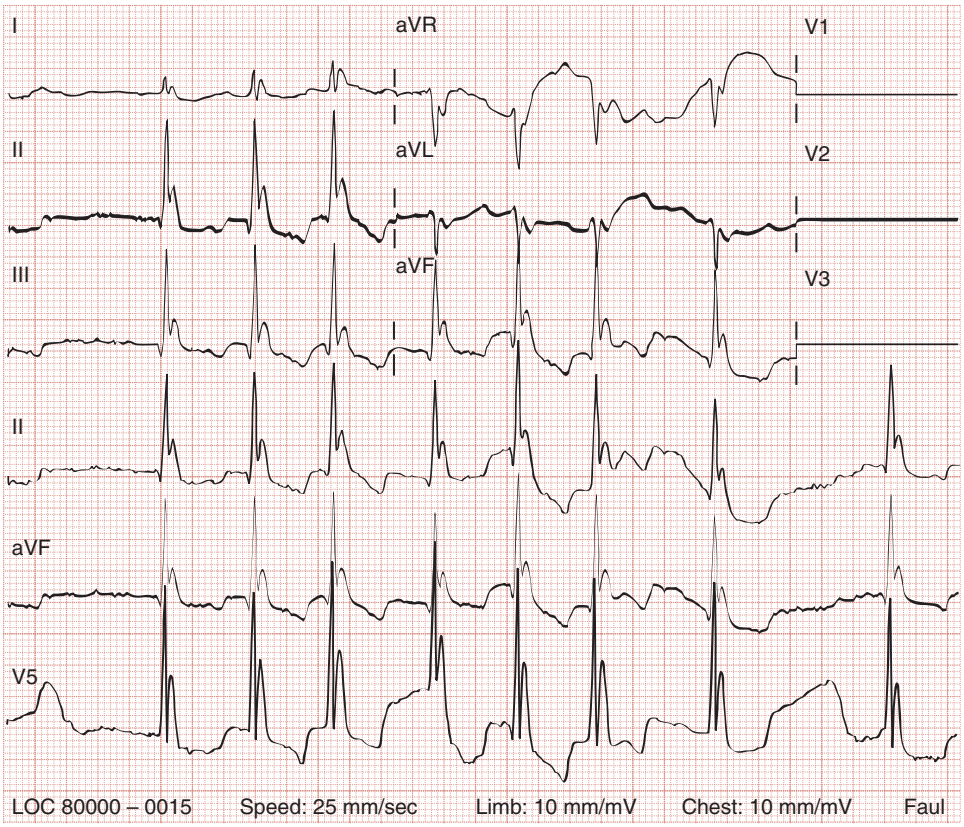


Figure 138-2. Hypothermic J waves.

Cerebral autoregulation is maintained with an increase in vascular resistance until 25° C. In cases of severe hypothermia, there is a disproportionately higher redistribution of blood flow to the brain. Visually evoked potentials are an objective measure of cerebral function and depend on cerebral blood flow. The potentials become smaller as the temperature decreases. Like the heart, the brain has a critical period of tolerance to hypothermia. There are temperature-dependent neural enzyme systems that are unable to function at temperatures that are well tolerated by the kidney.

Renal System

Simple exposure to cold induces a diuresis regardless of an individual's state of hydration. Hypothermia depresses renal blood flow, reducing it by 50% at 27° to 30° C. The kidneys then excrete a large amount of dilute urine, termed *cold diuresis*. Cold diuresis is essentially glomerular filtrate, which does not clear nitrogenous waste products. Severe hypothermia causes an initial relative central hypervolemia as a consequence of peripheral vasoconstriction. Cold diuresis may act as a volume regulator to diminish the vasoconstriction-induced capacitance vessel overload. Cold water immersion can further increase urinary output by 3.5 times, and ethanol doubles that increase.[22]

Respiratory System

Hypothermia initially stimulates respiration. This is followed by a progressive decrease in the respiratory minute volume, which is proportional to the decreasing metabolism. Carbon dioxide production decreases 50% with an 8° C fall in temperature. The normal stimuli for respiratory control are altered in severe hypothermia, and carbon dioxide retention with respiratory acidosis can occur.

Numerous other pathophysiologic factors adversely affect the respiratory system (Table 138-1). These include viscous bronchorrhea, decreased ciliary motility, and noncardiogenic pulmonary edema.

Predisposing Factors

Predisposing factors that contribute to the pathophysiologic changes accompanying core temperature depression can be categorized as those that decrease heat production, increase heat loss, or impair thermoregulation (Box 138-1).

Decreased Heat Production

Decreased thermogenesis is often secondary to an endocrinologic failure such as hypopituitarism, hypoadrenalism, or myxedema. Myxedema coma is several times more common in women, and up to 80% of these persons are hypothermic. Hypothyroidism is often occult in this setting. There is usually no available history of lassitude, dry skin, arthralgias, or cold intolerance.

Hypoglycemia with central neuroglycopenia also predisposes to hypothermia. Another cause of decreased heat production is malnutrition, which corresponds to a decrease in subcutaneous fat. Severe malnutrition, as with marasmus, contributes to heat loss. Kwashiorkor is less commonly associated with hypothermia because of the insulating effect of the hypoproteinemic edema.[12]

The young and the old are commonly at risk. The neonate has a large surface area-to-mass ratio, a relatively deficient subcutaneous tissue layer, and an inefficient shivering mechanism. Since neonates lack behavioral defense mechanisms, they are more likely to develop hypothermia.

Acute neonatal hypothermia is common after emergency deliveries or resuscitations. Many neonates are lethargic, fail

Table 138-1 Physiologic Characteristics of the Four Zones of Hypothermia

STATE	CORE TEMPERATURE °C (°F)	CHARACTERISTICS
Mild	35 (95)	Urine temperature 34.8° C; maximum shivering thermogenesis; increase in metabolic rate
	34 (93.2)	Amnesia and dysarthria develop; normal blood pressure; maximum respiratory stimulation
	33 (91.4)	Ataxia and apathy develop
Moderate	32 (89.6)	Stupor; 25% decrease in oxygen consumption
	31 (87.8)	Extinguished shivering thermogenesis
	30 (86)	Atrial fibrillation and other dysrhythmias; poikilothermia; pulse and cardiac output two thirds normal; insulin ineffective
	29 (85.2)	Progressive decrease in level of consciousness, pulse, and respiration; pupils dilated
Severe	28 (82.4)	Ventricular fibrillation susceptibility; 50% decrease in oxygen consumption and pulse
	27 (80.6)	Losing reflexes and voluntary motion
	26 (78.8)	Major acid-base disturbances; no reflexes or response to pain
	25 (77)	Cerebral blood flow one third normal; cardiac output 45% normal; pulmonary edema may develop
	24 (75.2)	Significant hypotension
	23 (73.4)	No corneal or oculocephalic reflexes
	22 (71.6)	Maximum risk of ventricular fibrillation; 75% decrease in oxygen consumption
Profound	20 (68)	Lowest resumption of cardiac electromechanical activity; pulse 20% of normal
	19 (66.2)	Flat electroencephalogram
	18 (64.4)	Asystole develops
	14.2 (57.6)	Lowest accidental hypothermia survival in an infant[109]
	13.7 (56.7)	Lowest accidental hypothermia survival in an adult[2]
	9 (48.2)	Lowest therapeutic hypothermia survival[102]

BOX 138-1 Factors Predisposing to Hypothermia

- Decreased heat production
  - Endocrinologic failure
    - Hypopituitarism
    - Hypoadrenalism
    - Hypothyroidism
    - Diabetes
  - Insufficient fuel
    - Hypoglycemia
    - Malnutrition
      - Marasmus
      - Kwashiorkor
    - Extreme exertion
  - Neuromuscular inefficiency
    - Age extremes
    - Impaired shivering
    - Inactivity
    - Lack of adaptation
- Increased heat loss
  - Environmental
    - Immersion
      - Nonimmersion
    - Induced vasodilation
      - Pharmacologic
      - Toxicologic
    - Erythrodermas
      - Burns
      - Psoriasis
      - Ichthyosis
      - Exfoliative dermatitis
    - Iatrogenic
      - Emergency deliveries
      - Cold infusions
      - Heatstroke treatment
- Impaired thermoregulation
  - Peripheral failure
    - Neuropathies
    - Acute spinal cord transection
    - Diabetes
  - Central failure/neurologic
    - CNS trauma
    - Cerebrovascular accident
    - Toxicologic
    - Metabolic
    - Subarachnoid hemorrhage
    - Pharmacologic
    - Hypothalamic dysfunction
    - Parkinson's disease
    - Anorexia nervosa
    - Cerebellar lesion
    - Neoplasm
    - Congenital intracranial anomalies
    - Multiple sclerosis
- Miscellaneous associated clinical states
  - Recurrent hypothermia
  - Episodic hypothermia
  - Sepsis
  - Pancreatitis
  - Carcinomatosis
  - Cardiopulmonary disease
  - Vascular insufficiency
  - Uremia
  - Paget's disease
  - Giant cell arteritis
  - Sarcoidosis
  - Shaken baby syndrome
  - Multisystem trauma
  - Shapiro's syndrome
  - Wernicke-Korsakoff syndrome
  - Hodgkin's disease

to thrive, and have a weak cry. Half have deceptively rosy cheeks. Late-onset hypothermia, which occurs after 72 hours of life, is commonly a result of septicemia. Hypothermia can occur in the shaken baby syndrome and may be a factor in some cases of apparent sudden infant death syndrome.

Homeostatic capability progressively decreases with aging. Thermal perception is altered, and elderly people manipulate the indoor ambient temperature less precisely. Most elderly patients are capable of normal thermoregulation but are prone to conditions, including immobility and systemic diseases, which interfere with heat production and conservation. Evidence exists that normal aging factors can predispose to hypothermia. Inability to sense cold, abnormal adaptive behavioral responses, and decreased peripheral blood flow reflect geriatric autonomic dysfunction.[23–25]

Increased Heat Loss

Many individuals often conserve heat poorly during exposure to the cold. Patients with erythrodermas, including psoriasis, exfoliative dermatitis, ichthyosis, eczema, and burns, can have increased peripheral blood flow. Iatrogenic causes of heat loss include exposure during resuscitations, massive cold infusions, overcooling of patients with heat stroke, and overzealous burn treatment.

Ethanol is metabolized at a slower rate in hypothermic individuals and interacts with every putative thermoregulatory neurotransmitter. It may directly damage the posterior hypothalamus and the mammillary bodies. Cutaneous heat loss increases through vasodilation, and shivering thermogenesis is decreased.

Ethanol is the most common cause of heat loss in urban settings.[8,17] Patients often lack protective adaptive behavior to avoid the cold. "Paradoxical undressing," which is the removal of clothing in response to a cold stress, is common.[26] Aging is associated with an increased sensitivity to the hypothermic actions of ethanol. Hypothermic alcoholic ketoacidosis also occurs. The incidence of hypothermia in patients with Wernicke's encephalopathy is common. Hypothermia can mask the usual clinical triad of ophthalmoplegia, confusion, and truncal ataxia. Intravenous thiamine can be both diagnostic and therapeutic.

Impaired Thermoregulation

Thermoregulation can be impaired centrally, peripherally, or metabolically. Skull fractures, particularly basilar fractures, and chronic subdural hematomas are implicated. Other causes include cerebrovascular accidents, neoplasms, anorexia nervosa, and Hodgkin's and Parkinson's diseases. The final common pathway in these disorders may be centrally mediated vasodilation. Cerebellar lesions produce choreiform, less efficient shivering.

In therapeutic or toxic doses, antidepressants, antimanic agents, antipsychotics, anxiolytics, and general anesthetics interfere with thermoregulation by impairing centrally mediated vasoconstriction. Overdosage of these medications and others (e.g., the organophosphates, heroin, glutethimide, and carbon monoxide) predisposes to hypothermia.

Peripheral thermoregulatory failure classically occurs after acute spinal cord transection. The interruption of the autonomic nervous system eliminates vasoconstrictive control and the patient effectively becomes poikilothermic. Neuropathies and diabetes are additional peripheral causes of heat loss. An abnormal plasma osmolality may explain hypothalamic interference in uremia, lactic acidosis, diabetic ketoacidosis, and hypoglycemia.[27]

Miscellaneous Causes

Hypothermia occurs in conjunction with several infections, most commonly overwhelming gram-negative sepsis, pneumonia, meningitis, and encephalitis. Other associated infections include bacterial endocarditis, brucellosis, malaria, syphilis, typhoid, miliary tuberculosis, and trypanosomiasis.

Medical conditions associated with hypothermia include carcinoma, pancreatitis without secondary infection, peritonitis from any cause, and severe cerebrovascular disease. Low cardiac output resulting from a myocardial infarction can induce hypothermia. Fetal and maternal bradycardia and hypothermia may result from magnesium sulfate infusion during preterm labor. Delayed recovery from neuromuscular blockade may also result from unrecognized hypothermia.

Traumatic Factors

Following trauma, hypotension and hypovolemia jeopardize thermostability.[28] In patients with major injuries, a fall in core and skin temperature with no compensatory shivering thermogenesis occurs. Thermoregulation is impaired, and heat production decreases.

Hypothermia may exacerbate blood loss by inducing a coagulopathy via three mechanisms: the coagulation cascade of enzymatic reactions is impaired, plasma fibrinolytic activity is enhanced, and platelets are sequestered and poorly functional.[29]

Traumatic injuries may be overlooked if hypotension or neurologic findings such as areflexia or paralysis are misattributed to hypothermia. Major risk factors for hypothermia in trauma patients include age; type of injury; level of intoxicants; transfusion requirements; and elapsed time spent in the field, emergency department, and operating room.

Hypothermia can only protect the brain from ischemia when it is induced before shock develops. This reduces adenosine triphosphate (ATP) use while the ATP stores are near normal. In traumatized patients, the ATP stores are already depleted. The target core temperature when rewarming a patient with an isolated head injury should balance neuroprotection against the adverse hematologic and immunologic consequences of hypothermia.[30]

CLINICAL FEATURES

When exposure is obvious, the diagnosis is simple. Appreciation of more subtle presentations helps facilitate the early diagnosis of mild to moderate hypothermia. Vague symptoms include hunger, nausea, confusion, dizziness, chills, pruritus, or dyspnea (Box 138-2). During an expedition, individuals may simply become uncooperative, uncoordinated, moody, or apathetic. Indoors, elderly patients may exhibit confusion or simply become less communicative and display lassitude or a peculiar "flat" affect. Subtle progression of mental deterioration or motor skill impairment may mimic senility. Symptoms such as slurred speech and ataxia may resemble symptoms of a cerebrovascular accident or intoxication.[27]

Some elderly people have a decreased ability to sense cold and thus fail to take appropriate adaptive action. The maladaptive phenomenon of *paradoxical undressing* is not uncommon.[26] The last preterminal effort of the victim may be related to the peripheral vasoconstrictive changes of profound hypothermia. The patient can be mistaken for a victim of sexual assault.

In urban settings, hypothermia is most commonly associated with ethanol ingestion or underlying illness. Other common presentations include strokes, overdoses, psychiatric emergencies, or coexistent major trauma.[17]

BOX 138-2 PRESENTING SIGNS OF HYPOTHERMIA

- Head, eye, ear, nose, throat
  - Mydriasis
  - Decreased corneal reflexes
  - Extraocular muscle abnormalities
  - Erythropsia
  - Flushing
  - Facial edema
  - Epistaxis
  - Rhinorrhea
  - Strabismus
- Cardiovascular
  - Initial tachycardia
  - Subsequent bradycardia
  - Dysrhythmias
  - Decreased heart tones
  - Hepatojugular reflux
  - Jugular venous distention
  - Hypotension
- Respiratory
  - Initial tachypnea
  - Adventitious sounds
  - Bronchorrhea
  - Progressive hypoventilation
  - Apnea
- Gastrointestinal
  - Ileus
  - Constipation
  - Abdominal distention or rigidity
  - Poor rectal tone
  - Gastric dilation in neonates or in adults with myxedema
- Genitourinary
  - Anuria
  - Oliguria
  - Polyuria
  - Testicular torsion
- Neurologic
  - Depressed level of consciousness
  - Ataxia
  - Hypesthesia
  - Dysarthria
  - Antinociception
  - Amnesia
  - Initial hyperreflexia
  - Anesthesia
  - Hyporeflexia
  - Areflexia
  - Central pontine myelinolysis
- Psychiatric
  - Impaired judgment
  - Perseveration
  - Mood changes
  - Peculiar flat affect
  - Altered mental status
  - Paradoxical undressing
  - Neuroses
  - Psychoses
  - Suicide
  - Organic brain syndrome
- Musculoskeletal
  - Increased muscle tone
  - Shivering
  - Rigidity or pseudo-rigor mortis
  - Paravertebral spasm
  - Opisthotonus
  - Compartment syndrome
- Dermatologic
  - Erythema
  - Pernio
  - Pallor
  - Frostnip
  - Cyanosis
  - Frostbite
  - Icterus
  - Popsicle panniculitis
  - Sclerema
  - Cold urticaria
  - Ecchymosis
  - Necrosis
  - Edema
  - Gangrene

Neurologic manifestations vary widely. A progressive decrease in the level of consciousness is usually proportional to the degree of hypothermia. Some patients, however, continue to be verbally responsive and display intact reflexes at 27° to 25° C.

Eye movement abnormalities and extensor plantar responses do not correlate directly with the degree of hypothermia. Cranial nerve signs may be seen with bulbar damage from central pontine myelinolysis. Above 22° C, it should be assumed that nonreactive dilated pupils reflect inadequate tissue perfusion and not hypothermia per se.

The rest of the neuromuscular examination may suggest the diagnosis. The patient's posture ranges from stiff to pseudo-rigor mortis to opisthotonos. Reflexes are usually hyperactive down to 32° C, then become hypoactive until they disappear around 26° C. Cremasteric reflexes are expectedly absent with testicular retraction. The plantar response usually remains flexor until 26° C. The knee jerk, when intact, is the last reflex to disappear and the first to reappear with rewarming. The diagnosis of an antecedent CNS disorder, including cord lesions, may be obscured by hypothermia.

Between 30° and 26° C, both contraction and relaxation phases of the reflexes are equally prolonged. If intact, the ankle jerk is helpful in diagnosing hypothermic myxedema. Myxedema prolongs the relaxation phase more than the contraction phase.

No psychiatric disorder improves when the patient is cold. Mental status alterations include anxiety, perseveration, neurosis, and psychosis. Many individuals who are functional in temperate climates decompensate in colder weather. Hypothermic-induced psychiatric presentations and suicide attempts are commonly misdiagnosed.[12]

DIAGNOSTIC STRATEGIES

Laboratory Evaluations

Acid-Base Balance

Blood gas analyzers warm blood to 37° C, which increases the partial pressure of dissolved gases. This results in an arterial blood gas (ABG) report showing higher oxygen and carbon

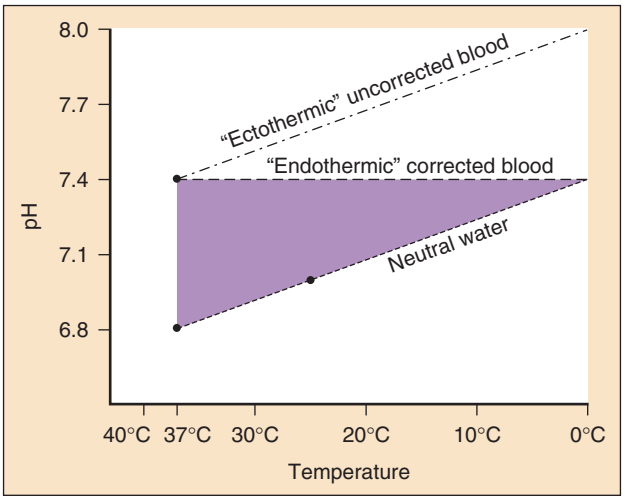


Figure 138-3. Neutrality reflects the pH of water at any given temperature. The pH of water is 6.8 at 37° C and 7.0 at 25° C. The physiologically ideal intracellular-to-extracellular 0.6 pH unit offset will be maintained if the arterial pH is kept uncorrected for temperature at 7.42.

dioxide levels and a lower pH than the patient's actual values. Optimal ABG levels in the setting of hypothermia dictate that correction of ABGs for temperature is unnecessary as a guide to therapy.[31–34] In fact, attempting to maintain a corrected pH at 7.4 and arterial partial pressure of carbon dioxide ($Paco_2$) at 40 mm Hg during hypothermia depresses cerebral and coronary blood flow and cardiac output and increases the incidence of ventricular fibrillation.[35] The ideal acid-base strategy is the ectothermic alpha-stat approach.[10] Simply put, the goal is an uncorrected pH at 7.4 and $Paco_2$ at 40 mm Hg.

Cold blood buffers poorly. In normothermia, when the $Paco_2$ increases 10 mm Hg, the pH decreases 0.08 units. At 28° C, the decrease in pH doubles. Because the neutral point of water at 37° C is a pH of 6.8, the normal 0.6-unit pH offset between blood and intracellular water should be maintained at all temperatures. Just as the neutral pH rises with cooling, so should actual blood pH (Fig. 138-3).

Intracellular electrochemical neutrality ensures optimal enzymatic function at all temperatures.[32] Relative alkalinity affords myocardial protection and improves the heart's electrical stability.[35] Carbogen could prove valuable in the treatment of accidental hypothermia because it flattens and shifts the oxyhemoglobin dissociation curve to the right.

Hematologic Evaluation

A patient's hematocrit can be deceptively high as the result of the decreased plasma volume. The hematocrit level increases 2% for every 1° C fall in temperature. A low-normal hematocrit level in a moderate to severely hypothermic patient should suggest acute blood loss or the possibility of a preexisting anemia.

A normal white blood cell count never excludes infection, especially if the patient is debilitated, alcoholic, myxedematous, or at either age extreme. Splenic, hepatic, and splanchnic sequestration in hypothermia decreases leukocyte and platelet counts.

Frequent evaluation of serum electrolytes during rewarming is essential. There are no safe predictors of their values or trends.[17] Changes occur in both membrane permeability and in the sodium-potassium (K^+-Na^+) pump. The patient's preexisting physiologic status, the severity and chronicity of hypothermia, and the method of rewarming alter the serum electrolyte values.

The plasma potassium level is independent of the primary hypothermic process. Hyperkalemia is often associated with metabolic acidosis, rhabdomyolysis, or renal failure. An important caveat is that hypothermia enhances the cardiac toxicity and obscures the premonitory electrocardiographic changes associated with hyperkalemia.

Hypokalemia is most common with chronic hypothermia. It results from potassium entering muscle, not a kaliuresis. A discrepant decline in serum potassium level despite a decreasing serum pH is caused by intracellular pH fluxes greater than extracellular pH fluxes.

Conditions associated with hypokalemia include preexisting diabetic ketoacidosis, hypopituitarism, inappropriate secretion of antidiuretic hormone, previous diuretic therapy, and alcoholism. If the potassium level is less than 3 mEq/L, supplementation may be necessary for treatment of gastrointestinal ileus or congestive heart failure during rewarming.

The blood urea nitrogen (BUN) and creatinine levels are elevated with preexisting renal disease or decreased clearance. Because of hypothermic fluid shifts, the hematocrit and BUN levels are poor indicators of a patient's actual fluid status.

The blood sugar level may also provide a subtle clue to the type of hypothermia. Acute hypothermia initially elevates blood sugar levels through catecholamine-induced glycogenolysis, diminished insulin release, and inhibition of cellular membrane glucose carrier systems. On the other hand, subacute and chronic hypothermia produce glycogen depletion, leading to hypoglycemia. Symptoms of hypoglycemia can be masked by hypothermia. A cold-induced renal glycosuria does not imply hyperglycemia nor guarantee normoglycemia.[27]

When hyperglycemia persists during rewarming, one should suspect hemorrhagic pancreatitis or diabetic ketoacidosis. Patients with the latter must be actively rewarmed past 30° C because insulin is ineffective below that temperature. Correction of hypoglycemia only corrects the level of consciousness to that of the corresponding level of hypothermia.

Severe hypothermia also causes serum enzyme elevation because of the ultrastructural cellular damage. Rhabdomyolysis is commonly associated with cold exposure.

Ischemic pancreatitis may result from the microcirculatory shock of hypothermia. The decreased pancreatic blood flow then activates proteolytic enzymes.[8] The amylase and lipase levels can correlate with mortality.

Hypothermic Coagulation

A physiologic increase in coagulation occurs with hypothermia, and a disseminated intravascular coagulation type of syndrome occurs. The cause may be catecholamine or steroid release, simple circulatory collapse, or release of tissue thromboplastin from cold, ischemic tissue.[29,36]

Hypothermic patients also develop coagulopathies because the enzymatic nature of the activated clotting factors is depressed by the cold. The clotting prolongation is proportional to the number of steps in the cascade. Because the kinetic tests of coagulation are performed in the laboratory at 37° C, the physician will see a disparity between the in vivo clinically evident coagulopathy and the deceptively "normal" prothrombin time, partial thromboplastin time, or international normalized ratio (INR) reported by the laboratory.[37] The only effective treatment is rewarming, not administration of clotting factors.[38]

The leukopenia and thrombocytopenia usually reverse with rewarming. Clinically significant coagulopathies occur, partic-

ularly in association with trauma. Cold-induced thrombocytopenia is observed with induced hypothermia. The mechanism may be either direct bone marrow suppression or splenic and hepatic sequestration. Platelet thromboxane B_2 production is also temperature dependent. Thrombocytopenia is more common at both age extremes.

The elevated viscosity seen with hypothermia may be exacerbated in patients with cryoglobulinemia or cryofibrinogenemia, both of which are more common in elderly patients. Cryofibrinogen, which is a cold-precipitated fibrinogen, is associated with the collagen vascular diseases, carcinomas, and coliform sepsis. The pathophysiology of cold hemagglutination results from cold agglutinins that produce either hemolysis or agglutination with thrombosis. This could explain the increase in coronary and cerebral thromboses in winter.

In summary, except in mild cases, the immediate laboratory evaluations should include glucose; ABGs uncorrected for temperature; complete blood cell count; a comprehensive metabolic panel including serum calcium, serum magnesium, and serum amylase/lipase levels; and coagulation studies. Baseline serum BUN and creatinine tests are indicated because renal failure may occur after rewarming in patients with chronic hypothermia.

A toxicologic screen is necessary by history or when the depression of the level of consciousness is inconsistent with the degree of hypothermia. Thyroid function studies, cardiac markers, and serum cortisol levels have selective utility.

The indications for radiography should be liberalized from normothermia. As examples, if the patient is not alert, spinal radiographs should be obtained. Bedside ultrasonography or computed tomography may show pancreatic calcifications, unsuspected pneumoperitoneum, small bowel dilation from hypothermia-induced mesenteric vascular occlusion, or colonic dilation associated with myxedema coma.[27]

MANAGEMENT

Patients who are cold, stiff, and cyanotic, with fixed pupils and inaudible heart tones, without visible thoracic excursions, continue to be successfully resuscitated.[2] Embarrassingly, some patients still recover completely in the morgue.

An adequate history includes available pertinent information regarding preexisting cardiac, pulmonary, neurologic, or endocrinologic disease. The duration of exposure, circumstances of discovery, associated injuries, and predisposing conditions should be documented. Initial management should emphasize the prevention of further heat loss.[39] The goals of prehospital care are to rescue, examine, insulate, and gently transport.[40,41]

If the patient is unresponsive and not shivering, presume the hypothermia is severe. At temperatures below 32° C, one should expect an irritable myocardium, a temperature gradient between the core and periphery, and relative hypovolemia.

In the emergency department, hypothermia should be confirmed and monitored with continuous core temperature evaluation. Every emergency department should have the equipment to accurately measure the core temperature. Standard oral thermometers record only down to 35° C. Oral temperatures are unreliable if the patient is uncooperative or tachypneic, or if the ambient temperature is low. Clinically, the rectal temperature is the most practical; however, it can lag behind core changes and is influenced by lower extremity temperatures and probe placement. The probe should be inserted to 15 cm and not placed in cold feces.

The tympanic temperature equilibrates most rapidly with the core temperature and is closest to the hypothalamic temperature. Infrared thermography should not be used alone in the setting of suspected hypothermia because the reliability of commercially available devices remains uncertain. If the patient is tracheally intubated, an esophageal probe reads falsely high with heated inhalation.

A Doppler measuring device may be necessary to establish the presence of a spontaneous pulse or blood pressure. The accuracy of pulse oximetry during conditions of poor perfusion and hypothermia is uncertain.[42] Similarly, end-tidal carbon dioxide measurements accurately assess tissue perfusion and tracheal tube placement only at normal temperatures. Commercially available devices do not function with humidified air used for airway rewarming.

Endotracheal intubation may be necessary unless the patient is alert or has intact protective airway reflexes.[7,17] Cold depression of ciliary activity allows secretory accumulation, with the production of frothy sputum and chest congestion. Failure to differentiate between this bronchorrhea and pulmonary edema may explain the conflicting reports of the association of hypothermia with pulmonary edema. Nasotracheal intubation is a noninvasive option when cold-induced trismus is present, unless there is a significant coagulopathy.

In a multicenter survey, endotracheal intubation was performed on 117 patients by multiple operators in various settings.[17] No induced dysrhythmias were recognized, as in several subsequent series. Factors commonly precipitating dysrhythmias include failure to preoxygenate, mechanical jostling, acid-base changes, and electrolyte fluctuations.

A nasogastric tube is indicated in patients with moderate and severe hypothermia after endotracheal intubation. Decreased gastric motility and gastric dilation occur commonly. Physical examination of the abdomen is unreliable because the cold can induce rectus muscle rigidity. A large percentage of moderate and severely hypothermic patients have decreased or absent bowel sounds. Because physical examination of the abdomen is unreliable, it is important to evaluate the patient carefully for an associated ileus, pancreatitis, or occult trauma.

In cases of moderate and severe hypothermia, indwelling bladder catheters with urine meter bags are essential to monitor urinary output and to help determine the severity of vascular fluid shifts.

Cardiac monitoring should be continued and peripheral or central intravenous catheters inserted as necessary. Inserting a central venous pressure catheter tip into the heart can precipitate dysrhythmias and should be avoided. Arterial catheters for continuous monitoring of intra-arterial blood pressure may rarely be necessary in selected profoundly hypothermic patients. The clinician should avoid placement of pulmonary artery catheters that risk perforation of the cold, stiff pulmonary artery.[43,44]

Volume Resuscitation

Patients with moderate or severe hypothermia are usually dehydrated, and they are also prone to thromboembolism resulting from the increased viscosity. During rewarming, a relatively high total plasma volume and low circulatory plasma volume are often present. As hypothermia develops, other effects include an increased peripheral vascular resistance with a decreased circulatory volume.[45]

Rapid volume expansion is critical. In hypothermic neonates, the mortality risk is dramatically lessened. Adult patients with moderate or severe hypothermia should initially receive a 250 to 500 mL fluid challenge of heated 5% dextrose in normal saline solution pending laboratory analyses. Lactated Ringer's solution should be avoided because the cold liver inefficiently metabolizes lactate.

Fluids administered intravenously should be heated to 40° to 42° C. This is done primarily to avoid worsening hypothermia, because the amount of heat provided only becomes significant with large-volume resuscitations.[46,47] There are many commercially available fluid and blood warmers. If unavailable, another option is to microwave intravenous fluids in plastic containers. A 1-L bag of crystalloid requires an average of 2 minutes on high power. The fluid should be shaken before administration to avoid hot spots. Rapid central venous administration, which may produce myocardial thermal gradients, should also be avoided.

There can be significant conductive heat loss through intravenous tubing. Long lengths of this tubing increase heat loss, especially at slow flow rates.[48] Countercurrent heat exchangers effectively heat crystalloids and blood from 10° to 35° C.

Normally, hypothermia induces an increased natriuresis. Preexisting gastrointestinal losses or previous diuretic treatment can also contribute to sodium loss. Patients with normal sodium and osmolality values may have preexisting sodium overload as a result of cirrhosis, nephrosis, or congestive heart failure; however, most patients will be free-water depleted, which elevates their sodium and osmolality values.

Hemoconcentration resulting from decreased plasma volume, fluid shifts, and increased vascular permeability usually is present. Hemodilution can occur from parenteral crystalloid administration, but a low hematocrit can also result from acute hemorrhage or preexisting anemia.

Advanced Life Support

Blood flow during CPR in patients with hypothermia differs from that during normothermia, when some flow results from phasic alterations in the intrathoracic pressure, not necessarily from direct cardiac compression.[49] During hypothermic cardiac arrest in swine, the cardiac output and cerebral and myocardial blood flows average 50, 55, and 31%, respectively, of those achieved during normothermic closed-chest compressions.[50]

In hypothermia, the heart is a passive conduit. The "thoracic pump" concept notes that the phasic alterations in the intrathoracic pressure are exerted equally on all cardiac chambers. The mitral valve remains patent during systole, and blood continues to circulate through the left side of the heart. This could explain the observation of Althaus and associates,[51] who noted that in one of three survivors at thoracotomy, "the heart was found to be hard as stone and it is hardly conceivable how effective external cardiac massage could have been." There are innumerable neurologically intact survivors after prolonged closed-chest compressions.[2,52,53]

Chest wall elasticity and pulmonary compliance are decreased with cold. Therefore, more force is needed to depress the chest wall sufficiently to generate intrathoracic pressure gradients. Pneumatic-powered thoracic compression devices are useful during prolonged resuscitations pending decisions regarding extracorporeal rewarming.[54] Other perfusion enhancers could include abdominal binding to inhibit paradoxical diaphragmatic motion and simultaneous compression ventilation.

Tissue decomposition, apparent rigor mortis, dependent lividity, and fixed dilated pupils are not always reliable criteria for withholding CPR in the hypothermic patient. Because intermittent flow may provide adequate support during evacuation, CPR should not be withheld just because continuous compressions cannot be assured.[55]

In a multicenter survey of 428 cases, 9 of the 27 patients receiving CPR initiated in the field survived, as did 6 of 14 patients with CPR initiated in the emergency department.[17] Since then, the literature has corroborated this observation. The rescuer should initiate CPR in cases of accidental hypothermia unless do-not-resuscitate status is documented and verified, obviously lethal injuries are present, chest wall depression is impossible, signs of life are present, or rescuers are endangered by evacuation delays or altered triage conditions.

PHARMACOLOGY

The efficacy of most medications is temperature dependent. Protein binding increases during hypothermia, and liver metabolism is decreased. Overmedication could be required to achieve a therapeutic response, and subsequent toxic levels would develop with rewarming. No medication should be given orally because of decreased gastrointestinal motility; none should be given intramuscularly because of poor absorption from vasoconstricted sites.

Cardiovascular

The effects of hypothermia on the autonomic nervous system vary. In primate studies, the sympathetic nervous system responds rapidly to cooling from 37° to 31° C. It then switches off around 29° C, which suggests that modest catecholamine support might be useful below that temperature.[56]

In general, pharmacologic manipulation of the pulse and blood pressure should be avoided. Vasoconstrictors may be dysrhythmogenic while having a minimal effect on the maximally constricted peripheral vasculature. Epinephrine and other vasoconstrictors should generally be avoided.

Inotropes usually are not necessary to support the blood pressure. Low-dose (2–5 μg/min) dopamine infusions should be considered in disproportionately hypotensive patients who do not maintain a mean arterial pressure of 60 mm Hg in response to crystalloids, colloids, and rewarming. To facilitate perfusion of a vasoconstricted cardiovascular system while on dopamine, some investigators add an infusion of low-dose nitroglycerin.

Dysrhythmia Treatment

Preexisting chronic premature ventricular contractions can be suppressed during hypothermia and recur during rewarming. Most hypothermia-induced dysrhythmias convert spontaneously during rewarming. Asystole that develops during rewarming is *not* a more ominous rhythm than VF. VF should be defibrillated at 2 W sec/kg up to 200 W sec. A successful reestablishment of electromechanical activity has been reported at 20° C.[57] If the defibrillation attempt is unsuccessful, active rewarming should be initiated with available equipment while CPR is continued. Defibrillation attempts are usually unsuccessful until the core temperature is well above 28° to 30° C. If unsuccessful, the core temperature should be raised above 30° C before further reattempts.[58]

Virtually all atrial dysrhythmias are common below 32° C and are associated with a slow ventricular response. Atrial fibrillation is common and considered innocent. It usually converts spontaneously during rewarming. Digitalization and calcium channel blockade are not warranted.

The ideal approach to ventricular dysrhythmias is unresolved. Lidocaine and propranolol have minimal hemodynamic effects during hypothermia. Their efficacy in treating ventricular dysrhythmias appears limited.

Although no longer available, bretylium tosylate was extremely effective in several animal studies before invasive maneuvers performed *after* induction of hypothermia. Several clinical chemical defibrillations with bretylium in cases of

severe hypothermia are reported.[27] The prophylactic value of bretylium or lidocaine during hypothermia has not been evaluated. In a canine model of severe hypothermic VF, neither amiodarone nor bretylium was effective.[59]

In cases of normothermia, group I ventricular antidysrhythmics directly decrease conduction velocity and possess indirect anticholinergic activity. In cases of hypothermia, at least one agent in this group, procainamide, reportedly increases the incidence of VF. Another drug in the group, quinidine, has prevented VF during induced profound hypothermia and during cardiac manipulation at 25° to 30° C.

Transvenous intracardiac pacing is extremely hazardous for hypothermia-induced bradydysrhythmias. External noninvasive pacing by means of large low-resistance electrodes is a successful alternative to emergency transvenous pacing in the rare setting of a profoundly disproportionate bradycardia.[60]

Failure to Rewarm

Cold exposure normally induces adrenal unresponsiveness to adrenocorticotropic hormone. A false diagnosis of decreased adrenal reserve in hypothermia is possible. The increase in adrenocorticotropic hormone level seen in hypothermic individuals may be a neurogenic or emotional response to the cold.

Acute cold stress initially stimulates cortisol secretion. The patient may already have a very high level as a result of an underlying stress. In clinical series, serum cortisol levels are commonly elevated. The percentage of cortisol bound to protein is increased with hypothermia, and therefore the active free fraction is decreased.

If a patient fails to rewarm, the historian should search for evidence of adrenocortical insufficiency or steroid dependence. At that juncture, administration of 30 mg/kg methylprednisolone sodium succinate or 250 mg intravenous hydrocortisone should be considered.

Empirical treatment with thyroxine should be reserved for patients thought to be myxedematous. Thyroid hormone replacement is recommended if a history of hypothyroidism is present, a suggestive neck scar is present, or a failure to rewarm occurs. After thyroid function study samples are drawn, 250 to 500 µg of levothyroxine should be administered cautiously intravenously over several minutes. Daily injections of 50 to 100 µg are necessary for 5 to 7 days. Hydrocortisone (100–200 mg) should be added to the first several liters of crystalloid fluid.

The absorption of levothyroxine is variable when it is administered orally or intramuscularly. Administration intravenously results in a smooth effect after the onset of action at 6 to 12 hours. This is evidenced by improvement in the vital signs and the rewarming rate. Half the dose is converted by the peripheral tissues into 1-triiodothyronine (T_3). If there is no improvement, 25 µg T_3 should also be given every 6 hours through a nasogastric tube.[27] An underlying infection also compromises thermogenesis.[61] In an urban setting, infection is the leading cause of failure to rewarm and of mortality.

Septicemia

Hypothermia compromises host defenses and predisposes to infection. The usual signs of infection, including fever, are absent. Shaking chills from sepsis may be mistaken for shivering. If a patient's mental status remains altered despite rewarming, CNS injury or infection should be suspected.

Diminished bone marrow release and circulation of neutrophils, along with impaired neutrophil migration and bacterial phagocytosis, are factors contributing to infection. In children younger than 3 months, prophylactic antibiotics after culturing are indicated. No reliable clinical or laboratory indicators of infection exist, but bradycardia, anemia, uremia, and serum glucose levels, as well as leukocyte abnormalities, are common clues.

The role of antibiotic prophylaxis in adults is less clear. Although gram-negative septicemia may be the cause of hypothermia, coexistent infections from gram-positive cocci, enterobacteriaceae, and oral anaerobes are common.

Elderly patients with thermoregulatory failure have a high risk of mortality and should be considered septic until proven otherwise. Routine antibiotic prophylaxis in hypothermic adults, unlike in elderly patients and in children, does not appear warranted. Antibiotics should be administered if the clinical picture is consistent with septic shock, if there is failure to rewarm, or if aspiration has occurred. Cellulitis, myositis, bacteriuria, or infiltrates present on chest radiographs all warrant immediate antimicrobial therapy.[12]

REWARMING

Since no controlled studies comparing rewarming methods in hypothermia exist, rigid treatment protocols would not be evidence based.[40,62–64] As a result, the clinician should consider the advantages, disadvantages, indications, contraindications, and specific guidelines for the various reported techniques of rewarming that follow.

Passive External Rewarming

Spontaneous passive external rewarming is noninvasive and is the treatment of choice for most patients with mild hypothermia. During passive external rewarming, the patient must be able to metabolically generate sufficient heat to maintain an acceptable rate of spontaneous rewarming. Elderly patients are commonly glycogen depleted, centrally hypovolemic, and not capable of normal cardiovascular or metabolic homeostasis.

The normal processes of heat dissipation are minimized by passive external rewarming. Cessation of evaporization and convection are coupled with insulation against further radiation of heat. This technique simply involves covering the patient with an insulating material in a favorable atmospheric condition. The ambient temperature should exceed 21° C. When the air is stationary, less heat is lost to conduction, convection, and radiation.

Below 30° C, humans are functionally poikilothermic. No shivering thermogenesis occurs. Shivering is the thermoregulatory neuromuscular response to cold that increases heat production from 250 to 1000 kcal/hr. Without it, the endogenously generated metabolic heat is insufficient to raise the core temperature. When the core temperature exceeds 32° C, the major source of heat production is shivering thermogenesis, unless complete glycogen depletion occurs.

Recommended rewarming rates vary between 0.5° and 2.0° C/hr. The rewarming rate should be rapid enough to avoid prolonged exposure to dysrhythmias.

Active Rewarming

Active rewarming is the direct transfer of exogenous heat to the patient. It can be accomplished by either external or internal techniques.

Cardiovascular instability and decompensation require rapid elevation of the core temperature (Box 138-3). Defibrillation is rarely successful at temperatures below 28° to 30° C. Active rewarming is indicated in patients with cerebrovascular accidents and other conditions that impair CNS control of

BOX 138-3 INDICATIONS FOR ACTIVE REWARMING

1. Cardiovascular instability
2. Moderate or severe hypothermia (<32.2° C)
3. Inadequate rate or failure to rewarm
4. Endocrinologic insufficiency
5. Traumatic or toxicologic peripheral vasodilation
6. Secondary hypothermia impairing thermoregulation

thermoregulation. Active rewarming is also indicated in patients when endogenous thermogenesis is insufficient or when glycogen depletion is present. These diseases are usually endocrinologic and include hypopituitarism, adrenal insufficiency, hypothyroidism, and Wernicke's encephalopathy. Active rewarming is also indicated if diabetic ketoacidosis is present because the core temperature must be elevated well above 30° C before insulin becomes effective.[65]

Pharmacologically induced peripheral vasodilation or acute spinal cord transection renders a patient incapable of sufficient thermogenesis, and such patients should be actively rewarmed. Active rewarming in patients with moderate or severe hypothermia is also indicated because of the potential for cardiovascular decompensation or ventricular irritability. Patients with severe hypothermia and a sustained perfusing rhythm do not necessarily require invasive extracorporeal rewarming techniques.[66]

Aggressive treatment of hypothermia in infants is also indicated. Rapid rewarming may be advantageous because it minimizes energy expenditures.[67] Vigorous monitoring for infectious, respiratory, hematologic, and metabolic complications is needed.

Active External Rewarming

Early concern with active external rewarming (AER) was voiced by Duguid and colleagues[68] in 1961, when 20 of their 23 patients died. Retrospective analysis of numerous clinical series notes widely varying mortality rates with AER.[7,17,65]

Various methods are available to conduct heat directly to the skin. Immersion in a bath of 40° C is one option. Disadvantages of this approach include the inability to monitor or resuscitate the patient in water and the difficulty of performing CPR on a floating body.

Other rewarming options include plumbed garments that recirculate warm fluids, hot water bottles, heating pads, forced-air warming systems, and radiant sources. Thermal injury to vasoconstricted hypoperfused skin is a common hazard with local heat application.[69]

Forced air warming systems efficiently transfer heat.[70–73] The Bair Hugger® circulates hot air through a "blanket." The air exits apertures on the patient side of the cover, which allows a convective transfer of heat. In one study in which accidental hypothermia victims were rewarmed in the emergency department, rewarming shock and core temperature afterdrop were not noted.[74] Both groups of patients were also treated with heated inhalation and warmed intravenous fluids. The use of forced-air warming systems is currently most practical in the emergency department.[74–76] Although these devices decrease shivering thermogenesis, afterdrop is minimized and heat transfer can be significant.

Arteriovenous anastomoses rewarming is another noninvasive AER technique first described by Vangaard in 1979.[77] Exogenous heat is provided by immersion of the lower parts of the extremities (hands, forearms, feet, calves) in 44° to 45° C water. The heat opens the arteriovenous anastomoses (AVAs). These organs are 1 mm below the epidermal surface in the digits.[78] As a result, there is an increased flow of warmed venous subcutaneous blood returning directly to the heart.

A permutation of AVA rewarming is negative pressure rewarming. Under hypothermic conditions, the AVAs remain closed during peripheral vasoconstriction. In combination with localized heat application, the application of subatmospheric pressure distends the venous rete and increases flow through the AVAs.

To initiate negative pressure rewarming, the forearm is inserted through an acrylic tubing sleeve device fitted with a neoprene collar. This allows an airtight seal to form around the forearm. After a 40 mm Hg vacuum pressure is created, heat is applied over the dilated AVAs.[79] The clinical practicality and efficacy of AVA rewarming is unclear.

Optimal candidates for AER are previously healthy patients with acute hypothermia. In these patients, minimal dehydration and pathophysiologic circulatory changes have occurred.[80] If AER is chosen and the extremities are vasoconstricted, the heat source should generally be applied only to the thorax. Application of heat to the extremities increases the cardiovascular load by increasing the metabolic requirements of the peripheral musculature. The depressed cardiovascular system may not be able to meet the demands, and cardiovascular collapse can occur.

Combining truncal AER with core rewarming is also successful. Some researchers believe that providing heated humidified oxygen and warmed intravenous fluids in addition to AER may anticipate and avert hypoxia, metabolic acidosis, core temperature afterdrop, and hypotension. If AER is chosen as the method of treatment for moderate or severe hypothermia, it should be combined with one of the active core rewarming techniques.

Active Core Rewarming

Numerous alternatives have been explored to achieve active rewarming of the core. These techniques minimize rewarming collapse in patients with temperatures below 32° C.

Airway Rewarming. Airway rewarming as an adjunctive active core rewarming technique has been explored in research laboratories and clinically since first suggested by Lloyd.[22] This simple technique is indicated in all cases of moderate or severe hypothermia.[81]

Advantages of heated humidified oxygen include noninvasiveness, cost, simplicity, assurance of adequate oxygenation, and avoidance of afterdrop. Additional benefits are the stimulation of pulmonary cilia, a decrease in pulmonary secretion viscosity, and a reduction of cold-induced bronchorrhea. Pulmonic absorption occurs without adverse effects on surfactant or increased pulmonary congestion.

The respiratory tract is a limited site for heat exchange.[46] Nevertheless, both the oxygen content and the temperature in the pulmonary vasculature rise. The myocardium is perfused by warmer oxygenated blood, stabilizing against intermittent temperature gradients.

A sufficient respiratory minute volume and complete humidification are necessary for maximal heat delivery. Because of the low thermal conductivity of dry air, ventilation with warm dry air provides negligible heat. Depending on the technique used (endotracheal tube more than mask), one should expect a rewarming rate between 1° and 2.5° C/hr.[7,17]

Heated mask ventilation is also of interest. A thermal countercurrent heat exchanger exists in the cerebrovascular bed of humans. This system, known as the rete mirabile, could preferentially rewarm the brainstem. Another option is heated inhalation through face mask continuous positive airway pressure.

Maintenance of sufficient oxygenation is also critical in moderate and severe cases. Fisher considered the effects of hypothermia, pH, $Paco_2$, and the level of 2,3-diphosphoglycerate on the shift of the oxyhemoglobin dissociation curve. In patients on cardiopulmonary bypass cooled to 28° to 30° C, the capacity of hemoglobin to unload oxygen to the tissue is less than half that found in normothermic patients.[82] Despite lower metabolic requirements, this decrease in "functional" hemoglobin, combined with a depressed respiratory minute volume, results in minimum oxygen reserves.

Some patients maintain a level of spontaneous respiration appropriate to the depressed carbon dioxide production. This is not the case in patients with coexisting toxicologic, traumatic, or metabolic depression of their respiratory centers. During spontaneous or assisted ventilation with heated ventilation, there is the flexibility to alter the fraction of inspired oxygen (Fio_2), monitor airway pressure, and deliver continuous positive airway pressure or positive end-expiratory pressure.

The technique for patients with spontaneous respirations requires a heated cascade nebulizer. An immersion heater can be connected to a hose with a warming wire. Because patients with a depressed level of consciousness do not complain of pain, it is essential to frequently check the temperature of the inspired air with an in-line temperature probe. The gas temperature should be maintained at 42° to 45° C. Most heater modules require modification to allow the temperature to reach 42° to 45° C and should be so labeled to avoid routine use.

Most humidifiers are manufactured in accordance with the International Standards regulations. The humidifier does not exceed 41° C close to the patient outlet with a 6-foot tubing length.

Strategies to circumvent the 41° C ceiling include reduction of tubing length, adding more heat sources, disabling the humidifier safety system, and placing the temperature probe outside the patient circuit.[83] Due to the modest clinical benefit in stable patients, circumventing the 41° C ceiling may not be worth the effort. The only report of thermal airway injury is in a patient ventilated via endotracheal tube for 11 hours with 80° C inhalant. A volume ventilator with a heated cascade humidifier can also deliver continuous positive airway pressure or positive end-expiratory pressure if needed during rewarming.

Complete airway protection averts aspiration. Hypothermia is associated with ileus, bronchorrhea, and depressed protective airway reflexes. Although the airway rewarming technique provides less heat than other forms of active core rewarming, it is safe, noninvasive, and practical.

Peritoneal Dialysis. This technique delivers dialysate at 40° to 45° C to the peritoneal cavity. Heat is conducted directly to the intraperitoneal structures. Heat is also conducted through the posterior parietal peritoneum to the solid viscera and through the hemidiaphragms to the heart and lungs.

A double-catheter system can increase the rate of rewarming with suction at the outflow. The usual clinically attainable rate is 6 L/hr. Two liters are infused, retained for 20 minutes, and then aspirated. Rewarming rates average 1° to 3° C/hr, depending on gradients and flow rates and dwell times.

An additional benefit of this invasive technique is hepatic rewarming, which reactivates depressed detoxification and conversion enzymes. Peritoneal dialysis can exacerbate preexistent hypokalemia; therefore, serum electrolytes should be carefully monitored. Peritoneal lavage rewarming should not be selected routinely for stable patients. It should be considered in severe cases and in combination with all available rewarming techniques for patients without spontaneous perfusion.[27]

Heated Irrigation. Heat transfer from irrigation fluids is usually very limited because the surface area available for heat exchange is minimal. Gastric or colonic irrigation can cause fluid and electrolyte fluxes. Exceeding 200- to 300-mL aliquots may force fluid into the duodenum; therefore, frequent fluid removal via gravity drainage minimizes "lost" fluid. A log of input and output is essential. A double-lumen esophageal tube and other modified Sengstaken tubes have been used.[84]

Closed thoracic lavage in accidental hypothermia is another option.[44,85,86] Two large-bore thoracostomy tubes are inserted into one or both hemithoraces. One is inserted anteriorly in the second or third intercostal space at the midclavicular line. The other is inserted between the fifth and sixth intercostal space in the posterior axillary line. Normal saline solution is heated to 40° to 42° C and sterilely infused into either tube and drained.[87] The dwell time for thermal transfer will be longest if the fluid is infused into the inferior tube. One should leave the inferior tube for drainage after rewarming.

The efficiency of heat transfer varies with the flow rate and dwell times. Pleural adhesions prevent adequate infusion rates and can result in a tension hydrothorax. Adequate drainage must be ensured to prevent intrathoracic hypertension.

Thoracic lavage should be reserved for the severely hypothermic patient who does not respond to standard techniques or the patient with another indication for a chest tube. It should be combined with all other available rewarming modalities in potentially salvageable cardiac arrest patients.[53,88,89] The rate of rewarming averages 3° C/hour.[86]

Mediastinal irrigation and direct myocardial lavage should only be considered in patients without spontaneous perfusion. The procedure requires a standard left lateral thoracotomy incision. The pericardium is not incised unless an effusion or tamponade is present. The heart is bathed in 1 to 2 L of an isotonic solution heated to 40° C for several minutes. The fluid is then removed and the lavage repeated. Internal defibrillation is attempted at 2° C intervals after the myocardial temperature exceeds 26° to 28° C. When a perfusing rhythm is achieved, lavage is continued until the myocardial temperature exceeds 32° C. A median sternotomy approach allows ventricular decompression in addition to direct defibrillation. Open cardiac massage of a cold, rigid, and contracted heart may not generate flow.[49,51]

Diathermy. Truncal diathermy may soon prove clinically useful. Diathermy involves the conversion of energy waves into heat. Large amounts of heat can be delivered to deep tissues with ultrasonic and low-frequency microwave radiation. Frostbite, burns, significant edema, and the presence of all types of metallic implants and pacemakers contraindicate diathermy.

Regional heating of hypothermic dogs after immersion does not damage tissue at 4 to 6 W/kg and rapidly elevates the core temperature. Zhong and associates[67] rewarmed 16 piglets with microwave irradiation "until they squealed and suckled." In a subsequent experiment, 20 of 28 human infants were successfully rewarmed with microwave irradiation at 90 to 100 W.

Extracorporeal Blood Rewarming. The four common techniques to rewarm blood are venovenous rewarming, hemodialysis, continuous arteriovenous rewarming, and cardiopulmonary bypass (CPB) (Table 138-2).[90–92]

Extracorporeal venovenous rewarming is an option for warming and recirculating the blood. With this technique, blood is removed, usually by a central venous catheter, heated to 40° C, and returned via a second central or large peripheral venous catheter. Flow rates of 150 to 400 mL/min have been achieved.[93,94]

The circuit is not complex and is more efficient than many other nonbypass modalities. There is no oxygenator, and since

Table 138-2 Extracorporeal Blood Rewarming Options

OPTIONS	CONSIDERATIONS
Venovenous circuit	CV catheter to CV or peripheral catheter rewarming No oxygenator/circulatory support Flow rates 150–400 mL/min ROR 2–3° C/hr
Hemodialysis circuit	Single- or dual-vessel cannulation Stabilizes electrolyte or toxicologic abnormalities Exchange cycle volumes 200–500 mL/min ROR 2–3° C/hr
CAVR circuit	Percutaneous 8.5F femoral catheters Requires blood pressure of 60 mm Hg systolic No perfusionist/pump/anticoagulation Flow rates 225–375 mL/min ROR 3–4° C/hr
CPB circuit	Full circulatory support with the pump and oxygenator Perfusate-temperature gradient (5–10° C) Flow rates 2–7 L/min (average 3–4 L/min) ROR up to 9.5° C/hr

CAVR, continuous arteriovenous rewarming; CPB, cardiopulmonary bypass; CV, central venous; ROR, rate of rewarming.

From Danzl DF: Hypothermia and frostbite. In Fauci AS, et al (eds): Harrison's Principles of Internal Medicine, 17th ed. New York, McGraw-Hill Professional, 2008.

the method does not provide full circulatory support, volume infusion is the only option to augment inadequate cardiac output.[95]

Standard hemodialysis is a widely available and practical rewarming technique. It is portable and efficient and should be considered in patients with electrolyte abnormalities, renal failure, or intoxication with a dialyzable substance. Two-way flow catheters allow cannulation of a single vessel. A Drake-Willock single-needle dialysis catheter can be used with a portable hemodialysis machine and external warmer. After central venous cannulation, exchange cycle volumes of 200 to 250 mL/min are possible.

Although heat exchange is less than with standard two-vessel hemodialysis, the ease of percutaneous subclavian vein placement is a major advantage. Hemodialysis via two separate single-lumen catheters placed in the femoral vein can achieve continuous blood flow at 450 to 500 mL/min.

Continuous arteriovenous rewarming is another option if the blood pressure is at least 60 mm Hg. As described by Gentilello, continuous arteriovenous rewarming involves the use of percutaneously inserted femoral arterial and contralateral femoral venous catheters.[28,96] The Seldinger technique is used to insert the 8.5F catheters. Heparin-bonded tubing circuits obviate the need for systemic anticoagulation. Continuous arteriovenous rewarming has principally been performed on traumatized patients.

The blood pressure of spontaneously perfusing traumatized hypothermic patients creates a functional arteriovenous fistula by diverting part of the cardiac output out the femoral artery through a commercially available countercurrent heat exchanger. The heated blood is then returned with admixed heated crystalloids via the femoral vein.

Continuous arteriovenous rewarming does not require the specialized equipment and perfusionist necessary for CPB. The average flow rates are 225 to 375 mL/min, resulting in a rate of rewarming of 3° to 4° C/hr. Since the catheters are 8.5F, the patient must weigh at least 40 kg.

Lastly, cardiopulmonary bypass utilizes the standard femoral-femoral circuit and includes arterial and venous catheters, a mechanical pump, a membrane or bubble oxygenator, and a heat exchanger.[97] A 16 to 30F venous cannula is inserted via the femoral vein to the right atrium/inferior vena cava junction. The tip of the shorter 16 to 20F arterial cannula is inserted 5 cm or just proximal to the aortic bifurcation. Transesophageal echocardiography can help evaluate ventricular load and valve function.

There are techniques to decrease the need for intravenous anticoagulation that previously limited clinical applicability. Heparin-coated perfusion equipment and the use of nonthrombogenic pumps can be coupled with the enhanced physiologic fibrinolysis seen in the first hour of CPB.[98,99]

Heated, oxygenated blood is returned via the femoral artery. Femoral flow rates of 2 to 3 L/min can elevate the core temperature 1° to 2° C every 3 to 5 minutes. In Splittgerber's review the mean CPB temperature increase was 9.5° C/hr.[100] Most pumps can generate full flow rates up to 7 L/min.

The optimal temperature gradient and bypass rewarming rates are unknown. An excessive temperature gradient between brain tissue and circulant can adversely affect electroencephalographic regeneration. The other concern is the possibility of increased bubbling if high perfusate temperature gradients are used. Most investigators use 5° to 10° C gradients.[101]

The major advantage of CPB in perfusing patients is the preservation of flow if mechanical cardiac activity is lost during rewarming. Other candidates for CPB are patients who do not respond to less invasive rewarming techniques, those with completely frozen extremities, and those with rhabdomyolysis accompanied by major electrolyte disturbances.

Of note, rapid acceleration of the rate of rewarming does not necessarily improve survival rates. Complications of rapid rewarming in severe hypothermia include disseminated intravascular coagulation, pulmonary edema, hemolysis, and acute tubular necrosis.

Extracorporeal blood rewarming should be attempted in hypothermic cardiac arrest patients when no contraindications to CPR exist. A realistic assessment of the risk-to-benefit ratio for debilitated patients with secondary hypothermia should be made. The lowest temperature in a survivor of induced hypothermia was 9° C.[102] Extracorporeal blood rewarming is unlikely to succeed below 5° C.[103] Resuscitation should be discontinued if frozen or clotted intravascular contents are identified.

DISPOSITION

Otherwise healthy patients who have mild primary accidental hypothermia (35–32.2° C) usually rewarm easily in the emergency department. They can be safely discharged if a warm environment is available.

Patients with more severe hypothermia (<32.2° C) almost always require admission.[104] These patients should be evaluated for the presence of underlying medical disorders (see Box 138-1). Cardiac monitoring should be considered in patients with persistent toxicologic or metabolic abnormalities. This is essential for those patients displaying cardiovascular instability or an inadequate rate of rewarming. Transferring patients to tertiary care centers is generally not necessary; however, some severely hypothermic patients are best managed in facilities with CPB capabilities.

OUTCOME

In the past, the treatment dictum was that "no one is dead until they are warm and dead." Some patients are cold and dead, and it would be useful and humane if they could be

safely identified.[105] Because of the variability of human physiologic responses, outcome is difficult to predict.[103,106–108] The type and severity of the underlying or precipitating disease process are the major determinants.[109] Patient age is not an independent predictor of mortality.

Trauma, infection, and toxin ingestions also affect survival unpredictably.[30,110] Outcome prediction based on the Glasgow Coma Scale score is unreliable. Further refinement of a hypothermia outcome score developed from a large database may enable multiple observers at different sites to assess treatment modalities and outcome predictors.[111] Significant predictors of outcome include asphyxia, prehospital cardiac arrest, a low or absent blood pressure, elevated BUN level, and the need for either endotracheal or nasogastric intubation in the emergency department.[92]

The search for a valid triage marker of death continues.[112–114] Grave prognostic indicators include evidence of intravascular thrombosis (fibrinogen <50 mg/dL), cell lysis (hyperkalemia >10 mEq/L), and ammonia levels greater than 250 mmol/L.[115] These indicators have not been prospectively validated.

KEY CONCEPTS

- Indications for active rather than passive rewarming include cardiovascular instability, temperature below 32° C, poor rate of rewarming, endocrinologic insufficiency, and vasodilation.
- One should consider hypoglycemia, hypovolemia, or an overdose if there is a tachycardia disproportionate to the temperature.
- The efficacy of most medications is temperature dependent. Overmedication to achieve an effect when the patient is cold could cause toxicity during rewarming.
- Kinetic laboratory tests of coagulation are performed at 37° C. Despite a clinically obvious coagulopathy, the values will be deceptively "normal."
- There are no safe predictors of serum electrolytes. Hypothermia enhances the cardiac toxicity of hyperkalemia and obscures premonitory electrocardiographic changes.
- Failure to rewarm despite good technique should suggest infection, endocrinologic insufficiency, or a futile resuscitation.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 139 Heat Illness

Melissa Platt and Salvator Vicario

PERSPECTIVE

Humans have been plagued by heat illness throughout recorded history, often as the result of military exercises, athletic events, or recreational activities. The ancient Greeks named a disease that resembled heatstroke *siriasis* after the dog star Sirius, which accompanies the summer sun. The U.S. Army reported at least 125 deaths from heatstroke during basic training in the years 1941 to 1944.[1] Modern military organizations continue to encounter heat illness because of the requirement to train unacclimatized troops with forced heavy physical exercise. Furthermore, athletes are also prone to heat illness. Between 1961 and 1971, 46 U.S. football players died of heatstroke. Heatstroke was once third only to head and spinal cord injuries and cardiac arrest as a cause of death among U.S. athletes.[2] When environmental heat stress is maximal, strenuous exercise is not required to produce heat illness.

The elderly and poor, often lacking adequate air-conditioning and nutrition, and those with preexisting disease are prone to heat illness during environmental extremes. In heat wave years in the United States, approximately 10 times as many deaths are reported as during non–heat wave years. It is also estimated that at least 10 times as many heat-aggravated illnesses occur because of myocardial infarction, cerebrovascular accident, and other causes. More than 700 excess deaths were caused by the heat during the 1995 heat wave in Chicago. The heat wave during the summer of 2003 is estimated to have caused 14,800 deaths in France, and climate models suggest an increase in both frequency and intensity of heat waves in temperate areas in the future.[3]

PRINCIPLES OF DISEASE

Physiology of Heat

Heat Production

Humans can be considered biochemical "furnaces" that burn food to fuel a complex array of metabolic functions. These chemical reactions consume substrate, generate usable energy, and produce by-products that must be eliminated for continued operation of the system. Water and carbon dioxide are produced and eliminated in large quantities, as are urea, sulfates, phosphates, and other chemical products. All of these reactions are exothermic and combine to produce a basal metabolic rate that amounts to approximately 100 kcal for a 70-kg person. In the absence of cooling mechanisms, this baseline metabolic activity would result in a 1.1°C hourly rise in body temperature.

Heat production can be increased up to 20-fold by strenuous exertion. Rectal temperatures as high as 42°C are recorded without ill effects in trained marathon runners. Metabolic factors, such as hyperthyroidism or sympathomimetic drug ingestion, can dramatically increase heat production. Environmental heat not only adds to the heat load but also interferes with heat dissipation. The physics of heat transfer as it relates to human physiology involves four mechanisms: conduction, convection, radiation, and evaporation.[4]

Conduction

Conduction is the transfer of heat energy from warmer to cooler objects by direct physical contact. Air is a good insulator; therefore, only approximately 2% of the body heat loss is by conduction. In contrast, the thermal conductivity of water is at least 25 times that of air.

Convection

Heat loss to air and water vapor molecules circulating around the body is termed *convection*. As ambient temperature rises, the amount of heat dissipated by convection becomes minimal, and once air temperature exceeds the mean skin temperature, heat is gained by the body. Convective heat loss varies directly with wind velocity. Loose-fitting clothing maximizes convective (and also evaporative) heat loss.

Radiation

Radiation is heat transfer by electromagnetic waves. Although radiation accounts for approximately 65% of heat loss in cool environments, it is a major source of heat gain in hot climates. Up to 300 kcal/hr can be gained from radiation when a person is directly exposed to the hot summer sun.[5]

Evaporation

Evaporation is the conversion of a liquid to the gaseous phase. Evaporation of 1 mL of sweat from the skin cools the body by 0.58 kcal. As ambient temperature rises, evaporation becomes the dominant mechanism of heat loss. Panting mammals such

as dogs have an oropharyngeal countercurrent flow mechanism (carotid rete mirabile) that results in selective cooling of the brain. In humans, respiratory and countercurrent mechanisms are minimal sources of heat loss, and the dominant mode of cooling in hot conditions is evaporation of sweat from the skin.

Heat Regulation

The regulation of body temperature involves three distinct functions: thermosensors, a central integrative area, and thermoregulatory effectors.

Thermosensors. Temperature-sensitive structures are located both peripherally in the skin and centrally in the body. Skin temperature changes, however, correlate poorly with changes in the rate of heat loss.[6] Thermosensitive neurons are in the preoptic anterior hypothalamus. They are activated when the temperature of the blood circulating through that area exceeds a "set point."

The skin temperature affects heat loss, since a person resting in a warm environment initiates sweating, even though the core temperature remains constant. In contrast, changes in core temperature are more potent in producing heat-dissipating responses than skin temperature changes.[7]

Central Integrative Area. The central nervous system (CNS) interprets information received from the thermosensors to properly instruct thermoregulatory effectors. The concept of a central thermostat by which an alteration shifts effector thresholds in the same direction fits a variety of clinical situations. For example, fever, the circadian rhythm of temperature variation, and the 0.5° C difference in rectal temperature after ovulation can be explained by variation of a thermal set point.

Thermoregulatory Effectors. Sweating and peripheral vasodilation are the major mechanisms by which heat loss can be accelerated. In a warm environment, evaporation of sweat from the skin is the most important mechanism of heat dissipation. Heat loss from the skin by convection and radiation is maximized by increased skin blood flow to facilitate sweating.

Humans possess apocrine and eccrine sweat glands. Apocrine glands are concentrated in the axillae and produce milky sweat rich in carbohydrate and protein. They are adrenergically innervated and respond to emotional stress as well as to heat. Most glands producing "thermal sweat" are eccrine glands. These are cholinergically innervated and distributed over the entire body, with the largest number on the palms and soles. Eccrine sweat is colorless, odorless, and devoid of protein. Individuals exercising in hot environments commonly lose 1 or 2 L/hr of sweat; loss of 4 L/hr for short periods is possible.

Cooling is best achieved by evaporation from the body surface; sweat that drips from the skin does not cool the body, and sweat evaporated from clothing is considerably less efficient. Each liter of completely evaporated sweat consumes 580 kcal of heat. The ability of the environment to evaporate sweat is termed *atmospheric cooling power* and varies primarily with humidity but also with wind velocity. As humidity approaches 100%, evaporative heat loss ceases.

The vascular response to heat stress is cutaneous vasodilation and compensatory vasoconstriction of splanchnic and renal beds. These vascular changes are under neurogenic control and allow heat to be dissipated quickly and efficiently, but they place a tremendous burden on the heart.[8] To maintain blood pressure, cardiac output must increase dramatically. For this reason, saunas and hot tubs may be dangerous for patients with cardiac disease. Cardiovascular and baroreceptor reflexes also affect skin blood flow. Reduced forearm sweating and vasodilation are observed in severely dehydrated subjects exercising in a warm environment.[9]

Acclimatization. *Acclimatization* is defined as "a constellation of physiologic adaptations that appear in a normal person as the result of repeated exposures to heat stress." Daily exposure to work and heat for 100 min/day results in near-maximal acclimatization in 7 to 14 days. This is characterized by an earlier onset of sweating (at a lower core temperature), increased sweat volume, and lowered sweat electrolyte concentration. Acclimatization is hastened by modest salt deprivation and delayed by high dietary salt intake.[10] As acclimatization proceeds, the sweat sodium concentration decreases while the volume increases.

The cardiovascular system plays a major role in both acclimatization and endurance training, largely resulting from an expansion of plasma volume.[11] Heart rate is lower and associated with a higher stroke volume. Other physiologic changes include earlier release of aldosterone, although acclimatized individuals generate lower plasma levels of aldosterone during exercise heat stress. Total body potassium depletion of up to 20% (500 mEq) by the second week of acclimatization can occur as a result of sweat and urine losses coupled with inadequate repletion.[11]

Although many similarities exist between thermoregulatory responses to heat and exercise, the well-conditioned athlete is not necessarily heat acclimatized. To maintain heat and exercise-induced adaptive responses, heat exposure needs to continue intermittently at least on 4-day intervals. Plasma volume decreases considerably within 1 week in the absence of heat stress.[11]

PATHOPHYSIOLOGY

Predisposing Factors for Heat Illness

Elderly patients, psychiatric patients, or those with chronic diseases who are taking medications predisposing to heat illness are prone to classic heatstroke during periods of high ambient heat and humidity. Adequate fluid intake is essential. Elderly patients sometimes dress inappropriately for hot weather; heat loss is maximized by light, loose-fitting garments.

Exertional heatstroke is most likely to occur in young, healthy people involved in strenuous physical activity, especially if they have not acclimatized to environmental factors that overwhelm heat-dissipating mechanisms. Fluid intake is the most critical variable. Dehydration can be minimized by education on work-rest cycles and fluid consumption and through provision of cool, pleasantly flavored fluids.

The goal is to maximize voluntary fluid intake and gastric emptying so that fluid can rapidly enter the small intestine, where it is absorbed. Gastric emptying is accelerated to 25 mL/min by large fluid volumes (500–600 mL) and cool temperatures (10–15.8° C). High osmolality inhibits gastric emptying; osmolality of less than 200 mOsm/L is optimal. Most commercially available electrolyte solutions contain excessive sugar. Hydration can be monitored by measuring body weight before and after training or athletic competition. An athlete with a loss of 2 or 3% body weight (1.5–2 L in a 70-kg man) should drink extra fluid and be permitted to compete only when within 0.5 to 1 kg (1 or 2 pounds) of the starting weight on the previous day. A weight loss of 5 or 6% represents a moderately severe deficit and usually is associated with intense thirst, scanty urine, tachycardia, and an increase in rectal temperature of approximately 2° C. Such athletes should be restricted to light workouts after hydration until they return to normal weight. A loss of 7% or more of body weight represents severe water depletion; the athlete should not participate in sports until examined by a physician.

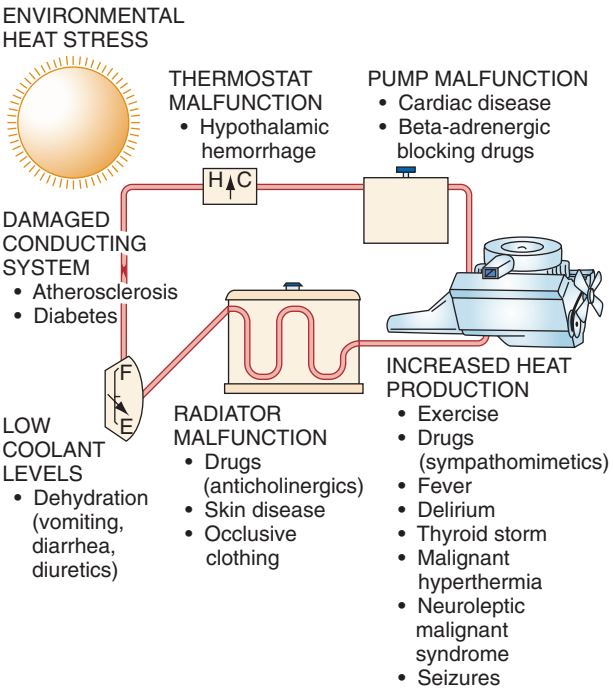


Figure 139-1. Predisposing factors for heat illness: an automotive analogy.

Wrestlers frequently fast, restrict food and fluid intake, and exercise vigorously wearing vapor-impermeable clothing to lose weight quickly so that they can compete in a lower weight class.[12]

The administration of salt tablets during strenuous exercise can cause delayed gastric emptying, osmotic fluid shifts into the gut, gastric mucosal damage, and hypernatremic dehydration. A 6-g sodium diet is sufficient for successful adaptation for work in the heat, with sweat losses averaging 7 L/day. Excessively high salt intake in relation to salt losses in sweat during initial heat exposure can impair acclimatization because of inhibition of aldosterone secretion. Excessive salt ingestion can also exacerbate potassium depletion.

Evaporative cooling can be lost when clothing inhibits air convection and evaporation. Loose-fitting clothing or ventilated fishnet jerseys allow efficient evaporation. Light-colored clothing reflects rather than absorbs light. Water evaporated from clothing is much less efficient for body cooling than is water evaporated from the skin.[13]

The body's heat dissipation mechanisms are analogous to the cooling system of an automobile (Fig. 139-1). Coolant (blood) is circulated by a pump (heart) from the hot inner core to a radiator (skin surface cooled by the evaporation of sweat). Temperature is sensed by a thermostat (CNS), which alters coolant flow by a system of pipes, valves, and reservoirs (vasculature). Failure of any of these components can result in overheating.

Effective circulation requires both an intact pump and adequate coolant levels. Individuals with cardiac disease or those taking beta-adrenergic blocking agents may be unable to increase their cardiac output sufficiently to produce the necessary peripheral vasodilation to dissipate heat. Dehydration caused by gastroenteritis, diuretics, or inadequate fluid intake predisposes to heat illness. Individuals working in the heat seldom voluntarily drink as much fluids as they lose and replace only approximately two thirds of net water loss ("voluntary dehydration"). Dehydration alone increases body temperature at rest by increasing the work of the sodium-potassium adenosine triphosphatase pump, which accounts for

BOX 139-1 WET BULB GLOBE TEMPERATURE

$$WBGT = 0.7T_n + 0.2T_g + T_a$$

T_n, "natural" wet bulb temperature; the temperature achieved by a thermometer covered with a moistened white wick and left exposed to the ambient environment

T_g, globe temperature; the temperature inside a blackened hollow copper sphere exposed to the ambient environment

T_a, ambient temperature

These measurements can be done manually or automatically calculated with the help of computer algorithms.

WBGT, wet bulb globe temperature.

25 to 45% of basal metabolic rate.[14] This is particularly true in cases of hypernatremic dehydration. The pipes and valves of the coolant system may be abnormal in diabetic or elderly patients with extensive atherosclerosis.

Radiator function depends on the skin and sweat glands. Occlusive, vapor-impermeable clothing hinders evaporative and convective cooling. Anticholinergic medications and drugs of abuse interfere with sweating and produce heat illness.[15] Various skin diseases, including miliaria (prickly heat rash), extensive burns, scleroderma, ectodermal dysplasia, and cystic fibrosis, are all risk factors. Anhidrosis can be secondary to either central or peripheral nervous system disorders as well.

Increased heat production causing heat illness most often accompanies exercise in hot, humid environments. Athletes and military recruits are commonly affected. When heat and humidity are extreme, exertion is not necessary to produce heat-related problems. Several indexes help objectify heat strain. The indexes can be divided into two categories: heat scales that are based on meteorologic parameters only and heat scales that combine environmental and physiologic parameters.[16]

The wet bulb globe temperature heat index is an excellent meteorological measure of environmental heat stress (Box 139-1). It includes the effects of temperature, humidity, and radiant thermal energy from the sun. When climatic conditions exceed 25° C wet bulb, even healthy people are at high risk if they choose to exercise. Above 28° C, exercise and strenuous work should be avoided or limited to extremely short periods.[17]

The heat strain index is widely accepted as an example of an index that includes environmental and physiologic factors. There are several variations and modified heat strain indexes in existence, with varying ease of use and accuracy (Fig. 139-2).[16]

Before the advent of air-conditioning, mortality increased threefold to fivefold in nursing homes and threefold in the general population during heat waves. Mortality in geriatric patients correlates with average weekly peak air temperature. Most deaths in the 2003 European heat wave occurred in elderly patients.[3] Microclimates conducive to heat illness are produced in the interiors of automobiles, tanks, and tents in the sun, as well as engine rooms, hot tubs, and saunas. Children are more susceptible to heat stressors because the higher surface area-to-mass ratios allow increased absorption of heat. They also have lower sweat rates per gland.[18]

Endogenous factors such as hyperthyroidism or pheochromocytoma can also drastically increase heat production. An overdose of sympathomimetics or stimulants such as amphetamines, cocaine, or phencyclidine can cause fatal hyperpyrexia. High ambient temperature is associated with a significant

NATIONAL WEATHER SERVICE
HEAT INDEX CHART

Temp.	Heat index F° (C°) Relative humidity (%) 40	45	50	55	60	65	70	75	80	85	90	95	100
110 (47)	136 (58)												
108 (43)	130 (54)	137 (58)											
106 (41)	124 (51)	130 (54)	137 (58)										
104 (40)	119 (48)	124 (51)	131 (55)	137 (58)									
102 (39)	114 (46)	119 (48)	124 (51)	130 (54)	137 (58)								
100 (38)	109 (43)	114 (46)	118 (48)	124 (51)	129 (54)	136 (58)							
98 (37)	105 (41)	109 (43)	113 (45)	117 (47)	123 (51)	128 (53)	134 (57)						
96 (36)	101 (38)	104 (40)	108 (42)	112 (44)	116 (47)	121 (49)	126 (52)	132 (56)					
94 (34)	97 (36)	100 (38)	103 (39)	106 (41)	110 (43)	114 (46)	119 (48)	124 (51)	129 (54)	135 (57)			
92 (34)	94 (34)	96 (36)	99 (37)	101 (38)	105 (41)	108 (42)	112 (44)	116 (47)	121 (49)	126 (52)	131 (55)		
90 (32)	91 (33)	93 (34)	95 (35)	97 (36)	100 (38)	103 (39)	106 (41)	109 (43)	113 (45)	117 (47)	122 (50)	127 (53)	132 (56)
88 (31)	88 (31)	89 (32)	91 (33)	93 (34)	95 (35)	98 (37)	100 (38)	103 (39)	106 (41)	110 (43)	113 (45)	117 (47)	121 (49)
86 (30)	85 (29)	87 (31)	88 (31)	89 (32)	91 (33)	93 (34)	95 (35)	97 (36)	100 (38)	102 (39)	105 (41)	108 (42)	112 (44)
84 (29)	83 (28)	84 (29)	85 (29)	86 (30)	88 (31)	89 (32)	90 (32)	92 (33)	94 (34)	96 (36)	98 (37)	100 (38)	103 (39)
82 (28)	81 (27)	82 (28)	83 (28)	84 (29)	84 (29)	85 (29)	86 (30)	88 (31)	89 (32)	90 (32)	91 (33)	93 (34)	95 (35)
80 (27)	80 (27)	80 (27)	81 (27)	81 (27)	82 (28)	82 (28)	83 (28)	84 (29)	84 (29)	85 (29)	86 (30)	86 (30)	87

Figure 139-2. National Weather Service Heat Index Chart.
Key:
- extreme danger
- danger

increase in mortality from cocaine overdose. Many younger patients who die from hyperthermia test positive for cocaine.[19] Heatstroke can occur with delirium resulting from ethanol withdrawal.[20] There are also reports of heatstroke occurring in well-trained military soldiers or athletes who ingest dietary supplements containing ephedrine.[21]

Certain patients undergoing general anesthesia rapidly experience severe hyperthermia, muscular rigidity, and acidosis. This syndrome, termed *malignant hyperthermia*, is the result of a genetically determined instability of skeletal muscle sarcoplasmic reticulum that allows inappropriate intracellular calcium release. Dantrolene, which lowers myoplasmic calcium, is effective in the prevention and treatment of this syndrome.[22]

Malignant hyperthermia is rarely seen in outpatient settings, but a clinically similar entity, *neuroleptic malignant syndrome*, is often encountered. This syndrome is induced by antipsychotic medications and is characterized by muscular rigidity, severe dyskinesia or akinesia, hyperthermia, tachycardia, dyspnea, dysphagia, and urinary incontinence. Although the lead-pipe rigidity and hyperthermia are reminiscent of malignant hyperthermia, the putative mechanism is different. Dopamine receptor blockade in the corpus striatum caused by haloperidol and similar agents produces severe muscle spasticity and dystonia, leading to overproduction of heat. Some antipsychotics also cause suppression of thirst recognition. Other miscellaneous risk factors include obesity,[23] fatigue, lack of sleep, and alcoholism.[24] Individuals with a history of heatstroke, with or without an inherent aberration that predisposed them to the initial episode, are at increased risk for a recurrence.

Fever versus Hyperthermia

It is both diagnostically and therapeutically important to identify patients suffering from a febrile response rather than heat illness. For many years, fever was attributed to pyrogens released by bacteria or viruses (exogenous pyrogens) or to cells undergoing autolysis phagocytic activity (endogenous pyrogens).[25] These circulating pyrogens would directly affect the thermoregulatory control center. It now appears that fever is the result of pyrogens triggering pathways involving cytokine receptors or other signals to reset the thermal set point in the preoptic area of the anterior hypothalamus to a new level above 37° C.[25]

Once this temperature is established, the thermoregulatory center uses all available heat-regulatory servomechanisms to maintain the new temperature. Thus, a patient with fever in an environment previously believed to be thermally comfort-

able begins to feel cold and chooses a warmer environment. This behavioral drive is coordinated with the autonomic mechanisms such as shivering to increase body temperature to the new set point. In most circumstances, temperature elevation is not a significant problem, and therapy is directed at the underlying disease state. Fever does not cause primary pathologic or physiologic damage to humans and does not require primary emphasis in the therapeutic regimen, which is directed at the underlying disease state.[26] However, if temperature-related physiologic changes such as febrile seizures or tachycardia in a patient with marginal cardiac reserve compromise the individual, temperature must be artificially regulated.

Since fever is the product of a molecular interaction that establishes a new physiologic thermal set point, therapeutic attempts to lower temperature are opposed by body mechanisms that attempt to maintain the new set point. Thus, attempts at whole-body cooling produce violent shivering and discomfort.[27] The use of agents to block the causative molecular interaction is the most clinically effective approach. Aspirin and other antipyretics block the action of the pyrogen at hypothalamic receptor sites through inhibition of prostaglandin synthesis.[28] These antipyretics are not effective against and should not be used to control environmental hyperthermia.

MINOR HEAT ILLNESS

Heat Cramps

Physiology

Heat cramps are brief, intermittent, and often severe muscular cramps occurring typically in muscles that are fatigued by heavy work. Heat cramps appear to be related to a salt deficiency. Heat cramps occur most commonly during the first days of work in a hot environment and develop in persons who produce large amounts of thermal sweat and subsequently drink copious amounts of hypotonic fluid.[29]

Clinical Factors

Athletes, roofers, steel workers, coal miners, field workers, and boiler operators are among the most commonly reported victims of heat cramps. Heat cramps tend to occur after exercise when the victim has stopped working and is relaxing (Box 139-2). In this respect, they differ from the cramps experienced by athletes during exercise, which tend to last for several minutes, are relieved by massage, and resolve spontaneously.

Heat cramps are occasionally confused with hyperventilation tetany, which can occur during heat exhaustion. The latter syndrome can be distinguished by the presence of carpopedal spasm and paresthesias in the distal extremities and perioral area. If accompanied by systemic symptoms, heat cramps may be part of salt-depletion heat exhaustion. Heat cramp victims exhibit hyponatremia, hypochloremia, and low serum sodium and chloride levels. Rhabdomyolysis or resultant renal damage is not present with isolated heat cramps.

BOX 139-2 HEAT CRAMPS: ESSENTIALS OF DIAGNOSIS

Cramps of most worked muscles
Usually occur after exertion
Copious sweating during exertion
Copious hypotonic fluid replacement during exertion
Hyperventilation not present in cool environment

Management

Heat cramps are usually rapidly relieved by salt solutions. Commercially available flavored electrolyte solutions are commonly ingested. Mild cases without concurrent dehydration are treated orally with 0.1 or 0.2% salt solution (two to four 10-grain salt tablets [56–112 mEq] or one fourth to one half teaspoon table salt dissolved in a quart of water), which is the general limit of palatability. Severe cases respond rapidly to intravenous isotonic solution (0.9% NaCl). Salt tablets are gastric irritants, delay gastric emptying, and are not recommended.[30]

Heat Edema

Physiology and Clinical Features

Swollen feet and ankles are often reported by nonacclimatized individuals, especially the elderly, who encounter climatic stresses of tropical and semitropical areas. Such individuals often have no underlying cardiac, hepatic, venous, or lymphatic disease. They commonly have assumed rigorous schedules with long periods of sitting or standing. The edema is usually minimal, not accompanied by any significant impairment in function, and often resolves after several days of acclimatization.

It is presumed that hydrostatic pressure and vasodilation of cutaneous vessels, combined with some degree of orthostatic pooling, lead to vascular leak and accumulation of interstitial fluid in the lower extremities. Simultaneously, aldosterone increases in response to the heat stress and perceived central volume deficit.

Awareness of this clinical presentation prevents overly vigorous diagnostic and therapeutic intervention. Brief diagnostic evaluation to rule out thrombophlebitis, lymphedema, or congestive heart failure is appropriate, but invasive diagnostic techniques or vigorous pharmacologic therapy is not indicated.

Management

No evidence exists that diuretic therapy is effective. Rather, simple leg elevation or thigh-high support hose should be used. In most individuals, the problem resolves either through adequate acclimatization or with the individual's return to a home climate.

Heat Syncope

Physiology and Clinical Features

Heat syncope is a perplexing disorder in which a host of serious and an even larger number of nonserious underlying mechanisms can also result in temporary loss of consciousness. The elderly have a special predilection for this disorder. Individuals adapt to a hot, humid environment by dilation of cutaneous vessels to deliver heat to the body surface. Thus, an increased portion of the intravascular pool is located in the periphery at any given time. Increasing blood flow to compliant cutaneous veins raises skin vascular volume at the expense of thoracic blood volume. Individuals who stand for protracted periods tend to pool blood in the lower extremities. Combined with volume loss and peripheral vasodilation, this pooling can result in inadequate central venous return, a concomitant drop in cardiac output, and cerebral perfusion inadequate to maintain consciousness.

Management

The disorder is self-limited because assumption of a horizontal position is curative. Individuals at risk for heat syncope should be warned to move often, flex leg muscles repeatedly when standing stationary, avoid protracted standing in hot environments, and assume a sitting or horizontal position when prodromal warning symptoms or signs occur. These include scintillating scotomata, tunnel vision, vertigo, nausea, diaphoresis, and weakness.

Prickly Heat

Physiology and Clinical Features

Prickly heat, also known as miliaria rubra, lichen tropicus, and heat rash, is an acute inflammatory disorder of the skin that occurs in tropical climates. It is the result of blockage of sweat gland pores by macerated stratum corneum and secondary staphylococcal infection. The acute phase is characterized by vesicles in the malpighian layer of the skin caused by dilation and rupture of the obstructed sweat gland ducts.

Clinically, this initially produces intensely pruritic vesicles on an erythematous base. The rash is confined to clothed areas, and the affected area is often completely anhidrotic. During approximately the next week, a keratin plug arises and fills these vesicles, causing a deeper obstruction of the sweat gland duct. The obstructed duct then ruptures a second time, producing a deeper vesicle within the dermis. This is known as the profunda stage, and it can persist for weeks. Profunda vesicles are not pruritic and closely resemble the white papules of piloerection; chronic dermatitis is a common complication.

Management

Chlorhexidine in a light cream or lotion is the antibacterial treatment of choice during the acute phase. Salicylic acid, 1%, can be applied three times daily to localized, affected areas to assist in desquamation, but it should not be used in children or over large areas because of possible salicylate intoxication. For diffuse or pustular rashes, erythromycin can be helpful.

Prickly heat can be prevented by wearing light, loose-fitting, clean clothing and the avoidance of situations that produce continuous sweating. Routine use of talcum or baby powder should be avoided.

HEAT EXHAUSTION

Physiology

Heat exhaustion (heat prostration) is a clinical syndrome characterized by volume depletion that occurs under conditions of heat stress. Two types of heat exhaustion are classically described: water depletion and salt depletion. *Water depletion* heat exhaustion results from inadequate fluid replacement by individuals working in a hot environment, usually laborers, athletes, military personnel, or incapacitated individuals without free access to water. Those working in the heat seldom drink as much as they lose and replace only approximately two thirds of net water loss. This "voluntary dehydration" results in progressive hypovolemia. Left untreated, water depletion heat exhaustion will progress to heatstroke.

Salt depletion heat exhaustion takes longer to develop than the water depletion form. It occurs when large volumes of thermal sweat are replaced by water with too little salt. It differs from heat cramps in that systemic symptoms occur. This syndrome is characterized by hyponatremia, hypochloremia, and low urinary sodium and chloride concentrations. Symptoms are similar to those seen in water depletion heat exhaustion; body temperature usually remains near normal.

BOX 139-3 HEAT EXHAUSTION: DIAGNOSIS

Vague malaise, fatigue, headache
Core temperature often normal; if elevated, less than 40° C (104° F)
Mental function essentially intact; no coma or seizures
Tachycardia, orthostatic hypotension, clinical dehydration (may occur)
Other major illness ruled out
If in doubt, treat as heatstroke

Clinical Features

The symptoms and signs associated with both types of heat exhaustion are variable and nonspecific and include weakness, fatigue, frontal headache, impaired judgment, vertigo, nausea and vomiting, and occasionally muscle cramps (Box 139-3). Orthostatic dizziness and syncope can occur. Sweating persists and may be profuse. The core temperature is only moderately elevated, usually less than 40° C, and signs of severe CNS dysfunction are not present.

Mild heat exhaustion and full-blown heatstroke represent extremes of the spectrum of heat illness, and intermediate cases may prove difficult to differentiate. Nevertheless, heat exhaustion should not be diagnosed in the presence of major CNS dysfunction (seizures and coma) or severe hyperthermia (>40.5° C). If uncertainty exists, measurement of hepatic transaminases may prove helpful. Elevations to several thousand units can be seen in patients with heat exhaustion or in healthy runners after a marathon, whereas in patients with heatstroke, such levels are usually in the tens of thousands after 24 hours.[31,32]

Management

Pure forms of either type of heat exhaustion are rare, and most cases of heat exhaustion involve mixed salt and water depletion. Heat exhaustion is primarily a volume depletion problem, and rapid recovery generally follows fluid administration. Decisions regarding the type of fluid and electrolyte replacements should be based on serum electrolyte measurements and the estimation of hydration status by clinical and laboratory parameters.

Patients with significant volume depletion or electrolyte abnormalities generally require intravenous fluids. If the patient is orthostatic, normal saline should be administered until he or she is hemodynamically stable. Free water deficits should be replaced slowly over 48 hours so as not to decrease serum osmolality more than 2 mOsm/hr. Overly rapid correction of hypernatremia is associated with seizures caused by cerebral edema.

Disposition

Young, otherwise healthy patients who do not have significant laboratory abnormalities and who respond rapidly to hydration do not require hospitalization. These patients can be discharged with instructions to drink plenty of fluids and avoid heat stress for 24 to 48 hours. Older patients, particularly those

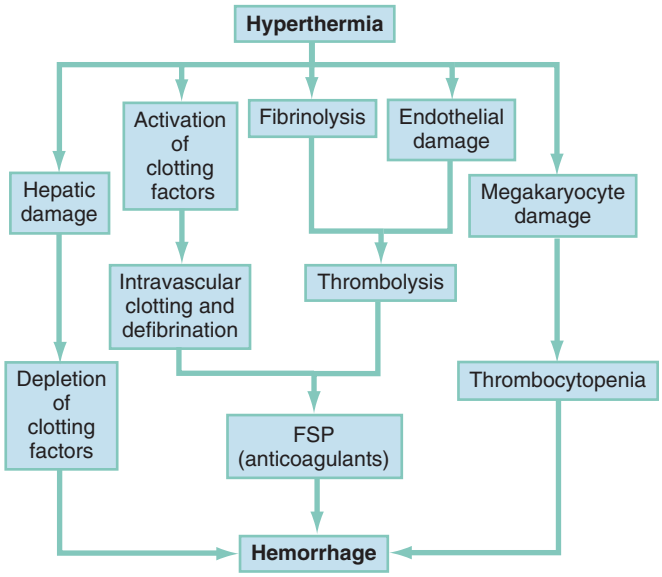


Figure 139-3. Pathogenesis of hemorrhage. FSP, fibrin split products.

BOX 139-4 HEAT EXHAUSTION: TREATMENT

Rest
Cool environment
Assess volume status (orthostatic changes, BUN, hematocrit, serum sodium)
Fluid replacement: normal saline to replete volume if patient orthostatic; replace free water deficits slowly to avoid cerebral edema
Healthy young patients usually treated as outpatients; consider admission if patient is elderly, has significant electrolyte abnormalities, or would be at risk for recurrence if discharged

BUN, blood urea nitrogen.

with cardiovascular disease or other predisposing factors described in Figure 139-3, require more cautious fluid and electrolyte replacement and frequent reassessment. They are best managed as inpatients (Box 139-4).

HEATSTROKE

In the previously discussed forms of heat illness, although the body temperature rises, homeostatic thermoregulatory mechanisms remain intact. Heatstroke is the catastrophic life-threatening emergency that occurs when these mechanisms fail. This failure results in elevation of body temperature to extreme levels, usually greater than 40.5° C (105° F), producing multisystem tissue damage and organ dysfunction.

Physiology

As heatstroke develops, energy will be insufficient to sustain thermoregulatory mechanisms, resulting in dramatic increases in core temperature and the clinical manifestations of heatstroke.[33] An exact temperature at which cellular damage begins to occur in an individual patient varies. Credible reports exist of full recovery despite rectal temperatures of 44.4° C to 46.5° C.[34] Damage is a function not only of temperature but also of the exposure time.[35] The resultant damage to tissues is a function of a complex interaction of body temperature, exposure time, work load, tissue perfusion, and individual factors, which vary markedly.

Neurologic dysfunction is a hallmark of heatstroke, and cerebral edema is common. Other pathologic changes include petechiae in the walls of the third and fourth ventricles and marked cerebellar Purkinje cell damage.[36] Interestingly, the hypothalamus, the predominant site of central thermoregulatory control, is usually not damaged.

Heat stress creates tremendous demands on the cardiovascular system, and patients who succumb to heatstroke show signs of circulatory failure. Although such pathologic changes are common, cardiac damage alone is not lethal.

Prolonged heat stress produces impressive increases in skin blood flow (peripheral vasodilation) and a reduction of the thermal gradient between the core and the skin. Functional hypovolemia is avoided by compensatory vasoconstriction of the splanchnic and renal vasculature. The resulting splanchnic and renal ischemia may explain the nausea, vomiting, and diarrhea observed in post–marathon runners. Hepatic damage is such a consistent feature of heatstroke that its absence should cast doubt on the diagnosis. This is manifested pathologically by centrilobular necrosis with extensive cholestasis.

If severe heat stress continues, compensatory splanchnic vasoconstriction will eventually fail. Failure to perfuse the skin with heated blood from the core results in a dramatically increased rate of heat storage. This produces elevated intracranial pressure, which, in combination with a reduction in mean arterial pressure caused by failure of compensatory splanchnic vasoconstriction, conspires to produce a decrease in cerebral blood flow. This results in the major CNS dysfunction characteristic of heatstroke.

Clinical Features

Heatstroke versus Heat Exhaustion

The onset of heatstroke is sudden, and the patient's level of consciousness is altered.[36] Prodromal symptoms lasting minutes to hours occur in approximately 20% of cases. These are nonspecific and may include weakness, dizziness, nausea, vomiting, anorexia, frontal headache, confusion, drowsiness, disorientation, muscle twitching, ataxia and signs of cerebellar dysfunction, and psychiatric symptoms ranging from anxiety and irritability to psychosis.[37,38]

These prodromal symptoms are reminiscent of the description of heat exhaustion. Heat exhaustion, particularly the water depletion variety, can progress to heatstroke if untreated. These two syndromes should be considered extremes on a spectrum of responses to heat stress. Heatstroke occurs when the thermoregulatory responses are overwhelmed and fail. If the patient is evaluated as this is occurring, differentiation between heat exhaustion and heatstroke is very difficult. If heatstroke cannot be excluded, efforts to cool the patient should begin immediately.

The usual manifestations of heatstroke include hyperpyrexia above 40.5° C, profound CNS dysfunction, and hot skin (Box 139-5). Persistent sweating can be observed in patients with rectal temperatures of 41.5° C to 42.4° C with heatstroke. In one large series of exertional heatstroke victims, sweating persisted in 50% of cases.[39] Therefore, the cessation of sweating is not the cause of heatstroke, and continued sweating does not preclude the diagnosis.

Although in heatstroke the core temperature is elevated above 40.5° C, significant cooling may occur in the out-of-hospital phase, and the first temperature obtained in the emergency department may not represent the original maximum core temperature.

BOX 139-5 HEATSTROKE: DIAGNOSIS

Exposure to heat stress, endogenous or exogenous
Signs of severe CNS dysfunction (coma, seizures, delirium)
Core temperature usually above 40.5° C (105° F), but may be lower
Hot skin common, and sweating may persist
Marked elevation of hepatic transaminases

CNS, central nervous system.

Table 139-1 Usual Characteristics of Heatstroke

EXERTIONAL	CLASSIC
Healthy	Predisposing factors/medications
Younger	Older
Exercise	Sedentary
Sporadic	Heat wave occurrence
Diaphoresis	Anhidrosis
Hypoglycemia	Normoglycemia
DIC	Mild coagulopathy
Rhabdomyolysis	Mild CPK elevation
Acute renal failure	Oliguria
Marked lactic acidosis	Mild acidosis
Hypocalcemia	Normocalcemia

CPK, creatinine phosphokinase; DIC, disseminated intravascular coagulation.

Classic Heatstroke versus Exertional Heatstroke

The two forms of heatstroke have significantly different presentations and manifestations: classic (epidemic) heatstroke (CHS) and exertional heatstroke (EHS) (Table 139-1).

Classic heatstroke occurs during periods of sustained high ambient temperatures and humidity, such as during summer heat waves. Victims are often elderly and poor and live in underventilated dwellings without air-conditioning. Debilitated patients who have limited access to oral fluids may develop water-depletion heat exhaustion, which progresses to heatstroke if untreated. Victims of CHS commonly suffer from chronic diseases, alcoholism, or schizophrenia, which predispose to heat illness. Such patients are often prescribed medications (e.g., diuretics, antihypertensives, neuroleptics, and anticholinergics) that impair the ability to tolerate heat stress. Sweating ceases in the majority of CHS patients. Factors such as advanced age, hypotension, altered coagulation status, and the necessity for endotracheal intubation on arrival at the emergency department predict a poor outcome despite successful cooling measures.[40]

In contrast, patients with EHS are usually young and healthy individuals whose heat-dispelling mechanisms are overwhelmed by endogenous heat production. Athletes and military recruits are typical victims.[41-43] Rhabdomyolysis and acute renal failure, rarely seen in patients with CHS, are common in patients with EHS.[44] Sweating is present in half the cases of EHS. Hypoglycemia may occur as the result of increased glucose metabolism and hepatic damage resulting in impaired gluconeogenesis. Coagulopathy is common. Hyponatremia with serum sodium levels less than 130 mmol/L has been detected in summer hikers in the Grand Canyon; many present with neurologic symptoms or seizures.[42]

Signs of profound CNS dysfunction dominate the early course of heatstroke. Delirium or coma is characteristic, but virtually any neurologic abnormality, including bizarre behavior, opisthotonus, hallucinations, decerebrate rigidity, oculogyric crisis, and cerebellar dysfunction, can be seen.[39] Convulsions occur in up to 75% of patients and can be precipitated by therapeutic cooling maneuvers. Profound muscle rigidity with tonic contractions, coarse tremor, and dystonic movements can mimic seizures. Pupils may be fixed and dilated, and the electroencephalogram may be isoelectric. All these changes are potentially reversible, although permanent damage, including cerebellar deficits, hemiplegia, dementia, and personality changes, is common in severe cases. Patients with heatstroke usually have hyperdynamic cardiovascular systems with low peripheral vascular resistance, tachycardia (up to 180 beats/min), and an elevated cardiac index. The central venous pressure (CVP) is usually elevated. The combination of elevated CVP with right-sided cardiac dilation suggests right-sided cardiac failure, which is also seen after shock or sepsis.[45] These changes are expected because skin blood vessels dilate to dissipate heat; however, this low peripheral vascular resistance has persisted in patients after reduction of body temperature to near normal.

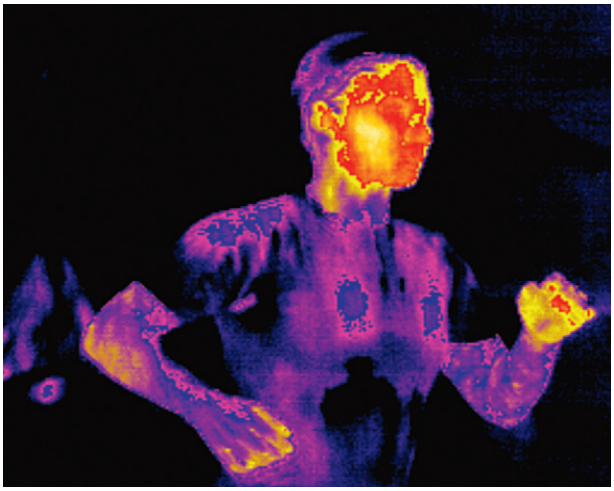


Figure 139-4. Human infrared image. Note that the palms and the face are substantially warmer than the rest of the body. (From Auerbach's Wilderness Medicine, 5th ed., Mosby, 2007, ch. 10, p. 233.)

Respiratory alkalosis is a physiologic response to active or passive heating and may be severe enough to produce tetany. Although most patients with CHS have respiratory alkalosis, those with EHS usually have a relatively pure lactic acidosis. Lactic acidosis is associated with a poor prognosis in cases of CHS but not necessarily in cases of EHS.

Aberrations in coagulation are common in patients with severe heatstroke, and their presence is a poor prognostic sign (Fig. 139-4). Abnormal hemostasis is manifested clinically by purpura, conjunctival hemorrhage, melena, bloody diarrhea, hemoptysis, hematuria, myocardial bleeding, or hemorrhage into the CNS.[46]

Hepatic damage is so consistently featured in heatstroke that its absence should cast doubt on the diagnosis. Hepatic injury is evidenced by markedly elevated levels of hepatic aminotransferases (serum aspartate transaminase and alanine transaminase). Jaundice typically appears 24 to 72 hours after the onset of severe heatstroke and gradually recedes if the victim survives. Survivors generally have no permanent impairment of liver function. Hypoglycemia with a serum glucose level less than 65 mg/dL is common in cases of exertional heatstroke.[47]

Renal damage is common. The initial urine specimen, usually obtained by catheterization, is a scanty, brownish, turbid fluid resembling machine oil. Microscopic examination

reveals proteinuria with abundant granular casts and red blood cells. Acute oliguric renal failure complicates 25 to 30% of EHS cases and 5% of CHS cases. Glomerular filtration rate, renal plasma flow, urine flow, and sodium excretion diminish markedly during exercise. Heavy physical exertion in hot climates produces acidic and maximally concentrated urine, which can result in acute oliguric renal failure when combined with hypotension and myoglobinuria.[29] Cocaine use is also associated with rhabdomyolysis and hyperthermia.[48]

Diarrhea, probably caused by intense splanchnic vasoconstriction, is commonly seen. Cooling aggravates the diarrhea, creating an unpleasant treatment problem. Pancreatitis is described with elevated serum amylase and lipase levels.

Diagnostic Strategies

Thermometry

Unfortunately, most standard measurements of body temperature vary significantly from the actual core temperature. Oral thermometry is affected by mouth breathing and is a poor approximation of the core. Rectal thermometry is less variable but responds to changes in core temperature slowly. Thermistors that are inserted 15 cm into the rectum offer continuous monitoring of temperature and less variability. Although slower to respond to changes in core temperature than tympanic temperature readings, rectal measurements are not biased by head skin temperature. An esophageal thermistor positioned adjacent to the heart is another option.

Placement of a tympanic temperature sensor directly on the tympanic membrane is difficult and is not used clinically. Commercially available infrared thermometers do not physically contact the tympanic membrane and are unreliable in detecting hyperthermia.[49] If a patient is being monitored with a catheter, pulmonary arterial temperature can be measured precisely with a thermistor catheter.

Only after the initial assessment and cooling have begun is the differential diagnosis relevant. When a history of collapse under conditions of heat stress is present, rapid improvement in mental status and blood pressure with cooling eliminates alternative diagnoses. If, however, the temperature does not respond and the patient does not recover neurologically, other causes of fever and coma must be considered (Box 139-6).

The history may be helpful; shaking chills suggest fever with an altered hypothalamic set point rather than heat illness. Meningitis and encephalitis can masquerade as heatstroke. In patients with heatstroke, the spinal fluid should be crystal clear, with occasional lymphocytic pleocytosis and elevated protein levels. Cerebral falciparum malaria, which presents a clinical picture of high fever and encephalitis, is seen in tropical areas where heat illness can also occur.

BOX 139-6 DIFFERENTIAL DIAGNOSIS OF HEATSTROKE

CNS hemorrhage
Toxins/drugs
Seizures
Malignant hyperthermia
Neuroleptic malignant syndrome
Serotonin syndrome
Thyroid storm
High fever/sepsis
Encephalitis/meningitis

CNS, central nervous system.

In patients with thyroid storm, the clinical symptoms resemble those of heatstroke. It should be suspected if the thyroid gland is enlarged or nodular, but a normal thyroid gland does not exclude the diagnosis. Thyroid function test results are elevated, but these are not available on an emergency basis. Fortunately, thyroid storm is rare, and some critical aspects of treatment, such as rapid cooling, coincide with those for heatstroke.

Drug-induced heat illness is an important consideration, particularly anticholinergic poisoning. Differentiation may be difficult because both heatstroke and anticholinergic poisoning produce hyperpyrexia, hot and dry skin, tachycardia, and abnormal mental status. Constricted pupils are present in many heatstroke patients.[50] Mydriasis should be present in patients with anticholinergic poisoning, and its absence argues strongly against this diagnosis. Typhoid fever, typhus, delirium tremens, and hypothalamic hemorrhage all produce symptom complexes similar to that of heatstroke.

Malignant hyperthermia and neuroleptic malignant syndrome are characterized by "lead pipe" rigidity. The serotonin syndrome can also mimic heatstroke because of the elevated body temperature tremors and CNS alterations that occur. Serotonin syndrome is classically a triad of mental status changes, autonomic hyperactivity, and neuromuscular abnormalities secondary to increased CNS serotonergic activity. Recent exposure to illicit or therapeutic medication is important.

Hepatic transaminase elevations may be diagnostically helpful. In most febrile states that include altered mental status or coma, these enzymes will be normal or minimally elevated, although they are usually dramatically elevated early in the course of heatstroke.

MANAGEMENT

It does not take long either to boil an egg or to cook neurons.

D. Hamilton[51]

Cooling

Immediate cooling is the cornerstone of treatment. Mortality correlates with the temperature and the number of dysfunctional organ systems, with an increased risk of death if patients present with anuria, coma, or cardiovascular failure.[3] Patients who present to the hospital with heat stroke have high mortality rates ranging from 21 to 63%,[3,52] and mortality increases significantly when cooling is delayed.[53,54] Cooling efforts take precedence over any time-consuming search for the cause. In the out-of-hospital setting, cooling should be initiated after removing the patient from the hot environment. When the patient arrives at the hospital, clothes should be removed, a thermistor probe should be inserted, and the temperature should be continuously monitored.

The ideal method of evaporative cooling uses a body cooling unit on which the patient lies suspended on a net surface while being sprayed with atomized 15°C water from above and below.[55] Air warmed to 45°C to 48°C is blown over the skin surface at 3 m/min. The unit, not widely available, maximizes evaporative cooling by maintaining cutaneous vasodilation and avoiding heat generation caused by shivering.

Less complex equipment can also be used to maximize evaporative cooling. Evaporative cooling is the most widely used cooling method. The combination of atomized tepid water at 40°C from a spray bottle and standing fans cool at rates comparable to both body cooling unit and immersion.[56]

BOX 139-7 Cooling Modalities to Lower Body Temperature in Heatstroke

Preferred

Evaporative cooling using large circulating fans and skin wetting
Ice water immersion

Adjuncts

Ice packs to axillae and groin
Cooling blanket
Peritoneal lavage (unproven efficacy in humans)
Rectal lavage
Gastric lavage
Cardiopulmonary bypass

Other evaporative techniques, including the use of downdraft from a helicopter, can be applied successfully.[57]

Immersion in ice water results in a rapid reduction of core temperature to less than 39° C within 10 to 40 minutes but complicates the resuscitation.[53] Vigorous skin massage to maintain cutaneous circulation has been advocated, but there is no objective evidence that this is efficacious. When the body temperature reaches 39° C, cooling measures should be discontinued to avoid hypothermic overshoot. Continuous monitoring is necessary to maintain the core temperature at 37° C to 38° C.[54]

Military studies of EHS patients treated with ice water immersion have reported no fatalities or permanent sequelae.[41] A mortality rate of 14% was reported in a study of 28 patients with CHS treated by immersion.[50] Immersion is technically difficult in the emergency department. Vasoconstriction from ice water immersion may be beneficial to hypotensive patients and may be better than evaporative cooling for victims in shock who have poor peripheral circulation.

Cooling modalities other than evaporation and immersion should be considered adjunctive treatments (Box 139-7). Application of ice packs to high heat transfer areas (neck, groin, and axillae) is commonly used. Cooling blankets may be a useful adjunct but will not produce rapid cooling if used exclusively. Cardiopulmonary bypass with a heat exchanger has been successful in the treatment of malignant hyperthermia.[58] Peritoneal dialysis with cold fluids, although successful in a canine model, remains untested in humans. Cold-irrigant gastric or rectal lavage will not provide significant heat exchange if used as the primary cooling modality.

Resuscitation

Aspiration and seizures are common in patients with heatstroke, and airway control is essential.[59] Hypoxemia may occur because of aspiration, pneumonitis and pulmonary infarction, hemorrhage, or edema. Metabolic demands are high, and normal pulmonary ventilation may be inadequate in this setting.

Circulatory fluid requirements are modest in some cases, averaging 1200 mL of isotonic crystalloid solution in the first 4 hours. Pulmonary edema occurs in patients with heatstroke and can be exacerbated by overzealous fluid administration. The use of a CVP catheter to monitor fluid resuscitation may be deceptive. Most patients have a hyperdynamic circulation with high cardiac index, low peripheral vascular resistance, and elevated CVP as a result of right-sided heart failure. These patients may require only modest intravenous fluids because cooling produces vasoconstriction and increases blood pressure.[60] Nevertheless, crystalloid resuscitation is essential.

Hypotension is common in patients with heatstroke and is usually caused by peripheral vasodilation resulting in high-output cardiac failure, in addition to dehydration. Blood pressure usually rises with cooling. If this does not occur, or if the patient monitored invasively has a low central venous pressure, a fluid challenge of 250 to 500 mL of 0.9% saline should be given rapidly while blood pressure, pulse, and urine output are monitored. If the blood pressure rises, further fluids are given with careful monitoring of the CVP. Aggressive fluid replacement is continued until the blood pressure reaches 90/60 mm Hg or the CVP exceeds 12 mL H_2O. Occasionally, patients exhibit hypodynamic responses with low cardiac index, elevated CVP, and hypotension. These patients may be cyanotic, whereas patients with hyperdynamic circulation are initially pink. This clinical observation can be helpful in identifying patients who may respond to catecholamines.

A variety of tachyarrhythmias commonly occur during heatstroke. These usually resolve with cooling, and electrical cardioversion should be avoided until the myocardium is cooled. The use of alpha-adrenergic agents such as norepinephrine is not recommended because they promote vasoconstriction without improving cardiac output or perfusion, decrease cutaneous heat exchange, and may enhance ischemic renal and hepatic damage. Atropine and other anticholinergic drugs that inhibit sweating should be avoided.

Because the pathophysiologies of heatstroke and fever differ, antipyretics are not indicated and may be harmful. Salicylates, particularly in large doses, can worsen hyperthermia by uncoupling oxidative phosphorylation and aggravate coagulopathies. Large doses of acetaminophen can result in further hepatic damage. The efficacy of dantrolene is not established.[61]

If rhabdomyolysis is present, maintenance of urinary output of at least 2 mL/kg/hr is required.[62] Urinary alkalinization has been supported by animal studies and retrospective reviews, and it should be considered early in patients with acidemia, dehydration, or underlying renal disease. Urine pH should be titrated to greater than 6.5. After volume repletion, administration of mannitol may be considered to increase intravascular volume and increase glomerular filtration rate. Mannitol should not be used in an oliguric patient.[63] Persistent anuria, uremia, or hyperkalemia is an indication for consideration of hemodialysis.

Hematologic evaluation should include arterial blood gas determination; complete blood cell count and platelet counts; electrolytes, blood urea nitrogen, glucose, creatinine, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, creatine phosphokinase, uric and lactic acid, and calcium levels; prothrombin and partial thromboplastin times; international normalized ratio; and fibrin degradation products and hepatic enzymes. Bedside cardiac markers should be considered. Acidosis is common, especially in patients with exertional heatstroke. Lactate levels are usually elevated; this may persist or even worsen with improved extremity perfusion.

Cooling modalities that drastically lower skin temperature may induce violent shivering; this increases metabolic heat production and may impede cooling. In this situation, intravenous benzodiazepines or chlorpromazine (25–50 mg intravenously) can be efficacious. Chlorpromazine has anticholinergic properties that can interfere with sweating and cause hypotension or, rarely, precipitate seizures. Therefore, its use should be reserved for instances when cooling is not adequate because of vigorous shivering.

Many patients are extremely agitated during the initial cooling period. Short-acting benzodiazepines can be used for sedation and to control seizures.[64] Barbiturates are less desir-

able for treatment of seizures since metabolism is altered by hepatic dysfunction.

Coagulopathies can occur during the first day of illness but are more common on the second and third days. Initial treatment after cooling should include replacement therapy with fresh frozen plasma and platelets.[46] The clinician should monitor the laboratory signs of disseminated intravascular coagulation (hypofibrinogenemia, elevated fibrin split products, prolonged prothrombin time, and thrombocytopenia).[46] The bleeding diathesis in patients with heatstroke may be the result of fibrinolysis. Although α-amino caproic acid can impede fibrinolysis, administration of this compound is associated with rhabdomyolysis and its use is not recommended in patients with heatstroke.

KEY CONCEPTS

- Antipyretics are ineffective and should not be used to control environmental hyperthermia.
- The symptoms and signs of heat exhaustion often mimic those of viral illnesses.
- Patients with exertional heatstroke are commonly diaphoretic.
- Rapid (convective) cooling of the potential heatstroke patient should be initiated before the differential diagnosis is firmly established.
- Heatstroke can cause right-sided cardiac dilation and elevated CVP, clinically resemble pulmonary edema, and yet require vigorous crystalloid resuscitation.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 140

Electrical and Lightning Injuries

Timothy G. Price and Mary Ann Cooper

PERSPECTIVE

Electrical Injury

The first recorded death caused by electrical current from an artificial source was reported in 1879 when a carpenter in Lyons, France, inadvertently contacted a 250-V alternating current (AC) generator.[1] The first U.S. fatality occurred in 1881 when an inebriated man passed out on a similar generator in front of a crowd in Buffalo, New York.

In the United States, electrical burns account for 4 to 6.5% of all admissions to burn units and approximately 1000 fatalities per year.[2] Occupational electrical incidents are uncommon but account for nearly 6% of all occupational fatalities annually.[3] Children have a predisposition to injuries from low-voltage sources, such as electric cords, because of their limited mobility within a relatively confined environment. During adolescence, a more active exploration of the environment leads to more severe high-voltage injuries or death. At the time of presentation, documentation of injuries is important not only for the immediate resuscitation of the victim but also for medicolegal reasons. Many electrical injuries eventually involve litigation for negligence, product liability, or worker compensation.

Lightning Injury

The incidence of injury and death from lightning is unknown since no agency requires the reporting of lightning injuries, and some victims do not seek treatment at the time of their injury. The incidence of lightning-related deaths in the United States has declined to an average of 62 people annually.[4] Lightning is fatal in 1 of 10 lightning strike victims.[5] In typical years, lightning kills more people in the United States than any other natural disaster except floods, and it is consistently among the top four weather-related killers (Fig. 140-1).

Participants in sports and recreational activities are common victims; mountain activities, golf, ball field games, and water activities account for the largest numbers of fatalities and injuries.[5] Outdoor workers, particularly on construction sites or on farms, are also vulnerable.[4] Lightning incidents often involve more than one victim when the current "splashes" to other individuals or as ground current spreads the electrical power throughout the area where a group is sheltered in a storm. The largest number of victims reported from a single lightning strike is 35 (28 people and 7 dogs). All of the victims were sleeping in a large tent, and 4 children and 4 dogs were fatally injured.[6]

Certain snowy conditions can also result in lightning and put skiers at risk for lightning injury. The formation of sleet and *graupel*, a type of frozen precipitation sometimes referred to as *snow pellets* or *soft hail*, reflects large differences in electrical potential in the atmosphere. Winter sports enthusiasts should recognize graupel and appreciate the associated lightning risks.[7]

PRINCIPLES OF DISEASE

Physics of Injury

The exact pathophysiology of electrical injury is not well understood because of the numerous variables that cannot be measured or controlled when an electrical current passes through tissue. With high voltage, most of the injury seems to be thermal, and histologic studies reveal coagulation necrosis consistent with thermal injury.[8,9] The theory of *electroporation* is that electrical charges insufficient to produce thermal damage cause protein configuration changes that threaten cell wall integrity and cellular function.[10]

The nature and severity of electrical burn injury are directly proportional to the current strength, resistance, and duration of current flow (Box 140-1). *Current strength* is expressed in amperes and is a measure of the amount of energy flowing through an object. Current is determined by the voltage and resistance.[11] Resistance is determined by the current's pathway through the body. The factors determining the severity of burn injury are summarized in Box 140-2.

Type of Circuit

One of the factors affecting the nature and severity of electrical injury is the type of circuit involved, either direct current (DC) or AC. High-voltage DC contact tends to cause a single muscle spasm, often throwing the victim from the source. This results in a shorter duration of exposure but increases the likelihood of traumatic blunt injury. Brief contact with a DC source can also result in disturbances in cardiac rhythm, depending on the phase of the cardiac cycle affected.

AC exposure of the same voltage tends to be three times more dangerous than DC. Continuous muscle contraction, or tetany, can occur when the muscle fibers are stimulated between 40 and 110 times per second. The standard frequency of electrical transmission in the United States is 60 Hz (cycles per second), which is near the lowest frequency at which an incandescent light appears to be continuously lit.

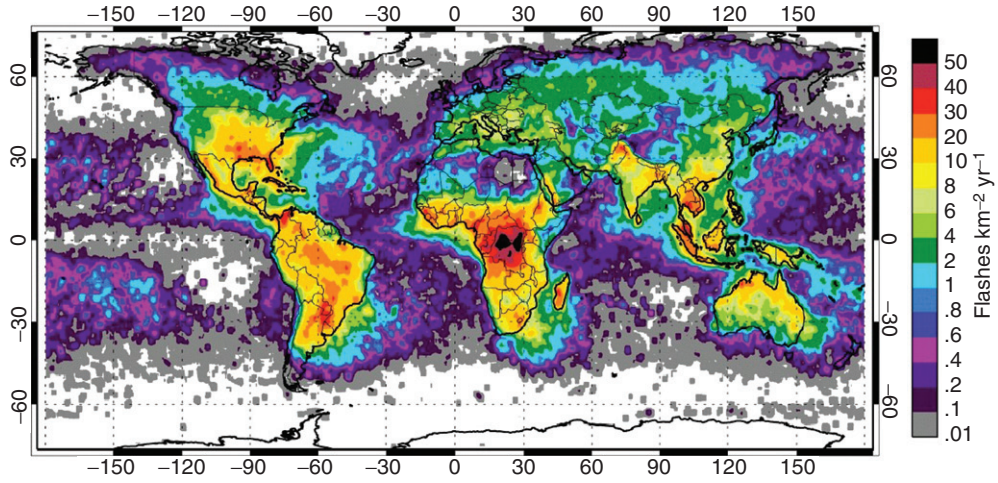


Figure 140-1. Global frequency and distribution of lightning as observed from space by the Optical Transient Detector. (From Christian HJ, et al: Global frequency and distribution of lightning as observed from space by the Optical Transient Detector. J Geophys Res 108[D1]:4005, 2003.)

BOX 140-1 ELECTROTHERMAL HEATING FORMULAS

$$P = I^2Rt$$

and

$$I = V/R$$

where
P = thermal power (heat), in joules
I = current, in amperes (A)
R = resistance, in ohms (Ω)
t = time, in seconds
V = potential, in volts (V)

BOX 140-2 FACTORS DETERMINING ELECTRICAL INJURY

Type of circuit
Duration
Resistance of tissues
Voltage
Amperage
Pathway of current

BOX 140-3 RESISTANCE OF BODY TISSUES

Least
Nerves
Blood
Mucous membranes
Muscle

Intermediate
Dry skin

Most
Tendon
Fat
Bone

The terms *entry* and *exit* are commonly used to describe electrical injury patterns. The terms *source contact point* and *ground contact point* are more appropriate, however, when referring to AC injuries. The hand is the most common site of contact via a tool that is in contact with an AC electrical source. Because the flexors of the hand and forearm are much stronger than the extensors, contraction of the flexors at the wrist, elbow, and shoulder occurs, causing the hand grasping the current source to pull the source even closer to the body. Currents greater than the "let-go threshold" (6–9 mA) can prevent the victim from releasing the current source, which prolongs the duration of exposure to the electrical current.

Resistance

Resistance is the tendency of a material to resist the flow of electrical current. It is specific for a given tissue, depending on its moisture content, temperature, and other physical properties. The higher the resistance of a tissue to the flow of current, the greater the potential for transformation of electrical energy to thermal energy. Nerves, designed to carry electrical signals, and muscle and blood vessels, because of their high electrolyte and water content, have a low resistance and are good conductors. Bone, tendon, and fat, which all contain a large amount of inert matrix, have a high resistance and tend to heat and coagulate rather than transmit current. The other tissues of the body are intermediate in resistance (Box 140-3).[12]

Skin is the primary resistor to the flow of current into the body. Skin on the inside of the arm or back of the hand has a resistance of approximately 30,000 Ω/cm^2. Hardened skin can have 20 to 70 times greater resistance (Table 140-1).[9] This high resistance may result in a significant amount of energy being expended at the skin surface as the current burns its way through deep callus, resulting in greater thermal injury to the skin but less internal damage than would be expected if the current is delivered undiminished to the deep tissues. As the duration of contact increases, however, the skin begins to blister and offer decreased resistance. A surge of current internally can cause extensive deep tissue destruction. Moisture also lowers resistance. Sweating can decrease the skin's resistance to 2500 to 3000 Ω/cm^2, and immersion in water causes a further reduction to 1200 to 1500 Ω/cm^2.

Amperage

Current, expressed in amperes, is a measure of the amount of energy that flows through an object. As defined by Joule's law, the heat generated is proportional to the amperage squared.[11]

Table 140-1 Skin Resistance

TISSUE	RESISTANCE (Ω/CM²)
Mucous membranes	100
Vascular areas	
Volar arm, inner thigh	300–10,000
Wet skin	
Bathtub	1,200–1,500
Sweat	2,500
Other skin	10,000–40,000
Sole of foot	100,000–200,000
Heavily calloused palm	1–2 million

Table 140-2 Physical Effects of Different Amperage Levels at 50 to 60 Hz

PHYSICAL EFFECT	CURRENT (MA)
Tingling sensation	1–4
Let-go current	
Children	4
Women	7
Men	9
Freezing to circuit	10–20
Respiratory arrest from thoracic muscle tetany	20–50
Ventricular fibrillation	60–120

Amperage depends on the source voltage and the resistance of the conductor and normally must be estimated in human electric exposures. Although the voltage of the source is often known, the resistance varies according to the involved tissues. In addition, as tissue changes occur secondary to the energy of the current flow, resistance may change markedly, rendering predictions of amperage difficult for any given electrical injury.

The physical effects vary with different amperages at 50 to 60 Hz, which is the AC frequency used in European countries and the United States (Table 140-2). A narrow range exists between the threshold of perception of current (0.2–0.4 mA) and *let-go current* (6–9 mA). The let-go current is the level above which muscular tetany prevents release of the current source. Thoracic tetany also can occur at levels just above this let-go current and result in respiratory arrest. Ventricular fibrillation occurs at an amperage of 60 to 120 mA. Dry skin in contact with a 120-V household source results in significantly lower current than the same voltage across skin submerged in water. This wet skin may result in current sufficient to cause electrocution with cardiac arrest with no surface burns.

Duration of Contact

The longer the duration of contact with high-voltage current, the greater the electrothermal heating and degree of tissue destruction. When carbonization of tissue occurs, the resistance to current flow increases. The physics differ with lightning. The extremely short duration and extraordinarily high voltage and amperage of lightning result in a short flow of current internally, with little, if any, skin damage and almost immediate flashover of current around the body.

Voltage

Voltage is a measure of the difference in electrical potential between two points and is determined by the electrical source. Electrical injuries are conventionally divided into low or high voltage, with 1000 V the most commonly used divider.[13] Although both can cause significant morbidity and mortality, high voltage results in greater current flow and has a greater potential for tissue destruction and amputations.

No fatalities are recorded from contact with the low voltages associated with long-distance communication lines (24 V) or telephone lines (65 V). Fatalities are reported, however, with exposure to 110-V household current, especially in special environmental circumstances such as bathtub-related electrocutions.

Pathway

The pathway of low, high, or lightning voltages determines the tissues at risk, the type of injury, and the degree of conversion of electrical energy to heat. Current passing through the heart or thorax can cause dysrhythmias and direct myocardial damage. Cerebral current can result in respiratory arrest, seizures, and paralysis. Current with ocular proximity can cause cataracts.

Truncal current causes less damage than current that passes through a single digit. As current density increases, its tendency to flow through the less resistant tissues is overcome. Eventually it flows through tissues indiscriminately, as if the body were a volume conductor, with the potential to destroy all tissues in the current's path. Because the current is often concentrated at the source and ground contact points, the greatest degree of damage is often observed there. Nevertheless, extensive deep destruction of the tissues may exist between these sites with high-voltage injuries, and the surface damage is often only "the tip of the iceberg." Damage to the internal structures of the body may be noncontiguous, with areas of normal-appearing tissue adjacent to burned tissue and with damage to structures at sites distant from the apparent contact points.

The pathway between contact points is a major determinant of the electrical field strength, which is the voltage per unit of length. For a given current, the shorter the distance between contact points, the greater the electrical field strength. Current from a 20,000-V power line passing from head to toe (approximately 2 m) results in an electrical field strength of 10,000 V/m. Approximately the same electrical field strength is created when 120-V household current passes between two close contact points on the mouth of a child chewing on a power cord (120 V/0.01 m). Although the electrical field strengths are similar, there is a tremendous difference in the amount of at-risk tissue in the respective pathways.[13,14]

Although lightning is governed by the same physical laws as artificial electricity, the rapid rise and decay of the energy complicates predictions of the extent of lightning injury more than artificial electrical injury. The most important difference between lightning and high-voltage electrical injuries is the duration of exposure to the current.

Lightning is neither a direct current nor an alternating current but, rather, a unidirectional massive current impulse. Lightning is classed as a *current*, rather than a *voltage*, phenomenon. The cloud-to-ground lightning impulse results from the breakdown of a large electrical field between a cloud and the ground that is measured in millions of volts. When connection is made with the ground, this voltage difference between the cloud and ground disappears, and a large current flows impulsively for a short time.

Mathematical modeling of a lightning strike to the human body is substantiated on animal models.[15] After lightning meets the body, current initially is transmitted internally, after which skin breaks down, and ultimately external "flashover" occurs. A fast flashover appreciably diminishes the energy dissipation within the body and can result in survival.[16]

Although lightning current may flow internally for an instant and short-circuit electrical systems, it seldom causes significant burns or tissue destruction. Burns and myoglobinuric renal failure are not a common injury pattern from lightning. More common manifestations include cardiac and respiratory arrest, vascular spasm, neurologic damage, and autonomic instability.

Lightning tends to cause asystole rather than ventricular fibrillation. Although cardiac automaticity may reestablish a rhythm, the duration of the respiratory arrest may cause secondary deterioration of the rhythm to refractory ventricular fibrillation and asystole.[17] This secondary arrest occurs experimentally in sheep. Other injuries caused by blunt trauma or ischemia from vascular spasms, such as myocardial infarction or spinal artery syndromes, also occur.[18-20]

Mechanisms of Injury

Electrical Injury

The primary electrical injury is the burn. Secondary blunt trauma results from falls or being thrown from the electrical source by an intense muscular contraction or the explosive force that may occur with electric flashes from circuit box or transformer accidents. Electrical burns are classified into four different types (Box 140-4).[21]

Heating of tissues secondary to current causes electrothermal burns. Usually, these burns are a result of a low-voltage shock with a limited affected area. Severe electrothermal burns can occur, however, if a person grips a high-voltage conductor. The prolonged flow of current can result in significant burns anywhere along the current path. Typically, the skin lesions of electrothermal burns are well-demarcated, deep, partial-thickness to full-thickness burns.

The most destructive indirect injury occurs when a victim becomes part of an electrical arc. An electrical arc is a current spark formed between two objects of differing potential that are not in contact with each other, usually a highly charged source and a ground. Because the temperature of an electrical arc is approximately 2500° C, it causes deep thermal burns at the point where it contacts the skin.[12] With electrical arcs, burns may be caused by the heat of the arc, electrothermal heating due to current flow, or flames that result from the ignition of clothing. Instead of a discrete arc, current may jump the gap by splashing across the entire body. These splash burns may cover a large portion of the body but are generally only partial thickness.[21]

At the time of presentation, it is often difficult to determine the mechanism of injury that caused an electrically injured patient's burns. Electrothermal heating is the main cause of muscle damage and is seen almost exclusively in high-voltage accidents with prolonged (seconds) contact and current flow.[21]

The histologic change in muscle injury that results from direct contact with an electrical source is coagulation necrosis with shortening of the sarcomere.[9,12] Muscle damage can be erratic, so areas of viable and nonviable muscle are often found in the same muscle group. Periosteal muscle damage may occur even though overlying muscle appears to be normal. Similar to the muscle damage, serious vascular damage usually occurs only after a high-voltage accident.

Vascular damage is greatest in the media; this can lead to delayed hemorrhage when the vessel eventually ruptures.[12] Intimal damage may result in either immediate or delayed thrombosis and vascular occlusion as edema and clots form on the damaged intimal surface of the vessel over a period of days. The injury is usually most severe in the small muscle branches, where blood flow is slower.[22] This damage to small muscle arteries, combined with mixed muscle viability that is not visible to gross inspection, creates the illusion of "progressive" tissue necrosis.

The absence of a pulse on initial examination may be a result of immediate arterial thrombosis or transient vascular spasm. Pulselessness resulting from vascular spasm should resolve within a few hours. If pulselessness persists after this time, serious vascular injury is likely.

Damage to neural tissue also may occur via several mechanisms. An immediate decrease in neural conductivity occurs with coagulation necrosis similar to that observed in muscle. In addition, it may suffer indirect damage as its vascular supply or myelin sheath is injured or as progressive edema results in a compartment syndrome. Evidence of neural damage may develop immediately or be delayed hours to days. The skull is a common contact point. Histologic studies of the brain reveal focal petechial hemorrhages in the brainstem, cerebral edema, and widespread chromatolysis (the disintegration of chromophil bodies of neurons).[12]

Lightning Injury

Lightning injury may occur by electrical mechanisms (Box 140-5) and by secondary blunt trauma.[23] Lightning strikes near the head may enter orifices such as the eyes, ears, and mouth to flow internally, which may help explain the myriad reported eye and ear symptoms and signs.

Injury from contact occurs when the person is touching an object that is part of the pathway of lightning current, such as a tree or tent pole. Side flash or splash occurs as lightning jumps from its primary strike object to a nearby person on its way to the ground.[18,24,25] Step voltage, a difference in electrical potential between a person's feet, may occur as lightning current spreads radially through the ground. A person is a far better conductor of electricity than the earth. A person who has one foot closer than the other to the strike point has a potential difference between the feet so that the lightning current preferentially flows through the legs and body rather

BOX 140-4 TYPES OF ELECTRICAL BURNS

Direct contact
  Electrothermal heating
Indirect contact
  Arc
  Flame
  Flash

BOX 140-5 MECHANISMS OF LIGHTNING INJURY

Direct strike
  Orifice entry
Contact
Side flash, "splash"
Ground current or step voltage
Blunt trauma

than the ground. This ground current is a common killer of large livestock such as cattle and horses because of the distance between their hind legs and forelegs.

Victims of lightning injury may also be exposed to low-current upward streamers or ball lightning. Cloud-to-ground lightning approaches the earth as charged downward leaders. As the leaders approach, the large electrical field induces a buildup of ground charges that surge upward as upward streamers. This upward surge can travel through objects, including people. If the upward streamer connects with a downward leader, a completed lightning strike occurs. Not all upward streamers connect. Individuals in the path of an upward streamer may be injured even in the absence of a completed lightning strike. Ball lightning is a mobile, luminous, spheroidal, floating or bouncing ball of plasma that lasts a few seconds before suddenly vanishing or exploding.[26] These glowing orbs have been observed traveling down power lines and the aisles of aircraft.

Blunt injury from lightning can occur from two mechanisms. First, the person may be thrown a considerable distance by the sudden, massive contraction caused by current passing through the body. Second, an explosive or implosive force occurs as the lightning pathway is instantaneously superheated then rapidly cooled after the passage of the lightning. The heating is seldom long enough to cause severe burns, but it does cause rapid expansion of air followed by rapid implosion of the cooled air as it rushes back into the void.

CLINICAL FEATURES

Patients with high-voltage injury commonly present with devastating burns. Patients with lightning injury and low-voltage injury may have little evidence of injury or, alternatively, may be in cardiopulmonary arrest. After the initial resuscitation of lightning and low-voltage injuries, other conditions may be identified. These patients may have significant residual morbidity from pain syndromes or cerebral damage.

Head and Neck

Electrical Injury

The head is a common point of contact for high-voltage injuries, and the patient may exhibit burns and neurologic damage. Cataracts develop in approximately 6% of patients with high-voltage injuries, especially whenever electrical injury occurs in the vicinity of the head. Although cataracts may be present initially or develop soon after the accident, they more typically appear months after the injury. Visual acuity and funduscopic examination should be performed at presentation. Hearing loss is much less common.[27]

Lightning Injury

Lightning strikes may cause skull fractures and cervical spine injury from associated blunt trauma.[18,19] Tympanic membrane rupture is commonly found in lightning victims and may be secondary to the shock wave, a direct burn, or a basilar skull fracture.[17] Although most patients recover without serious sequelae, disruption of the ossicles and mastoid, otorrhea, hemotympanum, perilymphatic fistulae, and permanent deafness may occur.[28,29]

Ocular injuries include corneal lesions, uveitis, iridocyclitis, hyphema, vitreous hemorrhage, optic atrophy, retinal detachment, and choroidoretinitis. As a result, dilated, unreactive pupils are not a reliable indicator of death. As with electrical injuries, cataracts may develop later in some patients.[17]

Cardiovascular System

Electrical Injury

Cardiac arrest, either from asystole or from ventricular fibrillation, is common in electrical accidents. Other electrocardiographic findings include sinus tachycardia, transient ST segment elevation, reversible Q-T segment prolongation, premature ventricular contractions, atrial fibrillation, and bundle branch block. Acute myocardial infarction is relatively rare. Damage to skeletal muscles may produce an increase in cardiac biomarkers leading to a spurious diagnosis of myocardial infarction.

Lightning Injury

In lightning injury, cardiac arrest may be caused by the electrical shock or induced vascular spasm.[30] Numerous dysrhythmias occur in the absence of cardiac arrest.[14] Nonspecific ST-T wave segment changes and prolongation of the Q-T interval may occur, and serum levels of cardiac enzymes are often elevated.[31,32] Hypertension is commonly present after lightning injury but usually resolves without treatment within a few hours.

Skin

Electrical Injury

Other than cardiac arrest, the most devastating injuries are burns, which are most severe at the source and ground contact points. The most common sites of contact with the source include the hands and the skull. The most common areas of ground contact are the heels. A patient may have multiple source and ground contact points. Burns in severe electrical accidents often appear as painless, depressed, yellow-gray, punctate areas with central necrosis, or the areas may be mummified.[12] High-voltage current often flows internally and can create massive muscle damage. If contact is brief, however, minimal flow may have occurred, and the visible skin damage may represent nearly all of the damage. Prediction of the amount of underlying tissue damage from the amount of cutaneous involvement is not possible.

A peculiar type of burn associated with electrical injury is the "kissing burn," which occurs at the flexor creases (Fig. 140-2).[12] As the current causes flexion of the extremity, the skin of the flexor surfaces at the joints touches. Combined with the moist environment that often occurs at the flexor areas, the

Figure 140-2. Kissing burn. (Courtesy of Mary Ann Cooper, MD.)

electrical current may arc across the flexor crease, causing arc burns on both flexor surfaces and extensive underlying tissue damage.

Electrical flash burns are usually superficial partial-thickness burns, similar to other flash burns. Isolated thermal burns may also be seen when clothing ignites. The total body surface area affected by burns in electrical injury averages 10 to 25%. Severe burns to the skull and occasionally to the dura may occur.

The most common electrical injury seen in children younger than 4 years is the mouth burn that occurs from sucking on a household electrical extension cord. These burns usually represent local arc burns, may involve the orbicularis oris muscle, and are especially worrisome when the commissure is involved because of the likelihood of cosmetic deformity. A significant risk of delayed bleeding from the labial artery exists when the eschar separates. Damage to developing dentition can occur, and referral to an oral surgeon familiar with electrical injuries is recommended.[33]

Lightning Injury

Deep burns occur in fewer than 5% of lightning injuries.[17,34] Patients may exhibit one or more of the following four types of superficial burns or skin changes: linear, punctate, feathering, or thermal burns.[10,17,34] *Linear burns* tend to occur in areas where sweat or water accumulate, such as under the arms or down the chest. These are superficial burns that appear to be caused by steam production from the flashover phenomenon. *Punctate burns* appear as multiple, small cigarette-like burns, often with a heavier central concentration in a rosette-like pattern. They range from a few millimeters to 1 cm in diameter and seldom require grafting. *Feathering burns* are not true burns because there is no damage to the skin.[34] Electron showers induced by the lightning create a fern pattern on the skin.[34] These transient lesions are pathognomonic for lightning injury and require no therapy (Fig. 140-3).[35] *Thermal burns* occur if the clothing is ignited or may be caused by metal that the person is wearing or carrying during the flashover.[21]

Extremities

Electrical Injury

In high-voltage injuries, muscle necrosis can extend to sites distant from the observed skin injury, and compartment syndromes occur as a result of vascular ischemia and muscle edema. Decompression fasciotomy or amputation is often necessary.[36] Massive release of myoglobin from the damaged muscle may lead to myoglobinuric renal failure.

Joint areas may exhibit more severe injury than the muscle along the long bone portions of an extremity. Burn injury becomes concentrated at joints because there is less cross-sectional area of muscle to conduct the energy than at long bone portions. There is also a much lower proportion of muscle versus more poorly conductive tendons that cross a joint surface. In addition, as the energy is concentrated in these areas, it may cause skin surface burns, particularly where skin surfaces touch, such as the antecubital fossae.

Vascular damage from the electrical energy may become evident at any time.[22] Neurovascular checks should be reassessed continually in all extremities. Because the arteries are a high-flow system, heat may be dissipated and cause little initial apparent damage but result in subsequent deterioration. In contrast, the veins are a low-flow system, allowing the heat energy to heat blood rapidly, with resulting thrombosis. Consequently, an extremity may initially appear edematous. With severe injuries, the entire extremity may appear mummified when all tissue elements, including the arteries, experience coagulation necrosis.

Damage to the vessel wall at the time of injury may also result in delayed thrombosis and hemorrhage, especially in the small arteries to muscle.[22] This ongoing vascular damage can cause a partial-thickness burn to progress into a full-thickness burn as the vascular supply diminishes to the area. Progressive loss of muscle because of vascular ischemia downstream from damaged vessels may mandate repeated deep débridements.[22]

Lightning Injury

Lightning injury may cause transient vasospasm so severe that the extremities appear cold, blue, mottled, and pulseless. This condition usually resolves within a few hours and rarely requires vascular imaging or surgical intervention.[17]

Skeletal System

As with electrical injury, numerous types of fractures and dislocations are reported with lightning injury. Fractures of the long bones are possible secondary to the trauma associated with electrical injury. Posterior and anterior shoulder dislocations caused by tetanic spasm of the rotator cuff muscles and spinal fractures occur.

Nervous System

Electrical Injury

In high-voltage injuries, loss of consciousness is usually transient, unless there is a significant concomitant head injury. Prolonged coma with eventual recovery also occurs. Patients may exhibit confusion, flat affect, and difficulty with short-term memory and concentration. Electrical injury to the central nervous system may cause a seizure, either as an isolated event or as part of a new-onset seizure disorder. Other possible causes of seizures, such as hypoxia and traumatic brain injury, should be considered. Neurologic symptoms may improve, but long-term disability is common. Lower extremity weakness is commonly undiagnosed until ambulation is attempted.[37]

In high-voltage exposures, spinal cord injury may result from fractures or ligamentous disruption of the cervical, thoracic, or lumbar spine.[37,38] Neurologic damage in patients without evidence of spinal injury can be immediate or delayed. Patients with immediate damage have symptoms of weakness,

Figure 140-3. Feathering burn. (Courtesy of Mary Ann Cooper, MD.)

and paresthesias develop within hours of the insult. Lower extremity findings are more common than upper extremity findings. These patients have a good prognosis for partial or complete recovery. Delayed neurologic damage may present days to years after the insult. Clinical presentations include ascending paralysis, or transverse myelitis.[38] Motor findings predominate. Sensory findings are also common and may be patchy and not match motor levels of impairment. Although recovery is reported, the prognosis is usually poor.[37]

Lightning Injury

On initial presentation, two thirds of seriously injured lightning patients have *keraunoparalysis*, which is a unique temporary paralysis secondary to lightning strike. It is characterized by lower and sometimes upper extremities that are blue, mottled, cold, and pulseless. These findings are secondary to vascular spasm and sympathetic nervous system instability.[39] Generally, this condition clears within a few hours, although some patients may be left with permanent paresis or paresthesias.

Paraplegia, intracranial hemorrhages, seizures, and electroencephalographic changes occur after lightning injuries.[31,32,39-42] Loss of consciousness for varying periods is common, and confusion and anterograde amnesia are almost universal findings. Peripheral nerve damage is also common, and recovery is usually poor.[43,44] A lightning strike to the head can cause a visual cortex defect that results in complex visual hallucinations.[45] A syndrome of delayed muscle atrophy caused by electrical injury of the nerves is described, even in the absence of cutaneous burns.[46]

Other Viscera

Electrical Injury

Injury to the lungs may occur because of associated blunt trauma but is rare from electrical current, perhaps because air is a poor conductor. Injury to visceral organs is also rare, but damage to the pancreas, liver, small intestine, large intestine, bladder, and gallbladder is reported.[47]

Lightning Injury

Pulmonary contusion and hemorrhage are seen with lightning injury.[19] Blunt abdominal injuries occur rarely. None of the other intra-abdominal catastrophes commonly associated with high-voltage electrical injury, such as gallbladder necrosis or mesenteric thrombosis, are seen with lightning injury.

Other Low-Voltage Injuries

An accurate history is essential to ensure that an apparent low-voltage injury was not caused by the discharge from a capacitor (as in the repair of a television, microwave oven, or computer monitor) or other high-voltage source. Although burns from low-voltage sources are usually less severe than burns from high-voltage sources, patients still may complain of paresthesias for an extended period, experience cardiac dysrhythmias, or have cataracts develop if the shock occurs close to the face or head.

As law enforcement use of electromechanical disruption devices (Tasers) increases, more subjects exposed to the associated electrical current will be evaluated in emergency departments. These devices deliver brief pulses of electrical energy that incapacitate the target subject. Taser use was listed as a contributory cause of death in 4 of 37 autopsy reports from restraint-related deaths.[48] The evaluation and treatment of people subdued with such devices should focus on wounds or retained fragments caused by the probes, secondary injuries associated with the induced fall, and the patient's organic or psychiatric conditions that prompted the officers' use of the device.

Complications

Electrical Injury

Cardiac arrest generally occurs only at the initial presentation or as a final event after a long and complicated hospital course. Many of the complications are similar to those of thermal burns and crush injuries, including myoglobinuria, infection, and clostridial myositis. The incidence of acute myoglobinuric renal failure has decreased since the widespread adoption of aggressive alkalinized fluid resuscitation. Fasciotomies or carpal tunnel release may be necessary for treatment of a compartment syndrome.[36] Tissue loss and major amputations are common with severe high-voltage injuries and result in the need for extensive rehabilitation.

Neurologic complications, such as loss of consciousness, peripheral nerve damage, and delayed spinal cord syndromes, may occur.[37,38,44] Damage to the brain may result in a permanent seizure disorder. Long-term neuropsychiatric complications include depression, anxiety, inability to continue in the same profession, aggressive behavior, and suicide. Stress ulcers are the most common gastrointestinal complication after burn ileus. Abdominal injuries from ischemia, vascular damage, burns, or associated blunt trauma may initially be overlooked.[12,47]

Lightning Injury

Complications of lightning injury fall into three categories: (1) those that could be reasonably predicted from the presenting signs, such as hearing loss from tympanic membrane rupture or paresthesias and paresis from neurologic damage; (2) long-term neurologic deficits similar to deficits associated with blunt head injury and chronic pain syndromes; and (3) iatrogenic complications that are secondary to overaggressive management.

In the past, patients with lightning injuries were often treated similarly to patients with high-voltage electrical injuries. These injuries, however, are distinctly different. The treatment of lightning victims seldom requires massive fluid resuscitation, fasciotomies for compartment syndromes, mannitol and furosemide diuretics, alkalinization of the urine, amputations, or large repeated débridements.[17,31]

DIFFERENTIAL CONSIDERATIONS

Electrical Injury

Electrical injuries are historically self-evident except in bathtub accidents, instances when no burns occur, or foul play. The mechanism of burn injury is relevant; flash burns have a much better prognosis than arc or conductive burns. Alterations in consciousness or seizures can be caused by the electrical injury or result from an associated traumatic brain injury.

Lightning Injury

The differential diagnosis of lightning injury is more complex, often because the incident is unobserved. It includes many of the causes of unconsciousness, paralysis, or disorientation of unclear etiology. Evidence of a thunderstorm or a witness to

the lightning strike may not be available, particularly when victims are alone when injured. The presence of typical burn patterns, such as feathering, may be helpful.

■ MANAGEMENT

Out-of-Hospital

Securing the Scene

When first reaching the scene, prehospital medical personnel should secure the area so that bystanders and rescuers do not sustain other injuries. For high-voltage incidents, the power source must be turned off. Although many approaches to achieving this goal are recommended, the safest approach is to involve the local power company in high-voltage accidents. Accidents involving discrete electrical sources that are disconnected easily through a circuit box or switch are easier to manage, although rescuers should still ensure that the power is off before approaching the victim. The use of electrical gloves by emergency medical service personnel is dangerous. A microscopic hole in a glove can result in an explosive injury to the hand, as thousands of volts from the circuit concentrate there to enter the glove.

Although a line may be on the ground and appear to be de-energized, it may have substantial current flowing from it to the ground, making the surrounding area dangerous. This ground current spreads out in a circle along and just below the surface of the ground. De-energized lines may be re-energized by automatic circuit reclosers resulting in surges of current.[49] During lightning incidents, nonhospital medical personnel must be vigilant because lightning *can* strike the same place twice.

Triage Considerations

Field evaluation of patients may involve triage of multiple victims. Traditional rules of mass casualty triage do not apply to lightning victims. Cardiorespiratory arrest is the major cause of death in lightning injuries.[17] In the absence of cardiopulmonary arrest, victims rarely die in the field. Triage of lightning victims should concentrate on victims who appear to be in cardiorespiratory arrest. When multiple victims are involved, the evaluation of victims who are breathing may be delayed because they are likely to survive the incident. Although intrinsic cardiac automaticity may ensue, the respiratory arrest caused by central nervous system injury often prevails. If the victim is adequately ventilated during the interval, perfusion may be maintained.

Initial Out-of-Hospital Resuscitation

Electrical injury victims may require a combination of cardiac and trauma care because they often have blunt injuries and burns and possible cardiac damage. Spinal immobilization is indicated whenever associated spinal trauma is suspected. Fractures and dislocations should be splinted, and burns should be covered with clean, dry dressings. All patients with conductive injury should receive a bolus of 20 mL/kg of isotonic fluid, and subsequent fluid management should be based on the patient's vital signs and clinical status.

Emergency Department

Assessment

The history obtained from bystanders and the nonhospital medical personnel regarding the type of electrical source, duration of contact, or environmental factors is helpful. An electrical injury should be treated similarly to a crush injury, rather than a thermal burn, because of the large amount of tissue damage that is often present under normal-appearing skin. As a result, none of the formulas for intravenous fluids based on percentage of burned body surface area are reliable. Standard crystalloid resuscitation in anticipation of myoglobinuria should be maintained. Cardiac monitoring is indicated for severely injured patients and for patients who have the indications listed in Box 140-6.[50] All patients with high-voltage injury and patients with low-voltage injury and cardiorespiratory complaints should have an electrocardiogram (ECG) and cardiac biomarker determinations. Although electrocardiographic changes and dysrhythmias are common with electrical injuries, anesthesia and surgical procedures performed in the first 48 hours of care can be accomplished without cardiac complications.[50,51]

BOX 140-6 INDICATIONS FOR ELECTROCARDIOGRAM MONITORING

- Cardiac arrest
- Documented loss of consciousness
- Abnormal ECG
- Dysrhythmia observed in out-of-hospital or emergency department setting
- History of cardiac disease
- Presence of significant risk factors for cardiac disease
- Concomitant injury severe enough to warrant admission
- Suspicion of conductive injury
- Hypoxia
- Chest pain

Most lightning victims behave as though they have had electroconvulsive therapy, with confusion and anterograde amnesia for several days. If any altered mentation or neurologic deterioration occurs after an electrical injury, a computed tomography scan is indicated to assess for intracranial hemorrhage.[17,42]

Lightning victims who do not experience cardiopulmonary arrest at the time of the strike generally do well with supportive therapy. Patients who have cardiopulmonary arrest may have a poor prognosis, particularly if there is hypoxic brain damage.[50,52]

Ancillary Tests

Electrical Injury

Patients sustaining an electrical injury should receive cardiac monitoring in the emergency department and an ECG despite the source voltage. The following laboratory tests may be considered in patients with evidence of conductive injury or significant surface burns: complete blood count, electrolyte levels, serum myoglobin, blood urea nitrogen, serum creatinine, and urinalysis. Patients with severe electrical injury or suspected intra-abdominal injury should also have pancreatic and hepatic enzymes measured and a coagulation profile obtained. If major débridements may be necessary, the emergency physician may consider ordering a type and crossmatch. Arterial blood gas analysis is indicated if the patient needs ventilatory intervention or alkalinization therapy. Patients should be evaluated for myoglobinuria, a common complication of high-voltage electrical injury. If the urine is pigmented or the dipstick examination of the urine is positive for blood, and no red blood cells are seen on microscopic analysis, the patient should be assumed to have myoglobinuria.

Creatine kinase (CK) levels and isoenzyme analysis should be performed. Peak CK levels predict muscle injury, risk of amputation, and length of hospitalization; the clinical value of a single level in the acute setting is not established. Cardiac biomarkers should be interpreted with care when diagnosing myocardial infarction in the setting of electrical injury. The peak CK level is not indicative of myocardial damage in electrical injury because of the large amount of injured skeletal muscle cells, which can contain a 20 to 25% CK-MB fraction. CK-MB fractions, electrocardiographic changes, thallium studies, angiography, and echocardiography correlate poorly in acute myocardial infarction after electrical injury. Other cardiac biomarkers (e.g., troponin) are not well studied in electrical injury but may prove useful in determining myocardial injury.

Radiographs of the spine should be obtained if spinal injury is clinically suspected or when patients cannot be assessed adequately because of altered mentation or the presence of other painful injuries. Angiography is not routinely indicated to plan débridements or amputations.[22] Technetium pyrophosphate scanning can be useful to detect areas of clinically unsuspected myonecrosis.[30,36] "Hot spots" may reflect 20 to 80% viable muscle and should be followed clinically.[36,53,54] CT or magnetic resonance imaging may be useful in the evaluation of associated trauma and is essential for evaluation of possible intracranial injuries.

Lightning Injury

In patients injured by lightning, an ECG should be obtained. Serum biomarkers for cardiac injury are indicated in patients with chest pain, abnormal ECGs, or altered mentation. The severity or nature of the injuries may require other laboratory studies. Radiographic studies, particularly cranial CT evaluation, may be indicated, depending on the patient's level of consciousness at presentation and throughout the evaluation and treatment.

Specific Therapies

Rhabdomyolysis

Victims of electrical injury who have heme pigment in the urine usually have myoglobinuria. Alkalinization of the urine increases the solubility of myoglobin in the urine, increasing the rate of clearance. Urine output should be maintained at 1 to 1.5 mL/kg/hr until all traces of myoglobin have cleared from the urine, while the blood is maintained at a pH of at least 7.45 using sodium bicarbonate. Furosemide or mannitol may be used to cause further diuresis. In contrast to high-voltage injuries, rhabdomyolysis is rare with lightning injuries.

Burn Wound Care

Cutaneous burns should be dressed with antibiotic dressings, such as sulfadiazine silver. Electrical burns are especially prone to tetanus, and patients should receive tetanus toxoid and tetanus immune globulin on the basis of their immunization history. Prophylactic administration of high-dose penicillin to prevent clostridial myonecrosis is controversial.

Extremity Injuries

Management of electrical injuries of the extremities entails surgical management, including early fasciotomy, carpal tunnel release, or amputation of an obviously nonviable extremity. Extremities should be splinted in a functional position to minimize edema and contracture formation. The hand should be splinted in 35- to 45-degree extension at the wrist, 80- to 90-degree flexion at the metacarpophalangeal joints, and almost full extension at the proximal and distal interphalangeal joints.

DISPOSITION

Electrical Injuries

Admission

Indications for admission for electrocardiographic monitoring are listed in Box 140-6. In general, when corporeal conduction is suspected, the patient should be admitted for 12 to 24 hours of cardiac monitoring. Most patients with significant electrical burns should be stabilized and transferred to a regional burn center for burn care and extensive occupational and physical rehabilitation.

Outpatient Management

Asymptomatic patients with a normal physical examination after low-voltage exposure can be reassured and discharged without performing any ancillary tests.[55] Patients with cutaneous burns or mild persistent symptoms can be discharged if they have a normal ECG and no urinary heme pigment. Outpatient referral is provided in the event that current symptoms persist or new symptoms (delayed cataracts, weakness, or paresthesias) develop.

Electrical injury during pregnancy from low-voltage sources may result in fetal demise. A prospective cohort study of electric shock in pregnancy suggested that electric shock usually does not pose a major fetal risk.[56] Nevertheless, obstetric consultation is advisable for all pregnant patients reporting electrical injury, regardless of symptoms at the time of presentation. Placental abruption, the most common cause of fetal death after blunt trauma, may result from even minor trauma, such as may be associated with electrical injuries. Patients in the latter half of pregnancy should receive fetal monitoring if there has been even minor blunt trauma and be considered high-risk patients for the remainder of their pregnancy.[14] First-trimester patients should be informed of the remote risk of spontaneous abortion and, if no other indications for admission exist, may be discharged with instructions for threatened miscarriage and close obstetric follow-up evaluation. The prognosis for fetal survival after lightning strike is most dependent on the extent of the mother's injuries. Fetal demise occurs in 50% of cases reported in the literature.[57]

Pediatric patients with oral burns may be safely discharged if close adult care is ensured. There is no evidence that an isolated oral burn correlates with cardiac injury or myoglobinuria. In general, these patients require surgical and dental consultation for oral splinting, eventual débridement, and, occasionally, reconstructive surgery. After appropriate consultation, if hospitalization is not deemed necessary, the child's parents should be warned about the possibility of delayed hemorrhage and receive instructions to apply direct pressure by pinching the bleeding site and to return immediately to the emergency department.

Lightning Injuries

Many of the signs of lightning injuries, such as lower extremity paralysis and mottling, confusion, and amnesia, resolve with time. After spinal cord and intracranial processes are excluded, observation is the mainstay of treatment.

Consultation with other specialists may be indicated for otic and ophthalmic damage. More severely injured patients

require trauma surgeon and cardiologist consultations, although with lightning injuries medical pathology predominates. If there is a history of a loss of consciousness or if the patient exhibits confusion, hospital admission and observation are suggested. After evaluation, if the ECG is normal, asymptomatic patients (including patients with feathering burns) may be discharged home with referral for follow-up from an ophthalmologist and other specialists as indicated.

KEY CONCEPTS

- High-voltage electrical injury causes significant tissue and organ damage along the path between the entrance and exit wounds. As a result, victims are often more severely injured than they initially appear. Injury assessment must be detailed, fluid requirements during resuscitation are much greater than one would calculate from the surface burns alone, and extensive tissue débridement is often necessary.
- Victims of lightning injury may appear to have significant injuries, but symptoms (extremities that are cold and pulseless, mottled skin, paralysis, and confusion) usually resolve with time. After spinal cord and intracranial injuries are excluded, observation is the mainstay of treatment.
- Patients with low-voltage electrical injury who have only minor cutaneous burns or persistent minor symptoms may be discharged safely if they have a normal ECG and no urinary heme pigment.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 141 Scuba Diving and Dysbarism

Richard L. Byyny and Lee W. Shockley

PERSPECTIVE

Underwater free diving (breath-holding) to salvage wrecks and to harvest seafood, sponges, coral, and mother-of-pearl has been practiced for more than 5000 years. Historic records indicate that the Persian King Xerxes employed a diver to recover sunken treasure in the fifth century BCE. Alexander the Great used divers to remove obstacles in the harbor of the city of Tyre in 332 BC.[1] Navies since the time of Alexander have used divers to construct defenses, sabotage enemy ships and harbor defenses, and salvage wrecks.

In an attempt to extend the duration of time underwater, some divers have used breathing tubes, such as hollow reeds; however, it is nearly impossible to use these at depths greater than 3 feet because of the underwater pressure restricting inspiration. Breathing bags (animal skins inflated with air) were also tried but made submersion impossible because of their buoyancy.

Shakespeare's description of Clarence's dream in *King Richard III** (1597) may have been influenced by reports of the first diving bell (1531). Subsequent inventions, including diving dresses, from the 16th to the 19th centuries allowed divers to remain underwater for prolonged periods at depths of up to 12 fathoms (72 feet).[2] The first diving dress (1715) was a reinforced, leather-covered barrel with watertight armholes and a viewing porthole.[2]

Colonel William Pasley, the officer in charge of a unit of the British Royal Engineers that salvaged the sunken warship HMS *Royal George* in 1840, observed symptoms in his divers: "Of the seasoned divers, not a man escaped the repeated attacks of rheumatism and cold."[3] At approximately the same time, similar symptoms and even fatalities were observed among caisson workers.† The ailment became known as caisson disease, but the construction workers on the Brooklyn Bridge (built from 1870 to 1883) attached the name "the bends" characterizing the symptoms that often caused the victim to bend forward in pain.[3] The first clinical description of caisson disease was by Paul Bert in 1878.[3] He correctly attributed the disease to nitrogen gas coming out of solution in the tissues during decompression. This led to the recommendation of slow ascents for pressurized workers and the development of the first recompression chambers.

Heavy diving helmets with surface-supplied air dominated underwater diving operations until the development of the *s*elf-*c*ontained *u*nderwater *b*reathing *a*pparatus (scuba). Scuba requires a demand regulator and high-pressure air tanks that allow the delivery of an air supply at an appropriate pressure for the depth of the diver. The significant breakthrough in making scuba possible was the invention of the Aqua-Lung by Jacques-Yves Cousteau and Emile Gagnan in 1943.[2] The lighter and less expensive scuba equipment does not require a surface supply of air and the support personnel that are necessary for helmet diving.

The sport of scuba diving is increasingly popular. Since 1967, more than 10 million people have been certified as scuba divers. Worldwide, more than 500,000 new diver certifications are issued annually. The rate of mortality in diving varies between 1.5 and 9 per 100,000 dives. The vast majority of amateur divers use compressed air, open-circuit scuba equipment at depths less than 130 feet of seawater (fsw).

Systems that use artificial mixtures of various gases are employed to extend the depths to which divers can descend. Some of these are used in sport diving, but their use is uncommon and is primarily limited to commercial applications (Table 141-1).

Other variations of supplying air for divers are closed-circuit and semi–closed-circuit diving apparati ("rebreathers") that use calcium hydroxide, $Ca(OH)_2$, to absorb expired carbon dioxide. Oxygen is then added to the decarboxylated gas prior to rebreathing. The advantages of rebreathers over compressed air scuba are that they are more efficient (less gas is used for a given time), allow deeper dives and longer bottom times, and generate few, if any, bubbles.

PRINCIPLES OF DISEASE

Medical emergencies encountered by scuba divers include those common to environmental exposures (e.g., hypothermia, sunburn, and physical trauma), those common to aquatic activ-

*Clarence: "Methought I saw a thousand fearful wracks; a thousand men that fishes gnawed upon; wedges of gold, great anchors, heaps of pearl, inestimable stones, unvalued jewels, all scattered in the bottom of the sea. Some lay in dead men's skulls; and in the holes where eyes did once inhabit there were crept, as t'were in scorn of eyes, reflecting gems, that woo'd the slimy bottom of the deep, and mocked the dead bones that lay scatter'd by." The Keeper: "Had you such leisure in the time of depth to gaze upon these secrets of the deep?"

†Caissons are construction chambers filled with pressurized air that permit working in a dry environment. They have been used in the construction of bridge footings and tunnels in places that would otherwise have been underwater.

ities (e.g., submersion accidents, motion sickness, and marine envenomations), and dysbarisms (problems unique to the sport of diving). *Dysbarisms* are illnesses that result directly or indirectly from exposure to increased ambient pressure. The pathophysiology of these conditions primarily results from volume-pressure changes within the air-filled cavities of the body and from increased dissolution of gases, particularly nitrogen, in body tissues.

Atmospheric pressure varies with altitude and weather patterns, but 760 mm Hg, or 14.7 pounds per square inch (psi), is the standard used at sea level. The pressure exerted on the human body at sea level is 1 atm. A scuba diver's depth gauge reads pressure in addition to the pressure at sea level (gauge pressure). Therefore, at sea level, a pressure gauge reads zero. The absolute pressure, or *atmospheres absolute* (ATA), is the total pressure on a diver, which is the sum of gauge and atmospheric pressure. Water is far denser than air and, as a diver descends, each foot of seawater exerts an additional pressure of 23 mm Hg or 0.445 psi on the diver. Whereas a mountain climber would need to ascend to 18,000 feet to reduce atmospheric pressure by 50% from sea level, a diver needs to descend only 33 feet in seawater (34 feet in freshwater) to double the atmospheric pressure.

To understand the pathophysiology of dysbarisms, one should be familiar with several of the laws of physics that define the behavior of liquids and gases (Table 141-2; Figs. 141-1 to 141-5). The human body is composed mostly of water and behaves as a liquid subject to Pascal's law, which states that a pressure applied to any part of a liquid is transmitted equally throughout. Pressure changes, however, do alter the volume within the air-filled spaces of the body, including the lungs, bowel, sinuses, and middle ear. These spaces compress on descent and expand on ascent according to Boyle's law, which states that at constant temperature, the absolute pres-

Table 141-1 Mixed Gas Diving

	OXYGEN	NITROGEN	HELIUM	OTHER
Air	21%	78%	Trace	1%
Nitrox I (EAN 32 or Nitrox 32)*	32%	68%	Trace	<1%
Nitrox II (EAN 36 or Nitrox 36)*	36%	64%	Trace	<1%
Normoxic Trimix (e.g., Trimix 19/30)†	19%	51%	30%	<1%
Hypoxic Trimix (e.g., Trimix 10/50)‡	10%	40%	50%	<1%

*Enhanced Air Nitrox, Oxygen Enriched Air, Nitrox, EANx, Safe Air, "devil gas," "voodoo gas."
†A normoxic mix, such as "19/30," is used in the 30-m (100 feet) to 60-m (200 feet) depth range.
‡A hypoxic mix, such as "10/50," is used for deeper diving, as a "bottom" gas only; it cannot safely be breathed at shallow depths where the oxygen partial pressure is less than 0.18.

Table 141-2 Pertinent Laws of Physics

GAS LAW	FORMULA	SIGNIFICANCE
Pascal's law: A pressure applied to any part of a liquid is transmitted equally throughout.	$\Delta P = pg\ (\Delta h)$ ΔP is the hydrostatic pressure. p is the fluid density. g is acceleration due to gravity. Δh is the height of fluid.	Pressure increases in a contained space are transmitted throughout; significant for IEBT and MEBT (see Fig. 141-1).
Boyle's law: At a constant temperature, the absolute pressure and the volume of gas are inversely proportional. As pressure increases, the gas volume is reduced; as the pressure is reduced, the gas volume increases.	$P_1{*}V_1 = P_2{*}V_2$	Relates to change in the volume of a gas caused by the change in pressure, due to depth, which defines the relationship of pressure and volume in breathing gas supplies (see Fig. 141-2).
Charles' law: At a constant pressure, the volume of a gas is directly proportional to the change in the absolute temperature.	$\frac{V_1}{T_1} = \frac{V_2}{T_2}$	Increasing pressure (filling a scuba tank) causes heat; cooling a tank decreases the pressure (see Fig. 141-3).
The *general gas law* combines these concepts to predict the behavior of a gas when the factors change.	$P_1{*}V_1/T_1 = P_2{*}V_2/T_2$ P_1 is the initial pressure. V_1 is the initial volume. T_1 is the initial temperature. P_2 is the final pressure. V_2 is the final volume. T_2 is the final temperature.	A means of relating pressure, volume, and temperature together in one equation when variables are not constant.
Dalton's law: The total pressure exerted by a mixture of gases is equal to the sum of the pressures (partial pressures) of each of the different gases making up the mixture, with each gas acting as if it alone was present and occupied the total volume.	$P_{Total} = P_1 + P_2 + P_3 + \ldots + P_n$	Nitrogen under pressure acts as if other gases were not present (see Fig. 141-4).
Henry's law: The amount of a gas that will dissolve in a liquid at a given temperature is directly proportional to the partial pressure of that gas.	$e^p = e^{kc}$ e is approximately 2.7182818 (the base of the natural logarithm). p is the partial pressure of the solute above the solution. c is the concentration of the solute in the solution. k is the Henry's law constant.	More nitrogen is taken into solution (e.g., serum) at high pressures than comes out of solution at lower pressures (see Fig. 141-5).

IEBT, inner ear barotrauma; MEBT, middle ear barotrauma.

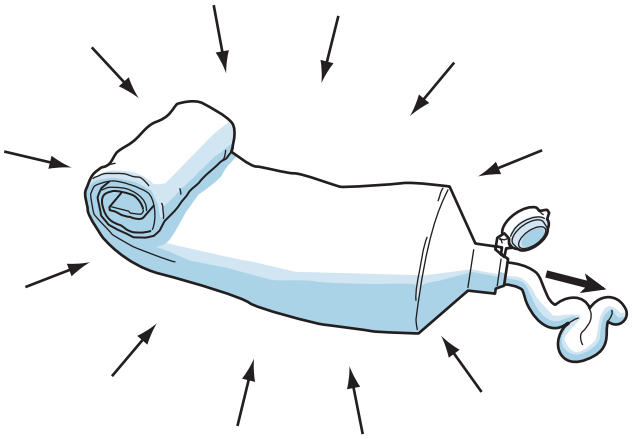


Figure 141-1. Pascal's law: A pressure applied to any part of a liquid is transmitted equally throughout.

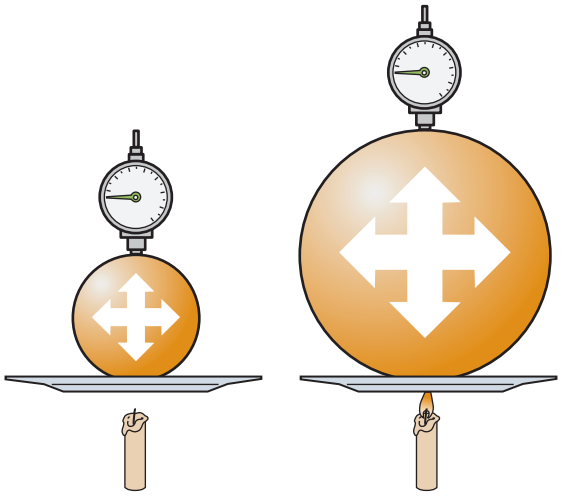


Figure 141-3. Charles' law: At a constant pressure, the volume of a gas is directly proportional to the change in the absolute temperature.

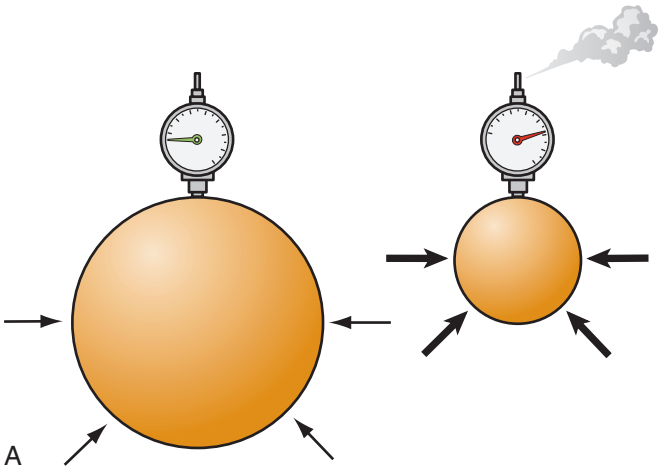


Figure 141-2. Boyle's law: **A,** At a constant temperature, the absolute pressure and the volume of gas are inversely proportional. **B,** As pressure increases, the gas volume is reduced; as the pressure is reduced, the gas volume increases.

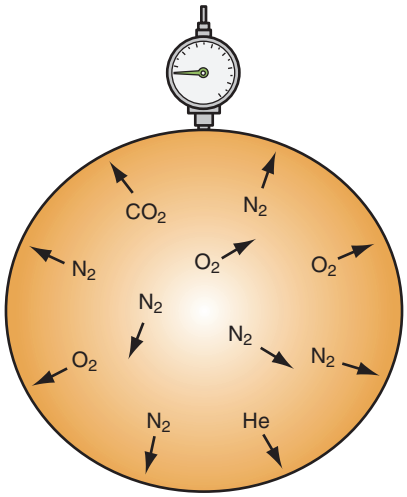


Figure 141-4. Dalton's law: The total pressure exerted by a mixture of gases is equal to the sum of the pressures (partial pressures) of each of the different gases making up the mixture, with each gas acting as if it alone was present and occupied the total volume.

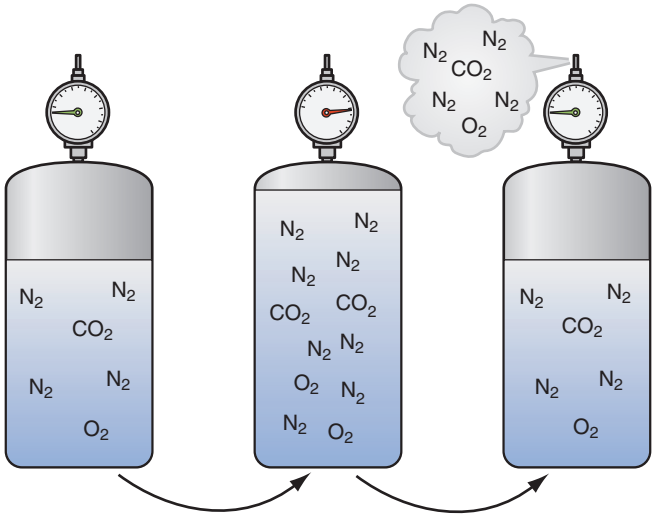


Figure 141-5. Henry's law: The amount of a gas that will dissolve in a liquid at a given temperature is directly proportional to the partial pressure of that gas.

sure and the volume of gas are inversely proportional ($PV = k$). As pressure increases, the gas volume is reduced; as the pressure is reduced, the gas volume increases.

When working with Boyle's law, the temperature of the gas is a constant value. However, temperature also affects the pressure and volume of a gas. Charles' law describes the relationships of temperature and volume. At a constant pressure, the volume of a gas is directly proportional to the change in the absolute temperature ($V_1/T_1 = V_2/T_2$). The general gas law ($P_1{*}V_1/T_1 = P_2{*}V_2/T_2$) combines the laws to predict the behavior of a given quantity of gas when any of the factors change.

Dalton's law states that the total pressure exerted by a mixture of gases is equal to the sum of the pressures (partial pressures) of the individual gases making up the mixture, with each gas acting as if it alone was present and occupied the total volume ($P_{total} = P_1 + P_2 + P_3 + \ldots + P_n$). Henry's law states that the amount of any gas that dissolves in a liquid at a given temperature is directly proportional to the partial pressure of that gas. At higher ambient pressures, the concentration of each component of air in solution with blood and tissues increases until a new steady-state concentration is achieved.

The gases in a diver's breathing mixture are dissolved into the body in proportion to the partial pressure of each gas in the mixture. The quantity of a particular gas that becomes dissolved is also governed by the length of time the diver is breathing the gas at the increased pressure and the inherent solubility of the gas. The dissolved gas in a diver's body, regardless of quantity, depth, or pressure, remains in solution as long as the pressure is maintained. As the diver ascends, however, increasingly more of the dissolved gas comes out of the solution and may form microbubbles in the circulation. A rapid ascent may reduce the pressure at a rate higher than the body can accommodate, and the bubbles (particularly nitrogen) may accumulate and disrupt body tissues and systems to produce decompression sickness (DCS). This is similar to the way that rapidly opening a bottle of soda allows bubbles of carbon dioxide to come out of solution rapidly.

If the ascent rate is controlled (i.e., through the use of the safe decompression tables or submersible dive computers), the gas is carried to the lung vascular bed and is exhaled before it accumulates to form significantly large or numerous bubbles in the tissues, similar to how opening a soda bottle slowly reduces the bubbling of the contained carbonated liquid.

Barotrauma, or injury caused by pressure changes, results when a diver is unable to equalize the pressure within air-filled structures to the ambient pressure of the environment during ascent or descent. The fractional changes in volume are greater near the surface. Thus, the greatest risk for barotrauma is in shallow water, where the proportional pressure changes are also the greatest.

CLINICAL FEATURES

Middle Ear Barotrauma

Middle ear barotrauma (MEBT), also known as barotitis or "ear squeeze," is the most common complaint of scuba divers. It is experienced by 30% of novice scuba divers and 10% of experienced divers.[4] The middle ear is an air-filled space with solid bony walls except for the tympanic membrane (Fig. 141-6). The eustachian tube is the only anatomic passage to the external environment.

As the diver descends, the water exerts increasing pressure against the intact tympanic membrane (TM). In normal circumstances, the diver performs various maneuvers to force air into the middle ear through the eustachian tubes, maintaining an equal pressure across the TM. If equilibration of middle ear pressure does not occur, the floppy medial third of the eustachian tube collapses shut, making any further attempts at equalization futile. Further pressure increases can cause the TM to rupture. The pain may or may not resolve as the TM ruptures. The ruptured TM, however, exposes the middle ear to cold water, inducing a transient nystagmus and vertigo secondary to caloric stimulation. In certain individuals, in whom the seventh cranial nerve passes unexposed through the middle ear, a facial palsy may occur.

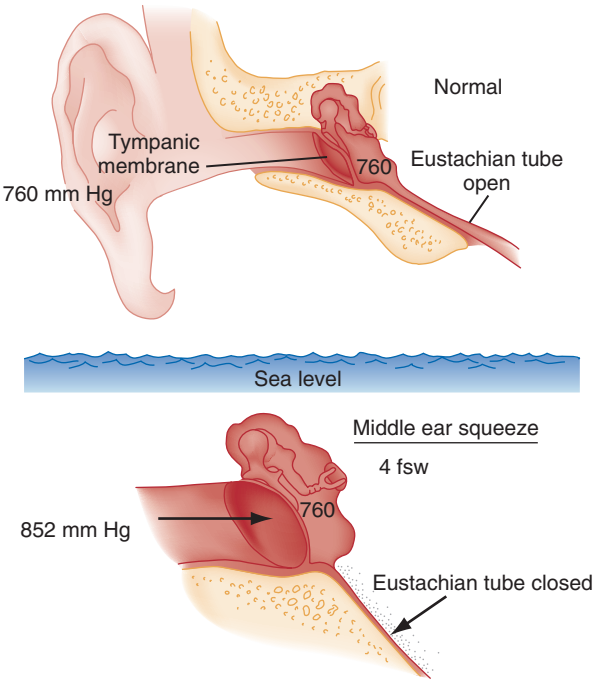


Figure 141-6. Anatomy of the ear and middle ear trauma. fws, feet of seawater. (From Kizer KW, VanHoesen KB: Diving medicine. In Auerbach PS [ed]: Wilderness Medicine, 5th ed. St. Louis, Mosby, 2007, p 1612.)

External Ear Barotrauma

External ear barotrauma is less common than MEBT and results from the outward bulging of the TM during descent. Normally, the external auditory canal is filled with water during descent. If, however, air becomes trapped in the external auditory canal because of obstruction from cerumen, stenosis, earplugs, or a tight-fitting wet suit hood, a relative negative pressure develops in the external canal resulting in local pain.

Inner Ear Barotrauma

Inner ear barotrauma (IEBT) results in damage to the cochleovestibular apparatus. It is much less common than MEBT but is associated with greater morbidity. Initially, the mechanism of damage is similar to that of MEBT in that a large negative pressure gradient develops in the middle ear if the diver is unable to equalize pressure during descent. Inward deflection of the TM is transmitted to the oval window of the cochlea through the ossicles. Movement of the oval window creates a pressure wave within the perilymph of the cochlea, which causes an outward distention of the round window into the middle ear. Sudden equilibration of pressure in the middle ear or a vigorous Valsalva maneuver may rupture the round window. Two other pathologic changes may not be associated with frank rupture of the round window: hemorrhage into

the inner ear and tearing of the labyrinthine (Reissner's) membrane.

Symptoms associated with IEBT include variable hearing loss, severe vertigo, nausea, tinnitus, and fullness in the affected ear. Signs include severe nystagmus, positional vertigo, ataxia, and vomiting. The degree of sensorineural hearing loss is variable.

The history and physical examination are probably as sensitive as operative visualization of IEBT.[5] The (Hennebert) fistula test may help. To perform this test, an insufflator and otoscope are used to compress and decompress air sequentially in the auditory canal. If nystagmus or vertigo is induced, the test suggests a perilymphatic fistula. Audiogram and tympanometric testing can provide objective data regarding the severity of sensorineural hearing loss and can detect concomitant conductive hearing loss. Distinguishing IEBT from inner ear DCS (a type of DCS II) can be challenging; if the diagnosis is in doubt, the patient should be treated as DCS II.

Barosinusitis

The air-filled maxillary, frontal, and ethmoidal sinuses are all susceptible to volume-pressure changes. Equilibration of pressure within the paranasal sinuses requires patent nasal passages. Obstruction by mucosal thickening, polyps, pus, or a deviated septum predisposes to sinus barotrauma. Pain is felt over the ethmoid, frontal, or maxillary sinuses during descent or ascent. The most commonly affected is the frontal sinus secondary to the relatively long and tortuous connection to the nasal passage. Epistaxis is common in barosinusitis.

Facial Barotrauma

Facial barotrauma results from negative pressure generation within the "artificial" airspace created by a dive mask over the eyes and nose. As water pressure increases during descent, a negative pressure develops within the mask, which must be equalized by forced exhalation through the nose. When this is not adequately performed, the large negative pressure gradient produces facial and conjunctival edema, diffuse petechial hemorrhages on the face, and subconjunctival hemorrhages. Rarely, optic nerve damage can result from severe facial barotrauma.

Temporomandibular Joint Dysfunction

Temporomandibular joint dysfunction can be seen in divers who experience teeth clenching and poor occlusion because of a poorly fitting regulator mouthpiece. The pain associated with this condition is typically felt in the region of the ear and can be mistaken for MEBT. Customized mouthpieces are available to relieve the problem.

Nitrogen Narcosis

Nitrogen narcosis, known as "rapture of the deep," results from the intoxicating effects of increased tissue nitrogen concentration at depth. Symptoms include euphoria, a false feeling of well-being, confusion, loss of judgment or skill, disorientation, inappropriate laughter, diminished motor control, and tingling and vague numbness of the lips, gums, and legs.[3] When breathing compressed air, symptoms typically begin to occur at approximately 100 feet and often become profound at depths greater than 150 feet.[3] There is a large degree of individual variability in susceptibility to nitrogen narcosis. Although the effects of nitrogen narcosis resolve with ascent to shallower depths, the diver may drown because of poor judgment or seriously impaired motor skills in the presence of a dive emergency. Because of the dangers of breathing nitrogen at increased partial pressures, the use of compressed air is not recommended for sport diving to depths greater than 120 feet.

Oxygen Toxicity

At elevated partial pressures for extended periods of time, oxygen can be toxic to the central nervous system (CNS) or lungs. Oxygen becomes toxic to the CNS when its partial pressure exceeds 1.6 ATA.* Oxygen partial pressures less than 1.4 ATA are unlikely to produce CNS toxicity. Symptoms of CNS oxygen toxicity may be remembered by the mnemonic VENTIDC[3]:

V: Visual symptoms (tunnel vision or blurred vision)
E: Ear symptoms (tinnitus)
N: Nausea or spasmodic vomiting
T: Twitching and tingling symptoms (small facial muscles, lips, or muscles of the extremities)
I: Irritability, confusion, agitation, and anxiety
D: Dizziness, clumsiness, incoordination, and unusual fatigue
C: Convulsions

Deep divers prevent oxygen toxicity by breathing mixed gases with decreased oxygen content (e.g., hypoxic Trimix). Breathing oxygen-enriched mixtures at depth makes a diver more susceptible to oxygen toxicity.

Pulmonary oxygen toxicity (low-pressure oxygen poisoning) can occur after 24 hours of exposure to partial pressures of oxygen in excess of 0.6 ATA.† The symptoms of pulmonary oxygen toxicity include a burning sensation or pain on inspiration and coughing. Pulmonary function gradually becomes normal after the exposure is terminated, but pneumonitis and permanent fibrosis are possible.

Contaminated Air

Rarely, other gases, such as carbon monoxide and carbon dioxide, can contaminate the air that is compressed into a tank. This can happen, for example, if the compressor intake is placed too close to the compressor's engine exhaust. As in the case of oxygen and nitrogen, the partial pressure of these contaminants in the tissues increases dramatically with depth, potentiating their clinical effects. The symptoms of hypercarbia or carbon monoxide poisoning are more severe at elevated partial pressures. Hypercarbia increases a diver's susceptibility to CNS oxygen toxicity.[3]

Rebreathers release microscopic calcium hydroxide or "soda lime" dust particles into the apparatus.[6] These particles are small enough and have geometric characteristics that allow them to be deposited in the alveoli. When soda lime comes

*A diver breathing compressed air would attain a partial pressure of 1.6 ATA of oxygen at a depth of 218 fsw. This far exceeds the depth to which sport divers would go. Treatment in a hyperbaric chamber with 100% oxygen attains this partial pressure at only 20 fsw. Therefore, hyperbaric treatment combines alternating periods of delivering 100% oxygen and air.

†A diver breathing compressed air would attain a partial pressure of 0.6 ATA of oxygen at a depth of 60 fsw. It is extremely unlikely that a sport diver would ever be exposed for the duration that is required to produce toxicity; however, long exposures to higher levels of oxygen, such as administered according to Recompression Treatment Tables 4, 7, and 8, may lead to pulmonary oxygen toxicity.

into contact with water, it forms a caustic liquid. In the event of a hose rupture allowing seawater contamination of the circuit, caustic burns to the mouth, throat, and airways may result. Chronic exposure to soda lime dust may contribute to long-term effects on respiratory function.

Decompression Sickness

The term *decompression sickness* refers to a spectrum of clinical illnesses that result from the formation of small bubbles of nitrogen gas in the blood and tissues.[7,8] The clinical expression of DCS depends on the location, destination, and degree of nitrogen bubble formation in blood and tissues. Small, asymptomatic venous gas emboli are common in the ascending diver and are filtered by the lungs without apparent permanent damage.[9,10] Persistent intravascular bubbles, however, elicit inflammatory cascades, cytokines, the complement system, platelet aggregation, and thrombosis.[11] Furthermore, the bubbles can cause mechanical obstruction, ischemia, and tissue hypoxia. Nitrogen is highly fat soluble, and the heavily myelinized white matter of the CNS is at particular risk for DCS.

The incidence of DCS is estimated to be 2.8 cases per 10,000 dives.[12] The potential for development of DCS increases with the length and depth of a dive. Other risk factors include age, obesity, fatigue, heavy exertion, dehydration, fever, cold ambient temperatures after diving, diving at high altitude, and flying after diving. Tobacco and ethanol use may also increase susceptibility to DCS. The risk of DCS is 2.6 times greater for men than women.[13] This difference is possibly due to risk-taking behaviors. There appears to be no increase in DCS in women who are taking oral contraceptive agents or menstruating during diving.

A patent foramen ovale (PFO) may be a risk factor for increased susceptibility to DCS. Sixty-five percent of divers who present with serious DCS have a PFO.[14] Reul and colleagues[15] report brain lesions in 27% of sport divers. This percentage is roughly the same as the prevalence of PFO or other right-to-left shunts in the general population. These multiple brain lesions may be caused by bubbles in the venous circulation that are not filtered by the vasculature of the lungs but enter the arterial circulation, even in the absence of other DCS symptoms.[16] Most sport divers do not undergo screening for PFO with echocardiographic bubble studies, and there is reason to believe that some PFOs may open only at increased ambient pressures so that bubble studies are negative if conducted at 1 ATA.[17]

The U.S. Navy dive tables estimate the amount of nitrogen that accumulates in the body during a dive to a particular depth for a specific duration.[3] The tables calculate a maximal dive time, called the "no-decompression limit," which represents the amount of time a diver may spend at a maximum depth and return to the surface without sufficiently exceeding the solubility of nitrogen at sea level to produce DCS. The diver still must ascend in a slow, controlled manner to allow the gradual release of nitrogen. Off-gassing continues after the diver has surfaced; it takes up to 12 hours at the surface for nitrogen stores to return to normal sea level values. Repetitive dives within several hours result in accumulation of tissue nitrogen and shorter no-decompression limits. Because dive tables are based on several assumptions regarding N_2 elimination, even strict adherence to these tables does not ensure that DCS will not occur.[3]

If the no-decompression limits are exceeded, underwater decompression stops are recommended. The depth and duration of these stops can be derived from the U.S. Navy Standard Air Decompression Dive Tables.[3]

Many sport scuba divers use submersible dive computers to calculate maximum dive times. These computers use mathematical algorithms to model nitrogen saturation in human tissues. Although they remove human calculation errors, such computers also tend to extend no-decompression times to their maximum limits. It is important to realize that divers can develop DCS even when within the no-decompression limits whether calculated by computer or derived from a dive table.

The clinical manifestations of DCS are divided into two categories—type I and type II. Type I DCS affects the musculoskeletal system, skin, and lymphatic vessels. Type II DCS involves any other organ system. Type II DCS is more commonly reported and more serious than type I (this may indicate recognition and reporting bias more than the actual incidences).

Type I DCS is also called the bends. It is experienced as variable and periarticular pain in the arms and legs. The elbow and shoulder joints are most commonly affected. Local tenderness and erythema are uncommon. Classically, the placement and inflation of a blood pressure cuff to 150 to 200 mm Hg on an affected joint produces relief of pain and helps confirm the diagnosis; however, the sensitivity of this maneuver was as low as 61% in one study.[18] Skin manifestations of type I DCS may include pruritus (niggles), erythema, and marbling. Pruritus without other signs, however, usually occurs only during decompression in hyperbaric chamber workers as a result of nitrogen diffusing through the skin; it is not considered a true form of DCS and is rare in scuba divers. Skin marbling, known as cutis marmorata (patchy cyanotic marbling of the skin), is a true form of DCS and results from venous stasis. It may begin as severe pruritus and progress into an erythematous rash and then to skin mottling. Cutis marmorata does not follow a dermatomal distribution and commonly involves the trunk and torso. Lymphatic obstruction by air bubbles can also occur, causing extremity edema.

Type II DCS includes symptoms beyond those described for type I DCS. These symptoms can involve the CNS, the inner ear, and the lungs. The CNS is particularly susceptible to decompression illness because of its high lipid content. The spinal cord, especially the upper lumbar area, is more often involved than cerebral tissue. Symptoms of spinal DCS include limb weakness or paralysis, paresthesias, numbness, and low back and abdominal pain. Limb symptoms often begin as a distal prickly sensation that advances proximally, followed by progressive sensory or motor loss. A dermatome sensory level occurs in some spinal DCS patients, often at the T12 to L1 dermatomes. Bladder symptoms, fecal incontinence, and priapism may occur. Unlike patients with spinal cord trauma, patients experiencing DCS may have patchy or unequally distributed sensory and motor findings.

Spinal DCS can occur alone or in combination with cerebral, inner ear, or pulmonary symptoms. Cerebral symptoms include mild to moderate headache, blurred vision, diplopia, dysarthria, unusual fatigue, inappropriate behavior, and a sense of detachment. Loss of consciousness in CNS DCS is rare (in marked contrast to the presentation in arterial gas embolism [AGE]).[19] Magnetic resonance imaging, computed tomography (CT), and single photon emission CT using technetium 99m-labeled hexamethylpropyleneamine can identify the bubbles of CNS DCS. However, no imaging studies are sensitive enough to exclude DCS, and the use of imaging should not delay transfer for definitive therapy.

Inner ear DCS is commonly called "the staggers." The symptoms of inner ear DCS are the same as those of IEBT and include nausea, dizziness, vertigo, and nystagmus.

Pulmonary DCS is called "the chokes." All divers are exposed to some degree of microbubble emboli to the lungs on ascent. The progression to symptoms probably depends on the number and volume of bubbles. The deposition of venous gas emboli in the pulmonary arterial circulation produces progressive dyspnea, cough, and chest pain. The cough may progress to paroxysmal fits with worsening pain.

The physical examination of patients suffering from pulmonary DCS may reveal cyanosis and hypotension in association with increased central venous pressure and pulmonary arterial pressure, right-sided strain on an electrocardiogram, and a decreased end-tidal CO_2 level. The condition may progress to respiratory arrest. Ancillary tests for pulmonary DCS not only are insensitive but also lead to unnecessary delays in treatment. Even after ascent from very shallow saturation dives, microbubbles in the venous circulation can be routinely detected by M-mode ultrasonography; however, their presence does not necessarily correlate with symptoms.[20-23]

DCS may be particularly dangerous to a developing fetus in the womb of a scuba diving mother because the majority of the fetal circulation bypasses the pulmonary bed through the foramen ovale and the ductus arteriosus. This bypass prevents the fetal lungs from acting as a filter for microbubbles. In addition, venous gas emboli may appear in the fetal circulation before they are apparent in the maternal circulation.[24,25] Human data on the effects of diving on pregnant women suggest a higher incidence of low-birth-weight infants, prematurity, congenital malformations, stillbirths, and spontaneous abortions.[26,27] There are no safe-diving tables that would protect a fetus from DCS; therefore, pregnant women should be advised to refrain from scuba diving.

Pulmonary Barotrauma

Without continuously expiring on ascent, a scuba diver who takes a full breath at 33 fsw will have twice the lung volume at the surface (Boyle's law). Because the volume expansion of the alveoli is limited, the increase in pressure either forces gas bubbles across the alveolar-capillary membrane or causes the wall of the alveoli to rupture. A differential pressure of only 80 mm Hg between the alveoli and chest wall, corresponding to a change in depth of 3 to 4 feet, is all that is required to force air bubbles across the alveolar-capillary membrane.[28] The greatest risk for pulmonary barotrauma occurs in less than 10 feet of water. Pulmonary barotrauma can result in the following five conditions: AGE, pneumothorax, pneumomediastinum, subcutaneous emphysema, and alveolar hemorrhage.

Risk factors sought from the dive and medical history may suggest the diagnosis of pulmonary barotrauma. In most cases, fast ascent, panic, problems regulating buoyancy, or running out of air is noted.

Scuba divers who suffer from asthma probably have a twofold increased risk for a dive accident compared with the general diver population.[29] There are six mechanisms by which asthmatics are at higher risk for pulmonary barotrauma:

1. Bronchospasm and mucus plugging predispose local regions of lung to injury.[30]
2. When air is compressed, it becomes denser. This may contribute to greater turbulent flow through narrow airways.
3. During scuba diving, there is a reduction in breathing capacity related to the effects of immersion. At 33 feet underwater, the maximum breathing capacity of a normal scuba diver is only 70% of the surface value. At 100 feet underwater, the reduction is approximately 50%.
4. When compressed air (from the scuba tank) expands in the regulator before delivery to the lungs, it cools (Charles' law). Breathing chilled air may trigger bronchospasm in asthmatics who have a cold-induced component of their disease.
5. Scuba diving takes some effort; asthmatics who have an exercise-induced component of their disease may experience bronchospasm.
6. Compressed air may be contaminated by pollen and other allergens.

Traditionally, asthmatics are advised not to dive. However, a consensus of experts at a 1995 Undersea and Hyperbaric Medical Society workshop proposed more liberal guidelines. The risk of diving is probably acceptable if the diving candidate with some asthmatic history demonstrates normal pulmonary function at rest (forced vital capacity [FVC], mid-expiratory flow, forced expiratory volume in 1 second, and forced expiratory flow between 25 and 75% of FVC) and after strenuous exercise. Asthma severity can wax and wane. Because symptoms may worsen for 4 to 6 weeks after an upper respiratory infection or during certain seasons, an asthmatic should refrain from diving until completely free of symptoms despite the pulmonary function criteria.

Arterial Gas Embolism

The most severe form of pulmonary barotrauma is AGE. It is the second leading cause of mortality among sport divers after drowning, accounting for approximately 30% of diving-related deaths.[28] Typically, it results when air bubbles are forced across the alveolar-capillary membrane, escape into the pulmonary venous circulation, and proceed through the left atrium and ventricle into the arterial circulation. Clinical symptoms and signs are in part the result of mechanical obstruction by gas bubbles. AGE can also result from a right-to-left shunt of venous bubbles, such as in a diver with a PFO.

Although air bubbles may embolize to any organ, the coronary and cerebral arteries are associated with the most serious consequences. Emboli to the coronary arteries may cause cardiac ischemia, myocardial infarction, dysrhythmias, or cardiac arrest. Dysrhythmias are also indirectly caused by centrally mediated autonomic dysfunction from cerebral emboli.[31,32] Mechanical occlusion of the cerebral vasculature from emboli, most commonly to the anterior and middle cerebral arteries, causes a variety of symptoms and signs similar in appearance to an acute stroke.

The clinical manifestations of AGE may be sudden, dramatic, and life-threatening. Divers who have supposedly "drowned" may actually have lost consciousness during ascent as a result of cerebral gas emboli. Any diver who has breathed compressed air at any depth underwater and who surfaces unconscious or who loses consciousness within 10 minutes of reaching the surface should be assumed to be suffering from AGE. The most common presentation of AGE includes a global alteration of consciousness, headache, dizziness, convulsions, and visual changes. Other common presenting symptoms and signs include cranial nerve symptoms, unilateral weakness, unilateral or bilateral sensory loss, ataxia, and speech changes.[28] Pulmonary symptoms, including dyspnea, pleuritic chest pain, and hemoptysis, occur in 25 to 50% of cases.[33]

Pneumothorax

When the air that escapes from alveoli as a result of pulmonary barotrauma crosses the visceral pleura, it may result in a pneumothorax. A tension pneumothorax is a rare complication.

The symptoms and signs of a pulmonary barotrauma-related pneumothorax are typical for a pneumothorax of any cause. Pulmonary barotrauma can also cause alveolar hemorrhage. Hemoptysis is coincident with chest pain and dyspnea.

Pneumomediastinum and Subcutaneous Emphysema

Pneumomediastinum results when air crosses the alveolar endothelium and dissects into the pulmonary interstitium. Most commonly, the air then travels into the neck, mediastinum, or pericardium. The manifestations of pneumomediastinum may include fullness in the neck, palpable subcutaneous crepitance, and a change in voice quality or timbre. Unless evidence of either hemodynamic instability or airway compromise exists, interstitial air or subcutaneous emphysema is not a life-threatening condition.

Alternobaric Vertigo

Alternobaric vertigo (ABV) results from an inability to equalize pressure within the middle ear during ascent. Although equalization during descent requires active maneuvers to maintain eustachian tube patency, air normally exits the middle ear without difficulty during ascent because the pressure within the middle ear exceeds ambient pressure. In the setting of mucosal edema or thickening within the eustachian tube, however, the passage of air may be impeded. The problem is typically unilateral. When the pressure gradient within the middle ear reaches 60 cm H_2O, increased labyrinthine discharge produces nystagmus, with the fast phase toward the affected ear. Clinically, the patient experiences a profound but transient sense of vertigo during ascent that may be associated with nausea and vomiting. Unlike those of IEBT, the symptoms are self-limited.

Barodontalgia

Occasionally, air that is trapped beneath a poorly filled dental cavity expands on ascent, leading to dental pain. This condition is relatively benign and self-limited.

Gastrointestinal Barotrauma

Serious gastrointestinal barotrauma is a rare condition in scuba divers. It results from the expansion of bowel gas in the small intestine and colon on ascent after diving. Predisposing factors include consumption of carbonated beverages, large meals, or gas-producing foods before diving as well as performing the Valsalva maneuver in the head-down position. Symptoms include eructation, flatulence, bloating, and crampy abdominal pain. In divers with inguinal or other hernias, the potential for expansion of trapped gas within the hernia exists, and expansion may result in incarceration or strangulation.[34] Gastric rupture is a rare complication.[35] Although gastrointestinal barotrauma is a rare entity, it must be suspected in the diver-patient with a provocative history and abdominal pain.

Pulmonary Edema

Pulmonary edema while scuba diving was first reported in 1981.[36] An increase in afterload (from vascular hyper-reactivity, possibly triggered by cold) combined with an increase in preload (from the hyperbaric underwater environment) may be the cause.

BOX 141-1 FOCUSED DIVE HISTORY

When was the first onset of symptoms?
What type of equipment was used? Compressed air, mixed gas, enriched air, rebreather? What was the source of the gas?
Did the dive approach or exceed decompression limits? Was a dive computer used?
What were the number, depth, bottom time, total time, and surface intervals for all dives in the 72 hours preceding symptoms (the dive "profiles")?
Were decompression stops used? Was in-water decompression attempted?
What was the time delay from the last dive to air travel?
Did the diver experience difficulty with ear or sinus equilibration? Did the pain occur on descent or ascent?
Was the diver intoxicated? Dehydrated? Working strenuously?
How long after the dive did symptoms present? Were they present at surfacing? Delayed? Progressive?
Is a medical history of ear or sinus infections or abnormalities present? Emphysema or asthma? Coronary artery disease? Patent foramen ovale? Neurologic illness?

DIAGNOSTIC STRATEGIES

Focused questions concerning the dive profile, including the depth and length of the dive and a careful assessment of when the symptoms first occurred, may provide important diagnostic clues (Box 141-1). A physician unfamiliar with the specifics of scuba diving may rely on the assessment of members of the dive group to determine whether maximum dive limits were approached. When making the diagnosis of a dive injury, it is helpful to think of the injuries in terms of occurring during descent, while at depth, or during ascent (Fig. 141-7).

The diagnosis of MEBT can be established by history and physical examination alone (Table 141-3). Symptoms include ear pain during descent, transient vertigo, and hearing loss. A grading system for MEBT based on symptoms and signs is useful in selecting treatment regimens (Table 141-4).[37,38] Other signs may include conductive hearing loss and, occasionally, unilateral facial paralysis.

DIFFERENTIAL CONSIDERATIONS

Most diving injuries have limited differential diagnoses that include medical disorders and trauma unrelated to dysbarism. The differential diagnosis of IEBT includes inner ear DCS, ABV, and isolated MEBT with a rupture of the TM. It is relatively easy to distinguish IEBT from MEBT and ABV because the vestibular symptoms associated with the latter two entities are transient and self-limited. When IEBT occurs simultaneously with MEBT, the presence of both may be documented by an audiogram, which demonstrates both a conductive and a sensorineural hearing loss.

The differentiation of IEBT from inner ear neurologic DCS is crucial, particularly because the treatments differ. A careful history is the most important tool in diagnosis. An IEBT is more likely when symptoms begin during descent or the diver relates a history of difficulty equilibrating or performing a vigorous Valsalva maneuver. If the dive profile is examined and the no-decompression limits are approached or exceeded and symptoms began soon after surfacing, inner ear DCS is more likely.[39]

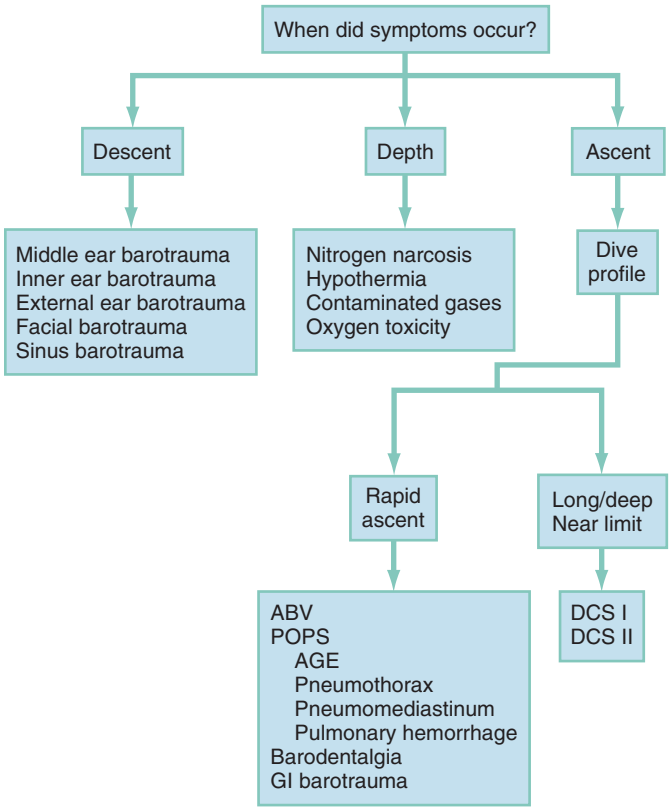


Figure 141-7. The approach to the injured diver. ABV, alternobaric vertigo; AGE, arterial gas embolism; DCS, decompression sickness; GI, gastrointestinal; POPS, pulmonary overpressure syndrome.

Table 141-3 Middle Ear Barotrauma, Inner Ear Barotrauma, and Alternobaric Vertigo

	MEBT	IEBT	ABV
Symptoms	Ear pain during descent	Ear pain during descent	Ear pain during ascent
	Hearing loss	Hearing loss	Transient hearing loss
	Possible transient vertigo	Severe vertigo and nausea	Nausea
Signs	Conductive hearing loss	Nystagmus	Nystagmus
	TM injury	Emesis	Emesis
	Unilateral face paralysis	Ataxia	TM injury
		Romberg's sign	
		Neural hearing loss	

ABV, alternobaric vertigo; IEBT, inner ear barotrauma; MEBT, middle ear barotrauma; TM, tympanic membrane.

Table 141-4 Grading of Middle Ear Barotrauma

GRADE	FINDINGS	TREATMENT
Type 1	Postdive symptoms with normal examination	Avoid diving until symptoms clear; systemic or topical decongestants
Type 2	Symptoms plus otoscopic findings without perforation	Avoid further diving until complete resolution; systemic or topical decongestants; nonnarcotic analgesics
Type 3	Symptoms plus otoscopic findings with perforation	Avoid further diving until complete resolution and healing; systemic and topical decongestants; consider prophylactic antibiotics, analgesics

Modified from Farmer JC: Ear and sinus problems in diving. In Bove AA, Davis JC (eds): *Diving Medicine,* 2nd ed. Philadelphia, Saunders, 1990.

Table 141-5 Decompression Sickness versus Arterial Gas Embolism

DECOMPRESSION SICKNESS	ARTERIAL GAS EMBOLISM
Dive History	
Depth and length dependent	Independent of dive profile
Decompression limits approached	Rapid ascent
Flying after diving	Inexperience
Diving at altitude	Out of air
Risk Factors	
Fatigue	Obstructive lung disease
Dehydration	Emphysema
Fever, hypothermia	Mucous plugging
Obesity	Patent foramen ovale
Strenuous activity	
Symptoms and Signs	
Progressive onset	Rapid onset
Spinal symptoms predominate	Cerebral symptoms predominate
Headache	Headache
Unusual fatigue	Loss of consciousness
Limb weakness or paralysis	Confusion
Paresthesias	Convulsions
Abdominal pain	Motor or sensory loss
Urinary retention	Cardiac dysrhythmias or arrest
Fecal incontinence	
Periarticular joint pain	
Skin marbling	
Vertigo or nystagmus	
Treatment	
Recompression	Recompression

The differentiation of inner ear DCS from barotrauma is based on the history, particularly the time of onset of symptoms. A history of difficulty equalizing the ears on descent, or the onset of symptoms early in the dive, suggests barotrauma. A history of a dive that approaches decompression limits, or the onset of symptoms during or soon after ascent, and the presence of other neurologic findings suggest DCS. A trial of recompression therapy is indicated if concern about DCS exists.

The differential diagnosis of pulmonary DCS includes AGE (Table 141-5). Although the treatment of both requires recompression therapy, attempts should be made to distinguish the

DAN On-Site Neurological Assessment for Diver's History

Last Name: _____ **First Name:** _____ **MI:** _____

Date: (mm/dd/yy): _____ **Time: (hh:mm)** _____

COMPLETED BY: _____

How do you feel? _____

Symptoms? _____

Did symptoms start during descent, on bottom, during ascent, or after surfacing? _____

_____

Dive profile, breathing gas, ascent and time of surfacing, recent dive history _____

_____

_____

_____

Unusual features of dive (e.g., out of air, rapid ascent) _____

Decompression computer, table _____

Difficulty with middle ear equalization? _____

Numbness, tingling? Where? _____

Pain? Where? What makes it better or worse? _____

Rate the pain on a scale of 0 (no pain) to 10 (the worst pain imaginable) _____

Shortness of breath? _____

Ringing or buzzing in ear? _____ Decreased hearing? _____

Dizziness? Vertigo? _____

"Vertigo" implies a sensation of the world spinning around. Vague "dizziness" is not vertigo.

Weakness? _____

Difficulty walking? If so, is this due to difficulty with balance or leg weakness? _____

Nausea, vomiting? _____ Able to urinate? _____

From "observer" (e.g., dive buddy, companion) _____

Confirm dive profile _____

His/her version of events _____

_____

_____

Did the diver breach safe procedures (e.g., ascent rate, out of air, was he/she breathing during ascent)?

_____

Has the diver been acting inappropriately? _____

Was there loss of consciousness, seizure? _____

Figure 141-8. The DAN On-Site Neurological Assessment for Diver's History.

two forms of injury. Almost all cases of AGE present within the first 10 minutes of surfacing, whereas DCS presents more typically after 10 minutes: 42% of pulmonary DCS symptoms begin within 1 hour of surfacing, 60% within 3 hours, 83% within 8 hours, and 98% within 24 hours.[3]

MANAGEMENT

Several invaluable resources are available for advice on the management of diving accidents. The Divers Alert Network (DAN), located at Duke University in Durham, North Carolina, is a membership association that provides courses on diving-related emergencies and publishes data on diving accidents and fatalities. Clinicians can locate the nearest hyperbaric chamber by calling DAN. DAN provides a 24-hour medical emergency hotline at 919-684-8111 and a nonemergency advisory line Monday through Friday, 9 AM to 5 PM Eastern time, at 919-684-2948. DAN also maintains a website with links to key information at http://www.diversalertnetwork.org. DAN uses a telephone intake form, the "DAN On-Site Neurological Assessment for Diver's History" (Fig. 141-8); familiarity with this form may enhance the emergency physician's communications with DAN.

The U.S. Navy has made available its most current diving manual (revision 5) at its website, http://www.supsalv.org/pdf/Diveman.pdf. It contains a wealth of information about diving

principles, equipment, and operations. It also has extensive information on diving medicine and recompression chamber operations.

Diving Disorders Requiring Recompression Therapy (Box 141-2)

Immediate treatment should include the administration of 100% oxygen. This reduces the bubble size by increasing the differential pressure for nitrogen diffusion out of the bubbles and speeds the washout of nitrogen from the tissues.[40] Recompression is the only definitive treatment for DCS (types I and II) and AGE. Treatment of DCS or AGE should not be withheld even if a significant time delay in transfer to a hyperbaric chamber is unavoidable. In-water recompression is risky, demanding, time-consuming, and not typically recommended.

Hyperbaric therapy for AGE should be initiated as soon as possible for optimal results, but there are cases of significant improvement even in the face of long delays until recompression.[41] Patients with AGE who are recompressed within 5 minutes of surfacing have a mortality rate of 5%, and there is an extremely low risk of morbidity among the survivors.[17] If recompression is delayed by 5 hours or more, the mortality rate increases to 10%, with 50% morbidity.[17] Although spontaneous resolution of symptoms may occur in patients with AGE, all patients should be recompressed. One rationale for this approach is that although microbubbles may clear from the cerebral circulation, secondary capillary edema and swelling may result in a delayed recurrence of symptoms. Furthermore, more subtle symptoms may be appreciated only after the resolution of more prominent ones. Finally, minor symptoms may progress, and the relapse rate is high in untreated cases.

Similarly, the prognosis for DCS when treated with recompression is generally good but depends on the severity of symptoms at onset and the delay to recompression. A delay to definitive recompression treatment is associated with a worse outcome in cases of severe DCS. Patients can obtain some benefit from recompression, however, even if treatment is initiated more than 24 hours after the dive. Recompression therapy for DCS may be initiated as late as 10 to 14 days after exposure if necessary.[42]

Monoplace hyperbaric chambers are compact, lightweight, and more widely available than multiplace chambers. Unfortunately, because of their design, most cannot be pressurized beyond 3 ATA (100 fsw) or deliver air-oxygen mixtures. Recompression therapy is usually performed based on U.S. Navy Treatment Tables (Fig. 141-9; Table 141-6). The 3 ATA limit renders some of the U.S. Navy Treatment Tables unsuitable for monoplace chambers. The small size of a monoplace chamber also prevents the unstable patient from receiving attendance within the chamber. The decision to bypass a monoplace chamber for a potentially more distant multiplace hyperbaric chamber must be weighed carefully in consultation with a hyperbaric specialist. The DAN hotline may be helpful in locating the closest suitable chamber.

BOX 141-2 Diving Disorders That Require Recompression Therapy

Decompression sickness (DCS) type I
DCS type II
Arterial gas embolism
Contaminated air (carbon monoxide poisoning)

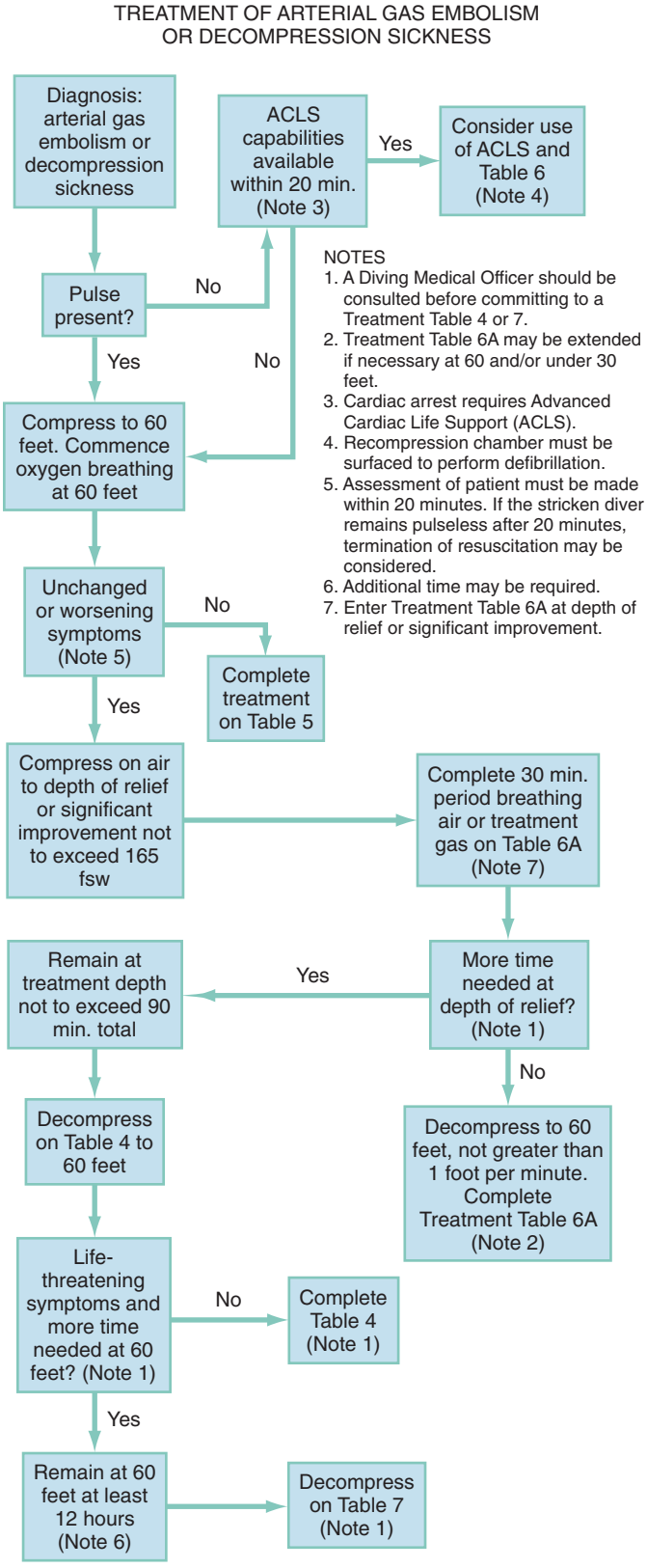


Figure 141-9. Treatment of arterial gas embolism or serious decompression sickness. (Modified from Figure 20-1 from Naval Sea Systems Command: U.S. Navy Diving Manual, revision 5. Published by direction of Commander of Naval Sea Systems, United States Navy, August 2005: Treatment of Arterial Gas Embolism or Serious Decompression Sickness.)

Table 141-6 Summary of the U.S. Navy Treatment Tables*

TREATMENT TABLE	MAXIMUM DEPTH	TIME REQUIRED (HR:MIN)	OXYGEN?	USED FOR
Treatment Table 5	60 fsw	2:15	Yes	DCS I Asymptomatic omitted decompression Treatment of resolved symptoms following in-water recompression Follow-up treatments for residual symptoms Carbon monoxide poisoning
Treatment Table 6	60 fsw	4:45	Yes	AGE, DCS I, DCS II symptoms where relief is not complete within 10 minutes at 60 feet or where pain is severe and immediate recompression must be instituted before a neurologic examination can be performed Cutis marmorata Severe carbon monoxide poisoning, cyanide poisoning, or smoke inhalation Symptomatic uncontrolled ascent Asymptomatic omitted decompression Recurrence of symptoms shallower than 60 fsw
Treatment Table 6A	165 fsw	5:50	Yes	AGE, DCS when severe symptoms remain unchanged or worsen within the first 20 min at 60 fsw
Treatment Table 4	165 fsw	39:06–40:36	If equipped	When it is determined that the patient would receive additional benefit at depth of significant relief, not to exceed 165 fsw
Treatment Table 7	60 fsw	48:00 minimum	If equipped	Heroic measure for treating nonresponding severe AGE or life-threatening DCS
Treatment Table 9	45 fsw	102:15	Yes	Residual symptoms remaining after initial treatment of AGE/DCS, selected cases of carbon monoxide or cyanide poisoning, smoke inhalation This table may also be recommended by the cognizant Diving Medical Officer when initially treating a severely injured patient whose medical condition precludes long absences from definitive medical care
Treatment Table 1A	100 fsw	7:52	Only used as a last resort when oxygen is not available	AGE, DCS: used if pain is relieved at a depth less than 66 fsw
Treatment Table 2A	165 fsw	13:33	Only used as a last resort when oxygen is not available	AGE, DCS: used if pain is relieved at depth greater than 66 fsw
Treatment Table 3	165 fsw	21:33	Only used as a last resort when oxygen is not available	AGE, DCS: used if symptoms are relieved within 30 min at 165 fsw

AGE, arterial gas embolism; DCS, decompression sickness.
*The times required listed in this table for the various treatment regimens do not include the time required for descent.
The treatment tables are from the U.S. Diving Manual Revision 5, Chapter 20, pp 41–50.
Available at http://www.supsalv.org/pdf/Diveman.pdf.

Ground transport to a hyperbaric facility is preferred over air transportation, if feasible, because an increase in altitude lowers the ambient pressure and allows microbubbles to expand. If air transportation must be used, it is important to maintain cabin pressure at less than 1000 feet. Commercial aircraft are typically pressurized to a cabin altitude of 5000 to 8000 feet in cruise flight (>30,000 feet). Most of these aircraft are capable of near–sea level cabin pressures if flying no higher than 20,000 to 25,000 feet. Because helicopters are not pressurized, it is recommended that they maintain an altitude of no more than 500 feet above the departure facility. The transferring physician can also consider transportation of the patient in a portable, monoplace chamber, if one is available.

The goals of recompression therapy are to reduce the mechanical obstruction of air bubbles, to facilitate the washout of nitrogen by increasing the tissue-blood nitrogen gradient, and to increase oxygen delivery to ischemic tissue. It is generally accepted that hyperbaric oxygen treatment is superior to hyperbaric air treatment for DCS or AGE. The selection of a treatment protocol for a particular patient, however, is best made by a qualified hyperbaricist. The U.S. Navy Treatment Tables are one of several widely accepted sets of treatment protocols. Patients suffering from DCS type I should be treated with recompression; the clinician should also search for symptoms of the more severe manifestations of DCS.

In addition to recompression therapy, several adjunctive treatments are advocated in the treatment of DCS and AGE. One hundred percent oxygen administered before recompression may facilitate the washout of inert gases. Intravenous fluid administration to ensure a urine output of 1 or 2 mL/kg/hr may facilitate tissue perfusion and washout of inert gases. The treatment or prevention of hypothermia may also help perfusion and off-gassing.

There are no medications that prevent or lessen the symptoms of DCS or AGE. Aspirin therapy (325–650 mg) or other platelet inhibitors may impede platelet aggregation in DCS.[28] Steroids have been advocated clinically for neurologic DCS and AGE; however, they have not been of benefit in animal studies and evidence implies that they may cause harm.[43] Lidocaine therapy—possibly because it reduces the cerebral metabolic rate, preserves cerebral blood flow, or reduces leu-

kocyte adherence to damaged endothelium—may prove useful in the treatment of DCS.[3,44]

Cardiac dysrhythmias may be refractory to standard treatments until the diver is recompressed. Seizures may be managed with benzodiazepines; however, mannitol should be avoided. Spinal DCS patients often develop urinary retention requiring bladder catheterization. Of note, endotracheal tube and urinary catheter balloons should be inflated with water or saline (not air) before initiating recompression therapy.

Transport of the patient with AGE in the supine position is recommended to maximize arterial-venous flow. The Trendelenburg position, once thought to reduce the degree of cerebral embolization, increases intracranial pressure, facilitates coronary gas embolization, and should be avoided.[45]

There is limited experience with carbon monoxide poisoning from contaminated air supplies in a diving environment. This condition should be treated immediately with normobaric 100% oxygen and may require hyperbaric oxygen therapy.

Diving Disorders Not Requiring Recompression Therapy (Box 141-3)

Prevention of MEBT requires that the diver equalize the pressure in both middle ears. Any diver who cannot clear both ears on the surface should not dive. The diver should never perform a forceful Valsalva maneuver during descent or ascent in order to clear the ears because of the risk of ABV, round or oval window rupture (descent), or pulmonary barotrauma (ascent). The prophylactic use of pseudoephedrine, 60 mg taken 30 minutes before diving, may reduce the incidence and severity of MEBT.[46] The use of this medication to facilitate diving with symptoms of an upper respiratory infection, however, is not recommended. Antihistamines should be avoided before diving. Sinusitis and upper respiratory infections increase the likelihood of suffering barotitis. Diving should be avoided for 2 weeks after the resolution of an upper respiratory infection.[47]

Treatment for uncomplicated serous otitis from MEBT includes topical nasal vasoconstrictors such as phenylephrine or oxymetazoline hydrochloride and repeated Frenzel maneuvers to displace the fluid through the eustachian tube. The Frenzel maneuver is performed by swallowing with a closed glottis, pursed lips, and pinched nose. If the physical examination reveals a ruptured TM, prophylactic treatment should also include an oral antibiotic. Oral steroids may speed recovery when a seventh nerve palsy is diagnosed in conjunction with a perforated TM, although this disorder is typically self-limited. Diving must also be suspended until the TM heals to prevent calorically induced vertigo.

BOX 141-3 Diving Disorders That Do Not Require Recompression Therapy

- Middle ear barotrauma
- External ear barotrauma
- Inner ear barotrauma
- Barosinusitis
- Facial barotrauma
- Nitrogen narcosis
- Oxygen toxicity
- Pneumothorax
- Pneumomediastinum
- Subcutaneous emphysema
- Alveolar hemorrhage
- Alternobaric vertigo
- Barodentalgia
- Gastrointestinal barotrauma
- Avascular osteonecrosis

Treatment of external ear barotrauma includes cleaning the external canal and removing foreign bodies. Earplugs should never be worn when diving.

A conservative treatment approach to IEBT includes bed rest for 5 to 7 days with the head elevated, avoidance of straining and the Valsalva maneuver, and decongestants to facilitate drainage of the middle ear. Early surgical intervention may benefit patients with total or near-total hearing loss but not isolated high-frequency hearing loss. All patients with IEBT should be provided referral to an otolaryngologist because IEBT suggests significant injury to the cochleovestibular system.

Treatment of barosinusitis is typically conservative, including the use of decongestants and, occasionally, antibiotics. If symptoms persist, referral for antrostomy should be considered, particularly to prevent future recurrences. The patient should be advised not to dive until any underlying respiratory infection or acute inflammatory process has resolved completely.

The victim of facial barotrauma may have a dramatic appearance, but the condition is usually benign and requires no specific treatment. The patient should be advised not to resume diving until facial edema has resolved.[48]

Nitrogen narcosis symptoms should resolve on surfacing when the partial pressure of nitrogen decreases. Seemingly persistent symptoms should prompt a search for other etiologies, such as DCS, cerebral AGE, contaminated air, and near drowning.

With the exception of AGE, none of the pulmonary barotrauma disorders (pneumothorax, pneumomediastinum, subcutaneous emphysema, and alveolar hemorrhage) requires recompression therapy. Treatment with 100% oxygen may aid in the resolution of the disorders. Although tube thoracostomy may not be required for the treatment of a small pneumothorax, such a tube should be placed if the diver is to undergo recompression therapy for concomitant AGE or DCS to prevent a tension pneumothorax. Catheter aspiration of the pneumothorax is an acceptable alternative to tube thoracostomy if the patient will not receive positive-pressure ventilation or recompression therapy.

The evaluation and management of pneumomediastinum includes serial chest radiographs to ensure that no coexisting pneumothorax develops and discharge with appropriate pain medication. One hundred percent oxygen therapy may hasten the resolution of symptoms. In the rare case of respiratory compromise, tracheal intubation may be required. Most important, the presence of interstitial pulmonary emphysema should alert the physician to the possible coexistence of more severe forms of pulmonary barotrauma. The need for a surgical decompressive treatment of subcutaneous emphysema alone is extremely unlikely. Supportive therapy to correct hypoxia is indicated in the treatment of alveolar hemorrhage.[49]

Careful equalization during a slow ascent can prevent the occurrence of ABV. Oral and topical decongestants may be indicated if symptoms persist. Occasionally, myringotomy is required.[50]

DISPOSITION

Decompression tables are based on the premise that the diver returns to an ambient pressure of 1 atm on surfacing. A further reduction in ambient pressure, however, occurs either when ascending in altitude after diving or when diving at altitude. Commercial airliners may be pressurized to a cabin altitude of 5000 to 8000 feet in cruise flight. Many cases of DCS have a

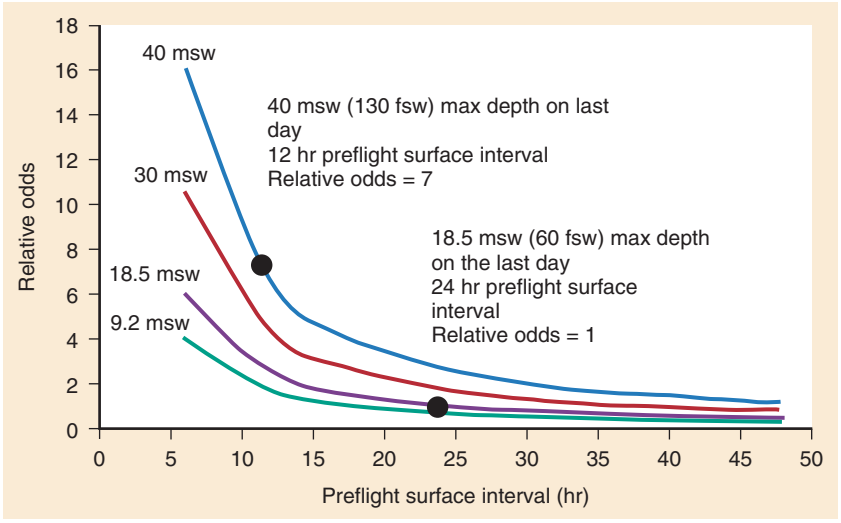


Figure 141-10. The risk of decompression sickness relative to flying. fsw, feet of seawater; msw, meters of seawater. (From Freiberger JJ, et al: The relative risk of decompression sickness during and after air travel following diving. Aviat Space Environ Med 73:983, 2002.)

delay in the onset of symptoms in divers who fly after diving even if they are symptom-free prior to departure. Divers who experience DCS symptoms before departure but nevertheless fly are more likely to have type II DCS, less likely to achieve complete relief after recompression, and more likely to have residual symptoms for at least 3 months.

The recommended postdive preflight surface interval (PFSI) before ascending to higher altitudes (or flying) depends on the diver's repetitive group designator (residual nitrogen time). The relative risk of developing DCS increases with greater residual nitrogen times and shorter PFSI (Fig. 141-10).[51] For example, the risk of developing DCS is seven times greater for PFSIs of 12 hours after a dive to 130 fsw than for PFSIs of 24 hours after a dive to 60 fsw.[51] Long PFSIs (up to 48 hours) may be necessary to reduce the risk of DCS after deep, multiday repetitive diving, particularly if the dives required decompression stops (exceeding the no-decompression limits).[52] Some dive computers calculate time-to-flight intervals, which tend to be somewhat shorter than most guidelines based on residual nitrogen timetables. Flying should be delayed for at least 12 hours after diving if less than 2 hours of total dive time was accumulated in the preceding 48 hours. For multiple-day, unlimited diving, flying should be delayed for at least 24 hours. It is prudent to admit all recompressed patients or to advise them to remain within 60 minutes of the hyperbaric facility for 24 hours. Patients recompressed after DCS or AGE should not fly for 72 hours.

The U.S. Navy's guidelines recommend that the patient not return to diving for 7 days after recompression for type I DCS and for 4 weeks after type II DCS.[3] The sport diver who experiences DCS type II symptoms or AGE should probably never dive again.

After treatment for pulmonary barotrauma, it is advisable to evaluate the diver with a spiral volumetric chest CT scan to determine whether there are any preexisting pathologic conditions (e.g., bullae) that could put the diver at risk for recurrence before further diving.[53] Chest CT is not recommended in routine medical screening before participating in scuba diving without a history of pulmonary barotrauma.

KEY CONCEPTS

- There is a large population of sport scuba divers at risk for diving injuries. The land-locked emergency physician may be confronted with these problems.
- The Trendelenburg position, once thought to reduce cerebral embolization, increases intracranial pressure and facilitates coronary gas embolization.
- The majority of dive injuries are diagnosed on the basis of the focused dive history and physical examination alone and are best differentiated into disorders of descent, disorders of depth, and disorders of ascent. The U.S. Navy Dive Manual and the Divers Alert Network (DAN) are valuable resources for the clinician presented with a diving emergency. Emergency physicians should be familiar with their local hyperbaric capabilities.
- With the exception of DCS, AGE, and, possibly, carbon monoxide poisoning from contaminated air, most dive-related disorders can be treated without recompression therapy. Recompression treatment is always recommended for patients with DCS and AGE.
- Before initiating recompression therapy, ensure that endotracheal tube and urinary catheter balloons are not inflated with air.
- After multiple-day unlimited diving, flying should be delayed for at least 24 hours.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 142 High-Altitude Medicine

Michael Yaron and Benjamin Honigman

EPIDEMIOLOGY

High-altitude illness represents a spectrum of clinical entities that have hampered the activities of mountaineers, merchants, military forces, aviators, and explorers throughout time. This illness is seen clinically in one of several forms that overlap and share a common pathophysiology. Acute mountain sickness (AMS) is the relatively benign and self-limited presentation, whereas high-altitude pulmonary edema (HAPE) and high-altitude cerebral edema (HACE) represent the potentially life-threatening manifestations of high-altitude illness.

Worldwide, it is estimated that approximately 40 million individuals live above 8000 feet, and 25 million live above 10,000 feet.[1] Rather than these high-altitude residents, the groups at risk for acute altitude illnesses are those who ascend into mountainous regions. Mountain sports activities and tourism are attracting increasing numbers of participants each year. This, combined with the rapid ascent made possible by air transportation, results in more unacclimatized individuals at risk for high-altitude illness. More than 1 million visitors travel annually to the remote high mountain ranges of Asia, Africa, and South America.[1] Approximately 35 million visitors travel annually to high-altitude recreation areas in the western United States.[1]

The incidence of high-altitude illness depends on many variables. The rate of ascent, previous altitude exposure, and individual genetic susceptibility are the most important factors.[2] Sleeping altitude, final altitude reached, and duration of stay at any altitude also play a role. AMS is very common (67% incidence) among mountain climbers on Mt. Rainier who ascend quickly (1 or 2 days) to 14,410 feet.[3] Trekkers who fly into the Khumbu region to explore the Mt. Everest area have a higher incidence of AMS (47%) compared with those who walk (23%).[4] Skiers who visit resorts in the western United States from sea level generally fly or drive to the region but sleep at relatively lower altitudes than the other groups mentioned. Among this population, AMS occurs in approximately 25%.[5] Given the large number (approximately 25 million) of visitors in Colorado each year, this is not a trivial matter. The incidence of HAPE varies from 0.01 to 2% in most studies but has reached 15.5% among soldiers flown directly to 14,500 feet without a chance to acclimatize at a lower altitude.[4,6] The incidence of HACE is lower, and although it usually occurs with HAPE, it can be seen as an isolated entity. Both HAPE and HACE are more common with a longer duration of visit and higher sleeping altitude.

Age may be a relative risk factor. Most studies on children suggest that they have the same incidence of AMS as adults.[7-10] One small study of tourists in Chile evaluated children 4 to 48 months old and found higher AMS scores and lower oxygen saturations compared to those of their parents.[11] Younger individuals (<20 years old) are more likely to develop HAPE, although HAPE is extremely rare in children younger than 2 years of age. Gender does not affect the incidence of AMS[2]; however, women may have less risk of developing HAPE.[4,5,12,13] No relationship appears to exist between AMS development and the menstrual cycle.[14]

The number of elders visiting mountain resorts is increasing. Many of these individuals have underlying health problems, including lung disease (10%), heart disease (25%), and hypertension (30%). Despite these conditions, the risk for AMS development in this subset of older adults may be less than that in other age groups.[2,15] Nevertheless, there are indications that elders may not react well to acute high-altitude exposure. Pulmonary vital capacity decreases almost one third in elders ascending from sea level to 14,000 feet for 1 week, producing a large decrease in both oxygen saturation and maximal oxygen uptake during exercise. For elders residing at moderate elevations, oxygen saturation is approximately 92% at rest.[15]

DEFINITIONS

Moderate altitude is between 8000 and 10,000 feet of elevation. Although most people do not experience significant arterial oxygen desaturation until they reach higher altitudes, high-altitude illness is common with rapid ascent above 8000 feet. Individuals with underlying medical problems may be predisposed to developing altitude illness at lower levels.

High altitude is between 10,000 and 18,000 feet. Most serious altitude illness occurs at these levels. The pathophysiologic effects of high altitude begin when the oxygen saturation of the arterial blood begins to fall below the 90% level. The sigmoidal shape of the oxyhemoglobin dissociation curve prevents a significant fall of arterial oxygen saturation (Sao_2) in most individuals until an altitude of approximately 12,000 feet. At this altitude, the steep portion of the curve is encountered, and rapid desaturation begins, with relatively small increases in altitude (Fig. 142-1). Some predisposed individuals may desaturate to less than 90% at altitudes as low as 8000 feet.

Extreme altitude is above 18,000 feet. At this height, complete acclimatization generally is not possible, and long visits above this level result in progressive deterioration.

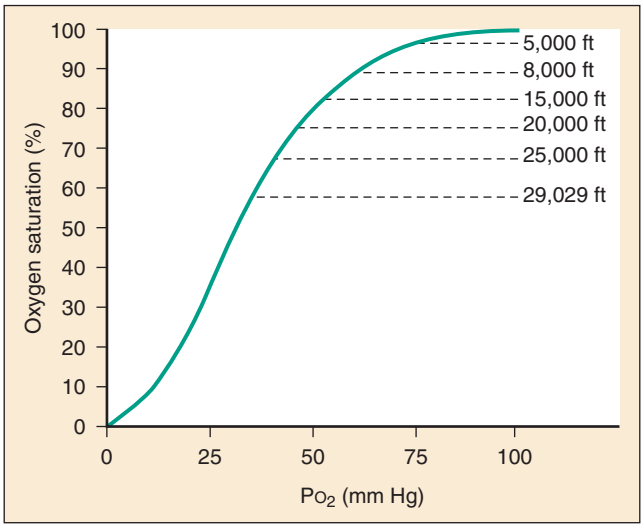


Figure 142-1. Oxygen-hemoglobin dissociation curve. Approximate oxygen saturations are marked for several altitudes. Po_2, partial pressure of oxygen. (Data for 15,000–29,029 feet from Sutton JR, et al: Operation Everest II: Oxygen transport during exercise at extreme simulated altitude. J Appl Physiol 64:1309, 1988.)

■ ENVIRONMENTAL CONSIDERATIONS

Barometric pressure decreases logarithmically as the altitude rises. The partial pressure of oxygen (Po_2) in the atmosphere also decreases as altitude rises, but it remains a constant 20.93% of the barometric pressure. The shape of the earth is slightly flat at the poles and bulging at the equator. The atmospheric envelope that surrounds the earth has a similar shape; therefore, the barometric pressure is lower at higher latitudes than it is at the equator. For example, it has been calculated that it would be impossible for a climber to reach the summit of Mt. Everest without supplemental oxygen if the mountain happened to be in a more northern latitude.[16]

The atmospheric envelope also undergoes a seasonal tide that causes a variation in its local thickness. This results in barometric pressures that are lower and "relative altitudes" that are higher during the winter season. Local weather can also have a significant effect on barometric pressure from day to day. A low-pressure front can reduce the barometric pressure 12 to 40 mm Hg (500–2500 feet) and result in a significant temporary increase in relative altitude.

■ ACCLIMATIZATION

The term *acclimatization* refers to the series of integrated adaptations that take place at high altitudes, which tend to restore the oxygen pressures within the tissues toward normal sea level values despite the lowered Po_2 of the atmosphere. These processes occur gradually and involve multiple respiratory, cardiovascular, and hematologic adjustments. Gradual ascents made by mountaineers over several weeks have allowed the successful summiting of many of the world's highest peaks, including Mt. Everest (29,029 feet), without supplemental oxygen and without the serious manifestations of altitude illness. If rapid exposure to extreme altitudes is attempted, acclimatization is impossible, and the individual loses consciousness and may die in a matter of minutes.

Acclimatization begins at the altitude that causes the oxygen saturation of arterial blood to fall below sea level values. The altitude at which this occurs depends on the rate of ascent, the duration of exposure, and individual physiology. People with preexisting conditions that reduce oxygen saturation or content will have a decreased altitude tolerance. Of particular importance are both acute and chronic cardiac and respiratory illnesses. Most healthy, unacclimatized visitors to high altitude will not desaturate significantly (to less than 90%) until they reach elevations higher than 8000 feet.[1]

The risk of high-altitude illness also depends on an individual's inherent ability to acclimatize. Some people acclimatize easily without any clinical symptoms developing, whereas others may transiently develop AMS during acclimatization. This variability may involve the genetic mediation of oxygen transport capabilities between individuals. Previous, successful acclimatization may be predictive of future responses in similar conditions.

The most important physiologic change that occurs during acclimatization is an increase in minute ventilation, causing a decrease in the partial pressure of carbon dioxide ($Paco_2$). The alveolar gas equation states that as the $Paco_2$ decreases, a corresponding increase in Pao_2 occurs, thereby increasing arterial oxygenation (Box 142-1). Thus, the level of ventilation determines alveolar oxygen for a given inspired oxygen tension.

When a person arrives at high altitude, the peripheral chemosensors in the carotid bodies respond to a decrease in Pao_2 and signal the respiratory control center in the medulla to increase ventilation. This increase in ventilation is known as the hypoxic ventilatory response (HVR), which can be inhibited or stimulated by numerous factors, including ethanol, sleep medications, caffeine, cocoa, prochlorperazine, and progesterone. The magnitude of the HVR varies among individuals and may be genetically predetermined.[17]

As ventilation increases, a respiratory alkalosis occurs that acts as a negative feedback system on the central respiratory center, limiting any further increase in ventilation. Within 24 to 48 hours of ascent, the kidneys excrete bicarbonate in an effort to compensate for the alkalosis. As the pH normalizes, ventilation rises slowly, reaching a maximum after 6 to 8 days. This process is facilitated by acetazolamide. The ability to achieve an adequate HVR varies and is related to the ability to acclimatize; thus, a poor HVR makes an individual more likely to fail acclimatization and develop AMS.[18] For the majority of people with intermediate hypoxic ventilatory responses, ventilatory drive probably has no predictive value for AMS development.[18] A low HVR and relative hypoventilation are implicated in the pathogenesis of both AMS and HAPE.[19]

The release of catecholamines on ascent stimulates the circulatory system to increase cardiac output. This is manifested by an elevation in heart rate, blood pressure, cardiac output, and venous tone.[20] Except at extreme altitudes, acclimatization results in the resting heart rate gradually returning to near sea level values. Resting relative tachycardia is evidence of poor acclimatization. As the altitude increases, a decrease in maximal heart rate capacity occurs and, at the limits of acclimatization, maximal and resting heart rates converge.

Another component of the acclimatization process is the hematopoietic response to high altitude, consisting of an

BOX 142-1 ALVEOLAR GAS EQUATION

$$Pao_2 = pio_2 - (Paco_2 / R)$$

Pao_2 = Partial pressure of oxygen in alveolus
Pio_2 = Partial pressure of oxygen in inspired air
$Paco_2$ = Partial pressure of oxygen in carbon dioxide in alveolus
R = Respiratory quotient

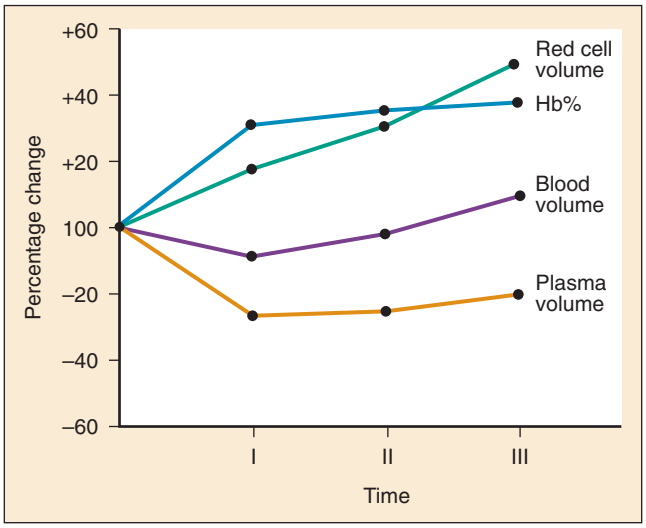


Figure 142-2. Acclimatization: Hematopoietic and volume adaptation. Point I, altitude 4000 to 5800 m, 18 weeks after arrival; point II, altitude 5800 m, 21 to 24 weeks after arrival; point III, altitude above 5800 m, 30 to 38 weeks after arrival. (Redrawn from Pugh LG: High altitudes. In Edholm AG, Bacharach AL [eds]: The Physiology of Human Survival. London, Academic Press, 1965, p 138.)

increase in both hemoglobin and number of red blood cells. An early increase of up to 15% occurs in mean corpuscular hemoglobin concentration after rapid ascent to high altitude. This is primarily a result of a fluid shift into the extravascular space. Long-term acclimatization leads to an increase in plasma volume and total blood volume. Erythropoietin is secreted in response to hypoxemia, which in turn stimulates the production of red blood cells, leading to new circulatory red blood cells in 4 or 5 days.[21] During the next 2 months, red blood cell mass increases in proportion to the degree of hypoxemia (Fig. 142-2).[22]

Hypoxemia also results in an increase in 2,3-diphosphoglycerate, resulting in a rightward shift of the oxyhemoglobin dissociation curve, favoring a release of oxygen from the blood to the tissues. This is counteracted by the leftward shift of the oxyhemoglobin dissociation curve caused by the respiratory alkalosis from hyperventilation. The result is an increase in oxygen-hemoglobin binding in the lung, which raises Sao_2.[23] This effect is thought to be helpful because individuals with mutant hemoglobin with a high oxygen-hemoglobin affinity acclimatize more efficiently at moderate altitudes than their normal counterparts.[24]

PATHOPHYSIOLOGY

The clinical syndromes of high-altitude illness are not discrete entities but represent a spectrum of intertwined pathophysiologic mechanisms. AMS and HACE represent differing manifestations of altitude illness on the same continuum, whereas HAPE appears to have an independent pathophysiology.

The symptoms of AMS develop several hours after arrival at high altitude, whereas the development of HAPE and HACE generally requires several days of altitude exposure. Since hypobaric hypoxemia occurs within minutes of arrival, it cannot be the direct cause of high-altitude illness. Instead, it appears to be the initiating factor for a complex pathologic process that leads to the development of the various clinical syndromes. The proposed mechanisms for the development of AMS, HAPE, and HACE are represented schematically in Figure 142-3.

A poor HVR resulting in relative hypoventilation may result from either the individual's genetic predisposition or extrinsic factors, such as medications, that decrease the ventilatory drive. Whenever the HVR is decreased, the protective effects of hyperventilation are lost and the hypoxemia of high-altitude exposure is exacerbated.

The periodic breathing associated with high-altitude exposure may result in periods of apnea during sleep, causing severe arterial oxygen desaturation, which further exacerbates hypoxemia.[25] Significant hypoxemia initiates multiple systemic responses that involve the circulatory, pulmonary, endocrine, and central nervous systems.

Hypoxemia alters fluid homeostasis, resulting in a generalized fluid retention followed by the shift of fluid into the intracellular spaces. This is manifested by peripheral edema, decreased urinary output, and increased body weight in patients with AMS. Several different mechanisms may account for these fluid shifts, including arginine vasopressin (AVP) levels and sympathetic stimulation that may be centrally mediated.[26,27] AVP levels are elevated in some cases of AMS and HAPE[28] and decreased in others.[29] Aldosterone, plasma renin, and atrial natriuretic levels are higher in people with AMS.[29-31]

The hypoxemia that results from high-altitude exposure causes pulmonary artery hypertension and elevated capillary pressures that play the cardinal role in the development of HAPE. Exercise and cold stress at altitude may increase hypoxemia and exacerbate pulmonary hypertension.[32,33] Pulmonary blood volumes and pulmonary hypertension are increased by sympathetic nervous system stimulation and catecholamine release.[34,35] In HAPE-susceptible individuals, pulmonary hypertension becomes severe and an uneven distribution of pulmonary vasoconstriction results in overperfusion, increased capillary pressures, distention, and leakage in the remaining vessels.[36-39] This explains the patchy nature of the infiltrate seen on a chest radiograph with HAPE (Fig. 142-4). The mechanism for the uneven vasoconstriction in HAPE may be due to decreased nitric oxide bioavailability at the pulmonary tissue level.[40-42] Overperfusion of a restricted vascular bed as the pathogenesis of HAPE is supported by the observation that people born with congenital unilateral absence of a pulmonary artery are very susceptible to HAPE.[43] These individuals deliver their entire cardiac output to one lung, predisposing them to overperfusion injury.

The importance of the excessive rise in pulmonary artery pressure in HAPE is emphasized since lowering the pressure during ascent prevents HAPE.[44] This implicates increased vascular pressure rather than inflammation as the primary cause of the vascular leak. The resultant mechanical shear forces lead to endothelial damage and changes in membrane permeability.[42] Inflammatory mediators appear to be a secondary response to the mechanical injury caused by overperfusion.[38,45] Once the vascular leak occurs and alveolar fluid accumulates, a defect in transepithelial sodium transport impairs the clearance of alveolar fluid and contributes to HAPE development.[46-48] Alveolar fluid clearance is up-regulated by beta-adrenergic agonists and inhaled beta-agonists that successfully prevent and treat HAPE.[48,49]

Preexisting inflammation may also be a risk factor for HAPE. A preexisting respiratory infection during ascent to high altitude increases susceptibility to HAPE, particularly in children.[50] Inflammation may "sensitize" the pulmonary endothelium to mechanical injury and increase susceptibility to HAPE during ascent.

The clinical manifestations of AMS/HACE are the result of central nervous system dysfunction. The speculative mechanistic theories involve altered cerebral hemodynamics and

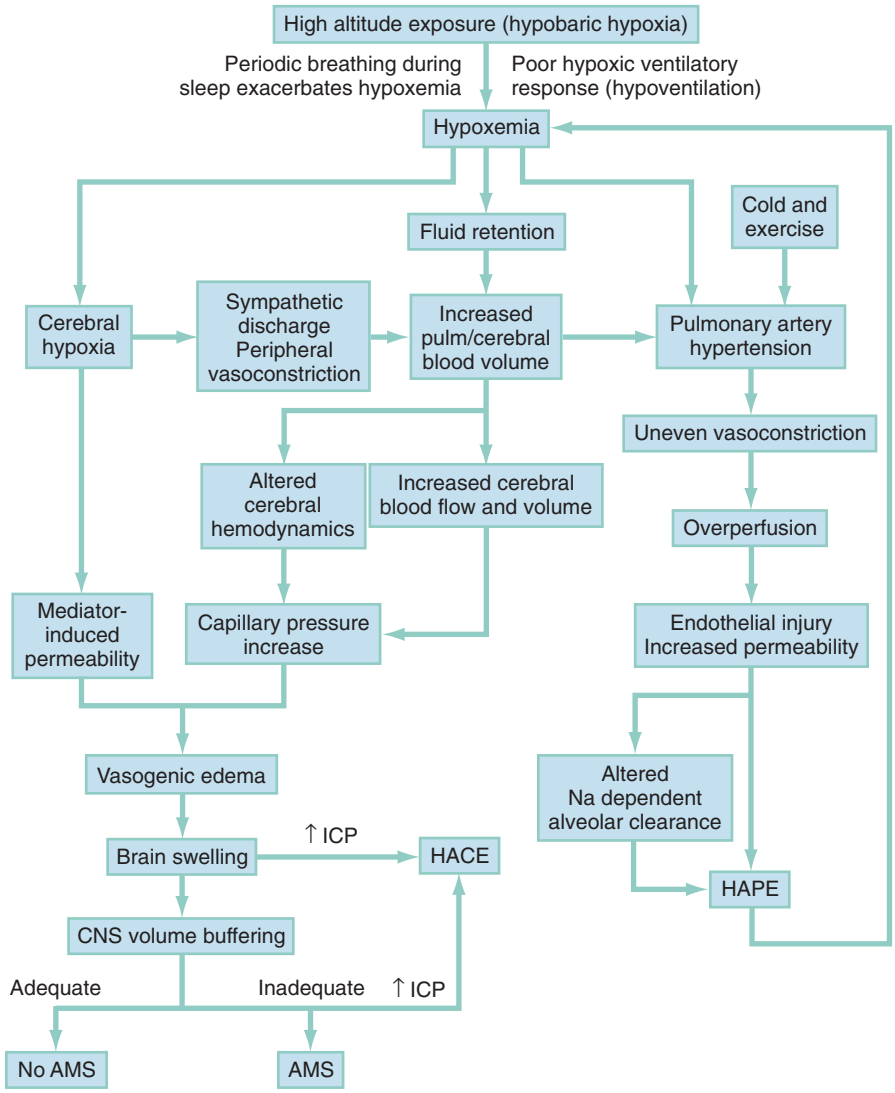


Figure 142-3. Proposed mechanisms for the development of acute mountain sickness (AMS), high-altitude pulmonary edema (HAPE), and high-altitude cerebral edema (HACE).
CNS, central nervous system; ICP, intracranial pressure.

biochemical inflammatory mediators.[51,52] The vasodilatory response to hypoxemia causes an increase of cerebral blood flow and cerebral blood volume.[53,54] Hypoxemia can also result in impaired vascular autoregulation that causes increased pressure transmission to the brain's capillary beds, resulting in vasogenic edema.[27,55,56] The addition of systemic hypertension with strenuous exercise at high altitude may overwhelm the brain vasculature, resulting in transcapillary leakage. In susceptible individuals, the vasodilatation, vasogenic edema, or associated changes in intracranial pressure may result in structural changes that cause pain-sensitive brain regions to be stretched or compressed, causing the sensation of headache in patients with mild AMS.[57-59]

Additional circumstances, however, may be necessary for the development of vasogenic edema. Biochemical inflammatory mediators may contribute to edema formation. Vascular endothelial growth factor, the inducible form of nitric oxide synthase, reactive cytokines, and free radical formation may mediate brain endothelial permeability. The roles that these play in altitude illness pathophysiology are unclear.[60-63] Magnetic resonance imaging (MRI) in patients with HACE reveals white matter changes consistent with vasogenic edema[64] (see Fig. 142-6). Vasogenic edema is also implicated in the origin of AMS. This breakdown of the blood-brain barrier is most likely the result of both mechanical factors and biochemical mediation of permeability.[53,65]

MRI data reveal that cytotoxic edema is also present in severe AMS.[66,67] Cytotoxic edema results from hypoxic cell damage most often associated with ischemic hypoxic insults. Failure of the adenosine triphosphate-dependent sodium pump allows sodium to accumulate within the cells, increasing intracellular water to maintain the osmotic equilibrium. Cytotoxic intracellular water accumulation may not be the primary mechanism for the development of HACE but, rather, the result of the increased cell ischemia initially caused by vasogenic edema.[64]

Hypobaria appears to play a role in the development of AMS. Sea-level experiments that expose subjects to hypoxia alone do not result in AMS; however, when hypoxia is combined with hypobaria, AMS does occur.[68,69] Although microbubble formation and fluid retention may be a mechanism, the exact role of hypobaria regarding altitude pathophysiology is unclear.[69]

These responses to hypoxia and altitude exposure occur in both susceptible individuals and those who remain free of AMS. Thus, there must be an overall permissive factor in a subject at risk for AMS that fails to compensate for brain swelling. Ross proposes and Hackett supports the "tight fit" hypothesis to explain AMS development and its inherent individual susceptibility.[53,70] The adequacy of the space to buffer changes in brain and cerebrospinal fluid (CSF) volume plays a key role in determining which individuals develop symptoms of

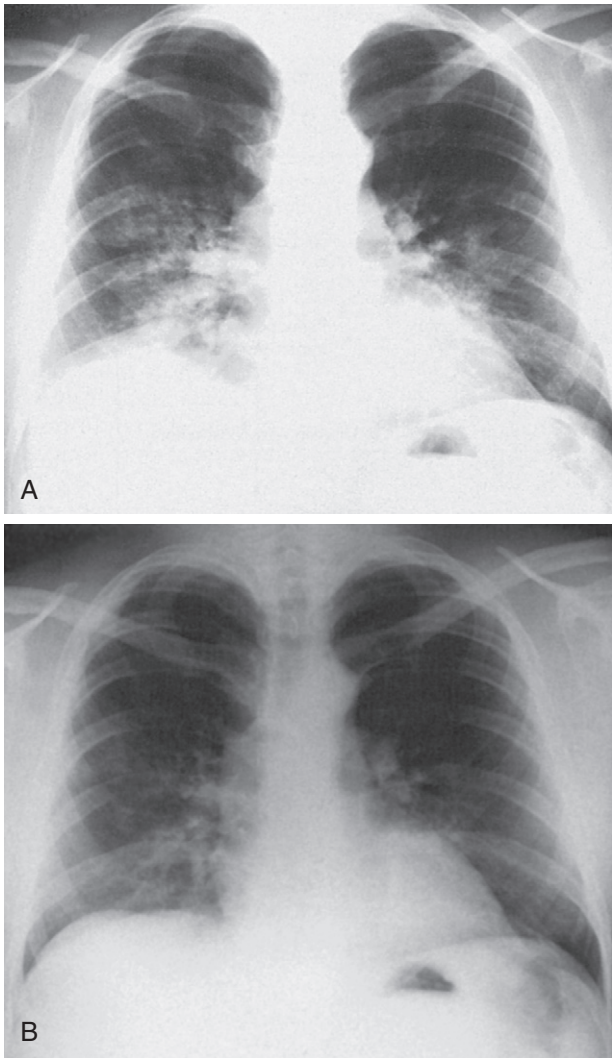


Figure 142-4. Chest radiograph of a patient with high-altitude pulmonary edema. **A,** Before treatment. **B,** After treatment. (Courtesy of Richard Nicholas, MD.)

altitude illness. As brain volume increases due to increased cerebral blood volume, the volume-buffering capacity of the central nervous system may prevent an immediate rise of intracranial pressure. As brain volume increases, the intracranial CSF is displaced via the foramen magnum into the space available in the spinal canal. Increased absorption of CSF by the arachnoid villi and decreased CSF production also occur. Individuals with less intracranial and intraspinal CSF buffering capacity have less compliance and become more symptomatic (i.e., develop AMS) from mild brain swelling. This tight fit hypothesis is supported by MRI and computed tomography studies.[53,70,71]

ACUTE MOUNTAIN SICKNESS

Clinical Presentation

The symptoms of mild AMS are very similar to those of a viral syndrome, an ethanol "hangover," or simple physical exhaustion. The vague nature of this presentation results in many misdiagnoses. In the setting of recent high-altitude exposure, these symptoms warrant a presumptive diagnosis of AMS until proven otherwise.

BOX 142-2 ACUTE MOUNTAIN SICKNESS

Incidence: 12 to 67%, varies with rate of ascent; rare below 8000 feet, most common with rapid ascent to altitudes greater than 10,000 feet
Symptoms and signs: Headache, anorexia, nausea, fatigue, dizziness, difficulty sleeping
Treatment: Mild cases are usually self-limited and do not require treatment; discontinue ascent, rest; for moderate case, administer acetazolamide, aspirin, or acetaminophen for headache; prochlorperazine for nausea; supplemental oxygen if available; descend if persistent or severe; add dexamethasone in severe cases
Prevention: Gradual ascent to allow acclimatization; high-carbohydrate diet, avoidance of ethanol or smoking; acetazolamide if ascent is rapid or known history of recurrent acute mountain sickness

To diagnose AMS, a patient must be in the setting of a recent gain in altitude, be at the new altitude for at least several hours, and report a headache *plus* at least one of the following symptoms: gastrointestinal upset (anorexia, nausea, or vomiting), general weakness or fatigue, dizziness or lightheadedness, or difficulty sleeping (Box 142-2).[72] The headache may vary from mild to severe, is generally bitemporal and throbbing in nature, and is worse during the night and on awakening or suddenly becoming upright. Anorexia and nausea, with or without vomiting, are common, and the other symptoms described can range in severity from mild to incapacitating. The disturbance of sleep caused by periodic breathing is common in all visitors to high altitudes but is exacerbated in the setting of AMS. The symptoms of AMS develop within a few hours after arrival at high altitude and generally reach maximum severity between 24 and 48 hours, followed by a gradual resolution. Most individuals become symptom free by the third or fourth day. Those who do not resolve their symptoms should descend because they may develop more serious manifestations of altitude illness, especially if they continue to ascend.

Among infants and very young children, AMS is manifested by increased fussiness, decreased playfulness, decreased appetite, and sleep disturbance.[8] In most cases of AMS in very young children, all of these symptoms are present. In children, many of the symptoms manifested by AMS can also result from the disruption of normal routine. A change in environment, sleeping accommodation, or eating habits can result in a fussy, unhappy child. In addition, the occurrence of an acute illness can also mimic AMS in young children. If occult bacteremia or another serious illness is suspected in a young child, descent to lower altitude is recommended to eliminate the confounding variable of altitude illness.

There are no diagnostic physical findings in cases of mild AMS. Although dyspnea on exertion is universal at high altitudes, dyspnea at rest is an early indication of HAPE, and a careful examination for pulmonary edema is indicated. Similarly, any evidence of cerebellar dysfunction, such as mild ataxia or alteration in mentation, mandates descent because of early evidence of HACE.

Management

The proper management of AMS must include adherence to the principle that after the symptoms of altitude illness occur, further ascent to a higher sleeping altitude is contraindicated. Halting ascent or activity to allow further acclimatization may

reverse the symptoms; however, continuing the ascent exacerbates the underlying pathologic processes and may lead to disastrous results. The presence of neurologic abnormalities (e.g., ataxia or altered mentation) or evidence of severe pulmonary edema mandates immediate descent because these signs indicate a progression of AMS to the more dangerous forms of altitude illness.

Mild AMS may be treated by stopping further ascent and waiting for acclimatization to occur. This may take 1 to 4 days. AMS that becomes worse or does not respond to maintenance of altitude, rest, and pharmacologic intervention mandates descent. A descent of 1500 to 3000 feet effectively reverses high-altitude illness in most cases. Descent should be continued until improvement is seen, and efforts to minimize exertion should be instituted during the descent.

Supplemental oxygen administration relieves AMS symptoms, including when given in small amounts (1-2 L/min) during sleep. In the wilderness, oxygen tanks are heavy and are usually unavailable in adequate amounts; therefore, oxygen therapy is usually reserved for the more serious manifestations of high-altitude illness. In resort settings, oxygen may be easily available for use in the hotel or condominium. Hyperbaric therapy that simulates descent is also effective.

Treatment of headache, nausea, and insomnia can be beneficial during the course of mild AMS. Aspirin, ibuprofen, and acetaminophen are useful for the treatment of headache; however, narcotic analgesics should be avoided due to depression of the HVR and the respiratory drive during sleep. For nausea and vomiting, prochlorperazine, unlike other antiemetics, stimulates the HVR.

Periodic breathing causes insomnia, which is best treated with the respiratory stimulant acetazolamide.[73] Doses of acetazolamide as low as 62.5 to 125 mg at bedtime may prevent periodic breathing and eradicate insomnia. Benzodiazepines and other sedative-hypnotics should be avoided because of their tendency to decrease ventilation during sleep. Some climbers experience unusual reactions to diazepam at high altitudes, including agitation, hallucinations, and disorientation. These reactions can occur in individuals who have previously used diazepam at lower altitudes without any difficulties.[74] Some studies suggest that low doses of benzodiazepines alone or in combination with acetazolamide are safe at high altitude.[75-78] Nonbenzodiazepine sleep agents (zolipedem and zaleplon) do not depress ventilation and may prove useful in AMS-related insomnia.[79]

Acetazolamide accelerates acclimatization and, if given early in the development of AMS, rapidly resolves symptoms. A dose of 250 mg of acetazolamide at the onset of symptoms and repeated twice daily is effective therapy for AMS.[80,81] The treatment of AMS in children has not been formally studied, but anecdotal experience supports the use of acetazolamide in children.[82] The dose for children is 2.5 mg/kg/dose given twice daily to a maximum of 250 mg.

Acetazolamide is a carbonic anhydrase inhibitor that induces a renal bicarbonate diuresis, causing a metabolic acidosis that increases ventilation and arterial oxygenation. This respiratory stimulation improves sleep when the hypoxemia caused by periodic breathing is eradicated by acetazolamide. The diuretic effects attenuate fluid retention common in patients with AMS. This agent also lowers CSF volume and pressure, which may play an additional role in its therapeutic and prophylactic use. Noncarbonic anhydrase inhibitory effects of acetazolamide include chemoreceptor effects on ventilatory drive, alterations of cerebral blood flow, relaxation of smooth muscles, and up-regulation of fluid resorption in the lungs.[83,84]

The most common adverse reactions to acetazolamide include paresthesias and polyuria. Less common reactions include nausea, drowsiness, tinnitus, and transient myopia. Carbonic anhydrase inhibition at the tongue causes dysgeusia, altering the flavor of carbonated beverages, including beer. Acetazolamide is a non-antibiotic sulfa compound that is usually well tolerated by individuals with an allergy to sulfa antibiotics. Approximately 10% of individuals allergic to sulfa antibiotics will experience an allergic reaction.[85] When feasible, administer a trial dose of acetazolamide in "sulfa allergic" patients prior to ascent. Acetazolamide should be avoided in breast-feeding mothers and pregnant women.

Dexamethasone is an effective alternative treatment for AMS. An initial dose of 8 mg is followed by 4 mg every 6 hours.[86] No significant adverse reactions are reported; however, symptoms can recur when the treatment is withdrawn. Although dexamethasone can resolve the symptoms of AMS, it does not play a role in acclimatization. Concurrent use with acetazolamide is advocated by some to promote acclimatization.[87] The mechanism of action is unclear. It is known to have anti-inflammatory properties, possibly reduce cerebral blood flow,[88] and block the action of vascular endothelial growth factor.[60] Reduction of AMS symptoms while using dexamethasone may be the result of these or its euphoric effects. We believe that dexamethasone should generally be reserved for use in the setting of acetazolamide intolerance or in more advanced cases of AMS, especially to help facilitate descent.

Prevention

Most of the symptoms of mild AMS are benign and well tolerated. These symptoms, however, can be unpleasant and debilitating to the point that travel, business, or vacation plans must be interrupted. Up to 50% of individuals with AMS report a decrease in activity.[5]

Slow ascent, allowing adequate time for acclimatization, is the best method of prevention; however, often the time constraints of most vacationers make slow ascent unrealistic. The major concern lies in the sleeping altitude during any individual ascent. Ideally, the first night should not be spent at an altitude higher than 9000 feet, with a subsequent increase of not more than 2000 feet each night. One extra night of acclimatization should be added for every 3000 to 4000 feet of altitude gain above 10,000 feet. If the journey begins at an altitude above 10,000 feet, then three nights should be spent acclimatizing before any further increase in sleeping altitude. Excursions during the day to higher altitudes with a return to a lower sleeping altitude aid in acclimatization.

Mild to moderate exercise is thought to aid in acclimatization; however, overexertion can contribute to the development of AMS.[32] Maintenance of adequate hydration is also recommended. Normal urine output and relatively clear (unconcentrated) urine reflect adequate hydration. Recommendations for hyperhydration are frequently given in the lay literature, yet no evidence supports this advice.[89,90] Drinking excessive amounts of free water may lead to hyponatremia and possibly complicate altitude illness.

In some cases, such as arrival at a high-altitude airport or the immediate dispatch of rescue personnel to high altitude, a slow ascent is impossible. Mountain climbers commonly ascend at rates that are higher than recommended, and some individuals continue to suffer AMS symptoms despite gradual ascent. Individuals who have a known susceptibility to the development of AMS and those for whom slow ascent is impractical may consider prophylactic pharmacologic intervention.

Numerous studies demonstrate the effectiveness of acetazolamide in preventing AMS in adults.[3,4,91] Lower dosages provide similar prophylaxis with fewer adverse reactions than

higher dosages. The ideal dose is debated. Many studies demonstrate that 250 mg twice daily starting 24 hours before ascent and continuing for the first 2 days at high altitude is effective. To avoid side effects, a lower dose for prevention is suggested. A dose of 125 mg given twice daily was effective in one study but not in another.[92,93] Although unstudied, the recommended dosage of acetazolamide for AMS prophylaxis for children is 2.5 mg/kg/dose up to 125 mg total given twice daily, and this weight-based approach may reduce side effects in smaller adults.

Dexamethasone also prevents AMS.[88] The lowest effective dosage is 4 mg every 6 hours.[94] Some patients experience the rapid onset of AMS after dexamethasone is discontinued. Dexamethasone does not facilitate acclimatization but, rather, reduces nausea and enhances mood. In most cases, dexamethasone use should be reserved for treatment of AMS rather than prophylaxis. Military or rescue personnel rapidly ascending to high altitude and individuals with acetazolamide intolerance are candidates for prophylaxis with dexamethasone. The combination of acetazolamide and dexamethasone may be more effective than either drug alone.[87]

Because of its antioxidant properties, *Ginkgo biloba* is proposed for preventive therapy of AMS. Although the results of several small studies were encouraging, a well-designed study showed no evidence that gingko is effective.[95]

Oxygen is an effective prophylactic modality for rescue personnel. Adequate supplies must be available to ensure the safety of all team members for the entire duration of the rescue. Air drops of oxygen can be lifesaving when weather or terrain prevents the immediate arrival of rescue personnel.

HIGH-ALTITUDE PULMONARY EDEMA

High-altitude pulmonary edema is the most common fatal manifestation of severe high-altitude illness (Box 142-3). Although HAPE is uncommon below 10,000 feet, it can occur, and even be fatal, at altitudes as low as 8000 feet. Episodes occurring between 8000 and 10,000 feet are usually related to heavy exercise, but at higher altitudes pulmonary edema can also occur at rest or with light activity.[36]

Some individuals are susceptible and experience HAPE with each ascent to altitude. Rarely, the congenital absence of a pulmonary artery exaggerates the pulmonary vascular response to hypoxia, resulting in recurrent HAPE at elevations lower than expected.[43] Many patients, however, have a single episode of HAPE and subsequently are able to return to high altitude without a recurrence. Conversely, those with previously uneventful high-altitude exposures may have HAPE develop in a future ascent.

Individuals who have been residents at high-altitude locations for extended periods may have pulmonary edema develop on re-ascent from a trip to low altitude. This phenomenon has been termed *reentry HAPE*. The incidence of reentry HAPE is not established; however, there seems to be an increased risk for children and young adults and possibly a greater incidence compared with HAPE experienced by low-altitude residents during their initial ascent.[96,97] This apparent increased susceptibility among children to develop HAPE is probably the result of developmental changes in pulmonary vascular reactivity and tone.

BOX 142-3 HIGH-ALTITUDE PULMONARY EDEMA

Incidence: 0.01 to 15%, varies with rate of ascent; rare below 8000 feet and more common above 14,500 feet; usually occurs 2–4 days after arrival at high altitude

Symptoms and signs: Dyspnea at rest, cough, fatigue, headache, anorexia, cyanosis, rales, tachypnea, tachycardia

Treatment: Patients with mild cases may recover with bed rest; moderate cases can be treated with bed rest and supplemental oxygen if clinical monitoring is available; severe cases require oxygen and descent; use hyperbaric therapy if available; if oxygen or descent are unavailable then nifedipine 10 mg every 4–6 hours or 10 mg followed by 30 mg slow release every 12 hours; consider tadalafil 10 mg every 12 hours (unstudied); inhaled beta-adrenergic agonist

Prevention: Gradual ascent and recognition of early AMS symptoms so that ascent is stopped before HAPE develops; with previous HAPE history, use nifedipine 20 mg slow release every 8 hours during ascent, then continue for 3 days (monitor for hypotension); or tadalafil 10 mg every 8 hours starting with ascent; or dexamethasone 8 mg every 12 hours starting 2 days prior to ascent; inhaled beta-adrenergic agonist; acetazolamide may be effective

AMS, acute mountain sickness; HAPE, high-altitude pulmonary edema.

Clinical Presentation

The initial symptoms of HAPE usually begin insidiously two to four days after arrival at high altitude. Most cases occur during the second night, but HAPE may develop rapidly, with early symptoms apparent after just a few hours at high altitude. Marked dyspnea on exertion, fatigue with minimal to moderate effort, prolonged recovery time, and dry cough are early manifestations of the disease. The symptoms of AMS usually occur concurrently with the development of HAPE.

As the HAPE patient deteriorates, usually through the night, the dyspnea intensifies with effort and is unrelieved by rest. Dyspnea at rest must be recognized as a red flag that warns of the development of a serious pulmonary problem. The cough becomes productive of copious amounts of clear, watery sputum, and in severe cases hemoptysis may be seen. As the condition intensifies, cerebral edema or simply severe hypoxemia causes central nervous system dysfunction, such as ataxia and altered mentation. Coma may follow and precede death in a few hours if oxygen therapy or descent is not instituted.

The physical examination reveals a few rales in patients with mild HAPE, usually found in the region of the right middle lobe, progressing to unilateral or bilateral rales and then to diffuse bilateral rales and also rhonchi and gurgles audible without the stethoscope. Cyanosis of the nail beds alone may progress to severe central cyanosis. Tachypnea and tachycardia become more pronounced as severity increases. Elevated temperatures are common, and a concurrent respiratory tract infection is occasionally seen, especially in children.[50]

Ancillary Tests

Chest radiographs can help elucidate the nature of the illness. The infiltrates seen in HAPE victims are alveolar and patchy in distribution, with areas of clearing between the patches. Unilateral infiltrates may be present in mild cases; however, bilateral infiltrates are seen in more advanced cases, with involvement of the right midlung field most common (see Fig. 142-4). Pleural effusion is rare but may be present in severe cases. The extent of the edema present on the chest radiograph roughly parallels the clinical severity. Of note, the

radiographic findings of cardiomegaly, bat-wing distribution of infiltrates, and Kerley B lines, which are typical of cardiogenic pulmonary edema, are absent in cases of HAPE.

Radiographic evidence for HAPE clears rapidly after initiation of treatment; some mild cases may clear in 4 to 6 hours, and most clear by 24 hours. Radiographs of patients with severe HAPE may reveal infiltrates that persist for as long as 2 weeks, even though the clinical symptoms have resolved.

An electrocardiogram reveals tachycardia and evidence of right heart strain, including right axis deviation, P wave abnormalities, tall R waves in the precordial leads, and S waves in the lateral leads.[36] Hemodynamic studies reveal increased pulmonary vascular resistance, elevated pulmonary artery pressures, and normal pulmonary wedge pressures. Echocardiography studies demonstrate high estimated pulmonary artery pressures, pulmonary vascular resistance, and normal left ventricular function.[35]

Differential Diagnosis

Pneumonia can be misdiagnosed in the setting of HAPE because the symptoms and signs of pneumonia are similar to those of HAPE. The incidence of pneumonia and the common organisms responsible for pneumonia at high altitude are unknown, but visitors to high altitudes may be predisposed to acquiring bacterial infections because of impaired T lymphocyte function.[98] Patients who present with symptoms compatible with pneumonia at high altitude should be treated for HAPE. If any doubt exists regarding the diagnosis of HAPE versus pneumonia, empiric antibiotic therapy should be initiated. Because of the mild immunosuppression coincident with high-altitude exposure, the treatment of any serious infectious illness at high altitude requires oxygen and descent in addition to local wound care and antibiotics.[98]

High-altitude bronchitis and pharyngitis are common problems among climbers. They may result from the increased ventilation of cold, dry air across the upper airway mucosa, causing mucosal inflammation. Copious sputum production is sometimes seen, and antibiotic therapy usually is not helpful. Coughing spasms may be severe and require codeine. Other therapeutic measures include hydration, lozenges, and steam inhalation.

Death from pulmonary embolism at high altitude is described.[99] Hypercoagulability results from altitude effects and hyperviscosity caused by elevation in hematocrit and dehydration. Venous stasis, caused by immobility when confined to a sleeping bag inside a tent, is also a predisposing factor for deep vein thrombosis. The symptoms and signs of pulmonary embolism can mimic those of HAPE; however, embolic disease tends to have a more rapid onset, and pleuritic chest pain is a more prominent feature.

Management

In remote settings, where oxygen and medical expertise may be unavailable, immediate descent is a lifesaving measure after diagnosing HAPE. Delaying descent while HAPE progresses or waiting for rescue personnel to initiate evacuation can prove fatal. Descents of 1500 to 3000 feet should be adequate for a rapid recovery. The recovered victim may be able to re-ascend in 2 or 3 days.

Warmth and rest are important in HAPE therapy to avoid cold- or exercise-induced pulmonary hypertension. Mild cases of HAPE can be treated without descent or oxygen with 1 or 2 days of bed rest. Oxygen administration increases the rate of improvement. Moderate cases can be treated without descent if bedrest and adequate supplies of supplemental oxygen are available. Any treatment plan that does not include descent mandates serial examinations by clinicians with experience in managing high-altitude illness.

On difficult terrain or in weather conditions that hamper efforts to descend, oxygen administration (or hyperbaric therapy) is a lifesaving measure. Rescue personnel should air drop oxygen supplies if immediate evacuation to lower altitudes will be delayed. High-flow rates of oxygen (6–8 L/min) by mask should be delivered initially to victims with severe HAPE until improvement is seen. Flow rates can then be lowered until recovery or descent is completed. Delivering oxygen with a continuous positive airway pressure mask is more efficacious than normal oxygen delivery.[100]

Hyperbaric therapy simulates descent without the administration of supplemental oxygen.[101] Several portable, lightweight (approximately 15 pounds), fabric hyperbaric chambers are available and pressurized manually (Fig. 142-5). These chambers generate 103 mm Hg (2 psi) above the ambient pressure. This simulates a descent of 4000 to 5000 feet at moderate altitudes, and at the summit of Mt. Everest it would simulate a descent of approximately 9000 feet. These devices can be lifesaving in patients with HAPE and HACE. Some nonambulatory patients are able to descend under their own power after a few hours in hyperbaric chambers.[102]

In treating HAPE, agents that lower pulmonary artery pressure, pulmonary blood volume, and pulmonary vascular resistance or enhance alveolar fluid clearance are useful but not as effective as oxygen and descent. Furosemide, 80 mg twice daily, is beneficial, and when combined with morphine for the initial dose, it results in even greater diuresis and clinical improvement. Some authors caution that deleterious dehydration may result from furosemide therapy and that the potential ventilatory depression caused by morphine can further increase the severity of the underlying hypoxemia of AMS.[36] Others argue that during the state of antidiuresis found with severe AMS, no documented deleterious effects from this treatment exist.[103]

Although furosemide may be useful, the advent of pulmonary vasodilators has displaced the use of furosemide for HAPE. Nifedipine, a pulmonary vasodilator, is especially useful when oxygen is unavailable or descent is impossible.[35,104] Nifedipine does not improve pulmonary hemodynamics as much as oxygen or descent, and it does not have an additive effect when administered with oxygen.[35] Treatment with 10 mg of nifedipine every 4 to 6 hours or 10 mg followed by 30 mg of a slow-release preparation administered once or twice daily is effective. A response to treatment with improvement

Figure 142-5. Gamow bag *(left)* and Certec bag *(right)*: lightweight, portable hyperbaric chambers. Note the attached foot-operated pressure pump. (Courtesy of Thomas Dietz, MD.)

in symptoms is usually noted within 15 to 30 minutes after the first sublingual dose.[104] Patients should be monitored for the development of hypotension during nifedipine administration.

Phosphodiesterase-5 inhibitors are less likely to produce hypotension, and although known to be useful for HAPE prevention, they have yet to be studied for HAPE therapy. Alveolar fluid clearance is upregulated by beta-adrenergic agonists, and inhaled beta-agonists have been used successfully for both prevention and therapy of HAPE.[48,49]

Disposition

Mild to moderate cases of HAPE can be treated with oxygen, rest, and careful monitoring. Resort doctors at moderate altitudes observe HAPE patients on oxygen therapy to ensure adequate oxygenation. These patients are then discharged to their hotel with supplemental oxygen and monitored for improvement or deterioration. In severe HAPE or milder cases that do not improve with therapy, descent is warranted. Rapid recovery is usually seen after descent to lower altitudes, and observation of the patient in the emergency department to ensure adequate room air oxygenation is generally adequate. Occasionally, admission to the hospital is indicated to maintain the Sao_2 greater than 90%. Hypocapnia, alkalosis, and radiographic evidence of HAPE may persist for several days. After oxygen saturation remains greater than 90% on room air and clinical improvement is apparent, the patient can be discharged. If the patient requires air travel to return home (cabin pressures equal approximately 8000 feet), additional recovery time before travel or arrangement for supplemental oxygen administration is advised. Detection of a heart murmur in a patient with HAPE should lead to an evaluation searching for cardiac structural anomalies that may increase pulmonary vascular resistance. An evaluation for underlying congenital heart disease is warranted after an episode of HAPE in a young child.

Prevention

As with all forms of serious altitude illness, a gradual ascent that allows time to acclimatize and immediate cessation of further ascent at the onset of symptoms are the most effective means of prevention. Individuals with a prior history of HAPE should also avoid extreme exertion during the first 2 days at altitude. With a prior history of HAPE, prophylactic therapy should be considered. Clinical experience suggests that acetazolamide prevents HAPE, and animal studies demonstrate its utility in reduction of hypoxic pulmonary vasoconstriction.[105-107] The nonspecific pulmonary vasodilator nifedipine, 20 mg (slow release) three times daily before ascent and continued at altitude for 3 days, is effective in preventing a recurrence of HAPE.[108] Phosphodiesterase-5 inhibitors are selective pulmonary vasodilators that increase cyclic guanosine monophosphate availability. Sildenafil (40 mg every 8 hours) and tadalafil (10 mg every 12 hours) are both effective in preventing HAPE.[44,109-111] The phospodiesterase-5 inhibitors have the added benefit that they are less likely to induce systemic hypotension than calcium channel blockers. Dexamethasone (8 mg every 12 hours) started 2 days prior to ascent also prevents HAPE. The mechanism for dexamethasone prevention is also due to pulmonary artery pressure reduction.[44]

HIGH-ALTITUDE CEREBRAL EDEMA

High-altitude cerebral edema is the least common but most severe form of high-altitude illness. Death from HACE at as low as 8200 feet is reported, although most cases occur above 12,000 feet. Mild AMS can progress to severe HACE with coma in as few as 12 hours. Although the usual time course is 1 to 3 days for the development of severe symptoms, it may occur in 5 to 9 days (Box 142-4).[112]

BOX 142-4 HIGH-ALTITUDE CEREBRAL EDEMA

Incidence: Lower than 1 or 2%, uncommon as a pure entity; usually associated with the presence of severe AMS and HAPE
Symptoms and signs: Ataxia, severe headache, nausea and vomiting, altered mentation, seizures, coma
Treatment: Immediate evacuation to a lower altitude; oxygen, bed rest, dexamethasone, and hyperbaric therapy while awaiting descent

AMS, acute mountain sickness; HAPE, high-altitude pulmonary edema.

Clinical Presentation

High-altitude cerebral edema is characterized by evidence of global cerebral dysfunction. The symptoms of severe AMS (headache, fatigue, and vomiting), as well as those of HAPE (cough and dyspnea), are usually present. HACE-specific signs include ataxia, generalized seizures, slurred speech, rarely focal neurologic deficits, and altered mentation. The latter can range from mild emotional lability or confusion to hallucinations and decreased levels of consciousness that may proceed to coma and death.[112] MRI of patients with HACE reveals white matter changes consistent with vasogenic edema (Fig. 142-6).[64]

Altered consciousness and cerebellar ataxia are the most sensitive signs for early recognition of HACE.[113] The early appearance of ataxia reflects the particular sensitivity of the cerebellum to hypoxia. Ataxia alone is an indication for immediate descent. Retinal hemorrhages are common but often occur as an isolated finding. Papilledema and, occasionally, cranial nerve palsy also occur in the setting of increased intra-

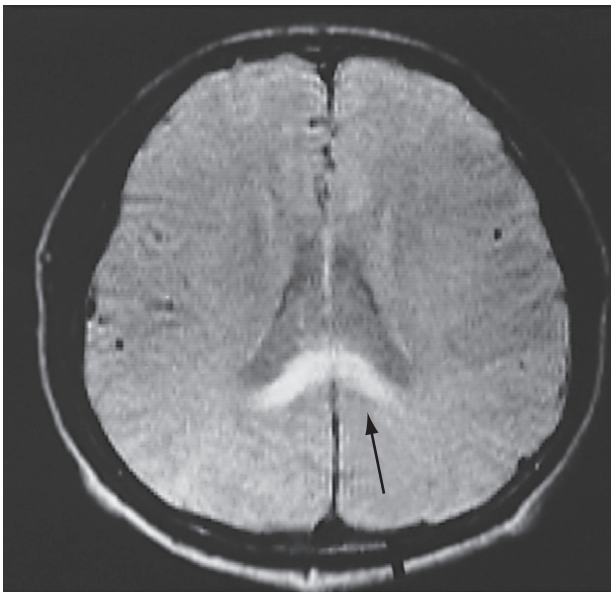


Figure 142-6. Axial proton-weighted magnetic resonance imaging scan of a mountain climber with high-altitude cerebral edema. *Arrow* demonstrates the markedly increased signal (edema) in the splenium of the corpus callosum. (Courtesy of Peter Hackett, MD.)

cranial pressure. Differentiating between HACE and stroke may be difficult. Although rare, the occurrence of cerebral thrombosis and transient ischemic attacks, in the absence of high-altitude illness, is documented at high altitude.[114,115] The absence of any other evidence for high-altitude illness, or signs that persist despite adequate treatment of high-altitude illness, suggests the presence of a vascular lesion.

Management

Early recognition and initiation of descent are the keys to successful therapy for HACE. High-flow oxygen should be administered, if available. Steroid therapy is recommended and may result in recovery from HACE without neurologic deficits. The initial dose of dexamethasone is 8 mg parenterally, or orally in mild cases, followed by 4 mg every 6 hours.

Patients with severely altered levels of consciousness require tracheal intubation and hyperventilation to control elevated intracranial pressures. Diuretics (e.g., furosemide) and hypertonic solutions (e.g., mannitol) decrease intracranial pressure. Many patients with HACE are already volume depleted from poor fluid intake, and diuretics may compromise adequate intravascular volume.

Hyperbaric treatment of HACE is also effective and may result in temporary improvement and allow self-rescue. Conversely, coma may persist for several days after descent to lower altitudes, so placement of HACE patients in a hyperbaric device may only delay the more comprehensive care available in the hospital setting.

Long-term neurologic deficits, such as ataxia and cognitive impairment, are reported after recovery from acute episodes of HACE. Both transient and long-lasting neurobehavioral impairments can occur in mountaineers after climbing to extreme altitude without experiencing clinical HACE.[116] Some of these sequelae can persist for 1 year. Because of the potential for long-lasting neurologic injury, the clinician who treats high-altitude illness must be extremely sensitive to the early manifestations of HACE. Early treatment for HACE generally results in good outcomes, but after coma is present, the mortality rate exceeds 60%.[117]

HIGH-ALTITUDE RETINAL HEMORRHAGE

High-altitude retinal hemorrhage (HARH) is the most common type of retinopathy in visitors to high altitude.[118] These hemorrhages are common at altitudes over 17,500 feet, although they can occur at lower levels.[119]

The exact incidence of HARH is unknown because most patients are asymptomatic, with HARH noted only on retinoscopy. HARH is not generally related to the presence of mild AMS but does seem to be related to strenuous exercise at high altitude. At any altitude, in the setting of severe HAPE or HACE, retinal hemorrhages are commonly noted.[119]

Hemorrhages are generally seen in the peripapillary area and throughout the fundus but usually spare the macula (Fig. 142-7). Retinal hemorrhages are self-limited and resolve without treatment in 2 or 3 weeks. With macular involvement, central scotomata may be noticed for several years, gradually resolving. In some cases, however, these visual defects are permanent. HARH is more likely to occur among individuals with a previous history of these hemorrhages. Usually, this does not pose a contraindication to return to high altitude unless the macular region is involved.

ALTITUDE AND UNDERLYING MEDICAL CONDITIONS

In individuals with diseases such as moderate to severe chronic obstructive pulmonary disease (COPD) and coronary artery disease, these illnesses are often aggravated by the relatively hypoxic atmosphere at higher elevations. They may have a more difficult time acclimating, which predisposes to the development of high-altitude illness. Table 142-1 describes the risk associated with travel to altitude in individuals with a variety of underlying comorbidities.

Respiratory Illnesses

Travelers with COPD to moderate altitudes have underlying anatomic and physiologic changes that predispose them to develop hypoxemia, sleep apnea, pulmonary hypertension, and ventilation disorders. COPD is a risk factor for the development of AMS.[5] Although oxygen saturation remains more than 90% in a healthy, awake individual until an altitude of 8000 feet, patients with COPD may desaturate below 90% at lower altitudes. Attempts to predict the need for oxygen use at altitude based on hypoxic breathing at sea level have resulted in the development of nomograms to predict arterial oxygen partial pressure at the expected high-altitude exposure (see Table 142-1). These have not been clinically useful. Travel to 5000 feet did not result in significant desaturation below 90% in one group of COPD patients and did not produce significant adverse effects on the systemic circulation in another group at 8000 feet.[120] High altitude increases hypoxic

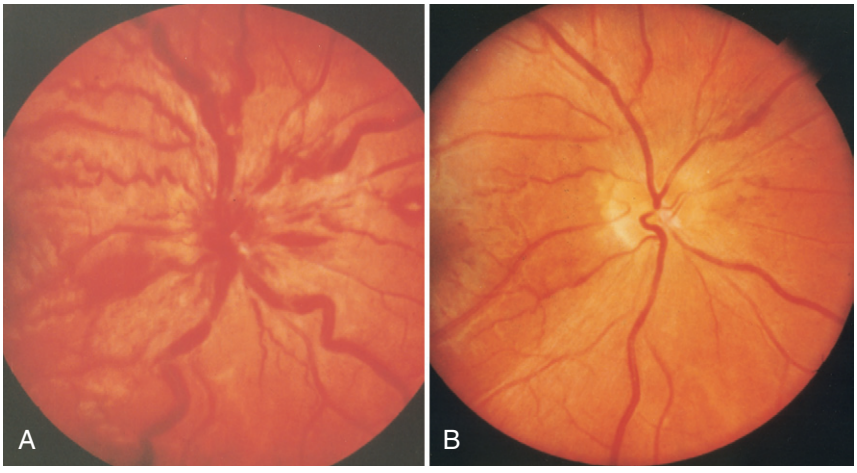


Figure 142-7. High-altitude retinal hemorrhages. **A,** Acute. **B,** After 1 week of resolution. (Courtesy of Charles Houston, MD.)

Table 142-1 Risk Associated with Travel to Altitude in Individuals with a Variety of Underlying Comorbidities

ADVISABILITY OF EXPOSURE TO HIGH ALTITUDE FOR COMMON CONDITIONS (WITHOUT SUPPLEMENTAL OXYGEN)
Probably No Extra Risk
Young and old
Fit and unfit
Mild obesity
Diabetes
Previous coronary artery bypass grafting (without angina)
Mild chronic obstructive pulmonary disease (COPD)
Asthma
Low-risk pregnancy
Controlled hypertension
Controlled seizure disorder
Psychiatric disorders
Neoplastic diseases
Inflammatory conditions
Caution
Moderate COPD
Asymptomatic pulmonary hypertension
Compensated congestive heart failure (CHF)
Morbid obesity
Sleep apnea syndromes
Troublesome arrhythmias
Stable angina or coronary artery disease
High-risk pregnancy
Sickle cell trait
Cerebrovascular diseases
Any cause of restricted pulmonary circulation
Seizure disorder (not on medication)
Radial keratotomy
Contraindicated
Sickle cell anemia (with history of crises)
Severe COPD
Symptomatic pulmonary hypertension
Uncompensated CHF

Modified from Hackett PH, Roach RC: High altitude medicine. In Auerbach P. (ed): *Wilderness Medicine*. Philadelphia, Elsevier, 2007, pp 2–36.

pulmonary vasoconstriction and may potentiate the development of cor pulmonale, which is known to adversely affect survival at sea level.[121] Colorado, for example, has a relatively low incidence of COPD but a higher mortality rate than expected from emphysema.[122] Individuals with chronic COPD should be advised of the potential need for oxygen supplementation when traveling to moderate altitude, especially if they are already using oxygen at sea level or if dyspnea or fatigue becomes worse. Use of a pulse oximeter that is readily available can guide the need for increased oxygen use.

Patients with asthma, on the other hand, may have fewer problems at altitude due to decreased allergens, pollutants, and decreased airflow turbulence. There have been no descriptions of asthma exacerbations at altitude, although at elevation oxygen saturations might be lower. Even those with exercise-induced bronchospasm do not have worsening symptoms while exercising at 5000 feet.[123] In addition, AMS incidence is not increased in asthmatic people.[123] People with asthma traveling to higher elevations should continue their usual medications and carry a rescue supply of bronchodilators and steroids.

Patients who ascend to high altitude with preexisting primary or secondary pulmonary hypertension should be considered HAPE susceptible, and those with primary pulmonary hypertension should be considered at increased risk for HAPE.[124] Patients with known pulmonary hypertension should be advised against travel to higher elevations. If travel cannot be avoided, then supplemental oxygen should be used. Prophylactic nifedipine SR, 20 mg twice daily for the duration of the stay at altitude, can prevent HAPE.[104] Phosphodiesterase-5 inhibitors and steroids may also be effective.[44]

Cardiovascular

Individuals with a history of congestive heart failure, angina, dysrhythmias, or coronary bypass surgery are rarely studied in this setting. In theory, people with a diseased myocardium should be advised to avoid trips to high altitude due to decreased environmental oxygen availability. However, no studies have reported increased mortality in visitors to these locations. To the contrary, long-term residents at high altitude may be protected from coronary artery disease due to increased collateral vessel formation or a decrease in the development of atherosclerosis.[125-127]

Several authors have safely exposed elderly people with known or suspected coronary artery disease to acute hypoxia at altitude, while breathing low oxygen mixtures, or when being placed in a hypobaric chamber.[128] In contrast, Levine and colleagues' investigation of elderly people with known coronary disease did demonstrate some risk.[129]

Patients with heart disease have increased sympathetic activity during the first 3 days at altitude, as do all travelers. The resultant increase in heart rate and blood pressure increases cardiac work and myocardial oxygen consumption and might increase dysrhythmias. Although both cardiac rhythm abnormalities and ST segment and T wave electrocardiogram changes are reported, none of these changes are associated with any clinical evidence of myocardial ischemia.[128,130] Limited data suggest no increased risk for sudden cardiac death or myocardial infarction at altitudes up to 8000 feet.

The small increase in heart rate and blood pressure that occurs when first visiting altitude might be expected to exacerbate angina in patients with known disease. Even when individuals with stable angina are exercised, there is conflicting evidence regarding the probability of inducing malignant dysrhythmias or untoward cardiac events.[129,131] In a study of 22 patients with recent percutaneous coronary intervention or coronary artery bypass graft with a submaximal exercise routine at 11,400 feet, there was no evidence of myocardial ischemia or significant arrhythmias despite an elevated oxygen demand, heart rate, and lactate level.[132] Travelers with heart disease who ascend to moderate altitudes do not appear to have an increased incidence of AMS.[5,15]

Recommendations for travelers with mild stable coronary artery disease should include gradual ascent, limitation of activity especially in the first few days at elevation, and continuation of antianginal and antihypertensive medications. Individuals who have more severe, symptomatic coronary disease or those in a high-risk group (low ejection fraction, abnormal stress test results, and high-grade ventricular ectopy) should avoid travel to high altitudes. Ascent to moderate elevations can be suggested on an individual basis with the previously mentioned precautions. Individuals with heart failure who travel to altitude may require increased use of diuretics to promote diuresis and promote acclimatization. Although not tested, acetazolamide prophylaxis may be useful for speeding acclimatization and preventing AMS and its accompanying fluid retention.[107] If the anticipated workload at altitude is greater than the individual is accustomed to at sea level, exercise stress testing at this increased workload before ascent should be considered.[133]

Hypertension

High-altitude travel produces a mild increase in blood pressure and heart rate in healthy individuals because of increased catecholamine activity and resultant sympathetic tone. This increase begins in the first few days after ascent, is maximal at 2 or 3 weeks, and returns to baseline values over time due to a down-regulation of adrenergic receptors if one stays at high altitude or on descent to sea level.[134,135]

The incidence of hypertension in sea-level dwellers traveling to high altitude is 10 to 25%.[136] Although there is no difference in blood pressure readings in either normotensive or hypertensive individuals when measured at low altitudes (3000 feet), significant increases occur in both blood pressure and heart rate at altitudes greater than 9800 feet.[137] This suggests that people with severe hypertension should travel only to moderate altitudes. For individuals who develop mild hypertension while traveling at altitude, treatment is not routinely necessary because the hypertension will rarely become dangerously high and will improve on descent. Although individual variability exists, patients with hypertension should be monitored frequently in the first few days at altitude and antihypertensive medications continued. For hypertensive patients with a rapid rise in blood pressure and who will be staying for several weeks, an alpha-blocker, nifedipine, or an ACE inhibitor should be considered.[138]

Sickle Cell Disease

Patients with sickle cell disease are affected by the hypoxemia occurring at low to moderate altitudes (5000–6500 feet). Up to 20% of patients with hemoglobin sickle cell and sickle cell–thalassemia disease may experience a vaso-occlusive crises, even under pressurized aircraft conditions.[139] Oxygen is therefore advised for air travelers who have sickle cell disease.

Although most people with sickle cell trait remain asymptomatic, this subgroup can experience the development of left upper quadrant pain as a result of splenic ischemia or infarction. Non-blacks, usually of Mediterranean origin, who have sickle cell trait may be more prone to the development of splenic infarctions than are blacks.[140,141]

Pregnancy

Studies of permanent high-altitude residents in Colorado and Peru show an increased incidence of complications in maternal, fetal, and neonatal life.[1] Infants born at high altitude have a lower birth weight compared to infants born at sea level. Fetal growth retardation at high altitude is believed to be the result of a reduction in uterine artery blood flow.

Pregnancy-induced hypertension, proteinuria, and peripheral edema (manifestations of toxemia and preeclampsia) are more common at high altitudes and may also be related to maternal hypoxemia.[142] Although hypertension in pregnancy is more common at high altitudes, no evidence exists for an increase in spontaneous abortions, abruptio placentae, or placenta previa.

Travel by pregnant women to moderate altitudes appears to be safe, but caution is advised for lowland women with normal pregnancies who wish to travel above 13,000 feet, for pregnant women who wish to remain at high altitude for a prolonged period, and for women with complicated pregnancies.

Radial Keratotomy

Although currently less popular, radial keratotomy may cause individuals to experience visual changes with ascent to altitude. This results from corneal swelling from ambient hypoxia because the cornea obtains its oxygen almost entirely by diffusion from the atmosphere. In normal corneas, this swelling is uniform. After radial keratotomy, the swelling is exacerbated and nonuniform secondary to the incisions.[143] Photorefractive keratotomy, which uses a laser technique that does not produce incisions but instead shaves the cornea, does not result in similar problems. Patients with radial keratotomy may require glasses of increasing refraction if they ascend to altitudes above 9000 feet.[144]

KEY CONCEPTS

- The symptoms of AMS can resemble a viral syndrome and include headache, nausea, anorexia, fatigue, and insomnia.
- The management of altitude illness must include adherence to the principle that after the symptoms occur and until symptoms resolve, further ascent is contraindicated.
- Dyspnea at rest is an early symptom of HAPE. As the HAPE patient's condition deteriorates, the dyspnea intensifies with effort and is unrelieved by rest.
- Cerebellar ataxia must be recognized as an early symptom of HACE, and descent is mandatory.
- Effective prophylaxis options for altitude illness include acetazolamide for AMS and nifedipine or tadalafil for HAPE. Dexamethasone should be reserved for acetazolamide intolerance or to facilitate descent with severe AMS.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 143 Drowning

David B. Richards and Andrew L. Knaut

PERSPECTIVE

Unintentional drowning accounted for 3308 deaths in the United States in 2004.[1] Worldwide, it is estimated that 500,000 people die after drowning annually, which exceeds mortality due to war.[2] Drowning is the fourth most common cause of accidental death in the United States. Among children 1 to 4 and 10 to 14 years old, drowning is second only to motor vehicle crashes as the leading cause of injury mortality.[1,3,4] Toddlers and older teenagers are at greatest risk of death by drowning, with annual incidences of 2.45 and 1.47 per 100,000, respectively.[1] Boys account for almost 80% of victims older than 1 year. Race plays a decided, although incompletely understood, role: Black males between ages 15 and 19 years have the highest annual incidence of drowning mortality (4.25 per 100,000), and black children between ages 5 and 14 years drown at more than three times the rate of white children of the same age.[1,5,6]

The incidence of drowning with nonfatal outcomes is less well known. The Centers for Disease Control and Prevention estimates that for every child who dies by drowning in the United States, five receive emergency department care for a submersion event, and half of these children require hospitalization.[6] Among all age groups, it is estimated that one to four hospitalizations secondary to nonfatal submersions occur for every drowning death.[7-9]

Submersion injuries occur in domestic settings such as swimming pools, hot tubs, bathtubs, and large buckets and in all forms of natural bodies of water. A review of all drowning deaths among individuals younger than 20 years in the United States during a 1-year period reveals that 55% of infants younger than 1 year who drown did so in bathtubs, and nearly 16% drown in large household buckets.[5] Most (56%) children 1 to 4 years old drown in artificial pools, whereas most (63%) deaths among older children occur in natural bodies of freshwater.[5] Drowning in the United States follows clear temporal patterns: Two thirds of pediatric deaths occur between the months of May and August, and most submersion injuries occur on weekends between the hours of noon and 8:00 PM.[7] Submersion victims older than 20 years are most often participating in water sports or using watercraft.

PRINCIPLES OF DISEASE

Definitions

Traditionally, the terminology used to describe submersion injuries has been confusing and impractical. In the past, *drowning* referred to death within 24 hours of suffocation from submersion in a liquid, whereas *near-drowning* described victims who survived at least 24 hours past the initial event regardless of the outcome. In 2005, the World Health Organization (WHO) published a new policy defining drowning in an attempt to clarify documentation and better track submersion injuries worldwide. Drowning was defined as "the process of experiencing respiratory impairment from submersion/immersion in liquid." Furthermore, the WHO policy states that "drowning outcomes should be classified as: death, morbidity, and no morbidity. … Use of the terms wet, dry, active, passive, silent, and secondary drowning should no longer be used."[2] As such, the term near-drowning should not be used, and the association of the term drowning with a fatal outcome should be abandoned.

Immersion syndrome refers specifically to syncope resulting from cardiac dysrhythmias on sudden contact with water that is at least 5° C less than body temperature. Proposed as mechanisms for the syndrome are vagal stimulation leading to asystole and ventricular fibrillation secondary to Q-T prolongation with a massive release of catecholamines on contact with cold water. The resultant loss of consciousness leads to secondary drowning. The risk of immersion syndrome is proportional to the difference between body and water temperature. Wetting the face and head before entering the water may prevent the inciting sequence of events.[3]

Risk Factors

Ethanol consumption in proximity with water is a major risk factor for submersion injury or death. Acute ethanol intoxication may be a contributing factor in 30 to 50% of drownings among adults and adolescents.[4,7] In one study of boating fatalities, most of which were due to drowning, an association between blood ethanol concentration and risk of death from drowning while using watercraft was established. Odds ratios of fatality from drowning followed a trend from 2.8 (95% confidence interval [CI] 1.6, 4.8) for a blood ethanol concentration (BEC) of 1 to 49 mg/dL to 37.4 (95% CI 16.8, 83.0) for a BEC of 150 mg/dL or greater compared with sober case controls.[10]

The relationship between swimming ability and the risk of drowning is unclear. No direct evidence exists to suggest that inexperienced swimmers are more likely to drown. On the contrary, skilled swimmers have greater exposure to water and may be more prone to submersion incidents.[11]

Numerous medical conditions confer an increased likelihood of drowning or submersion injury. Seizure disorders

sharply increase the chance of drowning among children and adolescents, and autism and other developmental and behavioral disorders increase risk in children.[12-14] Prolonged Q-T syndrome is also a risk factor for drowning. Laboratory studies show that immersion in cold water extends the Q-T interval. Interrogation of the automated internal cardiac defibrillator of a 12-year-old girl with prolonged Q-T syndrome who had a cardiac arrest on diving into the ocean revealed immediate further prolongation of the Q-T interval followed by a premature ventricular complex and subsequent ventricular tachycardia within 5 seconds.[15,16] This phenomenon may account for a significant proportion of immersion syndrome events and otherwise unexplained submersion injuries.

Pathophysiology

Unexpected submersion triggers breath-holding, panic, and a struggle to surface. Air hunger and hypoxia develop, and the victim begins to swallow water. As breath-holding is overcome, involuntary gasps result in aspiration. The quantity of fluid aspirated, rather than the composition, determines subsequent pulmonary derangement. The historical emphasis on pathophysiologic differences between freshwater and salt water aspiration with respect to resultant electrolyte imbalance, hemolysis, and fluid compartment shifting was based on animal studies conducted in the early 20th century.

Subsequent investigations have revealed that significant intravascular abnormalities do not occur until the amount of aspirated water exceeds 11 mL/kg of body weight, and autopsy studies show that most drowning victims aspirate less than 4 mL/kg.[17] In one review of the hospital treatment of 91 submersion victims, no patient required emergent intervention for a significant electrolyte abnormality.[18] Aspiration of 1 to 3 mL/kg of either freshwater or salt water destroys the integrity of pulmonary surfactant, leading to alveolar collapse, atelectasis, noncardiogenic pulmonary edema, intrapulmonary shunting, and ventilation-perfusion mismatch.[3] Profound hypoxia and metabolic and respiratory acidosis ensue, leading to cardiovascular collapse, neuronal injury, and, ultimately, death.

The classic hypothesis was that 10 to 15% of drowning victims die without aspirating a significant amount of water. Death from such "dry" drowning putatively results from severe laryngospasm causing hypoxia, convulsion, and death without fluid entering the lungs. An exhaustive review of the literature failed to corroborate this hypothesis.[19] Dry drownings more appropriately reflect deaths from causes other than simple submersion.

Many factors may influence the pathophysiologic sequence of events in submersion injury and affect the chance of survival, including age, water temperature, duration and degree of hypothermia, the diving reflex, and the effectiveness of resuscitative efforts. Because of a lower ratio of body mass to surface area, children develop hypothermia more quickly and to a greater degree after immersion in cold water than adults. Hypothermia lowers cerebral metabolic rate and is neuroprotective to some extent for victims of submersion injury.[20] Despite dramatic case reports of patients surviving prolonged submersion in cold water with full neurologic recovery, hypothermia is generally a poor prognostic finding. Cold water immersion speeds the development of exhaustion, altered consciousness, and cardiac dysrhythmia. The *diving reflex* may also play a protective role in infant and child submersions. Activation of the diving reflex by fear or immersion of the face in cold water shunts blood centrally to the heart and brain. Apnea and bradycardia ensue, prolonging the duration of submersion tolerated without central nervous system damage.[21]

CLINICAL FEATURES

Symptoms and Signs

Many submersion injuries are witnessed. Toddler drownings are an important exception, however, often occurring because of a lapse in supervision. Occasionally, the history of coughing, choking, or vomiting in a patient found near a body of water suggests the diagnosis. Signs of *pulmonary injury* may be obvious in a submersion victim who is hypoxic, cyanotic, and in obvious respiratory distress or arrest. More subtle clues, such as increased respiratory rate and audible rhonchi, rales, or wheezes, should alert the clinician to evolving respiratory compromise. Submersion victims swallow a significantly greater volume of water than is aspirated, and gastric distention from positive-pressure ventilation during rescue is common. As a result, 60% of patients vomit after a submersion event.[3] Aspiration of gastric contents greatly compounds the degree of pulmonary injury and increases the likelihood that acute respiratory distress syndrome will ensue. In addition, aspiration of particulate contaminants such as mud, sewage, and bacteria may obstruct the smaller bronchi and bronchioles and greatly increase the risk of infection both bacterial and fungal in nature.[22]

Victims with *central nervous system injury* may present with symptoms ranging from mild lethargy to coma with fixed and dilated pupils. Adverse neurologic findings on initial presentation do not preclude full neurologic recovery, although in general patients whose duration of submersion or resuscitation exceeds 25 minutes have an unfavorable outcome.[23] Central nervous system injury results from the initial hypoxic or ischemic insult and from the cascade of reperfusion injury that follows reestablishment of cerebral blood flow after an arrest. The release of inflammatory mediators and the generation of oxygen free radicals in the postresuscitative period contribute to cytotoxic cerebral edema, compromise of the blood-brain barrier, and increased intracranial pressure. Cerebral arteriolar vasospasm and enhanced platelet aggregation impede cerebral perfusion at the macrocirculatory and microcirculatory levels.[21]

Cardiac dysrhythmias may incite a submersion injury or develop as its consequence. Hypoxemia, acidosis, and, potentially, hypothermia are the primary factors responsible for dysrhythmias ranging from ventricular tachycardia and fibrillation to bradycardia-asystole. Electrolyte disturbances are rarely significant enough to be dysrhythmogenic.[18]

Other clinical sequelae of submersion injury may include acute *renal impairment*, present in approximately 50% of patients as the result of lactic acidosis; prolonged hypoperfusion; and, in some instances, rhabdomyolysis.[24] *Coagulopathy* as a consequence of associated hypothermia or disseminated intravascular coagulation may also occur.

Prognostic Factors

Many factors may help predict patients who will survive a submersion injury neurologically intact. Submersion victims who arrive in the emergency department alert with normal hemodynamics are unlikely to experience neurologic impairment. Circumstantial variables that portend a poor outcome include victim age younger than 3 years, submersion for longer than 5 minutes, and initiation of cardiopulmonary resuscitation (CPR) more than 10 minutes after rescue.[3,25] With the exception of victim age, however, such measurements are generally either unknown or inaccurately estimated at the time of a patient's arrival in the emergency department. Objective findings on emergency department arrival that are associated with

an unfavorable prognosis include hypothermia, severe acidosis, unreactive pupils, a Glasgow Coma Scale score of 3, and asystole or the need for ongoing CPR.[3,26-29] Neurologically intact survival is reported for individual patients even with several of these factors present, and none of several proposed scoring systems using combinations of these variables shows 100% predictive power.[25,27,30,31]

DIFFERENTIAL CONSIDERATIONS

The precipitants of a submersion injury, such as drug or ethanol intoxication, cardiac arrest, hypoglycemia, seizure, and attempted suicide or homicide, should be considered in a patient who is found unresponsive in the water. For pediatric victims, child abuse or neglect must also be considered as a potential etiology.

Potential head or cervical spine injury is an important consideration when a history of trauma is associated with the submersion. A review of 2244 cases of submersion injury in King, Pierce, and Snohomish counties in Washington state, however, identified only 11 (0.5%) patients with a cervical spine injury. Each patient had either clinical signs of serious trauma or a history of motor vehicle crash, fall from height, or diving into the water.[32] Unless such factors are present, routine cervical spine immobilization for submersion victims is not warranted.

DIAGNOSTIC STUDIES

Cardiac monitoring and an electrocardiogram must be obtained to determine the presence of significant dysrhythmias or Q-T prolongation. Pulse oximetry, capnography, and arterial blood gases should be monitored closely in all submersion victims for signs of hypoxemia, hypercarbia, and acidosis. Blood glucose, serum creatinine, and electrolytes should be obtained, although serum creatinine and electrolytes are usually normal on initial presentation. Similarly, complete blood count is often normal with the exception of leukocytosis. Toxicologic screening may be appropriate depending on the circumstances of the submersion. Subsequently, evidence of renal failure, hepatic dysfunction, and disseminated intravascular coagulation may be noted on laboratory testing.

The initial chest radiograph may underestimate the severity of pulmonary injury, although infiltrates or pulmonary edema may be evident within hours. Cranial computed tomography is rarely contributory initially unless significant trauma or other pertinent pathology is suspected. Magnetic resonance imaging of the brain may predict neurologic outcome after submersion injury, but its prognostic value is not optimal until 3 or 4 days elapse.[31,33]

MANAGEMENT

Salient details of the events surrounding the accident should be ascertained rapidly. Resuscitation of pulseless and apneic patients should be attempted initially in most cases because bystander estimates of total submersion time are often inaccurate. The clinical presentation of severe hypothermia often mimics death, and case reports exist of functional recovery for individuals submerged for 66 minutes.[34,35]

For a victim without vital signs, outcome depends on the interval preceding CPR. Mouth-to-mouth assisted ventilation should begin immediately, even before the victim is extricated from the water. Chest compressions are impractical before extrication but should be initiated as soon as the individual is placed on a solid surface. Maneuvers such as those proposed by Heimlich and Patrick to remove fluid from the lungs are ineffective and dangerous in a victim at risk for aspiration and may delay ventilation. Use of such maneuvers is not recommended unless there is reason to suspect airway occlusion by a foreign body.[36]

On arrival in the emergency department, cardiac monitoring and continuous pulse oximetry should be established. A core temperature obtained with a low-reading probe is indicated for any unstable or lethargic patient. Rewarming a hypothermic patient may suffice for hemodynamic stabilization and improvement in mental status. Bedside blood glucose measurement and empirical naloxone administration are warranted. In a spontaneously breathing patient, monitoring for signs of developing pulmonary injury should be established. Initial chest radiographs are often unremarkable even in the setting of serious and evolving pathology. Frequent arterial blood gas determinations are essential in submersion victims.

The decision regarding tracheal intubation should be based on clinical impression and objective determination of the adequacy of oxygenation and ventilation. Apparent or developing respiratory distress, the absence of protective airway reflexes, and significant associated head or chest injuries are indications. A $Paco_2$ greater than 50 mm Hg mandates intubation and mechanical ventilation. Patients unable to maintain an oxygen saturation greater than 90% or a Pao_2 greater than 60 mm Hg on high-flow oxygen require positive airway pressure to increase functional residual capacity, decrease intrapulmonary shunting, and reduce ventilation-perfusion mismatch. In an awake patient, this may be accomplished by face or nasal mask (continuous positive airway pressure), but the risk of potential gastric distention, vomiting, and aspiration must be considered. Otherwise, tracheal intubation and mechanical ventilation with positive end-expiratory pressure is necessary. The hemodynamic consequences of positive end-expiratory pressure must be monitored carefully because increased intrathoracic pressure may compromise venous return and cardiac output. Decreased cranial venous return may impede cerebral perfusion.

No consensus exists with regard to the appropriate length of resuscitative effort for hypothermic submersion victims in the emergency department. The safest parameter is to continue until the core temperature reaches at least 30° C to 35° C because cerebral death cannot be diagnosed accurately in hypothermic patients with temperatures below this level. This parameter may not always be practical, however, because brain-dead patients are often poikilothermic.

The administration of corticosteroids in the setting of submersion injury and potential acute respiratory distress syndrome does not improve outcome.[3,31] Similarly, empirical antibiotics do not increase survival and should be administered only to the rare patient who was submerged in grossly contaminated water or who shows signs of infection or sepsis.[3]

Interventions such as induced or permissive hypothermia aimed at attenuating reperfusion injury after anoxic brain insult are the focus of intense investigative effort, but no consensus exists regarding their use in submersion injury. A case report of twin toddlers with identical submersion injury and subsequent prolonged cardiac arrest indicates that therapeutic hypothermia may be a factor in influencing a good neurologic outcome. One twin was treated with therapeutic hypothermia for 72 hours and had a return to normal neurologic status. The other twin was not cooled and survived, but with significant neurologic impairment.[37] Reports such as this and studies in the resuscitation literature indicate an emerging role for therapeutic hypothermia in some drowning victims. Corticosteroid administration, barbiturate-induced coma, aggressive diuresis, neuromuscular blockade, and hyperventilation do not improve

neurologic outcome and, particularly in the case of hyperventilation, may be harmful.[21]

DISPOSITION

Symptomatic patients must be admitted for treatment. Patients with a history of apnea, unconsciousness, or hypoxia and any patients who manifest dysrhythmia or an abnormal chest radiograph also require admission. Patients who are asymptomatic on presentation to the emergency department, maintain a normal room air oxygen saturation, and have no chest radiograph or arterial blood gas abnormalities can be discharged safely after an observation period of 6 hours.[31,38] Careful instructions regarding symptoms or signs of delayed pulmonary complications are necessary, and the patient should be discharged in the care of a competent relative or friend.

Preventive Efforts

The mortality rate from drowning has decreased steadily since the 1990s in the United States.[1,4,31] A similar downward trend in submersion injuries is reported in Great Britain.[39] Although the exact causes of this decline are unknown, an increased public awareness of preventive measures and an emphasis on public education with regard to CPR and the dangers of ethanol use in conjunction with water-related activities have contributed significantly to the reduction in fatalities. A longitudinal study of drownings during a 21-year period in King County, Washington, notes that the incidence of death attributable to ethanol use has decreased by 81%.[3]

Parental education regarding the danger of pediatric drowning is an important focus of preventive effort. Inadequate supervision of children playing in or near water is one of the most common causes of pediatric submersion death, underscoring the importance of increasing awareness of the need for constant oversight of children in this setting.[9,40] Most pediatric submersion injuries in swimming pools occur at the victim's home.[9] In most cases, the child was last seen in the house, was left unattended for a moment, and entered the pool on an unfenced side closest to the home with no audible splash or screaming.[5] Adequate and fully circumferential fencing of residential pools is a current recommendation of the American Academy of Pediatrics. A meta-analysis of the literature regarding the efficacy of this preventive step reports an odds ratio of 0.27 for drowning or submersion in a properly fenced compared with a nonfenced pool.[40,41] Unfortunately, legislation requiring appropriate fencing is poorly adhered to, with only 40% of households compliant in one study.[42]

Pool covers are inadequate and potentially dangerous as barriers. Solar blankets do not support the weight of a child and can enmesh and obscure a struggling victim from view. A rigid pool cover may convey a false sense of stability to a child tempted to walk across its surface and is considered an insufficient substitute for effective four-sided fencing.[40]

Medical care providers are a vital resource for enhancing public awareness of the importance of these measures. The literature supports the concept that education in the emergency department with regard to drowning prevention can have a positive impact on patient and family awareness of steps to lessen the likelihood of catastrophic drowning or submersion injury.[43,44]

KEY CONCEPTS

- The fluid medium in which a submersion injury occurs (freshwater versus salt water) is usually of little clinical relevance; all significant submersions induce pulmonary injury and hypoxia based on the amount of water aspirated and the duration of submersion, not the water content.
- Aggressive pulmonary support is essential to optimizing the victim's chances for a favorable outcome.
- In submersion incidents, the Heimlich maneuver is reserved for patients with a suspected airway occlusion by a foreign body.
- No prognostic scale or clinical presentation accurately predicts long-term neurologic outcome; normal neurologic recovery is documented in patients with prolonged submersions, persistent coma, cardiovascular instability, and fixed and dilated pupils.
- Hyperventilation, steroids, dehydration, barbiturate coma, and neuromuscular blockade do not seem to improve outcome.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 144 Radiation Injuries

Christopher B. Colwell and Vincent Markovchick

HISTORICAL PERSPECTIVE AND EPIDEMIOLOGY

The technology of the 20th and 21st centuries has ushered in the nuclear age. Nuclear energy has significant peaceful industrial and medical uses, but it poses great potential danger as well. Although the safety record involving the use of radiation and radioisotopes is excellent overall, the hazards involved are well known as a result of the near-disaster that occurred at Three Mile Island in Pennsylvania in 1979, the disastrous accident at the Chernobyl Nuclear Power Station in the former Soviet Union in 1989, and the potential for disaster that occurred at a uranium processing plant in Tokaimura, Japan, in 1999.[1,2] The potential contamination of large numbers of people has and will continue to stress the capabilities of existing emergency medical systems.

The only wartime use of atomic and nuclear energy was the detonation of atomic bombs over Hiroshima and Nagasaki in 1945. Many nations now have nuclear weapons in their arsenals, however, and the possibility of terrorist groups obtaining and using such weapons does exist. Because the spent fuel from a nuclear power reactor can be reprocessed into plutonium, which can be used to produce nuclear weapons, more countries have now acquired the necessary raw materials to produce these weapons. The technology is available for the production and use of small, low-yield, tactical nuclear weapons and for megaton-yield, strategic nuclear weapons.

Although the proliferation of nuclear weapon technology and materials along with the growth of global terrorism raise new concerns about the possibility of a nuclear weapon being used by a rogue nation or terrorist group, a more likely scenario is the production and detonation of a "dirty bomb." In contrast to a nuclear weapon, which would be difficult to produce, a dirty bomb can be produced and detonated with relative ease. Perhaps the greatest threat from such a bomb lies in its potential to cause widespread terror from fear of radioactive contamination. Although the number of deaths and injuries resulting from a dirty bomb should not exceed those of a conventional explosion, the panic over radioactivity and evacuation measures and the prolonged cleanup efforts that would ensue could wreak havoc for months or years.

A dirty bomb can be produced from existing strontium-90 or cobalt-60 radioactive materials, such as radium and cesium-137 isotopes that are used in cancer therapy and found in many hospitals or university laboratories. Such a weapon can be produced by combining radioactive materials in solid or powder form with a conventional explosive that on detonation would send radioactive material into the area of the explosion and downwind. Although minimal to no harm would be likely from these sources of radiation, there would be tremendous psychological effects.[3,4]

It is technically much more difficult to produce a nuclear weapon than it is to manufacture a chemical or a biologic weapon. Use of a nuclear weapon by terrorists is highly unlikely unless they obtained such a weapon from existing stockpiles, which would include sources that may have been lost from governmental control in developing countries and areas of the former Soviet Union.

Injury from a nuclear explosion initially involves the mechanical effects of the blast wave that result in large-scale conventional types of blunt and penetrating trauma. Thermal or burn effects are the next threat, followed by the effects of ionizing radiation injury that occurs in proportion to the blast and thermal effects. In addition, radioactive fallout results from a nuclear weapon detonation on or above the ground. Detonation of a nuclear weapon could produce unimaginable devastation and injury from its immediate and long-term effects (Table 144-1).[5]

Accidents involving peacetime nuclear energy include exposure to and contamination by radioactive sources. The sources of this exposure are medical, industrial, and laboratory accidents that expose people to unacceptably high doses of radiation. Increased transport of such materials has resulted in an increased risk of accidents during transport. Emergency physicians are concerned primarily with the acute effects of exposure and contamination. The long-term effects continue to be studied in the large numbers of the populace exposed to radiation as a result of the Chernobyl accident.[1]

Nuclear Reactor Incidents

A nuclear weapon, as distinguished from a nuclear reactor, is designed to be autocatalytic (i.e., rather than being self-sustaining, the power grows without bounds after the chain reaction is initiated). The water-cooled nuclear reactors in U.S. power plants are designed to operate in their most reactive configuration. Any material or geometric change (except for removal of the control rods) renders them subcritical. In the graphite-moderated, steam-cooled reactors operating in the former Soviet Union, a nuclear excursion or accident can occur due to loss of coolant. This is what happened at Chernobyl.[6]

Every nuclear reactor should be housed within a containment structure to prevent the release of radioactivity in the

Table 144-1 **Approximate Distance from the Detonation Site at Which a 50% Fatality Rate Might Be Expected, According to the Size of a Nuclear Weapon**

YIELD (kT)	SHOCK WAVE	THERMAL RADIATION (M)	IONIZING RADIATION	
			INITIAL	RESIDUAL*
0.01	60	60	350	1270
0.1	130	200	460	2750
1	275	610	790	5500
10†	590	1800	1200	9600

*Data are for residual radiation (mostly fallout) in the first hour.
†At yields exceeding 10 kT, the lethal range of the fireball extends several times farther than the lethal range of either the blast or the initial radiation.
Data from the National Council on Radiation Protection and Measurements: Management of Persons Accidentally Contaminated with Radionucleotides (NCRP Report No. 65). Washington, DC, National Council on Radiation Protection and Measurements, 1980.

event of an accident. The Three Mile Island reactor has five layers of defense. It is for this reason that the accident in 1979 resulted in very little radiation being released into the environment. At Chernobyl, however, the containment structure failed, and all the radioactive material from the core of the reactor escaped into the environment. Although the amount of radioactive material released at Chernobyl was only approximately three times that released at Three Mile Island, failure of containment resulted in a 5000 times greater dose of radiation to all within a 10-mile radius of Chernobyl (40,000 mrem compared with 8 mrem from Three Mile Island).[1] Adding to the tragedy, the large amount of radioactive material released into the atmosphere at Chernobyl was carried aloft by prevailing winds, causing increased radiation exposure at long distances.

As a result of human error at a uranium processing plant in Tokaimura, Japan, 49 people were exposed to radiation, 2 of whom received a potentially lethal dose. Enriched uranium was mixed with nitric acid in an open vessel, resulting in Cherenkov radiation. This radiation is released when the speed of a charged particle in a transport medium is so high that it exceeds the velocity of light in that medium. A visible flash results from radiation emitted when the uranium reaches a critical mass and sets off an uncontrolled chain reaction for 20 hours.

Finally, a terrorist attack on a nuclear reactor could result in an atmospheric plume of radioactive iodine and noble gases released through a breach in the reactor core. These gases could have immediate health effects nearby, and long-term effects from radioactive iodine could occur at great distances from the reactor.

Radon Exposure

Radon gas is a major source of radiation exposure to the general public. Radon and its breakdown products are in the decay chain of uranium-238. Because uranium-238 has a long half-life and is distributed throughout the earth's rocks and soil, its decay products are ubiquitous. The decay scheme of radon results in the production of four heavy metal isotopes with short half-lives termed *radon daughters* (Fig. 144-1). These isotopes include alpha-emitting solids that can be inhaled and deposited in the tracheobronchial tree.

Radon-222 is a colorless, odorless, natural radioactive gas that moves by diffusion and pressure flow into basements and lower levels of buildings, where concentrations may reach hazardous levels. Radon daughters can be collected on filters, and alpha activity can be measured. The major source of radon gas is soil containing high levels of radon, such as uranium tailings used for landfill beneath buildings. Radon gas entry can be decreased by sealing basement cracks, and its removal can be enhanced by proper ventilation systems.[7]

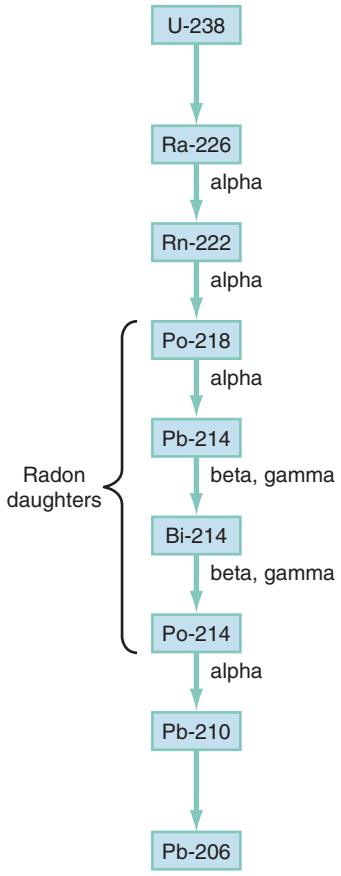


Figure 144-1. Radon and radon daughters in the major decay path of uranium-238. (Redrawn from Hart BL, Mettler FA Jr, Harley NH: Radon: Is it a problem? Radiology 172:593, 1989.)

Because radon and radon daughters result from the decay of uranium-238, uranium miners sustain some of the highest levels of occupational exposure. These individuals have an increased incidence of lung cancer and interstitial pulmonary fibrosis secondary to radon progeny exposure from inhalation of alpha particles.[8] It is estimated that radon exposure accounts for up to 33,000 lung cancer deaths in the United States each year, making radon the second-leading cause of lung cancer after cigarette smoking. Each year, 15,000 lung cancer deaths in the United States may result from indoor radon exposure; radon in homes may be a significant public health problem.[9]

PATHOPHYSIOLOGY OF RADIATION EXPOSURE

The electromagnetic spectrum (Fig. 144-2) encompasses a range from microwaves to gamma rays and includes long-wavelength, low-frequency, low-energy forms of nonionizing radiation and progresses to short-wavelength, high-frequency, high-energy forms of ionizing radiation. The frequency and length of these waves determine the energy, measured in units called *photons*. *Frequency* is the number of times per second the crest of a wave passes a given point, whereas *wavelength* is the distance between crests.

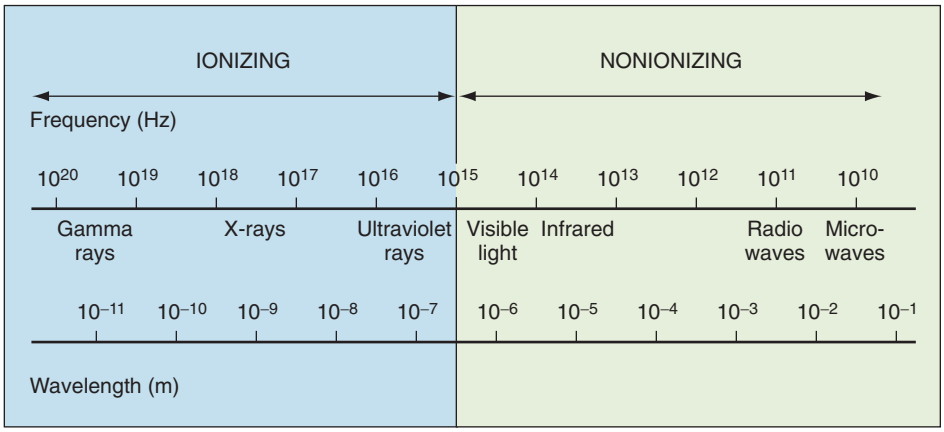


Figure 144-2. Electromagnetic spectrum.

Ionizing versus Nonionizing Radiation

Radiation is the transfer of energy in the form of waves, rays, or particles. The term *radioactivity* refers to the loss of particles (e.g., alpha, beta, or neutrons) or energy (e.g., x-rays and gamma rays) from an unstable atom that is spontaneously decaying. The spontaneous transformation of an unstable isotope to a stable one is referred to as decay, and it may involve the release of ionizing radiation. To understand the effects of radiation exposure on humans requires a distinction between ionizing and nonionizing radiation. *Nonionizing radiation* refers to all forms of the electromagnetic spectrum, with the exception of x-rays and gamma rays. Nonionizing (in contrast to ionizing) radiation has a long wavelength, low frequency, and low energy. Examples of nonionizing radiation include visible light, radar, radio and television broadcasting, garage door openers, microwave ovens, relay stations, medical diathermy, and satellite communications.

The primary adverse effects of nonionizing radiation are related to local heat production because the energy of nonionizing radiation is essentially all expended in heat. This effect depends directly on the intensity of the source, the distance from the source to the person exposed, and the duration of exposure.[5] Long-term exposure to microwave irradiation at some distance from the source has received extensive study. The most thoroughly researched example involves U.S. State Department employees exposed to long-term microwave irradiation in the U.S. chancery in Moscow. This building was subjected to a direct beam that resulted in exposed rooms having a higher power density than that usually found on the ground near transmission towers. After extensive study, it was concluded that no adverse health effects occurred from this exposure. This and other studies performed on various groups of workers exposed to radiofrequency radiation conclude that the present exposure levels (including microwaves) do not cause significant adverse health effects to the general public; specifically, there is no evidence of either decreased longevity or an increased incidence of cancer. The possibility of hazardous health effects resulting from low-level microwave exposure is an area of ongoing study.[10]

A microwave oven generates 2450-MHz microwaves. This megahertz wavelength can produce hyperthermia above a 25-mW level with a penetration of several centimeters. If a microwave oven has a door leak, a person can be exposed to the thermal effect of microwaves only by placing a body part in direct contact with the area. Electromagnetic waves dissipate at a rate directly related to the square of the distance from the source. In other words, exposure is cut to one fourth at twice the distance from the source. No thermal effect exists at a distance of several feet, but a potential exists for deleterious effects on electronic devices that are sensitive to the wavelength of this electromagnetic radiation.

Ionizing radiation has a short wavelength, high frequency, and high energy. The photons of ionizing radiation carry 1 billion times more energy than the photons of nonionizing radiation. Ionizing radiation induces injury by damaging DNA and other cellular components that can lead to cellular dysfunction or death. It is emitted in the form of alpha and beta particles, gamma rays, and x-rays.

Irradiation versus Contamination and Incorporation

Irradiation

A radioactive substance is one that emits ionizing radiation. It is referred to as a radionucleotide or radioisotope. If such radiation passes through a nearby object, the object is said to have been irradiated. With the exception of the situation in which there is direct exposure to neutrons, the object that has only been irradiated does not become radioactive. When a person has only been irradiated but not contaminated, such as the post–radiation therapy patient, no hazard exists to medical personnel, and the patient may be handled as any other emergency patient.

Contamination

Radioactive contamination is essentially radioactive particulate matter (alpha and beta particles) covering an exposed surface. Contamination is not an acute threat to the life of the patient or the provider, and its presence should not preclude instituting lifesaving measures for associated trauma. This radioactive particulate matter may emit radiation with an effect that is directly related to the time of exposure, distance from the source, and type of contamination. The four types of radiation that exist with the potential to contaminate are alpha, beta, gamma, and neutron radiation, and each presents different hazards (Fig. 144-3).

Alpha radiation consists of particles that are highly charged and composed of two protons and two neutrons. *Alpha particles* dissipate their energy quickly and travel only a few centimeters in the air. They cannot even penetrate paper and are therefore easily shielded. Even when directly contacting skin, penetration is limited to the thickness of the epidermis. Alpha radiation therefore presents a significant biohazard only when internalized. Alpha particles are produced by alpha emission from many of the heavy radioactive elements, such as pluto-

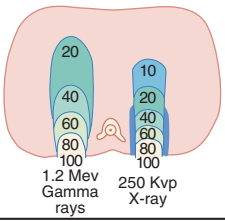
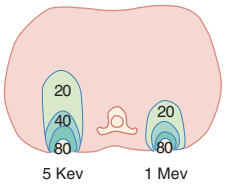
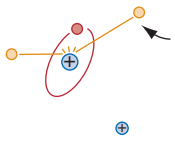
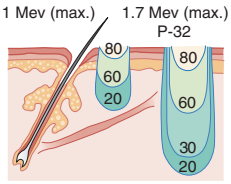
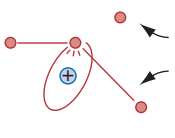
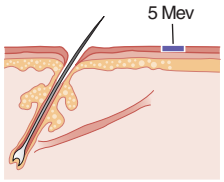
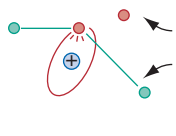
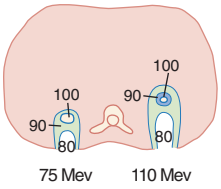
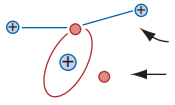
TYPE OF RADIATION	SYMBOL	USUAL SOURCE	PENETRATION OF EXTERNAL RADIATION	PRINCIPAL TYPES OF INTERACTION
X-rays Gamma rays	x γ	X-ray machines and accelerators Most radioisotopes emit a gamma ray following beta decay	 X- and γ rays penetrate deeply, for only a fraction of the rays interact with each layer of tissue	Ejected electron loses energy by causing additional ionization Deflected x- or γ ray may interact again some distance away Ionized atom formed after electron ejection
Neutrons	n	Neutrons are generally produced by critical assemblies, nuclear reactors, or accelerators	 Neutrons penetrate deeply, for only a fraction of the neutrons interact with each layer of tissue	 Deflected neutron may interact again some distance away Recoil proton loses energy by causing ionization
Beta particles	β	Most radioisotopes decay by beta emission, usually followed by gamma emission	 Penetration depends on energy of beta but is usually limited to less than 8 mm in tissue	 Ejected electron loses energy by causing additional ionization Deflected electron or beta particle causes additional ionization Ionized atom formed after electron ejection
Alpha particles	α	Many of the heavy radioactive elements such as plutonium decay by alpha particle emission	 Penetration is limited to about the thickness of the epidermis	 Ejected electron loses energy by causing additional ionization Deflected alpha goes on to cause additional ionization Ionized atom formed after electron ejection
Protons	p	Energetic protons are found only near particle accelerators	 Penetration depends on energy of the proton	 Deflected proton causes additional ionization Ejected electron loses energy by causing additional ionization Ionized atom formed after electron ejection

Figure 144-3. Types of radiation and possible external hazards. (Redrawn from Gould A, Cloutier RJ: Arch Environ Health 10:499, 1965.)

nium and uranium decay. Some Geiger-Mueller counters are not able to detect alpha particles, but are generally excellent for detecting beta and gamma radiation. Due to alpha particles' low penetrating ability, a proportional alpha counter with a special window must be used.

Beta particles have a smaller mass and charge than alpha particles and tend to have a greater velocity. They have a tissue penetration of approximately 8 mm and can cause significant burns to the skin surface, although these burns are not generally visible immediately after the exposure. Since clothing effectively shields covered areas, the primary danger is to exposed skin. Standard skin-cleansing procedures remove most of this contamination. The only means of detection is a radiation-sensing instrument (Geiger-Mueller counter), which all hospitals should have. If exposure to beta particles is allowed to continue, significant exposure to gamma radiation can occur because most radioisotopes decay by beta radiation followed by gamma emission.

Gamma rays are electromagnetic waves with no mass and no charge that travel quickly and penetrate tissue deeply, with a fraction of the rays interacting with every layer of tissue. Gamma rays are the most penetrating type of ionizing radiation and travel several meters in air and many centimeters into tissue. Gamma rays are emitted from radioisotopes after beta decay and are the primary cause of the acute radiation syndrome.

Neutrons are unique. When they are stopped, or "captured," after emission, they commonly cause a previously stable atom to become radioactive. This is the source of radioactive fallout. A surface burst of a thermonuclear weapon instantly vaporizes tons of surface soil, transforming it into highly radioactive material by the intense neutron bombardment. This cloud rises with the fireball and is carried away by the prevailing winds at high altitudes. Its radioactive particles ultimately descend as fallout.

Some gamma exposure also occurs with neutron exposure. In peacetime, significant neutron exposure is likely to occur only around nuclear reactors and accelerators. Quantization of the radioactive material induced by neutron irradiation is helpful in estimating neutron exposures and, sometimes indirectly, the dose of gamma radiation. The induced radioactivity is primarily sodium-24, which can be detected by a whole-

body counter or in blood samples. If neutron exposure is suspected, all feces and urine should be refrigerated and saved. All clothing, especially items containing metal parts, such as belt buckles, should also be saved for analysis of neutron-induced radioisotopes.

Incorporation

Incorporation occurs when a radioactive material is ingested, inhaled, or absorbed through an open wound.

TYPES OF EXPOSURE

- *External radiation* exposure results from partial-body or whole-body irradiation from an outside source. The patient may have received a lethal dose but presents no radioactive hazard to other people or the environment. Examples include accidental irradiation of personnel working with fissionable materials in laboratories or with nuclear reactors in nuclear power plants.
- *Incorporation and internal contamination* generally result from inhalation or ingestion of radioactive substances but can also occur from absorption of radioactive substances through open wounds. When this occurs, even alpha particles, which normally present no real health hazard with external exposure, can have long-term effects, including the development of lung cancer. The treatment of this type of exposure is often similar to that of acute poisoning with heavy metals.
- *External contamination* involves surface exposure to radioactive materials that remain in contact with the skin, such as dirt or liquids. Care must be taken to confine this contamination. Emergency treatment consists of removal of clothing and careful cleansing of exposed parts.
- *Wound contamination* involves exposure of an open wound to radioactive material that results in some degree of internal contamination.

Combinations of these types of radiation exposures can occur. The traumatic blast effects of a thermonuclear explosion could result in exposure to all types of radioactivity in addition to causing radioactively contaminated wounds.

CLINICAL FEATURES AND DIAGNOSTIC STRATEGIES

Symptoms and Signs

Radiation injury is caused by deposition of energy in tissue. This energy can lead to damage of cellular structures such as DNA from free radical formation. Cellular repair mechanisms will be less effective with more rapid delivery of higher doses of radiation. *Acute radiation syndrome* (ARS) is a symptom complex that occurs after whole-body irradiation. It varies in nature and severity depending on dose, dose rate, dose distribution, and individual susceptibility. This syndrome can result from external or internal exposure to radiation over a short period of time. The patterns of symptoms and signs of ARS overlap and contain many variables (Fig. 144-4).

The principal units used for expressing the dose of radiation absorbed in living tissue are the *gray* (Gy) (1 Gy = 1 joule of radiation absorbed per kilogram of tissue) and the *radiation absorbed dose* (rad) (1 rad = 100 erg per gram of tissue = 0.01 Gy). The *roentgen equivalent man* (rem) is the dosage of ionizing radiation equal to 1 rad of *x*-radiation (1 rad = 1 rem). A chest radiograph equals 45 mrem, and flying 3000 miles in a jet at 35,000 feet results in 4 mrem of exposure.

The relative sensitivity of organ systems exposed to the radiation determines the clinical symptoms. Since it is often difficult or impossible to accurately quantitate the absorbed dose of radiation, the symptoms and signs determine the diagnosis, therapy, and prognosis. The presence and timing of nausea and vomiting is an excellent screening tool to detect those who require more urgent medical investigation.[11] When

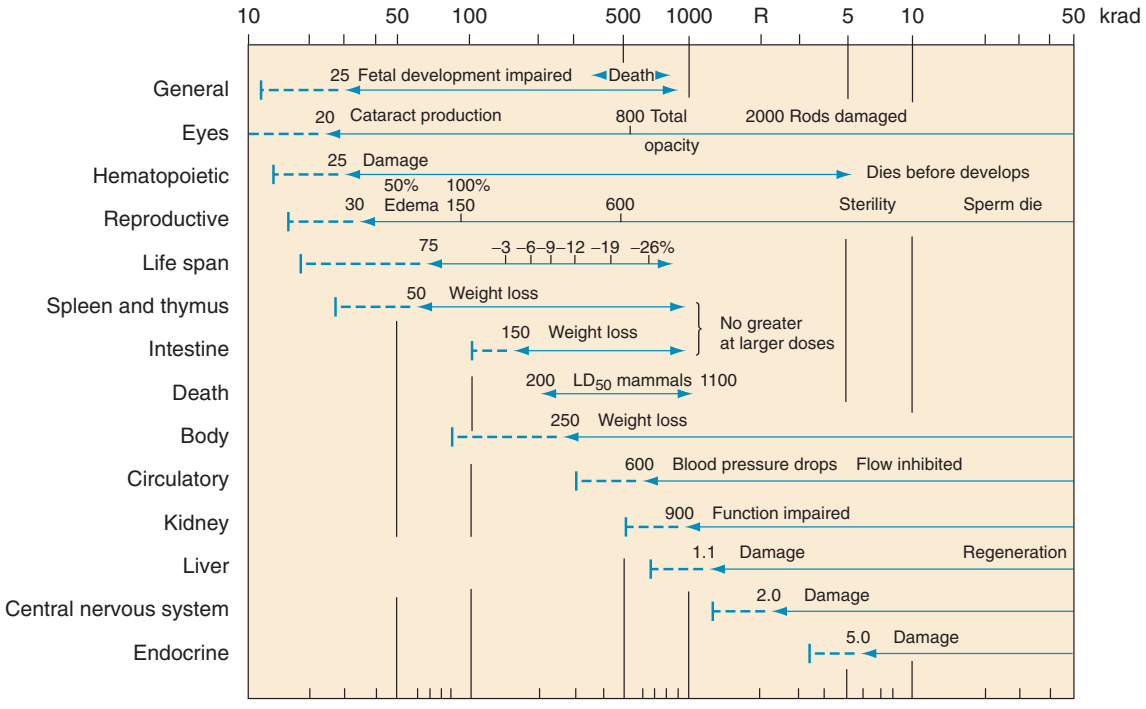


Figure 144-4. Organ and tissue sensitivity in mammals. The dose values are for whole-body, acute, x-ray, or gamma ray exposures. For low-intensity or fractionated exposure, the lines would be moved toward the right (higher doses). Radiosensitivity is directly related to the proliferative rate of the cells of the organs. (Redrawn from Auerbach PS, Gehr EC: Management of Wilderness and Environmental Emergencies. New York, Macmillan, 1983.)

Table 144-2 Prognosis According to the Lymphocyte Count within the First 48 Hours after Acute Exposure to Penetrating Whole-Body Radiation

MINIMAL LYMPHOCYTE COUNT PER MM²	APPROXIMATE ABSORBED DOSE (GY)	EXTENT OF INJURY	PROGNOSIS
1400–3000 (normal range)	0–0.4	No clinically significant injury	Excellent
1000–1499	0.5–1.9	Clinically significant but probably nonlethal	Good
500–999	2–3.9	Severe	Fair
100–499	4–7.9	Very severe	Poor
<100	≥8	Most severe	High incidence of death even with hematopoietic stimulation

the time to emesis is less than 4 hours after exposure, the effective whole-body dose is likely to be at least 3.5 Gy. If the time to emesis is less than 1 hour, the whole-body dose likely exceeds 6.5 Gy and the outcome may be fatal. In most radiation accidents, exposed individuals are not wearing a monitoring device that can measure high doses of radiation. The radiation dose must be estimated from its biologic effects. The earliest indicator of a significant radiation exposure is the decrease in the absolute lymphocyte count, which can occur within 48 hours after exposure (Table 144-2).[5]

Tissues with greater rates of cellular division, particularly the hematopoietic and gastrointestinal systems, are the most radiosensitive (see Fig. 144-4). With intense irradiation exposure, however, central nervous system (CNS) symptoms can result, even though the CNS has a low cellular turnover rate. Invariably, all organ systems are involved in whole-body irradiation. At doses less than 1 Gy (100 rem), most cells survive but may be susceptible to radiation-induced cancer. Leukemia can develop as quickly as 2 years postexposure, whereas solid tumors develop over several decades.[5,12,13]

The LD_{50} or median lethal whole-body dose (the dose that is lethal for 50% of test subjects), assuming proper medical care, is estimated to be approximately 4.5 Gy.[6] Whole-body exposure of 10 Gy is the maximal survivable dose even with the best medical therapy.[5] Doses greater than 20 Gy commonly produce CNS symptoms. These symptoms occur immediately after exposure and include headache, mental status aberration, prostration, vertigo, tinnitus, and sensory and motor changes. If the individual is exposed to a nonuniform dose and the gastrointestinal and hematopoietic systems are spared, there is a chance of survival after resolution of the CNS symptoms. If more than 20 Gy of whole-body exposure occurs, however, fulminating gastrointestinal and CNS symptoms ensue, sometimes within 30 minutes. This indicates a supralethal dose of radiation, and for triage purposes, the death of these patients should be classified as "impending" or "expectant." If medical resources are scarce, sedation and analgesia should be the only therapies. With whole-body exposure of more than 10 Gy, mortality approaches 100%. If the patient survives the CNS and gastrointestinal system insults, hematopoietic complications are lethal.

The gastrointestinal syndrome occurs regularly at doses higher than 1 Gy. In general, the higher the absorbed dosage, the sooner the onset of symptoms. In its mildest form, nausea and vomiting are short-lived. More protracted nausea and vomiting are seen with higher exposures. The onset of high fever and persistent bloody diarrhea are ominous signs. Death from hematopoietic system failure may result despite aggressive fluid and electrolyte therapy.

A latent period lasting 2 days to 4 weeks from the time of exposure often occurs before the signs of hematopoietic system involvement develop. The earliest sign is often pancytopenia resulting from marrow suppression. This hematopoietic syndrome includes leukopenia and thrombocytopenia with fever, increased susceptibility to infection, petechiae, and hemorrhagic diatheses. The absolute lymphocyte count 48 hours after exposure is a good predictor of hematopoietic system involvement (see Fig. 144-4). If the absolute lymphocyte count is greater than 1200/μL, it is unlikely that the patient has received a clinically significant dose of radiation. If the absolute lymphocyte count falls between 100/μL and 500/μL at 48 hours, a significant or even lethal dose of radiation should be suspected. A level in this range is an indication for protective isolation. Levels less than 500/μL suggest procedures such as the use of hematopoietic growth factors.[5,14] If a patient is symptomatic, serial complete blood counts should be performed. Hemorrhagic complications should be treated with platelet concentrates and whole blood or fresh frozen plasma when necessary. Anemia resulting from erythropoietic suppression is not generally of clinical significance.

Erythema from skin burns may be delayed in onset. When secondary to penetrating radiation, they indicate high exposure. Severe skin burns may be a result of nonpenetrating radiation, such as beta particle contamination without accompanying systemic symptoms. These burns can be prevented or tempered by early decontamination. When present, they should be treated as any thermal or chemical burn.

Skin changes that occur can help quantify radiation exposure. Epilation occurs after exposure to 3 Gy, erythema is seen after exposure to 10 Gy, wet desquamation occurs after 20 Gy, and necrosis occurs after 30 Gy of localized skin exposure.[5] These responses are similar to those of severe chemical burns.

A key historical point when evaluating a suspicious burn is whether the patient had contact with a hot object or caustic chemical. If the patient does not give a history that clearly explains the burn, particularly if there is a history of carrying a bright metal object that may have been a radioisotope source, the possibility of a radiation burn should be considered.

MANAGEMENT

Out-of-Hospital Care

The history obtained from field personnel is crucial. The exact type of exposure (external versus internal, whole body versus partial body) should be ascertained. If internal exposure is suspected, the portal of entry (inhalation, ingestion, or absorption) and the radioactive material involved should be investigated.

Reducing Exposure

The protection of providers involves reducing exposure to levels that are as low as reasonably achievable. The three classic and effective methods for reducing radiation exposure can be summarized as *time*, *distance*, and *shielding*. The absorbed dose is directly proportional to time. In addition, radiation exposure follows the inverse square law, and it decreases to one fourth at twice the distance from the source. Effective shielding varies from a sheet of paper for alpha particles to less than an inch of aluminum for beta particles and several inches of lead for gamma rays.

Decontamination

If the patient's condition permits, decontamination should usually be initiated at the scene because many communities lack emergency departments designed for this procedure. In an industrial or laboratory accident, each facility should have a specific protocol and equipment available to initiate the decontamination process. All out-of-hospital personnel should be trained in the decontamination process. Universal precautions, including rubber gloves, shoe covers, and respirators if airborne contamination is suspected, are very effective in protecting personnel and the work area from contamination. The only variation from normal universal precautions is a recommendation to wear two sets of gloves and to change the outer pair when appropriate to avoid cross-contamination.[15]

The patient's clothing should be removed and placed in plastic bags. If possible, soap and water cleansing of exposed skin should be performed. All materials, including wash water, should be placed in containers and labeled as radioactive waste. Performing these tasks at the scene minimizes contamination of the ambulance and the emergency department.

If the patient is unstable, rapid and partial decontamination procedures, such as clothing removal, should be initiated at the scene before expeditious transportation to an emergency department. Radio contact with the receiving hospital should be provided to the emergency department to facilitate preparations. If the community disaster plan has a designated hospital for radiation-contaminated victims, they should be transported directly to that facility. Physicians wishing to establish a comprehensive plan to manage radiation accident victims are referred to the National Council on Radiation Protection.[16]

Emergency Department

Every emergency department designated as a decontamination facility should have a radiation accident protocol. An excellent prototype is that published by Leonard and Ricks.[17] This protocol should be included in the policies and procedures manual and posted in the decontamination facility.

Preparation

The chaos that ensued in the wake of the Three Mile Island experience suggests that a community disaster plan should be developed with a predetermined individual empowered to make decisions regarding evacuation and other issues concerning the at-risk population. Upon notification of the numbers and types of patients involved in a radiation exposure accident, a decision should be made regarding implementation of a full disaster plan versus a limited response. The *radiation control officer*, usually a radiologist or pathologist, should be contacted immediately. The radiation control officer should monitor all patients and medical personnel with a radiation counter and should supervise the "cleanup" and the routing of patients to minimize "tracking," or spread, of contamination. The role of informational services is critical. Timely and accurate information and instructions should be given to a public relations person for dissemination to the news media to minimize the chaos and paranoia that inevitably result from such incidents.

Decontamination

Contaminated patients should be decontaminated in the field. If they arrive at the emergency department contaminated, they must enter through a separate, protected entrance or be isolated until a decontamination tent can be erected. Since the risk to emergency department staff from radioactive contamination is minimal with universal precautions, medical stabilization and treatment of the patient supersede decontamination efforts in a radiologic emergency.

There is a significant distinction between patients contaminated with radioactive material and those who arrive contaminated with chemical or biologic agents, where decontamination may need to take precedence. All medical personnel should wear protective, disposable clothing, including surgical gloves and shoe covers. Respirators are not required at the hospital but should be used by first responders who are entering a highly contaminated area.[5] The emergency suite should contain all equipment necessary for a major resuscitation. If decontamination occurs inside the emergency department, it must have a contained drainage and ventilation system to prevent the spread of waterborne or airborne radioactive contamination. In some hospitals, the only area equipped with such facilities is the autopsy room or morgue.

The radiation disaster plan may necessitate taking resuscitation equipment to this area and providing decontamination and initial care there if this cannot be done in a decontamination facility outside of the emergency department. As opposed to chemical and biologic hazards, radioactive contamination is relatively easy to detect with commonly available survey meters, such as a Geiger-Mueller (GM) instrument, often referred to as a Geiger counter. This should be available in any emergency department that may receive patients exposed to radioactive contamination. Although historically survey meters have not been able to detect alpha radiation, many of the newer devices can detect even small amounts of radioactive contamination and will typically be capable of distinguishing alpha, beta, and gamma radiation.

The patient should be undressed immediately, and all clothing should be placed in sealed containers labeled "radioactive waste." Removal of clothing can reduce contamination on the patient by 90%.[18] Exposed skin should be cleansed with soap and water. Overly aggressive skin washing should be avoided since abraded skin openings could allow increased absorption of radioactive material. Hair should be shampooed. All wastewater, washcloths, and towels should be saved in properly labeled containers. The cleansing process should be repeated as frequently as necessary until the area measures less than twice the background reading on the GM survey meter or until there is no significant reduction in the level of contamination between washes.[15] Long hair may need to be trimmed. The nails should be trimmed and meticulously scraped to remove contamination.

Wound Management and Treatment

If the patient has open wounds, the surrounding skin should be decontaminated by scrubbing with soap and water. Adhe-

sive, disposable surgical drapes should be applied, and the wounds should be prepared and irrigated with copious amounts of saline. Frequent monitoring for radioactive contamination determines when irrigation can be discontinued. Surgical débridement should be performed according to the usual indications of dirt and nonviable tissue or continued high readings of radioactive contaminants. The normal principles of wound closure should be followed for contaminated wounds. The wounds in patients who have received whole-body radiation greater than 1 Gy should be closed primarily to prevent infection.[5]

Since there is minimal risk to providers using universal precautions, emergency surgery or other necessary procedures should not be delayed due to contaminated skin or wounds. Surgical interventions should be performed within 48 hours of the injury when possible in patients who have suffered high-level radiation exposure and trauma. Acute radiation syndrome may be complicated by fluid and electrolyte disturbances. After 48 hours, surgical interventions may need to be delayed until hematopoietic recovery occurs.[15]

Treatment

The indications for pain management and antiemetics should be liberalized. Treatment of ARS should also focus on the prevention of infection. Neutropenia and fever should be managed with antibiotics, although routine enteric prophylaxis is not indicated.[19]

Internal Contamination

Oral ingestion of radionucleotides presents some special challenges. After ingestion, there is usually a variable time period prior to cellular absorption and uptake. Therapy with blocking or chelating agents is determined by the elements involved. A *blocking agent* is a chemical that saturates a tissue with a nonradioactive element, reducing the uptake of the radionucleotide. An example is potassium iodine (Lugol's iodine solution), which reduces the uptake of radioactive iodine. *Chelating agents* bind metals into complexes, which prevents tissue uptake and allows urinary excretion. Two examples of chelating agents are calcium disodium edetate and penicillamine, both of which treat radioactive lead poisoning. Ideally, these agents should be administered soon after exposure, before significant uptake of the radionucleotide can occur. A poison information center should be contacted for recommendations regarding the dosages of chelating and blocking agents and other treatment modalities, including induced emesis, cathartics, activated charcoal, and lavage.[20] All excretions (urine, feces, emesis, and lavage fluid) should be saved in specially labeled containers for dosimetry and proper disposal. The decision to treat suspected internal contamination should not be delayed for sample analysis, which typically will take 24 hours. Medications that may be administered to patients suspected of being internally contaminated with some radioactive isotopes are listed in Table 144-3.

Acute inhalation of radionucleotides is problematic. Emergent bronchopulmonary lavage may be effective in partial removal of the radioactive contaminants. Nasal swabs subsequently tested for radioactivity may help determine if inhalation of radioactive material has occurred. Chelating and blocking agents may be used if significant inhalation is suspected. Chronic low-level inhaled contaminants are more common, and long-term sequelae occur. Extensive cutaneous radiation fibrosis occurred in some survivors of the Chernobyl accident, and interferon therapy is of benefit.[21]

Table 144-3 Medication Options for Internal Contamination

MEDICATION	RADIOACTIVE ISOTOPE
Ferric hexacyanoferrate (Prussian blue)	Cesium –137, thallium
Ca- and Zn-diethylenetriamine penta-acetate (DTPA)	Plutonium, americium, curium
Potassium iodide	Radioiodine
Penicillamine	Radioactive heavy metal poisoning (lead)

Triage Classification, Further Treatment, and Disposition

Triage is facilitated by presenting symptoms into three categories: survival probable, survival possible, and survival improbable. The *survival probable group* consists of patients having either no initial symptoms or mild symptoms that subside within a few hours. Radiation exposure in this group is usually less than 2 Gy (200 rem or rads). The initial laboratory studies and serial complete blood counts reveal no depression of the leukocyte count.

The *survival possible group* includes patients in whom nausea and vomiting are relatively brief (lasting 24–48 hours), followed by an asymptomatic period. After the initial symptoms, these patients exhibit the typical hematologic changes of thrombocytopenia, granulocytopenia, and lymphopenia. The severity of these changes depends on individual susceptibility and the level of the initial radiation dose. These patients should be admitted for fluid and electrolyte therapy if vomiting is severe. Antiemetics may be ineffective. Also, protective isolation precautions are indicated, particularly if there is significant granulocytopenia at 48 hours.

The exposure dosage range for patients in the survival possible group is estimated to be 2 to 10 Gy, with the LD_{50} approximately 3 to 5 Gy. The LD_{50} varies depending on the vigor of supportive therapy. In mass casualty situations, the LD_{50} is in the range of 3.5 to 4.5 Gy. The concept of calculating the LD_{10} versus LD_{90} for human radiation exposure helps determine what level of therapeutic intervention is indicated. A patient who has received an LD_{90} exposure may survive only if hematopoietic growth factors are used, whereas a patient with an LD_{10} exposure may need only low-risk supportive care, such as reverse isolation and intravenous fluids.

The therapy for the survival possible group is based on the exact hematologic derangements. Platelet concentrates are recommended if the count falls below $25 \times 10^3/\mu L$. Appropriate broad-spectrum antibiotics should be considered only if clinical signs of infection appear. Prophylactic antibiotics may be indicated if serious gastrointestinal symptoms, such as vomiting and diarrhea, are present. Prophylactic antifungal agents, such as amphotericin B, may also be indicated. Acyclovir may be useful for oral herpes simplex infection. Colony-stimulating factors (cytokines) that induce bone marrow hematopoietic cells to proliferate may have substantial benefit, with little risk in victims predicted to have moderate or severe bone marrow failure.

Filgrastim and sargramostim, both used in treating patients with neutropenia resulting from myelosuppressive chemotherapy, are useful in radiation accident victims and may hasten recovery of neutrophil counts. Cytokine therapy (filgrastim (G-CSF) 5 μg/kg per day or sargramostim (GM-CSF)

250 μg/m^2 subcutaneously) is recommended in healthy individuals with no other injuries who receive exposures estimated to be in excess of 3 Gy and in patients with multiple injuries or burns who receive exposures in excess of 2 Gy. Intravenous hyperalimentation may be necessary for the successful treatment of the gastrointestinal syndrome.

The third group is the *survival improbable group*. The exposed dose range in this group is estimated to be greater than 10 Gy whole-body exposure. These patients experience rapid onset of fulminating nausea, vomiting, and diarrhea. Intense fluid and electrolyte and hyperalimentation therapy may initially stabilize these patients. They later experience bone marrow aplasia and pancytopenia that is generally fatal. If CNS symptoms appear early, the patient has received a very large dose of radiation. In mass casualty situations, these patients should be triaged into the "impending" or "expectant" death category and provided comfort care.

Consultative Resources

For questions about radiation exposure and injuries, the U.S. Department of Energy can be contacted 24 hours a day at the Radiation Emergency Assistance Center/Training Site (REAC/TS) in Oak Ridge, Tennessee (telephone, 865-576-1005; interactive website, http://www.orau.gov/reacts). For information about the training of physicians, REAC/TS can be contacted at 865-576-3131. The *Medical Management of Radiological Casualties Handbook* is available online at http://www.afrri.usuhs.mil. The Chemical/Biological Hotline of the National Response Center is 800-424-8802.

KEY CONCEPTS

- Contaminated patients are "radioactive"; irradiated patients are not.
- No danger to medical personnel from contaminated patients should exist if proper precautions and decontamination procedures are carried out.
- Decontamination should not delay or impede the stabilization of the patient in radiation emergencies.
- Careful evaluation of initial symptoms and signs is the most reliable indicator of the radiation dose received and the patient's prognosis.
- Most therapy is supportive and symptomatic except for exposures involving the ingestion or inhalation of radioactive material, when specific therapy with blocking or chelating agents may be indicated.
- Detonation of a "dirty bomb" would cause psychological terror and little or no radiation injuries.
- Formal consultation is available 24 hours a day and should be obtained when any patient with radiation injuries is evaluated.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 145 General Approach to the Poisoned Patient

Ken Kulig and Louis J. Ling

PERSPECTIVE

Most poisoned patients seen in the emergency department are adults with acute oral drug overdoses. Other common clinical scenarios include accidental poisoning in children; drug abuse through smoking, snorting, or intravenous routes; chronic poisoning, usually from environmental, industrial, and agricultural chemical exposure; medication reactions or interactions; and envenomation. Management requires both a general approach and specific actions directed at the particular toxin or toxins involved, as outlined in the various chapters in this section. Clinical studies have modified the management of poisoned patients, such as the use of gastric decontamination, but much of the toxicology literature, especially with unusual poisonings, remains case based. Regional poison centers and medical toxicologists have a concentrated experience in managing poisoned patients and can be called upon for advice and assistance, when necessary.

INITIAL APPROACH TO THE POISONED PATIENT

With rare exception, the priorities of care for a poisoned patient are identical to those for all patients coming to the emergency department. Patients who are contaminated with an agent that might injure health care personnel require decontamination before treatment to avoid disabling the hospital staff or the entire health care facility. Except for specific lifesaving antidotes against certain toxins, most poisoned patients require only supportive therapy for recovery. The initial workup should determine whether a specific patient has been exposed to an agent for which an antidote (or other specific treatment) exists.[1] A thorough poisoning history and toxicologic physical examination are followed by the selective use of laboratory tests.

After initial stabilization of a critically ill patient, specific antidote therapy is administered while a detailed history and physical examination are performed. Hypoglycemia must always be considered in a patient with altered mental status or seizures and should be evaluated by bedside glucose testing rather than empiric administration of hypertonic glucose solution.[2] *Naloxone* can be given to patients with respiratory depression while preparations are made to secure the airway because a positive response may obviate the need for intubation. *Flumazenil* is not indicated in an undifferentiated overdose patient, and its use should be limited to confirmed acute benzodiazepine overdose in a patient known to not be a regular benzodiazepine user (e.g., an adolescent who impulsively ingests a parent's benzodiazepine). Indiscriminate use may force a chronic benzodiazepine user into severe benzodiazepine withdrawal. Likewise, the patient may have ingested tricyclic antidepressants or other drugs likely to cause seizures. In either case, the use of flumazenil can carry a substantial risk of seizures. Patients with benzodiazepine overdose respond well to supportive care. *Thiamine* should be administered when dextrose is given to nutritionally compromised, alcoholic patients with altered mental status (100 mg in the maintenance intravenous line is sufficient and safe).[3]

A complete *overdose history* is required, particularly when the ingested agent is unknown or the patient is suicidal (Box 145-1). Valuable clues often come from unexpected sources, such as the patient's previous medical records, the pharmacy where prescriptions were filled, or the prescribing physician as listed on the patient's prescription bottles. Whenever possible, field personnel should bring the patient's medications to the hospital with them. If the ingested agent is a hazardous chemical (e.g., pesticide) that might endanger hospital personnel, it should be brought to the hospital in an airtight container or secured at the scene. Precise product identification information must be ascertained so that a hazardous materials reference system can be consulted. When it is suspected that the contents of the container are not the original product, the substance should be checked against the product label. It is easy to confuse the different types of chemical agents with agents with similar names found in many homes, and some may have specific properties that affect treatment. In rare cases, overdose patients may deliberately attempt to deceive caregivers by hiding the ingested agents.

Vital signs, including pulse oximetry, are important in the diagnosis of poisoning and should be measured accurately and repeated as indicated. At least one measurement of temperature should be included. Respirations should be counted, not estimated. A cardiac monitor or 12-lead electrocardiogram should be evaluated for QRS and QT intervals, morphology, and rhythm. The physical examination in a comatose patient should ensure that concomitant treatable conditions (e.g., intracranial hemorrhage and central nervous system [CNS] infection) are not missed. Focal neurologic findings could be possible indicators of intracranial catastrophe or severe head trauma.

The pupillary examination may give misleading information. Some opioid agonists, especially propoxyphene and pentazocine, may not produce the characteristic miosis of opioid

BOX 145-1 OBTAINING AN OVERDOSE HISTORY

- Obtain all prescription bottles and other containers when possible. Perform a pill count. Be sure that the bottles contain the medications listed. Identify any unknown tablets.
- Contact the prescribing physician(s) or the pharmacy as listed on the bottles to determine previous overdoses or other medications that the patient may have available. Identify underlying medical and psychiatric disorders and medication allergies. Review past medical records.
- Talk to the patient's family and friends in the emergency department. If necessary, call the patient's home to ask questions of others. The persons providing the important elements of the history should be identified in the chart.
- Search the patient's belongings for drugs or drug paraphernalia. A single pill hidden in a pocket, for example, may provide *the* most important clue to the diagnosis.
- Have family members (or the police) search the patient's home, including the medicine cabinet, clothes drawers, closets, and garage: such searches may also provide clues that make the diagnosis. This has the added benefit of involving the family in the patient's care.
- Always look for track marks on the patient. Consider body packing or body stuffing.

intoxication. When multiple drugs are ingested, the expected pupillary findings related to any particular agent may be modified or absent.

Physical stigmata of intravenous drug use (track marks) should be sought in both usual (e.g., antecubital fossa) and unusual (e.g., under the tongue and top of the feet) locations. A critical condition of unknown cause may be a result of "body packing" or "body stuffing," complicated by rupture of packets of cocaine, heroin, or amphetamines (see Chapter 152). Rectal, vaginal, and radiographic examination of the abdomen should be performed in these circumstances.

Other important physical findings are evidence of aspiration or noncardiogenic pulmonary edema on chest auscultation. Bowel sounds may be increased or decreased if agents affecting the cholinergic nervous system have been ingested. A rectal examination to detect melena or hematochezia may also provide evidence of suicidal ingestion of anticoagulant medication.

Unusual odors of the patient's breath, skin, clothing, vomitus, or nasogastric aspirate may also provide useful diagnostic clues (Table 145-1).[4] The absence of such odors, however, should not be taken as evidence that the agents listed are not present.

Table 145-1 Odors in Overdose History

ODOR	POSSIBLE INTOXICANT
Bitter almonds	Cyanide
Carrots	Water hemlock (cicutoxin)
Fishy	Zinc or aluminum phosphide
Fruity	Ethanol, acetone, isopropyl alcohol, chlorinated hydrocarbons (e.g., chloroform)
Garlic	Arsenic, dimethyl sulfoxide (DMSO), organophosphates, yellow phosphorus, selenium, tellurium
Glue	Toluene, other solvents
Pears	Chloral hydrate, paraldehyde
Rotten eggs	Disulfiram, hydrogen sulfide, *N*-acetylcysteine, dimercaptosuccinic acid (DMSA)
Shoe polish	Nitrobenzene
Wintergreen	Methyl salicylate

TOXIC SYNDROMES AND ANTIDOTES

The term *toxidrome* refers to a syndrome or constellation of physical findings that can be attributed to a specific class of toxins and can provide important clues to narrow the differential diagnosis.[1] The general rules outlined here have many exceptions, and polydrug overdoses may result in overlapping and confusing mixed syndromes. Nevertheless, this approach may confirm the history, provide the clinician with a starting point for management, and suggest useful laboratory tests. The most common toxidromes are the anticholinergic syndrome, sympathomimetic syndrome, opioid/sedative/ethanol syndrome, cholinergic syndrome, and serotonin syndrome (Table 145-2).

The *anticholinergic syndrome* occurs frequently because many common medications and plants have anticholinergic properties. Anticholinergic CNS poisoning causes mild temperature elevation and acute delirium with mumbling speech and typical "picking movements" of the fingers. Suppression of cholinergic inhibition of the heart rate leads to tachycardia. Inhibition of the secretory functions of the integument causes dry mouth and skin, and the face is typically flushed. Unopposed sympathetic drive of the ciliary apparatus causes wide papillary dilation. Most patients recover with supportive therapy, but the delirium may last a day or more. *Physostigmine* may be a useful antidote in carefully selected patients and quickly resolves the delirium. It should not be used with a possible cyclic antidepressant overdose where it is associated with asystole.

The *sympathomimetic syndrome* is usually seen after acute or chronic abuse of cocaine, amphetamines, or decongestants (e.g., phenylpropanolamine). Patients may be delusional; amphetamine, in particular, may cause complicated, intricate, and paranoid delusions. Seizures may occur, and the postictal state can contribute to the altered mental status. Blood pressure is usually elevated, the pulse is rapid (except with pure alpha-adrenergic agonists, which can cause reflex bradycardia), the pupils are dilated, and piloerection may be seen. In massive overdoses of sympathomimetic agents, cardiovascular collapse can occur with the development of shock and wide-complex dysrhythmias. This clinical picture can mimic that of overdose of cardioactive drugs or cyclic antidepressants. In contrast to the diaphoresis seen with anticholinergic syndrome, the skin in sympathomimetic syndrome is dry.

An extreme presentation of sympathomimetic excess can be excited delirium (Box 145-2). In this state, patients are agitated, hyperthermic, violent, and possess "superhuman strength." Frequently, many security personnel are required to control these individuals. These individuals may have a severe metabolic acidosis and hyperkalemia, which can cause sudden cardiovascular collapse. It is critical to sedate these patients and control hyperthermia aggressively while treating their acidosis and hyperkalemia simultaneously.

All sedative/hypnotic agents, when taken in sufficient dosage, cause general anesthesia with a complete loss of awareness and reflex activity. The CNS depressant (opioid/sedative/ethanol) syndrome is the most common toxic syn-

Table 145-2 Common Toxic Syndromes (Toxidromes)

Anticholinergic	
Common signs	Delirium with mumbling speech, tachycardia, dry flushed skin, dilated pupils, myoclonus, slightly elevated temperature, urinary retention, decreased bowel sounds. Seizures and dysrhythmias may occur in severe cases.
Common causes	Antihistamines, antiparkinsonians, atropine, scopolamine, amantadine, antipsychotics, antidepressants, antispasmodics, mydriatics, muscle relaxants, many plants (e.g., jimson weed, *Amanita muscaria*)
Sympathomimetic	
Common signs	Delusions, paranoia, tachycardia (or bradycardia with pure alpha-agonists), hypertension, hyperpyrexia, diaphoresis, piloerection, mydriasis, hyper-reflexia. Seizures, hypotension, and dysrhythmias may occur in severe cases.
Common causes	Cocaine, amphetamine, methamphetamine and its derivatives, over-the-counter decongestants (phenylpropanolamine, ephedrine, pseudoephedrine). In caffeine and theophylline overdoses, similar findings, except for the organic psychiatric signs, result from catecholamine release.
Opioid/Sedative/Ethanol	
Common signs	Coma, respiratory depression, miosis, hypotension, bradycardia, hypothermia, pulmonary edema, decreased bowel sounds, hyporeflexia, needle marks. Seizures may occur after overdoses of some narcotics (e.g., propoxyphene).
Common causes	Narcotics, barbiturates, benzodiazepines, ethchlorvynol, glutethimide, methyprylon, methaqualone, meprobamate, ethanol, clonidine, guanabenz
Cholinergic	
Common signs	Confusion, central nervous system depression, weakness, salivation, lacrimation, urinary/fecal incontinence, gastrointestinal cramping, emesis, diaphoresis, muscle fasciculations, pulmonary edema, miosis, bradycardia/tachycardia, seizures
Common causes	Organophosphate and carbamate insecticides, physostigmine, edrophonium, some mushrooms

Modified from Kulig K: Initial management of ingestions of toxic substances, N Engl J Med 326:1677, 1992.

BOX 145-2 TOXINS CAUSING DELIRIUM

Anticholinergics
Cocaine
Lithium
MAOIs
Mushrooms with muscinol/ibotenic acid
Phencyclidine
Salicylates
Sedative withdrawal
Solvents
Steroids
Sympathomimetics (cocaine, amphetamines)

MAOIs, monoamine oxidase inhibitors.

drome seen in the emergency department, and a depressed sensorium is its hallmark. Mixing agents in this class (e.g., ethanol and benzodiazepines) is common. As the drugs are absorbed at higher doses, the patient becomes increasingly obtunded, the deep tendon reflexes diminish, and, finally, the vital signs deteriorate as medullary drive of respiration and cardiovascular function is attenuated.

Respiratory depression is particularly pronounced with opioid overdose, and the respiratory rate is often diminished before decreases in blood pressure or pulse occur. The diagnosis of opioid overdose is confirmed by the use of naloxone (Narcan) or nalmefene (Revex) in adequate doses.[2,5] *Naloxone* has an elimination half-life of 1.1 hours, whereas that of nalmefene is 10.8 hours. *Nalmefene* is especially useful when the offending opioid has a very long elimination half-life (e.g., methadone, with a half-life of 15–40 hours). Close observation, investigation of alternative causes of depressed mental status when suggested by the clinical course, and airway intervention when indicated are the keys to successful management. Comatose patients often present without a history and need to be managed aggressively, securing the airway when needed. These patients may need basic labs and head CT if their presentation or course is suspicious for stroke, infection, or head trauma while considering a drug overdose alone or in combination with one of these medical conditions. A serum ethanol level that is not commensurate with the level of CNS depression raises suspicion of intracranial injury, hemorrhage, or infection.

The *cholinergic syndrome* is uncommon but important to recognize because lifesaving treatment is available. Cholinergic syndrome causes the patient to be "wet," as opposed to the anticholinergic syndrome, which causes the patient to be "dry." The wetness is manifest by profuse sweating and excessive activity of virtually the entire exocrine system, often accompanied by vomiting, diarrhea, and urinary incontinence. The mnemonic SLUDGE is used to recall the specific elements of the syndrome: *s*alivation, *l*acrimation, *u*rination, *d*efecation, *g*astrointestinal cramping, and *e*mesis. The CNS (e.g., confusion, coma, and seizures) and the skeletal muscles (e.g., weakness and fasciculations) can also be involved. The pupils are often miotic. Cholinergic syndrome is most frequently caused by organophosphate or carbamate pesticide exposure, which may be through unsuspected dermal contamination. Anticholinergic agents are also the foundation of "nerve agents" such as sarin, which was used in the Tokyo subway attack. Recognition of the syndrome led to the use of atropine and cholinesterase regenerators, with a subsequent good outcome in many patients.[6]

Serotonin syndrome ensues when there is a drug interaction involving the selective serotonin reuptake inhibitors (SSRIs) or an overdose of an SSRI.[7] Fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil), fluvoxamine (Luvox), and citalopram (Celexa) are commonly used SSRIs. Other drugs that are serotonin reuptake inhibitors (SRIs) also inhibit the reuptake of other neurotransmitters and are therefore not specific. These drugs include venlafaxine (Effexor), nefazodone (Serzone), and mirtazapine (Remeron). Drug interactions between many drugs can cause the serotonin syndrome described in Chapter 159. These drugs include the SSRIs,

SRIs, monoamine oxidase inhibitors (MAOIs), tryptophan, sympathomimetics, tricyclic and other antidepressants, meperidine, dextromethorphan, and lithium. Because of the long-lasting effects of the SSRIs, the syndrome can occur when one of the active agents is ingested even weeks after use of an SSRI has been discontinued.

Serotonin syndrome is characterized by altered mental status, fever, agitation, tremor, myoclonus, hyper-reflexia, ataxia, incoordination, diaphoresis, shivering, and sometimes diarrhea.[7] The diagnosis relies on the drug history, and it is difficult to distinguish serotonin syndrome from an overdose of cocaine, lithium, or MAOIs; the neuroleptic malignant syndrome; or thyroid storm. Patients may deteriorate slowly and become critically ill after an apparently benign manifestation.

As possible toxidromes are investigated, the use of specific antidotes should be considered (Table 145-3).

TOXICOLOGY LABORATORY

A toxicology screen (usually urine, sometimes blood and urine, and occasionally including gastric contents) only rarely results in identification of the ingested agent for three major reasons. First, the laboratory does not attempt to screen for many substances, even commonly ingested agents that are capable of causing critical illness (Box 145-3).[8]

Second, the urine screen is often performed soon after the ingestion, when the drug concentration is too low for a positive result. Even the drug responsible for life-threatening symptoms (e.g., tricyclic antidepressant) may be negative on the urine screen soon after ingestion. Other drugs, such as γ-hydroxybutyrate, are present relatively briefly in blood and urine and may therefore be negative in samples collected even on the same day.

Third, drugs found on screening may not be those responsible for the initial symptoms, especially if the drugs are not quantified (e.g., benzodiazepines and cocaine parent compound). In such cases, a positive screen may not relate to the patient's current findings and symptoms. Drugs with a large volume of distribution or high fat solubility may be detected in urine for a long time after the last dose. Cocaine metabolites may be detected for days and marijuana for weeks after the last exposure. Proper interpretation of urine screens requires consideration of the patient's current clinical condition. In addition, the results of toxicology screens are not usually available until many hours after most of the important treatment decisions are made. Screening results rarely change the clinical management of patients.[8] Toxicology screens are often very expensive, and their use is not warranted in most routine drug overdoses. The full toxicology screen is most useful in patients who (1) present with their first psychotic episode or (2) are critically ill for an unknown reason when identification of an otherwise unsuspected toxin may change management.

Alternatives to a full toxicology screen include (1) obtaining discrete drug levels (e.g., acetaminophen, which should be considered in almost all intentional ingestions), (2) a qualitative urine screen for drugs of abuse, or (3) no toxicology tests.[8,9] Quantitative measurements of suspected drugs may be helpful. In the agitated or seizing patient, elevated salicylate, theophylline, or lithium levels would significantly alter the management. Several commercial urine testing kits have a rapid turnaround time, primarily for drugs of abuse. Electrolyte levels help identify metabolic acidosis by the carbon dioxide content ("bicarbonate level"), which should be repeated if low to ensure that the acidosis is resolving. A persistent, unexplained metabolic acidosis should prompt urine examination for oxalate crystals (suggestive of ethylene glycol poisoning), a serum salicylate level, and methanol and ethylene glycol levels. A normal arterial blood gas or electrolyte measurement does not rule out such ingestion because metabolic acidosis is delayed and does not appear until after metabolism of the acids from ethylene glycol/methanol or until after erratic and slow absorption of salicylate. Arterial blood gas measurement is rarely helpful but may confirm when pulse oximetry is misleadingly low with carboxyhemoglobin and methemoglobinemia.

Rhabdomyolysis should be diagnosed by obtaining a serum CPK level when there is severe agitation or hyperthermia, or if the patient is thought to have been unresponsive for a prolonged period of time (i.e., by history of presence or pressure sores). A urinary dipstick for blood (myoglobin) and a serum creatine kinase should be checked. Rhabdomyolysis and its treatment are discussed in Chapter 125. Noncardiogenic pulmonary edema on a chest radiograph suggests opioid or salicylate overdose. Selective abdominal radiographs can detect smuggled packets. Some drugs are radiopaque (e.g., heavy

BOX 145-3 DRUGS, CHEMICALS, AND GROUPS *NOT DETECTED* BY A COMPREHENSIVE TOXICOLOGY SCREEN

Ammonia
Anesthetic gases
Antibiotics
Anticoagulants
Beta-blockers
Borates
Bromides
Caustics/corrosives
Colchicine
Cyanide
Digitalis glycosides
Disulfiram
Ergot alkuloids
Ethylene glycol
Fentanyl and its derivatives
Fluorides
H_2 antagonists
Hallucinogens (e.g., LSD)
Herbicides
Household products
Hypoglycemics
Insect repellents
Isoniazid
Laxatives
Lithium
Metals
Monoamine oxidase inhibitors
Most antihypertensives
Most cardiac medications
Muscle relaxants
Mushrooms
Newer antidepressants (e.g., fluoxetine, sertraline, paroxetine, bupropion, buspirone)
Nitrates/nitrites
NSAIDs
Paraquat
Pesticides
Phenol
Plants
Solvents
Thyroid hormone
Vitamins

NSAIDs, nonsteroidal anti-inflammatory drugs.

Table 145-3 Antidotes Used in the Emergency Department

TOXIN USED FOR	ANTIDOTE	DOSE AND COMMENTS
Acetaminophen	*N*-acetylcysteine	140 mg/kg PO, then 70 mg/kg q4h for up to 17 doses or 150 mg/kg IV load over 1 hr with 50 mg/kg over 4 hr followed by 100 mg/kg over 16 hr
Anticholinergics	Physostigmine	1–2 mg IV in adults, 0.5 mg in children over 2 min for anticholinergic delirium, seizures, or dysrhythmias
Arsenic, lead, and mercury	BAL	3–5 mg/kg IM only
	D-Penicillamine	20–40 mg/kg/day; 500 mg tid in adults; may cross-react with penicillin in allergic patients
Benzodiazepines	Flumazenil	0.2 mg, then 0.3 mg, then 0.5 mg, up to 5 mg; not to be used if patient has signs of TCA toxicity; not approved for use in children, but probably safe
Black widow spider bite	*Latrodectus* antivenin	One vial by slow IV infusion is usually curative; may cause anaphylaxis
Beta-blockers	Glucagon	5–10 mg in adults, then infusion of same dose per hour
	Insulin and glucose	10 U insulin with dextrose 25 g initially, then 0.1–1.0 U/kg/hr, 10–30 g/hr
Calcium channel blockers	Calcium	1 g calcium chloride IV in adults, 20–30 mg/kg/dose in children, over a few minutes with continuous monitoring. Repeat as needed
	Glucagon	5–10 mg in adults, then infusion of same dose per hour
	Insulin and glucose	10 U insulin with dextrose 25 g initially, then 0.1–1.0 U/kg/hr with 10–30 g/hr
Cyanide	Hydroxycobalamin	5 mg in 100 ml of NS over 15 min. Repeat if necessary
Cyanide, hydrogen sulfide	Sodium thiosulfate	50 mL of 25% (12.5 g; 1 ampule) in adults; 1.65 mL/kg IV in children
	Sodium nitrate	10 mL of 3% (300 mg; 1 ampule) in adults; 0.33 mL/kg slowly IV in children
	Hydroxycobalamin	50 mg in 50 mL given over 15 min
Digitalis glycosides	Digoxin-specific Fab	10–20 vials if patient in ventricular fibrillation; otherwise dose fragments based on serum digoxin concentration or amount ingested
Ethylene glycol	Fomepizole	15 mg/kg × 1, then 10 mg/kg q12h × 4, until ethylene glycol < 20 mg/dL. Adjust dose during dialysis
	Pyridoxine	100 mg IV daily
	Thiamine	100 mg IV
Hydrofluoric acid	Calcium gluconate	3.5 g in 5 oz of KY jelly topical; apply liberally to affected skin
Iron	Deferoxamine	15 mg/kg/hr IV; higher doses reported to be safe
Isoniazid, hydrazine, and monomethylhydrazine	Pyridoxine	5 g in adults, 1 g in children, if ingested dose unknown; antidote may cause neuropathy in very large doses
Lead	DMSA (succimer)	Reported useful for arsenic and lead as well; one 100-mg capsule per 10-kg body weight tid for 1 wk, then bid, with chelation breaks
	EDTA	75 mg/kg/day by continuous infusion; watch for nephrotoxicity, best done in hospital
Methanol	Folate or leucovorin	50 mg IV q4h in adults while patients have serious toxicity
	Ethanol	Loading dose, 10 mL/kg of 10%; maintenance dose, 0.15 mL/kg/hr of 10%; double rate during dialysis
	Fomepizole	15 mg/kg × 1, then 10 mg/kg q12h × 4, until methanol < 20 mg/dL. Adjust dose during dialysis
Methemoglobin-forming agents	Methylene blue	1–2 mg/kg IV, one 10-mL dose of 10% solution (100 mg) is typical for an adult without anemia
Opioids	Nalmefene	2 mg; much longer half-life than naloxone
	Naloxone	2 mg; less to avoid narcotic withdrawal, more if inadequate response; same dose in children
Organophosphates and carbamates	Atropine	Test dose, 1–2 mg IV in adults, 0.03 mg/kg in children; titrate to drying of pulmonary secretions
	Protopam	Loading dose, 1–2 g IV in adults, 25–50 mg/kg in children; adult maintenance, 500 mg/hr or 1–2 g q4–6h
Rattlesnake bite	*CroFab* antivenin	Five vials minimum dose by infusion in normal saline; increases in rate dependent on patient tolerance; may cause anaphylaxis
Serotonin syndrome	Cyproheptadine	4 mg PO as needed; no parenteral form available; antidote may cause anticholinergic effects
Sulfonureas	Octreotide	50 µg SC q12h, 5–10 µg/kg/24 hr IV
Tricyclic antidepressants	Bicarbonate	44–88 mEq in adults, 1–2 mEq/kg in children; best used by IV push and not by slow infusion
Valproic acid	Carnitine	100 mg/kg IV or PO loading dose with 25 mg/kg q6h

BAL, British anti-Lewisite; DMSA, dimercaptosuccinic acid; EDTA, ethylenediaminetetraacetic acid; TCA, tricyclic antidepressant.

metals, phenothiazines, potassium, calcium, and chlorinated hydrocarbons such as chloral hydrate), but radiography is rarely helpful in the evaluation of a poisoned patient except to monitor the decontamination of iron, lead, or body packets.[10]

DECONTAMINATION

Gastric decontamination rarely affects the clinical outcome in the undifferentiated poisoned patient and should not be undertaken routinely.[11,12] Children with accidental ingestion rarely consume enough drug to cause symptoms, and the fatality rate for those cases is less than 0.0025%.[13] Decontamination with activated charcoal (AC) has not been proven to improve outcome either in the undifferentiated overdose patient or in any specific poisoning. It should be considered only in the small number of cases in which it is early enough (<1 hour after ingestion) to make a difference or for medications of a type and in quantities that may be truly toxic beyond the requirement for supportive care. These medications include beta-blockers, calcium channel blockers, and cyclic antidepressants. Because gastric decontamination has not been shown to be of benefit and carries some risk, particularly if a nasogastric tube is required, it should be used selectively and with caution, if at all.[11,12,14-16]

If charcoal is used, 50 g of an oral slurry of AC is usually sufficient. If the patient is obtunded or uncooperative and the benefits of AC administration are thought to outweigh the risks (principally aspiration), intubation should be considered and the AC can be administered through a nasogastric tube. A cathartic, such as sorbitol, was formerly recommended to speed AC transit through the gut, but cathartics have never been shown to be of benefit and, in general, should be avoided. Repeated doses of sorbitol can cause dehydration. Agents that do not adsorb to charcoal include ions (e.g., acids and alkalies, lithium, borates, and bromides), hydrocarbons, metals (e.g., iron), and ethanol, but adsorption to charcoal does not equate to lesser toxicity or improved outcome.

Whole-bowel irrigation with a polyethylene glycol solution, although of no proven outcome benefit, rarely may be used in certain cases of severe, recent ingestion of lithium or metals such as iron or lead or in patients with ingestion of sustained-release formulations of highly toxic drugs. It has also been used to aid in the evacuation of drug packets from body packers.[17] Whole-bowel irrigation is unpleasant for both patient and staff, and it should be considered only after consultation with a toxicologist. It is typically done by placing a nasogastric tube and continuously infusing a bowel preparation solution, such as Go-Lytely, beginning at 1 or 2 L/hour and continued until the rectal effluents are clear.

Gastric lavage is rarely, if ever, indicated and should be considered only when a patient is seen within a few minutes (<1 hour) after the ingestion of a highly toxic substance (e.g., calcium channel blocker and cyclic antidepressant). Gastric lavage has not been shown to improve the clinical course or outcome of undifferentiated poisoned patients, although it has not been studied in selected higher risk populations.[18] In the rare circumstances in which gastric lavage is performed, a large (30-F or greater) orogastric tube is used, and specially designed lavage systems with large-bore tubes are available for this purpose. Syrup of ipecac has not been shown to change the clinical outcome of poisonings and is no longer used in emergency departments and rarely in out-of-hospital settings. Its use has been restricted because of its abuse by patients with bulimia.

Exposure of the eye to caustic chemicals and irritants requires immediate irrigation with large amounts of water or readily available fluid, as outlined in Chapter 151. It is more important to begin the irrigation immediately, preferably before transfer to the emergency department. Exposure to a gas does not require decontamination because the patient and rescuers are not at risk once the patient is removed from the toxic environment. The exception is when the patient's skin or clothing is contaminated with a liquid that is evaporating. The most important intervention to limit dermal exposure is to remove all clothing as soon as possible, ideally at the scene. Skin should be irrigated with warm water and with attention to skin folds and other areas that might be missed. This includes the axilla, beneath nails, behind the knees, the genitalia, and in the scalp. For hydrocarbons or solvents, soap can be added. The skin should not be abraded with overly aggressive scrubbing, which could increase skin absorption. Ideally, skin decontamination occurs as soon as possible after exposure, at an out-of-hospital site before transport.

DISPOSITION AND CONSULTATION

The decision to admit a patient is not difficult when the patient manifests serious toxicity. When the patient is minimally symptomatic but has ingested a potentially dangerous substance, the decision is more difficult. Identification of an agent that causes a particular risk for the patient, especially cardiovascular instability, seizures, or respiratory depression, generally mandates admission to the hospital or to an observation unit in the emergency department. A 6-hour period of observation for a minimally symptomatic patient is usually sufficient, except for some extended-release preparations. Patients with cardiac dysrhythmia, conduction disturbance, altered mental status requiring intubation, or the need for frequently titrated agents (e.g., pressors) should be admitted to the intensive care unit or a monitored inpatient unit. If the patient is acutely suicidal, a sitter or secure environment may be required.

Regional poison centers use a single nationwide toll-free number, 1-800-222-1222, and can provide specific, current advice, especially for more esoteric or unfamiliar poisons. Consultation with a medical toxicologist is particularly helpful when an uncommon agent has been ingested, the patient is not following the anticipated clinical course, or specific interventions such as administration of antibody therapy or dialysis are contemplated.

KEY CONCEPTS

- A thorough history from many sources is the key to toxicologic diagnosis.
- Common toxidromes should guide judicious use of antidotes.
- Minimally symptomatic patients do not benefit from toxicology screening or extensive laboratory investigation.
- Good supportive care is the key to management.
- Activated charcoal is rarely indicated in overdose, and other methods of gut decontamination (gastric lavage and whole-bowel irrigation) are virtually never helpful. Activated charcoal may decrease absorption of many drugs, but it has not been shown to improve outcome, and its use should be carefully weighed against potential complications.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 146 Acetaminophen

Robert G. Hendrickson and Nathanael J. McKeown

PERSPECTIVE

Acetaminophen is one of the most commonly used antipyretic and analgesic agents throughout the world. Acetaminophen may be found as an isolated product or in combination medications for the treatment of cold symptoms, pain, and headache. Given its widespread use and availability, acetaminophen toxicity is a concern in all intentional ingestions as well as in cases of therapeutic misadventures and drug abuse. Acetaminophen toxicity is one of the leading causes of hospital admission, antidotal use, and patient fatalities among ingested substances in the United States.[1]

Through significant study and experience, established protocols for the assessment and management of acute acetaminophen ingestion exist. Despite this, controversy continues to exist, and with new formulations in development, the management of acetaminophen ingestion promises to continue to evolve.

PRINCIPLES OF DISEASE

Acetaminophen is absorbed rapidly, with peak plasma concentrations generally occurring within 1 hour and complete absorption within 4 hours. Once absorbed, acetaminophen inhibits prostaglandin E_2 (PGE_2) synthesis, leading to antipyresis and analgesia. Inhibition of PGE_2 synthesis is either by direct COX-2 inhibition or inhibition of membrane-associated prostaglandin synthase.[2-4]

After therapeutic ingestion, acetaminophen is primarily metabolized by conjugation with glucuronide (40–67%) and sulfate (20–46%) into nontoxic metabolites that are excreted in the urine[5] (Fig. 146-1). A small percentage (<5%) is oxidized by cytochrome P_{450} 2E1 (CYP2E1) (and to a lesser extent 1A4 and 3A4) to a highly cytotoxic metabolic intermediary, *N*-acetyl-*p*-benzoquinonimine (NAPQI).[6-8] In therapeutic doses, NAPQI is short-lived, combining rapidly with glutathione and other thiol-containing compounds to form nontoxic metabolites that are excreted in the urine. With typical therapeutic acetaminophen dosing, glutathione stores and the ability to regenerate glutathione easily keep up with NAPQI production.

After large ingestions or repeated supratherapeutic ingestions, the amount of NAPQI produced begins to outstrip glutathione stores and the liver's ability to regenerate glutathione, leading to unbound NAPQI. The highly reactive electrophile NAPQI covalently binds to critical cell proteins in the liver, which initiates a cascade of events that lead to hepatic cellular death.[9] Renal injury may also occur with or without liver injury[10] and may be mediated by renal CYP enzymes[11,12] or activation of prostaglandin synthase.[13,14]

Acetaminophen-induced liver damage initially occurs in hepatic zone III (centrilobular) because oxidative metabolism is concentrated in this area. With severe toxicity, necrosis of the entire liver parenchyma may occur. The clinical effects of severe acetaminophen toxicity are the result of severe fulminant liver failure rather than a direct acetaminophen effect.[15] These effects include multiorgan failure, systemic inflammatory response syndrome, hypotension, cerebral edema, and death.[16]

The principal therapy for acetaminophen toxicity is *N*-acetylcysteine (NAC), which is effective via two separate mechanisms. Soon after overdose, NAC serves as a glutathione precursor and a sulfur-containing glutathione substitute (see Fig. 146-1), thereby detoxifying NAPQI and avoiding subsequent hepatotoxicity. In addition, NAC may decrease NAPQI formation by enhancing acetaminophen conjugation with sulfate to nontoxic metabolites.[17]

Even after acetaminophen hepatotoxicity is evident, NAC acts as a free-radical scavenger and an antioxidant and alters hepatic microcirculation and oxygen delivery.[18] In patients with acetaminophen-induced hepatic failure, intravenous (IV) NAC has been shown to decrease the rates of cerebral edema, hypotension, and death even when no acetaminophen remains.[16]

CLINICAL FEATURES

Acetaminophen toxicity leads to hepatic injury, which can progress to hepatic failure and renal failure. Early after acute acetaminophen ingestion, patients may be asymptomatic or have mild nonspecific symptoms (e.g., nausea, vomiting, anorexia, malaise, diaphoresis) (Table 146-1).

Liver injury becomes evident after a period of 8 to 36 hours as an elevation in aspartate aminotransferase (AST). Once liver injury has begun, patients may develop right upper quadrant (RUQ) pain or tenderness, vomiting, and jaundice. AST concentrations continue to rise and usually peak in 2 to 4 days, corresponding to maximal liver injury. Alanine aminotransferase (ALT), prothrombin time (PT), and bilirubin typically begin to rise and peak shortly after AST values. In severe toxicity, AST, ALT, and the PT may all be elevated within 24 hours (Fig. 146-2). With maximal liver injury, patients may develop signs and symptoms consistent with fulminant liver

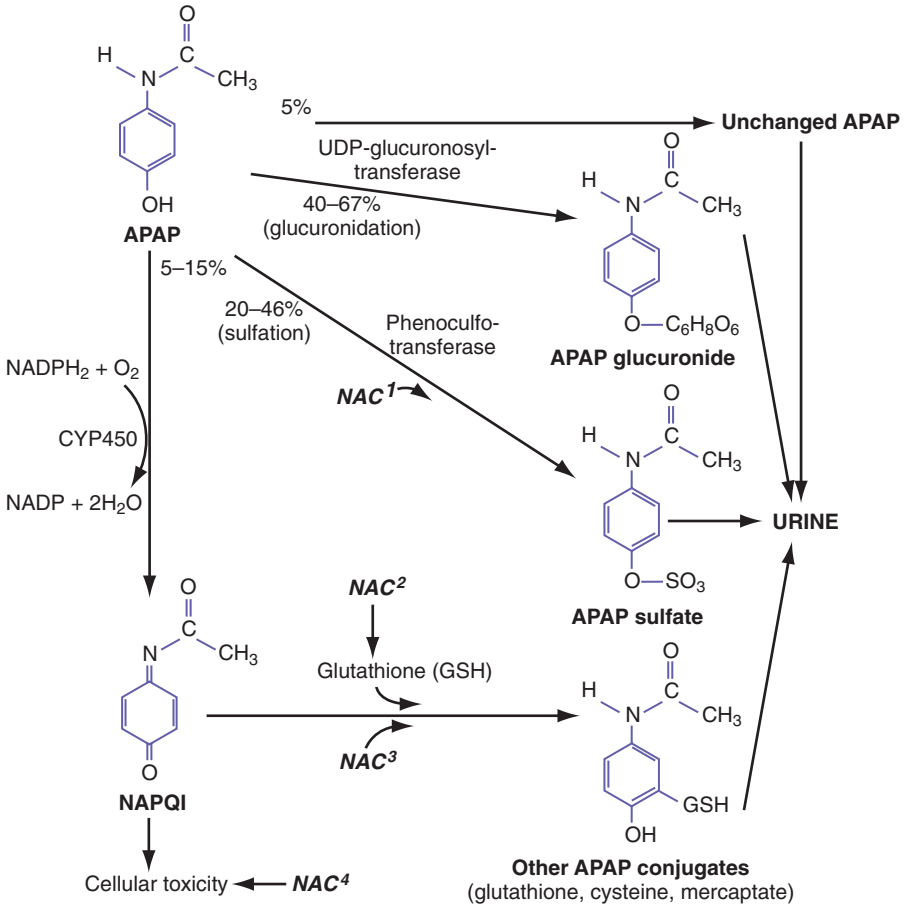


Figure 146-1. Acetaminophen (APAP) metabolism and *N*-acetylcysteine (NAC) mechanisms of action. NAC[1] enhances sulfation; NAC[2] serves as a glutathione (GSH) precursor; NAC[3] is a GSH substitute; NAC[4] may reduce systemic toxicity. NAPQI, *N*-acetyl-*p*-benzoquinonimine. (Modified from Smilkstein MJ: Acetaminophen. In Goldfrank LR, et al (eds): Goldfrank's Toxological Emergencies, 6th ed, Stamford, Conn, Appleton & Lange, 1998, p 547.)

Table 146-1 Time Course and Clinical Stages of Acetaminophen Toxicity

STAGE	TIME COURSE	NAME	SYMPTOMS	SIGNS
1	0–12 (up to 24–36) hr	Preinjury	Nausea, vomiting, anorexia, malaise	Elevated serum acetaminophen concentration
2	8–36 hr	Liver injury	Nausea, vomiting, right upper quadrant abdominal tenderness	Transaminitis (AST begins to rise 8–36 hr after ingestion)
3	2–4 days	Maximum liver injury	Liver failure (encephalopathy, coagulopathy, hemorrhage, acidosis)	Hemorrhage, ARDS, sepsis/SIRS, multiorgan failure, cerebral edema
4	>4 days	Recovery	None	Complete hepatic histologic recovery

ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; SIRS, systemic inflammatory response syndrome.

failure, including metabolic acidosis, coagulopathy, and hepatic encephalopathy. Death may occur from hemorrhage, adult respiratory distress syndrome, sepsis, multiorgan failure, or cerebral edema.[19] The risk of renal injury increases with the severity of hepatic injury, occurring in less than 2% of patients without hepatotoxicity and in 25% of patients with severe hepatotoxicity.[20-22]

If patients recover, transaminases return to baseline levels over a 5- to 7-day period, although complete histologic resolution of liver injury may take months. Once histologic recovery is complete, there are no long-term sequelae to the liver and patients are not at risk for chronic hepatic dysfunction.[23]

DIAGNOSTIC STRATEGIES

The primary goals of patient assessment after acetaminophen exposure are the determination of the patient's risk, diagnostic testing, and treatment with the antidote NAC when appropriate.

Acetaminophen exposures may be classified as acute or chronic, and each type requires different testing and risk assessment. An acute ingestion is generally considered to be a single ingestion, arbitrarily defined to be occurring within a 4-hour period. All other ingestions, including accidental repeated supratherapeutic ingestions and intentional ingestions spread over longer than 4 hours, can be considered to be chronic.

Risk Assessment with Acute Acetaminophen Ingestion

The initial diagnostic strategy of an acute ingestion is well established. The first step is to determine the patient's risk of acute acetaminophen exposure. Patients who report an acute

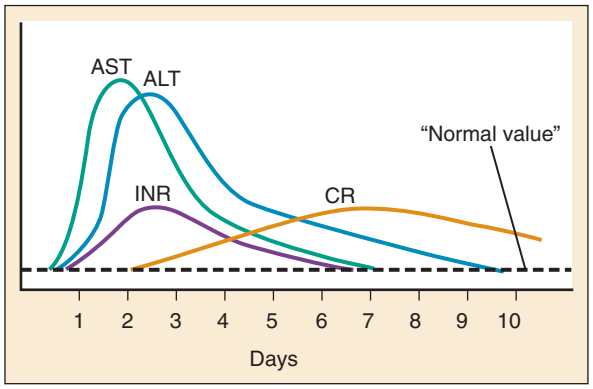


Figure 146-2. Illustration of a typical time course of rise, peak, and fall of laboratory values in patients with acetaminophen-induced hepatic dysfunction who survive. Peaks are not proportional. Not all laboratory abnormalities occur in all patients, and significant individual variation may occur. ALT, alanine transaminase; AST, aspartate transaminase; CR, creatinine; INR, international normalized ratio. (Adapted from Copyright Robert G. Hendrickson, MD.)

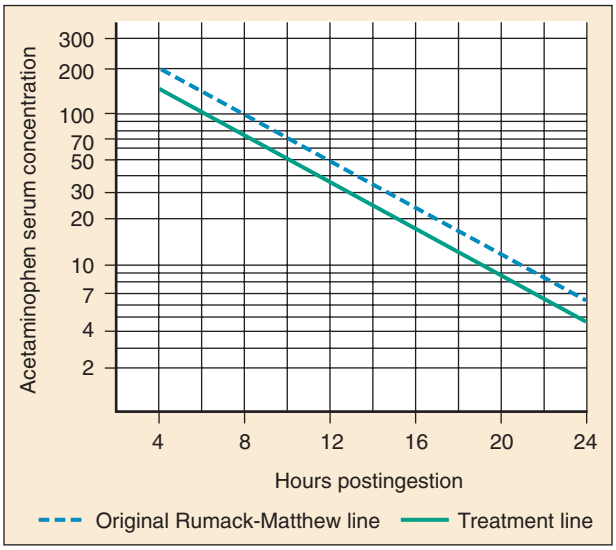


Figure 146-3. Treatment nomogram for acute overdose. The lower treatment line should be used for treatment decisions. (Modified from Rumack BH, Matthew H: Acetaminophen poisoning and toxicity. Pediatrics 55:871, 1975.)

intentional ingestion of acetaminophen require laboratory risk stratification regardless of the reported amount ingested. It is likely that significantly greater than 150 mg/kg in an acute ingestion must be consumed before significant liver toxicity is evident; however, historical factors may not be reliable. A serum acetaminophen concentration may be considered in all intentional overdoses because approximately 1.4 to 8.4% of patients with intentional ingestions who deny acetaminophen ingestion actually have a detectable concentration.[24-26]

Once a suggested exposure to acetaminophen is established, the next step is to establish a time of ingestion. If possible, this information should be corroborated by others. If no accurate time of ingestion can be determined, a worst-case scenario should always be considered (e.g., the last time the patient was seen prior to the ingestion).

Once a patient is determined to be at risk and a time of ingestion established or estimated, the next step is to determine a serum acetaminophen concentration 4 hours postingestion, or as soon as possible after 4 hours. The serum acetaminophen concentration and the time of ingestion determine the need for antidotal therapy by plotting the serum acetaminophen concentration against the time since ingestion on the treatment nomogram (Fig. 146-3), an adaptation of the Rumack-Matthew nomogram.[27] If the serum acetaminophen concentration is on or above the treatment line (that starts at 150 µg/L at 4 hr and decreases to 4.7 µg/L at 24 hr), then antidotal treatment with NAC should be initiated immediately. If the serum acetaminophen concentration is below the treatment line and the worst case scenario has been taken for the time of ingestion, then the patient requires no antidotal therapy.[28-30] Use of the treatment line is a highly sensitive approach and may be used for all acute ingestions.

Measurement of serum acetaminophen concentration prior to 4 hours is typically not necessary. It is possible that a serum acetaminophen concentration less than 10 µg/L between 1 and 4 hours after ingestion may exclude significant ingestion of acetaminophen; however, there are little data on which to base this conclusion. Absorption of acetaminophen may not be complete prior to 4 hours, and any serum acetaminophen concentration greater than 10 µg/L is difficult to interpret. Finally, serum acetaminophen concentrations measured prior to 4 hours cannot be plotted on the treatment nomogram. Fortunately, there is little need to treat patients prior to 6 to 8 hours after ingestion, as patients treated with NAC up to 6 hours after ingestion have no increased risk of hepatotoxicity regardless of their serum acetaminophen concentration.[31] For most patients, the risk of hepatotoxicity does not significantly increase unless NAC is delayed for 8 hours or longer after ingestion.[28,31] This is generally enough time for a serum acetaminophen concentration to be drawn at 4 hours and the laboratory evaluation to be completed. For patients at risk whose serum acetaminophen concentration cannot be obtained prior to 6 to 8 hours after ingestion, a loading dose of NAC should be considered.

Risk Assessment with Chronic Ingestion

If the ingestion is a repeated or chronic exposure, risk assessment is somewhat more complex, and the treatment nomogram cannot be used. The initial steps include determining if the patient is at risk for hepatotoxicity, evaluating the patient by measuring a serum acetaminophen concentration and an AST, and initiating therapy with NAC.

The risk of hepatotoxicity from chronic ingestion of acetaminophen is increased with both: (1) an increasing total dose of acetaminophen, and (2) a longer duration over which it has been ingested in supratherapeutic quantities. With this in mind, laboratory testing for serum acetaminophen concentration and AST should be initiated in any patient who fits the criteria in Table 146-2.[32]

Ingestion of therapeutic amounts of acetaminophen appears to be quite safe.[29,33] However, rare reports of transaminitis and liver injury during therapeutic dosing suggests that some patients may be at increased risk for liver injury, possibly due to genetic variation or to specific risk factors.[34] Patients who chronically ingest isoniazid (INH)[35,36] or ethanol[37-40] may have increased CYP2E1 activity and, therefore, be at higher risk for chronic acetaminophen toxicity. Similarly, patients who have prolonged fasting (e.g., malnourished, AIDS, severe prolonged vomiting)[41] and children with febrile illnesses[42-46] have been suggested to have higher risk. All of these risk factors are controversial and require additional study. Given that we are unable to accurately predict the rare patient at high risk, patients who have symptoms consistent with liver injury (e.g., RUQ pain or tenderness, jaundice) with the intake of

Table 146-2 **Indications for Initiating Testing for Serum Acetaminophen Concentration and AST in Chronic Acetaminophen Ingestions**[32]

Age ≥6 years old;	Ingestion of 10 g/d (or 200 mg/kg/d) [whichever is smaller] over a 24-hr period
or	Ingestion of 6 g/d (or 150 mg/kg/d) [whichever is smaller] over a 48-hr period
or	Symptomatic (e.g., RUQ pain/tenderness, jaundice, vomiting)
Children <6 years old;	Ingestion of 200 mg/kg/d over a 24-hr period
or	Ingestion of 150 mg/kg/d over a 48-hr period
or	Ingestion of 100 mg/kg/d over a 72-hr or longer period
or	Symptomatic (e.g., RUQ pain/tenderness, jaundice, vomiting)

AST, aspartate transaminase; RUQ, right upper quadrant.

acetaminophen merit risk determination regardless of the amount that they reportedly ingest.

Once serum acetaminophen concentration and AST are obtained, further risk assessment is necessary. Conceptually, patients with chronic ingestions may benefit from antidotal therapy if they have evidence of liver injury *or* if they have evidence of acetaminophen excess that may lead to liver injury. With this in mind, patients with chronic supratherapeutic acetaminophen exposure with significant elevations of AST (e.g., ≥50 IU) should be treated with NAC regardless of their serum acetaminophen concentration.[47,48] A higher cutoff for AST (e.g., twice normal, or >120 IU) has been suggested and may be safe, but is unstudied.[49] In patients with an AST that is not elevated (e.g., <50 IU), NAC should be initiated if their serum acetaminophen concentration is higher than expected. After a typical therapeutic dose of acetaminophen, serum acetaminophen concentration peaks below 30 μg/L and is less than 10 μg/L at 4 hours.[50,51]

All patients who do not require antidotal therapy should be educated to return to the emergency department if they develop signs of hepatotoxicity (e.g., RUQ abdominal pain, vomiting, jaundice).

Risk Assessment in Pregnant Women

Fetal acetaminophen toxicity is rare, but adverse outcomes have been reported in all stages of pregnancy.[52] Acetaminophen crosses the placenta and may be present in concentrations in the fetus that are as high as, or higher than, those in the mother.[52] In the early gestational period, acetaminophen toxicity can be associated with fetal death.[52] CYP enzymes appear in the fetus during the second trimester, and activity increases with gestational age, which may put the maturing fetus (e.g., third trimester) or newborn at risk of toxicity.[53]

The risk assessment and diagnostic approach to pregnant women, however, is the same as for nonpregnant women. In acute overdoses, a serum acetaminophen concentration should be drawn and plotted on the treatment nomogram. NAC therapy should be initiated if the serum acetaminophen concentration plots above the treatment line. With chronic exposure, if either the AST is above 50 IU or the serum acetaminophen concentration is above expected, NAC therapy should be initiated.

MANAGEMENT

Treatment of acetaminophen toxicity might sometimes include limiting gastrointestinal (GI) absorption, but the mainstays of management are providing supportive care and initiating NAC therapy when indicated.

Limiting Gastrointestinal Absorption

Gastric emptying by lavage is rarely indicated in cases of isolated acetaminophen overdose because of the very rapid absorption of acetaminophen and the availability of an effective antidote.[32] Early gastric emptying may be considered in cases of recent, life-threatening coingestions (see Chapter 145).

Activated charcoal (AC) effectively binds acetaminophen,[54] but there is no evidence that administration of AC translates into improved clinical outcomes. One small study suggests that, when given early (e.g., <2 hr after ingestion), AC may decrease the risk that a patient requires admission for antidotal therapy,[55] and some evidence exists for AC use more than 4 hours after ingestion.[56] However, methodologic issues limit the strength of these observations. Overall, there is insufficient evidence to support a recommendation for the routine use of AC in cases of acetaminophen poisoning presenting to the emergency department.

In those rare circumstances in which a clinician may want to give both oral (PO) AC and PO NAC simultaneously (e.g., decision to use PO NAC immediately after AC was given), absorption of the NAC is optimized by delaying the NAC for 1 to 2 hours, if possible.[57,58] Overall, though, the fact that NAC is of proven value in treating acetaminophen poisoning, and AC is not, is further argument to avoid using AC in patients with acetaminophen overdose. Both NAC and AC can increase vomiting.

N-Acetylcysteine

When indicated, NAC should be administered as early as possible. Delay of administration of NAC longer than 6 to 8 hours after ingestion increases the risk of hepatotoxicity (Fig. 146-4).[28]

Once the need for NAC is determined, it can be administered PO or IV. Both methods are efficacious in most situations, with advantages and disadvantages for each. All

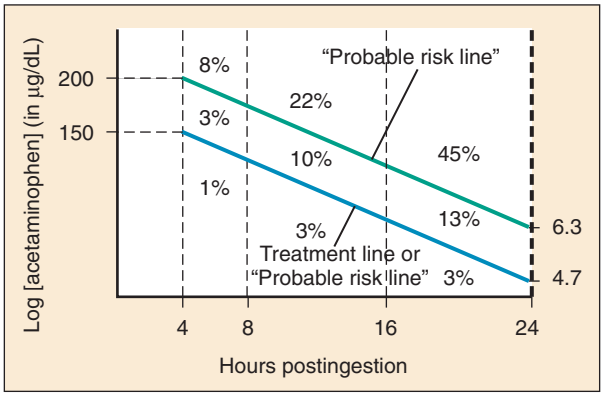


Figure 146-4. Risk of liver injury (aspartate transaminase > 1000 IU) based on initial acetaminophen concentration and time to administration of oral *N*-acetylcysteine. (Adapted from Rumack BH: Acetaminophen hepatotoxicity: The first 35 years. J Toxicol Clin Toxicol 40:3, 2002.)

Table 146-3 Side Effect Profile for NAC Formulations

NAC FORMULATION	COMMON SIDE EFFECTS	SEVERE SIDE EFFECTS
PO NAC	Vomiting (50%)[76]	Very rare
IV NAC	Mild anaphylactoid reactions (e.g., rash, flushing, pruritis, vomiting), 2–18%[61,66-69,77]	Severe anaphylactoid reactions (e.g., hypotension), <1%[63,67-69]

IV, intravenous; NAC, *N*-acetylcysteine; PO, by mouth.

formulations of NAC (PO or IV) are very effective when started within 6 to 8 hours of ingestion.[31,59-63] During this period, NAC's main role is to prevent hepatotoxicity by detoxifying NAPQI and decreasing NAPQI production. The risk of liver injury (i.e., AST > 1000 IU) in this group when treated with NAC is less than 4% and the mortality rate approaches zero[28,59,64] (see Fig. 146-4).

Both PO and IV NAC are equally effective in treating patients who present 8 to 24 hours after ingestion, although the overall rate of liver injury (i.e., AST > 1000 IU) in this group is significantly higher (approximately 30%).[59,60,65] Although early studies suggested that the PO formulation might be more effective than IV administration in patients treated 10 to 24 hours after ingestion, the differences between the effectiveness of PO and IV NAC likely reflect the length of therapy and dose of NAC, rather than the route.[60]

Once liver failure (e.g., coagulopathy, encephalopathy, etc.) is evident, however, the IV route is the only route that has been systematically studied.[16] IV NAC decreases the risk of hypotension, cerebral edema, and death in patients with acetaminophen-related hepatic failure.[16] Although PO NAC may be effective in this setting, there is inadequate published data to recommend its use when IV NAC is available.

The main differences between IV and PO NAC are in their side effect profiles (Table 146-3).

Approximately 2 to 6% of patients treated with IV NAC develop anaphylactoid reactions,[63,66-68] although rates of up to 14 to 18% have been reported in prospective trials.[69] The majority of these symptoms are mild and consist of transient skin rashes and flushing. More severe reactions have been reported in less than 1% of patients and include angioedema, bronchospasm, hypotension, and at least one death.[61,67-73] Symptoms typically occur within 30 minutes of the start of the loading infusion. These anaphylactoid reactions are dose-, rate-, and concentration-dependent.[61,66-68]

Anaphylactoid reactions are much less frequent with PO NAC. Skin rash, serious systemic reactions, and anaphylactic reactions are rarely reported with the PO formulation.[74,75] However, up to 50% of patients receiving PO NAC vomit, potentially delaying timely antidotal delivery.[76] PO NAC is extremely unpalatable largely due to a "rotten egg" odor and taste. Palatability may be improved by administering NAC diluted with either soda or juice and serving it in a covered container through a straw. Any dose that is vomited within 1 hour of administration should be repeated. Antiemetics (e.g., ondansetron, metoclopramide, etc.) are advisable prior to PO NAC dosing, but there are little data about effectiveness of this approach.

Anaphylactoid reactions to IV NAC are typically mild (e.g., flushing) and occur during the initial 15- to 60-minute infusion. Mild reactions can be managed with antihistamines (e.g., IV diphenhydramine) without stopping the infusion. Serious reactions can be managed by slowing or pausing the infusion, giving a fluid bolus, and administering diphenhydramine or IV glucocorticoids if necessary.[77] Epinephrine is rarely required. Although these reactions require close observation and treatment as necessary, they do not preclude subsequent doses.[77]

N-Acetylcysteine in Pregnancy

Treating the mother with NAC is safe and effective,[78] and NAC effectively crosses the placenta.[79] Administration of IV NAC to the mother has the theoretical advantage of increased NAC delivery to the fetus compared with PO NAC. IV administration circumvents first-pass metabolism, presumably exposing the fetal circulation to higher maternal serum concentrations. Once NAC is initiated, there is a paucity of published data to determine an appropriate length of treatment. All large published studies have continued therapy for 72 hours and, therefore, it is difficult to recommend a shorter protocol in the absence of published experience.[52]

Duration of Therapy

There are two well-established protocols for NAC administration: a 72-hour PO protocol and a 21-hour IV protocol.[28,80] At the completion of these protocols, NAC may be discontinued if the metabolism of acetaminophen is complete (i.e., serum acetaminophen concentration < 10 μg/mL) *and* there is no evidence of liver injury (AST concentration normal). However, the endpoint does not rely solely on the predetermined length of a protocol and should be extended if there is significant liver injury (AST concentration greater than normal) *or* acetaminophen metabolism is incomplete (serum acetaminophen concentration > 10 μg/mL). If extended, NAC therapy may then be discontinued once evidence of liver injury has resolved (e.g., encephalopathy and coagulopathy have resolved and AST is approaching normal) and acetaminophen is undetectable.

A variety of "short-course" protocols exist,[61,81-83] and all follow the logic described earlier; NAC may be discontinued once acetaminophen metabolism is complete *and* there is an absence of, or resolution of, acetaminophen-induced liver injury.[84] Decreasing the duration of a well-established protocol should be done thoughtfully and only in low risk patients (e.g., patients treated with NAC within 6–8 hr).

Supportive Care

Supportive care includes management of nausea and vomiting, hepatic injury, and renal dysfunction. Treatment of these problems is based on general treatment principles and is not acetaminophen-dependent (see Chapter 88).

DISPOSITION

Asymptomatic patients who fit the criteria for treatment should be treated with NAC and can be admitted to a medical ward or emergency department observation unit. The motivation behind any ingestion needs to be evaluated, and psychiatric consultation may be obtained when appropriate.

Patients showing evidence of severe hepatotoxicity and those at risk for fulminant hepatic failure may need to be admitted to a monitored bed in an intensive care unit, preferably a liver failure unit. These patients require frequent neurologic checks, monitoring of vital signs, and laboratory studies.

If a patient presents with established hepatotoxicity transfer to a higher level center that specializes in the care of patients with liver failure may be advisable, as is the case for any other patient presenting with liver failure. Clinical predictors of severe hepatic failure are listed in Table 146-4.

Table 146-4 Inpatient Predictors of the Severity of Illness in Patients with Acetaminophen Toxicity

SCORE	PREDICTIVE VARIABLES	OUTCOME PREDICTED	NOTES
Modified Kings College Criteria[85]	pH < 7.3 *or* Cr > 3.3 *and* INR > 5 *and* grade III *or* IV encephalopathy [patient comatose]	Death or transplant	Arterial pH is measured *after* fluid resuscitation.
APACHE II[86,87]	APACHE II score > 20	Death or transplant	Confounders include coingested medications that may alter the APACHE II score.
Lactate[88]	Lactate > 3.5 mmol/L prior to resuscitation	Death or transplant	Lactate was drawn a mean of 55 hr after ingestion. The predictive ability of an early lactate draw is unknown.

APACHE II, Acute Physiology and Chronic Health Evaluation II; Cr, creatinine; INR, international normalized ratio.

KEY CONCEPTS

- Acetaminophen concentration should be measured in cases of unknown or mixed overdoses. Acetaminophen is relatively clinically silent until serious hepatotoxicity ensues.
- Repeated supratherapeutic dosing of acetaminophen can lead to life-threatening toxicity.
- The treatment nomogram for NAC applies only to acute ingestions; the acetaminophen concentration at 4 hours postingestion is used to determine whether NAC therapy is indicated.
- For maximum benefit, NAC treatment should not be delayed beyond 8 hours after ingestion. If more than 6 to 8 hours has passed since ingestion, treatment should be started immediately, pending further assessment of the amount of ingestion and likelihood of hepatotoxicity.
- Late or prolonged administration of NAC is beneficial even after hepatotoxicity is evident.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 147

Aspirin and Nonsteroidal Agents

Donna L. Seger and Lindsay Murray

ASPIRIN

Perspective

The incidence of aspirin (acetylsalicylic acid [ASA]) overdose and related childhood deaths has decreased significantly in recent years. Reasons include pediatricians' preference for acetaminophen preparations, the Food and Drug Administration's mandate limiting 36 tablets of baby ASA to each bottle, and the use of child-resistant caps.

Unfortunately, the severity of this poisoning may be underestimated due to lack of familiarity with the clinical picture. Salicylate toxicity can cause metabolic acidosis, seizure, hyperthermia, pulmonary edema, cerebral edema, renal failure, and death. Morbidity and mortality are increased by delayed diagnosis in elderly patients with chronic medical problems and in young patients diagnosed with an acute illness.[1]

Principles of Disease

Pharmacokinetics

Salts of salicylic acid are rapidly absorbed intact from the gastrointestinal tract, with appreciable serum concentrations occurring within 30 minutes. Two thirds of a therapeutic dose is absorbed in 1 hour, and peak levels occur in 2 to 4 hours. Serum concentrations may rise for more than 12 hours after large ingestions (which may delay gastric emptying) or ingestions of enteric capsules.[2]

In the intestinal wall, liver, and red blood cells, aspirin is hydrolyzed to free salicylic acid, which reversibly binds to albumin (which contains a genetically determined variable number of salicylate-binding sites). In the liver, salicylate is conjugated with glucuronic acid and glycine (Fig. 147-1). A small fraction is hydroxylated. Free salicylate and its conjugates are eliminated by renal excretion. At therapeutic salicylate concentrations, elimination follows first-order kinetics, and excretion is proportional to salicylate concentration. When serum salicylate concentrations are greater than 30 mg/dL, however, elimination follows zero-order kinetics, and the metabolic rate is constant. The metabolic pathways become saturated, and the pH-sensitive urinary excretion of salicylic acid determines the half-life (which may approach 15–30 hr with toxic doses).[3]

Pathophysiology

Acid-Base Disturbances and Metabolic Effects. Salicylate stimulates the medullary respiratory center early and increases the sensitivity of the respiratory center to pH and carbon dioxide partial pressure (P_{CO_2}). Hyperventilation develops early, then subsequently becomes a compensatory mechanism to the metabolic acidosis. Prolonged high serum concentrations eventually depress the respiratory center. Respiratory alkalosis is compensated for by buffering of the hemoglobin-oxyhemoglobin system, the exchange of intracellular hydrogen ions for extracellular cations, and the urinary excretion of bicarbonate. Loss of bicarbonate decreases buffering capacity and intensifies the metabolic acidosis.[4,5]

Toxicity results primarily from interference with aerobic metabolism by uncoupling of mitochondrial oxidative phosphorylation. Inhibition of the Krebs dehydrogenase cycle increases production of pyruvic acid and increases conversion to lactic acid. Increased lipid metabolism increases production of ketone bodies. Metabolic rate, temperature, tissue carbon dioxide, and oxygen consumption are increased. Tissue glycolysis predisposes to hypoglycemia. (Hepatic gluconeogenesis and release of adrenaline may cause the less common hyperglycemia.) Inefficiency of anaerobic metabolism results in less energy being used to create ATP, and energy is released as heat, causing the hyperthermia frequently seen in salicylate poisoning.[4]

Only nonionized particles can cross the cell membrane and accumulate in the brain and other tissues. Because ASA has a low pK_a,[3,5] the majority of salicylate is ionized and little salicylate enters tissues at the physiologic pH of 7.4. However, as pH decreases, more particles become un-ionized, cross the cell membrane and blood-brain barrier, markedly increasing the movement of salicylate into the tissues and central nervous system (CNS).[4,5]

Fluid and Electrolyte Abnormalities

Significant potassium loss in salicylate toxicity is caused by (1) vomiting, secondary to stimulation of the medullary chemoreceptor trigger zone; (2) increased renal excretion of sodium, bicarbonate, and potassium as a compensatory response to the respiratory alkalosis; (3) salicylate-induced increased permeability of the renal tubules with further loss of potassium; (4) intracellular accumulation of sodium and water; and (5) inhibition of the active transport system, secondary to uncoupling of oxidative phosphorylation. The net result is rapid depletion of potassium stores.[4]

A salicylate-induced decrease in renal blood flow or direct nephrotoxicity may cause acute nonoliguric renal failure. Salicylate-induced secretion of inappropriate antidiuretic hormone may also affect renal function.[6]

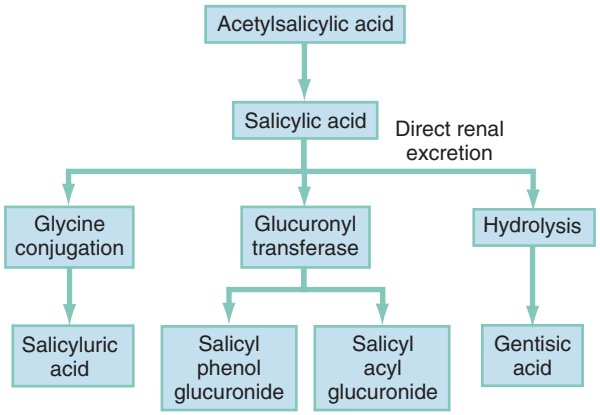


Figure 147-1. Aspirin metabolism.

Pulmonary and Cerebral Edema

The exact mechanism by which salicylate increases alveolar capillary membrane permeability is unknown. Theories include inhibition of prostacyclin, changes in platelet-vessel interaction, and neurogenic influences. In adults, the risk factors for salicylate-induced pulmonary edema include age older than 30 years, cigarette smoking, chronic salicylate ingestion, metabolic acidosis, neurologic symptoms, and serum salicylate concentration greater than 40 mg/dL. Risk factors in children include high serum salicylate levels, large anion gap, decreased serum potassium concentration, and low P_{CO_2}.[7]

Any alteration in sensorium is evidence of cerebral edema and is a grave prognostic sign. Factors causing cerebral edema are unknown. Patients with cerebral or pulmonary edema require immediate dialysis.

Chronic Ingestion Physiology

Physiologic changes of aging predispose elderly patients to toxicity from chronic therapeutic ingestion. Decreased liver blood flow rates decrease biotransformation of salicylate, and decreased renal function decreases salicylate clearance. Chronic ingestion of aspirin decreases albumin binding, which increases free salicylate. The free salicylate enters the cell, causing significant clinical illness with a relatively low serum salicylate concentration. A patient with chronic salicylate toxicity and a serum concentration of 40 mg/dL may be more ill than a patient with an acute ingestion and serum concentration of 80 mg/dL.[8]

Pediatric salicylism from supratherapeutic dosing may be more serious than acute ingestion. Sweating, fever, and tachycardia caused by salicylism may be attributed to underlying infection. Other sources of salicylate exposure include breast milk, teething gels, and percutaneous absorption of skin ointments, which have high concentrations of methyl salicylate.

Clinical Features

A toxic dose of aspirin is 200 to 300 mg/kg, and ingestion of 500 mg/kg is potentially lethal. The initial manifestations of acute salicylate toxicity include tinnitus, impaired hearing, hyperventilation, vomiting, dehydration, and hyperthermia. Salicylate-induced hyperpnea may manifest as increased respiratory depth without commensurate increase in rate. Hyperventilation is more common in adults, who usually have an initial respiratory alkalosis. Young children are predisposed to toxicity due to the metabolic acidosis, which increases tissue and CNS salicylate concentrations. Vomiting can occur 3 to 8 hours after ingestion. Serious dehydration can occur from hyperpnea, vomiting, and hyperthermia. CNS manifestations are usually associated with acidemia.

Shortness of breath and altered sensorium are caused by pulmonary and cerebral edema, respectively. Noncardiac pulmonary edema may be more common in children than scattered case reports suggest.[9] Failure to recognize salicylate toxicity as the cause of pulmonary edema increases the likelihood of morbidity and mortality in these patients.

Diagnostic Strategies

A serum salicylate concentration should be measured 6 hours or more after ingestion. A second sample should be obtained 2 hours later. If the second concentration is greater than the first, serial concentrations should be obtained to monitor continued absorption.

Prognosis and treatment of the acutely poisoned patient should be determined by the serum salicylate concentration; the dose of salicylate ingested; and the patient's age, clinical features, and acid-base status. Acid-base status can change quickly, and frequent monitoring of arterial pH is necessary to guide treatment. The Done nomogram should not be used to determine prognosis or treatment.

Salicylate-poisoned patients who require endotracheal intubation are extremely ill, and dialysis is indicated unless the intubation was undertaken because of toxicity of coingestants. Positive-pressure ventilation cannot maintain the respiratory rate required. Hemodynamic instability and worsening acid-base status usually follow intubation. Low pH and bicarbonate levels portend severe disease. The pH begins to drop when the patient is unable to compensate for the acidosis. Lactic acid accumulates, and serum bicarbonate is consumed. When pH is less than 7.4, and both P_{CO_2} and bicarbonate are low, the patient begins to decompensate hemodynamically. In the intubated patient or the acidotic patient with low P_{CO_2} and bicarbonate, hemodialysis should be undertaken.[10]

Differential Considerations

The symptoms of salicylism (hyperthermia, altered mental status or coma, pulmonary edema, and shock) mimic sepsis and the symptoms of many other diseases (Box 147-1). This is especially true with chronic ingestion—serum salicylate concentration is relatively low, and the severity of the poisoning is not recognized.[11] Death is caused by CNS depression and cardiovascular collapse.

Management

Treatment of salicylate toxicity has two main objectives: (1) to correct fluid deficits and acid-base abnormalities and (2) to increase excretion (Box 147-2). Strategies to limit absorption

BOX 147-1 Symptoms of Salicylate Toxicity

Asymptomatic: Occasional subjective but no objective manifestations
Mild: Mild to moderate hyperpnea tinnitis, sometimes with lethargy
Moderate: Severe hyperpnea, prominent neurologic disturbances, such as marked lethargy or agitation, but no coma or convulsions
Severe: Severe hyperpnea, coma, or semicoma, sometimes with convulsions

BOX 147-2 TREATMENT OF ACUTE SALICYLATE POISONING

Treat dehydration; maintain urine output at 2–3 mL/kg/hr with 5% dextrose (D_5) in lactated Ringer's solution or normal saline.
Correct potassium depletion.
Alkalinize urine.
- Obtain baseline arterial blood gas values.
- If pH is <7.4, administer sodium bicarbonate to obtain pH of 7.4 (50 mL bicarbonate increases serum pH by 0.1 in an adult).
- Infuse intravenous fluids: D_5 with 100–150 mEq bicarbonate/L.
- Monitor serum pH; do not cause systemic alkalosis.
- Do not attempt forced diuresis.

Monitor for dialysis indications:
- Coma, seizure
- Renal, hepatic, or pulmonary failure
- Pulmonary edema
- Severe acid-base imbalance
- Deterioration in condition
- Serum salicylate concentration ≥100 mg/dL after acute ingestion
- Serum salicylate concentration ≥40 mg/dL after chronic ingestion

have not been demonstrated to improve outcome and are not indicated in most cases. Gastric emptying, once widely recommended, is not of value.

Initial Evaluation

Perform a general physical examination, including vital signs (including oxyhemoglobin saturation and a counted respiratory rate and reliable temperature). Chest auscultation may provide evidence of pulmonary edema. Arterial blood gases are obtained early to rapidly assess acid-base and compensatory status.

Activated Charcoal

There is not sufficient evidence to support the administration of activated charcoal (AC) in acute or chronic salicylate poisoning. Early administration of AC somewhat reduces salicylate absorption, although an improved clinical outcome has not been demonstrated in overdose patients after a single dose or multiple doses of AC. Even when given within 1 hour of ingestion, there is no evidence that AC results in improved outcome, decreased toxicity, or alteration of therapy or course of the illness.[12]

Intravenous Fluids

Dehydration occurs early in salicylate intoxication because of the hypermetabolic state and should be treated with intravenous fluid. Potassium depletion must be corrected. Fluid administration should be guided by the patient's apparent deficit to maintain urine output of 2 to 3 mL/kg/hr and should not exceed the estimated replacement, because excessive fluid administration can worsen cerebral and pulmonary edema.

Additionally, the metabolic rate is increased in these cases. Intravenous fluid should contain dextrose, and the serum glucose level should be frequently monitored to prevent hypoglycemia. In animal studies, hypoglycemia consistently occurs with death.

Urinary Alkalinization

Because salicylates have a low pK_a and are renally excreted, alkaline urine traps the salicylate ion and increases excretion. Urinary alkalinization is advisable in patients with salicylate levels greater than 35 mg/dL, significant acid-base disturbance, or increasing salicylate levels. A urine pH of 7.5 to 8.0 is necessary to increase excretion. Sodium bicarbonate (1–2 mEq/kg) can be administered over 1 to 2 hours, with subsequent dosage adjustment determined by urinary and serum pH.

Urinary alkalinization is difficult to achieve because the excretion of salicylic acid in the urine decreases urinary pH. Additionally, potassium depletion must be corrected to attain an alkaline urine. Alkaline urine should not be produced at the cost of systemic alkalemia. Forced diuresis does not significantly increase salicylate excretion and may potentiate cerebral and pulmonary edema. Salicylate clearance varies in direct proportion to flow rate, but increases exponentially with pH.[13]

Hemodialysis

Hemodialysis is advisable in patients with the following: serum salicylate levels greater than 100 mg/dL in acute intoxication and 50 mg/dL in chronic salicylate poisoning; altered mental status; endotracheal intubation other than for coingestants; coma; renal or hepatic failure; pulmonary edema; severe acid-base imbalance; rapidly rising serum salicylate level; and failure to respond to more conservative treatment. Exchange transfusion can be considered in young infants or unusual cases of congenital salicylism.[14]

Pregnancy

Greater salicylate concentration on the fetal side of the placenta and relative fetal acidemia contribute to fetal distress from maternal salicylate poisoning. Salicylate poisoning during pregnancy is associated with fetal demise, and delivery of the distressed fetus should be considered if the fetus is viable.[15]

Disposition

In patients with acute intoxication, hospital admission is required for pulmonary edema, CNS symptoms (other than tinnitus), seizures, acidosis, electrolyte disorders, dehydration, renal insufficiency, or increasing serum levels. In patients with chronic intoxication, remarkably low serum salicylate concentrations may accompany severe salicylism. Any indication of infant salicylism requires hospital admission. The mortality rate for chronic salicylate intoxication is 25%, compared with a mortality rate of 1% following acute salicylate intoxication.

In patients with acute ingestion, a second serum salicylate concentration measurement is essential to determine whether the peak serum concentration has been attained. Patients should not be discharged unless the serum concentrations are decreasing. As in any case of intentional overdose, psychiatric evaluation is essential.

■ NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Perspective

The nonsteroidal anti-inflammatory drugs (NSAIDs) are a heterogeneous group of agents with variable analgesic, anti-inflammatory, and antipyretic activities. They are usually classified according to chemical structure, although classification based on cyclooxygenase (COX) selectivity may be more

clinically relevant. NSAIDs are widely prescribed for a variety of conditions. Ibuprofen and naproxen are available in over-the-counter and prescription strengths.

Principles of Disease

Physiology

The therapeutic anti-inflammatory effect of the NSAIDs is achieved by inhibition of COX and consequent blockade of prostaglandin production. Of the two discrete COX isoenzymes, COX-1, the constitutive enzyme, is concentrated in platelets, vascular endothelial cells, gastric mucosal cells, and renal collecting tubules. It is a physiologic maintenance enzyme, producing the prostaglandins critical for the autocrine-paracrine responses to circulating hormones and the maintenance of normal renal function, gastric mucosal integrity, and hemostasis. COX-2, the inducible enzyme, is expressed only in response to certain inflammatory stimuli. The benefits of NSAIDs are thus believed to result from COX-2 inhibition, whereas the principal gastrointestinal and renal adverse effects are attributed to inhibition of COX-1.

Traditional NSAIDs are nonselective and inhibit both COX-1 and COX-2. Newer, specific COX-2 inhibitors (e.g., celecoxib, rofecoxib, parecoxib, meloxicam) have fewer side effects than traditional NSAIDs while maintaining analgesic and anti-inflammatory efficacy. However, COX-2 inhibitors permit unopposed thromboxane A_2 production by platelets, thereby potentiating platelet aggregation, thrombosis, and vasoconstriction.[16] Therapeutic use of rofecoxib, particularly at higher doses, is associated with increased risk of myocardial infarction and stroke and has subsequently been withdrawn from the market.[17,18]

Pharmacokinetics

The NSAIDs are almost completely absorbed from the upper small intestine after oral administration. The presence of food may alter the site and timing of drug uptake. As weak organic acids (pK_a, 4–5), NSAIDs are largely nonionized in the stomach and readily diffuse across the bipolar layer lipid membrane of gastric-lining cells. Once intracellular, the drug can become ionized again at the relatively high pH of normal cytoplasm and become trapped within the mucosal cell. This relatively high local concentration of drug contributes to the frequent gastrointestinal symptoms associated with NSAIDs.

The NSAIDs are highly bound to plasma proteins, mainly albumin, and therefore have small volumes of distribution (0.10–0.17 L/kg). They are eliminated by hepatic biotransformation, principally oxidation and glucuronidation, with the metabolites being excreted in the urine. Metabolites are inactive, except for those of sulindac, nabumetone (inactive parent drugs metabolized to active agent in vivo), and phenylbutazone. Plasma half-lives are short (1–4 hr), except for naproxen (12–15 hr), oxaprozin (25–50 hr), piroxicam (45 hr), and phenylbutazone (50–100 hr). Elimination half-lives are not substantially prolonged in overdose.[19]

Clinical Features

Most NSAID overdoses, even with large amounts, are asymptomatic or cause only minor CNS or gastrointestinal disturbances. Experience with overdose of the newer COX-2 inhibitors is limited, but significant toxicity is not reported. Of all isolated celecoxib exposures reported to the Texas poison control centers over a 5-year period, no more than minor effects were reported and then in only 12% of cases.[20]

Ibuprofen is the most common NSAID ingested in overdose and is representative of the propionic acid derivatives. Despite rare case reports of coma, seizure, hypotension, hypothermia, upper gastrointestinal tract bleeding, acute renal failure, and metabolic acidosis, the vast majority of ibuprofen overdoses follow a benign, rapidly self-limiting course. About 50% of adults and 7% of children develop symptoms. Symptomatic overdose occurs only after ingestion of at least 100 mg/kg, and all those who develop symptoms do so within 4 hours of ingestion. Life-threatening symptoms or signs are rare, and most toxicity is a mild gastrointestinal or CNS disturbance that resolves in 24 hours.[21-25] Less common clinical effects include mild metabolic acidosis, muscle fasciculations, mydriasis, chills, diaphoresis, hyperventilation, mildly elevated systolic blood pressure, asymptomatic bradycardia, hypotension, dyspnea, tinnitus, and rash.

Reversible renal dysfunction is seen only after massive acute overdose and in association with a period of relative hypovolemia with hypotension.[21-26] It usually responds to supportive measures, although deaths have been reported.[27] Serum ibuprofen concentrations do not predict toxicity.[21]

Overdose with mefenamic acid, a fenamate, is associated with a relatively high incidence of seizures, which occur 2 to 7 hours after ingestion.[28] Rapid recovery is the rule with supportive care and intravenous benzodiazepines. Serum mefenamic acid concentrations correlate with seizures but do not aid in acute management.

Phenylbutazone, a pyrazolone, is now rarely used because of its association with aplastic anemia and agranulocytosis. Although rare, phenylbutazone overdose is much more severe than overdose with other NSAIDs.[29] Mild poisoning consists of nausea, abdominal pain, and drowsiness. Severely poisoned patients have early onset of abdominal pain, nausea, vomiting, hematemesis, diarrhea, restlessness, dizziness, coma, convulsions, hyperpyrexia, electrolyte disturbances, hyperventilation, alkalosis or acidosis, respiratory arrest, hypotension, cyanosis, edema, electrocardiographic abnormalities, or cardiac arrest. Late sequelae of severe poisoning (2–7 days) include renal, hepatic, and hematologic dysfunction. The clinical course is prolonged compared with other NSAID poisoning, reflecting the prolonged elimination half-lives of phenylbutazone and its principal metabolite, oxyphenbutazone.

Diagnostic Strategies

The diagnosis and assessment of severity and risk are based on history and clinical features. Plasma NSAID concentrations are not useful, but screening for acetaminophen should be done. Serum electrolyte levels, renal and hepatic function tests, serum salicylate level, urinalysis, and chest radiograph should be undertaken as indicated by specific clinical concerns.

Management

The management of NSAID overdose is supportive, and there is no specific antidote. Pyrazolone and fenamate overdoses are associated with significantly higher morbidity and should be managed more aggressively.

Children with ingestions of less than 100 mg/kg of ibuprofen do not require medical evaluation. Those who ingest more than 300 mg/kg should be evaluated. With ingestion of 100 to 300 mg/kg, children need treatment only if symptoms develop.

All patients with pyrazolone and fenamate ingestions should be evaluated in the emergency department. For other agents, emergency department evaluation is indicated if the amount

ingested is greater than five times the maximum daily therapeutic dose, the patient is symptomatic, or a suicide attempt is suggested.

There is no evidence supporting the use of gastric emptying or AC in cases of NSAID overdose, although AC has historically been used and it is not recommended. All patients with nontrivial overdoses should be observed until 4 hours postingestion and until symptoms are noted to be mild or improving. Hypotension, if it occurs, is managed with intravenous crystalloid solution. Although rarely indicated, and not subjected to study, extracorporeal membrane oxygenation has been successfully used to manage refractory hypotension following massive ibuprofen overdose.[30]

Because of high protein binding and rapid metabolism, urinary alkalinization, hemodialysis, or hemoperfusion is not clinically useful. Multidose AC reduces the elimination half-life of phenylbutazone by 30% and may be of benefit in cases of severe intoxication.[31]

Disposition

Patients who are mildly symptomatic or asymptomatic for more than 4 hours after an NSAID overdose do not require further medical care, other than possible psychiatric evaluation. Patients who have ingested a pyrazolone or fenamate may require longer observation for possible seizures. Admission to the ED observation unit until 8 hours after ingestion may be advisable, but studies have not been done to verify this. Patients who develop significant symptoms or signs of toxicity from the NSAID or a co-ingestant and who require supportive care should be admitted to the hospital or an emergency department observation unit for ongoing medical treatment. Patients with only gastrointestinal or neurologic symptoms may be observed in the emergency department until asymptomatic or improving. All patients for whom the ingestion represented a suicidal gesture need to undergo psychiatric assessment before hospital discharge.

KEY CONCEPTS

- ASA intoxication, especially chronic salicylism, should be considered in the differential diagnosis of altered mental status in the elderly.
- Potassium stores are rapidly depleted in patients with salicylate intoxication.
- The acute toxic dose of ASA is 300 mg/kg, and 500 mg/kg is potentially lethal.
- Acidosis signifies severe salicylism as unbound salicylate is moving into the cell.
- Signs of pulmonary or cerebral edema, coma, hepatic failure, circulatory collapse, refractory acidosis, or levels greater than 100 mg/dL require immediate hemodialysis.
- Hyperthermia, altered mental status, coma, pulmonary edema, and shock may be presenting signs of salicylism.
- Serial salicylate concentrations should be obtained after acute ingestion to ensure that the salicylate concentration is decreasing.
- Consider dialysis in patients with coma, seizures, renal failure, hepatic failure, pulmonary failure, or refractory acidosis or in acute cases in which serum levels are greater than 100 mg/dL.
- NSAID overdose, other than ASA, is usually self-limited, with predominantly gastrointestinal toxicity.
- Pyrazolones and fenamates can cause seizures.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 148 Anticholinergics

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PERSPECTIVE

Anticholinergic agents are divided into three main groups: (1) antimuscarinics, affecting the muscarinic acetylcholine (ACh) receptors; (2) neuromuscular blockers, blocking nicotinic ACh receptors; and (3) ganglionic blockers, affecting ACh sympathetic and parasympathetic nicotinic ganglia (Fig. 148-1). This chapter refers only to antimuscarinic agents, and the terms *anticholinergic* and *antimuscarinic* will be used interchangeably. The prototypical anticholinergic agents are the naturally occurring belladonna alkaloids—atropine, scopolamine (L-hyoscine), and hyoscyamine—found in many plant members of the Solanaceae family. Atropine is the major alkaloid of *Atropa belladonna,* an important pharmaceutical source of that drug. *Datura stramonium,* or Jimson weed, contains scopolamine, grows in almost all climates, and is often involved in plant-related belladonna poisoning.[1,2]

Physicians have used belladonna alkaloids for hundreds of years as mydriatics (Box 148-1).[3] The belladonna alkaloids and their synthetic congeners are used today as pupillary dilators (atropine, homatropine, tropicamide, cyclopentolate), as antispasmodics (dicyclomine), to decrease gastric secretions (propantheline), to prevent motion sickness (scopolamine), and to treat asthma (ipratropium) and bradycardia (atropine). Atropine and glycopyrrolate are used to dry airway secretions and block vagal responses to laryngoscopy and endotracheal intubation. The significant central nervous system (CNS) effects of scopolamine facilitate the induction of perioperative amnesia.

The anticholinergic antiparkinsonian agents are synthetic tertiary amine congeners of atropine and include benztropine (Cogentin) and trihexyphenidyl (Artane). They are used as second-line antiparkinsonian agents and to counteract the extrapyramidal side effects of neuroleptics. These agents readily cross the blood-brain barrier and exhibit central antimuscarinic effects.

Tolterodine (Detrol) and oxybutynin (Ditropan) are anticholinergic agents used for the management of urinary incontinence and bladder spasms. They have special selectivity for the muscarinic receptors of the urinary bladder. These agents do not penetrate the blood-brain barrier and thus do not cause significant CNS effects.

Many other drugs possess anticholinergic activity in addition to their main pharmacologic action. Some examples are the tricyclic antidepressants, the phenothiazines, and the antihistamines (H_1 blockers). Drugs that are structurally related to the tricyclics, such as carbamazepine (Tegretol) and cyclobenzaprine (Flexeril), also exhibit antimuscarinic effects.[4] In patients with significant toxicity from any of these drugs, the antimuscarinic effects provide valuable diagnostic clues (see Box 148-1; Box 148-2).

Inadvertent and intentional poisoning by anticholinergic drugs occurs commonly with over-the-counter agents such as diphenhydramine (Nytol, Benadryl, Sominex), and cyclizine (Marezine). Poisoning from drugs with toxicity limited to anticholinergic effects rarely results in death when adequate supportive care is provided. However, thermoregulatory dysfunction caused by impaired sweating may result in fatal hyperthermia in the agitated or seizing patient with an anticholinergic overdose.[5,6] Heatstroke fatalities have occurred in heat-exposed or exercising patients taking therapeutic doses of anticholinergics.[7,8] Deaths from trauma or drowning caused by perceptual distortion can also be attributed to anticholinergics.[9]

Poisonings with belladonna alkaloids are common. Deliberate ingestions of seeds or teas of the ubiquitous Jimson weed for their hallucinogenic effects have occurred in many cultures,[10] and its use as a recreational stimulant remains a problem among teenagers. Inadvertent poisonings have resulted from ingestion of commercially available herbal teas contaminated with atropine and from smoking herbal cigarettes.[11,12] A cluster of nonfatal scopolamine poisonings was described in New York City, when the difficult to detect drug was added to tourists' drinks to facilitate robbery. The tainting of heroin with anticholinergics leading to a complex toxidrome has also been reported in drug users in several eastern states of the United States.[5,6]

PRINCIPLES OF DISEASE

Atropine and atropine-like drugs inhibit muscarinic ACh receptors both centrally and peripherally at the end-organ sites of the parasympathetic nervous system (see Fig. 148-1). Although the term *anticholinergic* is commonly used, the most appropriate term to describe the pharmacologic action of these drugs is *antimuscarinic.* These drugs do not block the effects of ACh on nicotinic receptors in the ganglia or at the neuromuscular junction, with the exception of the synthetic quaternary amines. Muscarinic receptors affect smooth muscle function in the eye, intestinal tract, and urinary bladder. They also regulate sweat, salivary, and mucosal gland activity. Cardiac cholinergic receptors associated with vagal nerve fibers affect heart rate and conduction through the atrioventricular

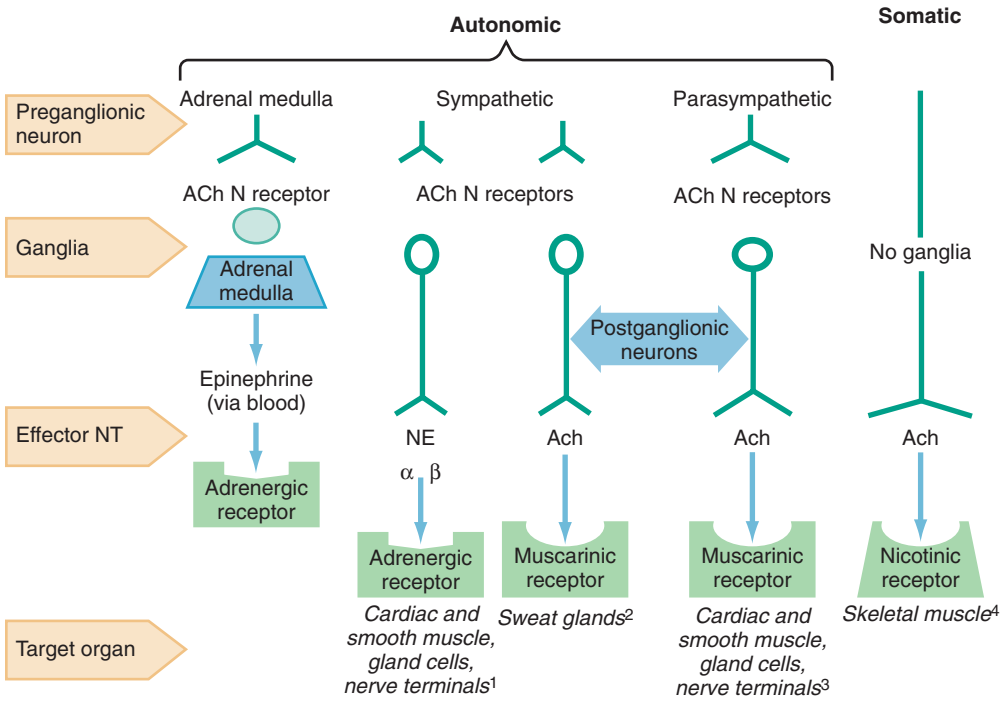


Figure 148-1. The sites of nicotinic and muscarinic acetylcholine receptors. Ach, acetylcholine; N, nicotinic; NE, norepinephrine; NT, neurotransmitter. [1]Causing tachycardia, hypertension, diaphoresis, mydriasis. [2]Causing diaphoresis. [3]Causing bradycardia, diarrhea, diaphoresis, urination, miosis, bronchospasm, bronchorrhea, lacrimation, salivation. [4]Causing fasiculations.

BOX 148-1 Drugs Exhibiting Primarily Anticholinergic Toxicity

Belladonna Alkaloids and Representative Synthetic Congeners
Atropine
Scopolamine
Homatropine
Cyclopentolate
Tropicamide
Propantheline (Pro-Banthine)
Ipratropium (Atrovent)

Antiparkinsonians
Benztropine (Cogentin)
Trihexyphenidyl (Artane)
Procyclidine (Kemadrin)
Biperiden (Akineton)
Ethopropazine (Parsidol)

Prototypical H_1-Receptor Blockers
Diphenhydramine (Benadryl)
Chlorpheniramine (Chlor-Trimeton)
Brompheniramine (Dimetane)
Cyclizine (Marezine)
Meclizine (Antivert)
Hydroxyzine (Atarax, Vistaril)
Dimenhydrinate (Dramamine)

Phenothiazine
Promethazine (Phenergan)

BOX 148-2 Drugs Exhibiting Anticholinergic Effects as Part of Toxic Manifestations

Tricyclic Antidepressants or Related Drugs
Cyclobenzaprine (Flexeril)
Carbamazepine (Tegretol)
Amitriptyline
Imipramine
Doxepin
Amoxapine
Desipramine
Nortriptyline
Glutethimide (Doriden)

Phenothiazines
Chlorpromazine (Thorazine)
Prochlorperazine (Compazine)
Mesoridazine (Serentil)
Thioridazine (Mellaril)

node. Muscarinic receptors in the CNS appear to be involved in new information storage, general perceptive and cognitive functions, and motor coordination.[13-16]

Generalized inhibition of muscarinic receptors by atropine results in tachycardia, pupillary dilation, loss of accommodation, inability to sweat, drying of mucosal surfaces, gastrointestinal paralysis, and urinary retention. In the CNS, muscarinic inhibition causes stimulation, seizures, coma, choreoathetosis, memory impairment, and perceptual and cognitive dysfunction.[13-19] The mnemonic "hot as a hare, red as a beet, blind as a bat, dry as a bone, mad as a hatter" aptly characterizes the more florid manifestations of the antimuscarinic syndrome. With increasing doses, CNS depression follows the initial stimulation. However, in adults, the CNS depression can predominate without CNS stimulation.[20] Various end organs manifest different but predictable sensitivities to antimuscarinic drugs. Salivation, bronchial secretions and sweating are suppressed first, followed by the onset of mydriasis and tachycardia. The least sensitive organs to antimuscarinic drugs are the bladder and the gastrointestinal tract.

Anticholinergics are generally rapidly absorbed and widely distributed throughout the body. Poisoning has been reported after ingestion, smoking, and topical absorption. However, with plant and seed ingestions or after an overdose, the onset of symptoms can be delayed.[21] Prolonged anticholinergic toxicity has also been reported, which may indicate slowed

gastrointestinal absorption of the ingested drug or residual drug in the gastrointestinal tract.[22,23]

CLINICAL PRESENTATION

The diagnosis of acute anticholinergic poisoning is suggested by the characteristic anticholinergic toxidrome. Mydriasis, dry mucous membranes, the absence of axillary sweat, flushed skin, fever, tachycardia, decreased or absent bowel sounds, and bladder distention from urinary retention constitute peripheral evidence of muscarinic blockade.[18,24-26] The patient is often alert and may be silly, agitated, violent, or incoherent. Visual hallucinations are common.[27] Central motor effects may manifest as myoclonus or choreoathetoid movements. Children are more sensitive to the CNS stimulant effects than adults and are more likely to have seizures, typically preceded by signs of CNS irritability or depression.[28] Massive ingestions are associated with coma and cardiovascular collapse.[23,29]

The agitated patient with anticholinergic overdose may have a greatly elevated temperature due to both increased motor activity and impaired heat exchange. In such cases, death secondary to hyperthermia supersedes the morbidity of the anticholinergic drug itself.[7,8,24] The hyperthermic patient may develop hepatic necrosis, rhabdomyolysis with myoglobinuric renal failure, cerebral edema, and disseminated intravascular coagulation.[30]

Patients with chronic anticholinergic poisoning may be difficult to diagnose. They develop organic mental symptoms that may be incorrectly attributed to dementia or underlying psychiatric illness. Significant peripheral anticholinergic signs are typically absent. Two likely settings for chronic anticholinergic toxicity are (1) the elderly patient taking anticholinergic drugs for parkinsonism or other chronic diseases and (2) the psychiatric patient receiving neuroleptic therapy and started on another anticholinergic drug.[14,18] Resolution of behavioral or cognitive symptoms after withdrawal of the offending drug confirms the diagnosis.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of the comatose, psychotic, delirious, or febrile patient is extensive, and serious alternative diagnoses should be considered and excluded.[17,31] Diagnoses to consider include toxicity and withdrawal from a variety of drugs, metabolic disorders, CNS infections, and other neurologic pathologies.[31]

The physical examination findings can be helpful. Patients with excessive sympathetic stimulation secondary to cocaine or amphetamine poisoning exhibit fever, tachycardia, and dilated pupils. Importantly, the finding of diaphoresis helps distinguish patients with sympathetic overload from those with anticholinergic effects; however, this finding can be absent in severely dehydrated patients. Marked nystagmus, diaphoresis, small pupils, and extreme agitation suggest phencyclidine poisoning. Lithium or monoamine oxidase inhibitor toxicity should also be considered.[32] These patients usually have tremors and significant hyper-reflexia or clonus, which are not characteristic of anticholinergic poisoning. Patients with serotonin syndrome often present with agitation.[33,34] These patients are often diaphoretic and have a tremor that is more prominent in the lower extremities. Neuroleptic malignant syndrome and malignant hyperthermia can also manifest similarly, but these patients display rigidity as a prominent physical examination feature.[34,35]

The nontoxicologic differential diagnosis of acute agitated delirium should consider metabolic, endocrine, infectious, neurologic, and neurosurgical emergencies. Nuchal rigidity or focality on neurologic examination, physical signs of systemic infection, hepatic failure, or thyroid disease suggest alternative diagnoses. The demonstration of hypoglycemia, hypoxia, uremia, or calcium abnormalities also suggests a nontoxic diagnosis.

Except for sinus tachycardia, electrocardiographic abnormalities from a pure anticholinergic overdose are unusual and should suggest a cardiotoxic agent with antimuscarinic side effects, such as a tricyclic antidepressant, carbamazepine, or a phenothiazine. (In the presence of hyperkalemia due to rhabdomyolysis, peaked T waves can be observed.)

DIAGNOSTIC STRATEGIES

Mildly symptomatic patients with well-established histories and consistent symptoms do not benefit from routine laboratory testing. In the seriously poisoned patient, laboratory investigation should include measurement of serum electrolytes, renal function, creatine phosphokinase, and glucose. Arterial blood gas measurements document disorders of oxygenation and ventilation and allow early detection of metabolic acidosis. Capillary blood glucose and oxygen saturation measurements are important first steps in the assessment of any patient with altered mental status. Thiamine should be administered to malnourished patients. An electrocardiogram should also be performed early, since certain anticholinergic medications such as tricyclic antidepressants and diphenhydramine can block sodium channels, causing QRS widening.[36]

Broad, nonspecific toxicologic screening is rarely useful in the acute setting, although it may retrospectively confirm a diagnosis in a seriously ill patient. However, patients with significant infectious or neurosurgical problems often have evidence of an incidental toxin. Therefore, a positive toxicology screen should not distract the physician from ruling out a more serious diagnosis.

In any case of intentional ingestion, serum acetaminophen levels should be obtained to exclude this common coingestant, especially because many over-the-counter products contain acetaminophen along with an antihistamine that causes the anticholinergic symptoms.

Computed tomography of the brain and a lumbar puncture exclude neurologic and neurosurgical emergencies in the patient who deteriorates, who fails to improve, or for whom the history or examination suggests an alternative diagnosis.

MANAGEMENT

In the emergency department, many patients with anticholinergic poisoning have no clear history of exposure. The patient is often unable to provide a history due to the delirium. Therefore, the diagnosis is often suggested solely on the basis of the physical examination fitting the muscarinic/anticholinergic toxidrome (Box 148-3). The general treatment of these poisoned patients proceeds with consideration of the broader differential diagnosis of the acutely agitated, febrile, or comatose patient.[17]

Agitation

The need for titrated sedation with a benzodiazepine, cooling, and hydration takes precedence over specific toxicologic concerns in these critically ill patients. Physical restraint alone is detrimental and is used only briefly to permit pharmacologic intervention.[37] Agitation should be controlled by titrating intravenous benzodiazepines to sedation. Benzodiazepines are preferred over phenothiazines and butyrophenones because exacerbation or induction of hypotension is unlikely, the

BOX 148-3 DIFFERENTIAL DIAGNOSIS OF DELIRIUM

Toxic
Steroids
Lithium
Salicylates
Anticholinergics
Sympathomimetics (cocaine, amphetamines)
Phencyclidine
Mushrooms containing muscimol/ibotenic acid (*Amanita* spp.)
Monoamine oxidase inhibitors
Solvents
Carbon monoxide
Sedative-hypnotic withdrawal

Metabolic
Sodium disorders
Hypoglycemia
Hypercarbia
Hypoxia, severe anemia
Calcium disorders
Uremia
Thyrotoxicosis
Hepatic encephalopathy
Hypertensive encephalopathy
Shock
Sepsis

Infectious/Inflammatory
Meningoencephalitis
Meningitis
Vasculitis

Neurologic/Neurosurgical
Cerebrovascular accident
Subarachnoid hemorrhage
Subdural/epidural hematoma
Frontal contusion
Postictal state
Temporal lobe seizures

possibility of seizures is decreased, and there are no added anticholinergic effects.[38] Pharmacologic restraints in the agitated patient prevent self-injury, severe hyperthermia, and the development of myoglobinuric renal failure from muscle injury. Control of the agitation also allows for a more thorough physical examination and for diagnostic procedures to take place. Intubation is generally not indicated as the sole treatment for agitation.

Hyperthermia

Deaths of agitated patients could be associated with unrecognized hyperthermia. The patient's core temperature should be measured with a flexible rectal probe. Aggressive temperature reduction with ice water or evaporative cooling with mist and fans should be the first priority in the severely hyperthermic patient. Benzodiazepines should be used to prevent shivering, which can hinder adequate cooling. The use of dantrolene sodium, a drug that decreases rigidity caused by abnormal calcium fluxes in muscle tissue in malignant hyperthermia, has no role in the treatment of hyperthermic patients who do not have muscle rigidity.[39] Antipyretic agents and simple cooling blankets are ineffective.

Seizures

Seizures should be treated with intravenous benzodiazepines. In the absence of an intravenous line, the intramuscular route can be effectively used for lorazepam or midazolam. Phenytoin is not useful in the management of most toxin-induced seizures. Status epilepticus is rare in anticholinergic poisoning and should suggest an alternative diagnosis.

Drug Removal

Decontamination of the patient with documented or strongly suggested anticholinergic poisoning must be individualized, based on time since exposure, type of anticholinergic agent involved, route of exposure, probable amount ingested, and severity of the clinical condition. Early gastric emptying (within 1 hour) may be considered for large ingestions, when an asymptomatic patient presents almost immediately after ingestion, but this rarely occurs. There is no evidence that gastric lavage improves outcome, and it is hazardous in agitated patients.

Activated charcoal has been shown to be efficacious in adsorbing diphenhydramine, tricyclic antidepressants, and phenothiazines.[40,41] However, there is no evidence that it improves outcome, and it should not be routinely used to decontaminate poisoned patients. Overall, there is insufficient evidence to support the use of either gastric emptying or activated charcoal (single or multiple doses) in patients with anticholinergic poisoning.

Physostigmine

Physostigmine is a naturally occurring acetylcholinesterase inhibitor, similar to neostigmine, pyridostigmine, and edrophonium. These agents block the degradation of ACh, which then accumulates in the synaptic space and overcomes the effects of ACh receptor blockade. Physostigmine, as a tertiary amine, is the only agent that can cross the blood-brain barrier and overcomes both central and peripheral muscarinic blockade.

The role of physostigmine in the management of anticholinergic overdoses has been controversial.[42] In the absence of anticholinergic blockade, physostigmine itself has significant toxicity. It can precipitate cholinergic excess, causing seizures, muscle weakness, bradycardia, bronchoconstriction, lacrimation, salivation, bronchorrhea, vomiting, and diarrhea. Even in documented cases of anticholinergic toxicity, seizures have been reported after the rapid administration of physostigmine.[43] Asystole has occurred after the administration of physostigmine for tricyclic antidepressant overdose,[44] so a conduction delay (QRS > 0.10 sec) or suggestion of tricyclic antidepressant ingestion is generally considered a contraindication to physostigmine administration.[45]

A retrospective study showed that physostigmine reverses delirium in 87% and agitation in 96% of patients with anticholinergic overdose.[46] Benzodiazepines controlled agitation in 24% of patients but did not reverse delirium. This study excluded patients with QRS widening unrelated to a bundle branch block.[46] Physostigmine can be used diagnostically in patients with obvious anticholinergic signs or suggested anticholinergic poisoning.[25,47] Reversal of coma or severe agitation and normalization of mental status may avoid the need for further diagnostic evaluation. Physostigmine should not be used in patients with suspected tricyclic antidepressant ingestion or as an empiric "coma" therapy.

To minimize toxicity, physostigmine should be infused over 5 minutes in an initial dose of 1 to 2 mg for adults and

0.02 mg/kg (max 0.5 mg) for children to control severe anticholinergic manifestations. This dose can be repeated in 10 to 15 minutes until a clinical response is obtained. The onset of action is within minutes of the drug's administration. Atropine should be available at the bedside, and the physostigmine infusion immediately stopped if signs of cholinergic excess develop. Since physostigmine has a relatively short duration of action of 1 hour, repeated doses may be required if clinical relapse occurs.[48]

DISPOSITION

Most patients with anticholinergic overdoses recover rapidly with sedation, temperature control, hydration, and observation. Patients who are alert, or have symptoms and vital signs that normalize during observation in the emergency department, do not require hospital admission. Patients with hyperthermia, agitation, coma, or seizures should be admitted to an intensive care unit.

The onset of symptoms after most anticholinergic ingestions is rapid; 4 hours of observation is adequate to exclude significant toxicity in an asymptomatic patient. Patients who have ingested *Datura stramonium* seeds should be observed for 8 hours because of delayed absorption.[49] Predischarge measures include psychiatric assessment, exclusion of other toxins including documentation of a nontoxic acetaminophen level, and assessment of a child's home situation.

KEY CONCEPTS

- Anticholinergic effects from medications and plants are extremely common.
- Lack of sweating is common with an anticholinergic and rare in a sympathomimetic toxidrome.
- Neither gastric emptying nor activated charcoal is of proven benefit in patients with anticholinergic poisoning.
- Hyperthermia and agitation should be aggressively treated with cooling and benzodiazepines.
- Physostigmine may be helpful in cases of severe toxicity with a known anticholinergic origin, but it has intrinsic toxicity and is not necessary in the vast majority of cases.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 149 Antidepressants

Elisabeth F. Bilden

PERSPECTIVE

Antidepressants consist of a wide variety of drugs, including cyclic antidepressants (CAs), selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), and miscellaneous agents (Table 149-1). Antidepressants can be classified based on structure or major mechanism of action.[1-3] Antidepressants account for only 4% of poisonings; however, they are involved in 23% of poisoning deaths and are the third most common cause of death from poisoning.[4] Overdoses with SSRIs result in lower morbidity and mortality than overdoses with tricyclic antidepressants (TCAs) and MAOIs.[4-8] Toxicity with miscellaneous antidepressants occurs less frequently than with TCAs and usually involves co-ingestants.[4,6,7]

CYCLIC ANTIDEPRESSANTS

Principles of Disease

TCAs and the tetracyclic antidepressant maprotiline have similar properties and are called CAs. The CAs are well absorbed from the gastrointestinal tract and reach peak plasma concentrations in 2 to 4 hours after therapeutic doses are reached.[1] Absorption is prolonged in overdose because the anticholinergic effect delays gastrointestinal motility and absorption. These pharmacokinetic data are compatible with the recommended 6-hour observation period in management of CA overdose (Fig. 149-1).[9,10] CAs are highly lipophilic, are extensively bound to plasma proteins, and have large volumes of distribution. CAs are metabolized predominantly by the liver.[1]

TCAs and their active metabolites have two basic structures: tertiary amines and secondary amines. All tertiary-amine TCAs are metabolized to secondary amines that are active. Amitriptyline forms nortriptyline, and imipramine forms desipramine. Amoxapine, a secondary amine, is metabolized to active intermediates by hepatic hydroxylation. Hydroxylation of other secondary-amine TCAs results in inactive metabolites.[1] The parent compounds and the active metabolites may undergo enterohepatic circulation.

Seven major pharmacodynamic effects of CAs result in characteristic signs and symptoms of toxicity and are manifested mainly in the cardiovascular and nervous systems (Box 149-1). Phase 0 myocardial depolarization is prolonged when sodium conductance is blocked through fast sodium channels.[11] This results in decreased conduction with a prolonged QRS complex (>100 msec) and negative inotropic effects.[11,12] Impaired excitation-contraction coupling within myocardial cells and diminished release of calcium from sarcoplasmic calcium stores decrease contractility.[11] $Alpha_1$-adrenoreceptor blockade can result in vasodilation in all vascular beds, causing hypotension from decreased preload and afterload. $Alpha_1$-blockade can decrease systemic vascular resistance, widen pulse pressure, and decrease pupil size.

Serotonin and norepinephrine reuptake inhibition within the central nervous system (CNS) predisposes to agitated delirium and seizures. Peripheral inhibition of catecholamine reuptake results in increased circulating catecholamines and initial hypertension.[13] Eventual metabolism of peripheral catecholamines by catechol-*O*-methyltransferase results in late hypotension and bradycardia.

Anticholinergic and antihistamine effects are associated with peripheral autonomic nervous system antimuscarinic effects (Box 149-2) and CNS effects of delirium, seizures, sedation, and coma (Box 149-3).[1] Potassium efflux blockade prolongs phase 3 of the myocardial action potential—repolarization—resulting in an increased duration of the QT interval. This increases the risk for developing torsades de pointes. CAs promote CNS excitation and seizures because of their indirect inhibition of γ-aminobutyric acid (GABA), the primary cerebral inhibitory neurotransmitter. CAs bind to the picrotoxin site of the $GABA_A$ receptor-chloride ionophore complex.

Clinical Features

CA poisoning initially manifests with anticholinergic symptoms, including sinus tachycardia and early hypertension (see Chapter 148). Severe poisoning is characterized by subsequent convulsions, coma, and cardiovascular collapse. CA toxicity should be considered in all patients with a decreased level of consciousness and prolonged QRS complex. Mental status changes do not predict the occurrence of seizures, and 23% of patients are awake and alert immediately before a seizure.[14]

Hypotension caused by CA poisoning can occur with or without QRS prolongation (>100 msec).[15] Hypotension can result from myocardial depression or peripheral vasodilation. Catastrophic cardiovascular collapse closely follows seizures in 13% of patients with CA-induced seizures.[14] Cardiovascular collapse is attributed to lactic acidosis, which impairs myocardial sodium conduction.

Patients can deteriorate rapidly, and even patients with trivial signs of poisoning on presentation can have a 50% mortality rate.[16] Because of rapid deterioration, death rates of 44%

Table 149-1 Antidepressants Approved by U.S. Food and Drug Administration

GENERIC NAME	TRADE NAME	MECHANISM OF ACTION
Tricyclics		
Amitriptyline	Elavil	5-HT and NE reuptake inhibition
Amoxapine	Asendin	NE reuptake inhibition DA_2 receptor inhibition
Clomipramine	Anafranil	5-HT and NE reuptake inhibition
Desipramine	Norpramin	NE reuptake inhibition
Doxepin	Sinequan	5-HT and NE reuptake inhibition
Imipramine	Tofranil	Same
Nortriptyline	Pamelor	NE reuptake inhibition
Protriptyline	Vivactil	Same
Trimipramine	Surmontil	5-HT and NE reuptake inhibition
Tetracylic		
Maprotiline	Ludiomil	NE reuptake inhibition
Selective Serotonin Reuptake Inhibitors		
Citalopram	Celexa	Selective 5-HT reuptake inhibition
Escitalopram	Lexapro	Same
Fluoxetine	Prozac	Same
Paroxetine	Paxil	Same
Sertraline	Zoloft	Same
Miscellaneous		
Bupropion	Wellbutrin	DA and NE reuptake inhibition
Desvenlafaxine	Pristiq	Same
Duloxetine	Cymbalta	5-HT and NE reuptake inhibition
Mirtazapine	Remeron	$Alpha_2$-adrenoreceptor antagonism*
		$5\text{-}HT_2$ and $5\text{-}HT_3$ receptor antagonism
Nefazodone		5-HT reuptake inhibition
		$5\text{-}HT_2$ receptor antagonism
Trazodone	Desyrel	Same
Venlafaxine	Effexor	5-HT and NE reuptake inhibition
Monoamine Oxidase Inhibitors (MAOI)		
Isocarboxazid	Marplan	MAOI
Phenelzine	Nardil	MAOI
Selegiline	Emsam	MAOI
Tranylcypromine	Parnate	MAOI

*With disinhibition of serotonin and norepinephrine neurotransmission (i.e., increased neurotransmission).
DA, dopamine; 5-HT, serotonin; NE, norepinephrine.

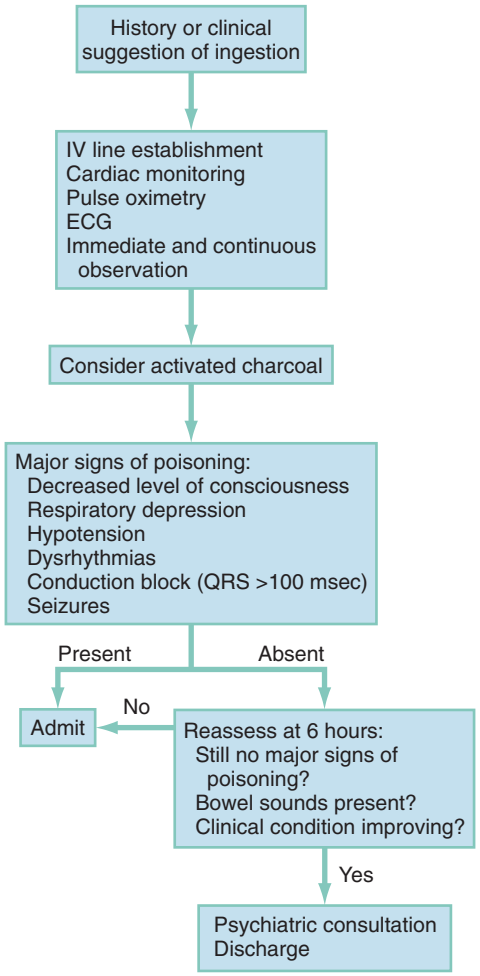


Figure 149-1. Algorithm for management of cyclic antidepressant overdose. (Modified from Cyclic antidepressant (CA) overdose. In Callaham M [ed]: Current Therapy in Emergency Medicine. Philadelphia, BC Decker, 1991.)

BOX 149-1 Major Pharmacodynamic Effects of Cyclic Antidepressants

1. Sodium channel blockade (quinidine-like membrane-stabilizing effects)
2. $Alpha_1$-adrenoreceptor blockade
3. Inhibition of reuptake of biogenic amines (e.g., norepinephrine, serotonin)
4. Muscarinic receptor blockade (anticholinergic effects)
5. Histamine receptor blockade (antihistaminic effects)
6. Potassium efflux blockade
7. Indirect $GABA_A$ antagonism caused by binding at picrotoxin receptor

GABA, γ-aminobutyric acid.

have been reported for patients en route to the hospital, many of whom were initially awake and alert with normal sinus rhythm.[16] Most serious complications develop within 30 to 60 minutes of presentation, usually while in the emergency department.[15]

CAs also can cause cardiogenic or noncardiogenic pulmonary edema. Acute myocardial infarction is rare in the setting of CA toxicity.[17] Amoxapine has fewer cardiac effects but a greater incidence of seizures. The tetracyclic, maprotiline, has more cardiac and CNS effects than TCAs.

Diagnostic Strategies

A history of CA overdose is the most helpful diagnostic indicator. A dose greater than 10 mg/kg or 1000 mg in an adult should be considered life-threatening. Patients who have an anticholinergic toxidrome, decreased level of consciousness, QRS prolongation (>100 msec), or rightward deviation of the terminal 40-msec QRS axis (R wave in aVR > 3 mm or R/S_{aVR} ratio of >0.7) should be considered to have CA poisoning until

BOX 149-2 PERIPHERAL NERVOUS SYSTEM EFFECTS OF CYCLIC ANTIDEPRESSANTS

Anticholinergic
Tachycardia
Hyperthermia
Mydriasis
Anhydrosis
Red skin
Decreased bowel sounds
Ileus
Urinary retention
Distended bladder

Alpha$_1$-Blockade
Reflex tachycardia
Miosis or midrange pupils

BOX 149-3 CENTRAL NERVOUS SYSTEM EFFECTS OF CYCLIC ANTIDEPRESSANTS

Excitation
Agitation
Delirium
Myoclonic jerks
Hyper-reflexia
Clonus
Seizures
Hyperthermia

Inhibition
Sedation
Coma

proven otherwise (Fig. 149-2).[18] With QRS prolongation greater than 100 msec in the limb leads, 30% of patients experience seizures; for prolongation greater than 160 msec, 50% develop dysrhythmias. CAs can induce an electrocardiogram (ECG) pattern consistent with the Brugada's syndrome, a genetic disorder resulting in sodium channel dysfunction. A right bundle branch block and ST segment elevation in the right precordial leads (V_1 through V_3) are seen.[19,20] CA toxicity is not fully excluded with normal ECG findings.

Quantitative serum toxicology tests for CAs are not usually available in a timely fashion and do not predict adequately the degree of toxicity. Qualitative laboratory tests may document only exposure. Neither serum toxicology tests nor laboratory tests are useful for clinical decision-making. Diagnosis, treatment, and disposition should be based on a clinical basis and with ECG and cardiac monitoring.[9,10]

Differential Considerations

The differential diagnosis of CA poisoning is extensive and includes intoxications by anticholinergic, psychiatric, and cardiac medications, especially type I antidysrhythmics. Many conditions cause sinus tachycardia and hypotension with a wide pulse pressure; however, QRS widening, seizures, or coma suggests CA poisoning.

Management

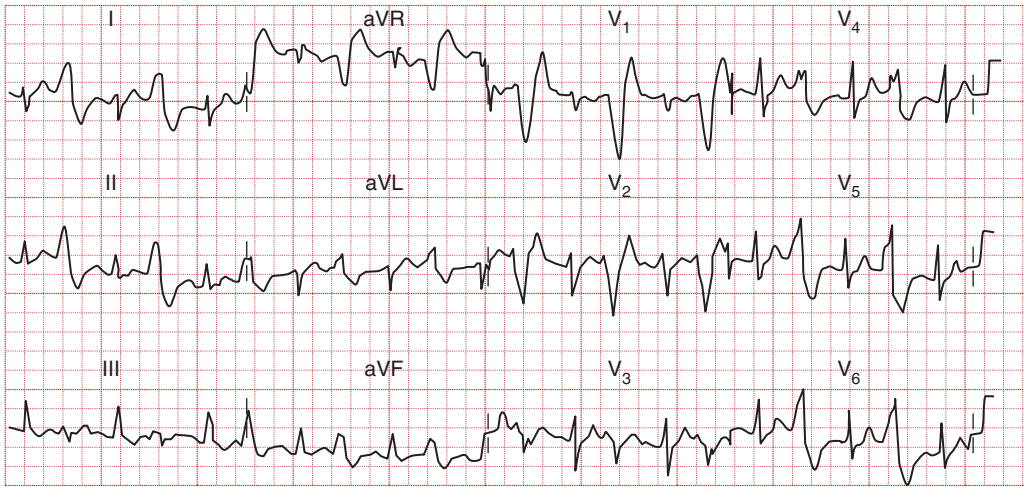
Treatment begins with assessment of airway and breathing. Endotracheal intubation should be performed if the patient is exhibiting a markedly decreased level of consciousness or if the level of consciousness is rapidly deteriorating. Respiratory depression, with attendant hypoxia and hypercarbia, significantly increases morbidity and mortality from CA poisoning. Patients with overdoses severe enough to require admission to the intensive care unit (ICU) have a high incidence of airway and breathing complications, with aspiration pneumonitis reported in 13 to 18% of patients.[21] The initial benign appearance of the patient's presentation may be deceptive; rapid deterioration with cardiac dysrhythmias, generalized seizures, and death can occur despite appropriate management.

Ventilatory support to avoid respiratory acidosis is crucial because acidosis inhibits conductance through fast sodium channels. Any patient with a significant CA overdose should have continuous pulse oximetry. Arterial blood gas determination or capnography may be helpful when ventilatory function is questionable despite normal oxygen saturations on pulse oximetry. Patients with low minute volumes, hypoxia, and acidosis can appear clinically to be ventilating adequately.

Gastric lavage and administration of activated charcoal within 60 minutes from time of significant ingestion is theoretically appealing, and despite the general lack of evidence for efficacy, the toxicity of these drugs is high and any decrease in the absorption may be helpful. If the patient is thought to have ingested sufficient CA to prompt gastric lavage, this should be preceded by intubation for airway protection, since the risk of deterioration is high. The use of physostigmine is not recommended. Seizures, cardiac arrest, and death have occurred when physostigmine has been used in CA overdose.[22]

Hypertension is usually mild and transient and requires no treatment (Table 149-2). Treatment of hypotension begins with isotonic crystalloids. If the QRS is greater than 100 msec, and the patient is symptomatic, with hypotension or a dysrhythmia, or if the patient is acidemic, intravenous (IV) sodium bicarbonate ($NaHCO_3$) also should be administered.[23] $NaHCO_3$ produces an alkaline pH and provides a sodium load and hypertonicity that increase sodium conductance through myocardial fast sodium channels.[11] Hyperventilation and hypertonic sodium chloride also enhance sodium conduction.[24] Hypertonic sodium chloride has been used for treating hypotension with QRS widening caused by CA-induced cardiotoxicity unresponsive to standard therapies.[25] Serum alkalinization is clinically effective in decreasing CA-induced intraventricular conduction delays. The major effect of increasing pH seems to be increased sodium conductance through myocardial sodium channels rather than the increase in plasma protein binding.[11] $NaHCO_3$ is administered by IV boluses of 1 to 2 mEq/kg until the QRS narrows or until serum pH increases to 7.50 to 7.55. After obtaining the desired endpoint with IV $NaHCO_3$ boluses, a continuous infusion can be maintained by adding three ampules of 8.4% $NaHCO_3$ (50 mEq/ampule, 100 mOsm/ampule) to 1 L of 5% dextrose in water. The initial IV infusion is started at a usual maintenance rate for IV fluids, based on the patient's weight. This initial $NaHCO_3$ infusion rate often must be maintained for at least 4 to 6 hours before the rate can be decreased. For a hypertonic continuous IV solution, four ampules of 8.4% $NaHCO_3$ can be added to 1 L of 5% dextrose in water. This infusion is occasionally necessary for refractory hypotension with a prolonged QRS or refractory ventricular dysrhythmias.

Excess $NaHCO_3$ and saline can worsen heart failure and should be avoided. Excessive alkalemia from combined use of hyperventilation and $NaHCO_3$ can result in complications, including death.[26] Repeat boluses and continuous IV infusion should be guided by serial measurements of arterial pH and QRS duration. When symptoms are refractory, hypertonic



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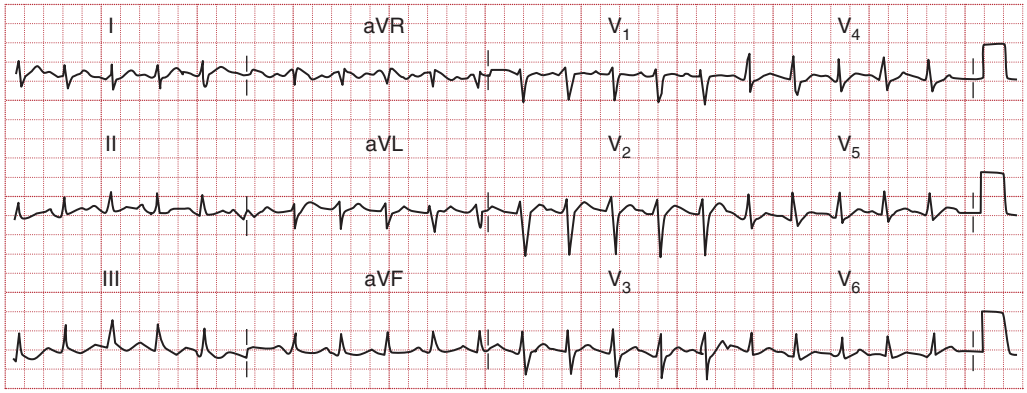

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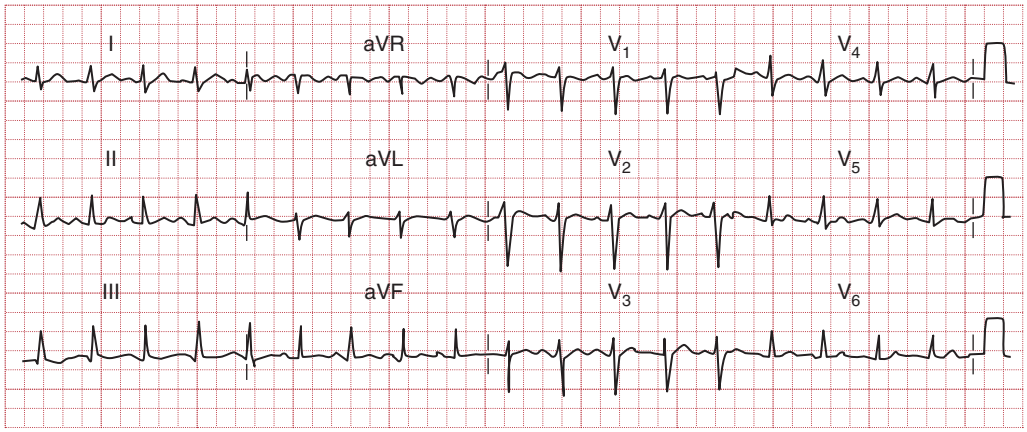


C

Figure 149-2. Electrocardiographic (ECG) changes in cyclic antidepressant poisoning. **A,** ECG of a 24-year-old woman who ingested 2.5 g of desipramine shows ventricular bigeminy, right axis deviation, wide QRS complex, long QT_c interval, and right deviation of terminal 40-msec QRS vector in limb leads, with prominent R wave in aVR. **B,** ECG of same patient after receiving bolus and continuous intravenous infusion of sodium bicarbonate shows sinus tachycardia, 90-degree axis, slight prolongation of QRS and QT_c intervals, and persistent right axis deviation of terminal 40 msec in limb leads. **C,** ECG of same patient 25 hours after ingestion and 4 hours after termination of sodium bicarbonate infusion shows persistent but improved sinus tachycardia, normalization of QRS axis and width, normalization of QT_c interval, and resolution of prominent R wave in aVR.

sodium chloride boluses can be used to treat hypotension and a wide QRS interval with ventricular ectopy.[25] If hypotension does not resolve, norepinephrine or dopamine is recommended.[8] High-dose dopamine (20–30 μg/kg/min) and norepinephrine (0.1–1 μg/kg/min) may be necessary for the direct $alpha_1$-agonist effect.[27] For inotropic support alone, dobutamine is controversial.[11] Vasopressin has been used to treat refractory hypotension following amitriptyline poisoning; and intralipid infusion has been used in an animal model to successfully treat hypotension due the fat-soluble drug clomipramine.[28,29]

Sinus tachycardia is usually well tolerated and does not require specific therapy. Beta-receptor antagonists and physostigmine should not be used.[23] Wide-complex tachycardia is

Table 149-2 Cardiovascular Complications of Cyclic Antidepressant Toxicity and Treatments

COMPLICATION	MECHANISM: CAUSE		TREATMENT
	CARDIAC	*PERIPHERAL VASCULAR*	
Hypertension (early and transient)	Positive chronotropism: Anticholinergic vagolytic effects Positive inotropism: Increased circulating catecholamines caused by reuptake inhibition	Initial vasoconstriction: Increased circulating catecholamines caused by reuptake inhibition	Not indicated
Hypotension	Negative inotropism: Fast sodium channel inhibition with impairment of excitation-contraction coupling	Vasodilation: Alpha$_1$-adrenoreceptor blockade	IV isotonic crystalloid IV $NaHCO_3$ if QRS >100 msec Norepinephrine or dopamine
Sinus tachycardia	Positive chronotropism: Anticholinergic vagolytic effects Positive chronotropism: Increased circulating catecholamines caused by reuptake inhibition	Reflex tachycardia: Alpha$_1$-adrenoreceptor blockade	Not indicated
Ventricular tachycardia (monomorphic)	Negative dromotropism: Fast sodium channel inhibition with QRS prolongation		IV $NaHCO_3$ Synchronized cardioversion Overdrive pacing
Ventricular tachycardia (polymorphic) (torsades de pointes)	Negative dromotropism: Fast sodium channel inhibition with QRS prolongation and resultant QT prolongation, and potassium efflux inhibition		Magnesium sulfate for torsades de pointes
Bradydysrhythmias (late and uncommon)	Negative dromotropism: Fast sodium channel inhibition Negative chronotropism: Impaired automaticity from threshold voltage elevation and slowing of phase 4 depolarization		ACLS algorithm for bradycardia
QRS prolongation, QT prolongation	Negative dromotropism: Fast sodium channel inhibition (potassium efflux inhibition), PR prolongation, rightward terminal 40-msec QRS axis deviation		IV $NaHCO_3$ for symptomatic QRS prolongation

ACLS, advanced cardiac life support; IV $NaHCO_3$, intravenous sodium bicarbonate.

not always ventricular tachycardia and can represent sinus tachycardia with aberrant conduction; however, treatment in either case is IV $NaHCO_3$.[11] Lidocaine is not consistently effective.[30] Phenytoin has been shown to increase the frequency and duration of episodes of ventricular tachycardia and is not recommended as an antidysrhythmic agent.[31] Type IA antidysrhythmics (quinidine, disopyramide, procainamide) and type IC antidysrhythmics (flecainide, moricizine, propafenone) are contraindicated because they also inhibit fast sodium channels. A transvenous pacemaker and overdrive pacing can be used for CA-associated polymorphic ventricular tachycardia (torsades de pointes) that is not responsive to magnesium. CA poisoning can result in increased threshold requirements for ventricular pacing and decreased electric cardioversion and defibrillation effectiveness. Bradydysrhythmias are rare and late in CA overdose.

QT prolongation, PR prolongation, and rightward terminal 40-msec QRS axis deviation do not mandate specific therapy.[11,23] Treatment with $NaHCO_3$, hypertonic sodium chloride, and hyperventilation does not completely correct QT prolongation, which involves not only sodium channel blockade, but also protracted repolarization from potassium efflux blockade.

Treatment of neurologic complications of CA poisoning includes early intubation with mechanical ventilation for coma (Table 149-3). Benzodiazepines should be used for agitation because they do not have the anticholinergic or cardiac conduction effects of some antipsychotic medications. Status epilepticus or prolonged seizures account for 20 to 30% of the seizures caused by CAs.[14,32] These seizures usually respond to IV lorazepam or diazepam.[14] Seizures refractory to other benzodiazepines have terminated with IV midazolam boluses of 2.5 to 10 mg and continuous IV infusions.[33]

If benzodiazepines fail to terminate prolonged or repetitive seizures, phenobarbital may be administered in a loading dose of 20 mg/kg, given at a rate of up to 50 mg/min in adults or up to 1 mg/kg/min in children. Propofol is also used to treat refractory seizures successfully.[34] A loading dose of 2.5 mg/kg is followed by continuous infusion of 25 to 200 µg/kg/min.[34] Phenytoin may cause more and longer episodes of ventricular tachycardia and is unlikely to be effective for seizures.[31] If maximal doses of benzodiazepines, phenobarbital, or propofol are ineffective, neuromuscular blockade and general anesthesia with continuous electroencephalogram monitoring are recommended to prevent rhabdomyolysis and hyperthermia caused by excessive muscle activity.

Table 149-3 Treatment of Neurologic Complications of Antidepressant Poisoning

COMPLICATION	TREATMENT
Coma	Endotracheal intubation Mechanical ventilation Supportive care
Seizures	Lorazepam or diazepam Phenobarbital, continuous intravenous midazolam infusion, or propofol
Hyperthermia	Cessation of seizures with benzodiazepines and phenobarbital Neuromuscular blockade with vecuronium during phenobarbital loading General anesthesia with continuous EEG monitoring Evaporative cooling Ice water bath

EEG, electroencephalogram.

Flumazenil is contraindicated, even if benzodiazepines are known coingestants.[35,36] Flumazenil counteracts the anticonvulsant activity of the co-ingested benzodiazepines. Seizures, ventricular tachycardia, and ventricular fibrillation can occur when flumazenil is used in mixed benzodiazepine-CA overdoses.[36]

Life-threatening hyperthermia (rectal temperature > 40° C) is best treated with control of seizures and neuromuscular blockade. A nondepolarizing neuromuscular blocker (e.g., rocuronium) is recommended if rhabdomyolysis and hyperkalemia with ECG changes are present. Evaporative cooling should be used until core temperature reaches 38.5° C. Forced diuresis, hemodialysis, and hemoperfusion are not helpful because CAs have large volumes of distribution, are highly bound to plasma proteins, and are minimally eliminated by the kidneys.

Disposition

Patients with known or possible CA overdoses require observation with continuous cardiac monitoring and pulse oximetry. After 6 hours of observation, patients may be discharged for psychiatric evaluation if they do not develop (1) ventilatory insufficiency, (2) desaturation on pulse oximetry, (3) QRS greater than 100 msec, (4) sinus tachycardia greater than 120 beats/min, (5) dysrhythmias, (6) hypotension, (7) decreased level of consciousness, (8) seizures, or (9) abnormal or inactive bowel sounds. Patients who exhibit any of these findings should be admitted to an ICU (see Fig. 149-1).[9,10]

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

SSRIs approved in the United States for treatment of depression are fluoxetine (Prozac), paroxetine (Paxil), sertraline (Zoloft), citalopram (Celexa), and escitalopram (Lexapro). Fluvoxamine (Luvox) is approved in the United States for treating obsessive-compulsive disorder. Combination medications also exist such as olanzapine with fluoxetine (Symyax).

Principles of Disease

SSRIs are well absorbed from the gastrointestinal tract and reach peak plasma concentrations 3 to 8 hours after achieving therapeutic doses. Controlled-release paroxetine reaches peak serum concentration 6 to 10 hours after ingestion. Because SSRIs have no significant anticholinergic effects, they are less likely than CAs to have delayed absorption. SSRIs are highly lipophilic, are extensively bound to plasma proteins, and have large volumes of distribution (12–97 L/kg).[1]

SSRIs are metabolized predominantly by the liver. The elimination half-life is about 15 hours for fluvoxamine, about 1 day for paroxetine and sertraline, 27 hours for escitalopram, 35 hours for citalopram, and 1 to 4 days for fluoxetine. Fluoxetine, sertraline, citalopram, and escitalopram have active metabolites that increase the duration of their effect. Fluoxetine is demethylated to its clinically active metabolite, norfluoxetine, with a half-life of 4 to 9 days.[1] The long half-lives of the SSRIs and their active metabolites explain the long interval necessary to avoid the life-threatening serotonin syndrome when stopping SSRI treatment and beginning MAOI treatment. MAOI therapy should not be initiated until at least 5 weeks after stopping fluoxetine and for at least 2 weeks after stopping the other SSRIs. Likewise, none of the SSRIs should be used for at least 2 weeks after stopping MAOI treatment. Minimal amounts of SSRIs are eliminated in the urine as unchanged drugs.

Enterochromaffin cells of the gastrointestinal tract contain 90% of the total serotonin in adults. Most remaining serotonin is in platelets and the CNS. In the CNS, serotonin is involved with mood, depression, anxiety, obsession, compulsion, perception of pain, migraine headaches, sleep, circadian rhythms, temperature regulation, and regulation of blood pressure. Serotonin's roles in the periphery involve regulating gastrointestinal motility and facilitating hemostasis by promoting vasoconstriction and platelet aggregation. The antidepressant effects of SSRIs are thought to be due to the blockade of presynaptic reuptake of serotonin at the 5-hydroxytryptamine type 1 ($5\text{-}HT_1$) autoreceptors, resulting in an increased concentration of intrasynaptic serotonin.[1]

Clinical Features

Overdose

The signs, symptoms, and morbidity and mortality rates for SSRI poisoning are much less than for CA poisoning. The organ systems most affected by excessive serotonin are the gastrointestinal tract, cardiovascular system, and CNS (Table 149-4). Overdose can cause sedation, agitation, tremor, hyper-reflexia, tachycardia, bradycardia, nausea, vomiting, abdominal pain, facial flushing, and dizziness. Syndrome of inappropriate secretion of antidiuretic hormone and priapism can occur rarely but are unique to specific substances. Severe overdose can cause seizures and cardiac toxicity, and the frequency of severe symptoms increases with coingestants.[37]

Fluoxetine. About 45% of adults and 90% of children who overdose on fluoxetine alone develop no symptoms.[3,38] Common symptoms of fluoxetine overdose include agitation, anxiety, restlessness, confusion, and hypomania.[39] Other milder symptoms are tachycardia, drowsiness, tremor, nausea, and vomiting. In children, 5% develop diarrhea, and 5% develop sleepiness.[3] QT_c prolongation, torsades de pointes, QRS widening, ventricular bigeminy, ventricular tachycardia, and seizures, with delayed onset 10 hours after ingestion, are rare with fluoxetine overdose.[39-41]

Fluvoxamine. Tachycardia, bradycardia, hypotension, ECG abnormalities, seizures, liver function abnormalities, coma, and death have been reported with fluvoxamine.[39] Status epilepticus and refractory hypotension also have been described with fluvoxamine toxicity.[42,43]

Table 149-4 Clinical Manifestations of Acute Fluoxetine Overdoses in Adults

NEUROMUSCULAR SYSTEM		CARDIOVASCULAR SYSTEM		GASTROINTESTINAL SYSTEM	
MANIFESTATIONS	%	MANIFESTATIONS	%	MANIFESTATIONS	%
Drowsiness	21	Sinus tachycardia	22	Nausea	6
Tremor	8	Hypertension	6	Emesis	6
Euphoria	2	Trigeminy	2	Abdominal pain	2
Headache	2	Junctional rhythm	2		

From Borys DJ, et al: Acute fluoxetine overdose: A report of 264 cases. Am J Emerg Med 10:115, 1992.

Citalopram. Gastrointestinal upset; mild CNS changes, such as dizziness and somnolence; and mild autonomic symptoms, such as tachycardia, are observed with ingestions of citalopram less than 600 mg.[2,8,44] QT_c prolongation has been observed after an ingestion of 400 mg.[44] At higher doses, QT_c prolongation, QRS widening, ventricular fibrillation, seizures, and death have been reported.[2,3,44] Seizures have been reported to start 14 hours after a citalopram and fluoxetine overdose.[45] Seizures and QT_c prolongation followed by torsades de pointes with cardiac arrest have been observed 13 hours following overdose.[46,47] A prolonged observation period beyond the routine 6-hour observation period is suggested following citalopram overdose.

Escitalopram. Limited information is available about this enantiomer of citalopram. Ingestion of 600 mg is associated with only minor effects, including drowsiness, agitation, and tachycardia. No seizures were reported.[48] Clinical toxicity is similar for overdose of citalopram when compared with escitalopram, with the most frequent symptoms being drowsiness, lethargy, tachycardia, and hypertension.[49]

Sertraline and Paroxetine. Mild symptoms after sertraline or paroxetine overdose are similar to symptoms with other SSRIs. Seizures and death have been reported with large doses of sertraline.[50] In general, deaths attributed to SSRI overdose usually are associated with polydrug poisonings involving significant co-ingestants.[8,50]

Serotonin Syndrome

Serotonin syndrome is a constellation of signs and symptoms manifesting as autonomic, neuromuscular, and mental status changes (Box 149-4).[1,51,52] Various drugs increase serotonin concentrations and serotoninergic neurotransmission (Table 149-5). Serotonin syndrome can occur when (1) a serotoninergic agent is added to an established medication regimen, (2) the dose of a serotoninergic agent is increased, or (3) high but usually therapeutic doses of a serotoninergic agent are taken.[51] Sternbach suggested diagnostic criteria for the serotonin syndrome (Box 149-5); these also could include signs and symptoms of severe disease, such as muscle rigidity, clonus, hypertension, and tachycardia.[51,53] The Hunter criteria are diagnostic decision rules for diagnosing serotonin toxicity (Box 149-6).[54]

Diagnostic Strategies

A history of SSRI dosage increase, SSRI overdose, or SSRI use with an incompatible drug is the most helpful diagnostic indicator. Urine and blood toxicology tests for SSRIs are not readily available nor clinically useful.

BOX 149-4 Clinical Manifestations of Serotonin Toxicity

Neuromuscular
Agitation
Akathisia
Anxiety
Ataxia
Bilateral Babinski's signs
Clonus
Coma
Confusion
Delirium
Diaphoresis
Dysarthria
Euphoria
Headache
Hyper-reflexia
Hyperthermia
Hypomania
Insomnia
Mania
Mydriasis
Myoclonus
Nystagmus
Piloerection
Rhabdomyolysis
Rigidity
Seizures
Shivering
Tremor

Cardiovascular
Cutaneous flushing
Hypertension
Hypotension
Sinus tachycardia
Ventricular tachycardia (rare)

Gastrointestinal
Abdominal cramps
Diarrhea
Salivation

Differential Considerations

The differential diagnosis of SSRI poisoning includes intoxications and pathologic conditions that cause sinus tachycardia, hypertension or hypotension, gastrointestinal upset, and seizures. In addition to these signs and symptoms secondary to SSRI overdose, SSRIs can produce serotonin syndrome (see

Table 149-5 Drugs Associated with Serotonin Toxicity

INCREASED SEROTONIN SYNTHESIS	INCREASED SEROTONIN RELEASE
L-Tryptophan*	Amphetamines
	Cocaine
	Codeine
	Dextromethorphan
	Fenfluramine
	Levodopa
	Pentazocine
	Reserpine
Decreased Serotonin Degradation (Monoamine Oxidase Inhibitors)	**Decreased Serotonin Reuptake**
Amphetamine metabolites*	Amphetamines
Clorgyline*	Carbamazepine
Iproniazid*	Citalopram
Isocarboxazid	Cocaine
Moclobemide*	Cyclic antidepressants
Pargyline*	Dextromethorphan
Phenelzine	Fluoxetine
Selegiline	Fluvoxamine
Tranylcypromine	Meperidine
	Methadone
	Paroxetine
	Sertraline
	Trazodone
	Venlafaxine
Direct or Indirect Serotonin Receptor Agonists	
Buspirone	
Electroconvulsive therapy	
Lithium	
LSD and other indoles*	
Mescaline and other phenylalkylamines*	
Sumatriptan	

*Not marketed in the United States.
LSD, D-lysergic acid diethylamide.

BOX 149-5 Sternbach's Diagnostic Criteria for Serotonin Syndrome

Adding a serotoninergic agent to a patient's established medication regimen or increasing the dose of a patient's serotoninergic agent.
At least three of the following signs and symptoms:
- Agitation
- Ataxia
- Diaphoresis
- Diarrhea
- Hyper-reflexia
- Hyperthermia
- Mental status changes (e.g., confusion, hypomania)
- Myoclonus
- Shivering
- Tremor

A neuroleptic has not been started or increased in dosage before the onset of the above signs and symptoms.
Other etiologies, such as infections, intoxications, metabolic derangements, and withdrawal, have been ruled out.

From Sternbach H: The serotonin syndrome. Am J Psychiatry 148:705, 1991.

BOX 149-6 Hunter Serotonin Toxicity Criteria: Decision Rules

In the presence of a serotonergic agent:

1. *If* (spontaneous clonus = *yes*), *then* serotonin toxicity = *yes*
2. *Else If* (inducible clonus = *yes*) *and* [(agitation = *yes*) *or* (diaphoresis = *yes*)], *then* serotonin toxicity = *yes*
3. *Else If* (ocular clonus = *yes*) *and* [(agitation = *yes*) *or* (diaphoresis = *yes*)], *then* serotonin toxicity = *yes*
4. *Else If* (tremor = *yes*) *and* (hyper-reflexia = *yes*), *then* serotonin toxicity = *yes*
5. *Else If* (hypertonic = *yes*) *and* (temperature > 38° C) *and* [(ocular clonus = *yes*) *or* (inducible clonus = *yes*)], *then* serotonin toxicity = *yes*
6. *Else* serotonin toxicity = *no*

From Dunkley EJC, et al: The Hunter serotonin toxicity criteria: Simple and accurate diagnostic decision rules serotonin toxicity. QJM 96:635, 2003.

Boxes 149-5 and 149-6). CNS and other infections, intoxications (e.g., methamphetamine, cocaine, other sympathomimetics), metabolic derangements (e.g., thyroid storm), sedative-hypnotic withdrawal, and strychnine poisoning should be considered in the differential diagnosis of serotonin syndrome. Clinically, serotonin syndrome can be difficult to distinguish from neuroleptic malignant syndrome. A history of precipitating medication use (SSRI vs. neuroleptic), more rapid onset of symptoms, and presence of clonus helps differentiate serotonin syndrome from neuroleptic malignant syndrome (Table 149-6).

Management

Activated charcoal may be considered, but SSRI toxicity is mild and rare so the overall potential risk-benefit consideration would argue against this. Hemodialysis and hemoperfusion are not indicated because SSRIs have large volumes of distribution and are highly bound to plasma proteins.[1] Forced diuresis is not helpful because minimal amounts of SSRIs and their active metabolites are eliminated in the urine.

Cardiovascular complications of serotonin toxicity include hypertension, sinus tachycardia, hypotension, and, rarely, ventricular dysrhythmias (Table 149-7).[51] Hypertension and tachycardia are usually mild and transient and require no treatment.[3] Hypotension is treated with isotonic crystalloids, and vasopressors are rarely necessary. Ventricular dysrhythmias should be treated with standard antidysrhythmic agents (e.g., lidocaine) (see Table 149-7).[3] QRS prolongation with fluoxetine toxicity has responded to IV $NaHCO_3$ treatment.[40]

Neurologic complications of SSRI overdose and serotonin syndrome are treated with benzodiazepines. Cyproheptadine, methysergide, chlorpromazine, and propranolol have been proposed as therapies, but have inconsistent effects. They have been used in isolated case reports of serotonin syndrome; however, none of these should be considered a proven therapy or diagnostic modality.[51] Cyproheptadine is available as a liquid that can be given through a nasogastric tube, beginning with an adult dose of 4 to 8 mg followed by 4-mg doses every 1 to 4 hours as needed to a maximum of 32 mg/day. For children, 0.25 mg/kg/day is given in divided

Table 149-6 Comparison of Serotonin Toxicity and Neuroleptic Malignant Syndrome

FACTOR MALIGNANT SYNDROME	SEROTONIN TOXICITY	NEUROLEPTIC
Dopamine antagonists	No	Yes
Serotonin agonists	Yes	No
Onset of symptoms	Within minutes to hours	Usually over days to weeks, may occur immediately
Hyperthermia, altered level of consciousness, autonomic dysfunction, muscle rigidity	Present in varying degrees	Almost universal for each sign
Leukocytosis, metabolic acidosis	Unusual	Very common
Elevated creatine kinase	Present in varying degrees	Very common
Hyper-reflexia, myoclonus	Present in varying degrees	Unusual
Treatment	Benzodiazepines, cyproheptadine	Bromocriptine
Resolution of symptoms	Resolution of symptoms begins but not complete in <24 hours; usually 24–48 hours to complete	Usually over days to weeks

Table 149-7 Treatment of Cardiovascular Complications of Selective Serotonin Reuptake Inhibitor Overdose and Serotonin Toxicity

COMPLICATION	TREATMENT
Hypertension	Not usually indicated Sodium nitroprusside if clinical signs of hypertensive emergency
Hypotension	Intravenous isotonic crystalloid, then norepinephrine or dopamine
Sinus tachycardia	Not usually indicated
Ventricular tachycardia	ACLS algorithm for ventricular tachycardia (lidocaine, synchronized cardioversion) IV $NaHCO_3$ if symptomatic with wide QRS complex
Bradydysrhythmias (rare)	ACLS algorithm for bradycardia

ACLS, advanced cardiac life support; IV $NaHCO_3$, intravenous sodium bicarbonate.

doses every 6 hours to a maximum of 12 to 16 mg/day depending on the child's age and weight. For children 2 to 6 years old, 2-mg doses can be given to a maximum of 12 mg/day based on the child's weight. For children 7 to 14 years old, 4-mg doses can be given to a maximum of 16 mg/day. Complications are rare, but cyproheptadine should be avoided in anticholinergic overdoses.

Disposition

Asymptomatic patients with known or suggested SSRI overdose should have a 6-hour observation period with cardiac monitoring before psychiatric evaluation and disposition. Because ECG abnormalities and seizures have been reported later in the course of citalopram overdoses, these overdoses warrant observation up to 12 hours.[45]

Patients with known or suggested serotonin syndrome should be admitted to a monitored inpatient unit for 24 hours of observation. The clinical course and treatment of serotonin syndrome is less defined than that of SSRI overdose. Serotonin syndrome can be fatal and may require ICU admission for potential complications (e.g., ventricular tachycardia, hypotension, coma, hyperthermia, rhabdomyolysis).

MISCELLANEOUS ANTIDEPRESSANTS

Bupropion (Wellbutrin, Zyban), trazodone (Desyrel), nefazodone, venlafaxine (Effexor), desvenlafaxine (Pristiq), duloxetine (Cymbalta), and mirtazapine (Remeron) are the seven antidepressants approved by the U.S. Food and Drug Administration that constitute the miscellaneous category. Serzone was withdrawn because of liver toxicity. The structures and mechanisms of action of the miscellaneous antidepressants are unique and unrelated to the CAs, SSRIs, and MAOIs.

Bupropion

Bupropion is available in immediate-release, sustained-release, and newer extended-release formulations. A sustained-release formulation of bupropion is approved for smoking cessation. Bupropion is well absorbed from the gastrointestinal tract, reaches peak concentrations in 2 hours for immediate-release formulations, and has a maximal serum concentration of metabolites at 3 to 4 hours. The sustained-release peak concentration occurs at 3 hours for the parent compound and at 5 to 6 hours for the metabolites. The extended-release parent compound peak concentration occurs at 5 hours and at 7 to 8 hours for the metabolites. Bupropion is highly lipophilic, is extensively bound to plasma proteins, has a large volume of distribution (20–30 L/kg), and is metabolized predominantly by the liver. It has a half-life of 10 to 21 hours. Bupropion has three metabolites; two are active and clinically significant, with half-lives longer than 20 hours. Bupropion inhibits dopamine reuptake and enhances dopaminergic neurotransmission. To a lesser extent, bupropion also enhances noradrenergic neurotransmission by inhibition of norepinephrine reuptake and has very little serotonin reuptake inhibition.[1]

Clinical Features

Bupropion's most significant toxic effect is seizure activity, which occurs not only with overdose but also when the maximal daily dose is exceeded.[55] At the recommended daily dose of 450 mg of immediate-release bupropion, the seizure incidence is 0.4%.[56] Incidence increases to 4% with dosages of 450 to 600 mg/day.[1] The incidence of seizure with the sustained-release formulation is 0.1%. Seizures cannot be predicted from ECG or cardiac monitoring, and there is no correlation between seizures and the presence of other symptoms.[57]

Patients who overdose on bupropion alone do not usually develop hypotension or coma, but concomitant overdose with

benzodiazepines can lead to coma or respiratory failure. The rare deaths associated with bupropion overdose usually involve co-ingestants.[58] Deaths due to bupropion alone have been reported, however.[59] Tachycardia, vomiting, agitation, lethargy, tremor, confusion, and drowsiness are the most common symptoms in adults and teenagers; vomiting is the most common symptom in children.[59] A significant number of intentional overdoses result in seizures.[59] Seizures are usually single and self-limited, but about 5% of patients develop status epilepticus.[59] Delayed onset of seizures has been recorded at 19 and 32 hours after ingestion of a sustained-release product.[60,61] These seizures were thought to be caused by the slow-release nature of the parent product and accumulation of its active metabolites.[61] Cardiovascular complications, including hypotension, bradycardia, intraventricular conduction delays, asystole, and death, have been recently reported.[60,62] A pharmacobezoar was noted in one fatal sustained-release bupropion overdose.[60]

Management

Bupropion-induced seizures should be treated with IV benzodiazepine (e.g., lorazepam, diazepam). Patients who have recurrent seizures or status epilepticus should be loaded with phenobarbital. Phenytoin is not indicated. If neuromuscular blockade is needed, continuous electroencephalographic monitoring should be performed. Activated charcoal is not indicated routinely in an isolated bupropion ingestion, considering the often benign course and the risk of aspiration during a seizure. ECG conduction delays (e.g., QRS/QT_c prolongation) resolve without specific treatment in many cases; however, they may require treatment if accompanied by hypotension or dysrhythmias.[62,63,64] $NaHCO_3$ has been used to successfully treat massive bupropion overdose with recurrent QRS widening and cardiac arrest.[64] Effective circulation followed treatment with a lipid emulsion for refractory cardiovascular collapse following an overdose of bupropion and lamotrigine.[65] Forced diuresis, hemodialysis, and hemoperfusion do not enhance elimination. Patients with an overdose of immediate-release bupropion require 8 hours of observation because seizures have occurred 8 hours after this overdose in the absence of other signs and symptoms.[55] With a sustained-release preparation, observation should be at least 12 hours. Because of limited data about overdose with the extended-release formula, a 24-hour observation period seems reasonable, given the finding of late onset seizures up to 24 hours following overdose of bupropion XL.[66] All of these observation periods should be extended if patients are otherwise symptomatic or experience a seizure during the observation period because of the risk of subsequent seizures.

Trazodone and Nefazodone

Trazodone and nefazodone are well absorbed from the gastrointestinal tract, reach peak concentration in 1 to 2 hours, are extensively bound to plasma proteins, and are metabolized predominantly by the liver. The half-life of trazodone is about 6 hours and nefazodone about 4 hours.[1,67] The major action of trazodone and nefazodone is inhibition of reuptake of serotonin, but neither is an SSRI.[1,60] They do not have antimuscarinic or antihistaminic effects.[1,39] Other pharmacodynamic effects include $alpha_1$-adrenoreceptor blockade, inhibition of norepinephrine reuptake, and postsynaptic $serotonin_2$-receptor blockade.[1] Hypotension in overdose is caused by $alpha_1$-adrenoreceptor blockade.[67] Trazodone and nefozodone overdoses are less toxic than CA and MAOI overdoses.[60,67,68]

Clinical Features

Clinical presentation of trazodone overdose is similar to SSRI overdose.[67] Cardiac toxicity has been reported with trazodone, but is rare. Trazodone also has been implicated in serotonin syndrome.[51,54] The most common manifestations of trazodone overdose are orthostatic hypotension with lightheadedness, drowsiness, lethargy, ataxia, nausea, and vomiting.[67] There are isolated reports of priapism, respiratory arrest, prolonged QT_c, ventricular dysrhythmias including torsades de pointes, bradycardia, hypotension, seizures, coma, and death. When trazodone overdose occurs with coingestants, morbidity and mortality rates are increased.[67,68] Because the two drugs are functionally similar, nefazodone most likely has similar toxicity to trazodone.

Management

Hypotension responds to boluses of IV crystalloids and usually does not require vasopressors.[67] Rare ventricular dysrhythmias should be treated with standard cardiac therapy. Neurologic complications of trazodone poisoning are treated similarly to neurologic complications of CAs (see Table 149-3). There is no proven efficacy of activated charcoal, and this is usually a more benign ingestion. Based on the pharmacokinetic data, forced diuresis, hemodialysis, and hemoperfusion have no benefit. After 6 hours of observation, asymptomatic overdose patients can receive psychiatric evaluation and disposition.

Venlafaxine, Desvenlafaxine, and Duloxetine

Venlafaxine is well absorbed from the gastrointestinal tract, reaches peak concentrations in 2 hours, has a large volume of distribution (≈7.5 L/kg), and undergoes extensive hepatic metabolism to form the active metabolite *O*-desmethylvenlafaxine (ODV). The half-life of venlafaxine is about 5 hours, and the half-life of ODV is about 11 hours.[1] The extended-release preparation, Effexor XR, reaches a peak concentration 6 to 7 hours after therapeutic dosing.[60] Venlafaxine and ODV inhibit reuptake of serotonin to a greater extent than norepinephrine and dopamine.[1,60] There is a dose-dependent blockade of sodium channels.[60,69,70] Desvenlafaxine, an oxidative metabolite of venlafaxine, is new, and information about its mechanism of action is limited at this time.

Duloxetine is well absorbed from the GI tract. It reaches peak concentration in about 6 hours if not taken with food and about 10 hours if taken with food. It has a large volume of distribution, is highly protein-bound, and has a half-life of 11 hours. The metabolites do not have significant pharmacologic activity. At low doses, duloxetine inhibits the reuptake of serotonin. At medium doses it inhibits serotonin and norepinephrine reuptake. At high doses, the reuptake of serotonin, norepinephrine, and dopamine is inhibited.[70]

Clinical Features

Most venlafaxine overdose patients are asymptomatic. Somnolence and sinus tachycardia are the most common symptoms. Seizures, life-threatening hypotension, QRS and QT_c prolongation, and death from venlafaxine overdose have been reported but occur more often in combination with coingestants.[60,71,72] Venlafaxine may not be as safe in overdose, however, as other serotoninergic drugs.[2,50,60] Rhabdomyolysis, hepatic failure, and renal failure have all been reported following venlafaxine overdose.[2] Massive venlafaxine overdose has resulted in arrhythmogenic death.[71] Serotonin syndrome has occurred when venlafaxine was used with MAOIs.[60]

The most common clinical effects to duloxetine exposure in one case series were neurologic. This included drowsiness or lethargy, irritability, agitation, tachycardia, confusion, and hallucinations. Drowsiness or lethargy was the most common effect. Tachycardia and nausea and vomiting were the next most common.[73]

Management

Standard supportive care is the foundation of overdose treatment. This includes $NaHCO_3$ for an increased QRS duration in the setting of hypotension. The rare instances of hypotension without QRS widening are treated with IV fluids, dopamine, and norepinephrine. There is no antidote. Cyproheptadine has been used in serotonin syndrome associated with venlafaxine and duloxetine. Benzodiazepines have been effective for venlafaxine-associated seizures. Forced diuresis, hemodialysis, and hemoperfusion have no role. After 6 hours of observation, longer for duloxetine, asymptomatic overdose patients can receive psychiatric evaluation and disposition.

Mirtazapine

Mirtazapine is well absorbed from the gastrointestinal tract, reaches peak concentrations within 2 hours after therapeutic doses, and is highly protein-bound. It is extensively metabolized in the liver to one active and two inactive metabolites. The elimination half-life of mirtazapine is 20 to 40 hours; the half-life for the active demethylated metabolite, normirtazapine, is about 19 hours.[60] Mirtazapine blocks presynaptic $alpha_2$-adrenergic receptors, increasing release of 5-HT and norepinephrine.[1,74,75] Mirtazapine blocks 5-HT_2 and 5-HT_3 receptors with high potency but has little effect on 5-HT_1 receptors; this results in fewer gastrointestinal effects compared with SSRIs.[1,74,75] To a lesser extent, mirtazapine antagonizes H_1 (histaminic), muscarinic, and peripheral $alpha_1$-adrenergic receptors; this can cause sedation, tachycardia, and hypotension.[1,74] Mirtazapine has fewer anticholinergic, antihistaminic, and antiadrenergic effects than CAs.

Clinical Features

In the few cases reported, somnolence, dizziness, anxiety, confusion, moderate hypotension, slight increase in systolic blood pressure, and mild tachycardia have occurred and resolved without specific treatment. No seizures or significant ECG changes were reported in two reports of isolated mirtazapine overdoses.[76,77] Sedation, tachycardia, and cognitive disorganization have been observed, but without permanent sequelae.[39,77,78] A case of mirtazapine along with co-ingestants was fatal.[79]

■ MONOAMINE OXIDASE INHIBITORS

Many drugs inhibit monoamine oxidases (MAOs).[1] Six drugs with significant MAO inhibition are marketed in the United States (Table 149-8).[1] MAOIs are well absorbed from the gastrointestinal tract, reach peak concentrations in 0.5 to 2.5 hours, are extensively bound to plasma proteins, and have relatively large volumes of distribution.[80] Tranylcypromine and selegiline have active metabolites that include significant amounts of amphetamine and methamphetamine.[81] Selegiline is now available in transdermal patch and oral dissolving tablet formulations. Minimal amounts of MAOIs are eliminated in the urine as unchanged drugs.

The MAO isoenzymes, MAO-A and MAO-B, inactivate direct-acting endogenous, biogenic amines, such as epinephrine, norepinephrine, and serotonin, as well as indirect-acting exogenous, biogenic amines, such as tyramine.[80-82] Effects of MAOIs include (1) inhibition of MAO; (2) MAOI effect on indirect sympathomimetics, such as amphetamine and methamphetamine, with the potential for enhanced CNS and peripheral nervous system sympathomimetic toxicity; (3) eventual depletion of norepinephrine stores; and (4) inhibition of pyridoxine phosphokinase and pyridoxine (vitamin B_6)-containing enzymes (Box 149-7).[80,81]

Table 149-8 Monoamine Oxidase Inhibitors (MAOIs)

MAOI Antidepressants in the United States	
Isocarboxazid (Marplan)	Irreversible* and nonselective
Phenelzine (Nardil)	Irreversible and nonselective
Tranylcypromine (Parnate)	Irreversible and nonselective
Antimicrobial in the United States	
Furazolidone (Furoxone)	Irreversible and nonselective
Antiparkinsonian in the United States	
Selegiline (Eldepryl)	Irreversible and selective MAO-B inhibitor
Antineoplastic in the United States	
Procarbazine (Matulane)	Irreversible and nonselective
Not Marketed in the United States	
Brofaromine	Reversible and selective MAO-A inhibitor
Cimoxatone	Reversible and selective MAO-A inhibitor
Clorgyline	Irreversible and selective MAO-A inhibitor
Iproniazid	Irreversible and nonselective
Mebanazine	Irreversible and nonselective
Moclobemide	Reversible and selective MAO-A inhibitor
Nialamide	Irreversible and nonselective
Pargyline	Irreversible and selective MAO-B inhibitor
Safrazine	Irreversible and nonselective

*Irreversible drugs have a much longer effect.

Clinical Features

The three presentations of MAOI toxicity are (1) MAOI overdose, (2) MAOI-food or MAOI-beverage interactions, and (3) MAOI-drug interactions.[80] These three presentations have different precipitating events, time to onset of symptoms, duration of symptoms, and major sign and symptom complexes (Table 149-9). All three presentations involve excessive sympathetic activity. The most common cardiovascular complications of interactions between foods, beverages, or drugs and MAOIs are hypertension and tachycardia. Reflex bradycardia can occur with severe hypertension.

Overdose

The clinical course of severe MAOI overdose occurs in four phases: (1) asymptomatic or latent, (2) neuromuscular and cardiovascular excitation with sympathetic hyperactivity, (3) CNS depression and cardiovascular collapse with hypotension and bradycardia late in severe overdoses, and (4) secondary complications caused by previous phases.[80] Onset of signs and symptoms after acute overdose usually occurs in 6 to 12 hours, but may be delayed 24 hours. Symptoms in acute MAOI overdose last for days (Table 149-10).

Table 149-9 Three Major Types of Monoamine Oxidase Inhibitor Toxicity

TOXICITY COMPLEXES	ONSET	DURATION	MAJOR SYMPTOM
MAOI overdose	Delayed for hours	Days	CNS sympathomimetic storms
MAOI-food or MAOI-beverage interaction	Minutes to hours	Hours	CNS and PNS sympathomimetic storms
MAOI-drug interaction	Minutes to hours	Hours to days	CNS and PNS sympathomimetic storms; serotonin syndrome

CNS, central nervous system; MAOI, monoamine oxidase inhibitor; PNS, peripheral nervous system.

Table 149-10 Clinical Manifestations of Acute Monoamine Oxidase Inhibitor Overdose

NEUROMUSCULAR SYSTEM MANIFESTATIONS	%	CARDIOVASCULAR SYSTEM MANIFESTATIONS	%
Agitation	67	Sinus tachycardia	67
Mydriasis	58	Hypertension	17
Rigidity	58	Hypotension	17
Hyperthermia	50		
Coma	50		
Hyper-reflexia	33		
Nystagmus	33		
Writhing	25		
Seizures	17		
Hallucinations	8		
Papilledema	8		

From Meredith TJ, Vale JA: Poisoning due to psychotropic agents. Adverse Drug React Acute Poisoning Rev 4:83, 1985.

BOX 149-7 Foods and Beverages Associated with Monoamine Oxidase Inhibitor Toxicity

Foods
- Aged, fermented, pickled, smoked, or tenderized meats and fish
- Aged cheeses
- Decayed or spoiled foods
- Broad beans
- Fava beans
- Bean curd
- Sauerkraut
- Yeast and meat extracts
- Ripe avocados
- Ginseng
- Chocolate
- Figs
- Raisins
- Bananas
- Soy sauce
- Miso soup

Undistilled Alcoholic Beverages
- Ales
- Beers
- Wines
- Sherry
- Vermouth

Seizures, coma, and muscular rigidity impair patients' abilities to keep airways patent, decrease ventilatory drive, and can produce rigid chest walls. Seizures, agitated delirium, myoclonus, muscular rigidity, and hyperthermia can result in rhabdomyolysis.[80] An overdose of 2 mg/kg (170 mg in an adult) can be lethal. Occasionally, hypotension, bradycardia, and asystole have been reported late in severe poisonings.[80] Initial release of norepinephrine can result in a decrease in the amount available for subsequent discharge from presynaptic vesicles. This situation may explain late CNS depression and cardiovascular collapse after earlier stimulatory phases of MAOI overdose.[80] Another potential cause of late bradycardic dysrhythmias is hyperkalemia from rhabdomyolysis. Long-term use of phenelzine has been associated with a sensorimotor peripheral neuropathy, probably from pyridoxine depletion.[83,84] Myocarditis due to massive phenelzine overdose has also been reported.[85]

Monoamine Oxidase Inhibitor–Food or Monoamine Oxidase Inhibitor–Beverage Interactions

Onset of sympathetic signs and symptoms with MAOI-food or MAOI-beverage interactions occurs in minutes to hours because ingested tyramine acts on the adrenal medulla to release endogenous biogenic amines (see Box 149-7). These interactions last only a few hours because of tyramine's short duration of action.

Monoamine Oxidase Inhibitor–Drug Interactions

Signs and symptoms of MAOI-drug interactions are sympathetic storm or the serotonin syndrome and begin minutes to hours after ingesting precipitating drugs (see Boxes 149-4 to 149-6 and Tables 149-5 and 149-6). Most MAOI-drug interactions occur in patients who are taking MAOIs regularly on an ongoing basis and ingest incompatible drugs, such as indirect-acting and mixed-acting (direct/indirect-acting) sympathomimetics, methylxanthines, antidepressants, opioids (e.g., meperidine), and other drugs that can cause serotonin syndrome (see Table 149-5; Box 149-8). These drugs produce excessive concentrations of endogenous biogenic amines that are not degraded because of MAO inhibition. Duration of MAOI-drug interactions is hours to days, depending on the precipitant's duration of effect, half-life, and formulation (e.g., sustained release, delayed release).

Differential Considerations

A recent or distant history of MAOI use alone or with food is the most helpful diagnostic clue. Urine and blood toxicology tests for MAOI levels are not readily available and are of little clinical value. The differential diagnosis of MAOI poisoning includes illnesses (e.g., thyroid storm, meningitis) and sympathomimetic intoxications (e.g., cocaine, amphetamines, theophylline, nicotine). Hypertensive emergencies, malignant hyperthermia, and heatstroke also are considerations in the differential diagnosis. Effects of MAO inhibition persist for

BOX 149-8 DRUGS THAT INTERACT WITH MONOAMINE OXIDASE INHIBITORS TO PRODUCE TOXICITY

Sympathomimetics

Indirect Acting

Amphetamines
Bretylium
Cocaine
Fenfluramine
Guanethidine
Ketamine
Methyldopa
Methylphenidate
Pemoline
Phencyclidine
Phentermine
Phenylpropanolamine
Pseudoephedrine
Reserpine
Ritodrine
Tyramine

Indirect Acting Mixed (Direct/Indirect Acting)

Dopamine
Ephedrine
Mephentermine
Metaraminol

Methylxanthines

Aminophylline
Caffeine
Oxtriphylline
Theophylline

weeks after cessation of MAOIs because MAO enzyme activity must be regenerated by synthesis of new MAO isoenzymes. Significant potential for MAOI toxicity can persist long after the drug has left the body.

Management

Sinus tachycardia does not usually require treatment. Beta-blockers can cause unopposed alpha$_1$-adrenoreceptor stimulation of the peripheral vasculature with vasoconstriction and worsening of the hypertension. Beta-blockers also can exacerbate the hypotension and bradycardia that can occur later in severe MAOI poisonings. Calcium channel blockers also are relatively contraindicated because of the potential for hypotension and bradycardia.[80]

Hypertension associated with MAOI toxicity can range from mild to life-threatening hypertensive emergencies. Mild hypertension does not require treatment. Hypertension with signs of impending or ongoing target-organ damage or with reflex bradycardia mandates treatment with sodium nitroprusside or phentolamine; both have rapid onset, easy titratability, and rapid resolution of effect when stopped, if hypotension develops later. An initial 5-mg bolus (adults) or 0.02 mg/kg to 0.1 mg/kg (children) of phentolamine is given over 1 minute.[80] The initial IV bolus can be repeated at 5- to 10-minute intervals as needed to lower the blood pressure to the desired range, followed by a phentolamine infusion to maintain the pressure. The initial dose of nitroprusside is 0.3 µg/kg/min, titrated to effect with a maximum rate of 10 µg/kg/min. Sodium thiosulfate can be used with continuous infusions of nitroprusside to prevent cyanide toxicity.

Reflex bradycardia is a beneficial compensatory response to significant, acute hypertension and decreases cardiac output; bradycardia should not be treated, unless it is associated with significant hypotension. Hypotension caused by MAOI toxicity usually occurs late in severe intoxications. If hypotension is associated with bradycardia, IV atropine should be administered until the bradycardia and hypotension resolve or a vagolytic dose of atropine has been reached (3 mg in adults or 0.04 mg/kg in children, with a minimum dose of 0.1 mg in children). Hypotension without bradycardia should be treated with IV isotonic crystalloids. A pacemaker is necessary for symptomatic bradycardia with accompanying hypotension that does not respond to atropine or agents such as epinephrine, dobutamine, or norepinephrine.[80] Initially a transcutaneous pacemaker can be used. Symptomatic, treatment-resistant bradycardia is often prolonged, however, and a transvenous pacemaker is optimal. Lidocaine is the drug of choice for ventricular dysrhythmias associated with MAOI toxicity

Neurologic complications of MAOI toxicity are treated similarly to neurologic complications of CA toxicity (see Table 149-3). Dantrolene, 2.5 mg/kg IV initially and repeated every 6 hours for 24 hours, seemed to be useful in a phenelzine overdose accompanied by life-threatening hyperthermia.[86] IV benzodiazepines may be used to control agitation. There is no antidote for MAOI toxicity, and forced diuresis, hemodialysis, and hemoperfusion are not effective.[80]

Disposition

The severity of acute MAOI overdoses is easily underestimated because signs and symptoms usually are not evident during the first 6 to 12 hours and may be delayed in onset for 24 hours. Patients with significant MAOI overdose or suggested serotonin syndrome should be observed for 24 hours. Symptomatic patients with known or suggested MAOI interactions with food, beverages, or drugs should be admitted to an ICU for at least 24 hours. Patients with possible food or drug interactions can be discharged if they remain asymptomatic for 6 hours.

DISCONTINUATION SYNDROME

Discontinuation syndromes with MAOIs, CAs, SSRIs, and various atypical antidepressants including venlafaxine and mirtazapine have been described.[87] A discontinuation syndrome has not yet been described for citalopram.[39] Symptoms depend on the agent and its mechanism of active action. With some SSRIs, insomnia, nausea, headache, sensory disturbances, hyperarousal, anxiety, agitation, tachycardia, and tremor have been reported.[87]

Restarting the drug and instituting a gradual taper over days to weeks generally reverses the discontinuation syndrome. Augmenting a drug that has a short half-life with another that has a long half-life may help to overcome the discontinuation syndrome.[87] Confusion and psychotic symptoms caused by stopping MAOIs may require hospital admission, restarting the MAOI, or treating with an antipsychotic medication.[87] Atropine and benztropine can help treat CA discontinuation symptoms because these symptoms reflect cholinergic rebound.[87]

A neonatal discontinuation syndrome, after in utero exposure to an SSRI in the third trimester of pregnancy, was described.[87] Symptoms included irritability, constant crying, shivering, increased tonus, eating and sleeping difficulties, and seizures.[88] Signs and symptoms began within a few days after birth and lasted 1 month.[88]

KEY CONCEPTS

- A patient with CA poisoning can deteriorate quickly.
- When in doubt, it is better to perform endotracheal intubation to prevent aspiration, hypoxia, or hypercarbia that can increase significantly the morbidity and mortality associated with CA poisoning.
- $NaHCO_3$ treats cardiac conduction abnormalities and negative inotropic effects of CA poisoning that result in ventricular dysrhythmias and hypotension with a wide QRS complex.
- The fatality rate for SSRI overdose is much lower than that for CA overdose.
- If serotonin syndrome is suggested, the patient should be admitted to a monitored unit for 24 hours of observation.
- Medication lists should be scrutinized for serotonin-enhancing drugs, and medications such as meperidine should be avoided in patients with SSRI overdose.
- Bupropion poisoning should be considered when seizures occur.
- Trazodone toxicity should be considered in a patient with priapism.
- If MAOI overdose is suggested or diagnosed, admission for 24 hours of observation is indicated, even if the patient is initially asymptomatic.
- MAOI toxicity should be considered in patients with hyperthermia, altered mental status, or muscular rigidity, such as those with meningitis, thyroid storm, neuroleptic malignant syndrome, malignant hyperthermia, and heatstroke.
- Hyperthermia must be treated aggressively to limit morbidity and mortality.
- The source of a food, beverage, or drug interaction with an MAOI should be identified to avoid recurrence and future complications.

ACKNOWLEDGMENT

The author would like to thank Frank G. Walter, MD, who was an author in the last three editions.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 150 Cardiovascular Drugs

David J. Roberts

Cardiovascular drugs rank among the most common causes of poisoning fatalities, both in children (third leading cause) and in adults (fifth leading cause). Of the scores of cardiovascular drugs, three—digitalis, propranolol, and verapamil—account for the majority of fatalities.

DIGITALIS

Perspective

Digitalis is derived from the foxglove plant, *Digitalis purpurea* (Fig. 150-1). Despite centuries of experience with digitalis, chronic and acute poisonings still occur. Dr. Benjamin Rush wrote in 1797, "I suspect the cases in which [digitalis preparations] were useful to have been either so few or doubtful and that the cases they had done harm were so much more numerous and unequivocal as justly to banish them from the *Materia Medica*."[1] Medication errors and toxic effects account for the most common causes (44%) of preventable iatrogenic cardiac arrests.[2]

Principles of Disease

Pathophysiology

In therapeutic doses, digitalis has two effects: (1) increasing the force of myocardial contraction to increase cardiac output in patients with heart failure; and (2) decreasing atrioventricular (AV) conduction to slow the ventricular rate in atrial fibrillation. The biochemical basis for its first effect is an inhibition of membrane sodium-potassium adenosine triphosphatase (ATPase), which increases intracellular sodium and calcium and increases extracellular potassium. At therapeutic doses, the effects on serum electrolyte levels are minimal. With toxic levels, digitalis paralyzes the Na-K pump, potassium cannot be transported into cells, and serum potassium can rise as high as 13.5 mEq/L.[3]

Digitalis exerts direct and indirect effects on sinoatrial (SA) and AV nodal fibers. At therapeutic levels, digitalis indirectly increases vagal activity and decreases sympathetic activity. At toxic levels, digitalis can directly halt the generation of impulses in the SA node, depress conduction through the AV node, and increase the sensitivity of the SA and AV nodes to catecholamines. Catecholamines, whether endogenous or administered by physicians to treat bradydysrhythmias or hypotension, probably play an important role in digitalis toxicity, and iatrogenic interventions may contribute to digitalis toxicity. Because bradydysrhythmias and tachydysrhythmias can appear and alternate in the same patient, administering one class of drugs to treat tachycardias may later contribute to more refractory bradycardias and AV block.

Digitalis also exerts three primary effects on Purkinje's fibers: (1) decreased resting potential, resulting in slowed phase 0 depolarization and conduction velocity; (2) decreased action potential duration, which increases sensitivity of muscle fibers to electrical stimuli; and (3) enhanced automaticity resulting from increased rate of phase 4 repolarization and delayed after depolarizations. These mechanisms account for an increase in premature ventricular contractions, the most common manifestation of digitalis toxicity. At toxic extremes, these effects result in a dangerous sensitivity to mechanical and electrical stimulation. Iatrogenic interventions with pacemaker catheters and cardioversion can result in asystole, ventricular tachycardia, and ventricular fibrillation.[4]

Unlike most cardiovascular drugs, digitalis can produce virtually any dysrhythmia or conduction block, and bradycardias are as common as tachycardias (Box 150-1). Unfortunately, none is peculiar to digitalis, and they can all occur in the setting of ischemic and other heart disease in the absence of digitalis. Digitalis intoxication remains a clinical rather than an electrocardiographic diagnosis.

The volume of distribution (V_d) of digoxin is 5 L/kg for adults but varies from 3.5 L/kg in premature infants to 16.3 L/kg in older infants.[5] This indicates that only a small fraction of digitalis remains in the intravascular space, and the drug is highly concentrated in cardiac tissue. The myocardial-to-serum ratio at equilibrium ranges from 15:1 to 30:1.[6] The V_d for digitoxin is 0.5 L/kg.

The elimination half-life of digoxin, which is primarily excreted in the urine, is 30 hours, and the half-life of digitoxin, which is metabolized in the liver, is 7 days.[6] Whereas digoxin undergoes only a small enterohepatic circulation, that for digitoxin is large, and multiple-dose charcoal treatment is clearly indicated for the latter.

Protein binding varies from 25% for digoxin to 95% for digitoxin.[6] The significant protein binding and large volume of distribution suggest that hemodialysis, hemoperfusion, and exchange transfusion are ineffective. The long half-lives suggest that temporizing measures such as pacemakers, atropine, and antidysrhythmic drugs might in the end cost more time, money, and lives than simply giving Fab fragments initially.

Figure 150-1. The foxglove plant, from which digitalis is derived.

BOX 150-1 DYSRHYTHMIAS ASSOCIATED WITH DIGITALIS TOXICITY

Nonspecific
PVCs, especially bigeminal and multiform
First-, second- (Wenckebach's), and third-degree AV block
Sinus bradycardia
Sinus tachycardia
Sinoatrial block or arrest
Atrial fibrillation with slow ventricular response
Atrial tachycardia
Junctional (escape) rhythm
AV dissociation
Ventricular bigeminy and trigeminy
Ventricular tachycardia
Torsades de pointes
Ventricular fibrillation

More Specific, but Not Pathognomonic
Atrial fibrillation with slow, regular ventricular rate (AV dissociation)
Nonparoxysmal junctional tachycardia (rate 70–130 beats/min)
Atrial tachycardia with block (atrial rate usually 150–200 beats/min)
Bidirectional ventricular tachycardia

AV, atrioventricular; PVC, premature ventricular contraction.

BOX 150-2 FACTORS ASSOCIATED WITH INCREASED RISK OF DIGITALIS TOXICITY

Renal insufficiency
Heart disease
- Congenital heart disease
- Ischemic heart disease
- Congestive heart failure
- Myocarditis

Electrolyte imbalance
- Hypokalemia or hyperkalemia
- Hypomagnesemia
- Hypercalcemia

Alkalosis
Hypothyroidism
Sympathomimetic drugs
Cardiotoxic co-ingestants
- Beta-blockers
- Calcium channel blockers
- Tricyclic antidepressants

Drug interactions
- Quinidine, amiodarone
- Erythromycin
- Verapamil, diltiazem, nifedipine
- Captopril

Elderly woman

BOX 150-3 NONCARDIAC SYMPTOMS OF DIGITALIS INTOXICATION IN ADULTS AND CHILDREN

General
Weakness
Fatigue
Malaise

Gastrointestinal
Nausea and vomiting
Anorexia
Abdominal pain
Diarrhea

Ophthalmologic
Blurred or snowy vision
Photophobia
Yellow-green chromatopsia (also red, brown, blue)
Transient amblyopia, diplopia, scotomata, blindness

Neurologic
Dizziness
Headache
Confusion, disorientation, delirium
Visual and auditory hallucinations
Paranoid ideation, acute psychosis
Somnolence
Abnormal dreams
Paresthesias and neuralgia
Aphasia
Seizures

Multiple drugs and disease states can negatively alter absorption, V_d, protein binding, and elimination and render the heart more susceptible to digitalis toxicity. The factors listed in Box 150-2 are especially important risk factors in chronic intoxication.

Clinical Features

The symptoms and signs of chronic digitalis intoxication are nonspecific. The most common symptoms—reported in more than 80% of cases—are nausea, anorexia, fatigue, and visual disturbance, but a variety of gastrointestinal, neurologic, and ophthalmic disturbances have also been linked to digitalis (Box 150-3). One should consider digitalis intoxication in any patient on maintenance therapy who develops consistent

Table 150-1 Chronic versus Acute Digitalis Intoxication

CHRONIC	ACUTE
Higher mortality (LL_{50} = 6 ng/mL)	Lower mortality
Potassium level normal or low	Potassium level normal or high
Ventricular dysrhythmias more common	Bradycardia and atrioventricular block more common
Usually elderly patients	Usually younger patients
Often need Fab fragment therapy	Often do well without Fab (*Caution:* many exceptions)
Underlying heart disease increases morbidity and mortality	Absence of heart disease decreases morbidity and mortality

symptoms, especially with new conduction disturbances or dysrhythmias.

Significant differences exist between acute and chronic intoxication (Table 150-1). Chronic poisoning has an insidious onset and is accompanied by a higher mortality rate. In cases of chronic intoxication, the LL_{50} (the level with a 50% mortality) is only 6 ng/mL.[7] The LL_{50} for acute intoxication is not known, but it is certainly much higher, especially in children. Chronically intoxicated patients almost always have underlying heart disease, which contributes to morbidity and mortality.

Diagnostic Strategies

Diagnosis and management rely heavily on readily available serum digoxin levels. It is the steady state, rather than peak level, that correlates with tissue toxicity and is used to calculate antidote dosages. Peak levels after an oral dose of digoxin occur in 1.5 to 2 hours, with a range of 0.5 to 6 hours.[6,8] Steady-state serum concentrations are not achieved until after distribution, or 6 to 8 hours after a dose or overdose, and may be only one fourth to one fifth of the peak level. The ideal serum digoxin concentration for patients with heart failure is considered to be 0.7 to 1.1 ng/mL.[9] Serum steady-state digoxin levels of 1.1 to 3.0 ng/mL are equivocal; that is, levels as low as 1.1 ng/mL have been associated with increased mortality rates,[10] and patients with levels up to 3.0 ng/mL can be asymptomatic.[11] The incidence of digoxin-incited dysrhythmia reaches 10% at a level of 1.7 ng/mL and rises to 50% at a level of 2.5 ng/mL.[12] A level drawn too soon after the last maintenance dose falsely suggests toxicity, especially in cases of chronic intoxication, in which significant morbidity and mortality can occur at levels of 2 to 6 ng/mL.[7] After an acute massive overdose in a patient who is rapidly becoming symptomatic, however, it may be impractical to wait 6 to 8 hours for the first reading.[13,14] It is unlikely that early levels exceeding 10 to 20 ng/mL will fade to clinical insignificance at 6 to 8 hours after ingestion.

Patients taking digitalis therapeutically often take diuretics as well, and they often have low serum and total body potassium levels. The acutely poisoned patient, in contrast, may have life-threatening hyperkalemia.

Differential Considerations

No sign or symptom, including dysrhythmia, is unique to digitalis poisoning, so the differential diagnosis is broad. Intrinsic cardiac disease as well as other cardiotoxic drugs must be considered. Central nervous system (CNS) depression or confusion may be secondary to various drugs and toxins as well as infection, trauma, inflammation, and metabolic derangements. Visual disturbances, should they be binocular, are often not reported by the patient, and the clinician should ask directly about them. Gastrointestinal disturbances are common and nonspecific and may be misdiagnosed as gastritis, enteritis, or colitis.

Management

With the availability of digoxin-specific fragment antigen-binding (Fab) antibodies (Digibind and DigiFab), all other therapies are considered temporizing.

There is no evidence to support gastric emptying for the treatment of digoxin overdose. Oral overdoses historically have been treated with activated charcoal, if it could be administered within 1 hour of ingestion, but no improvement in outcome has been established. Similarly, multidose charcoal has historically been used for digitoxin toxicity because of its prominent 26% enterohepatic circulation. This also is without proven benefit, however, and in any case, considerations of multidose charcoal are irrelevant with the widespread availability of antidigoxin antibody treatment as a specific antidote.

Electrolyte Correction

In cases of chronic intoxication, often exacerbated by hypokalemia, raising the serum potassium level to 3.5 to 4 mEq/L is an important early treatment. Potassium can be administered orally (which is safer) or intravenously (IV) although a rate more rapid than 10 to 40 mEq/hour is dangerous.

In acute poisoning, serum potassium may begin to rise rapidly within 1 to 2 hours of ingestion, potassium should be withheld, even if mild hypokalemia is measured initially. A serum potassium level greater than 5 mEq/L warrants consideration of digitalis antibody (ovine Fab fragment) treatment. If digitalis antibodies are not immediately available, severe hyperkalemia should be treated with IV glucose, insulin, and sodium bicarbonate. Although hypercalcemia can exacerbate digitalis intoxication, recent studies indicate that IV calcium can be safely given for hyperkalemia in the setting of digitalis intoxication.[15] Calcium salts should be administered over several minutes through a secure peripheral IV site or through a central venous catheter.

Many patients on diuretic therapy are also magnesium-depleted, even when the measured serum magnesium level is normal. If significant magnesium depletion is suggested, 1 to 2 g of magnesium sulfate can be given over 10 to 20 minutes (child: 25 mg/kg), followed by a constant infusion of 1 to 2 g/hour. Patients must be closely monitored for respiratory depression, which is usually preceded by progressive loss of deep tendon reflexes. Hypermagnesemia can exacerbate digitalis toxicity, but magnesium has been reported to reverse digoxin-induced tachydysrhythmias. It is prudent to infuse magnesium slowly and stop the infusion if heart block or bradycardia develops. Avoid magnesium in patients with renal failure. The role of magnesium in bradydysrhythmias and conduction blocks is less clear but probably dangerous because hypermagnesemia can impair impulse formation and AV conduction.

Atropine

Atropine is generally used for severe bradycardia and advanced AV block, with mixed results. Generally, an external or

transvenous pacemaker should be readied when bradycardia or AV block appears.

Pacing

Transvenous pacing has been a mainstay of treatment for several decades, but the catheter may induce ventricular tachydysrhythmias in a myocardium made irritable by digitalis. Iatrogenic accidents of cardiac pacing are frequent (14/39, 36%) and often fatal (5/39, 13%).[16] It may be safer to temporize with an external rather than a transvenous pacemaker while waiting for Fab fragments to take effect. Cardioversion and defibrillation can cause asystole after attempts to treat tachydysrhythmias. Lower energy settings, such as 25 to 50 J, may be less hazardous.

Carotid Sinus Massage

Carotid sinus massage may result in bradyasystole and cardiac arrest in the setting of digitalis toxicity.

Phenytoin and Lidocaine

Phenytoin and lidocaine are believed to be the safest of the antidysrhythmic drugs for controlling tachydysrhythmias in the setting of digitalis intoxication. Phenytoin may enhance AV conduction. Phenytoin has been infused at 25 to 50 mg/min to a loading dose of 10 to 15 mg/kg. Lidocaine can be given initially at a dosage of 1 to 3 mg/kg over several minutes, followed by an infusion of 1 to 4 mg/min (30–50 µg/kg/min).[17] Most other cardiac drugs (isoproterenol, procainamide, amiodarone, beta-blockers, calcium antagonists) may worsen dysrhythmias or depress AV conduction. Digoxin immune Fab fragments are the preferred therapy for dysrhythmias.

Fab Fragments (Digibind or Digifab)

The mortality rate before Fab fragment therapy was 23%, despite all of the interventions described.[18,19] Fab fragment treatment is well established in both chronic and acute poisonings, with a 90% response rate.[16,18-20] Nonresponders usually receive too little antibody or receive it too late. Other nonresponders are compromised by underlying heart or multisystem disease.

Digitalis antibodies are derived from sheep immunized with digoxin. Because the more antigenic Fab fragments are discarded, allergic reactions are less than 1% and routine skin testing is unneccessary.[20,21] Reactions have included erythema, urticaria, and facial edema, all of which are responsive to the usual treatment. Other expected reactions to Fab fragment neutralization of digitalis include hypokalemia, exacerbation of congestive heart failure, or increase in ventricular rate with atrial fibrillation.

Fab fragment treatment is best reserved for cases of serious cardiovascular toxicity rather than for routine or prophylactic administration of higher than expected serum levels. The primary indication for antibody treatment in cases of acute poisoning is hyperkalemia with a serum potassium level greater than 5.5 mEq/L or electrocardiographic changes. Although toxicity increases with greater body load, there is no clear correlation with amount ingested, especially in children, and many patients with large ingestions or high serum levels become only mildly symptomatic.[5] Fab fragment therapy should be used before transvenous pacing, which carries significant risk.

The median time to initial response is 19 minutes after completion of the Fab infusion, but complete resolution of digitalis-toxic rhythms may require hours.[19,22] Late administration of Fab fragments has resuscitated 54% of patients who have suffered cardiac arrest.[19,23] This antidote should be considered whenever hemodynamic compromise attends a digitalis-toxic dysrhythmia or heart block (Box 150-4).[24]

BOX 150-4 Recommendations for Administration of Digitalis Antibody Fragments

Adults

1. Severe ventricular dysrhythmias
2. Progressive and hemodynamically significant bradydysrhythmias unresponsive to atropine
3. Serum potassium greater than 5 mEq/L
4. Rapidly progressive rhythm disturbances or rising serum potassium level
5. Co-ingestion of cardiotoxic drugs such as beta-blockers, calcium channel blockers, or tricyclic antidepressants
6. Ingestion of plant known to contain cardiac glycosides *plus* severe dysrhythmias (rare)
7. Acute ingestion greater than 10 mg *plus* any one of factors 1 through 6 above
8. Steady-state serum digoxin greater than 6 ng/mL *plus* any one of factors 1 through 6 above

Children

1. Ingestion of greater than 0.1–0.3 mg/kg or steady-state digoxin greater than 5 ng/mL *plus* rapidly progressive symptoms or signs of digitalis intoxication *or* potentially life-threatening dysrhythmias or conduction blocks *or* serum potassium greater than 6 mEq/L
2. Co-ingestion of other cardiotoxic drugs with additive or synergistic toxicity
3. Ingestion of plant known to contain cardiac glycosides *plus* severe dysrhythmias (rare)

Current formulas for calculating Digibind or Digifab dosages are found in the package insert. There are at least three approaches. The first is empirical. A patient has a history of digitalis ingestion, consistent symptoms, and life-threatening dysrhythmias. There is no time to assess serum digoxin levels, either at 1 hour or in steady state. In such a situation, 10 vials should be administered over 30 minutes through a 0.22-µm filter for the average acute ingestion, and 4 to 6 vials for the average chronic ingestion. In cardiac arrest, 20 vials can be administered undiluted by IV bolus. The second approach uses a simple calculation when the ingested dose is known with reasonable certainty. One vial of Digibind or Digifab contains 38 mg of Fab fragments, which bind 0.5 mg of digoxin or digitoxin (Box 150-5). A third approach is to base the dosage on the steady-state serum digoxin or digitoxin level after 6 to 8 hours (Boxes 150-6 and 150-7). Because most assays measure both bound and unbound drug, digitalis levels will be elevated for up to 1 week, with values often greater than 100 ng/mL once Fab fragments have been administered. Newer methods can measure free digoxin, but it is more meaningful to follow the patient clinically.

Pediatric Considerations

Children at greatest risk are those on chronic digitalis therapy for heart disease. Children with healthy hearts have been known to tolerate massive acute oral ingestions without digitalis antibody treatment.[16] This excludes therapeutic errors, children taking digitalis therapeutically, and children with heart disease.

BOX 150-5 SAMPLE CALCULATION OF DIGIBIND OR DIGIFAB BASED ON INGESTED DOSE OF DIGOXIN OR DIGITOXIN*

Case: A toxic-appearing 40-year-old woman has ingested fifty 0.25-mg digoxin tablets

Body load = amount ingested × 0.8 (bioavailability of digoxin tablets)
= 12.5 mg × 0.8 = 10 mg

Dose of digoxin Fab fragments (in vials) = 10 mg ÷ 0.5 mg bound per vial
= 20 vials

*Formula from GlaxoSmithKline 2008.

BOX 150-6 SAMPLE CALCULATION OF DIGIBIND OR DIGIFAB BASED ON STEADY-STATE DIGOXIN CONCENTRATION*

Case: A toxic-appearing 4-year-old child weighing 20 kg has a digoxin level of 16 ng/mL 8 hr after ingestion of an unknown number of digoxin tablets

Dose (in number of vials) = (serum digoxin concentration × weight in kg) ÷ 100
= (16 × 20) ÷ 100
= approximately 3 vials

*Formula from GlaxoSmithKline 2008; assumes V_d = 5 L/kg.

BOX 150-7 CALCULATION BASED ON STEADY-STATE DIGITOXIN CONCENTRATION*

Case: A toxic-appearing 70-year-old man weighing 80 kg has a digitoxin level of 200 ng/mL (therapeutic = 10 to 35 ng/mL)

Dose (in number of vials) = (serum digitoxin concentration × weight in kg) ÷ 1000
= (200 × 80) ÷ 1000
= 16 vials

*Formula from GlaxoSmithKline 2008; V_d = 5 L/kg.

Dosage calculation and administration errors account for more pediatric digitalis intoxication and death than does accidental oral ingestion. Therapeutic errors—especially accidental IV overdoses—often result in death within 1 to 4 hours.

Signs and symptoms in children with digitalis poisoning are somewhat different (Table 150-2). Vomiting, somnolence, and obtundation is more common than in adults.[14,18] A CNS depression, in the absence of a history, might lead the clinician to suspect narcotic or sedative-hypnotic overdose, or even nontoxicologic causes such as head injury, metabolic disorder, or CNS infection. Conduction disturbances and bradycardias are more common than ventricular dysrhythmias in children, especially with acute ingestion.[6,14]

Table 150-2 Age Differences in Digitalis Intoxication

ADULT	PEDIATRIC
Toxic at lower levels	Asymptomatic at higher levels
Nausea, fatigue, and visual disturbances most common	Obtundation and vomiting more common than in adults
Tachydysrhythmias as common as blocks and bradydysrhythmias	Bradydysrhythmias and blocks most common
Allergic reactions to Fab fragments uncommon (<1%)	Allergic reactions extremely rare
V_d less variable (5–7.5 L/kg)	V_d more variable (3.5–6.0 L/kg in premature infants, 8.0–16.3 L/kg in infants 2–24 mo)

Disposition

All patients who are symptomatic for digitalis intoxication with hyperkalemia, dysrhythmia, AV block, or significant comorbidity should be admitted to the hospital or the emergency department observation unit for at least 12 hours of continuous cardiac monitoring. Patients with an acute ingestion of a large quantity of digoxin should be treated with Fab and admitted to an intensive care unit or coronary care unit until stabilized. All patients treated with antibodies require admission to an intensive care unit or a coronary care unit until their toxicity resolves.

■ BETA-ADRENERGIC BLOCKERS

Perspective

Beta-adrenergic blocking drugs became widely used in Europe in the 1960s for treatment of dysrhythmias. Their antihypertensive effects were later appreciated, and by the 1970s they were one of the most widely prescribed classes of drugs in the United States. Current indications include supraventricular dysrhythmias, hypertension, angina, thyrotoxicosis, migraine, and glaucoma. Overdose of propranolol is the most deadly, followed by acebutolol, oxprenolol, and alprenolol.[25]

Principles of Disease

Pathophysiology

Beta-blockers structurally resemble isoproterenol, a pure beta-agonist. They competitively inhibit endogenous catechol-

Table 150-3 Selected Characteristics of Common Beta-Blockers

	V_D (L/kg)	ISA	Elimination Half-Life (hr)	Lipophilic	Protein Binding (%)	MSE	Comments
Nonselective Beta-Blockers							
Propranolol	4	0	4	+	93	+	Most fatalities
Nadolol	1.9	0	10–20	0	20	0	Dialyzable
Timolol	1.4–3.5	0	3–5	+	10	0	Dialyzable
Pindolol	3–6	+	3–4	+	51	+	
Labetalol	10	0	4–6	0	50	+	Alpha-blockade also
Oxprenolol	1.3	+	2	+	78	+	
Sotalol	1.6–2.4	0	7–18	+	0	0	Class III and class II antidysrhythmic; torsades de pointes; dialyzable
Carvedilol	1.5–2	0	6–10	+	95	0	
Selective Beta-Blockers							
Metoprolol	5.5	0	3–4	+	12	0	
Atenolol	0.7	0	5–8	0	5	0	Dialyzable
Esmolol	2	0	0.13	0	55	0	
Acebutolol	1.2	+	2–4	+	26	+	QT prolongation, VT
Practolol	1.6	+	10–11	+		0	
Bisoprolol	2.9	0	10–12	0	30	0	
Betaxolol	5–13	0	12–22	0	55	0	

ISA, intrinsic sympathomimetic activity; MSE, membrane-stabilizing effect; V_d, volume of distribution; VT, ventricular tachycardia.

amines such as epinephrine at the beta-receptor. Catecholamine stimulation of beta-receptors results in the activation of adenyl cyclase, converting adenosine monophosphate (AMP) to cyclic AMP, which augments myocardial contraction (inotropy), enhances cardiac conduction (dromotropy), and accelerates heart rate (chronotropy). These are all $beta_1$ effects. Complex $beta_2$ effects include vascular (smooth muscle relaxation and vasodilation), liver (glycogenolysis, gluconeogenesis), lung (bronchodilation), adipose tissue (release of free fatty acids), and uterus (smooth muscle relaxation) effects. Equally important properties, which vary from one beta-blocker to another, include cardioselectivity, membrane-stabilizing effect, lipophilicity, and intrinsic sympathomimetic activity (Table 150-3). Although cardioselectivity is lost in overdose, cardioselective beta-blockers such as atenolol, metoprolol, and esmolol are associated with a lower mortality rate than propranolol, the oldest beta-blocker.

Beta-blockers are rapidly absorbed after oral ingestion, and the peak effect of normal-release preparations occurs in 1 to 4 hours.[26] Hepatic metabolism on first pass results in significantly less bioavailability after oral dosing than with IV injection (1:40 for propranolol). Volume of distribution for various beta-blockers generally exceeds 1 L/kg, meaning tissue concentrations exceed those of serum. Therefore, hemodialysis is not efficacious for most beta-blockers. Protein binding varies from 0% for sotalol to 93% for propranolol. Elimination half-lives vary from 8 to 9 minutes for esmolol to as long as 24 hours for nadolol and others (see Table 150-3).

Clinical Features

The most common initial sign remains bradycardia, which should draw attention to the possibility of cardiac drug overdose. Hypotension and unconsciousness are the second and third most common signs (Box 150-8). Much of propranolol's toxicity derives from its lipophilic nature and membrane-stabilizing effect that allow it to penetrate the CNS, leading to obtundation, respiratory depression, and seizures. Other beta-blockers do not have these effects. Seizures probably result from a combination of hypotension, hypoglycemia, hypoxia, and direct CNS toxicity. Surprisingly, bronchospasm is not problematic in cases of beta-blocker overdose, even with nonselective beta-blockers. The few cases of symptomatic bronchospasm respond to the usual bronchodilator nebulizations.

BOX 150-8 Manifestations and Complications of Beta-Blocker Overdose in Order of Decreasing Frequency*

1. Bradycardia (65/90 cases)
2. Hypotension (64/90)
3. Unconsciousness (50/90)
4. Respiratory arrest or insufficiency (34/90)
5. Hypoglycemia (uncommon in adults)
6. Seizures (common only with propranolol, 16/90)
7. Symptomatic bronchospasm (uncommon)
8. VT or VF (6/90)
9. Mild hyperkalemia (uncommon)
10. Hepatotoxicity, mesenteric ischemia, renal failure (rare or single case reports)

*Intoxication with beta-sympatholytics.
VF, ventricular fibrillation; VT, ventricular tachycardia.

Propranolol's membrane-stabilizing effect impairs SA and AV node function and leads to bradycardia and AV block. Ventricular conduction is also depressed, leading to QRS widening and occasional ventricular dysrhythmias.[27] Nadolol and acebutolol also have a significant membrane-stabilizing effect. These beta-blockers, like the tricyclic antidepressants, can cause ventricular dysrhythmias such as ventricular tachycardia, ventricular fibrillation, and torsades de pointes as well as the bradydysrhythmias more characteristic of beta-blockers in general. The intrinsic sympathomimetic activity of some beta-blockers such as pindolol and carteolol has led to some unusual manifestations such as sinus tachycardia instead of bradycardia and ventricular dysrhythmias. Labetalol is unique in that it also blocks alpha-adrenergic receptors, yielding an additional mechanism for hypotension. However, labetalol's beta-blockade is three to seven times more potent than its alpha-

blockade.[28] In contrast to digitalis, beta-blocker toxicity has a more rapid onset: life-threatening CNS and cardiovascular effects can occur 30 minutes after oral overdose. Patients ingesting delayed-release preparations may remain asymptomatic for several hours, affording a valuable therapeutic window.

Diagnostic Strategies

Diagnosis and management depend on the clinical picture since blood levels of beta-blockers correlate poorly with severity of intoxication and are not readily available. Most urine toxicology screens do not identify antidysrhythmic drugs and are not helpful.[29] Hypoglycemia is common in children, and bedside glucose determination should be done with obtundation. Known access of the patient to a beta-blocker and consistent clinical features such as obtundation, seizures, bradydysrhythmias, and occasionally tachydysrhythmias should lead the clinician to consider beta-blocker intoxication.

Differential Considerations

The combination of bradycardia and hypotension suggests beta-blockade or calcium channel blockade. Without a history of beta-blocker ingestion, the diagnosis can be challenging, especially when noncardiac effects such as CNS depression and seizures predominate. Sodium channel poisoning with QRS widening can occur, suggesting other antidysrhythmic drugs or cyclic antidepressants. The differential diagnosis also includes sedative-hypnotic drug overdose, hypoglycemic drug ingestion, opiate overdose, CNS injury or infection, endocrine-metabolic disorder, sepsis, and acute myocardial infarction.

Management

Immediate measures include IV fluids, supplemental oxygen, and monitoring of card for rhythm and respirations. Activated charcoal has been used in the first hour after overdose as a theoretical but unproven treatment. Similarly, multiple-dose charcoal (0.5 g/kg every 4 hr) has been recommended for beta-blockers that undergo enterohepatic or enteroenteric circulation, again without supporting evidence for an improvement in outcome. Specific management of dysrhythmias and hypotension should not be delayed by administration of charcoal. Evidence for improved outcome is also lacking but whole-bowel irrigation has been advocated for sustained-release preparations with a polyethylene glycol solution (OCL, GoLytely, CoLyte), administered orally or via nasogastric tube at 1 to 2 L/hour in adults or 20 mL/kg initially in children. With currently available evidence, gastric decontamination by activated charcoal or whole-bowel irrigation can neither be recommended nor criticized. Onset of toxicity is so uniformly early that absence of symptoms 4 hours after ingestion implies a low risk for subsequent morbidity unless a delayed-release preparation is involved.

Hypotension, Bradycardia, and Atrioventricular Block

Because bradycardia and heart block are usually attended by hypotension, catecholamines with chronotropic and dromotropic as well as inotropic and vasopressor effects should be chosen. Although therapeutic doses of beta-blockers may exacerbate Raynaud's phenomenon through an unopposed alpha effect, extreme peripheral vasodilation is the rule in cases of overdose. It is rare for one catecholamine to be equally effective against all four toxic effects, so combinations of drugs are often used in severe cases.

The first step in the treatment of beta-blocker overdose is bolus administration of atropine, glucagon, and crystalloid fluids. A dose of atropine may quickly wear off or be ineffective, so infusion of more potent drugs or cardiac pacing is usually necessary. Atropine (0.5 mg for adults, 0.02 mg/kg for children, minimum 0.10 mg) should be given before vagal stimuli such as tracheal or gastric intubation. Glucagon, which does not depend on beta-receptors for its action, has both inotropic and chronotropic effects.[30] Furthermore, it helps to counteract the hypoglycemia induced by beta-blocker overdose. Glucagon is given as a 5- to 10-mg IV bolus. Because of its short (20-minute) half-life, an infusion of 2 to 5 mg/hr (or for children, 0.05–0.1 mg/kg bolus, then 0.05–0.1 mg/kg/hr) should be started immediately after the bolus. With cumulative large doses, glucagon should be diluted in 5% glucose in water for constant infusion.[30] Side effects include nausea and vomiting in most patients, mild hyperglycemia, hypokalemia, and allergic reactions. The response to glucagon alone is often inadequate.

Sodium channel blockade, manifested by QRS widening, occasionally occurs with beta-blocker intoxication and may respond to infusion of sodium bicarbonate.

In hypotensive patients, 20 to 40 mL/kg of normal saline or Ringer's lactate solution can be infused and repeated. If hypotension or bradycardia persists, other cardioactive drugs are indicated. A single drug of choice after glucagon has not emerged, but many clinicians favor isoproterenol (isoprenaline in Europe), dopamine, or epinephrine.[31-33] Other catecholamines that have been successfully used include norepinephrine, dobutamine, prenalterol, metaraminol, and phenylephrine. Often, norepinephrine or dopamine is added to beta-agonists such as isoproterenol that lack vasopressor activity. Because patients are resistant to these drugs, the initial dose should be high and the infusion rates should be rapidly titrated to effect. A common mistake with cases of beta-blocker overdose is to timidly titrate catecholamine infusions within previously familiar ranges. In the setting of massive beta-blockade, much higher doses are usually needed, such as isoproterenol up to 200 μg/min, and the drug is titrated to effect.

High-dose (0.5–1 unit/kg/hr) insulin infusion for hemodynamically significant toxicity is often given before traditional pressors. Beta-blocker toxicity shifts myocardial energy preferences from free fatty acids to carbohydrates, and insulin increases myocardial carbohydrate uptake. Recent canine and porcine models showed the benefit of insulin infusion up to 10 units/kg/hr.[34,35] Glucose, usually in 5 to 10% solutions, is infused to maintain a serum glucose of approximately 100 mg/dL. The combination of glucose and high-dose insulin augments myocardial contraction independent of beta-receptors. Glucose and potassium should be monitored frequently during infusion and supplemented as needed to maintain euglycemia and eukalemia.

Refractory cases of bradycardia may respond to an external or transvenous pacemaker. Phosphodiesterase inhibitors such as aminophylline, amrinone, and milrinone have also been used as a final treatment to treat beta-blocker overdose in experimental animals and in humans. Like glucagon, they also help raise intracellular cyclic AMP levels and stimulate contractility.[36,37]

Calcium

Because deleterious effects on calcium transport may contribute to beta-blocker toxicity, IV calcium salts have been suggested for treating hypotension.[38,39] In animals, hypercalcemia as well as hypocalcemia can inhibit the action of glucagon,[40] and until more is known, calcium should be given cautiously

and less aggressively than for cases of calcium channel blocker overdose. Constant infusions are safer than boluses. Give 1 to 2 g over 5 to 10 minutes, monitoring closely for effect.

Ventricular Dysrhythmias

Although uncharacteristic, ventricular tachydysrhythmias do occur sometimes. Cardioversion and defibrillation are indicated for ventricular tachycardia and ventricular fibrillation, respectively, following American Heart Association guidelines. Pulsatile ventricular tachycardia or frequent ventricular ectopy can most safely be treated with lidocaine. Other antidysrhythmic drugs, especially of classes IA and IC, should be avoided because they may potentiate AV block or be prodysrhythmic because of an additive membrane stabilizing effect. Sotalol, unlike other beta-blockers, has class III as well as class II effects; that is, it prolongs the QT interval and can cause torsades de pointes and other ventricular dysrhythmias. Overdrive pacing with isoproterenol or a pacemaker and magnesium sulfate are specific therapies for torsades de pointes.

Extracorporeal Elimination and Circulatory Assistance

Hemodialysis or hemoperfusion may be beneficial for atenolol, nadolol, sotalol, and timolol, the beta-blockers with lower V_d, lower protein binding, and greater hydrophilicity.[41]

Unlike overdoses of acetaminophen and iron, cardiovascular drugs do not destroy tissue, and if circulation can be supported, complete recovery can be expected. An intra-aortic balloon pump or cardiopulmonary bypass can be lifesaving in cases of refractory hypotension.[42,43] The relatively short half-lives (hours rather than days) of beta-blocking and calcium-blocking drugs fall within the temporal range of such interventions. To be successful, such heroic measures must be taken before prolonged hypotension leads to multiorgan ischemic injury (Box 150-9). Because most patients recover with just supportive care, these expensive and invasive interventions should be reserved for drugs and circumstances, such as propranolol, verapamil, and mixed cardiotoxic overdoses, that are associated with higher rates of mortality.

Pediatric Considerations

Compared with adults, pediatric poisonings are rare. In the cases reported, CNS, cardiac, and metabolic toxicities are similar.[44] However, symptomatic hypoglycemia is much more common in children, especially in those who have been fasting, and occurs even after therapeutic doses. Therefore, serum glucose concentration should be measured in children. Risk factors include young age, fasting state, and diabetes mellitus. Obtunded children should receive empirical glucose, 1 to 2 mL/kg of 25% glucose IV. Generally, 5% glucose infusions have been sufficient to maintain euglycemia, especially with concomitant use of glucagon and catecholamines, which stimulate glucose release. Because glycogen mobilization is a $beta_2$ effect, hypoglycemia may be less common with the cardioselective ($beta_1$) blockers.

Seizures also occur in cases of pediatric beta-blocker overdose, but hypoglycemia is probably an important contributing factor. They are more common with the lipid-soluble beta-blockers propranolol and oxprenolol. Diazepam is effective.[25]

Children generally fare well after beta-blocker ingestion with symptoms in only 8 of 378 (2%) potential beta-blocker exposures in children.[44]

BOX 150-9 TREATMENT OF BETA-BLOCKER POISONING

Phase I (Resuscitation)
Boluses of atropine, glucagon, fluids

Phase II (Stabilization)
Infusions of
- Glucagon
- Insulin-glucose
- Catecholamines (epinephrine, norepinephrine, isoproterenol, dobutamine, dopamine, metaraminol)
- Phosphodiesterase inhibitors (amrinone)

Early cardiac pacing if no prompt response to chronotropic or dromotropic drugs
Peripheral arterial and pulmonary artery catheter monitoring if refractory hypotension
Consider hemodialysis of hydrophilic beta-blockers with low protein binding and low V_d

V_d, volume of distribution.

Disposition

Patients who remain completely asymptomatic for 6 hours after an oral overdose of normal-release preparations can be safely referred for psychiatric evaluation, with medical consultation for the first 24 hours. Patients ingesting sustained-release preparations should be admitted to a monitored bed, but those who remain asymptomatic 8 hours after ingestion are very unlikely to develop toxicity. Those who have been hypotensive, who have more than first-degree heart block, or who have hemodynamically significant dysrhythmias should be admitted to the intensive care unit.

CALCIUM CHANNEL BLOCKERS

Perspective

Verapamil and nifedipine, the earliest calcium channel antagonists, were introduced in Europe in the 1970s and in the United States in the early 1980s. Calcium antagonists have found many clinical applications: angina pectoris, hypertension, supraventricular dysrhythmias, hypertrophic cardiomyopathy, and migraine prophylaxis. Over 2000 cases of poisoning are reported annually to American poison centers. Most fatalities occur with verapamil, but severe toxicity and death have been reported for most drugs of this class.

Pathophysiology

Calcium channel antagonists block the slow calcium channels in the myocardium and vascular smooth muscle, leading to coronary and peripheral vasodilation. They also reduce cardiac contractility, depress SA nodal activity, and slow AV conduction. In cases of overdose, verapamil has the deadliest profile, combining severe myocardial depression and peripheral vasodilation. Both verapamil and diltiazem act on the heart and blood vessels, whereas nifedipine causes primarily vasodilation. As with beta-blockers, selectivity is lost in cases of overdose, and toxicity is fourfold, with negative effects on inotropy, chronotropy, dromotropy, and vasotropy.

All calcium channel blockers are rapidly absorbed, although first-pass hepatic metabolism significantly reduces bioavailability (Table 150-4). Onset of action and toxicity ranges from less than 30 minutes to 60 minutes, which has important implications for therapy. Peak effect of nifedipine can occur as early as 20 minutes after ingestion, but peak effect of sustained-release verapamil can be delayed for many hours. High protein

Table 150-4 Selected Characteristics of Some Calcium Channel Blockers

	V_D (L/KG)	HALF-LIFE (HR)	PROTEIN BINDING (%)	COMMENTS
Verapamil	4	3–12	90	Most fatalities; impairs contractility and cardiac conduction more than most other calcium antagonists
Diltiazem	1.7–5.3	3–7.9	70–80	Suppression of atrioventricular node similar to verapamil; myocardial depression otherwise less
Nifedipine	1.4–2.2	1–5	92–98	Vasodilation greatest effect
Nicardipine	0.64	8–9	95	Vasodilation
Nimodipine	0.94–2.3	1–2	95	No reports of oral overdosage (2005 *PDR*)
Amlodipine	21	30–50	98	Vasodilation
Bepridil	8	33–42	99	Class I as well as class IV antidysrhythmic; prolongs QT: torsades de pointes
Felodipine	10	10	99	Vasodilation
Isradipine	3	1.9–16	95	Vasodilation
Nisoldipine	4–5	7–12	99	Vasodilation

V_d, volume of distribution.

binding and V_d greater than 1 to 2 L/kg make hemodialysis or hemoperfusion ineffective. Fortunately (except with sustained-release preparations), their half-lives are relatively short, limiting toxicity to 24 to 36 hours.

Clinical Features

Severe calcium antagonism eventually affects multiple organ systems, but cardiovascular toxicity is primarily responsible for morbidity and mortality. Hypotension and bradycardia occur early, and other rhythm disturbances include AV block of all degrees, sinus arrest, AV dissociation, junctional rhythm, and asystole. Nifedipine overdose more commonly causes reflex sinus tachycardia from peripheral vasodilation. Calcium channel blockade has little effect on ventricular conduction, so QRS widening is not seen early on. Ventricular dysrhythmias are also uncommon except with bepridil, which has class I antidysrhythmic properties. This drug prolongs the QT interval in a dose-related fashion, and intervals greater than 520 msec are associated with increased risk of ventricular tachycardia, especially torsades de pointes (Box 150-10).

BOX 150-10 MANIFESTATIONS AND COMPLICATIONS OF CALCIUM CHANNEL BLOCKER POISONING

Cardiovascular: Hypotension, sinus bradycardia, sinus arrest, AV block, AV dissociation, junctional rhythm, asystole; ventricular dysrhythmias uncommon except with bepridil
Pulmonary: Respiratory depression, apnea; pulmonary edema; adult respiratory distress syndrome
Gastrointestinal: Nausea, vomiting, bowel infarction (rare)
Neurologic: Lethargy, confusion, slurred speech, coma; seizures (uncommon); cerebral infarction (rare)
Metabolic: Metabolic (lactic) acidosis; hyperglycemia (mild); hyperkalemia (mild)
Dermatologic: Flushing, diaphoresis, pallor, peripheral cyanosis

AV, atrioventricular.

Diagnostic Strategies

Serum levels of calcium antagonists are not readily available, nor do urine toxicology screens reliably detect this class of drugs. Blood samples should be obtained for measurement of glucose and electrolytes (including calcium and magnesium). Hyperglycemia secondary to insulin inhibition occurs occasionally, but the elevation is usually mild (150–300 mg/L), is usually short-lived (<24 hr), and generally requires no treatment.[45] A metabolic (lactic) acidosis occurs with hypotension and hypoperfusion.

An electrocardiogram should be promptly obtained, with special attention to atrial and ventricular rates and PR, QRS, and QT intervals. A prolonged QRS or QT interval suggests bepridil or a co-ingested cardiac toxin such as a tricyclic antidepressant.

Differential Considerations

Differential diagnosis is similar to that of beta-blocker cases. Until characteristic rhythm disturbances supervene, many other toxic, metabolic, traumatic, and cardiovascular disorders can cause hyptotension but less commonly cause bradycardia. Like the beta-blockers, calcium antagonists cause early toxicity, and symptoms can be expected within 6 hours of ingestion of normal-release preparations.[46] Toxicity can be delayed 12 to 24 hours with sustained-release preparations.

As with beta-blockade, CNS-depressive effects are common and include lethargy, confusion, and coma. Unlike beta-blockers, calcium antagonists seldom induce seizures. Pulmonary effects include noncardiogenic pulmonary edema and apnea can also occur. As with digitalis and beta-blocker overdose, nausea and vomiting are common.

Management

Initial management includes rapid establishment of vascular access, supplemental oxygen, cardiac monitoring, and frequent blood pressure measurement. Because of the rapid onset of toxicity with normal-release preparations, gastric emptying is dangerous and contraindicated. Vomiting is a powerful vagal stimulus that can exacerbate bradycardia and heart block. There is no evidence for improved outcome with activated charcoal. If activated charcoal use is contemplated despite this, it should be reserved for very early (<1 hr) presentations, or poisoning by a delayed-release preparation. Sorbitol should be avoided because hypotension frequently causes an ileus where residual sorbitol is metabolized to cause abdominal distension.

Hypotension and Bradycardia

Hypotension can be caused by myocardial depression, inadequate heart rate, or peripheral vasodilation. Atropine can be administered in the usual American Heart Association's recommended doses (0.5–1 mg, up to 3 mg for adults, and 0.02 mg/kg for children, minimum 0.1 mg). Atropine's effect has often been disappointing and short-lived, and multiple doses risk anticholinergic poisoning.[47] If symptomatic bradycardia or heart block persists, the next step is a pacemaker or chronotrope such as isoproterenol. A bolus of crystalloid fluid (20 mL/kg or more) should also be infused early. Intravenous calcium salts have traditionally been given to most patients. Their effect on contractility is considerable, but their effect on bradycardia, AV block, and peripheral vasodilation is often poor. The optimal dose of calcium is unknown. A reasonable dose is 6 g of calcium chloride, but some have given much higher calcium infusions, administering up to 30 g and raising the total serum calcium level to as high as 23.8 mg/dL.[48] Adverse effects of hypercalcemia include lethargy, coma, anorexia, nausea, vomiting, pancreatitis, polyuria, dehydration, and nephrocalcinosis. Most of these effects have been reported after weeks or months of hypercalcemia from malignancy or hyperparathyroidism. It is doubtful that hours or days of acutely induced hypercalcemia would be detrimental in the setting of massive calcium channel blockade. However, with *rapid* IV injection in animals and humans, bradycardia, AV block, AV dissociation, junctional tachycardia, ventricular ectopy, and ventricular fibrillation have been reported.[49] Extravasation of calcium salts can cause severe tissue necrosis. Administration through a central venous catheter is safer than through a peripheral IV line. Infiltration of calcium gluconate is less destructive than calcium chloride, but larger doses are necessary because it provides fewer calcium ions.

It is prudent to raise the total serum calcium level no higher than 14 mg/dL, which the endocrine and oncology literature define as the threshold of "severe" hypercalcemia. If ionized calcium levels are followed, it is probably wise not to exceed twice-normal levels. Adults should receive 10 to 20 mL of 10% calcium chloride slowly over 5 to 10 minutes, followed by a constant infusion of 5 to 10 mL/hour. Children can receive 10 to 30 mg/kg (0.1–0.3 mL/kg) of 10% calcium chloride initially. The serum calcium level can be as high as 18.2 mg/dL within 15 minutes after a bolus of just 5 mL of 10% calcium chloride, so levels should be measured later during the constant infusion.

As with beta-blocker poisoning, a monotherapeutic approach will probably succeed only for trivial overdoses. Most severely poisoned patients require addition of catecholamines to accelerate the heart rate (chronotropy), enhance AV conduction (dromotropy), and restore tone to peripheral vessels (vasotropy). Most experience and success have been reported with isoproterenol and dopamine, often in combination.[47] Isoproterenol infusion can begin at 2 to 10 µg/min (0.1 µg/kg/min in children), but much higher rates may be needed. Unlike beta-blocker overdose, however, the beta-adrenergic receptor remains intact, and lower catecholamine infusion rates have generally been effective (e.g., dopamine 5–30 µg/kg/min). Epinephrine, norepinephrine, and dobutamine have also led to successful outcomes.[50] Isoproterenol or dobutamine alone may not reverse or may even exacerbate peripheral vasodilation; therefore, it is logical to add a vasopressor such as norepinephrine, metaraminol, phenylephrine, or high-dose dopamine.

Glucagon has also been used for its inotropic and chronotropic effects, in doses similar to those advocated for beta-blocker poisoning. Bailey recently reviewed 30 controlled animal studies (no controlled human studies exist) of glucagon use in beta-blocker and calcium channel blocker overdose.[30] The results were somewhat disappointing: although it possibly increased cardiac output in beta-blocker overdose, its effect on survival was unclear; it increased heart rate and cardiac output in calcium antagonist overdose in animals, but it did not increase mean arterial pressure and appeared to have no effect on survival.

Insulin (0.5–1 µg/kg/hr) infusion has been effective in both animal trials and human cases.[51,52] Glucose (5–10% solutions usually suffice) is infused concurrently to maintain serum glucose at 100 mg/dL (usually 10–30 g/hr). Insulin euglycemia is thought to act by improving myocardial carbohydrate metabolism, thereby augmenting myocardial contraction. Serum glucose and potassium levels should be checked frequently to ensure that normal levels are maintained. Enthusiasm for insulin-glucose treatment is growing, and this therapy may prove safer and more efficacious than pressors. Finally, phosphodiesterase inhibitors such as amrinone (5 µg/kg/min) have been used to treat both calcium antagonist and beta-blocker poisoning, but experience with these agents is limited.[53]

If hypotension persists despite the preceding interventions, peripheral arterial and pulmonary arterial catheters should be inserted to precisely measure and coordinate the effects on blood pressure, pulmonary capillary wedge pressure, cardiac output, and peripheral resistance. Without such measurements, the clinician risks overtreatment with fluid and undertreatment with pressors, which may be needed in doses hitherto not encountered. As long as dysrhythmias are not aroused, cardiotonic infusions should be aggressively titrated to effect (Box 150-11).

Pediatric Considerations

Nifedipine, and probably other drugs in its class, joins the short list of medications that can kill a child with ingestion of a single tablet.[54,55] Seizures may be more common in children than adults and should be treated with diazepam, lorazepam, or calcium. Recommendations for calcium chloride administration in children range from 10 to 30 mg/kg (0.1–0.3 mL/kg of 10% calcium chloride) over 5 to 10 minutes, followed by an infusion.

Overall, death following calcium antagonist ingestion in children is rare. French poison centers reported 51 cases of pediatric diltiazem ingestion over 10 years without a single fatality.[56] The IV route of administration, as with digitalis, is much more dangerous. Even therapeutic doses of IV verapamil are considered contraindicated in infants with supraventricular tachycardia because of case reports of cardiovascular collapse and cardiac arrest after injection.[57]

BOX 150-11 Treatment of Calcium Channel Blocker Intoxication

Phase 1
Boluses of atropine, calcium, fluids

Phase 2
Catecholamine infusions
Calcium infusion
Insulin glucose infusion
Glucagon infusion
Phosphodiesterase infusion
Transcutaneous or transvenous cardiac pacing
Invasive monitoring

Phase 3
Consider intra-aortic balloon counterpulsation, cardiac bypass

Hyperglycemia occasionally occurs in children, but the elevation is usually short-lived. Although insulin has been administered in a handful of cases, it is generally not necessary, because the hyperglycemia usually resolves spontaneously within 24 to 36 hours.

A small number of children in refractory shock secondary to drug toxicity have been treated with intra-aortic balloon counterpulsation or cardiac bypass. For a toxin with a reasonably short half-life, although lethal, it does not directly cause irreversible tissue damage. Circulatory support during the day or two required for hepatic or renal elimination of the drug is potentially beneficial. In summary, aside from the differences previously noted, the presentation in children is similar to that in adults: rapid onset of toxicity with CNS depression, bradydysrhythmias, hypotension, and metabolic acidosis.

Disposition

Because the peak effect of normal-release calcium channel blockers commonly occurs in 90 minutes to 6 hours, patients who are totally asymptomatic for 6 hours after an ingestion can be safely discharged according to psychiatric needs. Symptomatic patients or those who ingested delayed-release preparations should be admitted to a medical or toxicology service for at least 24 hours of continuous cardiac monitoring.

NITRATES AND NITRITES

Nitrates (nitroglycerin, isosorbide mono- and dinitrate) are widely used as vasodilators in the treatment of heart failure and ischemic heart disease. They augment coronary blood flow as well as reduce myocardial oxygen consumption by reducing afterload. At lower doses nitrates primarily dilate veins, but at higher doses they also dilate arteries. Hypotension is a common complication, but usually responds to supine positioning, IV fluids, and reduction of dose. Hypotension is usually transient. Low-dose pressors are occasionally needed, but it is best to avoid them in the setting of acute coronary syndromes.

Intravenous nitroglycerin infusions are being used commonly in patients with acute pulmonary edema for afterload reduction. Infusions are usually initiated at 5 to 10 µg/min, but rates as high as 200 to 300 µg/min may be used. These doses may be beneficial in patients with pulmonary edema accompanied by acute hypertension, but hypotension may develop suddenly. Intravenous nitroglycerin has a rapid offset of action, so excessive fall in blood pressure usually responds to reducing or terminating the infusion. Use of nitrates is contraindicated in patients who have recently taken sildenafil (Viagra). Sildenafil and related drugs (vardenafil/Levitra and tadalafil/Cialis) inhibit type-5 phosphodiesterase, thereby relaxing vascular smooth muscle. These agents can prolong and intensify the vasodilating effects of nitrates, resulting in severe hypotension. If blood pressure does not rise with IV fluids, dopamine should be cautiously titrated, beginning at 5 µg/kg/min.

Nitrates are occasionally found in rural well water contaminated by livestock or fertilizer runoff. Oral nitrates may be converted to nitrites in the gastrointestinal tract, especially in infants, whose hemoglobin is also more susceptible to oxidation. However, most exposures are encountered in young adults, usually male, who inhale various alkyl nitrites (amyl, butyl, isobutyl, or ethyl nitrite) in the hope of enhancing or prolonging sexual pleasure. Because of the sound they make when broken open, these products are best known to abusers as "poppers." The popularity of poppers has waned in recent years as sales of sildenafil and related products have soared. Nitrites and nitrates are both potent vasodilators, and excessive use can cause headache, skin flushing, and orthostatic hypotension. Nitrites are also oxidizing agents that convert hemoglobin to methemoglobin, impairing oxygen delivery. Though most exposure is by inhalation, unintentional ingestion may occur, because nitrites are also used legitimately as food preservatives. A family of five developed methemoglobinemia after consuming a meal seasoned with sodium nitrite mislabeled as table salt.[58]

Patients with glucose-6-phosphate dehydrogenase deficiency are especially susceptible to the oxidative stress of nitrite exposure, and they may even develop hemolysis. When methemoglobin levels exceed 15%, a venous blood sample appears chocolate brown, and the skin appears blue even while patients look remarkably comfortable. Unlike most cases of cyanosis, supplemental oxygen does not improve the patient's color. Pulse oximetry is not reliable, and the partial pressure of oxygen remains normal in mild to moderate cases. This rare complication can be treated with IV methylene blue, but this antidote is usually not needed unless methemoglobinemia approaches 30% or the patient develops more reliable signs of distress, such as tachypnea, tachycardia, acidosis, and hypotension. The usual dose of methylene blue in adults is 1 to 2 mg IV over 5 minutes.

KEY CONCEPTS

Digitalis
- Consider digitalis intoxication in any patient with gastrointestinal or visual disturbance who presents with a new dysrhythmia or conduction disturbance.
- Dose digitalis Fab antibody fragments by body load of digitalis, not by body weight of patient.
- Use digitalis antibodies before pacing or other antidysrhythmic drugs, which may unnecessarily complicate treatment.
- Hyperkalemia in digitalis toxicity is best treated with IV Fab fragments. Conventional treatment with sodium bicarbonate, insulin, and glucose, as well as calcium, is also appropriate, especially when Fab fragment preparations are not immediately available.

Beta-adrenergic Blockers
- Beta-blocker intoxication usually causes AV block and bradydysrhythmias.
- Noncardiac symptoms such as obtundation, seizures, and hypoglycemia may predominate, especially early in the course and particularly with propranolol.
- Volume expansion, atropine, and glucagon are early measures used to restore normal heart rate and cardiac output. Absent a response, begin insulin-glucose infusion and titrate rapidly up to 1 unit/kg/hour as needed.

Calcium Channel Blockers
- Signs and symptoms of calcium channel blocker intoxication occur early after overdose.
- CNS depression is common; seizures are not.
- AV block and bradydysrhythmias predominate, except with bepridil.
- Volume expansion, calcium, and vasopressors have been the mainstays of treatment, but insulin-glucose infusion probably offers the most therapeutic benefit in cases of severe intoxication.

Nitrates and Nitrites
- Hypotension and methemoglobinemia are common presentations.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 151 Caustics

Paul M. Wax and Amy Young

PERSPECTIVE

Caustic or corrosive agents have the potential to cause tissue injury on contact with mucosal surfaces. Agents capable of causing chemical injury include alkaline and acidic corrosives. Alkalis accept protons, resulting in the formation of conjugate acids and free hydroxide ions. Lye is an example of an alkali caustic and refers to both sodium hydroxide (NaOH) and potassium hydroxide (KOH). Ammonia (NH_3) is another common alkaline corrosive. Acids are proton donors, as they dissociate into conjugate bases and free hydrogen ions in solution. Acidic caustics include hydrochloric acid (HCl) and sulfuric acid (H_2SO_4). The severity of caustic agents typically increases with a pH less than 3 or greater than 11. On the contrary, hydrofluoric acid (HF) is a relatively weak acid that can cause necrotizing injury and life-threatening systemic toxicity. Other chemicals that have caustic properties include phenol, formaldehyde, iodine, and concentrated hydrogen peroxide. This chapter discusses oral exposure. Dermal and inhalational exposures are discussed in Chapter 61 and Chapter 157, respectively.

Caustic exposures are either intentional suicidal ingestions or accidental ingestions in the pediatric and elderly populations. At least 85% of reported caustic ingestions are unintentional.[1] Transfer and storage of cleaners in alternative containers, such as soda bottles and jars, contribute to unintentional ingestion. Intentional ingestions have a greater degree of oropharyngeal sparing due to rapid swallowing but have a higher likelihood of serious injury.[2] More than half of suicidal patients who ingest caustic agents have a history of psychiatric illness.[3]

Prior to 1950, strong lye with concentrations greater than 50% made up a major portion of caustic ingestions in the United States leading to poor outcomes. To control the frequency of caustic ingestions especially in children, the Federal Caustic Act was passed in 1927 followed by the Federal Hazardous Substance Labeling Act of 1960 and the Safe Packaging Act of 1970.[4] Still, over 45,000 exposures involving caustic agents still occur in the United States every year.[5]

Presently, some household products such as liquid drain cleaners continue to have high concentrations of alkali (30% KOH) or acid (93% H_2SO_4) (Table 151-1). Commercial industries, farms (dairy pipeline cleaners containing liquid NaOH and KOH in concentrations of 8–25%), and swimming pool chemicals also contain caustics in high concentrations.[6]

Ingestion of crystals and solid particles can have prolonged tissue adherence, causing more severe burns. These ingestions are limited by immediate oral pain, usually causing them to be spit out sooner than a liquid agent. The ingestion of granular automatic dishwashing detergents is associated with devastating injuries.[7] Crystal drain cleaners have lye concentration as high as 74% NaOH and may cause proximal esophageal injury. Liquid dishwashing detergents and laundry detergents have a pH greater than 12, but because the titratable base content is significantly less, there is less risk of injury after ingestion.

Liquid household bleach typically contains dilute (5.25%) sodium hypochlorite (NaHClO), and ingestion rarely causes injury. Industrial-strength bleach may contain significantly higher concentrations of NaHClO, leading to esophageal necrosis. Toilet bowl cleaners contain hydrochloric acid as high as 26% HCl. General-purpose anticorrosive cleaners, such as 31% muriatic acid (HCl), are sold in gallon containers for home use and as swimming pool cleaners.

The alkali powder in air bags can cause ocular burns.[8] Perfume accidentally sprayed into the eyes can be caustic. Cement is alkaline and causes topical burns, typically on the knees.[9] Although hair relaxer creams contain NaOH and have a pH of 11.2 to 11.9, injuries after ingestion are usually limited.[4]

Caustic ingestions may occur when methamphetamine is produced from over-the-counter medications and household chemicals. Sulfuric acid, hydrochloric acid, NaOH, ammonium hydroxide, anhydrous ammonia, and metallic lithium are all used in the clandestine production of methamphetamine.[10] Severe caustic injuries in these situations can cause stricture formation, esophageal resection, and the need for colonic interposition.

More than 70 different pills can cause damage when they come in contact with esophageal mucus for prolonged periods.[11] Patients who take medications in the supine position, or who take pills without water, are at higher risk. Pills most likely to adhere are doxycycline, tetracycline, potassium chloride, and aspirin. Potassium chloride is particularly dangerous and has caused perforation into the aorta, left atrium, and bronchial artery.[11]

PRINCIPLES

Factors that influence the extent of injury from a caustic exposure include type of agent, concentration of solution, volume, viscosity, duration of contact, pH, and presence or absence of food in the stomach. The titratable alkaline reserve of an alkali or acid correlates with the ability to produce tissue damage.[12]

Table 151-1 Household Cleaning Products That Contain Caustic Chemicals

APPLICATION	PRODUCT (MANUFACTURER) CHEMICAL
Drain cleaner—liquid	Heavy Duty Liquid Drain Opener (Share), H_2SO_4 93% Drain Out Extra (Iron Out), KOH 30% Liquid-Plumr (Clorox), NaOH 0.5–2%, NaOCl 5–10% Maximum Strength Drain Opener (Enforcer), KOH 1–10%, NaOCl < 5% Drain Care Professional Strength Drain Opener, NaOH 5–15%
Drain cleaner—crystals	Heavy Duty Crystal Drain Opener (Roebic), NaOH 100% Crystal Drain Opener (Rohyme), NaOH 74% Crystal Drain Out (Iron Out), NaOH 30–60% Drano Pipe Cleaner (Johnson), NaOH 54%
Oven cleaner	Easy Off Heavy Duty Oven Cleaner (Reckitt), NaOH 4–6%
Rust remover	Rust Remover/Carpet Care (Johnson Wax Prof), HCl 10% Rust Stain Remover (Whink), HF 2.5–3% Rust Stripper (Certified), NaOH 50–75% Naval Jelly Rust Remover (Loctite), Phosphoric acid 25–30%
Toilet bowl cleaner	Instant Power Toilet Bowl Cleaner (Scotch), HCl 26% Bowl and Porcelain Cleaner (Cleanline), HCl 0.10% Bowl/Tile/Porcelain Cleaner (Share), Phosphoric acid 15–25% Husky 303 Toilet Bowl Cleaner, HCl 23% Misty Bolex Bowl Cleaner, HCl 26%
Swimming pool cleaner	Muriatic Acid, Aqua Chem (Recreational Water), HCl 31%

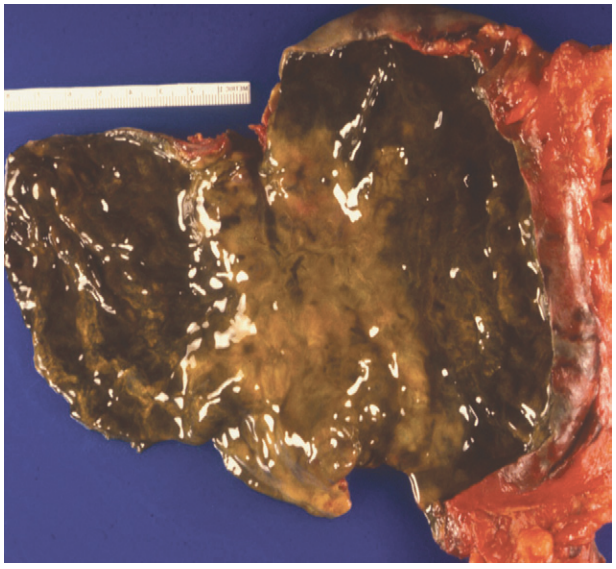


Figure 151-1. Gastric mucosa after ingestion of 35% potassium hydroxide.

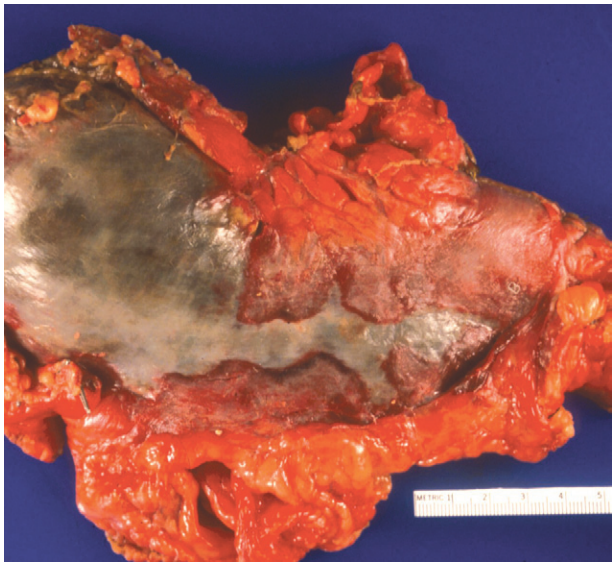


Figure 151-2. Gastric serosa after ingestion of 35% potassium hydroxide.

Figure 151-3. Esophagus after ingestion of 35% potassium hydroxide.

Concentrated forms of acids and bases generate heat resulting in superimposed thermal injury.[13]

Acidic compounds desiccate epithelial cells and cause coagulation necrosis. An eschar is formed thereby limiting further penetration. Because acids tend to have a strong odor and cause immediate pain on contact, the quantity ingested is usually limited. Because of resistance of squamous epithelium to coagulation necrosis, acids are thought to be less likely to cause esophageal and pharyngeal injury,[14] although severe esophageal and laryngeal burns may still occur. Acids can be absorbed systemically, causing metabolic acidosis, as well as damage to the spleen, liver, biliary tract, pancreas, and kidneys.

Alkaline contact causes liquefaction necrosis, fat saponification, and protein disruption, allowing further penetrance of the alkaline substance into the tissue. The depth of the necrosis depends on the concentration of the lye. A concentration of 30% NaOH in contact with tissue for 1 second results in a full-thickness burn.[15] Alkalis are colorless, odorless, and unlike acids, do not cause immediate pain on contact. Alkaline ingestions typically involve the squamous epithelial cells of the oropharynx, hypopharynx, and esophagus. The narrow portions of the esophagus, where pooling of secretions can occur, are also commonly involved.[13] Alkalis may also cause gastric necrosis (Figs. 151-1 and 151-2) and perforation. The esophagus can also be injured (Fig. 151-3).[16,17] Burns below the pylorus carry a worse prognosis than burns above the pyloris (50% vs. 9% mortality).[18]

Classically, the damage occurs in four steps. Initially, necrosis occurs, with invasion by bacteria and polymorphonuclear leukocytes. Vascular thrombosis follows, increasing the

damage. Over the next 2 to 5 days, superficial layers of injured tissue begin to slough. The tensile strength of the healing tissue may be quite low for up to 3 weeks following the caustic exposure, greatly increasing the chance of delayed perforation in some cases. Between 1 week and several months, granulation tissue forms, collagen is deposited, and a re-epithelization occurs in the burn area. Esophageal stricture may form over a period of weeks to years from contraction of the scar.

Caustic injury is categorized as first-, second-, and third-degree, similar to a thermal burn, based on appearance at endoscopy. The initial depth of injury found on esophagoscopy correlates with the risk of stricture formation. First-degree burns (also known as grade 1) consist of edema and hyperemia. Second-degree burns (grade 2) can be further divided into 2a, which are noncircumferential, and 2b, which are near-circumferential. Overall, second-degree burns are characterized by superficial ulcers, whitish membranes, exudates, friability, and hemorrhage. Third-degree burns (grade 3) are associated with transmural involvement with deep injury, necrotic mucosa, or frank perforation of the stomach or esophagus. Although grade 1 injuries do not progress to stricture, 15 to 30% of all grade 2 burns and up to 75% of circumferential grade 2 injuries of the esophagus develop strictures.[19] With full-thickness third-degree burns (grade 3), 90% result in stricture. Whether heat from the exothermic reaction increases the injury has never been quantified, but it has led to concerns regarding initial dilution or gastric lavage.[20,21]

CLINICAL FEATURES

Airway edema and esophageal/gastric perforation are the most emergent issues. Laryngeal edema occurs over a matter of minutes to hours. Systemic toxicity; hypovolemic shock; and hemodynamic instability with hypotension, tachycardia, fever, and acidosis are ominous findings. Small ingestions of potent substances can be as serious as larger ingestions. More than 40% of patients reporting to have "only taken a lick" have esophageal burns.[22] Patients present with oral pain (41%), abdominal pain (34%), vomiting (19%), and drooling (19%).[1] Many patients have wheezing and coughing. Others present with stridor and dysphonia. Chest pain is common. Visible burns to the face, lips, and oral cavity may be seen (Fig. 151-4). Skin burns can occur from spillage or secondary contamination after vomiting. Peritoneal signs suggest hollow viscous perforation or contiguous extension of the burn injury to adjoining visceral areas. Tracheal necrosis is one of the most frequent causes of death after caustic ingestion.[23]

Figure 151-4. Lip burn after exposure to 35% potassium hydroxide.

Studies present conflicting data correlating clinical symptoms with the severity of esophageal burns.[1,19,24] Oropharyngeal burns alone do not appear predictive of more distal injury, but prolonged drooling and dysphagia predicted significant lesions with 100% sensitivity and 90% specificity.[25] Vomiting and stridor may also be more predictive of burn injury.

Dysphagia usually subsides in 3 to 4 days. Patients with significant esophageal burns, particularly those that are circumferential, may develop esophageal stricture; 80% of strictures become apparent in 2 to 8 weeks. Symptoms include dysphagia and food impactions. Strictures that become symptomatic early are generally more severe. In one study of 86 adults admitted to the hospital after caustic ingestion, 18 developed complications and 6 died.[3]

Patients have an increase in esophageal cancer (1000-fold to 3000-fold increases) that develops 40 to 50 years after the caustic ingestion.[26] A recent long-term study showed that 1.8% of patients who ingested caustic soda developed esophageal cancer.[27] Nearly 3% of esophageal cancer patients have a history of caustic ingestion.[26]

Significant acid ingestions may be devastating and result in a higher mortality rate than alkali ingestions. The fulminant course of some acid ingestions may be due to systemic absorption of the acid, resulting in metabolic acidosis (which may also be the result of extensive tissue necrosis), hemolysis, and renal failure. In Russia, concentrated acetic acid ingestions account for 64% of caustic ingestions.[28]

DIAGNOSTIC STRATEGIES

The goal is to identify the extent and severity of the burn. Patients with chest and abdominal pain should have a chest radiograph and decubitus or upright abdominal studies to identify peritoneal and mediastinal air, denoting perforation or pleural effusion. Any suggestion of abdominal involvement should prompt abdominal computed tomography or ultrasonography.[29] Arterial blood gas determination may be useful after significant acid ingestions to monitor systemic metabolic acidosis. In cases of intentional overdose, co-ingestants should be considered.

Hydrofluoric acid exposures, whether inhalational, ingestion, or dermal (hand size or larger), require immediate cardiac monitoring to assess for QT_c prolongation, torsades de pointes, or other ventricular dysrhythmias. Rapid cardiac deterioration should be expected in these unusual cases.[30] Serum calcium and magnesium levels should also be determined, but empirical intervention with high-dose intravenous calcium chloride may be required for life-threatening dysrhythmias before confirmatory laboratory data are available.

The depth of burns cannot be predicted based on signs or symptoms. Noninvasive techniques (barium swallow) do not gauge the depth of burn injury. Endoscopy is contraindicated in patients with possible or known perforation. The finding of frank necrosis or obliteration of the lumen should result in termination of the endoscopic procedure. Patients with signs and symptoms (vomiting, drooling, stridor, or dyspnea) of intentional ingestion should undergo endoscopy within 12 to 24 hours to define the extent of the disease. Endoscopy performed too early may miss the extent or depth of tissue injury. Wound softening in the subacute phase when the likelihood of perforation is greatest makes late endoscopy (after 24 hours) more hazardous. A soft feeding tube or silk string can be placed in the esophagus, when burns are present, for future dilation. With the current flexible endoscopes, endoscopy should be continued past the area of burn and into the stomach, if possible.

Patients can be divided into four groups based on the results of endoscopy: (1) no esophageal/gastric injury, (2) gastric injury, (3) linear burns of the esophagus, and (4) circumferential burns.

MANAGEMENT

After a caustic ingestion, little can be done to attenuate the severity of the tissue injury. In evaluating a patient, the patient's history should include the time, amount, type of product ingested, and presence of suicidal ideations if any. Product labels are important in confirming the concentration of the chemical. If a sample is obtained, test the pH with litmus paper.

Early endotracheal intubation is warranted when airway compromise is suggested by hoarseness, throat pain, drooling, or edema. Intubation should also be undertaken early if significant exposure is suggested, before edema and secretions both threaten the airway and make intubation difficult or impossible. Blind nasotracheal intubation is contraindicated. When oral intubation is anticipated to be difficult or impossible because of edema and anatomic distortion, rapid-sequence intubation should be avoided and awake fiberoptic intubation or primary surgical cricothyrotomy may be necessary (see Chapter 1).

Patients who are suicidal may minimize their symptoms or have symptoms that understate the trauma. Intubation may not be enough to secure the airway. Hypoxia and an increased arterial-alveolar gradient warrant immediate bronchoscopy. In the suicidal patient, the physical examination and chest radiograph do not "rule out" pneumoperitoneum. Radiographs have low negative predictive values for detecting free air.[18]

Patients should have intravenous access and vigorous fluid resuscitation. In alert patients who are not vomiting and can tolerate liquids, small volumes (1–2 cups) of water or milk can be considered within the first few minutes after ingestion. Because injuries occur almost immediately, later dilution is not warranted. Forcing fluids is never indicated. Likewise, do not neutralize the ingested corrosive with weak acids or alkalis due to possible thermal reactions and worsening injury.

Inducing emesis, administering activated charcoal, and performing gastric lavage are not indicated. Careful nasogastric aspiration may be useful in the setting of significant acid ingestions presenting immediately after the event, given the ominous natural history of many of these cases and the somewhat lower risk of esophageal perforation compared with alkali ingestion.

Immediate surgical exploration is indicated for free air, peritonitis, increasing and severe chest and abdominal pain, and hypotension. Early and continuous hemodynamic monitoring is essential. The patient should be fully examined for evidence of dermal and ocular caustic exposures. Contaminated clothing should be treated as hazardous waste and disposed of using proper precautions.

Corticosteroid therapy remains controversial. Its use had been previously advocated to potentially prevent stricture formation.[31,32] The use of systemic corticosteroids in corrosive esophageal burns does not seem to be beneficial.[33] They can be harmful in perforation because they mask early signs of inflammation and inhibit resistance to infection. Prophylactic antibiotics may potentially mask evidence of impending perforation.

Children in developing countries often present late, sometimes months later, with a well-established stricture. These strictures are difficult to dilate and at risk for perforation. Recurrent strictures and repetitive dilatation treatment is expected.[34]

DISPOSITION

Surgical intervention is required in cases of hollow viscous perforation; early exploration may also be warranted in cases of suggested full-thickness burns.[17] Asymptomatic patients can undergo endoscopy in the emergency department or be discharged home with close follow-up monitoring. Children with a questionable history of ingestion should be observed even if they are asymptomatic and have no oropharyngeal burns. They can have a liquid diet. Symptomatic patients particularly those with potential for airway compromise require admission to the intensive care unit. If endoscopy is unavailable, the patient should be transferred to a facility where it can be performed. Psychiatric evaluation is indicated in patients with intentional or possibly intentional ingestion.

SPECIAL CASES

Ocular alkali exposures are true ophthalmologic emergencies. Immediate and aggressive lavage with at least 2 L of normal saline per eye is indicated in all cases except for frank perforation. Management is described in Chapter 61.

Dermal caustic exposures can also result in significant burn injuries (see Chapter 60). Clothing removal, copious irrigation, and local wound débridement are the most important initial treatment measures. Hydrofluoric acid burns warrant special attention. Although this is a relatively weak acid compared with HCl or H_2SO_4, the dissociated fluoride anion is problematic because of its extreme electronegativity. Deaths from HF, exposure have occurred after ingestion, after skin contact in areas as small as 1% of the body surface area, with concentrated HF, and after inhalation of HF vapor.[35] Systemic toxicity is characterized by immediate and profound hypocalcemia and dysrhythmias; cardiac monitoring and serum calcium monitoring are warranted in all but the most limited fingertip exposures.[36-38] Management is discussed in Chapter 61.

Povidone-iodine (Betadine) is used as a surgical scrub and is not a caustic agent, but ingestion of tincture of iodine can cause severe gastrointestinal injury and is potentially life-threatening. Gastric irrigation with starch or milk in these cases may convert iodine to the much less toxic iodide.

Ingestion of phenol or formaldehyde can also cause severe caustic injury to the gastrointestinal tract.[39,40] Both phenol and formaldehyde are general protoplasmic poisons and can cause protein denaturation and coagulation necrosis. Systemic symptoms, including dysrhythmias, hypotension, seizures, and coma, may also result from phenol ingestion. Acidosis may be quite prominent after formaldehyde ingestion due to its metabolism to formic acid. Phenol is well absorbed through the skin, and dermal exposure may result in burns and systemic toxicity. Although dermal decontamination of phenol exposures with low-molecular-weight polyethylene glycol has been suggested, irrigation with water may prove just as useful.

Ingestion of concentrated hydrogen peroxide (H_2O_2) may cause gastrointestinal burn injury and the formation of gas emboli.[41] Radiographic evaluation for the presence of gas in the chest or abdominal cavities, including the portal system, should be performed in symptomatic patients or those who ingest concentrated H_2O_2. Hyperbaric oxygen has been used successfully to treat gas emboli from H_2O_2 ingestion.[42]

Button (disk) batteries and conventional alkaline cylindrical batteries pose potential obstructive and chemical hazards if ingested. Ingestion of large 25-mm wafer-sized button batteries was a problem in the past but the smaller button batteries of today are less likely to cause esophageal obstruction. Button

batteries are usually made of a metallic salt (lithium, mercury, nickel, zinc, cadmium, or silver) bathed in NaOH or KOH. Obstruction can cause pressure necrosis, caustic injury due to leakage of alkaline medium, or electrical injury. Ulceration, perforation, and possible fistula formation occur but are uncommon. Heavy-metal toxicity in this setting has not been reported.[43]

Evaluation of button battery ingestions requires radiography to assess the position of the foreign body. Batteries lodged in the airway or esophagus require expeditious removal. Gastric or intestinal batteries can be treated with watchful waiting.[43] Checking the stool for passage of the batteries is recommended. Follow-up radiographs should be obtained in 1 week if the battery has not passed.

KEY CONCEPTS

- Ingestion of very small amounts of a caustic material (even a lick) can cause serious esophageal injury.
- All symptomatic patients should undergo endoscopy and be considered for admission.
- Asymptomatic patients can undergo endoscopy in the emergency department or be discharged with very close follow-up monitoring.
- Caustic ingestions can lead to esophageal stricture and a lifelong increased risk of esophageal cancer.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 152

Cocaine and Other Sympathomimetics

Rama B. Rao and Robert S. Hoffman

PERSPECTIVE

Cocaine, a naturally occurring plant-derived alkaloid, has been used for centuries as a medicinal product. For thousands of years in South America, the leaves of the cocoa plant (*Erythroxylon coca*) have been chewed for treatment of various ailments. In 1860, the pure alkaloid form was isolated and became a popular constituent of various beverages, pharmaceuticals, and therapeutic tonic but was banned from these products in 1914. At the peak of the cocaine epidemic in the early 1990s, it was estimated that 5 million people used cocaine regularly in the United States.[1] The drug is still popular, and the consequences of recreational cocaine use are profound. Between 1993 and 1995, 2000 unintentional cocaine-related deaths were reported in New York City.[2] Cocaine is also implicated in violent deaths and was detected in 25% of autopsies of fatal injuries in adults aged 15 to 44.[3] In 2003, 39% of drug misuse deaths were due to cocaine.[4]

Amphetamines are stimulants originally designed for use as decongestants and dietary aids that became popular as recreational drugs in the mid-20th century. Modifications of the amphetamine molecule, or illicit "designer" amphetamines, are inexpensively produced. The enhanced effects from these alterations add to the popularity of drugs such as 3,4-methylenedioxymethamphetamine (MDMA) and methamphetamines. Cocaine, amphetamines, and derivatives of amphetamines are called *sympathomimetics* (Box 152-1). These agents cause central nervous system (CNS) stimulation and a cascade of physiologic effects.

PRINCIPLES OF DISEASE

Pathophysiology of Cocaine

Acute cocaine use causes release of dopamine, epinephrine, norepinephrine, and serotonin. These neurotransmitters act on different receptor subtypes to cause many effects, but the most important are adrenergic stimulation by norepinephrine and epinephrine (see Box 152-1). Norepinephrine causes vasoconstriction by stimulating alpha-adrenergic receptors on vascular smooth muscle. Epinephrine increases myocardial contractility and heart rate through stimulation of beta$_1$-adrenergic receptors. In addition to causing catecholamine release, the reuptake of these stimulatory neurotransmitters from synaptic clefts is inhibited, altering the normal balance between excitatory and inhibitory tone in the CNS. Subsequent stimulation propagates peripheral catecholamine release (Fig. 152-1).

Cocaine also is a local anesthetic agent, slowing nerve impulses from neuronal pain fibers by blocking the inward movement of sodium across cell membranes (phase 0 of the action potential).[5,6] Sodium channel blockade across myocardial cells, similar to the class IA antidysrhythmic agents, is responsible for the occasional conduction abnormality with acute cocaine toxicity.

Cocaine metabolism occurs in the liver and the plasma. In the liver, the drug is metabolized primarily to the active metabolite norcocaine, which potentiates the parent drug. In the plasma, cocaine is metabolized to ecgonine methyl ester via pseudocholinesterase (plasma cholinesterase). This difference may account for the differences in duration of action with different routes of administration.[7] Ecgonine methyl ester may be protective because it is a vasodilator.[8] Genetic differences in the phenotypic expression of plasma cholinesterases may account for individual differences in susceptibility to cocaine toxicity.[9]

Benzoyl ecgonine is a nonenzymatic metabolite found in the plasma and is the metabolite identified by urine toxicology screens. Methylecgonidine and its metabolite ecgonidine are products of cocaine pyrolysis (crack).[10] Although less commonly assayed, methylecgonidine also can be identified in the urine.[10] The use of ethanol with cocaine may form cocaethylene, a metabolite that may potentiate the drug's stimulatory effects.[11]

Cocaine Formulations

Unpurified cocaine paste is converted to usable forms of cocaine. The crystallized freebase of the cocaine alkaloid is known as "crack cocaine." It is inhaled using a special "crack pipe" designed to tolerate the high temperature required to volatilize pure cocaine. The high lipid solubility and rapid transport from the lungs into the brain contribute to crack's rapid onset of action (Table 152-1). The water-soluble salts of cocaine (cocaine hydrochloride and cocaine sulfate) are available as a white crystalline powder that is taken intranasally or dissolved and injected intravenously. Oral administration is rare except for patients who are smuggling or concealing drugs.

CLINICAL FEATURES

The primary clinical effect of cocaine is the excitation of the sympathetic nervous system. Patients with moderate toxicity are alert and awake but may have diaphoresis, tachycardia,

BOX 152-1 CLINICAL EFFECTS OF SYMPATHOMIMETICS

Hypertension
Hyperthermia
Tachycardia
Mydriasis
Diaphoresis
Central nervous system excitation

mydriasis, and hypertension without organ damage. A more severely intoxicated patient may present agitated, combative, and hyperthermic. Signs and symptoms of end-organ damage may be present, including acute hypertensive emergencies. Patients may present with focal, acute pain syndromes; circulatory abnormalities; delirium; or seizures.

The clinical presentation depends on the dose, route of administration, and time to presentation after drug use. Additives, contaminants, or other drugs may alter the classic signs of acute cocaine intoxication. Patients who are "speedballing," using intravenous (IV) heroin and cocaine together, may be initially sedated, and administration of naloxone may precipitously reveal the underlying cocaine intoxication.

Mortality from acute cocaine overdose is significantly higher on days with ambient temperatures greater than 88° F.[12] The profound diaphoresis associated with cocaine may be absent or limited in cooler environments or if the patient is excessively dehydrated.

Initial assessment and treatment should focus on rapidly fatal complications, specifically hyperthermia, hypertensive emergencies, and cardiac dysrhythmias.

Hyperthermia

Acute psychomotor agitation with delirium increases the risk of hyperthermia.[13] Intoxicated patients have increased motor tone and generate heat. Vasoconstriction and dehydration can compromise cooling, resulting in life-threatening hyperthermia with core temperatures exceeding 106° F (41.1° C). Delay in recognition and management may increase the likelihood of death. Even with a normal temperature, increased motor tone can release intramuscular creatine kinase (CK) with rhabdomyolysis and its attendant renal and electrolyte complications.[14]

Hypertensive Emergencies

Acute cocaine-induced hypertension can seriously injure the cardiovascular system and CNS (see Chapter 83). Reported

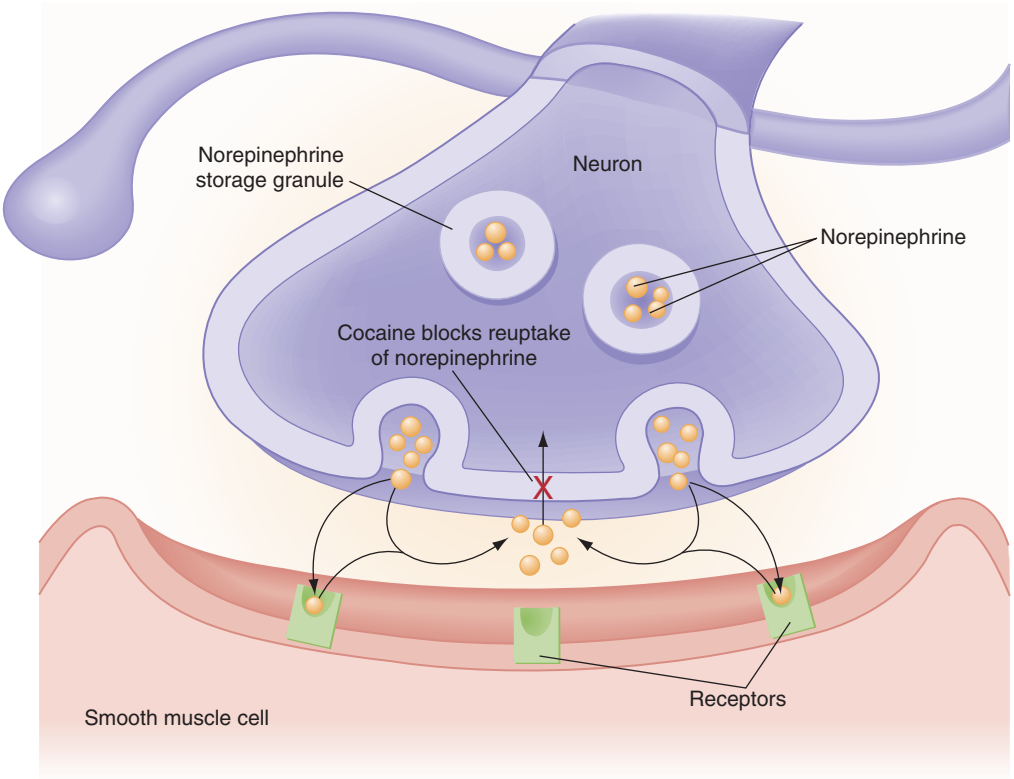


Figure 152-1. How cocaine increases sympathetic tone by increasing neurotransmitters in the synapse.

Table 152-1 Cocaine Pharmacology by Route of Administration

ROUTE	FORMULA	ONSET OF ACTION	PEAK EFFECT	DURATION
Inhalation	"Crack"	8 sec	2–5 min	10–20 min
Intranasal	Cocaine HCl	2–5 min	5–10 min	30 min
Intravenous	Cocaine HCl	Seconds	10–20 min	60–90 min
Oral	Cocaine HCl	30–60 min	60–90 min	Unknown
"Skin popping"	Cocaine HCl	Unknown	Unknown	Unknown

sequelae include aortic dissection,[15] pulmonary edema,[16] myocardial ischemia and infarction,[17] intracranial hemorrhage,[18] strokes,[19] and infarction of the anterior spinal artery.[20] Vasospasm can compromise perfusion to various organs. Intestinal infarctions and mesenteric ischemia can occur, particularly in body packers with large oral ingestions. Other local ischemic events include retinal vasospasm, renal infarctions, and placental insufficiency and infarction in the gravid uterus.[21]

Cardiac Dysrhythmias

A life-threatening dysrhythmia may not be noted until cardiac output abruptly diminishes, and the patient suddenly loses consciousness. Although sinus tachycardia is most common, atrial fibrillation and other supraventricular tachycardias can occur as a result of the surge in catecholamines. Torsades de pointes[22] or wide-complex tachycardias from blockade of fast sodium channels on the myocardium may deteriorate into poorly perfusing or fatal ventricular rhythms.[5,23] Transient conduction abnormalities consistent with a Brugada-type pattern have been associated with cocaine.[24,25] Hyperkalemia from rhabdomyolysis and myocardial ischemia can also cause dysrhythmias.

Other Complications

People who binge with continuous use over an extended time have a prolonged state of arousal, which causes catecholamine depletion, dehydration, and poor nutrition.

After the acute effects of cocaine have subsided, these patients with "cocaine washout" are profoundly sleepy but arousable and oriented, with normal vital signs or a mild sinus bradycardia.

Occasionally a patient has "crack dancing," a transient choreoathetoid movement disorder probably related to abnormalities in dopaminergic tone.[26] Deep vein thrombosis is reported with cocaine use, probably secondary to effects on coagulation. Paranoia, either drug-induced or from underlying psychiatric illness, may occur even after the acute effects of the drug subside. The neuropsychiatric effects of cocaine can alter behavior and judgment, increasing the risk of violent injuries.

Complications arise from the route of administration of cocaine. Inhalation of crack cocaine may cause oropharyngeal burns from the high temperature required to volatilize the drug.[27] Pneumothorax, pneumopericardium, and pneumomediastinum occur from inhalational barotrauma.[28] Intranasal cocaine use is associated with sinusitis and nasopalatine necrosis or perforation.[29] Intravenous users have a high risk of infection with blood-borne viruses, local abscesses, and systemic bacterial infections, including botulism, and endocarditis.[30] Transdermal injection of cocaine, or "skin popping," has similar types of complications. For a chronic user, addiction, or psychological dependence, is mediated through specific neurotransmitter pathways. Although there are no well-defined syndromes constituting cocaine withdrawal, patients may have strong cravings for the drug or a general feeling of dysphoria that is not physiologically life-threatening.[31]

DIAGNOSTIC STRATEGIES

Urine drug screening is unlikely to change treatment because it measures a cocaine metabolite (benzoyl ecgonine) that is typically present for 3 days after last use. In a few circumstances, however, urine drug screening may be beneficial: (1) to document possible abuse or neglect in a child with suggested exposure, (2) to confirm cocaine as the unknown substance in body packers, and (3) to differentiate paranoia from drug-induced or psychiatric causes.

An electrocardiogram (ECG) screens for dysrhythmias and conduction abnormalities from ischemia, hyperkalemia, or, more precipitously, QRS prolongation from sodium channel blockade. This blockade slows myocardial depolarization and results in a wide-complex tachycardia. The axis may be indeterminate or have a terminal rightward axis deviation similar to cyclic antidepressant toxicity. Cyclic antidepressants and cocaine share class Ia antidysrhythmic effects. Accurate diagnosis of chest pain is problematic. ST segment elevation is confounded by the presence of early repolarization.[32,33] Serial ECGs may be helpful.

Creatine kinase (CK), a nonspecific marker for muscle injury, is often elevated with cocaine use. The serum CK-MB fraction, troponin I, and troponin T are more specific in patients with atherogenic coronary disease, but it is uncertain how they apply to cocaine-related chest pain.[31,33,34] Some patients with elevations in CK-MB fail to show an elevation in either troponin I or troponin T.[34] Although the sensitivity and specificity of troponin and other serum enzyme markers are still being investigated for cocaine-related chest pain, cardiac enzymes should be measured as is done for other cardiac patients until cocaine-specific parameters are established. Severe, persistent headache despite normalization of blood pressure may occur with a subarachnoid hemorrhage and warrants head computed tomography and, if the scan is negative, lumbar puncture. Urinalysis should be checked for myoglobin, which indicates rhabdomyolysis.

DIFFERENTIAL CONSIDERATIONS

A differential diagnosis of acute cocaine intoxication considers the various causes of agitated delirium (Box 152-2). A thorough

BOX 152-2 DIFFERENTIAL DIAGNOSIS OF AGITATED DELIRIUM

- Metabolic causes
  - Electrolyte abnormalities
  - Hypoglycemia
  - Hypoxia
  - Uremia/hyperammonemia
- Structural lesions of the CNS
  - Trauma
  - Stroke
  - Hemorrhage
  - Mass
- Endocrine disease
  - Thyrotoxicosis
- Infections
  - Bacterial/viral meningitis/encephalitis
- Toxicologic causes
  - Sympathomimetic/stimulants
    - Cocaine
    - Amphetamines and derivatives
    - Caffeine
    - Phencyclidine/ketamine
  - Anticholinergics
  - Serotonin syndrome
  - Sedative-hypnotic withdrawal
- Heatstroke
- Postictal state

CNS, central nervous system.

assessment of mental status, vital signs, and physical examination can help direct and narrow the differential diagnosis. Conditions that may be indistinguishable from cocaine intoxication include sedative-hypnotic withdrawal, intoxication from amphetamines and amphetamine derivatives, and heatstroke. Phencyclidine intoxication may be distinguished by the presence of multidirectional nystagmus, but the treatment is similar. Patients with anticholinergic poisoning typically have urinary retention, dry skin, and minimally reactive pupils as distinguishing factors. Infection should be considered in all hyperthermic patients.

MANAGEMENT

A severely poisoned patient is combative and unable to cooperate in assessment of vital signs. These first few moments are crucial (Box 152-3). Because the patient's history is not always clear, the initial goal is to recognize and treat the rapidly life-threatening agitated delirium.

After initial airway assessment, patients may transiently require physical restraints to obtain complete vital signs and to secure IV access. If a chest restraint is used, a mesh vest is preferred to a jacket to help limit hyperthermia. The patient can receive empirical therapy with IV dextrose and thiamine or assessment with a bedside blood glucose monitor. Immediate pharmacologic sedation with IV benzodiazepines may be necessary, which, in adequate doses, restores inhibitory tone to the CNS and decreases excessive sympathetic outflow to peripheral tissues. Sedation also facilitates measurement of vital signs, particularly core temperature, continuous ECG monitoring, and completion of the physical examination.

Pharmacologic Sedation

In adults, IV diazepam can be administered in increments of 10 mg every 5 minutes until sedation is achieved. Diazepam has a rapid onset of action, is easily titratable, and has active metabolites for a sustained effect. Persistently increased motor tone reflects an inadequate diazepam dose, even if the patient appears sleepy. In wildly agitated patients in whom 20 to 30 mg of diazepam has no notable effect, the increments may be increased carefully by 20 mg each subsequent dose with close monitoring. Benzodiazepines also treat the choreoathetoid movements of crack dancing. Most cocaine intoxicated patients have salt and water depletion and require vigorous IV crystalloid replacement. If the cause of delirium is unclear, careful attention to the patient's respiratory status avoids the respiratory depression caused by excessive benzodiazepine administration in the presence of other sedative-hypnotic agents, such as ethanol.

Phenothiazines, droperidol, and haloperidol are ideally avoided if possible in patients thought to be acutely intoxicated with a sympathomimetic.[35] Although they have a rapid onset with intramuscular injection and CNS sedation is achieved, the anticholinergic effects of these agents can theoretically limit cooling by impeding diaphoresis and may also have associated dysrhythmic effects that may be additive to cocaine.

BOX 152-3 Initial Evaluation of Patients with Sympathetic Stimulation

- Rapid assessment of vital signs, especially core temperature
- Rule out hypoxia, hypoglycemia
- Pharmacologic sedation with benzodiazepines
- Electrocardiogram
- Urinalysis
- Serum creatinine phosphokinase

Hyperthermia

Cocaine-induced hyperthermia must be treated with rapid cooling (Box 152-4). Patients who sustain elevated core temperatures greater than 106° F (41° C) for more than 20 minutes are likely to stabilize transiently, then develop fatal multisystem organ failure, often heralded by disseminated intravascular coagulation. Patients should have continuous monitoring of core temperature with a rectal probe. Heat generated by agitation and increased muscle tone can be terminated by aggressive use of benzodiazepines, with neuromuscular paralysis and intubation as required. It is crucial to reduce core temperature to 102° F (38.8° C) within 20 minutes. Cooling blankets are insufficient. Ice water, wet sheets with large fans, and packing the entire body in ice with continuous monitoring of core temperature can be used. These patients often require aggressive fluid resuscitation.[36]

Hypertensive Emergencies

The goal in hypertensive emergencies is to promptly reverse the vasoconstriction of norepinephrine at peripheral alpha-adrenergic receptors. Benzodiazepines restore the CNS inhibitory tone on the peripheral nervous system. With evidence of end-organ damage, IV nitroglycerin or nitroprusside can be used.[37] Phentolamine, a direct alpha-adrenergic antagonist, is the antihypertensive of choice. It can be titrated slowly using repeat IV doses of 1 to 5 mg with blood pressure monitoring. In contrast to chronic hypertension, individuals with acute cocaine hypertension often have a normal blood pressure in the absence of the drug, and unless the patient's history suggests otherwise, a normal systolic and diastolic blood pressure should be the endpoint of therapy. Beta-adrenergic antagonists may cause paradoxical hypertension with cocaine.[38,39] Patients undergoing cardiac catheterization show decreased coronary artery diameter in the presence of cocaine and beta-adrenergic antagonists.[39,40] Beta-adrenergic antagonists use in cocaine toxicity or cocaine-related chest pain syndromes should be avoided while its role is investigated.[41-43] The treatment of cocaine-induced subarachnoid hemorrhage, myocardial infarction (MI), or aortic dissection differs from treatment

BOX 152-4 Management of Stimulant-Induced Hyperthermia

- Early identification of elevated core temperature
- Large-bore intravenous access with rapid infusion of crystalloid
- Sedation and muscle relaxation with benzodiazepines
- Rapid cooling within 20 min*
- Foley catheterization to monitor output
- Laboratory analysis for organ function
  - Serum chemistries/creatinine/CK
  - Liver function
  - PT/PTT/fibrin split products
  - Bacterial cultures†
- Urinalysis for myoglobinuria
- Paralysis and intubation if necessary

*Ideally with ice water immersion.
†Consider lumbar puncture or antibiotic therapy, especially in injection drug users.
CK, creatine kinase; PT, prothrombin time; PTT, partial thromboplastin time.

for other causes of the same conditions. The combined use of phentolamine and beta-adrenergic antagonists may result in profound hypotension and is inadequately investigated. Likewise, data on the use of labetalol are disappointing. The 2008 American Heart Association Guidelines consider beta-adrenergic antagonists potentially harmful.[43]

Dysrhythmias

Dysrhythmias from cocaine may be either atrial or ventricular. Atrial fibrillation and supraventricular tachycardias are likely due to sympathetic stimulation and often respond to benzodiazepines. Beta-adrenergic antagonists should be avoided.

When the cause of a wide-complex tachycardia from cocaine is unknown, an empirical sodium bicarbonate, 1 to 2 mEq/kg IV bolus, with closely recorded cardiac monitoring treats sodium channel blockade and potential cardiotoxicity from hyperkalemia.[6,44] Lidocaine, a class IB antidysrhythmic agent, may increase seizure risk and mortality and is therefore reserved for patients with ventricular dysrhythmias for whom bicarbonate therapy has failed and who have already received benzodiazepines. Lidocaine may be most useful for ventricular dysrhythmias with cocaine-associated MI. Amiodarone is not well studied, but may be beneficial for ventricular dysrhythmias.[45] Close monitoring is required for patients with a Brugada-type conduction pattern.[24,25]

Cocaine-Related Chest Pain

The causes of cocaine-related chest pain are diverse (Box 152-5). A chest radiograph may identify aspirated foreign bodies or pneumothorax or pneumomediastinum from inhalational barotrauma. Fever and shortness of breath should prompt consideration of pneumonia, pulmonary infarction,[46,47] or endocarditis with septic pulmonary emboli in IV drug abuse.

Cocaine acutely induces coronary vasoconstriction while increasing myocardial oxygen demand. Platelet aggregation is enhanced through prothrombogenic and antifibrinolytic pathways.[48,49] These cumulative effects can result in coronary insufficiency. Cigarette smoking acutely exacerbates these conditions. Chronic cocaine use may accelerate atherogenesis and induce left ventricular hypertrophy. All of these factors contribute to myocardial ischemia or infarction. Of nonfatal MIs in patients aged 18 to 45 years, 25% were attributed to cocaine, even after adjustment of other cardiac risk factors.[50]

Identifying a patient with a cocaine-related coronary syndrome is difficult. Patients may present hours to days after use, possibly due to vasoactive metabolites.[51] The patient may deny drug use and have atypical chest pain. Almost one third of cocaine-using patients meeting serum enzyme criteria for MI report pleuritic chest pain.[52] There are no clear predictors for patients at risk because age, route of drug use, time to presentation, and preexisting risk factors for coronary artery disease are inadequate for identifying patients sustaining MI.[52] Patients with positive serum enzymes for MI have significant angiographic stenosis.[53] Of patients without positive serum markers, 18% still have significant disease by angiogram.[53] Other predictors of significant disease in this group included elevated cholesterol and prior diagnosis of coronary disease or MI.[53] Patients with a history of coronary stent placement are at a high risk of thrombosis with cocaine use.[54]

As for most complications of cocaine use, benzodiazepines decrease myocardial oxygen demand by limiting peripheral stimulation and should be given early.[55] Aspirin and nitrates also should be administered.[51] In patients meeting ECG criteria for MI with persistent chest pain and hypertension and a clear history of acute cocaine intoxication, coronary vasodilation with IV phentolamine (1 mg) given slowly should be considered. This dose can be repeated, if needed, as long as the patient's blood pressure remains stable. Morphine sulfate also can be used to treat pain.[56] Patients with persistent chest pain and ST segments strongly suggestive of MI can be considered for percutaneous intervention in the catheterization laboratory or thrombolytic therapy, assuming there are no contraindications such as uncontrolled severe hypertension.

In contrast to non-cocaine-induced myocardial ischemia or infarction, beta-adrenergic antagonists, including labetalol, are contraindicated during acute cocaine toxicity because coronary vasoconstriction may worsen.[38,39,42,43] This contraindication also applies to patients with cocaine-related coronary syndromes who are not acutely intoxicated as alpha-adrenergic vasoactive metabolites may be responsible.

Heparin can be given, but fibrinolytic therapy is not well studied. Some mechanisms of cocaine-induced MI would be expected to respond to fibrinolytic agents. Patients failing vigorous treatment with nitrates and phentolamine who have known coronary artery disease or a previous ECG confirming new ST segment elevations may be candidates for fibrinolysis, although cardiac catheterization is preferable. The same contraindications apply as with non-cocaine-induced MI. Nuclear imaging studies also may provide more diagnostic information.[32,51,57]

Antiplatelet and glycoprotein IIb/IIIa inhibitors and calcium channel antagonists seem to be of benefit to some patients with MI or ischemia of atherosclerotic origin. Theoretically, these agents may counter some of the platelet aggregation enhanced by cocaine, but data investigating their use are lacking. Patients with cocaine-related chest pain without other risk factors who have normal ECGs and cardiac enzymes are at low risk for myocardial infarction. The role of provocative testing in these patients is unclear.[43]

BOX 152-5 CAUSES OF STIMULANT-INDUCED CHEST PAIN

- Noncardiac
  - Pneumothorax
  - Pneumomediastinum
  - Pneumopericardium
  - Aortic dissection
  - Pulmonary infarction
  - Infection
- Foreign body aspiration
- Cardiac chest pain
  - Endocarditis
  - Pericarditis
  - Ischemia/infarction
    - During acute intoxication
    - After acute intoxication
- Coronary stent thrombosis

Cocaine Body Packers

Before crossing international borders, "body packers" ingest cocaine that has been wrapped tightly into condoms or other latex products and sometimes coated in wax. Each packet can contain approximately 10 g of cocaine, and packers may swallow as many as 150 packets.[58,59] On arrival at the patient's destination, a cathartic is taken to stimulate gastrointestinal passage of the contraband for subsequent delivery and distribution. Body packers are likely to know the exact number of packets they ingested.

A body packer may present without symptoms to the emergency department. The body packer should be placed immediately on continuous cardiac monitoring, with large-bore IV

access. Diagnosis is made by history. An abdominal radiograph may confirm foreign bodies but cannot be used to count packets because plain radiographs have limited sensitivity in detecting an isolated or small number of packets. When uncertainty persists, a contrast study is warranted. Body packing also is used for transporting heroin and other illicit substances. Although heroin body packing rarely requires surgical intervention, an asymptomatic patient may refuse to identify the packet's contents. A urine toxicology screen may be useful because some fine quantities of drug may be directly ingested while swallowing the contraband. Body packers with a positive urine screen for cocaine metabolites should receive vigorous decontamination.

Rupture of a single cocaine packet can result in death because each packet contains almost 10 times the lethal dose. These patients may die suddenly. All cocaine body packers should be admitted to a monitored setting and given nothing to eat or drink. Patients with a leaking or poorly secured packet who become symptomatic meet the single absolute criterion for surgical removal of packets and are likely to die without prompt intervention. When evidence of cocaine toxicity is manifest, rapid transportation to the operating room may be the only way to save these patients. Benzodiazepines, neuromuscular blockade, or sodium bicarbonate administration may be required en route.

It is reasonable to administer activated charcoal (1 g/kg body weight) to an asymptomatic body packer whose airway is intact. Whole-bowel irrigation with polyethylene glycol solution facilitates gastrointestinal passage of the packets and cleanses the bowel in the event of emergent transport to the operating room.[56] Subsequent contrast studies may be required to evaluate for remaining packets. Computed tomography and contrast abdominal radiographs may fail to detect isolated packets that contain potentially fatal quantities of cocaine. Patients suggesting that they swallowed a larger number of packets than passed or who refuse to reveal the number ingested warrant continued bowel irrigation, observation, and repeat studies. Endoscopic retrieval is discouraged because of concern over packet rupture during the procedure.[59]

All packets passed in the stool, via endoscopic procedures, or in the operating room should be counted carefully and promptly given to law enforcement officials. When law enforcement is not yet involved, hospital legal counsel or risk management and the hospital ethics committee may be helpful in determining the disposition of the packets and ultimately of the patient when he or she is medically cleared.[59]

Body Stuffers

A "body stuffer" is an individual who attempts to conceal evidence of cocaine possession by swallowing the drug while pursued by law enforcement officials. These are usually unplanned events with generally small quantities of drug intended for personal use. The drugs are often swallowed in poorly sealed vials or glassine packets that may not be evident on radiographs. Generally, patients ingest nonlethal doses and are asymptomatic. Activated charcoal (50 g) can absorb any potentially released drug. Monitoring and whole-bowel irrigation should be performed if the quantity ingested is of concern or if signs of intoxication persist.[60] Stuffers rarely have fatal events, but these patients usually present with or develop symptoms in the first few hours.

DISPOSITION

Acutely intoxicated patients who need only observation or who respond quickly to sedation and do not develop complications can be discharged after the acute intoxication resolves. These patients may be extremely sleepy from catecholamine depletion, and it is best to discharge them with a responsible adult. Patients may be open to drug counseling and referral while in the emergency department. Patients who develop complications should be admitted to the intensive care unit for further treatment.

BOX 152-6 Admission Criteria for Cocaine-Related Chest Pain

- Persistent chest pain
- Electrocardiogram changes
- Dysrhythmias or conduction abnormalities
- CHF/cardiogenic shock
- Elevated enzymes
- Requiring vasodilation
- Preexisting CAD or stent placement
- Multiple risk factors for CAD

CAD, coronary artery disease; CHF, congestive heart failure.

Patients with chest pain (Box 152-6) who are acutely intoxicated and who show dynamic changes on the ECG, dysrhythmias, or congestive heart failure or patients requiring vasodilators or reperfusion should be admitted. These patients require further evaluation of the extent of preexisting reversible ischemia and intervention to encourage cessation of drug use.

The disposition of patients with chest pain who are not acutely intoxicated is less clear. Admission is warranted for patients with complications or ECG changes and patients requiring pharmacologic intervention. Other patients may be admitted for short-term observation to an emergency department observation unit or discharged, depending on the level of concern about underlying coronary artery disease.

Young patients who present after resolution of chest pain with normal, unchanging ECGs, no dysrhythmias, and few or no risks of coronary artery disease are likely to have a good outcome.[57] Complications such as congestive heart failure and ventricular dysrhythmias typically present within the first 4 hours.[17] After a 12-hour monitored observation period, patients with a benign clinical course and negative serum enzyme markers can be discharged.[57,61]

Body packers need to be observed until all packets have passed. Ideally, these patients have had three packet-free stools, a reliable packet count consistent with the ingestion, and a negative contrast radiographic study.[59] Body stuffers who receive activated charcoal, have normal ECGs, and remain asymptomatic with normal vital signs after 4 to 6 hours of observation may be discharged.

OTHER STIMULANTS

Amphetamines

Amphetamines enhance release of catecholamines from presynaptic nerve terminals by altering the pH of presynaptic vesicles. Amphetamines are usually taken as pills, but occasionally are crushed and injected. The subsequent CNS stimulation results in nearly identical sympathomimetic effects to those from cocaine, but not with the same frequency or intensity (see Box 152-1). Patients are at risk for hyperthermia, hypertensive emergencies, dysrhythmias, myocardial ischemia, and hyperkalemia associated with rhabdomyolysis. In contrast to cocaine, amphetamines do not block sodium channels and only minimally affect presynaptic reuptake of catecholamines. Although urine drug screens can identify amphetamines, they are of little utility in treating an intoxi-

cated patient. The management follows the same guidelines as for cocaine (see Box 152-3), although the duration of toxicity tends to be longer for amphetamines.

Methylenedioxymethamphetamine

Methylenedioxymethamphetamine (MDMA—"Ecstasy," XTC, Adam) is a chemically modified amphetamine originally taken orally at all-night dance parties, or "raves." Patients describe the euphoria allowing "closeness to others," so it is sometimes called the "love drug." The molecular structure of MDMA confers some serotoninergic properties that may account for the "shimmering" visual effects reported.

Along with the usual complications of amphetamines, MDMA can precipitate a life-threatening hyponatremia. MDMA or its metabolite may alter release of endogenous stores of vasopressin.[62] Although the exact mechanism is not understood, patients with MDMA-induced hyponatremia have concentrated urine samples with a relatively high urine sodium level, similar to syndrome of inappropriate antidiuretic hormone. Unless seizures or other neurologic events are present, patients can be treated supportively with fluid restriction. Urine can be tested for specific gravity, and a sample should be sent to the laboratory for electrolyte analysis and osmolality. Normal saline or other crystalloids may worsen the hyponatremia because these patients are likely to retain more free water than sodium. Their fluid intake should be restricted unless severe hypovolemia exists, and they should be treated with hypertonic saline for neurologic impairment. A newer treatment for hyponatremia includes vasopressin$_2$-receptor antagonists[63] but has not been described for these patients. In contrast to other amphetamines, chronic MDMA use causes potentially irreversible neurologic damage to serotoninergic neurons.[64] Other MDMA variants, such as 3,4-methylenedioxyethamphetamine (Eve), may cause similar complications (see Chapter 154).

Methamphetamine

Methamphetamine, known as "crank" and "crystal meth," is a fat-soluble, smokable, designer amphetamine. Complications from methamphetamine use are similar to those from other sympathomimetics. The duration of action can be significantly longer, however, with some paranoid delusions persisting for 15 hours. The production of methamphetamines requires a variety of metal salts, and lead toxicity from inappropriately produced drug is reported.[65] Injuries during illicit methamphetamine production or police raids include exposure to anhydrous ammonia, hydrochloric acid, sodium hydroxide, ether, and ephedrine, as well as burns and explosions.

Ephedrine and Ephedra

Ephedrine is another illicitly used amphetamine-like agent associated with complications of excessive sympathomimetic stimulation. Ephedra, a plant-derived product, also known as a Chinese herbal product, *ma-huang*, has been associated with strokes and deaths in adolescent users.[66] The U.S. Food and Drug Administration has banned all ephedra-containing dietary supplements.

Khat and Methcathinone

Khat is a stimulant agent naturally occurring in the leaves of the plant *Catha edulis*.[67] These leaves are chewed to extract the active compounds, cathinone and methcathinone, which are stimulants with sympathomimetic effects.[68] Management and disposition follow the same guidelines as that of cocaine. Smoking khat does not typically result in clinical effects because the agent degrades with pyrolysis. Illicitly manufactured methcathinone is known as "cat." Some methcathinone users experienced an extrapyramidal syndrome associated with elevated manganese levels likely resulting from an inadvertent contaminant during production or inadequate purification. The role of chelation therapy for elevated manganese levels is uncertain.[69]

KEY CONCEPTS

- Rapid sedation with an IV benzodiazepine is the key for most symptoms from cocaine and other stimulants.
- Hyperthermia is a high-risk sign, and body temperature must be reduced rapidly.
- Beta-adrenergic blockade may cause paradoxical hypertension and increase coronary vasoconstriction and is generally contraindicated.
- Wide-complex rhythms secondary to cocaine may respond to IV bicarbonate therapy.
- Cocaine body packers who become symptomatic need immediate surgery.
- Amphetamine symptoms and effects last longer than those produced by cocaine.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 153

Toxic Alcohols

Suzanne R. White

METHANOL

Perspective

Methanol is a colorless, volatile, slightly sweet-tasting alcohol. It is a product of natural fermentation and originally was manufactured from the distillation of wood. Methanol currently is produced almost exclusively by synthetic pathways. Certain products found in the home, including antifreeze; windshield washer fluid; carburetor fluid; duplicator fluid; hobby engine fuel; gasohol; dry gas; Sterno; glass cleaners; and thinners for shellacs, lacquers, adhesives, and inks may contain high concentrations of methanol. Methanol is a precursor in the manufacture of plastics, films, and dyes. Methanol is also found in formalin and embalming fluid. Illicit alcohol production remains a global source of methanol poisoning from products such as *chang'aa* (Kenya), *raki* (Turkey), and *tuica* (Romania).

Although epidemic poisonings from methanol are reported occasionally, most exposures are sporadic. In 2006, of the 2086 cases of methanol poisoning reported to American poison centers, 73% were unintentional, 8% had moderate to major complications, and 8 resulted in fatalities. Treatment delay is associated with increased morbidity, making early recognition of clinical and laboratory clues crucial.

Principles of Disease

Pharmacology and Metabolism

Methanol is absorbed rapidly from the gastrointestinal tract, and blood levels peak 30 to 60 minutes after ingestion.[1] Transdermal and respiratory tract absorption also has resulted in toxicity, especially in infants. Certain occupations, including painting, glazing, varnishing, lithography, and printing, are at high risk for inhalational exposure to methanol. Inhalational abuse of methanol is a recent trend that can result in toxic serum levels.[2] At low serum concentrations, the elimination of methanol follows first-order kinetics; at concentrations after overdose, zero-order kinetics predominate. A prolonged half-life of 24 to 30 hours results, which may be extended even further by the concurrent ingestion of ethanol. First-order elimination prevails at high levels (>300 mg/dL), possibly as a result of enhanced pulmonary elimination. Small amounts of ingested methanol may be exceptionally toxic. In adults, the smallest lethal dose reported is 15 mL of 40% methanol; 4 mL of pure methanol has led to blindness. With appropriate, timely treatment, however, survival without loss of eyesight has been reported despite extremely high levels. From a pediatric perspective, the ingestion of only 1.5 mL of 100% methanol in a toddler (0.15 mL/kg) is sufficient to produce a toxic blood level of 20 mg/dL. Any suggested pediatric methanol ingestion warrants aggressive evaluation and treatment.

Methanol itself has little toxicity, producing less central nervous system (CNS) depression and inebriation than ethanol. Metabolites of the parent alcohol are extremely toxic, however. Although small amounts of methanol are eliminated via renal and pulmonary routes, 90% is metabolized hepatically. Methanol is oxidized by alcohol dehydrogenase (ADH) to formaldehyde, which is rapidly converted by aldehyde dehydrogenase to formic acid (Fig. 153-1). Formic acid is the primary toxicant and accounts for much of the anion gap metabolic acidosis and ocular toxicity peculiar to methanol ingestion.[3] Through a folate-dependent pathway, formic acid is degraded to carbon dioxide and water.

Pathophysiology

Optic neuropathy and putaminal necrosis are the two main complications of severe methanol poisoning. Long-term morbidity takes the form of visual impairment, including blindness, and parkinsonian motor dysfunction, characterized by hypokinesis and rigidity. Formic acid has a high affinity for iron and, as such, inhibits mitochondrial cytochrome oxidase, halting cellular respiration.[4] Methanol metabolism in the cytosol and mitochondria may account for a second mechanism of adenosine triphosphate depletion.[5] Lactate accumulation resulting from hypotension or seizures further compounds the metabolic acidosis predominantly caused by formate. Other mechanisms of toxicity involve increased lipid peroxidation, free radical formation, and impaired protective antioxidant reactions.[4,6] Severe dysfunction of subcellular metabolism from methanol also has been linked to significant disturbance in proteolytic-antiproteolytic balance.[7]

The primary sites of ocular injury are the retrolaminar optic nerve and retina. Selective myelin damage to the retrolaminar optic nerve has been seen at autopsy in patients dying as a result of methanol toxicity. Müller cells, the principal glial cells of retinal neurons and photoreceptors, have been proposed as the initial target in methanol-induced visual toxicity. It seems that they alone harbor the enzymes necessary to metabolize methanol to formate. Histopathologic correlates suggest that retinal cells develop intra-axonal swelling, calcium influx, mitochondrial destruction, and microtubular disruption. Ultimately, interference with transport of essential proteins from the retinal neuron cell body to the nerve fiber axoplasm

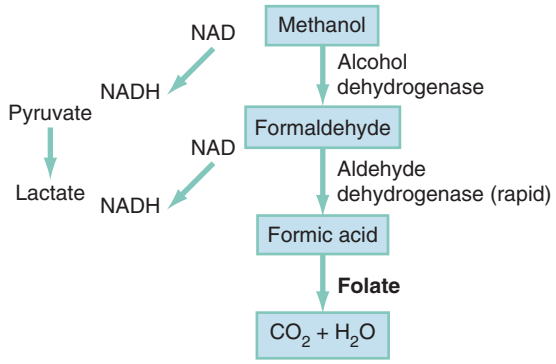


Figure 153-1. Metabolism of methanol.

results. Oligodendrocyte involvement results in myelin degeneration and leads to visual decrements. Acidosis may accelerate this process, by enhancing nonionic diffusion of formic acid into neurons and further increasing lactate production.[4] This self-perpetuating cycle of acidosis, termed *circulus hypoxicus*,[8] underscores the need for aggressive correction of pH to accomplish ion trapping of formate outside the CNS.

Methanol adversely affects other areas of the CNS, specifically the basal ganglia. Bilateral, symmetrical putaminal hypodensities, hemorrhages, or cystic lesions are characteristic, occurring in 13.5% of patients.[9] Necrosis is described in the subcortical white matter, spinal cord anterior horn cells, and cerebellum.[10] Acute signs and symptoms may be lacking or may take several days to develop, despite the presence of these radiographic findings. The cellular mechanisms of injury may be similar to the mechanisms of the ophthalmologic injury, but the reason for localization of neurologic damage to the basal ganglia is unknown.[9] Although some quantitative neuropathologic studies have shown high concentrations of formic acid within the putamen, others show that formate levels are not disproportionately elevated in these areas compared with levels in the blood or other tissues. Massive edema adjacent to the putamen shown by magnetic resonance imaging (MRI) suggests a possible localized disruption of the blood-brain barrier. Other proposed mechanisms for the vulnerability of this region include the unique pattern of arterial blood supply and venous drainage and greater metabolic activity.

Clinical Features

With individual cases of methanol poisoning, the history may be unobtainable or unreliable. The diagnosis should be considered in patients with altered mental status, visual complaints, or metabolic acidosis or in patients with occupations that put them at high risk for exposure. Because methanol is a poor substrate for ADH, a latency period exists between the time of ingestion and onset of visual or metabolic disturbance. The typical 12- to 24-hour latency may be shorter when large amounts are consumed or longer when ethanol is co-ingested (range 40 min to 72 hr).[1] In patients who present early, formic acid accumulation may be ongoing, with risk for significant toxicity despite being asymptomatic. When symptoms manifest, they are primarily neurologic, gastrointestinal, or ocular in nature.

Although methanol is less inebriating than ethanol, early symptoms of methanol poisoning are depressed mental status, confusion, and ataxia. Nonspecific complaints of weakness, dizziness, anorexia, headache, and nausea develop. In severe cases, coma and seizures may be seen. Although vomiting and abdominal pain commonly result from mucosal irritation, the absence of gastrointestinal complaints does not rule out a serious ingestion.[1] Abdominal tenderness, however, may be so severe that it suggests an acute surgical abdomen.[1] This may result from pancreatitis, and elevation of serum amylase is relatively common. Other authors have noted increased salivary amylase isoenzyme without pancreatic inflammation.

Visual disturbances are seen in 50% of patients, and their development may precede or parallel that of other clinical symptoms.[8] Patients may complain of cloudy, blurred, indistinct, or misty vision or may note yellow spots or, rarely, photophobia. The most common acute field defect is a dense central scotoma.[11] Some patients compare their visual symptoms with "stepping out into a snowstorm," a complaint unique to methanol ingestion. Patients can have a complete lack of light perception and total loss of vision. On examination, optic disk hyperemia is seen at 18 to 48 hours after ingestion. Peripapillary retinal edema follows, is most striking in the nerve fiber layer along the vascular arcades, and only rarely involves the macula.[5,11] Sluggishly reactive or fixed and dilated pupils indicate a poor prognosis. Pallor and cupping, indicative of optic atrophy, are late findings suggesting a poor prognosis for visual recovery. Occasionally, the fundus may appear normal, even in patients with visual symptoms.

Compensatory tachypnea heralds the onset of metabolic acidosis, which often may be severe, with reported serum bicarbonate concentrations of less than 5 mEq/L and an arterial pH less than 7.0. Early tachycardia has been noted, but in general, cardiovascular abnormalities are rare.[1] Hypotension and bradycardia, when present, are preterminal findings.[12] Historically, death was described in association with a peculiar, abrupt cessation of respiration, rather than with cardiovascular collapse.[1,13] Rarely, multiple organ failure develops.[12]

Prognosis after methanol ingestion seems to correlate with the degree of acidosis, time to presentation, and initiation of treatment within 8 hours of exposure.[1,14] Poor prognosis is associated with coma, seizures, or arterial pH less than 7.0.[12,15] A recent large outbreak was associated with a fatality rate of 44%.[16] Patients surviving the acute phase of toxicity may be left with permanent blindness or neurologic deficits, such as parkinsonism, toxic encephalopathy, polyneuropathy, cognitive dysfunction, transverse myelitis, primitive reflexes, or seizures.

Diagnostic Strategies

A severe anion gap metabolic acidosis is the hallmark of methanol poisoning. In some cases, this sign may be the only diagnostic clue. Because the onset of acidosis may be delayed 12 to 24 hours, the presence of a normal anion gap does not rule out methanol exposure. Absence of high anion gap acidosis has been described in cases with concomitant ethanol, lithium, or bromide ingestion. In methanol toxicity, this anion gap is due primarily to the presence of formic acid, with a variable contribution from lactic acid. Another classic laboratory finding in methanol toxicity is an elevated osmol gap. The osmolal gap is defined as follows:

$$\text{Osmol gap} = \text{measured serum osmolality} - \text{calculated serum osmolality}$$

Serum osmolality depends on the presence of low-molecular-weight solutes, primarily sodium, chloride, glucose, and blood urea nitrogen (BUN). One formula for calculating osmolality attributable to these solutes is as follows:

$$\text{Calculated serum osmolality (mOsm/kg)} = 2(Na^+) + [BUN/2.8] + [\text{glucose}/18] + [\text{ethanol (mg/dL)}/4.6]$$

The "normal" osmol gap is often cited to be less than 10 mOsm/kg when the preceding equation is used. This is an arbitrary number, and there is considerable variability in baseline osmolal gaps in patients, particularly children.[17] An osmol gap significantly greater than 10 mOsm/kg may be a useful aid in the diagnosis of toxic alcohol ingestion. Caution should be taken, however, in ruling out toxic alcohol ingestion with a "normal" osmol gap for several reasons. First, calculated serum osmolality results may vary among laboratories and must be done by the freezing point depression method. Also, delayed presentation after toxic alcohol ingestion may be associated with prior metabolism of most of the parent alcohol. Because only the parent compound is osmotically active, and because the charged metabolites are electrically balanced by sodium, there may be little or no osmol gap elevation in this setting. Finally, a toxic level of either methanol or ethylene glycol may be present with a gap of only 10 mOsm/kg. If there is clinical suggestion of toxic alcohol ingestion, direct measurement of the serum toxic alcohol level is necessary, and if not readily available, empirical treatment is warranted.[18] In addition to methanol, ethylene glycol, and isopropanol, other low-molecular-weight solutes, such as ethanol, acetone, propylene glycol, mannitol, glycerol, and ethyl ether, may cause elevated osmol gaps. Rhabdomyolysis, pancreatitis, and metabolic derangements, such as hypomagnesemia, hypokalemia, and hypophosphatemia, are also described with methanol poisoning.

Computed tomography may be indicated in an intoxicated patient with altered mental status. The characteristic finding of bilateral putaminal lesions suggests methanol poisoning, but this finding also may be seen with Leigh's syndrome, Wilson's disease, hypoxic-ischemic insult, encephalitis, and certain metabolic disorders. Ischemic necrosis, cerebral edema, or brain hemorrhages also may be noted. Follow-up scans may have prognostic value because parkinsonian features are unlikely to develop in patients whose putaminal lesions resolve within a short time frame.[19] MRI may also detect putaminal aberrations or optic neuropathy from methanol intoxication.

Differential Considerations

Methanol and ethylene glycol cause inebriation and are ingested as ethanol substitutes. The differential diagnosis of a patient with altered mental status includes hypoglycemia, head trauma, postictal state, carbon dioxide narcosis, hypoxia, infection, hepatic encephalopathy, other metabolic disorders, thiamine deficiency, endocrinopathy, drug abuse, and other poisoning. Patients who present with severe abdominal pain and altered mental status could slant the differential diagnosis toward a long list of intra-abdominal entities. When an anion gap acidosis is identified, however, the differential diagnosis must be tapered toward entities that cause this, and a primary decision must be made regarding whether the acidosis is a result of an ingested toxin or some other cause (e.g., mesenteric ischemia, diabetic ketoacidosis). Usually, the presence of an ingestion is admitted by the patient or strongly considered by the providers, but this is not always the case, especially when the patient has depressed mental status of unknown cause. Causes of an elevated anion gap in patients without evidence of renal failure, hypotension, hypoxemia, diabetes, seizures, or alcoholism include methanol, ethylene glycol, paraldehyde, isoniazid, iron, salicylates, toluene, or lactic acidosis from myriad toxicants, including metformin, carbon monoxide, cyanide, and cocaine. Ethylene glycol and methanol may cause a "double gap" (i.e., an osmol gap in addition to the anion gap). Other substances that contribute to an elevated osmol gap include isopropyl alcohol, ethanol, propylene glycol, mannitol, glycerol, and ethyl ether. Other situations in which double-gap acidosis may be encountered include diabetic ketoacidosis; alcoholic ketoacidosis; acetonitrile, methanol, ethylene glycol, and propylene glycol toxicity; multiple organ failure; chronic renal failure; and critical illness.[20] Hyperlipidemia and hyperproteinemia, by decreasing the measured sodium concentration, can increase the osmolal gap. Characteristically, isopropanol does not cause an increased anion gap.

Certain unusual characteristics of methanol and ethylene glycol intoxication lead to the specific diagnosis. The presence of ocular complaints unique to methanol poisoning is a valuable clue. Ethylene glycol ingestion often is associated with calcium oxalate crystalluria, which is not seen in methanol ingestion. Ultimately, the definitive diagnosis depends on the identification of the parent alcohol in the blood by laboratory tests that may not be routinely available. It is often necessary to start treatment based on clinical suggestion alone. Because the initial treatment for methanol and ethylene glycol is almost identical, identification of the specific toxic alcohol is not crucial to the initiation of therapy.

Management and Disposition

See the discussion on management in the following section on ethylene glycol.

ETHYLENE GLYCOL

Perspective

Ethylene glycol is a viscous, colorless, odorless, slightly sweet-tasting liquid. Because it lowers the freezing point of water, its primary utility is as a commercial antifreeze or coolant. Other sources include airplane deicing solutions, hydraulic brake fluids, and industrial solvents/precursors; it also is a component of certain paints, lacquers, and cosmetics. Most ethylene glycol poisonings occur with the ingestion of antifreeze. Unusual poisoning scenarios are described, including an epidemic after the contamination of water supplies and the intentional poisoning of an infant, presenting as an inherited metabolic disorder. In 2006, the American Association of Poison Control Centers reported 6135 exposures to ethylene glycol. Of those exposures, 74% were unintentional, and 11% resulted in moderate or severe effects; there were 34 fatalities. If treated early and aggressively, ethylene glycol poisoning is unlikely to result in death. Conversely, failure to recognize and treat ethylene glycol ingestion may result in multiorgan failure and death within 24 to 36 hours.[21]

Principles of Disease

Pharmacology and Metabolism

Absorption of ethylene glycol is rapid after ingestion. It distributes evenly to tissues with a volume similar to that of body water. Peak blood levels are reached within 1 to 4 hours after ingestion. In contrast to methanol and isopropanol, ethylene glycol is nonvolatile at room temperature so absorption via inhalation is unlikely. Reported half-lives range from 3 to 8.6 hours.[22] When metabolism is blocked by fomepizole or ethanol, the half-life increases to 11 to 15 hours or 17 hours, respectively.[23] The toxic and lethal doses of 100% ethylene glycol have been reported as 0.2 mL/kg and 1.4 mL/kg. At the other extreme, with therapeutic advances, patients who have ingested 3000 mL have survived.[24] Twenty-seven percent of ethylene glycol is excreted unchanged by the kidneys. The remainder is hepatically oxidized via ADH and other oxidative

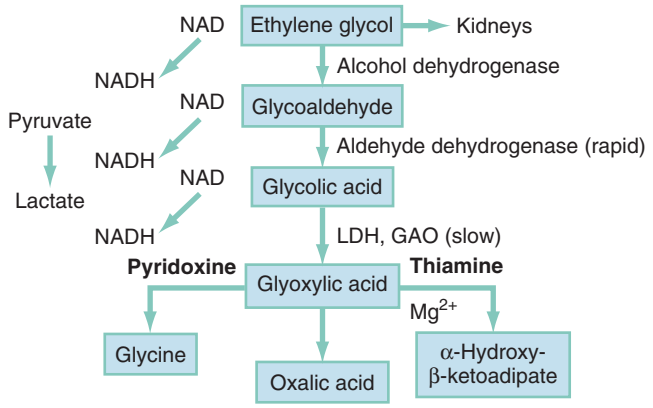


Figure 153-2. Metabolism of ethylene glycol. GAO, glycolic acid oxidase; LDH, lactate dehydrogenase; NAD, nicotinamide adenine dinucleotide; NADH, reduced form of nicotinamide adenine dinucleotide.

enzymes to various toxic organic aldehydes and acids (Fig. 153-2).

Pathophysiology

Unmetabolized ethylene glycol has limited toxicity, yet all metabolites are toxic. In humans, 2.3% of a dose of ethylene glycol ultimately is converted to oxalic acid, most of which is excreted in the urine. A fraction of oxalic acid combines with calcium to form calcium oxalate crystals, which precipitate in renal tubules, brain, and other tissues. Although calcium oxalate crystals previously were thought to be the most significant cause of renal toxicity, much of ethylene glycol's nephrotoxic effect now is known to stem from the direct cytotoxic action of the organic acid metabolites themselves. When administered to rats, the ethylene glycol metabolites glycolate, glyoxylic acid, and glycolaldehyde cause significant renal toxicity in the absence of calcium oxalate crystal deposition. Persistent deposition of these crystals has been observed in serial renal biopsy specimens despite recovery. An in vitro study on human proximal tubular cells showed that toxicity occurred primarily from the direct effect of oxalic acid, despite exposure to much higher levels of glycolate.[25] Other authors suggest that glycolate levels correlate better with disruption of CNS metabolism, the development of renal failure, and mortality.[26] An intermediary of glycolic acid metabolism, glyoxylic acid, theoretically can be shunted toward pyridoxine-dependent or thiamine-dependent pathways, which generate the nontoxic products glycine and α-hydroxy-β-ketoadipate (see Fig. 153-2). Based on this biochemical observation, both of these cofactors are routinely used in therapy.

Histologically, proximal renal tubular dilation with hydropic change and vacuolar degeneration, intratubular crystal deposition, and edema of the interstitium are seen. Relative sparing of the glomeruli is typical, although glomerular interloop space crystal deposition may occur. Glomerular function is preserved, but tubular dysfunction manifesting as protein leak is noted.[27] Neuropathologic changes induced by ethylene glycol include diffuse calcium oxalate deposition with petechial hemorrhages in the retina, brain, vessel walls, and perivascular spaces, with evidence of cerebral edema and chemical meningoencephalitis. Similar changes also have been noted in the liver, spleen, pancreas, pleura, lungs, pericardium, and blood vessel walls throughout the body. Myonecrosis occurs in skeletal and myocardial muscle, and rhabdomyolysis and myocardial dilation occur.[28] Fatty liver with focal necrosis has been noted.

The metabolism of ethylene glycol results in a profound anion gap metabolic acidosis caused mainly by glycolic acid.[29] Lactate elevation, triggered by the altered redox potential within cells and inhibition of the citric acid cycle by products of glyoxylate metabolism, is a minor contributing factor to the severe acidosis.[29]

Clinical Features

The clinical syndrome with ethylene glycol ingestion is divided into four stages: acute neurologic stage, cardiopulmonary stage, renal stage, and delayed neurologic sequelae stage. The severity of illness seen in each stage varies, as does progression through stages, which may be telescoped. Patients may die in any stage of ethylene glycol poisoning. Poor prognostic factors include hyperkalemia, severe acidosis, seizures, and coma. Metabolic acidosis and symptoms typically occur within 4 to 8 hours, but may be delayed for 12 hours or longer if ethanol has been co-ingested.

Stage I, the *acute neurologic stage*, occurs 30 minutes to 12 hours after ingestion. The parent alcohol causes approximately the same degree of inebriation as ethanol with CNS depression, slurred speech, nystagmus, ataxia, and vomiting. With large ingestions, more dramatic neurologic findings, such as hallucinations, convulsions, or coma, may be present during the early phase of intoxication. Ocular findings, similar to methanol intoxication, including decreased pupillary reflexes, decreased visual acuity, optic disk blurring, papilledema, and loss of color discrimination, are reported but methanol exposure was not ruled out in most of these case reports.

Stage II, the *cardiopulmonary stage*, occurs 12 to 24 hours after ingestion. Often, the patient exhibits mild hypertension and tachycardia. Tachypnea may reflect the underlying profound metabolic acidosis or may herald the onset of cardiogenic or noncardiogenic pulmonary edema.[8] The mechanism of acute respiratory distress syndrome (ARDS) is unclear but may be related to the toxicity of glycolic and glyoxylic acids and to the deposition of calcium oxalate crystals within the lungs. Pulmonary infiltrates are described during this phase. Circulatory collapse may occur as a result of myocardial depression. Hypocalcemia, rarely associated with tetany or cardiac dysrhythmia, occurs in 30% of patients as a result of systemic chelation of calcium by oxalate.[28] Myositis with muscle tenderness and creatine kinase (CK) elevation results from skeletal muscle inflammation and necrosis.

Stage III, the *renal stage*, occurs 24 to 72 hours after ingestion. In one epidemic of 36 patients, renal damage was noted in 67%.[28] Awake patients may complain of flank pain or have costophrenic angle tenderness. Calcium oxalate monohydrate or dihydrate crystalluria is seen in only 50% of cases.[30] Hematuria and proteinuria are common, however. As with other causes of acute tubular necrosis, oliguria is not always present but may develop 12 hours after ingestion and may progress to frank anuria. The outcome has not been well studied in patients who develop renal failure. Prolonged hemodialysis may be necessary, although recovery of renal function has been reported. Delayed onset of ARDS has been reported to occur during this stage, but more typically is seen in stage II. The degree of acidosis, delay in presentation, and glycolate levels correlate better with the development of renal failure than do ethylene glycol levels.[28,31]

Stage IV, the *delayed neurologic sequelae stage*, occurs 6 to 12 days after ingestion and typically manifests as cranial neuropathy.[32] All cases have been associated with renal failure. Facial diplegia, occasionally with deafness, is encountered most frequently. Other reported findings include dysarthria, dysphagia, tongue deviation, visual deterioration, and internal ophthalmoplegia. Delayed and persistent cognitive and motor deficits, such as ataxia, chorea, coma, and late personality

changes, also are reported. Total paralysis from severe axonal peripheral polyneuropathic degeneration with oxalate deposition is reported,[33] as is polyradiculopathy from nerve root (not distal) pathology. Although some improvement in neurologic status has been noted at follow-up, most patients are left with residual neurologic deficits. Some authors have coined this delayed syndrome *facial auditory nerve oxalosis*, based on heavy calcium oxalate crystal deposition along the subarachnoid portions of the seventh and eighth cranial nerves seen at autopsy.[34] It is unclear, however, what causal role calcium oxalate deposition plays. Direct mechanical injury from crystals, inflammatory response triggered by ethylene glycol metabolites, meningitis, and pyridoxine deficiency all have been proposed as mechanisms. Because the syndrome has been reported only since 1978, it is possible that the advent of hemodialysis has allowed more patients with potentially lethal ingestions of ethylene glycol to survive to display delayed neurologic complications.

Diagnostic Strategies

Useful laboratory tests for evaluating a patient with potential ethylene glycol toxicity include serum electrolytes, calcium, BUN, creatinine, serum glucose, serum osmolality, blood ethanol level, arterial blood gases, ethylene glycol level, electrocardiogram, and urinalysis. Although crystalluria is considered the hallmark of ethylene glycol ingestion, its absence does not rule out the diagnosis because less than half of patients have this finding.[30,35] Crystalluria may take the form of envelope-shaped calcium oxalate dihydrate crystals or needle-shaped calcium oxalate monohydrate crystals, which are occasionally mistaken for hippurate crystals.[8] Other crystal shapes and composites have been noted so that in the setting of combined anion and osmolal gap elevation, the presence of *any* type of crystalluria warrants a search for ethylene glycol. Monohydrate crystals are thought to be more specific for ethylene glycol poisoning.[30] Irrigating the urinary bladder with 50 to 100 mL of saline, centrifuging the irrigant, and examining the sediment for crystals may yield the diagnosis in patients who are already anuric. Other findings reflecting tubular dysfunction include decreased specific gravity, proteinuria, microscopic hematuria, pyuria, and cylindruria. Falsely elevated ethylene glycol levels may be seen in the face of elevated lactate or LDH with certain enzymatic assays.

Freshly voided urine can be examined for fluorescence with a Wood's lamp. Sodium fluorescein is added to antifreeze to aid in the detection of radiator leaks. Urinary fluorescence may be seen 6 hours after ingestion of fluorescein-containing antifreeze. Gastric contents and the patient's skin or clothing also may fluoresce under a Wood's lamp. The lack of fluorescence does not rule out ethylene glycol ingestion, however, because examiner sensitivity, specificity, and inter-rater reliability are low.[36] One study found urinary fluorescence in all specimens from children evaluated for conditions unrelated to poisoning.[37] Specimens should be collected in borosilicate glass test tubes or deposited directly onto gauze or filter paper because many plastic specimen containers and some glass tubes are fluorescent. The urine pH also should be checked and adjusted to 4.5 or greater before Wood's lamp examination.

Leukocytosis may be seen in ethylene glycol poisoning, with a typical white blood cell count of 10,000 to 40,000/μL, but is neither a sensitive nor a specific finding and is not of diagnostic value. The hematocrit and platelet counts are normal. One third of patients have hypocalcemia, which is most likely caused by calcium precipitation with oxalate.[34] QT prolongation on the electrocardiogram leads to the early diagnosis of hypocalcemia. Rarely, profound hypocalcemia resulting in seizures and tetany may occur. The CK can be elevated owing to toxic effects of ethylene glycol metabolites on muscle tissue.[38]

Similar to methanol, ethylene glycol often causes a profound anion gap metabolic acidosis when the metabolites glycolic acid and glyoxylic acid (and, to some extent, lactic acid) accumulate. Artifactual elevations of lactic acid levels may occur in the presence of glycolate with certain analyzers.[39] Similar to methanol toxicity, an elevated osmolal gap as measured by freezing point depression is a clue to the diagnosis of ethylene glycol toxicity. Lethal concentrations can be associated, however, with a normal or only slightly elevated osmolal gap. The cerebrospinal fluid may be normal or may display a cloudy or bloody appearance, increased protein or, most commonly, a polymorphonuclear pleocytosis.

Imaging studies show cerebral edema with decreased attenuation in the mediobasilar portions of the brain, typically with a return to isodensity within 1 week; this does not correspond to the clinical picture.[8] MRI in one patient with delayed cranial neuropathy showed gadolinium enhancement of cranial nerve V bilaterally, possibly secondary to calcium oxalate deposition. Electroencephalographic findings have been nonspecific.

Differential Considerations

Classically, patients who ingest ethylene glycol appear intoxicated without the odor of ethanol and have an anion gap metabolic acidosis, increased osmolal gap, and calcium oxalate crystalluria. Without evidence of alcoholic ketoacidosis or diabetic ketoacidosis, the differential diagnosis of the "double gap" should include methanol and ethylene glycol. The hallmark finding with late presentation is renal toxicity. Toxicant-induced acute renal failure is extensively reviewed elsewhere; substances commonly implicated include antimicrobials, nonsteroidal anti-inflammatory drugs, acetaminophen, halogenated hydrocarbons, radiocontrast media, metals, antineoplastic agents, and myoglobin. Hypocalcemia and a prolonged QT interval are important diagnostic clues. Toxicant-induced hypocalcemia is unusual and may be related to aminoglycosides, calcitonin, cisplatin, loop diuretics, interferon-alfa, mithramycin, pentamidine, and phosphate infusions. Healthy individuals with dietary excesses of vitamin C or foods rich in oxalate, such as tomatoes, garlic, spinach, rhubarb, cocoa, and tea, may exhibit calcium oxalate crystalluria.

Management

Methanol and ethylene glycol ingestions are treated essentially the same, and the following recommendations apply to both. As in any overdose setting, resuscitation and stabilization are paramount. Specific blood levels that confirm the presence of these substances may not be readily available, and a delay in instituting therapy can lead to irreversible organ damage or death. For any significant history of exposure, treatment should be initiated pending a confirmatory toxic alcohol blood level.

Because methanol and ethylene glycol are absorbed rapidly from the gastrointestinal tract, and gastric emptying has not been shown to alter clinical course or outcome and may be associated with complications, its use is restricted to patients who have ingested a substantial volume and arrive in the emergency department within 30 to 60 minutes of ingestion. Even in these cases, it is of dubious value. Activated charcoal is not useful. Obtunded patients should receive intravenous (IV) naloxone, dextrose (or have a bedside glucose determination), and thiamine, if clinically indicated. Forced diuresis is of no value and may cause pulmonary edema and ARDS. Early intubation may be indicated to protect the airway against

aspiration and in anticipation of further deterioration in mental status.

Regional poison control centers have developed management guidelines for ethylene glycol toxicity and can provide management advice at 800-222-1222. Key recommendations suggest that a patient with symptoms of ethylene glycol poisoning or in whom self-harm, misuse, or potentially malicious administration is a possibility should be referred to an emergency department immediately regardless of the dose reported. Conversely, the absence of symptoms shortly after ingestion does not exclude a potentially toxic dose and should not be used as a triage criterion. Inhalation exposures do not develop into systemic toxicity and can be managed out-of-hospital if the patient is asymptomatic. Patients with clinically significant mucous membrane irritation should be referred for evaluation. Decontamination of dermal exposures should include routine cleansing with mild soap and water. Removal of contact lenses and immediate irrigation with room temperature tap water is recommended for ocular exposures. If symptoms of eye injury are present, ophthalmologic consultation or follow-up may be helpful. Adults who ingest a "swallow" or children who ingest more than a witnessed taste or lick, or if the amount is unknown, of most ethylene glycol products should be referred immediately to an emergency department for evaluation. Gastrointestinal decontamination with ipecac syrup, gastric lavage, or activated charcoal is not recommended.[40]

Three treatment goals exist for patients with methanol or ethylene glycol toxicity: (1) correction of metabolic acidosis with bicarbonate; (2) ADH enzyme blockade, which inhibits the metabolism of methanol and ethylene glycol to toxic metabolites; and (3) removal of the parent alcohol and its metabolites by hemodialysis. The acidic metabolites of methanol and ethylene glycol can cause a profound bicarbonate-resistant metabolic acidosis, with several hundred milliequivalents of excess acid produced per hour.[41] In contrast to lactic acid, these acids are not metabolized to bicarbonate, and massive amounts of bicarbonate may be necessary merely for partial correction of the acidosis.[8] Early correction of metabolic acidosis may be beneficial in reversing methanol-induced visual impairment,[42] most likely related to the induction of a larger fraction of dissociated formic acid, which should decrease the amount of formic acid entering the CNS. Depending on the severity of the patient's acidosis, IV bicarbonate can be administered by intermittent boluses, an initial bolus followed by an infusion, or infusion alone. Boluses of 1 to 2 mEq/kg to attain a target serum pH of 7.45 to 7.50 followed by an infusion of 150 mEq/L of sodium bicarbonate in 5% dextrose at 1.5 to 2 times the maintenance fluid rate are suggested. With ethylene glycol, the potential for worsened hypocalcemia during the administration of large amounts of sodium bicarbonate should be considered.

To prevent further production of the toxic and acidic metabolites of methanol and ethylene glycol, metabolism of the parent compounds by the enzyme ADH must be blocked by either ethanol or fomepizole (Antizol). After significant toxic alcohol exposure, ADH blockade should be carried out in any adult or child with symptoms or with methanol or ethylene glycol levels greater than 20 mg/dL, even if asymptomatic. If ethanol is used to block ADH, the goal is to maintain the blood ethanol level between 100 and 150 mg/dL, which completely saturates ADH.[8] The affinity of ADH for ethanol is 10 to 20 times greater than for methanol and 100 times greater than for ethylene glycol. When methanol or ethylene glycol metabolism is blocked by ethanol, their half-lives increase to more than 30 hours or 17 hours, respectively. Prevention of methanol and ethylene glycol metabolism by ethanol explains the delayed toxicity seen in patients who ingest ethanol in combination with either of these substances. When dosing ethanol, it also is important to measure the patient's initial blood ethanol level. If it is greater than 100 mg/dL, a loading dose is unnecessary, and the patient can be started on a maintenance infusion (Table 153-1). The required maintenance dose of ethanol may nearly triple during hemodialysis because ethanol also is efficiently removed. Ethanol may be given orally or intravenously. Potential side effects of IV administration include CNS and respiratory depression, hypotension, vomiting, hypoglycemia, and thrombophlebitis, although even in children, adverse effects are limited.[43] Oral ethanol loading may be associated with gastritis. Initial close monitoring of serum ethanol and glucose levels every 1 to 2 hours is essential until a steady-state level of 100 to 150 mg/dL is achieved. Levels should be checked every 2 to 4 hours thereafter. Monitoring of ethanol therapy ideally is accomplished in the intensive care unit.

Similar to ethanol, fomepizole blocks the metabolism of methanol and ethylene glycol by ADH and prevents the formation of toxic metabolites.[23,44] When methanol or ethylene glycol metabolism is blocked by fomepizole, their half-lives increase to an average of 52 and 17 hours, respectively.[45] Fomepizole is a pregnancy category C drug; although not approved for use in children, its use has been reported.[46] Potential advantages of the use of fomepizole rather than

Table 153-1 Standard Range of Therapeutic Doses of Ethanol Based on Average Pharmacokinetic Values

	AMOUNT ABSOLUTE ETHANOL*	VOLUME (43% ORAL SOLUTION)†	VOLUME (10% IV SOLUTION)‡
Loading dose§	600 mg/kg	1.8 mL/kg	7.6 mL/kg
Standard maintenance dose (nondrinker)	66 mg/kg/h	0.2 mL/kg/h	0.83 mL/kg/h
Standard maintenance dose (chronic drinker)	154 mg/kg/h	0.46 mL/kg/h	1.96 mL/kg/h
Maintenance dose during dialysis (nondrinker)	169 mg/kg/h	0.5 mL/kg/h	2.13 mL/kg/h
Maintenance dose during dialysis (chronic drinker)	257 mg/kg/h	0.77 mL/kg/h	3.26 mL/kg/h

*Specific gravity = 0.79.
†Equivalent to 86 proof undiluted liquor (34 g ethanol/dL).
‡Equivalent to 7.9 g ethanol/dL.
§Assumes initial ethanol concentration is zero; dose is independent of chronic drinking status.
Modified from Barceloux DG, et al: American Academy of Clinical Toxicology practice guidelines on the treatment of ethylene glycol poisoning. Clin Toxicol 36:537, 1999.

ethanol include ease of administration, predictable pharmacokinetics, improved patient safety profile, a standardized and less complicated dosing regimen that does not require direct observation or frequent blood monitoring, longer duration of action, and lack of CNS depression.[47] Nonetheless, simply blocking toxic alcohol metabolism does not alter the toxicity of preformed metabolites. The use of neither fomepizole nor ethanol supplants the need for hemodialysis. The main disadvantage of the use of fomepizole is its acquisition cost. The dose is 15 mg/kg followed by 10 mg/kg every 12 hours for four doses. After five doses, the dose increases to 15 mg/kg every 12 hours until the ethylene glycol concentration is undetectable or less than 20 mg/dL *and* the patient is asymptomatic with a normal arterial pH. Dosing changes are required during hemodialysis. Side effects of fomepizole include headache, nausea, dizziness, inflammation at the site of infusion, rash, eosinophilia, and mild, reversible transaminase elevation. To date, no clinical trials have compared the relative efficacy, safety, or cost of fomepizole and ethanol in the treatment of ethylene glycol or methanol toxicity.

Rapid removal of the methanol or ethylene glycol through hemodialysis before they have been metabolized remains the cornerstone of therapy. In addition, hemodialysis, preferably using a dialysate high in bicarbonate, corrects acidosis and uremia, aids in fluid management and cardiovascular stabilization, and removes the toxic metabolites in late presenters. Hemodialysis decreases the half-life of methanol and ethylene glycol to 2.5 to 3.5 hours. Peritoneal dialysis and hemoperfusion are much less effective.[48]

Indications for hemodialysis in patients with methanol or ethylene glycol toxicity are controversial. In general, however, hemodialysis is indicated in patients who have metabolic acidosis, renal compromise, visual symptoms (methanol), deterioration despite intensive supportive care, or electrolyte imbalances unresponsive to conventional therapy.[8] Indications for hemodialysis are generally for patients who have metabolic acidosis, renal insufficiency, deterioration despite intensive care, electrolyte disturbance, or visual disturbances with methanol.[8] In addition, a blood level of either substance greater than 50 mg/dL usually calls for dialysis,[47,49] but in patients with normal kidneys, prolonged fomepizole treatment alone has been used without hemodialysis.[50,52] For ethylene glycol, a glycolic acid level greater than 8 mmol/L, an anion gap greater than 20 mmol/L, or an initial pH less than 7.30, predicts renal failure and the need for hemodialysis.[54] Methanol and ethylene glycol levels should be interpreted in the context of the clinical status and the time after ingestion. An acidotic patient with a low blood level after a delayed presentation requires more aggressive treatment than an asymptomatic patient with a high level.

The endpoint for hemodialysis is an undetectable serum ethylene glycol or methanol concentration and the disappearance of acid-base abnormalities and signs of systemic toxicity. Closure of the anion gap also may serve as an endpoint for hemodialysis in situations in which levels are not available or reliable (i.e., in patients with delayed presentation).

In methanol poisoning, the rate of the final degradation reaction of formic acid to carbon dioxide and water depends on the cofactor folate in primates (see Fig. 153-1). Studies in animals and limited human data suggest that formate metabolism is enhanced with the use of folate. Accordingly, 50 mg of leucovorin (folinic acid) should be given IV every 4 hours to adults with methanol toxicity. Likewise, the cofactors thiamine and pyridoxine have theoretical benefit based on their use in humans with primary hyperoxaluria, although no clinical trials have studied their efficacy in the treatment of ethylene glycol toxicity. Adequate cofactor levels minimize oxalic acid production by favoring the production of other, less toxic metabolites (see Fig. 153-2). Because underlying deficiencies of these vitamins may not be readily apparent in patients, empirical administration is reasonable. The recommended adult doses are thiamine, 100 mg IV every 6 hours, and pyridoxine, 50 mg every 6 hours for 2 days. With symptomatic hypocalcemia, IV calcium should be supplemented, albeit cautiously, to avoid further precipitation of calcium oxalate crystals in tissues. Asymptomatic hypercalcemia need not be treated. Magnesium is a cofactor along with thiamine for the detoxification of glycolic acid and should be replaced in patients who are deficient.

Disposition

Admission is generally necessary for patients undergoing treatment for ethylene glycol or methanol exposure. In addition, all patients with clinical or laboratory findings consistent with these ingestions should be admitted, even when the history is lacking or unavailable. Early consultation with a nephrologist for possible hemodialysis is necessary in the management of suggested toxic alcohol ingestion. If such services are not available, the patient should be given an ADH inhibitor and transferred to a setting where dialysis is available. A regional poison center or medical toxicologist may be contacted to guide management. An ophthalmologist can evaluate visual injury fully in patients with methanol poisoning. Neurologic consultation and follow-up monitoring of patients with either methanol or ethylene glycol toxicity are prudent given the potential for delayed or persistent neurologic sequelae.

Prevention

The addition of the bittering agent denatonium benzoate (Bitrex) to consumer automotive products containing 10% or more ethylene glycol or 4% or more methanol has been implemented. The effect of this effort has not yet been demonstrated to decrease exposure to these products in children.[54] Another opportunity for prevention is the substitution of less toxic glycols, such as propylene glycol, into commercial antifreezes.

ISOPROPYL ALCOHOL

Perspective

Isopropyl alcohol (isopropanol) is a clear, colorless liquid with a slightly bitter taste. It is the second most commonly ingested alcohol after ethanol. In 2006, the American Association of Poison Control Centers reported 21,181 isopropanol exposures: 88% were unintentional, and 3% involved moderate or major effects; there were 4 fatalities. Rubbing alcohols, which contain 70 to 91% isopropanol or ethanol, are frequent sources of exposure and may be tinted green or blue. Other sources include skin and hair products, nail polish removers, disinfectants, window and pine household cleaners, and antifreeze. Children experience toxicity most commonly from accidental ingestion, but inhalation and transdermal absorption during sponge bathing may occur. Isopropanol and its major metabolite acetone cause twice the CNS depression of ethanol, so intentional ingestion as an alcohol substitute is encountered frequently in adults. Isopropanol is not associated with the toxicity of ethylene glycol or methanol poisoning, and death after exposure is rare. The typical fatality involves a chronic, older alcoholic with mixed ethanol-isopropanol intoxication after a drinking binge.[55]

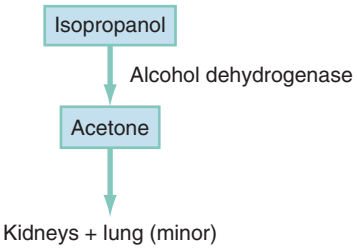


Figure 153-3. Metabolism of isopropanol.

Principles of Disease

Pharmacology and Metabolism

Absorption of isopropanol is rapid and complete; 80% of a dose is absorbed within 30 minutes of ingestion. The kidneys excrete 20% as unchanged isopropanol. A small portion is resecreted into the stomach and saliva; the remaining 80% is metabolized in the liver to acetone by ADH (Fig. 153-3). Acetone is excreted primarily by the kidneys, with small amounts expired through the lungs.

Isopropanol blood levels peak 30 minutes to 3 hours after ingestion, and elimination follows first-order kinetics, with a half-life of 3 to 7 hours.[56] In children, the half-life may be slightly shorter.[57] Acetone is eliminated more slowly, with a half-life of 22 hours. The rate of elimination of isopropanol may be increased by chronic ethanol abuse and decreased by hepatic damage.[55] A potentially lethal dose in adults is 150 to 240 mL (2–4 mL/kg), but adults have survived ingestions of 1 L (8–15 mL/kg).

Pathophysiology

Isopropanol is a potent CNS depressant, but the mechanism of action is unclear. Acetone is also a CNS depressant, and it has been suggested that coma may be prolonged by the extended elimination of this metabolite. The extent to which acetone contributes to coma is brought into question by the report of a patient who was awake and conversant, with acetone levels of 200 mg/dL. In large doses, isopropanol causes hypotension from peripheral vasodilation and direct myocardial depression. Topical effects include corneal de-epithelialization or dermal burns, described in premature infants as a result of skin de-esterification. Acetone does not seem to be shunted into the formation of acetoacetate or β-hydroxybutyrate; the finding of ketosis without acidosis is characteristic of isopropyl ingestion. No pathognomonic postmortem features are seen in isopropanol intoxication. Pulmonary congestion at autopsy is nonspecific and typical of deaths involving drug-induced CNS depression.[55]

Clinical Findings

Clinically, gastrointestinal and CNS complaints predominate. Intoxication may be suggested by apparent inebriation with the odor of acetone rather than ethanol detected on the breath. The patient may have headache or dizziness and may exhibit neuromuscular incoordination, confusion, and nystagmus. Severe ingestions may result in deep coma, which is prolonged compared with ethanol. Respiratory depression or failure may occur. Patients may have a loss of deep tendon, corneal, or protective airway reflexes and have an extensor response to plantar reflex testing.[58] Pupillary size varies, but miosis is most common.[59] Isopropanol is a gastrointestinal irritant; the patient may complain of abdominal pain, nausea, and vomiting. Gastritis can occur with dermal and oral exposure.[60] Hematemesis and upper gastrointestinal bleeding stem from gastritis, but are not commonly reported.

Hypotension, although rare, signifies severe poisoning, with a mortality rate of 45%. One case series found mortality only when coma and hypotension were present.[59] Sinus tachycardia is common, but other atrial and ventricular dysrhythmias are rare and generally found only with confounding hypoxia, acidosis, or shock. Hypothermia is frequent.[59] Rarely, myoglobinuria, acute tubular necrosis, hepatic dysfunction, and hemolytic anemia have been reported. Metabolic acidosis is not present with isopropanol intoxication unless accompanied by hypotension, gastrointestinal bleeding, or co-ingestants; this is a distinguishing clinical feature. Hyperglycemia may be noted, but hypoglycemia has not previously been described, even though it should be sought in patients who have altered mental status.

Diagnostic Strategies

Useful laboratory tests for evaluating a patient with isopropanol ingestion include an isopropanol level, serum electrolytes, BUN, creatinine, osmolality, serum and urine ketones, and arterial blood gas analysis. Peak isopropanol levels occur soon after ingestion, whereas acetone levels peak later at 4 hours after ingestion.[59] The most common laboratory abnormality is ketosis with little or no acidosis and normal blood glucose levels. The ketosis is from the metabolite acetone, which can be detected in the blood 15 minutes after ingestion and in the urine 3 hours after ingestion.[59] Acetone is uncharged, so it does not elevate the anion gap. Isopropanol and acetone contribute to the increased osmol gap. In theory, a 1-mg/dL increase in blood isopropyl alcohol concentration should result in a 0.17-mOsm/kg increase in serum osmolality.

One early laboratory clue to the diagnosis of isopropanol ingestion is "pseudo-renal failure," or isolated false elevation of creatinine with a normal BUN. This condition results from interference of acetone and acetoacetate by the colorimetric method of creatinine determination. Creatinine is expected to increase 1 mg/dL for every 100 mg/dL of acetone. A CK level should be checked because patients with isopropanol toxicity may have coma-induced myoglobinuria and rhabdomyolysis.

Differential Considerations

Patients who ingest significant amounts of isopropanol appear intoxicated or have depressed consciousness, and the differential diagnosis includes all of the causes of altered mental status in an alcoholic patient, as discussed previously. The presence of ketosis warrants a search for diabetic ketoacidosis, alcoholic ketoacidosis, salicylism, cyanide, or starvation ketosis. A distinguishing feature of isopropanol ingestion is the presence of ketosis without acidosis. An increased osmolal gap with acidosis mandates a search for other toxic alcohols. In the setting of a high or rising creatinine and normal BUN, acute rhabdomyolysis also should be considered. Other substances that falsely elevate creatinine are cimetidine, nitroethane, and nitromethane, often mixed with methanol in formulating radio-controlled vehicle fuel.[61] Detection of isopropanol in acetonemic patients not exposed to isopropanol (i.e., the conversion of acetone to isopropanol in vivo) is well described.

Management and Disposition

Neither gastric emptying nor activated charcoal administration is warranted. The patient should be intubated if unable to protect the airway, if intubation is indicated on the basis of co-ingestants, or if the patient's mental status is poor and

deteriorating. In contrast to methanol and ethylene glycol, ADH blockade with ethanol or fomepizole is not indicated. Hypotension should be managed with fluids and vasopressors as needed. If the patient remains hypotensive or has further vital sign deterioration despite these measures, dialysis is indicated. Some authors also recommend dialysis for isopropanol serum levels greater than 400 mg/dL.[53] Coma itself is not an indication for dialysis but may necessitate mechanical ventilation. Peritoneal dialysis and hemodialysis have been successful, but hemodialysis is much more effective and is preferred. Because of isopropanol's rapid absorption, patients who are hemodynamically stable without coma during the first 6 hours are at low risk for developing significant sequelae and generally do not require extracorporeal removal of isopropanol. The development of altered mental status within 2 hours is a clinical predictor of toxic blood isopropanol levels in children.[62] Care is otherwise supportive and includes rewarming, administration of thiamine, evaluation for hypoglycemia, and monitoring for gastrointestinal bleeding.

ACKNOWLEDGMENT

The author would like to thank Deborah Mouzon for her assistance with the preparation of this chapter.

KEY CONCEPTS

- Small doses (single swallows) of methanol and ethylene glycol may cause toxicity.
- A latent period before the development of symptoms is characteristic for ethylene glycol and methanol toxicity, especially when ethanol has been co-ingested.
- A double-gap acidosis (anion gap and osmol gap) should suggest methanol or ethylene glycol toxicity.
- Toxic alcohol exposure cannot be ruled out by a "normal" osmol gap.
- Therapy should begin immediately based on clinical suspicion of exposure to ethylene glycol or methanol. Acidosis should be corrected rapidly with bicarbonate, cofactors should be administered, and ADH should be blocked with ethanol or fomepizole.
- Because acidosis in the setting of exposure to either substance indicates toxic metabolite accumulation, immediate consultation for hemodialysis should be made, even before laboratory confirmation of toxic ethylene glycol or methanol levels.
- The presence of an osmol gap without acidosis is characteristic of isopropanol ingestion. Prolonged coma may be seen, and hypotension portends a poor prognosis.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 154 Hallucinogens

Binh T. Ly, Richard F. Clark, and Saralyn R. Williams

The term *hallucinogen* implies a single class of drugs, but these compounds have different chemical structures, mechanisms of action, and side effects. Most drugs usually do not produce actual hallucinations. Hallucinations are definitely not produced with marijuana, are possibly produced with phencyclidine (PCP), are occasionally produced with sympathomimetic amines, and are produced only with high doses of serotonergic agents. Almost any sympathomimetic compound can cause psychosis, paranoia, and other effects that some would classify as hallucinations but typically are misperceptions of real objects and more accurately termed *illusions*. This chapter describes serotonergic agents, sympathomimetic amines (entactogens), dissociative agents, and selected plants and fungi.

SEROTONIN-LIKE AGENTS

Perspective: Background and Epidemiology

Serotonin-like agents are a broad category of compounds that share chemical similarities to serotonin (5-hydroxytryptamine [5-HT]) or enhance serotonergic tone within the body. These agents include various lysergic acid derivatives and tryptamines. Serotonin-like agents produce changes in thought, mood, perception, and consciousness. Orientation to person, place, and time is preserved, but severe intoxication may cause confusion. Patients present to the emergency department because of acute panic reactions, massive ingestions, or accidental ingestions (e.g., children or adults who have ingested the drugs unknowingly). There is no addictive component in psychedelics and no euphoria-dysphoria cycle, as with cocaine, that would prompt a user to consume more. The rapid development of tolerance also limits the effect of repeated doses.[1]

LSD

Lysergic acid diethylamide (LSD), or "acid," is the most potent psychoactive drug. Doses of 1 to 1.5 μg/kg produce psychedelic effects. The typical dose taken for an acid "trip" is approximately 25 to 100 μg. LSD is sold in tablets (microdots), liquid, powder, and gelatin squares (window pane), but the most common form of LSD is "blotter" acid. Sheets of blotting paper are sprayed with LSD, dried, and perforated into small squares. Graphics are stamped onto the blotting paper in designs that include cartoon characters (e.g., Felix the Cat) or geometric designs (Fig. 154-1). Each sheet is composed of hundreds of squares that are placed sublingually or eaten whole. Massive ingestions are rare.

In addition to synthetic LSD, several plants contain alkaloids similar in structure and action to LSD. These plants include Hawaiian baby woodrose (*Argyreia nervosa*), Hawaiian woodrose (*Merremia tuberosa*), morning glory (*Ipomoea violacea*), and ololuique (*Rivea corymbosa*). Intoxication may result after ingestion of the seeds or an extract.[2]

Tryptamines

Substances in the tryptamines category are naturally occurring and synthesized. For centuries, Central and South American Natives have used tryptamine-containing beverages, *ayahuasca*, in their religious ceremonies. Recently, this plant-derived drink, which contains dimethyltryptamine (DMT) and 5-methoxy-dimethyltryptamine (5-MeO-DMT), has gained popularity in Europe and North America. Designer tryptamines can be synthesized and possess the psychotropic effects of their naturally found compounds.

Psilocybin and psilocin are naturally occurring tryptamines found in some species of *Psilocybe* (Fig. 154-2), *Panaeolus*, and *Conocybe* mushrooms.[3] Psilocybin is resistant to oxidation and remains active even when the mushrooms are dried or cooked. Street psilocybin sold as pills or capsules is usually substituted PCP or LSD. Misidentification and ingestion of other poisonous species is a danger of consuming mushrooms.

Naturally occurring tryptamines are found not only in plants and fungi but also in the parotid glands of the *Bufo* toad species. The venom of the Sonoran Desert or Colorado River toad (*Bufo alvarius*) contains the hallucinogenic substance 5-MeO-DMT, found in the drink ayahuasca. Smoking the dried venom results in psychoactive effects similar to those of 5-MeO-DMT.[4]

In addition to the tryptamines that occur in nature, designer tryptamines have been synthesized and are orally active.[5] Included in this group are α-methyltryptamine, diisopropyltryptamine, and diisopropyl-5-methoxytryptamine, which is also known on the streets as "foxy" or "foxy methoxy."[6] The effects of these synthetic derivatives are similar to those of naturally occurring tryptamines.

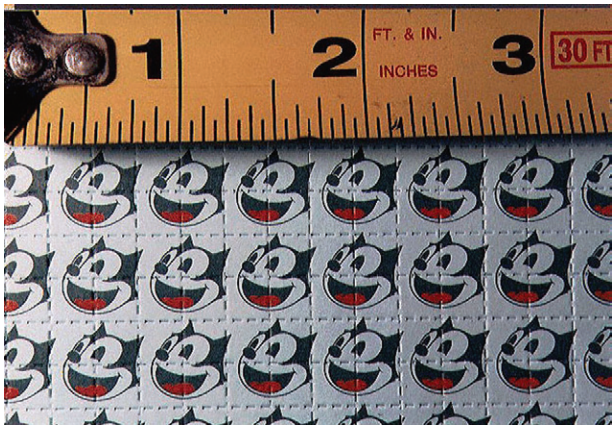


Figure 154-1. LSD blotters. (Copyright © 2001 Blotterart.com. Accessed at http://www.erowid.org.)

Figure 154-2. *Psilocybe cubensis* mushroom. (Copyright © 2003 Erowid.org. Accessed at http://www.erowid.org.)

Principles of Disease: Pharmacology and Pathophysiology

Understanding of these drugs is incomplete, but evidence indicates that these drugs act on serotonergic neurons, particularly the 5-HT_{2A} subtype class of serotonin receptors.[1,7] One theory postulates that midbrain raphe cells send signals to higher centers via serotonin and that psychedelics change these transmissions, causing increased activity in the cerebral cortex and the limbic forebrain.[8-10]

The onset of action of the psychoactive effects of LSD is usually within 30 minutes, with peak effects in 3 or 4 hours. The duration of effects may be approximately 12 hours. During the last half of the 12-hour effect, irritability, increased muscle tension (especially in the face), and paranoia can be present.[11] Psilocybin effects begin within 30 minutes of ingestion, with the psychedelic phase lasting 30 minutes to 2 hours. The effects then wane, with resolution by 4 to 6 hours.

Clinical Features

In Western society, psychoactive agents are taken for internal mental exploration or more commonly for "recreation" at music concerts, at the beach, or in the woods. Changes include loss of boundaries between the user and the environment; the sensation that colors and sounds are distorted and intensified; and the perception that usual objects appear novel, fascinating, or awe-inspiring. This state differs from the confusional and dissociative state produced by PCP. Users are usually aware that they are under the influence of the drug. A sense of euphoria is typical, but it may alternate with intense dysphoric experiences that are accompanied by suffering (e.g., that of dying or being born).

Acute panic reaction is the most common adverse reaction to psychedelics. Paranoid delusions and fear of impending death may be present. Behavior is either agitated or, occasionally, withdrawn. Sympathomimetic effects include dilated, reactive pupils and moderate increases in blood pressure, heart rate, and, rarely, temperature. Mydriasis seems to parallel the intensity of the trip. In contrast to PCP, nystagmus, ataxia, muscle rigidity, and increased secretions are not present.

The individual's altered perceptions may result in lack of awareness of dangers in the environment, resulting in injury. Psychosis after LSD trips is reported, and schizophrenia (overt and borderline) may worsen. Transient depression sometimes occurs after LSD use. Flashbacks, or post-hallucinogen perceptual disorder, are transient episodes of altered consciousness that occur months or years after an LSD trip. However, LSD use and these episodes have not been shown convincingly to have a cause-and-effect relationship.

Massive ingestions may result in a person becoming comatose and unresponsive to pain. The person may also be hyperactive with marked auditory and visual hallucinations. Fixed and dilated pupils, diaphoresis, vomiting, bleeding complications, and seizures may result.[12]

Euphoria and a distortion of reality usually occur after ingesting 1 to 5 *Panaeolus cubensis* mushrooms. Transient nausea is uncommon, and in contrast to peyote, vomiting is unusual. Larger doses (5–20 *P. cubensis* mushrooms) produce visual hallucinations. Few adverse reactions occur, and the incidence of "bad trips" or panic reactions is lower than with LSD. There are reports of seizures, coma, and hyperthermia after psilocybin use.

Diagnostic Strategies

Because most patients are either in a panic or brought in by a worried companion, the drug is usually known. Although mass spectrometry can identify psychedelics in serum, urine, or gastric contents, it is not available in the clinical setting, so diagnosis and treatment are based on clinical grounds. Even when tests are available, however, the results are delayed and only useful to confirm or document the event. Interference with routinely available drugs of abuse does not typically occur.

Differential Considerations

Other drugs or mixed ingestion are a possible source of the patient's symptoms, especially with coma or marked physiologic changes. PCP, cocaine, and amphetamines must be considered because their effects may require specific treatment. Schizophrenia may appear similar to psychedelic ingestion, but the time course is much longer.

Management

The basic principle of out-of-hospital care is reassurance and supportive care. If the patient is a danger to him- or herself or others, the patient may need to be restrained temporarily to

permit sedation or be sedated without need for restraint. There is no specific antagonist to the effects of serotonergic agents. An important therapeutic modality is empathic reassurance in a calm, quiet environment. The effects last for hours, but when they wear off, the patient feels normal again.

Benzodiazepines, such as lorazepam (1 or 2 mg intravenously, then titrated to effect), can be given safely to decrease agitation. Phenothiazines should be avoided in case the symptoms are actually caused by an anticholinergic drug and not a psychedelic. Butyrophenones, such as haloperidol or droperidol, may be given by intramuscular or intravenous injection in doses titrated to clinical response if the patient is violent and must be sedated. Monitoring for QT prolongation is recommended, if possible, when a butyrophenone is used.

Disposition

Patients with anxiety or panic reactions can be talked down and sent home with responsible family or friends. Patients who persist with confused or paranoid behavior should be admitted. If the diagnosis is in question, the patient should be observed for several hours for significant changes in the condition. Follow-up evaluation should be recommended with a psychiatrist, primary care physician, or drug counseling facility. Patients with massive ingestions or having incurred injuries or medical complications (rhabdomyolysis) may need admission to a monitored setting for serial reassessments.

■ ENTACTOGENS

Perspective: Background and Epidemiology

Hallucinogenic stimulants, also called entactogens, are structural analogues of amphetamine, mescaline, and *N*-substituted piperazines. These agents share effects in varying degrees of true stimulants and the serotonin-like hallucinogens.

Designer Amphetamines

New designer amphetamines were originally developed chemically to circumvent the law before the advent of the prospective standard for the Controlled Substances Act (CSA) and appear in drug communities each year. These agents include 3,4-methylenedioxymethamphetamine (MDMA, Ecstasy, XTC, or Adam), 3,4-methylenedioxyamphetamine (MDA), 3,4-methylenedioxyethamphetamine (Eve), paramethoxyamphetamine (PMA or death), and 4-methyl-2,5-dimethoxyamphetamine (serenity, tranquility, and peace [STP]).

MDMA is the best known of these agents. It was first synthesized in 1914 as an appetite suppressant. Recreational and psychotherapeutic use began in the late 1970s and has increased in recent years, especially on college campuses, where 39% of students have tried this drug.[13,14] Australian surveys report up to 20% of those age 20 to 29 years have used MDMA.[15] MDMA and MDA have been called "love drugs" because of claims from users that sexual pleasure and feelings are heightened, but the sympathomimetic effects of these drugs may produce erectile dysfunction. MDMA can produce euphoria, increase emotional awareness, and has been reported to improve interpersonal communications. The psychedelic and stimulant effects of MDMA are preferred over MDA by most users. Overt hallucinations of the type experienced with LSD are rare; however, sensory enhancement and distortion and illusions can occur. Because of these effects, Nichols suggested that these drugs represent a new drug class called *entactogens* (i.e., enabling the user to "touch within").[16] This concept is based on clinical effects in humans and on drug discrimination studies in laboratory animals.[17] MDMA was classified as a Schedule I drug by the Drug Enforcement Agency (DEA) in 1985.

Entactogens are predominantly used in three main settings: as "psychotherapeutic adjuncts," recreationally in small groups or by couples, and at dance clubs or "rave" parties. Some psychiatrists or psychotherapists have used entactogens as pharmacologic adjuncts to increase emotional awareness, interpersonal closeness, and introspection during psychotherapy.[18] MDMA is still being studied in low doses as an adjunct to therapy for anxiety.[19] Rave parties are all-night dances held in warehouses or dance halls. Nonstop dancing occurs to loud, repetitive, electronically synthesized "techno" music, and a variety of hallucinogens and amphetamine derivatives are consumed, especially MDMA. "Herbal ecstasy," known as mahuang or *ephedra*, is sometimes substituted for MDMA at these gatherings when MDMA is scarce. Although this herb contains ephedrine, its effects are not as psychedelic as MDMA. Ecstasy tablets may also contain other chemicals, such as amphetamine, methamphetamine, caffeine, and ketamine. MDMA is widely available and is sold in clubs, on the street, and at raves (usually 30–150 mg/pill), with a typical dose of 1 or 2 mg/kg.[20] The continuous muscular activity required during these parties may combine with MDMA and other psychostimulants to produce rhabdomyolysis and hyperthermia. Nine deaths in Canada associated with PMA were originally reported in 1974, but clusters of multiple deaths in association with PMA exposure have occurred in Europe and Australia.[21,22] Because of the popularity of MDMA, PMA is reportedly being sold under the guise of MDMA. Signs and symptoms of adrenergic excess occur before death, but whether PMA is more toxic in equipotent dosages than other amphetamines is not known.

Mescaline

Mescaline is usually consumed in the form of peyote "buttons," which are derived from the small blue-green cacti *Lophophora williamsii* and *Lophophora diffusa* (Fig. 154-3). The cacti grow in the deserts of the southwestern United States and Mexico. Peyote buttons are the round fleshy tops, which are removed and dried. Mescaline is the active hallucinogenic alkaloid found in the buttons of the cactus.

Peyote has been used in religious ceremonies for 8000 years. Mescaline is also contained in the San Pedro cactus (*Trichocer-*

Figure 154-3. *Lophophora williamsii* (peyote cactus). (Photo by Christopher B. Copyright © 2000 Erowid.org. Accessed at http://www.erowid.org.)

eus pachanoi) of South America and is used ritualistically by Andean Native Americans.[1] These cacti contain many other alkaloids, some of which are also psychoactive. The use of peyote is legal for members of the Native American Church in some states. Adverse reactions (e.g., panic) to peyote are rare in this structured religious use.[23] Mescaline has an onset of action of 45 to 60 minutes with a duration of effects of 4 to 8 hours. The central nervous system (CNS) and physiologic effects of mescaline use are similar to those of LSD, but more vivid hallucinations can occur. Nausea and vomiting are pronounced and almost always precede the hallucinogenic effects.

Piperazines

Recently, *N*-substituted piperazine compounds such as 1-benzylpiperazine (BZP or "A2"), 1-(trifluromethylphenyl) piperazine (TFMPP or "Molly"), and 1-(chlorphenyl)piperazine (CPP) have emerged as drugs of abuse and have been sold as safe, legal alternatives to MDMA and are referred to as "Legal E" or "Legal X" on Internet websites.[24,25] Although BZP was originally synthesized as a potential antihelmintic agent, there are currently no therapeutic applications for BZP or its congeners. Both in vitro and animal studies demonstrate that these piperazine compounds stimulated release of serotonin and other monoamines but were less potent in comparison to MDMA.[25] In 2002, both BZP and TFMPP were classified as Schedule I drugs due to their potential for abuse and hazard to the public. There are no deaths directly attributed to these piperazines, but fatalities occur in association with their use.[24]

Nutmeg

Nutmeg is a spice derived from the seed of the nutmeg tree, *Myristica fragrans*. Use of nutmeg as a natural and legal psychotropic agent was popularized in the 1960s. Despite lack of any in vivo human studies, myristicin and elemicin have been suggested as the agents responsible for intoxication because their chemical structures resemble that of mescaline. A proposed biotransformation of myristicin and elemicin would result in substances resembling known psychoactive agents, 3,4,5-trimethoxyamphetamine and 3-methoxy-4,5-methylenedioxyamphetamine.[26] Reports of intoxication are uncommon.[27,28] Ingestion of 5 to 30 g (1–4 tablespoons) of the spice is said to induce euphoria and hallucinations but is more likely to cause gastroenteritis.

Principles of Disease: Pathophysiology

The psychoactive effects of MDMA and other entactogens are thought to result from alterations in catecholamine neurotransmission at postsynaptic and presynaptic sites, particularly affecting 5-HT. These agents cause a release of serotonin, dopamine, and norepinephrine from nerve terminals, as well as inhibit catecholamine reuptake. Release of epinephrine and norepinephrine may produce the cardiovascular effects. MDMA and possibly other entactogens are serotonergic neurotoxins.[29,30] When MDMA is administered to nonhuman primates and laboratory animals, serotonin is released initially from serotonergic neurons followed by degradation of 5-HT projections. Magnetic resonance imaging shows significant neurodegeneration.[30] These effects may persist for weeks or longer after a single dose.[31] The significance of this neurotoxic effect for humans at the dosages taken is unknown.[32]

Psychostimulant-associated hyperthermia is well described in humans. Animal models exposed to entactogens develop hyperthermia in the absence of physical exertion but are less capable of regulating core body temperature in response to environmental hyperthermia.[33] In addition, increasing body temperature in the presence of MDMA or other entactogens seems to enhance serotonergic neurotoxicity.[34]

Hyponatremia resulting in seizures, stupor, and death is another complication of MDMA use not described as commonly with other amphetamines. Two hypotheses suggested for the hyponatremia are (1) excessive intake of free water because users of MDMA are advised to keep well hydrated by drinking lots of water[35] and (2) MDMA-mediated release of antidiuretic hormone.[36,37]

Clinical Features

MDMA effects last 3 to 5 hours. Blood pressure increases during the first hour and gradually returns to baseline within 6 hours. CNS effects of MDMA may persist for 6 to 12 hours. Larger dosages or greater frequency dosing of MDMA may lead to more frequent unpleasant side effects, such as agitation or confusion. Recreational users rarely report dysphoria.

Clinical effects expected from the entactogens would be similar to clinical effects of other amphetamine derivatives (see Chapter 152). Death after ingestion is most often linked to hyperthermia. Deaths at rave parties typically involve seizures and hyperthermia at recreational dosages. Dehydration and high ambient temperatures during rave parties may be contributing factors. The mechanism behind psychostimulant-induced hyperthermia is unclear but likely combines CNS factors and seizure activity with drug effects. Rhabdomyolysis can occur from a combination of direct toxic effects of the agent, extreme physical activity, and hyperthermia. Preexisting cardiac disease may contribute to sudden death, presumably from dysrhythmias.[38] MDMA may precipitate a hypertensive crisis in patients taking monoamine oxidase inhibitors, and it may precipitate serotonin syndrome when combined with other serotonergic agents.[20] MDMA and its analogues also have contributed to fatal overdoses.[39,40]

Diagnostic Strategies

Urine screening with immunoassay techniques can detect entactogens. Small dosages may not be detected, but larger doses test positive for amphetamine-methamphetamine.[41] Designer amphetamines, including MDMA, and their metabolites may be detectable with thin-layer chromatography methods.[42]

Differential Considerations

All sympathomimetic compounds, including cocaine, amphetamine derivatives, PCP, and LSD, can present with violent and psychotic behavior, convulsion, coma, and any combination of sympathomimetic signs and symptoms. Many of these reactions may not be from overdose but, rather, from idiopathic and unpredictable toxic reactions. Initial management is consistent for each of these compounds.

Management

Patients with panic reactions or violent psychotic episodes should be placed in a quiet environment and reassured. Diazepam, 2 to 10 mg, or lorazepam, 1 or 2 mg, can be administered orally to cooperative patients. Repeat doses of diazepam, 5 to 10 mg (intravenously [IV]), or lorazepam, 2 to 4 mg (intramuscularly [IM] or IV), can be used in violent subjects. Butyro-

phenones, such as haloperidol and droperidol, may also be used. Hypertension and tachycardia should be treated with liberal sedation. If necessary, alpha-adrenergic antagonists in combination with vasodilators may be used. Dysrhythmias should be treated in the usual manner.

Because hyperthermia is a common complication, a core temperature should be obtained. If the patient's temperature is greater than 40° C to 42° C, multiple organ damage often results in fatalities. Active cooling measures should be immediate and aggressive because the outcome strongly correlates with the presenting temperature and length of time the patient has been hyperthermic. Rapid sequence intubation, paralysis with a nondepolarizing neuromuscular blocker, intravenous fluid resuscitation, and water misting and fans should be used. Rhabdomyolysis, myoglobinuric renal failure, hepatic damage, and disseminated intravascular coagulopathy may accompany hyperthermia.[43,44] Treatment of hyponatremia should proceed in the usual manner. Aggressive pharmacologic management of nausea and vomiting may be necessary with peyote and nutmeg ingestions.

Disposition

Most patients with a toxic reaction or overdose to an entactogen who are not hyperthermic or do not have abnormal cardiac rhythms resolve their symptoms in several hours. Psychiatric assessment may be necessary if psychotic or abnormal thoughts or actions persist longer than this time period. Although urine screening will not guide treatment decisions, it may aid the psychiatrist in counseling.

Patients with ongoing or severe toxicity to these agents require admission to the hospital. Seizures, cardiac dysrhythmias, myoglobinuric renal failure, hepatic damage, and heat-related problems should be monitored in an intensive care unit or step-down unit. Direct sympathomimetic toxicity resolves over 24 hours, but sequelae may require prolonged hospitalization.

DISSOCIATIVE AGENTS

Perspective: Background and Epidemiology

PCP and ketamine are the two main agents included in the class of dissociative agents. They are similar in chemical structure and pharmacologic effect. PCP and ketamine are general anesthetics causing dissociation of the patient from the environment. They have analgesic and amnestic activity but do not cause respiratory or cardiovascular depression.

Phencyclidine

PCP was initially marketed for use as a general anesthetic; however, severe emergent reactions rapidly led to its recall. In the 1960s, PCP was sold as the "PeaCe Pill," which was consumed orally, but the effects were often unpredictable and unpleasant. In the mid-1970s, PCP was the most common cause of recreational drug-related emergencies. Its popularity decreased because of unpredictable effects, a long clinical course, dysphoria, and association with violence. In 1978, PCP was classified as a Schedule I drug.

Ketamine

The similarities between PCP and ketamine virtually guaranteed the eventual abuse of ketamine. Spurred by the rave party fad and the Internet (going by the names of "vitamin K" or "special K"), ketamine is one of the most rapidly increasing drugs of abuse in some areas of the United States, especially near the Mexican border. Preparations available on the street are often adulterated with various stimulants. The most common use of street ketamine is insufflation, but subcutaneous and intramuscular injection and even rectal infusion are done to achieve a level of intoxication or "high" known as the "K hole."

Dextromethorphan

Dextromethorphan is not truly a dissociative agent but does share a similarity in structure to PCP and other opioid compounds and its binding to the PCP site of the *N*-methyl-D-aspartate (NMDA) receptor. The abuse potential became reality in the 1990s with high school–age individuals (13–17 years) abusing dextromethorphan.[45,46] The Internet has also played a major role in popularizing the misuse of this agent. Referred to as "DXM," "Robo," and "skittles," dextromethorphan predominates on many Internet websites devoted to rave parties, drug use, and experimentation.

Principles of Disease: Pharmacology and Pathophysiology

Despite being simple molecules, the pharmacology of PCP and ketamine is complex, with agonist and antagonist actions at numerous sites, including the NMDA receptor, dopamine/norepinephrine/serotonin reuptake pump, sigma-opioid receptor, and cholinergic receptors.[47] PCP is well absorbed from any oral, nasal, or rectal mucous membrane and can be insufflated or smoked. It can be injected intramuscularly, subcutaneously, or intravenously. Ingested PCP is well absorbed in the small bowel, with onset between 15 and 60 minutes. When smoked, PCP produces symptoms within 5 minutes, with peak activity in 15 minutes.[48] Intoxication with PCP usually ranges from 8 to 16 hours, but it can be longer in chronic users. Although enterohepatic recirculation has been proposed, more likely causes are either gastrointestinal concretion or delayed release from lipid stores.[49]

Ketamine is only approximately one tenth as potent as PCP.[47] With ketamine, the intensity of intoxication is less pronounced, although in higher dosages the effects may parallel those of PCP. Duration of action of ketamine is typically shorter, with symptoms lasting approximately 1 hour after insufflation but may be prolonged 4 to 8 hours after an oral dose. PCP and ketamine are highly lipid-soluble agents that undergo extensive metabolism in the liver and are excreted eventually in the urine.

Dextromethorphan is the dextrorotatory isomer of the synthetic opioid levorphanol. Although typically classified as an opioid, its pharmacology is complex. It inhibits the uptake of serotonin and blocks the NMDA receptor at the PCP binding site.[50] At high dosages, dextromethorphan is an agonist at the sigma opiate receptor and naloxone has been reported to reverse intoxication.[51] Drug interactions with selective serotonin reuptake inhibitors and monoamine oxidase inhibitors are also reported.[52]

Clinical Features

Patients with PCP intoxication have a wide spectrum of findings, with autonomic signs and symptoms often similar to other sympathomimetic agents. Behavior may be bizarre, lethargic, agitated, confused, or violent. A blank or catatonic stare is common. Vertical, horizontal, and rotatory nystagmus is often present. Moderate hypertension and tachycardia may be present. Pupils usually are midsized and reactive, although

there may be miosis or mydriasis. Bizarre posturing, grimacing, and writhing may be seen.[53]

Other variable findings include ataxia, muscle rigidity, increased deep tendon reflexes, increased secretions, bronchospasm, hyperthermia, and seizures. The percentage of violent patients ranges from 10 to 40% for PCP, and controlling these patients may be the most challenging problem in the emergency department. "Superhuman" strength is possible because of the dissociative action of PCP. Patients have broken police handcuffs, fracturing bones in doing so, and have performed other destructive actions not normally possible. Although mild hypertension in PCP intoxication is common, hypertension requiring antihypertensive treatment is rare. Severe hypertension with PCP overdose has caused intracerebral hemorrhage but not as commonly as with cocaine or amphetamine.[54]

Hyperthermia can range from mild to life-threatening. Core temperatures of PCP victims can exceed 40° C and often go undetected for prolonged periods in the emergency department. Severe hyperthermia with temperatures greater than 42° C resembles heatstroke and is often associated with multiple organ damage.[55] Particularly susceptible organs are the kidneys, liver, heart, and brain. High-output congestive heart failure has been reported. The presumed mechanism is muscle damage from seizures, extreme muscular activity such as struggling against restraints, or prolonged immobility. Rhabdomyolysis and acute myoglobinuric renal failure are the most common serious medical complications. Renal function returns after several weeks in most cases. Among the most lethal complications of PCP are respiratory depression, apnea, and cardiac arrest.[53]

Although dextromethorphan has activity at opioid receptors, the typical triad of opioid intoxication (miosis, respiratory depression, and mental status depression) generally is not encountered.[56] Similar to meperidine, dextromethorphan intoxication may result in mydriasis through paralysis of the ciliary body.[57] More typical clinical findings are lethargy, agitation, slurred speech, ataxia, diaphoresis, hypertension, and nystagmus.[58] With higher doses, nausea and vomiting are common, and intoxication resembles that of LSD with euphoria and hallucinations. Dystonic reaction has been reported in a child after therapeutic administration.[50]

Diagnostic Strategies

Most hospital laboratories use radioimmunoassays that can detect urinary PCP with a detection limit of 5 ng/mL. Urine may be positive for 2 to 4 days after PCP use, but it can be positive for more than 1 week after chronic exposure. Serum screening for PCP is of little clinical benefit because levels correlate poorly with symptoms. Several substances may cross-react with urine screens for PCP, including dextromethorphan, due to their structural similarities. Chlorpromazine, methadone, ketamine, and diphenhydramine may also cross-react with some assays.[59] Because dextromethorphan is typically formulated as a hydrobromide salt, chronic use may result in spurious hyperchloremia with a low or negative anion gap due to interference of chloride analysis by the bromide ion in the autoanalyzer.[60]

Differential Considerations

PCP, ketamine, and dextromethorphan intoxications can mimic such diverse entities as head trauma, meningitis, catatonia, or heatstroke. Sympathetically mediated vital sign changes can be found in numerous other agents, including cocaine, amphetamine, and LSD. Antimuscarinic compounds, such as diphenhydramine, benztropine, and tricyclic antidepressants, can also simulate the tachycardia and altered mental status found with PCP or ketamine. Salicylate poisoning, thyrotoxicosis, and sepsis should be considered. Meningitis, intracerebral hemorrhage, and viral encephalitis can present with altered mental status of unclear etiology. Even with a PCP positive urine screen, the diagnosis is not certain unless a definite history of recent PCP, ketamine, or dextromethorphan use is obtained and other conditions have been eliminated.

Management

Out-of-Hospital

Life-threatening complications, such as apnea or seizures, should be stabilized before transport. The threat of violence to nonhospital care providers from patients with PCP poisoning makes it dangerous for only two or three nonhospital care providers to restrain these patients until additional help arrives. Oxygen and glucose testing should be deferred until the patient is controlled. Violent patients under the influence of PCP may have traumatic injuries.

Emergency Department

Patients with PCP toxicity can have unpredictable, violent behavior or sudden complications, such as cardiac arrest or seizures. Violent behavior, although possible, is less common with ketamine. Most patients with minor intoxication are alert, oriented, and neurologically normal after 4 to 6 hours.[54] All patients with signs of trauma or struggle should be evaluated for injuries. Reliable assessments of these individuals are difficult, and sedation and restraint are often necessary before diagnostic tests or examinations can be performed.

Chemical sedation or restraint is preferred to physical restraint in cases of PCP or ketamine intoxication, although temporary physical restraint may be necessary to ensure patient safety, establish intravenous access, and administer IV benzodiazepines. Assessment of mental status may not be as reliable after chemical sedation, but the benefits of protecting the staff and patient far outweigh the disadvantages. Haloperidol, 5 to 20 mg IM or IV, or droperidol, 2.5 to 10 mg IM or IV (noting the Food and Drug Administration black box warning), is usually an effective means of chemical restraint in these patients. These agents may antagonize CNS receptor sites that are responsible for much of the violent behavior in these individuals. Benzodiazepines such as lorazepam, 2 to 4 mg IV or IM, or diazepam, 5 to 10 mg IV, may be used in aggressive dosages to calm patients with all types of sympathomimetic poisonings. A well-coordinated team may be needed to apply hard restraints simultaneously to all four extremities and the body.

Comatose patients or patients with a questionable airway should be intubated to ensure adequate ventilation. Although PCP intoxication can cause mild hypotension, profound hypotension is probably the result of trauma or a mixed-drug ingestion, and the patient should be resuscitated with fluids. Seizures should be treated with IV benzodiazepines. Phenobarbital, 20 mg/kg IV, may be used for refractory seizures. Tachycardia does not require additional treatment except for sedation.

Hyperthermia (temperature >40° C) is common in severe cases of PCP poisoning. All patients with significant symptoms, psychosis, or history of violent behavior should have rectal temperatures measured. Individuals with elevated temperatures should be treated aggressively with active cooling measures.

Renal status and creatine kinase (CK) should be monitored to detect rhabdomyolysis and myoglobinuric renal failure. Urinary acidification had been used in the past to trap PCP in urine and aid elimination, but its use has been abandoned because of the insignificant renal clearance of the drug (10%) and the potential adverse impact of acid urine on myoglobin in renal tubules that is often present after PCP intoxication. Activated charcoal is of no value in acute intoxication, but a standard oral dose of 50 g may be considered when body packing is suspected. If patients have never been hyperthermic and have no signs of trauma, laboratory or other diagnostic tests are not needed.

Dextromethorphan poisoning can be managed with supportive care and measures to prevent injury to the patient. Sedation with a benzodiazepine may be used for agitation. The patient should improve over 4 to 6 hours. Many dextromethorphan cough and cold preparations also contain acetaminophen, so acetaminophen levels should be measured.

Disposition

For nonviolent patients with PCP intoxication, a quiet holding room is ideal for 4 to 6 hours of observation. Patients with violent behavior or obtundation often require admission to the hospital, where close observation and treatment of potential life-threatening complications can be accomplished. Serial chemistry evaluations, including serum creatinine and CK, should be monitored. Most of these patients can be medically cleared the next day.

MARIJUANA AND MISCELLANEOUS PLANTS AND FUNGI

Marijuana

Perspective: Background and Epidemiology

Marijuana is the most common illegal drug in the United States. It has been used medicinally since ancient times for conditions such as colic and asthma but has been illegal since 1937. The use of marijuana peaked in the late 1970s, with 20 million smokers, but declined during the 1980s. Today, there are more than 12 million users in the United States and more than 300 million regular users estimated worldwide.

Cannabis sativa and *Cannabis indica* plants are some of the earliest plants grown by humans. Bioactive substances derived from these plants are collectively called *cannabinoids*. The seedless flowering tops of the female plant are referred to as *sinsemilla* and are the commonly grown form of marijuana in the United States. The resin from the flowers is made into hashish. Marijuana is smoked or eaten blended into foods, such as brownies.

Principles of Disease: Pharmacology and Pathophysiology

Δ-9-Tetrahydrocannabinol (THC) is the main active agent of the more than 61 cannabinol compounds and approximately 300 other substances present in the cannabis plant.[61] Marijuana smoke also contains carbon monoxide, cyanide, acetone, and phenol, but not nicotine.[61,62] The most efficient route of THC delivery is by inhalation. Fifty percent of smoked THC is absorbed compared with 6% by ingestion.[63] Experienced users may be able to absorb higher doses with breath-holding techniques. Peak blood levels occur within 8 minutes of inhalation, with rapid distribution into tissues, especially tissues with high lipid content.[64] The duration of perceived effects is usually 2 to 4 hours when smoked and 6 to 12 hours when ingested.

Clinical Features: Acute Signs and Symptoms

Smoking leads to rapid and more predictable signs and symptoms. Ingestion can cause delayed and sometimes unpredictable effects. The most common effects from smoking marijuana include alteration of mood and usually relaxation and euphoria. The only reliable physiologic effects are a mild increase in heart rate and conjunctival injection.[65] Pupillary changes usually do not occur. Other acute peripheral changes include urinary retention, decreased testosterone levels, and decreased intraocular pressure.[66] Short-term memory is impaired, and the ability to perform complex tasks may be adversely affected.[67] Many users report excessive appetite after marijuana use.

The most common adverse reaction is panic, paranoia, or acute psychosis, particularly with novice users or individuals with preexisting psychiatric disease. These episodes are usually transient and reality testing remains intact. Even when "high-potency" marijuana is smoked continuously for hours, adverse effects are rarely seen. Users become more sedated as they continue to smoke but do not become unarousable. No deaths have been solely attributed to marijuana. Pediatric exposures to marijuana may lead to hypothermia, ataxia, nystagmus, tremor, tachycardia, injected conjunctiva, and labile affect.[68,69] Oral ingestion of potent marijuana in children can produce rapid onset of drowsiness, hypotonia, and lethargy, which can lead to coma and airway obstruction.[68,70]

Diagnostic Strategies

Marijuana screening is not helpful in the emergency department. Urinary metabolites of THC are detectable within 1 hour after smoking marijuana, but a positive urine test does not correlate with acute intoxication. A single marijuana cigarette can be detected for 72 hours when a 100 ng/mL cutoff level is used, and positive urine levels may persist for 3 months after chronic marijuana use.[71] Inadvertent or passive exposure to marijuana can produce positive urine testing.[72] False-positive urine screen results may be produced by efavirenz, ibuprofen, and naproxen.[73,74]

Differential Considerations

The presentation that most closely resembles marijuana intoxication is acute psychosis. Some individuals with underlying and preexisting psychiatric disorders may progress to overt psychosis after heavy or first-time marijuana use. Because marijuana is so readily available, it is commonly a cointoxicant used with ethanol and other psychotropic agents. Rarely, marijuana can be adulterated with other substances such as lead.[75]

Management and Disposition

Care of patients intoxicated from marijuana consists of prevention of injury and reassurance of those who have panic reactions. An extremely agitated patient can be sedated with oral or parenteral benzodiazepines. Children who are significantly symptomatic may require admission.

Salvia

Salvia divinorum is a perennial herb cultivated well outdoors in mild climates and is a member of the mint (*Lamiaceae*) family.[76] Common names for *S. divinorum* include "diviner's

sage," "mystic sage," "magic mint," "sage of the seers," "Sally-D," and "ska Maria Pastora." Although the plant has been used for divination and shamanism by the Mazatec Indians of Oaxaca, Mexico, *S. divinorum* has become popular in the past decade for recreational purposes because of its recognized hallucinogenic properties and continues to be sold legally by online vendors and "smoke" or "head" shops. In 2004, the DEA listed *S. divinorum* as a "drug of concern," but to date, it remains unscheduled under the CSA. Several states, however, have instituted or are considering legislation making possession, cultivation, and use of *S. divinorum* or its extracts illegal. Internationally, regulatory controls have been implemented in Australia and a number of European countries.[77]

The active ingredient in *S. divinorum* is salvinorin A (a.k.a. dvinorin A), a neoclerodane diterpene with selective agonist activity for kappa-opioid receptors (KORs), but it does not bind to delta- or mu-opioid receptors. Salvinorin A is the first naturally occurring non-nitrogenous KOR agonist with psychotropic properties and is the most potent plant hallucinogen discovered to date. The threshold dose of salvinorin A producing hallucinations is comparable to synthetic LSD and 4-bromo-2,5-dimethoxyphenylisopropylamine. Stimulation of KOR in the brain and spinal cord produces psychomimetic and analgesic effects, respectively. However, salvinorin A is distinct from more traditional hallucinogens because it does not bind to the 5-HT_{2A} serotonin receptors as is the case with LSD.[78]

Salvia is usually chewed and either spit out or swallowed, and it seems to be absorbed better from the oral mucosa than from the rest of the gastrointestinal tract. Effects produced as a result of oral mucosal absorption may persist for 1 hour. Dried leaves also can be smoked. Inhalation of smoke can produce symptoms within 1 minute that subside over 20 to 30 minutes. Sensations experienced are variable but include distortions of color and vision as well as auditory, visual, gustatory, and olfactory synesthesias that are confusions of the senses, such as seeing sounds, hearing touches, or smelling visions. *Salvia divinorum* is often used in conjunction with other agents, such as marijuana and MDMA.

Salvinorin A is not detected and is not known to cause interference with routine drug screens used in the clinical setting. Management of intoxication from *S. divinorum* is mainly supportive with emphasis on injury prevention. Use of naloxone, a non-specific opioid receptor antagonist, may theoretically be helpful in reversal of psychotropic manifestations.[79]

Kratom

Mitragyna speciosa Korth, or Kratom, is a tree indigenous to Thailand but is also found in tropical and subtropical regions of Asia and Africa. Its extracts have been used in Thailand and Malaysia for their euphoric effect as a substitute for opium or to moderate opium use by addicts.[80] The popularity of Kratom has grown due to reports of its successful use to attenuate symptoms of opioid withdrawal. Because Kratom remains easily obtainable from Internet sources, individuals are able to self-administer the perceived remedy, obviating the need for physician supervision.[81] The safety of such practice is unknown.

Although Kratom extract contains more than 25 alkaloids, mitragynine is the most abundantly found in the plant. Mitragynine is an indole alkaloid with structural analogy to yohimbine and has agonist activity at mu- and delta-opioid receptors producing euphoric, analgesic, and respiratory depressant effects. Despite its structural similarity to yohimbine, a selective antagonist of presynaptic alpha$_2$-adrenergic receptors, animal studies suggest that mitragynine is also an agonist at postsynaptic alpha$_2$-adrenergic receptors and blocks 5-HT_{2A} receptors.[79]

Typically, Kratom leaves are chewed, smoked, or brewed into a tea. Psychotomimetic effects occur within 5 to 10 minutes of use and may persist for 1 hour, with stimulatory effects at lower doses and opioid effects at higher doses. Opioid properties include analgesic, antitussive, antidiarrheal, and emetogenic effects.

Currently, there are no diagnostic tests available to detect the presence of Kratom alkaloids. Treatment of intoxication is mainly supportive. Although opioid activity has been demonstrated with Kratom, the effectiveness of opioid antagonists in reversing effects is inconsistent.

Iboga

Ibogaine is a naturally occurring indole alkaloid found in the roots of the African rain forest shrub *Tabernanthe iboga*. For many centuries, iboga has been ingested by indigenous peoples of western Africa as remedy for fatigue, hunger, and thirst and as a psychopharmacologic sacrament in religious ceremonies, and it is believed to enable contact with deceased ancestors. As with many plant-derived agents, ibogaine's physiologic effects are highly complex and may involve (1) opioid, (2) dopaminergic, (3) serotonergic, (4) glutaminergic, (5) GABAergic, (6) glutamatergic, (7) adrenergic, and (8) cellular ion channel signaling systems.

Although iboga in Western culture is used to ease opioid withdrawal and diminish craving of other abused drugs, the potential for abuse is high because hallucinogenic effect is extremely vivid. In contrast to other hallucinogens, the intensity of visual hallucinations from ingesting iboga is described to be pronounced with closed eyes.[82] There are no clinical tests, and diagnosis is dependent on a history of exposure because clinical findings are largely nonspecific and management is principally supportive. Since the first report in 1990, there have been 11 reported fatalities associated with ibogaine use within the 72 hours preceding death with a hypothesized cardiac etiology.[82]

Absinthe

Absinthe is a bitter, emerald green liqueur derived from an extract of the wormwood tree, *Artemisia absinthium*. The liqueur was popular in the 19th century, particularly among artists, poets, and playwrights, but has been illegal in most countries since the early 20th century. The legal sale of absinthe has resumed in several European countries and Japan, and with the Internet, there has been a resurgence in its use and popularity.

In addition to ethanol, the active ingredient of absinthe is thought to be α-thujone, an aromatic terpenoid related to camphor and turpentine. Although the mechanism is not clear, thujone is thought to antagonize the inhibitory γ-aminobutyric acid ($GABA_A$) receptor, which may explain the clinical effects observed with absinthe.[83] The acute clinical effects of absinthe are reported to be beyond ethanol alone and include confusion, delirium, euphoria, and hallucinations (auditory and visual). However, some doubt the plausibility of consuming a dose of thujone adequate to achieve the aforementioned neurotoxic effects given the low concentrations of the toxin present in spirits.[84] Nonetheless, thujone is a known proconvulsant in animals and may cause generalized clonic followed by tonic seizure activity.[85] Ingestion of an essential oil of wormwood has been reported to cause seizures complicated with

Figure 154-4. *Amanita muscaria* mushroom. (Photo by Mark Shubert. Copyright © 2004 Erowid.org. Accessed at http://www.erowid.org.)

renal failure secondary to rhabdomyolysis.[86] Treatment is supportive.

Isoxazole Mushrooms

Isoxazole-containing mushrooms include *Amanita muscaria*, *Amanita pantherina*, *Amanita gemmata*, and *Amanita cothurnata*. *Amanita muscaria* has a red or yellow cap with white warty structures on its surface and grows in forests of aspen, birch, fir, or pine trees (Fig. 154-4). It has been used by Siberians for centuries and is often described in folklore and fairy tales. Pharmacolinguistic evidence indicates that several modern religions began as *A. muscaria* cults.

The active ingredients are the isoxazole derivatives ibotenic acid and its decarboxylation product, muscimol, which are structural analogues of endogenous neurotransmitters glutamic acid (excitatory) and GABA (inhibitory) and thought to act at these respective receptor sites.[87] The excitatory effects characterized by elation, giddiness, hyperactivity, muscle tremors, and distortion of space-time begin approximately 20 to 60 minutes after ingestion and are likely mediated by ibotenic acid. Following is a phase of tiredness and deep "sleep" in which it may be difficult to arouse the patient. During this phase, vivid hallucinations and manic excitement may alternate with periods of deep sleep. The duration of effect is 6 to 12 hours. Management of the excitatory phase is similar to that of other hallucinogens previously described in this chapter. Prolonged sleep with *A. muscaria* ingestion requires only observation or supportive care. Tonic-clonic seizures are reported, but deaths are rare.

Because elements of isoxazole poisoning resemble manifestations seen with anticholinergic toxicity, these mushrooms have also been referred to as "anticholinergic" mushrooms; however, belladonna alkaloids are not present. Paradoxically, there has been a high incidence of mistreatment of *A. muscaria* ingestion with atropine because the name implies that it contains muscarine, a cholinergic toxin. However, the amount of muscarine is very small (<0.0002% in fresh specimens). Many textbooks recommend the use of atropine, but atropine may exacerbate the anticholinergic effects associated with isoxazole mushrooms. It is important to differentiate isoxazole-containing *Amanita* mushrooms from the deadly hepatoxic cyclopeptide-containing *Amanita* mushrooms, of which *A. phalloides* is a member.

KEY CONCEPTS

- Hallucinogens include many types of drugs with different associated effects.
- Diagnosis and management are based primarily on the history and physical examination.
- Reassurance and supportive care suffice for most patients.
- Aggressive sedation is necessary in agitated and violent patients.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 155 Heavy Metals

Larissa I. Velez and Kathleen A. Delaney

IRON

Iron, which is essential to the function of hemoglobin, myoglobin, many cytochromes, and many catalytic enzymes, can be extremely toxic when levels are elevated following an overdose or from accumulation in disease states.[1,2] The acute ingestion of iron is especially hazardous to children.[3] Ingestions of pediatric multivitamin formulations are the most common iron exposures. These occur in children younger than age 6 years and are minimally toxic. Life-threatening toxicity is associated with ingestion of potent adult preparations, such as prenatal vitamins. Serious iron ingestions in adults are usually associated with suicide attempts.[1,4,5]

Principles of Disease

Pharmacology

Under normal conditions, approximately 10% of ingested iron is absorbed from the intestine and bound to transferrin, using only 15 to 35% of the iron-binding capacity of transferrin. Normal serum iron levels range from 50 to 150 µg/dL. The total iron-binding capacity (TIBC), a crude measure of the ability of serum proteins—including transferrin—to bind iron, ranges from 300 to 400 µg/dL. It is higher than the serum iron level due to a low degree of saturation. When iron levels rise following a significant iron overdose, transferrin becomes saturated so that excess iron circulates as free iron in the serum. This unbound iron is directly toxic to target organs.[1,6]

When assessing the severity of an iron exposure, it is important to refer to the amount of elemental iron ingested because the toxicity of an iron compound depends on the amount of elemental iron it contains (Table 155-1). Different formulations of iron salts contain different percentages of elemental iron. The total amount of elemental iron ingested can be approximated by multiplying the estimated number of tablets by the fraction of elemental iron contained in the tablet. Ingestions of less than 20 mg/kg of elemental iron usually cause no symptoms. Ingestion of 20 to 60 mg/kg results in mild to moderate symptoms, and ingestion of more than 60 mg/kg may lead to severe morbidity. Although the dose of elemental iron associated with 50% mortality (LD_{50}) is reported to be 200 to 250 mg/kg, doses as small as 130 mg of elemental iron have been lethal in children.[7] A newer uncharged form of iron (carbonyl iron) is very slowly absorbed. There are no reported cases of serious toxicity or death from the ingestion of this compound.[8,9]

Pathophysiology

Iron has two distinct toxic effects: (1) it causes direct caustic injury to the gastrointestinal mucosa, and (2) it impairs cellular metabolism, primarily of the heart, liver, and central nervous system (CNS). The caustic effects of iron on the gut cause the initial symptoms of vomiting, diarrhea, and abdominal pain. Hemorrhagic necrosis of gastric or intestinal mucosa can lead to bleeding, perforation, and peritonitis.[6,7,10,11]

Unbound (free) iron moves into cells and localizes near the mitochondrial cristae, resulting in uncoupling of oxidative phosphorylation and impairment of adenosine triphosphate synthesis. Cell membranes are injured by free radical-mediated lipid peroxidation.[1,7,12]

Iron increases capillary permeability and induces both arteriolar and venodilation. Myocardial toxicity decreases cardiac output. Hydration of the iron molecule creates an excess of unbuffered protons, worsening metabolic acidosis.[1,7] This multitude of effects, combined with severe gastrointestinal fluid losses, can lead to the development of shock, cardiovascular collapse, and death.[1,7]

Clinical Features

The clinical effects of acute iron poisoning are described by five stages.[10] Phase I reflects the corrosive effects of iron on the gut. Vomiting occurs within 80 minutes of ingestion in more than 90% of symptomatic cases. Diarrhea, which can be bloody, follows. Phase II represents an apparent (but not complete) recovery that lasts less than 24 hours but can extend up to 2 days. Most patients recover after this point. Phase III is characterized by the recurrence of gastrointestinal symptoms, severe lethargy or coma, anion gap metabolic acidosis, leukocytosis, coagulopathy, renal failure, and cardiovascular collapse. Serum iron levels may have fallen to normal during this phase due to distribution into the tissues. Metabolic derangements due to iron poisoning include hypoglycemia, leukocytosis, and severe lactic acidosis from hypoperfusion and interference with cellular respiration. Early coagulation defects are probably related to direct effects of iron on vitamin K–dependent clotting factors.[13] Later coagulation defects are due to hepatic failure. Hypoglycemia and elevations of bilirubin, aspartate, and alanine aminotransferases are other markers of hepatotoxicity.[14] Phase IV, characterized by fulminant hepatic failure, occurs 2 to 5 days after ingestion. This is relatively rare, appears to be dose related, and is usually fatal.[14,15] Phase V represents the consequences of healing the injured

Table 155-1 Common Iron Preparations

COMPOUND	PERCENTAGE OF ELEMENTAL IRON
Ferrous sulfate	20
Ferrous fumarate	33
Ferrous gluconate	12
Ferric pyrophosphate	30
Ferrocholinate	14
Ferroglycine sulfate	16
Ferrous sulfate, dried	33
Ferrous carbonate, anhydrous	38
Carbonyl iron	100

Table 155-2 Toxicity of Iron by Amount Ingested and Peak Serum Levels

ELEMENTAL IRON (MG/KG)	PEAK SERUM IRON (µG/DL)	TOXICITY
<20	50–150	None
20–40	150–300	Mild
40–60	300–500	Moderate
>60	>500	Severe

Figure 155-1. Radiopaque iron tablets (*arrow*) seen on abdominal radiograph. (From Craig SA: Radiology. In Ford MD, Delaney KA, Ling LJ, Erickson T [eds]: Clinical Toxicology. Philadelphia, Saunders, 2001, p. 62.)

gastrointestinal mucosa. It is characterized by pyloric or proximal bowel scarring, which is sometimes associated with obstruction.[1,6,10]

Diagnostic Strategies

The presence of gastrointestinal symptoms suggests a potentially serious ingestion, whereas their absence is reassuring. A serum iron level measured at its peak, 3 to 5 hours after ingestion, is the most useful laboratory test to evaluate the potential severity of an iron overdose. Sustained-release or enteric-coated preparations may have erratic absorption, so a second level 6 to 8 hours after ingestion should also be checked. Peak serum iron levels of less than 350 µg/dL are generally associated with minimal toxicity, 350 to 500 µg/dL with moderate toxicity, and greater than 500 µg/dL with potentially severe toxicity (Table 155-2).[4] Because iron is rapidly cleared from the serum and deposited in the liver, iron levels may be deceptively low if measured late, even after a substantial ingestion.

TIBC has been used in the past as an indicator of free iron. However, TIBC is a crude test, and cases of serious toxicity have been reported even when TIBC exceeds the serum iron level.[8]

Although a negative radiograph does not rule out the presence of iron from chewable, liquid, and completely dissolved iron compounds, most tablets that contain a significant amount of elemental iron are radiopaque. The presence of tablets on a radiograph correlates with the severity of the ingestion (Fig. 155-1).[16,17]

Management

Gastric Emptying

Iron is not bound to activated charcoal, and neither gastric lavage nor ipecac effectively removes large numbers of pills. Iron tablets clump together as their outer coatings dissolve. Gastrotomy has been performed to remove iron from the stomach, but the success of whole-bowel irrigation generally obviates the need to consider surgery for the sole purpose of decontamination.[18]

For significant ingestions (>20 mg/kg of elemental iron), especially when tablets are identified on the abdominal radiograph, whole-bowel irrigation with a polyethylene glycol electrolyte lavage solution (PEG-ELS) (CoLyte, NuLytely, or GoLYTELY) is routinely recommended. The solution is either taken orally or administered through a nasogastric tube.[4,19] The usual rate of administration of PEG-ELS is 20 to 40 mL/kg/hr in young children and 1.5 to 2 L/hr for teenagers or adults, continued until the rectal effluent is clear and there is no radiographic evidence of pill fragments. This technique has been used in children, adolescents, and pregnant women without serious complications or electrolyte disturbances.[18,20,21] Common side effects include nausea, vomiting, abdominal cramping, and bloating. Whole-bowel irrigation is contraindicated in the presence of bowel obstruction, perforation, or ileus.[22]

Hemodialysis and hemoperfusion are not effective in removing iron due to its large volume of distribution. Exchange transfusions have been recommended for severely symptomatic patients with serum iron levels exceeding 1000 µg/dL.[23]

Deferoxamine

Deferoxamine chelates iron to form the water-soluble compound ferrioxamine, which can be renally excreted or dialyzed. One hundred milligrams will chelate 9.35 mg of elemental iron.[7] Deferoxamine may also limit the entrance of iron into the cell and chelate intracellular iron. Because of its short half-life, it is administered as a continuous infusion at a dose of 15 mg/kg/hr for up to 24 hours.[24] The maximum rate of administration is 35 mg/kg/hr. Rapid administration of deferoxamine can lead to hypotension, which is treated by reducing the initial rate of the infusion and slowly increasing

it to the desired rate.[8] Pregnancy is not a contraindication to deferoxamine. When calculating the dose in pregnancy, the prepregnancy weight should be used.

The presence of ferrioxamine turns the urine a "vin rosé" color, which reflects the excretion of chelated iron. Historically, the deferoxamine challenge test, which relied on detection of this color change, was used to diagnose the presence of free iron in the serum. The color change is difficult to detect, especially when the urine is dilute, resulting in false-negative results even in cases of serious poisoning. Falsely low serum iron values also occur in the presence of deferoxamine, so serum iron should be measured before its administration.[25]

Disposition

The asymptomatic patient who has ingested less than 20 mg/kg of elemental iron can be observed without further therapy. If the patient remains asymptomatic after 6 hours of observation, discharge is recommended.[1]

The patient who has ingested more than 20 mg/kg of elemental iron, or has pills visible on an abdominal radiograph, should receive whole-bowel irrigation. Abdominal radiographs can verify adequate gastrointestinal decontamination. The serum iron should be checked 3 to 5 hours after ingestion. A second iron level 6 to 8 hours after ingestion should be decreasing. Moderate gastrointestinal toxicity can be expected with peak levels of 300 to 500 µg/dL. If peak levels are less than 300 µg/dL, are not rising, and the patient is asymptomatic during 6 hours of observation, the patient can be discharged home. Patients with a serum iron level greater than 500 µg/dL or patients with any systemic signs of toxicity (mental status changes, shock, or high anion gap acidosis) require chelation with deferoxamine.[8]

When serum iron levels are not immediately available, elevations of the serum glucose level and leukocyte count are 100% specific for predicting serum iron levels greater than 300 µg/mL. A sensitivity of 50% limits their sole use as indicators of toxicity.[26] However, if the results of both these tests are normal, there are no signs or symptoms of toxicity during the 6-hour postingestion period, and the abdominal radiographs do not show pills in the gastrointestinal tract, the patient can be sent home.

LEAD

Lead poisoning is a disease of industrialization. It is the most common toxicologic problem of environmental origin in the United States.[27,28] Exposure usually results from ingestion or inhalation. Less often, it results from direct skin contact with organic lead compounds or from retained bullets in or near joints.[29] Approximately 3 to 4 million children (1 in 20) in the United States have toxic blood lead levels (BLLs).[27,30] Although the addition of lead to household paint and gasoline was banned in the United States in the 1970s, lead-based paint is still found in 30 million homes.[30] Other sources of toxic lead ingestions include curtain weights, buckshot, fishing weights, lead-contaminated soil or water, bootleg whiskey ("moonshine"), food or beverages stored or prepared in lead-soldered cans, lead-glazed pottery, and lead crystal decanters.[31] Herbal and folk remedies, toys, and numerous products imported from Asia and Mexico contain dangerous amounts of lead.[32,33]

Children typically present to the emergency department (1) following an ingestion of lead, (2) symptomatic with a possible exposure history, or (3) referred for management of an elevated BLL. Lead toxicity in adults most often results from inhalational exposure in the workplace, as well as from hobbies and related activities. It is estimated that more than 3 million workers in the United States are at risk for toxic lead exposure in industries such as lead smelting, battery manufacture, radiator repair, bridge and ship construction or demolition, soldering or welding, cable or tin can production, stained glass manufacture, lead-glazed or crystal pottery making, glass production, firing range operation, and lead-based paint abatement.[27,28] Hobbies at risk include making glazed pottery, target shooting at indoor firing ranges, soldering lead, smelting lead in the preparation of buckshot and fishing sinkers, repairing cars or boats, and remodeling homes. Lead toxicity should be considered in adults with compatible symptoms associated with these exposures.

Principles of Disease

Pharmacology

There is no known biologic need for lead. Its absorption is highest in malnourished children (approximately 40%) and in pregnant women.[34] Although 90 to 95% of lead is stored in cortical bone and teeth, it is also found in the brain, liver, and kidneys. Approximately 75% of the absorbed lead is eliminated by the kidneys, with the remainder absorbed through the skin, hair, sweat, nails, and gastrointestinal tract.[28]

Pathophysiology

Lead binds to sulfhydryl groups and other ligands and interferes with critical enzymatic reactions.[28] Its toxic effects are most prominent in the hematopoietic, neurologic, and renal systems.[34,35]

Anemia, the classic manifestation of hematopoietic toxicity, may be either normochromic or hypochromic. The severity of the anemia correlates directly with the BLL. Inhibition of heme biosynthesis results in the accumulation of heme precursors such as D-aminolevulinic acid and protoporphyrin.[34] In the peripheral nervous system, segmental demyelination and degeneration of motor axons result in peripheral neuropathies.[27] Wrist drop and foot drop are characteristic of adult lead poisoning. Lead toxicity also causes neuropsychiatric disorders. In children, elevated BLLs are associated with decreased intelligence (IQ) scores, hyperactivity, decreased attention span, overaggressive behavior, learning disabilities, criminal behavior, and subclinical sensorineural hearing loss.[36-42] Lead nephropathy is characterized by fibrosis in the proximal tubules, with relative sparing of the glomeruli. Hyperuricemic gout ("saturnine gout") can result from increased reuptake of uric acid by the tubular cells. Lead poisoning has also been correlated with hypertension.[43] Adults and children with acute toxicity may present with lead encephalopathy associated with increased capillary permeability and cerebral edema.[39]

Clinical Features

Symptoms of chronic, mild lead poisoning are slow in onset and nonspecific. The diagnosis is suspected by obtaining an accurate and comprehensive history of exposure to lead.

Acute exposure to lead can result in symptomatic poisoning. "Lead colic" is characterized by cramping abdominal pain with nausea, vomiting, constipation, and, occasionally, diarrhea.[39] Other characteristic symptoms and signs of acute toxicity include fatigue, anemia, peripheral neuropathy, renal impairment, and hepatic and CNS dysfunction. The CNS toxicity may manifest as mild headache or personality changes to full-blown encephalopathy with coma, convulsions, and papilledema. Permanent neurologic and behavioral sequelae may occur.[28]

Table 155-3 Serum Lead Levels and Symptomatology

	SYMPTOMS	
LEVEL (µG/DL)	**ADULTS**	**CHILDREN**
10	None	Decreased intelligence Decreased hearing Decreased growth
20	Increased protoporphyrin No symptoms	Decreased nerve conduction velocity Increased protoporphyrin
30	Increased blood pressure Decreased hearing	Decreased vitamin D metabolism
40	Peripheral neuropathies Nephropathy Infertility (men)	Decreased hemoglobin synthesis
50	Decreased hemoglobin synthesis	Lead colic
70	Anemia	Anemia Encephalopathy Nephropathy
100	Encephalopathy	Death

Diagnostic Strategies

Although capillary lead levels correlate well with BLLs, the most informative biomarker is a BLL.[44-47] The Centers for Disease Control and Prevention has defined a chronic BLL of greater than 10 µg/dL as toxic for a child. Acute exposure can result in levels up to 100 µg/dL (Table 155-3). Other ancillary data include findings on complete blood cell count, serum glucose, blood urea nitrogen, creatinine, electrolyte levels, and urinalysis. A peripheral smear may show basophilic stippling. Markers of hepatic injury may be elevated following acute exposure. Lead-containing paints and objects are radiopaque when present in sufficient quantities, and radiographs can confirm acute ingestion and monitor the effectiveness of whole-bowel irrigation. In cases of altered mental status, seizures, or coma, a computed tomography scan of the head will show cerebral edema associated with acute lead encephalopathy and rule out other causes for these symptoms. In children, plain radiographs of the wrist and knees may show increased metaphyseal activity manifest as "lead bands" or "lead lines" that are characteristic of chronic exposures.

Management

Acute Lead Encephalopathy

Acute lead encephalopathy can be rapidly fatal. The initial goals in management are to identify and treat all life-threatening conditions, followed by efforts to prevent further exposure to lead, minimize absorption of ingested lead, enhance its elimination, and prevent or reverse cellular pathology. Standard measures to control cerebral edema, including intubation and neurosurgical consultation for invasive monitoring of intracranial pressure, are indicated. When a severe poisoning is associated with ingestion or if radiopacities are seen on the radiograph, decontamination with whole-bowel irrigation is indicated.[48,49] Activated charcoal does not adsorb lead.

Chelation Therapy

The use of chelation in cases of acute lead poisoning is guided by the patient's clinical status and the BLL. Any patient with a BLL greater than 70 µg/dL, or with signs suggestive of encephalopathy, will require admission for parenteral chelation therapy. For these seriously poisoned patients, dimercaprol (or British antilewisite [BAL]) should be the first chelator given.[50] The dosage is 3 to 5 mg/kg (25 mg/kg/day), given by deep intramuscular injection every 4 hours for 2 days, followed by a dose every 4 to 6 hours for 2 more days and then every 4 to 12 hours for up to 7 days. Dimercaprol forms complexes that undergo both renal and biliary excretion. Adverse reactions to dimercaprol include nausea, vomiting, urticaria, pyrexia, hypertension, and hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency.[50] Since dimercaprol is diluted in peanut oil, it is contraindicated in patients allergic to peanuts. Dimercaprol is followed by calcium disodium ethylenediaminetetraacetic acid ($CaNa_2EDTA$), a highly effective lead chelator. Because of concerns that the chelated lead can cross the blood-brain barrier and worsen encephalopathy, the first dose of $CaNa_2EDTA$ is administered with the second dose of dimercaprol.[50] The dosage of $CaNa_2EDTA$ for patients with acute lead encephalopathy is 75 mg/kg/day or 1500 mg/m^2/day given intravenously or intramuscularly in two to four divided doses, with a maximum daily dose of 1 g in children and 2 g in adults. Adverse reactions include renal tubular injury and chelation of other metals, especially iron and zinc. $CaNa_2EDTA$ should be given only with adequate urine flow or with hemodialysis in the patient with renal failure.[51] It is important that $CaNa_2EDTA$ not be confused with sodium (Na) EDTA. The administration of NaEDTA has been associated with hypocalcemia and death from arrhythmias.[50,52]

The need for parenteral chelation therapy in asymptomatic or minimally symptomatic children is guided by the BLL. A BLL of more than 69 µg/dL mandates hospitalization and parenteral chelation therapy.[50] For less seriously poisoned patients, the dosage of $CaNa_2EDTA$ is 50 mg/kg/day or 1000 mg/m^2/day, given in two to four divided doses for up to 5 days.

Serum lead levels of 45 to 69 µg/dL in patients without vomiting or CNS symptoms can be managed in the outpatient setting using oral succimer (2,3-dimercaptosuccinic acid [DMSA]; Chemet).[50] The initial dose of DMSA is 10 mg/kg every 8 hours for 5 days, then 10 mg/kg every 12 hours for 14 days. The most common adverse reactions include nausea, vomiting, diarrhea, and transient elevations in liver transaminase levels. Although DMSA has been approved only for children, it is also used in adults.[45,53,54] Oral D-penicillamine should be used only in patients who do not tolerate succimer. The usual oral dose of D-penicillamine is 25 mg/kg every 6 hours for 5 days. D-Penicillamine is less efficacious than succimer and has more adverse reactions. Penicillin allergy is a contraindication to the use of D-penicillamine.

The key to managing chronic lead toxicity is the identification and reduction of sources of primary exposure. Any patient treated on an outpatient basis must be discharged to a lead-free environment. A BLL between 20 and 44 µg/dL in a patient who is asymptomatic or minimally symptomatic requires a more aggressive medical and environmental evaluation. Evidence indicates no need for chelation for children with a BLL lower than 45 µg/dL.[55] Children with lead levels of 10 to 19 µg/dL require family counseling about the symptoms and sources of lead exposure and careful follow-up, with frequent screening of BLLs.[50]

The treatment of adults with chronic poisoning is less aggressive than for children. If gastrointestinal symptoms or

CNS problems are present, hospitalization with parenteral chelation therapy is indicated. In the asymptomatic adult or the adult with only mild clinical problems, the only intervention needed is cessation of exposure. According to the Occupational Safety and Health Administration lead standard, workers with serum lead levels greater than 50 µg/dL must be removed from work.[56]

Disposition

Patients who have ingested a single lead foreign body (e.g., fishing sinker) will usually pass it harmlessly.[57] If the foreign body remains in the gastrointestinal tract after 2 weeks, removal should be considered to prevent lead toxicity.

Patients who are significantly symptomatic after an acute lead exposure and children with a BLL of 69 µg/dL or greater require hospitalization and chelation therapy. Patients discharged home on oral chelation therapy should not return to a contaminated environment. The health department should conduct an environmental assessment so that the primary source of lead exposure can be identified and further exposure prevented. Follow-up should be arranged with an experienced pediatrician, toxicologist, or occupational medicine physician.[58]

ARSENIC

Arsenic (As), a tasteless, odorless substance that looks like sugar, has an infamous history as an agent of homicide. Arsenic has also been implicated in many incidences of epidemic poisoning. Currently, arsenic exposure is primarily environmental and occupational. It is found in smelters and electric power plants that burn arsenic-rich coal. It is used in industry as a wood preservative and in the production of glass and microcircuits. Inorganic arsenicals are also used in rodenticides, fungicides, insecticides, paint, and tanning agents and as defoliants in the cotton industry. Arsenic is still used for medicinal purposes in the treatment of trypanosomiasis, amebiasis, and leukemia.[59] It has also been found as a contaminant in herbal remedies and drugs such as opium.[60] There are widespread reports of chronic arsenic poisoning associated with contaminated drinking water in underdeveloped countries.[61] Arsenic poisoning should be suspected if compatible symptoms occur with the use of these products or these possible exposures.

Principles of Disease

Pharmacology

Arsenic has no metabolic or biologic function. The elemental metal is poorly water soluble and is considered nontoxic. Of the two inorganic forms, trivalent arsenite (As^{3+}) is highly lipid soluble and is 5 to 10 times more toxic than the pentavalent arsenate (As^{5+}) form. The more toxic lipophilic trivalent arsenite form has a lower gastrointestinal absorption but is well absorbed by the skin. The pentavalent arsenate form, although less toxic, is water soluble and readily absorbed from the gastrointestinal tract. Absorbed arsenic is bound by hemoglobin, leukocytes, and plasma proteins. It is cleared from the intravascular compartment within 24 hours and concentrates in the liver, kidneys, spleen, lungs, and gastrointestinal tract. Arsenic crosses the placenta and can also accumulate in the fetus. Its affinity for sulfhydryl groups in keratin makes arsenic detectable in the hair, skin, and nails.[62] Arsine (AsH_3), a colorless and almost odorless gas, is extremely toxic.[63] It is immediately lethal at 250 ppm.[64] The excretion of arsenic and its metabolites occurs mainly through the kidneys.

Pathophysiology

Arsenic binds avidly to sulfhydryl groups, inhibiting critical enzymes such as lactate dehydrogenase and glyceraldehyde-3-phosphate dehydrogenase, a critical step in glycolysis. It also disrupts oxidative phosphorylation by replacing phosphorus in the formation of high-energy phosphate bonds (arsenolysis).[59] Arsine causes massive hemolysis. The exact mechanism is poorly understood.[65]

Clinical Features

Acute exposure to arsine gas is characterized by severe hemolysis that is associated with renal tubular injury. Gastrointestinal symptoms are common, and CNS and liver dysfunction can occur. The mortality rate is 25 to 30%. Exchange transfusions and plasma exchange have been used to remove arsine, which is tightly bound to the erythrocytes.[63] Urinary alkalinization can be used to decrease renal deposition of hemoglobin.

Acute gastrointestinal effects—nausea, vomiting, abdominal pain, and diarrhea—predominate as the initial manifestations of acute exposure to arsenic salts.[59,66-68] These symptoms can be so severe as to result in hematemesis and hematochezia. Within 30 to 60 minutes of exposure, patients complain of a metallic or garlicky taste. The patient can also develop encephalopathy with seizures and coma, respiratory failure associated with acute respiratory distress syndrome, and dysrhythmias associated with cardiac conduction disturbances.[69-71] In cases of severe poisoning, cardiovascular collapse and death ensue.[72] Less common complications include hepatitis, rhabdomyolysis, hemolytic anemia, renal failure, unilateral facial nerve palsy, pancreatitis, pericarditis, pleuritis, and fetal demise (Box 155-1).[68] The syndrome may be misdiagnosed as gastroenteritis or sepsis.

Weeks to months after the initial symptoms, chronic effects of arsenic poisoning appear, including characteristic lines in the nails (Mees' lines), painful sensorimotor neuropathy, and hyperkeratosis of the palms and soles.[59] Arsenic poisoning should also be considered in any patient with a history of severe or recurrent gastroenteritis/abdominal pain and unexplained dermatologic lesions associated with peripheral neuropathy. Finally, arsenic is a known human carcinogen.[59]

Diagnostic Strategies

Normal arsenic levels are 5 µg/L or less in blood or less than 50 µg/day in a 24-hour urine collection, which is the best way to diagnose the poisoning. Any urine level above 100 µg/day or 50 µg/L necessitates treatment. A spot urine sample may be falsely low because urinary excretion of arsenic is intermittent. Seafood contains arsenobetaine, which can increase urinary arsenic excretion to as high as 1700 µg/L.[73] Arsenobetaine, however, does not result in arsenic toxicity. For this reason, patients should refrain from eating seafood prior to testing whenever feasible, or the laboratory should be asked to speciate the type of arsenic measured.[74]

Other laboratory results may raise the suspicion of arsenic poisoning in the right clinical setting. Anemia, leukocytosis or leukopenia, and erythrocyte basophilic stippling are seen in the complete blood cell count. The results of renal function tests may be abnormal. Proteinuria, hematuria, and pyuria are also seen. The alanine aminotransferase, aspartate aminotransferase, and bilirubin levels may be elevated. In cases of chronic arsenic poisoning, the serum and urine arsenic levels may be undetectable, whereas hair and nail specimens can confirm the diagnosis.

BOX 155-1 ACUTE EFFECTS OF ARSENIC POISONING

Gastrointestinal
Violent gastroenteritis
Hematemesis/hematochezia
Jaundice
Pancreatitis
Dysphagia
Hepatomegaly

Cardiovascular
Third spacing with shock
Sinus/ventricular tachycardia
Prolonged QT interval, ST depression, T wave inversion
Torsades de pointes
Pericarditis

Respiratory
Respiratory failure
Adult respiratory distress syndrome
Pulmonary edema
Pneumonia

Renal
Proteinuria
Hematuria
Oliguria
Renal failure

Neurologic
Headache
Drowsiness
Delirium
Coma
Encephalopathy
Seizures

Arsenic in the gastrointestinal tract is radiopaque and can appear on a radiograph, although sensitivity is limited by rapid absorption and the ensuing gastroenteritis.[75]

Management

The initial management should address life-threatening conditions with supportive management of shock, dysrhythmias, and seizures. Activated charcoal does not adsorb arsenic and is of no value. Although there is no evidence for improved outcomes, orogastric lavage or whole-bowel irrigation should be considered only for very recent (<1 hr) ingestions or if radiopaque material is visualized on an abdominal radiograph. Hemodialysis removes arsenic in the setting of acute renal failure.[71] Exchange transfusions or plasma exchange should be considered very early after an arsine exposure.[63]

With a known history of exposure in a symptomatic patient, chelation should start as early as possible without waiting for laboratory confirmation of the arsenic levels. Intramuscular dimercaprol is the preferred chelator in patients who are critically ill. DMSA is a water-soluble analogue of dimercaprol that can be given orally.[76,77] D-Penicillamine has a high side effect profile, and its ability to chelate arsenic is inferior to that of dimercaprol and DMSA. Therefore, it should only be used when both dimercaprol and DMSA are unavailable. All patients receiving chelation for acute arsenic toxicity should be admitted. Chelation is not useful for arsine exposures.

BOX 155-2 SOURCES OF MERCURY

Elemental
Spill from mercury-containing devices
Gastrointestinal exposure from ruptured Cantor or Miller-Abbott tube
Inhalational exposure in the workplace/home
Deliberate injection or ingestion
Accidental ingestion

Salts
Accidental disk battery ingestion
Deliberate ingestion
Laxative abuse

Organic
Oral/dermal exposure to mercurochrome or thimerosal
Repeated injections of drugs containing thimerosal as a preservative
Exposure from occupational or agricultural accidents
Water/soil pollution
Consumption of contaminated seafood
Exposure to paint containing mercury

MERCURY

Mercury is a silver white metal, familiar to most as the only metal that is liquid at room temperature. It has a long history of medicinal uses as an antiparasitic, a diuretic, a cathartic, an antiseptic, and as a preservative in many vaccines.[78] Significant poisoning in the home has occurred when relatively small amounts of spilled mercury, such as that contained in a sphygmomanometer, were aerosolized by vacuuming or when mercury was heated on the kitchen stove to extract gold from ore.[79,80] Various other sources of mercury have also been implicated in intoxication (Box 155-2). Because of many industrial uses that include the manufacture of fluorescent lights, batteries, polyvinyl chloride, and latex paint, mercury is a common pollutant of air and water. This has led to restrictions in the consumption of fish caught in many local waters.[81,82]

Principles of Disease

Pharmacology

The most familiar form of mercury is elemental or metallic mercury, also known as "quicksilver." A common route of exposure to elemental mercury is the inhalation of volatilized vapor.[83] Aspiration of elemental mercury and intentional subcutaneous and intravenous injections also cause poisoning.[84] After inhalation, 74% of the metallic mercury is retained in the lungs. This can result in severe pneumonitis and acute respiratory distress syndrome.[85] Aspiration of elemental mercury results in primary pulmonary toxicity, in addition to CNS and renal toxicities.[86] Elemental mercury is not absorbed by the gastrointestinal tract, so ingestion does not normally lead to systemic toxicity unless it becomes trapped in diverticulae. Mercury is absorbed through the skin at 1% of the rate of inhaled mercury and is not a concern.

Inorganic mercury salts have two different valences, Hg^{1+} (*mercurous*) and Hg^{2+} (*mercuric*). Ingestion of either salt leads to significant gastrointestinal and renal toxicity.

The organic mercury compounds are categorized as either short chain (*alkyl*) or long chain (*aryl*). The major route of exposure to this type of mercury is through ingestion, but these compounds are also readily absorbed through the skin. These

organic forms classically result in delayed neurotoxicity with prominent ataxia, tremor, dysarthria, and tunnel vision.[81,87]

Pathophysiology

Mercury binds covalently to sulfhydryl groups, disturbing multiple cellular enzyme functions. Nephrotoxicity results from both direct damage and an immune reaction in the kidney.[79] The skin changes associated with mercury poisoning are also caused by an immune reaction. Mercury increases catecholamine levels by inhibition of catechol-*O*-methyltransferase, resulting in hypertension and tachycardia.[88,89] Atrophy of the cerebellum, postcentral gyri, and calcarine areas of the brain correlates with the symptoms of ataxia, sensory, and visual field disturbances.[90]

Clinical Features

The clinical manifestations of mercury poisoning depend on the acuity of the exposure, the route of exposure, and the chemical form of mercury. Inhalation of elemental mercury vapor results in the rapid onset of shortness of breath, fever, and chills that progresses to pneumonitis and respiratory distress.[80,85,91] Aspiration of liquid metallic mercury during medical procedures results in the rapid onset of tracheobronchial hemorrhage.[92]

Acute ingestion of inorganic salts typically causes a corrosive gastroenteritis with third spacing and hemorrhage. Patients complain of a metallic taste in the mouth and may have a grayish discoloration of the mucous membranes. Massive fluid loss results in shock and acute tubular necrosis. The manifestations of subacute or chronic inorganic mercury poisoning are neurologic (e.g., neurasthenia and erethism), renal (ranging from proteinuria to the nephrotic syndrome), and gastrointestinal (e.g., metallic taste, gingivostomatitis, loose teeth, burning sensation in mouth, hypersalivation, and nausea).[79,93]

Exposure to organic mercury compounds is not associated with acute toxicity. Neurologic symptoms develop over weeks to months. The neurologic and teratogenic effects of chronic exposure to methylmercury were well illustrated by the tragic poisoning of the population of Minamata, Japan, by fish caught in mercury-polluted water.[94] Slowly progressive fatal CNS injury was described following a minor topical exposure to dimethylmercury in a laboratory researcher (Table 155-4).[81,87,95]

Table 155-4 Mercury Intoxication Syndromes

TYPE OF MERCURY/ROUTE OF EXPOSURE	SIGNS/SYMPTOMS
Inhalation of metallic mercury	Hypoxemia Respiratory distress, ARDS Dyspnea, chest tightness Fever, chills Burning in mouth and throat Nausea, vomiting Bloody diarrhea Renal tubular necrosis
Aspiration of metallic mercury	Aspiration pneumonitis ARDS
Subacute/chronic inhalation of metallic mercury	Metal fume fever Neuropsychiatric symptoms Renal dysfunction Skin changes
Ingestion of inorganic mercury salts	Severe hemorrhagic gastroenteritis, shock, hypovolemia, third spacing Acute tubular necrosis in 24 hr, with albuminuria and hematuria
Subacute/chronic inhalation of inorganic mercury	Neurasthenia, erethism, acrodynia
Organomercury exposure (methyl-, diethyl-)	Delayed neurologic problems (ataxia, tremor, dysarthria), visual field constriction, hearing loss, spasticity, hyper-reflexia

ARDS, acute respiratory distress syndrome.

Diagnostic Strategies

Measurement of urine mercury levels is the most helpful test in confirming exposure and monitoring the effectiveness of chelation. For organic mercury compounds, which undergo little urinary excretion, serum levels must be used to confirm the diagnosis. "Normal" mercury levels are considered to be less than 10 µg/L in the blood or less than 20 µg/L in the urine. Blood levels greater than 35 µg/L and urine levels greater than 150 µg/L require intervention. No information is available on chelation at levels between 20 and 150 µg/L. Metallic mercury is radiopaque on plain radiographs, which can be ordered in cases of injection or ingestion of metallic mercury.[84]

Management

Initial management in the acutely poisoned patient should be aggressive support and decontamination. Gastric lavage with protein-containing solutions (e.g., milk and egg whites) may be beneficial in the decontamination of the gastrointestinal tract following ingestion of mercury salts. This is based on case reports only. Charcoal adsorbs very little mercury and is not recommended unless another serious co-ingestant is suspected. Ingested metallic mercury is generally harmless unless its passage is impaired by entrapment in a diverticulum or the appendix.[96]

For acute inhalational exposures, the patient should be removed from the source and supportive management provided. There is no role for prophylactic antibiotics or steroids. Suction and postural drainage are indicated in cases of acute aspiration of metallic mercury. Self-injection of metallic mercury often requires surgical débridement of infiltrated tissue.[84]

Help in the management of mercury spills can be obtained from the local hazardous materials team and the local health department.[83] Information on handling mercury spills can also be found at the Environmental Protection Agency website at http://www.epa.gov/hg/spills/index.htm. Sand or mercury decontamination kits that contain calcium polysulfide, which converts mercury to mercuric sulfide, should be used. Absorbable surfaces such as carpets should be removed. Attempts to remove mercury by vacuuming can volatilize the mercury and precipitate acute inhalational toxicity. Small spills, such as the contents of a home thermometer or a fluorescent bulb (amount = 30 ml or two tablespoons), can be scooped up with a stiff card or aspirated into a dropper placed onto a damp paper towel, sealed in a plastic bag, and ideally disposed of as hazardous waste. Mercury placed in household trash is incinerated and contributes to soil and water pollution and, ultimately, accumulation in the food chain.

Chelation Therapy

Chelating agents have thiol groups that compete with the enzyme sulfhydryl groups that bind mercury. BAL is used for

clinically significant acute inorganic mercury intoxication. Because it increases brain mercury levels in patients with methylmercury poisoning, BAL is contraindicated for patients poisoned with organic mercury compounds.[97] Although DMSA is not currently approved by the U.S. Food and Drug Administration for this indication, it is used for both acute and chronic mercury poisoning and may be the best chelator for methylmercury. D-Penicillamine is also used. It should be administered only after thorough gastrointestinal decontamination because mercury absorption from the intestinal lumen is enhanced by the penicillamines.

Disposition

In general, in cases of acute intoxication, the most toxic forms are the inorganic mercurials. Suicidal patients with such ingestions require decontamination and admission for supportive treatment. Patients who self-inject metallic mercury often need admission for surgical débridement. Patients with signs of neurotoxicity from an organomercurial also need admission. Most asymptomatic individuals can be followed closely with urinary testing as outpatients.

KEY CONCEPTS

- Ingestion of the salts of most metals causes severe gastrointestinal pain and emesis.
- Chelation with acute iron ingestion is guided by symptoms and two serum iron levels measured between 3 and 8 hours after ingestion.
- Patients with symptomatic acute lead exposures require immediate chelation. Asymptomatic or minimally symptomatic children with elevated BLLs require close follow-up and possible outpatient chelation. Parenteral chelation is indicated in children with lead levels greater than 69 μg/dL.
- Patients with a possible chronic heavy metal exposure and compatible symptoms should have further investigation and close follow-up.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 156

Hydrocarbons

David C. Lee

PERSPECTIVE: BACKGROUND AND EPIDEMIOLOGY

Human exposure to hydrocarbons (HCs) is a common problem. U.S. poison centers report 50,000 HC exposures annually, with the majority handled in an outpatient setting.[1,2] HC exposures that present to the emergency department (ED) generally can be classified into four types. The first is accidental ingestion involving children younger than age 5 years. This is the most common scenario causing fatality, and it usually involves significant pulmonary injury. Second is intentional inhalational abuse of volatile HCs. Recreational abuse has been a medical problem since solvent inhalation became popular during the late 1800s. Fatalities in this group will typically occur within distinct demographic groups (American Indians, homosexual males, and teenagers).[1,3] Third is accidental inhalational or dermal exposure to HC in the household or workplace setting. The fourth type is massive oral ingestion of HC in a suicide attempt.

PRINCIPLES OF DISEASE

Definitions and Terminology

HCs are a diverse group of organic compounds that contain hydrogen and carbon (Table 156-1). Most HCs (e.g., gasoline) are by-products of crude oil and are therefore called petroleum distillates. Some products, such as turpentine, are derived from pine oil, not petroleum. HCs can also be classified by their structure. The two main categories are straight chain HCs (aliphatic, such as propane) and those containing a benzene ring structure (aromatic, such as toluene). HCs can also have multiple nonorganic side chains. For example, halogenated HCs (e.g., carbon tetrachloride) usually will have one or more bromide, chloride, fluoride, or iodide moieties. Finally, HCs are used as the solvent base for many toxic chemicals such as insecticides and metals that in turn can cause a separate type of poisoning. Although the range of toxicity of HCs can vary widely, the majority of human exposures are confined to petroleum distillates.

Pathophysiology

Acute HC toxicity usually affects three main target organs: the lungs, the central nervous system (CNS), and the heart. Although certain HCs can enter the body through the skin or gastrointestinal (GI) tract, HCs cause the most damage via the lungs. Despite the fact that there are thousands of different types of HCs, their potential for acute toxicity depends mainly on four characteristics[4]:

1. Viscosity is the capacity to resist flow or change. Low viscosity allows a substance to spread rapidly, and a low-viscosity HC spreads easily into the airway and lungs. Thus, the lower the viscosity, the higher the toxicity. Viscosity is measured in Saybolt Seconds Universal (SSU), and substances with an SSU of less than 60 have the highest potential risk of aspiration. Lubricants and mineral oil have high viscosity and low toxicity, whereas furniture polish has low viscosity and high toxicity.
2. Volatility is the ease for a liquid to turn into a gas. High volatility gives an odor and enables a substance to displace alveolar oxygen. Butane and gasoline are types of HCs with high volatility.
3. Surface tension is the capacity for a substance to collect on a liquid surface. Low surface tension enables a substance (e.g., turpentine) to disperse easily.
4. Chemical side chains often increase potential toxicity. These toxic side chains include metals (e.g., arsenic), halogens (e.g., carbon tetrachloride), and aromatic structures (e.g., toluene).

Pulmonary Pathophysiology

The primary organ of toxicity for HCs is the lung. Fatalities after ingestion usually occur with an accompanying aspiration. Studies have shown that pulmonary toxicity is caused by aspiration rather than by GI absorption and hematogenous spread. A small amount of an HC in the trachea can be devastating, whereas a much larger amount of the same compound in the stomach can be benign.[5-7]

HCs affect the lungs through several mechanisms. HCs are usually poorly water soluble and are thereby able to penetrate into the lower airways, producing bronchospasm and an inflammatory response. Second, volatized HCs can displace oxygen in the alveolar space causing hypoxia. Third, HCs can cause direct injury to pulmonary alveoli and capillaries, producing distinct uniform lesions. Autopsy findings of these lesions include hyperemia, diffuse hemorrhagic exudative alveolitis with granulocytic infiltration, and microabscesses. Finally, HCs can inhibit surfactant function leading to alveolar instability and collapse. These mechanisms lead to alveolar dys-

Table 156-1 Spectrum of Hydrocarbon Toxicity

TYPE	EXAMPLE	USE	PATHOPHYSIOLOGY	COMMENTS
Aliphatic petroleum distillates	Methane Propane Butane Gasoline Kerosene Mineral spirits Mineral oil Naphtha Mineral seal oil Diesel oil *n*-Hexane	Fuels Liquid fuels Solvents Furniture polish Degreasers Multiple uses in chemical industry	Asphyxiants causing hypoxia and CNS depression Abused inhalants Pneumonitis when aspirated Abused inhalants CNS depression from fumes *n*-Hexane causes peripheral neuropathy	Sudden death from intentional inhalation Viscosity and volatility determine spectrum of toxicity Mineral seal oil has high aspiration potential Poor gastrointestinal absorption
Aromatic petroleum distillates	Toluene Xylene Benzene	Used in plastics, pharmaceutical, rubber, chemical, and solvent industries Degreasers	Highly volatile, lung aspiration Absorbed from gastrointestinal tract Abused inhalants	Inhaled toluene causes renal tubular acidosis Benzene causes aplastic anemia, leukemia
Wood distillates	Turpentine Pine oil	Solvent Household disinfectants	Well absorbed from gastrointestinal tract	Gastrointestinal/CNS toxicity
Halogenated hydrocarbons	Methylene chloride Chloroform Carbon tetrachloride Trichloroethylene Freon Methylbromide Lindane DDT	Solvents Cleaning fluids Degreasers Fire extinguishers Paint strippers Fumigants	Multisystem toxicity (CNS, renal, hepatic, cardiac) Inhalant abuse Highly lipid soluble	Methylene chloride metabolized to carbon monoxide Carbon tetrachloride is radiopaque Insecticides absorbed through skin
Related chemicals	Phenol Creosols	Disinfectants	Very corrosive	Phenol causes severe skin burns

CNS, central nervous system; DDT, dichlorodiphenyltrichloroethane.

function, ventilation perfusion mismatch, hypoxemia, and respiratory failure.[5-7]

Central Nervous System Pathophysiology

Certain HCs cause CNS depression (i.e., toluene, benzene, gasoline, butane, and chlorinated HCs). After respiratory exposure, most HCs passively diffuse through the pulmonary alveolus and are highly absorbed in blood and tissues. These HCs can cause euphoria, disinhibition, confusion, and obtundation. With an isolated single exposure, these effects usually have a rapid onset of intoxication and rapid recovery. For these reasons, substance abusers seek these HCs for recreational use. Inhalation of these substances avoids hepatic first-pass metabolism and generates high concentrations in the CNS. Chronic use of inhaled HCs can cause severe abnormalities in nervous system function, which include peripheral neuropathy, cerebellar degeneration, neuropsychiatric disorders, chronic encephalopathy, and dementia. More than 50% of patients who abuse toluene for more than 10 years will have cerebral cortical atrophy with histologic changes that include loss of neurons, diffuse gliosis, and axonal degeneration.[3,8]

Cardiac Pathophysiology

HCs can cause sudden death, especially after intentional inhalation. These compounds are thought to produce myocardial sensitization of endogenous and exogenous catecholamines, which then precipitates ventricular dysrhythmias and myocardial dysfunction. This is particularly true for halogenated and aromatic HCs (e.g., difluoroethane found in computer keyboard cleaning canisters).[9,10]

Other Pathophysiology

Various HCs have been reported to be toxic to other organ systems. Certain recognized syndromes include toluene-induced renal tubular acidosis, benzene-induced bone marrow toxicity and leukemia, methylene chloride–induced carbon monoxide poisoning, and chlorinated HC–induced centrilobular hepatic necrosis and renal failure. Direct skin exposure of certain HCs can cause extensive chemical burns.[3,11] HCs are often used as solvents for other chemicals that may have their own significant inherent toxicity.

CLINICAL FEATURES: SYMPTOMS AND SIGNS

There are several typical life-threatening clinical presentations of acute HC exposures. The first scenario is a child who has ingested an unknown quantity of an HC. Significant life-threatening poisonings usually have early respiratory symptoms, including cyanosis, coughing, grunting, noisy respirations, or repeated bouts of vomiting. These findings suggest aspiration. A patient may initially have mild symptoms and then develop tachypnea, dyspnea, bronchospasm, wheezing, rales, and fever within 6 hours.[12-18] A change in mental status can be a manifestation of hypoxia or hypercapnia, but it is also a direct effect of HCs. In extreme cases, these patients may present with frank respiratory failure. Additives or solutes in

Figure 156-1. Typical presentation of paint sniffer ("huffer") with paint around the face and sedation. (Courtesy of Chris Tomaszewski, MD, Carolinas Healthcare System.)

the HC base can produce varying symptoms (e.g., seizures from camphorated hydrocarbons or cyanosis from nitrite-induced methemoglobinemia). Pesticides are a classic example of such a toxic substance that is often placed in an HC base. With pesticide exposures, it can be very difficult to distinguish acute respiratory distress syndrome induced by HC aspiration from pulmonary edema induced by organophosphate exposures.

The second scenario is the solvent-abusing adolescent or adult. In the extreme case, these patients will be in cardiac arrest. Nonhospital medical personnel often describe an individual who has inhaled solvents, performed some type of physical activity, and then suddenly collapsed. This is thought to be due to cardiac sensitization by endogenous catecholamine and the ensuing development of dysrhythmias.[3,4,9,10] Various paraphernalia commonly include plastic bags used for "bagging" (a method of pouring HCs in a bag or container and then inhaling deeply) or an HC-soaked cloth used for "huffing" (a method in which abusers inhale through a saturated cloth). Other paraphernalia include gasoline containers, multiple butane lighters, and spray paint cans. These patients often have a distinctive odor because almost all of these products are volatile. They may have paint or a rash over the mouth and nose ("glue-sniffer's rash") (Fig. 156-1). These patients can also present to the ED with CNS intoxication comprising euphoria, agitation, hallucinations, confusion, and bizarre behavior. This may progress to CNS depression and seizures. Drug abusers who chronically inhale HCs may not be brought to medical attention specifically for treatment of their drug abuse but, rather, for behavioral problems or nonspecific medical symptoms caused by their abuse. The long-term chronic abuser may clinically appear similar to the long-term "skid row" alcoholic, with peripheral neuropathy, cerebellar degeneration, and encephalopathy.[19,20]

A third common scenario is the accidental dermal or inhaled (nonaspiration) respiratory exposure to HCs in the workplace or home. Fortunately, this is rarely life-threatening. Most cases do not seek medical care or are handled primarily through local poison control centers.[1,2] A very small percentage will seek treatment in the ED. Most of these patients will either be asymptomatic or have transient nonspecific symptoms such as headache, dizziness, or nausea. Those with significant respiratory exposure may have persistent pulmonary complaints and physical findings such as coughing, wheezing, and cyanosis. Patients with significant acute dermal exposures may have pain and evidence of chemical burns consisting of erythema, swelling, blistering, and dermal destruction.

The patient who intentionally ingests or intravenously injects HCs in a suicide attempt is rare. However, these patients can be difficult to treat because HCs are often ingested in combination with other substances. In the absence of aspiration or co-ingestion of another toxic substance, the massive oral ingestion of most commonly available HCs is not associated with significant morbidity or mortality. These patients risk aspiration if they vomit.

DIAGNOSTIC STRATEGIES

The diagnosis of HC poisoning is made on clinical grounds. In all cases, nonhospital medical personnel, family, and bystanders should be encouraged to bring the offending agent to the ED. The local poison control center may help to identify and verify substances containing HCs. When verification of an unknown substance is required, a reference laboratory is usually needed. Laboratory identification of HCs is usually time-consuming and not helpful in the ED management.

History and examination should focus on possible aspiration. These symptoms include cough, difficulty breathing, or shortness of breath. Signs of a significant exposure include tachypnea, tachycardia, wheezing, and hypoxemia. Patients with a significant HC exposure should have a chest radiograph taken. Radiographic changes can occur within 30 minutes of ingestion and may identify pathology not recognized by auscultation in more than 50% of cases.[13] Continuous pulse oximetry and arterial blood gases may also be helpful.

Patients who chronically abuse HCs often go to the ED for behavioral problems or nonspecific symptoms caused by their drug addiction. Similar to the intoxicated chronic alcoholic who is a common ED patient, these patients require close medical scrutiny to exclude underlying or secondary diseases. For example, chronic toulene abusers can develop acid-base disorders and indicate a need to measure electrolytes, blood urea nitrogen, creatinine, and urinalysis.

DIFFERENTIAL CONSIDERATIONS

In the most common fatal scenario—the child who ingests and then aspirates HC—the physician should be sure that no other toxic substances are involved. Organophosphate, salicylate, and paraquat poisonings can mimic the symptoms of HC aspiration. In the scenario of the recreational abuser, multiple drugs of abuse may be present. Behavioral disorders and confusion can be caused by hypoxia and respiratory compromise as well as from the drugs themselves. In the chronic abuser, it can be difficult to differentiate between a functional and an organic confusional state.

MANAGEMENT

Dermal exposures of HCs can cause extensive burns, and exposed patients should be decontaminated immediately. Contaminated clothing should be removed, and the skin should be washed with soap and copious lukewarm water. The GI decontamination of ingested HCs is controversial. The aphorism "the safest place in the body for hydrocarbons is the duodenum" holds true for most HCs regardless of the volume ingested. Routine gastric lavage or emesis should be avoided because HCs are much more toxic to lungs than to

the GI tract, where they also have a low potential for systemic absorption. Efforts at decontamination after the ingestion of a benign HC can result in aspiration, thereby converting a relatively nontoxic ingestion to a toxic aspiration. In certain situations, GI decontamination may be indicated. This is due to either the inherent toxicity of the HC or the toxicity of additives to the HC. A well-publicized mnemonic to describe most of these cases is *CHAMP*:

C—camphor, which can cause seizures and status epilepticus
H—halogenated HC, which can cause dysrhythmias and hepatotoxicity
A—aromatic HC, which can cause bone marrow suppression and cancer
M—metals (e.g., arsenic, mercury, and lead)
P—pesticides, which can cause cholinergic crises, seizures, and respiratory depression

Although the method of decontamination is controversial and there is scant literature to support the effectiveness of GI decontamination, use of a small-caliber nasogastric tube to evacuate stomach contents can be considered.[13,21]

Because HCs can cause sudden decompensation in a patient's pulmonary, cardiac, and CNS functions, all patients should be monitored with cardiac monitors and pulse oximeters in a well-observed area. In severe cases, early intubation for airway control and positive end-expiratory pressure have been advocated by several authors to minimize aspiration risks and counteract HC-induced alveoli collapse. However, no studies have proven this to be more beneficial than standard respiratory care. High-frequency jet ventilation and extracorporeal membrane oxygenation have both been used to treat children with respiratory failure secondary to aspiration.[22-25] Surfactant therapy has also been considered in these cases, but its benefit remains unproven.[26] Corticosteroids and antibiotics have not been shown to be beneficial in HC aspiration, but the differentiation between bacterial and chemical pneumonia may be difficult.[27] More than 50% of children with significant HC poisoning will develop a fever and leukocytosis.[13,15] Epinephrine and isoproterenol should be avoided unless required for cardiac resuscitation. Theoretically, exogenous catecholamine can cause dysrhythmias in HC-sensitized myocardium.

In most cases of HC ingestion or inhalation, supportive care and close observation and monitoring are the cornerstone of management. Currently, there are no specific antidotes for HCs.

DISPOSITION

Patients with exposures of known, relatively benign HCs should have a 4- to 6-hour period of observation. Patients who have ingested HCs and do not have symptoms should be monitored for a minimum of 6 hours with a reassessment that may include repeat physical examination, pulse oximetry, arterial blood gas measurements, and chest radiograph during the last hour of observation (Fig. 156-2). Any evidence of symptoms at this time mandates hospital admission and further observation. Asymptomatic patients with accidental exposures to HCs can be discharged after a period of observation with appropriate follow-up.[12]

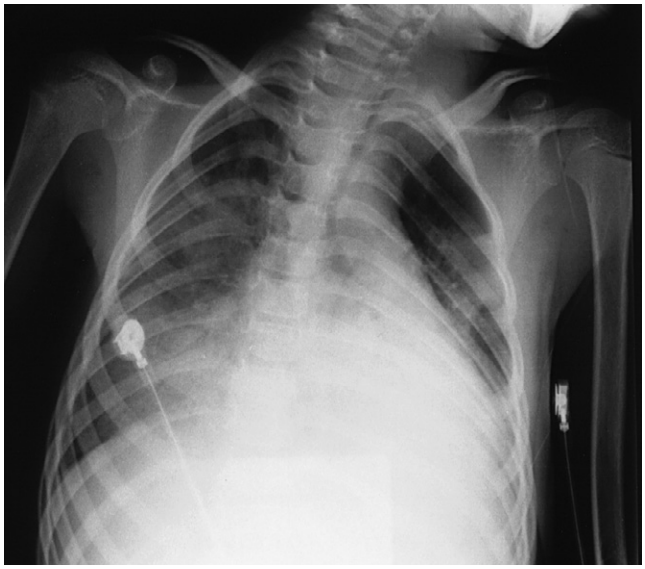


Figure 156-2. Chest radiograph of a patient with hydrocarbon ingestion 6 hours after exposure.

Patients who have ingested HCs and have symptoms suggestive of aspiration should be admitted for a minimum of 24 hours for observation. Patients who present after an episode of recreational HC use should also be observed for 4 to 6 hours. All patients in this category should be offered drug addiction counseling.[3]

KEY CONCEPTS

- The major toxic risk is with aspiration.
- Routine GI decontamination of HCs should be avoided.
- Symptoms can be delayed by several hours, so asymptomatic patients should be observed for an appropriate amount of time and given clear discharge instructions.
- Solvent-abusing patients are at risk for sudden cardiovascular collapse with exertion and should be kept calm and quiet.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 157 Inhaled Toxins

Lewis S. Nelson and Robert S. Hoffman

Airborne toxins typically produce local noxious effects on the airways and lungs. The respiratory tract can also serve as a portal of entry for systemic poisons. Inhalational exposure can be covert and indolent (as in occupational exposure to asbestos or urban exposure to photochemical smog) or fulminant and obvious. The circumstances and location of the exposure, the presence of combustion or odors, and the number and condition of victims assist in the diagnosis. Despite the array of possible toxic inhalants, identification of a specific inhalant is generally unnecessary because therapy is based primarily on the clinical manifestations (Table 157-1).

SIMPLE ASPHYXIANTS

Perspective

The vast majority of simple asphyxiations are workplace related and usually occur during the use of liquefied gas, while breathing through airline respirators or while working in confined spaces.[1] Since the advent of catalytic converters, most deaths from the intentional inhalation of automotive exhaust result from simple asphyxiation and not carbon monoxide poisoning.[2]

Principles of Disease

Most simple asphyxiants are inert and produce toxicity only by displacing oxygen and lowering the fraction of inspired oxygen (Fio_2). Exposed patients remain asymptomatic if the Fio_2 is normal. Carbon dioxide and nitrogen, both constituents of air, produce narcosis at elevated levels, but their predominant toxic effect is simple asphyxiation.

Clinical Features

Acute effects occur within minutes of onset of asphyxia and are the manifestations of hypoxia. A fall in the Fio_2 from normal, 0.21 (i.e., 21%), to 0.15 results in autonomic stimulation (e.g., tachycardia, tachypnea, and dyspnea) and cerebral hypoxia (e.g., ataxia, dizziness, incoordination, and confusion). Dyspnea is not an early finding because hypoxemia is not as potent a stimulus for this sensation as hypercarbia. Lethargy from cerebral edema is expected as Fio_2 falls below 0.1 (10%), and life probably cannot be sustained at an Fio_2 below 0.06 (6%).[3] Since removal from exposure terminates the hypoxia and results in clinical improvement, most patients present with resolving symptoms. However, failure to improve suggests complications of ischemia (e.g., seizures, coma, and cardiac arrest) and is associated with a poor prognosis.

Diagnostic Strategies and Differential Considerations

A consistent history, an appropriate spectrum of complaints, and rapid resolution on removal from exposure are generally sufficient to establish the diagnosis. Minimally symptomatic or asymptomatic patients do not require chest radiography or arterial blood gas (ABG) analysis. Definitive diagnosis ultimately requires scene investigation by a trained and suitably outfitted team. Determination of the exact nature of the gas is of limited clinical value but may have important public health implications. Since the presenting complaints offered by most exposed patients are nonspecific and protean (e.g., dizziness, syncope, and dyspnea), the differential diagnosis is extensive.

Management and Disposition

Management rarely requires specific therapy other than removal from exposure, supportive care, and possibly administration of supplemental oxygen. Neurologic injury or cardiorespiratory arrest should be managed with standard resuscitation protocols. Patients with manifestations of mild poisoning who recover after removal from the exposure can be observed briefly and discharged. Patients at risk for complications of hypoxia, such as those presenting with significant symptoms (e.g., coma) or with exacerbating medical conditions (e.g., cardiac disease), should be observed for the development or progression of posthypoxic complications.

KEY CONCEPTS

- Any gas can be an asphyxiant if it displaces sufficient oxygen from the breathable air.
- Appropriate therapy for asphyxiation includes removal from exposure, oxygen, and supportive care.

Table 157-1 Common Inhaled Toxins

INHALANT	SOURCE/USE	PREDOMINANT CLASS
Acrolein	Combustion	Irritant, highly soluble
Ammonia	Fertilizer, combustion	Irritant, highly soluble
Carbon dioxide	Fermentation, complete combustion, fire extinguisher	Simple asphyxiant; systemic effects
Carbon monoxide	Incomplete combustion, methylene chloride	Chemical asphyxiant
Chloramine	Mixed cleaning products (e.g., hypochlorite bleach and ammonia)	Irritant, highly soluble
Chlorine	Swimming pool disinfectant, cleaning products	Irritant, intermediate solubility
Chlorobenzylidenemalononitrile (CS)/chloroacetophenone (CN)	Tear gas (Mace)	Pharmacologic irritant
Hydrogen chloride	Tanning and electroplating industry	Irritant, highly soluble
Hydrogen cyanide	Combustion of plastics, acidification of cyanide salts	Chemical asphyxiant
Hydrogen fluoride	Hydrofluoric acid	Irritant, highly soluble; systemic effects
Hydrogen sulfide	Decaying organic matter, oil industry, mines, asphalt	Chemical asphyxiant; irritant, highly soluble
Methane	Natural gas, swamp gas	Simple asphyxiant
Methylbromide	Fumigant	Chemical asphyxiant
Nitrogen	Mines, scuba diving (nitrogen narcosis, decompression sickness)	Simple asphyxiant; systemic effects
Nitrous oxide	Inhalant of abuse, whipping cream, racing fuel booster	Simple asphyxiant
Noble gases (e.g., helium)	Industry, laboratories	Simple asphyxiant
Oxides of nitrogen	Silos, anesthetics, combustion	Irritant, intermediate solubility
Oxygen	Medical use, hyperbaric conditions	Irritant, free radical; systemic effects
Ozone	Electrostatic energy	Irritant, free radical
Phosgene	Combustion of chlorinated hydrocarbons	Irritant, poorly soluble
Phosphine	Hydration of aluminum or zinc phosphide (fumigants)	Chemical asphyxiant
Smoke (varying composition)	Combustion	Variable, but may include all classes
Sulfur dioxide	Photochemical smog (fossil fuels)	Irritant, highly soluble

■ PULMONARY IRRITANTS

Perspective

The pulmonary irritant gases are a large group of agents that produce a common toxicologic syndrome when inhaled in moderate concentrations. Although many of these agents can be found in the home, significant poisoning from consumer products is uncommon because of restrictions designed to reduce their toxicity. However, catastrophes such as the 1984 release of methyl isocyanate in Bhopal, India, which resulted in more than 2000 fatalities and 250,000 injuries, remain as an environmental risk. On a different scale, industrialization has increased ambient levels of sulfur dioxide, ozone, and oxides of nitrogen. These irritant gases frequently exacerbate chronic pulmonary disease.

Principles of Disease

Irritant gases dissolve in the respiratory tract mucus and alter the air-lung interface by invoking an irritant or inflammatory response. When dissolved, most of the gases produce an acid or alkaline product, but several generate oxygen-derived free radicals that produce direct cellular toxicity (Fig. 157-1). Pulmonary irritants are grouped by their water solubility (see Table 157-1).

Clinical Features

Highly water-soluble gases have their greatest impact on the mucous membranes of the eyes and upper airway. Exposure results in immediate irritation, with lacrimation, nasal burning, and cough. Although their pungent odors and rapid symptom onset tend to limit significant exposure, massive or prolonged exposure can result in life-threatening laryngeal edema, laryngospasm, bronchospasm, or acute lung injury (ALI), formerly known as "noncardiogenic pulmonary edema."[4] Poorly water-soluble gases do not readily irritate the mucous membranes, and some have pleasant odors (e.g., phosgene's odor is similar to that of hay). Since there are no immediate symptoms, prolonged breathing in the toxic environment allows the gas to reach the alveoli. Even moderate exposure causes irritation of

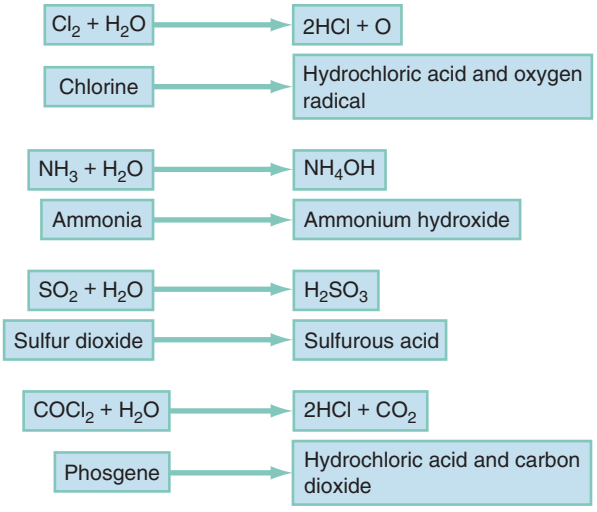


Figure 157-1. Sample reactions of pulmonary irritants reacting with water in the lung.

the lower airway, alveoli, and parenchyma and causes pulmonary endothelial injury after a 2- to 24-hour delay. Initial symptoms consistent with ALI may be mild, only to progress to overt respiratory failure and acute respiratory distress syndrome during the ensuing 24 to 36 hours.[5]

Gases with intermediate water solubility tend to produce clinical syndromes that are a composite of the other gases, depending on the extent of exposure. Massive exposure is most often associated with rapid onset of upper airway irritation and more moderate exposure with delayed onset of lower airway symptoms.[6]

Diagnostic Strategies and Differential Considerations

The evaluation of upper airway symptoms is usually done through physical examination but may require laryngoscopy. After exposure, swelling may occur rapidly or may be delayed, so a normal oropharyngeal or laryngeal evaluation may not exclude subsequent deterioration. Radiographic and laboratory studies have little role in the evaluation of upper airway symptoms.

Oxygenation and ventilation are assessed by serial chest auscultation and pulse oximetry, supplemented by chest radiography and ABGs in patients with cough, dyspnea, hypoxia, or abnormal findings on physical examination. No clinical tests can identify the specific irritant, and identification is not generally necessary for patient care, although knowing the causative agent may allow reduction of the observation period.

Bronchospasm, cough, chest tightness, and acute conjunctival irritation frequently follow allergen exposure, but the history generally suggests the diagnosis. ALI occurs after many physiologic insults, including trauma and sepsis, again highlighting the need for accurate history taking.

Management

Signs of upper airway dysfunction (e.g., hoarseness and stridor) mandate direct visualization of the larynx and immediate airway stabilization, if necessary. Given the potential rapidity of airway deterioration, early and frequent reassessment should be performed.

Bronchospasm generally responds to inhaled beta-adrenergic agonists; the role of ipratropium is not yet defined. Other than as a standard treatment for a comorbid condition, such as asthma, there is no clear indication for corticosteroids.[7]

Patients exposed to chlorine or hydrogen chloride gas receive symptomatic relief from nebulized 2% sodium bicarbonate solution.[6] Because the inflammatory cascade is not altered, however, the component of lung injury mediated by free radicals probably continues and causes delayed deterioration. Patients receiving inhalational bicarbonate therapy require extensive discharge instructions for signs and symptoms of pulmonary irritation or admission to the hospital.

Diagnosis of ALI or acute respiratory distress syndrome indicates the need for aggressive supportive care, including manipulations of the patient's airway pressures (e.g., continuous positive airway pressure and positive end-expiratory pressure). Exogenous surfactant and nitric oxide may have a beneficial role in toxin-induced acute respiratory distress syndrome, despite little support for its use in other forms of the syndrome.

Disposition

Patients exposed to highly water-soluble agents can be discharged if they are asymptomatic or improve with symptomatic therapy. After exposure to intermediate or poorly water-soluble agents, asymptomatic patients should be observed for increasing dyspnea for several hours before final disposition. Patients with substantial exposure to these agents or those in high-risk situations (e.g., underlying pulmonary disease, extremes of age, and poor follow-up) should be observed for 24 hours and may require hospitalization. All patients should be instructed to return if symptoms recur.

KEY CONCEPTS

- Highly water-soluble agents produce rapid irritation and predominantly upper respiratory tract symptoms such as bronchospasm.
- Poor water-soluble agents often produce delayed lower respiratory tract findings such as pulmonary edema.

SMOKE INHALATION

Perspective

Annually, 4000 people are injured or die in residential fires in the United States. Many of these casualties do not suffer serious cutaneous burns but, rather, die from smoke inhalation. This is a variant of irritant injury in which heated particulate matter and adsorbed toxins injure normal mucosa, similar to other irritant gases. In addition, carbon monoxide and cyanide are systemic toxins often discussed with the smoke inhalation syndrome because of their common origin.

Principles of Disease

Even at temperatures between 350° C and 500° C, air has such a low heat capacity that it rarely produces lower airway damage. However, the greater heat capacities of steam (approximately 4000 times that of air) or heated soot suspended in air (i.e., smoke) can transfer heat and cause injury deep within the respiratory tract.

The nature of the fuel determines the composition of its smoke, and because fires involve variable fuels and burning conditions, the character of fire smoke is almost always undefined to the clinician. Irritant toxins produced by the fire are adsorbed onto carbonaceous particles that deposit in the airways. The irritant substances damage the mucosa through mechanisms similar to those of the irritant gases, including generation of acids and free radical formation.

Clinical Features

Most smoke-associated morbidity and mortality relate to respiratory tract damage. Thermal and irritant-induced laryngeal injury may produce cough or stridor, but these findings are often delayed. Soot and irritant toxins in the airways can produce initial cough, dyspnea, and bronchospasm. Subsequently, a cascade of airway inflammation results in acute lung injury and failure of pulmonary gas exchange. The time between smoke exposure and the onset of clinical symptomatology is highly variable and dependent on the degree and nature of the exposure. Singed nasal hairs and soot in the sputum suggest substantial exposure but are neither sufficiently sensitive nor specific to be practical.[8]

Carbon monoxide (CO) inhalation should be routinely considered in these patients. Patients who are exposed to filtered or distant smoke (e.g., in a different room) or to relatively smokeless combustion (e.g., engine exhaust) inhale predomi-

nantly CO, cyanide, and metabolic poisons and do not sustain smoke exposure.

Diagnostic Strategies and Differential Considerations

Early death is caused by asphyxia, airway compromise, or metabolic poisoning (e.g., CO). Airway patency should be evaluated early, optimally with fiberoptic laryngoscopy. If evidence of significant airway exposure is present, such as carbonaceous sputum or hoarse voice, the airway should be examined by direct or fiberoptic laryngoscopy. Simply observing the patient for deterioration can result in airway compromise requiring rapid and, by then, very difficult airway intervention. Signs of alveolar filling or hyperinflation on chest radiography, abnormal flow-volume loop or diffusing capacity for CO on pulmonary function testing, or abnormal distribution and clearance of radiolabeled gas on ventilation scans can help predict lower airway injury.[9]

Metabolic acidosis, particularly when associated with a serum lactate level greater than 10 mmol/L, suggests concomitant cyanide poisoning.[10] Oxygenation should be assessed by co-oximetry because ABG analysis and pulse oximetry may be inaccurate in CO-poisoned patients.

With the obvious exposure history, the differential diagnosis is limited. Although it is often unclear whether inhalational injuries are thermal or irritant, the differentiation is clinically irrelevant. CO and cyanide should be considered in every case.

Management

The acute management of victims of smoke inhalation is identical to that of other irritant inhalational injuries. Rapid assessment of the airway and early intubation, as indicated, are critical because deterioration may be precipitous. Inhaled beta-adrenergic agonists are widely used but without evidence supporting their benefit. Optimal supportive care and maintenance of adequate oxygenation (e.g., suctioning and pulmonary toilet) are the most important aspects of care. Bronchoscopy with bronchoalveolar lavage is frequently recommended to clear debris and toxins from the distal airways. Corticosteroids, whether inhaled or systemic, are not indicated and are potentially harmful in patients with cutaneous burns.[11] Ibuprofen, antioxidants, exogenous surfactant, and high-frequency ventilation yield variably improved survival in experimental and clinical trials; none are generally considered as standard care. Antibiotics should be used only in patients with suspected infection.

Disposition

After the airway is examined and stabilized, patients with worrisome clinical findings (e.g., hoarseness and respiratory distress) and those with identifiers of substantial exposure (e.g., closed-space exposure and carbonaceous sputum) should be admitted to a critical care unit or transferred to a burn center. This decision will vary based on local resources, such as hospital capabilities or availability of a burn referral center.

KEY CONCEPTS

- Smoke inhalation injury is typically irritant in nature.
- Early visualization of the airway is essential. Early intubation prior to deterioration is critical if damage is present.
- Consider CO and cyanide in smoke inhalation.

CYANIDE AND HYDROGEN SULFIDE

Perspective

Hydrogen cyanide (prussic acid) is a gas with many commercial uses, particularly in synthetic fiber manufacture and fumigation. Hydrogen cyanide is occasionally noted to have the odor of bitter almonds. Cyanide in its salt form (e.g., sodium or potassium) is important in the metallurgic (e.g., jewelry) and photographic industries and is much safer to work with because of its low volatility. Cyanide salts do not have an odor under dry conditions. When cyanide salts are dissolved in water, hydrogen cyanide can leave the surface, particularly under acidic conditions. Cyanide is generated in vivo from precursors (cyanogens) such as amygdalin, found in apricot and other *Prunus* species pits, and from nitriles, a group of chemicals with many commercial uses.

Hydrogen sulfide poisoning most often occurs in petroleum refinery and sewage storage tank workers. Occasionally, well-intentioned would-be rescuers become victims, emphasizing the need for proper training and equipment. Hydrogen sulfide has a noxious odor similar to rotten eggs, which becomes unnoticeable with extremely high concentrations or prolonged exposure (*olfactory fatigue*).[12]

Principles of Disease

Gaseous cyanide is rapidly absorbed after inhalation and is immediately distributed to the oxygen-utilizing body tissues. Inhibition of oxidative metabolism by binding to complex IV of the electron transport chain within mitochondria occurs within seconds. The poisoned tissue rapidly depletes its adenosine triphosphate reserves and ceases to function (Fig. 157-2). Cyanide has no evident effect on other oxygen-binding enzyme systems, most notably hemoglobin. This is probably explained by the oxidation state of its iron moiety; cyanide binds only to oxidized iron (Fe^{3+}), whereas deoxyhemoglobin contains reduced iron (Fe^{2+}).

Hydrogen sulfide exerts its toxic effects both as a pulmonary irritant and as a cellular poison.[12] Its deadly metabolic effects are produced by a mechanism identical to that for cyanide poisoning. However, hydrogen sulfide's spontaneous dissociation from the mitochondria is rapid, allowing many patients to survive after brief exposure.

Clinical Features

Tissue hypoxia occurs within minutes, with the exact speed dependent on the route and nature of the exposure. Dysfunction of the heart and the central nervous system—the organ systems most sensitive to hypoxia—is characteristic of cyanide poisoning, manifesting as coma, seizures, dysrhythmias, and cardiovascular collapse. Metabolic acidosis develops due to diffuse cellular dysfunction and is associated with an elevated serum lactate. Cyanosis is not characteristic but can be present in profoundly poisoned patients. Given the extreme toxicity of cyanide, mild acute poisoning is uncommon. Patients with acute hydrogen sulfide poisoning have similar clinical manifestations, although many are recovering by the time of arrival in the emergency department.

Because cyanide and hydrogen sulfide prevent tissue extraction of oxygen from the blood, the oxygen content of venous blood remains high, approaching that of arterial blood. Clinically, this may appear as the "arterialization," or brightening, of venous blood to resemble arterial blood. A comparison of the measured venous (ideally but impractically mixed venous) and arterial oxygen contents may assist in the diagnosis of

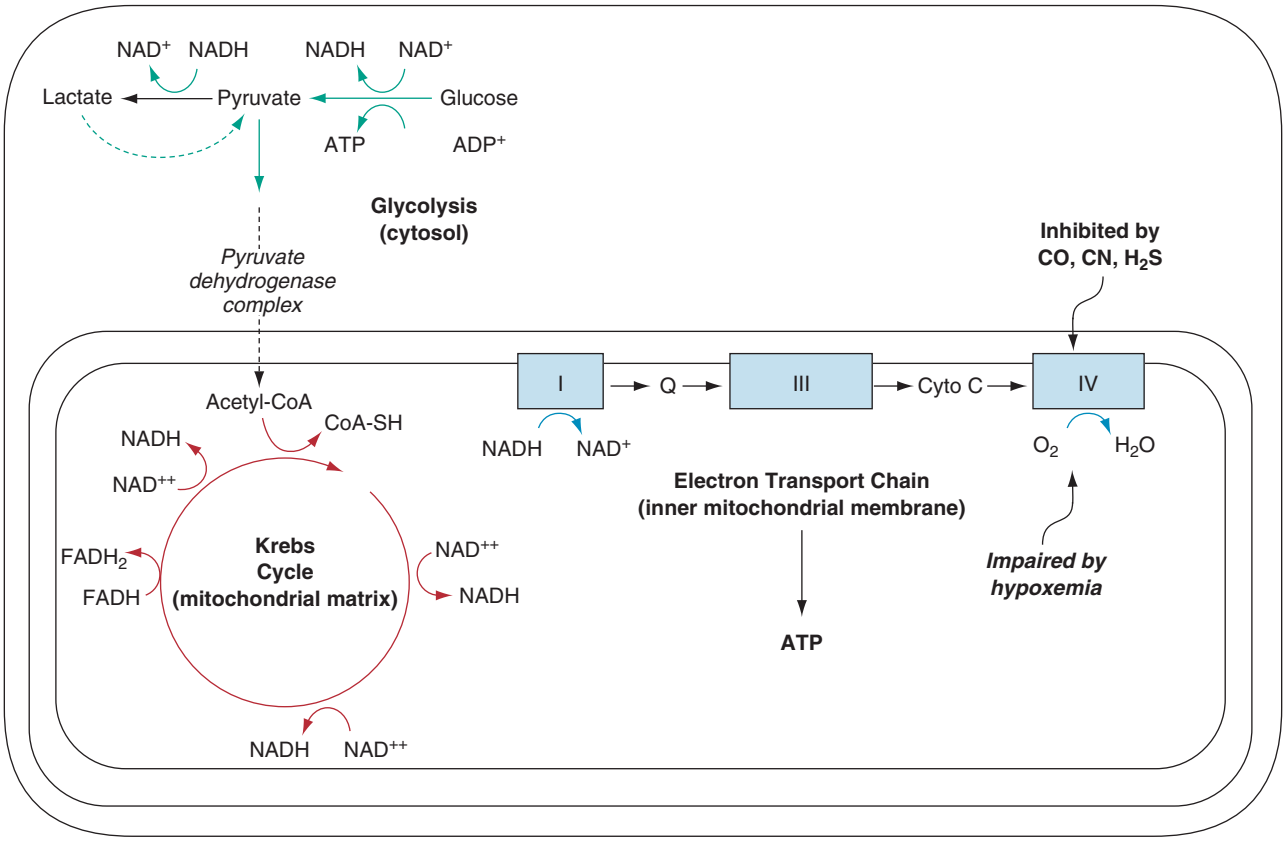


Figure 157-2. The complete metabolism of a molecule of glucose to energy is complex but occurs in two broad steps. The first step, anaerobic glycolysis, which occurs in the absence of oxygen, generates pyruvate, NADH, and adenosine triphosphate (ATP). Pyruvate then enters the Krebs cycle to create potential energy in the second step, through the reduction of NAD^+ to NADH and FADH to $FADH_2$. Similarly, fatty acid metabolism and protein metabolism produce $FADH_2$ and NADH, which also must be converted to ATP. These conversions occur in the mitochondrial membrane, where oxidative phosphorylation is linked to the electron transport chain, the last phase of which involves the transfer of electrons to molecular oxygen to form water. Cyanide (CN), hydrogen sulfide (H_2S), and carbon monoxide (CO) bind to and inhibit the last step, the Fe^{3+}-containing cytochrome aa_3 in complex IV, preventing further oxidation of NADH. This in turn hinders the Krebs cycle because the required regeneration of NAD^+ does not occur, and glucose metabolism is forced to end at pyruvate. For energy production to continue, NADH donates its electrons to pyruvate, creating lactate, and sufficient NAD^+ is regenerated for glycolysis to progress. Ultimately, energy failure and end-organ damage occur. CoA, coenzyme A; FAD, flavin adenine dinucleotide; NAD, nicotinamide adenine dinucleotide.

cyanide poisoning.[13] A low arterial-venous oxygen difference is suggestive of cyanide poisoning.

Patients surviving cyanide or hydrogen sulfide poisoning may have persistent or delayed-onset neurologic syndromes identical to those noted in patients with CO poisoning or cardiac arrest.[14]

Diagnostic Strategies and Differential Considerations

Obtaining the results of a serum cyanide level generally requires too much time for these to be of use in the emergency department, but these results can be useful for confirmation and documentation purposes. Technology exists for immediate cyanide determination but is not widely available. Rapid tests for hydrogen sulfide are not available.

In practice, the diagnosis must be based on the circumstances of exposure and a corroborative physical examination. Pulse oximetry and ABG analysis are accurate in cases of isolated cyanide or hydrogen sulfide poisoning. An increased anion gap metabolic acidosis and elevated serum lactate level are usually present. A lactate level greater than 10 mmol/L in a fire victim is highly predictive of cyanide poisoning.[9] An elevated carboxyhemoglobin concentration in a fire victim may suggest concomitant cyanide poisoning but may take too long to obtain and may falsely exclude patients exposed to combustion products of substances that generate only cyanide (e.g., certain plastics).

Rapid cardiovascular collapse, ventricular dysrhythmias, and seizures are typical and, in a fire victim, should suggest cyanide poisoning. However, each of these findings is also consistent with severe CO poisoning.[10] This differentiation may be important given the implication of the treatment for cyanide poisoning.

Management

Patients exposed to cellular poisons, including hydrogen cyanide and hydrogen sulfide, require individualized and specific therapy. The diagnosis can usually not be confirmed, and therapy is almost always empirical but should not be delayed in patients with suspected acute cyanide poisoning. In uncertain situations, antidotal therapy should be administered immediately.

Hydrogen Cyanide

The accepted goal of therapy is to reactivate the cytochrome oxidase system by providing an alternative binding site for the cyanide ion. There are two types of antidotal therapy for

cyanide. The cyanide antidote kit produces a high-affinity source of ferric ions (Fe^{3+}) for cyanide to bind. The kit has three components, and although the best results are likely attained when the entire kit is used, this may be impractical or dangerous, particularly for nonhospital providers. Because animal models and clinical evidence in humans demonstrate that sodium thiosulfate alone (the "third" part of the kit), in combination with oxygen and sodium bicarbonate, offers substantial protection, this should be the initial therapy administered by paramedics and during mass poisoning events. At all times, appropriate resuscitation measures including high flow oxygen and intravenous fluids should be provided.

Methemoglobin (MetHb) formation is the goal of the first two parts of the kit. Inhaled amyl nitrite or intravenous sodium nitrite are both effective, but the former should only be administered in patients for whom intravenous access cannot be obtained. Caution should be taken to minimize the provider's exposure to the volatile amyl nitrite because dizziness, hypotension, or syncope may occur. The dose of sodium nitrite for a previously healthy adult is 300 mg (10 mL of a 3% solution) given over 2 to 4 minutes, and dosing instructions for anemic patients and children are supplied with the kit. Sodium nitrite is a vasodilator, and hypotension may complicate a rapid infusion. Cyanide has a high affinity for MetHb and readily leaves cytochrome oxidase to form cyanomethemoglobin. Both free serum cyanide and cyanomethemoglobin are converted by sulfur transferase (*rhodanese*) to thiocyanate, which is renally eliminated. Since the rate of rhodanese function increases with the availability of sulfur donor, the third part of the antidote kit is the sulfur-containing compound sodium thiosulfate. The adult dose is 12.5 g intravenously (IV), which is provided as 50 mL of a 25% solution (1.65 mL/kg of 25% sodium thiosulfate in children). Generally, few, if any, adverse effects are associated with proper doses. The nitrite components of the cyanide antidote kit should be avoided in fire victims with possible simultaneous CO and cyanide poisoning. Since both CO and methemoglobin reduce oxygen delivery to the tissues, complications may arise. The use of the thiosulfate component alone in this subset of patients is recommended.

Hydroxocobalamin is a newer antidotal therapy that takes advantage of the high affinity of cobalt for cyanide. Upon binding cyanide, cyanocobalamin, or vitamin B_{12}, is formed. This antidote has been used for years in Europe and is rapidly gaining acceptance in the United States, including for use in mass poisonings. However, although it is approved by the Food and Drug Administration for treatment of known or suspected cyanide poisoning, its specific clinical role has not been fully explored.[15] The initial dose is 5 g IV over 15 minutes for adults and 70 mg/kg IV in children, up to an adult dose.[16] The known adverse effects are mild and include slight hypertension in those not cyanide poisoned and a bright red discoloration of the patient's skin. Due to the red drug's color, interference with certain spectrophotometric laboratory tests, including carboxyhemoglobin and possibly serum lactate, may prove consequential.[16] Blood samples should be obtained prior to the administration of the first dose of hydroxocobalamin.

There are insufficient clinical data to support the use of one cyanide antidote over the other. However, because hydroxocobalamin does not alter oxygen delivery, it should be safer than the nitrite-based antidote kit empirically in a fire victim. Direct comparison to thiosulfate alone has not been, and likely will never be, performed.[17]

Hyperbaric oxygen therapy has been advocated but is of no proven benefit and is not routinely indicated. In selected cases, when immediately available, its apparent value may lie in its ability to superoxygenate plasma and tissues, thus permitting higher levels of methemoglobinemia, particularly when CO poisoning is also present.

Hydrogen Sulfide

Since the bond between hydrogen sulfide and cytochrome oxidase is rapidly reversible, removal from exposure and standard resuscitative techniques are usually sufficient to reverse hydrogen sulfide toxicity. Use of the nitrite portion of the cyanide antidote kit is suggested to create MetHb for patients with severe or prolonged toxicity.[12] Sodium thiosulfate is unnecessary because hydrogen sulfide is not detoxified by rhodanese. There is no role for hyperbaric oxygen therapy in cases of hydrogen sulfide toxicity.

Disposition

All patients with symptomatic cyanide or hydrogen sulfide poisoning should be admitted to a critical care unit and observed for complications of tissue hypoxia. All patients should be followed for delayed neuropsychiatric symptoms.

KEY CONCEPTS

- An antidote for cyanide poisoning must be administered early.
- The sodium thiosulfate portion of the cyanide antidote kit is safe for empirical administration in any case in which cyanide poisoning is considered possible.
- Hydroxocobalamin is a safe and effective antidote, although its exact role in empirical therapy of fire victims is unclear.
- Patients with hydrogen sulfide poisoning generally respond to removal from exposure and ventilatory support.

CARBON MONOXIDE

Perspective

Carbon monoxide is the most common cause of acute poisoning death in developed nations and the most common cause of fire-related death.[18] CO is generated through incomplete combustion of virtually all carbon-containing products. Structure fires (e.g., wood), clogged vents for home heating units (e.g., methane), and use of gasoline-powered generators indoors are examples of the myriad means through which patients are poisoned by CO. Appropriate public health authorities (e.g., fire department and Department of Health officials) should be informed immediately about any potential public health risks that are identified during the care of a CO-exposed patient.

Principles of Disease

Carbon monoxide interacts with deoxyhemoglobin to form carboxyhemoglobin (COHb), which cannot carry oxygen. Hemoglobin binds CO tightly and forms a complex that is only slowly reversible. This allows the exposed individual to accumulate CO, even with exposure to low ambient concentrations. Although hemoglobin binding is the classically described mechanism of CO poisoning, it is relevant only to patients who are profoundly CO poisoned because a simple reduction in oxygen-carrying capacity due, for example, to anemia would not be expected to result in similar symptoms. However,

relevant to the management of pregnant patients, the fetus is always relatively hypoxic compared to the mother, and fetal hemoglobin binds CO better than adult hemoglobin.[19] In muscle, CO binds myoglobin, preventing its normal function, and this likely explains the development of atraumatic rhabdomyolysis.

Most important, CO affects cellular oxygen utilization at the tissue level. CO, similarly to cyanide, inhibits the final cytochrome complex involved in mitochondrial oxidative phosphorylation. This results in a switch to anaerobic metabolism and, ultimately, in cellular death.

Delayed-onset neurologic complications may be a manifestation of the hypoxic insult, although reperfusion injury and lipid peroxidation related to platelet-induced nitric oxide release may play a significant role.[20] By altering the platelet-associated nitric oxide cycle, the microvascular endothelium of the central nervous system undergoes free radical-mediated injury, resulting in localized inflammation and dysfunction. Animal models and human reports suggest that loss of consciousness during CO exposure may be necessary, and is certainly a risk factor, for the development of delayed neurologic sequelae.[21]

Clinical Features

Severe CO toxicity and cyanide poisoning have identical clinical presentations of asphxia: altered mental status, including coma and seizures; extremely abnormal vital signs, including hypotension and cardiac arrest; and metabolic acidosis. Unlike cyanide poisoning, however, mild CO poisoning occurs frequently, with headache, nausea, vomiting, dizziness, myalgia, or confusion as common presenting complaints. The neurologic assessment in these patients may yield normal findings or may demonstrate focal findings or subtle perceptual abnormalities. The often-touted cherry-red skin color in patients with cyanide or CO poisoning is a postmortem finding and is not noted in living patients.

Delayed neurologic sequelae are a well-documented phenomenon after CO exposure, although the frequency varies from 12 to 50%, depending on the definition and the sensitivity of the test used for their detection.[22] Patients develop a variety of neurologic abnormalities after an asymptomatic period ranging from 2 to 40 days.[21] The delayed neurologic effects can be divided into those with readily identifiable neurologic syndromes (e.g., focal deficits and seizures) and those with primarily psychiatric or cognitive findings (e.g., apathy and memory deficits). Although the latter form of delayed neurologic sequelae requires formal neuropsychiatric testing for detection, the impact of these abnormalities on the patient's daily function may be significant. Risk factors that predict the development of delayed neurologic sequelae include age and loss of consciousness. Since the majority of CO poisoned patients reaching the emergency department survive, prevention of delayed neurologic and neuropsychiatric sequelae is the predominant goal of therapy.

Diagnostic Strategies and Differential Considerations

Suspicion of CO poisoning relies on the history and physical examination findings. Co-oximetry, an inexpensive and readily available spectrophotometric laboratory method that can distinguish between the normal hemoglobins and COHb (and MetHb), confirms exposure to CO. Other laboratory tests only exclude other diagnoses. Severity of poisoning may not correlate with COHb levels; prolonged exposure to low levels can result in fatality with low COHb, but a brief, high-concentration exposure can produce a high COHb level with minimal symptoms.

The ABG measurement cannot be used as a diagnostic test for CO poisoning other than to identify the presence of a metabolic acidosis and a normal partial pressure of oxygen (Po_2). CO does not affect the amount of oxygen dissolved in the blood. Because the Po_2, a measure of dissolved oxygen, is normal in patients with CO poisoning, the calculated oxygen saturation will be normal even in the presence of substantial CO poisoning. Most pulse oximeters are inadequate for the detection of CO poisoning because COHb is essentially misinterpreted as oxyhemoglobin. Newer pulse oximeters (pulse co-oximeters) are capable of detecting COHb, as well as methemoglobinemia, but are not yet widely available.

Mild to moderate CO poisoning is a difficult diagnosis to establish clinically, and patients are easily misdiagnosed as having a benign headache syndrome or viral illness. CO poisoning should be suspected in every patient with persistent or recurrent headache, especially if a group of people have similar symptoms or if the headache improves soon after the person leaves an exposure site.

Patients with severe CO poisoning may present with coma or cardiovascular collapse, both of which have a broad toxicologic, metabolic, infectious, medical, and traumatic differential diagnosis. Many diagnoses are excluded by the medical history, physical examination, or standard laboratory testing. Given the relatively protean manifestations of CO poisoning, when seriously considered, it should be excluded by co-oximetry of an arterial or venous blood sample or pulse co-oximetry. Misdiagnosis can be catastrophic, particularly if the patient returns to the poisoned environment.

Management

Treatment begins with oxygen therapy, which serves two purposes. First, the half-life of COHb is inversely related to the Po_2; it can be reduced from approximately 5 hours on room air to 1 hour by providing supplemental 100% oxygen. Hyperbaric oxygen therapy (HBOT) further reduces the half-life to approximately 30 minutes. Altering the kinetics of COHb is only applicable to patients with extremely elevated COHb levels (e.g., >50%). Even then, few patients can be treated rapidly enough that enhanced CO clearance by HBOT would be lifesaving. Second, a sufficient Po_2 can be achieved with HBOT to sustain life in the absence of adequately functioning hemoglobin, but this is also relevant only to situations in which the COHb is extremely elevated. Thus, the primary indication for hyperbaric oxygen is to prevent delayed neurologic sequelae.

The controversy regarding the clinical utility of HBOT is largely related to the fact that a benefit is not identified immediately (as with life and death) but, rather, requires close follow-up and sophisticated testing. Although the literature base on which to make decisions is poor, several evidence-based reviews have suggested a limited role for HBOT, although this conclusion is disputed.[23-25] HBOT is associated with a reduction in the rate of delayed neurologic sequelae from approximately 12% without HBOT to less than 1%.[21] When HBOT administration is delayed more than 6 hours after exposure, its efficacy appears to decrease,[26] suggesting the need for rapid decision making. Similarly, evidence suggests that HBOT positively affects the development of the neuropsychiatric delayed neurologic sequelae after CO poisoning.[26,27] A randomized, double-blind study found that HBOT was superior to normobaric oxygen therapy (NBOT) at reducing the incidence of neuropsychiatric delayed neurologic sequelae at both 6 weeks and 1 year postpoisoning.[27]

However, it is not universally accepted that HBOT is useful in preventing the development of neuropsychiatric delayed neurologic sequelae. An earlier Australian study that compared HBOT to NBOT suggested that there was no benefit of HBOT on the development of neuropsychiatric delayed neurologic sequelae.[28] In this study, however, the majority of patients were suicidal and presumably depressed, a condition that interferes with performance on the neuropsychiatric testing needed to differentiate the two groups of patients. In addition to other methodologic flaws in the study (e.g., mean delay to hyperbaric oxygen of more than 6 hours, atypical hyperbaric regimen, unusual randomization protocol, and limited neuropsychiatric testing), the alternative to HBOT suggested by this study is continuous 100% NBOT for 3 or 6 days, which is unlikely to be accepted by both patients and the medical community.

Given the implications of poor tissue oxygenation due to the presence of COHb, many practitioners suggest that any patient with a neurologic abnormality or cardiovascular instability (e.g., syncope, altered mental status, myocardial ischemia, and dysrhythmias) is a candidate for HBOT.[29,30] This consideration should be relatively independent of the patient's COHb level, which correlates only weakly with toxicity. Patients with prolonged low-level exposure develop a "soaking" phenomenon, in which extremely high tissue concentrations of CO occur without the patient developing very high COHb levels.

In addition to using HBOT in those patients with obvious signs of tissue hypoxia, some institutions have set an arbitrary conservative COHb level of 25% at which asymptomatic or minimally symptomatic patients will be referred for HBOT. This seems appropriate, although some institutions use COHb levels of 40%, and others refrain from specifying a number. Special consideration is given for pregnancy because of the relative hypoxia of the fetus. Because fetal CO poisoning is associated with dysfunction and death, and HBOT appears to be safe in pregnancy, many institutions have lowered the standard for initiating hyperbaric oxygen therapy in a pregnant patient to a COHb level of 15%.[31]

Further study is still needed to define the optimal duration, pressure, and frequency as well as the cost-benefit and risk-benefit relationships of hyperbaric oxygen therapy. At this time, discussion with a regional HBOT center or poison control center is advisable. Patients with elevated COHb levels who do not require HBOT should be treated with normobaric oxygen therapy delivered by a tight-fitting non-rebreather face mask, at least until the symptoms resolve and the COHb levels fall. The total duration of such therapy is undefined, and although 3 days was suggested in one study,[28] most mildly CO-poisoned patients probably require no more than 6 hours of therapy.[32]

Simultaneous Carbon Monoxide and Cyanide Poisoning (Fire Victim)

Concurrent toxicity from CO and cyanide is widely reported and a major factor in the mortality associated with exposure to fire smoke.[10,33] Smoke inhalation victims who present with coma and metabolic acidosis can have severe CO poisoning, cyanide poisoning, or both. Nitrite-induced methemoglobinemia, which further reduces the tissue oxygen delivery, may be detrimental to patients with elevated COHb levels.

Sodium thiosulfate, administered without nitrites,[34] or hydroxocobalamin should be given to all smoke inhalation victims with coma, hypotension, acidosis, or cardiovascular collapse in whom cyanide poisoning cannot be rapidly excluded. If the COHb level is known to be low and the patient has persistent acidosis or hemodynamic instability, the complete cyanide antidote kit, including the nitrites, can be administered. Patients with high COHb levels undergoing therapy in a hyperbaric oxygen chamber can receive nitrite therapy while pressurized with little concern of decreasing the oxygen-carrying capacity. Alternatively, hydroxocobalamin, with or without sodium thiosulfate, can be administered in either of these last two situations.

Disposition

The decision to transfer a patient to a hyperbaric facility must consider the time delay to therapy, patient issues (e.g., burns and age), and potential transport-related complications.[35] At a minimum, prolonged NBOT should be administered, although the benefit of this remains undefined. Admission decisions should be based on the patient's clinical condition. All patients exposed to CO require close follow-up to evaluate for delayed neurologic sequelae.

KEY CONCEPTS

- Carbon monoxide poisoning is common and has important public health implications.
- Carbon monoxide poisoning can be obscure and should be corroborated with co-oximetry.
- Because the role of hyperbaric oxygen therapy in CO poisoning is controversial, consultation with a hyperbaric oxygen facility or poison control system may be helpful in cases of significant toxicity.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 158 Lithium

Oliver Hung

PERSPECTIVE

Lithium has been used as a medicinal agent since the mid-1800s, when lithium salts were popularized as a treatment for gout (lithium carbonate and lithium citrate), a sedative for manic patients (lithium bromide), and as a treatment for epilepsy (lithium bromide). In 1929, the soft drink "7 Up," whose original name was "Bib-Label Lithiated Lemon-Lime Soda," included lithium citrate as an ingredient (until 1950) and was marketed as a patent medicine to cure hangovers. In the late 1940s, lithium chloride was used as a salt substitute for patients requiring low-salt diets. However, in 1949, the Food and Drug Administration (FDA) banned the use of lithium because of several patient deaths attributed to lithium toxicity. Ironically, in the same year, a study by the Australian psychiatrist John Cade convincingly demonstrated the efficacy of lithium for the treatment of bipolar disorder. Use of lithium was prohibited in the United States until 1970, when the FDA reversed the ban on lithium and approved its use as a treatment for bipolar disorder. Despite the introduction of newer and safer medications, lithium is established as the most effective long-term treatment to prevent recurrences of mania and bipolar disorder.[1] Lithium treatment also appears to substantially decrease the risk of suicide and suicide attempts.[1] According to U.S. poison center data, in 2006 there were 5674 reported lithium exposures with 149 major outcomes (life-threatening or significant residual disability) and 7 deaths.[2]

PRINCIPLES OF DISEASE

The precise mechanism of action of lithium as a mood-stabilizing agent is not fully understood. Lithium increases serotonin release and serotonin receptor sensitivity, and it also inhibits norepinephrine and dopamine release from nerve terminals. Postulated mechanisms have begun to focus on cellular pathways, including intracellular signaling, neuronal plasticity/neurogenesis, and gene expression. These mechanisms include the inositol depletion hypothesis, glycogen synthase kinase-3 inhibition, and the arachidonic acid cascade hypothesis. In the inositol depletion hypothesis, lithium inhibits inositol monophosphatase, which depletes brain cell myoinositol and dampens phosphoinositide signaling.[3-5] Lithium's neuroprotective properties are attributed to its ability to inhibit glycogen synthase kinase-3. Finally, in the arachidonic cascade hypothesis, lithium reduces the amount of arachidonic acid recycled in brain cells. Bipolar disorder is thought to result from a hyperactive arachidonic acid cellular signaling cascade.

Immediate-release lithium is rapidly absorbed from the gastrointestinal tract. Peak plasma concentrations occur 0.5 to 3 hours after a single oral dose, with complete absorption within 8 hours. Sustained-release lithium preparations exhibit variable absorption, with a delayed peak of 6 to 12 hours. Ingestion of a single 300-mg lithium carbonate tablet increases the serum lithium level by approximately 0.1 mEq/L. After absorption, lithium distribution follows an open two-compartment model. Lithium is initially distributed in the extracellular fluid and then gradually redistributes in various tissue compartments (preferentially the brain, kidney, thyroid, and bone). Brain lithium distribution may take up to 24 hours following absorption. Approximately 95% of a single dose of lithium is excreted by the kidney. Lithium is freely filtered by the glomerulus, with 80% of filtered lithium reabsorbed by the proximal renal tubule. Lithium renal elimination is increased by factors that decrease glomerular filtration rate (e.g., dehydration) or sodium concentration (e.g., hyponatremia). Medications such as nonsteroidal anti-inflammatory drugs, diuretics, and angiotensin-converting enzyme inhibitors may increase lithium levels by interfering with renal lithium elimination.

Chronic lithium therapy is also associated with the development of nephrogenic diabetes insipidus, resulting in hyponatremia and dehydration, which may increase lithium levels. Fluid resuscitation and lithium cessation are usually sufficient in permanently reversing the effects of diabetes insipidus. Lithium also inhibits the synthesis and release of thyroid hormone. Hypothyroidism is a rare complication (5% of all patients) of chronic lithium therapy. Finally, lithium causes a temporary leukocytosis and was once investigated as a potential treatment for chemotherapy-induced neutropenia.

CLINICAL FEATURES

Clinical manifestations of lithium poisoning can be classified based on whether the poisoning is due to acute toxicity, chronic toxicity, or acute-on-chronic toxicity.

Acute toxicity represents an overdose of lithium in a patient without any lithium body stores. Gastrointestinal symptoms such as nausea, vomiting, and diarrhea are the earliest and most common presentation of toxicity. Lithium also causes electrocardiographic effects, including bradycardia, T wave flattening or inversion, and QT prolongation. Fortunately,

significant cardiac dysrhythmias following lithium poisoning are rare. Neurotoxicity is delayed because of the time required for lithium to distribute to the brain.

In chronic toxicity, the patient, who takes lithium regularly and has significant lithium body stores, develops toxicity because of increased absorption or decreased lithium renal elimination (e.g., dehydration, drug interactions, and renal insufficiency). Neurotoxicity is the predominant presentation. Mild toxicity may manifest as a worsening tremor. Progressively more severe signs of neurotoxicity include drowsiness, hyper-reflexia, confusion, clonus, coma, seizures, and extrapyramidal signs. The syndrome of irreversible lithium-effectuated neurotoxicity (SILENT) has been described and is defined as persistent neurologic dysfunction attributed to lithium toxicity persisting 2 months after lithium cessation.[6] Typical SILENT presentations include cerebellar dysfunction, persistent extrapyramidal syndromes, brainstem dysfunction, and dementia. The presence of fever is also considered a poor prognostic sign and possible precipitant of SILENT.[6]

Finally, in acute-on-chronic toxicity, a patient who is already taking lithium ingests an additional quantity of lithium in excess of the prescribed dosage. The clinical presentation is signs and symptoms of both acute and chronic toxicity, including gastrointestinal and neurologic symptoms.

Lithium use has also been implicated in the development of both neuroleptic malignant syndrome and serotonin syndrome. Serotonin syndrome usually results from the combination of serotonergic agents. Consequently, lithium should not be used in conjunction with serotonin agonists (e.g., monoamine oxidase inhibitor, selective serotonin reuptake inhibitors, dextromethorphan, buspirone, and meperidine). Lithium use is also considered a risk factor for neuroleptic malignant syndrome. The signs and symptoms of neuroleptic malignant syndrome, serotonin syndrome, and lithium toxicity are similar, with considerable overlap of symptoms (fever and neurologic deterioration). Fortunately, the initial treatment of lithium toxicity, serotonin syndrome, and neuroleptic malignant syndrome is the same and includes supportive care and discontinuation of the involved medication(s).

DIAGNOSTIC STRATEGIES

Since the signs and symptoms of lithium toxicity are nonspecific and are often delayed following acute overdose, a serum lithium level should be obtained in any patient suspected of acute or chronic lithium poisoning. Obtaining serum electrolytes may be helpful in patient management. Increased serum sodium may indicate lithium-induced nephrogenic diabetes insipidus, whereas the serum creatinine level may help determine whether extracorporeal removal is required. Thyroid functions should also be obtained if clinical thyroid disease is suspected. Finally, obtaining an electrocardiogram and a serum acetaminophen level should be considered for acute, intentional ingestions to evaluate for the presence of co-ingestants.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for lithium poisoning is extremely varied because of its nonspecific signs and symptoms. Consideration for alternate diagnosis can be based on whether the clinical presentation represents acute versus chronic lithium poisoning. Acute lithium poisoning typically presents with initial, prominent gastrointestinal symptoms that are similar to those of other drug overdoses. These include other metal salts (e.g., iron, arsenic, or mercury), salicylates, cardioactive steroids (e.g., digoxin), and theophylline. Chronic lithium poisoning, with its predominant neurologic symptoms, should raise concern for other neurologic conditions or central nervous system toxins, including central nervous system depressants, drugs that cause seizures, hypoglycemic agents, carbon monoxide, neuroleptic malignant syndrome, and serotonin syndrome.

MANAGEMENT

There is no antidote for lithium poisoning; consequently, the management of lithium toxicity includes selected gastrointestinal decontamination (for acute overdose only), techniques to increase the elimination of lithium (renal and extracorporeal) from the body, and supportive care.

Gastrointestinal Decontamination

Both oral activated charcoal and gastric lavage are ineffective in the management of lithium poisoning. Lithium is poorly adsorbed by activated charcoal.[7] Gastric lavage is ineffective for several reasons. The immediate-release lithium preparations are usually absorbed from the gastrointestinal tract too quickly for lavage or whole bowel irrigation to be effective. In addition, lithium-induced emesis would be expected to occur very quickly following an ingestion of immediate-release lithium, thereby limiting its own gastrointestinal absorption and making any attempt at gastric lavage potentially hazardous. Finally, sustained-release lithium tablets are too large to fit through an orogastric tube.

Whole-bowel irrigation with polyethylene glycol is the recommended gastrointestinal decontamination treatment for any overdose of sustained-release lithium preparation. It is the only form of decontamination that has demonstrated any efficacy in safely eliminating lithium in humans.[8] The recommended rate of administration is 2 L/hr in adults and 500 mL/hr in children via gastric tube until the rectal effluent is clear (4–6 hours).

Sodium polystyrene sulfonate (Kayexalate), a cationic exchange resin used to treat hyperkalemia, has been investigated as a gastrointestinal decontamination method for lithium poisoning. In animal models and in two human case reports (one volunteer and one overdose patient), administration of oral sodium polystyrene sulfonate (30 g every 6 hours for five doses) has been demonstrated to be effective in decreasing serum lithium levels.[7,9] However, it also significantly lowers serum potassium concentrations.[10,11] Because of limited patient experience and concerns about life-threatening hypokalemia, sodium polystyrene sulfonate is not recommended.

Techniques to Increase Elimination

Lithium can be removed by increasing renal elimination as well as by extracorporeal methods.

Fluid resuscitation with sodium chloride (normal saline) to correct hyponatremia and dehydration is the recommended method to maximize renal lithium elimination. Unless there are contraindications to aggressive volume expansion (e.g., renal insufficiency, congestive heart failure), administration of intravenous normal saline at a twice maintenance rate is recommended. Forced diuresis is not recommended because of the risk of causing hypernatremia and because of its variability in consistently increasing renal lithium elimination. Urinary alkalinization by intravenous sodium bicarbonate is also not recommended because it does not significantly increase renal lithium elimination compared with volume expansion by sodium chloride (normal saline) and because of the additional risk of hypokalemia and alkalemia.

The most effective technique to eliminate lithium from the body is hemodialysis. Endogenous lithium renal clearance is approximately 15 to 20 mL/min, whereas hemodialysis lithium clearance is approximately 100 mL/min.[12] Although hemodialysis substantially increases lithium elimination, its ability to decrease mortality or treat/prevent the syndrome of irreversible lithium-effectuated neurotoxicity has never been demonstrated.[12-15] Consequently, there is no evidence-based consensus to define the indications for hemodialysis for lithium poisoning. Hemodialysis is primarily used for clinical deterioration (e.g., seizures and decreased level of consciousness), inadequate endogenous lithium clearance (e.g., renal insufficiency), or inability to enhance renal elimination through volume expansion (e.g., congestive heart failure, cirrhosis, pancreatitis, and sepsis). Although it may not correlate directly with toxicity, hemodialysis is recommended for a serum lithium level greater than 4.0 mEq/L for acute toxicity and greater than 2.5 mEq/L for chronic toxicity. Continuous renal replacement therapies (e.g., continuous venovenous hemodialysis) have also been successfully utilized to treat lithium-poisoned patients.[16] Although their clearance rates are inferior to hemodialysis, they can be used in place of hemodialysis in hemodynamically unstable patient as well as in conjunction with hemodialysis in stable patients.

Because of the two-compartment model of lithium distribution in the body, serial lithium levels need to be monitored for increases after treatment due to redistribution from intracellular stores. In chronic lithium toxicity, rising lithium levels occur following hemodialysis, necessitating multiple hemodialysis treatments.

DISPOSITION

Hospital admission should be considered for any patient with suspected lithium poisoning with abnormal neurologic signs (e.g., hyper-reflexia, clonus, altered sensorium, or seizure) or any asymptomatic patient after acute overdose with increasing lithium levels. In addition, hospitalization at a center with emergency dialysis capability is preferable.

KEY CONCEPTS

- Lithium toxicity presents with nonspecific signs and symptoms.
- Consider lithium poisoning in any patient who is taking lithium and presents with an altered sensorium.
- Medications that impair renal function or environmental factors that lead to dehydration increase the risk of lithium toxicity.
- Early decontamination with whole-bowel irrigation and vigorous volume replacement are important in managing acute lithium toxicity.
- Consider hemodialysis in patients with severe signs and symptoms of neurotoxicity, inadequate renal function or inability to tolerate volume expansion (e.g., renal insufficiency and congestive heart failure), or a serum lithium level greater than 4.0 mEq/L in acute poisoning or greater than 2.5 mEq/L in chronic poisoning.
- Lithium has numerous drug interactions that may lead to adverse effects, including increased risk for lithium toxicity, increased lithium toxic effects, neuroleptic malignant syndrome, and serotonin syndrome.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 159 Antipsychotics

Mary A. Wittler and Eric J. Lavonas

PERSPECTIVE

The first antipsychotic, chlorpromazine, was used for the treatment of psychosis in France in 1951 and in the United States in 1954. Antipsychotic use has expanded significantly since then. The term *neuroleptic*, historically synonymous with antipsychotic medication due to the high degree of sedation produced by earlier drugs, is no longer appropriate because newer agents cause little sedation. The term *antipsychotic* is now preferred.[1] In 2006, U.S. poison control centers reported more than 4500 exposures to phenothiazines and 41,000 exposures to atypical antipsychotics, resulting in 1 and 11 deaths, respectively.[2]

PRINCIPLES OF DISEASE

Antipsychotic medications are used to treat agitation and psychosis caused by schizophrenia, mania, acute idiopathic psychosis, alcohol withdrawal hallucinosis, and Alzheimer's disease.[1] The antipsychotic medications are often divided into three broad categories based on their receptor profiles, clinical effects, and adverse effects (Table 159-1). All antipsychotic medications effectively treat the *positive symptoms* of psychotic disorders; they reduce hallucinations, control agitation, and aid in restructuring disordered thinking. In general, the low-potency neuroleptics are the most sedating at usual doses. Movement disorders, including extrapyramidal symptoms (EPS) and tardive dyskinesia (TD), are significant problems with both low-potency and high-potency neuroleptics. In addition to producing less sedation and fewer movement disorders, the atypical antipsychotic agents assist with the *negative symptoms* of psychotic disorders, such as flat affect, avolition, social withdrawal, and impoverished thought and speech. Although neuroleptic malignant syndrome (NMS) has occurred with all agents, it occurs least with the atypical antipsychotics.

ANATOMY AND PHYSIOLOGY

Antipsychotic drugs block dopamine receptors in several areas of the brain, including the cerebral cortex, basal ganglia, limbic system, hypothalamus, and chemoreceptor trigger zone.[1] All antipsychotic agents reduce the positive symptoms of schizophrenia by blocking the dopamine D_2 receptor subtype in the mesolimbic region of the brain. However, blockade of D_2 receptors in the nigrostriatal brain region produces undesired extrapyramidal movement disorders. In addition, blockade of D_2 receptors in the mesocortical brain region impairs cognition and worsens the negative symptoms of schizophrenia.[3] Atypical antipsychotic agents block both D_2 and serotonin 5-HT_{2A} receptors. These agents have lower affinity for dopamine receptor antagonism and more selective binding of D_2 receptors in the mesolimbic versus nigrostriatal areas of the brain, resulting in a lower frequency of EPS and TD. The serotonin receptor antagonism is thought to reduce EPS effects and improve the negative symptoms of schizophrenia.[4,5] Some atypical antipsychotics have serotonin 5-HT_{1A} receptor agonism, a functionally opposite effect of 5-HT_{2A} receptor antagonism, producing clinical effect in combination with D_2 receptor antagonism.[5,6] Antipsychotic medications also block other receptor types (see Table 159-1).

Some antipsychotic medications have additional clinical uses. The antiemetic effects of prochlorperazine, promethazine, and droperidol result from blockade of dopamine receptors in the chemoreceptor trigger zone of the medulla. Hydroxyzine controls itching by blocking histamine (H_1) receptors. Prochlorperazine and droperidol abort migraine headaches by preventing dopamine-mediated meningeal artery vasodilation. Chlorpromazine can treat severe hiccups. Haloperidol is the drug of choice for certain nonpsychiatric diseases characterized by movement disorders, including Tourette's syndrome and Huntington's chorea.[1]

PATHOPHYSIOLOGY

Extrapyramidal syndromes can be divided into two groups based on the time of onset after initiating drug therapy. The acute EPSs include dystonia, akathisia, and parkinsonism. These adverse effects are caused by blockade of nigrostriatal D_2 receptors and reduced by blocking muscarinic receptors.[7] The propensity for antipsychotics to produce EPSs is inversely related to the agents' muscarinic receptor antagonism.[5] The delayed-onset syndromes, including TD and tardive dystonia, develop after prolonged use of antipsychotic medications thought to occur from chronic dopamine receptor blockade in the nigrostriatal area leading to D_2 receptor upregulation and hypersensitivity to dopamine.[8-10] The pathophysiology of NMS, an idiosyncratic reaction to antipsychotic medication, is unknown, but it is thought to be from neuroregulatory dysfunction secondary to D_2 receptor blockade in the nigrostriatum and hypothalamus, leading to rigidity and hyperthermia, respectively.[11] There is no apparent association with ryanodine receptor (RYR) gene mutations, which are associated with malignant hyperthermia, in NMS patients.

Table 159-1 Selected Antipsychotic Agents Approved or Nearing Approval for Use in the United States

MEDICATION	RECEPTORS BLOCKED	CLINICAL EFFECTS	ADVERSE EFFECTS
Low Potency			
Chlorpromazine Chlorprothixene Fluphenazine Hydroxyzine Mesoridazine Molindone Perphenazine Prochlorperazine Promethazine Thioridazine	Dopamine D_2 (moderate affinity in mesolimbic and nigrostriatal areas) Acetylcholine muscarinic (generally strong affinity) Histamine H_1 (strong affinity) Alpha-adrenergic (moderate affinity) Dopamine D_1, D_3, D_4, D_5 (variable affinity)	Control positive symptoms of psychotic disorders: Hallucinations Delusions Agitation Disordered thoughts	Extrapyramidal syndromes (common) Tardive dyskinesia (common) Sedation (common) Orthostatic hypotension (common) Anticholinergic symptoms (common): Dry mouth Blurred vision Impaired sweating Constipation Weight gain Urinary retention Angle-closure glaucoma
High Potency			
Droperidol Haloperidol Loxapine Pimozide Thiothixene Trifluoperazine	Dopamine D_2 (strong affinity in mesolimbic and nigrostriatal areas) Acetylcholine muscarinic, histamine H_1. Alpha-adrenergic. (weak affinity) Dopamine D_1, D_3, D_4, D_5 (variable affinity)	Control positive symptoms of psychotic disorders	Extrapyramidal syndromes (common) Tardive dyskinesia (common) Sedation, orthostatic hypotension, and anticholingeric symptoms (uncommon in usual clinical doses)
Atypical			
Aripiprazole* Clozapine Olanzapine Quetiapine Risperidone Ziprasidone	Serotonin 5-HT_{2A} (strong) Dopamine D_2 (mild to moderate affinity, selective for mesolimbic areas) Dopamine D_1, D_3, D_4, D_5 (variable affinity)	Control positive symptoms of psychotic disorders Control negative symptoms of psychotic disorders: Social withdrawal Flattened affect Decreased activity Paucity of speech Pseudodementia	Extrapyramidal syndromes and tardive dyskinesia (uncommon)

*Aripiprazole has partial agonist activity at dopamine D_2 and serotonin 5-HT_{1A} receptors and antagonist activity at serotonin 5-HT_{2A} receptors.

Most antipsychotic medications produce cardiovascular side effects. The most common side effect is orthostatic hypotension with reflexive tachycardia due to alpha-adrenergic blockade. Many agents cause conduction delays, predominantly QT prolongation. Blockade of the delayed inward rectifier potassium current prolongs repolarization during the cardiac action potential and potentially causes torsades de pointes (TDP).[12,13] The degree of prolongation varies between antipsychotic agents, increasing with dose and with concomitant use of other drugs known to prolong the QT interval.[14,15] The phenothiazines, particularly thioridazine and mesoridazine, have the greatest risk of cardiac toxicity. QT prolongation has also been reported with the butyrophenones, haloperidol and droperidol.[12,14,16-18] The atypical antipsychotics produce less cardiotoxicity than the traditional agents, although most potentially cause repolarization abnormalities in therapeutic doses and overdose.[3,14,19-21] Ultimately, a correlation between QT prolongation and the occurrence of dysrhythmias or TDP has not been established.[4] Antipsychiotics are associated with an increased risk of sudden death, particularly in patients with heart disease. However, psychotic disorders themselves are associated with an increased risk of sudden death.

Clozapine produces agranulocytosis in 1 or 2% of treated patients[22]; however, this has been reduced to 0.4% after strict adherence to labeling requirements.[23] Although the mechanism of agranulocytosis is unknown, research supports an immunogenic cause.[24] Seizure rarely occurs with antipsychotic drugs, but clozapine has the highest seizure incidence. Drug dosing and the patient's seizure risk profile influence seizure susceptibility.[25] Some atypical antipsychotics have been associated with diabetes and dyslipidemia, especially clozapine and olanzapine, but the cause has not been established.[26]

CLINICAL FEATURES

Acute Overdose

In overdose, antipsychotic medications produce signs and symptoms that are exaggerations of the clinical effects. Most patients will develop symptoms within a few hours. Central nervous system (CNS) depression is universally present, ranging from mild sedation and confusion to coma and loss of brainstem reflexes. Airway reflexes can be impaired. Respiratory depression can occur after a massive overdose with profound CNS depression. Pupils can be of any size. Mild orthostatic hypotension is a common finding from alpha-adrenergic blockade. Overdose with low-potency antipsychotics can cause an anticholinergic delirium. EPS has been reported with the traditional and atypical antipsychotics.

Atypical antipsychotic overdose is similar to that of traditional antipsychotics. Overdoses are characterized by CNS depression and tachycardia.[27-34] Miosis may be present, potentially mimicking opioid toxicity.[35] Extremity twitching is common. With the exception of clozapine, seizures rarely occur in overdose. Acute EPS has been reported for risperidone overdose.[36]

Acute Extrapyramidal Syndromes

Acute dystonia manifests as involuntary motor tics or spasms that most often involve the facial, neck, back, or limb muscles.

Dystonic reactions usually develop within the first several doses of treatment or after a large increase in dosage.[37] *Oculogyric crisis*, characterized by continuous rotatory eye movements, has also been reported. *Laryngeal dystonia* is a rare but life-threatening form of dystonia that manifests as stridor, difficulty breathing, or a choking sensation.[38,39] Increased risk of death due to choking has been documented in schizophrenia patients.[40]

Akathisia, a subjective feeling of restlessness associated with objective motor restlessness, is often mistaken for worsening agitation, leading incorrectly to an increase in antipsychotic dose. Akathisia usually develops within the first few days of treatment,[38] but 40% of patients given 10 mg of intravenous (IV) prochlorperazine developed akathisia within 1 hour.[41]

A *parkinsonian syndrome* of bradykinesia, masked facies, shuffling gait, muscular rigidity, and resting tremor frequently develops during the first weeks of therapy with low-potency and high-potency neuroleptic-antipsychotic agents. *Perioral tremor* (rabbit syndrome), in which the lip and nose movements resemble those of a rabbit, can also develop after prolonged therapy.[1,42]

Tardive Dyskinesia

TD is a chronic movement disorder induced by prolonged use of antipsychotic medication. Typical signs of TD include quick, involuntary movements of the face (blinking, grimaces, tongue movements, and chewing), extremities, or trunk. Twenty percent of patients treated with long-term traditional antipsychotics are affected. The risk of development is much lower with the atypical agents. TD is difficult to treat and frequently permanent. Reducing the antipsychotic dose or changing to an atypical agent should be considered. TD improves in many patients switched to clozapine, but further clinical trials are needed to study other atypical antipsychotic agents.[38,43,44]

Respiratory dyskinesia, a variant of TD, is characterized by orofacial dyskinesia, dyspnea, dysphonia, and respiratory alkalosis. This chronic disorder often goes undiagnosed and can cause repeated bouts of aspiration pneumonia.

Neuroleptic Malignant Syndrome

NMS is a serious idiosyncratic drug reaction that typically develops during the first month of therapy but has occurred during stable drug regimens. Risk factors include rapid drug loading, high dosage, high-potency antipsychotics, parental formulations, dehydration, preceding psychomotor agitation, and previous episodes of NMS.[45,46] Other medications may contribute to NMS, including lithium, which inhibits dopamine secretion, as well as withdrawal from dopaminergic agents used to treat Parkinson's disease.[11,47,48] The incidence of NMS in patients treated with antipsychotics is approximately 0.02%, which is significantly lower than previous estimates of 3%.[45] The atypical antipsychotic agents, including clozapine, risperidone, olanzapine, quetiapine, and aripiprazole, have been associated with NMS.[49,50]

Table 159-2 lists the diagnostic criteria for NMS. Other features of NMS may include sialorrhea, dysarthria, dysphagia, metabolic acidosis, liver function elevations, sodium imbalance, dehydration, elevations in serum catecholamines, coagulopathy, generalized slowing on the electroencephalogram (EEG), pulmonary embolism, and renal failure.[46] Atypical presentations may lack full diagnostic criteria for NMS.[50-52]

Most patients develop the cardinal features of altered mental status, muscle rigidity, hyperthermia, and autonomic nervous system instability over several hours to days. However, the signs of NMS may develop gradually and in any order.[53] Agitation, often mistaken for worsening psychosis, may occur first. Physicians should consider discontinuing antipsychotic drugs in a patient who has developed one or more of the major manifestations of NMS. Most episodes resolve within 2 weeks after cessation of the offending medication, but some cases have lasted up to 6 months.[54,55]

Table 159-2 Diagnostic Criteria and Clinical Features of Neuroleptic Malignant Syndrome

CRITERIA/FEATURES	PREVALENCE
A. Development of severe muscle rigidity and elevated temperature associated with the use of a neuroleptic/antipsychotic medication	Rigidity: 97% Fever: 98%
B. Two (or more) of the following are present:	
1. Diaphoresis	98%
2. Dysphagia	
3. Tremor	
4. Incontinence	
5. Change in level of consciousness ranging from confusion to coma	97%
6. Mutism	
7. Tachycardia	88%
8. Elevated or labile blood pressure	61%
9. Leukocytosis	98%
10. Laboratory evidence of muscle injury (e.g., elevated creatine kinase)	95%
C. Symptoms in criteria A and B are not caused by another substance (e.g., phencyclidine), a neurologic or other general medical condition (e.g., viral encephalitis), or another mental disorder (e.g., mood disorder with catatonic features).	

Modified from American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed (TR). Washington, DC, *American Psychiatric Association*, 2000; prevalence data from Caroff SN, Mann SC: Neuroleptic malignant syndrome. *Med Clin North Am* 77:185, 1993.

Cardiovascular Toxicity and Dysrhythmias

The most common cardiac effect is sinus tachycardia with a normal QRS duration. If QRS prolongation is present, then another drug effect should be suspected. QT prolongation has been reported during therapeutic dosing of many antipsychotic agents. Therapeutic doses of thioridazine followed by ziprasidone prolonged the QT interval more than did risperidone, olanzapine, quetiapine, or haloperidol.[20,21] QT prolongation associated with TDP is a well-described adverse effect of thioridazine, mesoridazine, droperidol, sertindole, and high-dose IV haloperidol.[14,16,18,56-58] Among typical agents, thioridazine carries the greatest risk of cardiotoxicity.[16,59] Among atypical agents used during overdose, ziprasidone carries the greatest risk of QTc prolongation.[60-65] QT prolongation should be considered a "class effect" of all antipsychotic medications, but the clinical significance of QTc prolongation and the risk of TDP are not known.

Atrioventricular nodal block is a rare complication of overdose with chlorpromazine, thioridazine, and other older neuroleptics.[66]

Agranulocytosis

Clozapine produces agranulocytosis, with 75% of occurrences developing within the first 18 weeks after initiation of therapy, peaking at 3 months.[22] The concomitant use of other bone marrow–suppressing agents (e.g., carbamazepine) should be

avoided. Clozapine administration must be halted if the total white blood cell count falls below 3000 cells/mL or if the absolute neutrophil count is less than 1500 cells/mL. Agranulocytosis has not been reported after an acute overdose. Olanzapine, whose chemical structure is similar to that of clozapine, has been associated with neutropenia and agranulocytosis. All patients recovered after discontinuation of olanzapine.[67]

Seizures

Antipsychotic medications can lower the seizure threshold and induce epileptiform EEG abnormalities in many asymptomatic patients.[68] However, antipsychotic-induced seizures are rare except for clozapine, which causes a dose-related increase in risk of seizures (approximately 5% at high doses). Antipsychotics can be prescribed for patients with known seizure disorder.[68-70]

DIFFERENTIAL CONSIDERATIONS

Differential diagnostic considerations include a broad list of agents and clinical conditions that produce altered mental status, orthostatic hypotension, anticholinergic syndrome, seizure, QT prolongation, or TDP. Although the signs of NMS are similar to those of serotonin syndrome and heatstroke, the etiologies of these conditions are quite different (Table 159-3). Malignant hyperthermia should be considered in patients receiving inhalational anesthetics or succinylcholine.

DIAGNOSTIC STRATEGIES

Blood levels are neither readily available nor helpful in the management of an overdose with antipsychotic medication. As with any patient who presents with altered mental status, blood glucose and pulse oximetry readings should be obtained immediately. Other testing, such as brain computed tomography, lumbar puncture, serum acetaminophen measurement, and electrolyte measurements, may be required to screen for other causes. Olanzapine and clozapine have been associated with new-onset diabetes with ketoacidosis.[4]

An electrocardiogram (ECG) should be obtained in patients with significant antipsychotic overdose and in symptomatic patients taking thioridazine, mesoridazine, droperidol, or sertindole. Patients receiving high-dose IV haloperidol or droperidol for sedation require cardiac rhythm monitoring. If QT prolongation is present, serum potassium, calcium, and magnesium levels should be measured.

Patients who develop NMS, parkinsonism with marked muscle rigidity, or prolonged seizures are at risk for rhabdomyolysis and should have serum creatine kinase (CK), renal function, and urine myoglobin measured. A chest radiograph should be obtained if pulmonary aspiration is suspected. Patients taking clozapine or olanzapine who present with infection or fever should be checked for leukopenia.

Table 159-3 Differential Diagnosis of Neuroleptic Malignant Syndrome

DISEASE*	PATHOLOGIC MECHANISM	DIFFERENTIATING FACTOR	TIME COURSE	TREATMENT
Neuroleptic malignant syndrome	Impaired thermoregulation in hypothalamus and basal ganglia due to relative lack of dopamine activity	Antipsychotic medication use, muscular rigidity (diagnostic criteria in Table 159-2)	Gradual, progresses over several days	Stop offending medication(s) Hydration Active cooling Intravenous benzodiazepines to relax muscles and control agitation Neuromuscular blockade (nondepolarizing agents) Controversial: Bromocriptine or amantadine Dantrolene
Serotonin syndrome	Excess serotonin and dopamine levels in central nervous system	Medications (usually a combination) that increase serotonin levels (e.g., SSRIs, MAOIs, dextromethorphan, lithium, meperidine, tramadol, tryptophan); muscular rigidity	Usually rapid after introduction of new medication or increase in dose; can be gradual	Stop offending medication(s) Hydration Active cooling Cyproheptadine
Heatstroke	Environmental heat stress	Environmental exposure history; muscular rigidity rare	Rapid or gradual	Hydration Active cooling
Malignant hyperthermia	Genetic instability of sarcoplasmic reticulum, causing massive calcium release after administration of triggering medication	Occurs after administration of inhalational anesthetic or succinylcholine; muscular rigidity	Sudden, provoked by administration of anesthetic	Stop anesthetic Hydration Active cooling Dantrolene

*Other clinical entities to consider in the diagnosis of these conditions include Addison's syndrome, central nervous system infection, delirium tremens, hypocalcemia, hypoglycemia, hyponatremia, intracranial hemorrhage, lethal catatonia, poisoning (e.g., amphetamines, anticholinergics, cocaine, nicotine, salicylates, sympathomimetics, strychnine, theophylline), sedative-hypnotic drug withdrawal, sepsis, status epilepticus (including nonconvulsive status), tetanus, thalamic infarct, thyroid storm, and psychotic agitation.

MAOIs, monoamine oxidase inhibitors; SSRIs, selective serotonin reuptake inhibitors.

MANAGEMENT

Acute Overdose

Treatment is supportive; no specific antidote exists for antipsychotic medication overdose. Endotracheal intubation may be required to prevent aspiration or, less often, to support respiration. Hypotension is generally mild and responds to IV crystalloids. A vasopressor with alpha-adrenergic receptor agonism, such as norepinephrine, may be used if needed. If sedation and miosis suggest opioid intoxication, a trial of naloxone is warranted. Physostigmine and flumazenil are best avoided because of the risk of precipitating seizures.

Activated charcoal has no proven benefit. Activated charcoal should not be administered to a patient with a nonprotected airway to avoid aspiration of charcoal.

Acute Extrapyramidal Syndromes

Diphenhydramine, 25 to 50 mg IV, intramuscularly, or orally, or benztropine, 1 or 2 mg intramuscularly or orally, will usually control dystonic reactions. Benzodiazepines may also be effective. Akathisia can be treated with a lipophilic beta-adrenergic blocker (e.g., propranolol), anticholinergic agents, or benzodiazepines. Patients with EPS who respond to diphenhydramine or benztropine should continue on therapy for at least 48 hours to prevent recurrence.[38,71] In addition, patients should be referred to their treating physician, who may reduce the antipsychotic dose or change to an atypical agent as necessary. Benztropine, diphenhydramine, and the older antipsychotic medications all cause anticholinergic effects, so combination therapy may worsen dry mouth, blurred vision, and urinary retention.

QT Prolongation and Torsades de Pointes

Correction of hypokalemia, hypomagnesemia, and hypocalcemia shortens the QT interval. Treatment of TDP includes IV magnesium sulfate, overdrive pacing, and possibly isoproterenol. Administration of antiarrhythmic drugs that prolong the QT interval should be avoided.

Neuroleptic Malignant Syndrome

Treatment of NMS consists of supportive care and discontinuation of the offending medication. Agitation, psychomotor hyperactivity, and muscular rigidity should be treated with liberal doses of IV benzodiazepines. Lorazepam can be administered IV 1 or 2 mg every 3 minutes until muscle rigidity improves, to a maximum dose of 10 mg. In refractory cases or cases at risk of aspiration, rapid sequence induction, endotracheal intubation, and neuromuscular blockade with a nondepolarizing agent (e.g., rocuronium and vecuronium) are required. Hyperthermia should be managed with IV fluids and active external cooling with mist and fans. If rhabdomyolysis is present, IV hydration and urinary alkalization are used to prevent renal damage.

Bromocriptine and amantadine have been suggested as treatments for NMS but do not consistently show a benefit.[47,54,72,73] Bromocriptine is administered orally or via nasogastric tube, beginning with 5 mg every 8 hours and titrated to a maximum of 20 mg per dose. The dose of amantadine for NMS is 200 mg orally every 12 hours. Response to therapy requires at least 24 hours.[54] Bromocriptine has been linked to stroke, seizure, myocardial infarction, and severe hypertension in lactating or postpartum women, but not during treatment of NMS.[74]

Dantrolene, which inhibits the release of calcium from the sarcoplasmic reticulum, has also been suggested for NMS but has no proven benefit.[72,73,75] Because the muscular rigidity of NMS is thought to be due to dopamine blockade in the CNS rather than a muscle abnormality, dantrolene offers no advantage over benzodiazepines and neuromuscular blockade.

DISPOSITION

All patients with NMS and overdose patients with hypotension, coma, torsades de pointes, or airway compromise should be admitted to a critical care unit. Patients with a prolonged QT interval (QTc > 460 msec) and all patients with significant ingestions of thioridazine or mesoridazine should have at least 12 hours of cardiac monitoring.[76] Patients with less severe signs of toxicity should be observed in the emergency department for a minimum of 4 hours from the time of ingestion, with hospitalization for persistent or worsening signs and symptoms. Criteria for hospital discharge include return to normal mental status and resolution of any vital sign, metabolic, and ECG abnormalities. Psychiatric consultation may be necessary to assess the risk of suicide.

KEY CONCEPTS

- Extrapyramidal movement disorders are a common complication of antipsychotic medications and are treated with benztropine, diphenhydramine, and benzodiazepines.
- The most common finding in antipsychotic overdose is central nervous system depression. Treatment centers on supportive care, airway control, and cardiac monitoring.
- QT prolongation and torsades de pointes are potential complications from overdose of many antipsychotic medications, and they can occur with therapeutic doses of some agents.
- The neuroleptic malignant syndrome is characterized by altered mental status, hyperthermia, muscular rigidity, and autonomic instability. Supportive care includes airway management, benzodiazepines, neuromuscular blockade, and active cooling.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 160 Opioids

Christina Hantsch Bardsley

PERSPECTIVE

Opioid is a term that applies to all natural, synthetic, and semisynthetic agents with morphine-like actions. It is more inclusive than the term *opiate*, which refers only to natural agents. Both terms are derived from *opium*, the Greek word for juice in reference to poppy juice. Poppy juice contains more than 20 distinct natural alkaloids with morphine-like activity. The term *narcotic* refers to any agent that induces sleep and is nonspecific. Although the term narcotic persists, primarily in legal contexts, *opioid* is more precise and is the correct medical term for the family of agents that act on opiate receptors in the body. Finally, the term *endorphin* applies to any of the three endogenous opioid families: enkephalins, beta-endorphins, and dynorphins.[1]

Pharmacologic actions of opioids involve the gastrointestinal system, genitourinary system, cardiovascular system, pulmonary system, and central nervous system (CNS) and cause characteristic clinical effects. Sedation and analgesia are the most common therapeutic goals of opioid medications, which are available alone or in combination with other agents (e.g., acetaminophen and salicylates) for these purposes. Additional therapeutic goals of opioids and combination preparations include antitussive and antidiarrheal effects.

Misuse of pharmaceutical opioid preparations and use of illicit opioids are significant problems in the United States. According to the 2006 National Survey on Drug Use and Health, 506,000 Americans age 12 years or older have used heroin, including 338,000 current heroin users.[2] Injection is the most common route, followed by inhalation, smoking, and ingestion. Since the early 1990s, there has been a trend toward inhalation rather than injection. Prescription pain medications are used for nonmedical means by 5.2 million users in comparison to only 2.4 million cocaine users.[2] Opioids are second to sedatives/hypnotics/antipsychotics for substances involved in reported fatal exposures.[3] A multistate epidemic of nonpharmaceutical fentanyl-related overdoses resulted in more than 1000 deaths from April 2006 to March 2007.[4]

PRINCIPLES OF DISEASE

Anatomy and Physiology

Although opioids have been used for more than 5000 years, receptors and endogenous opioids have been recognized only since the 1970s.[1,5] Opioids have an incompletely understood physiologic role.

There are three established opioid receptors, known as *mu* or OP_3, *kappa* or OP_2, and *delta* or OP_1.[5] Opioid receptors are distributed throughout the CNS, concentrated in pain pathways and in areas associated with the perception of pain (e.g., periaqueductal gray matter, locus ceruleus, limbic system, and nucleus raphe magnus). Systemically, opioid receptors are localized in sensory nerve endings, on mast cells, and in the gastrointestinal tract.[5] Genetic variations in opioid receptors account for some of the interindividual differences in response to both endogenous and exogenous opioids. Several polymorphisms of the mu receptor have been identified, including A118G polymorphism, which is present in more than 34% of individuals.[6] The role of the opioid receptors in pain perception and the analgesic effects of exogenous opioids are discussed in detail in Chapters 186 and 187.

Pathophysiology and Pharmacology

Toxicity

Opioids include therapeutic agents and illicit substances. Toxicity occurs as a result of intentional overdose, intentional abuse, or adverse effect of therapeutic use. Although different opioids have receptor preferences in therapeutic or low doses, this specificity is lost at higher doses.

Opioids are well absorbed after gastrointestinal (oral and rectal) or parenteral administration but also through nasal, buccal, pulmonary, and transdermal routes, depending on the lipid solubility of the specific opioid.[1] Heroin is usually abused through intravenous and subcutaneous routes, but it is also absorbed after nasal administration because it is lipid soluble.[7] In general, opioid toxicity is less pronounced but more prolonged with oral ingestion than with parenteral administration.[1] Absorption of opioids after oral administration occurs in the small intestine. With therapeutic doses, absorption is complete within 1 or 2 hours. Absorption and clinical effects of toxicity may be prolonged after overdose, however, because gastric emptying is delayed.

Most opioids have a large volume of distribution. Clinical effects depend on lipid solubility, which affects the ease with which opioids and their metabolites cross the blood-brain barrier. All opioids undergo hepatic metabolism and renal elimination, and variations in hepatic and renal function are

important because metabolite activity may contribute to clinical effects and toxicity.[1] The half-lives of meperidine and normeperidine are prolonged with cirrhosis, and the elimination of normeperidine is decreased with renal insufficiency. These conditions increase the likelihood of normeperidine-related seizures, as do multiple or large doses.[8]

The pharmacokinetics of the specific agent determine the clinical course of opioid toxicity. Heroin peaks in the serum within 1 minute of intravenous injection, 3 to 5 minutes of intranasal administration, and 10 minutes of subcutaneous injection. Heroin's lipophilic nature allows for rapid transport across the blood-brain barrier into the CNS. In the CNS and blood, heroin is rapidly hydrolyzed to 6-monoacetylmorphine and then morphine (less lipid soluble). In the liver, morphine undergoes conjugation with glucuronic acid to form more water-soluble compounds that are excreted by the kidneys.[1]

Withdrawal

Because the half-life of heroin is 30 minutes and the half-life of methadone is 15 to 40 hours, withdrawal symptoms occur 4 to 6 hours after discontinuation of heroin compared with 24 to 48 hours after discontinuation of methadone.[9,10] Duration of symptoms is 7 to 10 days and 2 weeks, respectively. The degree of physical dependence that has developed is also important. With chronic opioid exposure, cellular adaptation results in upregulation of cyclic adenosine monophosphate (cAMP). When either the exposure is discontinued or an antagonist is administered, the result is a temporary elevation of cAMP levels and increased sympathetic activity above a normal baseline.

CLINICAL FEATURES

Toxicity

The toxidrome of opioid toxicity is CNS depression, respiratory depression, and miosis. Other potential findings in opioid toxicity are associated with toxicity from any opioid, but some features are unique to a specific agent or route of exposure.

Neurologic

CNS depression is a well-recognized manifestation of opioid toxicity. Hypoxia from CNS depression and respiratory depression also causes many neurologic complications. Dysphoria and acute psychosis may occur with an agonist-antagonist opioid. Excitatory effects may occur with opioid toxicity. Hypertonicity, myoclonus, and seizures have been reported with overdose of the synthetic opioids meperidine and propoxyphene. Meperidine-related seizures are probably caused by accumulation of normeperidine, especially after multiple or large doses or in patients with hepatic or renal insufficiency. Seizures may also result from hypoxia with overdose of any opioid.

Parkinsonian symptoms in intravenous drug abusers have been attributed to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), an unintended side product produced during synthesis of a meperidine analogue in street laboratories. MPTP injection is associated with accumulation of an MPTP metabolite in CNS cell mitochondria, focal lesions in the substantia nigra, and a syndrome clinically indistinguishable from idiopathic parkinsonism. The syndrome is irreversible in some patients.[11]

Spongiform leukoencephalopathy has been associated with inhalation of heated heroin, a practice known as "chasing the dragon." Patients present with psychomotor retardation, dysarthria, ataxia, tremor, and other neurologic abnormalities.[12] This syndrome is incompletely understood but is thought to be related to a combination of mitochondrial injury and hypoxia.[13] One report also associates heroin-induced movement disturbance with basal ganglia lesions.[14]

Serotonin syndrome is a clinical triad of mental status changes, autonomic instability, and neuromuscular changes (see Chapter 149) and may be fatal. Most cases involve an interaction between a serotoninergic agent and a second agent, usually a selective serotonin reuptake inhibitor or a monoamine oxidase inhibitor. Meperidine and dextromethorphan have serotoninergic properties and have been associated with serotonin syndrome.[8]

Respiratory

Opioids decrease respiratory rate and tidal volume in a dose-dependent manner by suppressing the sensitivity of the medullary respiratory center to hypercapnia.[1] Although it initially remains intact, the hypoxic drive is overridden in severe poisoning or when antagonistic stimuli (e.g., pain) are blocked. Overdose of an agonist-antagonist agent produces less significant respiratory depression, presumably because of mu receptor antagonism (Table 160-1). Central sleep apnea is associated with long-term opioid use and also occurs in those with acute increased opioid use from baseline. Continuous positive airway pressure is usually ineffective for treatment of sleep apnea in these patients.[15]

Bronchospasm is rare with heroin use in asthmatic and nonasthmatic patients and occurs mostly after inhalational exposure, but other routes are also implicated. The bronchospasm is often severe, prolonged, and refractory to beta-agonist therapy. Patients may require mechanical ventilation for several days. It is unclear whether the heroin, an adulterant, or a combination triggers the bronchospasm and whether the response is histamine mediated or the result of direct irritation.[7]

Acute lung injury occurs with therapeutic opioid use but is much more common after overdose.[16] The capillary leak is likely from hypoxia rather than a direct drug effect.

Ophthalmologic

In more than 90% of heroin overdoses, stimulation of mu receptors in the Edinger-Westphal nuclei of the third nerve results in miosis.[17] Miosis is not typically seen with meperidine, propoxyphene, or diphenoxylate-atropine (Lomotil) overdose. Toxicity from agonist-antagonists (e.g., pentazocine) or multiple agents may not produce miosis.

Otolaryngolic

Rapidly progressive sensorineural hearing loss has been reported with the use of hydrocodone. Genetic polymorphism producing altered metabolism and/or comorbidities have been suggested as causative factors.[18]

Cardiovascular

Opioids cause mild hypotension and relative bradycardia. Hypotension seems to be from histamine release and can be blocked by antihistamines (H_1 antagonists).[19] The hypotension is typically orthostatic and resolves with supine positioning. Propoxyphene and its metabolite, norpropoxyphene, may cause sodium channel blockade similar to that of type IA antidysrhythmic agents to produce widening of the QRS complex.[20]

Table 160-1 Select Opioid Doses and Associated Respiratory Depression

DRUG	ORAL DOSE (MG)*	INTRAMUSCULAR DOSE (MG)*	TIME TO ONSET OF RESPIRATORY DEPRESSION†
Codeine	200	120	Fast
Dextromethorphan	700	—	Fast
Dihydrocodeine	150	60	Fast
Diphenoxylate	300	—	Slow (or even more delayed)
Fentanyl	—	0.125	Very fast
Heroin	15	3	Fast
Hydrocodone	100	—	Fast
Hydromorphone	6	1.5	Fast
Levorphanol	1	2	Fast
Meperidine	250	100	Fast
Methadone	20	10	Slow (or even more delayed)
Morphine	70	10	Fast
Oxycodone	30	10	Fast
Oxymorphone	6	1	Fast
Paregoric	175	—	Fast
Propoxyphene	600	—	Fast

*Equivalent to 10 mg of intramuscular morphine.
†Varies with the drug and route of administration. In addition, the effects of a dose in any particular patient depend on multiple factors, including age, weight, and comorbid conditions. After intramuscular administration, *very fast* means 5 to 30 minutes, *fast* means 15 to 60 minutes, and *slow* means 1 to 4 hours. After oral administration, these time definitions are approximately doubled.

Gastrointestinal

Nausea and vomiting are common with therapeutic opioid use and also with overdose. Mechanisms include opioid-induced delayed gastric emptying, direct stimulation of the chemoreceptor trigger zone, and vestibular stimulation. Antihistamines and dopamine antagonists (e.g., chlorpromazine) may be effective in treatment.

Decreased gastrointestinal motility is a common finding with therapeutic use and overdose of opioids. Severe cases may develop ileus.[1] Increased biliary tract pressures and choledochoduodenal sphincter spasm occur with therapeutic dosing of many opioids, including morphine, meperidine, and codeine. Spasm is not always reproducible within the same patient but seems related more to individual susceptibility than to a specific agent. Presenting clinical symptoms mimic biliary colic and may respond to naloxone or glucagon.[21]

Genitourinary

Opioids can cause urinary retention from urethral sphincter spasm and decreased detrusor tone. Alpha-adrenergic antagonists may reverse this effect. Glomerulosclerosis and renal amyloidosis are seen in end-stage "heroin nephropathy" of chronic opioid addicts.[22]

Dermatologic

Pruritus, flushing, and urticaria occur after administration of certain opioids that release histamine (e.g., morphine) and do not represent a true allergy. Pruritus and erythema are often localized to the area of injection (e.g., along the vein through which the morphine was administered). Symptoms typically are controlled easily with antihistamines. Although all opioids have the potential to stimulate mast cell degranulation and histamine release, some (e.g., fentanyl) release only clinically negligible amounts of histamine and thus have good hemodynamic stability profiles.

Metabolic

Hypoglycemia occurs after opioid overdose, but the mechanism is unclear. Co-ingestants, especially ethanol, may contribute to this finding. Hypothermia has been reported, but the mechanism is unclear. Hyperthermia should prompt a search for infectious complications, particularly in intravenous drug users, and for co-ingestants (e.g., cocaine) or adulterants (e.g., tripelennamine and scopolamine).[23] "Cotton fever" is reported in intravenous drug users who strain suspended drug through cotton balls or cigarette filters to remove particulates. Filters are boiled to extract residual drug when supply is low. Cotton is a known pyrogen and can cause a benign fever in patients who subsequently "shoot the cottons" or inject the extracted residue from the filters.[24]

Withdrawal

Opioid withdrawal occurs in tolerant individuals when opioid use is discontinued or an antagonist is administered. Increased sympathetic discharge and adrenergic hyperactivity are responsible for the clinical symptoms and signs. In contrast to the typical toxidrome of opioid toxicity (CNS and respiratory depression and miosis), withdrawal is associated with CNS excitation, tachypnea, and mydriasis. Pulse and blood pressure are also increased. Although these can be uncomfortable, they are typically not life-threatening.[9,10]

Neurologic manifestations are prominent in opioid withdrawal. Restlessness, agitation, and anxiety are virtually universal, and seizures may rarely occur. Cognition and mental status are unaffected. Dysphoria and drug craving may be severe and prolonged.

Nausea, vomiting, diarrhea, and abdominal cramps are common in withdrawal. They can be significant and lead to dehydration and electrolyte abnormalities. Other symptoms may also include diffuse myalgias and insomnia with piloerection, yawning, lacrimation, rhinorrhea, and diaphoresis.

DIAGNOSTIC STRATEGIES

The diagnosis of opioid intoxication is usually based on history and physical examination. Diagnostic studies rarely assist in evaluation of patients suspected of opioid overdose. Other than hypoglycemia, specific laboratory abnormalities are not seen. When the patient has hypoxemia and pulmonary rales, a chest radiograph should be obtained to evaluate for acute lung injury. In the appropriate circumstances, an abdominal radiograph may identify packets of opioids or other illicit substances in a body packer. A case of QRS widening is thought to be associated with propoxyphene overdose but has not been validated.[20] If cardiac monitoring shows a prolonged QRS, a 12-lead electrocardiogram is advisable. With ingestion of an unknown opioid preparation, acetaminophen and salicylate levels should be checked because many prescription opioids are available in combination products. Likewise, many illicit opioid users are exposed to additional drugs and contaminants.[23,24]

Although opiates are detected on most qualitative urine toxicology screens, these are rarely helpful in acute situations. On some assays, several synthetic opioids are also detected because they cross-react or because they are metabolized to opiates, which are then excreted. Other agents, such as fentanyl and its derivatives, are missed on urine screens. Poppy seed ingestion can lead to a positive opiate screen for morphine and codeine; however, detection of 6-monoacetylmorphine, a specific metabolite of heroin, can confirm heroin use.[25]

As with opioid toxicity, no diagnostic test exists for opioid withdrawal.

DIFFERENTIAL CONSIDERATIONS

The diagnosis of opioid intoxication is usually obvious, based on history and physical examination, although patients with other intoxications or nontoxicologic conditions may have a similar physical examination. Other drugs that should be considered are clonidine (or a related drug), tramadol, valproic acid, γ-hydroxybutyrate, and sedative-hypnotic agents. The differential diagnosis encompasses all causes of depressed mental status, but the coexistence of miosis and respiratory depression greatly narrows the possibilities.

Opioid withdrawal is usually a straightforward diagnosis, and the patient often reveals it as the chief complaint. Simultaneous intoxication with, or withdrawal from, other classes of agents, especially CNS depressants and stimulants, may be seen.

MANAGEMENT

Attention to the airway, oxygenation, and ventilation is of vital importance in patients with opioid toxicity. If reversal is not achieved with antidote therapy, appropriate interventions include airway protection and ventilatory support. Patients with acute lung injury may require oxygen and positive-pressure modalities, such as bilevel positive airway pressure, continuous positive airway pressure, or mechanical ventilation with positive end-expiratory pressure. Circulatory support usually does not require more than a crystalloid infusion. Most opioids have a large volume of distribution and cannot be cleared by dialysis. There are no clinically effective techniques for enhanced elimination of opioids.

Gastrointestinal Decontamination

Gastrointestinal decontamination is often unnecessary because the antidote can reverse the effects. Whole-bowel irrigation can hasten passage of drug packets from body packers or patients with ingestions involving opioid combination products or multidrug ingestions. A single early dose of activated charcoal (1 g/kg in children and 50–100 g in adults) may be beneficial in some patients because gastrointestinal motility may be reduced.[26]

Antidote

Naloxone, a pure opioid antagonist, is the antidote most frequently used to reverse opioid toxicity. Naloxone has a rapid onset of action. For reversal of systemic opioid toxicity it is ineffective after oral administration secondary to the first-pass effect, but intravenous, subcutaneous, intramuscular, inhalational, and endotracheal routes can be used. Naloxone competitively binds opioid receptors and can reverse all the receptor-mediated actions of opioids. Naloxone is indicated for patients with opioid intoxication who have significant CNS or respiratory depression. The initial intravenous dose is 0.4 to 2 mg for adults and children, but 10 mg may be required to obtain a clinical response for synthetic opioids.

Naloxone can precipitate acute withdrawal in chronic opioid users. In this population, the dose should be started at 0.2 mg and slowly titrated. The duration of action of naloxone is 1 or 2 hours. Consequently, either repeat doses or a continuous infusion of two thirds of the effective initial dose per hour may be required.[1]

Naloxone has an excellent safety profile. Acute lung injury, hypertension, and dysrhythmia have been associated with use of naloxone after general anesthesia and in patients with underlying cardiac or pulmonary disease.[27] Whether naloxone is the cause of these complications is unproven. Idiosyncratic reactions and sympathetic discharge with precipitation of acute withdrawal have been proposed as explanations. The risk may be greater in those with ongoing hypoventilation prior to naloxone administration. Complete clinical recovery in response to naloxone is strongly suggestive of opioid overdose. Other intoxications, including valproic acid, clonidine, tramadol, captopril, and ethanol intoxication, may improve to lesser degrees with naloxone. Naloxone has been given to patients who have ingested these agents because of a presentation similar to opioid intoxication or suspicion of a mixed exposure that included opioids. The mechanism of these responses to naloxone is not established. Some of these drugs may have activity at opioid receptors.[27]

Nalmefene, another opioid antagonist, has a long half-life (8–11 hours) and duration of clinical effect. Intravenous nalmefene has a rapid onset of action in reversing opioid-induced CNS and respiratory depression. Alternate administration routes are oral, subcutaneous, and intramuscular. The initial intravenous dose is 0.5 to 1.5 mg (pediatric dose not established). Higher doses have been used but are associated with increased risk of adverse effects.[28,29] When a clinical response has been achieved with nalmefene, repeat doses or continuous infusions are generally not required; however, the duration of withdrawal symptoms may be longer with nalmefene. Naloxone remains the preferred antidote in patients at risk for withdrawal or other adverse effects and in patients with anticipated short duration of opioid toxicity. Seizures associated with opioid toxicity resolve with correction of hypoxia or administration of benzodiazepines.

Withdrawal

Opioid withdrawal is not life-threatening, but the potentially serious manifestations mandate attention to supportive and symptomatic care. When withdrawal is produced by adminis-

tration of naloxone, the symptoms are of short duration, and replacement opioids should be avoided.[9,10] Other patients with withdrawal can receive opioid replacement or other medications to alleviate symptoms. In addition, fluid and electrolyte replacement is important for patients with dehydration from gastrointestinal symptoms.

Methadone, a long-acting opioid, and l-α-acetyl-methadol (LAAM), an even longer acting opioid, provide opioid replacement to treat or prevent withdrawal in chronic heroin users admitted for other medical conditions. The onset of action of an initial dose of methadone of either 20 mg orally or 10 mg intramuscularly is 30 to 60 minutes. This initial dose typically controls significant symptoms.[9] Some symptoms, particularly drug craving, may be ongoing and require a subsequent dose after several hours. Maintenance methadone therapy requires doses every 24 hours or may be tapered daily. LAAM, a three dose per week opioid replacement, was discontinued by the manufacturer due to cardiac adverse events, including QTc prolongation.[9] In October 2002, the Food and Drug Administration approved a buprenorphine monotherapy product (Subutex) as well as a buprenorphine/naloxone combination product (Suboxone) for treatment of opioid addiction. As opposed to methadone, these treatments are not limited to use in traditional opioid treatment programs.[30] However, neither treatment is indicated in routine emergency department care.

Clonidine, a central alpha$_2$-agonist, is used for treatment of opioid withdrawal without opioid replacement.[9] Clonidine controls symptoms by suppressing sympathetic hyperactivity. It may also shorten the duration of withdrawal. The initial dose is 0.1 mg orally. Repeat doses may be given every 30 to 60 minutes; relatively large total doses may be required. As with opioid replacement, clonidine therapy is titrated to individual clinical response. Hypotension may limit the treatment but is not common in the setting of opioid withdrawal treatment. Patches for transdermal administration of clonidine are available, but onset of action is delayed 24 hours. Oral doses still must be given initially.

Buspirone is an azaspirone compound used to treat ethanol and nicotine addiction. Studies suggest that it may also be an option to treat withdrawal in opioid addicts, but further investigation is needed.[31]

DISPOSITION

Toxicity

Patients with opioid toxicity are usually treated successfully in the emergency department, sometimes in conjunction with the emergency department observation unit. Patients who receive naloxone should be observed for 2 hours to assess the extent of re-sedation. Asymptomatic patients can be observed in the emergency department until 4 hours after an ingestion, at which time they can be discharged with appropriate psychiatric evaluation or drug abuse counseling. Patients who have ingested an opioid with a longer half-life, active metabolite, or modified release preparation as well as patients with multiple drug ingestions involving an opioid may require longer observation periods.

Patients who have a known or potential overdose of diphenoxylate-atropine (Lomotil) should be observed in a monitored unit even if asymptomatic; this includes small children who may have ingested only a single tablet (2.5 mg of diphenoxylate or 0.025 mg of atropine). The metabolite of diphenoxylate, difenoxin, has a longer half-life and is five times more active than diphenoxylate, and it may cause delayed and prolonged toxicity. Delayed absorption, caused by each component of Lomotil and enterohepatic recirculation, may contribute as well.[32]

Patients with a known or potential ingestion of packets of illicit opioid drugs should be admitted until the packets are passed. Body packers and body stuffers remain asymptomatic until one or more of the packets leak.

Withdrawal

Patients with opioid withdrawal may be managed as outpatients. Clonidine may alleviate some of the symptoms of withdrawal but has a high incidence of postural hypotension. Patients with refractory complications (e.g., vomiting, dehydration, and electrolyte abnormalities) and patients with an uncertain diagnosis may require hospitalization. Some patients may need to be detoxified before entering chemical treatment programs. Substance abuse counseling and establishment of outpatient program referral should be completed before discharge.

KEY CONCEPTS

- Diagnosis of opioid intoxication is based on history, physical examination, and response to naloxone.
- The opioid toxidrome includes three prominent findings—CNS depression, respiratory depression, and miosis—but these may not be present in every patient.
- Early administration of reversal agents and airway management and attention to oxygenation and ventilation are crucial to management of patients with opioid toxicity.
- The duration of action of many opioids, especially after overdose, is significantly longer than that of naloxone. Patients responsive to naloxone should be observed for recurrence of opioid toxicity after the effect of naloxone has resolved.
- Opioid withdrawal syndrome does not include altered cognition. Patients with known or suspected opioid withdrawal who also have altered cognition should be evaluated for another etiology of the altered cognition.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 161 Pesticides

Cynthia K. Aaron, James W. Rhee, and Bram A. Dolcourt

PERSPECTIVE

Pesticides, a generic term used to refer to all pest-killing agents, include numerous chemicals intended for use as insecticides, herbicides, rodenticides, fungicides, and fumigants. Many of these chemicals are general protoplasmic poisons affecting a wide range of organisms, including humans. Although space does not allow a comprehensive discussion of each individual chemical that may produce human toxicity, numerous chemical classes are commonly used as pesticides. These classes have associated characteristic clinical pictures that are important to recognize because patients with acute (and occasionally chronic) exposures to these agents come to the emergency department. In addition, other pesticides with particularly unique mechanisms of toxic effects are described.

ORGANOPHOSPHATE AND CARBAMATE INSECTICIDES

The organophosphate insecticide triethyl pyrophosphate was first synthesized in 1859 but was not used to replace nicotine as a pesticide until World War II. After World War II, these compounds were used as chemical warfare agents, as organophosphorus and carbamate insecticides, and as medicinal agents. After the negative publicity associated with the organochlorine dichlorodiphenyltrichloroethane (DDT), organophosphate insecticides soon became some of the most common pesticides for home and industrial use. Since the late 1990s, with the increased awareness of terrorism, nerve agents have gained prominence as weapons of mass destruction.[1]

Principles of Disease

Organophosphorus insecticides are highly lipid soluble and are readily absorbed via dermal, gastrointestinal (GI), and respiratory routes.[2] This lipid solubility results in the storage of organophosphorus compounds in body fat, making toxic systemic levels possible from gradual or rapid accumulation from repeated low-level exposures. The parent compound and its metabolites are acetylcholinesterase inhibitors, and many parent organophosphorus compounds are less potent than their metabolites (e.g., parathion to paraoxon), which may result in delayed onset of clinical toxicity.

Organophosphorus pesticides work by persistently inhibiting the enzyme acetylcholinesterase, the enzymatic deactivator of the ubiquitous neurotransmitter acetylcholine. Because of the global penetration of organophosphorus compounds, inhibition occurs at tissue sites (true acetylcholinesterase and represented by erythrocyte or red blood cell [RBC] cholinesterase) and in plasma (circulating pseudocholinesterase).[3,4] Inhibition of cholinesterase results in the accumulation and subsequent prolonged effect of acetylcholine at a variety of neurotransmitter receptors, including the sympathetic and parasympathetic ganglionic nicotinic sites, postganglionic cholinergic sympathetic and parasympathetic muscarinic sites, skeletal muscle nicotinic sites, and central nervous system sites (Fig. 161-1).[2]

Clinical Features

Signs and Symptoms

The accumulation of acetylcholine results in a classic cholinergic syndrome, manifested by hyperactivity of cholinergic responses at the receptor sites indicated previously. The clinical syndrome of muscarinic acetylcholinesterase inhibition is commonly called the SLUDGE syndrome (Table 161-1). This syndrome represents postganglionic acetylcholine-induced hollow end-organ general hypersecretion,[2] resulting in clinical findings that include miotic pupils, lacrimation, rhinorrhea, sialorrhea, bronchorrhea, vomiting, diarrhea, and urinary incontinence. Bradycardia is a classic sign of the cholinergic syndrome, but the increased release of norepinephrine from postganglionic sympathetic neurons precipitated by excess cholinergic activity at sympathetic ganglia may result in normal or even tachycardic heart rates (nicotinic effect). Sympathetic hyperactivity can cause diffuse diaphoresis, although this response is mediated by cholinergic receptors at preganglionic (nicotinic) and postganglionic (muscarinic) sites. The most lethal components of acetylcholinesterase inhibition occur in the brain and neuromuscular junction. A combination of sympathetic stimulation, involvement of the *N*-methyl-D-aspartate receptor, and enhanced acetylcholine concentrations can lead to seizures.[5] At the neuromuscular junction, excess acetylcholine causes hyperstimulation of the muscles with secondary paralysis. Because the diaphragm is affected, cholinesterase poisoning leads to respiratory arrest.[6]

Although the usual clinical picture of acute organophosphorus poisoning is impressive, toxicity from gradual, cumulative exposure may be much more subtle. These patients commonly exhibit vague confusion or other central nervous system complaints; mild visual disturbances; or chronic abdominal cramping, nausea, and diarrhea.[7]

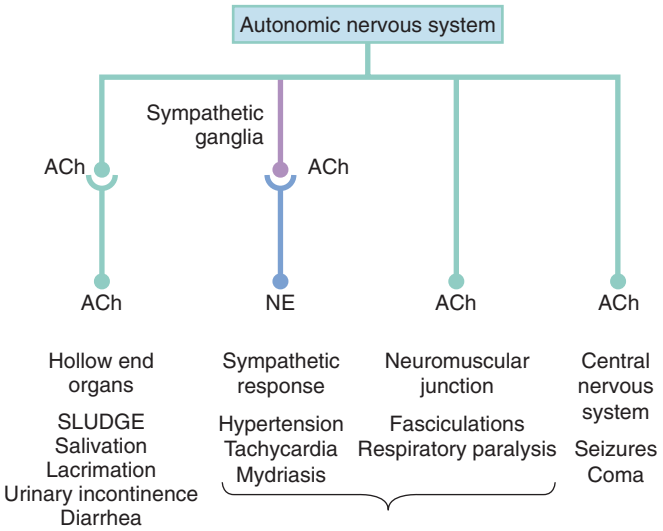


Figure 161-1. The autonomic nervous system (ANS) comprises the sympathetic and parasympathetic nervous systems. The sympathetic nervous system is also known as the thoracolumbar outflow, where the cell body lies in the spinal cord and the first synapse occurs in the sympathetic ganglia. The neurotransmitter in this first synapse is acetylcholine (ACh) (preganglionic), and the neurotransmitter in the postganglionic neuron with the target organ is norepinephrine (NE). In the parasympathetic nervous system (craniosacral outflow), nerves from the medulla and sacrum use ACh as the neurotransmitter in preganglionic and postganglionic target organs. The ANS is divided further into the muscarinic and nicotinic receptors, where atropine can block the muscarinic receptors but not the nicotinic receptors. The neuromuscular junction uses ACh as the effector neurotransmitter. In the brain, ACh is just one of several active neurotransmitters.

Table 161-1 SLUDGE Symptoms or DUMBELS

Salivation	**D**iarrhea/**D**iaphoresis
Lacrimation	**U**rination
Urinary incontinence	**M**iosis
Defecation	**B**radycardia/**B**ronchorrhea/**B**ronchospasm
Gastrointestinal cramps	**E**mesis
Emesis	**L**acrimation
	Salivation

Complications

Seizures and pulmonary hypersecretion, or bronchorrhea and bronchoconstriction, are prominent mechanisms of early morbidity and mortality in cases of poisoning from acetylcholinesterase inhibitors. Bronchorrhea is often incorrectly called noncardiogenic pulmonary edema because the origin of the excessive pulmonary fluids is from airway secretions and not transudation of fluid across the alveolar-capillary membrane. The obstruction of upper and lower airways, the potential intrusion of these bronchial secretions into alveolar sacs, and bronchoconstriction produce hypoxia, which is the primary concern in the initial stages of poisoning.[2]

Nicotinic hyperstimulation of skeletal muscle determines the ultimate morbidity and mortality of acetylcholinesterase inhibitors. Signs of skeletal muscle hyperactivity include involuntary twitches, fasciculations, and hyperactive reflexes. Muscle hyperactivity eventually gives way to muscle fatigue and paralysis, including the respiratory musculature and particularly the diaphragm.[6,8] Respiratory insufficiency may be delayed and result in death if not anticipated and corrected by mechanical or pharmacologic means.

Acetylcholinesterase inhibitors produce direct toxic effects on the central nervous system leading to neurologic signs of confusion, combativeness, seizures, and coma. Status epilepticus may occur in severely poisoned patients. Structural central nervous system damage may occur if seizures are not terminated rapidly.[9]

A unique effect of organophosphorus insecticides results from "aging," the irreversible conformational change that occurs when the organophosphorus agent is bound to the cholinesterase enzyme for a prolonged time. On average, for commercial organophosphorus agents some aging will occur by 48 hours, but aging may take longer. Once the enzyme has aged, an oxime antidote cannot regenerate the cholinesterase.

Diagnostic Strategies

Any patient with a full-blown cholinergic syndrome should be treated empirically without waiting for laboratory confirmation of decreased cholinesterase activity. Known or suspected exposure to cholinesterase inhibitors should be confirmed by ordering plasma and erythrocyte (RBC) cholinesterase levels. In acute exposures, the plasma cholinesterase levels decrease first, followed by decreases in RBC cholinesterase levels. The RBC cholinesterase level is more indicative of what is occurring at the nerve terminal.[3] Patients with chronic exposures may show only reduced RBC cholinesterase activity, with a normal plasma cholinesterase level. The true reflection of depressed cholinesterase activity is found in the RBC activity, and even a mild acute exposure may result in severe clinical poisoning. RBC cholinesterase levels recover at a rate of 1% per day in untreated patients and take approximately 6 to 12 weeks to normalize, whereas plasma cholinesterase levels may recover in 4 to 6 weeks. Other studies should focus on the evaluation of pulmonary, cardiovascular, and renal function and fluid and electrolyte balance. Patients presenting with no acidosis, or only a metabolic acidosis on the arterial blood gas, have lower mortality than those presenting with a respiratory or mixed acidosis.[10]

Differential Diagnosis

Few toxins or other clinical conditions produce the same symptoms as acetylcholinesterase inhibitors. A species of mushroom, *Amanita muscaria*, historically has been mentioned in the differential diagnosis, but it actually contains alkaloids that usually produce an anticholinergic (antimuscarinic) syndrome. A variety of conditions that induce excessive vagal responses (e.g., inferior wall myocardial infarction) may also produce some signs suggesting acetylcholinesterase inhibition, but other symptoms should make the primary cause apparent.

Management

Treatment is directed toward four goals: (1) decontamination, (2) supportive care, (3) reversal of acetylcholine excess at muscarinic sites, and (4) reversal of toxin binding at active sites on the cholinesterase molecule. Decontamination should start in the out-of-hospital phase of care to prevent greater absorption and subsequent toxicity and to protect care providers. Decontamination is particularly important in cases of dermal exposure; removal and destruction of clothing and thorough flushing of exposed skin may limit absorption and subsequent toxicity. Alternatively, dermal decontamination can be done with dry agents, such as military resins, flour, sand, or bentonite. Caregivers are at risk for contamination from splashes or handling of contaminated clothing. Treating personnel may be rotated

to limit their exposure to the organophosphates.[6] Caregivers should use universal precautions, including eye shields, protective clothing, and nitrile or butyl rubber gloves. In the case of ingestion, GI decontamination procedures are of questionable benefit because of the rapid absorption of these compounds. Profuse vomiting and diarrhea are seen early in ingestion and may limit[11] or negate any beneficial effect of additional GI decontamination.[12,13] Equipment, but not tissues, may be washed with a 5% hypochlorite solution to inactivate the cholinesterase inhibitor.

Because death is from airway and respiratory failure, supportive care should be directed primarily toward airway management, including suctioning of secretions and vomitus, oxygenation, and, when necessary, ventilatory support. Succinylcholine can be used for intubation but may have an extremely prolonged duration.[3] It is preferable to use a competitive neuromuscular blocking agent, such as rocuronium, for rapid sequence intubation in these patients, but increased dosing may be necessary. Although some authors have advocated the use of beta-blockers to control tachycardia, this may increase cardiovascular instability and worsen bronchospasm.[12,14] Most cardiovascular complications that occur in this setting rarely require specific therapy.

The definitive treatment of acetylcholinesterase inhibition starts with atropine.[2] A competitive inhibitor of acetylcholine at muscarinic receptor sites, atropine reverses the clinical effects of cholinergic excess at parasympathetic end organs and sweat glands. Large doses of atropine may be required.[15] Data suggest that the more rapid the atropinization, the faster control is obtained.[6,12,13] Suggested dosing is 1 or 2 mg of atropine (0.02–0.05 mg/kg) intravenously, with doubling of each subsequent dose every 5 minutes until there is control of mucous membrane hypersecretion and the airway clears.[6,12,13,16] If intravenous access is not immediately available, atropine may be administered intramuscularly. Patients may require 200 to 500 mg of atropine intravenously during the first hour, followed by prolonged continuous infusions of 5 to 100 mg/hr to maintain adequate secretion control.[16] Tachycardia and mydriasis may occur at these doses, but they are not indications to stop atropine administration. The endpoint of atropinization is drying of respiratory secretions, easing of respiration, and a mean arterial pressure greater than 60 mm Hg.[16] Animal evidence suggests that early rapid atropinization may limit seizure propagation and, in conjunction with diazepam, prevent status epilepticus.[9,17] Atropine is not active at nicotinic sites and does not reverse the skeletal muscle effects (e.g., muscle fatigue and respiratory failure).[3,13] Other anticholinergic medications such as diphenhydramine or ophthalmic agents may have benefit if atropine is scarce or unavailable; however, optimal intravenous dosing is not known.[18-20]

The second part of acetylcholinesterase inhibition treatment is the use of an oxime, such as pralidoxime (2-PAM, Protopam) or obidoxime (Toxigonin), to regenerate the organophosphate-acetylcholinesterase complex and restore cholinesterase activity at muscarinic and nicotinic sites.[3,6,13,21] There are various dosing regimens; the most common dose of pralidoxime is 1 or 2 g intravenously (pediatric dose, 25–50 mg/kg); additional doses may be given based on clinical response and serial cholinesterase levels. The medication may be given in a bolus of 1 or 2 g intravenously over 30 to 60 minutes every 4 to 8 hours or 500 mg/hr (pediatric dose, 10–25 mg/kg/hr).[21,22] The World Health Organization recommends an initial dose of 30 mg/kg followed by 8 mg/kg/hr continued for at least 24 hours or, if an infusion cannot be used, 30 mg/kg every 4 hours.[23] The infusion may be continued for several days with no adverse effects attributable to the pralidoxime; however, rapid administration can lead to hypertension, vomiting, and a transient reversible neuromuscular blockade.[24] The ideal dose of pralidoxime should be determined by monitoring the clinical condition of the patient and serial cholinesterase levels; the patient may require higher doses of oxime than recommended here. The World Health Organization recommended infusion dose of obidoxime is 4 mg/kg followed by 0.5 mg/kg/hr; alternatively, intermittent intravenous doses of 4 mg/kg, then 2 mg/kg, every 4 hours are given.[23] Pralidoxime and obidoxime can be administered by intramuscular injection. Indications for oxime therapy include respiratory depression/apnea, fasciculations, seizures, arrhythmias, cardiovascular instability, and use of large amounts of atropine. Oxime therapy can be used whenever the patient requires more than a limited amount of atropine (2–4 mg) to completely reverse the signs and symptoms of intoxication or in any patient who requires repeated doses of atropine. Oxime therapy and atropine are synergistic.

In the past, pralidoxime was only used within the first 24 hours because of aging of the organophosphate-acetylcholinesterase complex,[2] but not all organophosphates behave in a similar manner. Dimethyl and diethyl phosphoryl insecticides react differently at variable rates with acetylcholinesterase and oxime therapy. Many organophosphates are highly lipid soluble and slowly leach out of fat stores for up to 6 weeks, resulting in newly formed complexes with excellent reversal of the cholinesterase inhibition by pralidoxime clinically and by measurements of cholinesterase activity. Pralidoxime can also combine with unbound organophosphates and prevent their subsequent binding to nerve terminals. Even with optimal treatment, seriously intoxicated patients may require long-term supportive care, including ventilator support.[6,22]

In conjunction with atropine and oxime pralidoxime, patients with agitation, seizures, and coma should be treated with adequate doses of a benzodiazepine after the airway has been secured.[6,7,9,25] Although diazepam is most studied, any parenteral benzodiazepine may be used. The military has classically used diazepam autoinjectors for intramuscular use, but midazolam is the best intramuscular agent, with lorazepam as an alternate.

Sarin, soman, tabun, and VX are nerve agents that might be used in a terrorist attack. These agents have important differences from the common household or commercial organophosphorous insecticides. These agents tend to age very quickly, with tabun (GA) aging in 14 hours, sarin (GB) in 5 hours, soman (GD) in 5 or 6 minutes, and VX in 48 hours. Due to this rapid aging, reversal of nerve agent poisoning is very time sensitive. VX is an oily but highly toxic agent with low volatility. It does not readily vaporize, and because it has a low risk of inhalation, exposure is predominately transcutaneous. The other agents can be mostly dispersed into the air by explosion or vaporization, resulting in inhalation exposure. These agents do not require the extremely large doses of atropine but do require pralidoxime.[26-28] See Chapter 194 for further information on treatment.

New therapies for treatment of organophosphorus poisoning, including the use of *N*-acetylcysteine and exogenous acetylcholinesterase, show promise in research studies.[29,30] When added to anticholinergics, NMDA receptor antagonists may decrease organophosphorus compound–induced seizures.[31]

Disposition

Because of the prolonged effects of acetylcholinesterase inhibition, most patients with significant exposures require hospital admission. Occasionally, a person with chronic exposure, depressed cholinesterase levels, and mild visual or GI symptoms may be followed on an outpatient basis; however, some

patients, particularly those exposed to fenthion, initially present with signs and symptoms of mild exposure and progress to severe, life-threatening toxicity over time.[32] If plasma cholinesterase levels are available, they may be useful for treatment and disposition decisions. Asymptomatic or minimally symptomatic patients with normal or minimally depressed levels may be discharged after 4 to 6 hours with close outpatient follow-up to ensure that progressive toxicity does not occur. Patients with severely depressed levels (usually associated with significant symptoms) require admission and close monitoring, usually in a high-intensity care unit. Patients may develop rebound toxicity several days after apparently satisfactory response to initial treatment. Rebound toxicity may occur for many reasons, including persistent release of organophosphates from lipid stores.

A secondary syndrome, the intermediate syndrome (IMS), occurs 24 to 96 hours after exposure and consists of proximal muscular weakness specifically of the respiratory muscles. It is believed to be an abnormality at the neuromuscular junction. Patients with IMS present with respiratory failure several days after the acute cholinergic symptoms have resolved and may require several weeks of ventilatory support. It is theorized that this may occur as a result of inadequate initial oxime treatment or premature discontinuation of oxime therapy.[6,33] Oximes may be beneficial for IMS; however, this is controversial.[34] Finally, organophosphorus-delayed neuropathy has been reported as a different entity and affects an axonal enzyme, neurotoxic esterase, and leads to a peripheral sensorimotor neuropathy 7 to 21 days after exposure.[6]

CARBAMATE INSECTICIDES

Carbamate insecticides are another class of acetylcholinesterase inhibitors and are differentiated from the organophosphorus compounds by their relatively short duration of toxic effects. Carbamates inhibit acetylcholinesterase for minutes to 48 hours, and the carbamate-cholinesterase binding is reversible.[2] Although the clinical picture of acute carbamate poisoning may be identical to that of organophosphate poisoning, the toxic effects are limited in duration and patients may require only decontamination, supportive care, and treatment with adequate doses of atropine. Although the duration is limited in scope, patients may become just as sick and require assisted ventilation and seizure therapy. The use of pralidoxime is controversial in carbamate poisoning; an animal study suggests that pralidoxime administration may produce greater toxicity in cases of carbaryl (Sevin) poisoning, although the author has used pralidoxime in carbaryl-poisoned humans without adverse events.[35] Nevertheless, if doubt exists as to whether a severe poisoning is due to a carbamate or organophosphate, pralidoxime should be administered. It is the author's practice to use oximes when patients present with a cholinergic toxindrome and a history of exposure of organophosphorus or carbamate insecticides.

CHLORINATED HYDROCARBON INSECTICIDES

DDT, the prototype of chlorinated hydrocarbon insecticides (sometimes referred to as organochlorine insecticides), was first used extensively during World War II for the successful control of typhus and malaria and was used widely in the United States as a general insecticide after the war. Because of the effectiveness of DDT, many other chlorinated hydrocarbon insecticides were developed. These insecticides were used extensively in agricultural, commercial, and residential pest control. However, although these insecticides were very effective, their widespread use, long half-life, and persistence had negative ecologic repercussions. Many of these insecticides have been targeted as persistent organic pollutants by international agencies, leading to their restricted use.[36]

Although chlorinated hydrocarbon insecticides are no longer used in the United States for agricultural use, γ-hexachlorobenzene, better known as lindane (Kwell), is still used as a topical medicinal agent for the treatment of head lice and scabies. As a result, lindane is probably the most common cause of toxicity from an organochlorine compound in the United States. Given its toxicity, lindane is no longer a first-line agent for the treatment of scabies.[37] In 2001, California issued a ban on the use and sale of lindane, and other states are considering a ban on lindane.[36]

Principles of Disease

Chlorinated hydrocarbon pesticides are highly lipid soluble. They are readily absorbed through dermal, respiratory, and GI routes.[38] Dermal and GI exposures account for most clinical poisonings, including inappropriate external use of lindane or other compounds and the occasional accidental oral administration of lindane. Because they are so lipid soluble, these compounds are stored in fatty tissues, and repeated small exposures result in accumulation and eventual clinical toxicity.[39]

Chlorinated hydrocarbon insecticides primarily affect axonal membranes, resulting in neuronal irritability and excitation. Toxicity occurs in central and peripheral neurons.[40] Some of the organochlorines can inhibit the chloride channel of γ-aminobutyric acid (GABA) receptors, leading to decreased inhibition of the central nervous system.[41] Chlorinated hydrocarbons induce hepatic microsomal enzymes and produce hepatic tumors in some animals. This potential carcinogenicity is the basis for current human health concerns, but it is only theoretical. Chlorinated hydrocarbon insecticides, including chlorinated hydrocarbon solvents, may sensitize the myocardium to circulating catecholamines and increase susceptibility to ventricular dysrhythmias, such as tachycardia and fibrillation.[40]

Clinical Features

Signs and Symptoms

The primary clinical picture of acute or cumulative toxicity from chlorinated hydrocarbon pesticides is related to their neurotoxicity. Premonitory peripheral signs and symptoms, such as tremor or paresthesias, may be absent, and the first sign of toxicity may be the acute onset of seizure activity.[42] Additional signs include confusion, combativeness, and muscle twitching. Untreated, continued muscle activity can lead to hyperthermia, metabolic acidosis, and rhabdomyolysis with secondary acute tubular necrosis.[43] Because many of these agents are halogenated, ventricular dysrhythmias may occur from catecholamine sensitization and direct myocardial toxic effects. Immediate hepatotoxicity is unlikely without secondary hyperthermia or other metabolic complications.[40,44] Long-term exposure may result in neuropsychiatric symptoms.[45] Diagnosis may be difficult in chlorinated hydrocarbon pesticide exposure because the patient may be unable to provide a history. Nonhospital personnel are often in the best position to obtain information concerning pesticide availability and use and the situation surrounding the exposure. Another clue is the solvent odor and oily feel of the hydrocarbon solvent containing the highly lipid-soluble chlorinated hydrocarbon pesticides.

Diagnostic Strategies

Diagnosis must be confirmed by history or by investigation at the site of the exposure to establish the offending agent with certainty. No specific tests are readily available to confirm the diagnosis of chlorinated hydrocarbon pesticide poisoning. Some reference laboratories can measure fat and plasma levels, but results are difficult to interpret and seldom available during the acute phase of toxicity.[39,44] Ancillary laboratory and other studies should be based on the clinical condition, complications, and consideration of alternative diagnoses on an individual basis.

Differential Considerations

The differential diagnosis includes virtually every condition that produces seizures. The specific diagnosis depends on obtaining the history of significant acute or chronic chlorinated hydrocarbon pesticide exposure.

Management and Disposition

Skin decontamination with soap and water may reduce toxicity in acute dermal exposure. High lipid solubility results in rapid absorption, and delayed GI decontamination is not of benefit. Elimination of some chlorinated hydrocarbon insecticides can be increased, and repeat doses of cholestyramine (4 g orally every 8 hours) given during a mass exposure of chlordecone (a chlorinated hydrocarbon insecticide) enhanced the fecal elimination of this compound.[45-47]

The primary therapeutic objective is seizure control, which is best accomplished with short-acting benzodiazepines or barbiturates. Recurrent seizures or status epilepticus may require high-dose barbiturates and paralyzing agents (e.g., pancuronium or vecuronium) to prevent secondary morbidity from continuous motor activity in prolonged seizures. The seizure activity is usually self-limiting, lasting only 1 or 2 days even in severe cases.[42,46,48]

Continuous cardiac monitoring during the acute phase is indicated because of the potential for myocardial sensitization. Ventricular dysrhythmias are most likely to occur during seizure activity because of the high circulating catecholamine levels and other metabolic abnormalities present during seizures. Dysrhythmias should be treated with beta-adrenergic antagonists, such as propranolol, metoprolol, or esmolol, to reduce the effect of catecholamines on the myocardium.

Additional treatment should focus on the complications of prolonged seizure activity, such as rapid external cooling measures for hyperthermia. Metabolic acidosis is almost always transient and resolves spontaneously without treatment. Rhabdomyolysis and myoglobinuria should be anticipated. Other complications of seizures should be treated as indicated. Because of their high lipid solubility, chlorinated hydrocarbon pesticides are distributed largely in tissues and are not amenable to hemoperfusion, dialysis, or other attempts to enhance elimination.

Patients who have acute or cumulative chlorinated hydrocarbon pesticide toxicity require hospitalization until their seizures are controlled, complications have resolved, and they have returned to their neurologic baselines; this usually occurs within 1 or 2 days. Severe complications, such as renal failure from rhabdomyolysis, may prolong the clinical course.

■ SUBSTITUTED PHENOLS

The substituted phenols include dinitrophenol (DNP), pentachlorophenol, and dinitrocresol. These compounds have been used since the 1930s as insecticides, termiticides, herbicides, and wood preservatives. They are currently used in agricultural, commercial, and residential applications, including over-the-counter preparations for home gardeners. Substituted phenols such as DNP are abused as weight-reduction agents and occasionally are used in illegitimate weight-reduction operations.[49]

Principles of Disease

Substituted phenols are readily absorbed through the skin and GI tract, and aerosols may be absorbed through the respiratory tract. There is some potential for cumulative toxicity with repeated exposures, but much less so than with the organophosphorus and chlorinated hydrocarbon pesticides previously discussed.

Substituted phenols produce their toxicity by uncoupling cellular oxidative phosphorylation; this leads to inefficient production of high-energy phosphate substrates and increased cellular use of oxygen, glucose, and water, with subsequent excessive heat production.[50] These compounds are commonly used during the summer when the external heat predisposes users to increased toxicity.[51,52] In addition, nitro-substituted phenols may produce methemoglobinemia.

Clinical Features

Patients with substituted phenol toxicity present hypermetabolic and hyperthermic, tachycardic, tachypneic, and profusely diaphoretic. They may also have a relative hypovolemia from excessive insensible fluid losses through sweating and metabolic consumption. Loss of energy production in the brain results in neurologic changes ranging from confusion to seizures and coma. Renal and hepatic injury, and rhabdomyolysis with myoglobinuria, is common.[43] Because phenols are generally corrosive, patients with dermal exposures often have irritation or chemical burn, and some substituted phenols, such as dinitrophenol, produce a characteristic yellow staining of the skin or mucous membranes at the site of absorption. This same staining can be found throughout the internal organs at autopsy.[52]

Cataracts are a complication of long-term exposure. This condition was common in patients who used substituted phenols as part of a weight-reduction regimen and was partially responsible for the banning of this substance. The cataracts regress spontaneously after exposure is discontinued.[53]

Diagnostic Strategies

Laboratory evaluation of patients with substituted phenol toxicity is aimed at identifying deficiency of aerobic metabolic substrates, including oxygen, glucose, and water. A complete blood count may reveal hemoconcentration and a nonspecific leukocytosis. Electrolyte abnormalities depend on the duration and severity of symptoms, environmental factors, and complications or underlying disease states. Arterial blood gas measurements show varying degrees of acidosis, depending on the extent of anaerobic metabolic activity due to oxidative phosphorylation uncoupling and associated tissue hypoperfusion from dehydration. Serum enzyme determinations document the extent of hepatic, renal, and skeletal muscle injury. The presence of phenolic compounds in the urine of a patient with this clinical picture strongly suggests substituted phenol pesticides as the causative agent.

Differential Considerations

Acute toxicity from substituted phenol poisoning is difficult to distinguish from typical environmental heat-related emergencies or toxicity from sympathomimetics or salicylates. Continued evidence of hypermetabolic activity and metabolic acidosis after routine cooling measures, rehydration, and other supportive care should lead to a consideration of toxin-induced states. Persistent hyperthermia and acidosis in a weight lifter should trigger concern for DNP abuse. The presence of yellow staining virtually clinches the diagnosis.[52]

Management and Disposition

Initial treatment is directed toward control of body temperature; treatment of acidosis; protecting the kidneys, brain, and liver from hyperthermic damage; and providing the basic substrates for excessive metabolic activity—oxygen, glucose, and water.[52] If the chemical exposure is known or recognized, early decontamination of affected sites is important. Therapy should be directed toward prevention or minimization of the associated complications discussed previously.

Patients with mild toxicity can usually be stabilized after a few hours and discharged from the emergency department. Patients with significant organ system injury or a high likelihood of complications, such as prolonged or recurrent seizures, significant alteration of consciousness, and rhabdomyolysis, require admission, usually to the intensive care unit.

CHLOROPHENOXY COMPOUNDS

The chlorophenoxy pesticides were developed in the early 1940s and hailed as a selective herbicide particularly effective against broadleaf weeds. This class of herbicide developed a special notoriety during the Vietnam War as Agent Orange, a defoliant used in aerial spraying. Agent Orange consisted of a mixture of 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). 2,4,5-T is almost always contaminated with isomers of tetrachlorodibenzo dioxin. This concern regarding dioxin exposure has led to the extensive medical investigations of Vietnam veterans and severe restrictions on the production and use of 2,4,5-T.[54] Because of the relative safety and broadleaf selectivity of 2,4-D, however, most home gardeners have at least one chlorophenoxy compound on a shelf in their garages, and some old cans may contain 2,4,5-T or a mixture of both compounds.

Principles of Disease

Chlorophenoxy compounds may be absorbed through the skin, GI tract, and respiratory tract, but almost all significant poisonings occur as a result of accidental or intentional ingestion. The lipid solubility of these compounds is low, and excretion is fairly rapid, so cumulative toxicity from repeated exposures does not occur.[55]

Although skeletal muscle is the target organ for chlorophenoxy herbicides, the exact mechanism is obscure.[40,56] Depending on severity, muscular abnormalities may range from generalized muscle weakness to acute rhabdomyolysis. Higher doses may also uncouple oxidative phosphorylation and cause a hypermetabolic state similar to that seen with the substituted phenols.[40]

Clinical Features

Similar to most organic pesticides in an organic solvent, the chlorophenoxy herbicides may produce mild, nonspecific dermal and GI irritation with nausea, vomiting, and GI distress. Large exposures are likely to cause systemic symptoms ranging from diffuse myotonia and muscle fasciculations progressing to rhabdomyolysis, hyperthermia, and a hypermetabolic state with metabolic acidosis.[57]

Diagnostic Strategies

There are no specific tests for the detection of the chlorophenoxy compounds. Laboratory evaluation should be aimed at evaluating skeletal muscle injury and its complications. Severely poisoned patients require generalized organ system evaluation, including hepatic and renal function, because of the effects of rhabdomyolysis and hyperthermia.

Differential Considerations

Differential diagnostic possibilities include other causes of acute myopathy. The manifestation of chlorophenoxy compound toxicity is extremely rare, however, and without a definite history or strong suspicion of exposure, other explanations for acute myopathy should be pursued.

Management and Disposition

Treatment consists of initial skin decontamination, activated charcoal or gastric lavage with early presentation, and basic supportive care. Serious toxic effects develop within 4 to 6 hours after ingestion, and treatment can be directed toward the specific problems of muscle weakness, airway and ventilatory support, and rhabdomyolysis. Treatment of hyperthermia and acidosis has been discussed previously.

Asymptomatic or minimally symptomatic patients may be discharged with reassurance after 4 to 6 hours of observation. Patients with significant toxicity should be admitted for close observation and monitoring.

BIPYRIDYL COMPOUNDS

The bipyridyl (also called dipyridyl) compounds, paraquat and diquat, were first investigated in the late 1950s and early 1960s. They are extremely effective contact herbicides that are rapidly inactivated by the surrounding soil in the event of overspray. Paraquat is activated when exposed to sunlight, which led to its use as the herbicide of choice during aerial spraying of marijuana by the U.S. and Mexican governments. After spraying, however, growers simply would harvest the crops before the plants were exposed to enough sunlight to damage the plants, resulting in an apparently healthy harvest but one contaminated with paraquat. The burning of marijuana pyrolyzes paraquat into a nontoxic form, a fact that was lost in the warning messages dispensed by the government at that time.[58]

Principles of Disease

Of the two bipyridyl compounds in use, paraquat is the most clinically significant in terms of number of cases and toxic effects. Paraquat use is tightly regulated in the United States but is widespread throughout the world. Diquat is less regulated in the United States and is included in some formulations of Roundup. Paraquat is absorbed through the skin, GI tract, and respiratory tract. Almost all fatal exposures have resulted from the ingestion of paraquat, although a few case reports have involved extensive skin contamination.[59] Toxicity has occurred, but no fatal cases have been reported from inhalation of paraquat vapor or aerosols. Diquat is poorly

absorbed through intact skin, and most cases of toxicity result from ingestion.[60] A formulation change in Sri Lanka, adding an emetic—magnesium sulfate—and an alginate binder, decreased mortality by 9.5% in cases of intentional ingestion of paraquat.[61]

Paraquat's toxic effect results from the production of superoxides created during cyclic oxidation-reduction reactions of the compound in tissues. Lipid peroxidation of cellular membranes seems to be one significant pathway of cellular injury.[62,63]

Paraquat selectively concentrates in the lungs because of an amine uptake mechanism in alveolar cells. In addition, high concentrations of oxygen significantly increase the extent of paraquat-induced injury so that the lungs are the major target organ. The pathophysiologic lesions include direct injury to the alveolar-capillary membrane followed by surfactant loss, adult respiratory distress syndrome, progressive pulmonary fibrosis, and respiratory failure.[64] Paraquat damages other major organ systems by the same cellular membrane effects, including the liver, kidneys, heart, and central nervous system. Diquat has similar effects, with most of its toxicity concentrated in the kidneys and not preferentially in lung tissue.[60]

Clinical Features

Signs and Symptoms

Both agents are extremely corrosive and cause nausea, vomiting, and severe chemical burns of the oropharynx soon after ingestion. Patients who ingest concentrated paraquat frequently die as a result of esophageal perforation and mediastinitis before development of the characteristic progressive pulmonary injury. Patients with dermal paraquat exposures show significant skin irritation, and ocular exposures may produce severe corneal injury.[65]

The classic finding of paraquat-induced progressive pulmonary injury usually occurs over 1 to 3 weeks, although the clinical course varies considerably with severity of poisoning, involvement of other organ systems, and underlying medical problems.[64] This is not a factor in the emergency department, and the delayed pulmonary injury is not discussed here. In contrast to paraquat, diquat usually spares the lungs but produces similar toxicity in all other organ systems.[60]

Diagnostic Strategies

Paraquat is measurable in the blood, and the nomogram provides a fairly accurate prognosis. The assay is not readily available in the United States, and in most cases, by the time the results are obtained, nothing more can be done to change the eventual outcome. There is a qualitative bedside test that uses the reduction of paraquat or diquat in alkalinized urine by sodium dithionite, but the reagent frequently is not available.[57] Studies other than evaluation of caustic GI injury and pulmonary and renal damage should be directed toward secondary effects of the poisoning.

Differential Considerations

A person with acute paraquat or diquat ingestion is likely to present with the initial complaint of an acute corrosive injury; the differential diagnosis should encompass all corrosive agents. Successful therapeutic intervention for paraquat toxicity is extremely time dependent, and patient outcome depends on the history. Any patient who has evidence of pulmonary or other organ injury caused by paraquat exposure is probably already beyond recovery.

Management and Disposition

There are no studies comparing various treatment strategies, but the key to successful treatment of an acute paraquat exposure likely depends on early decontamination measures to limit absorption. Thorough skin cleansing is obvious and straightforward in dermal exposures. Careful gastric lavage and administration of activated charcoal may be lifesaving, but these measures should be undertaken in consultation with a poison center and may even be hazardous in the context of a corrosive ingestion. Early endoscopy and surgical intervention may be necessary if there is evidence of esophageal perforation and mediastinitis. Although Fuller's earth and bentonite are recommended as adsorbents in paraquat ingestions, activated charcoal is much more readily available in the United States and has equal, if not greater, efficacy.[66]

Although controversial, many toxicologists recommend rapid initiation of charcoal hemoperfusion to rapidly lower plasma paraquat levels and to limit pulmonary and other organ system uptake of paraquat. Many also recommend serial and combined hemoperfusion and hemodialysis, particularly during the first 24 hours after exposure.[67,68] There are multiple suggested treatment protocols for paraquat, such as *N*-acetylcysteine, low fraction of inspired oxygen, and cytoprotective agents such as amifostine, but no single therapy has proven consistently successful.[69,70]

Patients with any significant dermal paraquat exposure and all patients with ingested paraquat require hospitalization and consideration of enhanced elimination therapy. These patients should be observed and treated expectantly until paraquat levels are reported to be nonexistent or nontoxic.

PYRETHRINS AND PYRETHROIDS

Pyrethrins are naturally occurring insecticides of the yellow *Chrysanthemum cinerariifolium* and *Tanacetum cinerariifolium* and are among the oldest known insecticides, first used in the 1800s. Extracts of the dried flowers contain the active compound pyrethrum, which contains six naturally occurring pyrethrins. In addition, numerous synthetic derivatives, pyrethroids, have been produced and have greater chemical stability than the natural pyrethrins. Type II pyrethroids contain a cyano substituent and are among the more toxic formulations of this class. These present a potential danger to humans, but type II pyrethroids are generally less toxic than many of the other classes already discussed and are being used more commonly.

Principles of Disease

Because pyrethrins and pyrethroids are most commonly aerosolized, inhalation is the most likely route of exposure. The patient may not be aware of an exposure because pyrethrin and pyrethroid aerosols are used frequently as automated insect sprays in public areas, such as in airplanes. In these situations, concentrations rarely reach levels likely to produce symptoms in any but the most sensitized patient. Occasional ingestions have been reported, and significant toxicity is possible via this route. Systemic absorption via the dermal route is unlikely, but topical effects are possible. Most pyrethrins and pyrethroids are rapidly metabolized and deactivated in human exposure, so cumulative toxicity is not a problem. Piperonyl butoxide, which is added as an insect "knockdown" agent, may increase the toxicity of the pyrethrum derivatives.

Pyrethrins and pyrethroids have a variety of effects in humans and other mammals.[71,72] Clinically, the naturally

occurring pyrethrins can cause sensitization and allergic phenomena. This property does not occur with the synthetic pyrethroids. Both classes are associated with sodium channel blockade, slowing the rate of activation of the sodium channel and extending the time during which the channel is open. In addition, both classes affect GABA receptors, inhibiting chloride channel function. Less significant effects include potentiation of nicotinic cholinergic neurotransmission, enhancement of norepinephrine release, and inhibition of calcium adenosine triphosphatase interference with sodium-calcium exchange across membranes.[71,72]

Clinical Features

Allergic manifestations, including potentially life-threatening events, may occur after acute inhalation or dermal exposure. Inhalation exposure often occurs with the use of a pyrethrin-based aerosol in an enclosed, poorly ventilated space. Local effects include lacrimation, rhinitis, rhinorrhea, sneezing, throat irritation, and pharyngeal and laryngeal edema. Lower respiratory effects include cough, shortness of breath, chest pain, and wheezing. Skin rashes, consistent with a contact or allergic dermatitis, and photosensitivity may contribute to the dermatologic picture. There is potential for allergic cross-reactivity in patients who are allergic to ragweed.

Sodium channel-mediated and GABA-mediated chloride channel effects mediate neurologic signs and symptoms. Facial paresthesias have been reported, and seizures occur with massive ingestions.[71,72] Nonspecific symptoms, such as headache, fatigue, dizziness, and weakness, have been reported.

Diagnostic Strategies

No laboratory tests are available to measure pyrethrins or pyrethroids in a clinical setting.

Differential Considerations

The differential diagnosis of the signs and symptoms of pyrethrin or pyrethroid toxicity includes the usual causes of bronchospasm and seizures and other acute neurologic complications.

Management and Disposition

Decontamination, including removal from a contaminated environment or washing, should be the first step. Definitive treatment is supportive and directed at the respiratory and neurologic complications.

Disposition of a patient with exposure to pyrethrins depends on the severity of the underlying complications. If discharge from the emergency department is anticipated, the patient should be counseled with regard to the possibility of recurrent allergic phenomena on reexposure.

GLYPHOSATE

Glyphosate (Roundup) was introduced as a broad-spectrum nonselective herbicide in 1971 by the Monsanto Agricultural Company. It is the isopropyl ammonium salt of a noncholinesterase-inhibiting organophosphate herbicide. It is sold mixed with the surfactant polyoxyethylene amine (POEA). Because it is effective on broadleaf weeds and does not undergo photodecomposition, it is popular in the home market. Newer formulations of Roundup may contain diquat.

Principles of Disease

Glyphosate is poorly absorbed through the skin so that most exposures result from ingestion. The concentrated solution is extremely irritating, and patients may vomit with subsequent aspiration. The concentrated solution is provided as 41% glyphosate in 15% POEA. The directions state that it should be diluted to a 1% glyphosate solution.

Glyphosate is toxic to plants by inhibition of the enzyme 5-enolpyruvylskikimate-3 phosphatase-synthetase in the shikimic acid metabolic pathway. After application of glyphosate on the leaves, it is transported to the roots, where the enzyme is active. Humans lack this enzyme and are unlikely to develop toxicity. Reported toxicity is believed to result largely from the surfactant POEA and may reflect the direct corrosive effect from the amine salt, or it may uncouple oxidative phosphorylation.[73]

Clinical Features

Most ingestions of the dilute solution cause only minimal symptoms, including GI distress. Patients ingesting large volumes of dilute solutions or moderate volumes of concentrated solutions complain of sore throat, nausea, abdominal pain, and fever. They may develop vomiting, diarrhea, respiratory distress, noncardiogenic pulmonary edema, dysrhythmias, shock, coma, and renal failure. Acidosis reflects poor tissue perfusion and cardiovascular compromise.[73] Negative prognostic indicators include shock, acidosis, and persistent hyperkalemia.[73]

Diagnostic Strategies

The critical element in diagnosis is history of ingestion. Laboratory analysis may demonstrate an anion gap metabolic acidosis, hypoxemia, and hyperkalemia. Elevated transaminases may occur in 30% of ill patients, and signs of renal failure may develop in persistent shock states. The electrocardiogram may show ventricular dysrhythmias and secondary signs of hypoxemia.[73]

Differential Diagnosis

The differential diagnosis includes most corrosive ingestions and causes of shock. The findings of hyperkalemia and metabolic acidosis may suggest hydrofluoric acid ingestions. A normal ionized calcium level may help rule out hydrofluoric acid exposure. Any cause of aspiration should also be considered. The history is the most useful factor in the differential diagnosis.

Management and Disposition

Treatment is supportive. The patient may require positive-pressure ventilation to overcome the noncardiogenic pulmonary edema. POEA may also be a direct cardiac depressant; inotropic agents can be useful. Hyperkalemia should be treated in the usual manner with fluids, medications to shift potassium into the cell (e.g., bicarbonate, calcium, and beta-adrenergic agonists), and kayexalate. If there is an indication of significant corrosive ingestion, early endoscopy with placement of stent, high-dose steroids, and laparotomy may be considered.

Asymptomatic patients with small ingestions of dilute substances may be observed for 6 hours and discharged. Patients with complaints consistent with corrosive ingestions require admission and GI evaluation. Any patient with pulmonary complaints requires admission and intensive supportive care.

■ DEET

N,*N*-diethyl-*m*-toluamide or *N*,*N*-diethyl-3-methylbenzamide (DEET) is not a pesticide but an insect repellent. It is the most widely used chemical insect repellent in the United States. DEET was developed by scientists at the U.S. Department of Agriculture in 1946, patented by the U.S. Army soon thereafter, and released to the general public in 1957.[74] With the prevalence of Lyme disease and other concerning arthropod-borne diseases, the use of DEET has increased greatly. Formulations containing DEET range from 5 to 100%. The U.S. Army routinely used 75% solutions until 1987 but now uses a 35% time-release, polymer-based formulation. The American Academy of Pediatrics (AAP) recommends 30% as the maximum concentration that should be used in infants and children. The AAP does not recommend use of DEET in infants younger than 2 months.[75]

Principles of Disease

DEET is lipophilic and can be absorbed through the skin. Skin absorption and toxicity increase with repeated applications, increased ambient temperatures, sweating, and abraded, thin skin. Ingestion may lead to toxicity.[76] DEET primarily affects the central nervous system. Its mechanism of action is unknown. It may sensitize the skin and cause allergic reactions.

Clinical Features

Prolonged skin contact may lead to contact dermatitis, and prolonged contact with high concentrations has led to skin blisters. Patients who have ingested DEET or have repeated skin applications in a hot enclosed environment that enhances absorption have developed liver function test abnormalities and neurologic findings, including encephalopathy, seizures, movement disorders, and coma.[76] Most exposures to DEET result in no, or minimal, toxicity and should not preclude its use in susceptible populations in which significant arthropod-borne diseases are prevalent.[77]

Diagnostic Strategies

Exposure history is central to the diagnosis. Although DEET can be detected in urine, most laboratories are not able to do this testing during the acute toxicity phase. An electroencephalogram may be useful in a patient with coma or encephalopathy and seizures.

Differential Diagnosis

The differential diagnosis includes conditions that may cause encephalopathy, seizures, and movement disorders. Such conditions include drug intoxication, infectious causes, drug interactions, and structural defects.

Management and Disposition

Treatment is supportive. If DEET exposure is suspected, the skin should be thoroughly decontaminated. Oils or lipophilic agents should be avoided because they enhance skin absorption. After DEET ingestion, milk products and oil-containing foods should be avoided until the GI tract has eliminated the offending agent. Seizures should be treated with benzodiazepines.

Asymptomatic patients who have ingested DEET-containing repellents should be observed for 4 to 6 hours. Patients who develop neurologic symptoms should be admitted and observed.

KEY CONCEPTS

- All patients exposed to cholinesterase inhibitors should have skin decontamination. Emergency department personnel need to be protected during this process.
- Morbidity in cholinesterase inhibitor exposure results from early airway compromise secondary to copious secretions, status epilepticus, and late respiratory failure.
- Cholinesterase inhibitor exposure may include bradycardia or tachycardia, hypertension or hypotension, and miosis or mydriasis.
- The clinical endpoint for atropine administration is drying of airway secretions.
- Pralidoxime should be given to all organophosphorus-poisoned patients who require atropine regardless of time since exposure.
- With chlorinated hydrocarbon exposures, skin decontamination with protection of personnel is indicated.
- In chlorinated hydrocarbon exposures, catecholamine administration is avoided.
- Supportive care, temperature control, and seizure control are important.
- Rapid cooling and substrate provision (glucose) are the two most important therapies in substituted phenol toxicity.
- Diagnosis of chlorophenoxy compound toxicity depends on a history of accidental or deliberate ingestion.
- Rapid GI decontamination may be indicated in paraquat and diquat ingestions despite the corrosive injury.
- The predominant form of pyrethrin and pyrethroid toxicity is allergic.
- Small ingestions of dilute glyphosate solutions are GI irritants. Large or concentrated ingestions may cause acidosis, hyperkalemia, and noncardiogenic pulmonary edema.
- DEET should not be applied over abraded or raw skin.
- DEET applications to children should be restricted to 30% solutions, should not be used under occlusive clothing, and should be washed off completely between applications.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 162

Plants, Mushrooms, and Herbal Medications

Richard D. Shih

PERSPECTIVE

Botanicals such as plants, herbal products, and mushrooms have a long-standing and important place in medical history. Their use as therapeutic agents has been documented in the earliest of medical writings. The extraction of alkaloids from the opium poppy in the 1800s was a forerunner of modern pharmacology. The general public increasingly is using herbal products for medicinal purposes. Despite the tremendous growth in popularity of herbal products, data on herbal efficacy and toxicity are limited. This chapter does not focus on the medicinal use of natural products, but rather the toxicology related to their exposure or utility.

Epidemiology

Although plants, mushrooms, and herbal products all are derived naturally, they have different exposure patterns and epidemiology.

Unintentional Childhood Exposure

Unintentional childhood exposure occurs most commonly with plants. Approximately 5% of all poison center calls involve plants. Of these, about 75% involve children younger than 6 years. Most of these cases involve household plants with a limited amount of plant or toxin ingested, resulting in little or no toxicity.[1]

Misidentification of Botanical

Natural plant and mushroom gathering for personal ingestion is a popular activity. Mistakes while foraging commonly occur, with the potential for serious toxicity and death. In contrast to unintentional childhood exposures, foraging accidents usually involve adults and plants or mushrooms and are associated with a much larger toxin burden because a larger quantity of the botanical is ingested. Another type of botanical misidentification occurs with herbal products when plants used for herbal manufacture are misidentified by the manufacturer and incorrectly packaged and marketed.

Plants as Drugs of Abuse

Many plants and mushrooms are abused for their mind-altering potential, including hallucinogenic mushrooms, peyote, kava kava, and anticholinergic plants, such as jimsonweed.[2,3]

BOTANICAL IDENTIFICATION

Identification of the botanical in question is most useful, but most patients and medical professionals do not have any knowledge of botany or plant identification. The name of the plant or mushroom is often confusing because the scientific name is not typically known, and common names often overlap. Most emergency department personnel cannot identify common plants, such as mistletoe, holly berries, philodendron, and others. Several resources may be helpful, including plant atlases, CD-ROM plant databases, a local botanical expert, botanical garden personnel, or a poison center. Alternatively, digital photography of the plant or mushroom in question can be quickly e-mailed to a local expert to aid in identification.[4] With herbal products, the product name or herbal plant may be known. Because of the limited Food and Drug Administration (FDA) regulation, however, the purported herb might have been harvested from the wrong plant or contaminated with other toxic material.

Plants

Among more than 100,000 plant exposures reported to U.S. poison centers annually, most plant exposures occur in children (<6 years old), involve household plants, and 80% of exposed individuals never develop any toxicologic symptoms. Hospitalization for plant poisoning is rare, with fatalities occurring in less than one in a million exposures. Of thousands of different plant species, only a few are dangerously toxic.[5,6] More detailed discussion of specific plants focuses on plants that are most poisonous and most commonly implicated in human exposures.

Abrus precatorius

Abrus precatorius (Fig. 162-1), known as the jequirity pea, rosary pea, prayer bean, Seminole bean, Indian bean, and crab's eye, contains the toxin abrin, which affects protein synthesis, leading to cell death. The toxin is found in highest concentration in the seeds, which are used in jewelry or decoration. Because of their attractiveness, the seeds often are ingested by children. The hard, shiny coat causes most seeds to pass through the gastrointestinal tract without being digested. If the seeds are chewed or do not pass through the bowel rapidly and become digested, abrin is released; nausea, vomiting, and abdominal pain can be severe, and fluid and electrolyte balance is disturbed.[7–9] Systemic absorption of the

Figure 162-1. *Abrus precatorius* (jequirity pea or rosary pea). (Courtesy of Steven Setzer.)

toxin is limited because the protein is enzymatically digested. Rare parenteral exposure of small amounts is associated with severe toxicity and possible death. Treatment is supportive, with attention to fluid rehydration and electrolytes. Asymptomatic patients should be treated with activated charcoal, and whole-bowel irrigation may be helpful in moving numerous seeds more rapidly through the gastrointestinal tract.

Brassaia

The *Brassaia* is a popular indoor plant known as schefflera, umbrella tree, Australian umbrella tree, dwarf schefflera, rubber tree, and starleaf. This plant contains calcium oxalate crystals, which can cause mouth pain, but most ingestions cause mild or no symptoms.

Capsicum annum

Capsicum annum includes many types of peppers (e.g., chili pepper, red pepper, bell pepper) and contains the active toxin capsaicin. This alkaloid releases and depletes selected nerve terminals of substance P, causing a severe local inflammatory response, manifested by swelling, fluid exudation, and pain, which resolves rapidly as capsaicin depletes substance P. Capsaicin is not absorbed well through intact skin, but symptoms occur rarely, with prolonged and intense exposure.[10] Ingestions often cause gastrointestinal symptoms depending on the amount of toxin exposure. Most capsaicin exposures involve a pepper spray product, causing chemical conjunctivitis.[4] Keratitis can occur and is assessed with fluorescein. Treatment consists of local irrigation and analgesics. Despite their often dramatic appearance, cases resolve rapidly over several hours without sequelae.[11,12] Inhalation of capsaicin-containing powders is less common but can cause severe pulmonary exudation, potential acute respiratory distress syndrome, and death.[13] Treatment is supportive, but extracorporeal membrane oxygenation may be useful for acute respiratory distress syndrome.

Figure 162-2. *Cicuta maculata* (water hemlock). (Courtesy of Steven Setzer.)

Cicuta maculata

Cicuta maculata (Fig. 162-2), commonly known as water hemlock, contains the potent neurotoxin cicutoxin. Deaths from water hemlock are among the most commonly reported plant fatalities reported in the United States. Water hemlock has small white flowers at the ends of umbrella-like stems. They resemble *Daucus carota* (Queen Anne's lace) and *Heracleum lanatum* (cow parsnip). Mistaking water hemlock for one of these edible plants has been a common cause for exposure.[14] Ingestion of any part of the plant can lead to nausea, vomiting, and abdominal cramping. Severe toxicity is manifested by seizures, occurring within the first hour, which often are intractable and are a common cause of death. The toxic mechanism may be due to γ-aminobutyric acid (GABA) receptor antagonism. Fatality rates may be as high as 70%.[14] Aggressive supportive care is necessary, and asymptomatic suspected exposures should be treated aggressively with gastric lavage and activated charcoal. Patients often arrive in the emergency department with active seizures and should receive benzodiazepines and barbiturates.

Conium maculatum

Conium maculatum (Fig. 162-3), or poison hemlock, was purported to be used in the execution of Socrates. It is mistaken for several edible plants, such as *Daucus carota* (Queen Anne's lace) and *Heracleum lanatum* (cow parsnip). Poison hemlock contains the toxin coniine, which is similar to nicotine in structure and toxicity. The clinical picture and management resemble tobacco poisoning (see section on *Nicotiana tabacum*).[15,16]

Datura stramonium

Datura stramonium (jimsonweed) (Fig. 162-4) is one of numerous plants with alkaloids that have anticholinergic effects (see Chapter 148). The fruit is spiny and when opened contains 50 to 100 black seeds. All parts (including the seeds) contain the toxins atropine, hyoscyamine, and scopolamine, which are all potent anticholinergic agents.[17] One hundred seeds approximate 6 mg of atropine. Exposures are most commonly a result

Figure 162-3. *Conium maculatum* (poison hemlock). (Courtesy of Steven Setzer.)

Figure 162-4. *Datura stramonium* (jimsonweed). (Courtesy of Steven Setzer.)

of abuse for hallucinogenic effects, usually by smoking dried leaves or ingesting the seeds.[18,19] The clinical picture is that of anticholinergic toxidrome.[20,21] The symptoms can be prolonged several days if the overdose is due to ingestion of seeds. It is unclear if activated charcoal and gastric emptying measures are effective at decreasing the course of toxicity.[18] Physostigmine reverses the clinical symptoms.[18] Anticholinergic symptoms typically return as the effects of physostigmine wear off (see Chapter 148).

Dieffenbachia

Dieffenbachia (Fig. 162-5) has more than 30 different common names, including dumb cane, mother-in-law's tongue, dumb plant, and tuft root. Some of these names refer to the inability to talk that can occur after biting into parts of this plant. Typically the mucous membranes of the mouth are affected immediately with severe pain, swelling, and the sensation of biting into glass. Most cases are limited to the mucous membranes of the oropharynx. Rare cases of airway compromise have been reported.[22] The local effects are due to calcium oxalate crystals, packaged into bundles called *raphides*, which are found in cellular structures called *idioblasts*.[23,24] These idioblasts also contain proteolytic enzymes that are ejected out of the idioblasts with the oxalate crystals when plant parts are chewed. Because of the immediate pain, further exposure typically is

Figure 162-5. *Dieffenbachia.* (Courtesy of Steven Setzer.)

limited. Treatment is aimed at pain relief and local supportive measures, typified by feeding a symptomatic infant ice cream.[25]

Epipremnum aureum

Epipremnum aureum is a common household plant also known as pothos ivy, devil's ivy, hunter's robe, and golden pothos. Toxicity is due to calcium oxalate crystals,[5] the same toxin found in the *Dieffenbachia*, and the toxicity and treatment are similar.

Eucalyptus

Eucalyptus plants have common names, such as the silver dollar, lemon-scented gum, cider gum, and blue gum. These plants are not toxic but are implicated in frequent plant exposures.[26] The plants are used, however, to produce concentrated (approximately 70%) eucalyptus oil. Ingestion of small amounts (1–3 mL) has been reported to cause severe toxicity.[27] The predominant symptoms are neurologic, including mental status alteration, headache, ataxia, and seizures. Treatment for severe toxicity is supportive.

Euphorbia pulcherrima

Euphorbia pulcherrima (poinsettia) is a popular ornamental plant that is frequently implicated in plant exposures. It has a false reputation for being extremely poisonous. Ingestions are benign or cause minimal toxicity. However, contact dermatitis is relatively common with skin exposure.

Ilex

Ilex (holly) contains more than 400 different species and is frequently implicated in plant exposures. The plant's red and black berries are attractive to children and contain numerous toxins that are potent gastrointestinal irritants. Symptoms include nausea, vomiting, abdominal cramping, and diarrhea.

Nerium oleander

Nerium oleander (Fig. 162-6), or oleander, is one of many plants that contain toxic cardiac glycosides[28] structurally similar to

Figure 162-6. *Nerium oleander.* (Courtesy of Steven Setzer.)

Figure 162-7. *Phytolacca americana* (pokeweed). (Courtesy of Steven Setzer.)

digoxin. Ingestion of several leaves is unlikely to cause serious symptoms.[29,30] Large exposures from suicide attempts or misidentification of plants used for teas or herbal products can lead to severe toxicity or death. The cardiac glycosides are potent sodium-potassium adenosine triphosphatase inhibitors, and the symptoms they cause are similar to those of digoxin poisoning (see Chapter 150). Measurement of an abnormal digoxin level is only qualitative proof of exposure because the serum digoxin test can falsely measure nondigoxin cardiac glycosides. Conversely, a negative digoxin measurement does not rule out exposure because the level of cardiac glycoside cross-reactivity varies.[28] Treatment for suspected oleander ingestion includes multidose activated charcoal and digoxin-specific Fab antibodies (see Chapter 150)[29–33]; however, larger doses of Fab fragments generally are needed than for comparable digoxin poisonings. Initial empirical doses of 10 to 20 vials of digoxin-specific Fab fragments have been suggested.[32]

Nicotiana tabacum

Nicotiana tabacum is widely grown in the southeastern United States as a source for cigarette and cigar tobacco. Several *Nicotiana* species contain nicotine as their major toxin, which activates and subsequently blocks acetylcholine receptors in the central nervous system (CNS) and peripheral autonomic nervous system. Most exposures are ingestion of cigarettes or cigars by young children. Dermal exposure to workers harvesting plants and ingestion of wild plants mistaken for edible plants also have led to poisoning.[34]

The ingestion of one to two cigarettes has the potential to cause moderate poisoning in children. Most children ingesting cigarettes do not manifest toxicity. Patients not experiencing nausea and vomiting do not seem to be at risk for more severe toxicity.[35] Dermal exposure in tobacco workers has been called *green tobacco sickness*.[36,37] Nicotine is absorbed through the skin and occurs most severely when the skin or plant is wet. Exposure can be avoided by using proper protective equipment.

Symptoms begin shortly after absorption. Nausea, vomiting, salivation, lacrimation, diarrhea, hypertension, tachycardia, diaphoresis, agitation, and fasciculation are seen initially. More severe toxicity is manifested by seizures, respiratory depression (muscle weakness), and hyperthermia.[38] Treatment for ingestion is aimed initially at limiting absorption with activated charcoal. Other treatments are supportive in nature because no specific antidote for nicotine is available. Benzodiazepines are used for seizures and agitation. If severe salivation and lacrimation occur, atropine in 1-mg doses may be repeated until symptoms improve.

Phytolacca americana

Found in the eastern United States, *Phytolacca americana* (Fig. 162-7) is commonly known as pokeweed, poke, pokeberry, inkberry, scoke, American cancer, garget, phytolacca, and pigeonberry. Although the plant is poisonous, it can be detoxified by boiling it in water twice before use in salads or other recipes. Toxicity is seen when the plant is inadequately detoxified, or raw parts of the plant are eaten.[39] Symptoms begin shortly after ingestion and include severe nausea, vomiting, abdominal cramping, and diarrhea. Treatment is supportive.

Pyracantha

Pyracantha, commonly known as the firethorn, has small red, orange, or yellow fruit attractive to and commonly ingested by children. The plant is not toxic, but the thorny parts can penetrate skin deeply and are difficult to remove.

Rhododendron

Rhododendron includes more than 1000 species of azaleas and rhododendrons, including mountain laurel, dwarf laurel, rose bay, western Labrador tea, and Japanese pieris. Numerous structurally related toxins (diterpene polyalcohols) have been identified from these plants, including grayanotoxin, rhodojaponin, asebotoxin, and others.[40,41] These toxins bind to sodium channels and increase permeability (sodium channel openers), causing cardiovascular (e.g., bradycardia and hypotension) and gastrointestinal (e.g., nausea, vomiting, and abdominal pain) effects. Although ingestion of a few leaves is unlikely to cause

Figure 162-8. *Taxus* (yew). (Courtesy of Steven Setzer.)

symptoms, larger exposures can cause severe toxicity. Additionally, these plant toxins can be concentrated in honey. Large honey ingestions, "mad honey," can also lead to toxicity.[41,42] However, no deaths have been reported. Treatment is supportive; atropine and cardiac pacing have been used for bradycardia in rare cases.[42] Sodium channel-blocking agents, such as quinidine and procainamide, may have theoretical value in severe cases, although their efficacy is unclear.

Spathiphyllum

Spathiphyllum includes the peace lily, Mauna Loa, white anthurium, and snowflower. These plants contain calcium oxalates and have similar toxicity and treatment as *Dieffenbachia*.

Taxus

Taxus (yew trees) (Fig. 162-8) have a hard seed surrounded by a fleshy red cup (the aril). The aril portion is not poisonous, and the seed has a hard coat that limits toxin release in the gastrointestinal tract so that most ingestions are nontoxic. If the seed is masticated or leaves are ingested, cardiac (e.g., bradycardia and hypotension) and gastrointestinal symptoms (e.g., nausea, vomiting, and abdominal pain) may occur. Deaths from this plant have been reported, usually in the setting of a suicide and secondary to cardiac manifestations.[43,44]

HERBAL MEDICINES

Herbal products have gained an extraordinary amount of popularity over the past several decades. Although the highest usage is among immigrants and patients with difficult-to-treat diseases, such as advanced cancer and acquired immunodeficiency syndrome, these products are used by 30% of the general population.[45–48] Consumers often perceive herbals as more "natural" and thus "safer" and "harmless." Additionally, herbals are widely marketed as such, especially on the Internet.[49] One study of pregnant patients documented 45% herbal medicine usage during some point of their pregnancy.[50] Emergency department and surgical patients are also frequent users of herbal products.[51–53]

Herbal products are classified as dietary supplements and are not regulated as medications, even though they are used for their medicinal value.[53,54] Regulation of dietary supplements is limited. Safety, quality, and efficacy for medicines are the responsibility of manufacturers. For herbal products used as dietary supplements, of which there are thousands to hundreds of thousands of potential products, the burden of proving efficacy and safety lies with the FDA.[55–57]

Studies looking at the efficacy of herbal products are limited, with few randomized, controlled studies. Herbal manufacturers are not required to conduct these studies. Studies evaluating side effects, drug interactions, and toxicity are even less available.

Most herbal products have some direct pharmacologic action. The potency of these agents is usually limited, however. As a result, toxicity and side effects from the direct actions of herbal products are relatively uncommon.[58–63]

The lack of manufacturing quality control accounts for most toxicologic problems associated with their use. Four major types of toxicologic problems are associated with herbal product use, including (1) the misidentification of an herbal plant and toxicity resulting from a substituted plant, (2) contamination with nonherbal toxic material, (3) direct toxicity or overdose of the herbal product (Table 162-1), and (4) drug-herbal interaction (Table 162-2).

Misidentification of Herbal Plants

Incorrect plant identification and subsequent use in the production of herbal products have occurred on numerous occasions, leading to epidemic exposures with tragic outcomes. The following examples illustrate this problem.

Herbal Slimming Regimen, 1992

During the early 1990s, the Chinese herbs *Stephania tetrandra* and *Magnolia officinalis* were used for weight loss in Belgium. Many cases of interstitial fibrosis of the kidney occurred with the use of these herbal compounds. Analysis found that *S. tetrandra*, which was substituted for *Aristolochia fangchi*, contains the nephrotoxin aristolochic acid.[64,65]

Paraguay Tea, 1994

The South American herbal tea Paraguay tea is made from *Ilex paraguariensis*, used for urinary tract infections, cardiac insufficiency, and "lack of stamina." In 1994, several individuals had anticholinergic poisoning from Paraguay tea, after the manufacturer had purchased and mistakenly used other plant materials containing the belladonna alkaloids atropine, scopolamine, and hyoscyamine directly from farmers before packaging.[66]

Digitalis lanata, 1997

An herbal dietary supplement used for "internal cleansing" contained 14 herbal ingredients. Two patients developed complete heart block because one of the herbal ingredients, plantain, contained *Digitalis lanata* (a cardiac glycoside-containing plant).[67]

Dandelion Salad, 2004

Dandelion is a commonly ingested herb used as an appetite stimulant and diuretic. Many users grow and harvest their own plants. A 53-year-old woman who had ingested some homegrown dandelion developed persistent nausea, vomiting, and bradycardia with a heart rate between 30 and 40 beats per minute. Her bradycardia persisted for several days and had associated syncope. Her diagnosis was unclear until it was discovered that she had mistakenly harvested and ingested foxglove instead of dandelion.[68]

Table 162-1 Common Herbal Medications and Adverse Effects

HERBAL NAME	BOTANICAL NAME	USES	ADVERSE EFFECT
Bee pollen	*Apis mellifera*	General tonic	Allergic reactions
Betel nut	*Areca catechu*	Stimulant	Bronchospasm
Blue cohosh	*Caulophyllum thalictroides*	Menstrual cramps	Nicotinic effects
Boron		Astringent, wounds	Dermatitis, GI, hepatic, renal, CNS
Buckthorn	*Rhamnus frangula*	Laxative	Diarrhea
Canthardin	*Cantharis*	Aphrodisiac	GI, dermatitis, renal
Cat's claw	*Uncaria tomentosa*	AIDS, cancer, arthritis	None reported
Chamomile	*Matricaria chamomilla*	Fever, cough, colds, wounds	Allergic reactions
Chaparral	*Larrea tridentata*	Cancer, aging, general tonic	Hepatotoxicity
Comfrey	*Symphytum officinale*	Contusions and sprains	Hepatotoxicity
Compound Q	*Trichosanthes kirilowii*	AIDS	Pulmonary, CNS
Dandelion	*Taraxacum officinale*	Diuretic, appetite stimulant	None reported
Dong quai	*Angelica polymorpha*	Blood purifier, increase circulation	Anticoagulation, dermatitis
Echinacea	*Echinacea purpurea*	Common cold	Fever, nausea and vomiting
Ephedra	*Ephedra* spp.	Stimulant, asthma	Hypertension, tachycardia, CNS, MI
Fennel	*Foeniculum vulgare*	GI illnesses, cough	Allergic reactions
Fenugreek	*Trigonella foenumgraecum*	Expectorant, anti-inflammatory	None reported
Feverfew	*Tanacetum parthenium*	Migraines, antipyretic	Post-feverfew syndrome, rebound migraine
Garlic	*Allium sativum*	Infection, CAD, Htn	Dermatitis, GI
Germander	*Teucrium chamaedrys*	Gout, fever, dietary aid	Hepatotoxicity
Ginger	*Zingiber officinale*	Motion sickness, GI illness	None reported
Ginkgo	*Ginkgo biloba*	General tonic, depression, anxiety, memory	GI effects, bleeding effects, drug interactions
Ginseng	*Panax ginseng*	General tonic, depression, stress, anxiety, fatigue	Ginseng abuse syndrome
Glucosamine		Arthritis	None reported
Goldenseal	*Hydrastis canadensis*	Cutaneous wounds	GI, CNS, and pulmonary effects in overdose
Gordolobo yerba	*Senecio longiloba*	URI, fever	Budd-Chiari syndrome
Henbane	*Hyoscyamus niger*	Sedative, GI discomfort	Anticholinergic toxicity
Jimsonweed	*Datura stramonium*	Asthma	Anticholinergic toxicity
Juniper	*Juniperus communis*	UTI, kidney stones, appetite	Renal toxicity
Kava kava	*Piper methysticum*	Sedative, aphrodisiac	Euphoria, CNS
Kumbucha		Cancer, memory loss	None reported
Larkspur	*Delphinium consolida*	Diuretic, sedative	Lethargy, muscle paralysis
Licorice	*Glycyrrhiza glabra*	Cough, GI illnesses	Hypokalemia, drug interactions
Ma-huang	*Ephedra sinica*	General tonic, common cold	Sympathomimetic
Mate	*Ilex paraguayensis*	Stimulant	None reported
Milk thistle	*Silybum marinum*	General tonic, GI disorders	None reported
Mistletoe	*Viscum album*	GI illness, cancer, HIV	GI, bradycardia, CNS
Nutmeg	*Myristica fragrans*	Aphrodisiac, hallucinogen	CNS, GI
Parsley	*Petroselinum crispum*	UTI, kidney stones	Contact dermatitis
Pennyroyal	*Mentha pulegium*	Abortifacient, GI illnesses	Hepatotoxicity
Rose hips	*Rosa canina*	URI, vitamin C	None reported
Rue	*Ruta graveolens*	Menstrual disorders	Contact dermatitis, GI and CNS effects in overdose
Sage	*Salvia officinalis*	Antiseptic, wounds	Absinthism
St. John's Wort	*Hypericum perforatum*	Depression, anxiety	Drug interactions
Sassafras	*Sassafras albidum*	GI stimulant	Liver, carcinogen
Saw palmetto	*Serenoa repens*	Benign prostatic hypertrophy	GI effects
Scullcap	*Scutellaria lateriflora*	Nervous disorders, bitter tonic	Hepatotoxicity
Shepherd's purse	*Capsella bursa pastoris*	Hypertension, CHF, headaches, menstrual disorders	None reported
Siberian ginseng	*Eleutherococcus senticosus*	General tonic	None reported
Soy	*Glycine max*	Menopause, CAD	Carcinogen
Tonka bean	*Dipteryx odorata*	Whooping cough	Anticoagulant effect
T'u-san-chi	*Gynura segetum*	Stimulant tea	Budd-Chiari syndrome
Valerian	*Valeriana officinalis*	Sleep, anxiety, general tonic	Hepatotoxicity
Woodruff	*Galium odorata*	Diuretic, anxiety, menstrual disorders	Anticoagulant effect, CNS effects, hepatotoxicity
Wormwood	*Artemisia cina*	Worm infection, anxiety	Seizures, CNS effects
Yarrow	*Achillea millefolium*	Poor appetite, GI illnesses	Allergic reactions
Yew	*Taxus baccata*	GI illness, cancer	Dizziness, bradycardia
Yohimbine	*Pausinystalia yohimbe*	Sexual disorders, aphrodisiac	Hypertension, agitation, CNS effects

CAD, coronary artery disease; CHF, congestive heart failure; CNS, central nervous system; GI, gastrointestinal; Htn, hypertension; URI, upper respiratory infection; UTI, urinary tract infection.

Table 162-2 Common Herbal-Drug Interactions

HERBAL	DRUG	TYPE OF INTERACTION
Betel nut	Fluphenazine	Extrapyramidal effects
	Prednisone and salbutamol	Bronchospasm
Boldo	Warfarin	Increased INR
Chili pepper	ACE inhibitors	Cough
	Theophylline	Increased drug absorption
Curbicin	Warfarin	Increased INR
D-400	Oral hypoglycemics	Increased drug concentration and decreased serum glucose
Danshen	Warfarin	Increased INR
Devil's claw	Warfarin	Increased INR
Dong quai	Warfarin	Increased INR
Fenugreek	Warfarin	Increased INR
Garlic	Warfarin	Increased INR
Ginkgo	Aspirin	Increased platelet inhibition
	Blood thinners	Bleeding side effects
	Thiazide diuretics	Hypertension
	Warfarin	Increased INR
Ginseng	Warfarin	Decreased INR
	Ethanol	Increased ethanol clearance
Green tea	Warfarin	Decreased INR
Guar gum	Many drugs	Decreased absorption of drug
	Digoxin	Decreased drug concentration
Karela	Chlorpropamide	Decreased serum glucose
Licorice	Oral contraceptives	Hypertension, edema, hypokalemia
	Prednisolone	Alteration of pharmacokinetics
	Antihypertensives	Hypokalemia
Lycium	Warfarin	Increased INR
Ma-huang	Guanethidine	Sympathomimetic effects
	MAO inhibitors	Sympathomimetic effects
Mango	Warfarin	Increased INR
Oat bran	Lovastatin	Decreased drug concentration
Papaya	Warfarin	Increased INR
PC-SPES	Warfarin	Increased INR
Pectin	Lovastatin	Decreased drug concentration
Psyllium	Lithium	Decreased drug concentration
St. John's Wort	Selective serotonin reuptake inhibitors	Serotonin syndrome
	Theophylline	Decreased drug concentration
	Digoxin	Decreased drug concentration
	Cyclosporine	Decreased drug concentration
	Indinavir	Decreased drug concentration
	Irinotecan	Decreased drug concentration
	Nevirapine	Decreased drug concentration
	Oral contraceptives	Decreased drug concentration
	Simvastatin	Decreased drug concentration
	Warfarin	Decreased INR
Siberian ginseng	Digoxin	Increased digoxin levels
Soy	Warfarin	Decreased INR
Tamarind	Aspirin	Increased drug absorption
Wheat bran	Digoxin	Decreased drug concentration
Yohimbine	Tricyclic antidepressants	Hypertension

ACE, angiotensin-converting enzyme; INR, international normalized ratio; MAO, monoamine oxidase.

Contamination with Nonherbal Toxic Material

Contamination with nonherbal toxic material as a mechanism of herbal toxicity may be due to contamination of the products at the time of manufacture or consumer fraud. Because of the limited FDA regulation of herbal manufacturers, one of the major risks of herbal usage is the use of a product contaminated with a toxic substance. A study of Asian herbal patent medications sold in California found that 32% of these products were contaminated with heavy metals or undeclared pharmaceuticals.[69,70]

Lead, mercury, arsenic, cadmium, aluminum, tin, zinc, and copper all have been found in herbal products. The most common undeclared pharmaceuticals include ephedrine, chlorpheniramine, methyltestosterone, and phenacetin.[70,71] It is not clear why heavy metals are found in herbal products. Metal shavings have been added to herbal preparations to

increase selling price when the herbals are sold by weight. Some herbal products use the metal as an active ingredient with a purported medicinal benefit (e.g., lead in azarcon or mercury in cinnabar). Other cases involve contamination with the metals during the manufacturing process.[71–73] Consumer fraud in the herbal industry has been well documented on numerous occasions. Typically an FDA-controlled pharmaceutical product is mixed in with an herbal product, or the label did not list the pharmaceutical agent.

Chuifong Toukuwan was an herbal preparation that was associated with several cases of agranulocytosis. Analysis revealed that it contained phenylbutazone, indomethacin, and aminopyrine.[74] Gan Mao Tong was an herbal product found to contain phenylbutazone, causing aplastic anemia.[75] An undefined herbal preparation that was used "to avoid taking other medicine" was found to contain triamcinolone. A patient using the product for more than 1 year had several manifestations of steroid excess: thoracic compression fractures, proximal muscle weakness, and osteoporosis.[76] Tung shueh was an herbal product that was found to contain mefenamic acid and diazepam, causing gastrointestinal bleeding and acute interstitial nephritis.[77] Another herbal product was found to contain mefenamic acid, which caused acute renal failure necessitating hemodialysis. Dr. Tong Shap Yee's asthma pills were found to contain theophylline.[78] Leng Pui Kee herbal cough remedy was found to contain bromhexine.[78]

Direct Toxicity of Herbals and Herbal-Drug Interactions

Some herbal preparations can cause allergic reactions ranging from contact dermatitis to anaphylactic shock (Box 162-1).[79,80] Other herbal products are associated with uncommon idiosyncratic reactions, particularly hepatic toxicity (see Table 162-1). Herbal products are often taken in overdose. Not controlled by a prescription system, herbal medicines are seen as natural and safe so that "if one is good, then two or three is better." Direct toxicity is often due to this overuse. Herbs associated with specific toxicities and side effects are listed in Table 162-1.[81–90]

Concurrent herbal and pharmaceutical use is common and can cause drug interactions. Of U.S. adults, 18% who take prescription medications also use an herbal or mineral supplement, and 60% who use alternative therapies are unlikely to report this to their physicians.[91] Individuals often do not consider that herbs can potentially interact with conventional medicines, and serious drug reactions associated with an herbal product are less likely to be reported than reactions that occur with a conventional medicine. Common herbal-drug interactions are listed in Table 162-2.[58,92,93]

MUSHROOMS

U.S. poison center data estimate that five exposures take place for every 100,000 population per year. These exposures occur in three types of situations: (1) accidental ingestion of wild mushrooms by young children playing outdoors (which usually results in a small exposure), (2) mistaken selection of poisonous mushrooms while foraging for edible wild mushrooms intended for a meal (which leads to a larger toxin exposure and most of the severe cases of mushroom poisoning, including deaths), and (3) abuse of certain mushrooms for their mind-altering potential.[2,3] Mushrooms of abuse typically involve a young population that often abuses other drugs. Most of these cases do not come to medical attention and often involve other substances added to the mushrooms. Despite the potential for severe toxicity and death, most exposures are relatively benign.[94,95] Approximately 5% result in moderate poisoning, with only a few deaths reported per year.

Management of Mushroom Exposure

The prognosis depends on the specific species. Identification of the mushroom is the most helpful factor in deciding on a treatment plan. Techniques for mushroom identification are described in most mycology and toxicology textbooks. Local mycologists or a poison center may be helpful. If a specimen is available, it can be stored in a paper bag at room temperature for delivery. Alternatively, a digital picture can be taken and e-mailed.[4] Vomitus can be collected because mushroom parts

BOX 162-1 HERBALS ASSOCIATED WITH ALLERGIC REACTIONS

Agnus castus
Angelica
Aniseed
Apricot
Aristochol
Arnica
Artichoke
Asafetida
Balxum of Peru
Bee pollen
Bee venom
Black cumin oil
Boneset
Camphor
Capsaican
Cassia
Cedar wood oil
Celery
Chamomile
Chrysanthemum
Cinnamon
Cowslip
Curcumin
Dandelion
Echinacea
Elecampane
Euphorbia
Fennel
Feverfew
French marigold
Fucus
Garlic
Gingko
Gravel root
Guaiacum
Holy thistle
Hops
Hydrangea
Hydrocotyle
Inula helenium
Jasmine
Juniper
Kava
Lady's slipper
Lavender
Mai-Meu-Dong-Tang
Meadowsweet
Motherwort
Paprika
Parsley
Peppermint oil
Pilewort
Plantain
Pulsatilla
Rosemary
Rosewood
Royal jelly
Rue
Slippery elm
Tansy
Tea tree oil
Tung seed
Wild carrot
Yarrow
Ylang-ylang

Table 162-3 Mushroom Groups

GROUP/TOXIN	REPRESENTATIVE EXAMPLE	CLINICAL EFFECTS
Early onset of symptoms		
Coprine	*Coprinus atramentarius*	Disulfiram reaction with alcohol
GI toxin	Many species	Nausea, vomiting, diarrhea, abdominal pain
Ibotenic acid and muscimol	*Amanita muscaria*	Diverse CNS effects, including hallucinations, seizures, delirium, coma, agitation
Muscarine	*Clitocybe dealbata*	Peripheral cholinergic toxidrome
Psilocybin	*Psilocybe cubensis*	CNS effects, including hallucinations and euphoria
Late onset of symptoms		
Cyclopeptides	*Amanita phalloides*	GI effects followed by hepatotoxicity
Gyromitrin	*Gyromitra esculenta*	GI effects followed by seizures
Orellanine	*Cortinarius orellanus*	GI effects followed by renal toxicity

CNS, central nervous system; GI, gastrointestinal.

may be recovered. Despite these measures, the species is unknown in over 90% of ingestions. Because *Amanita* species are responsible for most deaths, a clinical strategy for differential diagnosis and management is most often used to identify the highest risk ingestions.

Mushroom Groups

Nine general groupings have been found to be useful for clinical management (Table 162-3). These groups can be classified into mushrooms with early onset of symptoms (0–4 hours postingestion), late onset of symptoms (>6 hours postingestion), or no symptoms (edible). Mushrooms with serious toxicity and potential for death are in the group that have late onset of symptoms. Particular attention should be paid to the timing of initial symptoms.[96–98] Mushroom species often grow together, and foragers frequently pick and eat more than one species of mushroom. The onset of early symptoms does not preclude the diagnosis of a more serious poisoning.

Early Onset of Symptoms

Gastrointestinal symptoms of nausea, vomiting, diarrhea, and abdominal cramps are common among many of the mushroom groupings (see Table 162-3). These symptoms are most predominant, however, in the gastrointestinal toxin group. This group contains numerous diverse mushrooms, many with unknown toxins. They cause symptoms rapidly (0.5–3 hours) after ingestion, and symptoms typically last 24 hours. Treatment is supportive, with good outcome expected.

CNS effects are associated with two groups of mushrooms, ibotenic acid/muscimol and psilocybin.[97–99] Psilocybin is structurally related to serotonin and lysergic acid diethylamide (LSD). Similar to LSD, hallucinations and CNS effects are prominent. This mushroom is most often used as a drug of abuse.[2,3] Ibotenic acid and muscimol are toxins that are structurally related to glutamic acid and GABA. Glutamic acid is an excitatory neurotransmitter, whereas GABA is an inhibitory one. Lethargy, hallucinations, seizures, or severe agitation begins within 1 to 2 hours after ingestion. Treatment for seizures and supportive care produce a good outcome.

The cholinergic toxidrome is associated with muscarine-containing mushrooms. Muscarine is structurally related to acetylcholine. Because of muscarine's quaternary structure, it does not cross the blood-brain barrier. Symptoms include salivation, lacrimation, urination, defecation, gastroenteritis, and emesis (SLUDGE). Atropine can be used for severe symptoms. Pralidoxime is not indicated because acetylcholinesterase inhibition is not involved.

The final mushroom group that causes early onset of symptoms occurs only with simultaneous ingestion of ethanol. These coprine-containing mushrooms cause a disulfiram-like reaction by blocking acetaldehyde dehydrogenase. The symptoms include flushing, nausea, vomiting, and headache. The onset of this reaction associated with ethanol can occur 30 minutes to several days after mushroom ingestion. Treatment is supportive and similar to disulfiram reactions from other causes.

Late Onset of Symptoms

Three groups of mushrooms cause late onset of symptoms (>6 hours postingestion): cyclopeptide, gyromitrin, and orelline/orellanine. The orelline/orellanine-containing mushrooms are infrequently found in the United States and there have not been any reported cases of toxicity in North America. The cyclopeptide group is responsible for most mushroom-related deaths in the United States.

The cyclopeptide mushrooms contain many species, of which *Amanita phalloides* is the most well known. Several cyclopeptide toxins have been identified (e.g., amatoxins, virotoxins, phallotoxins) that are thought to be responsible for toxicity.[100,101] Initial manifestations, such as severe nausea, vomiting, diarrhea, and abdominal cramping, begin 6 to 24 hours postingestion. Hydration and supportive care often lead to initial relief of symptoms and a relatively quiescent period. Hepatic toxicity followed by other end-organ involvement may ensue over the next several days to weeks. Progressive elevation of hepatic transaminases, jaundice, and hepatic encephalopathy can lead to death.

Many cases are misdiagnosed as gastroenteritis. Numerous noninvasive therapies have been suggested, including silibinin, thioctic acid, activated charcoal, high-dose penicillin, dexamethasone, vitamin C, cytochrome *c*, cimetidine, *N*-acetylcysteine, kutkin, and aucubin.[102,103] None of these therapies has been rigorously tested in human-controlled studies. Multidose administration of activated charcoal seems to be reasonable because of its ability to bind the toxins, availability, and relative safety; however, its effectiveness is unclear.

Numerous invasive therapies also have been proposed for use in cyclopeptide poisoning, including forced diuresis, hemodialysis, hemoperfusion, hemofiltration, plasmapheresis, and hepatic transplantation.[104–109] Similar to the noninvasive modalities, it is not clear if any of these therapies are effective. There have been several reports of successful transplantation in severe cases of poisoning[107–109]; however, it is uncertain what criteria should be used for selecting candidates.[110,111] Patients developing severe hepatic signs and symptoms should be considered for transfer to a transplant center.

Gyromitrin-containing mushrooms commonly are mistaken for edible mushrooms as they look similar to *Morchella* species (morel) mushrooms. The metabolites of this toxin cause GABA

neurotransmitter depletion similar to isoniazid toxicity, leading to excitatory CNS effects, such as headaches, agitation, and seizures. Effects also include nausea, vomiting, and possible hepatotoxicity. The onset of symptoms is at least 6 hours after ingestion. Because of its similarity to isoniazid toxicity, pyridoxine has been proposed as an antidote. It is unclear how effective this antidote is, but it is useful for gyromitrin-induced CNS effects because of its availability and safety profile.

Orelline/orellanine-containing mushrooms have been found in North America.[112] There have been no reports of toxicity associated with cases in the United States, however, with most reported cases in Europe. Symptoms begin 1 to 2 days after ingestion, with nausea, vomiting, abdominal pain, and headache. Renal toxicity manifests days to weeks after these initial symptoms and can progress to chronic renal failure.

Disposition

Initial management is aimed at ruling out mushroom groups associated with early onset of symptoms. If the patient remains asymptomatic after a 3-hour period of observation, the patient should be discharged with instructions to return if any symptoms manifest over the next 72 hours.

KEY CONCEPTS

- Plant exposures occur commonly in children and most commonly involve household plants. Most exposures cause little or no toxicity.
- Plants and mushrooms are often ingested for their mind-altering properties.
- Misidentification of plants and herbal products is a common cause for plant-induced and herbal product–induced toxicity.
- Natural plant and mushroom gathering for personal ingestion is a popular activity. Mistakes while foraging occur commonly, with the potential for serious toxicity and numerous fatalities.
- Herbal medicines increasingly are being used by the general public. Limited information is available regarding the efficacy and toxicity of these products.
- In the assessment of a patient exposed to a mushroom, the timing of initial symptoms and the assessment for associated symptoms constitute the most important data needed to make a differential diagnosis.
- A patient who has eaten or been exposed to a wild mushroom may have another medical condition actually responsible for the symptoms.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 163 Sedative Hypnotics

Leon Gussow and Andrea Carlson

BARBITURATES

Perspective

Barbiturates are discussed in do-it-yourself suicide manuals and have been implicated in the high-profile deaths of Marilyn Monroe, Jimi Hendrix, Abbie Hoffman, Margaux Hemingway, and the mass suicide of 39 members of the Heaven's Gate cult in 1997. Although barbiturates are still used for seizure disorders, their use as sedatives has declined significantly with the availability of safer alternatives, such as benzodiazepines, resulting in a decline from approximately 1500 barbiturate deaths per year in the 1950s to only six fatalities in 2006.[1]

Barbiturates are addictive, producing physical dependence and a withdrawal syndrome that can be life-threatening. While tolerance to the mood-altering effects of barbiturates develops rapidly with repeated use, tolerance to the lethal effects develops more slowly, and the risk of severe toxicity increases with continued use.

Principles of Disease

Barbiturates depress the activity of all excitable cells, especially those in the central nervous system (CNS) by enhancing the activity of γ-aminobutyric acid (GABA), the major central inhibitor. In acute overdose, barbiturates decrease neural transmission in autonomic ganglia, the myocardium, and the gastrointestinal tract and also inhibit the response to acetylcholine at the neuromuscular junctions.

The $GABA_A$ receptor is a protein complex found on postsynaptic membranes in the CNS. Structurally, it consists of several distinct receptor sites surrounding a chloride ion (Cl^-) channel (Fig. 163-1). GABA opens the chloride channel. The resulting flow of Cl^- into the cell increases the negative resting potential, hyperpolarizing and stabilizing the membrane. There are separate receptor sites for barbiturates and for benzodiazepines and a third site that binds GABA, ethanol, and meprobamate. Although barbiturates and ethanol can directly increase Cl^- conductance, benzodiazepines require the presence of GABA to affect Cl^- flow, which may account for the relative safety of benzodiazepines in comparison with barbiturates.

Barbiturates produce dose-related depressive effects, from mild sedation to coma and fatal respiratory arrest. In the early stages of intoxication, some patients experience euphoria. Barbiturates have no analgesic effect and can paradoxically increase the reaction to pain at low doses.

Barbiturates act directly on the medulla to produce respiratory depression. In therapeutic doses, this respiratory depression mimics that of normal sleep. Starting with doses approximately three times therapeutic, the neurogenic, chemical, and hypoxic respiratory drives are progressively suppressed. Since airway reflexes are not inhibited until general anesthesia is achieved, laryngospasm can occur at low doses.

Therapeutic oral doses of barbiturates produce only mild decreases in pulse and blood pressure, similar to sleep. With toxic doses, more significant hypotension occurs from direct depression of the myocardium along with pooling of blood in a dilated venous system. Peripheral vascular resistance is usually normal or increased, but barbiturates interfere with autonomic reflexes, which then do not adequately compensate for the myocardial depression and decreased venous return. Barbiturates can precipitate severe hypotension in patients whose compensatory reflexes are already maximally stimulated, such as those with heart failure or hypovolemic shock. Barbiturates also decrease cerebral blood flow and intracerebral pressure. Although hypnotic doses of barbiturates do not affect gastric emptying, higher doses can decrease gastrointestinal smooth muscle tone and peristaltic contractions and delay gastric emptying.

Barbiturates are classified according to their onset and duration of action: (1) ultrashort-acting (onset immediate after intravenous dose, duration minutes), (2) short-acting (onset 10–15 minutes after oral dose, duration 6–8 hours), (3) intermediate-acting (onset 45–60 minutes, duration 10–12 hours), and (4) long-acting (onset 1 hour, duration 10–12 hours) (Box 163-1). Only long-acting preparations have anticonvulsant effects in doses that do not cause sedation. Short- and intermediate-acting preparations are almost completely metabolized to inactive metabolites in the liver, while 25% of a phenobarbital (long-acting) dose is excreted unchanged through the kidney. Because phenobarbital is a weak acid (pK_a 7.2), alkalinizing the urine will increase the amount of drug present in ionized form, minimizing tubular reabsorption and increasing drug clearance. Short- and intermediate-acting barbiturates are not significantly affected by pH changes in this range.

Barbiturates cross the placenta, with fetal levels approaching those of the mother. They are also excreted in low concentration in breast milk. Use during pregnancy is associated with birth defects (category D).

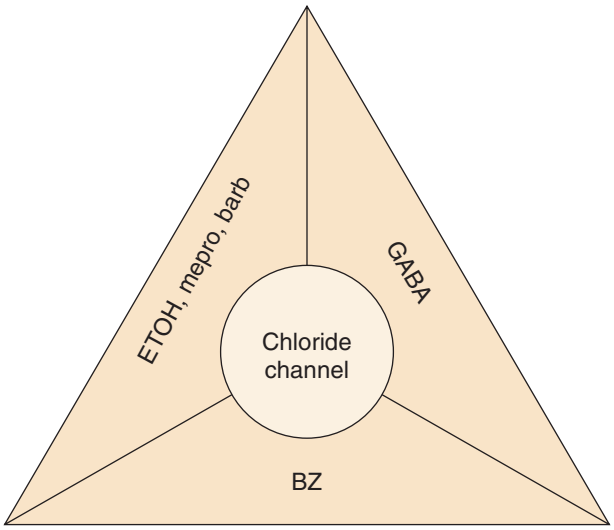


Figure 163-1. The γ-aminobutyric acid (GABA) receptor complex. BZ, benzodiazepine binding site; GABA, GABA binding site; ETOH, mepro, barb, binding sites for ethanol, meprobamate, and barbiturates, respectively.

BOX 163-1 BARBITURATES

Ultrashort-acting
- Methohexital (Brevital)
- Thiopental (Pentothal)

Short- and intermediate-acting
- Pentobarbital (Nembutal)
- Secobarbital (Seconal)
- Amobarbital (Amytal)
- Aprobarbital (Alurate)
- Butabarbital (Butisol)
- Butalbital (Fiorinal)

Long-acting
- Phenobarbital (Solfoton, Luminal)
- Mephobarbital (Mebaral)

Clinical Features

Mild barbiturate toxicity mimics ethanol intoxication, presenting with drowsiness, slurred speech, ataxia, unsteady gait, nystagmus, emotional lability, and impaired cognition.

In severe acute intoxication, CNS depression progresses from stupor to deep coma and respiratory arrest. Although pupils are usually normal or small and reactive, concomitant hypoxia can cause pupils to be fixed and dilated. Corneal and gag reflexes may be diminished or absent, muscle tone flaccid, and deep tendon reflexes diminished or absent. Flexor (decorticate) and extensor (decerebrate) posturing can occur in patients comatose from barbiturate intoxication. These neurologic signs are variable and do not always correlate with severity of intoxication or depth of coma. A fluctuating level of consciousness is commonly seen. High barbiturate levels depress gastrointestinal motility, delaying drug absorption. As the drug is metabolized and blood levels drop, peristalsis and drug absorption may increase, causing drug levels to rise.

The life threat of severe barbiturate toxicity is respiratory depression. Because respirations can be rapid but shallow, the degree of hypoventilation may not be apparent on clinical examination, but pulse oximetry or capnography will detect the ventilation compromise.

Hypotension is common in patients with severe intoxication, along with a normal or increased heart rate. Barbiturate overdose has been associated with noncardiogenic pulmonary edema. Altered pulmonary capillary permeability can be caused by hypoperfusion, hypoxia, or a direct effect of the drug. Pneumonia may be delayed.

A barbiturate withdrawal syndrome includes tremors, hallucinations, seizures, and delirium (similar to the delirium tremens of ethanol withdrawal). However, severe withdrawal occurs only following dependence on short- or intermediate-acting barbiturates (e.g., pentobarbital, secobarbital, amobarbital, or butalbital). Because these drugs are not commonly used, this syndrome is now rare.

Diagnostic Strategies

The therapeutic level of phenobarbital is 15 to 40 μg/mL (65–172 μmol/L). A serum level greater than 50 μg/mL can be associated with coma, especially in a patient who is not a chronic user. Levels greater than 80 μg/mL are potentially fatal. Serial phenobarbital levels may be helpful in monitoring effectiveness of treatment. Because barbiturates other than phenobarbital have high volumes of distribution, serum levels do not accurately reflect CNS concentrations or correlate with clinical severity. A positive urine screen establishes exposure to a barbiturate but does not prove that the drug is present in toxic amounts and should not be relied upon to explain decreased mental status.

Chest radiographs can detect noncardiogenic pulmonary edema or pneumonia. Computed tomography of the head should be obtained in comatose patients with evidence of trauma, focal neurologic signs, papilledema, or uncertain diagnosis.

Other causes of stupor and coma must be considered and ruled out. Since the electroencephalogram may be silent as a result of barbiturate overdose, no patient should be declared "brain dead" if barbiturates are present at therapeutic levels or greater.

Management

Since barbiturates have no specific antidote, management is based on supportive care, particularly with respect to the cardiovascular and respiratory systems. Severely intoxicated patients are unable to protect their airway adequately and have decreased ventilatory drive. Supplemental oxygen may suffice for patients with mild to moderate overdose, but intubation is often required. Long-term induced paralysis is rarely necessary, and additional sedation usually is unnecessary for mechanical ventilation. Careful fluid replacement should maintain a systolic blood pressure above 90 mm Hg and adequate urine output. Patients must be monitored for fluid overload and pulmonary edema. If vasopressors are necessary, dopamine is preferable to norepinephrine because of its renal vasodilating effects. Active warming should be initiated if the rectal temperature is less than 30° C.

Gastrointestinal Decontamination

Gastric emptying by lavage is not indicated. For large overdoses, there is evidence that clearance of phenobarbital is markedly increased with multidose activated charcoal (MDAC).[2–4] The dose of activated charcoal is 25 g every 2 hours in an adult; the pediatric dose is 0.5 g/kg every 2 hours. If vomiting occurs, a smaller dose or antiemetics should be used. MDAC can also be administered slowly through a nasogastric tube. Contraindications to MDAC include an unpro-

tected airway, so the patient is intubated before MDAC is initiated. Gastrointestinal obstruction or perforation is also a contraindication. Decreased peristalsis, such as that caused by opiate or anticholinergic overdose, is a relative contraindication to MDAC.[4] Although MDAC may shorten the duration of the intoxication, there is no evidence for improved outcome over that provided by supportive management of the airway and ventilation, and hemodynamic support.

Although alkalinizing the urine with $NaHCO_3$ has been recommended in the past, a recent nonrandomized study suggested that MDAC alone is most effective at increasing the drug's clearance.[5] The authors of that study hypothesize that alkalinization may interfere with the ability of the drug to diffuse across intestinal mucosa.

Hemodialysis or charcoal hemoperfusion is rarely needed but may increase clearance of phenobarbital in the presence of renal or cardiac failure, acid-base or electrolyte abnormalities, unstable cardiorespiratory status, or inadequate response to less invasive measures. Because phenobarbital is 40 to 60% protein-bound, hemoperfusion is sometimes advocated over hemodialysis; however, newer high-efficiency dialyzers using high blood flow rates may provide drug clearance greater than those achieved by hemoperfusion.[6]

Disposition

An asymptomatic patient who arrives in the emergency department (ED) after ingesting barbiturates should be observed until 6 hours postingestion and monitored for mental status changes, slurred speech, ataxia, hypotension, and respiratory depression. Onset of symptoms generally occurs within 1 hour of ingestion. Patients who remain asymptomatic and have no significant complicating co-ingestants or medical problems can be discharged or referred for psychiatric care. Patients who are still symptomatic 6 hours after arrival should be admitted for observation.

BENZODIAZEPINES

Perspective

Prior to 1950, drug options for treating anxiety were limited. While meprobamate, first synthesized in 1950, ultimately proved no safer than the barbiturates, its commercial success inspired the development of other nonbarbiturate anxiolytics. With chlordiazepoxide in 1960 and diazepam in 1963, benzodiazepines emerged as the principal agents for the treatment of anxiety. Cardiac effects and fatalities from pure benzodiazepine overdose are rare, and respiratory depression is less pronounced than with barbiturates. Additionally, drug-drug interactions involving benzodiazepines are uncommon.

Benzodiazepines remain among the most widely prescribed class of drugs (Table 163-1). With nearly 50 individual agents available worldwide, they account for two thirds of all psychotropic drug prescriptions.[7] Benzodiazepines are the most common prescription drugs for attempting drug-assisted suicide. Despite such frequent misuse, the vast majority of benzodiazepine overdoses follow a relatively benign clinical course. Children make up 10% of benzodiazepine overdose cases.

Principles of Disease

Benzodiazepines produce sedative, hypnotic, anxiolytic, and anticonvulsant effects by enhancing the inhibitory actions of GABA. Binding of a benzodiazepine to a specific benzodiazepine receptor potentiates GABA effects on the chloride channel at the $GABA_A$ receptor, increasing intracellular flux of chloride ions and hyperpolarizing the cell. The net effect is a diminished ability of the nerve cell to initiate an action potential, resulting in inhibition of neural transmission.

Three unique benzodiazepine receptors have been identified. The distribution of these receptors varies throughout the central and peripheral nervous systems. Classic benzodiazepines are nonselective, producing a broad range of clinical effects. Newer benzodiazepines interact selectively with a single receptor subtype to achieve a desired result, such as sedation, while minimizing unnecessary effects.

Pharmacokinetics

Benzodiazepines are rapidly absorbed orally. Intramuscular use of chlordiazepoxide and diazepam is limited by erratic absorption, but both lorazepam and midazolam are predictably absorbed after intramuscular injection. Following absorption, benzodiazepines distribute readily and penetration of the blood-brain barrier is facilitated by their highly

Table 163-1 Benzodiazepines

GENERIC NAME	BRAND NAME	USUAL DOSE	ORAL PEAK (HR)	HALF-LIFE (HR)	PARENT METABOLITE ACTIVITY
Alprazolam	Xanax	0.25–0.5 mg	1–2	6–27	Inactive
Chlordiazepoxide	Librium	5–25 mg	0.5–4	5–30	Active
Clonazepam	Klonopin	0.25–0.5 mg	1–2	18–50	Inactive
Clorazepate	Tranxene	7.5–15 mg	1–2	1–3	Active
Diazepam	Valium	2–10 mg	0.5–1	20–50	Active
Estazolam	ProSom	1–2 mg	2	8–28	Inactive
Flurazepam	Dalmane	15–30 mg	0.5–1	2–3	Active
Halazepam	Paxipam	20–40 mg	1–3	14	Active
Lorazepam	Ativan	0.5–2 mg	2–4	10–20	Inactive
Midazolam	Versed	0.025–0.1 mg/kg	1–2	1.5–3	Active
Oxazepam	Serax	10–30 mg	2–4	5–20	Inactive
Quazepam	Doral	7.5–15 mg	2	39–41	Active
Temazepam	Restoril	7.5–30 mg	1–2	3–19	Inactive
Triazolam	Halcion	0.125–0.25 mg	1–2	1.5–5.5	Inactive

lipophilic structure. In plasma, benzodiazepines are highly protein-bound.[7]

Metabolism of all benzodiazepines occurs in the liver. Oxazepam, temazepam, and lorazepam are directly conjugated to an inactive, water-soluble glucuronide metabolite that is excreted by the kidney. Other benzodiazepines must first be converted by the hepatic cytochrome P-450 system. Chlordiazepoxide, diazepam, flurazepam, and clorazepate are metabolized to active derivatives that are then slowly conjugated and excreted. The long elimination half-lives of these intermediates can cause accumulation in the body with repeated dosing. Triazolam, alprazolam, and midazolam are converted to hydroxylated intermediates that, although active, are very rapidly conjugated and excreted and do not contribute significantly to the drug's overall pharmacologic effect.[7]

Cytochrome P-450 processes may be significantly impaired in elderly patients or those with liver disease, leading to prolonged elimination of some benzodiazepines. Co-ingestion of drugs that also undergo cytochrome P-450 metabolism (e.g., cimetidine, ethanol) prolongs the half-lives of these benzodiazepines, but the clinical significance of these interactions is unclear.[8]

Clinical Features

Central nervous system depression is common in patients with benzodiazepine poisoning and ranges from mild drowsiness to coma. Significant respiratory depression is rare, but can be seen with large oral overdoses or during intravenous conscious sedation, particularly when the benzodiazepine is combined with an opioid such as fentanyl.[9] Hypotension is uncommon. Other complications include aspiration pneumonia and pressure necrosis of skin and muscles.

The vast majority of children develop symptoms within 4 hours of benzodiazepine ingestion. Ataxia is the most common sign of toxicity, occurring in 90% of patients. In children, respiratory depression occurs in less than 10% of cases and hypotension has not been reported.

Diagnostic Strategies

Any patient with altered mental status should have a blood glucose level rapidly determined. Qualitative immunoassays for benzodiazepines in urine are available but do not aid management decisions. Many of these tests detect only benzodiazepines that are metabolized to oxazepam glucuronide; therefore, clonazepam, lorazepam, midazolam, and alprazolam are not detected on a urine drug screen.[10] Serum drug concentrations are not routinely available and do not correlate with clinical severity.

The benzodiazepine antagonist flumazenil should not be routinely administered to patients with coma of unknown origin or suspected benzodiazepine overdose.[11] Any possibility of concomitant tricyclic overdose contraindicates flumazenil use.[9]

Differential Considerations

Benzodiazepine overdose is usually suspected or diagnosed because of the clinical presentation. Many patients are arousable and can provide supporting information. Atypical or focal findings can be clues to the presence of other conditions. Profound coma or cardiopulmonary instability with pure benzodiazepine overdose is rare, and the presence of either should prompt the search for a co-ingestant. Nontoxicologic causes of CNS depression should also be considered.

Management

General

Initial stabilization, including endotracheal intubation, must not be delayed by administering antidote. The vast majority of benzodiazepine overdoses can be managed expectantly. Activated charcoal is generally not beneficial in overdose.[12] MDAC, hemodialysis, and whole bowel irrigation are not indicated or effective in benzodiazepine overdose.

Antidote

Flumazenil, a nonspecific competitive antagonist of the benzodiazepine receptor, can reverse benzodiazepine-induced sedation after general anesthesia, procedural sedation, and overdose, but is not recommended for the reversal of benzodiazepine overdose in the ED. Although theoretical benefits of flumazenil use include cost savings and avoidance of procedures and tests such as endotracheal intubation and lumbar puncture, several studies have not been able to demonstrate an actual benefit.[13] Seizures and cardiac dysrhythmias can occur with flumazenil administration, and fatalities have been reported.[14–16] Flumazenil is especially hazardous when given to patients who are habituated to benzodiazepines, in whom acute benzodiazepine withdrawal, including refractory seizures, can be induced, and also when seizure-causing drugs (such as cocaine or a tricyclic antidepressant) have also been ingested, due to loss of the benzodiazepine's protective anticonvulsant properties. Co-ingestants that cause dysrhythmias, such as carbamazepine or chloral hydrate, may increase the likelihood of cardiac effects.[9] Other risk factors are summarized in Box 163-2. One study found that 12% of patients receiving flumazenil after known pure or mixed benzodiazepine overdose actually had a contraindication to its use.[17]

BOX 163-2 USE OF FLUMAZENIL

- Indications
  - Isolated benzodiazepine overdose in nonhabituated user (e.g., accidental pediatric exposure)
  - Reversal of conscious sedation
- Absolute contraindications
  - Known or suspected co-ingestant that lowers seizure threshold
  - Tricyclic antidepressants, cocaine, lithium, methylxanthines, isoniazid, propoxyphene, monoamine oxidase inhibitors, bupropion, diphenhydramine, carbamazepine, cyclosporine, chloral hydrate
  - Patient taking benzodiazepine for control of a potentially life-threatening condition (e.g., seizures)
  - Concurrent sedative-hypnotic withdrawal
  - Seizure activity or myoclonus
  - Hypersensitivity to flumazenil or benzodiazepines
  - Patient with neuromuscular blockade
- Relative contraindications
  - Chronic benzodiazepine user, not taking for control of life-threatening condition
  - Known seizure disorder not treated with benzodiazepines
  - Head injury
  - Panic attacks
  - Chronic alcoholism

The initial adult dose of flumazenil is 0.2 mg given intravenously over 30 seconds. A second dose of 0.3 mg may be given, followed by 0.5-mg doses at 1-minute intervals, to a total of 3 mg. Most patients respond within 3 mg. In children, the initial dose is 0.01 mg/kg (up to 0.2 mg). Because the duration of action of flumazenil is short (0.7–1.3 hours), resedation occurs in up to 65% of patients and requires either redosing or continuous infusion (0.25–1.0 mg/hr).

In summary, benzodiazepine overdose requires only supportive care (including, in some cases, intubation). Flumazenil may precipitate seizures or acute withdrawal. It should be used only in highly selected cases, such as small children with accidental poisoning or for reversal of accidental overdose of benzodiazepines during procedural sedation. When flumazenil is used, careful monitoring is necessary because of the risk for persistent respiratory depression or resedation. Use of flumazenil has not consistently altered outcome, complication rate, number of costly procedures performed, or duration of hospital stay in ED patients.[17]

Disposition

Patients remaining asymptomatic after 4 to 6 hours of ED observation may be medically cleared. For cases of deliberate overdose, appropriate psychiatric consultation should be obtained.

Benzodiazepine Withdrawal Syndrome

Abrupt discontinuation of a benzodiazepine in a chronic user results in a characteristic constellation of symptoms (Box 163-3). Risk for withdrawal is a function of both the dose of benzodiazepine and the duration of its use. Continuous treatment for more than 4 months is generally required before a patient is at risk for withdrawal. With abrupt discontinuation of a benzodiazepine, the most severe withdrawal symptoms are expected within several days to a week.[18] Use of flumazenil can precipitate immediate withdrawal symptoms. Treatment of withdrawal consists of restarting benzodiazepines.

FLUNITRAZEPAM

Flunitrazepam (Rohypnol) has been used in Europe, Asia, and Latin America for insomnia and preoperative sedation since 1975. Although never manufactured or sold in the United States, flunitrazepam has been implicated in many reports of "date rape" incidents. Flunitrazepam has been an active agent in the illicit drug market, where it is used to alter the effects of other drugs, including heroin and cocaine.[19]

Flunitrazepam has 10 times more affinity than diazepam for certain benzodiazepine receptors. Onset of CNS depression occurs within 30 minutes. The drug is most frequently ingested with alcohol, producing disinhibition and amnesia. Despite marked CNS depression, patients can usually be aroused with noxious stimuli. The half-life of the drug is 16 to 35 hours, but coma can be prolonged for up to 48 hours.[19] Flunitrazepam is easily obtainable outside the United States. The drug is not detected on routine urine drug screens but, if needed as evidence, urine should be collected and refrigerated or frozen and the local or state police crime laboratory contacted to arrange specific testing. Metabolites of flunitrazepam are detectable in the urine up to 72 hours after exposure.[20]

BOX 163-3 BENZODIAZEPINE WITHDRAWAL SYMPTOMS

Nonspecific
- Anxiety, depression, insomnia, tremor, tachycardia, sweating

Severe (rare)
- Visual hallucinations, delirium, seizures

BUSPIRONE

Buspirone (BuSpar) has been used for generalized anxiety since 1986. Unlike benzodiazepines, buspirone does not have any effect on GABA. Rather, it acts as a partial serotonin ($5\text{-}HT_{1A}$) agonist. To a lesser extent, it also antagonizes dopamine (D_2) receptors. Buspirone has no hypnotic, anticonvulsant, or muscle relaxant effects.

Buspirone has several advantages over benzodiazepines. The drug causes minimal CNS depression, even in combination with ethanol. Dosage adjustment is not needed for elderly patients. Chronic administration does not cause tolerance, and dependence does not occur. A withdrawal state after discontinuation has not been reported.

Only one case of isolated buspirone overdose has been published. That patient was lethargic and had a tonic-clonic seizure but recovered fully.[21]

ZOLPIDEM AND ZALEPLON

Zolpidem (Ambien) and zaleplon (Sonata) differ in structure from both the benzodiazepines and buspirone, and neither is detected on a benzodiazepine toxicology screen. They act selectively at a specific benzodiazepine receptor, producing sedation without many of the side effects seen with benzodiazepines. They have modest anxiolytic, muscle relaxant, and anticonvulsant properties. Significant drug interactions are rare. Compared with zolpidem, zaleplon causes less memory loss and sedation at therapeutic doses and is more rapidly eliminated.[22] Transient visual disturbances and hallucinations can occur in patients with normal levels of consciousness with both zolpidem and zaleplon.[22,23] Abuse of zolpidem is limited by vomiting, which may occur after a supratherapeutic dose. Both zolpidem and zaleplon are rapidly eliminated and lack active metabolites.[24]

Patients with zolpidem overdose do well with supportive care alone. Fatalities from isolated zolpidem overdose are rare. All published cases involve individuals found dead at home and are often associated with co-ingestants, particularly other sedative hypnotics or antipsychotics.[25] Drowsiness is by far the most common symptom. Coma and respiratory failure are rare, despite overdoses of up to 40 times the normal dose, although intubation may be required, particularly if there are co-ingestants.[26] Zolpidem overdose in children follows a similarly benign course. Drowsiness, ataxia, and hallucinations resolve within 10 hours.[27]

Overdose information for zaleplon is limited. In one case series, patients had CNS depression and mild hypotension. Arousal was temporally associated with flumazenil use in one patient.[28] The only published fatality involves a mixed drug overdose with unknown quantities of zaleplon and butalbital, with postmortem serum zaleplon concentration 40 times greater than therapeutic.[29] Adverse effects with therapeutic use include headache, anterograde amnesia, and transient visual hallucinations.[24]

ESZOPICLONE

Eszopiclone (Lunesta) has been marketed in the United States since 2005 for treating insomnia. It is the S-isomer of racemic zopiclone, which has been used for decades outside the United

States. Eszopiclone has a structure unrelated to those of benzodiazepines, barbiturates, zolpidem, and zaleplon.[30–34]

The mechanism of eszopiclone's action is not completely described but may involve a specific $GABA_A$ receptor close to or coupled with the benzodiazepine receptor.[30–33] Eszopiclone is rapidly absorbed, with a peak serum level at 1 hour and a half-life of 6 hours. It is metabolized in the liver to minimally active metabolites. The usual bedtime dose is 3 mg. It is recommended that elderly patients and those with hepatic insufficiency be treated with a lower (1 mg) dose.

Adverse effects seen with therapeutic use of eszopiclone include drowsiness, dizziness, dry mouth, unpleasant taste, nausea, and vomiting. Auditory and visual hallucinations have been reported.[35] Experience with eszopiclone overdose is limited, but treatment is supportive. A retrospective case review described 525 eszopiclone ingestions, but 259 of these patients had also ingested other drugs or chemicals.[32] The ingestions involved eszopiclone doses up to 210 mg and presented with mild to moderate symptoms at most. Two deaths occurred, both involving significant co-ingestants. A single case report described a 52-year-old man who developed coronary vasospasm and a ventricular fibrillation arrest after ingesting 45 to 60 mg of eszopiclone.[34] However, the arrest occurred approximately 20 hours after ingestion, and it is unclear what role, if any, eszopiclone played in causing the arrest.

CHLORAL HYDRATE

Perspective

Deaths related to chloral hydrate overdose were first reported in the medical literature in 1890. Chloral hydrate has a low therapeutic ratio and can produce significant, potentially fatal, toxicity. While chloral hydrate use is rare today, it is still occasionally prescribed as a sedative in the elderly and for sedation in children undergoing medical procedures. The hypnotic oral adult dose is 0.5 to 1.0 g. The toxic oral dose in adults is approximately 10 g and may be as little as 1.5 g in a child.[36]

The toxic effects of chloral hydrate include CNS depression, gastrointestinal irritation, cardiovascular instability, hepatitis, and proteinuria. The primary active metabolite of chloral hydrate, trichloroethanol, has a barbiturate-like effect on $GABA_A$ receptors and is responsible for most of the CNS depression seen with significant overdose.

Chloral hydrate is rapidly absorbed from the gastrointestinal tract and almost immediately metabolized to trichloroethanol by the enzyme alcohol dehydrogenase. Onset of action is 20 to 30 minutes.[37] Trichloroethanol is long-acting, with a half-life that can be significantly prolonged after overdose as metabolic pathways become saturated.

The combination of chloral hydrate and ethanol (the "Mickey Finn") potentiate each other's action to produce rapid loss of consciousness. Chloral hydrate increases the half-life of ethanol by competitively inhibiting the enzyme alcohol dehydrogenase, and the metabolism of ethanol generates NADH, a cofactor for the conversion of chloral hydrate to trichloroethanol.

Clinical Features

Chloral hydrate toxicity causes CNS and respiratory depression, gastrointestinal irritation, cardiovascular instability, and dysrhythmias. The combination of deep coma and cardiac dysrhythmia without hypoxia is characteristic of severe cases.

Mild chloral hydrate toxicity can mimic ethanol or barbiturates, with drowsiness, ataxia, and lethargy. A pear-like odor to the patient's breath or gastric contents may suggest the diagnosis. More severe toxicity includes miosis, muscle flaccidity, diminished deep tendon reflexes, hypoventilation, hypotension, and hypothermia.[36] Chloral hydrate is corrosive and causes nausea, vomiting, esophagitis, hemorrhagic gastritis and, more rarely, gastrointestinal perforation or necrosis.[36] Transient hepatic or renal dysfunction can also occur.

Dysrhythmias from chloral hydrate toxicity can be fatal. Chloral hydrate decreases myocardial contractility, shortens the cardiac refractory period, and increases the sensitivity of myocardium to catecholamines. Dysrhythmias include atrial fibrillation, supraventricular tachycardia, ventricular tachycardia, multifocal premature ventricular contractions, torsades de pointes, ventricular fibrillation, and asystole.[37] Hypotension results from inhibition of central neurovascular regulatory centers as well as impaired myocardial contractility.

MANAGEMENT FOR SEDATIVES

The key to management for all of these agents is support of cardiorespiratory function. Intubation may be required for airway protection or to support ventilation and oxygenation. Avoid naloxone or flumazenil, which may precipitate ventricular dysrhythmias.[36] Because chloral hydrate sensitizes myocardium to catecholamines, epinephrine and norepinephrine should also be avoided. Standard antidysrhythmic agents such as lidocaine do not appear effective against chloral hydrate–induced cardiac ectopy. The treatment of choice is a beta-blocker.[38] Intravenous propranolol can be given in adult doses of 0.5 mg until ectopy is suppressed, followed by an infusion of 1 to 2 mg/hr, titrated to a heart rate of 80 to 100 beats per minute. A short-acting agent such as esmolol can also be used. Torsades de pointes should be treated with intravenous magnesium or overdrive pacing. Type I antidysrhythmic agents such as quinidine should be avoided. Unstable patients not responding to conservative therapy can be treated with hemoperfusion or hemodialysis.[36]

OVER-THE-COUNTER SLEEP AIDS

Perspective

In the past, most over-the-counter (OTC) sleep aids contained a combination of an antihistamine (either methapyrilene or pyrilamine) and scopolamine. Some preparations also contained a bromide. For safety reasons, these products were reformulated in the late 1980s to contain diphenhydramine or doxylamine, now the only two drugs found in nonprescription hypnotics. Many preparations also contain acetaminophen or aspirin, added to create a nighttime pain reliever (Table 163-2). The availability and frequent use of these agents may explain why overdose is so common.

Principles of Disease

Diphenhydramine and doxylamine are antihistamines that also have hypnotic, anticholinergic, and weak local anesthetic properties. They act as competitive antagonists of H_1 histamine receptors and cause sedation by inhibiting the actions of acetylcholine on muscarinic receptors in the CNS.

The pharmacokinetic profiles of diphenhydramine and doxylamine are similar. Both are rapidly absorbed, with peak plasma levels occurring at 1 to 2 hours after administration. In the systemic circulation, they are highly protein-bound, with large volumes of distribution. Extensive metabolism occurs in the liver by the cytochrome P-450 system. The elimination half-life is 4 hours for diphenhydramine and 9 hours for doxylamine.

Table 163-2 Nonprescription Sedative Hypnotics, United States

BRAND NAME	ACTIVE INGREDIENT(S)
Alka-Seltzer PM effervescent tablets	38 mg diphenhydramine citrate 325 mg aspirin
Bayer PM Aspirin Plus Sleep Aid caplets	25 mg diphenhydramine hydrochloride 500 mg aspirin
Excedrin PM tablets, caplets or geltabs	38 mg diphenhydramine citrate 500 mg acetaminophen
Goody's PM powder	38 mg diphenhydramine citrate 500 mg acetaminophen
Maximum Strength Nytol QuickGels softgels	50 mg diphenhydramine hydrochloride
Nytol QuickCaps caplets	25 mg diphenhydramine hydrochloride
Simply Sleep caplets	25 mg diphenhydramine hydrochloride
Sleepinal Night-Time Sleep Aid capsules and softgels	50 mg diphenhydramine hydrochloride
Sominex Night-Time Sleep Aid tablets	25 mg diphenhydramine hydrochloride
Unisom Maximum Strength SleepGels	50 mg diphenhydramine hydrochloride
Unisom SleepTabs tablets	25 mg doxylamine succinate

Clinical Features

Impaired consciousness is the most frequent finding with diphenhydramine overdose. Somnolence, psychotic behavior, and agitation are common.[39] Anticholinergic effects may be apparent, as noted in Chapter 148. Apart from a lower incidence of psychosis, doxylamine has toxicity similar to that of diphenhydramine.[40] Seizures and rhabdomyolysis may occur with severe toxicity. Serious cardiotoxicity is rare.[41]

Diagnostic Strategies

Some comprehensive urine drug immunoassays will detect diphenhydramine. Quantitative serum levels of diphenhydramine or doxylamine are neither routinely available nor clinically useful. Serum acetaminophen and salicylate concentrations should be measured in patients with OTC sleep aid overdoses, because many preparations contain both a hypnotic and an analgesic. Measuring serum creatine phosphokinase and urinary myoglobin may help detect myoglobinuria.

Management

Management of mild to moderate toxicity from OTC sleep aid overdose is generally supportive. Specific details regarding anticholinergic toxicity are discussed in Chapter 148.

Disposition

Patients with minor sedation or anticholinergic effects that are resolving or who remain asymptomatic or are minimally symptomatic after a 4-hour observation period can be medically cleared. If the ingestion was in the context of self-harm, psychiatric evaluation is indicated. Other patients require inpatient observation in a monitored setting.

BOX 163-4 γ-HYDROXYBUTYRATE STREET NAMES

GHB	Liquid ecstasy
Grievous bodily harm	Liquid G
GBH	Somatomax
Georgia home boy	Soap
Gib	Salty water
Natural sleep-500	Scoop
Gamma-OH	Sodium oxybate
Gamma hydrate	Easy lay
Liquid X	Cherry menth
Organic quaalude	Fantasy
Liquid E	G-Riffick

γ-HYDROXYBUTYRATE

Perspective

Originally synthesized in the 1960s as an anesthetic in Europe and Japan, researchers later discovered that γ-hydroxybutyrate (GHB) was a naturally occurring metabolite of GABA. Since 1970, GHB has been used to treat narcolepsy and alcohol addiction, as well as alcohol and opiate withdrawal.[42]

A 1977 report that GHB may enhance the effects of steroids and the release of growth hormone resulted in marketing of the agent as a natural aid for increasing muscle mass. Numerous reports of adverse effects followed. In 1989, the U.S. Food and Drug Administration called for a voluntary withdrawal of the drug from store shelves. Its sale and manufacture were banned in 1990; however, illicit use of GHB increased along with the emergence of GHB precursors, γ-butyrolactone (GBL) and 1,4-butanediol (1,4-BD) (Box 163-4).[43] The Hillory J. Farias and Samantha Reid Date-Rape Drug Prohibition Act of 2000 made GHB a schedule I controlled substance. GHB has since been approved for the treatment of narcolepsy, under the trade name Xyrem (sodium oxybate, 0.5 mg/mL)[44] as a schedule III drug.

GHB remains a popular drug of abuse.[45] Recipes for home synthesis are widely available. Some individuals take GHB for its purported muscle-building and fat-burning actions, others for its psychoactive effects. The drug's euphoria-producing properties make it popular at "raves" (large, crowded youth parties with energetic dancing to rhythmic music for many hours).[46–48] Self-treatment of insomnia with GHB has been reported and can cause dependence.[49] CNS depression, amnesia, and disinhibition with GHB, especially mixed with ethanol, make this combination a potential agent in "date rape" situations.[50,51]

Chemical precursors to GHB are also commonly abused. GBL is rapidly converted to GHB by plasma lactonases. 1,4-BD is metabolized to γ-hydroxybutyraldehyde by the enzyme alcohol dehydrogenase, and then to GHB by aldehyde dehydrogenase.[52,53]

Principles of Disease

GHB binds to specific GHB receptors and at high concentrations to $GABA_B$ receptors.[54] The complex interaction between these two receptors may explain the sometimes paradoxical manifestations of GHB toxicity of somnolence and agitation. Through its action on the $GABA_B$ receptor, GHB decreases[55,56] release of dopamine.[42]

As underground laboratories often synthesize liquid GHB by mixing and heating butyrolactone and sodium hydroxide, careless preparation can result in residual unreacted base, causing significant caustic injury when the liquid is ingested.[43]

GHB is liphophilic and rapidly absorbed. Onset of symptoms occurs within 15 to 30 minutes and peak plasma levels within 20 to 60 minutes.[49] Unlike GABA, it readily crosses the blood-brain barrier. The half-life of GHB is 27 minutes but may increase at high doses.

GBL is an industrial solvent that is rapidly absorbed after ingestion and metabolized within minutes to GHB by peripheral and hepatic lactonases.[43] Before conversion to GHB, GBL itself is inactive and has no sedating effects.[42] It produces a clinical syndrome similar to that of GHB ingestion, but its effects are greater and more prolonged. In fact, GBL is more efficient at delivering GHB to the CNS than GHB itself.[57] GBL is available under a number of street names (Box 163-5).

1,4-Butanediol (1,4-BD) is converted after ingestion to GHB by the enzyme alcohol dehydrogenase.[53] Like GBL, it is used as an industrial solvent. Unlike GBL, 1,4-BD itself has sedative-hypnotic effects. Clinical findings are similar to GHB. When 1,4-BD and ethanol are ingested together, ethanol acts as a competitive inhibitor of alcohol dehydrogenase, so the toxic effects of 1,4-BD are delayed and prolonged, and the risk of death is increased.[53] 1,4-BD is available under a number of street names (Box 163-6).

In 2007, a children's toy marketed under the names Aqua Dots and Bindeez Beads was contaminated when 1,4-BD was substituted for a more expensive industrial solvent during the manufacturing process. The toy consisted of tiny brightly colored spheres that were readily ingested by toddlers, causing decreased levels of consciousness, coma, or apparent seizures.[58]

BOX 163-5 γ-BUTYROLACTONE STREET NAMES

Blue Nitro
Blue Nitro Vitality
Enliven
Fire Water
Gamma G
GH Revitalizer
GHRE (growth hormone release extract)
Nitro
NRG3
Remforce
RenewTrient
Revitalize Plus
Revivarant
SomatoPro
Verve 5.0

BOX 163-6 1,4-BUTANEDIOL STREET NAMES

Blue Raine
Dream On
Fubar
Inner G
Pine needle extract
Pine needle oil
ReJuv@Nite
Revitalize Plus
Serenity
SomatoPro
Thunder nectar
Weight belt cleaner
Zen

Clinical Features

Diagnosis of GHB intoxication is based on the history and clinical course. Rapid recovery from coma, or periods of agitation alternating with periods of decreased level of consciousness, is characteristic. Signs and symptoms are generally consistent with poisoning by other sedative-hypnotic agents. Hypothermia may occur.[47] In the presence of coma, bradycardia with or without hypotension may be seen and occasionally responds to stimulation alone.[47] Eye examination may reveal miosis with or without nystagmus. Behavioral changes are most common and range from aggression and delirium to coma.[47] A distinctive feature of GHB intoxication is respiratory depression with apnea, interrupted by periods of agitation and combativeness, especially stimulated by attempts at intubation that do not use RSI drugs. Emesis occurs in 50% of cases.[47] Generalized seizures may actually represent random myoclonic movements of the face and extremities. The dose-response curve of GHB is steep. An oral dose of 10 mg/kg results in hypotonia and amnesia, whereas 25 mg/kg induces sleep. A dose of 50 to 60 mg/kg produces anesthesia, and higher doses may cause coma associated with bradycardia, respiratory depression, vomiting, and myoclonic activity. The severity is also dependent on the dose and the concurrent use of alcohol or other psychoactive drugs.[49]

Diagnostic Strategies

GHB is not detected on most urine toxicology screens. If laboratory confirmation is required, specimens must be collected early to capture the parent compound, and gas chromatography-mass spectroscopy must be performed. The drug may be detected in urine up to 12 hours after ingestion.[59]

Poisoning with another sedative hypnotic can produce a similar clinical picture to that seen with GHB. Unique to GHB, however, is the relatively rapid resolution of symptoms. In the absence of a co-ingestant such as ethanol, most patients will awaken within 3 to 4 hours. Nearly all patients recover fully within 8 hours. Prolonged coma should prompt a search for another cause. Cardiac effects and refractory seizures are rare and suggest the presence of other agents.

Management

Because of the high incidence of emesis with GHB overdose, intubation for airway protection should be seriously considered in patients with significant CNS depression. In the absence of an identified difficult airway, rapid sequence intubation is the method of choice. Bradycardia unresponsive to stimulation can be treated with atropine. Treatment of isolated GHB ingestion is supportive. Patients should be protected from self-injury until resolution of symptoms. Physostigmine had been used as an antidote for GHB when used as an anesthetic agent, but the use of physostigmine is not generally recommended.[52,60]

Withdrawal

Similar to other sedatives and hypnotics, patients who suddenly stop GHB or its precursors after chronic, frequent use can experience a severe and potentially life-threatening withdrawal syndrome.[42,61,62] Because of the short half-life of GHB, symptoms of withdrawal usually begin within several hours of

the last dose. The typical patient will have been using these products for weeks or years, every 1 to 3 hours around the clock to avoid withdrawal symptoms.

Mild withdrawal presents with anxiety, tremor, and insomnia. This can progress to confusion, delirium, overt psychosis, paranoid ideation, hallucinations (visual, aural, and/or tactile), and autonomic instability. Diagnosis relies on a history of symptoms beginning after abruptly ceasing use of these products. The differential diagnosis includes withdrawal from other sedatives or hypnotics, delirium tremens, sympathomimetic toxicity, serotonin syndrome, neuroleptic malignant syndrome, CNS infection, and thyroid storm.

Initial treatment usually begins with high-dose benzodiazepines. However, GHB withdrawal may involve depleted levels of GABA.[61] Since the effect of benzodiazepines requires the presence of GABA, they may not be effective in controlling GHB withdrawal. Barbiturates, such as pentobarbital, which do not need GABA to be effective, are often required in cases of severe intoxication.[63]

These patients often require intensive care admission for high-dose sedatives to manage agitation and to monitor fluctuating vital signs. Rhabdomyolysis and severe hyperthermia should be ruled out. Deaths have been reported, sometimes many days after presentation and after apparent improvement.[61]

Disposition

Because of GHB's short half-life, symptoms often resolve while the patient is still in the ED. The patient generally regains consciousness spontaneously. No delayed toxicity is expected. Patients should be counseled about the seriousness of GHB intoxication.

KEY CONCEPTS

- Most patients with barbiturate intoxication will recover with observation and meticulous supportive care. The vast majority will not require gastric lavage, hemodialysis, or hemoperfusion.
- A urine toxicology screen positive for barbiturates does *not* prove that the patient's clinical condition is caused by the drug. Quantitative levels confirm the diagnosis. Serum barbiturate levels do not necessarily correlate with depth of coma or clinical outcome.
- Flumazenil should not be used in most benzodiazepine overdoses, because it can precipitate seizures. If it is used, patients must be monitored closely for persistent respiratory depression and for resedation after its use.
- Chloral hydrate–induced dysrhythmia should be treated with beta-blockade.
- Endotracheal intubation to protect against emesis and respiratory depression should be strongly considered for patients with GHB overdose and significant CNS depression.
- Withdrawal from GHB or its precursors can manifest with anxiety, tremor, and insomnia but can progress to a severe syndrome characterized by delirium and autonomic instability. Management of this syndrome often requires high-dose benzodiazepines or barbiturates.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

PART V

Special Populations

CHAPTER 164 General Approach to the Pediatric Patient

Robert A. Wiebe and Susan M. Scott

PERSPECTIVE

Background

Assessment of pediatric patients from the newly born through adolescence offers unique and varied challenges to the emergency care provider. Approximately 30% of all visits to a general emergency department (ED) are for issues related to pediatric patients. The vast majority of children in crisis are not seen in pediatric specialty hospitals, but in community hospital EDs. Although most pediatric visits to the ED are not serious, it is not uncommon to see true emergencies in infants and young children. Serious and life-threatening pediatric emergencies result from a wide variety of causes and require the health care provider to understand the unique anatomic, physiologic, immunologic, and developmental differences that make serious problems often difficult to recognize and the differential diagnosis dependent on the age of the patient.

Emergency care does not stop or start in the ED. An integrated emergency medical system that is capable of responding to the needs of children is a critical part of pediatric emergency care. Likewise, many critically ill or injured children cannot receive definitive care in small community hospitals. Therefore, a support network that includes interfacility transport resources and definitive care for pediatric patients must be part of an integrated system of emergency care for children. This chapter focuses on the role of the emergency physician in recognizing and assessing children needing emergency care.

Epidemiology

According to the National Center for Health Statistics, there were approximately 115,300,000 ED visits in the year 2003. In 2005, 20.5% of ED visits were for patients less than 18 years of age, and 28.2% of all children under 6 years of age in the United States had at least one visit to an ED in the past 12 months.[1] The National Hospital Ambulatory Medical Care Survey in 2005 demonstrated that the age group with the highest annual per capita ED visit rate was infants under 12 months of age, with 91.3 visits per 100 infants.[2] A recent survey revealed that pediatric patients were seen in an adult facility 89% of the time, with only 4% of departments having a separate area designated for the care of children.[3] The Emergency Pediatric Services and Equipment Supplement to the National Hospital Ambulatory Medical Care Survey revealed that 23% of EDs have a Pediatric Emergency Medicine specialist available, 62% have pediatric attending physicians available, and 71% have emergency medicine physicians on staff.[4] Only 6% of EDs have all the supplies as recommended by the joint American Academy of Pediatrics/American College of Emergency Physicians policy, "Care of Children in the Emergency Department: Guidelines for Preparedness."[5,6] Fifty percent of departments have at least 85% of the recommended supplies.

Data continue to suggest that health insurance status is not a significant cause of ED overcrowding.[7] Access to pediatric care is associated with a marked decrease in ED utilization regardless of insurance status, especially among the uninsured. The convenience of the ED, access without appointment, and lack of understanding by parents of the meaning of an emergency are the major factors related to pediatric nonurgent visits.[8]

Respiratory emergencies and trauma are the most common reasons for visits to an ED. Table 164-1 provides a list of the most common problems presenting to a pediatric ED. The most common diagnoses include acute respiratory infection, fever, otitis media and other head and neck infections, enteritis, and minor cuts and contusions. Injury is the most common cause of serious morbidity and mortality in children younger than 15 years and is responsible for 14.1 ED visits per 100 persons per year. In the pediatric age group, approximately 95% of these visits are for unintentional injuries that are largely predictable and preventable. Although the reasons for pediatric ED visits are many and varied, the care of critically ill or injured children should always focus on two physiologic events: shock and respiratory failure.

PRINCIPLES OF DISEASE

Pathophysiology

Anatomic and Physiologic Differences

Physical assessment of a pediatric patient requires attention to a variety of anatomic, physiologic, and developmental differences that vary with the age of the patient. It is sometimes difficult to separate anatomic and physiologic issues; for example, the large surface area-to-weight ratio in young infants can result in heat loss and temperature instability. Thus, it is important to maintain a neutral thermal environment during the physical assessment and stabilization process.

The relatively large head-to-body ratio and the small, weak neck of infants and young children make them particularly prone to head injuries. Blunt trauma to the chest and abdomen often results in injury to internal organs with minimal or no

Table 164-1 Chief Pediatric Complaints from Emergency Department Triage

COMPLAINT	NO. OF PATIENTS	PERCENTAGE OF TOTAL VISITS
Fever	19,754	19.3
Trauma/injury	11,650	11.4
Breathing difficulty	9979	9.7
Upper respiratory symptom	9004	8.8
Vomiting/diarrhea	7657	7.5
Abdominal pain	4460	4.4
Rash	4287	3.3
Ear complaint	3428	3.3
Genitourinary problem	3235	3.2
Soft tissue infection	1754	1.7
Seizure	1745	1.7
Eye complaint	1712	1.7
Sore throat	1562	1.5
Oral/dental complaint	1236	1.2
Headache	1229	1.2
Irritability	780	0.8
Chest pain	707	0.7
Foreign body	547	0.5
Behavior issue	392	0.4
Sexual abuse suspected	354	0.3
Total visits to triage	102,453	
Top 20 visits		82.6%

From Children's Medical Center of Dallas: 2003 ED Triage Statistics.

external signs of trauma. The elasticity of growing bones creates unique problems in pediatrics. Soft and pliable growing ribs will bend rather than break and transmit the forces of blunt trauma to the thoracic and upper abdominal organs. The weakest part of growing bones is the physeal plate or growth plate, and this area is injured more frequently than the surrounding ligaments. In a growing child, sprains are uncommon and physeal fractures result in nearly 20% of pediatric fractures. Recognition of growth plate injuries in children is critical to avoid imbalance in bone growth.

Anatomic differences between the pediatric and adult airway are important to understand for appropriate assessment and emergency support of the airway when required. The small airways of infants and young children are more prone to obstruction from secretions, which can result in relatively rapid deterioration ranging from respiratory distress to failure. Simple maneuvers such as deep suction of the upper airway can frequently have dramatic results in improving air movement in small infants. Because infants are often preferential nose breathers, nasal obstruction from secretions can result in significant airway compromise. An irritable and crying infant may just be learning to mouth breath when the nose is obstructed.

Youth also has its distinct advantages. Compensatory mechanisms to protect the infant or young child from decompensated shock, including increasing heart rate and shunting blood from the peripheral to more needed central circulation, are more effective in protecting the pediatric patient from serious consequences from shock.

Vital Signs

Table 164-2 provides normal ranges of vital signs. It is imperative for the provider to be familiar with these different values as they vary with age. Recognition and explanation for abnormal vital signs is one of the keys to success in the treatment of the ill patient.

Table 164-2 Normal Pediatric Vital Signs for Age*

AGE (YR)	RESPIRATORY RATE (BREATHS/MIN)	HEART RATE (BEATS/MIN)
<1	30–60	100–160
1–2	24–40	90–150
2–5	22–34	80–140
6–12	18–30	70–120
>12	12–16	60–100
Lower limits of systolic blood pressure†:		
0–28 days: 60 mm Hg		
1–12 months: 70 mm Hg		
1–10 years: 70 mm Hg + (2 × age in years)		

*From Dieckmann R, Brownstein D, Gausche-Hill M (eds): Pediatric Education for Prehospital Professionals. Sudbury, Mass, Jones & Bartlett, American Academy of Pediatrics, 2000, pp 43–45.
†From American Heart Association ECC Guidelines, 2000.

Normal heart rate varies with age. Tachycardia can be a product of fever, anxiety, pain, or fear but is also the first and most sensitive sign of cardiovascular compromise in the pediatric patient. When measuring the heart rate, the quality of the pulse can be extremely helpful, as can a comparison of the strength of the central and peripheral pulses in the same extremity. The quality of the brachial and radial pulses or the femoral and dorsalis pedis pulses palpated concurrently provides important information to differentiate cardiovascular compromise from benign causes of tachycardia. Bradycardia can be an ominous sign in the ill patient heralding cardiopulmonary failure and impending cardiac arrest.

Blood pressure measurement is a key component of the assessment of cardiovascular function and should be obtained in ill patients of all ages. Infants and young children have excellent compensatory measures for maintaining blood pressure in the presence of significant loss of circulatory volume. Compensatory mechanisms include an increase in heart rate and systemic vascular resistance. When these compensatory mechanisms fail and blood pressure drops below normal, the patient moves from a state of compensated to decompensated shock. Obtaining an accurate blood pressure in infants and small children can be challenging. The most common hurdle is the lack of cooperation by infants and small children. Another hurdle is the appropriate selection of the blood pressure cuff. The properly sized cuff should cover approximately two thirds of the circumference of the upper arm and extend at least 50% of the length of the upper arm.

The lower limit for acceptable blood pressure in children older than 1 year can be quickly estimated by using the following formula: systolic blood pressure (mm Hg) = 70 + (2 × age [in years]). The pulse oximetry waveform can also be used to determine systolic blood pressure. Observing for the return of a plethysmographic waveform of the pulse oximeter as the blood pressure cuff is deflated has been shown to correlate closely with conventional methods of blood pressure measurement.[9] Whenever possible, blood pressure should be obtained in all patients. An alert and crying infant with good peripheral pulses and normal mental status can be assumed to have adequate blood pressure, but this assumption can be misleading, and obtaining a blood pressure measurement in patients of all ages should be attempted.

As with the heart rate, respiratory rate varies with the age of the patient. Respiratory rate alone cannot be used to deter-

mine adequacy of ventilation. The respiratory rate must be compared with the adequacy of air exchange and work of breathing when assessing ventilation. Tachypnea can be the first and most sensitive sign of respiratory compromise in the pediatric patient. Tachypnea, however, is nonspecific and can also be a product of fever, fear, anxiety, or pain. In a febrile infant, the respiratory rate will increase by up to five respirations per minute for every degree centigrade in temperature elevation. Either a slow or rapid respiratory rate can be a sign of impending respiratory failure. Periodic breathing is a common reason for an ED visit by concerned, often first-time parents. It is not at all unusual for infants to have periodic breathing with episodes of apnea lasting up to 20 seconds. To be considered abnormal, periodic breathing must be associated with a drop in heart rate or oxygen saturation.

Vital signs at one given point in time may be quite difficult to interpret. Repeated measurement of the respiratory rate, heart rate, and blood pressure over time will provide a more accurate assessment of a patient's physiologic condition. Again, it is imperative that the provider find an explanation for any abnormal vital sign before disposition of the patient.

Developmental Issues

Knowledge of basic behavioral and developmental differences by age is important when assessing a pediatric patient. Table 164-3 summarizes age-related pediatric differences in motor function, problem-solving, language, and social/adaptive milestones during the first 2 years.

Neonates

During the neonatal period and early infancy, normal behavior consists of sleeping, feeding, and crying when hungry or experiencing discomfort. There is little or no eye contact and no social smile. Discomfort is usually nonspecific, and the cause of the irritability or crying may be difficult to interpret. It is essential in the assessment of the infant for the provider to listen to the parents and their concerns. A mother's "sense" of her child is often accurate and should be considered seriously.

Infants (12 Months or Younger)

By 2 to 3 months an infant has a social smile and responds to a friendly voice. Lack of appropriate social interaction can be worrisome. An infant with a glassy-eyed, "nobody home" stare can be easily distinguished from a normal infant who tracks lights or has a smiling face. Infants at this age have little or no understanding of language, but they will certainly respond to a calm and soothing voice. Of concern is a 6-month-old who does not acknowledge your presence. Normal behavior for this age includes any expression of curiosity or anxiety, such as crying. Children older than 6 months should be approached with caution. Infants at this age will cry when taken from the safety of their caregiver's arms. The emergency physician should anticipate stranger anxiety and examine the patient, whenever possible, in the lap of the caregiver. Distractions such as toys and penlights are useful to provide emotional control of the infant during the examination.

Toddlers (13 Months to 3 Years of Age)

During the toddler age, as language develops, it is important to talk directly to the child. It is important to realize that toddlers and preschoolers have more extensive receptive language than expressive language and can pick up fears and concerns from their parents and caregivers, making them apprehensive and fearful. If the patient appears stable, sitting and talking or playing with the patient first rather than performing the examination immediately upon entering the examination room can help establish a rapport. Praise and reassurance during the examination can go a long way in maintaining this rapport with the child.

Preschool Children (4 to 5 Years of Age)

Preschool children often fantasize, and such fantasies may result in irrational assumptions and even nightmares. The child may sense the fears and concerns of their caregivers and this may contribute to these assumptions. The cause of injuries or illnesses in preschoolers or loved ones may be misinterpreted as being a result of their own misbehavior. The provider can expedite the examination in a toddler by allowing the child to control some part of his or her experience, such as picking which ear the provider examines first.

School-Age Children (6 to 12 Years of Age)

As children reach school age, it becomes particularly important to explain procedures, answer questions, and address fears and concerns honestly. Privacy and modesty should be respected. Whenever possible, the child should be included in conversations, and historical information should be taken from both the child and parent. The powers of reasoning begin to mature, and a school-age child will often attempt to negotiate control over having painful or distasteful procedures performed. Choices and behavior limits should be given only when they do not compromise care. A child may be given some autonomy by allowing them to make choices in their care such as the choice to have blood drawn from the left arm or the right arm or be told that it is okay to cry but that it is important to keep the arm still.

Adolescents (13 to 19 Years of Age)

With adolescence comes independence and autonomy. Peer pressure becomes far more important than the behavior boundaries provided by the caregiver. Adolescents are risk takers and often have no fear of danger or injury. They rarely anticipate consequences and may lack common sense. Privacy and confidentiality should always be respected, and it is wise to separate adolescents from the caregiver when obtaining information and performing the physical examination. Adolescents should be given the opportunity to express their opinions and concerns about their own medical care.

CLINICAL FEATURES

Recognition of the pediatric patient at risk for decompensation and deterioration is a challenge to the health care provider forced to multitask in a busy ED. Despite the advanced technology available to the provider, the bedside evaluation of the patient is the key component to accurate evaluation and management. The initial assessment of the patient begins with the providers' examination of respiratory effort and circulation of the skin concurrently with their sense of the child's acuity, that is, "sick, not sick."

Pediatric Assessment Triangle

The pediatric assessment triangle (PAT) offers a sensible, orderly approach that can be used to assess children of all ages, identify abnormal cardiopulmonary physiology, and define the

Table 164-3 Developmental Milestones

AGE	GROSS MOTOR	VISUAL-MOTOR AND PROBLEM SOLVING	LANGUAGE, SOCIAL, AND ADAPTIVE
1 mo	Raises head slightly from prone position, makes crawling movements	Birth: visually fixes 1 mo: has tight grasp, follows to midline	Alerts to sound Regards face
2 mo	Holds head in midline, lifts chest off table	No longer clenches fist tightly, follows object past midline	Smiles socially (after being stroked or talked to) Recognizes parent
3 mo	Supports on forearms in prone position, holds head up steadily	Holds hands open at rest, follows in circular fashion, responds to visual threat	Coos (produces long vowel sounds in musical fashion) Reaches for familiar people or objects, anticipates feeding
4 mo	Rolls front to back, supports on wrists and shifts weight	Reaches with arms in unison, brings hands to environment midline	Laughs, orients to voice Enjoys looking around
5 mo	Rolls back to front, sits supported	Transfers objects	Says "ah-goo," orients to bell (localizes laterally)
6 mo	Sits unsupported, puts feet in mouth in supine position	Unilateral reach, uses raking grasp	Babbles Recognizes strangers
7 mo	Creeps	7–8 mo: inspects objects 7–9 mo: finger-feeds	Orients to bell (localizes indirectly)
8 mo	Comes to sit, crawls		"Dada" indiscriminately
9 mo	Pivots when sitting, pulls to stand, cruises	Uses pincer grasp, probes with forefinger, gestures, waves bye-bye, holds bottle, throws objects	"Mama" indiscriminately, understands "no" Starts to explore environment, plays gesture games (e.g., patty cake) 10 mo: "Dada" and "Mama" discriminately, orients to bell (directly) 11 mo: 1 word other than "Dada" and "Mama," follows 1-step command with gesture
12 mo	Walks alone	Uses mature pincer grasp, releases voluntarily, marks paper with pencil	Uses 2 words other than "Dada" and "Mama," immature jargoning (runs several unintelligible words together) Imitates actions, comes when called, cooperates with dressing 13 mo: uses 3 words 14 mo: follows 1-step command without gesture
15 mo	Creeps up stairs, walks backward	Scribbles in imitation, builds tower of 2 blocks in imitation	Uses 4–6 words 15–18 mo: uses spoon, uses cup independently 17 mo: uses 7–20 words, points to 5 body parts, uses mature jargoning (includes intelligible words in jargoning)
18 mo	Runs, throws objects from standing without falling	Scribbles spontaneously, builds tower of 3 blocks, plays in company of other children	Uses 2-word combinations Copies parent in tasks (sweeping, dusting), turns 2–3 pages at a time 19 mo: knows 8 body parts
21 mo	Squats in play, goes up stairs	Builds tower of 5 blocks	Uses 50 words, 2-word sentences Asks to have food and to go to toilet
24 mo	Walks up and down steps without help	Imitates stroke with pencil, builds tower of 7 blocks, turns pages 1 at a time, removes shoes, pants, etc.	Uses pronouns (I, you, me appropriately), follows 2-step commands Parallel play

Modified from Gunn KL, Nechyba C (eds): The Harriet Lane Handbook, 16th ed. St. Louis, CV Mosby, 2003.

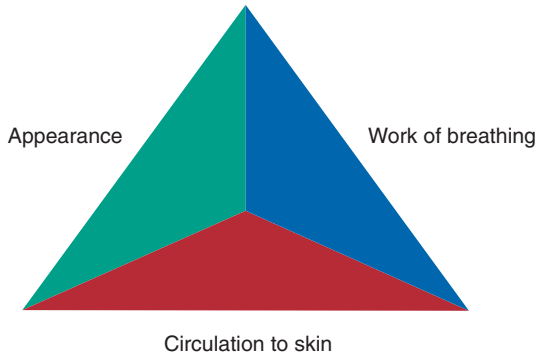


Figure 164-1. Pediatric assessment triangle.

urgency and need for lifesaving interventions. Before touching the patient, one should observe the child from a distance for visual and auditory clues. Figure 164-1 defines the three arms of the PAT: appearance, work of breathing, and circulation to the skin. This brief assessment rarely takes more than 30 seconds and adds to the initial discernment of "sick from well" (Table 164-4).[10,11]

Appearance

From a distance, one should quickly determine the general appearance of the child. A "hands-off" assessment of infants and young children can allow the examiner to gather critical information from a distance before upsetting the child with an invasive physical examination.

The evaluation of appearance can be remembered by the mnemonic TICLS: Tone, Interactiveness, Consolability, Look/Gaze, and Speech/Cry. Is the child interacting normally with the environment? Is the level of consciousness appropriate? Is the patient irritable, somnolent, lethargic, or appropriately responsive? When the brain is not adequately perfused, irritability is usually the first sign. This is followed by alternating irritability and lethargy, which, if left untreated, can progress to coma. Infants can be the most difficult to assess since their ability to interact with their surroundings is limited. The provider may need to rely on parents or caregivers, who can often recognize normal or abnormal behavior for their infant. The glassy-eyed, "nobody home" stare of a septic or brain-injured infant is not difficult to recognize. A high-pitched or cephalic cry is characteristic of any insult to the central nervous system. Simple observation of older children for proper tone, motor movements, and reaction to environmental stimulation is a good assessment of the appearance arm of the PAT. If the child is unusually irritable, allowing the patient to remain with the parent can help differentiate between behavior and pathology. Again, when in doubt a parent or caregiver can confirm whether the behavior is abnormal for the patient. Appearance, when normal, can insinuate that ventilation, oxygenation, and brain perfusion are at least adequate.

Table 164-4 Pediatric Assessment Triangle—Initial Assessment

APPEARANCE	WORK OF BREATHING	CIRCULATION TO THE SKIN
Tone	Abnormal sounds: stridor, grunting, snoring, wheezing	Pallor
Irritable, interactive	Abnormal positioning: sniffing, tripoding, refusal to lie down	Mottling
Consolable	Retractions	Cyanosis
Look/gaze	Head bobbing	Petechiae
Speech/cry	Nasal flaring	

Modified from Dieckmann R, Brownstein D, Gausche-Hill M (eds): Pediatric Education for Prehospital Professionals. Sudbury, Mass, Jones & Bartlett, American Academy of Pediatrics, 2000, pp 36–40.

Work of Breathing

Assessment of the work of breathing in infants and young children is best done from a distance. Once an infant begins to cry, it is difficult to make any reasonable interpretation of oxygenation and ventilation or to interpret breath sounds. One must listen carefully for audible abnormal airway sounds such as grunting, wheezing, stridor, and snoring. Grunting is an infant's or child's way of providing self-administered positive end-expiratory pressure to recruit collapsed or fluid-filled alveoli. The presence of inspiratory stridor alerts the examiner to upper airway obstruction. Muffled, hoarse, or abnormal speech can occur with trauma to the larynx or from a peritonsillar or peripharyngeal abscess. Assessment of the severity of wheezing should be determined by the presence of sounds that occur during both inhalation and exhalation, or just as expiratory sounds, and whether there is a prolonged expiratory phase. Observing for abnormal positioning can help determine the cause and severity of airway obstruction. A child assuming the "sniffing position" is attempting to best position the airway to overcome obstruction. Tripoding is often seen with severe respiratory distress in an attempt to maximize use of the accessory muscles of breathing (Fig. 164-2). The presence of intercostal, supraclavicular, and substernal retractions indicates an increased work of breathing (Fig. 164-3). Infants for the first several months of life may normally have abdominal breathing. Seesaw movements of the chest and abdomen are always abnormal. Nasal flaring and head bobbing can be seen in infants and young children with significantly increased work of breathing (Fig. 164-4).

Figure 164-2. Tripod position in a child with airway obstruction.

Figure 164-3. Intercostal retractions in a child with respiratory distress.

Figure 164-4. Nasal flaring in a child with respiratory distress from lower airway obstruction.

Effortless tachypnea, or rapid respirations with no increased work of breathing, is characteristic of a child compensating for metabolic acidosis by increasing the respiratory rate and driving the pH toward normal. It is important to remember that as a patient slips from respiratory distress to respiratory failure, work of breathing and the respiratory rate may both decrease. When this occurs, the appearance will change and a decrease in the level of consciousness will be evident.

Circulation to the Skin

Visual inspection of the skin can be used to quickly assess peripheral perfusion. Young children have excellent compensatory reserves, and with early and compensated shock, blood is shunted from the skin to vital organs. Compensated shock can be recognized by the presence of pallor. A pale child with a rapid heart rate should always be considered to be in shock until proved otherwise. As cardiac output is further compromised and perfusion to vital organs is decreased, the skin may

Figure 164-5. Cutis marmorata **(A)** and mottling of the skin **(B)**.

become mottled. Mottling is manifested by areas of vasoconstriction and vasodilation in a random pattern on the skin. It reflects loss of small vessel integrity and may be similar to what is seen in vital organs during multiple organ system failure. Mottling is usually an ominous sign. It is important to not confuse cutis marmorata with mottling in young infants (Fig. 164-5). Cutis marmorata is a lacy marbling of the skin caused by vascular instability. It is a normal finding and is commonly seen in infants in a cool ambient environment. Cyanosis may occur in the late stages of shock or with respiratory failure. Unless the child is cyanotic as a result of chronic primary cardiopulmonary problems or congenital heart disease, the development of cyanosis is an indication of respiratory failure or decompensated shock.

Table 164-5 summarizes how the PAT can be used to interpret specific physiologic abnormalities and the clinical condition of the patient.

Initial Hands-on Assessment

Two critical issues should be remembered when interpreting vital signs in children: first, one must remember to use age-appropriate standards (see Table 164-2); second, changes in vital signs over time are far more important than any single recording. A monitored and sleeping infant with an increasing heart rate cannot be ignored.

The initial hands-on assessment should be done in an orderly fashion by performing a stepwise assessment of airway,

Table 164-5 Interpretation of the Pediatric Assessment Triangle

PHYSIOLOGIC STATE	APPEARANCE	WORK OF BREATHING	CIRCULATION TO THE SKIN
Respiratory distress	Normal	Abnormal	Normal
Respiratory failure	Abnormal	Abnormal	Normal/abnormal
Compensated shock	Normal	Normal	Abnormal
Decompensated shock	Abnormal	Normal/abnormal	Abnormal
Brain injury/dysfunction	Abnormal	Normal	Normal
Cardiopulmonary failure	Abnormal	Abnormal	Abnormal

Modified from Dieckmann R, Brownstein D, Gausche-Hill M (eds): Pediatric Education for Prehospital Professionals. Sudbury, Mass, Jones & Bartlett, American Academy of Pediatrics, 2000, pp 30–57.

breathing, and circulation and resolving issues related to each before progressing to the next step.

Assessment of neurologic status or disability provides an opportunity for a more detailed objective measure of the child's appearance from the PAT. The Glasgow Coma Scale or its pediatric modification provides methods for assessing disability that can be used to monitor changes in mental status over time. The AVPU (alert, verbal, painful, unresponsive) scale is a simple alternative to assess whether the child is alert, responsive to verbal commands, responsive only to painful stimuli, or unresponsive.

Exposure of infants and young children can usually be performed more effectively with the parent's assistance. One should make every effort to maintain a neutral thermal environment to avoid unnecessary heat loss during the examination. Modesty can be preserved and cooperation can be improved by exposing body parts one area at a time.

Triage

The purpose of triage is to rapidly assess a patient and determine the urgency of evaluation and management. A number of triage scores have been devised, including the recently developed Canadian Pediatric Triage and Acuity Scale. This triage tool uses a five-level system. Table 164-6 uses a similar triage tool to list the 10 most common signs, symptoms, or problems categorized as triage level I in a busy inner-city ED in the United States. A triage level I patient is defined as one in shock or respiratory failure, unresponsive, or with absent or unstable vital signs. Traumatic injuries rank first for triage level I visits and rank third for triage level II visits. The second most common cause for a triage level I ED visit is seizures, which represent 16% of all triage level I visits. Respiratory failure is responsible for nearly 10% of all triage level I ED visits, and respiratory distress is the most common cause of triage level II visits.

Table 164-7 lists the 10 most common causes for triage level II visits. A triage level II patient is one who is considered to be an emergency with a potential threat to life, limb, or function; one who is lethargic, with significant respiratory distress; or one with severe pain. A level II patient requires physician assessment within 15 minutes of arrival to triage.

Table 164-6 Triage Level I Emergency Department* Visits

CATEGORY	NO. OF PATIENTS	PERCENTAGE OF LEVEL I VISITS
Trauma	369	56.3
Seizures	107	16.3
Respiratory failure	64	9.8
Altered consciousness	19	2.9
Sepsis	15	2.3
Cardiac problem	15	2.3
Diabetic ketoacidosis	11	1.7
Toxic ingestion	9	1.4
SIDS/CPR	8	1.2
Hypovolemic shock	4	0.6
Percentage of total		94.8
Total level I visits	655	64.0

*Children's Medical Center of Dallas, 2003; *N* = 102,453 visits.
CPR, cardiopulmonary resuscitation; SIDS, sudden infant death syndrome.

Table 164-7 Triage Level II Emergency Department* Visits

CATEGORY	NO. OF PATIENTS	PERCENTAGE OF LEVEL II VISITS
Respiratory distress	4132	33.0
Suspected sepsis/meningitis	881	7.0
Trauma/injury	786	6.3
Sickle cell disease complications	727	5.8
Diabetes complications	447	3.6
Genitourinary complaints	413	3.3
Ventriculoperitoneal shunt complications	388	3.1
Seizures	332	2.6
Hypovolemic dehydration	309	2.5
Oncology patient with fever	255	2.0
Percentage of total		69.2
Total level II visits	12,540	(12.2)

*Children's Medical Center of Dallas, 2003; *N* = 102,453 visits.

Clinical Interview

The initial contact with the child and parent will often determine the ultimate level of cooperation received and parent satisfaction with the visit. Parents who bring children to an ED for care usually perceive that their child has an emergency. Treating a family with respect, gentleness, and kindness goes a long way in ensuring a trusting patient-doctor relationship. If the family has been waiting a long time to see the doctor, start the conversation with a simple apology that expresses regret for the long wait. Introducing oneself to both the parents and child will facilitate a relaxed atmosphere for the interview.

Toddlers and early school-age children may be expected to say little during the interview process, but they should be allowed to provide answers to questions when appropriate. In an emergency setting, the chief complaint and present illness are the main focus for information gathering, but the past,

BOX 164-1 FOCUSED "SAMPLE" HISTORY

Signs/symptoms
Allergies
Medications
Past medical problems
Last food or liquid
Events leading to injury/illness

Modified from Dieckmann R, Brownstein D, Gausche-Hill M (eds): Pediatric Education for Prehospital Professionals. Sudbury, Mass, Jones & Bartlett, American Academy of Pediatrics, 2000, p 51.

family, and social history pertinent to the child's condition must also be explored. It is wise to not begin the interview with "What's the problem?" Parents do not like to consider their children or their conditions as "problems." A better approach would be "What brings you and your child to the emergency department today?" The "SAMPLE" mnemonic may be used to systematically obtain a focused history (Box 164-1). *Signs and symptoms* that describe the onset and nature of the chief complaint should be detailed. *Allergies* or drug reactions are recorded with information describing the characteristics of the reaction. *Medications* that the patient is currently taking are recorded, including the time and amount of the last dose. *Past medical problems* and special health care needs are detailed, including information about the pregnancy, labor and delivery, and current immunization status. Knowledge of the *last food and liquid given* is important if sedation, analgesia, airway management, or surgery is necessary. *Events* leading up to the injury or illness should be recorded. Gentle and soothing conversation throughout the physical examination often facilitates information gathering and reduces anxiety. The history is generally obtained while performing the secondary assessment.

Physical Examination

In infants and young children, the physical examination is not a stepwise process. It is neither a head-to-toe nor a toe-to-head evaluation. The examination should be performed in the least traumatic fashion by leaving painful or frightening components until the end and concentrating on high-value components initially. Children in late infancy through the toddler age should be left in the caregiver's lap during the majority of the examination.

Specific Disorders

Trauma

The initial assessment of the injured pediatric patient starts with a primary survey that includes careful assessment of the airway, adequacy of oxygenation and ventilation, as well as a search for signs of circulatory compromise. Once life-threatening abnormalities are identified and appropriate resuscitation efforts are begun, a careful and detailed secondary trauma survey is necessary to identify subtle but potentially life-threatening injuries. A systematic approach to pediatric trauma that includes a continuum of care from first responders through ED stabilization, interfacility transport, and definitive care will save lives.[12]

Attention to assessment of the cervical spine is a critical part of pediatric assessment. Because of the elasticity of the cervical spine in young children, spinal cord injuries without radiographic abnormalities (SCIWORA) can occur. These injuries result in ligamentous instability, which if ignored may result in significant morbidity or mortality. A history of neck pain, paresthesias, numbness, tingling, or focal neurologic findings must not be ignored even if cervical spine films are normal.[13] Because most out-of-hospital emergency medical systems require out-of-hospital providers to transport patients in complete spinal immobilization, it is important to obtain information from the transport professionals. Was the immobilization simply a precautionary measure by protocol? Was the child up, walking, and moving the neck before immobilization? Was there any history of pain, paresthesias, or evidence of neurologic injury? Such information can be helpful in determining whether the child needs radiographic imaging or can be clinically cleared from cervical spine immobilization. The decision to clinically clear a patient from immobilization can be considered if the patient is awake, alert, and cooperative with no distracting injuries and denies cervical spine tenderness. If at any time during the examination the patient complains of pain or has midline cervical tenderness, clinical clearance cannot be completed.

As the secondary trauma survey is systematically performed, continued attention to the PAT and primary survey is critical to identify ongoing bleeding or progressing respiratory problems. A pale trauma victim should have vascular access and blood available before or during the secondary survey.

Intentional injuries to children still result in more than 1200 deaths per year. Because these injuries are most commonly associated with blunt trauma, it is possible that no external evidence of injury will be apparent.[14] When historical indicators suggest possible child abuse, consultation with child protective services is mandatory. Box 164-2 lists historical indicators that should alert the heath care provider to the possibility of child abuse.[15] Examination of the skin for burns or bruises consistent with child abuse should be a part of any trauma survey. Box 164-3 summarizes bruises typically found in abused infants and children. See Chapter 64 for a more extensive discussion of these issues.

BOX 164-2 HISTORICAL INDICATORS OF CHILD ABUSE

Unexplained delay in seeking medical care.
History does not explain the injury.
History changes with time.
History is not consistent with the child's developmental abilities.
Child has "magical" injuries.

BOX 164-3 BRUISES SUGGESTIVE OF CHILD ABUSE

Any unexplained bruising in an infant under 9 months of age
Multiple bruises of different ages
Pattern injuries
  Handprints
  Belt marks
  Cord loop marks
  Linear marks from rigid objects
  Bite marks
Unusual distribution of bruises
  Neck
  Groin
  Inner aspect of thigh
Restraint marks on wrists or ankles

BOX 164-4 CLINICAL CROUP SCORE

Stridor	
None	0
Audible with stethoscope (at rest)	1
Audible without stethoscope (at rest)	2
Retractions	
None	0
Mild	1
Moderate	2
Severe	3
Air entry	
Normal	0
Decreased	1
Severely decreased	2
Cyanosis	
None	0
With agitation	4
At rest	5
Level of consciousness	
Normal	0
Altered	5

From Westley CR, Cotton EK, Brooks JG: Nebulized racemic epinephrine by IPPB for the treatment of croup. Am J Dis Child 132:484, © 1978. Reprinted by permission of Wiley-Liss, a division of John Wiley & Sons, Inc.

Medical Disorders

Seizures. Seizures are a common presenting complaint in the ED. Although most seizures in children are benign and self-limited, assessment must include attention to the airway and ventilation. An actively convulsing child must be quickly assessed for adequacy of oxygenation and ventilation. A nasal airway properly inserted can dramatically relieve airway obstruction and allow for assisted bag/mask ventilation when appropriate. As the child arouses from the postictal phase, the nasal airway should be removed to avoid vomiting. As a part of the secondary survey, the emergency physician should observe carefully for the character of the seizure and the presence or absence of any focal findings. Fever, central nervous system infections, and brain injury must always be considered in children with seizures and no history of childhood epilepsy. Other less common problems to rule out include intoxication, metabolic derangements, intracranial vascular anomalies, and tumor. Neonatal seizures can be very subtle and difficult to recognize. A seizure in this age group may be manifested as lack of an appropriate response to environmental stimuli, nystagmus, blinking eyes, or any fine repetitive movements.[16]

The Difficult Airway and Airway Obstruction. Recognition of a "difficult airway" can be a critically important issue in the assessment of seriously ill and injured children. Although scientific evidence for defining a difficult airway in children is limited, certain critical observations may be helpful. Dysmorphic features or physical conditions that limit the ability to completely open the mouth or that reduce neck mobility should suggest the possibility of a difficult airway. Although Mallampati grades have not been well studied in children, if the uvula cannot be visualized when opening the mouth, the patient should be considered high risk. Any evidence of upper airway obstruction in a child who is in impending respiratory failure should alert the emergency physician to the need of alternate airway devices or the possibility of surgical airway support.[17]

Scores that quantify the severity of upper and lower airway obstruction and disease are helpful tools to monitor response to therapeutic interventions. An example of a clinical croup score is detailed in Box 164-4.[18] The pediatric asthma severity score seen in Table 164-8 has been shown to be reliable, reproducible, and valid for assessing the severity of acute asthma in children 1 to 18 years of age.[19]

Altered Level of Consciousness. Altered level of consciousness accounts for approximately 3% of all critical ED visits. An orderly approach to the assessment of a child with altered level of consciousness is important to minimize organ damage and provide timely initial management. Quick assessment of the respiratory pattern can identify the irregular appearance of a Cheyne-Stokes breathing pattern, which consists of alternating periods of hyperpnea, followed by slowing ventilatory effort and periods of apnea. This respiratory pattern is typically found in children with increased intracranial pressure. Midbrain dysfunction will generally cause hyperventilation that is regular and rapid with normal oxygen saturation and low arterial partial pressure of carbon dioxide ($Paco_2$).

Examination of the eyes is helpful in sorting out causes of an altered level of consciousness. Pupils that are fixed and dilated in an unresponsive patient are always suggestive of

Table 164-8 Pediatric Asthma Severity Score

CLINICAL FINDING	DEFINITION	0	1	2
Wheezing	High-pitched expiratory sound absent wheezing heard by auscultation because of poor air exchange	None or mild	Moderate	Severe
Air entry	Intensity of inspiratory sounds	Normal or mildly diminished	Moderately diminished	Severely diminished
Work of breathing	Observed use of accessory muscles, retractions, or in-breathing	None or mild	Moderate	Severe
Prolongation of expiration	Ratio of duration of expiration to inspiration	Normal or mildly prolonged	Moderately prolonged	Severely prolonged
Tachypnea	Respiratory rate above normal for age	Absent	Present	
Mental status	Observation of the child's state of alertness	Normal	Depressed	

From Gorelick MH, Stevens MW, Schultz TR, Scribano PV: Performance of a novel clinical score, the Pediatric Asthma Severity Score (PASS), in the evaluation of acute asthma. Acad Emerg Med 11:10, 2004.

serious intracranial pathology and are never seen in patients unresponsive because of metabolic derangements. A unilaterally dilated pupil is secondary to increased intracranial pressure from mass lesions causing uncal compression on the third cranial nerve or due to direct ocular trauma. With significantly increased intracranial pressure, transtentorial herniation will increase pressure on the brainstem and result in asymmetrical pupils that become fixed and dilated. One should observe closely for equality of extraocular movements, nystagmus, and deviation of the eyes at rest. Funduscopic examination is helpful in identifying papilledema and retinal hemorrhages.

Assessment of motor movements including strength and tone is an important part of the secondary assessment for altered consciousness. One should observe closely for symmetry of movements as the absence of symmetry should signal the possibility of stroke and the presence or absence of abnormal posturing should alert the provider to the possibility of intracranial pathology and/or seizure.

Shock. Patients with trauma, sepsis, cardiac problems, diabetic ketoacidosis, diarrhea, vomiting, and ingestion of toxic substances may arrive at the ED in shock. The secondary survey will help differentiate causes of the shock state. Assessment of four organ systems in systematic fashion will help determine the etiology and severity of the shock and monitor response to treatment. The heart is the first organ to respond to a shock state and does so with an increased rate. Cardiac output is a function of stroke volume and heart rate, and when stroke volume decreases for any reason, the heart rate will increase. Careful examination of the heart by listening closely for a gallop rhythm, murmurs, indistinct or muffled heart sounds, or any dysrhythmia will help identify cardiogenic shock as the cause. The presence of these signs with development of hepatomegaly, especially after the administration of intravenous fluids, can also indicate the presence of cardiogenic shock. Tachycardia may be absent in patients with distributive shock. In the late stages of decompensated shock, bradycardia will occur as the shock progresses and can herald cardiopulmonary failure.

The second organ to respond to shock is the skin. In addition to the manifestations covered in the PAT, one should observe for skin temperature and signs of dehydration. The reverse thermometer sign can be of assistance in roughly judging the degree of hypovolemic shock. The examiner assesses skin temperature by running the fingers up the extremity to determine the point of cool/warm demarcation. During resuscitation, as reperfusion of the skin occurs, this point of warm/cold demarcation progresses peripherally. With early septic shock, the skin may appear warm and flushed. One must look closely for signs of dehydration, including tenting of the skin, a hollow-eyed appearance, or dry mucous membranes, which may suggest dehydration and hypovolemic shock. Capillary refill must be measured at or above the level of the heart to avoid erroneous results from venous flushing. In a neutral thermal environment, capillary refill longer than 2 seconds will be present in all forms of shock.

The third organ that objectively responds to the shock state is the brain. Irritability or a decrease in mental status is consistent with progressing shock.

The lungs respond to shock with tachypnea and hyperpnea. Hypovolemic shock will often be manifested as effortless tachypnea when the patient has become acidotic. Cardiogenic shock, distributive shock, and septic shock may also give rise to increased work of breathing, crackles, or wheezing (or any combination of the three).

Close and repeated monitoring of these four organ systems must be continued throughout the secondary survey and stabilization processes.

Children with Special Health Care Needs

Children with special health care needs account for a large number of emergency and urgent ED visits. In a child with developmental delay or significant neurologic problems, clinical assessment can be difficult and routine assessment tools may be limited in their usefulness. The caretaker is usually quite experienced and can often provide valuable information to assist in assessment. A behavior change recognized by the caretaker may be the only clue to a potentially serious illness or complication. For example, children with life-sustaining hardware such as ventriculoperitoneal shunts commonly come to the ED with nonspecific findings such as vomiting and headache, and change in behavior may be the only clue leading to an accurate diagnosis.

It is important to engage the parent to assist with baseline information and to seek specialty consultation from providers who are familiar with children who have special health care needs.

■ DIAGNOSTIC STRATEGIES

Noninvasive Monitoring

Noninvasive monitoring techniques such as oxygen saturation and end-tidal carbon dioxide measurements have become a routine part of pediatric assessment for a variety of illnesses and injuries. Pulse oximetry provides a valuable noninvasive and continuous measurement of arterial hemoglobin oxygen saturation, which has rapidly become a new "vital sign" for many illnesses. The role of pulse oximetry in monitoring children with respiratory distress and failure has been well defined. The use of pulse oximetry in children with cardiorespiratory problems is a valuable assessment tool and helps the clinician titrate the need for oxygen supplementation and respiratory support.

End-tidal CO_2 measurement is a noninvasive method for monitoring a variety of critically ill children that helps avoid repeated blood gas analysis. Studies have demonstrated that analysis of exhaled end-tidal CO_2 can be used to monitor respiratory failure, accurate endotracheal tube placement, and perfusion to peripheral tissues during the resuscitation of patients in shock. Measurement of end-tidal CO_2 and pulse oximetry can provide valuable assistance in monitoring children in both shock and respiratory failure. It is also a critical component of assessing correct placement of a tracheal tube after intubation has been performed.

The Pediatric-Ready Emergency Department

ED preparedness for the care of children is a special need that requires limited additional resources, but significant professional support and advocacy from both physicians and nursing staff. It is quite clear that the majority of hospitals with EDs will serve as pediatric receiving facilities for emergency care independent of size, volume, or availability of comprehensive resources. Hospitals without all the necessary resources must clearly be prepared to stabilize critical pediatric illnesses and injuries within their limitations and ensure timely transfer to facilities with available necessary resources. Guidelines for preparedness for the care of children in the ED are available.[5,6] The availability of protocols and policies that ensure timely transfer of critically ill and injured patients after stabilization is a part of the pediatric assessment process.

KEY CONCEPTS

- The physical and developmental stages of growth in pediatric patients provide challenges to the assessment of children in crisis.
- An understanding of age-related developmental issues and differences is important for performing an adequate pediatric assessment.
- One must establish rapport with pediatric patients to get cooperation in performing the examination.
- Abnormal vital signs always require explanation and resolution.
- The PAT provides a rapid assessment of severity and physiologic status and will provide a road map for the initial assessment of all pediatric patients.
- Continuing close monitoring and reassessment, especially following any intervention, is a key component to the evaluation and management of the ill or injured child.
- A neutral thermal environment should be maintained during the physical examination to avoid heat loss in infants who are critically ill.
- The presence of a difficult airway can be assessed in seriously ill or injured children by determining whether they are able to open their mouth wide enough for visualization of the uvula and normally extend and flex their neck.
- With special needs children, the caregiver can assist in determining baseline status.
- Beware the pale child: Pallor is a consistent and objective early sign of shock that cannot be ignored, especially in those with blunt trauma.
- Cervical spine: A large head with an elastic cervical spine may result in SCIWORA. Patients with this condition may not have any neurologic deficits, and cervical spine images may be normal. A history of transient paresthesia, numbness, tingling, or any focal neurologic findings, even if radiographs are normal, should be interpreted in this light and clinical clearance from immobilization should be delayed until further evaluation is performed.
- ED preparedness for pediatric emergencies: Guidelines for having a pediatric-ready ED are available through the American College of Emergency Physicians and the American Academy of Pediatrics.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 165 Pediatric Fever

Nathan W. Mick

Fever is the most common presenting chief complaint in pediatric patients presenting to the emergency department (ED), accounting for up to 20% of ED visits. Most cases of fever are viral in origin, benign in course, and resolve spontaneously. Fever tends to be of a higher clinical importance in younger children as they are immunologically immature and incompletely vaccinated. Management of children presenting to the ED varies dramatically depending on the age of the child with the following common, albeit arbitrary, divisions (0–28 days, 1–2 months, 2–3 months, 3–6 months, 6–36 months, 3 years to adulthood).[1] These divisions reflect differing immunologic and vaccination milestones as well as the spectrum of age-specific pathogens.

PERSPECTIVE

Definitions and Epidemiology

Fever is defined as any elevation in body temperature equal to or above 38.0° C and typically is the result of infection. The most reliable method to measure temperature is via a rectal thermometer, particularly in high-risk groups such as infants 0 to 3 months of age as axillary, oral, or tympanic thermometers are unreliable in this age group. The rectal route should not be used in patients who are potentially immunocompromised (i.e., children with fever who are receiving cytotoxic chemotherapy) due to the risk of mucosal damage, bacteremia, or transmission of infection. The cutoff for a clinically significant fever (i.e., one that triggers a laboratory evaluation) varies with the age and immunologic status of the child. A rectal temperature of 38.0° C is generally considered to be a clinically significant fever in an infant less than 3 months old, necessitating a thorough laboratory workup, whereas a toddler with a temperature of 39.5° C and an upper respiratory infection may not need any workup beyond a thorough history and physical. Fever is to be distinguished from hyperthermia, which is an elevation in the body's "set point." Causes of hyperthermia include bundling, heatstroke, salicylate ingestion, malignant hyperthermia as a complication of inhalational anesthetics, and elevation in temperature secondary to hypothalamic central nervous system (CNS) damage.

The cause of fever varies depending on the age of the child (Table 165-1). The vast majority of pediatric fever is due to infections, and the vast majority of infections are attributable to a viral source. Upper respiratory infections, viral gastroenteritis, croup, bronchiolitis, stomatitis, roseola, infectious mononucleosis, and varicella are all known causes of fever. Most viral illnesses are benign and self-limited, but infection with herpes simplex virus (HSV) at any age, or respiratory syncytial virus (RSV), particularly in the first month of life, can lead to significant morbidity and mortality.

Bacterial disease is also an important cause of fever in children. Serious bacterial illness (SBI) is typically defined as the presence of pathogenic bacteria in a previously sterile site and includes urinary tract infection (UTI), bacteremia, meningitis, osteomyelitis, bacterial gastroenteritis, bacterial pneumonia, cellulitis, or septic arthritis. Studies have found the risk of SBI in febrile infants less than 3 months of age to be between 6 and 10%, with children less than 28 days of age having the highest incidence.[2] Pathogens change during early infancy, with vertical transmission of organisms such as group B *Streptococcus*, *Listeria monocytogenes*, and HSV being more common in neonates. By 1 to 2 months of age, organisms such as *Streptococcus pneumoniae*, *Neisseria meningitidis*, and urinary pathogens (*Escherichia coli* or *Enterococcus*) become more common. In all children less than 3 months of age, the urinary tract is the most common site of infection, followed by bacteremia and meningitis. UTIs are more common in white children, particularly females, when compared with other races and is of higher prevalence in patients in whom no source for infection is found and who have higher temperatures (i.e., >39.0° C).[3]

Children under the age of 3 months may present with an apparent viral syndrome and still harbor serious bacterial illness. Levine and colleagues studied 1248 infants less than 60 days of age who had temperatures above 38.0° C. Of these children, 22% were positive for RSV. Although, overall, children with documented RSV had a lower incidence of concomitant SBI than those without RSV (12.5 vs. 7%), there was no significant difference in rates of SBI in children less than 28 days of age (14.2% in RSV-negative neonates vs. 10.1% in RSV-positive infants). Most of the bacterial infections were UTIs.[4] Older children 3 to 36 months of age with recognizable viral syndromes (e.g., croup, bronchiolitis, varicella, stomatitis) generally have a very low incidence of bacteremia. Greenes and coworkers found that among 1347 patients with fever above 39.0° C who had a recognizable viral syndrome, the risk of bacteremia was 0.2%.[5]

Occult bacteremia describes the presence of pathogenic bacteria in the bloodstream of a well-appearing febrile child in the absence of a focus of infection and was first described as a clinical entity in the 1970s.[6] The term typically refers to children 3 to 36 months of age who are highly febrile (>39.0° C) but appear well. Prior to the adoption of the conjugate vaccines

Table 165-1 Etiology of Fever in Children

AGE	BACTERIAL CAUSES	VIRAL CAUSES	OTHER
0–28 days of age	Group B *Streptococcus* *Listeria monocytogenes* *Escherichia coli* *Chlamydia trachomatis* *Neisseria gonorrhoeae*	Herpes simplex virus Varicella Enteroviruses Respiratory syncytial virus Influenza	Bundling Environmental
1–3 months of age	*Haemophilus influenzae* *Streptococcus pneumoniae* *Neisseria meningitidis* *E. coli*	Varicella Enteroviruses Respiratory syncytial virus Influenza	Bundling Environmental
3–36 months of age	*S. pneumoniae* *N. meningitidis* *E. coli*	Varicella Enteroviruses Respiratory syncytial virus Influenza Mononucleosis Roseola Adenovirus Norwalk virus Coxsackievirus	Leukemia Lymphoma Neuroblastoma Wilms' tumor
3 years to adulthood	*S. pneumoniae* *N. meningitidis* *E. coli* Group A *Streptococcus*	Varicella Enteroviruses Respiratory syncytial virus Influenza Mononucleosis Roseola Adenovirus Norwalk virus	Leukemia Lymphoma Neuroblastoma Wilms' tumor Juvenile rheumatoid arthritis

against *Haemophilus influenzae* type b (HIB) and *S. pneumoniae*, the incidence of bacteremia in this population was approximately 5%.[7,8] Vaccination has proven remarkably effective, nearly eradicating HIB as a significant pathogen and greatly reducing the burden of pneumococcal disease (Fig. 165-1).[9–11] Currently, the rate of occult bacteremia is below 1%, with pathogens such as *N. meningitidis* becoming proportionally more prevalent. Continued surveillance is ongoing to ensure that there is not a rise in invasive disease caused by nonvaccine serotypes. Urinary pathogens continue to be an important source of bacterial illness in infants and children, occurring in 2% of febrile children less than 5 years of age. Rates are highest in males less than 6 months of age (2.7%) and females less than 12 months of age (6–8%).[12,13]

Bacterial illness in school-aged children and adolescents includes focal infections such as streptococcal pharyngitis, cellulitis, and pneumonia, as well as bacteremia and meningitis. *N. meningitidis* has a bimodal distribution, with the highest incidence in children under 12 months of age (9.2/100,000 population). A second peak occurs during adolescence, when the rate of illness is 1.2/100,000 population, with a significant proportion of cases occurring in college students who reside in a dormitory setting (3.2/100,000 population).[14]

Although much less common than viral or bacterial infection, fever can also be a presenting sign of autoimmune diseases such as juvenile rheumatoid arthritis or Kawasaki disease (KD). CNS lesions such as brain tumors also can infrequently present with fever.

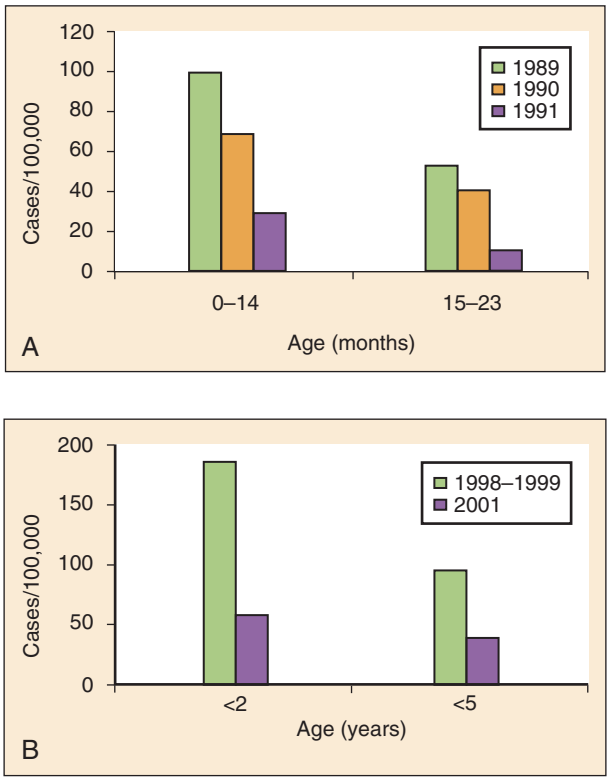


Figure 165-1. Decline in incidence of occult bacteremia after the introduction of the conjugate vaccine against *Haemophilus influenzae* **(A)** and *Streptococcus pneumoniae* **(B)**.

DISTINGUISHING PRINCIPLES OF DISEASE

Pathophysiology

The body's ability to fight infection varies with age. Maternal antibodies confer some protection after birth, but the infant's

immune system, particularly T-cell function and the ability to mount an immunoglobulin G response to infection, is initially inadequate. The immature neonatal immune system as well as exposure to certain pathogens during the birthing process (e.g., group B *Streptococcus*, *Chlamydia trachomatis*, *Neisseria gonorrhoeae*) places the newborn at particular risk for serious bacterial illness. Young infants are also at risk for disseminated infection as they are unable to mount the immune response needed to prevent a localized infection from spreading. Thus, a simple cellulitis, mastitis, omphalitis, or, rarely, gonoccocal eye disease can lead to sepsis or focal seeding of the CNS, making aggressive evaluation and treatment of such infections prudent. Immune function improves over the first 2 to 3 months of life, but the risk of SBI does not diminish appreciably until the primary series of vaccinations against HIB and pneumococcus is completed (6 months of age).

History

When dealing with a febrile child, history taking should focus on the length of illness, presence of localizing symptoms, as well as any pertinent past medical history. In infants less than 28 days of age, birth history, particularly the presence of potentially transmittable maternal infection (HSV or group B *Streptococcus*), is critically important. Immunization status, sick contacts, use of antipyretics prior to evaluation, and prior use of antibiotics are also important historical items. Defervescence after acetaminophen administration has not been shown to reliably exclude bacteremia.[15] Prior antibiotic use may mask the classic findings in diseases such as meningitis. Cough and congestion may suggest pneumonia or viral upper respiratory infection, whereas a harsh, barking, or seal-like cough is often a predominant complaint in viral laryngotracheitis (croup). Parents may report vomiting and diarrhea as a component of gastroenteritis or the presence of sore throat and lymphadenopathy with viral or streptococcal pharyngitis. A history of decreased oral intake or decreased urine output is frequently a complaint in gastroenteritis but may also be seen in patients with stomatitis as the painful aphthous ulcerations in the mouth make fluid intake difficult. Any history of lethargy, irritability, or altered mental status can be seen with severe dehydration but raises the specter of meningitis or encephalitis. A history of rash is seen in many viral illnesses such as roseola, but also may be seen in life-threatening conditions such as meningococcemia, Rocky Mountain spotted fever, or toxic shock syndrome (TSS). Complaints of headache and neck pain (meningitis or encephalitis) or ear pain (otitis media) are also important historical points.

Physical Examination

The physical examination of the febrile child should begin with a complete set of vital signs, including pulse oximetry. Hypoxia or significant respiratory distress manifested by tachypnea, grunting respirations, nasal flaring, or retractions may accompany sepsis or pulmonary infection. Stridor can be seen with croup but also can be seen with retropharyngeal abscess, epiglottitis, or bacterial tracheitis. Signs of shock such as hypotension or poor peripheral perfusion should be noted. Children typically mount a tachycardic response to fever, and hypotension is often a late and dire finding. Tachycardia is often due to the fever itself, but tachycardia out of proportion to the degree of fever is often seen in other conditions such as myopericarditis, hypovolemia, or dehydration. Greenes and colleagues found that in infants less than 12 months of age, heart rate increases linearly by 9.6 beats/min with each 1° C increase in body temperature; however, caution must be exercised in attributing tachycardia to fever alone.[16] Once oxygenation, ventilation, and perfusion have been assessed and deemed adequate, the physical examination should focus on a thorough search for focal infection. It should be noted that in young infants, particularly those less than 3 months of age, as well as in children who lack immunocompetence, fever may be the only presenting sign of serious illness, including meningitis. The physical examination in this age group is sufficiently insensitive to exclude serious bacterial illness, and clinicians should not be falsely reassured by a normal physical examination in small children.

Ancillary Testing

There are numerous laboratory and radiographic studies that can be used to evaluate the febrile child. Generally, testing should be directed at identifying the source of infection or evaluating for complications. Several guidelines exist for the evaluation of febrile children, although there is marked variation in adherence to these guidelines. Pantell and associates found that office-based practitioners followed published guidelines only 42% of the time when evaluating febrile children.[17] Clinicians with less experience and those based in the hospital tend to order more tests compared with more experienced clinicians and those practicing in an office setting.

White Blood Cell Count

An elevated white blood cell (WBC) count (>15,000/mm^3) can be an indicator of bacteremia but is also present in many viral illnesses. Leukopenia (<5,000/mm^3) can also be a sign of serious bacterial disease or early sepsis. An elevated WBC count is classically associated with pneumococcal disease, while infection with *N. meningitidis* and *H. influenzae* may be present even with normal WBC counts. Lee and colleagues found that the rate of pneumococcal bacteremia increased from 0.5% in highly febrile children (>39.0° C) with WBC between 10,000 and 15,000/mm^3 to 3.5% if the WBC was 15,000 to 20,000/mm^3, and up to 18% with WBC above 30,000/mm^3.[18]

The WBC differential has also been used to risk stratify febrile children in various models, with an increase in polymorphonuclear leukocytes (PMNs) and immature band forms increasing the risk of bacterial disease. A rise in PMNs is also seen early in some viral infections. An absolute neutrophil count (ANC) greater than 10,000/mm^3 suggests increased risk of pneumococcal bacteremia in febrile children; 0.8% for children with an ANC less than 10,000/mm^3 versus 8% for children with an ANC above 10,000/mm^3.[19]

Blood Culture

A blood culture is a useful diagnostic test when bacteremia is suspected. In infants and children, blood should be obtained after sterile preparation of the skin, which includes an alcohol preparation and swabbing of the skin with povidone-iodine solution, which is then allowed to dry. Many centers obtain blood for culture during intravenous catheter placement after sterile preparation of the skin has been performed. This technique has the advantage of eliminating a second venipuncture solely to obtain blood for culture, although the rates of contamination using this technique have been shown to be higher in children (9.1 vs. 2.8%).[20] The risks of contamination must be weighed against the risks and ability to obtain blood via a separate venipuncture. The yield of a single blood culture in infants and small children is actually quite good. Routinely sending more than one sample is generally not needed, and often accurate detection of bacteremia occurs even if only 0.5

to 1 mm of blood is obtained. The advent of automated blood culture systems led to the identification of true pathogens more quickly than traditional methods, often within 24 hours. Pathogens isolated in the first 24 hours are more likely to be true pathogens than bacteria isolated after 24 hours.[21]

Urinalysis and Urine Culture

Urinary tract infections are common causes of bacterial illness in febrile children. Accurate documentation of UTI is imperative both as a means to diagnose the cause of a fever as well as to identify those infants who need follow-up radiographic imaging (typically voiding cystourethrogram [VCUG] and/or renal ultrasound) to exclude anatomic abnormalities that will predispose them to further infection. The only reliable method to obtain urine in a non-toilet-trained child is through bladder catheterization or suprapubic aspiration. Bag collection of urine is notoriously unreliable as up to 85% of positive cultures from bag specimens will be false positives (defined as a culture growing a single organism with $<10^5$ colony forming units [CFU]/mL or a mix of two or more organisms), which then places these children at risk for unneeded costly, potentially painful, and expensive follow-up diagnostic testing. Obtaining urine via a clean catch specimen is appropriate for older toilet-trained children.

Urinary tract infection is defined as the combination of bacteriuria and pyuria. Bacteriuria in the absence of WBCs on microscopic examination represents asymptomatic bacteriuria. Urine is typically analyzed using a dipstick followed by microscopic analysis of a centrifuged specimen of urine. Hoberman and colleagues describe the test characteristics of an "enhanced" urinalysis, which is examination using a hemocytometer of an unspun specimen of urine for pyuria (defined as >10 WBCs/high-power field [hpf]) or presence of any bacteria/hpf in a Gram's stain of unspun urine. They report a negative predictive value of 99.8%, perhaps making urine culture unneeded if pyuria and bacteriuria are absent using the enhanced urinalysis method.[22] Many centers are not using this enhanced method. Because dipstick and microscopic analysis have lower sensitivities, most experts recommend sending urine for culture in high-risk groups (febrile girls <12 months of age, uncircumcised boys <12 months of age, and circumcised boys <6 months of age).

A positive urine culture is defined as the growth of greater than 10,000 CFU/mL from urine obtained from a catheterized or suprapubic sample. In older children, where urine is typically obtained from a clean catch specimen, a higher threshold of greater than 100,000 CFU/mL is typically employed.

Lumbar Puncture

A sample of cerebrospinal fluid (CSF) should be obtained from any child with signs and symptoms of meningitis. Fluid should be obtained using the smallest noncutting spinal needle possible (typically a 22-gauge spinal needle) and sent for cell counts, manual differential, Gram's staining, culture, and measurement of CSF protein and glucose. Meningoencephalitis due to HSV is a potential cause for fever, particularly in children, and if suspected, sending CSF for HSV polymerase chain reaction testing is indicated. The CSF in bacterial meningitis typically contains greater than 1000 WBCs/mL, although there is considerable overlap in the CSF profile of bacterial and viral meningitis, making a determination of viral or aseptic meningitis difficult based on CSF parameters such as cell count, protein, and glucose; thus, CSF culture of a pathogenic bacteria is the gold standard. A prediction rule has recently been developed and validated to differentiate bacterial from aseptic meningitis.[23] Children who lack all of the following criteria have a low risk (0.1%) of bacterial meningitis: positive CSF Gram's stain, CSF ANC of at least 1000 cells/μL, CSF protein of at least 80 mg/dL, peripheral blood ANC of at least 10,000 cells/μL, and a history of seizure before or at the time of presentation. This may obviate the need for empirical antibiotic therapy and hospital admission in some children who are at low risk for bacterial meningitis.

Contraindications to lumbar puncture include cellulitis over the proposed site of puncture, cardiopulmonary instability, bleeding dyathesis, focal neurologic deficits, and signs of increased intracranial pressure, including papilledema. In these patients, lumbar puncture should be deferred until the child is stable and blood should be obtained for culture, recognizing that up to 50% of children with meningitis will not have bacteremia.[24]

CSF contaminated by blood, or a traumatic lumbar puncture, can make interpretation of cell counts and differentials difficult. In these cases, fluid should be obtained for Gram's stain and culture and the child treated presumptively for meningitis until culture data are available. Nigrovic and coworkers have shown that risk factors for a traumatic lumbar puncture include operator experience, excessive patient movement during the procedure, advancing the needle with the stylet in place, and lack of local anesthesia.[25]

Stool Studies

Stool studies are indicated in patients in whom bacterial gastroenteritis may be a cause of fever. A stool guaiac for blood should be performed as well as a Gram's stain for WBCs. Presence of either in the febrile child should trigger a culture of stool for the presence of *Salmonella*, *Shigella*, *Campylobacter*, enterotoxigenic *Escherichia coli*, and *Yersinia* species. Patients with sickle cell disease are at particular risk for focal complications such as osteomyelitis from *Salmonella* infection.

Chest Radiography

Chest radiographs may be useful in the workup of the febrile child and are indicated when hypoxemia, respiratory distress, tachypnea, or focal findings on lung examination are present. Children younger than 6 months may present with tachypnea as the sole findings of bacterial pneumonia. Truly occult pneumonia can also occur, particularly in the highly febrile child (>39.0° C) without apparent source of fever. Bachur and associates found that the 26% of children with fever above 39.0° C and WBC counts greater than 20,000 had radiographic evidence of pneumonia.[26] Of note, this study was done in the era prior to the conjugate pneumococcal vaccine.

Rapid Viral Antigen Testing

Many clinical laboratories have the ability to perform rapid viral antigen testing for such common pediatric viral illnesses as influenza A and B and RSV. The presence of a viral "source" for the fever in an ill child may obviate the need for expensive, painful, and lengthy diagnostic workups for bacterial processes. Bonner and colleagues evaluated the impact of physician knowledge of the presence of a positive rapid influenza assay result.[27] The investigators studied 391 patients ages 2 months to 21 years who presented with classic signs and symptoms of influenza. Of these patients, over half had positive rapid assays for influenza and the investigators noted that significantly fewer laboratory and radiographic studies were ordered if the treating clinician was aware of these results. There were also fewer antibiotics prescribed.

RSV is also a frequent cause of fever in children. Levine and coworkers found that in febrile children less than 60 days of age, the presence of RSV reduced the risk of concomitant serious bacterial illness (12.5 vs. 7%), although in children under the age of 28 days, the risk reduction was not statistically significant (14.2 vs. 10.1%). Most of the serious bacterial illnesses in this study of RSV-positive children were UTIs.

SPECIFIC DISORDERS

General Approach to the Febrile Infant and Child

The initial approach to any child with a febrile illness is a rapid assessment for evidence of cardiopulmonary compromise or shock. Significant respiratory distress, hypoxemia unresponsive to supplemental oxygen, or altered mental status may necessitate intubation via rapid sequence induction and mechanical ventilation. Evidence of shock (poor perfusion, hypotension, altered mentation) should be aggressively treated with fluid resuscitation. An intravenous or intraosseous line should be placed and the initial resuscitative fluid should be 20 mL/kg of isotonic crystalloid. This should be repeated to a total of 60 to 100 mL/kg if signs of hypovolemia persist, after which the use of vasopressor therapy (dopamine 1–20 µg/kg/min or norepinephrine 0.1–3 µg/kg/min titrated to blood pressure) should be considered.

Every effort should be made to obtain appropriate specimens for culture (blood and urine), even in the critically ill child prior to antibiotic administration. Lumbar puncture may be deferred in the critically ill child until stabilization occurs. Empirical antibiotic therapy should be directed at the most likely causative organisms based on age. Sterilization of the CSF occurs quickly once antibiotic administration has been initiated: within 15 minutes to 2 hours in patients with meningococcal meningitis and within 4 to 10 hours in patients with pneumococcal meningitis.[28]

Serious Bacterial Illness

Infants 0 to 28 Days of Age

Children presenting with fever above 38.0° C who are less than 28 days of age are at particularly high risk for bacterial illness, with rates as high as 12% quoted in the literature.[29,30] Often, fever is the only manifestation of potentially life-threatening disease, and other signs and symptoms may be exceedingly subtle, and this has led to an aggressive approach to diagnostic testing, empirical antibiotic therapy, and hospitalization in this age group, even if the child is well-appearing.

Often, children in this age group present with nonspecific complaints such as irritability, lethargy, poor feeding, or grunting. Besides fever, other signs of serious illness include a bulging fontanel, mottled extremities, petechiae, or tachypnea. Bacterial pathogens in this age group include group B *Streptococcus*, *L. monocytogenes*, *N. meningitidis*, *S. pneumoniae*, and *E. coli*. Viral pathogens, including RSV and HSV, are also important considerations. Neonatal HSV infection in particular carries a high degree of morbidity and mortality and should be considered in any febrile neonate with a maternal history of genital herpes, who is ill-appearing, who presents with fever and seizure, who has cutaneous vesicles on physical examination, or who has evidence of transaminitis or coagulopathy. HSV meningoencephalitis should also be considered in patients with fever and CSF pleocytosis but a negative CSF Gram's stain. The risk period for HSV disease tends to be between 2 and 12 days of age (Fig. 165-2). Other noninfectious causes of a septic-appearing neonate include the acute salt-wasting crisis associated with congenital adrenal hyperplasia and undiagnosed ductal-dependent congenital heart disease.

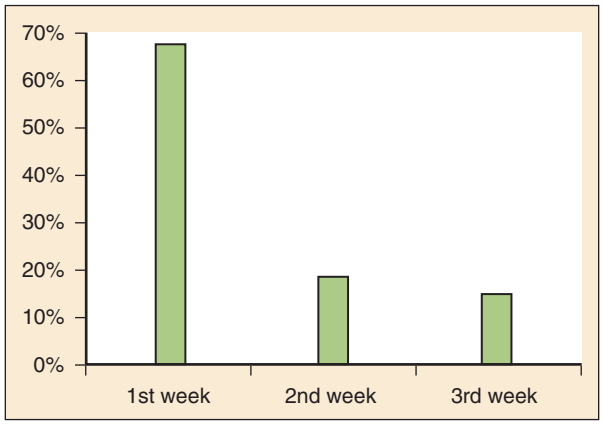


Figure 165-2. Age at presentation for neonatal herpes simplex virus infection.

Because of the high risk of bacterial pathogens and the difficulty in clinically assessing children younger than 28 days of age, these patients require an aggressive diagnostic evaluation, including a complete septic workup. This consists of a complete blood count (CBC), blood culture, urinalysis and urine culture, and lumbar puncture. Lumbar puncture is indicated even in the presence of a UTI due to the risk of concomitant meningitis.[31] All children in this age group should be admitted to the hospital on empirical antibiotics until culture data become available. Appropriate parenteral antibiotic regimens include ampicillin (100 mg/kg/24 hours divided every 6 hours) plus either gentamicin (5 mg/kg/24 hours divided every 8 to 12 hours) or cefotaxime (150 mg/kg/24 hours divided every 8 hours). Ceftriaxone should be avoided in infants under 28 days of age because of a theoretical risk of inducing acute bilirubin encephalopathy as ceftriaxone causes bilirubin to displace from its protein binding sites. Empirical acyclovir should be added if risk factors for HSV disease exist (60 mg/kg/24 hours, divided every 8 hours).

Infants 29 to 90 Days of Age

Although there is a relative consensus as to the evaluation and management of febrile infants younger than 28 days of age, there is debate about the appropriate workup for the slightly older febrile infants. Ill-appearing children of any age should have a complete sepsis evaluation performed and be admitted to the hospital on empirical antibiotic therapy. Appropriate antibiotic therapy for high-risk children would include coverage of neonatal pathogens such as *Listeria monocytogenes* and group B streptococci as well as coverage against *H. influenzae*, *N. meningitidis*, and *S. pneumoniae*. Ampicillin, 50 to 100 mg/kg every 6 hours, plus cefotaxime, 50 mg/kg every 8 hours parenterally, is one alternative. Vancomycin, 40 to 60 mg/kg intravenously (IV) every 6 to 8 hours, should be considered if *S. pneumoniae* resistant to penicillins and cephalosporins is suspected. Various strategies (herein referred to as the Rochester, Philadelphia, and Boston criteria) for the evaluation of well-appearing children have been reported, compared, and retested in the literature.[32–34] Each strategy has unique features, including the definition of fever (38.0 vs. 38.2° C), study population (0–3 months of age, 1–2 months of age, and 1–3 months of age), the clinical and laboratory variables studied, and disposition (hospitalization with/without antibiotics or outpatient treatment with/without antibiotics). Each strategy seeks to

Table 165-2 Summary of Major Strategies for the Management of Febrile Infants Less Than 3 Months of Age

	PHILADELPHIA	ROCHESTER	BOSTON
Age	29–60 days	≤60 days	28–89 days
Temperature	≥38.2° C	≥38.0° C	≥38.0° C
Examination	Well, no focus	Well, no focus	Well, no focus
Laboratory values (defines low risk)	WBC count <15,000/mm^3 Band: Neutrophil <0.2 UA <10 WBCs/hpf, (negative Gram's stain) CSF <8 WBCs/hpf (negative Gram's stain) CXR/stool negative (if obtained)	WBC count 5–15,000/mm^3 Absolute band count <1500 UA ≤10 WBCs/hpf Stool <5 WBCs/hpf (if obtained)	CSF <10 WBCs/hpf UA <10 WBCs/hpf WBC count <20,000/mm^3 CXR negative (if obtained)
High risk	Admission + IV antibiotics	Admit + IV antibiotics	Admit + IV antibiotics
Low risk	Home, no antibiotics	Home, no antibiotics	Home, empirical antibiotics
Performance	Sens 98% (92–100%) Spec 42% (38–46%) PPV 14% (11–17%) NPV 99.7% (98–100%)	Sens 92% (83–97%) Spec 50% (47–53%) PPV 12% (10–16%) NPV 98.9% (97–100%)	Sens not available Spec not available PPV not available NPV 94.6%

CSF, cerebrospinal fluid; CXR, chest radiograph; IV, intravenous; NPV, negative predictive value; PPV, positive predictive value; Sens, sensitivity; Spec, specificity; UA, urinalysis; WBC, white blood cell.

identify a set of low-risk criteria that, if met, will allow for less aggressive treatment or withhold empirical antibiotic therapy. The three main strategies are highlighted in Table 165-2. Baraff synthesized the recommendations of the Rochester, Philadelphia, and Boston criteria into an algorithm for the management of the previously healthy febrile infant 29 to 90 days of age (Fig. 165-3).[35] To be low risk, the child had to have been previously healthy with an uncomplicated nursery stay, be nontoxic clinically, and have no focal source of bacterial infection. Low-risk laboratory criteria in this schema included a normal WBC count (between 5000 and 15,000 WBCs/mm^3), less than 1500 bands/mm^3, a normal urinalysis (negative Gram's stain and <5 WBCs/hpf), and a negative CSF Gram's stain and cell counts (<8 WBCs/mm^3), if obtained. When diarrhea was present, less than 5 WBCs/hpf was the threshold for low risk. Once deemed low risk by these criteria, two options are available to the clinician based on the Philadelphia and Boston criteria. The first management strategy calls for a CBC, blood culture, urinalysis, and urine culture. Once these studies were obtained, the child could be discharged with close outpatient follow-up. The second option, based on the Boston criteria, calls for a complete sepsis evaluation including lumbar puncture, followed by empirical treatment with ceftriaxone (50 mg/kg IV or intramuscularly [IM]) and reevaluation within 24 hours. The important difference between these two strategies is that empirical antibiotics should not be administered unless a complete sepsis evaluation is performed, including a lumbar puncture. Otherwise, if the child returns for reevaluation and lumbar puncture is performed and CSF pleocytosis is found, pretreatment with antibiotics makes interpretation of culture results difficult. Thus, a child with a possible viral process may be condemned to inpatient admission and 14 days of parenteral antibiotic therapy.

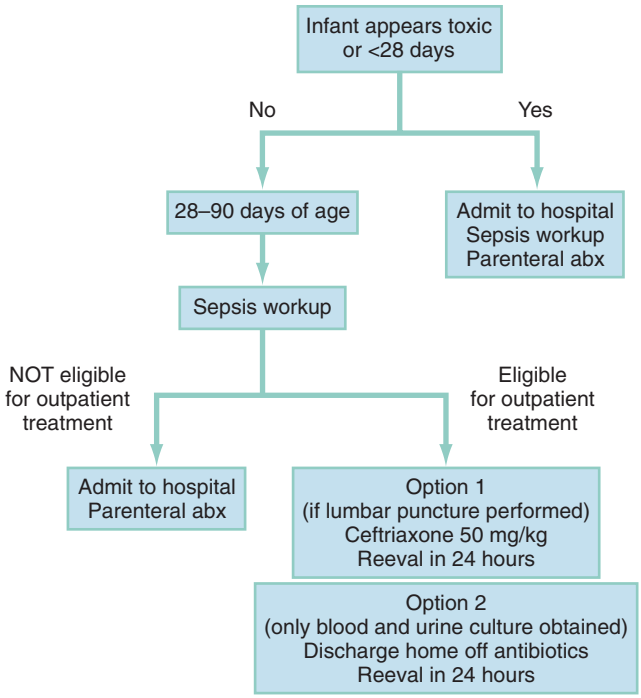


Figure 165-3. Algorithm for the management of febrile infants less than 3 months of age.

Infants 3 to 36 Months of Age

Fever in children 3 to 36 months of age is incredibly common and most cases represent self-limited viral illnesses. Common causes of fever in this age group include viral upper respiratory infections, croup, bronchiolitis, stomatitis (typically caused by HSV or coxsackievirus), gastroenteritis, roseola, and Fifth's disease (parvovirus B19 infection). Focal infections such as pyelonephritis, periorbital cellulitis, bacterial pharyngitis (group A *Streptococcus*), septic arthritis, retropharyngeal abscess, meningitis, as well as bacterial pneumonia also become common in this age group. Typically, these focal infections are apparent based on history and physical examination, and diagnostic testing and treatment should be directed accordingly.

The history in this age group should focus on the duration of illness, associated symptoms that may focus the evaluation, immunization history (particularly vaccination for *H. influenzae* type B and pneumococcus), and sick contacts. A thorough physical examination is essential to rule out serious focal infection such as meningitis. Young children may demonstrate inconsolable irritability or lethargy as the sole manifestations of meningitis; furthermore, classic meningeal signs such as nuchal rigidity are seen in less than 27% of infants (0–6 months) with bacterial meningitis.[36]

Prior research has focused on assessing children in this age group for the presence of occult bacteremia. It was found that a small percentage of highly febrile children (>39.0° C)

3 to 36 months of age were bacteremic.[35,37–40] These children were noted to be highly febrile but to lack any localizing signs of infection. No historical or physical examination findings were sufficiently sensitive or specific to identify cases of occult bacteremia, making universal diagnostic testing necessary.[41–43] A typical workup would include a CBC, blood culture, and empirical antibiotic therapy for children with WBC counts greater than 15,000/mm^3. Empirical antibiotics were justified based on studies that revealed treatment with antibiotics prevented focal sequelae of bacteremia such as meningitis and shortened the duration of fever.[44–46] Prior to the advent of almost universal immunization against *S. pneumoniae*, the rate of occult bacteremia was approximately 3%, and although up to 75% of the time pneumococcal bacteremia resolves without therapy, a small proportion of children develop sepsis or focal infections such as meningitis. Pneumococcal meningitis has a high degree of morbidity and mortality, including permanent neurologic disability, hearing loss, and death.[47,48] Since the advent of Prevnar (conjugate pneumococcal vaccine), the number of invasive pneumococcal infections caused by vaccine-serogroup isolates among eight U.S. children's hospitals has decreased more than 75% among children less than 24 months of age. Due to the decline in invasive pneumococcal disease brought on by vaccination, the cost-effectiveness of mandatory blood testing has been called into question.[49,50] Lee and colleagues evaluated the cost-effectiveness of various management strategies including:

- No workup
- Relying on clinical judgment
- Blood culture
- Blood culture plus empirical antibiotics
- WBC count plus blood culture and empirical antibiotics
- WBC count plus selective blood culture for WBC counts greater than 15,000 and empirical antibiotics

They found that at rates of pneumococcal bacteremia greater than 1.5%, obtaining a WBC count plus selective blood culture and empirical antibiotics were the most cost-effective approach. At rates of pneumococcal bacteremia less than 0.5%, strategies that utilized empirical testing and treatment were no longer cost-effective. They concluded that at lower rates of bacteremia, clinical judgment was more useful in selecting out high-risk populations who might benefit from selective testing and treatment.[51]

Although the incidence of pneumococcal bacteremia has declined in infants 3 to 36 months of age due to the aggressive campaign to vaccinate, infants 3 to 6 months of age have not yet completed the primary series of immunizations against *S. pneumoniae* and to a lesser extent, *H. influenzae*. Thus, highly febrile infants (>39.0° C) without an apparent source on examination should be considered at risk for occult bacteremia and consideration be given to obtaining a WBC count and blood culture as a screen. Empirical antibiotic therapy should be reserved for infants with WBC counts above 15,000/mm^3. It is important to note that although the conjugate pneumococcal vaccine contains antigens from the seven most common serotypes that cause invasive disease, there are approximately 90 serotypes that are capable of infecting humans. Continued bacterial surveillance is necessary to ensure that other serotypes do not rise in incidence to fill the void left by vaccination. It should also be noted that no clinical prediction algorithm correctly identifies all patients with meningococcal disease.[52] Additional signs and symptoms that may suggest meningococcemia are purpuric rash, bandemia, limb pain, and exposure to a person with the disease. An appropriate flow diagram for the workup of febrile infants 3 to 36 months of age is presented in Fig. 165-4.

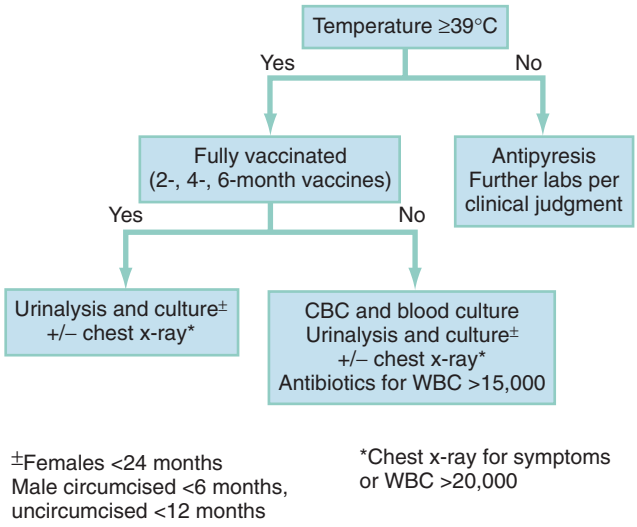


Figure 165-4. Algorithm for the management of febrile infants 3 to 36 months of age.

Children Ages 3 Years to Adulthood

The incidence of occult bacteremia decreases after 3 years of age. Focal infections such as streptococcal pharyngitis, septic arthritis, pneumonia, peritonsillar abscess (most often in adolescents), and cellulitis become more common. Viral pathogens are also common, such as infectious mononucleosis. Infection with atypical pathogens such as *Mycoplasma pneumoniae* should also be considered in children presenting with pneumonia. Skin infections secondary to community-acquired methicillin-resistant *Staphylococcus aureus* (CMRSA) are also becoming more common. CMRSA occurs in all age groups but has clustered among such children as wrestlers (associated with contaminated wrestling mats) and football players (infected equipment).[53,54] This diagnosis should be considered in all children who present with pyogenic skin infection and skin abscesses. Appropriate therapy includes incision and drainage of the abscess cavity and antibiotic therapy with trimethoprim-sulfamethoxazole for patients with large abscesses (>5 cm), with cellulitis, or with fever.[55]

There is also a second peak in incidence of meningococcal disease in adolescent children with an attack rate of 1.2 infections per 100,000 population. As opposed to infants, adolescents with meningococcal infection are more likely to present with meningococcemia (40 vs. 20%), shock at presentation (69 vs. 27%), and have a fatal outcome (22.5 vs. 4.6%). Meningococcal disease typically presents with one of three clinical syndromes: meningitis, bacteremia, or a combination of the two. College students residing in dormitories are at particular risk for infection with attack rates of 3.2/100,000 population.[56] The history in cases of meningococcal infection is often one of rapidly progressive fever, headache, and stiff neck. Shock, altered mental status or frank coma, petechiae or purpura, seizures, and myalgias are also seen. Some of the first signs of meningococcal infection include leg pain, cold hands and feet, or abnormal skin mottling.[57] Appropriate initial therapy for children suspected of having meningococcal infection is ceftriaxone, 100 mg/kg IV divided over 12 hours.

In January 2005, the Food and Drug Administration approved the meningococcal conjugate vaccine-4 (Menactra) for use in adolescents. This vaccine is a polysaccharide-protein conjugate

directed against the four serotypes that cause most cases of invasive meningococcal disease in humans. The American College of Immunization Practice recommends vaccination of adolescents at their 11- or 12-year-old well-child check up, and the American Academy of Pediatrics (AAP) has also advised that all college freshmen living in dormitories also be vaccinated. Use of the vaccine is associated with a 67% decrease in invasive disease and a 66% decrease in carriage rates.[58]

Febrile Seizures

Febrile seizures are a common cause of convulsions in children under the age of 5 years. They are defined as a seizure accompanied by fever without the presence of CNS infection. They typically occur in infants and children ages 6 months to 5 years. It is thought that the rapid rise or defervescence of a fever is the at-risk period, rather than the absolute height of the fever. Many parents worry about the subsequent risk of epilepsy after a febrile seizure, although studies have born out that the risk is only slightly increased. The risk of epilepsy in the general population is thought to be 0.5 to 1% while the risk in a patient who has had a febrile seizure is 1 to 2%. Although generally benign in course, febrile seizures can sometimes be the presenting complaint of infants and children with CNS infection such as meningitis. Febrile seizures are classified as either simple or complex. Simple febrile seizures are brief (<15 minutes), single, and nonfocal or generalized tonic-clonic. Complex febrile seizures are prolonged, recurrent (more than one within 24 hours), or typically focal.

Differentiating a benign febrile seizure from one that heralds CNS infection can be difficult. The AAP has published consensus guidelines for the evaluation and management of febrile seizures.[59] Laboratory and radiographic evaluation should be directed at finding the source of the fever, not driven by the seizure itself. The AAP suggests that a lumbar puncture be "strongly considered" after the first febrile seizure in infants younger than 12 months of age, in children who have received prior antibiotic therapy due to concern about missing CNS infection or in those who demonstrate symptoms or signs worrisome for meningitis. Routine referral for neuroimaging or electroencephalography is not indicated.[60] There is also no role for antiepileptic therapy after a single febrile seizure.

Parents should be warned that 33% of children who have a febrile seizure will have another one and that 75% of these will occur within a year. The younger a child is at the age of the first seizure, the more likely it is that a second one will occur. Children who seize at lower temperatures are also at higher risk for recurrence (35% at 38.5° C vs. 13% at 40° C).

Fever and Petechiae

The presence of a petechial rash in the setting of a febrile illness is classically associated with meningococcal infection. In fact, Baker and colleagues found that the incidence of meningococcal infection was 7 to 11% in patients hospitalized with fever and petechiae.[61] The rate of bacteremia of any cause was found to be much lower (1.9%) in an ED population. The differential diagnosis of fever and petechiae also includes disseminated intravascular coagulation, Rocky Mountain spotted fever, pneumococcal bacteremia, *Streptococcus pyogenes* infection, various viral infections, idiopathic thrombocytopenic purpura, Henoch-Schonlein purpura, and leukemia. Petechiae can also be caused mechanically from tourniquetting, wretching, or violent coughing. Petechiae due to vomiting or coughing is typically confined to the skin above the nipple line, but petechiae caused by serious bacterial illness can have any distribution.

Because of the risk of serious illness in children with fever and petechiae, blood should be obtained for CBC and blood culture. In cases associated with pharyngitis, testing for group A *Streptococcus* infection is indicated. Mandl and colleagues performed a prospective cohort study of 411 patients presenting to a pediatric ED with fever greater than 38.0° C and petechiae with the hopes of identifying clinical and laboratory criteria that would provide a means to screen for bacteremia.[62] They found that an abnormal WBC count (<5,000 WBCs/mm^3 and >15,000 WBCs/mm^3) or abnormal coagulation studies were predictive but not diagnostic of invasive bacteremia. Also, well-appearing children with normal WBC and coagulation studies were exceedingly unlikely to have invasive bacteremia. In their study, only two well-appearing children had bacteremia (*S. pneumoniae*), and this study was done in the pre-Prevnar era. Empirical antibiotic therapy (ceftriaxone, 50 mg/kg IV/IM) should be considered in all children presenting with fever and petechiae, even if an outpatient disposition is anticipated.

Kawasaki Disease (Mucocutaneous Lymph Node Syndrome)

Kawasaki disease is one of the most common vasculitides in childhood and should be considered in any infant or child with prolonged fever.[63] A more complete discussion on KD can be found in Chapter 169. Accurate diagnosis is important because the main complication of KD is the development of coronary artery aneurysms. Some patients will present with "incomplete KD," which occurs when not all diagnostic criteria are met. Despite the lack of classic findings, these children are still at risk for coronary complications. Laboratory abnormalities found in cases of KD include leukocytosis, thrombocytosis (platelet counts as high as 1,000,000/mm^3), and evidence of systemic inflammation with elevation in the erythrocyte sedimentation rate and C-reactive protein.

Children with suspected KD should be hospitalized and therapy with intravenous immune globulin (2 g/kg infused over 10–12 hours) and aspirin (initial dose 80–100 mg/kg daily divided every 6 hours).[64] Pediatric cardiology consultation for echocardiography is also indicated.

Toxic Shock Syndrome

Toxic shock syndrome refers to the toxin-mediated clinical syndrome that occurs with infection with *S. aureus*, although a similar illness is caused by infection with group A *Streptococcus*. The toxin implicated in TSS is an exotoxin termed TSS toxin 1. The syndrome is classically associated with tampon use by menstruating women, although cases also occur in males and prepubertal girls and also result from other sources of infection with *S. aureus*.[65–67]

Clinical manifestations of TSS include fever (>38.9° C), hypotension, diffuse erythroderma, as well as multisystem involvement. Patients may present with vomiting or diarrhea, severe myalgias, oropharyngeal hyperemia, or altered mental status. Laboratory abnormalities are common and include elevated creatine phosphokinase, elevated blood urea nitrogen or creatinine, transaminitis, and thrombocytopenia. The Centers for Disease Control and Prevention has developed a set of findings for case definition (Table 165-3).

Treatment of TSS involves aggressive fluid resuscitation as these patients typically have immense requirements and antistaphylococcal antibiotic therapy with clindamycin (25–40 mg/kg per day in three divided doses) as well as vancomycin (40 mg/kg per day IV in four divided doses).

Table 165-3 CDC Case Definition for Toxic Shock Syndrome

Fever: Temperature >38.9° C (102.0° F)
Hypotension: Systolic blood pressure 90 mm Hg for adults or less than fifth percentile by age for children <16 years of age; orthostatic drop in diastolic blood pressure by 15 mm Hg
Orthostatic syncope or dizziness
Diffuse erythroderma
Desquamation: 1–2 weeks after onset of illness, particularly involving palms and soles
Multisystem involvement (3 or more of the following organ systems)
Gastrointestinal: Vomiting or diarrhea at onset of illness
Muscular: Severe myalgia or CPK elevation >2 times the normal upper limit
Mucous membranes: Vaginal, oropharyngeal, or conjunctival hyperemia
Renal: BUN or serum creatinine >2 times the normal upper limit, or pyuria (>5 WBCs/hpf)
Hepatic: Bilirubin or transaminases >2 times the normal upper limit
Hematologic: Platelets <100,000/L
Central nervous system: Disorientation or alterations in consciousness without focal neurologic signs in the absence of fever and hypotension
Negative results on the following tests, if obtained
Blood, throat, or cerebrospinal fluid cultures for another pathogen (blood cultures may be positive for *Staphylococcus aureus*)
Serologic tests for Rocky Mountain spotted fever, leptospirosis, or measles

*Criteria for a probable case include a patient with fever >38.9° C, hypotension, diffuse erythroderma, desquamation (unless the patient dies before desquamation can occur), and involvement of at least three organ systems. A probable case is a patient who is missing one of the characteristics of the confirmed case definition.

BUN, blood urea nitrogen; CDC, Centers for Disease Control and Prevention; CPK, creatine phosphokinase; WBC, white blood cell.

Fever and Underlying Chronic Medical Illness

Oncology Patients

Children with cancer, particularly those undergoing treatment with cytotoxic chemotherapy, are at particular risk for sepsis and bacterial infection.[68] These life-threatening infections are most common during periods of profound neutropenia. Neutropenia is defined as an absolute neutrophil count of less than 500/mL or an absolute neutrophil count of less than 1000/mL and falling. Children with cancer also frequently have indwelling catheters, predisposing them to surgical line infections.

Causative organisms include both gram-positive and gram-negative bacteria. Staphylococci and streptococci as well as *Pseudomonas* are frequent pathogens. Often, patients with focal infection may not present with classic signs due to their leukopenia. Focal infections specific to cancer patients include stomatitis and typhlitis, which is a necrotizing enterocolitis of the terminal ileum and cecum.

Children presenting with fever and possible neutropenia require prompt evaluation. Blood should be obtained for a CBC and manual differential as well as culture. If a central line infection is suspected, a separate culture from the line should be obtained. Once appropriate laboratory studies are obtained, empirical antibiotic therapy should be initiated without waiting for the laboratory results. Appropriate monotherapy antibiotic regimens include cefipime, 50 mg/kg IV every 8 hours, or ceftazidime, 50 mg/kg IV every 8 hours. Vancomycin, 40 to 60 mg/kg every 6 to 8 hours, should be added for antistaphylococcal coverage in children with suspected central line infections or skin and soft tissue infections. Children with fever and neutropenia are rarely if ever treated as outpatients; if so, ceftriaxone, 50 mg/kg IV every 24 hours, is given and close follow-up is essential.

Acquired Immunodeficiency Patients

Children with the acquired immunodeficiency syndrome (AIDS) are at risk for bacterial infection due to a whole host of different organisms, some common, some uncommon. Infections specific to AIDS include cryptococcosis, infection with *Mycobacterium tuberculosis*, *Mycobacterium avium–intracellulare*, and *Pneumocystis jiroveci (carinii)*. Viral infections such as cytomegalovirus and Epstein-Barr virus are also common.

Laboratory evaluation should be directed by the history and physical examination, and early initiation of broad-spectrum antibiotic therapy is warranted.

Sickle Cell Disease

Febrile children with sickle cell disease are at particular risk for overwhelming infection.[69] In fact, infection is the most common cause of sickle cell–related death, occurring in up to 40% of patients. Recurrent episodes of splenic infarction leads to functional asplenia early on in life. Thus, these patients are at particular risk for infection with encapsulated organisms including *S. pneumoniae* and *H. influenzae*. Because of this risk of bacterial disease, it is recommended that all children with sickle cell disease should be completely immunized. Prophylaxis with penicillin is recommended in children under the age of 5 years, after which it can be safely discontinued in children who have not had a prior severe pneumococcal infection or surgical splenectomy.[70] The dose of penicillin is 125 mg orally (PO) twice daily until 3 years of age (at about 14 kg) and 250 mg PO twice daily after 3 years of age.[71]

High-risk criteria for bacterial infection include toxic appearance, temperature greater than 40° C, an abnormal WBC count (<5,000 or >30,000 WBCs/mm^3) and noncompliance with penicillin prophylaxis. Sickle cell patients are at particular risk for *Salmonella* osteomyelitis. All patients presenting with fever and sickle cell disease should have a CBC, reticulocyte count, and blood culture drawn. A reticulocyte count is important as many infections (e.g., parvovirus B19) can induce life-threatening aplastic crisis. It is important to remember that infection also predisposes children with sickle cell disease to acute chest syndrome.[72] Common causes of infection include *Chlamydia pneumonia*, *Mycoplasma*, RSV, *S. aureus*, and *S. pneumoniae*. Further laboratory and radiographic evaluation should be directed based on the presenting history and physical.

High-risk patients should be admitted for further evaluation and antibiotic therapy. Low-risk patients may be treated with a single dose of intravenous/intramuscular antibiotics, typically ceftriaxone, 50 mg/kg, and discharged to close outpatient follow-up. All patients should be reevaluated within 24 hours or sooner if the clinical condition deteriorates.

Osteomyelitis typically presents with fever and bone pain. As patients with sickle cell disease may have frequent bone pain due to vaso-occlusive crisis, the diagnosis often can be difficult. All patients should have a CBC with differential, erythrocyte sedimentation rate, and blood culture drawn, and a radionuclide bone scan may help to localize the infection. If *Salmonella* infection is suspected, a stool sample should be sent for culture.

Congenital Heart Disease

Children with congenital heart disease are at high risk for cardiovascular complications in the setting of febrile illness. Often, relatively minor viral illness can produce significant

Table 165-4 Modified Duke Criteria for the Diagnosis of Infective Endocarditis (IE)

Major Criteria

Positive Blood Cultures for IE

Typical microorganism for IE from two separate blood cultures
Viridians streptococci
Streptococcus bovis, including nutritional variant strains
HACEK group: *Haemophilus* species, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella* species, and *Kingella kingae*
Staphylococcus aureus
Community-acquired enterococci, in the absence of a primary focus; or
  Persistently positive blood culture, defined as recovery of a microorganism consistent with IE from blood cultures drawn more than 12 hours apart; or
  All of three or a majority of four or more separate blood cultures, with first and last drawn at least 1 hour apart
Single positive blood culture for *Coxiella burnetii* or antiphase I immunoglobulin G antibody titer >1:800*

Evidence of Endocardial Involvement

Positive echocardiogram for IE
TEE recommended in patients with prosthetic valves, rated at least "possible IE" by clinical criteria, or complicated IE (paravalvular abscess); TTE as first test in other patients*

Definition of Positive Echocardiogram

Oscillating intracardiac mass, on valve or supporting structures, in the path of regurgitant jets, or on implanted material, in the absence of an alternative anatomic explanation; or
Abscess; or
New partial dehiscence of prosthetic valve
New valvular regurgitation
Increase in or change in preexisting murmur not sufficient

Minor Criteria

Predisposition: Predisposing heart condition or intravenous drug use
Fever: 38.0° C (100.4° F)
Vascular phenomena: Major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway's lesions
Immunologic phenomena: Glomerulonephritis, Osler's nodes, Roth's spots, rheumatoid factor
Microbiologic evidence: Positive blood culture but not meeting major criterion as noted previously (excluding single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis); or
Serologic evidence of active infection with organism consistent with IE

*Echocardiographic minor criteria eliminated.
TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

changes in cardiac function, or make it difficult for children to be compliant with their oral medications. Children with congenital heart disease are also at risk for infective endocarditis. Infective endocarditis is heralded by fever and possibly a changing or worsening cardiac murmur. The modified Duke criteria for the diagnosis of endocarditis are presented in Table 165-4.[73]

Endocarditis is typically caused by *S. aureus*, viridians streptococci, *Streptococcus bovis*, enterococci, or infection with organisms from the HACEK group (*Haemophilus* species, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella* species, and *Kingella kingae S. aureus*). Children with suspected endocarditis should have blood cultures drawn and be admitted to the hospital for treatment and echocardiography. The American Heart Association recommends that initial antibiotic therapy be with ceftriaxone, 100 mg/kg IV or IM every 24 hours, or vancomycin, 40 mg/kg IV every 24 hours. Therapy is typically continued at least 4 weeks. Ceftriaxone can be combined with gentamicin, 3 mg/kg IV divided every 8 hours, if a shorter treatment duration (2 weeks) is desired.[74]

Ventriculoperitoneal Shunts

Children presenting with fever in the setting of ventriculoperitoneal (VP) shunts are at risk for shunt infection. If shunt infection is suspected, neurosurgical consultation should be obtained and a sample of CSF obtained. This is typically accomplished by sterile aspiration of fluid from the shunt reservoir. *S. aureus* and *S. epidermis* are the usual causative organisms. Because altered mental status may also accompany shunt infection, a computed tomography scan should be obtained to assess ventricular size. Children with suspected shunt infection are typically managed as inpatients and antibiotics should begin as soon as possible.

KEY CONCEPTS

- Fever is the most common complaint among pediatric patients presenting to the ED, although rates of bacterial illness are lower since the advent of universal vaccination for HIB and *S. pneumoniae*.
- Infants less than 3 months of age are at higher risk for bacterial illness with fever due to their immature immune systems and incomplete vaccination status, making aggressive workup of these children important.
- The most common cause of serious bacterial illness in children continues to be UTIs, and the only reliable method to obtain urine in a non-toilet-trained infant is through bladder catheterization or suprapubic aspiration.
- RSV is a common viral cause for fever and respiratory distress in infants, although the presence of RSV does not lower the risk of concomitant serious bacterial illness in children less than 28 days of age.
- Children presenting with fever and petechiae are at risk for infection with meningococcus; blood should be obtained for CBC and culture, and most children should be treated with empirical parenteral antibiotics.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 166

Pediatric Respiratory Emergencies: Upper Airway Obstruction and Infections

Mariann Manno

PERSPECTIVE

Respiratory distress from upper airway obstruction is an unusual but potentially catastrophic emergency in young children. It may be caused by a number of different processes, alone or in combination, including an acute infectious process, a congenital anomaly, or a foreign body in the airway or esophagus. A working knowledge of the anomalies and diseases of the upper airway is of primary importance in pediatric emergency medicine. Classification of airway pathology can be based on the anatomic location, the patient's age, the urgency of the symptoms, and whether it is a congenital or acquired lesion or an infectious or noninfectious process. The starting point for any classification is an appreciation of the unique aspects of pediatric airway anatomy.

DISTINGUISHING PRINCIPLES OF DISEASE

A number of differences between the adult and pediatric airway are important in airway management (Fig. 166-1). An infant's tongue is disproportionately large in relation to the mouth and protrudes back into the posterior of the pharynx. The tongue is a formidable obstacle when performing bag-mask ventilation and visualizing the airway. In the setting of hypotonia, posterior displacement of the tongue is the most common cause of functional upper airway obstruction. The infant larynx is more anterior and caudad, or higher in the neck relative to the cervical spine (at C3-4), than in an adult (at C4-5). The anterior aspect of the vocal cords is tipped inferiorly. The narrowest site of the infant airway is at the cricoid ring rather than the cords as in an adult. A child's epiglottis is relatively larger, longer, and omega shaped. It extends vertically beyond the opening of the cords, thus making a complete view of the airway difficult. The caliber of all airway structures is small; newborn tracheal length is 57 mm and laryngeal diameter is 4 mm. All cartilaginous supporting structures are soft, pliable, and prone to collapse. Finally, a prominent occiput allows passive flexion of the head and neck on the cervical spine. In aggregate, these anatomic features of the pediatric airway predispose infants and young children to functional upper airway obstruction and make airway intervention technically challenging.

The type and size of equipment required for management of the pediatric airway are derived from the anatomy just discussed. A face mask should be sized so that the top and bottom rims fit on the bridge of the nose (below the eye) and in the cleft of the chin. A straight (Miller) blade is generally used for endotracheal intubation in infants and young children because the tip of the straight blade lifts the epiglottis up and out of the line of vision of the airway. Endotracheal tube size is a function of the patient's size. For children older than 1 year, endotracheal tube size (internal diameter in millimeters) can be estimated by the formula (age in years/4) + 4; for uncuffed tubes, one should use one half size smaller except for 3.0-mm tubes. Alternatively, endotracheal tube size can be estimated by using a length-based measuring system such as the Broselow tape. Recent evidence suggests that cuffed endotracheal tubes may be used safely in children of all ages. Cuffed endotracheal tubes allow for the delivery of high pressures during ventilation without the air leak associated with uncuffed tubes and without increased complications such as subglottic stenosis.[1,2]

The spectrum of clinical findings in children who arrive at the emergency department with symptoms related to upper airway pathology is broad and includes the following general categories:

- Acute infections of the upper airway range in severity of presentation from the child with mild distress and self-limited signs and symptoms, to the child with abrupt onset of rapidly progressive airway obstruction.
- Undiagnosed congenital anomalies of the airway and surrounding structures may be manifested as chronic or progressive stridor or difficulty feeding. An infant with a congenital airway anomaly in whom an acute airway infection develops is at higher risk for decompensation and respiratory failure.
- Upper airway obstruction from a foreign body in the airway or esophagus can cause partial or complete airway obstruction and may require advanced airway management skills.

STRIDOR

Stridor is the classic sound associated with upper airway obstruction.[3–5] It is derived from the Latin *stridulus*, meaning harsh or grating. Stridor is caused by partial airway obstruction and the resultant turbulent airflow through a portion of the airway from the nose to the trachea. It is not a diagnosis in itself but an important sign that must be thoroughly investigated. Stridor should be timed in the respiratory cycle (inspiratory, expiratory, biphasic) and assessed in terms of quality (coarse, high pitched).

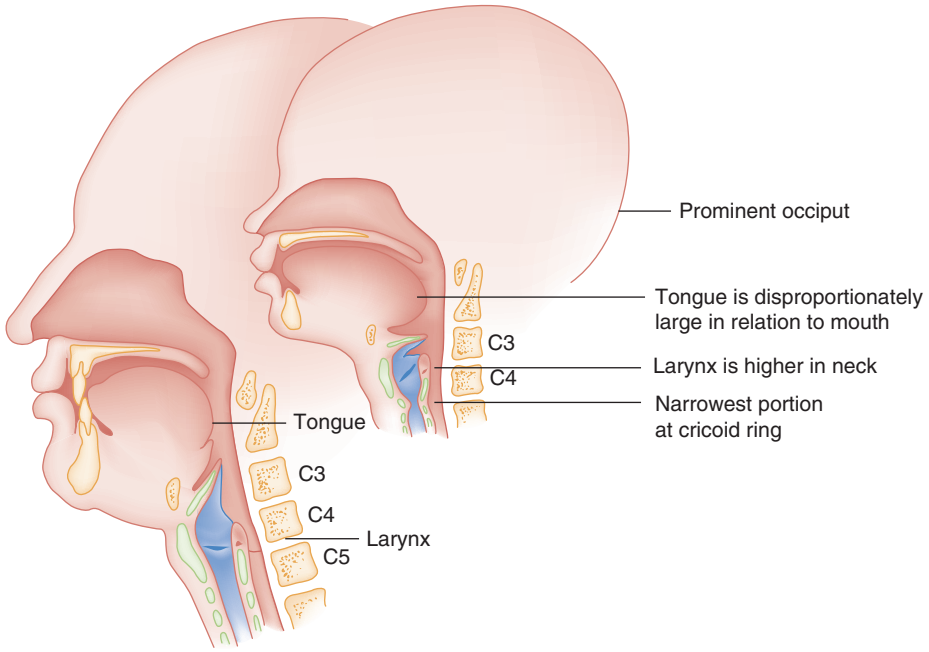
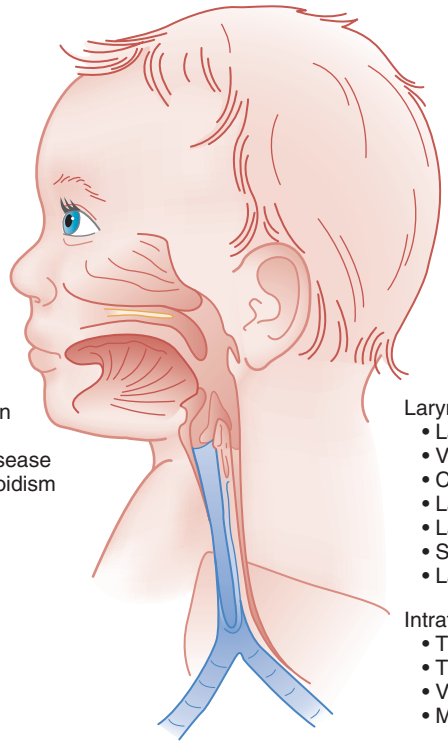


Figure 166-1. Comparison of adult and pediatric airways. (From Finucane BT: Principles of Airway Management. Philadelphia, FA Davis, 1988.)



Supraglottic
- Craniofacial
  - Pierre Robin
  - Treacher Collins
  - Hallermann-Streiff
- Macroglossia
  - Beckwith-Wiedemann
  - Down syndrome
  - Glycogen storage disease
  - Congenital hypothyroidism
- Choanal atresia
- Encephalocele
- Thyroglossal duct cyst
- Lingual thyroid

Laryngeal
- Laryngomalacia
- Vocal cord paralysis
- Congenital subglottic stenosis
- Laryngeal web
- Laryngeal cyst
- Subglottic hemangioma
- Laryngotracheoesophageal cleft

Intrathoracic
- Tracheomalacia
- Tracheal stenosis
- Vascular rings/slings
- Mediastinal masses

Figure 166-2. Regions and associated pathology of the pediatric upper airway. (From Simon NP, Simon N: Evaluation and management of stridor in the newborn. Clin Pediatr [Phila] 30:211, 1991.)

The airway can be artificially divided into four regions: the nose and pharynx, the supraglottic structures, the glottis and immediate subglottic area, and the intrathoracic trachea (Fig. 166-2). Stridor has different characteristics, depending on its exact origin in the airway (Table 166-1).

Stridor from the nose and pharynx has a sonorous, gurgling, and coarse quality. The voice may have a muffled or "hot potato" quality. An example of when this occurs is in the presence of a peritonsillar abscess. High-pitched, inspiratory stridor comes from the supraglottic and immediate subglottic trachea. Inspiratory stridor is heard with pathology in this region because the extrathoracic airway narrows with inspiration as a result of atmospheric pressure outside the airway being slightly higher than that inside the airway. The voice may sound hoarse or weak. Examples include viral croup and laryngomalacia.

Biphasic stridor is heard with inspiration and expiration and usually suggests a fixed lesion that does not change in size at the glottis or cricoid ring with respiration. Examples of conditions resulting in biphasic stridor are a laryngeal web and vocal cord paralysis. Stridor from the lower part of the trachea is usually expiratory. Bacterial tracheitis and a foreign body are examples.

Table 166-1 Causes of Stridor: Anatomic Location, Sound, and Etiology

FEATURES	SUPRAGLOTTIC	GLOTTIC	SUBGLOTTIC TRACHEA
Sound	Sonorous Gurgling Coarse Expiratory stridor	Biphasic stridor	High-pitched stridor Inspiratory stridor
Structures	Nose Pharynx Epiglottis	Larynx Vocal cords	Subglottic trachea
Congenital	Micrognathia Pierre Robin syndrome Treacher Collins syndrome Macroglossia Down syndrome Storage diseases Choanal atresia Lingual thyroid Thyroglossal cyst	Laryngomalacia Vocal cord paralysis Laryngeal web Laryngocele	Subglottic stenosis Tracheomalacia Tracheal stenosis Vascular ring Hemangioma cyst
Acquired	Adenopathy Tonsillar hypertrophy Foreign body Pharyngeal abscess Epiglottitis	Papillomas Foreign body	Croup Bacterial tracheitis Subglottic stenosis Foreign body

OVERVIEW OF THE EVALUATION AND MANAGEMENT OF A CHILD WITH AN UPPER AIRWAY OBSTRUCTION

Evaluation of a child with signs of airway obstruction begins with careful observation of the child at rest (work of breathing, respiratory rate, alertness, color) and during activity (crying, feeding). In most cases, observation and a carefully obtained history will provide most clues to the correct diagnosis. Important items to be elucidated in the history include the following:

- Onset and duration (acute, chronic)
- Associated symptoms (respiratory distress, fever, toxicity, drooling, cyanosis)
- Progression with age (number of bouts/severity of "croup" with increasing age)
- Exacerbations (supine vs. prone position, upper respiratory infection [URI], crying)
- Feeding pattern (dysphagia, feeding abnormalities)
- Airway procedures (intubation in the neonatal period)
- Choking episode (foreign body aspiration)
- Baseline noises, quality of cry and voice (location of obstructive lesion)

The initial physical examination includes assessment of the severity of respiratory distress (respiratory rate, retractions, flaring, heart rate) and the presence of respiratory failure (extreme distress, hypoventilation, altered mental status, dusky skin color, cyanosis, hypotonia). The character and timing of stridor, as well as the symmetry and quality of breath sounds, are important observations.

Definitive airway management always takes precedence over laboratory and radiographic tests in a patient with an acute airway emergency. In a stable patient with an uncertain diagnosis, an individualized diagnostic evaluation is important.

In the stable patient, radiographs of the soft tissues of the neck may be helpful and should include both lateral and anteroposterior views. These views are helpful to assess adenoid and tonsillar size, the contour of the epiglottis, the thickness of the retropharyngeal soft tissue space, the vallecula, the aryepiglottic folds, and the tracheal air column (Fig. 166-3).[6,7] Optimally, the child's head should be positioned in extension and the film taken during inspiration. Views of the chest may be helpful to assess heart size, location of the aortic arch, pulmonary pathology, and the trachea and bronchi.

Additional studies may be indicated in specific settings. Bedside fiberoptic nasopharyngoscopy can be performed without anesthesia, allows visualization and movement of supraglottic structures and vocal cords, and may permit fiberoptic-assisted intubation via the nasopharyngoscope. An esophagogram may help define lesions compressing the airway and trachea. Computed tomography (CT), magnetic resonance imaging (MRI), and fiberoptic and rigid bronchoscopy should be considered on an individual basis.

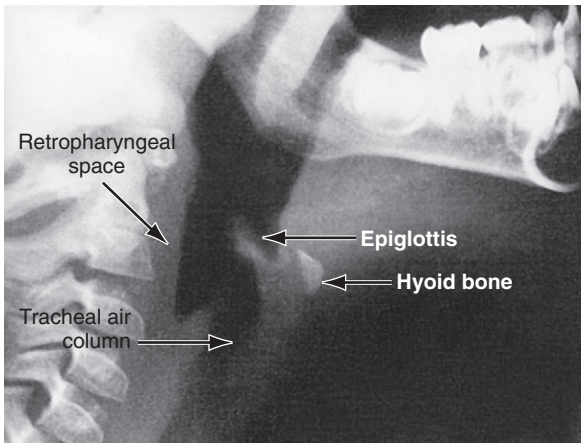


Figure 166-3. Normal appearance of upper airway structures on a lateral neck radiographic study. Note the hyoid bone, epiglottis, retropharyngeal space, and tracheal air column.

SPECIFIC DISORDERS

Supraglottic Airway Diseases

Perspective

The supraglottic portion of the airway includes the nose, pharynx, epiglottis, and surrounding structures. Pathology of the nose and pharynx is commonly associated with noisy, congested breathing and respiratory distress. Congenital lesions involving these structures may cause mild symptoms at baseline but dramatic distress when the patient is stressed with a superimposed infectious process. Among the congenital lesions with which the emergency physician should be familiar are choanal atresia, macroglossia, micrognathia, thyroglossal duct cyst, and lingular thyroid. Important acquired causes include nasal foreign body, nasal polyps, hypertrophic tonsils and adenoids, epiglottitis, retropharyngeal abscess, peritonsillar abscess, pharyngitis, mononucleosis, and upper airway foreign body. The most common ones are discussed in the following sections.

Congenital Lesions

Choanal atresia, the most common congenital anomaly of the nose, is caused by persistence of the bucconasal membrane or a bony septum in the posterior naris. Infants are "preferential nose breathers" because they breathe through their nose when their mouth is closed at rest and in order to suck and swallow. This breathing preference is a result of the posterior aspect of the soft palate extending downward and contacting the tip of the epiglottis. Bilateral choanal atresia is a life-threatening emergency that is identified shortly after birth. Infants with bilateral choanal atresia become acutely distressed and cyanotic at birth and are managed with an oral airway that opens the mouth to allow a passage for breathing. Surgical correction of the obstructing membrane is required. Unilateral choanal atresia may go undetected in the nursery and become apparent only when the normal, patent nares are obstructed by swelling or secretions, most frequently from a URI.

Macroglossia is associated with a number of conditions, including Down syndrome, glycogen storage disease, and congenital hypothyroidism. The tongue is abnormally large and protrudes posteriorly into the hypopharynx. The increased secretions and swelling associated with a URI exacerbate the underlying obstruction, and stridor or labored breath sounds are produced.

Micrognathia is associated with syndromes such as Pierre Robin and Treacher Collins. A small mandible posteriorly displaces the normally sized tongue. Signs of obstruction often worsen when the patient is supine.

Retropharyngeal Abscess

Perspective. A retropharyngeal abscess is a potentially life-threatening airway emergency resulting from infection of the retropharyngeal soft tissue space. The retropharyngeal space is a potential space between the posterior pharyngeal wall and the prevertebral fascia that extends from the base of the skull to the level of T2. It is rich in lymph tissue that drains the nose, pharynx, sinuses, and ears. An abscess may result from direct trauma, suppuration of lymph nodes, or hematogenous spread. Most cases are seen in children younger than 3 years. These infections are commonly polymicrobial, with *Streptococcus* and anaerobes the most commonly isolated organisms.[8] Several recent case reports highlight the emerging role of methicillin-resistant *Staphylococcus aureus* in these infections.[9]

Clinical Features. The variable manifestations of a retropharyngeal abscess often make it a challenging diagnosis in younger children. Common signs and symptoms include fever, sore throat, neck stiffness/nuchal rigidity, torticollis, trismus, neck swelling, drooling, stridor, and a muffled voice. In a prospective study of 17 patients with retropharyngeal abscess, stridor and airway obstruction were observed in half (56%) of the patients.[10] This common finding of acute airway obstruction in children is a function of the high position of the larynx in the neck. Such anatomy places the airway proximate to and easily compressed by the bulging retropharyngeal mass. In patients with airway compression, the clinical appearance may resemble epiglottitis. With less obvious signs of airway obstruction, patients can exhibit a mixture of symptoms (fever, neck stiffness, generalized toxicity) suggesting meningitis or sepsis. Complications of a retropharyngeal abscess can be serious: generalized sepsis, aspiration pneumonia, mediastinitis, and empyema.

Diagnostic Strategies. Careful evaluation of airway patency takes precedence in managing a child with a presumed retropharyngeal abscess.[11–19] Examination of the pharynx may reveal bulging of the posterior pharyngeal wall. A soft tissue lateral view of the neck may be helpful to establish the diagnosis; in the normal patient the width of the retropharyngeal space should not exceed the diameter of the adjacent vertebral body (Fig. 166-4). An air-fluid level is more commonly seen with perforations and anaerobic infections. Redundant soft tissue of the retropharyngeal space complicates interpretation of lateral neck films in young infants with a retropharyngeal abscess. Artifactual widening of a normal retropharyngeal space is commonly seen when the radiograph is taken with the head and neck in flexion or during exhalation (or both). CT may be beneficial in selected cases.

Management. The size of the abscess, the degree of airway obstruction, and the overall toxicity of the patient dictate management. The need for intubation or surgical drainage is determined on an individual basis, and these patients generally benefit from involvement of an ear, nose, and throat specialist.

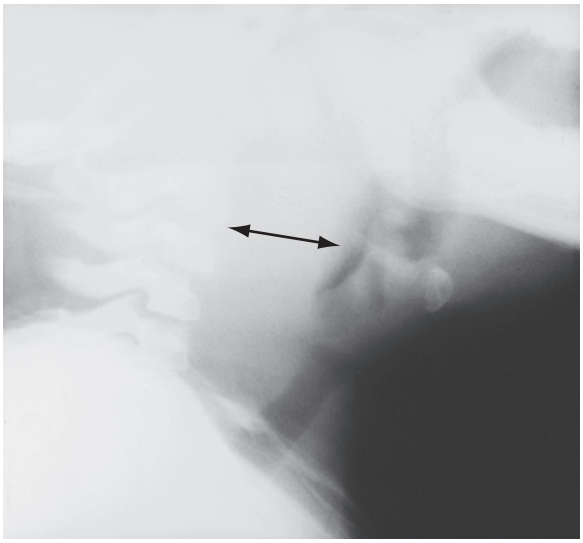


Figure 166-4. Retropharyngeal abscess. Note the widened retropharyngeal soft tissue space.

Perspective. Although still among the most feared pediatric emergencies, the incidence of acute epiglottitis has declined markedly since widespread administration of *Haemophilus influenzae* type b vaccine.[20–22] First licensed in 1985 for children 24 months old, the vaccine became available for immunization of infants 2 months of age in 1990. A study that compared epiglottitis before and after 1990 revealed a drop in the annual incidence of epiglottitis from 10.9 to 1.8 per 10,000 admissions.[23]

Principles of Disease. Epiglottitis is an invasive bacterial disease that causes inflammation and edema of the epiglottis, aryepiglottic folds, and surrounding supraglottic tissues. As these structures become inflamed and distended, they protrude downward and over the glottic opening. Historically it was caused by *H. influenzae* type b in children 3 to 7 years of age and occurred year-round. This traditional profile has changed.[24–26] In a survey of patients with epiglottitis since 1990, the average patient is older (80 vs. 35 months) with varying microbiology. *H. influenzae* type b is seen in a small minority of patients, and organisms such as group A beta-hemolytic *Streptococcus*, *S. aureus*, and *Streptococcus pneumoniae*[23] are more common. Noninfectious causes are rare and include thermal injury from swallowing hot liquids.[27,28]

Clinical Features. Epiglottitis is classically acute in onset. It is marked by high fever, intense sore throat, toxicity, and rapid progression. In one study, 85% of children with epiglottitis were symptomatic for less than 24 hours.[29] Children with epiglottitis appear anxious and maintain themselves in a "sniffing" or "tripod" position with the jaw jutting forward and the neck extended to maximize airway patency. As symptoms worsen, cough and phonation are usually absent. Drooling is prominent because of an inability to swallow. A study of children 2 to 18 years of age revealed that fever, difficulty breathing, irritability, change in voice or cry, stridor, and retractions were common initial symptoms that occurred in more than 80% of patients.[29] Singer and colleagues showed that in children younger than 24 months, toxicity, altered mental status, dyspnea, stridor, retractions, and fever were common initial symptoms.[30] Losek and coworkers in a study of 236 patients reported that 7 patients (3%) died.[29] The correct diagnosis of epiglottitis was not made in 11 of 58 (19%) children younger than 2 years and in 49 of 178 (28%) children between 2 and 18 years old. In the older patient (e.g., in adolescents), severe odynophagia or dysphagia in the absence of signs of pharyngeal swelling, erythemia, or exudates should raise suspicion for this diagnosis. The older patient is less likely to show dramatic signs of upper airway obstruction as compared with the younger child, because the diameter of the airway is relatively larger and thus takes a greater degree of swelling to produce symptoms. Incorrect diagnoses in patients who died included croup, summer virus, and pharyngitis. Croup was the most commonly assigned misdiagnosis and more often made in the setting of very young children or those in whom drooling or difficulty swallowing were not prominent.[29] A majority of patients with *H. influenzae* epiglottitis have bacteremia (50–75%).[31]

Diagnostic Strategies. Direct examination or manipulation of the pharynx should be avoided in cases in which epiglottitis is strongly suspected. Stimulation of the posterior of the pharynx with subsequent contraction of the pharyngeal muscles may increase airway obstruction. In adult patients this is less commonly a concern because of the relatively larger upper airway. A lateral neck radiograph can be helpful to confirm the diagnosis and should be evaluated for an enlarged epiglottis ("thumbprint sign"; Fig. 166-5), thickened aryepiglottic folds, lack of air in the vallecula, and a dilated hypopharynx. Careful observation of a child with suspected epiglottitis is essential. Laboratory tests, intravenous fluids and antibiotics, blood and epiglottis cultures, and sedation are all important considerations once the airway has been secured.

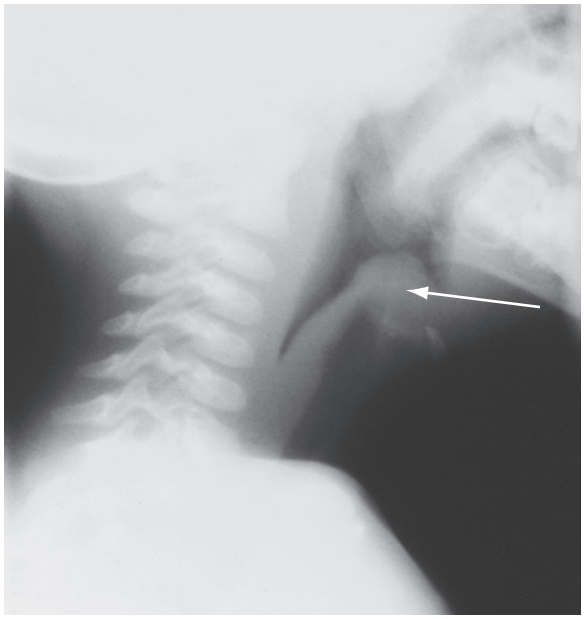


Figure 166-5. Epiglottitis. Note the "thumbprint sign" of the epiglottis and thickened aryepiglottic folds.

Management. The clinical features of classic epiglottitis are usually sufficiently characteristic that diagnostic tests are not necessary and should be avoided. The importance of securing the airway takes precedence over diagnostic evaluation. A "stable" patient who is maintaining a patent airway and adequate oxygenation should not be moved or repositioned for examination, laboratory tests, or radiography. Such patients should be carefully transported to a setting where definitive airway management can be achieved in a controlled fashion. If diagnostic studies are needed, constant and close observation is vital.

Careful decision-making is essential when a child with epiglottitis, or suspected epiglottitis, requires transport. A survey of pediatric intensive care and emergency physicians reported that half recommended intubation before interhospital transport in all cases. The remainder individualized the recommendation for pretransport intubation based in part on the referring physician's perceived ability to intubate the child.[32] Successful observation without intubation during transport has been reported.[33,34] However, this observation occurred in the selective setting of a pediatric intensive care unit (ICU) where several physicians with advanced training in anesthesia and pediatric critical care were on site at all times. Clearly, this is not the environment of most emergency departments and critical care units, and expeditious controlled intubation remains optimal management.

Unstable patients with respiratory failure require assisted ventilation. Bag-valve-mask ventilation should be attempted first and, if successful, continued until intubation can be performed by the emergency physician or anesthesiologist. If neither bag-valve-mask ventilation nor intubation is successful, more aggressive techniques such as needle cricothyroidotomy or tracheostomy may be indicated. Regardless of the approach to securing the airway, it is prudent for the emergency physician to as rapidly as possible consult other experts in airway management such as anesthesia (fiberoptic

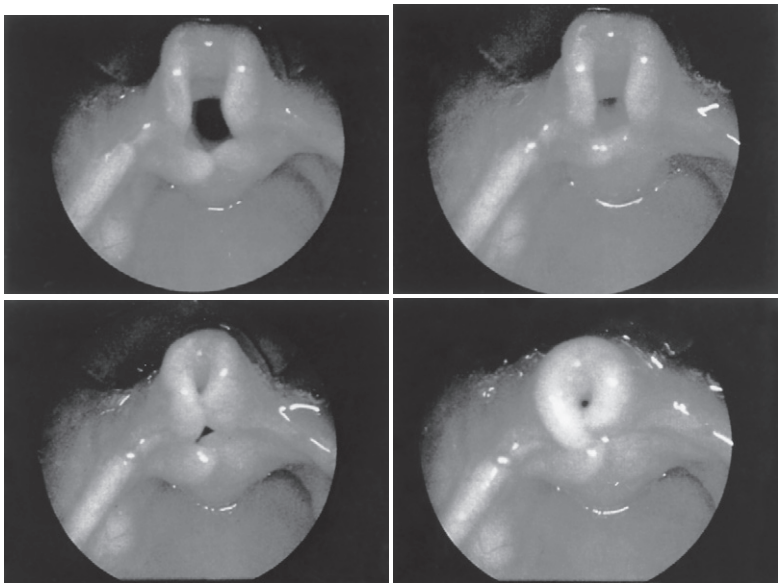


Figure 166-6. Laryngomalacia. Note the progressive obstruction with inspiration as the epiglottis and surrounding structures collapse into the glottic opening.

intubation) and head and neck or general surgery (surgical approaches) so that a plan of approach can be made and morbidity reduced.

Diseases of the Larynx

The larynx and vocal cords occupy an important region in the airway that is often associated with airway pathology causing obstruction. Many of these obstructing conditions are congenital lesions, including laryngomalacia, a laryngeal web, and vocal cord paralysis. Acquired lesions include laryngeal papillomas.

Congenital Lesions

Laryngomalacia, the most common cause of chronic stridor in infants,[35,36] is a result of incomplete development of the supporting cartilage of the larynx. With inspiration, the long, floppy epiglottis, arytenoids, and aryepiglottic folds are drawn into the larynx and create a partial obstruction (Fig. 166-6). Baseline inspiratory stridor begins shortly after birth and worsens with supine positioning and increased respiratory effort (crying, URI). Laryngomalacia is rarely associated with significant respiratory distress, feeding difficulties, or failure to thrive. Most patients experience complete resolution of symptoms by 2 years of age. Fiberoptic bronchoscopy has been used to confirm the diagnosis and exclude coexisting anomalies such as vocal cord paralysis and subglottic stenosis, which are found in approximately 20% of patients.

Vocal cord paralysis is the second most common cause of chronic stridor in infants. Bilateral vocal cord paralysis results in severe respiratory distress and stridor and is usually associated with serious central nervous system abnormalities such as Arnold-Chiari malformation. Unilateral vocal cord paralysis is most commonly left-sided and related to traction on the left recurrent laryngeal nerve at birth or compression from mediastinal structures. Infants with unilateral vocal cord paralysis have a hoarse, weak cry. Stridor often worsens with distress and improves with positioning of the affected side down.

A *laryngeal web* results from failure of complete canalization of the airway.[37] Most webs lie between the cords and appear as a partial anterior fusion (Fig. 166-7). The spectrum of symptoms reflects the size of the web. Small webs may cause a hoarse, weak cry and mild stridor. Larger, more complete webs are associated with aphonia and severe distress.

Figure 166-7. Large laryngeal web.

Laryngeal Papillomas

Laryngeal papillomas arise from the laryngeal epithelium and may result from perinatal or postnatal exposure to human papillomavirus. When acquired in the prenatal period, hoarseness, abnormal cry, and inspiratory stridor commonly occur by 3 to 4 years of age. Symptoms can progress to severe respiratory distress as the lesions enlarge and obstruct the larynx.

Subglottic Tracheal Diseases

The subglottic trachea is the origin of the high-pitched inspiratory sound commonly associated with upper airway obstruction. The subglottic space is the narrowest part of the airway in children younger than 8 years and is completely surrounded by the cricoid ring. Such anatomy predisposes this part of the airway to obstruction. Subglottic narrowing or stenosis can result from a congenital anomaly, inflammation from infection, and trauma associated with prolonged intubation.

Congenital laryngotracheal ("subglottic") stenosis is a result of a congenital defect in canalization of the subglottic trachea. Deformity of the cricoid ring is usually seen. Infants with severe stenosis have stridor at birth. Milder lesions may be asymptomatic until additional obstruction from infection or inflammation occurs. Subglottic stenosis is also an acquired condition that occurs after prolonged intubation or blunt trauma to the neck.

A *subglottic hemangioma* is a less common cause of stridor and subglottic airway obstruction in infants. The infant is usually asymptomatic at birth, but stridor (which may be biphasic) and cough develop within the first few weeks to months of life. Symptoms generally peak at 6 months as a result of rapid growth of the infant and the hemangioma during the first months of life. Respiratory symptoms worsen with crying and agitation. Cutaneous hemangiomas are seen in approximately half of cases. Hemangiomas of the airway may be seen on plain film as an asymmetrical lesion along the tracheal air column.

Viral Croup

Principles of Disease. Croup (laryngotracheobronchitis) is the most common cause of upper airway distress and obstruction in childhood. It occurs most commonly in late fall, early winter, and spring, with a peak incidence at 2 years (range, 6 months to 6 years) of age. Rarely, viral croup is seen in older, healthy children. Parainfluenza virus type 1 accounts for about half of cases, with parainfluenza virus types 2 and 3, respiratory syncytial virus, influenza A and B virus, and rhinovirus responsible for the remainder.[38] Croup is caused by inflammation, exudate, and edema of the loosely adherent mucosal and submucosal tissues of the subglottic space. The inflamed mucosa expands into the airway lumen because the cricoid forms a complete cartilaginous (nonexpanding) ring in this part of the trachea.

The true incidence of croup is uncertain. Most children with croup have an uncomplicated course, and many cases are managed without medical intervention. Only a small percentage of those who receive urgent care require hospitalization. Croup is recurrent in a small number of patients. A subset of children with croup have involvement of the lower airway and exhibit bronchoconstriction, lower airway edema, and atelectasis.

Clinical Features. Croup can generally be diagnosed clinically. Children with typical croup have a constellation of symptoms, including a barky cough, hoarse voice, and high-pitched, inspiratory stridor. These findings usually follow a prodrome of mild fever and URI symptoms lasting several days.

Scoring systems have been developed for assessment of croup and include an evaluation of worsening stridor, retractions, cyanosis, heart rate, and respiratory rate. Although a formal croup score is often not assigned in many clinical settings, the determination of mild, moderate, or severe croup should be based on careful evaluation of these five signs, as well as mental status and air movement. Mild croup is characterized by an intermittent barky cough, stridor with agitation but not at rest, mild tachypnea, and tachycardia. A child with mild croup is minimally distressed and well hydrated and has normal mental status. Moderate croup is characterized by audible stridor at rest, worsening stridor with agitation, a barky cough, and increased work of breathing (retractions, tachypnea, tachycardia). A patient with moderate croup may be fussy but is alert, interactive, and comforted by parents. Hypoxia is atypical in mild or moderate croup. When seen, it may signify concomitant lower respiratory disease, another disease process, or severe croup.

Laboratory tests are nondiagnostic. Radiographic studies of the neck are useful when the diagnosis is in doubt, but they do not change management. The classic finding in croup is a tapered narrowing of the normal shouldered appearance of the subglottic trachea such that it has the appearance of a pencil or steeple.

Management. Glucocorticoids are the mainstay of treatment of croup, resulting in reduced symptoms, need for aerosolized epinephrine, readmission to the emergency department, and shorter hospital stays.[39–41] Evidence for the use of routine steroids in croup was Geelhoed and Macdonald's comparison of the experience at Princess Margaret Hospital for Children before and after steroids became mandatory in the treatment of croup in patients in the ICU.[42] Before 1989, less than 5% of ICU patients received steroids. At that time, an average of 11% were intubated yearly, and the total ICU days were 129 (yearly average). Beginning in 1989, every child admitted to the ICU received 0.6 mg/kg dexamethasone intramuscularly. The intubation rate declined to 1% (yearly average), and total ICU days dropped to 21 (yearly average).

The role of oral, parenteral, and inhaled steroids in the treatment of croup has been debated for decades.[39] A meta-analysis of nine studies investigating steroid use in hospitalized patients with moderate croup suggested that (1) steroid therapy resulted in faster improvement in hospitalized patients, (2) steroids decreased the incidence of intubation, and (3) higher doses (>0.3 mg/kg dexamethasone) were more effective than lower doses.[40] Subsequent to this study, Geelhoed and Macdonald demonstrated that oral dexamethasone in doses as small as 0.15 mg/kg was as effective as higher doses in decreasing the duration of symptoms and hospitalization time.[43] Steroids in patients with mild croup have also been shown to improve symptoms and reduce the need for return to medical care.[44]

Budesonide is an inhaled steroid with potent topical anti-inflammatory properties. A single dose (2 mg) of nebulized budesonide was shown to shorten emergency department stay, decrease the rate of hospitalization, and cause a more rapid improvement in symptoms in children with mild to moderate croup evaluated in the emergency department.[41] Inhaled budesonide (2 mg per dose) was shown to be as effective as oral dexamethasone (0.6 mg/kg) in decreasing the duration of hospital stay, improving clinical symptoms, and decreasing the ongoing requirement for aerosolized epinephrine. Johnson and colleagues found intramuscular dexamethasone to be superior to nebulized budesonide in reducing rate of hospitalization,[40] while other studies have found the two treatments comparable.[45]

Aerosolized epinephrine, either racemic epinephrine (containing *d* and *l* isomers) or *l*-epinephrine, act on alpha-adrenergic receptors in the subglottic mucosa.[46] Through vasoconstriction, epinephrine reverses edema and relieves acute symptoms in a subset of patients. It is a temporizing measure with a quick onset of action (within 10 minutes) and duration of effect between 1 and 2 hours. Racemic epinephrine has traditionally been preferred over *l*-epinephrine because the racemic mixture has been associated with fewer cardiovascular side effects. However, the *l* form of epinephrine is the active isomer and has the same degree of safety and efficacy as racemic epinephrine[47]; either form may be used. The "rebound" phenomenon of epinephrine is defined as recurrence or worsening of the patient's pretreatment symptoms when aerosolized epinephrine wears off. This rebound is rarely clinically significant if steroids are given early in management.[48] Many patients with moderate croup benefit from aerosolized epinephrine. It has been demonstrated that a subset of these patients can be safely discharged from the emergency department after a post-treatment observation

period of 2 to 4 hours.[49,50] A retrospective study evaluating the policy of discharging selected patients after treatment with racemic epinephrine yielded favorable results. Of 50 patients discharged after the administration of epinephrine, none were subsequently hospitalized and only 1 required retreatment within 48 hours as an outpatient. Importantly, 92% were discharged on a regimen of steroids. The investigators recommend that children with moderate croup who have received aerosolized epinephrine can be safely discharged (1) after 2 hours of observation after administration of epinephrine, (2) if they are free of stridor and retractions, and (3) if they have access to follow-up care. They also recommend administration of steroids in these patients.[49] The decision to discharge after administration of aerosolized epinephrine should also be based on the patient's symptoms such as dehydration, preexisting airway pathology, and other congenital anomalies.

Cool mist has long been advocated as a useful therapy but has not been demonstrated to improve outcomes. It is hypothesized to act by moistening thickened secretions, thereby making them easier to mobilize out of the airway. A randomized trial of mist therapy in moderate croup showed no clear benefit in improving oxygen saturation, respiratory rate, or assessment times.[51]

A small percentage of patients with croup require admission. The decision to admit a child with moderate croup is based on a number of factors: the severity of symptoms at initial evaluation, persistence of respiratory distress, stridor at rest, oxygenation, response to treatment (humidification and aerosolized epinephrine), hydration, history suggesting airway pathology or recurrent croup, young age (<6 months), high fever, overall toxicity, and parental reliability (Box 166-1).

Severe croup is rare and associated with signs of impending airway obstruction and respiratory failure: fatigue, hypoxia, hypercapnia, abnormal mental status, extreme respiratory distress, and stridor. Since the advent of steroid administration, only an estimated 1 to 2% of patients with croup require intubation. Ideally, intubation should be performed under controlled circumstances. Orotracheal intubation with an endotracheal tube at least a half size smaller than expected for the child's size is often necessary. If the tube that can be passed is too small to allow adequate ventilation, tracheostomy may be required. The decision to extubate a child with severe croup is complex; age, coexisting congenital lesions, and length of intubation are all variables that should be considered.

Spasmodic Croup

Spasmodic croup is a somewhat indistinct clinical entity in which many of its features overlap those of viral croup. It is characterized by the sudden onset of severe stridor and a barky cough without a viral prodrome. It may be recurrent and has been associated with allergy and gastroesophageal reflux. Previous parainfluenza infection has been postulated as a predisposing condition for a hypersensitivity reaction on later exposure to the virus. There is little in the literature to delineate the difference between spasmodic and viral croup.

BOX 166-1 CROUP: INDICATIONS FOR ADMISSION

- Severe respiratory distress or failure
- Unusual symptoms (hypoxia, hyperpyrexia)
- Dehydration
- Persistence of stridor at rest after aerosolized epinephrine and steroids
- Persistence of tachycardia, tachypnea
- Complex past medical history (prematurity, pulmonary, cardiac disease)

Diseases of the Trachea

Obstruction of the trachea distal to the subglottic space can be a result of both congenital and acquired lesions.

Congenital Lesions

Tracheomalacia results from abnormally soft, undeveloped supporting cartilage of the tracheal rings. This diagnosis should be suspected in patients with a history of stridor that increases over the first few weeks of life and worsens with agitation, supine positioning, and infection. Plain radiographs are usually nondiagnostic, but dynamic studies such as fluoroscopy or ultrafast CT may be helpful.

Tracheal stenosis is a congenital anomaly that results from complete tracheal rings. Infants have persistent stridor and respiratory distress. Because the trachea is "fixed," symptoms worsen with agitation and age.

A *vascular ring* is an anomaly of the aortic arch and related vessels in which a ring is formed that encircles the trachea, esophagus, or both. Examples of "vascular rings" include a double aortic arch, right-sided aortic arch with a persistent left ligament, aberrant right subclavian artery, and a pulmonary sling. These conditions are rare and are often manifested in infancy with a variety of symptoms related to breathing and feeding. However, the nonspecific nature of the infant's symptoms and the low prevalence of these lesions often result in an initial incorrect diagnosis of croup or URI. In a retrospective review of 38 patients, the diagnosis was made in the first year of life in 87%. Stridor (50%), wheezing (53%), and dyspnea (45%) were the most common initial symptoms, followed by cough (34%), recurrent URI (32%), and dysphagia (32%). Sixty-three percent of these patients had associated cardiovascular anomalies.[52]

This diagnosis should be considered in any infant with persistent, unexplained respiratory and feeding problems. A chest radiograph revealing an abnormal (right-sided) location of the aortic arch may suggest the diagnosis in the emergency department. Definitive diagnosis requires further investigation. Traditionally, a barium esophagogram has been considered to be the single most important diagnostic procedure in patients with complete vascular rings (Fig. 166-8).[53] The need for additional studies such as CT, MRI, angiography, or bronchoscopy should be individualized. Importantly, the common association of congenital cardiac anomalies is a consideration in the workup of these patients.

Bacterial Tracheitis

Principles of Disease. Bacterial tracheitis (membranous croup, bacterial croup, pseudomembranous croup) is a relatively rare but serious cause of stridor and airway obstruction in children. Bacterial tracheitis was "reintroduced" by Jones and associates in 1979 after a period of almost 4 decades when it seemed to disappear as a clinical entity.[53] It generally affects younger children, with a peak incidence at approximately 3 to 4 years of age. However, bacterial tracheitis has been reported in patients well beyond this age group, thus making it a diagnosis seen in adolescence and young adulthood as well.

The pathogenesis of bacterial tracheitis is severe inflammation of the tracheal epithelium and the production of thick mucopurulent secretions. The lining of the trachea forms a loosely adherent membrane that sloughs into the lumen. Traditionally, *S. aureus* has been the organism primarily responsi-

ble for bacterial tracheitis. More recently, the microbiology of bacterial tracheitis has been better defined. In a review of bacterial tracheitis in 14 children, Brook reported that aerobic bacteria (43%), anaerobic bacteria (20%), and mixed anaerobic and aerobic flora (36%) were cultured. The predominant organisms recovered in tracheal secretions were *S. aureus* (5), *H. influenzae* type b (4), *Moraxella catarrhalis* (2), *Peptostreptococcus* species (4), *Prevotella* and *Porphyromonas* (4), and *Fusobacterium* species (2).[54] Others have reported *S. pneumoniae*, alpha-hemolytic and group A streptococci, and *Candida albicans*.

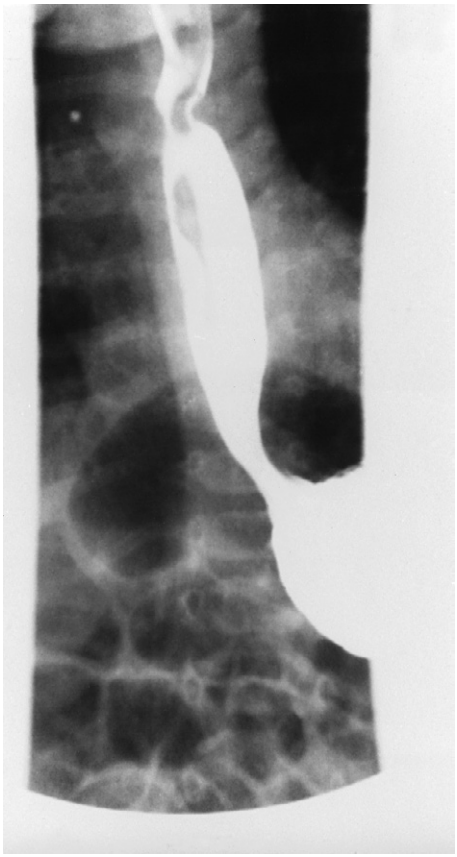


Figure 166-8. Barium esophagogram. Note the indentation of the esophagus caused by an encircling vascular ring.

Bacterial tracheitis is a secondary bacterial infection complicating a preexisting viral infection In 1983, Edwards and coauthors published two cases of *S. aureus* bacterial tracheitis in which influenza B was also cultured in one case and parainfluenza 2 was demonstrated in the other.[55] In a later series of 46 patients with bacterial tracheitis, concomitant viral respiratory cultures were positive in 72%.

Clinical Features. The clinical features of bacterial tracheitis overlap the symptoms of both croup and epiglottitis (Table 166-2). Patients experience a viral prodrome of fever, barky cough, and stridor. These symptoms typically intensify. The child appears toxic, and signs of airway obstruction and respiratory failure may develop acutely. Differentiating bacterial tracheitis from severe croup or epiglottitis on clinical grounds alone can be difficult. In a combined analysis of three studies, the correct initial diagnosis of bacterial tracheitis was made in only 4 of 26 patients. The admitting diagnoses in the remaining 22 patients were viral croup, epiglottitis, and aspiration.[56] In another report of 16 patients with bacterial tracheitis, an initial diagnosis of croup was made in 7 and acute epiglottitis in 2.[57] Features that suggest bacterial tracheitis include a viral prodrome followed by acute decompensation, symptoms atypical for croup (high fever, cyanosis, and severe distress), a poor response to usual treatment of croup (steroids and aerosolized epinephrine), and the presence of both inspiratory and expiratory stridor.

Diagnostic Strategies. Evaluation of a toxic-appearing child with bacterial tracheitis should be conducted expeditiously. Laboratory tests are nondiagnostic. The white blood cell count is normal or slightly elevated. Blood cultures are usually negative. Lateral and anteroposterior views of the neck and chest may be helpful. Findings on plain radiographs include subglottic narrowing, a ragged edge of the usually smooth tracheal air column, and a hazy density within the tra-

Table 166-2 Comparison of Croup, Epiglottitis, and Bacterial Tracheitis

	CROUP	EPIGLOTTITIS	BACTERIAL TRACHEITIS
Peak age	6 months to 3 years	3–7 years	3–5 years, but seen throughout childhood
Pathology	Subglottic inflammation, edema	Inflammation and edema of the epiglottis, aryepiglottic folds	Bacterial superinfection with inflammation of the tracheal mucosa, copious mucopurulent secretions obstructing the trachea
Organisms	Parainfluenzavirus, RSV, adenovirus	*Haemophilus influenzae*, Strep sp, *Staphylococcus aureus*	*Staphylococcus aureus* or mixed flora
Clinical features	Onset follows URI prodrome consisting of croupy cough, hoarse voice, low-grade fever, inspiratory stridor	Rapid progression of high fever, toxicity, drooling, stridor	Several-day prodrome of crouplike illness progressing to toxicity, inspiratory/expiratory stridor, marked distress
Laboratory and radiographic findings	Steeple sign on PA view of the neck, or normal	Thumbprint sign on lateral aspect of the neck, thickened aryepiglottic folds, loss of air in the vallecula	Normal upper airway structures, shaggy tracheal air column
Management	Steroids uncommon, aerosolized epinephrine	Intubation, antibiotics	Intubation common, antibiotics rare, intubation

PA, posteroanterior; RSV, respiratory syncytial virus; URI, upper respiratory infection.

cheal lumen. The epiglottis and supraglottic structures appear normal. In addition, the chest radiograph may reveal coexisting pneumonia. Bronchoscopy is both diagnostic and therapeutic and should be performed on an emergency basis. This procedure should allow for visualization of the supraglottic structures and larynx, exclusion of other pathology, suctioning of tracheal secretions and debris, and establishment of an artificial airway.

Management. In relatively few cases, severe distress requires immediate intubation and suctioning in the emergency department. Airway management in the setting of the operating room is preferred. These patients require hospital admission, intensive care, supplemental oxygen, fluid resuscitation, and broad-spectrum antibiotics.

Intubation has been required in the majority of patients. In six of eight series, intubation rates exceeded 70%. The remaining two reported intubation rates of only 30%.[56] The investigators postulated that the absence of aspiration pneumonia[58] and older age[59] are factors that may account in part for the decreased need for active airway management in some patients. Overall, recovery is slow. The duration of intubation in patients with bacterial tracheitis is reported to be 4 to 5 days, as opposed to 48 hours for croup and 54 hours for epiglottitis.[57] Reintubation after elective extubation was reported to be necessary in 4 of 10 patients because of recurrence of severe respiratory distress.[56]

Rare complications that have been reported in association with bacterial tracheitis include toxic shock syndrome, septic shock, postintubation pulmonary edema, and acute respiratory distress syndrome.[60]

Aeroesophageal Foreign Bodies

Airway Foreign Body

Perspective. Asphyxia after foreign body aspiration is a common cause of death in children. The majority of cases and deaths occur in toddlers younger than 3 years. A foreign body can lodge in any part of the airway and can move. Round-shaped foods are the most frequently aspirated objects: grapes, raisins, peanuts, and hot dogs.[61] Nonfood objects include a whole host of items. Conformable objects are the most difficult to manage and remove, and balloons, including those made from examination gloves found in physicians' offices, are the objects most likely to result in death.[62]

In general, objects that pass through the subglottic space will lodge in a bronchus, usually the right main stem bronchus, or in a more terminal part of the airway. Large objects that lodge in the upper airway and trachea tend to cause obvious and dramatic signs of upper airway obstruction: dyspnea, drooling, stridor, and cyanosis. They also carry the worst prognosis.

Clinical Features. An upper airway foreign body can cause partial or complete obstruction. A patient who is adequately oxygenated and is moving air should be initially allowed to maintain a preferred position, continue coughing to clear the obstruction, and breathe spontaneously.

Clinical signs of complete obstruction include poor air exchange, ineffective cough, severe distress, and cyanosis. The response to complete obstruction will be determined by the setting and available equipment. Outside a setting in which laryngoscopy and airway equipment are available, relief of a complete obstruction should follow the American Heart Association age-specific guidelines for obstruction by a foreign body.[63–65]

Diagnostic Strategies. In a child with an aspirated foreign body in the upper airway, there is often no time nor is it prudent to obtain diagnostic imaging. In a stable patient, a portable lateral neck radiograph and a chest radiograph may be obtained as long as the patient is allowed to maintain a position of comfort.

Management. Basic life support maneuvers to remove a foreign body in children include back blows and chest thrusts in infants and abdominal thrusts in children and adolescents. Choking infants younger than 1 year should receive a series of five back blows delivered between the shoulder blades, followed by five chest thrusts. Chest thrusts should be performed in a manner similar to chest compressions; the thumb encircling technique is preferred in infants.[65] The infant's head should be held below the trunk. Abdominal thrusts should not be performed in infants because of the possibility of injury to abdominal organs. Blind finger sweeps are not performed in infants or children because this maneuver may push the object further into the airway.[63]

In children older than 1 year, the Heimlich maneuver is used in children who are conscious and chest compressions in children who are unconscious.[65] When performing the Heimlich maneuver, the rescuer places the fist of one hand in the other hand and against the abdomen of the victim. Five thrusts are delivered between the waist and rib cage. The rescuer's hands should not be placed on the xiphoid. This maneuver is performed in the standing position in a conscious victim. An unconscious child should be placed supine with the rescuer kneeling astride the victim. In the hospital setting, the airway should be open with a jaw thrust and the patient assessed for respirations. If there is no chest rise, assisted ventilation with a bag-mask device (manual resuscitator) is indicated. If there is still no chest rise, laryngoscopy should be performed to visualize and remove the foreign body with pediatric Magill forceps.[65] If the foreign body cannot be seen in the pharynx or larynx, it may be located in the esophagus, where it could be pushing on the soft cartilage of the trachea and causing the obstruction. In this case, basic life support maneuvers may dislodge the foreign body into the mouth where it can be removed. If it appears within the subglottic space or trachea and cannot be removed, basic life support maneuvers may dislodge it into the oropharynx, or an attempt to push it into a main stem bronchus with an endotracheal tube may allow ventilation of the other lung but may result in irreversible airway obstruction. Recruiting additional expertise in the form of an ear, nose, and throat specialist, anesthesiologist, or general surgeon may be valuable.

The emergency physician should undertake emergency needle cricothyrotomy to access the airway in an obstructed patient who cannot be intubated nor bag-mask ventilated. A large intravenous catheter (14–18 gauge) is passed through the midline of the inferior edge of the cricothyroid membrane. When air is aspirated, the plastic catheter is advanced and connected to the adapter of a 3-0 endotracheal tube and then connected to a manual resuscitator. Needle cricothyrotomy kits are also commercially available. Jet ventilation devices or the use of wall oxygen flow may allow for greater ventilation than possible with a self-inflating manual resuscitator.[66] This is generally considered a temporizing measure that allows for oxygenation until another airway can be established.

KEY CONCEPTS

- *Retropharyngeal abscess.* A potentially life-threatening emergency in young children with signs of upper airway obstruction or meningismus, a retropharyngeal abscess is often related to oral trauma. It is most frequently caused by *Staphylococcus aureus*, group A streptococci, and anaerobes.
- *Epiglottitis.* In the post–*H. influenzae* type b vaccine era, the typical profile of epiglottitis has changed to include older patients. Group A *Streptococcus* causes the majority of infections; *H. influenzae* type b is the infectious agent in a minority of cases. The clinical features of epiglottitis are usually sufficiently characteristic that diagnostic tests are not necessary to make the diagnosis.
- *Croup.* Viral croup is the most common infection of the upper airway in young children and is often mild. The mainstays of managing moderate to severe croup include vaporized epinephrine and glucocorticoids. These patients can be discharged from the emergency department after a post-treatment observation period of several hours if they remain free of stridor and distress and have access to follow-up care.
- *Bacterial tracheitis.* The clinical features of bacterial tracheitis represent a progression from a viral URI to acute toxicity and marked respiratory distress. *S. aureus* is the most common cause of this infection. Bronchoscopy is both diagnostic and therapeutic and should be performed on an emergency basis.
- *Airway foreign body.* Children with an airway foreign body are managed with basic, followed by advanced, life support procedures for removal of the foreign body. Emergency cricothyroidotomy is reserved for obstructed patients who cannot be intubated or ventilated.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 167

Pediatric Respiratory Emergencies: Lower Airway Obstruction

Richard J. Scarfone and Jeffrey A. Seiden

ASTHMA

Perspective

Introduction and Epidemiology

Asthma is the most prevalent chronic disease of childhood, affecting almost 7 million children in the United States.[1] In the past 25 years, childhood asthma prevalence rates have more than doubled.[1] The public health burden posed by this disease, as assessed by emergency department (ED) visits, hospitalizations, and deaths, remains at a historically high level. About 3% of all ED visits among children are for asthma, accounting for 750,000 such visits annually.[1] Similarly, about 3% of all hospitalizations for children are due to asthma, totaling about 200,000 per year.[1] In addition, there are astonishing racial disparities among children with this condition. Compared with white children, black children have a 60% higher prevalence rate, a 260% higher ED visit rate, a 250% higher hospitalization rate, and a 500% higher death rate due to asthma.[1]

Thus, asthma is one of the few chronic diseases of childhood for which there have been increases in prevalence, morbidity, and mortality in recent decades. These trends are occurring despite unprecedented investments in terms of money, preclinical and clinical research, and national focus. The reasons for these trends are no doubt multifactorial and are beyond the scope of this discussion. This portion of the chapter will focus on the recognition, evaluation, and clinical management of children in the ED with acute asthma.

Distinguishing Principles of Diseases

Anatomy and Physiology

Asthma, a lower airway disease marked by bronchoconstriction, mucosal edema, and pulmonary secretions, may lead to respiratory failure if not treated in a timely or effective manner. Important anatomic and physiologic differences exist between children and adults that may hasten the development of respiratory failure, mandating that clinicians quickly recognize and take appropriate measures to reverse respiratory distress.

An upper respiratory infection (URI) associated with copious rhinorrhea, a common trigger of an asthma exacerbation, may significantly increase airway resistance. Further, a small decrease in the internal diameter of the upper airway causes a greater increase in resistance for the young child compared to the adult. In fact, just one millimeter of edema can decrease the cross-sectional area of the infant's airway by 75%.

Regarding the thorax, the young child has a compliant chest wall and horizontally located ribs. These factors limit use of the thorax to increase tidal volume; instead, ventilation is dependent on diaphragmatic movement. However, abdominal distention as might occur with crying or swallowing of air will impede diaphragmatic breathing. With the inability to significantly increase tidal volume, minute ventilation becomes rate dependent, quickly leading to fatigue.

An infant under 12 months of age has an oxygen consumption index that is double that of an adult, due to a higher rate of metabolism. Increased airway resistance and chest wall compliance necessitate more rapid breathing and increased energy expenditure. Increased work of breathing may account for as much as 15% of total oxygen consumption, at a time when oxygenation is poor. As a result, the child will develop hypoxemia quite rapidly in response to respiratory disease. The child with significant respiratory distress and inadequate oxygenation may become bradycardic, leading to cardiopulmonary arrest within minutes, if appropriate interventions are not undertaken.

Clinical Features

Clinical Evaluation

All acutely wheezing children arriving for ED care should be attached to a cardiorespiratory monitor and have oxygen saturation determined by pulse oximetry. If needed, supplemental oxygen should be provided. After this, the clinician may begin the clinical assessment.

History

In evaluating the child with acute wheezing, the treating physician should obtain a concise history, perform a brief and focused physical examination, determine the initial degree of illness, and initiate appropriate therapy. After therapy has begun, a more comprehensive history and physical examination can be conducted. The initial history should include questions regarding the child's age, duration and severity of symptoms, possible choking episode (foreign body aspiration), and recent medication use. The parents should be able to relate how the severity of this attack compares to that of previous exacerbations. A history of difficulty sleeping, eating, or speaking as a result of this attack suggests a moderate to severe

exacerbation. The names, doses, and frequency of administration of asthma medications recently received should be noted. A child who has been receiving very aggressive therapy with short-acting beta$_2$-agonists (SABAs) just prior to ED arrival may not respond favorably to that same therapy in the ED. Any comorbidities should be identified early in the clinical course.

A more comprehensive history should include questions regarding asthma triggers such as URIs, cigarette smoke, allergies, or exercise. Inquiries regarding fever and hydration status should be part of a complete review of systems. A past medical history of frequent asthma exacerbations, ED visits for asthma, or hospitalizations to either the general ward or the intensive care unit (ICU) would raise the concern for poorly controlled asthma. The impact that asthma has in the child's life may be gauged by the monthly frequency of daytime or nighttime symptoms such as cough, wheezing, shortness of breath, or chest tightness as well as missed days of school or restricted activity. A child who meets criteria for persistent asthma should be receiving daily anti-inflammatory therapy and those over age 5 years should be monitoring symptoms with a peak flow meter.[2] If the child is wheezing for the first time, then inquiries regarding other possible causes of wheezing (see Differential Considerations) should be made. Family and social histories should focus on asthma, cystic fibrosis, or atopic disease and the adequacy of support systems at home.

Physical Examination

The initial focused physical examination of the wheezing child should include obtaining vital signs and assessing the level of consciousness. A child who is anxious, restless, or lethargic may be hypoxemic. No single asthma score has been universally adopted to assess degree of illness or treatment responses.[3,4] Most asthma scores include key clinical factors such as respiratory rate, degree of wheezing, inspiratory to expiratory ratio, use of accessory muscles, and oxygen saturation in room air.[5] Such scores can assist in assessing the pretreatment degree of illness at ED triage, as well as tracking the child's response to therapy.

For a child with severe disease, wheezing may be audible without a stethoscope or, if aeration is extremely poor, no wheezing may be detected. Asymmetrical wheezing suggests pneumonia, pneumothorax, or the presence of a foreign body. Palpation of the chest and neck may reveal subcutaneous air, associated with a pneumomediastinum or pneumothorax. Following this initial assessment, the remainder of the physical examination may be performed. The most anxiety-provoking aspects of the examination such as otoscopy should be delayed until after treatment is well underway.

Diagnostic Strategies

Pulse Oximetry and Arterial Blood Gas

Adjunctive studies such as arterial oxygen saturation measured by pulse oximetry may assist in determining the initial degree of illness.[6] Pulse oximetry is noninvasive, inexpensive, and provides objective data regarding the degree of illness of a wheezing child. The oxygen saturation of any child with respiratory distress should be determined soon after ED arrival and supplemental oxygen should be provided if the oxygen saturation is 92% or less.

With the widespread use of pulse oximetry, physicians rarely need to obtain an arterial blood gas (ABG), especially if the sole purpose is to determine the partial pressure of oxygen. The acquisition of an ABG should be reserved for the child with severe disease to measure the extent of respiratory acidosis and hypercapnia. The timing of this test is important. For a severely ill child requiring admission to the ICU, it may be helpful to obtain this test after ED therapy has been initiated and after a clinical plateau has been reached. ABG results can then be used as a baseline that may be compared to subsequent results during the hospitalization. An apparently "normal" partial pressure of carbon dioxide ($Paco_2$) or pH may actually reflect severe disease. For example, a "normal" $Paco_2$ of 40 mm Hg in a child with extreme tachypnea and retractions suggests impaired ventilation and impending respiratory failure.

Peak Expiratory Flow Rate

Measuring the peak expiratory flow rate (PEFR) is a means of obtaining an objective assessment of exacerbation severity but it has limited utility in the evaluation of acutely ill children. Young children, in particular, may be unable to properly comply with this testing, and in one study just two thirds of children above age 5 years were able to complete PEFR testing during an asthma exacerbation.[3] Ideally, the PEFR should be determined with the child standing and the best of three attempts recorded. Therefore, moderately to severely ill or younger children may not be able to cooperate with this assessment.

Chest Radiographs

URIs marked by low-grade fever and coughing are common triggers of asthma exacerbations. These signs overlap with those found among children with pneumonia, making it difficult to determine the necessity of obtaining a chest radiograph (CXR) in the evaluation of an acutely wheezing child. No set of predictors has been found that can accurately identify children likely to have abnormalities on CXR.[7] Hyperinflation, interstitial markings, and atelectasis are common radiographic findings that may be seen in a wheezing child, but these should not result in initiating antibiotic therapy or other changes in management. More serious conditions associated with asthma such as pneumonia, pneumomediastinum, or pneumothoraces are much less common. Rarely is an unsuspected diagnosis made on the basis of a CXR in an acutely wheezing child, even if the child has never wheezed before.[8]

It should not be a routine practice to obtain CXRs for all wheezing children, even those who are wheezing for the first time or those who are being hospitalized.[8] CXRs should be considered for those with focal chest findings, fever, extreme distress, or history of choking. Reassessment after treatment to evaluate for the resolution of focal findings may further decrease the need for obtaining a CXR. This selective approach will be more cost-effective and lessen unnecessary radiation exposure and overuse of antibiotics. On the other hand, clinicians may have a lower threshold for obtaining CXRs for infants with first time wheezing because of a slightly greater likelihood of uncovering an anatomic abnormality.

Differential Considerations

Although most children with wheezing have asthma, other conditions must be considered. A differential diagnosis for childhood asthma is listed in Table 167-1. Of these conditions, bronchiolitis, laryngotracheobronchitis (croup), pneumonia, and gastroesophageal reflux are those that clinicians will encounter most often. Bronchiolitis is the one disease that is most commonly confused with asthma. Although the viruses associated with bronchiolitis infect children of all ages, clinical

Table 167-1 Differential Diagnosis of Asthma

CONDITION	DISTINGUISHING CHARACTERISTICS
Infections	
Bronchiolitis	Infant, preceding URI, seasonal, no history of atopy, no family history of asthma
Laryngotracheobronchitis (croup)	Inspiratory stridor, barky cough, fever, response to humidified air
Pneumonia	Focal wheezing, rhonchi, rales, grunting, fever
Tuberculosis	Diffuse adenopathy, weight loss, prolonged fever
Bronchiolitis obliterans	Prolonged cough and/or chest pain, inhalational exposure to toxin
Anatomic/Congenital	
Gastroesophageal reflux	Frequent emesis, weight loss, aspiration
Cystic fibrosis	Diarrhea, weight loss, chronic cough, salty sweat
Congestive heart failure	Rales, murmur, gallop, hepatosplenomegaly, cardiomegaly and/or pulmonary vascular congestion on chest radiograph
Tracheoesophageal fistula	Choking, coughing, cyanosis with feeds
Mediastinal mass	Chest pain, mediastinal density on chest radiograph
Vascular ring	Stridor, cyanosis, apnea, high-pitched brassy cough, dysphagia
Acquired	
Foreign body aspiration	History of choking, toddler, asymmetrical pulmonary examination, unilateral hyperinflation on chest radiograph
Anaphylaxis	Abrupt onset, urticarial rash, angioedema, history of allergies

bronchiolitis marked by wheezing is seen almost exclusively in those less than 12 months of age. Patients with bronchiolitis typically present between November and March. There is much clinical overlap between asthma and bronchiolitis and the two cannot be distinguished on physical examination findings alone. A complete discussion of bronchiolitis is included later in this chapter.

Croup may have a viral or allergic etiology and affects children from infancy through early school age. The hallmark of the disease is inflammation of the upper airway, resulting in a harsh, barky cough and inspiratory stridor. Symptoms are often worse at night. Asthma will not present with stridor alone, but a subset of children with croup may present with both stridor and wheezing and may be misdiagnosed with asthma.

Children with pneumonia may sometimes present with a component of wheezing, although respiratory rales or rhonchi are the usual auscultative findings. Infants and young children may also have high fever, cough, grunting, nasal flaring, or retractions, whereas more classic asymmetrical pulmonary findings are more easily detected in older children.

In addition to asthma, gastroesophageal reflux can account for recurrent wheezing in infants. In these children, poor lower esophageal sphincter function results in regurgitation and aspiration of gastric contents, leading to reflex bronchospasm. Young infants with recurrent wheezing, frequent "spitting up" of feeds, or failure to thrive should be referred for a diagnostic workup.

Management

For purposes of patient management, it is best to stratify children by degree of illness, based on the initial clinical assessment (Fig. 167-1). This will help to ensure the timely initiation of an appropriately aggressive approach for sicker children while minimizing adverse effects from unnecessary therapy among those with milder exacerbations. Of course, during the ED stay, the illness severity may change, making frequent examinations to assess response to therapy essential.

Mild Exacerbation

A mild exacerbation is characterized by alertness, slight tachypnea, expiratory wheezing only, a mildly prolonged expiratory phase, minimal accessory muscle use, and an oxygen saturation of greater than 95%. Children who are able to provide a PEFR should have a value greater than 70% of personal best. Patients with a mild exacerbation, especially those who were not receiving any asthma therapy prior to the ED visit, will usually require SABA therapy only. The Expert Panel of the National Heart, Lung, and Blood Institute (NHLBI) recommends that patients receive therapy every 20 minutes in the first hour of care.[2] Often, children with mild exacerbations improve promptly with just one or two SABA treatments. Many of these patients are managed without systemic corticosteroids. However, systemic corticosteroids may be given to those who are already undergoing a course of treatment with them prior to ED arrival or to those who do not respond promptly to SABA therapy (see later section on Moderate Exacerbation).

Due to its rapid onset of action, relatively long duration of action, and good safety profile, racemic albuterol has become the SABA of choice to treat children with acute asthma. Options for mode of delivery include small-volume nebulizers (NEBs) or metered dose inhalers with spacers (MDI-Ss), and recent studies have assessed the use of levalbuterol in this setting.

Nebulizers versus Metered Dose Inhalers with Spacers. There is considerable debate regarding the optimal method to deliver SABAs to children with acute asthma. About three fourths of pediatric emergency medicine physicians report using NEBs to administer SABAs, regardless of illness severity.[9] NEBs provide a passive means of receiving aerosolized medication. Precise coordination between respiration and aerosol delivery is not needed, and medications such as anticholinergics as well as humidified oxygen may be delivered concurrently with the SABA. However, delivery is inefficient, with only about 10% of the drug in the reservoir delivered to the small airways.[10–12] In addition, administration takes about 10 minutes, increasing respiratory therapy time and costs, and an external power source is needed, limiting portability.

On the other hand, spacers used with MDIs provide a reservoir of medication that is available to be inhaled. Therefore, precise coordination between actuation and inhalation is not needed and there is no need for breath-holding. Drug deposition in the oropharynx and systemic absorption is reduced with the employment of a spacer.[13] The decreased administration time associated with MDI-S use may result in reduced costs.[14–16] The portability of MDI-S allows older children to use them during the school day. Face mask–equipped spacers are available for children too young to use the spacer's mouth-

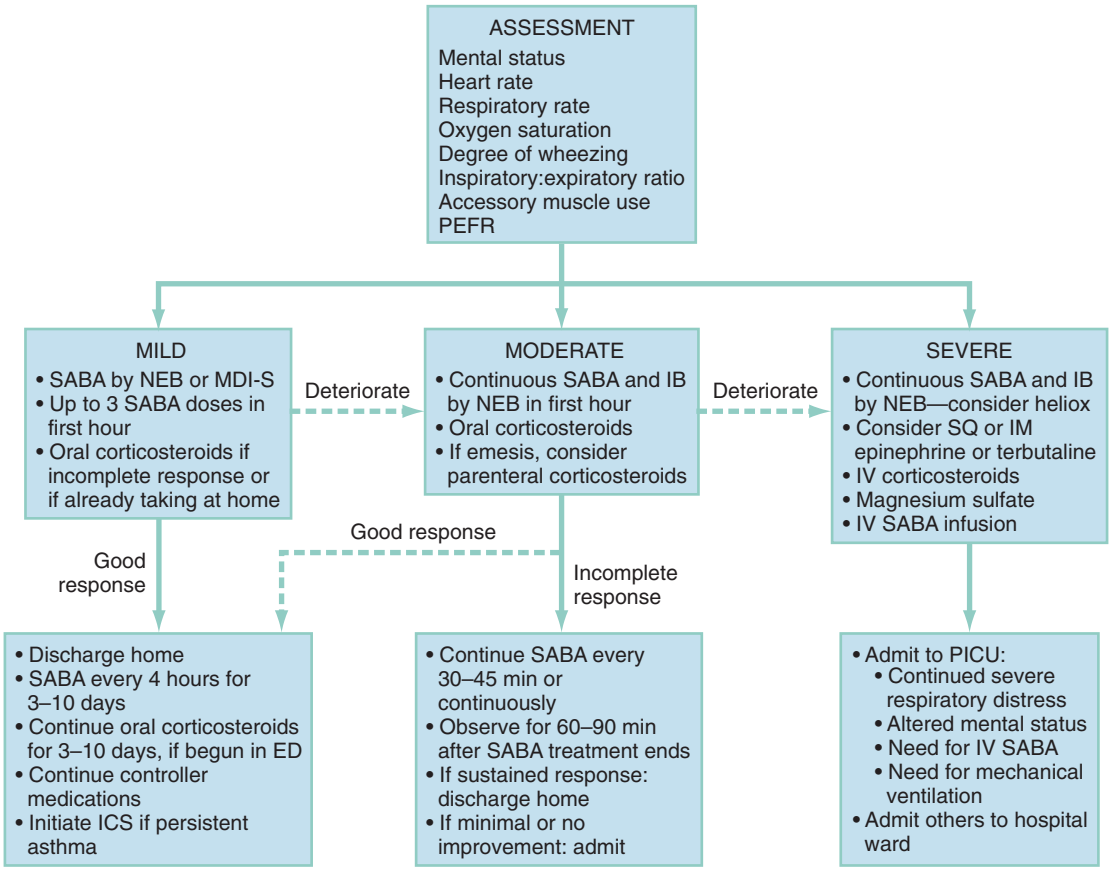


Figure 167-1. Emergency department management of acute asthma.

piece, although mouthpieces are preferable for older children to decrease nasal filtering of drug, which may reduce lung deposition.[17] Following each actuation, children should take five to eight breaths in order to completely empty the spacer.

These NEB disadvantages, along with the development and widespread use of spacers, have led investigators to assess the role of MDI-S to deliver SABAs in the ED. Numerous clinical trials and meta-analyses have consistently demonstrated that delivery by MDI-S is at least as effective as delivery by NEBs.[13,18–32] Among children 1 to 4 years old, MDI-S use was associated with a greater reduction in wheezing and a lower hospitalization rate.[16] One systematic review evaluated trials in which a total of 2066 children with acute asthma were randomized to receive SABAs by one of these two methods.[23] Those children treated with MDI-S had shorter ED length of stay and trended toward a reduced hospitalization rate. The American College of Chest Physicians and American College of Asthma, Allergy, and Immunology concluded that "both the NEB and MDI-S are appropriate for the delivery of SABA in the ED."[33] Thus, compared to NEBs, MDI-S administration has been shown to be equally effective for children of all ages,[16,22] with a wide range of illness severity and by multiple outcome measures.

Typically, when administering racemic albuterol by intermittent nebulization, a dose of 0.15 mg/kg is placed in the reservoir of a NEB. This dose is well established as one that is both effective and safe.[34,35] Optimal dosing for albuterol administered by MDI-S is not as well defined. A recent review assessed 10 randomized controlled trials comparing MDI-S to NEBs to deliver SABAs to children with acute asthma.[13] In some studies up to seven times more drug was placed in the NEB reservoir compared to that released by MDI-S, yet outcomes were similar. This reflects the inefficiency inherent with NEB delivery, with much drug being lost to the environment. Multiple puffs of SABAs delivered by MDI-S seems to be well tolerated, even by young children.[16,22] In one trial, children 1 to 4 years old treated with six puffs of albuterol by MDI-S had less tachycardia than those treated with 2.5 mg of albuterol by NEB.[16] The 2007 NHLBI guidelines state that "equivalent bronchodilation can be achieved either by high doses (4 to 12 puffs) of a short-acting beta agonist by MDI with a valved holding chamber … or by nebulizer"; they suggest a dose of four to eight puffs.[2] Table 167-2 provides recommended SABA doses stratified by the patient's weight.

Racemic Albuterol versus Levalbuterol. Another consideration in the use of SABAs is the potential role of levalbuterol. Racemic albuterol is an equal mix of the active R-albuterol and the inactive S-albuterol. R-albuterol produces bronchodilation as well as side effects such as tachycardia and tremors. S-albuterol was long thought to be inert. However, there is some evidence that S-albuterol may increase reactivity to histamine, have proinflammatory effects, and exhibit "characteristics of a typical contractile agent."[36–42] Further, there seems to be preferential retention of S-albuterol in the lungs of healthy volunteers[43–45]; this may account for diminished effectiveness with frequent dosing. Levalbuterol is pure R-albuterol without the S component. In theory, levalbuterol should be more effective than racemic albuterol at half the dose because there are no competing harmful effects from the S-isomer.

Studies assessing the use of levalbuterol to treat children with acute asthma have not consistently demonstrated this theoretical advantage. In the first of these clinical trials, levalbuterol (1.25 mg) was compared with racemic albuterol (2.5 mg) in the ED treatment of over 500 children with acute asthma.[46] The use of levalbuterol was associated with a

Table 167-2 Recommended Doses of Medications for Acute Asthma

Albuterol	0.15 mg/kg/dose (0.03 mL/kg/dose, max 1.0 mL) So:	
	<10 kg	2.5 mg (0.5 mL)
	11–19 kg	3.75 mg (0.75 mL)
	>20 kg	5 mg (1.0 mL)
Continuous albuterol	1.0 mg/kg/hr by nebulization (max 20 mg/hr)	
	<10 kg	10 mg/hr (2 mL/hr)
	10–20 kg	15 mg/hr (3 mL/hr)
	>20 kg	20 mg/hr (4 mL/hr)
Albuterol by MDI	Dose is not well established	
	<10 kg	2–4 puffs
	11–19 kg	4–6 puffs
	>20 kg	6–8 puffs
Levalbuterol	Half the recommended albuterol doses	
Ipratropium bromide	<20 kg	250 µg/dose
	>20 kg	500 µg/dose
L-epinephrine (1:1000) or terbutaline (1.0 mg/mL)	0.01 mL/kg/dose SC or IM (max 0.4 mL) May be repeated every 10–15 min	
IV terbutaline	10 µg/kg bolus over 10 min, then 0.1–0.3 µg/kg/min infusion Every 30 min, may increase infusion by 0.3 µg/kg/min to a max of 5 µg/kg/min	
Prednisone	2 mg/kg (max 60 mg), in ED 1 mg/kg/dose bid, home therapy	
Dexamethasone	0.6 mg/kg PO, 2 doses 24 hr apart	
IV methylprednisolone	1–2 mg/kg (max 125 mg)	
IV magnesium sulfate	50–75 mg/kg over 20 min (max 2.5 g)	

bid, twice daily; ED, emergency department; IM, intramuscularly; IV, intravenous; max, maximum; MDI, metered-dose inhaler; PO, orally; SC, subcutaneously.

decreased need for hospitalization. However, the baseline hospitalization rate in this study was quite high even though patients with all degrees of illness severity were enrolled. Subsequently, three other randomized trials comparing the ED use of the two drugs have failed to find a levalbuterol benefit.[47–49] These three studies analyzed children with a wide range of illness severities and baseline hospitalization rates and used various outcome measures such as asthma scores, pulmonary function tests, and hospitalization rates. Racemic albuterol was demonstrated to be as effective as levalbuterol under each of these circumstances.

To date, there are no published data assessing the use of continuously nebulized levalbuterol in the ED treatment of children with asthma. The acquisition cost of levalbuterol is over 10 times greater than racemic albuterol.[49] Until there are more compelling data to demonstrate conclusively that the additional costs of levalbuterol are offset by the need for fewer nebulizations, decreased length of ED or hospital stay, or decreased need for hospitalization, racemic albuterol should remain the drug of choice for children with acute asthma exacerbations.

Disposition. Most children with a mild exacerbation will be able to be discharged home. Those sustaining clinical improvement 60 minutes after the most recent SABA treatment may be discharged. SABAs should be continued for the next 3 to 10 days. If systemic corticosteroid therapy was administered in the ED, it should also be continued for 3 to 10 days. Children should continue all other asthma controller medications, including inhaled corticosteroids (ICS).

For those who are not already receiving ICS, it is unclear if prescribing them at ED discharge leads to improved short-term outcomes. Among adult asthmatics discharged from the ED after acute asthma exacerbations, the addition of inhaled flunisolide did not lead to improved outcomes.[50] Of note, though, compliance with the inhaled medication was low and many patients were lost to follow-up. On the other hand, adults randomized to inhaled budesonide following ED discharge had a marked decrease in relapse rates, frequency of SABA use, and asthma symptoms.[51] A review concluded that there is "insufficient evidence that ICS provide additional benefits" when added to systemic corticosteroids at ED discharge.[52] Pediatric emergency medicine physicians rarely prescribe ICS at ED discharge, even to children who have persistent asthma.[53]

Rather than prescribing ICS to prevent ED relapse, emergency physicians should consider longer-term goals for those with persistent disease. National guidelines state that ICS are the medications of choice when initiating long-term controller therapy for children with persistent asthma.[2] Further, these drugs are safe and well tolerated at recommended doses. Longitudinal studies show that daily use of ICS may decrease growth velocity, but these changes are small and reversible.[54,55] Therefore, ED physicians should identify children who, during the preceding month, have had frequent asthma symptoms, nighttime awakenings, and the need for frequent use of SABAs for asthma control. As stated by national asthma guidelines, initiation of ICS therapy at ED discharge "should be considered" for these patients.[2] Those already taking low doses of daily ICS may benefit from an increase in dosing.

In addition to prescribing medications, ED physicians should also provide asthma education at discharge. Some EDs employ the use of a video or DVD to provide standardized information to families while they undergo ED therapy. This education should include how to identify and avoid asthma triggers, a written asthma action plan explaining proper steps to take in response to an asthma flare, review of discharge medications, and proper MDI-S use. Also, follow-up asthma care within 1 to 4 weeks should be arranged.

Summary. For children with mild asthma exacerbations, racemic albuterol should be administered every 20 minutes, as needed (Fig. 167-1). Most children will respond promptly to therapy and be well enough to be discharged home after 1 or 2 treatments. Systemic corticosteroids may be considered for those who exhibit a suboptimal response to SABAs (see later section on Moderate Exacerbation). NEBs or MDI-S are each reasonable options to deliver SABAs intermittently. Table 167-2 lists recommended doses for SABAs and other asthma medications in the ED, and Table 167-3 provides a recommended strategy for SABA administration. Rather than base the method of delivery on the issue of efficacy, clinicians should assess other factors. The answers to questions such as the number of treatments a child is likely to need, the anticipated cooperation with a given delivery method, the need to deliver concurrent medications, and costs will help to guide decision-making.

Moderate Exacerbation

Children who are alert but very tachypneic with wheezing throughout expiration, an inspiratory:expiratory ratio of 1:2, and significant use of accessory muscles are experiencing a moderate asthma exacerbation. Typically, the oxygen saturation will be 92 to 95% and the PEFR will be 41 to 70% of the personal best. As with children experiencing more mild attacks,

Table 167-3 Short-Acting Beta$_2$-Agonists in Acute Asthma

	MILD	MODERATE	SEVERE
Delivery method	Intermittent NEB or MDI-S	Continuous by NEB for 1 hour, then reassess	Consider SC or IM Continuous by NEB
Comments	Most patients will need 1–2 treatments Allows for MDI-S teaching No IB needed	Not superior to MDI-S Easier to adhere to NHLBI guidelines for the first hour of therapy Concurrent IB therapy is more easily delivered	Better outcomes in severe asthma

IB, ipratropium bromide; IM, intramuscularly; MDI-S, metered dose inhaler with spacer; NEB, nebulizer; NHLBI, National Heart, Lung, and Blood Institute; SC, subcutaneously.

the cornerstone of therapy is aggressive SABA therapy. In addition, other medications such as ipratropium bromide (IB) and corticosteroids should be added and consideration should be given to delivering SABAs continuously.

Anticholinergics. Stimulation of airway cholinergic receptors results in reflex bronchoconstriction, which may be blocked with the use of anticholinergic agents such as IB. This medication is available as an MDI as well as a solution for nebulization that may be mixed directly with racemic albuterol. The MDI formulation should not be given to patients with allergy to peanut or soy because it contains soya lecithin; this is not a concern with the solution for nebulization.

Studies have shown that use of SABAs with IB is more effective than SABAs alone.[56,57] In a randomized, double-blind clinical trial, three doses of IB administered concurrently with the first three SABA treatments were shown to be superior to just one dose of IB.[56] In another study, over 400 children were randomized to receive racemic albuterol and prednisone alone or that therapy plus IB.[57] Those judged to be moderately ill did not experience an IB benefit. However, among those with an initial PEFR less than 50% predicted, the use of IB resulted in a significantly lower hospitalization rate. A recent systematic review and meta-analysis compared the use of SABAs plus anticholinergics with SABAs alone among children older than 18 months.[58] In the 16 trials assessed, combination therapy was associated with significantly lower hospitalization rates and improvements in asthma scores and pulmonary function testing. These investigators concluded that multiple doses of IB added to SABAs should be standard treatment for children with moderate to severe asthma exacerbations.

Clinical benefits following IB use may be delayed for up to 60 minutes.[56] However, it is inexpensive and since less than 1% is absorbed systemically, it is virtually free of adverse effects.[58] IB should be administered to children with moderate exacerbations. Three doses may be mixed with racemic albuterol and delivered concurrently and continuously by NEB in the first hour of care (see Table 167-3). This means of administration, although not superior to delivery by MDI-S, will help to ensure compliance with the goal of the equivalent of three NEB treatments in the first hour of care.[2] Alternatively, four to eight puffs of IB may be given every 20 minutes in the first hour of care,[2] but these children will also need to receive a substantial number of puffs of SABAs and, as clinicians care for other patients, there may be delays in receiving appropriately aggressive therapy.

Systemic Corticosteroids. There is compelling data to show that the prompt use of corticosteroids can decrease the need for hospitalization and that they should be used routinely for patients with moderate disease.[5,59–64] Clinicians must decide the optimal agent and route of administration.

Oral versus Parenteral. Two early clinical trials established the efficacy of parenterally administered corticosteroids in the ED. Compared with those treated with placebo, adults treated with intravenous (IV) methylprednisolone had a lower hospitalization rate,[59] as did children treated with intramuscular (IM) methylprednisolone.[60] Scarfone and colleagues were the first to demonstrate the efficacy of orally administered corticosteroids in this setting.[5] Children treated with frequent SABAs and oral prednisone had a reduced need for hospitalization compared to those treated with SABA therapy alone. Further, a meta-analysis determined that compared to placebo, oral corticosteroids were effective in reducing the need for hospitalization among children with acute asthma exacerbations.[63]

There have been few clinical trials directly comparing oral and parenteral therapy. In one small study, there were no differences in any outcome measures for children in the ED with moderate to severe asthma who were treated with equal doses of either IV or oral methylprednisolone.[65] The most recent NHLBI guidelines recommend using oral corticosteroids since this form of administration is less invasive and the benefits seem to be equivalent to parenteral therapy.[2,66,67] Further, oral corticosteroid therapy is inexpensive, the drugs are rapidly and completely absorbed, and this mode of administration provides the potential for out-of-hospital administration either at home or in a physician's office.

Prednisone versus Dexamethasone. As with SABAs, clinicians have a choice in the specific corticosteroid to be used. Oral prednisone has been the drug of choice in this setting. Significant clinical benefits begin 2 hours after administration, are most pronounced among the sickest children, and result in a decreased need for hospitalization.[5] Dexamethasone phosphate may be given orally or parenterally and has a substantially longer (36–72 hours) half-life than prednisone (18–36 hours).[68,69] Investigators recently treated children in the ED with either 0.6 mg/kg of dexamethasone or 2 mg/kg of prednisone in a randomized fashion.[69] Those in the dexamethasone group were provided one additional dose to take the following day, while those in the prednisone group were given a prescription for 4 additional days of prednisone. There were no differences in hospitalization or relapse rates or symptom persistence. Significantly fewer dexamethasone patients vomited the study drug in the ED and reported noncompliance with it after ED discharge. Of note is that Orapred, a more palatable form of oral prednisone, was not used in this study.

These data suggest that either dexamethasone or prednisone may be used in the treatment of moderately ill children with acute asthma. Given that clinical benefits from corticosteroids are delayed and that all moderately ill children will require corticosteroids whether or not they require hospitalization, they should be administered as soon as possible after ED arrival in an attempt to hasten clinical improvement and perhaps prevent the need for hospitalization.[61,64] Since SABAs are administered by inhalation and corticosteroids may be given orally, most children with a moderate asthma exacerbation can be managed without the insertion of an IV line. This avoids unnecessary pain and anxiety, as well as the delays in drug administration associated with IV line insertion. IM therapy is a reasonable option for children who vomit orally administered corticosteroids yet do not require an IV line for other reasons.

Inhaled Corticosteroids. The use of ICS for the ED treatment of acute asthma is an area of ongoing research. In three clinical trials, ICS were compared to oral prednisone in the ED setting.[70–72] Scarfone and colleagues treated children with either nebulized dexamethasone or oral prednisone.[70] The two groups had similar rates of hospitalization, although there was a trend toward greater rate of improvement among the dexamethasone-treated children. A potential limitation to the widespread use of nebulized dexamethasone is that it contains sodium bisulfite, a preservative that may induce wheezing among allergic individuals. Budesonide is an ICS that has a high topical activity and low systemic absorption[73] and is effective in the treatment of children with croup.[74,75] Investigators from India found that three nebulized doses of budesonide was superior to one dose of prednisone.[71] In another trial, fluticasone-treated children were more likely to be hospitalized and experienced a significantly smaller degree of improvement compared with those treated with prednisone.[72] Finally, investigators determined that children treated in the ED with inhaled triamcinolone had lower hospitalization rates and relapse rates compared to those treated with either prednisone or IV corticosteroids.[76]

Rather than replacing systemic corticosteroids, other investigators have assessed whether or not the addition of ICS to systemic therapy results in clinical benefits; however, few such studies have been performed in children and few have assessed the need for hospitalization.[77–79] Thus, the niche for ICS in the ED treatment of acute asthma is still being defined. Additional areas for further investigation include determining the optimal agent, the proper dose, the appropriate mode of delivery, and defining the patient population most likely to benefit from this therapy. At this time, there is no proven role for the routine use of ICS in the ED setting. Due to its greater bioavailability and proven benefits, moderately ill children should receive systemic corticosteroid therapy.

Intermittent versus Continuous. Children requiring very frequent intermittently nebulized albuterol may benefit from receiving albuterol continuously instead. In one clinical trial among asthmatic children, patients were randomized to receive the same total dose of albuterol nebulized either intermittently or continuously, over 2 hours.[80] Those in the continuous group had a greater mean improvement in their asthma scores and significantly less respiratory therapy time, although there were no differences in mean PEFR or admission rates. A systematic review found that those treated with continuously nebulized SABAs had lower rates of hospitalization, greater improvements in pulmonary function tests, and similar rates of adverse events compared with those treated intermittently.[81]

Perhaps the greatest advantage of continuous over intermittent therapy is one of a practical nature: it allows greater compliance with the goal of delivering the equivalent of three intermittent albuterol treatments in the first hour of care.[2] In addition, this method will result in less respiratory therapy time and costs, has been shown to be safe,[82,83] and may benefit the sickest patients the most.[84,85] On the other hand, young children may not tolerate a face mask for prolonged periods.

Many clinicians find it helpful to determine the total of racemic albuterol that would be delivered if three treatments were to be given intermittently over an hour, place that total dose in the NEB reservoir, and administer it continuously over an hour. Alternatively, a dose range may be used based on the child's weight (see Table 167-2).

Summary. A suggested approach to the management of children with moderately acute asthma is as follows. Supplemental oxygen should be provided if the initial oxygen saturation is 92% or less in room air. Albuterol and IB should be administered continuously by nebulization for 1 hour (see Fig. 167-1). This will ensure that an appropriate amount of each is delivered in the first hour of ED care. As soon as possible after ED arrival, a single dose of either oral prednisone or dexamethasone should be given. IM dexamethasone is an option for children who vomit the initial oral corticosteroid dose within 15 minutes of its administration or who vomit repeated doses.

After 1 hour of therapy, a clinical reassessment should be made; evaluation at this time is better than the initial assessment at predicting the need for hospitalization.[86] At this point, patients can generally be grouped into one of three categories: markedly improved, not improved or worse, or slightly improved. Children who are markedly improved may be observed without SABAs to ensure that there is no clinical deterioration. It is wise to delay a disposition decision until at least 60 minutes after the most recent SABA treatment so that a clinical relapse may be noted. In making the disposition decision, the clinician must determine the patient's physical examination findings and also consider the frequency of prior hospitalizations and ED visits and issues such as compliance and support systems. The medications and education to be provided at ED discharge are the same as outlined for those with a mild exacerbation.

Children who remain moderately ill after the first hour must continue to be treated aggressively with SABAs, either continuously or with frequent administration of intermittent therapy. If after 2 hours subjective and objective measures reveal that the degree of respiratory distress is unchanged or worse, then hospitalization is warranted. On the other hand, there will be a subset of patients who demonstrate some degree of clinical improvement at the 2-hour assessment but are not yet well enough to be sent home. One study showed that among prednisone-treated children who would have been hospitalized after 2 hours of ED therapy, less than half were actually hospitalized when aggressive SABA therapy was continued for an additional 2 hours and none returned to the ED within 48 hours of discharge.[5] Presumably, the onset of prednisone's effects allowed these children to avoid hospitalization. Therefore, continuing to treat such children with SABAs for a total of 3 to 4 hours, perhaps in an ED observation area, would be expected to avoid the need for many hospitalizations.

Severe Exacerbation

A severe exacerbation is characterized by restlessness or lethargy, extreme tachypnea and tachycardia, wheezing that is audible without a stethoscope, an inspiratory:expiratory ratio exceeding 1:2, significant use of accessory muscles, and an oxygen saturation less than 92%. Some older children with a severe exacerbation may have bradypnea because of a prolonged expiratory phase and wheezing may not be audible if aeration is markedly decreased. The PEFR will typically be less than 40% predicted, although most children will be too ill to use the peak flow meter.

Figure 167-1 provides an outline for the approach to managing severely ill children. They should be attached to a cardiorespiratory monitor and blood pressure cuff with continuous monitoring of oxygen saturation by pulse oximeter. As with the moderately ill child, supplemental oxygen and continuously nebulized albuterol and IB should be provided soon after arrival. To achieve an oxygen saturation of 95% or greater, it may be necessary to employ a non-rebreathing face mask. Severely ill children may be too sick to tolerate oral medications and will likely need an IV catheter for other indications. Therefore, an IV line should be established as soon as possible and a dose of methylprednisolone given.

Subcutaneous or Intramuscular Therapy. For children with very poor inspiratory flow, nebulized SABAs may not be effectively delivered to the smallest airways. Short inspiratory time, prolonged expiration, and low inspiratory pressures will impair delivery of inhaled medications. Here, subcutaneous (SC) or IM terbutaline or epinephrine should be used, especially if an IV line is yet to be established. Terbutaline may be preferable because it is a more selective agent with fewer side effects such as tremors, vomiting, or palpitations. Very ill anxious young children who are uncooperative with the inhalation treatments may also benefit from this therapy. There are no data to suggest one mode of administration is superior to the other, although IM therapy is recommended for children with bronchospasm due to anaphylaxis.[87] SC or IM therapy may be repeated every 10 to 15 minutes, as needed.

Magnesium Sulfate. There is accumulating evidence that magnesium sulfate may benefit adults and children with severe asthma. Recent meta-analyses determined that use of magnesium resulted in improved outcomes for both adults[88] and children.[89] In two separate trials, children with a suboptimal response to initial SABA therapy who were randomized to receive magnesium had significantly greater improvements in pulmonary function studies compared to those treated with placebo.[90,91] In contrast, Scarfone et al conducted a randomized, controlled trial assessing the use of 75 mg/kg of magnesium in asthmatic children.[92] They sought to determine if magnesium was efficacious as a component of *initial* therapy for children with moderate to severe exacerbation, without waiting to judge response to early albuterol therapy. No magnesium benefits were found for this population.

Magnesium is inexpensive and has minimal adverse effects.[93] The most common adverse effect is hypotension; this may be avoided by infusing the dose over 20 minutes. The most recent NHLBI guidelines recommend the consideration of magnesium for select patients; this represents a key difference from prior reports. At this point, existing literature indicates that magnesium should be considered for moderately ill patients who have a suboptimal response to SABAs, IB, and corticosteroids as well as for all severely ill children.

Intravenous Short-Acting Beta$_2$-Agonists. The NHLBI guidelines conclude that there are insufficient data to make recommendations regarding the use of IV SABAs.[2] Similarly, a recent systematic review of randomized, controlled trials failed to support this practice.[94] However, of the 15 studies included, just 3 were performed in children and just 3 assessed the combination of IV and inhaled SABAs compared to inhaled SABAs alone.[95–97] Rather than definitively demonstrating lack of efficacy, these data highlight the need for more and larger clinical trials.

Potential adverse effects from the use of IV SABAs are substantial and include dysrhythmias, hypertension, and hypokalemia. Due to the concern for toxicities, there is no role for initiating therapy with IV SABAs, even for severely ill children. However, for those who are poorly responsive to the interventions outlined above, with impending respiratory failure, the risk-benefit ratio shifts toward their use.

Heliox. Heliox is a low-density mixture (often in a 70:30 ratio) of helium and oxygen that results in less turbulent flow through narrowed airways. Theoretically, its use is associated with decreased work of breathing, less respiratory muscle fatigue, and a lower likelihood of ventilatory failure. In one trial, children with acute severe asthma treated with heliox had a significantly greater decrease in pulsus paradoxus and dyspnea index, and increase in PEFR, compared to others.[98] A more recent study compared the use of heliox versus oxygen alone to deliver continuously nebulized SABAs.[99] At 240 minutes, children in the heliox group had greater improvement as assessed by decreased asthma scores and need for hospitalization. However, after reviewing 10 clinical trials assessing the use of heliox, investigators concluded that there is insufficient evidence to support the use of heliox for all patients with asthma,[100] although it may be considered for severely ill children who are not responding to more conventional therapy.[2]

Mechanical Ventilation. When making decisions about the need for mechanical ventilation of the severely ill patient, one must assess the entire clinical picture, including duration of wheezing, illness severity, response to therapy, as well as ABG results. Making this decision based on the ABG results alone should be discouraged. For example, the child with a pH of 7.10 and a $Paco_2$ of 55 who shows marked improvement with IV SABA therapy may not require ventilatory assistance, yet the one with a pH of 7.18 and a $Paco_2$ of 50 who appears fatigued and is not responding to therapy probably does. Ketamine is a bronchodilator and is the drug of choice for sedation and analgesia of the asthmatic child who requires intubation.

With mechanical ventilation, air trapping with resultant pneumothorax is a major concern. *Permissive hypercapnia* is a term used to describe a strategy of minimizing tidal volumes and respiratory rate in order to minimize peak pressures. A degree of hypercapnia is accepted and may be treated with sodium bicarbonate. Enough expiratory time must be allowed for air exit from the lungs.

There are many potential therapies that are not recommended for the treatment of acutely ill asthmatic children. These include methylxanthines such as aminophylline, the routine use of antibiotics in the absence of known bacterial infection, aggressive hydration, chest physiotherapy, mucolytics, sedation, and noninvasive ventilation.[2]

Summary

Asthma is one of the few diseases in which there have been increases in prevalence, morbidity, and mortality in the past 2 decades. More than ever, physicians need to be vigilant in the recognition and treatment of children with acute asthma. In all cases, appropriate doses of albuterol should be given promptly and early use of multidose IB and corticosteroids is indicated for those who are moderately or severely ill. Aggressive use of SC or IM terbutaline, continuously nebulized albuterol, and magnesium is warranted for those who are severely ill, while IV SABAs are reserved for those not responding to the above therapy.

■ BRONCHIOLITIS

Perspective

Background

Bronchiolitis is an acute infectious disease that results in inflammation of the small airways in children younger than 2 years. This process manifests clinically as wheezing and increased work of breathing along with the typical signs and symptoms of a URI. Nearly all children are affected by the viruses that cause bronchiolitis at least once during their first 2 years of life, but it is more common for infants younger than 12 months to develop clinical bronchiolitis.

Epidemiology

Bronchiolitis is a seasonal disease, with most cases occurring between November and April in temperate climates. It

accounts for approximately 3% of all ED visits in the United States.[101] Overall, approximately 19 to 27% of children presenting to an ED with bronchiolitis are admitted for inpatient management.[101,102] This disease accounts for more than 20% of acute care hospitalizations for children younger than 1 year, and the total cost for all bronchiolitis-related hospitalizations is more than $500 million per year.[103] Hospitalization rates vary depending on many factors, and these rates have increased dramatically over the past 2 decades. In the United States, Hispanic children and those of Alaskan or American Indian descent are more likely to be admitted to the hospital after presenting with bronchiolitis.[101,104] Males and younger infants are also more likely to need admission.[105] Other factors that seem to be associated with hospitalization are poverty, household crowding, exposure to environmental tobacco smoke, and day care attendance.[106] Clearly, underlying chronic medical conditions, such as congenital heart disease or chronic lung disease, lead to a more severe course in patients with this disease.

Bronchiolitis is rarely fatal, with an average mortality rate of 2.0 per 100,000 live births in the United States. Low birth weight (<2500 g), low 5-minute Apgar score, high birth order, and young maternal age are all associated with an increased risk of death.[107,108] Breast-feeding, on the other hand, appears to be associated with a less severe clinical course.[109]

Distinguishing Principles of Disease

Etiology

Many viruses are implicated as the underlying cause for bronchiolitis. Respiratory syncytial virus (RSV) is the most common agent identified in children diagnosed with this disease, estimated to cause up to 70% of cases in previously healthy children.[110] Other viruses commonly isolated are parainfluenza, human metapneumovirus, influenza, adenovirus, and rhinovirus.[110–115]

Pathophysiology

Most respiratory viruses that cause bronchiolitis in children are transmitted from one host to another via fomites spread from hand to nose or via droplets produced by sneezing or coughing of respiratory secretions. Shedding of the virus often begins prior to the onset of significant clinical symptoms and can continue for 2 to 3 weeks in an immunocompetent infant. The typical incubation period is 2 to 8 days from the time of initial contact.[116]

In an infected patient, viral replication often begins in the epithelial cells of the upper airway before spreading to the mucosal surfaces of the lower respiratory tract. The infected epithelial cells are generally destroyed via lysis or apoptosis, which results in the desquamation of these cells and release of host inflammatory mediators.[117] Affected lungs demonstrate epithelial cell necrosis, monocytic inflammation and edema of the peribronchial tissues, and mucus and fibrin plugging of the distal airways upon histologic examination. These findings translate into the clinical findings of wheezing and lower airway obstruction in an infant with bronchiolitis. Younger infants, whose distal airways are of smaller caliber and whose immune systems lack active immunity to most respiratory viruses, are prone to more severe clinical symptoms.[106] Severe lower airway obstruction leads to air-trapping and atelectasis, resulting in mismatched ventilation and perfusion and hypoxemia. In addition, younger infants are at increased risk for fatigue, leading to hypercarbia and respiratory failure.

Clinical Features

Patient History

Typically, infants with bronchiolitis are less than 12 months of age and present during the winter months. The first symptoms are generally those of an upper respiratory infection, such as nasal congestion and copious rhinorrhea. This is followed within a few days by development of a tight cough, often associated with difficulty feeding. Some parents will report the presence of audible wheezing as well. A history of fever is common, though not universal, with one study reporting fever in approximately one third of patients admitted with bronchiolitis.[118] Very young infants may present with a history of apnea, and this may precede the onset of typical symptoms of respiratory infection. It is essential to ascertain information regarding the infant's hydration status, including the amount and frequency of oral intake, urine output, vomiting, and diarrhea.

A child's past medical history is important as well. Specifically, comorbidities such as congenital heart disease, chronic lung disease, or prematurity can significantly impact the clinical course of bronchiolitis. A past history or family history of wheezing or atopy may provide clues in differentiating bronchiolitis from asthma, particularly in the older infant. Other elements of the patient history that may be helpful are whether the child attends day care or if there are household contacts with respiratory symptoms.

Physical Examination

As in any pediatric patient, an assessment of vital signs and general appearance is crucial to the evaluation of an infant with bronchiolitis. Common vital sign abnormalities include fever, tachycardia, tachypnea, and hypoxia. Pulse oximetry is noninvasive, inexpensive, and provides objective data regarding the degree of illness of a wheezing child. The oxygen saturation (Sao_2) of any moderately or severely ill infant should be obtained soon after ED arrival as an adjunct to the physical examination. With the use of pulse oximetry, an ABG is generally unnecessary to assess a patient's oxygenation. Thus, the acquisition of an ABG should be reserved for those with severe disease to measure the extent of hypercarbia and respiratory acidosis. Irritability or lethargy may be present, especially in those infants with more severe disease. Nasal flaring and retractions are visible signs of respiratory distress that may be present. Lung auscultation often reveals decreased air movement, rales, rhonchi, wheezing, and an increased ratio of expiratory to inspiratory times. Using these physical examination findings, the clinician may stratify patients into mild, moderate, and severe categories of disease (Table 167-4).

The combination of poor feeding and increased insensible fluid losses often impacts an affected infant's hydration status. A careful assessment of the anterior fontanel, mucous membranes, and skin turgor can assist in determining whether an infant is dehydrated.

Complications

Clinicians caring for children with bronchiolitis need to understand the typical course of the disease, both for their ability to accurately diagnose and manage these patients and to advise parents about the recovery phase. The worst phase of the illness that may necessitate hospitalization generally occurs in the first few days, and median length of hospital stay has been reported to be between 2 and 3 days.[119,120] However, the entire course of illness can last much longer, with a median duration of 12 days.[121] Coughing and noisy breathing, in particular, can last for more than 4 weeks.

Table 167-4 Suggested Bronchiolitis Assessment Tool

	MILD	MODERATE	SEVERE
Feeding	Normal	Less	Poor
Sao_2 in room air	≥95%	92–94%	<92%
Respiratory rate (breaths/min)	<60	60–70	>70
Retractions	None/minimal	Intercostal	Substernal
Accessory muscle use	None	None	Neck or abdominal
Wheeze	None/minimal	Moderate expiratory	Severe inspiratory/expiratory, audible without stethoscope
Air exchange	Good, equal BS	Localized, decreased BS	Multiple areas of decreased BS

BS, breath sounds.

Bacterial acute otitis media (AOM) is the most common condition associated with bronchiolitis, with a prevalence of up to 60%.[122] The bacterial pathogens are similar to those recovered in other children with AOM; thus, it should be treated according to standard recommendations. Other concurrent bacterial infections are rare. In one study of more than 2000 children hospitalized with RSV bronchiolitis, approximately 1% also had a urinary tract infection (UTI).[123] Pathologic bacteremia and meningitis were not found in any of these patients. Similar rates of UTI without bacteremia are found in febrile children with clinical bronchiolitis, with or without documented RSV infection.[124] Infants less than 8 weeks old with fever and bronchiolitis present a unique dilemma for ED clinicians. The rate of serious bacterial infections (SBIs), defined as UTI, bacteremia, bacterial meningitis, or bacterial enteritis, among all febrile infants less than 8 weeks of age is reported to be up to 12%.[125,126] However, in infants with documented RSV infection or clinical bronchiolitis at the time of ED presentation, the rate of SBI is substantially lower.[127,128] In a large, prospective, multicenter study, Levine and colleagues reported that 7% of febrile infants less than 61 days of age who were RSV positive had a concurrent SBI, compared with 12.5% of those who were RSV negative. Of the patients with SBIs, most (82%) had a UTI. Bacteremia was rare and only occurred in infants less than 1 month of age. None of the RSV-positive infants had bacterial meningitis. As a result, most would advocate performing a workup for UTI in febrile infants between 1 and 2 months of age who are known to be RSV positive or have clinical bronchiolitis. Additional testing to obtain cultures of cerebrospinal fluid and blood may be done selectively. Similarly, these infants may not require empiric antibiotic therapy for presumed SBIs. On the other hand, in the first month of life, all febrile infants should undergo testing to evaluate for SBIs and be empirically treated with antibiotics regardless of RSV status.

Apnea is commonly reported in young infants with bronchiolitis, especially those who are admitted for inpatient management. Eight percent of admitted patients have a history of apnea, and nearly 3% will develop apnea during the hospital stay.[129,130] Risk factors for developing in-hospital apnea include age less than 1 month in full-term infants, postconceptional age less than 48 weeks in preterm infants, and a history of apnea prior to admission. The absence of all of these risk factors has a high negative predictive value for the development of in-hospital apnea.[130]

The long-term outcomes after bronchiolitis have also been examined extensively. It is clear that those who experience the disease in infancy have a higher prevalence of lower respiratory diseases, including asthma, in adolescence and adulthood.[131–134] Whether there is a causal relationship remains undetermined.

Differential Considerations

Asthma is the condition that has the most clinical overlap with bronchiolitis. Physical examination findings alone cannot distinguish the two. Younger age, presentation during winter months, antecedent URI symptoms, and the absence of prior or family history of atopic disease and wheezing all suggest bronchiolitis as the cause of wheezing in an individual patient. Some infants will have clinical features consistent with both conditions. For example, a 12-month-old may present in July with a URI and wheezing for the first time. For this child, a clinician may choose to initiate therapy for acute asthma. A complete discussion of other conditions that must be differentiated from bronchiolitis is included earlier in this chapter and in Table 167-1.

Diagnostic Strategies

Bronchiolitis should be diagnosed primarily on the basis of history and physical examination. Viral diagnostic testing can be performed on nasopharyngeal secretions using enzyme-linked immunosorbent assays, indirect fluorescent antibody detection, polymerase chain reaction, or viral culture. Generally, this is not warranted for those patients for whom outpatient management is sufficient. However, identifying a viral respiratory pathogen can be useful in certain situations. For example, if test results can be obtained rapidly, identifying a viral etiology may eliminate the need for further laboratory evaluation for infants who present with fever. In addition, having a specific viral diagnosis can allow for the appropriate cohorting of patients admitted for inpatient management, thus decreasing nosocomial transmission among patients and staff. Providers should exercise contact and droplet precautions until the causative viral agent is identified.

There is tremendous variability in the use of diagnostic imaging; in one series, a CXR was obtained for more than 70% of infants hospitalized with bronchiolitis.[135] In children with clinical findings that are typical for bronchiolitis, however, radiographic imaging is rarely necessary. Hyperinflation, atelectasis, and peribronchial cuffing are the findings most commonly associated with this disease. In ambulatory patients with acute lower respiratory infections, obtaining a CXR does not affect clinical outcome,[136] and this practice has been associated with increased usage of unnecessary antibiotics.[135] Further, the likelihood of a CXR revealing findings inconsistent with the clinical diagnosis of bronchiolitis is less than 1%.[137] Diagnostic imaging may be helpful in patients with severe distress, significant hypoxia, or an atypical presentation or clinical course. In summary, as recommended by the American Academy of Pediatrics (AAP) Subcommittee on Diagnosis and Management of Bronchiolitis, "clinicians should diagnose

bronchiolitis and assess disease severity on the basis of history and physical examination. Clinicians should not routinely order laboratory and radiologic studies for diagnosis."[138]

Management

Therapy

While the diagnosis of bronchiolitis is fairly straightforward, the management of children with the disease often presents clinicians with confusing and controversial dilemmas. The literature is often contradictory, making it difficult to reach a consensus. As a result, there exists wide practice variation in the management of bronchiolitis.[139–141] However, it is clear that a consistent, evidence-based approach to this disease can lead to more efficient and effective care.[130,142–145] Supportive care, such as providing hydration and supplemental oxygen, is the cornerstone of therapy for affected children.[138] A management strategy, stratified by the patient's initial degree of illness, is outlined in Figure 167-2.

SABAs are the treatment of choice for children with wheezing due to asthma. However, the evidence supporting their use in wheezing caused by bronchiolitis is less favorable than for asthma. In a recent meta-analysis of 22 clinical trials, a small short-term benefit in clinical score was observed for children with bronchiolitis treated with SABAs. This treatment had no significant effect on rates or duration of hospitalization. While rare, adverse effects such as tachycardia, decreased oxygen saturation, flushing, and hyperactivity occurred more frequently in children treated with SABAs.[146] Thus, the AAP does not recommend the routine use of SABAs for bronchiolitis; instead, clinicians should consider a trial of such medications to determine if a patient has a positive clinical response.[138]

Similar controversy exists with respect to the utility of nebulized epinephrine in treating bronchiolitis. A meta-analysis of 14 studies concluded that there is not enough evidence to support the use of epinephrine for inpatients, but it does provide some clinical benefit over other bronchodilators and placebo for outpatients.[147] Treatment does not decrease the rate of hospitalization, nor the length of hospital stay.[148] One difficulty with the use of epinephrine in the ED is that it is not a treatment that can be continued at home. Thus, nebulized epinephrine should be considered for children with moderate to severe distress in whom beta-agonist therapy was not effective and who will likely require hospitalization. As with SABAs, nebulized epinephrine should be continued only for those patients who demonstrate a clinical benefit.

Studies on the use of nebulized anticholinergic agents (e.g., ipratropium bromide) have not been conclusive. While one study in the ED setting reported a decreased need for additional treatment for patients receiving an anticholinergic medication in addition to SABAs,[149] a similarly designed ED study found no benefit.[150] There is currently not sufficient evidence to recommend the use of anticholinergic agents for young children with wheezing and suspected bronchiolitis.[151]

Many of the symptoms of bronchiolitis are a result of increased and thickened respiratory secretions. A great deal of literature supports the use of nebulized hypertonic saline in the treatment of cystic fibrosis, in which clearance of thickened secretions is vital.[152–154] Although there is not yet enough literature to definitively recommend its use for bronchiolitis, one recent study suggests that nebulized hypertonic saline is a safe medication that reduces the length of stay for hospitalized children.[155] Chest physiotherapy has also been examined as a means for clearing respiratory secretions. A meta-analysis of three randomized, controlled trials revealed no improvement in clinical score, length of stay, or oxygen requirement after chest physiotherapy.[156]

Systemic corticosteroids are well established as being effective treatment for wheezing due to acute asthma. Despite reports that more than half of infants may be prescribed corticosteroids when diagnosed with bronchiolitis,[141] well-designed controlled trials have demonstrated no benefit for their use in terms of rate of admission, clinical score, or any other outcome.[138,157,158] Specifically, Corneli and colleagues conducted a double-blind, randomized trial comparing oral dexamethasone with placebo in 600 children with acute moderate-to-severe bronchiolitis. The investigators concluded that oral dexamethasone had no significant effect on the rate of hospitalization, respiratory status after 4 hours of observation, or later outcomes, such as length of inpatient stay, repeat medical visits, and adverse events. Inhaled corticosteroids also provide no positive effect on clinical course.[159]

While infants with severe bronchiolitis requiring intensive care and mechanical ventilation frequently have concurrent or secondary bacterial infections,[160] this is an uncommon complication for most children. Despite some reports that clarithromycin may hasten recovery in RSV bronchiolitis,[161] there is no evidence for the routine use of antibiotics for bronchiolitis,

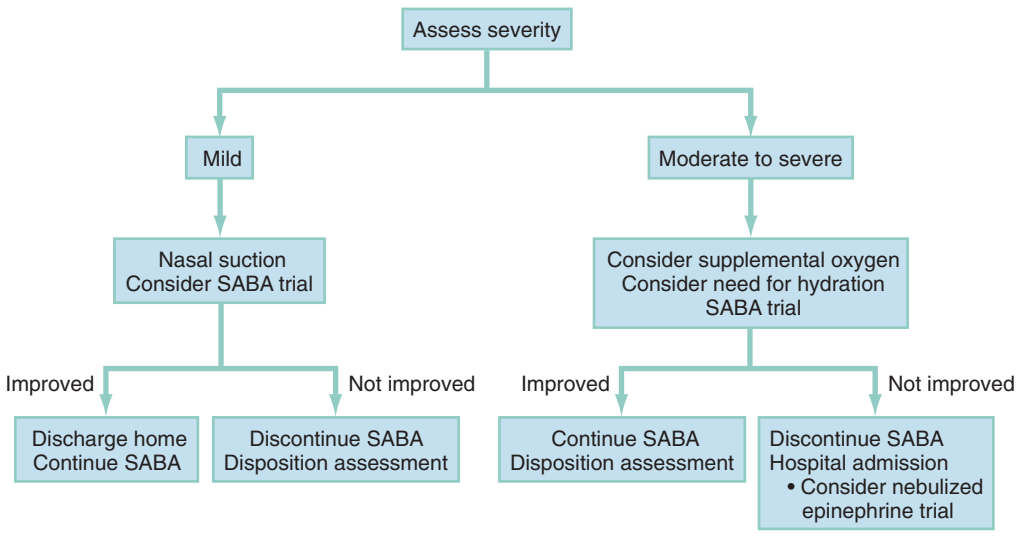


Figure 167-2. Emergency department management of bronchiolitis.

and they should be reserved for patients with true bacterial infections.[138,162]

Ribavirin is a specific antiviral agent directed toward treatment of RSV infections. Several smaller studies suggest a small benefit with respect to duration of mechanical ventilation and length of stay in patients with severe disease.[163] Its high cost and potential risks to caregivers, however, limit its role in routine management. Ribavirin may be indicated in selected cases of documented RSV bronchiolitis with severe respiratory compromise.[138]

Prophylaxis

Though ED clinicians generally do not have a role in administering preventive medications, they should be aware of the options available to their patients. Palivizumab (Synagis) consists of monoclonal antibodies against RSV. While RSV-specific immune globulin is not effective in treating the acute disease process,[164] palivizumab is quite effective in reducing hospitalization rates for RSV in certain high-risk populations.[165–168] It is recommended for most children younger than 24 months with chronic lung disease, congenital heart disease, or prematurity and is administered as a monthly intramuscular injection during the high prevalence months.[169]

Disposition

An essential component in the evaluation and management of bronchiolitis in the ED is the ability to predict the severity of its clinical course. Because it is a dynamic disease, evaluations at a single point in time may not be sufficient to fully estimate its severity; thus, serial examinations are necessary. A number of demographic and clinical features have been associated with a severe clinical course. These factors, which may mandate hospitalization, include age less than 3 months, gestational age less than 34 weeks, ill appearance, hypoxemia (Sao_2 < 95%), tachypnea (>70 breaths/min), and significant atelectasis on CXR (if obtained).[170] Most of the literature, however, focuses on inpatients. In addition to younger age and prematurity, a history of hemodynamically significant congenital heart disease, chronic lung disease, or an immunocompromised state have all been associated with higher morbidity and mortality among inpatients.[138,171,172]

Ultimately, the ED clinician must assess more than just the child's degree of respiratory distress. Patients for whom the respiratory symptoms negatively impact their ability to feed and maintain hydration warrant inpatient admission. Assessing the family's ability to continue supportive measures at home and to seek further medical care if necessary is central to the disposition decision. In children for whom outpatient management is deemed appropriate, expedient follow-up (within 24 hours) with a primary care provider is essential. If SABA therapy provides a sustained clinical improvement in symptoms in the ED, it should be continued as part of home therapy. On the other hand, for the subset of infants who fail to respond to SABA therapy yet meet other criteria for discharge, outpatient treatment with SABAs is not warranted. As in all of pediatric medicine, anticipatory guidance must be provided. Parents should be instructed about the signs of worsening respiratory distress, including poor feeding, retractions, increased tachypnea, lethargy, or irritability; seeking immediate medical care is warranted should these signs occur.

Summary

Bronchiolitis is a common respiratory disease in infancy that accounts for many ED visits and hospitalizations. It is primarily a clinical diagnosis based on key history and physical examination findings. Serious complications, such as apnea, are rare and mostly occur in very young infants or those with underlying medical conditions. Treatment is largely supportive, and the use of nebulized SABAs may be helpful for a subset of patients. Ultimately, ED clinicians must understand the dynamic and variable nature of bronchiolitis and be able to effectively predict the severity of its clinical course.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 168

Pediatric Respiratory Emergencies: Disease of the Lungs

David M. Stocker and Susan Kirelik

PNEUMONIA

Perspective

Background

Acute infections of the respiratory tract are among the most common infections of the human host. Although most of these infections involve the upper respiratory tract, physicians caring for children in the emergency department commonly encounter lower respiratory infections, most notably bronchiolitis and pneumonia. Bronchiolitis is primarily seen in children less then 2 years of age and is defined as wheezing and congestion due to a viral or bacterial lung infection. Pneumonia is an inflammation of the lung tissue and is most often due to an infection but occasionally may follow a noninfectious insult. Although the diagnosis of pneumonia may be suggested by clinical signs and symptoms, pneumonia is diagnosed by an abnormal chest radiograph showing pulmonary infiltrates. The clinical picture of pneumonia is variable and may range from a mild illness to life-threatening disease. Given the multiplicity of agents that can cause pneumonia and the limitations of diagnostic testing, determining a precise etiologic diagnosis may be difficult. Clinical, laboratory, and radiographic findings sometimes suggest a specific organism, but often the etiology remains unclear.

Epidemiology

Infection rates for pneumonia in children vary inversely with age, averaging 40 per 1000 in preschool-aged children and decreasing gradually to 7 per 1000 in 12- to 15-year-olds, with a male predominance of 2:1. Three fourths of all deaths from pneumonia result from bacterial infections.[1]

The causative organisms also vary with the age of the child. Because the organism is not definitively identified in most pneumonia cases, it is difficult to determine the true incidence of the specific etiologic agents.[2] Overall, it has been estimated that viral agents cause 60 to 90% of pneumonias.[3] Viral agents are more common in younger children. Bacteria predominate in neonates but are a less common causative agent in toddlers and older children. Outside of the neonatal period, the incidence of bacterial agents is stable throughout different age groups.[3] Mixed viral and bacterial infections or concomitant bacterial infections may occur in one third of pneumonias.[3–5] *Chlamydia trachomatis* is a unique cause of pneumonia in infants 3 to 19 weeks old. *Bordetella pertussis* classically occurs in children younger than 1 year but also occurs in older children and adolescents.[6,7] *Mycoplasma pneumoniae* is one of the most common causes of pneumonia among children older than 5 years and may play a role in younger children.[5,8] *Chlamydia pneumoniae* is more common in children older than 5 years but also may cause infection in younger children.[8,9]

Among bacteria, group B streptococci and gram-negative bacilli predominate in neonates. *Ureaplasma urealyticum* and *Listeria monocytogenes* may cause illness in infants younger than 3 months.[2] *Streptococcus pneumoniae* is the leading bacterial cause of pneumonia in all age groups beyond the newborn period; *Haemophilus influenzae* and *Staphylococcus aureus* are less common etiologic agents, most often seen in the first years of life. The incidence of *H. influenzae* type B disease has decreased by 90% since the onset of immunization of infants and young children.[10] The heptavalent pneumococcal conjugate vaccine, Prevnar (Lederle Laboratories/Wyeth-Ayerst Pharmaceuticals, Wayne, NJ), was licensed by the U.S. Food and Drug Administration in 2000 and is recommended as a primary series at 2, 4, and 6 months of age, with a fourth booster dose given at 12 to 15 months of age. Clinical trials suggested 85% protection against serotype-specific cases of bacteremic pneumonia.[11] Studies have also shown a decrease in carriage rates of the serotypes included in the day care setting.[12] Pneumococcal polysaccharide vaccines have been recommended for children older than 2 years at high risk for pneumococcal disease since 1985, but they are not immunogenic in younger patients. Pneumococcal vaccine has also been shown to provide some protection against viral pneumonia. One study found a 31% reduction in the incidence of pneumonia associated with seven respiratory viruses in hospitalized children. This may be because viral pneumonia in hospitalized children is often associated with concurrent pneumococcal infection.[13] Other, less common bacterial agents include group A streptococci, *Neisseria meningitidis*, and anaerobic bacteria, the latter being particularly common in the setting of aspiration pneumonia. Unusual causes of pneumonia include *Pseudomonas aeruginosa*, *Legionella pneumophila*, *Pneumocystis carinii*, and rickettsial infections. The incidence of *Mycobacterium tuberculosis* is increasing in the United States, particularly in urban and low-income areas and among nonwhite racial/ethnic groups. Infants and adolescents are at highest risk in the United States.

Respiratory syncytial virus (RSV) and parainfluenza are the most common viral agents in infants younger than 1 year. Viruses that may be responsible for neonatal pneumonia include rubella, cytomegalovirus (CMV), and herpes simplex

virus. Other viral agents include influenza, adenovirus, rhinovirus, enterovirus, measles, varicella, and Epstein-Barr virus. The immunocompromised host is susceptible to all the aforementioned causes of pneumonia and mixed and opportunistic infections, including bacterial, viral (CMV, varicella), protozoan (*P. carinii*), and fungal disease.

Principles of Disease

Pathophysiology

The lung is protected from infection by a variety of local and systemic immune mechanisms. Passively acquired maternal antibodies are important in protection against *S. pneumoniae* and *H. influenzae* infections during the first few months of life. Children with altered protective mechanisms are at increased risk for developing pneumonia; this includes children with congenital anatomic abnormalities (cleft palate, tracheoesophageal fistulas, pulmonary sequestration, congenital cystic adenomatoid malformation), immune deficiencies, neurologic alterations that predispose to aspiration (coma, seizures, cerebral palsy, general anesthesia), and alterations in quality of secreted mucus (cystic fibrosis [CF]).

Bacterial pneumonia and mycoplasmal infections are transmitted most often person to person by droplet aspiration. Asymptomatic upper airway colonization commonly occurs in children and may spread infection to other children.[14] Less commonly, bacterial pneumonia also may result from hematogenous spread from a distant focus or during primary bacteremia. Viral agents that cause pneumonia proliferate in the upper respiratory tract and spread contiguously to involve the lower respiratory tract. Viruses such as varicella, CMV, herpes simplex, Epstein-Barr, measles, and rubella also may infect the lung through hematogenous spread.

Clinical Features

Symptoms and Signs

History. Clinical symptoms and signs of pneumonia in pediatric patients vary with the age of the patient, specific pathogen, and severity of the disease. Infants younger than 3 months generally have respiratory symptoms, such as tachypnea, cough, retractions, and grunting, and nonlocalizing symptoms, including isolated fever or hypothermia, vomiting, poor feeding, irritability, and lethargy. Toddlers with *S. pneumoniae* may have nonspecific symptoms, such as high fever and lethargy, without respiratory symptoms. In general, with increasing age, signs and symptoms in children become more specific and are manifestations of generalized infection, lower respiratory tract disease, and associated extrapulmonary disease, although pneumonia in any child may have only a few or subtle manifestations. General symptoms related to the infection include fever and chills, headache, rigors, and malaise. Symptoms of lower respiratory tract disease may include cough and wheezing. Pleural irritation may cause chest, abdominal, or neck pain or result in neck stiffness. Vomiting or poor oral intake can be seen with pneumonia of any cause and may imply more severe disease or dehydration.

Other important points that should be elicited in the history include birth and immunization history (particularly pneumococcal and *H. influenzae* type B vaccination), sickle cell status, history of previous pneumonia or frequent infections, and presence of underlying chronic disease. Children with known respiratory (e.g., bronchopulmonary dysplasia or CF) or cardiac disease tend to tolerate pneumonia less well; children with primary or acquired immune deficiencies are prone to more severe and fulminant disease from common, uncommon, and opportunistic pathogens.

Physical Examination. Physical examination of a child with suspected pneumonia should begin by noting the general appearance and breathing pattern. Vital signs including oxygen saturation also should be evaluated on arrival. Important findings include toxicity, level of alertness and interaction, color, and state of hydration and perfusion. Fever most often is present with bacterial pneumonia but may be low grade or absent in neonates and patients with nonbacterial disease. Cardiovascular parameters may indicate dehydration or, rarely, shock. Tachypnea, although not universal, is the most sensitive indicator of pneumonia and may be the only manifestation in a young child.[15] The World Health Organization has published guidelines for the clinical diagnosis of pneumonia in developing countries and cites tachypnea and retractions as indicators of lower respiratory disease. Tachypnea is defined by the World Health Organization as a respiratory rate of greater than 50 breaths/min in infants younger than 1 year and greater than 40 breaths/min in children older than 1 year.[16] Other manifestations of lower airway disease may include cough, wheezing, nasal flaring, retractions, grunting, and use of accessory muscles. The characteristics of the cough may aid the diagnosis; a staccato and paroxysmal cough in an infant may indicate pneumonia caused by *C. trachomatis* or *B. pertussis*. A hacking quality is often present with *Mycoplasma* infection. Auscultatory examination of an older child may reveal rales, wheezing, and diminished breath sounds, often with dullness to percussion and associated decreased fremitus. Although these findings may be present, in a younger child the clinical findings are much less consistent; rales may be masked by poor inspiratory effort or noisy upper airway sounds.

Pleural irritation may cause abdominal tenderness or meningismus, and pulmonary hyperinflation may cause downward displacement of the liver and spleen. Extrapulmonary findings may include rhinorrhea, pharyngitis, stridor, or exanthems with viral infections; conjunctivitis with chlamydial disease; pharyngitis and exanthems with mycoplasmal pneumonia; or extrapulmonary infections, such as soft tissue abscesses, otitis media, sinusitis, meningitis, and pericarditis, with bacterial pathogens.

Specific Disorders

Bacterial Pneumonia

Perspective. *S. pneumoniae* is one of the most common bacterial agents causing pneumonia in children.[13] Children at increased risk for developing infection from *S. pneumoniae* are children with immune deficiency, chronic renal disease, or functional or anatomic asplenia, and Native Americans.[11] *S. aureus* pneumonia, although less common, tends to cause a more severe pneumonia, with more than 70% of all cases occurring in the first year of life.[17] Children with foreign body aspiration, immunosuppression, or skin infections may be at increased risk for *S. aureus* pneumonia. Progression of the disease is rapid, and empyema (90%), pneumatocele (50%), pneumothorax (25%), and bacteremia are common complications (Fig. 168-1). Since the mid-1990s, community-acquired methicillin-resistant *S. aureus* has been identified as an agent that may cause pneumonia in children. In contrast to classically described methicillin-resistant *S. aureus*, which is typically broadly resistant and nosocomially acquired, this agent is resistant to fewer antibiotics.[18]

Before widespread immunization, *H. influenzae* was the second most common bacterial cause of pneumonia. However,

Figure 168-1. Radiograph shows staphylococcal pneumonia with empyema and abscess on right. (Courtesy of Brianna Enriquez, MD, and Marianne Gausche-Hill, MD.)

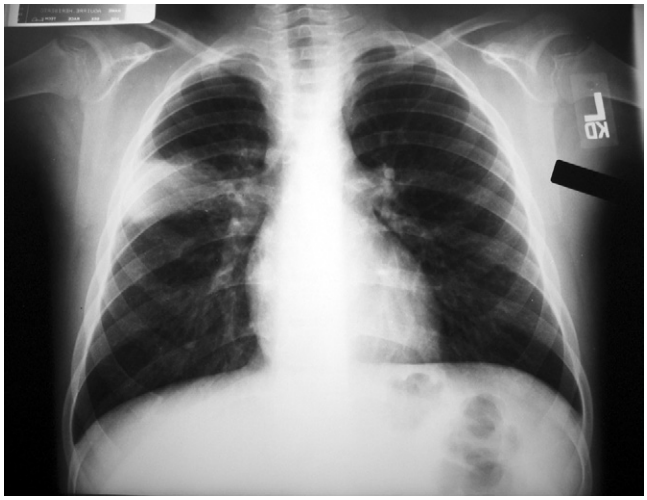


Figure 168-2. Radiograph shows pneumococcal pneumonia with infiltrate in right upper lobe. (Courtesy of Marianne Gausche-Hill, MD.)

its incidence has decreased by 90% since the onset of effective immunization.[10] Although *H. influenzae* previously was considered a disease of younger children, most cases now occur in older children.[19] Although often clinically indistinguishable from *S. pneumoniae, H. influenzae* pneumonia has a higher incidence of associated pleural effusions (25–75%) and bacteremia (75–95%).[20] Other foci of infection are more common and include meningitis, epiglottitis, septic arthritis, pericarditis, soft tissue infection, and otitis media.[20]

Although still uncommon, the incidence of group A streptococcal pneumonia may have increased since the 1980s. One study reported an increase in the incidence from 0.16 per 100,000 in 1992 to 0.35 per 100,000 in 1999 in Canada, whereas another study suggested stable rates since the 1980s.[21,22] Group A streptococcal pneumonia may occur sporadically and may occur as a complication of varicella.[21] It is typically a severe illness with abrupt onset and rapid progression to toxicity and a high fatality rate (30–60% fatality rate reported in a study of all ages).[21]

Clinical Features. Bacterial pneumonia beyond the neonatal period generally has a sudden onset and fever is almost universal (often temperature >39° C). Patients may or may not have a cough and often appear relatively toxic with tachypnea disproportionate to the fever. Confined rales or wheezes and localized decreased or tubular breath sounds commonly occur in older children, although the physical examination in a younger child may be completely unrevealing.

Diagnostic Considerations. Patients with pneumococcal infections often have a preceding dramatic presentation with high white blood cell (WBC) counts with associated pleural effusion and bacteremia in 10 to 30% of children.[23] Radiographic findings may show an alveolar infiltrate in a patchy or consolidated lobar (Fig. 168-2) or subsegmental distribution, although patients with bacterial pneumonia may have an interstitial infiltrate.[24] Bilateral involvement, pleural effusion, pneumatocele, and pneumothorax may occur with more severe disease. Although the WBC count may be normal with bacterial pneumonia, leukocytosis often occurs, sometimes exceeding 20,000/mm^3. Uncomplicated bacterial pneumonia often has a rapid response to institution of appropriate antibiotics; a stagnant or worsening clinical picture should prompt further investigation.

Management. Of particular concern is the emergence of resistance to penicillin and cephalosporins.[25] At this time, it seems that presentation and outcome of otherwise healthy children with pneumonia secondary to resistant pneumococcus may not differ significantly from the outcome of children with pneumonia secondary to penicillin-sensitive pneumococcus.[25–27] Pneumonia caused by *S. pneumoniae* may be complicated by empyema, pleural effusion, lung abscess, or necrotizing pneumonia. Since the 1990s, there seems to have been an increase in the incidence of such complications, with one study noting an increase from 22.6% in 1994 to 53% in 1999 in children hospitalized with pneumococcal pneumonia.[28] It does not seem that this increased incidence is related to intermediate resistant organisms. It is unclear if highly resistant organisms play a role.[28] High-dose amoxicillin is recommended for initial outpatient treatment of suspected pneumococcal pneumonia in children younger than 4 years; a standard dose may be used in older children who are immunocompetent (Table 168-1).

Viral Pneumonia

Viral pneumonia occurs more commonly in the winter and generally has a gradual onset over several days, often with associated cough, coryza, and low-grade fever. Tachypnea may be the only physical finding; however, retractions, rales, and wheezing are common, with grunting, cyanosis, lethargy, dehydration, and apnea apparent in more severely affected children. The diagnosis of viral pneumonia is often made clinically. Rapid antigen testing may be useful in the diagnosis of RSV or influenza A and B. Other viral agents may be diagnosed with culture of nasopharyngeal secretions. Although in the past the use of viral cultures was limited by the time required to grow viruses, improved culture techniques may yield results within 2 days and prove useful in a patient in whom cause needs to be established.

The WBC count is variable but tends to be less than 15,000/mm^3 with lymphocyte predominance. Radiographic findings typically include hyperinflation and peribronchial thickening with diffuse increase in interstitial findings. Patchy areas of consolidation may be present, representing lobular atelectasis or alveolar pneumonia. Although lobar consolidation and small pleural effusions may occur in viral pneumonia, these findings are more consistent with a bacterial cause.

Most viral pneumonias resolve without specific therapy. Because of the likelihood of bacterial superinfection and the

Table 168-1 Antibiotics for Treatment of Pediatric Pneumonia

AGE GROUP	AGENTS	OUTPATIENT TREATMENT	INPATIENT TREATMENT
0–12 wk	Group B *Streptococcus* Gram-negative bacilli (*Listeria monocytogenes*)		Ampicillin + cefotaxime *or* Ceftriaxone*
	Bordetella pertussis or *Chlamydia trachomatis*	Erythromycin estolate	Erythromycin estolate
12 wk to preschool age	*Streptococcus pneumoniae* (*Haemophilus influenzae*, *Staphylococcus aureus*, Group A streptococcus, *Neisseria meningitidis*)	Amoxicillin *or* Amoxicillin-clavulanic acid *or* Cefuroxime axetil *or* Azithromycin *or* Clarithromycin	Cefuroxime *or* Cefotaxime *or* Ceftriaxone *or* Clindamycin
	Mycoplasma pneumoniae or *Chlamydia pneumoniae*	Add erythromycin *or* Azithromycin *or* Clarithromycin	Add erythromycin (IV or PO) *or* Azithromycin (IV or PO) *or* Clarithromycin (PO)
	MRSA or critically ill		Add vancomycin
School age to adolescent	*M. pneumoniae* or *C. pneumoniae*	Erythromycin *or* Azithromycin *or* Clarithromycin *or* Tetracycline (>8 yr old) or fluoroquinolone (>16 yr old)	Cefuroxime *or* Cefotaxime *or* Ceftriaxone *or* Clindamycin *and* Macrolide
	MRSA or critically ill		Add vancomycin

*Ceftriaxone contraindicated in infants <1 month old.
MRSA, methicillin-resistant *Staphylococcus aureus*.

difficulty in differentiating between bacterial and viral pneumonia, antibiotics may be prudent in a more severely ill child. Potential complications include dehydration, local progression of the disease, bronchiolitis obliterans, and apnea (most commonly in the first 3 months of life).[29]

Mycoplasmal Pneumonia

Mycoplasmal pneumonia accounts for 10 to 20% of all pneumonias and was thought to occur most commonly in 5- to 18-year-olds. It is now clear that it also may play a significant role in younger children but is still rare in infants less than 1 year old.[30] Classically the onset is gradual and insidious, but some patients also may present with abrupt onset of symptoms similar to its bacterial counterpart.[5] Prodromal symptoms include fever, headache, and malaise followed several days later by a nonproductive, hacking cough. Patients also may present with pertussis-like illness. Other symptoms of infection may include hoarseness, sore throat, and chest pain; coryza is unusual. Children with mycoplasmal pneumonia generally appear nontoxic. Patients may have rales, with wheezing occurring less often. Pharyngitis, cervical lymphadenopathy, conjunctivitis, and otitis media may occur occasionally. Bullous myringitis, although rare, is believed to be indicative of *Mycoplasma*.[30] Rash is present in 10% of patients and may be urticarial, erythema multiforme, maculopapular, or vesicular.[31] The course may be complicated by pneumatocele, pleural effusion, pneumothorax, or bronchiectasis. *Mycoplasma*, typically thought to be a benign and self-limited infection, has been shown to play a significant role in exacerbating asthma and may cause chronic pulmonary structural abnormalities.[5]

Physical findings generally are less impressive than the radiographic picture; involvement is usually unilateral and in the lower lobes. The radiographic findings are protean, however, and may show lobar consolidation, scattered segmental infiltrates, or interstitial disease. Pleural effusions may occur but are uncommon. The WBC count is usually normal; the erythrocyte sedimentation rate tends to be elevated.

Laboratory diagnosis is problematic. Although used in the past, bedside cold agglutination testing is a poor indication of infection, especially in patients younger than 12 years old, and is rarely used today.[30] Infection often is diagnosed clinically and treated empirically. Diagnosis may be confirmed with acute and convalescent antibody titers; however, patients may take 4 to 6 weeks to seroconvert, and some patients may fail to mount an immune response.[5,31] Culture is not routinely available; polymerase chain reaction diagnosis at this time is available only from research laboratories.[5] Complications are varied but unusual and include hemolytic anemia, myopericarditis, neurologic disease (meningoencephalitis, Guillain-Barré syndrome, transverse myelitis, cranial neuropathy), arthritis, and rash.

Chlamydial Pneumonia

C. trachomatis is a common sexually transmitted infection, causing cervical infection in 2 to 30% of pregnant women.[9] It can be transmitted from the genital tract of infected mothers to their newborn infants, resulting in conjunctivitis in 22 to 44% and pneumonia in 5 to 20%.[9] An infant with pneumonia caused by *C. trachomatis* presents at 3 to 19 weeks of age after colonization with the organism at birth. The illness usually

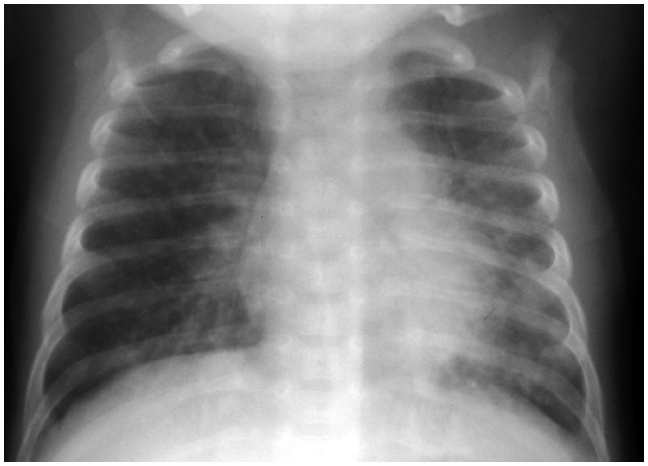


Figure 168-3. Radiograph shows chlamydial pneumonia in an infant. Note the symmetrical interstitial infiltrates. (Courtesy of Michael Diament, MD.)

begins with nasal congestion followed by cough. In half of the cases, conjunctivitis precedes the onset of respiratory symptoms. The infant is often afebrile, alert, and tachypneic, with a repetitive staccato cough. The cough may interfere with feeding or sleeping. It can resemble the paroxysms of pertussis and occasionally precipitates episodes of alarming respiratory distress. Mild retractions and diffuse inspiratory crepitant rales are noted on chest examination, with expiratory wheezing usually absent or minimal. Middle ear abnormalities are present in half of the cases.

The radiograph usually shows hyperinflation with bilateral and symmetrical diffuse interstitial infiltrates (Fig. 168-3). The total WBC count is usually normal but often with an eosinophilia of more than 400/mm^3.[9] Definitive diagnosis is made by isolating the organism in the tissue culture; diagnostic tests based on polymerase chain reaction are more sensitive than fluorescent antibody stain or tissue culture but may not be as specific. Although often a mild illness, chlamydial pneumonia may be complicated by apnea and hypoxemia. Treatment with erythromycin may shorten the course; however, the disease tends to be protracted with cough and tachypnea often requiring weeks to clear.

C. pneumoniae is a species of *Chlamydia* that is antigenically, genetically, and morphologically distinct from other *Chlamydia* species. *C. pneumoniae* infection is readily transmitted from person to person. *C. pneumoniae* may play a role in respiratory tract infections in infants and young children and may cause mild illness or asymptomatic infection in children and adults. As with *Mycoplasma*, *C. pneumoniae* may play a much greater role in pediatric pneumonia than previously thought. It also commonly may be present as a mixed bacterial infection.[5] *C. pneumoniae* has been reported to cause sore throat, fever, headache, pertussis-like cough, pneumonia, and influenza-like illness.[32] Outbreaks have been reported in schools, day care centers, military camps, adolescents, and families.[33] Infection with *C. pneumoniae* can trigger acute episodes of wheezing in children with asthma.

Pertussis

Pertussis, or whooping cough, is a respiratory tract infection seen most commonly in infants younger than 6 months (38% of cases are in children <6 months old, and 71% of cases are in children <5 years old). The incidence of pertussis increased in the 1980s and 1990s, especially in adolescents and adults, despite high immunization rates.[34]

The disease is characterized by three clinical stages: catarrhal stage, paroxysmal stage, and convalescent stage.[13] In infants, the disease begins with mild upper respiratory tract symptoms and cough; this catarrhal stage usually lasts 1 to 2 weeks. The disease progresses to severe paroxysms of a staccato cough followed by post-tussive emesis and may be accompanied by periods of cyanosis and apnea in infants younger than 6 months.[7] Classic whoop is rare, occurring only in 6% of patients, and is generally seen in children older than 2 to 3 years. Fever is often absent, and between paroxysms the examination is remarkably normal. Paroxysms sometimes may be induced on physical examination by gagging the patient. The paroxysmal stage lasts 2 to 4 weeks and is followed by a convalescent stage during which symptoms gradually wane. The duration of the illness in complicated cases may be 6 to 10 weeks.[7]

Immunization is only 80% effective in providing immunity after three doses: Pertussis still must be considered in an immunized infant, although the illness may be mild.[13] The WBC count is usually elevated, exceeding 15,000/mm^3 and occasionally 40,000/mm^3, with a marked lymphocytosis, although this finding may not be present in infants younger than 3 to 6 months old. The chest radiograph may show a "shaggy" right heart border or have clear lung fields. The organism is most easily recovered in the catarrhal or early paroxysmal stages and is rarely found after the fourth week of illness.[13] *B. pertussis* can be cultured from nasopharyngeal secretions. Cultures may be negative during the first week or after the fourth week of illness in immunized patients or patients treated with antibiotics.[13] Direct fluorescent antibody staining may be used, but this test has low specificity and variable sensitivity.[13] Diagnosis made by direct fluorescent antibody should be confirmed by culture.

Polymerase chain reaction may be more sensitive and specific, but availability is variable. Pertussis is a particularly severe disease in the first year of life; complications are common and include apneic episodes, seizures, secondary bacterial pneumonia, encephalopathy, and death. Pertussis has been increasing in incidence among immunized children and young adults who have waning immunity.[6] Adults are believed to be a significant source for the disease within the community. The illness in these patients does not follow the classic stages as described here. These patients have a mild but prolonged course. A dry cough is the predominant symptom, often lasting 3 weeks or more. All children younger than 6 months with presumed pertussis should be observed in the hospital because of the risk of apnea for monitoring and supportive care and should be treated with erythromycin. Other macrolides and trimethoprim-sulfamethoxazole are possible alternatives.[13] Antimicrobials have no effect on the disease progression after the paroxysmal stage is established but may be beneficial because they limit the spread of organism.

Aspiration Pneumonia

Aspiration pneumonia may be due to mechanical, chemical, or bacterial causes. Bacterial aspiration occurs in children with anatomic abnormalities and central nervous system disturbances that impair normal swallowing or protective airway reflexes. Pulmonary damage results from chemical (e.g., stomach acid) and bacterial (gastrointestinal and upper respiratory organisms) insults. Within several hours of the aspiration, the child may have the onset of cough, tachypnea, and fever. Physical examination commonly reveals rales and wheezing with cyanosis as the disease progresses. Radiographic findings include localized (right middle lobe, right lower lobe) and diffuse infiltrates, which are often bilateral.

Children with chronic disease and congenital, acquired, and iatrogenic immune deficiencies are susceptible to the aforementioned respiratory pathogens and to a multitude of opportunistic organisms, including *P. carinii*, CMV, and fungi. Presenting symptoms may be similar to normal hosts; however, the course tends to be more rapid, severe, and fulminant. Rigorous attempts to identify a pathogen are warranted, and patients should be hospitalized for this investigation and to await the results of cultures for monitoring, supportive therapy, and treatment with intravenous antibiotics active against a broad spectrum of organisms. If the patient fails to improve after initial therapy, obtaining tissue for diagnosis of potentially treatable organisms is necessary.

Diagnostic Strategies

Not every child suspected to have pneumonia requires laboratory or radiographic evaluation. A well-appearing child with cough and rales may be diagnosed clinically and treated as an outpatient. A child who appears ill or in whom the diagnosis is unclear requires further evaluation. Young children with high fever and leukocytosis may have an occult pneumonia. A chest radiograph should be considered in these patients.[35]

Laboratory Studies

Any child with pneumonia is at risk for hypoxemia and should have pulse oximetry to determine oxygen saturation. An arterial blood gas study is not needed in most patients but may be considered in a child with severe respiratory distress; it may be useful in following the effectiveness of respiratory status or ventilation. Serum electrolytes, blood urea nitrogen, and creatinine are useful in assessing the degree of dehydration and guiding fluid management when clinically relevant.

Further laboratory studies are obtained only as warranted to help identify the disease process and potential complications. The leukocyte count may be useful in differentiating causes of pneumonia; peripheral WBC counts greater than 15,000/mm^3, with predominance of mature and immature granulocytes, suggest bacterial infection, with pneumococcal pneumonia typically producing the highest WBC counts.[36] Marked leukocytosis and toxic granulation of WBCs also may help identify a child at risk for bacteremia and its potential complications. Normal to elevated WBC counts with lymphocytosis may be seen in viral infections, and eosinophilia suggests chlamydial disease. Increased WBC counts with extreme lymphocytosis typically are associated with pertussis, but this hematologic finding may be absent in infants younger than 6 months. Blood cultures may grow pathogens in only 1 to 10% of cases of bacterial pneumonia. Unfortunately, the contamination rate at most hospitals for cultures is in this range as well. In a well-appearing child with an uncomplicated pneumonia, blood culture is unlikely to be helpful.[2,37] When a blood culture is positive, however, it identifies the specific pathogen and should be considered in an ill patient in whom hospitalization with bacterial pneumonia is likely. Sputum cultures may be useful in adolescents but are technically very difficult and not useful in younger children.[38,39]

Patients with pleural effusions should have lateral decubitus radiographs to assess effusion size and loculation. Computed tomography scan is useful to provide greater detail of effusions and lung abnormalities in critically ill children with complicated pneumonia.[40] Routine computed tomography to establish the diagnosis is not recommended. Patients with significant effusions should have thoracentesis for diagnostic and therapeutic purposes. Although most suggestive of bacterial infection, parapneumonic effusions also occur with mycoplasmal and occasionally with viral infections.[41] The fluid should be sent for Gram stain and culture (anaerobic and aerobic bacterial) and cell count and differential, total protein, pH, and glucose determinations. Interpretation of pleural fluid in children follows adult guidelines (see Chapter 75). Cultures for rare pathogens may be considered if initial assessment is not diagnostic. Bronchoscopy with bronchoalveolar lavage may be useful in a severely ill child.

Nasopharyngeal viral cultures, antigen detection for specific viral or bacterial agents, and serum antibodies for specific agents may be helpful in determining certain etiologic agents. Although most pediatric patients with tuberculosis do not have pulmonary symptoms, skin testing for tuberculosis should be considered for patients with lobar pneumonia, pulmonary effusions, or hilar adenopathy, especially in immunocompromised children or children who have recently immigrated from less developed countries. Acid-fast bacilli often may be shown on an early morning gastric aspirate.[42] Sputum specimens generally are not helpful in a child younger than 8 years because of contamination by organisms of the upper respiratory tract.

Bacterial cultures of upper respiratory secretions are of no value and usually grow either normal flora or organisms that reflect only colonization. Although transtracheal sampling and direct aspiration from the lung may permit a more precise diagnosis, the invasiveness of these tests limits their usefulness. Evaluation of potential additional infectious foci should be guided clinically with particular attention to the meninges, pericardium, epiglottis, soft tissue, and joints to identify the offending pathogen and to delineate the disease process fully.

Radiology

A chest radiograph may be obtained to confirm or rule out an infiltrate. Rarely, a dehydrated child with pneumonia may have a normal study, and once they are rehydrated, the infiltrate becomes readily apparent. The radiograph also may provide clues as to the underlying disease process. Although great variability exists, bacterial pathogens classically produce alveolar infiltrates in a lobar distribution but may produce diffuse interstitial infiltrates.[43] Viral and chlamydial infections tend to appear as diffuse interstitial infiltrates, commonly with hyperinflation and atelectasis. Chest radiographs also identify multilobar disease, pleural effusions, pneumatoceles, and pneumothorax (Fig. 168-4). Hilar adenopathy may indicate tuberculosis or malignancy.

Children without comorbid conditions, who are without fever, unilateral wheezing, or tachypnea, are unlikely to have pneumonia and a chest radiograph is unnecessary. Further, a Cochrane review demonstrated that for non-ill-appearing children with less than 14 days of symptoms and clinical signs of pneumonia, chest radiography does not reduce subsequent hospitalization rate nor duration of symptoms.[44–46] Routine chest radiography is not beneficial in ambulatory children over 2 months with acute lower respiratory infections.[46]

Differential Considerations

The major conditions to be differentiated in children with pneumonia include bacterial pneumonias amenable to conventional antibiotics, viral disease, other unusual infectious causes (mycobacterial, protozoal, fungal), and noninfectious pathologic conditions (Box 168-1). Certain features help differentiate the common infectious causes (Table 168-2). As

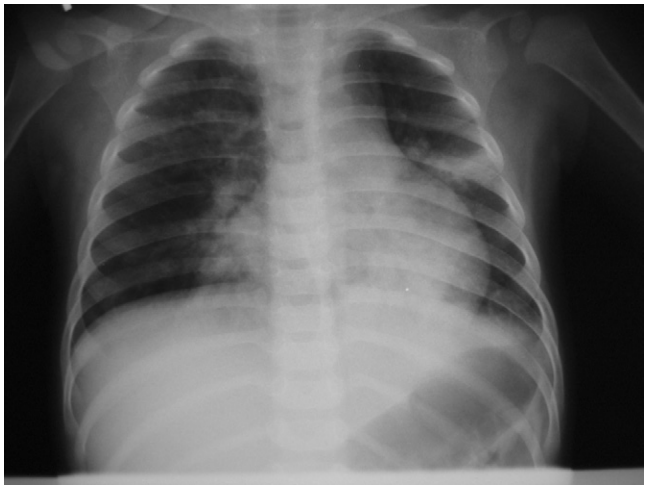


Figure 168-4. Radiograph shows multilobar pneumonia in a child with respiratory distress. (Courtesy of Marianne Gausche-Hill, MD.)

BOX 168-1 NONINFECTIOUS CAUSES THAT MAY PRESENT AS PNEUMONIA

- Radiologic technique
  - Inadequate inspiration
  - Breast shadow
  - Thymus
  - Uneven grid on film
  - Underpenetrated film
- Primary pulmonary
  - Asthma
  - Bronchiectasis
  - Atelectasis
  - Bronchopulmonary dysplasia
  - Cystic fibrosis
  - Pulmonary sequestration
  - Congenital cystic adenomatoid malformation
  - α_1-Antitrypsin deficiency
- Aspiration
  - Foreign body
  - Chemical
  - Recurrent caused by anatomic or physiologic disorders
- Primary cardiac
  - Congenital heart disease
  - Congestive heart failure
- Pulmonary infarction
  - Sickle cell vaso-occlusive crisis
  - Pulmonary embolism
- Collagen vascular disorders
- Acute respiratory distress syndrome
- Pleural effusion
- Neoplasm

From Boyer KM: Nonbacterial pneumonia. In Feigin RD, Cherry JD (eds): Textbook of Pediatric Infectious Diseases, 4th ed. Philadelphia, WB Saunders, 1998, pp 260–273.

detailed previously, each disease entity has certain classic historical, clinical, and laboratory findings. At the extremes of presentation, these diseases can be distinguished easily; however, the broad spectrum of illness for each process may make accurate diagnosis in an individual patient difficult. No specific feature reliably differentiates patients with bacterial infection from children with nonbacterial pneumonia. Because of limitations of reliably detecting bacterial pneumonia by culture technique, one should presume a bacterial cause in a child with a temperature greater than 39° C, clinical toxicity, lobar infiltrate, or pleural effusions. Although it is often difficult to make a precise etiologic diagnosis, consideration of host factors, epidemiology, and the clinical picture with judicious use of laboratory tests generally points the clinician toward the likely diagnosis and allows for effective patient management.

Complications

Several complications of pneumonia result from local and systemic effects of the infection. Pleural effusions or empyemas accumulate most often with bacterial pathogens (notably *S. pneumoniae*, *H. influenzae*, and *S. aureus*) but are occasionally associated with mycoplasmal, viral, and tuberculous pneumonia. An increase in the occurrence of such complications seemed to have occurred in the 1990s for reasons unknown.[47] Similarly, lung abscess, pneumatocele, and pneumothorax are local complications primarily seen with bacterial disease, particularly with *S. aureus*. Extensive pulmonary involvement of any cause may lead occasionally to hypoxia and progressive respiratory failure with multiple organ failure. Apnea without other symptoms is seen most often in viral, chlamydial, and pertussis infections in infants younger than 3 months. The most common systemic complication of pneumonia is dehydration, which occurs as a result of decreased intake from malaise and excessive respiratory effort and increased losses of fluid caused by vomiting, fever, and tachypnea. Another systemic complication of bacterial disease is the development of additional infectious foci resulting from bacteremia (e.g., meningitis, epiglottitis, pericarditis, septic arthritis, and soft tissue infections). Mycoplasmal pneumonia rarely is associated with meningitis, encephalitis, arthritis, and hemolytic anemia.

Management and Disposition

Infants Less Than 2 Months of Age

Treatment of pneumonia in a pediatric patient consists of appropriate antimicrobial use and supportive therapy (see Table 168-1). Because of the difficulty in identifying an etiologic agent, antibiotic choice is generally empirical. The three most important factors in directing management are the patient's age, likely pathogen, and degree of illness. An infant younger than 2 months with pneumonia should be admitted to the hospital. This age group is immunologically immature, and signs of sepsis may be subtle. Blood, urine, and cerebrospinal fluid cultures generally are indicated before initiation of antibiotics.

Infants 2 to 3 Months of Age

In an infant 2 to 3 months old, blood and urine cultures are appropriate. The decision to perform a lumbar puncture depends on clinical suspicion of central nervous system infection. Ampicillin plus an aminoglycoside or ampicillin and a third-generation cephalosporin would be appropriate initial antibiotic choices for an infant younger than 1 month (although ceftriaxone is contraindicated in infants <1 month old). Ampicillin and a third-generation cephalosporin are reasonable for an infant 1 to 3 months old. If *C. trachomatis* or *B. pertussis* is suspected, the infant also should be treated with erythromycin after appropriate diagnostic samples have been obtained; other macrolides or sulfonamides (trimethoprim-sulfamethoxazole)

Table 168-2 Pneumonia Syndromes

	BACTERIAL	VIRAL	*CHLAMYDIA*	*MYCOPLASMA*
Historical				
Age	Any	Any	4–16 wk	5–18 yr
Fever	High (>39° C)	Low grade	Usually none	Low
Onset	Abrupt, often after upper respiratory infection	Gradual	Gradual	Gradual
Cough	Productive	Nonproductive	Staccato	Hacking
Associated symptoms	Chest pain Focal infarct	Myalgias Rash Sore throat Coryza	Conjunctivitis	Headache Sore throat Rash
Physical	Toxic appearance			
Lungs	Confined rales	Diffuse rales Wheeze Stridor	Diffuse rales Rare wheeze	Unilateral rales
Chest radiograph				
Infiltrate	Lobar or segmental	Interstitial	Diffuse Interstitial	Lobar or diffuse
Pleural effusion	Occasional	Rare	None	Rare
Other	Pneumatocele Abscess	Hyperinflation Atelectasis	Hyperinflation	
Laboratory	Increased WBC granulocytosis	Normal or increased WBC count Lymphocytosis	Normal WBC count Eosinophilia	Normal WBC count
Pathogens (common)	*Streptococcus pneumoniae* *Haemophilus influenzae* *Staphylococcus aureus* <2 mo: Group B *Streptococcus* Gram-negative enterics *Listeria monocytogenes*	RSV Parainfluenza Influenza Adenovirus Enterovirus	*Chlamydia trachomatis*	*Mycoplasma pneumoniae*

RSV, respiratory syncytial virus; WBC, white blood cell.

may be an alternative in older infants and children.[13] Supportive therapy in this age group consists of fever control and intravenous hydration. A trial of inhaled beta-agonists may be indicated if the patient is wheezing or in significant respiratory distress; supplemental oxygen and respiratory support should be provided as needed. All infants should be monitored with continuous pulse oximetry because apnea and respiratory failure may be precipitous.

Infants and Children Greater Than 3 Months of Age

An older child with pneumonia should be categorized into likely bacterial, viral, or mycoplasmal disease if possible. Because no single pathognomonic test exists to differentiate bacterial from viral infection, the physician must base the presumptive etiologic diagnosis on clinical, radiographic, and laboratory findings. Although the categorization is not always clear, a toxic child with high fever, lobar consolidation, and leukocytosis is likely to have a bacterial process, whereas a child with a disease of gradual onset, low-grade fever, and interstitial infiltrate with air trapping is more likely to have a viral process.

If a viral agent is suspected and the child is not ill, antibiotics may be withheld. Uncomplicated bacterial pneumonia in immunocompetent children is safe to treat as an outpatient disease. A well-appearing infant or preschool-aged child with isolated pneumonia may be treated with oral antibiotics on an outpatient basis. In an infant beyond the neonatal period or a preschool-aged child, amoxicillin and amoxicillin-clavulanic acid are considered appropriate first-line agents. Cefuroxime axetil or high-dose amoxicillin (80–100 mg/kg/day) may be used when resistant *S. pneumoniae* is suspected. Azithromycin or clarithromycin also are considered appropriate first-line oral agents in this age group by some researchers.[2,39] One study of the treatment of pediatric community-acquired pneumonia showed no difference in clinical cure rate when azithromycin, erythromycin estolate, and amoxicillin-clavulanic acid were compared.[48] A macrolide is the first-line antibiotic choice in a school-aged child or adolescent in whom *M. pneumoniae* and *C. pneumoniae* are more common. Every child with bacterial pneumonia treated as an outpatient should be reevaluated within 24 to 48 hours. Patients who are not afebrile, clinically improved, and well hydrated should be evaluated at this time for possible admission to the hospital for parenteral antibiotic therapy. For patients in whom signs of bacteremia are present, a single dose of intramuscular ceftriaxone followed by outpatient oral therapy is recommended. In these cases, close follow-up monitoring is crucial.

For a patient who is admitted to the hospital, intravenous therapy with cefuroxime, cefotaxime, or ceftriaxone is appropriate. Addition of a macrolide should be considered if *M. pneumoniae* is a possible etiologic agent. Vancomycin should be added if methicillin-resistant *S. aureus* is suspected.[27] If an organism has been identified, an antibiotic with a more specific spectrum might be indicated.

Since the 1980s, *S. pneumoniae* has been developing increasing resistance to penicillin and other antibiotics; in general, this has not been clinically relevant because higher doses overcome the relative resistance. Clinical outcomes with intermediate resistance levels seem to be unchanged.[49] These patients

still respond to penicillin and the cephalosporins at higher doses. If the patient does not respond clinically after a trial of these agents or if the patient is critically ill, use of vancomycin with or without rifampin is recommended.[50]

Supportive therapy includes hydration and fever control with antipyretics. Appropriate laboratory testing should be performed to attempt identification of more virulent pathogens. The child should be examined for development of an additional infectious focus, and a repeat radiograph may be considered to determine spread or development of a pleural effusion.

Indications for hospitalization at the time of diagnosis include toxic appearance, vomiting or dehydration, respiratory compromise (distress, hypoxia, or inadequate ventilation), multilobar disease, pleural effusions, impaired immune function, and unstable social environments. Strong consideration should be given to hospitalizing children younger than 6 months because they are less tolerant of bacterial pneumonia than are older children. Supportive therapy for the inpatient should include maintenance of fluid and electrolyte balance and fever control, supplemental oxygen, inhaled bronchodilators, ventilatory assistance, and pleural fluid drainage as indicated. Parenteral antibiotic therapy should be administered until clinical improvement occurs. Other factors that influence duration of parenteral antibiotic treatment include the age of the patient, specific pathogen, presence of bacteremia, and any additional infectious foci.

A trial of bronchodilators may be worthwhile (aerosolized beta$_2$-adrenergic agent) even in the absence of wheezing and always should be considered in a patient with respiratory distress. Although this treatment is not always successful, if the child responds with diminished wheezing, improved aeration, or reduced work of breathing, one may continue with nebulized bronchodilators.

Children with neurologic or anatomic abnormalities who aspirate oral or gastric contents are susceptible to pneumonia predominantly from anaerobes. Penicillin and clindamycin are appropriate first-line antibiotic choices. In seriously ill patients, agents such as chloramphenicol, metronidazole, and cefoxitin may be more useful. Nosocomial infections should be treated with antibiotics also active against aerobes and gram-negative bacilli. Children with significant aspiration should be admitted to the hospital, and supportive therapy should include hydration, supplemental oxygen, oropharyngeal suctioning, and intubation of the trachea if airway reflexes are impaired or respiratory failure is manifest.

Long-term management of a child with pneumonia should include a clinical reevaluation 2 to 3 weeks after diagnosis. If the child had a prompt response to therapy and is entirely well at follow-up evaluation with a normal physical examination, a repeat radiograph is unnecessary.[51] If the child has undergone a complicated disease course (e.g., pleural effusion), has residual symptoms, or manifests any abnormality on examination, or if the illness is not the child's first episode of pneumonia, a chest radiograph should be obtained to ensure complete resolution of the disease. The follow-up radiograph should be performed 6 to 8 weeks after diagnosis.

In managing a child with pneumonia, it is essential to consider the age and clinical presentation of the child in delineating specific etiologic agents. Common pathogens may be treated as an outpatient disease in nontoxic patients; infants and children who exhibit some respiratory compromise may require parenteral antibiotics, support, and hospitalization. Over the past several years, the patterns of etiologic organisms have been changing. The spectrum of antimicrobial sensitivities also has changed, particularly with the emergence of penicillin-resistant *S. pneumoniae*. Repeat chest radiographs are indicated in children who fail a course of treatment; immunocompetent patients that respond to therapy may be followed clinically and a repeat chest radiograph is not necessary to document cure.

OTHER RESPIRATORY EMERGENCIES

Cystic Fibrosis

Perspective

Cystic fibrosis is an autosomal-recessive disease caused by a mutation in the CF transmembrane conductance regulator *(CTFR)* gene. In whites, approximately 1 in 25 is a carrier, and the disease has an incidence of 1 in 2500 births.[52] The disease also is present (in decreasing incidence) in Hispanics, Native Americans, African Americans, and Asians. Progressive lung disease and infection account for most of the morbidity and nearly all of the mortality in CF. Defects in chloride transport across the airway epithelium result in reduced ciliary clearance of thickened mucus, decreased antimicrobial effect of the airway surface, increased bacterial adherence, and innate secretion of inflammatory cytokines. All of these factors result in a unique sensitivity to bacterial infection of the airway.[53,54]

Diagnostic Strategies

Chest radiograph findings of CF include emphysema, peribronchial thickening, bronchiectasis, and focal infiltration, which may be linear or nodular in nature (Fig. 168-5). Crucial to the effective treatment of pulmonary infections in CF patients is the identification of pathogens involved, usually through sputum culture. Early childhood pneumonias in patients with CF are predominantly caused by *S. aureus* and *H. influenzae*.

Management

With the emergence of methicillin-resistant *S. aureus*, careful attention should be paid to antibiotic coverage. Patients on antistaphylococcal prophylaxis may be at increased risk for pseudomonal infections.[52] There is emerging evidence that CF patients also are at increased risk for hospitalization by nonbacterial pathogens.[55]

By 18 years of age, 80% of patients are colonized with *P. aeruginosa*. When colonization is established, it is generally considered permanent.[56] Acute infective exacerbations generally are managed by oral and intravenous antimicrobial drugs, typically a penicillin (e.g., ticarcillin or piperacillin) or ceftazidime combined with an aminoglycoside for purposes of synergy.[6] If a patient's previous sputum culture is available, care should be taken to ensure coverage of the last known bacterial pathogens. Resistant strains may benefit from imipenem or meropenem. Patients routinely are hospitalized for 10 to 14 days for the course of therapy.[52]

Burkholderia cepacia, a significant pathogen in CF patients, has been associated with an accelerated decline in clinical status and increased mortality. Generally, antimicrobial coverage is similar to that for *Pseudomonas*. Resistance is common, however, and the existence of differing colonization and resistance patterns of patients with CF necessitates respiratory isolation from other susceptible individuals.[57]

Clearance of thick mucoid secretions is vital for treatment. Patients may respond favorably to bronchodilator therapy and to mucolytics, such as inhaled *N*-acetyl cysteine, in the acute setting.[58] Chest physiotherapy often is provided by a

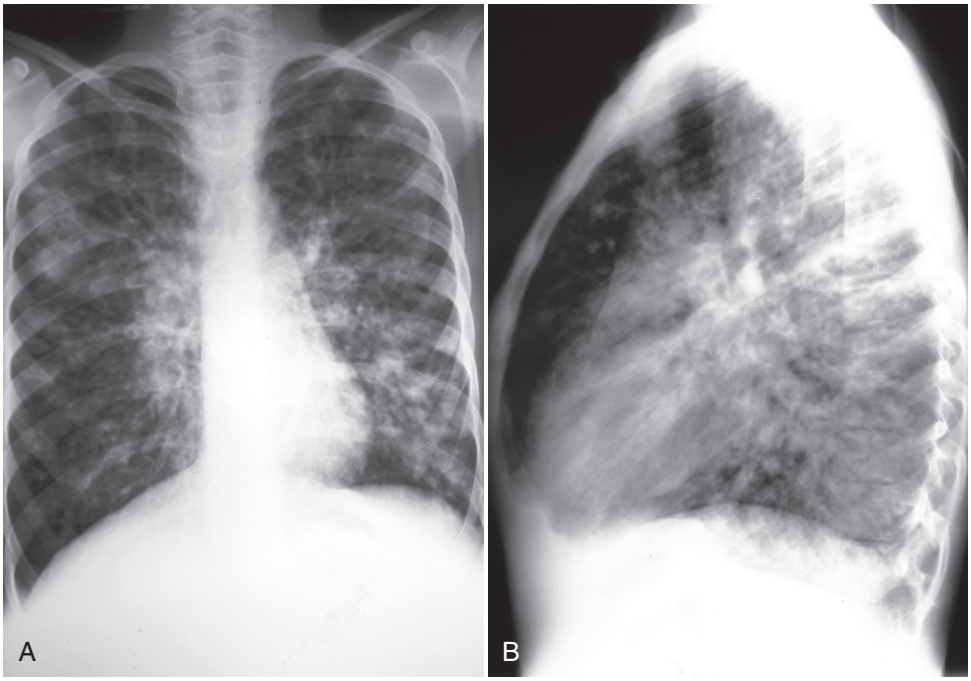


Figure 168-5. Posteroanterior **(A)** and lateral **(B)** radiographs of a teenager with cystic fibrosis. Note emphysema and nodular infiltrates. (Courtesy of Michael Diament, MD.)

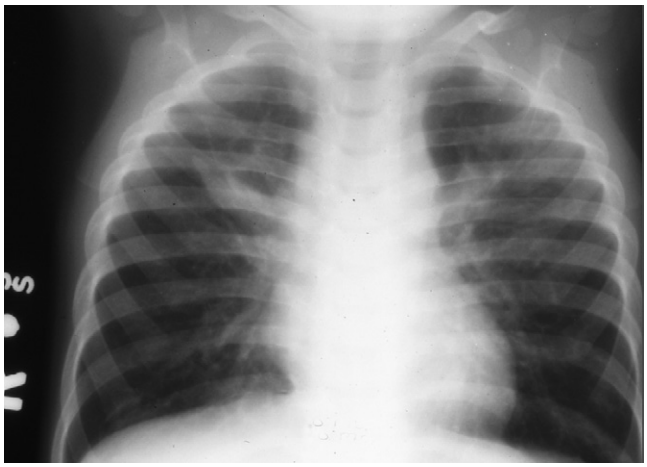


Figure 168-6. Radiograph of a child with bronchopulmonary dysplasia shows findings of chronic lung disease and hyperinflation. (Courtesy of Michael Diament, MD.)

high-frequency oscillator device. A flutter valve or a positive expiratory pressure mask also may be of assistance for improved mucoid clearance. Short-term control of inflammation may be obtained by inhaled corticosteroids.[59]

Chronic Lung Disease

Chronic lung disease (CLD) of infancy, also called *bronchopulmonary dysplasia*, is extremely common in premature infants and affects 40% of children with a birth weight of less than 1000 g.[60] The severity of disease is related to several factors, including degree of prematurity, use of peripartum steroids, damage incurred by ventilation in the neonatal period, and nutritional status.[61] Infants with CLD have greatly increased rates of hospitalization because of respiratory illness in the first year of life, approaching 65% in infants born weighing less than 1000 g.[62]

Immunizations are vital to the prevention of pneumonia in patients with CLD. All infants 6 to 23 months old should receive the influenza vaccine during the appropriate season. The heptavalent pneumococcal vaccine (Prevnar) and *H. influenzae* type B vaccine are especially vital for prevention of bacterial pneumonia.[63] In addition, monthly prophylaxis against RSV is administered to carefully selected patients with the monoclonal immunoglobulin palivizumab, which reduces the incidence of RSV disease and risk of subsequent hospitalization.[13,64]

Patients with CLD have increased airway resistance, decreased lung compliance, and obstructive lung disease. Pneumonia in patients with CLD may be complicated by a reactive airway component. Radiographs show marked hyperinflation and infiltrates if complicated by pneumonia (Fig. 168-6). Inhaled bronchodilators may be efficacious, although these medications may worsen air exchange in patients with concomitant airway malacia. Hypoxia and hypercarbia are common, despite an increased respiratory effort. Patients with severe CLD may be receiving long-term diuretic therapy to improve lung mechanics; care should be taken not to confuse pneumonia with cor pulmonale, which is especially prevalent in younger infants with chronic supplemental oxygen requirements.[60]

KEY CONCEPTS

- It may be difficult to determine the etiologic agent for pneumonia by clinical presentation, radiographic findings, or laboratory studies. Mixed infections occur commonly.
- Infants and younger children with pneumonia may have subtle or nonspecific signs and symptoms on presentation.
- Pertussis should be considered in a young infant with a lower respiratory tract infection, staccato cough, or episodes of cyanosis.
- *M. pneumoniae* and *C. pneumoniae* may play a role in pneumonia in a younger child.
- In patients with CF, defects in chloride transport across the airway epithelium result in reduced ciliary clearance of thickened mucus, which results in increased likelihood for pneumonia, especially those caused by *P. aeruginosa*.
- CF may respond favorably to bronchodilator therapy and to mucolytics, such as inhaled *N*-acetyl cysteine.
- Patients with CLD have increased airway resistance, decreased lung compliance, and obstructive lung disease; reactive airway disease and pneumonia are common in these patients.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 169 Cardiac Disorders

Alson S. Inaba and Timothy Horeczko

PERSPECTIVE

Pediatric cardiac disease has typically been divided into congenital and acquired disorders, with a further subdivision of the congenital heart disorders into cyanotic and acyanotic lesions. From a purely clinical standpoint, however, children with cardiac disorders present to the emergency department in one of two scenarios. In the first scenario, the child has signs and symptoms that may represent an exacerbation or complication of an already known underlying cardiac disorder. In cases with a known underlying cardiac disorder, early consultation with the child's cardiologist, along with comparisons of the child's previous and most recent diagnostic cardiac studies such as chest radiographs, electrocardiograms (ECGs), and echocardiograms, would also be extremely useful in the evaluation and management phases.

The second scenario represents more of a challenge to the emergency physician: the child with an undiagnosed congenital or acquired cardiac disorder who presents to the emergency department with nonspecific or concerning signs and symptoms (Box 169-1). This chapter focuses on some of the more common and life-threatening cardiac disorders in infants and children who present to the emergency department, with an emphasis on rapid evaluation, stabilization, and management of these disorders.

PRINCIPLES OF DISEASE

Fetal and Neonatal Circulation

Some of the key features of the fetal circulation that differ from that of a child are the presence of the ductus venosus, ductus arteriosus, and a patent foramen ovale. During fetal development, oxygenation of the fetal circulation bypasses the fetal lungs and is accomplished via the placenta. Blood that is oxygenated by the placenta flows to the fetus via the umbilical vein, bypasses the fetal liver via the ductus venosus, and returns to the fetal heart via the inferior vena cava. Blood returning from the inferior vena cava then enters the right atrium and is preferentially shunted across to the left atrium via the patent foramen ovale (Fig. 169-1). The blood in the left atrium is then pumped out of the aorta via the left ventricle. The oxygenated blood that is ejected through the ascending aorta is preferentially directed to the fetal coronary and cerebral circulations.

Deoxygenated blood that returns to the right atrium via the superior vena cava crosses the tricuspid valve and is pumped into the fetal pulmonary artery via the right ventricle. Since the fetal pulmonary vascular resistance (PVR) is higher than the fetal systemic vascular resistance (SVR), this deoxygenated blood bypasses the nonoxygenated fetal lungs via the patent ductus arteriosus (see Fig. 169-1). The poorly oxygenated blood enters the aorta via the patent ductus arteriosus and then mixes with the well-oxygenated blood in the descending aorta. The mixed blood in the descending aorta then returns to the placenta for oxygenation via the two umbilical arteries.

Once the infant is delivered and the umbilical cord is cut, expansion and aeration of the lungs causes a decrease in PVR, with a concomitant increase in pulmonary blood flow. Increased oxygenation causes a physiologic closure of the umbilical arteries, umbilical vein, ductus venosus, and ductus arteriosus. An increase in the pulmonary blood flow to the infant's left atrium also promotes closure of the foramen ovale. Complete anatomic closure of the foramen ovale does not occur until about 3 months of age. Although the ductus arteriosus functionally closes at about 10 to 15 hours of life, complete anatomic closure does not occur until about 2 to 3 weeks of life.

In the absence of any congenital cardiac defects, these transitional circulatory changes pose no physiologic problems to the infant. However, closure of the ductus arteriosus can pose life-threatening complications in neonates with specific congenital cardiac defects that are dependent on the patency of the ductus arteriosus for survival.

Pathophysiology of Cardiovascular Compensatory Responses

There are two fundamental and clinically useful physiologic formulas to keep in mind during the clinical assessment and management of cardiac disorders:

$$\text{Cardiac Output} = (\text{Stroke Volume}) \times (\text{Heart Rate})$$

$$\text{Blood Pressure} = (\text{Cardiac Output}) \times (\text{SVR})$$

The young myocardium is inefficient and unable to increase its contractility in response to demand.[1] When more cardiac output is needed, infants and children respond with an increase in heart rate. Therefore, bradycardia in infants and young children is an ominous sign that connotes a severely compromised cardiac output. Children develop the adult capacity to increase their stroke volume to improve overall cardiac output by 8 to 10 years of age.[2]

BOX 169-1 COMMON PRESENTING SIGNS AND SYMPTOMS OF CARDIAC DISORDERS IN INFANTS AND CHILDREN

- General
  - Fussiness
  - Lethargy
  - Poor feeding (with or without associated diaphoresis)
  - Poor growth
- Respiratory
  - Respiratory distress
  - Wheezing
  - Apnea
- Cardiovascular
  - Tachycardia
  - Shock
  - Paleness
  - Mottling
  - Cyanosis
  - Palpitations
  - Chest pain
  - Syncope
  - Various dysrhythmias

Based on the first physiologic formula, as stroke volume decreases, a compensatory increase in the heart rate will be necessary to preserve a normal cardiac output. A decrease in stroke volume can be produced by a weak "pump," decreased volume in the circulation, or both. The most common cause of decreased stroke volume in children is hypovolemia due to dehydration. Other causes of decreased stroke volume in children may be responsible (Box 169-2). Thus, tachycardia is the first compensatory cardiovascular response when the stroke volume is decreased. If tachycardia alone is not enough to maintain a normal cardiac output, the next compensatory physiologic mechanism to preserve perfusion is an increase in the SVR. This increase in SVR is exhibited as an increase in the diastolic blood pressure, which in turn accounts for a narrowed pulse pressure. The clinical examination of the extremities of a child with an increased SVR includes pallor, mottling, cool skin, a delayed capillary refill time (>2 seconds), and weak or thready distal pulses.

Pathophysiology of Cyanosis

Perspective

Cyanosis is a clinical sign caused by the presence of deoxygenated blood in the capillary beds, most readily observed in the mucous membranes, conjunctiva, nail beds, and skin. The presence of cyanosis usually means that there are at least 4 to 5 g/dL of deoxyhemoglobin in the blood, which correlates to an oxygen saturation of about 80 to 85%.[3] Pathophysiologically, central cyanosis results from a decrease in pulmonary ventilation/oxygenation, a decrease in pulmonary perfusion, shunting of deoxygenated blood directly into the systemic circulation, or the presence of abnormal hemoglobin. Cyanosis in the neonate can be due to a variety of cardiac, pulmonary, or hematologic causes. Cardiac causes of cyanosis include congenital lesions with right-to-left shunts as well as cardiac lesions with decreased or increased pulmonary blood flow. Common pulmonary causes of cyanosis include bronchiolitis, pneumonia, and pulmonary edema. Methemoglobinemia can be one of the hematologic causes of cyanosis.

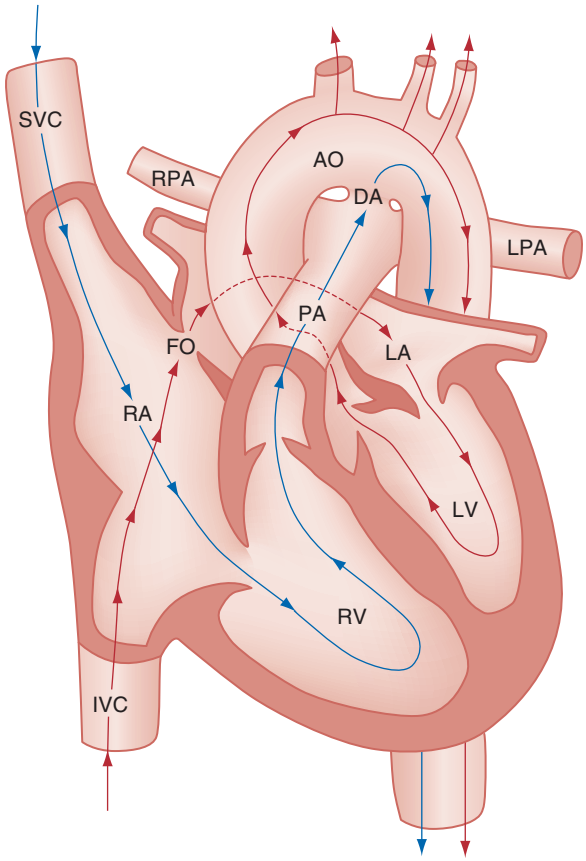


Figure 169-1. Normal intracardiac fetal circulation: Physiologic shunting through the patent foramen ovale (FO) and the patent ductus arteriosus (DA). Oxygenated blood from the placenta *(red arrows)* reaches the right atrium (RA) via the inferior vena cava (IVC). This well-oxygenated blood is preferentially shunted from the RA across to the left atrium (LA) through the FO and is then ejected out the left ventricle (LV) to the ascending aorta (AO). Deoxygenated blood *(blue arrows)* returning from the superior vena cava (SVC) preferentially travels from the RA into the right ventricle (RV) and then out through the main pulmonary artery (PA). Because of the high pulmonary vascular resistance in the fetal lungs, this deoxygenated blood bypasses lungs and enters the descending aorta via the DA. Thus, the areas of the fetal body that are perfused by arteries proximal to the DA receive well-oxygenated blood, whereas those areas of the body that are perfused by arteries distal to the DA receive blood with a mixed oxygenation. LPA, left pulmonary artery; RPA, right pulmonary artery.

BOX 169-2 ETIOLOGIES OF DECREASED STROKE VOLUME IN INFANTS AND CHILDREN

- Hypovolemia (most commonly secondary to dehydration)
- Congestive heart failure (acquired or secondary to underlying congenital cardiac defects)
- Myocarditis
- Hypertrophic cardiomyopathy with decreased diastolic filling
- Dilated cardiomyopathy with decreased systolic ejection
- Pericarditis or pericardial effusion with cardiac tamponade
- Tachydysrhythmias with decreased diastolic filling times

Clinical Features of Cyanosis

The region of the body that is cyanotic can provide important clinical clues as to the cause of the cyanosis. Central cyanosis involves the lips, tongue, and mucous membranes, whereas peripheral cyanosis (acrocyanosis) involves the hands and feet. Acrocyanosis is a common phenomenon in neonates caused by

Table 169-1 Clinical Clues to Help Distinguish between Cardiac and Pulmonary Etiologies of Central Cyanosis

	CARDIAC ETIOLOGY	PULMONARY ETIOLOGY
Respiratory status	May be "comfortably blue"	Respiratory distress
Response to crying	Worsening cyanosis	Improved cyanosis
Response to oxygen	Minimal to no improvement	Improvement with oxygen

Cyanosis due to severe pulmonary disease (e.g., severe pneumonia, tension pneumothorax, acute chest syndrome of sickle cell disease) may not show significant improvement with supplemental oxygen, but these children will also typically exhibit severe respiratory distress along with clinical cyanosis.

cold stress and peripheral vasoconstriction. Central cyanosis reflects a pathologic origin and is an ominous sign. Infants with cyanosis secondary to a congenital heart defect may not exhibit as much respiratory distress as compared with the infant with cyanosis due to a pulmonary cause. Thus, a cardiac cause for central cyanosis may be more likely than a purely pulmonary cause in the child who appears "comfortably blue." Another important clinical clue to the cause of central cyanosis is that cyanosis of cardiac origin usually worsens with crying, whereas cyanosis due to a pulmonary cause may improve when the infant cries.[4] Cyanotic congenital heart defects with right-to-left shunting will demonstrate a minimal improvement with supplemental oxygen, whereas cyanosis of a purely pulmonary origin typically exhibits a significant improvement with supplemental oxygen (Table 169-1).

CLINICAL FEATURES AND DIAGNOSTIC STRATEGIES: THE CARDIAC EVALUATION

The key elements that should be elicited in the history of a child with a known underlying cardiac disorder are listed in Box 169-3. Early consultation with the child's cardiologist or cardiac surgeon is extremely useful. The other important points to cover in the history of a child with a potential or suspected cardiac disorder are addressed in the subsequent sections of this chapter.

In addition to a well-focused history and physical examination, a chest radiograph and an ECG should be obtained on any child with a known or suspected cardiac disorder. Other ancillary studies that can also be useful include an arterial blood gas analysis, hemoglobin/hematocrit levels, digoxin levels in those patients on daily digoxin, serum electrolytes in those patients on daily diuretic therapy, and the 100% oxygen (hyperoxia) challenge.

History

The presence of certain maternal medical conditions have been associated with a higher incidence of cardiac disorders. For example, congenital heart blocks have been associated with maternal systemic lupus erythematosus and other collagen vascular disorders; infants of diabetic mothers have a higher incidence of cardiomyopathy.

Infants with an underlying congenital heart disorder may exhibit diaphoresis during feeds and poor weight gain secondary to congestive heart failure (CHF). The cause of the infant's hypoxia—cardiac or pulmonary—may be ascertained by the age at onset and the events surrounding a change in color. For example, an infant who sweats during feeding may exhibit a splanchnic steal from anomalous coronary arteries, causing transient ischemia, pain, color change, and diaphoresis that resolve after eating.[1] A child with an undiagnosed congenital heart defect may take longer to feed, frequently pausing to catch his or her breath, with subsequent poor weight gain and gradually increased work of breathing due to developing CHF and pulmonary edema. Respiratory tract infections are common during childhood and may cause an acute deterioration in a child with an underlying cardiac disorder. In turn, children with congenital heart disease (CHD) with large left-to-right shunts and increased pulmonary blood flow tend to have a higher incidence of lower respiratory tract infections. Acute respiratory distress in these patients may be from a combination of pulmonary and cardiac factors (e.g., CHF).

BOX 169-3 KEY ELEMENTS TO ELICIT IN THE HISTORY OF A CHILD WITH A KNOWN CARDIAC DISORDER

- Cardiac diagnosis
  - Congenital or acquired disorder?
  - Any episodes of previous decompensation (if so, are the current signs and symptoms similar to or different from those previous episodes)?
- Oxygen issues
  - Currently on home oxygen supplementation (continuous or only during feedings and sleep)?
  - Baseline oxygen saturation (room air or while on home oxygen)?
  - Any recent need for increasing the amount of supplemental oxygen?
- Medications
  - Names and dosages of all current medications (cardiac and noncardiac medications)?
  - Were any of these cardiac medications stopped recently (by the cardiologist or parental noncompliance)?
  - Any recent increases in the cardiac medications (reasons for the increase, previous dosage versus the current dosage, and the date this dosage was increased)?
  - Any new cardiac medications added recently and the reason for these additions?
  - Recent digoxin level if the patient is on daily digoxin therapy?
- Results of most recent studies (chest radiograph, electrocardiogram, echocardiogram, and cardiac catheterization)
  - When were the last studies performed, and what were the results?
  - Why were those studies performed (routine follow-up studies or obtained because of decompensation from baseline, or a planned evaluation for an upcoming surgical procedure)?
- Surgical procedures
  - Previous procedures and complications?
  - Any future planned procedures?

Chest Pain

The majority of pediatric chest pain cases are noncardiac in origin and benign in nature. Common causes include musculoskeletal or chest wall pain, costochondritis, asthma exacerbations, pneumonia, pleurisy, gastritis, and gastroesophageal reflux. An unusual cause of acute, nonradiating, left-sided chest pain in the adolescent is referred to as the *precordial catch syndrome* (also known as *Texidor's twinge*). The pain, which is located in the left periapical area of the chest wall, occurs

suddenly, often is exacerbated during inspiration, generally is not reproducible with chest wall compression, and usually resolves within a few minutes. Patients may state the pain took their breath away or they were afraid to move; usually it is of short duration and not associated with dysrhythmias or other sequelae. The cause is unknown and findings on physical examination, chest radiograph, ECG, and echocardiogram are all normal in these patients.

Chest pain or syncope on exertion may be due to an underlying cardiac condition and deserves a more thorough investigation, especially if there is a positive family history of sudden unexplained death in young adulthood. Myocardial involvement secondary to drug abuse (e.g., cocaine, amphetamines, crystal methamphetamine) should always be considered as a potential cause in any adolescent patient who presents with chest discomfort or pain. Pulmonary embolism is a possible cause of chest pain, especially in pregnant adolescent females or those who are taking oral contraceptive agents. The rare though life-threatening condition of aortic dissection must always be considered as a cause of chest pain in a patient with physical examination stigmata that are suggestive of a collagen vascular disorder, such as Marfan's syndrome. Patients with a known congenital heart defect or an acquired cardiac disorder (e.g., Kawasaki disease, acute rheumatic heart disease, myocarditis, pericarditis, cardiomyopathy) who present with chest pain also deserve a more thorough diagnostic evaluation.

Physical Examination

General Appearance and Pulses

All four extremities should be palpated for the presence and quality of pulses. The brachial and femoral pulses are the easiest to feel in infants. Bounding pulses are typically present in infants with a patent ductus arteriosus. Coarctation of the aorta should be suspected in any child with strong pulses in the upper extremities but weak pulses in the lower extremities. The pulse may be weak and thready in all extremities in a child who presents with CHF and shock.

Vital Signs and Blood Pressures

A mild resting tachypnea or tachycardia may be the only clinical clue to an underlying cardiovascular disorder. Age-related variables in heart rates, respiratory rates, and blood pressures often serve as a source of frustration and confusion to those clinicians who do not manage pediatric patients on a routine basis. Although there are numerous tables of pediatric vital signs with variations based on sleep or awake states, one can easily recall a rough estimate of the normal pediatric heart rates and respiratory rates based on a simplified table of pediatric vital signs (Table 169-2).[5] The methods to calculate the normal expected blood pressures and hypotensive blood pressures are also listed in Table 169-2.[6]

An accurate blood pressure reading is accomplished by using a cuff that covers two thirds of the upper arm or thigh. A cuff that is too narrow will overestimate the patient's true blood pressure and a cuff that is too large will underestimate the true blood pressure. Any child with a suspected cardiac disorder should have blood pressures measured in both arms. If the blood pressure in the left arm is significantly lower than the blood pressure in the right arm, a coarctation of the aorta proximal to the origin of the left subclavian artery should be suspected. Blood pressures must also be measured in the thighs in any child with a suspected aortic coarctation or documented hypertensive blood pressures in the upper extremities. The mere presence of femoral pulses does not rule out clinically the possibility of a coarctation of the aorta. Even with an appropriately sized cuff, the blood pressures in the thighs can be 10 to 20 mm Hg higher than the blood pressures in the upper extremities due to the lack of well-designed blood pressure cuffs for the legs. Therefore, if the measured blood pressure in the lower extremities is lower than the blood pressures in the upper extremities, coarctation of the aorta should be suspected. Pulse oximetry readings that are lower in the legs than in the upper extremities are also suggestive of either a coarctation of the aorta or a right-to-left-shunt across a patent ductus arteriosus.[7]

Table 169-2 Pediatric Vital Signs and Pertinent Formulas for Estimating Blood Pressure

Simplified pediatric vital signs[5]:

AGE GROUP	HEART RATE (BEATS/MIN)	RESPIRATORY RATE (BREATHS/MIN)
Newborn to 1 yr	140	40
1–4 yr	120	30
4–12 yr	100	20
>12 yr	80	15

Formulas to calculate the estimated normal blood pressures in children ≥1 year of age:

Estimated systolic blood pressure (SBP): [age in years × 2] + 90 mm Hg

Estimated diastolic blood pressure: 2/3 × [estimated SBP]

Minimum acceptable SPBs for age:

Newborn to 1 mo	60 mm Hg
1 mo to 1 yr	70 mm Hg
1–10 yr	[age in years × 2] + 70 mm Hg
>10 yr	90 mm Hg

Cardiac Auscultation

The intensity and degree of splitting of the S2 heart sound (which reflects closure of the pulmonic and aortic valves) is extremely important in a pediatric cardiologic evaluation. In normal children, both components (aortic closure and pulmonic closure) of S2 should be heard along the left upper sternal border (the pulmonic area). A widely split and fixed S2 suggests a physiologic problem resulting from either a constant volume overload to the right side of the heart (e.g., atrial septal defect) or a pressure overload to the right side of the heart (e.g., pulmonic stenosis). The classic congenital heart defect that is associated with a widely split and fixed S2 is the atrial septal defect. The intensity of the S2 component may be louder than normal in the child with pulmonary hypertension.

The third heart sound (S3), which is best heard along the lower left sternal border or the apex, can be a normal finding in children and young adults. S3 is produced by a rapid filling of the ventricles and is heard during early diastole, just after the S2 sound. A loud S3, however, is always pathologic and is due to dilated ventricles due to volume overload (e.g., CHF and large ventricular septal defects). The fourth heart sound (S4) occurs late in diastole, just before the S1 sound. The finding of an S4 is due to a decrease in compliance of a stiff, hypertrophic ventricle.

Cardiac murmurs are produced by turbulent blood flow through the heart. The presence of a cardiac murmur may not be associated with an underlying cardiac defect, however. The

BOX 169-4 A PATHOLOGIC ETIOLOGY OF A HEART MURMUR SHOULD BE SUSPECTED WITH ANY OF THE FOLLOWING CRITERIA

Diastolic murmurs
Systolic murmurs that are louder than a grade 3/6, continuous or associated with a thrill
Murmurs that are associated with abnormal heart sounds (clicks, rubs, or gallop rhythms)
Presence of cyanosis or respiratory distress
Bounding pulses or weak pulses
Abnormalities on the electrocardiogram
An abnormal cardiac silhouette, abnormal pulmonary vascularity or cardiomegaly on the chest radiograph

BOX 169-5 AUSCULTATION LOCATIONS OF COMMON SYSTOLIC MURMURS IN CHILDREN

Left upper sternal border (pulmonic area)
- Pulmonic valvular stenosis
- Atrial septal defects (due to an increased pulmonic flow)
- Innocent pulmonic ejection murmur
- Neonate pulmonic flow murmur
- Patent ductus arteriosus (a continuous, "machinery" sounding murmur)

Left lower sternal border
- Innocent vibratory Still's murmur
- Ventricular septal defects
- Endocardial cushion defects
- Tetralogy of Fallot
- Hypertrophic cardiomyopathy

Apex
- Innocent vibratory Still's murmur
- Mitral regurgitation
- Aortic stenosis
- Hypertrophic cardiomyopathy

Right upper sternal border (aortic area)
- Aortic stenosis
- Coarctation of the aorta

location, intensity, quality, timing, and radiation of the murmur determine whether the murmur is suggestive of an underlying cardiac pathologic condition. Although systolic murmurs can be present without any underlying anatomic abnormalities, diastolic murmurs are always considered pathologic in nature. Some of the other criteria that would suggest an underlying anatomic cardiac abnormality are listed in Box 169-4. Murmurs may be very difficult to appreciate in the noisy emergency department setting and given the degree of tachycardia that is often present even in normal infants. However, the location of the murmur may be a valuable clinical tool in determining the underlying anatomic origin of the murmur (Box 169-5).

Murmurs without any underlying anatomic abnormalities or hemodynamic significance are termed *innocent* or *functional* murmurs. All innocent murmurs are associated with normal ECGs and normal chest radiographs. Two of the most common innocent murmurs encountered in the pediatric population are the neonatal pulmonic flow murmur (also known as the peripheral pulmonic stenosis murmur) and Still's murmur. The pulmonic flow murmur of the neonate is due to the relatively thin walls and angulation of the right and left pulmonary arteries at birth. This systolic murmur is best heard at the left upper sternal border with radiation throughout the entire chest, axilla, and back. It usually disappears by 3 to 6 months of age. Persistence of a systolic murmur in the pulmonic area beyond this period should raise the possibility of a pathologic pulmonary arterial stenosis.

Another common innocent murmur in children is Still's murmur, which is a systolic murmur that typically occurs in children between 2 and 6 years of age. This systolic murmur is best heard along the left midsternal border. The distinctive quality of this murmur has been described as being "vibratory," "musical," "zippy," and "twanging" and results from turbulent flow. The distinct quality of this murmur helps to distinguish Still's murmur from a ventricular septal defect murmur, which has a harsher quality. The intensity of Still's murmur can be increased due to fever, excitement, exercise, or anemia.

The Hyperoxia Test

The hyperoxia test is an important bedside diagnostic tool to help differentiate between cardiac and pulmonary causes of central cyanosis. This test consists of assessing the rise in arterial oxygenation with the administration of 100% oxygen. An arterial blood gas is measured on room air (if tolerated) and repeated after several minutes of high-flow oxygen (100% O_2) is administered; the two blood gas analyses are then compared. When the child is breathing high-flow oxygen, an arterial oxygen partial pressure (Pao_2) of greater than 250 mm Hg virtually excludes hypoxia due to CHD—a "passed" hyperoxia test.[8] An arterial O_2 reading of less than 100 mm Hg (in a child without obvious pulmonary disease) is consistent with a right-to-left shunt and is highly predictive of CHD—a "failed" hyperoxia test.[8] Values between 100 and 250 mm Hg may indicate lesions with intracardiac mixing. Pulse oximetry is not an appropriate substitute for an arterial blood gas; it is not sensitive enough to determine "pass or fail" of the test, since a child breathing high-flow O_2 and registering 100% on pulse oximetry may actually have a Pao_2 of anywhere from 80 to 680 mm Hg.[1] Prolonged administration of 100% oxygen may cause some theoretical problems, such as closing the ductus arteriosus in those infants with critical left heart obstructions or by causing pulmonary vasodilation (which would potentially worsen pulmonary vascular congestion).[3] However, oxygen should not be withheld initially in critically ill infants; continuous reassessment is crucial in the evaluation and management of children with suspected CHD.[1]

Arterial Blood Gases

Patients with CHF exacerbation can exhibit respiratory acidosis (low pH and $Paco_2$) in addition to a low Pao_2. In contrast, children with compensated cyanotic congenital heart defects may have a normal pH despite a low Pao_2. Patients with congenital heart defects who are not experiencing respiratory failure are unlikely to exhibit elevation in $Paco_2$. Any cardiac condition that results in inadequate tissue perfusion (i.e., any of the acyanotic congenital heart defects that manifest in CHF) will exhibit a metabolic acidosis with or without a respiratory compensation.

Hemoglobin/Hematocrit Levels and Serum Electrolytes

The hemoglobin and hematocrit levels may reveal a compensatory physiologic elevation (i.e., polycythemia) in children with cyanotic congenital heart defects. Any concurrent medical illness or blood loss that produces an acute anemia could potentially precipitate an acute deterioration by compromising the oxygen carrying capacity in these children with an underlying congenital heart defect. A hemoglobin or hematocrit level

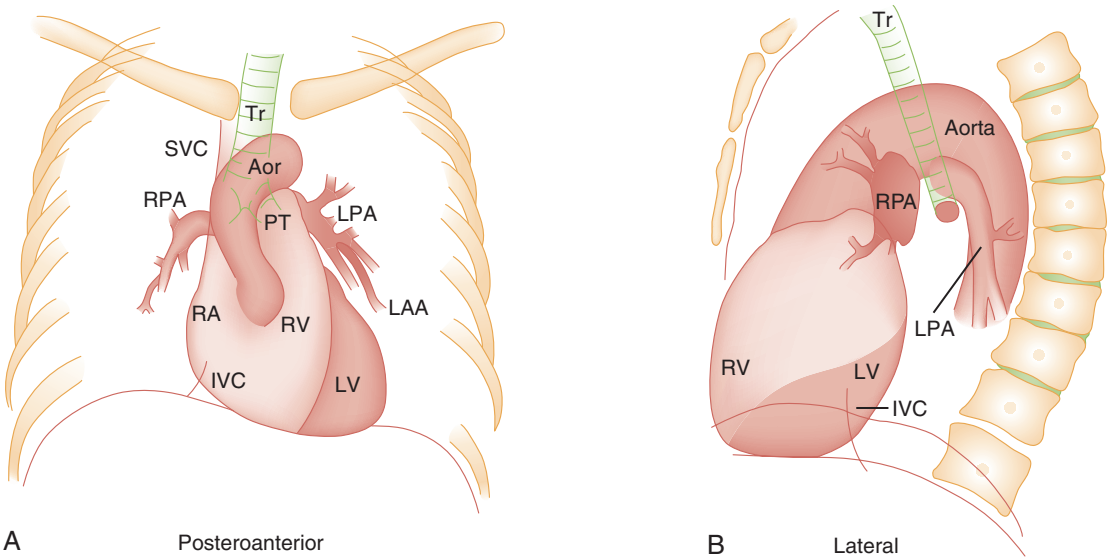


Figure 169-2. Diagrammatic representations of the anatomy of the chest radiograph. **A,** Normal heart in a young man. Posteroanterior projection. Aor, aorta; IVC, inferior vena cava; LAA, left atrial appendage; LPA, left pulmonary artery; LV, left ventricle; PT, pulmonary trunk; RA, right atrium; RPA, right pulmonary artery; RV, right ventricle; SVC, superior vena cava; Tr, trachea. **B,** Right lateral projection of a normal heart in a young man. IVC, inferior vena cava; LPA, left pulmonary artery; LV, left ventricle; RPA, right pulmonary artery; RV, right ventricle; Tr, trachea.

would also be helpful in evaluating whether a child's pallor is due to CHF or anemia. Serum electrolytes may be helpful when evaluating children with acute dysrhythmias or suspected metabolic acidosis and those children who are on chronic diuretic therapy.

Chest Radiograph

Three features of the chest radiograph (Fig. 169-2) that deserve special attention are (1) the cardiac size (cardiothoracic ratio), (2) the cardiac shape (silhouette), and (3) the degree of pulmonary vascular markings. The easiest method to determine the heart size in children is to determine the cardiothoracic ratio, which is obtained by comparing the largest transverse diameter of the cardiac shadow on the posteroanterior view of the chest radiograph to the widest internal diameter (measured from the inside rib margin to the widest point above the costophrenic angle) of the chest. The normal cardiothoracic ratio in children is approximately 50%. The cardiothoracic ratio is not very accurate in newborns and small infants, in whom a good inspiratory view is rarely obtained.[9] A cardiac silhouette that is larger than normal may be due to a shunt lesion, CHF, or a pericardial effusion.[9] An enlarged heart shadow on a chest radiograph more reliably reflects a problem with volume overload rather than pressure overload. Problems with pressure overload are better represented on the ECG.

The cardiac size can be falsely increased in infants due to the presence of the thymus, which can be seen in the mediastinum on the chest radiograph from birth until about 5 years of age. The thymic borders are typically wavy in appearance and sometimes can be seen as the classic "sail sign" along the superior right heart border (Fig. 169-3). The thymic shadow may not be radiographically visible in infants during times of physiologic stress but should reappear when the infant recovers.

The three classic cardiac silhouettes seen in patients with congenital heart defects are (1) the "boot-shaped" heart of tetralogy of Fallot (Fig. 169-4), (2) the "egg-on-a-string silhouette" of transposition of the great vessels, and (3) the "snowman-shaped" or "figure-of-8 heart" of total anomalous pulmonary venous return.

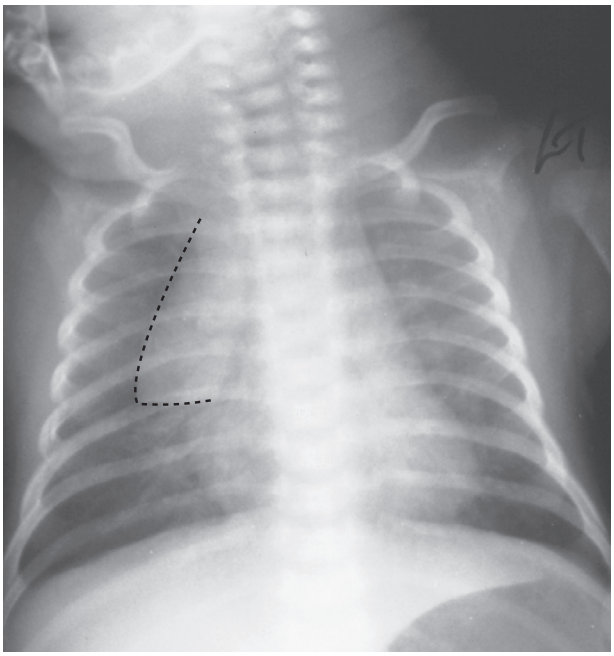


Figure 169-3. Thymic shadow demonstrating the "sail sign" along the right cardiac border *(dotted line)*.

The degree of pulmonary vascular markings is one of the key factors to consider when working through the differential diagnosis of congenital heart defects. An increase in pulmonary vascularity is present when the pulmonary arteries appear enlarged and extend into the lateral third of the lung fields or if there is an increased vascularity to the lung apices. Another criterion that suggests an increased pulmonary vascularity is when the diameter of the right pulmonary artery in the right hilum on the posteroanterior view of the chest is wider than the internal diameter of the trachea. The differential diagnosis of a cyanotic infant with decreased vascular markings includes tetralogy of Fallot, pulmonary atresia, or tricuspid atresia. The cyanotic infant with increased vascular markings may have transposition of the great vessels, total anomalous pulmonary

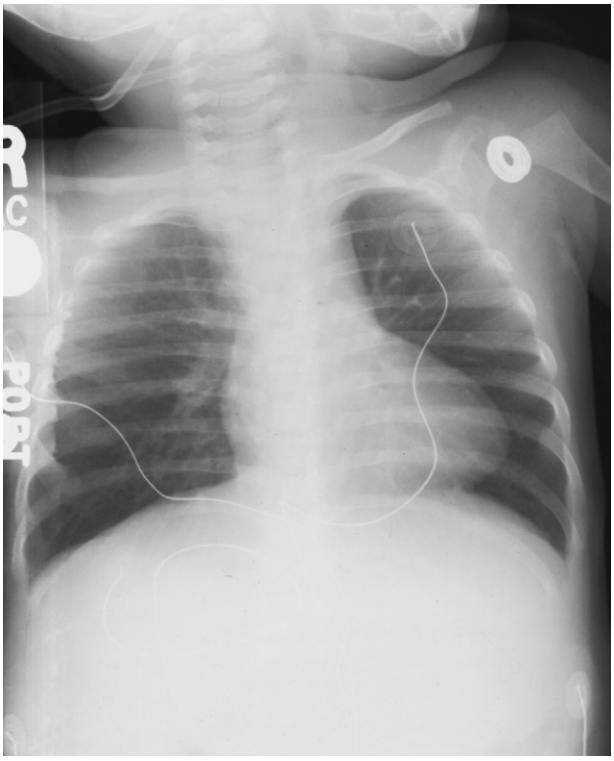


Figure 169-4. The classic boot-shaped heart of tetralogy of Fallot.

venous return, or truncus arteriosus. Increased vascular markings in an acyanotic infant are suggestive of an endocardial cushion defect, ventricular septal defect, atrial septal defect, or a patent ductus arteriosus.

In a normal left-sided aortic arch, the aorta descends to the left of the midline and displaces the tracheal air shadow slightly toward the right of midline above the level of the carina. In contrast to this, the tracheal air shadow may be midline or deviated toward the left in the presence of a right-sided aortic arch.[3] This finding is important to note, since a right-sided aortic arch is found in up to 25% of the children with tetralogy of Fallot.[9] Rib notching secondary to increased collateral blood flow along the intercostal vessels can sometimes be appreciated between the fourth and eighth ribs in older children with undiagnosed coarctation of the aorta but is rarely visualized in children with coarctation of the aorta who are younger than 5 years.[9]

Electrocardiogram

The ECG findings in infants and children can sometimes be problematic because various components of the ECGs change according to the child's age (Table 169-3).[6] At birth, the muscle mass of the right ventricle is greater than that of the left ventricle; this is demonstrated by right axis deviation on the neonatal ECG. By the end of the first month of life, the left ventricle assumes dominance. By 6 months of age, the left ventricular to right ventricular mass ratio is 2:1, which then reaches the adult ratio of 2.5:1 by adolescence. The durations of the PR interval, QRS complex, and QT intervals all increase with age.

Left axis deviation is present when the QRS axis is less than the lower limit of normal for the child's age and occurs with left ventricular hypertrophy and left bundle branch block. Right axis deviation is present when the QRS axis is greater than the upper limit of normal for the child's age and occurs with right ventricular hypertrophy and right bundle branch block. A "superior" QRS axis (0 to −180 degrees with an S wave in aVF greater than the R wave) may be suggestive of an endocardial cushion defect or tricuspid atresia.

Some of the more common indications for obtaining an ECG in a pediatric patient include chest pain, dyspnea, syncope, palpitations, and suspected dysrhythmias. Other indications for obtaining an ECG are in those children with known cardiac disorders who present with signs and symptoms that could reflect an acute decompensation of their underlying disorder. A rare but potentially fatal congenital cardiac abnormality that will demonstrate ECG abnormalities (i.e., ischemic changes) is the condition of the anomalous origin of the left coronary artery. These infants have a history of poor feeding, irritability, and failure to thrive, then suddenly present with cardiogenic shock secondary to myocardial ischemia.

Biochemical Markers

The utility and clinical accuracy of cardiac biochemical markers such as creatinine phosphokinase MB and cardiac troponin-T in the emergency department setting is currently limited in the pediatric population. Plasma homocysteine levels have been studied recently as a possible link to CHF in adults;

Table 169-3 Normal Electrocardiogram Values (PR, QRS, QTc, and QRS axes) in Infants and Children[6]

AGE	PR INTERVAL AVERAGE (UPPER LIMIT)	QRS DURATION AVERAGE (UPPER LIMIT)
0–1 mo	0.10 (0.12)	0.05 (0.07)
1 mo to 1 yr	0.10 (0.14)	0.05 (0.07)
1–3 yr	0.11 (0.15)	0.06 (0.07)
3–8 yr	0.13 (0.17)	0.07 (0.08)
8–12 yr	0.15 (0.18)	0.07 (0.09)
12–16 yr	0.15 (0.19)	0.07 (0.10)
Adult	0.16 (0.21)	0.08 (0.10)

The QTc interval should not exceed:
0.45 seconds in infants <6 months old
0.44 seconds in children and adolescents

Normal QRS axes in infants and children:

AGE	MEAN DEGREES (RANGE)
1 wk to 1 mo	+110 (+30 to +180)
1–3 mo	+70 (+10 to +125)
3 mo to 3 yr	+60 (+10 to +110)
>3 yr	+60 (+20 to +120)
Adults	+50 (−30 to +105)

Normal T wave axis in infants and children: (+) = upright T wave and (−) = inverted T wave

AGE	LEADS V1 AND V2	LEAD AVF	LEADS I, V5, AND V6
Birth to 1 day	+/−	+	+/−
1–4 days	+/−	+	+
4 days to adolescent	−	−	+
Adolescent to adult	+	+	+

however, there are currently no studies regarding plasma homocysteine levels in pediatric cardiac disorders.[9] Several recent studies have evaluated the use of plasma B-type natriuretic peptide levels in the assessment and management of CHF in adults.[10] Studies of B-type natriuretic peptide levels in children have demonstrated a similar correlation of elevated levels in children with CHF, and these also correlated to the clinical symptoms of heart failure and the ejection fraction as measured by echocardiography.[11] The clinician is urged to refer to the particular range of age-specific values from the laboratory kit used at his institution.

SPECIFIC DISORDERS

Congenital Heart Disease

Perspective

The incidence of CHD in the United States has remained fairly constant at approximately 1%, or 8 to 10 cases per 1000 live births. This equates to approximately 32,000 infants born each year with some form of CHD[12] (Table 169-4). Although a large percentage of CHD is now detected with prenatal ultrasonograms, one recent study also recommended routinely measuring pulse oximeter readings in all newborns prior to discharge from the nursery as an additional inexpensive screening tool for CHD.[13]

Clinical Features

The age, severity of symptoms, and time of presentation of a child with CHD vary depending on the specific defect, complexity and severity of the defect, and timing of the normal physiologic changes that occur as the fetal circulation transitions to that of a neonate (Table 169-5). The more severe or complex CHD lesions may not be clinically apparent immediately after birth. However, as the ductus arteriosus begins to close in the first several weeks of life, cardiac defects with obstructive lesions of the pulmonary or systemic circulations will be unmasked, and these infants will present clinically with acute cyanosis, shock, or both. Even the harsh systolic murmur of a large, isolated ventricular septal defect may not be heard until about the 4th to 6th week of life when the left-to-right shunt across the ventricular septal defect increases due to the decrease in the PVR. In general, the more severe the anatomic defect is (i.e., lack of pulmonary blood flow or lack of systemic blood flow), the earlier in life these conditions will manifest with cyanosis and shock.

Although CHD has been subdivided traditionally into cyanotic and acyanotic conditions, not all CHD lesions will fit neatly into a single category; some of the more complex defects have mixed pathophysiologic effects. Although the exact anatomic diagnosis of a CHD is dependent on echocardiography or cardiac catheterization, establishing the exact anatomic diagnosis is not entirely necessary in the emergency department setting.

Diagnostic Strategies

The emergency physician must rely on several key elements of the clinical examination in addition to chest radiograph and ECG findings (Box 169-6) to narrow the diagnostic possibilities. For example, using the data in Box 169-6, the presence of cyanosis, a grade 3/6 systolic-ejection murmur best heard at the mid-left sternal border, a boot-shaped heart, and decreased pulmonary blood flow on the chest radiograph with evidence of right ventricular hypertrophy on the ECG suggest tetralogy of Fallot. Only a brief discussion of some of the more common CHDs is presented in this chapter.

Management

The majority of children who present to the emergency department with shock due to dehydration and hypovolemia are typically given intravenous fluids in 20 mL/kg boluses. However, if a child with a suspected CHD presents to the emergency department in possible cardiogenic shock, one could consider using smaller 10 mL/kg boluses to prevent an iatrogenic complication of fluid overload. Frequent reassessment should be performed and the child's response after each 10 mL/kg bolus monitored to determine whether additional fluid boluses or inotropic agents are necessary.

Table 169-4 Incidence of Specific Congenital Heart Defects (CHDs)

DEFECT	PERCENT OF CHD
Acyanotic CHDs	
Ventricular septal defect	20–25%
Atrial septal defect	5–10%
Patent ductus arteriosus	5–10%
Coarctation of the aorta	8%
Pulmonic stenosis	5–8%
Aortic stenosis	5%
Cyanotic CHDs	
Tetralogy of Fallot	10%
Transposition of the great arteries	5%
Tricuspid atresia	1–2%
Total anomalous pulmonary venous return	1%
Truncus arteriosus	<1%
Pulmonary atresia	<1%
Ebstein's anomaly	<1%
Hypoplastic left heart syndrome	<1%
Hypoplastic right heart syndrome	<1%

Table 169-5 Symptomatic Presentation of Congenital Heart Defects (CHDs) and Time of Presentation

DEFECT	TIME OF PRESENTATION
CHDs That Present with Cyanosis	
Transposition of the great arteries	Birth to 2 wk
Total anomalous pulmonary venous return	Birth to 2 wk
Tricuspid atresia	Birth to 2 wk
Ebstein's anomaly of the tricuspid valve	Birth to 2 wk
Truncus arteriosus	Birth to 2 wk
Pulmonary atresia	Birth to 2 wk
Hypoplastic right heart syndrome	Birth to 2 wk
Hypoplastic left heart syndrome	Birth to 2 wk
Tetralogy of Fallot	Birth to 12 wk
CHDs That Present with Shock	
Coarctation of the aorta	From 1st wk on
Aortic stenosis	From 1st wk on
CHDs That Present with Congestive Heart Failure	
Ventricular septal defects	From 4 wk on
Patent ductus arteriosus	From 4 wk on

BOX 169-6 CLINICAL CLUES TO AID IN THE DIAGNOSIS OF CONGENITAL HEART DISEASE (CHD)

Presence or absence of central or peripheral cyanosis?
- Central cyanosis with minimal respiratory distress ("comfortably blue") is more suggestive of a CHD rather than a purely pulmonary etiology

Abnormalities in cardiac auscultation?
- Murmurs: systolic versus diastolic, location, and radiation
- Quality of S1, S2, and the presence of any clicks or gallops

Change in the degree of central cyanosis with crying?
- Worsening of cyanosis with crying suggests a cardiac rather than a purely pulmonary etiology

Response of the Pao_2 to the hyperoxia challenge (administering 100% oxygen)?
- Purely pulmonary causes of cyanosis:
- Pao_2 should rise to levels above 250 mm Hg
- Cyanotic CHD associated with an increased pulmonary blood flow:
- Pao_2 may occasionally reach as high as 150 mm Hg
- Cyanotic CHD associated with a decreased pulmonary blood flow:
- Pao_2 will not rise over 100 mm Hg

Chest radiograph abnormalities?
- Cardiac size and shape (one of the three classic cardiac silhouettes)?
- Boot-shaped heart: tetralogy of Fallot (TOF)
- Egg-on-a-string silhouette: transposition of the great vessels
- Snowman-shaped or figure-of-eight heart: total anomalous pulmonary venous return (TAPVR)
- Degree of pulmonary blood flow?
- Increased (acyanotic): atrial septal defect, Eisenmenger's syndrome, ventricular septal defect, patent ductus arteriosus, endocardial cushion defects (ECDs)
- Increased (cyanotic): transposition of the great arteries (TGA), TAPVR, hypoplastic left heart syndrome, truncus arteriosus
- Decreased or normal (acyanotic): pulmonic stenosis (PS), aortic stenosis, coarctation of the aorta
- Decreased (cyanotic): TOF, severe PS, Ebstein's anomaly, tricuspid atresia (TriA), pulmonary atresia, hypoplastic right heart syndrome

Electrocardiographic abnormalities?
- Evidence of chamber enlargement: right ventricular hypertrophy, left ventricular hypertrophy, biventricular hypertrophy, right atrial hypertrophy, or left atrial hypertrophy
- An abnormal superior QRS axis is suggestive of ECD or TriA

BOX 169-7 DUCTAL-DEPENDENT CARDIAC LESIONS IN THE NEONATE

Congenital heart diseases (CHDs) that require a patent ductus arteriosus to preserve blood flow from the aorta to the pulmonary circulation:
- Tetralogy of Fallot
- Tricuspid atresia
- Pulmonary atresia
- Hypoplastic right heart syndrome
- Transposition of the great vessels

CHDs that require a patent ductus arteriosus to preserve blood flow from the main pulmonary artery to the systemic circulation:
- Severe coarctation of the aorta
- Severe aortic stenosis
- Hypoplastic left heart syndrome

BOX 169-8 PROSTAGLANDIN E_1 (PGE_1) INFUSION PREPARATION FOR DUCTAL-DEPENDENT CONGENITAL HEART DISEASE[6]

Infusion rate 0.05–0.1 µg/kg/min

Available PGE_1 solution: 500 µg/mL (Alprostadil)—always follow the manufacturer's directions.
- Add one ampule (500 µg) PGE_1 to 250 mL of D_5W. This yields 2 µg/mL. To achieve 0.1 µg/kg/min, infuse at 0.05 mL/kg/min or 3 mL/kg/hr.

The above concentration of 2 µg/mL may be run as follows:

2-kg infant	0.1 mL/min or 6 mL/hr to achieve 0.1 µg/kg/min of PGE_1
2.5-kg infant	0.125 mL/min or 7.5 mL/hr to achieve 0.1 µg/kg/min of PGE_1
3-kg infant	0.15 mL/min or 9 mL/hr to achieve 0.1 µg/kg/min of PGE_1
3.5-kg infant	0.175 mL/min or 10.5 mL/hr to achieve 0.1 µg/kg/min of PGE_1
4-kg infant	0.2 mL/min or 12 mL/hr to achieve 0.1 µg/kg/min of PGE_1
4.5-kg infant	0.225 mL/min or 13.5 mL/hour to achieve 0.1 µg/kg/min of PGE_1
5-kg infant	0.25 mL/min or 15 mL/hour to achieve 0.1 µg/kg/min of PGE_1

From Siegfried BH, Henderson TO: Cardiology. In Gunn VL, Nechyba C (eds): The Harriet Lane Handbook: A Manual for Pediatric House Officers, 16th ed. Philadelphia, Mosby, 2002, p 123.

One unique pharmacologic intervention that can be lifesaving in infants involves the use of prostaglandin E_1 (PGE_1) to maintain the patency of the ductus arteriosus. CHD that manifests within the first 2 to 3 weeks of life with a sudden onset of cyanosis or cardiovascular collapse is typically due to ductal-dependent cardiac lesions (Box 169-7).[4]

Closure of the ductus arteriosus in patients with these specific cardiac lesions causes life-threatening situations due to either an interruption of blood flow to the lungs producing cyanosis (i.e., tricuspid atresia) or a disruption of blood flow to the systemic circulation producing shock (i.e., hypoplastic left heart syndrome).[4] Box 169-8 details one suggested method to prepare this potentially lifesaving PGE_1 infusion. The PGE_1 infusion is typically started at 0.05 to 0.1 µg/kg/min (the method of preparation described in Box 169-8). A known adverse reaction of a PGE_1 infusion is apnea; one should perform endotracheal intubation on these infants prior to the initiation of the PGE_1 infusion. Not only will intubation provide a secure airway, but controlled ventilation will also help decrease the infant's work of breathing. Other adverse reactions of a PGE_1 infusion include fever, seizures, bradycardia, hypotension, flushing, and decreased platelet aggregation.

Acyanotic Congenital Heart Defect

Acyanotic CHD can be further subdivided (Fig. 169-5) into obstructive lesions (i.e., pulmonic stenosis, aortic stenosis, and coarctation of the aorta) and lesions characterized by left-to-right shunts with an associated increase in pulmonary blood

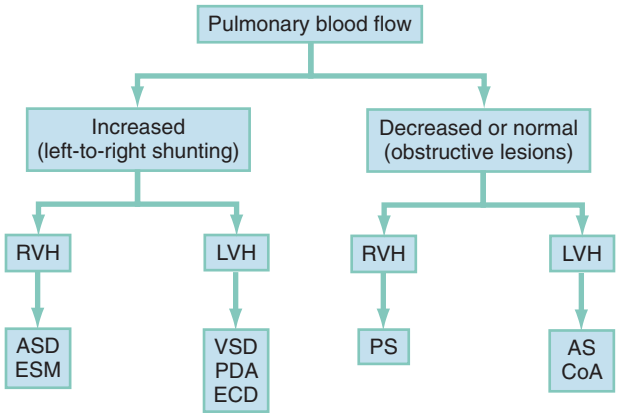


Figure 169-5. Clinical clues to diagnosing acyanotic congenital heart defects. AS, aortic stenosis; ASD, atrial septal defect; CoA, coarctation of the aorta; ECD, endocardial cushion defect; ESM, Eisenmenger's syndrome; LVH, left ventricular hypertrophy; PDA, patent ductus arteriosus; PS, pulmonic stenosis; RVH, right ventricular hypertrophy; VSD, ventricular septal defect.

flow (i.e., ventricular septal defects, atrial septal defects, patent ductus arteriosus, and endocardial cushion defects). These acyanotic lesions usually manifest within the first 6 months of life with symptoms of CHF; however, atrial septal defects can remain asymptomatic until adulthood.

Ventricular Septal Defect

Perspective. Ventricular septal defects are the most common congenital cardiac defects and account for 20 to 25% of all cases of CHD. Spontaneous closure occurs in 30 to 40% of all ventricular septal defects overall and in 50 to 70% of smaller ventricular septal defects.[14]

Clinical Features. The degree of symptoms is dependent on the size of the ventricular septal defects and the degree of PVR. Most ventricular septal defects are clinically asymptomatic (minimal to no left-to-right shunting) immediately after birth because of the high PVR. When the PVR decreases to the normal levels at 6 to 8 weeks after birth, left-to-right shunting can then occur and the typical systolic murmur of a ventricular septal defect will then be appreciated. Small ventricular septal defects may remain completely asymptomatic throughout childhood. Approximately 10% of the infants with large ventricular septal defects will eventually develop signs and symptoms of CHF (e.g., poor feeding and poor growth) by 2 to 3 months of age because of the increased pulmonary blood flow. Older children with ventricular septal defects may exhibit signs of decreased exercise tolerance and recurrent pulmonary infections. If moderate to large ventricular septal defects are not surgically corrected, irreversible changes in the pulmonary vasculature may begin to occur as early as 6 to 12 months of age, which will result in an elevation of the PVR and pulmonary hypertension. This in turn can lead to a reversal of the shunt direction across the ventricular septal defect to now become a right-to-left shunt, Eisenmenger's syndrome, with resultant cyanosis.

Diagnostic Strategies. The chest radiograph in children with small ventricular septal defects may be entirely normal, but cardiomegaly with increased pulmonary vascular markings is usually present with untreated moderate to large ventricular septal defects. The ECG of moderate-sized ventricular septal defects typically reveals left ventricular hypertrophy, but biventricular hypertrophy may be present in ventricular septal defects with large left-to-right shunting.

Management. All ventricular septal defects, regardless of the size of the defect, are at risk for bacterial endocarditis due to the high velocity of turbulent blood flow through them.

Traditional closure of ventricular septal defects required open heart surgery. Today, however, a transcatheter closure technique that avoids the inherent risks and complications of open heart surgery and cardiopulmonary bypass has supplanted traditional methods.[15–17]

Atrial Septal Defect

Perspective. Atrial septal defects account for 5 to 10% of all cases of CHD. The majority of infants and children with atrial septal defects remain clinically asymptomatic until adulthood. Spontaneous closure has been reported in up to 40% of the cases within the first 5 years of life.[14]

Clinical Features. Large atrial septal defects, or those associated with comorbid conditions such as bronchopulmonary dysplasia, can manifest with symptoms of CHF and pulmonary overcirculation (e.g., dyspnea with feedings, poor weight gain, and frequent lower respiratory tract infections).[3] The majority of atrial septal defects are discovered when a suspicious murmur is detected on a routine physical examination. A widely split and fixed S2 is a characteristic finding of atrial septal defects.

Diagnostic Strategies. The chest radiograph of children with atrial septal defects will reveal varying degrees of cardiomegaly, right atrial and right ventricular enlargement, and a prominent main pulmonary artery segment and increased pulmonary vascular markings. The ECG will reveal varying degrees of right axis deviation and right ventricular hypertrophy. All patients with unrepaired atrial septal defects will develop symptoms if pulmonary hypertension ensues. Patients with large atrial septal defects that are not detected and repaired are at risk for development of Eisenmenger's syndrome. Unlike ventricular septal defects, uncomplicated atrial septal defects are not associated with high risk of bacterial endocarditis because of the lower turbulence and velocity of blood flow through the atrial septal defects.

Management. Like ventricular septal defects, the traditional closure of atrial septal defects required open heart surgery to place a patch over the septal defect. Newer therapies involving closures with septal occluder devices placed via the transcatheter approach have been described.[18,19] Antiplatelet therapy during the 6-month period after placement of the device is typically given and is safe and effective in preventing thrombus formation on the surface of the septal occluder device.

Eisenmenger's Syndrome. Eisenmenger's syndrome can occur in any large left-to-right shunt defect that is not surgically corrected. When large left-to-right shunts are left untreated (i.e., large ventricular septal defects and atrial septal defects that are not surgically corrected), irreversible changes can occur in the pulmonary arterioles, leading to pulmonary vascular obstruction and pulmonary hypertension. As the degree of pulmonary hypertension increases, the PVR may then begin to exceed the SVR. This causes right-sided pressures to exceed those on the left, causing right-to-left shunting. The reversal in the direction of shunt flow produces cyanosis. Clinical features of patients who have developed Eisenmenger's syndrome include chest pain, dyspnea on exertion, and hemoptysis.[20]

Coarctation of the Aorta

Perspective. Coarctation of the aorta accounts for approximately 8% of all CHD, and up to 50% of patients with coarctation of the aorta also have an associated bicuspid aortic valve.[21] The area of coarctation can occur proximal to the insertion of the ductus arteriosus (preductal type) or distal to the insertion of the ductus arteriosus (postductal type). The majority of cases (89%) are of the postductal type.[21]

Clinical Features. The severity of the symptoms and the age at time of presentation are dependent on the location of the coarctation, the degree of narrowing, and the presence of any other associated cardiac defects. Infants with the preductal

type of coarctation of the aorta may also exhibit differential cyanosis if the ductus arteriosus remains open.[22] The upper half of the body is perfused with well-oxygenated blood supplied by the left ventricle and the ascending aorta. However, the lower half of the body will appear cyanotic, as it is largely perfused via right-to-left shunting of deoxygenated blood from the patent ductus arteriosus into the descending aorta.

Infants with the rarer preductal type of coarctation of the aorta will present with signs of circulatory failure and shock when the ductus arteriosus begins to close. Weaker pulses and lower blood pressures in the lower extremities as compared with the upper extremities are the classic physical examination findings in infants and children with coarctation of the aorta.

Most of the asymptomatic postductal cases of coarctation of the aorta are diagnosed as a result of a cardiology referral for a systolic murmur or a hypertension workup, but infants with severe postductal coarctation of the aorta can also present during the first few weeks of life with signs of circulatory failure and shock. If a child is discovered to have hypertension on a routine physical examination, it is mandatory to obtain blood pressure measurements in the lower extremities to assess the possibility of coarctation of the aorta. A systolic blood pressure in the right arm that is 15 to 20 mm Hg greater than that in the legs is sufficient evidence to suspect coarctation of the aorta because the systolic blood pressures in the legs are normally higher than that in the arms.[22] If the systolic pressure in the right arm is higher than that in the left arm, the area of coarctation is probably preductal and located proximal to the origin of the left subclavian artery.

Diagnostic Strategies. The chest radiograph will most often reveal a normal-sized cardiac silhouette and normal pulmonary vascular markings, but in children older than 5 years, it may exhibit notching along the lower borders of the posterior fourth to eighth ribs due to the pressure of the dilated collateral vessels. The absence of rib notching, however, does not rule out the possibility of coarctation of the aorta. The ECG typically reveals a left axis and left ventricular hypertrophy.

Management. Definitive surgical repair of coarctation of the aorta involves resection of the narrowed section of the aorta with an end-to-end anastomosis. Complications of undiagnosed cases are related to the resultant hypertension and can include heart failure, hypertensive encephalopathy, and intracranial hemorrhages.

Cyanotic Congenital Heart Diseases

Cyanotic CHDs are a result of either decreased pulmonary blood flow to the lungs or right-to-left shunting of desaturated blood directly into the systemic circulation. These cyanotic CHDs can be further subdivided into those conditions with an increased pulmonary blood flow and those lesions with decreased pulmonary blood flow (Fig. 169-6). The classic cyanotic CHD can be remembered by the "five T's": truncus arteriosus, transposition of the great vessels, tricuspid atresia, tetralogy of Fallot, and total anomalous pulmonary venous return. Other forms of cyanotic CHD include Ebstein's anomaly, pulmonary atresia, severe pulmonary stenosis, hypoplastic left heart syndrome, and hypoplastic right heart syndrome. Because many of these cyanotic heart lesions are usually detected either on prenatal ultrasonographic examinations or in the nursery, only tetralogy of Fallot is covered in this section.

Tetralogy of Fallot

Perspective. Tetralogy of Fallot accounts for approximately 10% of all cases of CHD and is the most common cause of cyanotic CHD beyond infancy. Tetralogy of Fallot is often associated with other cardiac defects, such as a right-sided aortic arch (25% of patients), atrial septal defect (10% of patients), and anomalous origin of the left coronary artery.[23] Tetralogy of Fallot arises from a single embryologic defect in which the subpulmonic conus fails to expand, resulting in the four abnormalities (Fig. 169-7): (1) right ventricular outflow tract obstruction; (2) a large, unrestrictive, malaligned ventricular septal defect; (3) an overriding aorta that receives blood flow from both ventricles; and (4) right ventricular hypertrophy secondary to the high pressure load placed on the right ventricle by the right ventricular outflow tract obstruction. These anatomic defects collectively result in decreased pulmonary blood flow and varying degrees of right-to-left shunting of deoxygenated blood across the ventricular septal defect.

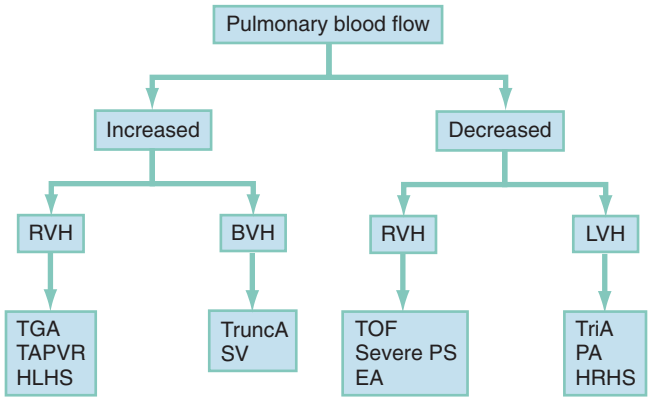


Figure 169-6. Clinical clues to diagnosing cyanotic congenital heart defects. BVH, biventricular hypertrophy; EA, Ebstein's anomaly; HLHS, hypoplastic left heart syndrome; HRHS, hypoplastic right heart syndrome; LVH, left ventricular hypertrophy; PA, pulmonary atresia; PS, pulmonary stenosis; RVH, right ventricular hypertrophy; SV, single ventricle; TAPVR, total anomalous pulmonary venous return; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; TriA, tricuspid atresia; TruncA, truncus arteriosus.

Clinical Features. The degree of cyanosis and the age of presentation are directly dependent on the degree of right ventricular outflow tract obstruction. Infants with tetralogy of Fallot typically have worsening of their cyanosis during crying and feeding. Older children with tetralogy of Fallot may have cyanotic exacerbations during periods of physical exertion. Infants who have milder forms of right ventricular outflow tract obstruction may be acyanotic and are sometimes referred to as having a "pink" tetralogy of Fallot. However, the majority of the cases of tetralogy of Fallot exhibit some degree of cyanosis. Infants with severe right ventricular outflow tract obstruction exhibit profound cyanosis within the first few days of life and may even require a PGE_1 infusion to preserve pulmonary blood flow via left-to-right shunting from the aorta into the main pulmonary artery via the patent ductus arteriosus.

The physical examination can reveal varying degrees of cyanosis and a systolic ejection murmur along the left sternal border. Chronic hypoxemia results in a compensatory polycythemia and varying degrees of clubbing of the fingers and toes.

Diagnostic Strategies. The chest radiograph of a patient with cyanotic tetralogy of Fallot (see Fig. 169-4) reveals decreased pulmonary vascular markings and a boot-shaped heart (secondary to a concave main pulmonary artery segment along the superior aspect of the left heart border). The heart size in tetralogy of Fallot is normal, and a right-sided aortic arch may be seen in 25% of the cases. The ECG of cyanotic tetralogy of Fallot reveals right ventricular hypertrophy and a right axis deviation. Children with "pink" tetralogy of Fallot may not initially exhibit any degree of right ventricular hypertrophy,

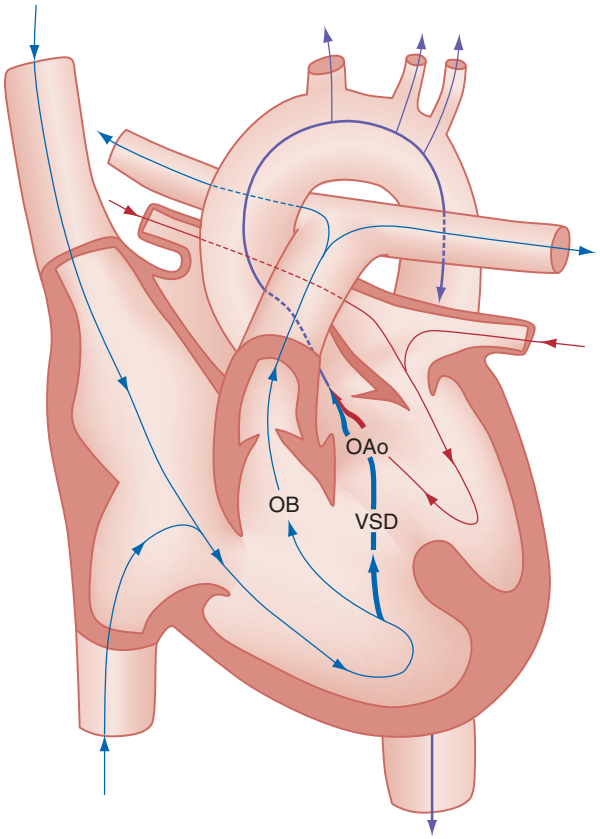


Figure 169-7. Diagrammatic representation of the right-to-left shunting that occurs in tetralogy of Fallot. Some of the deoxygenated blood *(thick blue arrow)* in the right ventricle is shunted across the ventricular septal defect (VSD) into the left ventricle. This deoxygenated blood mixes with the well-oxygenated blood from the lungs *(red arrow)*. The blood that is ejected out through the overriding aorta (OAo) therefore contains blood of mixed oxygenation *(purple arrows)*. The amount of deoxygenated blood that is shunted through the VSD *(thick blue arrow)* is dependent on a combination of factors, including the severity of right ventricular outflow tract obstruction (OB), the size of the VSD, and the degree of systematic vascular resistance (SVR). When the SVR falls (as occurs during a tet spell), more deoxygenated blood from the right ventricle will be shunted across the VSD into the systemic circulation, which results in hypoxia, metabolic acidosis, and worsening cyanosis.

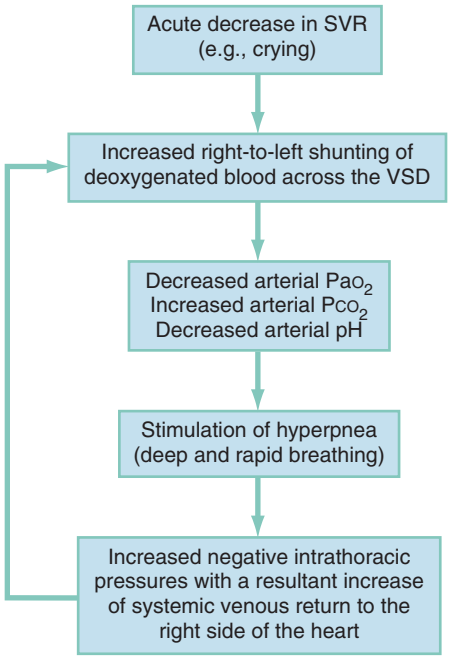


Figure 169-8. Pathophysiologic mechanisms of a hypoxic (tet) spell. SVR, systematic vascular resistance; VSD, ventricular septal defect.

but these acyanotic forms of tetralogy of Fallot gradually develop the cyanotic form by 1 to 3 years of age.

A potentially life-threatening complication of tetralogy of Fallot that can be seen in a patient who presents to the emergency department is the so-called "tet spell," which has also been referred to as the "hypercyanotic spell" or the "hypoxic spell." Although these hypoxic spells can occur in children with other forms of CHD, they are most commonly seen in infants and children with tetralogy of Fallot, and hence the term *tet spells*. These episodes occur most commonly in infants, with a peak incidence between 2 and 4 months of age.[23]

Any event that suddenly lowers the SVR, such as crying or defecation, will produce a large right-to-left shunt across the ventricular septal defect, beginning the vicious cycle of a hypoxic spell. Acute hypovolemia and tachycardia can also precipitate tet spells. The large right-to-left shunt through the ventricular septal defect bypasses the lungs, which then causes a decrease in the Pao_2, an increase in the Pco_2, and a fall in the arterial pH. These metabolic changes then stimulate the respiratory centers in the brain to produce hyperpnea (deep and rapid respirations), which increases the negative intrathoracic pressure during inspiration, causing an increase in the systemic venous blood return to the right side of the heart. This increased volume of blood in the right ventricle is then shunted through the ventricular septal defect through the combination of the existing right ventricular tract outflow obstruction and the acute decrease in the SVR. This in turn further decreases the arterial oxygen saturation, perpetuating the hypoxic spell (Fig. 169-8).

Clinically these hypoxic spells are characterized by periods of hyperpnea (rapid and deep respirations), uncontrollable crying, and worsening cyanosis. Limpness, seizures, cerebrovascular accidents, and even death have been reported with more severe tet spells. During a tet spell, the intensity of the murmur decreases because of less blood flow through the right ventricular tract obstruction and more blood being shunted from the right ventricle to the left ventricle through the ventricular septal defect.

Management. The overall treatment goals for tet spells (Box 169-9) are: (1) increasing the SVR, (2) abolishing the hyperpnea, and (3) correcting the metabolic acidosis. Although supplemental oxygen should be provided, this alone will not reverse a tet spell, since there is a decrease in the amount of

BOX 169-9 MANAGEMENT OF TETRALOGY OF FALLOT HYPOXIC SPELLS

Place the infant in the knee-to-chest position to increase the SVR, which decreases the right-to-left shunt across the VSD.
Provide supplemental oxygen (limited value by itself).
Morphine: 0.1–0.2 mg/kg intravenously (IV) or intramuscularly (IM)
Fentanyl: 1 µg/kg/dose IV or IM as an alternative to morphine
Sodium bicarbonate: 1 mEq/kg IV
Consider ketamine: 1–2 mg/kg IV or IM
Consider propranolol[6]: 0.01–0.2 mg/kg IV
Consider phenylephrine[6]: 0.01–0.02 mg/kg IV

pulmonary blood flow and an increase in the amount of right-to-left shunting across the ventricular septal defect. The infant should be picked up and placed in a knee-to-chest position. Older children can be placed in the squatting position. Both maneuvers are believed to increase the SVR and decrease the amount of systemic venous blood return to the right side of the heart. Morphine (0.1–0.2 mg/kg) has been traditionally given intramuscularly to suppress the respiratory center and thereby abolish the hyperpnea. A theoretical adverse effect of morphine, however, is that it can cause systemic vasodilation (further decreasing the SVR) via endogenous histamine release.[24] Although there are no current studies evaluating the use of other medications that may also suppress the respiratory centers, fentanyl and midazolam could be utilized for the same effect without the potential risk of endogenous histamine release. Ketamine (1–2 mg/kg intravenously or intramuscularly) has also been suggested for its sedative effect as well as for its effect on increasing the SVR.[23] Sodium bicarbonate can be given to correct any metabolic acidosis and reduce the respiratory center–stimulating effects of acidosis. Most infants respond to these measures and exhibit an improvement in their oxygenation and a decrease in their degree of cyanosis. Those infants whose condition does not improve with the above measures may require a vasopressor such as phenylephrine to increase the SVR and thereby decrease the degree of right-to-left shunting across the ventricular septal defect. An intravenous fluid bolus may also be considered to increase the volume of blood flow through the pulmonary artery. Propranolol has also been used as an adjunct to break the cycle of a tet spell. Although the exact pharmacophysiologic mechanisms by which propranolol accomplishes this is uncertain, it is thought to increase the SVR and perhaps promote an increase in the pulmonary blood flow by reducing spasms of the right ventricular outflow tract obstruction.

Palliative surgical procedures to increase the amount of blood flow temporarily to the pulmonary arteries are performed in infants with severe cyanotic tetralogy of Fallot. The most commonly performed procedure is the modified Blalock-Taussig shunt, in which an anastomosis is created between the subclavian artery and the ipsilateral pulmonary artery. Definitive surgical repair of tetralogy of Fallot consists of closing the ventricular septal defect and opening the right ventricular outflow tract obstruction by resection of the infundibular tissue. The mortality rate is 5 to 10% within the first 2 years after definitive surgical repair in uncomplicated tetralogy of Fallot cases. Complications that can occur after definitive surgical repair include complete heart block, ventricular dysrhythmias, and right bundle branch block (secondary to the right ventriculotomy). Bacterial endocarditis prophylaxis is still recommended after the definitive surgical repair of tetralogy of Fallot.

Postoperative Complications of Congenital Heart Defects

A variety of postoperative complications can be seen in patients who present to the emergency department weeks to months after cardiac surgery. The types of complications that could occur in each case depend on the original underlying cardiac defect as well as on the surgical procedure that was used to correct that defect. Some of the complications that may be seen in the emergency department include thrombosis of a shunt-conduit with decreased flow, increased shunt-conduit flow with resultant CHF, atrial and ventricular dysrhythmias, heart blocks, myocardial ischemia, and endocarditis. The size of the cardiac silhouette and the degree of pulmonary blood flow visualized on the chest radiograph may provide valuable clues as to whether there is an increased or decreased blood flow through a surgical conduit that was created to provide an improvement in blood flow to the pulmonary system.[25] Comparison of the child's other postoperative chest radiographs can help to determine whether there has been a change in the heart size and pulmonary vascularity.

The postpericardiotomy syndrome is an inflammatory pericarditis that can occur 1 to 6 weeks after any surgical procedure that involved a pericardiotomy. This immunologic phenomenon is believed to occur as a sequela of blood in the pericardial sac. This syndrome is characterized by fever, chest pain, and a pericardial effusion. A pericardial friction rub may be heard, depending on the amount of fluid that accumulates in the pericardial sac. The chest radiograph may reveal an enlarged cardiac silhouette, and the echocardiogram will confirm the diagnosis. Pericardiocentesis is rarely required but may be necessary if the amount of pericardial effusion is significant enough to cause a pericardial tamponade. The majority of cases will resolve within 2 to 3 weeks with bedrest and nonsteroidal anti-inflammatory medication.

Many of the above-mentioned postoperative complications, including the postpericardiotomy syndrome, can be avoided in children who undergo closure of patent ductus arteriosus, atrial septal defects, and ventricular septal defects via the transcatheter placement of various occluder devices.

Respiratory Syncytial Virus Infections in Infants and Children with Congenital Heart Defects

Respiratory syncytial virus (RSV) is the most common cause of lower respiratory tract infections in infants and children worldwide, with the majority of children being infected at least once by 2 years of age. Reinfection occurs commonly throughout life.[26] RSV lower respiratory tract infections account for more than 125,000 pediatric admissions annually in the United States, with a fatality rate of 6.3 deaths per 100,000 patients up to 4 years of age (Box 169-10).[27,28] Children with CHD who develop RSV infections tend to have a higher rate of intensive care unit admissions and require mechanical ventilation more frequently than those children who do not have CHD. Children with CHD who require hospitalization for RSV have a fatality rate that is two to six times greater than that of children without CHD.[27,28] RSV is responsible for a mortality rate of 40% in infants with CHD and up to 70% in infants with CHD and associated pulmonary hypertension.

Currently there are two products that can be used to prevent RSV infections. Both of these preparations require monthly administration prior to the onset of the peak RSV season, which typically runs from November through March in most states. The two currently available preparations are (1) palivizumab (Synagis), which is a humanized monoclonal antibody administered intramuscularly at a dose of 15 mg/kg and (2) RSV immunoglobulin (RespiGam), which requires intravenous administration at a dose of 750 mg/kg (which is equal to 15 mL/kg) and must be administered over a 4-hour period.[26] The use of palivizumab in the prevention of RSV infections in high-risk infants and children has largely replaced RSV

BOX 169-10 CONDITIONS ASSOCIATED WITH AN INCREASED RISK OF SEVERE OR FATAL RESPIRATORY SYNCYTIAL VIRUS INFECTIONS

Cyanotic or complex congenital heart defects
Pulmonary hypertension
Prematurity (especially those infants with bronchopulmonary dysplasia or chronic lung disease)
Immunodeficiency states

BOX 169-11 Recommendations for Palivizumab Administration in Children with Congenital Heart Disease (CHD)

CHD conditions that would benefit from palivizumab administration (15 mg/kg intramuscularly every 30 days during the respiratory syncytial virus season only):
- Cyanotic or complex CHD
- Congenital heart failure requiring medications
- Moderate to severe pulmonary hypertension

Children with hemodynamically insignificant CHD who do not require palivizumab administration:
- Secundum atrial septal defect
- Small ventricular septal defect
- Pulmonic stenosis
- Uncomplicated aortic stenosis
- Mild coarctation of the aorta
- Patent ductus arteriosus

immunoglobulin because palivizumab can be given intramuscularly, requires a 100-fold lesser volume, and has a 50-fold smaller protein load than RSV immunoglobulin.[29]

In 1998, the Food and Drug Administration gave approval for the use of palivizumab in preventing RSV lower respiratory tract infections in selected infants and children who were deemed to have a higher risk of severe infections. During the 4-year period from 1998 to 2002, several multicenter studies involving more than 24,000 subjects (including data from the Palivizumab Outcomes Registry) have demonstrated the efficacy of palivizumab in preventing hospitalizations of high-risk infants and children.[30] During this same 4-year period, another multicenter study involving six countries demonstrated a 45% relative reduction in hospitalization of 1287 high-risk children younger than 2 years with CHD who were given 15 mg/kg monthly intramuscular injections of palivizumab over a 5-month period.[29] This study also demonstrated a significant reduction in the total number of hospital days, supplemental oxygen requirement, total number of days in the intensive care unit, and total number of days requiring intubation in the group that received the monthly palivizumab intramuscular injections. Based on these results, the Food and Drug Administration in September 2003 gave approval for the use of palivizumab in infants and children with hemodynamically significant CHD (Box 169-11). The American Academy of Pediatrics emphasizes that prophylaxis with palivizumab should be initiated prior to the onset of the RSV season. Because RSV can persist on environmental surfaces for several hours, the best method to prevent the spread of RSV-contaminated secretions within the emergency department setting is meticulous hand washing and wearing a mask when caring for children with a documented or suspected RSV infection.

Congestive Heart Failure

Perspective

Congestive heart failure is defined as a clinical syndrome in which the cardiac output is unable to meet the hemodynamic and metabolic demands of the body. Although there is a wide array of causes of CHF, the primary cause in infants and children is CHD, which results in volume or pressure overload. Other causes of CHF include the anomalous left coronary artery in infants, myocarditis, endocarditis, rheumatic heart disease, pericardial effusions, anemia, cardiomyopathies, systemic hypertension, hypothyroidism, electrolyte imbalances, cardiac toxins, and dysrhythmias that compromise cardiac output.

CHF can result from a derangement in one of the four primary determinants of normal cardiac function: (1) excessive preload (e.g., large left-to-right shunts and severe chronic anemia); (2) decreased cardiac contractility (e.g., myocarditis); (3) excessive afterload (i.e., left-sided obstructive lesions); and (4) rhythm abnormalities that compromise cardiac output or stroke volume (e.g., paroxysmal supraventricular tachycardia and severe forms of heart block). The treatment of CHF depends on which of these four primary determinants of normal cardiac function are compromised. For example, inotropic agents and diuretics may be required in a child with volume overload and decreased cardiac contractility, whereas vasodilating agents may be required in a child with CHF due to an increased afterload.

Clinical Features

Although the clinical manifestations of CHF depend on the exact pathophysiologic cause of the CHF, common presenting signs and symptoms include tachycardia, a gallop rhythm, tachypnea with rales, hepatomegaly, peripheral edema, and decreased peripheral perfusion of the extremities. Wheezing and a chronic cough may also be the presenting symptoms of CHF.

Diagnostic Strategies

The chest radiograph typically reveals an enlargement of the cardiac silhouette and varying degrees of pulmonary congestion. An echocardiogram will be able to assess the ejection fraction as well as to identify underlying anatomic defects. Plasma B-type natriuretic peptide has been reported to be helpful in differentiating cardiac from pulmonary etiologies of dyspnea in children.[31] Other diagnostic studies to consider are case specific and depend on the suspected cause of the child's CHF.

Management

Acute stabilization of any child who presents with CHF includes administration of supplemental oxygen and agents to augment cardiac contractility and to improve cardiac output. Children who present in severe respiratory distress secondary to pulmonary edema may require intubation to support oxygenation and ventilation. Children with respiratory distress and air hunger due to pulmonary congestion may also benefit from elevation of the head and upper torso in addition to morphine sulfate (0.05–0.1 mg/kg/dose) administration. Continuous positive airway pressure or biphasic positive airway pressure ventilation may be useful initially to avert the need for endotracheal intubation. Plasma B-type natriuretic peptide levels have been shown to be elevated in children with CHF and have also been used to monitor the response to treatment regimens in patients with CHF.[11]

Diuretics and inotropic agents are the mainstay of treatment for the majority of children with CHF. Furosemide (Lasix) in a dose of 1 mg/kg is the most common loop diuretic used to increase renal perfusion and improve urine output. Digoxin has remained the most widely used inotropic agent to treat CHF in children (Table 169-6). With the proper use of furosemide and digoxin, most children with CHF will demonstrate a favorable response. The narrow therapeutic index of digoxin requires that levels be monitored very closely to prevent iatrogenic digoxin toxicity, which could cause a worsening of the preexisting CHF.

Table 169-6 Digoxin Dosing for Infants and Children with Congestive Heart Failure[6]

AGE	TOTAL DIGITALIZING DOSE (ORAL)*	DAILY MAINTENANCE DOSE (ORAL)
Premature	20 µg/kg/24 hr	5 µg/kg/day
Full term	30 µg/kg/24 hr	8–10 µg/kg/day
<2 yr	40–50 µg/kg/24 hr	10–12 µg/kg/day
2–10 yr	30–40 µg/kg/24 hr	8–10 µg/kg/day
>10 yr	0.75–1.25 mg/24 hr	0.125–0.25 mg/day

*The intravenous dose of digoxin is equal to 75% of the oral dose (except in children >10 years old, in whom the intravenous dose is the same as the oral dose).
The total daily digitalizing dose (TDD) is given as follows: ½ of the TDD given initially, followed by ¼ of the TDD given every 8–12 hours × 2 doses after the initial dose.
The daily maintenance dose is divided into a twice-daily dosing regimen (except in children >10 years of age, in whom the maintenance dose can be given as a single daily dosing regimen).
Intravenous digoxin is supplied as 100 µg/mL and 250 µg/mL solutions.
Oral digoxin suspension is supplied as a 50 µg/mL elixir.
Therapeutic range: 0.8–2.0 µg/L.
A lower dosing regimen may be required in those patients with renal failure since digoxin is excreted by the kidneys.

Other inotropic agents that are used for the treatment of CHF in infants and children are dopamine, dobutamine, and epinephrine (Table 169-7). Standardized drips have been established and have essentially replaced the "rule of six."[32] Dopamine is an endogenous catecholamine with complex cardiovascular effects. Dopamine can increase renal blood flow in low doses (2–5 µg/kg/min) and will increase the cardiac contractility and heart rate in moderate doses (5–10 µg/kg/min). Dopamine stimulates cardiac $beta_1$-adrenergic receptors both directly and indirectly through the release of endogenous norepinephrine stored in the cardiac sympathetic nerves. Due to this, some of the inotropic effects of dopamine may be reduced in those patients with decreased endogenous myocardial norepinephrine stores (i.e., patients with chronic CHF and neonates). At higher doses (10–20 µg/kg/min), dopamine will also increase the SVR, but excessive vasoconstriction may compromise end-organ perfusion at infusion rates greater than 20 µg/kg/min. If additional inotropic effects are required, the addition of either dobutamine or epinephrine infusions may be preferable to increasing the dopamine infusion greater than 20 µg/kg/min. The major toxicities of dopamine are tachycardia, vasoconstriction, and ventricular ectopy.

Dobutamine is a synthetic catecholamine with more selective cardiac inotropic effects and some $beta_2$-adrenergic vasodilatory effects. It is not a vasopressor per se, but could be a good adjunct in the treatment of low cardiac output states that are secondary to poor myocardial function. Dobutamine may have an advantage over dopamine in that it has fewer arrhythmogenic effects than dopamine and may also have a more direct effect on the enhancement of coronary blood flow. The main toxicities of dobutamine are tachycardia, ventricular ectopy, and hypotension.

Epinephrine is a potent inotrope and chronotrope and also increases the SVR. Epinephrine is useful in scenarios in which poor cardiac output is also associated with diminished systemic vascular tone. Toxicities associated with epinephrine include tachydysrhythmias, severe hypertension, hyperglycemia, lactic acidosis, and hypokalemia.

Amrinone and milrinone are newer inotropic agents that also have peripheral vasodilatory effects. These agents have been used in improving cardiac index in septic shock and in prevention of low cardiac output states for children with CHD. Side effects of these medications include profound hypotension, dysrhythmias, hypersensitivity reactions, fever, hepatotoxicity, and thrombocytopenia.

Another vasodilating medication that has been used for arterial and venous dilatory effects is nitroprusside. Nitroprusside has potent vasodilatory effects on both the systemic and pulmonary circulatory systems. This medication has a prompt onset of action and a short duration of action. Nitroprusside must be used cautiously in patients with either hepatic and/or renal impairment to avoid cyanide toxicity (severe metabolic acidosis and coma) or thiocyanate toxicity (irritability, seizures, abdominal pain, and vomiting).

Pediatric Dysrhythmias

Perspective

Dysrhythmias are not as common in children as they are in adults. The most common cause of cardiopulmonary arrest in infants and children is the untreated progression of respiratory failure or shock rather than a primary cardiac dysrhythmia.[33] Therefore, the most common arrest rhythm that will confront the emergency physician will be asystole or bradycardia rather than ventricular fibrillation or ventricular tachycardia. When confronted with a child with a primary cardiac dysrhythmia, the physician must identify and treat the underlying cause quickly and systematically. Children who are at risk for developing dysrhythmias are listed in Box 169-12. Various medications, drugs, and toxins can also precipitate dysrhythmias in children. Even those medications that are used to treat underlying cardiac problems such as digoxin, amiodarone, and procainamide can themselves precipitate dysrhythmias. Drugs of abuse (e.g., cocaine and crystal methamphetamine) and overdose of prescription medications (e.g., cyclic antidepressants) should always be considered when evaluating any previously healthy adolescent patient who presents with an acute dysrhythmia.

Pediatric dysrhythmias can be divided into three broad categories of rhythms based on their effect on the child's pulse: *slow* (sinus bradycardia and heart blocks), *fast* (supraventricular tachycardia or ventricular tachycardia with a pulse), or *absent* (ventricular tachycardia without a pulse, ventricular fibrilla-

Table 169-7 Inotropic and Load-Altering Agents Used in the Treatment of Congestive Heart Failure

	INOTROPE	CHRONOTROPE	VASCULAR EFFECTS	INFUSION RANGES
Dobutamine	+	+/–	Vasodilator	2–20 µg/kg/min
Dopamine	+	+	Pressor	2–20 µg/kg/min
Epinephrine	+	+	Pressor	0.1–1.0 µg/kg/min
Milrinone	+	No	Vasodilator	0.5–2 mg/kg bolus over 5 minutes followed by 5–10 µg/kg/min
Nitroprusside	No	No	Potent vasodilator	0.5–10 µg/kg/min

BOX 169-12 Conditions Associated with a High Risk of Developing Dysrhythmias

- Congenital heart defects (uncorrected defects and postoperative complications)
- Congenital complete heart blocks (e.g., maternal systemic lupus erythematosus)
- Myocarditis
- Rheumatic heart disease
- Kawasaki disease with involvement of the coronary arteries
- Cardiomyopathy
- Prolonged QT syndrome
- Aberrant atrioventricular conduction pathways (e.g., Wolff-Parkinson-White syndrome)
- Electrolyte abnormalities (e.g., potassium, calcium, and magnesium disturbances)
- Commotio cordis
- Profound hypothermia
- Hypoxia

tion, pulseless electrical activity, or asystole).[34] The most common dysrhythmia in children is supraventricular tachycardia, which occurs most commonly in infants and young children. Although supraventricular tachycardia can spontaneously occur in infants without any underlying structural cardiac defects, ventricular tachycardias typically are due to an underlying myocardial abnormality.

Clinical Features

Rhythm disturbances in infants can manifest with symptoms such as fussiness, lethargy, poor feeding, pallor, respiratory distress, or cardiogenic shock. Older children present with chest pain, palpitations, difficulty breathing, or syncope. The type and degree of severity of the presenting signs and symptoms must be taken into account when considering the evaluation and management of the specific dysrhythmia in each case.

Management

Not every child who exhibits a rhythm disturbance requires emergency intervention. Emergency treatment and stabilization of any dysrhythmia depend on two key clinical questions: (1) Does the child have a pulse? and (2) If a pulse is present, is it slow or fast and is the child hemodynamically stable or unstable? Children who have a pulse with good perfusion parameters (i.e., an alert child with strong distal pulses, warm extremities, and brisk capillary refill times) do not require emergency intervention unless they exhibit a rhythm that has the potential to rapidly degenerate into a more serious condition. Children who exhibit ECG evidence of conduction abnormalities (e.g., Mobitz type II second-degree heart blocks, complete heart blocks, prolonged QT intervals, or aberrant conduction such as the Wolff-Parkinson-White syndrome) may also warrant more emergency treatment.

A summary of the treatment algorithms for pediatric dysrhythmias and the most commonly used medications in treating these dysrhythmias are listed in Box 169-13. Although some medications can only be used to treat atrial tachycardias (e.g., the use of adenosine for supraventricular tachycardia) or ventricular tachycardias (e.g., the use of lidocaine for ventricular tachycardia), amiodarone and procainamide can be used for a wide array of both atrial and ventricular dysrhythmias, including supraventricular tachycardia and ventricular tachycardia.[35,36]

Bradydysrhythmias

Sinus Bradycardia. Bradycardia is defined as a heart rate that is slower than the lower limit of normal for a child's age. Based on the current definition by the American Heart Association (AHA) guidelines in Pediatric Advanced Life Support (PALS), clinically significant bradycardia in children is defined as a heart rate slower than 60 beats per minute that is associated with poor systemic perfusion.[34] Bradycardia is poorly tolerated in infants and children because they are not physiologically capable of increasing their stroke volume to maintain an adequate cardiac output in the face of significant bradycardia.

The most common cause for symptomatic bradycardia in infants and children is hypoxia. Therefore, the first step in the management of symptomatic bradycardia in children is to ensure adequate oxygenation and ventilation before automatically reaching for medications or pacing. Epinephrine is the first-line medication when treating symptomatic bradycardia in children that is not responsive to appropriate oxygenation and ventilation. This is in contrast to the treatment of bradycardia in adults, in which atropine is considered to be the first-line medication. If additional doses of intravenous or intraosseous epinephrine are required when treating symptomatic bradycardia, the dose should remain at standard dosing (0.01 mg/kg) and not be increased to the high dose (0.1 mg/kg) according to AHA and PALS guidelines. Atropine will have no effect on the denervated heart. If vascular access is not available, both epinephrine and atropine can be administered via the tracheal tube, although the intravenous route is preferred.

Other causes of bradycardia include hypothermia, increased intracranial pressure, heart blocks (congenital and acquired), a denervated heart status post–cardiac surgery, hypothyroidism, sick sinus syndrome, and various medications and toxins (e.g., digoxin, beta-blockers, calcium channel blockers, and cholinergic agents). One should consider emergency pacing for Mobitz type II second-degree atrioventricular block, complete third-degree heart block, or sick sinus syndrome.

Athletic adolescent patients may have resting baseline heart rates slower than 60 beats per minute and do not require emergency treatment if they are completely asymptomatic.

Tachydysrhythmias

Supraventricular Tachycardia

Perspective. Supraventricular tachycardia is the most common symptomatic dysrhythmia in infants and children.[34] In children younger than 12 years, the most common cause of supraventricular tachycardia is a reentry mechanism due to an accessory atrioventricular pathway.[37] No cardiac abnormalities are found in approximately half of the cases, and the Wolff-Parkinson-White syndrome is present in only 10 to 20%.[38] The QRS complex is narrow (<0.08 seconds) in up to 90% of the cases of pediatric supraventricular tachycardia.[39] The type of supraventricular tachycardia that occurs most commonly in infants and children involves a reentrant mechanism that utilizes an accessory pathway and the atrioventricular node. The orthodromic reentry phenomenon involves the normal antegrade conduction from the atria to the ventricles down the atrioventricular node with retrograde conduction back from the ventricles to the atria via the accessory pathway. Orthodromic conduction will produce a narrow QRS complex supraventricular tachycardia. The less common form of reentry mechanism is the antidromic form in which conduction from the atria to the ventricles first goes antegrade down the accessory pathway

BOX 169-13 SUMMARY OF PEDIATRIC DYSRHYTHMIA TREATMENT OPTIONS AND DEFIBRILLATION, CARDIOVERSION, AND MEDICATION IN RESUSCITATION

Simplified Summary of Dysrhythmia Treatment Options
- Asystole and pulseless electrical activity (PEA)
  - Cardiopulmonary resuscitation (CPR) and endotracheal intubation
  - Epinephrine
  - Consider and manage treatable causes (6 H's and 5 T's mnemonic).
- Ventricular fibrillation (VF) and pulseless ventricular tachycardia (VT)
  - Each defibrillation is followed immediately by 2 minutes of uninterrupted CPR (2 joules/kg for the first defibrillation followed by 4 joules/kg for all subsequent defibrillations).
  - Epinephrine is administered with the second defibrillation at 4 joules/kg (repeat epinephrine every 3–5 minutes followed by defibrillation).
  - Antidysrhythmic agents are administered with the third defibrillation at 4 joules/kg: amiodarone or lidocaine (if amiodarone not available) or magnesium (for suspected hypomagnesemia or torsades de pointes).

    Simplified VF/pulseless VT algorithm:
    Rhythm check (confirms VF or pulseless VT) → Defibrillation → 2 minutes of uninterrupted CPR (plus medications as indicated above)
- VT (with a pulse)
  - Unstable:
    - Immediate cardioversion (start at 0.5–1 joule/kg then 2 joules/kg)
  - Stable:
    - Amiodarone or lidocaine or procainamide (note: avoid concurrent use of amiodarone and procainamide)
- Supraventricular tachycardia
  - Unstable:
    - If intravenous access is immediately available, administer adenosine while preparing for cardioversion; otherwise perform immediate cardioversion if intravenous access is not available and/or if the patient is hemodynamically very unstable.
  - Stable:
    - Vagal maneuvers (ice water slurry to the face, Valsalva maneuver, blowing on an occluded straw or blowing on the tip of a syringe in an attempt to blow the plunger out)
    - Adenosine if vagal maneuvers fail
- Bradycardia (hypoxia is the most common etiology)
  - Unstable:
    - Ensure adequate oxygenation and ventilation.
    - Epinephrine
    - Atropine (if suspicion of increased vagal tone or cholinergic toxicity)
    - Cardiac pacing
  - Stable:
    - No emergent treatment required.

Defibrillation, Cardioversion, and Medications in Resuscitation
- Cardioversion
  - Start at 0.5–1 joules/kg; then may double the dose up to 2 joules/kg.
- Defibrillation
  - Start at 2 joules/kg; then double the dose to 4 joules/kg for all subsequent attempts.
- Adenosine
  - Start at 0.1 mg/kg (maximum = 6 mg); then may repeat at 0.2 mg/kg × 2 doses (maximum = 12 mg/dose).
- Epinephrine
  - Standard dose = 0.01 mg/kg (equals 0.1 mL/kg of the 1:10,000 solution) intravenously (IV) or intraosseous
  - High dose = 0.1 mg/kg (equals 0.1 mL/kg of the 1:1,000 solution) IV, IO, or via the ETT
  - TT (tracheal dose) = 0.1 mg/kg (equals 0.1 mL/kg of the 1:1,000 solution)
  - Neonatal doses: Always use the 1:10,000 solution as 0.01 mg/kg IV, IO, or umbilical venous catheter or 0.02–0.03 mg/kg via the TT
- Atropine
  - 0.02 mg/kg with minimum of 0.1 mg/dose to avoid paradoxical bradycardia. Maximum single dose is 0.5 mg in a child or 1 mg in an adolescent with an overall dosage total maximum of 1 mg in a child or 2 mg in an adolescent.
- Amiodarone
  - 5 mg/kg intravenous bolus for ventricular fibrillation or slowly over 20–60 minutes for stable ventricular tachycardia to avoid the hypotensive effects of amiodarone
  - Can be used to treat a wide array of both atrial and ventricular dysrhythmias in children due to its ability to slow conduction both through the atrioventricular (AV) node and within the ventricles.
  - Avoid concurrent use of other medications (e.g., procainamide) that can also prolong the QT interval.
- Procainamide
  - 15 mg/kg IV slowly over 30–60 minutes
  - Can be used to treat a wide array of both atrial and ventricular dysrhythmias in children due to its ability to slow conduction both through the AV node and within the ventricles.
  - Avoid concurrent use of other medications (e.g., amiodarone) that can also prolong the QT interval.
- Lidocaine
  - 1 mg/kg IV
  - Does not cause QT prolongation like amiodarone and procainamide.
- Magnesium
  - 25–50 mg/kg (maximum of 2 g) intravenous bolus for VF or pulseless VT (if suspect hypomagnesemia or torsades de pointes)

6 H's, 5 T's: hypovolemia, hypoxia, hydrogen ion (acidosis), hypo-/hyperkalemia, hypoglycemia, and hypothermia; toxins, tamponade, tension pneumothorax, thrombosis, and trauma.

From Ralston M, et al: Recognition and management of cardiac arrest. In PALS Provider Manual. Dallas, American Heart Association, 2006, p 153.

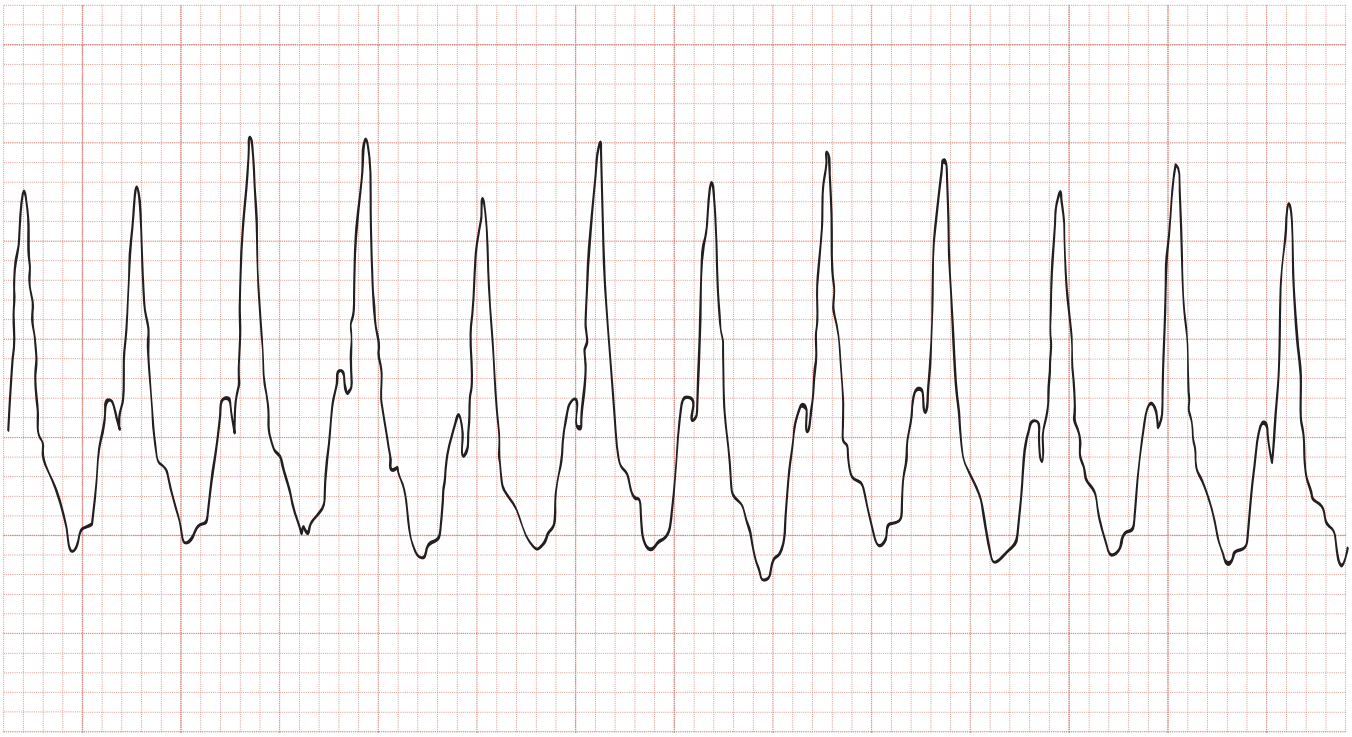


Figure 169-9. An example of an electrocardiogram showing a wide-complex supraventricular tachycardia at a rate of approximately 270 beats/min in an infant with Ebstein's anomaly of the tricuspid valve. This infant was in supraventricular tachycardia for approximately 2 days and presented with an acute exacerbation of her congestive heart failure, as evidenced by the cardiomegaly on the chest radiograph (see Fig. 169-10). Note that the cardiothoracic ratio in this infant is approximately 70%.

then retrograde back to the atria via the atrioventricular node. Antidromic conduction will produce a wide QRS complex supraventricular tachycardia. Supraventricular tachycardia in a child with a preexisting bundle branch block can also result in a wide-complex supraventricular tachycardia. The ECG in Figure 169-9 reveals a case of a wide-complex supraventricular tachycardia in a child with Ebstein's anomaly of the tricuspid valve who also presented with CHF (Fig. 169-10).

Clinical Features and Diagnostic Strategies. The width of the QRS interval in patients with pediatric supraventricular tachycardia is most commonly narrow-complex, with heart rates in infants usually greater than 220 beats per minute (Fig. 169-11). It is sometimes difficult to distinguish between sinus tachycardia and supraventricular tachycardia (Table 169-8).

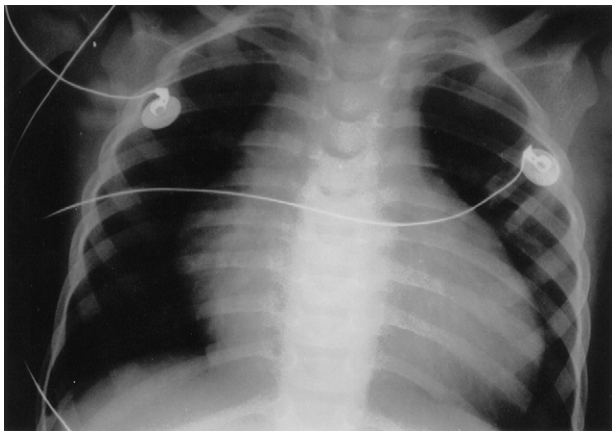


Figure 169-10. Chest radiograph of same infant as in Figure 169-9.

Infants with supraventricular tachycardia typically present with very nonspecific symptoms, such as fussiness and difficulty feeding. Although healthy infants can generally tolerate supraventricular tachycardia with heart rates approaching 300 beats per minute, if left untreated supraventricular tachycardia may begin to produce signs of CHF and shock. Older children with supraventricular tachycardia commonly present with palpitations, difficulty breathing, and chest discomfort.

Management. Management of supraventricular tachycardia depends on the hemodynamic stability of the child. If the child with supraventricular tachycardia is hemodynamically unstable and intravenous access in not available, immediate cardioversion starting at 0.5 to 1 joules/kg is the treatment of choice. If the child does not convert with this initial cardioversion attempt, the energy dose can be doubled up to 2 joules/kg on subsequent attempts. If the child is hemodynamically stable, vagal maneuvers or adenosine, or both, can be attempted initially before cardioversion, depending on the individual case scenario. Regardless of the method selected to convert the supraventricular tachycardia, a continuous rhythm strip should always be run to document the response to each conversion attempt. Vagal maneuvers (e.g., a bag containing a slurry of crushed ice and water to the face, blowing on an occluded straw, or blowing on the tip of a syringe) can be attempted before adenosine administration only in the child with hemodynamically stable supraventricular tachycardia. Application of ice to the face has been demonstrated to be a fairly effective method of converting supraventricular tachycardia in infants and children.[40,41] One method to perform this maneuver is to fill a plastic bag or surgical glove with a slurry of crushed ice and water, which is then placed over the infant's forehead, eyes, and bridge of the nose for 10 to 15 seconds. Care must be taken not to occlude the nose or mouth with the bag of ice water. External ocular pressure should be avoided, as it can be dangerous in children because excessive pressure

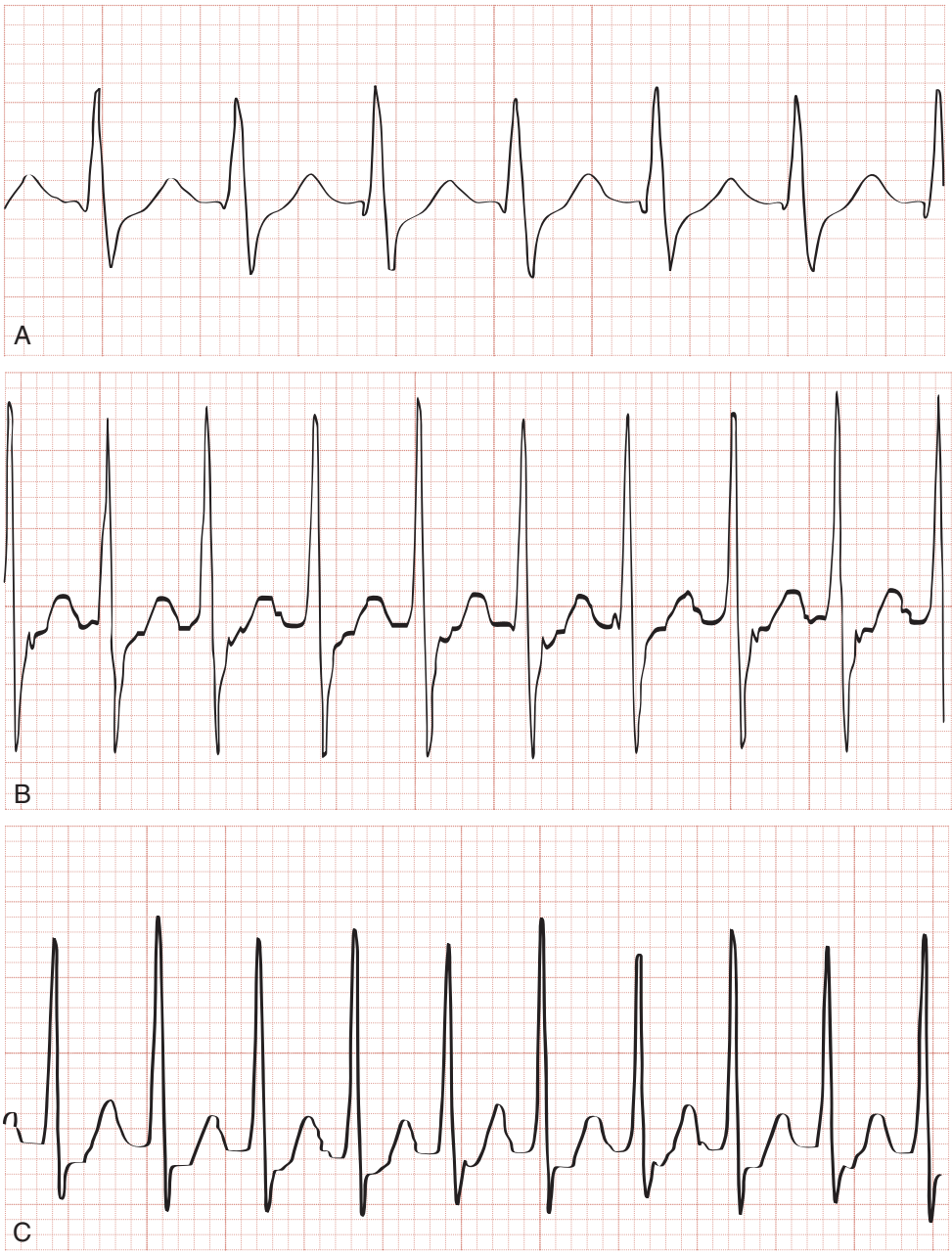


Figure 169-11. Three electrocardiographic examples of classic narrow-complex supraventricular tachycardia in children. The heart rate is approximately 240 beats/min in the first two examples (**A** and **B**) and approximately 270 beats/min in the third example (**C**).

Table 169-8 Clinical and Electrocardiogram (ECG) Features to Differentiate Sinus Tachycardia from Supraventricular Tachycardia in Children[34]

	SINUS TACHYCARDIA	SUPRAVENTRICULAR TACHYCARDIA
Precipitating event(s)	Dehydration, fever, pain	No precipitating event
P waves on ECG	Present	Absent
Heart rate varies with activity	Yes	No
Beat-to-beat variability	Yes	Constant R-R intervals
Heart rate in infants (beats/min)	Usually <220	Usually >220
Heart rate in children (beats/min)	Usually <180	Usually >180

can lead to a ruptured globe. Carotid massage is less effective and is not recommended as a vagal maneuver in infants or children.[34]

The initial dose of adenosine in children is 0.1 mg/kg with a maximum initial dose of 6 mg. If this initial dose of adenosine fails to convert the supraventricular tachycardia, the dose is then doubled to 0.2 mg/kg with a maximum of 12 mg/dose. This 0.2 mg/kg dose of adenosine can be attempted once more during the third adenosine dose. Elective cardioversion or esophageal overdrive pacing under conscious sedation may be

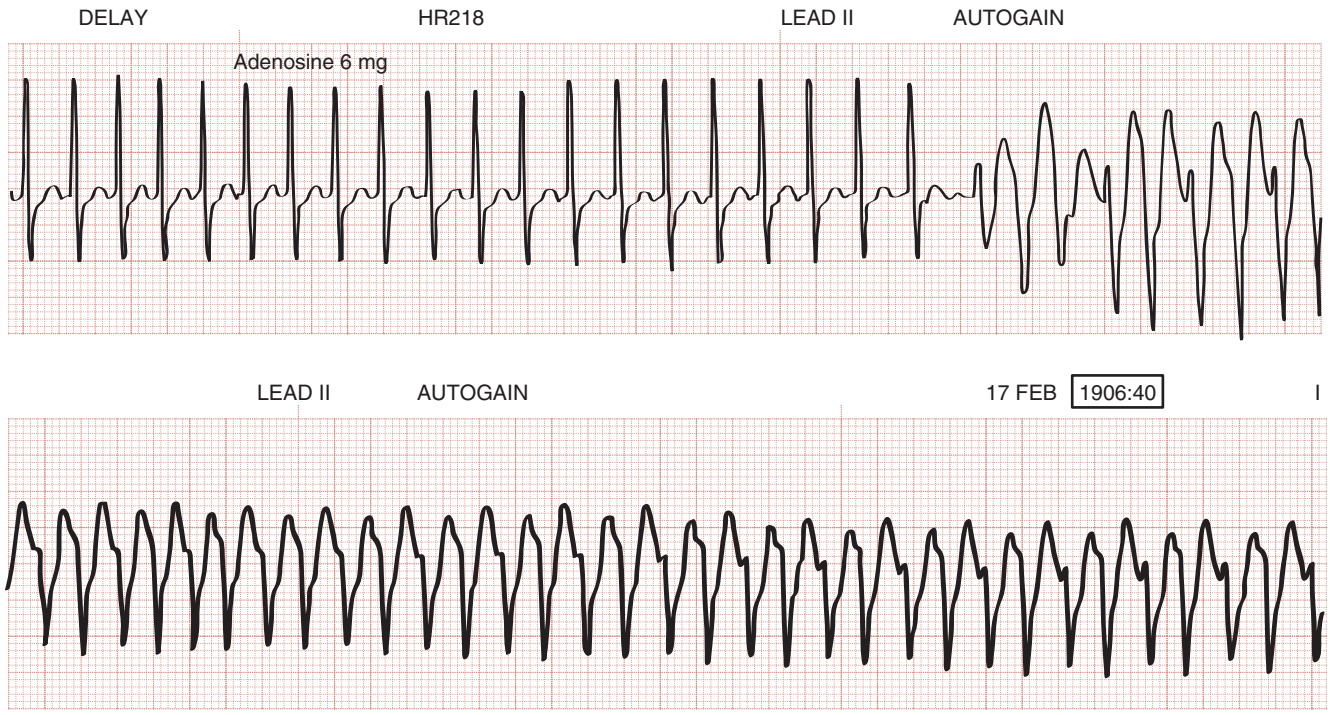


Figure 169-12. An example of adenosine-induced wide-complex tachycardia. A dose of 6 mg of adenosine was administered to this previously healthy 15-year-old girl who presented with a 6-hour history of palpitations. She had no previous cardiac problems except for intermittent palpitations in the past that always resolved spontaneously without any medical interventions. Once adenosine blocked the conduction through the atrioventricular node, a wide-complex tachycardia appeared on the electrocardiogram (ECG), which was probably due to antegrade conduction through an accessory pathway. During the 30 seconds of this wide-complex tachycardia, the patient remained alert with excellent perfusion parameters. This wide-complex tachycardia then spontaneously converted to normal sinus rhythm. Although the patient's postconversion ECG did not reveal an accessory pathway, Holter monitoring 1 month later detected the classic ECG findings of Wolff-Parkinson-White syndrome.

required in children who fail to convert with adenosine. Complications of adenosine administration include asystole and various dysrhythmias, including adenosine-induced wide-complex tachycardia (secondary to an occult accessory conduction pathway) (Fig. 169-12). The use of verapamil to convert supraventricular tachycardia in infants and younger children should be avoided because of the high incidence of profound hypotension and cardiovascular collapse when this medication is administered in this age group.[34]

Once the patient has been converted to sinus rhythm, a 12-lead ECG should be obtained to assess for the possibility of Wolff-Parkinson-White syndrome or any other underlying conduction abnormalities that may have predisposed the child to developing the supraventricular tachycardia.

Atrial Flutter and Atrial Fibrillation. Both atrial flutter and atrial fibrillation are rare in children and are usually associated with underlying heart conditions (i.e., CHD, status post–open heart surgical procedures that involved the atria, myocarditis, and digoxin toxicity). Hemodynamic stability of these two dysrhythmias depends on the rate of the ventricular response. Cardioversion is the treatment of choice for children who present with hemodynamically unstable atrial flutter or atrial fibrillation. The initial treatment priority in patients with hemodynamically stable atrial flutter and atrial fibrillation is first to slow down the rate of the ventricular response with medications such as digoxin, beta-blockers, or diltiazem. Once the ventricular rate is controlled, the rhythm can then be converted and suppressed with amiodarone, procainamide, or elective cardioversion. If the patient who presents with atrial flutter and atrial fibrillation is known to have an underlying Wolff-Parkinson-White syndrome, the four medications that should be avoided are the "A-B-C-D" medications (adenosine, beta-blockers, calcium-channel blockers, and digoxin), because all of these medications only block conduction down the atrioventricular node while leaving the accessory pathway wide open to conduct the atrial tachycardia to the ventricles at a potentially lethal rate.[42] Under these circumstances, amiodarone, procainamide, or cardioversion would be the safer alternative. Consultation with the cardiologist and initiation of anticoagulation should also be considered before conversion of either of these two atrial dysrhythmias in the hemodynamically stable patient to prevent a thromboembolic complication.

Ventricular Tachycardia. Ventricular tachycardia is not a common dysrhythmia in children. The majority of children with ventricular tachycardia have an underlying condition such as status post–cardiac surgery, myocarditis, prolonged QT syndrome, drug or toxin exposures (e.g., cyclic antidepressants), or electrolyte abnormalities. The treatment of ventricular tachycardia will depend on whether a pulse is present and on the hemodynamic status of the patient (Box 169-14). Torsades de pointes is a unique type of polymorphic ventricular tachycardia that is characterized by QRS complexes that change in polarity and amplitude. Prolonged QT syndrome, underlying congenital cardiac defects, hypomagnesemia, and various medications (e.g., cyclic antidepressants) have all been identified as known causes of torsades de pointes. The treatment of choice is intravenous magnesium. Class IA (i.e., procainamide) and class III (i.e., amiodarone) antidysrhythmic agents are both contraindicated in the treatment of torsades de pointes, because these two antidysrhythmic agents are capable of prolonging the QT interval, which could then precipitate the degeneration of the torsades de pointes into a more lethal rhythm.

BOX 169-14 CLINICAL CONDITIONS IN WHICH BACTERIAL ENDOCARDITIS SHOULD BE SUSPECTED IN A CHILD WITH AN UNDERLYING ANATOMIC CARDIAC DEFECT

- Fever of unknown etiology
- A change in the quality of the preexisting heart murmur or the presence of a new heart murmur
- Development of a neurologic deficit (secondary to central nervous system emboli)
- New-onset microscopic hematuria
- Splenomegaly
- Petechiae
- Splinter hemorrhages involving the conjunctiva, nail beds, palms, or soles
- Myalgias

Pulseless Rhythms

Ventricular Fibrillation and Pulseless Ventricular Tachycardia. Ventricular fibrillation and pulseless ventricular tachycardia account for approximately 10% of out-of-hospital cardiac arrest cases in which a terminal rhythm was recorded.[43,44] The survival rate for out-of-hospital ventricular fibrillation and pulseless ventricular tachycardia can be as high as 30%, whereas the survival rate from asystolic cardiac arrest is less than 1%.[31] In a recent study of in-hospital cardiac arrests, a shockable rhythm was present during some point of the resuscitation in 25% of the children.[45] The survival rate of children who initially exhibited shockable rhythms were higher than those children who presented with nonshockable rhythms. However the survival rates in those children who later developed a shockable rhythm at some time during their resuscitation were not as good.[45–47] Ventricular fibrillation should also be suspected as the arrest rhythm in cases of commotio cordis or in cases of sudden cardiac arrest. Current arrhythmia detection algorithms for automated external defibrillators (AEDs) appear to have a high sensitivity and specificity for detecting shockable rhythms in children; in July 2003 the AHA gave their approval for the use of AEDs in children 1 to 8 years of age (class IIB recommendation). When an AED is to be used on a child younger than 8 years (or <25 kg) the use of a pediatric attenuator device is strongly recommended in order to deliver a more pediatric-appropriate dose of defibrillation.[48,49] The American Academy of Pediatrics (AAP) also recently supported the use of AEDs in children.[50,51] There currently is still not enough clinical evidence to recommend for or against the use of AEDs in infants under 1 year of age.

The treatment algorithm and medication dosages for ventricular fibrillation and pulseless ventricular tachycardia are listed in Box 169-13. The 2005 PALS arrhythmia algorithms are basically the same as the 2000 treatment guidelines with one major change. Based on the 2005 PALS guidelines, ventricular fibrillation and pulseless ventricular tachycardia are now treated with single defibrillations followed immediately by 2 minutes of uninterrupted cardiopulmonary resuscitation (CPR).[40] Although a single shock with a biphasic defibrillator has a high likelihood of terminating ventricular fibrillation, the resulting rhythm is typically a nonperfusing rhythm, which therefore requires CPR in order to maintain perfusion to the heart and brain until normal cardiac contractility can resume.[40,52] Epinephrine is given with the second defibrillation and antiarrhythmic agents are added to the treatment algorithm with the third defibrillation. Although biphasic defibrillators can convert ventricular fibrillation at lower dosages than the previous monophasic defibrillators in adults, until more data are gathered on biphasic defibrillation dosages in children, the current AHA recommendation for pediatric defibrillation with biphasic defibrillators remains the same as for monophasic defibrillators (i.e., starting at 2 joules/kg followed by 4 joules/kg).

Asystole and Pulseless Electrical Activity. Asystole is the most common rhythm found in cases of out-of-hospital cardiac arrest in children and is associated with a less than 1% chance of survival.[53–55] The use of high-dose epinephrine has been deemphasized in the 2005 PALS guidelines.[40] The treatment algorithm and medication dosages for asystole and pulseless electrical activity are listed in Box 169-13. Pulseless electrical activity can either be a slow or fast rhythm and have a narrow or wide QRS complex.

The key to survival from any pulseless electrical activity rhythm is to rapidly identify and correct the underlying cause. The etiologies for pulseless electrical activity can be remembered by the "6 H's and 5 T's": hypovolemia, hypoxemia, hypothermia, hydrogen ion (acidosis) hypo-/hyperkalemia, hypoglycemia, hypothermia, toxins, tamponade, tension pneumothorax, thrombosis, and trauma.[34,40] The most common cause of pulseless electrical activity in children is profound hypovolemia. Therefore, an intravenous fluid bolus should always be considered as a therapeutic option during the treatment of pulseless electrical activity.

Bacterial Endocarditis

Perspective

Bacterial endocarditis involves an infection of the endothelial surfaces of the heart with a propensity for the valves. The incidence of bacterial endocarditis in children may be increasing slightly due to the many advances in surgical technology that are now allowing many children with very complex congenital heart lesions to survive. Children with indwelling intravenous lines with or without underlying CHD are also at risk for developing bacterial endocarditis. Although bacterial endocarditis most commonly occurs in children with an underlying CHD or an acquired cardiac lesion (e.g., acute rheumatic valvular heart disease), it can also occur in patients with no underlying anatomic defects of the valves or endocardium. In a series of 62 children with bacterial endocarditis, 19 (30%) of the children had normal cardiac anatomy.[56]

Factors that predispose children with underlying anatomic cardiac defects to bacterial endocarditis include dental procedures and other surgical procedures involving the respiratory, gastrointestinal, or genitourinary tracts. Those cardiac lesions with a more turbulent blood flow or a higher flow velocity are more prone to developing bacterial endocarditis secondary to a greater risk of endothelial surface damage, which then increases the risk of platelet deposition and vegetation formation. Cardiac lesions that carry this higher risk include ventricular septal defects, aortic valvular stenosis, tetralogy of Fallot, single ventricle states, prosthetic valves, and postoperative systemic-to-pulmonary shunts. Isolated secundum atrial septal defects carry a much lower risk for bacterial endocarditis because the shunt flow through the atrial septal defect is typically of a much lower velocity.

Clinical Features and Diagnostic Strategies

The early clinical manifestations of bacterial endocarditis may be very nonspecific. The child may simply present with only fever and tachycardia. However, bacterial endocarditis should be suspected in any child with an anatomic cardiac defect who presents with an unexplained fever. This diagnosis must always be considered in any child with a known CHD or an acquired cardiac lesion who presents with any of the condi-

tions listed in Box 169-14. A new heart murmur is present in fewer than 50% of the bacterial endocarditis cases.[57]

In addition to vigilance for the diagnosis of infective endocarditis—especially in children with CHD—the emergency physician should be aware of the indications for prophylaxis. In 2007 the AHA in conjunction with the AAP and the Infectious Diseases Society of America published revised guidelines for the prevention of infective endocarditis.[58] The changes simplify and greatly narrow the recommendations to provide prophylaxis for only the higher risk patients and procedures (Box 169-15). For those children for whom prophylaxis is recommended, the indications are (1) all dental procedures and (2) any manipulation or perforation of the gingival or oral mucosa.[58] It should be noted that antibiotic prophylaxis for infective endocarditis is no longer recommended for gastrointestinal and genitourinary procedures (Box 169-16). The committee found that it is still reasonable to give prophylaxis for procedures on the respiratory tract, infected skin, or musculoskeletal tissue only for high-risk patients (Table 169-9).[58]

Diagnostic studies to perform in a child with suspected bacterial endocarditis include a complete blood cell count, C-reactive protein (CRP) assessment, measurement of erythrocyte sedimentation rate, three blood cultures, chest radiography, and ECG. Cultures from scrapings of cutaneous emboli can also aid in the diagnosis. Although the definitive diagnostic study is the echocardiogram, it is only 80% sensitive in detecting the nidus of infection on the endocardium or valves.[59] *Streptococcus viridans* and *Staphylococcus aureus* are the two most common offending organisms recovered from the blood cultures of children with bacterial endocarditis. Recent studies have shown that in children with CHD, 60% of the cases caused by staphylococcal species are methicillin resistant and were associated with increased risk of mortality.[60]

BOX 169-15 Cardiac Conditions for Which Endocarditis Prophylaxis Is Reasonable

- Prosthetic cardiac valve or prosthetic material used for cardiac valve repair
- Previous infective endocarditis
- Congenital heart disease (CHD)*:
  - Unrepaired cyanotic CHD, including palliative shunts and conduits
  - Completely repaired congenital heart defect with prosthetic material or device during the first 6 months after the procedure†
  - Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or device (which inhibit endolethialization)
- Cardiac transplantation recipients who develop cardiac valvulopathy

*Except for those conditions above, antibiotic prophylaxis is no longer recommended for any other form of CHD.
†Prophylaxis is reasonable because endothelialization of prosthetic material occurs within 6 months after the procedure.
From American Heart Association: Prevention of infective endocarditis. Guidelines from the American Heart Association. Circulation 116:1736, 2007.

BOX 169-16 Procedures for Which Prophylaxis Is Recommended

- All dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa*
- Consider prophylaxis for incisional procedures on the respiratory tract, infected skin, or musculoskeletal tissue only for high-risk patients

*The following procedures do not need prophylaxis: routine anesthetic injections through noninfected tissue, dental radiographs, placement of removable prosthodontic or orthodontic appliances, adjustment of orthodontic appliances, placement of orthodontic brackets, shedding of deciduous teeth, and bleeding from trauma to the lips or oral mucosa.
From American Heart Association: Prevention of infective endocarditis. Guidelines from the American Heart Association. Circulation 116:1736, 2007.

Management

Antibiotics should be started immediately after blood culture samples have been obtained. Although the choice of intravenous antibiotics depends on the suspected source of seeding and the child's immune status, a common recommended regimen includes an aminoglycoside plus a penicillinase-resistant penicillin such as oxacillin. If methicillin-resistant staphylococci are suspected, vancomycin should also be included in the initial empirical antibiotic regimen.[61]

Bacterial endocarditis in the preantibiotic era was nearly always a fatal disease. Although the survival rate in patients with bacterial endocarditis has improved with the initiation of antibiotics, the current mortality rate is still 6 to 14%.[62] Compli-

Table 169-9 Regimens for Prophylaxis of Infective Endocarditis

		SINGLE DOSE 30–60 MINUTES BEFORE PROCEDURE	
SITUATION	**AGENT**	**ADULTS**	**CHILDREN**
Oral	Amoxicillin	2 g PO	50 mg/kg PO
Unable to take oral medications	Cefazolin or ceftriaxone	1 g IM or IV	50 mg/kg IM or IV
Allergic to penicillins or ampicillin—oral	Cephalexin *or*	2 g PO	50 mg/kg PO
	Clindamycin *or*	600 mg PO	20 mg/kg PO
	Azithromycin or clarithromycin	500 mg PO	15 mg/kg PO
Allergic to penicillins or ampicillin—unable to take oral medications	Cefazolin or ceftriaxone *or*	1 g IM or IV	50 mg/kg IM or IV
	Clindamycin	600 mg IM or IV	20 mg/kg IM or IV

IM, intramuscularly; IV, intravenously; PO, orally.
Adapted from American Heart Association: Prevention of infective endocarditis. Guidelines from the American Heart Association. Circulation 116:1736, 2007.

cations of bacterial endocarditis include systemic septic emboli, pulmonary emboli, central nervous system emboli with resultant neurologic deficits, dysrhythmias, CHF, myocarditis, myocardial abscesses, and valvular obstruction. Despite appropriate antibiotic treatment, surgical intervention to remove septic vegetations or valve replacements is sometimes necessary.

Myocarditis

Perspective

Myocarditis is an inflammatory condition of the myocardium with various infectious and noninfectious origins. In the United States, the most common cause is viral, with coxsackievirus B and enteroviruses accounting for the majority of cases. Other viral causes include echoviruses, influenza A, influenza B, adenovirus, varicella-zoster virus, Epstein-Barr virus, cytomegalovirus, and hepatitis B virus. Bacterial causes include *Corynebacterium diphtheriae*, *Streptococcus pyogenes*, *S. aureus*, *Mycoplasma pneumoniae*, *Borrelia burgdorferi*, and *Meningococcus*. Noninfectious causes include Kawasaki disease, acute rheumatic fever (ARF), collagen vascular disorders (e.g., systemic lupus erythematosus), toxins (e.g., cocaine and adriamycin), endocrine disorders (e.g., hyperthyroidism), and drug-induced hypersensitivity (e.g., penicillins, sulfonamides, phenytoin, carbamazepine).

Clinical Features

Myocarditis usually has a gradual onset with preceding upper respiratory tract infection symptoms. The presenting signs and symptoms of a child with myocarditis depend on the cause of the myocarditis, the age of the patient, and the degree of myocardial inflammation. The key to diagnosing myocarditis in infants and children is to suspect the diagnostic entity in the appropriate clinical setting. In mild cases, the only sign of myocarditis may be tachycardia. Tachycardia that is disproportionate to the degree of fever should alert the clinician to the possibility of myocarditis.[63] Other presenting signs and symptoms include fever, myalgias, fatigue, tachypnea, wheezing, abdominal pain, and chest pain. More severe cases of myocarditis can even present with signs and symptoms of acute CHF and various dysrhythmias. The physical examination may reveal a new murmur, a gallop rhythm, or a pericardial friction rub with muffled heart tones (if the myocarditis is also accompanied by pericarditis).

Diagnostic Strategies and Management

The evaluation and management of the child with myocarditis depend on the suspected cause and the presenting signs and symptoms. Blood cultures and viral titers should be considered in infectious and postinfectious cases. Appropriate antibiotics should be initiated immediately in cases with suspected bacterial origin. The chest radiograph in very mild cases may be normal, but in more advanced cases cardiomegaly will be evident. The ECG findings are usually nonspecific and can include low-voltage, nonspecific ST segment abnormalities, T wave inversions, atrioventricular blocks, and various other dysrhythmias. Creatine phosphokinase-MB, cTnT, CRP, and erythrocyte sedimentation rate may be elevated.

The echocardiogram is an essential component of the workup of any child with suspected myocarditis. The echocardiogram will not only be useful to assess the degree of left ventricular function, but it will also be able to detect any associated pericardial effusion that may accompany the myocarditis. Although an endomyocardial biopsy is rarely required, it is the definitive method to confirm the diagnosis and origin of myocarditis. If the endomyocardial biopsy is performed, it will typically demonstrate a myocardial inflammation with lymphocytic and monocytic infiltrates. The goal of treatment is to maintain adequate cardiac output and to control any associated dysrhythmias. Children who present in CHF may require inotropic support and diuretics. Digoxin and the various pressors must be used very cautiously in children with myocarditis because the inflamed myocardium is very sensitive to the dysrhythmogenesis of these medications. The use of beta-blockers is contraindicated,[63] and the routine use of immunosuppressive agents remains controversial.[64] Although the majority of children with acute viral myocarditis make a full recovery, a few patients will progress to develop dilated cardiomyopathy, which is characterized by dilated ventricles and impaired systolic contractility.

Pericarditis

Perspective

Pericarditis is an inflammatory process within the pericardial sac, which may not be associated with a pericardial effusion. The majority of cases of pericarditis in children are self-limited and follow a benign clinical course. In children, there is normally about 10 to 15 mL of fluid within the pericardial sac. A sudden increase or a large amount of fluid within this pericardial sac can cause a tamponade-induced decrease in stroke volume, which will cause a diminished cardiac output and hypotension.

Although the most common causes of pericarditis include bacterial and viral infections, other causes include ARF, systemic lupus erythematosus, uremia, postpericardiotomy syndrome, leukemia, lymphoma, and tuberculosis. Approximately 30% of pericarditis cases are due to bacteria such as *Pneumococcus*, *S. aureus*, *Meningococcus*, and *Haemophilus influenzae*.[2] Approximately 30% of the purulent bacterial pericarditis cases occur in children younger than 6 years.[24] Although viral causes are common, a viral pathogen is recovered in only 20 to 30% of the cases.[24] Common viral causes include coxsackieviruses, ECHO viruses, adenovirus, Epstein-Barr virus, and influenza viruses.

Clinical Features

The presenting signs and symptoms of pericarditis depend on the cause of the pericarditis as well as on the amount of fluid that has accumulated within the pericardial sac. Chest pain that varies with position is a common complaint with pericarditis. The chest pain that is classically associated with pericarditis is exacerbated with inspiration and the supine position but relieved when the patient sits up or leans forward. Tachycardia is also a common finding in patients with pericarditis. Other physical examination findings that have been associated with pericarditis include fatigue, tachypnea, neck vein distention, pulsus paradoxus, hepatomegaly, lower extremity edema, and thready distal pulses if heart failure is present. The cardiac auscultatory findings in a patient with pericarditis can include a harsh-sounding friction rub or diminished or muffled heart tones, if there is a significant amount of fluid within the pericardial sac. The pericardial friction rub, if present, is best heard when the patient sits up or leans forward. This friction rub of pericarditis can be distinguished from a pleural friction rub by having the patient hold his or her breath during auscultation. The friction rub of pericarditis will remain present during breath-holding while the pleural friction rub will no longer be heard while the patient holds the breath.

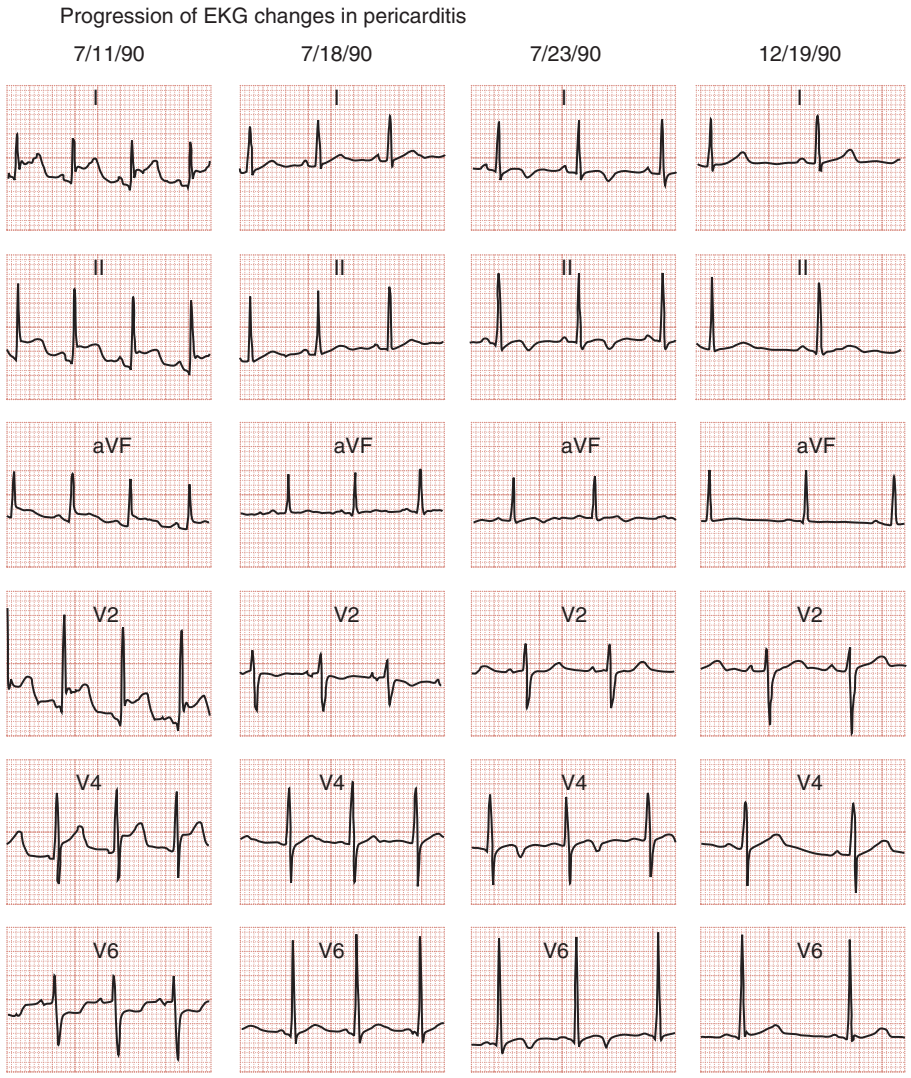


Figure 169-13. The classic electrocardiographic (ECG) progression of a patient with pericarditis. First phase: Diffuse ST segment elevation. Second phase: ST segments back to isoelectric, but decreased T wave amplitude. Third phase: T wave inversion. Fourth phase: Complete resolution. Notice that the first three phases of the ECG abnormalities of pericarditis in this patient are evident during the first 2 weeks of his illness. A follow-up electrocardiogram obtained 5 months later reveals a complete resolution of all the previous ECG abnormalities.

The chest radiograph in a child with pericarditis may not reveal an enlarged cardiac silhouette, depending on the amount of fluid that has accumulated within the pericardial sac. If there is a large collection of fluid within the pericardial sac, the heart shadow on the chest radiograph will resemble a "water bottle" silhouette. Approximately 50% of pericarditis cases also have an associated pleural effusion.[2]

The classic ECG findings of pericarditis include diffuse ST segment elevation and diffuse T wave inversions in all leads. The classic ECG changes associated with pericarditis evolve through four phases (Fig. 169-13). During the initial phase, there is diffuse ST segment elevation in all leads secondary to subepicardial inflammation; PR segment depression may also be seen. During the second phase, the previously elevated ST segments begin to return to isoelectric baseline and the T wave amplitudes begin to decrease with flattening of the T waves. During the third phase, although the ST segments are now back to isoelectric baseline, the T waves are now inverted. The fourth and final phase demonstrates complete resolution of the ST segment and T wave abnormalities. Diminished ECG voltages in all leads can also occur if there is a significant amount of fluid accumulated within the pericardial sac.

The diagnostic procedure of choice in any patient with suspected pericarditis is the echocardiogram, because this study will confirm both the presence and the amount of accumulated fluid within the pericardial sac. Although echocardiography cannot accurately quantify the exact amount of fluid that has accumulated within the pericardial space, the presence of an anterior and posterior fluid collection is suggestive of a large collection.

Management

The management of a child with pericarditis depends on both the suspected cause and the amount of fluid that has accumulated within the pericardial space. An emergency pericardiocentesis will be required in those patients who develop signs of acute cardiac tamponade. Any fluid that is aspirated from the pericardial space should be sent for routine cell counts, Gram's stain, and cultures. Anti-inflammatory agents and appropriate antibiotics should also be initiated based on the suspected cause. Steroids are reserved for refractory cases that are not responsive to the above agents and would be considered only after an infectious etiology is ruled out.[65]

Kawasaki Disease

Perspective

Kawasaki disease, originally described as mucocutaneous lymph node syndrome by Dr. Tomisaku Kawasaki in 1967, has emerged as a significant cause of acquired cardiac disease in children in the United States. An estimated 3000 to 5000 cases of Kawasaki disease are diagnosed annually in the United

BOX 169-17 DIAGNOSTIC CRITERIA FOR KAWASAKI DISEASE (KD)

I. Fever ≥5 days
II. At least four of the five following physical examination findings:
1. Bilateral, nonexudative bulbar conjunctival injection (bilateral scleral injection with perilimbic sparing).
2. Oropharyngeal mucous membrane changes (pharyngeal erythema, red/cracked lips, and a strawberry tongue).
3. Cervical lymphadenopathy (with at least one node >1.5 cm in diameter).
4. Peripheral extremity changes (diffuse erythema and swelling of the hands and feet during the acute phase or periungual desquamation during the convalescent phase of the illness). This diffuse palmar erythema seen in KD is in contrast to the discrete macular lesions of various viral illnesses (e.g., measles) that can sometimes be seen on the palms and soles.
5. A polymorphous generalized rash (nonvesicular and nonbullous). There is no specific rash that is pathognomonic for KD.

In a child with ≥4 criteria, the diagnosis may be made on day 4 of the fever.[67]

States. Up to 20% of untreated children develop some degree of coronary artery abnormalities.[66] This febrile, exanthematous, multisystem vasculitis is seen most commonly in children younger than 5 years of age with a male-to-female ratio of 1.5 : 1. The incidence is higher in Asian children and in certain geographic locations such as Hawaii. Although the exact cause of this vasculitis of small and medium-sized vessels remains unknown, early clinical recognition and initiation of high-dose aspirin and intravenous immunoglobulin therapies have improved the morbidity and mortality rates of Kawasaki disease in children.

Clinical Features

The key to prevention of the coronary artery complications of Kawasaki disease is first to recognize the clinical signs and symptoms of this disease. In addition to fever, the physical examination of a child with Kawasaki disease may reveal the typical findings as listed in Box 169-17 and illustrated in Fig. 169-14. The classic features of Kawasaki disease may manifest simultaneously or in series over days; a careful history and physical examination may elucidate the need for further testing. In addition, very young children may not have a classic presentation and require further investigation. All children with suspected Kawasaki disease, with either classic or incomplete features, should undergo echocardiography to detect the presence and degree of coronary aneurysm.[67]

Incomplete Kawasaki Disease

The classic presentation of Kawasaki disease is a clinical diagnosis of four or more of the five criteria in a child who is febrile five or more days. However, these strict criteria may miss a substantial number of children who present with incomplete Kawasaki disease. Any child may have an incomplete presentation, but this is mostly seen in infants less than 6 months old.[67]

The AHA's Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease has published consensus guidelines on the approach to incomplete Kawasaki disease.[67] The more inclusive criteria recommend that in a child who is febrile 5 days or greater, the presence of two or three criteria should prompt further testing. A CRP of 3 mg/dL or more and/or an erythrocyte sedimentation rate (ESR) of 40 mm/hr or more necessitate further laboratory investigation, such as those listed in Box 169-18. All of these children will also need echocardiography to assess coronary aneurysm, and the recommendation is to treat empirically those whose supplementary laboratory values (see Box 169-18) are positive for systemic inflammation while awaiting echocardiographic confirmation.[67]

Children with a CRP of less than 3 mg/dL and an ESR of less than 40 mm/hr may be followed daily and reassessed. It is important to note that the committee also added a stipulation that the infant 6 months or younger with fever of 7 or more days should also undergo supplemental laboratory testing, and if any signs of systemic inflammation are found, should have an echocardiogram. This underscores the current limits of diagnosis of Kawasaki disease, as well as the obligation to prevent the disastrous sequelae of aneurysmal development.

Differential Considerations

Measles can mimic Kawasaki disease but is rare in vaccinated children (i.e., a febrile illness with red eyes, a rash, and erythema of the oropharynx). The classic location, distribution, and progression of a measles rash starts on the head and face and progresses caudally. The rash of Kawasaki disease typically begins on the trunk and then spreads to the face and extremities. In contrast, Kawasaki disease can exhibit a polymorphous rash that is nonbullous and nonvesicular.

The palmar lesions of measles are discrete macular lesions (see Fig. 169-14F), whereas the palmar finding in children with Kawasaki disease is diffuse erythema, which may later lead to desquamation (see Fig. 169-14C).

Streptococcal disease, including pharyngitis and scarlet fever, can be confused with Kawasaki disease, but conjunctivitis and swelling of the hands and feet are unusual for streptococcal disease. Other infectious or autoimmune etiologies that may mimic Kawasaki disease include Rocky Mountain spotted fever and leptospirosis, or Stevens-Johnson syndrome and juvenile rheumatoid arthritis.[67]

As seen above, there are many imitators of Kawasaki disease. Conversely, this systemic vasculitis can affect any organ system, and thus mislead the clinician in diagnosis. For example, Kawasaki disease can present with nausea, vomiting, and abdominal pain in a febrile child, which may be mistaken for a surgical abdomen. In addition, a febrile, irritable child with Kawasaki disease may exhibit a cerebrospinal fluid pleocytosis and be misdiagnosed with viral meningitis. For this reason, Kawasaki disease should be included in the differential diagnosis of any child with several days of fever, rash, and nonpurulent conjunctivitis to avoid the pitfall of early diagnostic closure.

Clinical Course

Kawasaki disease is postulated to be caused by an infectious agent that enters the respiratory tract and initiates an oligoclonal immunoglobulin A response, which activates lymphocytes, cytokines, and proteinases that weaken vessel walls and predispose the entire circulation to aneurysms.[68] The main reason to recognize this disease entity in children is to initiate prompt therapies to prevent the cardiac complications of Kawasaki disease, which occur in two phases. Approximately 25% of patients develop mild diffuse myocardial inflammation. This occurs during the acute febrile period and is characterized by

Figure 169-14. Classic physical examination findings of Kawasaki disease. Note the bilateral nonexudative scleral injections (**A**) with perilimbic sparing (the thin margin of white sclera around the cornea), red-cracked lips with a strawberry tongue (**B**), diffuse palmar erythema (**C**), red soles (**D**), and the polymorphous exanthem (**E**). The diffuse palmar erythema of Kawasaki disease (**C**) is distinct from the palmar findings seen in other viral illnesses such as the discrete macular lesions on the palms in this child with measles (**F**).

BOX 169-18 SUPPLEMENTAL LABORATORY CRITERIA FOR KAWASAKI DISEASE

Albumin ≤3 g/dL
Anemia for age
Platelet count of ≥450,000/mm^3
White blood cell (WBC) count ≥15,000 mm^3
Elevation of alanine aminotransferase
Sterile pyuria of ≥10 WBCs per high-power field

From Newburger JW, et al: Diagnosis, treatment, and long-term management of Kawasaki disease: A statement for health professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. Circulation 110:2747, 2004.

tachycardia, a gallop rhythm, or nonspecific ST-T wave changes. Up to 5% of the children also exhibit some degree of CHF during this acute phase of their illness. This carditis usually resolves when the fever resolves. Pericardial effusions also occur in up to 20 to 40% of cases. Mild mitral and aortic regurgitation is also seen in 1 to 2% of untreated cases on echocardiographic examinations. This phase of the disease is mild and self-resolving. Therapy during this phase of the illness is primarily supportive.

The second phase of the disease involves coronary artery dilation, which usually peaks 2 to 4 weeks from the onset of the illness and is seen in 15 to 25% of the untreated patients with Kawasaki disease.[69] Without the appropriate treatment, 15 to 20% of children with Kawasaki disease go on to develop

coronary aneurysms within 1 to 3 weeks from the onset of their illness.[2] These coronary aneurysms can then lead to myocardial infarction, thrombosis, rupture, and a variety of ischemia-induced dysrhythmias. Significant risk factors for coronary aneurysmal formation include male gender, age younger than 1 year or greater than 8 years, a prolonged febrile period greater than 10 to 14 days, early myocarditis, anemia (Hgb < 10 g/dL), white blood cell count greater than 30,000, an increased band count, elevated ESR, elevated CRP level, low serum albumin levels, and aneurysms involving the renal, axillary, or iliac arteries and giant coronary aneurysms (>8 mm in diameter). Death from Kawasaki disease is primarily due to myocardial infarction secondary to coronary artery occlusion. Giant coronary artery aneurysmal rupture is rare. Although most of the fatalities that occur with Kawasaki disease occur within 6 weeks from the onset of the illness, sudden death can also occur many years after the illness. Prompt recognition and treatment have decreased this mortality rate from 2% to less than 0.01%.[66]

Management

The main goal of treatment during the acute febrile phase of Kawasaki disease is to provide supportive care and to decrease the inflammation of the myocardium and coronary arteries. The two major components of treatment include intravenous immunoglobulin (IVIG) infusion and high-dose aspirin therapy, which together have an additive effect. This combination of IVIG and high-dose aspirin, when initiated within 10 days from the onset of the illness, can substantially decrease the progression to coronary artery dilation and aneurysm formation as compared with aspirin therapy alone and results in a more rapid resolution of fever and the other indicators of acute inflammation.[66] However, despite prompt treatment with IVIG and high-dose aspirin, 2 to 4% of the children still develop coronary artery abnormalities.[66]

The current IVIG regimen involves an infusion of 2 g/kg over 10 to 12 hours. Side effects of IVIG include hypotension, nausea, vomiting, and seizures. Close cardiac monitoring during the IVIG infusion is mandatory. The 5 to 10% of children who receive IVIG who experience a persistent or recurrent fever after the initial dose of IVIG may be given a second infusion at the same dose. Approximately two thirds of those children who fail to respond to the initial dose of IVIG will improve with the second infusion.

Aspirin is initiated at 80 to 100 mg/kg/day orally divided into an every-6-hour dosing regimen until the child is afebrile for 48 to 72 hours (or longer). This dose is then decreased to 3 to 5 mg/kg orally each day until the laboratory study results return to normal, which typically occurs 6 to 8 weeks after the onset of the disease. Aspirin therapy is continued beyond this period only in those children in whom coronary artery abnormalities are present. Ibuprofen can antagonize the antiplatelet effects of aspirin and should be avoided during treatment.[67]

The use of corticosteroids as primary treatment has not been well established. A recent multicenter, randomized, double-blind study to determine the efficacy of the addition of methylprednisolone to initial conventional therapy showed no difference in clinical outcome, including dimensions of coronary artery aneurysms, length of hospital stay, and rate of re-treatment with IVIG.[70] The current recommendations include corticosteroids for refractory cases of Kawasaki disease, in which children are continued on high-dose aspirin, a second dose of IVIG is administered, and corticosteroids are added to decrease the risk of coronary artery aneurysm.[67,71] Other complications such as coronary aneurysmal thrombosis likewise have limited data to guide management. Therapeutic options include streptokinase, tissue-type plasminogen activator, and interventional cardiac catheterization.[67]

The follow-up of children with Kawasaki disease depends on the degree and presence of carditis and coronary artery abnormalities detected on the initial echocardiogram. Other imaging modalities used to follow aneurysmal parameters include electron-beam computed tomography, coronary magnetic resonance angiography, and multislice spiral computed tomography.[67] Those children with more severe cardiac abnormalities require very close follow-up by a cardiologist who is experienced in managing the cardiac complications of Kawasaki disease. Overall, prompt diagnosis and appropriate therapies can prevent coronary aneurysm formation in up to 95% of the cases as well as rapid symptomatic improvement in up to 90% of the cases.[72]

Acute Rheumatic Fever

Perspective

Acute rheumatic fever is the result of a delayed immune reaction of a group A streptococcal infection. ARF is one of the most common causes of acquired heart disease in children. In the United States, ARF most commonly occurs in children 5 to 15 years of age and has an attack rate of 0.3% in children with an untreated streptococcal infection. Although this disease affects multiple organ systems, carditis is the most serious complication.

Clinical Features and Diagnostic Considerations

The diagnosis of ARF is based on the Jones criteria (Box 169-19). In addition to the Jones criteria, there must also be evidence of an antecedent streptococcal infection, which can be documented with either a positive throat culture, a positive rapid streptococcal antigen test finding, or an elevated antistreptolysin O titer. The streptozyme test is not as reliable and therefore should not be used as a definitive test for evidence of an antecedent group A streptococcal infection.[73] The diag-

BOX 169-19 JONES CRITERIA FOR THE DIAGNOSIS OF ACUTE RHEUMATIC FEVER (ARF)

The diagnosis of ARF is based on the documentation of an antecedent streptococcal infection and either two major criteria or one major criteria + two minor criteria.

- Major criteria
  - Carditis
  - Migratory polyarthritis
  - Erythema marginatum
  - Subcutaneous nodules
  - Chorea
- Minor criteria
  - Clinical findings
    - Fever
    - Arthralgia
  - Laboratory findings
    - Elevated C-reactive protein or erythrocyte sedimentation rate
    - Prolonged PR interval
  - Supporting evidence of an antecedent group A streptococcal infection with either:
    - A positive throat culture or a rapid streptococcal antigen test
    - An elevated antistreptolysin O titer

nosis of ARF is made in a patient with a documented antecedent streptococcal infection who exhibits either two major criteria or one major plus two minor criteria. The most common presenting major criterion is the migratory polyarthritis, which commonly involves the larger joints of the extremities as well as the smaller tarsal joints in the foot and the smaller carpal joints in the hand. The carditis of ARF most commonly involves valvulitis of the mitral and aortic valves, which clinically manifests as occult mitral or aortic insufficiency. The murmur of mitral insufficiency is characterized as a holosystolic murmur best heard over the apex with radiation to the axilla. The murmur of aortic insufficiency is characterized as a diastolic murmur that is best heard over the base of the heart. Innocent murmurs that are normally exacerbated with fever can be mistaken for the murmurs of mitral or aortic insufficiency. The other cardiac manifestations of ARF include CHF, pericarditis, and various degrees of heart blocks. The two dermatologic major criteria (erythema marginatum and subcutaneous nodules) and chorea occur less commonly than the migratory polyarthritis and carditis. Chorea may occur as the only manifestation of ARF. If arthritis is used as a major component, arthralgia cannot be used as a minor component to make the diagnosis. Likewise, if carditis is used as a major component, then a prolonged PR interval cannot be used as a minor component.[73]

In addition to the ECG, CRP level, ESR, and documentation of an antecedent streptococcal infection, the diagnostic workup of ARF should also include a chest radiograph as well as an echocardiogram to evaluate the degree of cardiac involvement.

Differential Considerations

The differential diagnosis of ARF includes myocarditis, bacterial endocarditis, Lyme disease, systemic lupus erythematosus, juvenile rheumatoid arthritis, serum sickness, and septic arthritis.

Management

The acute management of ARF should first focus on stabilizing and treating any of the symptomatic cardiac manifestations of the illness, such as CHF or tamponade due to a pericardial effusion. Additional goals in ARF management include appropriate antibiotic therapy to eradicate the streptococcal infection, bedrest, and anti-inflammatory agents for the arthritis. The use of steroids in the treatment of carditis should only be employed under direction of a cardiologist. Another important aspect in the management of ARF is the prevention of recurrent attacks through the prophylactic use of penicillin, which can be given as monthly injections of 1.2 million units of benzathine penicillin G. Alternative prophylactic regimens include oral penicillin administered twice daily, or for penicillin-allergic patients, twice daily oral erythromycin. This prophylaxis with penicillin or erythromycin is required until 18 years of age at the minimum but can be continued for life, depending on the degree of cardiac involvement and the risk for recurrence.

Cardiac Causes of Sudden Death in Young Athletes

Perspective

The most common cause of sudden, unexplained death in athletes is various cardiac conditions, with only 15% of the cases stemming from noncardiovascular causes (Box 169-20).[74]

BOX 169-20 Cardiovascular Etiologies of Sudden Death in Young Athletes

Hypertrophic cardiomyopathy
Various congenital coronary artery anomalies
Prolonged QT interval syndrome
Various preexcitation syndromes (e.g., Wolff-Parkinson-White syndrome)
Commotio cordis
Aortic rupture secondary to Marfan's syndrome
Idiopathic dilated cardiomyopathy
Myocarditis
Coronary artery disease secondary to Kawasaki disease
Aortic stenosis
Mitral valve prolapse

The most common cardiovascular cause of sudden death in the athlete is hypertrophic cardiomyopathy, which accounts for up to 36% of the cardiovascular-related cases.[61]

Specific Disorders

Congenital Coronary Artery Anomalies. An additional 24% of the cases of sudden death are due to various anomalies of the coronary arteries.[75] Congenital coronary artery anomalies are difficult to detect from a clinical standpoint, but 37% of those individuals who died from congenital coronary artery anomalies did exhibit previous symptoms of exercise-induced syncope or chest pain.[76] The exact pathophysiologic mechanism of sudden death in individuals with congenital coronary anomalies is unknown. Although there are a variety of congenital coronary artery anomalies, the most common potentially lethal lesion is the anomalous left coronary artery in which the left main and right coronary arteries both arise from the right sinus of Valsalva. Individuals with this particular anomaly have a 46% incidence of sudden death, with more than 85% of the known cases of sudden death occurring during exercise.[77] Congenital coronary artery hypoplasia is another uncommon cause of exercise-induced sudden death. Any athlete with exertional syncope or chest pain should be evaluated by a cardiologist for the possibility of congenital coronary artery anomalies. If an anomaly is detected and surgically corrected, the athlete may resume full activity and participation in competitive sports.

Marfan's Syndrome. Individuals with Marfan's syndrome should be evaluated for potential cardiac abnormalities before being allowed to participate in competitive sports. Clinical manifestations of the disease include tall, slender habitus, striae atrophicae of the skin (multiple stretch marks on skin), disproportionately long extremities as compared to the trunk, scoliosis, pectus excavatum or carinatum, and dislocated lenses of the eye. Approximately 50% of patients with Marfan's syndrome have cardiac manifestations such as mitral valve prolapse or aortic dilation. The most serious cardiac complication of Marfan's syndrome is the progressive dilation of the aorta with the potential risk of aortic rupture, which most commonly involves the descending portion of the aorta. Therefore, patients with Marfan's syndrome should be prohibited from participation in contact sports. Those individuals who are known to have aortic dilation should also be prohibited from participation in any competitive sports regardless of the degree of contact involved.[75] All patients with Marfan's syndrome with or without cardiac involvement on their initial evaluation should be followed by a cardiologist with serial imaging studies of their aorta using echocardiography, magnetic resonance imaging, or computed tomography.

Hypertrophic Cardiomyopathy

Perspective. Although the nonobstructive form of hypertrophic cardiomyopathy is an uncommon cardiac malformation that occurs in only 0.2% of the general population, it is the single most common cardiac cause of sudden death in the young athlete.[77–79] Hypertrophic cardiomyopathy is a familial disease that is inherited in an autosomal dominant fashion with variable penetrance. The hypertrophy of the left ventricle in this condition is idiopathic in nature and not due to chronic pressure overload conditions such as systemic hypertension or aortic stenosis. The systolic left ventricular contractile function is vigorous but the thickened muscle of the left ventricle is stiff, resulting in impaired ventricular relaxation and high diastolic filling pressures.[80]

Sudden death in previously asymptomatic individuals with hypertrophic cardiomyopathy occurs during moderate or severe physical exertion. The proposed pathophysiologic mechanisms of sudden death during exertion in these individuals is thought to be due to a transient decrease of blood flow out through the aorta or to dysrhythmias secondary to the hypertrophied ventricular myocardium.

Clinical Features. Some individuals with hypertrophic cardiomyopathy have experienced previous "warning" episodes of chest pain, dyspnea, syncope, or palpitations during vigorous activities. A family history of sudden unexplained death in young adults should also alert the clinician to the possibility of hypertrophic cardiomyopathy. The majority of young athletes who die from this condition have the nonobstructive form of hypertrophic cardiomyopathy, and the classic loud systolic ejection murmur that is present with the obstructive form is not heard during the routine presports physical examinations.[81] Therefore, the standard presports screening physical examination may fail to detect the presence of nonobstructive hypertrophic cardiomyopathy in young athletes. If a systolic murmur along the lower left sternal border is heard on the routine screening physical examination of a young athlete, a Valsalva maneuver may help to differentiate the murmur of aortic stenosis from the systolic murmur associated with the obstructive form of hypertrophic cardiomyopathy. During the Valsalva maneuver, the venous blood return to the heart is decreased, which in turn transiently reduces the left ventricular size. The transient reduction in the size of the left ventricle will increase the degree of obstruction and thus cause an increase in the intensity of the systolic murmur heard with the obstructive form of hypertrophic cardiomyopathy. In contrast to this, the systolic murmur of aortic stenosis will decrease in intensity during a Valsalva maneuver due to the transient reduction of blood flow through the stenotic aortic valve.

Individuals who are suspected of having hypertrophic cardiomyopathy based on the above-mentioned exertional symptoms, a positive family history, or both should be referred to a cardiologist for a more extensive workup.

Diagnostic Studies. The ECG findings in individuals with hypertrophic cardiomyopathy typically reveal various degrees of left ventricular hypertrophy and left atrial enlargement. Other ECG findings include prominent Q waves in the inferolateral leads or diffuse T wave inversions. The most accurate study to make the diagnosis of hypertrophic cardiomyopathy is the echocardiogram, which will demonstrate various degrees of left ventricular hypertrophy most commonly involving the ventricular septum in up to 90% of the cases.[80] Those patients who have echocardiographic evidence of hypertrophic cardiomyopathy should be followed with serial echocardiographic examinations to monitor the progression of their condition.

Management. Although beta-blockers have been used in patients with hypertrophic cardiomyopathy, they have not been shown to prevent sudden death in these patients. The use of digoxin is contraindicated in patients with hypertrophic cardiomyopathy because its positive inotropic effect may worsen the left ventricular outflow obstruction. Sudden death in these patients with hypertrophic cardiomyopathy is thought to be due to exertion-induced ventricular fibrillation or pulseless ventricular tachycardia. Therefore, the current recommendation is that all individuals who are diagnosed with hypertrophic cardiomyopathy, as well as those individuals with an equivocal diagnosis of hypertrophic cardiomyopathy, should not participate in vigorous activities and competitive sports.

Prolonged QT Syndrome

Perspective. In 1957, Jervell and Lange-Nielsen first described the association of recurrent syncope, sudden death, and long QT interval in a series of deaf patients. Later, in 1963, Romano reported a similar association of symptoms with long QT intervals in patients with normal hearing. Both the Jervell-Lange-Nielsen and the Romano-Ward syndrome are inherited disorders with variable penetrance, characterized by a prolonged QT interval that has been associated with sudden death. The corrected QT interval (QTc) in normal individuals should not exceed 0.44 seconds in children or 0.42 seconds in adolescents. Individuals with QTc intervals greater than 0.55 seconds have a higher risk of sudden death. Prolongation of the QT interval predisposes the individual to ventricular tachycardia, torsades de pointes, and ventricular fibrillation, which is often initiated by a premature ventricular contraction occurring during the prolonged repolarization phase. In addition to the inherited syndromes of prolonged QT intervals, other causes of prolonged QT intervals include hypocalcemia, hypokalemia, hypomagnesemia, myocarditis, and medications (e.g., procainamide, erythromycin, cyclic antidepressants, phenothiazines, quinidine, organophosphates).

Clinical Features. Symptoms in the young athlete that are suggestive of QT prolongation include exercise-induced palpitations, chest pains, syncope, dizziness, or atypical seizures. The young athlete who develops any of these symptoms should be evaluated by a cardiologist, especially if the family history is positive for sudden unexplained death, cardiac problems, syncope, or deafness. Any young athlete who has been diagnosed with a prolonged QT syndrome should be prohibited from participation in competitive sports and vigorous activities. The growing popularity and presence of AEDs in public places and at sporting events can potentially save the lives of those athletes who suddenly collapse due to an underlying prolonged QT syndrome–induced nonperfusing ventricular dysrhythmia.

Management. Treatment of a prolonged QT interval depends on the cause. Correction of any underlying metabolic disorder and discontinuing a medication that induced the prolongation of the QT interval are the easiest conditions to correct. Magnesium sulfate is the drug of choice in the treatment of torsades de pointes. Antidysrhythmic agents that also can prolong the QT interval, such as procainamide and amiodarone, should be avoided. Therefore, the safest medication to use in a patient with prolonged QT interval-induced ventricular tachycardia or fibrillation is lidocaine. Beta-blockers have been used to prevent sudden ventricular dysrhythmias in those patients with the familial forms of QT prolongation. Adjunctive treatment in these selected patients also includes the insertion of pacemakers or internal defibrillators.

Commotio Cordis. The phenomenon of commotio cordis occurs when an object such as a baseball strikes the chest and produces sudden death. This phenomenon most commonly occurs in children between 5 and 15 years of age with no known predisposing cardiac conditions.[75,82] Although commotio cordis most commonly occurs in baseball, it has also been reported to occur in ice hockey, lacrosse, softball, and fist fights.[69] In a

few cases in which the cardiac rhythm was documented after the blunt trauma to the chest, the most common rhythm documented was ventricular fibrillation.[83] The majority of patients who sustain commotio cordis do not survive, especially if they are not rapidly treated with defibrillation. If an AED is not immediately available and the patient is completely unresponsive with no pulse after sustaining a direct blow to the chest, some practitioners have proposed that performing chest thumps during cardiopulmonary resuscitation may be of some benefit under this particular circumstance.

KEY CONCEPTS

- The possibility of a congenital heart defect should be considered in an infant who presents with central cyanosis that does not respond to 100% supplemental oxygen (hyperoxia challenge).
- Neonates with ductal-dependent cardiac lesions typically present within the first 2 to 3 weeks of life with either acute cyanosis or shock. Initiation of a PGE_1 infusion (0.05–0.1 µg/kg/min) will be lifesaving in these neonates.
- Treatment of a hypoxic tet spell first includes placing the infant in the knee-to-chest position and providing supplemental oxygen. Sedative agents can be used to decrease the infant's hyperpnea. Various medications can be used as adjunctive treatment to increase the SVR and thereby decrease the degree of right-to-left shunting across the ventricular septal defect.
- Prompt recognition of the clinical findings and symptoms of Kawasaki disease along with the rapid initiation of high-dose aspirin and IVIG infusion can prevent the formation of coronary aneurysms.
- Acute bacterial endocarditis should always be considered in a child with a known congenital heart defect or an acquired cardiac defect who presents with a fever of unknown origin, the development of acute neurologic deficits, new-onset microscopic hematuria, myalgias, splenomegaly, petechiae, or other signs of systemic embolization.
- Oxygen, diuretics (furosemide), and inotropic agents (digoxin) are the mainstay of treatment for infants and children who present with CHF.
- If vagal maneuvers fail to convert stable paroxysmal supraventricular tachycardia in children, rapid adenosine administration (0.1 mg/kg for the first dose followed by 0.2 mg/kg on repeat doses) is the treatment of choice. Verapamil should be avoided in children younger than 1 year due to its profound hypotensive effects.
- One should consider the use of lidocaine instead of amiodarone in cases of ventricular fibrillation or ventricular tachycardia due to medications (e.g., cyclic antidepressants) or toxins that prolong the QT interval.
- Young athletes with a positive family history of sudden unexplained death or exertion-induced symptoms such as chest pain, dyspnea, palpitations, or syncope should be evaluated by a cardiologist prior to their resumption of vigorous activity.
- The increased presence of AEDs in public places and at sporting events can potentially save the lives of more young athletes who suddenly collapse secondary to hypertrophic cardiomyopathy, prolonged QT syndromes, and commotio cordis.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 170 Gastrointestinal Disorders

Mark A. Hostetler

NEONATAL JAUNDICE

Perspective

Many infants become jaundiced during the newborn period, most often as a result of a benign, self-limited process. *Physiologic jaundice of the newborn* is the most common cause of neonatal jaundice and occurs in approximately 60% of normal newborns during the first week of life. *Breast milk jaundice* is the second most common cause of jaundice in the newborn period.

Principles of Disease

Bilirubin is formed by the breakdown of heme-containing proteins, primarily hemoglobin. Heme protoporphyrin is sequentially degraded into biliverdin and unconjugated bilirubin. Unconjugated bilirubin binds to albumin in the blood and is carried to the liver, where it is conjugated by glucuronyl transferase and excreted into bile. Jaundice may be caused by increased amounts of either unconjugated or conjugated bilirubin and becomes clinically apparent when the total bilirubin level reaches approximately 5 mg/dL. Conjugated hyperbilirubinemia occurs when the direct-reacting portion exceeds 2 mg/dL or is greater than 20% of the total.

The exact pathogenetic mechanism of breast milk jaundice is uncertain. Breast milk jaundice may be hormonally mediated or related to intestinal excretion and resorption of bile. Other causes of jaundice vary significantly, depending on the percent conjugation and age of the infant (Tables 170-1 and 170-2). Although jaundice in adults usually is the direct result of primary liver disease, infantile causes include a variety of extrahepatic causes—genetic, metabolic, infectious, and obstructive. The list of diagnostic possibilities in neonatal jaundice is extensive and requires careful consideration because the morbidity and mortality rates for many of these entities are high.

Clinical Features

Physiologic jaundice of the newborn is the most common cause of neonatal jaundice and occurs in approximately 60% of normal newborns during the first week of life. Affected infants are born with normal bilirubin levels that gradually increase to a peak level of 6 mg/dL on the third day of life and then decline to normal within 2 weeks. Breast milk jaundice is the next most common cause of hyperbilirubinemia in newborns. Affected infants exhibit the same gradual increase seen with physiologic jaundice. Levels continue to increase, however, and reach a higher peak level at 10 days to 3 weeks of life. Elevated levels may persist for 3 to 10 weeks and then gradually subside.

Toxic levels of bilirubin (greater than 20 mg/dL and dependent on age) may be associated with neurotoxicity, encephalopathy, and the development of kernicterus. Kernicterus is characterized by yellow staining in areas of the brain, including the basal ganglia. Clinical manifestations begin with poor feeding and lethargy and may progress to muscular rigidity, opisthotonos, seizures, and death. Survivors may have residual problems with coordination, hearing, and learning disabilities.[1] The cornerstones of therapy are phototherapy and exchange transfusion.

Diagnostic Strategies

Although physiologic jaundice of the newborn and breast milk jaundice are most common, it is important to identify truly pathologic causes of jaundice. Initial testing requires determination of fractionated levels of total and direct bilirubin. Box 170-1 lists indications for workup in infants presenting with hyperbilirubinemia. Conjugated (direct) hyperbilirubinemia is always pathologic. In such cases, a minimal workup should include a complete blood count (CBC) with peripheral smear and a Coombs' test for immune-mediated major blood group incompatibility. Ill-appearing infants also require finger-stick blood glucose measurement, electrolyte panel, urine assay for reducing substances, and serum ammonia determination to rule out inborn errors of metabolism.[2]

Differential Considerations

Birth history should be obtained to elicit any history of trauma, because large, resolving hematomas can result in jaundice. Family history should focus on identifying siblings or other relatives with a history of jaundice or genetic or metabolic disorders and any unexplained infant deaths. Tables 170-1 and 170-2 present full lists of differential considerations for jaundiced infants and children, respectively.

Infants with direct hyperbilirubinemia represent a special subset of patients. All infants with direct hyperbilirubinemia require hospital admission and evaluation for the cause of the jaundice based on history and presenting signs and symptoms. This evaluation may include any or all of the following: sepsis

Table 170-1 Differential Considerations for Hyperbilirubinemia in Infants

ETIOLOGIC CATEGORY	UNCONJUGATED (INDIRECT)	CONJUGATED (DIRECT)
Benign/physiologic	Physiologic jaundice of the newborn Breast milk jaundice	
Hemolysis	ABO incompatibility Physiologic breakdown of birth trauma hematoma (cephalhematoma) Intraventricular/intracranial hemorrhage Spherocytosis, elliptocytosis Sickle cell anemia Thalassemia Glucose-6-phosphate dehydrogenase deficiency Pyruvate kinase deficiency	
Infectious	TORCHS infections Urinary tract infection Sepsis	TORCHS infections Urinary tract infection Gram-negative sepsis Listeriosis Tuberculosis Hepatitis B Varicella Coxsackievirus infection Echovirus infection HIV infection
Obstructive	Meconium ileus Hirschsprung's disease Duodenal atresia Pyloric stenosis	Biliary atresia Choledochal cyst Bile duct strictures Inspissated bile syndrome Neonatal hepatitis Alagille syndrome Byler's disease Congenital hepatic fibrosis
Metabolic/genetic	Galactosemia Congenital hypothyroidism Crigler-Najjar syndrome Gilbert's syndrome	Galactosemia Tyrosinemia Glycogen storage disease type IV Niemann-Pick disease Wolman's disease Gaucher's disease Cholesterol ester storage disease α_1-antitrypsin deficiency Cystic fibrosis Dubin-Johnson syndrome Neonatal hypopituitarism Zellweger's syndrome Donohue syndrome (leprechaunism) Rotor syndrome
Miscellaneous		Drugs/toxins Parenteral nutrition

CMV, cytomegalovirus; HIV, human immunodeficiency virus; TORCHS, *o*ther infections, *t*oxoplasmosis, *r*ubella, *C*MV, *h*erpes, *s*yphilis.

BOX 170-1 Indications for Workup in Jaundiced Infants

- Jaundice appearing within 24 hours of birth
- Elevated direct (conjugated) bilirubin level
- Rapidly rising total serum bilirubin unexplained by history or physical examination
- Total serum bilirubin approaching exchange level or not responding to phototherapy
- Jaundice persisting beyond age 3 weeks
- Sick-appearing infant

workup, TORCHS (*t*oxoplasmosis, *o*ther infections, *r*ubella, *c*ytomegalovirus, *h*erpes, *s*yphilis) titers, basic metabolic studies, α_1-antitrypsin, sweat test for cystic fibrosis, ultrasound studies, radioisotopes (hepato-iminodiacetic acid [HIDA]/diisopropyl iminodiacetic acid [DISIDA]) scan, and liver biopsy. In children, hemolytic anemia, infection, and drugs are the most common causes of jaundice. The history should focus on travel, exposures, medications, and associated signs and symptoms such as fever, malaise, and weight loss. Gentle palpation of the liver is useful to estimate size, firmness, and tenderness and to distinguish hepatomegaly from liver inflammation.

Management

Treatment of infants with hyperbilirubinemia centers on the prevention of kernicterus. Guidelines for using phototherapy and exchange transfusion have been recommended by the American Academy of Pediatrics[3] (Fig. 170-1). Feeding should be continued to the extent possible because oral intake stimulates enterohepatic circulation and decreases bilirubin levels. Unless the infant is severely jaundiced, breast-feeding can be continued and supplemented with formula as needed. Infants

Table 170-2 Differential Considerations for Hyperbilirubinemia in Older Children

ETIOLOGIC CATEGORY	UNCONJUGATED (INDIRECT)	CONJUGATED (DIRECT)
Obstructive		Gallstones Tumor Choledochal cyst Bile duct stricture
Infectious		Hepatitis Sepsis Urinary tract infection
Genetic	Sickle cell Thalassemia Spherocytosis, elliptocytosis Glucose-6-phosphate dehydrogenase deficiency Pyruvate kinase deficiency Crigler-Najjar syndrome Gilbert's syndrome	Dubin-Johnson syndrome Rotor syndrome Wilson's disease Cystic fibrosis α_1-antitrypsin deficiency Glycogen storage disease
Other	Drug-induced hemolytic anemia Autoimmune hemolytic anemia Microangiopathic hemolytic anemia Hypersplenism	Cirrhosis Sclerosing cholangitis Cholestatic jaundice of pregnancy Drugs/toxins (acetaminophen, estrogens)

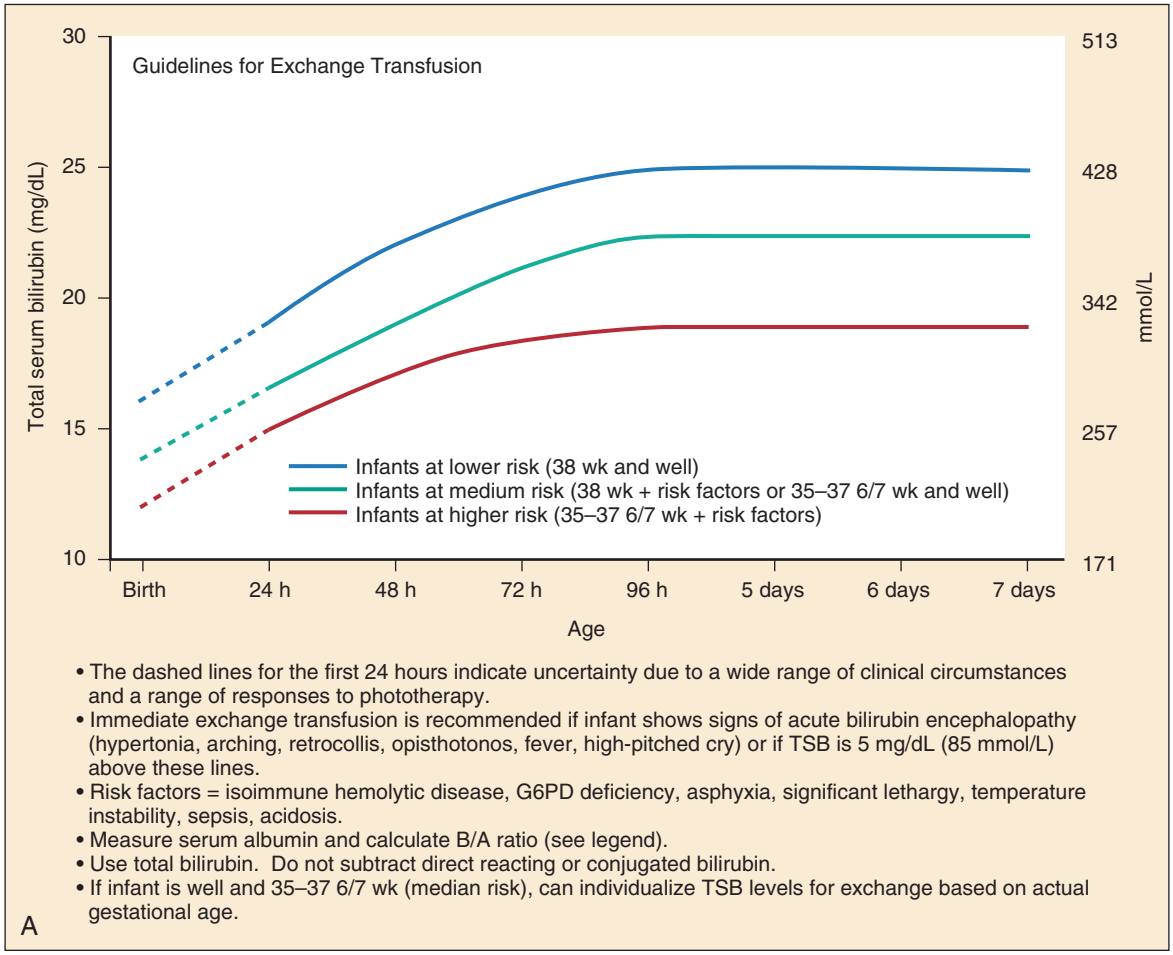


Figure 170-1. A, Guidelines for exchange transfusion in infants of 35 or more weeks' gestation. Note that these suggested levels represent a consensus but are based on limited evidence, and the levels shown are approximations. During birth hospitalization, exchange transfusion is recommended if the total serum bilirubin (TSB) rises to these levels despite intensive phototherapy. For rehospitalized infants, if the TSB level is above the exchange level, repeat TSB measurement every 2 to 3 hours and consider exchange if the TSB remains above the levels indicated after intensive phototherapy for 6 hours. B/A, bilirubin/albumin.

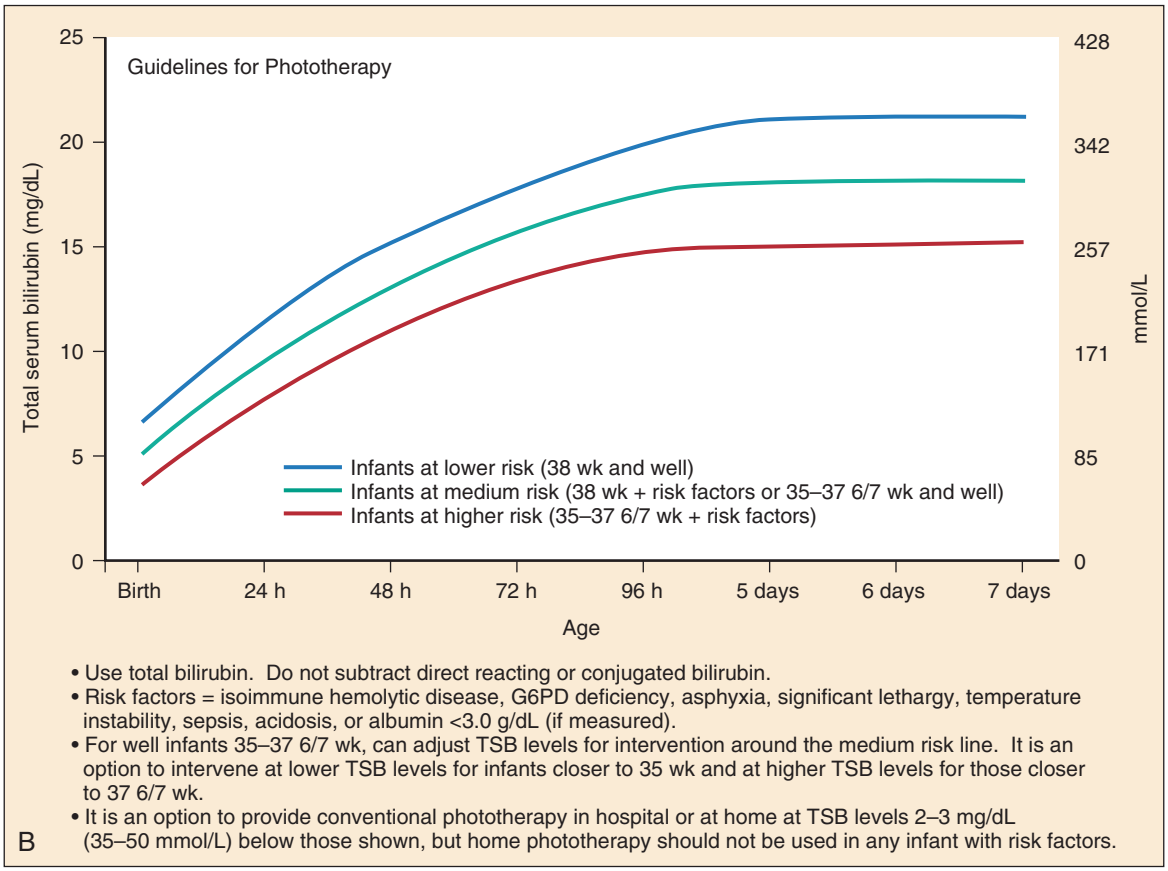


Figure 170-1, cont'd **B,** Guidelines for phototherapy in hospitalized infants of 35 or more weeks' gestation. Note that these guidelines are based on limited evidence, and the levels shown are approximations. The guidelines refer to the use of intensive phototherapy, which should be used when the TSB exceeds the line indicated for each category. Infants are designated as "higher risk" because of the potential negative effects of the conditions listed on albumin binding of bilirubin, the blood-brain barrier, and the susceptibility of the brain cells to damage by bilirubin. G6PD, glucose-6-phosphate dehydrogenase. (From American Academy of Pediatrics Clinical Practice Guidelines: Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics 114:305, 2004.)

who are premature or who have significant comorbidity require treatment at lower levels. Phototherapy often is now readily available on an outpatient basis.

Disposition

In general, infants with bilirubin levels greater than 18 to 20 mg/dL require hospital admission and phototherapy. All infants with direct hyperbilirubinemia require admission and workup.

HYPERTROPHIC PYLORIC STENOSIS

Perspective

Hypertrophic pyloric stenosis is the most common cause of infantile gastrointestinal (GI) obstruction beyond the first month of life. This condition occurs in 1 of every 250 live births.[4] Boys are affected at four times the rate of girls. Hypertrophic pyloric stenosis tends to run in families; however, the exact pattern of inheritance is unclear. The incidence rate is 1 in 14 if the father was affected; the rate is even higher if the mother was affected.[4] Whites are affected more often than African Americans, and the disease is rare in Asian Americans.

Principles of Disease

Infants are born with a normal pylorus, which undergoes hypertrophy only as time progresses. The exact etiology is unknown. As the pylorus continues to hypertrophy, there is progressive gastric outlet obstruction. As vomiting continues, the infant loses hydrogen and chloride ions through emesis of gastric juices. As this metabolic derangement worsens, the kidney attempts to retain hydrogen ions in exchange for potassium, resulting in a hypochloremic, hypokalemic metabolic alkalosis.

Clinical Features

Infants classically present at 2 to 6 weeks old with gradually progressive emesis that becomes projectile and remains nonbilious. Infants remain vigorous with a ravenous appetite. They rapidly finish an entire feeding, only to regurgitate the entire volume in a projectile fashion. In the later stages of the disease, children may exhibit visible waves of abdominal peristalsis in response to intense contractions against an obstruction. Children in the later stages of disease may exhibit marasmus—protein-calorie malnutrition—as a result of impaired nutrient absorption.

Diagnostic Strategies

Children may have a palpable pylorus, commonly referred to as an "olive" in the right epigastrium, on abdominal examination. Placing a nasogastric tube and emptying the stomach or placing the infant in the prone position often facilitates palpation. Hypertrophic pyloric stenosis may be confirmed by ultrasonography or upper GI series. Ultrasonography is the

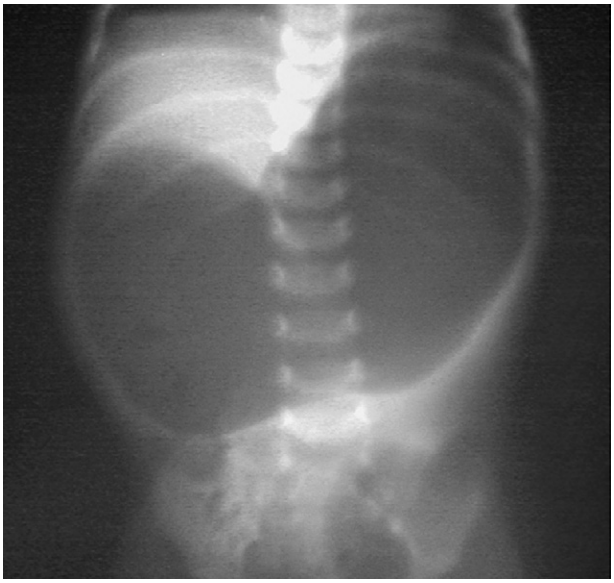


Figure 170-2. Plain radiograph of the abdomen revealing enlargement of the body and pyloric portions of the stomach; this is seen in advanced stages of hypertrophic pyloric stenosis. (Courtesy of Mark A. Hostetler, MD.)

diagnostic modality of choice because it is simple, readily available, and without serious complications such as aspiration. With both modalities, reported accuracy is greater than 95%. Ultrasound examination reveals a thickened pylorus, which is diagnostic.[5] A characteristic "string sign," reflecting passage of contrast material through the narrowed pyloric sphincter, can be seen in the upper GI tract. In advanced stages with complete obstruction at the pylorus, plain films may reveal an enlarged body of the stomach and pylorus (Fig. 170-2).

Differential Considerations

Etiologic possibilities vary depending on whether the course of vomiting has been sudden in onset, gradually progressive, or chronic. Details such as the frequency and volume of emesis also are important because they may have important implications regarding the severity of disease and the potential risk for dehydration or electrolyte disturbance. In infants, other major considerations in the differential diagnosis include gastroesophageal reflux and malrotation. The age of the child and the timing of vomiting provide important clues to the etiology. Reflux classically begins early in life, usually shortly after birth, and remains relatively constant. With pyloric stenosis, vomiting does not begin until 2 to 3 weeks of age and then becomes increasingly severe and projectile; the emesis is rarely if ever bilious. In neonates, bilious vomiting requires careful consideration to rule out the possibility of malrotation with volvulus.[6]

Many causes of vomiting do not have a true GI origin, including sepsis, increased intracranial pressure, middle ear disturbances, urinary tract infections, inborn errors of metabolism, pain, medications, and drug intoxications. Differential considerations for vomiting in children vary by age (Table 170-3).

Management

Treatment consists of fluid and electrolyte replacement and surgical consultation. Fluid resuscitation should begin with a 20 mL/kg bolus of normal saline, followed by additional boluses as necessary to treat signs of shock. When the patient is stable and shows no signs of shock, 5% dextrose and half-normal saline at 1.5 to 2 times maintenance may be administered. Potassium supplementation is often necessary. Hypertrophic pyloric stenosis is a chronic, progressive disease, not an acute ischemic process. Confirmatory radiographic diagnosis with ultrasonography may be done on a semi-urgent basis as symptoms warrant. Pediatric surgical consultation is mandatory, although usually not emergent. The definitive corrective surgical procedure is the Ramsteadt pyloromyotomy, which has an excellent track record of safety.[7] More recently, laparoscopic pyloromyotomy has gained increasing acceptance as being safe and effective.[8] Associated mortality is rare.

Disposition

Most children probably are best managed with hospital admission for rehydration and correction of electrolyte abnormalities, with imaging and surgical consultation done on a semi-elective basis.

MALROTATION WITH MIDGUT VOLVULUS

Perspective

Malrotation occurs in 1 in 500 live births and has a male predominance by at least 2:1.[9] Among infants with malrotation, volvulus eventually will develop in approximately 75%, and 75% of these infants present within the first month of life. Overall, 90% of patients present within the first year of life, although cases of adult midgut volvulus have been reported.[9] Bilious emesis is the hallmark presentation and is seen in greater than 75% of cases.[6,9,10] Malrotation with volvulus carries a mortality rate of 3 to 15%.[9]

Principles of Disease

During embryologic development, the GI tract rotates around the superior mesenteric artery. As it completes the rotation, the duodenum forms a C-loop and is fixed to the retroperitoneum in the left upper quadrant at the ligament of Treitz. The cecum becomes similarly fixed in the right lower quadrant. The duodenum and cecum normally come to lie widely separated and loosely connected by a broad-based mesentery. They are fixed firmly in position by peritoneal attachments called *Ladd's bands*. In cases of malrotation, the duodenum and the cecum do not rotate completely but end up in close proximity to each other, suspended in the midgut region by their vascular attachment containing the superior mesenteric artery. This unusually close proximity of the intervening mesentery results in a short stalk of mesentery that easily twists on itself, resulting in obstruction of the distal duodenum and compression of the superior mesenteric artery. Vascular compression results in ischemia of the bowel and, if not rapidly reversed, necrosis of the bowel wall in 1 to 2 hours.[9,12] Twisting of the pedicle also results in various degrees of obstruction secondary to Ladd's bands that are malpositioned and straddling the duodenum.

Bilious emesis is the hallmark presentation and occurs as a result of severe obstruction. Any pigmented staining of the vomitus suggests the presence of bile. When initially produced, bile is bright yellow and turns green only with time and oxidative exposures. Differential coloring of bile-stained emesis, yellow versus green, is not predictive of surgical pathology.

Table 170-3 Differential Considerations for Vomiting by Age

ETIOLOGIC CATEGORY	INFANCY	CHILDHOOD	ADOLESCENCE
Mechanical	Gastroesophageal reflux Malrotation with midgut volvulus Pyloric stenosis Meckel's diverticulum Intussusception Bowel obstruction Incarcerated hernia Tracheoesophageal fistula	Constipation Incarcerated hernia Meckel's diverticulum Bowel obstruction	Constipation Incarcerated hernia
Inflammatory/infectious	Necrotizing enterocolitis Gastroenteritis Sepsis Henoch-Schönlein purpura Meningitis Pneumonia Otitis media	Gastritis/gastroenteritis Otitis media Appendicitis Pancreatitis Henoch-Schönlein purpura Biliary tract disease	Gastroenteritis Appendicitis Pancreatitis Gastritis Biliary tract disease
Genitourinary	Urinary tract infection	Urinary tract infection	Urinary tract infection Pregnancy Testicular/ovarian torsion
Central nervous system	Hydrocephalus Intracranial hemorrhage Intracranial tumor	Migraine headache Hydrocephalus Intracranial hemorrhage Intracranial tumor Reye syndrome	Migraine headache Hydrocephalus Intracranial hemorrhage Intracranial tumor Glaucoma
Metabolic	Diabetic ketoacidosis Congenital adrenal hyperplasia Urea cycle defects Organic acidurias Amino acidopathies Fatty acid oxidation disorders	Diabetic ketoacidosis Urea cycle defects Fatty acid oxidation disorders	Diabetic ketoacidosis
Other/atypical	Occult trauma (abuse) Toxic ingestions Munchausen syndrome by proxy	Sickle cell Toxic ingestions Occult trauma (abuse) Munchausen syndrome by proxy	Sickle cell Toxic ingestions Occult trauma (abuse) Munchausen syndrome/ Munchausen syndrome by proxy

Clinical Features

Infants classically present with sudden-onset bilious emesis and abdominal distention.[13] The obstruction may be relatively high, however; consequently, a distended abdomen may not always be present. Infants usually appear quite ill and may present in shock.[14,15] Infants also may present with a history of intermittent, relatively mild episodes of emesis that suddenly become more intense. Although bilious emesis in a neonate always suggests the possibility of acute obstruction and volvulus, presenting manifestations in children may be nonspecific, such as abdominal distention or an ill appearance.[13,14]

Diagnostic Strategies

Diagnostic strategies may include obtaining a plain film of the abdomen, an upper GI series, or a computed tomography (CT) scan of the abdomen. Findings on plain abdominal films may include air-fluid levels suggesting obstruction, dilated loops overlying the liver, and a paucity of small bowel gas distally[12] (Fig. 170-3). In addition, a "double-bubble sign" may be present, representing a dilated stomach and obstructed proximal duodenum. Three different conditions are associated with this finding on plain abdominal films. The classic double bubble represents a dilated stomach and obstructed proximal duodenum, as noted, and is seen with duodenal atresia and malrotation with midgut volvulus. Duodenal atresia is limited to the newborn nursery and manifests within 24 hours of life. Malrotation with midgut volvulus typically manifests with bilious vomiting within the first month of life. The modified double-bubble sign seen with hypertrophic pyloric stenosis represents a dilated body of the stomach and pylorus and is associated with nonbilious emesis.

The diagnostic procedure of choice to determine midgut volvulus is the upper GI series, which reveals abnormal position of the duodenal C-loop (Fig. 170-4) and small bowel with a characteristic corkscrew appearance (Fig. 170-5).[12] An ultrasound scan may be obtained because of abdominal pain and may reveal abnormal positioning of the duodenal C-loop and superior mesenteric artery. The place of ultrasonography in the evaluation of children with midgut volvulus has yet to be determined, however.[10,11]

Differential Considerations

Vomiting in childhood is common and occurs across a wide spectrum of illnesses (see Table 170-3). Causes vary depending on the age of the child and whether the course of vomiting has been sudden in onset, gradually progressive, or chronic. Gastroesophageal reflux classically begins early in life, usually shortly after birth, and remains relatively constant. With pyloric stenosis, vomiting does not begin until the age of 2 to 3 weeks and then becomes increasingly severe and projectile. Acute obstruction causes sudden-onset vomiting, which may be bilious. In a neonate, bilious vomiting requires careful consideration to rule out the possibility of malrotation

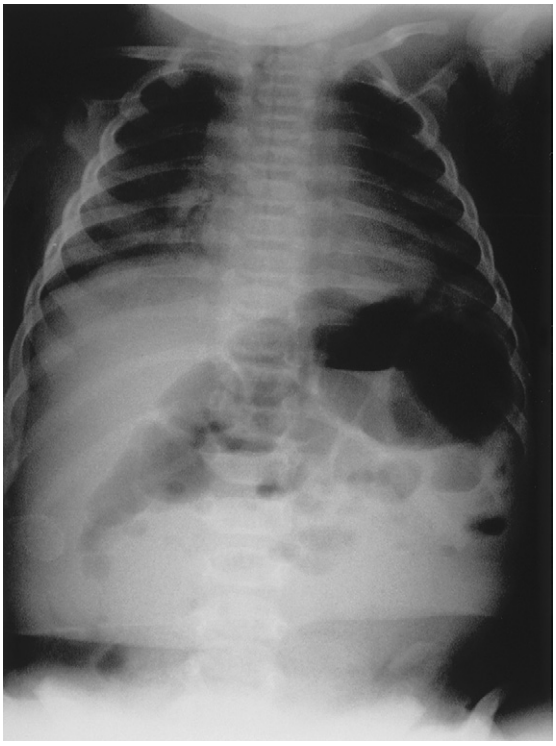


Figure 170-3. Upright abdominal radiograph obtained in an infant with bilious vomiting illustrates dilated loops of small bowel and a paucity of bowel gas distally, consistent with proximal obstruction secondary to malrotation with midgut volvulus. (Courtesy of Mark A. Hostetler, MD.)

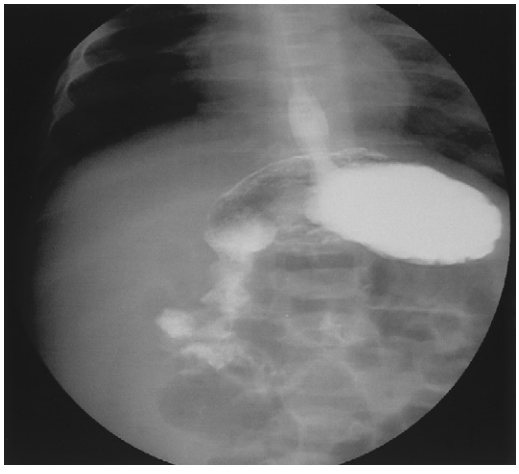


Figure 170-4. Upper gastrointestinal film, obtained in the same infant as in Figure 170-3, reveals abnormal positioning of the duodenal C-loop to the right of the spinal column, consistent with malrotation. (Courtesy of Mark A. Hostetler, MD.)

with volvulus.[13,14] Necrotizing enterocolitis (NEC) is another consideration because this life-threatening disease also manifests with obstructive signs and symptoms, including bilious emesis and abdominal distention. Whereas malrotation usually is associated with a paucity of small bowel air on plain films, NEC is characterized radiographically by diffusely dilated loops of small bowel. In addition, the presence of pneumatosis intestinalis is diagnostic of NEC but is not a feature of malrotation.

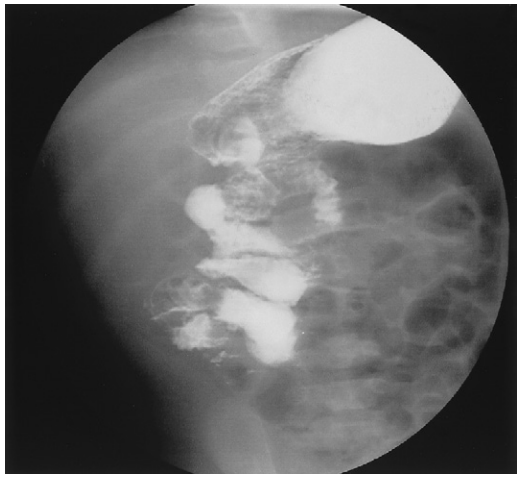


Figure 170-5. Another spot film from the upper gastrointestinal series obtained in the infant in Figure 170-3. This radiograph shows the characteristic corkscrew appearance seen on small bowel follow-through in patients with malrotation. (Courtesy of Mark A. Hostetler, MD.)

Management

Infants with bilious emesis of sudden onset who appear ill or have a distended abdomen require emergency consultation with a pediatric surgeon.[16] Intravenous access should be obtained and laboratory studies sent for CBC, electrolytes, and liver function tests. Repeated fluid boluses of normal saline, 20 mL/kg, are necessary until adequate circulation has been obtained. A finger-stick sample for blood glucose determination and specimens for blood and urine cultures should be obtained. A nasogastric or orogastric tube should be placed. After consultation with a pediatric surgeon, an upper GI series may be needed emergently. Ill-appearing infants require broad-spectrum, triple-antibiotic coverage with ampicillin, gentamicin, and either clindamycin or metronidazole. Time is of the essence in the evaluation and operative management of these patients. Rapid pediatric surgical consultation should be obtained in any neonate or infant with bilious vomiting even before obtaining diagnostic studies, especially infants who are ill-appearing. In contrast with hypertrophic pyloric stenosis, in which surgery does not need to be immediate, operative intervention must be rapid to save the bowel from necrosis.

Disposition

Patients suspected to have malrotation require definitive imaging and an immediate surgical evaluation. If the diagnosis is confirmed or equivocal, hospital admission and surgical management are required.

■ NECROTIZING ENTEROCOLITIS

Perspective

NEC is the most common GI emergency in neonates, affecting 2000 to 4000 infants in the United States every year.[17] NEC also is the most common cause of intestinal perforation occurring during the newborn period.[17] Because most affected infants are premature and acquire the condition in the neonatal intensive care unit, NEC usually is not considered a disease of the emergency department (ED). Many of these infants may be discharged relatively early, however, because they are "feeding and growing" and come to treatment in the first month of life. Ten percent of infants with NEC were full-term

babies.[18] Development of NEC is related closely to gestational age. In infants born at 24 to 28 weeks of gestation, NEC develops within 2 to 4 weeks of life[19]; in those born at 29 to 32 weeks of gestation, it is seen within 1 to 3 weeks of life. Among more mature, or full-term, infants, NEC tends to develop in the first week of life.[17] Complications in children who survive NEC may include strictures (seen in 10 to 20% of cases), fistulas, and short gut syndrome.

Principles of Disease

The exact pathomechanism in NEC is unclear but seems to be multifactorial. Proposed risk factors include prematurity, aggressive enteral feedings, birth-related hypoxic-ischemic insults, and infectious causes. Prematurity is the most common and universally accepted risk factor; 90% of all affected infants were premature at birth.[18,19] Rapid advancement of feedings also has been associated with increased rates of NEC.[20] Infection has been implicated as an important causative mechanism.[21] Evidence suggests that hypoxic-ischemic insults are not an independent risk factor for the development of NEC.[18] The primary pathologic event may be inflammation or injury to the intestinal wall, which begins in the mucosa and then extends transmurally. The distal ileum and proximal colon are more commonly affected, and the involvement may be continuous or patchy.[22]

Clinical Features

Infants with NEC present with feeding intolerance and emesis. Emesis may be either nonbilious or bilious. Occasionally, individual loops of bowel become distended with air and are palpable on abdominal examination. In the more severe stages of the disease, infants may be extremely ill-appearing, with hematemesis, hematochezia, and shock. NEC commonly is placed into one of three clinical stages based on criteria developed by Bell.[23] Stage I represents early or suspected NEC based on feeding intolerance, vomiting, or ileus. Stage II represents definite NEC as proved by abdominal radiographs showing intestinal dilation and pneumatosis intestinalis. Stage III represents advanced disease and is associated with perforation. Infants in this stage are acutely ill, with marked abdominal distention, metabolic acidosis, disseminated intravascular coagulation, and shock.

Diagnostic Strategies

Dilated loops of bowel are a common but nonspecific finding in stage I. Another early and more specific radiographic sign is the loss of a normal symmetrical gas pattern and replacement with an asymmetrical pattern of bowel gas, with a variable degree of dilatation. Intramural air (pneumatosis intestinalis) is specific for NEC and is present in stage II[23] (Fig. 170-6). Pneumatosis is present in 75% of patients with NEC.[18] Air also may be seen within the biliary tract (portal vein gas) or occasionally in the gastric wall ("pneumatosis gastralis") (see Fig. 170-6). Portal vein gas is present in 10 to 30% of cases.[18] Ultrasonography and barium enema, which have been described as adjunctive diagnostic imaging modalities in patients with suspected NEC, are rarely helpful in the ED. No individual laboratory features are diagnostic or specific for NEC.

Differential Considerations

Etiologic possibilities vary depending on whether the emesis is bilious and whether the course of vomiting has been sudden in onset, gradually progressive, or chronic (see Table 170-3).

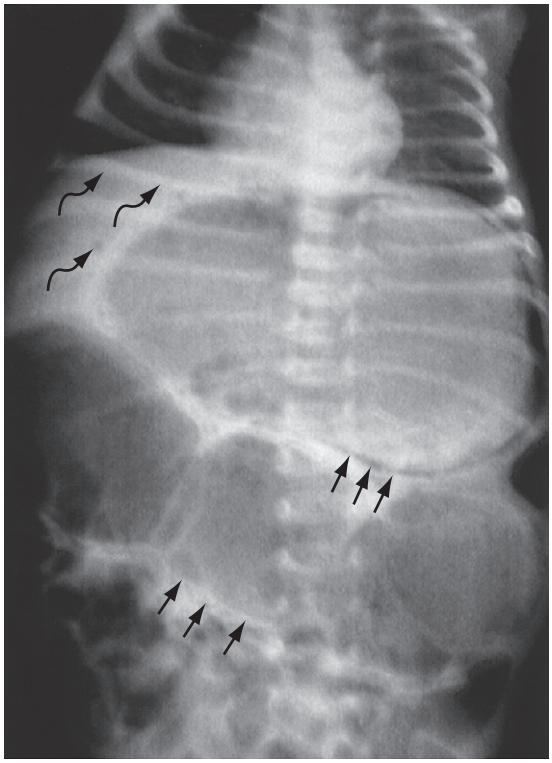


Figure 170-6. Plain radiograph obtained in an infant with necrotizing enterocolitis. *Shorter arrows* indicate air within the wall of the small bowel and gastric mucosa (pneumatosis intestinalis and gastralis). *Curved arrows* indicate air in the biliary tree (portal venous gas). (Courtesy of Mark A. Hostetler, MD.)

Gastroesophageal reflux classically begins early in life, usually shortly after birth, and remains relatively constant in character. Pyloric stenosis–related vomiting does not begin until 2 to 3 weeks of age and then becomes increasingly severe and projectile. In neonates, bilious vomiting requires careful consideration to rule out the possibility of malrotation with volvulus. As noted previously, with malrotation, a paucity of small bowel air usually is noted on plain films, whereas with NEC, diffusely dilated loops of small bowel typically are seen. In addition, the presence of pneumatosis is diagnostic of NEC but is not a radiographic feature of malrotation.

Management

Patients suspected to have NEC should receive nothing by mouth (i.e., be on NPO [*nil per os*] status), with placement of decompression of either an orogastric or a nasogastric tube for decompression of the stomach and small bowel. These patients frequently appear quite ill and may have periods of apnea or significant respiratory distress. The airway should be secured as indicated. Intravenous access should be established and routine laboratory studies performed, to include CBC, electrolyte panel, type and screen, and coagulation studies (prothrombin time/partial thromboplastin time [PT/PTT]). A bedside blood glucose value should be obtained. Cultures of the blood and urine also are indicated. Careful attention should be given to managing fluids and electrolytes because considerable third spacing of fluids may occur in these patients. Repeated fluid boluses at 20 mL/kg of normal saline should be administered until adequate circulation is obtained. These boluses may be augmented with dopamine or epinephrine drips as necessary for patients in refractory shock when euvolemia has been

achieved. Fluids should be continued with 5% dextrose in water and half-normal saline at a minimum of 1.5 to 2 times maintenance. Ill-appearing infants require broad-spectrum, triple-antibiotic coverage with ampicillin, gentamicin, and either clindamycin or metronidazole. Emergent consultation should be obtained from a pediatric surgeon. Patients with evidence of perforation, peritonitis, or gangrenous bowel require surgical intervention. Only one half to three quarters of patients with perforation have free air detectable on radiographs.[23]

Disposition

Children suspected to have NEC require hospital admission and pediatric surgical consultation.

GASTROESOPHAGEAL REFLUX

Perspective

Gastroesophageal reflux, one of the most common causes of vomiting during infancy, refers to the regurgitation of stomach contents into the esophagus.

Principles of Disease

Gastroesophageal reflux occurs as a result of an incompetent lower esophageal sphincter. Chronic reflux of gastric contents into the esophagus may result in esophagitis, aspiration, and, if severe, failure to thrive.

Clinical Features

Clinical manifestations occur along a wide spectrum of disease, ranging from occasional episodes of spitting up to severe, persistent vomiting and failure to thrive. Gastroesophageal reflux generally responds to conservative measures and resolves with age. The disorder may be associated with stereotypical opisthotonic movements, collectively referred to as *Sandifer's syndrome*. Affected children exhibit extension and stiffening of the arms and legs and extension of the neck, often accompanied by a shrill or guttural cry. It may be associated with a brief period of apnea and pallor as formula is refluxed into the esophagus. Sandifer's syndrome most commonly occurs shortly after feeding and usually is not associated with cyanosis.

Diagnostic Strategies

In the ED, the diagnosis of gastroesophageal reflux typically is made on the basis of a careful history and physical examination; however, for ill patients in whom the diagnosis is uncertain, other diagnostic studies are available with gastroenterology consultation, such as esophageal pH probes to check for reflux of acid, barium swallow, and direct visualization by endoscopy.

Differential Considerations

Children with gastroesophageal reflux exhibit nonbilious emesis that begins shortly after birth and is relatively constant over time. Typically, no sudden starting or ending point, as would be suggested by an acute obstruction, can be identified. Vomiting usually is neither gradually progressive nor projectile, as seen with pyloric stenosis. Most children with gastroesophageal reflux of milder severity continue to gain weight.

Management

Most infants respond to conservative measures, such as smaller feedings, frequent "burpings," thickening of formula with cereal, and maintaining a semi-upright position for 45 minutes to 1 hour after feeding. Pharmacologic regimens are reserved for more severe cases. Weight loss is an important historical feature and necessitates pediatric gastroenterology referral for evaluation. Children exhibiting failure to thrive or esophagitis often are placed on medical management with ranitidine and metoclopramide. Ranitidine, a histamine blocker, reduces gastric acid secretion. Metoclopramide increases lower esophageal tone, reduces pyloric sphincter tone, and increases gastric motility. Patients not responding to medical management occasionally require surgical intervention with a Nissen fundoplication, which involves wrapping a portion of the stomach around the esophagus to prevent the reflux.

Disposition

Most children can be discharged home safely with conservative measures. Children who exhibit failure to thrive should be referred to a pediatrician or pediatric gastroenterologist for consideration of pharmacologic management. Children with dehydration and children in whom other diagnoses have yet to be excluded may benefit from hospital admission and further evaluation.

INTUSSUSCEPTION

Perspective

Intussusception is the most common cause of intestinal obstruction in children younger than 2 years of age and occurs most commonly in infants 5 to 12 months of age.[12,23] An estimated incidence of 1 per 2000 children younger than 15 years of age, with a male predominance, has been reported.[23] Siblings of affected children have a relative risk 15 to 20 times higher than in the general population. The mortality rate for untreated intussusception is high.

Principles of Disease

The exact etiology of intussusception is unclear, but the most prevalent theory relates to a lead point that causes telescoping of one segment of intestine into another.[23] As the process continues and intensifies, edema develops and obstructs venous return, resulting in ischemia of the bowel wall. As ischemia of the bowel wall continues, peritoneal irritation ensues, and perforation may occur.

In younger children, lead points are most often the result of enlarged Peyer's patches secondary to a recent viral infection. In children older than 5 years, an underlying lesion is found in more than 75% of cases; lesions include Henoch-Schönlein purpura (HSP) vasculitis, Meckel's diverticulum, lymphoma, polyps, postsurgical scars, celiac disease, and cystic fibrosis.[24-28] Intussusception may occur at any point along the GI tract. Ileocolic intussusception are most common. Ileoileal intussusception may occur in children with HSP.

Clinical Features

The classic triad of clinical findings in intussusception consists of abdominal pain, vomiting, and bloody stools. All three features are present in less than one third of patients, however. Three quarters of patients with intussusception have two of these findings, and 13% have either none or only one.[28] In a

typical presentation, the child experiences cyclic episodes of severe abdominal pain. The pain typically lasts 10 to 15 minutes and has a periodicity of 15 to 30 minutes. During the painful episodes, the child is inconsolable, often described as drawing the legs up to the abdomen and screaming in pain. The clinical presentation occasionally does not include more typical evidence of pain; instead, the child presents with profound lethargy. Vomiting and diarrhea may be associated features. Blood may be present in either the stool or the emesis. Diarrhea containing mucus and blood constitutes the classic "currant jelly" stool most often associated with intussusception, although in actuality this finding is relatively infrequent. Children often have had a recent viral illness. Palpation of the abdomen may reveal a sausage-like mass in the right upper quadrant representing the actual intussusceptus and an empty space in the right lower quadrant representing the movement of the cecum out of its normal position. This combination of findings is called *Dance's sign* and is considered pathognomonic for intussusception. Its occurrence is relatively uncommon, however. Intussusception usually is not associated with a high fever; however, low-grade fevers may occur.

Diagnostic Strategies

Initial screening films should be obtained, with a minimum of two views of the abdomen. Attention should be focused on visualizing the entire colon and in particular the cecum. Films also should be examined for evidence of a soft tissue mass or mass effect, obstruction, a target sign (representing air in the intussusceptum as it telescopes into adjacent bowel), a meniscus sign (representing air compressed like a meniscus from invaginating bowel), and free air (Fig. 170-7). Normal findings on radiographs of the abdomen revealing complete visualization of the entire colon, including the cecum, make intussusception unlikely; however, indeterminate or nonspecific findings on films in which the entire colon cannot be visualized do not rule out intussusception and require additional imaging. Ultrasonography is the least invasive and most commonly used modality for visualizing intussusception.[29] Ileocolic intussusceptions are most common and are easily detected by ultrasonography, even in inexperienced hands.[30] The goal of the ultrasound exam is to visualize the ileocecal junction, which should be in the right lower quadrant but may be translocated into the right middle to upper quadrant. On the ultrasound scan, the intussusception mass appears as a multilayered or wrapped complex mass, and on longitudinal scan as a tube within a tube as the ileum projects up into the cecum (Fig. 170-8A and B). Because of the readily identifiable anatomic location, and the absence of ionizing radiation, this is usually the diagnostic imaging modality of choice. Contrast enemas may be both diagnostic and therapeutic and in intussusception will reveal a sharp cutoff at the point where the intussusceptum meets the contrast material (Fig. 170-9). Air contrast enemas are equally efficacious, have success rates averaging greater than 60%, and are preferred by some physicians over barium contrast studies.[29-33] Either type of enema requires readily available backup by a pediatric surgeon in the event of failure of the bowel to reduce or perforation. Before any radiologic studies are performed, intravenous access should be established and the patient should receive at least one

Figure 170-7. Plain radiograph obtained in a child with crampy abdominal pain and vomiting, later confirmed to have intussusception. Findings include a poorly defined soft tissue density in the right upper quadrant, obscuration of the liver edge, and focally dilated loops of small bowel, consistent with an acute obstructive process (intussusception). (Courtesy of Mark A. Hostetler, MD.)

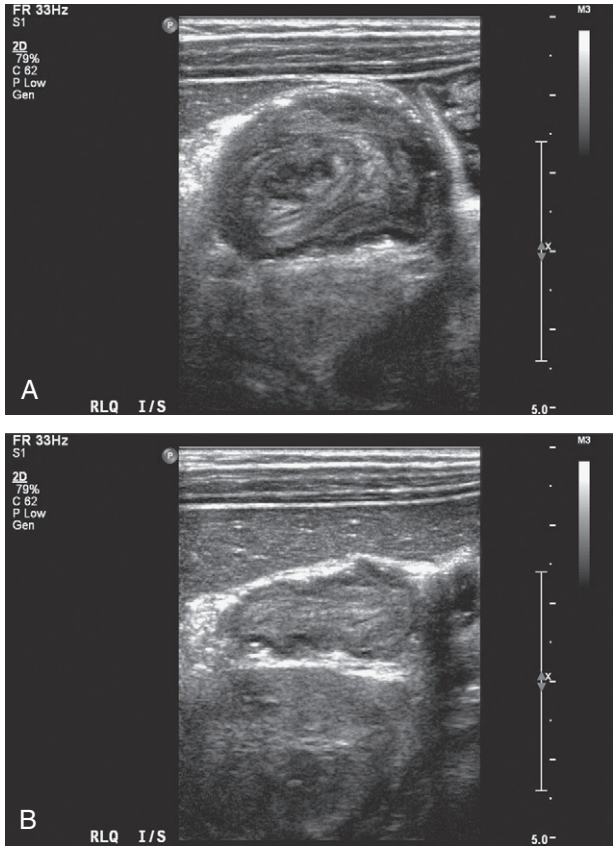


Figure 170-8. **A** and **B,** Abdominal ultrasound examination in a child with colicky abdominal pain and vomiting, later confirmed to have intussusception. On the transverse view (**A**), findings include a complex mass with a multilayered or rolled appearance. In the long view (**B**), the ileum can be seen protruding up into the cecum, forming the intussuscipiens-intussusceptum complex. (Courtesy of Mark A. Hostetler, MD.)

Figure 170-9. Contrast enema image obtained in a child with intussusception shows a sharp cutoff where the contrast material meets the intussusceptum and the acute obstruction. (Courtesy of Mark A. Hostetler, MD.)

20-mL/kg bolus of normal saline along with appropriate parenteral pain relief.

Differential Considerations

Differential considerations for abdominal pain in children by age are listed in Table 170-4. Slow, progressive onset of pain is more likely to be associated with appendicitis, constipation, or pancreatitis. Children with peritoneal irritation invariably lie still, often on the side with the knees bent, and refrain from all extraneous movement. Sudden onset of severe pain is associated most often with acute obstruction or vascular occlusion, as seen with intussusception, volvulus, or torsion of the testicle or ovary. Children with intussusception have severe colicky pain and often rock back and forth, frequently moaning or crying. Children with ischemic pain exhibit symptoms out of proportion to the findings on examination. They may appear diaphoretic, clammy, or pale and complain of excruciating abdominal pain, although exhibiting only mild tenderness to palpation and no localizing findings.

Management

Patients require intravenous access and screening CBC and electrolytes. Intravenous fluids are given in boluses of 20 mL/kg of normal saline until adequate vascular volume is achieved. Children should be maintained on NPO status. Nasogastric tube decompression may be necessary if there is evidence of significant gaseous distention. Prompt surgical consultation is required. Ill-appearing or febrile children require broad-spectrum, triple-antibiotic coverage with ampicillin, gentamicin, and either clindamycin or metronidazole. Diagnostic and therapeutic interventions depend on location and resources available. Patients may undergo an initial ultrasound exam, or if history and plain film findings suggest intussusception, the patient may go straight to either air or hydrostatic barium enema. Surgical intervention is required if the reduction is unsuccessful or if perforation occurs. The overall success rate for air contrast enema or barium enema approaches 90%. Intussusception may recur in 7 to 10% of radiologic reductions and in 2 to 5% of surgical reductions, usually within 24 hours. Admission for observation usually is recommended for all patients after reduction.[31]

Disposition

Children with suspected intussusception require definitive imaging with ultrasonography. Children with documented intussusception require reduction with either enema or surgery. Hospital admission is recommended for all patients after reduction.

Table 170-4 Differential Considerations for Abdominal Pain by Age

ETIOLOGIC CATEGORY	INFANCY	CHILDHOOD	ADOLESCENCE
Mechanical	Malrotation with midgut volvulus Intussusception Incarcerated hernia Meckel's diverticulum Hirschsprung's disease	Constipation Incarcerated hernia Meckel's diverticulum Bowel obstruction	Constipation Incarcerated hernia Meckel's diverticulum Bowel obstruction
Inflammatory/infectious	Necrotizing enterocolitis	Gastroenteritis Appendicitis Henoch-Schönlein purpura Pancreatitis Gastritis Biliary tract disease	Gastroenteritis Appendicitis Henoch-Schönlein purpura Pancreatitis Gastritis Biliary tract disease
Genitourinary	Urinary tract infection	Urinary tract infection	Urinary tract infection Nephroureterolithiasis Pregnancy, ectopic Pelvic inflammatory disease Testicular/ovarian torsion
Other/atypical	Colic Occult trauma (abuse) Toxic ingestions Munchausen syndrome by proxy	Pneumonia Diabetic ketoacidosis Sickle cell Toxic ingestions Occult trauma (abuse) Munchausen syndrome by proxy	Pneumonia Diabetic ketoacidosis Sickle cell Toxic ingestions Occult trauma (abuse) Munchausen syndrome/ Munchausen syndrome by proxy

HIRSCHSPRUNG'S DISEASE

Perspective

Hirschsprung's disease accounts for approximately 20% of cases of partial intestinal obstruction in early infancy. Hirschsprung's disease occurs at a rate of 1 in 5000 live births and is four to five times more common in boys. It usually is sporadic in occurrence but may be associated with Down syndrome or a variety of other anomalies of the GI, genitourinary, or central nervous system.[34]

Principles of Disease

Hirschsprung's disease represents congenital aganglionosis of the colon and is characterized by an absence of ganglion cells in the myenteric plexus of the distal colon.[34] The anus is invariably involved, with aganglionic bowel usually extending proximally 4 to 25 cm. Absence of colonic ganglion cells interferes with that segment's ability to relax, creating a functional obstruction. Stool accumulates proximal to the level of obstruction and produces dilation of the colon, the so-called megacolon.

Clinical Features

Neonates with Hirschsprung's disease often present in the nursery with failure to pass meconium. Infants brought to the ED may have a history of constipation and obstipation. Vomiting, irritability, and abdominal distention may be features. Symptoms and signs may be subtle and include a history of chronic constipation and poor weight gain or failure to thrive. Hirschsprung's disease usually is diagnosed in infancy; however, a spectrum of disease is recognized, and presentation may be later in life. Children who are ill-appearing with fever should be evaluated for enterocolitis and toxic megacolon. Enterocolitis is characterized by abdominal distention, bloody stools, fever, and an elevated white blood cell count.

Diagnostic Strategies

Plain films of the abdomen may reveal evidence of fecal impaction with proximal obstruction, air-fluid levels, and dilated colon. A barium enema revealing a narrowed aganglionic segment with proximal dilation is highly suggestive of Hirschsprung's disease.[34,35] The diagnosis is confirmed by biopsy or manometry.

Differential Considerations

Constipation is one of the most common causes of abdominal pain and vomiting in children.[35,36] Children in the process of "potty training" occasionally become pathologic in their ability to delay defecation. Pathologic causes of constipation are uncommon. In addition to Hirschsprung's disease, considerations include cystic fibrosis, infantile botulism, and hypothyroidism. An acquired variant of the disease also may occur in which other factors produce similar dilated colonic findings, resulting in acquired megacolon. Risk factors include anal fissures, fecal impaction, toilet training issues, and neuromuscular dysfunction secondary to neurologic disease, drugs, or metabolic causes.

The exact definition of constipation is elusive because it varies with age and diet. Infants during the first few months of life may have stool frequencies that range from one per feeding to one every other day, with breast-fed infants having more frequent stools than formula-fed infants. Frequency continues to decrease with age such that during the first year of life, infants may average two to three stools per day, and from 1 to 5 years of age, one or two per day. Defecation occurs as a combination of physiologic, behavioral, and psychological factors. Relaxation of the external sphincter required for defecation is under voluntary control, whereas relaxation of the internal sphincter is involuntary. Children with a history of unpleasant or painful experiences associated with defecation may contract the external sphincter voluntarily in an effort to delay defecation for as long as possible. Accumulation of stool over time causes the rectum to dilate and decrease its propulsive activity, resulting in an increasing capacity for stool and chronic constipation. Acute episodes may be the result of dietary changes, travel, lack of normal exercise, or stress.

Management

Initial management is focused on ensuring adequate fluid and electrolyte status. Abdominal films should be obtained. With evidence of acute obstruction, seen as marked dilation, decompression may be necessary. Decompression usually can be accomplished easily with a rectal tube. Children who are ill-appearing with fever should be evaluated for enterocolitis and toxic megacolon. Enterocolitis is characterized by abdominal distention, bloody stools, fever, and an elevated white blood cell count. Patients with enterocolitis require broad-spectrum, triple-antibiotic coverage with ampicillin, gentamicin, and either clindamycin or metronidazole. Urgent consultation should be made with a pediatric surgeon. Definitive therapy is surgical, with resection of the aganglionic segments. Acquired megacolon is managed by decompressing the colon and addressing the underlying problems.

Management of constipation requires three considerations: cleanout, maintenance, and behavior modification. Acute constipation is easier to manage because fewer functional problems are involved. The acute management of constipation usually is relatively easy and requires primarily the cleaning out of stool. Most experts recommend an approach that includes stool softeners or laxatives from above and suppositories or enemas from below. In milder cases, only the administration of enemas is necessary to soften feces and stimulate defecation. Tap water, Castile soap, and oil enemas all are generally equally efficacious. Maintenance includes keeping the stool soft for as long as necessary using stool softeners or laxatives. Dietary modifications include increasing fiber and water in the diet and avoiding foods that may be constipating. Management of chronic constipation is more difficult and usually requires a multidisciplinary approach with attention to behavior modification. Children with an underlying pathologic process, such as cystic fibrosis, may benefit from more intense measures, such as administration of large volumes of polyethylene glycol (GoLYTELY).

Disposition

Unless children are ill-appearing, most can be managed safely on an outpatient basis.

MECKEL'S DIVERTICULUM

Perspective

Meckel's diverticulum is the most common congenital malformation of the small intestine and follows the *rule of 2s*: The diverticulum is 2 cm wide and 2 cm long and usually located within 2 feet of the ileocecal valve. Moreover, the condition occurs in 2% of the population, and only 2% of affected patients

ever become symptomatic.[37] One half of all patients with the condition become symptomatic by the age of 2 years, and most present by age 20.[37]

Principles of Disease

Diverticula are remnants of the omphalomesenteric duct and contain bowel wall, with 60% containing heterotopic tissue.[38] This tissue most commonly involves gastric mucosa, but other types include pancreatic, duodenal, and endometrial tissue.[36-38] Bleeding occurs when acid secretion from ectopic gastric mucosa causes ulceration and erosion.

Clinical Features

Patients are classically boys younger than 5 years of age who present with massive, painless rectal bleeding of acute onset; however, it can occur at any age. Some children may have some complaints of abdominal cramping. The blood often is described as brick red in color. Complications may include intussusception, obstruction, perforation, and peritonitis.

Diagnostic Strategies

A technetium scan, also known as a Meckel's scan, is the diagnostic modality of choice and has an accuracy of 90% when ectopic gastric mucosa is present.[39] Administering pentagastrin, cimetidine, or glucagon may increase the sensitivity of the test.[40] CT scan of the abdomen may be obtained to look for signs of obstruction or if the diagnosis is unclear. Definitive diagnosis is confirmed by laparoscopy or laparotomy.

Differential Considerations

GI bleeding is uncommon in childhood. The first step in evaluating a child with suspected GI bleeding is to determine whether the substance is actually blood. Children commonly eat or drink substances containing dyes that lead to factitious changes in the stool's color. A simple Hemoccult test of the stool or Gastroccult test of the emesis can document the presence of hemoglobin. False-positive results may occur with red meat and iodine. Patients consuming products with bismuth (Pepto-Bismol), iron, and spinach may have black stools falsely appearing as melanotic; they test Hemoccult-negative.

After it has been determined that the substance is blood, the second step is to determine its origin. The location of bleeding often is difficult to determine but may be theorized based on the appearance of the blood. Hematemesis implies bleeding proximal to the ligament of Treitz. Blood exposed to gastric acids for any period of time develops the classic coffee-grounds appearance. Bright red upper GI bleeding implies either more proximal bleeding, such as from varices or esophagitis, or brisk gastric or duodenal bleeding. Bleeding that originates beyond the ligament of Treitz but proximal to the ileocecal valve results in melena. Hematochezia, with a visibly red to maroon appearance of the blood, implies bleeding from the descending colon. Distal lesions, such as fissures or hemorrhoids, can result in bright red blood. Barium contrast studies of the upper and lower GI tract sometimes are helpful; however, nuclear medicine scans (Meckel's scan) are the procedure of choice in detecting Meckel's diverticulum. Endoscopic examination has the highest rate of determining the location of bleeding; however, the diagnosis often is confirmed first on Meckel's scan.

In neonates, the most common etiologic category of gastrointestinal bleeding is idiopathic. Careful examination of the rectum should be performed, because the most identifiable cause for bleeding is a fissure or excoriation of the perirectal area. In young neonates, an Apt test may be performed to determine if the blood is maternal or fetal: One percent sodium hydroxide is added to the bloody stool. Fetal hemoglobin resists oxidation and remains pinkish red, whereas maternal hemoglobin changes to a dark brown color.

Another common cause for GI bleeding in infancy is milk protein allergy. Affected children typically are younger than 6 months of age with a history of sudden-onset mucoid, blood-streaked stools. Children otherwise appear well. Although the causative allergy most commonly is to milk protein, GI bleeding may occur with consumption of any protein and has been described in relation to soybean-based products. Children with persistent perianal excoriations and fissures refractory to standard emollients may be infected with group A streptococci and may benefit from treatment with an oral penicillin. Table 170-5 lists the differential considerations for GI bleeding in children by age.

Management

Management of GI bleeding begins with assessing and ensuring adequate circulatory status. Screening laboratory studies should include a CBC, coagulation studies (PT/PTT), and a type and screen. Two radiographic views of the abdomen should be obtained in patients in whom obstruction or perforation is suspected. A technetium scan is the imaging modality of choice to evaluate for Meckel's diverticulum. Consultation with a pediatric surgeon should be obtained.

Disposition

Children with suspected Meckel's diverticulum should undergo a Meckel's scan. Children with minor bleeding and normal findings on screening laboratory studies may be followed closely on an outpatient basis. Children with more active bleeding should be hospitalized for care by either a pediatric surgeon or a pediatric gastroenterologist.

■ HENOCH-SCHÖNLEIN PURPURA

Perspective

HSP, also known as anaphylactoid purpura, is a systemic vasculitis commonly associated with abdominal pain and rash. It is most common in children 4 to 11 years of age but also may occur in adults. HSP occurs most commonly in the spring after a viral upper respiratory infection. It also has been associated with insect stings and certain drugs.[41]

Principles of Disease

HSP is a hypersensitivity vasculitis with immune complex deposition with immunoglobulin A, mainly affecting the arterioles and capillaries. Although it is most well known for its characteristic petechial-to-purpuric rash, HSP is a systemic vasculitis and may affect any blood vessel. Less common manifestations are seen in cases in which the disease is more severe or widespread.

Clinical Features

Symptoms include abdominal pain, nausea, vomiting, and diarrhea. Patients most often are diagnosed clinically on the basis of the presence of a classic rash, abdominal pain, microscopic hematuria, and arthralgias. The classic rash is palpable purpura located on the buttocks and lower extremities (Fig.

Table 170-5 Differential Considerations in Gastrointestinal Bleeding by Pediatric Age Group

ETIOLOGIC CATEGORY	INFANCY	CHILDHOOD	ADOLESCENCE
Factitious	Swallowed maternal blood Dyes in foods/beverages Vaginal origin Urinary origin	Dyes in foods/beverages Swallowed nasopharyngeal blood Vaginal origin Urinary origin	Dyes in foods/beverages Swallowed nasopharyngeal blood Vaginal origin Urinary origin
Upper GI	Necrotizing enterocolitis Intussusception Gastroenteritis Gastritis	Esophagitis Gastroenteritis Gastritis Peptic ulcer disease	Esophagitis Gastroenteritis Gastritis Peptic ulcer disease
Lower GI	Necrotizing enterocolitis Intussusception Gastroenteritis Milk allergy Vascular malformation	Gastroenteritis Intussusception Meckel's diverticulum Inflammatory bowel disease Vascular malformation Henoch-Schönlein purpura Hemolytic uremic syndrome Colitis	Gastroenteritis Intussusception Meckel's diverticulum Inflammatory bowel disease Vascular malformation Henoch-Schönlein purpura Hemolytic uremic syndrome Polyps Colitis
Rectal	Rectal fissure	Rectal fissure	Rectal fissure Hemorrhoids Trauma
Other/atypical	Bleeding dyscrasia Occult trauma (abuse) Toxic ingestions Munchausen syndrome by proxy	Bleeding dyscrasia Toxic ingestions Occult trauma (abuse) Munchausen syndrome by proxy	Bleeding dyscrasia Toxic ingestions Occult trauma (abuse) Munchausen syndrome/ Munchausen syndrome by proxy

GI, gastrointestinal.

Figure 170-10. Henoch-Schönlein purpura in a 7-year-old child. Note typical red-purple rash on the lower extremities. (Courtesy of Marianne Gausche-Hill, MD.)

170-10). Up to 70% of patients with HSP have GI complaints. Microscopic hematuria occurs in 50%.[42] Intussusception may occur and may be atypical in that ileoileal intussusception is more common than the ileocolic intussusception that normally occurs. The syndrome often is relapsing and remitting over several weeks and may be associated with arthralgias. Neurologic involvement also may be a feature of HSP, although this manifestation is uncommon in children.[43]

Diagnostic Strategies

Patients most often are diagnosed clinically on the basis of the presence of a classic rash, abdominal pain, microscopic hematuria, and mild arthralgias. Screening studies should include a CBC with differential and platelet counts, urinalysis, blood culture, and sedimentation rate determination. Children with worrisome abdominal pain require CT to rule out ileoileal intussusception.

Differential Considerations

The most important entity in the differential diagnosis for this type of rash is meningococcemia, in which the patient has a fever and looks very ill. It is essential to rule out meningococcemia, because the condition is life-threatening and requires an entirely different approach to management involving hospitalization, fluid resuscitation, and intravenous antibiotics. The classic triad of palpable purpura, abdominal pain, and hematuria in an otherwise well-appearing child virtually ensures the diagnosis. Erythema nodosum occasionally is confused with the rash of HSP; however, in erythema nodosum the rash is described most often as subcutaneous purplish red nodules with the appearance of a bruise located on the extensor surfaces of the distal extremities. Erythema nodosum usually involves only the shins but in more severe cases also may involve the forearms, hands, and feet.

Management

Most children with HSP can be managed with close follow-up and require no treatment other than symptomatic support. Severe or intermittent abdominal pain in children with HSP is suggestive of intussusception; imaging to investigate this possibility should be done with a CT scan, because ileoileal

intussusception may occur and is not detected easily by ultrasonography. Management with steroids is controversial. Corticosteroids, at a dose of 1 mg/kg/day (maximum 60 mg), are reserved for patients with illness on the more severe end of the spectrum, with abdominal pain, hematuria, or arthralgias.

Disposition

Indications for hospital admission include uncertain diagnosis to exclude the possibility of meningococcemia, severe abdominal pain, and vomiting. Most patients can be managed safely with close outpatient follow-up.

■ INFLAMMATORY BOWEL DISEASE

Perspective

The two major entities included within the category of inflammatory bowel disease (IBD) are Crohn's disease and ulcerative colitis. Approximately 20% of patients present before the age of 20 years.[44] Most patients do not experience symptoms until adolescence, although childhood presentations have been described. IBD is rare in children younger than 1 year of age.[45]

Principles of Disease

Ulcerative colitis is an inflammatory disease primarily involving the mucosa and submucosa of the rectum and distal colon. *Crohn's disease* is a transmural inflammatory disease that may involve any portion of the intestinal tract. The most common area of involvement in cases with single-segment disease is distal ileum; however, multiple segments in different areas may be involved. Chronic inflammation may result in the formation of abscess, fistula, or stricture.

Clinical Features

Although patients experiencing complications frequently present to the ED, the diagnosis is rarely made in this setting. More commonly, children with known disease present in the midst of a flare, usually with bloody diarrhea and abdominal pain. Extraintestinal manifestations also occur and include fever, anemia, oral ulcerations, erythema nodosum, pyoderma gangrenosum, uveitis, liver dysfunction, and failure to thrive.[45] Some of these manifestations may occur even before the child has experienced any GI symptoms. The most feared complication is toxic megacolon, which classically manifests with abdominal pain, fever, and bloody diarrhea and is associated most often with ulcerative colitis.

Diagnostic Strategies

Flares of IBD are diagnosed by the presence of increased frequency of diarrheal or bloody stools and abdominal pain. Patients who are ill-appearing require plain films of the abdomen to rule out toxic megacolon. Patients with toxic megacolon usually have a fever, appear volume-depleted, and demonstrate significant abdominal tenderness to palpation. X-ray films reveal dilatation of the transverse colon to more than 6 to 7 cm in diameter. Free air also should be looked for, because perforation may occur. Screening laboratory studies should include a CBC with differential and platelet counts, type and screen, coagulation studies (PT/PTT), and electrolyte panel.

Differential Considerations

There are a wide number of differential considerations for abdominal pain and GI bleeding (see Tables 170-4 and 170-5). Gastroenteritis is the most common consideration in this clinical scenario. Children experiencing their first episode of IBD are much more likely to be misdiagnosed with an acute gastroenteritis. Children outside the usual age at presentation also are more likely to be misdiagnosed with gastroenteritis. Children with recurrent symptoms or a family history of IBD should be referred to a pediatric gastroenterologist for further evaluation.

Management

Steroids constitute the mainstay of treatment for acute exacerbations. Prednisone at a dose of 1 mg/kg/day (maximum 60 mg/day) usually is recommended and should be provided in consultation with a pediatric GI specialist. Other agents commonly used include sulfasalazine, azathioprine, and a host of other immunosuppressive agents. Management in the ED begins with attention to volume status and resuscitation with boluses of 20 mL/kg of normal saline until the volume status is adequate. Patients with suspected toxic megacolon require intravenous broad-spectrum, triple-antibiotic therapy (with ampicillin, gentamicin, and metronidazole) and immediate surgical consultation.

Disposition

Indications for admission include children who are dehydrated, febrile, or ill-appearing. Children with ongoing diarrhea productive of bloody stools usually benefit from intravenous fluids until the flare has been controlled. Children with evidence of toxic megacolon require surgical consultation and admission.

■ GASTROINTESTINAL FOREIGN BODIES

Perspective

Most GI foreign bodies occur in toddlers, who experience life by first putting it in their mouths. Children younger than 3 years of age are particularly at risk because of the combination of inappropriate mouthing of objects and a general lack of coordination in swallowing. Although food is the most common esophageal foreign body in adults, coins are most common in children.[46,47] Children with mental retardation swallow a variety of objects. Adolescents occasionally swallow objects in an attempt at suicide. Rectal foreign bodies are uncommon in the pediatric age group.

Principles of Disease

Most swallowed foreign bodies pass without difficulty. Foreign bodies may become lodged in any of three areas of normal physiologic narrowing: upper esophageal sphincter (cricopharyngeus muscle)/thoracic inlet (C6-T1), the aortic arch/tracheal bifurcation (T4-6), and the lower esophageal sphincter/diaphragmatic hiatus (T10-11). In general, 80 to 90% of objects that have made it into the stomach are passed without difficulty.[48]

Clinical Features

The classic clinical presentation is that of a child who is seen from across the room putting coins in his or her mouth. Children frequently gag and sputter as they attempt to swallow the

object. Aspirated objects generally produce persistent coughing, wheezing, or increased work of breathing. Objects that have been swallowed may result in the child's remaining asymptomatic or may produce symptoms ranging from persistent gagging to drooling and continuous dry heaves. Larger foreign bodies may compress the airway and cause significant respiratory distress. Rapidly progressive symptoms of dysphagia, pain, respiratory distress, or fever raise the possibility of a perforation. Perforation is uncommon, even with sharp objects such as straight pins. The ileocecal valve is the most common site for perforation, which occurs in less than 1% of patients.[48] Button batteries warrant special mention. Button batteries in the esophagus should be removed in as rapid a manner as possible because erosions and mediastinitis ultimately may occur. Button batteries in the stomach usually pass without difficulty and do not require removal unless they fail to pass the pylorus within 24 to 48 hours of ingestion.[49] Occasionally, objects pass into the stomach that are too large to pass through the pylorus; this is uncommon and is heralded by persistent vomiting. Long-present unrecognized foreign bodies may result in erosion, perforation, infection, stricture, or fistula formation.[50]

Diagnostic Strategies

Plain radiography is the most common method of visualizing location and is used to verify positioning past the lower esophageal sphincter into the stomach. Patients who are symptomatic after foreign body ingestion require imaging to determine location. Occasionally, patients who are asymptomatic also have objects remaining in the esophagus.[51] Radiographs should include anteroposterior and lateral views of the chest and neck (Fig. 170-11). The lateral view helps to delineate soft tissues in the hypopharynx and to evaluate for swelling, particularly if the foreign body is either unknown or of a nonradiopaque material. Often a single view of the neck, chest, and upper abdomen can be obtained easily in the pediatric patient. Unless the patient becomes symptomatic, repeat films are otherwise never necessary. Asking parents to sieve the stool typically is unproductive, and even sharp objects such as pins or razor blades usually pass through the GI tract without incident. Patients presenting with a history of button battery ingestion represent the exception in that they require repeat films to document passage beyond the pylorus. Rather than using standard radiography, some institutions have noted success with intradepartment fluoroscopy or hand-held metal detectors.[51-53] Contrast studies may be helpful to delineate nonradiopaque foreign bodies or to evaluate for perforations.

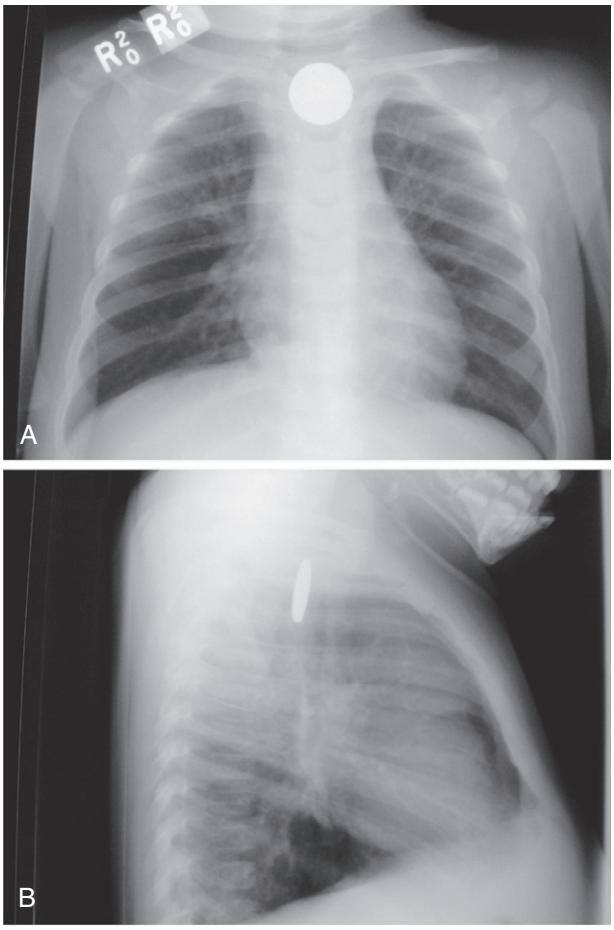


Figure 170-11. Plain radiographs obtained in a child with an esophageal coin foreign body. Posteroanterior (**A**) and lateral (**B**) views show the expected orientation for a coin lodged in the esophagus. (Courtesy of Mark A. Hostetler, MD.)

Differential Considerations

Not all foreign bodies are radiopaque and visible with standard radiography. Patients who remain symptomatic require further contrast-enhanced imaging or direct visualization.

Management

If the object has made it into the stomach, usually it will pass without incident, and no further treatment is necessary. If the foreign body is in the esophagus, most experts recommend removal within 24 hours to decrease the risk of aspiration and esophageal erosion. The preferred method by which to remove esophageal foreign bodies is controversial and varies by institution. Options include fluoroscopic Foley catheter removal, bougienage advancement into the stomach, endoscopic removal in the ED, and removal by rigid bronchoscopy under general anesthesia in the operating room. Foley catheter removal and bougienage do not require sedation in cooperative patients, but young children invariably require sedation in the operating room. With the latter two methods, the technique involves actually holding onto the foreign body, which—at least theoretically—decreases the chance of inadvertent aspiration. They also have the additional benefit of directly visualizing the integrity of the mucosa and evaluating for perforation. Gastric foreign bodies generally do not require removal. Indications for surgical removal of gastric foreign bodies include objects that are greater than 2 cm in width, objects that are greater than 5 cm in length, and objects that are sharp.

Disposition

Esophageal foreign bodies require removal as described previously. After foreign bodies have made it into the stomach, most pass without difficulty, and no further follow-up is necessary. Button batteries constitute the exception and necessitate follow-up films to document passage beyond the pylorus.

PANCREATITIS

Perspective

Pancreatitis is uncommon in childhood, especially in children younger than age 10. Pancreatitis has an incidence of approximately 1 case in 50,000 in children and carries a mortality rate

of 14%.[54,55] In adults, pancreatitis is associated most commonly with alcohol and biliary tract disease. In children, a fairly equal association of approximately 10 to 20% each has been documented for trauma, infection, structural disease, systemic disease, and drugs or toxins.[55] Mumps is the most common viral cause of pancreatitis and accounts for 10 to 15% of all cases.[55] Idiopathic causes account for 30% of cases.

Principles of Disease

Whether the result of trauma, obstruction, or inflammation, a series of events occurs, resulting in inflammation, edema, and autodigestion of pancreatic tissue by pancreatic enzymes. In severe cases, the inflammatory process may progress to necrosis and hemorrhage, resulting in necrotizing or hemorrhagic pancreatitis. Further complications include the formation of abscesses, pseudocysts, and fistulae.

Clinical Features

Patients classically present with complaints of severe epigastric pain that radiates to the back. Pain is gradually progressive and constant and often is associated with nausea and vomiting. Pain classically is described as being worse with eating. Significant abdominal tenderness usually can be elicited in the epigastric area, accompanied by voluntary guarding and hypoactive bowel sounds. The abdomen may be slightly distended.

Diagnostic Strategies

Screening laboratory studies reveal elevations in serum amylase or lipase. Plain films of the abdomen may be indicated to investigate the possibility of free air or obstruction. An ileus pattern is common, often with a sentinel loop of dilated small bowel noted in the left upper quadrant. An ultrasound or CT scan may be helpful to evaluate anatomy for congenital malformations or biliary tract disease and to evaluate for pseudocyst or abscess formation. In patients with pseudocysts, hemorrhagic pancreatitis may develop that may become life-threatening. For patients with respiratory distress, a chest film can be helpful to evaluate for a coexistent pleural effusion caused by the pancreatitis.

Differential Considerations

Slow, progressive onset of pain is more likely to be associated with appendicitis, constipation, or pancreatitis. Children with peritoneal irritation invariably lie still, often on the side with knees bent, and refrain from all extraneous movement. Sudden onset of severe pain is associated most often with acute obstruction or vascular occlusion as seen with intussusception, volvulus, or torsion. Differential considerations for abdominal pain in children by age are listed in Table 170-4; differential considerations for the causes of pancreatitis are listed in Table 170-6.

Table 170-6 Differential Considerations for Pancreatitis in Children

ETIOLOGIC CATEGORY	SPECIFIC DISORDER(S)
Trauma	Handlebar injury
Infectious	*Viral*: mumps, influenza A, EBV infection, CMV infection, hepatitis A and B, rubella, rubeola *Bacterial*: salmonellosis, leptospirosis
Structural	Choledochal cyst, duplication cyst, anomalous bile duct, duodenal stenosis Pancreas divisum Tumor Cholelithiasis
Systemic/genetic	Cystic fibrosis Glycogen storage disease Familial hyperlipidemias α_1-antitrypsin deficiency Sickle cell disease
Systemic/acquired	Systemic lupus erythematosus Kawasaki disease Hemolytic uremic syndrome Henoch-Schönlein purpura Crohn's disease Reye syndrome Diabetes mellitus
Drugs/toxins	Steroids, oral contraceptives Valproic acid Sulfasalazine, azathioprine Rifampin, pentamidine, metronidazole, tetracycline Thiazides, ethacrynic acid, furosemide Alcohol, L-asparaginase
Idiopathic	No definitive cause found

CMV, cytomegalovirus; EBV, Epstein-Barr virus.

Management

Management begins with attention to volume status and correction of electrolyte abnormalities if present. A bedside finger-stick blood glucose value should be obtained. Adequate pain relief with parenteral narcotics should be provided. The patient should be maintained on NPO status and given adequate fluids. Intravenous fluids are given in boluses of 20 mL/kg of normal saline until adequate vascular volume is achieved and then are followed by 5% dextrose in water and half-normal saline at 1.5 times maintenance. Antiemetics are indicated to help control nausea and vomiting. A nasogastric tube usually is not necessary or helpful, unless an ileus or persistent vomiting is present. Steroids and antibiotics are not indicated.

Disposition

Most children with pancreatitis require hospitalization, unless they have known or recurrent disease for which an outpatient regimen providing adequate analgesia and hydration is available.

APPENDICITIS

Perspective

Appendicitis is the most common surgical condition involving the abdomen, and the most common nontraumatic surgical emergency in children.[12] Approximately 200,000 appendectomies are performed every year, and appendicitis develops in approximately 1 of every 15 people in the general population sometime during their lifetime.[12,23,56] The peak age of incidence of appendicitis is between 9 and 12 years, and it is uncommon in children younger than 5 years of age.[12,23,56]

Acute appendicitis has an overall mortality rate of less than 1%. For unruptured appendicitis, the mortality rate is 0.1%; the mortality rate increases to approximately 3% for ruptured appendicitis. In children, the rate of appendiceal perforation before surgery varies, ranging from 17 to 40%, and is inversely

related to age, with higher rates of perforation occurring in younger age groups. In children younger than 2 years of age, perforation will have occurred in 90% by the time of surgery.

Principles of Disease

The appendix is a blind pouch that may become obstructed. After it is obstructed, a vicious circle is established, with increasing edema, vasocongestion, inflammation, ischemia, infarction, necrosis, and perforation. In adults, a thicker appendiceal wall protects against perforation, and a well-developed omentum aids in walling off the infection to prevent its diffuse spread. Children have neither, so rupture tends to occur earlier and diffuse peritonitis develops more readily.

Clinical Features

Patients classically present with a constellation of symptoms that includes abdominal pain, nausea, vomiting, fever, and anorexia. All of these symptoms are gradually progressive over 4 to 24 hours. Abdominal pain usually is described as vague, crampy, and periumbilical on origination, which then becomes more severe, constant, and localized to the right lower quadrant. Fever usually develops later, sometimes not until after the patient already has presented to the ED. Nausea and vomiting are progressive and most often are associated with anorexia. Patients occasionally may have a multiphasic course to their illness, which begins with the classic abdominal pain, with progression of symptoms until they suddenly resolve, followed several days later by development of fever, chills, and abdominal pain. This course represents acute appendicitis with spontaneous rupture and formation of an abscess.

Physical examination may reveal several classic findings. In patients with inflammation surrounding the appendix, peritoneal findings that localize to the right lower quadrant are typical. Pain occurs with movement, so the patient prefers to lie still. Patients are unable to jump up and down and complain that even rocking the bed or tapping their heels causes pain. The abdomen usually is quiet, with an absence of bowel sounds. Rebound tenderness can be elicited in the right lower quadrant. Rovsing's sign also may be present and consists of severe pain in the right lower quadrant occurring when the examiner presses in the left lower quadrant and rapidly releases the examining hand. Other findings associated with appendicitis include the psoas and obturator signs. The psoas sign is pain elicited by having the patient, in lateral decubitus position, hyperextend the right thigh at the hip, thereby stretching the psoas muscle, which overlies the inflamed appendix. The obturator sign similarly is pain elicited by having the patient internally rotate the flexed right thigh against resistance.

Diagnostic Strategies

Appendicitis may be diagnosed on the basis of history and physical findings alone. Patients with the appropriate constellation of findings consistent with appendicitis may not require any testing and can proceed directly to the operating room for either laparoscopic or open exploration. Patients in whom the diagnosis is suspected usually require some diagnostic workup. Screening studies should include a CBC with differential, urinalysis, and pregnancy test. An estimated 96% of patients with appendicitis have either an elevated white blood cell count greater than 10,000/μL or a left-shifted differential with more than 75% neutrophils.[57] Although an elevated white blood cell count supports the diagnosis, it is not specific for appendicitis. The appendix is in close proximity to the ureters, so appendicitis may induce some degree of sterile pyuria. Inflammatory changes related to appendicitis generally result in fewer than 5 to 10 white and red blood cells per high-power field and an absence of bacteria. Findings in excess of these amounts suggest a urinary tract etiology (e.g., infection, stone, mass, trauma). Consideration also may be given to adding a rapid streptococcal test in patients with a red or sore throat.

Figure 170-12. Fecalith in a child with appendicitis. (Courtesy of Marianne Gausche-Hill, MD.)

Diagnostic imaging options include plain films of the abdomen, ultrasonography, and limited CT scan of the appendix. Plain films help to rule out free air or obstruction and occasionally show an appendiceal fecalith, also called an *appendicolith* (Fig. 170-12). Although the presence of an appendicolith is essentially pathognomonic for acute appendicitis, it is present in only 10% of cases.[56] Ultrasound findings consistent with appendicitis include an enlarged, noncompressible appendix that is painful during scanning (Fig. 170-13A and B). A fecalith may be evident inside an enlarged and inflamed appendix—the so-called target sign.[58] Appendiceal ultrasound studies have a sensitivity, specificity, and overall accuracy of 90 to 95%.[58-61] Ultrasound imaging is particularly useful for evaluating for abscesses and fluid collections; however, a great deal of operator and reader variability is characteristic (Fig. 170-13C). Ultrasonography does not involve exposure to ionizing radiation. Using an ultrasound exam as an initial screen for appendicitis, in which only patients with negative or equivocal scans were required to undergo CT, resulted in a sensitivity of 96% and a negative predictive value of 98%.[62,63]

Limited CT of the appendix is the most recent technology to have emerged in terms of imaging.[64-68] Limited CT scans of the appendix have sensitivity and specificity rates of 95 to 100%.[65-68] The ready availability of appendiceal CT has been shown to reduce the negative laparotomy rate from 20% to 7%, with the highest accuracy reported using new focused appendiceal CT techniques with rectal contrast.[68] For patients with relatively low probability of appendicitis, CT may offer a cost-effective screening tool, particularly compared with inpatient admission and observation.[64] Imaging the pelvis and the right lower quadrant (with either CT or ultrasonography) not only establishes the diagnosis of appendicitis but also aids in identifying the two most common considerations in the differential diagnosis: IBD and mesenteric adenitis.[66-68] An important point is that CT scanning involves exposure to a significant amount of ionizing radiation, which places children at increased risk for future malignancies.[69] Beginning in the past decade, the number of CT scans has increased dramatically (nearly 700%),

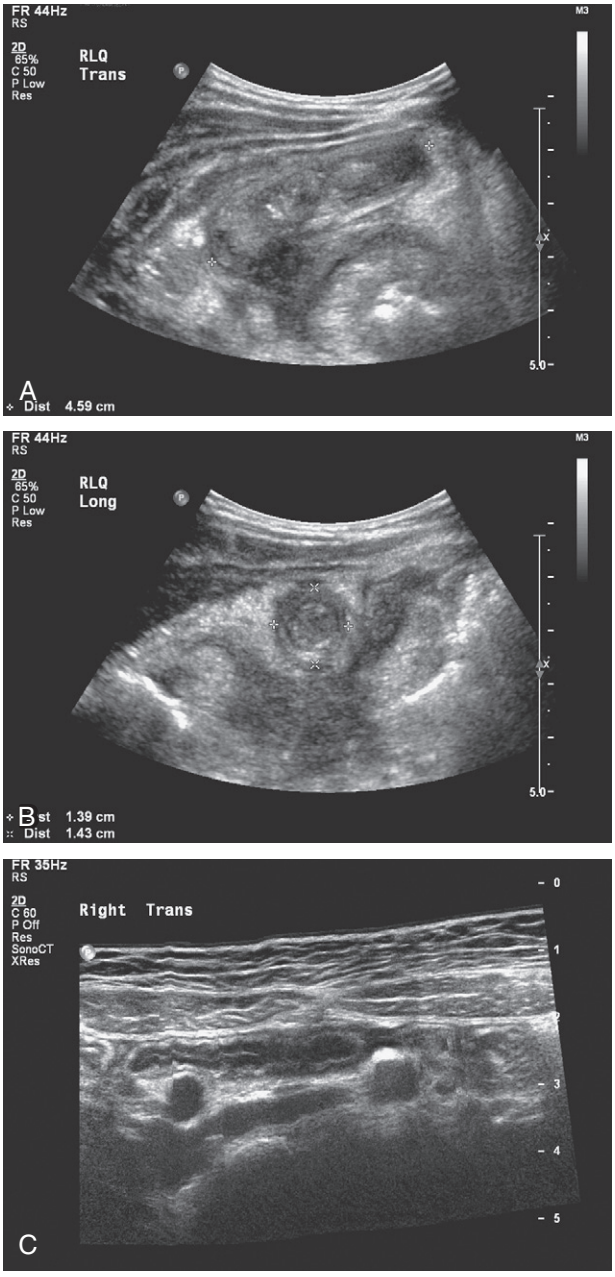


Figure 170-13. Ultrasound images obtained in children with appendicitis. Findings include an enlarged, noncompressible tube-like structure in the longitudinal view with an appendicolith (**A**), an enlarged, noncompressible structure seen in cross section (**B**), and in another patient, an enlarged, poorly compressible structure with moderate amount of free fluid consistent with acute perforation (**C**). (Courtesy of Mark A. Hostetler, MD.)

and appendicitis is believed to be the single primary reason accounting for its surge in use.[69] In weighing all of the risks and benefits, sequential imaging with ultrasonography followed by CT scan is likely to be the best choice.

Differential Considerations

Mesenteric adenitis is the most common condition associated with the signs and symptoms of appendicitis. It often is associated with significant diffuse tenderness and may localize in the right middle to lower quadrant. Children often lack fever, however, and do not have true peritoneal signs. Mesenteric adenitis usually follows a viral illness and results from nonspecific inflammation of mesenteric lymph nodes. It is perhaps even more common than appendicitis. Differential considerations for abdominal pain by age are listed in Table 170-4. Other considerations include nonaccidental trauma (abuse), malingering, and Munchausen syndrome.[69] Girls of reproductive age merit consideration of a gynecologic origin and require a pregnancy test and pelvic examination; the possibility of ovarian torsion, particularly if the pain seems to be severe and out of proportion to physical examination findings, should not be overlooked. Boys require an external genital examination to rule out the possibility of testicular torsion. Cryptorchidism in the face of acute abdominal pain should raise suspicion for testicular torsion.

Management

In patients with suspected appendicitis, NPO status should be maintained and an intravenous line established. Most patients have vomiting and anorexia and benefit from at least one fluid bolus of 20 mL/kg of normal saline and then administration of 1.5 to 2 times maintenance fluids with dextrose 5% in water and half-normal saline. Screening studies should be initiated, and appropriate consultation with a surgeon is indicated. Ongoing pain should be addressed adequately. Intravenous narcotics are safe and effective and should not alter the diagnostic accuracy of the physical examination. Patients with high fever, suspected perforation, or unusual delay to surgery require coverage with intravenous broad-spectrum antibiotics, which should be initiated in the ED after consultation with the surgeon.[70,71] A reasonable regimen for antibiotic therapy consists of ampicillin, gentamicin, and either metronidazole or clindamycin. Nasogastric tubes are reserved for patients with persistent nausea or vomiting related to abdominal distention or ileus.

Disposition

Children with appendicitis as documented by physical examination or diagnostic imaging are hospitalized for appendectomy. Patients with nonspecific symptoms and signs who do not undergo definitive diagnostic study can be hospitalized and observed for a period of 12 to 24 hours or, with adequate family and social support, can be discharged home with careful instructions to return for reexamination.

■ BILIARY TRACT DISEASE

Perspective

Biliary tract disease is uncommon in childhood and has causes distinct from those for disease in adults. In children, gallstones are associated with hemolytic disease, cystic fibrosis, total parenteral nutrition, sepsis, and dehydration.[72,73] Ceftriaxone also has been associated with sludging and biliary disease, particularly in neonates. Acute acalculous cholecystitis has been associated with Rocky Mountain spotted fever and a variety of bacterial infections including those due to *Salmonella* and *Shigella* organisms. Hydrops of the gallbladder (i.e., fluid distension of the gall bladder from chronic cystic duct inflammation or obstruction) is associated with viral upper respiratory or GI infections, Kawasaki disease, streptococcal pharyngitis, mesenteric adenitis, nephrotic syndrome, and leptospirosis.

Principles of Disease

Gallstones are classified as either cholesterol or pigment stones. Pigment stones occur in childhood, whereas cholesterol stones usually do not begin appearing until adolescence. Pigment stones result from the excess breakdown of red blood cells and

are seen most commonly in hemolytic anemia, such as from sickle cell disease and spherocytosis. Gallstones occurring in infants usually are associated with abdominal surgery, sepsis, necrotizing enterocolitis, or administration of total parenteral nutrition.[73] In young children, gallstones most commonly develop as a result of their hemolytic disease. Adolescents form gallstones in association with oral contraceptives, pregnancy, obesity, or underlying hemolytic disease. In acute acalculous cholecystitis, the ultrasound scan will reveal evidence of gallbladder inflammation in the absence of calculi. Hydrops of the gallbladder is an acute noninflammatory, noninfectious process that results in a markedly enlarged gallbladder without evidence of calculi.

Clinical Features

Similar to adult patients, pediatric patients usually present with right upper quadrant pain that radiates through to the back and may be associated with fever, nausea, and vomiting. Jaundice occurs in one third of patients.[73,74]

Diagnostic Strategies

Biliary tract disease usually is associated with elevations in liver enzymes and bilirubin; however absence of elevations does not exclude the diagnosis. Accordingly, right upper quadrant ultrasound imaging may be prudent in cases in which gallbladder disease is suspected. Elevations in alkaline phosphatase suggest cholestasis. Elevated white blood cell counts are nonspecific but if associated with fever may represent an acute infectious process (e.g., ascending cholangitis). Ultrasonography is the imaging modality of choice. It can determine the presence of gallstones, reproduction of pain on scanning (sonographic Murphy's sign), the amount of dilatation of the gallbladder and bile ducts, gallbladder wall thickness, and the anatomic configuration of the biliary and pancreatic collecting system. When ultrasound findings are equivocal or negative in the face of strong clinical evidence, the gold standard modality for biliary tract imaging is still considered to be cholescintigraphy (DISIDA scanning); rarely, percutaneous cholecystocholangiogram is necessary.[73] Although only 15% of gallstones in adults are calcified and visible on plain radiographs of the abdomen, 50% of stones are visible in children.[74,75]

Differential Considerations

Biliary tract disease is uncommon in children and requires consideration of underlying or coexistent disease. Differential considerations for abdominal pain by age are listed in Table 170-4.

Management

Management of biliary tract disease begins with attention to fluid and electrolyte status. Adequate pain control should be provided, usually with a parenteral opioid. Asymptomatic patients with incidental findings of gallstones require no further therapy in the ED and may be referred to a surgeon for outpatient care. Patients who are afebrile usually can be managed safely on an outpatient basis with adequate pain control. Febrile patients require hospital admission and intravenous antibiotics. A reasonable regimen for empirical antibiotic coverage consists of ampicillin and gentamicin, plus either clindamycin or metronidazole.

Several management options have been used in the treatment of children with cholecystitis: medical management with ursodeoxycholic acid to dissolve the stone, expectant management, and surgical management.[76] Laparoscopic cholecystectomy is considered safe and effective in children.[77]

Disposition

Indications for hospital admission include pain control, hydration, fever, and need for operation.

KEY CONCEPTS

- Physiologic jaundice of the newborn and breast milk jaundice are the most common causes of jaundice in the neonatal period.
- Direct hyperbilirubinemia in infants is always pathologic and requires a detailed workup.
- Hypertrophic pyloric stenosis manifests with gradually progressive nonbilious emesis that becomes projectile.
- Hypochloremic, hypokalemic metabolic alkalosis is the classic electrolyte abnormality for children with hypertrophic pyloric stenosis.
- Bilious vomiting in the neonate should immediately raise the suspicion of malrotation and volvulus.
- In infants with bilious emesis, a toxic appearance, a distended abdomen, or an acute obstructed pattern on abdominal radiographs constitutes a true surgical emergency.
- NEC occurs more commonly in premature infants, but 10% of affected infants are full term.
- Gastroesophageal reflux usually responds to conservative measures (positioning, thickening of formula, smaller and more frequent feedings).
- The classic clinical triad in intussusception comprises abdominal pain, vomiting, and heme-positive stools; however, the triad occurs in fewer than one third of patients.
- Children with intussusception may present without pain and with lethargy alone.
- Hirschsprung's disease is a common cause of constipation in the neonate and usually is manifested by delayed passage of meconium.
- Meckel's diverticulum classically manifests in children younger than 5 years of age with painless brick-red rectal bleeding.
- More than 90% of gastrointestinal foreign bodies pass without difficulty.
- Causes of pancreatitis in children include viruses, trauma, drugs, and toxins.
- Imaging strategies for children that include ultrasound examination followed by CT scan of the abdomen have been shown to reduce costs and negative laparotomy rates.
- Cholelithiasis is diagnosed with right upper quadrant ultrasound imaging; management strategies include medical and surgical approaches.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 171

Infectious Diarrheal Disease and Dehydration

Lei Chen

ACUTE INFECTIOUS DIARRHEA

Perspective

Diarrhea is defined as increased frequency, volume, and liquidity of stools. Worldwide, infectious diarrhea is one of the most significant contributors to morbidity and mortality and is responsible for 4 million to 5 million deaths per year in children younger than 5 years of age. Regional differences in resources, epidemiology, underlying general health status of the population, and availability of safe food and water affect the actual disease burden. In the United States, acute gastroenteritis historically accounts for 10% of hospital admissions of children younger than 5 years of age, estimated at 220,000 admissions per year; 300 to 400 deaths per year are caused by diarrhea, most occurring in the first year of life.[1,2] Children are at higher risk than adults for complications of diarrhea such as hypoglycemia, electrolyte abnormalities, and shock. This vulnerability is due to their smaller physical size, low physiologic reserve, and immature immune system.

In emergency departments (EDs) across the nation, intravenous therapy is widely used for treating volume depletion due to infectious diarrhea. Some potential serious complications have emerged as a result of exuberant use of parenteral rehydration. In many situations, diarrhea-related volume depletion can be treated by enteral replacement, either through oral intake or delivered by way of nasogastric and orogastric tubes. Recent vaccine advances have raised the hope that many viral cases of gastroenteritis can be prevented in the near future, at least in the developed world, where access to clean sources of water and food is a matter of course.[3]

Epidemiology

In developed countries such as the United States, infectious diarrhea is caused by viruses in 60% of cases; bacteria, 20%; parasites, 5%; and parenteral illnesses, 10%, with 5% caused by unknown agents. Rotavirus is the prototypical viral agent. Bacterial pathogens include *Salmonella*, *Escherichia coli*, and *Campylobacter jejuni*. *Giardia* and *Entamoeba histolytica* are common protozoal pathogens. Infectious diarrhea in children most often is contracted through the fecal-oral route and through poor food-handling practices. Daycare centers remain a main source of cases, with infection spread by handling diapers, fecal-oral transmission, and sharing toys. Causative agents may be endemic, epidemic with food- and water-borne outbreaks, or sporadic. For most agents, a large inoculum is required to transmit the illness. The exceptions are *Campylobacter*, *Giardia*, and *Shigella*, for which 10 to 100 organisms are sufficient to cause disease. Some groups are at higher risk for acquiring infectious diarrhea and suffer greater clinical consequences. Among these are premature infants and patients who are immunosuppressed or malnourished or who have a chronic disease. Recent hospitalization, treatment with broad-spectrum antibiotics, and travel to developing countries are additional risk factors.

Principles of Disease

Pathophysiology

Normally the gastrointestinal (GI) tract takes in, secretes, and absorbs a large quantity of fluids. Up to 9 L of fluid from diet and endogenous secretions enter the proximal bowel each day in the adult. In children, a proportionately larger volume of fluid per body weight is ingested and secreted to maintain homeostasis (e.g., 125 mL/kg per 24 hours in adults versus 220 mL/kg per 24 hours in newborns). Ninety percent of the fluid is absorbed in the small bowel and the remainder in the large bowel. Water follows osmotic gradients created by transport of electrolytes, sugars, and amino acids into the bloodstream. Both active transport– and passive transport–facilitated mechanisms are in place. Glucose and certain amino acids are absorbed by active carrier-mediated transport and coupled to sodium absorption. This concept of cotransporter is important in understanding the role of combination of dextrose and sodium in enteral rehydration.

Infectious diarrhea occurs when the fine balance is disrupted, either as a result of increased secretion from the GI tract or because of decreased absorption of fluids. Although this distinction is useful conceptually, cases of infectious diarrhea often occur through both mechanisms.

Secretory diarrhea is the result of the increased intestinal secretion caused by a variety of mechanisms. In the case of cholera, an enterotoxin causes an increase in cyclic adenosine monophosphatase (cAMP) in the endothelial cell, resulting in increased chloride and bicarbonate secretion. Enterotoxin-producing bacteria include *Salmonella* and *Shigella* organisms, *Vibrio cholerae*, *E. coli*, and *Clostridium difficile*. Noninfectious causes of secretory diarrhea are rare and include a variety of neurotransmitters such as prostaglandins, histamine, and other GI hormones. Clinically, secretory diarrhea often is characterized by absence of expected reduction in stool volume with

fasting, a stool pH greater than 6, and absence of reducing substances in the stool.

Osmotic diarrhea is caused by the presence of poorly absorbed solutes in the colon as a result of altered bacterial gut flora, damage to the mucosal absorptive surface, or ingestion of substances. These substances alter the normal mechanisms of fluid transport by creating an osmotic gradient across the bowel lumen. This results in movement of water and electrolytes into the luminal fluid. Typical acute viral gastroenteritis, caused by rotavirus or Norwalk-like virus, produces injury to the small bowel epithelium with consequent disruption of microvilli, thereby decreasing absorptive area and preventing normal fluid, electrolyte, and nutrient absorption. The illness is compounded when the colon is unable to cope with the large fluid volume. Diagnostic clues to an osmotic etiology are diarrhea that decreases or stops with fasting, a stool pH less than 5, and presence of reducing substances in the stool.

Dysentery is defined as diarrhea associated with blood and mucus in the stool. The presence of dysentery often implies that the infection has compromised the bowel wall. Acute inflammation, caused by enteroinvasive organisms such as *Salmonella*, *Shigella*, and *Campylobacter*, leads to infiltration of GI tract by neutrophils, which in turn release a host of enzymes and factors causing both increased secretion and decreased absorption by the intestinal tract. Although blood loss may be clinically appreciable, it usually is less significant than the fluid and electrolyte losses. Systemic infection should be suspected if clinical signs of prostration, chills, and fever are present, or if an elevated count or left shift is seen on a WBC count.

Diarrhea caused by altered motility, increased or decreased transit time (diabetes, scleroderma, neuromuscular disease), reduced surface area (short gut, celiac disease), or inhibited active ion transport is less common in children presenting to the ED.

Several physiologic factors predispose pediatric patients to more severe complications of infectious diarrhea. During growth and development, children undergo significant changes in the distribution and composition of body fluid compartments. Children have larger extracellular fluid compartments compared with adults and can therefore lose proportionately more fluids through the GI tract. Children have limited stores of metabolic substrates such as fat and glycogen. Young children often have limited ability to access fluids. They are therefore more susceptible to large fluctuations in fluid, electrolytes, or nutrients.

Extracellular fluid loss in acute diarrhea may lead to significant intravascular volume depletion, which in turn may lead to primary metabolic acidosis with varying degrees of respiratory compensation. The metabolic acidosis usually results from the loss of HCO_3^- in diarrheal fluid but also may be caused by renal tubular acidosis, excessive lactate production from poor tissue perfusion, and therapeutic interventions (e.g., salicylates). One effect of metabolic acidosis is an increase in minute ventilation. The maximum respiratory compensation in metabolic acidosis is a decrease in $Paco_2$ to 12 to 15 mm Hg, which may occur within minutes to hours of onset of the abnormality. Nonvolatile acids, especially sulfur and phosphoric acids, must be excreted by the kidneys; several hours to days will be required for this process to occur. On clinical examination, these children are hyperpneic, with deep and labored breathing, even when they are at rest. Patients with metabolic acidosis from diarrhea require restoration of intravascular volume to allow delivery of nutrient substrate and elimination of by-products of cellular metabolism, rather than rapid correction of the acid-base disorder with buffer alone. Restoration of intravascular volume often corrects what appears to be respiratory distress in the severely volume-depleted child.

Etiology

Acute diarrheal illnesses can be caused by viruses, bacteria, or protozoa. In developed countries such as the United States, viral causes predominate. In countries in which access to clean water and food supply is limited, bacterial agents contribute the major portion of the morbidity and mortality associated with infectious diarrhea.

Virus

The virus responsible for most cases of acute viral gastroenteritis and a disproportionate amount of morbidity caused by diarrheal illness in the United States is rotavirus.[3] This virus is endemic and accounts for nearly one third of the cases in children with diarrhea. The incidence peaks in the winter and spring in temperate climates. Rotavirus causes acute illness with vomiting and diarrhea that may or may not be associated with fever. The diarrhea usually is watery in consistency, and the volume may be large enough to result in significant and rapid intravascular volume depletion. Rotavirus also may cause symptoms of an upper respiratory tract infection. Most infections are transmitted person to person, probably through the fecal-oral route. There is also evidence that it may be transmitted through respiratory secretions as airborne droplets. The incubation period is 1 to 3 days. Postinfection excretion may be prolonged, ranging from 4 to 57 days.

Rotavirus selectively destroys the villus tip cells in the small intestine, leading to malabsorption and diarrhea. A proliferative response occurs, producing an abundance of incompletely differentiated cells in the gut mucosa. In the healthy host, repair of the epithelium and differentiation of the immature brush border take approximately 3 to 5 days and occur without specific intervention. In the chronically ill or malnourished child, the infection leads to complications beyond the usual brush border injury. Failure to repair the epithelium leads to the vicious circle of malnutrition and progressive epithelial injury.

Diagnosis is made by demonstration of the presence of antigens in stool specimens by enzyme immunoassay. Modern assays have up to 97% sensitivity and 97% specificity for rotavirus antigens in human stool. The test can be performed on undiluted stool without special preparation. An effective vaccine was available for a short time until it was noted to be associated with increased risk of intussusception, usually occurring 3 to 20 days after the administration. This vaccine was subsequently withdrawn from the U.S. market.[4]

Another live attenuated rotavirus vaccine, RotaTeq, was approved by the U.S. Food and Drug Administration (FDA) in 2006. In phase III trials it provided good protection from severe diarrheal diseases due to rotavirus.[4] The vaccine is now routinely administered to infants at 2 months, 4 months, and 6 months of age. To date, no association with intussusception has been reported. Nevertheless, vigilance for this problem is in order, and the diagnosis should be considered in a young infant presenting with signs or symptoms of intestinal obstruction, bloody diarrhea, or lethargy.

Norwalk-like viruses, now named *noroviruses*, are common pathogens in outbreaks of gastroenteritis in all age groups. These viruses can be transmitted person to person, as well as through contaminated food and water sources. Common-source outbreaks in long-term care facilities contribute significantly to morbidity and mortality among the residents. In addition, these agents most commonly are associated with out-

breaks of acute gastroenteritis on cruise ships and in schools and hospitals.

Hepatitis A virus (HAV) infections are seen as an acute febrile illness with anorexia, nausea, vomiting, and malaise. HAV invades the hepatocytes, causing immunologically mediated hepatocellular damage. In children, the infection may manifest as an anicteric illness and be misdiagnosed as a nonspecific viral gastroenteritis. HAV is not seasonal and is spread by a common food or water source with fecal-oral contamination. The incubation period is 2 to 6 weeks, and patients shed virus for 1 to 3 weeks beginning 1 to 2 weeks before symptoms develop. Subsequent lifelong immunity is the norm. Household contacts should be offered immunoglobulin prophylaxis. Two inactivated hepatitis A vaccines are available in the United States.

Bacteria

The common bacterial organisms causing acute diarrhea in the United States are, in order of frequency, *Salmonella* species, *Shigella* species, *Campylobacter jejuni*, and *Yersinia enterocolitica*. Enterotoxigenic, enteroinvasive, and enterohemorrhagic strains of *E. coli* also are found in the United States. Other, less common bacterial causes are *Clostridium perfringens*, *Clostridium difficile*, *Staphylococcus aureus*, *Vibrio cholerae*, and *Vibrio parahaemolyticus*, each accounting for less than 1% of cases.

Salmonella infections usually are divided into those caused by *Salmonella typhi* (typhoid fever) and those involving other species. Nontyphoid salmonellae account for more than 98% of the cases in the United States. Clinical syndromes include a carrier state, acute gastroenteritis, bacteremia, and a disseminated abscess syndrome. It is presumed that the salmonellae invade the mucosa and produce a cholera-like enterotoxin and a cytotoxin. Nontyphoid *Salmonella* gastroenteritis is an illness marked by nausea and fever, although it may manifest as dysentery or a cholera-like illness. Acute gastroenteritis occurs at any age but is most common in the first year of life. Animal reservoirs include poultry and reptiles, often kept as pets by young children. In general, antibiotics are not recommended for uncomplicated cases of acute gastroenteritis, because such therapy is ineffective in shortening the symptoms and can cause a prolonged carrier state. Antibiotic treatment is indicated in infants younger than 3 months of age or those with complications such as failure to improve within 5 to 7 days, bacteremia, or focal infection in the central nervous system (CNS), bone, joint, kidney, or pericardium. Ampicillin and trimethoprim-sulfamethaxazole (TMP-SMZ) usually are effective. Because of changing resistance patterns, susceptibility testing should be performed on all isolates.

Shigella species consist of four antigenic groups of 40 serotypes. *Shigella sonnei* is the most common cause of dysentery (diarrhea with significant blood, pus, and mucus) in the United States. Shigellosis usually begins as an enterotoxin-like secretory diarrhea with watery stools and fever that may progress to bacillary dysentery with or without systemic manifestations. Clinical illness varies from mild to severe, with some patients exhibiting abdominal cramps and tenderness. Shigellosis rarely infects infants younger than 3 months of age and is most common between 2 and 3 years of age. Symptoms usually are self-limited and resolve within 72 hours. Extraintestinal symptoms and signs are relatively common in children with *Shigella* infection and may include hallucinations, confusion, or frank seizures. Reactive arthritis can occur weeks after the infection. Rare complications of *Shigella* infection include bacteremia and hemolytic uremic syndrome (HUS). Antibiotics are reserved for patients with prolonged symptoms, dysentery, or underlying immune compromise. Approximately 50% of isolates are resistant to ampicillin and TMP-SMZ. Therefore, a fluoroquinolone (such as ciprofloxacin or ofloxacin) in adults or azithromycin in children is recommended for more severe illness.

Campylobacter species cause a significant proportion of diarrheal disease occurring worldwide. The organism is found in the GI tracts and feces of wild and domestic fowl, farm animals, and pets. Of the five types, *Campylobacter jejuni* and *Campylobacter coli* are the most common. Illness consists of abdominal cramps, diarrhea, chills, fever, and *Shigella*-like dysentery. The clinical presentation may be similar to that in acute appendicitis or other surgical conditions. Invasion of the mucosa with toxin production has been described. A 1- to 7-day incubation period is normal, and the illness usually lasts less than a week. *Campylobacter* organisms are transmitted by ingestion of contaminated food or water. Diagnosis is made by darkfield microscopy. Although azithromycin (12 mg/kg daily PO for 5 days) may shorten the course of the illness, most children do not need antibiotic therapy.

Y. enterocolitica is a relatively uncommon cause of simple self-limited diarrhea and vomiting in the United States. Diarrhea may be watery, mucoid, or bloody. As many as 6% of older children and adults may present with an appendicitis-like illness with right lower quadrant tenderness, usually as a result of reactive mesenteric adenitis.[5] The principal reservoirs for *Y. enterocolitica* are swine and cattle, with infections usually resulting from ingestion of undercooked pork or unpasteurized milk. Duration of the gastroenteritis may be prolonged, to 14 days or more. Antibiotics are indicated in cases of septicemia and extraintestinal infections.

C. difficile causes a spectrum of illnesses ranging from antibiotic-associated diarrhea to pseudomembranous colitis. Patients usually present with diarrhea, abdominal cramps, and fever. Other common features include abdominal tenderness to palpation and dysenteric stools, although asymptomatic infections and mild acute gastroenteritis also have been reported. *C. difficile* gastroenteritis most often occurs in hospitalized patients, with onset during hospitalization or within 60 days after antibiotic therapy. The organism is ubiquitous and transmitted by fecal-oral contamination. Asymptomatic infants can be colonized with the organism. The disease is thought to be brought on by the change in the gut flora as a result of antibiotic administration. Incubation time is unknown. The presence of pseudomembranes and friable rectal mucosa are characteristic. *C. difficile* toxin in the stool is diagnostic. Stopping the offending agent and adding therapy with metronidazole (30 mg/kg/day, divided, five times daily) or vancomycin (40 mg/kg/24 hours, divided, five times daily) for 7 to 10 days are indicated.

Ingested *C. perfringens* organisms produce an enterotoxin during sporulation in the gut that causes fluid collection in ileal loops and diarrhea. The result is a short-lived illness characterized by watery diarrhea, moderate to severe abdominal cramps, midepigastric pain, and an absence of fever. Vomiting is uncommon. Food source contamination, often from catered food services, is the usual source of outbreaks. The incubation time is 6 to 24 hours. Diagnosis is made by finding high spore counts in the stool; no specific treatment is required.

S. aureus produces the archetypal food poisoning from ingesting preformed enterotoxin, usually from contaminated food. Onset of symptoms is within hours of exposure. The illness is short-lived and self-limited. Nausea, vomiting, abdominal cramps, and diarrhea with a notable absence of fever constitute the typical pattern.

V. cholerae is an Asian-African organism that also is seen in South America. Most cases occur in travelers returning from endemic areas. A unique strain is endemic to the Gulf Coast of the United States. The disease is acquired through inges-

tion of contaminated water and food, such as undercooked shellfish and raw vegetables. Because a large inoculum is required, person-to-person transmission does not occur. Diarrhea is caused by a heat-labile enterotoxin that increases cyclic adenosine monophosphate (cAMP) through adenyl cyclase, resulting in inhibition of sodium reabsorption with chloride and fluid secretion into the gut. Antibiotic treatment should be considered for patients with moderate to severe diseases. Susceptibility testing is recommended because of changing resistance patterns.

Vibrio parahaemolyticus is commonly found in seawater, shellfish, and fish. Illness most commonly is associated with ingestion of contaminated raw or undercooked seafood. Diarrhea, abdominal cramps, and nausea are common, whereas vomiting, headache, fever, and chills are less common. The disease usually is self-limited and does not require treatment with antimicrobials.

E. coli is part of the normal flora in the lower GI tract. Several types within this species are recognized to cause disease. *E. coli* is identified by distinct groups of either somatic or flagellar antigens that determine virulence properties. The enterotoxigenic *E. coli* (ETEC) strain produces heat-stable and heat-labile toxins and colonization factor, which are important mediators of the illness called *traveler's diarrhea*. Travelers of all ages can be affected. The enteroinvasive *E. coli* (EIEC) strain is closely related antigenically and biochemically to *Shigella* species and causes a similar dysenteric illness. This form affects mostly adults and is often food-borne. The enteropathogenic *E. coli* (EPEC) strain is responsible for sporadic and endemic diarrhea in infants. This form does not produce toxins. The enterohemorrhagic *E. coli* (EHEC) strain, with *E. coli* O157:H7 being the prototype, produces bloody diarrhea without fever and is associated with the Shiga toxin. *E. coli* O157:H7 colonizes the lower GI tract in cattle and is an important cause of epidemics of bloody diarrhea and sometimes, hemolytic uremic syndrome (HUS).[6]

Controversy exists regarding indications for antibiotic treatment for *E. coli* diarrhea: Although such therapy may shorten the course in selected cases, it may be associated with increased risk for developing HUS[7] in cases of diarrhea caused by O157:H7. Although a meta-analysis failed to confirm the increased risk,[8] it is prudent to withhold antibiotics in diarrhea caused by EHEC.

Acute diarrheal illnesses in chronically ill and immunosuppressed patients often are due to the previously described agents, although they can be caused by several unusual organisms. In patients with acquired immunodeficiency syndrome, these infections may be acute, chronic, or recurrent and difficult to treat. Unusual organisms may include *Mycobacterium avium*, *Cryptosporidium*, cytomegalovirus, and adenovirus. Because of frequent antibiotic exposure, infections caused by *C. difficile*, *Candida albicans*, and *Pseudomonas aeruginosa* are more common in immune-suppressed patients.

Clinical Features

Diagnostic Findings. Although acute diarrhea in children often can be managed at home, it can cause significant fluid and electrolyte disorders. Indications for medical evaluation of children with diarrhea have been proposed.[9] Serious illnesses may be overlooked on cursory examination. The principal goal of the ED evaluation is to identify the fluid, electrolyte, acid-base, or nutrient deficits that may result from vomiting, diarrhea, or decreased oral intake.

It often is difficult to quantify the volume of diarrhea from the history. Helping the parent describe the stool relative to usual bowel habits may provide valuable information. The history should include specific information regarding the order of presentation, duration, and severity, and quantity if applicable, for each symptom. The clinician should solicit the presence or absence of fever, nausea, vomiting, hematemesis, abdominal pain, diarrhea, and hematochezia. The consistency and content of stools are important. The relationship of symptoms to eating and drinking should be established. It is helpful to know whether other persons in the household have a similar illness and whether previous episodes have occurred. A history of travel to endemic or epidemic areas may provide important information. Quantity and time of recent oral intake and information about recent pre-illness weight can be helpful. Information about orthostatic symptoms and the patient's activity level is desirable.

The physical examination should include close scrutiny of the vital signs, while keeping in mind that clinical signs are often insensitive and nonspecific for dehydration.[10] For example, tachycardia is sensitive but nonspecific, because there are many other causes of tachycardia such as fever and anxiety. On the other hand, hypotension is specific but insensitive, because children usually will maintain adequate blood pressure until severe intravascular depletion occurs. Capillary refill time and respiratory pattern are useful parameters to assess. Older children and adults may manifest symptoms at a lesser degree of volume depletion because of relatively smaller total body water and extracellular fluid volume. Important areas to emphasize with parents are addressed in Table 171-1.

Complications. The complications of acute diarrheal illness are reflected primarily in abnormalities of fluid, electrolytes, and acid-base status and in the systemic involvement from the infection. Hypoglycemia and metabolic acidosis are common in younger children yet manifest with nonspecific signs and symptoms. To inexperienced eyes, children may appear to

Table 171-1 Clinical Assessment of Degree of Dehydration

	MILD (<5%)	MODERATE (10%)	SEVERE (15%)
Signs and Symptoms			
Dry mucous membrane	±	+	+
Reduced skin turgor (pinch retraction)	–	±	+
Depressed anterior fontanel	–	+	+
Mental status	Alert	Irritable	Lethargic
Sunken eyeballs	–	+	+
Hyperpnea	–	±	+
Hypotension (orthostatic)	–	±	+
Increased pulse	–	+	+
Capillary refill	≤2 sec	>2 sec	>2 sec
Laboratory			
Urine			
Volume	Small	Oliguria	Oliguria/anuria
Specific gravity*	≥1.020†	≥1.030	≥1.035
Blood			
BUN	WNL†	Elevated	Very high
pH (arterial)	7.40–7.30	7.30–7.10	>7.10

*Specific gravity can provide evidence that confirms the physical assessment.
†Not usually indicated in mild or moderate dehydration.
+, present; –, absent; ±, variable.
BUN, blood urea nitrogen; WNL, within normal limits.
From Barkin RM, Rosen P: Emergency Pediatrics, 5th ed. St Louis, Mosby, 1999.

compensate well, only to sometimes undergo rapid decompensation. With severe illness or illness superimposed on underlying chronic conditions, children may arrive at the ED *in extremis*. Children may present in frank shock with lethargy, weakness, respiratory distress, anuria, cardiac dysrhythmia, seizure, or coma. It is vital to recognize early signs of shock, such as persistent tachycardia, hyperpnea, irritability, and lethargy, and to restore intravascular volume prior to decompensation.

Diagnostic Strategies. In children assessed to have significant dehydration from acute gastroenteritis, serum electrolytes and glucose should be assessed. Although not indicated in most cases of uncomplicated acute gastroenteritis, stool samples should be obtained for culture if specific therapy, hospitalization, or infection control measures may be indicated. Stool cultures also may be helpful if the patient has systemic involvement or underlying chronic medical complications or if the illness involves dysenteric features. In immunosuppressed patients and infants younger than 2 to 3 months of age or with possible bacteremia, a complete blood count, stool studies, and blood and other cultures are indicated. The stool study of primary utility in the ED evaluation is microscopic analysis for leukocytes and occult blood to differentiate dysentery from acute gastroenteritis. The presence of fecal leukocytes (more than 5 per high-power field) or blood indicates that the offending organism has crossed the mucosal barrier and that the risk of invasiveness has increased. Nearly 90% of children with acute diarrhea caused by *Salmonella* or *Shigella* organisms will have fecal leukocytes in the stool. Fecal leukocytes are also found in patients with *Campylobacter* organisms, *Y. enterocolitica*, invasive *E. coli*, and *V. parahaemolyticus*. Other studies such as stool electrolytes, fecal fat, culture, ova, and parasites are of greater interest and may be of help in follow-up management by the child's primary care physician. Stool culture, enzyme-linked immunoassay for rotavirus, and other tests are indicated in patients who have not responded in the expected manner or in whom the illness is of prolonged duration (more than 2 weeks) or has dysenteric features. Additional studies also are indicated if it is necessary to identify a cause for a community outbreak. Liver enzymes, bilirubin, and hepatitis serologic studies will be useful to identify the cause of hepatitis. Urinalysis can provide an indication of hydration, the presence of urinary tract infection, hepatitis, and potential renal injury.

Differential Considerations. Vomiting in children is a very common sign with an exhaustive list of causes. Young children have no social embarrassment or the personal distaste for vomiting (or diarrhea or crying) that often forces adults to bear the relative discomfort of the symptom. Children may vomit in response to pain, anxiety, or fear, as well as to other usual causes of nausea. Some general causes of vomiting are presented in Table 171-2. Diarrhea also is a common reason for parents to bring their children to the ED. Most often, diarrhea is associated with other features of acute gastroenteritis, but it may be the sole presenting complaint. Table 171-3 presents a brief list of causes of diarrhea in children. An important point is that although most children with diarrhea or vomiting, or both, have a relatively benign cause for their illness, other, more sinister, diagnoses should be considered in appropriate clinical settings.

Appendicitis is the most common surgical condition in children and adolescents. The signs and symptoms are notoriously variable. The presence of vomiting and diarrhea does not necessarily rule out the diagnosis of appendicitis, especially when the child has abdominal pain. Intussusception is another diagnosis to consider in a young child with vomiting and abdominal pain, with or without bloody stool. Bilious vomiting in a child should raise concern for intestinal obstruction, such as from midgut volvulus. Enterocolitis can be the presenting manifestation, as well as a subsequent serious complication, of Hirschsprung's disease. HUS is a rare but potentially fatal complication of enterocolitis caused by *E. coli* O157:H7 and *Shigella*.

Table 171-2 Common Causes of Vomiting in Children

ETIOLOGIC CATEGORY	CLINICAL SYNDROMES
Central nervous system	Infections, space-occupying lesion
Gastrointestinal	Obstruction, peritonitis, hepatitis, liver failure, appendicitis, pyloric stenosis, midgut volvulus, intussusception, inborn errors of metabolism
Drug	Ingestion, overdose, drug effect
Endocrine	Addisonian crisis, diabetic ketoacidosis, congenital adrenal hyperplasia
Renal	Urinary tract infection, pyelonephritis, renal failure, renal tubular acidosis
Cardiac	Congestive heart failure of any cause
Infection	Pneumonia, acute otitis media, sinusitis, sepsis
Other	Psychogenic, respiratory insufficiency

Table 171-3 Common Causes of Diarrhea in Children

ETIOLOGIC CATEGORY	CLINICAL SYNDROMES
Gastrointestinal	Malabsorption (e.g., milk intolerance, excessive fruit juice), intussusception, inflammatory bowel disease, irritable bowel syndrome, short gut syndrome
Drug	Ingestion, overdose, drug effect
Endocrine	Thyrotoxicosis, addisonian crisis, diabetic enteropathy, congenital adrenal hyperplasia
Renal	Urinary tract infection, pyelonephritis
Infection	Pneumonia, acute otitis media, sinusitis, sepsis
Other	Parental anxiety, chronic nonspecific diarrhea

Management. In addition to resuscitating children in shock, the priorities in ED management of children with diarrhea are (1) to consider other potential causes of diarrhea other than infectious diarrhea, (2) to assess for and treat underlying deficits and potential complications, and (3) to arrive at a microbiologic diagnosis. Table 171-4 lists the common infectious agents of diarrhea and the indicated treatment. Antidiarrheal compounds that impair GI motility, such as loperamide (Imodium), diphenoxylate, and atropine (Lomotil), have no role in the treatment of acute infectious diarrhea in young children, because they may prolong and exacerbate the disease and are potentially toxic.

Disposition

Most cases of childhood diarrhea can be managed on an outpatient basis by continuing routine formula or diet specific for age. Supplemental maintenance electrolyte solutions may be given. If home oral rehydration therapy is ordered, feeding

Table 171-4 Diarrheal Pathogens in Children and Specific Therapy

AGENT	SPECIFIC THERAPY BEYOND SUPPORTIVE CARE
Campylobacter jejuni	Azithromycin 12 mg/kg/day PO for 5 days *or* Erythromycin 30–50 mg/kg/day, divided, tid PO for 5–7 days
Clostridium difficile	Metronidazole 30 mg/kg/day, divided, qid PO for 7–10 days *or*
Escherichia coli	Azithromycin 12 mg/kg/day PO for 5 days *or* Trimethoprim-sulfamethoxazole 10 mg (TMP)/kg/day PO divided bid for 5–7 days
Giardia lamblia	Metronidazole 15 mg/kg/day PO, divided, tid for 5 days
Salmonella species	*In toxic infants <3 mo*: Ampicillin 200 mg/kg/24 hours q6h for 7–10 days *and* Gentamicin 5–7.5 mg/kg/24 hours q8h IV
Shigella species	Azithromycin 12 mg/kg/day PO for 5 days *or* Trimethoprim-sulfamethoxazole 10 mg (TMP)/kg/day, divided, bid for 5–7 days if susceptible
Yersinia enterocolitica	If patient is immunosuppressed, treat as for presumed sepsis
Vibrio	None; severe diarrhea or cholera may benefit from antibiotics

Data from Pickering LK, Baker CJ, Long SS (eds): Red Book: 2006 Report of the Committee on Infectious Diseases, 27th ed. Elk Grove Village, Ill, American Academy of Pediatrics, 2006.

BOX 171-1 Parent Instruction Sheet for Children with Vomiting and Diarrhea

1. Give clear liquids, as much as the child wants.
   a. Children younger than 2 years of age should be given a maintenance electrolyte solution, such as Pedialyte or Infalyte.
   b. Children older than 2 years of age may be given other clear fluids, such as decarbonated sodas, Gatorade, or clear soups.
2. If your child is vomiting, give clear liquids (as above) in small frequent volumes initially and advancing to normal volumes for the child's age as tolerated. It may be necessary to use teaspoons, cups, syringes, or ladles to administer the small volume. Fluid can be administered beginning 5 to 10 minutes after an episode of vomiting and should be continued despite the persistence of vomiting.
3. The child's diet may be advanced as soon as the vomiting has stopped and the child can tolerate fluids without vomiting. It is reasonable to wait 2 hours after the last episode of vomiting to resume feeding.
   a. Formula- or breast-feeding infants should be given their regular formula or returned to the breast.
   b. Older children should be given bland, starch-containing foods (bananas, rice, applesauce, and toast make up the popular "BRAT" regimen) in small quantities first and advancing to larger quantities and more complex items as the child's appetite returns.
4. The child may return to a regular diet as soon as the appetite returns and foods are desired.
5. Many foods may worsen diarrhea; pectin-containing foods, such as applesauce and other fruits and fruit juices, are not recommended until the diarrhea resolves.
6. Reduce the amount of cow's milk products in the diet until the diarrhea has lessened significantly.
7. Call your child's physician or return to the emergency department if any of the following occurs:
   a. The diarrhea or vomiting worsens in frequency or amount.
   b. The vomiting lasts for more than 24 hours.
   c. The stool or vomitus contains blood or the vomit becomes persistently green.
   d. The child has decreased urine output (not as many wet diapers), does not produce tears when crying, or becomes less active or difficult to arouse.

should resume as soon as vomiting subsides. Routine fasting for diarrhea illnesses is not recommended. Before discharge from the ED, careful and specific instruction regarding the signs and symptoms of expected improvement or complications must be given to the parents or caregiver (Box 171-1). Instructions should address proper hygiene and hand-washing techniques to prevent others from contracting the illness. Monitoring hand washing in daycare facilities has been shown to reduce bacterial contamination in children. Follow-up by the patient's primary care physician should be timely and should address concerns of worsening of the condition and complications that may have developed. Hospitalization may be warranted in cases of protracted vomiting, diarrhea with losses in excess of fluid administration, worsening clinical status despite therapy, presence of an underlying condition that would complicate therapy, or suspected systemic involvement. Very-low-birth-weight infants, because of low physiologic reserve and immature immune system, are at the highest risk for complications of acute gastroenteritis in the first year of life.

DEHYDRATION

Clinical Features

Dehydration, or decrease in total body water, can be caused by a variety of mechanisms. Broadly speaking, however, mechanisms of dehydration comprise three general categories: *decreased intake*, such as with stomatitis; *increased output*, such as with diarrhea and diabetes; and *increased insensible losses*, such as with fever. The severity of dehydration usually is measured as the acute weight (presumably fluid) loss as a percentage of preillness total body weight. More than 5% dehydration is considered significant and often can be identified by history and physical examination (see Table 171-1). Because preillness weights generally are not available, the clinician will need to rely on historical information, physical examination, and laboratory tests in assessing the severity of dehydration. Parental reports of history and observation are of significant value, with good sensitivity in detecting dehydration.[11] In a child who is dehydrated, initial physical exam may reveal an activity level lower than expected for age. The child may appear weak or lethargic. If the fontanel is still open, it may be sunken. The eyes appear sunken and the mucous membranes are dry (if the child has recently had something to drink, the mucous membranes may falsely appear moist). Tachycardia and hyperpnea may be present. The skin over the trunk should be examined for tenting (suggesting hypona-

Table 171-5 Types of Dehydration Reflected by Serum Sodium

PHYSICAL SIGN	DEHYDRATION TYPE BY SERUM SODIUM LEVEL		
	ISOTONIC: 130–150 MEQ/L	HYPOTONIC: <130 MEQ/L	HYPERTONIC: >150 MEQ/L
Skin			
Turgor	Poor	Very poor	Fair
Feel	Dry	Clammy	Thick, doughy
Mucous membranes	Dry	Dry	Parched
Sunken eyeballs	+	+	+
Depressed anterior fontanelle	+	+	+
Mental status	Lethargic	Coma/seizure	Irritable/seizure
Increased pulse rate	++	++	+
Decreased blood pressure	++	+++	+

+, ++, +++, relative prominence of finding.
From Barkin RM, Rosen P: Emergency Pediatrics, 5th ed. St Louis, Mosby, 1999.

tremia) or a doughy texture (suggesting hypernatremia) (Table 171-5). It is important to keep in mind that clinical signs and symptoms of dehydration are variable and often subtle.

Use of laboratory tests may be helpful in assessing children for etiology, severity, and complications of dehydration. A serum electrolyte panel and blood urea nitrogen (BUN), serum creatinine, and blood glucose determinations are the tests most commonly ordered.[12] Sodium concentration is important in identifying iso-, hypo-, or hypernatremic states for appropriate choice of therapy. A low serum HCO_3^- level may indicate loss of HCO_3^- in the stool or may reflect poor tissue perfusion. Newer noninvasive techniques for detecting dehydration have been described, such as ultrasound assessment of inferior vena cava diameter[13] and measurement of exhaled CO_2 as a marker for acidosis.[14] Children with dysentery should have BUN and serum creatinine measured and stool examined for *E. coli* O157:H7 to identify potential cases of HUS. Serum glucose level is important, because hypoglycemia is common in young children with viral gastroenteritis, and this test may help identify children with previously undiagnosed fatty acid oxidation disorders or other inborn errors of metabolism. Diabetes mellitus may manifest with vomiting and dehydration. In some cases it may be necessary to examine urine electrolytes and osmolality.

Differential Considerations

Most commonly, dehydration in children results from diarrhea and vomiting caused by infectious gastroenteritis. Table 171-6 lists some other causes of dehydration that should be considered when the GI tract is not primarily involved.

Table 171-6 Differential Diagnosis of Volume Depletion

FLUID LOSS CATEGORY	POTENTIAL ETIOLOGIC DISORDERS/CONDITIONS
Renal	Diuretics, renal tubular acidosis, renal failure, urinary tract obstruction, diabetes insipidus, diabetes mellitus, hypothyroidism, adrenal insufficiency, renal trauma, salt-wasting nephritis
Extrarenal	Third spacing (pancreatitis, peritonitis, sepsis), skin loss (burns, cystic fibrosis), lung loss, congestive heart failure, liver failure, hemorrhage

BOX 171-2 PRINCIPLES OF APPROPRIATE TREATMENT FOR CHILDREN WITH DIARRHEA AND DEHYDRATION

1. Oral rehydration solutions (ORSs) should be used for rehydration.
2. Oral rehydration should be performed as rapidly as possible.
3. Unrestricted diet is recommended as soon as dehydration is corrected.
4. For breast-fed infants, nursing should be continued.
5. For formula-fed infants, diluted formula is not recommended. Special formula is not necessary.
6. Additional ORS should be administered for ongoing diarrheal losses.

Adapted from King CK, et al: Managing acute gastroenteritis among children: Oral rehydration, maintenance, and nutritional therapy. MMWR Recomm Rep 52(RR-16):1, 2003.

Fluid and Electrolyte Management

Oral Rehydration Therapy

Oral rehydration therapy (ORT) is a safe and effective treatment for infants and children with mild to moderate dehydration.[9,15,16] ORT may be instituted even if the patient continues to vomit or has diarrhea. Children with severe dehydration, shock, lethargy, acute abdomen, suspected intestinal obstruction, sodium derangement, or significant underlying illness should be identified by means of a thorough history and physical examination and laboratory tests and be excluded from ORT. Some of these principles are illustrated in Box 171-2.

The ORT period in the ED may span 4 to 8 hours and provides an opportunity to educate the family in skills of evaluating and treating childhood diarrhea. A number of oral rehydration solutions (ORSs) have been shown to be effective. The main ingredients are water, glucose, sodium chloride, and bicarbonate in various concentrations (Table 171-7). Rehydralyte is an excellent initial solution for children with viral gastroenteritis. The volume of ORS is calculated in the following manner:

1. Estimate the degree of volume depletion as mild or moderate using information from the history, clinical signs, and physical examination.

Table 171-7 Common Oral Hydrating Solutions

SOLUTION	NA^+ (MEQ/L)	K^+ (MEQ/L)	CL^- (MEQ/L)	HCO_3^-/CITRATE (MEQ/L)	GLUCOSE* (G/DL)	MOSM/L
Rehydration						
Rehydralyte	75	20	65	30	2.5	270
WHO solution	90	20	80	10	2.0	310
Maintenance						
Lytren	50	25	45	30	2.0	
Pedialyte	45	20	35	30	2.5	270
Infalyte	50	25	45	34	1.9	200
Clear Liquids						
Gatorade	20	3			2.1	
Cola	3	0.1–0.9		7–13	10.0	
Ginger ale	4	0.2			9.0	

*May be long-chain oligosaccharide subject to hydrolysis.
WHO, World Health Organization.
From Barkin RM, Rosen P: Emergency Pediatrics, 5th ed. St Louis, Mosby, 1999.

2. Calculate the desired volume of ORS as 60 mL/kg for mild and 80 mL/kg for moderate volume depletion.
3. Administer 25% of the volume of ORS to be replaced each hour for the first 4 hours.
4. Monitor progress hourly and reevaluate after 4 hours.

This technique requires that the ED have the facilities and personnel to observe and monitor the patient for the 4 to 8 hours necessary to determine the success or failure of ORT. The parent or other caregiver can be taught to administer ORT. Nursing personnel also should instruct the parent in observation skills, methods of administering the fluid, and types of fluid that are considered appropriate for children with vomiting and diarrhea. During the monitoring period, a child who is unable to tolerate intake of the prescribed volume of fluid at the expected rate should receive intravenous fluids. It is important to determine and address whether the failure is the result of the child's inability to ingest the fluid, excessive fluid loss through vomiting or diarrhea, or poor technique or motivation on the parent's part. It usually is possible to maintain the fluid administration rate in children who continue to vomit by administering small volumes frequently. This may require, for instance, using a spoon or syringe to slowly drip the fluid by hand. Some success has been obtained with the use of nasogastric tubes. Emesis (volume-for-volume) and stool volume (5 mL/kg) losses are estimated and these amounts added to the replacement volume on an hourly basis. The patient is reassessed at the end of the first 4 hours. If the clinical examination indicates adequate volume repletion, the child may be discharged home with further specific instructions for parents regarding maintenance fluid requirements. If, on the other hand, the child still exhibits mild or moderate volume depletion on clinical examination but no deterioration in status has occurred, the child is reevaluated as if from the beginning, and another 4-hour trial is attempted. If the child is unable to ingest the appropriate volume, or if volume repletion is not achieved at the end of 8 hours, intravenous therapy should be initiated.

Intravenous Therapy

Some dehydrated children brought to the ED may not qualify for ORT, and others may fail to improve with ORT. These patients include those with circulatory collapse, shock, severe dehydration, increasing deficit or clinical deterioration during ORT, intractable vomiting, hypoglycemia, or sodium derangements.

Patients are evaluated in accordance with their immediate (emergency phase, phase I), short-term (repletion phase, phase II), and long-term (early refeeding phase, phase III) needs. During the *emergency* phase, the aim of fluid resuscitation is to restore circulatory volume. This fluid needs to be administered rapidly to prevent imminent serious morbidity or death. During the *repletion* phase, fluid and electrolyte derangements are reversed, and ongoing losses are replaced. This phase lasts 24 hours. In the *early refeeding* phase, long-term needs are addressed over the next few days, during which the body recovers fluid, electrolyte, and nutritional homeostasis. Immediate and short-term therapies are initiated in the ED, with subsequent phases carried out in the inpatient setting or at home as managed by the primary care physician. In clinical practice, this algorithm represents a continuum of care and not three distinct, separate phases. Monitoring of serum electrolytes, BUN, and blood glucose is indicated for patients receiving intravenous fluid therapy.

Emergency Resuscitation Phase

Rapid reexpansion of the intravascular space is the goal of immediate resuscitation and can be achieved with an isotonic crystalloid solution. Administering 20 mL/kg of 0.9% saline (or other appropriate isotonic crystalloid solution) IV at a rapid rate should result in reversal of signs of shock within 5 to 15 minutes. In critical situations, interosseous routes should be used if venous access is not immediately available. Patients should be reevaluated periodically, and those with excessive deficits should receive repeat boluses of 20 mL/kg until clinical improvement occurs. Signs of recovery include normalization of blood pressure measurements, improvement of mental status, and production of urine. Volume requirements greater than 60 mL/kg without signs of improvement warrant investigation for other conditions, such as septic shock, hemorrhage, capillary leak with third space fluid sequestration, congestive heart failure, and toxic shock.

A rapid determination of serum glucose is important. Children require glucose as an energy substrate and often have marginal stores available in illnesses. If the serum glucose is low (less than 50 mg/dL), rapid administration of dextrose 0.25 to 0.5 g/kg IV (in neonates younger than 3 months of age, 10% dextrose at 2 to 5 mL/kg is used) should correct the deficit. Glucose levels should be monitored (every 30 to 60 minutes until stable) to ensure improvement and to identify ongoing needs. Repeated episodes of hypoglycemia should raise sus-

picion for fatty acid oxidation defects and other inborn errors of metabolism.

Repletion Phase

After immediate resuscitation, appropriate fluid therapy for the patient should be determined. Calculations should take into account the fluids already administered and also should accommodate changes in the patient's clinical status. To allow accurate planning of the type and amount of fluid to be administered, volume replacement should proceed from the serum sodium level: hypernatremia (serum sodium level greater than 150 mEq/L), hyponatremia (sodium level less than 130 mEq/L), or isonatremia (sodium level of 130 to 150 mEq/L).

Isonatremic Volume Depletion

Isonatremic volume depletion is the most common form of volume depletion and results from relatively equal losses of sodium and water. No change in body fluid tonicity or redistribution of fluid between the extracellular and intracellular fluid spaces occurs. This results in loss of fluid from the extracellular space and, therefore, intravascular volume depletion. GI fluid loss with or without decreased intake or increased urine loss is the most common cause. Repletion fluids are outlined for a sample patient in Box 171-3. Generally, one half of the deficit fluids is given during the first 8 hours of repletion.

Note that the sample patient is mildly acidotic (HCO_3^- greater than 12 mEq/L) and that restoring intravascular volume results in improved tissue perfusion and correction of the metabolic acidosis. These calculations account for water and electrolyte requirements (maintenance and deficit) and demonstrate that use of a standard fluid preparation (0.9%, 0.45%, or 0.2% saline) permits close approximation of calculated requirements and facilitates treatment by relying on readily stocked supplies.

BOX 171-3 SAMPLE CALCULATION OF FLUID AND ELECTROLYTE REQUIREMENTS IN A PATIENT WITH ISONATREMIC VOLUME DEPLETION

Isotonic Volume Depletion: Management of Moderate to Severe Deficits

1. Initial findings
   a. Preillness weight: 10 kg (a 1-year-old)
   b. Degree of volume depletion: moderate (10%)
   c. Body weight on admission: 9 kg
   d. Electrolytes:

Na^+ 135 mEq/L	K^+ 5 mEq/L	Cl^- 115 mEq/L	HCO_3^- 12 mEq/L

2. Summary of fluid requirements

	H_2O (mL)	*Na^+ (mEq)*	*K^+ (mEq)*
Maintenance	1000 (100 mL/kg)	30 (3 mEq/kg)	20 (2 mEq/kg)
Deficit (100 mL/kg)			
ECF (60%)	600	84 (140 mEq × 0.6)	
ICF (40%)	400		30 (150 mEq × 0.4 × 50% correction)
TOTAL	1000 mL	84 mEq	30 mEq
Resuscitation fluids	200 mL	28 mEq	
Net deficit	800 mL	56 mEq	30 mEq

3. Fluid schedule

	Fluids	
Phase	*Calculation*	*Administered*
I (0–½ hr)	20 mL/kg	200 mL 0.9% NS or LR over 20–30 min
II (½–9 hr)	½ net deficit: 400 mL D_5W with 28 mEq NaCl and 15 mEq KCl	733 mL (~90 mL/hr) of D_5W 0.45% NS with 22 mEq KCl (~30 mEq/L) (this approximation facilitates care)
	⅓ maintenance: 333 mL D_5W with 10 mEq NaCl and 7 mEq KCl	
	TOTAL: 733 mL with 38 mEq NaCl and 22 mEq KCl	
III (9–25 hr)	½ deficit	1067 mL (~67 mL/hr) of D5W 0.45% NS with 28 mEq KCl (~26 mEq/L) (this approximation
	⅔ maintenance	

Notes

1. Fluid resuscitation is crucial during phase I. If initial response is poor, additional infusions are warranted. Generally, the initial emergency fluid bolus should be included as part of the deficit replacement.
2. Blood glucose should be assessed early, especially in children with prolonged vomiting, diarrhea, or inadequate intake. Early glucose infusion may be warranted.
3. If the patient is acidotic with HCO_3^- of ≤10 mEq/L or a pH < 7.1 on the basis of metabolic acidosis, one third of the sodium may be administered as $NaHCO_3$.
4. In the face of acidosis, serum potassium does not reflect total body deficit.
5. Adjust for fever (add 10% for each 1°C over 37°C), stool loss (5 mL/kg), or vomiting (volume for volume).

D_5W, 5% dextrose in water; ECF, extracelluar fluid; ICF, intracellular fluid; NS, normal saline; RL, Ringer's lactate.
Modified from Barkin RM, Rosen P (eds): Emergency Pediatrics, 5th ed. St Louis, Mosby, 1999.

Hyponatremic Volume Depletion

Hyponatremic volume depletion is a result of loss of relatively more sodium than water, resulting in extracellular water shift into the intracellular fluid space to maintain equal osmolarity. This results in a significant decrease in intravascular volume and hemodynamic compromise. This type of volume depletion usually is caused by GI fluid loss that has been replaced with hypotonic fluid. Specific signs and symptoms of hyponatremia are largely neurologic, ranging in severity from malaise and irritability to seizures and coma.

Appropriate management of hyponatremic dehydration for a sample patient is described in Box 171-4. If the serum sodium is 120 to 130 mEq/L, 5% dextrose in 0.9% saline is adminis-

BOX 171-4 Sample Calculation of Fluid and Electrolyte Requirements in a Patient with Hyponatremic Volume Depletion

Hypotonic Volume Depletion: Management of Moderate to Severe Deficits

1. Initial findings
   a. Preillness weight: 10 kg (a 1-year-old)
   b. Degree of volume depletion: moderate (10%)
   c. Body weight on admission: 9 kg
   d. Electrolytes:
      Na^+ 110 mEq/L K^+ 5 mEq/L Cl^- 90 mEq/L HCO_3^- 12 mEq/L
2. Summary of fluid requirements

	H_2O (mL)	*Na^+ (mEq)*	*K^+ (mEq)*
Maintenance	1000 (100 mL/kg)	30 (3 mEq/kg)	20 (2 mEq/kg)
Deficit (100 mL/kg)			
ECF (60%)	600	84 (140 mEq × 0.6)	
ICF (40%)	400		30 (150 mEq × 0.4 × 50% correction)
Sodium deficit*		125	
TOTAL	1000 mL	209 mEq	30 mEq
Resuscitation fluids	200 mL	28 mEq	
Net deficit	800 mL	181 mEq	30 mEq

3. Fluid schedule

Phase	*Calculation*	*Fluids Administered*
I (0–½ hr)	20 mL/kg	200 mL 0.9% NS or LR over 20-30 min
II (½–9 hr)	½ net deficit: 400 mL D_5W with 90 mEq NaCl and 15 mEq KCl	733 mL (~90 mL/hr) of D_5W 0.9% NS with 22 mEq KCl (~30 mEq/L) (this approximation facilitates care)
	⅓ maintenance: 333 mL D_5W with 10 mEq NaCl and 7 mEq KCl	
	TOTAL: 733 mL with 100 mEq NaCl and 22 mEq KCl	
III (9–25 hr)	½ deficit	1067 mL (~67 mL/hr) of D_5W 0.9% NS with 28 mEq KCl (~26 mEq/L) (this approximation facilitates care)
	⅔ maintenance	

*Sodium Deficit Calculation

A. Na^+ required to correct to 135 mEq/L = 135 mEq/L − 110 mEq/L (observed Na^+) = 25 mEq/L
B. Total body water (TBW) (L/kg) = 0.6 L/kg (preillness TBW) − 0.1 L/kg (water loss) = 0.5 L/kg
C. Preillness weight = 10 kg
Sodium deficit = A × B × C = 25 mEq/L × 0.5 L/kg × 10 kg = 125 mEq

Notes

1. Fluid resuscitation is crucial during phase I. If initial response is poor, additional infusions are warranted. Generally, the initial emergency fluid bolus should be included as part of the deficit replacement.
2. If a patient is acidotic with HCO_3^- of ≤10 mEq/L or a pH ≤ 7.1 on the basis of metabolic acidosis, one third of the sodium may be administered as $NaHCO_3$.
3. In the face of severe hyponatremia with decreased TBW in symptomatic patients, hypertonic 3% saline must be given to raise the serum sodium level to 125 mEq/L. A 3% saline solution contains approximately 0.5 mEq Na^+/mL. Patients may be given 3% saline 4 mL/kg IV over 10 minutes and the response monitored. Once seizures have stopped, half of the deficit may be corrected over the next 8 hours as outlined in the fluid schedule.
4. If excess water load is the cause, furosemide (Lasix) 1 mg/kg/dose IV may be used. During the subsequent diuresis, urinary sodium, potassium, and chloride should be measured and replaced milliequivalent for milliequivalent with 3% saline and supplemental potassium chloride.
5. Blood glucose should be assessed early, especially in children with prolonged vomiting, diarrhea, or inadequate intake. Early glucose infusion may be warranted.
6. In the face of acidosis, serum potassium does not reflect total body deficit.
7. Adjust for fever (add 10% for each 1°C over 37°C), stool loss (5 mL/kg), or vomiting (volume for volume).

D_5W, 5% dextrose in water; ECF, extracellular fluid; ICF, intracellular fluid; NS, normal saline; RL, Ringer's lactate.
Modified from Barkin RM, Rosen P (eds): Emergency Pediatrics, 5th ed. St Louis, Mosby, 1999.

tered, with one half of the daily fluid requirement given in the first 8 hours and the remainder over the succeeding 16 hours. Monitoring of serum electrolytes, BUN, weight, and intake and output is recommended. Rapid correction of hyponatremia can be associated with central pontine myelinolysis. Close monitoring of serum sodium is indicated to avoid correcting by more than 1 mEq/L per hour. Potassium chloride, 20 mEq/L, is added to the intravenous fluids after renal function is assessed. If the serum sodium is less than 120 mEq/dL, the patient will exhibit seizures, hyperexcitability, or other neurologic symptoms. In such cases, 3% saline (0.5 mEq sodium chloride/mL) should be administered according to the following formula:

$$3\%\ \text{saline (mL)} \times (10\,\text{mEq/L})(0.6)(\text{weight})/(0.5)$$

Avoiding too-rapid correction of serum sodium is warranted because of the risk for central pontine myelinolysis, as noted. This disorder has been reported in children, especially those undergoing fluid resuscitation for hyponatremic dehydration in diabetic ketoacidosis.[17,18] In some conditions causing hyponatremia, furosemide (1.0 mg/kg IV) or other diuretics have been recommended. The mechanism of action of the loop diuretics must be considered, because free water is excreted with an obligatory solute (sodium) loss. Diuretics may be used in combination with saline administration in an attempt to avoid sodium depletion.

Hyponatremic dehydration must be differentiated from another common cause of hyponatremia, the syndrome of inappropriate ADH secretion (SIADH). In this syndrome, caused by a variety of conditions, the kidneys inappropriately excrete sodium and retain water, resulting in low serum sodium and high urinary sodium concentrations. Treatment is with fluid restriction.

Hypernatremic Volume Depletion

Hypernatremic volume depletion arises with loss of relatively more water than sodium. It can occur if inappropriate types of fluids are given, if the fluid or formula is mixed incorrectly, or if fever or hyperventilation complicates the illness. This is the least common type of volume depletion because of a generally lower content of sodium in most modern infant fluids and formulas. Intracellular water shifts to the extracellular fluid space to maintain osmolar balance; therefore, intravascular volume is relatively preserved. Signs and symptoms specific to hypernatremia are "doughy" skin and altered CNS function (manifested as irritability, seizures, or high-pitched cry). Care must be taken not to administer hypotonic fluid at too fast a rate, because water will equilibrate across the cerebral blood-brain barrier almost immediately (long before the sodium is corrected), creating increased intracranial pressure. This type of dehydration should be corrected over 48 to 72 hours. Box 171-5 provides guidelines for the calculation of fluids and electrolytes for a sample case. Close monitoring of neurologic status and serum electrolytes is important during the period of rehydration.

Hospital-Acquired Hyponatremia

One of the complications that can develop during intravenous rehydration in children is acute hyponatremia. In children, this rare disturbance can lead to significant neurologic morbidity, including seizures, coma, and brain herniation, or even death. For acute hyponatremia to occur, two conditions have to be met: (1) an exogenous source of free water must be available, and (2) secretion of ADH must occur. Many experts, therefore, recommend using isotonic saline, rather than hypotonic saline, as the replacement intravenous fluid of choice in hospitalized children.[19,20] This practice is not universally accepted.[21] In any case, vigilance in monitoring the neurologic status of children undergoing intravenous rehydration is essential.

BOX 171-5 HYPERTONIC DEHYDRATION

A 2-week-old infant presents to the ED with a history of 1 day of poor breast milk intake. Weight yesterday at a well-baby visit was 4 kg; today the child weighs 3.4 kg. Laboratory study findings include serum Na^+ 155 mEq/L; K^+ 4.5 mEq/L; HCO_3^- 13 mEq/L.

Maintenance Therapy

100 mL/day for first 10 kg = 400 mL
Na^+ requirements = 3 mEq/kg × 4 kg = 12 mEq
K^+ requirements = 2 mEq/kg × 4 kg = 8 mEq

Total Fluid Deficit: 4.0 – 3.4 = 0.6 L

Free water deficits = observed Na^+ – ideal Na^+
(145 mEq/L)] × 4 mL/kg × wt (kg) = (155 – 145) × 4 mL/kg × 4 kg = 160 mL

Na^+ Deficit

The illness is less than 3 days in duration. Therefore, the fluid lost is 75% from the ECF and 25% of the ICF. Primary sodium reservoir is ECF.

$$\begin{aligned} Na^+\ \text{loss} &= (\text{ECF } Na^+ \text{ concentration}) \\ &\quad \times (75\%\ \text{of solute fluid deficit*}) \\ &= (140\,\text{mEq/L}) \times (0.75 \times 0.440\,\text{L}) \\ &= 46\,\text{mEq} \end{aligned}$$

NOTE: Solute containing deficit:
Total fluid deficit – free water deficit = 600 mL – 160 mL = 440 mL

K^+ Deficit (Primary Potassium Reservoir is ICF):

$$\begin{aligned} K^+\ \text{loss} &= (\text{ICF } K^+ \text{ concentration}) \\ &\quad \times (25\%\ \text{of solute fluid deficit}) \\ &= (150\,\text{mEq/L}) \times (0.25) \times 0.440\,\text{L} \\ &= 16\,\text{mEq} \end{aligned}$$

48-Hour Requirements = Maintenance + Deficits

Total deficits:
Fluid (mL) = (400 × 2) mL + 160 mL (free) + 440 mL (solute) = 1400 mL
Sodium (mEq) = 24 + 46 = 70 mEq
Potassium (mEq) = 16 + 16 = 32 mEq

Fluid Schedule

The fluid is administered in a step-wise fashion over 48 hours. One half the deficit is given in the first 24 hours; then the remainder is given over the next 24.

First Day Fluids = Maintenance + ½ Deficits

First day fluids = (400 mL + 12 mEq Na^+ + 8 mEq K^+) + ½ (600 mL + 46 mEq Na^+ 16 mEq K)
First day fluids = 700 mL D_5W + 35 mEq Na^+ + 16 mEq K^+
In practice (and after the calculations are done), the usual fluid that is required to rehydrate the child with hypertonic dehydration is either D_5W 0.2% NS or D_5W 0.45% NS, because it would appear that the *rate* rather than the type of fluid is most important. The volume of free water needed to lower a serum sodium concentration above 145 mEq/L is approximately 4 mL/kg of free water for each 1 mEq/L over 48 hours. Studies demonstrate that D_5W, D_5W 0.2% NS, and D_5W 0.45% NS all are acceptable if infused at a conservative rate, correcting deficits over 48 hours.

D_5W, 5% dextrose in water; ECF, extracellular fluid; ICF, intracellular fluid; NS, normal saline; RL, Ringer's lactate.
Modified from Barkin R, et al: Pediatric Emergency Medicine, 2nd ed. St Louis, Mosby, 1997.
*Calculated as (600 mL fluid deficit – 160 mL free water deficit).

KEY CONCEPTS

- *Identification of pathogen*: Stool studies are not indicated in most uncomplicated cases of acute gastroenteritis. Exceptions are those cases in which specific treatment, specific prophylaxis, or health precautions are required or in which the patient has systemic involvement or underlying medical complications or the illness involves dysenteric features.
- *Fecal leukocytes*: The presence of fecal leukocytes or blood indicates that the offending organism has crossed the mucosal barrier and that the risk of invasiveness has increased. Nearly 90% of patients with acute diarrhea caused by *Salmonella* or *Shigella* organisms will have fecal leukocytes in the stool.
- *Oral rehydration*: With oral rehydration therapy, resumption of feeding should begin as soon as vomiting subsides. Routine fasting with infectious diarrhea is not recommended. Patient and family instruction should address proper hygiene and hand-washing techniques to prevent others from contracting the illness.
- *Dehydration assessment*: The degree of volume depletion is estimated using information from the history, clinical signs, and physical examination. The desired volume of oral rehydration solution (ORS) is calculated as 60 mL/kg for mild and 80 mL/kg for moderate volume depletion; then 25% of the volume of ORS to be replaced is administered each hour for the first 4 hours.
- *Severe dehydration*: In severe dehydration, 20 mL/kg of 0.9% saline (or other appropriate isotonic crystalloid solution) given IV at a rapid rate should result in reversal of signs of shock within 5 to 15 minutes. Repeat boluses of 20 mL/kg are indicated until clinical improvement occurs, but volume requirements greater than 60 mL/kg without signs of improvement suggest other conditions, such as septic shock, hemorrhage, capillary leak with third space fluid sequestration, and heart failure.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 172

Genitourinary and Renal Tract Disorders

Maureen McCollough and Ghazala Q. Sharieff

PERSPECTIVE

This chapter discusses some of the more common causes of scrotal, testicular, and penile pain in children that precipitate a visit to the emergency department (ED). Also discussed are other renal or genitourinary tract disorders in this age group for which emergent treatment may be sought, including acute renal failure, urinary tract infections, and hypertension.

SPECIFIC DISORDERS

Penile Disorders

Priapism

Principles of Disease. *Priapism* is the engorgement of the dorsal corpora cavernosa, resulting in dorsal penile erection and ventral penile flaccidity. Sickle cell disease and leukemia are responsible for a majority of cases in children. Spinal trauma, immunosuppressive disorders, anticoagulation, and intracavernosal injection of agents such as papaverine, phentolamine, and prostaglandin-E1 also can result in priapism. Other drugs such as phenothiazines, sedative-hypnotics, selective serotonin reuptake inhibitors, antihypertensives, anticoagulants, and drugs of abuse (e.g., cocaine, alcohol, marijuana) may be causal.

The more common *low-flow priapism* is secondary to decreased venous outflow and is characterized by prolonged painful erection. *High-flow priapism* usually is painless and typically is associated with penile arterial laceration and excessive inflow of arterial blood, resulting in corporal engorgement. With prolonged engorgement of the corpora cavernosa, the resultant stagnation and hypoxia of the blood lead to the development of thrombosis and ischemia. Priapism complications include penile fibrosis, urinary retention, and impotence.

Clinical Features. Priapism is a clinical diagnosis and can be distinguished from other causes of erection by careful history and complete physical examination. The history should include past medical history with attention to previous treatment for anemia, leukemia, sickle cell disease, or drug abuse and current history of trauma or symptoms of immunosuppressive disease. Physical examination should be extensive and look for rash, lymphadenopathy, pale or jaundiced skin, or signs of a toxidrome. Although, as noted, priapism is a clinical diagnosis, laboratory studies may assist in isolating the cause of the condition. A complete blood count (CBC), hemoglobin electrophoresis, and coagulation studies may be useful in some cases. Diagnostic studies of penile blood flow may be indicated in cases for which the cause is unclear and may include magnetic resonance imaging (MRI), color Doppler cavernosonography, and technetium-99m penile scanning. Angiography is helpful in localizing the arterial bleeding site in high-flow priapism.[1]

Differential Considerations. The differential diagnosis for priapism in children differs from that in adults. In adults, penile erection from sexual arousal, urethral foreign bodies, Peyronie's disease, spinal cord injury, and penile implants may occur, but these etiologic factors would be rare in children. Anticoagulation, drugs of abuse, medications, trauma (including spinal trauma), Kawasaki disease, leukemia, and sickle cell disease all are associated with priapism in children.

Management and Disposition. Management centers on hydration, pain control, relief of urinary obstruction, and treatment of any other underlying conditions. Local anesthesia effected by dorsal nerve block using 1% lidocaine without epinephrine may be beneficial. Infiltration with hyaluronidase also may be effective. In patients with sickle cell disease, treatment is begun with oxygen, hydration, and analgesics. Low-flow priapism may respond to sitz baths or hot compresses, because the heat increases blood flow, thereby potentially relieving the obstruction.

In addition, cavernosal aspiration plus irrigation has been effective in patients with low-flow priapism. This procedure should be performed within the first few hours of symptom onset and rarely is beneficial after 48 hours. Phentolamine, phenylephrine (100 to 500 µg per dose for up to 10 doses; 10 to 20 mL of 20 µg/mL of solution given by intracavernous injection every 5 to 10 minutes), ephedrine, or 1:1,000,000 epinephrine often is added to the irrigation solution used in performing corporal aspiration. Alternatively, mix 1000 µg of phenylephrine in 100 mL of isotonic sodium chloride solution (10 µg/mL) and infuse 10–20 mL at a time. Parenteral vasodilators such as papaverine, hydralazine, and terbutaline also have been tried, with variable success.[2]

Exchange transfusion previously has been recommended; however, this treatment may not offer any advantage over conventional therapy and has been associated with serious neurologic sequelae, as in the so-called ASPEN syndrome (*a*ssociation of *s*ickle cell disease, *p*riapism, *e*xchange transfusion, and *n*eurologic events).[3,4] Patients with leukemia may respond with detumescence after chemotherapy is begun.

High-flow priapism in children is rare; accordingly, treatment modalities have not been well studied. High-flow states can be effectively addressed using arterial embolization. If

nonsurgical approaches are unsuccessful, a corpus cavernosa–glans shunt procedure may be necessary. In a recent case report, ultrasound-guided compression of the perineal arteriocavernous fistula was successful.[5] Interventions should be initiated within 12 hours of symptom onset to avoid long-term dysfunction and irreversible infarction.[6] Patients with persistent priapism or underlying disorders such as leukemia or sickle cell disease require hospitalization. Pediatric urologic consultation should be arranged as soon as possible. If the priapism has been treated successfully, then after some period of observation, the patient may be discharged home with urologic specialist follow-up.

Phimosis

Principles of Disease. *Phimosis* is a pathologic condition of the uncircumcised penis in which constriction of the foreskin prevents retraction of the prepuce from over the glans. It can result in pain, hematuria, and urinary outlet obstruction. Most cases are physiologic, representing normal development, and do not require intervention. Only 4% of newborn males have a fully retractable foreskin. This percentage increases with age: 25% of 6-month-olds, 50% of 1-year-olds, 80% of 2-year-olds, and 90% of 4-year-old boys have fully retractable foreskins.[7] Phimosis also may result from trauma, infections, chemical irritation, poor hygiene, congenital abnormality, or be a complication of circumcision.

Clinical Features. Phimosis is a clinical diagnosis. History may reveal that the foreskin is unretractable, along with narrowing or diversion of the urinary stream and bulging out of the foreskin with urination. Pain and hematuria may be accompanying features.

Management and Disposition. Because the ability to retract the foreskin fully is age-related, parents should be advised not to retract the prepuce forcefully. Gentle retraction with good hygiene should be stressed. If signs of urinary outlet obstruction are present, dilation of the prepuce or the urethral meatus or both can be performed by gentle use of forceps. With vascular compromise of the glans, a dorsal split procedure, circumcision, preputial plasty, or balloon dilation may be necessary.[8,9] Topical steroid treatment (with betamethasone valerate 0.6% cream) for 6 weeks has been 87% effective in reducing inflammation and treating phimosis.[10-12] In patients with severe stenosis, obstructive uropathy can result. In such cases, blood urea nitrogen (BUN) and serum creatinine levels should be obtained, and a renal ultrasound examination should be performed if signs of obstructive renal failure are present. Patients who are able to urinate and have no evidence of severe infection or ischemia can be discharged from the ED with outpatient urologic follow-up.

Paraphimosis

Principles of Disease. *Paraphimosis* is another pathologic condition of the uncircumcised penis in which the proximal foreskin cannot be returned to its anatomic position covering the glans penis, resulting in distal venous congestion with the potential for dire consequences. Paraphimosis can be caused by infection, masturbation, trauma, or hair or clothing tourniquets. Iatrogenic causes include failure to reduce the foreskin after a medical examination. Paraphimosis constitutes a true urologic emergency and can result in arterial compression, penile necrosis, and gangrene.

Clinical Features. The patient typically is anxious, and the history often reveals that the parents or the patient retracted the foreskin and then could not replace the foreskin back over the glans (Fig. 172-1). The history should include verification that the patient is uncircumcised, because hair tourniquet syndrome in a circumcised patient may mimic paraphimosis. Physical examination reveals a flaccid proximal penis with erythema and engorgement distal to the obstruction. The foreskin is retracted, and cellulitis may be present. The diagnosis of paraphimosis is based on clinical findings, but if a penile foreign body is a concern, radiographs can be obtained after relief of the vascular occlusion.

Figure 172-1. Paraphimosis in a 4-year-old uncircumcised boy. (Courtesy of Marianne Gausche-Hill, MD.)

Management and Disposition. Pain can be controlled either parenterally or by performing a local dorsal penile nerve block. Procedural sedation also may be necessary. Placing a finger of a rubber glove filled with ice water over the glans and foreskin can reduce the edema. Circumferential compression of the penis starting at the glans also can reduce the edema. Compression may need to be held for several minutes to achieve adequate reduction of edema. Manual reduction may be necessary, with application of gentle, steady pressure on the glans with both thumbs while the shaft is pulled straight (Fig. 172-2). Another method is to puncture the edematous foreskin with an 18- or 21-gauge needle.[13,14] The puncture may be followed by squeezing of the glans penis to further facilitate fluid drainage. Dorsal band traction has been performed in some cases by application of Adson forceps directly to the band formed by the retracted foreskin and applying traction and

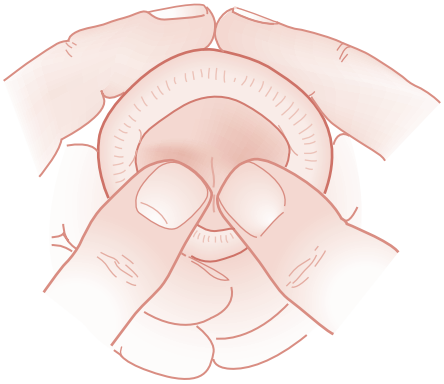


Figure 172-2. Paraphimosis reduction. (Courtesy of P.P. Kelalis.)

Figure 172-3. Balanoposthitis in an 8-month-old boy caused by candidal infection. (Courtesy of Marianne Gausche-Hill, MD.)

countertraction to loosen the constriction. If all such attempts fail, urologic consultation proceeding to circumcision or a dorsal slit procedure may be necessary. Patients can be discharged home after reduction if they are able to void spontaneously and urologic follow-up care can be arranged. Any evidence of cellulitis or necrosis warrants hospital admission, intravenous antibiotics, and urologic consultation.

Balanoposthitis

Principles of Disease. *Balanoposthitis* is an inflammation that involves the glans and the foreskin, occurring in up to 6% of uncircumcised males.[15] *Balanitis* involves the glans penis only. The primary cause of balanoposthitis is infection; however, chemical irritation, trauma, fixed drug rash, and contact dermatitis also can be contributory. Infectious organisms include gram-negative and gram-positive organisms, including group A beta-hemolytic streptococci and rarely *Neisseria gonorrhoeae* and *Chlamydia*.[16] Recurrent episodes of *Candida albicans* balanoposthitis should raise suspicion for diabetes mellitus.

Clinical Features. Physical examination reveals penile erythema, edema, and possibly a discharge (Fig. 172-3). Systemic symptoms and signs such as fever, vomiting, and diarrhea are unusual. Diagnosis is clinical and treatment is based on clinical findings; however, if symptoms are severe, the offending organism can be identified by culturing any discharge.

Management and Disposition. Management includes emphasis on adequate hygiene with sitz baths to reduce inflammation. Painful micturition can be addressed by having the child urinate while in a bath of warm water. In patients with cellulitis, antibiotic treatment with agents effective against *Staphylococcus aureus* and *Streptococcus pyogenes* is recommended. Seven days of a first-generation cephalosporin is an appropriate regimen. If group A beta-hemolytic streptococci are identified, a streptococcus-specific antibiotic is required.[17] Inflammation also can be treated with 0.5% hydrocortisone cream applied sparingly to the area. Candidal infections should be treated topically with antifungals; circumcision may be required for recurrent disease. Patients with a toxic appearance or those who exhibit evidence of cellulitis or constricting phimosis with uropathy should be hospitalized for appropriate management.

Complications of Circumcision

Principles of Disease. Circumcision usually is advocated for prevention of phimosis, paraphimosis, recurrent balanoposthitis, urinary tract infections, and penile cancer. Any of three techniques can be used: application of a Plastibell or Gomco clamp, excision, or a dorsal slit procedure. The choice of procedure is dependent on the preference of the operator. The most common complication of these procedures is hemorrhage, which usually is minor and can be controlled by direct pressure, silver nitrate application, or suture placement. Significant bleeding may be a sign of a blood dyscrasia. Localized, systemic, or urinary tract infection also can occur.

Management and Disposition. Postoperative pain usually resolves within 12 to 24 hours. Occlusive dressings can contribute to urinary retention and edema and should be removed. Stenosis of the now exposed urethral meatus may result from prolonged exposure to the ammonia in urine. Application of a Plastibell that is too small also can lead to meatal stenosis in 8 to 31% of cases.[18] Signs and symptoms include pain with urination, bloody discharge resulting from inflamed meatus, high-velocity stream, and the need to sit while voiding. Post-circumcision phimosis may result if excess foreskin remains. If the constriction is severe and urinary outlet obstruction occurs, dilation of the stenosis can be performed using a hemostat. Surgical revision usually is necessary.[19]

Skin bridges are small fibrotic bands that attach the glans to the penile shaft and may form after circumcision. Inclusion cysts result from smegma retained in the wound or from epidermis involution along the circumcision site. Like skin bridges, these are treated by surgical resection. These complications may be prevented by proper hygiene and application of an antimicrobial ointment to the circumcision site for 7 to 10 days after the procedure.

Penile Entrapment and Tourniquet Injuries

Penile rings, string, wire, and human hair tourniquets can result in penile venous and arterial occlusion. The patient presents with swelling of the glans, wherein the offending agent may be difficult to visualize because of edema of the coronal sulcus. In addition to the vascular supply, the dorsal penile nerve supply can be occluded. Urethral obstruction can be evaluated by means of a retrograde urethrogram, and Doppler ultrasonography can be performed to assess penile arterial blood flow. Once identified, the constriction is relieved, and the patient should not be discharged until spontaneous voiding is ensured. Urologic consultation may be necessary emergently if penile arterial flow is disrupted and the constricting object cannot be removed rapidly or signs of necrosis are present.

Zipper entrapment of the foreskin also can occur in children, typically those between 2 and 6 years of age. The zipper can be removed with bone or metal cutters or a mini-hacksaw to cut the median bar of the zipper[20,21] (Fig. 172-4). The zipper falls apart and the foreskin is freed. Although local anesthesia is not necessary, the patient may be quite anxious and require sedation before its removal. Success has been reported with soaking the penis in mineral oil before zipper removal.[22] Additional methods to release the foreskin under the zipper mechanism include simply cutting the zipper below the entrapment and pulling the two halves of the zipper apart, cutting the zipper teeth above and below the entrapment and using pliers, squeezing the median bar to allow for more room to disengage the trapped prepuce, and inserting a flat screwdriver between the faceplates of the zipper mechanism to pry open the faceplates and allow the prepuce to be released.[23-26] Parents should be instructed to encourage their children to wear underwear to decrease the risk of entrapment.

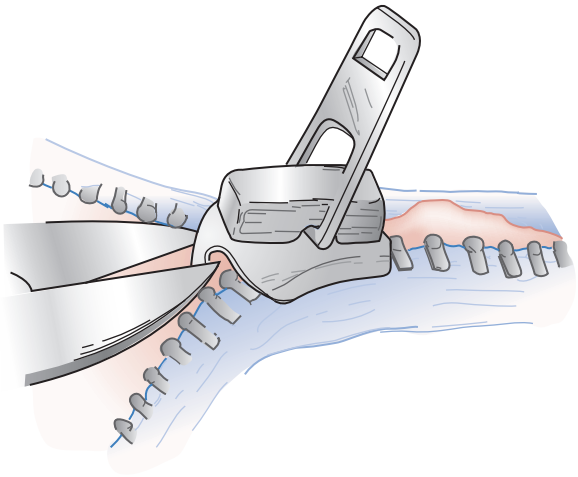


Figure 172-4. Release of zipper entrapment by cutting the median bar. (From Snyder HM III, et al: Genitourinary Trauma. In Fleisher GR, Ludwig S [eds]: Textbook of Pediatric Emergency Medicine, 4th ed. Philadelphia, Lippincott Williams & Wilkins, 2000.)

Scrotal Masses and Swelling

Epididymitis

Principles of Disease. *Epididymitis* is inflammation of the epididymis, which is located along the posterior aspect of the testicle. The most common cause is infectious, and the etiology varies by age. Adolescents should be evaluated for possible sexually transmitted diseases, such as *N. gonorrhoeae* and *Chlamydia trachomatis*. Patients may have a history of previous urinary tract infections, anatomic abnormalities, or previous genitourinary instrumentation. Urinary tract infections leading to epididymitis typically are caused by viruses or bacterial agents, such as *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus*, or *Pseudomonas aeruginosa*.

Clinical Features. Patients present with a painful, edematous scrotum and tenderness at the epididymis (Fig. 172-5). A urethral discharge may be present, particularly when the condition is secondary to a sexually transmitted disease. Systemic signs and symptoms such as nausea, vomiting, fever, and lower abdominal, scrotal, or testicular pain also may be present. Infants and young children may present with fever without other symptoms. Accordingly, the ED evaluation for all children with fever or other systemic symptoms or signs should include a complete examination, including a genitourinary examination.

Figure 172-5. Epididymitis in a 5-year-old boy; note mild swelling and erythema on the left. (Courtesy of Marianne Gausche-Hill, MD.)

As the edema increases, obliteration of the sulcus between the testis and epididymis occurs, making differentiation from testicular torsion extremely difficult. Relief of pain with scrotal elevation (Prehn's sign) is unreliable.

Diagnostic Strategies. Urinalysis and urine culture should be part of the ED evaluation for all infants and children younger than 2 years. In children 2 years of age or older, urine culture may be performed only if the urinalysis results indicate urinary tract infection. Lack of pyuria does not rule out epididymitis, because up to 50% of patients may have normal results on such studies. CBC may show leukocytosis, although this finding is nonspecific. Any urethral discharge should be cultured and sent for Gram's stain and tests for *N. gonorrhoeae* and *C. trachomatis*. Color-flow Doppler ultrasonography or radionuclide scintigraphy will reveal a normal testis and preserved or increased vascular flow toward the side of the inflamed epididymis.[27,28] Color Doppler ultrasonography should be performed in all children with suspected epididymitis and is the preferred diagnostic study because it does not require placement of an intravenous line and is more readily available at all hours of the day.

Management and Disposition. Scrotal elevation, placement of ice packs on the swollen area as tolerated, and nonsteroidal anti-inflammatory or narcotic medications are useful to control pain and inflammation. If urethral discharge is present, the adolescent patient should be treated for both *N. gonorrhoeae* and *C. trachomatis*. The treatment for sexually acquired epididymitis in children 9 years of age or older consists of ceftriaxone 250 mg IM, followed by doxycycline 100 mg PO twice a day or tetracycline 500 mg PO four times a day. Patients younger than 9 years should be treated with erythromycin 50 mg/kg PO per day, divided, four times a day. The course of treatment typically ranges from 7 to 14 days, depending on the antibiotic regimen. In children, nonsexually acquired epididymitis without evidence of urinary tract infection may be managed expectantly with analgesics for pain.[29] Infants with or without positive findings on urinalysis and young children with positive urinalysis findings may be treated with trimethoprim twice a day or cephalexin three times a day if a bacterial urinary tract infection is suspected. Other antibiotic options include oral erythromycin, clarithromycin, and azithromycin for patients who do not respond to other therapies, because *Mycoplasma genitalium* and *Ureaplasma urealyticum* may cause a more chronic form of epididymitis. Infants and children with epididymitis may be discharged for follow-up by their primary care physician, and urine cultures should be checked to determine definitively if urinary tract infection is present. Patients with systemic symptoms and toxicity should be admitted for intravenous antibiotic therapy with either ceftriaxone or cefotaxime. Children need close urologic follow-up to rule out any contributing anatomic abnormalities and to ensure that the antibiotic chosen treats the infecting organism.

Orchitis

Orchitis is a result of a bacterial or viral testicular infection leading to diffuse edema, pain, and discoloration of the scrotum. The most common pathogen is paramyxovirus, which can be the causative agent in up to 38% of postpubertal males with mumps-associated orchitis. Other etiologic agents include *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *Staphylococcus* or *Streptococcus* species, Epstein-Barr virus, coxsackievirus, arbovirus, enterovirus, *Brucella*, granulomatous disease, and filariae.

During the course of mumps, orchitis usually develops after the first week and manifests with tenderness and edema of the testis with discoloration of the scrotum. Bilateral cases are relatively rare, occurring in 2 to 5% of affected patients. If

epididymitis coexists, then a urethral discharge also may be present. Bacterial orchitis can result in scrotal abscess formation. Because orchitis typically is unilateral, fertility usually is maintained.

Doppler ultrasound imaging may be necessary to distinguish orchitis from testicular torsion. For patients with a clearly viral origin such as mumps, treatment is aimed at pain control (scrotal elevation, nonsteroidal anti-inflammatory agents, and possibly narcotics). When the diagnosis is unclear or when concurrent epididymitis is present, empirical treatment includes oral antibiotics with predominantly gram-negative organism coverage. Hospital admission is warranted for patients who have a toxic appearance or exhibit evidence of a scrotal or testicular abscess or in whom outpatient management has failed. Urologic follow-up should be arranged.

Testicular Torsion

Principles of Disease. Torsion of the spermatic cord is a common cause of an acutely painful scrotum. Delay in diagnosis and treatment can result in loss of spermatogenesis and, in severe cases, necrotic, gangrenous testes. Testicular salvage rates are time-dependent, with a 96% success rate if detorsion is performed less than 4 hours from symptom onset, decreasing to less than 10% if there is a greater than 24-hour delay to treatment.[30] The overall incidence of testicular torsion is 1 in 4000, with a peak incidence at age 13 years. Testicular torsion has been reported in all age groups, from the developing fetus to the elderly, but is most common in adolescence.

The testis enters the scrotum through the inguinal canal after descent from the abdomen. The peritoneum invaginates through the canal and partially covers the testis and epididymis, forming the tunica vaginalis. Typically, the tunica vaginalis attaches to the posterior wall of the hemiscrotum and superior pole of the testes to achieve testicular fixation. If the tunica completely covers the testis and attaches higher up on the spermatic cord (bell clapper deformity), proper testicular fixation does not occur, and there is a predisposition to torsion (Fig. 172-6). In intravaginal torsion, the testicle may rotate within the tunica vaginalis, thereby constricting the arterial blood flow. Extravaginal torsion is seen most commonly in neonates who are premature and also can occur antenatally. If the torsion is prolonged, testicular infarction and atrophy have been reported after as little as 4 hours of ischemia.

Clinical Features. Patients present with acute scrotal pain and swelling, an elevated testicle, and, typically, absence of the cremasteric reflex.[31] Although in one series the cremasteric reflex was absent in 100% of patients with torsion and in only 14% of patients with epididymitis, the presence of the cremasteric reflex does not preclude testicular torsion. Abnormal epididymal and testicular position also may be noted, with left-sided torsions slightly more common than right. Nausea, vomiting, and a low-grade fever also may be seen. In the patient with an undescended testicle who presents with abdominal pain, torsion should be a consideration.[32]

Diagnostic Strategies. Unless an alternative diagnosis is absolutely secure (e.g., epididymitis), the patient should be evaluated for testicular torsion. Alternatively, with a relatively confident clinical diagnosis of torsion, diagnostic testing should not delay appropriate management. Results of a urinalysis are rarely helpful as pyuria can be seen in cases of testicular torsion and epididymitis. The widely preferred diagnostic study for the prospect of torsion is color flow Doppler ultrasonography. This technique has a sensitivity of 79 to 86%, with a specificity of almost 100%, for detection of testicular torsion. In contrast with scintigraphy, it can be performed rapidly, often is available 24 hours a day, and does not require that an intravenous line be placed. Scintigraphy has a sensitivity ranging from 79

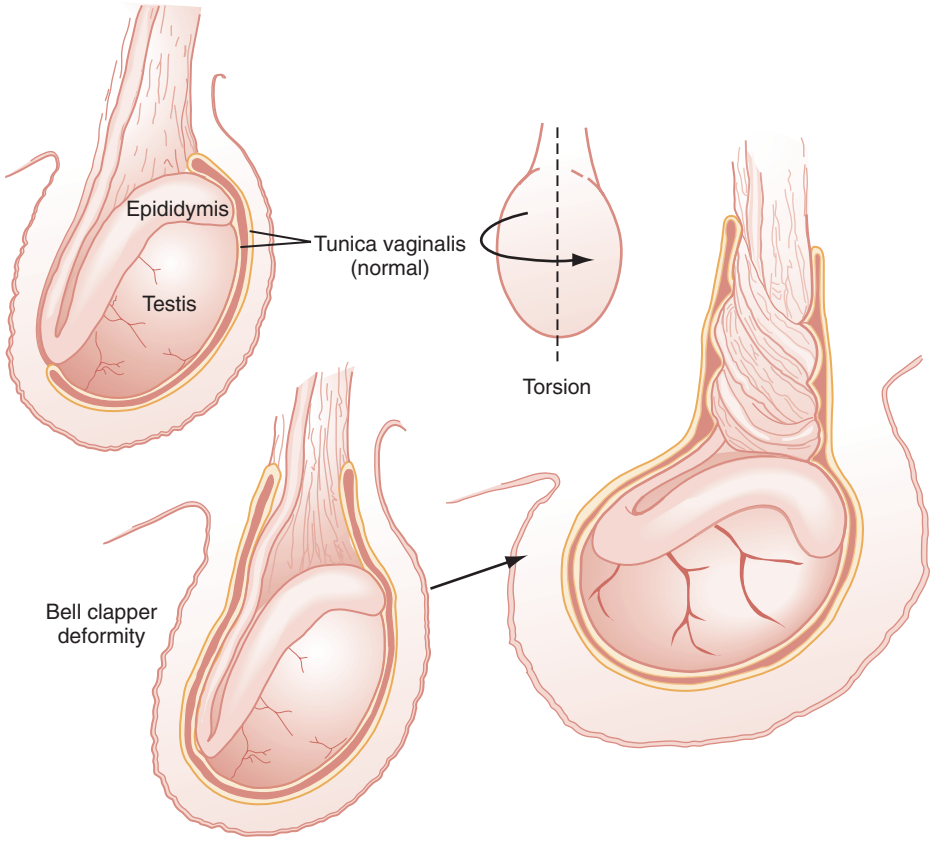


Figure 172-6. Anatomy of testicular torsion. (From Snyder HM III, et al: Pain–Scrotal. In Fleisher GR, Ludwig S [eds]: Textbook of Pediatric Emergency Medicine, 4th ed. Philadelphia, Lippincott Williams & Wilkins, 2000.)

to 100% and a specificity of 89 to 100%.[33-35] Magnetic resonance imaging (MRI) has recently been evaluated as another diagnostic modality, with a sensitivity in one study of 93% and specificity of 100%.[36] In cases of indeterminate ultrasound findings, the urology consultant should be notified for disposition decisions; in addition, scintigraphy may be performed as resources allow. When clinical suspicion is strong, surgical exploration should not be delayed for diagnostic studies, especially in patients in whom duration of symptoms is less than 12 hours.

Management. If the patient presents within 12 hours of symptom onset, immediate surgical exploration is indicated, predicated on clinical findings or confirmatory clinical studies.[37] Detorsion of the affected testicle is performed, followed by an elective orchiopexy of the contralateral side to avoid recurrence. Approximately 40% of patients have a bell clapper deformity of the contralateral testicle. Manual detorsion also may be performed by rotating the testicle in an "open book" fashion as viewed from below, from medial to lateral, until detorsion is complete.[38] Because the procedure is painful, sedation and pain relief should be considered before this intervention. Manual detorsion should be attempted only if there is a delay in getting a urologist to come in for operative detorsion and the patient has had continuous pain for less than 24 hours or if, in the judgment of the emergency physician, the time zone of opportunity to salvage the testis has not passed.

Torsion of the Testicular Appendage

The appendix testis is a remnant of the müllerian duct. The appendix testis is involved in 92% of the cases of testicular appendage torsion, and the appendix epididymis is involved in the remaining cases. The average age at occurrence is 10 years. Patients typically present with moderate pain of sudden onset that is localized to the involved hemiscrotum. The pathognomonic "blue dot" sign, a small area with a bluish hue less than 3 mm across located in the upper lateral portion of the hemiscrotum, is present in less than 25% of cases and represents the cyanotic appendage below the scrotal wall. If any doubt exists about the diagnosis, a nuclear radioisotope scan or color Doppler ultrasound study should be performed. Color Doppler ultrasonography reveals normal or increased flow to the affected testicle. Conservative therapy with analgesics usually is all that is indicated, with the involved appendage undergoing autoamputation within 1 week accompanied by resolution of symptoms.

Varicocele

A *varicocele* is a collection of venous varicosities of the spermatic veins in the scrotum caused by incomplete drainage of the pampiniform plexus. Incidence rates of 14 to 16% in adolescent males have been reported,[39] but varicoceles are rare in children younger than 10 years.[40] Left-sided varicoceles account for 85 to 95% of cases; however, bilateral varicoceles may be present in up to 22% of patients.[41] Intra-abdominal pathology should be suspected in cases of right-sided varicocele because these usually are caused by inferior vena cava thrombosis or compression of this vessel by tumors.[42] The acute presentation of a left-sided varicocele should raise suspicion for renal cell carcinoma with obstruction of the left renal vein. The dilated venous collection may be tender on physical examination, can be palpated superior and posterior to the testis, and usually is more pronounced with the patient in the upright position; therefore, the patient should be examined in both the standing and supine positions. Patients in whom scrotal swelling persists in the supine position should be evaluated with a computed tomography (CT) scan of the abdomen, with oral and intravenous contrast administration for conditions obstructing the renal vein. Varicoceles have been described as a "bag of worms" both in appearance and on palpation. Surgical correction may be required if the patient becomes symptomatic or has bilateral varicoceles.[43]

Idiopathic Scrotal Edema

Idiopathic scrotal edema is painless erythema and induration of the scrotum, with 77% of cases occurring before the age of 10 years. Two thirds of cases are unilateral, and no specific allergens have been identified. The condition is characterized by the development of painless erythema and induration of the scrotum, which may be pruritic. There is minimal tenderness on physical examination, but the edema and erythema may extend to the phallus, groin, and abdomen. Examination of the testes and epididymis reveals no palpable masses. Systemic signs and symptoms are rare. Patients can be discharged home with outpatient follow-up after an acute pathologic process has been ruled out. Most cases resolve spontaneously within a few days and do not require any specific treatment. Recurrence rates of up to 21% have been described.

Hydrocele

A *hydrocele* is a collection of fluid that accumulates in the tunica vaginalis. Communicating hydroceles result when the upper processus vaginalis fails to obliterate, leaving an open tract between the peritoneum and the scrotum. The tract is closed in noncommunicating hydroceles. Most hydroceles are right-sided. They may be present at birth, but they usually are painless and worsen with crying or exertion. Hydroceles often resolve spontaneously by the age of 18 months. Examination with transillumination reveals enlargement of the scrotum. Color flow Doppler ultrasonography or radionuclide scintigraphy may be necessary to determine the cause of the hydrocele and to exclude an acute pathologic process in patients with acute symptoms of pain; otherwise, asymptomatic patients can be discharged home with urologic follow-up. Patients with a hydrocele that has persisted for more than 1 year or who are older than 18 months should undergo ultrasonography to ensure that the hydrocele is not a reactive hydrocele caused by testicular tumor or inflammation.

Inguinal Hernia

Principles of Disease. Inguinal (direct and indirect) hernias are more common in males, with bimodal peaks before 1 year of age and then again after the age of 40 years. An indirect inguinal hernia occurs when the processus vaginalis does not obliterate in infancy and abdominal contents invaginate through this patent sac. Entrapment of mesentery, bowel, intraperitoneal organs, and the hernial sac can occur and is more common with small hernias. If the contents of the hernia can be returned to their anatomic position, the hernia is reducible; if the contents remain entrapped, it is incarcerated or irreducible. Hernias that remain incarcerated can undergo strangulation, with resultant necrosis of bowel or mesentery.

Clinical Features. Patients with incarcerated hernias may present with pain, edema extending to the scrotum, nausea, vomiting, and low-grade fever. Physical examination may reveal bowel sounds in the scrotal sac. If the inguinal mass can be palpated separately from the testes, it is possible to diagnose an inguinal hernia on clinical grounds alone. Rarely, the incarcerated and strangulated hernia can manifest as a tense blue mass in the scrotum.

Management and Disposition. The patient should be placed in the Trendelenburg position with an ice pack applied to the groin to reduce swelling; sedation may be necessary before reduction. Slow, gentle pressure should be applied to reduce the hernia. If the pressure technique is not successful in reducing the hernia, the opposite technique can be tried: The hernia mass can be "pulled" to straighten out the entrapped contents, thereby allowing them to slip back into the abdomen.

If the hernia cannot be reduced or strangulation is suspected (as indicated by fever, overlying cellulitis, or signs of peritonitis), the patient should receive fluid resuscitation, broad-spectrum parenteral antibiotics, and an emergent surgical consultation.[44]

Patients who are found to have a hernia on routine examination or who have had the hernia reduced and are without symptoms suggestive of incarceration or strangulation should be referred for surgical repair.

Carcinoma

Principles of Disease. Testicular and scrotal cancer represents approximately 1% of solid tumors in children. An increased incidence of testicular cancer, in both the undescended testicle and the contralateral descended testicle, has been noted in patients with cryptorchidism. Tumor types include teratomas, embryonal carcinomas, yolk sac tumors, choriocarcinomas, Leydig cell tumors, and Sertoli cell tumors. Lymphoma and leukemia can metastasize to the testicle as well.

Patients typically present with a painless unilateral mass palpated separately from the testis or may describe a feeling of fullness, tugging, or increased weight of the scrotum and testicular enlargement. A reactive hydrocele may be present in 7 to 25% of patients and can lead to a delay in diagnosis. Physical examination reveals a firm mass, smooth or nodular, that is not transilluminated. A complete physical examination looking for lymphadenopathy, petechiae, abdominal mass, hepatosplenomegaly, or gynecomastia should be performed.

Diagnostic Strategies. Diagnostic evaluation includes a CBC, urinalysis, urine human chorionic gonadotropin (produced by germ cell tumors) assay, and ultrasonography of the testis.

Management and Disposition. ED management includes prompt referral for urologic and oncologic consultation. Admission to the hospital to facilitate the evaluation may be necessary.

Urinary Tract Infections

Perspective. Sequelae of untreated urinary tract infections may include sepsis and renal scarring, and accurate and early diagnosis is important. At the same time, avoiding unnecessary evaluation and treatment of children at lower risk for these infections is cost-effective and minimizes the chance for iatrogenic harm. Diagnosing urinary tract infections in infants and young children can be challenging because the clinical signs often are nonspecific and obtaining useful urine specimens can be difficult.

Principles of Disease. The risk of developing urinary tract infections before the age of 12 years is approximately 3% for girls and 1% for boys. Neonatal boys are more susceptible to urinary tract infections than girls, but beyond that period, infections in females prevail. Girls younger than 2 years and uncircumcised boys younger than 6 to 12 months also are especially at risk.[45]

Seven percent of children younger than 2 years with a temperature greater than 39° C and presenting without a source for the fever have an occult urinary tract infection.[46,47] Moreover, up to 4% with a significant fever and an associated upper respiratory tract infection or acute otitis media also may have a urinary tract infection.[46,48] By comparison, the background prevalence of asymptomatic bacteriuria is estimated to be 1 to 2% in all children.[49]

On the basis of renal nuclear scans, it is estimated that 75% of children younger than 5 years with a febrile urinary tract infection have pyelonephritis.[46] Vesicoureteral reflux from the bladder into the ureter is a common cause of the pyelonephritis and renal scarring. Urinary tract infection in infants younger than 3 months is associated with bacteremia in up to 50% of cases; in children older than 3 months, the risk drops to 5%. Renal scarring can occur in 27 to 64% of children after pyelonephritis and may lead to renal failure and a risk of hypertension later in life.[46]

E. coli is the predominant cause of urinary tract infections in children, with *Klebsiella* species more likely to be the etiologic agents in newborn children. *Enterobacter*, *Proteus*, *Morganella*, *Serratia*, and *Salmonella* species also are important pathogens.[50] In neonates and young infants, bacteremia is considered the route of infection to the urinary tract. In older children, infection in the lower tract often is the source of upper tract infection. A common cause of urinary tract infections in toilet-trained girls is believed to be improper wiping after urination. Young girls should be taught to wipe from anterior to posterior (front to back) after urination.

Clinical Features

Infants and Children Younger than 2 Years. Signs and symptoms usually are nonspecific and include decreased oral intake, lethargy, jaundice, fever, vomiting, abdominal pain, and irritability. Young children may not be able to verbalize when urination is painful. It is assumed that a urinary tract infection in this age group represents upper tract disease and would therefore arise with more systemic symptoms and signs.

Children Older than 2 Years. Urinary tract infection in children older than 2 years can be either an isolated cystitis or upper tract disease with symptoms and signs of a more systemic nature. Cystitis usually is associated with local symptoms (i.e., suprapubic tenderness and dysuria). Clinical manifestations of pyelonephritis may include fever, costovertebral angle tenderness to palpation, abdominal pain, vomiting, and ill appearance. New-onset bedwetting also may be a sign of a urinary tract infection.

Diagnostic Strategies. Various techniques can be used for collecting urine samples from children. Because of the difficulty in cleaning the perineal area, the bag collection method is associated with an increased risk of contamination by periurethral flora, with false-positive results ranging from 12 to 83%.[46] Thus, the bag collection method is not recommended in infants and children who are not toilet-trained. Because urethral catheterization is almost always successful, suprapubic aspiration to obtain a urine sample is rarely needed.[49,50] A suprapubic bladder aspiration also is used for young infants because the expanded bladder is located more intra-abdominally. Chances of a full bladder and successful aspiration improve if 45 to 60 minutes have elapsed since the last diaper change. The use of ultrasonographic guidance has been advocated to enhance the probability of obtaining urine by the suprapubic and catheterization methods.[51,52]

Urethral catheterization is relatively simple and poses little risk, although it may be more difficult in uncircumcised boys or in young infants. There is a slight risk of both trauma to the urethra and the introduction of bacteria into the urinary tract with this technique. A 5F feeding tube can be used in young infants. Young male infants sometimes spontaneously urinate when the urethral meatus is cleansed; a midstream clean-catch urine specimen may then be obtained.

For a clean-catch urine sample from a toilet-trained child, the parent can clean the child's urogenital area with soap and

Table 172-1 Urinary Tract Infection Definitions Based on Collection Technique

URINE COLLECTION TECHNIQUE	INFECTION CRITERIA
Suprapubic bladder aspiration	10^2 CFU/mL, one pathogen
Urethral catheterization	10^4 CFU/mL, one pathogen
Midstream clean catch	10^5 CFU/mL, one pathogen, two cultures*

*Suspicious for urinary tract infection if only one culture yields positive result.
CFU, colony-forming units.
From Shaw KN, Gorelick MH: Urinary tract infection in the pediatric patient. Pediatr Clin North Am 46:1111, 1999.

BOX 172-1 Etiology of Dysuria in Children

Infection
Urinary tract infection, including cystitis or pyelonephritis
Vaginitis resulting from *Gardnerella*, *Trichomonas*, *Candida*, or sexually transmitted organisms
Pinworms
Balanitis

Irritation
Bubble bath, new soaps, or douches
Vaginal foreign body, such as retained toilet paper

Trauma
Sexual or physical abuse
Straddle injury (unintentional)
Self-stimulation or masturbation

Other
Labial adhesions
Renal stones or hypercalciuria

water before urination. Children can be instructed to sit backward on the toilet to urinate, allowing better access for obtaining the urine specimen. A urine sample with more than 10 white blood cells (WBCs) per high-power field and a large number of epithelial cells must be considered contaminated, and either an improved clean-catch method or catheterization must be tried. Females with a vaginal discharge, regardless of age, should be catheterized.

In children younger than 2 years, a urinalysis alone is not considered adequate for ruling out urinary tract infections. As many as 10 to 50% of patients with urinary tract infection can have false-negative results on urinalysis.[53,54] Nitrite and leukocyte esterase urinalysis markers have the highest combined sensitivity and specificity for detection of infection. If both markers are positive, the false-positive rate is less than 4%.[46] Gram's stain of the urine has a sensitivity of 93%.[46,55] Depending on the technique used to obtain the urine culture, criteria for a definitive diagnosis of urinary tract infection vary (Table 172-1).

Renal function tests are rarely abnormal but should be performed in children with hypertension, hematuria, proteinuria, or signs of dehydration. In general, blood cultures are not indicated in a majority of children with urinary tract infection. The true-positive rate for blood culture in the presence of a urinary tract infection is low, and the organism identified is invariably the same as the organism in the urine culture.[56]

Differential Considerations. Underlying renal disease or urinary tract abnormality considered in a child presenting with hypertension, hematuria, or difficulty with urination or should be suspected in children with elevated BUN or creatinine, electrolyte abnormalities, or acidosis on laboratory examination. CT of the abdomen may be necessary to delineate the extent of urinary tract abnormalities.

Several other causes of dysuria in children are recognized (Box 172-1). Irritants such as bubble bath or soaps may cause local irritation and dysuria. A retained foreign body in the vagina (such as toilet paper) can cause irritation or bacterial growth with associated dysuria and vaginal discharge. Pinworms in the genitourinary area can cause itching and scratching. Balanitis in uncircumcised boys also can cause dysuria and pyuria.

Accidental injuries to the genital area can cause abrasions or lacerations and subsequent dysuria. Sexual or physical abuse must be considered in any young child with a history of multiple urinary tract infections.

Management

Infants Younger than 2 Months. Young infants with urinary tract infections are at risk for associated sepsis. The age at which a urinary tract infection warrants hospital admission has decreased dramatically. Today, infants younger than 2 months of age are considered to be at high risk for the development of sepsis and should therefore be admitted to the hospital for intravenous antibiotic therapy (e.g., with gentamicin and ampicillin).[57,58]

Children 2 Months to 2 Years. Although inpatient treatment of children with suspected pyelonephritis has traditionally been recommended, studies now show that well-appearing children without signs of toxicity may be managed as outpatients.[59] A recent meta-analysis of data from both adult and pediatric studies found no significant evidence suggesting that oral antibiotic therapy is less effective than parenteral or initial parenteral therapy for treatment of severe urinary tract infection.[60] Community antimicrobial resistance patterns are important to consider in deciding on an appropriate antimicrobial. Rates of *E. coli* resistance to trimethoprim-sulfamethoxazole can be as high as 20 to 30% in some communities.[61] The first dose of a parenteral antibiotic and a double dose of an oral antibiotic appear to be equivalent. Because urinary tract infections in this age group are considered to be upper tract disease processes, a longer course of antimicrobials is indicated (e.g., 10 to 14 days). Although a review of studies found no difference in the frequency of positive urine cultures between short-course therapy (2 to 4 days) and longer-course therapy (7 to 14 days), most of these studies mixed children younger than 2 years with older children, including adolescents. Thus, the recommendation for short-course therapy in children younger than 2 years is not supported at this time.[62] Follow-up in 2 to 3 days is essential to evaluate the culture and sensitivity results and to assess clinical status. Additional outpatient follow-up, including appropriate imaging studies, is recommended to determine the presence of renal scarring, posterior urethral valves, or vesicoureteral reflux.[63]

Children Older than 2 Years. In older children with simple cystitis, a short 3-day course of antibiotics, such as trimethoprim-sulfamethoxazole or amoxicillin-clavulanate, is adequate. Shorter courses result in higher failure rates and are not indicated. In older children with pyelonephritis, a longer course of antibiotics (generally 14 days) is recommended. In the adult population, a more recent study shows that a 7-day course of a fluoroquinolone is as effective as a 14-day course of trimethoprim-sulfamethoxazole.[64] In children, fluoroquinolones are still contraindicated because of the presumed effect on cartilage growth.

Disposition. Children with signs of toxicity, urinary obstruction, or inability to take oral medications should be hospitalized for intravenous antibiotic therapy.[65] On discharge, parents

should be instructed to return if the child is unable to take the oral medication or if the symptoms worsen. The child may remain febrile for 48 hours despite adequate antimicrobial therapy. The child's clinical status should be checked in 48 to 72 hours, either in person or by telephone. At follow-up, the urine culture results should be checked to ensure appropriate antimicrobial therapy.[66]

Hematuria

Perspective. Hematuria is common in the pediatric population. *Hematuria*, defined as the presence of red blood cells (RBCs) on examination of two successive urine samples, has a prevalence rate of 1 to 2% in children ages 6 to 15 years of age.[67] *Microscopic* hematuria is defined as the presence of more than 5 RBCs/mm^3 and is detected using chemical reagent strips and microscopic urinalysis. *Persistent* hematuria is defined as positive results on three urinalyses over a 2- to 3-week period.[67] *Macroscopic* or *gross* hematuria is presence of blood in the urine visible to the naked eye and may be associated with clots.

Principles of Disease. Hematuria results from the entry of RBCs into the urinary tract. Inflammation, infection, trauma, or anatomic abnormalities can occur anywhere from the glomerulus to the urethra. The endothelium and basement membrane of the glomerulus usually are impervious to large proteins such as RBCs and hemoglobin, but myoglobin may pass freely. Damage to the glomerulus, however, may allow RBCs and hemoglobin to pass into the collecting system.

Urine with lysed RBCs tests positive for hemoglobin and negative for RBCs and may be pink in color. Urine containing myoglobin from muscle breakdown tests positive for hemoglobin and negative for RBCs. Evaluation of creatine kinase and fractionated bilirubin levels and hematocrit often can help differentiate hemoglobinuria from myoglobinuria. Not all red urine contains blood. Certain drugs or foods such as phenothiazines, ibuprofen, beets, and blueberries can cause reddish-colored urine. In neonates, urate crystals can cause red-tinged urine in the diaper. *Serratia marcescens*, a fecal pathogen, can cause a red pigmentation when left in the diaper. Bleeding from the vagina or rectum can sometimes be mistaken for blood in the urine.

Clinical Features. The history and physical examination should focus on signs of infection, trauma, or bleeding disorders. Signs of renal disease (e.g., hypertension), edema, rales, and cardiac murmurs are important findings. An examination of the genitalia may reveal inflammation or bleeding.

Differential Considerations. The etiology of hematuria comprises a diverse group of disorders and conditions (Box 172-2). Presence of RBCs in the urine as a result of trauma is discussed elsewhere.

Extrarenal causes of hematuria include urethral valves and meatal stenosis. Extensive exercise can also cause hematuria as a result of both direct renal trauma and ischemic injury.

Intrarenal disorders include pyelonephritis, renal or bladder tumors, poststreptococcal acute glomerulonephritis, and basement membrane disease of the glomerulus.

Systemic illnesses that cause hematuria such as Henoch-Schönlein purpura and hemolytic uremic syndrome (HUS) are discussed later in this chapter. Other systemic causes of hematuria include bleeding disorders, aspirin, and anticoagulants.

Diagnostic Strategies. A urinalysis that shows more than 5 RBCs per high-power field indicates hematuria. The presence of WBCs or leukocyte esterase should be noted. Casts in the urine or proteinuria demonstrates a glomerular origin for the hematuria. If glomerular disease is suspected, a throat culture, antibody test for streptococcus, complement studies, erythrocyte sedimentation rate determination, antinuclear antibody assay, or hepatitis B serology tests should be considered. If the patient has signs of hypertension, edema, or proteinuria, laboratory tests for electrolytes, total protein, and albumin should be ordered.[68]

BOX 172-2 ETIOLOGY OF HEMATURIA IN CHILDREN

Extrarenal
Trauma
Meatal stenosis or posterior urethral valves
Exercise
Menstruation or rectal bleeding
Foreign bodies
Cystitis, urethritis, or epididymitis

Intrarenal
Pyelonephritis
Renal or bladder stones or tumors
Poststreptococcal or idiopathic glomerulonephritis
Acute interstitial nephritis
Acute tubular necrosis
Basement membrane glomerular disease
Renal vein or arterial thrombosis
Recurrent familial hematuria
Polycystic kidney disease

Systemic
Henoch-Schönlein purpura
Systemic lupus erythematosus
Hemolytic-uremic syndrome
Infectious mononucleosis
Sickle cell disease or other hemoglobinopathies
Bacterial endocarditis or artificial cardiac valves
Bleeding disorders, warfarin, or aspirin
Medications such as amitriptyline or chlorpromazine, radiocontrast dyes
Munchausen syndrome or factitious

A 24-hour urine collection for creatinine and protein should be evaluated for asymptomatic hematuria. Urine and plasma calcium levels should also be measured.

Noncontrast helical CT is the current study of choice for the identification of renal stones. It has exceptional sensitivity and specificity for detection of calculi as small as 1 mm and can identify associated processes such as obstruction, hydroureter, hydrocalyx, and renal abscess. In addition, it is superior to intravenous pyelography in determining alternative diagnoses such as abdominal tumor.

Management. Management of the child with hematuria depends on the underlying cause. The management of the child with renal stones and renal tumors is discussed later on.

Disposition. The disposition of a child with hematuria depends on the underlying cause. Simple cystitis or pyelonephritis can be treated in the ED with follow-up by the child's primary care physician. A child diagnosed with a renal tumor or stone should be referred to a nephrologist or urologist. Children with acute renal failure, especially with those with signs of fluid overload or hyperkalemia, need to be hospitalized for appropriate management.

Renal Stones

Perspective. Renal stones result from a complex process of crystallization involving growth inhibitors and promoters and changes in urine pH and flow. Congenital abnormalities,

trauma, or infection also can be an inciting cause. An increased risk for hypercalciuria and the formation of renal stones often is inherited.

Principles of Disease. Renal stones are uncommon in children, with approximately 1 case diagnosed for every 1000 pediatric hospital admissions.[69] Calcium-containing stones are responsible for approximately 60% of all cases, followed by struvite (infection), uric acid, and cystine stones.[69] Renal stones are three to four times more common in white children than in nonwhite children. Family history also seems to play a role in the formation of kidney stones.[70]

Clinical Features. The signs and symptoms of renal stones in older children typically include colicky flank pain, vomiting, and hematuria. Younger children with renal stones also can present with less specific complaints, such as nontender abdominal pain, vomiting, or malaise. In a study from the United Kingdom, 17% of pediatric patients with renal stones were found to present with hematuria only, without flank or abdominal pain.[70] In the initial evaluation of children with possible renal stones, the history should ascertain potentially relevant factors including previous urinary tract infections, especially those caused by organisms such as *Proteus* species; family history of renal stones; and diet (including excessive vitamin use) and fluid intake.

Obstruction of the collecting system can sometimes lead to infection, papillary necrosis, or decrease in renal function. Fever in the presence of a renal stone should be taken as an indicator of upper tract infection.

Diagnostic Strategies. In children suspected of having renal stones, the urine should be checked for hematuria, leukocytes, and bacteria. The urine also should be strained and any crystals sent for analysis. Other laboratory tests to consider are CBC, electrolyte panel, and determination of BUN, creatinine, uric acid, total protein, and albumin. Ninety percent of renal calculi are visible on a plain abdominal radiograph, although stool can sometimes obscure the view. Other types of calcifications appearing on plain abdominal radiographs include gallstones, phleboliths, vessel or lymph node calcifications, and calcified malignancies. Plain films of the abdomen have no additional value over CT scan of the abdomen and should not be obtained in lieu of the CT scan.

Children with suspected kidney stones should have a noncontrast-enhanced CT scan of the urinary tract, called a CT urogram. A CT urogram may be obtained to define the anatomy and other potential causes of hematuria, such as a tumor or pyelonephritis; a CT urogram also avoids the use of nephrotoxic radiocontrast material. The intravenous pyelogram should be reserved for treatment centers without access to CT. Ultrasonography may be used in patients with a history of renal stones to follow the progress of a stone or in patients with frequent stones to eliminate the need for repeat CT scans and the attendant radiation exposure.

Differential Considerations. The differential diagnosis for colicky flank or abdominal pain in the pediatric patient generates a long list of possibilities. Gastroenteritis and constipation are more common causes of colicky abdominal pain in young children than kidney stones. Intussusception most commonly occurs in children younger than 2 years and can manifest with intermittent abdominal pain. In adolescents, biliary colic and intermittent gonadal torsion also must be considered.

Management. Initial pain management should include a narcotic analgesic in conjunction with a longer-acting nonsteroidal anti-inflammatory drug (NSAID). The analgesic effect of NSAIDs is directly related to the inhibition of prostaglandin-mediated contraction of the ureter and is characteristic of all NSAIDS (e.g., ibuprofen, naproxen, ketorolac). Patients with signs of volume depletion or with a history of fever, vomiting, or poor fluid intake should be adequately hydrated to improve urine flow and prevent urinary stasis, which may contribute to stone formation. Excessive fluid administration to increase urine flow, to enhance movement of the stone down the urinary tract, however, has not been proved to be effective.

After cultures have been obtained, children with infected urinary tracts with stones should be treated with antibiotics; hospitalization generally will be required. Children with larger renal stones may undergo shockwave lithotripsy as a therapeutic modality. In some centers, ureteroscopy also may be a management option for larger stones.[71]

Children with normal renal function and adequate pain control, without signs of toxicity or renal infection, can be safely discharged home with good follow-up. Follow-up with a nephrologist or urologist may include parathyroid hormone assay, analysis of fasting urine samples for calcium-to-creatinine ratio, or 24-hour urine collection for determination of calcium, magnesium, phosphorus, uric acid, oxalate, cystine, protein, and creatinine.[69,72]

Renal Tumors

Perspective. Abdominal masses in children are not uncommon, and in infants the vast majority are benign renal tumors or cysts.[73]

Principles of Disease. Renal tumors in children can range from the benign cystic nephroma to the more aggressive malignant rhabdoid tumor. The prognosis will depend on the type and staging of the renal tumor.

Clinical Features. The most frequent presentation for a child with a renal tumor is that of an abdominal mass found by the parent while bathing or dressing the child. Hematuria or pain is a less common presenting manifestation than in the adult population.

Diagnostic Strategies. Because a significant number of abdominal masses are the result of renal cysts, renal ultrasonography is the imaging study of choice. Ultrasonography can define the mass in question and is not associated with exposure to ionizing radiation. Laboratory tests should include CBC, platelet count, BUN, serum creatinine, urinalysis, and urine catecholamines. Urinary catecholamines are increased in 95% of patients with neuroblastoma but are normal in those with Wilms' tumor. Any solid masses found on ultrasonography will be better defined by CT of the abdomen. If the mass appears malignant, a CT scan of the chest is indicated to look for pulmonary metastases.[74]

Differential Considerations. Considerations in the differential diagnosis for a renal mass include cystic lesions such as those of polycystic kidney disease and severe hydronephrosis resulting from obstruction or severe reflux. Solid masses include Wilms' tumor, renal cell carcinoma, mesoblastic nephromas, and cystic nephromas.

Management and Disposition. Management depends on the function of the urinary tract. Because the renal mass typically involves only one kidney, renal function usually is maintained.

A preliminary diagnosis of the etiology of the mass should be obtained before discharge of the child from the ED. Well-appearing children with normal renal function for whom close follow-up can be ensured may be managed on an outpatient basis. Because of the potential seriousness of a renal tumor, hospital admission should be considered for all children. Consultations with a nephrologist, urologist, and hematologist-oncologist can be coordinated during the admission process.

Proteinuria

Perspective. The normal glomerulus is relatively impervious to albumin, a high-molecular-weight protein. Low-molecular-weight proteins, however, pass through the glomeruli and are reabsorbed in the proximal tubule. Proteinuria can result from either increased passage through the glomeruli or decreased reabsorption by the tubules. In most cases, proteinuria is benign and asymptomatic. If the amount of protein lost is significant, such as in nephrotic syndrome, the resultant hypoalbuminemia (albumin less than 2 g/dL and protein less than 4 g/dL) may cause ascites and generalized edema.

Principles of Disease. Proteinuria is a common finding in children. Trace to mild proteinuria (1+ to 2+) can be seen in up to 85% of children and adolescents screened, especially during the summer months.[75,76]

Clinical Features. Clinical features seen in a proteinuric child depend on the etiology of the proteinuria. Recent pharyngitis, presence of hematuria, changes in weight or urine output, or family history of proteinuria should be investigated. Abnormal findings may include hypertension, edema, ascites, or palpable kidneys in infants. A butterfly rash of systemic lupus or the purpuric rash of HSP may be evident.

Differential Diagnosis. Causes of proteinuria can be divided into glomerular and tubular. *Glomerular* causes include nephrotic syndrome, glomerulonephritis, and post-transplantation rejection. Transient causes of altered glomerular function include exercise, fever, and seizures. *Tubular* causes of proteinuria include heavy-metal poisoning, urinary tract infections, and diabetes; an asymptomatic tubular proteinuria also has been described.[75,76] False-positive results on urinary dipstick testing for proteinuria can be obtained when the urine is alkaline or when it contains mucus, blood, vaginal secretions, semen, or a significant number of inflammatory cells.

Orthostatic proteinuria is a benign condition characterized by the presence of protein in the urine collected with the patient in an upright position but not in samples collected from a supine child. Proteinuria that is persistent or associated with hematuria or other signs of renal disease usually is a sign of a more serious condition.

Diagnostic Strategies. Mild proteinuria (2+ or less; equivalent to 100 mg/dL or less) requires no further investigation unless there are signs of infection. Moderate proteinuria (3+ or greater; equivalent to 300 mg/dL or greater) necessitates additional evaluation with laboratory tests for serum total protein and albumin, serum electrolytes, BUN and serum creatinine, and urine culture. A 24-hour urine collection for protein also is indicated. The urine protein-to-creatinine ratio (urine Pr/Cr, expressed in mg/dL) in a random urine sample, however, correlates strongly with the protein levels found in a 24-hour urine collection.[75] Urine Pr/Cr less than 0.2 mg/dL is considered normal for children older than 2 years and for adults. Children 6 months to 2 years of age normally have a ratio of less than 0.5 mg/dL. A urine Pr/Cr greater than 3.0 mg/dL is consistent with nephrotic syndrome.

Antistreptolysin O (ASO) titer can be measured to identify a previous streptococcal infection as the cause of the proteinuria. In young children, renal ultrasonography detects polycystic disease or anatomic abnormalities. Referral to the child's primary care physician or a pediatric nephrologist for follow-up and renal biopsy is indicated. Renal biopsy may be indicated in patients with increased creatinine levels, low complement levels, or hematuria.[77]

Management. The approach to management for a child found to have proteinuria depends on the underlying cause. Management of children with poststreptococcal glomerulonephritis and nephrotic syndrome is discussed later in the relevant sections for these topics.

Disposition. A child with significant edema and ascites from the loss of albumin needs to be hospitalized. Children with significant hypertension resulting from glomerulonephritis or with marked impairment of renal function also need to be hospitalized. Well-appearing children for whom good follow-up can be ensured can be discharged home.

Poststreptococcal Glomerulonephritis

Perspective. Poststreptococcal glomerulonephritis (PSGN) is one of the sequelae of streptococcal pharyngitis and, less commonly, infections of the skin. Treatment of streptococcal pharyngitis with antibiotics has not been shown definitively to decrease the incidence of PSGN, as opposed to acute rheumatic fever, another sequela of streptococcal pharyngitis.

Principles of Disease. PSGN is not well understood but probably results from deposition of circulating immune complexes in the kidney.[78] This results in decreased glomerular filtration, allowing proteins to flow freely into the urine.

Clinical Features. PSGN most commonly occurs in children 3 to 7 years of age, usually with a history of pharyngitis with fever 2 weeks before the onset of glomerulonephritis. Symptoms either can be localized to the urinary tract, manifesting as hematuria or flank pain, or may be less specific, such as lethargy or generalized edema. Some children may present with more significant clinical signs such as pulmonary edema, cardiac arrhythmias, or significant hypertension. Renal failure is found in 2% of these patients.[79,80]

Diagnostic Strategies. Urinalysis shows significant blood and protein, with RBC casts in 60% of cases. Pyuria with granular or hyaline casts also may be found.

The ASO and immunoglobulin G levels are elevated in PSGN. Total complement levels, especially C3, are decreased in most patients during the first 2 weeks of the illness. The complement levels should return to normal within 3 to 4 weeks. The BUN is elevated; hyponatremia and hyperkalemia also may be present.[80]

Differential Considerations. Considerations in the differential diagnosis include the entities previously mentioned regarding proteinuria, including nephrotic syndrome and urinary tract infection.

Management and Disposition. Management includes restricting fluid and salt intake and sometimes using diuretics. A child with significant hypertension, congestive heart failure, or uremia requires hospitalization for inpatient management. Significant hypertension should be treated as outlined in the section on hypertension.

Children with mild symptoms in whom good follow-up can be ensured can be managed on an outpatient basis.

Nephrotic Syndrome

Perspective. Nephrotic syndrome is characterized by hypoproteinemia, proteinuria, and edema. *Primary nephrotic syndrome* applies to diseases limited to the kidney; renal biopsy is used to stratify patients and determine therapeutic and prognostic decisions. *Secondary nephrotic syndrome* results from systemic illnesses such as PSGN.

Principles of Disease. From 2 to 7 cases of nephrotic syndrome per 100,000 children are discovered each year.[77] Boys are affected twice as often as girls, but the distribution equalizes by adulthood. Primary nephrotic syndrome occurs more commonly in children younger than 5 years and secondary nephrotic syndrome more often in older children. Ninety percent of affected children have the primary disease,

with 85% having minimal change nephrotic syndrome, 10% focal sclerosis, and 5% mesangial proliferation (referring to the thin membrane-supporting capillaries surrounding the tubule of nephrons).

The etiology of primary nephrotic syndrome is thought to be idiopathic, but various theories involving bacterial or viral infections, allergic reactions (pollens, poison ivy), or drug ingestions (heroin, mercury) have been investigated.[77]

Clinical Features. Characteristics of nephrotic syndrome include edema, hypoalbuminemia, proteinuria, and hyperlipidemia. The onset of edema may be insidious, beginning with periorbital edema. As weight increases, pants and shoes may not fit. The edema progresses, but the child usually does not appear ill unless pulmonary edema or ascites is present. Other features may include anorexia, nausea, and vomiting secondary to edema of the intestine. Hypertension, hematuria, or oliguria may be present. Acute renal failure is rare in primary nephrotic syndrome.

Nephrotic children also are at risk for thrombosis, with a reported rate of thromboembolic complications of 2%.[81] Renal veins are particularly vulnerable to thrombosis, as characterized by flank pain, hematuria, and worsening renal function. Nephrotic children should not undergo punctures to deep vessels because of this risk of thrombosis.

Children with nephrotic syndrome taking corticosteroids also are at risk for side effects of corticosteroid use. Acute mood changes, from depression to mania, are associated with use of steroids. Irritability, excessive crying, and sleeping difficulties can result.

Because of steroid therapy and decreased levels of immunoglobulins, nephrotic children are at risk for bacterial infections, such as from *E. coli* and *Streptococcus pneumoniae.*

Diagnostic Strategies. Proteinuria in nephrotic syndrome is defined as excretion of greater than 3.5 g of protein per 1.73 m^2 per 24 hours or greater than 50 mg/kg per 24 hours. This corresponds to 3+ or 4+ on the dipstick reading. Specific gravity may be high because of the proteinuria. Microscopic hematuria also may be present. Total serum protein usually is low at 4.5 to 5.5 g/dL, and serum albumin is less than 2 g/dL.

Hyperlipidemia may occur because of the increased serum cholesterol. Hyponatremia may be present, but other electrolytes usually are normal. If an elevated cholesterol level is present, the lowered sodium level may be a combination of true and pseudo-hyponatremia. BUN and creatinine usually also are normal, and hemoglobin and hematocrit levels may be elevated because of hemoconcentration.

Chest radiographs sometimes show pleural effusions or pulmonary edema. The heart appears normal or small because of hypovolemia. An abdominal radiograph may reveal ascites, and ultrasonography may show a renal abnormality.

Renal biopsy is important for diagnostic and therapeutic decisions and should be performed in older children or in patients with evidence of hematuria, elevated BUN, or persistent hypertension or in whom the renal dysfunction fails to respond to steroids.

Differential Considerations. Other renal diseases that cause edema include glomerulonephritis and renal failure. A vasculitis or acute thrombosis of the renal vessels also must be considered. Gastrointestinal disorders that produce hypoproteinemia include cirrhosis, cystic fibrosis, and protein-losing enteritides.

Management. Despite the edema, children with signs of hypovolemia or shock need to be resuscitated with crystalloid. Hypertension may result from the intrinsic disease; prompt recognition and treatment of this condition are important.

After consultation with a pediatric nephrologist, patients between 12 months and 5 years of age with no gross hematuria and no large loss of protein or complement can be treated with corticosteroids. After the initial evaluation is completed, including a tuberculin test, prednisone at 2 mg/kg per 24 hours PO, divided, two or three times a day can be initiated. Relapses or steroid resistance may necessitate a second course of steroids.[77]

Diuretics such as furosemide, 1 to 2 mg/kg per 24 hours PO or IV in divided doses, may be necessary if respiratory distress or significant ascites is present. Salt restriction may be required. Fluid intake should be restricted only if edema is present despite salt restriction or if the child exhibits hyponatremia because of an impaired ability to excrete excess water.

The relatively immunocompromised status of nephrotic children increases the risk of infection. A fever or signs of peritonitis must be investigated thoroughly. A paracentesis should be performed and fluid sent for cell and differential counts, Gram's stain, and culture. Hospital admission and antibiotic therapy with agents with activity against *S. pneumoniae* and *E. coli* are appropriate.[77]

Disposition. Newly diagnosed patients should be hospitalized for initial evaluation, treatment, and education of both the child and the parents. Patients with signs of shock or respiratory distress should be admitted to the hospital after initial stabilization. Other patients with suspected bacterial infections, peritonitis, edema refractory to therapy, or evidence of renal insufficiency also should be hospitalized.

Acute Renal Failure

Perspective. *Acute renal failure* results from impaired glomerular filtration rate. Blood pressure, acid-base balance, removal of nitrogen waste, and fluid management all may be affected. The incidence of acute renal failure is unknown, but large children's hospitals may see 30 to 50 new cases each year.

Principles of Disease. Acute renal failure can be divided into three categories: prerenal, which involves decreased renal perfusion; renal (intrarenal), which is caused by parenchymal damage; and postrenal, which involves obstruction of the urinary tract (Box 172-3).

Causes of *prerenal* failure include hypovolemia resulting from a variety of factors (e.g., dehydration, burns, hemorrhage), shock (e.g., sepsis, anaphylaxis), and congestive heart failure (e.g., decreased cardiac output). Obstruction of the renal artery or thrombosis of the renal vein also can cause acute renal failure.

Intrarenal causes involve damage to the nephron. Glomerular damage most commonly results from PSGN. Systemic lupus erythematosus, HUS, and sepsis with hypoperfusion are systemic causes of renal failure. Tubular damage can result from heavy metal poisonings or hemoglobin-myoglobin in the tubules from a crush injury, burn, or hemolytic crisis. Cases of acute renal failure in dehydrated children after NSAID use have been reported.[82]

Postrenal failure resulting from an obstruction in the urinary tract may be caused by infection, tumor, renal stones, or posterior urethral valves. Bilateral obstruction of the kidneys usually is necessary for renal failure to occur.

Clinical Features. A child with acute renal failure acumulates nitrogen wastes shown by an increase in BUN and serum creatinine levels. A decrease in urine output is sometimes seen. A urinary output of 1 mL/kg per hour usually is considered adequate, but the output may be lower if the patient is dehydrated. Nephrotoxic agents such as certain aminoglycosides can actually increase the urinary output because of renal tubular damage, but BUN and serum creatinine levels are still elevated.

BOX 172-3 ETIOLOGY OF ACUTE RENAL FAILURE IN CHILDREN

Prerenal
Decreased intravascular volume or dehydration
- Burns or hemorrhage
- Third spacing
- Sepsis

Decreased cardiac output
- Cardiac shock

Decreased renal arterial blood flow

Intrarenal
Glomerular disease
- Poststreptococcal and other glomerulonephritis
- Pyelonephritis

Systemic causes
- Hemolytic uremic syndrome
- Henoch-Schönlein purpura or other vasculitides
- Systemic lupus erythematosus
- Sepsis or other causes of prolonged decreased perfusion

Toxins
- Heavy metal poisonings such as lead, gold
- Myoglobin or hemoglobin deposits
- Antibiotics such as aminoglycosides
- Anticonvulsants such as phenytoin
- Radiocontrast dyes

Postrenal
Obstructive lesions
- Nephrolithiasis or tumor
- Posturethral valves
- Intra-abdominal tumor obstructing urinary flow
- Infection

Renal vein thrombosis

Acute renal failure can result in life-threatening complications that must be recognized and treated promptly. These include severe hyperkalemia, pulmonary edema or fluid overload, hypertensive encephalopathy, septic shock from renal obstruction and infection, and seizures from metabolic abnormalities or encephalopathy.[83]

Diagnostic Strategies. Preliminary laboratory tests should include CBC; determination of electrolytes, calcium, phosphorus, BUN, and serum creatinine; and a urinalysis with microscopy and culture. Diagnostic studies such as ASO titer (for acute PSGN), C3 complement (for lupus), total serum albumin, cholesterol, and albumin-to-globulin ratio (for nephrotic syndrome and cirrhosis) may be obtained. RBC casts in the urine indicate glomerulonephritis. WBC casts indicate infection as an etiologic disorder, whereas hyaline casts suggest dehydration or acute tubular necrosis.[84]

Ultrasonography is the imaging modality of choice for the preliminary evaluation of obstructive causes of renal failure. A noncontrast CT urogram also can readily identify the site of obstruction and avoids the use of nephrotoxic radiocontrast material. A voiding cystourethrogram shows extrinsic pressure on the bladder by posterior urethral valves.

Differential Considerations. Significant dehydration can result in temporary decreased urine output and a slight rise in BUN and serum creatinine. After hydration and repletion of intravascular volume, urine output should improve and the elevated BUN and creatinine should resolve. Processes that can result in retention of fluids with associated renal failure include liver disease and decreased cardiac output.

Management. The initial management of a child with acute renal failure depends on the clinical evaluation. If hypovolemia resulting from dehydration or blood loss is thought to be the cause of the renal failure, immediate rehydration is necessary. A 20-mL/kg bolus of crystalloid should be given to prevent possible progression to acute tubular necrosis. If no urinary response is obtained after two boluses of crystalloid, diuretics may be useful in the euvolemic patient. Furosemide 1 mg/kg per dose every 2 to 6 hours IV may be tried if there is no evidence of obstruction. Bumetanide, 0.015 to 0.1 mg/kg per dose every 6 to 24 hours IV (maximum of 10 mg per 24 hours), can be useful if furosemide has no effect. Mannitol, 0.75 g/kg per dose every 6 hours IV, also may be helpful but is contraindicated if there is evidence of obstruction.

If the child is considered euvolemic and has no urine output despite diuretic therapy, renal-dose dopamine should be initiated (2 to 5 µg/kg per minute). Consultation with a nephrologist is necessary.[83]

If hypertension with encephalopathy develops, a controlled 10 to 20% reduction in blood pressure should be achieved using nitroprusside or other intravenous blood pressure agents. Oral medications such as nifedipine or captopril are useful but are associated with the risk of a precipitous drop in blood pressure. Overaggressive reduction in blood pressure can result in hypoperfusion of central target organs such as the brain, heart, and kidneys that have become accustomed to higher perfusion pressures. Further discussion of hypertensive emergencies and treatment can be found in Chapter 83.

Hyperkalemia can result in cardiac dysrhythmias. Potassium levels higher than 6.5 mEq/L may cause changes on the electrocardiogram (ECG) such as peaked T waves and, if significant, widened QRS complexes. Hyperkalemia with resultant ECG changes such as loss of the p wave or widened QRS complex should be treated with calcium chloride 20 to 30 mg/kg per dose (0.2 to 0.3 mL/kg per dose) given IV over 10 to 15 minutes (maximum of 500 mg or 5 mL per dose). Calcium alters the cardiac cells' action potentials, thereby decreasing the risk of arrhythmias. The calcium dose may be repeated in 5 minutes.

Sodium bicarbonate, 1 to 2 mEq/kg per dose IV every 4 hours, also can be administered. The resultant alkalosis helps move the potassium intracellularly by exchanging H^+ for K^+. Continued therapy with sodium bicarbonate should be administered in conjunction with pediatric nephrology services because of the risk of increasing volume load with repetitive dosages of sodium. Potassium-binding agents such as sodium polystyrene sulfonate (Kayexalate) are administered orally or rectally and exchange Na^+ for K^+ in a 1:1 ratio.

Glucose (50% dextrose in water), 0.5 to 1 g/kg, should be given along with regular insulin (1 unit for every 4 g of glucose administered). The insulin temporarily shifts the potassium intracellularly.

Nebulized albuterol also can be be used to shift potassium temporarily into the cells and lower serum potassium by 1 to 1.5 mEq/L over 30 minutes.[85] Severe cases and those associated with renal failure should be immediately referred to a pediatric nephrologist for emergent dialysis.[83]

Acute renal failure may lead to seizures caused by either hypertensive encephalopathy or a metabolic derangement—most commonly hyponatremia resulting from dilution of the sodium by free water. Intractable hyponatremic seizures may rarely necessitate the use of hypertonic saline (3% sodium chloride). Each mL/kg of 3% sodium chloride increases the serum sodium by approximately 1 mEq/L. A child with hyponatremic symptoms such as seizures will often improve after receiving 3 to 5 mL/kg of 3% sodium chloride.

Normal saline (0.9%) is relatively hypertonic compared with serum and therefore also may be helpful in correcting the hyponatremia. Water restriction along with the administration of saline usually is only a temporary treatment, because many of these hyponatremic patients ultimately require dialysis.

Sodium bicarbonate will correct a persistent metabolic acidosis and maintain pH 7.1 or greater and a serum bicarbonate level of 15 mEq/L. The base deficit can determine the amount of bicarbonate needed:

$$\text{Base deficit} = [0.6 \times (\text{body weight in kg}) \times (\text{desired bicarbonate level} - \text{observed level})] \div 2$$

One-half the replacement is given in the first 3 hours, with the remainder given over the next 24 hours.

Hemodialysis or peritoneal dialysis may be indicated for refractory fluid overload associated with hypertension, congestive heart failure, pulmonary edema, severe hyperkalemia, hypo- or hypernatremia, metabolic acidosis, myoglobinuria resulting from burn or crush injuries, or HUS with hemoglobinuria or encephalopathy.[83]

Disposition. All children with acute renal failure should be admitted to the hospital. Any child with signs of congestive heart failure, pulmonary edema, significant hyperkalemia, or acidosis should be admitted to a monitored bed.

Hypertension

Perspective. *Hypertension* is defined as a systolic or diastolic blood pressure higher than two standard deviations above the mean for the age and sex of the patient (Table 172-2). This diagnosis requires three or more accurately measured blood pressures over the course of several weeks. A correct cuff size should be chosen (i.e., the air bladder should cover 80 to 100% of the circumference and two thirds of the length of the upper arm).[79] It is recommended that all children receive yearly blood pressure measurements starting at the age of 3 years.[79] A child who is in pain or agitated may have falsely elevated blood pressure readings.

Principles of Disease. Hypertension occurs throughout childhood in both boys and girls. It probably occurs more often in black children than in white children, just as in the adult population. Predisposing factors include obesity, physical inactivity, and a strong family history. Metabolic syndrome, a combination of insulin resistance, hypertension, and hyperlipidemia, may affect up to 50% of overweight adolescents.[86]

Just as in adulthood, primary or essential hypertension is unrelated to a second systemic disease. Children diagnosed with primary hypertension are more likely to become adults with hypertension.[58] Secondary hypertension results from endocrinologic, cardiac, neurologic, or other factors such as exposure to certain drugs or poisons (Box 172-4). In children with significant hypertension, the underlying cause usually is renal (as in glomerulonephritis) or renovascular.

Table 172-2 Blood Pressure Limits in Children

AGE (YEARS)	BLOOD PRESSURE: UPPER LIMIT (MM HG)	
	SYSTOLIC	DIASTOLIC
0–2	110	65
3–6	120	70
7–10	130	75
11–15	140	80

From Daniels SR: Consultation with the specialist. The diagnosis of hypertension in children: An update. Pediatr Rev 18:131, 1997.

Clinical Features. There are a variety of clinical presentations of hypertension in children. First, asymptomatic or mildly symptomatic hypertension may show up in routine vital signs measured in children evaluated in the ED for unrelated illnesses. When asked, these children may complain of headaches, abdominal pain, irritability, or nosebleeds. Sometimes personality changes and difficulties in school are noted.

Urgent hypertension results in severe elevations in systolic or diastolic blood pressures (younger than 10 years of age: systolic blood pressure 160 mm Hg or higher, diastolic blood pressure 105 mm Hg or higher; older than 10 years of age: systolic blood pressure 170 mm Hg or higher, diastolic blood pressure 110 mm Hg or higher) but without signs of end-organ damage.

In children experiencing a hypertensive emergency, clinical signs of end-organ damage will be present. A severe elevation in blood pressure is associated with acute neurologic changes or encephalopathy, pulmonary edema, myocardial ischemia, or proteinuria. The ECG may show signs of ischemia or ventricular hypertrophy. Chest radiography may reveal cardiomegaly or pulmonary edema. Hypertensive emergencies require prompt recognition and treatment. However, overaggressive treatment of long-standing hypertension can produce relative hypotension, leading to worsening neurologic deficit.

Hypertensive encephalopathy symptoms include headache, vomiting, altered mental status, visual disturbances (including blurry vision and diplopia), and seizures or stroke. Papilledema, decreased retinal venous pulsations, and cranial nerve palsies may be found on examination. The diagnosis is confirmed when the symptoms and signs subside rapidly after the blood pressure is lowered. Headache alone, without any other associated symptoms or signs, generally is not considered to represent a hypertensive emergency.

Diagnostic Strategies. In addition to a thorough history and physical examination, laboratory and radiologic studies performed in the ED often can determine both the cause of the hypertension and whether a hypertensive emergency exists (Box 172-5).

Differential Considerations. Any situation that causes undue agitation or pain in a child can cause a transient rise in blood pressure. Therefore, the diagnosis of hypertension in a pediatric patient should be based only on carefully measured blood pressures in a nonagitated child over several weeks. Secondary hypertension is more likely in symptomatic younger children, especially those without a strong family history.

Other disorders with presentations similar to that of hypertensive encephalopathy include meningitis, brain tumor, intracerebral hemorrhage, stroke, and uremia. These conditions, however, generally produce only a mild increase in the systolic blood pressure[87]; CT or lumbar puncture also can help identify these other diagnoses.

Management. The management of hypertensive emergencies also is discussed in Chapter 83. When a child with severe hypertension is seen in the ED, questions should focus on a history of hypertension, urinary tract infections, hematuria, edema, or umbilical artery catheterization. A history of joint pain or swelling, palpitations, weight loss, flushing of the skin, or drug ingestion or a family history is important to ascertain.

A physical examination emphasizing the central nervous system and cardiopulmonary system is indicated. Examination of the fundus may reveal papilledema or hemorrhages. Signs of congestive heart failure or a difference in the upper and lower extremity blood pressures should be noted. A renal

BOX 172-4 ETIOLOGY OF HYPERTENSION IN CHILDREN

Primary
Essential hypertension

Secondary

Renal
Glomerulonephritis
Henoch-Schönlein purpura
Pyelonephritis
Obstruction or reflux
Polycystic kidney disease
Diabetic nephropathy
Trauma
Renal transplant or hemodialysis
Tuberous sclerosis
Systemic lupus nephritis

Endocrine
Pheochromocytoma
Cushing's syndrome
Congenital adrenal hyperplasia
Corticosteroid treatment
Hyperthyroidism
Neuroblastoma
Ovarian tumor

Cardiac
Congestive heart failure
Coarctation of the aorta

Vascular
Hemolytic-uremic syndrome
Kawasaki syndrome
Renal artery thrombosis or stenosis

Neurologic
Central nervous system tumor or infection
Central nervous system trauma or abuse
Increased intracranial pressure
Guillain-Barré syndrome

Neoplastic
Neuroblastoma
Wilms' tumor
Pheochromocytoma
Adrenal carcinoma

Drugs
Corticosteroids
Cocaine
Sympathomimetics
Oral contraceptives
Phencyclidine
Beta-blocker or clonidine withdrawal
Lead, mercury

Others
Iatrogenic fluid overload
Volume overload from end-stage renal disease

BOX 172-5 DIAGNOSTIC EVALUATION IN HYPERTENSIVE CHILDREN

Hypertensive Emergency?*
1. History of medications or drugs, or family history of cardiovascular disorders
2. Symptoms of headache or chest pain
3. Physical examination focused on acute neurologic changes, funduscopic abnormalities, pulmonary edema
4. Urinalysis for significant protein
5. Chest radiograph for cardiomegaly or congestive heart failure
6. Electrocardiogram for ventricular hypertrophy

Primary or Secondary Cause?
Laboratory and radiologic tests to consider:
1. Urinalysis and urine culture
2. Urine catecholamine assay
3. Complete blood count with platelet count
4. Blood smear
5. Sodium, potassium, chloride, carbon dioxide, calcium, phosphorus, magnesium, uric acid measurement
6. Blood urea nitrogen, creatinine determinations
7. Serum C3 complement assay, antistreptolysin O titer, antinuclear antibody assay
8. Plasma renin level
9. Computed tomography urogram or intravenous pyelogram
10. Voiding cystourethrogram
11. Renal ultrasound scan
12. Renal arteriogram

*Evidence of end-organ damage.

cause of the hypertension may be revealed by the presence of peripheral edema or palpable kidneys. An abdominal or flank bruit suggests renovascular hypertension. Initial laboratory tests should include a CBC, electrolytes, BUN, creatinine, urinalysis, urine culture, chest radiograph, and ECG.

A child in whom clinical findings are consistent with a hypertensive emergency (e.g., acute end-organ damage as found by physical examination, laboratory, or radiologic results) should have intravenous access and be monitored with continuous blood pressure readings; an arterial catheter is preferable. The goal of therapy is to reduce the mean arterial blood pressure by 10 to 20% over several minutes to hours, depending on the nature of the emergency. Headache and vomiting require blood pressure control over several hours, whereas intracranial bleeding or herniation requires reduction over several minutes. Beta-blockers are contraindicated in patients with decreased cardiac output and clinical signs of congestive heart failure. Oral nifedipine is contraindicated in patients with signs of end-organ damage, such as intracerebral bleeding, because of the inability to control the amount of blood pressure reduction. To avoid overaggressive treatment and resultant relative hypotension, medications that can be controlled by intravenous infusions are preferred (Table 172-3).

A hypertensive urgency is severe hypertension without evidence of end-organ damage. These patients should be started or restarted on antihypertensives to prevent end-organ sequelae. Angiotensin-converting enzyme inhibitors or calcium

Table 172-3 Medications Used in Hypertensive Emergencies

MEDICATION	DOSE	TIME TO REPEAT DOSE	DURATION OF EFFECT	SIDE EFFECTS
Nitroprusside	0.3–0.5 µg/kg/min IV (max 10 µg/kg/min)	30–60 min	During infusion	Headache, abdominal pain, chest pain, gastrointestinal upset, seizures, thiocyanate and cyanide toxicity*
Hydralazine†	0.1–0.2 mg/kg IV (max 20 mg) slowly over 15 min	10–20 min	4–12 hr	Tachycardia, skin flushing, headache, vomiting, diarrhea, hypotension
Labetalol‡§	May bolus 0.2–1 mg/kg IV (max. 20 mg), then 0.4–1 mg/kg/hr IV (max. 3 mg/kg/hr)	10 min	6 hr, but variable	Gastrointestinal upset, headache, sedation
Esmolol‖¶**	Load 100–500 µg/kg IV over 1–2 min, then maintenance 25–100 µg/kg/min	10 min	During infusion	Similar to labetalol
Phentolamine	0.1 mg/kg/dose IV (max 5 mg)	30 min	30–60 min	Tachycardia, abdominal pain

*Avoid in pregnancy.
†Use with caution in renal patients.
‡Avoid in asthma, pulmonary edema, and heart block.
§Avoid in second and third trimesters of pregnancy.
‖With inadequate response, readminister loading dose or increase maintenance dose by 25–50 µg/kg/min every 5–10 minutes.
¶Usual maintenance range: 50–500 µg/kg/min.
**Morphine may increase esmolol levels.
Note: Diazoxide is no longer recommended because of the associated potential for an acute drop in blood pressure.

channel blockers are useful as first-line agents and usually are well tolerated. The child may be observed for a few hours after administration of the medication to evaluate effectiveness or complications. With no evidence of acute end-organ damage, the child can be safely discharged home, assuming that good follow-up can be ensured.

Children with mildly elevated blood pressures (5 to 10 mm Hg above normal) unrelated to the ED visit require repeated blood pressure measurements before treatment for hypertension is begun. If the blood pressure is moderately elevated and the patient is asymptomatic, appropriate management consists of discharge home for outpatient workup of the hypertension and follow-up with the patient's primary care physician for monitoring of blood pressure values. Thiazide diuretics or beta-blockers may be started at low doses.

Disposition. A child with evidence of a hypertensive emergency (i.e., acute end-organ damage) must be hospitalized for evaluation and care in a monitored bed. A child with significantly elevated blood pressure, but without evidence of end-organ damage, can be discharged home if good follow-up can be ensured.

Henoch-Schönlein Purpura

Perspective. *Henoch-Schönlein purpura* is an immunoglobulin A–mediated systemic vasculitis involving the small blood vessels supplying the skin, gastrointestinal tract, and joints.[88] The peak incidence is between 4 and 7 years of age, with an overall occurrence rate of 13.5 episodes per 100,000 children annually.

Principles of Disease. Immune complex deposition results in a systemic vasculitis, with up to 33% of patients experiencing recurrences.[89] Approximately 50% of affected children have a history of previous upper respiratory tract infection, and as many as 75% have group A beta-hemolytic streptococci cultured from the oropharynx. Other theorized predisposing factors include exposure to cold weather, certain foods, drugs, and insect bites. Varicella-zoster virus, *Mycoplasma* species, parvovirus, *Campylobacter enteritidis*, parvovirus B19, and Epstein-Barr virus also have been implicated.

Clinical Features. The hallmark of Henoch-Schönlein purpura is a palpable, purpuric, or petechial rash most prominent on the lower extremities, starting at the lateral malleoli and extending to the buttocks. The cutaneous manifestations are the initial presenting complaint in 50% of patients. Arthralgia or arthritis occurs in 65 to 85% of patients[90] and usually involves the knee and ankle joints. Gastrointestinal manifestations are present in up to 65% of patients, with the most common symptom being dull periumbilical pain resulting from bleeding into the intestinal wall. The abdominal pain typically occurs concurrent with or immediately after onset of the rash; however, in up to 15% of patients, abdominal pain can be the initial complaint.[91] A self-limited glomerulonephritis manifested by hematuria develops in 25 to 50% of children. This condition progresses to chronic renal insufficiency in less than 1% of these patients. Children presenting with acute renal failure, nephritic syndrome, or hypertension are more likely to have unfavorable outcomes such as chronic renal failure.[92] Testicular involvement occurs in up to 35% of patients; they may present with severe scrotal edema that resembles acute testicular torsion.

Diagnostic Strategies. There are no specific tests to confirm the diagnosis of Henoch-Schönlein purpura, and recognition of the disorder can be difficult if the classic rash is absent at the time of presentation. Screening tests such as urinalysis, BUN and serum creatinine determinations, CBC, and coagulation studies may be needed to rule out other pathologic conditions. Ultrasound findings in patients with abdominal pain typically include evidence of intraluminal hematomas and duodenal wall thickening.[93] Intussusception also may complicate the disease.

Differential Considerations. Considerations in the differential diagnosis include meningococcemia, Rocky Mountain spotted fever, intussusception, trauma, appendicitis, thrombotic thrombocytopenic purpura, juvenile rheumatoid arthritis, bacterial endocarditis, systemic lupus erythematosus, kidney stones, and primary renal disease.

Management. Treatment of Henoch-Schönlein purpura remains controversial because most cases resolve spontaneously and do not require therapy. NSAIDs can be used to treat joint pain, but close attention must be paid to renal function. Corticosteroids have been used to treat severe renal or gastrointestinal involvement. A recent meta-analysis of data on the use of steroids for Henoch-Schönlein purpura found these agents to be effective in reducing the time to resolution of abdominal pain and reduced the odds of developing persistent renal disease.[94] Prednisone or methylprednisolone pulse therapy has shown some benefit, but an acute surgical process must be excluded before initiation of steroids.[93] Therapy for patients with severe renal involvement also includes intravenous immunoglobulins, although promising results also have been seen in patients with severe abdominal pain.[95] Other treatment options for patients with severe Henoch-Schönlein purpura–related nephropathy include early treatment with oral immunosuppressants[96] and possibly the use of methylprednisolone and urokinase pulse therapy.[97] A nephrologist should be consulted for appropriate management of patients with renal involvement, and good follow-up must be ensured.

Disposition. Patients with only the skin manifestations of Henoch-Schönlein purpura usually can be discharged home with symptomatic therapy for the joint pain and malaise. An NSAID or acetaminophen usually is sufficient, but close follow-up should be ensured. Patients with abdominal pain or renal involvement should be admitted for further evaluation and treatment.

Hemolytic-Uremic Syndrome

Perspective. HUS continues to be one of the most common causes of acute renal failure in children.[98] It most commonly affects infants and children, with a mean age at presentation of 3 years, but is rare after 5 years of age. There is no sex predilection, and outbreaks can be sporadic or epidemic, especially when the disorder is related to the most common offending agent, verotoxin produced by *E. coli* serotype O157:H7. Transmission is through person-to-person contact and also exposure to contaminated food, such as unpasteurized dairy products or beef.[99] Other causes of HUS include *Shigella* organisms, *S. pneumoniae*, *Aeromonas*, human immunodeficiency virus, and drugs; hereditary, familial, and idiopathic forms are recognized as well.

Principles of Disease. Renal compromise is the result of injury to the renal vascular endothelium induced by viral or bacterial agents or the toxins released. Microangiopathic hemolytic anemia then results from injury to the RBCs by fibrin strands along the narrowed blood vessels. Platelets, complement, and fibrin also are deposited in the glomerular lumen, leading to a decrease in glomerular filtration rate and renal failure.

Clinical Features. Patients with HUS present with watery diarrhea, crampy abdominal pain, and occasionally fever. From 2 to 3 days after onset of symptoms, patients experience increased abdominal pain with bloody stools, the latter developing in up to 89% of patients by day 5.[100] Other pathologic features may include toxic megacolon, ischemic colitis, intussusception, perforation, or delayed colonic stricture. After the prodromal gastroenteritis, patients experience sudden onset of hemolytic anemia, thrombocytopenia, and acute renal insufficiency, with possible progression to renal failure. In a meta-analysis published in 2003, death or end-stage renal disease occurred in 12% of cases of diarrhea-associated HUS, and 25% of survivors demonstrated long-term renal sequelae.[101] Pancreatic insufficiency resulting in insulin-dependent diabetes mellitus also has been reported. There are reports of HUS occurring in association with urinary tract infection as well.[102]

Central nervous system irritability may develop and may result in seizures in 40% of patients. Hypertension occurs in up to 50% of patients and may contribute to the development of encephalopathy. HUS recurrences have been associated with a 30% mortality rate.

Diagnostic Strategies. Leukocyte counts and C-reactive protein levels were found to be significantly higher in patients with toxin-producing *E. coli* O157:H7.[99] The peripheral blood smear shows microangiopathic changes such as teardrop cells, helmet cells, microspherocytes, and burr cells. WBC counts may be elevated, and the platelet count may be less than 50,000/μL. The hemoglobin can be as low as 5 g/dL as a result of the rapid hemolysis that occurs.

Differential Considerations. Considerations in the differential diagnosis of HUS include thrombocytopenic thrombotic purpura, ulcerative colitis, intussusception, and other causes of acquired hemolytic anemia.

Management. Supportive therapy and early peritoneal dialysis account for the reduction in current mortality rates to less than 5%. Patients should be rehydrated; however, it is important not to overload these children with fluids. Hyperkalemia is common and should be treated with sodium bicarbonate, calcium gluconate or chloride, dextrose and insulin, and sodium polystyrene sulfonate (Kayexalate). Patients with severe hyperkalemia, hyperphosphatemia, or severe metabolic acidosis require dialysis.

Packed RBCs (5 mL/kg over 4 hours) typically are administered if the hemoglobin falls below 6 g/dL. Platelet transfusions are required only for life-threatening bleeding or before an invasive procedure. Hypertension is responsive to calcium channel blockers, labetalol, captopril, or nitroprusside in refractory cases. Seizures typically respond to benzodiazepines and phenytoin; however, if they are secondary to hyponatremia, treatment with 3% saline (4 mL/kg) may be indicated. Treatment for the colitis itself also is supportive only, because antimotility agents may lead to toxic megacolon. To date, no randomized trials have been conducted to show the effectiveness of antibiotics for the prevention of the development of HUS. Accordingly, because antibiotics may enhance the release of verotoxin from the bacteria, antibiotics should be avoided.[103] Hyperglycemia, ketonemia, and acidosis secondary to pancreatic islet cell necrosis are managed with insulin therapy.

Idiopathic HUS may be treated with plasmapheresis, especially if neurologic involvement is present. If this therapeutic measure is unsuccessful, renal transplantation may be required. Unfortunately, idiopathic HUS also can recur in the transplanted kidney.

Disposition. Patients with HUS require hospital admission, and consultation with a pediatric nephrologist and a urologist should be arranged. Early dialysis and supportive therapy result in return to baseline renal function in up to 90% of patients with acute renal failure.

KEY CONCEPTS

- *Priapism*: In low-flow priapism, cavernosal aspiration plus irrigation has been effective when performed within the first 48 hours, and preferably within a few hours, of symptom onset. Phentolamine, phenylephrine, ephedrine, or 1 :1,000,000 epinephrine often is added to the irrigation solution used in performing corporal aspiration.
- *Phimosis and paraphimosis*: Use of steroid cream is first-line therapy for phimosis. In paraphimosis involving vascular compromise of the glans penis, a dorsal split procedure may be necessary.
- *Testicular torsion*: Delay in diagnosis and treatment can result in loss of spermatogenesis and, in severe cases, a necrotic, gangrenous testis. Testicular salvage rates are time dependent, with a 96% success rate if detorsion is performed less than 4 hours after symptom onset; with greater than a 24-hour delay in time to treatment, the success rate decreases to less than 10%.
- *Varicoceles*: Left-sided varicoceles account for 85 to 95% of the cases; intra-abdominal pathology should be suspected in cases of right-sided varicoceles because these usually are caused by inferior vena cava thrombosis or compression of this vessel by tumors.
- *Urinary tract infections*: In children younger than 2 years, a urinalysis alone is inadequate for ruling out urinary tract infections because this study yields false-negative results in as many as 10 to 50% of patients.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 173 Neurologic Disorders

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PERSPECTIVE

Many acute neurologic manifestations of disease that precipitate a visit to the emergency department (ED), such as seizure, vertigo, ataxia, or headache, appear in both adults and children. However, associated signs and symptoms and diagnostic considerations in children are quite different from those in the adult population. Moreover, bacterial meningitis, once a predominantly pediatric disease, is now mainly a disease of adults; yet it remains imperative to recognize subtle signs and symptoms of this lethal disease in infants and young children.

ACUTE BACTERIAL MENINGITIS

Perspective

Despite advances in medical care, acute bacterial meningitis (ABM) remains a potentially life-threatening emergency. Nationwide mortality rates for treated cases are 20 to 30% in neonates and adults and 2% in infants and children.[1] With the recommendation in 1991 that all infants, starting at 2 months of age, receive the conjugated vaccine against *Haemophilus influenzae* type b, the incidence of bacterial meningitis caused by this organism has been reduced in children by more than 99%.[1,2] Even with the best care, however, 10 to 30% of survivors of meningitis of all types demonstrate persistent, functionally important disabilities.[3,4] These include hearing deficits, seizures, learning and behavioral problems, and cognitive impairments.

Neonates

Group B streptococci account for more than one half of the cases of neonatal meningitis; *Escherichia coli* and other coliforms are responsible for another one fourth of cases.[5] The incidence of early-onset group B streptococcal disease has declined as a result of intrapartum prophylaxis. However, late-onset disease (after 7 days of life) has not.[6] *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Neisseria meningitidis*, group D streptococci, *Ureaplasma urealyticum*, *H. influenzae* type b, and nontypable strains are less common pathogens in neonatal infection. *Listeria monocytogenes* rarely is the agent of meningitis in neonates but is important because of its prevalence within some immigrant groups, its association with unpasteurized dairy products, and its resistance to cephalosporins.[5,6]

Infants and Children

Beyond the neonatal period, in the United States, *S. pneumoniae* and *N. meningitidis* account for 90% of the documented cases of ABM. Unusual pathogens include *Salmonella* species, *Campylobacter* species, *L. monocytogenes*, group G streptococci, *Francisella tularensis*, group B beta-hemolytic streptococci, and several anaerobic organisms.[1,2] Recent advances involving the heptavalent pneumococcal conjugate vaccine (PCV7), which has been recommended for all children younger than 2 years of age, have dramatically reduced the number of cases of bacterial meningitis caused by invasive pneumococcal disease.[7]

Principles of Disease

Host factors influence the degree of susceptibility to meningitis. Newborn infants younger than 1 month of age, particularly those born prematurely, are at greatest risk for ABM owing to their immunologic immaturity. Other groups predisposed to ABM include males, Native Americans, African Americans, malnourished persons, indigent urban dwellers, daycare center attendants, and patients with compromised immune status from sickle hemoglobinopathies, acquired immunodeficiency syndrome (AIDS), asplenia, renal disease, hepatic disease, diabetes mellitus, or dysgammaglobulinemia, as well as those undergoing immunosuppressive treatment, including corticosteroid therapy.

Bacterial meningitis is thought to develop through the interconnection of (1) infection of the respiratory tract, (2) development of bacteremia, (3) invasion of the meninges, and (4) inflammation of the meninges and brain.[6] Invasion of the meninges by bacterial pathogens is facilitated by mechanical disturbances. These include recent neurosurgical procedures such as ventriculoperitoneal shunt placement and lumbar puncture and skull fracture with a persistent cerebrospinal fluid (CSF) leak. Congenital or developmental central nervous system (CNS) abnormalities also predispose affected patients to bacterial seeding of the CNS. These include neurenteric fistula, intracranial cysts, and epidermoid or dermoid tumors, often with an associated congenital dermal sinus tract.

For ABM to occur, organisms must gain entrance into the subarachnoid space. On rare occasions, this occurs as a direct extension from a contiguous focus, such as sinusitis, mastoiditis, or otitis media. In a majority of cases, the bacterial organism gains access to the bloodstream and hematogenously seeds

through inflamed capillaries within the choroid plexus. Most cases of ABM follow a progression of events. After exposure and nasopharyngeal colonization, invasion of the blood occurs. The organism can be recovered from the bloodstream in up to 90% of patients with CSF culture–proven bacterial meningitis.

If bacteria gain entrance into the subarachnoid space, they replicate. Bacterial cell wall constituents are liberated into the CSF. Host inflammatory mediators and cytokines, including interleukin-1, tumor necrosis factor, and platelet-activating factor, are produced and secreted by CNS macrophages and endothelial cells. As a result of an inflammatory response, vascular and parenchymatous cerebral changes occur. These include vasculitis, microthrombus formation, occlusion of venous sinuses, reduced blood flow, increased permeability of the blood-brain barrier, increased intracranial pressure, diffuse cerebral edema, and intracerebral hemorrhage.[8]

Clinical Features

In three fourths of children ultimately diagnosed with ABM, the clinical presentation is subacute, evolving over 2 to 5 days. At onset, affected children typically exhibit a variety of symptoms and signs such as fever, malaise, decreased interest in surroundings, irritability, alteration in sleeping pattern, anorexia, nausea, vomiting, or diarrhea. These findings are nonspecific, seen with equal frequency in children who are suffering from trivial and self-limited illnesses.[9] If the patient is examined early in the course, physical signs may be subtle or lacking.

Children with this insidious presentation have a better prognosis than patients with ABM who present with a rapid progression of signs and symptoms. In one fourth of children with ABM, an acute illness with manifestations such as vomiting, fever, and lethargy develops in less than 24 hours. In such patients, the diagnosis is rarely missed.[10] Those with fulminant illness exhibit a higher risk for death as well as for both immediate and long-term complications.[11]

In addition to the invasiveness of the offending organism, the other variable with the greatest impact on clinical expression is the age of the patient. As a rule, the younger and smaller the infant, the more nonspecific and ambiguous the symptoms and signs of ABM.[1,3,5]

The cutaneous expression of ABM may be a helpful finding suggestive of specific organisms. Petechial and purpuric eruptions may suggest meningococcemia but also can be seen in cases of pneumococcal disease and *H. influenzae* meningitis. Herpes simplex virus (HSV) infections in the neonate are suggested by blisters or erosions in or around the eye, mouth, or skin. These lesions also may be seen in patients with bullous impetigo, candidal infections, varicella, listerioses, or syphilis.[6]

Neonatal Period (Up to the Age of 1 Month)

The clinical findings with ABM in the neonate are nonspecific and may include altered vital signs, behavioral changes, neurologic aberrations, dermatologic lesions, and gastrointestinal manifestations (Table 173-1). In the first 30 days of life, patients who present to an ED with a temperature of 38° C (100.4° F) or higher are found to have serious bacterial illness and ABM in 4 to 15% and 1 to 2% of cases, respectively.[11,12] The absence of fever does not eliminate the possibility of serious bacterial infection, because more than one half of neonates with meningitis are afebrile or exhibit hypothermia. Other vital sign changes include tachycardia, bradycardia, tachypnea, and apnea. Apnea with cessation of breathing for longer than 20 seconds may signify either seizure activity or a nonspecific medullary respiratory center dysfunction.

Table 173-1 Clinical Findings with Bacterial Meningitis

FEATURE	NEWBORN	INFANT/CHILD
General	Apnea Tachypnea Hypothermia Hyperthermia Bradycardia	Fever Shaking chills Myalgia Neck, backache Tachycardia
Behavioral	Restlessness Paradoxical irritability Lethargy	Malaise Irritability Lethargy
Neurologic	High-pitched cry Nystagmus Vacant stare Seizure Opisthotonos Altered tone Nuchal rigidity Bulging fontanel	Altered mentation Focal neurologic signs Hearing deficit Seizure Gait disturbance Photophobia Nuchal rigidity Kernig's, Brudzinski's signs
Dermatologic	Cyanosis Petechiae Purpura Delayed capillary refill Livedo reticularis	Cyanosis Petechiae Purpura Delayed capillary refill
Gastrointestinal	Altered feeding Diarrhea Vomiting Abdominal distention Jaundice	Anorexia Nausea Vomiting

Neonates have a limited behavioral repertoire. Within that range, even subtle changes in behavioral patterns can reflect early meningeal involvement. Restlessness, listlessness, increased or decreased sleeping time, and irritability may be clues. Irritability in a neonate without meningeal invasion generally is alleviated by human contact. Increased irritability with cuddling should suggest the diagnosis of ABM. Neurologic manifestations of ABM in the neonate may include high-pitched cry, incessant cry, absent cry, or moan. A vacant stare, hypertonicity, trembling chin, or bicycling motion of the extremities suggests a seizure. Focal or generalized tonic-clonic activity, although possible, is less commonly seen. Nuchal rigidity occurs in less than 25% of cases of neonatal ABM. A bulging fontanel and diastasis of the sutures, both hallmarks of an increased intracranial pressure (ICP), are present in approximately 15% of the cases of neonatal ABM.

Skin rashes are infrequent manifestations of neonatal meningitis.[13] One clue may be generalized pallor accompanied by indistinctly outlined truncal patches of blue discoloration (livedo reticularis). Difficulty feeding and unusual stooling patterns are nonspecific gastrointestinal features. Nonprojectile vomiting may appear in the course of meningitis, becoming projectile only after ICP has increased. Increased stool volume, irritability during defecation, abdominal distention, hepatomegaly, and jaundice can develop with meningitis.

One Month to 12 Months

In young infants (younger than 3 months of age), symptoms of serious bacterial illness are similar to those in the neonate, but as the infant grows older, the social repertoire and motor capability expand, allowing for greater opportunity to assess

for alteration in behavior or for signs and symptoms of bacterial meningitis. Nuchal rigidity, although not commonly present, is highly predictive for ABM in this age group. The absence of nuchal rigidity does not preclude the possibility of CNS infection; however, other signs often are present, such as poor tone, decreased interactiveness, inconsolability, alteration in gaze and focus, and a weak cry.

One Year to 5 Years

The cardinal features in this age group are fever, headache, vomiting, and stiff neck. Obtundation and lethargy also are common findings with meningitis but are nonspecific. After the first year of life, neck stiffness with difficulty flexing the neck is reliably seen during the acute phase of meningitis. A patient rarely may exhibit torticollis.[14] The clinician can attempt to elicit nuchal rigidity by forced flexion of the neck with the child in the supine position. However, this method is less reliable than attempting neck flexion with the child seated with both legs outstretched. Both of these maneuvers involve passive motion that many children voluntarily resist. More reliable methods that result in fewer false-negative and false-positive results involve active neck motion on the part of the child. In a toddler, a distracting object can be used to attract eye contact, and the active range of neck motion can be determined. Additionally, the neck stiffness that accompanies ABM may be displayed in both the prone and supine positions when the child's shoulders are placed at the edge of the examining table and minimal support of the occiput or forehead is provided manually. Presence of Kernig's sign (flexion of the hip 90 degrees with subsequent pain on extension of the leg) and Brudzinski's sign (involuntary flexion of the hips and knees following passive flexion of the neck performed with the patient supine) is less reliable. Kernig's and Brudzinski's signs are seen in approximately 43% and 66%, respectively, of children with ABM.[15]

Older Than 5 Years

Headache, fever, stiff neck, and alteration of sensorium are common presenting signs and symptoms in children older than 5 years, as they are in the adult patient with ABM.

Diagnostic Strategies

Lumbar Puncture

Indications

Lumbar puncture is indicated in any child in whom bacterial meningitis is suspected. Patients to be considered as candidates for this procedure include those with classic signs and symptoms such as fever, stiff neck, and photophobia, but in infants and children, classic signs often are absent. In a study by Walsh-Kelly and colleagues, nuchal rigidity was present in only 27% of infants younger than 6 months of age with bacterial meningitis. By 12 months of age, 71% showed nuchal rigidity; this rate rose to greater than 95% by 19 months of age.[16] Therefore, the decision to perform a lumbar puncture in children with suspected meningitis should be based primarily on the constellation of presenting signs and symptoms.

Nuchal Signs. A lumbar puncture should be performed in ill children who exhibit nuchal rigidity or a Kernig sign or Brudzinski sign and who have suspected meningitis. These three signs of meningeal irritation also can be seen in patients with parameningeal disease states other than ABM, so caution must be exercised in these cases.

Suspected Sepsis in Young Infants. A bacterial infection is the most likely etiologic disorder in any infant younger than 3 months of age who is ill.[12] Current practice advocates that the possibility of severe bacterial infection must be pursued with an ill young infant. No distinguishing features differentiate sepsis from meningitis in this age group. Because 50% of neonates with acute meningitis are bacteremic at the time of the initial evaluation, and because an intracranial infection subsequently develops in 25% of bacteremic neonates, blood cultures and lumbar puncture should be undertaken concomitantly.[17,18] In infants older than 1 month but younger than 3 months of age, history and physical examination, even if augmented with selective laboratory investigations (excluding lumbar puncture), may fail to identify those infants with a serious bacterial infection such as ABM. Thus, a lumbar puncture should be performed as part of the sepsis evaluation.[19,20]

Toxic Appearance. A lumbar puncture also should be considered in any case in which a global assessment of the child's clinical condition suggests overall toxicity. Such observations include a blunted response to social overtures, poor perfusion, altered motor tone, and abnormal cry. Febrile pediatric patients of all ages with a toxic appearance have an increased incidence of severe bacterial infections, including ABM.[11] Focal infections have been implicated as a source of dissemination of organisms into the CNS. Establishing an apparent infectious source for a particular presentation does not preclude the possibility of a more serious suppurative focus that may be intracranial.

If the patient exhibits clinical manifestations that are more severe than anticipated for an extracranial focus of infection, a lumbar puncture should be performed.

When obvious clues to the source of an apparent infectious process exist and an initial lumbar puncture yields negative findings in the face of increasing severity of illness, additional information can be obtained by repeating the lumbar puncture. The CSF composition may change from normal cellularity to marked pleocytosis within as little as 30 minutes.[21] Thus, later reexamination of the CSF may be invaluable in establishing the nature of an occult intracranial infection.

Febrile Illness after Intimate Contact. All children who have prolonged and close physical involvement with persons found to have a serious bacteremic illness require prompt medical evaluation. In particular, fever developing after intimate contact with patients with meningococcal or *Haemophilus* disease is a strong indication for lumbar puncture in this age group.[22]

Febrile Seizures. Children 6 months to 5 years of age who have experienced a simple febrile seizure and who appear well (alert, active, playful) are extremely unlikely to have meningitis.[23] Generally, patients who exhibit complex features of the febrile seizure are at increased risk for meningitis.

Lumbar puncture should be *considered* in patients who have characteristics that increase their risk for ABM or who show signs and symptoms of ABM. The historical features are age younger than 1 year, exposure to another child with meningitis or serious bacterial infection, and a physician visit within 48 hours before the febrile seizure. Children with febrile seizures who exhibit any clinical sign associated with increased risk for intracranial infection, including lethargy, decreased motor tone, doll's eye sign, inability to fix and follow, decreased response to painful stimuli, nuchal rigidity, full fontanel, petechiae, and poor skin perfusion, should undergo lumbar puncture.

Fever and Petechiae. Trivial to life-threatening infectious disease can cause fever and petechiae. No current optimal strategy has emerged for evaluating febrile children with petechial eruptions. Well-appearing febrile children with localized petechiae, especially above the nipple line and with no purpura are

unlikely to have invasive bacterial disease. Patients at highest risk for invasive bacterial disease are more likely to appear ill or to have generalized petechiae and purpura or signs of meningeal irritation.[24] In the high-risk group, unless contraindicated by coagulopathy, lumbar puncture should be performed to exclude concurrent meningitis.[25]

Sepsis Suspected in an Abnormal Host. Immunocompromised pediatric patients are at risk for the development of both opportunistic infections and invasive illness from pathogens common to all children. Immunologically incompetent children may not exhibit the typical manifestations of intracranial infections, including nuchal rigidity.[26] An immune-impaired child who experiences only a change in mental status, however, should be suspected of having meningitis. CSF parameters in these patients are less sensitive indicators of the presence of bacterial meningitis compared with normal host response to a bacterial invasion of the meninges. A lumbar puncture nonetheless should be performed in the process of excluding sepsis in a compromised host.

Penetration of Dura. Fracture through the paranasal sinuses or anterior or middle cranial fossa and penetrating nasal injury or instrumentation may lead to dural tears. Such defects constitute a potential portal of entry for microorganisms into the CNS. Evidence of CNS infection generally is seen within 2 weeks of the initial injury, but clinical manifestations may be delayed for years. Persistent CSF otorrhea or rhinorrhea may be encountered but is not a clinical prerequisite for posttraumatic meningitis. When patients with a recent or remote history significant for craniofacial trauma develop any constellation of symptoms suggestive of meningitis, lumbar puncture should be performed after a computed tomography (CT) scan.

Acute Hearing Loss. Hearing loss has been identified in up to one third of patients with ABM. Hearing impairment may be identified in the acute phase or become apparent only in the postmeningitic period. Of significance, hearing loss may precede the onset of systemic complaints and herald the appearance of meningitis. This is especially true for patients with an inner ear fistula or basilar skull fracture. Acute hearing loss should be an indication for lumbar puncture in patients with traumatic injury, which may have directly inoculated organisms into the labyrinth or basilar subarachnoid space, and in patients who have symptoms suggestive of meningitis.

Contraindications

Herniation of the temporal lobes through the tentorium or herniation of the cerebellar tonsils through the foramen magnum rarely occurs in patients with meningitis and increased ICP. Most children with ABM exhibit some mental status changes, but rapid onset and progression to deep coma (Glasgow Coma Scale score less than 8) usually reflect increased ICP, and lumbar puncture is contraindicated.[27] Focal neurologic signs suggestive of an abscess are further contraindications to lumbar puncture in children.

Positioning and Precautions

When not contraindicated, emergency lumbar puncture with CSF examination should be performed to confirm a presumptive diagnosis of ABM (Box 173-1). Patients with suspected bacterial meningitis should have the procedure completed in the lateral decubitus position with spine flexed and knees drawn upward toward the chest, with shoulders and back perpendicular to the table. Opening pressure should be obtained if possible with the patient in this position. In circumstances in which opening pressure measurement cannot be obtained, an alternative position is sitting with the thighs flexed toward the abdomen.

BOX 173-1 Indications for Lumbar Puncture in Suspected Acute Bacterial Meningitis

- Signs or symptoms of meningitis or toxic appearance
- Suspected neonatal sepsis
- Febrile infant younger than 2 months of age
- Sepsis suspected in an abnormal host
- Documented bacteremia
- Febrile illness after intimate contact with person with meningitis or serious bacterial infection
- Febrile seizure
- Fever and petechiae

In the stable monitored patient, the potential for complications is sufficiently low that sampling the CSF should be routine. Lumbar pain can be eliminated in all pediatric patients with the use of an anesthetic agent. Prevention of post–lumbar puncture cephalgia is enhanced by using smaller-gauge needles, restricting the sample fluid volume to 3 mL, and reinserting the stylet before removing the needle. The small risk of introducing bacterial skin flora is reduced with proper aseptic technique. Causing meningitis by performing a lumbar puncture in the course of a bacteremic illness is a theoretical concern but does not occur. The information obtained from the lumbar puncture outweighs this hypothetical risk.

Standard Cerebrospinal Fluid Interpretation

A standard CSF examination includes bacterial culture and Gram's stain from tube 1, protein and glucose assessment from tube 2, and blood cell count from tube 3. In cases of culture-proven bacterial meningitis, up to 6% of patients have normal glucose and protein levels, few white blood cells, and a negative result on Gram staining.[15] Patients who have received antibiotics before their first lumbar puncture merit special mention. Although the CSF can be sterilized after the administration of antibiotics in the ED, especially in cases of pneumococcal and meningococcal disease, the CSF profile often is unaffected for more than 12 to 24 hours after therapy.[6]

Glucose. The CSF glucose concentration must be interpreted in relation to a concomitant serum glucose value. The normal steady-state CSF-to-serum glucose ratio is approximately 0.6. Hypoglycorrhachia, as defined as a ratio below 0.4, is characteristically found in cases of ABM with common pathogens and with *Mycobacterium tuberculosis*. Hypoglycorrhachia also may be associated with viral meningitis, although CSF glucose in such cases typically is normal.

Protein. The normal CSF protein range is 40 to 170 mg/dL in newborns and 15 to 45 mg/dL in children. Normal to modest elevations in protein concentration occur in the course of viral meningitis. Higher levels of protein are encountered with ABM. After a traumatic lumbar puncture, each 800 to 1000 red blood cells elevate the protein level by 1 mg/dL.

Cellularity. A representative cellularity profile is presented in Table 173-2. Unfortunately, these numbers have been largely derived from healthy or non–systemically ill children.[28] The standard "panic values" that have been quoted often are greater than 2 standard deviations above the mean or are figures that are seen in only 5 to 10% of studied populations. Cellularity that exceeds these typical threshold values can be seen with conditions that indirectly influence the CNS; however, such cases should be considered to represent possible ABM and treated accordingly. These conditions include generalized seizure, shigellosis, and parameningeal focus of infections such as otitis media, sinusitis, and mastoiditis.[29]

Table 173-2 Reported Values for Cerebrospinal Fluid Cellularity

AGE	TOTAL WHITE BLOOD CELLS/μL		
	MEAN	RANGE	THRESHOLD EXCEEDED
Preterm	7	0–44	>9
Term newborn	8	0–32	>22
0–4 weeks	11	0–50	>35
4–8 weeks	7	0–50	>10
>8 weeks	2	0–8	>6

Patients with suspected sepsis or with foci of infection distant from the CNS such as pneumonia also may have increased cellularity. Classically in ABM, the total white blood cell count ranges from 1000 to 20,000/mm^3.[15] A white blood cell count of greater than 2000 is present in more than one third of cases of ABM.[30] Significant pleocytosis also can accompany aseptic meningitis.

Of note, the practice of "correcting" for white blood cells in bloody CSF samples may have little scientific support. Underestimation of the white blood cell count may occur in the setting of culture-positive meningitis. Furthermore, consideration should be given to other illnesses, such as herpes simplex virus encephalitis, in which an increased number of red blood cells may be seen in the CSF.[6]

In the first month of life, up to 60% of the cells in the normal CSF are polymorphonuclear leukocytes (i.e., neutrophils) (PMNs). Beyond 1 month in the normal state, not more than 3 PMNs/mm^3 should be seen. Shortly after invasion of the meninges, white blood cells can be sampled from the lumbar space. Traditional teaching suggests that a rise in PMNs is characteristic of ABM. However, PMNs and bands may be present in patients with viral meningitis as well.[31]

Gram's Stain. The probability of visualizing bacteria on a Gram's stain depends on the number of bacterial organisms present at the time of sampling. One fourth of the smears yield positive results with 10^3 or more colony-forming units (CFUs) per milliliter; 60% of the smears show positive results with 10^3 to 10^5 CFUs/mL, and 97% show positive results with 10^6 CFUs/mL. A positive result on Gram staining necessitates immediate antibiotic therapy, even in the absence of increased white blood cells and protein levels or decreased glucose level in the CSF.

Other Cerebrospinal Fluid Tests

Antigen Detection. Commercial antigen detection kits are available for detecting the common pathogens causing ABM. Microbial antigens in CSF are detected by coaglutination, latex agglutination, countercurrent immunoelectrophoresis, enzyme-linked immunosorbent assay, and centrifugation-augmented solid-phase immunoassay. Because antigens remain measurable after antibiotic treatment, antigen detection proves to be most effective in cases of partially treated meningitis or in patients in whom the CSF Gram's stain and culture results are negative and ABM is strongly suspected. In any meningitic state, either untreated or pretreated, the CSF antigen detection kits are most sensitive when more than 500 white blood cells are present in the CSF.[32] The antigens typically are present at high levels in the CSF for several days, even after parenteral antibiotics have been initiated. A positive CSF assay result provides reliable bacteriologic diagnosis. A negative antigen test result cannot exclude the diagnosis of ABM.

Cytokines. Assayed concentrations of C-reactive protein, various interleukins, tumor necrosis factor, and prostaglandins are elevated with ABM.[33] These assays require sophisticated techniques and expensive equipment and take 5 hours to complete. For these reasons, the assays are of little utility in the ED setting.

Polymerase Chain Reaction Testing. The diagnosis of meningitis caused by HSV and enterovirus can be determined using PCR-based testing (for these organisms) in CSF. PCR assays for the detection of pneumococci are still experimental.[6]

Other Laboratory Testing Instruments

The performance of other diagnostic tests in addition to CSF analysis should be guided by the clinical situation. Blood cultures are of proven value in the patient with ABM. A pretreatment blood culture will identify the organism recovered from the CSF in 86 to 92% of cases. Culture of specimens from body surfaces and orifices (e.g., nose and throat) is not helpful in identifying the causative pathogen. Positive results on culture from urine, stool, and pleural space samples substantiate systemic bacterial disease but do not ensure the presence of an intracranial infection with the same organism.

Determination of serum electrolytes and serum glucose may be helpful because changes in body water content and electrolytes may be a feature of ABM. The serum sodium level may be below 135 mEq/L in more than one half of the patients at the time of presentation.[34] The blood glucose level should be estimated rapidly with a glucose oxidase tape, because hypoglycemia secondary to poor intake, vomiting, and metabolic derangements is a common complication. The estimated value should be confirmed with a serum sample submitted for electrolyte determinations.

No hematologic profiles can consistently identify pediatric patients with ABM; nevertheless, a complete blood count is warranted, because the total white blood cell count and platelet counts may aid prognostic risk assessment. Either thrombocytopenia or neutropenia at admission may be an ominous feature.

At the time of establishing the diagnosis of ABM in a moderately ill patient, arterial blood gas determination can be performed in selected cases as indicated by apparent hypoventilation or hypoxia or presence of signs of metabolic acidosis.

A Gram-stained smear of a petechial or purpuric lesion may reveal an offending organism causing systemic invasion.[35] Serum C-reactive protein assay, erythrocyte sedimentation rate determination, and measurements of the various cytokines can be used to support the diagnosis of systemic bacterial infection. These tests yield nonspecific findings, however, and cannot be used to include or exclude a diagnosis of ABM. Elevated pretreatment values may be tracked to determine the most effective duration of therapy for ABM.

A urine specimen should be submitted for analysis. If the patient is pretreated with antibiotic agents, urine microbial antigen detection should be performed. Urine antigen detection may be positive in up to 87% of pretreated cases of ABM. A midstream clean-catch voided specimen or urine acquired by catheterization should be submitted. Urine from a bag specimen that is potentially contaminated by fecal material may yield false-positive results as a result of cross-reactivity with *E. coli* organisms.[36]

Radiology

CT of the head should be performed when the clinical findings suggest subdural empyema, cavernous sinus thrombosis, lateral sinus thrombosis, cerebral hemorrhage, brain tumor,

brain abscess, or a parameningeal focus of infection. CT of the head without contrast should be performed on an emergency basis when the patient exhibits signs and symptoms of elevated ICP. Concern for raised ICP is warranted if the patient has cranial nerve palsy, absence of retinal venous pulsations, altered pupillary responses, papilledema, focal seizure, hemiparesis, ataxia, obtundation, persistent vomiting, decorticate or decerebrate posturing, or bradycardia unassociated with hypoxemia.[15] A decision to image the head or other body parts (such as the chest) must not delay antibiotic administration for patients with ABM. If patients with a ventriculoperitoneal shunt demonstrate fever or signs of increased ICP, they also should undergo CT before tapping of the shunt for CSF.

Differential Considerations

Any of the manifestations of ABM can be expressed in a single patient. The most common presentation involves a combination of thermal instability, altered behavior, blunted mental status, and neck stiffness. The differential diagnosis for this constellation comprises infectious, metabolic, traumatic, and miscellaneous conditions (Box 173-2).

Many conditions cause a child to appear ill. Any infectious agent can cause clinical illness in children, particularly in the first months of life. Infants with infectious disease exhibit altered affect, including significant changes in mental status, strongly suggesting an intracranial pathologic process. Beyond infancy, children may exhibit a toxic appearance with any focal infection or with extensions from a primary focus leading to systemic invasion.[10] In addition to infection, a change in mental status may be noted with endocrinopathy, hypoglycemia, electrolyte imbalance, metabolic disease, uremia, seizure, unintentional trauma, abusive head injury, intussusception, or exposure to toxins.

Nuchal rigidity provokes strong consideration of ABM. However, neck stiffness associated with altered mentation or neurologic deficit can occur with spontaneous intracranial hemorrhage, hemorrhage into brain tumor, epidural abscess, or brain abscess. Other causes of stiff neck include retropharyngeal abscess, peritonsillar abscess, and torticollis.

BOX 173-2 Differential Diagnosis for Acute Bacterial Meningitis

Infectious
Septicemia
Rickettsemia
Encephalitis
Subdural empyema
Spinal epidural abscess
Intracranial epidural abscess
Viral meningitis
Fungal meningitis
Tuberculous meningitis
Myocarditis
Shigellosis

Traumatic
Shaken baby syndrome
Closed head injury

Metabolic
Hypoglycemia
Ketoacidosis
Hyponatremia
Hypernatremia
Uremia
Urea cycle defect

Miscellaneous
Intussusception
Intoxication
Toxic exposure
Seizure disorder
Brain tumor
Arteriovenous malformation
Ruptured dermoid cyst

Viral Meningitis

In the first few years of life, the signs and symptoms of bacterial and viral meningitis can be indistinguishable.[37] Beyond 1 year of age, a majority of children with viral meningitis have a relatively mild illness compared with children with ABM. Fever and retro-orbital or frontal headache are frequent symptoms of both diseases. Gastrointestinal disturbances such as anorexia, nausea, and diarrhea are more common with viral meningitis. Generalized myalgia also may be a feature, and patients often complain of neck ache or neck stiffness. However, reduction in active neck flexion is uncommon.

Modest elevation of PMNs in CSF specimens coupled with normal glucose level, normal to slightly elevated protein concentrations, and a negative result on Gram's staining is anticipated with viral meningitis. These laboratory findings can confirm a clinical suspicion of viral meningitis. However, atypical features such as hypoglycorrhachia or significant pleocytosis can be found in 20% of encounters. This blurs the distinction between the two states and may alter management. Decision rules have been proposed to distinguish viral from bacterial meningitis, but their usefulness in clinical practice may be limited if they cannot identify every case of ABM. Nigrovic and colleagues, however, demonstrated a low risk (0.1%) for bacterial meningitis in children who lack the following criteria: positive CSF Gram's stain, CSF absolute neutrophil count (ANC) of at least 1000 cells/μL, CSF protein of at least 80 mg/dL, peripheral blood ANC of at least 10,000 cells/μL, and a history of seizure before or at the time of presentation.[38]

Management

Management priorities for ABM include airway protection, oxygenation, and volume resuscitation with monitored preservation of organ function. If the capillary refill time is delayed more than 2 seconds or the patient is hypotensive, the patient should be treated for shock. A bolus infusion of 20 mL/kg of normal saline or lactated Ringer's solution should be provided while an indwelling urinary catheter is inserted. Up to 40 mL/kg should be provided as bolus infusions. If vital signs fail to stabilize after an infusion of 40 mL/kg of crystalloid solution and a urine flow of 0.5 mL/kg per hour or greater cannot be maintained, pressors should be given. In the patient without shock, an hourly infusion rate should be established that provides normal maintenance fluids. Fluid restriction, previously advocated, may be deleterious to the patient's survival and neurologic recovery.

Beyond support of cardiopulmonary and hemodynamic status, initial management of ABM includes prevention of hypoglycemia, control of seizures, and administration of agents to maintain cerebral blood flow.

Antibiotic Therapy

Intuitively, it makes biologic sense to advocate expeditious antibiotic administration for the patient suspected to have

ABM. In reality, no studies have shown that a duration of any given time frame arbitrarily chosen to constitute an "excessive delay" affects morbidity or mortality; however, most experts agree that antibiotics should be administered within 1 to 2 hours of presentation in patients with suspected ABM. The timing of antibiotic administration in a patient with CNS syndrome compatible with ABM should be driven by the specifics of the clinical scenario. A conservative approach for children with suspected ABM consists of treatment with empirical antibiotics and hospitalization for observation. Strategies to stratify patients into low- and high-risk categories as a basis for appropriate management (i.e., to restrict hospitalization and antibiotic therapy to children with suspected bacterial meningitis) have been proposed. The following four categories are offered:

Nontoxic, low-risk: In a non-pretreated patient with no evidence of systemic toxicity in whom the clinical picture is suggestive of viral meningitis, if the CSF indices confirm a clinical suspicion of viral meningitis (negative result on Gram's stain, few white blood cells in the CSF, and normal CSF protein and glucose levels), antibiotics can be withheld in consultation with the patient's primary care physician or a neurologist. Another option is to discharge the patient and schedule a repeat lumbar puncture within 12 hours after antibiotic therapy. These strategies are not without risk, because it often is difficult to distinguish viral meningitis from other infections such as Rocky Mountain spotted fever or ABM. If biochemical parameters or cytologic assessment findings resemble those in ABM, it is appropriate to begin empirical antibiotic therapy and hospitalize the patient for observation.

Nontoxic, high-risk: A patient with no evidence of toxicity but with high-risk historical factors (such as pretreatment with antibiotics, exposure to an invasive organism [*H. influenzae* or *N. meningitidis*], or age younger than 1 year) prompting increased concern for ABM requires blood culture and lumbar puncture for CSF analysis. If the spinal fluid is cloudy, antibiotic therapy should begin immediately rather than being withheld pending complete CSF analysis. In symptomatic patients exposed to a person with meningococcemia, appropriate management consists of a full range of cultures, empirical antibiotic therapy, and hospitalization for observation until the results of all cultures are known, because the absence of meningitis does not rule out the presence of meningococcal disease.

Critical, stable: For the patient with classic signs of ABM who has a protected airway, adequate ventilation, normal perfusion, and no evidence of coagulopathy and is assessed as being in critical but stable condition, a blood culture with phlebotomy and a second culture with placement of an intravenous catheter, urinalysis and culture, blood chemistries, and a complete blood cell count are recommended, after which a lumbar puncture is performed. Antibiotics should be administered immediately after lumbar puncture and before the results of the CSF or other studies become available from the laboratory.

Critical, unstable: A patient with a CNS syndrome, abnormal vital signs for age, an unprotected airway, ongoing seizure activity, focal neurologic deficit, or coagulopathy is considered to be in critical and unstable condition. The risk for an adverse outcome as a result of diagnostic lumbar puncture is magnified, especially if the procedure is carried out before the patient is stabilized. Patients with clinical signs of increased ICP may experience fatal cerebral herniation (even if CT findings are normal) after a lumbar puncture.[27] Two blood culture samples and blood and urine specimens for antigen detection should be obtained. Antibiotics should be administered and the lumbar puncture deferred.

Table 173-3 Empirical Antibiotics for Treatment of Acute Bacterial Meningitis

AGE	FIRST INTRAVENOUS DOSE	
	ANTIBIOTIC	MG/KG
0–4 weeks	Ampicillin	50–100
	plus	
	Gentamicin	2.5
	or	
	Cefotaxime	50
4 weeks–2 months	Ampicillin	100
	plus	
	Cefotaxime	50
	or	
	Ceftriaxone	100
	or	
	Chloramphenicol	25
>2 months	Cefotaxime	50
	or	
	Ceftriaxone	100
	plus	
	Vancomycin	15

ED antimicrobial treatment decisions are empirically based. The choice of agents should be based on knowledge of the prevalent organisms responsible for intracranial infections and the regional patterns of their antimicrobial susceptibility. The initial regimen chosen for treatment should be broad enough to provide coverage for the various pathogens typical for the age group being treated (Table 173-3).

In the newborn, no single antibiotic has bactericidal activity against all of the possible organisms commonly encountered. The most widely used combination therapy consists of ampicillin with an aminoglycoside or ampicillin plus cefotaxime, which is equally effective. For infants older than 1 month and younger than 3 months of age, in the absence of any evidence for presence of unusual organisms, conventional therapy is ampicillin and a third-generation cephalosporin. Beyond the age of 3 months, monotherapy with a third-generation cephalosporin provides adequate coverage, except in cases involving resistant strains of *S. pneumoniae*. When gram-positive cocci are identified on the CSF Gram's stain, the combination of a broad-spectrum cephalosporin (e.g., cefotaxime, ceftriaxone) and vancomycin is now routinely recommended.[39]

Steroid Therapy

The role of dexamethasone therapy for ABM has long been the focus of clinical interest. Consensus opinion suggests that for infants beyond 8 weeks of age, dexamethasone can mitigate some neurologic sequelae, particularly hearing loss in cases of ABM caused by *H. influenzae*. The beneficial effect, if any, of dexamethasone on morbidity and mortality caused by other bacteria is less well defined.[1]

Use of dexamethasone is not without risk. The most commonly reported deleterious effect of dexamethasone is gastrointestinal bleeding. The anti-inflammatory effects of dexamethasone have led to a false sense of clinical improvement, overshadowing the failure of the chosen antibiotic to eradicate an invasive organism. Reduced penetration of vancomycin with dexamethasone therapy has been

demonstrated.[40] As a potentially universal distribution of cephalosporin-resistant and penicillin-resistant *S. pneumoniae* approaches, reducing the penetrating effect of vancomycin may cause undue harm. In summary, it is best to adhere to the latest recommendations of the American Academy of Pediatrics (AAP) and limit the use of dexamethasone for the presumptive treatment of *H. influenzae* meningitis (a rare disease in the United States). Logistically, 0.15 mg/kg dexamethasone can be administered only after completion of the Gram's stain interpretation or on finding a positive result on assay for *H. influenzae* antigens.

For optimal management, close observation is mandated for the patient with newly diagnosed and treated ABM. Vital signs, systemic perfusion, and level of consciousness can rapidly change. Complications from the disease state such as shock or seizure, or from interventions such as anaphylaxis or post–lumbar puncture herniation of cerebral contents, can be addressed only if the patient undergoes continuous monitoring.

Acyclovir

The issue of empirical treatment of a neonate or young infant (younger than 3 months of age) with acyclovir is controversial because identification of infected infants is challenging. Acyclovir should be administered in an ill or febrile infant with a history of maternal HSV infection, presence of vesicles on the skin, seizure, or focal neurologic signs. Use of acyclovir also should be considered in atypical presentations of sepsis or meningitis.[6] The dose of acyclovir is 20 mg/kg IV every 8 hours for 21 days in full-term immunocompetent infants. Polymerase chain reaction assay for HSV should be performed in these cases.

Disposition

A child newly diagnosed with ABM is best managed by experienced physicians and nurses who are capable of addressing critical care needs. When available, the best resource is a hospital that can provide pediatric intensive care. If transfer of the patient to another hospital is necessitated by the lack of appropriate inpatient pediatric care, the composition, expertise, and equipment of the interfacility transport team are important. Accordingly, the relevant logistics are best worked out in advance of the actual patient encounter.

SEIZURES

Perspective

A *seizure* is a paroxysmal event characterized by a change in behavior of the patient; it is caused by abnormal and excessive activity of a group of cortical neurons. The clinical appearance of the seizure depends on the location and extent of brain involved. *Epilepsy* is defined as the occurrence of two or more *unprovoked* seizures.

Seizure disorders are among the most common neurologic disorders of childhood. In children, the incidence is the highest in the first year of life.[41]

Principles of Disease

Pathophysiology

The young, immature nervous system is more susceptible to seizures. Early in development, excitatory activity predominates and inhibitory systems are undeveloped.[42] This is known as the period of vulnerability. A paucity of synaptic connections and alterations in the synthesis of neurotransmitters also may play a role.

Seizures and Brain Damage

It is well known that children with epilepsy are at a significant risk for cognitive impairment and behavioral abnormalities. Distinguishing the relative contributions of the effect of the seizures themselves from the underlying CNS pathology and from the effect of anticonvulsants is difficult. A single prolonged seizure has been shown to damage the brain, particularly the temporal lobes and hippocampus.[43] Additionally, a growing body of evidence points to the lasting effect of repetitive, brief seizures in early childhood.[44]

Clinical Features

Classification of Seizure Type

One of the first priorities in evaluating a child with a seizure is to determine the seizure type and, if possible, the seizure syndrome. Seizures are classified into two main types: partial (consciousness is maintained) and generalized (consciousness is lost) (Box 173-3). In *complex partial* seizures, the patient experiences a change in level of awareness and may exhibit bizarre behaviors, including staring, lip smacking, wandering, or picking at clothing. In *simple partial* seizures, the patient experiences no change in mentation.

Generalized seizures may be *convulsive* or *nonconvulsive*. *Absence* seizures are generalized nonconvulsive seizures that consist of a brief arrest of consciousness and movement (i.e., for 5 to 10 seconds); no postictal drowsiness occurs. It may be difficult to differentiate a brief complex partial seizure from an absence seizure in children.

Classification of Epilepsy: Epileptic Syndromes

An *epileptic syndrome* is characterized by a specific triad of patient age at onset, seizure types, and electroencephalo-

BOX 173-3 CLASSIFICATION OF SEIZURES

Partial (focal, local) seizures
Simple partial seizures (consciousness maintained)
  With motor signs
  With autonomic symptoms and signs
  With somatosensory or special sensory symptoms
Complex partial seizures (consciousness impaired)
Generalized seizures (convulsive and nonconvulsive)
  Absence seizures
  Atypical absence (marked change in tone, not rapid in onset or cessation)
  Myoclonic seizures
  Clonic seizures
  Tonic seizures
  Tonic-clonic seizures
  Atonic seizures
Unclassified epileptic seizures (includes all seizures that cannot be classified because of inadequate or incomplete data)

From Commission on Classification and Terminology of the International League Against Epilepsy: Proposal for revised clinical and electroencephalographic classification of epileptic seizures. Epilepsia 22:489, 1981.

BOX 173-4 MODIFIED CLASSIFICATION OF EPILEPTIC SYNDROMES

I. Idiopathic epileptic syndromes (focal or generalized)
  A. Benign neonatal convulsions
  B. Benign childhood epilepsy
    1. With central midtemporal spikes (benign rolandic epilepsy of childhood)
    2. With occipital spikes
  C. Childhood/juvenile absence epilepsy
  D. Juvenile myoclonic epilepsy
  E. Idiopathic epilepsy otherwise unspecified
II. Symptomatic epilepsy syndromes (focal or generalized)
  A. West syndrome (infantile spasms)
  B. Lennox-Gastaut syndrome
  C. Early myoclonic encephalopathy
  D. Epilepsia partialis continua
  E. Aquired epileptic aphasia (Landau-Kleffner syndrome)
  F. Temporal lobe epilepsy
  G. Frontal lobe epilepsy
  H. Post-traumatic epilepsy
  I. Other symptomatic epilepsy not otherwise specified
III. Other epilepsy syndromes of uncertain or mixed classification
  A. Neonatal seizures
  B. Febrile seizures
  C. Reflex epilepsy
  D. Other unspecified

Data from Flomin O, Nield L, Kamat D: Seizure medications: A review for the primary care pediatrician. Clin Pediatr 44:383, 2005.

graphic findings. Identification of the epileptic syndrome provides information on prognosis and informs management decisions. Epileptic syndromes of infancy and childhood have been well described. Several of these syndromes are reviewed below (Box 173-4).

Infantile Spasms

Infantile spasms manifest during the first year of life and consist of rapid jackknife flexor or extensor spasms that appear in clusters. The electroencephalogram (EEG) shows *hypsarrhythmia*, an abnormal pattern characterized by slow waves of high voltage and disorganized spike activity.

Approximately two thirds of children with infantile spasms have an underlying CNS disorder such as a congenital brain malformation or tuberous sclerosis. The outcome is poor. Only one half will attain remission of seizures, and the large majority will be mentally retarded. Treatment is notoriously difficult. In the United States, use of adrenocorticotropic hormone (ACTH) has traditionally been the treatment of choice, although prednisilone treatment is being used with increasing frequency.[45]

Childhood and Juvenile Absence Epilepsy

Childhood and juvenile absence epilepsy begins most commonly between 4 and 12 years of age and is characterized by frequently recurrent absence seizures. The parent may note that the child "spaces out" and does not respond for a few seconds. Bursts of spike-and-wave activity at 3 per second on the EEG during an absence spell are indicative of this syndrome. Generalized convulsive seizures occur in up to 50% of the patients. Hyperventilation can trigger absence spells and can be used to diagnose absence epilepsy. Treatment is with ethosuximide; if convulsions also occur, then valproic acid or lamotrigine should be used.[46] The prognosis is excellent, and children usually outgrow this disorder.

Benign Rolandic Epilepsy of Childhood

Benign rolandic epilepsy of childhood is a partial epilepsy occurring between the ages of 3 and 13 years. Classically, the seizure occurs during sleep and involves the face; secondary generalization may occur. The typical EEG pattern is one of central temporal (rolandic) spikes, particularly during sleep. The prognosis is excellent; the seizures cease by 16 years of age. Carbamazepine, phenytoin, and valproic acid all are equally efficacious. Considerable controversy has emerged regarding whether brief seizures in this benign epilepsy syndrome warrant treatment at all.[47]

Lennox-Gastaut Syndrome

Lennox-Gastaut syndrome is characterized by mental retardation, multiple seizure types, and a classic EEG pattern of "slow" spike and wave. The age at onset is between 1 and 8 years, and the syndrome may evolve from infantile spasms. The patient usually demonstrates multiple different seizure types and seizure control may be difficult. Traditionally, valproic acid has been the first-line agent. In the past several years, however, several new anticonvulsants, including lamotrigine, topiramate, and felbamate, have shown promise for the treatment of Lennox-Gastaut syndrome.[48]

Febrile Seizures

A *febrile seizure* is defined as a seizure occurring in the presence of fever without CNS infection or other cause. To satisfy the criteria for a *simple* febrile seizure, the seizure must be generalized, last less than 15 minutes, and occur in a child between 6 months and 5 years of age who is neurologically and developmentally normal.[49] Febrile seizures affect approximately 3% of children. Simple febrile seizures typically occur early in the course of the febrile illness. Almost half the children with a febrile seizure have a documented temperature of less than 39° C. *Complex* febrile seizures are diagnosed when multiple seizures occur during the same illness, seizures are prolonged (longer than 15 minutes), or the seizures have a focal component.

Thirty percent of children with a simple febrile seizure have a recurrence; of these, one half will have a third event.[50] The younger the age at onset, the more likelihood of recurrence. Children with simple febrile seizures have a 2 to 3% chance of developing epilepsy (compared with a 1% rate of epilepsy in the general population). Children with complex febrile seizures have a significantly higher risk. Treatment with long-term anticonvulsants does not affect the later risk of epilepsy.[51] Acetaminophen and ibuprofen have not been shown to decrease the likelihood of recurrence.[52]

Rectal diazepam (Diastat) is safe and effective for terminating prolonged or repetitive febrile seizures and should be available for home use in the child with recurrent, prolonged febrile seizures.[53] Long-term anticonvulsant use is rarely warranted.[49] Reassurance and education constitute the mainstays of management.

Neonatal Seizures

The frequency of seizures is higher in the first month of life than at any other time in childhood.[54] Neonatal seizures may be subtle: apnea, sustained eye deviation, chewing, or limb bicycling movements may be the only apparent changes. A high incidence of subclinical electrographic seizures has been described.[55] Focal clonic movements usually are associated with an underlying structural lesion.

BOX 173-5 Etiology of Neonatal Seizures

Hypoxic-ischemic encephalopathy
CNS infection
Intracranial hemorrhage
Cerebral infarction
Chromosomal abnormalities
Congenital brain abnormalities
Metabolic disturbances
  Hypoglycemia
  Hypocalcemia
  Hypomagnesemia
  Pyridoxine dependency
  Inborn errors of metabolism
  Drug withdrawal or intoxication

CNS, central nervous system.

BOX 173-6 Episodic Disorders That May Mimic Seizures

Newborns
Jitteriness
Benign neonatal sleep myoclonus
Nonepileptic apnea
Opisthotonos
Normal movement

Non Newborn
Breath-holding spells
Rigors/chills
Gastroesophageal reflux (Sandifer's syndrome)
Migraine
Benign paroxysmal vertigo of childhood
Syncope
Neurovascular event
Sleep disorders
  Sleep myoclonus
  Narcolepsy
  Nightmares, night terrors, somnambulism
Tics/stereotypies
  Infantile shuddering attacks
  Paroxysmal choreoathetosis or dystonia
Psychological
  Psychogenic seizures
  Panic attack

Although the causes of neonatal seizures are numerous, a relatively few etiologic disorders account for a majority of cases (Box 173-5). These include hypoxic-ischemic encephalopathy, intracranial infection, congenital brain malformation, cerebrovascular events, and metabolic disturbances, particularly hypoglycemia and hypocalcemia. Although inborn errors of metabolism are rare, early treatment can be lifesaving. A dose of 50 to 100 mg of pyridoxine will immediately stop the seizure and normalize the EEG in a neonate with the rare disorder of pyridoxine dependency.

Neonatal seizures also may predispose the affected infant to the development of cognitive and behavioral difficulties, as well as an increased risk of epilepsy, later in life.[55] Ultimately, the prognosis is dependent on the etiology of the seizure.

Status Epilepticus

Convulsive status epilepticus constitutes a true neurologic emergency; it is associated with high morbidity and mortality rates that increase with duration of the seizure activity. *Status epilepticus* is defined as continuous seizure activity for 30 minutes or longer or occurrence of sequential seizures over a similar period without full recovery of consciousness between seizures. In clinical practice, any seizure lasting more than 5 minutes warrants intervention.[56] Although the diagnosis of convulsive status usually is obvious, the duration of the seizures often is underestimated because the intensity of the jerking tends to diminish with time. The importance of careful observation cannot be overstated.

Status epilepticus occurs significantly more frequently in children than in adults, particularly in those younger than 1 year of age.[57] Febrile illness is by far the most common precipitant of status epilepticus in children. Medication change, toxic ingestion, idiopathic epilepsy, metabolic derangements, and congenital abnormalities are the next most common. Although morbidity and mortality rates both are significantly lower than in adults, they are still significant at 30% and 4%, respectively. Complications in patients with prolonged status epilepticus may involve any and all organ systems.

Nonconvulsive status epilepticus is marked by an altered mental status. Patients may demonstrate confusion, unresponsiveness, abnormal motor movements, twitches, lip smacking, or automatisms. An EEG can confirm the diagnosis and should be obtained if nonconvulsive status is suspected. A benzodiazepine is the therapeutic agent of choice.

Etiology of Seizures and Differential Considerations

The first task of the ED evaluation is to determine whether the event in question was truly a seizure. Not all paroxysmal events are seizures (Box 173-6).

Syncope is one of the more common disorders mistaken for a seizure. This entity is characterized by a sudden, usually brief loss of consciousness and motor tone. It results from a reversible decrease in cerebral blood flow precipitated by cardiogenic or noncardiogenic causes. The patient usually complains of light-headedness and blurry vision and appears pale and sweaty, with clammy skin. Postictal confusion does not occur. Trembling and stiffening are common. Vasovagal syncope is quite common in otherwise healthy children and does not warrant further workup unless it is recurrent. Because vasovagal syncope generally occurs when the child is standing, cardiogenic syncope, such as from prolonged QTc syndrome, should be considered if the child is not standing at the time of the event.

Breath-holding spells occur in 4 to 5% of children, primarily between the ages of 6 and 18 months. Breath-holding spells are triggered by pain or emotional upset. During expiration, the breath is held and the child becomes cyanotic or pale; this may progress to loss of consciousness. The infant initially is limp but may exhibit a brief period of clonic movements or opisthotonos. The average attack lasts approximately 40 seconds.[58]

Migraines may mimic seizures, particularly when accompanied by an aura, motor dysfunction, clouding of consciousness, or vomiting.

Disorders of sleep are distinguished by excessive daytime sleepiness or by disordered nighttime sleep. *Narcolepsy* is characterized by daytime sleep attacks, sleep paralysis, hypnagogic hallucinations (vivid hallucinations while falling asleep), and cataplexy (sudden loss of motor tone). Cataplexy may be mistaken for atonic or absence seizures. *Nocturnal enuresis* may

raise concern for a nighttime seizure with incontinence. *Night terrors* (pavor nocturnus) occur when the child suddenly appears to awaken and cries out. The child usually is unresponsive and inconsolable, and the event concludes with the child's returning to sleep. *Sleepwalking (somnambulism)* and *sleeptalking (somniloquy)* are quite common among school-aged children.

Movement disorders may mimic seizures. *Tics* are rapid, repetitive, brief involuntary movements that occur intermittently and in flurries. Those most commonly seen are eye blinking and head shaking. Patients do not lose consciousness. *Shudder attacks* are uncommon but easily mistaken for seizures. They have been described as looking like the classic reaction to the chill experienced when cold water runs down the back. *Paroxysmal choreoathetosis* is an abnormal motor movement that may be spontaneous or triggered by the child's movement.

Behavioral or psychiatric disturbances can manifest with behaviors that may appear epileptic. *Panic attacks* may be mistaken for complex partial seizures. The patient has a sudden sensation of intense fear accompanied by shortness of breath, dizziness, palpitations, sweating, choking, chest discomfort, and fear of dying. *Psychogenic seizures* are involuntary events that mimic seizures. Many children with psychogenic seizures also have epileptic seizures. Prolonged EEG monitoring may be necessary to differentiate an epileptic seizure from a psychogenic seizure.

Infants with gastrointestinal reflux may exhibit *Sandifer's syndrome*, characterized by episodes of abnormal posturing, arching of the back, and torticollis.

Etiology of Seizures in Children

After the diagnosis of seizure is made, the seizure type and the etiology should be determined. Seizures can be divided into three main etiologic categories: acute symptomatic, remote symptomatic, and idiopathic seizures (Box 173-7).

Acute symptomatic seizures are provoked by an acute event. Febrile seizures are the most common cause of acute symptomatic seizures in children. Remote symptomatic seizures are due to an earlier, or remote, CNS lesion. Examples include head trauma (nonacute), congenital brain malformation, and any other chronic brain injury. Idiopathic seizures have no definable cause.

Acute Symptomatic Seizures

Meningitis should always be considered in any patient with seizures and fever, particularly children. A child whose mental status is normal both before and after the seizure is unlikely to have meningitis.

Hypoglycemia (defined as a blood glucose concentration less than 60 mg/dL in adults and less than 40 mg/dL in children) may cause acute seizures. Hyponatremia (serum sodium concentration less than 125 mEq/L) and hypernatremia (serum sodium greater than 150 mEq/L) are both associated with seizures. Hypernatremia most commonly is caused by dehydration.

Hypocalcemia and hypomagnesemia may lead to muscle spasms, paresthesias, hyperactive reflexes, weakness, tetany, and seizures. Hypocalcemic seizures are a common cause of neonatal seizures.

Post-traumatic seizures occur in as many as 15% of children after head injury. *Impact seizures*, occurring within 1 hour of a head trauma, are not associated with severe injury or with the later development of epilepsy. *Early post-traumatic seizures* (occurring within the first week of injury) may arise from cerebral edema or intracranial hemorrhage, laceration, or contusion. Phenytoin is effective in preventing early post-traumatic seizures but does not influence the development of late-onset epilepsy.[59]

Brain tumors cause a wide variety of symptoms depending on their location and the type of tumor. In children, tumors usually are infratentorial and therefore rarely cause seizures.

Stroke, both hemorrhagic and ischemic, may manifest with seizures. Congenital heart disease, sickle cell anemia, and

BOX 173-7 ETIOLOGY OF ACUTE AND REMOTE SYMPTOMATIC SEIZURES

- Febrile seizures
- Infectious processes
  - Meningitis
  - Encephalitis
  - Brain abscess
  - *Shigella* infection
  - Neurocysticercosis
- Traumatic lesions
  - Cerebral contusion
  - Hemorrhage—subdural, epidural, subarachnoid, intraparenchymal
  - Impact seizure
- Toxic conditions
  - Drug intoxication (see Box 173-8)
  - Drug withdrawal
- Metabolic disturbances
  - Hypoglycemia
  - Hyponatremia
  - Hypernatremia
  - Hypomagnesemia
  - Hypophosphatemia
  - Hepatic or renal disorder
  - Hyperosmolar states
  - Inborn errors of metabolism (e.g., aminoacidurias, organic acidurias, mitochondrial diseases)
  - Pyridoxine dependency syndrome
- Neoplastic disease
- Vascular disorders
  - Arteriovenous malformation
  - Subarachnoid hemorrhage
  - Intraparenchymal hemorrhage
  - Cerebral venous thrombosis
  - Ischemic infarct
  - Hypertensive encephalopathy
- Neurocutaneous disorder
  - Neurofibromatosis
  - Tuberous sclerosis
  - Sturge-Weber syndrome
- Neurodegenerative disorder
- Miscellaneous
  - Eclampsia
  - Dialysis
  - Post-immunization
  - Hypoxia
  - Hypoxic-ischemic encephalopathy
  - Ventriculoperitoneal shunt malfunction
  - Cerebral dysgenesis
  - Cerebral palsy
  - Intrauterine infection (e.g., TORCH)
  - Primary epilepsy

TORCH, *t*oxoplasmosis, *o*ther agents, *r*ubella, *c*ytomegalovirus, *h*erpex simplex.

BOX 173-8 DRUGS THAT MAY CAUSE SEIZURES

Anesthetic Agents
Etomidate
Enflurane
Methohexital
Lidocaine

Antibiotics
Penicillin
Beta-lactams
Quinolones
Isoniazid
Metronidazole

Anticholinergics
Phenothiazines
Butyrophenones
Tricyclic antidepressants

Anticholinesterases
Organophosphates
Physostigmine

Anticonvulsants
Carbamazepine
Phenytoin

Antidepressants
Tricyclic antidepressants
SSRIs
Bupropion
Fluoxetine
Monoamine oxidase inhibitors

Antidysrhythmics
Mexiletine
Tocainide
Procainamide

Antihistamine
Diphenhydramine

Antipsychotics
Phenothiazines
Chlorpromazine clozapine
Thioridazine
Butyrophenones
Haloperidol

Antitumor Agents
Chlorambucil
Cyclosporine

Beta-blockers
Sympathomimetics
- Cocaine
- Amphetamines
- Phenylpropanolamine
- Methylphenidate

Other Agents
Baclofen
Camphor
Carbon monoxide
Cyanide
Radiocontrast agents
Ethanol: severe intoxication or withdrawal
Flumazenil
Hypoglycemic agents
- Insulin
- Oral hypoglycemics

Lead
Lithium
Narcotics
- Fentanyl
- Meperidine

Nicotine
Oxygen
- Hyperbaric oxygen therapy

Theophylline

homocystinuria are major risk factors for ischemic stroke in children. Vascular malformations such as arteriovenous malformations may cause hemorrhagic stroke.

Numerous drugs are known to cause seizures. Cyclic antidepressants, cocaine and other stimulants, antihistamines, and isoniazid are the most common agents of drug-induced seizures. Drugs that may be associated with seizures are summarized in Box 173-8. Seizures also may occur during drug withdrawal, usually within 48 hours of drug cessation. Drug withdrawal in the neonate is a significant issue. Withdrawal of benzodiazepines and barbiturates leads to an abstinence syndrome similar to ethanol withdrawal.

Reflex seizures are precipitated by a specific, identifiable stimulus. For example, viewing television and playing video games may induce seizures in photosensitive children.[60]

Remote Symptomatic Seizures

Causes of remote symptomatic seizures include congenital brain malformations, neurocutaneous disorders, cerebral palsy secondary to brain lesions such as neonatal infarct, hypoxic-ischemic encephalopathy, or neonatal meningitis.

Diagnostic Strategies

The initial diagnostic evaluation is directed toward determining if the event in question was indeed a seizure and, if so, identifying a specific underlying cause. If the patient arrives in the ED actively convulsing, immediate attention is turned to stopping the seizure.

A complete history is key to establishing the diagnosis of a seizure or epilepsy. Effort should be made to obtain a description from an eyewitness as well as an account from the patient himself or herself. The history should include:

1. *Events leading up to the attack*: What was the patient doing at the time? Did the patient become confused or complain of dizziness, a bad smell, flashing lights, or anything else?
2. *The event itself*: Did the patient get stiff or limp? Did the patient shake? Was there a loss of consciousness? Did the eyes or head turn in one direction? Was there incontinence? Having the observer demonstrate the movements can be very helpful.

3. *Events directly after the attack*: Was the patient lethargic or confused? For how long? Did the patient remember the event? The occurrence of postictal confusion, headache, or fatigue can help differentiate a seizure from a nonepileptic event.[61]
4. *Possible precipitants of seizures*: Has there been recent fever, illness, rash, head trauma, drug use, or medication or supplement use?
5. *Risk factors for epilepsy*: Past history of meningitis, head injury, febrile seizures, congenital anomalies, or developmental delay, or a family history of epilepsy, as well as the presence of unusual birth marks may be elicited.
6. *Previous history of abnormal movements, staring spells, or myoclonus*: It is not uncommon for a patient with a first generalized tonic-clonic seizure to have underlying, undiagnosed absence epilepsy.

In a patient with known epilepsy, it is important to determine whether any doses of anticonvulsant have been missed. The general physical examination should look for signs of systemic disease that can cause seizure. Particular attention should be paid to detect evidence of meningitis, head trauma, drug use, dehydration, hypertension, and heart disease. Skin lesions, such as café-au-lait spots or hypopigmented nevi, may point to a neurocutaneous disorder. An abnormal head circumference may point to hydrocephalus or abnormal brain growth.

A careful neurologic examination also is an essential part of the ED evaluation of the child who has experienced a seizure. The examination should assess for signs of increased intracranial pressure, focal neurologic deficits, and developmental delay.

Management

The management of four categories of seizures—febrile seizures, afebrile seizures, neonatal seizures, and status epilepticus—is described next. Box 173-9 provides an overview of the approach to a child with a seizure.

Febrile Seizures

As mentioned earlier, a febrile seizure is defined as a seizure accompanied by fever without CNS infection occurring in children between 6 months and 5 years of age.[62] In general, a child in this age range who had a brief seizure in the setting of fever and in whom the neurologic examination reveals no abnormalities can be assumed to have had a simple febrile seizure. The evaluation should be directed toward the diagnosis of the cause of the fever. According to the AAP recommendations, lumbar puncture is not necessary in children older than 18 months in whom the clinical findings are not suggestive of meningitis. Lumbar puncture should be considered in children between 12 months and 18 months of age and *strongly* considered in children younger than 12 months of age, because signs of meningitis can be subtle in this age group.[63] EEG, blood workup, or neuroimaging generally is not required.

BOX 173-9 SUMMARY APPROACH TO THE CHILD WITH A SEIZURE

- Determine if the event was truly a seizure.
- Determine seizure type.
- Identify precipitating factors (e.g., hypoglycemia, hypocalcemia, electrolyte imbalance, low anticonvulsant levels, fever, trauma, CNS infection, toxin) and treat accordingly.
- Determine if anticonvulsant therapy is appropriate at this time.

CNS, central nervous system.

Afebrile Seizures

Laboratory Studies. Laboratory tests generally include determinations of calcium, glucose, urea, electrolytes, and magnesium.[64] However, such studies are rarely abnormal in the child who is neurologically normal after a brief seizure.[65] Toxicology screening should be considered if drug exposure is a concern. Anticonvulsant levels should be measured if the patient is on such medication and testing is available for a particular agent.

A lumbar puncture is mandated in the patient with an abnormal mental status or other signs of meningitis, regardless of whether or not fever is present. Most patients exhibit signs of an altered mental status in the postictal period. If the concern for meningitis is low, the clinician may opt to observe the patient over the next few hours; if the patient returns to baseline, a lumbar puncture often can be avoided. A prolonged seizure can cause a mild elevation of white blood cells in the CSF, presumably from a transient disruption of the blood-brain barrier. CSF should be sent for cell counts, protein, glucose, culture, and PCR for herpesvirus.

Radiography and Other Imaging

Consensus is lacking regarding the need for neuroimaging in patients who come to the ED after a first seizure. Emergent imaging should be performed in a patient with new focal deficits, persistent altered mental status, recent trauma, persistent headache, or partial-onset seizures.[67] A witnessed generalized convulsion may have begun as a partial-type seizure before secondarily generalizing; it is important to question both the eyewitness and the patient about events at the onset of the seizure. Children with generalized unprovoked seizures and normal examinations usually do not require acute imaging. At follow-up evaluation, further evidence, such as a focal abnormality on the EEG, may indicate a need for neuroimaging, which can be done at that time. Children with a history of previously treated epilepsy do not need neuroimaging unless a change in clinical status occurs.

If imaging is indicated in the acute period, either CT or magnetic resonance imaging (MRI) may be used. Although MRI provides superior anatomic detail, the patient often needs sedation. Therefore, CT, which provides rapid imaging and is highly sensitive for detecting acute blood and fractures, is the imaging study of choice in the patient with head trauma or who is potentially unstable.

Special Procedures

The EEG is the most important laboratory test for evaluating the patient with a seizure. It rarely needs to be performed in the acute situation unless nonconvulsive status epilepticus is suspected. The EEG helps determine the seizure type, specific epilepsy syndrome, and risk for recurrence.[65] Transient postictal slowing may occur for several days after a seizure.

Techniques such as sleep deprivation, hyperventilation, and photic stimulation enhance the sensitivity of the EEG. Ideally, all EEGs should be performed with the patient awake, drowsy, and asleep.

Treatment of Specific Causes of Acute Seizures. Hypoglycemia is treated intravenously with 25% dextrose, 2 to 4 mL/kg. Severe hypo-

natremia may be treated with the intravenous administration of 3% saline (4 mL/kg infused over 30 minutes) to raise the serum sodium level to 125 mEq/L. The remainder of the correction should occur slowly over the next 24 hours. Hypernatremia is corrected slowly over 48 hours. Hypocalcemia is treated with 10% calcium gluconate, 100 mg/kg IV; the patient should be on a cardiac monitor during the infusion. With most toxic ingestions that cause seizures, no antidote is available. Ingestions involving isoniazid constitute one exception; a dose of 1 mg of intravenous pyridoxine for each 1 mg of isoniazid ingested should be administered (5 mg is given for an unknown amount of isoniazid ingestion).

Patients suspected to have meningitis should be started on empirical antibiotic therapy (see Table 173-3). Additionally, the patient with altered mental status, focal seizures, and red blood cells in the CSF should be treated empirically for herpes encephalitis with acyclovir, 20 mg/kg per dose (15 kg per dose in children greater than 12 years) every 8 hours.

Neonatal Seizures

The common underlying causes of neonatal seizures differ from those in older children and adults (see Box 173-5). Initial diagnostic testing is summarized in Box 173-11. Glucose, calcium, magnesium, and electrolytes are sent immediately. If findings are normal, lactic acid, ammonia, and pH determinations should be considered. Lumbar puncture should be performed and fluid sent for cells, protein and glucose determinations, culture, and herpes PCR assay; clinical assessment for meningitis is not reliable in young infants. Imaging should be obtained. Head ultrasound scans may be obtained in a child who is not stable enough to be moved. Otherwise, head CT or MRI studies should be obtained.

Empirical antibiotic therapy should be started in affected infants (see earlier section on meningitis). Acyclovir (20 mg/kg per dose every 8 hours) is initiated if herpes encephalitis is a clinical concern. Hypoglycemia is corrected with 2 mL/kg IV of 10% dextrose solution. Hypocalcemia is treated with 10% calcium gluconate (1 mL/kg given over 5 to 10 minutes with heart rate monitoring and ongoing close inspection of the infusion site) or calcium chloride (20 mg/kg). Hypomagnesemia, which may be associated with hypocalcemia, is treated with a 0.25 mL/kg of 50% solution magnesium sulfate IM.

Phenobarbital, 20 mg/kg, is loaded; additional doses of 5 to 10 mg/kg may be given if necessary. Phenytoin and fosphenytoin are erratically absorbed and have an unpredictable rate of metabolism in young infants; these agents are given only if seizures continue after phenobarbital. The dosage of fosphenytoin is 20 PE/kg. Benzodiazepines may be useful but are associated with hypotension and respiratory depression; they should be used with caution. Continued seizures may be treated with midazolam infusion.[44] If seizures are refractory to medical treatment, empirical treatment with pyridoxine, 50 to 100 mg IV, is indicated. This will abort seizures in the rare child with pyridoxine dependency syndrome.

The diagnostic assessment of neonatal seizures is fairly straightforward and includes metabolic testing, lumbar puncture and CSF analysis, and neuroimaging (Box 173-11).

Status Epilepticus

Status epilepticus constitutes a true medical emergency. The patient is positioned to maximize ventilation and to prevent physical injury; the cervical spine must be protected if trauma cannot be ruled out. Oxygen is administered by nasal cannula or face mask, and a large suction catheter should be available to suction secretions. In the younger patient, the tongue may obstruct the airway; a nasopharyngeal airway will keep the tongue forward and improve respiratory status.

If the airway is compromised, respiratory failure occurs, or there is evidence of increased ICP, the patient should be intubated. Do not paralyze unless absolutely necessary, because this will mask signs of seizure activity. If needed, short-acting neuromuscular blockers, such as succinylcholine and vecuronium, should be used.

Monitor heart rate, blood pressure, and respiratory rate and pulse oximetry and treat hyperthermia with antipyretics and cooling blankets. Place an intravenous line and send blood samples for electrolytes, glucose (including rapid blood glucose), calcium, magnesium, renal function, liver function, antiepileptic levels (if indicated), and CBC. Urine should be sent for toxicology.[68]

Correct any metabolic abnormalities (see previous section on afebrile seizures). If necessary, an intraosseous line may be used.

Begin anticonvulsant treatment as quickly as possible. The three most commonly used agents to treat convulsive status epilepticus are benzodiazepines, phenytoin, and barbiturates.[56] Table 173-4 presents a summary of these medications. Benzodiazepines, particularly diazepam and lorazepam, usually are the initial drugs used in the treatment of status epilepticus. They diffuse quickly into the CNS, rapidly terminating seizure activity 70% of the time.[69] The recommended pediatric intravenous dosage for lorazepam is 0.1 mg/kg (maximum 8 mg) given at a rate of 1 to 2 mg per minute; the recommended intravenous dosage for diazepam is 0.2 to 0.5 mg/kg (maximum of 10 mg) at a rate of 2 mg per minute. Hypotension, respiratory depression, and impaired consciousness may occur.

Rectal diazepam may be used if intravenous access cannot be obtained. The dosage is 0.5 mg/kg (maximum 20 mg). If Diastat, a rectal preparation of diazepam, is not available, the intravenous preparation may be instilled through a lubricated feeding tube inserted 4 to 6 cm into the rectum. Buccal and intranasal midazolam preparations are effective, although not yet commonly used; dosages are 0.4 mg/kg and 0.2 mg/kg, respectively.[70]

If the seizure continues, a second dose of benzodiazepine is given. If the seizure is ongoing, then fosphenytoin or phenytoin is loaded. Patients who already are on phenytoin should receive phenobarbital in a loading dose of 20 mg/kg.

Fosphenytoin is a water-soluble phosphate ester of phenytoin (prodrug) that is rapidly converted in plasma to phenytoin. Unlike phenytoin, fosphenytoin can be administered intramuscularly, can be administered with common intravenous solutions, and is substantially less cardiotoxic and less sclerosing to the vasculature. Additionally, it can be given three times more rapidly than is possible with phenytoin. Fosphenytoin produces plasma concentrations similar to those achieved for phenytoin in the same time period.

The standard loading dose of phenytoin is 18 to 20 mg/kg at a rate of 1 mg/kg per minute, not exceeding 50 mg per minute. The loading dosage of fosphenytoin is 18 to 20 PE (phenytoin equivalents)/kg at 150 mg per minute. Monitoring cardiovascular status, including blood pressure and ECG, is recommended with use of either medication. If hypotension results, the rate of infusion is decreased. If the seizure continues, phenobarbital is given in a loading dose of 20 mg/kg at a rate of 1 mg/kg per minute (maximum dose of 50 to 75 mg per minute). An additional dose of 10 mg/kg of phenobarbital may be given if necessary. Significant side effects include depressed consciousness, apnea, and hypotension; these complications are more pronounced in the presence of benzodiazepines.

Table 173-4 Antiepileptic Drug Therapy for Status Epilepticus

REGIMEN	DRUG	INITIAL DOSE MG/KG	RATE	REPEAT DOSE	TIME TO STOP SEIZURE	COMMENTS
1	Lorazepam *or* Diazepam	0.05–0.1 IV/IO (max 8 mg) 0.2–0.5 IV/IO/PR (max 10 mg)	2 mg/min 2 mg/min	q 15 min (twice) q 15 min (twice)	2–3 min 1–3 min	Watch for respiratory depression
2	Fosphenytoin *or* Phenytoin	20 mg PE/kg IV 20 mg/kg IV	150 mg PE/min 50 mg/min	10 mg PE/kg 10 mg/kg	10–30 min	Monitor for hypotension, arrhythmia No glucose in line
3	Phenobarbital	20 mg/kg IV	1 mg/kg/min	10 mg/kg	20–30 min	Be prepared to intubate Avoid neuromuscular blockade if possible Monitor for hypotension
4	Levitaracetam *or* Valproic acid	20–30 mg/kg IV (max 3 g) 20 mg/kg IV	5 mg/kg/min 5 mg/kg/min	No No	5 min 5 min	 Do not use if concern of underlying liver or metabolic disease
	Midazolam drip *or* Propofol *or* Pentobarbital	0.2 mg/kg bolus (max 10 mg) 1–2 mg/kg bolus 10–15 mg/kg over 1 hour	0.1 mg/kg/hr 2–10 mg/kg/hour 0.5–1 mg/kg/hour			Monitor EEG to burst suppression pattern

IO, intraosseous [administration route]; PE, phenytoin equivalent.

When status epilepticus is refractory to these medications, any of several options may be tried. Concurrent EEG monitoring is very helpful at this point. The patient should be intubated if this has not yet occurred.

One option is use of inhalational anesthetics (e.g., thiopental, 4 mg/kg IV), although this is difficult in an ED setting and is rarely used.[56] Levitaracetam (Keppra) is playing an increasing role in the management of status epilepticus. Another option is intravenous valproic acid (Depacon), 20 to 30 mg/kg (max 3 g), loaded at 5 mg/kg/minute. Valproic acid should not be used if underlying liver or metabolic disease is a possibility.

Midazolam is a safe and effective benzodiazepine that is extremely effective in terminating status epilepticus refractory to conventional agents. A bolus of 0.2 mg/kg is administered by slow intravenous injection, followed by infusion of 0.1 mg/kg per hour.[71] The dose is increased every 15 minutes as necessary to a maximum of 10 µg/kg per hour. Tachyphylaxis may occur, necessitating high doses.

Propofol also has been shown to be highly effective in the treatment of refractory status. An initial intravenous bolus of 1 to 2 mg/kg is followed by infusion of 2 to 10 mg/kg per hour.[72] Propofol is contraindicated in children on the ketogenic diet.

Pentobarbital (10 to 15 mg/kg IV given over 1 hour, followed by 0.5 to 1.0 mg/kg per hour) also is effective. However, severe hypotension, cardiovascular toxicity, and postinfusion weakness are common complications.

Nonconvulsive status epilepticus is more difficult to recognize and often requires EEG for diagnosis. Treatment is with benzodiazepines or intravenous valproic acid.[73]

Once the seizure has been effectively terminated, neuroimaging and lumbar puncture are indicated.

Disposition

Hospitalization is unnecessary for most patients after a first, brief unprovoked seizure so long as findings on the neurologic examination are normal and follow-up evaluation is possible. EEG and imaging studies can be done on an outpatient basis as necessary.

Children with simple febrile seizures can almost always be sent home. Warden and Hauser and their colleagues outlined advice to be given to families in the ED[74,75] (Box 173-10).

A child with a prolonged febrile seizure, or multiple seizures, may be given a prescription for rectal diazepam (Diastat) (0.5 mg/kg PR rounded up to the nearest 2.5 mg, to a maximum of 10 mg in young children and 20 mg in older children) after consultation with the child's neurologist or primary care physician. Instruct parents that Diastat is given *only* if a seizure continues beyond 5 minutes. Additionally, the parents should familiarize themselves with proper usage *before* an emergency. If the medication is administered, parents should call EMS for transport to the ED for further evaluation.

Children who have had a prolonged seizure or in whom the neurologic examination is not back to the child's baseline should be admitted to the hospital. If adequate follow-up evaluation cannot be arranged, or if extreme parental anxiety is a factor, hospitalization also is recommended. Children with acute symptomatic seizures other than febrile seizures usually will need to be hospitalized for appropriate management of the underlying disorder (Box 173-11).

Initiating Anticonvulsant Therapy

The decision to start anticonvulsant prophylaxis must balance the risk for recurrence of seizure against the potential complications associated with long-term medication use.

Side effects of medication are common and include sedation, dizziness, blurred vision, ataxia, gastrointestinal disturbances, and cognitive and behavioral changes. Idiosyncratic reactions include hepatotoxicity, agranulocytosis, aplastic anemia, rash, Stevens-Johnson syndrome, and serum sickness.

Two thirds of children with a first unprovoked seizure never experience a recurrence.[75] The risk of recurrence is increased

Table 173-5 Summary of Commonly Used Anticonvulsants in Children

DRUG	SEIZURE TYPE	AVERAGE DAILY MAINTENANCE (MG/KG/DAY)	THERAPEUTIC LEVEL (μG/ML)	DOSE-RELATED SIDE EFFECTS*	IDIOSYNCRATIC EFFECTS
Carbamazepine (Tegretol)	Partial, GTC	10–20	6–12	Ataxia, nystagmus vertigo,	SIADH, aplastic anemia, Stevens-Johnson syndrome, hepatotoxicity
Diazepam (Diastat)	Clusters	0.5 mg/kg rectally PRN	Not routinely measured	Respiratory depression	
Ethosuximide	Absence	15–30	40–100	Nausea, GI distress	Aplastic anemia, Stevens-Johnson syndrome
Phenobarbital	Partial, GTC	3–6	15–40	Hyperactivity, decreased IQ	Angioedema, serum sickness
Phenytoin (Dilantin)	Partial, GTC	4–7	10–20	Ataxia, nystagmus, vertigo, hirsutism, gum hyperplasia	Stevens-Johnson syndrome, aplastic anemia
Valproic acid (Depakene, Depakote)	Absence, myoclonic, atonic, GTC	15–60	40–120	Thrombocytopenia, weight gain, tremor, platelet dysfunction	Hepatotoxicity, pancreatitis, aplastic anemia, Stevens-Johnson syndrome
Gabapentin	Partial, GTC	900–3600 mg/day	Not routinely measured	Cognitive abnormalities, exacerbation of preexisting hyperactivity	
Lamotrigine	Partial, GTC, absence, Lennox-Gastaut syndrome	5–15 (1–5 if on valproic acid)	Not routinely measured	Dizziness, diplopia, ataxia	Stevens-Johnson syndrome (especially if used with valproic acid)
Levitaractam	Partial, GTC, myoclonic	20–40	Not routinely measured	Agitation, somnolence	
Topiramate	Partial, GTC, myoclonic, Lennox-Gastaut syndrome	5–9	Not routinely measured	Kidney stones, weight loss, psychomotor slowing	Hepatotoxicity, glaucoma, hyperthermia

*Not including sedation and dizziness.
GI, gastrointestinal; GTC, generalized tonic-clonic; IQ, intelligence quotient; SIADH, syndrome of inappropriate antidiuretic hormone.
Data from Flomin O, Nield L, Kamat D: Seizure medications: A review for the primary care pediatrician. Clin Pediatr 44:383, 2005; and Bourgeois BF: Broader is better: The ranks of broad-spectrum antiepileptic drugs are growing. Neurology 69:1734, 2007.

BOX 173-10 Advice to Parents about Simple Febrile Seizures

- Febrile seizures occur in 2 to 5% of all children between the ages of 6 months and 5 years.
- These seizures may appear frightening to observers but generally are harmless.
- Simple febrile seizures often occur in the first 24 hours of the febrile illness and occur only once. If the seizure recurs, your child should be reevaluated.
- A febrile seizure may be manifested by body stiffening, twitching of the face and/or arms and legs, eye rolling, jerking of the arms and legs, staring, or loss of consciousness.
- Febrile seizures generally last less than a minute but can last up to 15 minutes.
- Your child may appear not to be breathing and the skin color may become darker; if so, call 911 or emergency personnel and lay the child on the floor on his or her back. Do NOT place your fingers in the child's mouth.
- Febrile seizures do not cause brain damage or paralysis.
- A child who has febrile seizures has only a slightly increased risk of developing a seizure disorder compared with a child who never had a febrile seizure.
- Febrile seizures tend to run in families.
- Febrile seizures can recur with subsequent febrile illnesses. Medicines generally are not given to prevent simple febrile seizures.
- Using medicines such as acetaminophen or ibuprofen for fevers has not been shown to prevent febrile seizures.

From Hauser WA, et al: Risk of recurrent seizures after two unprovoked seizures. N Engl J Med 338:429, 1998.

with concomitant Todd's paralysis, neuroimaging or EEG abnormalities, developmental delay, a family history of epilepsy, a remote symptomatic seizure, or occurrence of the first seizure during sleep. If none of these risk factors is present, the 5-year recurrence risk is only 21%.[76] No evidence is available to show that early treatment with anticonvulsant medications alters the later risk of epilepsy.[77] Neither is there evidence showing that a single self-limited seizure causes neurologic sequelae, although a point of concern is that frequent brief seizures may indeed cause neurologic sequelae.[78]

Balancing the foregoing information, anticonvulsants generally are started only after a second unprovoked seizure and, if

BOX 173-11 DIAGNOSTIC ASSESSMENT OF NEONATAL SEIZURES

Metabolic Testing (Screening)
Blood glucose
Calcium
Magnesium
Electrolytes
Ammonia
Lactate
pH

Lumbar Puncture and CSF Exam
Cells
Protein/glucose
Cultures
Herpesvirus PCR assay
Lactate
Aminoacids

Neuroimaging
Head ultrasound exam
Head CT
Brain MRI

CSF, cerebrospinal fluid; CT, computed tomography; MRI, magnetic resonance imaging; PCR, polymerase chain reaction.

possible, after consultation with the patient's primary care provider or a neurologist. Keep in mind that a patient's first convulsion may not be the patient's first seizure. Absence seizures are commonly missed for long periods of time.

Patients with acute symptomatic seizures coupled with a risk factor for recurrence, such as cerebral hemorrhage, meningitis, or contusion, should be treated in the initial period with prophylactic anticonvulsants such as phenytoin or fosphenytoin. When the patient is stable, the decision to continue or discontinue treatment is made.

The choice of medication is dictated by the seizure type and syndrome and the side effect profile of the agent. Drug levels must be monitored with the older anticonvulsants, but most of the newer anticonvulsants do not necessitate monitoring.

Phenytoin, phenobarbital, valproic acid, and carbamazepine all are excellent medications for management of generalized and partial seizures. Phenytoin is a poor long-term choice in children because of the associated development over time of hirsutism, gum hyperplasia, and facial coarsening. Phenobarbital is rarely used in children older than 2 years of age because of the common occurrence of hyperactivity, sleep disturbances and lower intelligence quotient (IQ). Phenobarbital frequently is used in infants, however, because of its consistent absorption and excellent safety profile. Valproic acid is associated with a relatively high incidence of hepatotoxicity, particularly in children younger than 2 years of age; it is more effective in generalized seizures than in focal seizures. This leaves carbamazepine as the most likely choice for the management of partial epilepsy. Carbamazepine is available in a sustained-release preparation. Oxcarbazepine (Trileptal), a prodrug of carbamazepine, is available as well, and blood monitoring is not necessary with this agent.

Valproic acid commonly is the first-line agent for treatment of primary generalized epilepsy and is particularly useful with myoclonic and absence seizures. Carbamazepine and phenytoin can worsen absence seizures and myoclonus. Ethosuximide is quite effective for absence seizures, although it is not effective for convulsive seizures.

In the last decade or so, several new anticonvulsants have been approved by the U.S. Food and Drug Administration (FDA). These include gabapentin, felbamate, lamotrigine, topiramate, zonisamide, oxcarbazepine, levetiracetam and rufinamide. Their use is increasing in the pediatric population both for add-on therapy and for first-line monotherapy. Table 173-5 provides a summary of the commonly used anticonvulsants in children.

Decision to Withdraw Anticonvulsant Therapy

Many practitioners consider withdrawal of anticonvulsants if the patient has remained seizure-free for longer than 2 years.[79] The likelihood of recurrence is increased if age at onset was more than 12 years, there is a family history of epilepsy, a history of atypical febrile seizures, remote symptomatic epilepsy, or EEG abnormalities. No consensus has emerged regarding the length of time of withdrawal; medication tapers lasting anywhere from several weeks to several months have been used.

HEADACHES IN CHILDREN

Perspective

Headache is a common problem in children and adolescents. Even though a majority of patients have benign causes of headaches, which usually can be diagnosed by a careful history and physical examination, neuroimaging using CT or MRI or both may be necessary in selected cases. Proper diagnosis, treatment, and close monitoring of these patients are extremely important to ensure that no serious cause for the headache has been overlooked.

Studies of schoolchildren have indicated that 40% of children will experience a headache by 7 years of age and 75% will experience a headache by the time they are 15 and also that migraine (one of the most common causes of headache in childhood) occurs in 1% of children by 7 years and 5% of children by 15 years of age. Studies in the United States have found that the highest incidence (246 episodes per 100,000 person-years) of migraine headache is in boys 10 to 14 years of age.[80]

Principles of Disease

Several pathophysiologic theories have emerged to explain the mechanisms of headache. The *vascular theory* proposes that headaches are produced by dilation of intracranial or extracranial arteries. The change in vessel diameter triggers the auras before and the pain during a headache; the dilatation may be relieved by vasoconstrictive drugs, such as ergots. The *neuronal theory* proposes that headaches are due to a primary dysfunction of the brain; a wave of spreading neuronal depression is accompanied by decreased cerebral blood flow. Serotonin (5-hydroxytryptamine [5-HT]) may be a key mediator in this cascade of events. Serotonin agonists have been shown to relieve migraine pain. The *trigeminovascular theory* is an integrated hypothesis that combines elements of both theories. The trigeminal nerve makes synaptic connections with cerebral blood vessels, and the headache is an expression of the nerve–blood vessel interaction.[81]

Clinical Features

Headaches can be classified into five temporal patterns: acute, acute recurrent, chronic progressive, chronic nonprogressive, and mixed. An *acute* headache is new in onset and different from previous headaches; it can herald a broad range of conditions ranging from a viral illness to a subarachnoid hemorrhage.

Acute recurrent headaches can be expressed as periodic events separated by pain-free intervals. *Chronic progressive* headaches occur over weeks to months. They can signify serious medical disorders such as brain tumors or arteriovenous malformations. *Chronic nonprogressive* headaches usually occur for years and are classified as primary headaches (as opposed to secondary symptomatic headaches). *Mixed* headaches are a combination of acute recurrent headaches (migraine) superimposed on a pattern of daily chronic nonprogressive headaches.[81,82]

The primary goal of the ED evaluation is to differentiate symptomatic headaches from primary headaches such as migraine or tension headaches. The history is critical in investigating children's complaints of headache and is the most important component of the evaluation for determining the correct diagnosis. Both the patient and family members should be asked about specific factors related to the headache. Rothner has created a patient questionnaire to generate a "headache database" from which clinicians can formulate a diagnosis, which is presented in Box 173-12.[82]

In addition to the important questions in Box 173-12, the clinician must focus on a detailed history of the neurologic system to identify any related symptoms (e.g., lethargy, ataxia, seizures, weakness, visual disturbances) and a general review of other organ systems. Warning signs of symptomatic headaches include recent onset, occurrence with straining or athletic endeavors, association with neurologic symptoms, change in headache pattern, nocturnal awakening, and bilateral occipital headaches. Additional information related to the past medical history (e.g., history of recent head trauma, neurologic or psychiatric disorders, hospital admissions, medications) also is important to obtain.

The physical examination, including vital signs, must be performed in a careful manner with particular attention to those findings unique to children. Height, weight, and head circumference should be compared with standard percentiles and the child's previous growth history; a change in the rate or direction of growth may indicate the presence of an intracerebral mass or hydrocephalus. Blood pressure also should be carefully measured, with use of age-appropriate cuff size and percentiles for age. The child's head also should be auscultated for bruits associated with arteriovenous malformations, and a skin examination should be performed to look for stigmata of neurocutaneous disorders such as neurofibromatosis. The neurologic examination should begin with assessment of the child's mental status, language, and level of consciousness and also should include assessment of cranial nerves; gait analysis; cerebellar, sensory, and motor function testing; and evaluation of deep tendon reflexes. The ophthalmologic examination should include pupillary reactivity, visual acuity, extraocular movements, and funduscopy. Observation of interactions between the patient and family members also may provide clues to potential family problems, depression, or anxiety.

BOX 173-12 PATIENT QUESTIONNAIRE TO GENERATE HEADACHE DATABASE

- Do you have more than one type of headache?
- How did the headache begin?
- Was there associated trauma or infection?
- How long has the headache been present?
- Are the symptoms worsening or staying the same?
- How often do the symptoms occur and how often do they last?
- Do the headaches occur at any special time or circumstance?
- Are the headaches preceded by warning signs?
- Where does it hurt?
- What is the quality of the pain? Is there pounding or a sharp sensation?
- Do you have any associated symptoms during the headache? Abdominal pain? Is there any nausea or vomiting?
- Do you stop what you are doing during the headache?
- Do you have any other medical problems?
- Are you taking other medications?
- Are there activities that make the headache worse?
- Does any medication make the headache better?
- Does anyone in your family have headaches?
- What do you think is causing your headache?

Data from Lewis DW, Rothner DA: Headache in children and adolescents. In Johnson RT, Griffin JW, McArthur JC (eds): Current Therapy in Neurological Diseases, 6th ed. Philadelphia, Mosby, 2002

Headache Syndromes and Differential Considerations

The list of differential considerations for headache is extensive (Box 173-13).[83]

Acute Headache

The acute headache is a common problem in children and adolescents and accompanies many infectious processes. In the absence of other signs of CNS involvement (such as nuchal rigidity or alteration in level of consciousness), headaches in febrile children usually do not constitute evidence of CNS infection. In fact, nonspecific viral illnesses represent a majority of diagnoses in children presenting to the ED with an acute headache.

The most common cause of subarachnoid hemorrhage in young adults is a ruptured cerebral aneurysm. In younger children, rupture of an arteriovenous malformation that is near the subarachnoid space may cause subarachnoid and intraparenchymal hemorrhage. A common site of bleeding is the anterior cerebral artery with resulting pressure on the third cranial nerve. Varying degrees of ptosis, lateral deviation of the eye, and pupillary dilatation may be seen with this type of aneurysm.

If subarachnoid hemorrhage is suspected, CT of the head (non–contrast-enhanced) should be performed as soon as possible. If the CT scan does not show subarachnoid blood, a lumbar puncture must be performed, because head CT findings are normal 5 to 10% of the time, especially if only a small

BOX 173-13 DIFFERENTIAL DIAGNOSIS FOR HEADACHE

Aneurysm/arteriovenous malformation
Congenital malformation (e.g., Dandy-Walker syndrome)
Hydrocephalus
Hematoma—subdural, epidural (acute), intraparenchymal
Hypertension
Infectious: viral illness, abscess, meningitis, encephalitis
Metabolic
Neoplasm
Pseudotumor cerebri
Subarachnoid hemorrhage; berry aneurysm rupture
Toxic (medication, cocaine abuse, analgesia rebound)
Trauma

Data from May A, Goadsby PJ: The trigeminovascular system in humans: Pathophysiologic implications for primary headache syndromes of the neural influences on the cerebral circulation. J Cerebr Blood Flow Metab 19:115, 1999.

amount of bleeding has occurred. The first and last samples taken in the lumbar puncture are examined for cells to eliminate the possibility of a "traumatic tap" (in which the number of red blood cells would be expected to decrease by the last tube) and the presence or absence of xanthochromia.

Localized acute headaches commonly are due to sinusitis, otitis media, dental disorders, or traumatic head injury. Dental disorders usually are accompanied by pain localized to the teeth, gums, or jaw. Temporomandibular joint dysfunction usually is associated with unilateral pain in the ear, jaw, or mouth. Headache associated with trauma must always be carefully investigated for the possibility of subdural or epidural hematomas, fractures, and leptomeningeal cyst—a "growing" skull fracture in a child 3 years of age or younger with a history of recent trauma. Ophthalmologic problems such as astigmatism, refractory errors, eye strain, or squint also are occasionally responsible for headaches in children.

Chronic-Progressive Headache

The chronic-progressive headache category is composed of disorders that cause progressive severe headaches in children. The development of increased ICP, which can be caused by brain tumors, pseudotumor cerebri, hydrocephalus, brain abscess, or intracranial bleeding, is a major problem in this category. Headache that awakens the child or is present on first awakening is a classic symptom of increased ICP. Impaired venous outflow in the supine position leads to excess fluid (blood, CSF, or edema) inside the skull, leading to increased pressure. Nocturnal or morning emesis also may suggest increased ICP. The physical examination may show symptoms or signs of increased ICP (papilledema, brisk reflexes, cranial nerve deficits, upturning toes in response to stimulation of the sole of the foot, decreased level of consciousness) as well as focal symptoms related to the location of the lesion (e.g., hemiparesis, ataxia, visual field deficits).

Headaches may be the first symptom of a brain tumor and as such occur with increasing frequency with age. In a recent study, 18% of 0- to 5-year-olds, 52% of 6- to 10-year-olds, and 68% of 11- to 20-year-olds who had brain tumors presented with headaches. Only 38% of primary brain tumors were diagnosed within the first month after the onset of symptoms.[84] More than 50% of these patients had at least three associated symptoms or signs, such as nausea, vomiting, visual effects, problems with walking, weakness, and changes in personality, school performance, or speech. The most common neurologic findings were papilledema, abnormal eye movements, ataxia, abnormal tendon reflexes, and abnormalities on the visual examination.[84]

Clinical findings with pseudotumor cerebri (idiopathic intracranial hypertension) are secondary to the increased ICP and include papilledema, sixth cranial nerve palsy, and visual field obstruction. This condition is more common in females and in younger children than in older age groups and is associated with obesity; use of outdated tetracycline; presence of otitis media or head trauma; use of vitamin A, steroids, birth control pills, or tetracycline; presence of menstrual irregularities or diseases that produce obstruction of the CSF pathways; and obstruction of the major venous sinuses. By definition, neuroimaging findings are normal. The lumbar puncture usually demonstrates elevated pressure, often greater than 20 cm H_2O, and normal CSF protein and glucose levels. Neuroimaging should precede lumbar puncture when increased ICP is suspected. Treatment can include diuretics and repeated lumbar puncture for incremental removal of CSF.[85] Hydrocephalus may be related to a previous episode of meningitis, subarachnoid hemorrhage, or head injury or may be congenital.

Brain abscess can result from meningitis, head trauma, chronic otitis media and sinusitis, or septic embolization in children with congenital heart disease. Focal neurologic signs as well as fever and headache also may be present, but the patient may look surprisingly well. Before a lumbar puncture is performed and the opening pressure is measured, CT of the head with and without contrast enhancement should be performed to determine whether a mass lesion is present. CSF findings usually include a mild leukocytosis (10 to 200 leukocytes/μL), slightly elevated protein level, and normal glucose level. The CSF smear and culture usually do not reveal any organisms.

Subdural hematoma is associated with head trauma. Symptoms include those associated with increased ICP; seizures and other focal neurologic deficits also may be present. The diagnosis is confirmed by neuroimaging. Postconcussive headaches are common. These headaches can be severe and associated with dizziness and vomiting. Chronic progressive headache also can be a symptom of systemic diseases such as hypertension, collagen vascular disease, hypothyroidism, Lyme disease, mononucleosis, or inborn errors of metabolism.

Migraine Headache

The diagnosis of migraine is based on symptoms of recurrent headaches separated by pain-free intervals. A revised classification of migraine syndromes has been made for pediatric migraine (Box 173-14).[86,87]

Migraine headaches are classified primarily into migraine with and without an aura. *Migraine without an aura*, also known as *common migraine*, is the most common type of pediatric and adolescent migraine and includes the following criteria: more than five attacks that last 2 to 72 hours (untreated), plus a minimum of two of the following criteria—unilateral location, pulsing quality, moderate to severe intensity, and aggravated by routine physical activities—and accompanied by at least nausea and/or vomiting and photophobia and phonophobia.

The main features that differentiate the pediatric from the adult migraine headache are a shorter duration (1 to 48 hours), unilateral or bilateral pain, and the presence of either photophobia or phonophobia. In children, malaise, irritability, and dizziness commonly occur before the onset of the headache.

Migraine with an aura, previously known as *classic migraine*, is diagnosed when at least two episodes occur with the following criteria: (1) reversible symptoms arising from focal cerebral or brainstem dysfunction, (2) gradual development of the headache over more than 4 minutes or several symptoms that

BOX 173-14 1998 REVISED CRITERIA FOR PEDIATRIC MIGRAINE WITHOUT AN AURA

A. Five or more attacks fulfilling features B through D below
B. Headache attack lasting 1–48 hours (*adults*: 2–72 hours)
C. Headache has at least two of the following features:
   1. Either bilateral or unilateral (frontal/temporal) location (*adults*: unilateral)
   2. Pulsating quality
   3. Moderate to severe intensity
   4. Aggravated by routine physical activities
D. At least one of the following accompanies headache:
   1. Nausea and/or vomiting
   2. Photophobia and/or phonophobia (*adults*: both photo- and phonophobia)

occur in succession, (3) aura with a duration of less than 60 minutes, and (4) the appearance of a headache either before, simultaneously with, or within 60 minutes of the aura. In children, auras most commonly are visual, but sensory, motor, and psychic auras do occur.[86]

Hemiplegic migraine is characterized by the sudden onset of hemiparesis or hemisensory loss along with headache in the contralateral hemisphere. This type of migraine is seen more frequently in children than in adults. Even though symptoms usually last for hours or days, affected persons rarely are left with permanent deficits. *Ophthalmoplegic migraine* is characterized by severe unilateral eye pain and headache, followed by ipsilateral third nerve palsy of variable degree. Less commonly, the fourth and sixth cranial nerves may be affected. *Basilar artery migraine*, also common in children, manifests with a combination of visual symptoms (e.g., transient bilateral blindness, blurred vision) and visual hallucinations, vertigo, ataxia, loss of consciousness, and drop attacks. An *acute confusional state* consists of a change in personality, orientation, or behavior. The *Alice in Wonderland syndrome* includes perceptions of distortion in body images and shapes. Objects appear either much larger (macropsia) or smaller (micropsia) before, during, or after a headache.

Migraine variants are common. *Abdominal migraine* is characterized by recurrent abdominal pain, nausea, vomiting, and recurrent headaches. Benign paroxysmal vertigo is manifested as the sudden onset of vertigo, pallor, and nystagmus. *Paroxysmal torticollis* is defined as recurrent episodes of head tilt associated with headache, nausea, and vomiting. Of note, this is a diagnosis of exclusion. A child with a head tilt, vomiting, and headache must first be evaluated for a posterior fossa lesion. *Ocular migraine* is characterized by transient monocular visual blurring to blindness with bright flashes of light.

Epilepsy and migraine headache are distinct clinical syndromes, yet they share several characteristics such as aura, vertigo, nausea, pallor, loss of consciousness, drowsy postictal state, confusion, and transient focal neurologic deficits. The incidence of seizures is higher in patients with migraine than in the general population. The differentiation of these two clinical entities may be difficult in certain cases. Headache as the sole manifestation of a seizure is uncommon; however, headaches frequently may follow tonic, tonic-clonic, and brief complex partial seizures. Bilateral frontal throbbing headaches also may follow episodes of status epilepticus. Further neurologic evaluation including EEG may occasionally be necessary to try to distinguish between these two syndromes.

Chronic Nonprogressive Headache

Chronic nonprogressive headache commonly is seen in the adolescent population. Included in this category of headache are muscle contraction headache, depressive equivalents, and conversion headaches. The International Headache Society classification of headaches refers to these types of headaches as *tension headaches*. The symptoms of this type of headache include bilateral or unilateral; nonthrobbing, pressing, or band-like tightness of mild to moderate intensity; and the absence of nausea, vomiting, and aura. These headaches are further classified as either episodic (10 to fewer than 15 episodes/month lasting 30 minutes to 7 days) or chronic (more than 15 episodes/month for greater than 6 months).

Cluster Headache

Cluster headache is a distinctive headache syndrome more commonly seen in male patients. The syndrome rarely is seen in those younger than 10 years of age. Cluster headache is characterized by one to several attacks recurring each 24 hours, over several weeks to months, with headache-free periods between the cluster headaches. The headache-free periods may last from months to years. The pain is throbbing, severe, and unilateral; occurs over the same orbitotemporal region; and is associated with ipsilateral scleral injection, lacrimation, nasal stuffiness, and, less often, partial Horner's syndrome. The pain lasts 30 minutes to several hours and can occur at any time of day or night.

Diagnostic Strategies

The diagnosis of a specific headache syndrome usually is determined by the history and physical examination. The primary goal of the ED evaluation is to eliminate the possibility of an intracranial lesion or serious extracranial pathologic condition. Skull radiographs and EEG are of limited value in this setting for the routine evaluation of children with chronic headaches.

Radiology

CT of the head and cranial MRI are excellent studies to evaluate patients with headaches.[88,89] MRI is particularly useful in detecting abnormalities in the sella turcica, temporal lobes, posterior fossa, and cervicomedullary junction. MRI also is better at detecting arteriovenous malformations and low-grade tumors. In general, MRI provides superior anatomic detail compared with CT scan. However, a patient cannot be closely monitored during MRI. Therefore, CT is the modality of choice in the potentially unstable patient and for the detection of acute bleeding. Indications for the use of neuroimaging are presented in Box 173-15.[85]

Laboratory and Special Procedures

Lumbar puncture occasionally is helpful in the evaluation of patients with headache. If the possibility of a mass lesion is a concern (as suggested by history of early-morning headaches

BOX 173-15 INDICATIONS FOR RADIOLOGIC IMAGING IN PATIENTS WITH HEADACHE

Strongly Indicated If . . .
- Abnormal neurologic examination findings
- Signs and symptoms of elevated intracranial pressure
- Meningeal signs plus focal neurologic findings or altered mental status
- Progressive and/or new neurologic signs
- Significant head trauma
- Severe nocturnal headaches that awaken the patient from sleep or are present on awakening
- Severe (characterized by patient as "worst headache of my life") headaches of increasing frequency and duration
- Presence of ventriculoperitoneal shunt
- Chronic progressive headache

Consider If . . .
- Headache or vomiting on awakening
- Unvarying location of headache, especially occipital
- Persistent headache plus no family history of migraine
- Neurocutaneous syndrome
- Age younger than 3 years (limited verbal skills)

Data from Qureshi F, Lewis D: Managing headache in the pediatric emergency department. Clin Pediatr Emerg Med 4:159, 2003.

and vomiting or focal neurologic findings on physical examination), radiologic imaging should precede the lumbar puncture. The lumbar puncture is a necessary procedure to determine the presence of an infectious process, hemorrhage, or pseudotumor cerebri.

In a patient with suspected chronic progressive headaches, the headaches may be a symptom of a systemic disease. Laboratory tests that may be considered include CBC; urinalysis; erythrocyte sedimentation rate determination; antinuclear antibody assay; liver function studies; thyroid function studies; serum lipid assay and determination of serum magnesium, lactate, and pyruvate concentrations; and a Lyme disease titer.

Management

Treatment of primary childhood headaches requires attention to initial pharmacologic management as well as reassurance, removal of potential triggering factors, and initiation of a behavioral management program. A headache diary is important to help the patient identify potential triggers and the effects of medications. Common triggers include reduction in sleep, perimenstrual stress, missed meals, and foods such as caffeine, chocolate, processed meats, alcohol, hard cheeses, red wine, monosodium glutamate, yeast extracts, nuts, figs, aspartame, and sauerkraut. Children with primary headaches are not hospitalized for care unless the diagnosis is uncertain and a serious cause of secondary headache is being considered.

Migraine

Treatment of migraine headache includes analgesics, vasoconstrictors, sedatives, triptans, antiemetics, and other modalities.[91-94] The patient should be placed in a quiet and safe environment. Simple analgesics and rest are the first line of treatment for patients with migraine as well as nonmigraine headache. These medications include acetaminophen (10 to 15 mg/kg per dose, 650 to 1000 mg for children 12 years of age and older) and the nonsteroidal anti-inflammatory drugs (aspirin, 10 to 15 mg/kg per dose, 650 to 1000 mg for patients 12 years and older; ibuprofen, 5 to 10 mg/kg/dose, 400 mg for those 12 years and older; or naproxen, 2.5 to .0 mg/kg per dose, 250 to 300 mg for those 12 years of age and older, to a maximum daily dose of 1250 mg).

For severe migraine episodes, more potent analgesics may be needed. These include ketorolac tromethamine (Toradol), a nonsteroidal anti-inflammatory which can be used parenterally in children who are vomiting (0.5 mg/kg IV or IM every 6 hours, to a maximum dose of 30 mg); codeine (0.5 to 1.0 mg/kg per dose every 4 to 6 hours orally, to a maximum dose of 60 mg); and oxycodone (0.05 to 0.15 mg/kg PO per dose every 4 to 6 hours, to a maximum dose of 5 mg every 6 hours). Combination medications, such as Fiorinal (butalbital, aspirin, and caffeine), Fioricet (butalbital, acetaminophen, and caffeine), and Midrin (isomethetpene, acetaminophen, dichloralphenazone) also are effective. The dose is 1 or 2 capsules in children older than 12 years of age. Caution should be used in prescribing these medications. In addition to producing an analgesic effect, these medications may produce alterations of emotional state, sedation, and psychological dependence.

In the adolescent population, vasoconstrictor drugs are used less commonly than in the adult population. Antiemetic agents, although not as well studied in the pediatric as in the adult population, also may be considered. This group includes promethazine (in children: 0.25 to 0.5 mg/kg per dose IM or PR every 4 to 6 hours as needed; in adults: 12.5 to 25 mg every 4 to 6 hours as needed); metoclopramide (oral, IV) 0.5–2 mg/kg per dose PO or IV q 4–6 hours (<10 mg); and prochlorperazine (in children weighing more than 10 kg or older than 2 years of age: PO or PR 0.4 mg/kg per 24 hours, divided, three to four times per day, or IM 0.1 to 0.15 mg/kg per dose, three to four times per day). Dystonic reactions with antiemetics are more common in children, so these agents must be used with caution in this population. Brousseau, in one of the few pediatric randomized clinical trials examining the efficacy of prochlorperazine compared with ketorolac for the treatment of acute migraine, found that by 60 minutes, a greater reduction in headache pain was obtained in the prochlorperazine group—even though 30% of patients in each group experienced some recurrence of headache symptoms.[95]

Sumatriptan is a selective 5-HT_1 receptor agonist that can mediate cerebral vasoconstriction and block inflammatory response and can be administered orally, intranasally, or subcutaneously. A recent review of medication trials of triptans in children with migraine highlighted the important finding that randomized clinical trials found no difference in outcome between the control and the experimental groups.[90] In another pediatric study, however, a 78% response rate was obtained within 60 minutes using a single subcutaneous administration of 0.06 mg/kg.[91] Finally, nasal sumatriptan (5 to 20 mg, repeated in 2 hours, to a maximum daily dose of 40 mg) has been shown to be effective in the adolescent population,[92] along with oral preparations of 25 to 50 mg (repeated in 2 hours, to a maximum daily dose of 200 mg). Sumatriptan should be avoided in persons with cardiac disorders or hypertension and in patients who have received an ergot alkaloid in the preceding 24 hours. Other newer 5-HT_1 agents such as zolmitriptan (Zomig) (at doses of 2.5 mg intranasally and 5 mg PO) compare favorably with sumatriptan. Cluster headaches, which are brief and may not respond to oral therapy, can be treated with inhalation of oxygen at 4 to 5 L per minute, the ergot alkaloid Cafergot, or sumatriptan.[82]

The use of pharmacologic agents for prophylaxis in children with migraine headache requires careful observation and follow-up evaluation by the child's primary care physician. The indications for use of these medications include more than two to three headaches per week and interference with lifestyle, particularly missed schooldays or inability to participate in social activities. In keeping with or perhaps reflecting the high spontaneous remission rate of childhood migraine, the placebo effect of many medications is very high. Controlled studies are extremely limited. Medications that have been used include propranolol (initiated slowly at a dose of 2 to 4 mg/kg per day, divided, three times a day; contraindicated in asthma patients), amitriptyline (initiated at a dose of 25 mg at bedtime for adolescents; a baseline ECG is recommended), calcium channel blockers, anticonvulsants (particularly valproic acid), cyproheptadine, and naproxen sodium. Cyproheptadine, valproic acid, and naproxen are available in liquid form, which is a valuable feature in the pediatric population. Methysergide should be avoided in children owing to serious side effects, including retroperitoneal fibrosis. Amitriptyline may be useful for adolescents with a diagnosis of migraine and muscle contraction headaches and in depressed children with headaches.

■ PEDIATRIC ATAXIA

Perspective

Ataxia comes from the Greek word *ataktos* meaning "lacking order" and describes a pathologic abnormality of organization or modulation of movement.[96]

Pathophysiology

Ataxia can be caused by congenital abnormalities or can be acquired. Congenital ataxia is associated with CNS abnormalities. Acquired ataxia can be acute, episodic, or chronic. The chronic ataxias are usually caused by inherited metabolic or genetic disorders. Most commonly, ataxia is caused by cerebellar dysfunction. Lesions in the corticospinal tract or dorsal columns of the spinal cord may also be causative.

Clinical Features

Most children with ataxia are seen in the first few days after onset, usually because of a refusal to walk, unsteadiness of arm movements, or the sudden development of a wide-based "drunken" gait. The history should identify any recent infection, injury, inadvertent drug ingestion, or other family members with the same problem. Mental status usually is normal in cases of postinfectious ataxia. If it is abnormal, the possibility of ingestion, acute disseminated encephalomyelitis, or stroke should be considered. Nystagmus is common if the cerebellum is affected. Papilledema or cranial nerve palsies suggest hydrocephalus or a lesion.[97]

Differential Considerations

In children, 40% of ataxia cases are caused by acute cerebellar ataxia (Box 173-16). Boys are more commonly affected, with the highest incidence at ages 2 to 4 years. Seventy percent of patients have a history of recent illness with multiple causative agents, but varicella virus is the most common, with up to 26% of cases associated with varicella. Coxsackievirus and echovirus are other etiologic agents. The disease is thought to be due to an autoimmune phenomenon leading to cerebellar demyelination.[97] Symptoms and signs are maximal at onset, with the extremities more seriously affected more than the trunk and ranging from unsteadiness and wide-based gait to complete inability to walk. Mental status is normal, and nystagmus is common. Fever and seizures are uncommon.[9]

Acute postinfectious demyelinating encephalomyelitis can also cause ataxia and occurs in the recovery phase of a viral illness or vaccination. It is distinguished from acute cerebellar ataxia by alteration in consciousness and multifocal neurologic deficits as well as fever and the frequent occurrence of seizures.[96,97]

Brainstem encephalitis can involve the cerebellum, causing ataxia in association with focal neurologic abnormalities and respiratory irregularities. Etiologic agents include Epstein-Barr virus, *L. monocytogenes*, and enteroviruses.[96]

Up to 32% of cases of acute childhood ataxia are due to drug toxicity, most commonly from ingestion of anticonvulsants, benzodiazepines, alcohol, or antihistamines and less commonly from exposure to organic chemicals or heavy metals. The ataxia usually is accompanied by lethargy, confusion, and inappropriate speech or behavior. Nystagmus may be present as well.[96]

Approximately 45 to 60% of all childhood brain tumors arise in the brainstem or cerebellum and can manifest with slowly progressive ataxia. Acute decompensation can occur with the development of hydrocephalus or hemorrhage into the lesion.[96]

Head injuries with cerebellar contusion or hemorrhage can cause ataxia. In patients with neck injuries, ataxia can be caused by vertebral artery dissection. Posterior circulation strokes are rare in children but should be considered after neck trauma with possible vertebral artery dissection as a cause for the ataxia.[98]

The opsoclonus-myoclonus syndrome consists of ataxia, rapid chaotic multidirectional eye movements, and myoclonic jerks of the extremities, head, trunk, and face. Most commonly, this is seen as a presenting manifestation of neuroblastoma or ganglioneuroblastoma in which the ataxia is thought to be due to a paraneoplastic autoimmune phenomenon involving cross-reactivity of tumor and cerebellar antigens.[96] Spontaneous vertebral artery dissections also have been reported in children without a known history of trauma.[98]

Ataxia can be seen in patients with basilar migraine and can be associated with vertigo, hemiparesis, cranial nerve dysfunction, nausea, vomiting, or headache.[96]

Loss of sensory input to the cerebellum can cause a sensory ataxia. Clinical manifestations will include a Romberg sign, decreased deep tendon reflexes, and impaired proprioception and vibration sense. Fifteen percent of patients with Guillain-Barré syndrome have sensory ataxia. In the Miller-Fisher variant of Guillain-Barré syndrome, the triad of ataxia, areflexia, and ophthalmoplegia of vertical gaze is characteristic.[96]

Transient ataxia can be present in the ictal or postictal phase of seizures.[96] Inborn errors of metabolism also can manifest with ataxia, which can develop acutely or be intermittent, depending on dietary intake or the presence of other illness. Such disorders should be considered when ataxia is accompanied by lethargy, encephalopathy, vomiting, diarrhea, or unusual body odor. Defects in urea acid cycle enzymes called aminoacidurias, as well as defects in pyruvate and lactate metabolism, can cause such signs and symptoms. Other inherited disorders such as Niemann-Pick, Tay-Sachs, and Wilson's diseases also can cause ataxia.[96] Repeated attacks of ataxia also can be the presenting manifestation of multiple sclerosis.

A discussion of all of the genetic disorders that can cause ataxia would be too vast to be included here, but the two most common genetic disorders are Friedreich's ataxia and ataxia telangiectasia.

Friedreich's ataxia is a disorder of autosomal recessive inheritance characterized by progressive gait and limb disturbance. It is caused by mutation in the gene encoding a mitochondrial protein, frataxin, that results in loss of gene function. Affected patients demonstrate dysarthria, lower limb areflexia, and proprioceptive sensory loss and high-arched feet (pes cavus). Most patients are unable to walk by the age of 30 years. The

BOX 173-16 ETIOLOGY OF CHILDHOOD ATAXIA

- Acute cerebellar ataxia
- Acute postinfectious demyelinating encephalomyelitis
- Brainstem encephalitis
- Drug ingestion
- Guillain-Barré syndrome
- Metabolic disorders
  - Amino acidopathies
  - Mitochondrial disorders
  - Organic acidopathies
  - Urea cycle disorders
- Migraine headaches
- Multiple sclerosis
- Neoplasm
- Opsoclonus-myoclonus syndrome
- Recurrent and chronic genetic ataxias
- Seizures
- Stroke
- Vertebral artery dissection

Adapted from Ryan M, Engle E: Acute ataxia in childhood. J Child Neurol 18:309, 2003.

most common cause of death is cardiomyopathy causing intractable congestive heart failure, as well as respiratory compromise from severe kyphoscoliosis.[96]

Ataxia telangiectasia is a disorder of recessive inheritance caused by gene mutation that manifests as a truncal ataxia in infancy that leaves most patients wheelchair bound by the age of 12 years. Oculocutaneous telangiectasias usually appear by age 3 to 5 years. These patients also demonstrate dysarthria, nystagmus, dystonic posturing, myoclonic jerks, and accelerated aging. They have deficient IgA and decreased IgE and IgM levels. They suffer from frequent sinus and pulmonary infections, as well as a 50- to 100-fold risk for development of leukemia and lymphoma. The mean age at death from this disorder is 20 years.[99]

Diagnosis

The key to making the diagnosis is taking a complete history and performing a thorough physical examination. In particular, testing cerebellar function by looking for dysmetria and dysdiadochokinesia is helpful.[100] Urine and serum toxicologic studies are the laboratory tests most likely to prove diagnostic. CT and MRI findings usually are normal in patients with postinfectious ataxia, but demyelination, tumor, hydrocephalus, or traumatic injuries may be identified. CSF analysis may show mild pleocytosis or lymphocytosis in acute postinfectious ataxia; findings are normal in most other cases. EEG is recommended for patients with altered consciousness and fluctuating clinical signs. A pattern of epileptiform discharges or slowing is seen in 66% of children with acute cerebellar ataxia. EEG also can diagnose nonconvulsive or convulsive seizures. The EEG pattern is normal in the opsoclonus-myoclonus syndrome. Electromyography may be helpful if sensory ataxia is suspected and may help diagnose Guillain-Barré syndrome. Urinary catecholamines can be assayed to diagnose neuroblastoma. Testing for newborn errors of metabolism includes a CBC; liver function tests; measurement of blood ammonia, lactate, pyruvate, and ketone levels; and determination of acid-base status. Other tests include plasma and urinary amino acid assays, urine organic acid assay, determination of serum biotinidase level, and CSF lactate assays. Genetic or other specialized testing also may be required. In the absence of developmental delay or positive family histories, however, these investigations for inborn errors of metabolism are unlikely to be helpful.[100]

Management

Children with ataxia usually require hospital admission for a complete evaluation. Consultation with a pediatric neurologist should be sought for patients in whom the cause of the ataxia is not evident on the ED evaluation.

Most children with acute cerebellar ataxia recover completely. Improvement is seen within a week and complete recovery in 3 months for 50% of children. Sixty-six percent to 90% recover completely. Some children exhibit persistent gait disturbances, ataxia, and delayed speech development. Evidence is lacking for improved outcomes with immunosuppressive therapies. Recovery is slower from acute postinfectious demyelinating encephalopathy. Corticosteroids may hasten recovery. Relapse can occur in up to 10% of children. Most children recover fully, but some are left with significant permanent sequelae. Brainstem encephalitis should be treated with broad-spectrum antibiotics effective against *L. monocytogenes*; acyclovir should be included to provide coverage for varicella and other viruses until an organism is discovered. Patients with Guillain-Barré syndrome will need to be hospitalized and may require intravenous immunoglobulins and plasmapheresis to reduce circulating antibodies.

PEDIATRIC VERTIGO

Perspective

Vertigo is defined as an illusion of movement, a sensation that the external world is revolving around an individual (objective vertigo) or that the affected person is revolving in space (subjective vertigo). Vertigo is well recognized to occur in the pediatric age group and has many potential causes.

Pathophysiology

Disease processes that affect the balance of the vestibular, visual, and proprioceptive systems can cause vertigo by impairing the neural activity of the vestibular nucleus. Diseases of the ear, the eighth cranial nerve, the neck, the brainstem, or, rarely, the eye all can lead to vertiginous symptoms. Vertigo is characterized as *central* or *peripheral*, depending on whether the cause is in the CNS or not.

Clinical Features

Vertigo often manifests with dizziness. There may be a history of sudden falls, grasping for support, or unwillingness to move. Review of symptoms should include those related to the ear, such as otalgia, hearing loss, or tinnitus. Other important historical features that should be asked about include headache, loss of consciousness, head trauma or barotrauma, and family history of migraine and seizure disorders.

Diagnostic Strategies

To determine the cause of vertigo, patients can be divided into those who have hearing loss and those who have normal hearing. In the group with hearing loss, further characterization of the loss as conductive or sensorineural in character and identification of the presence of trauma, and whether the causative disorder involves the CNS or the peripheral nervous system from the labyrinth or eighth cranial nerve, will help in diagnosis (Fig. 173-1).

Differential Considerations

Although not as common in the pediatric age group as in adults, vertigo has many potential causes (Box 173-17).[101] It usually is helpful to separate those conditions that cause vertigo into those with and those without associated hearing loss.

Benign paroxysmal vertigo of childhood is defined by the repeated occurrence of vertiginous episodes lasting seconds to minutes, with occasional vomiting, which usually remits spontaneously for months to years. The most frequent cause of benign paroxysmal vertigo of childhood is a migraine headache,[99] with vertigo occurring as the aura of an episode.[109]

Patients with basilar artery migraines also present with vertigo; hemiparesis; ataxia; palsies of the third, sixth, or seventh cranial nerve; drop attacks; and blindness in various combinations followed by migraine headache. Children with benign paroxysmal vertigo of childhood or basilar migraines usually have a family history of migraine headaches.[101]

Benign positional vertigo is rare in children, and the earliest age at which it has been reported is 11 years.[101] It is believed to be due to an otolith that has moved out of its normal position in the utricle and can occur spontaneously as well as after trauma.

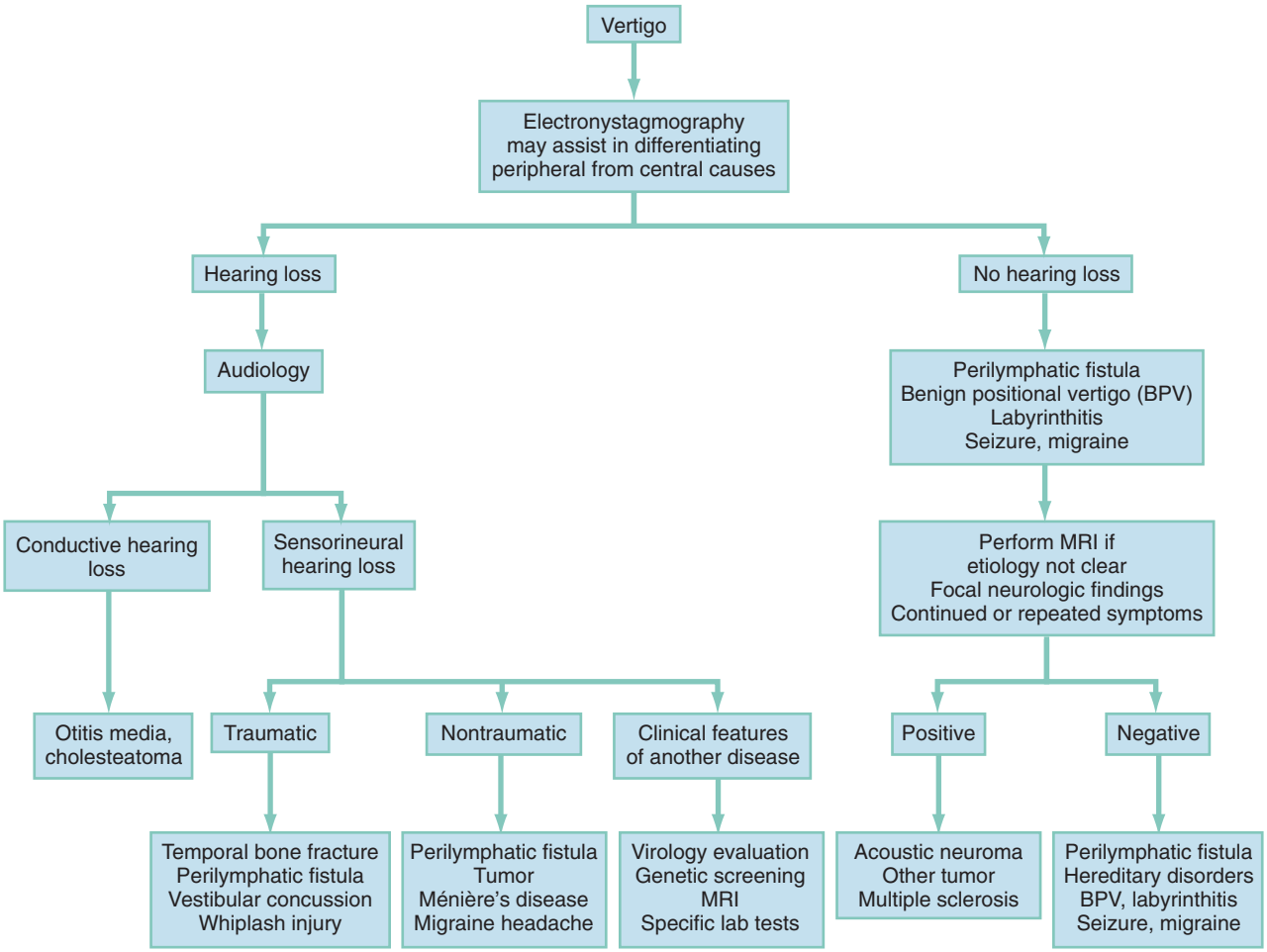


Figure 173-1. Vertigo evaluation. MRI, magnetic resonance imaging. (Adapted from Rudolph C, Rudolph A [eds]: Rudolph's Pediatrics, 21st ed. New York, McGraw–Hill, 2003, pp 1246–1247.)

BOX 173-17 ETIOLOGY OF PEDIATRIC VERTIGO

Central vertigo
Atrioventricular malformations
Brain abscess
Chiari malformations
Demyelinating disorders
Encephalitis
Meningitis
Migraine headaches
Neoplasm
Seizures
Trauma
Peripheral vertigo
Alport syndrome
Benign paroxysmal torticollis
Benign paroxysmal vertigo of childhood
Benign positional vertigo
Cholesteatoma
Diabetes mellitus
Down syndrome
Labyrinthine dysplasia/aplasia
Labyrinthine concussion
Labyrinthitis
Lyme disease
Otitis media—suppurative and serous
Ototoxins
Ocular disorders
Pendred syndrome
Perilymphatic fistula
Radiation
Stenosis of the internal auditory canal
Syphilitic inner ear disease
Thyroid disease
Trauma
Usher syndrome
Vestibular neuronitis
Waardenburg syndrome

Adapted from Rudolph C, Rudolph A (eds): Rudolph's Pediatrics, 21st ed. New York, McGraw-Hill, 2003, p 1248.

Ménière's disease, a syndrome with a combination of vertigo, fluctuating hearing loss, and tinnitus, is responsible for 1.5 to 4% of cases of pediatric vertigo.[102,103]

Vestibular neuronitis manifests with vertigo without hearing loss. A viral infection is thought to be the cause. Sixty percent of patients have a preceding cold. It manifests with severe vertigo that resolves in a few days, after which the child will have vertigo only with rapid head movements, which persists for weeks or months until central compensation occurs.[104]

Labyrinthitis is an inflammatory process involving the inner ear membranous labyrinth. It manifests with vertigo, hearing loss, and tinnitus. Viruses such as cytomegalovirus, rubella virus, and rubeola virus are etiologic agents. Bacterial labyrinthitis also can occur, usually associated with meningitis.[105] Lyme disease and syphilis each may cause vertigo if the inner ear is affected.[105] Neurofibromatosis can manifest with vertigo if it involves the superior vestibular nerve. Café-au-lait spots should be looked for. Other genetic syndromes also are associated with vertigo (see Box 173-16).[105]

Ototoxic drugs such as aminoglycosides and chemotherapeutic drugs can be a cause of vertigo, usually in association with hearing loss (Box 173-18).[105] Cerebellar and brainstem lesions on occasion also manifest with vertigo. Cranial nerve deficits associated with vertigo may indicate a lesion or tumor.[104]

Multiple sclerosis can have vertigo as one of the symptoms, and vertigo is the presenting symptom in 5 to 12% of cases.[104] Endocrine disorders such as thyroid disease or diabetes mellitus have rarely been reported to cause vertigo.[104]

In post-traumatic vertigo, disturbances of cochlear and vestibular functions are the most common etiology of late-onset vertigo from head injury in children. If labyrinthine damage is caused by trauma (labyrinthine concussion), vertigo, gait unsteadiness, and swaying toward the affected side are present along with nausea and vomiting. Symptoms and signs subside over a period of 4 to 6 weeks. Signs of vestibular dysfunction may be present many years after the injury. Positional nystagmus with the quick component toward the uninvolved side usually is present. Vestibular concussions can cause vertigo without hearing loss following a blow to the parietal-occipital or temporal-parietal region. It normally is continuous for several days followed by improvement but may reoccur intermittently with certain head positions. Displacement of an otolith is thought to be responsible.[106]

Temporal bone fractures (especially transverse) also may cause vertigo by injury to the eighth cranial nerve or the otic capsule. It also may cause sensorineural hearing loss.[107] Whiplash injuries to the neck also can cause vertigo, with up to 50% of patients experiencing hearing loss or tinnitus. Post-traumatic migraine and seizures also can cause vertigo and occur in 5 to 7% of patients with closed head injuries.[106]

Perilymphatic fistula manifests with sensorineural hearing loss of sudden onset. It frequently is associated with congenital cranial deformities and congenital abnormalities of the ear. However, barotrauma (flying, extreme coughing, retching, or straining) or direct trauma also can be a cause. There is leakage of fluid from the oval or round window into the middle ear. Having the patient perform a Valsalva maneuver may precipitate vertigo. Hennebert's sign, which consists of nystagmus and vertigo after negative pressure is induced in the ear by a pneumatic otoscope, may be a feature.[101] Treatment usually consists of surgical repair.

Ocular disorders such as convergence insufficiency, strabismus, and amblyopia have been reported to cause a sensation of vertigo, and treatment of these disorders will eliminate the vertigo in children.[107]

BOX 173-18 CAUSES OF VERTIGO WITH AND WITHOUT HEARING LOSS

Hearing Loss

Conductive

Otitis media with effusion

Chronic suppurative otitis media or cholesteatoma should be considered

Sensorineural

Perilymphatic fistula

Tumor

Ménière's disease

Migraine headache

Genetic syndromes

Temporal bone fracture

Vestibular concussion

No Hearing Loss

Acute Vertigo

Perilymphatic fistula

Benign positional vertigo

Seizure

Labyrinthitis

Recurrent or Chronic Vertigo

Acoustic neuroma

Multiple sclerosis

Diagnostic Strategies

For most patients, the final diagnosis for the cause of the vertigo may not be able to be made in the ED. A complete physical examination including otologic and neurologic evaluation is important. Looking for nystagmus and cerebellar testing are especially critical. Having the child hop as well as stand from a seated position on the floor with eyes open and closed may reveal vestibular dysfunction. Looking for physical signs of other disease processes such as café-au-lait spots in neurofibromatosis may aid in diagnosis. If a Valsalva maneuver or Hennebert maneuver initiates vertigo, the cause probably is a perilymphatic fistula.

Vertical nystagmus is always from a central cause. Nystagmus from peripheral causes tends to extinguish or diminish after rapidly repeated stimulation, whereas central nystagmus does not. Helpful laboratory tests in the vertiginous patient include glucose and electrolyte assessment, thyroid function tests, and viral titers or serologic studies (e.g., for Lyme disease or syphilis), as the physical examination dictates.[101,105] The Hallpike-Dix positioning maneuver may help to diagnose benign positional vertigo.[104] A CT or MRI scan is indicated only in cases of central vertigo.

Management

Management of the vertiginous patient depends on the underlying cause, which may not be evident in the ED.[108] For acute symptomatic relief, vestibular suppressants such as meclizine or diazepam may be helpful. Otoliths causing inappropriate stimulation may be restored to their proper place by Epley's maneuver.[101,109] Vestibular rehabilitation exercises that encourage patients to move the head while viewing a stimulus may assist in vestibular adaptation and reduce symptomatology.[101] Follow-up including examination, testing, and treatment by a neurologist or an otolaryngologist for vertiginous patients is

recommended. Highly symptomatic children may need to be admitted to the hospital.

SYNCOPE

Perspective

Syncope is defined as a sudden, reversible, typically brief loss of consciousness and muscle tone (between 20 and 60 seconds) that usually reverses without intervention. The exact incidence of syncopal episodes is not known, but 15 to 25% of children and adolescents experience one episode by young adulthood.[110,111] The peak incidence occurs between 15 and 19 years of age, and females are affected more frequently than males. The presentation of these events can be quite frightening to the patient and those who witness them (parents, teachers, peers, coaches). Gordon and coworkers found that in a group of pediatric patients presenting to the ED, a mean of six diagnostic tests were performed per patient, 40% of these patients were admitted to the hospital, and total charges averaged $3000 per patient, yet significant pathologic conditions were found in less than 10% of the patients.[112]

Principles of Disease

The causes of syncope can be divided into autonomic, cardiac, and noncardiac. The most common cause of syncope is reflex syncope (also called autonomic, vasovagal, neurocardiogenic, or vasodepressor syncope or fainting). Venous pooling and decreased preload associated with prolonged standing normally are compensated for by reflex tachycardia and increased sympathetic tone. Patients who are prone to syncope demonstrate a cardioinhibitory response causing bradycardia or a vasodepressor response causing hypotension or, most commonly, a combination of both. Patients with cardiac syncope have decreased CBF resulting from poor cardiac filling or contractility, elevated afterload, or cardiac arrhythmias.

Clinical Features

Patients can experience syncope during intercurrent illnesses, with mild dehydration, during menstruation, or after vigorous exertion. In those with situational syncope, typical triggers may include emotion, pain, hyperventilation, shower, cough, swallowing, urination, or defecation. Before the event, they may experience dizziness, light-headedness, weakness, nausea, chest discomfort, palpitations, blurred vision, headache, tremulousness, and anxiety. After the event, loss of consciousness is brief (usually for less than 20 seconds), and the patient is described as ashen-appearing, with sweating and coolness of the extremities.[113] Other examples of conditions associated with neurally mediated syncope are postural orthostatic tachycardia syndrome, chronic fatigue syndrome, and pandysautonomia.[114] Patients with postural orthostatic tachycardia syndrome and pandysautonomia experience orthostatic palpitations rather than straightforward syncope, do not appear healthy between events, and complain of fatigue and exercise intolerance. Patients with pandysautonomia also exhibit thermoregulatory impairment, sweating, and bowel dysfunction.[114] Although cardiac causes of syncope are rare, they can be life-threatening and should be suspected when the episode occurred during exercise or physical activity. Noncardiac causes include seizures. Helpful features to differentiate seizures from syncope include the following: seizures usually occur in a supine rather than an upright position, convulsions occur before rather than after the loss of consciousness, and warm, flushed or cyanotic-appearing skin, rather than pale and sweaty skin, is characteristic.

Diagnosis

Evaluation of the patient begins with obtaining a description of the event, previous episodes, and past personal and family history. A detailed description of the event and particular note of any presyncopal symptoms or signs such as sweating, nausea, pallor, visual changes, or onset with a rapid change in position can suggest vasovagal syncope. A thorough physical examination with determinations of orthostatic heart rate and blood pressure performed with the patient in supine, sitting, and standing positions and a detailed neurologic examination are essential. A baseline electrocardiogram should be obtained to rule out structural heart disease or an arrhythmia. If the history, physical examination, and electrocardiogram are typical for a neurally mediated event, further testing is not usually required. Family history of sudden death, early infarction or arrhythmia, previous personal history of fatigue with a known arrhythmia or heart defect, syncope preceded by chest pain or palpitations, occurrence of syncope during exercise, occurrence of syncope without a prodrome, recurrent syncope (more than two or three episodes), and a syncopal event with neurologic sequelae all warrant additional testing.[115]

Differential Considerations

Cardiac causes of syncope may be life-threatening. Such disorders include underlying structural abnormalities of the heart, such as cardiomyopathies (hypertrophic, dilated, and restrictive), postoperative congenital heart anatomic changes (Mustard, Fontan), congenital coronary artery abnormalities, myocarditis, aortic stenosis, and pulmonary hypertension. Other cardiac abnormalities include those classified as electrical disorders, such as long QT syndrome, Wolff-Parkinson-White syndrome, atrioventricular block, idiopathic ventricular fibrillation, or Brugada's syndrome. Patients with an underlying cardiac abnormality merit further investigation, which may include 24- to 48-hour Holter monitoring, an echocardiogram, or exercise stress testing. Tilt-table testing can be used after diseases such as myocarditis, hypertrophic cardiomyopathy, and long QT syndrome have been ruled out, because such testing in this subgroup can have fatal consequences.

Common noncardiac causes of syncope include neurologic disorders (seizures, migraines, tumor, and vertigo), breath-holding spells, electrolyte abnormalities (hypoglycemia), hyperventilation (hypocapnia), endocrinopathies, toxins (carbon monoxide), and drugs of abuse.

Management and Disposition

Syncope is a common pediatric problem and usually has a benign, neurally mediated cause. Certain groups of patients may have an increased risk for cardiac syncope and should eventually be referred to a pediatric cardiologist for evaluation. These include athletes, patients with eating disorders or chronic fatigue, persons who use illicit substances, and survivors of congenital heart disease.[111]

The approach to management of patients with neurocardiogenic syncope is primarily one of education, involving avoidance of potential triggering events (hot, crowded environments; volume depletion) and recognition of the early signs and symptoms to allow timely maneuvers to abort the syncopal episode (e.g., assuming a supine position, ingesting fluids, leg-crossing). The patient and the family must be reassured that these events are not life-threatening. A simple approach is to

encourage liberal fluid intake and to increase dietary salt intake. In a subgroup of patients with recurrent syncope or recurrent dizziness, however, a trial of an appropriate medication may be warranted. No large pediatric randomized studies have been conducted to investigate this application of such medications, which include beta-blockers, fludrocortisone, selective serotonin reuptake inhibitors, and alpha-agonists.[115]

KEY CONCEPTS

- Signs and symptoms of bacterial meningitis vary by age and can include nonspecific manifestations such as irritability and lethargy in infants and young children.
- A careful and detailed history is instrumental in determining whether or not an event was a seizure. If the event was a seizure, the history should delineate what type of seizure occurred (partial or generalized) and whether the clinical event fits into a known epilepsy syndrome.
- Status epilepticus constitutes a neurologic emergency that carries high morbidity and mortality rates. Usual initial treatment is with lorazepam followed by fosphenytoin or phenytoin.
- For patients experiencing a febrile seizure, ED management should include a review with family members of appropriate first aid, use of antipyretics, recurrence risk and risk for epilepsy, and follow-up care with the child's primary care physician.
- The possibility of acute symptomatic, or provoked, seizures should always be considered, particularly because many of the causes of such seizures are treatable.
- A majority of headaches in children have nonserious causes that usually can be diagnosed by a careful history and physical examination.
- Radiologic evaluation using CT or MRI, or both, may be necessary to rule out secondary causes of headache such as intracranial hemorrhage, subarachnoid hemorrhage, brain abscess, or brain tumor.
- A toxicology screen is the test with the highest diagnostic yield for acute onset ataxia in children. The most common cause of benign positional vertigo in children is a migraine headache. Vertigo with hearing loss has a significantly different etiology than vertigo with no hearing loss.
- Most children with ataxia require hospitalization for evaluation and diagnosis.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 174 Musculoskeletal Disorders

Kemedy K. McQuillen

PERSPECTIVE

Each year there are more than 11 million pediatric injury-related emergency department (ED) visits, 14.3% of which are due to fractures and dislocations.[1]

As a result of the physiologic and anatomic differences between children and adults, pediatric patients are susceptible to problems that do not affect the adult population. An understanding of these differences helps the emergency physician appropriately diagnose and treat musculoskeletal complaints in children. This chapter reviews the general principles and physiology of the pediatric musculoskeletal system, highlights the more common pediatric fractures, and describes musculoskeletal problems specific to the pediatric population.

PRINCIPLES OF DISEASE

Anatomy and Physiology

Several factors distinguish the pediatric musculoskeletal system from that of the adult. The most striking difference is the presence of a physis or growth plate. The physis is made up of proliferating cartilage cells between the metaphysis and epiphysis. Because it is composed of cartilage, the growth plate is the weakest part of the bone and is more likely to separate before the adjacent tendon or ligament tears. Accordingly, sprains are less frequent in the pediatric population than in the adult population, and physeal injuries are common.

Another factor that influences pediatric musculoskeletal injuries is the presence of a thick, physiologically active periosteum that is easily stripped from the bony cortex. When injuries occur, the periosteum often is torn on the convex side (i.e., the reverse aspect of a bone subjected to a deforming force) while remaining intact on the concave side (the aspect directly incurring the force of injury). In any case, the periosteum acts as a tether to reduce the amount of fracture displacement and, when it remains intact, aids in fracture reduction. The great bone-forming potential of the periosteum also facilitates the healing process: Callus formation is vigorous, and nonunion almost never occurs.

Growing bone is more porous, more pliable, and less dense than adult bone. These characteristics result in less strength, thus making children more susceptible to fractures. However, although it takes less force to cause deformation, pediatric bone is more likely to buckle when compressed or to bow when bent. Finally, because the bones are still growing, the potential for remodeling is greater with metaphyseal fractures. Growth can compensate for postreduction imperfections in both apposition and alignment, with deformities occurring in the plane of motion having the greatest potential for remodeling.

Fracture Patterns

As with fractures in adults, description of pediatric fractures includes the bony location (diaphysis, metaphysis, physis, or epiphysis), configuration, relationship of fracture fragments to one another (angulation and displacement), and relationship of fracture fragments to adjacent tissue (open or closed). The inherent differences between pediatric and adult bone result in fracture configurations that are not found in the adult population. Pediatric fractures can be classified as follows:

- *Plastic deformation*: Bone is bowed with no obvious cortical disruption.
- *Torus fracture* (buckle fracture): Buckling of bone without cortical disruption; it tends to occur because of compression failure of the bone at the metaphyseal-diaphyseal junction (Fig. 174-1). These fractures may be immobilized with a splint or cast or, if they involve the distal end of the radius, a Futura splint (Velcro wrist splint)[2] or Prelude[3] backslab. The Futura splint and Prelude backslab can be removed by the family or primary care provider in 3 to 4 weeks, thereby obviating the need for orthopedic follow-up. Buckle fractures also may be treated with a soft cast[4,5] or a plaster splint.[6]
- *Greenstick fracture*: Bone and one cortex are disrupted; the periosteum on the fracture's compression side remains intact (Fig. 174-2).
- *Complete fracture*: The fracture propagates completely through the bone; included are transverse (Fig. 174-3), spiral (Fig. 174-4), oblique and comminuted (Fig. 174-5) fractures.

The presence of a relatively weak cartilaginous physis in growing bone makes physeal injury common in the skeletally immature. Although injuries to the physis can occur at any age, they are more common during rapid skeletal growth. The Salter-Harris classification system is the most frequently used tool to describe physeal injuries. This classification system is based on the extent of involvement of the physis, epiphysis, and joint (Table 174-1). Types I and II Salter-Harris injuries (Figs. 174-6 and 174-7) do not involve the germinal layer of

Figure 174-1. Buckle fracture of the distal end of the radius. Treatment consists of immobilization for 3 to 6 weeks.

Figure 174-2. Greenstick fracture of the radius. This fracture may need to be completed to achieve an anatomic reduction.

Figure 174-3. Transverse fractures of the radius and ulna.

Figure 174-4. Spiral fracture of the femur.

Figure 174-5. Comminuted fractures of the tibia and fibula.

Figure 174-6. Salter-Harris type I fracture of the fibula. The only finding on examination was point tenderness over the distal end of the fibula. Radiographic findings include soft tissue swelling over the growth plate, with minimal physeal widening.

Table 174-1 Salter-Harris Fracture Classification

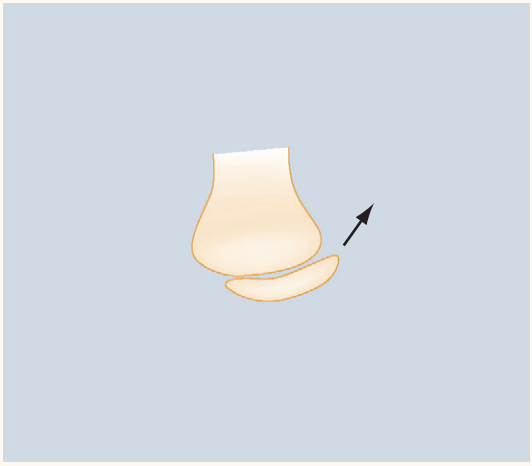
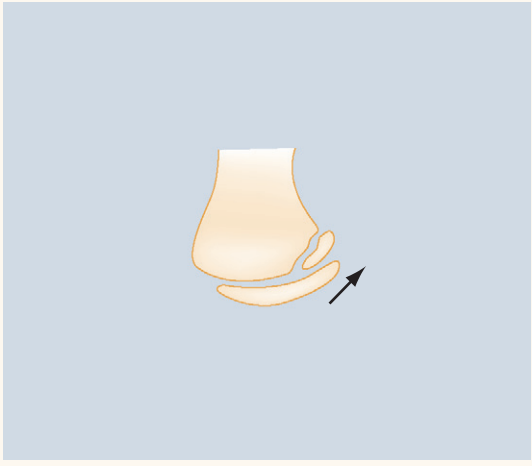
Type I	Fracture extends through the physis (see Fig. 174-6)	
Type II	Fracture extends from the physis into the metaphysis (away from the joint space)	

Table 174-1 Salter-Harris Fracture Classification—cont'd

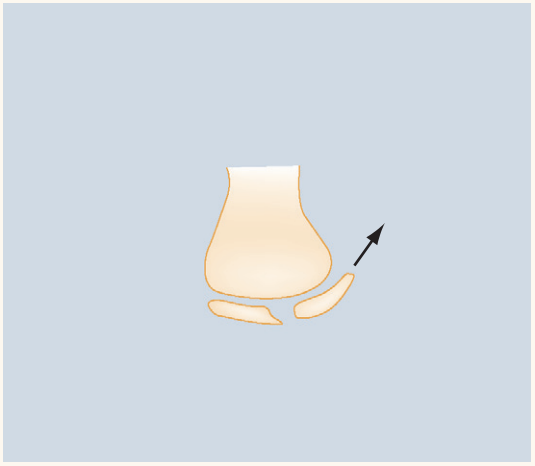
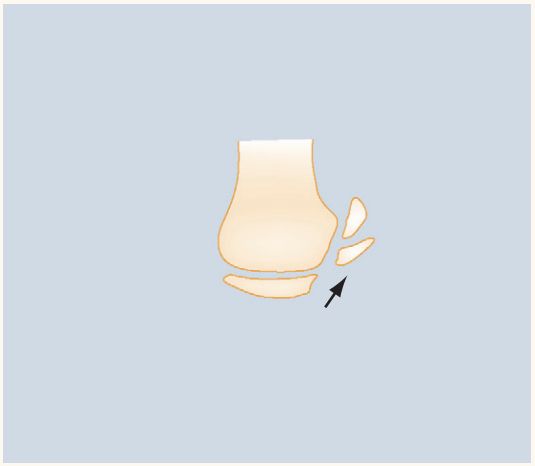
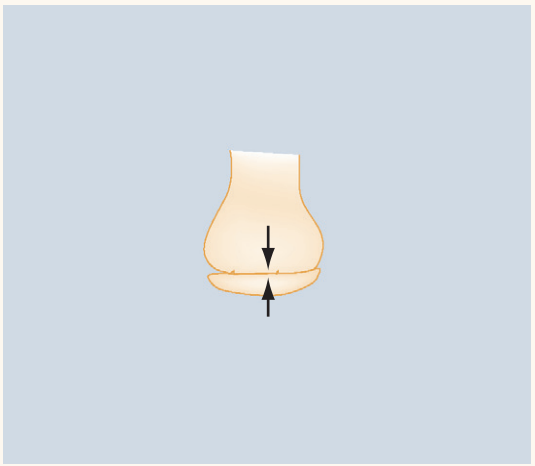
Type III	Fracture extends from the physis into the epiphysis (toward the joint space) (see Fig. 174-8)	
Type IV	Fracture extends from the physis into the metaphysis and epiphysis (see Fig. 174-9)	
Type V	Crush injury of the physis (see Fig. 174-10)	

Figure 174-7. Salter-Harris type II fracture of the radius. The triangular piece of the metaphysis is referred to as the Thurston-Holland segment.

Figure 174-9. Salter-Harris type IV fracture of the proximal phalanx.

Figure 174-8. Salter-Harris type III fracture of the middle phalanx.

Figure 174-10. Salter-Harris type V fracture of the distal end of the radius. The crush injury has obliterated the physis.

the growth plate; therefore, the risk for growth arrest is small. In general, the higher the Salter-Harris classification, the greater the damage to the growth plate and the greater the likelihood of growth arrest or limb length abnormalities (Figs. 174-8 to 174-10 [Salter Harris III to V]). Type II fractures are the most common Salter-Harris injury and account for approximately three fourths of all growth plate injuries.

SPECIFIC DISORDERS

Clavicle Fracture

The clavicle is one of the most frequently broken bones in children.[7] The physis of the clavicle does not close until the age of 23 to 25 years and is at risk for injury until that time. Midshaft fractures account for approximately 85% of all clavi-

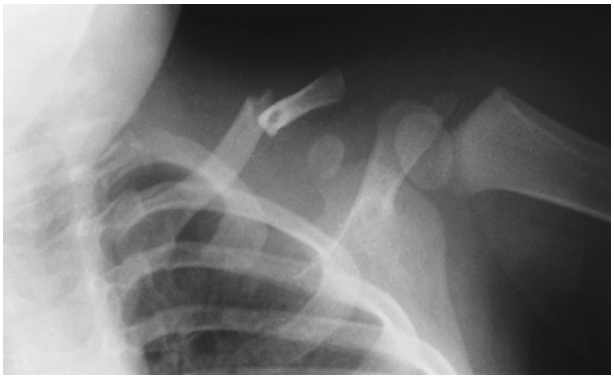


Figure 174-11. Fracture of the middle third of the clavicle.

cle fractures; distal and proximal fractures account for approximately 10% and 5%, respectively. The usual mechanism of injury is a fall on the shoulder or, less commonly, direct trauma to the bone itself. The child typically supports the affected side with the other hand and tilts the head toward the side of the fracture. Physical examination reveals point tenderness at the fracture site, with or without an obvious bony deformity. With a minimally displaced fracture, shoulder motion may be tolerated. Otherwise, range of motion of the shoulder is limited by pain. Although complications are rare, the proximity of the clavicle to the great vessels and brachial plexus calls for a thorough neurovascular evaluation; severe posterior dislocations can cause compression of the trachea, subclavian vessels, or brachial plexus. The proximity to the pleural cap also may result in pneumothorax.

An anteroposterior (AP) radiograph of the clavicle (Fig. 174-11) confirms the diagnosis. If clinical suspicion is high and the AP view does not reveal a fracture, a 30-degree cephalic view can be helpful. Specialized imaging studies are rarely needed, although computed tomography (CT) and duplex ultrasonography may be considered with proximal, posteriorly displaced fractures.[8]

Clavicle fractures do not require anatomic reduction for healing or function; therefore, treatment is directed at maintaining comfort with splinting, ice, and analgesics. Distal clavicular fractures in adolescents, however, may require surgical management. Figure-of-eight splinting helps bring the clavicle out to length, relieves muscle spasm, and minimizes motion at the fracture site. Previously the treatment of choice, immobilization with the figure-of-eight splint has fallen out of favor with some physicians because of the risk for brachial plexus palsy with long-term use. Alternatively, a sling with or without a swath can be used to provide comfort by supporting the upper extremity and relieving the suspensory forces usually maintained by the clavicle. Most clavicle fractures heal without any problems, except for the development of bony callus at the fractures site; the younger the patient, the greater the potential for remodeling of this deformity. As the fracture stabilizes and the comfort level improves, range-of-motion exercises can be started, with gradual progression in intensity. Younger children generally require shorter periods of immobilization (2 to 4 weeks) than those used in adolescents and adults (4 to 8 weeks). Rehabilitation includes early range of motion and strengthening of the rotator cuff. Patients may return to contact sports when there is no tenderness at the fracture site or pain with ROM and they have achieved normal strength.

Although surgical intervention is uncommon with clavicle fractures, orthopedic consultation should be obtained if the fracture is open, if there is neurovascular compromise or associated rib cage fractures, or if there is greater than 100% displacement of the fracture fragment with severe skin tenting.

Clavicle fractures also can occur during childbirth and represent more than 90% of obstetric fractures. They occur equally in boys and in girls and on the right and on the left sides. Symptomatic neonatal clavicle fractures in the immediate postnatal period are characterized by "pseudoparalysis" of the affected arm; asymptomatic fractures may not be noticed until 10 days of age, when the bony callus becomes apparent. The diagnosis is made with radiographs.

Table 174-2 Gartland Classification for Extension-Type Supracondylar Fractures

Type I	Nondisplaced fracture
Type II	Displaced fracture with intact posterior cortex
Type III	Displaced fracture with no cortical contact
	A: Posteromedial rotation of the distal fragment
	B: Posterolateral rotation of the distal fragment

Modified from Gartland JJ: Management of supracondylar fractures of the humerus in children. Surg Gynecol Obstet 109:145, 1959.

Supracondylar Fractures of the Humerus

Supracondylar fracture is the most common elbow fracture in the pediatric population. Most such fractures are sustained in children younger than 8 years. Until that age, the tensile strength of the ligaments and joint capsule is greater than that of the bone itself; the weaker bone therefore yields to the stronger ligament complex around the joint.[9]

Supracondylar fractures are classified as flexion or extension according to mechanism of injury. The *extension* type of fracture constitutes 95% of all supracondylar fractures and typically results from a hyperextension injury to the elbow incurred in a fall onto the outstretched arm. In this injury the olecranon is forcefully driven into the olecranon fossa, and the forces are concentrated in the supracondylar area. This mechanism results in failure of the anterior cortex and displacement of the distal fragment posteriorly in relation to the proximal fragment. With extension-type supracondylar fractures, the degree of displacement and continuity of the cortex are further defined by the Gartland classification[10] (Table 174-2). In the less common *flexion* type of supracondylar fracture, the elbow is flexed when it hits the ground, and energy is transferred from the posterior aspect of the proximal end of the ulna to the distal end of the humerus. This mechanism results in a supracondylar fracture with anterior displacement of the distal fragment and failure of the cortex posteriorly.

Children with supracondylar humerus fractures may present with anything from mild swelling and elbow pain to a grossly displaced humerus. Gentle palpation is useful in determining the site of injury; however, manipulation should be avoided because movement may cause further neurovascular damage. Children with extension-type supracondylar fractures hold the affected arm in extension with an S-shaped configuration of the elbow and exhibit a prominence at the olecranon. Children with flexion-type supracondylar fractures hold the arm in flexion and exhibit an empty space where the olecranon should be. In all cases it is important to carefully assess distal neurovascular status. Motor and sensory function should be evaluated by assessing the radial, ulnar, and median nerves (Table 174-3). Two-point discrimination on the fingers provides a sensitive means of assessing sensory status: an abnor-

Table 174-3 Neurologic Examination of the Distal Upper Extremity

	EXAMINATION COMPONENT	
NERVE	**MOTOR**	**SENSORY**
Radial	Wrist extension	Thumb and first finger web space
Ulnar	Wrist flexion and adduction	Little finger
Median	Wrist flexion and abduction Thumb opposition	Thumb, index, and middle fingers Radial aspect of palm of hand
Anterior interosseous	Distal phalanx flexion (thumb/first finger)	None

Table 174-4 Sequence of Ossification around the Elbow: CRITOE

OSSIFICATION CENTER	AGE AT APPEARANCE	AGE AT CLOSURE
*C*apitellum	6–12 months	14 years
*R*adial head	4–5 years	16 years
Medial (*I*nternal) epicondyle	5–7 years	15 years
*T*rochlea	8–10 years	14 years
*O*lecranon	8–9 years	14 years
Lateral (*E*xternal) epicondyle	9–13 years	16 years

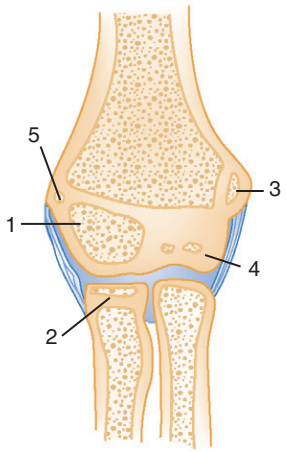


Figure 174-12. Ossification centers of the elbow: 1, capitellum; 2, radial head; 3, medial epicondyle; 4, trochlea; 5, lateral epicondyle. (From Connolly JF: DePalma's Management of Fractures and Dislocations. Philadelphia, WB Saunders, 1981.)

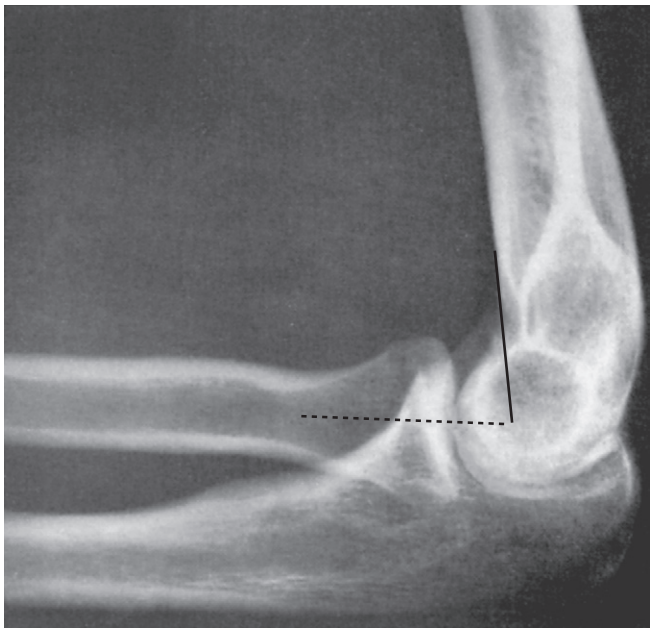


Figure 174-13. Lateral radiograph demonstrating the bony relationships in a normal elbow. The anterior humeral line *(solid)* and proximal radial line *(dashed)* bisect the capitellum. (From Weissman BN, Sledge CB: Orthopedic Radiology. Philadelphia, WB Saunders, 1986.)

mal value (greater than 6 mm) indicates a deficit. Vascular assessment should include evaluation of radial and brachial pulses and capillary refill of the hand. Patients should have ongoing assessment for the development of compartment syndrome of the forearm. With pain on flexion or extension of the fingers, forearm tenderness, or pain that is disproportionate to the injury, compartment pressures should be measured immediately. Unrecognized ischemic injury can result in Volkmann's ischemic contracture, which is characterized by fixed elbow flexion, forearm pronation, wrist flexion, metacarpophalangeal (MCP) joint extension, and interphalangeal flexion.

Radiographic evaluation of any elbow injury should include an AP view of the extended elbow and a lateral view of the flexed elbow. If these views do not show a fracture but clinical suspicion is high, oblique views are helpful. Even with proper radiographs, diagnosis of a pediatric elbow fracture can be difficult. The elbow is largely cartilaginous during early childhood, and the six secondary centers of ossification around the elbow can camouflage or be mistaken for fractures (Fig. 174-12). These ossification centers can be remembered by the mnemonic CRITOE—*c*apitellum, *r*adius, *i*nternal (medial) epicondyle, *t*rochlea, *o*lecranon, and *e*xternal (lateral) epicondyle. The approximate ages at which these sites ossify may be estimated at 1, 3, 5, 7, 9, and 11 years, respectively (Table 174-4).

Bony relationships are helpful in evaluating a radiograph for the presence of a supracondylar fracture (Fig. 174-13). A true lateral view should demonstrate a figure-of-eight appearance of the distal humerus with bisection of the capitellum by the anterior humeral line. If the capitellum falls posterior to this line, an extension-type supracondylar fracture is likely. In all views, the proximal end of the radius and radial neck should point to the capitellum. Baumann's angle also is helpful in diagnosing subtle supracondylar fractures[11] (Fig. 174-14). This angle is formed by a line drawn to follow the growth plate of the capitellum transected with a line that runs perpendicular to the axis of the humerus. The angle should be approximately 75 degrees. Baumann's angle should be the same in both elbows, and differences between elbows can be used to detect subtle supracondylar fractures. Postreduction alterations in Baumann's angle reliably predict the final carrying angle.[12]

Fat pads also provide a means for detecting occult supracondylar fractures. A lateral radiograph with the elbow flexed at 90 degrees may show an anterior fat pad protruding from the coronoid fossa. This finding is normal unless the pad is bulging

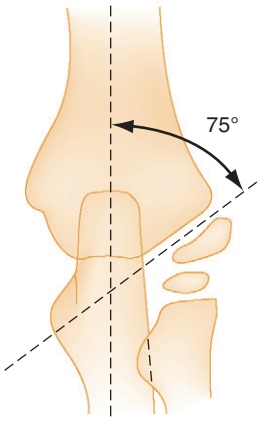


Figure 174-14. Baumann's angle in a normal elbow on an anteroposterior radiograph. (From Worlock P: Supracondylar fractures of the humerus: Assessment of cubitus varus by the Baumann angle. J Bone Joint Surg Br 68:755, 1986.)

Figure 174-15. Lateral radiograph of a supracondylar fracture with an anterior fat pad "sail sign" and a posterior fat pad.

or in the shape of a ship's sail. This "sail sign" may indicate fluid in the joint, although alone it may not be a reliable predictor of a fracture. The posterior fat pad, however, sits snugly within the olecranon fossa and should never be seen unless there is a fracture around the elbow. In this case, blood pushes the fat pad laterally, thereby making it visible on a lateral radiograph of the elbow. Accordingly, visualization of a posterior fat pad suggests the presence of an occult fracture around the elbow. The presence of a posterior fat pad without an obvious fracture warrants obtaining oblique views of the elbow (Fig. 174-15), splinting, and follow-up.

Plain radiographs usually are sufficient for diagnosing supracondylar fractures; however, if the diagnosis remains in question after AP, lateral, and oblique radiographs are obtained, ultrasound imaging may be useful in infants,[13,14] and magnetic resonance imaging (MRI) may be useful in older children.[15] With strong clinical suspicion, some orthopedic surgeons bypass MRI in favor of an intraoperative arthrogram.

ED treatment of supracondylar humeral fractures is determined by displacement and neurovascular status. A pale, pulseless cold hand mandates emergency consultation with an orthopedic surgeon. If an orthopedic surgeon is unavailable and the vascular supply has not been restored, reduction should be attempted (Fig. 174-16). If necessary, reduction can be performed by a single operator: With the patient supine, the shoulder held in 90 degrees of forward flexion, and the elbow slightly flexed, both hands are placed on the arm proximal to the fracture and both thumbs are placed on the posterior aspect of the fracture fragment. Then, while the thumbs are directed distally, the fragment is lifted onto the distal metaphysis. The return of blood supply is marked by the hand becoming warm and pink. If perfusion does not improve, another reduction may be attempted, with care taken to not entrap the brachial artery and median nerve. Multiple attempts at reduction increase the likelihood of neurovascular injury and swelling; therefore, no more than two reductions should be attempted. A supracondylar fracture with a pulseless hand that is warm and pink does not need to be reduced and should be splinted as it lies so that vascular status is not further compromised. The elbow should be splinted in relative extension, because too much flexion in conjunction with swelling may obstruct the brachial artery and contribute to limb ischemia.

Gartland type I fractures can be splinted in the ED with the arm maintained in 90 degrees of flexion and neutral rotation. Hospital admission is not required, but referral to an orthopedic surgeon the next day is recommended. Gartland type III fractures require immediate orthopedic consultation and should be treated by either closed reduction and percutaneous pinning or open reduction and internal fixation in the operating room. Treatment of a partly displaced type II fracture is controversial. Some surgeons reduce and pin it in the operating room, whereas others perform closed reduction and keep the arm immobilized in a cast. Treatment of displaced supracondylar fractures by closed reduction and casting is associated with higher complication rates than is treatment by closed reduction and pinning; therefore, most such fractures are treated with pinning and casting for 3 to 4 weeks.

The primary complications of supracondylar fractures are related to neurovascular injury. Type III fractures are at greatest risk, with neurovascular compromise occurring in as many as 49% of patients.[16] The median nerve is involved in half of the cases and is associated with posterolateral displacement. The radial nerve is involved in almost one third of patients and is associated with posteromedial displacement. Brachial artery injuries, including arterial entrapment, laceration, intimal tears, or compression from compartment syndrome, occur in approximately 40% of patients and are found with either type of displacement. Fortunately, the brachial artery has many branches around the elbow, and flow to the forearm and hand can be maintained even when the brachial artery is injured.

Despite the frequency of neurovascular deficits immediately after the accident, most nerve palsies are caused by stretching or contusion and resolve spontaneously. The typical course for nerve injuries is complete resolution. Although motor function usually returns within 12 weeks, sensory function may not return for 6 months or longer.[17] If clinical or electromyographic evidence of nerve recovery is lacking after 5 months, exploration and neurolysis are indicated.[18] Volkmann's ischemic contracture (contracture deformity of the fingers, hand, and wrist) and permanent limb disability are the end result of untreated vascular injury. This complication is extremely rare and easily prevented by close observation and evaluation for the development of compartment syndrome. A few supracondylar fractures heal with a "gunstock" deformity; however, the combination of varus, hyperextension, and medial rotation of the limb is not a functional problem and, except in severe cases, requires no treatment. Severe cases can be corrected by humeral osteotomy.

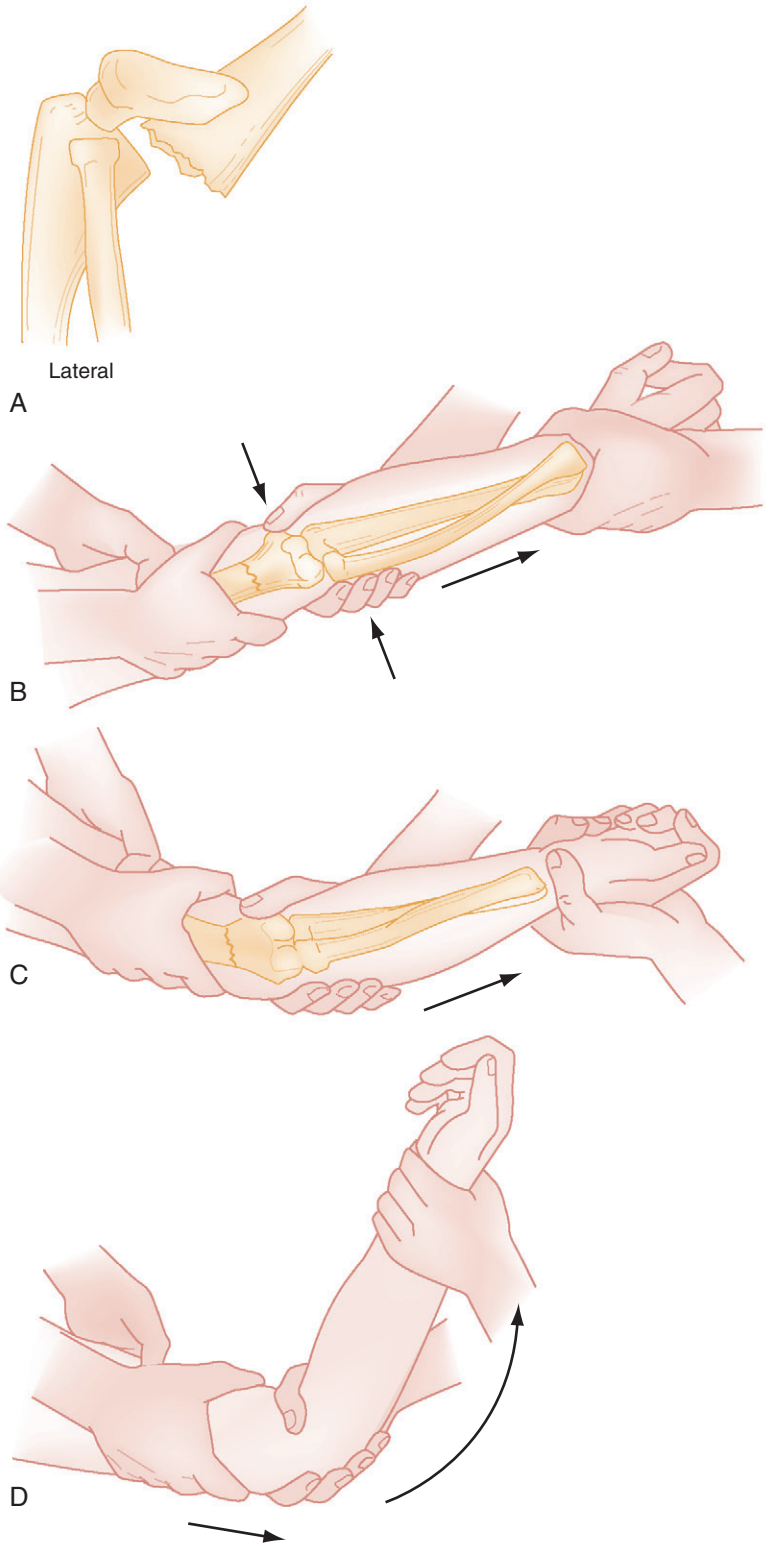


Figure 174-16. Steps in reduction of a displaced supracondylar fracture, seen in **A. B,** The assistant fixes the arm of the patient while the physician grasps the patient's wrist and applies steady traction in line with the long axis of the arm while keeping the forearm in the neutral, thumb-up position. **C,** If the distal fragment is displaced laterally, it is pushed inward with the physician's other hand. If it is displaced medially, it is pushed outward. Throughout manipulation, traction is maintained. **D,** After length is restored and the medial and lateral displacement is corrected, the physician's thumb is placed over the anterior surface of the proximal fragment with the fingers behind the olecranon, and the elbow is gently flexed. The arm is then immobilized with the forearm pronated; laterally displaced fractures are immobilized with the forearm supinated. (From Geiderman JM, Magnusson AR: In Rosen P, Barkin R [eds]: Humerus and Elbow in Emergency Medicine: Concepts and Clinical Practice, 4th ed. St Louis, CV Mosby, 1998.)

Monteggia Fracture-Dislocation

Monteggia fracture-dislocations are characterized by a fracture of the proximal third of the ulna plus dislocation of the radial head. The radiographic evidence can be very subtle, with only a minor greenstick fracture or bowing of the ulna. Isolated ulna fractures are rare in children; therefore, with all such fractures, AP and lateral radiographs of the elbow should be obtained to rule out dislocation of the radial head. The radial head should align with the capitellum on all radiographs of the elbow; if it does not, then a Monteggia injury should be suspected. (A radiograph showing a classic Monteggia injury can be found online at http://www.hawaii.edu/medicine/pediatrics/pemxray/v1c15.html.)

Monteggia fracture-dislocations require urgent referral to an orthopedic surgeon for closed reduction of the radial head dislocation and repair of the ulna fracture. Complications include permanent radial head dislocation, valgus deformity of the arm, loss of pronation, and late radial nerve palsy.

Nursemaid's Elbow

In one study, radial head subluxation, or nursemaid's elbow, was the most common upper extremity injury in children younger than 6 years presenting to a pediatric ED.[19] It typically occurs when axial traction is placed on an extended and pronated arm, as when the child is pulled up or swung by the arms. It also may occur when the child falls onto the outstretched arm, sustains minor direct trauma to the elbow, or simply twists the arm. In infants, radial head subluxation can occur when an extended arm is caught beneath the infant's body while being rolled over. In pathoanatomic terms, subluxation occurs when the annular ligament becomes loosened from the head of the radius and slips into the radiocapitellar joint, where it becomes entrapped (Fig. 174-17).

Nursemaid's elbow occurs in children a few months to 5 years of age and has a peak incidence between 2 and 3 years of age.[20] It has been reported in children younger than 6 months[20] and has been seen in children as old as 9 years. This injury has a slight predilection for girls.

The history often includes an event involving a mechanism consistent with the injury followed by acute onset of arm pain that may or may not be localized to the elbow. The affected arm is held against the body, with the elbow slightly flexed and the arm pronated. Physical examination is significant for lack of swelling, erythema, ecchymosis, or deformity. Examination may reveal mild tenderness to palpation of the radial head. Pain is elicited with supination, pronation, and elbow flexion.

The diagnosis of nursemaid's elbow is made clinically, and radiographs are not necessary. If, however, significant point tenderness, swelling, or ecchymosis is present or if the history suggests another injury, such as a supracondylar fracture, radiographs should be obtained. Although not commonly used as a diagnostic procedure, ultrasound imaging may demonstrate a widened space between the radial head and the capitellum.[21]

Radial head subluxation is an orthopedic injury that is easily reduced without sequelae. Classically, the affected elbow is gripped with the clinician's thumb over the radial head, and with the other hand, the clinician flexes and supinates the patient's arm. As the radial head relocates, the clinician feels it click or "clunk" under the thumb. Hyperpronation of the forearm also is effective in reducing radial head subluxation. As is done in the flexion-supination maneuver, the child's affected elbow is held with the clinician's thumb over the radial head, but then flexion-supination is replaced with hyperpronation of the forearm. Success rates range from 80[20] to 92%[22] with supination and from 93[23] to 98%[24] with pronation. Pronation also may be less painful to the patient[24,25] and is the reduction method of choice.[24] After successful reduction, the child typically uses the arm normally within 10 minutes. This may be delayed in younger children and when the injury occurred more than 4 to 6 hours before reduction. Neither splinting nor orthopedic referral is required after a successful reduction.

Failure to reduce the subluxation of nursemaid's elbow may result from improper reduction technique; swelling of the annular ligament as a result of edema, hemorrhage, or hematoma; or disruption of the annular ligament. Persistence of the subluxation also is more likely if reduction is attempted 12 hours or longer after the injury.

If two attempts at reduction fail to restore normal use of the arm, alternative diagnoses should be entertained. Because of the similarity in clinical findings, children also should be assessed for fractures of the clavicle and elbow. If no other pathologic process is found and the child is still not using the arm, a posterior splint should be applied with the elbow kept at 90 degrees and the forearm in supination. Follow-up evaluation with an orthopedic surgeon should be arranged for the next day.

Parents should be cautioned to avoid traction on the forearm and elbow, because recurrence rates of radial head subluxation range from 5 to 39%, depending on the referral population studied.[20,22,24] With recurrent subluxations, immobilization in a posterior splint with the elbow maintained at 90 degrees and the forearm supinated may be warranted. The need for open reduction or repair of the annular ligament is exceedingly rare.

Toddler's Fracture

Toddler's fractures are oblique nondisplaced fractures caused by low-energy torsional forces applied to the very porous bone of infants and young children. Previously, it referred only to tibial fractures in children between 9 and 36 months of age, but the term is now applied more loosely. The mechanism of injury can be as mild as the child's twisting on the leg while walking or a fall from an insignificant height. In some instances, the mechanism of injury may be unknown. The child will exhibit a limp or may refuse to walk on the affected leg. Some

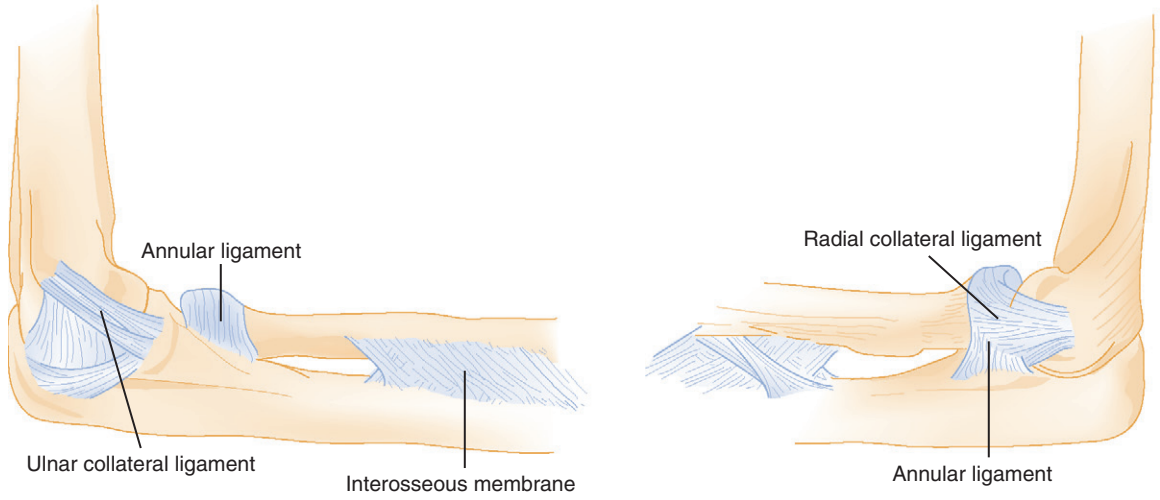


Figure 174-17. Nursemaid's elbow. In a nursemaid's elbow injury, as an axial force is applied, the annular ligament around the radial head is dislodged. The ligament is then partially dislocated into the radiocapitellar joint when the arm is released. (From Simon R, Kownigsknecht S: Emergency Orthopaedics: The Extremities, 2nd ed. E Norwalk, Conn, Appleton & Lange, 1987.)

Figure 174-18. Toddler's fracture.

children will revert to crawling and can crawl without pain. Examination may show mild swelling of the leg and point tenderness. Gentle twisting of the lower part of the leg may elicit pain.

AP and lateral radiographs may reveal a spiral or oblique fracture extending downward and medially through the distal third of the tibia (Fig. 174-18). An internal oblique radiograph is helpful if evidence of fracture is absent on the AP or lateral view. If findings on all views are negative, consideration should be given to fractures elsewhere in the limb. If no fracture is apparent, the child should be splinted for comfort and radiographs repeated in 10 days, at which time periosteal new bone or sclerosis of the fracture edges will make the fracture visible. If findings on these radiographs are negative and the child is still limping, further evaluation should be undertaken to rule out osteomyelitis and malignancy. Bone scans often are helpful in assessing a limping toddler and are more sensitive than plain radiographs for detection of fractures. Treatment of a toddler's fracture consists of use of a below-knee walking cast for approximately 3 weeks.

The presence of a spiral fracture without an appropriate history may raise concern for nonaccidental injury (i.e., child abuse). Midshaft fractures, which are more common in abused children, and tibial fractures in nonambulating children, as well as other unexplained or frequent injuries, should prompt further evaluation.

Skeletal Aspects of Nonaccidental Injury

Perspective. Fractures are the second most common manifestation of child abuse, second only to soft tissue injury, and are present in up to 70% of physically abused children. Fractures associated with child abuse occur in the very young: 50% in children younger than 12 months[26] and 94% in children younger than 3 years.[27] With child abuse, a timely and accurate diagnosis is imperative, because children who are returned to an abusive home face a 35% chance of repeated abuse and a 10% chance of death.

No fracture is pathognomonic for abuse, but certain fracture patterns are more worrisome than others. Any fracture in a child younger than 1 year, fractures at different stages of healing, and bilateral or multiple fractures indicate a need for thorough assessment for intentional (nonaccidental) injury. Injuries that are especially concerning include complex skull fractures, rib fractures, metaphyseal fractures, and vertebral fractures or subluxations. Midshaft humeral and scapular fractures are nearly always associated with abuse, as are approximately 70% of femoral fractures in children younger than 1 year.

Specific Disorders and Injuries

Diaphyseal Fractures

Although multiple fractures at different stages of healing are strongly suggestive of child abuse, the most common manifestation of child abuse is an isolated diaphyseal fracture, which occurs four times as often as classic metaphyseal fractures. The humerus, femur, and tibia are the most frequently fractured long bones; the radius and ulna are the most infrequently fractured. With the exception of supracondylar fractures, all fractures of the humerus in children younger than 3 years are strongly suggestive of abuse.[28]

Metaphyseal Fractures

Although less common than diaphyseal fractures, metaphyseal fractures are more specific for child abuse. Metaphyseal fractures most commonly affect the tibia, femur, and proximal end of the humerus. *Corner fractures* and *bucket handle fractures*, which may be the same fracture viewed in two different projections, result from violent shaking or forceful pulling or twisting of an infant's limb. The diagnosis is made by careful evaluation of high-quality plain radiographs. The tight adherence of the periosteum at the metaphysis precludes an active periosteal response, making these fractures difficult to diagnose even in the healing stages. Additionally, after healing these fractures may not be visible due to rapid bone remodeling. Bone scans, although sometimes helpful, are difficult to interpret because of the normally increased radionuclide uptake in the metaphyseal area.

Rib Fractures

Rib fractures are present in 5 to 27% of cases of child abuse, with 90% of such fractures occurring in children younger than 2 years. The young pediatric rib cage is very compliant, and considerable force is required to break a rib. Accordingly, rib fractures are seldom seen in unintentional injury and are almost never seen after cardiopulmonary resuscitation.[29,30] When present, post-resuscitation rib fractures are anterior and also may be multiple.[30] In a child younger than 3 years, the positive predictive value of a rib fracture as an indicator of intentional trauma approaches 100%.[31]

With nonaccidental injury, posterior rib fractures are most common and result from maximal mechanical stress as the rib is levered over the transverse process of the vertebral body when infants are grasped and shaken. The ribs fail mechanically at the head or neck. Abuse-related rib fractures tend to be multiple and symmetrical and may be difficult to diagnose acutely on standard radiographs. Repeating the radiographic exam at 7 to 10 days after the injury is advised if findings on the initial films are negative but the level of clinical suspicion is high. Radiographic findings include callus formation or widening of the rib neck as a result of apposition of new bone subperiosteally. Bone scans can be helpful in detecting fractures in the acute setting.

Skull fractures are the second most frequent orthopedic injury in abuse and occur more commonly in abuse cases than from unintentional trauma.[26] Eighty percent occur in infants younger than 1 year, and although complex skull fractures are more suspicious for abuse, linear skull fractures are the most common type. Standard skull radiographs may not be adequate for diagnosis and are reported to miss more than 25% of head injuries. Children who meet high-risk criteria (the presence of rib fractures, multiple fractures or facial injury, or age younger than 6 months) should undergo CT or MRI to assess for occult head injury.[32]

Periosteal New Bone Formation

Periosteal new bone formation, which is one of the most common findings in cases of abuse, reflects separation of the periosteum from the bone and may be the only manifestation of orthopedic trauma related to child abuse. It may be present with or without a fracture. It results from shaking, from acceleration-deceleration forces applied to an unsupported limb, or from forceful gripping.

Diagnostic Strategies: Radiology. Conventional skeletal radiography is the screening examination of choice in cases of suspected physical abuse. Unsuspected fractures are found in 22% of physically abused children and are more common in the very young. A complete skeletal survey is recommended for all physically abused children younger than 2 years and for all infants younger than 1 year with evidence of abuse or neglect. Complete skeletal surveys are rarely indicated in children older than 5 years; in children between 2 and 5 years of age, the need for a skeletal survey is determined on a case-by-case basis. A skeletal survey consists of an AP view of the extremities (including the hands and feet), frontal and lateral views of the thoracolumbar spine (including the ribs), and an AP and lateral skull series. In cases in which abuse is strongly suspected but radiographic findings are negative, bone scanning serves as an adjunct and is complementary to the skeletal survey in detecting injury. It is sensitive for detection of subtle rib, spine, and diaphyseal trauma, especially in the acute setting, but because the radiographic abnormalities can persist for years, it is not reliable in determining the age of the fracture.

Differential Considerations. Although most cases of intentional injury are easily diagnosed with a thorough history and physical examination, certain conditions can be confused with child abuse. Metaphyseal cupping and spurring and periosteal new bone formation are two normal variants that radiographically are almost identical to the findings in cases of child abuse. These features are seen in more than 40% of normal infants. They appear between 2 and 3 months of age and may persist until 8 months of age. These findings can be differentiated from child abuse by subtle radiographic clues: normal-variant infantile metaphyseal spurs are in continuity with normal bone and cortex, and physiologic periostitis is bilateral, confined to the diaphysis, and smooth and lamellar in appearance. Physiologic periostitis also tends to be more obvious on the medial aspect of the bone and most commonly involves the femur, although it also is seen in the humerus and tibia. Radiographic differentiation between normal variants and trauma-related injury is extremely difficult, and the clinical findings must be taken into account.

Osteogenesis imperfecta (OI), a heritable disorder of connective tissue, is an alternative cause of multiple fractures with minimal trauma. In the United States, the estimated incidence is 1 in 20,000 persons. This estimate includes cases in children in whom the condition is diagnosed within 1 year of birth but does not include milder forms of the disease that are not diagnosed until later in life. Accordingly, the true incidence of OI may be significantly higher. Most types of OI have been linked to mutations in type I collagen genes that interfere with either the synthesis or the construction of collagen subunits. Clinical features include bone fragility, ligament laxity, defective dentinogenesis, short stature, scoliosis, middle ear deafness, blue sclera and tympanic membranes, and misshapen skull. On radiographs, the bones are diffusely osteopenic, with thin cortices and attenuated trabecular patterns. The long bones have narrow diaphyses, and bowing and fractures are common (Fig. 174-19).

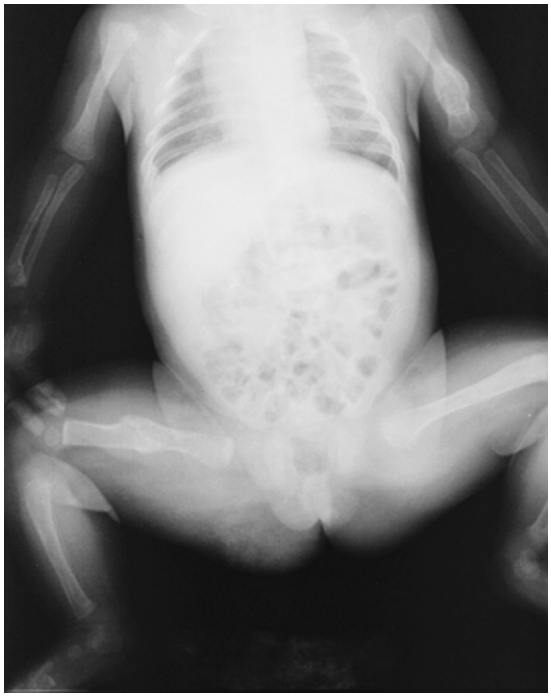


Figure 174-19. Radiograph obtained in a child with osteogenesis imperfecta. Note the narrow diaphyses, osteopenia, and multiple fractures.

Four types of OI are recognized, with clinical presentations ranging from intrauterine demise to occurrence of multiple fractures in an infant to almost complete absence of symptoms in an adult (Table 174-5). The diagnosis of OI is made on the basis of the history, physical examination, and radiographic findings. Confirmation is by skin biopsy and culture of dermal fibroblasts for evaluation of type I collagen. However, because the molecular basis for the entire spectrum of disease has not been established, up to 10% of cases of OI would be missed with skin biopsy alone.[33] ED management of children with OI includes appropriate orthopedic referral for fractures and primary care referral for hearing evaluation.

In addition to musculoskeletal complaints, children with OI are predisposed to abdominal pain and neurologic abnormalities. The abdominal pain is thought to be related to the trefoil-shaped pelvis and acetabular protrusion associated with OI. These structural abnormalities narrow the pelvic outlet, resulting in partial rectosigmoid obstruction and subsequent constipation or obstipation. Neurologic abnormalities associated with OI result from basilar impression. Basilar impression, or elevation of the floor of the posterior cranial fossa, is reported to occur in 25% of patients with OI.[34] It is seen most frequently in children with OI type IVB (71%), and one half of the patients with this type of OI will have neurologic signs or symptoms of compression of the posterior fossa structures.[34]

Table 174-5 Classification of Osteogenesis Imperfecta

TYPE	INHERITANCE	BONE FRAGILITY	SCLERAE*	OTHER FEATURES
I	Autosomal dominant	Mild to moderate Onset of fractures after birth Most fractures in preschool years	Blue	Most common form Presenile hearing loss Type A: normal teeth Type B: dentinogenesis imperfecta
II	Autosomal dominant—new mutation; autosomal recessive	Very severe Lethal in perinatal period	Dark blue	Subtypes A, B, and C based on radiographic findings
III	Autosomal dominant—new mutation; autosomal recessive	Moderate to severe Severe osteoporosis Fractures at birth with progressive deformity	Normal	Occasional deafness
IV	Autosomal dominant	Mild to moderately severe More severe than type I	Normal, gray or blue in infancy Normal by adolescence	Occasional deafness Type A: normal teeth Type B: dentinogenesis imperfecta

*Blue sclerae are normal in infants up to 4 months of age.

The signs (nystagmus, facial spasm, nerve paresis, pyramidal signs, and papilledema) may predate the symptoms (headache, neuralgia, imbalance, weakness, and incontinence). The most serious outcomes with basilar impression include brainstem compression, respiratory arrest, and sudden death. Any neurologic changes in a patient with OI mandate neurosurgical evaluation.

Several metabolic abnormalities can be associated with frequent fractures and radiographic abnormalities. *Rickets*, which results from vitamin D or calcium deficiency or hyperparathyroidism, can be manifested by diffuse osteopenia, fraying of the metaphysis, fractures, periosteal new bone formation, widening of the physis, and well-defined transverse stress fractures in the shafts of long bones. The diagnosis can be confirmed with laboratory testing. *Menkes' kinky hair syndrome*, a rare disorder of X-linked recessive inheritance involving inadequate copper absorption, is characterized by wormian (intersutural) skull bones, osteopenia, and metaphyseal fractures and spurring. Affected children have sparse, kinky hair with abnormal dentition and exhibit developmental delay. Serum levels of copper and ceruloplasmin are low and confirm the diagnosis. *Hypervitaminosis A*, although a rare cause of fractures, results in a thick periosteal reaction of tubular bones, most frequently the ulna and metatarsals, and widening of the cranial sutures. The epiphyses and metaphyses are normal. The diagnosis is based on the history and vitamin A levels.

Congenital syphilis also can mimic nonaccidental injury. Skeletal findings in congenital syphilis frequently are diffuse and symmetrical and involve the long bones, skull, and small bones of the hands and feet. Radiographic findings include osteolytic defects, periosteal reaction, and metaphyseal lucencies parallel to the physis. The diagnosis is confirmed by serologic testing.

Developmental Dysplasia of the Hip

Perspective. Developmental dysplasia of the hip (DDH), formerly known as "congenital dislocation of the hip," is abnormal formation of the hip joint that occurs between organogenesis and fetal maturity.[35] It encompasses a spectrum of disease ranging from "subluxatable" ("loose") hips to frank dislocation of the hips.

In white neonates, the incidence of dysplasia is 1%, and the incidence of dislocated hips is 0.1%. DDH is more common in Native American populations and less common in African American, Korean, and Chinese populations. An apparent familial predilection for the development of DDH has been reported; one British study noted that more than 20% of children who required treatment for DDH had a positive family history.[35] DDH is more common in girls and most frequently is unilateral (80%). With unilateral involvement, a predilection for the left side is characteristic. Associated birth factors include oligohydramnios, breech presentation, torticollis, talipes equinovarus, metatarsus adductus, and firstborn status.[36] Postnatally, swaddling infants with their hips and knees in extension predisposes to dislocation.

Principles of Disease. The etiology of DDH is not entirely clear. Three theories have been postulated: mechanical issues related to fetal position and environment, primary acetabular dysplasia, and ligamentous laxity which is enhanced by maternal relaxin hormone. Each theory has merit, and a combination of factors that contribute to the development of DDH is most likely.

Clinical Features. DDH may be diagnosed at birth, or despite frequent and appropriate physical examinations, it may not be discovered until later in life. In one study, 6% of children with documented DDH had normal findings on physical examination at birth.[35] Conversely, in more than 50% of infants found to have unstable hips at birth, spontaneous stabilization occurs within 3.5 days.[37]

The clinical manifestations of and physical examination findings with DDH are as diverse as the disease itself. This variability is due to differences in the severity of the dysplasia and the progressive changes that occur over time. Up to 4 to 6 months of age, the diagnosis of DDH is based on physical examination findings of leg length, skinfold, and range-of-motion asymmetry and abnormal findings on the Barlow provocative test and the Ortolani reduction maneuver. Skinfold asymmetry (Fig. 174-20) can be noted in the groin, below the buttock, and along the thighs. Although skinfold asymmetry is not specific for DDH, being present in approximately 30% of infants with normal hips, it is sensitive, and the diagnosis of DDH is very unlikely in infants with normal skinfold symmetry. Range of hip motion also is helpful in diagnosing DDH; any asymmetry in hip flexion, abduction, and external rotation should prompt further investigation. Although the general physical examination can be helpful in assessing hip stability, the physical diagnostic cornerstones for diagnosing DDH in young infants are the Ortolani reduction maneuver and the Barlow provocative test. The Ortolani reduction maneuver is performed in an attempt to reduce a dislocated hip back into normal position, and the Barlow provocative test detects a

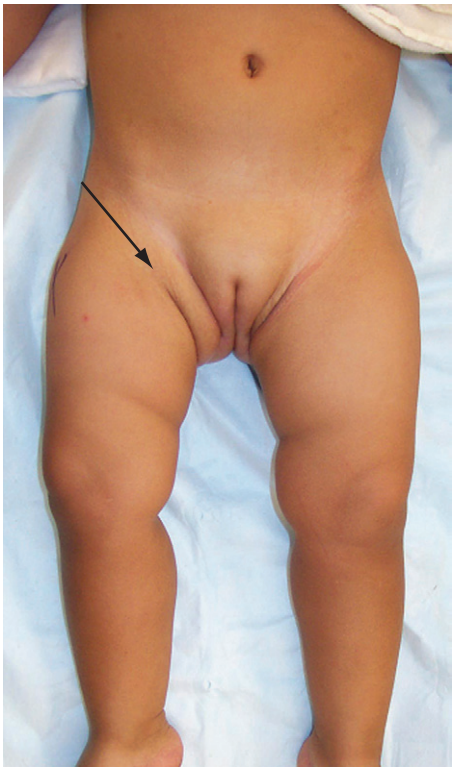


Figure 174-20. A 21-month-old child with right hip dislocation. Note the asymmetrical skinfolds in the upper thigh *(arrow)*. (From Storer SK, Skaggs DL: Developmental dysplasia of the hip. Am Fam Physician 74:1310, 2006.)

BOX 174-1 ORTOLANI AND BARLOW MANEUVERS

Ortolani (Reduction) Maneuver

1. Stabilize the pelvis with one hand.
2. With the other hand, slightly abduct the infant's hip.
3. With the index and long fingers over the greater trochanter, pull up the thigh to gently reduce the hip.

Barlow (Provocative) Test

1. Stabilize the pelvis with one hand.
2. Place the thumb on the inner aspect of the thigh near the lesser trochanter.
3. Adduct the hip.
4. Exert downward pressure on the thigh with the thumb and push it into the table.

subluxatable or dislocatable hip (Box 174-1). Abnormal findings include the presence of a "clunk" with the Ortolani test and any abnormal movement between the femoral head and the acetabulum with the Barlow maneuver.

After approximately 4 to 6 months of age, soft tissue contractures develop, the Ortolani and Barlow tests yield less information in detecting unstable hips, and range-of-motion abnormalities become more apparent. Parents may notice limited or asymmetrical leg movements or difficulty with diapering. Findings on examination include limited abduction (Fig. 174-21), relative shortening of the ipsilateral femur (*Galeazzi's sign*) (Fig. 174-22), and skinfold asymmetry. In children with bilateral DDH, the diagnosis is even more difficult beyond the first few months of life because of the absence of asymmetry. After the development of contractures, physical findings in bilateral DDH include widening of the perineum,

Figure 174-21. A 3-year-old child with a left hip dislocation. Note the limited abduction. (From Storer SK, Skaggs DL: Developmental dysplasia of the hip. Am Fam Physician 74:1310, 2006.)

Figure 174-22. Galeazzi's sign in a 7-month-old girl with left hip dislocation: Apparent inequality of femur length is manifested as asymmetry in the level of the patient's knees. (From Storer SK, Skaggs DL: Developmental dysplasia of the hip. Am Fam Physician 74:1310, 2006.)

abduction less than 60 degrees, and the appearance of abnormally short thigh segments.

With the onset of walking, gait asymmetry or asymmetrical in-toeing or out-toeing is a clue to the presence of DDH. Adduction and flexion contractures, a Galeazzi sign, hyperlordosis, and a waddling gait are common features. Clinical observation of the appropriate maneuver reveals a *Trendelenburg sign*: While standing, the patient lifts one leg up at a time, and because the gluteal muscles are weakened on the affected side, the pelvis drops to the opposite side. With bilateral DDH, children have a wide-based waddling gait.

Diagnostic Strategies. Radiographs of infant hips are extremely difficult to interpret and may provide a false sense of security if the findings seem normal. Before the child is 3 to 6 months old, at which time the femoral head ossifies, an abnormal relationship between the upper end of the femur and the acetabulum may not be apparent. Additionally, in infants with unstable but nondislocated hips, radiographs will show the hip in position, so its instability goes undetected. Before femoral head ossification, a better diagnostic test is ultrasonography.[38] Because a large percentage of infants will have abnormal ultrasound findings in the first week of life, with many of these abnormalities resolving within a few weeks,[35] it is best to delay ultrasound imaging in children with nondislocated but possi-

bly unstable hips until 4 to 6 weeks of age. Children with dislocated hips require immediate ultrasound examination. Plain radiographs are useful after the age of approximately 6 months. A standard AP radiographic view of the pelvis with both legs extended in neutral abduction is then sufficient for diagnosis. Radiographic findings may include displacement of Shenton's line (a curvilinear line defined by the medial border of the femoral neck and the superior border of the obturator foramen) and a widened acetabular angle; angles greater than 30 degrees are abnormal, and those greater than 40 degrees indicate dislocation (Fig. 174-23).

Management. Treatment of DDH is most successful when begun early, and delay in detection can be associated with a significantly worse outcome. Patients with untreated abnormalities of the hips that persist beyond the newborn period are at risk for osteoarthritis, pain, abnormal gait, leg length discrepancy, and decreased agility. For this reason, all children who are seen in the ED should have their hips examined until they are able to walk. Neonates who have a dislocated hip at birth should be referred to a pediatric orthopedist immediately. When a newborn has a loose but nondislocated hip, referral can be made within 2 weeks. Children with loose hips who are seen after the newborn period should be referred to a pediatric orthopedic surgeon immediately.

The essential basic goal of treatment is concentric reduction of the hip. After concentric reduction, stability must be obtained so that when the leg is allowed to move, it does not subluxate or dislocate. This position is maintained until all of the dysplastic features of the bone and cartilage have resolved. The two most important complications are failure to achieve these goals and aseptic necrosis of the femoral head.

In the first 6 months of life, use of the Pavlik harness is the mainstay of treatment. It is a dynamic splint that allows movement while preventing hip extension or adduction. Other treatment options include application of the Craig and von Rosen splints.[39] If these modalities are unsuccessful, application of a hip spica cast usually is the next choice. Beyond 6 months of age, use of a hip spica cast or fixed orthosis is required. Surgical release of contracted muscles may be necessary in older infants and children, and open surgical reduction is required if complete closed reduction is not achieved. Femoral or pelvic osteotomy (or both) may be necessary to reduce and stabilize dislocated hips in children older than 18 months.[40] Beyond the age of 4 years in bilateral cases and 8 years in unilateral cases, reduction should not be attempted. The risk of aseptic necrosis and the potential for a poor result are too high.[36]

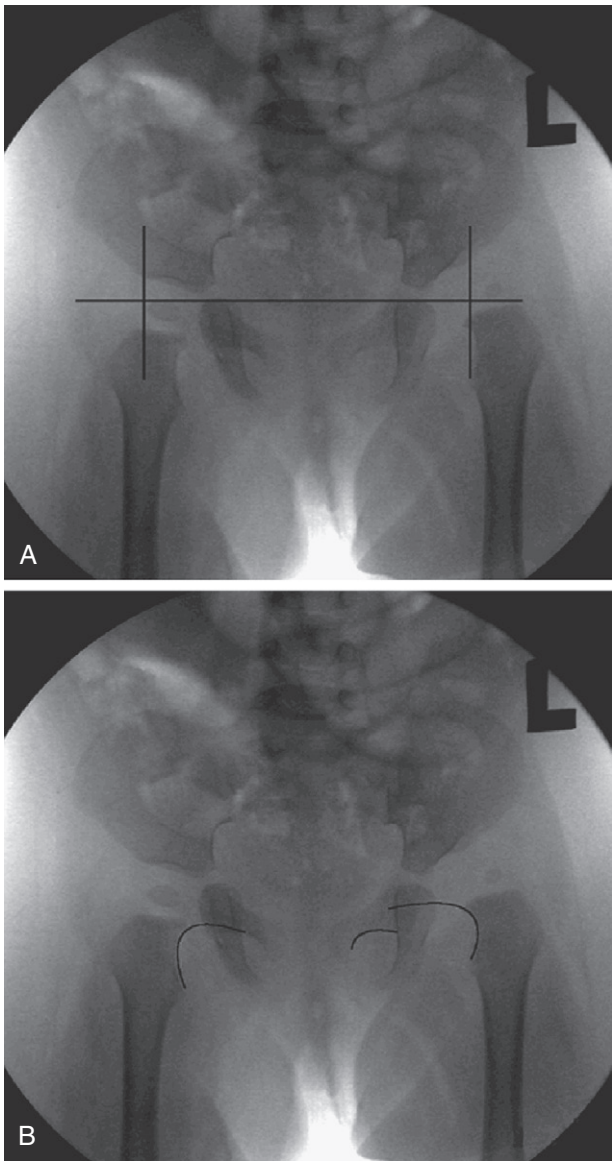


Figure 174-23. Anteroposterior radiographs obtained in a 7-month-old girl with developmental dysplasia of the left hip. **A,** The *horizontal line* is Hilgenreiner's line; the *vertical lines* are Perkin's lines. Note that the femoral head on the right (normal) side lies in the inferomedial quadrant formed by those lines. The left hip is dislocated; its femoral head lies in the superolateral quadrant. **B,** Shenton's line is disrupted on the left (dislocated) hip. (From Storer SK, Skaggs DL: Developmental dysplasia of the hip. Am Fam Physician 74:1310, 2006.)

Hip Pain in Children

Perspective. Hip pain in children is an extensive topic with myriad causes (Box 174-2). The extensive differential diagnosis precludes an in-depth review of the topic in this chapter, but an overview of some of the more common causes of hip pain in children is presented next.

BOX 174-2 CAUSES OF HIP PAIN IN CHILDREN

Trauma
Hip or pelvis fractures
Overuse injuries

Infection
Septic arthritis
Osteomyelitis
Myositis
Lyme disease

Inflammation
Transient synovitis
Juvenile rheumatoid arthritis
Rheumatic fever

Neoplasm
Leukemia
Osteogenic or Ewing's sarcoma
Metastatic disease

Hematologic Disorders
Hemophilia
Sickle cell anemia

Miscellaneous
Legg-Calvé-Perthes disease
Slipped capital femoral epiphysis

Transient Synovitis

Transient synovitis is the most common cause of hip pain in childhood.[41] It is a self-limited condition caused by a nonpyogenic inflammatory response of the synovium. Although it has been reported in children as young as 3 months and occasionally occurs in adults,[42] its peak incidence is between 3 and 6 years of age. Transient synovitis of the hip affects boys more commonly than girls and has a slight predilection for the right side. Less than 5% of cases are bilateral. Approximately one half of the patients are seen acutely, usually within the first 3 days of the onset of symptoms, whereas the other half have a more insidious course, with symptoms occurring for weeks to months before medical evaluation.[43] Although most commonly affecting the hip, transient synovitis also can affect the knee.

The etiology of transient synovitis is unknown. Current theories imply an association with active or recent infection, trauma, or allergic hypersensitivity. At least one half of the children with transient synovitis have or recently have had an upper respiratory illness.[44] One study demonstrated a fourfold rise in viral titer in 45% of patients and elevated serum interferon levels, consistent with a concurrent viral infection, in 43% of patients with transient synovitis.[45] Trauma commonly is associated with transient synovitis, but no clear relationship has been demonstrated. Similarly, a causal association with an allergic reaction to an infectious agent has been suggested but not proved.

It is estimated that transient synovitis of the hip may occur in up to 3% of children. Hip or groin pain is the most common initial finding, but referred pain to the medial aspect of the thigh or knee is found in 10 to 30% of patients. Affected patients either walk with a limp or, with severe pain, refuse to walk at all. The leg is held in flexion with slight abduction and external rotation. On examination, passive movement usually is pain-free; however, pain and a slightly decreased range of motion may be noted with extreme internal rotation or abduction. Although most children with transient synovitis tend to otherwise be well, some will have a low-grade fever and malaise.

The diagnosis of transient synovitis is one of exclusion and relies on the history and physical examination in combination with limited laboratory testing and AP and "frog-leg" lateral radiographs of the pelvis. Laboratory tests are used to help distinguish children with transient synovitis from those with septic arthritis. In transient synovitis, laboratory values may be normal or may reveal mild elevations in the white blood cell count and erythrocyte sedimentation rate (ESR), both consistent with a nonspecific inflammatory process. Multiple studies have attempted to define criteria to help differentiate transient synovitis from septic arthritis. Clinical decision rules have included the presence or absence of fever, the ability to bear weight, white blood cell counts, the inflammatory markers ESR and C-reactive protein (CRP), side-to-side differences in the width of the joint space on radiographs, and previous visits to a health care provider for related symptoms. Kocher and colleagues found four independent multivariant predictors of septic arthritis: fever, inability to bear weight, ESR of 40 mm/hour or higher, and a serum white blood cell count greater than 12,000 cells/μL. Patients with three of the four predictors had a 93% chance of having septic arthritis, and those with all four had a 99% likelihood of pyarthrosis.[46] A subsequent study to validate these findings showed that patients with none of the predictors had a 2% probability of septic arthritis; those with one of four criteria had a 9.5% probability; with two of four, a 35% probability; with three of four, a 73% probability; and with all four predictors, a 93% probability of septic arthritis.[47] When this algorithm was tested at another institution, however, the presence of all four Kocher criteria predicted septic arthritis only 59% of the time.[48] In general, in children with transient synovitis and septic arthritis, the overlap of laboratory values and historical features is too great to provide a foolproof diagnostic algorithm.

Although radiographs of the hip and pelvis tend to be normal in appearance with transient synovitis, they are helpful in excluding other diseases. Radiographic findings consistent with transient synovitis include medial joint space widening, an accentuated pericapsular shadow, and *Waldenström's sign*, which is lateral displacement of the femoral epiphysis with surface flattening secondary to effusion. However, these findings also are apparent in Legg-Calvé-Perthes disease and, if present, mandate close follow-up or further investigation with MRI. If joint aspiration is necessary to clarify the diagnosis, ultrasonography can be used to guide hip joint aspiration. Effusions are present in 60 to 70% of cases of transient synovitis; however, they also are present with septic arthritis, osteomyelitis, acute slipped capital femoral epiphysis (SCFE), Legg-Calvé-Perthes disease, rheumatoid and infectious arthritis, malignancy, and osteoid osteoma. Accordingly, the presence of an effusion on ultrasonography cannot be used to distinguish transient synovitis from other causes of hip pain.[49] Nuclear scintigraphy in patients with transient synovitis is helpful in differentiating transient synovitis from osteomyelitis (with or without septic arthritis), Legg-Calvé-Perthes disease, and SCFE. Scintigraphy may demonstrate differential uptake in the capital femoral epiphysis, with decreased uptake early in the course of the disease and increased uptake later on. The early changes also are seen with very early Legg-Calvé-Perthes disease and suggest that some children with transient synovitis experience ischemia of the capital femoral epiphyses. This ischemia may be caused by an intracapsular effusion that tamponades vessels along the femoral neck. These ischemic findings have not yet been shown to have clinical significance.

Most cases of transient synovitis can be managed at home with close follow-up by the child's primary care provider. Generally, these children have a mild limp and, if treated with nonsteroidal anti-inflammatory drugs, often show clinical improvement with relief of symptoms. A complete blood count and determination of ESR should be performed, and radiographs should be obtained. Patients with severe symptoms, fever, and an elevated ESR should be evaluated for septic arthritis. If there is any doubt about the diagnosis, immediate orthopedic consultation is necessary.

Treatment of transient synovitis is twofold: (1) rest of the affected joint achieved with non-weightbearing or, in cases associated with extreme pain, bedrest and (2) reduction of the inflammatory process with anti-inflammatory medications. Temperatures should be monitored closely, and any fever should be reported to the physician. Children are allowed a gradual return to activity as the pain subsides, and full unrestricted activity is permitted when the hip is completely pain-free with no evidence of a limp. Although many children with transient synovitis have an effusion, aspiration of the joint is not routinely performed, and there is no strong evidence that aspiration shortens the clinical course or prevents osteonecrosis. Repeat examination is recommended for all children within 12 to 24 hours and then again after 10 to 14 days if the symptoms have not resolved.

The prognosis for children with transient synovitis is excellent. Up to 75% of patients have complete resolution of pain within 2 weeks and 88% within 4 weeks. The remainder may

have less intense but persistent pain for up to 8 weeks. Relapse is possible, although infrequent, and usually occurs within 6 months. In general, long-term sequelae of transient synovitis are infrequent; these may include asymptomatic coxa magna (enlargement and deformity of the femoral head and neck caused by hypertrophy of cartilage secondary to inflammation) and mild degenerative cystic changes of the femoral neck. These changes persist for years and may be accompanied by radiographic degenerative change, but they do not tend to cause long-term functional disability. Additionally, a small number (2%) of cases of transient synovitis follow a clinical and radiographic course consistent with Legg-Calvé-Perthes disease. Whether this is due to ischemia of the capital femoral epiphyses during the early stages of synovitis or reflects an initial misdiagnosis is unclear. It is recommended that children with persistent symptoms undergo ultrasonography to evaluate for the presence of an effusion. Persistent joint effusion beyond 4 to 6 weeks may be associated with the subsequent development of Legg-Calvé-Perthes disease.[50] Some experts recommend routine 6-month follow-up radiographs for all children with transient synovitis,[43] whereas others reserve radiographs for children who remain symptomatic.[51]

Acute Septic Arthritis

Septic arthritis refers to microbial invasion and infection of the joint space. Bacterial pathogens are common in patients with acute septic arthritis, whereas fungal and mycobacterial pathogens tend to be associated with a more indolent septic arthritis. Acute septic arthritis occurs in all age groups but is more common in children: 70% of cases occur in children younger than 4 years, and the peak incidence is between 6 and 24 months. Boys are affected twice as frequently as girls. Predisposing factors include preceding viral infection, trauma, immunodeficiency, hemoglobinopathy, hemophilia with recurrent hemarthroses, diabetes, intravenous drug abuse, rheumatoid arthritis, and intra-articular injections or operations. In 75% of cases of septic arthritis, the pathologic process involves the joints of the lower extremity, with the knee being most commonly and the hip second most commonly involved. Other affected joints, in order of involvement, include the ankle, elbow, shoulder, and wrist. More than 90% of the cases are monoarticular.

Hematogenous seeding, local spread, or traumatic or surgical infection may cause septic arthritis. In children, it most commonly results from hematogenous spread as bacteria pass into the synovial space through the highly vascular synovial membrane. The synovial membrane lacks a limiting basement membrane, which facilitates bacterial translocation. The bacteria then bind to bone and cartilage, initiating an inflammatory response that breaks down the joint by two mechanisms: directly through the effects of proteolytic enzymes and indirectly through pressure necrosis caused by accumulation of purulent synovial fluid.

Contiguous spread of infection from osteomyelitis to the joint space occurs in approximately 10% of cases and is more common in newborns and young infants. In these children, blood vessels cross the physis, thereby connecting the metaphysis and epiphysis and allowing bacteria direct access into the joint space. Additionally, the joint capsules of the hip and shoulder overlie the bony metaphyses of the femur and humerus, facilitating direct extension of osteomyelitis into these joint spaces.

The most common bacterial causes of septic arthritis are listed in Table 174-6. In all age groups, *Staphylococcus aureus* is the most common cause of septic arthritis and infection, with community-acquired MRSA becoming more common.[52] In addition to the organisms listed in Table 174-6, additional causative organisms include *Neisseria gonorrhoeae* in neonates and sexually active adolescents, *Pseudomonas aeruginosa* and *Candida* species in intravenous drug abusers, *Salmonella* species in children with sickle cell disease, and gram-negative bacteria in immunosuppressed children. *Kingella kingae*, a fastidious gram-negative coccobacillus that colonizes the respiratory and oropharyngeal tracts in children, has been implicated as a common cause of osteoarticular infections in young children. Culture and *K. kingae*–specific polymerase chain reaction (PCR) assay were used by Chometon and colleagues to identify *K. kingae* as the causative agent in 45% of osteoarticular infections in their series.[53] Studies from Israel indicate that 40 to 50% of culture-negative septic arthritis cases in children younger than 2 years of age may potentially be attributable to *K. kingae*.[54] Fortunately, *K. kingae* is susceptible to a wide array of antibiotics that are given empirically to young children for septic arthritis.

Table 174-6 Septic Arthritis Pathogens and Treatment

AGE	ORGANISM	TREATMENT
Birth to 2 months	Group B streptococci *Staphylococcus aureus* Gram-negative rods *Neisseria gonorrhoeae*	Nafcillin, 50 mg/kg, and cefotaxime, 50–75 mg/kg
2 months to 5 years	*Staphylococcus aureus* *Streptococcus pneumoniae* *Streptococcus pyogenes* *Kingella kingae* *Haemophilus influenzae*	Nafcillin, 50 mg/kg, and ceftriaxone, 50 mg/kg (consider vancomycin, 10 mg/kg)
5 years to 12 years	*Staphylococcus aureus* *Streptococcus pyogenes*	Nafcillin, 50 mg/kg, and ceftriaxone, 50 mg/kg (consider vancomycin, 10 mg/kg)
>12 years	*Staphylococcus aureus* *Neisseria gonorrhoeae*	Nafcillin, 50 mg/kg, and ceftriaxone, 50 mg/kg (consider vancomycin, 10 mg/kg)

The clinical picture of septic arthritis varies with age: Infants tend to have fever, failure to feed, lethargy, pseudoparalysis of the extremity, and pain with diaper changes. In one study, however, neonates (younger than 1 month) were found to have less fever and fewer systemic signs of illness than in older infants, thus making the diagnosis even more difficult.[55] Most older children have systemic signs and symptoms of fever, malaise, poor appetite, and irritability, as well as localized symptoms of pain and limp or refusal to walk. With septic arthritis, the onset of symptoms is more acute than with osteomyelitis. Physical examination reveals local erythema, warmth, and swelling. If the hip is affected, it often is held in flexion, abduction, and external rotation. Range of motion is decreased because of pain and muscle spasm, and passive joint movement is painful. In infants, joint dislocation may be observed.

Laboratory studies helpful in diagnosing septic arthritis include a white blood cell count, ESR, CRP assay, blood cultures, and evaluation of joint fluid. Use of the white blood cell count and ESR is discussed in the section on transient synovitis. It should be noted that the ESR rises 24 hours or more after the onset of signs and symptoms of infection, so it may not be helpful during the first day of illness. CRP levels may be a better monitor than the ESR for septic arthritis. The CRP assay is a simpler test that requires only a fingerstick sample

of blood. The CRP level rises more quickly than the ESR, typically is elevated at the time of the initial evaluation, and, with appropriate therapy, will normalize within a week; by contrast, the ESR will not normalize for more than a month.[56] In patients with septic arthritis, the peripheral white blood cell count, ESR, and CRP generally are elevated, although occasionally CRP is normal, especially with *K. kingae* infection.[57]

Blood cultures should be included in the evaluation of a child with suspected septic arthritis. Culture results are positive in 20 to 50% of cases,[56] when positive they not only help direct antibiotic treatment but also provide an organism for serum bactericidal testing as the child progresses to oral antibiotics.

If *N. gonorrhoeae* infection is suspected, special media are required for cultures of joint fluid, blood, pharynx, skin lesions, cervix, urethra, vagina, and rectum. Urine, urethral, cervical, and vaginal specimens also can be obtained for nucleic amplification testing.

If the patient has signs or symptoms of pharyngitis, a throat swab should be sent for culture of *S. pyogenes*. Antibody titers to antistreptolysin O and anti-DNAase B also may be helpful in establishing a causative organism.

Evaluation of synovial fluid is the standard modality for diagnosing septic arthritis. If septic arthritis is being considered, joint aspiration should be performed without delay and the sample sent for Gram's stain, aerobic and anaerobic cultures, cell count with differential count, glucose determination, and a mucin clot test. The mucin clot test is a test of the integrity of hyaluronic acid, which tends to be degraded when bacteria are present. It is performed by placing two drops of 5% acetic acid into a mixture of 4 mL of water and 1 mL of synovial fluid while stirring with a glass rod. A normal result is formation of a tight rope of mucin. The test result is considered positive for infection if the fluid's consistency changes to that of curdled milk as the clot flakes and shreds. Abnormal mucin clot test results are found with septic arthritis and rheumatic fever; however, with rheumatic fever, a fibrous band resembling a tethered rope forms on the glass stir rod. The synovial fluid in patients with septic arthritis tends to be turbid or grossly purulent, with a white cell count greater than 40,000 cells/μL and a predominance of polymorphonuclear cells. Synovial glucose may be low (synovial fluid glucose: blood glucose less than 0.5) and protein and lactate elevated (Table 174-7). Because of the intrinsic immunoglobulins in the synovial fluid, results on culture of the fluid will be positive in only one half of the children in whom the clinical picture is consistent with septic arthritis. Joint fluid should be inoculated directly into blood culture bottles to enhance identification of fastidious organisms such as *K. kingae*.[57] Culture specimens may need to be incubated for a week or longer.[54]

In septic arthritis, plain radiographs of the hip may be normal in appearance or, in the presence of a large joint effusion, may show periarticular soft tissue swelling, widening of the joint space, obliteration or displacement of the gluteal lines, and asymmetrical fullness of the iliopsoas and obturator soft tissue planes. Late in the course of infection, subchondral bone erosions and narrowing of the joint space are seen. Ultrasonography is much more sensitive than plain radiography for detecting hip effusion and provides direct visualization of the fluid and needle during joint aspiration. Scintigraphy also may be useful in diagnosing septic arthritis; during the "blood pool" or delayed images of the joint, symmetrical uptake in periarticular tissue on both sides of the joint is seen. Scintigraphy is diagnostic of septic arthritis earlier than other imaging techniques and is a useful adjunct in identifying associated osteomyelitis or avascular necrosis of the femoral head. CT can confirm the presence of an effusion but does not differentiate septic from nonseptic arthritis. Changes in signal intensity and femoral epiphysis perfusion seen on MRI may provide diagnostic clues in attempting to differentiate septic arthritis from transient synovitis.[58,59]

Septic arthritis requires immediate hospital admission, antibiotics, and surgical intervention. Surgical options range from needle aspiration to open surgical drainage, but no randomized, controlled trials have compared these two treatment approaches. Some experts recommend surgical drainage in all infants and young children with septic arthritis, because needle aspiration has been shown to be inferior in this population.[60] Indications for surgical drainage in children with septic arthritis include involvement of the hip joint, the presence of large amounts of pus or debris in the joint, loculated fluid, recurrence of joint fluid after four or five aspirations, and lack of clinical improvement within 3 days of the initiation of appropriate therapy.[61-64] In joints other than the hip, the need for surgical drainage is determined on a case-by-case basis.

Empirical antibiotic therapy for septic arthritis is directed against the most likely organisms as dictated by patient age and comorbid conditions (see Table 174-6). Treatment may then be changed after culture and sensitivity results are known. If a pathogen is not isolated but the patient is improving, initial antibiotic therapy is continued. If a pathogen is not identified and the patient is not improving, reaspiration of the joint or the possibility of a noninfectious process should be considered. To maximize culture results, antibiotics should not be given until a specimen of joint fluid is obtained. Initial treatment should be parenteral to ensure adequate serum antibiotic concentrations. After the patient's clinical condition is stabilized, oral antibiotic therapy can be instituted. In general, doses two to three times those used for mild infections are sufficient. Response to therapy is measured by clinical improvement and assays for acute phase reactants (CRP and ESR).

The mortality rate associated with septic arthritis has fallen to less than 1%, but the morbidity remains significant. Sequelae

Table 174-7 Synovial Fluid Findings in Different Types of Arthritis

CONDITION	CHARACTER	WBC COUNT (CELLS/μL)	PMNs (%)	MUCIN CLOT	OTHER
Normal	Clear; yellow	<200	<10	Good	
Juvenile rheumatoid arthritis	Turbid	250–50,000	50–70	Fair to poor	50% with decreased complement
Reactive arthritis	Cloudy to turbid; may be clear	1000–150,000	50–70	Fair to poor	Increased complement
Lyme arthritis	Turbid	500–100,000	>50	Poor	
Septic arthritis	Turbid; white-gray	10,000–250,000	>75	Poor	Low glucose High lactate

PMNs, polymorphonuclear leukocytes (neutrophils); WBC, white blood cell.

include leg length discrepancy, persistent pain, limited range of motion and ambulation, and ischemic necrosis of the femoral head. Predictors of a poor outcome include infection of the hip and shoulder, adjacent osteomyelitis, a delay of 4 days or more before antibiotic and surgical intervention, and prolonged time to sterilization of synovial fluid.

Legg-Calvé-Perthes Disease

Idiopathic avascular necrosis of the proximal femoral epiphysis, also known as Legg-Calvé-Perthes disease, is named after the men who independently described it in the early 1900s. It usually occurs between the ages of 3 and 12 years, with the peak incidence between the ages of 5 and 7 years. Legg-Calvé-Perthes disease has been reported in teenagers, as well as in children as young as 2 years. Boys are affected three to five times more frequently than girls, and the disease is familial approximately 10% of the time. The disorder is bilateral in up to 20% of cases. Legg-Calvé-Perthes disease is associated with breech presentation, later birth order (with the third to sixth children in a family particularly affected), lower socioeconomic status, higher parental age, lower birth weight, attention-deficit/hyperactivity disorder, delayed bone age, short stature, passive smoke inhalation, infection with human immunodeficiency virus, and chronic renal disease. The increased incidence of Legg-Calvé-Perthes disease in Japanese, Asians, Eskimos, and central Europeans and the decreased incidence in Native Australians, Native Americans, Polynesians, and African Americans suggest that racial factors also may play a role. Trauma often is related to the onset of symptoms , but a direct relationship between the two has not been clearly established. Thrombophilia also may be associated with Legg-Calvé-Perthes; however, studies are conflicting.

Despite extensive research, the etiology of Legg-Calvé-Perthes disease remains unclear. Ponseti and colleagues[65] suggested that the disease is a local manifestation of a transient generalized disorder of epiphyseal cartilage. Their histologic studies showed thickening and disorganization of the growth plate, which could block penetration of the blood vessels and render the femoral epiphysis avascular. Other etiologic theories involve abnormalities in the vascular anastomotic network around the femoral epiphysis, increased blood viscosity leading to infarction, and abnormalities in growth hormone.

On clinical examination, children with Legg-Calvé-Perthes disease initially exhibit a limp of insidious and stuttering onset. Associated pain, when present, usually is related to activity and relieved by rest. The pain tends to be localized to the groin or referred to the anteromedial aspect of the thigh or knee region. Symptoms and limp severity usually are worse at the end of the day. On examination, children have limited hip motion, particularly abduction and internal rotation. Early in the course of disease, the limited abduction is secondary to synovitis and muscle spasm. As the disease progresses, limitation of motion is due to deformity of the femoral head, and with time, the limited abduction may become permanent. Children with Legg-Calvé-Perthes disease demonstrate a positive result on Trendelenburg testing (see the earler section, "Developmental Dysplasia of the Hip") accompanied by thigh, calf, and buttock atrophy related to disuse. With advanced disease and femoral head collapse, limb length discrepancy may be noted.

The role of laboratory evaluation in the diagnosis of Legg-Calvé-Perthes disease is limited to ruling out other causes of hip pain (e.g., septic arthritis) when the diagnosis is in question or to evaluating for hormonal, metabolic, or genetic causes in patients with bilateral hip involvement.

Legg-Calvé-Perthes disease is diagnosed and staged by plain radiographs obtained in the AP and frog-leg lateral views. This radiographic survey shows the extent of epiphyseal involvement and the stage of the disease and also provides prognostic information. Radiographic "head at risk" signs that are associated with poor results include a radiolucent V-shaped defect in the lateral epiphysis and adjacent metaphysis (*Gage sign*), speckled calcification lateral to the capital epiphysis, diffuse metaphyseal reaction (metaphyseal cysts), lateral capital femoral epiphysis subluxation, and a horizontal physis. These prognostic signs help guide treatment. In early Legg-Calvé-Perthes disease, radionuclide bone scanning may be diagnostic before the development of abnormalities on plain film. Bone scintigraphy also has been shown to provide accurate information concerning the extent of the necrotic process, as well as the degree of vascularization and hence the stage of the disease. Scintigraphy, however, was not able to predict disease outcome.[66] When compared with plain radiographs and bone scan, MRI gives earlier and more reliable information about the extent of necrosis of the femoral head. MRI also is better than scintigraphy at showing revascularization. Despite the usefulness of MRI in early Legg-Calvé-Perthes disease, its role in healed Legg-Calvé-Perthes disease is limited because it provides no additional information regarding the configuration and structure of the femoral head beyond that from plain radiography.[66] Arthrography is useful in delineating flattening of the femoral head, demonstrating the hinge abduction phenomenon with abduction of the leg, and, in conjunction with plain films or CT, diagnosing osteochondritis dissecans after Legg-Calvé-Perthes disease.

There are four radiographic classification stages of Legg-Calvé-Perthes disease: initial, fragmentation, reossification, and healed. Radiographic findings in the *initial* stage include a femoral head that appears smaller than the opposite unaffected femoral head, widening of the medial joint space, a subchondral lucent zone (subchondral collapse—the so-called crescent sign), an irregular physeal plate, and a blurry and radiolucent metaphysis (Fig. 174-24). In the *fragmentation* phase, the repair aspects of the disease become more prominent. The epiphysis begins to fragment, and areas of increased radiolucency appear as new bone forms, as well as areas of increased radiodensity. During the *reossification* stage, the repair process continues as normal bone density returns, radiodensities replace radiolucencies, and alterations in the shape of the femoral head and neck become apparent. The *healed* stage is the final radiographic stage of Legg-Calvé-Perthes disease, and radiographs of the proximal one third of the femur obtained during this stage of the illness will demonstrate any residual deformities.

Multiple prognostic classification systems of Legg-Calvé-Perthes disease have been devised. In general, a poor prognosis is associated with a greater degree of deformity of the femoral head and acetabulum at maturity, disease onset in

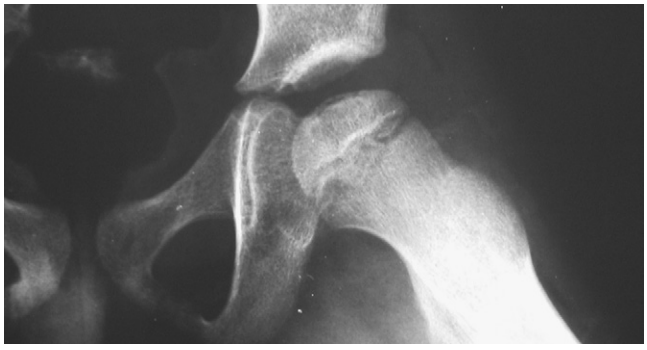


Figure 174-24. Crescent sign (subchondral lucent zone) in early Legg-Calvé-Perthes disease. (Courtesy of Marianne Gausche-Hill, MD.)

children 6 to 8 years of age or older, female gender, and prolonged duration of disease.

When the diagnosis of Legg-Calvé-Perthes is suspected, orthopedic consultation is recommended. Goals in the treatment of Legg-Calvé-Perthes disease are to improve range of motion, prevent deformity, limit growth disturbance, and prevent degenerative joint disease. Treatment is not indicated in all affected children, but when indicated, it must be started in the initial or fragmentation phase of the disease. Treatment is recommended for patients who have a poor prognosis based on clinical and radiographic findings. The cornerstone for treatment of Legg-Calvé-Perthes is referred to as "containment": The femoral head is contained within the acetabulum to equalize pressure on the head and subject it to the molding action of the acetabulum to maintain the spherical nature of the femoral head. Containment can be achieved through nonoperative or operative methods, and optimal treatment is determined on a case-by-case basis.

Residual deformities resulting from Legg-Calvé-Perthes disease follow four patterns: coxa magna, premature physeal arrest, irregular head formation, and osteochondritis dissecans. Despite these deformities, most patients with childhood hip disease are capable of bony remodeling with subsequent improvement in femoral head deformities. During their early years, regardless of radiographic appearance, patients with Legg-Calvé-Perthes disease tend to do well.[67] A majority (70 to 90%) of patients are active and pain-free and have good range of motion 20 to 40 years after the onset of symptoms. Only patients with flattened irregular femoral heads at the time of primary healing or premature physeal closure experienced clinical deterioration and increasing pain.[68] Later in life, function becomes markedly reduced, with degenerative joint disease developing in a majority of patients by their 50s and 60s.[67] With noncontainment treatment, however, the outcome is not as good. Yrjonen found that at an average of 35 years of follow-up, 48% of patients had evidence of degenerative joint disease and 17% either had undergone total hip arthroplasty or had clinical symptoms that warranted total hip arthroplasty.[69]

Slipped Capital Femoral Epiphysis

SCFE refers to posterior and inferior slippage of the proximal femoral epiphysis on the metaphysis. The femoral head sits securely in the acetabulum, whereas the epiphysis separates from the femoral neck through the growth plate. The average annual incidence of SCFE ranges from 0.2 (in Japan)[70] to 10.8 (in the United States) per 100,000 children, with boys being affected almost twice as frequently as girls.[71] The peak incidence is during the adolescent growth spurt: boys between 12 and 16 years of age (mean age, 13.5 years) and girls between 10 and 14 years of age (mean age, 11.5 years). The age at diagnosis decreases with increasing obesity. A majority of children with SCFE have delayed skeletal maturation, with bone age being as much as 20 months behind chronologic age. African American and Hispanic children are affected more frequently than white children. The literature reports SCFE to be bilateral in up to 80% of cases, although 30 to 40% of these cases are asymptomatic and discovered only on screening radiographs. In unilateral cases, the left hip is affected twice as often as the right.

SCFE is associated with endocrine disorders (hypothyroidism, panhypopituitarism, hypogonadism, and growth hormone administration), renal osteodystrophy, and radiation therapy. Most cases of SCFE, however, are idiopathic and associated with obesity. The etiology of idiopathic SCFE is unknown. It is likely to be multifactorial and related to biomechanical factors such as obesity and physeal architecture, as well as hormonal factors that weaken physeal strength. Obesity results in increased shear forces across a more vertically and posteriorly oriented growth plate that has been weakened by architectural irregularities and hormonal changes of puberty. The consequence is slippage of the epiphysis inferiorly and posteriorly in the direction of the weight-bearing force.

The traditional classification of SCFE was based on the duration of symptoms, with acute slippage defined as symptom duration of less than 3 weeks, chronic slippage defined as symptoms for 3 weeks or longer, and acute-on-chronic slippage defined as symptom duration of more than 3 weeks with a recent sudden exacerbation. This classification has been replaced by one based on stability: in *stable* SCFE, ambulation is possible (with or without crutches), whereas in *unstable* SCFE, ambulation is not possible (with or without crutches).[72] This classification system is preferred over the traditional classification because it does not rely on patient or parent recall for duration of symptoms and provides information regarding prognosis.

The signs and symptoms of SCFE vary with its stability. Children with stable SCFE have symptoms of intermittent limp and pain of several weeks' to months' duration. Stable SCFE is found in approximately 95% of all cases.[73] The pain of SCFE may be localized to the hip but more commonly is poorly localized to the thigh, groin, or knee. Atypical manifestations of SCFE include weakness and easy fatigability of the affected limb and limping on exertion. With continued slippage, internal rotation, flexion, and abduction are lost, and parents and children may note progressive external rotation and shortening of the involved lower extremity with subsequent difficulty in daily activities such as tying shoes. On examination, children initially have a slight loss of internal rotation and experience pain only at the extremes of motion. Their gait is antalgic, and muscle atrophy is minimal. As the slip becomes more severe, the gait becomes more antalgic, internal rotation is lost, abduction and flexion of the hip increase, thigh and gluteal muscle atrophy is more pronounced, and leg length discrepancy develops. A frequently seen sign associated with SCFE can be elicited during passive flexion of the affected hip: As flexion is increased from an extended position, the thigh abducts and externally rotates.

Unstable SCFE in children typically initially comes to attention after a sports-related injury or a fall with a twisting injury. These children experience acute onset of extreme pain and, on examination, hold the hip in flexion, external rotation, and abduction. The children resist any type of movement of the affected leg, and if unstable SCFE is suspected, no passive movement should be attempted for fear of further displacing the epiphysis.

The diagnosis of SCFE is made with AP and lateral radiographs of both hips. With stable slippage, AP and frog-leg lateral pelvic radiographs should be obtained. When an unstable slip or a minimal slip is suspected, a cross-table radiograph replaces the frog-leg lateral view. Early in the course of SCFE, the initial slippage is posterior, so the AP view is normal in appearance or shows widening of the physis; the slip is better seen on the lateral projection (Fig. 174-25). Early findings on lateral radiographs include a minimal posterior step-off at the anterior physeal plate or widening of the growth plate. On AP radiographs, signs of slippage include Klein's line and the blanch sign of Steele. *Klein's line* is a line drawn along the superior margin of the femoral neck. With a normal hip, the line intersects with or falls within the epiphysis, whereas in a hip with a slipped epiphysis, the line does not come in contact with the epiphysis. The *blanch sign of Steele* is a crescent-shaped area of increased density in the proximal portion of the femoral neck that is created by superimposition of the

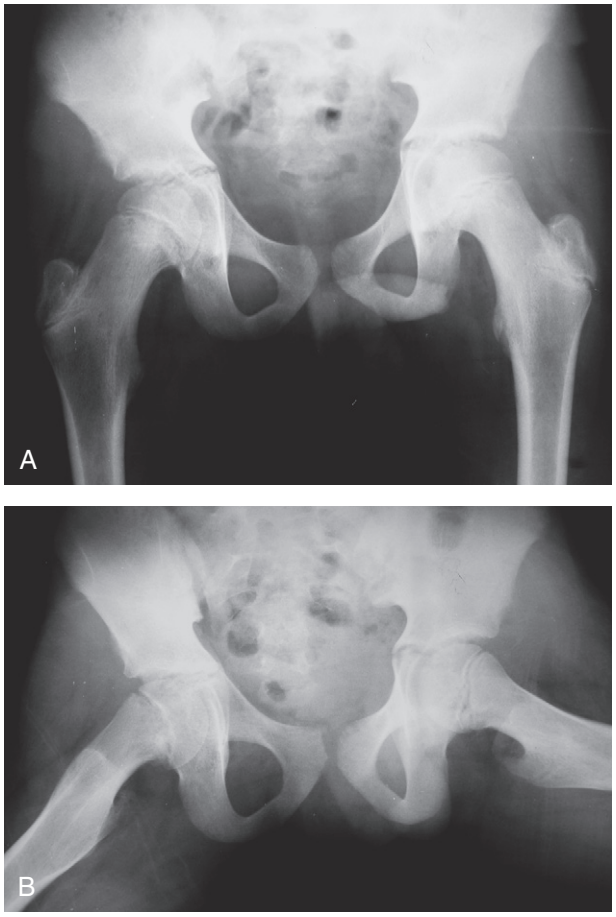


Figure 174-25. **A,** Anteroposterior radiograph of the pelvis with a unilateral slipped capital femoral epiphysis; note widening of the physis on the right as compared with the left. **B,** Early inferior and posterior slippage is evident on the lateral view. (**A** and **B,** Courtesy of Marianne Gausche-Hill, MD.)

posteriorly displaced epiphysis on the femoral neck. The femoral metaphysis of the affected hip also appears to be more laterally displaced from the medial wall of the acetabulum. As the slip continues, the epiphysis continues to be displaced inferiorly and posteriorly relative to the metaphysis. Over time, remodeling smooths away the superior and anterior portions of the femoral neck, and in an attempt to buttress the slippage, callus is formed at the inferior and posterior portions of the femoral neck. Unstable slips in children without previous symptoms will not be associated with evidence of bone healing or remodeling.

Ultrasonography has been used in the diagnosis of SCFE but offers little, if any, information beyond that provided by conventional radiography. CT and MRI can be used to confirm and quantitate epiphyseal displacement in patients who have symptoms but no radiographic findings suggestive of SCFE.

Slip severity is described in either of two ways. The simplest classification describes the amount of *displacement of the femoral head* on the femoral neck. In mild SCFE, the amount of displacement is less than one third, moderate SCFE has displacement between one third and one half, and severe SCFE is marked by displacement of the femoral head by more than one half the width of the femoral neck. A more accurate description of the magnitude of slippage is obtained by measuring the *epiphyseal-shaft angle of Southwick*. On a frog-leg lateral radiograph of the pelvis, a line is drawn between the anterior and posterior tips of the epiphysis at the physeal plate level. A second line is then drawn perpendicular to the epiphyseal line. Next, a line is drawn along the midshaft of the femur. The epiphyseal-shaft angle is formed by the intersection of the perpendicular and the femoral shaft lines. The magnitude of slip displacement is the angle of the involved hip minus the angle of the normal hip. If involvement is bilateral, 12 degrees is used as the control angle. Mild SCFE involves displacement of less than 30 degrees, a moderate slip is between 30 and 50 degrees, and severe displacement is greater than 50 degrees.

When SCFE is diagnosed in the ED, non-weight-bearing status is assigned immediately, and the child is provided with either crutches or a wheelchair; an urgent orthopedic consultation should be obtained. For a stable slip, definitive treatment is best performed within a few days; however, hospital admission is prudent. With an unstable slip, some orthopedic surgeons recommend immediate fixation.

The goals of treatment are to prevent further slippage and achieve physeal stability, avoid complications, and maintain adequate hip function. A stable slip can be fixed with internal fixation (pinning), bone graft epiphyseodesis, corrective osteotomy, or spica cast immobilization. Most orthopedic surgeons recommend internal fixation with a single central screw. Failure of this repair is very rare and, with new techniques that avoid opening the hip joint, it has become a procedure associated with minimal blood loss and wound complications and minimal need for hospitalization and rehabilitation. Postoperatively, non-weightbearing or touch-toe weightbearing for 4 to 6 weeks is followed by a gradual return to normal activity. Running and contact sports may be resumed once the physis is closed. With unstable SCFE, controversy has arisen regarding the timing of the surgery, the optimal number of fixative devices that should be used, whether reduction should be performed, and whether preliminary traction and bedrest should be used before surgery. Treatment is dependent on the degree of slippage and the preference and experience of the orthopedic surgeon.

The two most worrisome short-term complications of SCFE are avascular necrosis and chondrolysis; the risk for either process increases with the severity of the initial slippage.[74] Avascular necrosis has been reported to occur in 10 to 15% of children with SCFE. The risk is higher with unstable SCFE,[75,76] greater degrees of slippage, and multiple attempts at reduction.[76] In children with stable slips treated by single-screw internal fixation without reduction, reported rates of avascular necrosis are as low as zero to 5%.[78]

Chondrolysis occurs in approximately 5% of patients with SCFE, with an increased incidence in children with greater degrees of slippage. Chondrolysis may develop before and as a result of treatment. It should be suspected when pain and loss of motion are disproportionate to the severity of the slip. On radiographs, loss of articular cartilage may be seen. When SCFE is treated by spica cast immobilization, the rate of chondrolysis is reported to range from 19 to 67%.[77,79] Approximately 50% of cases of chondrolysis will resolve; however, it may progress to such severe pain and contractures that hip arthrodesis is needed.

Other complications of SCFE include nonunion, premature closure of the epiphyseal plate, and degenerative changes. Degenerative hip arthritis develops gradually over decades and has an earlier onset with more severe degrees of slippage.

Apophyseal Injuries

Perspective and Principles of Disease. The apophysis is a cartilaginous structure that serves as a site for insertion of tendons on the growing bone. It has its own growth plate that has a slower rate of growth than the nearby epiphyseal plate. Apophysitis is

unique to patients with skeletal immaturity and involves inflammation of this actively growing bony prominence that is under great tensile stress. Common apophyseal injuries include medial epicondylitis, Osgood-Schlatter syndrome, and Sever's disease.

Apophysitis may be secondary to a single episode of macrotrauma or may follow repetitive microtrauma to the secondary center of ossification, which causes multiple tiny avulsion fractures. This scenario sets up an inflammatory cycle that is perpetuated by continued activity and trauma to the apophysis.

Growth also contributes to the development of apophysitis. As the musculoskeletal system goes through a growth spurt, muscle development lags behind bony development. This difference in development leads to a muscle-tendon imbalance manifested as tight and inflexible muscle groups in which excessive stress is placed on the apophyseal centers at which these muscles insert.

The true incidence of apophysitis is unknown. One study found an incidence of 18% in a population of 1000 patients seen at an urban general pediatric clinic over a 4.5-month period.[80] Another study, which looked at patient visits to a sports medicine clinic, found an incidence of 31%.[81] Children between 8 and 15 years of age most frequently are affected, with involvement of different apophyseal centers affected at different ages.

Specific Disorders/Injuries

Osgood-Schlatter Syndrome

In 1903 Osgood and Schlatter independently reported traumatically induced apophyseal injury to the tibial tubercle in adolescents.[82] This entity, now known as Osgood-Schlatter syndrome, is the most common of the apophyseal disorders.[83] It is found most commonly in boys between 10 and 15 years of age and in girls between 8 and 13 years of age and frequently is bilateral. Boys are affected more often than girls, although this trend is changing as more girls are becoming increasingly involved in competitive sports. Bilateral involvement is found in 20 to 30% of patients.

Clinically, patients with Osgood-Schlatter syndrome have tenderness, pain, and swelling at the site of insertion of the patellar tendon on the tibial tubercle. The tibial tubercle may be prominent and the quadriceps tight. Pain is worsened with activities such as running or jumping that cause the quadriceps to contract, thereby stressing the tubercle. Extension of the knee against resistance causes pain, but resisted straight leg raises are painless. Osgood-Schlatter syndrome is a clinical diagnosis, and radiographs generally are not indicated. If obtained, however, lateral radiographs of the tibial tubercle may be normal in appearance or may show an enlarged, fragmented, and irregular tibial tuberosity with or without an overlying bony ossicle. Ultrasonography, which has been proposed as a diagnostic tool by some experts, may reveal pretibial swelling, fragmentation of the ossification center, insertional thickening of the patellar tendon, or excessive fluid collection in the infrapatellar bursa.[84]

Treatment of Osgood-Schlatter syndrome is conservative and symptomatic. Initially, the pain can be effectively managed with ice and modification of activity, with or without nonsteroidal anti-inflammatory medications. The use of a patellar strap may help to relieve symptoms. After the acute inflammatory process has resolved, treatment focuses on strengthening and stretching of the quadriceps muscles. Mild pain during activity is not an absolute contraindication to participation; however, with more severe symptoms, the risk of avulsion of the tibial tubercle should be weighed against the benefits of competing. In rare instances, conservative therapy is insufficient and a 2- to 3-week trial of crutches is required. Steroid injections have been used in the past but are not currently recommended owing to the associated risk of patellar tendon rupture. Complete recovery without residual pain or weakness is the rule. Recovery usually occurs within weeks but, in some cases, may not be complete until the underlying growth plate is closed. However, if the patient reaches skeletal maturity and is still symptomatic, consideration should be given to surgical removal of the tibial tubercle or the bony ossicle overlying the tibial tubercle (or both).

Sever's Disease

Sever's disease is an apophysitis of the calcaneus due to traction by the gastrocnemius-soleus complex. It initially was described in 1912[85] and commonly manifests as posterior heel pain in an 8- to 13-year-old athlete. It is bilateral in 60% of cases. As with other apophyseal injuries, pain is exacerbated by activity. Sever's disease can be associated with growth or tight heel cords or other biomechanical abnormalities. Impact sports, especially those that involve running, and sports in which cleats are worn frequently are implicated in the development of Sever's disease.

Patients have pain at the insertion site of the Achilles tendon and plantar fascia on the calcaneus. Tenderness is elicited when the calcaneus is squeezed bilaterally. Dorsiflexion of the ankle is restricted due to tight heel cords. Radiographs may be normal in appearance or may show partial fragmentation and increased density of the calcaneal apophysis, although these findings also can be seen in normal feet.

As in Osgood-Schlatter syndrome, treatment of Sever's disease is conservative and symptomatic. Treatment consists of ice, massage, stretching of the plantar fascia and involved muscles (gastrocnemius-soleus complex and ankle invertors or evertors), nonsteroidal anti-inflammatory drugs, and addition of shock-absorbing shoe inserts. Heel cups also have been found to be helpful, but they must be accompanied by stretching to avoid exacerbating the calf muscle contracture. Patients in whom conservative management fails have been found to have bone bruising and edema in the calcaneal metaphysis and apophysis, suggesting that calcaneal stress fractures may be the cause of persistent heel pain. Modification of activity and a trial of crutches for 3 to 4 weeks may be necessary.[86] Plantar fasciitis can cause heel pain as well, but patients will experience tenderness along the plantar fascia, especially at the attachment of the fascia to the calcaneus. Treatment involves the use of anti-inflammatory agents, rest, and relaxation of the plantar fascia with heel support pads.

Little League Elbow

Little League elbow is a term used to describe a group of injuries of the elbow including apophysitis, medial epicondylitis, and osteochondritis dissecans of the radial head and capitellum. The injury involves an overuse phenomenon resulting in inflammation at the site where the forearm flexor muscles originate. As its name suggests, it commonly affects baseball pitchers in children's leagues and is associated with overhead arm motion. It also is seen in other skeletally immature overhand athletes, including tennis players. Little League elbow is caused by the excessive forces placed on the medial side of the elbow during the late cocking and acceleration phases of throwing.

Patients tend to be preadolescents in whom pain on the medial aspect of the elbow is associated with diminished throwing effectiveness and decreased throwing distance. Examination reveals localized tenderness and swelling over the medial epicondyle and pain with resisted flexion of the

wrist. There may be a slight flexion contracture. Radiographs may be normal in appearance or may show fragmentation, sclerosis, and widening of the medial epicondylar apophysis. Treatment consists of a regimen of ice, nonsteroidal anti-inflammatory drugs, and modification of activity. Throwing is restricted until the symptoms have resolved. After resolution of the pain, the patient can begin a program of muscle stretching and strengthening, with a gradual return to throwing. During recovery, alteration of the throwing style to reduce the degree of sidearm delivery is advisable. Recovery usually takes 4 to 6 weeks. If pain returns during resumption of pitching, rest should be reinstituted. Patients with persistent pain, locking or decreased range of motion of the joint, or lateral elbow pain should be evaluated for avulsion fractures, loose bodies, and osteochondritis dissecans.

To minimize the risk of developing medial epicondylitis in children's league pitchers, the American Academy of Pediatrics recommends limiting the number of pitches to 200 per week or 90 pitches per outing[87]; however, the USA Baseball Medical and Safety Advisory Committee recommends lower pitch counts: 75 to 125 pitches per week or 50 to 75 pitches per outing, depending on age.[88] Preseason conditioning, use of proper pitching mechanics, and gradual increases in the amount and intensity of throwing are other preventive measures.

Apophysitis of the Hip

Apophyseal injuries of the hip involve sites around the hip where major abdominal and hip muscles either originate or insert: the anterior superior iliac spine, the anterior inferior iliac spine, the iliac crests, and the ischial tuberosities. Dancers and distance runners most commonly are affected. Patients with apophysitis of the hip experience dull pain near the hip that is related to activity. Treatment includes strengthening and stretching of the abdominal and hip muscles and restriction of activity.

Avulsion Fractures

Apophysitis tends to have an insidious onset; therefore, any patient with sudden onset of apophyseal pain after an acute traumatic event should be evaluated for an avulsion fracture of the apophysis or the adjacent bone. Such fractures occur when the muscular attachments to the apophyses are pulled off during strong active contractions against resistance, such as with a single powerful throw. Examination will reveal localized tenderness and swelling. The diagnosis usually is readily apparent on plain films (Fig. 174-26); however, bone scan and ultrasonography may play a role when the diagnosis is in question. Ultrasonography is advantageous because it involves no radiation exposure, it can detect a fracture before the development of an ossification center, and it provides a dynamic examination. Findings consistent with an avulsion fracture include a hypoechogenic zone, increased distance to the apophysis, dislocation of the apophysis, and mobility of the apophysis on dynamic examination.[89] Treatment of an avulsion fracture is based on the degree of separation: If the displacement is minimal (less than 2 cm with a hip avulsion and less than 5 mm with avulsion of the medial epicondyle[90]), immobilization for 4 to 6 weeks with subsequent slow resumption of activities usually is sufficient. With widely separated avulsion fractures, some experts recommend open reduction and fixation.[90]

Figure 174-26. Avulsion of the inferior iliac spine in a child with hip pain after kicking a soccer ball. (Courtesy of Marianne Gausche-Hill, MD.)

KEY CONCEPTS

- Knowledge of the pediatric musculoskeletal system is imperative for appropriate evaluation and treatment of the skeletally immature patient.
- Child abuse must be suspected in children younger than 3 years with nonsupracondylar humerus fractures, femur fractures, rib fractures, and complex skull fractures.
- Children with displaced supracondylar fractures are at significant risk for neurovascular injury and should have frequent evaluations to assess for compartment syndrome.
- All children who are not yet walking should have a thorough hip evaluation on any visit to the ED.
- All patients with a gait disturbance need a thorough physical examination and directed laboratory and radiographic evaluation.
- Septic arthritis constitutes a medical and surgical emergency that mandates immediate orthopedic consultation.
- Examination of the hip is warranted in all patients with knee pain.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 175 General Approach to the Pregnant Patient

Laurie J. Morrison

PERSPECTIVE

Epidemiology

Remarkable trends in the epidemiology of fertility have emerged that may have an impact on the demographic and diagnostic profile of patients encountered in today's emergency department (ED). The birth rates and fertility rates for all races, and the mean age at menarche in both the United States and Canada have fallen over the past decade. The age-specific fertility rate has declined in women younger than 30 years, and the rate of multiple births is rising.

The National Center for Health Statistics reported the number of U.S. live births for the year ending December 2005 to be 4.12 million with a birth rate of 14 per 1000 population for all races. In Canada during the year 2006-2007, the birth rate was 10.8 per 1000 population, with 352,848 births. Over the past 5 years Canada has witnessed a rise in the birth rate, with the mean age for mothers giving birth of 29.2 years. Women aged 30 to 34 years of age contributed 31.4% of this growth, whereas fertility rates in women younger than 20 years of age continue to decline.[1] The 2008 report from the U.S. National Center for Health Statistics noted that the birth rate for women younger than 25 years, the principal childbearing age, had fallen from 43% in 1990 to 38% in 2004.[2] The overall birth rate for teens aged 15 to 19 dropped from 15% in 1990 to 12% in 2004,[2] which resulted in a historic low of 72 pregnancies per 1000 women.[2] Nearly one half of all pregnancies in the United States occur among unmarried women, and this number is rising, increasing from 2.7 million in 1990 to 2.8 million in 2004, whereas rates among married women continue to fall, from 4.1 million in 1990 to 3.5 million in 2004. Pregnancy outcomes in the United States vary across the black, Hispanic, and white populations. The rate of pregnancies resulting in live births varies from 69% in non-Hispanic whites and 98% in Hispanic women to 50% for non-Hispanic blacks, whereas the rate of pregnancy resulting in abortion in non-Hispanic blacks is triple the rate (37%) for non-Hispanic whites (12%) and Hispanic women (19%).[2] The median age at menarche for adolescent American girls fell from 15.5 years in 1900 to 12.3 years in 2000[3] (Fig. 175-1).

From 1980 to 1997, the number of twin births in the United States rose 52% (from 68,339 to 104,137), and triplet and higher-order births rose 404% (from 1377 to 6737 births). At the same time, differences in twin birth rates between non-Hispanic white and non-Hispanic black mothers disappeared. Non-Hispanic white women were more than twice as likely as non-Hispanic black or Hispanic women to have a triplet birth.[4]

Statistical data concerning the pregnant patient demographics and frequency of use of the ED and the diagnostic profile are incomplete because most observational data sets group perinatal and pregnancy as "other medical diagnosis," which accounts for less than 2% of visits to the ED in the United States and Canada[5]; however, persons between the ages of 18 and 44 account for approximately 20% of all ED visits, so the risk of an unknown pregnancy complicating the diagnosis may be higher than anticipated.[6] A study of random pregnancy tests performed on female trauma patients revealed that 2% were pregnant.[7,8] Even when the chance of pregnancy was remote, female patients seeking treatment in the ED had a pregnancy rate of at least 10%.[8]

Pregnant patients may present with (1) symptoms and signs related to an undiagnosed, normal pregnancy (abdominal discomfort, nausea, urinary frequency, breast swelling and tenderness, fatigue, or near-syncope); (2) symptoms and signs related to complications of pregnancy (see Chapter 176); or (3) clinical manifestations of chronic medical illnesses that may be exacerbated by pregnancy (see Chapter 177). This chapter covers the following aspects of a normal pregnancy: common initial signs and symptoms, diagnostic tests, and considerations regarding treatment and referral.

Definitions

Gravidity refers to the number of pregnancies that the patient has had. This number includes all normal and abnormal pregnancies, including the current one.

Parity is the total number of times that the patient has given birth, regardless of outcome. Multiple births are counted individually for the purpose of calculating parity. Parity can be divided into four distinct categories; they usually are written on the chart parenthetically, adjacent to the parity level, and separated by hyphens. The four categories are identified by the letters T-P-A-L and refer to numbers of term infants, preterm infants, abortions, and children currently living (e.g., G10 P9 [6-1-2-7]).

Gestational age refers to the number of completed weeks of pregnancy from the last menstrual period.[7] A *term infant* is a child born between 38 and 42 completed weeks of gestation, a *preterm infant* is born before 38 completed weeks of gestation, and a *post-term infant* is born any time after 42 weeks' gesta-

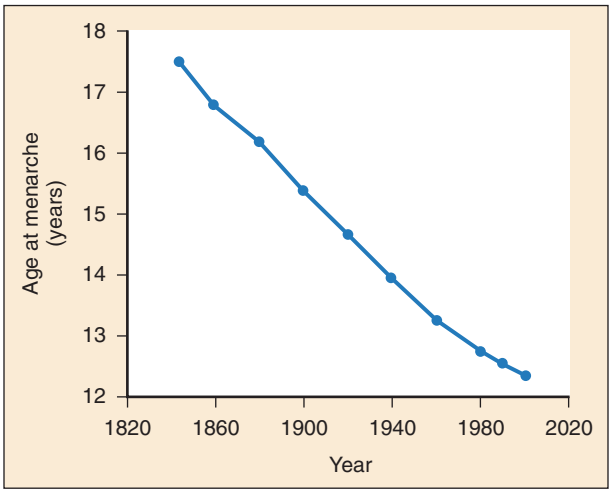


Figure 175-1. Age at menarche among European girls during the past 150 years. (Modified from Tanner JM: Growth at Adolescence. Oxford, Blackwell, 1962; Cunningham FG, et al: Williams Obstetrics, 19th ed. E Norwalk, Conn, Appleton & Lange, 1993; and MacDonald PC, et al: Recurrent secretion of progesterone in large amounts: An endocrine/metabolic disorder unique to young women? Endocr Rev 12:372, 1991.)

tion.[9] The conceptus is considered an *embryo* from conception until after the 8th week, when it is termed a *fetus*. An *abortus* is a fetus or embryo removed or expelled from the uterus during the first half of gestation (20 weeks or earlier) and that weighs less than 500 g or measures less than 25 cm.[9] *Premature* labor occurs before 37 weeks' gestation, and *postmature* labor occurs beyond 42 or 43 weeks' gestation.

CLINICAL FEATURES

History

It is prudent practice to suspect pregnancy in all female patients of childbearing age presenting to the ED. Cyclic ovulation occurs on average for 38 years. Out of a possible 10,000 ovarian follicles, 500 achieve ovulation.[9] Thus, there are "500 opportunities for pregnancy which likely can be achieved by sexual intercourse on any one of 1500 days. Physicians of all specialties must be constantly vigilant and sensitive to the possibility that women of reproductive age may be pregnant irrespective of their presenting complaint."[9]

The reliability of the sexual and menstrual history has been notably poor. Ramouska and colleagues reported that 11.5% of women with abdominal pain or vaginal bleeding had positive pregnancy tests, in contrast with their perception that there was "no chance" that they were pregnant.[8,9] Missed diagnosis of pregnancy in adolescents was associated with failure to document a sexual or menstrual history. Adolescents rarely mentioned the possibility of pregnancy at triage (10%), and 10% denied being sexually active.[10]

Early signs and symptoms of pregnancy elicited during the history include cessation of menses, anorexia, nausea, easy fatigability, urinary frequency, breast swelling and tenderness, and the perception of fetal movement (quickening at 16 to 20 weeks).

Cessation of menses becomes suggestive of pregnancy at 10 days or longer after the time that menstruation is expected. Intermittent, spontaneous vaginal bleeding or vaginal discharge is common during the first half of pregnancy, particularly in multiparous women. Most women without cervical lesions experience bleeding on or before the 40th day of pregnancy. This bleeding has been interpreted by some investigators to be physiologic in origin and a result of implantation.[11] Nevertheless, any patient presenting to the ED with vaginal bleeding during pregnancy should be considered to be at risk for a pathologic cause for the bleeding until proved otherwise.

It is possible to calculate the estimated date of conception in a regularly menstruating woman who has 28-day cycles and can give a reliable history. Franz K. Nägele, a German obstetrician in the 18th century, developed Nägele's rule, which is still the current standard: Add 7 days to the date of the first day of the last menstrual period and subtract 3 months.

Physical Examination

During the last half of pregnancy, the physical examination should be done with the patient in the left lateral recumbent position, to avoid precipitating the supine hypotension syndrome.

Vital signs in a pregnant patient are essentially the same as those in a nonpregnant patient. The only changes are seen in the heart rate and blood pressure. The resting heart rate increases approximately 10 to 15 beats/minute. Blood pressure in the brachial artery is highest in the sitting position, lowest when lying in the left lateral position, and intermediate in the supine position, except in pregnant women who have supine hypotension syndrome. Pathologic hypertension of pregnancy is defined as a sustained rise of 30 mm Hg systolic or 15 mm Hg diastolic over baseline values on at least two occasions, 6 hours or more apart.[9]

Fetal heart activity should be included as the fifth vital sign in the evaluation of a pregnant patient. It can be auscultated with a stethoscope at 17 weeks of gestation, on average, and by 19 weeks in nearly all pregnancies in nonobese women. With the use of Doppler ultrasonography, fetal cardiac activity can be detected as early as 8 weeks; however, it is more commonly heard by 10 weeks. It is possible to detect fetal heart activity at 48 days' gestation with echocardiography.

Auscultation of the pregnant abdomen reveals numerous findings that may be confusing. In addition to fetal heart sounds, it may be possible to identify sounds of fetal movement, the maternal pulse, maternal bowel sounds, and the fundic and uterine souffle. The fundic or umbilical cord souffle is created by blood rushing through the umbilical arteries. The whistling sound created is timed with the fetal pulse and present in 15% of pregnancies. The uterine souffle is a soft blowing sound timed with the maternal pulse and usually heard in the lower portion of the uterus. It is a function of blood flow through the dilated uterine vessels and can be heard in pregnancy and in women with uterine myomas or large tumors of the ovaries.[9]

Breast tenderness and fullness are common manifestations of pregnancy that can be appreciated on gentle physical examination. Objective breast changes include darkening of the areolae, greater prominence of the glands of Montgomery around the nipple, engorgement of the breasts with tiny bluish venules, and presence of colostrum at the nipple with gentle massage of the breasts. This milky material may persist for months or even years, especially if the patient continues to breast-feed.

Increased skin pigmentation (melasma gravidarum) and abdominal striae occur not only in pregnancy but also in women who ingest estrogen-progestin contraceptives.

Braxton-Hicks contractions are painless contractions that occur spontaneously and irregularly early in pregnancy. They also occur in patients with hematometra and those with uterine myomas. These contractions are not reliable for the diagnosis of pregnancy; however, they do not occur in ectopic preg-

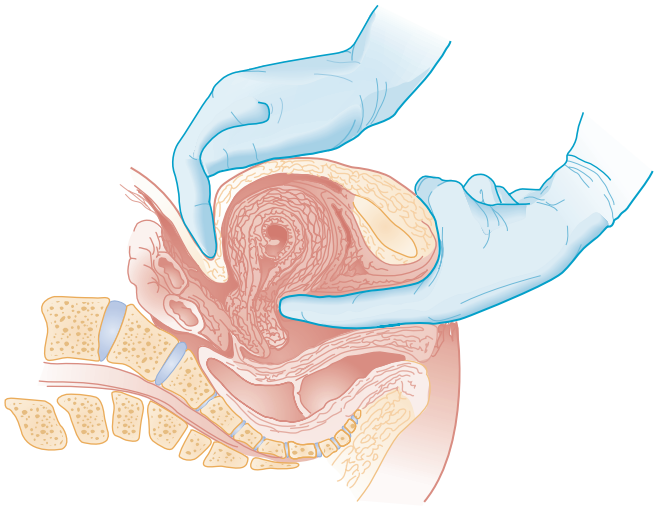


Figure 175-2. Hegar's sign. The softness and compressibility of the lower uterine segment can be so extreme that the fundus and cervix may even feel like separate organs. (Modified from Willson JR, et al: Obstetrics and Gynecology, 5th ed. St Louis, CV Mosby, 1975.)

nancy, so their presence may be helpful in excluding the existence of an ectopic pregnancy.[9]

Uterine enlargement can be felt in nonobese women. At 6 to 8 weeks the uterus is approximately the size of an orange. At 12 weeks the top of the fundus should be at the level of the symphysis pubis, at 16 to 20 weeks at the level of the umbilicus, and at 36 to 38 weeks at the level of the xiphoid process of the sternum. Thereafter, the fetus descends into the pelvis, and fundal height may decrease accordingly.[12]

At approximately 6 to 8 weeks of pregnancy, Hegar's sign can be appreciated during an internal pelvic examination. Hegar's sign is softening of the lower uterine segment caused by hyperemia. In some cases the softening is sufficient to allow the examiner to easily distinguish the cervix from the fundus on palpation. It can be found in other conditions; however, it is not as easily detected as it is in pregnancy (Fig. 175-2).

The vaginal mucosa becomes hyperemic during pregnancy and with any other condition that causes congestion of the pelvic organs. In response, the color of the mucosa of the vaginal walls changes from pink to blue to violet and can be visualized at the vaginal introitus (Chadwick's sign).[13]

At midpregnancy the fetus can be detected by ballottement or palpated through the maternal abdominal wall in a nonobese patient. The fetus floats in a large volume of amniotic fluid. Thus, with ballottement, pressure exerted on the uterus causes the fetus to sink and then rebound to its original position. Palpating the outline of the fetal body becomes easier near the end of pregnancy; however, subserosal myomas can simulate the fetal head and small parts, or both.[9]

DIAGNOSTIC STRATEGIES

Laboratory Tests

Determination of urine or serum human chorionic gonadotropin (hCG) is important in clinical management. Applications include diagnosis and monitoring of pregnancy and diagnosis and evaluation of the course of neoplastic trophoblastic disease or response to treatment (i.e., hydatidiform choriocarcinoma, gonadal teratoma, a carcinoma with ectopic secretion of hCG).[14]

Human CG assays are referenced to standard hCG preparations. Thus, the reference standard should always be noted in comparing results. One nanogram of hCG equals 9.3 mIU of the international reference standard provided by the World Health Organization (used in this chapter) and equals 5.0 mIU of the second international standard.[15]

Biologic assays for hCG are now only of historical interest. Since the 1960s, all hCG assays have been immunoassays. Enzyme-linked immunosorbent assay (ELISA) for hCG is the state-of-the-art pregnancy test. ELISA offers greater user convenience and has a sensitivity for levels of hCG between 25 and 50 IU/L.

Over the years the pregnancy test has undergone a number of refinements. Antibodies are selected that act against the purified β subunit of hCG, and this modification has resulted in improved sensitivity for low levels of hCG in the presence of luteinizing hormone. The development of monoclonal antibodies has improved specificity for the purified β subunit of hCG.

The fundamental process of ELISA involves an antibody adherent to a solid-faced support (usually plastic) that binds to a region of the hCG molecule. A second antibody chemically linked to an enzyme (for example, alkaline phosphatase) binds to another side of the trapped hCG molecule. The hCG molecule is sandwiched between the two antibodies. Excess enzyme-linked antibody is washed away, and a color developer is added and becomes blue when it comes in contact with the enzyme (Fig. 175-3). The antibodies can be polyclonal or monoclonal. Many variations exist with respect to the solid-faced support and the method of developing the color reaction.

In 1988 the first one-step pregnancy test became available. It was developed and patented by Unipath and is sold as Clearblue One Step. This test uses monoclonal antibodies specific for the β subunit of hCG. It includes a unique built-in control that shows a blue line when the test is complete and performed correctly.[16] This test appeals to consumers because it is rapid (requiring less than 5 minutes), requires no manipu-

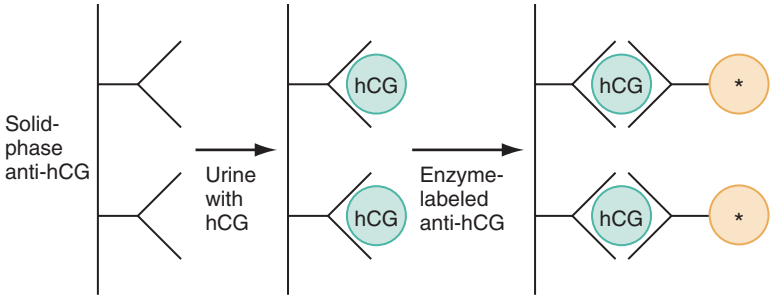


Figure 175-3. The principle of enzyme immunoassay (also sometimes known as "sandwich" or "immunometric" assay). hCG, human chorionic gonadotropin. (Modified from Chard T: Pregnancy tests: A review. Hum Reprod 7:701, 1992.)

lation by the user, offers hygienic sample handling, provides clear and easy-to-read results, and has a sensitivity level of hCG between 25 and 50 mIU/mL. This level of sensitivity means that more than 95% of pregnancies within 3 days after missed menses will be detected by a home pregnancy device.[17] For detection to occur on the day of missed menses, a lower sensitivity level of 12.5 mIU/mL is required. A study in 2001 compared routine urinary hCG point-of-care qualitative tests performed by nurses in the ED versus laboratory tests and found the former to be equally accurate and much faster, shaving 35 minutes off wait times for results.[18]

A well-designed ELISA applied to urine is not affected by drugs or a concurrent physiologic state. The only exception is in patients taking exogenous hCG for induction of ovulation.[19]

Normal hCG levels in men and premenopausal women range from 0.02 to 0.8 IU/L. Postmenopausal women may have higher levels.[20] The blastocyst begins to secrete hCG 7 days after fertilization.[21] Thus, the hCG released can be detected as early as 6 to 8 days after conception.[22,23]

The initial doubling time is fast and has been attributed to the actual process of implantation. This is followed by a slower rate of doubling as trophoblast hCG and maternal circulatory hCG levels equilibrate[23] (Fig. 175-4). Human CG levels peak at 7 to 10 weeks of pregnancy, with a mean value of 50,000 IU/L and a range of 20,000 to 200,000 IU/L.[24]

Human CG testing becomes positive in 98% of patients 7 days after implantation, which coincides with the time of the expected period. When a test with a sensitivity of 25 to 50 IU/L is used, a negative result 1 week from the expected time of the missed period essentially guarantees that a woman is not pregnant.[19]

The minimum number of false-positive results can be attributed to postmenopausal status, abortion in the first trimester, exogenous hCG for induction of ovulation, or an hCG-secreting tumor. Levels of hCG may take as long as 60 days to return to zero after an abortion.[25] Persistent elevation of hCG beyond 60 days after abortion may indicate an incomplete abortion, a twin pregnancy with only one fetus removed, or an ectopic pregnancy.[4]

The hCG assay continues to be the standard for the diagnosis of pregnancy. Routine clinical detection of pregnancy by ultrasonography is not possible until 6 weeks' gestation, when the hCG level is 1000 IU/L or more.[26-28]

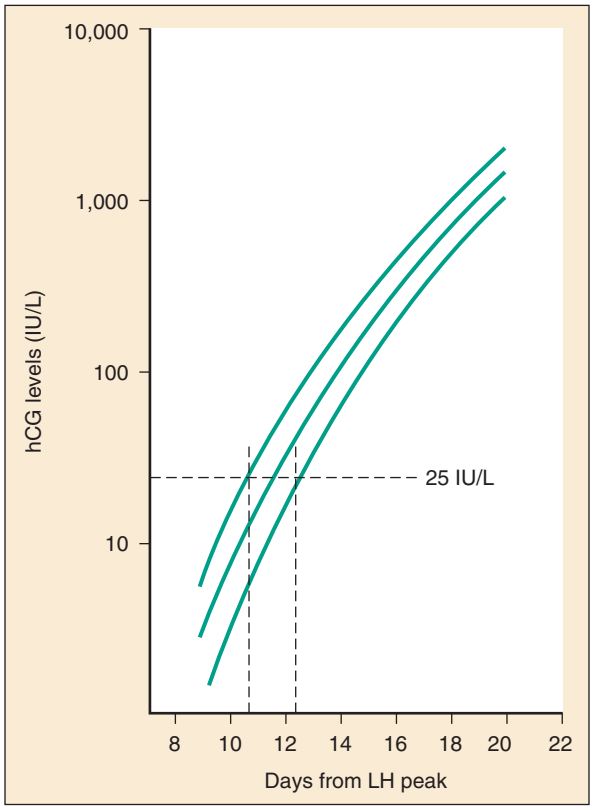


Figure 175-4. Levels of circulating human chorionic gonadotropin (hCG) in early pregnancy, showing that an assay with a sensitivity level of 25 IU/L would yield a positive result in some subjects between 10 and 11 days after the peak in luteinizing hormone (LH) and in most subjects at 12 to 13 days after the peak. (Modified from Chard T: Pregnancy tests: A review. Hum Reprod 7:701, 1992.)

Radiology

Ultrasonography

Ultrasonography is reliable for the diagnosis of intrauterine pregnancy during the first trimester. In addition to diagnosis, it also locates the embryo and assesses gestational age and viability. Transabdominal sonography is more commonly used; however, transvaginal sonography may be necessary during the first trimester if transabdominal sonography is not diagnostic.

Sonography during the second trimester is used to survey fetal anatomy. The anatomic survey includes the cerebral ventricles, four-chamber view of the heart, spine, stomach, urinary bladder, umbilical cord insertion on the abdominal wall, and kidneys.[29]

Much debate exists about whether ultrasonography should be performed as part of routine prenatal screening in all pregnancies. The National Institutes of Health Consensus Conference in 1984 concluded that sonographic studies performed during pregnancy are safe.[30] Genetic screening of pregnancy requires an accurate gestational age based on biparietal diameter; accordingly, ultrasonography at 15 to 16 weeks is a routine component of maternal genetic screening.

Transabdominal Sonography. Transabdominal ultrasound examination at 4 to 5 weeks of gestation can identify the presence of a small white gestational ring. This sonographic finding disappears after the 11th week of gestation.[9]

At 6 weeks the gestational sac can be visualized by transabdominal sonography (Fig. 175-5). Presence of the sac is con-

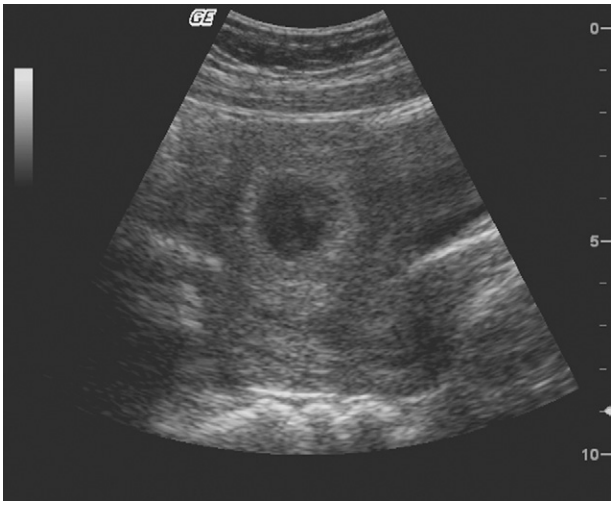


Figure 175-5. Transabdominal ultrasound image showing a gestational sac with no fetal pole or yolk sac. (Courtesy of Andrew A. Common, MD.)

firmed when two central uterine echoes are visualized within the hypertrophied endometrium. This diagnostic echo is called the double decidual sac sign. A healthy pregnancy can be determined by correlating the size of the sac with gestational age and quantitative hCG values.[31] At 8 weeks the fetal pole and fetal heart activity can be visualized reliably with transabdominal ultrasonography in a normal pregnancy.

Transvaginal Sonography. Transvaginal sonography affords greater resolution than transabdominal sonography and does not require a full bladder. Transvaginal ultrasound examination can identify an intrauterine gestational yolk sac at 5 weeks' gestation. This finding correlates with a quantitative hCG value of more than 1800 IU/L.[32] Fetal heart motion can be detected with transvaginal ultrasound evaluation at 6 weeks' gestation and correlates with an hCG level of 6770 IU/L and a crown-rump length of 2 mm.[9]

An intrauterine pregnancy can be diagnosed by sonographic findings in the following order of appearance: the double ring sign, the double gestational sac, the intrauterine fetal pole, and intrauterine fetal heart activity (Fig. 175-6). The gestational sac is eccentrically positioned within an asymmetrically thickened decidua. An ectopic pregnancy can be difficult to distinguish from a normal pregnancy and may be seen sonographically as a pseudosac or fluid collection centrally placed in the uterine cavity and surrounded by symmetrically thickened endometrium.[33]

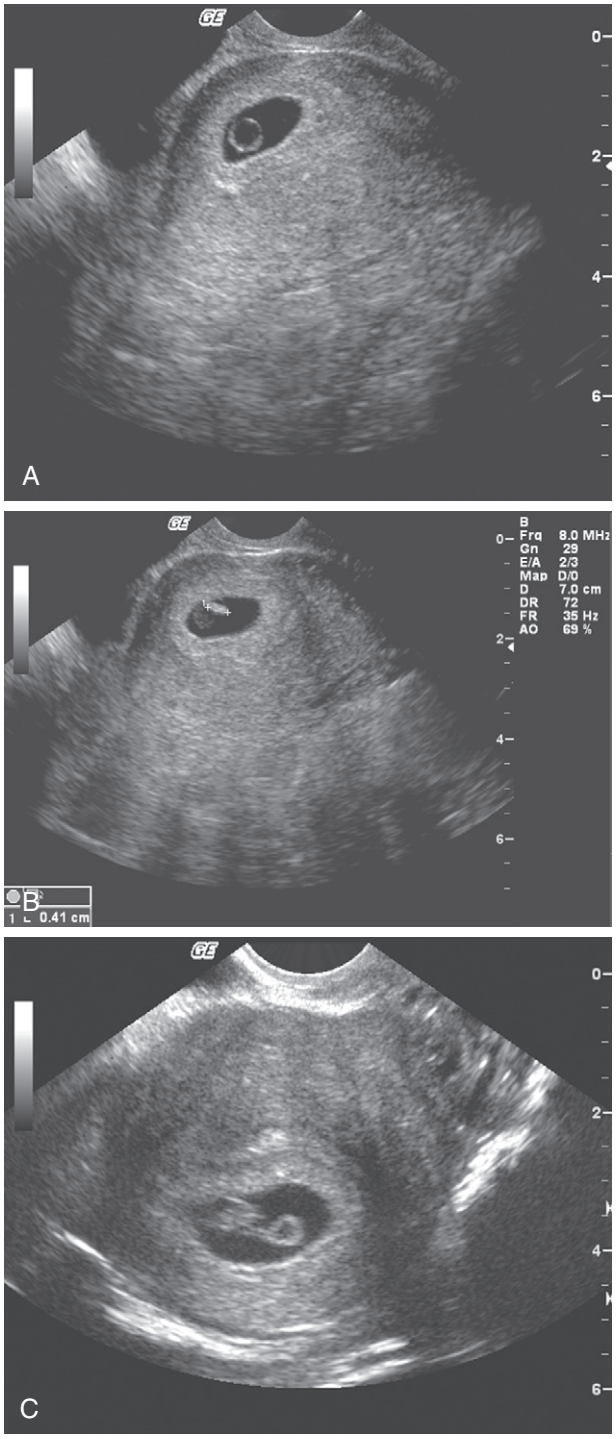


Figure 175-6. Transvaginal ultrasound images. **A,** Yolk sac. **B,** Fetal pole. **C,** Fetal pole, vitelline duct, and yolk sac. (Courtesy of Andrew A. Common, MD, and Derek Muradali, MD.)

Magnetic Resonance Imaging

No significant side effects have been documented to date with the magnetic field and radio waves used in magnetic resonance imaging (MRI). Gadolinium is the most common intravenous contrast agent, and allergic reactions with this agent are rare. The effects of strong magnetic fields on the fetus are unknown, so the consensus is that use of this imaging modality should be avoided in pregnant women.

Plain Radiographic Fetal Identification

The fetus can be reliably recognized by plain radiography after 16 weeks' gestation. Fetal foci of ossification can be identified as early as 14 weeks.[9]

Diagnostic Imaging Considerations in Pregnant Patients

The decision to perform imaging investigations in a pregnant patient must take into consideration the risk to the developing fetus from radiation exposure and the inherent risks with such investigations for the mother, balanced with the risk to the mother and fetus associated with missing the diagnosis because of reluctance to use available diagnostic imaging techniques. The potential for adverse outcomes with intrauterine fetal exposure to the radiation used in radiography is minimal. Case-control studies report a slight but statistically significant increase in the relative risk for childhood cancer.[34] Radiation is a dose-dependent teratogen.[35] The fetal central nervous system is most vulnerable to the teratogenic effects of radiation at 8 to 15 weeks after conception. The fetal dose of radiation is estimated from the ovarian or uterine dose. Pregnant women exposed to less than 5000 mrad have pregnancy outcomes similar to those in control subjects.[36] A study of childhood cancers in the offspring of female radiologists revealed a cancer frequency of 0.16% in children exposed to 1000 mrad of radiation in utero. In comparison, the frequency of cancer is 0.07% among children who were not exposed to radiation in utero.

Table 175-1 summarizes the estimated fetal radiation exposure associated with the more common diagnostic imaging modalities. Radiation exposure depends on the equipment and technique, and estimates listed may not be generalizable to every radiology department.

A thoughtful, common-sense approach to the differential diagnosis will provide a sound basis for imaging investigations that will undoubtedly be in the best interests of the mother and the fetus. It is important not to defer investigations that are medically necessary, so long as the anticipated fetal doses are less than 5000 mrad.[37]

Table 175-1 Fetal Radiation Exposure with Various Imaging Modalities

PROCEDURE	ESTIMATED FETAL RADIATION EXPOSURE (MRAD)
Chest plain film with an abdominal shield	<1*
Chest CT with an abdominal shield	<10*
Abdomen plain film	240*
Abdomen CT: with and without contrast	2000 and 1000*
Cardiac catheterization: with and without pelvic fluoroscopy	1300 and 100*
Head CT	<10*
Unilateral venography without an abdominal shield	305
Limited venography with an abdominal shield	<50
Pulmonary angiography via femoral access	405
Pulmonary angiography via brachial access with an abdominal shield	<50
Perfusion lung scan using ^{99m}Tc-MAA:	
3 mCi	18
1-2 mCi	6–12
Ventilation lung scan using:	
^{133}Xe	3–20
^{99m}Tc-DTPA	7–35
^{99m}Tc-SC	1–5
Ventilation-perfusion scan	<50

*Data from Duke University and Duke Medicine Division of Radiation Safety: Fetal radiation dose estimates. Available at: http://www.safety.duke.edu/radsafety/fdose/fdxray.asp; accessed May 6, 2008.

CT, computed tomography; DTPA, diethylenetriaminepenta-acetic acid; MAA, microaggregated albumin; SC, sulfur colloid.

Modified from Ginsberg JS, et al: Thrombotic complications in the obstetric patient. In Coleman RW, et al (eds): Hemostasis and Thrombosis: Basic Principles and Clinical Practice, 3rd ed. Philadelphia, JB Lippincott, 1994.

DIFFERENTIAL CONSIDERATIONS

Considerations in the differential diagnosis with early pregnancy include myomas, hematometra, adenomyosis, and an extrauterine mass or masses. Patients with these diagnoses, excluding hematometra (a blood collection or retention in the uterus), typically have persistent regular menses. The enlarged uterus in these nonpregnant conditions generally is firmer and less elastic and boggy than it is in pregnancy.[9]

Spurious pregnancy is imaginary pregnancy or pseudocyesis (false phantom). It usually occurs in women nearing menopause or in women who have an overwhelming desire for pregnancy. The associated increase in abdominal girth generally is attributable to fat deposition, fluid accumulation, or intestinal gas. The menses may become unpredictable with respect to timing, duration, and amount of flow. This condition can be associated with changes in the breasts, including enlargement, galactorrhea, and increased areolar pigmentation. Patients may have morning sickness of psychogenic origin. The associated use of phenothiazines may cause amenorrhea, hyperprolactinemia, breast enlargement, and galactorrhea. Women with this condition may perceive fetal movements. Most commonly these movements can be attributed to muscular contractions of the abdominal wall and normal gastrointestinal peristalsis.[9]

The diagnosis is confirmed by the presence of a small uterus and a negative pregnancy test result. The challenge in this condition is convincing the affected woman of the lack of pregnancy and addressing the underlying reason for this delusion.

SPECIFIC DISORDERS

Perspective. In general, a pregnant patient should be treated and assessed in the same way as for all other patients. However, the normal physiologic changes of pregnancy may mask or unmask underlying medical conditions. In addition, consideration should be given to the increased medical risks of pregnancy (e.g., deep vein thrombosis) and risk to the fetus associated with diagnostic imaging or surgical interventions.

Headache

The most common headache during pregnancy is a muscle contraction headache.[38] The patient usually has had a history of headaches before the pregnancy. The headaches begin on waking and increase in intensity during the day. The headache is described as a broad band, squeezing or constricting in quality, and localized to the vertex. The paracervical muscles are taut, and palpation usually reproduces or exacerbates the pain. During pregnancy these headaches are worsened by postural changes and psychosocial stress. Commonly used abortive medications for migraines in pregnancy include acetaminophen (e.g., Tylenol), non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin, opioids, tryptans, antiemetics, and caffeine.[39] From 18 to 86% of classic migraine sufferers experience remission from attacks during pregnancy, particularly women with menstrual migraines.[39-41] Therefore, any headache in a pregnant patient requires investigation, except a typical headache in a patient with a known primary headache disorder.[39,42]

Brain tumors enlarge during pregnancy and shrink temporarily postpartum.[43] Most brain tumors become symptomatic during the second half of pregnancy, and they account for 10% of maternal deaths during pregnancy. Both pituitary gland and prolactin-secreting adenomas swell during pregnancy. Headache usually develops during the first trimester and precedes visual changes by approximately 1 month.[38] Occasionally, central venous thrombosis may occur during pregnancy and mimic eclampsia. The lack of proteinuria and hypertension points to the former diagnosis.[38] Central venous thrombosis is an unusual cause of postpartum headache that is associated with a mortality rate of 40%.[38]

Pseudotumor cerebri is benign intracranial hypertension in the absence of a mass lesion and hydrocephalus. Symptoms and signs often include headache and papilledema. Other associated findings include decreased visual acuity, loss of color vision, defects in visual fields, and horizontal diplopia caused by abducens nerve palsy.[38] Pseudotumor cerebri associated with pregnancy usually occurs in obese women and begins during the third to fifth months of pregnancy. Symptoms resolve spontaneously after 1 to 3 months.[44]

Spontaneous subarachnoid hemorrhage accounts for 10% of maternal deaths. Reviews of the risk for subarachnoid hemorrhage in pregnant versus nonpregnant patients have been conflicting. The absolute risk has been estimated to be between 1 in 2000 and 1 in 10,000. In a majority of cases, the intracranial bleeding is attributable to rupture of an arteriovenous malformation or a ruptured intracranial aneurysm. The overall risk for rupture of an arteriovenous malformation is identical in

pregnant and nonpregnant patients without previous bleeding at 0.031 per patient-year.[45] Arteriovenous malformations usually bleed during the second trimester and during labor. Berry aneurysms initially bleed during the third trimester, and the incidence of bleeding increases as the pregnancy advances.

Nearly one third of cases of spontaneous subarachnoid hemorrhage are a result of bleeding disorders, bacterial endocarditis, metastatic tumor, and sickle cell disease. Cerebral hemorrhage is the most common cause of death in toxemia. It occurs in 60% of patients who die after becoming eclamptic.[38]

New-onset headache or a change in the usual pattern of headache pain during pregnancy or the postpartum period warrants a closer look. A thorough history and a detailed physical examination with emphasis on visual field and funduscopic examination can, in most cases, exclude the aforementioned serious disorders.

Chest Pain

The diagnosis of cardiac disease is complicated by the fact that the signs and symptoms of a normal pregnancy are suggestive of heart disease. Pregnancy is associated with easy fatigability, dyspnea, orthopnea, palpitations, syncope, peripheral edema, chest discomfort, and reflux. Triggers for further cardiac evaluation include progressive orthopnea, dyspnea severe enough to limit activity, paroxysmal nocturnal dyspnea, syncope during or immediately after exertion, hemoptysis, and chest pain in an ischemic distribution at rest or associated with exertion, anxiety, or anger.[38]

Cardiovascular findings are altered in normal pregnancy. Peripheral edema is present in 80% of pregnant women. A third heart sound and systolic murmurs are common. Diastolic murmurs and systolic murmurs of grade higher than II/VI warrant investigation. Other worrisome signs include cyanosis, clubbing, pulmonary rales, distended neck veins throughout the cardiac cycle associated with hepatomegaly and peripheral edema, persistent split S_2, and criteria of pulmonary hypertension (left parasternal lift and a loud P_2).[38]

The pregnant patient is predisposed to thrombolytic disease as a result of increased venous pressure, decreased distal venous flow, and significant venous stasis from compression of the pelvic veins and inferior vena cava by the enlarging uterus. Other predisposing factors may include the antepartum use of oral contraceptives before conception and the propensity for stasis secondary to lack of activity in the workplace and at home as the pregnancy progresses.[9] The annual incidence of thromboembolism is five times higher in postpartum women than in pregnant women.[46] The incidence of deep vein thrombosis is three times higher than that of pulmonary embolism; however, the incidence of deep vein thrombosis during pregnancy has remained constant over the last 30 years, whereas that of pulmonary embolism during pregnancy doubled.[46] This increased risk for pulmonary embolism in pregnancy should prompt thorough evaluation of pregnant patients who present with pleuritic chest pain, syncope, acute right-sided heart failure, or more subtle signs such as unexplained fever, dyspnea, or tachycardia.

Abdominal Pain

Displacement of the abdominal contents by the expanding uterus during pregnancy causes abdominal discomfort that may be associated with nausea, vomiting, gastroesophageal reflux, delayed gastric emptying, bowel irregularity, urinary frequency, and back and buttock pain. These findings may complicate the clinical assessment of a pregnant woman with abdominal pain. Delay in diagnosis or failure to diagnose and treat underlying pathologic conditions may result in maternal and fetal morbidity and death.

Obstetric causes of abdominal pain early in pregnancy include vascular congestion of the pelvic tissues, round ligament tension, ectopic pregnancy, and threatened abortion. Later in pregnancy, considerations in the obstetric differential diagnosis should include Braxton-Hicks contractions, toxemia, premature labor, abruptio placentae, and rupture of the uterus.[38] Nonobstetric causes include all diagnoses seen in a nonpregnant patient (e.g., cholecystitis, pyelonephritis, renal colic, ovarian torsion, salpingitis, corpus luteum cyst rupture or torsion, degeneration of a uterine myoma). Common surgical diseases that may complicate pregnancy include appendicitis, gallbladder disease, and intestinal obstruction.

The incidence of appendicitis in pregnant patients is equal to that in nonpregnant patients, but the perforation rate is higher. The state of pregnancy results in delays in diagnosis of appendicitis that contribute significantly to maternal and fetal morbidity and mortality.[47] The perinatal mortality rate for women with nonperforated appendicitis is 4.8%. It rises, however, to 27.8% in those experiencing perforation at the time of surgery. The perforation rate is as high as 30% during the third trimester.[48]

The diagnosis of appendicitis is more difficult during the latter half of pregnancy, but it is challenging even in early pregnancy. Anorexia, nausea, and vomiting are symptomatic of appendicitis and may be misinterpreted as hyperemesis of pregnancy. As the uterus enlarges, the appendix moves upward and outward toward the right. As the appendix moves higher, the omentum is unable to surround the appendix and contain the infection if rupture occurs. Thus, appendiceal rupture in pregnant women results in generalized peritonitis.[9] A retrospective review comparing magnetic resonance imaging (MRI) findings with surgical confirmation of disease suggests that MRI is useful for triaging pregnant patients with acute abdominal and pelvic pain.[49] When available, MRI should be considered in this setting, particularly during the first trimester of pregnancy, because of the higher levels of radiation exposure associated with computed tomography (CT) of the abdomen.

Musculoskeletal Pain

Hand symptoms are common during pregnancy. The median nerve is at risk for compression distally within the carpal tunnel. Approximately 25% of pregnant women complain of hand symptoms compatible with median nerve compression, but only 2.3% are actually found to have carpal tunnel syndrome.[50] Symptoms of carpal tunnel syndrome include the classic triad of burning pain, numbness, and tingling in the thenar area or median nerve distribution. The patient often is awakened from sleep with the onset of symptoms. In 80% of cases, the symptoms are bilateral. Tapping over the median nerve at the wrist (Tinel sign) or hyperflexing the wrist (Phalen's test) reproduces the symptoms and is diagnostic. Because the symptoms usually resolve during the postpartum period, only supportive treatment is required. A sleep splint applied with the hand in slight flexion resolves the symptoms in 80% of patients.[51]

Postural changes in the cervical spine, the shoulder girdle, and the lumbar spine result in pregnancy-related posterior pelvic pain and low back pain. Lordosis is exaggerated and becomes progressively more symptomatic during pregnancy. Low back pain usually is localized to the lumbar region just above the sacroiliac joint, worsened by forward flexion at the waist, and results in decreased range of motion and tenderness

to palpation of the erector spinae muscles. The pain may radiate to one or both of the legs. The nature of the referred pain lacks the radicular quality of discogenic pain and does not extend beyond the knee.[38] Patients should avoid wearing high-heeled shoes because this will increase the lumbar lordosis with exacerbation of the pain. Swimming and conditioning exercises are recommended.[38] Pregnancy-related posterior pelvic pain is hypothesized to occur because of asymmetrical sacroiliac joint laxity. It is important to distinguish this from low back pain, because the treatments are different. Pregnancy-related pelvic pain is a stabbing pain in the buttocks, distal and lateral to the L5-S1 area, which may or may not radiate to the posterior thigh or knee, with a normal range of motion at hips and spine. The *posterior pelvic pain provocation test* has a positive predictive value of 0.91 for pregnancy-related pelvic pain. The test is performed with the patient in the supine position with the hips and knees bent at 90 degrees: The examiner applies pressure with one hand at the knee along the long axis of the femur from anterior to posterior while using the other hand to stabilize the pelvis at the contralateral anterior iliac spine. A positive test result is gluteal pain on the side of femoral pressure.[52]

Meralgia paresthetica is a painful dysesthesia along the lateral aspect of the thigh caused by entrapment of the purely sensory lateral femoral cutaneous nerve as it passes beneath the inguinal ligament. This condition develops during the third trimester in obese pregnant women or in pregnant women with excessive and rapid weight gain. It resolves during the postpartum period without treatment.[38]

Trauma

Trauma is the leading cause of death in young men and women. The American College of Obstetricians and Gynecologists reports that 1 in every 12 pregnancies is complicated by physical trauma.[53] Trauma is the leading cause of maternal death secondary to nonobstetric etiologic conditions or disorders.[54] One study suggests that fetal mortality after trauma is significantly associated with higher injury severity score (of 28 or higher), lower final hemoglobin level, higher number of transfusions, longer hospital stay, and a higher incidence of disseminated intravascular coagulation.[55] A retrospective institutional review over 5 years demonstrated that older maternal age, first-trimester presentation, elevated serum lactate, and high injury severity score were associated with poor fetal outcome.[56] Other studies have not demonstrated a correlation between injury severity scores and maternal and fetal morbidity, and their authors advocate enhanced clinical vigilance for the unexpected in caring for obstetric trauma victims (see Chapter 34).[57]

Domestic Violence

Up to 35% of all ED visits by women are due to injuries or illnesses related to domestic violence. Domestic violence is conservatively estimated to occur in 10 to 20% of North American spousal relationships. Estimates of abuse during pregnancy vary widely, ranging from less than 1% up to 37%. The wide variation in estimates is attributable to different study designs, definitions of abuse (Table 175-2), and sample population demographics.[58-67] Moreover, it generally is accepted that violence in the home is underreported and the prevalence is higher than studies estimate.

Violence may begin or increase during pregnancy.[67-71] Prevalence estimates in 1997 based on cross-sectional survey data obtained from interviews with 261 pregnant women suggest that 33.3% of women will report abuse when asked. Of the 261 women interviewed, 26.7% were African Americans, 25.2% were of Hispanic origin, and 58.3% were white women.[72] Pregnant teenagers are at even greater risk for abuse from parents and partners.[73] Other significant demographic variables associated with abuse and pregnancy can be classified under the major headings of social instability, unhealthy lifestyle, and physical health problems.[70] Abused pregnant women are more commonly of lower educational levels, unmarried, unemployed, eating an unhealthy diet, abusing drugs and alcohol, and experiencing an unplanned pregnancy; they may also delay seeking prenatal care[70,74,75] (Table 175-3). Evidence of physical abuse is more common in the facial area in a nonpregnant patient,[67] whereas blunt abdominal trauma is the most common injury type in a pregnant patient.[70,71] Blunt abdominal trauma can result in miscarriage, abruptio placentae, fetal loss, premature labor, fetal fractures, low birth weight, and premature delivery. Other common injury sites in abused pregnant patients are the breasts and genitals.

Table 175-2 Frequency of Abuse in Pregnant Women Attending a Prenatal Clinic ($N = 1014$)*

No abuse	70.3%
Pushing, shoving, slapping	23.5%
Emotional abuse (includes verbal abuse, being allowed no money, being kept away from family and friends)	21.2%
Kicking, biting, hitting with fist	13.2%
Damage to property or pets	12.0%
Throwing objects to intimidate	11.2%
Serious threat to life	5.8%
Choking, strangling	5.6%
Sexual abuse	5.3%
Using a knife, gun, or other weapon	3.7%

*Some women reported abuse in more than one category.
Modified from Webster J, et al: Domestic violence in pregnancy: A prevalence study. Med J Aust 161:468, 1994.

Not all abuse is physical abuse (see Table 175-2). Emotional abuse, including intimidation by the aggressor to maintain an abused woman in the abusive relationship, has been well described.[76,77] Most abused women remain in the relationship, and few have any knowledge of the support services available to them.[70] Abused pregnant women often suffer from low self-esteem, despair, anxiety, fear, withdrawal, post-traumatic stress disorder, passivity, learned helplessness, and depression and have high rates of attempted suicide.[76,77]

Abused pregnant women may have vague physical symptoms, including headache, fatigue, insomnia, choking sensations, gastrointestinal complaints, pelvic pain, and backache. These symptoms may be manifestations of a deep depression or of a conversion reaction related to the adversity of the home environment.

Abused pregnant women do not believe that they have any control over the health of their fetus. They hold a strong belief that chance is the major determinant in fetal outcome. This perception and the associated behavior (e.g., cigarette smoking, alcohol and drug abuse) are unlikely to change unless the abused women leave their abusive situation. Only then will they be able to improve their sense of power and self-esteem and make changes in their behavior that are in the best interest of the fetus.[70]

Identification and appropriate follow-up are paramount in the ED management of an abused pregnant patient. Most abused patients will not volunteer information regarding domestic violence unless specifically asked. They are more likely to disclose such information to another woman or medical

Table 175-3 **Frequency of Socioeconomic/Psychosocial Characteristics among Nonabused versus Physically Abused Pregnant Women**

CHARACTERISTIC	NO. OF PATIENTS (%)		*P* VALUE*
	NONABUSED (*N* = 512)	ABUSED (*N* = 36)	
Unmarried	69/503 (13.7)	35/36 (97.2)	≤.001
Failed to complete high school	41/488 (8.4)	25/33 (75.8)	≤.001
Born in Canada†	275/496 (55.4)	21/35 (60.0)	NS
Unemployed or receiving social assistance	133/498 (26.7)	27/35 (77.1)	≤.001
Pregnancy unplanned	151/503 (30.0)	32/36 (88.9)	≤.001
Regularly smokes cigarettes	63/506 (12.5)	26/36 (72.2)	≤.001
Regularly drinks alcohol	83/430 (19.3)	23/33 (69.7)	≤.001
Uses illicit drugs	6/501 (1.2)	20/36 (55.6)	≤.001
Unhealthy diet	31/499 (6.2)	10/36 (27.8)	≤.001
Previous emotional problems	19/499 (3.8)	22/36 (61.1)	≤.001
Aware of abuse services	245/416 (58.9)	18/34 (52.9)	NS

*The chi-square test was used to compare figures.
†Origin of study; included as parameter reflecting immigrant status.
NS, not significant.
Modified from Stewart DE, Cecutti A: Physical abuse in pregnancy. CMAJ 149:1259, 1993.

personnel of either sex who offer protection, support, and access to help and who are very sympathetic.[70,71] Fear that an abused woman will be offended by direct questioning is unfounded.[70]

It is important to include direct queries about abuse when taking a history from a patient in the absence of her partner. Direct questioning may take the form of the following: "How do you and your partner resolve disagreements?" "Have you been hit or hurt by anyone in the last year?"[70] "Are you concerned for your safety or the safety of your children?" "Many women come to the emergency department with similar problems and are victims of violence. Could this be what happened to you today?"[78]

The history also should ascertain the status of the current pregnancy, satisfaction with the spousal relationship, the nature and location of injuries, the need for medical treatment in the past and present, the level of violence at home, awareness of access to social and legal services, and the safety of children at home. With respect to child safety, it is well documented that spousal abuse is associated with child abuse.[63,76]

The patient's account of the abuse should be accepted in a nonjudgmental manner. Subsequently, however, it is essential to communicate that such abuse is unacceptable and likely to escalate in the future. This should be followed by an offer to assist the patient in developing a safety plan, which should include community resources and information regarding protection, legal rights, and emergency shelters for her and her children.

If a pregnant patient is found to be at high risk and living in dangerous circumstances, it is prudent to arrange for immediate shelter or hospital admission. All patients identified as victims of abuse should be referred to social services, community support groups, and if appropriate, substance abuse programs; referral for psychiatric and high-risk obstetric consultations may be indicated as well.

ED staff should receive education regarding the issues surrounding victims of domestic violence and how to deal with a victim effectively, cooperatively, and expeditiously. In addition, it is important for the ED to develop strong links with battered women's services and to display posters and pamphlets about domestic violence and local resources.[70]

MANAGEMENT

Perspective

The assessment and care of pregnant patients require specialized equipment and access to specific ancillary tests. Basic equipment for the management of all obstetric and gynecologic emergencies includes a variety of specula and a Doppler ultrasonographic device for fetal heart readings. The specula should be available in at least four blade widths: extra narrow at 16 mm (e.g., Miltex Pedersen), narrow at 22 mm (e.g., Miltex Pedersen), regular at 25 mm (e.g., Pedersen), and wide at 35 mm (e.g., Graves). Speculum blades are available in three lengths: small at 7.7 cm, medium at 10.2 cm, and large at 17.8 cm. The medium-length Pedersen speculum provides adequate exposure for most women. Virginal or postmenopausal women may require a narrow or extra narrow speculum with a 10.2-cm-long blade. Pelvic examination of obese patients or patients in whom the vaginal walls are loose and redundant may necessitate the use of a Graves speculum.

Appropriate diagnostic imaging (transabdominal and transvaginal sonography, as well as color Doppler ultrasonography or impedance plethysmography) and laboratory testing (both quantitative and qualitative hCG testing) should be available at all times. Access to MRI should be available by previous arrangement if equipment is not on site. If ready access to a high-risk obstetric unit is not available, prearranged agreements for transport to specialized centers for high-risk obstetric patients and neonates should be in place.

Health Promotion and Disease and Injury Prevention in Pregnancy

For some patients, the ED is where the diagnosis of pregnancy is first made and the time when the patient is introduced to both the emotional and physiologic realities of pregnancy. For others, the ED is simply the only source of prenatal care.

After complications of pregnancy and comorbid conditions have been excluded, pregnant patients should initially be counseled, appropriately referred, and encouraged to partici-

pate in regular prenatal care. The proportion of American women beginning prenatal care during the first trimester has consistently increased since the early 1990s, with a rate of 83.9% reported in 2004.[79] Statistics suggest that timely care rose 10% during the 1990s and continued to rise until 2003.[79-81]

Although the time for prenatal counseling often is limited in the ED, such counseling can have a positive impact on both fetal and maternal health. The following discussion is not inclusive of all prenatal issues; however, it does outline some of the most commonly identified risks and patient concerns, along with the appropriate advice that should be given.

Use of Seat Belts, Helmets, and Air Bags

The use of three-point seat belt restraints should be emphasized. There is no evidence that these restraints will increase the chance of fetal injury. The proper use of seat belts is a good predictor of a favorable maternal and fetal outcome in the case of vehicular trauma.[82] The lap belt should be snugly and comfortably placed low across the maternal pelvis, below the uterine corpus and fundus and across the thighs, with the shoulder belt positioned between the breasts and no excessive slack allowed anywhere in the belt.[83] The National Highway Traffic Safety Administration does not consider pregnancy to be an indication for the deactivation of air bags and recommends the combined use of seatbelts and air bags.[84] All patients should be encouraged to wear helmets when riding a bicycle or a motorcycle, whether voluntarily or in compliance with the law. The latter modes of transportation are ill advised during pregnancy and certainly inappropriate during the third trimester.

Safe infant feeding should be reinforced. It is inappropriate and unsafe to breast-feed in a moving vehicle. Similarly, it is unsafe to remove the child from the restraining device to bottle-feed while in a moving vehicle.

Sexual Intercourse during Pregnancy

Sexual intercourse is considered harmless for a normal pregnant female. Most texts recommend abstinence during the last 4 weeks of pregnancy or when abortion or preterm labor is threatened.

Safety of Douching during Pregnancy

Certain guidelines must be adhered to for the proper use of douches during pregnancy. Hand-held bulb syringes are prohibited because of the risk of air embolism. The height of the douche bag should be limited to 2 feet or less above the level of the hips to prevent high fluid pressure. The nozzle should not be inserted more than 8 cm into the vagina.

Travel Restrictions during Pregnancy

Generally, travel is not prohibited during pregnancy. Airlines allow unrestricted travel for women with normal pregnancies (and no history of premature labor) up to 35 to 37 weeks of gestation. Only short trips are allowed with more advanced pregnancy and require a doctor's letter of assurance that delivery is not imminent. It should be emphasized to the pregnant traveler that she should walk about at least every 2 hours to minimize the risk for thromboembolism. Cosmic radiation exposure for casual travelers is trivial. Pregnant airline employees or frequent flyers should consult a physician during pregnancy because their cosmic radiation exposure is increased.[85]

Immunization during Pregnancy

The Advisory Committee on Immunization Practices posts guidelines for immunization during pregnancy on the CDC website. Immunization of pregnant women should be guided by risk-versus-benefit logic. Relative indications for vaccination consist of three guiding principles: (1) the risk of exposure is high, (2) the infection could cause harm to the mother or infant, and (3) the vaccine is unlikely to cause harm. Live virus vaccines generally are contraindicated during pregnancy because of the theoretical risk of transmission of the virus to the fetus. If a pregnant patient has received a live virus vaccine in the 3 months before the pregnancy, she should be referred for counseling on the potential risks to the fetus.[86] Comprehensive and specific guidelines for each vaccine are updated and posted on the CDC website (http://www.cdc.gov/vaccines/pubs/ACIP-list.htm).

Importance of Regular Appropriate Exercise

Suitable regular exercise should be encouraged during pregnancy because it helps prevent venous stasis and thromboembolic disease, maintain regular bowel movements, improve posture and perineal muscle strength, and regulate weight gain. Sedentary lifestyles and work activities that are performed predominantly in the sitting position should be discouraged. The American College of Obstetrics and Gynecology recommends that healthy pregnant women without medical or obstetric complications adhere to the standard of exercise for nonpregnant patients recommended by the CDC and the American College of Sports Medicine. The standard aimed at improving health and well-being includes an accumulation of 30 minutes or more of moderate activity daily. Pregnant patients with comorbid conditions require exercise also and should engage in regular exercise with close medical supervision.

Patients should be encouraged to strengthen the abdominal muscles; stretch the lower part of the back; balance pectoralis muscle strength with that of the trapezius, rhomboids, and latissimus dorsi; strengthen the cervical spine flexors; and perform regular pelvic tilt exercises in all positions to correct the postural imbalance of pregnancy and relieve discomfort.

Appropriate exercise includes low-impact and aquatic aerobics. High-impact activities should be avoided, especially during the latter half of pregnancy. Aggressive abdominal exercises are discouraged after 12 weeks of gestation because they may exacerbate the development of diastasis recti. Moderate regular abdominal strengthening exercises will minimize the lordosis of pregnancy. The Aerobics and Fitness Association of America recommends that exercise intensity during pregnancy be limited to an exercise heart rate range of 55 to 70% of the age-predicted maximum heart rate; class time should not exceed 1 hour and 15 minutes, including the time for stretching and relaxation exercises; and frequency should not exceed three times a week.

Diet, Vitamin Supplementation, and Weight Gain Recommendations

It is not recommended that pregnant patients take routine multivitamin supplementation; however, iron supplements may be recommended, especially during the latter half of pregnancy. It also is recommended that 1 mg of folic acid be taken daily, beginning 1 month before conception and continuing throughout the first trimester to reduce the risk for neural tube defects.

The American College of Obstetricians and Gynecologists recommends an average weight gain for pregnant women of

between 10 and 12 kg.[87] The normal physiologic changes of pregnancy account for approximately 9 kg. The remainder is maternal fat storage.[88] The CDC makes weight gain recommendations according to prepregnancy weight: underweight women, 13 kg; normal-weight women, 11 kg; and overweight women, 7 kg.[89]

Appropriate Management of Pregnant Patients with Substance Abuse Problems

The risks of smoking, illicit drug use, and excessive alcohol consumption during pregnancy are widely known to the lay public; however, despite warnings, some pregnant women continue to smoke and imbibe excessively. Cigarette smoking during pregnancy has declined steadily since 1989, to 12.9% in 1998 and 10.7% in 2005.[79] Nonetheless, tobacco use by pregnant teenagers continues to be high, with a reported rate of 19% in 2005. The U.S. Department of Health and Human Services Substance Abuse and Mental Health Services Administration concluded from its National Household Survey on Drug Abuse (1996-1997 database) that among women 15 to 44 years of age who were currently pregnant, 2.5% used one or more illicit drugs in the past month, 1.3% engaged in "binge" alcohol use, and slightly less than 20% were past-month cigarette smokers. *Binge drinking* was defined as drinking five or more drinks on the same day at least once during the previous 30 days. In comparison with a nonpregnant cohort, women who abuse substances reported curtailing their use during pregnancy and resuming use postpartum. Substance abuse during pregnancy was more frequent in unmarried women without a high-school education. The prevalence decreased as the amount of adult education increased. The prevalence of drug abuse during the last month of pregnancy showed no difference between Hispanic and white pregnant females. Drug abuse during pregnancy was significantly more common among black than among Hispanic patients.[90]

KEY CONCEPTS

- An important principle of the ED evaluation is that any female patient of childbearing age should be assumed to be pregnant; 11.5% of women with abdominal pain or vaginal bleeding have a positive result on pregnancy testing even when they have stated that there is "no chance" that they are pregnant.
- Accurate vital signs are best obtained with pregnant patients in the left lateral decubitus position.
- ELISA is the state-of-the-art urine pregnancy test. It offers excellent user convenience and has a sensitivity for levels of hCG between 25 and 50 IU/L.
- The decision to perform diagnostic imaging investigations in a pregnant patient must take into consideration the risk to the developing fetus from radiation exposure, the inherent risk of such investigations for the mother, and the risk to the mother and the fetus associated with missing the diagnosis because of reluctance to use available imaging techniques.
- In general, a pregnant patient should be treated and assessed in the same way as all other patients. However, the normal physiologic changes of pregnancy may mask or unmask underlying medical conditions.
- The ED encounter is an opportunity to reinforce or provide primary education and advice on health promotion and disease and injury prevention in pregnancy.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 176

Acute Complications of Pregnancy

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PERSPECTIVE

Acute complications of pregnancy can appear in all trimesters of pregnancy and can pose challenges in diagnosis and management. Life-threatening disorders of pregnancy, such as ectopic pregnancy in early pregnancy, pregnancy-induced hypertension in mid- and late pregnancy, and abruptio placentae in late pregnancy, are relatively common, and recognition and management of them should be an integral part of the emergency physician's knowledge base. The emergency physician must consider the signs and symptoms, week of gestation, and stability of the patient when developing management strategies.

PROBLEMS IN EARLY PREGNANCY

Miscarriage

Perspective

Spontaneous miscarriage is common in pregnancy. Early pregnancy loss (positive human chorionic gonadotropin [hCG] finding but less than 6 weeks after last normal menstrual period) occurs in approximately one fourth of pregnancies.[1,2] The overall embryonic and fetal loss rate after implantation ranges up to one third of detectable pregnancies. The risk of miscarriage rises with increasing maternal age (fivefold increase in those older than 40 years compared with those 25–29 years), increasing paternal age, alcohol use, increased parity, low prepregnancy body mass index, maternal stress, and history of vaginal bleeding.[3] Approximately 80% of miscarriages occur during the first trimester; the rest occur before 20 weeks of gestation. Fetal demise after 20 weeks of gestation or when the fetus is more than 500 g is considered premature birth.

Threatened or actual miscarriage is a common patient presentation in the emergency department (ED). Approximately one fourth of clinically pregnant patients experience some bleeding. It is widely estimated that approximately 50% of all women who have bleeding during early pregnancy miscarry, although the risk is probably higher in the ED population.[4,5] Those with a history of bleeding who do not miscarry have otherwise fairly normal pregnancies, although they have approximately twice the risk of premature birth and low-birth-weight infants.[6]

Principles of Disease

Pathophysiology. The two major causes of miscarriage are uterine malformations and chromosomal abnormalities. In some cases, the ovum never develops (anembryonic gestation). In the majority of early miscarriages, fetal death precedes clinical miscarriage, often by several weeks. Although clinical symptoms of miscarriages are most common between 8 and 12 weeks of gestation, sonographic evidence in most cases demonstrates death before 8 weeks; if fetal viability can be demonstrated by heart activity and a normal sonogram, the subsequent fetal loss rate is only 3.4%.[7]

Chromosomal abnormalities are associated with approximately 40% of miscarriages. Maternal factors that increase the risk of miscarriage include congenital anatomic defects, uterine scarring, leiomyomata, and cervical incompetence. Other conditions associated with increased miscarriage rates include toxins (e.g., alcohol, tobacco, and cocaine), autoimmune factors, endocrine disorders including luteal phase defects, and occasional maternal infections.[2]

Terminology. Several stages of miscarriage are recognized. In *threatened miscarriage*, the patient has bleeding but a closed internal cervical os. The risk of miscarriage in this population is estimated at 35 to 50%, depending on patient demographics and severity of symptoms.[4] If the internal cervical os is open, the miscarriage is considered inevitable. If products of conception (POCs) are present at the cervical os or in the vaginal canal, the miscarriage is termed *incomplete*. *Completed* miscarriage occurs when the uterus has expelled all fetal and placental material, the cervix is closed, and the uterus is contracted. Establishing the diagnosis of completed miscarriage is difficult in the ED unless a gestational sac is visualized because the cervix may close after an episode of heavy bleeding and clot passage without or after only partial expulsion of POCs. Unless an intact gestation is passed and recognized, completed miscarriage should be diagnosed only after a dilation and curettage (D&C) with pathologic confirmation of gestational products; a sonogram demonstrating an empty uterus with a prior known intrauterine pregnancy (IUP); or by reversion to a "negative" pregnancy test result, which may take up to several weeks.

Missed abortion is a relatively obsolete term referring to clinical failure of uterine growth over time. The terms *anembryonic gestation* (when no fetus is seen) and *first-* or *second-trimester fetal*

death (failure to see fetal heart activity in a fetus with at least a 5-mm crown-rump length) are more appropriate.

Clinical Features

Patient history should include the estimated length of the gestation; time since last menstrual period; symptoms of pregnancy (and loss of pregnancy symptoms); degree of bleeding; duration of bleeding; the presence of cramps, pain, or fever; and attempts by the patient to induce miscarriage. The severity of symptoms does not correlate well with the risk of miscarriage, although cramping and passage of clots are thought more likely to occur as the miscarriage becomes inevitable.[4]

The assessment of the patient who experiences first-trimester vaginal bleeding includes a careful abdominal examination to evaluate for tenderness or peritoneal irritation from a potential ectopic pregnancy as well as to determine uterine size (the uterus should not be palpable abdominally). Pelvic examination should be performed to evaluate whether the cervix is closed or open, to look for clots or POCs, and to determine the degree of vaginal bleeding, as well as uterine size and tenderness. The cervix should be gently probed with a ring forceps (not a Q-Tip) to determine whether the internal os (1.5 cm deep to the external os) is open or closed. This is unnecessary in the patient who has a clearly open os or visible POCs but can be safely performed during the first trimester as long as the forceps are used gently and do not penetrate the cervix more than 2 or 3 cm. In the patient with second-trimester bleeding, probing should not be done because the uterus is more vascular and the organized placenta may overlie the cervical os. Parous females normally have an open or lax external os, a finding of no significance. The adnexa may be enlarged, often unilaterally, either because the corpus luteum is cystic or because the pregnancy is ectopic. Significant adnexal or uterine tenderness should always raise the possibility of an ectopic pregnancy. Much less commonly, pelvic infection can cause uterine and adnexal tenderness during early pregnancy.

Any tissue that is passed should be suspended in saline or tap water (or viewed under low-power microscopy) to differentiate sloughing endometrium and organized clot from chorionic villi, which form fronds and appear feathery in the saline suspension. Except in the rare instance of heterotopic pregnancy (combined intrauterine and ectopic pregnancies), this reliably excludes ectopic pregnancy. Passage of tissue called the *decidual cast* in ectopic pregnancy can easily be confused with intrauterine miscarriage if the physician does not confirm the absence of chorionic villi in the tissue.[8]

Diagnostic Strategies

A hemoglobin determination is useful to provide a baseline measurement and to evaluate the degree of bleeding in females whose bleeding persists. In addition, an Rh (*Rhesus*) type should be obtained. Ultrasonography is the primary means of evaluating the health of the fetus as well as its location (Table 176-1). Because historical and clinical estimations of gestational age are often inaccurate, ultrasonography is useful to provide an accurate measure of fetal age and viability (Box 176-1).

In the stable patient with threatened miscarriage, observation over time may be sufficient to determine when intervention is needed, as long as ectopic pregnancy has been excluded. Serial quantitative hCG levels are used to assess the health of the fetus if sonographic findings are indeterminate or if the gestational age is less than 6 or 7 weeks. The sonographic "discriminatory zone" is defined as the quantitative hCG level at which a normally developing IUP should reliably be seen. This is considered to be 6500 mIU/mL for transabdominal ultrasonography and 3000 mIU/mL by transvaginal ultrasonography.[9] Ultrasonography can be performed or repeated when hCG levels rise to 3000 mIU/mL. If hCG levels are flat or decline, or if sonographic criteria for fetal demise are demonstrated (see Box 176-1), the patient should be referred to an obstetrician for follow-up to be sure the miscarriage completes.

Table 176-1 Landmarks for Gestational Age and hCG by Transvaginal Ultrasonography

FINDING	WEEKS FROM LMP	β-HCG (MIU/ML)
Gestational sac (25 mm)	5	1000
"Discriminatory zone"	5–6	1500–2000
Yolk sac	6	2500
Upper "discriminatory zone"	6–7	3000
Fetal pole	7	5000
Fetal heart motion	8	17,000

hCG, human chorionic gonadotropin; LMP, last menstrual period.
Adapted from Dart RG: Role of pelvic ultrasonography in evaluation of symptomatic first-trimester pregnancy. Ann Emerg Med 33:310, 1999.

BOX 176-1 SONOGRAPHIC CRITERIA FOR ABNORMAL PREGNANCY WITH TRANSVAGINAL ULTRASONOGRAPHY

- No gestational sac at β-hCG level of 3000 mIU/mL
- No yolk sac with gestational sac of 13 mm (or at 32 days since last menstrual period)
- 5-mm crown-rump length with no fetal heart tones
- No fetus with gestational sac of 25 mm mean diameter
- No fetal heart tones after 10–12 weeks' gestational age

β-hCG, human chorionic gonadotropin.
Adapted from Dart RG: Role of pelvic ultrasonography in evaluation of symptomatic first-trimester pregnancy. Ann Emerg Med 33:310, 1999.

Differential Considerations

Of greatest concern is the possibility of ectopic pregnancy, which can masquerade as a threatened miscarriage in the early stages. Even in the patient with painless vaginal bleeding, the diagnosis of ectopic pregnancy must be considered. For this reason, early ultrasonography is imperative to locate the pregnancy in the patient who has bleeding or pain.

Other diagnoses should also be considered. A small amount of bleeding occurs at the time of implantation of the blastocyst into the endometrium and occasionally at the time of the first missed menses. Molar pregnancy is also characterized by vaginal bleeding, usually during the late first trimester or the second trimester. This condition can be identified by ultrasonography. Cervical and vaginal lesions can also cause local bleeding and can usually be seen on vaginal inspection.

Management

After assessment of hemodynamic status and management of blood loss, a patient with a threatened miscarriage requires very little specific medical treatment. Anti-D immunoglobulin should be administered if the patient is Rh-negative (unless the father is also known to be Rh-negative). A 50-μg dose is used during the first trimester and a full 300-μg dose after the

first trimester.[10] Ectopic pregnancy should always be considered, and ultrasonography should be employed urgently if risk factors for ectopic pregnancy are present or if the patient has pain. Although ectopic pregnancy can be associated with painless bleeding,[8] this occurs less frequently than bleeding associated with pain. Ultrasonography can be scheduled more routinely at a later time in the patient without significant pain as long as the patient is aware that the potential for ectopic pregnancy exists until excluded by identifying an IUP. In the patient who is planning pregnancy termination, prompt referral should be encouraged and chorionic villi confirmed at the time of uterine evacuation.

Unless an IUP is diagnosed, the patient with threatened miscarriage should be given careful instructions to return if she has signs of hemodynamic instability, significant pain, or other symptoms that might indicate ectopic pregnancy (so-called ectopic precautions). In conjunction with gynecologic colleagues, an ED protocol is useful to determine when follow-up sonographic evaluation and serial hCG measurements should be obtained. In addition, studies have indicated that low progesterone[11] and low inhibin A[12] levels can also be predictors of early pregnancy loss, although they are not in widespread use.

Fifty percent or more of women with threatened miscarriage who are seen in the ED ultimately miscarry. Treatment to "prevent" miscarriage is not useful because most fetuses can be shown to be nonviable 1 or 2 weeks before actual symptoms occur. In the vast majority of cases, spontaneous miscarriage is the body's natural method of expelling an abnormal or undeveloped (blighted) pregnancy. Thus, a major goal of early management should be patient education and support. Patients should be advised that moderate daily activities will not affect the pregnancy. Tampons, intercourse, and other activities that might induce uterine infection should be avoided as long as the patient is bleeding, and she should return immediately for fever, abdominal pain, or a significant increase in bleeding. Cramping from a known IUP can be safely treated with oral synthetic narcotics, if needed. If the patient passes tissue, it should be brought to a provider to examine for POCs because differentiation of fetal parts or villi from decidual slough or casts is difficult.

Patient counseling is paramount with threatened miscarriage. Determination of fetal viability can be helpful in either reassuring the mother or preparing her for probable fetal loss. Miscarriages are associated with a significant grieving process, which is frequently more difficult because early pregnancy is unannounced and early fetal death is not publicly recognized. Because many women consider that small falls, injuries, or stress during the first trimester can precipitate miscarriage, patients should be reassured that they have done nothing to cause miscarriage. It is important to make them aware that miscarriage is common, grieving is normal, and counseling may be beneficial.[13] A follow-up appointment should be scheduled after miscarriage to support the patient in resolving such issues.

Treatment of the patient with inevitable miscarriage includes observation, dilation and evacuation, or D&C to remove the remaining intrauterine contents. When the miscarriage is incomplete, the uterus may be unable to contract adequately to limit bleeding from the implantation site. Bleeding may be brisk, and gentle removal of fetal tissue from the cervical os with ring forceps during the pelvic examination often slows bleeding considerably.

Management of patients with presumed completed spontaneous miscarriage is more complicated. If the patient brings tissue with her, this should be sent to the pathology department for evaluation. Unless an intact gestational sac or fetus is visualized, it is rarely clear clinically whether miscarriage is "complete." Studies have shown that in women with a history consistent with miscarriage who have minimal remaining intrauterine tissue as determined by ultrasonography, expectant management is safe, but only if ectopic pregnancy can be excluded.[14] If endometrial tissue is not seen with ultrasonography, bleeding is mild, and gestational age is less than 8 weeks, curettage is frequently unnecessary and the patient can be safely followed by a gynecologist for serial hormonal assays. Up to 80% of women with first-trimester miscarriage complete the miscarriage without intervention. However, the need for later visits and procedures may be decreased by uterine curettage, particularly if the fetal pole or a gestational sac is visible on the sonogram at the time of evaluation.[14] Medical management with misoprostol instead of D&C is also an option and has a success rate of 84%.[15] The patient should be instructed to return if uncontrolled bleeding, severe pain or cramping, fever, or tissue passage occurs. Follow-up is recommended in 1 or 2 weeks to ensure that the miscarriage is complete.

After miscarriage, the patient should be advised that fetal loss, even during the first trimester, can cause significant psychological stress. Follow-up in 1 or 2 weeks with a gynecologist should be provided. Some physicians prescribe antibiotics after D&C (usually doxycycline or metronidazole), particularly in patient populations at high risk for genital tract infections. Ergonovine or methylergonovine (0.2 mg PO twice daily) can be used to stimulate uterine involution. The patient should be advised to return if signs of infection (fever or uterine tenderness) occur, if bleeding resumes, or if further tissue is passed.

Ectopic Pregnancy

Perspective

Ectopic pregnancy, or pregnancy implanted outside the uterus, is an increasingly frequent problem that poses a major health risk to women during the childbearing years. It is the third leading cause of maternal death, responsible for 6% of maternal mortality.[16] The incidence of ectopic pregnancy has risen steadily over several decades and now accounts for approximately 2% of all pregnancies. Although the incidence of ectopic pregnancy is highest in women age 25 to 34 years, the rate is highest among older women and women belonging to minority groups. Simultaneous intrauterine and extrauterine gestations (heterotopic pregnancy) have historically been rare, occurring in approximately 1 in 4000 pregnancies; more recently, women who have undergone assisted reproduction techniques with embryo transfer have demonstrated a risk of one of the pregnancies being ectopic of 4% or greater.[17] The incidence of ectopic pregnancy among women presenting to the ED with vaginal bleeding or pain in the first trimester is consistently approximately 10% in several series.[18,19]

Principles of Disease

Implantation of the fertilized ovum occurs approximately 8 or 9 days after ovulation. Risk factors for an abnormal site of implantation include prior tubal infection (50% of cases), anatomic abnormalities of the fallopian tubes, or abnormal endometrium (host factors). These result in failure of the embryo to implant in the endometrium. The risk of ectopic pregnancy increases approximately threefold after a patient has had pelvic inflammatory disease (PID). In recent studies, one fourth of patients with ectopic pregnancies have had tubal surgery, including tubal sterilization or removal of ectopic pregnancy.[20] If the patient is currently using an intrauterine device,

BOX 176-2 RISK FACTORS FOR ECTOPIC PREGNANCY

- Tubal surgery (for tubal sterilization or ectopic pregnancy)
- Pelvic inflammatory disease
- Smoking
- Advanced age
- Prior spontaneous abortion
- Medically induced abortion
- History of infertility
- Intrauterine device

Modified from Bouyer J, et al: Risk factors for ectopic pregnancy: A comprehensive analysis based on a large case-control, population-based study in France. Am J Epidemiol 157:185, 2003.

increased risk can occur from complicating PID or from failure of the intrauterine device to prevent ectopic pregnancy as well as preventing endometrial implantation. All forms of contraception except intrauterine device use and tubal sterilization decrease the incidence of ectopic pregnancy. After an ectopic pregnancy, the risk of a subsequent ectopic pregnancy was 22% in one series of women trying to conceive again (Box 176-2).[21]

When abnormal implantation occurs in the fallopian tubes, on the ovaries, or in the cervix, the pregnancy usually grows at a less than normal rate, which can result in abnormally low or declining hCG production. Leakage of blood occurs intermittently through the tubal wall or out the fimbrial ends, with spillage into the peritoneal cavity. Bleeding and other symptoms are usually intermittent. Three outcomes are possible: Tubal abortion may occur into the peritoneal cavity or vagina, spontaneous involution of the pregnancy may occur, or rupture of the pregnancy with internal or vaginal bleeding may result. Implantation in the uterine horn (cornual pregnancy) is particularly dangerous because the growing embryo can use the myometrial blood supply to grow larger (10–14 weeks of gestation) before rupture occurs.

Clinical Features

The classic clinical picture of ectopic pregnancy is a history of delayed menses followed by abdominal pain and vaginal bleeding in a patient with known risk factors. Unfortunately, this history is neither sensitive nor specific. Risk factors for ectopic pregnancy are absent in almost half of patients. Fifteen to 20% of patients with symptomatic ectopic pregnancy have not missed a menstrual period, and occasionally the patient has no history of vaginal bleeding. Abdominal pain is most commonly severe, peritoneal in nature, and constant. Shoulder pain implies free fluid in the peritoneal cavity and is very suggestive of an ectopic pregnancy with significant hemorrhage. The pain of ectopic pregnancy can also be crampy, intermittent, or even absent.[8,22]

The physical examination findings in ectopic pregnancy are likewise variable. Vaginal bleeding, uterine or adnexal tenderness, or both in the patient with a positive pregnancy test result should trigger consideration for ectopic pregnancy. Tachycardia is not always present, even with significant hemoperitoneum; hemoglobin is usually normal and hypotension may be seen.[22] The presence of peritoneal signs, cervical motion tenderness, or lateral or bilateral abdominal or pelvic tenderness indicates increased likelihood of an ectopic pregnancy. If significant peritoneal irritation is present, pain can preclude accurate bimanual examination. Adnexal masses are felt in only 10 to 20% of patients with ectopic pregnancy.[8,22]

Vaginal bleeding is often mild. Heavy bleeding with clots or tissue usually suggests a threatened or incomplete miscarriage, although the patient with an ectopic pregnancy who has decreasing hormonal levels may experience endometrial sloughing, which can be mistaken for passage of fetal tissue. Passed tissue should be examined, as with cases of miscarriage, in tap water or saline (or under low-power microscopy). Unless fetal parts or chorionic villi are seen, ectopic pregnancy should not be excluded in the patient with bleeding or passage of "tissue."

Diagnostic Strategies

Because both the history and the physical examination of the patient with ectopic pregnancy are insensitive and nonspecific, ancillary studies are required to locate the pregnancy in any patient who has abdominal pain or vaginal bleeding and a positive pregnancy test result. Technologic advances have allowed accurate detection or exclusion of ectopic pregnancy in the assessment of the woman with first-trimester vaginal bleeding or pelvic pain. Ultrasonography and hormonal assays are the most commonly used ancillary tests. In addition, laparoscopy can be the most efficient diagnostic tool in some instances.

Ultrasonography. Ultrasonography is the primary method used to locate early gestation, establish gestational age, and assess fetal viability. Transabdominal ultrasonography is most useful for identifying IUPs with fetal heart activity and excluding ectopic pregnancy (except in patients at high risk for heterotopic pregnancy due to infertility procedures).[9] Transvaginal ultrasonography is more sensitive, recognizes IUP earlier than transabdominal ultrasonography, and is diagnostic in up to 80% of stable patients presenting in the first trimester.[23] In general, an indeterminate ultrasound usually does not result in a diagnosis of normal pregnancy; one series of more than 1000 pelvic ultrasounds reported that 53% of indeterminate ultrasounds resulted in a diagnosis of embryonic demise, 15% were ectopic pregnancies, and only 29% had an IUP.[23] However, correlation of sonographic results with quantitative hCG measurements can add to the predictive value. With hCG less than 1000 mIU/mL, the risk of ectopic pregnancy increases fourfold; ultrasonography is still diagnostic in a significant minority of patients (one third of patients with ectopic pregnancy), although the accuracy of sonographic findings may decrease.[19,24] Normal pregnancy is unlikely if no gestational sac is seen by transvaginal ultrasonography with an hCG level greater than 3000 mIU/mL, but the differential diagnosis includes both miscarriage and ectopic pregnancy.[24] Unfortunately, levels of approximately 1500 mIU/mL develop in only approximately half of patients with ectopic pregnancies (see Table 176-1).[5,9]

Indeterminate sonograms, which demonstrate neither an IUP nor extrauterine findings suggestive of ectopic pregnancy (Box 176-3), occur in approximately 20% of ED evaluations of women with first-trimester bleeding or pain. Ectopic pregnancy is more likely among this subgroup with indeterminate sonograms if the hCG level is less than 1000 mIU/mL and when the uterus is empty. Endometrial debris and fluid in the uterus do not exclude ectopic pregnancy.[25]

Hormonal Assays. The quantitative hCG levels have two primary uses in ED evaluation: Serial levels can be used in the stable patient who can be followed as an outpatient, and a single level can be correlated with sonographic results for improved interpretation. hCG levels normally double every 1.8 to 3 days for the first 6 or 7 weeks of pregnancy, beginning 8 or 9 days after ovulation. An initial quantitative level can be measured at the time of the ED visit, particularly if the sono-

BOX 176-3 SONOGRAPHIC FINDINGS IN THE PATIENT WITH SUSPECTED ECTOPIC PREGNANCY

Diagnostic of Intrauterine Pregnancy (IUP)
- "Double" gestational sac
- Intrauterine fetal pole or yolk sac
- Intrauterine fetal heart activity

Diagnostic of Ectopic Gestation
- Pregnancy in fallopian tube (Fig. 176-1)
- Ectopic fetal heart activity (Fig. 176-2)
- Ectopic fetal pole

Suggestive of Ectopic Gestation
- Moderate or large cul-de-sac fluid without IUP
- Adnexal mass without IUP*

Indeterminate
- Empty uterus (Fig. 176-3)
- Nonspecific fluid collections (Fig. 176-4)
- Echogenic material
- Abnormal sac (Fig. 176-5)
- Single gestational sac

*Complex mass most suggestive of ectopic pregnancy, but cyst can also be seen with ectopic pregnancy.

Adapted from Dart RG: Role of pelvic ultrasonography in evaluation of symptomatic first-trimester pregnancy. Ann Emerg Med 33:310, 1999.

Figure 176-1. Pregnancy in the fallopian tube, diagnostic of an ectopic pregnancy. (Courtesy of Mary Ann Edens, MD.)

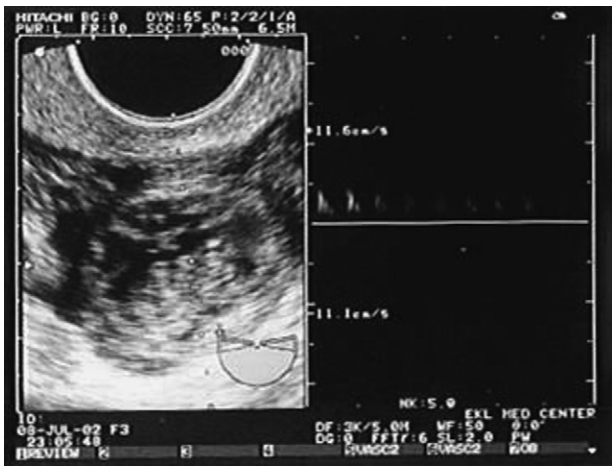


Figure 176-2. Fetal heart movements detected by ultrasonography in the fallopian tube, diagnostic of an ectopic pregnancy. (Courtesy of Mary Ann Edens, MD.)

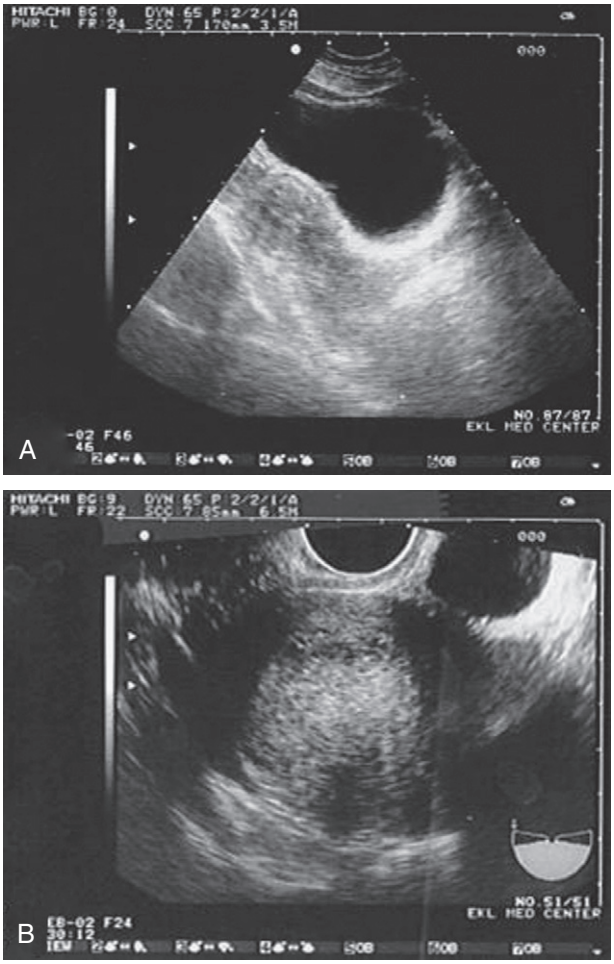


Figure 176-3. Ultrasonography showing an empty uterus, indeterminate for diagnosis of an ectopic pregnancy. (Courtesy of Mary Ann Edens, MD.)

Figure 176-4. Ultrasonography showing fluid around the fallopian tube. (Courtesy of Mary Ann Edens, MD.)

gram is indeterminate or the gestational age is estimated as less than 6 weeks. A repeat level should be measured 48 to 72 hours later. Levels that fall or double slowly are associated with abnormal pregnancy, either intrauterine or ectopic. However, rising hCG levels can be seen during early ectopic pregnancy, with falling levels of hCG seen initially in only 40% of ectopic pregnancies. Twenty-one percent of women with an ectopic pregnancy in one series had an initial rise in hCG at a rate consistent with an IUP.[26]

Figure 176-5. Ultrasonography showing a gestational pseudosac. (Courtesy of Mary Ann Edens, MD.)

Single quantitative hCG levels can also be useful in conjunction with ultrasonography; normal IUPs should be visible transvaginally at 3000 mIU/mL hCG (see Table 176-1). A benign course for ectopic pregnancy cannot be assumed with low hCG levels; ruptured ectopic pregnancies requiring surgery have been reported with very low or absent levels of hCG.[27]

Serum progesterone levels have been studied as an additional or alternative marker to determine which patients need further evaluation and follow-up for possible ectopic pregnancy. Progesterone rises earlier than hCG in normal pregnancy and plateaus with levels greater than 20 ng/mL, so measuring serial levels over time is not necessary. Levels less than 5 ng/mL exclude viable IUP (with rare exceptions) and could be useful when hCG levels are low, ultrasonography is indeterminate, and the clinician is considering D&C or laparoscopy. The ability of a progesterone level to differentiate ectopic pregnancy from a failed IUP is limited, however, and it is not a standard tool for evaluation.[28]

Other Ancillary Studies. Culdocentesis is not commonly used in stable patients with suspected ectopic pregnancy if ultrasonography is available. Culdocentesis is less sensitive and specific than ultrasonography for detecting hemoperitoneum, and several series report a nondiagnostic (i.e., dry) tap in approximately one fourth of patients.[29] Culdocentesis could be considered, however, to verify hemoperitoneum in the unstable patient who cannot tolerate the time required for ultrasonography or when emergency transfer is being considered for gynecologic consultation and definitive care.

Dilation and evacuation can be used in patients without a viable IUP or ectopic pregnancy on ultrasonography to differentiate intrauterine miscarriage from ectopic pregnancy. Identification of chorionic villi in endometrial samples is seen in approximately 70% of patients and excludes ectopic pregnancy (except in infertility patients). Identification of chorionic villi can be made even in 50% of women with an empty uterus on ultrasonography and limits the need for laparoscopy to exclude ectopic pregnancy in this population.[30]

Although invasive, laparoscopy is extremely accurate as a diagnostic (and therapeutic) procedure for possible ectopic pregnancy. It is the diagnostic treatment of choice in the unstable first-trimester patient with frank peritoneal signs and is also indicated in patients with significant peritoneal fluid or an ectopic gestation in the pelvic cavity. Medical alternatives for management of ectopic pregnancy have resulted in decreased indications in stable patients.[31]

Differential Considerations. The spectrum of clinical presentations in ectopic pregnancy is wide, so the differential diagnosis includes essentially all first-trimester complications. Threatened miscarriage, the most common alternative diagnosis, can be recognized by sonographic evidence of an IUP, either healthy or failed. Hypovolemia may be seen, particularly in incomplete miscarriage, but hypotension without significant vaginal hemorrhage is highly suggestive of ectopic pregnancy. Identification of fetal parts or chorionic villi in tissue expelled or obtained during D&C is useful to confirm a complication of IUP, although this is not sufficient to exclude ectopic pregnancy in the patient who has received infertility treatment and has an increased risk of heterotopic gestation.

A ruptured corpus luteum cyst should also be considered in the patient who has first-trimester bleeding associated with peritoneal pain or irritation. The corpus luteum normally supports the pregnancy during the first 7 or 8 weeks. Rupture causes pelvic pain and peritoneal irritation. Ultrasonography is helpful if it reveals an IUP (except in patients with in vitro fertilization). During early gestation, when ultrasonography is nondiagnostic, free fluid is usually visible by ultrasonography and serial observation may be required. If the patient is unstable (especially if an IUP cannot be identified by ultrasonography), laparoscopy or, rarely, laparotomy may be required to differentiate between the two conditions.

Management

Classically, approximately 20% of women with ectopic pregnancies manifest signs and symptoms warranting immediate intervention.[32] This includes patients with significant hypovolemia, large amounts of peritoneal fluid, or an open cervical os. For patients with significant signs of hypovolemia, rapid volume resuscitation should be instituted with intravenous fluids and blood products as necessary, and a baseline hemoglobin level and type and crossmatch should be obtained. A D&C or evacuation procedure with examination of endometrial contents for products of conception can be performed urgently in the unstable patient with an open cervical os.

If the patient remains unstable, immediate surgery is warranted. Laparoscopy may be indicated for patients who stabilize with treatment or for those who are hemodynamically stable but exhibit significant peritoneal signs. One study reported that identifying free fluid in Morrison's pouch on bedside ultrasonography predicted the need for operative intervention in the majority of cases in patients with suspected ectopic pregnancies.[33] All patients with ectopic pregnancy who are Rh-negative should be given Rh immunoglobulin 50 μg intramuscularly, unless the father is known to be Rh-negative.

The majority of patients who seek treatment for bleeding or pain during the first trimester of pregnancy are stable. In such patients, the goal should be to exclude ectopic pregnancy in a timely manner. In the patient with significant pain by history or examination, or significant risk factors for ectopic pregnancy, ultrasonography should be performed before discharge. If the results are indeterminate, a quantitative hCG may be helpful in determining the patient's risk for ectopic pregnancy.

In low-risk patients with only minor symptoms or bleeding, ectopic pregnancy is still a possibility. Two general outpatient approaches can be considered. In most institutions, ultrasonography is the initial screening tool (Fig. 176-6), performed by the emergency medical team or by radiology personnel. If an IUP is not seen, quantitative hCG levels help stratify patients by risk. Cost, availability, and convenience will drive the ordering of ancillary studies in different institutions. In all

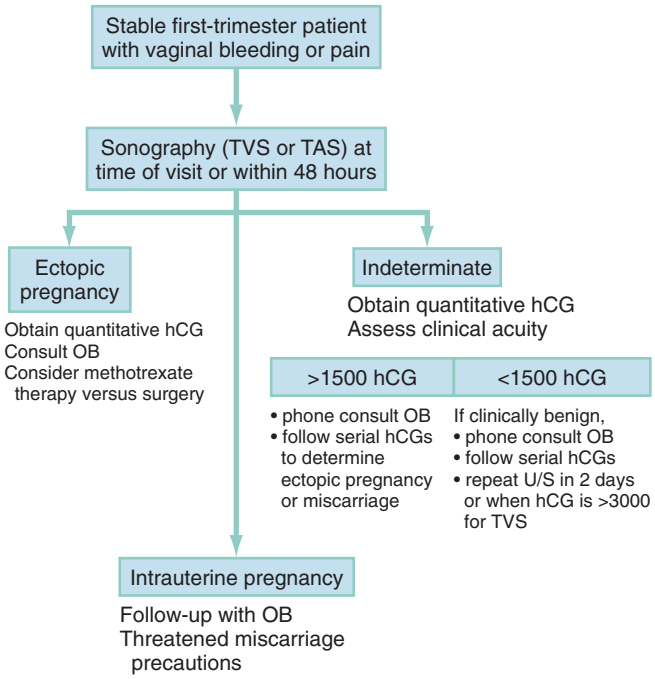


Figure 176-6. Management of vaginal bleeding or pain in the stable first-trimester pregnant patient. hCG, human chorionic gonadotropin; OB, obstetrics specialist; TAS, transabdominal ultrasonography; TVS, transvaginal sonography.

cases, if the patient is discharged, careful instructions are given for symptoms that would require her earlier return (ectopic precautions).

An alternative strategy using hCG first has also been used. However, waiting times for the serum assay can increase length of stay in the ED. In addition, ultrasonography is usually diagnostic of IUP or ectopic pregnancy, even if the hCG level is less than 1000 mIU/mL.[18,23] In most hands, the initial sonogram provides more rapid and accurate information at the time of an ED visit.

A significant minority of patients have indeterminate sonographic results and hCG levels less than 1500 mIU/mL. When the hCG levels never rise to the discriminatory zone, the differential diagnosis includes intrauterine fetal demise and ectopic pregnancy. Early D&C with identification of POCs can be useful to the patient with nonrising hCG levels to detect chorionic villi and confirm a failed IUP or to strongly suggest ectopic pregnancy.[30] Alternatively, hCG levels can be followed until they reach zero, particularly if initial levels are low.

Although laparotomy may be required for emergency patients who have ectopic pregnancies, an increasing number of surgeries are being performed through the laparoscope. Salpingostomy is preferred to salpingectomy if the patient is stable and the procedure is technically feasible. Overall, the advent of transvaginal ultrasonography has resulted in a decreased number of surgeries and a trend toward nonoperative management.[33]

Medical management has become standard in many areas for the stable patient with minimal symptoms and is cost-effective when considering subsequent fertility.[31] Methotrexate is the drug most commonly used to treat early ectopic pregnancy. It causes destruction of rapidly dividing fetal cells and involution of the pregnancy. Medical treatment is most often used for patients with a tubal mass less than 4 cm in diameter, no fetal cardiac activity, and no sonographic evidence of rupture. Although there is no agreed upon cutoff for single-dose methotrexate, a systematic review found that patients with an hCG of greater than 5000 mIU/mL had an increased failure rate.[34] Medical therapies are associated with an 85 to 93% success rate, with no significant difference between single- and multiple-dose protocols.[35,36] Pelvic pain is common (60%) in patients receiving methotrexate, even when used successfully.[37] Indications of methotrexate failure and need for rescue surgery include decreasing hemoglobin levels, significant pelvic fluid, or unstable vital signs. All patients receiving methotrexate require close follow-up until the hCG level reaches zero, which may take 2 or 3 months.

Molar Pregnancy

Gestational trophoblastic disease (molar pregnancy) comprises a spectrum of diseases characterized by disordered proliferation of chorionic villi. In the absence of fetal tissue, the pregnancy is termed a *complete hydatidiform mole*. More rarely, if fetal tissue is present and trophoblastic hyperplasia is focal, it is called an *incomplete mole*. In approximately 19% of molar pregnancies, neoplastic gestational disease develops, with persistence of molar tissue after the pregnancy has been evacuated.[38] Metastatic disease can develop, requiring chemotherapy and intensive oncologic management.

Early molar pregnancy is usually not clinically apparent. Many patients present with abdominal pain, nausea and vomiting, or vaginal bleeding, and it may be difficult to differentiate these patients from those with threatened miscarriage or ectopic pregnancy by historical features alone.[39] Patients sometimes seek treatment for apparent persistent hyperemesis gravidarum from high circulating levels of hCG, bleeding or intermittent bloody discharge or failure to hear fetal heart tones during the second trimester is the usual initial clue to diagnosis. If molar pregnancy spontaneously aborts, it is usually in the second trimester (before 20 weeks), and the patient or physician may note passage of grapelike hydatid vesicles. Uterine size is larger than expected by date (by more than 4 weeks) in approximately 30 to 40% of patients. Theca lutein cysts may be present on the ovaries as a result of excessive hormonal stimulation, and torsion of affected ovaries can be seen.

The diagnosis of hydatidiform mole is based on the characteristic sonographic appearance of hydropic vesicles within the uterus, described as a "snowstorm" appearance (Fig. 176-7). Alternatively, cystic changes are seen in partial molar pregnancies. In some cases, partial molar pregnancy is detected only on pathologic examination of abortion specimens.[40] Complications of molar pregnancy include preeclampsia or eclampsia (which can develop before 24 weeks of gestation); pulmonary embolization of trophoblastic cells; hyperemesis gravidarum; and significant uterine bleeding, either acute or chronic. Ultrasonography usually provides the diagnosis of complete molar pregnancy, either in the second-trimester patient who has "threatened miscarriage" or during sonographic assessment for fetal well-being and size. However, ultrasonography is only 58% sensitive, and diagnosis of partial mole is made in 17% of cases.[40] Up to two thirds of molar pregnancies are diagnosed by pathologic specimens after miscarriage.[40]

COMPLICATIONS OF LATE PREGNANCY

Vaginal Bleeding in Later Pregnancy

Perspective

Bleeding during the second half of pregnancy occurs in approximately 4% of pregnancies. Only 20% of miscarriages

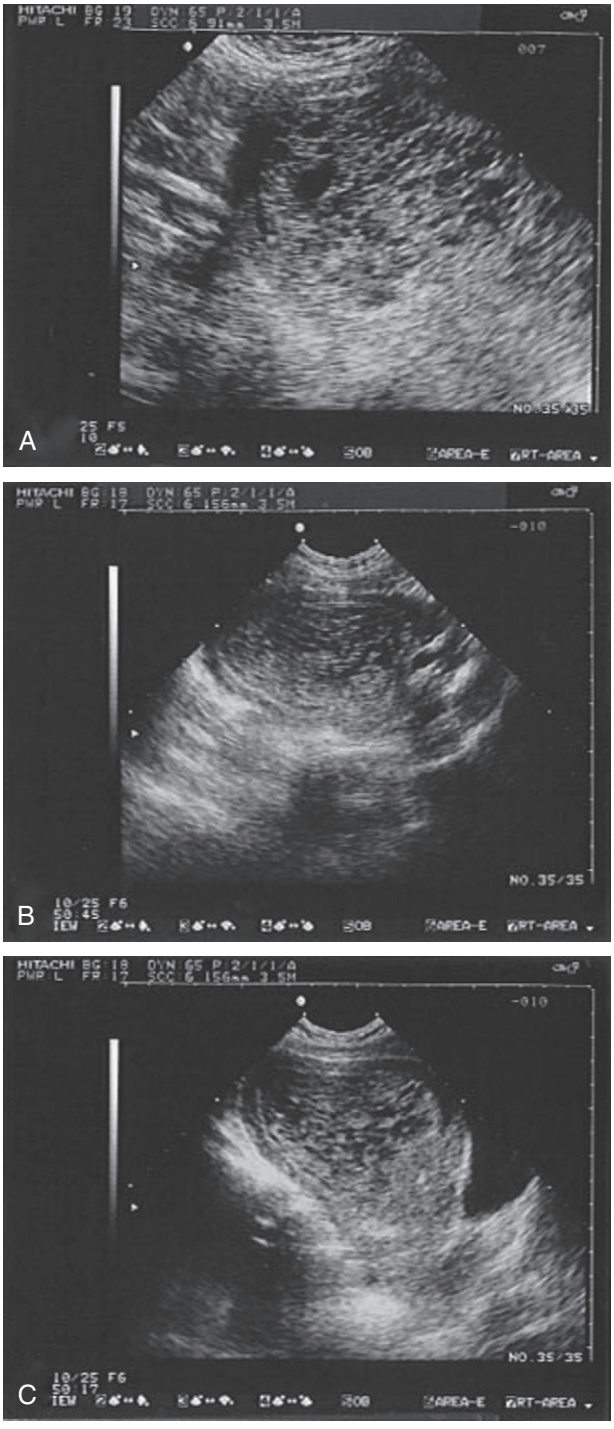


Figure 176-7. Ultrasound showing molar pregnancy. (Courtesy of Mary Ann Edens, MD.)

occur after the first trimester, and the most important differential diagnoses after 12 to 14 weeks of gestation are abruptio placentae and placenta previa. Often, the cause is not determined, although occult marginal placental separations (which can be recognized only by placental inspection at delivery) are held to be a common source of bleeding from above the cervix. Other causes of late vaginal bleeding include early labor, various cervical and vaginal lesions, lower genital tract infections, and hemorrhoids.

Bleeding during the second trimester before the fetus is potentially viable (14–24 weeks) is not benign. One third of fetuses are ultimately lost when maternal bleeding occurs. Management is supportive and expectant because fetal rescue is impossible at this level of fetal immaturity. In the third trimester, vaginal bleeding is still associated with significant morbidity in approximately one third of women, but the treatment includes consideration of urgent delivery.[41]

Abruptio Placentae

Principles of Disease. Abruptio placentae, or separation of the placenta from the uterine wall, is believed to account for approximately 30% of episodes of bleeding during the second half of pregnancy. In addition, small subclinical or marginal separations may go undetected until the placenta is examined at delivery and probably account for many of the other self-limited episodes of bleeding for which no diagnosis is made. In cases of nontraumatic abruptio placentae, apparently spontaneous hemorrhage into the decidua basalis occurs, causing separation and compression of the adjacent placenta. Small amounts of bleeding may be asymptomatic and remain undetected until delivery. In other instances, the hematoma expands and extends the dissection; bleeding may be concealed or may be clinically apparent if dissection occurs along the uterine wall and through the cervix. Placental separation can be acute or can be an indolent problem throughout late pregnancy.

Abruptio placentae is most clearly associated with maternal hypertension and preeclampsia; it is also more common with increasing maternal age and parity, a history of smoking, thrombophilia, prior miscarriage, prior abruptio placentae, and cocaine use.[41,42] Placental separation can also be associated with blunt trauma to the abdomen. In such instances, the cause appears to be shearing of a nonelastic placenta from the easily distorted elastic uterine wall at the time of traumatic impact. Women who reported physical violence during pregnancy were twice as likely to have an abruption than women who did not report any violence.[43]

Clinical Features. Vaginal bleeding occurs in 70% of patients with abruptio placentae.[43] Blood is characteristically dark and the amount is often insignificant, although the mother may have hemodynamic evidence of significant blood loss. Uterine tenderness or pain is seen in approximately two thirds of women; uterine irritability or contractions are seen in one third. With significant placental separation, fetal distress occurs and the maternal coagulation cascade may be triggered, causing disseminated intravascular coagulation.[41]

There is a wide spectrum of severity of symptoms and risk in placental separation. Up to 20% of women will have no pain or vaginal bleeding.[42] Assessment is generally based on clinical features, coagulation parameters, and signs of fetal distress. Slight vaginal bleeding, little or no uterine irritability, the absence of signs of fetal distress, and normal coagulation characterize mild abruption. As the separation becomes more extensive, it is associated with more vaginal bleeding (or hidden maternal blood loss), increased uterine irritability with or without tetanic contractions, declining fibrinogen levels, and evidence of fetal distress and maternal tachycardia. In cases of severe abruptio placentae (15% of cases), the uterus is tetanically contracted and very painful, maternal hypotension results from visible or concealed uterine blood loss, fibrinogen levels are less than 150 mg/dL, and fetal death can occur. Ultrasonography is insensitive in the diagnosis of abruptio placentae, often because the echogenicity of fresh blood is so similar to that of the placenta. Symptomatic or even fetus-threatening abruption can occur in the presence of a negative sonogram.[41]

Fetal distress and death occur in approximately 15% of patients with abruptio placentae due to interruption of placental blood and oxygen flow. Risk of fetal death increases in

proportion to both the percentage of placental surface involved and the rapidity of separation. Fetal distress may result from the loss of placental blood flow, associated maternal hemorrhage (into the uterine cavity or externally), increased uterine tone, or resultant disseminated intravascular coagulation. Maternal death can result, usually from coagulopathy or exsanguination. Fetomaternal transfusion occurs in a significant minority of patients. Placental separation also predisposes the mother to amniotic fluid embolism.

Differential Considerations. The main alternative diagnosis in the woman with late-pregnancy bleeding is placenta previa, which is usually associated with painless, bright red bleeding and must be excluded with ultrasonography. Lower genital tract or rectal lesions and bloody show (blood-tinged cervical mucous plug) are also considerations.

In the patient with abdominal pain but no vaginal bleeding, abruptio placentae with concealed hemorrhage must be distinguished from other causes of abdominal pain in later pregnancy: complications of preeclampsia, pyelonephritis, various liver diseases, gallbladder disease, appendicitis, and ovarian torsion. Uterine irritability caused by abruptio placentae can also be confused with early labor; in one series, almost one fourth of patients were misdiagnosed as having premature labor until fetal distress occurred. If the patient has acute catastrophic hypotension, amniotic fluid embolus (with or without abruptio placentae) and uterine rupture must be considered.[41]

Placenta Previa

Principles of Disease. Placenta previa, or implantation of the placenta over the cervical os, is the other major cause of bleeding episodes during the second half of pregnancy. The risk of placenta previa is increased with maternal age, multiparity, smoking, and prior cesarean section.[44] Bleeding occurs when marginal placental vessels implanted in the lower uterine segment are torn, either as the lower uterine wall elongates or with cervical dilation near the time of delivery. Early bleeding episodes tend to be self-limited unless separation of the placental margin is aggravated by iatrogenic cervical probing or onset of labor.

Clinical Features. Painless, fresh vaginal bleeding is the most common symptom of placenta previa. In approximately 20% of cases, some degree of uterine irritability is present, but this is usually minor. Vaginal examination usually reveals bright blood from the cervical os. Digital or instrumental probing of the cervix should never be done during the second half of pregnancy because it can precipitate severe hemorrhage in the patient with an asymptomatic or minimally symptomatic placenta previa. In the ED, speculum examination of the vagina and cervix should be performed only in those settings in which obstetric consultation is not readily available. It should be limited to an atraumatic partial speculum insertion to identify whether the bleeding is coming from the cervical os (and a presumed placenta previa), hemorrhoids, or a vaginal lesion that might not require urgent management.

Most cases of placenta previa identified during the midtrimester resolve by the time of delivery as the lower uterine segment elongates and the placenta no longer overlaps the cervical os. Central or total previa (which occurs in approximately 20% of cases) can, however, cause severe hemorrhage, with risk of exsanguination for the fetus and mother.

Diagnostic Strategies. Ultrasonography is the diagnostic procedure of choice for localizing the placenta and diagnosing placenta previa. Accuracy is excellent; visualization of the placenta as well as the internal cervical os is required. The bladder should be emptied prior to examination for suspected placenta previa to avoid overdiagnosis of placenta previa. Transvaginal ultrasonography is safe and even more accurate for visualizing the relationships between the placenta and the internal os.[45]

Management

Patients who experience vaginal bleeding during late pregnancy should have immediate obstetric consultation and arrangements for safe transfer to an appropriate obstetric facility. Initial management consists of maternal stabilization, with establishment of two large-bore intravenous lines and fluid resuscitation, as well as continuous fetal monitoring if available. A baseline hemoglobin level should be obtained, and blood should be sent for type and crossmatch; baseline coagulation studies including platelet count, prothrombin time, and partial thromboplastin time should be performed; and fibrinogen level and the presence of fibrin split products should be determined. The normal fibrinogen level in pregnancy is 400 to 450 mg/dL; values below 300 mg/dL indicate significant consumption of coagulation factors.

Blood loss requiring transfusion can occur in patients with placenta previa or abruptio placentae. Fresh frozen plasma or fresh whole blood may be needed because of the coagulopathy associated with significant abruptio placentae. Fetomaternal hemorrhage can occur with abruption. If the Rh-negative patient has not yet received her routine Rh immunoglobin prophylaxis at 28 weeks, 300 μg of Rh immune globulin should be administered within 72 hours (unless the father is known to be Rh-negative).[46] Transfer to the obstetric unit should be expedited if the patient is stable, or it should be done after initiation of resuscitation if she is unstable. If transfer to another hospital is required, a high-risk transfer team should be used if bleeding is significant or if the fetus is in distress. Although the bleeding source may not be identified or may be relatively benign, assessment is best accomplished by obstetricians who are accustomed to evaluating late-pregnancy complications and who can perform emergent cesarean section if needed.

In the obstetrics unit, fetal monitoring is continued. Ultrasonography is used primarily to locate the placenta and diagnose placenta previa; it may not be reliable in confirming the diagnosis of abruptio placentae. Occasionally, subplacental hemorrhages of abruptio placentae can be seen and changes in size of the collection can be monitored. If evidence of placenta previa is absent or equivocal, vaginal examination is performed in the delivery suite, where emergency cesarean section can be performed if uncontrolled bleeding is encountered.

Patients who have significant abruptio placentae may require early delivery (either vaginal or surgical, depending on fetal status). If placenta previa is diagnosed or if abruptio placentae is considered mild, the patient is admitted for close monitoring. The goal is to support the patient, ideally until fetal maturity is demonstrated and a successful delivery can be accomplished.

Pregnancy-Induced Hypertension (Preeclampsia and Eclampsia)

Perspective

Hypertension is observed in approximately 6 to 8% of pregnancies and is generally divided into several categories.[47] Gestational hypertension occurs during pregnancy, resolves during the postpartum period, and is recognized by a new blood pressure reading of 140/90 mm Hg or higher. Preeclampsia is gestational hypertension with proteinuria (>300 mg/24 hours), and eclampsia is the occurrence of seizures in the patient with

signs of preeclampsia. Progression of preeclampsia to eclampsia is unpredictable and can occur rapidly. Pregnancy-aggravated hypertension is chronic hypertension with superimposed preeclampsia or eclampsia. Chronic or coincidental hypertension is present before pregnancy or persists more than 6 weeks postpartum.[47]

Approximately 2 to 7% of pregnancies are complicated by pregnancy-induced hypertension. The incidence of actual eclampsia has progressively declined, but it is still one of the major causes of maternal mortality. The risk of pregnancy-induced hypertension is greatest in women younger than 20 years; primigravidas; those with twin or molar pregnancies; those with hypercholesterolemia, pregestational diabetes, or obesity; and those with a family history of pregnancy-induced hypertension.[48]

Principles of Disease

Gestational hypertension/preeclampsia is a vasospastic disease of unknown cause unique to pregnant women. Vasospasm, ischemia, and thrombosis associated with preeclamptic changes cause injury to maternal organs, placental infarction and abruption, and fetal death from hypoxia and prematurity. The cause of eclampsia is not known, but recent research has centered on vascular responsiveness to endogenous vasopressors in the preeclamptic woman. Vascular responsiveness is normally depressed during pregnancy, which is a high-output, low-resistance state. Gestational hypertension is characterized by an even greater elevation in cardiac output, followed by an abnormally high peripheral resistance as the disease develops clinical manifestations. In patients with preeclampsia, the cardiac output eventually drops as peripheral resistance rises.[49] The cause of these changes is not known, but endothelial dysfunction is purported to release vasoactive mediators and result in vasoconstriction.[50] Antiplatelet agents during pregnancy have been reported to reduce the risk of development of preeclampsia, supporting the premise of an imbalance between levels of thromboxane and prostacyclin in preeclampsia.[51]

The vasospastic effects of gestational hypertension/preeclampsia are protean. Intravascular volume is lower than in normal pregnancy, central venous pressures are normal, and capillary wedge pressures are variable. Liver effects are believed to be due to hepatocellular necrosis and edema resulting from vasospasm. Renal injury causes proteinuria and may result in decreased glomerular filtration. Microangiopathic hemolysis may result from vasospasm, causing thrombocytopenia. Central nervous system effects include microvascular thrombosis and hemorrhage, as well as focal edema and hyperemia.[48]

Clinical Features

Signs and Symptoms. The patient with gestational hypertension has mild systolic or diastolic blood pressure elevation, no proteinuria, and no evidence of organ damage. Mental status assessment, testing of reflexes, abdominal examination, liver function studies, and coagulation studies should all yield normal results. Preeclampsia is associated with kidney changes and, in severe cases, other end-organ symptoms. Edema is often difficult to assess because pregnancy is normally associated with excess extracellular fluid and dependent edema, and it is no longer used as a criterion for recognizing preeclampsia. Proteinuria (>300 mg/24 hours) is variable at any given time and may not be detectable in a random urine specimen.[47]

In cases of severe preeclampsia, diastolic blood pressure can exceed 110 mm Hg, proteinuria is more severe, and there is evidence of vasospastic effects in various end organs. Central nervous system effects commonly include headache or visual disturbances. Thrombocytopenia may be present, liver function test findings may be elevated, and the liver is often tender. Renal dysfunction may be indicated by oliguria and elevated creatinine levels in addition to proteinuria.

Complications. The HELLP syndrome is a particularly severe form of preeclampsia that develops in 5 to 10% of women who have preeclamptic symptoms and is characterized by *h*emolysis, *e*levated *l*iver enzymes, and *l*ow *p*latelet count (<100,000/mL). Prothrombin time, partial thromboplastin time, and fibrinogen level are all normal, and blood studies reveal microangiopathic hemolytic anemia. Other complications of preeclampsia include spontaneous hepatic and splenic hemorrhage and abruptio placentae.

The most dangerous complication is eclampsia, which is the occurrence of seizures or coma in the setting of signs and symptoms of preeclampsia. Warning signs for development of frank eclampsia include headache, nausea and vomiting, and visual disturbances.[52] Elevated total leukocyte count, creatinine, and aspartate aminotransferase are also predictive of increased morbidity for the patient with severe preeclampsia.[53] Particularly in early eclampsia before 32 weeks of gestation, seizures may develop abruptly and hypertension may not be associated with edema or proteinuria.[54] One third of eclamptic seizures occur after delivery, usually during the first 48 hours but occasionally as many as 28 days after delivery.[55] After 48 hours postpartum and without predelivery signs of preeclampsia, other diagnoses such as intracranial hemorrhage should be considered. Maternal complications of eclampsia include permanent central nervous system damage from recurrent seizures or intracranial bleeding, renal insufficiency, and death.

The maternal mortality rate from eclampsia has been reduced with modern management and is currently less than 1%. Perinatal mortality has also decreased, although it remains 4 to 8%.[48] Causes of neonatal death include placental infarcts, intrauterine growth retardation, and abruptio placentae. In addition, fetal hypoxia from maternal seizures and the complications of premature delivery mandated by the maternal condition contribute significantly to fetal mortality and morbidity.

Diagnostic Strategies

The patient who has severe preeclampsia should have an intravenous line and fetal monitoring initiated in a quiet but closely observed area. Blood testing should include complete blood cell count, renal function studies, liver function tests, platelet count, and coagulation profile. A baseline magnesium level should also be obtained. In the patient with actual seizures, serum glucose should be tested. If a history of preeclampsia is not obtained or the symptoms are refractory to magnesium sulfate therapy, a computed tomography (CT) scan of the head should be performed to exclude cerebral venous thrombosis or an intracranial bleed, either of which can occur in pregnancy (with or without pregnancy-induced hypertension) and may require specific treatment. CT scan abnormalities can be seen in half of patients with eclampsia. Patchy hemorrhage and microinfarcts of the cortex are characteristic and may be due to loss of cerebral autoregulation in patients with severe pregnancy-related hypertension. Diffuse cerebral edema can also be seen.[56]

Differential Considerations

Peripheral edema is common in normal pregnancy, and it may be difficult to differentiate normal edema from that of early preeclampsia. Differentiation of gestational hypertension from

preexistent hypertension is often impossible if no record of normal blood pressure is available. Seizures during pregnancy may be due to epilepsy as well as to other intracranial catastrophes, such as thrombosis or hemorrhage.

Management

In the patient who has mild preeclampsia, appropriate management includes documentation of blood pressure and reflexes, weight, and testing to ensure normal end-organ function. Accurate determination of gestational age by ultrasonography is needed to allow optimal management if symptoms progress. Limitation of physical activities (including bedrest) is the only demonstrated means of reducing blood pressure and allowing the pregnancy to be sustained longer. Definitive treatment is delivery of the fetus. Arrangement for close follow-up is important for patients who are not hospitalized.

Hospitalization is usually required for patients with sustained hypertension above 140/90 mm Hg and signs of severe preeclampsia. Baseline laboratory studies to identify end-organ effects in the liver, kidney, and hematologic systems should be obtained. Both diuresis and antihypertensive therapy have been remarkably unsuccessful in improving fetal outcome or prolonging pregnancy. Admission does, however, allow the obstetrician to accurately assess fetal age and well-being, maternal organ function, and the effect of bedrest on blood pressure before deciding the optimal timing of delivery.[47]

Fulminant or severe preeclampsia, with marked blood pressure elevation (>160/110 mm Hg), associated with epigastric or liver tenderness, visual disturbance, or severe headache, is managed in the same way as eclampsia (Box 176-4). The goal is prevention of seizures and permanent damage to maternal organs. Magnesium sulfate is given for seizure prophylaxis.

Seizures and coma are the hallmarks of eclampsia, the ultimate consequence of preeclampsia. As in all seizure patients, hypoglycemia, drug overdose, and other causes of seizures should be excluded with appropriate tests. Eclamptic seizures are controlled in almost all patients by adequate doses of magnesium sulfate, although the mechanism of action remains elusive. Magnesium has little antihypertensive effect but is the most effective anticonvulsant, preventing recurrent seizures while maintaining uterine and fetal blood flow. The goal of magnesium sulfate therapy is to terminate ongoing seizures and prevent further seizures. A loading dose of 6 g IV magnesium, followed by 2 g IV/hr, is recommended. Magnesium administration should be accompanied by clinical observation for loss of reflexes (which occurs at approximately 10 mg/dL) or respiratory depression (which occurs at levels >12 mg/dL, although actual serum magnesium levels are rarely monitored). The infusion should be stopped if signs of hypermagnesemia are seen; such patients may require assisted ventilation. Calcium gluconate, 1 g given slowly into a secure vein, will reverse the adverse effects of hypermagnesemia.[48]

Despite ongoing controversy, the familiarity, physiologic advantages to the fetus, wide margin of safety, and high success rate in controlling seizures make magnesium sulfate the first-line drug in patients with eclampsia. Several reports highlight an international consensus that magnesium sulfate is more effective than nimodipine, phenytoin, or diazepam for prophylaxis against or treatment of eclamptic seizures.[57,58] If seizures persist after the recommended doses of magnesium sulfate have been administered, further therapy should be given in conjunction with obstetric consultation and a careful search for other causes of seizures (e.g., hypoglycemia and intracranial bleed) should be instituted.

Although magnesium sulfate is not a direct antihypertensive, the hypertension associated with eclampsia is often controlled adequately by stopping the seizures. Rapid lowering of blood pressure can result in uterine hypoperfusion, so specific antihypertensive treatment is initiated only if the diastolic blood pressure remains above 105 mm Hg after control of seizures. Many patients do not require specific antihypertensive treatment after treatment with magnesium sulfate. The antihypertensive used most often by obstetricians is hydralazine. The dose is 5 mg IV, with repeated doses of 5 to 10 mg IV every 20 minutes as needed to keep the diastolic blood pressure below 105 mm Hg. Nimodipine and labetalol have also been reported to be safe and effective, although they are less widely used.[48] Other antihypertensive agents are not well studied in this population because there are specific risks to uncontrolled lowering of blood pressure and loss of uteroplacental blood flow.

Although total body water in the eclamptic patient is excessive, intravascular volume is contracted and the eclamptic patient is very sensitive to further volume changes. Hypovolemia results in decreased uterine perfusion. Thus, diuretics and hyperosmotic agents should be avoided in patients with eclampsia. Although intravascular volume expansion in the face of volume contraction, increased systemic resistance, and vasospasm would seem reasonable, invasive monitoring has demonstrated that vasospasm is not reversed with intravenous fluid administration. Rather, excessive intravenous fluids increase extravascular fluid stores that are difficult to mobilize postpartum, resulting in a higher incidence of pulmonary edema in patients treated aggressively with fluid therapy. Invasive pulmonary artery pressure monitoring may be required for accurate fluid management in the eclamptic patient.

BOX 176-4 MANAGEMENT OF ECLAMPSIA AND SEVERE PREECLAMPSIA

- Control seizures with magnesium sulfate.
- Control hypertension after seizure control if diastolic blood pressure >105 mm Hg.
- Draw initial laboratory studies to assess organ injury:
  - Complete blood count and platelet count
  - Liver function tests
  - BUN, creatinine
- Monitor urine output: maintain at <25 mL/hr.
- Limit intravenous fluid administration unless significant losses occur.
- Avoid diuretics and hyperosmotic agents.
- Perform a CT scan of head if consciousness is decreased or seizures persist, lateralizing signs are present, or there are other concerns.
- Initiate steps to delivery.

BUN, blood urea nitrogen; CT, computed tomography.
Modified from Pritchard J, et al: The Parkland Memorial Hospital protocol for treatment of eclampsia: Evaluation of 245 cases. Am J Obstet Gynecol 161:261, 1989.

Amniotic Fluid Embolus

Perspective

Amniotic fluid embolus (AFE) is the release of amniotic fluid into the maternal circulation during intense uterine contractions or uterine manipulation or at areas of placental separation from the uterine decidua basalis (abruptio placentae), triggering a rapidly fatal anaphylactoid-type maternal response. Although AFE most commonly occurs during labor, in which

circumstance the maternal mortality rate is 25% or higher, it can also occur after induced abortions and miscarriages and spontaneously during the second and third trimesters. AFE can also occur after amniocentesis or in association with abruptio placentae after abdominal trauma. Although it is a rare syndrome, AFE is responsible for 13 to 30% of maternal deaths and is the fifth leading cause of direct maternal death.[59]

Clinical Features

Amniotic fluid embolus should be suspected during the second or third trimester of pregnancy, particularly in the setting of uterine manipulation or contraction, when a patient experiences sudden hypotension, hypoxia, and coagulopathy. The embolization of amniotic fluid and the particulate matter suspended in it triggers a profound immunologic response when it enters the maternal circulation. Half of the cases of mortality occur during the first 2 hours when vasospasm, release of vasoactive substances, and mechanical plugging of vessels, particularly in the maternal pulmonary vascular tree, trigger abrupt cardiopulmonary collapse.[59] In survivors, disseminated intravascular coagulation, acute respiratory distress syndrome, and left ventricular dysfunction develop. An initial seizure is seen in approximately 10% of patients. Bleeding diathesis may be the initial sign in some women.

Diagnostic Strategies

When AFE is suggested, a complete blood cell count, coagulation studies, arterial blood gases, and chest radiograph should be obtained. Urinary output should be monitored after urinary catheter placement. The diagnosis is usually made with certainty only at autopsy, with the finding of fetal hairs, squamous cells, and debris in the maternal circulation. Because squamous epithelial cells can be seen normally in the maternal pulmonary circulation, the typical clinical syndrome is also required for diagnosis.[59]

Differential Considerations

Catastrophic pulmonary embolus, drug-induced anaphylaxis, and septic shock must be considered in the differential diagnosis. Seizure occurs in patients with eclampsia, but in that condition hypertension, rather than cardiovascular collapse, should be observed. Coagulopathy may be seen in patients with preeclampsia (HELLP syndrome), abruptio placentae, or other chronic coagulopathies seen in the nonpregnant patient.

Management

Amniotic fluid embolus is uncommon, so treatment is mainly anecdotal and based on animal studies. The most helpful modalities appear to be high-flow oxygen, support of ventilation and oxygenation with intubation, aggressive fluid resuscitation, inotropic cardiovascular support, and anticipation and management of consumptive coagulopathy. A few reports have indicated that plasma exchange may be helpful to remove triggering cytokines.[60] Adequate management usually requires invasive hemodynamic monitoring in an intensive care unit.

Rh (Anti-D) Immunization in Pregnancy

Rh immunization occurs when an Rh-negative woman is exposed to Rh-positive fetal blood. Small numbers of fetal cells enter the maternal circulation spontaneously throughout pregnancy, but the maternal immune system is only triggered by significant loads of fetal cells, which can occur during the third trimester and at delivery. Sensitization occurs in up to 15% of Rh-negative women carrying Rh-positive fetuses. To prevent this, anti-D immunoglobulin (RhoGAM) is routinely administered to Rh-negative mothers (if the father is Rh-positive or his status is unknown) at approximately the 28th week of gestation to protect the mother from spontaneous sensitization, which occurs during the third trimester. Transplacental hemorrhage can also occur during uterine manipulation, threatened miscarriage (even without fetal loss), spontaneous miscarriage, surgery for ectopic pregnancy, and amniocentesis, although the risk is not clear. Anti-D immunoglobulin should be administered when these events occur. A dose of 50 μg can be used if the patient is at less than 12 weeks of gestation, although many pharmacies only carry the 300-μg dose, which can also be given. After 12 weeks, a 300-μg dose should be given. The half-life of immunoglobulin is 24 days, and it needs to be administered within 72 hours of a sensitization event to prevent antibody development.[10]

The Kleihauer-Betke test of maternal blood has been used to detect fetal cells in the maternal circulation. Unfortunately, the test is difficult to perform, not immediately available in most emergency laboratories, and only sensitive enough to detect 5 mL of fetal cells in the maternal circulation. Because only 0.1 mL of fetal cells is required to sensitize the mother, routine immunoglobulin administration has been recommended in situations likely to result in sensitization. Patients with third-trimester bleeding are not at increased risk of sensitization compared with patients with normal pregnancy; RhoGAM should be administered only if the patient did not receive her prophylactic dose at 28 weeks.[46] In instances of significant blunt trauma to the uterus, the Kleihauer-Betke test should be ordered to detect the rare large fetal transfusions that may require specific fetal blood therapy or administration of additional immunoglobulin to the mother. The standard dose (300 μg) is sufficient to prevent maternal immunization for fetal transfusions of up to 15 mL of red blood cells or 30 mL of whole blood.[10]

■ MEDICAL AND SURGICAL PROBLEMS IN THE PREGNANT PATIENT

Perspective

Clinicians must be aware of a variety of illnesses, both related and unrelated to pregnancy, that may have altered symptomatology, risk, and treatment in the pregnant patient (Tables 176-2 and 176-3).

Abdominal Pain

Gynecologic Problems

Several gynecologic diseases must be considered in evaluating the pregnant patient who has abdominal pain. These include threatened miscarriage and ectopic pregnancy, which were discussed previously in this chapter. A patient with either complication of pregnancy can complain of nonspecific abdominal pain, either in the midline or laterally, and may show intermittent or constant symptoms. A careful history can be helpful in differentiating gradual progression of inflammatory or infectious diseases (e.g., ovarian cyst expansion or, rarely, PID) from sudden peritonitis caused by spillage of blood or cyst fluid into the peritoneal cavity or from the colicky pain of renal stones or the ischemic pain of ovarian torsion. In addition, examination of the abdomen, back, and pelvis helps localize the pain to areas and specific organs, thus narrowing

Table 176-2 Differential Diagnosis of Abdominal Pain in Pregnancy

DIAGNOSIS	GESTATIONAL AGE	COMMENTS
Gynecologic		
Miscarriage	<20 wk, 80% <12 wk	Ultrasonography to confirm location
Septic abortion	<20 wk	Fever, uterine tenderness
Ectopic pregnancy	<14 wk	Must always consider in first trimester until intrauterine pregnancy confirmed
Corpus luteum cyst	<12 wk	Sudden focal peritoneal pain; no fever
Ovarian torsion	Especially <24 wk	Ischemic pain
Pelvic inflammatory disease	<12 wk	Very rare
Chorioamnionitis	>16 wk	Tender uterus, fever; amniocentesis reveals white blood cells
Abruptio placentae	>16 wk	Focal uterine tenderness, fetal distress, variable bleeding
Preeclampsia	>20 wk	Hypertension, proteinuria, edema, right upper quadrant pain
Nongynecologic		
Appendicitis	Throughout	Guarding may be less prominent; location changes
Cholecystitis	Throughout	Confirm with ultrasonography
Hepatitis	Throughout	Confirm with liver function tests
Pyelonephritis	Throughout	Flank pain, fever, positive catheterized urinalysis

Table 176-3 Differential Diagnosis of Common Symptoms in Pregnancy

DIAGNOSIS	GESTATIONAL AGE	COMMENTS
Vaginal Bleeding		
Miscarriage	<20 wk	Usually no fetal heart activity at 8 weeks; decreasing hCG
Ectopic pregnancy	<14 wk	Evaluate with ultrasonography
Molar pregnancy	12–24 wk	No fetal heart tones, characteristic sonogram
Cervical lesions	Throughout	Perineal and vaginal inspection
Vaginitis/cervicitis	Throughout	White blood cells on wet mount, with culture
Placenta previa	>16 wk	Ultrasonography to localize placenta
Abruptio placentae	>16 wk	Ultrasonography to exclude previa; fetal distress, tenderness
Seizure		
Eclampsia	>24 wk	Blood pressure >140/90 mm Hg; usually history of PIH, edema, proteinuria
Amniotic fluid embolus	>12 wk	Hypotension, respiratory distress, DIC
Epilepsy	Throughout	History; lack of PIH findings
Dyspnea		
Pulmonary embolus	Especially 6 wk prepartum and postpartum	Usual diagnostic studies
Dyspnea of pregnancy	>24 wk	Exclude other causes
Pulmonary infection	Throughout	Examination; roentgenography
Amniotic fluid embolus	>12 wk	Uterine manipulation, bleeding diathesis, hypotension
Jaundice		
Cholestasis of pregnancy	>24 wk	Well patient; itching and jaundice
Hepatitis	Throughout	Abnormal liver function tests
Acute fatty liver	>24 wk	Rapid liver failure; coma, seizures, hypoglycemia
Bleeding Diathesis		
Eclampsia	>24 wk	Blood pressure > 140/90 mm Hg; proteinuria, edema, HELLP syndrome
Amniotic fluid embolus	>12 wk	Respiratory distress, cardiovascular collapse
Abruptio placentae	>20 wk	Uterine tenderness; vaginal bleeding; fetal distress

DIC, disseminated intravascular coagulation; hCG, human chorionic gonadotropin; HELLP, hemolysis, elevated liver enzymes, low platelets; PIH, pregnancy-induced hypertension.

the differential diagnosis and guiding the selection of ancillary studies.

Appendicitis

Perspective. Appendicitis is the most common surgical emergency in pregnant patients. The incidence of appendicitis in pregnant patients is the same as that in nonpregnant patients, but delays in diagnosis contribute to an increased rate of perforation, which results in significant fetal mortality and maternal morbidity.[61,62] During the first half of pregnancy, diagnostic findings are usually similar to those in the nonpregnant woman, but the clinical picture becomes less classic during the second half of pregnancy.

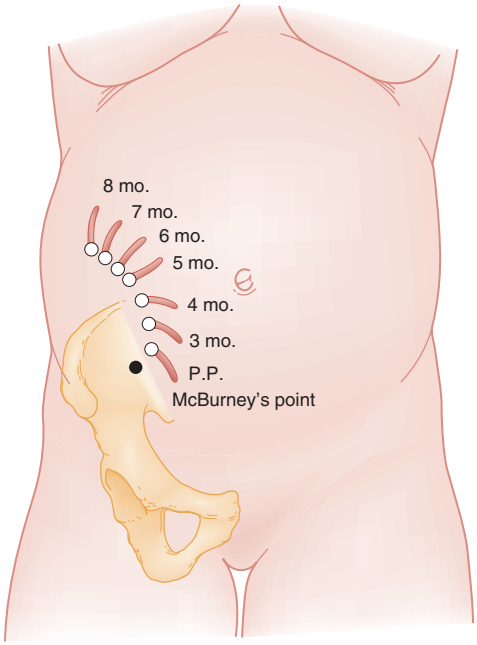


Figure 176-8. Locations of the appendix during succeeding months of pregnancy. In planning an operation, it is better to make the abdominal incision over the point of maximal tenderness unless there is great disparity between that point and the theoretical location of the appendix. P.P., postpartum. (From Gabbe SG, et al [eds]: Obstetrics: Normal and Problem Pregnancies. New York, Churchill Livingstone, 2007; as modified from Baer JL, Reis RA, Arens RA: Appendicitis in pregnancy. JAMA 98:1359, 1932.)

Principles of Disease. Traditionally, the appendix was thought to displace counterclockwise out of the right lower quadrant after the third month of gestation, with its ultimate location deep in the right upper quadrant, superior to the iliac crest (Fig. 176-8). However, a study has questioned this finding; it found that in only 23% of pregnant patients did the location change from the right lower quadrant, even in the third trimester.[62] Displacement of the abdominal wall away from the abdominal viscera can result in difficulty palpating organs and loss of signs of parietal peritoneal irritation. The physiologic increase in white blood cell count and erythrocyte sedimentation rate in pregnancy must also be considered when evaluating the patient with possible appendicitis because these may confuse the overall clinical picture.

Clinical Features. The gastrointestinal symptoms of appendicitis, such as anorexia, nausea, and vomiting, mimic those of pregnancy, particularly during the first trimester, making such symptoms relatively nonspecific. Right-sided abdominal pain is the most constant finding, although this is less reliable later in pregnancy. Peritoneal signs are likewise most common during the first trimester. Lack of fever, leukocytosis, or tachycardia has been reported.[63,64] The cause of these differences in clinical findings in pregnant patients with appendicitis may be a blunted inflammatory response from elevated maternal levels of pregnancy-related steroids. Pyuria without bacteruria is seen in up to 58% of patients.[65]

Because of confounding factors, the misdiagnosis rate for appendicitis is 30 to 35% overall in pregnancy, with a 40 to 50% rate of removal of normal appendix during the third trimester.[63,65,66] In contrast to the relative safety of performing an exploratory laparotomy or laparoscopy during pregnancy, the risk of fetal loss and maternal morbidity from failure to diagnose appendicitis and perforation is considerable, so clinical vigilance is required even in the absence of classic signs. In later pregnancy, when peritoneal signs are often absent and the uterus obscures normal physical findings, diagnosis is frequently delayed and the perforation rate may approach 25%.

Differential Considerations. Pyelonephritis, cholecystitis, nephrolithiasis, and pregnancy-related diseases such as ectopic pregnancy, broad ligament pain, corpus luteum cyst leakage, and ovarian torsion must be considered in the patient who has right-sided abdominal pain. Pyelonephritis is the most common condition that is confused with appendicitis. During its migration, the appendix takes up a position very near the kidney, resulting in a high incidence of pyuria and flank pain (see Fig. 176-8). In cases of appendicitis, unless there is coincident urinary tract infection, the urine is free of bacteria, a feature distinguishing it from pyelonephritis. Salpingitis, another common misdiagnosis, is very rare in pregnancy, although it can occur before 12 weeks of gestation.

Diagnostic Strategies. Leukocytosis is common in pregnant patients with appendicitis, although it is rarely high enough to distinguish it from the physiologic leukocytosis of pregnancy. Pyuria in a catheterized urine specimen suggests pyelonephritis, but it is also seen in 20% of patients with appendicitis.[63] Bacteruria is uncommon. Ultrasonography, using graded-compression techniques, may reveal a noncompressible tubular structure in the right lower quadrant consistent with appendicitis. Studies regarding the diagnostic utility of ultrasonography in the diagnosis of appendicitis are limited but suggest that it has a high positive predictive value but a low negative predictive value.[65,67] Given the low radiation risk to the fetus, the noninvasive nature of the test, and its utility in evaluating other complications, some authors have recommended that ultrasonography should be the initial test of choice when appendicitis is suspected, especially in the first and second trimesters.[64,65] Castro and colleagues[68] reported the utility of helical CT in diagnosis, with fetal radiation exposures of only 300 mrad, using rectal contrast and a limited study. Otherwise, laparoscopy or laparotomy is the diagnostic procedure of choice in the pregnant patient suspected of having appendicitis. Early exploration is to be encouraged even more in pregnant than in nonpregnant patients because of the variability of clinical signs and the increased fetal risk if diagnosis is delayed.

Management. The pregnant patient with suspected appendicitis should be admitted to the hospital after appropriate consultation with surgeons and obstetricians. Ultrasonography or CT scan should be considered as diagnostic options. The patient should be kept on nothing by mouth (NPO) status, with intravenous fluid hydration to maintain intravascular volume. Although prompt surgery is required if the diagnosis is clear, in unclear cases a period of inpatient observation may allow clarification of signs and symptoms.

Gallbladder Disease

Perspective. Cholelithiasis is present in approximately 5% of pregnant women and is the second most common nonobstetric surgical condition in pregnant patients. The natural history of asymptomatic cholelithiasis is believed to be similar to that in nonpregnant women, with less than half of patients with gallstones developing symptoms.[69,70]

Principles of Disease. Changes in gallbladder kinetics are believed to be due to high pregnancy-related steroid levels. Progesterone decreases smooth muscle tone and induces gallbladder hypomotility and cholestasis, causing an increased risk of stone formation. In addition, pregnancy induces changes in bile composition and increased cholesterol secretion, thus increasing the incidence of cholesterol stone formation.[71]

Clinical Features. The signs and symptoms of acute cholecystitis during pregnancy are the same as those in nonpregnant

women. Epigastric or right upper quadrant pain and tenderness and nausea predominate. Leukocytosis must be interpreted carefully because of the increased white blood cell count seen normally in pregnancy. Likewise, a slightly elevated amylase level can be normal during pregnancy, and alkaline phosphatase, which is produced by the placenta, may be twice the nonpregnant level. A history of self-limited pain episodes associated with food intake is useful in suggesting the diagnosis.

Diagnostic Strategies. Ultrasonography is a reliable means of recognizing stones within the gallbladder, although it may not differentiate symptomatic from asymptomatic stones. In the patient with right upper quadrant pain, simultaneous sonographic evaluation of the liver is useful but technically difficult, particularly during the third trimester, when subcapsular liver hematomas and other intrinsic hepatocellular disease can occur but the liver may be obscured under the ribs.

Differential Considerations. Pyelonephritis should always be considered in the patient with right upper quadrant pain with or without fever. During the third trimester, appendicitis can also be associated with right upper quadrant pain. Hepatitis and fatty liver infiltration occur in pregnancy; liver distention and inflammation associated with pregnancy-induced hypertension can also cause right upper quadrant pain. In addition, spontaneous intrahepatic bleeding can occur in late pregnancy, mimicking cholecystitis. Because of the potential for other serious diseases, diagnostic studies should always be performed to verify a clinical diagnosis of symptomatic cholelithiasis and cholecystitis in pregnancy.

Management. The patient who has fever, leukocytosis, prolonged pain, or evidence of cholecystitis should be made NPO and given IV fluid hydration, adequate pain control, and broad-spectrum antibiotics. These patients must be admitted for inpatient management. Some patients can be managed medically for prolonged or complicated cholecystitis. Patients with obstructive jaundice, gallstone pancreatitis, or sepsis or patients who fail conservative management should have surgery. Discharge should be considered only in patients with uncomplicated and sonographically proven cholelithiasis who do not meet admission criteria after consultation with an obstetrician. Pregnant patients with symptomatic cholelithiasis have a high rate of symptomatic relapse and increased severity of disease with each relapse.[72] Early follow-up should be arranged and the patient should be given careful instructions to return if she experiences fever, vomiting, or persistent pain. In one study, one third of pregnant women with biliary colic failed conservative treatment but were treated safely, often using newer laparoscopic techniques.[73]

Liver Disorders

Perspective. Pregnancy is associated with several unique liver abnormalities in addition to more usual hepatic diseases. Clinicians should recognize the various symptoms of liver disease during pregnancy as well as the hepatic diseases unique to pregnant women. Liver metabolism increases during pregnancy, but hepatic blood flow is unchanged and little change occurs in liver function. Bilirubin, transaminases, lactate dehydrogenase, and prothrombin times are unchanged from the nonpregnant state. Albumin levels decrease secondary to an increase in maternal circulating plasma volume. Alkaline phosphate levels may be up to double the nonpregnant values, and amylase levels may also be slightly elevated.[74-76]

Hepatitis. Hepatitis is the most common cause of liver disease in pregnancy, accounting for 40% of cases of jaundice in pregnancy. Management and treatment are supportive and unchanged from those for nonpregnant patients. Hepatitis E, however, has been reported to have a more aggressive course in pregnancy.[76] Maintaining adequate nutrition is a priority. Vertical transmission of hepatitis B can occur if the disease is not recognized. Prophylaxis should be administered to the newborn.

Acute Fatty Liver of Pregnancy. Acute fatty liver of pregnancy is a disorder of the third trimester that can result in hepatic failure, complicated labor, and fetal mortality. The disease is rare, occurring most often in primiparous patients and patients with twin gestations.

Principles of Disease. The cause of acute fatty liver of pregnancy is unknown, although studies suggest that a deficiency in the fetus's fatty acid metabolism leads to an accumulation of hepatotoxic metabolites in the maternal circulation.[76-79] Microscopically, fatty infiltration of the hepatocytes with edema and vacuolization can be seen, but there is no necrosis or inflammation. Liver function returns to normal after delivery if the patient can be supported through the acute phase. Although up to 50% of patients have signs of preeclampsia, the two are not clearly related.[76] The diagnosis must be differentiated from viral hepatitis and HELLP syndrome, which have similar disease presentations and laboratory findings but, again, are not clearly related.[76,77]

Clinical Features. Nausea and vomiting or liver dysfunction during the third trimester should trigger consideration of a diagnosis of acute fatty liver. In addition, nonspecific flulike symptoms, such as anorexia, fatigue, and headache, occur initially.[80] The right upper quadrant and/or epigastrium is usually tender. The disease may progress to coagulopathy, jaundice, seizures, disseminated intravascular coagulation, and hepatic encephalopathy. The diagnosis is often delayed secondary to the multiple differential considerations.[81]

Diagnostic Strategies. Typically, leukocytosis is present, the platelet count and fibrinogen level are low, prothrombin time and partial thromboplastin time are elevated, and fibrin split products are present. Hypoglycemia may occur. Serum transaminase levels are elevated, although rarely above 1000 U/L (a distinguishing feature from hepatitis), and should be measured in all patients who have systemic gastrointestinal symptoms during the third trimester. In contrast to Reye's syndrome, the serum ammonia level is only mildly elevated. Hyperuricemia is usually present. Bilirubin is elevated late in the course of the disease. The CT scan is usually normal, as is the sonogram. Liver biopsy is used to make the definitive diagnosis.[82]

Differential Considerations. Liver tenderness and coagulopathy most often suggest preeclampsia during the third trimester.[82] Jaundice and increases in aminotransferase level are distinguishing features because they are unusual in cases of liver disease associated with pregnancy-induced hypertension. Similarly, rapid progression of hepatic failure, hypoglycemia, and coagulopathy is unlikely in cases of preeclampsia. The patient with viral hepatitis is likely to have more marked elevations in transaminase levels. Drug-induced hepatic failure should be excluded by history and toxicologic screen for acetaminophen or other toxins if appropriate. Cholecystitis may be distinguished by ultrasound, but it may also be characterized by right upper quadrant pain; it is not associated with coagulopathy or progressive liver failure.

Management. The patient with acute fatty liver of pregnancy requires immediate stabilization if experiencing seizure or coma. Hypoglycemia may occur, which should be rapidly corrected with dextrose. Coagulation parameters should be assessed. Fluid resuscitation and replacement of clotting factors may be required, and the patient should be admitted to an obstetric service capable of managing this serious disease. The diagnosis is usually made with liver biopsy if the disease

has not progressed to severe coagulopathy. Rapid delivery is usually advisable when the diagnosis has been established. The route of delivery is dictated by the patient's clinical course and hemodynamic status. Fresh frozen plasma, platelet transfusions, and glucose may be needed to sustain the patient until delivery can be accomplished. After delivery, infants of mothers with acute fatty liver of pregnancy are at risk for postpartum hypoglycemia and liver dysfunction and therefore should be monitored closely.[82]

Intrahepatic Cholestasis of Pregnancy. Intrahepatic cholestasis of pregnancy, also termed *idiopathic jaundice of pregnancy*, *icterus gravidarum*, or *pruritus gravidarum*, is a rare syndrome that occurs during the third trimester of pregnancy. It is the second most common cause of jaundice in pregnancy, after hepatitis. Histologically, the disease is characterized by cholestasis and dilated canaliculi in the biliary tree. The liver is normal. It is more common with increasing maternal age, with multiple gestations, and in the winter months.[76,80]

Clinical Features. Generalized pruritus and mild jaundice are the hallmarks of intrahepatic cholestasis of pregnancy. Only 20% of patients present with this combination, however, and 80% present with pruritis alone. The pruritis usually begins in the palms and soles and ascends to the trunk. Although insomnia and fatigue occasionally accompany the pruritus, the patient appears nontoxic, without fever, vomiting, diarrhea, or significant malaise. The bilirubin level is rarely above 5 mg/dL, the alkaline phosphatase level can be elevated 7- to 10-fold, and transaminase levels are in the normal range. Resolution occurs when the woman delivers. Although maternal outcome is favorable, women with intrahepatic cholestasis of pregnancy are at increased risk for preterm delivery, meconium passage, and intrauterine fetal demise.[76,80,83]

Differential Considerations and Management. Exclusion of more serious entities, such as viral hepatitis, acute fatty liver, drug-induced cholestasis, or complicated cholecystitis, is required. Outpatient management is appropriate, provided the diagnosis is clear and the patient has close obstetric follow-up. Some authors advocate aggressive fetal surveillance and delivery after fetal lung maturity to improve fetal outcome.[76] Symptomatic treatment with antihistamines, ursodeoxycholic acid, bile salts, guar gum, benzodiazepines, and other medications has been tried with variable success.[80,84]

Hyperemesis Gravidarum

Nausea and vomiting are common in pregnancy, particularly from 6 to 20 weeks of gestation. *Hyperemesis gravidarum* is defined as nausea and vomiting that causes starvation metabolism, weight loss, dehydration, and prolonged ketonemia and ketonuria. It occurs in a small minority of pregnant patients. The cause of hyperemesis gravidarum is not clear; associations have been made with increasing estradiol and hCG levels, as well as with maternal cytokines.[85,86] Several studies have suggested an increased infection rate with *Helicobacter pylori* in patients with hyperemesis gravidarum.[87-89] Initial management involves rehydration with intravenous fluids, antiemetics, and demonstration of ability to take oral hydration. Patients may require enteral nutrition. Most standard antiemetics are in Food and Drug Administration category C and are used successfully to treat hyperemesis gravidarum. A short course of oral prednisolone has been reported to be therapeutic for intractable hyperemesis.[90,91] Oral vitamin B_6 has also been reported to be helpful.[89] Bilirubin and alkaline phosphatase levels can be mildly elevated but should return to normal levels after delivery. Hyperemesis may be complicated by liver disease and abnormal liver function tests, which are expected to resolve with supportive treatment.[92]

Thromboembolic Disease in Pregnancy

Principles of Disease

Thromboembolic disease accounts for almost 20% of obstetric mortality, making it the leading cause of death in pregnancy.[16] Pregnancy is a hypercoagulable state, with increased coagulation factors and stasis as pregnancy progresses and significant vascular trauma at the time of delivery. The risk of venous thrombosis increases during pregnancy to five or six times that of nonpregnant women. Although the risk is increased throughout pregnancy, it is highest during the puerperium. Women who smoke, are overweight, are older than 35 years, have varicose veins, or have a prior superficial venous thrombosis or history of a hypercoagulable state, as well as women who deliver prematurely or have postpartum hemorrhage, are at higher risk.[93-96]

Clinical Features

As in nonpregnant patients, clinical signs of pain, tenderness, and swelling are poor predictors of deep vein thrombosis in pregnancy. The clinical diagnosis of pulmonary embolus is likewise difficult. Although tachypnea, tachycardia, dyspnea, and pleuritic pain are commonly associated with pulmonary embolus, the symptoms are nonspecific and may be associated with such diverse diseases as hepatic inflammation, pyelonephritis, and diaphragmatic impingement from a normal gravid uterus.

Diagnostic Strategies

An arterial blood gas analysis should be undertaken, although it may be difficult to interpret. Arterial blood gases in pregnancy normally show a respiratory alkalosis from progesterone-induced respiratory stimulation, and the alveolar-arterial (A-a) oxygen difference is normal (the pregnant normal A-a gradient can be as high as 20 mm Hg) in the majority of patients with pulmonary embolus.[97] A chest radiograph (shielding the pelvis and uterus) should be obtained to exclude other disease processes that may mimic a pulmonary embolus. The diaphragm is normally symmetrically elevated during late pregnancy.

Noninvasive impedance plethysmography is highly accurate for the exclusion of deep vein thrombosis but lacks sensitivity for the exclusion of nonobstructive thrombi. Due to its widespread availability, Doppler ultrasonography has superseded noninvasive impedance plethysmography as the first-line test for the diagnosis of deep venous thrombosis. Both tests, however, are useful in the diagnosis of deep vein thrombosis of the femoral or popliteal veins in pregnancy, and these studies provide the least risk to the patient. Abnormal flow study results can be found in the normal patient studied in the supine position during late pregnancy, so positive results should be confirmed with the patient positioned on her left side. An unequivocally abnormal flow study finding is sufficient reason to treat the pregnant patient in most cases. However, normal leg study results can be seen with isolated iliac vein disease, which is common in pregnancy and requires imaging with magnetic resonance imaging or CT for diagnosis. If thromboembolic disease is suspected, serial indirect Doppler testing or CT may be required.[98] The risk of anticoagulation usually outweighs the risk of definitive studies when the diagnosis is equivocal.

Technetium-labeled ventilation-perfusion scans expose the fetus to less than 50 mrad of radiation, making them safe in all trimesters. One study found that only 2% of pregnant women

had high-probability scans; no adverse events occurred during follow-up in 104 women who were not heparinized and had normal or nondiagnostic scans.[99] Helical CT scanning provides an alternative for the diagnosis of pulmonary embolus in pregnancy. The average fetal radiation dose in helical CT scans is less than that from ventilation-perfusion scans, making it a potentially attractive alternative, although studies of its accuracy in pregnancy have not been done.[100] A pulmonary angiogram may be required if the diagnosis of pulmonary embolus is unclear after less invasive studies have been performed.

Management

Warfarin (Coumadin) is contraindicated during pregnancy because of its teratogenic effects and high risk of abortions and fetal hemorrhage. Heparinoids are used to treat thromboembolic disease during pregnancy. Unfractionated heparin carries a poorly understood risk of fetal osteoporosis, thrombocytopenia, prematurity, or miscarriage. In general, acute anticoagulation with intravenous heparin is followed by subcutaneous heparin twice daily, usually continued for 3 to 6 months postpartum in patients who have deep vein thrombosis or pulmonary embolus during pregnancy. Patients receiving this treatment require laboratory testing every 1 or 2 weeks, and the efficacy of anticoagulation may be variable in pregnancy. Low-molecular-weight heparin is considered safe in pregnancy and offers several advantages over unfractionated heparin: decreased bleeding risk, reliable pharmacokinetics, decreased risk of heparin-induced thrombocytopenia, fixed dosages, less frequent dosing, and decreased risk of osteoporosis and thrombocytopenia.[101-105] In patients with a history of deep vein thrombosis or pulmonary embolus, prophylaxis for subsequent gestations is usually recommended.[106-108]

Genitourinary Infections

Urinary Tract Infection

Principles of Disease. Although the risk of asymptomatic bacteruria (9%) does not increase in pregnancy, it appears that pregnancy predisposes the patient to develop symptomatic lower and upper tract genitourinary infections.[109,110] Uterine pressure exerted on the bladder and ureters, poor emptying of the bladder with voiding, and progesterone-induced smooth muscle relaxation that inhibits ureteral peristalsis all appear to contribute to increased risk of infection during pregnancy.

Identification of patients with asymptomatic bacteruria by prenatal screening in early pregnancy identifies approximately 95% of individuals at risk for subsequent bacteruria during the pregnancy. Because up to 30% of women who have asymptomatic bacteruria will develop pyelonephritis if untreated, treatment of bacteruria is cost-effective and important.[111,112]

Clinical Features and Diagnostic Strategies. The pregnant patient who comes to the emergency department with lower urinary tract symptoms (e.g., dysuria, frequency, and urgency) or upper tract symptoms (e.g., fever, malaise, or back pain) should have a pelvic examination and evaluation of an uncontaminated urine specimen (preferably catheterized). There is a predominance of right-sided symptoms during pregnancy, probably the result of increased mechanical forces on the right ureter, but left-sided flank pain or bilateral symptoms may be caused by pyelonephritis. Rarely, urinalysis may yield normal results or cultures may produce negative findings, either because of failure to report lower colony counts or because of complete obstruction of the involved ureter.

The major risk of asymptomatic and lower urinary tract infection is spread to the renal parenchyma. Acute pyelonephritis carries considerable morbidity in pregnancy, including maternal sepsis, permanent renal injury, and premature labor.[112] The risk of prematurity can be minimized by effective treatment and continued monitoring for recurrence. The development of premature labor in the woman who has pyelonephritis is ominous and can be prevented only by aggressive recognition and treatment earlier in pregnancy.

Differential Considerations. Vaginitis, herpes genitalis, chlamydial infection of the urethra, or ovarian torsion can masquerade as urinary tract symptoms. A history of external dysuria (burning at the perineum with urination) suggests herpes or vaginitis. A pelvic examination should be performed to obtain cervical cultures and to identify perineal or vaginal causes of dysuria. Appendicitis, cholecystitis, pancreatitis, and liver diseases in pregnancy must be considered in the differential diagnosis of upper urinary tract infection. Back pain may also be a sign of premature labor. Careful evaluation of an uncontaminated catheterized urine specimen is essential to making the correct diagnosis.

Management. Patients with asymptomatic bacteruria or lower urinary tract signs and symptoms should be treated with 7 to 10 days of an antibiotic that is active against usual urinary pathogens and is safe in pregnancy.[112,113] The most common choices are a cephalosporin, a nitrofurantoin, or a sulfonamide (except during the third trimester). Single-dose therapy for these infections during pregnancy has been proposed but may not be appropriate in an emergency department population with questionable follow-up and a relatively high incidence of occult upper urinary tract infection.

Patients with fever, back pain, and evidence of acute pyelonephritis in pregnancy are usually admitted for intravenous antibiotic administration, although outpatient parenteral therapy can be effective and safe in selected patients.[112,114] In such cases, aggressive intravenous hydration, obstetric consultation, and urine cultures should be initiated. At least one parenteral dose of antibiotics should be given, with antibiotic coverage guided by known organism susceptibilities in a given hospital. Because the resistance of *Escherichia coli* to ampicillin is considerable in most regions, cephalosporin or a combination of a penicillin and an aminoglycoside (which must be carefully monitored because of variable clearance by infected kidneys) is the usual intravenous medication administered. Cultures must be performed to ensure that the original choice of antibiotic was correct, and the patient must have a repeat culture and be followed closely after treatment.

Vaginitis

Bacterial Vaginosis. Bacterial vaginosis (formally known as *Gardnerella* vaginitis or *Haemophilus vaginalis* vaginitis) is an overgrowth of multiple endogenous vaginal bacteria, in some cases producing excessive discharge and vaginal malodor. Prevalence rates for bacterial vaginosis in pregnancy are estimated at 15 to 20%. Bacterial vaginosis is associated with an increased risk of chorioamnionitis, subclinical PID, premature rupture of membranes, fetal prematurity, and postpartum endometritis after vaginal delivery. Therapy during the second trimester is recommended even when the patient is asymptomatic to prevent the sequelae of premature rupture of membranes. Management includes a 7-day course of metronidazole or a 7-day course of clindamycin. Intravaginal treatment is not recommended in pregnant patients.[113,115]

Candida albicans *Vaginitis.* The incidence of vulvovaginal candidiasis is increased during pregnancy by high levels of estrogen and other steroids. It is not increased in the pregnant patient

who has recently been on antibiotics,[116] and there is no association of *Candida* colonization with adverse pregnancy outcomes.[117] Oral azoles are contraindicated in pregnancy because of an association with adverse fetal outcomes.[118] Treatment with vaginal azoles for 7 days during pregnancy is considered safe, with an estimated 85 to 100% cure rate.[113] Recurrent disease may require a vaginal culture to confirm diagnosis and to identify unusual candidal species (e.g., *Candida glabrata*) that may be resistant to conventional treatment. Longer treatment or treatment of a potential *Candida* reservoir in the patient's partner may also be required.

Trichomoniasis. Trichomoniasis is a sexually transmitted vaginitis caused by a protozoan parasite, *Trichomonas vaginalis*. Of patients who have trichomoniasis, 50% are asymptomatic. Symptoms include vaginal itching, malodorous discharge, or vaginal irritation. Diagnosis is made by direct visualization or protozoans on wet mount. The recommended treatment is metronidazole, a one-time dose of 2 g, for symptomatic patients only.[113] The organism is rarely aggressive during pregnancy but is associated with adverse pregnancy outcomes if untreated.[119]

Sexually Transmitted Diseases in Pregnancy

Sexually transmitted diseases are treated in pregnant patients according to the latest Centers for Disease Control and Prevention guidelines. In general, the tetracyclines and quinolones are contraindicated in pregnant patients. Treatment of genital tract infections may be important in preventing preterm labor and the morbidity of prematurity.

Chlamydia trachomatis *Infection.* *Chlamydia trachomatis* infection is the most common sexually transmitted disease, both in the United States and worldwide. Its prevalence is currently three to five times that of *Neisseria gonorrhoeae* infection.[113] Clinical diagnosis is difficult during pregnancy because cervical mucus is usually cloudy and contains white blood cells. Routine chlamydia screening during pregnancy is important to prevent complications of preterm labor and postpartum endometritis, both of which are more common in patients who have chlamydial cervical infections.[120] Chlamydial infections of infants born to infected mothers include conjunctivitis and pneumonitis. Treatment during pregnancy or breast-feeding is azithromycin (single 1-g dose), which improves compliance and decreases gastrointestinal side effects.[121] Treatment with a 7-day course of erythromycin base or amoxicillin is an acceptable alternative. Tetracyclines are contraindicated in pregnancy.[113]

Herpes Simplex Infection. Herpes simplex virus infections pose a significant risk in pregnancy to both the mother and the newborn. Women who have genital herpes during the third trimester have a 30 to 50% increased risk of transmission compared with women with herpes simplex virus infection in the first trimester (1%). The virus can be transmitted prenatally via transplacental infection or ascending vaginal infection and via vaginal delivery, particularly when herpetic lesions are present. Infections in the neonate often are disseminated or involve the central nervous system, causing significant morbidity and mortality. In the emergency department, culturing of new suspected herpetic lesions of the cervix, vagina, or perineum identifies patients at risk for perinatal complications. Although the risk of oral acyclovir and valacyclovir use in pregnancy is not well-known, it is recommended for first-episode genital herpes. Suppressive therapy can reduce the need for cesarean section in women whose first clinical episode of genital herpes simplex virus occurred during pregnancy but may not eliminate the need for cesarean section in women with recurrent herpes simplex virus.[113,122-124] Treatment should be undertaken with obstetric consultation and careful patient monitoring.

Neisseria gonorrhoeae *Infection.* Gonococcal infection of the cervix occurs during pregnancy in 1% of women. Symptoms are similar to those in nonpregnant women. Salpingitis is rare but may develop during the first trimester from upper genital extension of cervical infection. Some practitioners believe that the incidence of the disseminated infection is increased in pregnant patients because of elevated progesterone levels and increased vascularity in the area of the cervix. Gonococcal arthritis is the most common manifestation of gonococcal dissemination. Diagnosis and treatment of gonococcal infections are unchanged by pregnancy, and treatment includes cephalosporins or spectinomycin.[113] Treatment for possible coexistent chlamydial infection is recommended for pregnant and nonpregnant women. The major complications of third-trimester gonococcal infection are neonatal gonococcal ophthalmia and sepsis.[113,119]

Upper Genital Tract Infection

Pelvic Inflammatory Disease. Pelvic inflammatory disease is very rare in pregnancy and does not occur after the first trimester. Differential diagnosis includes ectopic pregnancy, septic abortion, and appendicitis, all of which are more common. In the patient with suspected infection, smears or cultures for chlamydia and gonorrhea should be obtained. Given the risk of endometrial infection in pregnancy and the need to consider other diagnoses, pregnant patients who have suspected PID require hospital admission and intravenous antibiotics.[113]

Chorioamnionitis. Chorioamnionitis is the infection or inflammation of the placenta and fetal membranes. After 16 weeks of pregnancy, the chorioamniotic membranes adhere to the cervical os and may become infected. The risk is increased in women with preterm labor. Chorioamnionitis is diagnosed by the findings of fever, maternal and fetal tachycardia, and uterine tenderness in a patient past 16 weeks of pregnancy. Leukocytosis can be suggestive of chorioamnionitis but is not diagnostic. The diagnosis is confirmed by amniocentesis. Patients should have blood cultures drawn. Vaginal and cervical cultures for group B strep, *E. coli*, chlamydia, and gonorrhea should also be obtained. Urgent obstetric consultation should be obtained, and hospital admission for intravenous antibiotics is required. Patients are usually treated with intravenous ampicillin and gentamicin. Vancomycin, clindamycin, or erythromycin may be substituted in the penicillin allergic patient.[125,126]

Acknowledgment

We thank Dr. Jean Abbott for her work on prior editions of this chapter.

KEY CONCEPTS

- The emergency physician must determine the type of miscarriage (incomplete, complete, inevitable, and threatened) because management priorities for these patients are different.
- The history and the physical examination of the patient with ectopic pregnancy are insensitive and nonspecific; therefore, ancillary studies are required to locate the pregnancy in any emergency department patient who has abdominal pain or vaginal bleeding and a positive pregnancy test result.
- The major conditions associated with vaginal bleeding in the second half of pregnancy include abruptio placentae and placenta previa. Patient history, physical examination, and results of ultrasonography must be used together by the emergency physician to distinguish these conditions.
- Appendicitis is the most common surgical emergency in pregnancy, and the presentation of these patients may not be classic, leading to a misdiagnosis rate of 30 to 35% overall in pregnant patients.
- The treatment of eclampsia includes magnesium sulfate for seizures, reduction of blood pressure, and delivery of the fetus.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 177

Chronic Medical Illness during Pregnancy

Kirsten K. Calder and Edward J. Newton

This chapter focuses on the care of the pregnant patient with selected chronic medical illnesses. Recognition of chronic disease is an important aspect of screening in these patients and can prevent adverse outcomes for both the mother and the fetus.

PRINCIPLES OF DISEASE

The physiologic changes that occur in pregnancy may exceed the patient's underlying compensatory mechanisms, resulting in initial symptom onset or rapid decompensation of medical illness during pregnancy. Certain chronic medical conditions also pose a serious threat to the mother's health or result in a poor fetal outcome. Finally, some medical illnesses result in a difficult delivery or the need for special resuscitation measures in the neonate.

The incidence of pregnancy in chronically ill patients is increasing because of improved survival of patients with diseases such as diabetes, epilepsy, renal failure, and various cancers. Also, the demographics of pregnancy are changing in that maternal age at the time of first pregnancy is increasing. Advances in assisted reproduction, including in vitro fertilization and oocyte donation, have made it possible for older women—including those who are postmenopausal—to become pregnant. Older pregnant women experience an increased rate of antepartum and intrapartum complications and are more likely to have comorbid conditions such as cardiovascular disease.[1]

SPECIFIC DISORDERS

Asthma

Asthma is the most common pulmonary problem in pregnancy, affecting up to 8.4% of gestations, and the prevalence appears to be increasing.[2] The overall effect of pregnancy on asthma seems to be that one third of patients will experience a worsening of the disease, one third will experience improvement, and the other third remain unchanged. The exact effect of asthma on the fetus remains controversial. Some studies show an increased risk of complications including preeclampsia, gestational diabetes mellitus, prematurity, and intrauterine growth retardation.[3,4]

Several changes in respiratory physiology during normal pregnancy affect the management of asthma in this context; both the tidal volume and the minute ventilation rise, increasing up to 50% by term. This increase in minute ventilation, or "hyperventilation of pregnancy," lowers the resting P_{CO_2} by an average of 8 to 10 mm Hg to a P_{CO_2} of 32 mm Hg. In response to chronic hyperventilation, there is a compensatory increase in the renal excretion of bicarbonate, with serum levels averaging 19 mEq/mL. The net result is a slight respiratory alkalosis, with a serum pH ranging from 7.40 to 7.45. It is important to keep these "normal" values in mind when gauging the severity of an asthma exacerbation in the pregnant patient.

The treatment strategy in the care of the pregnant asthmatic patient is to achieve normal pulmonary function, prevent acute exacerbations, and minimize use of short-acting rescue beta-agonists. Acute asthma exacerbations pose a significant maternal and fetal risk, and the pregnant patient should be managed as aggressively as the nonpregnant patient.[5] In fact, patients whose asthma is well controlled are generally expected to have normal pregnancies, and the risks from inadequately treated disease outweigh the risks of therapy.[5,6]

The inhaled beta-agonist agents are generally considered as safe in pregnancy (Tables 177-1 and 177-2).[5,7] As in the nonpregnant patient, inhaled short-acting beta-agonists are first-line agents for acute asthma exacerbations. Long-acting agonists are also recommended for maintenance use in patients with moderate or severe disease.[5] Although safe from a teratogenic perspective, these medications are powerful tocolytics and will usually halt active labor. Selective agonists are preferred because nonselective agents such as epinephrine theoretically decrease uteroplacental blood flow via beta-mediated effects.

Corticosteroids remain a core component of maintenance treatment for asthma in the pregnant patient. In fact, current data support the safety of inhaled corticosteroids,[7] and their chronic use is recommended in all asthmatic patients except those with mild intermittent disease.[5] Use of systemic corticosteroids is sometimes necessary on a chronic basis in patients with severe persistent asthma and as a short burst in patients with exacerbations that exhibit inadequate or poor response to initial beta-agonist therapy. However, corticosteroids have a possible association with cleft deformities, preterm delivery, low birth weight, and preeclampsia.[3,5,7-10] These complications may also be related to uncontrolled asthma, but inhaled delivery is preferred over systemic dosing.

The methylxanthine theophylline has been shown to be safe in pregnancy at therapeutic doses and is an acceptable alternative medication for maintenance therapy.[5,7,11] There are limited data for chromolyn sodium and the newer leukotriene receptor antagonists (montelukast and zafirlukast),[12] but all are

Table 177-1 Gestational Effects and Treatment of Medical Illnesses during Pregnancy

MEDICAL ILLNESS	GESTATIONAL CONCERNS	TREATMENT
Asthma	Fetal—IUGR, PTD, hypoxia, meconium-stained amniotic fluid, fetal loss Maternal—preeclampsia, gestational hypertension, gestational diabetes, hyperemesis gravidarum, need for labor induction	Treatment of acute exacerbations is the same as for the nonpregnant patient. Fetal monitoring for exacerbations during the third trimester is recommended even in the absence of maternal hypoxia. Maintenance therapy also unchanged with the following precautions: **Corticosteroids:** inhaled agents preferred to limit side effects, but oral route may be necessary with severe, persistent disease; patients on long-term steroids require "stress dose" hydrocortisone during labor and delivery **Methylxanthines:** safe but debatable benefit; use only in refractory disease; reduced clearance during pregnancy may result in maternal toxicity and fetal tachycardia **Leukotriene receptor antagonists:** avoid zileuton
Acute coronary syndrome	Fetal—perinatal death, PTD Maternal—uterine hemorrhage and abruption (related to use of antiplatelet, antithrombotic, and fibrinolytic agents)	Standard medical therapy is the same as for the nonpregnant patient, although antiplatelet, antithrombotic, and fibrinolytic agents should be avoided when delivery is imminent. Avoid maternal hypotension when using nitrates—may result in fetal distress. Avoid beta-blockers in the first trimester (teratogenic). Coordinate definitive care (fibrinolytics vs. PCI) with cardiology.
Valvular heart disease	Fetal—perinatal death, PTD Maternal—decompensated heart failure, thromboembolism, death	Subcutaneous heparin therapy indicated for patients with prosthetic valves and atrial fibrillation. Avoid warfarin. **Mitral stenosis:** diuresis and beta-blockade; valvuloplasty or open cardiac surgery for severe symptomatic disease; consider pregnancy termination in patients with atrial fibrillation or severe stenosis **Mitral and aortic regurgitation:** diuresis in patients with pulmonary congestion; surgical therapy for acute regurgitant lesions; consider pregnancy termination in patients with symptomatic disease **Aortic stenosis:** avoid hypotension and the supine hypotensive syndrome—position left lateral decubitus; vigorous fluid replacement during delivery; valvuloplasty or open cardiac surgery for severe symptomatic disease
Hypertension	Fetal—perinatal death, IUGR, PTD Maternal—progression of target end-organ damage, superimposed preeclampsia, abruption	Fetal cyanide poisoning might develop after several hours of sodium nitroprusside—avoid prolonged infusions. The most commonly used agents include methyldopa, labetalol, and hydralazine. Avoid beta-blockers in the first trimester (teratogenic). Avoid ACEIs and ARBs.
Iron-deficiency anemia	Fetal—low birth weight, PTD, low fetal iron stores, fetal loss (with severe anemia) Maternal—preeclampsia, high-output heart failure (rare); effects on maternal mortality unclear	Oral iron supplementation is indicated to improve maternal iron stores. Several over-the-counter preparations are available. There is a delay from onset of therapy to increase in serum hemoglobin. Parenteral iron replacement is safe and effective, although rarely required. Transfusion is rarely required but may be necessary with severe symptomatic anemia.
Sickle cell anemia	Fetal—fetal loss, IUGR, PTD, and premature rupture of membranes Maternal—↑ need for cesarean section, preeclampsia, infection, heart failure, pulmonary infarction, ↑ incidence of painful crises; maternal mortality low with treatment; false-positive Apt and Kleihauer-Betke tests 2° to persistent hemoglobin F	Management of pain crises and infections is the same as for the nonpregnant patient, with rest, hydration, narcotic analgesia, supplemental oxygen, and antibiotics as indicated. Narcotic analgesics should not be withheld, but the need for neonatal respiratory support should be anticipated if delivery is imminent. Prophylactic transfusion is not indicated. Fetal monitoring and assessment of fetal well-being are indicated for viable pregnancies. Chronic maintenance care includes pneumococcal vaccination, supplemental folate, and usually iron. Hydroxyurea has been discouraged during pregnancy, but few adverse fetal effects have been reported in humans.
Epilepsy	Fetal—various congenital malformations associated with AEMs, fetal hypoxia and bradycardia, fetal loss Maternal—variable changes in seizure frequency; alterations in AEM levels; increased seizure frequency secondary to voluntary medication noncompliance; abruption, anemia, hyperemesis gravidarum, preeclampsia, need for labor induction and cesarean section, premature rupture of membranes	Management of status epilepticus is the same as for the nonpregnant patient. Maintenance therapy should be coordinated by the patient's neurologist (or primary care practitioner) and obstetrician—in general, a single AEM given at the lowest effective dose is recommended. Patients with pregravid seizure control with AEM monotherapy should continue their current regimen. There is limited experience with newer AEMs, but these are likely to have a more favorable side effect profile. Folate supplementation is mandatory for patients taking older AEMs. Administer oral vitamin K to the mother during the last month of pregnancy and parenteral vitamin K to the newborn.

Table 177-1 Gestational Effects and Treatment of Medical Illnesses During Pregnancy—cont'd

MEDICAL ILLNESS	GESTATIONAL CONCERNS	TREATMENT
Myasthenia gravis	Fetal—transient neonatal myasthenia syndrome Maternal—variable changes in disease severity; arrest of labor; disease exacerbation in the postpartum period	Management is the same as for the nonpregnant patient. Ventilatory support is the most important aspect of therapy; note that patients with myasthenia gravis are relatively resistant to depolarizing paralytic agents—higher doses may be required. Pyridostigmine therapy can be continued. Patients on maintenance corticosteroids require "stress dose" hydrocortisone during labor and delivery. Plasmapheresis is safe during pregnancy.
Diabetes mellitus—insulin-dependent, non-insulin-dependent, and gestational	Fetal—congenital malformations; macrosomia; IUGR; fetal loss; neonatal hypoglycemia, jaundice, hypomagnesemia, and hypocalcemia Maternal—preeclampsia, "brittle" diabetes, ↑ need for cesarean section; mothers with GDM have ↑ risk for development of postpartum diabetes	Every attempt should be made to maintain maternal serum glucose of 100 mg/dL. Note that insulin requirements decrease during the immediate postpartum period and the mother may not need insulin for 24–48 hours after delivery. Insulin therapy—using either intermittent dosing or continuous subcutaneous infusion—is standard care for patients with both IDDM and NIDDM. Management of DKA is the same as for the nonpregnant patient with the addition of an assessment of fetal well-being and continuous fetal heart monitoring. GDM is often manageable with diet alone but may require insulin therapy when fasting plasma glucose remains >105 mg/dL.
Hyperthyroidism	Fetal—PTD, low birth weight, fetal thyroid dysfunction, fetal loss Maternal—preeclampsia, heart failure	Management of thyroid storm is the same as for the nonpregnant patient and includes a search for the underlying precipitant. Therapy for hyperthyroidism in the absence of thyroid storm: **Reversal of sympathetic effects:** propanolol in standard doses is useful until thyroid hormone synthesis has been blocked by thioamides **Thioamides:** both propylthiouracil and methimazole at the lowest effective dose are acceptable **Surgical therapy:** thyroidectomy is useful in refractory cases **Other:** avoid iodide if possible; hydrocortisone decreases peripheral conversion of T_4 to the more active T_3 and can be used during pregnancy Radioactive iodine is absolutely contraindicated.
Hypothyroidism	Fetal—congenital malformations, low birth weight, fetal loss, fetal thyroid dysfunction, and goiter Maternal—preeclampsia, abruption, postpartum hemorrhage, ↑ need for cesarean section	Maintenance therapy includes levothyroxine 0.15 mg/day. Appropriate treatment prevents adverse obstetric and fetal outcomes. Myxedema coma is rare, but when present, treatment is the same as for the nonpregnant patient.
Tuberculosis	Fetal—fetal loss, low birth weight, PTD; fetal and neonatal tuberculosis Maternal—preeclampsia; potential for delayed diagnosis and treatment out of concern for the fetus	**PPD positive/chest radiograph negative:** 6- to 9-month course of isoniazid (starting after the first trimester) for patients with recent conversion (<2 years); patients who have been PPD positive >2 years may defer treatment until after delivery but should still be offered a course of isoniazid since it is safe in pregnancy **Active tuberculosis:** 9-month course (starting immediately) of isoniazid plus rifampin or ethambutol **Multidrug-resistant tuberculosis:** warrants aggressive therapy without regard to potential teratogenicity Pyridoxine is mandatory for all patients receiving isoniazid.
HIV/AIDS	Fetal—HIV infection, PTD, fetal loss; neonatal drug withdrawal if the mother uses intravenous drugs Maternal—postpartum endometritis, uterine bleeding (in the setting of thrombocytopenia)	**Antiretroviral therapy:** 1. Highly active antiretroviral therapy (HAART) should be offered to all pregnant patients with HIV and viral load >1000. The HAART regimen should include zidovudine (AZT) to prevent vertical transmission of the virus. 2. There are specific HAART drug-related concerns during pregnancy—decisions regarding therapy are best made by appropriate specialists. 3. AZT monotherapy is not recommended except in those patients with a low viral load who do not wish to take HAART. In these cases, AZT is appropriate to reduce disease transmission. Cesarean section is recommended with viral load >1000. Opportunistic infections require standard therapies despite the potential fetal effects.
Syphilis	Fetal—congenital syphilis, fetal loss, PTD, IUGR, nonimmune hydrops	Primary, secondary, early latent (<1 year): benzathine penicillin G (BPG), 2.4 million units IM × one dose Late latent (>1 year or unknown duration): BPG, 2.4 million units IM weekly × three doses Neurosyphilis: aqueous penicillin G, 2–4 million units IV q4h × 10–14 days or procaine penicillin G, 2.4 million units IM, and probenecid, 500 mg PO q6h × 10–14 days

ACEI, angiotensin-converting enzyme inhibitor; AEM, antiepileptic medicine; AIDS, acquired immunodeficiency syndrome; ARB, angiotensin II receptor blocker; DKA, diabetic ketoacidosis; GDM, gestational diabetes mellitus; HIV, human immunodeficiency virus; IDDM, insulin-dependent diabetes mellitus; IUGR, intrauterine growth retardation; NIDDM, non-insulin-dependent diabetes mellitus; PCI, percutaneous coronary intervention; PTD, preterm delivery.

Table 177-2 Drugs Used in the Treatment of Acute Asthma Exacerbations during Pregnancy

PHARMACOLOGIC CLASS	EXAMPLES	DOSAGE	COMMENTS
Inhaled beta-agonists	Albuterol Levalbuterol	2.5–5 mg every 20 min 1.25–2.5 mg every 20 min	Inhaled beta-agonists first-line therapy May also be administered via MDI Up to three doses in first hour; continuous use in severe exacerbations
Injectable beta-agonists	Epinephrine Terbutaline	0.3–0.5 mg SC (1:1000 or 1 mg/mL) every 20 min 0.25 mg SC (1 mg/mL) every 20 min	No proven benefit over inhaled dosing Up to three doses in first hour
Systemic corticosteroids	Prednisone Prednisolone Methylprednisolone	Dosage applies to all preparations Initial inpatient therapy: variable dosing; need at least 120–180 mg/day Outpatient burst therapy: 40–60 mg/day for 3–10 days	No benefit of intravenous dosing over oral except in patients with impending respiratory failure who can't take oral medications
Inhaled anticholinergics	Ipratropium bromide	0.5 mg every 20 min	Not first-line therapy; should be used with beta-agonists Consider for use in patients with severe exacerbations
Smooth muscle relaxants	Magnesium sulfate		Limited data on its use for asthma in pregnancy

From NAEPP Expert Panel Report: Managing asthma during pregnancy: Recommendations for pharmacologic treatment—2004 update. J Allergy Clin Immunol 115:34, 2005.

Table 177-3 Hypertensive Disorders of Pregnancy

	CHRONIC HYPERTENSION	GESTATIONAL HYPERTENSION	PREECLAMPSIA	CHRONIC HYPERTENSION WITH SUPERIMPOSED PREECLAMPSIA
Definition	1. Hypertension* that antedates pregnancy	Hypertension diagnosed after 20 weeks of gestation in the absence of proteinuria or other evidence of preeclampsia	Hypertension that begins after 20 weeks of gestation occurring in association with new-onset proteinuria (≥300 mg/24 hr)	1. Hypertension that antedates pregnancy in association with new-onset proteinuria
	2. Hypertension diagnosed prior to 20 weeks of gestation			2. Sudden increase in proteinuria in a woman with chronic hypertension* and proteinuria prior to 20 weeks of gestation 3. Hypertension that antedates pregnancy in association with sudden increase in blood pressure
	Comment: rarely, preeclampsia presents prior to 20 weeks of gestation	*Comment:* may progress to preeclampsia; may also represent previously undiagnosed hypertension		4. Hypertension that antedates pregnancy in association with decreased platelets or elevated liver transaminases

*Defined as blood pressure ≥140 mm Hg systolic or ≥90 mm Hg diastolic.

From Roberts JM, et al: Summary of the NHLBI working group on research on hypertension during pregnancy. Hypertension 41:437, 2003; and the National Institutes of Health: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. NIH Publication No. 04-5230, August 2004.

considered class B (presumed safety) during pregnancy. Magnesium sulfate has received a good deal of attention in the acute treatment of refractory asthma exacerbations because it has a wide safety profile and potent bronchodilator properties. Although large doses of magnesium have been used for the treatment of eclampsia, at this time there are insufficient data to support routine use of magnesium in this patient population.

Perhaps the most important tenet of treatment to recognize is that if the mother is hypoxic, the fetus is hypoxic as well. In addition, the fetus is more sensitive to hypoxia; thus, a normal maternal oxygen saturation does not preclude fetal distress. Supplemental oxygen should be administered to all pregnant patients with an acute asthma exacerbation.

Hypertension

Chronic Hypertension and Hypertensive Emergencies

Chronic hypertension is defined as elevated blood pressure that is present before the onset of pregnancy or that begins prior to the 20th week of gestation. It affects up to 5% of pregnancies and represents a significant source of maternal and fetal mortality and morbidity (see Table 177-1).[13,14] The emergency physician may be required to provide therapy for hypertensive emergencies in patients with chronic hypertension and to differentiate between the various hypertensive disorders of pregnancy (Table 177-3).

In the treatment of chronic hypertension in pregnancy, the physician must balance the goal of reducing maternal blood

pressure with the requirements to maintain cardiac output and minimize adverse effects for both mother and fetus. Precipitous and marked decreases in blood pressure may significantly diminish uteroplacental blood flow. Treatment of patients with mild disease does not have an appreciable effect on perinatal outcomes, nor does it reduce the incidence of superimposed preeclampsia. In addition, these patients are likely to have a decrease in blood pressure without pharmacologic agents due to normal physiologic changes that occur in pregnancy, and they may be successfully managed without medications.[14-16] On the contrary, patients with more severe hypertension, patients with evidence of end-organ damage, and patients on more than one pregestational antihypertensive medication probably need maintenance medical therapy (see Table 177-1).[15,16] Lifestyle modification is a potential mode of therapy, but it is unclear whether dietary and weight restrictions are safe in the gravid patient.[14]

Decisions regarding maintenance therapy are most appropriately made by the patient's primary care practitioner in conjunction with her obstetrician. However, the emergency physician may be called upon to make treatment decisions for patients with severely elevated blood pressure and for patients with superimposed eclampsia. Nearly all of the major classes of antihypertensive agents are acceptable in the pregnant patient, with the exception of angiotensin enzyme inhibitors and angiotensin II receptor blockers. Diuretics are also considered second-line agents because of concerns regarding plasma volume constriction (see Table 177-1).[15,16] Hydralazine and labetalol are the agents most commonly used for hypertensive emergencies associated with eclampsia and are also appropriate for such emergencies in the patient with chronic hypertension. Sodium nitroprusside can cause fetal cyanide toxicity after several hours of infusion and is considered a second-line agent (Table 177-4).[15]

Diagnosis of preeclampsia in the pregnant patient with chronic hypertension is challenging but necessary (see Chapter 176). Patients with chronic hypertension are more likely to develop preeclampsia, a situation that results in increased morbidity and mortality compared with either process in isolation. Coexistence of the two disorders should be suspected in the following situations: (1) new onset of proteinuria after 20 weeks of gestation in a patient with known hypertension and (2) pregnant patients with hypertension and proteinuria prior to 20 weeks of gestation who develop thrombocytopenia, increased transaminase levels, or an acute increase in proteinuria or blood pressure (see Table 177-3).[14]

Pulmonary Hypertension

Primary (idiopathic) pulmonary hypertension, Eisenmenger's syndrome (pulmonary hypertension associated with intracardiac left-to-right shunts), and secondary vascular pulmonary hypertension have extremely high mortality rates in association with pregnancy, ranging from 30 to 52%. The majority of deaths are a result of heart failure.[17] Unfortunately, mortality is unaffected by peripartum management in most cases, although some patients benefit from selective pulmonary artery vasodilators such as prostacyclin and inhaled nitric oxide.[17] The primary goals of the emergency physician are to ensure high right ventricular filling pressures by maintaining adequate volume status and to obtain early consultation with obstetrics and cardiology. Patients with early gestations should be referred for elective pregnancy termination.

Cardiac Disorders

Acute Coronary Syndromes

Coronary artery disease is rare in pregnant women, with a population-based study noting a diagnosis of acute myocardial infarction (AMI) in up to 6.2 per 100,000 deliveries.[18] Prior mortality rates were reported to be approximately 20%, but more recent studies reveal rates ranging from 5.1 to 7.3%.[18-20] Normal physiologic changes of pregnancy such as increased cardiac output and reduced oxygen-carrying capacity secondary to physiologic anemia have the potential to exceed the threshold for angina if a fixed coronary artery stenosis is present. Certain conditions are also associated with an increased risk of pregnancy-related AMI, including advanced maternal age, thrombophilia, hypertensive disorders, anemia, diabetes mellitus, and tobacco use.[18,19] AMI can occur anytime during the gestational period but peaks during the last trimester and peripartum period. Twenty-seven to 41% of events occur in the 6 weeks after delivery.[18,19] Because increases in cardiac output peak during labor and delivery, maternal mortality from AMI is higher intrapartum than during the antepartum or postpartum periods.[19]

A significant percentage of pregnant women with AMI have normal coronary arteries—reported to be 29% of those patients who underwent angiography.[20] Other pathophysiologic mechanisms besides atherosclerosis that cause AMI in the pregnant patient include coronary artery dissection, coronary artery aneurysm, and vasospasm. The relative significance of these lesions varies according to the gestational period. Atherosclerotic disease causes the majority of AMIs in the antepartum period, whereas the incidence of coronary artery dissection is increased postpartum.[20] Pulmonary embolus, reflux esophagitis, biliary colic, and aortic dissection are all more common than myocardial ischemia during pregnancy and need to be considered in the differential diagnosis. Unfortunately, some women continue to use illicit drugs during their pregnancy, and it is important to consider cocaine use in the pregnant patient presenting with chest pain.

Table 177-4 Antihypertensive Agents for Hypertensive Emergencies

ANTIHYPERTENSIVE AGENT	DOSE	COMMENT
Hydralazine	5 mg IV, then 10 mg IV every 20–30 min until target blood pressure is achieved	Consider another agent if inadequate response despite administration of 25 mg
Labetalol	20 mg IV; subsequent dosing with 40 mg, then two doses of 80 mg every 10 min until target blood pressure is achieved	Consider another agent if inadequate response despite administration of 220 mg Standard contraindications apply
Sodium nitroprusside	Infusion rates vary—start at 0.25 μg/kg/min	Use only if other agents not effective—fetal cyanide toxicity is possible after several hours

National Institutes of Health: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. NIH Publication No. 04-5230, August 2004.

The diagnosis of angina is often clinical. Because normal pregnancy is often associated with electrocardiographic changes such as ST wave depression and T wave inversion, additional evaluation may be necessary. Echocardiography is useful in correlating suspicious electrocardiographic findings with wall motion abnormalities. The enzymatic diagnosis of myocardial infarction is unchanged except during and immediately after delivery, when troponin is preferred over creatinine kinase and myoglobin, which are both elevated above baseline during this time period. Angiography for the patient with suspected angina is generally avoided because the large dose of radiation poses a risk to the fetus, but it can be used in certain clinical situations with the preferred time of intervention being the second trimester.[16] Radionuclide studies carry a lower radiation risk than does angiography but are also avoided unless absolutely necessary.

Treatment of AMI during pregnancy is similar in most respects to treatment of the nonpregnant patient. Survival of the mother is the primary concern, and therapy to improve maternal outcome should not be withheld. Standard treatment includes antiplatelet agents, nitroglycerin, beta-blockers, and antithrombotic agents. However, there are potential adverse effects of such therapy on the mother and fetus (see Table 177-1), and emergent consultation with cardiology is recommended. Regarding antiplatelet agents, aspirin remains the first-line agent. There is limited experience with clopidogrel and eptifibatide, but both have been used successfully and are considered safe from a teratogenic standpoint. Heparin has long been considered the antithrombotic agent of choice in pregnant patients, but newer low-molecular-weight agents, specifically dalteparin and enoxaparin, appear to be efficacious and safe and are deemed appropriate for use.[21] Heparin is preferable for patients in the late third trimester because there is a more predictable response to protamine sulfate should labor begin.

Experience with thrombolytic therapy in pregnancy is extremely limited and is much more extensive in the setting of stroke and pulmonary embolism.[22] Although such therapy may reduce maternal and fetal mortality, pregnancy is considered a relative contraindication to its use. Reported adverse effects have included maternal hemorrhage, maternal death, placental abruption, preterm delivery, fetal death, and fetal intracranial hemorrhage, although the causal relationship in many of these cases is unclear because neither tissue plasminogen activator nor streptokinase cross the placenta. The majority of patients had favorable maternal and fetal outcomes, but most were being treated for indications other than AMI.[20,22] Because thrombolytic therapy precludes major surgery and epidural anesthesia in the hours to days immediately after administration, the emergency physician must carefully consider whether to use these agents in pregnant women who are close to term, especially if the need for cesarean delivery is anticipated. Because of the lack of data and potential risks of fibrinolytics in gravidas, emergent percutaneous intervention is the treatment of choice for definitive management of AMI.

In the setting of peripartum AMI, labor should be conducted with continuous monitoring of both the mother's hemodynamic status and fetal well-being. There are benefits and risks of both vaginal and operative delivery. Cesarean section avoids prolonged exertion by the mother but subjects the patient to general anesthesia if use of antithrombotic agents precludes epidural catheter placement. In addition, surgical delivery places the patient at risk for typical postoperative complications, such as infection, hemorrhage, and thromboembolism. Therefore, assisted vaginal delivery is preferred unless there is an obstetric reason for cesarean section.[20] Resolution of angina may occur during the postpartum period as physiologic demands lessen, but its occurrence during pregnancy merits a complete cardiac evaluation for acute coronary syndrome.

Valvular Heart Disease

Maternal valvular heart disease can be congenital or acquired and is one of the leading causes of nonobstetric death. Acquired valvular disease is mainly the result of rheumatic fever and endocarditis. In the United States, most cases of significant congenital heart disease are identified and corrected surgically before puberty. The ability of patients to tolerate pregnancy without significant adverse effects depends on the type and severity of the lesion. Mild to moderate lesions (New York Heart Association classes I and II) are often associated with good outcomes. On the other hand, mitral stenosis (beyond class I), advanced aortic stenosis, aortic and mitral lesions associated with moderate to severe ventricular dysfunction or pulmonary hypertension, and mechanical prosthetic valves requiring anticoagulation can result in significant maternal mortality and require directed therapy (see Table 177-1).[16,23]

Mitral Stenosis. Mitral stenosis is the most commonly encountered valvular lesion in pregnancy and is also the most important lesion to detect in early pregnancy because maternal mortality is appreciable.[16] The increased resting heart rate seen in normal pregnancy shortens left ventricular diastolic filling time and consequently results in decreased stroke volume. The demand for increased cardiac output during pregnancy creates a vicious cycle in which further acceleration of heart rate occurs. This tachycardia, combined with the expanded plasma volume of pregnancy, ultimately produces high left atrial pressures, pulmonary vascular congestion, and the symptoms and physical findings typical of left ventricular failure. Even patients with asymptomatic pregestational mitral stenosis warrant close cardiology follow-up with echocardiography at frequent intervals during gestation.[16]

Treatment is aimed at reducing plasma volume and slowing the heart rate (see Table 177-1). Surgical intervention is indicated in patients with refractory symptoms despite optimal medical management and in patients with pulmonary hypertension. The preferred procedure is percutaneous balloon valvotomy, which is associated with good maternal and fetal outcomes when performed in experienced centers.[16,23]

Aortic and Mitral Regurgitation. In most cases, chronic regurgitant lesions are well tolerated during pregnancy and may even improve as the reduced systemic vascular resistance of pregnancy allows more forward and less regurgitant flow. In addition, this effect is aided by the increase in heart rate and shortened diastole that occur in pregnancy.[16,23] When necessary, medical therapy consists of diuresis and, possibly, vasodilators. Patients with acute mitral regurgitation due to ruptured chordae do not fare as well and may require surgical therapy.[16,23]

Aortic Stenosis. Symptomatic aortic stenosis during pregnancy usually occurs in the setting of a congenital bicuspid valve and is uncommon.[16,23] Patients with aortic stenosis tend to have good pregnancy outcomes, and conservative management is often possible. Severely symptomatic patients may need percutaneous valvotomy in an experienced institution, although this procedure is risky for both the mother and the fetus.[16,23]

Prosthetic Heart Valves. Anticoagulation for the pregnant patient with a prosthetic heart valve is complicated. Warfarin is considered to be contraindicated during weeks 6 through 12 of gestation, although the risk of embryopathy is likely low when the dose is ≤5 mg/day.[16,23] In addition, because warfarin crosses the placenta, there is a risk of fetal bleeding. Neither unfractionated heparin (UFH) nor low-molecular-weight heparin

(LMWH) cross the placenta or are teratogenic, but there are problems with their use in pregnancy. The response to UFH is more unpredictable in the pregnant patient, and frequent monitoring of the activated partial thromboplastin time is indicated. Even with frequent monitoring, the risk of thromboembolism is significantly increased. LMWH is an acceptable alternative to UFH in pregnant patients with thromboembolic disease, but there are limited data on its use in the gravida with a mechanical valve.[16,23] As a result, use of LWMHs in patients with prosthetic heart valves is not recommended at this time.[16,21,23]

Hematologic Disorders

Anemia

By far the most common medical complication of pregnancy is anemia. The physiologic adaptations to pregnancy include expansion of plasma volume in excess of the increase in red blood cell (RBC) mass. This results in the dilutional, physiologic anemia of pregnancy with nadir hemoglobin occurring near the beginning of the third trimester. Any type of anemia can complicate pregnancy, but the three types most commonly involved are iron deficiency, folate deficiency, and sickle cell hemoglobinopathy.

Iron-Deficiency Anemia. Iron-deficiency anemia is common, occurring in approximately 20 to 25% of pregnancies in industrialized countries. Apart from chronically low or marginal iron stores in many women, diversion of maternal iron to the fetus for development of its own RBCs and iron stores and increased maternal demand for iron exacerbate the deficiency during pregnancy. Pregnant patients are also subject to other causes of iron-deficiency anemia, such as malnutrition, chronic underlying disease, and blood loss from the gastrointestinal or genitourinary tracts.

Anemia in pregnancy is defined by the World Health Organization as a hemoglobin (Hgb) concentration less than 11 g/dL. Because of physiologic dilution, this level may be slightly lower after the 25th week of gestation. Mild, dilutional anemia (Hgb between 9 and 11 g/dL) confined to the later stages of pregnancy has little impact on obstetric outcomes.[24] On the other hand, severe anemia (<6 to 7 g/dL) and nondilutional anemia occurring early in pregnancy are associated with preterm delivery and low birth weights.[24-26] The diagnosis of iron-deficiency anemia is most accurately made in the very early stages of pregnancy because serum ferritin, the preferred test, is affected by the dilutional effect of increased plasma volume occurring later in pregnancy. After the first trimester, other blood tests performed in combination may be necessary. The use of RBC indices is not a reliable screening tool because microcytosis and hypochromia are not reliably present in pregnant patients.

Iron supplementation to increase maternal iron stores (see Table 177-1) is indicated in women with iron deficiency even though it remains unclear as to whether such therapy improves perinatal outcomes. Patients with an otherwise uncomplicated physiologic anemia can be expected to have good obstetric outcomes without therapy and do not require iron treatment. The use of prophylactic supplementation in women with normal Hgb (>11 g/dL) and normal iron stores (ferritin >20 μg/L) is controversial. A trial found that iron supplements for such women prior to 20 weeks of gestation did not reduce the prevalence of preterm delivery or development of anemia later in pregnancy but did result in an increase in birth weight.[27] Another trial found that the incidence of both preterm delivery and low birth weight was reduced in women on prophylactic iron.[28]

Folate-Deficiency Anemia. Folate deficiency is one of a number of causes of megaloblastic anemia, a condition characterized by abnormal DNA synthesis and ineffective RBC production. The incidence of folate deficiency in pregnancy is low (4%) in developed countries but remains higher in other populations.[29-31] The risk of developing folate deficiency is increased in patients with multiple gestations, preexisting malnutrition, hyperemesis gravidarum, malabsorption syndromes, and alcoholism. Use of certain antiepileptic medications also places women at increased risk for deficiency.

Iron-deficiency and folate-deficiency anemias often coexist, making the peripheral blood smear difficult to interpret. Measurement of serum and RBC folate levels is indicated in cases of suspected folate deficiency, but both have limitations. Serum folate is noted to exhibit a rapid response to folate intake, and low levels may normalize within days after a folate-rich meal. Serum folate is also affected by the hemodilution of pregnancy. RBC folate levels are more static and are indicative of folate status several months prior to analysis. RBC folate levels may be misleading in more acute cases and are affected as well by the increase in RBC production that occurs in pregnancy.

As is the case for iron deficiency, effects on the fetus depend on the degree of anemia, with the most significant complications being neural tube defects (NTDs) and preterm delivery.[32-34] Folate supplementation reduces the risk of NTDs,[32,33] and oral folate supplementation with 0.4 to 1.0 mg daily is routinely recommended during pregnancy and prior to conception.[35] Women at higher risk for NTDs (e.g., NTDs in prior pregnancy) are advised to take higher doses of folate at 4 mg daily.[35]

Sickle Cell Anemia. Sickle cell disease (SCD) is one of the major sources of maternal and fetal complications in the United States. The details of the pathophysiology and genetics of SCD are discussed in Chapter 119, but it is useful to review the most common phenotypes that affect pregnancy. The sickle gene can be homozygous (hemoglobin SS or SCD), and this form of the disease is responsible for most pregnancy complications. The sickle gene can also be heterozygous with normal hemoglobin A (sickle cell trait or hemoglobin SA), in which case symptoms are rare except under extreme environmental conditions. The hemoglobin S can also be heterozygous with a large number of abnormal hemoglobins such as hemoglobin C, several variants of thalassemia, and other rare hemoglobin variants, and each variant has its own complication profile. Of these, the most relevant in terms of pregnancy complications is hemoglobin SC.

Patients with SCD are subject to many chronic medical problems secondary to a variety of pathophysiologic mechanisms, including sickling of RBCs, anemia, immunosuppression caused by autosplenectomy, and the need for repeated transfusion. Median life expectancy is in the fifth decade for both sexes affected by SCD, and female fertility is generally unaffected, so it is likely that the emergency physician will encounter pregnant patients with the disease. Reported maternal complications in patients with SCD include preterm labor, premature rupture of membranes, maternal infections, more frequent pain crises, and an increased need for cesarean delivery.[36,37] Despite these complications, the maternal mortality rate is less than 1% with current treatment.[37]

SCD also results in adverse effects on the fetus (see Table 177-1). Placental infarction is common, with small-for-gestational-age and low-birth-weight infants resulting from placental insufficiency.[38] A high rate of fetal loss has been noted in the past, although a recent study found no increase in the rate of perinatal death.[37] An incidental complication is that the Kleihauer-Betke test to distinguish fetal from mater-

nal blood will yield false-positive results because of the persistence of hemoglobin F in the mother.

Management of SCD during pregnancy is similar to that of the nonpregnant patient (see Table 177-1). Folate supplementation is standard even in the nonpregnant state because of the increased turnover of RBCs, although the recommended daily dose of folate increases to 4 mg during pregnancy.[39] Supplemental iron is controversial because of the potential for iron overload. The need for therapy is best determined by the appropriate specialists after a complete analysis of relevant hematologic parameters. Prophylactic transfusion to achieve a predetermined hemoglobin level has not been found to improve pregnancy outcomes, although it may reduce the number of acute pain crises.[40] Transfusion is reserved for patients with symptomatic anemia, cardiopulmonary instability, acute chest syndrome, and preeclampsia and possibly for patients with increasingly frequent pain crises. It is also used preoperatively for anticipated blood loss in patients undergoing cesarean section.[39,40] Hydroxyurea is not recommended for use in pregnancy because of potential teratogenicity.[39]

Neurologic Disorders

Epilepsy

Epilepsy is the most common neurologic complication of pregnancy but remains relatively rare, affecting less than 1% of all gestations.[41] Epilepsy refers to a broad spectrum of seizure disorders that range from relatively benign and infrequent seizures to a disabling condition with daily, poorly controlled generalized convulsions; therefore, care must be individualized. Management of epilepsy during pregnancy must balance the risk of increased frequency and duration of seizures to both the mother and the fetus against the teratogenic risks of antiepileptic medications (AEMs).

The effect of pregnancy on epilepsy is variable. Most (65%) epileptic patients experience no change in their seizure frequency, whereas 20% experience more frequent seizures and 15% experience less frequent events.[42] A decrease in plasma drug concentrations is expected with the older AEMs due to alterations in the plasma volume, protein binding, and renal clearance that occur in pregnancy. In addition, some patients engage in voluntary noncompliance with medications to avoid teratogenic effects on the fetus. Data for the "newer" agents are less robust, but decreased drug concentrations also occur with lamotrigine, oxcarbazepine, and levetiracetam.

The primary adverse fetal complication in these pregnancies is congenital malformations. Of primary concern is the risk of NTDs with valproic acid and carbamazepine and facial clefts/cardiac anomalies with phenytoin and the barbiturates. There is a two- or threefold increase in the incidence of serious congenital malformations in offspring of epileptic mothers taking these drugs, and the risk is even higher if the mother is taking more than one agent.[41,43,44] Controversy exists regarding whether infants of epileptic patients not taking AEMs have an increased incidence of congenital malformations compared with the general population. Studies comparing these infants with infants born to mothers without epilepsy noted a similar incidence of malformations.[43,44] Data are limited, but preliminary results suggest that the newer agents also have a rate of congenital malformations similar to the general population.[45-47]

Care should be provided by specialists in high-risk obstetrics and neurology disciplines; however, emergency physicians may be forced to confront this problem in several clinical scenarios—the pregnant patient with a first-time seizure or status epilepticus and the patient with epilepsy who is found to be pregnant.

New-Onset Seizure. Pregnant patients may seek treatment for idiopathic new-onset seizures; however, drug toxicity or withdrawal, head injury, meningitis, stroke, and eclampsia should be considered as possible causes. The most important of these is eclampsia. Patients in the immediate postictal phase often manifest hypertension resulting from massive sympathetic discharge, and even those with normal pregnancies may have mild edema of the lower extremities. Consequently, urinalysis should be performed to search for proteinuria, which may be the only differentiating factor in the initial assessment of these patients. After a period of observation, elevated blood pressure in the noneclamptic patient will likely revert to normal. If the patient remains hypertensive or manifests other signs of eclampsia, magnesium sulfate and other agents are indicated to prevent further seizures and to control blood pressure. In patients who do not manifest signs of eclampsia, investigation of the cause of the seizure should proceed as with the nonpregnant patient (see Chapter 100).

Status Epilepticus. Any potential seizure etiology, including eclampsia, may result in status epilepticus. Despite this, status epilepticus in pregnancy is relatively rare, and limited data are available regarding its occurrence and therapy. Observations from a pregnancy registry note that status epilepticus may occur at any time during gestation and even at delivery. It may also occur in patients who have been seizure-free throughout their pregnancy.[42] Older reports note a high fetal and maternal mortality, but recent data support a much lower complication rate.[42]

The risk of untreated status epilepticus to both the mother and the fetus clearly outweighs the potential for adverse teratogenic effects, and standard resuscitative measures as well as drug therapy are indicated. Continuous fetal monitoring should be instituted as soon as possible and the mother positioned in the left lateral decubitus position to avoid the supine hypotensive syndrome.

Pregnant Epileptic Patient. Patients with epilepsy coming to the emergency department for unrelated reasons may be found to be pregnant. Although no immediate change in their therapeutic regimen needs to be made, these patients should be advised of the potential risk of AEMs in pregnancy and be referred to appropriate specialists. Unintentional pregnancy is seen even in patients taking oral contraceptives because AEMs can cause increased clearance of these medications, thereby reducing their efficacy.

There are significant obstetric complications related to prolonged seizure activity, and long-term treatment with an AEM for most patients with seizures is warranted (see Table 177-1). Patients who have nonconvulsive seizure disorders or who are seizure-free for a sufficient period prior to conception are candidates for nonpharmacologic observation, but this decision should be deferred to the patient's primary physician or neurologist. Because phenytoin, carbamazepine, valproate, and possibly other AEMs interfere with folate metabolism, oral supplementation with at least 0.4 mg/day is recommended for all women of childbearing age taking these drugs. Higher doses are recommended for women using valproic acid and carbamazepine, which are known to cause NTDs. Enzyme-inducing AEMs such as carbamazepine, phenytoin, and phenobarbital have been reported to cause neonatal vitamin K deficiency and hemorrhagic complications. It has been recommended that mothers taking these certain AEMs be given oral vitamin K during the last month of gestation, but data indicate that the actual risk of hemorrhage is low and possibly related to prematurity.[48]

Multiple Sclerosis

Multiple sclerosis (MS) affects approximately 400,000 Americans and is twice as common in women as in men. The peak age at onset is 20 to 35 years of age, which overlaps peak childbearing years. The disease is characterized by intermittent episodes of central nervous system demyelination with consequent neurologic impairment that follows a relapsing-remitting course. Progressive neurologic deficits and permanent disability develop in certain patients.

The impact of pregnancy on the course of MS has been closely studied in various cohorts of women, and a pattern has emerged. Like other autoimmune diseases, the frequency and severity of exacerbations of MS improve because of the immunosuppressant effects of pregnancy. This effect is most pronounced in the third trimester. During the 3 months after delivery, the rate of relapse increases and then returns to the prepregnancy baseline.[49,50] Pregnancy does not seem to have any significant long-term adverse effects on disease progression.[49,50] On the other hand, children of parents with MS have an increased susceptibility to develop MS, reflecting at least a partial genetic component to the disease.

Maternal relapse rate is unaffected by epidural anesthesia,[49] and decisions regarding anesthesia should be based solely on obstetric considerations. Labor may be complicated by fatigue and uncoordinated voluntary motor activity in pushing, but generally pregnancies in these patients progress without undue complications.[51]

Spinal Cord Injury

Because spinal cord injury (SCI) occurs mainly in young people and usually does not impair fertility, there is a relatively large population of paraplegic and quadriplegic patients who become pregnant. Although many of these pregnancies are uneventful, these patients are at risk for certain complications.

The incidence of urinary tract infection is increased as a result of neurogenic changes and the need for catheterization. These infections may progress to pyelonephritis during pregnancy, with the subsequent increased risk of fetal loss, prematurity, and maternal sepsis. The increased coagulability of pregnancy combined with chronic immobilization results in an increased incidence of venous thrombosis and pulmonary embolus.

A unique problem in the patient with SCI is the detection of the onset of labor, which may be painless and precipitous. Patients with spinal cord lesions below T10 to T12 have an intact uterine nerve supply and will experience labor pains; however, with lesions above T10, labor may be imperceptible or experienced as only mild abdominal discomfort. In addition, 85% of patients with high lesions (above T5 to T6) experience potentially life-threatening autonomic dysreflexia.[52] This manifests as severe paroxysmal hypertension, headache, tachycardia, diaphoresis, piloerection, mydriasis, and nasal congestion. Because the response is not specific to labor and may be precipitated by distention of bowel or bladder, other causes must be pursued as well. Pregnant patients with SCI who have these symptoms should be assessed for cervical dilation and have uterine contractions monitored. Emergency department treatment is directed at restoring normal blood pressure with nitroprusside, nitroglycerin, or hydralazine. Definitive therapy is with regional anesthesia. Both spinal and epidural anesthesia obliterate and prevent this response and should be used as soon as possible during labor for all women with SCI.[52] Because of the difficulty in detecting labor, pregnant patients with SCI are sometimes admitted for observation near term.

Myasthenia Gravis

Myasthenia gravis is a rare disorder in which autoimmune destruction of the postsynaptic cholinergic receptor results in profound muscle fatigability. Treatment with cholinesterase inhibitors can supply additional acetylcholine to achieve virtually normal muscle contractility but must be titrated to avoid precipitating a cholinergic crisis. Adjustments in medication dosing are frequently required to preserve this balance.

The effect of pregnancy on myasthenia gravis is unpredictable in the individual patient, but overall approximately one fifth to one third of patients experience exacerbation of disease, with the remainder having improvement or no change in disease severity.[53,54] Several important pregnancy complications are associated with myasthenia gravis. Because of weight gain, anemia, and other physiologic adjustments of pregnancy that may result in fatigue, the distinction between normal pregnancy symptoms and myasthenia may be difficult. Most deliveries are accomplished vaginally without complication in treated patients, and studies have found that assisted and surgical delivery in myasthenia gravis patients is usually performed not for exacerbations but, rather, for obstetric reasons.[54] Nonetheless, assisted delivery with vacuum extraction has been recommended to facilitate the second stage of labor.[54]

Up to 30% of neonates born to mothers with myasthenia gravis develop a transient neonatal myasthenic syndrome via placental transport of acetylcholine receptor antibodies.[54] The onset of neonatal myasthenia is typically within the first hours of life but may be delayed by a period of days. Manifestations include poor feeding and suck, diminished reflexes, hypotonia, and respiratory failure. As with adults, the symptoms respond to cholinesterase inhibitors, but treatment should be done in an intensive care unit setting. The duration of the syndrome depends on the clearance of maternal antibodies, and these neonates should be observed for at least 1 week.

Treatment in the emergency setting is no different than treatment for nonpregnant patients (see Table 177-1). Assessment of pulse oximetry, forced vital capacity, and arterial blood gas parameters will guide respiratory therapy. For patients presenting with weakness, a "Tensilon challenge test" to distinguish myasthenic from cholinergic crisis is appropriate after initiation of appropriate ventilatory support. Standard medical treatment should be continued during labor and delivery in order to maximize motor strength. Epidural anesthesia is also recommended to reduce pain and fatigue. Sedatives and other agents that increase fatigue should be avoided during this time. The physician should be aware that 30% of patients experience an exacerbation during the postpartum period as the protective immunosuppressant effect of pregnancy dissipates.[53,54] In addition, puerperal infections place the patient at risk for disease exacerbation and warrant aggressive therapy.[54]

Renal Disorders

Several alterations in renal hemodynamics occur during pregnancy. Both the glomerular filtration rate (GFR) and effective renal plasma flow increase by 30 to 50% compared with the nonpregnant state. Because no substantial alterations are present in the production of creatinine or urea nitrogen, levels of these solutes decrease from low normal nonpregnant values of 0.7 and 12.0 mg/dL to 0.5 and 9.0 mg/dL, respectively. Thus, blood urea nitrogen and creatinine levels considered normal in nonpregnant women (creatinine > 0.8 mg/dL and blood urea nitrogen > 12 mg/dL) indicate underlying renal impairment and warrant further investigation.

The primary factors that determine how renal disease affects pregnancy outcome are the degree of underlying dysfunction

and the presence of hypertensive disorders. In general, patients with mild insufficiency (creatinine < 1.4 mg/dL) and no hypertension can expect good pregnancy outcomes and preserved renal function. On the other hand, patients with moderate to severe renal dysfunction have a much higher risk of further decline in renal function as well as adverse obstetric outcomes, including preeclampsia, placental abruption, fetal loss, preterm delivery, low birth weight, and an increased need for cesarean section.[55-57] Worsening of underlying renal function is more likely in patients with decreased GFR who also have associated proteinuria and/or hypertension.[56-58] Because worsening renal function is manifested by hypertension and proteinuria, differentiation from preeclampsia can be difficult. In this setting, it is best to treat the patient for presumed preeclampsia with the caveat that magnesium administration be performed judiciously based on serum magnesium levels.

Pregnant women with chronic renal failure require aggressive and timely management to optimize their chances for a successful gestation without causing further deterioration in renal function. Baseline renal function studies are done early in pregnancy and then reassessed every 4 to 6 weeks. Evidence of renal function deterioration or the development or exacerbation of hypertension warrants admission for specialized inpatient care. Hemodialysis is indicated for creatinine levels greater than 3.5 to 5 mg/dL. In patients undergoing dialysis, sessions are more frequent and more prolonged to minimize azotemia.[59]

Metabolic and Endocrine Disorders

Diabetes

Three types of diabetes are involved in pregnancy: type I, or insulin-dependent diabetes mellitus (IDDM); type II, or non-insulin-dependent diabetes mellitus (NIDDM); and gestational diabetes mellitus (GDM). Although NIDDM is sometimes considered a more benign form of disease, the risk of malformations is the same for both NIDDM and IDDM.[60,61] Maternal and fetal complications relate more to inadequate glycemic control as well as the presence of vascular complications or severe renal insufficiency rather than to the type of diabetes. All pregnant patients with diabetes are considered "brittle" and require regular follow-up by appropriate specialists. In addition, all patients, including those with GDM, should perform routine self-monitoring of glucose.

Maternal Complications. The physiology of glucose regulation during pregnancy is complex. During the first half of gestation, the sensitivity to insulin increases as a result of increased circulating estrogen. When combined with emesis, increased use of glucose by the placenta and fetus, and a decrease in hepatic glucose production, hypoglycemia occurs more easily. Consequently, patients with IDDM are at risk for severe hypoglycemia during early pregnancy and insulin dosage should be decreased. During later gestation, however, there is progressive insulin resistance that peaks during the third trimester and then falls again during labor and the immediate postpartum period. Pregnancy also predisposes to ketosis, and this effect is exacerbated in the setting of emesis. Specific adverse pregnancy-related outcomes are more common and include preeclampsia, preterm delivery, and the requirement for cesarean delivery.[62,63]

The effects of pregnancy on underlying diabetes vary depending on the organ system. The data are limited, but pregnancy is not advised for diabetic patients with significant coronary artery disease because of the cardiovascular demands of pregnancy and the high mortality of AMI during pregnancy.[62] Patients with diabetic nephropathy are at increased risk for preeclampsia and the subsequent requirement for preterm delivery.[62] The renal effects of pregnancy depend on the severity of underlying disease. Patients with mild to moderate renal dysfunction do not seem to experience permanent disease progression. On the other hand, women with more severe renal dysfunction are at increased risk for progression to end-stage disease.[60,62] Retinopathy may worsen acutely during pregnancy, especially in patients with high HbA_{1c} and hypertension and in the setting of aggressive control of hyperglycemia.[62,64] Laser therapy of preexisting retinopathy is recommended prior to conception.[60,62] Autonomic neuropathy does not accelerate during pregnancy,[64] but the combination of hyperemesis gravidarum and gastroparesis often causes problems. Frequent vomiting results in dehydration and inadequate intake of food that can result in hypoglycemic episodes if the insulin dosage is not adjusted accordingly.[60]

Diabetic ketoacidosis (DKA) occurs in up to 10% of diabetic patients during pregnancy and may represent the initial presentation of diabetes. DKA is most commonly seen in patients with IDDM but also complicates pregnancies in women with NIDDM and GDM.[62] Common precipitating events include the typical factors seen in nonpregnant patients, such as insulin noncompliance and infection. Other pregnancy-specific factors are hyperemesis, use of beta-mimetic medications for tocolysis, and use of corticosteroids to hasten fetal lung maturity. The serum pH may be deceptively normal in a pregnant patient with DKA because the initial pH tends to be higher in pregnancy due to physiologic hyperventilation. Loss of gastric acid through vomiting will also counteract the metabolic acidosis of diabetic ketoacidosis. In addition, serum glucose may be only moderately elevated because the fetus continues to secrete insulin and use glucose. Maternal mortality is rare in appropriately treated DKA. Fetal mortality rates are relatively high, ranging from 10 to 35%.[62]

Fetal Complications. Diabetes has many deleterious effects on the fetus (see Table 177-1). The rate of congenital malformations in patients with prepregnancy diabetes is increased three- or fourfold compared to the nondiabetic population, with anomalies being more likely in pregnancies with poor glycemic control.[62,63,65] Glucose crosses the placenta, and prolonged fetal exposure to maternal hyperglycemia induces fetal pancreatic hyperplasia and high insulin production. Elevated insulin levels in turn promote fetal growth, resulting in macrosomia. Conversely, preeclampsia and placental infarction secondary to vascular disease may result in impaired fetal development.[62,63] After delivery, continued high insulin secretion in the absence of a maternal glucose supply results in a significant rate of neonatal hypoglycemia. Because these infants are more likely to be preterm, hyperbilirubinemia and respiratory problems are also more frequent.[62,63] Long term, it is likely that poor metabolic control during pregnancy leads to an increased risk of impaired glucose tolerance, obesity, and NIDDM in affected offspring.[60,62,66,67]

Management. Treatment of NIDDM and IDDM requires individualized and carefully adjusted insulin administration with the goal to maintain strict glycemic control while avoiding hypoglycemia. Ideally, HbA_{1c} values should not be greater than 6% (see Table 177-1).[60,62] Frequent self-monitoring is recommended, and these patients should also have frequent office visits with their practitioner throughout the duration of pregnancy.[62] It is preferable to achieve glycemic control prior to conception in order to minimize the risks of malformations and other complications.[60] Treatment of DKA does not differ from treatment given in the nonpregnant state except that fetal viability and well-being should be assessed.

The timing and mode of delivery depend on whether there exist obstetric or maternal complications. In the absence of

suspected problems, vaginal delivery at term is recommended.[60] Elective delivery is indicated in the setting of poor metabolic control, significant diabetic complications, and fetal macrosomia with suspected birth weight greater than 4500 g.[62] Delivery is timed to avoid fetal growth into the macrosomic range while allowing for sufficient fetal lung maturity. If corticosteroids are administered, very close glucose monitoring is required because insulin requirements are likely to increase. Progression beyond term is not recommended.

Gestational Diabetes

GDM is defined as glucose intolerance that begins (or is first detected) during pregnancy. As the incidences of both NIDDM and IDDM have increased, so has that of gestational disease.[68] GDM has little impact on perinatal mortality if detected and addressed; however, untreated disease increases the likelihood of fetal macrosomia and adverse perinatal outcomes.[67,69,70] GDM is also a risk factor for the subsequent development of nongestational diabetes. Patients at increased risk for NIDDM include those with obesity, whereas patients with evidence of islet cell immunity are at risk for development of IDDM.[67,71]

The exact means of screening for GDM is controversial, but all pregnant patients should undergo some form of screening, even if it is accomplished simply by obtaining a clinical risk profile.[72] The American Diabetes Association advocates selective laboratory assessment in patients at high risk for GDM. This group includes patients older than 25 years; certain high-risk ethnic groups; and patients with obesity, known first-degree relatives with diabetes, a personal history of diabetes or glucose intolerance, and a personal history of poor pregnancy outcome.[67] A positive screening test at 24 to 28 weeks of gestation via measurement of serum glucose 1 hour after a 50-g oral load is an indication for a formal 3-hour glucose tolerance test.

The majority of patients with GDM achieve metabolic control with dietary therapy. Traditionally, insulin administration is indicated if dietary control is unsuccessful (see Table 177-1).[67,72] Standard practice is to avoid oral medications because they cross the placenta and have the potential for teratogenicity. However, studies comparing insulin with glyburide in GDM found that the latter provided similar glycemic control without an increase in adverse pregnancy outcomes.[73] Preliminary investigations of metformin have found this agent to be safe for use in pregnancy, but further study is recommended prior to its widespread use.[74] There are very limited data for other oral medications.

Thyroid Disorders

The peak incidence of thyroid disease is in women of childbearing age. Both hypoactivity and hyperactivity lead to obstetric complications and warrant specific therapy. As with other organ systems, there are physiologic changes in thyroid function that occur in normal pregnancies. Human chorionic gonadotropin (hCG) is structurally similar to thyroid-stimulating hormone (TSH) and stimulates the thyroid gland. As a result, women with normal pregnancies may experience a temporary suppression in TSH production and slightly lower TSH levels during the first trimester, which mirrors the high circulating hCG levels seen at this gestational period.[75,76] This hCG-mediated effect may lead to a transient hyperthyroidism if hormone levels are markedly increased. Estrogen increases the amount of thyroid hormone binding proteins, which ultimately leads to an increase in the amount of total T_4 and T_3 even though free hormone levels remain normal. After 10 to 12 weeks of gestation, the fetus makes its own thyroid hormone but still requires placental transport of iodine and adequate maternal intake of this element (200 μg/day).

Hyperthyroidism

The most common cause of hyperthyroidism is Graves' disease, in which autoimmune thyroid-stimulating immunoglobulin G results in increased production and release of thyroid hormone. Because the symptoms of hyperthyroidism resemble the physiologic changes expected during pregnancy in many respects, the diagnosis may not be immediately evident. Patients with Graves' disease have disease-specific findings, including a diffusely enlarged, soft, mildly tender thyroid gland; exophthalmos; and dermopathy. Other symptoms, such as dyspnea, heat intolerance, hyperemesis, tachycardia, palpitations, systolic flow murmurs, increased appetite, and fatigue, are common to both conditions, making clinical diagnosis difficult. In cases of suspected hyperthyroidism, thyroid function studies are indicated and will confirm the presence of disease.

There are several obstetric concerns for both mother and the fetus in the setting of untreated hyperthyroidism (see Table 177-1).[76] Thyroid storm is the most serious manifestation of the disease. It may be precipitated by stressors such as infection and delivery, and it manifests with fever, dysrhythmias, myocardial dysfunction, mental status changes, and circulatory collapse. In addition to the more general complications stemming from thyroid hormone excess, Graves' disease places the fetus at risk for autoimmune-mediated thyroid dysfunction via placental transfer of maternal thyroid-stimulating immunoglobulins (TSIs). Up to 17% of neonates of mothers with Graves' disease and positive TSI values have transient hyperthyroidism lasting 3 to 12 weeks. The condition gradually clears as maternal antibodies are metabolized. Manifestations are potentially severe and include irritability, tachycardia, goiter, cardiomegaly, congestive heart failure, premature craniosynostosis, low birth weight, and failure to thrive.[77] These infants also have an increased mortality rate, so the condition must be recognized promptly and treated aggressively with typical therapies.

The mainstay of treatment of hyperthyroidism (see Table 177-1) consists of antithyroid drugs. Propylthiouracil has traditionally been preferred over methimazole because of an increased potential for adverse congenital drug effects from the latter. Both drugs cross the placenta and can cause fetal hypothyroidism. Consequently, maternal thyroid function should be assessed periodically during pregnancy with the goal of keeping free thyroxine in the high normal range. Most patients respond to pharmacologic manipulation, although thyroidectomy may be considered in severe cases. Use of iodine-131 radionuclide to ablate the maternal thyroid is contraindicated because it will also destroy the fetal thyroid gland.

Additional therapy with beta-blockade to mitigate the hemodynamic effects of sympathetic stimulation may be required in certain cases pending adequate disease control with antithyroid medications. In the nonpregnant patient, iodides may be used to transiently block the release of stored T_4 from the thyroid gland and inhibit organification of iodide. However, the fetal thyroid is extremely sensitive to iodide, which may result in neonatal goiter and hypothyroidism. Therefore, iodide is considered class D in pregnancy, and its use should be reserved for severe cases with duration of therapy limited to a period of days. As with other autoimmune conditions, transient improvement of Graves' disease during pregnancy is common, with rebound and clinical deterioration occurring after delivery.

Postpartum Thyroiditis

Postpartum thyroiditis (PPT) is a common but relatively benign condition that develops in approximately 7% of parturients within 9 months of delivery.[78] Patients typically experience transient hyperthyroidism, transient hypothyroidism, or transient hyperactivity followed by transient hypoactivity.[78] Symptoms are typical for type of impairment, although they are often mild. Pharmacologic treatment may be required; however, the need for medication seems to be confined to those patients with hypothyroidism.[76] Occasionally, patients with transient hyperthyroidism require beta-blockers, but antithyroid drugs are not helpful because pathophysiology relates to release of preformed thyroid rather than excess thyroid hormone production. Approximately 30% of patients with PPT develop permanent thyroid failure, and this percentage is increased to more than 50% if one considers just the patients with postpartum hypothyroiditis.[79,80]

Hypothyroidism

The most common cause of hypothyroidism is Hashimoto's thyroiditis. Overt hypothyroidism is often associated with infertility, so most cases seen during pregnancy are less severe or subclinical forms or occur in patients already undergoing levothyroxine therapy for known disease. Undiagnosed subclinical hypothyroidism may manifest during pregnancy as physiologic adjustments result in a greater requirement for thyroid hormone production. In addition, iodine deficiency may be exacerbated by pregnancy because renal losses of iodine increase as the glomerular filtration rate increases and as the fetus diverts iodine for its own thyroid hormone synthesis.

Approximately 3 to 5% of women of childbearing age have subclinical hypothyroidism[81] and, unfortunately, these patients may remain asymptomatic. When signs and symptoms do occur, they are identical to those in the nonpregnant state. Myxedema coma is extremely rare but must be considered along with other causes of coma in a pregnant patient.

As with hyperthyroidism, there is an increased incidence of adverse maternal and fetal effects (see Table 177-1).[76,82,83] The majority of patients who are already undergoing treatment for hypothyroidism will require an increased dosage of levothyroxine during pregnancy, and close monitoring of thyroid function is recommended as soon as possible after conception.[75] Treatment for newly diagnosed patients consists of the replacement of thyroid hormone with the goal being to achieve a normal TSH level.[76] In women with preexisting hypothyroidism, levothyroxine dosage requirements may increase significantly during pregnancy, and it is suggested that doses be increased by 30% as soon as pregnancy is diagnosed.[75]

Undiagnosed and untreated subclinical hypothyroidism results in increased perinatal mortality and adverse neurologic and cognitive outcomes for affected infants.[82-84] It is unclear whether this effect is directly related to abnormal thyroid function or whether it results from the associated increase in preterm delivery.[85] The issue of whether to provide routine prenatal screening for hypothyroidism remains controversial. At the very least, screening should include anyone at risk for disease, and some sources recommend assessment of TSH levels in all women prior to conception or as soon as possible after becoming pregnant because targeted screening may miss up to one third of affected women.[84,86-88]

Congenital hypothyroidism, associated with cretinism and severe mental retardation, occurs in approximately 1 in 3000 births in the United States. It is most often the result of sporadic fetal thyroid agenesis or ectopy rather than maternal thyroid dysfunction.[89] Diagnosis is often difficult because clinical signs and symptoms may be masked by maternal thyroid hormone. Congenital hypothyroidism is successfully treated with hormone replacement begun in the first days of life, and screening for congenital hypothyroidism is mandated in most developed countries.

Systemic Infections

Tuberculosis

Acquisition and presentation of tuberculosis is unchanged during pregnancy. However, the effect of tuberculosis on pregnancy is unclear. Some studies reveal a significant increase in gestational complications (see Table 177-1), but these outcomes are likely significantly influenced by the site of disease and specifics of treatment or lack thereof. One study found no significant increase in gestational complications in 111 pregnant patients with properly treated tuberculosis.[90] Complications are more likely in patients with inadequate or delayed treatment, delayed diagnosis, and extrapulmonary (extranodal) tuberculosis.[91,92] Neonatal tuberculosis acquired via exposure to undiagnosed and untreated active disease places infants at significant risk for acquiring tuberculosis during the first year of life, with significant mortality. In addition, congenital tuberculosis is possible after the fetus becomes infected via the placenta or aspiration of infected amniotic fluid. The latter is rare if the mother has received appropriate therapy.

Current recommendations are to administer a tuberculin skin test early in pregnancy to all patients at high risk for disease and to obtain a chest radiograph if the purified protein derivative (PPD) skin test is positive or if the patient's signs and symptoms suggest tuberculosis. Universal screening should be considered in urban areas with a high prevalence of disease. Definitive treatment varies depending on the duration of PPD positivity and whether the patient has active disease (see Table 177-1).[93,94] Isoniazid, ethambutol, and rifampin in their usual doses have not been shown to be teratogenic to human fetuses and are acceptable during pregnancy. On the other hand, streptomycin causes fetal ototoxicity, and little is known about the safety of other second-line agents during pregnancy. These less commonly used agents should be avoided except in the case of multidrug-resistant disease.

Human Immunodeficiency Virus and Acquired Immunodeficiency Syndrome

The human immunodeficiency virus (HIV) is one of the leading health problems in pregnancy. In 2005, 27% of reported cases of HIV/acquired immunodeficiency syndrome (AIDS) in the United States were in women, with the majority being in women of childbearing age.[95] Estimates of the seroprevalence of HIV in pregnant women vary on a regional basis. In the United States, the overall prevalence is low but also varies depending on the population, with increased rates seen in inner-city and other high-risk populations.

The mechanism of vertical transmission is multifactorial. The majority of cases are thought to occur during delivery through exposure to maternal blood and secretions; other infants are likely infected in utero or via breast-feeding. Various factors influence the rate of transmission. The most important is maternal viral load, although infection can occur even with maternal HIV RNA greater than 1000 copies/mL.[96-100] Other contributing factors for transmission include vaginal infections, intravenous drug use, low birth weight, and prolonged rupture of membranes.[96,101,102] Vertical transmission

of HIV in the United States has declined significantly since its peak in the early 1990s due to the implementation of a number of interventions, including routine voluntary testing, antiretroviral therapy (ART), use of elective cesarean section, and avoidance of breast-feeding.[100,103] However, vertical transmission remains a concern in women without adequate prenatal care as well as a global concern. It is estimated that perinatal infection occurs in approximately 20% of deliveries if the mother is untreated, whereas the previously mentioned interventions reduce this rate to less than 1 or 2%.[97,98,100,102,103] Because of this beneficial effect, it is recommended that all pregnant women undergo screening during their routine prenatal evaluation. Rapid HIV screening is recommended for women in labor whose HIV status is unknown.[104]

Treatment of the pregnant patient with HIV includes appropriate ART as well as standard therapy for opportunistic infections (see Table 177-1).[105] Optimal therapy to prevent vertical transmission includes three stages: antepartum administration of highly active antiretroviral treatment (HAART), intrapartum ART dosing, and treatment of the infant with 6 weeks of zidovudine.[96] In HIV-infected mothers without prenatal care, intrapartum ART followed by postexposure treatment of the infant reduces the likelihood of infection but is less effective than the recommended three-stage regimen.[96] Elective cesarean section is recommended in mothers with a viral load greater than 1000 copies/mL. It is also reasonable to present cesarean delivery as an option for patients with lower viral loads because transmission does occur even at these low levels.[100]

Even in the setting of ART, commonly used serologic tests to detect antibodies for HIV yield positive results in virtually all neonates born to HIV-positive mothers because of placental transfer of maternal antibodies. These antibodies may be present for up to 18 months and are not necessarily indicative of infection. The preferred means of diagnosis of perinatal HIV is via use of assays to detect viral RNA or DNA. These infants should also be monitored clinically. Infants with AIDS typically present with lymphocytic interstitial pneumonitis, recurrent bacterial infections, *Pneumocystis* pneumonia, encephalopathy, thrush, and generalized wasting.[106] Recent analysis reveals that HAART therapy in infants and children is extremely effective in reducing HIV-related morbidity and mortality.[107]

The effects of pregnancy in women with symptomatic HIV infection include an increased incidence of prematurity, stillbirth, and low birth weight and also gestational diabetes. Seropositive mothers who undergo cesarean delivery also have an increased risk of postpartum endometritis and other maternal infections, with the highest rate of infection seen in women who have an emergent procedure.[108,109] It is also important to consider the effect of ART on pregnancy outcomes. A few agents, such as efavirenz, have teratogenic potential and are avoided in pregnancy. However, most antiretroviral medications are considered safe in this regard. Several studies have not found an increase in adverse outcomes with the possible exception of preterm delivery or low birth weight when protease inhibitors are used.[110-114]

The effect of pregnancy is also a matter of debate. An observational cohort study in which a majority of women were using HAART found that pregnancy had no impact on the rate of disease progression.[115]

Syphilis

The incidence of primary and secondary syphilis among females in the United States steadily declined between 1990 and 2004 but increased during 2005 and 2006, with a current rate of 1 case per 100,000 women.[116] Fortunately, the incidence of congenital syphilis (CS) is declining, but the disease remains a concern among those patients without access to adequate prenatal care and prenatal syphilis screening.[117]

Syphilis causes numerous gestational complications (see Table 177-1), but its most significant sequela is CS. This syndrome is characterized by clinical abnormalities such as hepatosplenomegaly, osteochondritis, jaundice, rash, lymphadenopathy, rhinitis, Hutchinson's teeth, and anemia. Perinatal mortality for cases occurring from 1992 to 1998 was 6.4%.[118] If untreated, vertical transmission rates are high but can be reduced significantly with appropriate penicillin therapy.[119] Screening for all pregnant patients is indicated at the first prenatal visit and again in the early third trimester and at delivery for high-risk patients.[104] Either Venereal Disease Research Laboratory (VDRL) or rapid plasma reagin (RPR) testing can be used to detect nontreponemal antibody. Pregnancy may cause false-positive results for nontreponemal studies, so confirmation using specific treponemal tests is indicated for a positive VDRL or RPR study. Patients with latent syphilis and those whose titers fail to respond to therapy should undergo cerebrospinal fluid analysis to screen for tertiary syphilis. In addition, fetal ultrasonography prior to the 20th week of gestation is indicated to assess for abnormalities consistent with CS.

Treatment is identical to that given to nonpregnant patients using benzathine penicillin G (see Table 177-1).[104] Penicillin-allergic patients should undergo skin testing and desensitization if the skin test result is positive because alternative therapy is not reliably effective in preventing congenital syphilis.[104] Treatment failures are rare with appropriately administered penicillin but do occur. Failures leading to CS are more likely in mothers with secondary syphilis, high VDRL levels, and an interval from treatment to delivery of less than 30 days. They are also more likely in the setting of preterm delivery.[119,120]

Hepatitis

Hepatitis B. The prevalence of hepatitis B virus (HBV) infection among pregnant women varies depending on the population studied. In U.S. urban areas, 0.14 to 5.79% of pregnant women are positive for HBsAg, with Asians having the highest seroprevalence.[121] The rate of vertical transmission depends on the acuity of maternal infection and when during the gestation it occurs. Perinatal transmission approaches 90% in mothers who are seropositive for HBsAg and HBeAg and is also more likely if the mother has acute infection during the third trimester or first few months postpartum or if she is a chronic carrier.[104,122] Of infants who develop HBV infection, up to 90% become chronic carriers as adults and are at risk for complications such as cirrhosis and hepatocellular carcinoma.[104]

Routine screening for HBV during early pregnancy is recommended because treatment with hepatitis B immunoglobulin and hepatitis B vaccine is very effective in reducing the rate of vertical transmission.[122,123] Treatment failures do occur in the setting of maternal seropositivity for HBeAg and HBV DNA.[124] Women at risk for sexually transmitted disease (STD) and women with hepatitis should be retested at delivery.[104] Vaccination against HBV is currently recommended for all infants in the United States. The treatment schedule and the need for additional therapy with immunoglobulin vary depending on maternal seropositivity. Infants of HBsAg-positive mothers should receive hepatitis B immunoglobulin and the first dose of vaccine within 12 hours of birth. Two additional doses of vaccine are administered at a later date. Pregnancy is not a contraindication to either therapy. All HBsAg-negative gravidas at risk for STDs or who are seeking STD treatment should receive the vaccine.[104,122] Pregnant patients who are

exposed to HBV should receive both hepatitis B immunoglobulin and vaccine.[122]

Hepatitis C. As with HBV, the prevalence of hepatitis C infection among pregnant women varies depending on the population, ranging from less than 1% to approximately 5%. Vertical transmission is rare in mothers with anti-hepatitis C antibodies and no circulating hepatitis C virus (HCV) RNA.[125,126] However, perinatal transmission is significantly increased by the presence of HCV viremia, occurring in approximately 4 to 6% of cases. The transmission rate is even higher in the setting of co-infection with HIV.[125-127] Unfortunately, there is little definitive data regarding the use of cesarean delivery to prevent HCV transmission.[128] No available vaccine exists to prevent hepatitis C, although testing of potentially infected neonates is advised to identify those at risk for chronic hepatitis.

Inflammatory Disorders

Rheumatic diseases or collagen vascular diseases are characterized by sterile inflammation in multiple anatomic sites. The most common rheumatic diseases encountered in pregnancy are systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Patients with collagen vascular disease may have preexisting cardiovascular or renal compromise and may not tolerate the increased intravascular volume and other physiologic changes that occur during pregnancy. The following discussion focuses on SLE, which is the rheumatic disease responsible for the majority of gestational complications. Most of the treatment guidelines for SLE are relevant to other rheumatologic disorders as well.

Systemic Lupus Erythematosus

SLE primarily affects women of reproductive age, and fertility is usually unaffected. The disease course during pregnancy is a matter of controversy, but analyses indicate that acute flares occur in less than one third of patients in clinical remission at the time of conception. These flares tend to be mild and involve the skin and musculoskeletal system.[129,130] The gestational effects of SLE also depend on the underlying severity,[131] and it is best for women to achieve good disease control prior to pregnancy. Many patients have acceptable outcomes, but lupus pregnancies are associated with an increased rate of complications, including hypertensive disorders, preterm delivery, intrauterine growth retardation, fetal loss, and need for cesarean section.[129,130,132,133] The risk of preeclampsia is markedly increased in patients with preexisting lupus nephritis.[134,135] As with other renal disease, increasing proteinuria warrants a careful evaluation to distinguish between lupus glomerulonephritis and preeclampsia. The presence of abnormal urine sediment, increasing titers of anti-DNA antibody, and decreasing levels of C3 and C4 point to lupus nephritis.[129]

Numerous other organ systems in addition to the kidneys are involved in SLE, and differentiation from pregnancy-related changes may be difficult. Mild thrombocytopenia occurs in normal pregnancies and is also common in patients with SLE, although the clinical significance varies from patient to patient. Anemia is a frequent complication of lupus and magnifies the normal dilutional anemia of pregnancy. Various musculoskeletal and cutaneous symptoms associated with pregnancy, such as arthralgias and facial and palmar erythema, can also resemble active SLE. In addition, preexisting lupus rashes become more erythematous because of the increased cutaneous blood flow during pregnancy. Neurologic disease in SLE may manifest as psychosis, seizures, chorea, or peripheral neuropathy. The incidence of these complications is low during pregnancy, although the occurrence of seizures in late pregnancy in patients with coexistent hypertension and renal insufficiency may pose a diagnostic dilemma between the neurologic effects of SLE and eclampsia.

Other Rheumatologic Diseases

Rheumatoid arthritis is characterized by chronic, destructive, symmetrical joint inflammation. Less common manifestations include the development of subcutaneous nodules, neuropathy, pleuropericarditis, and vasculitis. Systemic symptoms, including weight loss, lymphadenopathy, and fatigue, are common. Because the median age at onset is later with RA, this disorder is seen less frequently than SLE in the pregnant population.[132] Approximately two thirds of patients with RA experience an amelioration of symptoms during pregnancy, although often an exacerbation follows delivery.

Patients with other rheumatologic diseases, including scleroderma, Raynaud's phenomenon, and polymyositis, tend to have good pregnancy outcomes in the setting of good disease control. Birth weights are lower in the offspring of these patients likely as a result of the underlying vasculopathy.[136,137]

Treatment

The rheumatologic diseases are very similar with respect to the therapeutic approach. Corticosteroids form the basis of treatment for most disease complications and exacerbations. These drugs may result in a minimally increased risk of cleft deformities (data are inconclusive) but have not been found to have any other significant teratogenic effects and are considered relatively safe to use for disease control in these patients.[9,10] Steroid use during pregnancy does have a dose-related effect on intrauterine growth retardation and predisposes the patient to GDM and hypertension, so close monitoring is advised.

Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) are also a mainstay of therapy in many patients with rheumatic diseases and may be used in pregnancy. There are potential adverse effects of aspirin and NSAIDs on gestation, including miscarriage when taken early in pregnancy and premature closure of the fetal ductus arteriosus, increased maternal hemorrhage, and prolongation of gestation and labor when taken later in pregnancy. There are also conflicting data regarding an increased risk for gastroschisis, cleft defects, and cardiac defects with NSAID use.[138-140] If a true association exists, the risk for these anomalies remains extremely small in absolute terms. Use of these agents after 32 weeks of gestation should be avoided to minimize the risks of maternal and fetal hemorrhage and premature ductus closure.

Acute flares often require institution of cytotoxic drugs. Cyclophosphamide and methotrexate are contraindicated during the first trimester and should be used only in extreme circumstances because of their teratogenicity and abortifacient properties. Azathioprine has a much more favorable safety profile because of its use in renal transplant patients, and it is the cytotoxic agent of choice during pregnancy. Although the drug and its metabolites cross the placenta, it does not appear to have any major teratogenic effects.[141] Cyclosporine also seems to lack teratogenicity and is an acceptable alternative to azathioprine.[142]

The antimalarial agent hydroxychloroquine is also used in the treatment of SLE and RA. This medication has been found to be safe during pregnancy, and its use may allow for a decrease in corticosteroid dosage.[143,144] In addition, patients who have been maintained on hydroxychloroquine prior to conception experience an increased rate of disease flares when the agent is discontinued.[143]

KEY CONCEPTS

- The physiologic demands of pregnancy may cause previously occult medical conditions to become apparent.
- The physiologic adjustments of pregnancy alter the normal ranges for certain laboratory values. The adjusted values need to be considered in interpreting results.
- The possibility of pregnancy must be considered in the differential diagnosis of certain conditions, including new-onset seizures or status epilepticus (eclampsia), glucose intolerance (GDM), persistent vomiting (hyperemesis gravidarum), and thyroid disorders.
- The immunosuppressive effects of pregnancy may cause temporary improvement in inflammatory and autoimmune conditions. This beneficial effect is lost in the postpartum period, resulting in exacerbations of asthma, thyroid disorders, and myasthenia gravis. Medication requirements can change drastically during pregnancy and the postpartum period.
- Certain medical conditions in the mother result in neonatal complications requiring special resuscitative measures.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 178

Drug Therapy in Pregnancy

Rania Habal

PERSPECTIVE

The placenta was previously believed to act as a barrier, excluding toxins from the fetal circulation and protecting the fetus from environmental and pharmacologic exposures. In 1961, when an epidemic of amelia, a rare malformation characterized by an absence of limbs, was linked to the use of thalidomide during pregnancy, the vulnerability of the fetus to medications came into focus. Thalidomide was a sedative-hypnotic agent introduced in 1956. It immediately became popular in the treatment of nausea and vomiting during the first trimester of pregnancy, but in the years that followed, it was established that thalidomide was the agent responsible for the amelia/phocomelia epidemic. By the time thalidomide was withdrawn from the market, an estimated 5850 children were affected worldwide.[1] Similarly, it took an epidemic of debilitating congenital anomalies and deaths in the children of fishermen in Minamata, Japan, to recognize the teratogenicity of environmental pollutants.[2,3] Minamata disease was due to the ingestion of fish contaminated by methylmercury, an industrial by-product that was dumped into Minimata Harbor in the early 20th century. These two events sparked the development of numerous control agencies to oversee the safety of drugs in pregnancy and numerous environmental protection laws.

Thalidomide's legacy continues to haunt physicians worldwide. Many physicians are reluctant to prescribe medications to pregnant women or to nursing mothers. However, only a few medications have been identified as teratogens, and medication use during pregnancy is extremely common. In a worldwide survey of more than 14,000 patients, the World Health Organization reported that more than 86% of women used at least one prescription drug while pregnant. In a similar survey in the United States, more than 80% of pregnant women reported using medications during pregnancy, with 30% using more than four drugs.[4] The contribution of these substances to the incidence of birth defects is thought to be low, accounting for 1 to 3% of all live birth defects.[5,6]

The emergency physician must understand when the maternal benefit of prescribing a particular agent will outweigh any potential risk of fetal harm, and he or she must be able to discuss those risks and benefits with the patient.

PRINCIPLES OF DISEASE

Major birth defects affect 3 to 5% of all live births.[6] Most are of unknown etiology, but 1 to 3% of these are thought to be due to pharmaceutical agents.[5,6] A *teratogen* is any chemical, pharmacologic, environmental, or mechanical agent that can cause deviant or disruptive development of the conceptus.[5-7] Included in this definition are physical malformations, growth retardation, fetal demise, and functional impairment.[6] Although serious effects on the mother are identified immediately, a drug's teratogenic effect may not be apparent for years. Malformations may range from subtle neurobehavioral effects to devastating physical deformities and physiologic effects, including death.[5-7] Why one pregnancy would be affected and not another remains to be elucidated. Highly teratogenic medications seem to be few in number, estimated at well below 50 agents (Box 178-1).[7,8]

When examining the effects of substances on the outcome of pregnancy, it is important to keep in mind that the process of establishing the risk and safety of drugs in pregnancy is tedious and often flawed. For ethical reasons, few controlled prospective human studies analyzing the risk-benefit relationship for any given exposure are available. As a result, much current knowledge has been derived from case reports, case-controlled studies, or cohort studies, which are inherently weak in establishing a causal relationship,[1,5,6,9] and from animal research. Knowledge extrapolated from animal models, although valuable in determining risk initially, is not always applicable to humans.[1,5,6,9]

In evaluating data on the relationship between an exposure during pregnancy and a particular outcome, a multitude of confounding factors make the determination of a causal link difficult. The genetic background of the fetus, the timing and duration of the exposure, environmental factors, the occurrence of multiple exposures and the presence of nutritional deficits, maternal illness, and illicit drug use all contribute to the outcome of pregnancy.[1,5-9] In the presence of maternal illness, for example, the outcome of pregnancy may be related to the medical condition and not the medication, and separating the risks of an anomaly from the expected background risk may be difficult.

The study of teratogenicity is also hindered by several additional factors. First, the history of drug or environmental exposure is often obtained in retrospect, after 9 months of pregnancy and the delivery of an abnormal infant. By that time, significant recall bias may have been introduced, which may depend on the outcome of the birth.[9] Second, because many pregnancies are spontaneously aborted before maternal knowledge that conception has occurred, the cited prevalence of drug-induced birth defects may not be accurate.[5,6,8,9] Finally, as in the case of diethylstilbestrol, teratogenicity may not be appar-

BOX 178-1 DRUGS AND AGENTS CONSIDERED HUMAN TERATOGENS AND DEVELOPMENTAL TOXINS

Alkylating agents (busulfan, chlorambucil, cyclophosphamide, etc.)
Lead*
Aminopterin and methotrexate*
Lithium*
Amnioglycosides (streptomycin and others)
Methimazole
Amiodrone
Methylmercury*
Androgens*
Methylene blue
Angiotensin enzyme inhibitors*
Misoprostol
Carbamazepine
Nonsteroidal anti-inflammatory agents
Carbon monoxide
Paramethadione, trimethadione*
Chlorobiphenyls*
Phenytoin*
Cocaine*
Polychlorinated biphenyls*
Corticosteroids
Progestins
Coumarin derivatives*
Quinine
Danazole
Diethylstilbestrol*
Tetracycline*
Ergotamine
Ethanol (in large doses)*
Tobacco
Fluconazol (in high doses)
Iodine
Thalidomide *
Ionizing radiation*
Trimethadione*
Isotretinoin (systemic) *
Valproic acid*
Statins

*Teratogen.
Modified from Shepard TH: Catalog of Teratogenic Agents, 12th ed. Baltimore, Johns Hopkins University Press, 2008; and Fine JS: Reproductive and perinatal principles. In Goldfrank LR, et al (eds): Goldfrank's Toxicologic Emergencies, 8th ed. New York, McGraw-Hill, 2006, pp 465–485.

BOX 178-2 FOOD AND DRUG ADMINISTRATION CLASSIFICATION: TERATOGENIC RISK OF DRUGS

Class A: Controlled studies have shown no risk. Adequate well-controlled studies in pregnant women have failed to show risk to fetus.
Class B: No evidence exists of risk for humans. Animal studies show risk or are negative, but no human studies have been done.
Class C: Use may engender risk for fetus. Human studies are lacking, and animal studies may be positive or lacking. Potential for benefit may outweigh potential for harm.
Class D: Positive evidence of risk is based on studies or postmarketing data. Potential for benefit may outweigh potential for harm.
Class X: Drugs are contraindicated in pregnancy based on human or animal studies or postmarketing reports that indicate benefit is clearly outweighed by risk.

ent for years after birth. Large population studies are needed to understand the connection between the outcome of a pregnancy and an associated in utero exposure.[10]

Classification of Teratogenic Risk

To aid physicians in determining the teratogenic potential of a particular medication, the U.S. Food and Drug Administration (FDA) has published a classification system that assigns risk based on currently available human and animal studies and case reports. Drugs are assigned one of five letters—A, B, C, D, and X—depending on the strength of evidence for their safety or teratogenicity (Box 178-2). The FDA classification system has been criticized as oversimplistic and perhaps inaccurate because it relies on data that are generally of poor quality. In addition, using this classification, more than 90% of drugs approved in the United States between 1980 and 2000 were assigned an undetermined teratogenic risk.[11] Furthermore, some clinicians believe that the classification system conveys the incorrect impression that there is a gradation of reproductive risk from exposure across categories (i.e., that risk increases from A to B to C to D to X) and that the drugs within a given category present similar reproductive risks.[12] The FDA has acknowledged these problems, and in 2008 it proposed new rules regarding drug labeling during pregnancy and the elimination of the current ABCDX pregnancy categories. A number of clinical teratology resources, such as TERIS, REPROTOX, and REPRORISK (Shepard's catalogue of teratogenic agents), are now available online. These databases assign teratogenic risk to drugs based on a consensus of opinion of an expert panel.

Drug Transfer across the Placenta

The degree to which the fetus is affected by a given pharmaceutical agent and the nature of that effect depend on multiple factors. The transport of maternal substrates to the fetus and of waste products from the fetus to the mother is established during week 5 of gestation.[1,5,8,13] Drug transfer across the placenta occurs most commonly by simple passive diffusion or by protein transport. A thin layer of trophoblastic cells is all that separates maternal from fetal circulation. The degree to which a drug gains access to fetal circulation depends on molecular size, ionic state, lipid solubility, and the extent of protein binding. Drugs with a molecular weight of less than 5 kDa readily diffuse. Anionic forms diffuse through the lipid layer more readily than ionized forms. Free drug diffuses more readily than a drug that is bound to plasma proteins. Because fetal pH is slightly more alkalotic than maternal pH, weak organic acids (e.g., salicylate) may become ion trapped in the fetal circulation, increasing fetal exposure.[1,5,8,13]

Drugs may affect the fetus through a variety of mechanisms. Some drugs may alter the availability of substrates, such as vitamins, glucose, oxygen, and amino acids, needed for normal nutrition and growth.[1,5,8,13] Others may directly affect cellular growth and differentiation. The age of the fetus is crucial in determining the impact of any given exposure. During the time of organogenesis (days 21–56 of fetal life), the fetus is much more vulnerable to toxic insults.[1,5,8] The major body organs are formed during this period, and exposure to a terato-

gen at this time may result in major anatomic defects. The central nervous system (CNS) develops over a longer period (10–17 weeks) so that later exposures may affect neurologic development and subsequent function. Exposure after the period of organogenesis may affect the growth and development of the fetus but does not have an impact on organogenesis; however, it most likely affects fetal growth.[1,5,8]

Drug Transfer during Lactation

For the most part, drugs and substances that are ingested or injected by the mother diffuse passively into milk and then back into the maternal circulation for excretion.[14] The amount of drug diffusing into milk depends on many factors. Lipid-soluble and nonionic substances diffuse more readily, and highly protein-bound substances diffuse less readily.[14] Whether a substance is concentrated in maternal milk or not, the neonate generally is able to detoxify it with no adverse effects, and only a few drugs pose a serious danger to a breast-feeding infant.[14] The interruption of breast-feeding should not be advocated except in rare situations of known drug toxicity to the infant.[15]

Table 178-1 summarizes the compatibility of medications and their effects in pregnancy and lactation.

DRUG THERAPY DURING PREGNANCY

In general, the health of the fetus is directly related to the health of the mother. Physicians should never withhold life-saving medications from pregnant patients because of a reported risk to the fetus and should resuscitate pregnant patients according to Advanced Life Support Guidelines. Physicians may also prescribe any agent that presents maternal benefits that outweigh the risks to the fetus. Included in this category are therapeutic medications for asthma, arrhythmias, status epilepticus, and HIV.

Analgesic Agents

Acetaminophen (paracetamol) is safe throughout pregnancy. It is widely used during pregnancy and has not been associated with an increase in the incidence of congenital malformations when therapeutic doses are used.[16,17] Statements about its safety also apply to acute and chronic overdose conditions.[18,19] However, there is an increase in the incidence of spontaneous abortion and fetal demise, especially when antidote treatment with *N*-acetylcysteine is delayed.[18-20] Acetaminophen is safe during lactation because only a small amount is excreted into breast milk, and the amount that does get through is tolerated by the neonate's sulfhydration pathway.[15,16]

Aspirin appears to be safe throughout pregnancy when used in small doses. Early studies of aspirin use during pregnancy linked it to an increased risk of perinatal and neonatal bleeding, increased risk of postmaturity, significant prolongation of labor, low birth weight, neonatal hypoglycemia, metabolic acidosis in the newborn, and neonatal death.[16,17] However, in the Perinatal Antiplatelet Review of International Studies Collaboration (PARIS) study, low doses of aspirin were actually found to be beneficial and to reduce the risk of preeclampsia, premature birth, and adverse perinatal outcomes.[23] Furthermore, a number of recent meta-analyses in humans failed to demonstrate a teratogenic effect to aspirin, although there was a trend toward a slightly increased incidence of gastroschisis when used in the first trimester.[21,22]

Non-aspirin NSAIDs should be avoided in the first and third trimesters but are considered safe in the second trimester. Use of NSAIDs in the first trimester has been associated with a small increase in cardiac defects, oral clefts, and gastroschisis.[16,17,24] Use of NSAIDs at or near term has been associated with premature closure of the ductus arteriosus, periventricular hemorrhages in the offspring, oligohydramnios, and fetal nephrotoxicity.[16,17] Additionally, a number of population-based cohort studies have found that NSAIDs are associated with an increased risk of spontaneous abortion, preterm birth, and low birth weight.[25] NSAIDs in general appear to be safe during lactation when used for short durations.[16,17]

The short-term use of opiates appears to be safe in pregnancy. Because opiates' sedative effects extend to the fetus, caution should be used when prescribed at term. Chronic use of opiates is discouraged in general because it may result in maternal as well as fetal addiction. Because opiates are poorly concentrated in milk, opiate analgesia may be used safely during breast-feeding.[15]

Antibiotics

First- through fourth-generation penicillins and their derivatives (including procaine, benzathine, clavulanate, sulbactam, and tazobactam) are considered safe for use in pregnancy, as is oral probenecid.[16,17,26,27] Penicillins are considered safe during breast-feeding, but their use may interfere with culture results if a neonatal fever workup is required.[15-17]

First- through fourth-generation cephalosporins appear to be safe for use during pregnancy, although there are no controlled studies examining their safety.[16,17,26-28] Some cephalosporins are excreted into breast milk and may have the same implications on the workup of neonatal sepsis as described for penicillin.[15-17]

Chloramphenicol is safe during pregnancy except at term. No relationship has been found between the use of chloramphenicol and congenital anomalies.[16,17,27,29] Although it is considered safe throughout most of pregnancy, chloramphenicol should be used with caution at term. It has been associated with the development of cardiovascular collapse (the "gray baby" syndrome) in a neonate.[16,17,26,27] The safety of chloramphenicol during breast-feeding is unknown; however, due to its potential toxicity, it is not recommended for use during lactation.[15–17]

The macrolides erythromycin, azithromycin, and clarithromycin are considered to be safe for use in pregnancy and compatible with breast-feeding, although there are no well-controlled studies examining their effects on the fetus.[15–17] Some reports have linked erythromycin to pyloric stenosis, but these studies were not controlled.[16,17,26,27] The estolate salt of erythromycin has also been associated with the development of hepatotoxicity in pregnant women and should be avoided during pregnancy.[16,17,26,27] Clarithromycin has been associated with an increased risk of fetal and embryonic death as well as congenital malformations in animal species. To date, however, this has not been shown in humans. In addition, a prospective controlled multicenter study comparing the outcomes of pregnancies exposed to clarithromycin to matched controls did not find any differences in the types or patterns of malformations between the two groups.[29,30] However, there appeared to be an increased number of spontaneous abortions in exposed women, which may have been due to confounding factors, and further studies are warranted. Azithromycin is poorly

Text continued on p. 2320

Table 178-1 Summary of Medication Safety in Pregnancy and Lactation

MEDICATION	PREGNANCY	LACTATION
Analgesic agents		
Acetaminophen or paracetamol	Safe (B)	Safe
Nonsteroidal anti-inflammatory drugs (NSAIDs)		
Salicylate	Not recommended (D)	Safe for short-term use
Other NSAIDs	Not recommended (D)	Safe
Opiates: Most opiates are considered safe for short-term use but are all reclassified in category D if used for prolonged periods or if used in high doses at term (due to respiratory depression in newborn). Do not use opiates combined with aspirin or NSAIDS.		
Morphine—short-term use	Safe (C)	Safe
Fentanyl—short-term use	Safe (C)	Safe
Methadone	Safe (B/C)	Safe
Meperidine—short-term use	Safe (C)	Safe
Codeine	Possible risk (C)	Not advised if longer than 2 days
Oxycodone—short-term use	Safe (C)	Probably safe
Hydrocodone—short-term use	Safe (C)	Probably safe
Hydromorphone—short-term use	Safe (B)	Probably safe
Oxycodode—short-term use	Safe (B)	Probably safe
Antibiotics: Use of antibiotics near term may interfere with culture results in neonates.		
Penicillins		
First-generation penicillins: penicillin G, benzathine penicillin, bicillin, penicillin VK	Safe (B)	Safe
Second-generation penicillins: oxacillin, dicloxacillin, nafcillin	Safe (B)	Safe
Third-generation penicillins: ampicillin, ampicillin-sulbactam, amoxicillin, amocillin-clavulanate	Safe (B)	Safe
Fourth-generation penicillins: ticarcillin, ticarcillin-clavulanate, piperacillin, piperacillin-tazobactam, carbenicillin	Safe (B)	Probably safe
Cephalosporins		
First generation: cephalexin, cefazolin, cefadroxil	Safe (B)	Safe
Second generation: cefuroxime, cefaclor, cefoxitin, cefprozil	Safe (B)	Safe
Third generation: cefdinir, cefotaxime, ceftazidime, ceftriaxone, cefpodoxime, ceftizoxime	Safe (B)	Probably safe
Chloramphenicol: *Do not* use at term because it can cause "gray baby syndrome."	Safe until term (C)	Possible toxicity
Macrolides		
Erythromycin: *Do not* use estolate salt.	Safe (B)	Safe
Azithromycin	Safe (B)	Safe
Clarithromycin	Probably safe (C)	Probably safe
Sulfonamides: May cause kernicterus in newborn if given in third trimester.	Not recommended near term (C)	Safe, except in premature infants or infants with G6PD deficiency or hyperbilirubinemia
Quinolones		
First generation: nalidixic acid	Moderate risk (C)	Safe
Second generation: ciprofloxacin, norfloxacin, ofloxacin	Small risk (C)	Probably safe
Third generation: levaquin	Small risk (C)	Probably safe
Fourth generation: gatifloxacin, moxifloxacin	Small risk (C)	Probably safe
Aminoglycosides	Not recommended (D)	Safe
Clindamycin	Safe (B)	Safe
Vancomycin	Safe (B)	Safe
Linezolid: Maternal benefit may outweigh risks to fetus or embryo.	Unknown (C)	Safety unknown
Tetracyclines	Not recommended (D)	Not recommended
Nitrofurantoin: May cause hemolytic anemia in newborn if used in third trimester.	Safe (B), except in third trimester	Probably safe
Metronidazole	Contraindicated in first trimester, safe in second and third trimesters (B)	Not recommended
Antifungals		
Nystatin	Safe (B/C)	Safety unknown
Clotrimazole	Safe (B/C)	Safety unknown
Ketoconazole	Probably safe (C)	Probably safe
Fluconazole	Not recommened in high doses (C)	Safe
Terbinafine	Low risk (B)	Not recommended

Table 178-1 Summary of Medication Safety in Pregnancy and Lactation—cont'd

MEDICATION	PREGNANCY	LACTATION
Antituberculous medications in general present a maternal benefit that is much greater than the fetal or embryonic risk and may be prescribed during any stage of pregnancy when indicated.		
INH	Safe (C)	Probably safe
Rifampin	Probably safe (C)	Probably safe
Ethambutol	Safe (C)	Probably safe
Antiviral agents		
Antiherpetic medications		
Acyclovir	Safe (B)	Safe
Valacyclovir	Safe (B)	Safe
Famciclovir	Small risk (B)	Potentially toxic
Anti-influenza agents		
Amantadine	Possible risk (C)	Safety unknown
Oseltamivir	Safe in animals (C)	Safety unknown
Anti-HIV medications in general present a maternal benefit that is much greater than the fetal or embryonic risk and may be prescribed during any stage of pregnancy when indicated.		
Reverse transcriptase inhibitors		
Zidovudine	Caution in first trimester (C)	Not recommended
Lamivudine	Caution in first trimester (C)	Not recommended
Didanosine	Caution in first trimester (B)	Not recommended
Tenovir	Caution in first trimester (B)	Not recommended
Indinavir	Caution in first trimester (C)	Not recommended
Protease inhibitors		
Ritonavir	Caution in first trimester (B)	Not recommended
Nelfinavir	Caution in first trimester (B)	Not recommended
Anticoagulants		
Warfarin	Contraindicated	Safe
Heparin	Safe (B)	Safe
Low-molecular-weight heparin	Safe (B)	Safe
Thrombolytics: Benefits to the mother generally outweigh the risk to the fetus.		
Alteplase	Safe (C)	Probably safe
Reteplase	Safe (C)	Probably safe
Urokinase	Safe (B)	Probably safe
Streptokinase—no human data	Safe in animals (C)	Hold breast-feeding
Tenectaplase—no human data	Safe in animals (C)	Hold breast-feeding
Anticonvulsants: Benefits to the mother outweigh the risks to the fetus and embryo. Monotherapy is recommended. Use of highly teratogenic anticonvulsants is recommended in refractory cases only.		
Carbamazepine	Teratogen (D)	Probably safe
Valproic acid	Teratogen (D)	Probably safe
Phenobarbital	Not recommended (D)	Not recommended
Phenytoin	Teratogen (D)	Safe
Lamotrigine	Small risk in animals (C)	Not recommended
Levetiracetam	Small risk in animals (C)	Safety unknown
Topiramate	Small risk in animals (C)	Safety unknown
Gabapentin	Small risk in animals (C)	Probably safe
Sedative-hypnotics		
Benzodiazepines: Results are inconsistent. There may be a small risk of abnormalities. In the acute short-term treatment of status epilepticus, agitated delirium, and alcohol or benzodiazepine withdrawal, benefits to the mother outweigh risks to the fetus or embryo. Not recommended for long-term use.		
Diazepam—low risk in first and third trimesters	Safe acutely; unsafe for chronic use (D)	Potential toxicity
Lorazepam—low risk in first and third trimesters	Safe acutely; unsafe for chronic use (D)	Potential toxicity
Chlordiazepoxide—low risk in first and third trimesters	Safe acutely; unsafe for chronic use (D)	Potential toxicity
Oxazepam—low risk in first and third trimesters	Safe acutely; unsafe for chronic use (D)	Potential toxicity
Midazolam—low risk in first and third trimesters	Safe acutely; unsafe for chronic use (D)	Potential toxicity
Barbiturates		
Methohexital	Safe (C)	Safety unknown
Thiopental	Safe (C)	Safety unknown
Ketamine: Risk mainly with high doses close to delivery.	Safe (B)	Probably safe after 12 hr
Propofol	Safe (B/C)	Not recommended
Etomidate	Safe (B/C)	Probably safe
Paralytic agents		
Depolarizing agents		
Succinylcholine	Low risk, especially around delivery (C)	Probably safe
Nondepolarizing agents		
Rocuronium	Limited data (C)	Probably safe
Vecuronium	Limited data (C)	Probably safe

Continued

Table 178-1 Summary of Medication Safety in Pregnancy and Lactation—cont'd

MEDICATION	PREGNANCY	LACTATION
Antiarrythmics: In cases of refractory arrhythmias, the benefits to the mother may outweigh risks to the fetus or embryo.		
Adenosine	Safe (C)	Safe
Amiodarone	Not recommended (D)	Contraindicated
Digoxin—caution in third trimester (oxytocic)	Safe (C)	Safe
Disopyramide	Caution in third trimester (B)	Probably safe
Encainide	Limited data (C)	Probably safe
Flecainide	Limited data (C)	Not recommended
Quinidine	Safe (C)	Not recommended
Procainamide	Safe (C)	Not recommended
Ibutilide	Risk in animals	Not recommended
Lidocaine	Safe (B)	Probably safe
Sotalol	Probably safe (C)	Not recommended
Antihypertensives		
Angiotensin antagonists		
Angiotensin-converting enzyme inhibitors	Not recommended (D)	Some are safe
Angiotensin II receptor antagonists	Not recommended (D)	Safety unknown
Beta-blockers		
Labetalol	Probably safe (C)	Probably safe
Atenolol	Caution in second and third trimesters (D)	Potential toxicity
Esmolol	Caution in third trimester (C)	Safety unknown
Metoprolol	Caution in second and third trimesters (D)	Potential toxicity
Propranolol	Caution in second and third trimesters (D)	Probably safe
Calcium channel blockers		
Diltiazem—tocolytic	Probably safe (C)	Probably safe
Verapamil	Probably safe (C)	Probably safe
Amlodipine	No data (C)	No data
Nifedipine—not sublingual	Probably safe (C)	Probably safe
Diuretics: Caution for dehydration and electrolyte abnormalities.		
Furosemide	Low risk (C)	Probably safe
Bumetanide	Low risk (C)	Probably safe
Ethacrynic acid	Low risk (B)	Probably safe
Torsemide	Low risk (B)	Probably safe
Hydrochlorothiazide—contraindicated in gestational HTN	Safe (B)	Safe
Nitrates		
Nitroprusside	Some risk (C)	Potential toxicity
Nitroglycerin	Probably safe (C)	Probably safe
Vasodilators		
Hydralazine	Safe (C)	Safe
Alpha effectors		
Clonidine	Caution in third trimester (C)	No data
Other		
Methyldopa	Safe (B)	Safe
Fenoldopam	No data (B)	No data
Medications used in the treatment of asthma, allergies, and upper respiratory infection: For asthmatic patients, maternal benefits outweigh risks to fetus or embryo.		
Beta-adrenergics considered safe for short-term use		
Epinephrine	Risk (C)	Potential toxicity
Metaproterenol	Safe (C)	Probably safe
Salmeterol	Limited data (C)	Probably safe
Albuterol	Safe (C)	Probably safe
Terbutaline	Low risk (C)	Probably safe
Anticholinergic agents		
Ipratropium	Safe (B)	Probably safe
Mast cell stabilizers		
Cromolyn sodium	Safe (B)	Probably safe
Leukotriene inhibitors		
Zafirlukast	Risk (B)	No data
Zileuton	Risk (C)	Not recommended
Montelukast	Risk (B)	No data; probably compatible

Table 178-1 Summary of Medication Safety in Pregnancy and Lactation—cont'd

MEDICATION	PREGNANCY	LACTATION
Corticosteroids safe for short-term use: Human data suggest an increased risk of orofacial clefts.		
Prednisolone	Risk (C)	Safe
Prednisone	Risk (C)	Safe
Methylprednisolone	Risk (C)	Safe
Antihistamines		
Chlorpheniramine	Safe (B)	Not recommended
Diphenhydramine	Safe (B)	Not recommended
Dimenhydramine	Safe (B)	Not recommended
Doxylamine	Safe (B)	Not recommended
Hydroxyzine	Risk (C)	Not recommended
Meclizine	Safe (B)	Not recommended
Cetirizine	Probably safe (B)	Not recommended
Fexofenadine	Class C	Safe
Loratadine	Probably safe (B)	Safe
Decongestants		
Pseudoephedrine	Risk (C)	Probably safe
Antiemetics		
Dopamine antagonists		
Promethazine	Safe (C)	Not recommended
Prochlorperazine	Safe (C)	Potential toxicity
Metoclopramide	Safe (B)	Potential tocxicity
5-HT_3 antagonists—generally safe		
Dolasetron	Low risk (B)	Probably safe
Granisetron	Low risk (B)	Probably safe
Ondansetron	Safe (B)	Probably safe
Medications used in the treatment of diabetes		
Insulin	Safe (B)	Safe
Sulfonylureas		
Glipizide	Low risk (C)	Probably safe. Caution: Nursing infants should be monitored.
Glyburide	Low risk (C)	Probably safe. Caution: Nursing infants should be monitored.
Metformin	Moderate risk (C)	Probably safe
Pioglitazone	Moderate risk (C)	Probably safe
Rosiglitazone	Moderate risk (C)	Probably safe
Antacids		
H_2 blockers		
Famotidine	Low risk (B)	Probably safe
Ranitidine	Safe (B)	Probably safe
Nizatidine	Low risk (B)	Probably safe
Cimetidine	Safe (B)	Safe
Proton pump inhibitors		
Omeprazole	Low risk (C)	Safety unknown
Esomeprazole	Low risk (B)	Safety unknown
Lansoprazole	Low risk (B)	Safety unknown
Pantoprazole	Low risk (B)	Safety unknown
Antidotes and toxicology: When indicated, the benefits to the mother will outweigh the possible risks to the fetus.		
Antidote: acetaminophen overdose		
N-acetylcysteine	Safe (B)	Safe
Universal antidote		
Charcoal	Safe (B)	Safe
Antidote: iron toxicity		
Deferoxamine	Probably safe (C)	No data
Antidote: digitalis		
DIG Fab	No data (C)	No data
Antidote: benzodiazepines		
Flumazenil	No data (C)	No data
Antidote: toxic alcohols		
Fomepazole	No data (C)	No data
Antidote: cyanide poisoning		
Hydroxycobalamine	Safe (B)	Safe
Antidote: methemoglobinemia		
Methylene blue	Risk noted (C)	Not recommended

Continued

Table 178-1 Summary of Medication Safety in Pregnancy and Lactation—cont'd

MEDICATION	PREGNANCY	LACTATION
Antidote: narcotics		
Naloxone	Safe (B)	Safe
Universal antidote		
PEG-ELS	Safe (B)	Safe
Antidote: anticholinergics		
Physostigmine	No data	No data
Antidote: organophosphates		
Pralidoxime	No data	No data
Antidote: isoniazid overdose		
Pyridoxine	Safe (B)	Safe
Antidote: lead poisoning		
Succimer	No data	No data

G6PD, glucose-6-phosphate dehydrogenase; PEG-ELS, polyethylenegycol-electrolyte lavage solution.

concentrated in breast milk and may be the preferred agent in lactating mothers.[15-17,27]

Sulfonamides are safe for use in the second trimester and possibly safe in the first trimester, but they should be avoided at term. The primary use of sulfonamides in the emergency department is in the treatment of uncomplicated urinary tract infection, and in this circumstance, sulfamethoxazole is combined with trimethoprim. Trimethoprim is a folate antagonist and has traditionally been contraindicated in pregnancy because of an increased risk of neural tube defects. The sulfonamides readily cross the placenta to the fetus during all stages of gestation. Fetal levels may reach 90% of maternal plasma concentrations. Although sulfamethoxazole has been associated with an increase in congenital malformations in animals, most reports of sulfonamide exposure during pregnancy in humans have failed to demonstrate such an association.[16,17] Sulfonamides are contraindicated in pregnancy near term because they theoretically compete with bilirubin for protein-binding sites, leaving large amounts of free bilirubin to diffuse, be deposited in the infant's brain, and cause kernicterus.[16,17,31,32] To date, however, this complication has not been reported in neonates, presumably because free bilirubin is effectively cleared by the placental circulation. In contradistinction, kernicterus has occurred in newborns exposed to sulfonamides after birth.[16,17] Sulfonamides are excreted into breast milk in low concentrations and are generally tolerated by a healthy neonate. They should be avoided, however, in ill or premature infants and in infants with hyperbilirubinemia or glucose-6-phosphate dehydrogenase deficiency.[15]

Aminoglycosides should be avoided during pregnancy. These drugs readily cross the placenta and their use in pregnancy has been linked to fetal ototoxicity and nephrotoxicity, especially when high doses are used.[16,17] Gentamicin is secreted in small amounts in breast milk and is poorly absorbed from the gastrointestinal tract. It is compatible with lactation.[15-17]

Tetracycline should be avoided during pregnancy because it has been associated with the development of fatal fatty liver in pregnant women.[16,17,26,27] It readily crosses the placenta and reaches the fetus, where it chelates calcium, causing abnormalities in bone growth and staining of decidual teeth. Tetracycline has also been associated with fetal genitourinary anomalies, inguinal hernias, and limb abnormalities.[16,17,26,27] Doxycycline does not bind to calcium and is associated less with stained teeth than is tetracycline. Also, it does not appear to cause an increase in any type of congenital malformation. Despite these findings, doxycycline is not advocated for long-term use in pregnancy.[16,17,26,27]

Because tetracycline binds to breast milk calcium, only a small amount reaches the nursing infant, and it may be used for short periods (≤10 days) during breast-feeding.[15-17] Because it does not bind to breast milk calcium, doxycycline is present in greater quantities in breast milk and is not recommended for use for prolonged periods.[15-17,26,27]

Fluoroquinolones have been linked to numerous toxic effects on bone and cartilage growth in animal models and have been discouraged from use during pregnancy, particularly during the first trimester.[15-17,26,27] A 1998 prospective multicenter study, however, found no increase in premature birth, fetal distress, low birth weight (<2500 g), birth weight, or motor development when fluoroquinolones were used during pregnancy.[33] The American Academy of Pediatrics (AAP) considers fluoroquinolones to be compatible with breast-feeding, because breast-fed infant plasma levels are low.[15,27]

Clindamycin has not been associated with birth defects in humans, and animal studies have failed to link clindamycin to congenital abnormalities in the offspring.[16,17,26,27] The AAP considers clindamycin to be compatible with breast-feeding.[15]

Vancomycin has not been linked to birth defects in humans.[16,17,26,27] Reports of auditory abnormalities and renal insufficiency in neonates of mothers treated with vancomycin are believed to be false positives.[34] Vancomycin is excreted into milk but not well absorbed by the GI tract. Its effects on the nursing infant have not been studied.[16,17]

Linezolid has been linked to embryonic death, decreased weight, and abnormalities in cartilage and ossification in animal studies, but there is no information regarding its effects in humans. Its use in pregnant women should be limited to cases in which the maternal benefit will outweigh possible risk to the fetus.[16,17]

Nitrofurantoin has not been linked to birth defects in animals or humans. However, there are rare reports of hemolytic anemia in the newborn when the drug is used near term, independent of glucose-6-phosphate dehydrogenase deficiency.[16,17,35]

Human data on the use of metronidazole during pregnancy are mixed.[16,17,27] Because metronidazole is mutagenic and carcinogenic in mice, many physicians avoid prescribing it during pregnancy. An analysis of pooled data from case-control and cohort studies, however, did not reveal any increased incidence of congenital malformations even when metronidazole was used in the first trimester.[36] It is therefore considered safe for use in the second and third trimesters, but because of its potential mutagenic effects it is not recommended for use in the first trimester.[16,17,27] Furthermore, the AAP recommends using metronidazole with caution during lactation.[15-17]

Antifungal Medications

Nystatin has a long safety profile during pregnancy and lactation. It is poorly absorbed from skin, mucous membranes, and the GI tract, and it is considered the antifungal agent of first choice for treatment of mucocutaneous fungal infections.[16,17,27] Clotrimazole, miconazole, and ketoconazole seem to be safe during pregnancy and lactation because they have not been associated with major birth defects. However, in a case-control study, a minor increase in the incidence of hypoplastic left ventricle was reported. In addition, ketoconazole is teratogenic in rats. For these reasons, clotrimazole, miconazole, and ketoconazole are considered second-line treatment of fungal infections in pregnancy.[16,17,27] Fluconazole is teratogenic in high doses (>400 mg/day) and has been associated with an increased incidence of craniofacial and cardiovascular defects in offspring and multiple abnormalities of the skeleton and cartilage.[16,17,27,37] These anomalies were not noted when lower doses were used or with single-dose (150 mg) therapy for vaginal candidiasis.[16,17]

Ketocanazole, fluconazole, and itraconazole are excreted into breast milk. Based on the safe use of ketocanazole in neonates and the lack of negative reports, it is considered compatible with breast-feeding.[15-17]

Antituberculous Agents

Untreated tuberculosis places the mother and fetus at greater risk than does the use of antituberculous medications. In addition, in a review of antituberculous treatment during pregnancy, no association was found between these medications and congenital malformations.[16,17,27,38] Rifampin crosses the placenta and occasionally has been implicated in case reports of congenital anomalies and with hemorrhagic disease of the newborn.[16,17] Because there are no controlled studies documenting these effects, rifampin continues to be recommended as first-line therapy along with isoniazid for treatment of pregnant women with tuberculosis. Ethambutol crosses the placenta but has not been associated with any congenital defects.[16,17,27] All three antituberculous medications are considered compatible with breast-feeding.[15-17]

Antiviral Agents

Antiherpetic Drugs

Acyclovir is a purine analogue commonly used in the treatment of herpesvirus infections. During pregnancy, acyclovir is indicated for life-threatening maternal herpes simplex virus infections, such as disseminated disease, herpes encephalitis, and varicella pneumonia, which carries a maternal mortality of 44% if untreated.[16,17,27,39] The Centers for Disease Control and Prevention also recommends treatment of the first episode of genital herpes during pregnancy with oral acyclovir.[39,40] In humans, acyclovir readily crosses the placenta and reaches higher concentrations in fetal circulation than in maternal circulation. There are no reports of teratogenicity or adverse effects in the fetuses or newborns of mothers using acyclovir or valaciclovir.[16,17,27,39-41] Famciclovir was associated with congenital cardiovascular anomalies, hepatotoxicity, and death.[16,17] Acyclovir is concentrated in milk, in which levels may be higher than in plasma. Because there are no reported adverse outcomes in infants of mothers taking acyclovir or infants treated with acyclovir for disseminated herpes, it is considered safe during breast-feeding.[15-17]

Anti-influenza Drugs

Amantadine appears teratogenic in some animals but not others. Its use in pregnant women is very limited, and one cannot draw any conclusions.[16,17]

Oseltamivir has no effect on embryonic or fetal development in animal studies. There appear to be no reports of its use in pregnancy, but based on its safety in animals, it may be used in human pregnancy, albeit cautiously.[16,17]

Anti-HIV Drugs

Anti-HIV drugs may be indicated immediately after a needlestick injury or sexual contact with an infected individual. No specific pattern of birth defects has been described with the use of these drugs, but there are a number of unanswered questions relating to the drugs' mutagenesis and carcinogenesis and their long-term effects on the liver, heart, and reproductive system.[15-17]

Animal and human data suggest that didanosine, lamivudine, stavudine, zidovudine, and zalcitabine present some risk, albeit small, of structural malformations and mitochondrial dysfunction in the developing fetus. However, even if a negative association is proven, the risk of morbidity and mortality from HIV infection far outweighs the risk of toxicity of most of these substances.[15-17,40,42] Similarly, no specific pattern of birth defects has been described with protease inhibitors such as ritonavir and nelfinavir. When indicated, the benefits of treatment outweigh the drugs' toxicities.[15-17,42]

Anticoagulants

Warfarin (Coumadin) is a known human teratogen and affects 4 or 5% of exposed fetuses. The risk from exposure is greatest during 6 to 9 weeks of gestation and seems to be dose dependent.[16,17,27] The fetal warfarin syndrome is associated with multiple abnormalities, such as hypoplasia of the nasal bones, midline dysplasia including agenesis of the corpus callosum, optic atrophy and blindness, mental retardation, seizures, and stippling of the bones with scoliosis and shortening of limbs.[16,17,27,43] Because warfarin is so highly protein bound, only a little is secreted into milk, and use by breast-feeding mothers is acceptable.[16,17] Caution should be used in breast-feeding premature infants because they may be at increased risk for intraventricular hemorrhage.[16,17]

Unfractionated heparin is a highly charged heterogeneous molecule with a molecular weight between 5 and 35 kDa. It does not cross the placenta and does not present a direct risk to the fetus. Early reports on the use of heparin for the prevention or treatment of venous thromboembolism during pregnancy concluded that the risks to the fetus from prematurity, stillbirth, and hemorrhage might affect one third of infants. Recently, however, the increased risks previously associated with heparin were determined to be related to underlying maternal medical problems rather than heparin.[16,17,26,27] When anticoagulation during pregnancy is required, heparin is considered the agent of choice.[16,17,44] Its use is sometimes associated with maternal osteopenia and immune-mediated thrombocytopenia.[16,17,27] Patients need careful monitoring for these adverse effects. The risk of maternal hemorrhage at delivery is significant. Because of its high molecular weight, heparin is not excreted in breast milk and is compatible with breast-feeding.[15-17]

Low-molecular-weight heparin may be used during pregnancy and in the postnatal period for therapeutic or prophylactic anticoagulation.[16,17,27] All currently available low-molecular-weight heparin products have been used safely

during pregnancy. Data are limited, however, because of their relatively recent introduction.

Thrombolytic agents have been used successfully in pregnant women in cases of life-threatening pulmonary embolus or myocardial infarction. Experience with these agents during pregnancy, however, remains limited. To date, no teratogenic effects have been reported in humans, but maternal hemorrhage occurred when alteplase was used during the intrapartum period.[16,17,45] Most thrombolytics are thought to be compatible with breast-feeding because of their short half-life.[16,17]

Anticonvulsants

The occurrence of generalized seizures during pregnancy has been associated with an increased risk of spontaneous abortion, hypoxic injury to the fetus, and impaired neuropsychological functioning.[16,17] Anticonvulsants are known teratogens, however, and 30% of neonates exposed to commonly used anticonvulsants exhibit congenital anomalies.[16,17,27,46] The risks for birth defects increase with the duration of exposure and with the number of agents used.[16,17,27,46] In an observational study of 25 epilepsy centers, it was noted that valproate use during pregnancy was associated with the most frequent serious adverse effects on the pregnancy and fetus (20.3% incidence of serious adverse outcomes) compared with phenytoin, carbamazepine, and lamotrigine (10.7, 8.2, and 1.0%, respectively).[47] Despite the risks, most practitioners believe that it is important to control seizures during pregnancy. Monotherapy is the most appropriate option and is recommended at the lowest effective anticonvulsant dose. Dividing the daily dose to decrease peak plasma levels may be considered. Adjustment of the dosage upward is often required to maintain adequate seizure control.[16,17]

Phenytoin is a human teratogen that readily crosses the placenta. The parent compound and all metabolites have been identified in fetal tissues. Of chronically exposed fetuses, 5 to 10% develop the fetal hydantoin syndrome.[16,17,27,48] This syndrome is characterized by varying degrees of ossification abnormalities of the extremities and digits; craniofacial abnormalities including cleft lip and palate; impaired growth; delayed neurologic development; and cardiovascular anomalies, including atrial septal defects, ventricular septal defects, coarctation of the aorta, and endocardial cushion defects. Phenytoin has also been associated with hemorrhagic disease of the newborn, presumably because it competitively inhibits placental transport of vitamin K.[16,17,27,48] To avoid this rare complication, some clinicians have advocated the use of vitamin K during the last month of pregnancy, but evidence does not support its use.[47] Phenytoin has been linked to a variety of tumors in infants. Phenytoin use is considered safe in breast-feeding.[15-17]

Carbamazepine use during pregnancy is associated with a syndrome similar to fetal hydantoin syndrome, which is thought to be secondary to a toxic, teratogenic metabolite and not the parent compound.[16,17,27,49] In one study, carbamazepine was associated with a twofold increase in major congenital abnormalities in exposed fetuses compared with nonexposed fetuses.[16,17,27,49] These abnormalities include craniofacial defects, fingernail hypoplasia, neural tube defects, and developmental delay. Carbamazepine has also been reported to induce hemorrhagic disease of the newborn.[39] The use of carbamazepine is considered compatible with breast-feeding.[15-17]

Valproic acid, a class D medication that should not be used in pregnancy, is an eight-carbon, branched-chain carboxyl acid that has been approved for the treatment of absence seizures since 1978.[16,17,27,50] It is teratogenic in laboratory animals and in humans. It readily crosses the placenta and concentrates in the fetus. Many authors have described a syndrome of defects associated with the use of valproic acid. The characteristics of the syndrome include multiple minor facial anomalies, low birth weight, delayed neurologic development, congenital heart defects, neural tube defects, hypospadias, strabismus, nystagmus, tracheomalacia, afibrinogenemia, and hyperglycemia.[16,17,27,50] Valproic acid is present in breast milk in low levels and is considered safe during breast-feeding.[15-17]

Phenobarbital is considered a class D medication in pregnancy. It is associated with a slightly increased risk of congenital abnormalities, including congenital heart disease and cleft lip or palate and some minor malformations associated with the fetal hydantoin syndrome.[16,17,46] It is occasionally associated with hemorrhagic disease in the newborn and may result in neonatal withdrawal. Breast-fed infants of mothers taking phenobarbital have developed toxicity characterized primarily by sedation. These infants must be monitored closely for sedation while breast-fed and after breast-feeding for symptoms of withdrawal.[15-17]

Newer Anticonvulsant Medications

No adequate studies of human teratogenicity have been published regarding felbamate, levetiracetam, gabapentin, and lamotrigine, but they appear to be safe during pregnancy. Lamotrigine has been associated with a slightly increased incidence of cardiovascular, craniofacial, gastrointestinal, and genitourinary birth defects.[16,17,51] Safety in lactation is unknown.

Cardiovascular Medications

Antidysrhythmics

Adenosine is a naturally occurring compound that is metabolized quickly in the body. It has been used safely throughout pregnancy and is the drug of choice for terminating maternal supraventricular tachycardia,[52] despite the absence of large-scale studies.[16,17,27,48] Adenosine has also been used safely in terminating incessant tachycardia in the fetus.[53] Adenosine is likely safe in lactation.[16,17]

Amiodarone, a class D agent, is not recommended in pregnancy, except in refractory cases of supraventricular and ventricular tachycardias of the mother or the fetus.[54,55] It contains large amounts of iodine and has been associated with congenital goiter and transient neonatal hyperthyroidism and hypothyroidism.[16,17,56,57] In addition, amiodarone use during pregnancy has been linked to many congenital abnormalities, including growth retardation, structural cardiac abnormalities, corneal deposits, and developmental delay.[16,17,54] Because of its high iodine content, its excretion into milk, and its long elimination half-life, amiodarone should not be used in nursing mothers.[16,17]

Digoxin, disopyramide, and quinidine are all considered safe for use during pregnancy and lactation.[16,17] None have been linked to congenital defects in humans or animals. Of the three agents, digoxin and quinidine have the longest safety records in pregnancy and are first-line agents for the treatment of significant maternal dysrhythmias.[16,17] They have also been successfully used in fetal tachycardia.[58,59] However, maternal overdoses of digoxin resulting in fetal death have occurred.[60] Although considered safe during pregnancy, disopyramide has been associated with premature uterine contractions and labor.[61]

Lidocaine is a weak base. It rapidly crosses the placenta and becomes ion trapped in the fetus. There is no evidence of a

link between lidocaine and any fetal malformations.[16,17] High doses used near term are associated with neonatal CNS depression, apnea, hypotonia, seizures, and bradycardia. Lidocaine is considered compatible with breast-feeding.[15-17]

Procainamide is also well tolerated and should be considered a first-line treatment of wide-complex tachydysrhythmias during pregnancy.[55,58] The use of procainamide in nursing mothers is controversial because it and its metabolite, *N*-acetyl procainamide, have been found in breast milk.[15-17]

Encainide and flecainide are newer class IC antiarrhythmic agents that are structurally related to procainamide. Both have been used safely to terminate maternal and fetal tachycardia.[16,17] A few negative fetal effects have been noted with the use of flecainaide, including hyperbilirubinemia, hepatotoxicity, and loss of fetal heart rate variability.[62,63] Both encainide and flecainide are found in breast milk. Although experience with encainide is limited, the AAP considers flecainide compatible with breast-feeding.[16,17]

Ibutilide is a class III antiarrhythmic used to terminate atrial fibrillation and flutter. Although there are no reports of its use in pregnancy in humans, when used in high doses, ibutilide was found to be teratogenic in rats.[16,17] Ibutilide may be used in refractory cases in which the benefits of therapy outweigh any fetal risk.[16,17]

Sotalol does not appear to have teratogenic effects in animals.[16,17] It has been used in pregnant women to treat hypertension. In these cases, bradycardia in the newborn was noted, which persisted for 24 hours. Sotalol has also been used successfully to terminate in utero fetal supraventricular tachycardia.[64]

Isoproterenol is indicated for refractory high-grade atrioventricular block and for torsades de pointes associated with prolonged QT interval. Data from animal studies have not shown any association between isoproterenol and developmental toxicity. It is also considered compatible with breast-feeding.[16,17]

Vasopressors

Dobutamine is an inotrope used in the setting of cardiac dysfunction and sepsis. Data from animal studies have not revealed any untoward reproductive effects. Effects in humans are not known, but one case report did not reveal any effects on the fetus.[16,17,65]

Dopamine and other vasopressors offer a maternal benefit that far outweighs the possible deleterious effects on the fetus and should not be withheld if indicated. Dopamine has been associated with increased uterine vascular resistance in animal studies, but no significant fetal side effects directly related to the drug have been reported. In addition to its use in maternal shock, dopamine has been successfully used in low doses to improve cardiac and urine output in patients with preeclampsia and oliguria.[66]

Epinephrine has been used to treat shock from any cause during pregnancy. However, it has been associated with anoxic injury to the fetus, intracranial hemorrhage, and an increased incidence of inguinal hernias.[16,17,67] Safety during breast-feeding has not been studied.

Norepinephrine is associated with an increased incidence of cerebral hemorrhage, skeletal abnormalities, and a significant decrease in placental blood flow and fetal oxygenation in animal studies.[16,17,68] Its safety during breast-feeding has not been studied.

Antihypertensives

Hypertension complicates 12% of pregnancies and accounts for 18% of maternal deaths in the United States.[69] Previously, the most commonly used drug in hypertensive emergencies was hydralazine, but other medications currently available, such as labetolol and nifedipine, appear to be as effective and possibly safer than hydralazine.

Angiotensin-converting enzyme (ACE) inhibitors are classified as category D drugs and are contraindicated for use during pregnancy. ACE inhibitors are embryocidal in animals and increase the rate of stillbirths in some species. Although they seem to be safe in humans during the first trimester of pregnancy, many adverse fetal effects have been noted with their use during the second and third trimesters, precluding their use.[16,17,37,70] Reported adverse neonatal effects include oligohydramnios, anuria, renal agenesis resulting in death, increased risk of stillbirth, intrauterine growth retardation (IUGR), fetal skull abnormalities, pulmonary hypoplasia, respiratory distress syndrome, and fetal and neonatal hypotension. Captopril and enalapril are considered compatible with breast-feeding.[15-17]

Angiotensin II receptor antagonists should be avoided during pregnancy because their use has been reported to result in fetal abnormalities similar to the abnormalities seen with ACE inhibitors, including renal agenesis, neonatal anuria, oligohydramnios, IUGR, persistent patent ductus arteriosus, abnormal ossification, and death.[16,17] Their safety in lactation is unknown.

Beta-blockers have become a first-line treatment for hypertension in pregnancy.[71,72] All beta-adrenergic blocking agents cross the placenta. The most experience with beta-blockers has been with women requiring treatment during the last trimester of pregnancy, at which time they seem to be safe. Long-term in utero exposure and first-trimester exposure have not been studied.[16,17,37] Labetalol is the antihypertensive of choice during pregnancy.[71,72] It has not been associated with any teratogenic effects in animal studies. Human reports of its use in the treatment of hypertension during pregnancy have not revealed any significant effect on the fetal birth weight or fetal heart rate.[16,17,37] Transient neonatal hypotension and bradycardia may be observed when used at term. However, compared with traditional therapies for pregnancy-induced hypertension, labetolol appeared to reduce the blood pressure more smoothly than either hydralazine or diazoxide.[16,17,71,73] Furthermore, it was associated with fewer cesarean sections than either of the two drugs.[73] Atenolol and metoprolol are considered safe in pregnancy but only when used for short periods of time.[16,17,73] There are reports of fetal harm when atenolol is used in the first trimester. Atenolol has also been associated with IUGR when used for prolonged periods during pregnancy, and when given near term, it is associated with persistent beta blockade in the newborn.[16,17,73] Similarly, propranolol is associated with fetal and neonatal adverse effects, especially when doses exceeding 160 mg/day are used. These adverse effects include IUGR, hypoglycemia, bradycardia, respiratory depression at birth, and hyperbilirubinemia. Esmolol has also been associated with fetal bradycardia, neonatal bradycardia, and hypotonia as well as fetal distress requiring emergent cesarean section.[74] It should therefore be used only if the benefits to the mother outweigh the risks to the fetus and if other options have failed. Beta-blockers are reportedly safe in breast-feeding, but close monitoring of the infant for adverse effects is recommended.[15-17]

Calcium channel blockers are indicated in the treatment of hypertension and a number of supraventricular rhythm disturbances during pregnancy.[16,17,71] Nifedipine and cardizem have also been used as tocolytic agents. In addition, verapamil has been used to terminate maternal as well as fetal tachycardia.[75] Despite negative reproductive studies in animals, the calcium channel blockers are used extensively during the second and

third trimesters in humans and are considered safe for use during these stages of pregnancy.[16,17,37,76] Whereas cardizem appears to be safe at all stages of pregnancy, nifedipine was associated with fetal distress secondary to maternal hypotension when it was used sublingually.[16,17] In addition, when used in conjunction with magnesium, nifedipine appeared to potentiate the neuromuscular blocking effects of magnesium, resulting in profound muscle weakness, difficulty in swallowing, and paradoxical respirations.[77] Calcium channel blockers are considered safe for use during breast-feeding.[15-17]

Thiazide diuretics have been used successfully for the treatment of hypertension in pregnancy but may result in electrolyte abnormalities in neonates when given near term.[16,17,71] An increase in perinatal mortality and congenital defects possibly caused by volume depletion has been reported.[16,17] First-trimester use has been associated with an increase in congenital anomalies.[16,17] Diuretics are not recommended for the treatment of pregnancy-induced hypertension because of the maternal hypovolemia characteristic of this disease. Other risks to the pregnancy include higher rates of uterine inertia and meconium staining.[78] In the neonate, there is a higher incidence of hypoglycemia, thrombocytopenia, hyponatremia, hypokalemia, and death from maternal complications.[16,17] Moreover, thiazide diuretics may have a direct effect on smooth muscle and inhibit labor. Bendroflumethiazide, chlorthalidone, and hydrochlorothiazide are considered safe during breast-feeding.[16,17] Loop diuretics are generally not used in pregnancy unless indicated for congestive heart failure. They have not been found to cause major adverse outcomes in the fetus.

Hydralazine is safe in pregnancy. It was previously considered the drug of choice for the parenteral treatment of acute severe hypertension during pregnancy.[71] However, it has been associated with higher rates of maternal hypotension compared to labetolol, which may affect perinatal outcome.[16,17,37,71] It is also associated with a lupus-like syndrome, which has been reported in both mother and neonate.[16,17,37,79] Because other agents, particularly labetalol, are safer and just as effective, hydralazine is no longer recommended as a first-line agent in the treatment of hypertensive emergencies in pregnant women.[71] Hydralazine is safe in lactation.[16,17,79]

Methyldopa is considered safe in pregnancy, and most reviews have not linked it to any adverse effects on the pregnancy.[16,17] Many clinicians still use it as first-line therapy to treat hypertension during pregnancy. Methyldopa is compatible with breast-feeding.[31]

Clonidine has been safely used throughout pregnancy, but experience during the first trimester is very limited.[80] A few insignificant adverse fetal effects attributable to clonidine have been reported. Transient neonatal hypertension has been reported in neonates with in utero exposure to clonidine.[16,17,37,80] Its effects on breast-feeding neonates are unknown, but it is considered to be compatible with breast-feeding.[15-17]

Nitroglycerin has not been shown to cause fetal harm in animal studies. Limited reports in humans do not show any major effects on the fetus or neonate. Nitroglycerin is rarely used during pregnancy, but it appears to be a safe, effective, rapidly acting and short-acting agent.[16,17,81] It appears to be effective in relieving intrapartum fetal distress related to uterine hyperactivity.[81]

Nitroprusside use for the treatment of hypertensive emergencies in pregnancy has the same advantages and disadvantages seen in nonpregnant patients.[16,17,71] Advantages include its rapid onset, rapid metabolism, and rapid excretion. Disadvantages of nitroprusside include the need for constant monitoring and cumbersome administration. During prolonged administration of high doses, nitroprusside may result in cyanide toxicity. It readily crosses the placenta, and fetal levels of cyanide can increase as high as twice maternal levels. Standard doses do not seem to subject the fetus to major risk of toxicity, but with the availability of safer alternatives, notably labetalol, nitroprusside is considered a second-line agent.[16,17,37] When used, it is recommended to monitor plasma and red blood cell cyanide and maternal pH. Nitroprusside is considered a category C medication. No data are available on its use during breast-feeding.

Asthma, Allergy, and Upper Respiratory Infection Medications

Pregnant women with asthma are at risk of neonatal death, preterm birth, low-birth-weight infants, preeclampsia, and small-for-gestational-age infants.[71,82] Asthmatic mothers may also have a higher rate of chorioamnionitis, hypertensive disorders of pregnancy, cesarean section, and prolonged hospital stay compared to control mothers.[82,83] Better asthma control has been associated with an improved outcome.[71]

The beta-adrenergic medications albuterol, metaproterenol, and terbutaline are safe for use in pregnancy. None have been linked to congenital anomalies.[16,17] Beta-adrenergic agents have also been used during the last trimester to treat premature labor. Adverse reactions are related to the drugs' cardiovascular and metabolic effects, which are transient and generally well tolerated by the fetus.[16,17,83,84] Transient hyperglycemia followed by insulin secretion may also occur, resulting in neonatal hypoglycemia, especially in diabetic patients.[16,17] Long-term use of albuterol has not been associated with adverse effects. Albuterol is compatible with breast-feeding.[15-17] Long-acting beta-agonists also appear to be safe during pregnancy.[16,17,83]

Ipratropium has not been found to be teratogenic in numerous animal models. Although there are few human data, ipratropium seems to be safe for use during pregnancy and lactation.[15–17]

Cromolyn sodium is safe in pregnancy. Cromolyn has not been associated with any significant risk of birth defects or negative perinatal outcomes.[16,17,82,83]

Corticosteroids are commonly used during pregnancy for the treatment of various disorders, including autoimmune diseases, hyperemesis gravidarum, and asthma. Inhaled corticosteroids are the main therapy for the prevention of asthma exacerbations during pregnancy. Oral corticosteroids are the mainstay of therapy for acute exacerbations of asthma. Although they are not considered human teratogens, there may be a slightly increased incidence of orofacial clefts when oral steroids are used during the first trimester.[16,17,37,85] Furthermore, their use in the third trimester has been linked to an increased incidence of preterm delivery, low birth weight, preeclampsia, and cataracts in the newborn.[16,17,37,85] Other authors have also raised concerns about the development of congenital adrenal hyperplasia in newborns.[16,17] Prednisone is considered safe during breast-feeding.[15-17]

Data on the use of leukotriene antagonists in pregnancy are limited. One study did not find an association with congenital abnormalities, but there was a slight increase in intrauterine growth restriction. However, these results should be interpreted with caution because of the small sample size of the study.[86] Zileuton is mutagenic in animal studies and should be avoided during pregnancy and lactation.[16,17]

Antihistamines have been safely used in the treatment of allergic reactions during pregnancy and as antiemetics in the treatment of nausea and vomiting during pregnancy. Antihis-

tamines have been linked to the development of retrolental fibroplasia (retinopathy of prematurity) in premature infants when given during the last 2 weeks of pregnancy.[16,17] A meta-analysis that reviewed 24 studies involving more than 200,000 patients confirmed the safety of antihistamines, including chlorpheniramine, diphenhydramine, doxylamine, hydroxyzine, and meclizine, during pregnancy.[87] The newer generation antihistamines, such as cetirizine and loratadine, also appear safe during pregnancy.[88] They may be acceptable alternatives for severe allergies if the first-generation antihistamines are not tolerated.[16,17] First-generation antihistamines are not recommended during breast-feeding because they may inhibit lactation. In addition, neonates receiving antihistamines appear to develop serious adverse CNS effects, including seizures, especially when premature.[15-17]

Decongestants are not recommended during pregnancy.[16,17] Decongestants with strong vasoconstrictive properties, such as phenylpropanolamine and pseudoephedrine, cause placental vasoconstriction, resulting in an increased incidence of abnormalities typically associated with placental vascular disruption, such as gastroschisis and intestinal atresia.[16,17,83]

Gastrointestinal Medications

Phenothiazines, such as promethazine, chlorpromazine, perphenazine, and metoclopramide, are dopamine antagonists commonly used in the treatment of nausea and vomiting during pregnancy, and they have not been linked to congenital abnormalities. Caution should be used with chlorpromazine because it may cause hypotension and also with promethazine at term because it may cause respiratory depression.[16,17,89]

Ondansetron, a serotonin 5-HT_3 receptor antagonist, has not been linked to any fetal malformations, but it may not offer any additional antiemetic activity compared to the phenothiazines.[16,17,89] Newer 5-HT antagonists, such as dolasetron and granisetron, also appear to be safe during pregnancy, although experience is limited.[16,17,89] These agents are most likely compatible with breast-feeding.[15-17]

The H_2 receptor antagonists ranitidine, famotidine, and cimetidine have not been linked to any congenital malformations and appear to be safe for long-term use during pregnancy and lactation.[15-17] However, one report has linked the use of antacids during pregnancy to an increased incidence of asthma during childhood.[90]

Diabetes Medications

Insulin has been used safely during pregnancy and lactation for many years and is the drug of choice for glucose control in pregnancy. Sulfonylurea drugs traditionally have not been used during pregnancy. They are regarded as possibly teratogenic and less effective than insulin in the control of gestational diabetes.[16,17] Sulfonylurea drugs have also been associated with neonatal hypoglycemia when used at term.[16,17] In reality, there is little information about their use during pregnancy, and in a randomized study, glyburide proved to be as effective and safe during pregnancy as insulin.[16,17,91] Glyburide and glipizide are highly protein bound and are not likely to pass into breast milk; nursing infants should be monitored.[16,17]

Metformin has not been associated with fetal malformations in animals, and there are no controlled studies analyzing its effect in humans.[16,17] Metformin has been associated with serious adverse effects in adults, including severe life-threatening metabolic acidosis and hepatotoxicity. Because of its potential for serious effects in adults, metformin is not recommended for use in lactating mothers.[16,17,92]

Anesthetics and Sedatives

The short-term use of benzodiazepines during pregnancy appears to be safe. However, the safety of benzodiazepines during pregnancy has been debated because data on the fetal effects of these drugs have been inconsistent. Some case reports have linked their use during the first trimester of pregnancy to increased risk of oral clefts, but in a meta-analysis of pooled data from the cohort studies, no association was found between fetal exposure to benzodiazepines and the risk of oral clefts.[93] Different benzodiazepines also have been linked to different effects and risks. Lorazepam, for example, has been linked to anal atresia; clonazepam has been associated with congenital cardiac abnormalities; and oxazepam and diazepam have been linked to specific dysmorphic features, CNS abnormalities, and growth defects.[16,17] Midazolam, on the other hand, has not been linked to any developmental abnormalities. Neonates exposed to benzodiazepines may exhibit signs of toxicity, including apnea, cyanosis, unresponsiveness, hypotonia, poor feeding, and withdrawal symptoms characterized by irritability and tremulousness.[16,17] Because of the reported risk of apnea, it is recommended that neonates exposed to benzodiazepines through breast-feeding be monitored closely.[15-17]

Ketamine is a rapidly acting dissociative anesthetic that is commonly used in pediatric procedural sedation and may be used in rapid sequence intubation (RSI). It has not been associated with any developmental malformations.[16,17,94] Ketamine has a dose-related oxytocic effect, and in high doses it has been associated with uterine tetany, increases in maternal blood pressure and heart rate, and increased neonatal muscle tone. Neonatal depression has also been reported.[16,17,94] Ketamine may remain in breast milk for 12 hours.[16,17]

Propofol is a rapidly acting sedative anesthetic that rapidly crosses the placenta. It has not been linked to any congenital defects when used in pregnancy.[16,17,94] When high doses are used at term, it can cause neonatal respiratory and CNS depression. Propofol is excreted in breast milk in negligible amounts.[16,17]

Thiopental is an ultra-short-acting barbiturate that may be used during RSI or for persistent status epilepticus. It has not been linked to any congenital defects when used during pregnancy, but a slight reduction in birth weight has been noted when high doses are used.[16,17,94]

Etomidate is an ultra-short-acting hypnotic agent that is commonly used for procedural sedation or RSI. No reports on developmental effects of etomidate have been published. However, newborns of mothers undergoing cesarean section with etomidate were found to have significant reductions in serum cortisol concentrations 1 hour after delivery.[16,17,95] The significance of this effect remains to be elucidated. No data on breast-feeding were found.

Paralyzing Agents

Succinylcholine is a depolarizing neuromuscular blocking agent used in RSI for its rapid onset of action and short duration of paralysis. It has not been associated with any congenital defects, although there is limited experience with its use in early pregnancy in humans.[16,17,94] In addition, it does not appear to have any effects on the newborn, except in rare cases of neonates with pseudocholinesterase deficiency.[96] As occurs in adults with the same condition, newborns with cholinesterase deficiency exhibit prolonged respiratory depression and paralysis.[96] Succinylcholine in lactation has not been

studied; however, it is probably safe because it is hydrolyzed quickly.[16,17,96]

Rocuronium and vecuronium are nondepolarizing neuromuscular blocking agents used in RSI. The effects of neuromuscular blocking agents on organogenesis are not known, but these agents are not thought to pose a significant teratogenic risk.[16,17,94] Because of their chemical properties, very little of either drug crosses the placenta, and very little is excreted in milk.[16,17,94] Their effects on lactation are unknown but probably would be minimal.[16,17]

Antidotes

N-acetylcysteine has been used successfully and without untoward effects in pregnant women who have overdosed on acetaminophen.[18,19] No teratogenic effects have been reported.

Deferoxamine is indicated for iron toxicity occurring from iron overdose or from multiple transfusions in thalassemia patients. It has been associated with developmental effects on ossification in some animal species.[16,17] Experience in humans is limited, but it does not appear to affect the fetus.[99] The effects of deferoxamine on the nursing infant are not known.

Dimercaprol or British antilewisite is a metal chelating agent that is used as an antidote for acute mercury, lead, arsenic, and gold poisoning. It has also been used in Wilson's disease. It is teratogenic in mice and has been associated with increased mortality, growth retardation, cleft facial features, cerebral herniation, and abnormal digits, but experience in humans is limited.[16,17,97] In certain cases of heavy metal poisoning, the maternal benefits of dimercaprol use outweigh its potential risks to the unborn fetus. Breast-feeding is not recommended for patients poisoned by heavy metals.

Flumazenil is a benzodiazepine antagonist. No teratogenic effects have been reported in animals, and data on humans are very limited.[16,17] Its use in pregnancy depends on the potential maternal benefit compared to possible risks to the fetus.

Fomepazole is a competitive inhibitor of alcohol dehydrogenase indicated in cases of methanol and ethylene glycol poisoning. Its use during pregnancy has not been studied in animals or humans. Its safety during pregnancy is not known.[16,17] In cases of toxic alcohol poisoning, the benefits of treatment of the mother outweigh the possible risks to the fetus. Use of ethyl alcohol in these situations may also be considered.

Activated charcoal is not absorbed and is probably safe for use in pregnancy and lactation, although there are no published studies regarding the effects of charcoal use during pregnancy.[16,17]

Digoxin fragment (DIG Fab) therapy is indicated for life-threatening digoxin overdose and is being studied for treatment of preeclampsia. There are very few case reports of the use of DIG Fab immune globulin during pregnancy. A conclusion on the effects of DIG Fab cannot be made based on these reports. However, in cases of life-threatening digitalis overdose with arrhythmias, the benefits of treatment of the mother may outweigh the risk to the fetus. DIG Fab is not likely to be excreted in large amounts in milk, and it is probably safe for use during lactation.[16,17]

Hydroxycobalamin is a vitamin that is indicated in the treatment of cyanide toxicity. Studies in animals do not reveal an association with any developmental abnormality.[16,17]

Methylene blue is used in the treatment of methemoglobinemia. In the past, it was injected into the amniotic sac to identify twins and to detect rupture of the membranes, but these practices were associated with hemolytic disease in the newborn, hyperbilirubinemia, and deep blue staining of the newborn.[16,17,98] Methylene blue in pregnancy has also been associated with an increased incidence of intestinal obstruction and atresia in the newborn.[99] The effects on nursing infants are unknown but probably minimal.[16,17]

Naloxone, used to reverse the effects of opiates in an overdose, readily crosses the placenta. Naloxone has not been associated with reproductive abnormalities; however, its use in opiate-addicted mothers may precipitate withdrawal in both mother and term fetus.[16,17] It is compatible with breast-feeding.[15]

Physostigmine is an anticholinesterase agent indicated in cases of severe anticholinergic poisoning associated with delirium. Experience with the medication during pregnancy is limited, and its effects on the developing fetus are unknown.[16,17] Use of physostigmine at term was associated with only mild decreases of Apgar scores at 1 and 5 minutes.[100]

Polyethylene glycol (PEG) is not absorbed systemically. It is probably safe for use in pregnancy and lactation, although there are no reports on the effects of PEG in pregnancy.[16,17]

Pralidoxime is indicated for organophosphate/cholinergic poisoning because it is able to reactivate cholinesterase. Experience with pralidoxime in pregnancy is limited, and its effects on fetal development are not known.[16,17] In cases of organophosphate poisoning, the benefits to the mother generally outweigh the possible risk to the fetus.

Pyridoxine is a vitamin required for good maternal health and good fetal development. It is indicated in isonizid poisoning and in gyromytrin mushroom poisoning. Its use has been advocated in some for nausea and vomiting of pregnancy and gestational hypertension and diabetes. It has not been associated with any adverse developmental effects, and it is safe in lactation.[16,17]

Succimer is a lead chelator that is indicated in lead poisoning. It has been linked to congenital defects in animal models, possibly due to effects on zinc and copper metabolism.[16,17] Experience with the use of succimer in pregnancy is limited to case reports of women poisoned with lead. No conclusions can be drawn on its teratogenic effects.[101]

KEY CONCEPTS

- Chemically induced birth defects are believed to be responsible for approximately 1 to 3% of anomalous births.
- The age of the fetus is crucial in determining the impact of any given exposure; during the time of organogenesis (days 21–56 of fetal life) when major body organs are formed, exposure to a teratogen may result in major anatomic defects.
- Certain medications, such as anticonvulsants, warfarin derivatives, NSAIDs, sulfonamides, fluoroquinolones, ACE inhibitors, and oral hypoglycemic agents, are known teratogens or cause potential toxic effects in the newborn and should be avoided, if possible, during pregnancy.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 179

Labor and Delivery and Their Complications

Shoma Desai, Sean O. Henderson, and William K. Mallon

PERSPECTIVE

Emergency department (ED) births are rare. In most cases, the emergency physician will identify patients in labor and triage them to the obstetric service for urgent management, maintaining a continuum of care with their primary providers. Because some births are precipitous and obstetric resources may not be immediately available, the emergency physician must possess the basic skills for intrapartum management of both normal and abnormal deliveries. In addition, a general knowledge of postpartum care is required in case of the occasional out-of-hospital delivery.[1-3]

Limitations of the Emergency Department

The ED is a suboptimal location for the management of a complicated delivery. The obstetric suite has experienced personnel and better resources, including tocodynamometry, fetal scalp electrodes, intrauterine pressure monitors, vacuum extractors, and forceps. Also, the obstetrician usually has prenatal care information for each patient that helps to optimize maternal and fetal outcomes. Such information includes accurate gestational dates, the presence of multiple gestations, estimated fetal weights, detailed maternal pelvimetry, placental anatomy, amniocentesis results, maternal blood type and Rh factor, and prior documented obstetric complications. This information allows the obstetrician to anticipate complications of labor and delivery. It is difficult, if not impossible, to obtain these data in the ED while preparing for imminent delivery.[4] Finally, in certain situations, cesarean section is the best way to ensure successful delivery. This surgical option is not available in the ED except in dire perimortem circumstances.

Epidemiology of Emergency Delivery

In 2004, the perinatal mortality rate in the United States was 6.2 per 1000 live births and fetal deaths (>20 weeks of gestation).[5] Extensive epidemiologic data regarding the subgroup of ED deliveries are lacking. However, it has been established that delivery complications and mortalities do occur with greater frequency in the ED. In fact, the perinatal mortality rate for ED deliveries has been approximated at 8 to 10%.[6]

There are multiple causes of the "high-risk" ED delivery profile. The ED is often selected by an obstetric population with unexpected complications. Antepartum hemorrhage, premature rupture of membranes (PROM), eclampsia, premature labor, abruptio placentae, precipitous delivery, malpresentation, and umbilical cord emergencies are overrepresented in the ED population.[6]

Psychosocial factors further skew the epidemiology of ED deliveries. Women who present with precipitous deliveries often have had very little or no prenatal care.[7] Pregnant women who have drug or alcohol problems or are victims of domestic violence represent a disproportionate number of patients who deliver in the ED. Women who are unaware or in denial of their pregnancies, or immigrants without access to other medical care, also present to the ED when labor begins.[8-10] For each of these groups, all of which are compromised by psychosocial factors, inadequate prenatal care makes the subsequent delivery high risk.

Patient Transfer Considerations

Because of the high risk associated with ED delivery, patients should be transported to a facility that has obstetric and neonatal resources as appropriate. The management of a premature infant may require highly specialized intensive care that is unavailable at many community hospitals. The desire to transfer a woman with an impending high-risk delivery to such a facility must be tempered, however, by clinical and medicolegal judgment.[11,12]

Medicolegal Considerations

Transfer, with resultant en route delivery, can be disastrous for the mother and fetus. Such a transfer also violates federal law. The Consolidated Omnibus Reconciliation Budget Act (COBRA) of 1989 was based on an "inappropriate" obstetric transfer.[13] Federal law has identified labor as a condition unsuitable for transfer because of its unstable nature. Although the intent of this legislation is to protect women from medical and financial "dumping," COBRA also may force emergency physicians to perform difficult high-risk deliveries that might have better outcomes if transferred.[14]

Nursery Requirements

For many ED deliveries, labor will have progressed to a point where tocolysis is contraindicated and delivery is imminent. Generally, this is the point when the mother feels the urge to push or the head is crowning. Whenever possible, a neonatologist or pediatrician should attend high-risk preterm (<36 weeks' gestation) deliveries, and preparations for neonatal

BOX 179-1 LEVELS OF NURSERY CARE

Level 1 Nurseries
These nurseries care for infants presumed healthy. In such units, screening and surveillance are primary responsibilities.
"Rooming-in" units are encouraged, with emphasis on support of breast-feeding and assessment of parenting skills.

Level 2 Nurseries
These nurseries care for infants >30 weeks' gestation and >1200 g who require special attention short of circulatory or ventilator support and major surgical procedures. A high percentage of the patients in such nurseries have had obstetric complications (e.g., birth trauma, fetal distress, and obstetric anesthesia).

Level 3 Nurseries
These nurseries are staffed and equipped to care for all newborn infants who are critically ill, regardless of the level of support required. They are regional institutions serving as referral centers for other nurseries and for this reason are often linked with transport services.

Perinatal Centers
A perinatal center provides services to high-risk mothers and to infants requiring level 3 nursery care. Ample data show a higher neonatal survival rate for high-risk pregnancies cared for in such centers.

resuscitation and high-level nursery care should be initiated (Box 179-1).[15]

NORMAL DELIVERY

Although the epidemiology and high complication rate associated with ED births demand caution, most are normal deliveries. Knowledge of normal labor and delivery mechanics aids safe vaginal delivery and facilitates the identification of complications.

Whenever a woman in the third trimester of pregnancy seeks treatment in the ED, the possibility that she is in labor must be considered. A wide array of nonspecific symptoms may herald the onset of labor. Abdominal pain, back pain, cramping, nausea, vomiting, urinary urgency, stress incontinence, and anxiety can all be symptoms of labor. After 24 weeks' gestation, any medical assessment should include the mother and the fetus because fetal viability becomes established near that time. In addition, given the generally high-risk nature of this patient population and the abundance of bodily fluids that the health care provider and newborn are exposed to during delivery, serologic testing for infectious disease may be warranted. With the development of rapid bedside testing technology, human immunodeficiency virus (HIV) and hepatitis screening before delivery is indicated in a significant group of patients presenting with active labor.

Distinguishing False from True Labor

Braxton Hicks contractions, or false labor, must be differentiated from true labor. During the third trimester, the uterus develops into a contractile organ. After 30 weeks of gestation, the previously small and uncoordinated contractions of the uterus become more synchronous and may be perceived by the mother. Braxton Hicks contractions do not escalate in frequency or duration, in contrast to the contractions of true labor. By definition, this muscular activity is associated with minimal or no cervical dilation or effacement. Examination should also reveal intact membranes. Care not to rupture the membranes is important to avoid inducing labor prematurely. If the diagnosis remains in doubt, external electrical monitoring of uterine activity can be utilized to rule out true labor. Any discomfort associated with false labor is usually relieved with mild analgesia, ambulation, or change in activity.

Unlike false labor, true labor is characterized by cyclic uterine contractions of increasing frequency, duration, and strength, culminating in delivery of the fetus and placenta. In contrast to Braxton Hicks contractions, true labor causes cervical dilation to begin, marking the first stage of labor.

Bloody Show

Early in pregnancy, the cervix becomes increasingly vascular and develops edema, giving the cervix a boggy texture. The vascularity of the cervix also increases, giving rise to Chadwick's sign (a blue-violet coloration). At the onset of labor, the cervical mucus plug is expelled, resulting in what is called a *bloody show*. The bleeding associated with the process is slight, and usually only a few dark red spots are noticed. The dark color is due to its venous origin, and it is admixed with the mucous components of the cervical plug. The significance of a bloody show is that it is a fairly reliable indicator of the onset of true labor, specifically stage 1. Bloody show is not a contraindication to vaginal examination for determination of cervical effacement and dilation. If bleeding continues or is of a larger volume, more serious causes should be suspected, such as placenta previa and placental abruption, which are contraindications for a vaginal examination.

Stages of Labor

First Stage of Labor

The first stage of labor is the cervical stage, ending with a completely dilated, fully effaced cervix. It is divided into a latent phase, with slow cervical dilation, and an active phase, with more rapid dilation. The active phase begins once the cervix is dilated 3 cm.[16] In multiparous women, the active phase can progress rapidly into stage 2 of labor (delivery of the fetus). Most women who deliver in the ED arrive while in the active phase of stage 1 or in early stage 2 labor (Fig. 179-1).[6]

The duration of the first stage of labor averages 8 hours in nulliparous women and 5 hours in multiparous women. During this time, frequent assessment of fetal well-being is important. For low-risk pregnancies, fetal heart tones should be auscultated approximately every 15 minutes. For higher risk pregnancies, continuous external electrical monitoring may help identify fetal distress, allowing appropriate intervention.[17]

Abdominal examination using Leopold's maneuvers may confirm the lie of the fetus (Fig. 179-2). After labor has begun, particularly during the active phase of stage 1, Leopold's maneuvers are difficult to use. The firm contractions of the uterus prevent the identification of fetal "small parts." Other modalities of assessing the lie, such as ultrasonography, may be necessary if presentation remains in question.[18]

Maternal examination also provides a rough guide to gestational age. At 20 weeks' gestation, the uterine fundus reaches the umbilicus. Approximately 1 cm of fundal height is added per week of gestation until 36 weeks. At that time, the fundal height decreases as the fetus "drops" into the pelvis (Fig. 179-3). These estimates help to establish gestational age rapidly.

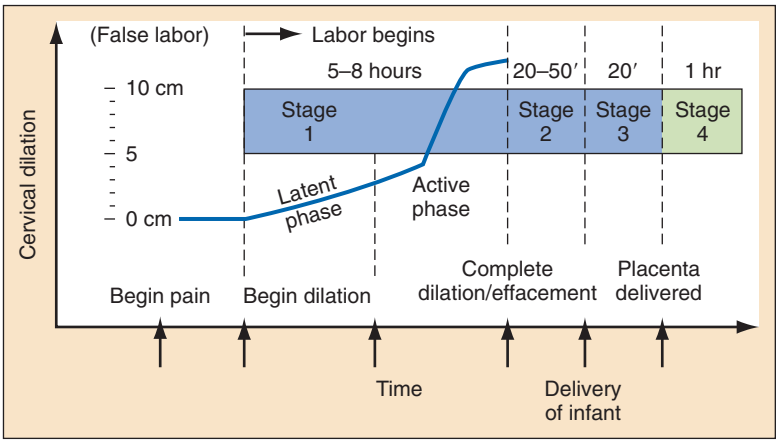


Figure 179-1. Stages of labor and delivery. Stage 1, cervical stage; stage 2, fetal expulsion; stage 3, placental expulsion (20 minutes); stage 4, uterine contraction (1 hour postpartum).

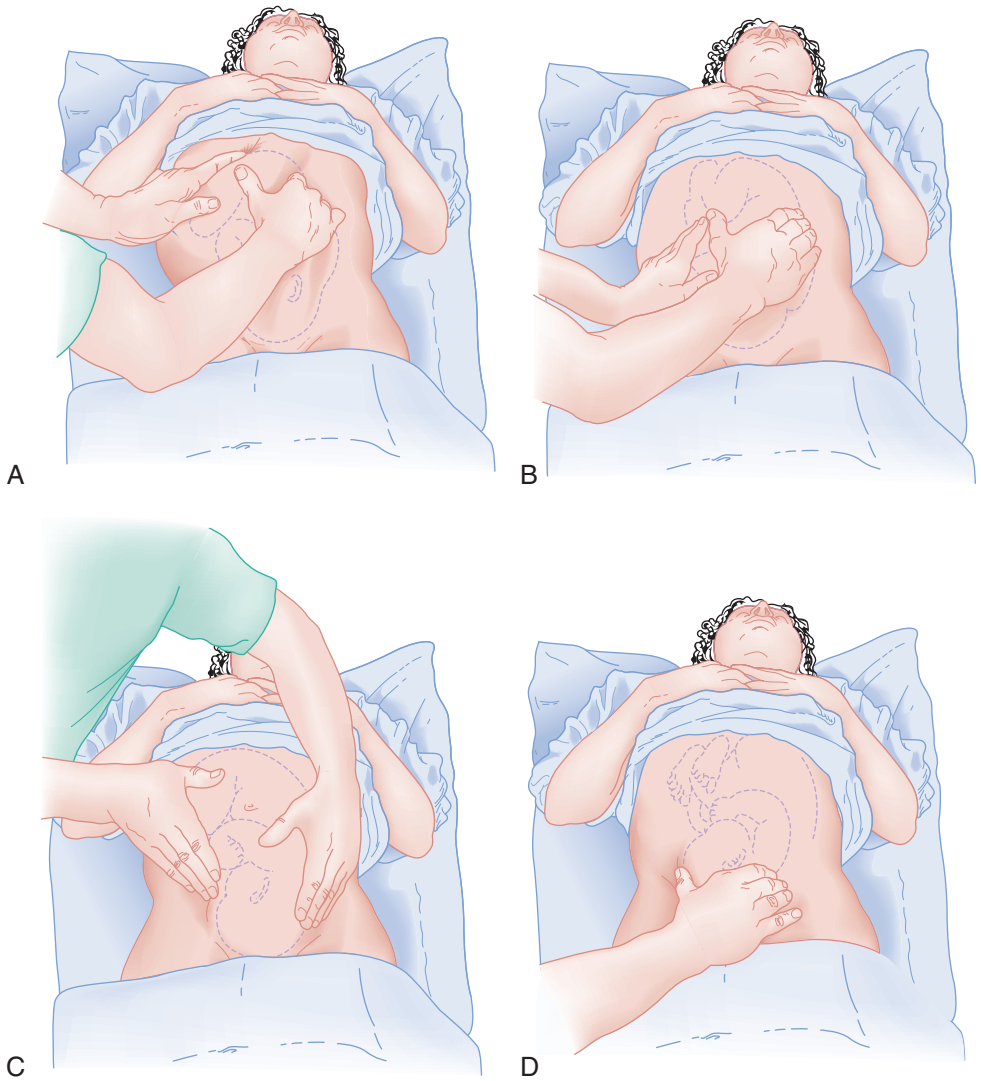


Figure 179-2. Leopold's maneuvers. **A,** The first Leopold maneuver reveals what fetal part occupies the fundus. **B,** The second Leopold maneuver reveals the position of the fetal back. **C,** The third Leopold maneuver reveals what fetal part lies over the pelvic inlet. **D,** The fourth Leopold maneuver reveals the position of the cephalic prominence. (Modified from Willson JR, et al: Obstetrics and Gynecology, 9th ed. St. Louis, Mosby, 1991.)

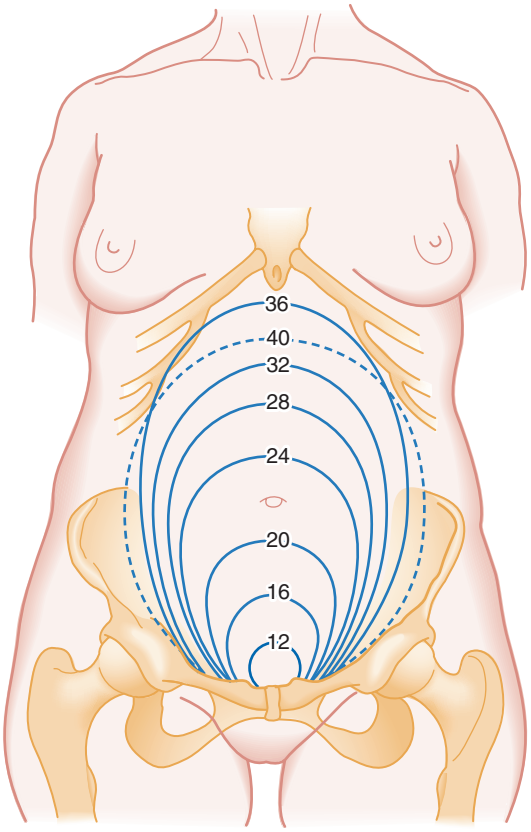


Figure 179-3. Height of fundus by weeks of normal gestation with a single fetus. *Dotted line* indicates height after lightening. (Modified from Barkaukas V, et al: Health and Physical Assessment. St. Louis, Mosby, 1994.)

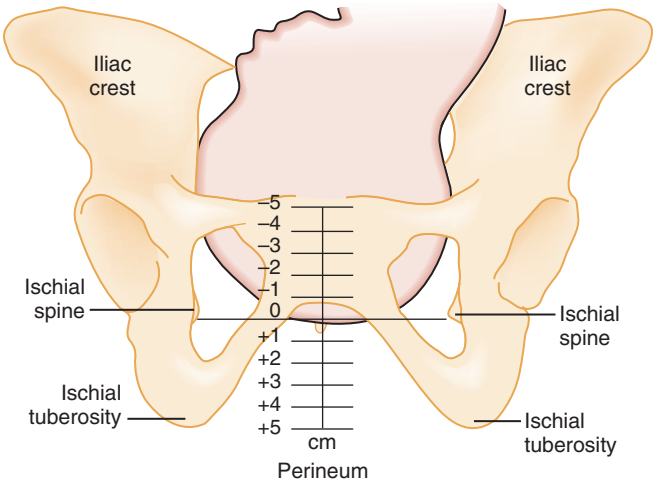


Figure 179-4. Fetal stations. The level of the ischial spines is considered "0" station. The silhouette of the infant's head is shown approaching station +1. (Courtesy of Ross Laboratories, Columbus, Ohio.)

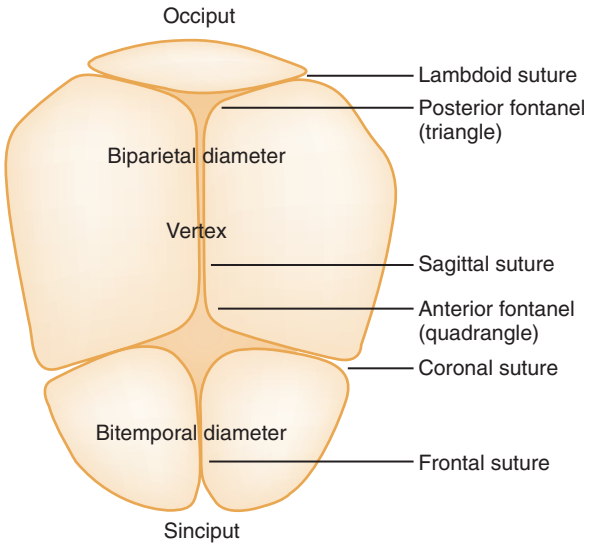


Figure 179-5. Bony landmarks of the fetal skull. (Modified from Willson JR, et al: Obstetrics and Gynecology, 9th ed. St. Louis, Mosby, 1991.)

The accurate determination of the stage of labor depends on examination of the cervix. A sterile approach using sterile gloves, a sterile speculum, and povidone-iodine (Betadine) solution is indicated to prevent ascending infection, such as chorioamnionitis. On pelvic examination, the clinician should determine the following:

1. *Effacement* refers to the thickness of the cervix. A paper-thin cervix is 100% effaced.
2. *Dilation* indicates the diameter of the cervical opening in centimeters. Complete, or maximum, dilation is 10 cm.
3. *Position* describes the relationship of the fetal presenting part to the birth canal. The most common position of the head is occiput anterior.
4. *Station* indicates the relationship of the presenting fetal part to the maternal ischial spines (Fig. 179-4).
5. *Presentation* specifies the anatomic part of the fetus leading through the birth canal.

In 95% of all labors, the presenting part is the occiput, or vertex. On digital exam, a smooth surface with 360 degrees of firm bony contours and palpable suture lines is noted. Palpation of the suture lines and the fontanels where they join allows the examiner to determine in which direction the fetus is facing. Three sutures radiate from the posterior fontanel, and four radiate from the anterior fontanel (Fig. 179-5). The lateral margins should be examined carefully for fingers or facial parts that indicate compound or brow presentations.

When the clinician suspects rupture of membranes, a sterile speculum examination should be performed. This may reveal pooling of amniotic fluid. Two tests used to confirm the presence of amniotic fluid include a fernlike pattern when the fluid is allowed to dry on a microscope slide and the use of nitrazine paper, which should turn blue, indicating an alkaline amniotic fluid (pH > 6). Although vaginal blood, cervical mucus, semen, and infection can interfere with results, sensitivities of both nitrazine paper and ferning in detecting amniotic fluid are nearly 90%.[19]

Of note, if vaginal bleeding is evident, both digital and speculum examination of the pelvis should be deferred until ultrasound can be obtained to rule out placenta previa.

Second Stage of Labor

The second stage of labor is characterized by a fully dilated cervix and accompanied by the urge to bear down and push with each uterine contraction. The fetal station is advanced to +3, with crowning of the presenting part as expulsion begins. Stage 2 uterine contractions may last 1 or 2 minutes and recur after a resting phase of less than 1 minute. The median duration of this stage is 50 minutes in nulliparous women and 20

minutes in multiparous women. More rapid progression through stage 2 should be anticipated for low-birth-weight premature infants. A prolonged second stage of labor is defined as more than 3 hours in nulliparous women if regional anesthesia is administered, more than 2 hours in nulliparous women without anesthesia or multiparous women with regional anesthesia, and more than 1 hour in multiparous women without regional anesthesia.[20] Prolonged second stage of labor is associated with an increase in maternal complications, including postpartum hemorrhage, infection, and severe vaginal lacerations.[21]

Antenatal Fetal Assessment. The assessment of any woman in the third trimester includes an assessment of fetal well-being. After 24 weeks' gestation, the fetal condition should affect clinical decision-making. During labor and delivery, the identification of fetal distress and appropriate intervention can reduce fetal morbidity and mortality.

There are currently three methods of assessing a fetus in utero. Clinical monitoring, electrical monitoring, and ultrasonography all have a role in the assessment of the fetus.[22,23] External electrical monitoring and ultrasonography merit consideration for use in the care of women laboring in the ED. The machinery for both technologies is portable and easy to use, making them attractive to the emergency physician.[24,25] These modalities can provide real-time information helpful for diagnosing fetal distress and assisting with intrapartum decision making.

Electronic Fetal Monitoring. Intrapartum fetal assessment by electronic fetal monitoring is most useful during stage 1 of labor. Electronic fetal monitoring confirms labor and may help diagnose fetal distress. Tracings of fetal heart rate and uterine activity provide information that, when combined with clinical data, can presage fetal damage and provide a window for intervention.

Uterine activity is measured transabdominally via a pressure transducer, creating a recording of the contraction frequency. Because the measurements are indirect, the strength of the contractions correlates poorly with the tracing. The tracings are position and placement sensitive. Documentation of organized cyclic uterine contractions confirms the onset of labor and rules out Braxton Hicks contractions that are too disorganized to register in this manner. Premature onset of labor can also be diagnosed. Finally, this type of external electrical monitoring may be used to determine the efficacy of administered tocolytic agents.

Fetal heart rate tracings have several components that can be assessed: baseline heart rate, variability, accelerations, decelerations, and diagnostic patterns. Baseline heart rate, by definition, is maintained for 15 minutes in the absence of a uterine contraction and is the most important aspect of fetal heart rate monitoring.

Variability can be instantaneous (beat-to-beat) or long term over intervals of 1 minute or more. Both types of variability are indicators of fetal well-being. Accelerations of heart rate are an important component of long-term variability. Accelerations occur during fetal movement and reflect an alert, mobile fetus. Brief periods of umbilical cord compression also can cause accelerations by decreasing the venous return and reflexively generating fetal tachycardia. Meanwhile, decreased variability may indicate fetal acidemia and hypoxemia or may be a side effect of a wide array of drugs. Analgesics, sedative-hypnotics, phenothiazines, and alcohol have all been reported to cause decreased variability.

Decelerations in fetal heart rate are more complicated, and their interpretation must be integrated with the clinical situation. There are three types of deceleration: variable, early, and late (Fig. 179-6). These terms refer to the timing of the deceleration relative to the uterine contraction.

Variable and early decelerations are common. Present on more than 50% of all tracings, these heart rate changes can represent physiologic reflexes associated with head compression in the birth canal or intermittent cord compression. Variable decelerations that are persistent and repetitive usually indicate repeated episodes of umbilical cord compression. The resultant hypoxia and acidosis may cause fetal distress. Attempts to shift maternal and fetal weight off the umbilical cord by changing position are indicated. If these variable decelerations continue, the situation calls for efforts to hasten the delivery or, if obstetric backup becomes available, to perform an emergency cesarean section.

Late decelerations are more serious and most often indicate uteroplacental insufficiency. The tracing contours are generally smooth, with the heart rate nadir occurring well after maximal uterine contraction. The lag, slope, and magnitude of late decelerations correlate with increasing fetal hypoxia. Late decelerations are particularly ominous in association with poor variability, nonreactivity, and baseline bradycardia. Immediate delivery to prevent further hypoxia is indicated when these findings are present. The need for newborn resuscitation should be anticipated and preparation for critical care established for these deliveries. Overall, 30% of infants with late decelerations have good outcomes. The remaining 70% have suboptimal outcomes related to either the underlying pathologic condition or hypoxia.

Finally, the clinician should be aware of the significance of sinusoidal tracings. Tracings of this type have low baseline heart rates and little beat-to-beat variability. The sinusoidal tracing is an ominous finding that is often premorbid. The differential diagnosis includes erythroblastosis fetalis, placental abruption, fetal hemorrhage (trauma), and amnionitis.

Ultrasonography. Ultrasonographic techniques have wide application in obstetric care. In the third trimester or during labor, ultrasonography can provide crucial information pertaining to impending delivery. When a technician and radiologist are available, the gestational age, biophysical profile, amniotic fluid index, as well as a survey of fetal and placental anatomy may be discerned (Table 179-1).[25-27] The parameters of

Table 179-1 Biophysical Profile: 30 Minutes of Ultrasonographic Observation

ELEMENT ASSESSED	NORMAL SCORE = 2	ABNORMAL SCORE = 0
Fetal heart rate reactivity	2 accelerations >15 beats/min for >15 sec	<2 accelerations
Amniotic fluid index	1 pocket >1 cm in orthogonal planes	No large pockets
Fetal muscle tone	1 episode of active flexion-extension with full return to flexed posture	<1 episode or slow, incomplete actions
Body movements	3 discrete moves	≤2
Breathing motions	1 episode of fetal breathing of at least 60 sec duration during 30 min of observation	No breathing activity *or* The absence of 1 episode of fetal breathing of at least 60 sec duration during 30 min of observation

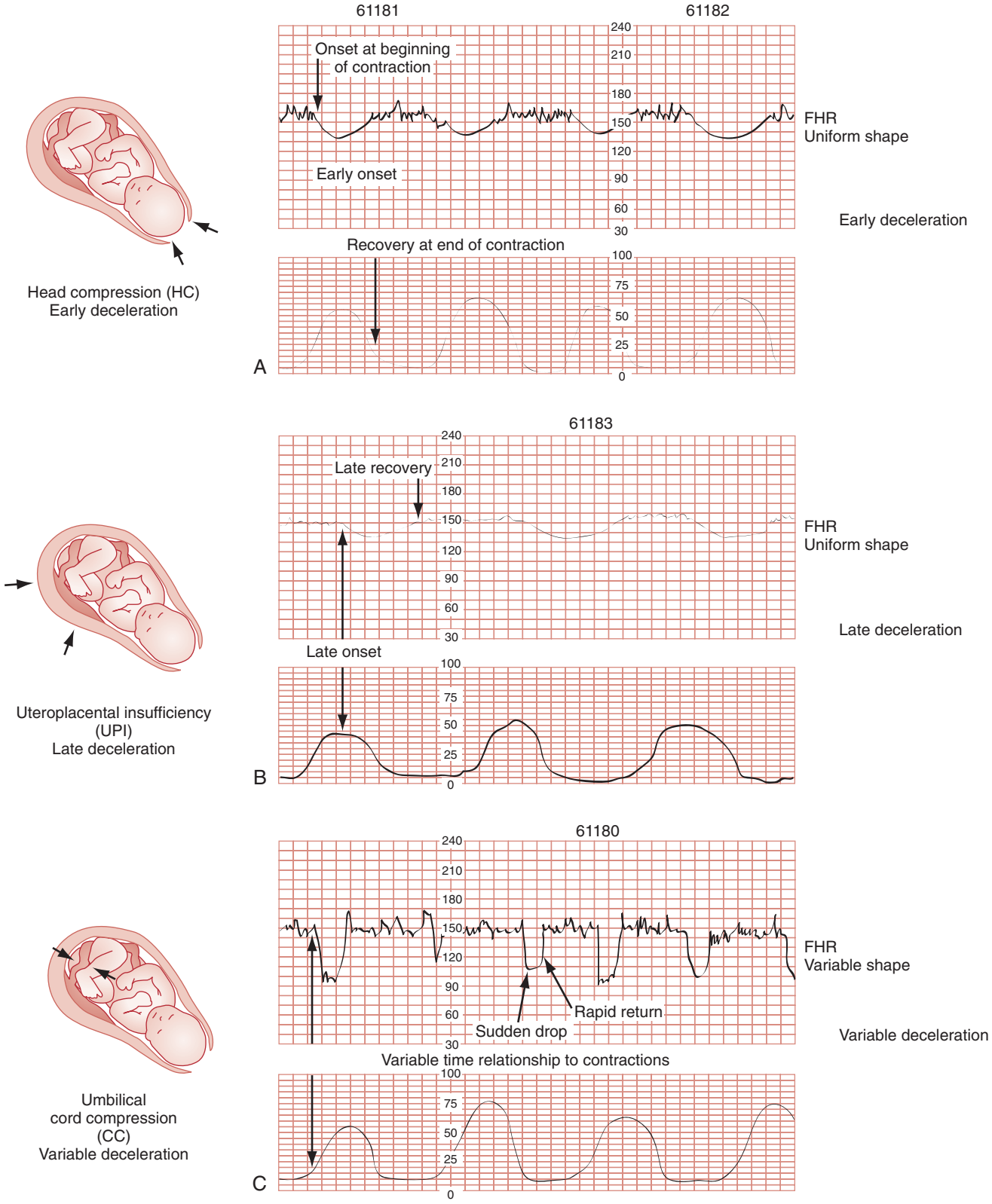


Figure 179-6. Deceleration patterns of the fetal heart rate (FHR). **A,** Early deceleration caused by head compression. **B,** Late deceleration caused by uteroplacental insufficiency. **C,** Variable deceleration caused by cord compression. (Modified from Lowdermilk DL, et al: Maternity and Women's Health Care, 6th ed. St. Louis, Mosby, 1997.)

BOX 179-2 THIRD-TRIMESTER ULTRASONOGRAPHY: POSSIBLE INDICATIONS

- Determine number of fetuses
- Establish fetal presentation
- Identify fetal heart motion
- Locate placenta
- Measure amniotic fluid
- Determine gestational age
- Survey fetal anatomy
- Diagnose cord prolapse
- Diagnose third-trimester bleeding
- Rule out abruption

immediate interest in the ED are fetal viability (specifically in utero gestation and fetal heart rate), lie, and presentation. Ultrasonography may also reveal multiple gestations, allowing for preparation and early communication with other specialists (from obstetrics, neonatology, and anesthesia).[28] In 1991, the American College of Obstetricians and Gynecologists made recommendations regarding the indications for ultrasonography in the third trimester (Box 179-2). A 2- to 5-MHz transducer is appropriate for all bedside transabdominal sonographic assessments. Transvaginal ultrasonography is relatively contraindicated in the peripartum period, particularly in the cases of premature rupture of membranes and placenta previa.[28]

Delivery. As stage 2 of labor progresses, preparation for delivery should be underway. A radiant warmer should be available and heated. Neonatal resuscitation adjuncts, such as a towel, scissors, umbilical clamps, bulb suction, airway management equipment (oxygen, bag/mask device with appropriate-sized masks, and endotracheal intubation and suctioning equipment for meconium), and equipment to achieve vascular access, should be available. Most deliveries require only basic equipment to cut and clamp the umbilical cord, suction the mouth and nose, and dry and stimulate the infant. A nurse should be at the bedside to coach and provide reassurance to the mother.

The mother should be placed in the dorsal lithotomy position and prepared for delivery. The Sims position, or left lateral position with knees drawn toward the mother's chest and back to the physician, is also an acceptable position for delivery. The vulva and perineum are cleared and gently scrubbed, directing all mucoid debris and feces away from the introitus. A repeat sterile examination to assess labor progression and confirm presentation may be performed. Some firm digital stretching of the perineum, particularly posteriorly, may prevent tears and lacerations later in delivery.

Controlled, coordinated expulsion with coaching to sustain each push aids with crowning and delivery of the head. When the fetus is crowning, care should be exercised to have the delivery occur in a slow, controlled manner. Precipitous delivery is more likely to cause maternal injuries, such as perineal, rectal, urethral, labial, vaginal, and uterine lacerations, and fetal injuries.[29,30]

The most vulnerable moment is when the fetal head begins to stretch and distend the perineum. Instructing the mother to pant and not push slows the passage of the head and the shoulders as indicated. Calm communication between the physician and the mother is the best way to maintain control of the delivery. With a controlled delivery, routine performance of an episiotomy is not recommended. Instead, use of the modified Ritgen maneuver facilitates most normal deliveries.[30]

In the modified Ritgen maneuver, a towel-draped, gloved hand is used to stretch the perineum and gently exert pressure on the chin of the fetus. The second hand puts pressure on the occiput superiorly, guiding the head into slight extension. When at the perineum, this slight extension of the head promotes delivery by positioning the head so that its smallest diameter passes through the pelvic outlet and perineum.

After the head is delivered, the physician should allow the head to rotate toward the maternal thigh and clear the fetal face and airway. Bulb suctioning of the nares and oropharynx optimally is done before proceeding with the delivery. Clearing the oropharynx at this time minimizes the likelihood of aspiration of blood, meconium, and debris collected during descent through the birth canal. Coordination with the mother is important to prevent uncontrolled fetal expulsion.

Next, the shoulders, usually anterior shoulder first, clear the perineum. The shoulders often deliver spontaneously, with little effort by the physician. First, gentle downward traction on the head promotes delivery of the anterior shoulder. A subsequent upward motion pulls the posterior shoulder through the pelvic outlet, minimizing maternal trauma. If delay occurs in delivery of the shoulders, the potential for shoulder dystocia should be considered.

As the infant clears the perineum, attention focuses on the umbilical cord. The infant should be kept low or at the level of the perineum to promote blood flow into the infant from the placenta. The cord is clamped and cut. Clamps should be placed 4 or 5 cm apart, with the proximal clamp 10 cm from the infant's abdomen. An adequate umbilical stump is important for venous access if the child requires resuscitation.

The infant is now clear of the mother and can be wrapped in towels and moved to the warmer. Gentle drying with a towel and suctioning usually provide adequate respiratory stimulation. If not, flicking the soles of the feet and rubbing the back are other modalities. Apgar scores at 1, 5, and 10 minutes after birth should be documented.

Episiotomy. Previously, the need for episiotomy in normal deliveries was an area of controversy. The original potential benefit of episiotomy included the substitution of a straight surgical incision for a ragged, uncontrolled traumatic laceration. Theoretically, the surgical approach decreased the incidence of severe rectovaginal tears. This rationale led to widespread routine episiotomy, with a medial incision used in the United States and a mediolateral incision used in the Commonwealth countries.

Recent literature has shown that both types of incisions increase maternal morbidity and are no longer recommended for uncomplicated deliveries. Women receiving episiotomies have been shown to have a higher incidence of perineal trauma and maternal blood loss during delivery and more pelvic pain, sexual dysfunction, and urinary incontinence in the postpartum period.[31]

Episiotomy should be performed only for specific indications, such as shoulder dystocia or breech delivery. When the decision is made to use an episiotomy, the procedure should be done before excessive stretching of the perineal muscles occurs but near the time of delivery to avoid excessive bleeding. Common practice is to cut the episiotomy when the head is visible during a contraction and the introitus opens to a diameter of 3 or 4 cm. Most authors currently recommend a mediolateral incision to avoid perineal tears and rectal involvement; this is particularly true for a complicated delivery in which lacerations extending the surgical incision are likely (Fig. 179-7).

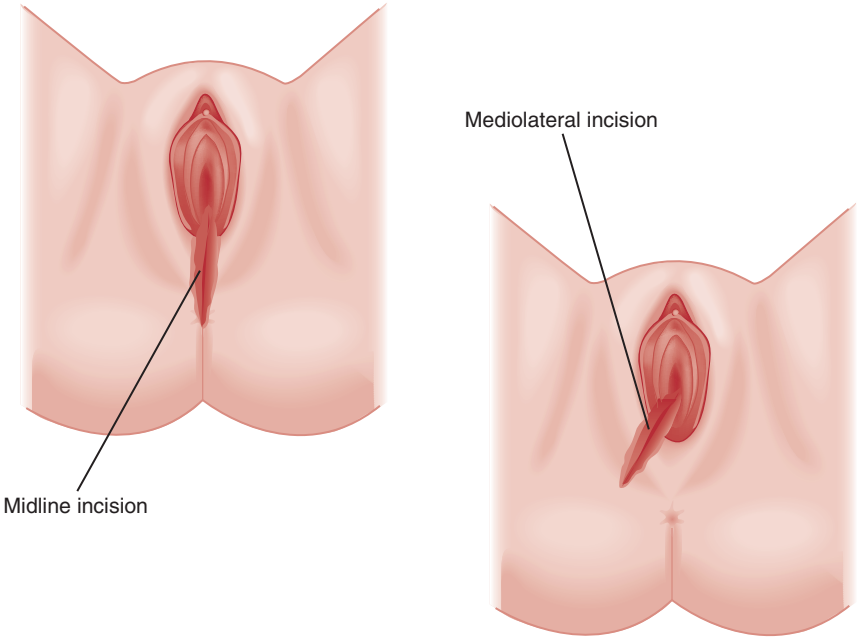


Figure 179-7. Mediolateral episiotomy incision is preferred over a strictly midline incision. (Redrawn from http://www.aurorahealthcare.org/healthgate/images/exh44028a_ma.jpg.)

Table 179-2 summarizes some of the adjuncts used in normal labor and delivery, with recommendations regarding their use in the high-risk setting of an ED delivery.

Third Stage of Labor

The third stage of labor involves the delivery of the placenta and is a time of patient observation with frequent checks of the tone and height of the uterine fundus. Signs of placental separation include the following:

1. The uterus becomes firmer and rises.
2. The umbilical cord lengthens 5 to 10 cm.
3. There is a sudden gush of blood.[32]

These signs usually occur within 5 to 10 minutes of the delivery of the infant but may extend to 30 minutes. Beyond 18 minutes, the risk of postpartum hemorrhage increases and is, in fact, up to six times more likely after 30 minutes.[33] Although the placenta may be delivered expectantly, active management reduces the length of the third stage of labor and thereby decreases the risk of postpartum hemorrhage. Active management includes the administration of uterotonics, gentle traction of the clamped umbilical cord with mild pressure applied above the symphysis pubis, and uterine massage after delivery.[34] Be aware that any attempt to deliver the placenta before it separates is contraindicated.

Examination of the placenta and umbilical cord is an essential part of the delivery process. Abnormalities of the cord should be noted at this time. Also, a segment of the umbilical cord should be kept available as a source of cord blood.

Normally a three-vessel structure, the umbilical cord is filled with a connective tissue known as *Wharton's jelly* and is approximately 50 to 60 cm long and 12 mm in diameter. Normal architecture places the two umbilical arteries on either side of the single umbilical vein. A two-vessel cord (one umbilical artery) occurs in 1 of 500 deliveries, is more common in African Americans, and is a result of aplasia or atrophy. Approximately

Table 179-2 Risk-Benefit Analysis of Routine Adjuncts to Normal Labor and Delivery

PRACTICE OR PROCEDURE	RISK	BENEFIT	UTILITY IN THE ED
NPO status and IV hydration	Fluid overload, osmolar and acid-base disturbances	Venous access, decreased risk of aspiration	Yes
Enemas	Time-consuming	Reduced pain caused by constipation	Minimal to none
Pubic shaving	Infections and irritation	None	None
Nitrous oxide analgesia	Incomplete pain control	Self-administered, minimal fetal side effects, noninvasive	Yes
Narcotic analgesia	Neonatal depression	Excellent pain control	As needed
Regional anesthesia	Technically difficult, incomplete pain control	Excellent pain control when technically successful (paracervical or pudendal block)	Variable (operator-dependent)
Electronic fetal monitoring	Increased incidence of surgical intervention	Early diagnosis of fetal distress	Variable (operator-dependent)
Ultrasonography	None	Rapid augmentation of database	Yes (operator-dependent)
Amniotomy	Augmented labor, prolapsed umbilical cord	None	No
Episiotomy	Poor maternal outcomes	None for uncomplicated delivery	No
Ritgen maneuver	None	Decreased birth trauma	Yes

IV, intravenous; NPO, nothing by mouth.

30% of two-vessel cord infants have congenital defects. An association also exists between fetal structural anomalies and placental vascular occlusion or thrombosis.[35]

The placenta should also be examined for abnormalities. Clots adherent to the uterine aspect may indicate placental abruption. Accessory lobes (succenturiate placenta if completely separate) and abnormal cord insertion are common abnormalities. The umbilical cord and placenta routinely should be held for pathologic review.[36] The discovery of an incomplete placenta or membranes should alert the emergency physician to the possibility of postpartum complications and should be documented.

Fourth Stage of Labor

The fourth stage of labor refers to the first hour after delivery of the placenta and is a critical period because postpartum hemorrhage is most likely to occur during this time. Thus, careful examination and repair of any vaginal lacerations should be performed. The cervix and vaginal fornices should be visually inspected to avoid missing deep lacerations as a result of delivery.

At this point, oxytocin is infused to promote contraction of the uterus and control hemorrhage. The uterus should be evaluated frequently for tone and massaged transabdominally if any sign of relaxation exists. Oxytocin should not be given before delivery of the placenta because this may result in the trapping of placental fragments or may hinder the delivery of an undetected twin.

BOX 179-3 FACTORS LINKED TO PRETERM LABOR

Demographic and Psychosocial
Extremes of age (>40 yr, teenagers)
Lower socioeconomic status
Tobacco use
Cocaine abuse
Prolonged standing (occupation)
Psychosocial stressors

Reproductive and Gynecologic
Prior preterm delivery
Diethylstilbestrol exposure
Multiple gestations
Anatomic endometrial cavity anomalies
Cervical incompetence
Low pregnancy weight gain
First-trimester vaginal bleeding
Placental abruption or previa

Surgical
Prior reproductive organ surgery
Prior paraendometrial surgery other than genitourinary (appendectomy)

Infectious
Urinary tract infections
Nonuterine infections
Genital tract infections (bacterial vaginosis)

SPECIFIC DISORDERS

Third-Trimester Complications Associated with Delivery

Obstetric problems in the third trimester often result in the initiation of labor. Premature labor, premature rupture of membranes, and third-trimester bleeding are relatively common complications. The fundamental question to be addressed in these settings is whether the fetus would fare better in utero or delivered.

Premature Labor

Premature, or preterm, labor and fetal immaturity are the leading causes of neonatal mortality. *Preterm labor* is defined as uterine contractions with cervical changes before 37 weeks of gestation. Women with premature labor are a heterogeneous group. Many underlying conditions result in preterm labor, which accounts for 11% of all pregnancies but 70% of all perinatal mortality.[37] Factors linked to this problem include substance abuse, reproductive history, uterine anomalies, iatrogenic complications, infections, and lifestyle or psychosocial stressors (Box 179-3).[38] The unexpected nature of premature labor often results in an ED visit. When delivery is not imminent, the patient can be moved to the obstetrics unit for further care.

Clinical Features. The diagnosis of preterm labor requires the identification of uterine activity and cervical changes before 37 weeks of gestation. Early maternal signs and symptoms include an increase or change in vaginal discharge, pain resulting from uterine contractions (sometimes perceived as low back pain), pelvic pressure, vaginal bleeding (usually bloody show), and fluid leak.

Diagnostic Strategies. If uterine contractions and cervical changes are present and the estimated fetal weight on ultrasonography is less than 2500 g, the diagnosis of premature labor is likely. The differentiation of false labor (Braxton Hicks contractions) from true labor is best done by electrical monitoring. Ultrasonography may also aid in the diagnosis because fetal breathing movements make the diagnosis of false labor unlikely. The initial evaluation of a woman with possible preterm labor should include urinalysis, complete blood count, and pelvic ultrasonography. If delivery is not imminent, these studies can be performed in the ED or obstetrics area, whichever would provide the best monitoring. When possible, these patients should be transferred to a perinatal center with an associated intensive care unit.

Management. A viable fetus and healthy mother are indications for medical management directed toward the prolongation of gestation. Preterm labor should not be postponed with medical management in the cases of intrauterine demise, major congenital anomalies, eclampsia, or, most important, PROM.[38] When patients with PROM, fetal disorders, and maternal contraindications are excluded, only one fourth of all women in premature labor are candidates for medical management.[39]

The treatment of preterm labor involves multiple modalities. Tocolytics to palliate labor and fetal maturation therapy combined with bedrest and hydration are used in hopes of prolonging pregnancy (Box 179-4). These patients optimally should be transferred to an appropriate center before delivery whenever possible because medical management fails in more than 25% of preterm patients in whom it is attempted.[40]

Tocolysis. The two classically used tocolytics were magnesium sulfate and beta-mimetic drugs. Other medications that have been shown to be as or more effective include prostaglandin synthetase inhibitors (nonsteroidal anti-inflammatory drugs [NSAIDs]) and calcium channel blockers.[41,42] When indicated and in coordination with an obstetric consultant, tocolytics initiated in the ED may arrest premature labor, preventing imminent delivery in 75 to 80% of patients for 48 to 72 hours.[37]

BOX 179-4 COMMONLY USED TOCOLYTIC AGENTS

Magnesium sulfate
- 4–6 g IV bolus over 30 min
- 2–4 g/hr IV infusion

Terbutaline
- 5–10 mg PO q4–6 h
- 0.25–0.5 mg SC q 30 min–6 h
- 10–80 µg/min IV

Ritodrine*
- 10 mg PO q2–4 h
- 5–10 mg IM q2–4 h
- 50–350 µg/min IV

Isoxsuprine
- 20 mg PO q4–6 h
- 0.05–0.5 mg/min IV

IV, intravenously; SC, subcutaneously; PO, orally.
*Ritodrine is currently discontinued in the United States.

BOX 179-5 CONTRAINDICATIONS TO TOCOLYSIS

Absolute
- Acute vaginal bleeding
- Fetal distress (not tachycardia alone)
- Lethal fetal anomaly
- Chorioamnionitis
- Preeclampsia or eclampsia
- Sepsis
- Disseminated intravascular coagulopathy

Relative
- Chronic hypertension
- Cardiopulmonary disease
- Stable placenta previa
- Cervical dilation >5 cm
- Placental abruption

Table 179-3 Drug and Labor Interactions

DRUG	EFFECT ON LABOR
Barbiturates	In anesthetic doses can stop labor
Alcohol	Decreases oxytocin release, smooth muscle relaxant
Cocaine	Increased prematurity, placental infarction
Caffeine or aminophylline	Increased duration of labor
Narcotics	Increased latent phase, slow dilation (minimal effect once in active labor)
Atropine, scopolamine	Lower uterine segment relaxation, decreased frequency of contractions
Halothane	Strong inhibition of labor
IV nitroglycerin	Profound uterine relaxation

IV, intravenous.

Magnesium Sulfate. Magnesium sulfate competitively inhibits calcium uptake into smooth muscle and allows relaxation. Women treated with magnesium require monitoring. Magnesium produces respiratory and neurologic depression at elevated levels, exacerbated by renal insufficiency. Pulmonary edema and cardiac dysrhythmias have also been reported.[37] These effects can be reversed rapidly by the administration of calcium-containing solutions (i.e., 1 g of 10% calcium gluconate solution). Because women with premature labor are at risk for ascending infections, early treatment with antibiotics is often indicated during magnesium therapy (Table 179-3).[43]

Beta-Mimetics. Beta-mimetics (ritodrine and terbutaline) cause smooth muscle relaxation by activating enzymes that bind calcium to the sarcoplasmic reticulum. This effect is mediated by $beta_2$-receptors that increase cyclic adenosine monophosphate concentrations in the myometrium. The beta-mimetic is titrated to effect since the dosage needed to eliminate uterine activity is unpredictable and varies. Only side effects limit beta-mimetic administration. They freely cross the placenta and cause fetal tachycardia. In one meta-analysis, beta-mimetics and magnesium sulfate had similar efficacy in eliminating contractions.[42]

Pulmonary edema is the main adverse effect of high-dose beta-mimetics. This complication is more likely to occur in mothers with preexisting cardiac disease, multiple gestations, and maternal infection. This form of pulmonary edema is high-output failure and tends to occur when there is sustained maternal tachycardia greater than 120 beats/min. Beta-mimetics should be gradually titrated according to uterine activity and maternal heart rate. Eventually, tachyphylaxis and receptor down-regulation decrease the effectiveness of these drugs over 24 to 48 hours.[40]

$Beta_1$-related side effects can be problematic in diabetic mothers. $Beta_1$ stimulation can lead to diabetic ketoacidosis and the usual cascade of metabolic and electrolyte abnormalities.[44] Surveillance of the urine for glucose and ketones is recommended. Fetal heart stimulation can result in increased cerebral perfusion pressures. A premature infant's central nervous system vasculature is delicate and may not tolerate these changes. Beta-mimetics are associated with an increased incidence of fetal intraventricular hemorrhage.[45]

NSAIDs. The prostaglandin synthetase inhibitors, specifically indomethacin and sulindac, have been shown to be as or more effective than magnesium and the beta-mimetics in multiple trials. However, in the fetus, pulmonary hypertension, patent ductus arteriosus constriction, renal insufficiency, necrotizing enterocolitis, and intraventricular hemorrhage have been reported with NSAID use. Potential maternal side effects include a prolonged bleeding time and renal insufficiency.[42,46]

Calcium Channel Blockers. Calcium channel blockers have also been used as tocolytics with success. Nifedipine or nicardipine may be given. Onset is more rapid than that of magnesium, and the maternal and fetal side effect profiles are good.[41,42]

Aggressive titratable tocolytics are best for the initial 24 to 48 hours of preterm labor. After uterine contractions have been stopped, the patient can usually be maintained on oral agents, although the benefits of maintenance tocolysis, studied to date primarily with beta-mimetics and magnesium, have yet to be shown.[42] The contraindications to tocolytics are important to review before initiating these therapies (Box 179-5). Any patient receiving tocolytics should be externally monitored (electrically) for signs of fetal distress.

Premature Rupture of Membranes

Clinical Features. PROM, also known as *amniorrhexis*, is defined as rupture of the amniotic and chorionic membranes before the onset of labor. PROM affects 3% of all gestations.[47] During pregnancy, the chorionic and amniotic membranes protect the fetus from infection and provide an environment that allows fetal growth and movement. The amniotic fluid is constantly exchanged by fetal swallowing and urination and umbilical cord transfer. The fetal airway also contains a secreted fluid that allows for fetal breathing movements, promoting fetal

respiratory development. This fluid is produced at 5 mL/kg/hr at term gestation and is resorbed rapidly by the pulmonary lymphatics, blood vessels, and upper airway at birth.

The word *premature* in PROM refers to rupture before labor, not to fetal prematurity. In 10 to 15% of PROM cases, the fetus is at or near term, and PROM may result in normal labor. When PROM is associated with fetal prematurity, there is significant fetal morbidity and mortality. PROM is the inciting event in one third of all preterm deliveries.

After the membranes rupture, the period from latency to the onset of labor varies. Longer latent periods are common earlier in pregnancy, and the latency shortens as gestational age increases. At term, labor is a desirable result of PROM, but with fetal immaturity labor is problematic because delivery would result in fetal complications, such as hyaline membrane disease.

Diagnostic Strategies. The diagnosis of PROM usually can be established by history and physical examination. The patient usually describes a spontaneous gush of watery fluid followed by a mild persistent seepage. In most cases, the patient suggests the diagnosis and usually is correct. Urinary incontinence or excess vaginal or cervical secretions are occasionally confused with PROM.

Examination of women with potential PROM should be performed under sterile conditions to prevent ascending infection. Direct digital examination of the cervix should be avoided. The incidence of infection has been shown to be proportional to the number of examinations. The identification of amniotic fluid was previously discussed. Table 179-4 summarizes the bedside testing modalities available to confirm the diagnosis of PROM. Visualization of the cervix for prolapsed cord or abnormal fetal presentation (prolapse of a small part) should be done during the uterine evaluation for effacement and dilation. Cultures for group B streptococci, *Chlamydia*, and gonorrhea should be obtained.

Management. When the diagnosis of PROM is established, management depends on several factors: gestational age and maturity of fetus, the presence of active labor, the presence or absence of infection, the presence of placental abruption, and the degree of fetal well-being or distress.[48] Obstetric consultation and admission are indicated.

Gestational age may be well known by menstrual history and previous ultrasonographic scans. In the absence of such data, immediate ultrasonography provides an estimated gestational age quickly. Fetal maturity is a more complex determination. Beyond 36 weeks of gestation, fetal pulmonary maturity is likely. If the gestational age is less than 36 weeks, testing the amniotic fluid for the lecithin-to-sphingomyelin ratio or for phosphatidylglycerol can establish maturity. Fluid pooling in the posterior vaginal vault can be used for this purpose.

In the immature fetus (24–31 weeks of gestation), administration of corticosteroids can accelerate pulmonary maturation. The benefit of this strategy has been shown with preterm labor; however, this therapy is less well documented for PROM. In PROM, treatment with steroids seems to decrease the incidence and severity of hyaline membrane disease, but it may increase the risk of maternal infectious complications. Rupture of the membranes also stimulates fetal lung maturation, making it more difficult to establish a treatment benefit in PROM compared with preterm labor. When gestational age is less than 26 weeks, the latent interval to delivery is often 1 week. Tocolytics are an obvious choice, but their use is controversial. When tocolytics are used, the goal is to temporize, allowing time for therapy to take effect. These treatment decisions should be coordinated with the receiving obstetrician.

All patients with PROM should be assessed for intra-amniotic infection. Infectious complications should be diagnosed and treated before the mother develops overt clinical signs of infection. Preterm PROM is usually treated with intravenous penicillin and erythromycin. Treatment of term PROM is indicated when the patient is group B streptococcus positive or has not been tested. The signs and symptoms of chorioamnionitis are late manifestations of advanced infection and are discussed next.[48]

Table 179-4 Bedside Testing for Premature Rupture of Membranes

METHOD	RESULT
Nitrazine	Amniotic fluid pH 7.1–7.3 turns nitrazine paper yellow; >7.3 is blue
Ferning	Amniotic fluid crystallizes
Smear combustion	Amniotic fluid, when flamed, turns white and crystallizes
	Vaginal secretions caramelize and turn brown

Chorioamnionitis

Chorioamnionitis occurs when vaginal or cervical bacteria ascend into the uterus, instigating an inflammation of the chorion and amnion layers of the amniotic sac.[49] It occurs in 1 to 10% of all pregnancies, and risk factors include prolonged labor, premature rupture of membranes, excessive vaginal examinations, and recent amniocentesis. Box 179-6 summa-

BOX 179-6 Chorioamnionitis Evaluation

Fluid in Vaginal Vault
Phosphatidylglycerol

Cervical Cultures
Escherichia coli and other gram-negative bacteria
Neisseria gonorrhoeae

Vaginal Cultures
Chlamydia spp.
Mycoplasma hominis
Group B streptococci
Ureaplasma urealyticum

Amniocentesis Studies
Gram's stain (group B streptococci)
Culture
Glucose
Lecithin-to-sphingomyelin ratio

Maternal Signs and Symptoms
Premature rupture of membranes
Uterine tenderness
Fever
Tachycardia
Malodorous vaginal discharge
Leukocytosis

Fetal Signs and Symptoms
Decreased activity
Abnormal biophysical profile (ultrasonographic examination)
Fetal tachycardia
Decreased variability of fetal heart rate

rizes the findings and evaluation of chorioamnionitis. Chorioamnionitis may result in prolonged first- and second-stage labor and decreased responsiveness to oxytocin. Early, aggressive treatment, even before evidence of infection occurs, decreases neonatal morbidity and delays delivery, allowing fetal maturation.[50,51]

Vertical Transmission of Human Immunodeficiency Virus

Emergency deliveries may involve women who are known to be HIV positive in addition to women who are infected but have never been tested. The latter group generally includes pregnant women with little or no prenatal care who are at risk for precipitous delivery. Transmission may occur in the antepartum, intrapartum, or postpartum period (breast-feeding). Because intrapartum transmission accounts for up to 75% of vertically transmitted HIV infections, antiretroviral therapy upon presentation, even while labor progresses, can decrease vertical HIV transmission.[52] Potential mechanisms of transmission include microtransfusion during contractions, absorption of virus through the mucous membranes, and even invasion through the epithelium. Risk factors for transmission include high viral loads, prolonged rupture of membranes, maternal drug use, vaginal delivery, and breast-feeding (Table 179-4).[53,54]

In November 2002, the Food and Drug Administration approved the OraQuick Rapid HIV-1 Antibody Test (OraSure Technologies, Bethlehem, Pa).[55] Point-of-care testing for HIV with a median turnaround time of 45 minutes realistically allows the clinician to initiate intrapartum and neonatal antiretroviral therapy when the test is positive. As usual, serologic confirmation is recommended, but emergent interventions can proceed based on the bedside result.[56] Since 1994, it has been known that immediate treatment during labor can significantly decrease vertical transmission to the newborn.[57,58]

A positive HIV test in some cases may allow for a change in the method of delivery. Cesarean section decreases the rate of HIV transmission compared with vaginal delivery methods. In a 1999 meta-analysis from the United States and Europe, vertical HIV transmission was decreased by cesarean section with an odds ratio of 0.43 (95% confidence interval, 0.33–0.56). The protective effect of surgical delivery over other delivery methods persisted even when the data were stratified for receipt of antiretroviral therapy.[59] This finding was tempered by a reported increase in maternal morbidity and mortality in HIV-positive women undergoing cesarean section, namely an increased incidence of endometritis, maternal sepsis, pneumonia, and transfusion. Therefore, cesarean section may be reserved for only high viral load patients.[60]

Ideally, decisions regarding the mode of delivery and the need for antiretroviral therapy can be made before the rupture of membranes. The risk of transmission increases after that time and continues to increase as the fetus traverses the birth canal.[61] When antiretroviral therapy and elective cesarean section are employed, the likelihood of vertical transmission is reduced by 87% compared with that for women receiving neither intervention.[59]

This relatively new diagnostic and therapeutic burden on the emergency physician faced with an imminent delivery is challenging. Data indicate that antiretroviral treatment and the mode of delivery make labor a true emergency for an HIV-positive patient. In addition, pregnant women with advanced HIV disease have a higher incidence of premature births, postpartum endometriosis, and perinatal mortality.[54]

Currently, the main obstacle to this type of care is the availability of point-of-care HIV testing. Since the late 1990s, the results supporting this approach have become increasingly robust and seem to justify the efforts.[62,63]

Complicated Delivery

Perspective

Complicated deliveries, involving dystocia, malpresentation, and multiple gestations, are potentially life-threatening emergencies. The emergency physician cannot "solve" these obstetric problems with cesarean section and will therefore face the prospect of an extremely high-risk vaginal delivery. As expected, these abnormal deliveries increase the risk of fetal and maternal complications. Aggressive attempts to obtain obstetric, neonatal, and anesthesia support are warranted. If the delivery proceeds in the ED, preparations for maternal and neonatal resuscitation should be made rapidly.

Principles of Disease

Knowledge of abnormal labor and its anatomy and physiology is important for the clinician facing a complicated delivery. Intrapartum management skills will enable the emergency physician to proceed with delivery in an efficient, capable manner.

Dystocia and Malpresentation. Dystocia, or abnormal labor progression, accounts for one third of all cesarean sections and half of primary cesarean sections. Because rapid surgical resolution is unavailable to the emergency physician, intrapartum management skills are important.

Dystocia can be divided into three etiologic categories. Labor fails to progress when there are problems related to the pelvic architecture (the passage), when there are fetal size or presentation problems (the passenger), and when uterine expulsive forces are inadequate. Although it is useful to consider these causes independently, dystocia is usually caused by a combination of factors. Presentation problems are particularly important because they become apparent during stage 2 of labor and require immediate action.

In order of increasing incidence, brow, face, shoulder, and breech presentations are the most common malpresentations (Table 179-5). True fetopelvic disproportion is much less common. Cesarean section is indicated when labor arrest or cord prolapse coexists with these presentations.[64]

Breech Delivery

Perspective. Breech is the most common malpresentation, occurring in approximately 4% of all deliveries. Three types of breech presentation exist: frank, incomplete, and complete (Fig. 179-8; Box 179-7). The main mechanical problem with breech presentations is that the buttocks and legs do not provide a sufficient wedge, hindering cervical accommodation of the relatively larger head. In addition, because the presenting part does not completely occlude the cervical opening, umbilical cord prolapse may occur.

The terminology for breech deliveries is complicated. By convention, the presentation (frank, incomplete, and complete) is followed by the relationship of the fetus to the birth canal, using the fetal sacrum as a reference point. The mode of delivery used also has specific terminology. *Spontaneous breech delivery* refers to vaginal delivery without manual aid,

Table 179-5 Relative Incidence of Malpresentations

MALPRESENTATION	INCIDENCE
Breech presentation	1/25 live births
Shoulder dystocia	1/300 live births
Face presentation	1/550 live births
Brow presentation	1/1400 live births

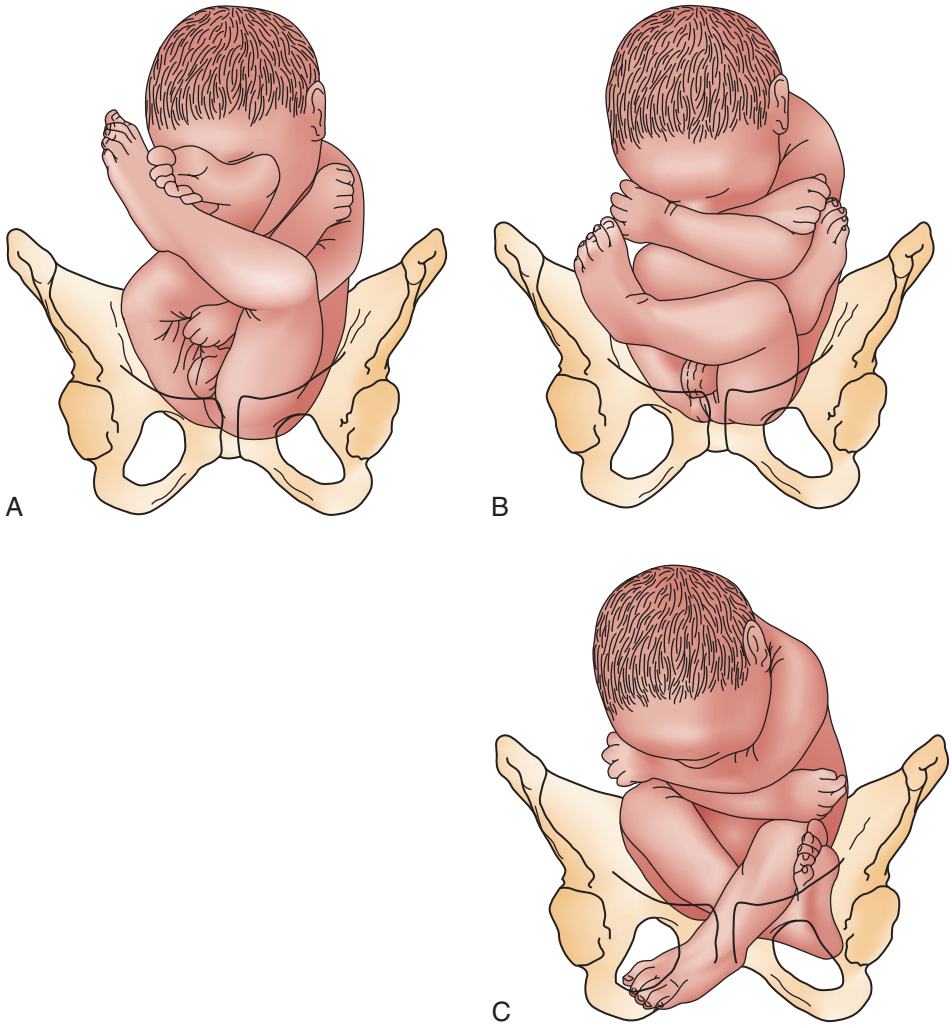


Figure 179-8. Breech presentations. **A,** Frank breech presentation. **B,** Complete breech presentation. **C,** Incomplete breech presentation. (Modified from Cunningham FG, et al: Williams Obstetrics, 19th ed. Norwalk, Conn, Appleton & Lange, 1993.)

BOX 179-7 BREECH PRESENTATIONS

Frank Breech
60–65% of all breech presentations
Hips flexed, knees extended
Buttocks act as good dilating wedge
Incidence of cord prolapse approximately 0.5%

Complete Breech
Least common, occurs in approximately 5% of all breech presentations
Hips and knees flexed
Buttocks act as good dilating wedge
Incidence of cord prolapse is 5–6%

Incomplete Breech
25–35% of all breech presentations
Incomplete hip flexion, single or double footling
Poor wedge
Increased incidence of prolapsed cord (15–18%)

almost always of a small premature infant. *Assisted breech delivery* and *partial breech extraction* are terms that apply when delivery is manually assisted after the umbilicus clears the perineum. The head may be delivered by intrapartum maneuvers or forceps. *Complete breech extraction* consists of the application of traction to the lower extremities or groin before delivery of the buttocks. This approach is never indicated for a singleton breech because it increases the chances of head entrapment. Confusion arises because the word *complete*, as used here, describes the mode of delivery, not the presentation.

Slightly less than 4% of deliveries are breech. Correlated with this abnormal presentation are several factors: prematurity, multiparity, fetal abnormalities, prior breech presentation, polyhydramnios, and uterine abnormalities.[65]

Overall, one third of breech fetal deaths are believed to be preventable. Asphyxia is often due to umbilical cord prolapse or entrapment of the head. Fetal head and neck trauma can occur if inappropriate delivery techniques are used. Scheduled cesarean section for these patients reduces the potential for emergency room presentation. Since the 1990s, however, obstetricians have been attempting to decrease cesarean rates. As part of this process, some centers have proposed a trial of labor and vaginal delivery for selected full-term infants with frank breech presentations.[66] Therefore, the potential for the emergency physician to encounter a breech presentation may be increasing.

Diagnostic Strategies. Before labor, Leopold's maneuvers facilitate the diagnosis of breech presentation. In the case of breech presentation, Leopold's first maneuver identifies a firm, round mass (the head) in the fundus of the uterus. The third maneuver reveals the softer breech at the pelvic inlet. For the emergency physician, active labor restricts the use of Leopold's maneuvers; thus, vaginal examination is required.

The differentiation of a vertex presentation from a breech by tactile vaginal examination is not always simple. Any time

a fontanelle is not identified on examination, a breech presentation should be suspected. During the vaginal examination, it is helpful to remember that the face and the skull have a complete circle of bone, whereas the anus is flanked by bone on only two sides.

If time allows, immediate ultrasonographic studies or plain radiographs are indicated to obtain information on the position of the fetal arms and neck. If the fetus has a hyperextended neck, vaginal delivery is associated with a 70% incidence of spinal cord injuries. If possible, labor should be delayed to allow cesarean section.[67] Likewise, if the arms are over the head, they increase the dystocia when the head enters the birth canal. If ultrasound reveals anencephaly or massive hydrocephaly, vaginal breech delivery should be allowed to continue because cesarean section is undesirable.

Management. Premature infants in the breech position often deliver spontaneously without difficulty. As the infant comes to term, dystocia becomes increasingly common. When committed to a vaginal delivery, knowledge of breech dystocia mechanics may allow atraumatic delivery. The key goals are to maximize the size of the passage and to minimize the dystocia of the aftercoming head. Box 179-8 summarizes the actions associated with successful vaginal breech delivery.

The Mauriceau maneuver is the use of the fetal oral aperture to flex the fetal neck and draw in the chin. Because fetal neck extension is associated with cord injuries and worsening dystocia, this maneuver is crucial to successful vaginal delivery. While the Mauriceau maneuver is used, the fetal pelvis should be supported to avoid abdominal injuries. Generous episiotomy may even be necessary to facilitate the Mauriceau maneuver in a full-term infant. If the aftercoming head cannot be delivered quickly, the chances of good fetal outcome are poor. For term infants, labor arrest, asphyxia, and/or brachial plexus injuries are potential complications of vaginal breech deliveries.

BOX 179-8 VAGINAL BREECH DELIVERY

Actions to Do as Able

Monitoring fetal heart rate
Focused history
Diagnosis of breech lie
Cervical dilation and station determination
Ultrasonography or plain radiography
Evaluation for prolapsed cord if spontaneous rupture of membranes
Episiotomy
Knee flexion and sweep out legs
Pulling out a 10- to 15-cm loop of cord (room to work) after umbilicus clears perineum
Use of bony pelvis as means of holding infant
Keeping face and abdomen away from symphysis, and using rotation to deliver the more accessible arm
Mauriceau maneuver

Actions to Avoid

Inappropriate transfer with delivery en route
Misdiagnosis of cervical dilation
Iatrogenic rupture of membranes (cord prolapse)
Moving patients or leaving unmonitored
Traction on the fetus during delivery
Grasping fetus by the waist, causing abdominal organ injury
Arm entrapment over head
Neck hyperextension

Shoulder Dystocia

Perspective. Shoulder dystocia is the second most common malpresentation, occurring in 1 in 300 deliveries. In contrast to a breech presentation, which may be diagnosed antepartum, shoulder dystocia develops intrapartum. Maternal and fetal factors are associated with shoulder dystocia. Maternal factors include diabetes, obesity, and prolonged second stage of labor; fetal factors include macrosomia, postmaturity, and erythroblastosis fetalis. The combination of prenatal data, estimated fetal weight, and fetal biometry cannot reliably identify most deliveries complicated by shoulder dystocia. The fact that shoulder dystocia responds well to a variety of intrapartum maneuvers means that delivery skill is an important determinant of fetal outcome.

The consequences of shoulder dystocia can be devastating. As with breech presentation, infant complications are more common and severe than maternal complications. Asphyxia, traumatic brachial plexus injuries, and humeral and clavicular fractures contribute to a complication rate of 20%.[68] Maternal complications are related to traumatic delivery and include vaginal, perineal, and anal sphincter tears as well as urinary incontinence.[69]

Diagnostic Strategies. Shoulder dystocia is diagnosed clinically by the inability to deliver either shoulder. The fetal head may appear to retract toward the maternal perineum. This finding is known as the "turtle sign." Traction on the head extends and abducts the shoulders, increasing the bisacromial diameter and worsening the dystocia. Figure 179-9 shows the normal and abnormal relationship of the shoulders to the birth canal and illustrates why the bisacromial diameter is an important element of fetal biometry.

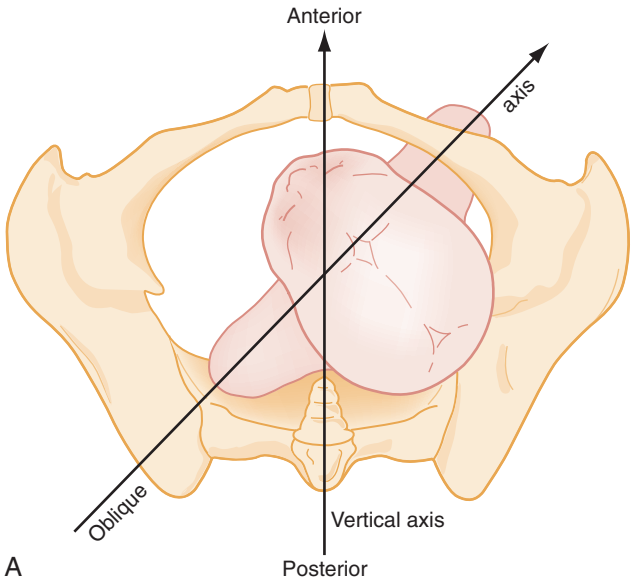
Normally, the shoulders negotiate the maternal pelvis in sequential fashion, anterior shoulder first. With shoulder dystocia, both shoulders attempt to clear the maternal pelvis simultaneously. In addition to the turtle sign, examination often reveals that the fetal shoulders are on a vertical axis (rather than oblique). These findings in combination with an arrested delivery confirm the diagnosis of shoulder dystocia.[70]

Management. When shoulder dystocia becomes evident, knowledge of intrapartum delivery maneuvers can be lifesaving. Successful vaginal delivery is most likely when a directed sequential approach to each maneuver is used. Rapid resolution of shoulder dystocia is important to avoid fetal asphyxia and resultant central nervous system injury. A head-to-body time interval over 6 to 8 minutes is considered critical in the development of these sequelae.[68] Obstetric and neonatology assistance may improve the outcome, and aggressive attempts to obtain help in these areas are warranted.

Initial attempts to resolve shoulder dystocia involve increasing the anteroposterior diameter of the passage. An episiotomy may be used for fetal maneuvering by allowing access to the posterior shoulder. Anteriorly, draining the bladder with a Foley catheter can generate room.

The most important first step is to use the McRoberts' maneuver (Fig. 179-10). Maternal leg flexion to a knee-chest position may disengage the anterior shoulder, allowing rapid vaginal delivery to follow. This maneuver "walks" the pubic symphysis over the anterior shoulder and flattens the sacrum, helping the fetus to pass through the birth canal one shoulder at a time. This method, although requiring very little effort, is successful in 40% of shoulder dystocia cases when used alone.[71]

If the McRoberts' maneuver does not free the anterior shoulder, suprapubic pressure may accomplish the goal. Pressure may slip the anterior shoulder beneath the pubis or cause the posterior shoulder to retreat into the hollow of the sacrum. Digital pressure on the posterior shoulder (via the episiotomy) may help facilitate posterior shoulder retreat.



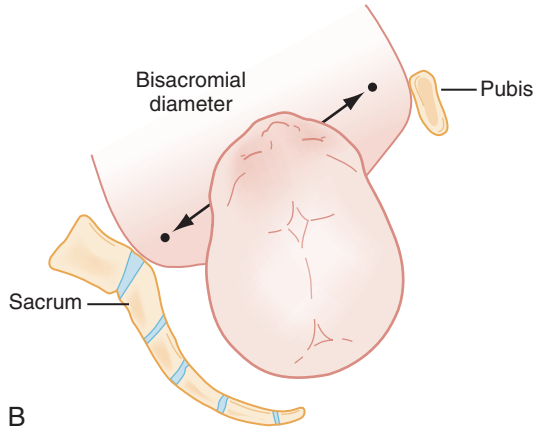


Figure 179-9. **A,** Normal delivery. As the fetal head rotates, the shoulders assume an oblique position and enter the pelvis one at a time. **B,** Shoulder dystocia. Both shoulders attempt to clear the pelvis simultaneously, forcing the bisacromial diameter into the opening.

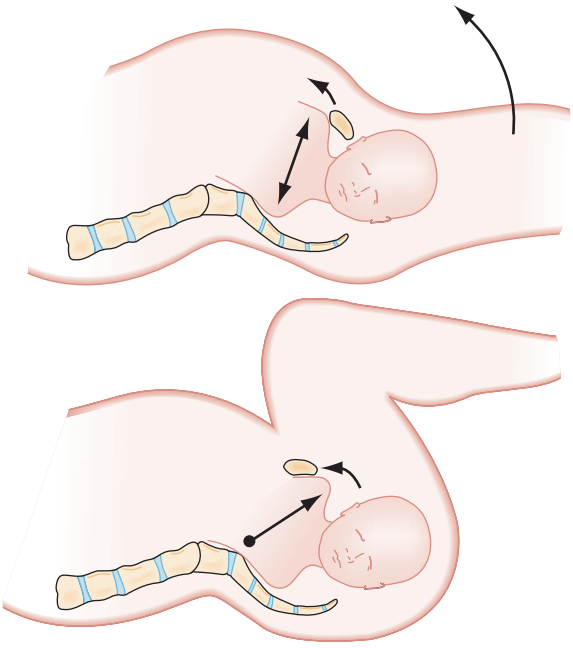


Figure 179-10. McRoberts' maneuver. **Top,** Bisacromial diameter pinned behind pubic symphysis. **Bottom,** Removing the maternal legs from the stirrups and putting the knees up to the chest fulcrum the pubic symphysis over the impacted anterior shoulder.

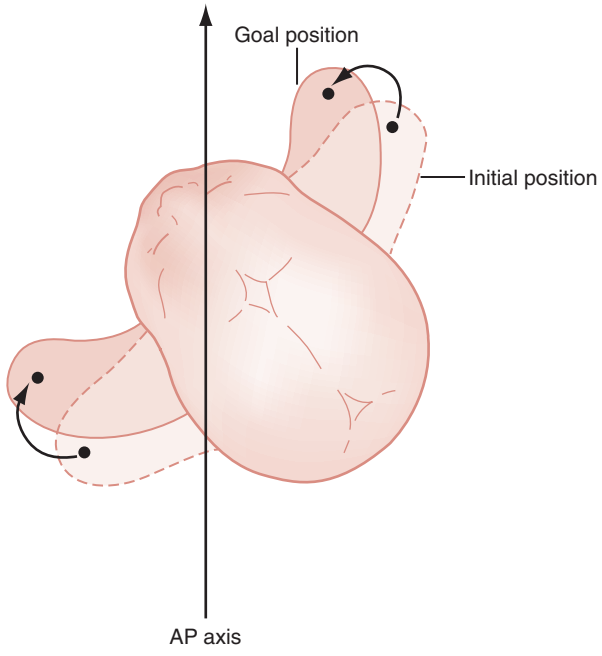


Figure 179-11. Rubin's maneuver decreases the bisacromial diameter. AP, anteroposterior.

Use of these intrapartum maneuvers resolves most cases of shoulder dystocia. However, if delivery is still impossible, more drastic interventions are warranted. Decreasing the bisacromial diameter may be possible by pushing the most accessible shoulder toward the fetal chest (Rubin's maneuver; Fig. 179-11). Often, both shoulders assume the same attitude, decreasing the bisacromial diameter and allowing delivery. Attempts to manipulate the shoulders for Rubin's maneuver may be transabdominal, via the introitus (anterior shoulder), or via the episiotomy (posterior shoulder).

If the shoulders remain undeliverable, the next step is to use Wood's corkscrew maneuver. In this process, the impacted shoulders are released through rotation of the fetus 180 degrees. Fetal rotation is achieved by pushing the most accessible shoulder in toward the chest.[72] The fetal axilla can be snared with a digit, or a hand can be slid in along the fetal spine to sweep the hips and generate rotation. Wood's corkscrew maneuver is difficult to perform but should be attempted before reaching for an arm. A slightly oblique anteroposterior position for the shoulders provides the largest passage through the pelvic outlet.

At this juncture, if the fetus remains trapped and several attempts have failed to yield delivery, consideration of delivery of an arm is appropriate. A hand is introduced along the posterior aspect of the posterior shoulder. This would be a tight fit, requiring tactile identification of fetal anatomy. The posterior arm is swept across the chest, bringing the fetal hand up to the chin. Attempts to splint the humerus may prevent fractures and brachial plexus injuries. The fetal hand is grasped and pulled out of the birth canal across the face, delivering the posterior shoulder. The mnemonic *HELPER* (Box 179-9) has been proposed to help keep these steps organized and to

BOX 179-9 HELPER MNEMONIC FOR SHOULDER DYSTOCIA

Help
Obstetrics, neonatology, anesthesia
Episiotomy
Generous, possibly even episioproctotomy
Legs flexed
McRoberts' maneuver
Pressure
Suprapubic pressure, shoulder pressure
Enter vagina
Rubin's maneuver or Wood's maneuver
Remove posterior arm
Splint, sweep, grasp, and pull to extension

facilitate a sequential approach. These steps successfully deliver almost all cases of shoulder dystocia.

Face, Brow, and Compound Presentations. Face and brow presentations yield a larger engaging aspect of the fetal head and predispose to labor arrest. Although these abnormal presentations can be diagnosed with ultrasonography or Leopold's maneuvers, most are discovered during labor via vaginal examination. Approximately half are discovered during the second stage of labor.

The engaging diameter of the head in vertex position is approximately 0.8 cm less than a face presentation and 1.5 cm less than a brow presentation. Face presentations are described using the chin as a reference point (e.g., mentum anterior). Face presentation is managed expectantly. The obstetric adage "if a face presentation is progressing, leave it alone" arises from the fact that mentum anterior presentations usually deliver vaginally and mentum transverse presentations frequently rotate to become mentum anterior. Brow presentations, occurring when the fetal head is partially flexed, also spontaneously convert to vertex or face presentations in more than 50% of cases.[65]

A persistent mentum posterior face and brow presentation cannot be delivered vaginally if the fetus is full term. The resultant labor arrest requires symphysiotomy or cesarean section. Prolongation of the second stage is the most common outcome of both of these malpresentations at term. For the emergency physician, this prolonged second stage may provide a window during which obstetric help may arrive.

Compound presentations are those in which an extremity enters the birth canal with the head or breech. Small and premature fetuses generally proceed to vaginal delivery without incident.

Labor arrest and umbilical cord prolapse are accepted indications for cesarean section in the setting of face, brow, and compound presentations. Manipulation of a compound presentation, including attempts to reduce the hand or arm, increases the rate of cord prolapse. Therefore, manipulation attempts are contraindicated. Cord prolapse rates are 10 to 20% even without manipulation. Close monitoring and careful examination are indicated.

Multiple Gestations

Perspective. Although twin gestations accounted for less than 1% of all deliveries historically, there has been a recent increase in the frequency of twin and triplet or higher births (65 and 500%, respectively) due to the increasing use of infertility treatments.[73] In 2003, twin deliveries accounted for 31.5 per 1000 live births. Because multiple gestation deliveries have a higher incidence of preterm labor and low birth weights, both maternal and fetal complication rates are correspondingly increased.[74]

Diagnostic Strategies. Most women with multiple gestations have the situation identified well before the third trimester. In patients who have had little or no prenatal care, bedside ultrasonography allows rapid diagnosis and early preparation. The stages of labor for twins and other multiple gestations are similar to the stages for a singleton. Nulliparous women experience longer labors than multiparous women, with an overall labor duration that is similar to that of singleton pregnancies. Of importance to the emergency physician is a relatively short latent phase of labor, with rapid progression to the active phase. The active phase is usually longer, however. The prolongation of the active phase is due to overdistention of the uterus plus malpresentation and may allow time for obstetric assistance to arrive.

Vertex twin A and vertex twin B occur in approximately 40% of deliveries. In the remaining 60%, one or both of the twins has a malpresentation, usually twin B.[75] Delivery problems with twin B cause most of the preventable perinatal mortality of twin gestation.[76]

Management. The presentation of the twins is an important determinant for the safety of vaginal delivery. Twins who are vertex-vertex, the most common presentation, can be delivered vaginally. If twin B is nonvertex, some obstetricians recommend cesarean section to prevent delivery-related complications for twin B. External cephalic version may also be attempted to convert twin B to a vertex lie and then proceed to vaginal delivery. Breech extraction is a third, more difficult, option. The general consensus is that if twin A is nonvertex, cesarean section is the preferred route. In such cases, efforts should be made to delay delivery until an operative approach can be used.[77,78] Proceeding vaginally can result in the "stuck twin" syndrome and lead to poor outcome.

The interval between the delivery of twin A and twin B is variable. Although in most cases twin B delivers in minutes, prolonged interdelivery times with good fetal outcomes have been reported. When twin B does not follow rapidly, in utero assessment is important to document fetal well-being. If fetal heart tracings are reassuring, the delivery of twin B (especially nonvertex) should not be hastened. Repeat ultrasonographic evaluation may be utilized to confirm twin B's presentation and well-being during the interdelivery period.

After every emergency department delivery, particularly deliveries that are precipitous or that occur in the out-of-hospital setting, the mother should be examined for the possibility of twins. Ongoing labor may be confused with postpartum cramping, only to have twin B and all of the potential complications surprise the clinician. This situation is particularly relevant for women with inadequate prenatal care and low-birth-weight infants.

Umbilical Cord–Related Emergencies

Perspective

Umbilical cord–related complications can occur in normal and abnormal deliveries. Immediate intervention is required to prevent fetal morbidity and mortality. The spectrum of cord-related emergencies includes prolapsed cord, nuchal loops of the umbilical cord, body coils, cord knots, and entangled cords in monoamniotic twins. Cord length is believed to be proportional to fetal activity in utero during the first and second trimesters. Excess cord length increases the potential for umbilical cord complications of all types. Because the umbilical cord supplies the fetus with all of its oxygen, interruption of cord circulation before establishment of fetal respiration is a life-threatening emergency. Fetal asphyxia caused by cord

Table 179-6 Conditions Associated with Umbilical Cord Prolapse

PRESENTATION	INCIDENCE (%)
Vertex	0.14
Breech	2.5–3.0
Frank breech	0.4
Complete breech	5
Incomplete breech	10
Shoulder	5–10
Compound	10–20
Face or brow	Rare

circulation compromise is potentially preventable with appropriate delivery interventions.

Umbilical Cord Prolapse

Clinical Features. Umbilical cord prolapse occurs when (1) the umbilical cord precedes the fetal presenting part or (2) the presenting part does not fill the birth canal completely. Most instances of cord prolapse are unexpected and develop during the second stage of labor.

Cord prolapse has a variable rate of association with different fetal presentations. Compound, shoulder, and breech presentations all yield gaps and a relatively poor dilating wedge. Table 179-6 summarizes the rates of umbilical cord prolapse with various fetal presentations. Overall, malpresentations account for 50% of cord prolapse cases; therefore, prolapse may be the first indication of a malpresentation.[79] The incidence of cord prolapse is reported to range from 0.3 to 0.6% of all deliveries and associated perinatal mortality ranges from 8.6 to 49%.[80,81]

Diagnostic Strategies. Umbilical cord prolapse may be overt or occult, requiring a pelvic examination to reveal the umbilical cord lying beside the presenting part. The diagnosis also may be made with Doppler ultrasonography. In most cases, the diagnosis is obvious, and the cord is encountered at the perineum or introitus.

Management. Whenever a prolapsed cord occurs with a viable infant, cesarean section is the delivery method of choice. If surgical delivery is available, maneuvers to preserve umbilical circulation should be instituted immediately. The mother should be placed in the knee-chest position with the bed in Trendelenburg as the presenting part is digitally elevated off the umbilical cord.[82] It is crucial that the mother be instructed *not* to push, to avoid further compression of the cord. Placement of a Foley catheter and instillation of 500 to 750 mL of saline into the bladder may help lift the fetus off the cord, particularly in the first stage of labor.

Preparation for an emergency ("crash") cesarean section should be underway. The time from prolapse to surgical intervention is an important factor in fetal outcome. Perinatal mortality rates of approximately 15% are reported for prolapsed cord deliveries; however, if cesarean section can be done within 10 minutes, the mortality rate decreases to 5%.[83] These numbers have implications for the availability of obstetric and surgical backup for the ED.

If surgical delivery cannot be done in a timely fashion, funic reduction (manual replacement of the cord into the uterus) and rapid vaginal delivery may be the only options available. The same maneuvers to decrease cord compression are used, and the umbilical cord is pushed gently, in a retrograde fashion, above the presenting part. Manipulation and cord trauma should be kept to a minimum because the resultant vasospasm can cause fetal hypoxia. After funic reduction, the development of umbilical cord body coils or nuchal loops is common and should be anticipated.[84]

Subsequent to delivery, the physician should be prepared for resuscitation of a distressed newborn. If one is available, a neonatologist should attend the delivery.

Cord Entanglement

The umbilical cord can also become entangled with itself, spontaneously knotting. Umbilical cord knots are related to intrauterine movements early in pregnancy. Approximately 4 or 5% of stillbirths are found to have knots that are believed to have caused fetal demise. Despite this association, cord knots can persist without problems as long as perfusion is maintained.

Loose umbilical cord knots pulled tight at delivery may cause fetal distress. As with cord prolapse, this situation must be resolved quickly to prevent fetal asphyxia. Rapid delivery with avoidance of further cord traction optimizes fetal outcome. No specific interventions exist to deal with this problem.

Long umbilical cords are associated with true knots as well as entanglements and prolapse. Because the fetal limbs are short and flexed in most presentations, they are rarely involved. Loops around the neck and body do occur, however. Umbilical cord loops can be single or multiple, and there are reports of six nuchal loops. Risk factors for excessive cord length include increasing parity and fetal weight. Although generally benign, they may result in fetal complications, such as nonreassuring fetal status and respiratory distress.[85]

During delivery, loose nuchal cords should be reduced at the perineum. Loose body coils usually disentangle spontaneously. The reduction process may be aided by slipping them over the extremities or forward over the head. Occasionally, loops are tight enough to impede delivery and cannot be reduced. The solution is to cut the clamped cord and deliver the infant rapidly. The high frequency of nuchal loops (one in five births) means that the emergency physician should expect to encounter this problem.

Maternal Complications of Labor and Delivery

Perspective

Maternal complications of labor and delivery include postpartum hemorrhage, uterine inversion and rupture, amniotic fluid embolism, infections, and more. Many of these problems can be managed nonsurgically. When severe, however, these complications threaten the reproductive future and the life of the mother, and they may require emergent surgical intervention.

Postpartum Hemorrhage

Clinical Features. Postpartum hemorrhage is the most common complication of labor and delivery. Defined as hemorrhage greater than 500 mL, it affects 5 to 10% of all deliveries and accounts for up to 25% of obstetric deaths.[86,87] Postpartum hemorrhage is divided into primary and secondary categories. The primary category includes blood loss that occurs within the first 24 hours, and the secondary category is hemorrhage 24 hours to 6 weeks after delivery. The clinical picture is as expected with any type of hemorrhage, although due to maternal adaptations during pregnancy, the patient may not show signs of shock until more than 1500 mL of volume is lost.[88]

Differential Considerations. The differential diagnosis of primary postpartum hemorrhage includes uterine atony, genital tract trauma, retained placental tissue, and coagulopathies, or the "four Ts": tone, trauma, tissue, and thrombin.

Uterine Atony. The most common cause of serious immediate postpartum hemorrhage is laxity of the uterus after delivery. It accounts for 75 to 90% of postpartum hemorrhage cases.[89] Postpartum bleeding from the placental implantation site normally is limited by contraction of the myometrium, constricting the spiral arteries. If the uterus cannot or does not contract, ongoing hemorrhage will occur. Predisposing factors include overdistention of the uterus (multiple gestations and polyhydramnios), prolonged labor, chorioamnionitis, use of tocolytics, and general anesthesia with halogenated compounds. Despite the myriad causes, uterine atony is a diagnosis of exclusion. Physical examination to rule out obstetric trauma and retained products of conception must be done before reaching the diagnosis. On examination, the uterus is palpable as a soft, boggy mass.

After other causes have been excluded, therapy to augment myometrial contraction should be instituted to prevent further hemorrhage. Two-handed uterine massage may stimulate uterine contraction. One hand exerts pressure transabdominally while the other supports the uterus via the introitus. Uterotonics in conjunction with massage usually provide enough stimuli to control bleeding. Blood should be typed, crossmatched, and available for resuscitation should these measures fail.

Maternal Birth Trauma. Maternal birth trauma is the second most common cause of postpartum hemorrhage, accounting for 20% of the cases. Uncontrolled delivery, macrosomia, and malpresentation all may result in maternal birth-related trauma. Although genitourinary structures are most commonly involved, any part of the birth canal–associated anatomy may be injured, with resultant postpartum hemorrhage. Tears and lacerations may involve the perineum, rectum, cervix, vagina, vulva, and urethra. Blood vessels beneath the vulvar or vaginal epithelium can also be injured without frank hemorrhage, resulting in the formation of large, contained hematomas. These hematomas may go unrecognized for hours, gradually enlarging and eventually resulting in hemorrhagic shock. This type of hemorrhage should be suspected whenever there is evidence of ongoing blood loss and no identifiable obstetric site of bleeding (a firm uterus and negative examination for lacerations). Delayed postpartum hemorrhage at these sites can also occur and is often a diagnostic challenge.

Tears. Vaginal tears, especially posteriorly over the ischial spines, should be diagnosed early by postpartum exploration rather than hours later when the mother is hemorrhaging. The vulva, including periurethral structures, should be examined. Although minor tears may be left, any laceration involving subcutaneous tissue should be repaired with absorbable suture.

The most common sites of tears are the vaginal, perineal, and rectal structures. Tears are classified as first, second, third, and fourth degree. First-degree tears involve the perineal skin and vaginal mucous membranes without involvement of the underlying fascia and muscle. Second-degree lacerations extend through the skin into the fascia and muscles of the perineal body but not into the rectal sphincter. Third-degree tears involve the skin, mucous membranes, perineal body, and anal sphincter. Fourth-degree tear involvement extends through all layers, including the rectal mucosa. These lacerations are also associated with tears in the region of the urethra.

The repair of these tears and the repair of episiotomies are virtually identical. Commonly, repair of the episiotomy is delayed until the placenta is delivered, which allows an uninterrupted approach to potentially complicated repairs. The goal of these repairs is to restore anatomy and provide hemostasis with a minimum of suturing. Third-degree and fourth-degree tears should be repaired by the obstetrician in an operating room.

Retained Products of Conception. Approximately 10% of postpartum hemorrhage cases are due to retained placental tissue. Normally, the plane of cleavage between the zona basalis and the zona spongiosa results in clean separation of the placenta from the uterus. When this occurs, the placental tissue delivers as a single unit, without evidence of fragmentation. Occasionally, accessory placental tissue exists as succenturiate placenta, but this also should cleave normally and deliver spontaneously.

Any placental defect or evidence of accessory placental tissue may signify a retained cotyledon. Retained fragments prevent myometrial constriction and result in hemorrhage. Inappropriate traction on the placenta during stage 3 of labor can result in tears with retained products of conception, which may cause immediate and delayed postpartum hemorrhage. Ultrasonography may be utilized in the diagnosis of retained placenta, with an empty or fluid-filled uterus providing a high negative predictive value and an expanded endometrium or solid echogenic masses within the uterus providing evidence of retention.[28,90]

Treatment requires removal of the remnant placental tissue. Digital uterine exploration with blunt dissection of the fragments from the myometrium allows myometrial contraction. Normal placental tissue cleaves away easily, allowing removal. Abnormally adherent tissue is not freed by this mechanism.

Placenta Accreta, Increta, and Percreta. Placenta accreta, increta, and percreta describe various degrees of abnormal placental attachment to the uterus. Placental villi may invade the myometrium at the site of implantation, firmly rooting the placenta and obliterating the normal cleavage plane. Thus, abnormal attachment results in retained products of conception and postpartum hemorrhage. When the placenta adheres to the myometrium without the intervening decidua basalis, it is termed *placenta accreta*. In *placenta increta*, the villi extend into the myometrium. In *placenta percreta*, the placenta penetrates the full thickness of the myometrium.[91]

The incidence of these placental disorders is 1 in 2000 to 7000 deliveries. Placenta accreta occurs in 80% of these cases. Associated risk factors include multigravidity, prior cesarean sections, placenta previa, previous curettage, and uterine infections.

Management

Uterine Exploration and Placental Removal. In the face of ongoing hemorrhage and retained products of conception, attempts to remove the placenta manually are indicated. The procedure entails risk of infection, perforation, and increased hemorrhage but may be the most expeditious way to control bleeding.[92] Before beginning, the patient should be on a monitor, good vascular access should be established, and blood products should be available.

The umbilical cord is traced through the cervical os to the placenta, allowing the identification of a placental margin. The placental membranes are digitally perforated, and the placenta is gradually divided from the myometrium. The palmar surface of the hand should be directed toward the placenta, taking care to avoid uterine perforation. After placental removal, the uterus should be explored for retained cotyledons. Removal of any further fragments still present requires curettage of the uterine cavity by an obstetrician. Placenta accreta, percreta, and increta may be diagnosed in this way because these are not digitally dissectible.

Once emptied, the uterus can be stimulated to contract. Uterine massage, oxytocin, and prostaglandins all may be used.

Uterine Packing. Uterine packing to decrease postpartum hemorrhage was widely used previously but now is uncommon. For the emergency physician, this technique may be used to create tamponade, preventing further blood loss. The procedure has limited morbidity and is straightforward. The physician introduces 15 to 20 yards of 4-inch gauze with a ring forceps and packs it into the uterus using a layering technique. A special "uterine packer" is available to help direct gauze high into the uterus but is not necessary.

Opponents of packing point out that an atonic uterus may accommodate a large volume of packing and blood without effective tamponade. Packing may also increase the risk of postpartum infection even when prophylactic antibiotics are given. As with all uterine manipulation and instrumentation, some risk of perforation also exists. Because dilation and curettage and hysterectomy sometimes are not available to the emergency physician, the importance of uterine packing as an option is increased. This approach is a temporizing measure.[93]

Pelvic Vessel Embolization. Pelvic bleeding postpartum can be difficult to control. Hysterectomy as a solution results in infertility and brings with it all the complications of general anesthesia and major surgery. Radiographic embolization of the bleeding vessels by an interventional radiologist is another option. The procedure does not require an anesthesiologist, operating room, or obstetrician and may, in fact, be more available on an emergent basis. The success rate of embolization is estimated to be 90%.[94]

A catheter is placed in the aorta and fluoroscopically guided to the bleeding sites that are imaged by radiopaque dye. The vessels are embolized with absorbable gelatin sponges placed via the catheter. Common sites of bleeding include the uterine artery, pudendal artery, and hypogastric artery. Because only the smallest involved branches are embolized and recanalization usually occurs, future reproductive capability is generally preserved.[95]

Uterotonic Agents. The use of uterotonic agents, although commonly applied upon delivery of the placenta, also has special application in the case of postpartum hemorrhage. Uterotonics, such as oxytocin, ergot alkaloids, and prostaglandins, control bleeding by inducing myometrial contraction. Oxytocin is considered to be first-line treatment, given either intramuscularly or intravenously. Ergot alkaloids, such as methergine and ergotamine, may induce hypertension and are therefore contraindicated in patients with preeclampsia or other comorbid conditions. Finally, prostaglandins may also be used, although the F class is contraindicated in asthma.[84]

Hysterectomy. Most postpartum hemorrhages are controllable with uterotonics and massage or uterine exploration for products of conception. Rarely, hemorrhage continues despite the interventions outlined. Life-threatening obstetric bleeding may require emergency hysterectomy. The desire to preserve the patient's reproductive capabilities must not be given priority if her life is in jeopardy.[96]

A speedy search for the refractory cause of hemorrhage is warranted because coagulopathies may complicate obstetric hemorrhage. Disseminated intravascular coagulation (DIC) can occur as a consequence of placental abruption, eclampsia, amniotic fluid embolism, postpartum infections, and dilution of clotting factors caused by aggressive volume resuscitation. Also, retained products of conception and dead fetal tissue contain excess thromboplastin, which can initiate DIC. All women with severe postpartum hemorrhage should be evaluated for DIC. As with DIC from nonobstetric causes, clinical signs of bleeding are associated with hypofibrinogenemia, thrombocytopenia, and elevated levels of fibrin split products and D-dimer.[97]

Appropriate management entails hemodynamic support as well as correction of coagulopathies. In fact, recent investigations have reported the successful use of recombinant factor VIIA for severe cases of postpartum hemorrhage.[98]

Uterine Inversion

Uterine inversion is an uncommon but serious complication of delivery that occurs during stage 4 of labor. The resultant postpartum hemorrhage can be severe and life-threatening, accounting for a maternal mortality rate of up to 15%. Uterine inversion is relatively rare, complicating 1 in 2000 deliveries.[99] It is classified by duration as well as degree of inversion. Risk factors include forceful traction on the umbilical cord (especially in conjunction with a fundal placenta), placenta accreta, maternal congenital abnormalities of the uterus, fundal pressure during delivery, use of magnesium sulfate in the antepartum period, and primiparity.[99,100]

Clinical Features. Clinically, the patient notes the sudden onset of severe abdominal pain. Abdominal examination reveals tenderness and an absence of the uterine corpus, which is potentially visualized at the cervical os or bulging from the introitus. Profuse bleeding leading to hemodynamic instability can also occur. Ultrasound may assist in making the diagnosis. Once uterine inversion is identified, the appropriate mobilization of resources should begin simultaneously with efforts to reestablish the correct anatomic position of the uterus.

Management. The highest likelihood for successful repositioning of the inverted uterus is immediately after inversion occurs. If the placenta is still adherent, it should not be removed until after repositioning. Removing the placenta while the uterus is inverted is associated with excessive blood loss. The initial attempt to reposition the uterus should be to push the fundus upward via the introitus. Digital pressure should be directed toward the mother's umbilicus along the long axis of the uterus. Contraction of the cervical uterine segments can create a muscular ring, preventing repositioning. Therefore, all uterotonic agents should be withheld immediately upon diagnosis of uterine inversion.

If initial attempts fail and a cervical ring develops, pharmacologic attempts to relax the uterus are indicated. Sedation and tocolytics can be used to facilitate uterine replacement. Terbutaline and magnesium sulfate have been used successfully to relax cervical rings. When the uterus has been repositioned, the muscle relaxants should be halted, and oxytocin and prostaglandin therapy should be initiated. Firm manual pressure via the introitus should be maintained until uterine contraction begins, the cervical ring contracts, and the uterus can no longer invert.

If all these measures fail and obstetric/anesthesia backup becomes available, halogenated anesthetics may be used to induce relaxation of the cervical rings with or without an attempt at surgical repair.[99]

Uterine Rupture

Criticism of the high rate of cesarean delivery in the United States has led to an advocacy of vaginal birth after cesarean (VBAC). Prior cesarean section is no longer an automatic indication for repeat cesarean delivery. The high success rate and relative safety of VBAC are countered partly by the risk of uterine rupture. Dehiscence of a surgical scar occurs in 0.6% of VBAC deliveries.[101] As more women have VBACs, emergency physicians can expect to encounter uterine rupture.

Clinical Features. Uterine rupture is an unpredictable event occurring late in pregnancy or as stage 1 of labor transitions to the active phase. It is defined as a full-thickness uterine wall perforation. The severity of rupture ranges from simple scar dehiscence to complete fetal extrusion. It may be spontaneous, but it is most often liked with previous uterine surgery.[102]

This diagnosis should be entertained when appropriate because significant fetal mortality is associated with the event. As the degree of fetal expulsion through the rupture increases, the fetal mortality rate increases as well. Minimal fetal extrusion results in a perinatal mortality rate of less than 1%, whereas complete extrusion results in a 10 to 20% mortality rate. Maternal death is rare, but significant hemorrhage is common, complicating one third of cases. Maternal genitourinary injury may also occur in association with uterine rupture.

Diagnostic Strategies and Difficulties. The diagnosis of uterine rupture is sometimes difficult because pain is not always present. Risk for uterine rupture with VBAC generally cannot be predicted based on maternal characteristics except that women with a prior classic, or T-shaped, incision and women who have had more than three cesarean sections are at increased risk. Intrapartum vaginal bleeding may signal the problem, but its absence by no means precludes rupture. Prolonged fetal heart rate deceleration, indicating fetal distress, is the most reliable sign of fetal extrusion.[28] Emergency ultrasonography may reveal a protruding amniotic sac, hemoperitoneum, and/or the site of myometrial rupture; however, good sensitivity data are lacking.[102]

Management. If uterine rupture is suspected, delivery should be hastened to limit fetal hypoxia. Emergency cesarean section is the best method to speed delivery and repair the injury. The American College of Obstetricians and Gynecologists guidelines for uterine rupture identify a 30-minute window of opportunity that maximizes fetal outcome.[103] At surgery, the maternal condition dictates whether uterine repair or hysterectomy is indicated. In the absence of opportunity for emergency laparotomy, appropriate interventions remain speculative. Uterotonic agents (especially ergonovine) may enlarge the rupture and are contraindicated.

Amniotic Fluid Embolism

Amniotic fluid embolism is a rare and catastrophic complication of labor and delivery. The incidence rate is 6.0 and 14.8 per 100,000 in primigravid and multiparous deliveries, respectively.[104] Although the mechanism is not well understood, it is thought to involve the spread of amniotic fluid through the maternal vasculature, activating either a procoagulant or anaphylactic cascade. Uterine trauma at or around the time of delivery, amniocentesis, and miscarriage also may result in amniotic fluid embolism. The diagnosis is usually clinically evident with the sudden onset of dyspnea, hypoxia, altered mental status, seizure, or hemodynamic collapse. DIC frequently follows and maternal mortality is high. In more than half of amniotic fluid embolism patients, postpartum bleeding due to coagulopathy occurs. Central hemodynamic monitoring, vasopressors/inotropes, and DIC management may be needed.[105-107]

Postpartum Endometritis

Perspective. Puerperal infections affect 5% of all vaginal deliveries and 10% of all cesarean sections. Operative delivery, prolonged rupture of membranes, lack of prenatal care, prolonged stage 2 labor, use of intrauterine monitoring, and frequent vaginal examinations have all been linked to these ascending gynecologic infections.[108] Of all puerperal deaths, 8% have infection and sepsis as a direct or contributing factor.[109] Causative organisms for these infections include gram-positive cocci and gram-negative coliforms. Less commonly, *Chlamydia* and *Mycoplasma* species have been implicated.

Clinical Features. Endometritis is the most common puerperal infection, usually developing on the second or third day postpartum. Typically, the lochia has a foul odor and the white blood cell count is elevated. Fever and abdominal pain indicate greater severity of infection, often warranting inpatient care and intravenous antibiotics. Often, a coexistent surgical wound infection is present. A search for retained products of conception is indicated, particularly if bleeding is ongoing.

Management. Treatment is empirical and directed at the most likely organisms. Clindamycin in conjunction with an aminoglycoside is usually used, although second- and third-generation cephalosporins are acceptable alternatives.[110] Most patients with postpartum endometritis require admission.

Postpartum Cardiomyopathy

Perspective. For unclear reasons, the postpartum period is associated with the relatively sudden onset of cardiomyopathy in healthy women without evidence of prior cardiac disease. Estimates indicate that postpartum cardiomyopathy (PPCM) occurs in 1 of 4000 pregnancies and is more common in African American and multiparous women. Proposed etiologies include viral, immunologic, toxic, and genetic factors, but in most cases no specific cause is found.[111] Mortality rates for PPCM range from 18 to 56%.

Clinical Features. Symptom onset varies, as does the severity of the cardiomyopathy. Onset is usually days to weeks after delivery, and symptoms range from mild fatigue to acute pulmonary edema. PPCM is often unrecognized in its milder form, leading to the consensus that the condition may be more prevalent than reported. Dyspnea on exertion, orthopnea, and fatigue may be easily misinterpreted as normal in a mildly anemic woman who is breast-feeding a new infant at home. The clinician should not dismiss these symptoms because congestive heart failure and dysrhythmias may ensue.

Management. Treatment with diuretics, vasodilators, and oxygen relieves the symptoms in many cases. Angiotensin-converting enzyme inhibitors are contraindicated if PPCM occurs during the last month of pregnancy (owing to teratogenicity) but should be considered a mainstay of treatment postpartum. Amlodipine (a dihydropyridine calcium channel blocker) may also have a role in the treatment of PPCM.[112,113]

Cardiac function returns to normal in half of patients with PPCM during the following 6 months. Others have residual left ventricular dysfunction and a cardiac mortality of 85% during the next 5 years. The presence of cardiomyopathy after one pregnancy does not predict recurrence during subsequent pregnancies.[114] Most obstetricians recommend against future pregnancies, however, believing that there is some residual cardiac function impairment. If such a pregnancy cannot be avoided, it should be considered high risk and followed closely.

Postpartum Depression

Perspective. Although likely underdiagnosed, it is estimated that postpartum depression affects 10 to 15% of mothers. Although in many cases it is self-limited, the condition has been recognized as having important consequences for the mother, infant, and family. Risk factors for postpartum depression include previously diagnosed depression and neuroticism, inadequate

spousal support, adverse socioeconomic factors, recent life stressors, and emergency delivery.[115]

Clinical Features. Postpartum depression patients present with symptoms not unlike those of other major depressive disorders. These symptoms include depressed mood, anhedonia, loss of appetite, insomnia, fatigue, decreased concentration, feelings of guilt and worthlessness, and suicidal ideation.[116] Most women with postpartum depression do not have vegetative signs or symptoms. Symptoms peak at 10 to 12 weeks postpartum, although some cases are diagnosed up to 1 year postpartum.[117]

When unrecognized, these women are at high risk for suicide and may come to the ED with overdoses or other manifestations of a suicidal attempt.[118]

Management. Early identification and referral are the key components of therapy. Dismissal of postpartum fatigue as normal, without considering the diagnosis of postpartum depression, can be disastrous. Not only does this condition contribute to marital discord, maternal risk for suicide, and even infanticide, but also studies have shown that children of depressed mothers have an increased incidence of delayed cognitive, psychological, neurologic, and motor development.[119] Therefore, sensitivity to the possibility of postpartum depression is crucial to successful treatment. The disposition of inpatient psychiatric care with suicide precautions may be required, as deemed appropriate.

KEY CONCEPTS

- ED deliveries should be considered high risk. Antepartum hemorrhage, PROM, eclampsia, premature labor, precipitous delivery, malpresentation, and umbilical cord emergencies are all overrepresented in emergency deliveries.
- Women in labor who present to the ED are generally best cared for in the obstetric suite. Women with the urge to push or with the head of the infant crowning are at imminent risk of delivery, which should take place in the ED. The transfer of a woman with an impending high-risk delivery to a perinatal center must be tempered by clinical and medicolegal judgment.
- Most ED deliveries require only basic equipment to cut and clamp the umbilical cord and to dry and suction the infant. However, the ED should have the equipment and staff available to care for a newborn requiring further resuscitation.
- Maternal complications of labor and delivery include obstetric trauma, postpartum hemorrhage, uterine inversion and rupture, amniotic fluid embolism, coagulation disorders, and infections. Many of these problems can initially be managed nonsurgically in the ED.
- Deliveries complicated by dystocia, malpresentation, or multiple gestations are life-threatening emergencies. The clinician must develop strategies to treat each of these potential complications of delivery.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 180 The Elder Patient

Diane M. Birnbaumer

There are no diseases of the aged, but simply diseases among the aged.

Leonard Larson, 1960

PERSPECTIVE

The population of the United States is becoming more elderly, with the proportion of people older than age 65 years increasing at twice the rate of younger people. In 2000, 12.4% of the population was older than age 65 years, and by 2045 one in five people may be older than that age.[1] With the first baby boomer turning 62 years old in January 2008, estimates are that 365 people per hour will reach this milestone during the next decade, and the fastest growing subset of the U.S. population is people age 85 years or older. This group is also the fastest growing population seen in the emergency department (ED). Approximately 35% of total health care dollars are spent on patients older than age 65 years.[2]

These changing demographics affect the practice of emergency medicine. Elders account for 6.4 million of the 110 million ED visits; this number reflects a 34% increase in ED visits by this age group from 1993 to 2003.[3] Nearly half of these patients are admitted. This group accounts for nearly 43% of all ED admissions and 47% of all critical care admissions.[4] Because the number of ED visits for the elderly is expected to nearly double by 2013, the health care impact of this age group will be enormous. In general, elderly patients presenting to the ED are more likely to have an emergent condition than younger patients and spend a longer time being evaluated in the ED.[5]

PRINCIPLES OF DISEASE

Physiologic Changes of Aging

Physiologic changes of aging affect virtually every organ system and have many effects on the health and functional status of elders (Table 180-1). Heart disease is the leading cause of hospitalization and death.[2] Increased peripheral vascular resistance with aging leads to an increased risk of hypertension. Decreased inotropic and chronotropic cardiac functioning compromises the patient's ability to respond to physiologic stressors. Atherosclerosis is common and contributes not only to the rate of heart disease but also to the risk of vascular conditions (e.g., stroke, mesenteric ischemia, peripheral vascular disease, aortic dissection, and abdominal aortic aneurysm).

Elders are at higher risk for infections due to decreases in antibody titers. Prostate disease and also incomplete bladder emptying in women with pelvic floor abnormalities predispose to urinary tract infections. Microaspiration increases the risk of pneumonia, and fragile, aging skin prone to injury and breakdown increases the risk of infections of the skin and soft tissues. *Immunosenescence* of cell-mediated immunity predisposes patients to reactivation of latent diseases (e.g., tuberculosis) and may be associated with increased susceptibility to neoplasms. Cancer is the second most common cause of hospitalization and death in older patients.[2]

Fractures are the fifth leading cause of hospitalization, reflecting the high rate of osteoporosis, particularly in women. Arthritis is the most prevalent outpatient disease in elders because of the wear on the cartilaginous joints, particularly of the knees, hips, and hands.[2] Arthritis greatly affects quality of life, and these patients report fair or poor health approximately three times more often than patients without arthritis.[6]

Although the physiology of aging often affects a patient's functional status, laboratory values are usually within the normal range. Abnormal laboratory values in elders should be evaluated as abnormal findings and should not be attributed to "normal effects of aging."

Pharmacologic Considerations

Polypharmacy, drug interactions, and misuse and abuse of medications in elders are crucial health care issues. Elders currently consume more than 30% of the prescription drugs in the United States, and this figure is projected to increase to 50% by 2020. More than 40% of elders use 5 or more drugs weekly, and more than 10% use 10 or more.[7,8]

Although multiple medications may be necessary to treat the medical problems that occur with aging, significant adverse health effects may result. Underlying medical problems, multiple physicians, changing pharmacokinetics of aging, and treating side effects of one medication with another drug are all contributory. Twelve to 30% of admitted elders have adverse drug reactions or interactions as a primary or major contributing factor to their admission, and 25% of these drug reactions or interactions are serious or life-threatening.[9]

Pharmacokinetics may change with age. Altered gastrointestinal motility and blood flow, decreased lean body mass, increased proportion of adipose tissue, decreased creatinine clearance, and decreased hepatic blood flow all may alter the absorption, distribution, and clearance of medications. Despite these changes, the bioavailability of most medications is not

Table 180-1 Physiologic Changes of Aging and Potential Effects

PHYSIOLOGIC CHANGE	POTENTIAL EFFECT
Nervous System	
Decreased efficiency of blood-brain barrier	Increased risk of meningitis Potential for exaggerated medication responses
Decreased response to changes in temperature	Impaired thermoregulation
Alteration of autonomic system function	Variations in blood pressure; risk of orthostatic hypotension Reduced erectile function Urinary incontinence
Alterations in neurotransmitters	Slowing of complex mental functioning
Skin/Mucosa	
Atrophy of all skin layers	Decreased insulation Increased risk of skin injury Increased risk of infection
Sweat glands decreased in number or activity	Potential for hyperthermia
Musculoskeletal System	
Progressive bone loss	Increased risk of fractures
Atrophy of fibrocartilaginous and synovial tissues	Joint instability and pain Impaired balance and mobility
Decrease in lean body mass	Alteration in pharmacokinetics
Increase in proportion of adipose tissue	Alteration in pharmacokinetics
Immune System	
Decrease in cell-mediated immunity	Increased susceptibility to neoplasms Tendency to reactivate latent diseases
Decreased antibody titers	Increased risk of infection
Cardiovascular System	
Decreased inotropic response	Less efficient response to myocardial wall stress
Decreased chronotropic response	Decreased maximal heart rate
Increased peripheral vascular resistance	Increased blood pressure
Decreased ventricular filling	Changes in organ perfusion
Pulmonary System	
Decreased vital capacity	
Decreased lung/airway compliance	Increased airway resistance
Decreased chemoreceptor response to hypercapnia/hypoxemia	Potential for rapid decompensation
Decreased ventilatory drive	Decreased Pa_{O_2} and increased Pa_{CO_2}
Decreased diffusion capacity	Decreased Pa_{O_2}
Hepatic Function	
Decrease in hepatic cell mass	Reduced ability to regenerate
Decrease in hepatic blood flow	Alteration in pharmacokinetics
Alterations in microsomal enzyme activity	Alteration in pharmacokinetics
Renal System	
Decrease in renal cell mass	Decreased drug elimination
Thickening of basement membrane	Decreased drug elimination
Reduced hydroxylation of vitamin D	Risk of hypocalcemia, osteoporosis
Decrease in total body water	Alteration in pharmacokinetics
Decreased thirst response	Risk of dehydration/electrolyte abnormalities
Decreased renal vasopressin response	Risk of dehydration/electrolyte abnormalities
Gastrointestinal System	
Decrease in gastric mucosa	Increased risk of gastric ulcer
Decrease in bicarbonate secretion	Increased risk of gastric ulcer
Decrease in blood flow to gastrointestinal system	Increased risk of perforation
Decreased epithelial cell regeneration	Longer healing times

significantly altered in elders. Medication interactions and side effects pose significant problems, however, particularly because so many elders take multiple medications. Emergency physicians unwittingly may contribute to this problem by adding a new medication at discharge that may have an adverse drug interaction with a patient's preexisting medications. In addition, the altered pharmacokinetics in elders necessitates caution when medications are administered in the ED, particularly sedative-hypnotics and narcotics. A rule of thumb is "start low and go slow."

Several medications frequently used in the outpatient elder population are "potentially inappropriate medications." This

list includes, but is not limited to, narcotic analgesics, nonsteroidal anti-inflammatory agents, sedative-hypnotics, muscle relaxants, and antihistamines.[10-12] These agents are generally not recommended for use in this patient population and should be used sparingly.

The medications most often implicated in adverse reactions in elders in the ambulatory setting are cardiovascular medications, followed by diuretics, nonopioid analgesics, hypoglycemics, and anticoagulants.[13] Caution should be used when prescribing any of these classes that can contribute to morbidity and mortality in this group.

Narcotics and sedative-hypnotic agents can decrease cognition and increase the risk of falls and accidents. Diuretics may cause dehydration or electrolyte imbalance. Nonsteroidal anti-inflammatory drugs (NSAIDs) may have serious and potentially lethal side effects. The toxicity of NSAIDs includes azotemia, worsened hypertension, and congestive heart failure as a result of sodium retention. Gastrointestinal toxicity ranges from bleeding to perforation.[14] The data support using extreme caution when prescribing NSAIDs. These complications can be seen in patients taking widely available over-the-counter formulations of these drugs. There is a significant increase in cardiovascular risk with the use of COX-2 inhibitors.

Due to these concerns, pain management is difficult. Although a "first, do no harm" philosophy is laudable, treatment of pain is one of the most important remedies physicians have to offer. Three major considerations influence the choice of medication for elderly patients. First, chronic pain (e.g., arthritis pain) may require different treatment from an acute painful condition (e.g., wrist fracture). Second, the patient's underlying medical problems, social situation, and baseline functional status need to be considered. Third, starting with low doses, then titrating upward to effect, is the safest strategy.

Overall, *acetaminophen* has the highest safety profile in elders and often is the drug of choice for chronic painful conditions (e.g., degenerative joint disease). Although inadvertent excessive dosing can occur, acetaminophen is safe and should be considered first-line management for chronic pain and acute conditions causing mild to moderate pain.

NSAIDs effectively ease pain, but these agents have a ceiling analgesic effect. Increasing the dose increases the risk of side effects without increasing the analgesic benefit. These agents in low doses should be used as second-line agents after acetaminophen in chronic or acute painful conditions.

Narcotics may be necessary for acutely painful conditions and chronic conditions refractory to acetaminophen or NSAIDs. The common side effect of constipation can be problematic, and older patients need to be instructed to exercise regularly, eat high-fiber foods or supplements, and remain well hydrated. Because these agents may decrease cognition, start with low doses and titrate upward as needed.

Psychosocial Issues

The possibility of drug dependence and ethanol abuse should be considered when treating elders. Ethanol dependence is a factor in 14% of elders who present in the ED and is more prevalent than suspected.[15,16] These patients often present with gastrointestinal complaints or after falls or other trauma. Iatrogenic dependence on prescription drugs, particularly sedative-hypnotics, is also more prevalent than suspected. The routine use of sedative-hypnotics should be avoided and duration limited. Dependence on these drugs may cause decreased cognition, and withdrawal from these agents can be life-threatening.

Psychiatric disease in elders often manifests in atypical fashion. Depression, a common problem, may manifest as agitation, anxiety, and somatic complaints, in addition to the typical depressive symptoms.[17,18] Depression often follows chronic illness, loss of physical mobility, diminished cognitive function, bereavement from the death of a spouse or long-time friend, and financial pressures, all of which are common features of old age. Social isolation and loss of independence produce a sense of helplessness and hopelessness that may result in suicidal ideation or action. Certain types of depression, such as "late-life delusional depression" and involutional depression, occur exclusively in old age. In addition, depression may be caused by medication side effects or reversible physiologic conditions (e.g., thyroid disease and malnutrition). Elders often respond to pharmacologic treatment of depression but are prone to develop adverse effects from antidepressants; selective serotonin reuptake inhibitors seem to be safer. A phenomenon known as *sundown syndrome* occurs in elderly demented patients, who become highly agitated and disoriented after dark when visual sensory input is diminished and the environment becomes unfamiliar.

EVALUATION AND CLINICAL FEATURES

The evaluation of elders is often difficult. Elders living independently have an average of 3 medical problems, which increases up to 10 for those living in care facilities. Underlying illnesses complicate the evaluation. Many emergency physicians are uncomfortable evaluating elders because a specific complaint is significantly more difficult than managing the same problem in a younger patient. Use of ancillary services can be increased by 50% in elders, most likely because of vague or atypical presentations and complicated medical backgrounds.

History

Obtaining a medical history from an elderly patient requires meticulous and painstaking work. Cognitive and physical deficits must be recognized, and physicians often need to be creative and thorough to obtain adequate information.

Cognitive deficits may compromise an elder's recall and result in an inaccurate medical history. Enlisting family members, consulting with the patient's primary care physician, and reviewing past medical records may be necessary. Particular attention should be paid to past medical and surgical problems and to the patient's current medications, including over-the-counter and herbal preparations.

Physical deficits also may impede the history-taking process. Sequelae from previous strokes (e.g., aphasia) are usually obvious. Hearing impairments affect communication and can lead to dangerous misunderstandings. Elders tend to lose high-frequency hearing earlier than other ranges, so physicians should lower the pitch of their voice and speak loudly while ensuring the patient's privacy. Hearing loss can be embarrassing for the patient; thus, the physician should address the issue with sensitivity to allow for adequate communication while maintaining the patient's dignity.

Physical Examination

Due to the physiologic changes that occur with aging, the physical examination may be misleadingly benign in an elder, despite the presence of a potentially lethal illness. In addition, medications may alter the response of elders to physiologic stressors. Antihypertensives, particularly beta-blockers, may alter the patient's ability to mount tachycardia in response to hypovolemia or sepsis or may predispose the patient to hypotension.

Of elders with a serious infection, 30% present with a blunted or absent fever response.[19] The temperature measurement must be accurate; an oral temperature may be spuriously low, so a rectal temperature should be measured when fever is uncertain in a patient with a possible infectious disease. When fever is present, elders are much more likely to have a serious (nonviral) infection than are younger patients.[20] Of febrile elders presenting to an ED, 89% have an infectious disease. Approximately one third are respiratory tract infections, one fifth are urinary tract infections, and nearly 20% are bacteremia or sepsis.[20] Fever in an elder must be taken seriously, with appropriate ancillary testing and a low threshold for admission. A lack of fever does not exclude infection.

DIAGNOSTIC STRATEGIES

Because of the difficulty in obtaining accurate histories and the often poor sensitivity of physical findings in elders with significant underlying disease, more diagnostic tests are generally obtained for these patients than for their younger counterparts who present with similar complaints.[5] This increased use of resources is appropriate because the accuracy and timeliness of diagnosis are critical in elders, who suffer greater morbidity and mortality with delays in definitive treatment.

SPECIFIC DISORDERS

Myocardial Infarction

The incidence of atypical presentation of acute myocardial infarction (AMI) increases with age.[21,22] In patients older than 85 years, atypical presentation of myocardial infarction may be anticipated, and a lack of chest pain may be the rule. Only 2 to 6% of elders with AMI, however, have an asymptomatic presentation.[21] A painless myocardial infarction is more common with increasing age and occurs more often in women than men.[22-24] Sudden onset of dyspnea may be the only presenting complaint in elders with myocardial infarction. Other presenting complaints include syncope, flulike symptoms, nausea, vomiting, confusion, and weakness.[22-24] The prognosis for AMI in elders who present atypically is the same as that for elders who present typically; atypical presentations are not more benign.

Infections

Elders are more prone to infectious diseases than are younger patients, with greater morbidity and higher mortality from these diseases. Common infections occur regularly, but aging causes this population to be more susceptible to unusual organisms. Although immunosenescence is a contributory factor, predisposing illnesses and institutionalization are more significant causes of this increased risk. Hospitalization increases the risk of nosocomial infection. Instrumentation and catheterization are also significant risk factors for acquiring infectious diseases.

Evaluating infections may be difficult because 48% of elders with proven bacterial infections do not have a fever at presentation.[20] In addition, the sensitivity of an elevated white blood cell count and bandemia is poor—approximately 44 and 32%, respectively.[19]

Several infections, particularly pneumonia, urinary tract infections, and sepsis, occur more often in elders. *Pneumonia* is one of the 10 leading causes of hospitalization and death.[2] The elderly are more prone due to decreased vital capacity, decreased lung and airway compliance, less ventilatory drive, and poorer ciliary function. Combined with decreased cough response and increased esophageal reflux with microaspiration, pneumonia is the leading cause of hospitalization due to infection in the elderly. Pneumococcus is still a common cause, but gram-negative organisms are also common, as are mixed infections. Reactivation of *tuberculosis* also must be considered in this age group.

Urinary tract infections are common in elders. The incidence of bacteriuria is 20% in men older than age 70 and 20% in women ages 65 to 70, increasing to 23 to 50%, respectively, in men and women older than age 80.[25] Laxity of the pelvic floor and urinary incontinence are significant risk factors in women, whereas prostate enlargement is a significant risk factor in men. The incidence of urinary tract infections increases dramatically in patients with chronic indwelling catheters.

Abdominal Pain

Abdominal pain may be the most difficult presenting complaint to evaluate in elderly patients. Despite this difficulty, most patients have a specific diagnosis made in the ED. Two thirds of elders with abdominal pain are admitted, and nearly one fifth go directly to the operating room.

The differential diagnosis (Table 180-2) of abdominal pain differs significantly from that of younger patients, particularly in regard to the number of serious and potentially life-threatening causes. The pathology in more than 60% is surgical in nature, a rate nearly double that of younger patients. There is a 10-fold higher risk of mortality compared with younger patients.[26]

Due to the physiologic changes of aging, even life-threatening causes of abdominal pain may present with few or no alarming findings. Elders may complain of vague abdominal pain despite the occurrence of a catastrophic process. The complication rates of typically benign processes in younger patients are dramatically higher in older patients. With aging, the abdominal musculature decreases, and patients are less able to manifest guarding and rebound. In addition, the omentum shrinks and is less able to contain intra-abdominal processes. Atherosclerotic disease, with its resultant decrease in blood flow, causes increased perforation rates in diseases such as cholecystitis and appendicitis. This increased rate of vascular disease also contributes to higher rates of vascular causes of abdominal pain, such as mesenteric ischemia and leaking or ruptured abdominal aortic aneurysms.[27] The high prevalence of gallstones in elders leads to an increased risk of cholecystitis.

Due to the vague presentation and high rate of serious disease, evaluating an elderly patient with abdominal pain often requires an extensive battery of laboratory and radiographic tests.[28] Elders with potentially catastrophic intra-

Table 180-2 Differential Diagnoses of Abdominal Pain in Elderly Patients

DISORDER	INCIDENCE (%)
Cholecystitis/biliary colic	12–41
Nonspecific abdominal pain	9.6–23
Appendicitis	2.5–15.2
Obstruction	7.3–14
Hernia	4–9.6
Perforation	2.3–7
Pancreatitis	2–7.3
Diverticular disease	3.4–7

abdominal processes may not present with a fever or an elevated white blood cell count.[29,30] As a result, ancillary diagnostic ultrasonography, computed tomography, radionucleotide studies, and, occasionally, angiography may be important.[27] Since many elders with abdominal pain have a serious disease, consider admission and close observation when symptoms persist and the diagnosis remains unclear. If the patient is not admitted, a prolonged period of ED observation or reevaluation within 12 hours is prudent.

Major Trauma

Major trauma in elders (see Chapter 36) is relatively uncommon, constituting 8 to 15% of cases in major trauma databases. Elder trauma patients, however, experience higher mortality and poorer functional recovery for a given trauma score.[31,32] In any elderly trauma patient, the circumstances leading to the injury need to be determined. For any elder patient who presents with a fall, the circumstances of the fall should be questioned. Although mechanical falls occur, falls may be due to potentially serious or life-threatening medical causes such as syncope, hypovolemia due to dehydration or bleeding, cardiac or cerebrovascular disease, or medications.[33] Motor vehicle crashes, particularly involving a single vehicle, may result from transient loss of consciousness due to dysrhythmias, syncope, medication side effects, transient ischemic attacks, strokes, or myocardial infarctions.[34] These serious medical problems require simultaneous diagnosis and treatment in the setting of trauma and may be as important as or more important than the traumatic injuries.

The presence of comorbid illness and the limited physiologic reserve in the cardiopulmonary and renal systems often complicate the trauma resuscitation in this age group. More aggressive ventilatory support and early use of invasive hemodynamic monitoring are indicated to guide volume resuscitation. Shock is poorly tolerated in elders because hemodynamic compensation is limited, and end-organ failure occurs earlier.

Certain injuries are more common and severe in elders. A subdural hematoma may occur after relatively trivial head trauma, and chronic subdural hematoma may present as progressive dementia with only subtle neurologic findings. Increasing ankylosis of the spine, osteoarthritis, and decreased bone density as a result of osteoporosis render the geriatric cervical spine more susceptible to fracture. Preexisting pulmonary pathology and a brittle thoracic wall account for the greater severity of pulmonary contusions and the higher incidence of rib fractures and resultant complications (e.g., atelectasis and pneumonia). Skeletal fractures are more common and lacerations of atrophic skin are more difficult to repair and more prone to infection. This thin skin is also prone to decubitus breakdown in patients who are immobile, even for short periods such as during spinal immobilization on a backboard.

■ PREVENTIVE CARE

Immunizations

Pneumonia, influenza, accidents, and adverse medical events are among the top seven causes of death in elders.[2] These conditions account for 15% of admissions and are potentially preventable. Annually, 36,000 adults die of complications from influenza and pneumococcal infections, and most of these deaths occur in elders. Immunization would reduce the incidence of clinical and serologic influenza by half in this patient population. The Centers for Disease Control and Prevention (CDC) has a goal of an 80% immunization rate for patients in high-risk groups, including elders. The actual vaccination rate falls significantly below this goal. In patients 65 years old, 66 and 62% were vaccinated for influenza and pneumococcus, respectively, with the lowest rates among multiracial ethnic groups and people of lower socioeconomic means.[35] As a result, the CDC recommends that potential vaccination sites be extended to include walk-in clinics and EDs. Elders who have not been hospitalized or seen their primary care physician in the previous 3 years average at least one visit to an ED, and many are willing to be vaccinated there.

Despite this information, controversy exists regarding vaccination of elders in the ED. Emergency physicians can be reluctant to give vaccinations, citing time constraints and their concern regarding delivering primary care. Considering the low threshold in the ED to administer the tetanus vaccine, it seems feasible that influenza and pneumococcal vaccination programs could be relatively easy and effective in the ED.

Falls

In combination with vaccinations, education about accident prevention in the home could have a considerable impact on the overall morbidity and mortality in elders. Falls and adverse medical events are the seventh leading cause of death in elders.[2] A primary care or social service provider more appropriately supplies this instruction. The ED, however, may be an additional resource for providing educational services to elders on a case-by-case basis, particularly in reference to any specific incident that led to the need for emergency care. The leading cause of falls in elders is related to the use of pharmacologic agents, often prescription drugs.[36] Reviewing the patient's medications, searching for agents that might cause decreased cognition or dehydration, and addressing the need for these agents with the patient and the primary care provider could decrease significantly the risk for falls. In addition, informing the patient's primary care provider that the patient has fallen may facilitate education by the primary physician.

KEY CONCEPTS

- Polypharmacy and side effects of prescription and nonprescription drugs often occur in elders and should be considered in their evaluation.
- Physiologic changes that occur with aging make the clinical evaluation of elders difficult. Because of the difficulty in obtaining accurate histories and the often poor sensitivity of physical findings in elders with significant underlying disease, more diagnostic tests are generally obtained for these patients than for their younger counterparts who present with similar complaints.
- The immunosenescence that accompanies aging may blunt the fever response to infection and cause a less elevated white blood cell count.
- Myocardial infarction frequently presents atypically in elders as dyspnea, syncope, weakness, confusion, or abdominal complaints, often in the absence of accompanying chest pain.
- Abdominal pain in elders is often caused by surgical conditions that may require extensive evaluation in the ED, including radiographic studies.
- Elderly trauma patients have a higher morbidity and mortality than their younger counterparts because of exacerbation of underlying medical problems.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 181

The Immunocompromised Patient

Michael J. Burns

PERSPECTIVE

Compared to individuals with an intact immune system, infections in immunocompromised patients are more common, are more severe, progress more rapidly, are more often fatal, and are caused by a wider variety of microorganisms.[1,2] Many factors, often interrelated, cause patients to become immunocompromised and predispose them to develop infections with potentially pathogenic microorganisms. These include disruption of the body's protective surfaces such as skin and mucosal barriers (oral and respiratory mucosa and intestinal and genitourinary surfaces); disorders (e.g., lymphoma, asplenism, and myeloma) that directly impair the function of the body's immune system; drugs and irradiation that suppress or alter immune function; alterations in body substances (hyperglycemia) or solid organ function (kidney and liver failure); as well as malnutrition, aging, and exposure to antimicrobial agents that inhibit the normal protective resident bacterial flora.

PRINCIPLES OF DISEASE

The body's defense mechanisms consist of surface barriers, such as skin, enzymes, and mucus, as well as innate (natural) and acquired (adaptive) responses. Innate responses occur to the same extent regardless of how often the body encounters the infectious agent, whereas acquired responses improve on repeated exposure.[3] Innate immunity is activated immediately upon exposure to an infecting agent, rapidly controlling replication and allowing the requisite 3 to 5 days for the adaptive component to clone sufficient T and B cells to respond more specifically.[4]

Non-Microbe-Specific Immunity

Physical Barriers

The first line of defense against microorganisms consists of physical barriers, including skin, gastrointestinal and respiratory mucosa, and gastric acid. Cutaneous acidity inhibits dermal bacterial growth. In addition, mucous membranes are continually bathed in secretions that contain antimicrobial enzymes, other proteins, and immunoglobulin G (IgG) and secretory IgA.[5]

In the respiratory tract, mucociliary transport and the cough reflex remove particulate matter and microbes, but this mechanism is impaired with smoking and ineffective cough. Mechanical ventilation or tracheostomy introduces large numbers of microbes that often overwhelm natural clearance.[6]

Gastric acid and pancreatic enzymes have antibacterial properties that prevent overgrowth in the upper gastrointestinal tract. Normal peristalsis and mucosal shedding help maintain normal gut flora. Alterations in these factors increase susceptibility to infection. Broad-spectrum antibiotics alter normal flora, permitting overgrowth of pathogens such as *Candida* species, multiantibiotic-resistant bacteria, and *Clostridium difficile*.

Acute Phase Response

The metabolic changes that occur during systemic infection and inflammation constitute the acute phase response. The liver manifests a stress response by decreasing albumin synthesis while increasing production of proteins that enhance phagocytosis and assist in complement activation. One of these proteins is *C-reactive protein* (CRP), sometimes measured clinically as a nonspecific indicator of infection or inflammation. Muscle proteolysis is also part of this response and may result in the weight loss characteristic of chronic inflammatory or infectious states.

Invading microorganisms activate the acute phase response, which is not microbe specific. The response delivers humoral and cellular immune components to sites of inflammation and initiates antibody responses. Cytokines, platelet-activating factor, and hormone-like proteins, including interferons, are secreted from various immune cells and play important roles in mediating this response.[7] Clinically, these cytokines result in migration and adhesion of polymorphonuclear leukocytes and monocytes to sites of bacterial invasion. These cells release granules of substances that vasodilate and increase vascular permeability, leading to edema, warmth, and redness, but also allow both phagocytic cells and humoral components to concentrate at the site of infection.

A family of distinct transmembrane proteins, called toll-like receptors, which mediate recognition of extracellular microbial products such as endotoxin, are vitally important in the innate immune response.[5] They are present on many cell types, including macrophages, neutrophils, dendritic cells, mucosal epithelial cells, and endothelial cells. They recognize pathogen-associated molecular patterns, generate signals that lead to activation of innate immune responses, and help bridge innate and adaptive immune responses.

The reticuloendothelial system, composed of tissue macrophages and their blood-borne counterparts, monocytes, removes particulate matter, including microbes, from the lymph and blood. The tissue component is concentrated in the lymph nodes, spleen, liver, marrow, and lung and has particular affinity for encapsulated bacteria such as pneumococci, meningococci, and *Haemophilus influenzae*. The vital importance of this non-microbe-specific system is demonstrated by the overwhelming sepsis from encapsulated organisms in patients with asplenia.

Adaptive (Microbe-Specific) Immunity

Humoral Immunity

Antibodies. Antibodies are produced by B lymphocytes, and each B cell produces a single microbe-specific antibody type. Stimulation by an antigen (or microbe) causes proliferation of this particular B cell so that large quantities of a specific circulating antibody can be produced. Furthermore, B cells are active in presenting antigens to T lymphocytes, which promotes cell-mediated immunity.

Immunoglobulins. IgM is the first immunoglobulin to appear in response to a new antigen. Although it has less affinity at binding antigens than IgG, IgM provides some recognition of antigens and begins B cell proliferation before the subsequent development of IgG.[8] Clinically, IgM is detectable earlier in serum than IgG and serves as a marker for a patient's early response to acute infection.

Secretory IgA is the predominant immunoglobulin present in gastrointestinal fluids, nasal and oral secretions, tears, and other mucous fluids. IgA inhibits cell adherence of viral, bacterial, and protozoan pathogens and therefore prevents invasion by organisms through the respiratory or gastrointestinal tract.[9,10]

IgE, which is expressed in high concentration on the surface of mast cells and basophils, is responsible for immediate-type hypersensitivity responses. Mast cells and IgE are important in defense against helminthic pathogens.

IgG, which accounts for 75% of the total immunoglobulin mass, is widely distributed in tissues. It crosses the placenta and provides fetal immunity during the first 6 months of life. Congenital or acquired deficiencies of IgG lead to infection with encapsulated organisms because the predominant subtype (IgG2) has affinity for the dense polysaccharides of bacterial cell capsules, such as those of *Streptococcus pneumoniae* and *H. influenzae*.

Complement. The complement cascade, consisting of a complex interaction of 30 proteins, is another crucial component of humoral response. Complement is important in producing inflammation and leukocytosis and in recruiting leukocytes to sites of infection by production of chemoattractants. Complement also neutralizes viruses, enhances opsonization of bacteria, and produces bacterial cell wall and membrane lysis.

Both IgG and IgM, when in contact with an antigen, activate the classical pathway, whereas molecules with repeating chemical structures (e.g., bacterial cell walls and capsules) activate the cascade through the alternative pathway. Components of C3, the merging point of the classical and alternative paths, provide opsonization and modulate the response of lymphocytes (cell-mediated immunity). Opsonization is important in defense against infection with *S. pneumoniae*, *Streptococcus pyogenes*, *H. influenzae*, and *Staphylococcus aureus*. The terminal leg of the cascade, C5 through C9, forms the membrane attack complex, which inserts into cell walls and membranes and leads to cell death.

Individuals with inherited complement deficiencies are predisposed to frequent and recurrent infections with *S. pneumoniae*, *H. influenzae*, and especially *Neisseria meningitidis* and *Neisseria gonorrhoeae*.[11] The risk of meningococcal infection is increased several thousandfold and most often develops in people deficient in C3 and in late complement components (C5–C8). Paradoxically, the disease is usually milder with complement deficiency, and mortality is likewise reduced 5- to 10-fold.[12] This suggests that the host response may be, in part, responsible for the severity of disease in normal individuals and is attenuated in complement deficiency. People with meningococcemia should be tested for inherited complement deficiencies because they may benefit from immunization.

Acquired deficiencies of complement function may develop in people with rheumatologic diseases, especially systemic lupus erythematosus (SLE). Approximately 40% of patients with SLE have an inhibitor of C5a-derived chemotaxis in their serum that results in enhanced susceptibility to infection.[13]

Cell-Mediated Immunity

Cell-mediated immunity (CMI) generally includes immune responses that are mediated by T lymphocytes, natural killer (NK) cells, and mononuclear phagocytes. CMI is vitally important in the control of infections caused by microbes that survive and replicate intracellularly, including most viruses, and some bacterial (obligate and facultative intracellular types), fungal, and protozoan pathogens.

Only 5% of lymphocytes are in circulating blood. Most mature and are active in the marrow, thymus, spleen, and lymph nodes. The latter two sites expose T cells to circulating antigen from invading microbes.[5] Specialized antigen-presenting cells in the lymphoid system sequester antigen and antigen-antibody complexes and present them to T cells. This process involves internalization and processing of the antigen, followed by formation of peptides that bind to a cell surface molecule called the *major histocompatibility complex* (MHC). Only with this specific presentation can a T lymphocyte become activated against a particular antigen.

Two major types of T lymphocytes are CD4 (helper cell) and CD8 (suppressor cell), corresponding to type II and type I of MHC, respectively. CD4 lymphocytes provide help for other cells in the immune system, including enhanced B cell antibody production and production of cytokines. CD8 lymphocytes are generally cytotoxic and mediate the eradication of virally infected target cells and certain tumors. A decline in the number of CD4 cells, with predominance of CD8 cells, is responsible for the increased susceptibility to infection in patients with acquired immunodeficiency syndrome (AIDS).[5] Despite the cytotoxicity of CD8 cells, immunity is reduced without adequate numbers of CD4 cells.

Patients with defects in CMI are at increased risk for disseminated infection with intracellular bacteria, such as *Mycobacterium tuberculosis*, *Listeria monocytogenes*, and *Salmonella* species. The deoxyribonucleic acid (DNA) viral infections, such as cytomegalovirus, herpes simplex, and varicella zoster, also affect these patients more severely, as do fungal infections with *Candida*, *Cryptococcus*, *Mucor*, *Aspergillus*, and *Pneumocystis*. Finally, some protozoa are pathogenic without intact CMI, as infections with *Toxoplasma gondii* demonstrate.[14,15] Some infections are seen only below a certain CD4 cell count. *Pneumocystis* pneumonia is seen almost exclusively in patients with counts less than 200 cells/mL, whereas almost all patients with

toxoplasmosis or cryptococcal meningitis have counts less than 100 cells/mL.

NK cells, closely related to lymphocytes but neither B nor T cells, are important in the innate immune response and are found in high concentrations in blood and spleen.[5] NK cells recognize infected cells and respond by directly killing these cells, and they secrete cytokines that activate macrophages to destroy phagocytosed microbes. These cells are very important in defense against intracellular microbes, particularly viruses and intracellular bacteria such as *L. monocytogenes*.

Granulocytic Phagocytes. Granulocytic phagocytes are the cellular effectors of microbe killing, engulfing them and enzymatically lysing their cell membranes or walls. Two major types are polymorphonuclear leukocytes (also called neutrophils) and macrophages (the tissue version of circulating monocytes). Macrophages have surface receptors that recognize nonvertebrate carbohydrates such as mannose, which form the cell wall of some microorganisms. Hence, they can identify and attack "invaders" rather than "self."

Two other types of granulocytes, eosinophils and basophils, are less involved in the ingestion of organisms.[16] Eosinophils mediate the destruction of certain parasitic helminths through release of toxic proteins. Normally only 3% of total granulocytes, this cell type can reach 20% during times of high parasite load. Basophils (rare in circulation) and their tissue counterparts, mast cells, have high affinity for IgE. When exposed to antigens, they release granules with histamine, prostaglandins, and leukotrienes, which affect the allergic-inflammatory response with increased vascular permeability, bronchospasm, and vasodilation.[3]

Neutrophils constitute 90% of circulating granulocytes and spend only 6 to 8 hours of their average 4-day life in circulation (the remainder in tissues). Effective antibacterial activity depends on the ability of neutrophils to travel to sites of infection—a process known as *chemotaxis*. The locomotion of neutrophils along vascular endothelium is facilitated by adherence to cell surface proteins whose production is enhanced in the acute phase response.[16]

One half of all neutrophils that leave the bone marrow circulate in the plasma. The other half become marginated, adhering to endothelium, primarily in the lungs, liver, and spleen. During periods of stress or with endogenous or exogenous catecholamines or corticosteroids, these neutrophils demarginate and enter the circulation. As long as the patient is not neutropenic, demargination causes an increased peripheral neutrophil count composed of mature cells, whereas with infection, an increased proportion of immature (band) forms is typically seen.

Neutrophils (and macrophages in tissue) bind to and ingest bacteria—a process called *phagocytosis*. This process is enhanced by proteins called *opsonins* that bind to bacterial surfaces. CRP, one of the acute phase response proteins, fulfills this function for certain bacteria, including *S. pneumoniae*. IgG and complement protein C3b also opsonize bacteria, again illustrating the interdependence of the immune system. Actual killing takes place within granulocytes when cytoplasmic granules enzymatically produce potent oxidants. Granulocytes further control bacterial proliferation at the site of infection by elaborating lactoferrin, which locally binds free iron necessary for bacterial replication.

In addition to phagocytosis, macrophages (located in the spleen, alveoli, liver, and lymph nodes) modulate the immune response by presenting antigens to lymphocytes and releasing cytokines and complement components. Activation of macrophages to ingest bacteria depends on interaction with interferon-γ, a cytokine manufactured by T cells.[5] Thus, the once clear demarcation between cellular and humoral immunity is breaking down as more is understood about the interdependent immune system.

SPECIFIC IMMUNOCOMPROMISED STATES

Solid Organ Transplants

See Chapter 182.

Cancer

Patients with cancer frequently have multiple immune defects that predispose them to infection, such as neutropenia and impaired T cell and B cell function, which are induced by cancer chemotherapy or by the disease process. Other factors leading to infection are defects in physical barriers (skin and mucous membranes), including cytotoxic effects of chemotherapy on cells lining the gastrointestinal tract. In addition, splenic dysfunction or splenectomy, use of long-term intravascular catheters, frequent use of complex invasive diagnostic and therapeutic procedures, toxic effects of radiation therapy, and frequent colonization with antimicrobial-resistant pathogens are predisposing factors. Cancer treatments (e.g., allogeneic bone marrow and autologous stem cell transplantation, platelet transfusion, granulocyte colony-stimulating factor, and implanted central venous catheters) increase survival during episodes of profound immunosuppression, allowing patients to receive more intense cytotoxic cancer chemotherapy regimens. This results in long survival of patients with neoplastic diseases that were formerly rapidly fatal. Despite many advances in supportive care, infections continue to result in serious morbidity and mortality. Furthermore, increasing resistance to antimicrobials is occurring among common pathogens, along with the emergence of new opportunistic pathogens. Infection is much more common in patients with acute leukemia and lymphoma (75% of patients) and multiple myeloma (50% of patients) compared to those with solid tumors.[17] Factors predisposing to infection in immunocompromised patients are listed in Box 181-1.

Neutropenia

Principles of Disease. Neutropenia is defined as a neutrophil count of less than 500 cells/mL, including band forms, or less than 1000 cells/mL and expected to fall to less than 500.[18,19] It usually results from cytotoxic chemotherapy or radiation therapy or the disease process, especially in hematologic malignancies. In addition, cancer chemotherapeutic agents and radiation therapy can cause functional defects in granulocytes. The risk of febrile neutropenia and mortality is higher in the first one or two cycles of multicycle cytotoxic chemotherapy regimens.[20]

The incidence and severity of infection in cancer patients with neutropenia are inversely proportional to the absolute neutrophil count and directly proportional to the duration of neutropenia. Although the incidence begins to rise as the neutrophil count falls below 500 cells/mL, most severe infections and almost all bacteremias occur when the neutrophil count is less than 100 cells/mL.[21] Fever in the neutropenic patient is defined as a single temperature of 38.3°C (101°F) or higher or a temperature of 38.0°C (100.4°F) or higher over 1 or 2 hours.[19] In neutropenic patients, the temperature should be measured orally or tympanically, not rectally. Although fever can be suppressed or lessened by immunosuppressive agents such as corticosteroids and nonsteroidal anti-inflammatory

BOX 181-1 THE IMMUNOCOMPROMISED PATIENT: FACTORS PREDISPOSING TO INFECTION AND THE MOST COMMON PATHOGENS

Neutropenia

Bacteria

Gram-negative bacilli
- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Pseudomonas aeruginosa*
- *Enterobacter* sp.
- *Serratia* sp.
- *Citrobacter* sp.
- *Proteus* sp.
- *Stenotrophomonas maltophilia*

Gram-positive cocci
- *Staphylococcus epidermidis*
- *Staphylococcus aureus*
- Viridans streptococci
- Less common: *Enterococcus* sp.

Gram-positive rods
- *Corynebacterium* sp.
- Less common: *Bacillus* sp.

Fungi

Candida sp.
Aspergillus sp.
Less common: *Mucor* sp., *Rhizopus* sp., *Trichosporon beigelii*, *Fusarium* sp., *Pseudallescheria boydii*

Cellular Immune Dysfunction

Bacteria

Listeria monocytogenes
Salmonella sp.
Mycobacterium tuberculosis
Mycobacterium avium-intracellulare
Legionella sp.
Nocardia sp.

Fungi

Cryptococcus neoformans
Histoplasma capsulatum
Coccidioides immitis
Candida sp.
Aspergillus sp.
Pneumocystis jirovecii (formerly *carinii*)

Viruses

Herpes simplex
Varicella zoster
Cytomegalovirus
Epstein-Barr
Less common: Measles, adenovirus

Parasites

Toxoplasma gondii
Cryptosporidium sp.
Stronglyoides stercoralis

Humoral Immune Dysfunction (Antibody Deficiency)

Bacteria

Streptococcus pneumoniae
Haemophilus influenzae
Neisseria meningitidis
S. aureus

Splenectomy/Functional Asplenia

Bacteria

S. pneumoniae
H. influenzae
N. meningitidis
Capnocytophaga canimorsus
Bordetella holmesii

Parasites

Babesia sp.

Complement Deficiency

Bacteria

N. meningitidis
S. pneumoniae
H. influenzae

drugs, most cancer patients with infection manifest fever despite the use of these agents.[22] Also, although it is uncommon, immunocompromised patients can have serious local or systemic infections without fever, manifested by unexplained tachypnea or tachycardia, mental status changes, metabolic acidosis, increased volume requirements, rapid changes in serum glucose or sodium, or acute abdominal pain. Because cancer patients with severe neutropenia or a history of splenectomy can develop the rapid onset of life-threatening infections, urgent evaluation and initiation of antimicrobial therapy in the emergency department are essential.

The most common sites of infection in neutropenic patients are the lung (25%); mouth and pharynx (25%); gastrointestinal tract (15%); skin, soft tissue, and intravascular catheters (15%); perineum and anorectal area (10%); urinary tract (5%); and nose and sinuses (5%).[23] Pneumonia and anorectal infection are more likely to be associated with bacteremia. Bacteremia may occur without an obvious source despite intensive investigation. Historically, the most important bacteria are three gram-negative bacilli—*Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*—and four gram-positive cocci—*Staphylococcus epidermidis*, viridans group streptococci, *Enterococcus* species, and *S. aureus*. Many centers that treat large numbers of cancer patients have noted a decrease in these gram-negative bacilli and an increase in infections caused by others, such as *Enterobacter*, *Citrobacter*, and *Serratia* species, which are capable of rapidly developing resistance to cephalosporins and extended-spectrum penicillins. Anaerobes are uncommon but may be important in certain mixed infections (e.g., mouth, abdominal, and perianal).

During the past 25 years, infection with gram-positive organisms (e.g., coagulase-negative staphylococci, *S. aureus*, viridans streptococci, and *Enterococcus* species) has increased and this is now the leading cause of bacterial infection (50–70% at some centers) in febrile neutropenic cancer patients in the United States, Canada, and Western Europe. Gram-negative organisms still predominate in developing countries.[24,25] With the exception of viridans streptococci, most of these gram-positive organisms do not produce immediately life-threatening infections compared with the rapid lethality of many gram-negative infections. Life-threatening bloodstream infections caused by viridans streptococci (especially *Streptococcus mitis*) are common in many cancer centers and often respond poorly to penicillins and cephalosporins. Risk factors for serious viridans streptococcal infections include aggressive cytoreduction therapy for acute leukemia or allogeneic bone marrow transplantation (especially after high-dose cytosine arabinoside treatment), profound neutropenia, and severe oral mucositis. Other factors

include prophylactic use of trimethoprim-sulfamethoxazole (TMP-SMX) or fluoroquinolones, use of antacids or H_2 receptor antagonists, and childhood.[26,27]

Aspergillus and *Candida* species are the most common fungi producing infection in cancer patients with fever and neutropenia.[23,28,29] They are most likely to develop in neutropenic patients treated with broad-spectrum antimicrobials and whose fever has persisted for more than 7 days. *Aspergillus* species usually produce necrotizing infections in the lung or sinuses. Pulmonary aspergillosis often presents with pleuritic pain, hemoptysis, and localized wheezing. The chest radiograph demonstrates pleural effusion or focal infiltrates. Computed tomography (CT) is more sensitive in detecting pulmonary infiltrates compatible with aspergillosis, and it may demonstrate a distinct halo of low attenuation surrounding a pulmonary infiltrate. This pattern is highly suggestive of invasive aspergillosis, although mucormycosis and other disorders may mimic the halo. Invasive aspergillosis originating in the paranasal sinuses may extend to the surrounding bone and brain. Often, an initial red-purplish lesion on the nasal turbinate or palate turns pale and then black as vascular invasion produces infarction of the mucosa and bone. The black eschar on the nose or palate is easily misdiagnosed as dried blood. Patients presenting with head or facial pain or swelling, or proptosis, should be rapidly evaluated for invasive aspergillosis and mucormycosis. *Candida* species produce infections of the skin, oral cavity, and esophagus as well as fungemia. The sudden onset of generalized rash consisting of pinkish-purple, nontender subcutaneous nodules is characteristic of candidemia.

Less common fungi producing infection in these patients include *Mucor* and *Rhizopus* species (necrotizing pneumonia and sinusitis), *Trichosporon* species (pneumonia and fungemia), and *Pseudallescheria boydii* (soft tissue infection). Other than *Candida* species, these fungi are rarely found in blood cultures. Specific diagnosis requires biopsy.

Clinical Features. Certain clinical findings are characteristic for specific pathogens (Table 181-1). Noninfectious causes of fever also need to be considered, such as drug toxicity, drug allergy, transfusion reactions, and pulmonary emboli.[17] Fever is frequently the only sign of infection because these patients are unable to mount a full inflammatory response at a site of infection.[23] Usual symptoms and signs of infection may not be present, especially when the neutrophil count is less than 100 cells/mL. When pneumonia develops, purulent sputum may be absent, and the initial chest radiograph may not show an infiltrate. Pyuria may be absent in the presence of urinary tract infection. Areas of cellulitis may have diminished or absent induration and redness and no purulent drainage. Tenderness may be the only finding in perineal and anal infections. The neutropenic patient with a documented infectious cause of fever may be difficult to distinguish from the patient with fever not caused by infection. The performance of a procedure before the onset of fever, the presence of chills, "toxic appearance," and lack of localized findings do not help determine whether the patient is bacteremic.[30] Only 20% of febrile neutropenic patients have a clinical focus of infection identified at presentation, and only 30% of patients have positive blood cultures.

Mucositis involving the mouth and other mucous membranes is a painful and debilitating condition that commonly occurs in cancer patients receiving intense chemotherapy. It is a frequent prelude to viridans streptococcal bacteremia, which can produce sudden onset of acute respiratory distress syndrome, a toxic shock–like syndrome, rash, and pneumonia.

Diagnostic Strategies. The emergency evaluation of the cancer patient with fever and neutropenia should include a meticulous search for subtle symptoms and signs of inflammation at common sites: oral cavity and pharynx, lower esophagus, lung, skin, perineum including anus, bone marrow aspiration sites, vascular catheter sites, and tissue around the nails.[21] In nearly two thirds of patients, the initial evaluation does not identify a focus of infection.[22] Two sets of blood cultures should be obtained. If the patient has a central venous catheter, cultures of blood should be obtained from one lumen of a multilumen catheter and from at least one peripheral site. Specimens for culture should also be obtained from any site of inflammation, including inflamed or draining catheter exit sites. Patients with severe mucositis should have herpes simplex cultures performed if not on antiherpes prophylaxis, and they should have a smear for *Candida* pseudohyphae. Complete blood count, electrolytes, transaminases, blood urea nitrogen, and creatinine should be obtained to plan management and to monitor the occurrence of drug toxicity.

Urine culture should be obtained if symptoms or signs of a urinary tract infection are present, if a urinary catheter is in place, or if the urinalysis is abnormal. Examination of the cerebrospinal fluid is not recommended as a routine procedure unless subtle symptoms or signs of meningitis are present.

A chest radiograph should be obtained even when symptoms or signs of pneumonia are absent. If the chest radiograph is negative or inconclusive but there is still suspicion for pneumonia, high-resolution CT or thin-section multislice CT scanning of the chest without contrast should be obtained because

Table 181-1 Characteristic Clinical Findings in Neutropenia That May Be Associated with Infection with Specific Pathogens

CHARACTERISTIC CLINICAL FINDINGS	SUSPECT PATHOGENS
Ulcerative lesions in the mouth	Viridans streptococci, herpes simplex, *Candida*, anaerobes
Necrotizing skin lesions	*Pseudomonas aeruginosa*, *Aeromonas hydrophila*, *Aspergillus*, *Mucor*
Nontender subcutaneous nodules	*Nocardia*, *Cryptococcus*
Nontender pink skin papules	*Candida*
Black eschar of nose or palate	*Aspergillus*, *Mucor*
Generalized macular red rash	Viridans streptococci
Right lower quadrant abdominal pain, tenderness, distention, bloody diarrhea	Typhlitis (neutropenic enterocolitis) caused by *P. aeruginosa*, *Escherichia coli*, *Clostridium septicum*
Perineal pain and tenderness without inflammation or abscess	Gram-negative bacilli, anaerobes
Redness or pain at vascular catheter sites	Coagulase-negative staphylococci, *Corynebacterium*, *Bacillus* species

pneumonia is often detected by chest CT in febrile neutropenic patients with normal findings on chest radiograph.[31] CT evaluation of the sinuses should be performed if facial pain or swelling is present. In patients with abdominal pain and tenderness, CT scanning of the abdomen is useful for diagnosing neutropenic enterocolitis ("typhlitis"), a necrotizing infection of the bowel wall that usually affects the cecum. This is more commonly seen in acute leukemia and is not generally treated surgically. Ultrasonography over a subcutaneous tunneled catheter tract and its vein of insertion may reveal the presence of an abscess or infected thrombus.[32]

In patients with diarrhea, stool testing for *C. difficile* toxin as well as culture for routine bacterial pathogens should be obtained. *C. difficile* colitis occasionally produces abdominal pain in the absence of diarrhea. *Cryptosporidium parvum*, a protozoan, may cause profuse, watery diarrhea and is detected by acid-fast staining or immunofluorescence testing of stool.

Management of Febrile Neutropenia

Antibiotic Therapy. Broad-spectrum antimicrobial therapy should be initiated promptly in the febrile neutropenic patient if the neutrophil count is less than 500 cells/mL or if the neutrophil count is 500 to 1000 cells/mL and is expected to drop.[19] Moreover, even afebrile neutropenic patients who have symptoms and signs (e.g., abdominal pain and tenderness) compatible with an infection should be treated empirically (Table 181-2).

Use of a single antimicrobial agent is preferred in most patients because there is no conclusive evidence of a benefit from multiple drugs.[33,34] Factors that must be considered when

Table 181-2 Selected Antimicrobial Agents Useful in the Immunocompromised Patient

DRUG	DOSAGE		PRECAUTIONS/COMMENTS
	ADULT	CHILD (AGE > 28 DAYS)	
Aminoglycosides			
Gentamicin	2 mg/kg loading dose, then 5 mg/kg/day IV q8–12h, *or* 5–7 mg/kg IV once daily	Same as adult	Decrease maintenance dose in elderly or with renal dysfunction
Tobramycin	Same as gentamicin	Same as adult	
Amikacin	10 mg/kg/day loading dose, then 15 mg/kg/day IV q12h or once daily	Same as adult	
Extended-Spectrum Penicillins/β-Lactamase Inhibitors			
Piperacillin/tazobactam	4.5 g IV q6h	240–400 mg/kg/day IV q6h	For *Pseudomonas aeruginosa*, administer with aminoglycoside
Cephalosporins			
Ceftazidime	1–2 g IV q6–8h	150 mg/kg/day IV q8h	Both active against *P. aeruginosa*, but cefepime more active than ceftazidime against gram-positive organisms and some resistant gram-negative bacilli
Cefepime	1–2 g IV q8h	150 mg/kg/day IV q8h	
Carbapenems			
Imipenem/cilastatin	0.5–1 g IV q6h	60–100 mg/kg/day IV q6h	Adjust dose in elderly or with renal dysfunction.
Meropenem	0.5–1 g IV q8h	60–120 mg/kg/day IV qh8	Seizures associated with imipenem. May be cross-allergenic with penicillin. Broad-spectrum against gram-positive and gram-negative organisms, including *P. aeroginosa* and anaerobes.
Other			
Aztreonam	1–2 g IV q8h	120 mg/kg/day IV q6h	Active against gram-negative bacilli including *P. aeruginosa* Not active against gram-positive organisms Safe in penicillin-allergic patient
Vancomycin	15 mg/kg IV q12h	40 mg/kg/day IV q6–12h	Infuse over 2 hr (flushing, hypotension with rapid infusion)
Amphotericin B	0.5–1.5 mg/kg/day IV once daily	Same as adult	Refer to infectious disease or pharmacology text
Acyclovir			Infuse over 1 hr
Herpes simplex, mucocutaneous*	5 mg/kg IV q8h *or* 400 mg PO three times a day	250 mg/m^2 IV q8h *or* 15 mg/kg/day PO q4h	
Herpes zoster			
Not severe†	800 mg PO five times a day	20 mg/kg PO four times a day	
Severe	10 mg/kg IV q8h	500 mg/m^2 IV q8h	Elderly: 7.5 mg/kg IV q8h
Primary varicella	10 mg/kg IV q8h	500 mg/m^2 IV q8h	

*Alternative for herpes simplex: famciclovir 250 mg three times a day, or valacyclovir 1 g two times a day PO.
†Alternative for herpes zoster: famciclovir 500 mg three times a day, or valacyclovir 1 g three times a day PO q8–12h.

choosing an antimicrobial agent include renal and hepatic function, drug allergies, suspected site of infection or organism, and cost. Antimicrobial resistance varies widely, and in the absence of a written hospital-specific protocol, immediate consultation with an oncologist or an infectious diseases specialist may be of great assistance.

Monotherapy with intravenous cefepime, ceftazidime, imipenem, meropenem, or piperacillin-tazobactam is preferred, with an aminoglycoside (gentamicin, tobramycin, or amikacin) added for the more seriously ill patient.[19,23,35,36] Monotherapy, without an aminoglycoside, may be advantageous in the patient with mild to moderate renal dysfunction or for patients on nephrotoxic agents such as cisplatin, cyclosporine, or amphotericin B. Ceftazidime-resistant gram-negative bacilli are common pathogens at some centers. In addition, ceftazidime is the least active against gram-positive organisms, compared with cefepime, cefotaxime, or ceftriaxone. Cefepime, a broad-spectrum cephalosporin with excellent activity against both gram-positive and gram-negative organisms including *P. aeruginosa*, is now preferred at many centers. The carbapenems imipenem and meropenem provide excellent activity against gram-negative organisms (including *P. aeruginosa*), gram-positive organisms, and anaerobic bacteria. None of the antimicrobial agents previously listed is active against vancomycin-resistant *Enterococcus* species or methicillin-resistant staphylococci.

For patients who are allergic to β-lactam antibiotics (e.g., penicillins, cephalosporins, imipenem, and meropenem), coverage of gram-negative bacilli, including *P. aeruginosa*, can be provided by aztreonam. Because aztreonam is not active against gram-positive or anaerobic bacteria, it should be combined with an antimicrobial such as vancomycin. If anaerobes are suspected (i.e., oral, abdominal, or perianal infection) in the β-lactam allergic patient or in the patient receiving cephalosporin monotherapy, an antianaerobic drug such as clindamycin or metronidazole should be administered. Empirical treatment with intravenous fluoroquinolones is not recommended in the febrile neutropenic cancer patient because of frequent prophylactic use of these agents in the cancer patient, risk for rapid emergence of resistance in gram-negative bacilli, and predisposition to *C. difficile* infection.[19,37,38]

When a focus of infection is identified, empirical therapy should cover the most likely pathogens causing infections at the site. For example, patients with pneumonia may need coverage for *Legionella* (fluoroquinolone, azithromycin, doxycycline, or erythromycin), *Pneumocystis* (TMP-SMX), or fungi (amphotericin B) in addition to standard antibacterial coverage. Agents effective against anaerobes (clindamycin, metronidazole, imipenem, meropenem, and piperacillin-tazobactam) should be considered for patients with perianal or oral infection and those with abdominal pain, who may have appendicitis, diverticulitis, or typhlitis (neutropenic enterocolitis). Acyclovir should be considered for patients with ulcerative or vesicular lesions who may have herpes simplex or varicella zoster virus infections. Ganciclovir may be required to treat cytomegalovirus infection, which is rare in febrile neutropenic cancer patients. Foscarnet may be needed for acyclovir-resistant herpes simplex or ganciclovir-resistant cytomegalovirus infections. In patients with severe mucositis and febrile neutropenia, a carbapenem or extended-spectrum penicillin is preferred for empirical treatment rather than a higher-generation cephalosporin because of superior efficacy against viridans streptococci.

Routine empirical use of vancomycin for the febrile neutropenic cancer patient is not recommended because of concern about the development of vancomycin-resistant organisms.[26,39,40] Randomized clinical trials show no survival advantage when vancomycin is in the initial therapy for all neutropenic patients, even those with indwelling catheters. Because most infections with gram-positive bacteria are indolent, vancomycin therapy can be safely delayed for 24 to 48 hours in most patients until a vancomycin-requiring gram-positive infection is identified.[41]

Indications for initial empirical vancomycin therapy include serious catheter-related infections, known colonization with penicillin-resistant pneumococci or methicillin-resistant *S. aureus*, and positive blood culture for gram-positive organisms before final identification and susceptibility testing. Other indications include shock, severe mucositis, prior fluoroquinolone prophylaxis, and institutions in which methicillin-resistant *S. aureus*, vancomycin-susceptible enterococci, and *S. mitis* are frequent pathogens.

Amphotericin B (and its lipid formulations) is the drug of choice for treatment of invasive fungal infections in patients with neutropenia.[19,39,42] Up to one third of febrile neutropenic patients not responding to 1 week of antibiotics have systemic fungal infections, usually *Candida* or *Aspergillus*. Antifungal agents, such as caspofungin, voriconazole, or posaconazole, may be indicated in selected cases. Empirical use of fluconazole is not recommended because of lack of activity against *Aspergillus* and some *Candida* species.

Cell Stimulation Therapy. To prevent and treat neutropenia, some centers routinely use human recombinant hematopoietic or colony-stimulating growth factors (G-CSF-filgrastim, pegfilgrastim; GM-CSF-sargramostim) to stimulate the proliferation and maturation of bone marrow progenitor cells and increase the number and function of these committed cell populations. Although safe and well tolerated, they are very expensive. Treatment with these agents after chemotherapy may shorten the hospital stay and the duration of fever, but no good evidence exists that they prolong survival or affect the frequency of severe infections. Many authorities recommend that use of these agents should be limited to high-risk neutropenic patients, such as those with severe sepsis, multiorgan failure, or recurrent febrile neutropenia and elderly patients.[19,43,44]

Risk Assessment for the Patient with Febrile Neutropenia, Including the Concept of Brief Observation and Early Discharge of the Low-Risk Patient. Febrile neutropenic cancer patients can be classified into high-risk and low-risk groups.[19,45-47] Factors associated with high-risk patients include (1) status as inpatient when fever and neutropenia develop; (2) the presence of comorbid medical conditions; (3) uncontrolled cancer; (4) acute leukemia; (5) hemodynamically unstable; (6) evidence of organ failure; (7) the presence of pneumonia, severe soft tissue infection, infection of a central line, abdominal pain, neurologic or mental status abnormalities; and (8) neutropenia expected to last more than 10 days. These patients should always be treated in the hospital with intravenous antibiotics.

Low-risk patients generally have an excellent outcome with therapy and are clinically stable outpatients with solid tumors, lymphomas, or chronic leukemia who lack any of the high-risk factors noted previously and who are not on fluoroquinolone prophylaxis. Low-risk patients with fever and neutropenia may be treated in the hospital with oral antibiotics, such as ciprofloxacin plus amoxicillin-clavulanate (or ciprofloxacin plus clindamycin in penicillin-allergic patients).[47-50] Furthermore, oral antibiotic therapy with early discharge is safe and effective in carefully selected low-risk patients.[51-53] Hospitalization exposes low-risk patients to potential iatrogenic complications and antimicrobial-resistant nosocomial pathogens, and early discharge followed by outpatient treatment allows an improved quality of life. Low-risk patients may be hospitalized initially, stabilized over 12 to 48 hours, and then discharged to continue parenteral or oral antibiotics. Some

authorities recommend a period of observation less than 12 hours, which may allow discharge from the emergency department, an observation unit, or physician's office.[47] The patient should be observed for at least 2 hours after administration of the first dose of antibiotics and only discharged after consultation with the patient's oncologist. Patients sent home need adequate instructions, family support, and easy access to a hospital in case of emergency.[47,54,55]

Non-neutropenic Conditions

The Solid Cancer Patient without Neutropenia. Most solid cancer patients who develop fever and infection are not neutropenic. Infections often occur after surgical procedures and may include wound infection, deep abscess, or perforated viscus. Infections may be associated with central venous catheters, urinary catheters, stents, and prosthetic devices. In addition, solid tumor patients with large tumor lesions may develop obstructive infections (of bronchus, bile duct, or ureter). The spectrum of microorganisms includes a wide variety of indigenous organisms (bacterial, fungal, and viral) as well as nosocomial multiantibiotic-resistant pathogens.

Prompt initiation of antimicrobial therapy in the febrile non-neutropenic solid cancer patient is not always indicated. Rapid surgical intervention may be more important than the urgent initiation of empirical antibiotics. In febrile non-neutropenic cancer patients who are not ill-appearing and have no identified focus of infection, it may be appropriate to obtain cultures and observe the patients. After consultation with an oncologist, some of these patients can be discharged home from the emergency department with close follow-up. Indications for urgent antibiotics in these patients include signs of sepsis, mental status changes, lactic acidosis, shock, abdominal pain, history of splenectomy, or identification of a focal site of infection.[56,57]

Impaired Cell-Mediated Immunity. The T cell defects resulting from impaired CMI in cancer patients usually result from cancer chemotherapy or corticosteroid treatment. The cancer impairs CMI in patients with Hodgkin's disease, non-Hodgkin's lymphoma, and hairy cell leukemia.

Bacterial Infections. *Listeria monocytogenes* is one of the more common bacterial organisms infecting cancer patients with impaired CMI.[58-61] *Listeria* infection is also seen in patients with organ transplants, diabetes, cirrhosis, and AIDS and in those receiving high-dose corticosteroids. No early characteristics distinguish *Listeria* infection from bacteremias caused by other organisms. Meningitis, which may be accompanied by cerebritis or brain abscess, is the most common focus of infection and may present with personality changes or focal neurologic signs.[62] Cerebrospinal fluid examination frequently does not reveal the organism on Gram's stain, but protein is elevated and pleocytosis is present. Treatment should be with ampicillin and gentamicin. TMP-SMX is the alternative drug for patients with penicillin allergy. Vancomycin is not effective in treating *Listeria* infections even when showing in vitro susceptibility. Cephalosporins, such as ceftriaxone and cefotaxime, are not active against *Listeria*.

Infections caused by *Salmonella* species are common in patients with impaired CMI and usually present with fever with or without enteritis.[63] Bacteremia can result in infection of bones, joints, central nervous system, and endovascular devices. Multidrug-resistant *Salmonella* species are increasing. Treatment usually includes a third-generation cephalosporin or a fluoroquinolone because many isolates have become resistant to ampicillin and TMP-SMX.[64]

Patients with solid tumors, lymphoma, and leukemia (especially hairy cell leukemia) are at increased risk for pneumonia from *Legionella* species, with the highest risk in cancer patients receiving high-dose corticosteroids.[65,66] Non-*pneumophila* species of *Legionella* (e.g., *Legionella micdadei* and *Legionella bozemanii*) are particularly common in these patients.[67] Clinical and radiographic manifestations of *Legionella* infection in the immunocompromised patient often differ from those in the immunocompetent host. For example, pleuritic chest pain may be a prominent symptom in the former and may mimic pulmonary embolism. These patients can have fever without any other symptoms of pneumonia despite the presence of radiographic pulmonary infiltrates. In addition, the chest radiograph may reveal an expanding pulmonary nodule or cavitation of a nodule or infiltrate rather than the usual lower lobe alveolar filling defects. Hyponatremia (serum sodium <130 mEq/L) is particularly common. Although gastrointestinal and neurologic symptoms and elevated serum transaminase levels are common in patients with *Legionella* infections, these are not more common in patients with *Legionella* than in those with other causes of pneumonia. The treatment of choice for immunocompromised patients with *Legionella* is a fluoroquinolone or azithromycin (alternatively, doxycycline or erythromycin, each combined with rifampin).

Nocardiosis is an uncommon but often severe bacterial infection caused by a weakly acid-fast gram-positive branching filamentous rod. It occurs in cancer patients, in those on high-dose corticosteroids, and in others with defective CMI.[68,69] Subacute pneumonia with nodular infiltrates is the most common manifestation, but *Nocardia* may also produce cellulitis, subcutaneous abscesses, meningitis, and brain abscess. Diagnosis requires biopsy, tissue stains, and culture. Treatment is with sulfonamides often combined with other agents.

Mycobacterial Infections. Tuberculosis and other mycobacterial diseases may produce severe disease in those with defective CMI and present as fever of undetermined origin, pneumonia, lymphadenopathy, or skin lesions.[70,71] It is easily mistaken for signs caused by the patient's underlying disease or treatment. Disseminated nontuberculous mycobacterial infections are more common in patients with hairy cell leukemia or chronic myelogenous leukemia.

Fungal Infections. Infections with *Cryptococcus neoformans* and *Cryptococcus gatti* occur in patients with Hodgkin's and non-Hodgkin's lymphoma, chronic myelogenous leukemia, and chronic lymphocytic leukemia, especially those taking high-dose corticosteroids.[72] Patients with HIV infection, solid organ transplants, diabetes, renal insufficiency, and cirrhosis are also at risk, as are patients on prolonged high-dose corticosteroids for connective tissue diseases. Meningitis is the most common manifestation, often presenting with the insidious onset of low-grade fever and subacute (and often intermittent) headache. Many other organ systems can become infected, including the lung, skin, bones, and joints. Diagnosis is made by measuring cryptococcal antigen (not antibody) in serum and CSF and by fungal cultures and tissue biopsy.[73]

Impaired CMI may result in reactivation of *Histoplasma capsulatum* and *Coccidioides immitis* with resultant disseminated disease. Infections with *Candida* species are also common in cancer patients with defective CMI, but disseminated disease is less likely than in patients with neutropenia. Invasive aspergillosis may develop in cancer patients receiving high-dose corticosteroids but not as commonly as in those with organ transplants or prolonged neutropenia. *Pneumocystis jirovecii* (formerly *carinii*) pneumonia is most common in patients with AIDS, leukemia, and lymphoma and in patients with solid tumors taking high doses of corticosteroids.

Parasitic Infections. Reactivation of central nervous system infection with the protozoan *T. gondii* occurs most often in cancer

patients with lymphoma and leukemia as well as in HIV infection. *Strongyloides stercoralis*, an intestinal nematode, is the only helminthic organism producing severe infection in patients with deficient CMI, almost exclusively in those receiving high-dose corticosteroids.[74,75] Larvae of the parasite disseminate from intestine to the lung and other organs, including the central nervous system and skin. Wheezing, cough, dyspnea, hemoptysis, and rash are common symptoms. Chest radiographs may show focal or diffuse infiltrates. Dissemination is often accompanied by bacterial infection, usually caused by enteric gram-negative bacilli carried by the parasites from the intestinal tract. Diagnosis includes examination of sputum and stool for parasites. Treatment of choice is ivermectin, with thiabendazole as a less effective alternative.

Viral Infections. The most common viruses producing serious infections in cancer patients with defective CMI are varicella zoster, herpes simplex, and cytomegalovirus.[76] Visceral dissemination is common in primary varicella in nonimmune immunocompromised children and adults. When a nonimmune immunocompromised child or adult is exposed to varicella, varicella zoster immune globulin (VariZIG, an investigational product available in the United States under an expanded access protocol) can be given within 96 hours of exposure to ameliorate the disease.[77] Herpes zoster infection is common in cancer patients, particularly those with Hodgkin's and non-Hodgkin's lymphoma and leukemia. Disease usually remains localized to the primary dermatome, but dissemination occurs in approximately 11% of patients. Dissemination is usually limited to the skin, but visceral involvement (lung and liver) occasionally occurs. Skin lesions in primary varicella or zoster often become hemorrhagic in these patients.

Reactivation of herpes simplex virus is common, resulting in severe mucocutaneous infection in oral or genital areas. Spread may occur to the esophagus, lungs, or other organs. Herpetic lesions in cancer patients tend to be larger and deeper than those in the immunocompetent patient. Acyclovir given intravenously is the treatment of choice for varicella zoster and herpes simplex infections in immunocompromised patients, but some authorities recommend oral famciclovir or valacyclovir for stable patients.

Cytomegalovirus infection may occur in cancer patients treated with corticosteroids. Measles virus, although uncommon, may produce severe infection with defective CMI. Fever, rash, pneumonia, and encephalitis are common manifestations. Immune serum globulin may be given after exposure to ameliorate disease. Common community respiratory viruses, such as respiratory syncytial virus, influenza, and adenovirus, may produce severe or fatal pneumonia.[78]

Humoral Immune (B Cell) Defects. Hypogammaglobulinemia is common in patients with chronic lymphocytic leukemia and myeloma. Low immunoglobulin levels predispose to infections with encapsulated bacteria, such as *S. pneumoniae*, *H. influenzae*, and *N. meningitidis*.[79-82] Pneumonia is the most common manifestation, but sepsis, otitis media, cellulitis, and urinary tract infection may occur. After receiving cytotoxic agents and corticosteroids for treatment, these patients become susceptible to infections associated with impaired CMI as well as bacterial infections caused by *S. aureus* and gram-negative bacilli. Regular infusions of intravenous immunoglobulin may decrease the incidence of infection but do not prolong survival. Patients should receive pneumococcal vaccine, but many do not respond.

Disruption of Natural Barriers. Disruption of natural anatomic barriers (e.g., mucous membranes and skin) by ulcerating tumors, chemotherapy, radiation, diagnostic and therapeutic procedures, and catheters can lead to infection by gram-positive and gram-negative organisms, including anaerobes.[83] Oral mucositis, a debilitating and intensely painful condition associated with radiation therapy and high-dose chemotherapy, frequently results in serious local and systemic infections, including life-threatening sepsis with viridans streptococci.[84,85] Cancers may cause partial or total obstruction of body lumens and cavities. Stenosis of a lumen may result from radiation. Bronchial obstruction by tumor can lead to pneumonia. Obstruction of the urinary tract may result in infection. Gastrointestinal tract obstruction can lead to perforation and peritonitis.

Opportunistic Infections Mimicking Neoplasm. Infectious agents can produce laboratory, radiologic, or physical findings that resemble those caused by the spread of tumor. For example, mass lesions in the brain caused by *Nocardia* or *Toxoplasma* can be mistaken for cancer metastases. *Aspergillus*, *Mucor*, *Rhizopus*, and related fungi invade blood vessel walls and produce thrombosis, which may result in Budd-Chiari syndrome (hepatic vein obstruction), nephrotic syndrome, or oculomotor palsy that may be misattributed to the spread of tumor. Renal vein thrombosis can be caused by infection with gram-negative bacilli. *Candida* fungus balls may develop in one or both ureters, producing a picture of postrenal obstructive uropathy. *Histoplasma*, *Pneumocystis*, *Legionella*, *Aspergillus*, *Nocardia*, and other organisms can produce pulmonary nodules and be mistaken for pulmonary metastases.

Pulmonary Infections in the Immunocompromised Patient. In neutropenic cancer patients, pneumonia is commonly caused by gram-negative bacilli early in neutropenia and by fungal organisms such as *Aspergillus* late. In those with impaired CMI, cytomegalovirus, *Pneumocystis*, *Legionella*, *Nocardia*, mycobacteria, and fungal infections predominate. Pneumococcal pneumonia is most common in patients with impaired humoral immunity. Patients with primary lung cancer or with pulmonary metastases from other cancers develop postobstructive pneumonia, lung abscess, and empyema related to *S. aureus*, gram-negative bacilli, and anaerobes. Mimics of pneumonia in the immunocompromised host include pulmonary emboli and infarction, congestive heart failure, metastatic or primary carcinoma, lymphangitic spread of carcinoma, alveolar hemorrhage, leukoagglutinin reactions, and radiation- and drug-induced pneumonitis.[86] An acute presentation of "pneumonia" suggests bacterial pneumonia, pulmonary emboli, congestive heart failure, or pulmonary hemorrhage. Subacute presentation suggests a fungal, nocardial, mycobacterial, or viral etiology (Table 181-3).[87,88]

Diabetes

Diabetic patients have increased susceptibility to infection because of defects in immune function, excess substrate for fungal and bacterial growth, vascular insufficiency related to microangiopathy and atherosclerosis, and sensory neuropathy that leads to wound neglect.[89-91]

Neutrophil and monocyte/macrophage functions are impaired in diabetic patients, including adherence to bacteria, chemotaxis, phagocytosis, and intracellular killing. These defects are exacerbated by hyperglycemia and improved by tight glucose control. Although decreased lymphocyte proliferative responses to phytohemagglutinin and certain pathogens are described, cellular immunity appears normal or only minimally affected by diabetes. Humoral immunity is normal in diabetics.[92,93]

Infections seen with increased frequency in diabetic patients include rhinocerebral zygomycosis (formerly mucormycosis) caused by *Rhizopus* and *Mucor* species; malignant (or necrotizing) otitis externa caused by *P. aeruginosa*; pneumonia caused

Table 181-3 Pulmonary Infiltrates in the Immunocompromised Patient: Common Patterns of Disease and Differential Diagnosis

DIFFUSE BILATERAL INFILTRATES	FOCAL OR PATCHY INFILTRATES
Viruses	Bacterial pneumonias, including *Legionella*
Cytomegalovirus	Fungi
Respiratory syncytial virus	Invasive pulmonary aspergillosis
Influenza, parainfluenza	Zygomycosis (mucormycosis)
Adenovirus	*Fusarium*
Varicella	*Pseudallescheria*
Pneumocystis jirovecii	Tuberculosis
Fluid overload and pulmonary edema	Nontuberculous mycobacteria
Acute lung injury due to transfusion of blood products	Nocardiosis
Radiation damage	Pulmonary embolus
Chemotherapy-induced toxicity	
ARDS due to viridans streptococcal bacteremia	
Bronchiolitis obliterans	
Pulmonary hemorrhage	
Progression of disease (lymphangitic spread of carcinoma, leukemic infiltrates)	

by *S. aureus* and gram-negative bacilli; tuberculosis, emphysematous cholecystitis, and urinary tract infections including emphysematous cystitis and pyelonephritis; polymicrobial necrotizing fasciitis involving the perineum (Fournier's gangrene) and lower extremities; and psoas abscess, spinal epidural abscess, and foot infections with osteomyelitis. Diabetics are not more likely to develop pneumococcal pneumonia but are more likely to become bacteremic and have a higher mortality rate.

Alcoholism and Cirrhosis

Alcohol consumption predisposes to infection through direct suppression of the immune system, alterations in blood flow, depression of mental status, and delay in seeking medical care.[94]

With alcoholic cirrhosis, there is deficient hepatic clearance and killing of bacteria by reticuloendothelial cells, as well as splenic hypofunction.[95] Complement deficiency occurs because the liver is the primary site of C3 synthesis. Neutrophils show impaired recruitment to infective sites and defective chemotaxis and phagocytosis.[96,97] Cellular immune deficiency occurs and is exacerbated by malnutrition. Bactericidal activity of IgM antibody against gram-negative pathogens such as *E. coli* and *H. influenzae* is decreased.

Acute ethanol intoxication is associated with granulocytopenia and diminished leukocyte mobilization that is reversible with abstinence. Ethanol intoxication interferes with most respiratory tract defense mechanisms, resulting in alterations of normal flora, impaired mechanical and cellular clearance because of a suppressed cough reflex, decreased ciliary motility, and resultant aspiration. These effects are often compounded by malnutrition, cigarette smoking, and chronic lung disease. Alcoholics exhibit an increased incidence of oropharyngeal colonization by gram-negative bacteria (35–59% of ambulatory alcoholic patients) compared with control subjects (14–18%). Alcoholics are also more likely to aspirate because of loss of reflex glottic closure associated with acute intoxication, withdrawal seizures, and encephalopathy.

Common infections include spontaneous bacteremia and sepsis caused by *E. coli*, *K. pneumoniae*, *Salmonella*, streptococci, *Vibrio vulnificus*, and *Aeromonas*; spontaneous bacterial peritonitis, usually caused by *E. coli*, *K. pneumoniae*, *S. pneumoniae*, or enterococci; pneumonia related to pneumococci, gram-negative bacilli (*E. coli*, *K. pneumoniae*, and *H. influenzae*), and anaerobes; tuberculosis; meningitis caused by *S. pneumoniae* and *L. monocytogenes*; and skin and soft tissue infections with *S. aureus*, streptococci, and gram-negative bacilli. Nasopharyngeal and cutaneous diphtheria also occurs.[98]

Renal Failure

Infections cause up to 20% of all deaths among patients with chronic renal failure and are the second most common cause of mortality after coronary artery disease.[99,100] Disruption of cutaneous barriers at vascular access sites and peritoneal dialysis catheter sites as well as numerous immune system defects are responsible for the increased incidence of infection. Uremic pruritus with excoriation, epidermal and sweat gland atrophy, dryness, and vesicular eruptions also compromise the cutaneous barrier. Reduced renal clearance of unknown toxins, nutritional deficiencies, and administration of immunosuppressive medications lead to aberrant immune regulation early in the course of renal failure.

Chronic kidney failure leads to a state of generalized immune hyporesponsiveness. Neutrophils show reduced mobility, chemotaxis, adherence, phagocytosis, and intracellular bactericidal activity, and leukopenia is commonly present. CMI is severely impaired, with decreased activation and proliferation of T lymphocytes and reduced NK cell activity, which cannot be reversed by hemodialysis. Furthermore, humoral immunity is adversely affected, resulting in deficient production of certain IgG subclass antibodies. Poor response to vaccines is common but can be improved by reinforced vaccination schedules, increased vaccine dosage, and adjunct immunomodulators.[101]

Additional predisposing factors to infection in uremic patients include low serum albumin, iron overload, increased intracellular calcium, circulating low-molecular-weight uremic toxins, metabolic acidosis, circulating inhibitors to chemotactic factors, decreased production of endogenous pyrogens, and invasive vascular procedures for dialysis access. The annual mortality rate from sepsis in dialysis patients is increased 100 to 300 times.[102]

Skin and soft tissue infections, especially those caused by *S. aureus*, are particularly severe in diabetics and in those with peripheral vascular disease or peripheral neuropathy. Vascular access site infections are usually caused by *S. aureus* but occasionally by gram-negative bacilli and enterococci. Patients using central venous catheters for dialysis have much higher rates of sepsis compared to fistulas or grafts. Bacteremia may lead to hematogenous osteomyelitis, usually involving the ribs or thoracic vertebrae, as well as endocarditis, meningitis, epidural abscess, and septic arthritis. Although the incidence of pneumonia is not increased overall in renal failure, it is often more severe, and there is an increased incidence of *Legionella* pneumonia. Tuberculosis as well as fungal infections caused by *Candida* species, *Cryptococcus*, *Histoplasma*, and *Coccidioides* occur with increased frequency. In addition, *C. difficile* colitis occurs more frequently and is more severe in patients with chronic renal failure. Infections of the urinary tract are more prevalent, with urinary bladder catheterization the most frequent predisposing factor. There is a poor correlation between the presence of pyuria and urinary tract infection in these

patients. *Candida* infection of the urinary tract may develop in patients with chronic renal failure treated with broad-spectrum antibiotics.

Up to two thirds of patients receiving chronic ambulatory peritoneal dialysis have peritonitis in their first year, and one third may be forced to discontinue dialysis because of recurrent infections. *S. aureus* and *S. epidermidis* predominate, followed by streptococci, gram-negative bacilli, and *Candida* species. Fortunately, peritoneal dialysis patients have much lower rates of sepsis than those on hemodialysis.

Splenectomy, Hyposplenia, and Functional Asplenia

The spleen is the most important organ in the reticuloendothelial system and the primary site for IgM synthesis, the first early immune response of the body. Opsonin production in the spleen facilitates phagocytosis of bacteria by intracellular macrophages. Patients without a spleen also have decreased production of neutrophils, NK cells, and immunomodulating cytokines.[103,104]

The spleen is the principal site of clearance of *S. pneumoniae* from the blood. Splenectomy or functional asplenia predisposes to overwhelming pneumococcal infection and fulminant infection with other encapsulated organisms (*H. influenzae*, *N. meningitidis*, and *Capnocytophaga canimorsus* after dog bites) and gram-negative bacilli (*E. coli* and *P. aeruginosa*). Asplenic people who become infected with *Babesia microti*, a malaria-like protozoan transmitted by tick bite in the United States, develop severe and often fatal hemolysis. Human granulocytic anaplasmosis (formerly ehrlichiosis), another tick-borne infection, is severe and sometimes fatal in asplenic patients. In addition, the gram-negative coccobacillus *Bordetella holmesii* produces a non-life-threatening acute febrile illness with bacteremia in patients with asplenia. Pneumococcal sepsis represents 50 to 90% of cases. Most healthy adults who die after fulminating pneumococcal sepsis have had a splenectomy or have a congenitally small or abnormal spleen.[105-108]

Overwhelming postsplenectomy sepsis is rare, and the true incidence is unknown due to lack of prospective studies.[109] The risk is greater in children than in adults, with children younger than 2 years at greatest risk. The risk is highest in the first few years after splenectomy but persists throughout life into old age. People undergoing splenectomy for a hematologic disorder or lymphoma are at much higher risk for overwhelming postsplenectomy infection (OPSI) than are those undergoing splenectomy for trauma. This is probably because of the occurrence of splenic implants (splenosis) or accessory spleens in traumatized patients. Patients with functional asplenia from sickle cell anemia or thalassemia major are at high risk for overwhelming bacterial infections as well.

Functional hyposplenism occurs in a variety of conditions besides sickle cell disease, including sickle cell–hemoglobin C disease, ulcerative colitis, celiac disease, sarcoidosis, amyloidosis, rheumatoid arthritis, and SLE. The presence of anatomic or functional hyposplenism may be recognized by finding Howell-Jolly bodies in red blood cells on a peripheral blood smear.

When OPSI occurs, often no obvious source of infection is found. Prodromal symptoms, such as fever, rigors, malaise, myalgias, headache, vomiting, and diarrhea, may be present for 1 or 2 days.[110] Patients seen at this time may be misdiagnosed as having a viral illness, gastroenteritis, or food poisoning. Abrupt deterioration then occurs over hours, with rapid progression to septic shock with disseminated intravascular coagulation, purpura, and multiorgan dysfunction. The mortality rate is high (50–70%), with younger children having the highest mortality rate. In addition, meningitis without overwhelming infection or shock is a common presentation of pneumococcal infection in asplenic patients.[111] When fever develops in a person at risk for this disorder, treatment with an antimicrobial agent effective against *S. pneumoniae* should be initiated without delay. After blood culture is performed, the patient should receive ceftriaxone or cefotaxime, with addition of vancomycin in areas where penicillin resistance is prevalent. Clindamycin, levofloxacin, and moxifloxacin are alternatives for patients with serious penicillin allergy.

Use of pneumococcal vaccine in patients at risk is especially important now that antimicrobial-resistant *S. pneumoniae* is prevalent.[112] Asplenic people should be immunized against pneumococcus, *H. influenzae* type B, *N. meningitidis*, and influenza virus. People with functional hyposplenism related to serious underlying diseases often respond poorly to pneumococcal vaccine. Children should receive prophylaxis with oral penicillin or amoxicillin up to age 5 years and for at least 1 or 2 years after splenectomy, provided that they have not had an invasive pneumococcal infection and have received pneumococcal immunizations. Long-term antimicrobial prophylaxis is generally not recommended in adults. These patients should have standby oral antibiotics at home (amoxicillin-clavulate, levofloxacin, or moxifloxacin) with instructions to self-administer at the first sign of infection, and they should be provided with information and a medical alert bracelet. Fatal pneumococcal infection has occurred in patients immunized with pneumococcal vaccine who were also taking penicillin. An emergency department–based pneumococcal vaccine program, if implemented, could reduce mortality in high-risk patients while remaining cost-effective.[113,114]

IMMUNOSUPPRESSIVE THERAPY

Corticosteroids

High doses of corticosteroids alter the distribution and function of neutrophils, monocytes, and lymphocytes.[115] Corticosteroids suppress inflammation and enhance susceptibility to infection by impairing the mobilization and function of neutrophils and mononuclear cells at sites of primary lodgment of microorganisms in tissues. Corticosteroids inhibit neutrophil adherence to endothelium, decrease chemotaxis of neutrophils and monocytes, and inhibit phagocytosis and intracellular killing of microorganisms. Corticosteroids also severely impair CMI, probably a result of inhibition of the migration of lymphocytes to the site of antigen challenge, inhibition of lymphokine production, and consequent inhibition of lymphocyte proliferation. They also inhibit both classical and alternative pathways of complement activation. The hyperglycemia that occurs with corticosteroid use also contributes significantly to infection risk. Moreover, patients receiving high-dose corticosteroids have infection risks related to anatomic abnormalities of the underlying disease, treatment with other immunosuppressive agents, cancer chemotherapeutic agents, radiation, and implantation of foreign bodies.[116-118]

Acute administration of corticosteroids produces marked alterations in circulating leukocyte numbers. Basophils, eosinophils, and monocytes decrease, whereas neutrophils are increased. These changes occur within 4 to 6 hours and abate by 24 to 48 hours after a single steroid dose. There is a redistribution of lymphocytes, predominately T cells, out of the circulation, resulting in lymphocytopenia. Acute or chronic corticosteroid therapy has little effect on serum immunoglobulin levels.

The most common infections occurring in patients receiving high-dose corticosteroids are those caused by pyogenic bacte-

ria (*S. aureus*, streptococci, and gram-negative bacilli). Despite the profound depression of CMI that occurs in patients taking corticosteroids, these patients generally have few infections commonly recognized as associated with defective CMI. The most common are tuberculosis and severe or disseminated infections caused by varicella zoster and herpes simplex viruses. Patients receiving moderate doses of corticosteroids for asthma and other disorders are at increased risk for lethal primary varicella infection.[119] Other infections seen with corticosteroid use include those caused by *Listeria*, *Salmonella*, *Legionella*, *Nocardia*, *Candida*, *Aspergillus*, *Cryptococcus*, *Histoplasma*, *Coccidioides*, *Pneumocystis*, *Toxoplasma*, *Cryptosporidium*, and *Strongyloides*. Patients with neurologic diseases have much higher rates of infectious complications than patients with intestinal, hepatic, or renal disease. The infectious complications related to corticosteroid use increase with doses of prednisone equivalents of greater than 20 mg/day in adults, with total doses of more than 700 mg, and with treatment longer than 30 days. The risk of adrenal suppression can be decreased by using prednisone doses less than 7.5 mg/day, giving doses early in the day, avoiding split doses, and using alternate-day dosing.

Corticosteroids decrease leukocyte accumulation at inflammatory sites, and the whole cascade of responses leading to local manifestations of infection is slowed. These effects result in late presentation of serious infections. The ability of parietal cavities to localize sepsis is reduced. In addition, prolonged administration of corticosteroids results in delayed wound healing. For example, skin sutures should be left in place 50 to 100% longer than in normal patients. Short-term treatment has little effect on wound healing.[120]

The diagnosis of peritonitis resulting from perforation of colonic diverticula, appendicitis, peptic ulcer, or another primary intra-abdominal condition is particularly difficult.[121] These patients have abdominal discomfort, but they may have few abdominal findings and need rapid and aggressive investigation for life-threatening abdominal disease. CT scan of the abdomen and pelvis and surgical consultation may be needed emergently in these patients. Broad-spectrum antimicrobials to cover for gram-negative enteric bacilli and anaerobes should be administered without delay.

Other complications unrelated to the effects on the immune system include iatrogenic Cushing's syndrome, peptic ulcer disease, benign intracranial hypertension (pseudotumor cerebri), glaucoma, posterior subcapsular cataract, pancreatitis, avascular necrosis of bone (especially the femoral and humoral heads), psychosis, poor wound healing, hyperglycemia, diabetic ketoacidosis, hyperosmolar nonketotic diabetic coma, myopathy, and osteoporosis, resulting in vertebral compression fractures and other spontaneous fractures. In addition, adrenocortical insufficiency may occur on withdrawal of therapy.

Other Immunosuppressive Medications

Commonly used immunosuppressives include cyclosporine, tacrolimus, sirolimus, mycophenolate, azathioprine, methotrexate, and cyclophosphamide. They treat a wide variety of conditions, including rheumatoid arthritis, psoriasis, nephrotic syndrome, and inflammatory bowel disease, and they are used in the prevention and treatment of organ transplant rejection.[122] These drugs depress immune function, especially CMI. In addition, they have a narrow therapeutic window, wide-ranging toxic side effects, and many significant drug-drug and drug-food interactions. Patients may present to the emergency department for evaluation of symptoms caused by an adverse drug reaction or an infection. Before altering current medications, the physician needs to check carefully for drug interactions. For a more detailed discussion of the toxic effects of these agents, refer to Chapter 182.

New immunomodulating agents that inhibit tumor necrosis factor, interleukins, and other cytokines treat a variety of immune-mediated inflammatory diseases, including rheumatoid arthritis, psoriasis, and inflammatory bowel disease. These drugs include infliximab, etanercept, adalimumab, rituximab, basiliximab, daclizumab, abatacept, anakinra, and leflunomide. Serious infections, including bacterial sepsis, are reported after treatment with several of these agents, especially reactivation of latent *M. tuberculosis* infection, frequently disseminated and extrapulmonary at presentation.[123-127] These drugs may also cause impaired wound healing, so skin sutures should be left in place for a longer amount of time than is usual.[128]

KEY CONCEPTS

- Fever in cancer patients with chemotherapy-induced neutropenia indicates infection until proved otherwise, most often caused by gram-positive and gram-negative bacteria but also by a wide variety of fungal, viral, mycobacterial, and protozoal organisms.
- Rapid diagnosis and early initiation of therapy are essential in preventing serious morbidity and mortality in immunocompromised patients who often have subtle or unusual presentations and are difficult to diagnose. Early use of broad-spectrum antibiotics is indicated after appropriate cultures of all potential sites of infection, including intravascular catheters.
- Diabetics, alcoholics, and patients with renal failure, cirrhosis, and collagen vascular diseases all have varying degrees of immunosuppression.
- Patients with functional or surgical asplenia are at high risk for overwhelming sepsis from encapsulated bacteria, especially pneumococci.
- High doses of corticosteroids cause profound dysfunction of neutrophils and mononuclear cells and impair cell-mediated immunity, resulting in a marked increase in infections caused by pyogenic bacteria, varicella zoster and herpes simplex viruses, tuberculosis, and a wide variety of other bacteria, fungi, and parasites.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 182

The Solid Organ Transplant Patient

Matthew T. Keadey

PERSPECTIVE

The successful rehabilitation of patients with end-stage renal, pulmonary, hepatic, and cardiac failure through organ transplantation is one of the great achievements of modern biomedical science. Because 1-year survival rates for all solid organ transplants exceed 80% and many patients survive much longer, increasing numbers of transplant patients with complications are being seen in the emergency department (ED).

PRINCIPLES OF DISEASE

Transplanted organs are devoid of their native innervations and have surgical anastomoses to a variety of structures, including vessels, heart chambers, bronchi, ureters, intestines, and even the bladder, depending on the allograft. Pain is therefore an unreliable sign of underlying disease. Furthermore, the normal inflammatory and immunologic responses to infection and malignancy are impaired. Subtle symptoms and signs may be the harbingers for serious complications of organ transplant, and each complaint merits careful investigation. Even in the most advanced stages of severe disease, patients may have few specific complaints and physical findings. Anatomic relationships must be considered to anticipate leakages or blockages of vital anastomoses. The baseline physiologic capacity of the allograft will aid in interpreting chief complaints in the context of possible organ failure. Small changes in allograft function may be a harbinger of an episode of rejection.

Transplant organ complications can generally be classified into one of four categories: anatomy, infection, rejection, and drug toxicity. In any transplant patient presenting to the ED, each category must be considered in the differential diagnosis. Often, the exact etiology is not determined until the patient is admitted to the hospital. Time since transplant must also be considered in the evaluation. This information can help the clinician focus his or her investigative efforts and tailor treatment regimens.

Anatomy

Anatomic complications of solid organ transplants can be categorized into three groups: vascular, nonvascular anastomosis, and complications related to surgery. Often, these present early in the post-transplant course, but delayed presentations can occur.

Vascular complication can include both arterial and venous structures. Acute thrombosis of arteries may lead to fulminate organ failure. This is especially true in liver transplant recipients in whom the hepatic artery is the sole source of blood flow for the biliary system. Arterial stenosis may also develop later in the course, with its effects typically determined by the degree of blood flow restriction. Pseudoaneurysms may also develop, possibly leading to arterial rupture, which is heralded by hypovolemic shock and a precipitous drop in the patient's hematocrit.

Nonvascular organ anastomosis may include bile ducts, bronchi, and ureters. Complications related to these structures include leaks and obstructions that often lead to acute graft dysfunction. Early identification is vital in leading to salvage of the graft. Leaks often present with pain and may lead to abscess formation. Conservative therapy may include antibiotics and percutaneous drainage. Refractory or severe cases may require surgical intervention. Obstructions may occur due to scar tissue, migration of stents, or stone development. If untreated, graft dysfunction may lead to infections such as cholangitis and pyelonephritis. Bronchial leaks may cause a pneumothorax or pneumomediastinum. Prolonged leaks may lead to abscess formation in the thorax, requiring antibiotics and surgical drainage.

Complications related to the surgery are directly associated with the procedure but not specific to the transplanted organ. These may include problems related to technique that lead to hematoma or lymphocele formation. Any cause of fever in the acute postoperative period must be evaluated for complications specific to the transplanted organ as well as other common causes of postoperative fever.

Infection

Lifelong immunosuppression is generally necessary for all recipients of solid organ transplants. Because of this, infection is the primary cause of mortality after transplantation. Two thirds of transplant patients have at least one significant infection, most commonly nosocomial during the surgical recovery period or subsequently community acquired (Box 182-1).[1,2]

Signs of infection in this patient population are often blunted by an impaired inflammatory response. Minimal complaints or the chief complaint of a fever in an afebrile patient may herald a severe infection. Aggressive management usually translates into increased patient survival and graft function.[1]

Primary sources of infection in transplant recipients include pretransplant, community acquired, transmission from organ donor, and nosocomial. Transplant patients may be vaccinated,

BOX 182-1 INFECTIOUS PATHOGENS IN TRANSPLANT PATIENTS

Exposure before Transplantation
Tuberculosis
Histoplasmosis
Coccidioidomycosis
Blastomycosis
Strongyloides stercoralis
Hepatitis B and C
Human immunodeficiency virus
Cytomegalovirus (CMV)
Epstein-Barr virus (EBV)
Varicella zoster virus
Herpes simplex virus

Community-Acquired Exposure after Transplantation
Influenza
Primary varicella
Salmonellosis
Tuberculosis and fungal infections (see above)
Legionellosis
Nocardiosis
Cryptococcosis
CMV
EBV

Nosocomial Exposure
Aspergillosis
Legionellosis
Pseudomonas aeruginosa and other gram-negative bacilli

Modified from Gorbach S (ed): Infectious Diseases. Philadelphia, Saunders, 1992.

but live viral antigens should be avoided. Close family members should not be given live vaccines due to the risk of transmission. The timing of infection can be separated into three periods: first month post-transplant, between 1 and 6 months post-transplant, and more than 6 months post-transplant. These distinctions are helpful in predicting the etiologic agents of the infection.

First Month after Transplant

Infections occurring in the first month after transplantation are likely to be related to the transplant procedure, catheters, and intubation. In addition, the typical causes of postoperative fever must always be considered in the workup. Nosocomial pathogens are prominent, and management is similar to that for any immunosuppressed patient recently discharged from the hospital.[2]

1 to 6 Months after Transplant

Infections occurring from 1 to 6 months after transplant are divided into two general types: immunomodulating viral infections and opportunistic infections. Immunomodulating viruses include cytomegalovirus (CMV), hepatitis B and C, BK polyomavirus, human herpesvirus 6, and Epstein-Barr virus (EBV), whereas opportunistic infections include *Pneumocystis*, *Listeria*, and fungal species.

CMV is the most important and prevalent immunomodulating virus 1 to 6 months after transplantation.[1] CMV infection may produce disease in multiple systems, but pneumonitis is particularly common and may present insidiously. CMV infection may be primary or due to reactivation from latent viral particles found in lymphocytes. Typically, signs of CMV infection occur at a median of 40 days after transplant. Survival from CMV infection is improving due to earlier diagnosis from aggressive use of bronchoscopy and treatment with gangcyclovir and CMV-specific immunoglobulin. Prophylaxis with gangcyclovir reduces CMV incidence and death due to infection, but the use of routine gangcyclovir is associated with a number of potential unwanted side effects.[3] Because the risk of CMV infection is greatest during antilymphocyte therapy, some transplant centers only administer gangcyclovir selectively during the treatment period. Despite these advances, however, CMV infection is still often fatal.[4,5]

Active CMV infection can also trigger or exacerbate organ rejection. CMV is linked to a particular form of glomerulopathy in renal allograft recipients, as well as acute hepatic dysfunction and the disappearing bile duct syndrome of chronic hepatic allograft dysfunction.[6,7] Furthermore, both acute cardiac dysfunction and accelerated coronary artery atherosclerosis of chronic heart transplant rejection are linked to CMV.[8,9]

EBV infection causes similar clinical effects as those caused by CMV. EBV contributes to the net state of immunosuppression and can cause a mononucleosis-like syndrome associated with lymphadenopathy, weakness, and low-grade fevers. Because CMV and EBV often coexist, it is unknown whether EBV alone causes or triggers graft rejection independently. EBV is also implicated in B cell lymphoproliferative syndrome, which is histologically similar to polymorphic B cell lymphoma.[10]

6 Months after Transplant

Six months or more after transplant, patients with functioning solid organ allografts receiving immunosuppression therapy are divided into three groups relative to infection susceptibility: healthy transplant, chronic viral infection, and chronic rejection.

Healthy Transplant. Healthy transplant patients have no chronic immunomodulating viral infections and a functioning allograft. They have a mildly increased susceptibility to normal community-acquired infections, such as influenza, urinary tract infection, and pneumococcal pneumonia.

Chronic Viral Infection. Progressive disease may develop as a result of the combination of viral immunomodulating infections and long-term immunosuppression. Progressive liver disease due to recurrent or acquired viral hepatitis may occur as well as hepatocellular carcinoma. B cell lymphoproliferative disorder associated with EBV infection may also develop.[1,2]

Primary varicella infection may lead to rapid dissemination with pneumonia, pancreatitis, hepatitis, encephalitis, and disseminated intravascular coagulation. Patients who are varicella zoster virus (VZV) seronegative need high doses of intravenous (IV) varicella zoster immune globulin after any exposure. Therapy can be lifesaving if it is administered early before dissemination occurs.[1,2]

Reactivation of latent VZV infection, manifested as cutaneous herpes zoster, affects at least 10% of solid organ transplant recipients. Fortunately, reactivation of VZV is usually confined to a single dermatome and does not disseminate. Hospitalization for IV acyclovir therapy should be considered because this speeds healing but does not change the incidence of painful neuralgia. Facial zoster specifically involving the cornea, however, and disseminated infections found in more than one dermatome are indications for admission.[1]

Herpes simplex virus (HSV) reactivation is common after solid organ transplants and can manifest as oral or anogenital lesions, more often ulcers than vesicles. Some transplant centers prescribe oral acyclovir for 3 to 6 months after transplantation, whereas others choose to treat HSV immediately

at the first sign of recurrence.[11] Typically, these patients can be treated as outpatients if they tolerate oral medications and pain is controlled.

Chronic Rejection. Patients with chronic rejection require ongoing aggressive immunosuppressive treatment to protect the allograft. These patients are at highest risk of life-threatening opportunistic infections with fungi (e.g., *Candida*, *Cryptococcus*, *Coccidioides*, *Blastomyces*, and *Histoplasma*), bacteria (e.g., *Listeria* and *Nocardia*), and parasites (e.g., *Pneumocystis*, *Toxoplasma*, and *Strongyloides*).

Fungal infections are distinct to geographic regions and typically present with subacute respiratory complaints associated with fever and focal, disseminated, or miliary infiltrates on chest radiograph.[1] Invasive candidiasis and aspergillosis are also problems in the chronically immunosuppressed group. Primary infections in the lungs, gastrointestinal (GI) tract, or nasal sinuses lead to fungemia and seeding of IV lines and wounds. Treatment is with antifungal agents such as amphotericin B, paying special attention to potential renal toxicity.

Diverticulitis is the principal bacterial GI infection observed in transplant patients considered to have chronic rejection. Inflammation is suppressed with chronic steroid therapy, leading to an increased incidence of perforation before diagnosis. Patients complain of an insidious onset of pain, change in bowel habits, and sometimes fever, but they typically lack peritoneal signs. Transplant patients also have increased susceptibility to invasion of the mucosa with salmonellae (nontyphoidal) and *Listeria*. Both organisms can be present as acute diarrheal syndromes that progress to bacteremia or meningitis.[1,2]

Pulmonary infection with *Nocardia asteroides* may occur in transplant patients. Primary infection is subacute, with cough, fever, pleurisy, purulent sputum, and subsequent metastatic infection of the brain and skin. Seizures or subcutaneous nodules may be the presenting complaint with primary *Nocardia* infection.

Pneumocystis carinii pneumonia (PCP) is often found in combination with CMV infection because CMV inhibits alveolar macrophage function (Fig. 182-1). Fortunately, its incidence is reduced with prophylactic low-dose trimethoprim-sulfamethoxazole (TMP-SMX). Without prophylaxis, infection develops 1 to 6 months after transplantation and presents subacutely with fever, nonproductive cough, progressive dyspnea, and an interstitial infiltrate on chest radiograph. Differentiation from CMV pneumonia is impossible without bronchoscopic confirmation. Treatment of PCP includes IV TMP-SMX and steroids, depending on the degree of hypoxia.

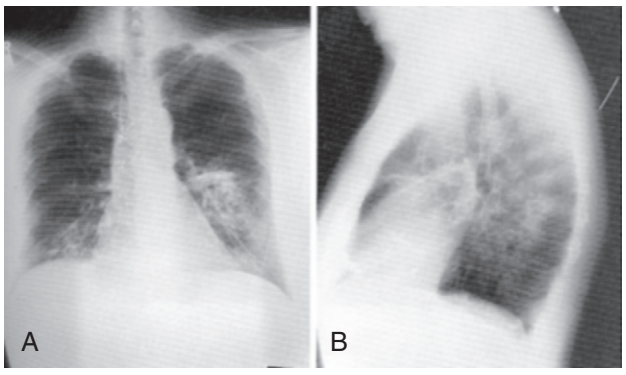


Figure 182-1. **A** and **B,** Bilateral perihilar and lower lobe alveolar infiltrates in a cardiac transplantation recipient from *Pneumocystis carinii*. (From Tewari S, Maurer J: Pulmonary considerations of organ transplantation. In Ginnes LG, Cosimi AB, Morris PJ [eds]: Transplantation. Malden, Mass, Blackwell Science, 1999, p 617.)

Disseminated toxoplasmosis is a particular problem in heart transplant patients. Toxoplasmosis can lay dormant in the tissues, especially the heart, and be reactivated during immunosuppression, resulting in myocarditis, brain abscesses, or diffuse encephalitis. Typically, treatment of toxoplasmosis is a combination IV sulfadiazine and pyrimethamine daily for more than 4 weeks.

Strongyloides stercoralis, an intestinal nematode that normally causes few or no symptoms, can become an invasive pathogen. During immunosuppression, a *hyperinfection syndrome* can develop, causing a necrotizing hemorrhagic enterocolitis. The exaggeration of the parasite's normal life cycle has a major impact on the GI tract and lungs (hemorrhagic pneumonia). Disseminated strongyloidiasis occurs when the larvae migrate from the GI tract into all portions of the body. Dissemination and hyperinfection are associated with gram-negative bacteremia and meningitis secondary to impairment of the blood-gut barrier.

Mycobacterial disease can present as opportunistic reactivation or a primary infection. Even disseminated disease can be clinically silent, with invasion of the bowel, skin, and GI tract. Pulmonary disease can be absent, miliary, or cavitary (Fig. 182-2). Treatment is a significant problem because typical agents used to treat mycobacteria can cause graft dysfunction.[1,2]

Rejection

The course of rejection may vary from patient to patient, but each individual typically has a lifelong course of a waxing and waning immune response to the allograft, mandating ongoing surveillance of allograft function. Differentiating infection and rejection is often difficult. Determination is often made only after biopsy of the transplanted organ or positive culture results are identified.

Rejection typically occurs in three phases: hyperacute, acute, and chronic. *Hyperacute rejection* is rare with careful donor-recipient matching. It typically occurs in the immediate perioperative period. *Acute rejection* occurs within the first

Figure 182-2. A 22-year-old male with a kidney transplant who presents with fever and a cough who was diagnosed with reactivated tuberculosis by sputum analysis.

months after transplantation. It usually presents with constitutional symptoms and signs of transplant organ insufficiency. Expeditious laboratory assessment, including possible allograft biopsy, can confirm the diagnosis of rejection, and the appropriate adjustment can be made in the patient's immunosuppressant regimen. Acute rejection can occur at any time if immunosuppressants are stopped. *Chronic rejection* has a time course of years and results in the gradual failure of the transplanted organ.[12]

Drug Toxicity/Immunosuppression

Pharmacology of Immunosuppression

The greatest advancement in the treatment of patients with transplanted organs is the advent of effective immunosuppressants. Immunosuppressive therapy requires correctly timed drug combinations to establish a delicate balance between immunosuppression, rejection, and susceptibility to infection. Multiple agents are used, and patients are commonly on more than one agent. Regimens are typically transplant center specific, but most include a calcineurin inhibitor, an antimetabolite, and varying dosages of steroids. Recognizing the side effects, toxicities, and potential drug interactions of immunosuppressant medications is an important component in the care of any transplant patient.

Allogenic bone marrow transplantation from the solid organ donor is being investigated as a means of immunosuppression. If successful, bone marrow transplantation may revolutionize how solid organ rejection is treated and how immunosuppression is achieved.

Calcineurin Inhibitors

Cyclosporine. A variety of immunosuppression strategies are being tested, but the current mainstay of transplant immunosuppression is cyclosporine.[13,14] Cyclosporine inhibits both cellular and humoral immunity by binding to cyclophilins, which block cytokine transcription and production, thereby inhibiting lymphocyte signal transduction. The result is a potent immunosuppression of helper-inducer T cells, without affecting the suppressor T cell subset.[13,15] The helper-inducer T cells enhance antibody recognition and production by B cells.

Cyclosporine has significant risks. It exhibits dose-related nephrotoxicity, which is additive to other nephrotoxic drugs typically used after transplant, such as amphotericin B, aminoglycosides, and high-dose TMP-SMX. Cyclosporine causes renal tubular injury and direct renal artery vasospasm in a dose-dependent manner, leading to systemic hypertension in many recipients.[13] Hypertension must be treated aggressively using standard regimens to preserve renal function and prevent atherosclerosis. Cyclosporine may also aggravate hyperlipidemias, leading to atherosclerosis.[16] Therefore, monitoring blood levels and renal function is routine during therapy.

Cyclosporine causes hyperuricemia and gout in transplant patients. The nephrotoxic effects of cyclosporine complicate the management of gouty attacks in renal transplant patients.[17]

Cyclosporine levels are altered by many common post-transplant medications (Table 182-1). Drugs that inhibit cytochrome P450 metabolism, such as erythromycin and ketoconazole, produce elevated cyclosporine levels and enhanced toxicity.[18] Treatment with rifampin can increase metabolism, which triggers episodes of organ rejection. Cyclosporine also causes hepatotoxicity, hyperkalemia, hirsutism, tremor, and gingival hyperplasia.[13]

Tacrolimus. Tacrolimus is a macrolide compound that binds to lymphocyte proteins and inhibits cytokine synthesis. Used as either primary or rescue therapy for allograft rejection, tacrolimus is effective for rejection in all types of solid organ transplants.[19,20] Due to an improved side effect profile and more effective immunosuppression, tacrolimus is more commonly used. Of patients discharged after liver transplantation in 2002, more than 88% had tacrolimus in their regimen.[21]

As with cyclosporine, tacrolimus causes nephrotoxicity as well as neurotoxicity. In combination with steroids, tacrolimus is more likely than cyclosporine to lead to diabetes. Tacrolimus can also cause anorexia, diarrhea, dyspepsia, and nausea. Macrolide antibiotics should not be prescribed to patients taking tacrolimus because they may cause increased levels of tacrolimus, leading to potential toxicity.[19]

Table 182-1 Drug Interactions with Cyclosporine

AGENT	PHARMACOKINETIC ACTION	EFFECT
Carbamazepine Nafcillin Phenobarbital Phenytoin Rifampin	Induce cytochrome P450 enzymes	Decreased half-life and immunosuppressive effect
Colchicine Diltiazem Fluconazole Fluoroquinolones Ketoconazole Macrolide antibiotics Oral contraceptives Verapamil	Inhibit cytochrome P450 enzymes	Increased half-life and potential drug toxicity or immunosuppression
Aminoglycosides Amphotericin B Cimetidine Nonsteroidals Sulfur	Interact at a glomerular or tubular level	Increased nephrotoxicity

Antimetabolites

Azathioprine. Azathioprine is an antimetabolite derivative of 6-mercaptopurine. Long an important component of immunosuppressive therapy in solid organ transplants, azathioprine functions by inhibiting both deoxyribonucleic acid and ribonucleic acid synthesis, resulting in a suppression of lymphocyte proliferation. It is typically used in combination with other agents.[22] Since the introduction of the calcineurin inhibitor class, the use of azathioprine has been reduced due to an improved side effect profile.

Azathioprine is a bone marrow toxin, and patients exhibit dose-related neutropenia. The drug is given at the minimum effective dose to maintain a peripheral white blood cell count of 4000 to 6000/mL. Azathioprine may also cause hepatic dysfunction and other GI disturbances.[22]

Mycophenolate Mofetil. Mycophenolate mofetil (MMF) prevents and suppresses organ rejection after solid organ transplantation.[23,24] MMF is an antimetabolite with more potent and selective inhibition of lymphocytic proliferation. It reduces the incidence of acute rejection but with no significant change in the long-term survival of transplant recipients or their allografts.[15,22]

MMF has the advantage of a low side effect profile, and it should be used concomitantly with cyclosporine and corticosteroids when the patient can tolerate oral medication. The

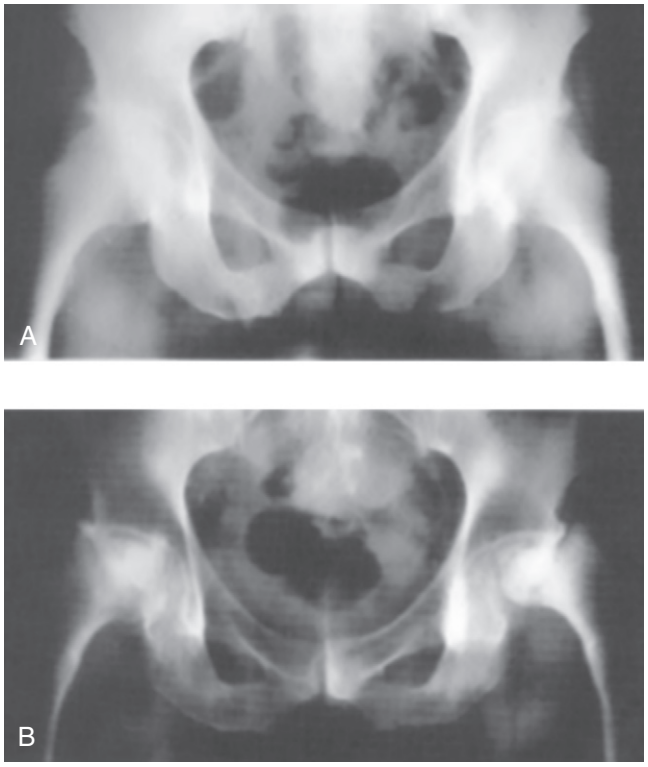


Figure 182-3. Radiographic appearance of a 24-year-old renal transplant patient with early (**A**) and late (**B**) findings consistent with avascular necrosis from chronic steroid use. (From Walker RG: Steroids and transplantation. In Ginnes LG, Cosimi AB, Morris PJ [eds]: Transplantation. Malden, Mass, Blackwell Science, 1999, p 121.)

mostly mild effects resulting from its GI and hematologic toxicity include abdominal pain, nausea, diarrhea, gastroenteritis, leukopenia, and thrombocytopenia. Because magnesium and aluminum antacids interfere with the absorption of MMF, care should be exercised when treating the GI symptoms.[24]

Corticosteroids. Corticosteroids have been used for immunosuppression since the 1960s. Glucocorticoids have a wide range of effects on the immune system, specifically the T lymphocytes. Because of the significant long-term toxic effects associated with chronic glucocorticoid administration, every effort is made to minimize glucocorticoid usage. *Combination therapy*, in which two or more immunosuppressants are administered simultaneously, decreases the reliance on long-term, high-dose glucocorticoid administration for allograft survival.[23]

Long-term corticosteroid therapy causes osteoporosis, cataracts, GI bleeding, glucose intolerance, skeletal myopathy, bone disease, and adrenal suppression (Fig. 182-3).[25] Acute administration may lead to glucose and electrolyte abnormalities as well as altered mental status. Acute withdrawal or severe illness may lead to an addisonian crisis.

Antilymphocyte Monoclonal Antibody Preparations. OKT3 and antithymocyte globulin are used in short courses to reverse allograft rejection.[23,26] OKT3 is a mouse-derived monoclonal antibody to T cells. When used against acute rejection, it is administered intravenously for 10 to 14 days, usually in the hospital initially because chills, fever, hypotension, and headache often occur. Pulmonary edema may also develop in overhydrated, oliguric patients. OKT3 is effective in more than 90% of first rejections. Patients can develop antibodies against these agents, which limits the duration of therapy and availability for repeat use.[15]

OKT3 toxicity is common because of T cell activation and lymphokine release caused by these agents. When receiving these agents, patients are at increased risk of infection with opportunistic pathogens, particularly CMV. An increased risk of lymphoproliferative disease also exists.[23,26]

SPECIFIC DISORDERS

Clinical Features

The pertinent clinical features of organ transplant complications are as extensive as the elements of the history and physical examination. Allograft rejection symptoms are usually vague and nonspecific. Complications of the organ often result in localized symptoms and dysfunction of the allograft. The clinical features of infectious complications depend on the nature of the pathogenic organism, location of the infection, and level of immunosuppression. The resuscitation of a traumatized transplant patient should focus on standard injury patterns. However, careful attention must be paid to maintaining the appropriate level of immunosuppression and watching for the typical transplant-related complications.[27] Every complaint and finding in the organ transplant recipient must be examined in the most suspicious light to avoid missing catastrophic illness.

Diagnostic Strategies

Transplant patients should undergo careful and often extensive laboratory and radiographic evaluation to rule out myriad infectious etiologies, assess allograft function, and survey for signs of drug toxicity. Laboratory assessments should include organ-specific measures of function as well as a careful search for evidence of infection. When suspected, appropriate cultures and serologies should be obtained. Radiologic interventions focus on sources of infection and the relevant anatomy of the patient's allograft.

MANAGEMENT

Heart Transplant

General Approach

Human heart transplantation was first performed in 1967. More than 3000 procedures are done annually in the United States. The 5-year survival rates for adults and children are 72 and 80%, respectively.[28] Typically, the recipient heart is removed and replaced by the donor heart (orthotopic transplant), but occasionally the recipient heart is left in place with the donor heart anastomosed to the native vessels (heterotopic transplant) (Fig. 182-4).

Patients are usually discharged from the hospital within 2 or 3 weeks. In the Stanford experience, 37% of heart transplant patients made at least one ED visit in the ensuing 3 years (range, one to six visits). The most common complaints are fever (37%), shortness of breath (13%), GI problems (nausea, vomiting, and diarrhea) (10%), and chest pain (9%). Sixty percent of these patients are admitted, compared with an overall ED admission rate of 15%, reflecting an appropriately high concern for rejection or localized or systemic infection. The most common ED diagnoses are sepsis (18%), rejection (11%), and pneumonia (8%).[16]

In trauma, the diagnosis of myocardial contusion is established in these patients by usual means, notwithstanding the lack of a gold standard. Treatment for the transplanted heart should not differ from that for native hearts. Baseline tachy-

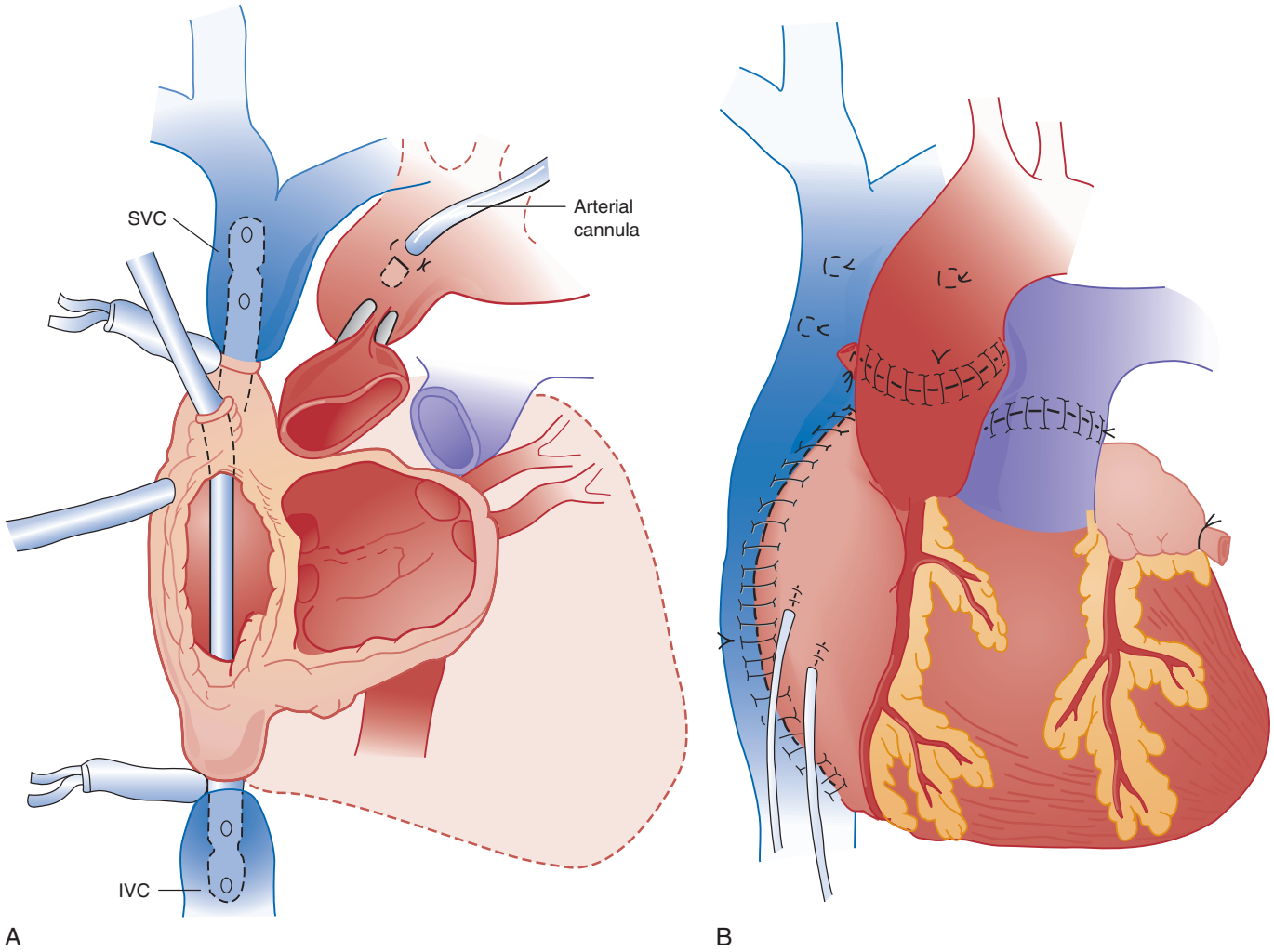


Figure 182-4. **A** and **B,** Typical anastomoses of an orthotopic heart transplant. IVC, inferior vena cava; SVC, superior vena cava. (From Hunt SA, Schroeder JS, Berry GJ: Cardiac transplantation, mechanical ventricular support, and endomyocardial biopsy. In Furster VL, et al [eds]: Hurst's The Heart. New York, McGraw-Hill, 2001, pp 729–730.)

cardia is expected, due to denervation of the vagus nerve. Despite the absence of a pericardium, scarring and adhesions may result in clinical tamponade with pericardial fluid or blood. Blind pericardiocentesis is discouraged.[27]

Infection and rejection are the leading causes of mortality in the first year. Any heart transplant patient presenting to the ED with congestive heart failure (CHF), fever (>38° C), shortness of breath, hypoxia, hypotension, poorly controlled hypertension, or new dysrhythmia should be admitted. Chest pain is rarely related to cardiac ischemia because the denervated heart is incapable of producing angina.[29] Accelerated atherosclerosis of the graft vessels is the hallmark of chronic rejection. Ischemia is manifested as CHF, ventricular dysrhythmias, hypotension, syncope, or sudden death.[30,31] CMV infection also appears to be a risk factor for accelerated atherosclerosis.[9,18,32]

Drug Toxicity

Lifelong immunosuppression is required in these patients. Most centers use a three-drug regimen of cyclosporine, prednisone, and azathioprine. Each drug has potential for toxicity, and the combination of cyclosporine and prednisone aggravates the hyperlipidemias common to many of these patients.[16,33]

Rarely, cyclosporine toxicity can result in a neurotoxic syndrome of seizures, confusion, cortical blindness, and quadriplegia, possibly progressing to coma. Seizure management is with standard anticonvulsants.[34-36]

Rejection

Acute rejection occurs in 75 to 85% of patients within the first 3 months. Its manifestations may be subtle with cyclosporine included in the immunosuppressive regimen. Previously, rejection was obvious, with decreased QRS voltage, a new S3 heart sound, or new-onset CHF or atrial dysrhythmias. These features are now present only during episodes of severe rejection, and the diagnosis of rejection is made by endomyocardial biopsy showing lymphocyte infiltration or myocyte necrosis.[1,16] Because most episodes of early or mild rejection are asymptomatic, frequent biopsies are performed to monitor the success of the immunosuppressive regimen.[37,38]

Acute rejection is treated with increased doses of corticosteroids (methylprednisolone, 500–1000 mg/day) and cyclosporine or with OKT3 or antithymocyte globulin. Immunosuppression is continued lifelong, with endocardial biopsies at least every 3 to 6 months.[38,39]

The transplanted heart maintains a rate of 100 to 110 beats/minute without parasympathetic tone. The electrocardiogram

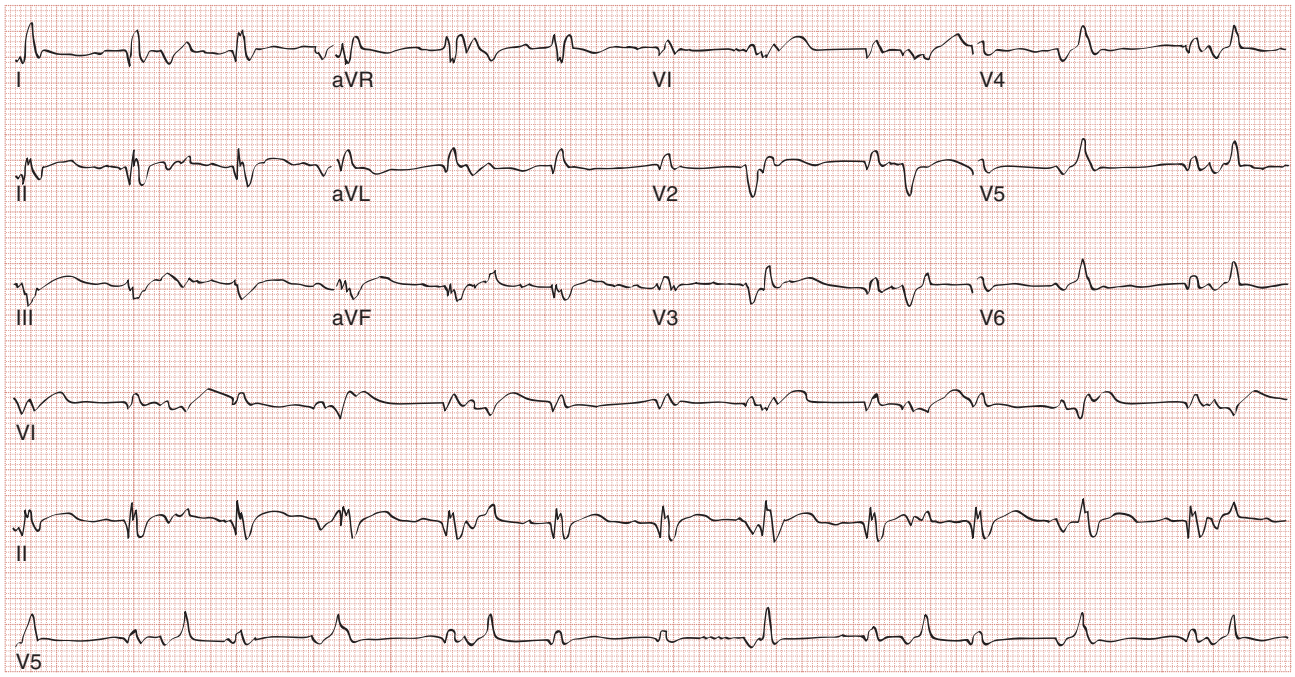


Figure 182-5. A 68-year-old male status postheterotopic heart transplant; native heart rate of 55 and donor heart rate of 75 beats per minute.

(ECG) typically demonstrates two P waves. One wave is from the native sinus node in the posterior right atrium, which is often left in place. The second P wave is from the donor sinoatrial node, which should conduct to the ventricles as usual with a normal PR interval. In the rare heterotopic heart transplant, bizarre ECGs may be seen that do not conform to normal standards (Fig. 182-5).

The transplanted heart rate can increase with exercise or stress through the effects of endogenous catecholamines, up to 70% maximum for age. Exogenous pressor drugs work well in the transplanted heart. Up-regulation of beta-adrenergic receptors appears to occur in the graft, with a slightly enhanced response to norepinephrine and isoproterenol.[34,39-41] Typical antihypertensive agents can be used as in the nontransplant patient. Atropine is ineffective due to vagal denervation.

Infection

Infection in heart transplant patients has many causes. One fourth of deaths after transplant result from infection. The most vulnerable period is the first 3 months, when immunosuppression is maximal. Although one third of patients will have a major infection develop in the first year, life-threatening infection after 1 year is rare.[1,18]

In the first month, nosocomial infection predominates, with the usual gram-positive and gram-negative bacteria. After the first 3 months, patients experience an overall 20% per year rate of infection. The most common skin infection is herpes zoster, which is treated with high-dose acyclovir. Nausea, vomiting, or diarrhea should prompt a search for CMV by culture and serologic testing.[2,16,37]

All heart transplant patients with fever should be aggressively evaluated unless a minor source of infection such as an upper respiratory infection is obvious. The diagnostic workup in the ED can include blood and urine cultures, computed tomography (CT) scan, lumbar puncture, and bronchoscopy. In addition, complete blood count, glucose, serum chemistries, blood urea nitrogen and creatinine, chest radiograph, and ECG are recommended. In one series of 131 ED visits by such patients, 23 patients were admitted with a diagnosis of "rule out sepsis," and in 12 (52%) an infecting organism was identified.[16,34,38]

Any new headache with or without visual changes may be the first symptom of meningitis or brain abscess, and CT scan of the head and a lumbar puncture should be obtained. Fever, lethargy, headache, altered mental status, or seizures are presenting signs of *Listeria*, cryptococcal meningitis, *Toxoplasma gondii*, or brain abscesses from *Nocardia* or *Aspergillus*. A more definitive diagnosis can often be made through biopsy of a mass lesion or drainage of an abscess. This often obviates the need for lumbar puncture. Aseptic meningitis occurs in 10 to 14% of patients treated with OKT3 approximately 6 to 10 days after therapy.[1,18]

Due to the attendant risk of endocarditis, antibiotic prophylaxis should be provided for invasive procedures likely to cause bacteremia, such as abscess drainage and urethral catheterization. Endotracheal intubation requires no such prophylaxis. VZV immune globulin is recommended as soon as possible when seronegative patients are exposed to chickenpox or herpes zoster.[2,16]

Liver Transplant

Liver transplants have 1- and 3-year survival rates of 86 and 76%, respectively.[28] Complications are common, and loss of function of the graft organ is rapidly life-threatening.

Anatomic Considerations

The typical liver transplant is connected to its host via five anastomoses (Fig. 182-6). The vessels are connected first, allowing organ reperfusion. The biliary system is then reconstructed and often stented with a T tube to prevent stenosis. In the early post-transplant period, T tubes may be replaced if restenosis develops. The most common vascular complication is hepatic artery thrombosis, which most commonly occurs early in the post-transplant period. Severe graft dysfunction is invariable and mortality approaches 75%.[42]

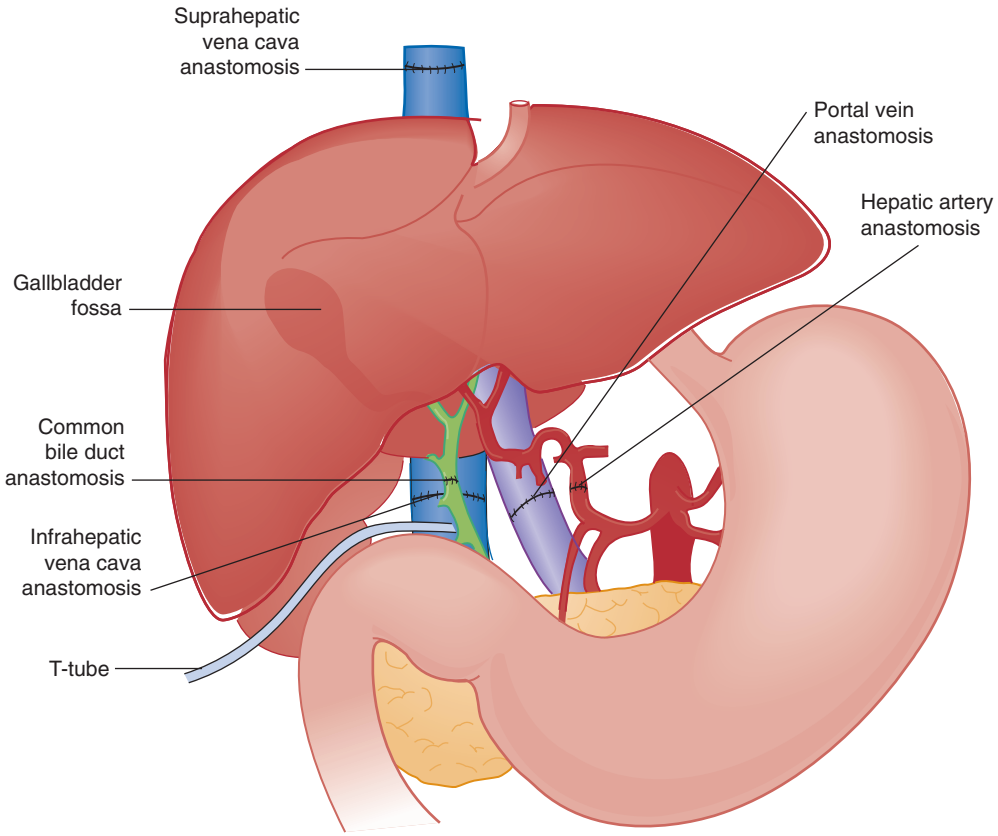


Figure 182-6. Typical anastomoses of an orthotopic liver transplant. (From Powelson JA, Cosimis AB: Liver transplantation. In Ginnes LG, Cosimi AB, Morris PJ [eds]: Transplantation. Malden, Mass, Blackwell Science, 1999, p 352.)

Rejection

Liver transplant rejection is the norm despite immunosuppressive therapy. Rejection often begins 1 or 2 weeks after surgery, with fever, right upper quadrant pain, and elevated bilirubin and transaminases. Leukocytosis may occur but is nonspecific. Related conditions that simulate graft rejection are mechanical biliary obstruction, primary nonfunctioning graft, ischemia from thrombosis of vascular anastomoses, viral infections, drug toxicity, and recurrent primary disease.[43-46]

As soon as transplant rejection is suspected, treatment with high-dose methylprednisolone should begin. Hospitalization is routine. If this fails to diminish the rejection episode, OKT3 monoclonal antibodies are again used in addition to polyclonal antilymphocyte globulin.[43]

Infection

After the first postoperative month, opportunistic infections replace the common postsurgical complications. Viral (CMV and HSV), fungal (*Aspergillus*, *Candida*, and *Cryptococcus*), protozoan (*Pneumocystis* and *Toxoplasma*), and unusual bacterial (*Nocardia*, *Legionella*, and *Listeria*) infections occur. In addition, ascending cholangitis due to colonization of biliary stents with staphylococcal species, enterococci, and gram-negative organisms is common. Subsequent injury to the graft during biopsy or cholangiogram can cause cholangitis or liver abscess.

Kidney (Renal) Transplant

With survival rates of 96% at 1 year and 91% at 3 years, renal transplants are highly successful.[28] Injury of the transplanted kidney is rare, despite its location in the retroperitoneal area of the anterior pelvis, where it may be at risk from direct blows as well as seat belt injuries.[27]

Infection

The classic example of bacterial infection in transplanted organs is pyelonephritis in renal allografts. It often occurs in the first month after surgery during high-dose immunosuppression. During this period, an increased risk of sepsis exists. Gram-positive organisms associated with wound infections and gram-negative organisms are the predominant causes. Pyelonephritis occurs in 35% of patients during the first 4 months but can be prevented with prophylactic antibiotics. All patients with transplant who have pyelonephritis are admitted for aggressive antibacterial therapy.[47,48]

Hepatitis C virus (HCV) infection is the most common cause of hepatitis in renal transplant patients. It may be transferred to the recipient by blood transfusion or through the donor organ because pretransplant antibody testing is a poor predictor of latent HCV infection. Liver disease develops in approximately 50% of seropositive patients, occurring approximately 4 months after transplantation. Most patients develop chronic hepatitis with accompanying immune defects and susceptibility to sepsis and spontaneous bacterial peritonitis. Pretransplant screening is the only avenue of prevention.[1,48]

Rejection

Early kidney transplant rejection is mediated through T lymphocytes against antigen donor tissues, including cytotoxic CD8 and CD4 cells. In addition, B lymphocytes, natural killer cells, and macrophages infiltrate the foreign tissues. The B lymphocytes manufacture specific antibodies, which results in microvascular lesions impairing perfusion.

Chronic transplant rejection occurs after several years of adequate function and is a result of nephrosclerosis. This process involves proliferation of the vascular intima of renal vessels with marked decrease in the lumen size. Systemic

hypertension ensues as the graft fails from ischemia, with resultant tubular and glomerular atrophy.

With cadaveric kidney transplants, histocompatibility differences are almost universal and routinely require long-term immunosuppressive therapy. This is accomplished with a combination of azathioprine, prednisone, and cyclosporine. On diagnosis of acute rejection, high-dose methylprednisolone (500–1000 mg) is begun daily and continued for 3 days. After 6 to 12 months, many patients only need lower doses (10–20 mg/day).[47,48]

Clinically, renal graft rejection presents as fever, swelling and tenderness over the allograft, and decreased urine output. A subtle rise in serum creatinine should prompt great concern. Renal ultrasound should be performed to rule out obstruction, abscess, vascular thrombosis, and perirenal collections of blood, pus, or lymph.[48] Early consultation with the nephrologist is prudent.

Lung Transplant

The lung may be transplanted alone or in combination with the heart, with 1-year survival rates of 76 and 56%, respectively.[28] Lung transplants are usually done unilaterally, except for cystic fibrosis. Unequal lung sounds are to be expected. There is no published experience with lung injury following transplant. Comparison of chest radiography with preinjury studies is critical in the evaluation of trauma. Chest tube placement on the transplanted side may be difficult because of adhesions and loculations.[27]

Rejection

Although still rare, lung transplantation is increasing in frequency; more than 800 are performed annually in the United States.[28] Most patients develop early rejection, and 25 to 40% have chronic rejection. An episode of acute rejection can occur as early as a few days after transplantation or as late as several years. Clinically, the patient presents with cough, dyspnea, and fever. Rales and rhonchi are heard, with deterioration in oxygenation and pulmonary function. Early rejection is often accompanied by infiltrates on chest radiograph. When rejection occurs more than a month after transplantation, 75% of radiographs are normal or unchanged. The diagnosis of rejection is made by transbronchial biopsy showing lymphocytic infiltration.[18,49-51]

Suspected episodes of acute rejection are treated with high-dose methylprednisolone (500–1000 mg/day). This is successful in reversing most episodes, but OKT3 can be used in refractory cases.[50]

Chronic lung transplant rejection is a leading cause of late morbidity and mortality. Antecedent acute rejection and CMV pneumonia are risk factors. Pathologically, vascular sclerosis and progressive limitation to airflow occur from obliterative bronchiolitis. Rejection can occur several years after transplantation, but the mean time to onset is 8 to 12 months. Clinically, this rejection mimics an upper respiratory infection or bronchitis. If dyspnea is a component of the presenting complaint, a search for transplant rejection should be initiated.[50,52]

Chronic rejection is treated with high-dose methylprednisolone (500–1000 mg/day), with the first dose begun in the ED. Antilymphocyte antibodies are used as well, but relapse of the rejection episode is common.

Infection

Transplanted lungs are highly susceptible to pneumonia because they can be colonized by bacteria during the ventilator stage of the brain-dead donor. After transplant, diminished mucociliary clearance, decreased cough reflex due to denervation, and defective function of alveolar macrophages are present. The most common infections are caused by gram-negative bacteria such as *Pseudomonas* and by *Staphylococcus aureus*. Antibiotic therapy should be aggressively directed toward any pathogenic bacteria cultured from the tracheobronchial tree. Community-acquired pneumonia must be considered as well. *Pneumocystis* pneumonia is uncommon because of routine prophylaxis with TMP-SMX.[1,50]

CMV pneumonia is the most common opportunistic pulmonary infection after lung transplantation. Patients are at highest risk between 3 weeks and 4 months. Clinically, CMV infection closely resembles transplant rejection. Tissue biopsy and viral culture are required to differentiate the two entities. Treatment with ganciclovir is effective. Colonization by *Candida* is common, but not invasive disease. *Aspergillus* provides the most significant fungal threat to the transplanted lung. Reactivation of tuberculosis is rare.[50,51]

Pancreas Transplant

The pancreas may be transplanted singly or in combination with a kidney. This is typically secondary to diabetes. Pancreatic transplants have a high complication rate, with 1-year graft survival rates as low as 72%. Because the exocrine functions of the allograft pancreas are usually drained into the bladder, genitourinary complaints are also common. Duodenocystostomy fistula may form in the early post-transplant period. The clinical findings are abdominal pain, tenderness, hyperamylasemia, leukocytosis, and elevated serum creatinine. Other types of pancreatic transplant complications include urinary tract infections, hematuria, reflux pancreatitis, rejection, and pancreatic graft thrombosis.[53-55]

Anatomic considerations are important when these patients suffer major trauma because pancreas transplants are placed in the pelvis overlying the iliac vessels.[27] Exocrine secretions are drained into the bladder for excretion, and patients have a chronic non–anion gap acidosis through loss of bicarbonate into the bladder. This should not be confused with lactic acidosis. These trauma patients should not require exogenous insulin, unless the graft is injured. Positive amylase on peritoneal lavage (CT is recommended if the patient is stable) can result from either native organ or graft trauma or from a ruptured bladder. CT scanning should be done with rectal contrast, in addition to IV and oral, to better define the native and transplanted pelvic organs.[27]

Islet cell transplantation is under investigation as a treatment for diabetes mellitus. If successful, this procedure may negate the need for future solid organ pancreas transplants and the resultant complications.

PSYCHOLOGICAL ASPECTS OF ORGAN TRANSPLANTATION

The psychological issues that surface while under consideration for or after reception of an organ transplant impact many patients. Organ transplantation is no longer considered experimental, and it is a common therapeutic option for end-stage organ failure. Strong emotions naturally occur and should be acknowledged in donors, recipients, and transplanters.

Transplant programs widely employ psychosocial selection criteria. Generally, the cardiac programs have the most stringent criteria. The side effects of lifelong immune suppression or steroid withdrawal can include anxiety, depression, and insomnia. On the other hand, successful transplantation often improves psychological well-being. Transplant social workers

can provide awareness of and access to the social network that should surround each transplant recipient. Long-term compliance with all aspects of treatment will minimize graft rejection.[56]

DISPOSITION

Patients with solid organ transplants presenting to the ED have a much higher than average rate of hospitalization.[28,46] The insidious nature of the diseases affecting this immunosuppressed population mandates a thorough approach to evaluation. If organ rejection, infection, or drug toxicity is evident, local transplantation specialists should be consulted. Physicians without significant transplant experience should contact the patient's transplant center to obtain consultation and coordinate follow-up care. Patients who are discharged require careful instructions and close follow-up.

KEY CONCEPTS

- The possibility of organ rejection, infection, or drug toxicity should be considered in all organ transplant patients who present to the ED despite subtle presentations.
- A patient's inability to take oral immunosuppressants for even a single day should be considered an emergency condition.
- When prescribing care in the ED, the physician must be careful to avoid drug interactions and toxicity.
- Infections that occur from 1 to 6 months after transplantation are generally immunomodulating viruses such as CMV or opportunistic infections.
- Close family members of transplant patients should not receive live viral antigen vaccines due to the risk of transmission.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 183 Alcohol-Related Disease

John T. Finnell and David B. McMicken

PERSPECTIVE

Epidemiology

The disastrous effects and widespread incidence of alcoholism are well known to the emergency physician. Motor vehicle collisions, drowning, suicides, homicides, divorce, violent crime, child abuse, unemployment, and disruption of the family are often either directly or indirectly associated with excessive alcohol consumption. The tragic effects of alcohol not only affect the individual drinker but also have far-reaching implications for the family, community, and workplace. There are an estimated 68.8 million emergency department (ED) visits, with a rate of 28.7 per 1000 U.S. population.[1] The 5-year mortality rate among alcohol-intoxicated ED patients was 2.4 times that of a comparison group in one study.[2]

A simple, rapid, and respectful screening test for alcoholism is the four *CAGE* questions: Have you ever felt

- The need to ***C***ut down on your drinking?
- ***A***nnoyed by criticism of your drinking?
- ***G***uilty about your drinking?
- The need to drink an ***E***ye opener in the morning?

Positive answers to two or more of these questions are sufficient to identify individuals who require more intensive evaluation.[3] Also, a positive answer to the question, "Have you ever had a drinking problem?" plus evidence of alcohol consumption in the previous 24 hours provides greater than 90% sensitivity and specificity as a screening tool for identifying alcoholism.

Alcohol is the most common recreational drug taken by Americans, and per capita consumption is increasing. Alcoholism affects approximately 12% of individuals in the United States during a lifetime.[4] Alcoholism permeates all levels of society and is the leading cause of preventable mortality and morbidity, with a cost to the nation estimated to be greater than $185 billion annually.[5] An estimated 18 million alcoholics live in the United States. With more than 100,000 alcohol-related deaths occurring each year, alcohol is the third leading cause of preventable death in the United States.[6]

Definition and Natural History

A precise definition of alcoholism is difficult. A proposed definition encompassing the features of alcoholism is "a primary chronic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations." The disease is often progressive and fatal. It is characterized by impaired control over drinking, preoccupation with and use of alcohol despite adverse consequences, and distortions in thinking, most notably denial. Each of these symptoms may be periodic or continuous.[7] Alcoholism is present when drinking adversely affects an individual's physical health, ability to function in society, or interpersonal relationships. Certainly, the patient who has a dependence on ethanol can be labeled "alcoholic."

Hazardous or "at-risk" drinking is defined by the National Institute on Alcohol Abuse and Alcoholism as follows:

Men: more than 14 drinks per week *or* more than 4 drinks per occasion
Women: more than 7 drinks per week *or* more than 3 drinks per occasion
Age older than 65: more than 7 drinks per week *or* more than 1 drink per occasion

Harmful drinkers present with negative consequences related to alcohol.

The cause of alcoholism is not completely understood but appears to be a complex interaction between biologic and environmental factors. Genetic variability of enzymes for alcohol metabolism may be a risk factor supported by family, twin, and adoption studies.[8] A large study, entitled the Collaborative Studies on Genetics of Alcoholism (COGA) is now identifying additional gene loci.

The natural history of alcoholism is variable, and it may appear in any patient despite age or social status. The age of onset of alcoholism continues to decrease. Up to 6% of high school seniors drink daily, and it is not unusual to see children younger than 16 years of age who have already graduated from an alcohol detoxification program.[9] Many individuals also begin drinking heavily after age 60.

The fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)* has two categories for substance disorders that include alcohol abuse. It lists criteria for substance abuse and substance dependence.[10] The chronic *substance abuse* of alcohol eventually leads to *acquired tolerance*, a condition in which increasingly larger doses of alcohol are required for the same effect. An *inborn tolerance* also exists. There is a wide variance in abnormal behavior independent of the patient's drinking experience.

Continued alcohol abuse progresses to *substance dependence*, defined in *DSM-IV* as a maladaptive pattern of substance use leading to clinically significant impairment, as manifested by three or more of the following occurring in the same 12-month period:

1. Physiologic dependence, as evidenced by tolerance or withdrawal
2. Alcohol taken in larger amounts or over a longer period than was intended
3. Persistent desire or unsuccessful efforts to control alcohol consumption
4. Great amount of time spent in activities necessary to obtain alcohol or recover from its effects
5. Important social, occupational, or recreational activities forsaken for sustained alcohol use
6. Continued alcohol use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol

PRINCIPLES OF DISEASE: METABOLISM OF ALCOHOL

Ethanol is rapidly absorbed from the stomach and small intestine. It is distributed uniformly to all organ systems, including the placenta. The oxidation of alcohol is a complex process involving three enzyme systems, all contained in the hepatocyte. The pharmacokinetic properties of alcohol metabolism are well-known. The class I alcohol dehydrogenase (ADH) isoenzymes, ADH1A, ADH1B, and ADH1C, oxidize ethanol. ADH1B and ADH1C have polymorphic properties with distinct kinetic properties. At the ADH3 locus, two alleles account for pharmacokinetic differences of 2.5-fold in maximum velocity of ethanol oxidation.[11]

$$\text{Ethanol} \xrightarrow[\text{NAD}\rightarrow\text{NADH}]{\text{Alcohol dehydrogenase}}$$

$$\text{Acetaldehyde} \xrightarrow[\text{NAD}\rightarrow\text{NADH}]{\text{Alcohol dehydrogenase}}$$

$$\text{Acetyl coenzyme A} \xrightarrow[\text{Cycle}]{\text{Citric acid}} \text{CO}_2 + \text{H}_2\text{O}$$

An alternative pathway, the *microsomal ethanol-oxidizing system* (MEOS), can be induced by chronic alcohol exposure. The primary component of MEOS is the molecule cytochrome P450, which exists in several variants. The variant most important for alcohol metabolism is cytochrome P450 2E1 (CYP2E1). Many effects of alcoholism are produced by the toxic byproducts (hydrogen and acetaldehyde), the acceleration of metabolism of other drugs, and activation of hepatotoxic compounds by these metabolic pathways.

Although the liver is the major site of ethanol metabolism, other tissues contribute to its metabolism. ADH is found in the gastric mucosa, but the gastric metabolism of alcohol is decreased in women and those of Asian decent. This increased bioavailability of ethanol or decreased first-pass metabolism may explain the enhanced vulnerability of women to acute and chronic complications of alcohol.

Studies have shown two alcohol elimination curves. The alcohol elimination rate approximates zero-order kinetics (constant rate) for lower ethanol levels and first-order kinetics (the amount of drug removed over time is proportional to the concentration of the drug) for higher levels, especially in chronic alcoholics. The MEOS pathway may account for the increased elimination rate at higher blood levels.

The absorption and elimination rates of alcohol vary by individual and depend on many factors: diet, gender, body weight and habitus, speed of consumption, gastric motility, the presence of food in the stomach, smoking history, age, whether the person is a chronic alcohol consumer with enzyme induction and high-activity MEOS, advanced cirrhosis, the presence of ascites, and the state of nourishment.[12] There is enormous variation among patients in the rate of disappearance of ethanol from the blood, ranging from 9 to 36 mg/dL/hr in published data.

Table 183-1 Physiologic Effects and Blood Alcohol Levels

BLOOD ALCOHOL CONCENTRATION (MG/DL)	EFFECTS*
20–50	Diminished fine motor control
50–100	Impaired judgment; impaired coordination
100–150	Difficulty with gait and balance
150–250	Lethargy; difficulty sitting upright without assistance
300	Coma in the novice drinker
400	Respiratory depression

*These effects are for the occasional drinker. Chronic drinkers can function at much higher alcohol concentrations because of tolerance. On the other hand, patients may become comatose with low levels of alcohol in mixed alcohol-drug overdose.

Although the clearance rate may be as high as 36 mg/dL/hr in some chronic drinkers, 20 mg/dL/hr is a reasonable rate to assume in a typical intoxicated ED patient. This holds true for adults, adolescents, and children. In the unusual circumstance that an accurate prediction of the rate of clearance is required, a second measurement should be obtained several hours after the initial value.[13]

Physiologic effects vary directly with the blood alcohol (Table 183-1). Diminished fine motor control and impaired judgment appear with alcohol concentrations as low as 20 mg/dL (0.02 mg%), but wide individual variability exists. Chronic alcoholics can exhibit impressive tolerance. The *blood alcohol concentration* (BAC) of a person cannot be accurately determined without quantitative testing. More than 50% of the adult population are obviously intoxicated with a level of 150 mg/dL (0.15 mg%). As the ethanol level rises, the patient's level of consciousness declines, eventually ending in coma. Death is caused by aspiration or respiratory depression.

In most states, the legal level of intoxication while driving is 80 mg/dL (0.08 mg%). Many states now allow administrative driver's license revocation at BACs as low as 20 mg/dL (0.02 mg%). There is not an illegal BAC for activities other than driving.

Alcohol via passive diffusion will be present anywhere there is water in the body. Hence, expired breath alcohol or saliva can be used to obtain a reliable approximation of BAC in a cooperative patient. This value can be used as a rapid screen for alcohol intoxication.[14,15] The breath alcohol level can be falsely low with uncooperative patients.

DIFFERENTIAL CONSIDERATIONS

Acute alcohol intoxication is a diagnosis of exclusion. Before assuming that a patient's behavior is caused only by alcohol, other conditions should be considered. Hypoglycemia, hypoxia, carbon dioxide narcosis, mixed alcohol-drug overdose, ethylene glycol or methanol poisoning, hepatic encephalopathy, psychosis, severe vertigo, and psychomotor seizures can manifest in a manner similar to ethanol intoxication. The possibility of occult head trauma and the presence of associated metabolic disorders should be considered after alcohol intoxication has been established. Adequate history from paramedics and family, repeated physical examinations by the same clinician, and diagnostic adjuncts can help resolve this dilemma.

MANAGEMENT

Comatose or stuporous patients need to have their airway and ventilation evaluated, with endotracheal intubation performed as necessary. Gastric lavage and activated charcoal are of little

value in ethanol overdose because of the rapid absorption of alcohol but may be appropriate in a suspected mixed drug-alcohol overdose.

Ethanol is similar to general anesthetics that act on the lipid moiety of cell membranes. Because there are no specialized receptors for alcohol, a specific antagonist does not exist.

Thiamine (100 mg intravenously [IV]) to prevent or treat Wernicke-Korsakoff syndrome, glucose (dextrose, 25–50 g IV) for hypoglycemia, and naloxone (0.8 mg IV) for possible opioid ingestion are considered in comatose patients. Whenever possible, hypoglycemia should be documented before the empiric administration of glucose. With the airway maintained and respirations supported, the patient's liver eventually metabolizes the alcohol, and the patient should recover.

Glucose (dextrose, 25 g IV) produces a dramatic response in alcohol-induced hypoglycemic patients. Unlike hypoglycemia of other causes, alcohol-induced hypoglycemia may be unresponsive to glucagon because of depleted liver glycogen stores. Although Wernicke's encephalopathy is a medical emergency, alcohol-induced hypoglycemia is a much more common condition with serious and permanent morbidity if left untreated. Therefore, thiamine can be given in a timely fashion, but glucose therapy should not be delayed.[16]

Intoxicated patients require evaluation and treatment in the ED regardless of their obstreperousness. Inappropriate discharge and failure to diagnose are two common areas of liability when treating the alcohol-dependent patient. The theoretical liability for detention by reasonable restraint is less than the potential liability for injury sustained by the alcohol-dependent patient or an innocent bystander after premature discharge. Discharge (after excluding significant abnormal laboratory values or suspected head injury) can be considered when a patient is clinically sober and able to dress, walk, and function independently. In ideal circumstances, a concerned, sober adult is available and willing to take responsibility for and remain with the patient for the next 24 to 48 hours.

ALCOHOL WITHDRAWAL SYNDROME

Principles of Disease

The neurophysiology of alcohol withdrawal is complex and not fully understood. Chronic alcohol consumption has a depressant effect on the central nervous system (CNS). The hallmark of alcohol withdrawal is CNS excitation with increased cerebrospinal fluid (CSF), plasma, and urinary catecholamine levels.

Chronic alcohol consumption affects central adrenergic alpha-receptors, glutamate, central adrenergic beta-receptors, the inhibitory neurotransmitter γ-aminobutyric acid (GABA), and dopamine turnover. The effectiveness of lofexidine and clonidine ($alpha_2$-adrenergic agonists), propranolol and atenolol (beta-blockers), haloperidol (dopamine blocker), and benzodiazepines and propofol (GABA transmission blockers) in suppressing the signs and symptoms of alcohol withdrawal supports this concept.[17,18]

Differential Considerations

Alcohol withdrawal syndrome can initially be confused with acute schizophrenia, encephalitis, drug-induced psychosis, thyrotoxicosis, anticholinergic poisoning, and withdrawal from other sedative-hypnotic–type drugs. It may be difficult to differentiate between alcohol withdrawal and alcohol-induced hypoglycemia.

Acute schizophrenia usually has its onset in adolescence or early adulthood. Manifestations include multiple bizarre delusions and a flat affect with the patient otherwise oriented. The patient in alcohol withdrawal is usually older (20s or 30s), hyperactive, and often disoriented. An important distinction: the schizophrenic patient will typically describe auditory hallucinations, whereas the alcoholic patient in withdrawal will more often describe visual hallucinations.

Encephalitis can produce headache, confusion, fever, and seizures. Thyrotoxicosis is more common in women, and its features include irritability, insomnia, tremor, weight loss despite a good appetite, palpitations, and frequent stools. Physical examination may reveal lid lag, tachycardia, and a bruit over the thyroid. No relationship exists between the onset of encephalitis or thyrotoxicosis and alcohol consumption.

Anticholinergic poisoning can occur with several different drugs or plant ingestion. The classic clinical picture is a patient with dry mouth, dry eyes, dry skin, hypoactive bowel sounds, urinary retention, and delirium. Amphetamine and cocaine intoxications produce anorexia, insomnia, and physical signs of CNS sympathetic overactivity.

In opioid withdrawal, patients complain of abdominal pain and diarrhea, the mental status is usually normal, the patient is afebrile, and seizures are uncommon (with the exception of meperidine). In contrast, patients with major alcohol withdrawal are usually disoriented and febrile and may have seizures.

Signs of alcohol withdrawal usually begin 6 to 24 hours after a decrease in the patient's usual intake of alcohol. If patients manifest withdrawal 3 days or more after their last drink, drugs with a longer half-life should be considered. The barbiturate and benzodiazepine withdrawal syndromes usually progress more slowly, with a higher frequency of seizures later (7 vs. 2 days), and status epilepticus is more common than with alcohol withdrawal.

Clinical Features

Isbell and colleagues' classic 1955 study confirmed the relationship between alcohol and the withdrawal syndrome.[19] They documented that the severity of signs and symptoms depends on both the dose and the duration of ethanol consumption. The withdrawal syndrome may occur any time after the blood alcohol level starts to fall. Therefore, only a reduction, not the abrupt cessation, of ethanol intake may result in withdrawal.

The withdrawal syndrome usually develops 6 to 24 hours after the reduction of ethanol intake and lasts 2 to 7 days. The alcohol withdrawal state ranges from mild withdrawal with insomnia and irritability to major withdrawal with diaphoresis, fever, disorientation, and hallucinations.

Minor alcohol withdrawal occurs as early as 6 hours and usually peaks at 24 to 36 hours after cessation of or significant decrease in alcohol intake. It is characterized by mild autonomic hyperactivity: nausea, anorexia, coarse tremor, tachycardia, hypertension, hyper-reflexia, sleep disturbances (e.g., insomnia and vivid dreams), and anxiety.[20]

Major alcohol withdrawal occurs after more than 24 hours and usually peaks at 50 hours but occasionally takes up to 5 days to manifest after the decline or termination of drinking. The syndrome is characterized by pronounced anxiety, insomnia, irritability, tremor, anorexia, tachycardia, hyper-reflexia, hypertension, fever, decreased seizure threshold, auditory and visual hallucinations, and, finally, delirium.[21]

Delirium tremens is the extreme end of the spectrum and consists of gross tremor, frightening visual hallucinations, profound confusion, agitation, and a hyperadrenergic syndrome characterized by a temperature greater than 101°F, a blood pressure greater than 140/99 mm Hg, and tachycardia. It seldom appears before the third postabstinence day. Only 5% of patients hospitalized for alcohol withdrawal develop

delirium tremens. Other causes of delirium to be considered in the alcoholic patient include sepsis, meningitis, hypoxia, hypoglycemia, hepatic failure, and intracranial bleeding. True delirium tremens is rare and is not synonymous with alcohol withdrawal.

Management

Out-of-Hospital Care

The alcohol-dependent patient in withdrawal may also have a mixed alcohol-drug ingestion, occult head trauma, or cervical spine injury. Patients who are unable to sit without assistance or have an altered mental status require IV access. Naloxone (0.8 mg) and glucose (dextrose, 25 g) may be given in an IV bolus. Rapid blood glucose testing is preferable, but glucose may be given for altered mental status if this testing is not readily available. Thiamine should be given as soon as possible after glucose. The airway should be maintained and respirations supported. Emergency medical service personnel should monitor the patient's vital signs and neurologic status. The cervical spine should be immobilized if trauma is suspected. It is usually best to withhold additional treatment until the patient can be evaluated in the ED. Emergency medical service personnel should be alert for other medical disorders that accompany alcoholism, such as pneumonia, sepsis, gastrointestinal bleeding, pancreatitis, hepatic failure, hypoglycemia, and intracranial hemorrhage.

Hospital Care

Initial Assessment. Family, friends, bystanders, or paramedics may give more reliable historical data than the patient. Accurate vital signs are essential. This may require a rectal temperature. Hyperthermia, hypothermia, tachypnea, or tachycardia may suggest serious disorders that often accompany the alcohol-dependent patient. These disorders should be considered during this first assessment.

A rapid, thorough examination should be done with attention to the level of consciousness, signs of hepatic failure, or coagulopathy. Signs of trauma are sought, such as subcutaneous emphysema, ecchymosis, subconjunctival hemorrhage, hemotympanum, Battle's sign, or palpation for fractures. The neurologic examination should search for focal findings, including central facial nerve palsy, hemiparesis, asymmetry of reflexes, or asymmetry of pupillary response.

Treatment Plan. The alcohol withdrawal syndrome should be promptly recognized and treated. Treatment is necessary (1) to provide relief from anxiety and hallucinations; (2) to halt progression to major withdrawal and withdrawal seizures; (3) to allow detection of a treatable primary psychiatric illness; (4) to prepare the patient for long-term alcohol abstinence with the lowest risk of new drug dependence; and (5) to calm the patient and allow adequate examination for the detection of medical illnesses that typically accompany alcoholism, such as gastritis, dehydration, pancreatitis, pneumonia, electrolyte disorders, and hepatitis.

In combination with appropriate chemical sedation, detention by reasonable restraint may be an option to prevent potential injury that patients may inflict on themselves or the hospital staff. Appropriate restraints are preferable to allowing decision-challenged patients to sign an "against medical advice" form and be discharged.

Pharmacologic Intervention. Patients suffering from alcohol withdrawal should receive pharmacologic intervention along with supportive care. The ideal drug for alcohol withdrawal would have a rapid onset, a wide margin of safety, a metabolism not dependent on liver function, and limited abuse potential. Although no one drug class fits all these requirements, benzodiazepines are clearly the mainstay of treatment.

Benzodiazepines. The benzodiazepines have superior anticonvulsant activity, have the least respiratory and cardiac depressive effect of all the CNS depressants, and can be given parenterally in the uncooperative patient. By interacting with receptors linked to the GABA-associated chloride ion channel, benzodiazepines substitute for the withdrawal of the GABA-potentiating effect of alcohol and abate withdrawal signs and symptoms.[22]

Numerous benzodiazepines have been studied. No evidence of clear superiority of any one benzodiazepine exists. Lorazepam has good bioavailability with oral, intramuscular (IM), and IV routes. It is rapidly and completely absorbed from IM sites in agitated patients with no IV access. Lorazepam's half-life is intermediate (7–14 hours), and it reaches a steady state in 36 to 48 hours without active metabolites. Excessive sedation, confusion, and ataxia are potential complications of all benzodiazepines with prolonged half-lives. Lorazepam is metabolized (conjugated) in the liver, yielding inactive products. Although lorazepam's half-life increases in patients with cirrhosis or liver failure, it is much less than the increase with chlordiazepoxide. Lorazepam's elimination is only minimally altered in patients with renal failure and in the elderly.

Lorazepam may be given IV in a dose of 1 to 4 mg, depending on the severity of the withdrawal. Dosing can be repeated at 5- to 15-minute intervals for patients in severe withdrawal. An IM dose of 1 to 4 mg can be used every 30 to 60 minutes until calm, then every hour as needed for light somnolence. The oral schedule for moderate withdrawal is 6 mg/day in three divided doses, tapering the amount by 1 or 2 mg/day over 4 to 6 days. Diazepam can be given in a dose of 5 mg IV every 5 to 10 minutes (2.5 mg/min) in major withdrawal until the patient is calm. The dose can be repeated in 5 to 10 minutes. If the second dose of 5 mg is not working, consider 10 mg for the third and fourth doses every 5 to 10 minutes. If this is not effective, consider 20 mg for the fifth and subsequent doses until adequate sedation is obtained.[23,24] Because of erratic absorption, diazepam should not be given IM.

The dosage of benzodiazepines required for alcohol withdrawal is highly variable. Practically, the dose is titrated to the patient's agitation. Massive IV drug doses have been required in patients with delirium tremens, including a recorded 2640 mg of diazepam and 35 mg of haloperidol over 48 hours, 75 mg of midazolam in 1 hour, and 2850 mg of midazolam over 5 days.[25]

Butyrophenones. Haloperidol, a dopamine antagonist, can be considered in patients with major alcohol withdrawal or delirium tremens not responding to IV benzodiazepines. Haloperidol is more potent than chlorpromazine, has lower anticholinergic properties, and has less propensity to cause cardiovascular side effects or lower the seizure threshold. Haloperidol has little effect on myocardial function or respiratory drive, and its safety and efficacy by the IV, IM, or oral route in the ED have been established. Haloperidol has no anticonvulsant properties, however extrapyramidal effects may be seen. In 2008, Ortho-McNeil placed a black box warning on haloperidol for elderly patients with dementia-related psychosis. Elderly patients with dementia-related psychosis treated with antipsychotic drugs such as haloperidol have 1.6 to 1.7 times the risk of death compared with placebo-treated patients. Caution should be used in patients who may be susceptible to a prolonged QTc. Droperidol has similar effects as haloperidol. In 2001, the Food and Drug Administration issued a black box warning regarding QTc prolongation and torsades de pointes following droperidol use; nevertheless, droperidol remains a

safe and effective treatment for agitated patients.[26] Dystonic reactions occur with both haloperidol and droperidol.

Haloperidol and lorazepam in combination are safe and may be synergistic, with haloperidol for the hallucinations and lorazepam for the hyperadrenergic effects. Use in extremely high doses in patients with serious underlying medical illness has been documented in several studies: 240 mg of haloperidol and 480 mg of lorazepam given over 24 hours in a patient and 485 mg of haloperidol over 8 hours in another patient without significant adverse effects. Some advocate an aggressive protocol with escalating doses of the combination of haloperidol and lorazepam.[27]

Emergency Department and Outpatient Approaches

Rapid, aggressive control of alcohol withdrawal is crucial. The cornerstone of treatment is a benzodiazepine. Lorazepam is preferable because of its previously discussed qualities.

An initial test dose of lorazepam may be given IV in a dose of 1 to 4 mg, depending on the severity of the withdrawal. Dosing can be repeated at 5- to 15-minute intervals for patients in severe withdrawal. An IM dose of 1 to 4 mg can be used every 30 to 60 minutes until a patient is calm and then every hour as needed for light somnolence. Patients remain under observation or are admitted until the manifestations of withdrawal do not progress after the effects of the benzodiazepine have dissipated.[22]

Outpatient treatment consists of lorazepam, 1 or 2 mg three times a day in a tapering dose for 3 to 6 days; chlordiazepoxide, 25 to 100 mg three times a day in a tapering dose for 3 to 6 days; or diazepam, 30 mg once a day tapered over 5 days depending on the severity of symptoms. Adequate diet, abstinence, and participation in a rehabilitation program in the community are also desirable. Any patient requiring 300 mg of chlordiazepoxide or 60 mg of diazepam per day to control withdrawal should be considered for admission. Patients with major alcohol withdrawal (disorientation, hallucinations, diaphoresis, or fever) are admitted. Doses approximately equivalent to 100 mg of chlordiazepoxide are 20 mg of diazepam and 5 mg of lorazepam.[22]

Adjunctive Therapy

Patients being treated for major alcohol withdrawal should receive thiamine (100 mg IV) and magnesium (2 g IV). Although magnesium sulfate does not decrease the severity of withdrawal symptoms, the incidence of delirium, or seizures, it carries no significant risk (with adequate renal function) or cost. In the nonacute setting, oral magnesium supplementation in chronic alcoholics improves liver function tests, electrolyte balance, and muscle strength.[28] Multivitamin preparations may be considered for chronic malnutrition. Although their clinical benefit is not proved, they carry no significant risk or cost.[18]

If present, volume depletion can be corrected with normal saline. Reversal of electrolyte and metabolic disorders (hypomagnesemia, hypophosphatemia, hypokalemia, and acidosis) benefits the patient, but it does little to abate the withdrawal syndrome.

Phenothiazines are contraindicated because they can produce hypotension, lower seizure threshold, disturb central temperature regulation, and cause extrapyramidal effects in the dosages required to calm patients in alcohol withdrawal.

ALCOHOL-RELATED SEIZURES

Among the many medical problems related to alcohol abuse, the differential diagnosis and management of seizures are one of the most challenging and controversial (Box 183-1). Patients presenting to the ED with seizures should be questioned about alcohol intake. In 20 to 40% of seizure patients presenting to an ED, the seizures are related to alcohol use or abuse.[29] Alcohol is a causative factor in 11 to 24% of patients with status epilepticus.[30,31] In states where alcohol sales are restricted on Sundays, EDs may see a spike in alcohol-related seizures on Mondays.[32]

BOX 183-1 Differential Diagnosis of Alcohol-Related Seizures

Withdrawal (alcohol or drugs)
Exacerbation of idiopathic or post-traumatic seizures
Acute intoxication (amphetamines, anticholinergics, cocaine, isoniazid, organophosphates, phenothiazines, tricyclic antidepressants, salicylates, lithium)
Metabolic (hypoglycemia, hyponatremia, hypernatremia, hypocalcemia, hepatic failure)
Infectious (meningitis, encephalitis, brain abscess)
Trauma (intracranial hemorrhage)
Cerebrovascular accident
Sleep deprivation
Noncompliance with anticonvulsants

The primary consideration in the initial care of seizure patients who use alcohol is the recognition of treatable, life-threatening causes. These causes include, but are not limited to, CNS infection, metabolic disorders, and intracranial hemorrhage. Alcohol may act in one of several ways to produce seizures in patients with or without underlying foci: (1) by its partial or absolute withdrawal after a period of chronic intake; (2) by an acute alcohol-related metabolic disorder (e.g., hypoglycemia and hyponatremia); (3) by creating a situation leading to cerebral trauma; (4) by precipitating seizures in patients with idiopathic or post-traumatic epilepsy; (5) by lowering the seizure threshold in patients with prior existing intracerebral disease states; or (6) by persistent heavy ingestion of alcohol, independent of alcohol withdrawal. Moreover, alcoholics are more susceptible to other disorders associated with seizures, including neurosyphilis, acquired immunodeficiency syndrome, brain abscess, and meningitis.[33-35]

Alcohol Withdrawal Seizures

Descriptions of alcohol withdrawal seizures (AWSs) were based on data collected by Victor and Brausch on 241 alcohol abusers with seizures or an alcohol-related illness complicated by seizures.[36] Seizures occurred 6 to 48 hours after the cessation of drinking. Ninety percent had one to six generalized tonic-clonic seizures. Sixty percent experienced multiple seizures within a 6-hour period. However, data suggest seizure recurrence can be reduced to 3% with lorazepam administration following the initial seizure.[37] The incidence of partial seizures, common with post-traumatic epilepsy, is increased in alcohol withdrawal. Regardless, first-time seizures and partial seizures warrant an evaluation for intracranial pathology.

The term *alcohol withdrawal seizure* is reserved for seizures with the characteristics described by Victor and Brausch.[36] The term *alcohol-related seizure* (ARS) is used to refer to all seizures in the aggregate associated with alcohol use, including this subset of AWS.

Management

After ensuring airway, breathing, and circulation (ABC), treatment should start by quickly establishing intravenous access.

If the patient has altered mental status, thiamine, magnesium, dextrose, and naloxone should be considered. An empirical glucose bolus should not be used if an accurate determination of blood glucose is quickly possible.[38]

Although magnesium administration does not decrease the severity of withdrawal symptoms, the incidence of delirium, or seizures, it carries no significant risk or cost. In the nonacute setting, oral magnesium supplementation in chronic alcoholics improves liver function tests, electrolyte balance, and muscle strength.[28] Multivitamin preparations may be considered for the patient's IV fluid for chronic malnutrition. Their clinical benefit is not proven.

Treatment with 2 mg of lorazepam IV reduces the risk of recurrent seizure in chronic alcoholics from 3 to 24%.[37]

It is often difficult to rule out a CNS infection in alcoholics because of concomitant hyperthermia, serum leukocytosis, and CSF pleocytosis. Although fever may suggest meningitis, it may be found in intracranial hemorrhage, brain abscess, alcohol withdrawal, toxic ingestions, and infections outside the CNS. Temperature can rise as a result of tonic-clonic seizure. Although there were few infections found in a retrospective series of 140 patients presenting with ARS, if CSF infection is a possibility, IV antibiotics should be started, blood cultures obtained, and a lumbar puncture (LP) undertaken.[32] An LP may be delayed until a space-occupying lesion is ruled out with computed tomography (CT) scanning, but antibiotics should not be delayed if meningitis is a possibility.

Patients Presenting with a Normal Neurologic Exam

New-Onset Alcohol-Related Seizures

Patients with new-onset ARS should be thoroughly evaluated. This includes alcoholics who claim to have had seizures but for whom no documentation or an appropriate workup is available.[39,40] Metabolic disorders, toxic ingestion, infection, and structural abnormalities should be considered. Laboratory and radiographic testing including electrolytes, blood urea nitrogen, creatinine, glucose, anticonvulsant levels, and brain CT scan may be necessary. Of 259 patients presenting with their first ARS, clinical management was changed in 3.9% based on head CT results.[41]

If the initial physical exam, imaging studies, and laboratory tests are within normal limits, patients who remain seizure free and symptom free with no sign of withdrawal after 4 to 6 hours of observation may be discharged. These criteria may be difficult to meet; therefore, admission may be considered.

It may be unclear whether the patient has had a pure AWS or a new-onset seizure disorder in the setting of alcohol ingestion. Long-term treatment with antiepileptic drugs (AEDs) is not necessary in unprovoked new-onset seizures that have resolved or when a clear cause of seizures, such as alcohol consumption, can be identified. Optimal outpatient treatment includes follow-up and referral to a detoxification/rehabilitation program. Ideally, the help of a concerned family member or friend, who is not a drinking partner and can remain with the patient for at least 1 or 2 days, is helpful.

Seizures in the Alert Patient with a History of Seizures during Prior Withdrawal

The risk of seizure increases significantly in alcoholic patients with manifestations of alcohol withdrawal who relate a history of AWS.[43,44] Detoxification with benzodiazepines reduces AWS and should be initiated early because most AWSs occur within the first 24 hours after alcohol withdrawal. An initial dose of 2 mg of lorazepam or 5 mg of diazepam can be given intravenously. These doses frequently need to be repeated.[45] The patient is observed for 4 to 6 hours before he or she is considered for discharge. Prescribing benzodiazepines or AEDs upon discharge carries its own hazards. Prescribing benzodiazepines (other than a short 3- to 6-day tapering dose for withdrawal) may increase the potential risk of addiction. Using AEDs, such as phenytoin, in a potentially noncompliant patient may paradoxically increase the number of seizures by having large fluctuations in blood levels. The poorly compliant alcoholic patient may do better without outpatient anticonvulsants for a concurrent seizure disorder.[43] The ideal disposition is referral to a detoxification/rehabilitation unit.

Alert Patient with a Seizure before or after Presentation

The alcoholic patient with a known history of ARSs who experiences a single seizure or a short burst of seizures should be treated with benzodiazepines. These patients can usually be discharged after monitoring of neurologic status for 4 to 6 hours.[37]

Patients with an Abnormal Neurologic Presentation

New-Onset Partial Seizures

Partial seizures are reported to account for 24 to 51% of ARS.[46] Conversely, studies have shown that 17 to 21% of partial ARS patients have structural lesions (hematomas, tumors, vascular abnormalities, or stroke).[47] These primary causes of partial ARS, such as prior head trauma, may be easily missed in the history taking. As a result, an emergent CT scan is indicated to evaluate new-onset partial seizures.

The patient with a history of a focal ARS who has been previously evaluated does not require an emergency CT scan, provided a return to baseline occurs promptly. A patient presenting with a focal ARS with subsequent normal neuroimaging can be managed with supportive care, observation for 4 to 6 hours, and a benzodiazepine for withdrawal signs or symptoms. Appropriate follow-up should be arranged.

Status Epilepticus

Although fewer than 8% of ARS patients go into status epilepticus, alcohol is implicated in 15 to 24% of status epilepticus cases.[48] Status epilepticus may also be the first presentation of ARS. The most common cause of status epilepticus is discontinuation or erratic compliance with an anticonvulsant drug regimen, followed by ARS.[30,31] However, status epilepticus may arise for a variety of reasons and is often multifactorial.

Initial interventions for the alcoholic in status epilepticus include stabilization of the ABCs, administration of thiamine and glucose as indicated, and treatment with a benzodiazepine. Lorazepam and diazepam are both effective in terminating seizures in status epilepticus. Lorazepam is preferable because its anticonvulsant effect lasts several hours, whereas diazepam's anticonvulsant effect lasts only 20 to 30 minutes.[41,49-52]

Obtundation

The obtunded or stuporous alcohol-dependent patient with a history of seizure activity poses a diagnostic challenge. The patient's decreased level of consciousness (LOC) may be the result of a postictal state, occult head trauma, unrecognized

metabolic disorder, or poisoning. The first diagnostic task is to quickly determine the possibility of hypoglycemia (diagnosed and reversed at the bedside in minutes) and the evaluation of other metabolic and toxic causes of altered mental status. Patients with an acute alteration in mental status should undergo an emergent head CT if they are not demonstrating expected and obvious improvement.

No History of Seizures, No Current Seizure

In the alcoholic patient in withdrawal who lacks a history of seizures, benzodiazepines generally have sufficient anticonvulsant activity to prevent withdrawal seizures.

Phenytoin-Anticonvulsant Conundrum

Phenytoin has no significant benefit over placebo in preventing recurrence of AWS. Considering the risks of phenytoin and because it has no demonstrated benefit in the setting of AWS, it is not indicated for the treatment of AWS. The sudden withdrawal of phenytoin may potentiate the convulsive effects of alcohol withdrawal. Withdrawal seizures may occur in epileptic patients withdrawn from phenytoin.[29,53]

Alcoholic patients with preexisting seizure disorders pose a dilemma when they are supposed to be taking antiepileptic drugs but their blood levels suggest noncompliance. This is especially problematic when their epileptic attacks are uncommon and appear to occur exclusively in the context of alcohol withdrawal. Some of these patients may have AWS and may have been misdiagnosed. Others may have a seizure disorder that appears to be confined to the setting of alcohol withdrawal. Such patients have demonstrated that they cannot maintain compliance with their treatment.

A patient currently taking AEDs for an antecedent seizure disorder who presents with a seizure while intoxicated falls into a different category. Such an episode could be an isolated event in a usually compliant patient without a history of chronic alcohol abuse. In this patient, a seizure in the setting of a subtherapeutic AED level may represent the consequences of noncompliance with AED or sleep deprivation versus AWS.[43]

OTHER CLINICAL FEATURES AND MANAGEMENT

Cardiovascular Effects

Acute and chronic ethanol consumption can affect the mechanical function of the heart, produce dysrhythmias, and exacerbate coronary artery disease (CAD). It may alter myocardial function by direct toxic effects, associated hypertension, or indirectly by altering specific electrolytes. Acute intoxication can decrease cardiac output in both alcoholic and nonalcoholic patients with preexisting cardiac disease.[53]

Studies have linked moderate alcohol consumption (up to two drinks per day in men and one in women) to a protective effect from CAD. As much as 50% of the relative risk reduction of CAD can be explained by increased levels of high-density lipoprotein (HDL) and its subfractions HDL-2 and HDL-3. Genetic variations in the ADH allele may account for these changes. Low to moderate alcohol consumption decreases platelet aggregation, raises plasma levels of endogenous tissue plasminogen activator,[54] and lowers insulin resistance. Experimental data suggest that alcohol may have antioxidant properties, produce effects on smooth muscles through interactions with nitric oxide, and alter plasma total homocysteine levels.[55,56]

Studies suggest that moderate alcohol consumption, through a reduced risk of CAD, may also protect individuals from congestive heart failure (Box 183-2).[57] All of these beneficial effects are lost in heavy drinkers, in whom chronic alcoholism is associated with hypertension and congestive cardiomyopathy.

BOX 183-2 RISKS AND BENEFITS OF LIGHT, MODERATE, AND HEAVY DRINKING

Light/Moderate Drinking

Risks		*Benefits*	
Established	Heavy drinking	Probable	Decreased risk of coronary heart disease Decreased risk of ischemic stroke Decreased risk of gallstones
Unresolved	Breast cancer Fetal damage	Possible	Decreased risk of diabetes Decreased risk of peripheral vascular disease
Unlikely	Bowel cancer Hemorrhagic stroke High blood pressure		

Heavy Drinking

Risks		*Benefits*
Noncardiovascular	Liver cirrhosis Pancreatitis Certain cancers Accidents Homicides Suicides Fetal damage Degenerative central nervous system disorders	None
Cardiovascular	High blood pressure Arrhythmia Hemorrhagic stroke Cardiomyopathy	

From Klatsky A: Drink to your health? Sci Am 288:74, 2003. Copyright © Scientific American, Inc.

The typical patient with alcoholic cardiomyopathy is a man older than 30 years with a greater than 10-year history of chronic alcohol intake. The signs and symptoms are no different from those of low-output congestive heart failure of other causes: dyspnea, palpitations, weakness and fatigue, jugular venous distention, poor R wave progression, nonspecific electrocardiographic abnormalities, and biventricular enlargement on a chest radiograph. Echocardiography shows four-chamber enlargement with decreased left and right ventricular contractile function. Up to one third of chronic alcoholic patients have left ventricular dysfunction demonstrated by a radionuclide ventriculogram, usually coexisting with skeletal muscle disease. Women appear to be more sensitive to the toxic effects of alcohol on striated muscle and are at greater risk for cardiomyopathy and myopathy. The diagnosis is made by obtaining a history of prolonged alcohol use and excluding hypertensive, coronary, valvular, and congenital disease.

Heavy alcohol consumption (more than 2 ounces a day) has a detrimental effect on those with preexisting CAD. It can reduce exercise tolerance, induce coronary vasoconstriction, and raise heart rate and blood pressure.[58] Additive cardiovascular effects of ethanol and nicotine contribute to dysrhythmias and sudden death in patients with CAD. In one study, nearly half the patients with alcohol withdrawal had prolongation of the QT interval. Prolonged QT can precipitate a dysrhythmia, resulting in sudden death.[59] There is an increased incidence of sudden death among heavy drinkers regardless of concomitant CAD or smoking.

Supraventricular (usually atrial fibrillation) and ventricular (usually transitory ventricular tachycardia) dysrhythmias, labeled "holiday heart," have been documented in alcoholic patients who have been drinking heavily. One study reported that alcohol contributes to or causes new-onset atrial fibrillation in approximately two thirds of patients younger than 65 years. Alcohol also affects cardiac function indirectly by lowering potassium and magnesium levels. Data from the Framingham Heart Study indicate that patients with lower levels of potassium and magnesium have higher rates of dysrhythmias.[60]

Left ventricular ejection fractions improve with either abstinence or sustained decrease of alcohol consumption starting at 1 year and continue to improve over at least 4 years. Tachydysrhythmias as a result of episodic drinking commonly revert to sinus rhythm with abstinence and do not require immediate intervention if the patient is hemodynamically stable. Nevertheless, correction of electrolyte abnormalities is prudent.

Pulmonary Effects

Alcohol reduces the mobilization of alveolar macrophages and their bactericidal capacity. Their impairment is greatest in alcoholics with hepatic cirrhosis. These effects, along with aspiration, decreased airway sensitivity, concomitant smoking, and malnutrition, probably account for the increased incidence of pneumonia, particularly lobar pneumonia, among alcoholic patients.[61]

At least 80% of alcoholics are smokers, making it difficult to distinguish between alcohol-induced and tobacco-induced injury to the lungs. The high prevalence of respiratory disease in alcoholics is largely caused by smoking. Chronic alcohol abuse has been shown to increase the risk of developing adult respiratory distress syndrome.[62,63]

Alcohol induces bronchospasm in some asthmatics and increases ventricular ectopy and sleep apnea in patients with chronic obstructive pulmonary disease. Alcoholic patients with hepatic cirrhosis can have hypoxemia as a result of precapillary shunting in their lungs. Hyperventilation and respiratory alkalosis are also seen with hepatic cirrhosis. One or two drinks per day decrease the risk of pulmonary embolus and deep vein thrombosis in elderly patients.[64]

Gastrointestinal and Hepatic Effects

Esophagus and Stomach

Alcoholic patients have a higher incidence of esophagitis, gastric cancer, and esophageal carcinoma than the general population. Acute alcohol ingestion also decreases lower esophageal sphincter pressure, delays gastric emptying, and disrupts the normal gastric mucosal barrier. Vomiting is common among drinkers. Forceful or persistent emesis can lead to a Mallory-Weiss tear or Boerhaave's syndrome.

Gastrointestinal Bleeding

Alcohol is closely associated with gastrointestinal bleeding. Causes include Mallory-Weiss tears, esophagitis, esophageal varices, acute and chronic gastritis, thrombocytopenia, portal hypertensive gastropathy, qualitative and quantitative platelet disorders, and prolonged clotting times. Alcohol may exacerbate gastric mucosal damage when combined with nonsteroidal anti-inflammatory drugs (NSAIDs), but ethanol is not a risk factor for peptic ulcer disease. An inverse relationship exists between consumption of alcohol, particularly wine, and active *Helicobacter pylori* infection. Peptic ulcer disease is the most common cause of bleeding in alcoholic patients with upper gastrointestinal hemorrhage as well as in those who do not drink.[65]

Liver

The liver is the primary site of ethanol metabolism. Hepatic damage has been recognized for centuries as the hallmark of chronic alcohol abuse. Obesity potentiates the severity of alcohol-induced liver damage.[66] The production of cytokines such as tumor necrosis factor alpha is one of the earliest events in many types of liver injury. This cascade may trigger the production of other cytokines that together enlist inflammatory cells, kill hepatocytes, and initiate healing through fibrogenesis. There is no one test that can be used to diagnose alcoholic liver disease (ALD) reliably. However, the ratio of aspartate transaminase (AST) to alanine transaminase (ALT) greater than 1.5 suggests that alcohol is the cause of liver injury.[67] ALD is the most common liver disorder in the Western world and, along with hepatitis C, is a leading cause of liver transplantation.

The earliest, mildest, and most common liver change seen in alcoholism is the accumulation of macrovesicular fat in the hepatocytes, predominantly involving triglycerides. Alcoholic fatty liver is usually asymptomatic, associated with mild elevations of AST and ALT. It is usually detected by the finding of hepatomegaly on physical examination or abnormalities on ultrasonography or CT but is confirmed by liver biopsy. Fatty liver is a reversible disorder if the patient can refrain from drinking.[68]

Alcoholic Hepatitis

Alcoholic hepatitis is more serious than fatty infiltration and develops in up to 35% of heavy drinkers.[69] These individuals usually have right upper quadrant pain, a tender enlarged liver, fever, jaundice, leukocytosis, and altered liver function tests. AST levels are usually less than 500 IU/L, and ALT levels are typically less than one half the AST levels. Alcoholic hepatitis

has a range of clinical manifestations, from mildly symptomatic hepatomegaly to fulminant hepatic failure. The severity of the disease can be estimated in the ED by a prolonged prothrombin time/international normalized ratio (INR)[70] or with the use of discriminant factor.[71] Model for End-Stage Liver Disease is also very helpful to predict mortality in these patients.[72]

Emergency department evaluation includes complete blood count, electrolytes, blood urea nitrogen, creatinine, glucose, prothrombin time/INR, liver function tests, and urinalysis. If the patient has an abnormal prothrombin time/INR and is actively bleeding, fresh frozen plasma should be started in the ED. Steroids are indicated in severe cases (encephalopathy and coagulopathy).[73] Steroids are contraindicated in patients with gastrointestinal bleeding or concurrent infection. In those who are contraindicated for steroid treatment, pentoxifylline has been shown to be beneficial.[74] Up to 80% of patients who continue to drink after having alcoholic hepatitis eventually develop cirrhosis.

Alcoholic Cirrhosis

Cirrhosis is the disruption of the normal architecture of the liver by scarring and regenerating nodules of parenchyma. Alcoholism is the most common cause of cirrhosis in the United States and is responsible for approximately 50% of all cirrhotic deaths.

Alcoholic cirrhosis usually requires 10 to 15 years of chronic drinking, often punctuated by one or more episodes of acute alcoholic hepatitis. The clinical outcome is determined by the development of complications of portal hypertension and by hepatic dysfunction. It is unknown why hepatic damage develops in some alcoholic patients and not in others exposed to identical amounts of alcohol. The disorder was originally described as "nutritional cirrhosis," but it has been shown that alcohol, independent of malnutrition, produces liver damage. Alteration of the normal hepatic architecture by fibrosis and nodule formation may eventually lead to portal hypertension. Portal hypertension may be complicated by ascites and esophageal varices.

Hepatitis C antibodies are found in one third to one half of alcoholics with ALD, presumably from shared risk factors. Patients with ALD and hepatitis C have histologically more severe disease, shorter survival, and increased rates (by a factor of 10) of cirrhosis and liver cancer.[75]

No specific medical therapy exists for ALD other than abstinence, proper diet, and management of the subsequent hepatic decompensation (i.e., ascites and encephalopathy). A 60% decrease in mortality has been associated with decreasing the amount of alcohol consumed over 1 year.[76] Although cirrhosis is irreversible, its progression may be halted with abstinence.

Pancreas and Intestines

The association of ethanol with pancreatitis is well established, but the exact pathogenesis is unclear. Hypotheses include reflux of duodenal contents and bile into the pancreatic duct, obstruction by a plug of pancreatic juice rich in proteins, and a direct toxic effect of ethanol. Ethanol abuse is associated with both acute and chronic pancreatitis.

The diagnosis of alcoholic pancreatitis can be difficult because asymptomatic alcoholics may have an elevated amylase level. In addition, up to 30% of patients with acute alcoholic pancreatitis have an amylase value within normal limits. Serum lipase rises after amylase and remains elevated longer. It appears to be a more reliable indicator of alcoholic pancreatitis, especially when more than three times normal.[77] Alcohol is only one of several causes of acute pancreatitis; other causes include biliary tract disease, hypercalcemia, hypertriglyceridemia, penetrating peptic ulcer, abdominal trauma, and reactions to various drugs. Alcohol is the leading cause of chronic pancreatitis.

Diarrhea and impaired intestinal absorption are common problems of the chronic alcoholic. Alcohol increases small intestine transit time and decreases brush border enzyme activity. Thiamine, vitamin B_{12}, amino acids, folic acid, and glucose all have impaired absorption in alcoholics. Dietary deficiencies in folic acid and protein, pancreatic insufficiency, abnormal biliary secretion, and direct toxic effects of ethanol on the gastrointestinal tract all contribute to malabsorption. Abstinence and adequate nutrition reverse the diarrhea and much of the malabsorption.[68]

Neurologic Effects

Altered Mental Status and Coma

A potential pitfall is ascribing the cause of the patient's altered mental state to acute intoxication without considering other conditions. Coma or an altered mental state may be caused by acute intoxication, mixed alcohol-drug overdose, postictal states, head trauma, hypoglycemia, shock from gastrointestinal bleeding or sepsis, hypothermia, hyperthermia, hepatic encephalopathy, methanol-isopropyl alcohol-ethylene glycol poisoning, or Wernicke-Korsakoff syndrome.

These potentially catastrophic diagnoses are usually detected by a thorough history and physical examination, a blood alcohol level (coma is rare in patients with blood alcohol levels <200 mg/dL), and close observation (an intoxicated patient's LOC should constantly improve over time). Patients with a less than classic presentation or course should have appropriate laboratory analysis and a head CT scan.

Neuropathy

A symmetrical sensorimotor polyneuropathy is common after chronic alcohol abuse, usually in the lower extremities. Its causes are thought to be a combination of nutritional deficiency with thiamine or vitamin B_{12} deficit and a direct neurotoxic effect of alcohol. Burning pain and paresthesia are common complaints. Findings on physical examination include loss of light touch, decreased pinprick, and reduced lower extremity deep tendon reflexes. Distal muscle weakness is a late finding. The neuropathy may lead to nonhealing ulcers on the feet. Treatment of alcoholic neuropathy is abstinence, adequate diet, and thiamine. Complete recovery is rare.

"Saturday night palsy" or "honeymooner's syndrome," an entity caused by radial nerve compression, consists of wrist drop. The patient usually has spent the night with the arm drooped over the back of a chair, bench, or a companion, compressing the radial nerve against the humerus and producing a neurapraxia. With radial nerve neurapraxia, function usually returns after a few weeks to months.

Wernicke-Korsakoff Syndrome

Wernicke's encephalopathy, a medical emergency with a mortality rate of 10 to 20%, remains a clinical diagnosis and is often unrecognized.[18] Contemporary criteria require two of the following signs: (1) dietary deficiencies, (2) oculomotor abnormalities, (3) cerebellar dysfunction, and (4) either an altered mental state or mild memory impairment.[78]

Genetic and environmental factors may play a part in the pathogenesis of this disorder. A thiamine-dependent enzyme, transketolase, is deficient or less active in some patients with

Wernicke-Korsakoff syndrome. This may explain why the disorder develops in only a few alcoholics. People with transketolase deficiency are asymptomatic until they are stressed by thiamine deficiency. Protracted vomiting, inadequate diet, and malabsorption all contribute to thiamine deficiency in the alcoholic.[79]

Korsakoff psychosis or amnesic state, also called alcohol-induced persisting amnestic disorder, is a disorder with recent memory impairment, inability to learn new information or recall previously learned information, apathy, and confabulation. Although common, confabulation is not essential for the diagnosis. Age older than 40 years and many years of heavy alcohol use are risk factors. The onset may be abrupt or insidious.

Alcoholics with altered mental status should receive thiamine (100 mg IV) and either a rapid blood glucose determination or empirical dextrose (25 g IV). Treatment for Wernicke-Korsakoff syndrome consists of abstinence, adequate diet, and thiamine. The ophthalmoplegia and nystagmus usually have a good response to thiamine within hours to days. The ataxia and mental changes may take days to weeks to improve and usually have a poorer prognosis. Less than 25% of patients show any real recovery, 50% show some recovery, and the remainder show no response despite adequate thiamine replacement. Because magnesium is a cofactor for this enzyme system, serum levels should be corrected.

Patients with Wernicke's syndrome require admission and aggressive thiamine and magnesium repletion. Recovery is variable in the Korsakoff or alcohol amnesic state.

Cerebrovascular Accident

As with CAD, many studies show that drinking light to moderate amounts of alcohol may decrease the risk of ischemic stroke. Conversely, heavy drinking is linked to an increased risk of intracranial hemorrhage and ischemic brain injury. Chronic alcohol consumption is believed to increase the risk of hemorrhage through alcohol-induced hypertension, impaired hemostasis, decreased circulating levels of clotting factors, excessive fibrinolysis, and disseminated intravascular coagulation. In addition, cardiac dysrhythmias or cardiomyopathy may precipitate thromboembolic phenomena.[33] Fifty percent of middle-aged patients (45–55 years) with no apparent cause for their cerebrovascular accidents suffer from alcoholism.[10]

Myopathy

Several studies have reported elevated creatine kinase in patients who had been on drinking sprees. Although these patients are asymptomatic, many have muscular tenderness on examination. Cardiomyopathy often coexists in these patients. Both acute and chronic forms of this myopathy are recognized. Many chronic alcoholics have mild proximal muscle weakness and muscle atrophy on examination.

Type II muscle fiber atrophy is found in chronic alcoholic myopathy. The role of ethanol, toxic metabolites, hypokalemia, hypocalcemia, hypomagnesemia, hyponatremia, malnutrition, unrecognized compression or crush injury, and other factors in the pathogenesis of atrophy remains to be determined.[80]

Movement Disorders

Alcohol withdrawal is associated with tremor, ataxia, and myoclonus. Acute alcohol consumption ameliorates essential tremor and myoclonus. Persistent tremor is occasionally seen in chronic alcoholism. This alcoholic tremor may persist up to 1 year after abstinence. Although the pathophysiology is poorly understood, studies have confirmed that essential tremor and alcoholic tremor are distinct entities.[81]

Alcoholic Cerebellar Degeneration

Characterized by ataxia of the extremities, cerebellar ataxia of alcoholism results in a wide-based stance and uncoordinated gait. Lower extremity involvement predominates, although the arms may rarely be involved. Pathologic changes consist of degeneration of elements in the cerebellum, especially the Purkinje cells. The diagnosis is based on history, physical examination, and magnetic resonance imaging or CT (which show severe cerebellar atrophy). Treatment consists of abstinence, adequate nutrition, and thiamine.[82]

Infections

Alcohol is an immunosuppressive drug. Animal and human studies have implicated acute and chronic ethanol ingestion in causing decreased serum bactericidal activity, impaired mononuclear phagocyte function, diminished cell-mediated immune functions, reduced delayed hypersensitivity reaction, and defective polymorphonuclear neutrophils. Neutropenia may be found in up to 8% of hospitalized alcoholics.[83]

Alcohol ingestion prevents the normal delivery (chemotaxis) of polymorphonuclear neutrophils to sites of bacterial infection. Chronic alcohol exposure depresses the development and expression of cell-mediated immunity. This depression may contribute to the high incidence of tuberculosis and head, neck, and upper gastrointestinal cancers in alcoholics. Alcohol's suppression of macrophage function reduces the reticuloendothelial system's ability to clear particles. This may contribute to spontaneous bacteremia, spontaneous peritonitis, and pneumonia. Primary antibody response to new antigens is also depressed. Malnutrition and liver failure also contribute to an immunocompromised state in the alcoholic.

The most common infection seen in alcoholism is pneumonia. Associated risk factors for pneumonia in alcoholics include smoking, decreased ciliary function, decreased surfactant production, depressed cough reflex, malnutrition, and poor oral hygiene. Although alcoholic patients may contract a variety of bacterial pneumonias, *Streptococcus pneumoniae* is still the most common organism. Periods of alcoholic stupor with incomplete glottic closure and subsequent aspiration can lead to aspiration pneumonia or lung abscess. *Klebsiella pneumoniae*, classically associated with alcoholism, is currently more common in patients with cytotoxic chemotherapy, hematologic malignancy, and transplantation than in the chronic alcoholic. In addition, these infections now tend to be nosocomial rather than community acquired.[83]

Alcoholism is also associated with a 55 times higher incidence of *tuberculosis* than that of the general population. Alcoholism does not seem to influence the long-term relapse rates in tuberculous patients if they have closely supervised therapy of adequate duration. Homeless alcoholic patients are an important reservoir of tuberculosis in the United States. Spontaneous bacterial peritonitis occurs in cirrhotic patients with ascites and has a high mortality rate (50–90%). A common presentation consists of fever, abdominal pain, and leukocytosis. *Escherichia coli*, *K. pneumoniae*, and *S. pneumoniae* are the most common bacteria cultured from the ascitic fluid. Patients with ascites and fever should have a diagnostic paracentesis as part of their evaluation.

Hepatitis C appears to be related to concomitant IV drug use rather than the direct effect of alcohol abuse. Alcoholism is associated with a high prevalence of unsafe sexual behavior

and human immunodeficiency virus (HIV) seropositivity,[84] with greater immunologic changes in HIV-1-positive patients who also consume alcohol.[85]

The most serious impairment of host defenses occurs with alcoholic cirrhosis and liver failure. Chronic alcoholics with cirrhosis develop spontaneous bacteremia and have a higher incidence of bacterial endocarditis. Alcoholism and cirrhosis increase the mortality rate in pneumococcal meningitis.

Fever in the chronic alcoholic may have a wide variety of causes. The most common infection remains pneumonia. Occult urinary tract infections are more common than expected. The most common noninfectious causes of fever are alcohol withdrawal and alcoholic hepatitis. A leukocytosis is associated with both, often making the differentiation from infection difficult. Both infectious and noninfectious causes may coexist, as well as multiple sources of infection. Most febrile alcoholics without an identifiable source are best served by hospitalization.

Endocrine Effects

Alcohol dependence adversely affects many endocrine systems. Both peripheral thyroid hormone dysfunction and central hypothalamic-pituitary-thyroid axis deregulation are seen.[86] Male hypogonadism and feminism are seen in chronic male alcoholics. Alcohol's effects on both the testes and the hypothalamus decrease testosterone production in men.[87] Alcohol may cause impotence by CNS sedation, secondary depression, or decreased testosterone production. Decreased testosterone, increased estrogen (in patients with liver disease), and increased prolactin can lead to decreased libido, feminization, and gynecomastia in male alcoholics and to abnormalities in lactation and menstruation in women. In female alcoholics, increased levels of testosterone and estrogen are found. Estrogen replacement therapy may increase hormonal levels threefold and thus increase the risk of cholelithiasis and breast cancer.[88]

It is difficult to distinguish between obesity, alcoholism, and Cushing's syndrome because facial fullness, weakness, fatigue, and easy bruising related to thinning of the skin can be present in all three conditions. An alcohol-induced pseudo–Cushing's syndrome has also been described that resolves with abstention.[87]

Metabolic Effects

Carbohydrates

Alcohol-induced hypoglycemia occurs in 1 to 4% of intoxicated ED patients. It is more frequently seen in chronic alcoholics.[89] Coma, seizures, hemiparesis, and a variety of other neurologic signs have been described in patients presenting with alcohol-induced hypoglycemia. Starvation, depletion of liver glycogen stores, decreased plasma cortisol levels, impaired release of growth hormone, and inhibition of gluconeogenesis contribute to this phenomenon.

Hyperglycemia and diabetes may be found in chronic alcoholism. However, studies in men that explored the association between light to moderate alcohol use and risk for type 2 diabetes suggest that an inverse relationship may exist.[90] Alcohol abuse can lead to chronic pancreatitis, resulting in underproduction of insulin by the damaged pancreatic cells. Alcohol also impairs peripheral glucose utilization, causing a relative insulin resistance (similar to type 2 diabetes). In diabetic patients, alcohol can induce hypoglycemia and also mask the signs of hypoglycemia. This effect has been found to be more prominent in the fasting state.[91]

Ethanol can be found as an active ingredient in hundreds of prescription and nonprescription drugs. Concentrations of 60% or greater can be found in some oral preparations, which pose a potential threat to the pediatric patient by producing profound intoxication or alcohol-induced hypoglycemia. Children are particularly susceptible because of smaller glycogen stores and delayed diagnosis. Hypoglycemia can also be seen with aspirin intoxication, prior gastric bypass surgery, hypothermia, or overwhelming sepsis.

Lipids

A reversible hypertriglyceridemia occurs in many chronic alcoholics. Ethanol increases hepatic synthesis of triglycerides. Abstention is necessary to reduce elevated triglyceride levels. Except for its relationship to fatty infiltration of the liver, the clinical significance of this hyperlipidemia is unknown.[92]

Uric Acid

Hyperuricemia is common with heavy drinkers. Alcohol increases urate levels by inhibiting renal clearance of urate, and it increases urate synthesis by enhancing the turnover of adenine nucleotides. Although alcohol use can exacerbate primary gout, it is unlikely that alcohol alone can induce secondary gout.

Electrolytes

Ethanol has numerous effects on electrolytes and mineral metabolism, as summarized in Table 183-2. Hyponatremia and hypokalemia are common findings in active drinkers. Vomiting, diarrhea, magnesium depletion, malnutrition, and metabolic alkalosis contribute to these abnormalities.

Alcoholism is the most common cause of severe magnesium deficiency in adult outpatients. Thirty percent of alcoholics are magnesium deficient as a result of malabsorption, malnutrition, diarrhea, vomiting, and increased urinary losses. Correcting the magnesium level has been shown to improve liver enzyme levels and to correct other electrolytes.[16,28]

Hypocalcemia is common in alcoholic patients with magnesium depletion. The mechanism is related to diminished parathyroid hormone secretion, decreased tissue responsiveness to parathyroid hormone, decreased vitamin D metabolism, and decreased calcium release from bone independent of parathyroid hormone. Correction of magnesium depletion is necessary to restore calcium to normal levels. Hypoalbuminemia, pancreatitis, or vitamin D deficiency may also contribute to low serum calcium or low total body stores of calcium in alcoholic patients.[93]

Hypophosphatemia is found in 30 to 50% of admitted patients with alcoholism. Phosphorus depletion results from malnutrition, vomiting, respiratory alkalosis, diarrhea, enhanced release of calcitonin, phosphate-binding antacids, and urinary loss (related to vitamin D deficiency and secondary hyperparathyroidism). Hypophosphatemic patients are often found to have low magnesium levels.[94] Rehydration, carbohydrate repletion, and parenteral alimentation further exacerbate phosphorus depletion. Glucose bolus and infusion have been shown to produce a significant decrease in serum inorganic phosphate levels. Severe hypophosphatemia (<1 mg/dL) has been associated with acute respiratory failure; myocardial depression; dysfunction of erythrocytes, leukocytes, and platelets; CNS irritability; and rhabdomyolysis.

Although chronic alcoholics requiring admission often have potassium, magnesium, and phosphate depletion, empirical treatment with potassium and phosphate is discouraged.

Table 183-2 Effect of Ethanol on Mineral Metabolism

MINERAL	CAUSE OF DEPLETION	ADDITIONAL EFFECT OF COMPARTMENT SHIFTS	CONSEQUENCES
Magnesium	Alcohol Diarrhea Poor intake Phosphate depletion Hyperaldosteronism	↓ Hyperventilation ↓ Free fatty acids	Pseudohypoparathyroidism Myopathy Potassium depletion Phosphate depletion ECG abnormalities Seizures
Phosphorus	Poor intake Diarrhea Metabolic alkalosis Hypomagnesemia	↓ Metabolic alkalosis ↓ Respiratory alkalosis ↓ Glucose (refeeding) ↑ Hypoparathyroidism (secondary to hypomagnesemia) ↑ Rhabdomyolysis	Rhabdomyolysis Platelet dysfunction WBC dysfunction CNS dysfunction Cardiac failure Renal tubular acidosis
Calcium	Poor intake Steatorrhea Hypovitaminosis K	↓ Hypoparathyroidism (secondary to hypomagnesemia) ↓ Rhabdomyolysis ↓ Hypovitaminosis D ↓ Hyperphosphatemia ↓ Pancreatitis ↓ Hypoalbuminemia ↑ Recovery from rhabdomyolysis	Tetany Seizures
Potassium	Poor intake Metabolic alkalosis Hyperaldosteronism Diarrhea	↓ Glucose (refeeding) ↓ Hyperventilation ↑ Rhabdomyolysis	Weakness Paralysis Myopathy Sudden death

↓, out of plasma; ↑, into plasma.
CNS, central nervous system; ECG, electrocardiographic; WBC, white blood cell.
From Kaysen G, Noth R: The effects of alcohol on blood pressure and electrolytes. Med Clin North Am 68:239, 1984.

Serum levels and renal function should be determined. Unintended hyperkalemia and hyperphosphatemia can produce significant morbidity, and phosphate infusion exacerbates hypocalcemia if present. Because most magnesium is intracellular, a normal serum magnesium level does not necessarily mean that total body magnesium levels are normal. If the serum level is normal, total body levels may be either normal or low. As long as renal function is adequate, empirical magnesium treatment can be considered. Abstinence and a proper diet resolve electrolyte and nutritional deficiencies in the ambulatory alcoholic patient who is healthy enough to be treated as an outpatient.

Correcting these problems is usually the responsibility of the admitting physician. Therapy may be initiated in the ED. In most cases, oral supplementation is sufficient. To correct more severe cases of hypokalemia and hypophosphatemia, 20 mEq of potassium phosphate per liter of IV solution can be given. Two grams (16.2 mEq) of magnesium sulfate (maximum 30–40 g/day) may be given IV at a rate not to exceed 150 mg/minute (equivalent to 1.5 mL of 10% solution).

Alcoholic Ketoacidosis

Alcoholic ketoacidosis most frequently occurs in severe chronic alcoholics who have had a recent binge followed 1 to 3 days later by protracted vomiting, decreased food intake, dehydration, and abstinence. Nausea, vomiting, and abdominal pain are common presenting complaints.[95]

These patients have tachypnea, dehydration, ketonuria, and little or no glucosuria. Serum glucose levels are usually less than 200 mg/dL. Normal blood pH may be found despite ketonemia because of coexisting respiratory alkalosis and metabolic alkalosis.

The exact mechanism responsible for the increase in ketone bodies is unclear. Acute starvation superimposed on chronic malnutrition, as well as release of an alcohol-induced block in ketogenesis allowing marked ketosis, may explain the disorder. An increased ratio of reduced (NADH) to unreduced nicotinamide adenine dinucleotide (NAD) in the alcoholic predisposes to the accumulation of β-hydroxybutyrate and the inhibition of gluconeogenesis, which may underlie the common occurrence of hypoglycemia in alcoholic ketoacidosis.

Alcoholic patients with metabolic acidosis present an interesting dilemma. Most of these patients have an increased anion gap acidosis. In addition, a very high osmolal gap (>25 mOsm/kg) is very specific (88%) for methanol or ethylene glycol ingestion.[96] Quick examination of a urine specimen in the ED can be helpful in determining the cause of the acidosis: Glucosuria may suggest diabetes; crystalluria can be seen in ethylene glycol poisoning; low specific gravity, proteinuria, and casts can be seen in renal failure; leukocytes and bacteria are present with urosepsis; and significant ketones in an otherwise normal urine may indicate starvation or alcoholic ketosis.

Treatment of alcoholic ketosis consists of normal saline, glucose, thiamine, and correction of hypokalemia. This can be accomplished with 5% dextrose in normal saline and either 30 mEq of potassium chloride or 30 mEq of oral potassium. Bicarbonate is seldom necessary for the uncomplicated case but may be considered in the rare patient who has a pH less than 7.1. If no serious complicating illness is present, the ketosis is reversed in 12 to 24 hours with this treatment.

Clinical improvement may be detected within hours of therapy. Nevertheless, most patients with alcoholic ketoacidosis need 1 or 2 days of inpatient treatment to correct fluid, electrolyte, and nutritional balance.[6]

Hematologic Effects

The alcoholic presents the clinician with a myriad of hematologic abnormalities. The direct toxic effect of ethanol and its metabolites, secondary nutritional deficiency, and hepatic disease, individually or in combination, affect red blood cells (RBCs), white blood cells (WBCs), platelets, hemostasis, and the immune system.[97]

Anemia

Several mechanisms are responsible for anemia, which is common in the alcoholic. Megaloblastic anemia resulting from folate deficiency is the most common anemia in alcoholics. The mean corpuscular volume (MCV) is typically increased but may be normal when iron deficiency coexists. Malnutrition, inability of the cirrhotic liver to store folate, excessive urinary loss, and malabsorption decrease folate stores. Alcohol accelerates the development of megaloblastic anemia in individuals with depleted folate stores (MCV > 100 fL) by an unknown mechanism.

Macrocytosis is the most common hematologic manifestation of the chronic alcoholic. It may be caused by folate deficiency, reticulocytosis (the younger reticulocytes are larger), liver disease (producing an abnormal lipid coating of RBC membrane), or vitamin B_{12} deficiency. The most common condition is idiopathic macrocytosis of alcoholism.

Iron deficiency anemia is common among alcoholic patients and usually is a result of blood loss from the gastrointestinal tract. Alcoholics are subject to chronic inflammatory diseases such as endocarditis, tuberculosis, empyema, lung abscess, malignancy, and hepatic disease. These chronic inflammatory illnesses can produce the anemia of chronic disease, a mild microcytic or normocytic anemia in which the serum iron is low, the total serum iron–binding capacity is low or low-normal, and serum ferritin is increased. With iron deficiency anemia, the serum iron is decreased, the total serum iron–binding capacity is elevated, and serum ferritin is decreased.

Ethanol also has a direct toxic effect on erythropoiesis. Bone marrow biopsies reveal vacuolization of erythroid precursors, resulting in decreased reticulocytosis and a reversible sideroblastic anemia. Sideroblastic anemia, usually in the presence of malnutrition with pyridoxine deficiency and folate deficiency, occurs in 25 to 30% of anemic alcoholics.

Hemolytic Syndromes and Erythrocyte Abnormalities

A variety of hemolytic syndromes have been associated with alcoholism. Zieve syndrome is a transient hemolytic anemia with hyperlipidemia and fatty infiltration of the liver. Acquired stomatocytosis, a condition characterized by abnormally shaped RBCs that are susceptible to hemolysis and acanthocytosis (spur cell anemia), has been associated with alcohol abuse. Zieve syndrome and stomatocytosis may be reversed with abstinence. Spur cells are RBCs with spicules. Spur cell hemolytic anemia is frequently linked to alcoholics with cirrhosis. With jaundice and splenomegaly, spur cell hemolytic anemia is usually fatal. When severe hemolysis is present, remission is rare.[98]

These syndromes are associated with liver disease, which alters the lipid composition of the RBC membrane, and congestive splenomegaly, which produces hemolysis. Severe hypophosphatemia (<1 mg/dL) can also result in hemolysis. The pathogenesis of these syndromes, specificity for alcoholism, and relationship to membrane injury or hemolytic anemia are uncertain.[97]

Leukocyte Abnormalities

Leukopenia is often seen in the alcoholic patient and has several possible causes. Sepsis, folate deficiency, and hypersplenism all lead to a decreased WBC count. Alcohol has a direct toxic effect on WBC production in the bone marrow. Granulocyte mobilization (chemotaxis) and adherence are also impaired, resulting in a decreased inflammatory response.

Platelet Disorders

Thrombocytopenia can occur with folate deficiency, sepsis, disseminated intravascular coagulation, or splenic sequestration. The direct toxic effects of alcohol decrease measured survival time and impair production of platelets in the bone marrow, but marrow toxicity will rarely reduce the platelet count below 30,000. Qualitative platelet function is also impaired. Binge drinking is associated with a reactive thrombocytosis potentially responsible for acute stroke and sudden death.[99]

Hemostasis

Alcoholic patients develop a bleeding diathesis for many reasons, including thrombocytopenia, qualitative platelet disorders, deficient production of hepatic clotting factors, gastrointestinal variceal formation, and vitamin K deficiency. A complete blood count, peripheral smear, platelet count, reticulocyte count, thrombin time, prothrombin time/INR, and partial thromboplastin time are required to evaluate episodes of significant bleeding. Bleeding associated with coagulation abnormalities may require immediate intervention. Fresh frozen plasma can be given for immediate correction of coagulation factor depletion; vitamin K (10 mg IV) takes 6 to 10 hours to reverse the vitamin K–dependent factors II, VII, IX, and X. Because of poor diet and impaired hepatobiliary function, alcoholics may have insufficient vitamin K storage and benefit from vitamin K delivery. However, alcoholic patients with profound liver failure are unable to produce precoagulation factors II, IV, VII, IX, and X, and vitamin K therapy is futile. Platelet transfusions should be started in the ED for adult patients with active bleeding whose platelet count is less than 50,000/mL.

Oncologic Effects

Worldwide, an annual total of 389,000 cases of cancer representing 3.6% of all cancers are alcohol related.[100] Chronic alcohol use is associated with an increased incidence of upper alimentary and respiratory tract cancers. The direct or indirect mechanism (e.g., tumor promoter) producing this relationship remains to be explained. Increasingly, acetaldehyde appears to play an important role in the carcinogenic effects on the upper digestive tract.[100] Ethanol may promote carcinogen activation by its effect on the cytochrome P450 system through (1) nutritional deficiencies (particularly vitamin A) that accompany prolonged heavy drinking, (2) contaminants such as nitrosamines and hydrocarbons, or (3) increased permeability of mucous membranes to other carcinogens.[101] Smoking certainly has an additional role as a cause of neoplasia and is difficult to isolate in these studies.

In general, alcohol increases the risk of cancer of the mouth, pharynx, larynx, and esophagus. Chronic hepatitis B infection may sensitize the liver to alcohol, producing hepatocellular carcinoma. Women who consume two to five drinks per day have a relative risk of 1.41 for invasive breast cancer compared with nondrinkers.[102] Moderate alcohol consumption leads to an increased risk of colorectal and prostate cancer.[103] The association is less clear between alcohol consumption and lung or pancreatic cancer.[104]

Hypothermia

Acute alcohol ingestion is one of the most common precipitating factors for accidental hypothermia and exacerbates hypothermia of other causes. Several studies have implicated acute

ethanol ingestion in 33 to 73% of patients presenting with a core temperature less than 35° C.[105] Alcohol is associated with the following: depressed hypothalamic thermoregulation, peripheral vasodilation producing heat loss, CNS depression, sepsis, inability to shiver, hypoglycemia, and an increased risk of environmental exposure. Hypothermia may be the presentation of Wernicke's syndrome, possibly caused by lesions of the posterior hypothalamus, hypoglycemia, or sepsis. Intoxicated patients also may have slower rewarming rates.

Psychiatric Effects

Forty-five percent of alcohol-dependent adults are diagnosed with one or more additional psychiatric conditions during their lifetime. Of alcoholic men admitted to a psychiatric ward, approximately 40% have a psychiatric disorder unrelated to substance abuse. In particular, antisocial personality disorder, schizophrenia, mood disorders, and anxiety disorders are found in this group. Up to 17% of all alcoholics eventually die by suicide.[106,107]

Depression and antisocial personality are the two most common psychiatric disorders that correlate with alcoholism, with a prevalence in most studies of 30 to 60%, respectively. Chronic alcohol use can produce an imbalance in the serotoninergic system. This imbalance may lead to increased anxiety, aggression, and depression. Interestingly, aggressive behavior is linked more strongly to depression than to alcohol dependence.[108] Secondary depression may be caused by alcoholism, or the primary affective disorder may be present with secondary alcoholism. Mild depressive symptoms are also common in alcohol withdrawal. Antisocial individuals are at high risk for alcoholism and drug dependence, although an unstable, unhappy childhood environment appears to be more important to the development of sociopathy than alcohol. Alcoholism, major depression, and antisocial personality all predispose to suicide attempts, and interaction among the three is particularly dangerous.

As many as 50% of alcoholic women exhibit symptoms of other psychiatric disorders. Although many patients turn to alcohol because of a primary psychiatric illness, alcohol can produce anxiety, hallucinations, paranoia, and depression and has been associated with a nearly twofold increased risk of suicide.[106]

An alcoholic patient who presents with an apparent psychiatric disorder poses a diagnostic dilemma. Does the patient have a primary affective disorder with secondary alcoholism, or is the patient manifesting anxiety or depressive behavior because of alcoholism? In general, alcoholic patients with psychiatric disorders are best treated with medications that are specific for their psychiatric condition.[2]

Many alcoholics with mild depression have spontaneous resolution of symptoms with abstinence. Nevertheless, depression meeting *DSM-IV* criteria is best treated with antidepressants.[109,110] If abstinence can be achieved, underlying psychiatric disorders are more easily diagnosed and treated.

■ ALCOHOL-DRUG INTERACTIONS

Alcohol is associated with a vast number of drug interactions (Table 183-3). These may occur through several mechanisms: (1) altered absorption; (2) enhanced metabolism and activated toxic metabolites through the hepatic CYP2E1 pathway; (3) additive or synergistic effects; (4) disulfiram-ethanol–like reactions; and (5) congeners, which are compounds found in alcoholic beverages. In general, chronic alcoholism is associated with an increased rate of drug clearance resulting from enhanced metabolism and enzyme induction (cytochrome P450 system). Conversely, acute alcohol intoxication reduces clearance for other drugs, increasing their serum concentration because of competition for a partially shared detoxification pathway.[111]

Altered Absorption

Propranolol may delay gastric emptying and thus prolong gastric contact. Other compounds, such as erythromycin and metoclopramide, may increase gastric emptying.

Enhanced Metabolism and Toxic Metabolites

Most alcohol is metabolized by ADH. A small percentage of alcohol is metabolized by the MEOS–cytochrome P450 system, which is also responsible for the metabolism of various drugs. The MEOS metabolic pathway is enhanced in chronic alcoholics. Therefore, the induction of MEOS is associated with the acceleration of the degradation of these other drugs. For example, the half-lives of warfarin, phenytoin, and isoniazid are 50% shorter in abstaining alcoholics than in nondrinkers. Barbiturates, diazepam, propranolol, and rifampin may have increased rates of clearance when taken by chronic alcoholics. This effect can persist for days to weeks after the cessation of drinking.[68,112]

Acetaminophen is the most widely used analgesic in the United States and is often recommended to alcoholic patients instead of NSAIDs to prevent gastritis. Chronic alcohol ingestion may enhance acetaminophen hepatotoxicity by accelerating the biotransformation to a toxic metabolite. There are a few case reports of severe or lethal acetaminophen toxicity in alcoholics taking therapeutic doses of the analgesic. Greatly elevated AST levels (3000 to 48,000 in one series), increased ALT levels, and greatly elevated prothrombin/INR times help to distinguish acetaminophen hepatotoxicity from alcoholic hepatitis.[111] Increased vulnerability seems to occur immediately after cessation of drinking. A synergistic effect apparently occurs with alcohol, fasting, and acetaminophen use in combination with depleted glutathione stores. Other studies have failed to demonstrate increased hepatotoxicity after acetaminophen overdose in heavy drinkers versus nondrinkers.[113]

Additive or Synergistic Effects

Alcohol has long been known to have additive or even synergistic effects with several drugs. Acute intoxication decreases the rate of drug metabolism, which is at least partially explained by competition for the same enzymatic process in the liver. For example, ethanol has additive sedative effects when taken with first-generation antihistamines, barbiturates, cyclic antidepressants, benzodiazepines, phenothiazines, propoxyphene, propofol, and narcotics. Alcohol may also increase the activity of methyldopa and nitroglycerin. Alcohol can increase tetracycline levels by 30%. Selective serotonin reuptake inhibitors do not appear to affect alcohol kinetics or psychomotor performance.

When cocaine and ethanol are taken concomitantly, a third drug is formed. Cocaethylene is a neurologically active compound, significantly more toxic than cocaine to the heart, liver, and brain, which is more addicting and more lethal than cocaine alone. Cocaethylene produces a higher incidence of confusion, lower mean Glasgow Coma Scale (GCS) scores, and a higher incidence of violent trauma and more often requires endotracheal intubation.[114] Hemodynamically, these patients demonstrate an elevated heart rate (1.5–5 times normal) and blood pressure greater than that with either drug alone. Sudden death is increased 18- to 25-fold over that associated with use

Table 183-3 Effects and Mechanisms of Alcohol-Drug Interactions

CLINICAL EFFECT	MECHANISM	DRUGS INVOLVED	COMMENTS
Increased blood alcohol levels	Inhibition of gastric ADH	Cimetidine Ranitidine Aspirin	Debatable role
Increased blood alcohol levels	Increased rate of gastric emptying	Cisapride Erythromycin	
Liver damage	Increased hepatotoxicity (chronic or "heavy" alcohol use)	Acetaminophen Isoniazid Phenylbutazone	"Heavy" drinkers can experience severe consequences even with therapeutic doses.
	Decreased metabolism of drug (acute alcohol use)	Narcotics Barbiturates Benzodiazepines Chloral hydrate Warfarin	"Binge" drinkers may develop toxicity from standard doses.
May require higher dosages	Induction of enzymes	Benzodiazepines Phenytoin Propranolol Warfarin	Chronic alcoholics
Increased bleeding time		Aspirin NSAIDs	
Sedation		Antihistamines	
Psychomotor impairment		Barbiturates Benzodiazepines Narcotics Tricyclic antidepressants	
	Disulfiram-like reactions	Oral hypoglycemics Antibiotics: metronidazole Sulfonamides Griseofulvin Cefoperazone Nitroglycerin	
Hypoglycemia		Long-acting oral hypoglycemics	
Hypotension		Aldomet Hydralazine Nitroglycerin	

ADH, alcohol dehydrogenase; NSAIDs, nonsteroidal anti-inflammatory drugs.

Data from Fraser AG: Pharmacokinetic interactions between alcohol and other drugs. Clin Pharmacokinet 33:79, 1997; and Adams WL: Interactions between alcohol and other drugs. Int J Addict 30:1903, 1995.

of cocaine alone. Plasma levels of cocaine in this combined group were higher than in those who used cocaine alone.[115]

Gastrointestinal Bleeding

Ethanol increases aspirin-induced prolongation of bleeding time and reduces the metabolism of warfarin, leading to increased anticoagulant effects. There is an increased risk of upper gastrointestinal bleeding when alcohol is combined with NSAIDs. This may be the most dangerous additive or synergistic effect of alcohol.[116]

Disulfiram and Similar Reactions

Most patients pretreated with disulfiram (Antabuse) who then consume even small amounts of alcohol experience an extremely unpleasant reaction. These patients develop a hypersensitivity to ethanol and experience a direct response within 15 minutes and lasting 30 minutes to several hours. The reaction consists of skin flushing on the head that spreads to the trunk, along with nausea, vomiting, headache, chest and abdominal discomfort, diaphoresis, vertigo, palpitations, and confusion. A severe reaction may produce hypotension, seizures, and dysrhythmias. Disulfiram-ethanol reaction is thought to occur by either the accumulation of acetaldehyde secondary to inhibition of the aldehyde dehydrogenase enzyme, which may be deficient in some Asians, or another unknown toxic factor. This incapacitating reaction has been used to discourage chronic alcohol ingestion.

A similar but milder disulfiram-ethanol–like reaction has been described when alcohol combines with several different drugs. The reaction may occur days to weeks after the last dose of medication. Four cephalosporins (cefamandole, cefoperazone, cefotetan, and moxalactam), metronidazole, chloramphenicol, griseofulvin, nitrofurantoin sulfonamides, all sulfonylureas, and chloral hydrate have been reported to produce this reaction when combined with alcohol ingestion. Life-threatening toxic reactions between griseofulvin and small amounts of ingested alcohol have been reported.[117]

Treatment for disulfiram reaction is symptomatic and includes IV fluids, dopamine for persistent severe hypotension, observation, an antiemetic, and cardiac monitoring.

Congeners

Congeners are compounds in alcoholic beverages other than ethanol and water. Some beers and wines contain tyramine. Hypertensive crisis may occur in patients treated with monoamine oxidase inhibitors who drink these alcoholic beverages.

Oral Hypoglycemics

Oral hypoglycemic agents and alcohol can interact and produce unpredictable glucose levels. Profound hypoglycemia can occur when alcohol and oral hypoglycemic agents are combined. Patients taking metformin may have an increased risk for developing lactic acidosis when combined with heavy drinking. A disulfiram-ethanol–like reaction has been described with many hypoglycemic agents.[112]

THE ADOLESCENT PATIENT

Injury is the most common cause of adolescent morbidity and mortality. Alcohol is often associated with these injuries.[118] Adolescent drinking is associated with a myriad of negative consequences, including suicide, driving under the influence and resultant fatalities, unsafe or increased sexual activity, sexual assault, and date rape. Seventy-eight percent of high school students have tried alcohol, and 30% admit to binge drinking at least once a month.[119]

The age of drinking onset may be an indicator for increased risk of alcohol-related injury. Adolescents who began drinking regularly before age 14 years were at least three times more likely to be diagnosed with alcohol dependence than those who began drinking at age 21. In addition, adolescents who began drinking before age 21 were significantly more likely, during their lives, to have been injured while under the influence of alcohol.[120]

Adolescent drinkers account for nearly 20% of all alcohol consumption, spending an estimated $22.5 billion.[121]

THE ELDERLY PATIENT

Active problem drinking is found in 14% of elderly (older than 65 years) ED patients. Fifty percent of older people drink alcohol, and 2 to 4% meet criteria for alcohol abuse or dependence. Common screening tests (e.g., CAGE) tend to be less sensitive in this age group. Alcohol may exacerbate underlying disease by masking anginal chest pain, worsening hypertension, and inducing dysrhythmias.[122] However, elderly people consuming low to moderate levels of alcohol may have a decreased risk for developing dementia and heart failure.[123] More than 90% of people age 65 or older use more than one prescribed medication.[124] Aging alters gastrointestinal absorption, lowers volume of distribution, diminishes homeostatic responses, and reduces renal and hepatic function.[112] Elderly people also demonstrate increased end-organ sensitivity, particularly involving the CNS, with concomitant drug use. Therefore, elderly patients are at increased risk for alcohol and drug interactions.

Elderly patients are also more likely to have neuropsychiatric complications of alcoholism. Sleep problems, anxiety, depression, and dementia are often observed. Alcohol has been involved in one third of suicides in elderly people. Older subjects have also been shown to perform less well on tests of perception and attention than younger subjects at all blood alcohol levels. This may result in an increased risk of fractures from falling and osteoporosis.

Overall, prognosis is age related with respect to cirrhosis. One study reported a 1-year mortality rate of 50% in those older than 60 versus 7% for those younger than 60.[68]

PREGNANCY

More than 2000 scientific reports have confirmed alcohol's teratogenic effects. According to the National Institute on Drug Abuse, almost 19% of all children born in the United States have been exposed to alcohol during gestation.[125] Pregnant women who reported any use of alcohol, binge drinking, or frequent drinking were more likely to be older than 30 years, employed, and unmarried.[126]

Fetal alcohol syndrome is characterized by a triad of CNS defects, including mild to moderate mental retardation; dysmorphology, involving mostly facial structures; and growth deficiencies, usually consisting of short status and microcephaly.[127] Fetal alcohol syndrome is now considered the most common identifiable source of mental retardation. Children exposed to prenatal alcohol exhibit increased activity levels, cognitive and attention deficits, perseverative behavior, and language and motor problems, which persist into adulthood.[128]

Ethanol rapidly diffuses across the placenta and is distributed to all fetal tissue with a predilection for gray matter. Although infants of mothers who drink heavily have the poorest outcome, children of mothers who consume only two or three alcoholic drinks a day also display abnormalities. Even in the absence of growth retardation or congenital abnormalities, children born to women who consume excessive alcohol during pregnancy appear to be at increased risk for attention deficit disorders. These findings are referred to as *fetal alcohol effects*.

No known safe amount of alcohol consumption during pregnancy exists. The American Academy of Pediatrics recommends abstinence from alcohol for women who are pregnant or who are planning a pregnancy.[129]

TRAUMA

Alcohol and trauma are inextricably linked. Independently, the tragic effects of each are numerous; in combination, they are staggering. Injury is the leading cause of death between the ages of 1 and 44 years. It accounts for more than 500,000 injuries per year. In the United States, alcohol is the major risk factor for virtually all categories of intentional and unintentional injury. Besides increasing the frequency and severity of injury, alcohol significantly complicates the management of the trauma victim.[3] Alcohol intoxication often complicates the initial assessment of injury severity, resulting in an increased need for invasive diagnostic and therapeutic procedures (e.g., intubation, CT scan, and intracranial pressure monitoring).[130]

Alcohol may diminish the patient's capacity to respond to hemorrhagic shock by altering hemodynamic effects and acid-base balance. Volume depletion as a result of the diuretic effect of alcohol or vomiting can impair the reserve of the intoxicated trauma patient. Peripheral vasodilation caused by alcohol may contribute to hypotension and hypothermia. Although these effects may be minimal, they underscore the need for early and adequate fluid resuscitation in these patients. Intoxicated patients with severe non-neurologic trauma may have lower blood pressures and carbon dioxide levels (indicative of a compensatory hyperventilation) on hospital arrival than sober patients. More important, a poorly understood cardiac depressant effect also increases the depth of shock and volume requirements for resuscitation. Alcohol-induced skin vasodilation may be accompanied by an increase in skeletal muscle, mesenteric and renal bed constriction, and left ventricular stroke. Thus, the overall effect on systemic vascular resistance and blood pressure may be balanced.[131]

Intoxication renders the signs and symptoms of intra-abdominal and retroperitoneal injury less reliable than usual. If the risk of an intra-abdominal injury exists, further evaluation (e.g., ultrasonography and CT) should be considered.

Alcohol intoxication predisposes to abdominal wall laxity and thus less protection from blunt trauma.[131] These patients

are also likely to have full stomachs, increasing the risk of gastric injury after trauma and predisposing to vomiting and aspiration, especially during airway management. The fatty liver changes of alcoholism can result in hepatomegaly. Portal hypertension in alcoholics may produce splenomegaly. These organs can become more vulnerable to the effects of trauma because of their enlarged size, protrusion beneath the protection of the ribs, and increased intracapsular pressure.

Alcohol intoxication contributes to CNS injury in many ways. It is associated with aggressive behavior, impaired reflexes and coordination, and inappropriate avoidance responses. A higher degree of trauma to the spinal cord and much worse neurologic and functional recovery occur in patients who are intoxicated during trauma compared with sober patients.[132] Experimental evidence suggests that alcohol acts synergistically with mechanical injury of the spinal cord to amplify the trauma response by increasing edema formation within the contused tissue.[133]

No consensus exists on the indications for an emergency CT scan in patients with "minor head injury" (loss of consciousness, post-traumatic amnesia, GCS score of 14–15, and normal neurologic examination). One disturbing prospective study found that GCS plus 1 hour of observation was unable to predict positive head CT scans in intoxicated patients with minor head trauma. Patients with signs of head trauma and focal or generalized seizures need an urgent CT scan. CT scans of the head should be performed for any patient with deteriorating mental status, focal neurologic findings, new-onset seizures even without obvious signs of history of trauma, failure to improve over time, or mental status changes out of proportion to the degree of intoxication.[134]

The good news is that during the past 20 years, there has been a decline in the number of alcohol-related fatalities. Five states (Hawaii, Illinois, Indiana, Pennsylvania, and Utah) have enacted mandatory hospital and/or provider reporting laws.[135]

ADMISSION GUIDELINES AND DISPOSITION

Optimal outpatient therapy for chronic alcoholics includes involvement of concerned family or friends to ensure that the patients take their medications properly, appear at their follow-up appointments, abstain from alcohol, and maintain an adequate diet. Alcoholic patients who undergo outpatient treatment need close supervision; therefore, a follow-up clinic appointment within 24 to 48 hours should be considered.

Most alcoholics suffer from a combination of medical, psychiatric, and social problems. Hospitalization is often necessary to diagnose and treat these multiple problems. Moreover, with alcoholics who are no longer able to care for themselves, hospitalization is often dictated for this reason alone. Unfortunately, many managed care and Medicaid plans limit or do not cover inpatient detoxification. In choosing medical versus psychiatric admission, a medical illness usually takes priority.

Acute Intoxication

Acute intoxication alone seldom requires admission. However, combined alcohol-drug overdose or associated medical, psychiatric, or social problems may require hospitalization. Acute alcohol intoxication is a diagnosis of exclusion reached after adequate observation to ensure that the altered mental status resolves.

Alcohol levels that may be tolerated by an adult can be lethal in children. It is prudent to admit children with acute intoxication unless close psychosocial follow-up can be ensured. Children presenting with hypoglycemia or medical complications should be admitted. Child abuse or neglect should be considered.

Alcohol Withdrawal

Patients with signs of major withdrawal (fever, hallucinations, confusion, and extreme agitation) require admission. Patients with mild alcohol withdrawal can be observed in the ED. After 4 to 6 hours of observation and treatment, the alert, oriented patient whose vital signs, physical examination, and appropriate laboratory analysis are within normal limits may be released. Optimally, the patient can be sent to an alcohol treatment center or sent home with an accompanying competent adult for continued observation over several days.

Seizures

Patients experiencing their first ARS may be admitted. Admission allows initiation of drug therapy, diagnostic evaluation, and continued monitoring of the patient's status. However, the alcoholic patient with a first-time ARS may be discharged to a suitable social situation when (1) the patient's alcohol withdrawal is mild and easily controlled either by supportive care or with low-dose benzodiazepines; (2) the diagnostic workup, including a head CT scan, is unremarkable; (3) the patient has had less than two seizures; and (4) the patient has been observed to be alert and oriented, with normal vital signs, physical examination, and laboratory studies, during the 6 hours since the last seizure, and appropriate outpatient follow-up can be ensured.

Patients with a documented history of ARS can be discharged if they have had no more than two ARSs during a 6-hour period with a lucid interval between seizures and are observed to be seizure free and at baseline mental and physical status for at least 6 hours after their last ARS. Three to five brief, self-limited seizures may occur with alcohol withdrawal seizures. Nevertheless, admission for patients with two or more seizures is advised because of the potential for deterioration to status epilepticus. This is especially appropriate in the malnourished, immunocompromised, homeless, or noncompliant alcoholic patient.

Patients with partial seizures or focal neurologic findings on physical examination require admission unless these findings have been previously documented. Patients with seizures associated with head trauma or with mixed alcohol-drug withdrawal are admitted. Status epilepticus or recurrent seizures during observation in the ED indicate a lack of seizure control also requiring hospitalization.

Psychiatric and Social Problems

Alcoholic patients requiring admission with acute intoxication, ARS, alcohol withdrawal, or medical or surgical disorders are usually best managed on acute care floors rather than by a general psychiatric service. Some psychiatric and social conditions in the alcoholic can be better handled on a general psychiatric unit, including psychosis, exacerbation of schizophrenia, depression with suicidal tendencies, any patient who is a danger to self or others, or alcoholic hallucinosis with an otherwise clear sensorium.

Patients who are no longer able to care for themselves may also require admission. Although these patients' ultimate destination is a rehabilitation center or a board-and-care program, hospitalization may be necessary to rule out medical or psychiatric illness and to treat impending withdrawal symptoms. Patients who wish to stop drinking are usually admitted to a

detoxification unit to treat impending withdrawal. Data and interest are increasing for outpatient drug therapy in alcohol dependence. The Food and Drug Administration has approved disulfiram, naltrexone, acamprosate, and topiramate for treatment of alcohol dependence.[2] Naltrexone, ondansetron, acamprosate, or acamprosate plus naltrexone have had mixed results facilitating abstinence.[136,137] The role of medications in combination with behavioral therapy is actively investigated.[138,139] Brief intervention—10 to 15 minutes of counseling—can decrease drinking compared with no intervention.[140] Referral and brief intervention are warranted.[141] Most communities have either an Alcoholics Anonymous chapter or a treatment center for anyone who desires help with alcohol. In smaller communities, clergy or social workers can usually arrange rehabilitation.

Alcohol kills—it kills the alcoholic and it kills unintended victims by the acts of inebriated people. Whatever medical, psychological, or social problem brings the alcoholic to the ED, the underlying problem is alcoholism and the ultimate goal is abstinence. This disease surely progresses if alcoholism is not recognized and if the patient is never given the opportunity to participate in a rehabilitation program.[142] The emergency physician can intervene on behalf of the patient and the public.

KEY CONCEPTS

- Moderate alcohol consumption is defined as one or two drinks per day in men and one in women.
- Benzodiazepines are the mainstay of treatment for alcohol withdrawal and alcohol withdrawal seizures.
- Inappropriate alcohol consumption or alcohol dependence should be considered in ED patients in almost any clinical situation, including trauma, potential drug-alcohol reactions, pneumonia, cardiomyopathy, new-onset atrial fibrillation, hepatitis, gastrointestinal bleeding, pancreatitis, altered mental status, depression, suicide, magnesium deficiency, and anemia.
- Minor alcohol withdrawal occurs as early as 6 hours and usually peaks at 24 to 36 hours after the cessation of or significant decrease in alcohol intake.
- Major alcohol withdrawal occurs after more than 24 hours and usually peaks at 50 hours (but occasionally takes up to 5 days) after the decline or termination of drinking.
- Delirium tremens is the extreme end of the alcohol withdrawal spectrum and consists of gross tremor, profound confusion, fever, incontinence, frightening visual hallucinations, and mydriasis.
- Not all alcohol-related seizures are alcohol withdrawal seizures.
- "Brief intervention" in the ED can decrease drinking and its long-term consequences.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 184 Substance Abuse

Stephen A. Colucciello and Christian Tomaszewski

PERSPECTIVE

The use and abuse of psychoactive substances are not unique to our country or century. People utilized hallucinogenic plants to achieve altered states of consciousness in prehistoric times, and psychoactive substances have been used in all eras and cultures ever since. As Osler remarked, "The desire to take medicine is, perhaps, the great feature which distinguishes man from other animals."[1] The human cost of substance abuse is high, and deaths secondary to psychoactive substances are common. In the United States, illicit drug use resulted in approximately 17,000 deaths in 2000 (Table 184-1).[2]

A major barrier to appropriate recognition and treatment of substance abuse is the lack of a precise definition. The American Psychiatric Association defines it as a maladaptive pattern of drug use associated with some manifest harm to the user or others.[3] Physicians have a very difficult time recognizing such abuse when up to 44% of emergency department (ED) patients report underlying chronic pain syndromes.[4] Chronic pain may not manifest the typical overt sympathetic changes or physical findings of acute pain.[5] Therefore, emergency physicians constantly walk a tightrope between undertreating legitimate pain and inappropriately rewarding substance abusers with controlled medications.

EPIDEMIOLOGY

A variety of stereotypes come to mind when compiling the profile of a substance abuser. These stereotypes pose dangerous traps for the clinician. Physicians are likely to ignore the possibility of drug intoxication in the well-dressed businessman or in those at the extremes of age. Yet children may ingest psychoactive substances they find on coffee tables or floors after parties or passively inhale smoke in rooms where drugs are used. Some parents deliberately give psychoactive substances to their children to calm or abuse them.

Increasing numbers of teens are ingesting dextromethorphan-containing over-the-counter (OTC) products such as Coricidin HBP Cough & Cold tablets.[6] These are known on the streets as Triple C, Red Devils, Red C, Red Box, or Skittles. Other dextromethorphan compounds include cough medicines, such as NyQuil or Robitussin DM, which provide the sought-after high known as the "robo-buzz." Teens abusing such preparations may present to the ED with anticholinergic syndromes and demonstrate tachycardia, hypertension, mydriasis, somnolence, or agitation.[7] Adolescents may also abuse medication used to treat obsessive-compulsive disorder and attention deficit/hyperactivity disorder. Methylphenidate has been a particular concern. Tablets can be abused orally, or they can be crushed and the powder injected or snorted. Despite its abuse potential, experts disagree regarding the extent to which methylphenidate is diverted from therapeutic use to abuse in preteens and adolescents.[8]

The elderly also abuse substances, and geriatric patients may suffer new-onset psychosis as a result of sympathomimetic abuse or drug withdrawal. Drug use is frequent among pregnant women, resulting in both maternal and fetal morbidity. Up to 7% of women delivering babies have urine toxicology screens that are positive for illicit drugs.[9] Manifestations of abuse may be acute, as in abruptio placentae or premature birth, or insidious, producing growth retardation and birth defects. Drug problems are more prevalent among the disadvantaged minority and lower socioeconomic groups. As a result, these groups bear the brunt of drug-related problems, such as incarceration, acquired immunodeficiency syndrome, and tuberculosis.

The Drug Alert Warning Network (DAWN), sponsored by the Substance Abuse and Mental Health Services Administration Office of Applied Studies, collects data from hospital EDs and medical examiners that include drug-related visits or deaths. The data consist of patients who abuse illegal drugs or use legal substances for a nonmedical purpose. According to DAWN, the drugs of misuse or abuse most commonly involved in deaths include cocaine, opiates/opioids, antidepressants, benzodiazepines, and miscellaneous (anxiolytics, sedatives, and hypnotics).[10]

For 2005, DAWN estimates that 816,696 ED visits involved an illicit drug: Cocaine was involved in 448,481, marijuana in 242,200, heroin in 164,572, and stimulants (including amphetamines and methamphetamine) in 138,950 ED visits. Other illicit drugs (phencyclidine [PCP], Ecstasy, and γ-hydroxybutyric acid [GHB]) were much less frequent.[11] In addition, 598,542 ED visits involved nonmedical use of prescription or OTC pharmaceuticals or dietary supplements, an increase of 24% between 2004 and 2005.[11] The majority of these visits (55%) involved multiple drugs. Benzodiazepine abuse increased 19%, opiate/opioid abuse increased 24% overall, and methadone abuse–related visits increased by 29%. Among the central nervous system agents, opiate/opioid analgesics accounted for a third of all ED visits, and oxydocodone products, hydrocodone products, and methadone were implicated in more than 130,000 ED visits.

Table 184-1 Complications of Illicit Drug Use

Infectious
Hepatitis
Pneumonia
Skin abscess
Brain abscess
Endocarditis
HIV
Osteomyelitis
Botulism
Gangrene

Cardiovascular
Cardiomyopathy
Aortic dissection
Myocardial infarction
Dysrhythmias
Pseudoaneurysms
Arteritis
Hypertension

Neurologic
Stroke
Drug-induced parkinsonism
Dystonia
Vasculitis
Intracerebral hemorrhage
Cerebral atrophy
Radiculopathy
Leukoencephalopathy

Pulmonary
Chronic lung disease
Pulmonary hypertension
Pulmonary edema
Eosinophilic pneumonia
Pneumonitis
Barotrauma (pneumomediastinum)
Pulmonary fibrosis
Emphysema

Psychosocial
Unemployment
Inadequately treated depression
Conduct disorders
Hallucinations
Suicide
Homicide

Miscellaneous
Dental caries and periodontal disease
Rhabdomyolysis
Thrombophlebitis
Tattooing
Placental abruption
Congenital malformations

PHARMACOLOGY

Knowledge of drug interactions assists in the diagnosis and care of substance abuse victims. A careful medication history for all legal and illegal drugs, including ethanol, may pinpoint the source of an adverse reaction. For example, a variety of agents can increase the effects of cocaine. Some abusers co-ingest small amounts of organophosphates to decrease pseudocholinesterase activity and prolong the effects of cocaine.[12] The co-ingestion of ethanol and cocaine results in an active metabolite, cocaethylene, which also enhances and magnifies cocaine's effects. Serotonin syndrome, manifested by muscle rigidity, hyperthermia, diarrhea, and seizures, may result when sympathomimetic drugs are taken concurrently with selective serotonin reuptake inhibitors such as fluoxetine. Amphetamines elevate serotonin either directly or by reversible inhibition of monoamine oxidase (MAO). In fact, a selective serotonin reuptake inhibitor can result in flashbacks in prior amphetamine users. MAO inhibitors can provoke hypertensive crisis in patients taking sympathomimetics. Interactions between agents commonly prescribed for patients with human immunodeficiency virus (HIV) and recreational drugs may be associated with serious clinical consequences because protease inhibitors and nonnucleoside reverse transcriptase inhibitors can inhibit or induce the cytochrome P450 system.[13]

Figure 184-1. Freon abuser. (Copyright Stephen Colucciello.)

Some common chemicals in the home and workplace have an intoxicating effect that may be unexpected. Solvents, paint, lacquers, glues, aerosols, refrigerants, and other propellants (Fig. 184-1) are readily accessible for abuse among children and teens. Inhaled hydrocarbons, such as toluene, are rapidly absorbed and easily pass through the lipophyllic blood-brain barrier to give an inexpensive high.

Illicit drug laboratories have poor quality control, and many drugs are combined or "cut" with other substances to increase profits. Up to 50% of street samples lack the alleged drug. Some additives, such as local anesthetics or sugars, may be innocuous, but others, such as strychnine, may be lethal. Other drugs, such as PCP, are misleadingly sold as a different drug, such as lysergic acid diethylamide (LSD). During the 1990s, many doses of purported Ecstasy (MDMA) actually contained amphetamine drug mixtures or even simple caffeine or ephedrine.[14,15] Drug combinations and unanticipated additives or substitutions may produce a clinical picture discordant with what the patient claims to have taken.

"Look-alike" drugs may also have toxic effects. Teens in particular may take look-alike or "knock-off" drugs that look like a desired product such as Ritalin or Coricidin in the hopes of getting a desired "high," when in reality they may suffer unanticipated effects from an unrelated medication sold by an unscrupulous dealer.

CLINICAL FINDINGS

History

A drug history should be obtained from patients reporting drug reactions, acute anxiety or other psychiatric problems, and acute cardiopulmonary or neurologic symptoms. This information should include use of legal and illegal substances, prescription and OTC medications, vitamins, herbals, tonics, and potions. When appropriate, the physician should specifically ask if the patient is suicidal. The physician who is neutral and nonjudgmental in approach is more likely to obtain accurate information.

Patients should be asked what they believe their son or daughter took and when. The "street name" may be unfamiliar to the emergency physician; for a list of more than 2300 street terms that refer to specific drugs, visit http://www.whitehousedrugpolicy.gov/pdf/street_terms.pdf.[16] Regardless, this is no guarantee that the purported ingestant is pure or unadulterated; therefore, history is no substitute for careful examination, which may provide more reliable clues. Nonhospital personnel, family members, and friends may be able to offer additional information. Patients who are brought from the scene of a club, "rave," or circuit party with altered mental status may be under the influence of a "club drug" such as MDMA (Ecstasy), GHB, flunitrazepam (Rohypnol), or ketamine. Other club drugs, such as "Verve" and "Jolt," are sold on the Internet as precursor molecules to GHB, known as γ-butyrolactone. These dangerous drugs are especially appealing to teens.[17]

Intravenous drug abusers are likely to have infectious complications such as septic pulmonary emboli, skin or brain abscesses, endocarditis, or HIV-related disease.

The RAFFT score is useful in detecting substance abuse in adolescents, and a positive response to one or more of the following questions warrants further evaluation[18]:

Relax: Do you drink/use drugs to relax, feel better about yourself, or fit in?
Alone: Do you ever drink/use drugs while you are by yourself, alone?
Friends: Do any of your closest friends drink/use drugs?
Family: Does a close family member have a problem with alcohol or drugs?
Trouble: Have you ever gotten into trouble from drinking or using drugs?

Physical Examination

Documentation of vital signs is essential. Although fever may suggest infection or drug reaction, temperatures are frequently neglected in violent or agitated patients. Because rapid mouth breathing, dry mucous membranes, and agitation all produce unreliable oral temperatures, a rectal temperature can confirm suspected hyperthermia. Patients should be undressed and completely examined, with particular attention paid to the skin, eyes, and nervous system.

Physical examination includes evaluation for specific toxidromes. The presence of diaphoresis, mydriasis, tachycardia, hypertension, abnormal mental status, and hyperactive bowel sounds suggests sympathetic overload. In comparison, anticholinergic syndrome has these same features with the exception of dry skin and mouth and absent bowel sounds. The neurologic examination should incorporate a mental status evaluation, addressing both the level of consciousness and appropriateness of affect. Dental disease, with extensive caries, has traditionally been attributed to methamphetamine use, but it is common in other forms of chemical dependency.[19] The skin provides important clues to substance abuse, such as residue of drugs on the hand or face or track marks from intravenous drug use.

DIFFERENTIAL DIAGNOSIS

It is dangerous to assume that abnormal behavior or altered mental status in the unkempt young patient is due to drug intoxication. Many serious illnesses can manifest as an overdose ("OD"), including sepsis, meningitis, encephalitis, head trauma, unintentional poisoning (e.g., carbon monoxide), hypothermia, heatstroke, intracranial hemorrhage, complex seizures, and drug withdrawal. Hypoglycemia and other metabolic and endocrine derangements are important considerations. Similarly, drug intoxication should be considered in the differential diagnosis of altered mental status or abnormal vital signs regardless of age.

COMPLICATIONS

Illicit drugs produce a wide variety of complications involving all major organ systems. They are responsible for up to 5% of intensive care admissions, generating 10% of costs.[20] Neurologic complications are especially prominent. Almost 10% of strokes occur secondary to drug abuse.[21] Cerebral infarction, cerebral and cerebellar hemorrhage, and subarachnoid bleeding are often secondary to use of cocaine and amphetamines and, occasionally, PCP or heroin.[22] Single generalized tonic-clonic seizures are common with substance abuse, and status epilepticus can occur. Although sympathomimetics such as cocaine and amphetamines are responsible for the majority of seizures, heroin, tricyclic antidepressants, and PCP play a significant role. Withdrawal from benzodiazepines and alcohol can also result in status seizures.

The dangers of substance abuse extend far beyond the toxic effects of a particular drug. Associated hazards include HIV infection, not only secondary to intravenous injection but also from the promiscuous lifestyle associated with the drug culture. HIV seroprevalence is 12.7% among injection drug users and 7.5% among crack smokers.[23]

Recent declines in HIV incidence among intravenous drug abusers are encouraging, but resurgences have been associated with needle sharing and inadequate methadone treatment.[24] Accompanying this phenomenon is a decrease in hepatitis B and C among injection drug users in some U.S. cities.[25] Almost 20% of cocaine abusers have a positive skin (tuberculosis) test result in some locales. Sexually transmitted disease is common, especially in the sex-for-drugs culture of crack cocaine. Syphilis in particular is endemic among crack abusers.

The lungs are target organs for impurities in intravenous drugs, and pyrogens become trapped in this massive filter. This can produce "cotton fever," characterized by high fever, tachycardia, and tachypnea 10 to 20 minutes after injection.[26] This benign self-limited illness contrasts with the long-term restrictive and obstructive lung diseases that accompany the prolonged intravenous abuse of methylphenidate. Right-sided endocarditis is a frequent sequela of chronic intravenous drug abuse, and the nonspecific flulike symptoms that accompany this disease can mislead the clinician. In addition to endocarditis and acquired immunodeficiency syndrome, intravenous drug abusers develop septic pulmonary emboli, cellulitis, botulism, tetanus, and other infectious complications. They may develop unusual sites of osteomyelitis or septic arthritis involving the lumbar spine or sternoclavicular or sacroiliac joints.

Psychiatric complications of substance abuse are frequent and include anxiety, depression, suicidal ideation, mood swings, paranoia, and panic attacks. Paranoia and depression and associated suicide attempts are common among stimulant abusers, and hallucinations of parasites under the skin (formication) are frequent in those addicted to amphetamines. Sympathomimetics are strongly associated with aggressive behavior and street crime. Traumatic injuries are endemic among substance abusers and arise from both assault and motor vehicle crashes. In addition, psychedelic drugs, such as LSD and PCP, can prompt extreme behavioral change that can in turn lead to traumatic injuries. Occasionally, trauma can be occult, and the unwary physician may overlook a stab wound in a

patient whose clinical picture is predominated by drug-induced agitation.

DIAGNOSTIC ADJUNCTS

All patients with acute alterations in mental status require either a bedside glucose test strip measurement or the empiric administration of 50% dextrose solution. Patients who are unstable hemodynamically or with altered mental status need assessment of electrolytes, blood urea nitrogen, and creatinine. The complete blood cell count is of little value, except to follow serial hemoglobins if occult trauma or hemolysis is suspected. Arterial blood gas may be useful in assessing acid-base status as well as measuring oxygenation and ventilation. Rhabdomyolysis, most likely seen with sympathomimetic abuse or prolonged periods in the same body position as may occur with abuse of downers (e.g., barbiturates), is best detected by measurement of serum creatinine kinase or myoglobin.[27] Rhabdomyolysis is usually defined as creatinine kinase levels more than five times the upper limit of normal. Dipstick urinalysis may screen positive for hemoglobin without accompanying red blood cells but is insensitive for this condition. The electrocardiogram will occasionally diagnose a myocardial infarction in patients with drug-related chest pain.

The use of qualitative toxicology screens is controversial, but these are less important than the patient history and clinical status. Although unsuspected drugs may be detected, this knowledge rarely affects acute patient management.[28,29] Emergency physicians are often confused about which drugs are screened for on their own hospital's toxicology panel. Quantitative levels of suspected substances, such as acetaminophen or acetylsalicylic acid, may be valuable in certain circumstances. A new generation of rapid bedside urine toxicology screens may provide timely information, but their use requires further study.[30]

MANAGEMENT

Agitation

Few antidotes exist for psychoactive drug intoxication, and with a few notable exceptions, treatment is supportive. Violent or agitated patients require sedation. Benzodiazepines such as lorazepam (Ativan) can best sedate patients with sympathomimetic symptoms, whether due to drug intoxication or withdrawal. For other patients, intramuscular butyrophenones, such as haloperidol (Haldol) and droperidol (Inapsine), are rapidly effective and generally safe; however, droperidol has a black box warning from the Food and Drug Administration (FDA) for QT prolongation and potentially torsades de pointes. In September 2007, the FDA added a warning stating that "torsades de pointes and QT prolongation have been observed in patients receiving haloperidol, especially when the drug is administered intravenously or in higher doses than recommended. Haloperidol is not approved for intravenous use."[31] Phenothiazines are not recommended in the drug-intoxicated patient because of their strong anticholinergic effects and potential to produce hypotension and lower the seizure threshold.

Body Packers and Stuffers

The body *stuffer* swallows loosely packaged drugs, or the raw drug itself, in an attempt to conceal contraband on arrest. The body *packer* (a "mule") delivers professionally packaged drugs in his or her intestines, usually on a flight from another country. In many cases, these packets can be visualized radiographically.[32]

There is considerable debate regarding the best approach to these patients; some recommend activated charcoal for body stuffers and whole bowel irrigation for body packers, whereas others adopt a less aggressive approach.[33,34] In asymptomatic cases, the patient's right to refuse care usually supersedes local laws for forcible removal of such evidence. Patients who are significantly confused from drug effects (or comatose) are incapable of refusing lifesaving interventions.

Referral

After acute medical issues have been managed, substance abusers should be asked whether they would like help in overcoming their addiction. Studies show that intervention may be most successful for abusers of heroin, nonprescribed methadone, and benzodiazepines. Users of crack cocaine appear to be more resistant to treatment.[35]

Drug Seeker

As the front line in medical care, EDs are confronted by patients with drug-seeking behavior, typically for pain medication or benzodiazepines. Although only 1% of ED patients have a formally recorded diagnosis of substance abuse, as many as 27% of ED patients are actually in need of substance abuse treatment.[36] This drug-seeking behavior is described as a compulsion for seeking and taking drugs after prolonged use of a certain drug.[37] Although physicians should not "feed the habit" of drug seekers, their quandary is that inadequate pain management is internationally considered poor medicine and unethical.[38]

EDs need to judiciously provide pain medication to avoid long-term problems from undertreatment of real acute pain. However, an overly liberal approach can contribute to addictive behavior with repeated drug seeking. It is difficult for the individual physician to screen effectively for drug seeking or abuse on just a single encounter. Self-admission would be the easiest screen, but 90% of patients who abuse opioids deny it.[36] Although not sensitive, a prior history of drug or alcohol abuse may identify patients at risk for abuse of opioids, the most commonly abused agents of the prescription drug seeker.[39] Repeated visits for the same complaint, rapid dose escalation, unusual and multiple allergies, and demands for specific agents (often in specific milligram amounts) are all warning signs of potential drug seeking.[40] Unfortunately, there is no reliable finding that can consistently identify drug seeking while not penalizing legitimate medication seekers.

In response to this problem, both individual hospitals and some states are starting to track patients who habitually receive opiate prescriptions.[41] The effectiveness of such programs is not known. Some locales have had success with pain guidelines that restrict the use of opiates to proven conditions, with electronic flagging of habitual visitors who present for medical care.[40] Such approaches may work if done in conjunction with referral to chronic pain clinics or detoxification centers. A multipronged approach that combined counseling, denial of narcotic prescriptions in the ED, and referral to a single pharmacy resulted in a 72% decrease in ED visits by frequent users.[42] Restriction or removal of meperidine (which is highly intoxicating with potential for serious adverse effects) from EDs can result in decreased visits and fewer substance-abusing patients.[43]

Beyond facility-wide policies, individual physicians can attenuate drug-seeking behaviors. Avoiding the use of meperidine, which reinforces drug-seeking behavior, is an excellent

strategy.[44] In addition, the use of long-acting narcotics such as methadone and specialized forms of oral morphine decreases the reinforcement of drug-seeking behavior while providing compassionate pain alleviation.[45] Finally, concerned refusal, explaining to the patient that opioids or other controlled substances are not appropriate, may be helpful but only if other physicians in the group or community agree on such a strategy for a particular patient.[46]

KEY CONCEPTS

- Substance abuse can affect people from all socioeconomic groups and all ages.
- For the majority of patients with toxin-induced violent behavior, intramuscular butyrophenones such as haloperidol (Haldol) are safe and rapidly effective sedating agents. In patients with suspected sympathomimetic (e.g., cocaine and amphetamines) intoxication, benzodiazepines such as lorazepam (Ativan) should be utilized.
- Presenting to an ED with a complication of substance abuse may be a "teaching moment." Substance abusers should be offered drug treatment services.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 185

Evaluation and Management of Children with Special Health Care Needs

Terry Adirim

PERSPECTIVE

Children who are developmentally or physically disabled, have chronic illnesses, or are technology dependent for mobility or survival have special health care needs. In 1998, the Federal Maternal and Child Health Bureau provided a definition of children with special health care needs (CSHCN) to assist states in their systems development activities. This definition was conceived with the input of various constituencies, including CSHCN program directors, parents, and health care professionals. The following definition has become widely accepted within the pediatric community:

"Children with special health care needs are those who have or are at increased risk for a chronic physical, developmental, behavioral, or emotional condition and who also require health and related services of a type or amount beyond that required by children generally."[1]

The prevalence and characteristics of the CSHCN community depend on the definition used. Using the federal definition, in 2001 it was estimated that almost 13% of children in the United States experienced a special health care need.[2] There was a higher prevalence among older children, boys, and non-Hispanic white and black children, and after adjustment for demographic factors, families in poverty were more likely to have a CSHCN.

Advances in medical science and technology have been instrumental in allowing children with complex medical problems to survive beyond the neonatal period. Moreover, family-centered care has been the goal for the care of these children and, as a result, many are living at home instead of in institutions. These children are frequent users of the emergency medical system. Acutely ill children with special health care needs account for 24% of pediatric emergency department (ED) visits at tertiary care hospitals.[2] Emergency medical services (EMS) are typically activated during the time of a crisis. This crisis may occur because of equipment failure or panic by the caregiver who is fatigued or new to caring for the special needs child. However, a survey of 100 families with CSHCN conducted at a tertiary care urban pediatric center demonstrated that although 97% of the families had sought emergency care in the past, only 23% of the caregivers had ever called 911 before, and 93% had driven their child to the hospital during an emergency. Families may transport their children either to the nearest community hospital or to their "home" institution, which is likely to be a tertiary care center. Most EMS jurisdictions transport to the nearest "appropriate" medical facility.

Children with special health care needs are usually cared for by adults who have been trained to manage their child's daily care. In general, families are knowledgeable about their child's medical conditions and technological needs. Families may have detailed medical plans that specify such things as the size of tubes, how often to change tubes, dosages of medications, and ventilator settings. One example of a program that provides information to medical care providers is the American Academy of Pediatrics and American College of Emergency Physician's "Emergency Preparedness for Children with Special Health Care Needs Program."[3] This is an emergency notification program whose purpose is to communicate specific information to medical caregivers about the special needs child's conditions and medications. An emergency information form (EIF) is completed by the child's primary care physician or family and is carried with the child. Programs have also been developed to assist EMS personnel, such as "EMS Outreach," a tertiary care hospital–based program developed in the Washington, DC, metropolitan area. Enrollees in the EMS Outreach program complete a medical information form that caregivers carry with them. This information is disseminated to area EMS systems so that EMS providers are aware of the specific needs of the CHSCN within their jurisdictions. The information is kept in a database and is updated every 6 to 12 months. Although most caregivers are adept at handling many of their children's emergencies, caregivers seek help for a variety of reasons, including the need for respite, equipment malfunction, an overwhelming medical problem, and help with transport to the child's home hospital.

PRINCIPLES OF DISEASE

General Issues for Children with Special Health Care Needs

CSHCN differ from well children in a variety of ways. Some CSHCN may be neurologically impaired and therefore developmentally delayed. Their physical growth may be limited, resulting in their being smaller than other children of the same age. As a result, medical personnel cannot rely on age- and weight-based norms and should either ask caregivers for this information or use length-based tapes when estimating weight, calculating drug dosages, and determining fluid management. Developmentally delayed children may have vital signs that differ from those expected for "healthy" children of the same age. For example, baseline vital signs are altered in children

with cardiac conditions or on mechanical ventilators, and a child with unrepaired complex congenital heart disease may have a baseline pulse oximetry reading in the low 80s. Some children with lung diseases may have respiratory rates higher than expected, yet these higher respiratory rates are considered their baseline.[4] Also, some children may have sensorineural deficits such as blindness and deafness that may make assessment challenging. Medical care providers need to be aware of these situations.

Care must be taken when treating and moving developmentally delayed children as they tend to become frightened easily with quick motions and unfamiliar sights and sounds. Using a calming tone while speaking at a developmental level the child can comprehend can decrease anxiety and most likely increase cooperation. Allowing parents to be at the bedside is vital for all children, but most especially for these children. Moving children with musculoskeletal disorders can best be accomplished with slow, deliberate motions so as not to frighten the child. The child's caregivers are the best resource when determining the most appropriate methods for communicating with or moving a special needs child.

SPECIFIC DISORDERS

Airway/Pulmonary Conditions

Tracheomalacia

Tracheomalacia is a condition of abnormally weak tracheal walls due to the loss of supporting cartilage and structural integrity. This frequently causes collapse of the trachea on inspiration. Tracheal collapse is most prominent during times of increased airflow, such as when the infant is coughing, crying, feeding, or has an upper respiratory infection.

There are three causes of tracheomalacia: (1) congenital or intrinsic tracheal anomaly (occurring within the trachea), which may be associated with a tracheoesophageal fistula (a patent connection between the trachea and esophagus); (2) extrinsic defects (occurring outside the trachea) such as abnormal development of the vasculature around the trachea that may create a ring, which places pressure on the trachea and interferes with airflow; and (3) acquired malacia, which occurs in children with prolonged intubation or chronic tracheal infections.

Medical management for tracheomalacia consists of symptomatic treatment. A child may experience respiratory compromise with simple viral infections. Racemic epinephrine may decrease swelling of the upper airway under these circumstances. It is prudent to observe these children in the hospital until they are no longer compromised. For children with severe tracheomalacia, a stent or rigid piece of cartilage may be surgically placed in the collapsed area of the trachea to establish permanent patency. Infants with vascular rings may have constricting vessels surgically divided and reattached to surrounding structures in order to release the pressure on the trachea. In rare instances, tracheostomies are placed in order to provide a patent airway until the child's airway grows and strengthens. Fortunately, infants often outgrow tracheomalacia.

Regardless of the underlying cause, infants and children with tracheomalacia who are in respiratory distress present with similar signs and symptoms, including cough, prolonged expiratory phase, stridor, accessory muscle use, and hypoxia.

Bronchopulmonary Dysplasia

Bronchopulmonay dysplasia (BPD) is a chronic lung disease occurring in infants, which is characterized by stiff lungs and chronic exacerbations. BPD is a worldwide problem with 5000 to 10,000 new cases reported each year and ranking with cystic fibrosis and asthma as the most common chronic lung disease in infants.[3]

BPD develops primarily in low-birth-weight infants who have respiratory distress syndrome (RDS), a lung disease common in premature babies. Babies born prior to 32 weeks' gestation may not have enough surfactant to keep their alveoli open.[4] However, BPD development is not limited to RDS survivors. BPD may result from alveolar damage caused by other lung diseases, exposure to prolonged high oxygen concentrations, or use of mechanical ventilation after birth (due to conditions such as neonatal pulmonary hypertension, pneumonia, or other infections or trauma to the lungs), all of which can cause harmful chemical reactions in the lungs.[5]

A combination of fewer air sacs and a lack of surfactant can result in abnormally stiff lungs. This increases the work of breathing for affected infants who can quickly become fatigued. As the child progressively weakens, carbon dioxide builds up in the lungs and blood. Respiratory infections can also worsen the inflammatory response in the lungs, leading to more fluid in the lungs and bronchospasm. Other emergencies directly related to BPD include pulmonary edema, aspiration of food or stomach contents into the lungs, and apnea. Signs and symptoms of BPD can vary in severity depending on the infant's lung maturity. They may include tachypnea, retractions, paradoxical respirations, abnormal posturing, and wheezing.

BPD causes the most difficulties during the first year of life, which is when most deaths from this disorder occur. Problems after the first year become increasingly uncommon. The most common long-term lung complication of BPD is asthma, which occurs in approximately half of patients. Other less common complications include apnea during infancy, gastroesophageal reflux, pulmonary hypertension, high blood pressure, pulmonary edema, aspiration, subglottic stenosis, and tracheomalacia. Infants who have BPD are at risk for frequent hospitalizations because of their borderline respiratory reserve, hyperactive airway, and increased susceptibility to respiratory infection.

Treatment for BPD involves symptomatic relief. Home management may include oxygen, bronchodilators, corticosteroids, diuretics, antibiotics and, in rare cases, ventilator support through a tracheostomy.

Tracheostomy Tubes

Tracheostomy tubes are placed to facilitate mechanical ventilation, provide a bypass of the upper airway, or keep the airways clear of secretions. The more common conditions for which tracheostomy tubes are placed include tracheal stenosis, tracheomalacia, certain craniofacial anomalies, bronchopulmonary dysplasia, muscular dystrophy, spinal cord injury, and traumatic brain injury.

Because the tubes are available from several manufacturers, their sizing and markings vary. Common brands include Shiley, Bivona, Hollinger, Portex, and Berdeen. Typically, the sizes are marked on the packaging and on the flange, or wings, of each tube. They range in size from 00 for newborns to 7.0 for older adolescents.[6] The inner and outer diameter ranges are provided so that comparisons between brands can be made. They range from 2.5 mm for infants to 10.0 mm for adolescents and adults. This information is helpful for emergency personnel when replacing a tracheostomy tube or when choosing an endotracheal tube for oral intubation or use through a stoma. The inner diameter of a tracheostomy tube should be used to choose the endotracheal tube size for insertion through a stoma. Tracheostomy tubes also come in various lengths.

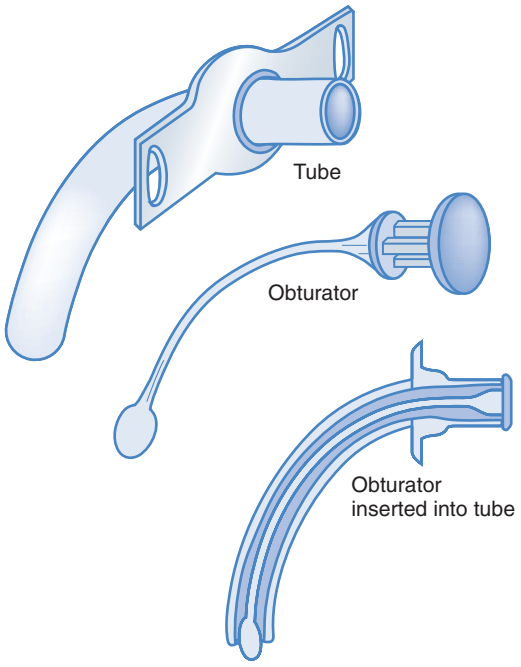


Figure 185-1. Single-cannula tracheostomy tube. (Adapted from Susan Gilbert in Teaching Resource for Instructors in Prehospital Pediatrics [TRIPP]; www.cpem.org.)

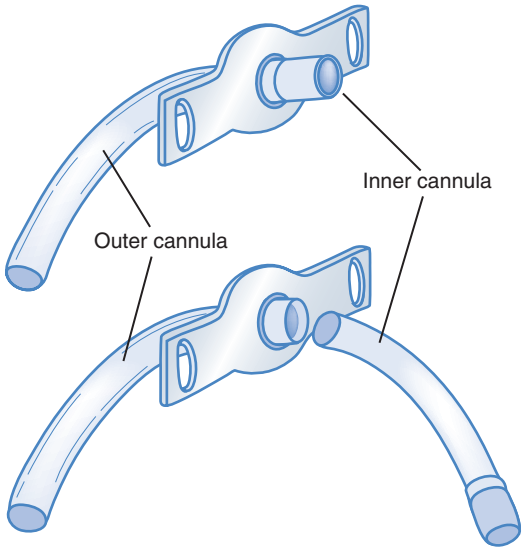


Figure 185-2. Double-cannula tracheostomy tube. (Adapted from Susan Gilbert in Teaching Resource for Instructors in Prehospital Pediatrics [TRIPP]; www.cpem.org.)

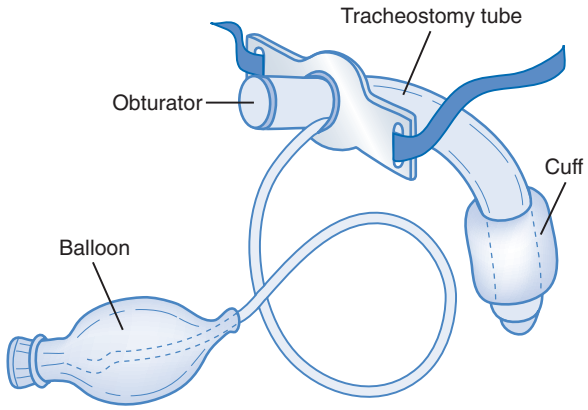


Figure 185-3. Cuffed tracheostomy tube. (Adapted from Susan Gilbert in Teaching Resource for Instructors in Prehospital Pediatrics [TRIPP]; www.cpem.org.)

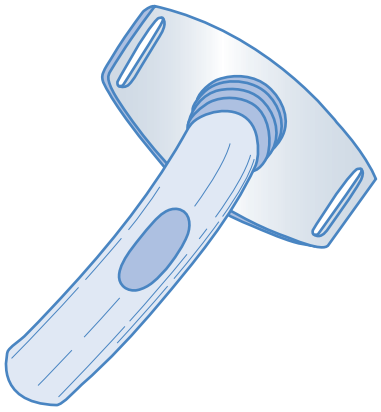


Figure 185-4. Fenestrated tracheostomy tube. (Adapted from Susan Gilbert in Teaching Resource for Instructors in Prehospital Pediatrics [TRIPP]; www.cpem.org.)

Neonatal tubes are shorter than pediatric tubes, although the inner diameters may be the same.

There are several types of tracheostomy tubes and attachments: single-cannula tubes (Fig. 185-1), double-cannula tubes (Fig. 185-2), cuffed tubes (Fig. 185-3), and fenestrated tubes (Fig. 185-4).[7] Neonates, infants, and young children use single-cannula tracheostomy tubes. As a child's trachea gets larger, a double-cannula tube can be used. This contains an outer tube that stays in the stoma and an inner tube that is removable for cleaning and pulmonary toilet. Tracheostomy tubes for older children and adolescents have an inflatable cuff to keep the tube in place and to prevent air leaks. Fenestrated tubes have a hole in the cephalic portion of the tube that redirects air into the upper airway to allow the child to speak and breathe through the nose and mouth. This is facilitated by a decannulation plug that is attached to the opening of the tube.

Attachments to the tracheostomy tube may include a tracheostomy nose, a tracheostomy collar, and a speaker valve. A tracheostomy nose is placed over the external opening of the tracheostomy tube of a non–mechanically ventilated child to provide air filtration and humidification. A tracheostomy collar is used to provide humidified air or supplemental oxygen to the non–mechanically ventilated patient. A speaker valve is an attachment that redirects airflow through the upper airway to facilitate speech.

Tracheostomy Emergencies

Children with tracheostomy tubes seek emergency care for three primary reasons: (1) an exacerbation of the underlying pulmonary disease, (2) blockage of the tube by a mucous plug, or (3) equipment failure. Signs and symptoms of respiratory distress include nasal flaring, retractions, increased respiratory rate, decreased breath sounds, decreased oxygen saturation, cyanosis, wheezing, rales, and increased secretions.

Sudden onset of respiratory distress may suggest a mucous plug or equipment failure rather than a pulmonary infection, which is usually heralded by a more progressive deterioration of respiratory status and fever. Airway assessment should include inspection of the tracheostomy tube for patency.

For the child experiencing an exacerbation of pulmonary disease, infection and reactive airway disease are the most

likely possibilities. Acute treatment for wheezing includes administration of a bronchodilator by nebulizer through the tracheostomy or in-line with the ventilator in a mechanically ventilated child. In a child with a fever, infection should be considered, chest radiography and tracheostomy cultures obtained, and antibiotic coverage provided. The need for hospitalization is determined by a combination of factors including age, medical history, severity of illness, and diagnosis. Medical personnel should consider transporting medically complex children to their home hospital for care by physicians who know them best.

For the child with sudden onset of respiratory distress, suctioning the tracheostomy tube may be helpful. Approximately 2 to 3 mL of normal saline should be instilled prior to suctioning. If suctioning two to three times does not relieve the obstruction or respiratory distress, then the medical provider should change the tracheostomy tube because there may be a thick mucous plug obstructing airflow through the tube. As with any procedure, the practitioner should be prepared and have the appropriate supplies available; an endotracheal tube can be used as a substitute in the appropriate size if a tracheostomy tube is not available. Also, parents and caregivers often have spare equipment in their "go" bags that can be used (for troubleshooting, see Table 185-1).

Apnea

Apnea in infants and young children is defined as a cessation in breathing for more than 20 seconds or associated with a change in color, limpness, altered mental status, or bradycardia. Apnea occurs more frequently in infants born prematurely and generally reflects immature neurologic and respiratory control mechanisms. These pauses in respiration may be due to central apnea, which is the result of an absence of a neurologic signal to the respiratory muscles. Underlying causes include encephalitis, brainstem infarction or tumor, neuromuscular disorders such as muscular dystrophy, or thoracic restrictive disorders such as kyphoscoliosis. These children are

Table 185-1 Medical Devices: Common Problems and Solutions

DEVICE	PROBLEM	ACTION
Tracheostomy	Obstruction	Attempt assisted ventilation with high-concentration oxygen Attempt to suction Change tracheostomy tube Ventilate through stoma Transport
	Dislodged	Replace tracheostomy Provide assisted ventilation with high-concentration oxygen through the stoma Transport
	Unable to reinsert	Attempt to place a tracheostomy tube one size smaller If attempt fails, attempt to place a similar size endotracheal tube If attempt fails, provide assisted ventilation through stoma or through the child's mouth while blocking the stoma
Home ventilator	Respiratory distress	Ask parents to check whether ventilator is functioning properly Assist in adjustment of ventilator Assess tracheostomy for obstruction Remove patient from ventilator and provide assisted ventilation
Pacemaker	Failure	Assess heart rate and perfusion Treat for shock Follow appropriate PALS guidelines Transport
Central intravenous catheter	Dislodged or damaged	Apply direct pressure to stop bleeding Clamp or tie exposed catheter to prevent further blood loss Assess and treat patient for hemothorax and shock Transport
	Air embolism	Clamp the line Place patient on left side with head down Administer high-flow oxygen Transport
Central venous catheter site	Signs of infection at the site	Treat as a potentially serious infection Transport
Oral or nasal feeding catheter	Dislodged	Remove catheter Have patient seek medical attention for tube reinsertion
Surgically placed feeding catheter	Dislodged	Cover open stoma with gauze Transport promptly
	Abdominal distention or obstruction	Unclamp tube Decompress stomach (aspirate air/fluids) Transport
CSF shunt	Failure or obstruction	Treat ABCs Keep head elevated Give anticonvulsants for seizure activity Follow appropriate PALS guidelines for arrhythmias

ABCs: airway, breathing, and circulation; CSF, cerebrospinal fluid; PALS, pediatric advanced life support.
Adapted from Adirim T, Smith E: Special Children's Outreach and Prehospital Education. London, Jones and Bartlett, 2005.

discharged home from the hospital on an apnea monitor. Apnea monitor alarms often result in ED visits. The apnea monitor should be transported with the child to the hospital. Most monitors contain a computer chip that records information that can be downloaded into a computer at the home hospital to determine the origin of the monitor alarms (high or low heart rate, apnea, or artifact). This diagnostic procedure can be expedited when the child is transported to his or her home hospital.

The most common type of childhood apnea is obstructive apnea, which is caused by an occlusion in the upper airway at the oropharyngeal level or by gastroesophageal reflux disease (GERD). GERD occurs when the lower esophageal sphincter opens, causing stomach contents to pass into the esophagus during or after a meal. Younger children tend to outgrow this condition. Those who continue to be symptomatic can experience complications such as a chronic cough, recurrent pneumonia, difficulty swallowing, recurrent vomiting, and weight loss. Symptoms can often be controlled with positioning, diet, medications, and, in rare circumstances, surgery.

Mixed apnea is central apnea that is followed by an obstructive apnea event. Obstructive sleep apnea may be managed by providing oxygen during sleep or through nasal continuous positive airway pressure (CPAP), which may be delivered through a nose mask or tracheostomy. Central apnea is managed with supplemental oxygen and CPAP but also responds to medications that stimulate the respiratory system or mechanical ventilation.

Home Mechanical Ventilation

Many children with tracheostomies are also mechanically ventilated. Indications for mechanical ventilation include severe lung disease and abnormal respiratory drive either from central causes or secondary to paralysis. Some children are dependent on ventilators 24 hours a day, some while asleep, and others for part of the day.

There are two types of ventilators: pressure-cycled ventilators and volume ventilators. Pressure-cycled ventilators tend to be used in infants. They are set to deliver a given pressure with each breath. Volume ventilators give a tidal volume with each breath. There are two common modes of ventilations: intermittent mandatory ventilation (IMV) and controlled mechanical ventilation (CMV). IMV mode delivers a mechanical breath between the patient's own respirations to ensure that the patient achieves a certain number of breaths per minute. The ventilator synchronizes its breaths with the patient's breaths. On the other hand, with CMV, the ventilator is set to deliver a certain number of breaths per minute whether or not the patient can breathe without assistance. Some ventilators have an assist control mode in which the ventilator gives a breath at the same time the patient takes a breath to augment the patient's effort.

There are five types of home ventilator alarms: (1) low pressure/apnea, (2) low power, (3) high pressure, (4) setting error, and (5) power switchover. The causes of a low-pressure alarm include a loose or disconnected circuit, a leak in the circuit, and a leak around the tracheostomy site. The low-power alarm indicates the internal battery is near completion and the ventilator will need to be plugged into an electrical outlet. A high-pressure alarm indicates that either there is an obstructed circuit or the patient is having bronchospasm. A setting-error alarm indicates the setting has been improperly adjusted. Under these circumstances the patient should be manually ventilated until the ventilator can be set properly. The power-switchover alarm sounds whenever the ventilator switches from AC power to battery power. When this happens, check to ensure that the battery is powering the unit before pressing the "alarm silent" button.[7]

Possible causes of respiratory distress in a ventilator-dependent child include airway obstruction (e.g., obstructed tracheostomy tube), an obstruction or leak in the ventilator tubing, problems with the oxygen supply, equipment failure involving the ventilator, or a medical condition. If a ventilator-dependent child is found to be in respiratory distress and the cause is not easily determined, the child should be taken off the ventilator promptly and ventilated with a manual resuscitator (bag device). Manually ventilating the child can help determine if the equipment has failed or a medical condition is responsible.

Congenital Cardiac Conditions

Congenital cardiovascular defects are the most common forms of malformations in newborns, with a reported incidence ranging from 4 per 1000 to 50 per 1000 live births (see Chapter 169).[8] The diagnosis is established within the first year of life in 40% of patients with congenital heart disease (CHD).[9] Left untreated, the condition proves fatal in most cases before age 20.[10] Cardiovascular defects are considered to be the leading cause of neonatal death due to congenital abnormalities. However, from 1979 to 1997 mortality due to CHD declined by 40% due to early diagnosis, improved surgical treatment, and advances in medical technology.[11] When an infant is born with a severe cardiac anomaly, interventions are primarily directed toward maximizing home health care until definitive surgery can be performed, although some defects cannot be surgically corrected.

Complex CHD is divided into acyanotic and cyanotic lesions.

Acyanotic Lesions

Acyanotic lesions account for most cases of CHD. With acyanotic defects, there is no mixing of desaturated (poorly oxygenated venous) blood in the systemic arterial circulation. The defects are associated with left-to-right shunts and obstruction to the ventricular outflow. Left-to-right shunts cause oxygenated blood from the left side of the heart to mix with deoxygenated blood from the right side of the heart. Long-term left-to-right shunting of blood leads to complications, and therefore these infants should receive surgical repair as soon as possible. Some of the more common acyanotic cardiac lesions involve a defect in the septum. These include atrial septal defects (ASDs), ventricular septal defects (VSDs), and atrioventricular canal defects (endocardial cushion defect or atrioventricular septal defect). The atrioventricular canal defects are more serious and almost always require surgical repair. VSDs in the muscular part of the septum often close on their own and only need to be repaired surgically if they are large and cause serious symptoms. Small ASDs have a very high rate of spontaneous closure, so surgical correction is delayed until the child is 3 to 4 years of age. However, if the defect is large and untreated, the patient may present with congestive heart failure or pulmonary hypertension as a result of volume overload. Typical later findings on cardiac exam include a fixed, split S_2 sound.[7]

Obstructive Lesions

Obstructive lesions obstruct ventricular outflow. Some of these include pulmonary stenosis, aortic stenosis, and coarctation of the aorta. Infants with pulmonary stenosis have mild defects that are usually asymptomatic. Signs and symptoms of aortic

stenosis depend on the severity of the condition. Most children are asymptomatic even though mild stenosis can worsen over time. Symptoms of worsening stenosis include fatigue, dizziness, syncope, and chest pain. A balloon valvuloplasty or surgery is performed to correct aortic stenosis. Coarctation of the aorta represents 8 to 10% of all CHD and is commonly associated with Turner's syndrome.[7] The child is often asymptomatic at birth; however, newborns with critical coarctation can develop symptoms as early as a week after delivery. The signs and symptoms include poor feeding and weight gain, breathlessness, and signs of circulatory shock. Patients may present with weak peripheral pulses, significantly higher blood pressure readings in the upper extremities than in the lower, or congestive heart failure. The condition is repaired surgically.[7]

Cyanotic Lesions

Cyanotic defects are less common congenital cardiac conditions. Blood from the arteries and the veins mixes in the heart, causing baseline low blood oxygen levels. (Normal pulse oximetry readings can range from the 60s to the low 90s in unrepaired cyanotic defects.) The degree of cyanosis may vary with age, activity, and the severity of defect. In many instances survivability depends on shunting between the right-sided pulmonary circulation and the left-sided systemic circulation. This shunting allows unoxygenated blood to mix with oxygenated blood. Two openings that allow this mixing to occur after birth are other associated cardiac abnormalities such as ASDs and VSDs. Acidosis is common and can develop quickly because of decreased ventilatory reserve. This type of heart disease can result in a true life-threatening emergency since circulatory collapse is imminent after the development of acidosis. Cyanotic cardiac defects include hypoplastic left heart syndrome, tetrology of Fallot, transposition of the great arteries (TGA) (Fig. 185-5), tricuspid atresia, pulmonary atresia, and truncus arteriosus. The most important management issues for these children are prevention and treatment of heart failure and acidosis and maintenance of oxygen saturation in the child's "normal" range, which may be below 90%.

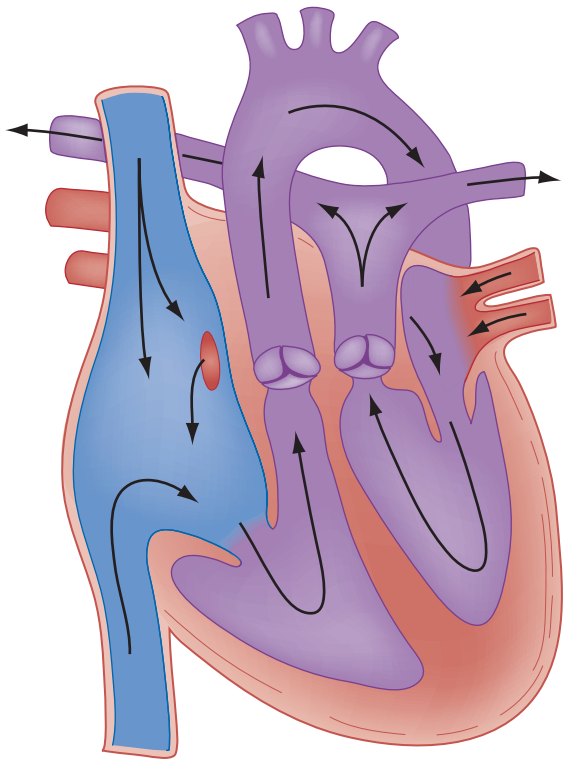


Figure 185-5. Transposition of the great arteries.

Children with complex CHD are often small for age, and some may be developmentally delayed. When a child with complex CHD presents to the ED for treatment, asking the caregivers about the child's usual appearance, usual oxygen saturation, and developmental age is extremely helpful in managing the child's care. It is also useful to know which cardiac procedures the child has undergone to anticipate complications. Table 185-2 is a summary of the more common procedures and their complications.

Neurologic Conditions: Cerebral Palsy and Seizures

Cerebral Palsy

Cerebral palsy (CP) is the leading cause of childhood disability.[12] CP is a group of disorders affecting the development of movement that is attributed to nonprogressive disturbances that occur in the developing fetal or infant brain. The motor disorders are often accompanied by one or more of the following: disturbances of sensation, cognition, communication, perception, or behavior or a seizure disorder.[13] Premature birth is the most common associated historical factor, and prenatal maternal infection and multiple pregnancies have also been associated with CP.[14]

CP is classified based on the type of movement disorder and the area of the body involved: spastic, athetoid, ataxic, mixed and hemiplegia, diplegia, or quadriplegia. The most common form, spasticity, is defined as a velocity-dependent resistance to stretch. When the extremities of a child with the spastic form of CP are stretched beyond their range of motion, the muscles contract and increase resistance. Clonus, an extensor plantar response and persistent primitive reflexes, is characteristic. Since CP is a movement disorder, gross motor skills are delayed. There is a lack of coordination and differential strength and tone in the musculature of the child. Treatment is focused on managing spasticity. Some of the treatments include daily range-of-motion exercises, casting, and splinting. Some children may take oral medications (baclofen, diazepam, and clonidine) to improve muscle spasticity or to decrease the drooling that is evident in 10% of children with CP, caused by poor oromotor control combined with decreased sensation and poor head control.[9]

Intrathecal Baclofen Pump. Some children with CP are now treated with baclofen pumps inserted directly into the thecal sac surrounding the spinal cord. Baclofen is directly infused into this space by a small pump via continuous infusion. Baclofen acts by binding to receptors in the spinal cord, thereby inhibiting spinal reflexes. Complications include overdose when the pump is filled incorrectly or programming is inaccurate. Overdose can lead to respiratory depression and death. Some less serious side effects of the medication include drowsiness, dizziness, hypotension, headache, and nausea. If presented with a comatose child with CP on a baclofen pump, the physician must maintain the child's airway, breathing, and circulation until the pump is urgently stopped with a specialized device. If this device is not readily available, then emptying the reservoir with a 22-gauge needle is an alternative treatment. This can be done by locating the pump in the abdominal wall and inserting the needle in the center of it. Another complication is medication withdrawal due to pump failure, which is usually the result of tube obstruction or faulty

Table 185-2 Congenital Cardiac Repairs and Their Complications

PROCEDURE	CARDIAC LESION PALLIATED OR REPAIRED	DESCRIPTION	MOST COMMON COMPLICATIONS
Modified BT shunt	HLHS	Palliative procedure to augment pulmonary blood flow; used prior to complete repair of lesions with single ventricle physiology.	Thrombosis of the shunt. Diagnosis is made by echocardiography or CT angiography. Another rare complication is a seroma adjacent to the shunt causing airway compromise or cardiac tamponade.
BDG shunt	HLHS	Palliative procedure to shunt systemic venous blood to pulmonary artery; originally created to palliate tricuspid atresia and other underdeveloped right heart lesions.	Pulmonary arterial venous fistulas, which cause ineffective gas exchange.
Modified Fontan and Hemi-Fontan	Tricuspid atresia HLHS Hypoplastic right ventricle with pulmonary atresia Double inlet ventricle	Creates a circulation where the systemic venous blood enters the pulmonary circulation directly, bypassing the right ventricle.	Pulmonary arteriovenous malformations, protein-losing enteropathy, elevated systemic or right atrial pressures, thrombosis in the right side of the heart and the Fontan conduit, pulmonary effusions, arrhythmias, progressive exercise intolerance, anastomotic stenosis, and hepatomegaly.
Norwood procedure	HLHS	The purpose is to create a systemic circuit in children with one ventricle physiology; this is done in three stages because pulmonary vascular resistance is high in newborns.	This procedure is done in three stages to avoid complications and to allow child to grow.
Norwood, stage 1	HLHS	This is done during the first days after birth. This establishes a connection between the right ventricle and the systemic arterial system, creates sufficient pulmonary venous return, and establishes pulmonary blood flow with a systemic to pulmonary shunt such as a modified BT shunt.	Thrombosis of the shunt.
Norwood, stage 2	HLHS	This procedure is usually done when the pulmonary vascular resistance has decreased to normal at about 3–6 months of age. A cavopulmonary shunt is created; either a BDG or hemi-Fontan is performed to accomplish this. The BT shunt is removed during this stage.	Pulmonary arterial venous fistulas.
Norwood, stage 3	HLHS	This is the modified Fontan procedure. This stage completes the separation of the pulmonary and systemic circulations.	Pulmonary effusions, pericardial effusions, ascites, hepatomegaly or SVC syndrome, protein-losing enteropathy, and cardiac failure.
	TGA	The aorta and the coronary arteries arise from the RV instead of the LV, and the PA emanates from the LV, which creates a parallel circulation. The definitive procedure, the Jatene arterial switch, is performed within the first weeks of life. This procedure involves transaction of the 2 arteries, switching them to their respective ventricles, and also moves the coronary arteries as well.	Dilatation of the neoaortic root (AV regurgitation is rarely seen); risk of coronary artery occlusion or stenosis. If the definitive surgery correction cannot be done in the first days of life, then a first procedure may be done at 1–3 days of life if there is no connection between the 2 circulations (e.g., VSD)—the Rashkind procedure where a balloon catheter creates a hole in the atrial septum.
Rastelli	TGA with VSD and LVOT obstruction Pulmonary atresia with VSD Double outlet right ventricle with PS or PA	Alternative procedure for patients who cannot undergo arterial switch. This procedure bypasses the LVOT. First the LVOT is closed off, a tunnel is created between the LV and into the aorta, the VSD is enlarged, and the RV to the PA flow is augmented by a pulmonary allograft.	LVOT and right-sided conduit obstruction; highlate mortality.

Table 185-2 Congenital Cardiac Repairs and Their Complications—cont'd

PROCEDURE	CARDIAC LESION PALLIATED OR REPAIRED	DESCRIPTION	MOST COMMON COMPLICATIONS
ASD repairs		If small, sutured closed (primary repair). If larger, a pericardial or prosthetic patch used for closure. Small secundum ASDs can be closed during cardiac catheter procedure with a clamshell device. Other types of ASDs (sinus venosus or coronary sinus) must be performed with an open surgical repair.	Incomplete closure with clamshell occurs more often than open procedures; pericardial effusions; postpericardiotomy syndrome; thrombus formation on device; arrhythmias.
VSD repair		Small lesions in the muscular septum may close spontaneously; large VSDs are repaired at 3–6 months; surgical repair is an open procedure and involves placement of a patch.	Injury to conduction tissue—heart block; residual defects, tricuspid valve insufficiency.
Tetrology of Fallot repair	Repair of VSD and RVOT obstruction	Definitive repair occurs at age 3–6 months; type and extent of repair are dependent on extent of RVOT.	Pulmonary insufficiency; residual pulmonary stenosis; hypertrophied RV leading to RV dysfunction and cardiac failure.
AVC repair	Complete, partial, and transitional defects	Surgical repair occurs at 4–6 months; type and extent of repair are dependent on extent of lesion. Ranges from suturing defects to patches.	AV node and the bundle of His are at risk of injury during repair and therefore heart blocks are seen; mitral regurgitation.

ASD atrial septal defect; AV, atrioventricular; AVC, atrioventricular canal; BDG, bidirectional Glenn (shunt); BT, Blalock-Taussig (shunt); CT, computed tomography; HLHS, hypoplastic left heart syndrome; LVOT, left ventricular outflow tract; PA, pulmonary atresia; PS, pulmonary stenosis; RVOT, right ventricular outflow tract; SVC, superior vena cava; TGA, transposition of the great arteries; VSD, ventricular septal defect.
From Gaca AM, Jaggers JJ, Dudely LT, Bisset GS: Repair of congenital heart disease: A primer—Part 1. Radiology 247; 3:617, 2008.

pump programming. Symptoms of withdrawal include increased spasticity, tachycardia, blood pressure changes, severe hyperthermia, and rhabdomyolysis, possibly progressing to multisystem failure and death.[15]

Intellectual Disability. Intellectual disability, also known as mental retardation, is commonly found in CP. Approximately 30 to 50% of children with CP have significant intellectual disabilities. Most have milder cognitive deficits and learning disabilities. Some children with CP have normal intelligence, so asking parents about their child's developmental level is important. Often the term *developmental delay* is used interchangeably with mental retardation. Mental retardation has a specific definition, however. Mental retardation is a fixed disability characterized by significant limitations both in intellectual functioning and in adaptive behavior as expressed in conceptual, social, and practical adaptive skills.[16] Developmental delay is a failure to achieve age-appropriate milestones; these children have the potential to "catch up" and to eventually progress normally with their growth and development.[6]

Seizures

Seizure disorders affect approximately 10% of children who are disabled, compared with only 0.5% of healthy children. Seizures are divided into multiple categories. Children with seizure activity often have normal intelligence, and their seizures can be well controlled by anticonvulsant medication.[17] "Breakthrough" seizures generally occur as a result of toxic or subtherapeutic blood levels of seizure medication for a variety of reasons. These include but are not limited to poor absorption of their medication secondary to a gastrointestinal illness, missing one or more doses of anticonvulsant medication, medication dosages not being appropriately adjusted for the child's growth, or a lowered seizure threshold such as from an illness or accidental multidosing of a patient's medication. For patients with multiple abnormalities, seizure activity is generally more severe and is more difficult to control with anticonvulsant medications.

Children with CP or other brain abnormalities are more likely to experience status epilepticus. Status epilepticus is a condition of generalized convulsions in adults and older children (>5 years old) for 5 minutes continuously or two or more discrete seizures without full recovery of consciousness.[18] Early intervention is important. Treatment initially includes benzodiazepines, which are often effective; if two doses of a benzodiazepine are not effective, subsequent doses are not likely to work, and phenytoin (Dilantin) or fosphenytoin (Cerebyx) is considered the next line of medication.[19] (See Chapter 173 for a complete discussion of the management of childhood seizures.)

Vagal Nerve Stimulators

Vagal nerve stimulators (VNS) are implantable devices used to prevent seizures. Intractable epilepsy affects approximately 20 to 30% of patients with seizures. Newer antiepileptic drugs and surgical procedures decrease seizure frequency in a significant number of patients. Even among this group, up to 10% continue to have disabling seizures. For these patients, VNS provides hope for better seizure control.

The VNS is an implantable device that looks like a pacemaker. It is implanted by a neurosurgeon just under the skin in the chest. In the small number of children who have had VNS placed, most have seen a reduction in seizure frequency of 50%.[20] How the VNS works on the brain is not known. The vagus nerve is a peripheral nerve that leads directly to the brain and it is there that the VNS has an effect.

The VNS is programmed to provide baseline intermittent stimulation of the left vagus nerve. Although the VNS system delivers stimulation automatically in regular pulses all the time, a magnet can be used to deliver extra electronic stimulation in between cycles. The patient or caregiver activates the device by placing a handheld magnet over the device implanted in the chest.[21] Patients who can sense that they are about to experience a seizure can activate the VNS themselves by passing the magnet over the device. Out-of-hospital providers who encounter a seizing patient with a VNS should assist the caregiver with its activation or seek advice from medical control. Children with VNS devices should otherwise be treated as other seizing patient, with careful attention to airway, breathing, and circulation. A magnet can also be used to stop the stimulation by holding the magnet over the device. Sometimes the patient may want to shut the stimulation off. Some of these include when eating if the stimulation causes problems with swallowing, when the patient plans to speak or sing in public as the stimulation can change one's voice, and if the stimulation causes discomfort.[22,23]

Myelomeningocele and Hydrocephalus

Myelomeningocele (or spina bifida) refers to a gap in the vertebral arches. The most common types of spina bifida are spina bifida occulta, the milder form, and spina bifida associated with malformation of the spine and attachment of the sac—a condition known as myelomeningocele. The rate of spina bifida in the United States has decreased markedly since the introduction of folic acid to the diets of women of childbearing age.

Clinical presentation depends on the level of the defect. The condition results in partial or complete paralysis and loss of sensory function (not always symmetrical) with motor loss. In addition, the child may present with loss of bladder or bowel control, cognitive impairments, visual deficits, and seizure disorders. Bladder and bowel dysfunction is very common among children with spina bifida. In such cases, there is incomplete emptying of the bladder, predisposing the child to urinary tract infections. Management of such cases requires emptying of the bladder by urinary catheterization several times a day. Hydrocephalus associated with Chiari malformation (displacement of the brainstem and part of cerebellum downward through the skull) occurs in greater than 68% of children with spina bifida.[24] One should always assume that children with spina bifida are allergic to latex.[25]

Ventriculoperitoneal Shunts

Ventriculoperitoneal (VP) shunts are catheters that are inserted into the ventricles within the brain and then threaded under the skin from the skull to the peritoneum where excess cerebral spinal fluid (CSF) is drained (Fig. 185-6). Hydrocephalus occurs when an obstruction occurs somewhere in the CSF circulation system. If the obstruction occurs beyond the lateral ventricles, then they enlarge with CSF, increasing intracranial pressure. Hydrocephalus can be seen in formerly premature infants who sustained an intracranial hemorrhage during the neonatal period, in children with brain tumors, and posttraumatically. Also, children with spina bifida (myelomeningocele) often have hydrocephalus if they have an Arnold-Chiari malformation that obstructs CSF flow.

Within the first 3 postoperative months, although rare, a child with a VP shunt can develop an infection of the shunt track. Symptoms include fever, ill appearance, erythema over the shunt site or tubing, tenderness over the tubing, abdominal pain and tenderness, vomiting, and altered mental status. If a VP shunt infection is suggested, CSF should be drawn from the shunt by a neurosurgeon and sent for cell count and culture. Broad-spectrum antibiotics should be administered pending cell count and culture results; however, likely organisms include *Staphylococcus epidermidis*, *Staphylococcus aureus*, and, rarely, *Haemophilus influenzae*. Neurosurgeons should manage all shunt infections.

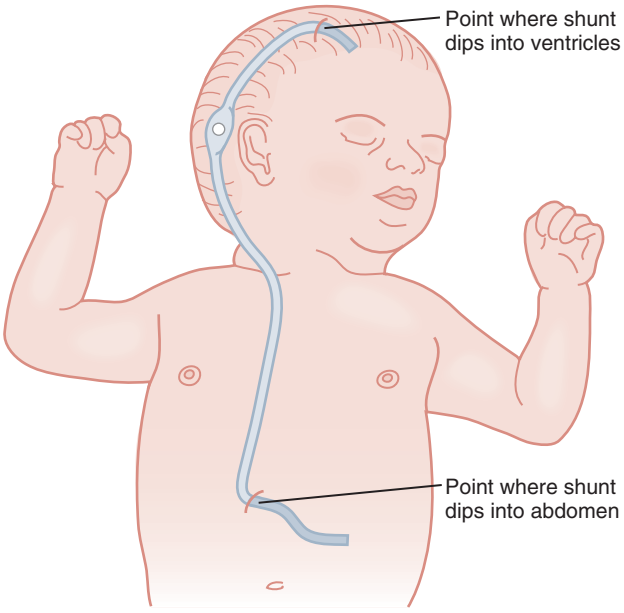


Figure 185-6. Ventriculoperitoneal shunt. (Adapted from Susan Gilbert in Teaching Resource for Instructors in Prehospital Pediatrics [TRIPP]; www.cpem.org.)

Peritonitis is another complication of VP shunts. The tip of the shunt empties into the peritoneal cavity and as a foreign body can serve as a nidus for infection. Signs and symptoms include fever, vomiting, abdominal pain and tenderness, and abdominal distention. Management is similar to that for VP shunt infections and should include diagnostic lab work, broad-spectrum antibiotics, and consultation with the neurosurgeon.

The more common complication of a VP shunt is shunt obstruction or malfunction. This can occur with an increase in protein in the CSF that causes a blockage in the tubing or as a result of a mechanical disruption in the shunt tubing. This can cause a buildup of CSF in the ventricles and an increase in intracranial pressure. Signs and symptoms include headache, nausea, vomiting, irritability, altered mental status, ataxia, change in vital signs, and a bulging fontanel in an infant. Initial management should include elevating the child's head and managing the patient's airway, breathing, and circulation. Stable patients should have head computed tomography performed, and a neurosurgeon should be consulted as soon as possible. The definitive treatment is surgical shunt revision.[6]

Gastrostomy Tubes

Gastrostomy tubes are placed in children who need long-term nutritional supplementation or cannot take food by mouth. There are many conditions that necessitate placement of an artificial feeding tube including severe developmental delay, coma, short bowel syndrome, swallowing difficulties, burns to mouth and esophagus, failure to thrive, and chronic diseases that affect nutrition such as cystic fibrosis.

Gastrostomy tubes are surgically or endoscopically placed feeding catheters. These tubes include gastrostomy tubes

(G tubes), jejunostomy tubes (J tubes), and percutaneous endoscopic gastrostomy tubes (PEGs or buttons). J tubes are placed in children with GERD. The tube is placed in the stomach and then passed through the junction between the stomach and jejunum, bypassing the stomach. PEGs are placed by gastroenterologists either at the bedside or in the outpatient procedure area.

There are three potential gastrostomy tube emergencies. (1) The tube can leak gastric contents, (2) become obstructed, or (3) come completely out. When presented with a child who has any of these problems, assessment of hydration status is important, especially in those children who are totally dependent on their feeding tubes for hydration and nutrition. One should inquire about prescribed medications and whether any doses were missed.

In children experiencing leaking around the catheter, management focuses on delineating and fixing the cause of the leak. Possible causes of leakage include balloon deflation, coughing, constipation, bowel obstruction, and seizure. Addressing the cause may solve the problem; otherwise, consultation with the subspecialty service that manages the child's tube may be necessary (Table 185-3).

Sometimes the child's G tube becomes clogged with medication or food. Obstructed tubes can be cleared with either Coca-Cola or a proteolytic enzyme solution; otherwise, they need to be replaced.

G tubes that have fallen completely out of the patient need to be replaced as soon as possible, so the stoma does not constrict and make replacement difficult. Gastrostomy-jejunostomy tube placement is more problematic because after placing a tube in the stomach, passing the tube to the jejunum is usually done under fluoroscopy by a radiologist familiar with this procedure. For G tube replacement, the physician should ask when the tube was first inserted. For tubes that are less than 3 months old, consultation with the person or service that performed the procedure is necessary because the track may not yet be fully formed and insertion by a practitioner not adept at replacing these tubes may create a false track.

When performing the reinsertion procedure, a similar size gastrostomy tube should be used. Parents often have an extra tube with them. If cases when the ED does not have access to G tubes (the Mic-Key type of tube is easiest to use), using a Foley catheter to temporarily keep the stoma open is acceptable until definitive placement can occur. Once the G tube is replaced, tube placement can be confirmed by instilling a small amount of diatrizoate meglumine (Gastrografin) dye into the tube (15–30 mL) and obtaining two radiographic views to observe the tube and dye in the stomach. Confirma-

Table 185-3 Troubleshooting Gastrostomy Tubes/Buttons

PROBLEM	POSSIBLE CAUSATION	ACTIONS
Nausea, vomiting, cramping, and/or diarrhea	Too rapid feeding Feeding too cold Spoiled formula or a change in formula	Increase feeding time. Ensure feeding is at room temperature.
Leakage of stomach contents	*Mechanical* Broken or sticking valve Malpositioned tube wedged into the gastric mucosa Balloon not inflated properly *Organic* Increased volume of feeding (too much gas or formula) Constipation Ileus Pneumonia (from coughing), seizures	Place insertion obturator, decompression tube, or 8- to 10-Fr suction catheter into shaft of button so it moves the flex valve. Anti-reflux valve makes popping sound when it moves back into closed position. Ensure balloon is fully inflated. Check stomach residual, readjust method of feedings as appropriate. Evaluate for other organic causes and treat accordingly.
Blockage of button	Feeding or medications too thick or remain in shaft too long	Flush button with 5–10 mL of tap water after using. Use thin solutions with well-crushed meds. Use insertion obturator or 8- to 10-Fr suction catheter to gently try to push the plug through.
Accidental removal of button	Vigorous pulling on the button Spontaneous deflation of the gastrostomy balloon	Insert gastrostomy tube to keep stoma open. As a last resort, a Foley catheter with an anti-migration device may be inserted into the stoma. Tube must be securely taped in place. Immediately transport to tertiary hospital for button replacement. Button length may be too long.
Stoma site irritation Maceration due to moisture Gastric acid burn from leakage of gastric contents Purulent mucus	Regular cleaning not effective Incomplete drying Feeding spillage with incomplete cleaning Leakage of gastric contents from or around tube Excessive granulation tissue	Button length may be too short. Do not use occlusive dressing, gauze, tape, or creams. Rotate button 360° once a day. Clean site daily with soap and water. Clean site with 1/3 strength hydrogen peroxide if irritated. Consider using a skin barrier cream and H_2 blocker for gastric burns.
Balloon leaks or ruptures	Silicone balloons generally last about 3 months; however, life of balloon may vary	Replace gastrostomy button.

From Adirim T, Smith E: Special Children's Outreach and Prehospital Education. London, Jones and Bartlett, 2005.

Table 185-4 Potential Central Line Emergencies and Physician Management/Considerations

External catheter dislodgement	Direct pressure to skin site Clamp line near the exit site Place a peripheral IV to continue necessary fluids and medications Do chest radiograph to locate distal end of catheter Consider a dye study to determine location of catheter tip Obtain surgical consultation
Complete catheter dislodgement	Direct pressure to skin site Place a peripheral IV to continue necessary fluids and medications Obtain surgical consultation to determine disposition
Damaged catheter	Clamp catheter proximal to the break with a hemostat wrapped in gauze Estimate blood loss Observe for symptoms of air embolus If PICC line in place, remove it For other partially implanted lines, repair catheter if >2 in. of the line exit from the skin
Bleeding at catheter entry site	Direct pressure to entry site Estimate blood loss Place a peripheral IV to continue necessary fluids and medications Do chest radiograph to locate distal end of catheter Consider a dye study to determine location of catheter tip Obtain surgical consultation
Internal bleeding	Direct pressure to site Observe for symptoms of hemopneumothorax Place a peripheral IV to continue necessary fluids and medications Do chest radiograph to locate distal end of catheter Consider a dye study to determine location of catheter tip Obtain surgical consultation
Catheter occlusion	For problems withdrawing blood, try placing the child in various positions (arms high, laying supine, etc.) Attempt to gently aspirate the clot using a 10-mL syringe half filed with NS placed directly onto the male Leur lock of the catheter Consider using a fibrinolytic agent
Dislodgement of blood clot	Never force fluids through the catheter! Pulmonary embolism may result Observe for tachycardia, tachypnea, hypoxemia, and chest pain Immediately stop infusion of fluids Clamp catheter
Air embolus	Observe for *sudden* changes: tachypnea, chest pain, shortness of breath, or loss of consciousness Clamp system, place child on left side in a head down position, give oxygen
Fever	Consider patient bacteremic or septicemic until proven otherwise Sepsis can quickly develop in immunosuppressed children Evaluate for source of infection Begin broad-spectrum antibiotics Admit to the hospital for antibiotic therapy
Reactions from home nutrient or medication infusions	Immediately stop infusion of medications and begin infusion of NS Treat signs of allergic reaction with Benadryl, steroids, and subcutaneous injections of 1:1000 epinephrine if symptoms are severe

IV, intravenous; NS; normal saline; PICC, peripherally inserted central venous catheter.
From Adirim T, Smith E: Special Children's Outreach and Prehospital Education. London, Jones and Bartlett, 2005.

tion of replacement of the G tube is indicated when the track is relatively new (placed within 1 month of ED visit), when the tube is difficult to replace, or when there is any doubt that the tube is in the stomach. Patients should not be discharged home without a definitive G tube placement. Discussion with the subspecialty service that manages the tube is important for further advice. If there is a delay in G tube replacement, then assessment of hydration is important. For the child who cannot take fluids orally, intravenous hydration may need to be considered.[6]

Central Venous Catheters

Central venous catheters, or central lines, are used to deliver medications, blood products, and nutrition directly into a central vein. There are a number of circumstances when a child would need a central venous line, including children with cancer who need chemotherapy, children with sickle cell disease who need frequent transfusions, children with infections who need long-term antibiotic therapy, and various conditions in which nutritional supplementation is needed, such as in short bowel syndrome.

There are three types of catheters. Peripherally inserted central venous catheters (PICC) are long catheters inserted into the cephalic vein via the antecubital fossa. The catheter is advanced into the subclavian vein. These tubes are placed in children who need temporary venous access, such as for antibiotic therapy. These tubes can be placed by nonsurgeons. Potential complications include infection, obstruction, and easy dislodgement because they are not sutured in place (Table 185-4).

Tunneled central venous catheters are placed surgically. They are inserted directly into a central vein, most commonly the subclavian, cephalic, or external jugular. There are three

common types: Broviac, Hickman, and Groshong. The first two are most commonly used in children. The distal ends rest outside the chest and can have one to three ports. Implanted vascular access ports (Port-A-Cath, PAS Port, and Med-A-Ports) are also common in children. The insertion sites and method are the same as for the tunneled central venous catheters. The distal end of the catheter consists of a reservoir that is covered with a self-healing rubber septum. This reservoir rests subcutaneously, and a special needle is needed to access this line. The advantages of the implanted vascular ports are that they only need to be flushed with heparin once a month and after each access, as opposed to daily heparin flushes, and they are hidden and so may be more acceptable to older children for whom body image is more of an issue.

Circumstances where a child with a central line presents for emergency treatment include damage to the catheter, air embolus, catheter dislodgement, and fever. Catheters that are damaged should be clamped proximal to the break with a hemostat. With catheters that are dislodged, the practitioner should apply direct pressure at the entry site to stop or prevent bleeding. This is a potential life-threatening emergency. The child should be brought to a facility that can repair or replace the catheter. Air emboli in the tubing can cause sudden onset of respiratory distress, chest pain, and altered mental status. If an embolus is suggested in a child with a central line, the child should be placed on his or her left side and given oxygen. Peripheral IV placement should be considered.

Fever is a common problem in children with central lines. The line is a foreign body that can act as a direct conduit for microorganisms, a situation that is especially problematic for immunocompromised children who can easily develop sepsis. Treatment of these children should include obtaining blood samples for complete blood count and cultures and administering broad-spectrum antibiotics until culture results are known. Neutropenic patients (absolute neutrophil count <500) should be admitted to the hospital for IV antibiotics pending blood culture results.[6] If the febrile child with a central line is not immune suppressed and appears well, discharging the child home with appropriate follow-up is appropriate. In borderline cases, consultation with the child's physician can aid in making disposition decisions.

KEY CONCEPTS

- CSHCN are frequent users of the health care system. Parents and caregivers often know their children's issues very well. They may have information cards or notebooks describing their child's conditions and equipment and listing medications, or the child may be wearing medical jewelry. Listen to the caregivers when treating CSHCN.
- CSHCN may be physically smaller than children of the same chronologic age, may have vital signs outside the range of normal for age, and may also be developmentally delayed. Ask caregivers what is normal for their child.
- Most children with special health care needs suffer the same typical diseases as their normal counterparts. Treatment of CHSCHN should begin with assessment of the child followed by assessment of medical equipment. When in doubt regarding the best course of action, maintain the child's ABCs while seeking consultation from the child's pediatrician or surgeon.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 186 Pain Management

James R. Miner, Paul M. Paris, and Donald M. Yealy

PERSPECTIVE

The assessment and treatment of pain are parts of the chief complaint in up to 70% of patients in the emergency department (ED).[1-5] Pain can be present in a wide variety of physical and psychosocial situations but is almost always present in the setting of tissue injury. Pain can therefore be assumed to be present in patients with physically apparent disease or injury, even in those who cannot effectively communicate their condition.

A wide variety of options are available for the treatment of pain. Despite being easy to identify and having effective treatments available, the treatment of pain is often extremely difficult to do effectively in the ED and is often one of the most challenging and frustrating aspects of the practice of emergency medicine.[6-10]

Patients' perceptions of their ED care are highly influenced by pain treatment, and satisfaction with emergency care often depends on the techniques and timeliness of analgesia as well as the discharge plans for pain relief.[11,12] In every interaction with a patient in pain, a balance must be struck between relieving the patient's suffering in the ED and during the subsequent recovery and in appropriately diagnosing and treating the underlying medical condition.

Other than the obvious fact that relieving pain is associated with less suffering for a patient, a growing body of evidence supports the importance of effective pain management as a central aspect of the treatment of disease. Acutely, unrelieved pain is associated with a variety of potential negative physiologic outcomes, including increases in sympathetic outflow, peripheral vascular resistance, myocardial oxygen consumption, and the production of carbon dioxide; hypercoagulability; and decreases in gastric motility and immune function. Poorly treated acute pain can aid in the development of chronic pain syndromes and vegetative symptoms, as well as increasing the need for pain treatment during the recovery period.[13-20] Pain during subsequent procedures may actually increase if successful analgesia was not provided during previous procedures.[21] It is likely that a patient's experience of pain increases the ability to perceive pain from similar stimuli in the future, leading to increased pain in patients who receive inadequate analgesia during future painful events.[22]

The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) requires hospitals to develop comprehensive programs for the measurement, treatment, documentation, and institution of quality improvement efforts related to acute pain management. These requirements were established at the same time that the treatment of pain in the ED was undergoing increased scrutiny through clinical research. The improvement in pain management in the last decade may be due to both factors.[23-28]

There are many ways to treat pain, and very few single approaches are clearly superior to all other options. Uncontrolled pain should be considered a medical emergency with the estimated degree of pain playing a role in the determination of a patient's overall acuity for triage. Pain estimations, using both provider- and patient-derived scales, should be obtained and recorded for patients as frequently as any vital sign. Important terms relating to analgesic practices are listed in Box 186-1.

PATHOPHYSIOLOGY

Pain can be generally described as nociceptive or neuropathic. Nociceptive pain results from the activation of sensory neurons that signal pain (nociceptors) in response to noxious stimuli. Neuropathic pain results from signal processing changes in the central nervous system (CNS). It is usually described as burning, tingling, or shooting pain and includes neuropathies and deafferentiation. Both types of pain involve both peripheral and central sensitization involving a complex array of mediators to sensitize peripheral nociceptors and perpetuate thalamic signals. An overview of the physiologic process of pain is in Figure 186-1. At each level in the physiologic process of pain production or transmission, interventions are available to alter the process.

Pain Conduction Pathways

The perception of pain can be divided into four separate processes, the pain detection system (transduction), the pain transmission system, the pain modulation system, and the pain expression system (perception) (see Fig. 186-1). The transduction of painful sensory input is initiated by activation of the nociceptors, with subsequent depolarization of their axons. The axons relay information (afferent input) to their cell bodies located in the dorsal root ganglion just lateral to the spinal cord.[29] Central dendrites of these first-order neurons synapse in the dorsal horn, where sensory input is modulated. The signal then travels through the spinothalamic tracts and posterior columns to synapse in the reticular system and the thalamus. From there the signal is projected to the cerebral cortex.

BOX 186-1 DEFINITIONS OF TERMS RELATED TO ANALGESIA

Amnestic—an agent the suppresses the formation of memories
Local anesthesia—creating an area of insensibility to pain by the injection of a local anesthetic agent
Analgesia—relief from pain
Hypnotic—an agent that promotes the onset of sleep
Narcotic—a term with legal implications describing opioid agents together with various central nervous system depressant drugs of abuse
Nociceptor—a receptor that is sensitive and responsible for transmitting pain stimuli
Noxious stimulus—a stimulus that is damaging or potentially damaging and results in sensation of pain
Opiate—a naturally occurring derivative of opium alkaloid that binds opiate receptors and produces effects similar to those of the endogenous endorphins
Opioid—a naturally occurring (includes all opiates) or semi-synthetic derivative of opium alkaloid that binds opiate receptors and produces effects similar to those of the endogenous endorphins
Pain—an unpleasant sensory and emotional experience arising from actual or potential tissue damage or described in terms of such damage
Procedural sedation—pharmacologically producing a state of sedation or dissociation with amnesia for pain control during a painful procedure (see Chapter 187)
Sedative—an agent that decreases a patient's awareness

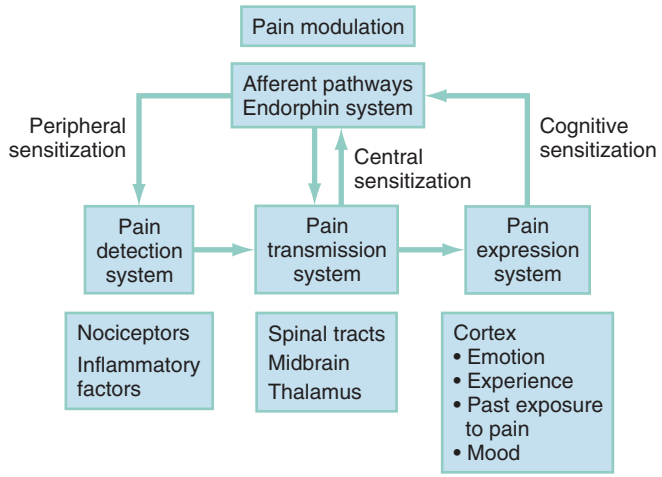


Figure 186-1. The pain system algorithm.

Pain Detection

The somatosensory system is responsible for the detection of pain as well as tactile, proprioceptive, and thermal sensations. Pain transduction occurs when noxious stimuli are translated into electrical activity by sensory nerves. Receptors responsible for detecting pain are called nociceptors. Nociceptors include sensory nerves that are capable of detecting mechanical, thermal, or chemical stimulation. Several different subtypes of nociceptors are present in cutaneous tissues, including mechanoreceptors, polymodal nociceptors (PMNs), and a variety of thermoreceptors.[29] Most nociceptive input is from PMNs, which respond to intense chemical, thermal, and mechanical stimuli.

The principal difference between a nociceptor and a non-nociceptive sensory neuron is that stimulation of a nociceptor causes pain. In general, nociceptors have a higher threshold of activation than a typical sensory neuron. The threshold of activation of a nociceptor can be increased or decreased by a variety of chemical mediators (prostaglandin, cyclic adenosine monophosphate, leukotrienes, bradykinins, serotonin, substance P, thromboxanes, platelet-activating factor, and endorphins) and by thalamic sensory efferent nerves. This is called peripheral sensitization. Trigger points are areas of frequent or constant low-level sensory stimulation (e.g., scar tissue or a degenerative joint) that have developed sensitized nociceptors that perceive pain from otherwise innocuous stimuli.

Information Transmission

Peripheral Nerve Fibers

All sensory neurons are composed of a cell body, which is located in the dorsal root ganglia, and a receptor located within a given dermatome (cutaneous input), sclerotome (input from bones), or myotome (input from muscle), connected by an axon. The discrete areas covered by each nerve provide a sensory map of the body surface. Table 186-1 is a classification system of peripheral nerve fibers that describes the roles of the different fibers. A-δ and C type fibers are responsible for the transmission of pain. A-δ fibers transmit sharp initial pain that persists as long as the inducing stimuli, and C fibers transmit dull, aching, or burning pain that persists longer than the initial stimuli. The relative concentration of nerve fiber types varies in different tissues. Muscle C fibers, for example, produce aching, poorly localized pain in response to violent contraction or stretch, ischemia, or inflammation. In joints, afferents respond to noxious movement of the joint, the threshold of which is sensitized by chemicals present during inflammation (accounting for the pain with normal movement associated with arthritis or after an injury). The periosteum has the lowest pain threshold of all the deep tissues and is supplied by both A-δ and C fibers, whereas cortex and marrow have very few nociceptors.

Pain Transmission

Dorsal Horn

The dorsal horn is the gray matter in the posterior aspect of the spinal cord (Fig. 186-2). The dorsal horn acts as an integration system where sensory input is filtered, attenuated, or amplified before being relayed to other spinal segments or the cortex.

The dorsal horn is structured in layers called laminae. Each lamina receives specific types of nerve fibers, and the various laminae are connected by multiple interneurons. The dorsal horn is a processing center for incoming information and is extensively involved in the modulation of nociceptive input. Visceral, muscle, bone, and cutaneous afferents converge here, which probably accounts for the cutaneous allodynia associated with painful visceral, muscular, or bony stimuli. Differentiation between innocuous stimuli and nociceptor input occurs due to a higher frequency of discharge from painful stimuli in cells called wide dynamic range neurons (WDRNs) as they receive the input. WDRNs receive modulating input from a variety of chemical (opioids, substance P, or inflammatory factors) and efferent and afferent pathways.

Lamina II has projections to laminae I that influence the WDRNs there, making these laminae the likely primary modulating source on afferent painful impulses.

Laminae V receives A-δ and C fiber input and projects to both the spinothalamic and spinomesencephalic tracts, which account for many of the reflex responses to pain.

Table 186-1 Peripheral Nerve Fibers

FIBER	FUNCTION	MYELIN	MEAN DIAMETER (μM)	ASCENDING TRACT	CONDUCTION VELOCITY (M/S)
A-α	Skeletal muscle motor	Deep	12–20	Ipsilateral dorsal column	70–120
A-β	Light touch and pressure	Superficial	5–15	Contralateral spinothalamic tract	30–70
A-γ	Motor	Superficial	6–8	Ipsilateral dorsal column	15–30
A-δ	Sharp pain (mechanoreceptors, thermoreceptors, PMNs)	Superficial	1–4	Contralateral spinothalamic tract	12–30
B	Sympathetic		1–3	Preganglionic	3–15
C	Long-lasting burning pain	Superficial	0.5–1.5	Contralateral spinothalamic tract	0.5–2

Adapted from Paris PM, Uram M, Ginsburg MJ: Physiological mechanisms of pain. In Paris PM, Stewart RD (eds): Pain Management in Emergency Medicine. Norwalk, Conn, Appleton & Lange, 1988.

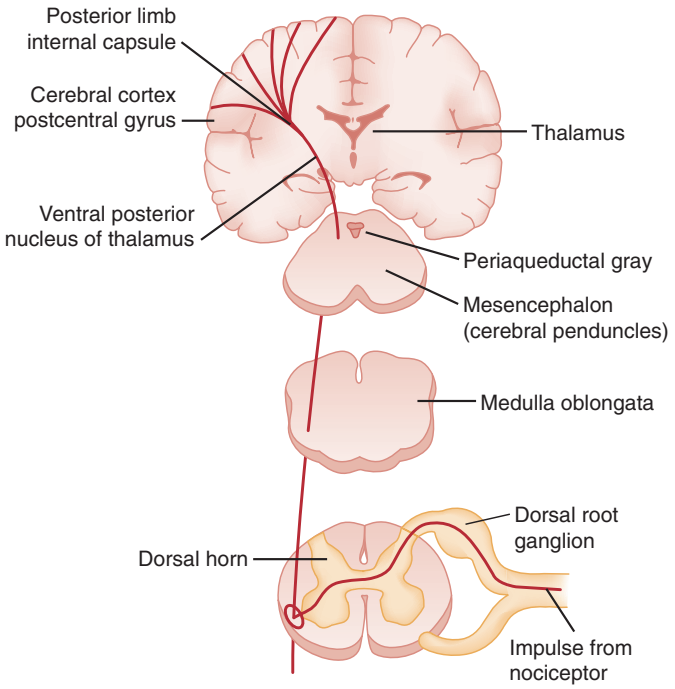


Figure 186-2. Diagram tracing the path of the major tract that carries pain stimuli to the brain, the lateral spinothalamic tract.

Visceral Pain

The quantity and type of stimuli that produces pain varies among visceral structures. The myocardium, for example, is sensitive to ischemia but not mechanical stimulation. The intestines can by cut, crushed, or burned without pain, but traction or distention produces pain. The quality of visceral pain is different from somatic pain. Somatic pain is initially sharp and later becomes burning or throbbing in nature as the response is modulated. Visceral pain tends to be poorly localized, dull, and aching, with pronounced autonomic activation relative to somatic pain. This is likely due to the fact that the ratio of A to C fibers is 1:10 in visceral nerves and 1:2 in cutaneous nerves.

Visceral pain often produces referred pain. For example, periumbilical pain is often associated with appendicitis. This occurs because the visceral afferents supplying the small bowel travel through the celiac ganglia and splanchnic nerves to enter the spinal cord at T10. This sensitizes the dorsal horn at T10, leading to sensitization of all the dorsal horn nociceptive neurons, which leads to the perception of pain in the T10 dermatome. As the appendicitis progresses, the pain localizes to the right lower quadrant as the inflammation extends to the parietal peritoneum, which has the same nerve supply as the overlying myotome and dermatome.

Ascending Tracts Associated with Pain

Fibers carrying pain impulses exit the dorsal horn and ascend the spinal cord to the brain. The predominant pathways for pain conduction are the spinothalamic tract, the spinomesencephalic tract, and the spinoreticular tract, located in the anterolateral aspect of the spinal cord (Fig. 186-3). The spinothalamic tract is the most important for pain transmission. Lesions in this tract (the anterolateral portion of the spinal cord) cause the loss of pain sensation in the contralateral side below the lesion. The cell bodies of this tract are in laminae I and V of the dorsal horn. Axons cross the midline within two spinal segments of their origin and then ascend the tract. The axons synapse in the ventroposterolateral nucleus of the thalamus and the posteromedial thalamus, where they then project to the cortex.[29] As these tracts ascend, they add fibers to the anteromedial border, producing an organization with sacral segments located dorsolaterally and cervical segments located anteromedially.

The spinoreticular tract ends in synapses in the reticular formations of the medulla, pons, midbrain, and intralaminar thalamic nuclei, which ultimately project to the limbic forebrain. The spinoreticular tract is an important part of the suprasegmental reflex responses to pain and serves as a direct link between the reticular arousal centers and the dorsal horn. Spinomesencephalic tract fibers synapse in the periaqueductal gray matter and other midbrain nuclei, where they likely activate a system of descending pain inhibitory signals that project from the periaqueductal gray matter.

The dorsal columns of the spinal cord mostly transmit innocuous sensory information but may also play a role in pain through modulation of the spinothalamic tract. In addition to providing discriminatory information to localize pain, sensory input may activate cortical descending pathways that modulate the dorsal horn response to nociceptive input. The spinothalamic tract then provides precise localization of the nociceptive data, whereas the spinoreticular and spinomesencephalic tract input serves to arouse the body to ongoing tissue damage, activating the neuroendocrine, emotional, and autonomic reflexes associated with pain.[30]

Thalamus

The thalamus receives input from the spinoreticular and spinomesencephalic tracts in the medial and intralaminar nuclei, which they project to a wide area of the cortex and the limbic

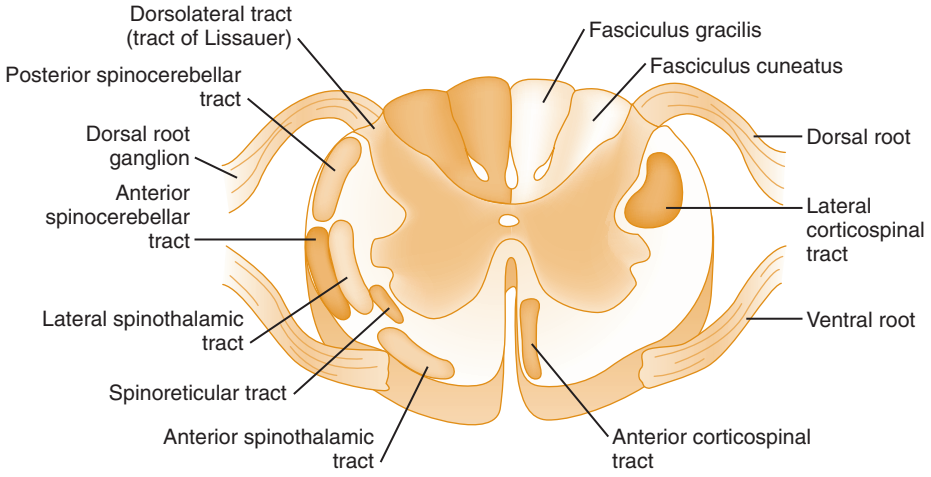


Figure 186-3. Cross section of entire spinal cord with all major tracts labeled. Spinothalamic tract synapses in the thalamus, with third-order neurons ascending the somatosensory cortex.

system. The spinothalamic tract and the periaqueductal gray matter project to the ventroposterolateral and ventroposteromedial nuclei, which also receive input from descending fibers from the somatosensory cortex. It then projects to a wide area of the cortex. Cerebrovascular disease or injury to the thalamus can produce central neuropathic pain syndromes in the absence of its modulating effect on pain.

Pain Modulation

Impulses from nociceptors are modulated by descending tracts both peripherally and in the spinal cord. The two primary descending pathways appear to be primarily serotonergic and noradrenergic, and originate in the midbrain (periaqueductal gray matter and locus ceruleus) and medulla (nucleus raphe magnus and nucleus reticularis gigantocellularis). They are transmitted to the spinal cord via the dorsolateral funiculus. Electrical stimulation of this pathway produces analgesia comparable to that produced with opioids. Stimulation of the thalamus can also produce analgesia.[31] Inputs to this system come from the frontal cortex, the limbic system, the hypothalamus, the reticular system, the locus ceruleus, and the spinal cord. Multiple neurotransmitters are involved in these pathways, including serotonin, norepinephrine, and substance P. It is believed that the activation of this system is responsible for effects such as placebo, acupuncture, and TENS units.

Central Sensitization

Central sensitization involves the amplification of nociceptive signals. It is mediated by multiple substances such as nitric oxide, glutamate, substance P, aspartate, prostaglandins, leukotrienes, norepinephrine, and serotonin. It can occur in the presence of chronic pain or as the result of damage at any point along the pain transmission system. It is described in the setting of traumatic and degenerative conditions of the spinal cord and brainstem and can be associated with thalamic strokes, multiple sclerosis, Parkinson's disease, Arnold-Chiari formation, and cervical stenosis.

Pain Expression

The transduction, transmission, and modulation of pain stimuli develop the perception of the subjective emotional experience of pain. Many factors other than the stimulation of nociceptors influence the final perception of pain. The discrete cognitive processes and pathways involved in the interpretation and experience of painful stimuli remain a mystery and are affected by factors such as cultural expectations, personality, experiences, and the underlying emotional state. Many of these factors, and therefore the subsequent perception of pain, can be greatly influenced by both pharmacologic and nonpharmacologic interventions. For drugs such as nitrous oxide and low-dose opioids, much of their effect is on the cognitive interpretation and emotional reaction to pain rather than on the transmission of the pain stimulus. Noninvasive techniques (e.g., distraction and hypnosis) can limit pain perceptions and increase tolerance. Changes in a way a person experiences pain based on previous experiences and learned behaviors are referred to as cognitive sensitization.

Reflex Responses to Pain

There are two types of reflex responses to nociceptor input: spinal segmental (or suprasegmental) and cortical. Spinal reflexes are generated by the transmission of nociceptive impulses from the dorsal horn to motor and autonomic neurons in the spinal cord, provoking responses such as tachycardia, vasoconstriction, paralytic ileus, and muscle spasm.[32] Suprasegmental reflexes are transmitted through ascending tracts to the brainstem, hypothalamus, and cortex, where withdrawal reflexes and autonomic responses occur in conjunction with conscious responses. The autonomic reflex responses to pain are variable and cannot be used to quantify pain in an individual.[33,34] Reflex responses to nociceptive input are summarized in Box 186-2.

Endorphin System

The endorphin system is a neuroendocrine system that serves to modulate responses to pain and stress. It consists of widely scattered neurons that produce three types of opioids: beta-endorphin, the met- and leuenkephalins, and the dynorphins. These opioids act as neurotransmitters and neuromodulators at three major classes of receptors—mu, delta, and kappa—and produce analgesia and counter the stress response. These receptors are described in Table 186-2.

Under normal circumstances, the endorphin system serves to decrease pain and stress after a person has adequately dealt with the inciting noxious stimuli. It normally is a responsive system that can have an increased or decreased effect in order to produce the appropriate response to a painful event. Like other neuroendocrine systems, it produces feedback inhibition of itself with increasing stimulation. During prolonged periods of pain with high levels of stimulation, the system can become

BOX 186-2 REFLEX RESPONSES TO PAIN

Increased Sympathetic Tone
Vasoconstriction producing increased peripheral resistance
Increased cardiac output from increased stroke volume and heart rate
Increased blood pressure
Increased metabolic rate and oxygen consumption
Decreased gastric tone (delayed gastric emptying; can progress to ileus)
Decreased urinary tract tone (leads to urinary retention)

Endocrine Responses
Decreased insulin production
Increased cortisol
Increased antidiuretic hormone
Increased growth hormone
Increased renin, angiotensin II, aldosterone
Increased glucagons
Increased catecholamines

Respiratory Responses
Hyperventilation

Cortical Responses
Anxiety and fear

Table 186-2 Opioid Receptors

OPIOID RECEPTOR CLASS	EFFECTS	ASSOCIATED ENDOGENOUS ENDORPHIN
Mu 1	Euphoria, supraspinal analgesia, confusion, dizziness, nausea, low addiction potential	Beta-endorphin
Mu 2	Respiratory depression, CV and GI effects, miosis, urinary retention	Beta-endorphin
Delta	Spinal analgesia, CV depression, decreased brain and myocardial oxygen demand	Enkephalin
Kappa	Spinal analgesia, dysphoria, psychomimetic effects, feedback inhibition of endorphin system	Dynorphin, beta-endorphin
Epsilon	Hormone	Beta-endorphin
Gamma	Dysphoria, psychomimetic effects	Beta-endorphin

CV, cardiovascular; GI, gastrointestinal.

less responsive and less effective at modulating the pain response.

Like their endogenous counterparts, the opioid drugs, or opiates, act at these same receptors to produce both analgesia and undesirable side effects.[35] As these drugs are given over a prolonged period, they inhibit the endogenous endorphin system, blunting its response to pain and stress and decreasing the overall effect of the endorphin system. As these drugs are tapered off, the normal effects of the endorphin system resume.

Table 186-3 Acute versus Chronic Pain

	ACUTE PAIN	CHRONIC PAIN
Inciting Factor	Associated pathology present and recovery is expected	Associated pathology either not identifiable or is not expected to improve, recovery either unpredictable or not expected
Relation to Healing	Pain improves as the injury heals and limitation of activity due to pain assisting healing	Neither pain nor injury expected to improve, pain may limit activities that could improve condition
Psychosocial Effects	Limited to acute stress reaction	Negative effects a prominent feature of disease
Treatment	Analgesics, immobilization	Psychosocial aspects must be addressed, analgesics play a smaller role

Acute versus Chronic Pain

Acute pain is usually associated with an identifiable pathologic condition and serves an adaptive function by warning the individual that an illness or injury exists, motivating the person to stop any activity that is causing the pain, look for a cause, seek help, and avoid the stimulus in the future.

Acute pain becomes chronic pain when the pain pattern persists, in changed or unchanged form, after the original physiologic insult has apparently resolved. All chronic pain starts as acute pain, but only a small subset of patients with acute pain go on to develop chronic pain (Table 186-3). The physiologic transition from acute to chronic pain is a complex process with both physiologic and psychosocial components. It is likely that the development of chronic pain is related to the treatment of acute pain.

Acute pain serves an important purpose in that it stimulates a person to protect the injured area and seek help, and the neurochemical factors that contribute to pain generally are a part of the recruitment of tissue repair mechanisms.[36] As an injury heals, these adaptive responses may become maladaptive if the pain persists, leading to a decreased range of motion and decreased function of the area that could lead to increased susceptibility to injury and pain. Pain also causes a stress response, which is also initially adaptive in the face of injury. A prolonged stress response, however, causes an impaired immune system, hypercoagulable states, sleep disturbances, anxiety, and depression.[15,16,37] Chronic pain is very common, and a large number of patients with chronic pain are seen in the ED.[4,38]

It can be difficult to determine at what point an adaptive pain response becomes maladaptive or at what point acute pain becomes chronic. When a clear physiologic injury is related to the pain and its progression can be assessed, the determination is more straightforward. If an injury can be identified and can be expected to improve, the pain can be considered acute. Chronic pain is not related to tissue injury or is related to tissue injury that is not expected to resolve, is past the time by which it should have resolved, or is expected to progress.

MANAGEMENT PRINCIPLES

Pain Assessment

The early, accurate recognition and assessment of a patent's pain are the most important aspects of effective acute pain management.[39] When pain is inadequately treated, inaccurate assessment is very likely the root cause of the problem.[6]

The degree to which a person experiences pain is a complex and subjective interaction between the physical stimulus and the patient's cognitive and emotional state. It is clear, however, that the degree of pain a patient perceives is not directly determined by the degree of physiologic injury. Patients in the ED with the same injury may display completely different amounts of pain.[39] Therefore, pain treatments, analgesic requirements, and the way a patient describes pain cannot be uniformly described based on the nature of a patient's injury, and each patient must be individually and repeatedly assessed.

The assessment of pain depends on the patient's ability to communicate the nature of the painful experience to the physician and on the physician's ability to obtain this information. Unfortunately, there is no test or physiologic index to measure pain reliably.[40-47] Objective observations, such as hypertension, diaphoresis, or tachycardia, do not correlate well with the degree of pain present.[8,33,42] Pain assessment is made through an indirect estimation by the patient's caregivers. Since pain cannot be objectively measured, a physician's assessment depends on communication with the patient, both verbal and nonverbal. Barriers to communication between patients and physicians, including linguistic, socioeconomic, and cultural differences, limit the ability to assess pain. Because effective treatment is based on the assessment of pain, patients who have difficulty communicating are at particular risk of undertreatment of their pain (oligoanalgesia). Groups at risk include infants and children; patients whose cultural background differs significantly from the treating physician's; and patients who are developmentally delayed, cognitively impaired, under severe emotional stress, or mentally ill.[4,8,39,48-51] The accurate assessment of pain in the face of communication barriers is a difficult yet important challenge to overcome in treating pain adequately.

Oligoanalgesia

Oligoanalgesia, the inadequate treatment of pain, is detected in most studies of pain in the ED.[4,52-65] Data from the National Hospital Ambulatory Medical Survey evaluated all isolated closed fractures of extremities and clavicle and showed that only 64% of patients received an analgesic and only 42% received an opioid.[52] Children, the elderly, and patients from social and ethnic minorities exhibit oligoanalgesia the most frequently.[4,51,66,67]

Even when analgesia is administered in the ED, there frequently is a long delay. When opioids are used, they frequently are given in subtherapeutic doses. One study of trauma centers shows that of the 38% of patients who received an analgesic, the average time of administration of the first dose of analgesic was 109 minutes after arrival.[56]

For a wide variety of reasons patients do not receive adequate analgesia, and they are not all related to the assessment of pain. Many are due to misconceptions about the safety and efficacy of various treatments and about the effect of pain treatment on a patient's evaluation.

Pain Measurement

The use of numeric rating scales, employing a verbal 0 to 10 "none to worst imaginable" score, are ubiquitous in the ED and other settings where acute pain is managed or inflicted.[66] Visual analogue scales, usually consisting of a 10-cm straight line with anchors at either extreme (similar to verbal scales), are used in research in order to provide continuous data for analysis but offer little practical advantage over verbal reports for clinical use.[40,43,67-69] Including a pain scale as a part of vital signs is now mandated by the Joint Commission (Fig. 186-4)[70] and is a routine part of care. This encourages clinicians to initially and frequently communicate with patients to assess their pain and its response to interventions in order to improve the management of their pain.[59,71]

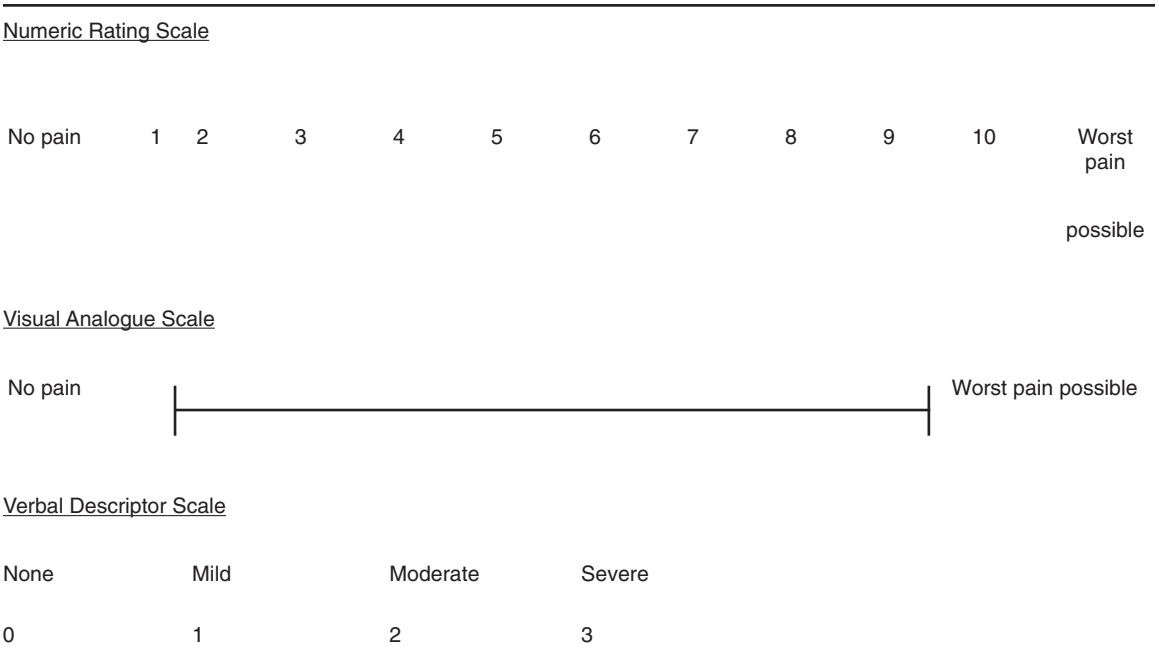


Figure 186-4. Common pain rating scales.

Patient-derived pain scales are only useful if the patient can understand the question being asked. Using a numeric or verbal rating scale requires understanding the language it is being asked in or being able to read the anchors. It also requires an ability to assign a concrete value to the abstract concept of pain. In general, children younger than 7 years are unable to successfully accomplish this. The FACES pain scales are designed for children younger than 7 who are verbal and may be used to describe their pain.[72] These scales have a series of cartoon faces expressing a range of emotions from happiness to severe distress. The child is asked point to the face that corresponds to how he or she feels. These scales require less of an abstract reference than numeric and verbal scales and are useful in assessing toddlers and cognitively impaired adults.[73]

In preverbal children, observer-derived scales may be used. These include scales such as the Modified Pre-Verbal, Early Verbal Pediatric Pain Scale (M-PEPPS),[74] and the Children's Hospital of Eastern Ontario Pain Scale (CHEOPS)[75] for preverbal children and the CRIES scale for neonates.[76] These scales use a scoring system for observed criteria that is reproducible between observers, making them useful for research, but they have little clinical utility over the physician's or parents' overall impression of the child's pain.[77]

Although these scales are validated for use in the ED, a great deal of variability is described both within and between patients for a given stimulus.[43,78] Numeric rating scales can be used as communication tools between the patient and the physician to talk about pain, but care must be taken against using the scores derived from the scale as an absolute indicator of pain. The score a patient uses to describe pain has as much to do with how much he or she wants action to be taken on that report as it does a description of the pain relative to previous experiences. A patient reporting 10/10 pain probably wants something to be done about it. If other concerns are more pressing, the patient may describe the pain from the same injury as 2/10. As a patient undergoes treatment, changes in the pain scores represent satisfaction from the treatment and a desire for further treatment, more than any change in the condition. Nevertheless, pain scores remain the most accurate measure of assessing a patient's pain and pain treatment and should be used frequently during the assessment of patients with pain. Treatment should be targeted to a goal of reducing the pain score (e.g., by 50% or to below 3/10) rather than a particular (maximum) dose of the analgesic.

Treatment

The basic approach to the treatment of pain can be broken into four main treatment groups: (1) acute pain, (2) chronic pain, (3) recurrent pain, and (4) chronic pain of malignancy. Therapy for groups 2–4 should involve a long-term multidisciplinary approach in order to treat the multiple manifestations of these diseases, where the plan from the emergency physician fits in as part of an ongoing strategy.

Acute and chronic pains have different physiologic etiologies and thus require different treatment approaches (Fig. 186-5). The main difference in the treatment of acute versus chronic pain, in terms of the treatment of the actual perception of pain, is that it cannot be assumed that chronic pain will resolve, and treatments that are sustainable with side effects that can be controlled must be selected.

Chronic Pain

The assessment of pain in the absence of acute or obvious physical injury requires a great deal of communication skill on the part of the physician and the patient. Many patients with chronic pain develop a great deal of experience, some of it adaptive and some maladaptive, in describing their pain and interacting with physicians in order to receive pain treatment.[79] Many behaviors such as exaggerating symptoms or attempting to manipulate providers develop around the patient's low expectations of receiving pain relief. These behaviors, combined with the negative psychosocial effects and sense of futility associated with chronic pain, can complicate the evaluation process and the care of chronic pain patients.

The assessment of chronic pain can represent some of the most challenging situations in which to obtain an accurate history. Patients who are having a difficult time describing their pain should be encouraged with detailed questions about the pain, combined with multiple examples, comparisons, and summarizing statements, in order to facilitate accurate communication. Assuring the patient that the questions are intended to aid understanding and to enable treatment of symptoms as effectively as possible can facilitate the development of a common goal and help establish the trust necessary to develop an effective treatment strategy.

Patients with chronic pain can present either with an exacerbation of their chronic pain in the setting of their ongoing

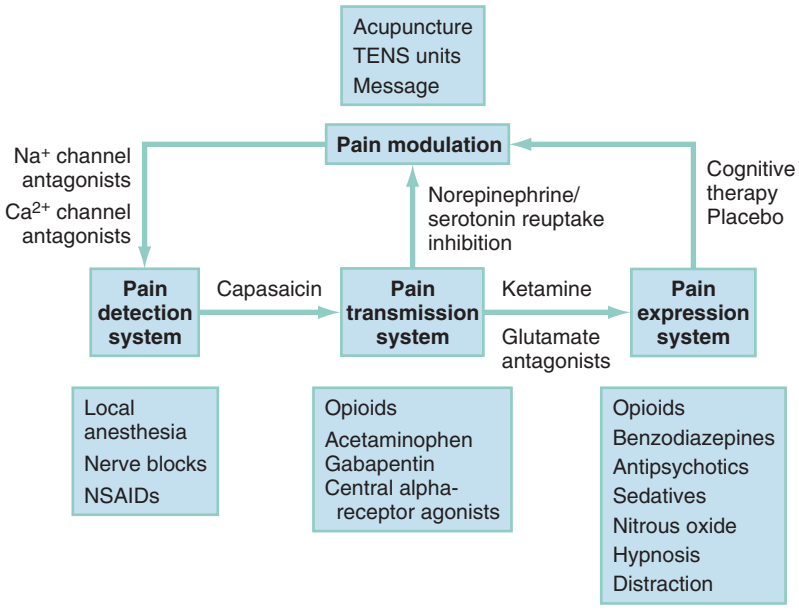


Figure 186-5. Sites for pain treatment algorithm.

therapy or with untreated chronic pain due to a gap in or a lack of appropriate treatment. These two situations require different treatment approaches. For chronic pain patients with an exacerbation in their pain exceeding the pain control of their usual treatment strategy, treatment can be approached in a similar fashion to acute pain, with the goal of controlling the exacerbation and returning them to their baseline therapy. Many patients with chronic pain, however, are in comprehensive treatment programs, most of which involve a "contract" with respect to where they will seek their care (e.g., not in an ED) and their medications (always from the pain center). For such patients, review of the pain management plan in the medical records or contact with the physician on call for the pain center is desirable before embarking on a treatment strategy.

Patients with chronic pain who have a gap in their baseline treatment or have never established appropriate treatment for chronic pain (e.g., patients who have linked together the acute treatment plans of multiple providers but lack a consistent treatment approach) require an approach that takes into account the fact that a chronic pain treatment plan needs to be established.

Patients with no ongoing treatment plan who are identified as having chronic pain should have a basic chronic pain treatment plan implemented during their ED visit. Patients should be using acetaminophen if not contraindicated and an nonsteroidal anti-inflammatory drug (NSAID) if it can be tolerated. Tramadol may be helpful in certain cases, and adjuvants appropriate for neuropathic or central pain may be added if appropriate. Opioids should not be prescribed until these other treatments are maximized and should be added in addition to these other therapies rather than as an alternative.[80] In general, opioids for chronic pain management are in the domain of the ambulatory pain center or primary care physician and should be avoided in the ED and by prescription on discharge.

Recurrent Pain

Recurrent pain is a subset of chronic pain and describes patients who have few symptoms in between repeated episodes of similar pain It can include such disorders as back pain, myofascial pain syndrome, migraine syndrome, sickle cell disease, and inflammatory bowel disease. The approach to the treatment of recurrent pain in the ED is similar to that of acute pain, except that prevention must be considered and strategies that can be safely repeated should be employed. Therapies that may suppress future episodes, such as physical therapy for back pain, should be planned to start in between exacerbations.

Chronic Pain of Malignancy

Chronic pain due to malignancy is approached differently from other causes of chronic pain. Chronic malignant pain is similar to acute pain in its relation to ongoing nociceptive stimulation and similar to chronic pain in its duration and psychobehavioral effects. The medications used, for the most part, are similar to those used for acute pain. Similarly to chronic pain, the psychosocial effects of the pain must also be addressed as part of an effective treatment strategy. Patients with a significant change in the pattern of their chronic pain caused by cancer or a terminal illness, as with other chronic pain patients, should be evaluated for a new process to account for the pain. Opioids, especially in long-acting or transdermal preparations, should be used liberally to bring pain relief in patients with terminal illnesses.[7]

Neuropathic Pain

Usually, activation of the sympathetic system does not result in pain. In the setting of nerve injury, however, it appears to modulate the development of hyperalgesia and allodynia and is associated with a wide variety of neuropathies. Complex regional pain syndrome (CRPS) is a term that includes most sympathetically maintained pain.[81] CRPS type 1 (sometimes referred to as reflex sympathetic dystrophy) develops after an injury and is usually in the distribution of a peripheral nerve.[82] It is associated with hyperalgesia, allodynia, changes in skin blood flow, and sympathetic dysfunction. CRPS type 2 (sometimes referred to as causalgia) is associated with burning pain and allodynia in the distribution of an injured nerve and is not usually associated with sympathetic symptoms. Some evidence indicates that CRPS can be prevented with opioids prior to the occurrence of an injury[83,85] and that opioids are ineffective after the injury.[84] Clonidine, *N*-methyl-D-aspartate receptor antagonists, and γ-aminobutyric acid (GABA) receptor agonists are more effective than opioids for these conditions.[85]

Antidepressants have effects on neuropathic pain that do not depend on their mood effects.[86] A meta-analysis of 39 placebo-controlled trials using first-generation tricyclic antidepressants found benefits in a variety of chronic pain syndromes.[87,88] They are generally used as analgesics for central and neuropathic pain but can be useful as antidepressants in most chronic pain conditions. For chronic pain that is not thought to be central or neuropathic, other antidepressants, such as serotonin reuptake inhibitors, may be safer and more effective.

Several anticonvulsants, including gabapentin, phenytoin, carbamezepine, and valproic acid are described for neuropathic pain with lancinating or burning properties. Carbamezepine is used most frequently for trigeminal neuralgia, postherpetic neuralgia, and diabetic neuropathy. Gabapentin is described for both types of CRPS, postherpetic neuralgia, and diabetic neuropathy.[89-91]

Acute Pain

Acute pain follows injury and usually disappears as the injury heals. When the cause is uncertain, establishing a diagnosis is a priority, but symptomatic treatment of pain should be initiated promptly, titrated to an acceptable level of relief, and continued while the investigation is proceeding. It is rarely appropriate to delay analgesic use until a diagnosis is made. There is no evidence that the administration of adequate doses of opioid analgesia to establish patient comfort impairs the physician's ability to diagnose the cause of the painful condition. To the contrary, administration of analgesia may enhance the accuracy of physical examination. For example, when the woman with severe pelvic pain receives adequate analgesia before pelvic examination, she is more likely to be able to assist the physician in localizing the pain to one side or the other.[92,93]

Analgesic Agents

Opioid Analgesic Agents

In 1680, Sydenham wrote "Among the remedies it has pleased Almighty God to give to man to relieve his sufferings, none is so universal and so efficacious as opium."[94] Centuries later, this statement is still accurate, and titrated opioids are the mainstay of therapy for acute pain. The beneficial effects of opioids have been well documented for centuries, as have their toxic-

ity and potential for abuse. Opioids, however, are often poorly used in clinical practice.[53] Concerns about inducing opioid toxicity or dependence and a poor understanding of the pharmacokinetics of the drugs lead to inadequate dosing and excessively infrequent dosing intervals. The safety of the short-term use of opioids for acute pain, however, in terms of both toxicity and their likelihood of causing future dependence, is shown in a wide variety of studies.[92,93] Opioids should be the first-line agents in the management of acute severe pain. Table 186-4 lists commonly used opioid agents.

Mechanism of Action and Toxic Effects. Opioids bind to specific endorphin system receptors located throughout the nervous system that suppress pain detection peripherally, modify pain transmission in the spinal cord and thalamus, and alter the perception of pain at the level of the cortex. A variety of endorphin receptors are currently defined (see Table 186-2), and the unique actions of various opioids are determined by the specific binding properties of the agent to the various receptors.

Opioids also suppress the medullary cough center (antitussive) and decrease the medullary sensitivity to carbon dioxide (respiratory depression). They can activate the chemoreceptor trigger zone, causing nausea or vomiting, but this is relatively infrequent. They decrease bowel motility and smooth muscle function, causing constipation and, rarely, urinary retention. To a varying degree, some opioids destabilize mast cells in a dose-dependent fashion, causing histamine release, with urticaria, pruritus, and, sometimes, orthostatic hypotension. Any

Table 186-4 Opioid Analgesics

NAME	INITIAL PARENTERAL DOSE	INITIAL ORAL DOSE	DURATION OF ACTION	EQUIPOTENT IV DOSE	EQUIPOTENT PO DOSE	COMMENTS
Morphine	0.1 mg/kg	0.5 mg/kg	3–4 hr	10 mg	50 (single dose)	Standard opioid for comparison
Hydromorphone	0.015 mg/kg	0.075 mg/kg	2–4 hr	1.5 mg	7.5 mg	Inactive metabolites make it superior in patients with renal or hepatic disease
Methadone	0.1 mg/kg	0.2 mg/kg	4–8 hr	10 mg	20 mg	Used for opioid addiction treatment and chronic pain, half-life longer than duration of action
Fentanyl	1.5 µg/kg	3 µg/kg	0.5–1.5 hr	100 µg	NA	Oral dose actually transmucosal absorption, metabolites inactive, transcutaneous patches used for chronic pain
Oxycodone	0.1 mg/kg	0.15 mg/kg	3–4 hr	10 mg (IV)	15 mg	Excellent bioavailability makes it an effective oral agent
Codeine	1.3 mg/kg	2.5 mg/kg	2–4 hr	130 mg	200 mg	Pronounced peripheral effects (constipation, nausea and vomiting, cough suppression)
Hydrocodone	NA	5–15 mg	3–4 hr	NA	30 mg	Commonly used in preparations with acetaminophen, more potent than codeine
Meperidine	0.75 mg/kg	3 mg/kg	2–3 hours	75 mg	300 mg	Toxic metabolite normeperidine accumulates at normal doses, no indications relative to other available opioids
Oxymorphone	0.01 mg/kg	0.1 mg/gk (rectal)	3–4 hr	1 mg	10 (PR)	Rectal dosing more predictable than other agents
Propoxyphene	0.5 mg/kg	1 mg/kg	2–4 hr	50 mg	100 mg	Combination with acetaminophen inferior to acetaminophen alone, no indications for use
Alfentanil	10–20 µg/kg	NA	8–12 min	1 mg	NA	Short duration due to redistribution, duration of action increases with the size of the dose
Sufentanil	0.1 µg/kg	NA	1–1.5 hr	10 µg	NA	Minimal cardiovascular side effect
Remifentanil	0.5–1 µg/kg	NA	4–6 min	50 µg	NA	Used as a continuous infusion
Nalbuphine	0.4 mg/kg	0.1 mg/kg	3–4 hr	40 mg	NA	Mixed agonist/antagonist, Decreased respiratory depression relative to other opioids, limited analgesic effect, used in perinatal period

IV, intravenous; NA, not applicable; PR, per rectum.

of these side effects can significantly limit therapy, especially in the acute setting. The occurrence of these side effects varies among individual patients and opioids, but tolerance of many of them develops shortly after the initiation of therapy. Most patients tolerate opioids very well, and prompt relief of severe pain often reduces nausea and vomiting.

The most common side effect of opioids is constipation, related to opioid binding to receptors located in the antrum of the stomach and proximal small bowel.[95] Tolerance to this does not develop with prolonged use. Some opioids may cause less constipation than others, and parenteral and transdermal administration routes may be superior to oral (PO) due to decreased exposure of the gut to the opioids.[96,97] Constipation can be anticipated with long-term (more than a few days) opioid use, and an active laxative, such as senna, lactulose, or bisacodyl, should be prescribed as needed.

Nausea and vomiting can occur with the administration of opioids, especially in opioid naïve patients,[98] but routine coadministration of an antinauseant with the opioid, once an almost universal practice, is not indicated. It is impossible to distinguish whether the nausea and vomiting are caused by the opioid or the acute pain for which it is administered. Nausea and vomiting in the context of persistent acute pain after opioid administration require additional opioid and an antinauseant, such as promethazine, prochlorperazine, or one of the 5-HT_3 receptor antagonists (e.g., ondansetron).

True immunoglobulin-mediated allergies are rare for morphine and other opioids, but many patients experience mild pruritus of the trunk and face after parenteral administration. This is related to histamine release from opioid receptors on mast cells and does not constitute an allergy to opioids. Often, it appears as localized urticaria that tracks up the vein after intravenous (IV) administration of an opioid, especially morphine. Rarely, bronchospasm may be seen in patients with reactive airway disease. The effect usually subsides rapidly, and no treatment is required.

Sedation and respiratory depression can occur with opioid administration for acute pain but are usually mild and self-limited. The underlying mechanism of respiratory depression is central stimulation of the mu receptor. The combination of opioids with other sedating agents, such as benzodiazepines, can increase the likelihood of respiratory depression. Patients with underlying hepatic or renal dysfunction may be at increased risk because of inability to clear the drug normally. Respiratory depression rarely occurs in the context of acute severe pain, and fear of respiratory depression should not deter the clinician from adequately relieving the pain. Pain is a powerful physiologic stimulant of respiratory drive, however, and if the source of the pain is removed, such as by local anesthesia or the reduction and stabilization of a fracture, patients who had previously tolerated a dose of an opioid may develop respiratory depression.[99] Transient respiratory depression usually responds to simple verbal or tactile stimulation and rarely requires reversal.

Tolerance and physical dependence are common with prolonged use of opioids. Physical dependence is defined by the occurrence of opioid withdrawal syndrome following abrupt cessation, rapid dose reduction, or administration of an antagonist. Tolerance is a phenomenon that occurs after prolonged exposure to opioids and is characterized by the diminution of an opioid's effect over time. Normal expected results of the prolonged use of opioids should be accounted for in planning the use of opioids for extended periods and do not represent addiction. Addiction is a potential risk associated with prolonged opioid use, which often limits the use of opioids.[100] The term *addiction* refers to a neurobiologic disease, with many factors influencing its development and manifestations. It is characterized by compulsive drug use, continued use despite harm, and craving. The iatrogenic creation of opioid addiction, a new addiction where one did not previously exist, is a relatively rare phenomenon.[101] The results of the Boston Drug Collaborative Study show that only 4 in 11,892 inpatients treated with opioid analgesic agents developed new opioid abuse.[102]

Pseudoaddiction describes patient behaviors that may occur when pain is undertreated.[103] Patients with unrelieved pain may become focused on obtaining medications and otherwise seem inappropriately "drug-seeking." Behaviors such as illicit drug use and deception can occur in the patient's efforts to obtain relief. Pseudoaddiction can be distinguished from true addiction in that it resolves when pain is effectively treated.

Suggestion of Drug-Seeking Behavior. Some patients feign or exaggerate pain in order to receive opioids.[104] A physician's perception that a patient is drug-seeking is associated with decreased treatment of the patient's pain and is associated with a patient's ethnic background, making this perception a possible source for bias in the treatment of pain.[39] Care must be taken both to identify such behavior when it exists and to do so accurately. A patient should be given the benefit of the doubt until it is clear that he or she is trying to deceive care providers to obtain medication. Primary providers, chronic pain specialists, and others should note patient contracts, prescription details, and patterns of possible nontherapeutic drug-seeking in the paper or electronic medical record, using objective terms and descriptions.[105] Patients with repetitive episodes may benefit from a multidisciplinary review to establish specific recommendations for their care when they present to anyone other than their primary pain management provider.

Administration

The goal of the administration of opioids is to attain effective analgesia with minimal adverse effects and then to maintain it. The effects of opioids vary among individuals. There is no "ceiling effect" to their potency, neither is there a standard, fixed, or weight-related dose that can produce a given clinical effect. The correct dose a particular patient requires at a particular time can only be determined by repeated assessment of the degree of pain relief and any adverse effects the patient may be manifesting. The use of opioids therefore requires titration based on frequent and accurate assessments of the effects of any dose given.[94] The most effective and safest way to achieve pain relief is to use a deliberate IV titration.

The intramuscular (IM) route of administration of opioids has several disadvantages and is not advised for treatment of acute pain (Box 186-3). The principal limitation is that it does not allow effective titration. The time to achieve significant pain relief from an IM injection varies from 20 to 60 minutes, offering no advantage over the PO route. If the dose is inade-

BOX 186-3 Disadvantages of Intramuscular Opioid Administration

Pain on injection
Delayed onset of action
Inability to predict effect
Inability to titrate dosage
Diurnal variation in level achieved
Disease state may affect level achieved
Level dependent on muscle used

quate, the patient must experience another painful injection and wait another 20 to 60 minutes to determine whether effective analgesia is achieved. If too large a dose is given, the patient is at risk of side effects.

Most patients are best treated with PO agents if mild to moderate pain exists and IV agents if pain is moderate to severe. If an IV line cannot be established and the patient cannot tolerate PO medications, the subcutaneous (SC) route is preferable to the IM route because the injection is less painful. The rate of absorption for an SC injection is almost identical to one given by the IM route.

Opioids can be delivered through the PO transmucosal or intranasal mucosal route.[106,107] The opioid buprenorphine can be given by sublingual route. Fentanyl is available in an impregnated, sweetened matrix called a Fentanyl Oralet (PO transmucosal fentanyl citrate). Nasal fentanyl, butorphanol, and sufentanil also produce rapid clinical effects.[77,108,109]

The optimal use of IV opioids requires administering an initial "loading" dose, assessing its analgesic effect, and then administering frequent (every 10–15 minutes) repeated doses until analgesia is achieved, followed by doses at regular intervals to prevent the return of significant discomfort. The best way to determine the need to administer another dose of opioid is to use the patient's subjective impression. Patient-controlled analgesia uses a computerized delivery system that allows patients to self-administer a prescribed dose of opioid based on their own determination of need. Patient-controlled analgesia has been demonstrated to be safe and effective for sickle cell pain crisis in a pediatric ED.[110]

Specific Agents

Morphine. Intravenous morphine is often the first choice for treatment of acute severe pain in ED patients and is the opioid analgesic agent with which all other opioids are compared. When administered IV, morphine reaches its peak of action in 15 to 20 minutes and has a half-life of 1.5 to 2 hours in healthy young adults and slightly longer in the elderly. Its duration of action is 3 to 4 hours. An appropriate loading dose for acute severe pain is 0.1 to 0.15 mg/kg IV, augmented by repeated doses of 0.05 mg/kg every 15 minutes until pain is relieved. Oral administration of morphine can be an effective option for moderate or severe outpatient pain, but only 20% of the ingested dose reaches the tissues after first-pass metabolism. There is no validity to the perception that morphine causes more smooth muscle spasm than other opioids and should be avoided in patients with biliary or renal colic.

Morphine is hydrophilic in nature, which delays its transport across the blood-brain barrier relative to more lipophilic opioids and delays its onset of action. This results in it having a longer duration of action (4–5 hours) than its half-life (2–3 hours). Morphine is primarily metabolized by conjugation into a 3-conjugate and 6-conjugate form in the liver. The 3-conjugate form (normorphine) has no opioid analgesic activity and rarely has been associated with CNS side effects (e.g., tremors, myoclonus, delirium, or seizures) when used repetitively over a long period and allowed to accumulate. This risk, although small, is greatest in elder patients and those with renal insufficiency but is rarely an issue in the ED. Less of the 6-conjugate than the 3-conjugate form is created in the chemical preparation. This form is a strong mu and delta receptor agonist and plays an important role in morphine's efficacy and the duration of its clinical effect.

Meperidine. Meperidine (Demerol), although once widely used, has several disadvantages compared with morphine and other parenteral opioids and has no role in the ED management of acute pain. The duration of action of meperidine is only 2 to 3 hours, which is less than that of morphine. Perhaps the greatest disadvantage of meperidine is that it is metabolized by the cytochrome P_{450} system to the active metabolite normeperidine, which is produced in much larger quantities than the toxic metabolite of morphine at therapeutically equivalent doses, and causes CNS toxicity. Normeperidine has a half-life of 12 to 16 hours and blocks muscarinic receptors, resulting in significant anticholinergic effects and subsequently causing agitation and delirium. This eventually leads to seizures, hallucinations, and psychosis as the drug accumulates. Normeperidine is renally excreted and has a longer half-life in patients with decreased renal function. Repeated doses of meperidine should be avoided.

Of particular concern is the potentially lethal interaction of meperidine with monoamine oxidase inhibitors. Meperidine can also cause a serotonin syndrome in patients who are taking a selective serotonin reuptake inhibitor or other serotonin agonist. Meperidine is no longer a formulary drug at many hospitals.

Hydromorphone. Hydromorphone is a semisynthetic derivative of morphine that is a potent analgesic agent, increasingly used in the management of acute pain in the ED. This P_{450} metabolite of hydrocodone is seven times more potent than morphine when given parenterally and has a similar duration of action to morphine. Although 7 mg of morphine is equivalent to 1 mg of hydromorphone, nurses are more likely to administer the "low" milligram doses of hydromorphone to patients with acute pain than the "higher" equipotent doses of morphine.[111,112] Pruritis, nausea, and vomiting may occur less frequently than with morphine at equianalgesic doses. It is conjugated primarily into hydromorphone-3-glucuronide (H3G) in the liver and is excreted renally. H3G is for the most part inactive, so hydromorphone is better tolerated than morphine in elderly patients and those with hepatic impairment. Patients with renal insufficiency may be at some risk of neurotoxicity after prolonged exposure due to H3G accumulation. True allergy to opioids is rare, but patients allergic to morphine do not always have cross-reactivity with hydromorphone. Hydromorphone can be given IV or PO. A rectal (PR) preparation is available in the form of 3-mg PR suppositories.[94]

Fentanyl. Fentanyl is a synthetic opioid that is highly lipophilic and produces analgesia within 1 to 2 minutes after IV infusion. It also redistributes rapidly, and its duration of action is only 30 to 60 minutes. It is metabolized by the P_{450} system into inactive metabolites. Drug accumulation and toxicity may occur after tissue saturation following a prolonged infusion, but this is unlikely to happen during acute therapy. Fentanyl's short duration of action makes it highly titratable and ideal for use in patients who require serial examinations, such as trauma patients with possible occult head injury.

Fentanyl releases less histamine than morphine, is associated with fewer peripheral effects at an equianalgesic dose, and thus is an excellent choice for treating pain in patients with bronchospastic lung disease. It is more frequently associated with respiratory depression with regular use than morphine, and patients receiving infusions of the drug should be monitored with direct observation, supplemented by pulse oximetry or capnography. ED use of fentanyl is associated with a very low (1.1%) incidence of potentially serious complications.[113–115] High or repeated doses of fentanyl may produce muscle rigidity. This side effect usually occurs with anesthetic doses greater than15 μg/kg and may be so severe that it interferes with respiration but is exceedingly rare at doses used for analgesia. This rigidity does not uniformly respond to naloxone but is abolished by neuromuscular blockade. Fentanyl can be administered IV, transmucosally,[115] or transdermally.

Nebulized fentanyl is described for the treatment of acute pain in patients without IV access at doses of 3 μg/kg,[77,108] as has intranasal administration.[116,117]

Oxycodone. Oxycodone is a strong opioid agonist that is highly bioavailable in PO form. It is widely available in combination with acetaminophen or aspirin as well as by itself. It is also available in long-acting PO formulations. Its bioavailability is described to be between 0.60 and 0.85, which is higher than other opioids. It is quickly and efficiently absorbed, with abuse potential. Oxycodone is not available in a parenteral form in the United States, although studies have found its IV form to be equianalgesic to morphine. Similar to the other opioids, oxycodone's analgesic effects are dose-dependent. A 15-mg dose has a similar efficacy to 10 mg of IV morphine. The onset of action of PO oxycodone is 20 to 30 minutes.[118]

Oxycodone is a prodrug that undergoes hepatic metabolism into oxymorphone, a strong opioid agonist that principally accounts for its analgesic effects, and the inactive metabolite noroxycodone. Similarly to codeine, 10% of patients do not metabolize oxycodone well and do not generate the functional metabolite, which means that they require very large doses of oxycodone to achieve analgesia. This effect can also be caused by agents that compete with oxycodone for CYP2D6 metabolism, such as neuroleptics, tricyclic antidepressants, and selective serotonin reuptake inhibitors. Cases of serotonin syndrome are reported when serotonin reuptake inhibitors and oxycodone are given together.[119,120]

Hydrocodone. Hydrocodone is metabolized in the liver to hydromorphone. It provides greater pain relief when combined with acetaminophen or NSAIDs than either component does alone. In two small studies, hydrocodone-acetaminophen (5 mg/500 mg) provides similar analgesia to codeine-acetaminophen (30 mg/500 mg) in patients with acute musculoskeletal pain or those who had undergone dental surgery.[121,122] Hydrocodone may cause more drowsiness and dizziness but less nausea than codeine. It is less effective than oxycodone-acetaminophen combinations.[123] Hydrocodone is usually administered alone, 5 to 20 mg PO every 4 to 6 hours. Hydrocodone-acetaminophen combination tablets are commonly prescribed as one to two tablets every 4 hours as needed for pain.

Codeine. Codeine is a commonly prescribed opioid, usually in combination with acetaminophen. Codeine is a weak opioid receptor agonist and has little role in the ambulatory treatment of pain, unless oxycodone is not available. Codeine is thought to exert its effects through metabolism into morphine and other metabolites in the liver.

Approximately 10% of the population metabolizes codeine poorly and experiences nausea, constipation, and pruritus without pain relief. Although often prescribed for mild to moderate pain, codeine is a poor choice because of its tendency to cause side effects, especially nausea, cramping, and constipation, at doses that provide limited analgesia.

Propoxyphen. Propoxyphene has limited indications for use. Many studies show its analgesic efficacy to be no better or only marginally better than placebo.[124] Its metabolite, norpropoxyphene, can accumulate with repeated or large doses and can cause refractory seizures, respiratory arrest, and significant risk of death from torsades de pointes.[125] There is little evidence to support its use alone or combined with acetaminophen for acute pain, and it generally should not be used in the ED or prescribed for outpatient management of pain.[126]

Methadone. Methadone has several unique features that distinguish it from other opioids. It has no known neurotoxic or active metabolites, has high bioavailability, and, in addition to being a strong opioid agonist, has *N*-methyl-D-aspartate antagonist and serotonin reuptake–blocking properties. It has a slow elimination half-life of 27 hours due to its lipophilicity and tissue distribution. This slow clearance of methadone is the basis for its use in maintenance therapy, because it can delay the onset of opioid withdrawal symptoms for up to 24 hours. The duration of its analgesic effects, however, is closer to 6 to 8 hours. The discrepancy between the duration of action of analgesia and the duration of the prevention of withdrawal symptoms is due to the biphasic elimination of the drug and its redistribution.[127]

Naloxone. Naloxone is an opioid antagonist that can be given IV, IM, SC, or via an endotracheal tube. It reverses the effects of opioids and is usually used in the setting of severe adverse events or recreational opioid overdose. It can precipitate physiologic withdrawal in patients who are opioid-dependent. Its duration of action is 45 minutes, which is shorter than that of most opioids, so care must be taken to monitor for the recurrence of the adverse event for which it was given after this time period. It is usually given in repeated titrated doses of 0.2 mg IV, until the adverse effect of the opioid is reversed. Careful titration allows for the smallest dose possible to be given so that as much of the analgesic effect of the opioid can be maintained as possible.

Tramadol. Tramadol is a synthetic oral compound that is a weak mu agonist with some serotonin and norepinephrine reuptake qualities. Its analgesic properties are thought to be primarily due to mu receptor agonism. Tramadol-induced analgesia, however, is only partially reversed by naloxone, suggesting its other properties play a role. Tramadol, as a selective mu agonist, should not cause physiologic dependence. Since its release, however, it has been associated with abuse and withdrawal similar to that of other opioids, but at a low enough rate that it remains an unscheduled drug. It is metabolized in the liver by the cytochrome P_{450} system. One of its metabolites, M1, has an even greater mu-receptor affinity than tramadol and has an elimination half-life of 9 hours. Tramadol appears to have effects on GABA, norepinephrine, and serotonin receptors and the reuptake of the neurotransmitters, which may serve to activate descending pain modulation pathways.

Compared with traditional opioids, tramadol has a more favorable side effect profile and may present a lower risk of addiction with chronic use. The most common side effects, nausea, vomiting, dizziness, orthostatic hypotension, and sedation, are seen in as many as 17% of patients using it for chronic pain, with slightly lower rates occurring in patients receiving controlled-release versions.[128] The occurrence of these side effects increases dramatically with increasing doses. Reports of overdose and fatalities have led to the addition of past or present histories of addiction to opioids as a contraindication for the drug. The use of tramadol with other serotonergic medications (selective serotonin receptor inhibitors, monoamine oxidase inhibitors, and serotonin norepinephrine reuptake inhibitors) is associated with serotonin syndrome.[129]

Tramadol is an efficacious pain medication at low doses. At increasing doses, it is associated with nausea and vomiting, limiting its use to low doses and effectively giving a ceiling to its therapeutic effect. Tramadol 37.5 mg combined with acetaminophen 325 mg has similar efficacy to hydrocodone 5 mg combined with acetaminophen 325 mg.[130]

Opioid Agonist-Antagonist Analgesic Agents

The agonist-antagonist group of opioids was synthesized in an attempt to provide analgesia with little or no respiratory depression and abuse. It is believed that the analgesia provided by these agents is caused by agonist action at the kappa receptors, whereas the ceiling on respiratory depression is

caused by antagonism of the mu receptors. They have rates of abuse similar to those for standard opioids and a ceiling effect to their analgesia that limits their use to situations in which brief, limited analgesia is needed and respiratory depression is the principal adverse effect of concern—such as in the perinatal period. Nalbuphine can be used in these situations. Its major advantage is decreased respiratory depression. The half-life is 3.5 hours, and the effects of renal or hepatic disease on metabolism are not completely known. The usual therapeutic parenteral dose is 10 mg, but as with all other opioids, the dose must be individualized.

Opioid Use in Abdominal Pain

Historically, it was recommended that pain treatment be withheld from patients with abdominal pain in order to avoid confounding the diagnosis. These recommendations date from the turn of the 20th century, predating modern diagnostic techniques, and have no place in modern emergency care. Multiple studies confirm the safety of providing effective opioid analgesia to patients with undiagnosed abdominal pain, and no study has demonstrated any adverse effects.[131-139]

Nonopioid Analgesic Agents

Acetaminophen. Acetaminophen is the first-line agent for the treatment of both acute and chronic pain. It is the safest pharmacologic option for pain in children and adults. It has a high toxic-to-therapeutic ratio and lacks significant drug interactions compared with other pain medications.

Although acetaminophen has been in use since the 1880s, its pharmacologic mechanism of action is unknown. It has known analgesic and antipyretic activity, with no known peripheral anti-inflammatory effects. Its activity may be due to the inhibition of prostaglandin endoperoxide H_2 synthase and a cyclooxygenase isoenzyme centrally.[140] It may also effect the activation of beta-endorphin centrally.[141] The analgesic actions of acetaminophen are comparable in magnitude to those of NSAIDs,[142] and the analgesic effects of the combination of acetaminophen with an NSAID are additive.

Acetaminophen is metabolized in the liver primarily through conjugation to sulfate or glucuronides. A minor pathway for the oxidative metabolism of acetaminophen produces the toxic metabolite *N*-acetyl-*p*-benzoquinone imine (NAPQI). NAPQI requires glutathione for detoxification and elimination. Hepatic toxicity can occur when glutathione pathways are overwhelmed by an increase in NAPQI or a decrease in glutathione. Hepatic toxicity is rare with ingestions less than 10 g in a 24-hour period unless underlying liver disease exists or there is concomitant ethanol abuse. In the latter cases, therapeutic doses can cause clinical hepatotoxicity.[143]

Acetaminophen is generally well tolerated when used at therapeutic doses. Mild rashes are reported, as is bone marrow suppression, manifested by neutropenia, thrombocytopenia, and agranulocytosis. Its use is associated with several important drug interactions. Many anticonvulsants, including phenytoin, barbiturates, and carbamazepine, induce hepatic microsomal enzymes. Increased conversion of acetaminophen to its toxic metabolite may occur in patients who are taking anticonvulsants, but this is rarely of clinical significance in the context of the usual doses for pain management.

Although uncommon, drug interaction resulting in an increased international normalized ratio is reported for patients taking both acetaminophen and warfarin, particularly among patients taking high doses of acetaminophen (>9100 mg/week).[144,145] Chronic use of acetaminophen should be avoided in patients with hepatic or renal disease. Renal failure reportedly can worsen with acetaminophen use, but the mechanism is unknown.[146] Patients with a history of salicylate hypersensitivity characterized by urticaria have an 11% cross-reactivity to acetaminophen, and the agent should be used with caution in this group.[147]

For mild analgesia and fever reduction, acetaminophen is the first-line agent and is a first choice for use in combination with other agents, usually opioids, in the treatment of patients with more severe pain. Acetaminophen is available in many formulations, including caplets, tablets, and liquid and PR formulations. The recommended dose of acetaminophen for an adult is 650 to 1000 mg every 4 to 6 hours, not to exceed 4000 mg/day.

Nonsteroidal Anti-inflammatory Agents

NSAIDs inhibit cyclooxygenase (COX) and, as a result, the synthesis of prostaglandin, a key mediator of inflammation. The analgesic effect of NSAIDs is peripherally mediated by decreasing prostaglandin and effectively raising the threshold of activation of nociceptors. NSAIDs have synergistic effects with opioids and can reduce the amount of opioids needed to achieve pain relief in a patient.

Two COX isoenzymes mediate prostaglandin synthesis. COX-1 is present in all cells and plays an important role in homeostatic functions. COX-2 is induced by injury or inflammation and generates prostaglandins as part of the inflammatory process. Nonselective NSAIDs inhibit both COX-1 and COX-2, which results in multiple beneficial effects (reduction of inflammation, pain, and fever) but also some important undesirable effects.

As a group, and because of their wide use, NSAIDs are responsible for more serious drug-related side effects than any other class of analgesic drugs.[148] The major side effects of NSAID analgesic agents are gastrointestinal (GI) bleeding, renal failure, anaphylaxis, and platelet dysfunction. The majority of these side effects occur in patients who are taking NSAIDs for chronic conditions. It is estimated that more than 100,000 hospital admissions and approximately 16,500 deaths each year from GI bleeding are related to NSAID use for osteoarthritis and rheumatoid arthritis.[149] One survey estimated that for every 100,000 people taking NSAIDs each year, there are 300 GI-related deaths, 5 liver-related deaths, 4 renal-related deaths, and some congestive heart failure–related deaths.[150]

Limited evidence suggests that prostaglandins promote bone formation and that NSAIDs might inhibit the process, but this has not been established through properly conducted studies.[150,151] There is no evidence that short term use of NSAIDs for analgesia after fracture is deleterious to healing.

In addition to prostaglandin, cyclooxygenase helps generate prostacyclin, a vasodilator that increases GI mucosal perfusion. In the stomach, COX-1 increases bicarbonate and mucus production, important for protecting the mucosal lining. Inhibition of COX-1 compromises these protections, predisposing patients to ulcerations and bleeding, which are then exacerbated by concomitant NSAID-induced platelet dysfunction.[152]

COX-1 and COX-2 affect the cardiovascular system through the production of endothelial prostacyclin (vasodilatory) and thromboxane (platelet aggregation). Inhibition of COX-1 produces antiplatelet activity that may be cardioprotective by inhibiting thromboxane production more than prostacyclin. Inhibition of COX-2 inhibits prostacyclin production more than thromboxane and may produce prothrombotic effects, increasing the risk of cardiovascular events. In the case of nonselective COX inhibitors, these two effects appear to balance each other out, resulting in few changes in cardiovas-

cular risk in studies of these drugs. In the case of selective COX-2 inhibitors, this may result in an increase in cardiovascular risk.[153-155]

Prostaglandin produced by COX-1 causes renal vasodilation that maintains renal blood flow and the glomerular filtration rate (GFR). Inhibition of COX-1, especially in volume-depleted patients, can result in decreased GFR and even acute renal insufficiency. Sodium and water retention, hypertension, hyperkalemia, and acute renal failure may also ensue, especially in patients with congestive heart failure.

The most common adverse effect of NSAIDs is GI mucosal injury. In patients taking NSAIDs continuously for 1 year, 10 to 60% will develop abdominal pain, dyspepsia, or nausea and 2 to 4% will develop symptomatic ulcers.[156] Risk factors include age, concomitant use of warfarin or corticosteroids, congestive heart failure, diabetes, and coronary artery disease. There is evidence that cytoprotective agents such as misoprostol and proton pump inhibitors reduce this risk.[157] The relative risk for causing GI effects of the various NSAIDs are listed in Table 186-5.

Drug Interactions

Aspirin. NSAIDs may impair the cardioprotective effect of aspirin, although the available evidence is unclear and the use of daily aspirin for cardiac prophylaxis should not deter the prescribing of an NSAID for acute pain or inflammation.[158,159]

Oral Anticoagulants. The antiplatelet effects of NSAIDs add to the anticoagulant properties of warfarin, compounding the risk of significant bleeding complications, especially from GI ulcers. Furthermore, NSAIDs displace protein-bound warfarin and cause subsequent increases in prothombin times at a constant warfarin dose.[160] NSAID use is generally avoided in patients who are taking warfarin.

ACE Inhibitors. Concurrent use of NSAIDs with angiotensin-converting enzyme (ACE) inhibitors may impair renal function and impair the antihypertensive effects of ACE inhibitors.

Diuretics. Patients who are taking diuretics have a greater risk of developing renal failure because of NSAID-mediated decreased renal blood flow. Also, the natriuretic response to diuretics depends in part on prostaglandin-mediated vasodilatation.

Glucocorticoids. Patients on corticosteroids have an increased risk of peptic ulcer disease. NSAIDs should generally be avoided in patients concurrently taking glucocorticoids unless closely supervised by an ambulatory care physician.

Lithium. NSAIDs enhance lithium reabsorption and may directly reduce lithium excretion, leading to increased lithium levels. CNS symptoms (drowsiness, confusion, vertigo, convulsions, or tremors), cardiac dysrhythmias, and QRS widening are warnings of lithium toxicity. The lithium dosage should be reduced when an NSAID is prescribed.

Methotrexate. Chronic coadministration of NSAIDs and methotrexate have resulted in prolonged, elevated blood levels of methotrexate, resulting in severe toxicity. A possible mechanism may be the decreased renal perfusion caused by NSAIDS, decreasing the elimination of methotrexate.

Nonselective Cyclooxygenase Inhibitors

NSAIDs combine analgesia and anti-inflammatory effects with low abuse potential and much different side effects from those for the opioids. Oral NSAIDs can be as effective as PO opioids for mild to moderate pain. Parenteral NSAIDs are available in many countries (only ketorolac is available in the United States) but offer little advantage over their PO forms.[157] Different patients respond differently to both the effects and the side effects of different NSAIDs; some experimentation may be necessary to determine the best choice for a particular patient. No particular NSAID is proven superior for any indication. Drug selection should depend on availability, side effect profile, convenience, and cost. Patients at risk for adverse events using NSAIDs are listed in Box 186-4.

Ketorolac Tromethamine. Ketorolac is the first nonopioid analgesic agent available for parenteral use in the United States, but it is rarely indicated because 60 mg of ketorolac administered IM is not superior to 800 mg of PO ibuprofen, which is easier to administer at a fraction of the cost.[161-163] Ketorolac's main use is in the early treatment of renal colic (accompanied by a loading dose of IV morphine), a pain mechanism for which NSAIDs are particularly effective. If the patient can tolerate PO medication, 800 mg of PO ibuprofen is given instead.

Ibuprofen. Ibuprofen is the most widely used drug in the NSAID class. It is available over the counter in a variety of preparations, including tablets, liquid suspension, and sup-

Table 186-5 Risk of Serious Gastrointestinal Effects of Nonselective NSAIDs[149,150]

NSAID	RELATIVE RISK OF SERIOUS GI TOXICITY
COX-2 inhibitor	0.6
Ibuprofen	1.0
Diclofenac	1.8
Sulindac	2.1
Naproxen	2.2
Indomethacin	2.4
Tolmetin	3.0
Piroxicam	3.8
Ketoprofen	4.2
Ketorolac	24.7
Risk Reduction When Added to Ibuprofen[164]	
Proton pump inhibitor	0.09
Misoprostol	0.57

GI, gastrointestinal; NSAIDs, nonsteroidal anti-inflammatory drugs.

BOX 186-4 Patients at Risk for Adverse Events Using NSAIDs

1. Patients who are dehydrated or hypovolemic or who have impaired renal function are at increased risk for decreasing renal function or renal failure.
2. Patients with liver disease or congestive heart failure, in particular, those already taking ACE-inhibitors, ABRs, or diuretics, in whom liver or heart conditions may worsen.
3. Elder patients, particularly those at risk for GI and renal events.
4. Patients with asthma and known aspirin hypersensitivity are at an increased risk of bronchospasm.
5. Women in the third trimester of pregnancy. NSAIDs may prolong gestation or prematurely close the ductus arteriosus.
6. Patients who use tobacco or ethanol or who have a history of gastritis or peptic ulcer disease are at risk for peptic ulcer and GI bleed.

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; GI, gastrointestinal; NSAIDs, nonsteroidal anti-inflammatory drugs.

pository. Ibuprofen is rapidly absorbed in the upper GI tract and has minimal interaction with other medications. The adult analgesic dose is 400 mg, and the anti-inflammatory dose is 600 to 800 mg. No NSAID has been shown to be more effective as an analgesic than ibuprofen 400 mg, including ibuprofen 800 mg.[161,164,165]

COX-2-Specific Inhibitors

The discovery of two distinct cyclooxygenase isoenzymes (COX-1 and COX-2), one (COX-2) associated mostly with pain and inflammation, raised hope that an effective new class of analgesics could be developed. These would control pain and inflammation with fewer adverse effects (particularly GI mucosal injury) than traditional NSAIDs. Despite great initial promise, a dramatic pricing differential, and intensive marketing, the two classes of NSAIDs (nonselective COX inhibitors and selective COX-2 inhibitors) perform similarly in clinical use, with similar side effect profiles. Agents that selectively inhibit COX-2 are expected to cause less ulceration and have a lower risk of bleeding. COX-2 has been identified in normal gastric mucosa, however, and selective inhibitors may not confer any GI-protective advantage. COX-2 inhibitors may have prothrombotic effects from greater inhibition of prostacyclin than thromboxane, thus increasing the risk of cardiovascular events. COX-2 inhibitors also decrease renal perfusion, thereby decreasing renin activity and reducing sodium excretion by the same amount (approximately 20%) as NSAIDs.

No studies on COX-2 inhibitors' effectiveness in pain relief have been conducted in ED settings. COX-2 inhibitors are superior to placebo and equivalent to COX-1 inhibitors in treating acute postoperative dental pain, postoperative orthopedic pain, primary dysmenorrhea, and osteoarthritis. There are no studies comparing COX-2 inhibitors' efficacy in renal colic, biliary colic, acute gout, headache syndromes, sickle cell crisis, or acute musculoskeletal or soft tissue injury. COX-2 inhibitors should not be combined with NSAIDs because of their similar pharmacologic effects. COX-2 inhibitors have similar interactions as NSAIDs with ACE inhibitors, antihypertensive agents, anticoagulants, and lithium.

Given their price, potential for adverse cardiovascular events related to long-term use, and lack of superior safety or efficacy compared with nonselective NSAIDs, there is little or no role for COX-2 inhibitors in the ED or as a discharge prescription.

Skeletal Muscle Relaxants

Skeletal muscle relaxants are advocated as an adjunct to analgesics in the management of musculoskeletal pain with a "spasm" component, principally back pain. Despite the common use of skeletal muscle relaxants, relatively little data exist on their role in the treatment of pain. Studies show that muscle relaxants, such as cyclobenzaprine, are indistinguishable from ibuprofen in analgesic effect but have an increased side effect profile. Although a Cochrane Systematic Review claims that skeletal muscle relaxants are more effective than placebo with respect to relieving acute low back pain, it is not possible to discern any differential or additive effect to that of NSAIDs when the primary trials are reviewed.[166] These drugs have not been found to be of benefit in the treatment of chronic low back pain, which is their most common use.[167] Skeletal muscle relaxants should not be used in the management of acute musculoskeletal pain as a substitute for proper doses of effective analgesics unless there is a high degree of anxiety accompanying the pain, and an anxiolytic is felt to be helpful. In that case, a benzodiazepine, such as diazepam, 5 mg three times daily, may be an effective adjunct for pain control. Based on (a lack of) outcome benefit, there is no indication for the prescription or use of the other muscle relaxants shown in Table 186-6.

Table 186-6 Selected Muscle Relaxants and Mechanisms of Action

MEDICATION	MECHANISM
Baclofen	GABA agonist
Benzodiazepines	GABA agonist
Carisoprodol	Sedative
Chlorzoxazone	Sedative
Cyclobenzaprine	Tricyclic antidepressant (sedative)
Metaxalone	Sedative
Methocarbamol	Sedative
Orphenadrine	Antihistamine (sedative)
Tizanidine	Central alpha$_2$-agonist

GABA, γ-aminobutyric acid.

Benzodiazepines have hypnotic, anxiolytic, antiepileptic, and antispasmodic properties. Muscle relaxation is probably due to GABA-mediated presynaptic inhibition at the spinal cord level but has not been shown to be clinically relevant. Diazepam is the most commonly used benzodiazepine for muscle spasm.[167]

Nitrous Oxide/Oxygen Mixtures

Nitrous oxide/oxygen mixtures can be used in the ED or the out-of-hospital care setting to reduce anxiety in patients and to manage mild to moderate pain states. The analgesic and anesthetic properties of nitrous oxide were discovered more than 200 years ago. Combined with oxygen, a mixture of nitrous oxide and oxygen in a 50:50 ratio is safe when self-administered by the patient. This technique is one of the original forms of patient-controlled analgesia. Nitrous oxide and oxygen administered by nasal mask have long been used by dentists. Experience in emergency medicine with nitrous oxide/oxygen mixtures has been greatest in the ratio of 50:50 with self-administered hand-held masks.[168,169]

The actual mechanism of analgesia and anxiolysis is not fully delineated, but it is known to diffuse through tissue membranes and is poorly soluble in blood. In the two-tank self-administered system, a fixed-ratio nitrous oxide/oxygen mixture is delivered to the patient through a demand valve activated when the patient inhales through a face mask or mouthpiece. A pressure of 3 to 5 cm H_2O must be produced within the mask or mouthpiece to activate the flow of gas. This element provides safety for the patient-controlled aspects of the system since patients must initiate a breath and hold the mask to their face to receive the medication.

In 10 to 15% of patients, nitrous oxide is ineffective.[168] It is much more potent as an anxiolytic than as an analgesic agent. As with all analgesic agents, its success should be determined by the patient's subjective feedback. When necessary, nitrous oxide can be supplemented with other analgesics.

Nitrous oxide/oxygen mixtures are relatively or absolutely contraindicated in patients with a decreased level of consciousness who are unable to follow instructions, patients with a head injury, or those with decompression sickness. Patients with severe chronic obstructive pulmonary disease who retain CO_2 should be given nitrous oxide/oxygen mixtures carefully because the mixture contains 50% oxygen. Because nitrous

Table 186-7 Characteristics of Common Local Anesthetic Agents

AGENT	POTENCY (LIPID SOLUBILITY)	DURATION (MIN)	ONSET	COMMENTS
Procaine	1	60–90	Slow	Solutions of 0.5–2%, used in infiltration and blocks
Tetracaine	8	180–600	Slow	Topical in the eye
Lidocaine	3	90–200	Rapid	Most commonly used agent, 1.5 times as toxic as procaine
Mepivacine	2.4	120–240	Very rapid	Less potent than lidocaine, less toxic
Bupivacaine	8	180–600	Intermediate	Long acting, used in infiltration and blocks
Etidocaine	6	180–600	Rapid	Twice as toxic as lidocaine, used mostly in epidurals

Modified from Paris PM, Weiss LD: Narcotic analgesics: The pure agonists. In Paris PM, Stewart RD (eds): Pain Management in Emergency Medicine. Norwalk, Conn, Appleton & Lange, 1988.

oxide does diffuse into body cavities, it can worsen a pneumothorax or bowel obstruction.[56]

Minor side effects of the analgesic gas mixture are reported in 5 to 50% of patients. The most common adverse effect is light-headedness, with paresthesias and nausea reported less frequently. No documented adverse hemodynamic effects have occurred with the self-administered forms of this agent. This safety has also been confirmed in the out-of-hospital care setting.[170,171]

Side effects usually resolve within minutes of discontinuation. Chronic use or abuse of nitrous oxide is associated with vitamin B_{12} antagonism and secondary hematologic effects as well as development of a myelopathy.[172,173]

Nitrous oxide requires an effective scavenging and ventilation system to avoid accumulation and toxicity in health care workers, and this requirement has limited its use in EDs.

Local Anesthesia

Mechanism of Action

Peripheral nerves are responsible for transmitting pain information from the pain receptors to the spinal cord. Each fiber consists of an axon surrounded by a covering called the Schwann cell. A *myelinated* axon is one that is covered by the projection of a Schwann cell that wraps itself many times around the axon, which is called the *myelin sheath*.

Local anesthetics are much more effective at penetrating unmyelinated or lightly myelinated fibers than heavily myelinated ones. This differential explains the fact that ordinarily local anesthetic agents provide sensory block without a motor block (see Table 186-1).

Local anesthetic agents reversibly block the sodium channels of the lipid membrane and prevent the sudden influx of sodium ions into the axon, blocking depolarization and the action potential. After injection of a local anesthetic, tissue buffers increase the pH of the solution surrounding the agent, driving some of the water-soluble acidic form of the agent to its lipid-soluble nonionic form. The lipid-soluble phase of the drug is able to penetrate the lipid membrane of the axon where it then ionizes and enters the sodium channel, blocking the channel's ability to allow sodium to enter the cell.

Classes of Local Anesthetic Agents

Local anesthetic agents are chemical compounds that consist of an aromatic and an amine group separated by an intermediate chain. The class that has an ester link between the intermediate chain and aromatic portion is called amino esters and includes procaine, chloroprocaine, and tetracaine. Amides have an amide link and include lidocaine, mepivacaine, prilocaine, bupivacaine, and etidocaine. Esters are unstable in solution and are metabolized in the body by the plasma enzyme cholinesterase. The amides, after absorption into the body, are destroyed by enzymes in the liver.[174]

Specific Agents

Each local anesthetic has a predictable effect when used in appropriate doses and by the appropriate route. The main considerations in the clinical use of these agents are potency, duration of anesthesia, and the speed of onset (Table 186-7).

Potency. The ability of a local anesthetic drug to penetrate the lipid membrane of the axon determines its potency. Agents that have a high lipid solubility (e.g., tetracaine, etidocaine) are more potent than those with a low lipid solubility (e.g., procaine, mepivacaine). Less potent local anesthetics must be given in more concentrated forms and in larger doses to achieve an equivalent effect.

Duration of Anesthesia. Agents that bind well to protein in the sodium channel are longer acting and provide anesthesia of long duration. Tetracaine and bupivacaine have a high affinity for protein and provide long-lasting anesthesia, whereas procaine, which is poorly bound, does not.

Onset of Action. In most cases, it is helpful to have an anesthetic agent that acts quickly. The speed of onset of any local anesthetic agent is directly related to how quickly that agent, after injection, can diffuse through tissues to the nerve and through the nerve membrane. After injection, the agent is in two forms, ionized and nonionized. The amount of drug in the nonionized form is determined by its pK_a (the pH at which 50% of the solution is nonionized and 50% is ionized). Because only the nonionized form of the drug diffuses into the nerve, solutions with a low pK_a have a more rapid onset of anesthesia. Local anesthetic agents with higher pK_as take effect more slowly. At a tissue pH of 7.4, 5% of tetracaine (pK_a 8.5) is in the nonionized form compared with 35% of lidocaine (pK_a 7.9) solution. Low tissue pH (5 or 6) in surrounding infected tissue delays the onset of local anesthesia in situations such as abscess incision and drainage, because the anesthetic primarily remains in an ionized state. The onset of action of a local anesthetic can be hastened by the alkalinization of the solution carrying the drug, which also decreases its irritant effect (pain) on injection. This can be done by adding sodium bicarbonate solution to the anesthetic at a ratio determined by the pK_a of the agent (e.g., 1:10 for lidocaine).[175,176]

Several other factors influence the clinical performance of local anesthetic agents. In the clinical dosages used, these agents (except cocaine) are vasodilators, which tend to shorten the duration of anesthesia. Injection of the solutions into vascular tissues not only shortens the duration of anesthesia but also increases systemic absorption and the (small) chance of systemic toxicity. For these reasons, epinephrine is often added to local anesthetic solutions.

Allergy. Patients sometimes provide a history of allergy to local anesthetic agents, but it is usually not an immunoglobulin-mediated true allergy. Allergy to ester agents is most probably caused by the preservative methylparaben and its breakdown products. True allergy to the amide group is exceedingly rare. When allergy is reported, it is often caused by one of the preservatives used. Because the two groups do not cross-react, if a patient gives a history of allergy to an agent of one group, an agent from the other group can be used. In one study, 236 patients with reported adverse reactions to local anesthetics were tested using commercial preparations of unrelated local anesthetics. No patient exhibited systemic reactions.[177] In those patients who insist they are allergic to all "-caine" anesthetic agents, and the allergy is believed to be legitimate (a very rare circumstance), diphenhydramine can be used; 1 mL of a 50-mg/mL ampule can be diluted to 5 to 10 mL (1–0.5% solution) and can be used for local infiltration or nerve block. Diphenhydramine may cause direct tissue toxicity and should be avoided when possible in areas with poor collateral circulation.[178,179]

Local and Systemic Toxicity

Local Toxicity. Local anesthetic agents are directly toxic to tissue, depending on the concentration. Some investigators have claimed that the use of a vasoconstrictor in the anesthetic solution produces a reduction in blood flow that increases the wound healing time and the vulnerability of the wound to infection, but this has never been demonstrated.

Nerve blocks are preferable to local infiltration for wounds that are extensive or contaminated. Epinephrine-containing solutions have traditionally been avoided on digits, the penis, ears, or the nose. Literature, however, suggests that dilute epinephrine can be used safely on digits and possibly these other areas as well.[180] A comprehensive review of the use of epinephrine in digits concludes that it is safe when diluted to 1:200,000 or less, but it should not be used in patients with vascular disease.

Systemic Toxicity. Systemic toxicity of local anesthetics occurs when a sufficient quantity of the drug accumulates in the body so that sodium channel blockade occurs in the heart or the brain. There is a dose-related clinical progression of local anesthetic toxicity from subtle neurologic symptoms to seizures to cardiovascular collapse.

All local anesthetics produce systemic toxicity at sufficiently high blood or CNS concentrations. Each local anesthetic has a range of therapeutic safety, beyond which systemic toxicity is more likely to occur. Table 186-8 provides a guideline to safe doses that can be administered for local anesthesia. Overdosage may occur more commonly in patients with large wounds and in very small patients. The more lipophilic agents (e.g., etidocaine, bupivacaine) are more cardiotoxic. Cardiac toxicity may also be increased for epinephrine-containing anesthetics when inadvertent IV injection occurs. Special care should be exercised in children and when performing certain blocks known to produce high blood levels of the anesthetic agent (e.g., intercostal). In pediatric patients, total dose guidelines are important, and the maximum dose should be calculated before administration.

A wide variety of symptoms may be experienced from local anesthetic toxicity. These include light-headedness, headache, paresthesias, tinnitus, decreases in the level of awareness, and muscle spasm.[181] The degree to which CNS symptoms are experienced is directly related to the blood level of the local anesthetic. At the extreme, CNS toxicity may result in seizures. The clinical progression usually begins with a circumoral paresthesias, dysarthria, and a report of tinnitus or a similar auditory phenomenon, followed by a decreased level of consciousness and progressing to confusion, seizures, and coma. Longer-acting, more potent agents (e.g., bupivacaine and etidocaine) are more likely than lidocaine to cause CNS symptoms at lower blood levels.[181] Local anesthetic-induced seizures should be treated with IV benzodiazepines. Local anesthetic agents also have direct effects on cardiac automaticity, conductivity, contractility, and vascular tone. In animal experiments, the cardiac toxicity of bupivacaine is commonly seen before the CNS toxicity, and this toxicity is exacerbated by epinephrine.

Management of cardiovascular collapse caused by toxic levels of local anesthetic agents should follow standard advanced cardiac life support guidelines. Unless the overdose is massive, the toxicity should be relatively short-lived because of the redistribution of the lipophilic agents.

Table 186-8 Guidelines for Maximum Doses of Commonly Used Local Anesthesia Agents*

AGENT	WITHOUT EPINEPHRINE	WITH EPINEPHRINE
Lidocaine HCl†	3–5 mg/kg	7 mg/kg
Mepivacaine HCl	8 mg/kg	7 mg/kg‡
Bupivacaine HCl§	1.5 mg/kg	3 mg/kg

*All maximum doses should be reduced 20–25% in very young, old, and very sick patients.
†A lidocaine level of 0.5–2.0 µg/mL may be reached for every 100 mg of lidocaine infiltrated for blocks.
‡Epinephrine adds to the potential cardiac toxicity of this drug.
§Not to be used for pudendal blocks or intravenous regional anesthesia. Not recommended for children younger than 12 years old.
Adapted from Stewart RD: Local anesthesia. In Paris PM, Stewart RD (eds): Pain Management in Emergency Medicine. Norwalk, Conn, Appleton & Lange, 1988.

BOX 186-5 TECHNIQUES THAT CAN BE USED TO REDUCE THE PAIN OF INJECTION

Buffering of local anesthetic agents
Counterirritation
Slowing rate of injection
Use of topical anesthetics
Warming solution
Distraction techniques

Reducing the Pain of Injection

Counterirritation by scratching, jiggling, or repetitively pinching the skin during needle puncture or injection reduces discomfort[182] (Box 186-5). The addition of sodium bicarbonate to lidocaine immediately before injection significantly reduces patient discomfort.[175] A standard solution of sodium bicarbonate (8.4% in 50 mL) can be added to a syringe containing lidocaine in a ratio of 1:10 (e.g., 1 mL bicarbonate to 10 mL lidocaine, or 0.5 mL to 5 mL). Buffered lidocaine can be stocked in the ED and is effective for up to 1 week.[183] Bupivacaine can also be buffered, but the ratio should be 1:50 (i.e., 0.1 mL bicarbonate to 5 mL bupivacaine). Slow injection attenuates pain of infiltration to a greater degree than buffering of the solution.[184] Injection of local anesthetic into the edges of the laceration is less painful than injection through intact skin surrounding the wound.[185] When time permits, warming the anesthetic or the application of a topical anesthetic agent can also greatly decrease the initial sensation associated with needle injection.[176]

Topical Anesthesia

Topical anesthetics are generally of two types: those that can be applied to intact skin and those used on open skin. The agents are absorbed and exert their anesthetic effect on adjacent superficial nerves. The topical application of local anesthetics must be done with just as much caution as used with injected anesthetics to avoid systemic toxicity. The dose of topical anesthetic should be monitored to avoid applying doses associated with toxicity. As with injectable local anesthetic agents, topical solutions are often described in terms of percent of agent; 1% equals 10 mg/mL of anesthetic, and 5% solution has 50 mg/mL.

Topical agents are particularly useful in children and in patients who are afraid of needles. They don't provide anesthesia to the same degree as SC infiltration or nerve blocks but provide a substantial decrease in the intensity of superficial stimuli. The long application time necessary for effective analgesia can be a principal drawback of these agents; however, in some patients the ritual of applying the topical anesthetic and delaying the procedure until there will be less pain can be an effective tool in controlling pain and the response to subsequent interventions.

Topical Anesthetics Applied to Intact Skin

Eutectic Mixture of Local Anesthetics. Eutectic mixture of local anesthetics (EMLA) is a mixture of lidocaine and prilocaine in an alkaline oil mixture in which the anesthetics occur primarily in their nonionized form, allowing them to diffuse through the skin. The term *eutectic* refers to mixtures that result in a melting point higher than that of either agent alone. The mixture should be applied on the desired area with an occlusive dressing 30 to 60 minutes before the desired procedure is performed. Heating the EMLA for 20 minutes improves analgesia but is less effective than a routine 60-minute application with or without heat.[186] The duration of action after a 60-minute application is 1 to 5 hours. Indications for the use of EMLA include venipuncture, arterial puncture, lumbar puncture, or arthrocentesis when a 30- to 60-minute delay in performing the procedure is not an impediment. EMLA can be applied in triage, particularly for pediatric patients, whose IV can then be started later in the ED with little or no pain.

Ethyl Chloride and Fluori-Methane sprays. Ethyl chloride and fluorimethane sprays are occasionally used for superficial analgesia. The agents evaporate quickly and cool the skin, providing brief (<1 minute) local anesthesia due to the cold. The induced analgesia is brief, and any injection or incision should be made immediately after the application of the agent causes a brief "frosting" effect in which the skin blanches white.

Agents Applied to Mucosal Surfaces

Cocaine. This agent is unique among local anesthetic agents because it is a potent vasoconstrictor in addition to being an anesthetic and can be applied to mucosal surfaces. It is frequently used in the nose, where a 4% (40 mg/mL) solution provides rapid anesthesia for the treatment of epistaxis and other procedures on the nose. Although the maximum safe dose is unknown, more than 200 mg should not be exceeded in adults. Cocaine should not be used in patients with known coronary artery disease because it may cause coronary artery vasoconstriction.

Lidocaine. Both 2 and 4% solutions of this drug are available in a viscous matrix for use on mucosal surfaces. It can be used in nasal procedures, including the passing of nasogastric tubes and gastric lavage tubes. It can be used for urethral anesthesia during Foley catheter placement as well, but to be effective it must be injected into the urethra with a catheter-tip syringe and be in contact with the area for 5 to 20 minutes. Lidocaine spray (4%) decreases the discomfort of nasogastric tube insertion. Lidocaine spray (4 or 10%) is useful for upper airway anesthesia, including intranasal use.

Tetracaine. This potent ester is used for surface anesthesia of the cornea. It stings when placed in the eye, but only for 10 to 15 seconds, after which there is profound corneal anesthesia.

Benzocaine. Almost insoluble in water, benzocaine remains on mucous membranes in the mouth and is used commonly to provide superficial analgesia for oral procedures and pain.

Agents Applied to Open Skin

Tetracaine, Adrenaline, and Cocaine. The combination of tetracaine, adrenaline (epinephrine), and cocaine (TAC) was popular in the past but has been largely replaced with lidocaine, epinephrine, and tetracaine (LET), which does not contain cocaine. Between 5 and 10 mL of this combination of agents is applied to the open wound using sterile cotton, which is then covered and held in place for 10 to 20 minutes. Anesthesia has been described in approximately 85% of cases of wounds of the scalp and face and a lower percentage of extremity wounds.[187] Application of the solution to mucous membranes (eye, intranasal) can result in toxic blood levels of both tetracaine and cocaine and should be avoided.[188]

Lidocaine, Epinephrine, and Tetracaine. LET is as effective and less expensive than TAC.[189,190] To account for the 20-minute onset, one study showed success when the application was administered at the time of triage in children with a simple laceration.[191]

Intravenous Regional Anesthesia (Bier Block)

The IV regional anesthesia procedure known as Bier block is an effective and rapid technique to anesthetize extremities for fracture reduction or repair of extensive wounds. The method involves the IV injection of a local anesthetic agent (lidocaine, prilocaine) into a previously exsanguinated limb. This procedure has been adapted for use in the ED in the form of a minidose of 100 mg of lidocaine and is described in procedure manuals. A safe alternative is to use the relatively nontoxic local anesthetic agent prilocaine.

Nonpharmacologic Interventions

Transcutaneous Electrical Nerve Stimulation

TENS systems uses electrical stimulation to induce analgesia, likely through the activation of descending sensory pathways and modulation of nociceptive signals at the level of the spinal cord. TENS units include a pulse generator, amplifier, and electrodes. Studies show varying degrees of effectiveness, and the devices are rarely, if ever, indicated for use in the ED.[192,193]

Hypnosis

The induction of hypnosis allows patients to refocus attention away from pain and anxiety-producing stimuli to other images and feelings. Hypnosis can be used as an adjunct to pharmacologic interventions or, in some cases, as a substitute. Hypnosis can be induced with only brief interventions on the part of the clinician.[194,195] Hypnosis is usually not possible in the ED because of time constraints and distracting ambient noise.

Pain Management in Children

Pain in children is both more difficult to assess and more challenging to treat. When used properly, most of the interventions described in this chapter can be used in children. The same general principles that apply to providing analgesia to adults apply to children. The major difference in providing analgesia to children is the difficulty of accurately assessing the perception of pain, particularly in the very young.[196]

The general approach to a child can be important in developing a trusting relationship with both child and parent. Both verbal and nonverbal cues from the child and parents must be observed and appreciated, taking into account the unique developmental aspects of each age group. Threatening equipment should be de-emphasized (e.g., syringes, scissors, and suture holders should be kept out of sight of the child). Play therapy and a slow, friendly, nonthreatening manner can be helpful. The decision to separate children from their parents must be individualized but should be avoided when possible. Parents can help distract the child and reinforce the suggestions of the medical team.[197]

Most of the principles relating to the pharmacokinetics of drugs, including absorption, distribution, and elimination, are similar for children and adults. In neonates and infants younger than 3 months old, opioid clearance is delayed, plasma drug levels are higher due to decreased protein binding, and the blood-brain barrier is immature and more permeable to opioids. Opioids must be given carefully to this age group and at smaller weight-based doses than used in older children. Neonates also require smaller doses of local anesthetics due to decreased protein binding and slower metabolism. For mild pain, acetaminophen can be very effective in doses of 15 mg/kg PO or 20 mg/kg PR every 4 hours. Sucrose solutions have been shown to be effective agents in this age group, 25% applied to a pacifier and given PO.

Pain Management in Elder Patients

Approximately 80% of elder patients have at least one chronic ailment commonly associated with pain.[198] Elders are more sensitive to analgesics, especially opioids, and reduced dosing achieves adequate analgesia while avoiding side effects. Opioids, even in conservative doses, may produce sedation, confusion, or constipation, and the patient and caregivers should be alerted to this possibility. NSAIDs are used in reduced doses or avoided altogether because of their potential for adverse effects on GFR.

The assessment of pain in elder patients can be complicated by depression, dementia, and atypical patterns of pain presentation.[199] As with children, careful attention must be paid to the assessment of pain in the elderly due to communication barriers.

Out-of-Hospital Analgesia

Out-of-hospital providers frequently encounter patients with painful conditions, and patients obtain pain relief more quickly when pain medications are started by out-of-hospital personnel,[200] but pain control in the out-of-hospital setting is challenging to perform adequately.[201-203] Protocols for the administration of fentanyl and morphine exist in most EMS systems and are usually limited to single-dose therapy prior to obtaining orders from the medic control physician.[204] No difference in the relative value of using fentanyl or morphine is found.[205]

The out-of-hospital environment is less controlled than the ED, and the information about a patient's underlying condition is more limited, making the safe administration of pain medications more difficult. As in the ED, establishing rapport with the patient, providing calm reassurance, and using careful movement and handling, including proper splinting, are the first steps to which pharmacologic support can be added. Pain can be assessed in the out-of-hospital setting using numerical and verbal rating scales as it would in the ED.[206]

Unfortunately, moderate to severe pain is treated infrequently in the out-of-hospital environment.[207,208] The study of lower extremity or hip fractures shows that only 18% of patients received an analgesic.[209] Another study of suggested extremity fractures shows that despite a protocol allowing the use of either morphine sulfate or nitrous oxide, among 1073 patients, analgesia was administered to only 18 patients (1.8%). The National Association of EMS Physicians encourages the increased use of analgesics in the out-of-hospital environment.[210] Self-administered 50% nitrous oxide offers many advantages for use in the field. Morphine 0.05 mg/kg is a safe dose for out-of-hospital use and should be considered the first-line agent for severe pain.[211]

TREATMENT ENDPOINTS

Pain is a subjective experience, and using pain relief as the endpoint of treatment results in a subjective marker of treatment success or failure. In the ED, management of acute pain should target a specific desired endpoint; for example, reduction of the patient's self-reported pain score to 3 or less, or by 50% of the starting level. Pain medication, usually IV opioids, is ordered by frequent titration to reach that specific endpoint, usually with a caveat regarding total dose that might prompt a reorder. For example, "morphine sulfate 10 mg IV loading dose, then morphine sulfate 5 mg IV every 10 minutes until the patient reports pain as 3/10 or less. Please notify me if more than 30 mg administered in any 60-minute period." This allows the nurse to titrate the medication to the patient's pain and to feel comfortable that he or she knows when to alert the clinician that the patient is requiring larger than anticipated doses. Pain orders that are wide-ranging or vague should be avoided, because they frequently lead to underdosing and inadequate pain relief. An example of such an order is "morphine sulfate 6 mg IV now, and repeat 2 to 6 mg IV every 20 to 40 minutes as needed for pain."

KEY CONCEPTS

- Patient pain should be rapidly relieved and frequently reassessed in tandem with diagnostic evaluations.
- Titrated IV opioid analgesics are the principal therapeutic approach to the treatment of moderate and severe acute pain; the IM route has several disadvantages and is not recommended.
- Morphine, fentanyl, and hydromorphone are the preferred agents for the majority of opioid indications in the ED.
- There is no validity to the belief that morphine causes more smooth muscle spasm than other opioids and should be avoided in patients with biliary or renal colic.
- Topical and local anesthetics can be used to treat pain associated with the majority of ED procedures and should be considered for use in all isolated painful conditions.
- Low tissue pH (5 or 6) in infected tissue delays the onset of local anesthesia.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 187

Procedural Sedation and Analgesia

David Burbulys and Kianusch Kiai

PERSPECTIVE

The performance of painful diagnostic and therapeutic procedures is common in emergency care. Many of these are associated with significant anxiety, especially in children.[1,2] Procedural sedation and analgesia (PSA) has therefore become a fundamental and required skill for emergency physicians and an integral part of the core training of emergency medicine residents.[3-5]

PSA improves the quality of patient care and satisfaction through relief of pain and anxiety and by facilitating the success of therapeutic or diagnostic procedures.[5,6] These include fracture or joint reduction, incision and drainage of abscesses, cardioversion, tube thoracostomy, lumbar puncture, complex wound repair and imaging studies in young or uncooperative patients.

Many of the agents used for PSA have the potential to cause significant respiratory, cardiovascular, or central nervous system (CNS) depression.[7-15] The Joint Commission, the American College of Emergency Physicians, and the American Society of Anesthesiology have produced expert consensus or evidence-based documents concerning its use.[2,5,6,16] With the advent of these guidelines, PSA has become a safe, common, and practical emergency department (ED) procedure. This has been further improved by the development of shorter-acting, more effective drugs and the utilization of noninvasive monitoring devices.

With the wide variety of procedures and patient populations, the ability to individualize PSA and maximize the risk-benefit ratio for each unique situation is a necessary skill. This can be best achieved through a detailed understanding of: the preprocedural patient assessment, the protocols delineating the required personnel and their roles, the supplies and equipment required, the specific drugs used (including their routes of administration, dosages, effects, interactions, and complications), consideration for special populations and patient monitoring, recovery, and discharge criteria.

Terminology

Anxiolysis is a state of decreased apprehension concerning a particular situation in which the patient's level of awareness does not change.

Analgesia refers to the relief of pain without the intentional alteration of mental status, such as occurs in sedation. An altered mental state may be a secondary effect of the medications administered for this purpose.

Dissociation is a trancelike cataleptic state induced by an agent such as ketamine and characterized by a profound analgesia and amnesia. Protective reflexes, spontaneous respirations, and cardiopulmonary stability are retained.

Sedation is a controlled reduction of environmental awareness.

Procedural sedation and analgesia is a technique of administering a sedative or dissociative agent, usually along with an analgesic, to induce a state that allows the patient to tolerate unpleasant procedures while maintaining adequate spontaneous cardiorespiratory function. It is intended to result in a depressed level of consciousness that allows the patient to maintain oxygenation and airway control independently and continuously. The drugs, doses, and techniques used are not likely to produce a loss of the protective airway reflexes.[6]

Prior terminology defined three levels of sedation: conscious sedation, deep sedation, and general anesthesia. The term *conscious sedation* was often misinterpreted, confusing, and imprecise. It was coined in 1985 to describe lightly sedated dental patients.[14,17,18] It was then further incorporated into pediatric sedation guidelines to distinguish an easily arousable level of sedation from the more advanced techniques of deep sedation, in which patients are difficult to arouse, or general anesthesia, in which patients are not arousable. Despite the focused intent of these definitions, practitioners quickly labeled all levels of procedural sedation taking place outside the operating room as "conscious sedation."

In 2001, The Joint Commission adopted the American Society of Anesthesiologists (ASA) definition of sedation and analgesia that was created in 1999 to better describe the continuum of sedation and analgesia (Fig. 187-1). Although this truly is a continuum, the ASA divided PSA into four distinct subgroups. These include minimal sedation, moderate sedation, deep sedation, and general anesthesia. A fifth category, dissociative sedation, has since been added. This new nomenclature is more intuitive, clear, and logical.

Minimal sedation (anxiolysis) is a drug-induced state during which patients respond normally to verbal commands. Although cognitive functions and coordination may be impaired, ventilatory and cardiovascular functions are unaffected.

Moderate sedation (formerly called "conscious sedation") refers to a drug-induced depression of consciousness during which patients respond purposefully to verbal commands, either

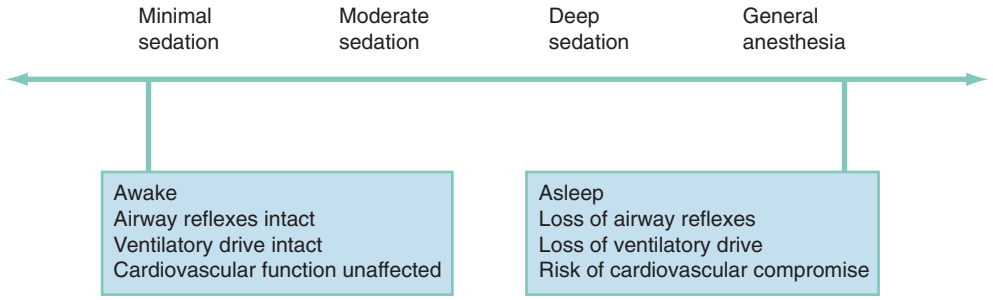


Figure 187-1. Schematic representation of the sedation continuum. As increasing doses of nondissociative agents are given, patients move along the sedation continuum, experiencing a progressive decline in their level of consciousness and an increased risk of adverse respiratory and cardiovascular events. If medication administration continues, the patient will ultimately reach a state of general anesthesia with loss of protective airway reflexes and ventilatory drive. The transition from one level of sedation to the next is often difficult to predict and varies from patient to patient.

Table 187-1 American Society of Anesthesiologists Physical Status Classification

CLASS	DESCRIPTION	EXAMPLES	SEDATION RISK
I	Normal and healthy patient	No past medical history	Minimal
II	Mild systemic disease without functional limitations	Mild asthma, controlled diabetes	Low
III	Severe systemic disease with functional limitations	Pneumonia, poorly controlled seizure disorder	Intermediate
IV	Severe systemic disease that is a constant threat to life	Advanced cardiac disease, renal failure, sepsis	High
V	Moribund patient who may not survive without procedure	Septic shock, severe trauma	Extremely high

alone or accompanied by light tactile stimulation. Reflex withdrawal from the painful stimulus is not considered a purposeful response. No interventions are required to maintain a patent airway, and spontaneous ventilation is adequate. Cardiovascular function is always maintained.

Dissociative sedation is a trancelike cataleptic state induced by the dissociative agent ketamine and characterized by profound analgesia and amnesia, while protective airway reflexes, spontaneous respirations, and cardiopulmonary stability are maintained.

Deep sedation describes a drug-induced depression of consciousness during which patients cannot be easily aroused but respond purposefully after repeated or painful stimulation. The ability to independently maintain ventilatory function may be impaired. Patients may require assistance in maintaining a patent airway, and spontaneous ventilation may be inadequate. Cardiovascular function is usually maintained.

General anesthesia is a drug-induced loss of consciousness during which patients are not arousable even by painful stimulation. The ability to independently maintain ventilatory function is often impaired. Patients often require assistance in maintaining a patent airway, and positive-pressure ventilation may be required because of depressed spontaneous ventilation or drug-induced depression of neuromuscular function. Cardiovascular function may be impaired.[6,14]

The progression from minimal sedation to general anesthesia truly is a dynamic continuum that lacks distinct separation between stages. The transition from one level of sedation to the next is often difficult to predict and varies from patient to patient. The sedation continuum is not drug-specific, and levels from mild sedation to general anesthesia can be achieved with virtually all of the PSA agents. Because of this, it is recommended that clinicians administering PSA be competent in the skills required to treat patients in a least one level greater than the intended level of sedation.

Approach to Procedural Sedation and Analgesia for Procedures

Patient Assessment

To date, no outcome-based studies have demonstrated clear benefit from extensive evaluation beyond vital signs, mental status, and airway and cardiopulmonary assessment prior to PSA.[19] Despite this, consensus guidelines suggest that an increased risk of adverse events may exist in select subsets of patients. These include the extremes of age, patients with difficult facial or neck anatomy or any other reason for potential intubation or bag-valve-mask ventilation difficulty, and patients with underlying significant disease states. A patient's general physical status is conventionally categorized according to the ASA's classification system (Table 187-1). Most practice guidelines require that a history and focused physical examination be performed and documented prior to PSA. There is no literature to support the need for routine diagnostic testing other than diagnostic testing driven by the patient's current status, including comorbidities.

The patient's age; current illness or injury for which the PSA is intended; underlying medical problems (comorbidities); previous experiences or problems with PSA or general anesthesia; drug allergies and current medications; and tobacco, drug, and alcohol use are reviewed and recorded. A directed physical examination focuses on the vital signs, the heart and lungs, and evaluation of the airway for potential difficulty providing bag-valve-mask ventilation or intubation.

A discussion including the risks, benefits, and potential side effects of PSA should take place with patients or their families before the procedure. Written consent is obtained, unless this is not possible. Patient selection is important to the safety of the sedation. Not every patient is an appropriate candidate for PSA in the ED. Depending on the clinical circumstances, a patient with an anticipated difficult airway or an ASA classification of III or IV may require consultation with an anesthesiologist. It may be advisable in some cases to have the anesthesiologist perform the sedation or to undertake the

procedure in the operating room under more controlled circumstances.

Preprocedural Fasting

The need for preprocedural fasting in PSA remains controversial. Currently the ASA recommends a period of 2 hours following ingestion of clear liquids and a period of 6 hours following the ingestion of other liquids or solids prior to PSA, but there are no outcome studies to support these recommendations. These guidelines are based on expert consensus and extrapolated from data describing circumstances when patients received sedation to the level of general anesthesia followed by the manipulation of their airway during intubation and extubation.[20] PSA in the ED attempts to avoid both of these specific situations.

Many studies fail to support the notion that gastric emptying has any effect on the incidence of complications or outcome with PSA.[20-29] There have been no published studies demonstrating an increased risk of aspiration following a liquid or solid meal and no studies showing a benefit of fasting prior to PSA. In one prospective observational study of more than one thousand children, no differences with airway complications, emesis, or other adverse effects were observed between various groups of patients classified by their preprocedural fasting status.[27] During PSA, the combination of vomiting and the loss of the airway protective reflexes is an extremely rare occurrence. Furthermore, most episodes of vomiting and aspiration occur during airway manipulation, which is also very unlikely to occur during PSA. The issue of the risk of free reflux during deep sedation has not been well studied.

Although recent food intake is not a contraindication for administering PSA, risks of pulmonary aspiration and the benefits of providing PSA are weighed in accordance with the needs of each individual patient.[5,30] Some procedures, such as reduction of a dislocated joint, should not be delayed for consideration of fasting status, while others, such as abscess drainage, are not as time-sensitive, and the sedation plan can be adapted accordingly.

Personnel

The Joint Commission and most institutional policies suggest that PSA providers have: adequate training to administer the agents effectively and safely, the skills to monitor the patient's response to the medications given, and the expertise needed to manage all potential complications.[6] This generally implies that PSA in the ED must be supervised by an emergency physician or other appropriately trained and credentialed physician. It is also recommended that a qualified support person (nurse, respiratory therapist) be present for the continuous monitoring of the patient. Such support persons should focus on the patient's status and not take part in the procedure. They should also be able to recognize and respond to the complications of PSA. They may assist with minor, interruptible tasks; however, they should have no other responsibilities that would interfere with the level of monitoring and documentation appropriate for the planned level of sedation. They should be free to monitor the patient from the start of the procedure through the completion of the recovery phase.[6]

Supplies and Equipment

Procedural sedation and analgesia may result in an allergic reaction, oversedation, respiratory depression, or, rarely, cardiopulmonary arrest. The incidence of these complications depends on patient selection, the drugs used, the rate and dosage of administration, and specific patient sensitivities. Consequently, appropriate equipment to monitor the patient's condition at all times; to manage airway complications, allergic reactions, and drug overdoses; and to treat respiratory or cardiopulmonary arrest should be readily available. Supportive equipment must include oxygen, suction, patient-monitoring devices, basic and advanced airway management equipment, a monitor/defibrillator/pacer, advanced life support medications, reversal or rescue agents, and vascular access equipment (Box 187-1).

BOX 187-1 Equipment for Procedural Sedation and Analgesia

In the Room:
- High-flow oxygen source
- Suction
- Airway management equipment
- Monitoring equipment
  - ECG monitor*
  - Pulse oximeter
  - Blood pressure monitor
  - Capnography*
- Vascular access equipment
- Reversal agents
- Adequate staff

Readily Available:
- Defibrillator
- Resuscitation drugs

*Suggested, not required
ECG, electrocardiogram.

In most situations, the agents used for PSA in adult patients should be administered intravenously. Nearly all adults undergoing PSA in the ED should therefore have an intravenous (IV) line placed prior to the procedure. This need in children is less clear and depends on the presence of comorbid conditions and the choice and route of drug to be administered. If the procedure is likely to be lengthy, or if multiple doses of drugs will be needed, an IV line should be considered.

The requirement for supplemental oxygen, and its benefits during PSA, have not been well studied and remain somewhat controversial. Supplemental oxygen may prevent hypoxemia in many patients; however significant respiratory depression in these patients may not be detected because of their normal oxygen saturation. This may delay the recognition of respiratory compromise and hypercarbia.[31-34] On the other hand, transient hypercarbia is not harmful, and maintenance of adequate oxygen saturation is much more important. The use of capnography eliminates this issue, because ventilatory status is displayed continuously (see following section). Because there are little scientific data to guide the clinician, the use of supplemental oxygen should be in accordance with institutional protocols and at the discretion of the treating physician. In general, though, there is little to advise against the use of supplemental oxygen when administering PSA to a patient in the ED.

Monitoring

The most important aspect of monitoring during PSA is the visual observation and assessment of the patient. The patient's ability to follow commands in response to varied levels of stimulation is useful in quantifying the level of consciousness. Furthermore, the patient's ventilatory status may be readily

evaluated by direct observation. Other components of monitoring, which should be documented, include respiratory rate, heart rate, blood pressure, oxygen saturation, and perhaps cardiac rhythm and capnometry.[35-43] Pulse oximetry is a reliable and important monitoring adjunct, but it does not obviate the need to observe the patient.

There is no evidence that cardiac monitoring during PSA is of any benefit.[44,45] In older patients, or in those with a history of cardiovascular disease, hypertension, or dysrhythmia, the use of continuous electrocardiographic monitoring is advised. In young healthy patients without underlying significant disease this may be safely replaced by continuous pulse oximetry, which also displays the heart rate. Nevertheless, given the wide availability, continuous electrocardiographic monitoring is commonly used for all patients by protocol.

Capnometry or capnography measures end-tidal CO_2 partial pressure and may be useful to detect cases of inadequate ventilation earlier than with oximetry and prior to the onset of hypoxemia. Several studies have demonstrated this, but none have shown an effect on outcome to date.[30-32,35-37,39-43,46-51] Although the benefit of adding capnometry to oximetry and visual monitoring remains unclear, it is well described in the anesthesia literature and may be considered useful when direct patient observation is difficult or impossible or when supplemental oxygen is being administered. Capnography should be used when deep sedation is planned, as respiratory depression is common in patients undergoing deep sedation.

The Bispectral index (BIS) is monitored via a noninvasive device attached to the patient's forehead and derives a depth of sedation level via frontal lobe electroencephalographic measurements. It has been used in the operating room as an objective measure of sedation depth.[52-59] Studies have shown that it may be beneficial in preventing oversedation in PSA and reducing the time to discharge. These investigations have also suggested that its use may better guide the depth of sedation endpoint than traditional sedation scales have, and it may have further benefit for PSA in children as they frequently require deeper levels of sedation to prevent movement.[60-64] Early ED studies for its use in PSA to discriminate between mild-to-moderate and moderate-to-deep levels of sedation have not been reliable nor has it been shown to be predictive of patients sedated to the point of general anesthesia from those with lesser degrees of sedation.[58,65-72] BIS monitoring may have a beneficial role for emergency medicine use and PSA in the future, but requires more investigation before its possible uses and benefits can be completely defined.

If it is necessary to transfer the patient outside the ED, every attempt should be made to provide the same level of monitoring during the transport that was used within the department.

The highest risk of serious adverse events generally occurs within 5 to 20 minutes of receiving the last dose of IV medication and at the completion of procedures, when the patient remains sedated but is no longer receiving the painful stimulus.[9-13,73,74] Patients should continue to be monitored most closely at these times, and this should continue until clinical recovery has occurred (see following section).

Recovery

Monitoring as part of the PSA routine should continue until patients are spontaneously awake and able to function independently, even though they may not be completely back to baseline function or ready for discharge. Drowsy patients should not be left unattended, particularly when they are in other areas of the hospital. If patients are transported out of the ED before they have completely returned to baseline function, a trained caregiver with appropriate monitoring equipment and resuscitative supplies must accompany them.

Discharge Criteria and Instructions

Prior to discharge, a normal mental status and baseline cognitive and motor function should be achieved. The patient should be able to follow commands, speak clearly, and ambulate or sit unassisted (infants). Vital signs and respiratory status should be back to baseline and within normal limits. Residual pain should be addressed. Nausea should be minimal, and vomiting should be resolved. It is preferable that all patients, including adults, be sent home with a responsible adult, but if this is not possible, the patient must remain in the ED until normal baseline has been achieved.[73]

Patients should be advised not to drive or participate in other dangerous activities for 12 to 24 hours. Despite the short clinical duration of most of the agents used, many people may exhibit subtle signs of cognitive deficits and mild drowsiness. It is therefore preferable that they be accompanied by a responsible adult at home for 4 to 8 hours. For children, light play at home should be the extent of activities with no bicycle riding, swimming, or other complex motor activity until the next day. An antinauseant and progressive diet is helpful if nausea or vomiting is experienced. Standard discharge instructions should also be provided for the presenting complaint and all should be instructed to immediately return if any confusion or respiratory symptoms arise.

Pharmacology

In selecting agents, one must consider the effects desired, the risks and benefits, and the logistics of administration for each situation. The ideal agent would provide analgesia, anxiolysis, amnesia, and somnolence. It would have a rapid onset and offset with predictable results and have no adverse effects. This agent, of course, does not exist.

When the procedure is unpleasant, but not painful (e.g., endoscopy), pure sedation may be the desired endpoint, and agents such as benzodiazepines, barbiturates, etomidate, or propofol sometimes are used alone. These agents do not provide pain relief and should not be used as the sole agent when pain management is also desired. Analgesic agents such as opioids or nitrous oxide are often added to a sedative agent to provide analgesia for painful procedures. Ketamine, on the other hand, may be an excellent single drug choice for painful or stimulating procedures in children and for some adult applications (e.g., fracture reduction). Usually, a combination of analgesic and sedative agents is required. One must be cautious as their side effects are frequently potentiated.

The specific agents for PSA and dosage recommendations for adult patients are provided in Table 187-2 and for pediatric patients in Table 187-3. Benefits and adverse effects are provided in Table 187-4. Individual agents are discussed in greater detail in the following sections.

Route of Administration

Route of administration should also be determined by the procedure and the specific patient. In most situations, IV titration to the desired level of sedation and analgesia provides the safest, most rapid, and most predictable results. Drugs given by the intramuscular (IM), oral (PO), transmucosal (TM), intranasal (IN), or rectal (PR) route generally have a slower onset of action, are difficult to titrate, have unpredictable results, and may lead to prolonged sedation. These routes are virtually never used for PSA in adults. In children, however,

Table 187-2 Procedural Sedation and Analgesia Agents—Recommended Adult Starting Dosages

AGENT	CLASS	MAIN EFFECT	ROUTE	USUAL STARTING DOSE
Fentanyl	Opioid	Analgesia	IV	1 µg/kg
Morphine	Opioid	Analgesia	IV	0.1 mg/kg
Midazolam	Benzodiazepine	Sedation Amnesia	IV	0.05 mg/kg
Methohexital	Barbiturate	Sedation Amnesia	IV	1 mg/kg
Pentobarbital	Barbiturate	Sedation Amnesia	IV IM	2 mg/kg 4 mg/kg
Ketamine	Phencyclidine derivative	Dissociation Analgesia Sedation Amnesia	IV IM	1–2 mg/kg 4–5 mg/kg
Etomidate	Imidazole derivative	Sedation Amnesia	IV	0.1 mg/kg
Propofol	Alkylphenol derivative	Sedation Amnesia Antiemetic	IV	0.5 mg/kg
Nitrous oxide	Anesthetic gas	Analgesia	Inhaled	30–70%

IM, intramuscular; IV, intravenous.

Table 187-3 Procedural Sedation and Analgesia Agents—Recommended Pediatric Starting Dosages

AGENT	CLASS	EFFECT	ROUTE	USUAL STARTING DOSE
Fentanyl	Opioid	Analgesia	IV TM	1 µg/kg 10 µg/kg
Morphine	Opioid	Analgesia	IV	0.1 mg/kg
Midazolam	Benzodiazepine	Sedation Amnesia	IV IM PO PR IN	0.1 mg/kg 0.1 mg/kg 0.5 mg/kg 0.5 mg/kg 0.2 mg/kg
Methohexital	Barbiturate	Sedation Amnesia	IV PR	1 mg/kg 25 mg/kg
Pentobarbital	Barbiturate	Sedation Amnesia	IV IM	2 mg/kg 4 mg/kg
Ketamine	Phencyclidine derivative	Dissociation Analgesia Sedation Amnesia	IV IM PO PR IN	1–2 mg/kg 4–5 mg/kg 10 mg/kg 10 mg/kg 6 mg/kg
Etomidate	Imidazole derivative	Sedation Amnesia	IV	0.1 mg/kg
Propofol	Alkylphenol derivative	Sedation Amnesia Antiemetic	IV	0.5 mg/kg
Nitrous oxide	Anesthetic gas	Analgesia	Inhaled	30–70%

IM, intramuscular; IN, intranasal; IV intravenous; PO, oral; PR, rectal; TM, transmucosal.

ketamine has been shown to provide consistent and predictable results when given IM.[13,75-78] Nitrous oxide has predictable behavior when used as an inhalational PSA agent in children but is also usually used as an analgesic adjunct to a sedating agent.[79-82] In pediatric patients, the benefits of IV drug administration may be outweighed by the difficulty and distress to the patient in obtaining IV access. In this situation, drugs given by the alternative routes may be preferred.

Drugs should be administered by titrated slow IV bolus to minimize hypotension or respiratory depression in many situations. Lower initial doses should be chosen in sensitive patients or when drugs from multiple classes are being administered. It is important to allow adequate time between doses to achieve and assess peak effect before a further dose is given.

Opioids

Parenteral opioids are commonly used as analgesics before performing painful procedures. For PSA, an opioid is rarely optimal as a single agent, and most clinicians combine an opioid with a sedative-amnestic agent to balance sedation-amnesia and analgesia with the least likelihood of respiratory depression. The most commonly used opioids in the ED for

Table 187-4 Procedural Sedation and Analgesia Agents—Benefits and Adverse Effects

AGENT	ROUTE	ONSET (MINUTES)	DURATION (MINUTES)	ADVANTAGES	ADVERSE EFFECTS
Fentanyl	IV TM	1–2 10–30	30–40 60–120	Rapid onset Short duration ↓Histamine release Minimal CV effects	Respiratory depression Rigid chest syndrome
Morphine	IV	10	240–360	Longer lasting	Hypotension Respiratory depression
Midazolam	IV IM PO PR IN	1–2 10–15 15–30 10–30 10–15	30–60 60–120 60–90 60–90 45–60	Rapid onset Short duration Easy to titrate Multiple routes	Respiratory depression
Methohexital	IV PR	<1 5–10	4–7 20–60	Rapid onset Short duration Airway reflexes maintained	Respiratory depression Apnea Hypotension
Pentobarbital	IV	1–2	30–60	Rapid onset Airway reflexes maintained	Respiratory depression Apnea Hypotension Prolonged recovery
Ketamine	IV IM PO PR IN	1 5 30–45 5–10 5–10	15 15–30 120–240 15–30 30–120	Airway reflexes maintained No respiratory depression Predictable	Emergence phenomena Emesis Laryngospasm ↑ICP and ↑IOP
Etomidate	IV	<1	5–10	Rapid onset Short duration Minimal CV effects Cerebral protective	Respiratory depression Myoclonus Adrenal suppression
Propofol	IV	<1	8–10	Rapid onset Short duration Antiemetic Cerebral protective	Respiratory depression Hypotension Injection pain
Nitrous oxide	Inhaled	1–2	3–5	Rapid onset Short duration Minimal CV effects	Expansion of gas-filled structures Emesis

CV, cardiovascular; ICP, intracranial pressure; IM, intramuscular; IN, intranasal; IOP, intraocular pressure; IV intravenous; PO, oral; PR, rectal.

PSA are fentanyl and morphine. These are often combined with benzodiazepines such as midazolam for moderate sedation and used in smaller doses to provide analgesia during deep sedation with etomidate or propofol. Meperidine historically was used for PSA but is no longer recommended because seizures are commonly associated with the accumulation of its long-lasting metabolite, normeperidine.

Fentanyl

Fentanyl has many advantages as an analgesic agent for PSA, given its rapid onset of action, short duration of activity, lack of histamine release, and favorable cardiovascular profile.[32,83-85] Fentanyl rapidly crosses the blood-brain barrier and produces analgesia in as little as 90 seconds. Serum levels rapidly decline from peak concentrations because of extensive tissue uptake followed by hepatic metabolism. It has a duration of action of 30 to 40 minutes and a serum half-life of approximately 90 minutes. These properties permit the administration of multiple small doses that can be easily titrated to the desired clinical effect. Because fentanyl readily creates a reservoir in the adipose tissue, accumulated large doses may result in a progressively increasing duration of effect. This does not generally occur in doses less than 10 μg/kg.[86-88]

For deep sedation, a single dose of 1 to 2 μg/kg of fentanyl is often given before the sedating agent. For moderate sedation, fentanyl can be titrated, along with a sedative agent, often midazolam, depending on whether the clinician feels that more sedative effect (midazolam) or analgesic effect (fentanyl) is required. Dosing should begin at 1 μg/kg and be slowly titrated upward every 1 to 2 minutes until the desired level of analgesia is achieved. Sufficient analgesia for painful procedures under moderate sedation usually is accomplished with dosages of 2 to 3 μg/kg and under deep sedation with 1 to 2 μg/kg. Lower doses should be used in elderly patients or when other CNS depressants have been previously administered (e.g., ethanol).

Respiratory depression is more likely at higher doses, when given rapidly, or when combined with other CNS depressants such as benzodiazepines or alcohol. Other side effects may include vomiting and pruritus, although these are less common than with other opioids. Hypotension and bradycardia are rare but may occur with high doses. Chest wall rigidity and glottic spasm, which may make ventilation difficult, are unique complications seen with very high doses (anesthetic) of fentanyl given rapidly (generally > 15 μg/kg). Many of these adverse effects may be readily reversed by naloxone. The exception to this is chest wall rigidity, which may not reliably be antagonized and may require neuromuscular blockade and intubation to enable adequate ventilation.[89-92] This complication is very rarely reported with the dosages of fentanyl used for PSA.

In children, PO TM fentanyl has been used widely as a premedication for anesthesia and IV placement. It has also been used for PSA when IV access is not feasible.[93-96] This is generally in the form of a fentanyl-impregnated, sweetened matrix in lozenge form on a holder; the fentanyl lollipop. Transmucosal delivery allows rapid onset of action by avoiding first-pass metabolism in the liver. It has been shown to decrease activity and relieve pain in 10 to 30 minutes with scores similar to comparable IV doses of fentanyl.[97] Despite this fairly rapid onset, TM delivery does not allow for easy titration. The general dosage is 10 to 15 µg/kg. Larger doses have been shown to cause more nausea and vomiting without improving analgesia or activity scores. The combination of TM fentanyl and TM midazolam has not been shown to have additional benefit over either agent used singularly for laceration repair in the ED and has been shown to increase adverse events.[98-100] Its use prior to other agents such as propofol has not been studied well. The use of TM fentanyl for PSA has largely been limited by unacceptable levels of nausea and vomiting, which approach 20 to 40 % of patients.[94,96,100-107]

Morphine

Morphine is poorly lipid-soluble and penetrates the blood-brain barrier more slowly after small bolus injections. Ten to 30 minutes is required before its peak effects are seen, although when used for PSA, morphine performs in similar fashion to fentanyl, with comparable recovery times. A general starting dosage of 0.1 mg/kg is commonly used and then titrated to desired effect as with fentanyl (see preceding section). Morphine has much more histamine release and therefore is more likely to produce hypotension, especially in preload-dependent patients. It has similar potential to other opioids for producing respiratory depression, especially when used with other CNS depressants such as benzodiazepines. Morphine undergoes hepatic metabolism to an active metabolite followed by renal excretion. Insufficiency of either organ system may lead to increased serum half-life.

Benzodiazepines

Benzodiazepines are potent amnestic, hypnotic, and anxiolytic medications. They also have anticonvulsant and purported muscle relaxant properties but do not have analgesic effects. Because of this, they are commonly coadministered with an analgesic agent such as fentanyl or morphine. They may be given IV, IM, PO, IN, or PR but are virtually always used via IV for PSA in adults.[100,108-122] Midazolam is the most commonly used agent, because of its favorable pharmacokinetics.

Midazolam

Midazolam has many advantages for PSA given its rapid onset of action and short duration of activity compared with other benzodiazepines. Its amnestic properties also appear to be superior to many of the others.[123] The starting IV dose is 0.05 mg/kg. Children may need slightly higher doses. Onset of sedation is generally within 1 to 2 minutes, and the duration of action is 30 to 60 minutes. Alternatives to the IV route are often used in children, particularly when sedation alone, without analgesia, is desired as for performance of a radiologic study. With IM administration the same doses may be used, but the onset of duration is delayed. Oral doses are often used in children, with a recommended starting dose of 0.5 mg/kg. Sedation is generally achieved within 30 minutes. Rectal administration may also be useful with doses of 0.5 mg/kg. The response by this route may be less predictable, and it is generally not accepted by older children. Intranasal administration may be useful but is irritating and often difficult in older children as well. The starting dose for this route is 0.2 mg/kg and results in sedation in 10 to 15 minutes. Of note, 1% of children younger than 5 years may experience a paradoxical reaction and become excited and agitated when given midazolam. If necessary, the agitated state is reversible by flumazenil. Midazolam has been shown to be an extremely safe and effective agent for PSA, both alone and when used in combination with fentanyl.[124-129]

Side effects include dose-dependent hypoventilation and hypoxemia. Apnea and hypotension are uncommon, but occur more often at high doses or when other CNS depressants such as opioids are used. Headache, nausea, emesis, coughing, and hiccups have been shown to occur, although rarely. Lower doses should be used when other agents such as analgesics are given concomitantly and in the elderly. Prolonged effects may be seen in elderly patients or those with liver dysfunction due to decreased hepatic or first-pass metabolism. Midazolam is highly lipophilic and its effects may be greatly amplified in obese patients, resulting in an increased plasma half-life of up to 8 hours with high or repetitive doses. Chronic alcohol users who do not have liver dysfunction may require relatively high doses of midazolam to achieve the same clinical effects.

Barbiturates

Barbiturates are also potent hypnotics, with amnestic and anticonvulsant effects. They do not have analgesic properties. Before the widespread use of midazolam and the advent of propofol for deep sedation, barbiturates were commonly used for brief painless procedures, but they are much less commonly used now. They are not commonly combined with other agents, due to their narrower therapeutic window. The most useful barbiturate PSA agents are methohexital and pentobarbital. These drugs generally have a brief procedural effect due to redistribution, but large or repetitive dosages may lead to significantly prolonged sedation due to their actual plasma half-life.

Methohexital

Methohexital is a highly lipophilic ultra-short-acting barbiturate with a rapid onset of amnesia and deep sedation in 30 to 60 seconds. It does not provide analgesia, and an opioid, such as fentanyl, is required for painful procedures. The concomitant use of fentanyl or another opioid increases the risk of apnea. Intravenous doses of 1 mg/kg produce unconsciousness for approximately 5 minutes. It may also be administered PR in children at a dose of 25 mg/kg but has a more variable effect and longer onset and duration of action.

Depressed respiratory drive and apnea are more common than with other agents but are generally transient and mild. Most patients respond to supplemental oxygen and repositioning of the airway. Its use in the ED appears to be safe and effective, particularly for brief orthopedic joint reductions, cardioversions, and radiologic imaging procedures. Only a small percentage of patients require brief periods of assisted ventilation. In several studies, no ED patients have required intubation or change in disposition after receiving methohexital for PSA.[130,131] Methohexital does have the potential to cause significant hypotension as well and should be used with caution in patients with hemodynamic instability or occult blood loss. It also may cause activation of the respiratory reflexes, inducing coughing, hiccups, and, rarely, laryngospasm. In contrast to the other barbiturates, methohexital may worsen or precipi-

tate seizures, and it is prudent to avoid it in patients with a known seizure disorder.[130,132,133] Propofol has largely supplanted methohexital for PSA because it has more reliable, consistent effects, is easily titrated, and can be administered as an infusion for longer procedures.

Pentobarbital

Pentobarbital is also a barbiturate sedative agent, best used via IV for nonpainful diagnostic studies. Its onset of action is generally within 1 to 2 minutes, with a duration of 30 minutes. It is usual to start with an initial dose of 2 mg/kg and titrate to effect with subsequent doses of 1 to 2 mg/kg every 30 seconds as needed. The predominant complications with pentobarbital are respiratory depression, hypotension, and prolonged recovery.

Ketamine

Ketamine is a well-studied, safe, and predictable agent for use in the pediatric population for PSA.[78,128,129,134-141] It is gaining popularity for use in adults as well.[137,142,143] It is a derivative of the street drug phencyclidine and is classified as a dissociative agent. It causes disruption between the thalamoneocortical and limbic systems, preventing the higher centers from perceiving visual, auditory, or painful stimuli. Due to this, its use leads to profound analgesia, amnesia, and catalepsis. It does not produce unconsciousness, but rather a trancelike state. Patients often experience nystagmus, roving eye movements, and random movements of the extremities unrelated to painful stimuli. Parents observing procedures in which ketamine is used may be disturbed at seeing this and should be forewarned.

Ketamine has several advantages over other PSA agents.[78,128,134,135,144,145] The most notable are its profound analgesic effect and the lack of significant or frequent respiratory depression. The protective airway reflexes, such as coughing, swallowing, and muscular tone of the tongue and pharynx are well maintained or slightly enhanced. Its use further leads to blockade of catecholamine reuptake, and blood pressure is generally well supported. It also induces bronchial smooth muscle relaxation and is well tolerated in patients with reactive airway disease. It has a fast onset and offset and is predictable when given by the IV or IM route. Following administration, it is rapidly distributed and taken up by the cerebral tissues. The effects are maintained until the drug redistributes into the peripheral tissues and is metabolized by the liver. Due to this mechanism, repeat doses are well tolerated in longer procedures with predictable results.

Ketamine may be given by multiple routes but is used almost exclusively by the IV route in adults. Following an IV dose of 1 to 2 mg/kg, a dissociative state results in approximately 1 minute with duration of action of approximately 15 minutes. Complete recovery generally requires 1 to 2 hours. Similar cataleptic results may be seen with an IM administration of 4 to 5 mg/kg in approximately 5 minutes, with effects lasting 15 to 30 minutes. For pediatric sedation, ketamine is generally administered by the IV or IM route but may also be given PO (10 mg/kg), PR (10 mg/kg), or intranasally (6 mg/kg). These other routes are infrequently used due to variable onset of action, slow offset, and less predictable results.

The most common side effect seen with ketamine is the emergence phenomenon.[74,146,147] This occurs in approximately 15% of patients and is mild in almost all. They may wake up with unpleasant, vivid dreams or hallucinations or complain of nighttime awakenings due to unpleasant dreams for several days following its administration.[148-150] Less than 1 to 2% of patients have significant emergence agitation. This is more commonly seen in female patients, adolescents or adults, and in those with underlying psychiatric disorders. Its rare occurrence, especially in children, should not limit ketamine's use when indicated. Some studies have suggested that preprocedural or concurrent administration of midazolam may mitigate this reaction, but others have disputed its utility. Some practitioners feel that a tranquil state and preprocedure pleasant imagery prior to drug administration may also be of benefit.[137,138,140,148]

Other side effects seen with ketamine use are transient apnea, laryngospasm, and emesis.[13,151] These are also rare but more common with rapid IV administration. Doses given slowly, at a rate of 0.5 mg/kg/min, may limit much of this. Ketamine also stimulates tracheobronchial and salivary secretions. Since airway reflexes are maintained, this generally isn't a concern except in young children. In young children, and any patient undergoing airway examination (e.g., fiberoptic laryngoscopy), pretreatment with glycopyrrolate, 0.01 mg/kg given 10 minutes before the ketamine, may be beneficial. Postrecovery nausea and vomiting are also frequently seen but generally short-lived.

Significant laryngospasm has been seen in infants younger than 3 months and in children with upper respiratory tract infections. It is recommended that ketamine be avoided in these patients. Due to catecholamine-mediated hypertension and tachycardia, ketamine should also be avoided in those with significant cardiovascular or coronary artery disease. Ketamine also increases intracranial and intraocular pressure and should be avoided in those with significant head trauma, CNS abnormalities, or open globe injuries.

Etomidate

Etomidate is a short-acting sedative-hypnotic agent that is structurally unrelated to the other PSA agents and has no analgesic properties. Its use leads to the very rapid onset of profound sedation and hypnosis by enhancing neurotransmission at γ-aminobutyric acid receptors. Etomidate has been used for deep sedation because of its rapid onset, short duration of action, and, most importantly, minimal effects on respiratory and cardiovascular function.[152-164]

Following IV administration, sedation occurs in approximately 1 minute, and patients recover in 5 to 10 minutes. Etomidate induces deep sedation that borders on general anesthesia with higher doses and may be more difficult to titrate than the other sedative hypnotic agents. It is generally administered IV, with an initial dose of 0.1 mg/kg given slowly over 1 to 2 minutes. Additional doses of 0.05 to 0.1 mg/kg may be administered every 2 to 3 minutes until the desired level of sedation is achieved. Smaller initial doses should be considered when it is combined with analgesic agents or in the elderly. Because it has little effect on the cardiovascular system and is cerebral protective, it is an excellent choice for patients who have the potential for hemodynamic instability or increased intracranial pressure.

Adverse effects that may limit its usefulness include apnea, respiratory depression, myoclonus, nausea, vomiting, and adrenal suppression.[153,154,162,165-168] These side effects are more common with rapid IV administration, when higher doses are used, and in older patients. Although respiratory depression is rare and generally transient, few patients may require brief periods of assisted ventilation. Myoclonus is also typically described as mild and brief but at times may interfere with the procedure. Vomiting is unlikely with dosages administered in the ED. Etomidate suppresses adrenal function by inhibiting 11-β-hydroxylase activity. This is not a concern when a single sedating dose is used (see Chapter 1).[169-173]

Propofol

Propofol is another short-acting sedative-hypnotic agent that is structurally unrelated to the other PSA drugs and has no analgesic properties. It has an extremely rapid onset, a short duration of action, and predictable efficacy for inducing deep sedation. Sedation quickly clears completely, permitting superior titration and earlier recovery and discharge.[174-177] Propofol also possesses potent antiemetic properties and decreases intracranial pressure. It does not provide analgesia and is frequently preceded by an opioid for painful procedures. As with all sedative agents, the addition of an opioid may increase the risk of deeper than anticipated sedation, respiratory depression, apnea, and hypotension.[41,174,178-184]

Propofol is administered by an initial IV bolus dose of 0.5 mg/kg that is then titrated every 3 to 5 minutes by 0.25- to 0.5-mg/kg aliquots to the desired sedation level. Children may require slightly higher dosing than adults. The onset of sedation occurs in less than 1 minute, and patient recovery is in 10 minutes. For procedures lasting longer than this, additional boluses of 0.5 mg/kg may be administered, or a continuous infusion of 3 to 6 mg/kg per hour may be titrated to the desired level of sedation. Smaller doses should be used when sedating elderly patients or when administering propofol with analgesics.

Adverse effects include dose-dependent respiratory depression, apnea, hypotension, and pain on injection. Other agents such as opioids may intensify these effects. In most cases apnea is transient, and patients often respond to repositioning of the airway or, rarely, a brief period of assisted ventilation. Propofol commonly results in a transient drop of systolic and diastolic blood pressure, which generally responds to fluid administration and is well tolerated in healthy patients. When given by rapid bolus, or to patients with hypovolemia, this can be significant and should be avoided. Pain associated with propofol injection occurs in the majority of patients and can be reduced with small infusions of IV lidocaine under tourniquet prior to its administration.

Nitrous Oxide

Nitrous oxide is a gas that, when used in combination with oxygen, provides excellent analgesia to supplement procedural sedation. It defuses rapidly across the alveoli in the lungs, providing a predictable and rapid onset in 1 to 2 minutes and rapid elimination in 3 to 5 minutes.

Nitrous oxide is administered as a 30 to 70% mixture with oxygen by a demand-valve mask or mouthpiece held by the patient. It must be administered with at least 30% oxygen to avoid hypoxemia. A 30% concentration may be less than effective for PSA, especially in children, whereas a 70% mix may result in the loss of protective airway reflexes.

The need for a scavenger device and proper ventilation exhaust have limited the use of nitrous oxide in the ED. Because nitrous oxide rapidly defuses into gas-filled pockets, it can potentially worsen conditions such as pneumothoraces, small-bowel obstructions, decompression sickness, chronic obstructive pulmonary disease, and middle ear effusions. High concentrations may lead to nausea and vomiting, respiratory depression, and general anesthesia.

Reversal and Rescue Agents

Careful titration of PSA drugs to the desired level of sedation is the goal. At times, unanticipated deeper levels of sedation may be reached, and respiratory depression or apnea may be experienced. Airway repositioning, supplemental oxygen, and bag-valve-mask ventilation may be required. If these periods are prolonged, partial or complete reversal of agents such as opioids or benzodiazepines may be necessary. Elective reversal of PSA following the completion of the procedure is not recommended.[185-187]

Naloxone

Naloxone is a competitive antagonist of opioids and has been effectively used for the reversal of opioid-induced respiratory depression during PSA. It has a rapid onset of action and a mean plasma half-life of approximately 45 minutes though its clinical effects last only 15 to 30 minutes. Resedation is generally not a problem for patients who have been given fentanyl or morphine in doses recommended for PSA. Nevertheless, these patients should be observed for a minimum of 1 hour after the administration of naloxone. It is especially important for patients who have received large doses of fentanyl to ensure that redistribution of fentanyl within the body does not result in the recurrence of sedation.

Naloxone may be administered IV, IM, subcutaneously, or via endotracheal routes, but is almost universally given via IV. The smallest dose necessary to restore respiratory effort should be used, because reversal of the opioid's respiratory depressant effect is matched by reversal of the analgesia. Initial dosing depends on the patient and the specific goals desired. For partial reversal, titrated doses of 0.1 to 0.2 mg may be used every 1 to 2 minutes to desired effect. Complete reversal is almost never desirable and requires doses of 1 to 2 mg. Similar dosages may be used in children. In patients who are opioid-dependent these doses may precipitate an acute withdrawal state. Smaller initial doses should be considered. Large doses of naloxone may also make it more difficult to control postprocedure pain. Naloxone use has little risk, but pulmonary edema, seizure, and dysrhythmia rarely have been reported.

Flumazenil

Flumazenil is a competitive antagonist of benzodiazepines. Although it reverses the sedation effect of benzodiazepines, it is not as effective for reversing respiratory depression. In general, when oversedation occurs, brief support of ventilation permits the patient to recover sufficient spontaneous respiration without the need for reversal. Flumazenil has a rapid onset of action in 1 to 2 minutes, a peak effect in 5 to 10 minutes, and a half-life of 45 to 90 minutes. Continuous patient monitoring must be ensured when it is used to reverse respiratory depression associated with longer lasting benzodiazepines because resedation is likely. Flumazenil has also been shown to be effective in reversing paradoxical excitement in children.

It is generally titrated in doses of 0.1 to 0.2 mg IV every 1 to 2 minutes to the desired effect. A maximum dose of 1 mg is generally sufficient. Common pediatric doses of 0.02 mg/kg are generally used, with a maximum of 0.2 mg. It should be used with extreme caution in patients with benzodiazepine dependence or a history of seizures as it may precipitate life-threatening status epilepticus. Routine reversal is not recommended.

Drug Selection and Administration

When choosing a strategy for PSA, it is important to consider the type of procedure being performed (painful or not), the length of the procedure, specific procedural requirements (anxiolysis vs. immobility), and whether sedation may need to be prolonged. The need for IV access generally is an issue only

in small children. Planned adjuncts, such as topical, local, or regional anesthesia are also considered. Patient factors, including age, medications, alcohol and drug use, and comorbid conditions are considered when selecting both the agent and the initial dose. Procedures needing sedation may be broadly divided into three categories: nonpainful procedures requiring immobilization (e.g., computed tomography, magnetic resonance imaging), low-pain high-anxiety procedures (e.g., laceration repair, lumbar puncture), and highly painful high-anxiety procedures (e.g., fracture or joint reduction, tube thoracostomy, abscess drainage, cardioversion). These are summarized in Table 187-5 for adult patients and Table 187-6 for pediatric patients.

For brief nonpainful procedures requiring complete immobilization, IV midazolam, etomidate, and methohexital are excellent initial choices. For longer procedures, PO midazolam, PR methohexital, or IV pentobarbital may be indicated. Intravenous propofol should also be considered and may become the agent of choice as its use becomes more commonplace in the ED. Nitrous oxide may be an alternative if complete immobilization is not required.

For briefly painful procedures requiring minimal to moderate sedation and where topical or local anesthetics may be used (e.g., reduction of a glenohumeral dislocation for which intra-articular lidocaine will be used), midazolam is a reliable and safe choice. Intravenous propofol (preceded by a modest dose of fentanyl) is an excellent choice for deep sedation (e.g., cardioversion, joint reduction, and other highly painful procedures). Ketamine has been extensively studied by both the IV and IM route for children and is highly effective with a large margin of safety. The same may be said for IV midazolam plus fentanyl in both the adult and pediatric populations.

Special Considerations for Pediatric Populations

Performing painful procedures on children in the ED is often distressing for the parent and the provider as well as the child. This often includes obtaining IV access as well as more traditional procedures. In many cases, a calm and reassuring bedside manner, combined with distraction techniques, may be highly successful. Child life practitioners, coloring books, toys, video games, and television may often be helpful.

The advent of ultrafast spiral computed tomography scanners has nearly eliminated the need of sedation for this procedure. For prolonged computed tomography studies or magnetic resonance imaging, deep sedation is generally required in young children. The need and desire for IV access in children should also be considered when planning PSA. Agents such as midazolam may be very effective in infants, but they do not

Table 187-5 Adult Drug Selection Strategies

PROCEDURE TYPE	EXAMPLES	RECOMMENDATION	ALTERNATIVES	COMMENTS
Nonpainful	Radiologic imaging	Midazolam (IV)	Propofol (IV)	Midazolam has considerable support and safety
Low pain, high anxiety	Central line placement Lumbar puncture	Midazolam (IV)	Propofol (IV) Ketamine (IV)	Analgesia may be accomplished with local or topical agents frequently
High pain, high anxiety	Fracture or joint reduction Abscess drainage Burn débridement Cardioversion Chest tube placement	Midazolam + fentanyl (IV) Propofol + fentanyl (IV)	Etomidate + fentanyl (IV) Ketamine (IV, IM)	There are far more data supporting the safety of fentanyl and midazolam, although the other choices have significant support

IM, intramuscular; IV, intravenous.

Table 187-6 Pediatric Drug Selection Strategies

PROCEDURE TYPE	EXAMPLES	RECOMMENDATION	ALTERNATIVES	COMMENTS
Nonpainful	Radiologic imaging	Midazolam (PO) Methohexital (PR)	Midazolam (IV) Methohexital (IV) Ketamine (IV, IM) Propofol (IV) Pentobarbital (IV)	IV access is often not required
Low pain, high anxiety	Laceration repair Lumbar puncture Foreign body removal Sexual assault examination	Midazolam (PO, IV)	Ketamine (IV, IM) Propofol (IV)	Analgesia may be accomplished with local or topical agents frequently
High pain, high anxiety	Fracture or joint reduction Abscess drainage Burn débridement	Ketamine (IV, IM) Fentanyl + midazolam (IV)	Propofol + fentanyl (IV)	There are far more data supporting the safety of ketamine or fentanyl and midazolam, though propofol and fentanyl have significant support

IM, intramuscular; IV, intravenous; PO, oral; PR, rectal.

reliably ensure immobility in young children except at high doses.[7,15,128,188-193] Methohexital and pentobarbital have demonstrated efficacy for sedating children for these longer imaging procedures.[132,156,175,189,190,194-201] Ketamine has been the most extensively studied and has been shown to be highly effective with a large margin of safety.[74,128,192,202,203] The use of these drugs may largely be supplanted by propofol use in the future as studies continue to show its efficacy and safety in pediatric PSA.

For mildly painful procedures such as laceration repair or lumbar puncture, topical agents such as cream eutectic mixture of local anesthetics (EMLA); or tetracaine, adrenaline, or cocaine (TAC); or lidocaine, epinephrine, tetracaine (LET) gels in combination with TM or PO midazolam may preclude the need for placement of an IV line.

Brief painful procedures or those requiring deeper sedation may be accomplished with a single IM injection of ketamine. Longer procedures or those requiring IV PSA agents require venous access. This should be considered a mildly painful procedure in itself, and distraction techniques, PO midazolam, and topical agents such as EMLA should be considered if time and the situation permits. Guidelines for patient preparation, personnel requirements, monitoring, drug administration, recovery care, and discharge criteria for children receiving IV PSA are similar to those outlined for adults.

With PSA in children, it is essential that drug dosages be calculated precisely using the child's current weight and not the parent estimate. Equipment to manage the airway and resuscitation supplies must be size-appropriate, and the physician must be skilled in pediatric airway management and resuscitation.

Chloral hydrate, a pure sedative-hypnotic agent, has been historically popular for sedating children for a wide variety of procedures. It offers no advantage to currently available agents.[204-206] It has a poor safety record, delayed onset of 45 minutes, prolonged recovery time of hours, and residual sedation of nearly a day. Its use should be discontinued. Likewise, the combination of meperidine (Demerol), promethazine (Phenergan), and chlorpromazine (Thorazine), also known as DPT, is not recommended. It has an unacceptable rate of sedation failure, prolonged sedation times, high risk of respiratory depression, and frequent dystonic reactions.[207]

KEY CONCEPTS

- PSA has become commonplace and should be approached as a complex procedure requiring high-level skills and knowledge.
- Propofol is an excellent agent for deep sedation in the ED.
- Preprocedural fasting is controversial, and guidelines are a benchmark for minimizing risk.
- Pulse oximetry is mandatory during sedation, and end-tidal CO_2 partial pressure should be monitored if deep sedation is the goal.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 188 The Combative Patient

Louise Kao, Gregory P. Moore, and Kenneth Jackimczyk

PERSPECTIVE

Background

Combative patients are among the most difficult patients emergency physicians (EP) encounter. Often brought in against their will, they are agitated, confrontational, nearly impossible to examine, and may physically harm themselves or others. The EP must control the patient and the situation, diagnose and treat reversible causes of violence, and protect the patient and staff from harm.

Epidemiology

Violence is referred to as our nation's shameful epidemic. Injury is the leading cause of death in persons younger than 44 years, and homicide is the second leading cause of death in persons from age 15 to 24 years.[1] Rates of firearm violence are higher in the United States than in any other industrialized country,[2,3] and the rate of death from firearms is eight times higher in the United States.[4] For each death there are an estimated 19 additional injuries requiring hospitalization.[5] The high lifetime cost of treating gunshot injuries is a public health issue, as a large proportion of the expense is covered by U.S. taxpayers.[6,7]

The emergency department (ED) is a volatile environment due to high stress, illness, prolonged waiting times, and frequent lack of communication. The 24-hour open door policy, availability of potential hostages, and widespread accessibility of drugs and weapons compound the potential for violent behavior. Among hospital workers, the majority of assaults occur in the ED, psychiatric ward, waiting rooms, and geriatric units.[8] Up to 50% of human services providers become victims of violence sometime during their careers.[9,10] In a survey of 242 emergency care workers in five Midwestern hospitals, the majority report being verbally threatened, and 51% of physicians and 67% of nurses report being physically assaulted at least once in the past 6 months.[11] Another survey of attending physicians (n = 171) in Michigan EDs reports that 75% experienced a verbal assault and 28% a physical assault in the last 12 months; 82% were occasionally fearful of workplace violence.[12] An ED census of at least 50,000 patients annually or an average waiting time of at least 2 hours is significantly associated with an increased incidence of violence.[13,14] Despite these obvious risks, providers are typically not trained in the identification and management of combative patients.

Patients armed with lethal weapons pose a serious threat to ED staff. The carriage of weapons in the ED population is estimated at approximately 4 to 8%.[15,16] One large urban hospital ED with a metal detector reports confiscating an average of 5.4 weapons a day.[17] At this center, 26.7% of major trauma patients seen in the ED over a 14-year period were initially armed with lethal weapons (84% knives and 16% guns). Unfortunately, predicting weapons carriage in any particular patient is impossible.[18] Therefore, it is prudent to assume that all violent patients are armed until proven otherwise, especially those presenting with major trauma.

Identification of potentially violent patients is difficult, with male gender, prior history of violence, and drug or ethanol abuse the only positive predictors.[19-23] Ethnicity, diagnosis, age, marital status, and education are not reliable identifiers. A study conducted in an outpatient psychiatric setting finds that the incidence of violent behavior occurring after psychiatric evaluation does not vary with the experience of the psychiatrist.[20] Actuarial prediction of patient violence in a 6-month time period using criteria such as age, drug use, and prior history of violence is substantially more accurate than prediction of future violence by evaluating attending psychiatrists.[24] The prediction, prevention, and control of violent outbursts in the ED is difficult. Appreciation of the potential for violence, preparedness, and proper utilization of verbal techniques and physical or chemical restraints assists the patient while preventing injury.

PRINCIPLES OF DISEASE

Pathophysiology

The pathogenesis of violent behavior is conjectural. Potential causes include environmental, historical, interpersonal, biochemical, genetic, hormonal, neurotransmitter, and substance abuse disorders.[25,26] Psychiatric illness is also a risk factor, with schizophrenia (paranoid and nonparanoid), personality disorders, mania, and psychotic depression most frequently associated with violence.[23,25,27-29] Delusional schizophrenic patients become violent, believing that others are attempting to harm them. They may also have auditory hallucinations commanding harm to others. Antisocial and borderline personality disorder patients typically do not feel remorse for their violent actions. The patient with acute mania is unpredictably dangerous because of emotional lability, a situation in which pleasantness can quickly turn to aggression. Substance abuse

disorders are consistently associated with violent behavior in both psychiatric and nonpsychiatric populations.[22,23,30,31]

Biologically, the serotonin system controls aggression and inhibition, with diminished serotonergic function possibly disinhibiting aggression against self and others.[32-36] Generalized brain dysfunction may predispose patients to violence by disruption of the regulation of aggression, particularly in the prefrontal and temporal cortex.[37-40] Research in cerebral imaging documents both functional and structural impairments in violent criminals and antisocial patients.[41,42] Genetic and hormonal influences are also implicated in the neurobiology of aggression.[43,44]

MANAGEMENT

Risk Assessment

Evaluation of the combative patient begins with risk assessment and attention to safety measures. Violence often erupts after a period of mounting tension. The astute practitioner may identify verbal and nonverbal cues and subsequently have the opportunity to defuse the situation.[29,45] In a typical scenario, the patient first becomes angry, then resists authority, and finally becomes confrontational and violent. When physicians have a "gut feeling" that a dangerous situation may be developing, they should take appropriate precautions.[46] Violent behavior may also erupt without warning, especially in patients with an organic brain syndrome (OBS), so clinicians should not feel overly confident in their ability to sense impending danger.

An obviously angry ED patient should always be considered potentially violent. Provocative behavior, an angry demeanor, pacing, loud or pressured speech, tense posture, gripping arm rails intensely, frequently changing body position, pounding walls or throwing things, and clenched fists are all symptoms and signs of impending violence. The patient should be removed from contact with other belligerent accomplices, as well as from other provocative patients, to prevent escalation. A quiet area with a window or direct observation is optimal. Since increased waiting times correlate positively with violent behavior,[8,13,14] consider evaluating the potentially violent patient expeditiously to prevent escalation of aggression. Often, the perception of preferential treatment will defuse patient anger.

All patients should be screened for weapons before the interview. The use of metal detection is ideal before ED entry. The practice of undressing patients and placing them in a gown is useful both as a nonconfrontational search for weapons and for easy identification in the event of patient escape from the ED. Although screening and searching patients for weapons may appear to be a violation of privacy, routine disarming of all ED patients results in an increased feeling of safety for both patients and staff.[16,47]

The ideal setting for the patient interview should emphasize privacy but not isolation.[27,46] Some EDs have seclusion rooms specifically designed for interviewing potentially dangerous patients.[48] Security should be nearby and the door left open to facilitate both intervention and escape. The patient and interviewer may be seated roughly equidistant from the door, or the interviewer may sit between the patient and the door. Blocking the door, however, poses a risk of harm to the clinician if the patient feels the urge to escape. Ideally two exits should be available and doors should swing outward. The clinician should have unrestricted access to the door and never sit behind a desk. The room should not contain heavy or potentially dangerous objects that may be thrown. There must be a mechanism for alerting others of danger, such as a panic button or a code word or phrase that summons security (e.g., "I need Dr. Armstrong in here"). For personal protection, earrings, necklaces, and neckties should be removed. Personal accessories that may be used against the EP, such as a stethoscope or scissors should be removed. The physician should be aware of any objects within the room or on the patient's body, such as pens, watches, or belts that may be used as weapons.[45,46,49,50]

Verbal Management Techniques

The patient should be made as comfortable as possible, and the interviewer should adopt an honest and straightforward manner. In some cases, an agitated patient may be aware of their impulse control problem and welcome limit-setting behavior by the clinician (e.g., "I can help you with your problem, but I cannot allow you to continue threatening me or the ED staff."). The interviewer should act as an advocate for the patient. Offering a soft chair or something to eat or drink (not a hot liquid, which may be used as a weapon) may help to establish trust. A significant percentage of patients relax at this point, because offering food or drink appeals to their most basic human needs and builds trust. The interviewer should adopt a nonconfrontational demeanor and be an attentive and receptive listener without conveying weakness or vulnerability. The interviewer should respond verbally in a calm and soothing tone of voice. It is also important to stand at least an arm's length away and avoid prolonged direct eye contact, approaching the patient from behind, or sudden movements.[46]

A key mistake when interviewing a potentially violent patient is failing to address the issue of violence directly.[20,45,51] The patient should be asked relevant questions regarding suicidal or homicidal ideations or plans, possession of weapons, history of violent behavior, and current use of intoxicants. Acknowledgment of the obvious (e.g., "You look angry.") may help the patient to begin sharing emotions. If the patient becomes more agitated, it is important to speak in a conciliatory manner and offer supportive statements, such as "You obviously have a lot of will power and are good at controlling yourself," to help defuse the situation. If this is not successful, a respectful offer of medication or restraints to the patient if another health care provider is close by may prevent further escalation.

Counterproductive approaches to the combative patient include argumentation, machismo, or condescension. These inappropriate strategies challenge patients to "prove themselves." An open threat to call security personnel also invites aggression. The clinician must be aware of her or his own reactions to the patient and avoid countertransference of anger. The deception of a patient (e.g., "I am sure you will be out of here in no time.") only invites violent consequences once the lie is uncovered. The unsuspecting nurse or colleague who follows the interviewer may be victimized.

It is especially important not to deny or downplay threatening behavior. If verbal techniques are unsuccessful and escalation of violence occurs, the physician should leave the room and summon help.

Physical Restraints

Physical restraint should be considered when, despite a professional and proper approach to the combative patient, verbal techniques are unsuccessful. The use of restraints can be humane and effective in facilitating diagnosis and treatment of the patient, while preventing injury to the patient or medical staff.[49,52-54] The liability one incurs for restraining a patient

against his will is negligible compared with the potential liability for allowing a patient to lose control and cause physical harm.[46]

Indications for emergency seclusion and restraint include the prevention of imminent harm to the patient, to others, and to the environment or as part of an ongoing behavior treatment program.[46,55] Seclusion or restraint may be contraindicated due to the patient's clinical or medical condition. Seclusion should not be used in an unstable patient who requires close monitoring and should be avoided when the patient is suicidal, self-abusive, self-mutilating, or has had an intentional ingestion of drugs or poisons.[29,49,56] Restraints should not be applied for convenience or as a punitive response for disruptive behavior. If available, a colleague should document agreement with the application of restraints, mentioning the specific indications (e.g., "I restrained Mr. Smith because he told me he was going to beat me up and then took a swing at me" is preferable to "I restrained Mr. Smith because he was violent").

The implementation of restraints should be systematic, and an ED protocol should be in place. This protocol begins when the examiner leaves the room after verbal techniques are unsuccessful. It may be helpful to consider the application of restraints as a procedure analogous to running an advanced cardiac life support code.[45] The restraint team ideally consists of at least five people, including a team leader. The leader, whether a physician, nurse, or security officer, will be the only person giving orders and should be the person with most experience in implementing restraints. Before entering the room, the leader outlines the restraint protocol and warns of anticipated danger (e.g., the presence of objects that may be used as weapons). All team members should remove personal objects that the patient could use against them. If the patient is female, at least one member of the restraint team should be female to potentially mitigate allegations of sexual assault.

The team enters the room in force and displays a professional, rather than threatening, attitude. Many violent individuals calm down at this point, as a large show of force protects their ego (e.g., "I would have fought back but there were too many against me."). The leader speaks to the patient in a calm and organized manner, explaining why restraints are needed and what the course of events will be (e.g., "You require a medical and psychiatric examination as well as treatment."). The patient is instructed to cooperate and lie down to have restraints applied. Some patients are relieved at the protection to self and others afforded by restraints when they feel themselves losing control. Even if the patient suddenly appears less dangerous, however, once the decision to restrain is made, do not negotiate.

If physical force becomes necessary, one team member restrains a preassigned extremity by controlling the major joint (knee or elbow). The team leader controls the head. If the patient is armed, two mattresses can be used to charge and immobilize or sandwich the patient. Restraints are applied securely to each extremity and tied to the solid frame of the bed (not side rails, as later repositioning of side rails also repositions the patient's extremity). Leather is the optimal type of restraint because it is physically stronger material and less constricting than typical soft restraints. For this reason, gauze should not be used. Soft restraints may help restrict extremity use in the semicooperative patient but are likely to be less effective in the truly violent patient who is continuing to struggle and attempt escape. If chest restraints are used, it is vital that adequate chest expansion for ventilation is ensured. The application of a soft Philadelphia collar to the patient's neck minimizes head banging and biting. Whenever possible, the treating physician should not actively participate in restraint application to preserve the physician-patient relationship. The restraining of patients on their sides helps prevent aspiration, although restraint supine with the head elevated is more comfortable and allows a more thorough medical examination while providing some protection against aspiration.[29,57] Once the patient is immobilized, announcing "the crisis is over" will have a calming effect on the restraint team and the patient.

After restraints are successfully applied, the patient should be monitored frequently and positions changed to prevent neurovascular sequelae such as circulatory obstruction, paresthesias, and rhabdomyolysis associated with continued combativeness. A standardized form should be developed for physically restrained patients. Documentation should include the specific indication for restraint and, ideally, colleagues' agreement that restraints are necessary.

Sudden, unexpected deaths are reported in restrained patients.[58-62] Although healthy volunteers, when restrained and undergoing physical exertion, do not appear to experience clinically significant positional asphyxia,[63-65] the combative ED patient often suffers from other conditions that may predispose to increased morbidity. Patients who are cocaine- or stimulant-intoxicated or restrained in the prone position appear to be uniquely at risk for adverse outcomes.[58-61] Increased sympathetic tone and altered pain sensation are postulated to allow exertion beyond normal physiologic limits in these patient. Sympathetic induced vasoconstriction may impede clearance of metabolic waste products. Alteration of respiratory mechanics in an acidemic patient resulting from restraint position could be a contributing factor by impairing respiratory compensation. As a general guideline, the prone restraint position should be avoided when possible and chemical sedation used when a patient continues to struggle against physical restraints.

The Joint Commission on Accreditation of Health Care Organizations (JCAHO) has guidelines governing the use of restraint and seclusion for behavioral health patients. Educational materials regarding seclusion and restraint are available at http://www.jointcommission.org/. Several essential elements must be provided in a restraint situation including:

1. Hospital policies and procedures guide appropriate and safe use of restraint.
2. The implementation of restraint or seclusion is limited to emergencies where imminent risk of harm exists to the patient or others.
3. Staff is trained and competent to apply restraint safely.
4. Staff is trained to minimize the use of restraint.
5. Patients in restraint are regularly evaluated and monitored.
6. Orders for restraint use are provided by licensed practitioners and are time-limited.
7. Medical records document that the use of restraint or seclusion are consistent with organizational policy.

Chemical Restraints

Chemical restraint may be necessary to control an agitated patient and may be used in conjunction with physical restraint. The ideal pharmacologic agent should be effective with multiple routes of administration, nonaddictive, immune to tolerance, and have a low side effect profile. Antipsychotic medications, also called neuroleptics, are useful for rapid tranquilization due to their high therapeutic index, lack of tolerance to the desired effects, and lack of addictive potential. Classic antipsychotics block dopaminergic receptors and also have variable effects on cholinergic, adrenergic, histaminic, and serotonergic receptors. Antipsychotics can be divided into low potency (e.g., chlorpromazine, mesoridazine, thioridazine), midrange potency (e.g., loxapine, molindone), and high

potency (e.g., haloperidol, fluphenazine, thiothixene, trifluoperazine). The incidence of sedation, hypotension, and seizures is highest in the low-potency group, and the incidence of extrapyramidal symptoms (EPS) is greatest in the high-potency group.

Until recently, haloperidol (Haldol) has been recommended as the drug of choice to sedate violent patients as it was the only neuroleptic agent with an intramuscular (IM) or intravenous (IV) route of administration. Haloperidol is generally administered at dosages of 2.5 to 10 mg IM at 30- to 60- minute intervals, with half doses used in the elderly.[66-69] After IM injection, effects are typically seen in 10 to 30 minutes, with most patients requiring less than three doses to achieve the desired effect. Although no ceiling dose has been established, it has been recommended that patients not receive more than six doses in 24 hours. Using the lowest effective dose minimizes the risk of side effects.[70] Of note, haloperidol is not approved for IV administration by the U.S. Food and Drug Administration (FDA); however, it has been used safely and effectively via this route with such widespread acceptance that FDA approval will most likely be deferred indefinitely.

Droperidol (Inapsine), an analogue of haloperidol, has also been used with success at doses of 5 to 20 mg IM to control an agitated patient.[66,71-73] Compared with haloperidol, droperidol has a shorter duration of effect, a lesser incidence of EPS, and a greater incidence of sedation and orthostatic hypotension.[68] The use of droperidol has been limited since it was given a black box warning in 2001 by the FDA for cases of QT prolongation and torsades de pointes.[74-77]

The most common side effects of haloperidol and droperidol include sedation, orthostatic hypotension, and EPS. Extrapyramidal symptoms are not dose-related, can occur after one dose, and may occur up to several days after administration.[68] After acute administration, patients may develop akathisia (extreme restlessness) or acute dystonia, which may manifest as involuntary turning or twisting movements seen in the neck (torticollis), back (opisthotonos), and eyes (oculogyric crisis). Rarely, the mouth and tongue can be affected, compromising the airway. The treatment for each of these symptoms is benztropine (Cogentin), 1 to 2 mg, or diphenhydramine (Benadryl), 25 to 50 mg, either IM or IV. Relief generally occurs within minutes. Haloperidol and droperidol have negligible anticholinergic properties and are often coadministered with anticholinergic agents (benztropine or diphenhydramine) in order to attenuate dystonia.[78]

Neuroleptic malignant syndrome (NMS) is an idiosyncratic reaction that leads to autonomic instability. Symptoms include hyperthermia, hypertension, and lead-pipe rigidity of extremities. This reaction occurs in an estimated 0.2% of patients receiving antipsychotic medications.[69] Clinicians should be familiar with this syndrome when administering antipsychotic medications. If NMS develops, supportive care should be administered and further neuroleptic medications withheld.

Some neuroleptic medications (especially phenothiazines such as chlorpromazine) may lower seizure threshold; therefore the use of neuroleptics in sympathomimetic-intoxicated patients has been controversial. In clinical practice, seizure activity occurring after haloperidol or droperidol administration appears to be a rare event.[73,79] In addition, haloperidol has been found in an animal model to prevent seizures in cocaine and amphetamine intoxication.[80]

Conduction disturbances, specifically prolongation of the QT interval and in some cases torsades de pointes, have been reported in patients sedated with haloperidol.[81-84] A 2007 FDA alert recommends electrocardiographic (ECG) monitoring in patients receiving IV haloperidol due to the possible risk of QT prolongation and torsades de pointes.[85]

Rapid tranquilization with newer medications is considered safe and effective in the treatment of psychotic and potentially assaultive patients.[53,68,69,86] Atypical antipsychotic agents (e.g., risperidone, olanzapine, quetiapine, ziprasidone) have largely replaced typical antipsychotics in the first-line treatment of schizophrenia due to increased efficacy on both positive and negative symptoms and a significantly decreased incidence of movement disorders compared with typical antipsychotic agents such as haloperidol.[68-70,78] The use of atypical antipsychotic agents to treat the acutely agitated or psychotic patient in the ED setting has been historically limited by slow titration regimens and the lack of an IM route of administration. Intramuscular formulations for some of the atypical antipsychotics have since been developed and appear to offer promising additions to our current pharmacologic armamentarium when treating the combative patient acutely. They also allow for a smooth transition to oral dosing in those patients requiring ongoing antipsychotic therapy.[53,68,87-89]

In several randomized, double-blind, and placebo-controlled studies, atypical antipsychotics have proven useful. Olanzapine at 2.5 mg and 5.0 mg IM is equivalent to lorazepam 1 mg IM in controlling acute agitation in elderly patients with Alzheimer's or vascular dementia.[90] Olanzapine 10 mg IM is superior to lorazepam 2 mg IM in controlling acute agitation in patients with bipolar mania.[91] Olanzapine doses of 5, 7.5, and 10 mg IM are more rapidly effective than haloperidol 7.5 mg IM in controlling acute agitation in patients with schizophrenia.[92,93] The most common side effect noted is mild hypotension. QTc prolongation is comparable with that from placebo, and olanzapine is significantly less likely than haloperidol to produce dystonia and movement disorders.[94] In addition, olanzapine IM produces distinct calming rather than nonspecific sedation.[95] Olanzapine, however, has significant anticholinergic properties and can potentially exacerbate an anticholinergic delirium. A Cochrane Collaboration review of olanzapine IM concludes that it may be valuable in managing acute agitation, but more studies are needed.[96] Olanzapine IM is FDA approved for the treatment of acute agitation associated with bipolar I mania and schizophrenia. Recommended dosing for olanzapine IM is 2.5 to 10 mg initially, followed by up to two more doses 2 to 4 hours apart, for a total maximum dose of 30 mg.[97,98]

Intramuscular ziprasidone at doses of 10 and 20 mg is effective in reducing acute agitation in patients with underlying psychotic disorders.[99,100] A randomized, open-label study comparing ziprasidone and haloperidol for the treatment of acute psychosis finds that ziprasidone (10 mg IM followed by 5–20 mg q4–6 hr) is superior to haloperidol (2.5–10 mg IM and q4–6 hr) in reducing agitation and improving scores on psychiatric assessments as measured every 24 hours for 3 days.[99] The most common side effect is dose-related sedation. An observational study of ziprasidone IM in 110 adult patients with acute agitation (35% substance-related) seen in a psychiatric ED reports rapid efficacy and decreased total restraint time compared with historical controls.[101] A randomized, double-blind trial comparing droperidol at 5 mg IM, ziprasidone at 20 mg IM, and midazolam at 5 mg IM to treat acute undifferentiated agitation in the ED (primarily intoxication related) finds that adequate sedation is delayed with ziprasidone relative to the other agents, rescue medication is required more frequently with midazolam, and the most common adverse events are mild respiratory depression and akathisia.[102]

Ziprasidone has more effect on the QTc interval than olanzapine, haloperidol, or risperidone.[69] In a regulatory study, ECGs performed at the times of peak plasma concentrations of various antipsychotics show that ziprasidone averaged a 16 ms increase in the QTc interval from baseline.[103] Others,

however, report no significant differences in the QTc interval between ziprasidone IM and haloperidol IM.[86,104] An observational study of pediatric patients prescribed ziprasidone reports a mean increase in QTc of 28 milliseconds, although no patient had a QTc greater than 500 milliseconds.[105] There are two reports of torsades de pointes associated with ziprasidone use, both involving polydrug exposures.[106,107] Ziprasidone IM is FDA approved for the control of acute agitation in patients with schizophrenia. Recommended dosing is 10 mg IM every 2 hours or 20 mg IM every 4 hours, not to exceed 40 mg/day. Ziprasidone is not recommended for those patients with known QTc prolongation or who are at risk for QTc prolongation.[88,108,109]

Aripiprazole 9.75 mg IM in several double-blind, randomized, placebo-controlled studies is equivalent to haloperidol IM (6.5 mg or 7.5 mg) in the treatment of acute agitation in patients with schizophrenia, with a lower incidence of EPS.[110-112] Aripiprazole 9.75 mg IM and 15 mg IM in another study is equivalent to lorazepam 2 mg IM in the treatment of acute agitation in patients with bipolar disorder.[113] Aripiprazole IM is FDA approved for the treatment of acute agitation associated with schizophrenia or bipolar disorder. Recommended doses are 5.25 to 15 mg IM, repeated every 2 hours, to a maximum of 30 mg.[114]

Although these newer intramuscular atypical antipsychotic agents appear to be effective in the chemical restraint of specific populations of agitated patients, their use in the ED treatment of the combative patient with undifferentiated agitation is not fully defined at this point. The atypical antipsychotics may evolve as first-line treatment of acute agitation in psychiatric patients.[53,69,115]

Benzodiazepines can also be used for rapid tranquilization of an agitated patient, with lorazepam proving superior to other benzodiazepines due to rapidity of action, effectiveness, short half-life, lack of active metabolites, and IM or IV route of administration.[52,69,116] Benzodiazepines are especially useful in the patient who is agitated due to intoxication or withdrawal while still maintaining efficacy in acute psychosis.[23] Recommended doses of lorazepam start with 2- to 4-mg increments IV, IM, or orally (PO) and are titrated upward as needed, up to 120 mg in 24 hours.[66] Midazolam, a shorter acting benzodiazepine, has been compared with lorazepam and haloperidol in the severely agitated patient.[117] Midazolam 5 mg IM was compared with lorazepam 2 mg IM or haloperidol 5 mg IM in a randomized, prospective, double-blind trial and has a more rapid onset of action but also a shorter duration of activity than either lorazepam or haloperidol. The most common side effects of benzodiazepines are sedation, confusion, ataxia, and nausea. Respiratory depression is the most significant risk when benzodiazepines are used in a patient who is already under the influence of a potential respiratory depressant such as ethanol.

Antipsychotics and benzodiazepines can be used alone or in combination. The combination of lorazepam with haloperidol has been studied prospectively and was superior to either drug alone in a randomized, double-blind, multicenter trial.[116] ED patients with undifferentiated agitation were treated with lorazepam 2 mg, haloperidol 5 mg, or both in combination. Doses were repeated as needed at hourly intervals, up to six times. Patients were reevaluated hourly for efficacy, vital signs, and presence of side effects for a total of 12 hours. Patients receiving combination therapy improved significantly more in the first 3 hours than those receiving either drug alone, and more patients experienced EPS in the haloperidol-alone group than in the combination group, possibly because of a greater number of doses needed. Based on these findings, combination therapy has been endorsed for rapid tranquilization of the acutely agitated patient for optimal effect and minimal side effects. The use of 5 mg of haloperidol IV or IM with 2 mg of lorazepam IV or IM, repeated every 30 minutes to effect, is often recommended to treat the combative patient with undifferentiated agitation and without contraindications to these medications.[52,68,88,115,118,119] Half doses should be used in the elderly. These medications are compatible within the same syringe for up to 16 hours.[120]

Rapid tranquilization calms patients so they can cooperate in their evaluation and treatment and avoid harming themselves or others. Although obscuring the mental status with medication can confuse the clinical diagnosis, these considerations must be weighed against placing the patient and medical staff at increased risk by withholding effective medications. In addition, physical restraint alone, especially in a struggling patient, may increase the risks for patient morbidity and mortality.

Assault

Unfortunately, physical assault may occur despite appropriate precautions and interventions. If assaulted, immediately summon help. Maintain a sideward posture, keeping the arms ready for self-protection. If faced with a punch or a kick, deflect with an arm or a leg. If choking is attempted, tuck the chin in to protect the airway and carotids. If bitten, do not pull away but rather push toward the mouth and hold the nares shut to entice opening of the mouth. If threatened with a weapon, try to appear calm and comply with demands.[46] Adopt a nonthreatening posture and avoid sudden movements. Do not attempt to reach for the weapon. Avoid argument, despair, or whining. Attempt to establish a human connection with the hostage taker.[27,121] Offering to administer to other ill or injured hostages allows a hostage to appear less expendable. Do not bargain or make promises, and do not lie, as the consequences could be disastrous. Reassure the hostage taker that someone authorized to hear the complaint or demand should arrive promptly.[121] If a weapon is put down, do not reach for it but rather attempt to verbally resolve the crisis while awaiting the arrival of security personnel. Legal authorities can be called on to provide a professional hostage negotiator if one is needed.

Each hospital should have a plan of action for cases of extreme violence.

The plan should include prevention and safety measures, a means for rapid notification of security and police personnel, evacuation plans, medical treatment, and crisis intervention.[46,121,122] A novel approach uses a violence management team trained in the preceding techniques to provide a mechanism for dealing with aggressive patients and protecting the staff.[123]

■ CLINICAL FEATURES

History and Physical Examination

Once combative patients are controlled, they need to be evaluated for organic causes of their agitated behavior. Separating functional from organic disease is a challenging task complicated by the fact that many patients with psychiatric disorders suffer from organic medical disorders that may worsen their symptoms. Patients who exhibit violent behavior that is caused or exacerbated by an organic problem may rapidly deteriorate if the medical issues are not addressed in a timely fashion. A focused history and physical examination assists the physician in differentiating functional from organic illness and facilitates a cost-effective and timely diagnosis.

Several historical features distinguish functional (psychiatric) from organic (medical) illness. Patients older than 40 years who have a new onset of psychiatric symptoms are more likely to have an organic cause.[124,125] Also, elders are at higher risk for organic delirium due to medical illness or adverse reactions to medications. Patients with a history of drug or ethanol abuse may exhibit violent behavior as a manifestation of an intoxication or withdrawal syndrome. The acute onset of agitated behavior, as well as behavior that waxes and wanes over time, suggests an organic origin. Most psychiatric patients are alert and oriented and have a past psychiatric history. Table 188-1 lists clues for distinguishing functional from organic causes of violent behavior.

The history of present illness should include psychiatric, medical, family, and social information, including suicidal ideation, medication use, and any recent changes to prescribed medications. Often family and friends can provide valuable details, as the agitated patient may not be a reliable source of information. When available, they should be interviewed independently from the patient. Medical records may detail medical and psychiatric history as well as prior history of violence. Drug and ethanol use is an important part of the history, as substance abuse is highly correlated with violent behavior.

The patient should be asked for permission for the physician to perform a thorough physical examination to search for an organic cause of violent behavior and uncover any resulting injury. Patient restraint may be necessary to accomplish even the most rudimentary physical examination. The importance of obtaining routine vital signs including temperature and performing a thorough mental status and neurologic examination cannot be overemphasized. Patients with persistently abnormal vital signs, a clouding of consciousness, or focal neurologic findings are more likely to suffer from organic disease and require further diagnostic evaluation. A careful physical examination should focus on the patient's general appearance (e.g., hygiene, nourishment, tremors) and vital signs, evidence of trauma or needle tracks, characteristic odors, neurologic and mental status examination, and signs of a possible toxidrome (Table 188-2).[126]

DIAGNOSTIC STRATEGIES

Diagnostic studies should be guided by the information obtained from the history and physical examination. Although some authors advocate a standardized panel of laboratory and radiographic studies for patients with psychiatric symptoms, most recommend tailoring diagnostic studies based on clinical findings.[118,124,127-130]

A rapid blood glucose determination and pulse oximetry should be obtained on all combative patients. Patients younger than 40 years of age with a prior psychiatric history, a normal physical exam including vital signs, a calm demeanor, normal orientation, and no physical complaints likely require no further diagnostic testing.[129] Additional studies that may be useful in selected patients include serum electrolytes, blood and urine toxicology screening, serum ethanol, thyroid function panel, cranial imaging, and electroencephalography (EEG).[25,28,46,124] A lumbar puncture may be performed if a CNS infection is suggested. Specific medication levels may be determined when toxic levels would affect therapy. An ECG may be useful in elders and in the setting of a suggested intentional ingestion. Patients who may have intentionally ingested a toxic substance should also have an acetaminophen level measurement, as this potentially fatal ingestion may be difficult to diagnose clinically and has an effective treatment.

An additional consideration in the diagnostic workup must be the concern of the psychiatrist who will ultimately evaluate the patient. Although serum ethanol and toxicology screening may not significantly influence a patient's treatment, the psychiatrist may use them to assess the degree to which ethanol

Table 188-1 Distinguishing Organic from Functional Etiology of Violent Behavior

	ORGANIC		FUNCTIONAL
Clinical feature	Delirium	Dementia	
Onset	Acute	Gradual	Gradual
Age of onset	Any	>50 years	<40 years
Alertness	Altered	Normal	Normal or hyperalert
Orientation	Impaired	Normal	Normal
Hallucinations	Common, can be visual/auditory/tactile	None	Auditory in schizophrenia, otherwise uncommon
Symptom picture	Fluctuating	Stable	Stable
Abnormal vital signs	Common	Uncommon	Uncommon
Psychiatric history	No	No	Yes

Table 188-2 Vital Signs and Toxic Syndromes

TOXIN	BP	P	RR	T	PUPIL SIZE	SKIN	EXAMPLE
Sympathomimetic	↑	↑	↑	↑	↑	Wet	Cocaine
Anticholinergic	↑/↓	↑	↑/↓	↑	↑	Dry	Diphenhydramine
Cholinergic	↑/↓	↑/↓	—	—	↓	Wet	Pesticides
Opiates	↓	↓	↓	↓	↓	—	Morphine
Sedatives	↓	↓	↓	↓	↑/↓	—	Lorazepam
Withdrawal (ethanol, sedative-hypnotics)	↑	↑	↑	↑	↑	Wet	Benzodiazepine withdrawal

BP, blood pressure; P, pulse; RR, respiratory rate; T, temperature; —, no change.
Adapted from Olshaker JS, Browne B, Jerrard DA, et al: Medical clearance and screening of psychiatric patients in the emergency department. Acad Emerg Med 4:124, 1997.

or drug use contributes to the patient's behavioral issues.[124,131] Ideally, an agreement on a diagnostic strategy should be reached between the psychiatrist and EP prior to referral. Unnecessary diagnostic testing prolongs ED length of stay and delays definitive psychiatric care.

■ DIFFERENTIAL CONSIDERATIONS

Violent behavior often occurs in association with head trauma, hypoxia, hypoglycemia, electrolyte imbalance, infections (particularly herpes encephalitis), drug intoxication or withdrawal or adverse reaction, and metabolic and endocrine derangements.[27,46] Uncommon organic causes include seizures (e.g., temporal lobe, limbic); tumors, particularly those in the limbic system; limbic encephalitis; multiple sclerosis; porphyria; Wilson's disease; Huntington's disease; sleep disorders; hyperparathyroidism; and vitamin and mineral deficiencies (e.g., folate, vitamin B_{12}, niacin, and vitamin B_6).[132] In the ED setting, drug and ethanol intoxication or withdrawal are the most common diagnoses in combative patients.[29,57] The mnemonic FIND ME (*f*unctional, *i*nfectious, *n*eurologic, *d*rugs, *m*etabolic, *e*ndocrine) helps to organize a diagnostic search for the cause of violence (Box 188-1).

Medical Clearance

The EP often provides "medical clearance" for the psychiatric or combative patient. It must be recognized that "medical clearance" is a misnomer and that on completion of the ED evaluation the patient is not "cleared" of all possible medical conditions.[127,133] In addition, there is no standard process of providing what may be more accurately termed a "focused medical assessment."[118]

The incidence of organic disease in patients presenting with psychiatric complaints ranges from 24 to 80%.[124,134,135] The more relevant issue for the EP is to detect medical problems that are causing or contributing to the patient's violent behavior. Misattribution of aberrant organic behavior in a patient with known psychiatric pathology is a common cause of litigation.[136] The EP should recognize that most psychiatrists rely on their medical assessment of the patient. Low risk patients with functional illness can be rapidly referred for psychiatric evaluation once they are calm and able to cooperate with a therapeutic psychiatric interview. Patients who are identified by a focused history and physical examination as being at higher risk for an acute organic illness require further diagnostic studies.

Once the medical screening evaluation is completed the findings should be communicated to the consulting psychiatrist. The medical record should reflect that the evaluation showed no evidence that an acute medical condition caused or contributed to the patient's behavior. If the cause of the patient's violent behavior is drug or ethanol intoxication, the patient should be observed until he has reached the point where a therapeutic interview can be conducted by the psychiatrist. Alternatively, the patient may be transported to a facility where observation can occur until the effects of the intoxicants have abated. Rather than pronouncing the patient "medically clear," the EP should clearly document his findings and recommendations to the consulting psychiatrist.

Preparing the Emergency Department to Prevent Violence

The risk of violence in the ED should be minimized in a cost-effective manner without creating a hostile or negative environment. The prevention of violence is best accomplished by developing a system that includes ongoing staff education, adequate personnel, and a well-designed physical structure. The personnel and features used in an institution's violence prevention program must be selected based on the assessment of risk in each facility.

BOX 188-1 PROBLEMS ASSOCIATED WITH VIOLENCE

Psychiatric
- Schizophrenia
- Paranoid ideation
- Catatonic excitement
- Mania
- Personality disorders
  - Borderline
  - Antisocial
  - Delusional depression
  - Post-traumatic stress disorder
  - Decompensating obsessive-compulsive disorders
- Homosexual panic

Situational Frustration
- Mutual hostility
- Miscommunication
- Fear of dependence or rejection
- Fear of illness
- Guilt over disease process

Antisocial Behavior
- Violence with no associated medical or psychiatric explanation (these patients may be managed by the police or security)

Organic

Diseases
- Delirium
- Dementia
- Trauma
- CNS infection
- Seizure
- Neoplasm
- Cerebrovascular accident
- Vascular malformation
- Hypoglycemia
- Hypoxia
- AIDS
- Electrolyte abnormality
- Hypothermia or hyperthermia
- Anemia
- Vitamin deficiency
- Endocrine disorder

Drugs
- Unanticipated reaction to prescribed medication (especially sedatives in brain-injured or elderly patients)
- Alcohol (intoxication and withdrawal)
- Amphetamines
- Cocaine
- Sedative-hypnotics (intoxication or withdrawal)
- PCP
- LSD
- Anticholinergics
- Aromatic hydrocarbons (e.g., glue, paint, gasoline)
- Steroids

AIDS, acquired immunodeficiency syndrome; CNS, central nervous system; LSD, lysergic acid diethylamide; PCP, phencyclidine.

Security Personnel

A well-trained and responsive security force is a key element of any hospital security system. Such personnel are expensive, and their expertise is often sacrificed quickly during budget curtailments, so decisions regarding the type and number of guards are often made on an economic basis. The use of guns by hospital security personnel is controversial, as is allowing other armed law enforcement officers into the ED. Other devices such as the Taser, stun gun, and mace are suggested as less lethal alternatives to guns.

Patient Searches

Searching patients for weapons as they enter the ED is permissible when performed in a nondiscriminatory manner.[121] Warning signs should be prominently displayed, perhaps reading: "For the safety of patients and staff, individuals entering the ED may be screened for weapons." Almost all patients and families will cooperate with searches and may actually feel safer as a result.[47] Clear written policies regarding searches and disposal of contraband must be distributed to the staff and closely followed.

Alarm Systems

The goal of any alarm system is to obtain rapid appropriate response with a minimum of false alarms. A tiered alarm system is usually best. Panic buttons in each room activate a central buzzer in the department. Several designated ED personnel respond initially and then judge the level of response needed. Every ED should have at least one telephone with a direct line to police or security in case additional personnel are deemed necessary. A verbal code (e.g., "Dr. Armstrong to Room 9") is also a useful adjunct.[46]

Limited Access to the Emergency Department

Controlling flow into the ED can be an effective method of preventing violent acts. High risk departments should limit access to one or two entrances, especially during the evening hours. Bulletproof glass barriers and buzzer access systems are useful as well.

Use of a Designated Room

ACEP recommends that most EDs contain at least one secure examination room with shatterproof ceiling lights, a solid ceiling, heavy indestructible chairs, a well-secured restraint bed, two doors that can be locked from the outside, and an emergency distress button that can be activated unobtrusively.[121] If desired, this room can be set up for video monitoring by security or ED staff.

One large urban county hospital with a high incidence of violent behavior in the ED is equipped with a large security force, metal detectors, a bulletproof Plexiglas triage area, a keypad security entry, controlled entryway into the ED, and metal bars to prohibit cars from driving into the department.[17] The hospital reports no incident of weapons-related violence or injury in the ED since these measures have been implemented.

Prevention

The concepts of primary, secondary, and tertiary prevention of violence can be applied to the ED environment.[13] Primary prevention refers to trying to control those factors that encourage the development of frustration and aggression. Long waiting times are associated with development of violent behavior. Attempts to shorten waiting times and make the waiting room environment as pleasant as possible may diminish previolent aggression. The presence of surveillance cameras and a visible security force also act as deterrents.

Secondary prevention of violence involves response to previolent agitation and aggression. Successful intervention involves the recognition of risk and implementation of de-escalation techniques. Staff should be trained to recognize previolent individuals who should be seen in a timely manner. Often the aura of preferential treatment defuses the situation.[123] Training of staff in techniques for managing violence leads to increased staff confidence and comfort while decreasing the rate of aggressive incidents.[137,138]

Tertiary prevention refers to limitation of the actual act of violence itself once it has occurred. Physical and chemical restraints are used, and security and police intervention are often needed. Protocols for dealing with the violent patient are important to minimize risks to the patient and staff. Enhanced security measures may be indicated in an ED with substantial risk for violence.

Violence is increasingly a major public health issue, with increased focus on improving surveillance and universal preventive measures to target large populations.[139-141] Physicians are increasingly aware of their role in reducing violence. Firearm regulations, hospital security mandates, and legislation for education of practitioners in the prevention and treatment of violence represent current controversies in which EPs should have a voice. A proposed agenda for violence prevention for emergency medicine includes improvements in medical education, research, and clinical practice, as well as involvement with public education and advocacy.[142]

KEY CONCEPTS

- ED staff should be trained to recognize potentially violent individuals and to intervene with de-escalation techniques.
- The ED should have a written plan of action to deal with violence that integrates the activities of ED staff, hospital administration, security, and local authorities.
- The EP should be familiar with the use of physical and chemical restraints.
- The possibility of an organic (medical) cause of aggressive behavior should be considered in all violent patients, even those with known psychiatric disease.
- ED leadership should be proactive in attempting to create an environment that is safe and supportive for both patients and staff.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 189

The Difficult Patient

Robert J. Vissers and Norman Kalbfleisch

PERSPECTIVE

Certain patients consistently arouse negative reactions in health care providers. These negative reactions may be initiated by a patient's appearance, apparent attitude, interactive style, or presenting complaint. Difficult patients can rapidly disrupt the harmony and efficiency of an emergency department (ED). Such patients have been referred to with a number of pejorative terms, such as *gomer*, *crock*, and other even less complimentary slang terms of disdain. They may receive suboptimal medical care, impede patient flow, and adversely influence the quality of care given to other patients, thus posing a medicolegal risk. Moreover, recurrent exposure to such patients, in the absence of a well-thought-out approach to dealing with them, may lead to escalating frustration for staff, promote unprofessional behaviors, and contribute to eventual burnout.

Historically, the medical literature has largely ignored the possibility of physicians harboring negative feelings toward any type of patient. Anger, hatred, and frustration are traditionally considered feelings that physicians should disown in favor of humor, compassion, and integrity. Although the latter are admirable attributes, to deny the presence of negative reactions is unrealistic. Physicians are as human as the patients they serve. Not until Freud coined the term *countertransference* were the negative reactions that patients can arouse in physicians actually recognized for their potential effect on care and used as diagnostic tools.

Good interpersonal skills are essential to the maintenance of the patient-physician relationship.[1] Although some clinicians have more natural abilities in this area than others, the myth that these skills are intuitive and cannot be taught is erroneous.[2] Teaching communication and relationship-building skills is now a priority of most medical schools and many primary care specialties.[3] The need for guidelines for teaching and evaluating interpersonal skills within emergency medicine residency programs has only recently been addressed.[2,4,5] The Accreditation Council for Graduate Medical Education (ACGME) has identified professionalism and interpersonal communication skills as two of the six core competencies required in the curriculum of all U.S. residency programs, including emergency medicine, prompting greater interest in research and education in these areas. Although it remains a challenge to measure the effectiveness of these initiatives, innovative curricula on professionalism and communication are being implemented in emergency medicine residencies.[6-9]

DISTINGUISHING PRINCIPLES

Difficult patients are often referred to as "problem patients," "disruptive medical patients," "unwanted patients," and, less diplomatically, "hateful patients."[10] Patients with personality disorders are commonly included in this group because of their rigid, maladaptive personality traits. Difficult patients, however, do not necessarily have personality disorders and may fall into one of several other familiar patient categories (e.g., drug seekers, hostile patients, malingerers, and ED repeaters).

There is no universally agreed on definition of the difficult patient. We define the difficult patient as *one who interferes with the physician's ability to establish a normal patient-physician relationship*. This impaired patient-physician relationship is often, but not necessarily, associated with negative feelings toward the patient.

PATHOLOGY OF THE PATIENT-PHYSICIAN RELATIONSHIP

An understanding of the difficult patient-physician relationship is hampered by a tendency to view it as a consequence of some inherent problem with the patient. Physician characteristics and the ED environment also play a role.[5,11-13]

Physician Factors

Impaired communication is a common problem in all forms of interpersonal relations and is often exaggerated in the medical setting. Patient satisfaction is highly correlated with patients' beliefs that clinicians listen to them and understand their requests, coupled with the perceived professionalism of the physician.[14] Despite this, physicians continue to focus on their own medical agenda, which may differ from patients' concerns. When confronted with patients who have difficult social situations, physicians exacerbate the problem when they refuse to deviate from their own rigid medical model.

Physicians often have preconceived notions regarding how patients should behave when they are ill and tend to rapidly categorize them as either the acceptable "truly sick" patient type or the "burdensome, difficult" patient type. Patients placed within the former category are excused for their symptoms, but patients in the latter category are not. Patients may also be judged as difficult when cultural differences or language barriers interfere with the develop-

ment of a mutual understanding between patient and physician.[13]

Physician failure to provide sufficient and interpretable information to patients about their diagnosis, treatment, and follow-up evaluation is another area of common communication breakdown. Studies show that in 20 minutes of patient-physician interaction, only 1 minute is reserved for educating patients about the illness.[15] Personal biases and prejudices also affect patient treatment.[11,16] The rapid formulation of an opinion based solely on appearance is a skill that physicians rely on to quickly form a "gestalt" about a patient. This is an essential skill for an emergency physician. To assume that such preconceived notions are influential only in a positive way, however, is unrealistic.

Emergency Department Factors

The ED is an environment plagued with distractions and frequent interruptions, rarely approaching the comforting atmosphere that many patients expect and deserve.[17] A sense of urgency and strict time constraints are often present. Patient assessments are sometimes conducted in suboptimal environments, such as hallways. The physician interaction is often perceived to be brief and punctuated by interruptions, which may imply to the patient that the physician does not care or that their evaluation is incomplete.[17-19] Patients may enter the encounter frustrated because of a lack of choice regarding their physicians or facilities and upset because of long waiting times, and physicians may enter the encounter biased by nursing comments or stressed by the prospect of losing control of the department while trying to deal with these particularly challenging patients.[13]

The Cycle of Impaired Patient-Physician Relationships

Difficult patients are deemed to make unreasonable demands on physicians (Fig. 189-1). Physicians react with negative feelings and may direct negative actions toward the patient. Patients are sensitive to these negative reactions, feel threatened with abandonment, and attempt to sustain the relationship by escalating symptoms. Physicians experience greater frustration at the maladaptive behavior of the patients, and so the cycle is perpetuated.

The consequences of this impaired relationship for the patient include failure to identify the real problems, missing medical diagnoses, "another poor experience" with the medical establishment, and premature or inappropriate discharge.[1] The negative effect on the staff is manifested by frustration, a sense of failure and defeat, fear of litigation, and the development of unconstructive stereotypes and unrecognized prejudices, all of which may contribute to eventual professional burnout.

STRATEGIES FOR TREATING THE DIFFICULT PATIENT

This section discusses the treatment of difficult patients from three approaches: general strategies, dealing with negative reactions, and crisis intervention.

General Strategies

Box 189-1 lists several general strategies that are helpful in dealing with difficult patients.

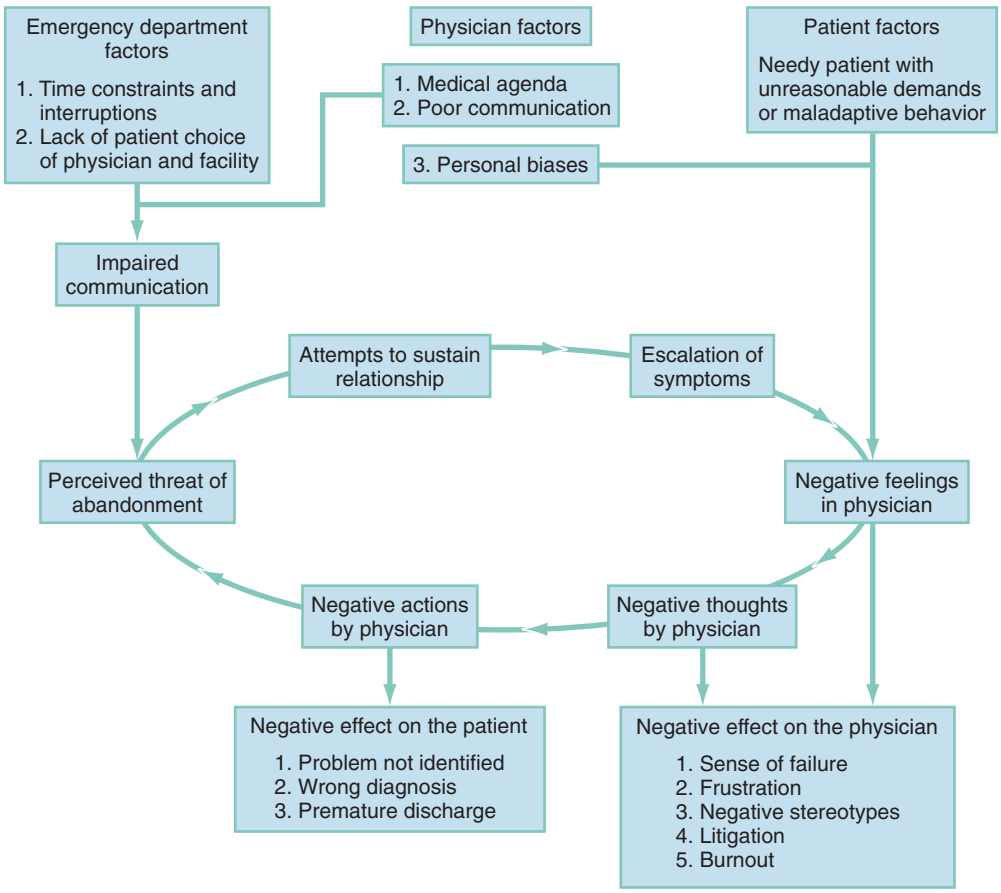


Figure 189-1. Cycle of the impaired patient-physician relationship.

BOX 189-1 GENERAL STRATEGIES FOR DEALING WITH DIFFICULT PATIENTS

Be supportive.
Structure the interview.
Set limits.
Point out impasses.
Share your reactions.
Redirect the interview.
Take time out.
Use teamwork.
Understand the patient's agenda.

Be Supportive

Being supportive is not always the natural response to difficult patients because of the negative feelings they arouse in the physician. Nevertheless, initiating the interaction with a clear and explicit demonstration of concern and empathy may be the single most powerful tool at one's disposal. Some physicians are concerned that seeming to be "soft" with a demanding or entitled patient may exacerbate the situation. To the contrary, expressing a respectful and empathetic concern for their problem effectively disarms many patients who are preparing for a long and arduous battle to be taken seriously. The possible news that there is no immediate solution available is more willingly received by patients who are convinced that they have been heard and believe the physician's desire to help is sincere.

Connecting emotionally with the patient can take time. Initially addressing a smaller concern in a caring and respectful manner can build trust and create greater rapport and compliance. For example, a patient who seeks treatment for self-inflicted lacerations but who will not cooperate with a history aimed at assessing suicidal risk is often more candid after the physician has rendered appropriate wound care in a nonjudgmental way.

Structure the Interview

Setting self-imposed time limits for contact with difficult patients helps control the anxiety associated with falling behind in a busy ED.[1] Flexibility in the structure of the assessment may be necessary. It is fair and appropriate to tell the patient of the need to excuse oneself to care for other patients. The fulfilled promise of returning to complete the next element of the assessment helps build trust and rapport.

Set Limits

It is helpful to share the ground rules of reasonable behavior with patients. For example, profane patients should be reminded that they are entitled to treatment but that their language may offend other patients. The physician may suggest they censor their remarks or be escorted from the area.

Point Out Impasses

At times, patient expectations and physician limit setting produces an impasse. When this occurs, it may be necessary to agree to disagree. Some issues can be resolved by pointing out impasses and giving the patient a chance to help solve the problem. Impasses sometimes can be resolved if difficult issues are set aside and returned to later in the interview. This fundamental approach to negotiations is generally underutilized in the ED.

Share Your Reactions

Pointing out impasses may not be effective if a patient senses annoyance or frustration in the physician. It may be helpful at such times to share one's feelings explicitly with the patient while continuing treatment.

Redirect the Interview

Some patients love to talk about issues unrelated to the problem at hand. Pursuing trivial or chronic complaints should be avoided. Patients often require redirection to focus on issues that have some potential for resolution. Asking them to take a chronologic approach in discussing a specific concern may help keep them on track.

Take Time Out

Physicians occasionally feel unable to contain their frustration. One should feel comfortable retreating from the room and returning when both parties have regained their composure.

Use Teamwork

Individuals who intimidate or split the staff are much more easily treated from the outset with teamwork. This is especially important with violent patients requiring restraint when a show of strength in numbers may defuse potentially dangerous situations. A more subtle, but equally important, application of teamwork is in the treatment and discharge planning of patients with complex problems who require an especially well-organized, multidisciplinary approach involving medical and support services in the community. Occasionally, if available, the benefit of a "second opinion" from an emergency medicine colleague can help identify the difficult patient and allow the treating physician to regain clinical perspective.

Understand the Patient's Agenda

Sometimes physicians ask themselves, "Why is this patient here?"[1] It is often productive to ask the patient the same question in a nonjudgmental fashion. The patient may have an easily satisfied, although unanticipated, agenda. This may be as simple as needing a bus ticket to get home or reassurance that there is no immediate danger of dying from some minor disorder. When the patient's needs are not as easily met, a clear understanding of the purpose of the visit may allow the opportunity to set more realistic goals.[20]

Dealing with Negative Reactions

Although negative reactions make dealing with difficult patients an unpleasant experience, they can also provide valuable diagnostic information. Physicians should accept these reactions as understandable responses to a patient's unpleasant behavior and use them to their advantage.[1]

Physicians typically have similar reactions to certain patient behaviors. The variations in these reactions depend on the individual physician's personality style, previous experiences, and unrecognized prejudices. Physicians must know their own reactions to specific behavioral patterns to use them as diagnostic aids.

Early recognition of these reactions may, in addition to their diagnostic value, allow the physician to analyze them

as the first step in preventing failure in the therapeutic relationship.[11,13]

Negative Thoughts about the Patient

Negative thoughts about patients have the greatest potential to adversely affect patient care. Patients are often placed into such stereotyped categories as "drug addict," "malingerer," or "crock." These labels may describe individual patients more or less accurately, but the potential exists for physicians to make inaccurate and potentially dangerous assumptions based on the biases linked to these labels.

The process of assigning patients to epidemiologic categories is a normal part of clinical judgment. Certain categories are used to help define the likelihood of encountering diseases in particular patient populations, thereby influencing decisions regarding investigation, treatment, and disposition. The danger in dealing with difficult patients is that this process can result in inaccurate assumptions about patients and compromise patient care.

Inaccurate assumptions about patients based on prejudicial, stereotyped labels are called *cognitive distortions*. The following case exemplifies the effect cognitive distortions can have on clinical decision-making.

An injection drug user requests analgesia for severe neck pain after minor trauma. The physician labels the patient a drug seeker and assumes the complaints to be fictitious. After becoming aware of the physician's assumption, the patient becomes belligerent and aggressive. He is escorted from the ED by security. A few days later, he returns with quadriplegia resulting from a cervical epidural abscess.

The physician assumed the patient was malingering because of past experience with injection drug users and did not consider other legitimate explanations for the patient's behavior. This phenomenon, known as "all-or-none" thinking, leads to the real disease being overlooked.

Negative Self-Perceptions

Self-directed negative thoughts by physicians often reflect a sense of inadequacy or despair. Some patients contribute to the problem by criticizing their care in ways that reinforce the physician's feelings of inadequacy. Unreasonable expectations of patients, coupled with their secret conviction that no one can really help, combined with the all too prevalent rescue fantasies of physicians, create a potent recipe for physician frustration, which in the long term can contribute to eventual burnout.

Negative Behaviors

Physician behaviors can be the most obvious manifestations of negative feelings and thoughts. Examples include rudeness, sarcasm, and indifference toward patients. A patient may receive an incomplete clinical evaluation, and unnecessary ancillary tests may be performed, as an attempt to compensate. Physical or chemical restraint use, administration of naloxone, or the performance of other procedures may be used inappropriately or punitively. Analgesics may be withheld or used sparingly. Faulty communication may result in misunderstood discharge instructions and poor compliance. Impaired patient-physician relationships may lead to a refusal of care, forcing treatment against patients' wishes, or resulting in them leaving against medical advice.[21]

Although patients can suffer at the hands of physicians, the potential exists for the reverse to occur. Dissatisfied patients with incorrect diagnoses and poor follow-up instructions are prone to initiate successful malpractice suits against physicians.[1] The physician may become the victim of patient violence.[22] Negative physician behaviors can also have an effect on the rest of the ED staff. Actions viewed by colleagues as inappropriate can compromise team morale and functioning. Physicians who are feeling angry, demoralized, and stressed may vent their frustrations on team members or consulting services, resulting in a further deterioration of the immediate situation and potential damage to long-term working relationships.

Strategies for Managing Negative Reactions

Six strategies are helpful in managing physicians' negative reactions toward patients.

Maintain Appropriate Emotional Distance

Physicians should avoid reciprocating hostile reactions offered by patients. This may be difficult to resist and is best accomplished by maintaining sufficient emotional distance so as to avoid taking the patient's behavior personally. This "detached concern" must be balanced with sufficient emotional investment to convey a sense of caring and empathy for the patient.[11]

Generate Alternatives to Negative Reactions

Instead of applying negative labels, physicians should attempt to view the patient as a victim of circumstance. Patients do not choose the social and genetic pool into which they are born. They do not choose to be abused children, to suffer from psychiatric disorders, or to experience many of the life events that lead to an ED visit. They are entitled to high-quality care, delivered with courtesy and empathy, despite their behavior.

Attempt to Understand the Patient's Behavior as a Symptom

The second step in managing negative reactions is to recognize that patients relate to the world in a particular way because of their condition, culture, and circumstances. The condition may include a variety of medical and psychiatric problems, intoxication, cognitive impairment, or personality disorders or traits. The behaviors that one finds so disturbing should be recognized as the symptoms resulting from these conditions. Cultural differences and social circumstances can result in behaviors that seem irrational or difficult if the underlying issues are not understood. When attempting to maintain a compassionate approach to a particularly troubled and troubling patient, it is sometimes helpful to imagine how difficult one would find it to *be* that patient.

Look for the Cognitive Distortion

Cognitive distortions are best identified by looking for evidence that patients or situations are being stereotyped. Physicians should be aware of the effects on clinical judgment that arbitrary inferences and all-or-none thinking have on interactions with patients.[23]

Find a Rational Response to Cognitive Distortions

The initial reaction to the elderly schizophrenic patient presenting with chest pain might be to discount the symptoms as delusional. Psychosis, however, is not protective against ischemic heart disease, and the principle of first considering the

most potentially life-threatening diagnosis serves both the patient and physician well in the ED.

Place Negative Reactions in Perspective by Viewing Them in Context

The ED is a stressful work environment. An expectation exists that emergency physicians will deal with problems quickly and effectively. Patients who thwart physicians' attempts to perform accordingly may be identified as undesirable. Such patients are difficult to view objectively when one is feeling overwhelmed. The frustration resulting from dealing with such difficult situations may produce an exaggerated response to a patient's behavior. Recognizing this may help reduce the loss of objectivity that leads to problems with patient care.

Although dealing with negative reactions is not the panacea for dealing with difficult patients, it provides the foundation for restructuring one's interactions with them in a way that will ultimately benefit the patient clinically and the physician emotionally.

Crisis Intervention

Some presenting complaints such as "can't sleep," "nervous stomach," "anxiety," and "can't cope" are especially likely to produce a sense of frustration and dread among caregivers. Attempts to deal with such complaints directly often prove unfruitful, partly because the patient's seemingly exaggerated affect interferes with effective communication. These are, however, all signs of a patient presenting in crisis.[24]

Anatomy of a Crisis

A crisis occurs when a hazardous event is encountered and customary problem-solving strategies prove ineffective.[24] People experience crises of various intensities many times in their lives; common examples include the death of a loved one, the loss of a job, serious illness, and domestic violence. The usual response of an individual to such stress is to experience an inner tension that mobilizes coping skills. Different problem-solving behaviors are then tried based on previous experience.

If an effective means of resolving the crisis is chosen, the person returns to a more organized state. If a resolution to the crisis is not easily found, a period of disorganization follows. During this time, the person experiences intense emotions such as confusion, anxiety, fear, anger, and despair. It is during the state of emotionally charged disorganization that a person may seek help at the ED.

Patients in crisis will, by the nature of their complaints and behavior, fall into the category of "the difficult patient" whether or not they actually are a "difficult person." It is important to be able to apply certain techniques of crisis intervention when dealing with such patients.

Dealing with the Crisis

Recognizing the Crisis. The presenting complaint of a patient in crisis may be a description of an event, situation, emotion, or physical symptom that can be vague or specific (domestic violence, inability to cope, anxiety, unwell, headache). Patients who present with crisis-related symptoms are a heterogeneous group. At one end of the spectrum are patients who have chief complaints that describe some type of emotional suffering and who do not require a traditional "medical" workup. At the other extreme are patients who need to be reassured in absolute terms about the absence of serious disease before their anxiety is alleviated. Between these two extremes are patients who partially understand how their circumstances might be contributing to their suffering. They can accept the idea that "the effect of stress often produces these kinds of physical symptoms." Many patients, however, are justifiably unwilling to accept this explanation until they believe their medical complaint has been adequately assessed. This usually requires no more than a careful history and physical examination followed by reassuring communication from the physician, and the patients' perception that the complaint is taken seriously. Some patients who are in severe crisis need to be taken through the steps of formal crisis intervention. The complex nature and considerable time required for this are often beyond the scope of practice of a busy emergency physician. The unfortunate increase in the length of stay for psychiatric patients in the ED, due to diminishing resources for these patients, may provide an opportunity for social workers, psychiatrists, or psychiatric nurse practitioners to employ this technique. A recognition of the patient in crisis is critical to creating a functional patient-physician relationship, addressing their underlying illness, and beginning the process of intervention (Box 189-2).

BOX 189-2 FIVE BASIC STEPS IN CRISIS INTERVENTION

Recognizing the crisis
Gathering basic information
Understanding the development of the crisis
Reproducing the peak tension of the crisis
Finding the solution

Gathering Basic Information. The first step in crisis intervention, after recognition of the crisis, involves gathering general information about the patient's home environment, work situation, personal relationships, and social involvements. The purpose of basic information gathering is to place the patient and the crisis into context before exploring the crisis itself. This step is time-consuming and cannot be rushed, and it needs to be performed by providers other than the emergency physician.

Understanding the Development of the Crisis. A structured interview is performed to obtain information about the sequence of events leading up to the crisis and the nature of the crisis itself. The objective is to understand the situation while keeping the interview organized and directed so that the patient can describe events without being overwhelmed by the emotion attached to them.

Reproducing the Peak Tension of the Crisis. Once the crux of the crisis is identified, the care provider should proceed to help the patient express the intense emotions associated with the situation. Through empathetic, active listening, the person in crisis is allowed to experience the previously overwhelming emotions in a safe context. This places the care provider in a position of trust and sets the stage for problem solving.

Finding the Solution. In the final phase of crisis intervention, the physician reframes the circumstances in objective, realistic, and understandable terms for all those concerned in order to facilitate a solution to the problem. Possible solutions to the crisis are then suggested, with participation from the involved parties, and the best plan for resolution is implemented. It is important that this be a joint effort and that the patient have some ownership of the solution.[24]

SPECIFIC APPROACHES FOR DEALING WITH DIFFICULT PATIENTS: PUTTING IT ALL TOGETHER

The various management strategies described here can be consolidated to formulate a practical approach to dealing with

difficult patients. The first step is the recognition of specific behavior types, rather than traditional diagnoses. These behavior types describe the most difficult patients seen in the ED. Patients displaying some, but not all, characteristics of a certain behavioral type may still be amenable to the management strategies for that type.

Behavioral Classification

Individuals with personality disorders frequently present as difficult patients. Although reliably establishing the diagnosis of a personality disorder during the typical brief ED encounter is difficult, an awareness of those personality disorders having a high prevalence in the ED helps ease communication with colleagues when the diagnosis has been previously established (Box 189-3).

An alternative to the traditional diagnostic categories for classifying difficult patients is based on four specific behavioral presentations and the negative reactions they produce.[25] We have adapted this classification system, using more neutral terms. The behavioral categories are *dependent patients*, *entitled patients*, *intractable patients*, and *self-destructive patients*. Through recognition of the difficult patient's maladaptive behavior and identification of the physician's subsequent negative reactions, patients can be placed into one of these behavioral categories. The behavioral categories in turn suggest effective treatment strategies for each patient type (Table 189-1).

Dependent Patients

Dependent patients see physicians as inexhaustible sources of compassion and understanding. Their initially reasonable requests rapidly escalate into repeated demands for reassurance, affection, analgesia, or other forms of attention. They are excessive in their gratitude; however, the more care they receive, the more their needs multiply. Initially, the physician

BOX 189-3 COMMONLY ENCOUNTERED PERSONALITY DISORDERS

Borderline Personality Disorder
Pattern of instability of interpersonal relationships, self-image, and affect that is accompanied by marked impulsiveness beginning by early adulthood and present in a variety of contexts. It may be indicated by five or more of the following:
1. Frantic efforts to avoid real or imagined abandonment
2. A pattern of unstable and intense interpersonal relationships characterized by alternating extremes of idealization and devaluation
3. Identity disturbance: markedly and persistently unstable self-image or sense of self
4. Impulsiveness in at least two areas that are potentially self-damaging (e.g., spending, sex, substance abuse, reckless driving, binge eating)
5. Recurrent suicidal behavior, gestures, threats, or self-mutilating behavior
6. Affective instability caused by a marked reactivity of mood (e.g., intense episodic dysphoria, irritability, or anxiety usually lasting a few hours and only rarely more than a few days)
7. Chronic feelings of emptiness
8. Inappropriate, intense anger or difficulty controlling anger (e.g., frequent displays of temper, constant anger, recurrent physical fights)
9. Transient, stress-related paranoid ideation or severe dissociative symptoms

Antisocial Personality Disorder
Pattern of disregard for and violation of the rights of others since the age of 15 years as indicated by three or more of the following:
1. Failure to conform to social norms with respect to lawful behaviors as indicated by repeatedly performing acts that are grounds for arrest
2. Deceitfulness, as indicated by repeated lying, use of aliases, or conning others for personal profit or pleasure
3. Impulsiveness or failure to plan ahead
4. Irritability and aggressiveness, as indicated by repeated physical fights or assaults
5. Reckless disregard for safety of self or others
6. Consistent irresponsibility, as indicated by repeated failure to sustain consistent work behavior or honor financial obligations
7. Lack of remorse, as indicated by being indifferent to or rationalizing having hurt, mistreated, or stolen from another

Dependent Personality Disorder
Pattern of pervasive and excessive need to be taken care of that leads to submissive and clinging behavior and fears of separation beginning by early adulthood. It may be indicated by five or more of the following:
1. Has difficulty making everyday decisions without an excessive amount of advice and reassurance from others
2. Needs others to assume responsibility for most major areas of his or her life
3. Has difficulty expressing disagreement with others because of fear of loss of support or approval
4. Has difficulty self-starting projects or doing things (because of a lack of self-confidence in judgment or abilities rather than a lack of motivation or energy)
5. Goes to excessive lengths to obtain nurturing and support from others, to the point of volunteering to do things that are unpleasant
6. Feels uncomfortable or helpless when alone because of exaggerated fears of being unable to care for self
7. Urgently seeks another relationship as a source of care and support when a close relationship ends
8. Is unrealistically preoccupied with fears of being abandoned

Paranoid Personality Disorder
Pattern of distrust and suspiciousness of others, such that their motives are interpreted as malevolent, beginning in early adulthood as indicated by four or more of the following:
1. Suspects, without sufficient basis, that others are being exploitive, harmful, or deceitful
2. Is preoccupied with unjustified doubts about the loyalty or trustworthiness of friends or associates
3. Is reluctant to confide in others because of unwarranted fear that the information will be used maliciously against him or her
4. Reads hidden demeaning or threatening meanings into benign remarks or events
5. Persistently bears grudges (i.e., is unforgiving of insults, injuries, or slights)

BOX 189-3 COMMONLY ENCOUNTERED PERSONALITY DISORDERS—cont'd

6. Perceives attacks on character or reputation that are not apparent to others and is quick to react angrily or to counterattack
7. Has recurrent suspicions, without justification, regarding the fidelity of spouse or sexual partner

Histrionic Personality Disorder

Pattern of excessive emotionality and attention seeking beginning by early adulthood as indicated by five or more of the following:

1. Is uncomfortable in situations in which the center of attention is someone else
2. Interaction with others is often characterized by inappropriate sexually seductive or provocative behavior
3. Displays rapidly shifting and shallow expression of emotions
4. Consistently uses physical appearance to draw attention to self
5. Has style of speech that is excessively impressionistic and lacking in detail
6. Shows self-dramatization, theatricality, and exaggerated expression of emotion
7. Is suggestible (i.e., easily influenced by others or circumstances)
8. Considers relationships to be more intimate than they actually are

Narcissistic Personality Disorder

Pattern of grandiosity, need for admiration, and lack of empathy beginning by early adulthood as indicated by five or more of the following:

1. Has a grandiose sense of self-importance (e.g., exaggerates achievements and talents, expects to be recognized as superior without commensurate achievements)
2. Is preoccupied with fantasies of unlimited success, power, brilliance, beauty, or ideal love
3. Believes self to be "special" and unique and can only be understood by, or should associate with, other special or high-status people (or institutions)
4. Requires excessive admiration
5. Has a sense of entitlement (i.e., unreasonable expectations of especially favorable treatment or automatic compliance with their expressed expectations)
6. Is interpersonally exploitive (i.e., takes advantage of others to achieve personal ends)
7. Lacks empathy, is unwilling to recognize or identify with the feelings and needs of others
8. Is often envious of others or believes that others are envious of him or her
9. Shows arrogant, haughty behaviors or attitudes

Adapted from American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Washington, DC, American Psychiatric Association, 2000.

may feel powerful and unique. Dependent patients give the message "You're the only doctor who cares" and the physician often believes it. As the demands escalate, the physician's patience diminishes and initial feelings of inflated self-esteem are replaced with feelings of frustration, exhaustion, and failure. This leads to a natural desire to discharge or refer these patients, along with their demands, to another unfortunate physician. The patient leaves feeling rejected and then begins the same vicious cycle with the next physician. Patients with certain personality disorders (dependent, borderline, and histrionic), somatoform disorders, malingering, and chronic psychiatric disorders often fall into this behavior category.[1,26]

Dependent patients are best treated early in the relationship before the help-rejection cycle is fully established. Some of their earliest identifying features are the negative reactions they produce in physicians. The replacement of physicians' strong feelings of self-esteem by frustration and failure is a diagnostic clue to this type of patient. Although it is important to be supportive with such patients, it is imperative to set limits as tactfully and firmly as possible. Physicians should point out their own limited time and resources. Reasonable expectations for the patient must be established while giving assurances that one will try to help. After appropriate management, disposition should be arranged, and written discharge instructions with defined criteria for return visits to the ED should be provided. The need for follow-up visits with the appropriate primary care provider should be emphasized.

Dependent patients are especially likely to seek solutions to their problems at the ED in times of crisis. Looking for the underlying issues and structuring the interview along the lines of crisis intervention can assist in finding a satisfactory resolution to the patient's problem.

Entitled Patients

Very important persons (VIPs) are often well-informed, independent professionals who may be knowledgeable in medical matters. They spend their professional lives in a position of authority and control. The traits that make them successful in the workplace, however, can cause them to be demanding, fault-finding, and self-entitled patients.

Entitled patients also seem to have endless needs, but instead of helplessness or seduction, they use intimidation, hostility, and threats to attain their often unreasonable demands. Entitled patients fear being helpless and dependent on physicians. They use a shield of entitlement to protect themselves. An example is the lawyer who, in his refusal to accept his illness, roams from physician to physician demanding repeated tests and opinions, while threatening to sue the previous physician who had tried to help him. Physicians experience the natural responses of disgust, anger, and antagonism when faced with such patients. There may be an urge to enter into a power struggle with the patient. The other common temptation is to accept the patient's terms at the price of compromising his or her care. Occasionally, the physician may even experience shame at being unable to meet the patient's unrealistic demands. The maladaptive behaviors of entitled patients are commonly seen in people with paranoid and narcissistic personality disorders, as well as in addicted patients and VIPs.[26]

Because the behavior of the entitled patient stems from insecurity, it is important to be supportive. While reassuring patients that they are entitled to good medical care, physicians must set limits that unreasonable demands will not be met. Prolonged debates with the patient about diagnostic and therapeutic options should be avoided. Recommendations about management options should be offered and patients left to

Table 189-1 Management Strategies: Putting It All Together

BEHAVIORAL CLASSIFICATIONS	ASSOCIATED TRADITIONAL DIAGNOSTIC CATEGORIES	SUGGESTED MANAGEMENT STRATEGIES
Dependent Patients		
Excessive needs for attention, reassurance, analgesia.	Personality disorders: dependent, histrionic, borderline	Try to view the patient's neediness as a symptom. Be supportive while setting limits on patient expectations.
Uses helplessness and seduction.	Malingerers, chronic psychiatric patients	May need crisis intervention.
Physician initially feels special, then drained and frustrated.		Follow-up with appropriate, consistent physician.
Patient increases needs when ultimately rejected.		
Entitled Patients		
Fear of loss of power causes entitled behavior.	Personality disorders: paranoid, narcissistic	Be supportive of entitlement to good care while setting limits on unreasonable demands.
Uses intimidation, name dropping, hostility, and threats.	Substance abusers	Allow patients to choose between reasonable treatment options.
Physician feels intimidated, angry, sometimes inadequate.	VIPs	Avoid power struggles.
Potential for litigation.		
Intractable Patients		
Excessive needs for attention met by having unsolvable problems with multiple visits, doctor shopping, poor compliance, and no hope for successful treatment.	Personality disorders: antisocial, borderline Malingerers	Distinguish from other complicated patients, and manage appropriately.
Physician feels frustrated, angry, but fears "sharing" pessimism and missing significant illness.		Beware of cognitive distortions that may obscure significant illness.
Cycle of "help me, but nothing helps."		Be supportive while setting reasonable expectations.
Self-Destructive Patients		
Disregard for own health and repeated visits for serious illness.	Borderline personality disorder Substance abusers	Provide appropriate medical care.
Often overtly self-destructive, denying of illness.	Chronically suicidal patients	Learn to deal with own negative and nihilistic reactions to patients.
Physicians feel frustrated, helpless, angry, and guilty for wishing the patient success.		Look for signs of depression and consider psychiatric referral as needed.

VIPs, very important persons.

exercise their autonomy in choosing their preferred course. At the same time, physicians must communicate their acceptance of the patients' rights to exercise this control and that their decision will not jeopardize subsequent access to appropriate care.

Intractable Patients

Intractable patients, like dependent and entitled patients, have insatiable needs for emotional support. They are, however, neither seductive nor dependent in their behaviors. They present the antithesis of entitlement; they believe nothing will help. Intractable patients desperately seek help despite the failure of all previous medical assistance. Their history is punctuated by multiple emergency visits and behaviors that are self-defeating, covert, and manipulative. These negative behaviors undermine treatment and antagonize physicians, creating feelings of anger, self-doubt, and frustration. Patients with borderline and antisocial personality disorders and malingerers often fall into this behavioral category.[26]

Malingerers are among the most difficult patients presenting to the ED. Malingering is the intentional production of false or grossly exaggerated physical or psychiatric symptoms, motivated by external incentives that are unrelated to illness.[27] These patients may be seeking narcotics, shelter, or monetary compensation; may be attempting to avoid work or criminal prosecution; or may simply be lonely.

Malingering represents deceptive, manipulative behavior and is coded in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV), as a "problem" rather than a mental disorder.[26] This contrived behavior must be distinguished from the psychiatric illness of somatoform disorders. Somatization is the involuntary production of symptoms without the patient's awareness. Unlike malingerers, somatizers are not motivated by any conscious desire for secondary gain.

Repeaters are patients who frequent the ED excessively to the point that most staff know them by name. Although chronic schizophrenics often fall into this category, this behavior can occur in any patient with poor coping skills and maladaptive responses to psychosocial stressors. The easy accessibility of the ED often makes it the only support system immediately available to chronically decompensated patients. Despite the perception that "frequent flyers" are often inappropriate in their ED utilization, studies demonstrate that frequent users

are in poor health and require medical attention more often than less frequent users.[28,29]

Geriatric patients with multiple medical problems and those abandoned in the ED by caretakers who are no longer willing or able to meet their needs are also patient types that deserve special attention. Although these patients have problems that are often difficult to solve, the patients themselves are not necessarily difficult people.[30]

Intractable patients elicit strong negative reactions from physicians and are sometimes identified by the feelings of futility that they produce in their caregivers. Their multiple, vague complaints that defy diagnosis and successful treatment often cause them to be labeled as "crocks," along with dependent patients.

Intractable patients pose a particular risk of missed diagnosis or premature discharge. Physicians must avoid the temptation to overreact with cognitive distortions and dismiss the possibility of genuine illness in the patient. Intractable patients should be distinguished from other complicated patients, evaluated for conditions that require immediate intervention, and provided appropriate management and disposition. Alternatively, there may be a tendency to inappropriately launch into extensive investigations if the behavior type is not recognized. Collateral information from previous medical records and other caregivers is valuable in providing diagnostic guidance.

Because this type of behavior stems from a need for a relationship and fear of rejection, it is important for physicians to be supportive. The belief that showing empathy only encourages maladaptive behavior is generally untrue. To the contrary, an escalation of symptoms usually follows when these patients interpret a physician's lack of concern as rejection.

Nevertheless, limits should be set regarding patients' expectations. Physicians should use this strategy while acknowledging the difficulty of the patients' problems and sharing their deep concern, and perhaps even pessimism, regarding the outcome of the investigations and treatment. It is helpful to make statements such as, "You know, Mr. Jones, you obviously have a very difficult problem here. You've seen lots of doctors and had lots of tests and treatments that don't seem to be helping much. There is no way, given the limited resources available in the ED at 11 o'clock on a Friday night, that we are going to be able to get to the bottom of this. What I can do is examine you and do some tests to make sure that there is no new, serious problem going on tonight. Then you will be able to follow up with your regular doctor on Monday." In this way the physician can communicate both an interest in the patient and empathy for his condition while setting limits on expectations. Both the physician and patient then understand the "contract" and have a way of terminating the encounter satisfactorily.[20]

Self-Destructive Patients

Self-destructive patients are particularly difficult to treat. Unlike intractable patients, they do not seek help. Rather, they are repeatedly brought to the ED because of their neglectful and self-destructive behaviors. Their ability to deny their problems is profound and sets up the maladaptive cycle of "nothing is wrong and nothing will help." Yet their behaviors often require repeated heroic efforts to save their lives. Their chronic self-destructive behaviors may temporarily meet their immediate needs of shelter and food and perhaps, paradoxically, some of the attention they outwardly reject. This lethal cycle usually leads to a premature death. The *substance abuser*, the *violent patient*, and the *suicidal patient* are included in this category of difficult patient.[10]

It is not surprising that ED staff respond to such patients negatively, feel frustrated and helpless, and may even secretly wish them success in their self-destructive efforts. These are among the most difficult patients to treat. In reality, physicians can do little apart from providing appropriate care for the multiple presentations characteristic of this type of patient. The greatest obstacle for physicians may be to come to terms with their own complacency about the survival or demise of such patients. The lack of real concern about whether they live or die or, worse, actually wishing that they would die, is repugnant and produces feelings of self-recrimination. Our inability to relate to the self-destructive decisions made by these individuals contributes to our complacency about their plight. Remembering our own human weaknesses or risk-taking behaviors and viewing their seemingly incomprehensible behavior as a difference in degree rather than in kind may help us to have more empathy for them.[11] Being supportive is important. Signs of depression in the patient may indicate the need for psychiatric referral. These patients should be screened for risk of suicide and, when appropriate, held for psychiatric evaluation following medical stabilization.

SUMMARY

Dealing with difficult patients is a common problem in the ED. The impaired patient-physician relationships associated with them have multiple negative implications for both patients and physicians. Their treatment may be optimized by using the general principles discussed in this chapter, by dealing realistically with one's own negative reactions, and by using techniques of crisis intervention where appropriate. These strategies are best applied within the context of a behavioral classification that avoids pejorative terms and stereotypes, labels that differentiate them from "worthier" patients.[11] Although this approach is not a panacea for dealing with difficult patients, the framework may help physicians render appropriate care while minimizing personal frustration, medicolegal exposure, and eventual physician burnout.

One of the great challenges of medical practice is to maintain humanity when caring for these difficult and highly vulnerable individuals. By focusing on their humanity, we have the best chance of preserving our own.[11] It is easy to care for patients who generate sympathy and noble to care for those who do not.[13]

In the end, the ability to accept distressing behavior as a symptom and to treat even the most irritating individuals with compassion and kindness may be the key to surviving them. When asked how he had avoided burnout after decades in emergency medicine, one well-known patriarch of the specialty simply responded, "You've got to love the patients."[31] This is a tall order, and not meant in the literal sense. But the degree to which we can show caring and empathy, even to the unlovable, may be the key to maintaining the quality of our care, our satisfaction with the specialty, and our long-term survival in practice.

KEY CONCEPTS

- Difficult patients may elicit negative reactions in caregivers, resulting in undesirable implications for both themselves and their caregivers.
- Managing the difficult patient can be optimized by understanding the multiple factors contributing to the impaired physician-patient relationship.
- Behavioral classifications should be used instead of pejorative stereotypes when characterizing difficult behaviors.
- General and specific strategies, including understanding our own reactions, are helpful in dealing with the impaired physician-patient relationship.
- The ability to accept difficult behaviors as symptoms and treat even the most difficult patient with kindness is central to providing good care while avoiding personal frustration, medicolegal repercussions, and physician burnout.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

PART VI

Emergency Medical Services

CHAPTER 190

Emergency Medical Services: Overview and Ground Transport

Thomas H. Blackwell

PERSPECTIVE

Development of Emergency Medical Services

Before the advent of civilian ambulance services, the sick and injured were transported by any means available, including passerby motorists, wagons, farm machinery, delivery carts, buses, or taxicabs. Figure 190-1 depicts the early Larrey ambulance used during the Napoleonic Wars, the Rucker Wagon used during the American Civil War, and a modern ambulance used today. In 1865, the Commercial Hospital in Cincinnati established the first hospital-based ambulance service. Four years later, the first city service began at New York's Bellevue Hospital[1].

In 1965, the President's Commission on Highway Safety recommended a National Accident Response Program to decrease death and injury from highway accidents.[2] Results from a second national survey by the National Academy of Sciences—National Research Council were used to draft a white paper entitled "Accidental Death and Disability: The Neglected Disease of Modern Society."[3] Published in 1966, this document described the hazardous conditions of emergency care provision at all levels and outlined the necessary building blocks for future EMS maturation. These national efforts were the impetus for congressional legislation that directed the U.S. Department of Transportation (DOT)—National Highway Traffic Safety Administration (NHTSA) to develop a program for improving emergency medical care.

During the mid-1960s, out-of-hospital cardiac care included field defibrillation programs in Belfast, Northern Ireland, and cardiac arrest research in several U.S. cities.[4,5] In 1969, the first National Conference on EMS convened, resulting in the development of a curriculum, certification process, and national registry for the emergency medical technician-ambulance (EMT-A). By 1972, the U.S. Department of Labor recognized the EMT as an occupational specialty.[6] Interested physicians and nurses later provided advanced educational courses and practical experiences for the EMTs, and thus began the paramedic providers.[7,8]

Additional programs prompted Congressional passage of the EMS Systems Act of 1973 (P.L. 93-154), which authorized funding that dramatically improved the development of comprehensive regional EMS delivery systems. Efforts to improve pediatric emergency care occurred in 1984 when Congress adopted the Emergency Medical Services for Children (EMS-C) initiative through the Health Services, Preventive Health Services, and Home Community Based Services Act of 1984 (P.L. 98-555).[9] An Institute of Medicine (IOM) study, released in 1994, promoted the concept of EMS-C becoming integrated not just into existing EMS systems but into comprehensive systems of care provision, including injury prevention, primary and definitive care, and rehabilitation services.[10]

More than 40 years since publishing the 1966 white paper, the IOM released a report on the status of emergency care entitled "The Future of Emergency Care in United States Health System." The report focused on three separate, yet related, topics: (1) emergency care: at the breaking point, (2) emergency medical services at the crossroads, and (3) emergency care for children: growing pains.[11-13]

A major focus included the need to strengthen the integration of EMS into the entire healthcare system, because lack of such coordination often results in patients being diverted from overcrowded to inappropriate or distant facilities. The recommendation was to ensure that the delivery of emergency medical and trauma care is organized into a coordinated, regional system such that patients receive care at the most appropriate facility based on their injury or illness. Additional recommendations targeting EMS improvement included national accreditation for paramedic educational programs, adopting a national certification system for individual state licensure, and recognizing common levels of EMS certification across the United States.

The concern for inadequate funding for EMS systems operations and disaster response was also addressed. Recommendations included Congress developing regionally funded, multiyear demonstration projects that encourage states to identify and test strategies for creating seamless systems of care, workforce strengthening, evidence-based practices, and disaster preparedness. It was further recommended that an advisory committee be created to work with the Centers for Medicare and Medicaid Services to improve reimbursement and policies related to reimbursement.

Finally, a small, yet significant, proportion of EMS transports involve the pediatric population; thus, it is often difficult for prehospital providers to maintain the knowledge and skills necessary to care for critically ill or injured children. Many plans, including disaster preparedness, often neglect children. As such, the IOM report recommended several items, most importantly that the care of children be integrated into the overall EMS system and not separated from adults, with pediatric emergency care competencies being defined and training enhanced to maintain those competencies. Because it is diffi-

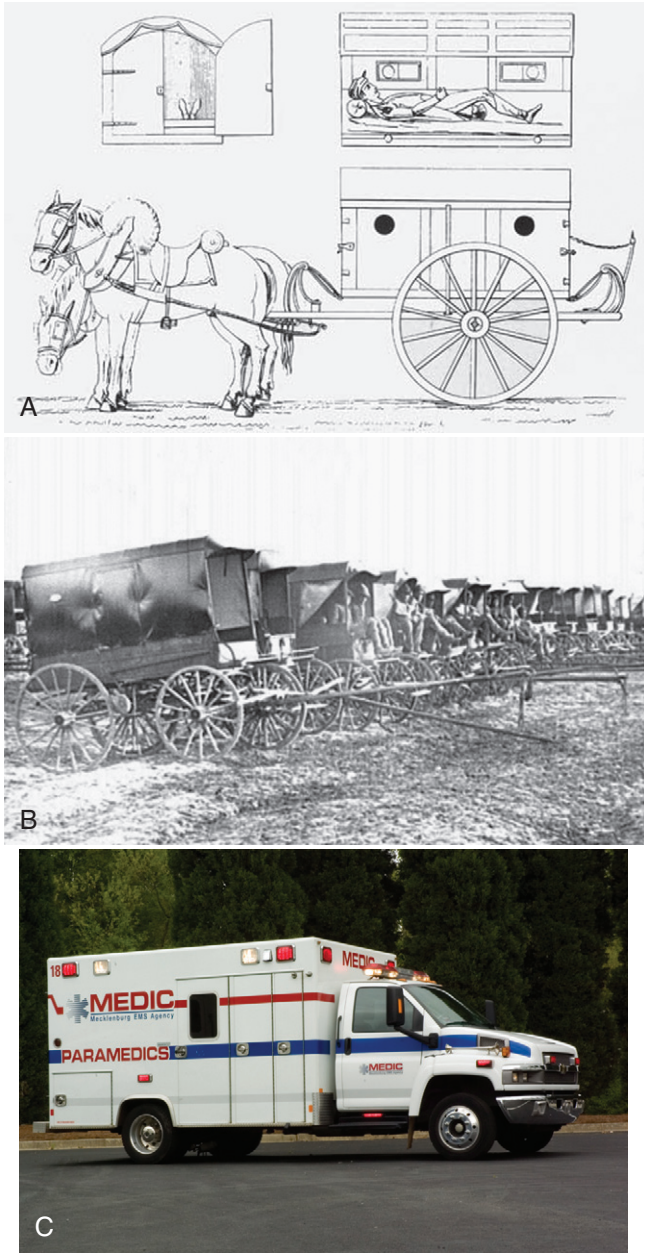


Figure 190-1. Larrey's Flying Ambulance (**A**), Letterman's Rucker Wagon (**B**), and the modern ambulance used today (**C**). (**A**, courtesy of the National Library of Medicine, History of Medicine Division; **B**, courtesy of the Library of Congress, Prints and Photographs Division, LC-88171-2585 DLC; and **C**, courtesy of Monroe Hicks, Mecklenburg EMS Agency, Charlotte, North Carolina.)

cult to ascertain whether systems have targeted the pediatric population, the IOM further recommended that a pediatric coordinator be included in all EMS systems to advocate for ensuring equipment, medications, training, and protocols are appropriate for children.

Each of the three IOM reports supported the concept of the federal government developing national standards for emergency care performance indicators and evaluation and protocols for triage, treatment, and transport of patients. To accomplish this objective, a lead federal agency should be identified. Debate exists whether EMS at a national level should remain under the NHTSA or reside in other applicable agencies (e.g., Health and Human Services, Homeland Security). Regardless, the parent organization must ensure that research is supported to improve the knowledge base and support evidence for the practice of out-of-hospital medical care.

Emergency Medical Service Systems

Multiple EMS system designs exist, all predicated on the type of community served. While this is a local decision, all states incorporate an administrative office that governs or oversees the provision of EMS activities. Typically the role is not to direct any individual service, but to assist in planning, licensing services, and establishing or enforcing the scope and standards for practice. Other functions may include training, examining, certifying and recertifying providers, record keeping, data collection, and auditing or investigating programs. A description of systems for the 200 most populous cities in the United States is periodically published in the *Journal of Emergency Medical Services*.[14] For simplicity, the following categorization of systems will be used: private and public agencies; basic life support (BLS) and advanced life support (ALS) services; and single-tiered, multitiered, and first responder systems.

Private and Public Agencies

Where local government has not assumed primary responsibility for EMS services, communities may depend on private providers. Financial responsibility varies but usually depends on federal reimbursement (Medicare or Medicaid) and user fees. A local government subsidy may or may not supplement the operation. If multiple providers are serving one jurisdiction, calls may be allocated by rotation or specified zone coverage. Dispatching varies depending on the system but may be by the provider or by a central agency. Medical direction is often provided by a contracted physician or physician oversight board.

Hospital-based EMS systems are few in number and may be managed by a single hospital or hospital corporation. Not all hospital-based EMS programs are considered private, in that the hospital may be a division under local or state government or operating under a public authority. Like private models, financial responsibility is usually in the form of user fees, with or without additional subsidy. Dispatching may be provided by a local public safety agency that may also be responsible for police and fire communications. An emergency physician from a sponsor or base hospital typically provides medical direction for these systems.

A public utility model is a hybrid between private and public design that allows local government to contract with a private or public provider. The successful bidder for service becomes a contracted entity that agrees to provide the specified services (ALS, BLS, or both) to the catchment area and, depending on the arrangement, may bill the patient directly or receive uniform reimbursement. Depending on local structure and interagency agreement, dispatching may be performed by an existing public safety organization or by the parent company. Medical direction is usually a specified individual subject to contractual terms.

When government officials were faced with planning and establishing EMS systems during the early maturation periods, many decided that the fire department was the logical choice to incorporate EMS. Fire stations were strategically located throughout the community, and personnel were already used to providing emergency response. Firefighters could be cross-trained as a firefighter-paramedic or dedicated to either fire or EMS function with the opportunity for transfer. Public EMS systems that were not incorporated into fire departments evolved into their own separate entity, referred to as a municipal third-service system. Such agencies are operated by local municipalities and are endorsed and supported by local government. Many cities have been successful in combining

police, fire, and EMS under a global public safety agency, with all department heads or chiefs reporting to one manager or administrator. Financially, public EMS systems may be supported by a tax base, which may or may not be supplemented by user fees. Regardless of design, medical oversight for a municipal EMS system may be provided by a physician appointed and contracted by a local hospital, an advisory council, or medical oversight board.

Basic Life Support and Advanced Life Support Service

BLS describes the provision of emergency care without the use of advanced therapeutic interventions. Skills include airway management (oral and nasal airways, bag-mask ventilation), cardiopulmonary resuscitation (CPR), hemorrhage control, fracture and spine immobilization, and childbirth assistance. Defibrillation using an automated external defibrillator (AED) is often included by many BLS systems. Services are provided by certified or medical first responders or emergency medical technicians (EMTs) certified at the basic level (EMT-B).

BLS systems may be associated with poor survival rates from out-of-hospital cardiac arrest, especially those not incorporating AED technology.[15,16] Alternatively, there is debate on the effectiveness of ALS for medical and traumatic emergencies.[17,18] Despite this evidence, few urban communities across the United States operate solely at the BLS level. Many rural and some suburban EMS services rely on volunteers who may not wish to become advanced-level providers. Because these services may have low call volumes, it becomes more difficult for personnel to maintain advanced skills and a proficient knowledge base.[19] Also, such communities may not have access to medical supervision or hospital sponsorship for ALS care.

Systems categorized as ALS offer a more comprehensive level of service by highly educated providers, usually certified at the intermediate or paramedic level (EMT-I or EMT-P, respectively), or equivalent levels depending on individual state certifications. Provider skills include advanced airway interventions, intravenous (IV) line placement, medication administration, cardiac monitoring and manual defibrillation, and certain invasive procedures. Most EMS systems in urban cities operate at the ALS level of care.

The number of EMT-Ps in any jurisdiction has come under scrutiny, in that cities with more paramedics per capita tend to have lower survival rates.[20] Although this may seem implausible, one explanation might be that the number of patient encounters per paramedic decreases and the sharpness of skills degrades when that community is saturated with paramedics.

Single-Tiered, Multitiered, and First-Responder Systems

In a single-tiered system, every response regardless of the call type receives the same level of personnel expertise and equipment allocation (all BLS or ALS). Multiple-tiered systems use a combination of ALS and BLS levels depending on the nature of the call. Differences in cost and effectiveness between a mixed ALS-BLS service and an all ALS service have been debated. Currently, there is a steady decrease in systems that provide mixed ALS-BLS care.[21,22] A single-tiered ALS response may prove to be cost-effective in specific locales, ensures the capability of providing a consistent advanced level of care to all patients regardless of illness or injury severity, and obviates the potential for undertriage or overtriage by 9-1-1 telecommunicators. Alternatively, a multitiered system may meet the needs of individual communities or agency infrastructure. This design often meets with employee satisfaction and has the potential to preserve ALS resources for higher priority calls, in that BLS transport of nonurgent patients allows for ALS ambulances to be available for potential critical responses.

Regardless of single- or multiple-tier design, EMS systems usually include first-responder (FR) services as part of their structure. The FR, usually a police officer or firefighter, is the nontransport BLS or ALS provider who quickly responds to the scene of an emergency to provide initial care before definitive medical care and transportation assets arrive. The FR quickly assesses the situation and patient(s), determines whether additional resources are required, initiates patient care, and provides advance information to responding personnel.

The design of an EMS system is targeted toward providing quality patient care in the briefest period of time following unexpected injury or illness. A desirable and cost-effective design might include BLS nontransport FRs with short response times (average 2–4 min), having the capability of providing early defibrillation and airway support, coupled with ensuing ALS care and transport services.[23]

Levels of Provider and Scope of Practice

At the federal level, NHTSA is responsible for developing the National Standard Curriculum for the different certification levels. Individual state legislation is responsible for provider levels recognized, initial and continuing medical education requirements at each level, testing, and time intervals for course completion and recertification. The following sections outline the DOT recommendations for the four common levels of provider with suggested hours of training and incorporated skills (Table 190-1).

First Responder

The FR is typically the first to arrive on the scene of an incident. Initial scene and patient assessment, along with limited life-saving interventions, are primary functions. Along with CPR and basic airway management skills, the FR should be able to control hemorrhage and initiate spinal immobilization.

The four elements referred to as the "chain of survival" by the American Heart Association (AHA), which decrease mortality from out-of-hospital cardiac arrest, are early access to care, CPR, defibrillation, and advanced airway management and medications.[24] Because early defibrillation may improve the odds of survival of out-of-hospital cardiac arrest, the use of an AED should be a mandatory procedure for the FR.[25,26]

The DOT recommends 40 hours of didactic instruction for the standard FR course and 16 to 36 hours for refresher training. A clinical rotation is not part of the curriculum.[27]

Emergency Medical Technician—Basic

The EMT-B is the minimum level required to staff a BLS ambulance and is commonly used for nonemergency and convalescent transport services. In addition to the skills of the FR, the EMT-B is also involved with triage, more detailed patient assessment, and transportation. Like FRs, EMT-Bs should have the capability of providing early defibrillation.[28]

In 1995, NHTSA released the revised EMT-B curriculum. The initial course requires approximately 110 hours of instruction and includes 46 lessons, each with cognitive, effective, and psychomotor objectives.[29] Many states have expanded the course to include more skills such as AED use, epinephrine autoinjections, albuterol administration by hand-held nebulizer or metered-dose inhaler, and IV fluid therapy. For recertification, the DOT recommends a 24-hour refresher course,

Table 190-1 EMS Provider Level Training and Skills

EMS PROVIDER LEVEL	DOT RECOMMENDED HOURS OF TRAINING	SKILL SET
First responder	Initial: 40 hr Refresher: 16–36 hr	Initial scene and patient assessment and stabilization Basic airway skills CPR Control hemorrhage Spinal immobilization
EMT—Basic	Initial: 110 hr Refresher: 24-hr refresher course, 48 hr of continuing education, and a BLS course every 2 years	First responder skills plus: Triage and detailed patient assessment AED May assist in some systems: Use of epinephrine autoinjectors for anaphylaxis; albuterol for wheezing
EMT—Intermediate	Initial: 300–400 hr and includes didactic and clinical experience	EMT—basic skills plus: Endotracheal intubation Manual defibrillation IV line placement Limited pharmacologic treatments May assist in some systems: Laryngeal mask airway
EMT—Paramedic	Initial: 1000–1200 hr Refresher: 48-hr refresher course, 24 hr of yearly continuing education, and BLS and ALS courses at the pediatric and adult levels	EMT—intermediate skills plus: Cardiac rhythm recognition Expanded pharmacologic treatments Needle decompression of a tension pneumothorax Needle or surgical cricothyrotomy Transthoracic cardiac pacing

AED, automated external defibrillator; ALS, advanced life support; BLS, basic life support; CPR, cardiopulmonary resuscitation; DOT, Department of Transportation; EMT, emergency medical technician; IV, intravenous.

48 hours of continuing education, and a BLS course every 2 years.

Emergency Medical Technician—Intermediate

The EMT-I was established to allow a more comprehensive approach to care when paramedic services were unavailable or unobtainable. Many states recognize the EMT-I certification, but others designate alternative, but comparable, levels depending on specific skills and procedures. The intermediate level is useful for rural systems because it supplies an ALS for less cost and educational time expended. The scope of practice for the EMT-I varies across the United States. Most systems allow the EMT-I to establish an IV line and to manually defibrillate. Limited administration of medications and use of adjunctive airway devices (e.g., blind insertion airway device or laryngeal mask airway) may be integrated skills.

The DOT recommends 300 to 400 hours of initial education that includes didactic classroom lectures combined with hospital and field experiences.[30]

Emergency Medical Technician—Paramedic

The EMT-P is the most advanced out-of-hospital provider. Paramedics have the capability to address most out-of-hospital emergencies. The scope of practice includes a wide variety of therapeutics and procedures including cardiac rhythm recognition, expanded pharmacologic treatments, and advanced airway interventions. Other important invasive procedures include needle decompression of a tension pneumothorax, needle or surgical cricothyrotomy, and transthoracic cardiac pacing.

A recent revision of the National Standard Curriculum for the EMT-P calls for approximately 1000 to 1200 instructional hours, including didactic, clinical, and field education. All course content focuses on technical and professional competency. Additional modules are included that allow programs to incorporate an expanded scope of practice.[31] With the expansion of EMS technology and management career options, many paramedic educational programs have advanced from 1-year certificate curriculums to 2-year associate or 4-year baccalaureate degrees. Recertification requirements include a 48-hour refresher course, 24 hours of yearly continuing education, and BLS and ALS courses at the pediatric and adult levels.

Material Resources

Prior to the mid-1960s, few if any regulations governed system design, operations, and equipment. As EMS development progressed, guidelines for emergency vehicle specifications were adopted by the DOT and equipment lists were proposed. Today, the American College of Surgeons, the ACEP, and the EMS-C Program continue publishing documents that recommend design, equipment, and medications for ambulances.[32,33]

Medications

During the 1980s, many believed that prehospital drug administration was unjustified and simply delayed hospital transport.[34,35] Moreover, there is a profound paucity of outcomes-based research into the use of various medications in the out-of-hospital environment.[36] There is significant evidence for early defibrillation and certain advanced cardiac life support medications, which are carried by most ALS services.[37] The wide variety of alternative medications is less uniform. This includes respiratory and anaphylaxis medications, preparations for altered mental status, analgesics, and antiemetics. Medications are traditionally administered in the field by the parenteral route, but the intranasal route is becoming popular for certain preparations. The beneficial aspects are that absorption is rapid with an onset of action similar to parenteral administration. Two medications that are commonly administered intranasally are naloxone for narcotic overdose and midazolam for pediatric seizure.[38,39]

Equipment

Basic ambulance equipment should include items necessary for emergency procedures (i.e., airway support, hemorrhage control, fracture and spine immobilization, childbirth), personal protection, patient movement, and basic rescue procedures. Additional patient care equipment is predicated on the level of provision outlined by the system design.

Ambulances

Three basic ambulance vehicle designs are recognized by the DOT: type I, type II, and type III. Both type I and type III ambulances incorporate a modular patient compartment mounted on a conventional truck and van chassis, respectively. The type II vehicle is a standard van. The larger medium-duty vehicle, mounted on a business-class chassis, has become popular in recent years. This configuration requires less periodic maintenance and offers extended service time. Each ambulance manufacturer promotes various interior cabinetry and all include sufficient lighting, outlets for 110-volt equipment, suction, oxygen systems, and external audible and visual warning devices. The six-pointed blue star, or "Star of Life," surrounding the staff of Aesculapius is recognized worldwide as the standard symbol for EMS.[40]

Communications

Integral to out-of-hospital care systems, EMS communications involve multiple components, all interlinked to support expedient patient care. Effective communication systems include public information and education programs regarding general access to care, technology to ensure simplified access, means of call prioritization and management of available resources, protocols for providing emergency patient care instructions prior to EMS arrival, ability to communicate with allied agency and hospital personnel, educational opportunities for telecommunicators, and quality improvement processes.

Access

Since 1973, the 9-1-1 universal emergency access telephone number has been adopted by many communities throughout the United States. Basic 9-1-1 service simply connects a caller to a central communications center or public safety answering point (PSAP). Most primary PSAPs are under the domain of law enforcement. Although many of these handle all public service (police, fire, EMS) calls, many larger cities have secondary PSAPs for fire and EMS. Enhanced 9-1-1 provides additional information by immediately displaying the caller's telephone number and address.

Emergency Medical Dispatch

Dispatching encompasses multiple elements that assist patients in receiving expeditious medical care.[41] It is estimated that 30% of EMS calls are for nonemergent conditions, with only 15 to 20% being considered critical or life-threatening.[42]

The emergency medical dispatcher (EMD) is responsible for ascertaining the primary medical condition and severity. Communication centers that model their dispatch response protocols on priority use a finite list of common chief complaints, each having associated predetermined questions. Answers to these questions ultimately dictate a predefined response mode. Depending on the response assigned and system configuration, an ambulance (BLS or ALS) and possibly an FR resource is dispatched to respond in an emergency or nonemergency mode. When critical conditions are identified, the EMD may proceed in giving specific prearrival instructions to assist the caller in providing critical interventions prior to EMS arrival. These include procedures such as opening and clearing an airway, performing CPR, controlling hemorrhage, and assisting with childbirth. Such assistance dramatically narrows the response time interval for receiving emergency medical care.

Systems Status Management

Depending on system size, population served, and resources available, the use of systems status management has proven beneficial for many services. Based on historical data, high-performance or peak-demand periods of the day coupled to service areas or call location can be identified so that coverage plans or posting assignments may be instituted. Such mechanisms place ambulances at predetermined locations where potential calls are likely to occur. Response vehicles may be equipped with an automatic vehicle locator that functions as a telemetry unit, or global positioning satellite system that provides a site interface with the computer-aided dispatch system. This site information is helpful when staging or redeployment of vehicles is required during periods of high call volume or when resources are limited.

Field Communications

While at the scene or during transport, EMTs usually have the capability of communicating with hospital staff. A consultative patient report may be given to receive medication or intervention orders, or simply for arrival notification. EMS providers should also have the capability of communicating with all allied public safety agencies for mutual aid purposes, mass casualty situations, or disaster responses. If air medical services are available, EMS and fire personnel must have the capability of communicating with the helicopter pilot and crew members. Scene personnel must relay landing zone information and potential hazards to the pilot and should provide a preliminary patient report to the medical crew.

MEDICAL DIRECTION

An EMS medical director is a physician with specialized interest and knowledge of patient care activities unique to the out-of-hospital environment. Medical oversight must extend from the communications center through all components of field care. Typically, a contractual arrangement for services provides the physician with administrative authority to implement patient care protocols, to interact with all aspects of the system, and to remove a provider from practice if medical care or behavior is substandard. Published guidelines describing the activities and performance of an EMS medical director have been prepared by ACEP, National Association of Emergency Medicine Services Physicians (NAEMSP), NHTSA, and Health Resources and Services Administration (HRSA).[43-45]

Medical direction consists of off-line (indirect) and on-line (direct) control. Off-line medical control includes protocol development, personnel education, prospective and retrospective patient care review, and other quality improvement processes. Direct medical control concerns real-time interaction between a physician or designee and the field provider.

Indirect Medical Control

Medical accountability for patient care activities is the basis for indirect medical control and functions either

before a patient is encountered (prospective) or after hospital transport has occurred (retrospective). Patient care guidelines and protocol development for EMTs and EMDs, continuing medical education, medicolegal policies, and quality and performance improvement processes are important elements.

Protocols

Perhaps the most important duty of the medical director is to develop patient care protocols. Protocols serve as preestablished practice guidelines that define the standard of care for most illnesses or injuries encountered in the out-of-hospital setting. Operational issues, such as hospital designation and destination policies, termination of resuscitation, and patient transport refusal, may be included. Depending on state regulations, protocols may include standing orders for particular clinical situations in which EMTs may perform certain procedures or administer medications for predefined patient conditions prior to communication with hospital personnel. Protocol development should be driven by system resources and patient needs and should include guidelines for triage and care of specific patient populations, including trauma patients, newborns, and children.

Regardless of local communication protocols, out-of-hospital providers should always be able to discuss a case with a physician for clarification or guidance when clinical questions or controversial situations arise. Furthermore, hospital notification is always important when critical patients are being transported.

Education

Medical directors should be familiar with and actively involved in local or regional educational programs for initial and continuing education courses for all levels of EMT certification. Course curriculum development and administration, evaluation, and revision processes should be understood. Systems that incorporate their own educational programs allow for modifications that reflect intrinsic needs of the system and the providers.

Field personnel and telecommunicators must be given regularly scheduled courses that improve competency in knowledge and skills. Instructional formats and resources to accomplish educational objectives may include didactic classroom lectures, skill labs, direct field observation, or distance learning models for self-paced opportunities. Standardized core content is important for maintaining consistency and quality of care.

Quality and Performance Improvement

Once patient care protocols are developed and implemented, there must be mechanisms, such as retrospective patient care report review or direct field observation, for evaluating individual and system performance and patient outcome. Deviations from specific protocols may reflect problems with individual EMTs, medical control personnel, or the protocol itself, each requiring education and reevaluation. Deficiencies, both operational and clinical, must be identified for appropriate remediation to occur, which may be in the form of counseling, educational instruction, or revisions of system design or patient care protocols.[46] Competency, knowledge retention, and skill performance are measurable parameters. Time standards (e.g., out-of-chute time [time from ambulance notification to deployment], response time, and scene time) are equally important measures.[47]

Direct Medical Control

Direct medical control is the concurrent direction of EMTs providing patient care. This may be in the form of radio or telephone communications or by direct scene observation and may be considered centralized or decentralized. In a centralized system, a selected hospital is designated as the lead facility (base station hospital, resource hospital, or sponsor hospital) and is responsible for providing all direct medical control orders and notification regardless of the receiving facility. In a decentralized system, each hospital functions as a base station, providing direction to EMTs transporting patients to its facility.

Personnel responsible for direct medical control must be knowledgeable about the entire EMS system, receiving facilities, protocols, medication formulary and equipment, administrative and operational issues, and medicolegal implications for certain presenting situations. Systems whose protocols include standing orders may only require direct communication for specific reasons. Thus, while these medical and administrative protocols may guide EMTs through most circumstances, medical control consultation may assist with medicolegal issues, situational problems at the scene, patient nontransport, or a multitude of potential ethical dilemmas that may be encountered. Nevertheless, direct medical control is usually invaluable for notifying a receiving facility for treatment room and staff preparation when critical or potentially critical patients are being transported.

OUT-OF-HOSPITAL MEDICAL CARE AND CONTROVERSIES IN MANAGEMENT

Airway Support and Respiratory Emergencies

Interventions

Respiratory complaints account for a significant number of EMS responses. Basic measures to control and support a patient's airway include manual maneuvers (e.g., chin lift or jaw thrust), oral and nasopharyngeal devices, and use of bag-mask ventilation. At a more advanced level, interventions may include blind-insertion airway devices (e.g., Combitube or laryngeal mask airway), which have been shown to enable faster placement and provide improved minute ventilation. Studies have shown that basic-level EMTs were able to successfully place laryngeal mask airways in simulated arrest models and also demonstrated an improved minute ventilation with these devices when compared with bag-valve mask ventilations.[48,49] Similar studies have demonstrated that laryngeal mask airways are more successful than endotracheal intubation for paramedics, because they provide a faster technique, require fewer attempts for successful insertion, and improve ventilation.[50,51]

Commonly used by air medical services, drug-assisted intubation (DAI) and rapid sequence intubation (RSI) procedures have recently expanded in ground transport services, despite a lack of supporting evidence. Several long-standing programs have achieved great success using RSI; however, others have not appreciated the benefits and have questioned the usefulness.[52,53] Several studies have challenged the effectiveness of out-of-hospital intubation, particularly in view of an alarming incidence of esophageal intubation in some systems and poor outcomes with the use of RSI for head-injured patients.[54,55] One prospective, randomized study of pediatric out-of-hospital airway management concluded that in the urban setting, bag-mask ventilation may be superior to intubation in

certain patient groups.[56] Although controversy exists and the debate will continue, most would agree that in order to have a successful airway management program, the educational and quality management component must be meaningful and should be as comprehensive and compulsive as possible.[57] For programs using DAI or RSI procedures, the experiential component should include operating room time and simulator sessions. Ideally, training would also occur in an ED setting where patients requiring emergent intubation would potentially have the full complement of confounding variables (e.g., combative status, full stomachs, blood and vomit in the airway).

Traditionally used in the hospital, continuous positive airway pressure (CPAP) is intensifying in the out-of-hospital setting. The effectiveness of out-of-hospital use of CPAP has been demonstrated; however, patient outcome studies have been limited.[58,59] Out-of-hospital use would require strict protocols that would outline such variables as indications and contraindications, clinical applications, mental status assessment, hemodynamic status, and mechanisms for transferring the patient at the hospital.

Medications

Most advanced programs have adopted the use of clinically proven medications for bronchospasm, chronic obstructive pulmonary disease, and anaphylaxis, but no studies have demonstrated benefit to administration of these medications in the out-of-hospital environment. While some studies might be considered unethical (e.g., an out-of-hospital study of epinephrine for anaphylaxis), others (e.g., out-of-hospital use of beta$_2$-agonists or steroids for asthma, or loop diuretics for pulmonary edema) could easily be performed, with the results far from certain. Pending further studies, most systems have adopted the position that these medications do not harm patients in the out-of-hospital setting, may be helpful, and may provide comfort and clinical improvement for most patients experiencing varying degrees of respiratory distress. The overhead related to training and maintenance of knowledge related to these additional, probably unnecessary, medications is rarely considered.

Cardiovascular Emergencies

Interventions

Previous research has demonstrated the effectiveness of early defibrillation for terminating ventricular fibrillation and improving survival rates from sudden cardiac death.[60] Advances in technology have improved such that defibrillators, traditionally used by paramedics, are now used by a variety of public safety responders and bystanders. Public access defibrillation (PAD) programs are being implemented throughout the country, with devices being placed in high-volume, populous, and secluded areas such as airports and airplanes, casinos, and office buildings.[61] The effectiveness of PAD is currently being investigated.[62] The acquisition and transmission of out-of-hospital 12-lead electrocardiograms is becoming more prevalent as well. Although expensive to implement, several studies have revealed minimal delays in scene time while obtaining the ECG, and a shorter time to intervention (thrombolytic administration or catheterization lab admission) by using this technology.[63,64]

Although the statistics for cardiac arrest survival across the United States are dismal, those that do survive may suffer some degree of hypoxic encephalopathy. Recent evidence suggests that cooling patients who achieve a spontaneous return of circulation following cardiac arrest, especially with ventricular fibrillation as the initial rhythm, achieve higher survival rates and level of neurologic functioning.[65,66] The explanation may be due to several mechanisms, including a decrease in neuronal cell oxygen consumption, cell membrane protection, slowing of degradative reactions resulting from reperfusion, and limiting acidosis.[67] International guidelines now call for the institution of hypothermia for patients who are resuscitated from cardiac arrest, and many out-of-hospital systems have implemented protocols that may include administration of chilled saline, sedation, or neuromuscular blockers, in coordination with receiving hospital emergency departments.

Medications

Traditional cardiac medications recommended by advanced cardiac life support are used by most ALS systems. Recent investigations involving amiodarone as an out-of-hospital agent to terminate refractory ventricular fibrillation have resulted in higher survival rates to hospital arrival; however, improvement in survival to discharge is still not significant.[68] Whether amiodarone should replace lidocaine for out-of-hospital ventricular fibrillation requires further investigation, although many systems have already made this expensive change. The use of out-of-hospital fibrinolytic agents for acute ST elevation myocardial infarction has not gained wide acceptance and may only be a useful intervention for systems having prolonged transport times, or if hospitals may not have catheterization or intervention facilities available. Future recommendations for out-of-hospital use of these agents remains speculative.

Traumatic Emergencies

Interventions

Interventions for specific medical emergencies, such as cardiac arrest (i.e., defibrillation, intubation, IV and medication administration), may be effectively performed while on the scene or prior to hospital transport. Alternatively, it is widely accepted that most interventions for traumatic injuries should be performed while en route to the hospital, and all efforts should be extended to reduce on-scene time.

The issue of IV fluid administration has gained controversy over the past several years. High-volume IV fluid for hemodynamic instability resulting from traumatic injury has traditionally been the accepted standard in most out-of-hospital care systems. Recent data, however, support a paradigm shift to restrictive or hypotensive resuscitation for penetrating truncal injuries. Restoration of hemodynamic stability with fluid resuscitation prior to definitive surgical hemostasis may lead to increased morbidity.[69] Likewise, the use of the pneumatic antishock garment has been shown to increase mortality rates in penetrating torso injuries and is no longer recommended.

Similar to medical patients, definitive airway support by endotracheal intubation may be beneficial for severely injured patients although these benefits of intubation in improving patient outcome have not been clearly delineated. To be successful, paramedics must exhibit the technical skills to rapidly place the endotracheal tube correctly, assess the placement, and move the intubated patient appropriately. In addition, providing the correct minute and tidal volumes is equally important. Overzealous personnel subconsciously delivering hyperventilatory rates may impair cardiac output and cause further tissue damage. Patients sustaining blunt head injury pose special problems that must be expeditiously addressed and resolved. Intubation provides a solid means of providing ventilatory assistance and airway protection, but the procedure and postintubation care may negate these potential benefits.

BOX 190-1 EMTALA REQUIREMENTS FOR PATIENT TRANSFERS

Complete certification (risks and benefits) of transfer
Informed consent obtained from the patient or family
Appropriate transportation (equipment and personnel) arranged
Treatment and stabilization performed
Acceptance from receiving facility ensured
Appropriate patient care data sent (fax or with patient)

EMTALA, Emergency Medical Treatment and Active Labor Act.

Attempting to intubate head-injured patients may result in dental or soft tissue damage in those patients with clenched teeth, and intracranial pressure may be exacerbated from an intact gag reflex or from subsequent regurgitation. Recent studies on the use of RSI in head-injured patients reveal that patients experience significant hypoxia and bradycardia during the procedure, and outcome is actually worse.[48] Thus, the role of RSI in prehospital airway management in trauma patients is in question, just as it is for medical patients.

INTERFACILITY AND SPECIALIZED TRANSPORTS

Transportation between health care facilities may occur for several reasons including patient preference, unavailable diagnostic or therapeutic resource availability at the transferring facility, or managed care requirements that patients be cared for in predesignated hospitals following stabilization. Hospital corporations engaged in networks or alliances that share resources and services depend on interhospital transport systems to convey patients to allied institutions for specialized tests or procedures. Likewise, critical patients admitted to less specialized facilities may need to be transferred to tertiary care or designated trauma centers. Whereas long-distance transports may be best accomplished by air medical services, regional or local transports should use ground systems. These may be provided by either local EMS resources or those owned and operated by the hospital.

Interfacility transfer of patients that is medically indicated must fall under a set of requirements referred to as the Emergency Medical Treatment and Active Labor Act (EMTALA).[70] Although the EMS system providing the transport plays a key role, these guidelines primarily involve particular information and obligations that must be satisfied by the transferring and receiving facility prior to transfer. It is important to note that an unstable patient should not be transferred to another facility at the request of a managed care organization unless the transferring hospital is incapable of providing standard care and the receiving hospital does have the capability to manage the condition and foreseeable complications. Box 190-1 lists various requirements that must be completed prior to transferring a patient to another facility.

Depending on patient condition, specialized transport services may function at the BLS or ALS level, providing emergency or nonemergency transportation. Patient transfers considered ALS may include interhospital (either ED or intensive care unit) neonatal or high-risk infant, critical cardiac, or trauma transports. Personnel configuration depends on system design and level of care provided. Many programs use a nurse-paramedic combination. Patients requiring specialized care may need the services of specifically trained individuals, such as respiratory therapists, neonatal nurses, or other specialized critical care personnel. The presence of a physician is not mandatory but may be useful in selected cases.

As with any EMS activity, all interfacility transports should be reviewed for appropriateness of transfer and medical care provided. In 1993, The Practice Management Committee of ACEP updated the 1990 policy statement on interfacility transfers.[71]

Table 190-2 EMS Resource and Contact Information

RESOURCE	URL
Advocates for EMS	www.advocatesforems.org
American Ambulance Association	www.the-aaa.org
American College of Emergency Physicians	www.acep.org
Centers for Disease Control and Prevention	www.cdc.gov
Commission on Accreditation of Ambulance Services	www.caas.org
EMS Division, NHTSA	www.nhtsa.dot.gov/people/injury/ems
Maternal and Child Health Bureau, EMS-C	www.ems-c.org
National Association of EMS Educators	www.naemse.org
National Association of EMS Physicians	www.naemsp.org
National Association of EMTs	www.naemt.org
National Association of State EMS Officials	www.nasemsd.org
National Registry of EMTs	www.nremt.org

EMS, emergency medical services; EMT, emergency medical technician; NHTSA, National Highway Traffic Safety Administration.

THE FUTURE

Providing quality, efficient, and responsible health care to the right patient, in the right setting, at the right time will always be laudible objectives for any system, but there is a need for research to demonstrate which interventions are conducive to better patient outcome. As the call volumes increase, it is imperative that systems focus on those interventions, from both the training and health care delivery perspectives, that are known to be of benefit. Agencies and organizations involved in EMS development and oversight are listed in Table 190-2.

Acknowledgments

The author wishes to express thanks to Joey, Alex, and Marty for the release time required to complete this chapter.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 191

Air Medical Transport

Ira J. Blumen, Howard Rodenberg, and Stephen H. Thomas

PERSPECTIVE

The history of air medical transport (AMT) dates back to World War I. The French Air Services evacuated soldiers from Serbia using fixed-wing aircraft (airplanes) as ambulances as early as 1915. The first recorded use of a U.S. military air ambulance was in 1918 when an airplane was converted to accommodate a patient in a semirecumbent litter in the rear cockpit. In 1926, the United States Army Air Corps was formed and flew injured troops more than 150 miles from Nicaragua to a hospital in Panama. In World War II, more than 1.1 million sick and wounded soldiers were airlifted to the United States during the last 3 years of the war. The Korean War introduced the rotor-wing aircraft (helicopter) to AMT. In August 1950, a Bell 47 flew the first of more than 20,000 medical evacuations in Korea. Wounded servicemen were strapped to litters outside the aircraft and transported from battalion aid stations to waiting hospital units. During the Vietnam War, Operation Dustoff transported nearly 1 million injured patients to hospitals.

The impact of AMT on the wounded soldier can be shown by comparing time to definitive care and mortality. During World War II, the average time from injury to definitive care was 6 to 12 hours, with a mortality rate of 5.8%. In Korea, the time was 2 to 4 hours, with 2.4% mortality. In Vietnam, the time was 65 minutes, and mortality was less than 1%.[1] Encouraged by the military experience, civilian AMT in the United States was propelled by the 1969 start of the first hospital-sponsored, fixed-wing air medical program. The first civilian helicopter emergency medical services (HEMS) program in the United States was established in 1972.

AVIATION PHYSIOLOGY

A working knowledge of aviation physiology is vital to understanding the effects of AMT on pilots, medical personnel, and patients.

Boyle's Law

The cornerstone of aviation physiology is *Boyle's law*, which states that the volume of a unit of gas (a specified number of molecules) is inversely proportional to the pressure on it. In concrete terms, Boyle's law means that as altitude increases (and atmospheric pressure decreases), the molecules of gas grow apart, and the volume of the gas expands. With descent (increasing atmospheric pressure), the molecules are condensed, and gas volume contracts.

Physiologic difficulties from expansion and contraction of gases within the closed spaces of the body may occur with any change in altitude. Squeeze injuries occur on descent and are common causes of barotitis and barosinusitis. Air trapped within the sinus or middle ear cavities cannot be equalized with ambient pressure, and the air within the space contracts, pulling mucosal and neurovascular elements with it. Reverse squeeze injuries occur on ascent. The decrease in barometric pressure leads to an increased volume of the air trapped within the space, exerting pressure on adjacent bony, neurovascular, or parenchymal structures. Ascent injuries can also include barotitis media, barosinusitis, conversion of a simple pneumothorax into a tension pneumothorax, and rupture of a hollow viscus by expansion of intestinal gas. The operation of medical equipment containing closed air space can also be affected. Intravenous flow rates, the pressure in air splints and in pneumatic antishock garment suits, and endotracheal tube cuff volumes may be altered with altitude.

Charles' Law

Charles' law follows from the volume effects of Boyle's law. *Charles' law* notes that as the temperature on a volume of gas rises, the volume of the gas also increases. The molecular dispersion seen with increases in gas volume at altitude (Boyle's law) means there is less chance of molecular collision with resulting generation of heat. Charles' law explains why the ambient temperature decreases with increased altitude.

Dalton's Law

Dalton's law states that the total barometric pressure at any given altitude equals the sum of the partial pressures of gases in the mixture ($P_t = P_1 + P_2 + P_3 \ldots P_n$). As pressure is reduced, expansion of gases creates increasing distances between molecules, and the quantity of oxygen available for respiration decreases. Although oxygen still constitutes 21% of the atmospheric pressure, each breath brings fewer oxygen molecules to the lungs, and hypoxia results (Table 191-1). The clinical effect of Dalton's law is manifested as a decrease in partial arterial oxygen tension with increasing altitude.

The most threatening feature of hypoxia is its insidious onset. Physiologic responses include an increased rate and depth of respirations and an increase in heart rate. With prolonged exposure, oxygen supply to the brain is insufficient to support cerebral metabolism. Signs and symptoms of cerebral

Table 191-1 Effects of Altitude on Oxygenation

ALTITUDE (FT)	BAROMETRIC PRESSURE (MM HG)	P_{O_2} (MM HG)	P_{AO_2} (MM HG)	P_{ACO_2} (MM HG)	OXYGEN SATURATION (%)
Sea level	760	159.2	103.0	40	98
8,000	565	118.4	68.9	36	93
10,000	523	109.6	61.2	35	87
15,000	429	89.9	45.0	32	84
18,000	380	79.6	37.8	30.4	72
20,000	349	73.1	34.3	29.4	66
22,000	321	67.2	32.8	28.4	60

P_{AO_2}, partial pressure of alveolar oxygen; P_{ACO_2}, partial pressure of arterial carbon dioxide.

hypoxia include headache, nausea, drowsiness, fatigue, and, finally, unconsciousness and death. Although the onset and severity of symptoms may vary with individuals, no one is exempt from the effects of hypoxia, including patients and air medical flight crew.

Henry's Law

Henry's law states that the mass of gas absorbed by a liquid is directly proportional to the partial pressure of the gas above the liquid. Henry's law has its most familiar applications in diving medicine, in which the increased pressure exerted on gases in the body at depth forces the gases into solution in the bloodstream. Rapid ascent from depth causes the gas to come out of solution within the bloodstream, resulting in decompression sickness or dysbarism. Henry's law does not carry the same weight in aviation medicine because the degree of change in atmospheric pressure per unit of distance is considerably less than the degree of change in water. Sudden decompression at high altitude similarly may result in dysbarism, however.

Additional Stresses of Flight

Other stresses of flight that can affect the patient or crew include temperature fluctuations, dehydration, noise, and vibration. Temperature changes may produce increases in metabolic rate and oxygen consumption. Prolonged exposure can result in motion sickness, disorientation, fatigue, and impaired performance.

As altitude increases and the air cools, the amount of moisture in the air decreases significantly. To prevent dehydration during AMT, fluid intake (oral or intravenous) must be monitored carefully, and all patients should receive humidified medical oxygen. Noise and vibration may represent the most ubiquitous stresses encountered in AMT; both may interfere with patient assessment or the function of medical equipment. Long-term exposure may result in fatigue, nausea, visual or vestibular disturbances, ear damage, and deterioration in task performance. Hearing protection should be worn during aircraft operations by the patient and crew.

■ PRINCIPLES OF AIR MEDICAL TRANSPORT SYSTEMS

Administrative Structure

Air medical services may take several forms. Despite a tremendous growth of independent (private) operations in the United States in recent years, the most common type of helicopter service remains the hospital-sponsored operation transporting patients from outlying referral centers or accident scenes to tertiary care centers. A single hospital or a consortium of institutions may sponsor these flight programs. In 2008, there were approximately 219 dedicated HEMS programs operating 668 helicopters—twice as many aircraft as there were in 1998. Single hospitals or consortiums accounted for 71% of the programs but only 50% of the helicopters; the remaining 50% of the helicopters were operated as independent (private) operations.[2] Public service agencies may also sponsor air medical services. Vehicles used by these programs are often multifunctional aircraft that serve in medical, search and rescue, fire suppression, and law enforcement roles. The Military Assistance to Safety and Traffic (MAST) program operated by the U.S. Armed Forces may transport ill or injured patients when no civilian service is available and when MAST aircraft, equipment, and personnel are not being used for the unit's primary military mission. Funded by tax dollars, these programs are often operated at no cost to the patient. In the United States, public-use and MAST helicopters account for more than 160 additional helicopters available for patient transport.[3]

There is no accurate accounting of the number of fixed-wing air ambulances companies or airplanes. Although some hospitals do sponsor fixed-wing AMT, it is more common for these programs to be private fee-for-service operations.

Types of Missions

Air medical missions may involve primary or secondary response. Primary responses ("scene flights") are responses in which the aircraft serves as the sole means of patient transport to a receiving facility. Aircraft involved in secondary responses—interfacility transport—move patients from outlying hospitals to facilities offering higher levels of care.

AMT missions may also be classified according to the level of care provided. This may include critical care transport, advanced life support, specialty care transport, or basic life support.

Air Medical Aircraft

Although the ground ambulance remains the primary means of out-of-hospital and interfacility patient transport, the use of the air ambulance has grown significantly since the 1970s. No one aircraft is ideal for the needs of all air medical programs or for all patients. The vehicle selected should meet the mission requirements of the program for the types of patients to be transported and the anticipated service area.

Helicopters (Rotor-Wing Aircraft)

The helicopter offers several advantages over other transport vehicles. Traveling "as the crow flies" at speeds of 120 to 180 mph, helicopter transport time is often 75% less than that

Figure 191-1. Confined spaces within helicopters may make performing procedures more challenging. (Photo courtesy of Ira Blumen, MD.)

for an equivalent distance by ground transport. The service area of helicopter programs is generally up to 150 to 200 miles from its base of operations. The rotor-wing aircraft has the ability to avoid common traffic delays and ground obstacles and can fly into locations that may be inaccessible to other modes of travel. Helicopter landing zone requirements are a disadvantage compared with ground ambulances but offer an advantage over the airport requirements of airplanes.

Disadvantages to rotor-wing flight include the presence of noise and turbulence, which may interfere with patient evaluation, monitoring, and management. Weather considerations may significantly limit the availability of helicopter transport. In small and medium-sized helicopters, cramped patient compartments and weight limitations (compared to ground ambulances) may limit the number of transport personnel or equipment that can be carried. Occasionally, this may compromise optimal patient care in the transport environment (Fig. 191-1).

Many helicopter programs permit flight only under visual flight rules. When the weather conditions (ceiling and visibility) fall below established program minimums, a program may decline to undertake a transport for safety reasons. However, an increasing number of programs are equipping their helicopters and training their pilots for instrument flight rules (IFR) to allow safe travel in less favorable weather conditions. With the aid of new technology, HEMS programs and hospitals are working together in many areas of the country to develop IFR approaches to private-use hospital helipads. IFR flight does not facilitate travel to the scene of an accident or to hospitals that are not equipped for an instrument approach.

Airplanes (Fixed-Wing Aircraft)

Although rotor-wing missions attract more media attention, fixed-wing flights constitute a significant portion of AMT operations. Fixed-wing aircraft provide increased range; greater speed; and often more patient, crew, and equipment capacity than do rotor-wing vehicles. Decreased cabin noise and turbulence create fewer patient management problems, and pressurization can combat the impact of physiologic gas laws. Fixed-wing operations are limited, however, to areas that have airports, runways of appropriate length or condition, and refueling facilities. During fixed-wing transports, patient transfers require multiple vehicles (i.e., hospital to ground ambulance to airplane).

Various fixed-wing aircraft are available for medical transport. These range from unpressurized light planes with single- or twin-piston engines to pressurized turboprops and jets. The selection of the ideal aircraft depends on the nature of the air medical mission.

Air Medical Flight Crew

Air medical crew members represent the broad spectrum of health care providers. AMT services that provide critical care transport, advanced life support, or specialty care transport must staff the vehicle with a minimum of two medical personnel to provide direct patient care.[4,5] Most AMT programs in the United States provide critical care transport teams composed of one registered nurse (RN) and an additional crew member. Some fixed-wing AMT services provide basic life support staff with a minimum of one certified/licensed emergency medical technician-basic (EMT-B).

For some AMT programs, crew configuration may be dependent on the mission (adult, pediatric, neonatal, or obstetrics). Data compiled from 1984 to 2005 show that the RN/paramedic team is most often used (>60%) in helicopter and airplane transports. Other combinations, including RN/RN (8%), RN/EMT, RN/physician, RN/respiratory therapist, and EMT-paramedic/EMT-paramedic, account for less than 5% each.[6]

Flight nurses generally have extensive experience in intensive care units or emergency departments. They may be specialized within the transport team to care for adult, pediatric, or neonatal patients. Paramedics often make their greatest contribution in the transport of critical patients from the scene of illness or injury. Respiratory therapists bring expertise in airway and ventilator management and oxygen delivery systems. Flight physicians may be residents, attending physicians, or medical directors of flight programs. Early research focused on the specific benefit of the onboard physician.[7-10] Although the answer to this question remains controversial, it is clear that the crew used by an AMT program must be explicitly tailored to the needs of the community and the patients it serves.

The AMT environment imposes unique considerations on the air medical flight crew that can influence their ability to provide patient care. Human factors work has shown that most medical care procedures are more difficult to perform in an AMT vehicle than in other ground-based settings.[11] Auscultation of the lungs, palpation of pulses, performance of cardiopulmonary resuscitation, endotracheal intubation, and recognition of visual alarms are all impaired while aloft.[12-15] In addition, fatigue, motion sickness, an erratic pattern of work activity, and the high risk involved in AMT operations may affect task performance significantly.[16]

Medical Direction

All air medical services require the active involvement of a physician as air medical director, who is responsible for supervising, evaluating, and ensuring the quality of medical care provided by the AMT team.[17] Emergency physicians play a significant role, with nearly 50% of all air medical directors having a background in emergency medicine.[18] The air medical director must have the final authority over all clinical aspects of the air medical service. The medical director should ensure that the medical personnel have adequate training and qualifications to deliver appropriate medical care, that appropriate medical equipment and supplies are available, and that the correct vehicle is selected for transport. Medical care policies and procedures should be established, including specific pro-

visions for online and offline medical control. The Air Medical Physician Association and the National Association of EMS Physicians have established guidelines for the medical director of an air medical service.[19,20]

Safety

Safety is the predominant concern of air medical operations, and ensuring safe conduct is a fundamental part of every flight program.[21] Safety must also be an overriding consideration of medical and public safety personnel when considering the risks and benefits of AMT for every patient being transferred. Continual training of aircraft pilots and mechanics is essential, and both participate in ensuring the airworthiness of the vehicle. Medical personnel must be proficient in the emergency operations of the aircraft and the routine procedures in and around their helicopter or airplane. Crew fatigue and other self-imposed stresses that could affect safety, such as the use of prescription or over-the-counter medications, tobacco, and alcohol, must be scrupulously avoided.

Weather requirements or "minimums" must be strictly enforced. On receipt of a flight request, the pilot must verify the weather conditions and the condition of the aircraft. To ensure impartiality, the pilot should not be told of the patient's condition or acuity. The pilot always has the right to decline a mission because of aircraft or weather considerations. These decisions must not be influenced or reversed by administrators, flight crew, or other parties.

A practice that should be avoided with regard to helicopter transport and poor weather conditions is "helicopter shopping." The Federal Aviation Administration (FAA) has found that this dangerous operational practice has been a factor in several fatal HEMS accidents. *Helicopter shopping* refers to the practice of a requesting EMS agency or hospital calling numerous HEMS operators until one agrees to accept a flight—without disclosing with the accepting HEMS operator that other programs have declined the flight due to bad weather.[22,23] Although there may be circumstances in which a subsequent program can safely undertake and complete the flight, helicopter shopping can lead to an unsafe situation in which a program initiates a flight that it would have declined if it had been aware of all of the facts surrounding the request. In 2006, the FAA issued a letter to all state EMS directors describing helicopter shopping and requesting that they take action to prohibit this practice.[24]

Landing Zones

Helicopter landing zones are inherently dangerous places. The most obvious risk of injury is from impact with rotor blades. This danger is heightened during ground operations because the blades dip lowest to the ground at the slower rotor speeds associated with engine start-up and shutdown. Injuries also may occur as a result of debris being propelled through the air by "rotor wash," increased noise levels and an inability to hear warnings, and slippery surfaces found on exposed landing sites.

Many hospitals have designated landing areas that are appropriately lit and secured (Fig. 191-2), with fixed coordinates and predesignated liftoff and approach patterns. Most primary responses occur at unmarked sites, however. Ground personnel must be trained to designate and secure a safe landing zone for helicopter operations (Box 191-1). AMT programs have an obligation to help train ground staff on proper landing zone setup and conduct (Box 191-2).

Helicopter flights direct to the scene of an accident pose a unique risk to AMT due to potential hazards near the landing zone. This is especially true at night. In response to this, some out-of-hospital care providers and flight programs have found it beneficial and safer to utilize a rural or community hospital helipad to rendezvous. For some hospitals and emergency physicians, this has raised concerns regarding Emergency Medical Treatment and Active Labor Act (EMTALA) responsibilities to provide a medical screening exam for these patients. In May 2004, the Centers for Medicare and Medicaid Services (CMS) resolved this concern; CMS stated that the use of a helipad on hospital property that has a dedicated emergency department does not trigger EMTALA as long as the helipad is being used as a helistop for EMS personnel to rendezvous with air medical transport to complete the transport of a patient to a tertiary care or the closest appropriate facility.[25]

Figure 191-2. Landing zone safety is paramount to delivery of patients to hospitals. (Photo courtesy of Dan Lemkin, MD.)

Another adjunct to landing zone safety and night operations in general is the increasing utilization of Night Vision Goggles (NVG). A growing number of AMT programs are equipping their aircraft with NVGs and training their pilots and medical crews to use this sophisticated technology. NVGs dramtically magnify ambient light from the moon or stars to illuminate the ground, as well as natural terrain and man-made obstacles that could interfere with safe flight or landing.

Integration of AMT within Emergency Medical Service Systems

AMT should be an integral resource within a comprehensive EMS system. Integration begins with the establishment of geographic service areas. Service areas may be determined based on program mission description, aircraft range and speed, the placement of specialty centers and receiving facilities, and the location and mission of air medical programs in adjacent regions. Population densities are also key factors. Helicopters are generally less useful in urban settings because of the proximity of health care facilities and a lack of open and safe landing zones. Paramedics, EMTs, and other public safety personnel should be provided with guidelines specifying when AMT should be considered. These protocols are best developed by EMS medical directors in close collaboration with their air medical colleagues.

■ CLINICAL CONCEPTS AND PATIENT CARE

Although virtually all types of patients have been transported by air medical services, definitive prospective data indicating which patients will benefit from flight are lacking. Many ques-

BOX 191-1 Safety of Personnel Approaching and Disembarking a Helicopter

- Vehicles and personnel should be kept at least 100 ft from the landing zone.
- Spectators should be kept at least 200 ft from the landing zone.
- No smoking or running is permitted within 50 ft of the helicopter.
- All items (e.g., IV lines, poles) should be kept below shoulder height.
- The flight crew opens and closes aircraft doors.
- The flight crew directs and supervises the loading and unloading of the patient and equipment.
- Ground personnel should use eye and ear protection.
- Approach the helicopter *only* when signaled to do so by the pilot or an onboard crew member.
- Approach and depart the helicopter *only* forward of the rear cabin door and in a crouched position with your head down.
- *Never approach or depart from the rear of the helicopter.*
- Stay clear of the tail rotor; it is virtually invisible and extremely dangerous.
- If the aircraft is parked on a slope, approach and depart on the downhill side (greatest clearance under the blades).
- Keep the landing zone clear of (or hold on to) all loose articles (e.g., hats, scarves, sheets, pillows).
- Protect patient from the dust and debris.
- Follow the flight crew's instructions at all times.
- In disaster situations and mass casualty incidents, victims, witnesses, and spectators may become hysterical or exhibit signs of an acute situational reaction. These individuals must be kept clear of the landing zone and helicopter *at all times*. Injured victims who exhibit this behavior should *not* be triaged for helicopter transport, or they should be transported *only* with adequate physical or chemical restraints in use.
- *If you do not know, ask.*

Courtesy of University of Chicago Aeromedical Network (UCAN), University of Chicago Medical Center, and Illinois Association of Air and Critical Care Transport (IAACCT), 2008.

BOX 191-2 Landing Zone (LZ) Requirements for Air Medical Transport

Landing Area

- LZ should be as close as possible to the scene or hospital entrance, but not so close that it may interfere with ground operations or patient care.
- LZ should be at least 100 × 100 ft.
- LZ should be as flat and level as possible.
- LZ *must* be clear of debris.

Hazards and Obstructions

- Identify all potential hazards that may be on the ground or near the approach/departure path of LZ.
- LZ should be clear of wires, poles, trees, buildings, vehicles, and spectators.
- Road cones, ropes, tape, and barricades are *not* recommended for use near LZ.
- Perimeter of LZ should be at least 50 ft away from potential obstructions and hazards.
- LZ should be located *upwind* from any hazardous material incident.

Approach and Departure Path

- Path should point into the wind and be free of obstruction to an altitude of 500 ft above the surface.
- Path should *not* pass over command posts, treatment areas, or operationally congested areas on the ground.

Day Operations

- Use radio communications and hand signals.
- Stand with your back to the wind.

Night Operations

- Use radio communications and lighting to designate LZ.
- Spotlights should be directed at the top of possible hazards, *not* toward the approaching or departing aircraft.
- Position a portable light, vehicle headlights, emergency vehicle flashing lights, flare, or chemical stick at each corner, with a fifth light upwind.
- Nonessential lights should be turned off.

Light Sources

- Lights *must* be clear of LZ.
- If portable, lights *must* be well secured.
- *Never* point lights toward an approaching or departing helicopter.

Wind Indicator

- Indicator may be a wind sock, flag, flare, or smoke.
- Indicator *must* be clear of LZ.
- If portable, indicator *must* be well secured.

Courtesy of University of Chicago Aeromedical Network (UCAN), University of Chicago Medical Center, and Illinois Association of Air and Critical Care Transport (IAACCT), 2008.

tions regarding the triage of patients to air or ground transport, the efficacy of air medical care, and the effects of AMT on morbidity and mortality in medical and surgical conditions remain unanswered. In an effort to ensure that AMT resources are used wisely, the Air Medical Physician Association has established a detailed medical condition list for the appropriate use of AMT.[26] A more general approach to the need for AMT is illustrated in Box 191-3.

Trauma

Although there are some analyses of HEMS use for secondary (interfacility) missions, the vast majority of trauma studies have addressed air medical utilization for scene response.[27–29] There are data from Pennsylvania and California brain-injured patients undergoing out-of-hospital intubation demonstrating HEMS-associated improvements in both morbidity and mortality in patients with traumatic brain injury.[30,31]

Methodologic heterogeneity precludes formal meta-analysis of the AMT outcomes data. However, in considering the mortality benefit that appears to be associated with HEMS, existing data support an estimate of 20 to 35% survival improvement, or the saving of three to six lives (perhaps fewer for pediatric patients) per 100 air medical trauma flights.[32-39] Furthermore, trauma systems experts' finding that HEMS represents the *only* modality by which nearly 28% of U.S. residents have timely (i.e., within 1 hour) access to level I or II trauma centers emphasizes the vital role of AMT in care of the injured patient.[40] Studies have also presented data that suggest lack of HEMS benefit, but these studies are a small minority and are limited by confounding and methodologic quirks such as inclusion of a preponderance of transports to nontrauma centers.[41,42]

On the other hand, seminal work in HEMS casts doubt on the supposed logistical advantages of helicopter dispatch.[43] Faster times to trauma centers are not required for air medical accrual of outcomes benefit. Studies conducted from regions as disparate as California and The Netherlands demonstrate HEMS mortality benefit but find similar scene-to-trauma center times for ground and air transports.[39,44] Even so, it seems clear that for many patients, factors other than speed are responsible for AMT's benefits.

AMT is unlikely to improve outcome in those whose injuries are either trivial or grave. For instance, if the Injury Severity Score's 75-point scale is collapsed into five ordinal categories, analysis finds a significant association between helicopter transport and improved mortality in the middle three categories (survival odds ratios range from 2.1 to 2.6).[45,46]

Cardiac Disorders

The ability to study HEMS-related outcomes benefit in acute coronary syndrome is limited by the lack of validated scores that can be used to stratify risk and predict outcome. There are data demonstrating the use of helicopter transport to extend the ability of primary angioplasty centers, with outcomes of patients flown from a distance equaling outcomes of patients presenting primarily to the cardiac referral center.[47,48]

Although HEMS could conceivably shorten door to percutaneous coronary intervention (PCI) time by transporting patients rapidly from hospitals without PCI capability to a referral center, in some circumstances the patient will be best served by receiving thrombolytic therapy in the sending hospital and then being transported by the most appropriate mode of transport (air or ground ambulance). In other situations, however, pre-hospital and interfacility helicopter transport can play an important contributory role in extending regional cardiac care systems and primary PCI to many patients.

Stroke

With the advent of time-critical therapy for ischemic stroke, HEMS has played an increasing role in the regionalization of acute neurologic care. Early studies demonstrating safety of transport of post-thrombolysis stroke patients have been complemented by case series illustrating the increasing use of helicopter interfacility transport for stroke.[49,50] However, once a patient has received thrombolysis, the risk-benefit analysis for air versus ground transport may be altered. For many patients, ground ambulance transport will be appropriate. For other patients, however, the referring physician may determine that AMT is still warranted. Case reports and series have demonstrated the utility of air medical dispatch for primary (scene) transport of patients with strong suspicion of stroke.[51-53] In one region, ground EMS providers were able to identify stroke with accuracy (nearly four out of five air-transported patients had the diagnosis confirmed), and helicopter-transported patients comprised nearly one fourth of the stroke center's thrombolysis volume.[52] The use of strict triage definitions keeps inappropriate calls for AMT to acceptably low levels while allowing for a significant extension of the geography served by an individual stroke center.[52]

BOX 191-3 Criteria for Air Medical Transport (AMT)

1. Distance to the closest appropriate facility is too great for safe and timely transport by ground ambulance.
2. Patient's clinical condition requires that the time spent in transport be as short as possible.
3. Patient's condition is time critical, requiring specific or timely treatment not available at the referring hospital.
4. Potential for transport delay associated with ground transport is likely to worsen the patient's clinical condition.
5. Patient requires critical care life support during transport that was not available from the local ground ambulance service.
6. Patient is located in an area inaccessible to regular ground traffic, impeding ambulance egress or access.
7. Local ground units are not available for long-distance transport.
8. Use of local ground transport services would leave the local area without adequate EMS coverage.
9. For interfacility medical transport, the requesting physician based on his/her best medical judgment and information available at that time of transport determined the need for AMT.
10. For scene medical transport, the requesting authorized out-of-hospital provider based on applicable policy, his/her best medical judgment and information available at that time of transport determined the need for AMT.

Courtesy of University of Chicago Aeromedical Network (UCAN), University of Chicago Medical Center, 2008. Based on Association of Air Medical Services: Position paper on the appropriate use of emergency air medical services. J Air Med Transport 9:29, 1990; and Determination of Medical Necessity for Air and Critical Care Medical Transportation. Position Statement of the Air Medical Physician Association. Revised April 13, 2002. In Blumen IJ (ed): Principles and Direction in Air Medical Transport. Salt Lake City, Utah, Air Medical Physician Association, 2006.

Pregnancy

With appropriate triage, obstetric air transport can counterbalance risks of delivering an infant in a helicopter's confined space, with benefits of transporting a high-risk pregnancy in the prepartum phase.[54] Series demonstrate that with helicopter transport, high-risk obstetric patients (and their subsequently born neonates) from distant hospitals have outcomes as good as those presenting primarily to the obstetric referral center.[54,55]

Neonates and Children

The use of AMT to extend the reach of neonatal care centers is reported from many settings.[56,57] The most rigorous analysis suggests that long-distance AMT allows for infants from remote areas to achieve outcomes as good as those achieved with infants born in urban centers. Although neonates are vulnerable to physiologic deterioration, air transport is associated with no more derangement in oxygenation and ventilation than is transport (with the same team) by ground vehicle.[56]

Many areas depend on AMT to deliver critically ill or injured children to regional pediatric centers. Although speed of transport may be an important consideration, the emphasis is often more on the transport *team* than on the *mode* of transport. Experienced pediatric transfer teams often bring a level of expertise unavailable to the pediatric patient in the outlying hospital.[58] Appropriate training, experience, and competency are essential for those responsible for the transport of critically ill or injured children.[59] Depending on regional AMT and pediatric resources, the transport team may be a regularly scheduled transport team or a pediatric specialty team. Several studies have compared pediatric transports conducted by specialty pediatric teams versus regularly scheduled transport teams. Specialized pediatric transport teams, including services providing extracorporeal membrane oxygenation, were found to have comparable outcomes and fewer adverse events.[60-62]

EFFICACY AND COST-EFFECTIVENESS

Cost-benefit is deservedly an area of increasing focus for AMT. Part of the problem lies in the imperfections of current triage (e.g., for trauma) and the inability to precisely identify, in prospective manner, which patients will truly benefit from helicopter EMS. However, it is equally true that in some regions there is little, if any, guidance regarding when air medical dispatch is indicated.[63] Using endorsed guidelines for air medical dispatch, EMS regional authorities should collaborate to generate criteria best for their own systems, with constant refinement as indicated by rigorous utilization review.[64]

Fortunately, compared to the cost-benefit ratios of widely accepted medical interventions, AMT is well within the accepted range per quality-adjusted life-year saved.[65-68] One Scandinavian study, with a large proportion of rural transports, concluded, "The analysis indicates that the benefits of ambulance missions flown by helicopters exceeds the costs by a factor of almost six."[69] Another group from the region estimates that HEMS contributes to the cost-effectiveness of primary PCI; even when patients were transported from longer distances (and by air), the cost-effectiveness of primary PCI over time is maintained.[70] Other investigators have demonstrated the favorable cost-effectiveness of helicopter stroke transports.[71]

Cost-effectiveness determinations are not straightforward. It is difficult to calculate true cost-effectiveness for helicopter use for transports that would otherwise not occur (as with high-risk obstetrics cases)[54] or would deliver patients outside critical time windows (as for stroke or cardiac transports).[49,72] There is no ground transport option capable of rapidly moving through rush hour traffic in Los Angeles or getting patients from coastal islands to neurointerventional or cardiac catheterization suites.[49,54] Because HEMS represents the only mechanism by which more than 80 million U.S. citizens have timely access to mortality-improving high-level trauma center care,[73] it is obvious that some form of air transport is a "must-have" for some U.S. EMS regions. The direct bearing on the cost-effectiveness calculations is not difficult to understand: If a region must have air medical assets for some group, then it is most reasonable to amortize the "overhead" costs across all transported patients.

Also, air transport costs should be compared with those of the real-life alternative mode of transport. In many cases, AMT is arguably less expensive than the alternative.[74] Unfortunately, the job of assessing HEMS' cost-effectiveness is rendered difficult by the extremely limited amount of information on cost-effectiveness of ground EMS.[75] Crew and patient safety are issues in both air and ground systems.

FUTURE OF AIR MEDICAL TRANSPORT

AMT faces many challenges. The dramatic increase in the number of medical helicopters in the United States since the late 1990s has heightened concerns for their inappropriate use. AMT services work best when they are integral to and enhance an overall system of out-of-hospital care and interfacility transport. Systems must be in place to educate requesting agencies and professionals regarding the appropriate use of available air and ground resources. At the same time, flight programs must be more vigilant in terms of triage. It also seems that advances in ground-based EMS and the availability of critical care ground ambulances for interfacility transports are offsetting many of the assumed benefits of AMT. However, geographic issues, the regionalization of specialty services, the development of new highly time-sensitive therapies, and the need to transport patients quickly over long distances will require that there be systems in place to continually assess the potential value of initiating or continuing AMT.

Research into these issues is a key facet of the future of AMT. The challenge with HEMS and outcomes research is not *whether* but, rather, *in whom* there is benefit. Currently, the major dilemma facing helicopter transport outcomes researchers is the identification of triage variables that can prospectively (i.e., at the time of transport vehicle selection) guide utilization of the air medical resource.[63,64,76]

Safety must be the priority in AMT. AMT programs, aviation operators, air medical associations, and regulatory agencies continue to address this issue. However, it is important to remember the significant role that requesting and receiving personnel can also play with regard to AMT safety and the safe transport of their patients.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 192

Tactical Emergency Medical Support and Urban Search and Rescue

Richard B. Schwartz and John McManus

TACTICAL EMERGENCY MEDICAL SUPPORT (TEMS)

Perspective

Law enforcement agencies in the 21st century face an increase in terrorist threats and new challenges, including organized opposing forces, military-type weapons, direct fire, hostage and barricade situations, and potential toxic hazards. As these threats have increased, so has the recognition of the need for integrated medical support of tactical operations.[1,2] Tactical emergency medical support (TEMS) is the specialty of emergency medical services (EMS) established to maintain safety, health, and welfare for combat medical units and special operations civilian law enforcement units, such as special weapons and tactics (SWAT) teams, hostage rescue teams, and special emergency rescue teams.[2-4] These specially trained teams are composed of highly trained and specially equipped personnel who are tasked with mitigating and responding to many different high-risk situations.[5-8] Events such as the World Trade Center bombings and hurricane Katrina have demonstrated the need for many nonhospital health care personnel to use some of these current military out-of-hospital medical strategies.

Tactical Medical History

The principles of TEMS have largely been developed through lessons learned from military conflicts. Civilian TEMS structure most closely emulates the medical support structure of military special operations units such as Army Special Forces, Navy Seals, Army Rangers, and Air Force Pararescuemen.[2,5] These small, unique tactical units frequently operate outside the normal realm of military operations remote from dedicated medical resources, often for long periods of time.

In the civilian setting, snipers, mass demonstrations, riots, and fire bombings gained notoriety as new forms of urban conflict in the United States during the late 1960s and early 1970s, which led to the formation of the first SWAT unit. In 1996, there were more than 5000 SWAT teams in the United States supporting local, state, and federal agencies.[9] Essentially today, more than 90% of municipalities with a population greater than 50,000 have a SWAT team. With the evolution of these specialized law enforcement tactical teams, the need for military-style EMS support began to emerge.

Due to the dangerous environment, SWAT team members are at high risk for injury, with a casualty rate of 33 injuries per 1000 officer missions.[1] Suspects are injured at the rate of 18.9 injuries per 1000 officer missions and bystanders are injured at the rate of 3.2 per 1000 officer missions. It was recognized that traditional EMS providers were not properly trained or equipped to enter these unique and sometimes remote austere environments to care for casualties.[1,2,10,11] In fact, basic EMS training still emphasizes that personnel should wait until the "scene is safe" before rendering medical care to patients. Past incidents such as shootings at Columbine High School in Littleton, Colorado, Ruby Ridge in Idaho, the University of Texas in Austin, and the Mormon Library in Salt Lake City proved that sequestering medical personnel far from the area of operations leads to delays in definitive trauma care, with potentially higher morbidity and mortality.[10-13] The tactical environment necessitates the medical provider possess a unique training and skill subset to utilize a different set of field assessment and treatment priorities and strategies for monitoring and sustaining health maintenance. Provision of tactical medical care has now become an integral part of preplanning for federal, state, and local tactical teams in response from lessons learned.[2,5]

The inadequacy of the previously discussed civilian trauma model for application in tactical situations was expounded upon by Butler and Hagmann in their landmark 1996 paper.[11] Since this publication, the principles of "tactical combat casualty care" (TCCC) have been refined and now applied on today's battlefield[2,14-19] as well as in most civilian TEMS teams.[20,21] TCCC is a set of principles that aim to prevent further casualties, accomplish the tactical mission, save the maximum number of lives, and minimize morbidity of the injured. The TCCC guidelines are based on treating the leading preventable causes of battlefield death, which include hemorrhage from a compressible site, tension pneumothorax, and airway compromise.[22,23] In the most recent TCCC guidelines, attention to hypothermia prevention, intravenous access, improved en route care, and pain management techniques are also addressed.[20]

Goals of Tactical Emergency Medical Support

In the early years, TEMS role was for care and evacuation of wounded. This role has evolved with more emphasis on mission planning, primary care, preventive medicine, and emergency care of illness and injury. Although the primary goal of TEMS is to enhance the law enforcement mission, the tactical medical role involves a continuum of care that includes maintenance of team health; reconnaissance of environmental and situational aspects of the mission;

Table 192-1 Goals of Tactical Emergency Medical Support

Enhance mission accomplishment
Prepare medical threat assessment
Monitor the medical effects of environmental conditions
Reduce death, injury and illness, and related effects among team members, innocents, and perpetrators
Reduce lost work time
Maintain good team morale
Maintain health of team and provide preventive medicine
Coordinate with surrounding agencies and hospitals
Decrease liability
Possess basic forensic knowledge and crime scene preservation

coordination of local emergency medical support; creation of evacuation plan and routes; and assessment of future medical needs of the team, perpetrators, bystanders, and possible hostages.[2,5,24] Implementation of an effective tactical medical support program is directed at achieving several important goals (Table 192-1).

Tactical Team Structure, Training, and Integrated Medical Support

SWAT team and combat TEMS structure and size vary throughout the United States according to location and purpose. The typical team is composed of assault teams, which make initial contact with suspects, and arrest teams, which support the assault team. There are also rescue teams, backup teams, and hostage and negotiation teams. A unit commander supervises the operation from a command post.[2,4,5]

The TEMS component of a tactical unit, like team structure, varies widely throughout the United States. Some SWAT teams use "standby" EMS personnel, whereas others have physician-only TEMS providers. Much like the military Special Forces, many civilian tactical law enforcement agencies are now integrating medical support into the tactical team in order to enhance mission success.[1,2,5]

Although not ideal, the minimal medical coverage at a tactical location should be the use of standby civilian EMS personnel in a predetermined location. The standby EMS personnel treat casualties that are brought to them but are unable to assist in medical preplanning or inner perimeter rescue. This minimal medical support for tactical missions may be inadequate for some missions, given the high degree of potential injury and delay in definitive care.

Law enforcement agencies using integrated medical support have varying medical qualifications. The use of EMT-Bs for medical coverage has the advantage of availability and modest cost. Medical directors may be able to train basic providers with an enhanced skill set in order to provide appropriate medical care for tactical support. However, the increased skill set possessed by advanced nonhospital providers makes them favorable in a TEMS environment.[5,12] In a small number of jurisdictions, emergency physicians and residents provide medical oversight for TEMS units and are also deployed as medical operators in the tactical environment.[5,7] Although physician providers offer a broader scope of practice and do not require direct medical control, they usually have limited out-of-hospital experience and also require tactical training. In addition, as the law enforcement mission takes on additional roles overseas there is a growing need for forward surgical teams similar to military forward surgical teams that can function in remote areas. The Medical College of Georgia has developed one such surgical resuscitation team that has been deployed in support of law enforcement operations.

Figure 192-1. Special response team training for the extraction of an injured suspect. Note that the suspect is secured with handcuffs to ensure the safety of the team and bystanders. (Photo by Richard Schwartz.)

Training Issues

The tactical environment is different from the traditional EMS environment. Traditional EMS doctrine taught personnel to ensure the scene is "safe" before attempting to render care.[25] This principle is not possible in some tactical situations. Tactical training needs to take into account team tactics and movement; cover and concealment; equipment issues; nuclear, biological, and chemical training; rappelling; weapons familiarity; and noise and light discipline training.[2,5,26] Also, routine training needs to be done in basic rescue tactics, tactical room entries, open area rescues and tactics, movement under fire, cover and concealment, officer down drills, and, in some systems, firearm training (Fig. 192-1). Furthermore, many teams are now training all team members on medical management for lifesaving interventions.

In the military and operational environments, there is a significant increase in the number of penetrating traumatic injuries (gunshot, fragmentary, and blast propellant wounds, etc.).[23,27] Due to the increased complexity and number of combat casualties and the possibility that civilian TEMS providers may be exposed to such, additional training and knowledge of the TCCC guidelines are important for the operational and tactical medic. Although advanced trauma life support may be applicable to the emergency department management of trauma patients in both civilian and military hospitals, it was not created for combat or tactical out-of-hospital

Table 192-2 Phases of Tactical Combat Care

Care under fire
Tactical field care
Casualty evacuation care

medicine.[11,28-31] The three goals of TCCC are to (1) treat the casualty, (2) prevent additional casualties, and (3) complete the mission.[2,12] TCCC is divided into three distinct phases to provide the correct medical interventions at the correct time in the continuum of out-of-hospital care (Table 192-2).

Care under Fire. In terms of medical delivery in the civilian tactical environment, the area is usually divided into three zones—cold, warm, and hot.[2,26] These zones are based on tactical environment, threat level, and treatment options, which are based on a risk-benefit ratio relative to the medical provider and patient. The cold zone is a safe environment with no threat to injury. This zone is outside the inner perimeter and regular EMS treatment principles usually apply. In the warm zone, threat is not considered immediate but still exists. Finally, the hot zone is characterized by possible direct exposure to hostile fire.

As such, *care under fire* refers to care being rendered in the "hot zone." In this zone, the medic and casualty are under direct effective hostile fire. Care in this phase is very limited but not nonexistent. When care may be rendered, airway management, the first medical priority in routine out-of-hospital medicine, is best deferred until the tactical field care phase due to difficulty maintaining the airway during evacuation under direct fire. Also, cardiopulmonary resuscitation and C-spine immobilization have little or no role in the treatment of penetrating injuries in this phase and are not a priority in the combat environment.[2,11,32-34] Recommended care is limited to placing the casualty in rescue position if possible, achieving adequate hemostasis, and evacuation of the casualty to a safer "zone" or "phase" of care if possible.

Uncontrolled extremity or otherwise compressible hemorrhage remains the leading cause of preventable battlefield death, and 7 to 9% of all fatalities since the Korean conflict have resulted from wounds potentially amenable to first aid.[23] During the current conflict in Iraq and Afghanistan, newer tourniquets, hemostatic agents, and dressings and intravenous therapies have been developed, researched, and fielded by the military with unprecedented speed.[27] During the "care under fire" phase, hemorrhage control is ideally gained through the use of tourniquets. Although shunned for many years, tourniquets have reemerged as the standard of care in this environment due to low complication rates, ease of use, rapid application, and effectiveness in stopping blood loss.[2,35-38] Most tourniquets used previously were improvised with rubber tubing, rifle slings, belts, and so on and not specifically fabricated as they are today. Improvised tourniquets such as rubber surgical tubing are not recommended and should be used with extreme caution.[39] Several case series and reports have found that tourniquet use on the current battlefield has not resulted in increased limb loss or permanent disability even among patients thought to have had tourniquets applied unnecessarily.[38,40]

Many types of tourniquets are available. The tourniquet in use on today's battlefield by the U.S. Army is the combat action tourniquet, which has received very good reviews from current operators in the field.[35,41] Based on current literature, both the U.S. and the Israeli military, the International Committee of the Red Cross, and civilian agencies in the United States have embraced tourniquets as an initial hemorrhage control option during a care under fire phase in order to achieve rapid control of bleeding.[37] The current TCCC recommendation is for liberal use of appropriate tourniquets for uncontrolled extremity hemorrhage in the tactical environment.

Tactical Field Care. The second phase of care, tactical field care, is medical treatment rendered in the warm zone. This phase consists of medical care that is delivered while the medic and casualty are still under threat of injury but not under direct, effective hostile fire. Simply by dragging a casualty 5 feet around the corner of a building could transition the medic from care under fire to tactical field care. Care in this phase focuses on several areas that have been shown to increase morbidity and mortality in tactical environments if not addressed.[11,23,27] Airway establishment and maintenance is first addressed in this phase of treatment. Next, breathing issues such as tension pneumothorax and open pneumothorax (sucking chest wound) may need to be addressed in this phase of care. Circulatory issues such as tourniquet replacement with direct pressure dressings or advanced hemostatic agents and correct fluid therapy are then addressed. Intravenous (IV) access needs to be established. Hypothermia prevention, adequate analgesia, prophylactic antibiotics, and appropriate use of cardiopulmonary resuscitation are also addressed in this phase.[2,31]

Advanced Hemostatic Agents. The ideal out-of-hospital hemostatic agent ideally would require little training; be nonperishable, durable, flexible, and inexpensive; adhere to the wound only; pose no direct risk of disease; not induce a tissue reaction; and effectively control hemorrhage from arterial, venous, and soft tissue bleeding. There is no single ideal advanced hemostatic agent that currently meets all of these criteria for either military or civilian use. However, many hemostatic agents have been used successfully for uncontrolled hemorrhage on today's battlefield and have contributed to reduced morbidity and mortality in penetrating combat trauma.[42-44]

Three agents are utilized in current military operations: QuikClot (Z-Medica, Wallingford, Conn.), HemCon bandage (HemCon, Tigard, Ore.), and ChitoFlex (HemCon). Newer agents are being fielded.

Intravenous Hemostatic Agents. In the future, optimal out-of-hospital hemorrhagic control in the combat environment may also involve use of IV agents. In selected combat nonhospital settings, appropriate use of factor VIIa and blood products may help reduce coagulopathy and mortality.[45,46] Also, hemoglobin-based oxygen carrying resuscitative fluids may become available.

Tension Pneumothorax. The second leading cause of potentially preventable battlefield death is tension pneumothorax, accounting for 3 or 4% of all fatal injuries.[23,47] McPherson and colleagues[47] studied radiologic and autopsy examinations of 978 fatalities from the Vietnam conflict; 15 of the casualties with identified tension pneumothorax lived long enough to be treated by a medic, but none underwent needle decompression and all of them died.

Although needle thoracostomy is a controversial procedure in the civilian trauma setting for adults, current TCCC guidelines recommend consideration of needle decompression in casualties with chest trauma and progressing respiratory distress.[2,31,48]

Airway Management. The third leading cause of potentially preventable battlefield death is airway compromise.[2,8,47] Although the incidence in the conflicts in Iraq and Afghanistan is unknown and is currently being studied, historically airway compromise is responsible for approximately 1% of fatal injuries on the battlefield. According to Bellamy's analysis from the Vietnam era, approximately 80% of these injuries are due to facial or neck trauma causing obstruction and compromise of the airway.[10]

Initially, in an unconscious patient with intact upper airway anatomy at risk for airway compromise, the recovery position and minimally invasive adjuncts such as the nasal pharyngeal and the oral pharyngeal airway are emphasized. However, given the high incidence of trauma as a cause of airway obstruction, the cricothyroidotomy is taught as the definitive airway management technique on the battlefield if simple maneuvers fail. Traditional methods providing ventilation, such as endotracheal intubation, the laryngeal mask airway, the combitube, or the King laryngeal tube airway, may not be as feasible in tactical situations. The initial training requirements as well as maintenance issues for these skills for all military medics are simply not practical. Furthermore, use of white light required for laryngoscopy may draw enemy fire on the battlefield. Finally, based on the best available data, many patients needing airway management will likely have disrupted upper airway anatomy, for which these skills would not be successful and cricothyroidotomy would be indicated.

Intravenous Access and Fluid Resuscitation. The tactical environment often makes IV access difficult, and alternate techniques and routes may be needed to establish access.[25,48-50] Medics therefore are trained to obtain intraosseous (IO) access for fluid administration. Several newer IO devices are utilized in both civilian and combat tactical environments, including the EZ-IO, the Pyng FAST-1 sternal IO, and the Bone Injection Gun.

The current recommendations for IV resuscitation on the battlefield focus only on those patients with signs of hemorrhagic shock. Because the majority of combat casualties present with non-life-threatening penetrating extremity injuries, the number of casualties actually requiring IV fluids in the field is few. TCCC guidelines recommend an infusion of 500 mL of Hextend, followed by an additional 500 mL in 30 minute if shock is still present.[25]

Hextend, a colloid, is the recommended fluid of choice over crystalloid solutions. Hextend remains in the intravascular space longer, requiring significantly less volume than crystalloids. These factors are critical when supplies must be carried in the medic's pack. Future battlefield resuscitation strategies may include hypertonic saline, or combinations of hypertonic solutions and colloids. A growing scientific literature supports this "hypotensive resuscitation" strategy.[25,51,52]

Hypothermia Management. Hypothermia has been well recognized as an independent contributing factor for increased morbidity and mortality in trauma patients. Studies have shown hypothermia to be associated with increases in acidosis, coagulopathy, multiple organ failure, length of hospital stay, and mortality.[53,54] In the austere environment, prolonged out-of-hospital times, cold fluid administration, and environmental factors affect the patient's core temperature, as does bleeding that results in hypoperfusion, which alters the body's thermoregulation and results in hypothermia.

TCCC emphasizes prevention of hypothermia (<34° C) in patients with penetrating trauma. Prevention of heat loss should start as soon as possible after wounding. This is optimally accomplished in a layered manner. Several new devices are being tested and fielded in the combat out-of-hospital setting for hypothermia prevention.

Analgesia. The tactical environment exacerbates the typical challenges found in treating acute pain and has the additional obstacles of a lack of supplies and equipment, delayed or prolonged evacuation times and distances, devastating injuries, provider inexperience, and dangerous tactical situations. Studies have shown that failure to recognize and appropriately treat acute pain may result in an increased incidence of chronic pain and post-traumatic stress disorder.[55]

Finally, other newer agents and routes of delivery are being utilized on the battlefield to treat analgesia. Oral transmucosal fentanyl citrate has been found to relieve moderate to severe pain on the battlefield and is currently carried by many Special Forces medics.[56] Also, ketamine has been utilized successfully as an out-of-hospital analgesic in the combat setting.[57] Ketamine in subanesthetic doses is an almost ideal analgesic because of its profound pain relief, its role in preventing opioid hyperanalgesia, and its large margin of safety.

Triage and Advanced Vital Signs. It has been hypothesized that some trauma deaths may be preventable if the severity of blood loss can be recognized earlier during out-of-hospital medical care.

In an attempt to provide new possibilities for more efficient algorithms that may assist in determination of treatment and evacuation priorities for patients with unrecognized hypovolemia, new and more accurate noninvasive indicators of the underlying physiologic status in trauma patients who have initial normal systolic blood pressure and Glasgow Coma Scale have been investigated and implemented in current combat operations. Some of these indicators of hypovolemia include derived physiologic variables (e.g., shock index, pulse pressure, and field trauma score)[58,59] and continuous "real-time" variables (e.g., electrocardiogram R wave amplitude and heart rate variability).[60,61] The National Association of EMS Physicians, with funding from the Centers for Disease Control and Prevention, has led an effort to standardize mass casualty triage. Through this project, a new triage system has been developed that utilizes the principles of TCCC. This system is called Sort Assess Life Saving Triage and has been endorsed by multiple organizations, including the American College of Emergency Physicians.

Combat Casualty Evacuation Care. Combat casualty evacuation care is the third phase of care. It is rendered to the casualty in the cold zone and while the casualty is evacuated to definitive medical care. Care now begins to closely approximate traditional civilian field medical care and includes advanced life support en route to the receiving facility, often a trauma center (Fig. 192-2).[25]

Figure 192-2. Combat casualty evacuation care is usually provided via aeromedical transport or advanced life support ambulance in the civilian setting. (Photo courtesy of the *Augusta Chronicle* and Andrew Davis Tucker.)

TEMS Environment

Training

Practicing effective medical care in the tactical environment requires TEMS personnel to be well educated, trained, and equipped. Integrated "team" training allows the medical support members to understand their roles and learn all aspects of tactical law enforcement operations and fundamentals on how to approach the tactical medical arena. Unique medical scenario-driven protocols should be developed and rehearsed with the tactical team. These specialized protocols may require advanced practice, and they require medical control approval that should also satisfy state or federal regulations.[2,5,62]

Equipment

The medical equipment selected and carried by TEMS providers varies and is based on usage, size, weight, budget, training, experience, and mission type. Use of conventional EMS medications and equipment with bright markings and color coding is often discouraged in the tactical environment in order to maintain concealment.

Remote Patient Assessment

Remote patient assessment is another function of TEMS and is done when a person is injured and medical personnel must assess the patient from a distance using binoculars, gun scopes, night vision goggles, cameras, and microwave radar motion detectors.

Hazardous Materials

Incidents involving clandestine drug labs and weapons of mass destruction are also considerations in a TEMS environment. Rapid decontamination must be taught and practiced by tactical teams because adequate decontamination is usually not available in the inner perimeter.[63,64]

Forensic Science

Basic knowledge of forensic science is important in order to recognize and preserve evidentiary items. Documentation of wound and blood patterns should be done. All evidence should be collected appropriately and the chain of custody honored.[65]

Medical Threat Assessment

Medical threat assessment (MTA) is the accounting for all variables that may affect the health and welfare of the tactical team, the perpetrators, nearby civilians, and possible hostages. The MTA is an essential component of the preplanning phase and should be integrated into the tactical operation.[2,5,66] Once the MTA is complete, a plan is then developed based on the medical intelligence addressing each possible situation, with the realization that the plan may change as the mission evolves.

Preventive Medicine

The maintenance of the tactical team's health is an important aspect of a TEMS program. Poor health has been shown to directly correlate with poor job performance and mission failure.[67-69]

Liability

Because special operations lend themselves to high litigation and possible disability, TEMS providers need to ensure they have proper malpractice and disability coverage.[5,70]

URBAN SEARCH AND RESCUE

It was hard to breathe. The air was thick and choking. It looked as though black snow had fallen, covering everything.

It was as dark as a tunnel and the air was as thick as soup. Despite repeatedly scooping chunks of dust and debris from my mouth and nostrils, I inhaled and swallowed large quantities.

It took an hour to wash off the layers of dust, which by now had become like a layer of concrete.

Drs. Kelly and Prezant, New York City Fire Department, during the September 11, 2001, terrorist attacks.

Perspective

Urban search and rescue (US&R) is the science of responding to, locating, reaching, medically treating, and safely extricating victims entrapped by collapsed structures.[71] US&R is a "multihazard" discipline because it may be needed in a variety of emergencies and disasters, including natural disasters (e.g., earthquakes, hurricanes, etc.) and man-made disasters (e.g., terrorist attacks, building and structure collapse, hazardous materials spills, etc.).[72,73] Federal activation of US&R teams occurs when local and state resources have been overwhelmed and there has been a request from a state governor to the President for the activation of federal response assets. In addition, in catastrophic events the activation of military assets may be required to assist in a support role of other local, state, and federal assets.[74] In order for responding resources to be effective, they must be highly trained, quickly deployable, mobile, and self-sufficient.

Components and Structure of a US&R Team

The responding team must mobilize quickly to accomplish its objectives and must not place additional demands on the already stressed infrastructure. Figure 192-3 shows the organizational structure of a Federal Emergency Management Agency (FEMA) US&R team.[72] There are 28 FEMA US&R task forces throughout the continental United States that are trained and equipped to handle structural collapse.

An effective US&R team needs both properly trained personnel and appropriate equipment. The equipment cache should allow the task force to be totally self-sufficient for the first 72 hours and to be capable of 24-hour operation for 10 days.[72,75] The FEMA equipment cache is divided into five groups—rescue equipment, medical equipment, technical equipment, communications equipment, and logistics equipment. The medical equipment cache was designed to treat the unique medical needs of trapped victims as well as the medical needs of the team. The medical cache contains enough supplies to handle 10 critical cases, 15 moderate cases, and 25 minor cases. The cost of the entire cache is approximately $2 million.[72,75]

Coordination and cooperation with local resources and other teams is critical.[71,76] The US&R team is integrated into the Incident Command System (ICS) at the disaster.

The search team is responsible for developing and implementing a plan to search the area for victims. The search team can be subdivided into two teams—a *canine search team* and a *technical search team*. The canine team uses specially trained

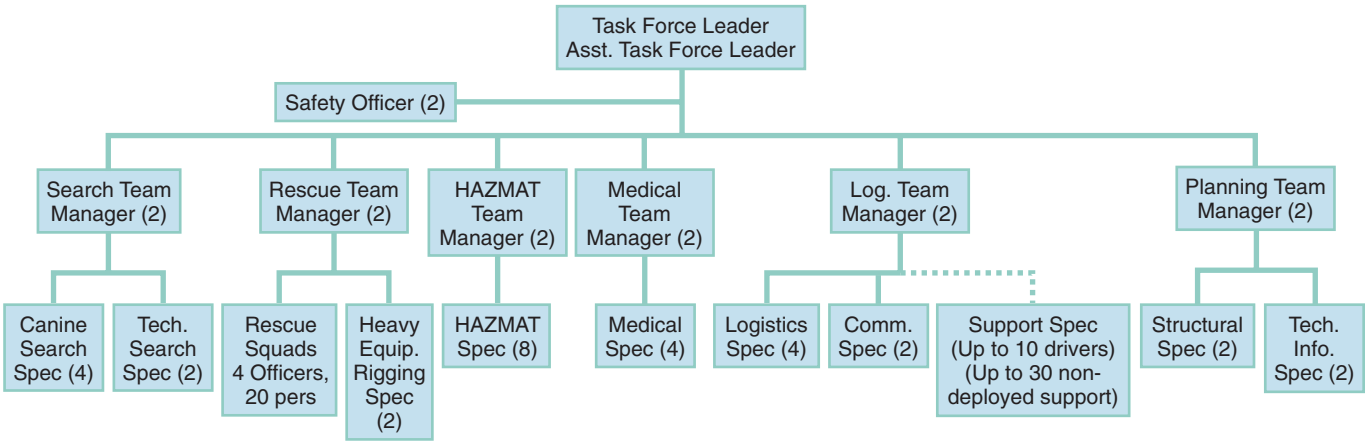


Figure 192-3. Structure of a FEMA US&R team.

dogs to locate trapped victims. The technical team uses specialized microphones, listening devices, cameras, and fiberoptic devices to locate victims in confined spaces. The search team is responsible for locating victims and identifying probable areas where victims may be found.

The rescue team is composed of rescue specialists. Once a victim or potential victim is located, the rescue team is responsible for breaching the area and creating a safe entrance to, and exit from, the victim's position.

The technical team is composed of various specialists, including structural specialists, hazardous materials specialists, heavy rigging and equipment specialists, technical information specialists, and communications specialists.[76] These specialists work collaboratively to ensure a safe and efficient operation.

The logistics team is responsible for all the equipment needs, including inventory, issuing, and record keeping.[76]

Finally, the medical component is composed of medical personnel who are responsible for the medical needs of both the task force personnel and the victims. Typically, the medical personnel are emergency physicians and paramedics.[76,77]

BOX 192-1 Medical Intelligence Gathering Prior to Deployment

- Type of disaster and predicted numbers and types of potential victims
- Capabilities of the team to deal with the medical aspects of the situation, including dealing with injured team members
- Local emergency department's level of functioning; trauma center status and location
- Local EMS resources
- Location of planned triage staging area
- Communications with local resources (EMS, police, emergency departments, fire and rescue, etc.)
- Weather, environment, or hazardous materials issues
- Availability of other resources (military, NDMS, DMAT, etc.)

DMAT, disaster medical assistance team; EMS, emergency medical services; NDMS, National Disaster Medical System.

Medical Team Operations in Urban Search and Rescue

A number of unique considerations must be addressed for US&R. As with TEMS, team physicians must realize that they will be operating outside of their usual environment and that they are not in charge overall. Typically, the physician on the team works with the team leader and the managers of the other components. To do this efficiently, the physician should be familiar with the capabilities and training of all the members on the team and the ICS. Cross-training of team members is ideal.[71,76-78]

Medical Team Tasks

Predeployment. The job of the medical team in the predeployment phase is to ensure that the entire team is fit and functional for deployment and that the medical equipment cache is organized and up-to-date.[77] The perceived medical threats in the deployed area must also be addressed (e.g., endemic disease, water contamination, insect threats, existing medical support, etc.). A family and communication support system should also be set up before the deployment.

Deployment. The medical team is responsible for much more than just treating the victims. Medical intelligence information needs to be collected and addressed (Box 192-1). A plan is required for transfer and transport of victims and for fatality management.

The medical action plan is critical for ensuring smooth operations and must be updated as conditions or knowledge changes.[71,76,77] The medical component of a US&R team needs to be able to provide care for its own team members, whose needs may exceed those of the victims. The medical team also needs to assess the adequacy of team members' rest and sleep and the psychological effects of the situation.[76,77] In addition, the US&R medical assets must be integrated with the overall medical response that is guided under Emergency Support Function Number 8, "Public Health and Medical." This includes integration with existing medical resources, disaster medical assistance teams, TEMS resources, military resources, and public health. If there is a canine search component, the medical team should receive some sort of basic veterinary training before deployment.[76,77]

Confined Space Issues

A *confined space* is defined as any space with limited access and ventilation. The physician and medical team must be prepared to work in this setting during a deployment and must be aware of issues related to team and victim safety, air purification, and structural dynamics related to collapse or impending collapse.[76,77]

Specific Disorders in Urban Search and Rescue

US&R teams will typically be responding to the aftermath of earthquakes, collapsed structures, terrorist bombings, hurricanes, and other natural and man-made disasters.[71,77] Reviews of the literature have identified the types of medical problems and conditions that might be encountered.[71,72,77,78] Most of the medical conditions are those encountered in the emergency department and are handled similarly. The following clinical problems occur with much greater frequency in the US&R environment: crush syndrome, compartment syndrome, particulate inhalation, hazardous materials exposures, and blast injuries.[71,77] Since the terrorist attacks of September 11, 2001, there has also been an emphasis on preparing the US&R teams for the medical response to weapons of mass destruction.

Crush Injury and Crush Syndrome

Compartment syndrome is defined as crush injury caused by swelling of tissue inside the confining fibrous sheath of a muscle compartment, which can cause further destruction of the intracompartment muscle and nerves. Compartment syndrome is discussed in Chapter 46.

Crush syndrome is defined as the systemic manifestations caused by crushed muscle tissue. This typically occurs when blood flow is restored to the crushed tissue and the toxins are released systemically. It is estimated that 3 to 20% of earthquake victims, and up to 40% of survivors of multistory building collapses, will develop crush syndrome.[79,80] Early hydration of the victim in the rubble before, during, and after extrication can lessen the renal effects of crush syndrome.

Crush injury and crush syndrome can result from objects that have fallen on the patient or from the patient's own body weight. The amount of time required for crush syndrome to develop depends on both the amount of pressure and patient factors. It can occur within 1 hour if the pressure is severe, but it usually takes 4 to 6 hours to develop.

Pathophysiology of Crush Syndrome. The cause of muscular injury in crush injury is not fully understood and controversial. The intracellular contents of the cell include lactic acid, potassium, myoglobin, uric acid, enzymes, leukotrienes, thromboxane, phosphate, and others. There is also increased capillary permeability. This can lead to edema and third spacing of fluid.[81,82] These effects occur locally until the tissue is released and reperfused. This is why victims can be trapped for days with severe crush injury and appear stable when reached by rescuers only to deteriorate soon after being rescued. There are reports of patients going into cardiac arrest soon after rescue.[81-83] When the crushed area is released, there is a release of all the intracellular contents that have been building up locally into the systemic circulation, causing systemic symptoms. The major causes of early death due to crush syndrome are hypovolemia due to third spacing of fluid and dysrhythmias due to severe metabolic acidosis and hyperkalemia. Delayed causes of death include renal failure, acute respiratory distress syndrome, sepsis, ischemic organ injury, disseminated intravascular coagulopathy, and electrolyte disturbances.[79-82]

Management of Crush Syndrome. Early aggressive therapy is essential for prevention of crush syndrome, and it should begin before extrication.[81] All victims who have an obvious crush injury or are immobilized for 4 hours or more should be considered to have crush injury. The severity of the crush syndrome may be related to the number of extremities with crush injury. In a Japanese study of earthquake victims, the incidence of acute renal failure due to crush syndrome was 50% for one involved extremity, 75% for two involved extremities, and 100% for three or more involved extremities.[79] Once a victim is located, the medical component needs to be actively involved with the rescue process and begin treatment before extrication. Cardiovascular instability is commonly seen in crush syndrome.[82] As extrication is being done, continuous cardiac monitoring is recommended. Adequate hydration is recommended along with the usual management of hyperkalemia (e.g., insulin/glucose, ion exchange resins, beta-agonists, and dialysis). The current guidelines taught in the FEMA medical specialists course recommend IV calcium only for arrhythmias that do not respond to other measures or when there is a documented severe hypocalcemia.[77] It has been suggested that an average-sized adult may require up to 12 L/day of fluids to sustain a forced diuresis of 8 L/day to prevent renal complications. Continued monitoring of the patient's vital signs, hydration status, and urine output should be done to guide fluid administration until more invasive monitoring is available.[78] Alkalinization of the urine to prevent renal failure has been recommended in crush syndrome but has not been subjected to proper study, and the effects of the alkalinization, if any, are impossible to separate from those of the volume fluid used. Rhabdomyolysis and its relationship to renal failure are discussed in Chapter 125.

Other Medical Problems in US&R

Another unique medical problem in US&R is dust and airway contamination. During earthquakes and building collapses, a tremendous amount of dust is released into the air. During the first 48 hours of rescue efforts at the World Trade Center (WTC), 90% of the 10,116 New York City Fire Department rescue workers evaluated at the WTC site reported an acute cough often accompanied by nasal congestion, chest tightness, or chest burning, but only 3 required hospitalization for respiratory symptoms (Fig. 192-4). During the 6 months after the attacks, 322 firefighters and one EMS worker had WTC-related cough severe enough to require more than 4 weeks of sick leave.[84] The victim of a collapsed structure should be assumed to have some sort of dust contamination. Evaluate the airway for any evidence of burns or hazardous materials exposure. During the extrication process, monitor the patient's airway and be prepared for deterioration. If considering intubation, it is better to do it early before edema obstructs the

Figure 192-4. Massive amounts of dust and contaminants can exacerbate existing medical conditions, such as asthma and chronic obstructive pulmonary disease, during US&R operations. (Photo by Jeff Orledge.)

airway, making the procedure more difficult. Medical management of the victim reached after prolonged entrapment is very different from the typical trauma setting. The "scoop and run" approach of the trauma patient is not always appropriate or possible.

Hypothermia may also be an issue for patients subjected to environmental conditions. Stabilization, extrication, and ongoing treatment should also be directed at the prevention or reversal of hypothermia, as discussed previously.

KEY CONCEPTS

- The hostile environment that is intrinsic to combat and urban SWAT team operations requires specialized training and planning for medical personnel.
- Determining medical capability for the hot, warm, and cold zones of a conflict area requires evaluation of local characteristics, the nature of the threat, team safety, and community resources.
- US&R teams have many integrated components. Typically, the medical component is the smallest part of the team but has some of the greatest responsibilities.
- Medical problems, including crush syndrome, compartment syndrome, exacerbation of respiratory illness, and hypothermia, will be encountered in US&R.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 193

Disaster Preparedness

Carl H. Schultz and Kristi L. Koenig

PERSPECTIVE

Disasters occur in all areas of the world and cause harm to people, property, infrastructures, economies, and the environment. Harm to people includes death, injury, disease, malnutrition, and psychological stress. Recent catastrophes include earthquakes in Iran (2003) and Pakistan (2005) (Fig. 193-1); devastating tsunamis in the Indian Ocean involving multiple countries, including Sri Lanka, Indonesia, and India (2004); massive hurricanes in the southern United States (2005); severe flooding in Mozambique (2000) and France (2003); tornadoes in Arkansas, Tennessee, and Kentucky (2008); and global adverse weather conditions related to the El Niño phenomenon (2003 and 2004). These types of events are likely to become more common in the future. Increasing population density in floodplains and in earthquake- and hurricane-prone areas and the effects of global warming point to the probability of future catastrophic disasters with millions of casualties.

Factors that indicate an increasing probability of mass casualty incidents include (1) terrorist activity; (2) increasing population density in floodplains, seismic zones, and areas susceptible to hurricanes; (3) production and transportation of thousands of toxic and hazardous materials; (4) risks associated with fixed-site nuclear and chemical facilities; (5) the possibility of catastrophic fires and explosions; and (6) global warming. For example, the U.S. Geological Survey has identified approximately 35 volcanoes in the western United States and Alaska that are likely to erupt in the future. Mt. Hood, Mt. Shasta, and the volcano underlying Mammoth Lakes in California are near population centers. Because of the rising population density in these areas, hazards from volcanic activity are increasing.

Given this probability and the increasing role of emergency medicine in disaster preparation, mitigation, response, and recovery, this chapter discusses disaster planning and operations with emphasis on the role of the emergency physician. The emergency physician has extensive responsibilities for community disaster preparedness and disaster medical services, particularly regarding terrorism.[1] In its June 2001 position paper, the American College of Emergency Physicians outlined the scope of emergency medicine's involvement in preparedness and response to terrorism and stated its belief that "hospital emergency departments will be the first and most critical line of defense for detection, notification, rapid diagnosis, and treatment" and that "emergency department personnel will become the *first responders* to a covert biological attack."

A committed emergency department alone is insufficient to provide hospitals with a successful disaster preparedness program. Institutional commitment by every hospital department and the administration is necessary to coordinate effectively with systemwide resources for disaster management. This is especially critical for creation of hospital surge capacity.[2-4]

Surge Capacity

The concept of surge capacity has emerged as a way to manage an event that produces a sudden influx of casualties with medical and health needs that exceed current hospital resources.[5] This can occur due to either the volume or types of victims. The three basic components of the surge capacity system are commonly referred to as the three S's of staff (hospital personnel), stuff (supplies and pharmaceuticals), and structure (physical location and management infrastructure). A complete discussion of surge capacity is beyond the scope of this chapter but has been published elsewhere.[3,4]

NATURE OF DISASTERS

Definitions

One of the challenges facing those responsible for disaster preparation is that no standard definition of *disaster* exists. Some events that have been routinely classified as disasters clearly are not. For example, many would consider a plane crash a disaster, yet it may not even approach overwhelming the resources of the local responders. Because disaster medicine is multidisciplinary and depends on the integration of multiple levels of responders, the use of a common, precise terminology is essential.

In general terms, an event can be considered a disaster when it overwhelms response capabilities. These response capabilities can change in diverse environments or even in the same location at different times of the day or days of the week. For example, a multiple-vehicle collision with 6 critically injured patients and 12 patients with minor injuries could overwhelm both the emergency medical services system and the hospital in a small rural community. In an urban area with multiple hospitals that participate in a trauma system, however, this same event could be handled with routine resources. Thus, it is the functional impact on the specific area that is the key concept in determining whether a disaster exists.

Figure 193-1. Large-scale catastrophes, such as this earthquake in Pakistan (2005), have the potential to cause much injury and psychological stress.

Classic Terminology

Many terms have been used in an attempt to describe disasters. The words *internal* and *external* refer to a hospital setting to help distinguish whether an event has occurred within the hospital grounds (internal) or in the community (external). This concept distinguishes between preparing for casualties to arrive at the hospital and dealing with casualties or resource problems within the hospital. This geographic distinction between internal and external may be useful, but it has severe limitations. Many events can be both internal and external to the facility at the same time (e.g., major earthquake or hurricane). Furthermore, simply identifying the location of the event does not answer the critical question: How are response capabilities affected?

An etiologic descriptor for an event is another customary classification. It does not matter whether a disruption in the ability of the hospital to respond is caused by nature or by humankind. The key consideration is what needs to be done to mitigate and then to rectify the situation. Thus, although the terms *natural* and *man-made* are prevalent disaster descriptors, they generally do not add anything of value and therefore some experts have advocated to remove them from the disaster lexicon, particularly because the cause of the event may be unclear in its initial aftermath.

Some definitions have been based on the number of casualties. As previously described, the absolute number of patients is much less important than whether their medical and health needs exceed the resources to care for them. Another scheme divides disasters into three levels. Level I denotes a situation in which local resources are adequate to care for casualties. For example, the 2002 collision between a freight train and commuter train in Orange County, California, was managed effectively by local responders. Level II means that regional mutual aid is required to respond to the event. This was the case at the Hyatt Regency Hotel in Kansas City in 1981 when two skywalks collapsed, killing 114 people and injuring hundreds. Level III incidents require state and federal aid. The attack on the World Trade Center in 2001 (Fig. 193-2) and Hurricane Katrina in 2005 were such events, causing such massive destruction that federal disaster medical assistance teams were deployed to New York and Louisiana, respectively, to provide medical personnel and supplies.

One model eliminates the word *disaster* and replaces it with the acronym for potential injury-creating event, *PICE*.[6-8] The PICE nomenclature is an attempt to resolve the issue regarding diverse meanings for *disaster*. This model is referenced in the Joint Commission standards and in publications from several countries. The PICE system is discussed here to help clarify important concepts in describing an event.

Potential Injury-Creating Event Nomenclature

The acronym PICE and its modifiers concisely describe the critical features of most types or degrees of disaster.[6-8] The same occurrence can have different effects at different points in time; thus, as an event evolves over time, its description may change.

Modifiers are chosen from a standardized group of prefixes along with a stage to indicate the need for outside medical assistance (Table 193-1). The first prefix (column A) describes the potential for additional casualties. The second prefix (column B) describes whether local resources are overwhelmed and, if so, whether they must simply be augmented (disruptive) or whether they must first be totally reconstituted (paralytic). The third prefix (column C) shows the extent of geographic involvement.[6-8]

The stage rating scale defines the likelihood that outside medical assistance will be needed either to augment or to completely reconstitute resources.[6-8] Stage 0 means that there is little or no chance. Stage I means that there is a small chance and requires placing outside medical help on alert. Stage II means that there is a moderate chance and outside help should be placed on standby. Stage III means local resources are clearly overwhelmed and requires the dispatch of outside resources and commitment of personnel. For example, a multivehicle collision with a dozen injuries and several deaths in a large city would be a stage 0, whereas in a small rural town it might be a stage III (Table 193-2).

A PICE can be either static or dynamic. *Dynamic* implies an evolving situation in which it is too soon after the incident to determine the numbers and types of casualties and the impact on the hospital. Alternatively, a *static* situation results if 10

Figure 193-2. The World Trade Center attack of 2001 overwhelmed local resources and necessitated state and federal help.

Table 193-1 PICE Nomenclature

PREFIX					
A	*B*	*C*	PICE STAGE	PROJECTED NEED FOR OUTSIDE AID	STATUS OF OUTSIDE AID
Static	Controlled	Local	0	None	Inactive
Dynamic	Disruptive	Regional	I	Small	Alert
	Paralytic	National	II	Moderate	Standby
		International	III	Large	Dispatch

PICE, potential injury-creating event.

Table 193-2 PICE Nomenclature Examples

World Trade Center attack, September 11, 2001	Dynamic, paralytic, local PICE, stage III
Los Angeles civil disturbance	Dynamic, paralytic, regional PICE, stage I
Northridge earthquake	Dynamic, disruptive, regional PICE, stage II
Oklahoma City bombing	Dynamic, disruptive, local PICE, stage I

PICE, potential injury-creating event.

BOX 193-1 Six Critical Substrates for Hospital Operations

Physical plant
Personnel
Supplies and equipment
Communication
Transportation
Supervisory managerial support

BOX 193-2 Examples of Paralytic PICE

Destructive
Bomb explosion
Earthquake
Fire
Civil unrest

Nondestructive
Snowstorm
Employee strike
Power failure
Water supply cutoff

people are injured in an incident and little potential for further harm exists.[6-8]

In some situations, enhancing routine operations is not sufficient or possible. A PICE can completely overwhelm the capability to mount a normal response so that a substitute plan for recovery must be used. Situations that require significant reconstitution of critical resources are termed *paralytic*.[6-8] Within the hospital, there are six critical elements necessary to provide a response (Box 193-1).[9] If one or more of these resources are compromised, they must be reconstituted or a substitute must be implemented. Such paralytic events can be either destructive or nondestructive (Box 193-2).[6]

Hazard Vulnerability Analysis

An important consideration in disaster planning is an awareness of the types of events for which the hospital or community is vulnerable. The classic example is the monumental risk from earthquakes in the central United States resulting from the combination of the New Madrid fault and the limited seismic safety requirements for buildings in that area. The planner must learn what types of support are available from outside agencies (e.g., hazardous materials decontamination from fire departments and information from poison control centers). Although awareness of such resources is critical, contingency plans must be available when such assistance is not accessible.

After performing a hazard vulnerability analysis, emergency planners should consider the most probable events and prepare for them. There must also be planning for events that are rare but catastrophic.[10] The major peacetime threat to life and limb in the United States is probably a large earthquake in a densely populated area or a terrorist attack. The disaster planner must proactively identify all such hazards and prepare contingency plans for each.

TRIAGE

The term *triage* derives from the French verb, *trier*, meaning "to sort." The concept of triage was used as far back as Napoleon's time to assign priorities to treatment of the injured when resources were limited. Priority is given to the most salvageable patients with the most urgent conditions. The emergency department uses triage in the hospital setting on a daily basis, but the focus of such triage must be changed under disaster conditions.[11,12] Standard emergency department triage is intended to identify the most seriously ill patients first and ensure that they receive rapid care. The goal of disaster triage is slightly different—that is, "to do the most good for the most people." In other words, there is a shift from focus on individual patients to focus on the entire affected population. It can be very difficult for physicians to realize that to achieve the goal of maximizing benefit to an entire population of patients, they may need to let some patients die with only comfort care. Under true disaster conditions, cardiopulmonary resuscitation should not be performed.[13]

Routine Multiple-Casualty Triage

To assist in understanding triage techniques, it is useful to consider a routine out-of-hospital event with multiple casualties (e.g., a multivehicle collision). In such situations, rescue personnel often use a Simple Triage and Rapid Treatment (START) technique that depends on a quick assessment of respiration, perfusion, and mental status.[14] Initially, all victims who are able to walk are asked to move away from the immediate incident area. These patients are classified as green, or "walking wounded," and are reassessed after the more immediately critical patients are triaged.

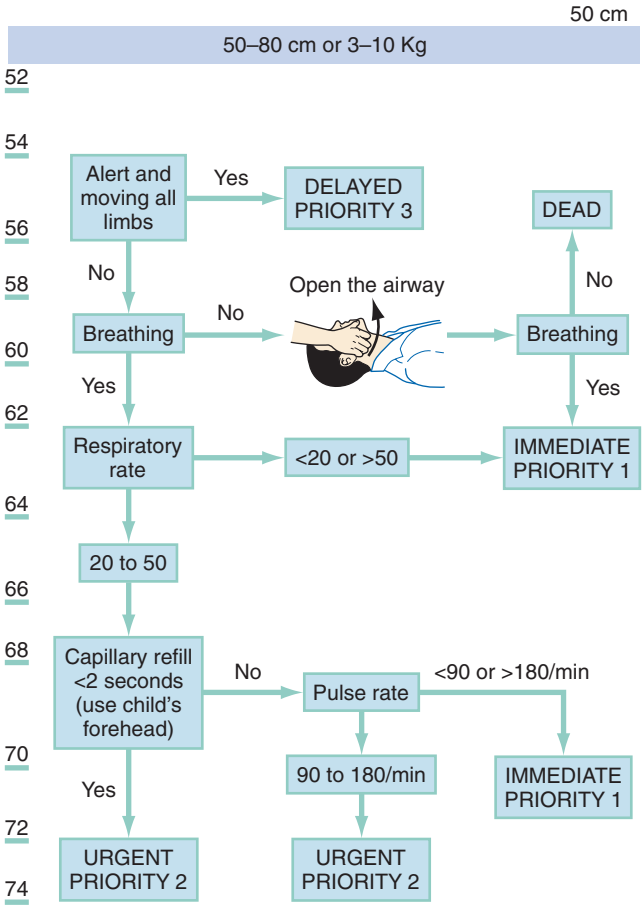


Figure 193-3. Pediatric Triage Tape algorithm for a child 50 to 80 centimeters in length.

The Pediatric Triage Tape (PTT) and JumpSTART have been proposed for the triage of children. JumpSTART is a modification of the START triage protocol that includes an additional step of five rescue ventilations for children presenting apneic and modification of criteria for hypoventilation and tachypnea, as well as for a decrease in mental status. The PTT utilizes criteria that change in proportion to increasing victim size. The parameters for a child 50 to 80 cm in length are illustrated in Figure 193-3. In a comparison of sensitivity and specificity between the PTT and JumpSTART in pediatric trauma patients, the PTT demonstrated superior outcomes.[15] Both START and the PTT appear to be useful tools, but neither has been adequately evaluated in disaster situations.[16,17]

As illustrated in Figure 193-4, a rescuer can assess each patient in seconds, quickly checking respiratory rate, pulse, and ability to follow commands (mental status), and divide them into the remaining three categories: red (immediate), yellow (delayed), and black (deceased). The only patient care interventions provided during this process are the opening of an obstructed airway and direct pressure on obvious external hemorrhage. At this point, patients are generally transported to a hospital for definitive care. Most often, patients arrive with a color-coded triage tag and are reassessed and retriaged by the hospital staff (Fig. 193-5).

Catastrophic Casualty Management

Triage during a widespread, catastrophic disaster differs from triage performed in routine out-of-hospital and hospital settings. The number of victims is vastly increased, and medical resources are severely limited or even initially absent. Patients may remain on scene for an extended period and must be frequently reassessed. In addition, the triage process is decentralized, occurring at multiple sites, or compartments, simultaneously throughout the disaster zone. Rather than a single scene or localized disaster, this can be thought of as a compartmentalized disaster. Lastly, patients tend to seek care at the closest hospital, a phenomenon known as *convergence*. Hospitals close to the disaster scene are overwhelmed, whereas hospitals located only a few miles away may receive few, if any, patients.

To address these considerations, the secondary assessment of victim endpoint (SAVE) system of triage was developed.[17] The SAVE triage system is designed to identify patients who are most likely to benefit from care available under austere field conditions in a resource-poor environment. When combined with the START protocol, SAVE triage is useful for any scenario in which multiple patients experience a prolonged delay in accessing definitive care.

The SAVE methodology is designed for use by health care providers under two conditions: (1) for those working within the disaster zone who begin caring for patients immediately but may not be able to transport patients to a definitive care facility for days and (2) for those caring for patients within hospitals where demand for resources exceeds supply. This second situation can occur as hospitals attempt to increase surge capacity. It is immediate and dynamic rather than delayed and static. Although there are many elements in common with other triage systems, rapid transport to a functional medical center within the ideal "golden hour" may not be possible.

The SAVE triage methodology divides patients into three categories: (1) those who will die regardless of how much care they receive, (2) those who will survive whether or not they receive care, and (3) those who will benefit significantly from austere field interventions. Only those patients expected to improve receive more than basic care and comfort measures. Using SAVE, patients are separated into these three categories so resources can be focused appropriately. The decision to place patients in a particular group is based on field outcome expectations derived from existing survival and morbidity statistics.[18] An example is a situation in which three victims require chest tubes (two victims require one tube each and one victim requires two tubes), but only two chest tubes are available. The SAVE principles guide providers to place their last two chest tubes into the two victims that need it rather than into the single victim requiring two tubes.

During the triage process, individuals who would most benefit from early transport should be marked as "first out," in case an evacuation opportunity occurs. These would be victims with medical problems readily treatable at a hospital but untreatable and fatal in the field. A patient requiring surgery for intra-abdominal hemorrhage is a common example.

Since nuclear, biologic, and chemical terrorism has become a threat, new triage systems are under development.[11,19] These systems attempt to incorporate the added threats from exposure and contamination into the triage process. One such method for biological casualties triages many individuals to home observation rather than hospitalization to optimize resource utilization and minimize the spread of the infectious agent.[19] In addition, responders must be protected from secondary contamination or exposure; therefore, part of the triage algorithm must include a risk assessment and determination of whether, and what type of, personal protective equipment

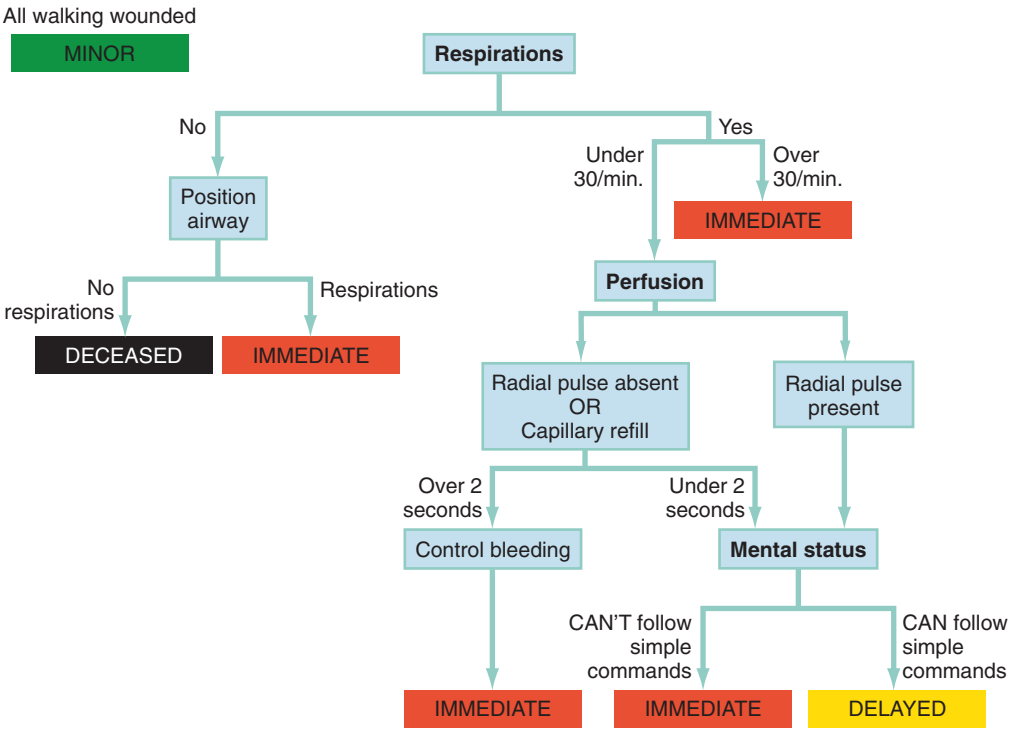


Figure 193-4. Simple Triage and Rapid Treatment (START). Victims who can walk are identified first and triaged into the "minor" category. Those remaining are triaged using the algorithm. (Modified from Triage-START and SAVE. In Medical Disaster Response Training Course Syllabus. Dana Point, Calif, Medical Disaster Response, 1993.)

must be donned prior to assessing patients. A quick determination is critical to prevent patient deaths from traumatic injuries while awaiting medical care from responders concerned about their own health and safety. This is particularly true in a "combined event" scenario such as an event involving a radiologic dispersion device. Also associated with terrorism incidents are large numbers of *psychogenic casualties*—those who believe they were exposed but actually were not and those at risk for post-traumatic stress disorder. The emergency plan must include a mechanism to assess and sort these individuals so as not to overwhelm the emergency department and also provide mental health care. While performing triage, the emergency physician must also consider the effects of extremes of age, underlying disease, and multiple injuries when assessing the potential prognosis for a given patient. Fortunately, the treatment of many nontraumatic emergencies can be accomplished with field interventions that do not consume extensive resources. Therefore, patients with such illnesses should usually be triaged to the treatment area.

Special Triage Categories

To maximize personnel resources, disaster victims who would normally be triaged to the observation area can be triaged to the treatment area if they possess special skills valuable to the medical team (e.g., medical expertise and translation skills). By increasing the number of functional team members, the effectiveness of the overall response will improve. The guiding principle supports the disaster triage goal of maximizing benefit to the most people.

■ OUT-OF-HOSPITAL RESPONSE

Emergency Medical Services System Protocols

To prepare adequately, hospitals must be familiar with and involved in the development of county or regional plans. For example, some emergency medical services systems use automatic systems such that each hospital may be expected to accept a predetermined number of critically ill or injured and minor patients without previous notification.

Physicians working at hospitals should be familiar with community disaster management operations, including the function of the emergency operations center.[9] Mutual aid agreements with other hospitals or regions should be considered for situations in which the hospitals become overwhelmed or require evacuation.

Incident Command System

Some form of an incident management system is now a standard component of emergency command and control throughout the United States. It provides a flexible management structure on which to organize a response.[20] The federal version, known as the National Incident Management System (NIMS), is incorporated into the National Response Framework and provides strategic guidance on the U.S. government's involvement in disaster response. All states must utilize an incident management system, and it must be compliant with NIMS.[21] By standardizing an organizational structure and using common terminology, an incident command system provides a management configuration that is adaptable to events involving a multiagency or multijurisdictional response. At the most basic level, there are five functional elements in the organizational structure: (1) incident command, (2) operations, (3) planning, (4) logistics, and (5) finance. The principles of an incident command system can also be applied to the hospital setting through implementation of a Hospital Incident Command System. With this type of organizational infrastructure and the flexibility to expand and collapse as needed, an orderly and efficient response to any incident can be accomplished. Because hospitals cannot anticipate every contingency, a system such as the Hospital Incident Command System assists with planned improvisation. The Joint Commission (formerly known as JCAHO) standards require use of an incident management system in health care facilities.

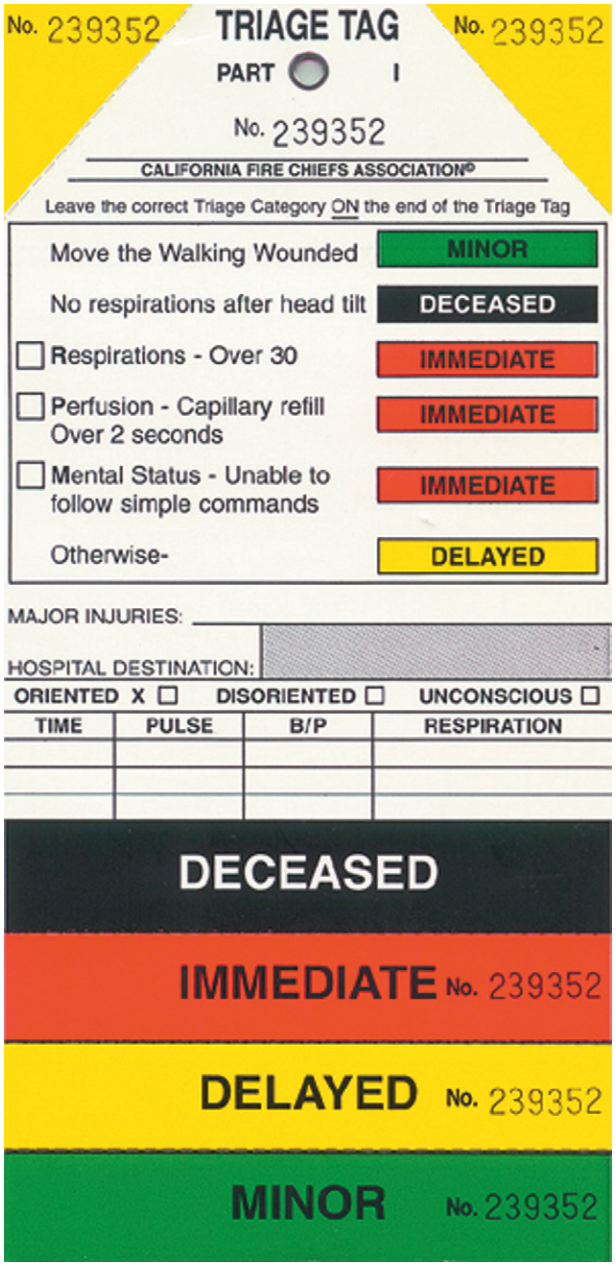


Figure 193-5. Triage tag to be used in multicasualty or disaster patient assessments.

Incident Command

The incident commander has overall management responsibility for the incident. Physicians should understand that they are not in charge at the scene of an out-of-hospital incident.[21] In general, nonhospital providers can manage the scene, and physicians should remain at the hospital to provide definitive care. When a physician is on scene, the best way to assist is to ask the incident commander where medical help is most needed.

The incident commander may choose to appoint a command staff to handle public information, safety, and interagency liaisons.[20] When an event involves multiple jurisdictions, a unified command is established that coordinates a common and consistent action plan to make the best use of available resources.

Operations Section

The operations section has a chief who is responsible for the management of all incident tactical activities.[20] This section can be expanded and subdivided into branches (e.g., law, fire, and medical) and divisions. Operations also manages the resources assigned to staging areas. Ambulances, personnel, and supplies must be staged outside the perimeter of the scene and directed in as needed rather than converging on the disaster site, potentially disrupting activities and blocking the exodus of patients. It is under the operations section that all medical triage and care is provided.

Planning Section

The planning section collects, evaluates, and disseminates information regarding incident operations and the status of resources. This section also develops incident action plans and conducts planning meetings.[20]

Logistics Section

The logistics section's chief is responsible for providing facilities, services, and material in support of the incident. This includes procuring equipment and supplies, providing food and medical support, and meeting transportation needs.[20]

Finance Section

The finance section is responsible for maintaining records on personnel and equipment, providing payments to vendors for supplies and use of equipment, and determining the cost of various alternatives for strategic planning.

Organization of the Out-of-Hospital Disaster Scene

The disaster site is organized into several distinct areas. The command post is the nerve center of the operation and contains the incident commander and section chiefs. A staging area for incoming personnel and equipment should be established on the outer perimeter. If air evacuation is needed, a safe landing zone must be identified. A casualty collection point and morgue should be designated. In conjunction with an incident command system, this structure brings order to the response.

PLANNING AND HOSPITAL RESPONSE

Comprehensive Emergency Management

The comprehensive emergency management all-hazard approach to disaster preparedness is now required by the Joint Commission. Comprehensive emergency management consists of four phases: (1) mitigation, (2) preparedness, (3) response, and (4) recovery.[22,23] *Mitigation* involves taking actions to reduce the impact of identified hazards. Training, drills, and cataloging resources are examples of *preparedness* activities. *Response* includes assessment of the situation and coordinating resources. Finally, *recovery* consists of a return to normal operations and debriefing to critique the response and provide psychological support to the rescuers.

As required by the Joint Commission, a hospital's disaster or "emergency management" plan must address events that occur both inside (internal) and outside (external) the institution.[23] Because some incidents affect both internal and exter-

nal operations, a hospital emergency management program should contain plans that address all circumstances.

Hospital Disaster Response Plan

A disaster event can disrupt daily, routine hospital functions. This can represent an infrastructure failure (e.g., loss of electric power and water) or a threat to the safety of patients and hospital personnel (e.g., labor dispute). Because the response varies from postponing elective surgery to facility evacuation, every hospital department must participate in the planning process. At a minimum, the disaster plan should (1) clearly delineate the circumstances in which the plan is activated; (2) identify the command structure with defined lines of authority and responsibility; (3) describe a response strategy for each anticipated incident; (4) estimate an incident's impact on safety and hospital function, providing for evacuation if necessary; and (5) list essential information, such as critical telephone numbers (e.g., elevators, key personnel, and pay telephones), community agencies (emergency medical services, police, and public health), and sources of vital supplies (water, oxygen, and drugs).[22]

After plan activation, the primary role of the emergency department is to assess and treat individuals with illness or injury. In the absence of casualties, other hospital departments primarily manage disasters that disrupt hospital operations. Nevertheless, the medical director of the emergency department should continuously monitor the response process.

In the unlikely event that evacuation of the emergency department is necessary, evacuation routes and relocation destinations that have been planned in advance maximize safety and efficiency. When resources are plentiful, emergency department patients in critical condition are assigned the highest priority for evacuation and transport. Less ill patients receive a lower priority.[24] When resources are limited (e.g., in the event of a large-magnitude earthquake), the reverse strategy applies. The least critically ill patients receive the highest priority for evacuation.

Another scenario would be an event occurring in the community that results in a sudden influx of patients requiring emergency care at hospitals. This type of incident has no direct impact on hospital capacity or function. Participation in the planning and execution of the hospital disaster response is an important administrative responsibility.[13] Available data guiding development of disaster strategies are incomplete, but an effective disaster response can be created by reviewing the essential components of disaster plans and the previous experience of hospitals.[13,22,24] A member of the emergency department must have a leadership role in the planning and implementation of the disaster plans.

Basic Components of a Hospital Comprehensive Disaster Response Planning Process

Interdepartmental Planning Group

The interdepartmental planning group has the responsibility for hazard identification and disaster preparedness activities. Frequently referred to as the *disaster* or *emergency preparedness committee*, it is composed of representatives from all departments vital to the hospital's response, including administration, medical staff, nursing, safety, security, the emergency department, and engineering. Additional input may occasionally be necessary from outside agencies (e.g., fire department, hospital suppliers of goods and services, and emergency medical services agency).

The committee must be structured to ensure that the plan is properly constructed, tested, and executed. Hospital resources must be provided to support the planning process and testing of the plan, and there must be a detailed educational program for all affected hospital staff.[23,25]

Resource Management

A full inventory of the hospital's resources must be available. In addition to equipment, space, and personnel within the institution, potential support from outside the hospital must be sought. It is also necessary to develop contingency plans to compensate for lost resources (e.g., failure of hospital computers during a power outage). Augmentation of such resources is critical to successfully increase the hospital's surge capacity.[3,4,26]

Strong relationships with community agencies (e.g., fire department and regional emergency medical services system) are important to ensure a coordinated disaster response. Hospitals located near companies using large amounts of hazardous materials are required by Title III of the Superfund Amendments and Reauthorization Act to participate in local emergency planning committees.[27]

Command Structure

An organized system establishing lines of authority and decision responsibility must be in place. This system should designate a command center where the disaster response can be coordinated and create a clear chain of command. This prevents confusion if certain individuals are missing, a common situation on nights and weekends. The command center should contain sufficient equipment to support command and control functions, even if the center must be moved as a result of hospital damage.

Media

The media can be an important source of information but can also significantly disrupt the hospital's disaster response. Therefore, arrangements should be made in advance for a designated individual to coordinate all media interactions and for these briefings to occur in a designated location. Media coordinators should inform reporters of the time they will receive their next update so they do not intrude on response operations while trying to obtain information. A strong media liaison can facilitate dissemination of important information to the public, such as that no blood shortage exists so that individuals refrain from coming to the hospital to donate blood. In fact, crisis and emergency health risk communication is now an important part of managing the disaster response and can significantly impact the public's perception of events.[28] Security should be involved in managing the media response to the hospital and in preventing media from interfering with triage and treatment of patients.

Communication

Communication systems are probably the most important, but also most vulnerable, component of a disaster plan.[13,24] Redundant systems are essential. Those responsible for mobilizing the emergency response require access to at least one other communication system besides the telephone (which is frequently one of the first systems compromised during a disaster). Two-way radios are often used, as are pay telephones, independent fax lines, and cellular phones. Another option is the use of satellite phones and wireless hand-held devices to

transmit e-mail messages. Runners are useful for intrahospital communication if all else fails.

Personnel

The disaster plan must include a roster of all critical positions and personnel and establish a reliable method for their mobilization. Several individuals should be assigned to each position in case some personnel cannot be reached. A protocol for managing volunteers is also crucial. A large group of uncontrolled volunteers descending on a hospital can be as disruptive as the disaster.[29]

Credentialing volunteer health professionals in a timely manner so hospitals can utilize their services during a disaster remains a challenge. A federally supported program known as the Emergency System for Advance Registration of Volunteer Health Professionals (ESAR-VHP) is attempting to address this problem. When completed, it will provide a system for credentialing volunteer health care providers in advance of a disaster so they will have emergency privileges should the need for their services arise.[30] There remain significant challenges with such a system, including whether sufficient numbers of providers will participate, how well qualified they will be, and whether they will have competing obligations during a disaster. An alternative system that permits hospitals to recognize each other's credentialing process through a shared database shows promise. Not only will this alternative system facilitate participation by most health care providers but also it permits hospitals to grant emergency privileges within minutes after a disaster.[30]

Patient Management

A systematic approach to patient management is necessary to maximize resources. This includes protocols for decontamination, triage, patient prioritization, evacuation, and control of patients' families. Alternative use of hospital facilities must be anticipated, such as the conversion of a parking lot into a clinic area for suturing lacerations or a decontamination zone. Provisions for patient identification and treatment documentation are also important to facilitate federal and third-party reimbursement at the conclusion of the disaster.

Training Exercises

Disaster exercises are one of the more effective ways of familiarizing hospital staff with their responsibilities. All hospital departments should participate, and community agencies should be involved. The Joint Commission requires two drills a year; these should mimic incidents that are likely to occur.

REVIEW OF HOSPITAL AND COMMUNITY DISASTER RESPONSE EXPERIENCE

Disaster plan implementation is complex and difficult. Much can be learned from reviewing previous disaster response experiences, resulting in improved implementation strategies. The following discussion highlights potential problem areas.

Focal Disasters

Most disasters experienced by hospitals are focal in nature. Hospital function is typically unimpaired. The majority of problems encountered are related to a sudden increase in patient volume and acuity or arrival of patients with illnesses not usually treated at that facility (e.g., burns, radiation exposure, and severe acute respiratory syndrome).

Hospitals frequently experience difficulty in effectively using and interfacing with community resources. Field triage must allocate patients rationally, and transfer agreements must be in place to facilitate interhospital movement of patients and evacuation of patients to alternate care sites.

Media access must be controlled. During the Loma Prieta earthquake in 1989, a news helicopter occupied a nearby community hospital's only landing zone, preventing the possibility of landing a medical helicopter.

Redundant communication systems must be in place. Typical backup systems to the telephone are radios and cellular phones, but the frequencies can be overloaded in both systems. Two-way radios are reliable and should be part of the communications network. Satellite phones are also an option.

Catastrophic Disasters

In a large-scale disaster, paramedics may be unavailable to assist in patient transfers or hospital evacuations. Disaster medical assistance teams and urban search and rescue teams will deploy, but their time to arrival on scene may be variable. Each individual hospital may have to remain self-sufficient for 48 to 72 hours or longer.[31] Generator problems are frequent; they either fail altogether (as they did during the Loma Prieta earthquake) or supply insufficient power to meet emergency needs (as during the Northridge earthquake). Evacuation plans must not require elevators for this reason. Telephone service will cease as lines are disrupted or deliberately restricted by the phone company. Cellular phones may function within a local area, but failure is likely if more distant sites within the city are dialed. Hospital radios designated for disaster use must have the hardware secured to prevent earthquake damage.

Under catastrophic conditions, mobilizing personnel is more difficult. Because telephone communication is unreliable, at least one additional system for contacting personnel at home must be in place. An alternative is to institute an automatic response system.

After earthquakes or explosions, immediate access to structural engineers is important. In the Northridge earthquake, eight hospitals in the Los Angeles area sustained enough damage to force evacuation of at least one patient. Four institutions completely evacuated their facilities in the first 24 hours, including two hospitals that met the most current structural earthquake standards. Further structural damage was subsequently identified, and two additional hospitals were forced to evacuate completely in the next 2 weeks. Ultimately, four of these hospitals were permanently closed and demolished.[24]

Catastrophic earthquakes can cause extensive casualties, including large numbers of patients with crush syndrome and lacerations. Up to 90% of victims with serious but survivable injuries are rescued by local responders and volunteer citizens in the first 24 to 48 hours. Therefore, special medical teams such as disaster medical assistance teams and urban search and rescue teams may not significantly affect survival if they arrive after more than 48 to 72 hours. If hospitals are not functional and no backup plan exists, immediate advanced medical care will not be available, and many people will die. Therefore, planners must include a backup system to provide medical care at nonhospital alternate care sites.

Need for Local Response

Currently, it is not possible for outside assistance to arrive in force during the crucial first 48 hours. Therefore, an alternative source of immediate, sophisticated medical care is necessary.

It appears this is best provided by local responders who can begin caring for patients soon after the event.[32] The Medical Disaster Response Project is the most advanced model of a local medical response to such a disaster. Developed by emergency physicians in Southern California, the Medical Disaster Response Project has two components: (1) training of health care providers in the management of disaster victims under austere conditions and (2) placement of sophisticated medical supplies at designated sites within the community.[31] Under this plan, victims could receive rapid, advanced medical care from surviving volunteer health care providers even if hospitals were destroyed.

Toxic Disasters (Hazardous Material)

Hospitals in the vicinity of major chemical industries, transportation corridors, or probable terrorist targets (e.g., major theme parks or nationally symbolic buildings) should be aware of potential hazards from incidents involving chemical and radioactive substances and be prepared to decontaminate large numbers of individuals exposed to these hazardous substances. Effective decontamination of victims and the need for safety measures on the part of rescue personnel to prevent secondary contamination are critical.[33] Decontamination equipment must be stored near the emergency department, and the staff must be trained in its use. This location must be known to personnel.[34] When such an emergency occurs, there is little time to search the hospital for the necessary supplies.

Ideally, patients contaminated with hazardous chemicals should first be brought to a designated decontamination area containing a warm water shower with a container to hold drainage water. Victims should remove all clothing. Clothing and valuables are bagged, tagged, and stored. Contaminated patients must never be brought into regular patient care areas because of the danger of contaminating other patients, hospital staff, and equipment. In 1994, paramedics unsuspectingly transported a patient contaminated with a degradation product of dimethyl sulfoxide to an emergency department in Riverside, California. Before detecting the presence of the hazardous material, six health care workers were exposed, including an emergency physician. The emergency physician experienced a near-fatal exposure and required intubation and an extensive stay in the hospital's intensive care unit. Uncontrolled spread of the toxin resulted in evacuation and temporary closure of the emergency department.[35]

The emergency department must close off the air intake vents in rooms containing contaminated patients so toxic products do not enter the ventilation system and circulate to other areas of the hospital. Rescue personnel and hospital staff should be protected by gowns, gloves, and masks and, if necessary, supplied air respirators. The goals are to reduce the initial level of external contamination, contain the contamination that remains, and prevent further spread of these potentially dangerous substances to other patients and staff members.

CHEMICAL, BIOLOGIC, RADIOLOGIC, NUCLEAR, AND EXPLOSIVE TERRORISM

In addition to the familiar threat from hazardous materials, there is a new challenge: a potential attack by terrorists using biologic, radiologic, or chemical weapons (see Chapter 194). Although somewhat similar to hazardous materials situations, management of patients exposed to weapons of mass destruction (WMD) requires new knowledge and skills. Expertise in the management of patients attacked with unconventional weapons is important, but emergency physicians should also be familiar with treatment of blast injuries. High explosive events, including suicide bombers, remain the most probable type of terrorism.

The most likely radiation source used by terrorists will probably not come from the detonation of a nuclear weapon. Instead, simple radiologic devices, such as those used by hospitals for radiation therapy, are believed to be the source of choice. They do not explode and give no warning of their presence. Terrorists can also dismantle such devices and incorporate the radioactive source into an explosive radiologic dispersion device ("dirty bomb"). Therefore, providers must recognize the presentation of patients suffering from radiation exposure to make the diagnosis. In addition to damage from radiation, these casualties may also suffer blast injuries. Patients who are irradiated but not externally or internally contaminated pose no threat to emergency department personnel.

One of the greatest challenges with respect to WMD is the detection of biologic weapons. Patients exposed to many of the biologic agents initially present with vague symptoms associated with flulike illnesses. Decontamination is not a priority unless the exposure is immediate; standard precautions are generally sufficient.

Unlike radiologic or biologic weapons, chemical agents produce symptoms quickly. The challenge is decontamination and treatment. Approximately 80% of mass casualty decontaminations are performed at hospitals. Therefore, hospitals must be prepared to decontaminate patients outside the emergency department. Personal protective equipment is also an issue for responders because of the risk of exposure during the decontamination process.[34,36]

DISASTER STRESS MANAGEMENT

Emergency health care providers experience high levels of stress responding to the needs of disaster victims. If this excessive stress exceeds the capacity of normal coping mechanisms, it can potentially interfere with job performance and produce disturbing symptoms, including depression, sleep disturbances, increased use of alcohol and drugs, irritability, and anxiety. Post-traumatic stress disorder can result. In an attempt to reduce the psychological impact of these events on medical responders, various therapeutic techniques have been introduced throughout the years and are collectively known as *critical incident stress management*. This formal process of resolving emotional conflict utilizing mental health professionals is now widely practiced.

In general, the longer the delay between exposure to the critical incident and subsequent psychological intervention, the smaller the chance for a successful outcome. Therefore, the critical incident stress management process is designed for rapid implementation. During the incident, stress management staff or even a colleague can provide on-scene intervention. The goal is to assist the health care worker in regaining emotional control by facilitating communication of feelings and reactions through listening and support.

If a critical incident has profoundly affected participants, and if symptoms are still present many hours later, urgent assistance is provided in the form of defusing. The critical incident defusing process is coordinated by mental health and peer support staff and focuses on information and venting of emotions. This process often takes place away from public view to protect confidentiality. If the psychological stress is severe, the process transitions to formal care provided by psychiatrists or psychologists.[37] Data from previous experiences suggest that such intervention can assist providers in maintaining job performance and satisfaction.

DISASTER MANAGEMENT AND RESPONSE ORGANIZATIONS WITHIN THE U.S. GOVERNMENT

Department of Homeland Security

The Department of Homeland Security (DHS), a cabinet-level department formed after the terrorist attacks of September 11, 2001, is the federal government's lead organization for emergency management activities in the United States. The Federal Emergency Management Agency (FEMA) has been incorporated into DHS and retains its name. DHS has a coordinating responsibility for the entire spectrum of disasters irrespective of their size or etiology. DHS assists state and local organizations to mitigate, prepare for, respond to, and recover from emergencies and is a major source of funding for these endeavors. In 2003, the President directed that the DHS develop a National Incident Management System and a National Response Plan. Existing federal plans, including the National Response Plan, were then incorporated into the National Response Framework.

Urban Search and Rescue

When a building collapses because of an earthquake, terrorist bombing, structural failure, or other reason, various challenges confront rescue and medical personnel.[38] Some victims require field amputations to facilitate extrication,[38] and use of urban search and rescue teams and effective emergency medical care may improve the outcomes of such lifesaving efforts. This national system of multidisciplinary task forces is designed for rapid deployment to the sites of collapsed structures.[39] The medical team's responsibilities include caring for task force members, victims recovered by search and rescue activities, and the search team's dogs. There are now WMD urban search and rescue teams trained by FEMA to respond to nuclear, biologic, and chemical terrorist attacks.

Department of Health and Human Services

On December 19, 2006, the President signed the Pandemic and All-Hazards Preparedness Act (S. 3678) into law and created a new position, the Assistant Secretary for Preparedness and Response (ASPR), within the Department of Health and Human Services (DHHS). The office of the ASPR oversees the department's responsibilities for emergency preparedness and response activities, including the National Disaster Medical System (NDMS) and the Hospital Preparedness Cooperative Agreement Program, the coordination of the Medical Reserve Corps, the ESAR-VHP, the Strategic National Stockpile, and the Cities Readiness Initiative.

National Disaster Medical System

The NDMS is a federally coordinated initiative designed to augment the emergency medical response capability of the United States in the event of a catastrophic disaster. This system is a cooperative program of four agencies in the federal government: the Department of Defense, the DHHS, the DHS, and the Department of Veterans Affairs (VA). Although oversight of the NDMS has moved between federal departments, the DHHS currently has the lead for the NDMS. The NDMS provides an interstate medical mutual aid system linking the federal government, state and local agencies, and private sector institutions to address the medical needs of victims of catastrophic disasters. Its medical response element includes dozens of volunteer civilian disaster medical assistance teams that supplement the local medical infrastructure.

In a disaster, the NDMS is activated when state resources are overwhelmed and the governor makes a request for federal assistance. The disaster medical assistance teams must meet specific NDMS standards. Throughout the NDMS, emergency physicians are taking key roles in defining training standards, the deployment of clinical services, and the administration of field operations and in developing the concept of a civilian-federal disaster response capacity during national emergencies.

Centers for Disease Control and Prevention

The Centers for Disease Control and Prevention (CDC), based in Atlanta, is a U.S. federal agency under the DHHS. Its major responsibilities include preparing for and responding to public health emergencies (e.g., disasters) and conducting investigations into the health effects and medical consequences of these events. The major aims of CDC researchers are to assess the risks of death and injury and to develop strategies for preventing or mitigating the impact of future disasters. Other responsibilities of CDC staff in the area of emergency preparedness and response include (1) rapid assessment of the health and medical needs of disaster victims in the immediate postdisaster period; (2) development and maintenance of national systems for acute environmental hazard surveillance; and (3) provision of epidemiologic, sanitary, laboratory, and other relevant scientific support services to agencies involved in disaster planning and response.

Metropolitan Medical Response System

Metropolitan Medical Strike Teams (MMSTs) are highly trained, readily deployable, and fully equipped groups of medical, fire, and rescue professionals. As a component of the larger Metropolitan Medical Response System (MMRS), they support other local personnel in treating the victims of a chemical, biologic, or nuclear attack. In 2008, the MMRS expanded to include 125 participating jurisdictions. Although composed of local personnel, MMSTs are under the direction of the DHS. Their goal is to enhance local planning and response capability. However, hospital and community planners must still create an independent response because MMSTs require 90 minutes or longer to deploy.[40] MMSTs are equipped with chemical agent monitoring devices, protective equipment, and pharmaceutical supplies.

Department of Veterans Affairs

The VA has not traditionally been regarded as a disaster response entity. However, one of the VA's four mandated missions is emergency management. A unique feature of the VA is that its facilities and personnel are situated nationwide, and these are used to support federal health and medical assistance to state and local governments during disasters. The VA has highly trained specialty personnel who can support disaster medical activities. In addition to the vast pool of human resources, the VA provides large amounts of the pharmaceuticals and expendable supplies for on-site disaster support. For example, the VA purchases the contents of the CDC's Strategic National Stockpile. VA support is coordinated through the DHS and DHHS, as the lead federal agency for health and medical response. In addition to the VA's role in the federal response to disasters, as the largest integrated health care system in the nation, it has a well-developed hospital emergency management program. The VA *Emergency Management Program Guidebook* is an open-source reference that provides up-to-date information on emergency management concepts

and various templates for emergency operations plans and hazard vulnerability assessment tools for hospitals.[41]

The Military

On April 17, 2002, Secretary of Defense Donald Rumsfeld announced the formation of the Northern Command, or NorthCom, to assume responsibility over all military forces that operate within the United States in response to external threats and in support of civil authorities. Furthermore, Secretary Rumsfeld stated that NorthCom will "help the department better deal with natural disasters, attacks on U.S. soil, or other civil difficulties. It will provide for a more coordinated military support to civil authorities such as FBI, FEMA, and state and local governments."

FUTURE DIRECTIONS

The field of disaster medicine has become a major subspecialty within emergency medicine, and a section for disaster medicine has been organized within the American College of Emergency Physicians and the Society for Academic Emergency Medicine. There are also numerous national and international forums for the presentation of disaster medical research results. Since the American College of Emergency Physicians first defined a disaster medicine curriculum suitable for residencies and fellowships, a number of disaster medicine fellowships have been established in the United States and elsewhere.[42] In the 21st century, disaster medicine will continue to develop as a professional activity and unique academic specialty.

KEY CONCEPTS

- The increasing likelihood of mass casualty incidents and high public expectations for an appropriate and timely response mandate careful and complete interagency planning.
- Mass casualty planning must account for the fact that traditional transport and communications systems will break down.
- Field personnel must be specifically trained in mass casualty triage and stabilization because austere field conditions change management strategies.
- All plans must protect caregivers and rescue personnel.
- Critical incident stress management may be highly desirable after an event and must be planned for in advance.
- Planners should establish and exercise a hospital-based incident management system.
- A plan must be in place to manage convergence of volunteers, address credentialing issues, and work with the media.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 194

Weapons of Mass Destruction

Carl H. Schultz and Kristi L. Koenig

PERSPECTIVE

The practice of emergency medicine now has another challenge: the possibility of an attack by terrorists using nuclear, biologic, chemical, or high-explosive weapons. Although conventional explosives remain the most common weapon used by terrorists, the risk from nuclear, biologic, and chemical agents may increase over time. The nomenclature for these weapons remains controversial. Some authors have proposed the use of *weapons of mass effect* or *weapons of mass disruption*. The military uses the acronym CBRNE, pronounced "see-burn-ee" and referring to *c*hemical, *b*iologic, *r*adiologic, *n*uclear, and *e*xplosive. This chapter uses *weapons of mass destruction* (WMD) because of its wide acceptance.

The results of an attack with WMD, although admittedly of low probability, are potentially catastrophic. According to a World Health Organization estimate, 50 kg of anthrax spores aerosolized above a city of 5 million people would result in 100,000 deaths, with an additional 150,000 people seriously infected. The cost of managing 100,000 cases of anthrax exposure is estimated at $26 billion by the Centers for Disease Control and Prevention (CDC).[1] Given these considerations, most authorities believe that preparedness for such threats must be improved.

Children are particularly vulnerable to these weapons. They breathe at a faster rate than adults, increasing their relative exposure to aerosolized agents. Some chemicals, such as sarin, are heavier than air, so they tend to accumulate at the level where children are more likely to inhale them. Children have a greater surface area-to-volume ratio and their skin is thinner. This makes them more susceptible to agents that act on or through the skin. They have smaller fluid reserves and higher metabolic rates. Therefore, they are more vulnerable to dehydration from vomiting and diarrhea and suffer increased toxicity from a given exposure, such as to radioactive iodine (I^{131}).

The use of biologic and chemical agents dates back to biblical times, although the threat from radiation and nuclear detonation is relatively new. Assyrians poisoned the wells of their enemies using rye ergot in the 6th century BC. The Mongols catapulted bodies infected with bubonic plague over the walls of Kaffa in the 14th century. The British Army gave American Indians blankets taken from individuals infected with smallpox during Pontiac's Rebellion in 1763. During World War I, the Germans effectively used chlorine and mustard agent against the advancing Allied armies. The Japanese killed hundreds to thousands of Chinese citizens with bubonic plague during World War II by spraying towns with fleas infected with *Yersinia pestis*. Saddam Hussein employed a mustard agent against the Iranians during the Iran-Iraq War in the 1980s.

The use of WMD has been predominantly by the military during times of conflict. In recent history, however, the use of these agents has taken an ominous turn. Nonaffiliated groups have begun using WMD directed at civilians to achieve political ends. The Bhagwan cult sprayed salad bars in Oregon with *Salmonella* in an attempt to influence an election in 1984.[2] The Aum Shinrikyo used the nerve agent sarin in an unsuccessful 1994 assassination attempt on three judges in Matsumoto, Japan. This same group used sarin again in the 1995 Tokyo subway attack that killed 11 people.[3] The United States experienced multiple anthrax hoaxes during 1997 and 1998, motivated by personal or political agendas. Terrorists initiated an actual anthrax attack using the U.S. mail in 2001 that resulted in 11 deaths. The perpetrator's identity and motivation remain unknown. No one has yet used radiologic or nuclear devices in a successful terrorist attack, but at least one attempt has occurred. In addition, several highly radioactive sources have been stolen from U.S. medical facilities, and a Russian dissident, Alexander Litvinenko, was assassinated with a radiologic agent (polonium-210) in 2006.

Many agents are potential candidates for weaponization, and some represent a substantial risk (Box 194-1). Management strategies for patients exposed to WMD are frequently similar to strategies for hazardous materials exposure. However, several features associated with WMD make these events unique (Box 194-2). Additional knowledge and skills are required in the evaluation and treatment of WMD victims. These plans represent only one small part of an overall comprehensive emergency management strategy for all hazards (see Chapter 193). Names of departments, bureaus, and agencies that can assist with planning and response to WMD events are listed in Table 194-1.

NUCLEAR AND RADIOLOGIC DEVICES

Terrorists selecting radiation as a means to inflict casualties are unlikely to employ nuclear weapons. These devices are heavily guarded, difficult to move due to their size and weight, and easy to detect. Although Russia acknowledges that 50 to 100 of its 1-kiloton "suitcase" nuclear weapons are missing, the problems of purchasing, moving, and detonating these devices

BOX 194-1 Potential Agents of High Concern for Use as Weapons of Mass Destruction

Chemical
Nerve agents
- Sarin
- Soman
- Tabun
- VX

Mustard agent

Biologic
Anthrax
Plague
Smallpox

Radiologic
Simple device
Dispersal device

BOX 194-2 Features of Weapons of Mass Destruction Threat

Fear of unknown or unfamiliar
Lack of training for hospital personnel
Lack of equipment, including personal protection and diagnostic aids
Potential for mass casualties
Psychological casualties
Crime scene requiring evidence collection and interaction with law enforcement
Potential for ongoing morbidity and mortality (dynamic situation)

are formidable. Sabotage at nuclear power stations is possible, but given tight security, multiple safety systems, and thick concrete housings surrounding the reactors, the threat is probably low.

Instead, simple radiologic devices, such as those used by hospitals for radiation therapy, are thought to be the source of choice. These sources are plentiful. They do not detonate on their own and give no warning of their presence, unless dispersed by a conventional explosive (radiologic dispersal device). Thefts of radiotherapy sources have occurred in the United States. Accidental dispersion from a stolen hospital therapy source in Brazil resulted in the screening of 112,000 people for contamination. A total of 249 people were found to be exposed, 4 of whom ultimately died.[2] Placement of such a device at an information kiosk in a crowded mall during a busy holiday shopping season would silently expose countless persons to significant radiation.

Ionizing radiation, regardless of its type, causes injury at the cellular level, usually by damaging DNA. Rapidly dividing cells are the most sensitive. Patients develop symptoms within hours to days, depending on the dose. Common syndromes associated with radiation exposure include dermal burns, bone marrow failure, and gastrointestinal dysfunction (e.g., vomiting and gastrointestinal bleeding) (see Chapter 144). A U.S. Department of Homeland Security task force developed an expert consensus document on medical treatment of radiologic casualties, and the results were subsequently published in the peer-reviewed literature.[4]

A basic emergency department radiation protocol must address decontamination, triage, staff safety, personal protective equipment (PPE), and diagnostic procedures that emphasize radiation monitoring. Victims presenting to the emergency department will suffer from three types of exposure: irradiation, internal contamination, and external contamination. Irradiated victims have been exposed to a beam of radiation, similar to someone undergoing a chest x-ray. They are not radioactive and pose no threat to emergency department personnel.

Contaminated patients are more challenging, and early involvement of the radiation safety officer is critical. This individual evaluates the degree of the victim's contamination and monitors radioactivity levels throughout the decontamination process. Internally contaminated patients present a therapeutic challenge because they have radioactive material inside their bodies (e.g., lungs and gastrointestinal tract) or incorporated into their cells. They should be placed in an isolation room, where all secretions and bodily fluids can be collected. Various medications are available for administration to internally contaminated patients and can limit uptake or facilitate removal of certain radioactive elements. These medications include Radiogardase (Prussian blue) for cesium and thallium ingestions and diethylenetriamine pentaacetic acid (DTPA) for plutonium exposure. Health care providers can receive assistance by calling the Radiation Emergency Assistance Center/Training Site (REAC/TS; http://orise.orau.gov/reacts) at 865-576-3131 (emergency number: 865-576-1005).

Externally contaminated victims have radioactive material on their skin or clothing and are decontaminated by removal of clothing and washing with soap and water. Washing by protected personnel must continue until monitoring by the radiation safety officer demonstrates the absence of radioactivity. If present, wounds are decontaminated first. After the wounds are covered with a sterile, waterproof dressing, the remaining skin is washed. Hospitals must be prepared to decontaminate patients because historical data suggest that up to 80% of patients do not receive this intervention before

Table 194-1 Resources and Contacts for Planning and Response to Events Involving Weapons of Mass Destruction

ORGANIZATION	WEBSITE	TELEPHONE
Radiation Emergency Assistance Center/Training Site (REAC/TS)	http://orise.orau.gov/reacts	865-576-3131
State and local health departments	http://www.statepublichealth.org/index.php http://www.cdc.gov/other.htm#states	
Centers for Disease Control and Prevention (CDC)	http://www.bt.cdc.gov	800-CDC-INFO
Federal Bureau of Investigation (FBI)	http://www.fbi.gov	
Federal Emergency Management Agency (FEMA)	http://www.fema.gov	800-621-FEMA
U.S. Army Medical Research Institute of Chemical Defense	http://chemdef.apgea.army.mil	

arrival.[2] Decontamination before hospital entry is crucial because these individuals can expose caregivers to radiation and contaminate the entire hospital through the ventilation system. Removal of clothing and covering the head with a surgical cap can reduce contamination by 80% to permit stabilization in the decontamination unit, but complete decontamination should occur before exposure of unprotected staff if the patient's medical condition permits.

Initial triage of radiation casualties is based on their overall pathologic condition, not on exposure.[5] Even patients who have received a lethal dose of radiation do not die immediately as a consequence of the ionizing exposure. Therefore, a patient in acute distress from a myocardial infarction or urosepsis would be triaged ahead of a radiation victim with stable vital signs, regardless of the dose received. If a radiation casualty also suffers a severe injury or illness, immediate intervention is required. For example, most morbidity and mortality associated with a radiologic dispersion device are related to traumatic injuries from the explosion and not to radiation exposure.[4]

In addition to patient contamination, the radiation safety officer is responsible for monitoring the exposure of hospital staff. All personnel involved in the care of contaminated patients should wear dosimeters, which measure the amount of radiation received by the wearer. The safety officer tracks the amount of radiation received by each staff member and can remove a health care worker from the area if the exposure is too high. Radiation monitoring is complex, and the radiation safety officer should be involved as early as possible. Hospitals should consider conducting disaster drills that include casualties suffering radiation injuries.

Although many radioactive elements are candidates for use in a terrorist attack, I^{131} and related isotopes deserve additional discussion because of heightened interest. I^{131} is found only after a nuclear detonation or in reactor fuel rods. Although not impossible, the probability that terrorists could tap either of these sources is very small. The use of I^{131} in a radiologic dispersal device is very unlikely due to its short half-life (8 days). Even if such a device could be made, it is extremely unlikely that the radiologic dispersal device could disperse sufficient radioactive material to pose an immediate health hazard.[6] Given these facts, the probability that any significant exposure of the population (especially children) to I^{131} will occur is equally small. The large number of childhood thyroid cancers that occurred after the accident at the Chernobyl nuclear power plant was due mostly to situations that will not occur in the United States. These include delayed reporting of a breach in the reactor containment vessel preventing timely evacuation, failure to quarantine contaminated milk and vegetables, and significant iodine deficiency in the exposed children.[7] Nonetheless, concern regarding treatment to prevent thyroid cancer after potential exposure to I^{131} remains. Current recommendations for treatment with potassium iodide, which blocks uptake of I^{131} by the thyroid, are listed in Table 194-2. Caveats for using this table include increasing the amount of potassium iodide for adolescents approaching 70 kg to the adult dose (130 mg) and monitoring thyroid-stimulating hormone and free T_4 levels in neonates when possible. Nonpregnant adults older than 40 years are unlikely to benefit from this intervention.

Table 194-2 Treatment with Potassium Iodide (KI) for Radioactive Iodine Exposure

SUBPOPULATION	PREDICTED EXPOSURE (RAD)	KI DOSE (MG)	NUMBER OF 130-MG TABLETS
Adults >40 yr	>500	130	1
Adults 18–40 yr	≥10	130	1
Pregnant/lactating women	≥5	130	1
Children 3–18 yr	≥5	65	½
Children 1 mo–3 yr	≥5	32	¼
Neonates, birth–1 mo	≥5	16	⅛

BIOLOGIC WEAPONS

By convention, biologic weapons are divided into three groups: bacteria, viruses, and toxins. A characteristic shared by these agents is their ability to be dispersed as an aerosol. Because this is the most effective means to expose a large population, aerosol dispersal is the most likely route that terrorists will use to deploy such weapons. Therefore, victims will have respiratory signs and symptoms. Dermal contact and ingestion are also potential pathways for exposure, and some agents are effective by these routes. People infected in the 2001 U.S. anthrax attack were inoculated via aerosol and dermal exposures. However, it is logistically more difficult to produce large casualty numbers using nonrespiratory portals of entry, so agents spread primarily by injection or through the gastrointestinal tract are less likely candidates for wide deployment. If the goal is to disrupt the economy or spread fear among the population, then almost any type of release will suffice, whether or not people actually die.

Patients exposed to biologic agents usually present with vague symptoms associated with flulike illnesses. Unless a biologic attack is announced or suspected, the emergency department staff may not realize they are treating victims. Indeed, it is not always possible to distinguish natural occurrences from engineered outbreaks of diseases. Therefore, personnel must be vigilant and at least consider the possibility of a bioweapon exposure when warning signs are present (Box 194-3). For example, large numbers of patients suddenly presenting with "the flu" not during flu season should cause concern. For these reasons, health surveillance will be paramount in identifying agents and potential sources. The emergency department must have a working relationship with local and state health departments as well as local law enforcement and stay apprised of CDC and Department of Homeland Security guidelines.

Several infectious agents with potential for use as biologic weapons can spread in a hospital environment. Examples include Ebola and smallpox.[2,8] Hospitals need protocols for PPE and patient isolation to ensure a safe environment.[9-12] Fortunately, such protocols are similar to those applied to other infectious diseases (Box 194-4). Implementation of such precautions is credited with halting the in-hospital spread of the Ebola virus in the 1995 Zaire outbreak. Decontamination

BOX 194-3 SIGNS SUGGESTING BIOLOGIC WEAPON DEPLOYMENT

Syndromes
Pulmonary symptoms, pneumonia
Rashes
Sepsis syndrome
Influenza symptoms

Epidemiology
Multiple, simultaneous events
Dead animals
Large patient numbers with high toxicity and death rate

BOX 194-4 RECOMMENDATIONS FOR PREVENTION OF IN-HOSPITAL TRANSMISSION OF CONTAGIOUS AGENTS

1. Isolate patient in single room with adjoining anteroom.
2. Have handwashing facilities and personal protective equipment (PPE) available in anteroom.
3. Use negative air pressure if possible.
4. Use strict barrier precautions: PPE, gowns, gloves, HEPA filter respirators, shoe covers, protective eyewear.
5. Alert hospital departments that generate aerosols: laboratory (centrifuges), pathology (autopsies).

is not a priority unless the exposure is immediate. Standard (universal) precautions are generally sufficient, and special suits (e.g., levels A, B, and C) are unnecessary.[13]

Current assessment suggests that three biologic agents—anthrax, plague, and smallpox—represent the greatest threat.[14]

Anthrax

Bacillus anthracis, a gram-positive spore-forming bacterium, is the causative agent of anthrax ("woolsorter's disease"). The spores are extremely hardy and can survive for years in the environment. The disease is caused by exposure to the spores, not the bacilli in their vegetative state. It is normally a disease of sheep, cattle, and horses and is rarely seen in developed countries because of animal and human vaccination programs. Disease in humans can occur when spores are inhaled, ingested, or inoculated into the skin. The spores germinate into bacilli inside macrophages. The bacteria then produce disease by releasing toxins (e.g., protective antigen, edema factor, and lethal factor) that cause edema and cell death.

Russia and the United States have successfully developed anthrax into a biologic weapon. The effectiveness of this agent was clearly demonstrated by two events: an accidental release of spores from a biologic weapons facility in the former Soviet Union town of Sverdlovsk in 1979 and the intentional distribution of anthrax spores through the mail along the eastern seaboard of the United States in 2001. After the Sverdlovsk release, at least 66 people died downwind from the compound during the next several weeks, and animal cases of anthrax were reported 30 miles away.[15,16] The ability of non-state-sponsored terrorist groups to develop anthrax as a weapon is uncertain. The Japanese organization Aum Shinrikyo made several attempts to disperse anthrax throughout Tokyo without success.[1] The perpetrator of the U.S. anthrax attack remains unidentified. However, many experts speculate that this individual was not a foreign national, given that the strain of anthrax used in the attack (Ames strain) was developed by the U.S. government.

Inhalational anthrax is the most lethal form of the disease and is caused by inhaling spores into the lungs. The mortality rate was thought to exceed 90%. However, the data from the 2001 anthrax exposure call this figure into question (5 deaths in 11 cases). Although the actual mortality rate is unknown, it is probably in the 50% range.[17,18] The minimum number of spores required to produce disease is unknown. The original number quoted in the literature, 10^4 spores, appears high given recent experience.[19] After phagocytosis by macrophages, the spores germinate and are transported to the tracheobronchial lymph nodes, where the bacteria multiply. Over 2 to 10 days, patients develop a flulike illness, with malaise, fever, and nonproductive cough. This initial phase can be delayed for more than 1 month in some patients. Within 24 to 48 hours, abrupt deterioration occurs, with overwhelming sepsis, shock, hemorrhagic mediastinitis, dyspnea, and stridor. A chest radiograph obtained at this time may show a widened mediastinum and hilar adenopathy, but typical radiographic findings are not dramatic and could be missed (Fig. 194-1). Computed tomography scanning of the chest is more sensitive and should be performed if the disease is suspected. Bloody pleural effusions can also occur, and examination of the lung fields frequently reveals consolidation. This can easily be confused with pneumonia (Fig. 194-2). Death usually results within 3 days, and 50% of patients develop hemorrhagic meningitis. Human-to-human transmission has not been reported with inhalational anthrax.

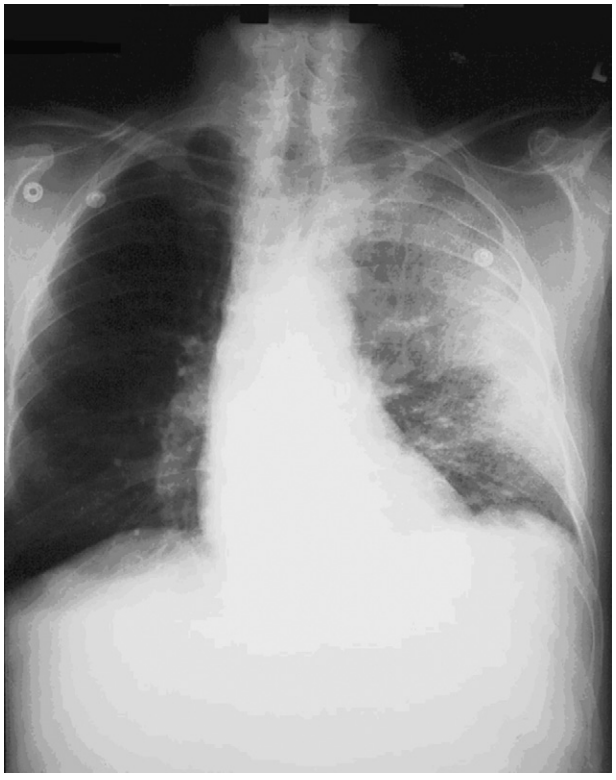


Figure 194-1. Chest radiograph of anthrax patient showing diffuse left lung consolidation consistent with pneumonia. There is no mediastinal widening. (Courtesy of the U.S. Centers for Disease Control and Prevention.)

Initial diagnosis is generally made clinically, based on a flulike or septic illness; a suspicious chest radiograph or computed tomography scan demonstrating hilar adenopathy, infiltrates, or pleural effusions; and a reason to consider anthrax in the first place (e.g., current outbreak or warning from authorities). Several clinical algorithms exist that attempt to separate patients with influenza from those with anthrax.[20,21] Unfortunately, they are based on a handful of anthrax cases, and their usefulness remains in doubt.[18] Sputum culture, Gram's stain, and blood cultures are not helpful until late in the course of the disease. Tests to confirm the diagnosis of inhalational anthrax include the polymerase chain reaction for identification of anthrax markers in pleural fluid, serologic detection of immunoglobulin to protective antigen, and immunohistochemical testing of biopsy specimens.

In addition to inhalational anthrax, cutaneous anthrax can occur in any area where large numbers of spores are released, as was the case in the United States in 2001. This form of the disease occurs when spores are introduced into the skin, usually through open wounds or abrasions. The mortality rate is approximately 20% without treatment and 1% with treatment. Antibiotics do not affect the course of local disease but

Figure 194-2. Chest computed tomography scan of an anthrax patient showing pulmonary consolidation and effusions. (Courtesy of the U.S. Centers for Disease Control and Prevention.)

Figure 194-3. Child with cutaneous anthrax. (From Roche KJ, Chang MW, Lazarus H: Images in clinical medicine: Cutaneous anthrax infection. N Engl J Med 345:1611, 2001.)

BOX 194-5 TREATMENT FOR ANTHRAX

Cutaneous Anthrax *without* Toxicity

Adults

Ciprofloxacin, 500 mg PO bid
or
Doxycycline, 100 mg PO bid
or
Amoxicillin, 500 mg PO tid

Children

Ciprofloxacin, 20–30 mg/kg/day PO divided bid (max 1 g)
or
Doxycycline, 4.4 mg/kg/day PO divided bid (max 200 mg)
or
Amoxicillin, 20–40 mg/kg/day PO divided tid (max 1500 mg)

All doses given for 7–10 days.

Inhalational, Cutaneous, or Gastrointestinal Anthrax *with* Toxicity

Adults

Ciprofloxacin, 400 mg IV q12h
or
Doxycycline, 100 mg IV q12h
or
Penicillin G, 4 million units IV q4h

Children

Ciprofloxacin, 20–30 mg/kg/day IV divided q12h (max 800 mg)
or
Doxycycline, 4.4 mg/kg/day IV divided q12h (max 200 mg)
or
Penicillin G, 100,000–400,000 U/kg/day IV divided q4h (max 24×10^6)

All doses given until toxicity resolves. Then switch to oral form. Treat for 60 days or until patient receives three doses of vaccine.

Postexposure Prophylaxis

Same drugs and dosage as for cutaneous anthrax *without* toxicity. Treat for 60 days or until patient receives three doses of vaccine.

are used to prevent dissemination and death. After an incubation period of 1 to 5 days, a papule develops, progressing to form a large vesicle over the next several days. Severe edema occurs around the lesion and is associated with regional lymphadenitis. The lesions are not tender, and the patient may or may not be febrile (Fig. 194-3). After approximately 1 week, the lesion ruptures, forming a black eschar (thus the name *anthrax*, from the Greek word for "coal"). In the next 2 or 3 weeks, either the eschar sloughs off and the illness is over or the organism disseminates and the patient dies. As with inhalational anthrax, the diagnosis is predominantly clinical. Confirmation is established by culturing of the lesion, punch biopsy, or serologic testing. A total of 11 cutaneous anthrax cases occurred in the United States after the 2001 attack.[22]

A few cases of gastrointestinal anthrax and oropharyngeal anthrax are also possible after a terrorist attack. These rare manifestations usually occur with the ingestion of insufficiently cooked, contaminated meat. The mortality rate is approximately 50%. After ingestion, the spores are transported to regional lymphatic tissue, where symptoms develop after a 2- to 5-day incubation period. Patients with oropharyngeal anthrax present with sore throat and neck swelling from cervical and submandibular lymphadenitis. The tonsils are also frequently involved, and symptoms are associated with fever and toxicity. Dysphagia and respiratory distress often follow. Gastrointestinal anthrax begins with nausea, vomiting, and fever associated with mesenteric lymphadenitis. Patients then experience severe abdominal pain, hematemesis, ascites, and bloody diarrhea and may present with an acute abdomen.

Treatment

Traditional treatment for anthrax infection has been penicillin. However, weapons-grade anthrax is probably resistant to penicillin (although this was not the case with the U.S. attack). Current treatment recommendations reflect this fact (Box 194-5).[1,2] These consensus recommendations include fluoroquinolones and tetracycline for all children, regardless of age. Balancing the potential risks of such drugs against the consequences of infection by drug-resistant anthrax strains, the benefits justify the recommendations. Nontoxic victims with cutaneous anthrax can be treated as outpatients with oral ciprofloxacin or doxycycline for 7 to 10 days. Victims with inhala-

tional, cutaneous, or gastrointestinal disease and toxicity require intravenous therapy with ciprofloxacin or doxycycline plus at least two other antibiotics (e.g., rifampin, clindamycin, imipenem, or an aminoglycoside). Patients can be switched to oral antibiotics when toxicity resolves. Other modalities that may be helpful include chest tube drainage of pleural effusions and possibly tracheal intubation and mechanical ventilation.[22] Surprisingly, the latter intervention did not improve mortality. All patients intubated after the U.S. anthrax attack died.[17,19]

Treatment must continue for 60 days or until the patient has received three doses of the anthrax vaccine, given on days 0, 14, and 28. The complete vaccine course requires 18 months. This treatment regimen is also recommended for children and pregnant women. If the anthrax strain proves susceptible, patients can be switched to intravenous penicillin or oral amoxicillin. In vitro studies suggest that ofloxacin or levofloxacin can be substituted for ciprofloxacin.[1]

For postexposure prophylaxis, oral ciprofloxacin (500 mg) or doxycycline (100 mg) twice a day is recommended. Amoxicillin can be substituted if sensitive strains are identified. Antibiotic prophylaxis must continue for 60 days or until patients have received at least three doses of the vaccine. The vaccine is approved by the U.S. Food and Drug Administration (FDA) for adults but not for children. A review by the Institute of Medicine found the vaccine both safe and effective for prophylaxis against inhalational anthrax.[23]

Plague

Plague has been a human pathogen since antiquity. Many regions of the world, including Asia and India, are currently witnessing the third pandemic of plague, and this affliction is endemic in the western half of the United States. Plague is caused by *Yersinia pestis*, a gram-negative bacillus. It is normally a disease of rodents that is transmitted to humans through the bite of an infected flea or by inhalation. Three forms of the disease exist: pneumonic, bubonic, and septicemic plague. The bacteria do not form spores and die rapidly in the environment. However, they are viable for days in dry sputum, flea feces, and human remains. Dogs are relatively resistant to infection, but cats are highly susceptible and could form a reservoir for maintaining the disease in a human population. Recovery is followed by temporary immunity.

Primary pneumonic plague results when bacilli are inhaled into the lungs. It has a mortality rate approaching 100% if not treated early. Pneumonic plague will be the most frequently encountered form of the disease because terrorists are likely to use aerosolization as the method of dispersal. After an incubation period of 2 or 3 days, victims develop sudden onset of fever, chills, and a flulike illness. This is followed within 24 hours by a fulminant pneumonia associated with hemoptysis, systemic toxicity, respiratory failure, circulatory collapse, and death. The pneumonia is classically lobar, but any x-ray pattern is possible, including acute respiratory distress syndrome. Six to 10% of victims develop plague meningitis. Coagulation abnormalities and hepatocellular injury occur. The coagulopathy is characterized by ecchymoses, disseminated intravascular coagulation, and acral gangrene ("black death"). The gangrene is caused by bacterial production of the coagulase enzyme in areas of the body where the temperature drops below 37° C. This causes blood to clot in fingers, toes, and the nose, with resultant infarction and gangrene. If the victims survive, long-term rehabilitation is required. Pneumonic plague is transmissible human to human.

Bubonic plague occurs when organisms are inoculated into the skin, usually from a flea bite. During the 2- or 3-day incubation period, the bacilli migrate to regional lymph nodes, where they multiply and cause inflammation and necrosis of lymphatic tissue, resulting in large, tender nodes, or buboes. Typically, buboes develop in the groin, axilla, or cervical region and are so painful that the patient will refrain from moving the affected area (Fig. 194-4). Individuals experience fever, chills, and weakness. In approximately 25% of patients, vesicles or ulcerations occur at the site of the flea bite. The buboes are usually nonfluctuant but rarely can suppurate. Organisms can be aspirated from the nodes for diagnosis, but incision and drainage is not recommended because the lymphadenitis resolves with antibiotic treatment, and practitioners could become infected if exposed during the procedure.

Figure 194-4. Child with bubonic plague demonstrating axillary bubo. (Courtesy of Frederick M. Burkle, Jr., MD, MPH.)

During the next week or more, the bacteria disseminate in approximately 50% of patients with bubonic plague. These victims develop septicemic plague or secondary pneumonic plague and die if untreated. Those with septicemic plague experience endotoxemia, shock, disseminated intravascular coagulation, and coma. If bacteremia does not occur, most victims recover. A small percentage of those infected by fleas develop septicemic plague without detectable buboes. Direct human-to-human transmission does not occur with bubonic or septicemic plague. However, both of these conditions can lead to secondary pneumonic plague, which is communicable. Therefore, initial isolation (for the first 48 hours) is recommended for all patients with plague.

Differential Diagnosis

The preliminary diagnosis of plague is clinical. Few diseases other than plague cause fulminant gram-negative pneumonia associated with hemoptysis in previously healthy individuals. The same can be said for diseases that cause lymphadenopathy. Cat-scratch disease, tularemia, and staphylococcal or streptococcal infections are all in the differential diagnosis. However, the extremely tender nature of the lymphadenopathy and the toxicity of the patient strongly suggest plague. Once the disease is suspected, Gram's stain and culture of sputum, blood, cerebrospinal fluid, or lymph node aspirate are helpful. State health departments or the CDC can test specimens for the presence of the capsular antigen using direct fluorescent antibody staining. Polymerase chain reaction also holds promise. Unfortunately, all laboratory tests require several days to complete, so initial management decisions must be based on clinical findings.

Treatment

Antibiotic treatment is essentially the same for all three types of plague (Box 194-6).[24] The same caveats for the use of fluoro-

BOX 194-6 TREATMENT FOR PLAGUE

Parenteral Therapy

Adults
- Streptomycin,* 1 g IM bid
- Gentamicin, 5–7 mg/kg once daily IM or IV
- Doxycycline, 100 mg IV bid
- Ciprofloxacin, 400 mg IV bid
- Chloramphenicol, 25 mg/kg IV qid

Children
- Streptomycin,* 15 mg/kg IM bid (max 2 g/day)
- Gentamicin, 2.5 mg/kg IM or IV tid
- Doxycycline, 2.2 mg/kg IV bid (max 200 mg/day)
- Ciprofloxacin, 15 mg/kg IV bid (max 800 mg/day)
- Chloramphenicol, 25 mg/kg IV qid

Pregnant women: Same as above but exclude streptomycin and chloramphenicol.

Oral Therapy

Adults
- Doxycycline, 100 mg bid
- Ciprofloxacin, 500 mg bid
- Chloramphenicol, 25 mg/kg qid

Children
- Doxycycline, 2.2 mg/kg bid (max 200 mg/day)
- Ciprofloxacin, 15 mg/kg bid (max 1 g/day)
- Chloramphenicol, 25 mg/kg qid

Pregnant women: Same as above but exclude chloramphenicol.

*Although streptomycin is recommended as first-line treatment, it may not be readily available.

quinolones and tetracycline in children with anthrax also apply to plague. In the case of pneumonic and septicemic plague, treatment must be started within 24 hours of symptoms to improve outcome. Antibiotics are given for a minimum of 10 days. As patients improve, oral antibiotics are substituted for intravenous therapy to complete the course. Respiratory isolation of patients with pneumonic plague is necessary for 4 days after beginning antibiotics to guarantee sterilization of sputum. Patients with septicemic and bubonic plague require isolation for 48 hours. If they do not develop pneumonia or draining lesions during this time, isolation can be discontinued. Nonseptic patients with mild bubonic plague can be treated at home with oral doxycycline or tetracycline for 10 days.

The mainstay of prophylaxis against plague remains oral antibiotics. A vaccine exists but has no value in an acute outbreak. It is effective only against bubonic disease and requires several months to impart immunity. The drugs for prophylaxis are tetracycline, doxycycline, ciprofloxacin, chloramphenicol, and possibly trimethoprim-sulfamethoxazole for children.

Smallpox

Smallpox was eradicated in 1980 as a naturally occurring disease. The only known repositories of the variola virus, the etiologic agent of smallpox, are in the United States and Russia. However, Russia was successful in weaponizing the virus, which may have been sold or smuggled out of the country.[8] The effectiveness of Russia's weaponized strain was demonstrated in 1971 when an individual became infected while traveling on a ship 15 km downwind from a Soviet bioweapons test site (Vozrozhdeniye Island in the Aral Sea).[25] In addition, most of the world's population is no longer fully immune to infection because vaccination against smallpox ceased 20 years ago. Given its high infectivity and lethality, this makes smallpox an excellent biologic weapon.

The variola virus is spread as an aerosol. It can survive for 24 hours, possibly 48 hours, in the environment. The occurrence of smallpox in hospital employees whose only exposure was handling laundry from infected people is testimony to its viability. Approximately 30% of exposed people become ill. One infected person has the potential to infect up to 20 other individuals. People are infectious from the time the rash first appears until the scabs fall off (1 or 2 weeks). Anyone exposed to smallpox must be quarantined and observed for 17 days to rule out infection.

The disease manifests clinically in several forms. Variola major and variola minor represent 90% of the cases. Variola major is the classic form—a more severe illness with a mortality rate of 30%. Variola minor is a milder form, with less toxicity, fewer pox, and a mortality rate of 1%. Two other forms of the disease, hemorrhagic and malignant (or flat) smallpox, are seen in 10% of cases; the mortality rate is greater than 90%. Patients with hemorrhagic smallpox develop symptoms earlier and become toxic quickly. Instead of pox, their rash is characterized by petechiae and hemorrhage. Death occurs in 5 or 6 days. Those with malignant smallpox have a similar course, but their rash is characterized by soft, flattened lesions that never progress to pustules. If they survive, the lesions resolve without forming scabs.

The infection begins when the virus is inhaled. After migrating to regional lymph nodes, the virus replicates for 3 or 4 days and then asymptomatically spreads to the spleen, bone marrow, other lymphoid tissue, and liver. A second viremia occurs 8 to 12 days later and is associated with fever, prostration, and headache. Mental status changes can occur. During this phase, which lasts 2 or 3 days, the virus localizes to the skin and pharyngeal mucosa. A maculopapular rash soon appears, which becomes vesicular and finally pustular. The rash first appears on the face and forearms, later spreading to the legs and trunk. All the lesions in any one area of the body are the same age (Fig. 194-5). During the next 8 to 14 days, the pustules crust over and separate from the skin, leaving pitted scars.

A clinical algorithm developed by the CDC can assist in assessing the probability that an individual has smallpox. It relies on three major and five minor criteria. The major criteria are a febrile prodrome, classic smallpox lesions, and lesions in the same stage of development. The minor criteria are centrifugal distribution of pustules; first lesions on the oral mucosa, face, or forearms; toxic appearance; slow evolution of lesions; and pustules on the palms and soles. A patient with all three major criteria is at high risk and should be isolated and reported

Figure 194-5. Man with smallpox. (From the U.S. Centers for Disease Control and Prevention Public Health Image Library.)

to public health authorities and law enforcement agencies immediately. Patients with the febrile prodrome and either four minor criteria or one other major criteria are at moderate risk. Consultation with infectious disease and dermatology specialists should be sought and tests ordered to confirm varicella. If smallpox cannot be ruled out after these interventions, the patient should be treated as high risk. If a patient does not have the febrile prodrome or has the prodrome but no other major criteria and has fewer than four minor criteria, the individual is at low risk for smallpox. These patients can be managed as clinically indicated.[26]

Differential Diagnosis

As with anthrax and plague, the initial diagnosis of smallpox is clinical. Other illnesses resembling smallpox include chickenpox, herpes simplex, and monkeypox. Unlike variola, the rash associated with chickenpox (varicella) is seen first on the trunk and then spreads to the extremities and face. In addition, the pustules are in different stages of evolution in any one area of the body. If the first case seen is hemorrhagic or malignant smallpox, the diagnosis will probably be missed until more typical cases present. To confirm the diagnosis, vesicular fluid or scabs were traditionally sent for electron microscopic examination. Polymerase chain reaction techniques appear promising for rapid viral identification, with sensitivities and specificities in the 98% range.[27]

Treatment

No effective therapy exists for victims infected with smallpox who become symptomatic. However, potential antiviral agents, such as cidofovir, show promise. In mice exposed to a lethal cowpox challenge, administration of an oral lipid prodrug of cidofovir in modest doses once a day for 5 days produced 100% survival.[28] Vaccinia immunoglobulin (VIG) has no role in the treatment of active disease. Some practitioners suggest that most smallpox patients should be isolated at home or other nonhospital facilities because the virus spreads easily in a hospital environment and the disease is currently untreatable.[8]

The best strategy for containing the disease is vaccination of the susceptible population. Vaccinating an immunocompetent individual within 3 days of exposure will prevent or significantly ameliorate illness. Vaccination up to 7 days after exposure may prevent death. Complications from vaccination with vaccinia virus occur and can be fatal. Groups at risk for these adverse consequences include pregnant women and people with eczema, human immunodeficiency virus infection, and immunosuppressive conditions (e.g., malignancy, chronic steroid use, and hereditary immunodeficiencies). Given the seriousness of the disease, the current recommendation is to vaccinate these individuals and simultaneously administer 0.3 mg/kg of VIG intramuscularly (IM). For people who develop complications from the vaccine (e.g., progressive vaccinia, ocular autoinoculation, and eczema vaccinatum), the dose of VIG is 0.6 mg/kg IM and is divided over 24 to 36 hours. Ribavirin can be administered but is considered experimental. VIG is not indicated for vaccinia-associated encephalitis.

The smallpox vaccine supply situation has improved dramatically in the United States. The CDC has 100 million doses of the traditional smallpox vaccine (Dryvax). These vials can be diluted 5:1 to produce a total of 500 million doses without any decrement in the vaccine's efficacy.[29] In 2004, a British company delivered an additional 209 million doses of a second-generation vaccine derived from the same vaccinia virus used in Dryvax but grown in cell cultures. In addition, work is commencing on production of an improved modified vaccinia ankara vaccine. The virus used in the modified vaccinia ankara vaccine is so attenuated that it does not replicate in a human host. This may make it safe for administration to immunocompromised individuals.

CHEMICAL WEAPONS

Unlike victims of biologic weapons, casualties exposed to chemical agents manifest symptoms quickly, from immediately to a few hours after contamination.[30] Therefore, surveillance and recognition are less problematic. The challenge is decontamination and treatment.

Terrorism with chemical weapons produces casualties similar to those seen in hazardous materials incidents, and medical management is comparable. However, the unique features of such events, including the volume of patients and the risk of hospital contamination, necessitate additional preparation. For example, the Tokyo subway attack using sarin in 1995 resulted in 11 deaths and more than 5000 patients converging on local emergency departments. Although the majority of these patients had subclinical exposure or psychological symptoms alone, the health care system was severely taxed. Secondary contamination by direct contact or vaporization occurred in ambulances and at the hospitals.[3]

Health care facilities must have protocols in place to deal with the eventuality of chemically contaminated patients (Box 194-7).[31,32] Current recommendations for levels of PPE and types of decontamination facilities necessary in a hospital setting are inconclusive.[33]

The four basic classes of chemical agents are nerve, vesicant (blistering), blood, and pulmonary (choking). Although all have potential for use as weapons, the nerve agents and vesicants are thought to represent the greatest threat.

Nerve Agents (Sarin, Tabun, Soman, and VX)

Nerve agents are organophosphates. They inhibit the enzyme acetylcholinesterase, blocking the degradation of acetylcholine at the postsynaptic membrane. Acetylcholine accumulates, resulting in overstimulation of muscarinic and nicotinic receptors. Symptoms are receptor dependent. Stimulation of muscarinic receptors produces miosis, salivation, rhinorrhea, lacrimation, bronchorrhea, bronchospasm, vomiting, and defecation. The major life threat associated with this syndrome is ventilatory compromise from profound bronchorrhea and bronchoconstriction. Stimulation of nicotinic receptors produces muscle fasciculations, flaccid paralysis, tachycardia, and hypertension. Unlike typical organophosphates, exposure to nerve agents has not been associated with urination. In addition, bradycardia is rare, and miosis does not respond to systemic therapy.[2]

BOX 194-7 EMERGENCY DEPARTMENT PREPAREDNESS FOR CHEMICAL WEAPONS OF MASS DESTRUCTION

- Community-based hospital planning
- Personnel trained in recognition, mass casualty triage, and treatment
- Decontamination facility with protocols (runoff water, warm water, etc.)
- Personal protective equipment readily accessible and compliant with regulations
- Rapid access to antidotes, cyanide kits, and anticonvulsants
- Hospital incident management system in place
- Knowledge of how to access experts quickly

Nerve agents also cause direct central nervous system toxicity that manifests as seizures, coma, and apnea. In survivors, residual central nervous system effects manifest as psychological changes that can last 4 to 6 weeks. These manifestations are caused by chemical effects, not stress.

A preliminary diagnosis of nerve agent exposure is based on clinical findings. Important features include muscle fasciculations and miosis, which are sufficient to justify treatment pending further evaluation. Diagnosis is confirmed by measuring red blood cell cholinesterase levels. This test is not readily available, however, so treatment must begin before test results are known.

Terrorists are most likely to employ the nerve agents sarin (designated GB) and VX. Sarin exists as a liquid at room temperature but represents primarily a vapor threat because of its high volatility. Symptoms occur within seconds after inhaling vapor and peak at 5 minutes. There are no delayed effects; patients remaining asymptomatic 1 hour after possible exposure have not been contaminated. They can be sent home. VX is a thick liquid with low volatility. It represents a liquid threat only. Victims generally develop symptoms after skin exposure. The median lethal dose (LD_{50}) for VX is 10 mg, a droplet slightly larger than a pinhead. Death from doses of this size occurs in less than 30 minutes. Delayed symptoms occur, so individuals must be observed for 18 hours before potential contamination can be ruled out.

Decontamination of victims exposed to sarin vapor requires only removal of clothing. People contaminated with VX or liquid sarin must have their clothing removed and then must be decontaminated using showers. When the level of exposure or the involved agent is uncertain, full decontamination is prudent. Responders caring for patients in the presence of liquid sarin exposure may require level A or B protective suits.

Treatment

The treatment of nerve agent victims depends on the form (liquid or vapor) and level of exposure (mild, moderate, or severe) (Box 194-8). Three drugs are the mainstay of treatment: atropine for the muscarinic effects (improves ventilation), pralidoxime chloride (2-PAM) for the nicotinic effects (reverses paralysis), and diazepam for the prevention and treatment of seizures (Box 194-9). The dose of atropine is titrated to the drying of respiratory secretions and not to heart rate or pupil size. If diazepam is unavailable, other benzodiazepines can be used. 2-PAM is most effective if administered within 4 to 6 hours of sarin exposure. After this period, the drug's impact wanes due to "aging," defined as the permanent attachment of sarin to the acetylcholinesterase enzyme. Hypertension can occur during 2-PAM administration and is controlled by intravenous phentolamine, 5 mg for adults and 1 mg in repeated doses for children.

An autoinjector kit (Mark I) approved by the FDA consists of two cartridges, one containing atropine (2 mg) and the other 2-PAM (600 mg). Mark I kits are available as part of civilian pharmaceutical caches strategically located throughout the United States. An autoinjector containing 10 mg of diazepam is also available. Doses should be adjusted for pediatric and elderly patients. Using the Mark I kits to treat these populations can be problematic because of difficulty in adjusting the dose. An alternate solution is to inject the medication into a sterile vial. The drug can then be re-aspirated in an appropriate amount for the patient's weight or age and administered.[34]

BOX 194-8 TYPE AND DEGREE OF NERVE AGENT EXPOSURE

Vapor Exposure (Sarin)
Mild: Rhinorrhea and miosis
Moderate: Mild symptoms plus increased secretions, wheezing/dyspnea, muscle weakness/fasciculations, or gastrointestinal effects
Severe: Apnea, seizures, loss of consciousness, flaccid paralysis, or major involvement of two organ systems

Liquid Exposure (VX)
Mild: Localized sweating and fasciculations where a drop touches the skin; no miosis; may be delayed for 18 hours
Moderate: Gastrointestinal effects; miosis uncommon; may be delayed for 18 hours
Severe: Apnea, seizures, loss of consciousness, flaccid paralysis, or major involvement of two organ systems; occurs in less than 30 min at or above LD_{50}

Vesicants (Mustard)

Vesicants (blistering agents) are chemical warfare agents that induce blister formation when contacting skin. Terrorists could use several of these compounds, but mustard is considered the chemical of choice. Mustard is a liquid at room temperature but has both liquid and vapor toxicity. Injury from mustard exposure occurs in 1 or 2 minutes, but symptoms do not develop for 4 to 8 hours. The exact mechanism is unknown, but the agent damages DNA, causing eventual cell death. Mustard has both local and systemic toxicity. Local effects occur from direct exposure to the skin, eyes, and airway. Systemic effects result from the impact of absorbed mustard on the bone marrow. Treatment is supportive and includes decontamination (to prevent secondary contamination) and airway maintenance. Although no specific antidote for mustard is currently available, a topical iodine preparation shows promise.

BOX 194-9 TREATMENT FOR NERVE AGENT EXPOSURE*

Vapor
Mild: Observe for 1 hr, then release; no treatment
Moderate: One or two Mark I kits IM *or*
Atropine, 2–4 mg IV, may repeat every 5–10 min as needed, *and* 2-PAM, 1 g IV over 30 min, may repeat every hour as needed
Severe: Three Mark I kits IM and one diazepam autoinjector IM *or*
Atropine, 6 mg IV, may repeat 2 mg boluses IV every 5–10 min, *and* 2-PAM, 1 g IV over 30 min, repeat every hour for total of 3 g, *and* diazepam, 5 mg IV, may repeat as needed

Liquid
Mild: One Mark I kit IM *or*
Atropine, 2 mg IV, *and* 2-PAM, 1 g IV over 30 min
Moderate: Same as for vapor
Severe: Same as for vapor

Pediatric Doses
Atropine, 0.02 mg/kg IV
2-PAM, 15 mg/kg IV over 20–30 min
Diazepam, 0.2–0.3 mg/kg IV

*Give atropine before attempting intubation. Otherwise, airway resistance will inhibit ventilation. Continue atropine until secretions are dry (usually ≤20 mg). In hypoxic patients, IV atropine has been reported to cause ventricular fibrillation, so consider using IM atropine.

When applied within 1 hour after mustard exposure to the skin of guinea pigs, an iodine-tetraglycol solution reduced vesicle formation and signs of inflammation.[35] Application more than 1 hour after exposure was not effective.

Eye damage from mustard exposure varies from conjunctivitis to corneal ulcer and perforation; however, only 1% of patients have permanent eye damage. Severe pain is frequently associated with mustard injury and causes significant blepharospasm. Irrigation is beneficial if performed within minutes of exposure but ineffective once symptoms occur. Standard treatment includes mydriatics, topical antibiotics, oral analgesics, and petroleum jelly applied to the lids to prevent adhesions. Topical steroids are indicated only within the first 24 hours.

The hallmark of mustard injury is skin blisters resembling second-degree burns. Within 4 to 8 hours of exposure, erythema and burning occur, followed by vesicle and bulla formation. Most vapor injuries do not involve the entire dermis, so wounds will not require skin grafting. If liquid exposure occurs to skin, full-thickness burns may result. The patient should be decontaminated by removing clothing and washing with water or a dilute bleach (1 : 10 hypochlorite) solution. Decontamination immediately after exposure prevents further injury to the patient, but delayed decontamination is indicated to protect staff. Treatment is supportive and includes standard burn wound management, analgesia, and tetanus prophylaxis. An important exception is fluid resuscitation. Fluid losses from mustard injury are much less than those associated with thermal burns. Therefore, standard burn formulas for fluid administration do not apply, and caution must be used to avoid overhydration.

The degree of airway injury after mustard exposure is dose dependent. Mild exposure causes irritation of the nose, sinuses, and pharynx and can be treated with cool, humidified mist. Moderate exposure extends to the larynx and upper trachea and may require treatment with oxygen, continuous positive airway pressure, or even intubation. Severe exposure involves the lungs, producing hemorrhagic necrosis of the bronchioles. Pulmonary edema is rare. Intubation is usually required, and patients may benefit from positive end-expiratory pressure and in-line bronchodilators. Steroids are of questionable benefit, and antibiotics should only be given for established infection.

Systemic toxicity from mustard is caused by bone marrow suppression. Absorbed mustard kills stem cells, causing the white blood cell count to decline after 3 to 5 days. Survival is rare if the white blood cell count falls below 200, which generally occurs when greater than 50% of the total body surface area is involved from exposure to liquid agent. Death after mustard exposure usually results from secondary infection.

Blood Agents (Cyanide)

Blood agents such as cyanide bind to cytochromes within mitochondria and inhibit cellular oxygen use. Low-dose exposures result in tachypnea, headache, dizziness, vomiting, and anxiety. Symptoms subside when the patient is removed from the source. At higher doses, the symptoms progress to seizures, respiratory arrest, and asystole within minutes of exposure.

Victims should be removed from the area, have their clothing discarded, and receive oxygen. If no improvement occurs, the cyanide antidote is given. This has traditionally been the sequential administration of amyl nitrate, sodium nitrite, and sodium thiosulfate. However, the FDA has approved intravenous hydroxocobalamin for treatment of cyanide exposure. The initial dose is 5 mg and can be repeated if necessary.[36]

Pulmonary Agents (Phosgene and Chlorine)

Pulmonary or choking agents cause an inflammatory reaction when they come into direct contact with the eyes and upper airway. They can be life-threatening if inhaled. No specific antidote exists. Treatment is mainly supportive and consists of removing the patient from the source, decontamination, airway maintenance, bronchodilator administration, and eye irrigation.

KEY CONCEPTS

- Emergency department preparedness for a radiation incident must address decontamination (an external free-standing decontamination unit is best), triage, staff safety, PPE, and diagnostic procedures that emphasize radiation monitoring. The emergency personnel should make sure they know their radiation safety officer.
- Management of acute life-threatening conditions takes priority over radiation-associated issues.
- Aerosol dispersal is a likely route that terrorists may use to deploy biologic weapons, so victims will present primarily with respiratory complaints.
- In addition to "flulike" symptoms, anthrax typically causes mediastinal widening, pulmonary consolidation, and pleural effusions best seen on chest computed tomography scans.
- Smallpox can spread in a hospital environment; thus, patients suspected of having smallpox should be admitted to locations separated from the rest of the hospital.
- Decontamination is a key activity in the management of patients exposed to chemical agents, and hospitals must provide this intervention.
- Nerve agents are organophosphates, and patients exposed to these agents are treated with large doses of atropine (repeated frequently), pralidoxime, and benzodiazepines.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

PART VII

The Practice of Emergency Medicine

CHAPTER 195

Medical Literature and Evidence-Based Medicine

Kelly D. Young and Roger J. Lewis

PERSPECTIVE

Medicine is an empirical science based on the experiences and insights of past and contemporary practitioners. Because the clinical experience of an individual physician is a small fraction of the experience of the medical profession as a whole, the advancement of medical science depends on physicians' abilities to assemble, organize, and disseminate information in order to learn from the experience of others.

The Medical Literature

During the past several decades, medical literature has exploded.[1,2] Thirty years ago, physicians could understand most medical publications. Currently, reports frequently use sophisticated statistical analyses that are unfamiliar to most clinicians.[3] Emergency physicians and other practitioners are increasingly aware that the quality of the research reported must be evaluated before the results can be considered valid and clinical practice altered. Also, the results of quality research may not be applicable if the population studied differs greatly from the patient population in the emergency physician's clinical practice. Even a clinician who possesses the analytical skills necessary to understand the modern medical literature will find it difficult to remain current, given the rate at which medical studies relevant to emergency medicine are published. Thus, the emergency physician must have a plan to identify, select, and read high-quality, relevant articles. Furthermore, the emergency physician must understand a number of principles to be able to analyze published studies critically.

The first step toward achieving these goals is to identify a small number of journals on which to focus.[4,5] Most high-quality studies relevant to emergency medicine are published in fewer than a dozen journals. Once a list of 6 to 12 journals is compiled, back issues can be skimmed to determine the average number of relevant articles in each issue. Those journals that publish the highest number of articles directly relevant to an emergency physician's clinical practice should then be selected.[4] An emergency physician in full-time clinical practice should probably focus on 2 to 6 journals per month. Regular pamphlet or audiotape updates reviewing recent literature relevant to emergency medicine can be purchased and used as a supplement to journal review. Articles should be pulled and read in full, however, before results are accepted and clinical practice is altered.

Possible articles should then be screened to evaluate the relevance of the study question and population and to determine whether the methodology is of sufficient quality to warrant reading the article in more detail. Quality and clinical relevance vary greatly in the peer-reviewed literature.[4] Only articles that meet high standards for methodologic quality should be read in detail.[1,2] The emergency physician must learn to differentiate high-quality studies from poor-quality studies with unreliable results. Practitioners who understand the concepts presented in this chapter will have the basic foundation to differentiate good from poor studies and to focus their reading on those studies most likely to yield results that warrant a change in clinical practice. Additional guidance can be obtained from the *Journal of the American Medical Association*'s *Users' Guides to the Medical Literature* series (http://www.cche.net/usersguides/main.asp).[6]

A steadily increasing amount of attention is being paid to the importance of rigorous methodology in the design and execution of clinical trials.[3,7-9] A poorly designed statistical analysis can yield misleading results, but a trial is more likely to be weakened by a poorly chosen question, an inappropriate study population, or other methodologic errors that bias the results.[10-17] Thus, although some degree of statistical literacy is important, the practitioner must also understand nonstatistical issues in the design and analysis of clinical studies.[6,10-17]

TYPES OF CLINICAL STUDIES

Studies can be divided into two categories, cross-sectional and longitudinal (cohort), based on when the measurements are made on the study population.[12] In a cross-sectional study, data are obtained from a population of patients at a single point in time, whereas in a longitudinal study, data are obtained from a population of patients over a period of time.

Cross-Sectional Studies

Many epidemiologic studies are cross-sectional. Although a cross-sectional study cannot prove a causal relationship between a risk factor or treatment and an outcome, strong associations between identified variables in cross-sectional studies are suggestive of such effects.[18]

Many important observations can only be made using cross-sectional studies because, for practical and ethical reasons, some variables cannot be artificially manipulated to determine

their effect on patient outcome.[18] Furthermore, the effect may be so delayed that a longitudinal study is impractical. An example is a study examining the association between cigarette use and lung cancer. It would be unethical to expose a nonsmoking population to the effects of cigarettes, and even if one were to identify a population that would voluntarily use cigarettes, it would be impractical to observe subjects long enough for malignancies from cigarette smoking to appear. However, a cross-sectional study of self-reported cigarette use and the diagnosis of lung cancer that examines a population of subjects at a single point in time can easily demonstrate an association.

Longitudinal Studies

In a longitudinal, or cohort, study, a population of patients is enrolled in the study and measurements are made over a period of time.[11,12] Longitudinal studies can be observational, if no intervention is made, or they can be interventional.

Longitudinal Observational Studies

In a longitudinal observational study, data are collected from a group, or *cohort*, of patients over time, but no intervention is made. A longitudinal observational study can be either prospective or retrospective. In a *prospective* observational study, patients who meet specific eligibility criteria are identified, and data are prospectively gathered over time.[12] Prospective observational studies are valuable for defining the course of a particular disease treated with standard therapies and for identifying subgroups of patients with differing prognoses. If an association is noted between treatment and outcome in a prospective observational study, the association should be verified in a prospective interventional randomized clinical trial.

Although an observational study cannot prove a causal relationship, associations between initial patient characteristics or specific treatments and subsequent outcome can be detected. Such associations can be measured more accurately in a prospective longitudinal study than in a cross-sectional study because both the original patient characteristics and the subsequent outcome are determined prospectively. When these are determined prospectively, any associations observed are more likely to be true and not a result of bias.

In a *retrospective* observational study, medical records of patients with certain initial characteristics who are treated over time are reviewed and data abstracted. As with all retrospective studies, retrospective observational studies are subject to recording bias, problems with missing information, and other methodologic limitations. Because retrospective studies have these additional sources of bias and limitations, prospective studies provide higher quality evidence than retrospective studies. Prospective studies, however, are usually more difficult and time-consuming to perform.

Longitudinal Interventional Studies (Clinical Trials)

Interventional studies, which must be prospective, involve the artificial manipulation of a patient's therapy to determine the effect of an investigational treatment.[11,12] An interventional study can be controlled or uncontrolled, and, if controlled, it should be randomized.

In an *uncontrolled* interventional study, all patients who meet defined eligibility requirements are given the investigational therapy, and their outcomes are determined. Although such studies are useful for defining the rate of successful therapy in a well-defined population of subjects, the lack of a control group makes it difficult to estimate the relative effectiveness of the new therapy compared with another therapy. Previous experience with the standard treatment, in the form of a historical control group, can be used for comparison to the group receiving the new therapy. The use of such historical control groups is unreliable and often leads to an overestimate of the relative effectiveness of the new investigational therapy.[16] Medical care generally is becoming more effective, and thus the results of modern studies tend to yield better patient outcomes, even if the investigational treatment has no inherent advantage over the therapy received by the historical control patients.[16]

In a *controlled* clinical trial, some patients are given the new investigational treatment, and some patients (*control group*) are given a standard treatment.[11,12] The purpose of the control group is to define the effectiveness of the standard therapy in a group of patients as similar as possible to the group receiving the investigational therapy. To obtain two groups of patients who are nearly identical with respect to all characteristics that might influence the outcome of their disease, it is important that no external or subjective factors influence the assignment of treatment.[11,17] Each patient must have the same chance of receiving each therapy. For this reason, assignment to control or therapy groups should be randomized.

It is extremely important that control patients be given a therapy that is at least as effective as the best currently available treatment. It is unethical for a control group to receive an inferior treatment simply to demonstrate that a new treatment has some effectiveness.[19-22]

In general, longitudinal interventional studies provide the highest quality evidence, although this is controversial.[23-25]

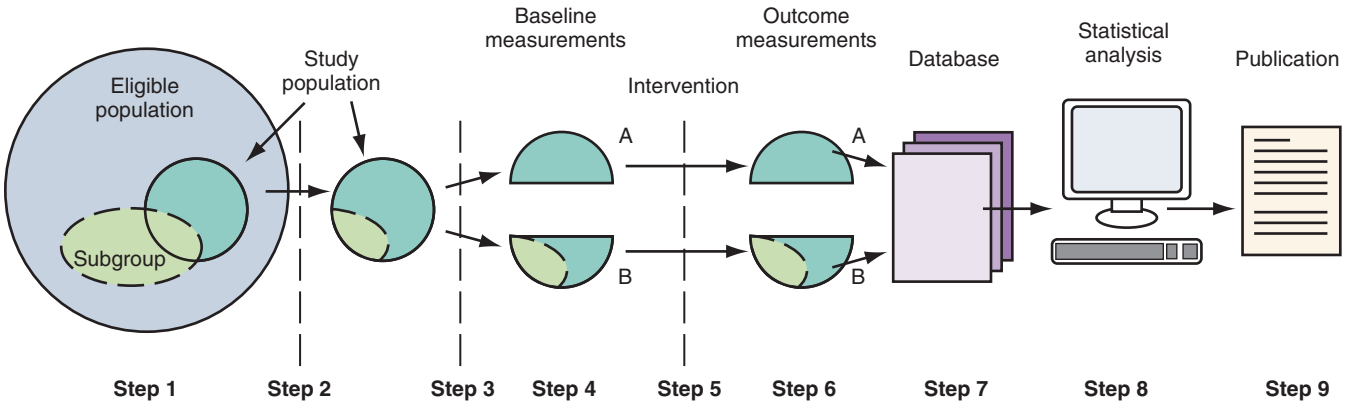
RANDOMIZED LONGITUDINAL INTERVENTIONAL STUDY (CLINICAL TRIAL)

The steps in a randomized clinical trial assume that a worthwhile research question has been defined (Fig. 195-1). No matter how well designed the study, if the research question is not well-defined and not clinically useful, the intended audience will not find the study's results valuable.[26] The research question must also be prospectively defined; it is not appropriate to gather data and then devise a research question to fit the data. A good research question clearly defines four elements: (1) patient population and problem to be studied, (2) intervention to be applied to the treatment group, (3) comparison (control) intervention, and (4) outcome of interest.

Even if these four elements are well-defined, the research question must still have relevance for the emergency physician. For example, a study that compares oral and parenteral antibiotics (treatment and comparison interventions) for the prevention of meningitis (outcome) in well-appearing febrile children with occult bacteremia confirmed by positive blood culture (patient population) is less useful to the emergency physician than a similar study including all well-appearing febrile children because results of blood cultures are not typically available in the emergency department.

Step 1: Definition of Patient Population

Assuming an appropriate research question has been selected, the first step is to define the patient population to be studied.[27,28] The original patient population defined in the research question may be modified slightly by practical factors in study design. For example, although an investigator may want to study all asthmatic patients presenting to the emergency department, it may only be practical to study those presenting when investigators are available (*convenience sample*). Explicit



Step 1: Definition of the patient population	Step 2: Recruitment and enrollment of patients	Step 3: Randomization	Step 4: Measurement of baseline characteristics	Step 5: Treatment or intervention	Step 6: Collection of data on outcome	Step 7: Data management	Step 8: Statistical analysis	Step 9: Presentation and publication of results
Problem 1: Heterogeneous population (confounding variables), poorly chosen inclusion criteria	**Problem 2:** Bias in recruitment, self-selection by potential subjects	**Problem 3:** Imbalance of important confounding characteristics, inadequate blinding	**Problem 4:** Imbalance of confounding characteristics is not detected	**Problem 5:** Unequal compliance or attrition	**Problem 6:** Subjects lost to follow-up, poorly defined outcomes	**Problem 7:** Data entry errors, data reduction errors or bias	**Problem 8:** Type I and type II errors, ill-advised comparisons or subgroup analysis, covariate imbalance	**Problem 9:** Overextrapolation of results, failure to recognize limitations of or biases in results
Solution 1: Population defined in terms of emergency department presentation, confounding characteristics considered in definition of population	**Solution 2:** Consecutive enrollment, records of nonenrolled but eligible patients	**Solution 3:** Effective randomization and blinding, stratified randomization	**Solution 4:** Planned prospective measurement of important confounding characteristics	**Solution 5:** Intention-to-treat analysis of final data, measurement of compliance, procedures to encourage compliance	**Solution 6:** Multistep plans to obtain follow-up data, unambiguous definitions of treatment outcome	**Solution 7:** Data verification, double data entry, value-limited data entry, appropriate forms design	**Solution 8:** Small number of comparisons, planning of analysis, adequate sample size, multivariate modeling	**Solution 9:** Peer review, replication of results by other investigators, educated readership

Figure 195-1. Implementation and analysis of a prospective randomized, controlled clinical trial.

inclusion and exclusion criteria must be defined before enrolling any patients, and these criteria must be uniformly applied in determining which patients are eligible to participate in the study. For the study to be most applicable to emergency medicine, the population should be defined in terms of clinical characteristics that are observable in the emergency department. On the other hand, groups of patients defined by their clinical characteristics in the emergency department are highly heterogeneous.[13] Some patients in the population may have more severe disease than other patients or may have a completely different cause for their symptoms.

When reading a study, one should look to see that the patient population is well-defined and reasonably comparable to one's own patient population.[6] If important segments of the population are excluded (e.g., those with severe disease), the study results are not applicable to this subgroup. Researchers should not generalize their conclusions to patients not included in their study population.

Step 2: Recruitment and Enrollment of Patients

Once a patient population is defined, the next step is to recruit patients for enrollment in the study. To the extent possible, all patients meeting the predefined eligibility requirements for the study should be enrolled. The method of recruitment and enrollment should ensure that there is no systematic tendency to exclude a subgroup of patients from the study who meet the inclusion criteria. If such a *selection bias* exists, it will make the results of the study inapplicable to the types of patients that were excluded.[11,29] For example, if a study of head trauma patients specifies that informed consent must be obtained from the patient within the first half hour of presentation to the emergency department, there will be a systematic tendency to exclude patients with head trauma severe enough to result in an altered level of consciousness.

Even in a study that is appropriately designed, patients may self-select, resulting in selection bias. For example, patients of low socioeconomic status may be less likely than patients of high socioeconomic status to give consent for participation in clinical studies. Thus, although the disease may affect people in all socioeconomic strata, the study results may apply only to patients of high socioeconomic status similar to those who participated in the study.

To minimize selection bias, studies should aim to achieve consecutive enrollment of all patients who meet inclusion criteria. Furthermore, patients who meet eligibility criteria but are not subsequently enrolled should be counted to allow an estimation of the possible extent of any selection bias that might exist.[10] When reading a study, one should look for information on eligible patients who were not enrolled. A significant number of such patients may indicate selection bias. Researchers should explain why these patients were missed and should justify the validity of their results despite missed patients by showing, for example, that demographics and disease characteristics of missed patients were similar to those of enrolled patients.

Step 3: Randomization

The third step in conducting a clinical trial is to randomize enrolled patients to the different treatments being compared.

The purpose of this randomized allocation is to create two groups of patients who, other than receiving different treatments, are as nearly identical as possible.[11]

Stratified randomization can be used to ensure that important confounding factors are equally distributed in the control and test groups.[11] In a stratified randomization, patients with the stratifying characteristic are randomized independently of those without the characteristic. For example, in a study of therapy for closed head injury, patients with severe closed head injury as defined by a low Glasgow Coma Scale score could be randomized independently of those patients with a higher Glasgow Coma Scale score. This would help ensure that the control and test groups have equal fractions of patients with severe and mild closed head injury.

Whenever possible, both the patient and the treating physician should be "blinded" (*double blinding*) to the therapy given.[11] Such blinding is important to ensure that both the patient and the investigating physician can make unbiased estimates of endpoints, including the occurrence of undesirable side effects. Recently, increasing importance has been placed on subjective outcomes, such as quality-of-life assessments made by the patient. Blinding is especially important to ensure that the patients' expectations regarding the effect of the new therapy do not influence their assessment of this type of outcome.

The quality of the randomization in a controlled clinical trial is important because studies that are inadequately randomized are more likely to "find" a positive treatment effect.[30] Similarly, studies in which blinding is inadequate, so that the patient or the treating physician might be able to determine the treatment that the patient actually receives, are more likely to yield false-positive results.[15] When reviewing a clinical trial, one should look for truly random treatment assignment and adequate blinding procedures. For example, in a trial in which patients are enrolled if determined to be sufficiently "stable" by the physician and assignment to therapy or control is alternated, a physician with the bias that the therapy is not efficacious may avoid enrolling a patient by deeming the patient unstable if the physician knows that the next patient will be assigned to the treatment group. A better method of randomization would be assignment by a computerized randomization program, such that no pattern of assignment can be discerned by the enrolling personnel.

Step 4: Measurement of Baseline Characteristics

The fourth step is to measure the characteristics of patients enrolled in the study before therapy. The purpose of these baseline measurements is to detect imbalance between the control and test groups in characteristics that might influence each patient's chance for a successful outcome. Factors that might influence patient outcome and that are not controlled by the investigators are termed *confounding variables*. For example, the initial cardiac rhythm is a confounding variable in a study that compares different treatments for out-of-hospital cardiac arrest. If one group includes more patients in ventricular fibrillation and the other group has more patients in asystole, the intervention given to the first group will appear to be more efficacious. The influence of confounding characteristics must be anticipated, and those characteristics should be prospectively measured for all patients enrolled in the study. Subgroups of the overall patient population often have specific confounding characteristics (see Fig. 195-1). If a clinically significant difference in outcome is ultimately detected between the two treatment groups, the baseline characteristics of the treatment groups should be compared to ensure that the observed difference in outcome did not occur because the two patient groups were not initially equivalent.[11] When reading a study, one should look to see that important confounders were measured and that they did not differ significantly between the groups studied.

Step 5: Treatment or Intervention

The next step is to administer the experimental treatment to the test group and the control treatment to the control group. Although the control and test patients should be nearly identical in their underlying characteristics, the two groups often have unequal compliance with therapy. For example, in a placebo-controlled study of an oral medication, patients taking the active drug may find that it causes gastrointestinal discomfort, whereas those taking the placebo treatment might not experience such an effect. Therefore, patients taking the active agent may be less compliant with therapy. Unequal compliance complicates the interpretation of the outcome data.

Step 6: Collection of Data on Outcome

The sixth step is to determine the outcome of each patient. Definitions of treatment success and treatment failure must be explicitly defined before any data are collected. Sometimes a trial is initially designed to investigate the effects of therapy on one outcome, but during data analysis investigators notice an apparently significant effect on a different outcome. Such a serendipitous finding may be true but can also result from chance because there are generally many such possible findings, and the study was not originally designed to investigate each of these possible outcomes. Such findings can be reported as interesting and warranting further investigation but should not be reported as reliable conclusions.

A difficulty with the collection of outcome data arises if too many subjects are lost to follow-up. This is more likely to occur in studies that evaluate the long-term effects of therapy. Patients who are lost to follow-up may have different characteristics than those patients who keep their follow-up appointments. For this reason, lack of complete follow-up in the study population can bias the results of the study.

Ensuring high rates of follow-up in studies of outpatient therapy is notoriously difficult. One approach is to create a multistep plan to obtain follow-up, with specific procedures to be followed if patients miss their first, second, or even third follow-up appointment. When reading a study, one should look at the percentage of patients lost to follow-up and look for a systematic effort to maintain good follow-up.

Step 7: Data Management

Once patients have been enrolled and have had their baseline characteristics measured, treatments administered, and outcomes determined, all this information must be organized and stored in a format that allows analysis of the data. Data should be collected on a form that limits and organizes the information. In general, information to be recorded on the data form should be highly structured, with categorical variables limited to a small number of possibilities and with very little (or no) unformatted "fill-in-the-blank" information requested. Such structure is required if the resulting data are to be analyzed statistically.

Errors may be introduced when data are entered into the database from data sheets. Bias can be introduced if certain types of data (e.g., written phrases in a patient questionnaire) must be reduced to a smaller number of categoric responses during the data entry procedure. Databases should be designed

to ensure that the data listed are reasonable. For example, the electronic database should not allow entry of patient temperatures that are incompatible with life or negative blood pressures. When reviewing a study, one should look for data categorizations that are clear and clinically useful. For example, a study of postresuscitation neurologic outcomes would be most useful to the emergency physician if patients were categorized as "normal," "mildly impaired," "severely impaired," or "dead" versus the more vague terms "good" or "poor" or by the results of a detailed neuropsychological battery of tests.

Step 8: Statistical Analysis

The next step is to analyze the data. Careful planning of the statistical analysis to be performed is required to minimize the chance of erroneous conclusions. Only a small number of comparisons should be made, and the study should be designed to have an adequate sample size to reliably detect a clinically important treatment effect.[31-35] The comparisons to be conducted must be defined prospectively, as well as any specific subgroups of patients that will be considered separately. Any imbalance in confounding baseline characteristics should be accounted for in the statistical analysis. Specific statistical tests are discussed later.

Step 9: Presentation and Publication of Results

Once the clinical trial data have been statistically analyzed, conclusions can be drawn from the results of the study. During the preparation of a manuscript describing the study and its conclusions, the investigators must be careful not to overextrapolate the results. Care must be taken to explain limitations in the study design and to enumerate factors that might bias the results of the study or at least limit its applicability to different patient populations. One purpose of the peer review process is to ensure that appropriate care is taken in interpreting the clinical trial results.

The enthusiasm of most investigators and clinicians for the results of a clinical trial is partly determined by the direction of the results.[36] For example, a trial that shows a highly effective new therapy for a serious disease is interesting and exciting. On the contrary, a trial that shows that a previously unstudied therapy has no advantage over the currently accepted treatment may be less interesting. Because positive results are inherently more interesting, it is commonly believed that clinical trials yielding positive results are more likely to be published than those with negative results. This effect is termed *publication bias*.[37-39]

However, studies have shown that trials with negative results may be less likely to be submitted for publication but, once submitted, are as likely to be published as trials with positive results.[37,39] Thus, publication bias may be the result of a *file drawer problem*, meaning that study results that are negative sometimes end up in the file drawer instead of in manuscripts submitted for publication.[40]

Publication bias and the file drawer problem are serious threats to the validity of the medical literature taken as a whole. If negative trials are selectively excluded from the medical literature, an ineffective treatment may appear to be at least partially effective because those (possibly poorly designed) studies that show some positive treatment effect are selectively submitted for publication. Meta-analyses or systematic reviews often utilize only published research. It may be unethical to subject patients to the risks and discomforts of participation in a clinical study and not publish the results, especially if participation did not result in any direct benefit to the patient.

Publication bias and other sources of bias can be especially problematic in pharmaceutical or commercially sponsored clinical research. Commercial studies are less likely to report unfavorable conclusions.[41] Data from industry-sponsored research may go unpublished or may be difficult to obtain for subsequent review.[42] When reading a clinical trial, one should determine what agency or company funded the research and consider what biases, if any, might have been introduced.

DATA ANALYSIS

Classic Hypothesis Testing

Data from clinical trials are usually analyzed using *P* values and classical hypothesis testing.[3,7,8] In classical hypothesis testing, two hypotheses that might be supported by the data are considered. The first, called the *null hypothesis*, states that no difference exists between the groups being compared with respect to the measured outcome of interest.[7] For example, in a study examining the use of a new sympathomimetic agent for blood pressure support in patients with sepsis, the null hypothesis might be that there is no difference between the average systolic blood pressure achieved with the test agent and that achieved with the control agent. The *alternative hypothesis* states that the groups being compared are different.[7] In this example study, the alternative hypothesis might be that the test agent results in a 10 mm Hg greater average systolic blood pressure than the control agent. The magnitude of the difference between the two groups defined by the alternative hypothesis is called the *treatment effect* (Tables 195-1 and 195-2).

Table 195-1 Steps in Classical Hypothesis Testing

STEP	DESCRIPTION
Define the null hypothesis	There is no difference between the groups being compared. For example, in a clinical trial the null hypothesis might be that the response rate in the treatment group is equal to that in the control group.
Define the alternative hypothesis	The alternative hypothesis might be that the response hypothesis rate in the treatment group is greater than that in the control group by a given amount.
Calculate a *P* value	This calculation assumes that the null hypothesis is true. One determines the probability of obtaining the results found in the data or other results even more inconsistent with the null hypothesis. This probability is the *P* value.
Accept or reject the null hypothesis	If the probability of observing the actual data, or more extreme results, under the null hypothesis is small ($P < \alpha$), then we should doubt that hypothesis. The idea is that if the probability under the null hypothesis of observing the actual results is very small, then there is a conflict between the null hypothesis and the observed data, and we should conclude that the null hypothesis is not true.
Accept the alternative hypothesis	If we reject the null hypothesis, we accept the alternative hypothesis by default.

Table 195-2 Terms Used in the Design of Clinical Trials

TERM	DEFINITION
Alpha (α)	Maximum *P* value to be considered statistically significant; the risk of committing a type I error
Alpha error	Type I error
Alternative hypothesis	Hypothesis considered an alternative to the null hypothesis; usually the alternate hypothesis is that there is an effect of the studied treatment on the measured variable of interest; also called *test hypothesis*
Beta (β)	Risk of committing a type II error
Beta error	Type II error
Null hypothesis	Hypothesis that there is no effect of the studied treatment on the measured variable of interest
Power	Probability of detecting a treatment effect the size of the treatment effect sought (i.e., obtaining a *P* value < α), given alpha, and the sample size of the clinical trial; power = 1 – β
P value	Probability of obtaining results similar to those actually obtained, if the null hypothesis were true
Type I error	Obtaining a statistically significant *P* value when, in fact, there is no effect of the studied treatment on the measured variable of interest; also called *false positive*
Type II error	Not obtaining a statistically significant *P* value when, in fact, there is an effect of the treatment on the measured variable of interest that is as large as or larger than the effect the trial was designed to detect; also called *false negative*

Modified from Lewis RJ: An introduction to the use of interim data analyses in clinical trials. *Ann Emerg Med* 22:1463, 1993.

The treatment effect defined by the alternative hypothesis must be set before data are collected. The treatment effect should be large enough to be clinically important but small enough such that showing no difference between the groups rules out any clinically important treatment effect. In an interventional study, the difference defined is ideally the minimum treatment effect thought to be clinically significant (i.e., that which would lead to a change in clinical practice). Sometimes a larger treatment effect is defined because designing a study to reliably detect the smallest clinically significant treatment effect would require too large a sample size.[32-35] When evaluating the results of a clinical trial, one should look for the size of the treatment effect that the trial was designed to detect.

Once the null and alternative hypotheses are defined, the null hypothesis is "tested" to determine which hypothesis (null or alternative) will be accepted as true. The process of testing the null hypothesis consists of calculating the probability of obtaining the observed results, or results that are even more inconsistent with the null hypothesis, assuming the null hypothesis is true. This probability is the *P* value.[7]

If the *P* value is less than some predefined value, denoted alpha (α; usually 5% or .05), the null hypothesis is rejected as false, and the alternative hypothesis is accepted as true. In other words, if the null hypothesis were true, the probability of obtaining data like that obtained or even more extreme results by chance alone is less than alpha.

Type I Errors

A type I error occurs when the investigator concludes that a difference has been demonstrated between two groups when no such difference exists.[7,8,43] It is a type of *false positive*. When data are analyzed using *P* values, a type I error occurs when a statistically significant *P* value is obtained but there is actually no underlying difference between the groups being compared. Because the *P* value is the probability of obtaining results equal to or more extreme than those actually observed, assuming there is actually no difference between the groups being compared, the risk of a type I error is equal to alpha, the maximum *P* value considered statistically significant, when the groups are fundamentally the same.[7,43]

Type II Errors, Power, and Sample Size

A type II error occurs when a difference exists between the two groups and that difference is as great as that defined by the alternative hypothesis, but when a nonsignificant *P* value is obtained.[7,32-35] In other words, there really is a difference between the two groups, but the trial failed to demonstrate this difference. A type II error is a type of *false negative* and is commonly denoted beta (β).

The *power* of a trial is the probability of detecting a treatment effect of a given size, if one truly exists.[32-35] Studies are usually designed to have a power of .80 or greater. Because the power of the trial is the chance of finding a true treatment effect, the quantity (1 – power) is the chance of missing a true treatment effect (i.e., risk of committing a type II error).[32,34] The value of (1 – β), or the power, and the magnitude of the treatment effect the clinical trial is designed to detect (defined by the alternative hypothesis) determine the sample size required for the study.[35]

The smaller the size of the treatment effect the study is designed to detect, the larger the required *sample size* will be for a given value of alpha (the maximum significant *P* value) and for a given power. For any given treatment effect, a smaller maximum significant *P* value or a larger power will also require a larger sample size. Surprisingly, clinical studies are often published with negative results even though the studies did not have a sample size sufficient to detect reliably a clinically significant treatment effect.[32-35]

When reading a study, one should look for a statement about the power of the study. Generally, a power of .80 or greater is desirable. The treatment difference tested should not be too large, such that smaller clinically important treatment differences may still exist even after a "negative" result. Power and sample size should be estimated before beginning the study; a "post hoc power analysis" after the data have been collected is not recommended.

Statistical Tests

Depending on the characteristics of the data being analyzed, different statistical tests are used to determine the *P* value (Table 195-3). Student's *t*-test and Wilcoxon rank sum test are used to compare continuous variables (e.g., serum glucose level and respiratory rate) between two groups of patients. If there are three or more groups of patients, one-way analysis of variance (ANOVA) and the Kruskal-Wallis test are used to compare continuous variables between the groups. The chi-square test and Fisher's exact test are used to detect associations between treatment and outcome when both the treatment and the outcome are categoric variables (e.g., placebo vs. active drug, lived vs. died, and admitted vs. discharged).

Table 195-3 Common Statistical Tests

STATISTICAL TEST	DESCRIPTION
Student's *t*-test	Used to test whether the means of measurements from two groups are equal, assuming that the data are normally distributed and that the data from both groups have equal variance
Wilcoxon rank sum test (Mann-Whitney test)	Used to test whether two sets of observations have the same distribution; similar in use to the *t*-test, but does not assume the data are normally distributed
Chi-square test	Used with categoric variables (two or more discrete treatments with two or more discrete outcomes) to test the null hypothesis that there is no effect of treatment on outcome; assumes at least five expected observations of each combination of treatment and outcome under the null hypothesis
Fisher's exact test	Used similar to chi-square test; may be used even when fewer than five observations are expected in one or more categories of treatment and outcome
One-way analysis of variance (ANOVA)	Used to test the null hypothesis that three or more sets of continuous data have equal means, assuming the data are normally distributed and that the data from all groups have identical variances; may be regarded as a *t*-test for three or more groups
Kruskal-Wallis test	Nonparametric test analogous to one-way ANOVA; no assumption is made regarding normality of the data; may be regarded as a Wilcoxon rank sum test for three or more groups

Student's *t*-test and one-way ANOVA are examples of parametric statistical tests. Parametric tests make assumptions about the underlying distribution of continuous variables. Both the Student's *t*-test and ANOVA assume that the data are normally distributed (i.e., distributed in a bell-shaped curve around the central mean) and that the different groups yield data that have equal variance.

When the data to be analyzed are not normally distributed, the *P* value should be obtained using a nonparametric test.[7,8,44] Nonparametric tests are distribution free in that they do not rely on the data to have any particular underlying distribution. The nonparametric alternative to a *t*-test for unpaired samples is the Mann-Whitney test, or Wilcoxon rank sum test. For a statistical comparison of paired measurements, the Wilcoxon signed rank test can be used. The nonparametric alternative to one-way ANOVA is the Kruskal-Wallis test. The *t*-test may be used inappropriately when the data are unlikely to be normally distributed. If it is unclear whether the data are normally distributed, it is preferable to use the nonparametric test.

Confidence Intervals

Often, the primary goal of a clinical trial is not simply to obtain a "yes-no" answer to the question of whether or not a treatment has any efficacy at all but, rather, to estimate the magnitude of the treatment effect. This goal of measuring the effect of the treatment arises if another treatment is known to be effective. On the other hand, if no effective treatment is available, a new therapy may be adopted even if the study shows only the possibility of effectiveness.

When the primary goal of a study is to measure or estimate a treatment effect, the results should be reported using confidence intervals.[45-49] In general, a confidence interval is a range of treatment effects within which the true treatment effect falls with a given degree of certainty. For example, a 95% confidence interval will contain, within its limits, the true size of the treatment effect 95% of the time.[48,49] Confidence intervals are easily calculated for most data.[49] Advanced statistical methods may be required to report confidence intervals for data with non-straightforward (e.g., normal or binomial) distributions.[50]

Situations may arise in which a *P* value and confidence interval can lead to different qualitative interpretations of the same clinical trial results. Suppose one is studying a treatment for a disease that has no known effective therapy. If the 95% confidence interval for the treatment effect ranges from −2 to 30%, where the treatment effect is measured as the change in the absolute percentage of patients with a good outcome, many clinicians would interpret this as showing that although the therapy may have little benefit, it has the possibility of having significant benefit (improving the outcome for up to 30% of patients). Thus, many clinicians would adopt the therapy as appropriate, given the lack of an effective alternative. If classical hypothesis testing had been used to analyze the same data, a nonsignificant *P* value would have been obtained. Many clinicians would then interpret the study as failing to show efficacy and conclude that the therapy was not appropriate for clinical use.[45-49]

When reading a study, one should look beyond the *P* values to the size of the treatment effect found and the width of the confidence intervals. If *P* is reported as significant (usually <.05), one should make sure that the difference is clinically significant. For example, a difference in reduction of temperatures by 0.5° C between two antipyretics may not be clinically significant but would be statistically significant in a sufficiently large study. Issues such as cost, palatability, and adverse effects are likely to be more important in choosing between the two antipyretics. If *P* is reported as not significant (usually >.05), the practitioner should ensure that the confidence interval is not so wide that a clinically important treatment effect is still possible, as in the previous example.

Multiple Comparisons

Whenever two groups of patients are compared statistically, even if they are fundamentally identical, a statistically significant *P* value can be obtained by chance.[7,43] If the maximum significant *P* value (alpha) is .05, there is a 5% chance that a statistically significant *P* value will be obtained when no true difference exists between the two patient populations. This risk of a false-positive *P* value occurs each time a statistical test is performed. When *multiple* comparisons are performed, whether they are "pairwise comparisons" of more than two groups of patients or the comparison of many different characteristics between two groups of patients, the risk of at least one false-positive *P* value is increased because the risk associated with each test is incurred multiple times (Table 195-4).[31,51,52] For a small number of tests, the overall risk of at least one type I error is roughly equal to the maximum significant *P* value used for each individual test multiplied by the total number of tests performed. This rough equality is the basis for the Bonferonni correction.[7,11,31]

The *Bonferonni correction* is a method for reducing the overall type I error risk for the whole study by reducing the maximum *P* value used for each of the individual statistical tests ("test-

Table 195-4 Probability of at Least One Type I Error (False Positive) When Performing Multiple Comparisons*

NUMBER OF COMPARISONS	PROBABILITY OF AT LEAST ONE TYPE I ERROR
1	.05
2	.10
3	.14
4	.19
5	.23
10	.40
20	.64
30	.79

*Between identical groups with $\alpha = .05$.

wise risk"). The desired overall risk of a type I error (usually .05) is divided by the number of statistical tests to be performed, and this value is used as the maximum significant *P* value for each individual test. For example, if five comparisons are to be made, a maximum significant *P* value of .01 should be used for each of the five statistical tests.

The Bonferonni correction controls the overall risk ("study-wise risk") of a type I error at the expense of an increased risk of a type II error. Because each statistical test is conducted using a more stringent criteria for a statistically significant *P* value, there is an increased risk that each test might miss a clinically important difference and yield a *P* value that is non-significant using the new criterion of $P < .01$.

Specific statistical tests have been developed to compare three or more groups of patients, such as the one-way ANOVA, Kruskal-Wallis test, chi-square test, and Fisher's exact test (see Table 195-3). These tests, which do not use the Bonferonni correction, can be useful for detecting differences among three or more groups with relatively high power while controlling the overall risk of a type I error. Their disadvantage is that although they can detect a difference among three or more groups of patients, they do not define *which* pairwise differences are statistically significant. When reviewing positive studies with multiple study groups or multiple comparisons, one should consider the increase in type I error and check for the use of statistical methods accounting for multiple comparisons or appropriate for more than two study groups.

Interim Analyses of Accumulating Data

During a clinical trial, data accumulate sequentially and contain increasingly more information on the effectiveness of the treatments being compared. Often, however, these data are not analyzed until the trial has been completed and all patients have been enrolled. This type of fixed sample size design has the disadvantage of possibly enrolling more patients than are necessary to obtain a reliable result. It is often advantageous to plan one or more interim analyses of the data to be conducted before the full sample size has been reached to determine whether a reliable conclusion can be drawn from the data and the trial can be terminated early. Because this is a type of multiple comparison, such interim analyses must be planned in advance to avoid increasing the type I error rate.[11,52-54] When reading a study reporting results of an interim analysis, one should look to see that the interim analysis was planned and not performed because a casual observation of the data showed interesting or promising results.

Subgroups

Any group of patients is heterogeneous; this is especially true for groups of patients defined by presenting signs and symptoms in an emergency department setting. Some of the patients within such a group may have a more severe form of the disease in question, and some patients may have a coexisting disease that modifies the original disease process. Almost any group of patients can be considered to have multiple subgroups, each of which is more homogeneous than the overall group.

Because of this heterogeneity, a treatment effect that is detected within the entire group may or may not exist for a particular subgroup of the original population, or vice versa.[55-57] Therefore, the data from subgroups of patients are often analyzed separately. In some circumstances, this is important in determining which therapies are most effective in clinically important subgroups of patients.[55,56]

When subgroups of patients are to be analyzed, they should be defined prospectively. Unfortunately, studies with an overall negative result may emphasize a positive treatment effect found only in a subgroup defined after data collection. Although such findings may warrant brief discussion and further investigation, they are unreliable because analyzing data from all possible after-the-fact subgroups requires the use of multiple statistical comparisons, which increases the chance that the finding represents a type I error.

Even if the subgroups were defined before the acquisition of any of the clinical trial data, testing for a treatment effect in each subgroup potentially increases the risk of a type I error. Also, because each subgroup of patients is smaller than the entire study population, the analysis of these subgroups may have low statistical power, which increases the chance of a type II error.

Additional problems can occur if the subgroups of patients are not defined properly.[55,56] A "proper" subgroup of patients is defined by signs, symptoms, or laboratory results that are available at the initial presentation and that are not modified by the treatments being compared. An "improper" subgroup of patients is defined by signs, symptoms, or laboratory findings that can, in principle, be modified by the treatments being administered. For example, in a study that compares different volumes of fluid resuscitation for patients with septic shock, an improper subgroup of patients might be defined by a low systolic blood pressure after fluid administration (the so-called refractory shock group). Conversely, a proper subgroup would be defined by a low systolic blood pressure before any fluid administration.

Because of the possible association between the subgroup assignment and the treatment being administered in an improperly defined subgroup, improper subgroups cannot be used to assess the effectiveness of therapies. It is a common error in many retrospective studies to compare such improper subgroups of patients. When reading a study reporting results in subgroups of patients, one should look to see that the subgroups were prospectively and properly defined and consider whether the characteristics defining the subgroup are available in the emergency department.

Multivariate Models

Multivariate modeling is a statistical tool used to determine the association between two or more independent (predictor) variables and a single dependent (outcome) variable. For example, a multivariate model might be used to determine the simultaneous effects of the patient's age and initial systolic blood pressure on the patient's chance of survival after penetrating abdominal trauma.

The two most common types of multivariate models in medical literature are multivariate linear regression models and multivariate logistic regression models. *Linear regression models* are used to determine the effects of two or more variables on a continuous outcome variable, such as blood pressure. *Logistic regression models* are generally used when the outcome is binary, such as survival (lived vs. died) or admission to the hospital (admitted vs. discharged).

Multivariate models offer several advantages over univariate analyses.[58-60] In a *univariate analysis*, the effect of a single predictor on the outcome is studied in isolation, often using the statistical tests discussed previously. Multivariate models are more akin to "real-life" clinical decision making, whereby a clinician considers several factors such as demographics (e.g., age and gender), history elements, and physical examination findings in deciding a patient's likely diagnosis or clinical course. They can determine which subsets of variables have significant effects on the outcome.

Multivariate models allow one to control for *confounders*, variables associated with the predictor one wishes to study that may also affect the outcome. For example, in studying the effect of alcohol intake on the outcome of lung cancer diagnosis, tobacco smoking may confound the findings because patients with high alcohol intake are more likely to also smoke, and smoking increases lung cancer. A multivariate model that includes both predictors, alcohol intake and smoking, allows one to look at the isolated effect of alcohol intake while holding the effects of other predictors (smoking) constant.[58]

An example of this phenomenon was illustrated in a study of the predictors of mortality in patients with ruptured abdominal aortic aneurysm.[61] Univariate analysis did not reveal the emergency department-to-operating room time interval to be a significant predictor of mortality, whereas in the multivariate model, prolonged emergency department-to-operating room time was clearly a significant predictor. Patients with longer emergency department-to-operating room times likely presented with other findings that made their diagnosis less clear, or the need for intervention appear less urgent, and that were also associated with improved survival, such as higher initial systolic blood pressure and higher hematocrit. In the multivariate model, the effect of emergency department-to-operating room time could be assessed while holding such confounders as initial blood pressure and hematocrit constant.

The disadvantage of multivariate modeling is that it is more complex than univariate analysis. Certain statistical assumptions must be met, such as normal distribution of the outcome and independence of the predictor variables. Sometimes a single data point with an extreme value for a predictor or outcome variable, termed an *outlier*, exerts undue effects in the model. Regression diagnostics should be performed to assess that the statistical assumptions have been met and that no outliers are exerting undue effect.[58]

If two or more predictor variables interact (e.g., alcohol intake exerts an effect only in men, and not women, such that there is an interaction between the two predictors alcohol intake and gender), an *interaction term* must be included in the model. If two or more predictor variables give redundant information (e.g., the predictors age and arrest etiology may give redundant information for the outcome survival from pediatric cardiopulmonary arrest because the vast majority of infants have an arrest etiology of sudden infant death syndrome), the model is said to have *multicollinearity*, and this may require revision of the model.[58]

Authors should report statistics that measure the "goodness of fit," or how well the model explains the observed data. However, the model may display good fit using these statistics and still be missing an important predictor variable or contain more predictor variables than necessary. Ultimately, investigators and readers need to have a basic understanding of the disease under study to determine that all the likely significant predictors have been accounted for in the model.[58]

When reading studies using multivariate models, one should look for the use of independent predictor variables that make clinical sense. One should check the reporting of statistics measuring goodness of fit as well as discussion of regression diagnostics performed.

Importance of Prior Probabilities

Occasionally, statistical tests yield surprising results. Unexpected results are especially difficult to interpret using classic hypothesis testing. Consider a clinical trial that uses a randomized, double-blind controlled design to compare two antibiotics for prophylaxis of infectious complications of tube thoracostomy, with the development of local wound infections or empyema as the primary endpoint. Suppose no statistically significant difference is found in the rate of infectious complications, but a statistically significant difference in mortality is noted between the two treatment groups ($P = .03$). It seems inherently unlikely that the choice of prophylactic antibiotic would affect survival without affecting the infection rate. This is an example in which the apparent conclusion of the trial has a very low *a priori probability* of being true. In other words, the a priori probability that the choice of prophylactic antibiotic could influence survival after traumatic injuries without affecting infection rates is exceedingly small.

Two possible explanations exist for such results. First, the antibiotic may have a true effect on survival by a previously unknown mechanism. The results of the trial would then be a true positive. Second, the results of the study might be a type I error, with the statistically significant P value occurring by chance, even though the antibiotic has no effect on survival. The second explanation seems more likely than the first because the chance that the antibiotic exerted its effect through a previously unsuspected mechanism is small. Thus, despite the fact that a statistically significant P value was obtained, it is unlikely that a true treatment effect exists. Classical hypothesis testing is most likely to be misleading when the alternative hypothesis being tested has a very low a priori probability of being true.[62]

The chance of any particular interpretation of data being correct depends both on the a priori probability of that conclusion being true and on the data supporting that conclusion.[62] An entire branch of statistical reasoning, Bayesian statistics, has been developed to incorporate a priori information quantitatively into the interpretation of data. Bayesian analysis is analogous to usual clinical reasoning in which laboratory test results are interpreted in light of the patient's underlying risk of disease.[62,63] For example, the proper interpretation of nonspecific T wave abnormalities in an electrocardiogram (ECG) depends on the patient from whom the ECG is obtained. If the ECG is obtained from a patient with multiple cardiac risk factors and typical ischemic chest pain, the T wave abnormalities should be considered suggestive of myocardial ischemia. If, on the other hand, the ECG is obtained from a young, healthy adolescent with a very low chance of having cardiac disease, the T wave abnormalities should be considered a normal variant. This use of a priori risk of disease in interpreting data is common in clinical practice. Similar logic should be used in the interpretation of data from a clinical study, especially when the conclusion would have been considered very unlikely before the study was performed.[62-64]

When reviewing studies, one should consider the results in the context of one's knowledge base. Is there scientific basis

for the results? Are the results in congruence with other research in this area? Have the results been corroborated in subsequent studies?

Data Dredging or Torturing

It is surprisingly common for large databases containing many hundreds or even thousands of patient records to be created without clear prior definition of what questions are to be asked of the data. A typical example of this type of database is a trauma registry. When such databases are analyzed, the number of different questions that could be asked (or hypotheses tested) is enormous. In the case of a trauma registry, many tens of variables potentially associated with an adverse outcome are collected. It is tempting to test statistically for an association of each of these variables with survival in an attempt to find combinations of variables that predict outcome. When such exploratory data analyses are performed without clearly defined hypotheses, the analyses may entail a very large number of statistical tests. Each one of these statistical tests carries the risk of a type I error. If enough hypotheses are tested, one is virtually assured of obtaining some statistically significant *P* values, even if none of the variables are associated with outcome.

Multiple comparisons are also made, although only implicitly, when large collections of data are visually inspected by an investigator searching for trends or associations. The investigator may make dozens of mental comparisons, most of which show little obvious difference among the groups being compared. Often, however, some "interesting" differences are noted and brought to the attention of the statistician for statistical testing. The statistician may then find a statistically significant difference but is unaware that many comparisons were made by the investigator in searching for one or a few promising comparisons.

This process of making a large number of implicit or explicit comparisons in searching for possibly important differences is called *data dredging* or, more pejoratively, *data torturing*.[65] Such undirected analyses of large databases virtually always yield statistically significant *P* values that are meaningless. Thus, even when working with large collections of data, it is essential that the comparisons to be made are defined before the inspection or collection of the data and that the total number of comparisons is kept to a minimum. The risk of false-positive results from data dredging is especially high when the hypotheses tested were unlikely to have been chosen before the data collection. In other words, hypotheses that are motivated by the same data used to test them are much less likely to be true than hypotheses that are defined before the data collection, based on independently known associations or concepts.

Not all studies performed on large preexisting databases are examples of data dredging. When reviewing such studies, one should look to see that the hypothesis was defined prior to any manipulation of the database. The hypothesis should be based on independent observations and corroborated by previous research (basic science, animal, or clinical).

Intention-to-Treat Analysis

The effectiveness of any therapy is determined both by the therapy's inherent efficacy and by the emergency physician's ability to administer the therapy to the patient. For example, in the case of an oral medication, the effectiveness will be decreased if patients find the medication's side effects to be intolerable and are noncompliant. Similarly, an invasive procedure will be less effective, on average, if it can only be performed successfully in a minority of patients. To estimate accurately the effectiveness a therapy will have in clinical practice, the emergency physician must properly account for those patients for whom a treatment is initiated but cannot be completed. This is the purpose of an intention-to-treat analysis.[66]

In an intention-to-treat analysis, patients are considered to be members of the treatment group to which they were originally assigned, regardless of whether they take the prescribed medication or the appropriate therapy is successfully administered to them.[66] For example, in a trial that examines the use of an oral agent, patients would be considered to be part of the test group if they were originally prescribed the test medication, even if they freely admit to never having taken any of the tablets.

In a study of out-of-hospital intubation, children were randomized to receive bag-valve-mask (BVM) ventilation alone or BVM ventilation followed by endotracheal intubation (Fig. 195-2).[67] The populations of children were inherently heterogeneous; some children had sudden infant death syndrome, and others had closed head injury. The initial population was well randomized to the two interventions. Children with sudden infant death syndrome were substantially easier to intubate (because of their flaccid state) in the out-of-hospital setting than children with closed head injury, but their overall survival rate was much lower.

The goal of the analysis of the data was to determine the effect of out-of-hospital endotracheal intubation on survival. The correct way to group the data is to consider all patients initially assigned to the endotracheal intubation group as belonging to that group, whether or not they were successfully intubated. Thus, of 199 patients, 116 patients were assigned to the endotracheal intubation group and 83 patients were assigned to the BVM ventilation group. Considering all patients in the endotracheal intubation group, whether or not they were successfully intubated, the overall survival rate is 7.7% (9/116). Similarly, considering all patients in the BVM ventilation group, the overall survival rate is 9.6% (8/83). Thus, the results of the study show a small trend toward improved survival with BVM ventilation.

Alternatively (but incorrectly), one might group the data according to the treatment actually received.[66] In this case,

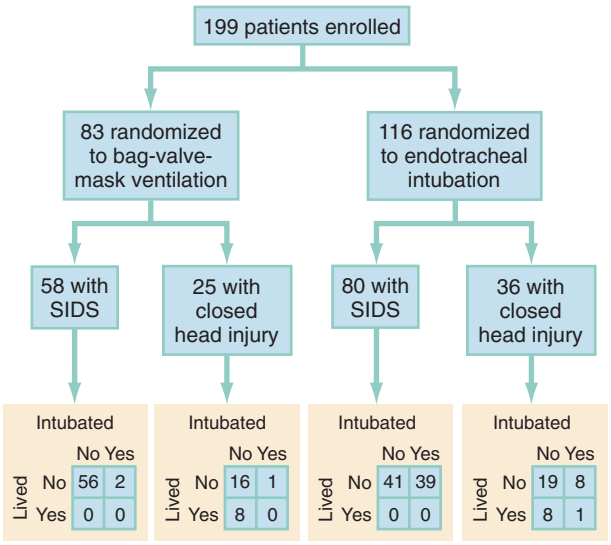


Figure 195-2. Results from a clinical trial comparing the use of bag-valve-mask ventilation with the use of endotracheal intubation in patients requiring advanced airway management in an out-of-hospital setting. SIDS, sudden infant death syndrome.

children initially assigned to the endotracheal intubation group but not successfully intubated might be considered to be members of the BVM ventilation group because that was the treatment they actually received. If one counts all children who received only BVM ventilation, the overall survival rate in that group is 10.8% (16/148). Similarly, if one considers only children who were *successfully* intubated as the members of the endotracheal intubation group, the overall survival rate in that group is only 2.0% (1/51). This is because more children with sudden infant death syndrome are successfully intubated because of their flaccid state, but these children have lower survival rates. Similarly, children with closed head injury may be more combative and difficult to intubate but have higher survival rates than those with sudden infant death syndrome. This type of analysis then suggests that endotracheal intubation is extremely harmful. Whenever there is an association between compliance or the ability to administer an intended treatment and the patient's baseline chance of a successful outcome, analysis by treatment received does not accurately estimate the effect of the therapy in an actual patient population.

Even when an intention-to-treat analysis is used to analyze study results, extrapolation of the results to the general population may be unreliable if the compliance in the general population is lower than that in the study population.[68] This is a common problem because study populations tend to be highly compliant compared with the general population. When reviewing a study, one should look for an intention-to-treat analysis rather than analysis by treatment received. In addition, one should assess whether one's patient population is likely to be as compliant as the study population or, in the case of a procedure, whether one is likely to be able to perform the procedure with the same rate of success.

Meta-analysis

Meta-analysis, or systematic review, is a statistical method for quantitatively combining the results of multiple clinical trials that investigate identical or similar therapies for a specific disease to obtain more accurate estimates of the effectiveness of the treatment.[69] Unlike the traditional review article, a meta-analysis emphasizes the quantitative estimation of the treatment effect observed in all the available studies taken as a whole and usually provides an estimate of the reliability or quality of the results of each study. Meta-analyses can be powerful tools in practicing evidence-based medicine because they collate the results of many or all available studies.[70]

Studies with poor design have been shown to be more likely to find an apparent positive treatment effect. A meta-analysis that includes many poorly designed studies tends to bias the results toward showing a positive treatment effect, even if no such effect exists. Methods for controlling and measuring the effect of poorly designed studies on the results of the meta-analysis have been developed and are often termed *sensitivity analyses*.[71] One method is to first perform the meta-analysis using only studies of the highest quality and then to sequentially include studies of increasingly lower quality to determine whether this causes a directional shift in the results. This approach requires a relatively objective measurement of study quality. Numerous scales and methods for defining study quality have been developed.[72,73]

Publication bias, whereby smaller studies with negative results (i.e., no treatment effect shown) are not submitted for publication, may affect the validity of the conclusions drawn by a meta-analysis.[70] Authors of meta-analyses must strive to include all available trials, often requiring search strategies beyond a simple MEDLINE search. Other methods may include hand searching of relevant review articles and identified studies' reference lists, contacting commercial sponsors and investigators to seek unpublished data, and searching nontraditional bibliographical databases.[74] Problems can arise when pharmaceutical companies withhold data from commercially sponsored trials.[42]

Funnel plots are used to assess for publication bias.[71] Authors plot trial size or quality score against treatment effect. One would expect a funnel-shaped plot, whereby smaller and lower quality trials have a wide base centered around the mean treatment effect, whereas larger and higher quality studies, because they provide more accurate estimates of the treatment effect, make up the narrower top of the funnel. If a portion of the funnel is missing, such as the smaller studies with no treatment effect, this is indicative of publication bias.

Sometimes discrepancies arise between meta-analytic results and subsequent results from a large randomized clinical trial, leaving the reader wondering which results are correct.[75] Discrepancies may be due to bias introduced in the meta-analysis due to heterogeneity of studies included, poor quality of studies included, or publication bias.[75,76] Discrepancies may also be due to differences in inclusion or exclusion criteria or in definitions of outcomes. For example, a meta-analysis of studies that included patients at high risk for preeclampsia found calcium supplementation to be effective prophylactic therapy, whereas a single large trial that included only low-risk patients found calcium supplementation to have no effect.[77] Because of the inclusion of multiple trials, a meta-analysis may incorporate results from thousands of patients, and small treatment effects may reach statistical significance. Such small treatment effects may be false positives arising from inadvertent bias in poorly designed studies or from an artifact of the meta-analysis. Alternatively, the results may be true but clinically unimportant, or they may be true, clinically important, and warrant a change in clinical practice. The discerning reader must consider the size of the treatment effect and possible bias introduced by the meta-analysis methodology and studies included to determine which of the previous conclusions is most likely.

When reviewing a meta-analysis, look for (1) assessment of the quality of trials included, (2) comprehensiveness of the search strategy for studies to include and assessment of possible publication bias, (3) narrow confidence intervals indicating a large number of patients, and (4) the majority of the highest quality studies to agree with the overall conclusion. Even when results are statistically significant, consider whether the size of the treatment effect is clinically significant and, combined with consideration of the costs and risks of the therapy, warrants a change in clinical practice.

CHANGING PRACTICE BASED ON A RESEARCH STUDY

After reading the publication of results from a clinical research study, clinicians must decide whether the results of the study should cause them to change their clinical practice. There are several factors to consider when making this decision, the most obvious being the quality of the study and the results themselves. Other factors to consider include the context of the study within the available literature; the similarity of the clinician's practice setting and the clinician's likely ability to achieve results similar to those in the study; and the risks, benefits, and costs of changing clinical practice.[78]

For the clinician to change clinical practice based on the results of a study, first the study must be high quality. Generally, well-done systematic reviews of multiple randomized clinical trials provide better evidence than a single randomized

Table 195-5 Checklist for Assessing Quality of Research Studies

Longitudinal Interventional Study (Clinical Trial)	
Study population	Inclusion and exclusion criteria well defined, identify a population large enough to be clinically important, and can be applied in the emergency department setting
Enrollment	Enrollment as complete as possible (e.g., consecutive patients meeting enrollment criteria) Missed patients accounted for and not systematically different from study participants (selection bias)
Controlled	Control group similar to intervention group except for treatment received (usually requires randomization) Contemporaneous (not historical) control group
Randomized	Truly randomized allocation of treatments Study personnel unable to influence treatment group assignment Blinded assignment to treatment groups (patients, clinicians, and study personnel all blind to treatment group)
Outcomes	Important potential confounders measured and accounted for by randomization or statistical analyses High compliance with treatments between study groups Small number of patients lost to follow-up and patients lost to follow-up not systematically different between study groups or different than those not lost to follow-up Appropriate, clinically relevant outcome definitions Those determining outcomes blinded to treatment group allocation Outcome difference between groups clinically significant as well as statistically significant Uncertainty in outcome difference quantified by use of confidence intervals or similar methods
Statistical analysis	Correct statistical procedure used (see Table 195-3) Treatment effect to be detected established a priori Sample size calculation performed prior to starting study Intention-to-treat analysis performed (patients analyzed in the groups to which originally assigned, despite actual treatment received)
Conclusions	Limitations and potential biases explained Conclusions not overextrapolated outside study population or study protocol
Additional Considerations	
Multiple comparisons	If multiple study groups or multiple comparisons were made, appropriate statistical procedures to account for this were used Interim analyses were planned a priori and conducted according to plan
Subgroups	Subgroups reported were defined prior to beginning the study (prospectively defined) and limited in number If multiple subgroups studied, statistical procedures are used to account for multiple comparisons or the number of subgroups is small Adequate sample size in important subgroups Subgroups defined by characteristics available to the clinician at initial presentation (proper subgroups)
Multivariate models	Independent predictor variables included in the model make clinical sense and include all important variables "Goodness of fit" statistics reported and regression diagnostics performed
Meta-analysis or systematic review	Comprehensive search strategy used to identify potential trials to include Quality of trials assessed Sensitivity of results to exclusion of lower-quality studies assessed Funnel plot used to assess publication bias Narrow confidence intervals indicate a large number of patients Majority of highest-quality studies agree on overall direction of treatment effect

clinical trial, and randomized clinical trials provide better evidence than observational or cross-sectional studies, while recognizing that some clinical questions do not lend themselves to randomized interventional trials. Also generally, prospective studies provide higher quality information than retrospective studies (e.g., chart review studies). Table 195-5 summarizes key study characteristics to look for when evaluating research studies.

Once the study is determined to be of sufficient quality to believe that the results are valid, those results should be interpreted in the context of related medical literature and experience. The next section of this chapter reviews evidence-based medicine principles to be used in gathering and evaluating evidence from the medical literature. If the current study is an outlier in its conclusions, and equally high-quality studies in the literature do not support changing clinical practice, the clinician should consider waiting for further evidence. Expert guidelines and editorials may help the clinician weigh the available evidence and consider possible causes of differing results between studies.

The clinician must decide whether the study's patient population and health care practice setting is similar enough to the clinician's to make the study results relevant to the clinician's practice (a type of external validity). A study performed in a population from the East Coast demonstrating Lyme disease to be a common cause of meningitis may not be relevant to a clinician practicing in an area with low prevalence of Lyme disease. A study showing the utility of a particular intervention applied within 60 minutes of the patient's arrival to the emergency department may not be relevant to a clinician who works in a health care setting that is unable to provide that intervention in the same time frame. The study's inclusion and exclusion criteria must be closely examined to determine whether the clinician's patient population sufficiently matches the study population, and the study protocol must be examined to determine whether the clinician would be able to

provide similar care. Often, simply by virtue of being a research study protocol with the added advantages of having research personnel focused on patient enrollment and study completion, compliance and follow-up are better than in a typical clinical setting.

Finally, the clinician must perform an informal cost analysis before changing clinical practice. If an intervention is extremely costly, even if it was shown unequivocally to provide some benefit, the costs may outweigh the benefits. Some costs may not be financial, such as potential adverse effects and "opportunity costs," whereby receipt of one therapy results in the loss of the opportunity to receive another proven therapy. Clinical practice should only be changed when, on balance, the potential benefits outweigh the costs. This cost-benefit analysis may differ according to patient population, health care system, and individual circumstances.

EVIDENCE-BASED MEDICINE

Evidence-based medicine (EBM) refers to the systematic gathering of information from the medical literature, often regarding the effectiveness of a particular treatment or the diagnostic accuracy of a particular test, with the intent to apply that evidence in diagnostic or management decisions related to an individual patient.[79,80] Although a specialized vocabulary has evolved, including both old and new terms (Table 195-6), the practice of EBM essentially involves the systematic application of long-established principles of medical literature analysis that until recently were often unknown by or impractical for the medical practitioner.

The fundamental steps in EBM are (1) to define precisely the clinical question being asked in terms that can be addressed by clinical studies; (2) to gather the available medical literature related to the question defined; (3) to assess the relevance, validity, and quality of the evidence contained in each study; and (4) to summarize the available evidence so that diagnostic and management decisions can be made for the individual patient based on the recovered information.[79]

Step 1: Definition of Clinical Question

The first step in the practice of EBM is to define the clinical question clearly. The process of developing a well-formulated clinical question consists of several parts. First, the practitioner must define the population of patients similar to the individual patient motivating the search. The goal is to define a group of patients broad enough that they are likely to have been studied in clinical trials but specific enough that they are similar to the patient. Second, the practitioner must define the treatments or diagnostic approaches being considered. This involves defining the alternate approaches that might be used by reasonable practitioners in similar situations. Third, the practitioner must define the outcome of interest. The outcome of interest should be important to the patient and definable in terms of measurable quantities.

The steps required to define the clinical question in EBM practice are similar to the steps required to define a good hypothesis for a clinical trial: (1) the population for a clinical trial should be clearly defined, (2) the interventions to be used should be reasonable and well-defined, and (3) a

Table 195-6 Terms Used in Evidence-Based Medicine

TERM	DEFINITION
Bias	Tendency to yield a result that lies to one side or the other of the true value; an error that is not centered around zero
Critically appraised topic (CAT)	Summary of the results of an analysis of the evidence relevant to a particular clinical question
Likelihood ratio, negative (LR–)	Probability that a negative test result would occur in a patient with the disease in question divided by the probability that a negative test result would occur in a patient without the disease in question (generally <1)
Likelihood ratio, positive (LR+)	Probability that a positive test result would occur in a patient with the disease in question divided by the probability that a positive test result would occur in a patient without the disease in question (generally >1)
Negative predictive value	Fraction of patients with a negative test result who, in fact, do *not* have the disease in question
Number needed to treat (NNT)	Number of patients who must be treated with the better of two treatments so that one additional "good" outcome is obtained
Odds	Probability of an outcome divided by the probability of the outcome not occurring
Odds ratio	Odds of the outcome of interest occurring in one group of patients divided by the odds of the outcome of interest occurring in another group
Positive predictive value	Fraction of patients with a positive test result who, in fact, *do* have the disease in question
Post-test odds	Odds of the outcome of interest (e.g., particular disease being present), once a particular test result (positive or negative) is known to have occurred; equal to the pretest odds times the likelihood ratio for the test result obtained
Post-test probability	Probability of the outcome of interest once a particular test result is known to have occurred
Pretest odds	Odds of the outcome of interest before the test result is known
Pretest probability	Probability of the outcome of interest before the test result is known
Relative risk	Probability of an outcome in one group divided by the probability of the same outcome in another group
Reliability	Degree with which a clinical trial or diagnostic test is likely to yield consistent results when repeated
Sensitivity	Fraction of patients with the disease in question who have a positive test result
Specificity	Fraction of patients without the disease in question who have a negative test result
Validity, external	Degree to which the results from a study accurately reflect what would happen to similar patients who were not enrolled, including patients at other locations
Validity, internal	Degree to which a study accurately measures the outcomes for the enrolled study population

single clinically relevant and measurable outcome must be defined.

Step 2: Collection of Evidence

The second step in the practice of EBM is to gather the available evidence.[79,81-84] Although a variety of resources might be used to accomplish this, the practitioner generally begins by searching one of the available electronic databases of published medical literature (e.g., MEDLINE). In addition, the physician may want to search one of the databases of known clinical trials (e.g., Cochrane Collaborative) because these databases often include the results from studies that have not been published or are not available on MEDLINE. Initially, the goal is to cast a very wide net to gather as many of the available studies as possible.[79]

Step 3: Analysis of Studies for Validity, Reliability, and Relevance

The third step in the practice of EBM is to analyze each of the gathered studies to determine its validity, reliability, and relevance. The *validity* of a study is the degree to which the results are likely to represent "truth." When the clinical question involves the effect of a therapeutic intervention, a double-blind, randomized clinical trial is generally believed to be the most valid type of study. The external validity of a study may be reduced if the patient population in the study is too dissimilar to the patient motivating the current activity or if the clinical setting is substantially different from the physician's practice setting. Threats to internal validity include inadequate blinding, inadequate or no randomization, and use of historical controls or, worse, absence of controls.

The *reliability* of a study refers to the degree to which the results of the study are likely to be the same if the study were repeated in the same clinical setting using another group of similar patients. A study may have reduced reliability if the sample size is too small or if some of the study procedures were poorly defined and therefore difficult to repeat consistently (e.g., if some interventions were decided by individual treating physicians).

The *relevance* of a study is the degree to which the results, specifically the outcome or outcomes measured, directly address the clinical question being posed. Thus, a study is less relevant if the outcome used in the study is different than the outcome deemed most clinically important. For example, long-term survival may be the most clinically important endpoint for a particular condition, whereas the available clinical trials may use survival at 24 hours as their endpoint. This leaves open to question whether differences observed in survival at 24 hours would lead to differences in long-term survival.

Step 4: Summary of Most Useful Evidence

Based on these considerations, the practitioner of EBM proceeds to the fourth step, summarizing the available evidence from the studies that are the most valid, reliable, and relevant. For each of these studies, the size of the treatment effect or the accuracy of the diagnostic strategies should be noted. In the case of a binary outcome (e.g., lived vs. died or admitted vs. discharged), the *number needed to treat* is a useful measure of the size of the treatment effect.[80] The utility of diagnostic tests is best measured by positive and negative likelihood ratios. Other useful measures of diagnostic accuracy include sensitivity, specificity, positive predictive value, and negative predictive value.[85-87]

Step 5: Application to Patient and Critical Appraisal

Once the available evidence from high-quality studies is summarized, the practitioner is ready to apply the information to the care of the individual patient. To save the information, however, it is useful to create a summary of the entire EBM process, briefly describing each step and the results from each step. Such summaries are sometimes called *critically appraised topics*, which can be saved for future reference.[88] Such "shortcut reviews" performed by others are available in journals or online (http://ebem.org/cgi-bin/index.php), but results must be interpreted in light of the specific study question, comprehensiveness of the search for evidence, and the appraisal process used.[89]

SUMMARY

For the educated reader, the medical literature provides an ever-expanding view of knowledge regarding the effectiveness of medical therapy. A qualitative understanding of the concepts described in this chapter allows the emergency physician to distinguish high-quality studies with results that warrant a change in clinical practice from poor-quality studies that, at best, only suggest important questions to be studied.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 196

Observation Medicine and Clinical Decision Units

Malcolm Mahadevan and Louis Graff, IV

PRINCIPLES OF OBSERVATION MEDICINE

Observation services are an extension of emergency department (ED) services specifically designed to address unmet patient needs. Observation services improve patient care by continuing the evaluation and management of selected ED patients who would otherwise require admission for acute care services. With observation, 80% of these patients can be sent home without the need for hospitalization. The cost to evaluate and treat these patients is half that incurred by admission.[1,2] In addition, the physician threshold for extended evaluation (traditionally provided with hospitalization) is lowered. Patients with atypical signs and symptoms are more fully evaluated to rule out serious conditions such as acute myocardial infarction or acute appendicitis. Thus, in addition to lower costs, there is also a simultaneous decrease in the inadvertent release home of patients with serious disease.[1]

An ED observation unit is a designated area to provide these short-term services for up to 24 hours. Names given to observation units vary and include *chest pain unit*, *clinical decision unit*, and *rapid diagnostic treatment unit*. An ED-based observation unit is not a holding unit. A holding unit stems from hospital overcrowding and is an area where patients admitted to the hospital are held passively until they can be transferred to an inpatient hospital bed.

Two categories of patients benefit from extension of the usual 2- or 3-hour ED visit to up to 24 hours. One group is selected ED patients with a critical diagnostic syndrome (Box 196-1). These are patients whose diagnoses are unclear after the initial ED evaluation and who will benefit from further evaluation during observation. They are either admitted if found to have a serious disease or released home. The second group is ED patients with selected emergency conditions (see Box 196-1). Those patients not successfully treated during the traditional ED treatment period benefit from further treatment in an observation unit.

THE OBSERVATION APPROACH

The traditional ED encounter lasts 2 or 3 hours. The physician performs a history and physical examination and orders laboratory and radiologic tests. When the test results return, the physician either admits the patient to the hospital or discharges the patient home.

The observation approach adds a third option at the completion of the ED evaluation. The patient is treated and further tested for up to 24 hours. After the observation period, patients are then admitted to the hospital or discharged home.

Observation begins with the physician writing the observation orders. The patient is transferred to the observation unit from the main ED. An observation unit chart is started with treatment and investigations are begun. The observation orders include the clinical impression, the reason for observation, the therapeutic evaluation plan, expected outcome, criteria and time frame for disposition, and the physician responsible for the patient's care and disposition. The responsible physician may be the emergency physician or the patient's private physician or a consultant.

Adequate staffing of the observation unit is crucial for the success of the program. The patient receives services for an average 12 to 24 hours beyond the ED visit. The amount of nursing staff required is proportional to the type and intensity of treatments offered, the number of beds, whether the beds are monitored or nonmonitored, and the patient acuity. The average staff is one registered nurse per four to six patients in monitored beds and one registered nurse per six to nine patients in nonmonitored beds. The number of full-time equivalents of nursing staff is calculated to meet these staffing needs.

Staff nursing skills should be broad based and include the ability to care for patients of all ages with a wide spectrum of conditions. They should have the ability to provide critical care when needed and frequent assessments of patients under their care. Nurses should be able to provide prolonged patient and family interactions, including hygiene care, meals, and emotional support. These are all skills present in emergency nurses. When nonemergency nurses are recruited for the observation unit, they should be cross-trained, serving some shifts each month in the ED.

Additional physician staffing is also required for the observation unit. Managing ED patients in the observation unit for an additional 12 to 14 hours requires approximately a doubling of the physician service for a single patient.[3] Calculations of the physician staffing for the amount of additional services will be approximately one full-time equivalent for every 2000 patients observed per year. As with the nurses, physicians in the observation unit must have broad-based knowledge and experience in the management of a wide variety of disease processes.

BOX 196-1 CONDITIONS APPROPRIATE FOR OBSERVATION

Evaluation: Critical Diagnostic Syndromes	Treatment: Emergency Conditions
Abdominal pain	Asthma
Chest pain	Atrial fibrillation
DVT	Congestive heart failure
Gastrointestinal bleed	Dehydration
Syncope	Infections
Trauma	Pneumonia
Blunt abdominal	Pyelonephritis
Blunt chest	
Penetrating abdominal	
Penetrating chest	
Head injury	

DVT, deep vein thrombosis.

Emergency physicians possess the skill sets necessary for observation medicine. The emergency physician is ultimately responsible for the care of the patient and needs to provide clear leadership at all times.

Patients and staff involved in the observation process should be well informed about the goals and benefits provided by the extended service. Well-written, condition-specific, observation protocols ensure a continuum of care, including the transfer of patient care at shift change. The services provided in an ED observation unit are equivalent to inpatient services, albeit at an accelerated pace.

Consultants must be available to the observation unit as they would to any inpatient service. They provide therapeutic and management advice and assist in the serial examinations of patients as requested. The observation unit must identify needs, notify the consultant, assemble all the needed information, and carry out the consultant's recommendations within the shortest time frame possible.

Residents and medical students are included in the functioning of the observation unit because exposure to the observation approach is an integral part of their training program. Emergency residents specifically need training in this area of emergency medicine through clinical practice, lectures, and review of published literature. Residents from other specialties benefit from the exposure by having a better understanding of the role of observation medicine and its applicability in a select group of ED patients.

The amount and type of ancillary personnel needed in the observation unit depend on the size and type of services offered in the unit. An observation unit that offers chest pain evaluation may require different ancillary personnel than one that does not. Personnel may be from outside the department or function full-time in the observation unit (e.g., respiratory therapists). They may also be personnel who have not traditionally been available to the ED, such as psychiatric nurses. Also crucial for proper functioning of the unit are adequate secretarial and clerical staff.

The structure of the observation unit will determine its clinical effectiveness and financial viability. Models for the structure of the observation unit are reviewed in the American College of Emergency Physicians textbook *Emergency Department Design*.[4] An observation unit that is properly designed and located adjacent to the ED will result in a 50% lowered cost compared with traditional hospital admission while providing equivalent or improved quality of patient care.

Designating and empowering an emergency physician to manage the observation unit is critical for success. The complexity of patient care is multiplied when an ED adds observation services. The manager develops and implements clinical protocols for efficient quality patient care. The manager schedules and supervises the observation unit staff and leads the continuous quality improvement team monitoring the observation unit's functioning.

CLINICAL CONDITIONS

Evaluation of Critical Diagnostic Syndromes

Abdominal Pain

Traditional Approach. Abdominal pain is one of the most frequent complaints seen in the ED and accounts for 4 to 8% of all visits.[5] The typical ED evaluation of the abdominal pain patient includes a thorough history, physical examination, and the appropriate diagnostic tests. Within the short time frame of 2 or 3 hours, patients are given a provisional diagnosis and are either hospitalized or sent home.

Problem with Traditional Approach. The ED evaluation is inadequate for many patients, and in 40% of patients the origin of abdominal pain is never determined. Acute appendicitis is the most common abdominal surgical emergency and illustrates the inadequacies of the traditional approach. The diagnosis of acute appendicitis is missed in 20 to 30% of cases (false-negative decisions). In addition, 20 to 30% of patients taken to surgery for acute appendicitis are found to have no abnormality (false-positive decisions).[5]

Observational Approach. With observation, the ED evaluation is extended from 2 or 3 hours to up to 23 hours (Box 196-2). After the initial history and physical examination of the patient, the physician makes an estimate of the probability that the patient actually has appendicitis. Those patients deemed to have an intermediate probability of disease are ideal candidates for the observational approach.[6] Patients who are immunocompromised or pregnant and those at the extremes of age often benefit from observation. Elders in particular benefit from observation because surgical problems are often missed due to diminished diagnostic precision with increasing age.[7]

During the period of observation, the patient is usually kept fasted and hydrated intravenously. Serial abdominal examinations are repeated at 4-hour intervals and laboratory tests repeated as appropriate. Imaging and consultations are also arranged during this time frame. Patients without appendicitis will experience improvement of their pain and have had completion of diagnostic workup and exclusion of surgical disease.[8] Patients should be hospitalized if they have no improvement, have clinical deterioration, or have surgical pathology diagnosed by testing. In patients who do have appendicitis, signs and symptoms will continue or worsen.[8]

BOX 196-2 OBSERVATION CRITERIA FOR ABDOMINAL PAIN

Vital signs stable
Intermediate probability of appendicitis
or
Low probability of appendicitis with risk factor

Risk Factors
Pregnant
Elderly (>65 yr)
Young (<3 yr)

Physician decision-making improves with observation. With observation, physicians' false-positive surgeries can nearly be eliminated. Intensive observation with serial physical examinations at least every 8 hours rather than once per day decreases the false-positive rate from 20 to 30% to 5%.[9,10] The use of a period of observation can also help identify many patients whose diagnoses may be missed during the initial ED evaluation. The appendicitis patient whose diagnosis is missed in the ED often has few clinical signs or symptoms of appendicitis on presentation, making diagnosis difficult.[11] Physicians delaying disposition decisions on questionable cases can avoid these false-negative decisions. Because appendicitis patients develop more signs and symptoms during short-term observation, whereas those without the disorder clear their signs and symptoms, fewer patients have an unclear clinical picture after observation. With observation, a physician's false-negative decisions (missed appendicitis diagnosis) can be significantly reduced.[11] Missing the diagnosis at the time of initial evaluation has been found to delay surgery up to 72 hours.[11] Complications (perforation and abscess formation) occur with delays in making the diagnosis of appendicitis and are proportional to the missed diagnosis rate.[11] Physicians who observe rather than discharge abdominal pain patients with low probability of appendicitis lower their missed diagnosis rate, avoiding potential perforations and abscess formation.

Chest Pain

Traditional Approach. The main focus of the ED evaluation in chest pain patients is twofold: (1) assessment of the probability that the patient has an acute myocardial infarction (AMI) or acute coronary ischemia (ACI) and (2) assessment of the risk of the patient having a life-threatening event. These two assessments help determine the appropriate setting for further testing and monitoring. The probability of AMI is traditionally assessed in the ED with a directed history, physical examination, electrocardiogram (ECG), and an initial measurement of creatine kinase-MB (CK-MB) and troponin I.[12]

Patients with clear evidence of AMI on ECG are potential candidates for immediate reperfusion therapy with either thrombolytics or emergency angioplasty. This subset is at high risk for life-threatening events and best managed in the coronary care setting with close monitoring. This approach has been shown to improve survival in patients with AMI.

Depending on the evaluating physician's threshold, chest pain patients without definite evidence of AMI at initial evaluation are generally admitted to the hospital to confirm or exclude ("rule in" or "rule out") ACI or AMI. Patients who are judged to have low probability of ACI after the initial evaluation are released home for outpatient follow-up.

Problem with Traditional Approach. The poor performance of initial diagnostic tests makes the evaluation of chest pain highly dependent on clinical judgment. The initial ECG is diagnostic in only 50% of AMI patients,[13] and the initial CK-MB measurement has a sensitivity of only 35%.[14] Reliance on physician judgment has resulted in as many as 5% of AMI patients being discharged home.[1,15] AMI patients not identified at the initial evaluation and released from the ED have up to a 25% risk of poor outcome.[1] This has led to emergency physicians erring on the side of admitting patients to the hospital in an attempt to avoid missing the diagnosis of AMI. The increased sensitivity of a more liberal admission policy results in two thirds of patients admitted for chest pain having a noncardiac cause for their symptoms.[1] The cost of this inefficiency has been estimated to be billions of dollars.[4] Despite this liberal admission policy, missed AMI is the leading cause for malpractice suits against emergency physicians.[16]

BOX 196-3 Observation Criteria for Chest Pain

Nontraumatic chest pain
Low probability of disease or risk of adverse event
Stable vital signs
Normal cardiac markers
Nondiagnostic electrocardiogram
Cocaine-induced chest pain

Observational Approach. The emergency physician can use the observation unit to extend the evaluation of patients with chest pain (Box 196-3). When used principally for such a purpose, the observation unit has been termed a *chest pain unit*. The chest pain unit has been successful in increasing the sensitivity and specificity of the evaluation process.[17] Patients with low to intermediate risk of AMI are transferred to the observation unit. Patients unsuitable for observation unit evaluation include those who have a high probability of acute myocardial ischemia as evidenced by unstable vital signs, ECG findings of acute myocardial infarction, or persistent or recurring chest pain consistent with unstable angina.

The physician identifies patients with low probability for ACI by using one or more risk stratification tools. Risk stratification based on classic risk factors alone has been shown to be a poor predictor of short-term outcome.[18] Risk stratification based on ECG findings is more reliable. The Brush ECG criteria[19] classify low risk as the absence of ST segment elevation or depression, T wave inversion or strain, new (or presumed new) Q waves, left bundle branch block, or paced rhythm. Another useful risk stratification tool is the Goldman protocol, which uses history, physical examination, and ECG findings to classify patients into high (>70%), moderate, or low (<7%) risk.[20] The Agency for Health Care Policy and Research criteria use the Goldman protocol to determine the risk of ischemia (low, moderate, or high) and the likelihood of complications.[21] Another tool is the acute cardiac ischemia time insensitive predictive instrument. This uses the ECG findings, patient age, patient gender, and the presence or absence of chest pain to assign a probability of acute ischemia.[22]

Patients admitted to the observation unit are first evaluated to rule out a myocardial infarction. They are serially tested with cardiac markers and ECGs. CK-MB estimation at 0, 3, 6, and 9 hours after presentation has 100% sensitivity, 98% specificity, and 100% negative predictive value in the detection of AMI.[17] Other useful serum cardiac markers are the troponins (I and T) and myoglobin. Patients who present more than 24 hours after symptom onset have negative CK-MB and myoglobin testing findings, but troponin T or I remains positive for up to 6 days. Patients are monitored with continuous ECG monitors equipped with dysrhythmia alarms and memory storage capabilities. Continuous ECG ST segment monitoring can detect dynamic ST segment changes indicative of ischemia, which, when present, indicates an increased likelihood for an adverse cardiac event.[23]

After evaluation to exclude AMI, the patient is evaluated for possible ACI. This may be performed before release of the patient from the observation unit or at follow-up evaluation within 72 hours of discharge. The most common testing modality used is exercise stress testing. Patients who obtain their target heart rate without ECG evidence of ischemia can be released home. They have an annual mortality rate of less than 1%.[24] The performance of exercise testing depends on the ability of the patient to exercise adequately, gender (women have higher false-positive rates), interpretability of the resting

ECG, and the availability of the test. Other testing modalities include stress echocardiography and technetium (^{99m}Tc) sestamibi scanning.

Approximately one third of ED chest pain patients are candidates for observation, with 80 to 85% released home after observation.[1] This reduces the hospitalization rate from 60 to 70% to 40 to 50%.[1] The cost of evaluation with observation is half that of traditional evaluation with hospitalization.[1] The safety and cost-effectiveness of the observation approach have been confirmed in four randomized clinical trials.[1,25-27] The use of observation units for chest pain evaluation is becoming the standard in U.S. hospitals.

Deep Vein Thrombosis

Traditional Approach. The primary objectives for the treatment of deep vein thrombosis (DVT) are to prevent pulmonary embolism, reduce morbidity, and prevent or minimize the risk of developing postphlebitic syndrome. Patients with suspected DVT are usually hospitalized when diagnostic testing is unavailable in the ED or the diagnosis has been confirmed and further management is required. Traditionally, anticoagulation with unfractionated heparin has been administered by continuous intravenous infusion for 5 to 7 days while oral anticoagulation is instituted.[28] The anticoagulant response to this treatment varies markedly among patients, and therefore the dosage must be monitored by coagulation profiles.[29]

Problem with Traditional Approach. New modalities for investigation and treatment have made it possible to manage DVT on an outpatient basis rather than with hospitalization. There are new, less invasive investigative tests and newer therapeutic agents that do not require monitoring of coagulation profiles.

Observational Approach. The role of the observation unit in the management of patients suspected of having DVT is for diagnostic testing as well as initiation of therapy using low-molecular-weight heparin (LMWH) and patient education. Patients often present during the night or on weekends when definitive tests for DVT (e.g., Doppler ultrasonography) are not available. The patient may have a positive D-dimer test finding, which requires a confirmatory definitive test because of its poor specificity.[30] In these circumstances, the patient can be anticoagulated for the short term with one dose of LMWH (enoxaparin 1 mg/kg twice daily) until the diagnosis can be clarified. If the diagnosis is confirmed, the patient can be admitted or treated as an outpatient based on hospital protocol. Patients considered for outpatient management are instructed on how to administer the medication. They are educated about DVT as well as its complications and possible side effects of the LMWH. Appropriate follow-up evaluation is also arranged before discharge. This approach has been shown to result in patients spending 67% less time in the hospital and having greater physical activity and social functioning than their standard heparin cohorts.[31] Outpatient management is not recommended if the patient has proven or suspected concomitant pulmonary embolism, significant comorbidities, extensive ileofemoral DVT, active bleeding, renal failure, or poor follow-up compliance. LMWH is administered by subcutaneous injection in doses adjusted for the patient's weight, without laboratory monitoring.

Outpatient testing with venous compression ultrasonography has become readily available.[32] It is both sensitive and specific for the diagnosis of proximal (femoropopliteal) DVT.[33] When repeated compression ultrasonography was compared with impedance plethysmography, compression ultrasonography was superior in detecting DVT.[32] It has been proven to be a safe method of deciding when to administer anticoagulation.[30] The D-dimer assay has also been shown to be a useful adjunct to compression ultrasonography in outpatient testing.

Upper Gastrointestinal Bleeding

Traditional Approach. Most patients with upper gastrointestinal bleeding (UGIB) are admitted to the hospital after initial ED assessment and stabilization.

Problem with Traditional Approach. UGIB is a common and potentially life-threatening condition with an overall mortality rate of 6 to 10%.[34] However, most cases of UGIB are self-limited, and 80% of patients have only one bleeding episode.[35]

Observational Approach. Not all patients with UGIB do poorly, suggesting that outpatient management is possible if patients at high risk for further bleeding can be identified. Prognostic indicators include the patient's age, heart rate, systolic blood pressure, orthostatic changes in blood pressure or pulse, color of stool or emesis, anticoagulant use, and comorbid conditions.[36] In an attempt to refine diagnostic accuracy, risk assessment, and disposition, several scoring systems have been developed. Some practitioners use hemodynamic stability, intensity of bleeding, and underlying health status as predictors of rebleeding, need for surgery, and mortality.[37] Some use a period of observation with early endoscopy to identify the patient who can be discharged early. Patients found to have clean-based ulcers at endoscopy have a rebleeding rate of 0 to 2% and virtually never require urgent intervention for recurrent bleeding and can be released. Utilization of this approach has been proven to be both safe and cost-effective, including a prospective clinical trial that demonstrates that 24% of patients can avoid hospitalization with cost savings of $990 per patient.[38]

Syncope

Traditional Approach. Syncope is caused by a spectrum of disease entities. ED evaluation includes a thorough history, physical examination, and 12-lead ECG. Patients with evidence of possible myocardial ischemia or a cardiac cause of their syncope are usually admitted to the hospital because cardiac syncope has a high risk of death (up to one third will have a poor outcome).[39] Those with concomitant heart failure have a 25% mortality rate at 30 days.[40] On the other hand, patients with noncardiac syncope have a low risk of adverse events (1%) and can be managed as outpatients.[39]

Problem with Traditional Approach. Attempts to exclude a possible cardiac cause for syncope usually result in 25 to 40% of patients being hospitalized for further evaluation and management.[40] The traditional ED evaluation identifies only 50% of patients with a serious cause of their syncope,[41] and this has often resulted in a liberal admission policy; however, one study found that only 12% of patients had a serious cause for syncope that justified hospitalization.[42]

Observational Approach. Extending the ED with a period of observation is a strategy to reduce unnecessary hospitalizations (Box 196-4). Patients with a cardiac syncope have a poor prognosis and need to be identified. These patients often do not have chest pain as a symptom, but they may have ischemic changes on ECG, arm or shoulder pain, or prior history of exercise-induced angina. A "rule out myocardial infarction" evaluation with serial ECG and enzyme measurement may be the only way to identify these patients. Prolonged ECG monitoring can point to a specific cause in up to one fifth of patients, with half of all abnormalities detected in the first 24 hours.[43] The 1-year risk of dysrhythmia or death in syncope patients correlates with four factors: an abnormal ECG, history of ventricular dysrhythmia, history of heart failure, and age older

BOX 196-4 OBSERVATION CRITERIA FOR SYNCOPE

Low to intermediate risk of adverse event
Stable vital signs
Loss of consciousness <10 min
No focal acute neurologic signs
Normal electrolytes and blood count
No objective evidence of ischemia or injury by electrocardiographic or cardiac markers
No history of congestive cardiac failure

than 45 years.[44] Patients with none of these risk factors have only a 4.4% rate of adverse events at 1 year and may be appropriate for outpatient evaluation. In contrast, patients with three or four risk factors have a 58% adverse outcome rate and should be admitted to the hospital. Patients with one or two risk factors have intermediate risk and may be appropriate for outpatient evaluation with observation. Patients unsuitable for observation include those who have abnormal neurologic findings, abnormal ECG or cardiac enzymes, history of trauma before syncope, or loss of consciousness for longer than 15 minutes.

During the observation period, serial examination of patients is carried out, including vital signs, with the majority of patients safely discharged home without hospitalization.[45] Continuous ECG monitoring, consultation, serial cardiac enzymes, and further tests such as two-dimensional echography of the heart, psychiatric assessment (associated with up to 25% of cases of syncope), and tilt table testing should be arranged when appropriate. Tilt table testing is a useful investigation in patients with recurrent syncope when heart disease is not suspected. Up to 60% of patients who have vagally mediated syncope can be detected by this modality.[46] The period of observation can also identify patients with cardiac dysrhythmias or sinus pauses who are candidates for more extensive diagnostic evaluation in the hospital.

Transient Ischemic Attack

Traditional Approach. More than 300,000 people suffer a transient ischemic attack (TIA) each year.[47] For most patients, it is a transient event that will not recur if they take an aspirin each day. However, for 1 in 10 patients, it is a warning sign that they will suffer a stroke unless they are appropriately evaluated and treated.[48] Traditionally, the patient is assessed in the ED with history, physical examination, lab tests, ECG, and head computed tomography (CT) scan. Most patients are then hospitalized for serial clinical evaluations, a neurology consultation, carotid Doppler testing, echocardiography, and cardiac monitoring.[49]

Problem with Traditional Approach. The problem with the traditional approach is that most TIA patients are admitted to the hospital. After 3 days of evaluation, few will be found to have carotid or heart disease requiring an intervention. The opportunity for improvement is to develop a more cost-effective approach.

Observational Approach. Observation is an alternative to hospitalization for those TIA patients with a negative ED evaluation for whom the emergency physician still has concern. An accelerated diagnostic observation protocol was compared to acute care hospitalization in a prospective randomized clinical trial. All patients had full evaluation in the observation unit or inpatient floor.[49] Clinical outcomes were equivalent with the two approaches, but the observation unit was more efficient (length of stay, 25 hours vs. 61 hours) and had lower costs ($890 vs. $1547).[50]

Trauma

There are more than 30 million trauma-related ED visits annually.[51] Patients with serious injuries require hospitalization for definitive therapy, whereas those with minor injuries can be discharged after treatment in the ED.

The problem with the traditional ED approach is that many patients have injury patterns or actual injuries that fall somewhere between the two scenarios just described. If these patients are released home, there is a risk that some will have poor outcomes as a result of missed injuries. On the other hand, because the majority of these patients do not have serious injuries, admitting this group to the hospital will result in a waste of scarce health care resources.

Observation units have been found to be an efficient and useful strategy in the evaluation and management of trauma victims.[52] With observation, selected patients can be evaluated further to determine the need for admission. One study of 20,000 patients treated in an ED observation unit during a 12-month period found that 3% of patients were admitted to the observation unit, with 86% safely discharged home without the need for admission.[52]

Blunt Abdominal Injury

Traditional Approach. Current ED management of blunt abdominal trauma (BAT) patients includes history taking, physical examination, blood analysis, plain radiography, ultrasonography, and CT scan. After initial stabilization and exclusion of other major injuries in the ED, most patients suffering BAT are admitted to the hospital for further evaluation and monitoring.

Problem with Traditional Approach. The initial evaluation is inadequate for accurate disposition of many BAT patients. One third of patients who do not have any symptoms or signs suggestive of intra-abdominal injury may actually have significant injury.[53] Also, because none of the present modalities for investigating the presence of injury is 100% sensitive, many patients with initially negative investigations are hospitalized.

Observational Approach. BAT patients appropriate for observation include those who, after initial evaluation, have no clear evidence of serious injury on physical examination but remain at risk for serious injury because of the mechanism of the injury or the individual's personal health (e.g., on anticoagulants). Evaluations during observation for up to 23 hours include repeat physical examinations, laboratory testing, imaging, and specialty consultations. Patients are hospitalized if their condition deteriorates during the observation period or if, after testing, they are found to have serious internal injury. Patients with negative findings on evaluation and the ability to tolerate feeding can be safely released home. Patients who have sustained significant BAT by mechanism of injury or have equivocal findings on abdominal examination should undergo further testing, such as CT scan, to detect occult injury.[54] Ultrasonography (focused assessment by sonography in trauma [FAST]) is being increasingly used in the initial evaluation of the patient with BAT because it is a rapid noninvasive study with 99% specificity for detecting abdominal injury.[55] However, it cannot be used to rule out serious intra-abdominal injury because a meta-analysis of 62 trials found the overall sensitivity of FAST to be only 79%.[55] CT alone is not adequate to rule out serious injury, with sensitivity of only 80 to 95%.[56] Observation alone in patients with BAT is not sufficient because up to 20% of patients with significant injury will not have abdominal tenderness or develop it even after a short period of observation.[56] Thus, the prudent approach to

patients with significant BAT without clear evidence of intra-abdominal injury is the utilization of a diagnostic test, such as CT, together with a period of observation.

Penetrating Abdominal Injury

Traditional Approach. Most patients with penetrating abdominal injury are hospitalized for further evaluation, which may include wound exploration in the operating room and additional diagnostic testing.

Problem with Traditional Approach. Many of these hospitalizations are unnecessary because only two thirds of patients with abdominal stab wounds have a breach of the peritoneum, and two thirds of these do not sustain visceral injury.[57]

Observational Approach. A period of observation can identify those patients who do not require surgical intervention. Patients undergo serial examinations by the physician, further diagnostic testing, and specialty consultation. Those without evidence of peritoneal perforation or visceral injury after evaluation are sent home after proper wound care.

The conservative approach to penetrating abdominal wounds was developed in the 1970s. Those without peritoneal breach can be safely sent home after wound care and a period of observation without the need for hospitalization. Those with stab wounds to the abdomen with peritoneal breach but a negative finding on diagnostic laparoscopy or imaging with CT scan or ultrasonography can be safely managed in an observation unit.[57-60] Patients with significant intra-abdominal injuries identified during observation are admitted; the 70 to 90% of patients without such injuries are released home.[57,61] Gunshot wounds are often more difficult to evaluate than stab wounds. However, patients who appear to have tangential gunshot wounds can avoid surgery with observation if they are hemodynamically stable and have initial negative test findings. Penetrating wounds manifest differently in children than in adults.[62] Initial diagnostic testing with CT and diagnostic peritoneal lavage in children detects only 50% of injuries, with only 30% of patients having localized tenderness. Observation can help avoid unnecessary surgery in patients without injury and avoid missing the diagnosis in those without clear evidence of injury.

Blunt Chest Trauma

Traditional Approach. Many patients who have a history of blunt chest trauma (BCT) in high-velocity accidents are admitted to the hospital to rule out myocardial or pulmonary contusion.

Problem with Traditional Approach. Very few patients admitted to the hospital with BCT from high-velocity accidents without initial evidence of injury are found to have serious injury during hospital evaluation.[63]

Observational Approach. Patients with isolated BCT who are otherwise stable with normal ECG are suitable for a period of observation to exclude myocardial injury. During the period of observation, patients are monitored with continuous ECG, specifically assessing for dysrhythmias. Serial enzyme determinations, such as troponin level, are also carried out to detect evidence of myocardial injury. Those patients with sternal fractures or other evidence of higher risk of intrathoracic injury should be considered for transesophageal echocardiogram.[64] Those with negative evaluations during the period of observation are released home for outpatient follow-up.

Much of the period of observation in patients with BCT focuses on identifying the presence and prognosis of myocardial contusions. The overall incidence of cardiac-related complications in these patients is low (0.1%).[65] Patients with blunt cardiac trauma who have complications usually have an abnormal ECG or abnormal CK-MB or troponin level at presentation. Conversely, a normal ECG and CK-MB and troponin levels correlate with the lack of clinically significant complications.[66,67] Patients who have isolated chest wall contusions and no abnormality of serial CK-MB, troponin, or ECG abnormalities or dysrhythmia during 6 to 12 hours of ECG monitoring are unlikely to have complications.

Penetrating Chest Injury

Traditional Approach. Patients with penetrating chest injury present with a spectrum of severity ranging from severe life-threatening injury requiring urgent operative intervention to hemodynamically stable patients with a negative initial evaluation. Most patients presenting with penetrating chest injuries are admitted to the hospital. Often, even those with a negative initial evaluation are admitted to exclude serious injury to the heart, lungs, and the major blood vessels.

Problem with Traditional Approach. The accuracy of this approach is limited because many patients with evidence of injury are admitted but have no further deterioration or need for medical therapy. On the other hand, there are those without obvious evidence of serious injury who will have a negative outcome if released after the initial evaluation.

Observational Approach. A period of observation combined with diagnostic imaging can improve clinical decision-making. Patients with evidence of a small pneumothorax or hemothorax can be monitored for deterioration. Those without evidence of serious injury but of concern to the physician can likewise be observed for complications. During the period of observation, patients are monitored for respiratory or hemodynamic compromise. Repeat chest radiographs can detect the development of hemothorax or pneumothorax. Patients who deteriorate during the period of observation require hospitalization.

The safety and efficacy of managing asymptomatic stab wound victims in the short-term observation unit have been clearly established in multiple studies.[68-70] A total of 5 to 15% will require hospitalization because of development of delayed pneumothorax, subcutaneous emphysema, hematemesis, or pneumopericardium.[68] In addition, the majority of stab wound victims with small pneumothoraces or hemothoraces will be treated solely with a chest tube without further surgical intervention. Major trauma centers can manage many of these patients as outpatients without hospitalization with use of a period of observation.

Patients with penetrating wounds to the cardiac area of the chest (between the nipples), the region of the great vessels, or the thoracoabdominal area usually require more intensive testing to exclude injury not only to the heart, major vessels, and lungs but also to the diaphragm and the abdominal organs. Echocardiography may detect pericardial fluid or tamponade in patients with penetrating injury in close proximity to the heart.[71-73] Patients with small effusions may be observed in a monitored setting with serial examinations, whereas patients with large effusions should be treated surgically.[73] Patients with a negative echocardiography can be observed in the observation unit. Even patients with small effusions may have sustained a serious injury, so the intensity of monitoring needs to be high.

Treatment of Emergency Conditions

Asthma

Traditional Approach. More than 20 million people in the United States are afflicted with asthma. Acute exacerbation of asthma

is a common ED presentation, with estimated annual admissions exceeding 450,000.[2] Traditionally, therapy is provided in the ED for 2 to 4 hours, consistent with national guidelines.[74] Initial assessment includes history, physical examination, oxygen saturation, and peak expiratory flow rate (PEFR) or forced expiratory volume in 1 minute. Treatment consists of beta-agonists, magnesium sulfate, and steroids, where appropriate. Patients who do not improve after 3 or 4 hours of treatment are hospitalized for further management.

Problems with Traditional Approach. With this approach, one third of patients are hospitalized.[75] This translates into an estimated medical cost of $1.2 billion annually.[76] Another pitfall in the traditional ED treatment of asthma is that short encounter times do not allow for identification and aggressive treatment of patients with a higher tendency for relapse. This leads to repeat ED visits, additional medical costs, and diminished quality of life.

Observational Approach. An alternative to hospitalization for patients failing ED treatment is the use of an extended, short-term intensive protocol for 8 to 12 hours in an observation unit.[2] With extended treatment, 80% of such patients can be discharged home.[2] Inclusion criteria for observation unit management are failure of standard initial management and continued respiratory distress and good response to initial management but high risk for relapse (Box 196-5). Increased risk of relapse is indicated by a history of numerous asthma-related ED or clinic visits within the past year, using more outpatient medications (including home nebulizers), and longer duration of symptoms.[75] Exclusion criteria include unstable vital signs, evidence of impending respiratory failure ($Paco_2$ > 45 mm Hg, Pao_2 < 55 mm Hg), or severe airway restriction (PEFR < 80 L/min after first inhaled beta-agonist treatment). Exclusion criteria also include factors that correlate with unsuccessful treatment during observation. These include a previous ED visit in the past 10 days, previous intensive care unit admission or intubation, hospitalization during the previous year, three or more ED visits in the past 6 months, use of oral steroids for more than half of the previous year, and peak flow after the third beta-agonist treatment that is less than 32% of predicted.[2]

Therapy in the observation unit is a continuation of ED treatment with handheld nebulized beta-agonists every 2 to 4 hours and repeated steroids at 6 hours after initial therapy. Patients are managed up to 23 hours but generally are admitted to the hospital if they do not respond within 12 hours. Patients are released from the observation unit when they are not in respiratory distress, have minimal residual symptoms, and have a PEFR of 70% or greater of predicted or personal best. Before discharge, there should also be patient educational activities and assessment of inhaler techniques. Patients should be initiated into daily diary keeping as well as a log of PEFR before and after treatment. Appropriate follow-up monitoring should also be arranged.

A prospective randomized clinical trial of observation versus traditional hospitalization of ED asthma patients who did not "break" in the first 3 or 4 hours of ED treatment found no difference in relapse rates at 8 weeks, but it found significant differences in the length of stay (9 hours vs. 59 hours), patient satisfaction, and quality of life and also cost savings of $1000 per patient.[2] Patients treated in the observation unit had higher patient satisfaction according to four parameters: received service wanted, recommendation of service to others, satisfaction with service, and overall satisfaction compared with inpatient care. Observation unit patients also reported fewer problems with care received, communication, emotional support, physical comfort, and special needs. Observation has also been shown to have utility in the management of pediatric patients with asthma. Of those who would otherwise require hospitalization, 30 to 70% can be successfully managed as outpatients with the observation unit.[77]

BOX 196-5 Observation Criteria for Asthma

Failed standard emergency department management
Stable vital signs
Peak flow after third beta-agonist >32% predicted
No concomitant illness (e.g., pneumonia, heart failure)
Successful emergency department management but high risk for relapse
Risk of relapse
- Second visit to emergency department within 10 days
- Previous intubation or intensive care unit admission
- Hospitalization in past year
- Three or more emergency department visits in 6 mo
- Oral steroids for more than 6 mo

Atrial Fibrillation

Traditional Approach. Atrial fibrillation is a relatively common condition that occurs in 2 or 3% of adults and is the most common sustained cardiac dysrhythmia in patients presenting to the ED.[78,79] The goals in management of acute atrial fibrillation are hemodynamic stabilization, symptom relief, prevention of thromboembolism, resolution of the dysrhythmia, and exclusion of serious pathologic causes of the dysrhythmia. The majority of patients who present to the ED with new-onset atrial fibrillation or acute atrial fibrillation are hospitalized.[80]

Problem with Traditional Approach. Recently, the necessity of admitting the majority of patients with acute atrial fibrillation has been questioned. It is recognized that new-onset atrial fibrillation for most patients is a transient dysrhythmia with no serious precipitants and a benign prognosis. One retrospective analysis of 216 patients admitted for atrial fibrillation found that one third of patients did not actually require admission to the hospital.[80]

Observational Approach. The observational approach to new and acute atrial fibrillation has been validated in a number of clinical trials.[81] The period of observation is usually 8 to 12 hours. During observation, patients are treated to rectify their dysrhythmia and evaluated for serious precipitants of their condition. After observation, 80 to 90% of patients can be discharged home without hospitalization.

Observation extends the ED evaluation of the patient for underlying medical conditions that may have precipitated the arrhythmia (Box 196-6). These include AMI, congestive heart failure, electrolyte abnormalities, and hyperthyroidism. AMI is excluded as a precipitant with serial cardiac enzyme testing over 6 to 9 hours. The period of observation is also used to

BOX 196-6 Observation Criteria for New-Onset Atrial Fibrillation

Normal electrolytes and blood count
Stable vital signs
No physical finding of heart failure
Jugular venous distention, ankle edema, S3 gallop
No history of heart failure
No symptoms of myocardial ischemia
No objective evidence of ischemia by electrocardiographic or cardiac markers

detect structural heart disease with the use of echocardiography where appropriate. Patients are excluded from observation if they exhibit hemodynamic instability, comorbid conditions, heart failure, chest pain, or significant coronary artery disease.

Observation is also used to extend the treatment period of the patient. The spontaneous conversion rate for patients with acute atrial fibrillation is 50 to 70% within the first 24 hours.[82] Patients who spontaneously convert have a low rate of structural heart disease.[82] Those who do not spontaneously convert in the first 8 hours can be converted chemically or electrically.[83] After cardioversion, the patient needs to be observed. This is especially true for patients converted with the newer class III antidysrhythmic agents (e.g., ibutilide), which have the potential for serious side effects, such as torsades de pointes (5% of patients), sinus bradycardia, and sinus arrest.[83,84] The risk of thromboembolism in patients with atrial fibrillation of less than 48 hours' duration is less than 1%, so patients who convert can be released home without need for anticoagulation.[85]

Congestive Heart Failure

Traditional Approach. Congestive heart failure (CHF) is highly lethal, with 37% of men and 33% of women dying within 2 years of diagnosis. The 6-year mortality rate is 82% for men and 67% for women, which corresponds to a death rate fourfold to eightfold greater than that of the general population of the same age.[86] Patients who present to the ED with CHF undergo history taking and physical examination and investigations, including chest radiography. Treatment is begun with oxygenation, diuretics, inotropic agents, and vasodilators where appropriate. Most CHF patients treated in the ED are eventually hospitalized.

Problem with Traditional Approach. CHF is highly prevalent, affecting approximately 1% of people in their 50s and increasing progressively with age to afflict 10% of people in their 80s.[86] It is an increasing problem; more than 2 million Americans have the disease and 400,000 new cases are diagnosed each year.[86] One third of patients with CHF require hospitalization each year, one third get readmitted each year, and one third die within 2 years.[86] The annual cost to the health care system of managing patients with heart failure admitted to the hospital has been estimated at $28 billion.[47] Between 80 and 87% of patients diagnosed with CHF are hospitalized.[87-88]

Observational Approach. Observation is a strategy to avoid hospital admission of patients with CHF that results in great cost savings (Box 196-7). Selected patients can be safely managed in an observation unit.[87-89] Such patients include those with a high probability of successful treatment with short-term extension of the ED visit. Patients should also have low severity of illness. They should not be hypoxic, should not have pulmonary edema or hypotension, and should not have objective evidence of AMI, hemodynamic instability, or serious comorbid conditions.[87-89] B-type natriuretic peptide (BNP) has been used to streamline decision making. Patients with BNP levels between 100 and 500 pg/mL are suitable candidates for observation unit care because a large proportion of these patients should be able to be discharged home. The test has a negative predictive value of greater than 95% and a positive predictive value of 70 to 95%. It correlates with pulmonary capillary wedge pressure, and because its half-life is less than 30 minutes, serial measurements during observation can evaluate the effects of therapeutic interventions.[90,91]

Therapy and evaluation are a continuation of the initial 2- or 3-hour ED visit for up to 23 hours. Continuous ECG monitoring for dysrhythmias is performed because up to 30% of CHF patients have dysrhythmias.[92] Inotropic agents can be infused and the patient educated about preventable causes of the exacerbation. Therapy may include continuous infusion of loop diuretic (0.05–0.1 mg/kg/hr) titrated hourly to a net fluid balance of –1 mL/kg/hr. In most patients with acute exacerbation of chronic CHF, the cause of their exacerbation is preventable, such as failure to take their medications or dietary indiscretion. The opportunity to provide patient education, medication review, and consultations with dietary and social service where necessary is fully utilized because this has been shown to improve compliance with therapy.[93] Patients are discharged home when their symptoms are adequately controlled, all reversible causes of morbidity are treated or stabilized, and adequate outpatient support and follow-up care are arranged. With observation, the focus of ED care can shift from providing only episodic treatment for CHF patients to providing more comprehensive and preventive care.[93]

Compared with acute care hospitalization, observation has a much reduced length of stay and significantly lower costs.[93]

Dehydration

Traditional Approach. Dehydration is often the presenting symptom of an underlying disease state and can affect the very young to the very old. Patients are often admitted for intravenous hydration to correct fluid and electrolyte imbalances or for further diagnostic evaluation.

Problem with Traditional Approach. Patients with dehydration are often hospitalized because short ED visits do not allow for full correction of fluid and electrolyte disorders or extensive evaluation for underlying causes. A common cause of ED return visits is dehydration due to initially inadequate therapy and evaluation.[94]

Observational Approach. The goals of observation unit therapy are adequate treatment of fluid and electrolyte abnormalities and identification of the underlying cause of symptoms. Appropriate patients for observation include those with acceptable vital signs and mild to moderate dehydration (Box 196-8). They should have self-limited or treatable causes not requiring hospitalization, with mild to moderate electrolyte abnormalities. Another group of patients appropriate for observation are those with hyperemesis gravidarum. Patients unsuitable for observation are those with unstable vital signs, cardiovascular compromise, underlying chronic medical illness, severe dehydration or electrolyte abnormalities, or associated condi-

BOX 196-7 OBSERVATION CRITERIA FOR HEART FAILURE

High probability of successful treatment
Physician clinical judgment that observation is safe and nil or one risk factor: hypoxia, hypotension or syncope, anasarca, pulmonary edema, or respiratory distress
No objective evidence of ischemia or injury: electrocardiographic or cardiac markers

BOX 196-8 OBSERVATION CRITERIA FOR DEHYDRATION

Stable vital signs
Limited or treatable cause of illness
Mild to moderate electrolyte abnormalities
No cardiovascular compromise
Hyperemesis gravidarum

tions not amenable to short-term therapy (e.g., bowel obstruction, diabetic ketoacidosis, and sepsis). Interventions include intravenous rehydration, serial examination and vital signs, and antiemetics. The patient is released home when there are acceptable vital signs, resolution of symptoms, tolerance to oral fluids, and normal electrolytes. If the patient does not fulfill the discharge criteria or serious underlying pathology is found, he or she is admitted to the hospital.

Infections

Pneumonia

Traditional Approach. Each year, approximately 600,000 patients are hospitalized with pneumonia, at a cost of almost $4 billion.[95] Many of these patients are admitted after initial ED evaluation. Physicians often rely on subjective criteria such as clinical appearance when selecting patients for hospital admission.[96]

Problem with Traditional Approach. There is great variation in the admission rates for pneumonia.[97] Emergency physicians tend to overestimate the risk of death in patients with pneumonia, which has resulted in many low-risk patients being hospitalized unnecessarily.[96]

Observational Approach. Observation is appropriate for those patients whom the physician is concerned may not do well as outpatients (Box 196-9). This concern can be based on physician clinical judgment or a severity of illness index. Fine and associates[96] developed a prediction rule to estimate which pneumonia patients would be at higher risk for mortality. They reviewed medical records of more than 14,000 patients hospitalized with pneumonia and identified 14 key clinical variables (e.g., age, sex, coexisting illness, vital signs, and mental status) and 7 key laboratory variables (e.g., blood urea nitrogen, glucose, hematocrit, arterial oxygen, and pleural effusion on chest radiograph). They then weighed each of these variables into a cumulative point total (PSI index) and assigned each patient to one of five mortality risk groups ranging from class I, which includes patients with a low risk (60-day mortality risk <0.5%) who can be treated as outpatients, to class V, which includes patients with a high risk (60-day mortality risk >30%) who should be treated as inpatients. Patients in class III are at intermediate risk, and traditionally one half are admitted and one half are treated as outpatients. By use of the PSI to risk stratify patients, physicians can avoid hospitalization of many low-risk patients.[98] Intermediate-risk patients (class III) are good candidates for a period of observation to clarify their need for hospitalization. Irrespective of the patient's risk as judged by PSI, some patients are not appropriate for observation but should be admitted: those with immunocompromise, pulmonary tuberculosis, high suspicion of pulmonary embolism, or hypoxia (Table 196-1).

During observation, patients are treated with antibiotics, oxygen therapy, and pulse oximetry monitoring. Hydration is given either orally or intravenously. After 10 to 12 hours of treatment in the observation unit, the patient is reevaluated and a decision about disposition is made. Patients who deteriorate during the observation period or have a saturation of less than 90% on room air after observation should be admitted to the hospital.

BOX 196-9 Observation Criteria for Pneumonia

Low risk of death (1–5%): clinical judgment or severity index
No risk factors for poor outcome: immunocompromised, neuromuscular disorder, pulmonary tuberculosis, cystic fibrosis
No objective evidence of ischemia or injury: electrocardiographic or cardiac markers

Table 196-1 Use of Pneumonia Severity Index (PSI) for Admission Decisions

Step 1: Assess Arterial Oxygenation for All Patients
Is pulse oximetry < 90% or Po_2 < 60 mm Hg?
YES: Inpatient therapy recommended **NO:** Go to Step 2

Step 2: Are Any of the Following Present?
- Patient 51 years of age or older
- Coexisting medical conditions listed in Step 3
- Physical examination findings listed in Step 3

YES: Go to Step 3 **NO:** Risk Class I, go to Step 4

Step 3: Compute Risk Score (Sum of Applicable Points)

Risk Factor	*Points*
Demographic factors	
Age in years (age –10 for women)	
Nursing home resident	10
Coexisting medical conditions	
Neoplastic disease	30
Liver disease	20
Congestive heart failure	10
Cerebrovascular disease	10
Renal disease	10
Physical examination findings	
Altered mental status	20
Respiratory rate ≥ 30/min	20
Systolic blood pressure < 90 mm Hg	20
Temperature < 35° C or ≥ 40° C	15
Pulse ≥ 125/min	10
Laboratory and radiographic findings	
Arterial pH < 7.35	30
BUN ≥ 30 mg/dL	20
Sodium < 130 mEq/L	20
Glucose ≥ 250 mg/dL	10
Hematocrit < 30%	10
Po_2 < 60 mm Hg or O_2 sat < 90%	10
Pleural effusion by chest x-ray	10
Total score (sum of all points)	

Step 4: Recommended Initial Site of Treatment

Risk Score	*Risk Class*	*Treatment Site*
Not applicable	I	Outpatient
<71	II	Outpatient
71–90	III	Observation
91–130	IV	Inpatient
>130	V	Inpatient

BUN, blood urea nitrogen.

Pyelonephritis

Traditional Approach. Pyelonephritis is a serious infection that frequently results in hospitalization for intravenous hydration and antibiotic administration.

Problem with Traditional Approach. Many patients who are admitted with pyelonephritis are judged retrospectively not to have had the condition. In addition, many patients with pyelonephritis are at very low risk for developing complications.

Observational Approach. Observation is appropriate for adult, nonpregnant women who appear to have uncomplicated pyelonephritis. Patients receive an initial dose of intravenous antibiotic, intravenous fluids, antiemetic, and antipyretic. Laboratory tests include complete blood cell count, urinalysis, and

urine and blood cultures. Patients who are clinically stable and able to tolerate oral fluids are released home after 12 hours of treatment.

Outpatient management of selected pyelonephritis patients with observation has been shown to be safe and effective. Only 5 to 25% of patients require hospitalization after the period of observation.[99,100] At 3-week follow-up examination, 2 to 6% have developed complications and require hospitalization.[99,100] With a period of observation and careful follow-up evaluation, selected patients with pyelonephritis can be successfully managed without hospital admission.[100]

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 197 Emergency Ultrasound

Vivek S. Tayal and Casey M. Glass

PERSPECTIVE AND DEFINITIONS

Emergency ultrasound (US) is the simultaneous performance and interpretation of sonographic examinations at the bedside of the patient in a focused manner to diagnose, monitor, and treat emergency medical conditions.[1,2]

Emergency US is an emergency clinician-performed study.[1,3,4] Although the operator is typically an emergency physician,[1,3,4] he or she may be an emergency physician assistant, nurse practitioner, emergency medicine (EM) resident, or trained emergency nurse or paramedic—all under the supervision of a trained, credentialed emergency physician.[5,6] Emergency physicians who have advanced training in ultrasound imaging are also known as emergency sonologists. Emergency US is typically performed in hospital emergency departments but may also be performed in other areas of the hospital, emergency stand-alone centers, out-of-hospital mobile transport such as ambulances or helicopters, disaster scenarios, military engagements, international rescue work, and remote settings such as space, sea, or land centers with limited or no medical access.[1,7-14]

Emergency US is a different paradigm in which the same physician or clinician performs and simultaneously interprets the examination in addition to integrating the results in the clinical scenario.[1,15] This is unlike other specialties, such as radiology, cardiology, and obstetrics and gynecology, that often use a trained technologist to perform the examination and a physician in that specialty to interpret or "read" the examination.[16,17]

Emergency US examinations are typically focused examinations of an area of the body, organ system, or physiologic pattern or goal-directed investigations of an emergency symptom or sign. Not all pathology will be detected by such examinations. Additionally, the physics of ultrasound may limit the detection of pathology or create pseudopathology that causes diagnostic difficulty. The primary limitation of such studies is the experience and skill of the performing physician.

HISTORY

A half century of scientific work in many countries produced the initial clinical medical uses of US in the 1950s by physicians interested in its advantages over traditional imaging, including noninvasiveness, lack of ionizing radiation, and superior resolution.[17]

Emergency physicians started using US in the 1980s as a way to rule out emergent "silent" diagnoses, such as ectopic pregnancy, intraperitoneal hemorrhage, hemopericardium, cholelithiasis, renal colic, and aortic aneurysm. A model curriculum was created by a Society for Academic Emergency Medicine (SAEM) task force that initiated formal guidance for emergency US programs.[18,19] Due to resistance within hospitals from traditional imaging specialties such as radiology and cardiology, the American Medical Association House of Delegates, led by the American College of Emergency Physicians (ACEP), carried a resolution suggesting that hospital credentialing committees follow specialty-specific guidelines for US-based credentialing.[20]

Specialty-specific guidelines were created in 2001 by ACEP that specified emergency US scope of practice, primary applications, training pathways, the number of procedures required for training prior to credentialing, quality assurance and documentation guidance, and training course outlines.[1] Today, more than 95% of emergency medicine residencies teach US, and approximately 30% of community hospitals have instituted bedside US performed by emergency physicians.[21,22] New applications are being described, including procedural guidance.

TRAINING, CREDENTIALING, AND ACCREDITATION

Emergency US is one of three competency assessments required of EM residents by the Residency Review Committee for Emergency Medicine.[6,23,24] For emergency physicians in practice, initial training often takes place through continuing medical education courses followed by a period of proctoring or supervision.[1,25]

APPLIED ULTRASOUND PHYSICS AND INSTRUMENTATION

By definition, US is sound greater than 20,000 Hz; US is a longitudinal, mechanical, and directional wave that is transmitted through mediums. US is kinetic energy, so all users of this technology should use the ALARA (as low as reasonably achievable) principle by performing procedures only when needed and limiting the time of sonographic investigation.[26]

US waves are characterized by their amplitude (deflection from a baseline), wavelength (the wave cycle distance, usually measured in microns), and frequency (the number of cycles per second). Modern diagnostic US transducers emit at millions of cycles per second or MHz. The frequency of the transducer can be adjusted to improve image quality; lower

frequencies penetrate deeper tissue at the expense of resolution, whereas higher frequencies improve resolution but cannot penetrate deeper structures.

M-mode or motion mode displays received waves over both time and distance and is used to calculate rates, speeds, and distances by sending a steered one-dimensional line across tissue. The most familiar display is B-mode or brightness mode, which graphs the amplitude of reflected US waves as shades of gray from black to white on a monitor screen. As sound hits reflective interfaces, it returns to the transducer at higher amplitudes than waves that continue through tissue. In addition, sound can be attenuated, refracted, and reverberated away from the transducer. These reflections or lack thereof create a brightness graph that is depicted in two planes creating the two-dimensional image. One can adjust the brightness of the image by changing the overall gain or change the amount of gain at certain depths, which is called time-gain compensation (TGC). This allows for a more discrete amplification of sound at different levels. By increasing overall gain or amplification and TGC at different levels, one can adjust for the loss of returning information.

US resolution can be described as axial, in the long axis of the transducer, or lateral, perpendicular to the long axis of the transducer. Typically, higher probe frequencies produce higher axial resolution. The focus of the transducer is the image area where the US beam produces the best lateral resolution. The area from the probe to the focus is called the near field, and that from the focus to the end of the image is called the far field. The best imaging with maximum reduction in artifacts occurs at the focus.

Focal zones can be increased for more resolution, but frame rate (the speed at which the screen updates the image) will decrease, causing a slow-motion image that is poor for imaging moving tissues. One can also change from a sector transducer (a curved abdominal or phased array transducer) to a linear transducer for better lateral resolution on the edges of the transducer.

Some machines allow the adjustment of dynamic range, which is the ratio of initial intensity and final intensity of returning echoes. Adjusting dynamic range allows for more contrast (e.g., echocardiography) or more gray scale (e.g., soft tissue). Harmonics is another technology that listens for multiples of the frequency sent out and often cleans up images near the screen such as in the gallbladder, apex of the heart, or soft tissue of skin.

Doppler US shows the velocity of moving structures, typically red blood cells, thus representing flow. Color flow Doppler shows direction (by red or blue colors representing flow in opposite directions) and velocity of flow (by degrees of brightness of the color, where lighter is higher velocity). Power Doppler or power angiography is also a representation of velocity of flow, but it describes only the presence of flow and not direction.

Gray scale US has the best resolution when the direction of the probe and sound waves are perpendicular to the object because the sound is reflected back up to the transducer. Doppler US has the best resolution with the probe parallel or less than 60 degrees from the direction of blood flow. This often means realignment by tilting of the probe to create better imaging based on the mode of US.

Other US terms and artifacts commonly used are listed in Table 197-1.

Table 197-1 Common Definitions

Window—soft tissue where transducer is placed to interrogate tissue in the body
Anechoic—without sounds (black)
Echogenic—with sounds (white)
Hyperechoic—with more reflected sounds than adjacent tissue (more echogenic)
Hypoechoic—with less sound than adjacent tissue (less echogenic)
Shadowing—sound blocked by a reflective barrier
Enhancement—more echogenicity due to increased velocity of sound, typically behind a fluid-filled structure such as the bladder or gallbladder
Reverberation—an artifact that results from multiple reflections at a given interface, often in parallel
Mirror image—a propagation speed artifact that repeats images that are beyond a strong reflector (e.g., diaphragm), creating a mirror image
Lateral cystic shadowing—a refraction artifact seen on the edge of cystic structures causing an artificial shadow
Beam width artifact—a volume-averaging artifact causing artifactual echoes in the inferior aspect of anechoic structures or spaces

EQUIPMENT

A variety of US machines are available, including palm size, laptop, cart based, and combination devices. US machines have controls for gain, depth, and freeze and have print or acquire image controls. Additional controls including TGC, frame rate, measurement, dynamic range, M-mode, power Doppler, color directional Doppler, spectral Doppler, patient ID, transducer selection, and image review. Images are produced in digital stills, digital video clips, thermal paper stills, or DVD or video recordings.

Modern multifrequency probes can select among several US frequencies to maximize either tissue penetration or image quality depending on the application. Probe design and footprints (the actual transducer surface area touching the patient) can be divided into three categories: flat linear array probes, curved linear array probes, and phased array probes. Flat linear probes give a square or rectangular picture with excellent lateral resolution at the expense of width of field. Curved linear array probes, which give a wider field of view at the expense of lateral resolution, are usually used for deep tissue penetration applications, such as evaluation for pregnancy or abdominal aortic aneurysm. The endocavitary probe is a highly curved linear array probe that is most commonly used for endovaginal evaluation. Phased array probes offer a smaller footprint than curved linear array probes and were originally developed for cardiac evaluations, but they can also be used for abdominal studies. They offer excellent image quality for the evaluation of moving structures but with worse resolution of static structures.

APPLICATIONS AND CATEGORIZATION

In 1994, SAEM categorized US applications broadly into abdominal, cardiac, obstetric/gynecologic, and special applications.[18] In 2001, ACEP developed specialty-specific guidelines that categorized applications more narrowly to include trauma, pregnancy, abdominal aortic aneurysm (AAA), and cardiac for pericardial effusion and cardiac activity, biliary, renal, and procedural applications.[1] Recent studies have investigated emergency US in diagnosing deep vein thrombosis (DVT) and pneumothorax.[4] New applications include soft tissue, ocular, and musculoskeletal studies.[27-32] Therapeutic applications of transcranial Doppler are being studied by emergency physicians.[33]

The most common uses of US by community emergency departments in decreasing order are trauma, cardiac (cardiac arrest and pericardial effusion), AAA, pelvic, biliary, procedural, renal, and DVT.[22]

Procedural guidance can assist many emergency percutaneous procedures such as vascular access, torso cavities evacuation (e.g., thoracentesis, paracentesis, and pericardiocentesis), arthrocentesis, lumbar puncture, abscess drainage, nerve blocks, and other percutaneous procedures.[4]

Emergency US is used in clinical pathways or algorithms to rapidly identify or exclude emergency medical conditions.[34,35]

Trauma Ultrasound

The trauma US exam is also called the focused assessment with sonography in trauma (FAST) examination.[4,36,37] The trauma examination originally focused on the peritoneal space, as an evaluation for hemoperitoneum, using the right flank, left flank, and pelvic windows for detection of dependent peritoneal fluid and pleural effusion.[38,39] Newer versions include the EFAST (extended FAST) for the evaluation of potential pneumothorax and FASTER for evaluation of the extremities.[40]

The FAST exam is based on the premise that fluid within the peritoneum circulates throughout the abdomen and pelvis and settles in dependent spaces.[41,42] The volume of fluid required for a positive US depends on the site of injury and site of sonographic detection but generally 250 mL or greater is required, and nearly 600 mL of fluid is necessary to cause a positive flank stripe when fluid is from the pelvis.[43] Pericardial fluid is contained within the parietal and visceral pericardium. Once a certain volume is reached, the pressure in the pericardial space increases exponentially, causing pericardial tamponade.[44] Generally, 50 mL is required to cause a hemodynamic compromise in a patient without prior pericardial inflammation. However, tears in the pericardium that communicate with the pleural space or even the peritoneum can cause false-negative exams. Pleural fluid can be detected by US, but this is dependent on the position of the body.[45] Pneumothorax detection is based on the absence of the normal sonographic sliding of the visceral and parietal pleura.

The indications for the torso trauma US examination (often called the EFAST) include the need to detect any of the following in an injured or ill patient: pathologic free intraperitoneal fluid (typically hemoperitoneum, uroperitoneum, bile, or bowel contents), hemopericardium, hemothorax, or pneumothorax.[46] Typically, fluid in the peritoneum, pericardium, and pleural cavity is anechoic, but it can have echogenicity with clotting, depending on the age of the clot. Compared with other fluid-filled structures in the abdomen and pelvis, peritoneal free fluid generally has sharp edges and an irregular shape, whereas most visceral or vascular structures have intrinsically smooth oval contours and less abrupt edge detail.

The FAST technique uses a low- to middle-frequency probe (2–5 MHz) to evaluate dependent peritoneal spaces, pleural spaces, and the pericardium. Within the peritoneum, dependent spaces include the following, grouped by tissue window: right flank—this evaluates the hepatorenal space, also called Morison's pouch (Fig. 197-1), the right subphrenic space, and the right costophrenic angle; left flank—this evaluates the perisplenic space between the diaphragm and spleen, the splenorenal space, the perirenal space, and the left subphrenic space; and suprapubic view—this view is performed by placing the transducer superior to the pubic bone with a full bladder to visualize the pouch of Douglas in females and the retrovesical space in men. Extra views include the paracolic gutters inferior from the flank views and medial from the iliac spine to visualize free fluid surrounding the bowel.[47]

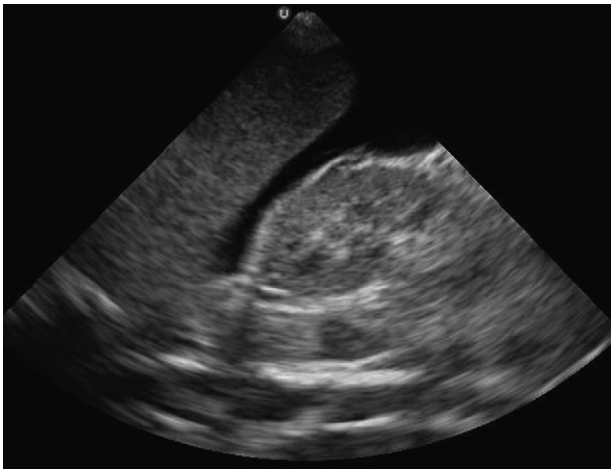


Figure 197-1. Free fluid in the peritoneum in Morison's pouch seen from right flank.

The typical cardiac views include the transverse subcostal images, which visualize the four cardiac chambers and pericardial space, whereas the sagittal subcostal view assesses the pericardial space and the inferior vena cava with regard to its collapsibility and diameter, indicating right heart pressures. A good alternative in patients with long chest walls or obesity is the parasternal view, which assesses the anterior and posterior pericardial spaces.

For pleural fluid, the superiorly angled flank views allow visualization of the costophrenic angles. The evaluation for pneumothorax utilizes either a low-frequency probe at a shallow depth or, more typically, a high-frequency probe for better resolution, placed at the anterior chest in the second intercostal space for anterior pneumothorax and at the axilla for large pneumothoraces and pleural effusion.

The sensitivity of the FAST exam ranges from 60 to 99%, and its specificity ranges from 80 to 99%.[48-50] The large range of sensitivity is related to the comparative gold standard used for each study, with clinical endpoints suggesting higher accuracy. The trauma US does not capture every peritoneal injury, although the need for intervention on undetected injuries has not been studied. Randomized, controlled trials show reduced morbidity, time to operating room, and charges for patients with US use during resuscitation,[51,52] and a positive US increases the odds ratio of laparotomy.[53]

Patients with traumatic pericardial effusions have reduced times to operative management and reduced mortality rates with US,[44] but the mediastinal injuries more common in blunt trauma have not been assessed without transesophageal echocardiography.[54] Pleural effusion has been studied with variable accuracy.[55] US diagnoses pneumothorax with excellent sensitivity and specificity compared to plain chest x-ray and variable accuracy compared to computed tomography scanning.[56]

There are certain patient populations in whom FAST evaluation has limited performance. In patients with penetrating chest injuries, the use of the FAST exam seems to be efficacious for both pericardial and nearby peritoneal injuries,[57] but in patients with purely anterior penetrating trauma to the abdomen, the sensitivity of trauma US is poor because significant bowel injuries can occur without significant hemoperitoneum.[58,59]

The accuracy of the FAST exam in children is very similar to that in adults, but caution is advised because many pediatric

injuries can be observed or treated nonoperatively with angiography.[60] In obstetric patients, the few observational studies that have been performed have shown reasonable sensitivity and specificity, although abruption and fetal viability may necessitate an earlier operative course.[61]

In patients with pelvic fractures, there have been mixed results, with sensitivity from 20 to 80%.[62-64] More important, the detection of free fluid in an unstable patient with a pelvic fracture may be due to uroperitoneum from bladder injury rather than hemoperitoneum from vascular injury, clouding the decision for laparotomy versus pelvic embolization.[64] In addition, retroperitoneal injuries to the genitourinary tract are not assessed with four-quadrant FAST exam.

Pelvic Ultrasound

Pelvic US by emergency physicians was initiated to address one of the epidemics of the modern era—ectopic pregnancy.[65-69] Typically, pelvic US is used to confirm intrauterine pregnancy, thereby indirectly excluding ectopic pregnancy in the vast majority of patients.[70,71] Other uses during pregnancy include detection of fetal viability, incomplete abortion, ectopic pregnancy, and molar pregnancy. Nonpregnancy pelvic US uses include the detection of tubo-ovarian abscesses, masses, and hemoperitoneum in the hemodynamically unstable patient.[72]

Indications for sonographic evaluation of the first-trimester pregnant patient include symptoms or signs that suggest an ectopic pregnancy, molar pregnancy, fetal demise, or for dating the pregnancy. Standard definitions for intrauterine pregnancy describe a gestational sac with a yolk sac or fetal pole within the fundus of the uterus (Fig. 197-2).[70] An embryonic or fetal demise has US findings of a fetal pole greater than 5 mm without fetal heart rate or a gestational sac greater than 20 mm in diameter without a fetal pole. A molar pregnancy appears as an echogenic, cystic uterus with disorganized echoes and is associated with high β-hCG concentrations without the sonographic finding of intrauterine pregnancy. Findings of an ectopic pregnancy include a chorionic ring or gestational sac with evidence of a yolk sac or fetal pole outside the uterus or in an abnormal location in the uterus, such as the cornu or cervix.[73] Excluding the groups of IUP, embryonic demise, molar pregnancy, and ectopic pregnancy, there is a class called "indeterminate," which may account for 20% of pregnant patients presenting to the ED in the first and early second trimesters. Heterotopic pregnancies can occur at a rate of 1/5000 and be detected by the same techniques and definitions.[74]

Pelvic US is performed by either transabdominal or endovaginal techniques. The transabdominal technique utilizes a low-frequency transabdominal transducer placed over the lower abdomen suprapubically. Ideally, the patient has a full bladder, which provides a sonographic window, but this may not be necessary if the uterus is large or the patient is thin. Advantages of the transabdominal technique include wider field of view, detection of large pelvic masses, and greater depth of field. In the endovaginal technique, the transducer is placed in the vagina, optimally with an empty bladder to visualize the same structures. Endovaginal transducers are high frequency, providing excellent axial resolution but poor penetration of distant structures. Early intrauterine yolk sacs and fetal poles within gestational sacs may be detected more clearly, and ectopic pregnancies can be identified with more accuracy. Endovaginal US can detect small (7 mL) amounts of peritoneal fluid. Endovaginal US in the hemodynamically compromised patient has replaced culdocentesis for detection of ruptured ectopic pregnancy.

Emergency physician-performed pelvic US has reduced the morbidity of ectopic pregnancy by shortening the time to diagnosis and operating room treatment, and it has resulted in greater initial detection of abnormal pregnancy, reduced emergency department patient throughput times, and increased patient satisfaction with emergency department care.[66,68,75-78]

Pelvic US in nonpregnancy states has shown good accuracy for tubo-ovarian abscess and improved decision-making for female patients with right lower abdominal pain.[79]

Cardiac Ultrasound

The use of cardiac US by emergency physicians is presentation and symptom specific and focused in nature. Indications include cardiac arrest, possible pericardial effusion, trauma, chest pain, hypotension, and for procedural guidance. Cardiac US is often combined with other applications to form algorithms and protocols for certain symptoms or signs, such as dyspnea or hypotension.

Cardiac US is performed through the transthoracic and transabdominal windows using small curvilinear or phased array transducers. Typical views include the subcostal four-chamber and long-axis views, parasternal long-axis view, parasternal short-axis view, and apical four-chamber view. Although most emergency physicians are very comfortable with the subcostal view from the FAST exam, the parasternal long-axis view is a good alternative and good window for left ventricular assessment.[80,81] In addition, the apical four-chamber view provides excellent comparison of the right and left ventricles in terms of size and function.

Cardiac US performed by emergency physicians shows good accuracy in detection of pericardial effusion (Fig. 197-3),

Figure 197-2. Intrauterine pregnancy with fetus on endovaginal scanning.

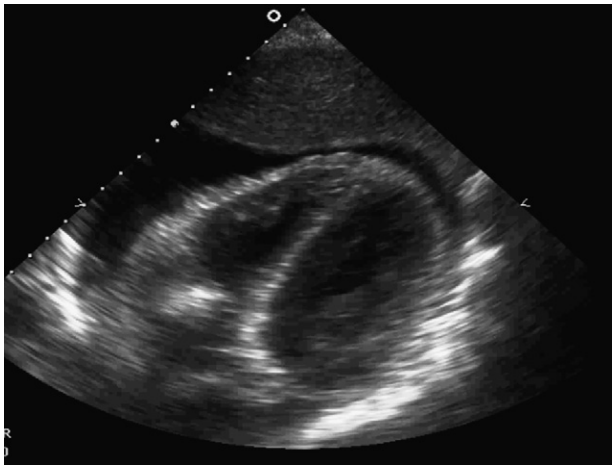


Figure 197-3. Pericardial effusion in subcostal view.

assessment of left ventricular function, and evaluation of patients with undifferentiated shock. In addition, aspects of cardiac US are being used for the assessment of intravascular volume status, cardiac output, and in the evaluation of dyspnea.

In cardiac arrest, US detects ventricular motion in both asystole and pulseless electrical activity (PEA).[82-86] In asystole, two studies have shown poor prognosis in the absence of sonographic ventricular activity.[84,85] Use of cardiac US in PEA and near-PEA states can be diagnostic for pericardial effusion.[82] Cardiac US can detect pseudo-asystole by revealing ventricular fibrillation or coordinated cardiac contractions without a palpable pulse.[86] Cardiac US can detect ventricular capture when the patient is paced, transcutaneously or by a transvenous pacer. It can also identify pneumothorax, another treatable cause of cardiac arrest.[83]

Emergency cardiac US is diagnostic for detection of both medical and traumatic pericardial effusions.[87] In patients with dyspnea, pericardial effusion is detected with excellent accuracy.[88] In trauma, use of cardiac US reduces time to operative intervention and reduces mortality in patients with penetrating cardiac injury.[44] Detection of effusions in blunt trauma has also been described. Patients with cardiac US performed by emergency physicians for pericardial effusion have significantly reduced hospital length of stay and charges.[89]

Cardiac US is used for detection of pericardial effusions, chamber enlargement, and global activity in chest pain syndromes.[90] In chest pain, US has been studied for the evaluation of pericardial tamponade, pulmonary embolus, cardiogenic shock, aortic dissection, pneumothorax, and bony chest wall fracture.[87,91,92]

US protocols have been developed to evaluate patients with undifferentiated hypotension.[93-97] Cardiac US windows with the addition of abdominal views can assess for effusion, global ventricular activity, ventricular chamber size, inferior vena cava (IVC) size and respiratory change, peritoneal fluid, and abdominal aortic aneurysm. Such a combined US protocol rapidly narrows the differential diagnosis. Sepsis is the most common diagnosis for patients with hyperdynamic ventricular activity.[97]

Central pressures can be estimated by examining the IVC size and collapsibility.[98,99] Several studies show that this technique has good accuracy in assessing blood loss and as a marker of hypovolemia. Correlation studies have show moderate agreement between CVP and IVC measurements, with actual cardiac qualitative assessment as good as or better than the IVC measurements.

Cardiac US is also a procedural guide for placement of transvenous pacer wires and for pericardiocentesis. Transvenous pacer wires are often placed through central veins, and placing them into the right ventricular apex can be difficult. US facilitates placement by imaging the wires in real time as they pass through the tricuspid valve and approach the apex of the right ventricle. US can also document ventricular capture. The probe is placed in the subxiphoid space for both applications.

Abdominal Vascular Ultrasound

Abdominal aortic aneurysm is another silent disease for which US has been used by emergency physicians for diagnosis and management of patients with flank, abdominal, or back pain and for evaluating unexplained hypotension in the older patient.[100-103] The use of US to detect aortic dissection in the chest and the abdomen has been described but is not common.[104-106]

The technique involves imaging of the aorta from the subxiphoid space to the umbilicus to evaluate for dilation above a diameter of 3 cm (Fig. 197-4). Due to the increased incidence of infrarenal aneurysm, the technique must visualize the aorta from diaphragm to the aortic bifurcation. Fusiform aneurysms are more common, but saccular aneurysms can also be present, necessitating imaging in both the transverse and longitudinal planes.[107] If an aneurysm is found, a peritoneal view of Morison's pouch is performed to detect intraperitoneal fluid.

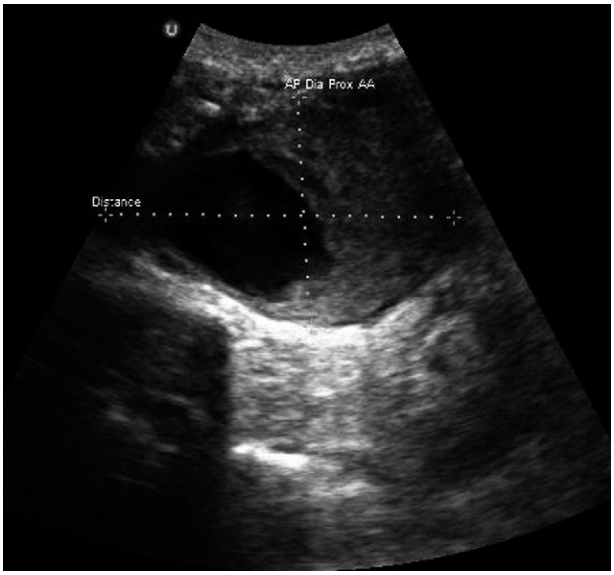


Figure 197-4. Large abdominal aortic aneurysm with echogenic intraluminal clot.

Emergency physician use of US for AAA detection has shown good accuracy compared to other imaging modalities and laparotomy.[100-102,108] It also has management implications in older patients with lower back pain, where elimination of the presence of AAA can lead to other management decisions. Screening for AAA in the emergency department with US has been shown to be effective.[109]

Aortic dissection may be detected by a combination of abdominal and cardiac scanning.[106] Anywhere in the aorta, a linear echogenic flap across the lumen of the aorta is suggestive of dissection, with color Doppler possibly detecting different flows on either side of the flap. The cardiac US signs include unexplained pericardial effusion; a dilated aortic root; aortic insufficiency; and a linear echogenic flap seen in the ascending aorta, aortic arch (via a suprasternal notch), or descending aorta.

Biliary Ultrasound

Biliary US to detect gallstones and associated cholecystitis was one of the early applications in emergency medicine.[110-112] The sonographic technique involves a modified biplanar approach to the right upper quadrant to evaluate the gallbladder and surrounding area. A complete evaluation includes visualizing the common bile duct. The diagnosis of cholelithiasis is made after identification of echogenic foci within the gallbladder lumen with shadowing (Fig. 197-5). Other image patterns include stones that will not shadow, sludge, and the wall echo sign of a gallbladder full of gallstones. Signs of cholecystitis include a dilated gallbladder, increased gallbladder wall thickness, sonographic Murphy's sign, and pericholecystic fluid. A nonmobile stone in the gallbladder neck is highly suggestive of eventual cholecystitis.[113] A common bile duct

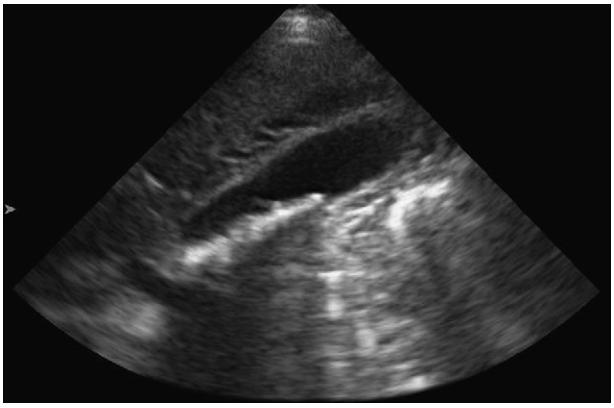


Figure 197-5. Echogenic layering gallstones seen in gallbladder with posterior shadowing.

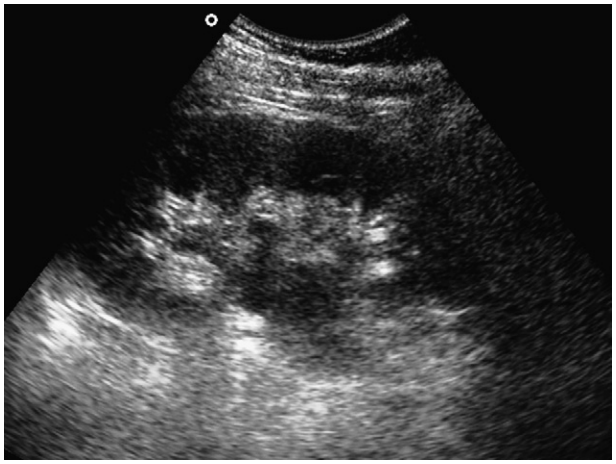


Figure 197-6. Hydronephrosis in renal pelvis and calyces.

greater than 6 mm in people younger than 60 years and less than 10 mm in elders may indicate choledocholithiasis. Biliary US has been shown to be fast and accurate, with a sensitivity of 94% and a specificity of 96% in detecting gallstones.[110,114,115] Biliary US has a primary role compared to nuclear medicine testing.[112]

Renal Ultrasound

Renal or urinary tract US is one of the early applications for the diagnosis of urinary obstruction, resulting in hydronephrosis. The lack of ionizing radiation and the rapidity of renal US make it an attractive option for the investigation of unexplained flank, back, or groin pain.

The performance of renal US includes biplanar views of the kidneys with emphasis on dilation of the calyceal system and pelvis of the respective kidney. In addition, visualization of the bladder can diagnose secondary hydronephrosis from an obstructed bladder stone and may demonstrate nonobstructive bladder jets through the use of Doppler US. The windows for the two kidneys are very similar to the trauma flank series with the exception that the patient may be rolled on the opposite side so that the transducer may be placed more posteriorly on the back if needed. The bladder view is performed suprapubically, and calculations of volume may be made with on-machine calculators or by formulas.

Renal US has a sensitivity of 83% and a specificity of 92% in detecting hydronephrosis (Fig. 197-6).[116,117] Genitourinary tract obstruction protocols have shown great sensitivity in eliminating renal obstruction from a differential diagnosis.[118] Bladder US is useful for detection of a full bladder and the presence of a Foley catheter and also for procedure guidance (superpubic aspiration or Foley placement).[119-124]

Extremity Vascular Ultrasound

The swollen extremity often requires sonographic imaging to assess for DVT. Emergency physicians commonly utilize compression US to rule out DVT.[125-128]

The two-level compression technique involves visualizing the compressibility of the common femoral and popliteal veins, whereas the three-level technique adds visualization of the compressibility of the junction of the superficial femoral and deep femoral veins (Figs. 197-7 and 197-8). Upper extremity veins have been investigated, but this is not a common application because Doppler is needed for sampling of the subclavian vein, which is not compressible under the clavicle.[129]

Figure 197-7. Deep vein thrombosis with layering clot in popliteal vein seen on compression ultrasound.

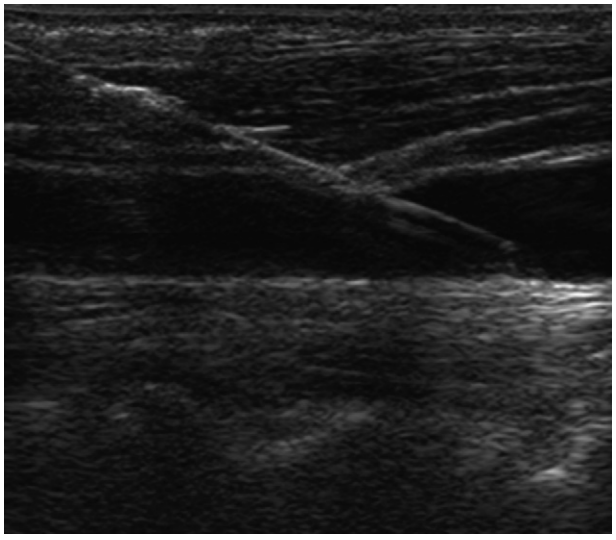


Figure 197-8. A needle in an internal jugular vein for procedural guidance.

The accuracy of this technique ranges from 70 to 99%, depending on operator experience.[130,131] Hospital charges and time in the emergency department are reduced for patients who have venous US performed by emergency physicians to rule out DVT.[132,133]

Thoracic and Tracheal Ultrasound

Thoracic applications include the detection of pleural effusion, pneumothorax, as well as other pathologic lung states. The technique of thoracic US utilizes a low-frequency probe to survey for pleural effusions and a high-frequency probe to detect pleural lines and related artifacts. Pleural fluid appears as an anechoic collection above the diaphragm. In addition, the lung may be collapsed and visualized as an echogenic floating structure. Normally, the parietal and visceral pleural lines slide against each other, and lack of sliding is the finding most consistent with pneumothorax.[134,135] Confounding factors include adhesions of the pleura, chronic obstructive pulmonary disease, and prior pneumothorax. A lung point sign is the edge of the pneumothorax where the lung is still adherent to the parietal pleura, and part of the image shows no sliding until the lung moves into the interspace with respirations.[136] The accuracy of US for detection of pneumothorax is better than that of plain chest x-ray in the acute setting, but there are concerns regarding reduced accuracy after 24 hours.[137-139]

Severe pneumonia is visualized as echogenic "liver-like" echogenicity as the lung accumulates fluid with consolidation. Peripneumonic collections are common and may indicate inflammation.

Pulmonary edema is indicated by the presence of comet tails, which are reverberation artifacts that reflect from the parietal pleural interface into the lung. Normally found in dependent areas of the lung, the widespread distribution of these artifacts in an apical lung may indicate increased lung congestion.[140,141]

Tracheal US has been explored for the confirmation of endotracheal intubation with relatively good sensitivity and specificity.[142,143] The dynamic movement of the endotracheal tube creates a flutter through the recognized shadow of the airway, but static US seems to lack accuracy.[144,145] This technique may have a role in patients in cardiac arrest or with equivocal end-tidal carbon dioxide, and it has been used in pediatric patients with significant decreased time to confirmation compared with chest radiography.[146]

Ocular Ultrasound

Ocular US has been described for intraocular pathology such as retinal detachment, retinal hemorrhage, vitreal hemorrhage, intraocular foreign body, dislocated lens, and retro-orbital hemorrhage.[30] The eye is an excellent acoustic window, and short-duration gray scale US over a closed eyelid can visualize both the anterior and the posterior chamber well. In addition, the optic nerve sheath diameter can be measured behind the eye, reflecting intracranial pressure.[32,147-149]

Soft Tissue Ultrasound

US in soft tissue is facilitated due to the lack of air and bone in the skin and subcutaneous tissue except in the hand and foot. Soft tissue US is used to differentiate cellulitis from abscess, for detection of foreign bodies and hernia, and for the evaluation of other soft tissue pathology.[27,28,150] The technique involves the use of a high-frequency linear transducer to image the soft tissue from normal skin to the abnormal area. Cellulitis or edema will cause an echogenic pattern with cobblestoning between fat lobules. Abscesses are irregular hypoechoic to anechoic collections within the subcutaneous layer but may connect with the surface. US is diagnostic in soft tissue disease states such as cellulitis, abscess, and necrotizing fasciitis.[150-153] In the ABSCESS study, clinical exam had a sensitivity of 86% and specificity of 70%, whereas US had a sensitivity of 98% and specificity of 88%. Management in half of the patients with clinical cellulitis was changed based on results of US.[27]

US can detect peritonsillar abscess with differentiation of cellulitis versus abscess, and it can be used for guidance of peritonsillar aspiration.[154] It can also detect early Ludwig's angina with abscess in the soft tissues and fascia of the face.[155]

Detection of foreign bodies is characterized by variable echogenicity in the tissue with unexpected shadowing beneath the foreign body. Metal foreign bodies may have characteristic highly reflective echogenicity and ring-down artifacts. Bedside US has had variable accuracy for detection of foreign bodies in simulated cases but better accuracy in clinical settings.[156-158] Use of a water bath may aid the detection of superficial foreign bodies.[159]

Musculoskeletal Ultrasound

The use of US for musculoskeletal disorders is focused on joint effusion and fractures. US is excellent for detecting fluid in joints and confirming effusions and guiding drainage procedures.[29,160,161] Joint effusions typically are anechoic or echogenic, depending on type and age. Diagnosis of ligamentous injuries and muscular avulsion and hemorrhage has also been reported.[162-164] Muscular and tendon abnormalities are detected by anechoic and heterogeneous abnormalities. Detection is often assisted by movement of the limb. Tendons and their anistrophic longitudinal fibrils can be visualized near joints, with pathologic tears appearing as a discontinuity of the tendon. Muscles are hypoechoic with echogenic borders. Tears or hemorrhage may be seen as interruption of this normal pattern.[164] Water bath techniques provide a better acoustic window for very shallow tissue such as fingers.

In addition, the characteristic reflection of bone with immediate shadowing can be used to visualize normal bone and its contour. Detection of fractures requires identification of a defect in the bony cortex.[40,164-166] The ability to image the bony cortex can be useful for guidance of fracture reduction.[167] Comparison with the contralateral side may also be helpful.

US is accurate in the detection of fractures, joint effusions, and hematomas.[160,167-169] Prospective evaluation of finger fractures demonstrates good accuracy.[169] Other fractures studied include femur, sternal fracture, rib fracture, and forearm fractures.[40]

US is also used to guide anesthetic blocks and hematoma blocks.[170-172]

Transcranial Doppler Ultrasound

Transcranial Doppler US has been used by some emergency physicians for detection of abnormal flow patterns in the brain and for detection and treatment of middle cerebral artery strokes. An advanced procedure, typically using a phased array transducer over a bone or orbital window in the skull, color Doppler and spectral Doppler scanning is performed at different levels of intracranial vessels for detection of abnormal patterns.[173]

Testicular Ultrasound

Testicular scanning is an advanced US application that requires visualization of the normal and symptomatic testicle using a

high-frequency probe. The normal testicular structures, including the normal homogeneity of the testicle, are evaluated, and Doppler scanning is performed for evaluation of normal venous and arterial flow. Absence or a difference in flow from the unaffected side indicates possible torsion, whereas increased flow indicates epididymitis. Experienced emergency physicians accurately diagnosed testicular pain with a sensitivity of 95% and specificity of 94% in a study of 36 patients, which included 3 patients with torsion.[174]

Abdominal Bowel Ultrasound

The use of bedside US for evaluation of appendicitis, diverticulitis, and other bowel pathology is an area of increasing interest. There has been variable experience with the use of graded compression US to detect appendicitis, with reported sensitivity of 67% and specificity of 92%.[175] The novel use of US to detect diverticular disease and hernias has been described.[176,177]

Ultrasound for Procedural Guidance

In 2001, in response to the Institute of Medicine report "To Err Is Human," the Agency for Healthcare Research and Quality (AHRQ) sanctioned a report on actions that may improve patient safety.[178] The report contains a recommendation for US guidance for internal jugular central line insertion. Since then, the use of US for procedural guidance has expanded for almost every known emergency procedure, but especially vascular access.

There are several key concepts regarding procedural guidance with US. Procedural guidance can be static or dynamic.[179] Static guidance suggests that US has been placed over the anatomic area, and the area is marked while angle and distance information is noted. Dynamic guidance describes procedures performed with real-time US visualization of the needle entering the anatomic area.

There are two approaches to vein cannulation: transverse, where the vein appears as a circular structure on the screen, and longitudinal, where the vein appears as a tubular structure along the width of the screen. In the transverse approach, the probe's long axis is centered transverse (90 degrees) to the long axis of the anatomic area, guiding the needle to bisect the probe at its center gives centering and depth information. In the longitudinal axis, the probe is placed along the long axis of the anatomic area, and the needle is introduced in the long axis of the probe, giving depth and trajectory information.

US guidance for central line insertion has been the most studied application and most advocated use among US-guided procedures.[180-182] Both the AHRQ and the National Institute for Health and Clinical Excellence have recommended US guidance for central line insertion.[183,184] US guidance for internal jugular (IJ) central line insertion can be recommended as a best practice and safe practice.[180,185]

US permits the physician to assess the IJ for overlap with the carotid artery, vessel diameter, and the presence of luminal clot or vessel obliteration.[186] IJ central line insertion has been studied in the emergency department, intensive care unit, and radiology suite. In the emergency department, there is decreased time to flashback and improved success in the difficult stick patient and improved overall success rate, first attempt rate, reduced time to insertion, and reduced complication rate with US guidance for IJ cannulation.

Femoral vein insertion has been studied in cardiac arrest patients, and improved cannulation rate and reduced complications have been reported.[187] Several maneuvers can optimize the success rate of femoral vein cannulation, including reverse Trendelenburg position and placing pressure on the iliac vein proximal to the femoral vein.[188]

Studies of US-guided subclavian insertion suggest that US does not contribute to procedural success because of a lack of a convenient window for the subclavian vein. At the location where the vein is usually cannulated, visualization is obstructed by the clavicle. However, more laterally, toward the junction of the axillary vein and subclavian veins, the vein can be visualized in the chest wall.[189,190] Although it may be cannulated there, the more difficult challenge may be inserting the catheter through the pliable soft tissue of the anterior-superior chest.[191] The supraclavicular fossa is a window for central line insertion, and the subclavian and brachiocephalic veins may be imaged from this site.[192]

Emergency physicians are able to use US to insert peripheral intravenous catheters in difficult patients with high success rates.[193-195] Nurses have also been taught to use US for peripheral venous guidance.[196,197]

Arterial access, including radial artery aspiration and cannulation, is more successful with the use of US guidance.[198,199]

Numerous other procedures using US guidance have been described in emergency practice. They are listed in Table 197-2.

Table 197-2 Ultrasound Guided Emergency Procedures

ULTRASOUND	PROCEDURE
Vascular access	Central venous access[182,210,211] Internal jugular vein Subclavian near axillary vein Subclavian with superclavicular approach Femoral vein Peripheral vein[193,197,212] Basilic Brachial Cephalic Forearm veins Intraosseus needle[213] Arterial cannulation[198,214] Radial artery Arterial sampling[215]
Torso fluid collections	Paracentesis[216,217] Thoracentesis[218] Pericardiocentesis[219]
Cardiac	Pacer placement[220–223]
Musculoskeletal	Arthrocentesis[29,224,225] Hip Knee Other joints Fracture reduction Foreign body removal[226] Tendon sheath injection[227]
Soft tissue	Abscess drainage[228] Hernia reduction[229]
Anesthesia	Interscalene Peripheral nerves Axillary[192] Femoral nerve[230] Hematoma block
Airway	Endotracheal tube placement[231–234]
Urinary bladder	Superpubic aspiration and cystostomy[235–237] Foley guidance[238]
Neurologic	Lumbar puncture[239–243]

Out-of-Hospital Ultrasound: Disasters and Remote Settings

US has been used in various settings, including out-of-hospital, the military battlefield, disaster settings, critical care settings, and international medicine settings. The use of US has been described in European and other settings that utilize physicians in the out-of-hospital arena, including ground, helicopter, air, and space.[9,200-204]

The military was a source of funding for small compact US machines and has been an extensive user of US in combat situations, including the frontline, combat support hospital, and tertiary hospital settings.[8,205,206]

US in disaster and other mass casualty situations has been described, including their use during the Armenian earthquake of 1988. With smaller, more compact machines, US capability may become part of disaster facilities and plans.[207]

INTEGRATION INTO EMERGENCY MEDICINE PRACTICE

US technology has rapidly been integrated into emergency medicine practice due to the need for effective, noninvasive, nonpainful, portable imaging techniques.[208] US, whether introduced in medical school, residency, or clinical practice, is a skill that requires constant attention with hands-on practice and interpretation.[15,209] However, with the integration of US into emergency medicine practice, emergency care has become more rapid, efficient, safe, and accurate.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 198

Multiculturalism and Care Delivery

Edward Bernstein, Judith Bernstein, and Thea James

Every day, in emergency departments throughout the United States, physicians encounter challenging cases that require an appreciation of cultural differences. Lack of understanding of the role of cultural factors can have an adverse effect on physician-patient communication and trust. Health outcomes can also be negatively affected, as demonstrated by a large body of literature on racial and ethnic disparities in types of interventions and outcomes for heart and lung disease. Race, culture, ethnicity, class, gender, economic conditions, spirituality, and sexual orientation define health and illness for patients and affect both access to health care and the quality of services received. Missing these cues may lead to medical errors.[1,2]

The American College of Emergency Physicians (ACEP) Code of Ethics, 1998–99, commits emergency physicians to "protect the rights and best interests of the most vulnerable … [and] secure access to emergency and other basic health care for all."[3] This code also recognizes that "denial of emergency care or delay in providing emergency services on the basis of race, religion, ethnic background, social status, type of illness or injury, or ability to pay is unethical." Lewis Goldfrank, past president of the Society of Academic Emergency Medicine (SAEM) and a member of the Institute of Medicine, and Robert Knopp, Deputy Editor of *Annals of Emergency Medicine*, comment in an editorial about ethnic disparities in emergency department analgesia prescription:

> With the legacy of racism and the growing body of medical evidence indicating differential care in the emergency department and other medical specialties, we believe that the burden of responsibility has now shifted so that the medical profession must now demonstrate that physicians are providing appropriate and timely care for all.… Our integrity as a profession and as a nation hangs in the balance.[4]

The purpose of this chapter is to provide the knowledge base in cultural competence that is essential to meet patient needs, improve health outcomes, reduce racial and ethnic disparities, and achieve professional goals.

RATIONALE FOR CULTURAL COMPETENCE

Changing Demographics: New Challenges for Emergency Physicians

We live in a global community, and both the U.S. population and the types of health problems seen by emergency physicians are constantly changing. In 2000, the U.S. Census Bureau estimated that 12% of the U.S. population was foreign born and 20% spoke a language other than English at home.[5] It is projected that by 2030 the proportion of Hispanics will increase from 13 to 20%, and racial and ethnic minority representation in the United States will exceed 40%.[6]

These figures do not speak to the diversity within these groups. The category Hispanic, for example, is an ethnic grouping counted in the race category of the census, but it fails to capture the significant range of diversity represented by Spanish speakers. Hispanics may share some cultural practices and speak similar versions of the Spanish language but have major differences in vocabulary, history, socioeconomic status, cultural identity, what they call themselves (Hispanic or Latino), levels of acculturation, health beliefs, habits, access to care, and health outcomes.

What do these changes in demographics mean to practicing emergency physicians? The ACEP Code of Ethics challenges us to recognize ethnic and racial differences in health care access and outcomes, to advocate for equity, and to work with other health organizations and providers to contribute to eliminating these disparities.

Racial and Ethnic Disparities in Health Care Access and Outcomes

In the past decade, both financial and nonfinancial barriers to access for racial and ethnic minority populations have been thoroughly documented. These include high rates of uninsurance, lack of prenatal care, hospitalizations for ambulatory-sensitive diagnoses (an indicator of reduced access to primary care), and concentration of minorities in areas of physician shortage.[7] In 2003, the Institute of Medicine (IOM) produced a report commissioned by the U.S. Congress in which more than 100 studies assessing the quality of care for racial and ethnic minorities living in the United States were analyzed.[8] According to the IOM report, minorities received fewer needed services and procedures than whites, after controlling for insurance status, income, and other access factors. These findings applied to a wide range of health conditions, such as cancer, cardiovascular disease, HIV/AIDS, diabetes, and mental illness. The findings identified cultural and linguistic barriers, fragmentation of the health care system, and differences in sites of care delivery and insurance coverage as explanatory factors. The authors suggest that unconscious bias, prejudice, stereotyping, and physician uncertainty of severity may influence clinical decision-making and allocation of services and procedures. Patient preferences may account for some of the range of distribution of services, but preference alone is insufficient to explain health care disparities. The report concludes that "racial and ethnic disparities in health care exist, and

because they are associated with worse outcomes in many cases, they are unacceptable."

The IOM report also discussed important nonfinancial barriers to access, such as the unequal distribution of physicians in areas where minority populations live. In particular, the number of racial and ethnic minorities living in medically underserved areas is three times the proportion of minorities in the general population. Poor urban communities with high African American and Hispanic representation averaged 24 physicians per 100,000 people compared with 69 physicians per 100,000 in communities with low representation. Although minority physicians are more likely to serve patients with Medicaid or no insurance, enrollment of minorities in health profession schools has been declining for African Americans, Hispanics, American Indians, and Alaskan Natives.[9] In fact, the American Association of Medical Colleges (AAMC) reported that in four states with restrictions against affirmative action, in the year following enactment, there was a 17% decline in applications and a 26% decline in matriculation to medical schools from underrepresented minority groups.[10] A survey conducted in 1997 by the SAEM Task Force on Women and Minorities found that 59% of residency-affiliated sites had no minority faculty member.[11] Dr. Jordan Cohen, president of AAMC, argues that "to achieve diversity in the health profession is not someone else's problem; it is a problem for the profession, for all of us who are concerned about the future of access to health care and the quality of health care that we are going to be able to provide our society."[12]

The National Institutes of Health National Center for Minority Health and Health Disparities, created by Congressional Public Law 106-525 to oversee research in health care disparities, reports that improvements in health have not been universal during the past two decades: "Striking disparities in the burden of illness and death" exist for African Americans, Hispanics, Native Americans, Alaskan Natives, Asians, and Pacific Islanders. Despite a decade of attention focused on racial and ethnic health care disparities, progress in narrowing critical gaps in life expectancy has been slow. Life expectancy for blacks as a whole is 73.2 years versus 78.3 years for the white population—a gap of 5.1 years. For black males versus white males, the gap is even larger (6.2 years). Lower life expectancy for blacks is accompanied by higher rates of cardiovascular disease, cancer, infant mortality, maternal mortality, birth defects, asthma, diabetes, stroke, intentional injury inflicted by others, sexually transmitted disease, and mental illness.[13,14] The reliability of data for Hispanics is limited by inaccurate reporting of race/ethnicity on birth and death certificates, the healthy migrant effect, and the possibility that migrants may return to their country of origin when they become ill or disabled.

Factors Contributing to Disparities in Health Outcomes

In the past decade, reports have been regularly published in major peer-reviewed journals about disparities in the use of diagnostic tests and procedures, access to appropriate treatment modalities, and waiting times to receive care in emergency departments.[15,16]

Test and Treatment Options: Physician-Patient Communication Failure?

Studies document clearly that both Hispanics and African Americans receive fewer analgesics for extremity fractures[17-20] and for musculoskeletal pain[21] than white patients in the emergency department setting, despite no evidence of difference across race and ethnicity in the ability to discriminate painful sensation.[22,23] In secondary analyses of the National Hospital Ambulatory Medical Care Survey data for 1993 to 2005, opioids were less likely to be prescribed to African Americans (23%) and Hispanics (24%) for pain relief than whites (31%),[24,25] and these differences were greatest for patients with the most severe pain.[24] Disparities in emergency department pain treatment continue to persist a decade after identification of racial and ethnic differences in analgesic administration.

Evidence from other specialties corroborates that differences in provision of medically appropriate procedures and therapies are often related to race and ethnicity. In the case of preventive measures, for example, elderly African Americans and Hispanics are less likely to receive influenza and pneumococcal vaccine, and Hispanics are less likely to have a blood pressure check or a cholesterol level within the past 2 years.[26] In the domain of surgery, the operative rate for certain lung cancers was 76.7% for whites and 64% for African Americans, and the 5-year survival was 34.1 and 26.4%, respectively.[27] The authors concluded that if blacks had undergone surgery, the 5-year survival rate would have been similar. An accompanying editorial suggests that the medical establishment take some responsibility for the racial discrimination that results in inadequate emphasis on prevention or insufficiently aggressive care for African Americans.[28]

These issues also apply to disparities between black and white populations with respect to cardiovascular disease. After adjusting for severity and coexisting conditions, African Americans are less likely to undergo either angioplasty or bypass surgery than whites, and differences are more significant for those predicted to benefit most from revascularization.[29] A multicenter emergency department study found racial disparities in access to cardiac catheterization for African Americans and other non-whites with acute myocardial infarction and unstable angina. The researchers also found that African American patients were less likely to receive a timely electrocardiogram or an assay for cardiac markers,[30] and doctors were less likely to prescribe anti-ischemic medications.[31]

In recent years, racial and ethnic disparities in emergency department treatment decisions have also been identified for admission following a diagnosis of pancreatitis,[32] for care related to mild traumatic brain injury[33,34] and headache,[35] for rate of appendicitis rupture,[36] and for underdiagnosis of psychiatric disease.[37]

Discrimination and Health Outcomes

Deleterious health consequences that result from racial discrimination have been well documented.[38-42] In a study of the nation by state, in states where more respondents to the General Social Survey indicated that blacks lacked innate ability, there was a closely associated increase in age-adjusted black mortality that was considerably stronger than the correlation for mortality and socioeconomic status.[43] Mechanisms used to cope with the stress of racism have been shown to backfire by adding to health risks, as in the case of smoking, substance abuse, and overeating.[44,45] Racism-induced stress has been shown to be negatively associated with disease entities such as diabetes, hypertension, depression, and preterm birth.[46-50] Similar experiences have been described for homosexuals vis-à-vis homophobia.[51]

Race-Based Medical Decision-Making

Racism, sexism, and homophobia can interfere with the establishment of trust and the delivery of effective medical care if providers create or establish barriers based on their own

internal biases, prejudices, and negative reactions to racial or cultural characteristics, such as skin color or clothing styles. Patients read these reactions clearly during an encounter with a provider. A barrier is created, and the opportunity for a good medical outcome may be lost. Provider biases against people with certain stigmatized diseases, such as HIV and substance abuse, can also create barriers to effective health care. When primary care physicians viewed scripted video interviews with hypothetical patients with chest pain who had similar symptoms, risk factors, vital signs, and thallium stress test and electrocardiographic findings, they were less likely to refer African American women for cardiac catheterization than men and whites, even though the scripts varied only by race and gender.[52] Disparities profiling can result in both under- and overdiagnosis and thus contribute to medical error.[53,54]

Failure of Trust

Patients from minority communities have reason to be skeptical about the validity of medical research and the appropriateness of medical recommendations. Participants in the Tuskegee study, for example, were not notified when effective treatment for syphilis became available because researchers wished to investigate the natural course of the disease.[55] Middle-class African American patients often rate their physician interactions as less participatory than when the doctor is of the same race as the patient.[56,57] Yet this option for physician-patient congruence is rarely available to minority patients because only 4% of physicians are black, whereas 12% of the population is black.[8]

In the Agency for Health Quality Research National Healthcare Disparities Report, blacks and Hispanics were found to be more critical of the patient-provider relationship than were whites. A higher percentage of adult blacks and Hispanics rated their health care at less than 6 on a scale of 1 to 10 in the past year and believed that they would have received better care if they were of a different race or ethnicity. The report provided evidence confirming perceptions of a lower quality of medical care. For example, when black and Hispanic adults older than 65 years were hospitalized for pneumonia, they were less likely than comparable whites to have blood culture samples drawn and antibiotics administered in accordance with current recommendations. Hispanics with myocardial infarction were less likely to receive aspirin or a beta-blocker on admission and discharge. In comparison to white dialysis patients, fewer blacks and Hispanics in need of a kidney were registered on waiting lists for transplant or had received a transplant within 3 years.[58]

Language and Effective Medical Care

According to the 2000 U.S. census, 47 million Americans (18%) speak a language other than English at home, 21.3 million speak English less than very well, and 10.7 million speak English not at all or not well.[59] Patients with limited English proficiency are more likely to defer needed services, leave against medical advice, miss appointments, fail to adhere to treatment regimens, lack a regular provider, and report poorer health status.

Transcribed audiotapes of medical encounters in a pediatric emergency department setting were studied to ascertain differences in communication error rates for patients who were aided by professional hospital interpreters compared with those who had an ad hoc interpreter (e.g., family, friend, or nonprofessional hospital worker) and those who had no interpreter available. They found that communication errors occurred equally among the ad hoc and the no interpreter groups. These errors included left out words (52%), incorrect words (16%), substituted words (13%), interjected personal views (10%), and added words (8%). The errors of ad hoc interpreters were more likely to result in clinically significant medical errors, such as omitting drug allergies and giving inaccurate instructions on dosing and route of administration.[60] The use of untrained nonprofessional employees as interpreters resulted in serious translation errors, including omissions, additions, and substitutions for what the patient is trying to say, and the use of relatives, particularly children, may violate privacy and disrupt family norms of authority.[61-64]

A cross-sectional survey at a public hospital emergency department suggested that there is a patient-perceived need for interpreter services, and the highest patient satisfaction ratings are obtained when patients can communicate directly with their physicians.[65] Satisfaction ratings for patients using ad hoc interpreters are lower, and rates are lowest when an interpreter should have been used but was unavailable. In one retrospective study of Spanish-, Haitian Creole-, and Portuguese Creole-speaking patients presenting to the emergency department with chest pain, headache, and abdominal pain, the investigators found that the use of trained interpreters was associated with increased intensity of emergency department services, reduced emergency department return rate, increased clinic utilization, and lower charges during the next 30 days, without any simultaneous increase in length of stay or cost of visit.[66]

A statewide emergency department patient satisfaction survey in Massachusetts indicated that non-English speakers were less satisfied with their emergency department care, were less willing to return for care, and reported more problems with emergency care.[67] The authors state that interpreter service is likely to improve the satisfaction of this group.

Evolution of New Standards for Health Care

In response to the identification of unacceptable differences in both health care provision and health care outcomes, state Medicaid regulations and Health Plan Employer Data and Information Set criteria now reflect the need to establish quality performance measures to ensure access to appropriate services for culturally diverse populations.[68] A new standard of care has been established that requires institutions and practitioners to provide for medical needs in the patient's primary language and in a manner compatible with patients' health beliefs and practices. Health care institutions and providers are asked to collect data stratified by race, ethnicity, and language and to institute quality improvement efforts when cross-cultural differences in outcomes of care, process indicators, or patient satisfaction are detected. They are asked to develop culturally competent systems of care based on an assessment of the organization's mission, goals, policies, practices and services, staff training needs, and the current diversity of the staff.

After the assessment process, health care organizations must identify opportunities to improve the cultural competence of the organization and its delivery of health care services to a diverse population. At the top of the list is the improvement of interpreter services. Hospitals are asked to establish minimum performance standards for interpreters that include training in culturally specific medical language and code of ethics. These requirements have been codified as a set of standards for culturally and linguistically appropriate services (CLAS Standards) by the Office of Minority Health and the Agency for Health Care Research and Quality and published in the Federal Register (December 15, 2000).[69] In spring 2000, the Massachusetts legislature took a positive step in the

direction of compliance with these standards by passing a law requiring all emergency departments to provide interpreter service and authorizing the state to provide Medicaid reimbursement for interpreter services.

Culturally Competent Approach to Language Barriers

In 1996, the SAEM Task Force on Physician-Patient Communication identified lack of a common language as the most common barrier to communication in the emergency department. Professional medical interpreters were recommended for the following reasons: (1) confidentiality, (2) medical knowledge and a common vocabulary with the provider, and (3) fluency.[70] Two emergency department case reports illustrate this point.[71]

A 50-year-old Mexican American man who spoke only Spanish was seen in the emergency department because of "chest pain." Because no translator was available, an electrocardiogram and chest radiograph were ordered. The electrocardiogram was normal; the chest radiograph showed a widened mediastinum suggestive of a dissecting aortic aneurysm. An aortogram was subsequently performed, which demonstrated a normal aorta. At some point, a Spanish-speaking physician was able to elicit a 1-year history of difficulty swallowing and regurgitation of food. A barium swallow was performed, which revealed achalasia.

A 22-year-old Vietnamese man arrived in the emergency department unresponsive and comatose with small, reactive pupils. Naloxone hydrochloride and 50% dextrose in water were administered without response. The medical history was obtained from a family member who spoke some English. It consisted of brief answers to specific questions and was not helpful diagnostically. A lumbar puncture and examination of the cerebrospinal fluid ruled out meningitis. A clerk later recalled that a child with the same last name was admitted the previous day for headache, nausea, and vomiting caused by carbon monoxide poisoning. In retrospect, it was clear that the history obtained from a family member who was under stress and giving vague answers to pointed questions was inadequate. The authors conclude that "a trained bicultural translator can effectively elicit the history as conceptualized by the patient or family and translate it both linguistically and in the format of Western medicine."

The previous example also illustrates that bilingualism is necessary but not sufficient. There are nuances and sociocultural assumptions in both languages as well as nonverbal cues that must be communicated along with words for effective diagnosis, treatment, and disposition. The medical interview is the heart of the medical encounter between physician and patient, yet in an interpreted interaction, neither patient nor physician is in a position to judge the accuracy or completeness of a lay interpreter's translation. Clearly, omissions, additions, opinions, guesses, and distortions can lead to serious mistakes and unnecessary diagnostic procedures.

Standards and certification for medical interpreters are needed to ensure consistency and quality. The Massachusetts Medical Interpreter Association recommends that standards cover interpretation, the cultural interface, and ethical behavior. Because the meaning inherent in the message is rooted in culturally specific beliefs, values, assumptions, customs, and norms, and language is itself an expression of culture, it may be necessary for a medical interpreter to go beyond a literal interpretation to explain unstated assumptions and to find new ways of communicating untranslatable words or concepts. In addition to maintaining confidentiality, the medical interpreter has an ethical burden to uphold the trust of both parties and assure them that the considerable power associated with the interpreter's role will not be abused and that information will be faithfully conveyed without interjecting the subjective opinions and thoughts of the interpreter. Even with such qualified interpreters, the emergency physician still needs to monitor the flow of the interview and, from time to time, clarify meaning and ensure understanding. This can be done by having the interpreter repeat what he or she thought the patient meant and asking the patient to repeat what the interpreter said. It is important to observe the interaction for phrase length as an indication of material not translated or added by the translator.

Using Cultural Competence to Cross the Barrier of Different Beliefs, Values, and Life Experiences

Both physicians and patients have a culture that they bring into the examining room. Differences between their cultures have an impact on the physician-patient encounter. Awareness of one's own values and those of others can enhance both satisfaction and health outcomes. The SAEM task force report cautioned, however, that it is dangerous to hold strong preexisting assumptions about any cultural group because variations within cultures often exceed variations between them. A patient who is thoroughly acculturated into American society may be offended by a health care provider's attribution of traditional beliefs. Even in the context of a busy emergency department encounter, it is necessary and feasible to get to know the individual patient sufficiently to make a rough assessment about level of acculturation, or at least to ask rather than to assume.

In some cultures, the diagnosis of specific diseases can be particularly problematic. For example, in African American and Puerto Rican communities, cancer is often perceived as a fatal disease. Patients may therefore avoid initial evaluation or choose no treatment when diagnosed, even when the cancer is identified at an early stage and the prognosis is good. A health care provider who understands these health beliefs and concerns can work collaboratively with patients to provide health information in a format that the patient can accept.

Alternative healing systems have strong cultural roots. In 1997, the U.S. population made an estimated 629 million visits to providers of alternative health care—approximately 243 million more visits than to conventional health care providers and an increase of 47% since 1990. An estimated 44% used at least one complementary alternative therapy in 1997.[72]

Folk medicine is too diverse for providers to know all possible practices, but emergency physicians need to know some of the more common therapies and ask their patients about them. For example, more than a few emergency physicians have called social workers to investigate children with apparent bruises caused by coining, which involves vigorous rubbing of the skin with coins and warm oil (tiger balm) to release the "bad wind" (reduce fever). These parents, who have attempted to help their children by using health care practices that are widely accepted in their communities of origin, feel accused, and the trust between the physician and the family may be irrevocably lost. Similarly, herbal remedies can be effective or at least harmless, but occasionally they can be toxic, as in the case of clay ingestion by pregnant women, the use of marijuana tea to treat asthma, and powders containing high concentrations of lead oxide to treat *empacho*, a condition in which it is believed that a substance (usually food or saliva) gets "stuck" to the walls of the stomach or intestines, causing an obstruction. Specific uses of folk medicine need to be elicited respectfully in a careful history and evaluated. Recommendations can

then be presented nonjudgmentally, and alternative folk remedies that are benign can be prescribed along with needed allopathic medications.

The practitioner and the patient will inevitably bring different beliefs and values to the medical encounter; the key to cultural competence is respectful negotiation of these differences without imposing the power of physician expertise, thus protecting patient autonomy. If patients are satisfied, they will carry out follow-up recommendations and return to the emergency department in the future when they need emergency care.

In a review of Hispanic cultural practices, Flores suggests a five-step approach for the pediatric emergency department that is applicable to all emergency medicine: The physician should (1) explain that he or she is aware that a given folk illness exists; (2) ask whether the parent or patient has ever heard of it; (3) ask whether the patient has the folk illness now; (4) ask what treatment the patient is receiving for the condition; and (5) suggest alternatives to harmful folk remedies, accommodating wherever possible (nonjudgmentally) to folk illness beliefs and practices, and integrating the use of harmless folk remedies into the treatment plan when the patient so desires.[73]

Interpreting the Culture of Medicine to Patients from Diverse Backgrounds

There are inherent conflicts between the culture of medical care, particularly emergency department culture, and the cultures of many patients. Physicians are expert in diagnosing and treating *diseases*, which represent abnormal structures or functions of the human body (the pathophysiology of disease states). On the other hand, patients experience *illness*, a subjective, feeling state that is interpreted through the lens of culture and has a personal and social meaning. The patient is an expert in his or her own illness and its effects on daily living, whereas a physician is expert in the effects of diseases on organ systems. Both ways of looking at the world have validity, but they are radically different.[74] Unfortunately, the culture of medicine tends to recognize only its own interpretation and perspective. A culturally competent approach recognizes both and works to integrate the best of both worlds.

A patient may have very high blood pressure, HIV, or early cervical cancer and not experience symptoms. If patients do not feel sick and experience no alteration in functioning, they may not accept a physician's diagnosis. There may be conflict between the patient's perception of causality and the physician's, as in the case of the differences between the medical diagnosis of hypertension and the commonly accepted view of hypertension as "high blood" in the African American community.[75]

On the other hand, a patient may feel sick—be ill, weak, and dizzy, with extreme fatigue or abdominal pain—yet the physician is unable to diagnose a disease despite a thorough history, physical examination, testing, and appropriate consultation. For example, *susto*, an illness recognized by Mexican Americans, causes listlessness, insomnia, depression, and anorexia and is believed to be caused by exposure to a frightening experience. Treatment requires the patient to speak openly about the events that led to the susto, followed by bedrest and a ritual that includes prayers, incantations, and *barridas* (sweeping of the body with an egg, a candle, or herbal teas).[76]

To be most effective, physicians need to investigate how patients view the causality of their illnesses and how they experience them in order to negotiate a therapeutic intervention. Exploration might take the form of comments and questions such as, "Help me to see through your eyes how you understand this problem. Have you or someone you know experienced it before?" The role of the physician is to accept the patient's experience as uniquely his or hers or, when possible, reframe it in terms of medical knowledge. Then both physician and patient will be satisfied with the outcome of the encounter.

Role Expectations in Western Medicine: Opportunity for Misunderstanding

The culture of medicine, especially in emergency medicine, has its own set of patient expectations, rules and regulations, language, and dress distinctions that reflect a hierarchy of authority, a characterization of patients as good or bad, and different sets of behaviors toward patients depending on the category to which they have been assigned. The "good emergency patient" is acutely ill but waits patiently until called without complaining, requesting pain medications, getting angry, or being loud or disruptive. The "good patient" understands the triage system and provides a clear, concise, pertinent history with enough information for accurate diagnosis. The "good patient" does not take up physician time with minor complaints, feelings, or tangentially related information. The "good patient" accepts invasive examinations and procedures without protest, agrees to admission or to a discharge plan, does not require long explanations of rationale for treatment, and has a support system in place for a safe discharge. A "good patient" who does not speak English brings someone to interpret, someone who can bridge the cultural divide and help with transportation upon discharge. A "good patient" does not moan, scream for a nurse or doctor, or act violently. A "good patient" does not have family members who are emotionally upset, stir up trouble, or challenge providers. A "good patient" uses seat belts, maintains personal hygiene and normal weight, takes prescribed medications, avoids drugs and cigarettes, and exercises. "Good patients" share a trust, understanding, and belief in scientific, modern, technological medicine and its value. Because they comprehend the physician's explanation of causality—for instance, bacterial infection as a cause of pneumonia—they agree to a discharge plan and adhere to a treatment regimen. They understand medical jargon and require very little explanation and ask a minimum of questions. "Good patients" help maintain the flow through the emergency department, whereas their opposites obstruct the flow. "Good patients" get better; the "bad patient" keeps coming back, has chronic recurrent conditions, and has confusing or difficult to resolve problems.

Thus, it is not surprising and no fault of their own that people from different cultures may find it impossible not to violate one of the many rules and regulations of the emergency department. Every medical encounter is potentially a cross-cultural experience, and negotiating the divide is a challenge for both patients and providers. Cultural competence involves a reframing of many of these unstated rules because they prevent us from looking beneath the surface and addressing real problems. When a patient comes in with vague complaints, there may be a social stressor that has tipped the balance of mental health. There may be circumstances that the patient does not feel comfortable sharing with the provider because of cultural, racial, or language barriers, or there may have been an overload of negative stimuli related to racial and ethnic discrimination—a crisis for the person and the body this person inhabits.[77,78] People from minority cultures experience stressful events daily that the white provider, secure in his or her socioeconomic status and membership in the dominant majority, can only imagine: being passed by the 15th taxi in a

row because "it's not safe to pick up blacks"; being followed in a department store because you and your friend were speaking Spanish; having to "dress up" to go to the store to avoid a possible humiliating moment; or standing in line to register at a hotel, dressed in professional clothing, and being asked by a white person in line, "Hey, can you take my baggage to my room?" In each of these cases, assumptions were made about the person on the basis of a stereotype related to physical appearance or presumed country of origin. There is mounting evidence that these types of negative encounters engender clinical depression and anxiety and contribute to hypertension and other medical sequelae. If a patient self-defines as having an emergency by showing up at the emergency department, the problems that cause that person to come deserve our respect.

A study of racial and ethnic patterns of emergency department use found that four times as many African Americans and Hispanics as whites report the emergency department as a source of care.[79] Patients who "overuse or abuse" the emergency department are seen as "bad patients," but the reasons given in this study for patients' use of the emergency department are entirely rational: (1) Individuals seen in the emergency department need not request an appointment to receive care; (2) emergency departments provide sophisticated medical technology; (3) emergency departments operate 24 hours a day; (4) emergency department services are often covered by health insurance and other options are not; (5) emergency departments have a tradition of free care; (6) many communities lack culturally competent private practitioners; and (7) emergency departments are often close to inner-city neighborhoods, whereas many primary care providers have abandoned the city center environs for the suburbs. These reasons may explain, at least in part, why U.S. emergency departments had an estimated 115.3 million visits in 2005.

To practice good medicine in this health care and social environment, emergency physicians must critically question and reframe the moralistic good patient/bad patient paradigm. We, like our patients, are at the whim of forces beyond our control, and both patients and practitioners will experience higher levels of satisfaction if these issues are addressed directly. Patients must take responsibility for their own behaviors whenever possible, but physicians can and should work with health care institutions to adopt policies that improve access to culturally competent health care. These actions can help create a safe environment for both practitioners and patients.

RECOMMENDATIONS

Diversity among the emergency department patient population poses a challenge to emergency physicians. Recognition of cultural differences, knowledge about diverse cultures, awareness of the health impact of cultural beliefs and practices, and sensitivity to patients' needs can reduce access barriers and improve clinical outcomes and hospital-community relationships, while reducing the number of repeat visits and the cost of health care. Diversity education also creates a rich environment for conceptualizing and researching health problems.[80,81]

There are many opportunities for emergency departments and their institutions to improve their care of multicultural communities. These include plans to address problems related to (1) a lack of protocols for patient care; (2) a lack of resources for translation and cross-cultural interpretation; (3) an incorrect perception that attention to cultural competence adversely affects flow and efficiency; (4) a lack of cross-cultural teaching guidelines and standards in medical education; (5) inadequate recruitment and retention of minority residents, faculty, and practitioners; and (6) a lack of pathways for communication and collaborative work with communities.

Concrete recommendations, based on the CLAS standards, have been proposed for pediatric emergency settings and can be applied universally: (1) Institutions should employ trained medical interpreters and a diverse workforce; (2) pharmacies should label prescriptions and provide medical instructions in the patient's primary language; (3) administrators should post multilingual signs and ensure that handouts and forms are translated; (4) quality improvement programs should collect and analyze data and provide information to monitor

BOX 198-1 BASIC SKILLS IN AN INTERCULTURAL CURRICULUM

Communicate an interest in and respect for the patient's culture.
Tactfully and respectfully ask for general cultural information (e.g., herbal remedies, acupuncture, coining, moxibustion, or other cures attempted).
Elicit the patient's understanding of and beliefs about illness or health problems.
Request information regarding folk medicine beliefs—for instance, "mal ojo" (the evil eye or evil spirit) among Mexican Americans, voodoo among Haitians, yin and yang among Chinese patients, "rootwork" among African Americans, and "spiritism" (the ability of spirits to make people sick or cure them) among Puerto Ricans.
Interpret verbal and nonverbal behaviors in a culturally relevant manner.
Negotiate a culturally appropriate health care plan with the patient and his or her family as partners.
Demonstrate an ability to work as a team with a medical interpreter in the bilingual medical encounter.

From Goldstein E, et al: Intercultural medicine. In Jensen N, Van Kirk J (eds): A Curriculum for Internal Medicine Residency. Philadelphia, American College of Physicians, 1995.

BOX 198-2 POLICIES FOR INSTITUTIONAL IMPROVEMENT

Educate emergency department personnel about the circumstances of patients' lives and the interesting cultures that have evolved to deal with these circumstances using a variety of formats:
1. A series of hospital inservices to provide information about each specific patient group that uses the institution
2. Small focus groups with patients to improve our understanding of our patients' needs and begin the process of freeing providers from racial and ethnic stereotypes that create barriers to good medical care
3. Training utilizing videotapes and role-playing exercises to enhance movement along the cultural competence continuum

Meet with community organizations to build trust and create partnerships for preventive education.
Hire employees who reflect the culture, ethnicity, and socioeconomic background of emergency department patients to improve the quality of services.
Provide interpreter services, visual aids, and other educational materials in a variety of languages, and provide multilingual health education classes.
Participate as an institution in community health fairs.

outcomes based on race/ethnicity; and (5) a diverse group of patients should be enrolled in research studies to improve outcomes.[82]

Recommendations from the IOM report for a series of additional legal, regulatory, and policy measures were highlighted in an *Academic Emergency Medicine* editorial and include the following: (1) patients in public managed care organizations should have the same patient bill of rights as patients in private health maintenance organizations, (2) the number of health care providers who are members of racial and ethnic minority groups should be increased, (3) resources must be adequate to enforce penalties for civil rights violations, (4) incentives to promote disparities should be stringently limited, (5) health care professionals should have opportunities for cross-cultural education, (6) patient participation in decision-making should be enhanced through education, (7) community health care workers/advocates should assist patients to negotiate the health care system successfully, (8) the diversity of faculty and residents must be improved, (9) a cross-cultural curriculum should be developed for residency training and continuing education, and (10) physicians must educate themselves and the general public about the need to eliminate racial and ethnic disparities in health care.[83]

SUMMARY

Changing demographics manifest themselves in a diverse emergency department patient population, and emergency department practitioners must learn to be culturally competent and promote systemic change to provide quality care. Essential cultural competence tools for providers include recognition of cultural differences, respect for individual opinions and perspectives about health and illness, and, most important, the ability and willingness to negotiate differences to offer the best opportunity for good health care outcomes. Culturally appropriate health care systems must be incorporated into emergency departments, which serve as the gateway to our health care institutions.

Basic skills proposed in an intercultural curriculum developed by Goldstein and associates for internal medicine residents can apply equally to emergency physicians (Box 198-1).[84] Policies that will promote cultural competence, increase patient satisfaction, and improve health outcomes include those listed in Box 198-2.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 199

Process Improvement and Patient Safety

Shawna J. Perry, Robert L. Wears, Pat Croskerry, and Marc J. Shapiro

PERSPECTIVE

The overall process of patient care in the emergency department (ED) begins with the initial decision by the patient (or caregiver or family) to seek emergency assistance and ends with the patient's disposition and follow-up. The care process is highly complex, with many separate components, people, and interfaces with other processes in the health care organization (Fig. 199-1). This complexity, among other things, provides many opportunities for process failures, "errors," and adverse outcomes. Although process failures in health care have been studied for decades, most of that effort originated from outside of the field of health care, with health care professionals largely unaware of it.[1]

This began to change in the early 1990s when the Harvard Medical Practice Study reported that almost 4% of hospitalized patients suffered significant adverse events during their care and that almost 30% of these were due to human "error."[2] The study noted that failures in ED care accounted for only approximately 3% of all adverse events, but it estimated that more than 90% of adverse ED events were judged to be preventable. This study and others ultimately led the Institute of Medicine (IOM) to issue a report in 1999 titled *To Err Is Human: Building a Safer Health System*.[3] This report provoked the interest of the media and the general public and thrust the issue of safety in health care onto the national agenda. The major accomplishment of the IOM report was the introduction of some of the fundamental concepts regarding safety in complex systems for the first time into the world of health care. The most transforming concept was the idea that failures (or "errors") in care were not the result of bad decisions or bad individuals but were instead intrinsic properties of the processes of care in the health care system. Thus, efforts to reduce these failures should be focused on changing the processes of care rather than identifying, retraining, or punishing the workers.

The response within health care was mixed. Most health care professionals focused on the projected number of deaths due to "error," arguing that they were either too high[4,5] or too low,[6] and a third, smaller group argued that the concept of "error" was essentially contestable and thus an approach aimed at counting "errors" was fundamentally flawed.[7] The transforming concept of "system failure" rather than "human error" gradually gained acceptance, despite going against the natural human tendency to believe that individuals cause outcomes. This viewpoint is problematic because it undermines a clinician's sense of free agency; health care providers prefer not to view themselves as trapped in a system that is moving inexorably toward a bad outcome.

Within emergency medicine, safety and quality have been addressed by task forces, interest groups, and special sections examining the practice of emergency care, its processes, and environments using tools from the "science of safety"[8] to improve performance and cultivate patient safety. A basic curriculum for teaching about safety at the undergraduate level was developed with similar efforts taking place to implement safety concepts into medical education.[9]

Interesting lines of research on the safety and processes within emergency care have been performed, with a number of patient safety case reports published in the emergency medicine literature.[10] Chisholm and colleagues[11] reported that emergency physicians are interrupted, on average, approximately once every 6 minutes and that two thirds of those interruptions cause a change in task; this is important because both interruptions and task switching frequently lead to process failures. Fordyce and associates[12] reported that self-detected errors occurred in almost 20% of all ED cases but that only 2% were associated with adverse events. Fordyce and associates' work emphasizes that errors are ubiquitous but only rarely combine with other factors to produce adverse events, and it supports the notion that focusing on eliminating errors is not likely to be a productive strategy for improvement.

Coiera and colleagues[13] studied emergency physicians in Australia and reported high communication loads and found similar levels of interruptions. Morey and coworkers[14] reported that specific training of emergency physicians and nurses to work together in teams led to reductions in failures and improved performance. Perry and colleagues[15,16] identified a number of unexpected yet highly consequential failures of information technology that were difficult to detect, some occurring during emergency resuscitations. Wears and Perry[17] noted ergonomic shortcomings in the workplace and pointed out their potential for contributing to failures in care. Hall and colleagues[18] identified significant delays related to ED layout, with time to assessment of chest pain patients being greater for patients placed behind a door or who were 25 feet or farther away from the physicians assigned to care. These examples of safety research in emergency care demonstrate the wide range of known and unknown contributors to patient safety and the importance of the work processes that overlay this very complex work environment.

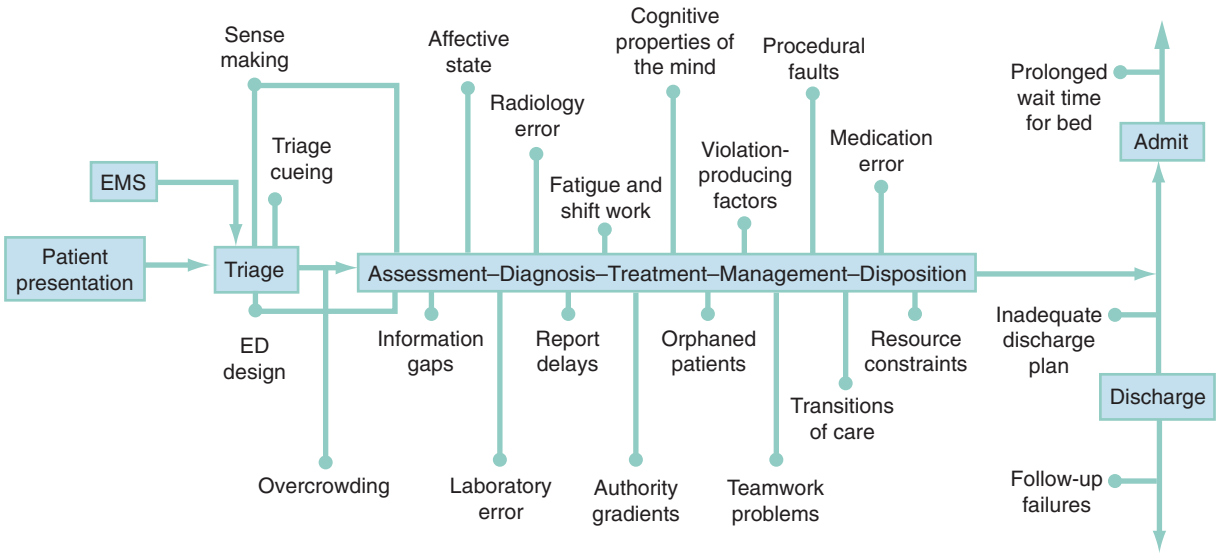


Figure 199-1. Process mapping showing sources of failures. The overall process is highly simplified and presented as a linear model of a patient's trajectory. (The actual process is much more complex, involving multiple simultaneous patients at different stages and loops within a given patient's trajectory.) Sources of failure may occur in parallel or at multiple stages in the sequence and are often additive in their overall effect on patient safety.

SOURCES OF FAILURE IN EMERGENCY CARE

Many characteristics of emergency medical practice make it vulnerable to failures (Table 199-1).[19-26] This section focuses on some of the principal factors that contribute to adverse outcomes and how they might be better managed to improve safety.

Emergency Department Design/Human Factors and Ergonomics

Two frequently overlooked contributors to lowered safety in any work environment are the design of the workspace and the engineering of the tools, technology, and procedures used to do the work.[27] This is especially true for EDs because the majority were not designed for the care actually being delivered there.[28] Emergency department caregivers are required to adapt to the space by creating "work-arounds" to cope with the limitations and impediments of the workspace.

Consistency is rarely found in equipment across or between areas. For instance, the blood pressure monitor in the ED is often not the same type or model as that used in the radiology department when the patient goes for diagnostic tests. In addition, tools and technology are seldom developed or assessed for their "user-centered design" or ability to be integrated into existing workspace and the associated hazards for doing so. This is most apparent with regard to health information technology, which is often introduced for improving safety and quality; however, embedded latent features that can produce clinical failures that are "hard to see" have been demonstrated.[29,30] Study of computerized physician order entry by Koppel and colleagues[31]showed that the software facilitated 22 types of medication error risks; for example, displays that prevented a coherent view of the patients' medications and inflexible ordering formats that generated wrong orders. Other contributors to information technology failure within health care are the lack of usability testing,[32] delays in in-service training, and failure to reassess the impact of the new technology and changes in clinical work following pre- and postimplementation.[33]

Table 199-1 Characteristics of the Emergency Department That Affect Performance

INTRINSIC*	EXTRINSIC†
Human cognitive properties	High communication load
High levels of uncertainty	Poor teamwork
High decision density	Overcrowding
High cognitive load	Production pressures
Narrow windows of opportunity	High ambient noise levels
Multiple interruptions/ distractions	Information gaps
Low signal-to-noise ratio‡	Report delays
Surge phenomena§	Inadequate staffing
Novel or infrequently occurring conditions	Poor feedback
	Inexperience
Patient factors (e.g., acuity, language, delirium)	Inadequate supervision
	Sleep deprivation/sleep debt
	Fatigue
	Multiple transitions of care
	Poorly designed procedures
	Emergency department layout

**Intrinsic* factors are intimately part of the nature of emergency care and as such are not amenable to change but instead must be compensated for.*

†*Extrinsic* factors are in principle manageable and typically relate to resource constraints.

‡*Low signal-to-noise ratio* refers to the low likelihood of a critical diagnosis compared with a benign diagnosis for similarly presenting symptoms and findings (e.g., subarachnoid hemorrhage *vs.* tension headache).

§*Surge phenomena* refers to the rapid changes in volume and acuity, routinely experienced in many emergency departments.

The contribution of poor design to the difficulty in maintaining safety in a health care environment is generally overlooked by staff, who cope with these difficulties as "part of the job."[17] Vigilance is the common solution but despite caregivers' best efforts cannot be sustained given competing demands for their attention. This increases the risk of a failure not being

recognized as linked to the workplace, the procedures, or the equipment, despite being "tightly coupled" to any or all of these.

Overcrowding

Emergency department overcrowding has long been recognized as a major source of time-delay failures and a threat to patient safety.[34,35] It is important to understand that such delays are not simply an inconvenience to the patient but may give rise to significant adverse events. For example, patients with atypical presentations of severe illness who have been mis-triaged to low levels of acuity may experience inordinate and, occasionally, fatal delays. In other cases, such as community-acquired pneumonia, cellulitis, lacerations, and others, more expedient care may significantly improve the course of the illness. A significant proportion of patients who leave without being seen may have serious illness and incur delays in diagnosis and treatment. At the other end of the process, when the patient is ready for admission to the hospital from the ED, further time-delay errors may occur (see Fig. 199-1). Not only do such delays create throughput problems for the ED and contribute to overcrowding by front-end loading or "entry block" but also they give rise to discontinuities in care and may lead to adverse events that are difficult to identify because they manifest once the patient has left the ED.[36-38]

Information Gaps

Missing information is common in emergency care and can significantly affect quality of care.[39] Hospital records, especially discharge summaries, details of past medical history, and other important information is often difficult to access in an expedient manner, even with electronic medical records. Referral notes sent in by family doctors with the patient may not reach the emergency physician or may not contain relevant or significant details. In these situations, emergency physicians make clinical decisions and take action on the basis of incomplete, limited, or erroneous information. Emergency clinicians often end up not seeking additional or clarifying information due to time pressures, patient volume, or limited methods for obtaining more information (e.g., referring physician's office is closed), essentially accommodating to this "gap" in continuity of care and the associated increase in patient risk.[40]

Performance-Shaping Factors

Blaming individuals for "errors" in the ED contributes little to an understanding of risk, vulnerability, and failure. A wide variety of ambient, systemic conditions in the ED contribute to the majority of adverse events and near misses that occur (see Table 199-1). Some performance-shaping factors can be considered to be "intrinsic," part and parcel of the milieu of emergency medicine and thus not amenable to direct control (e.g., cognitive workload, multiple distractions and interruptions, and high acuity). These factors must be managed by strategies for buffering or mitigating their effects. In contrast, other "extrinsic" performance-shaping factors typically reflect limitations of resources (e.g., staffing ratios, production pressure, and ED layout). When resources are limited, a tradeoff can occur in the ability of the ED to provide safety and quality in patient care. This condition is referred to as RACQITO (*r*esource *a*vailability *c*ontinuous *q*uality *i*mprovement *t*rade-*o*ff),[41] a concept derived from speed-accuracy tradeoffs described in industrial settings.

BOX 199-1 VIOLATION-PRODUCING FACTORS

Gender
Mood
Ill health
Risk-seeking/risk aversion
Normalization of deviance
Maladaptive group pressures (groupthink)
Maladaptive copying behavior
Underconfidence/overconfidence
Perceived authorization to deviate
Authority gradient effects (obeying authority figure or absence of disapproving authority figure)
Likelihood of detection

Based on an original schema by Williams JC: Assessing and reducing the likelihood of violation behavior—Preliminary investigation. In Proceedings of an International Conference on the Commercial and Operations Benefits of Probabilistic Safety Assessment. Edinburgh, Institute of Nuclear Engeneess, 1997; adapted for emergency medicine in Crosherry PG, Wears RL: Safety in emergency medicine. In Markovchick V, Pons P (eds): Emergency Medicine Secrets, 3rd ed. Philadelphia, Hanley & Belfus, 2003. A summary can also be found in Reason J: Managing the Risks of Organizational Accidents. Aldershot, UK, Ashgate, 1997.

Violation-Producing Factors

Although at first one might think that violations of organizational policies, rules, and procedures would always be culpable causes of failures and adverse events, the modern approach to safety has pointed out that some violations are actually necessary for the safe functioning of the system, and others fall somewhere in between.[42] Aside from recklessness, drug use on the job, moral failings, and other egregious acts, research in other domains has identified other factors that are associated with the occurrence of rule and safety violations (Box 199-1). The "normalization of deviance"[43] is an accumulated tolerance of small variances from safe operating conditions that develops over time, ultimately compromising safety. This is evidenced in overtaxed EDs coping with overcrowding of patients (e.g., performing evaluation and management of patients in hallways). Violations can also occur in response to perceptions of authority. They may occur through a directive supporting violation from an authority figure (e.g., nursing supervisors order admitted patients moved to inpatient beds without calling to report if there are delays in reaching inpatient nurses), the absence of a disapproving authority (e.g., physicians leaving shifts early and the medical director does not address the behavior), or from an individual's self-perception that he or she is authorized to disregard or deviate from prescribed procedures (e.g., ED electrocardiograms done on patients in chairs because there are no available stretchers).

Fluctuations in mood can also contribute to violations for a variety of reasons and will result in inconsistent clinical performance; males are more likely to break safety rules and engage in more risk-taking behavior than females.[42] Risk-seeking and risk-averse attitudes have been associated aspects of decision-making in the ED.[44]

Teamwork

Good teamwork is essential to the safe practice of emergency medicine, but emergency caregivers are not trained or evaluated as teams. Teamwork training in other fields, such as aviation, has been successful in reducing failures related to poor communication, cross-monitoring (observing others' behaviors to reduce risk of failure and share workload), and authority

gradients (both within and between professions).[45] Work on transferring teamwork training principles to emergency medicine suggested that teamwork failures were involved in approximately 40% of malpractice cases.[46] The lack of cross-monitoring across team members and the failure of advocacy or assertion on behalf of the patient by caregivers to avoid patient harm were two of the most frequent factors identified. A multidisciplinary teamwork training course implemented in nine EDs showed a significant improvement in quality of team behaviors and a sixfold decrease in observed clinical errors.[14] Teamwork is not a specific fix for any one type of error, but it should be viewed as one type of adaptable human factor intervention with a set of teachable skills and behaviors capable of increasing system resilience and safety, which are hallmarks of high-reliability organizations.[47]

Teamwork training requires a change of culture, which can be difficult for ED staff. Institutional and ED leadership must be fully committed to the process before implementing teamwork training for all staff. Resistance to behavioral change is likely to be encountered, and it will be necessary to demonstrate the clinical relevance of this training. High-fidelity medical simulation supported by audiovisual feedback offers the educational methodology to help clinicians and staff understand the necessity of behavioral change.[48] A major unanswered question is how to embed teamwork behaviors into medical training and how to sustain the behaviors over time.

Authority Gradients

Almost all human groups have some form of authority gradient among members. This hierarchy can be based on profession (e.g., doctors have greater authority than nurses) or organizational rank (e.g., attending physicians have more authority than residents). Ideally, information between team members should flow freely, but this may not occur if low-authority members are inhibited by differences in seniority, stature, expertise, profession, or social status. There are clear examples of cases in which authority gradients have been responsible for adverse events.[49] A work environment in which all team members feel comfortable expressing their viewpoint, especially if it is a dissenting one, requires cultural change that can begin with the physicians who occupy the highest authority position in the clinical setting. Authority figures have the ability to initiate change by recognizing the value of perspectives other than their own and eliciting them from other clinicians and staff (e.g., asking a patient's nurse what he or she thinks may be going on with the patient). Senior clinicians are in a powerful position to bridge gradients by fostering open communication through multidisciplinary rounds, demonstrating that they are approachable (e.g., acknowledging staff by name), and the use of clinical narratives from their own experience that illustrate near misses and judgment failures.[50]

Cognitive Properties of the Mind

The human mind has characteristic dispositions to respond to particular stimuli and contexts in specific ways. A great deal of effort has gone into identifying and describing these; more than 30 *cognitive dispositions to respond* have been described.[17,51,52] A number of strategies have been proposed to reduce the adverse outcomes associated with cognitive dispositions to respond.[53]

The overall process of patient care in the ED is driven by a process of making clinical sense out of multiple sets of fragmented, tangential, and interrupted stimuli. This is aimed at making an accurate diagnosis if possible or, more commonly, a useful framing of the problem, which can determine management and disposition. Although many diagnoses, such as lacerations, dislocations, fractures, and foreign bodies, are self-evident, others (e.g., chest pain, fever, headache, abdominal pain, and syncope) are often associated with high levels of diagnostic uncertainty and are more likely to lead to problems. Cognitive biases can frequently be identified in retrospect following diagnostic failures,[54] but the problem of hindsight bias makes this identification problematic.[55]

In addition to cognitive mental properties, the emotional state of the physician can affect his or her decision-making; this has been referred to as *visceral bias*.[17,52] Relatively little attention has been directed at the important role of affective bias in decision-making. Although processes such as countertransference, fundamental attribution error,[41] and the economy of perception that underlies stereotyping are well understood in psychology, health care workers are typically less aware of them (e.g., "She's a drug seeker," "He's a frequent flyer," and "She just wants attention") and their effect on clinical interactions.

Fatigue and Shift Work

Both fatigue and shift work contribute to performance failures,[56] but relatively little research has been directed at their respective impacts on clinical performance in the unique milieu of the ED.[57] Although the two are often considered together, they are different entities and exert both qualitatively and quantitatively different effects on performance.[58] Fatigue has a number of determinants separate from those associated with shift work (Fig. 199-2).

Shift work has extensive, well-documented, detrimental effects on health that, in turn, have an impact on well-being and job performance.[59] Importantly, it leads to disruption of circadian rhythms that inevitably result in sleep deprivation. Circadian dyssynchronicity largely occurs through missing sleep in the *anchor period*, approximately midway through the sleep phase when core temperature and arousal level are at their lowest. It has been stated that the performance degradation of someone who has been up all night is roughly equal to that of a person with a blood alcohol level of 0.1% (Box 199-2).[60]

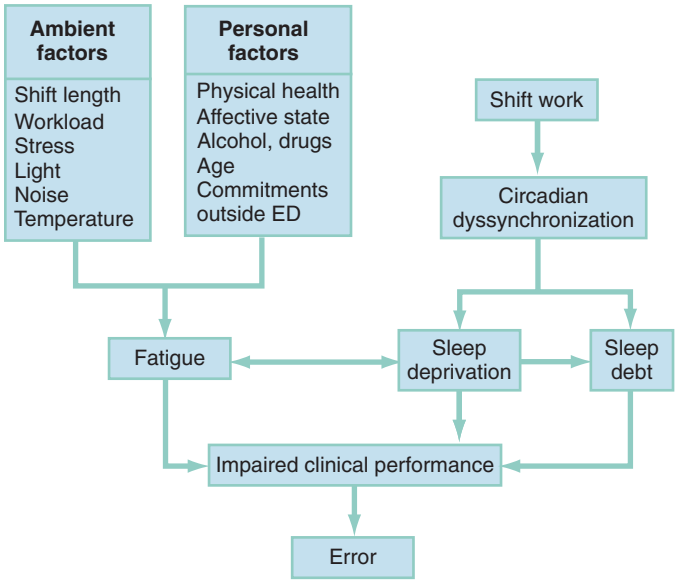


Figure 199-2. Relationships between shift work, fatigue, and performance.

BOX 199-2 EFFECTS OF SLEEP DEPRIVATION

- Longer reaction time
- Lapses in attention or concentration
- Lost information
- Errors of omission
- Poor short-term memory
- Poor mood (increased confusion, stress, and irritability)
- Reduced motivation
- Distractibility
- Sleepiness
- Poor psychomotor performance
  - At circadian low points
  - When sedentary
  - On long, difficult, or externally paced tasks with no feedback
  - In unchanging surroundings, particularly with reduced light or sound, or with low motivation, interest, or novelty

Adapted from Bonnet MH: Sleep deprivation. In Kryger M, Roth T, Dement WC (eds): Principles and Practice of Sleep Medicine. Philadelphia, Saunders, 2000, pp 53–71.

BOX 199-3 RATIONAL APPROACHES TO SHIFT WORK

- Optimize circadian-friendly schedules
  - Forward rotating (clockwise with circadian rhythms)
  - Rapid changes
  - Minimize consecutive nights (1 or 2)
  - 24–48 hr off after nights
  - Allow social time, including some weekends
  - 8-hr shifts (absolute maximum 12 hr)
  - Institute regular, predictable template
- Employ proper sleep hygiene
  - Use a sleep-friendly room: room-darkening blinds, "white noise" (e.g., electric fan) or earplugs, no phones, family aware
  - Maintain a regular sleep routine
  - Try anchor sleep
  - Avoid caffeine, alcohol, and drugs
  - Prophylactic naps
- Modulate circadian rhythms
  - Exercise
  - Consider bright light
- Eat healthy
  - Eat a balanced diet
  - Avoid junk food
  - Keep regular mealtimes
- Promote a healthy lifestyle and work style
  - Promote a personal healthy lifestyle
  - Educate friends and family about shift work issues
  - Educate colleagues about shift work issues
  - Advocate for department improvements in working conditions
  - Advocate for shift worker–friendly community services
- Avoid pharmaceuticals
  - Use caffeine in moderation, prn
  - Do not use sedatives or stimulants
  - Avoid alcohol before sleep

Adapted from Jha AK, Duncan BW, Bates DW: Fatigue, sleepiness, and medical errors. In *Making Health Care Safer: A Critical Analysis of Patient Safety Practices.* Evidence Report/Technology Assessment No. 43, AHRQ publication 01-E058. Rockville, Md, Agency for Healthcare Research and Quality, 2001; and Frank JR: Shiftwork and emergency medicine practice. Can J Emerg Med 4:421, 2002.

The acute effects of sleep deprivation are well-known, but the chronic effects are less appreciated. Invariably, working a night shift results in less sleep the following day, and subsequent sleep is often disrupted and fragmented in the struggle to restore the circadian rhythm before the night-shift cycle repeats itself. This results in the accumulation of a *sleep debt* that has a significant impact on performance. A study of anesthesia residents on a normal work schedule, with no on-call duty in the preceding 48 hours, showed daytime sleepiness scores comparable to those of patients with narcolepsy or sleep apnea.[61] The on-call schedule of these subjects (five periods per month) entailed considerably less sleep deprivation and fragmentation than an average emergency physician's schedule. Increasing age is associated with decreased tolerance for sleep deprivation.[62]

Performance declines as work hours increase,[63] but the optimal shift length in the emergency department is unknown and difficult to delineate for several reasons. The relationship with workload or acuity is not well appreciated, and some workers exhibit contradictory incentives, such as preferring to work longer shifts to get more days off. More recovery time between shifts might be expected to enhance job performance, but these issues remain relatively unexplored. A survey of emergency physicians found a preference for 8-hour over 12-hour shifts,[64] but it is not known whether job satisfaction in the ED translates into improved clinical performance and fewer adverse events. Other ambient conditions within the ED, competing commitments outside the ED, age, ill health, and other factors all contribute to fatigue, with evidence pointing toward additional health implications for emergency physicians.[65,66]

The appropriate management of shift work and fatigue to improve patient safety is not well understood, and further research is needed in this area. In most high-hazard industries, the assumption is that fatigue and long, aberrant work hours lead to poor performance; however, in the health care industry, concerns regarding discontinuity of care and difficulties in changing medical culture have obscured these issues. Given that medical personnel, like all human beings, function suboptimally when fatigued, efforts to reduce fatigue and sleepiness should be undertaken, and the burden of proof should be in the hands of the advocates of the current system to demonstrate that it is safe.[60] In the meantime, shift scheduling should be optimized to reduce the impact of circadian disruption, and ED personnel should practice good sleep hygiene. Some basic approaches have been reviewed (Box 199-3).[59,63]

PROBLEM AREAS IN EMERGENCY CARE

The mechanisms of failure within the ED are remarkably variable, with a cadre of known and unknown contributors. Areas of consistent concern within emergency medicine include triage, technical procedures, laboratory and radiographic tests, transitions in patient care, orphaned patients, and medications.

Triage

The point of entry of all patients into the ED is through triage. Triage, or sorting by acuity, is by definition an abbreviated decision-making process that can never be completely safe because of the limited information available, lack of time invested, and the variety of presentations of illness and injury. An additional problem is that there is a low "signal-to-noise"

ratio for a number of serious conditions (i.e., when the incidence of a serious condition is far exceeded by that for a benign condition, but their clinical presentations are similar). Inevitably, the triage process involves tradeoffs between sensitivity and specificity. Undertriage for a particular patient would have a greater potential for an adverse event than overtriage, whereas overtriage affects resource utilization and may have an impact on the care of other patients.

Triage assessments are important contributors to process failures and adverse events. Beyond treatment delays, which can occur with undertriage or be produced by overtriage, an incorrect assessment may be the triggering event that initiates a chain of failures. Geography can become destiny, and an inappropriate triage to a specific treatment area may create a bias in the minds of the treating clinicians and staff. The use of five-level triage systems for adults and children, with excellent inter-rater reliability, offers an opportunity to reduce the risk associated with undertriaging.[67,68]

Technical Procedures

The practice of emergency medicine requires proficiency in a wide range of procedures with varying degrees of difficulty. Patients who require procedures are at greater risk for adverse events.[12] Contributors to this higher risk include not only problems with proficiency but also a low frequency for use of higher risk procedures. Critical procedures, such as cricothyrotomy, pericardiocentesis, and endotracheal intubation, are rarely performed in many EDs. When they are needed, they are highly consequential events under significant time pressure for intervention, therein reducing opportunity for refreshing skills prior to performing the procedure. The acquisition and especially the maintenance of a requisite level of skill is an important problem in emergency medicine. Simulation techniques have considerable potential here[69] but require both capital and human investment to be effective.

Laboratory

The interface between the ED and its ancillary services is critically important. Failures can occur at three phases of laboratory processes. Preanalytic errors mostly occur through inappropriate collection of specimens due to lapses in technique, timing, and identification of both patient and specimen. Analytic errors refer to those that arise directly from the testing process. Postanalytic errors occur after the test result has been obtained and can take many forms (e.g., keyboard entry errors, overlooked or lost data, and failure of results to reach physician). Studies on a blood bank and a stat lab both found that the majority of failures occurred in the pre- and postanalytic stages, with less than 5% in the analytic stage.[70,71] Overall, the laboratory defect rate is less than 1%, but the number of exposures is very large. Of the failures that do occur, up to 50% may have a moderate impact, with up to 8% having a severe impact on patient care.[72]

Radiology

Radiographic imaging is a critical aspect of diagnosis and management in the ED. Although patient identification and wrong-side problems are important sources of failure, the majority lie in interpretation. Assuming the radiologist's interpretation to be the criterion standard, the rate of errors in interpretation by emergency physicians and residents may be as high as 16% for plain radiographs and more than double that rate for computed tomography scans.[73] Clearly, not all misinterpretations are consequential, and emergency physicians typically seek the advice of the radiologist when they recognize difficult interpretations. The introduction of digital imaging and picture archiving communications systems has resulted in new patient safety issues related to usability, the effect of monitor resolution on interpretation, and reconciliation of ED physician and radiology readings.[74] Significant interpretation errors can be detected with prompt review of all films by the emergency physician and radiologist, but effective procedures are required to ensure that timely and appropriate feedback and review occurs. This approach has been demonstrated to substantially reduce the rate of clinically important misinterpretations.[75]

Transitions in Patient Care

The need for 24-hour access to care and the fragmented nature of health care delivery require the occurrence of transitions of care between providers, either within the ED (at shift changes) or between the ED and other care areas (when patients are admitted, transferred, or discharged). The shift "sign-over" or "handoff" is generally thought of as a communication activity performed for the transfer of clinical information, but it also embodies the transfer of responsibility and authority from one provider to another. The sign-over also conveys general situational awareness (e.g., the state of the department, hospital, and city) and provides a forum for reviewing decision-making and treatment plans.

There has been little study of these transitions of care, despite their ubiquity and importance to the specialty.[20,76] Sign-overs are highly variable in their content, the number of individuals involved, the physical configuration (e.g., walking, stationary, and at bedside), the tools used to facilitate the transition (e.g., white boards, medical records, and written notes), and the length of the transition process. Although widely regarded as providing a major contribution to adverse events, sign-overs also provide an opportunity for review of decision-making by clinicians and may provide opportunities for recovery by bringing "fresh eyes" to a patient's case.[20,76]

Potential threats to high-quality transitions include the following:

- Interruptions during the turnover (e.g., phone calls and sidebar conversations) can cause a loss of focus and lead to the omission of important information.
- Lack of consistent structure to the turnover: Although the traditional case presentation narrative is generally followed (chief complaint, history, physical examination, initial laboratory results, impression, and plan), the case presentation format does not automatically remind participants of pending or as yet uncompleted tasks.
- Patients are commonly "marked" in ways that can sometimes be helpful but sometimes harmful, especially for at-risk groups such as the homeless, psychiatric patients, alcoholics, or drug abusers.

Common sense and well-meaning approaches such as standardizing verbal content and compulsory use of sign-over checklists risk extinguishing latent safety features inherent to them without further research of this complex and vital work tool for emergency medicine and health care overall.

Orphaned Patients

Orphaned patients are those who have suffered temporary loss or diminished supervision or accountability for their ED care. This may occur at several stages in the process. Patients who are seen and assessed at triage and then wait in the waiting

area are temporarily orphaned. Those who are brought in by paramedics sometimes remain on stretchers for hours before being admitted to the ED. Patients who leave without being seen or before treatment is completed have "orphaned" themselves. Patients can also be temporarily orphaned out of the ED for radiographic studies or other special tests. Occasionally, patients get "lost in the shuffle" and are overlooked at shift change, or they may get "lost" after one or more consultations with other services. With prolonged wait times, occult conditions can mature to serious and potentially catastrophic levels. A significant cause of orphaning in some EDs is the "boarding" of admitted patients because no inpatient beds are available. In such cases, patients may be put in holding areas in or adjacent to the ED and receive sporadic care from a succession of caregivers who know increasingly less about their conditions. The risk of harm to patients caught in this "gap" within the ED is not well studied.[40,77]

Medications

Medication errors constitute the largest proportion of failures in most general studies, with failures occurring in all six steps of the process (prescription, transcription, dispensing, administration, monitoring, and discharge).[78] Many EDs take on the dispensing role, obviating input from the pharmacy, where many errors are corrected. In addition, team communication errors can contribute to many failures: missed medications, wrong medications, and duplicate dosing. Pediatric patients are at higher risk; drug errors are no more common than in adults, but they are typically more serious.[79,80]

The presence of a pharmacist on the clinical team has been shown to reduce medication errors in several settings.[81] There is great interest in the potential for computer technologies, such as bar coding or computerized physician order entry, to enhance medication safety. However, despite some successful demonstrations, widespread implementation has not occurred, and there is evidence that such systems introduce new problems to replace old ones.[82] The Institute for Safe Medication Practices has recommended certain problematic practices be avoided in writing orders or prescriptions.[83] Success in this area will require more than just individual attentiveness; nurses, unit secretaries, and pharmacists will have to feel comfortable challenging improper usage by physicians.

CONCLUSION

The safe management of patients in the ED depends on a multiplicity of processes. All appear vulnerable to failure, yet all have the potential for improvement through judicious process management. Efforts by front-line workers will not be sufficient, and so considerable effort will be required at the administrative or "blunt end" of the system.[84]

Safety in complex dynamic environments, such as the ED, is itself dynamic. *Safety is a "nonevent" because it is evidenced by the absence of things that should not or do not occur*, such as administering a medication to the wrong patient. It cannot be banked for future use but is created by workers in a well-designed and supportive organizational environment. Achieving safe performance in settings such as the ED is analogous to fighting a guerilla war: There are no dramatic victories, but there are occasional horrific defeats, with no end in sight. The establishment and maintenance of successful safety cultures within health care will require constancy of purpose by health care organizations, a willingness to adopt new ideas and tools from outside of health care, and commitment to continued effort and investment.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 200 Bioethics

Kenneth V. Iserson

PERSPECTIVE

Definitions

Ethics is the application of values and moral rules to human activities. *Bioethics*, a subset of ethics, uses ethical principles to find reasoned and defensible solutions to actual or anticipated moral dilemmas facing clinicians. The moral precepts that underpin ethical decisions are derived from a variety of sources, including individual, cultural, and community value systems. Unlike the law, which is relatively rigid and, particularly in the case of scientific and medical issues, can lag years or even decades behind modern developments, the bioethical construct allows a greater flexibility in decision-making. This is a crucial factor in the emergency department (ED), which demands reasonable action. Emergency physicians (EPs) often are called on to identify a patient's personal, cultural, religious, or community values and to balance these values with their own personal and professional ethos. A working knowledge of bioethics greatly enhances the EP's ability to make reasonable, ethical decisions in the limited time frame common to the practice of emergency medicine.[1]

Unlike professional etiquette, which relates to standards governing the relationships and interactions between practitioners, bioethics deals with relationships between practitioners and patients, practitioners and society, and society and patients. Issues within the realm of professional etiquette include billing, referrals, advertising, competition, conflicts of interest, professional courtesy, employment and supervision of auxiliary personnel, the use of secret remedies and exclusive methods, and the location and appearance of an office, ED, or urgent care center. These are quite different from bioethics' concerns of basic moral values and patient-centered issues. Although the two areas occasionally overlap, each relies on different standards, values, and problem-solving methods.

Ethics and Emergency Medicine

In the ED, the focus is inevitably on the inherent "medical" nature of each case; therefore, it should come as no surprise that ethical dilemmas often are not recognized as being in the ethical rather than the strictly medical realm. A second, related failing of the specialty is to misperceive ethics as embodying the "commands" of secular or religious law, or as a discipline that describes irresolvable issues.[1]

This chapter addresses a number of ethical issues in emergency medicine. What follows are brief discussions of the relation of law to bioethics; bioethical values and principles; moral imperatives in emergency medicine; ethical oaths and codes; applying bioethics to clinical situations; bioethical dilemmas in emergency medicine; a rapid decision-making model for ethical dilemmas; advance directives; the relationship between consent, decision-making capacity, and surrogate decision makers; ethical issues in resuscitation; and ethical issues in public policy.

BIOETHICS AND THE LAW

Basic Considerations

Emergency physicians often look to the law for answers to knotty dilemmas. Yet, except in the rare cases of "black-letter law," wherein very specific actions are delineated, they are best served by turning to bioethical reasoning and using bioethics consultations. It is said that good ethics makes good law but that good law does not necessarily make good ethics. Societal values are incorporated both within the law and within ethical principles and decisions. Laws are rules of conduct established by legislatures, administrative agencies, courts, or other governing bodies. They often vary from locale to locale and are enforceable only in the jurisdiction where they prevail. By contrast, ethics is more universal, incorporating the broad values and beliefs of correct conduct. The primary differences between law and bioethics are shown in Table 200-1.

Modern bioethics developed during the past 4 decades because the law often has remained silent, inconsistent, or morally wrong on matters vital to the biomedical community. The rapid increase in biotechnology, the failure of both the legal system and legislatures to deal with new and pressing issues, and the increasing liability crisis drove the medical community to seek answers to the difficult questions practitioners had to work through on a daily basis.

Although bioethical principles do not change because of geography (at least not within one culture), interpretation of the principles may evolve as societies change. The same evolution occurs within the law. For example, elective abortion, once illegal in most U.S. jurisdictions, is now legal in most circumstances and jurisdictions. Likewise, all basic ethical

Table 200-1 Relationship between Law and Bioethics

BIOETHICS	FUNCTION/PRINCIPLE	LAW
✓	Case-based (casuistic)	✓
✓	Has existed since ancient times	✓
✓	Changes over time	✓
✓	Strives for consistency	✓
✓	Incorporates societal values	✓
✓	Basis for health care policies	✓
	Some unchangeable directives	✓
	Formal rules for process	✓
	Adversarial	✓
✓	Relies heavily on individual values	
✓	Interpretable by medical personnel	
✓	Ability to respond rapidly to changing environment	

Adapted from Iserson KV: Ethical principles—emergency medicine. In Schears RM, Marco CA (eds): Ethical Issues in Emergency Medicine. Emerg Med Clin North Am 24:515, 2006.

BOX 200-1 COMMONLY ACCEPTED MORAL RULES

Moral rules govern actions based on ethics and codes of conduct. These can justifiably be enforced and their violation punished. Although none of these rules is absolute, they all require one not to cause evil. Somewhat paradoxically, however, they may not require either preventing evil or doing good.

1. Do not kill.
2. Do not cause pain.
3. Do not disable.
4. Do not deprive of freedom.
5. Do not deprive of pleasure.
6. Do not deceive.
7. Keep your promise.
8. Do not cheat.
9. Obey the law.
10. Do your duty.

Modified from Gert B: Morality: A New Justification of the Moral Rules. Oxford, Oxford University Press, 1988.

principles do not have universal support, just as the values implicit in many legal changes have divided U.S. society.

Rights and Duties

Significant overlap exists between legal and ethical decision-making. Frequently there is concurrence on basic issues. On occasion, clarity within the law can lead to clearer thinking in bioethics, and vice versa. Both law and bioethics, for example, use the term *rights*, as in "patients' rights" and "the right to die." This term, often used to advance an ethical argument about medical care, frequently is misunderstood or applied erroneously. A legal right is a demand that a person can make on another person, embodied in *in personam* rights, or against the state for recognition and enforcement of this demand, as in *in rem* rights. Most rights involved in bioethical discussions are *in rem* rights. These most often are negative rights because they entail someone else's duty to refrain from doing something. A common source of ethical conflict is between "active rights," the right to act or not act as one chooses, and "passive rights," the right to not be acted upon by others in certain ways.[2]

Without a duty to act, there can be no rights. Both a moral and a logical connection exist between the rights and the duties of individuals; one cannot exist in the absence of the other. In general, a duty is an action required by the rights of others, the law, a higher authority, or one's conscience.[2] This obligation to act can be based on an individual's personal values, professional position, or other commitments.[3] For the physician, this duty to act is a role responsibility, at least specifically as a physician and possibly at all times. The role-duty link occurs "whenever a person occupies a distinctive place or office in a social organization, to which specific duties are attached to provide for the welfare of others or to advance in some specific way the aims or purposes of the organization."[4] In this circumstance, performance is not predicated on a guarantee of compensation but, rather, on a concern for another person's welfare.[5] The EP has just such a duty.

VALUES

Values are the standards by which human behavior is judged. Values are learned, usually at an early age, through indoctrination into the birth culture: from observing behavior and through secular (including professional) and religious education. Although many of these learned values overlap, each source often claims moral superiority over the others, whether the values are generic and cultural, legal norms, religious and philosophical traditions, or professional principles.[6,7] Societal institutions incorporate and promulgate values, often attempting to solidify old values even in a changing society. In a pluralistic society, clinicians treat people with multiple and differing value systems, so they must be sensitive to alternative beliefs and traditions.

This section discusses the role of religious, patient, institutional, and professional values, including professional oaths and codes specific to emergency medicine.

Religious Values

Organized religions are recognized as keepers of society's values. Even though various religions may appear dissimilar, most hold the golden rule, "Do unto others as you would have them do unto you," as a basic tenet. Other moral rules that are common to most religions are listed in Box 200-1. Problems surface in trying to apply religion-based rules to specific bioethical situations. For example, although "Do not kill" generally is accepted, the activities that constitute killing, active or passive euthanasia, or merely reasonable medical care vary with the interpretation of the world's religions as they do with the interpretations of various philosophers.[8-10] As members of a democracy with significant populations practicing a number of religions, EPs should behave in a manner consistent with each patient's values. The underlying question must be "What is the patient's desired outcome for medical care?"

Not only religious but also family, cultural, and other values contribute to patients' medical care decisions. Without asking, it is impossible to know what decision a specific person would make. An important point is that religion influences modern secular bioethics, which uses many religion-originated decision-making methods, arguments, and ideals. In addition, clinicians' personal spirituality may allow them to relate better to patients and families in crisis.[9]

Good versus Evil

The terms *good* and *evil* can be used to illustrate a stark dichotomy in ethical thought and values. The following is a current set of definitions that may help the physician find solutions to ethical problems. *Good* can be defined as what no rational person will avoid without a reason. Examples are freedom, pleasure, health, wealth, and knowledge. *Evil* can be defined as what all rational persons desire to avoid for themselves and for others they care about. Examples are untimely death, pain, disability, and loss of freedom or pleasure.[11] Rational persons with deeply held religious beliefs may, for example, refuse blood transfusion, choosing a likelihood of death over the permanent pain and anguish they feel would ensue if they should violate their religious injunction.

Patient Values and Ethical Decisions

A key to making bedside ethical decisions is to know the patient's values. Although many people cannot answer the question "What are your values?" physicians can get an operational answer by asking patients what they see as their goal of medical therapy and why they want specific interventions. The responses represent concrete expressions of patient values. In patients who are too young or are deemed incompetent to express their values, it may be necessary for physicians either to make general assumptions about what a normal person would want in a specific situation or to rely on surrogate decision-making. But with patients who are able to reason and communicate, care must be taken to discover what they hold as their own, uncoerced values.

Although each individual is entitled, and perhaps even required, to have a personal system of values, certain values have become generally accepted by the medical community, the courts, legislatures, and society at large. Autonomy and individual dignity, for example, are two such values: They have been considered fundamental and often are given overriding importance. Although some groups disagree about each of these values, this dissension has not affected their application to medical care.

FREQUENTLY CITED BIOETHICAL PRINCIPLES

Nonmaleficence and Autonomy

The basic tenet all medical students are taught is nonmaleficence: "First, do no harm." This credo, often stated in the Latin, *primum non nocere*, derives from the recognition that physicians can harm as well as help. With the physician's fallibility recognized, patient autonomy is and has been for several decades the overriding professional and societal bioethical value. Autonomy recognizes an adult person's right to accept or reject recommendations for medical care, even to the extent of refusing all care, if that person has appropriate decision-making capacity. It is the counterweight to the medical profession's long-practiced paternalism (or parentalism), wherein the practitioner determines what is "good" for the patient, regardless of whether the patient agrees. Coupled with paternalism is coercion, the threat or use of violence to influence behavior or choice. The august figure in white combined with implied or explicit threats remains a potent force for counteracting patients' wishes. The thrust of modern bioethics is to respect patients by honoring their autonomy (Box 200-2).

BOX 200-2 COMMONLY ACCEPTED SOCIETAL AND BIOETHICAL VALUES

Autonomy: Self-determination: a person's ability to make personal decisions, including those affecting personal medical care. Autonomy is the opposite of paternalism.
Beneficence: Doing good. A duty to confer benefits. Production of benefit.
Confidentiality: The presumption that what the patient tells the physician will not be revealed to any other person or institution without the patient's permission.
Distributive justice: Fairness in the allocation of resources and obligations. This value is the basis of and is incorporated into society-wide health care policies.
Nonmaleficence: Not doing harm, prevention of harm, and removal of harmful conditions.
Personal integrity: Adhering to one's own reasoned and defensible set of values and moral standards.

Beneficence

At the patient's bedside, beneficence (doing good) and confidentiality (holding information in confidence) have been long-held and nearly universal tenets of the medical profession. Similarly, personal integrity (the adherence to one's own moral and professional standards) is basic to thinking and acting ethically.

Justice

The concept of comparative or distributive justice suggests that a society's comparable individuals and groups should share similarly in the society's benefits and burdens. Many society-wide decisions affecting thoughts and actions about the allocation of limited health care resources are based on this principle. Yet for individual clinicians to limit or terminate care on a case-by-case basis is an erroneous extrapolation of the perceived need to limit health care resource expenditures.[7] Distributive justice is a policy concept, rather than a clinical model.

Truth-Telling

Personal integrity involves adhering to one's own reasoned and defensible set of values and moral standards and is basic to ethical thought and action. Integrity includes a controversial value within the medical community—truth-telling. Some people feel that the patient has the right to know the truth, no matter what the circumstances, and have championed absolute honesty. Yet many of these same people, when patients themselves, have been appalled by their physician's lack of sensitivity when relating unfavorable medical news.[12] In this context, being honest does not mean being brutal; truth is best tempered with a modicum of compassion.

Physicians accept a lack of truth-telling, depending on the circumstances. When patient harm may result from failing to disclose the truth, such as happened in the infamous Tuskegee experiments on black men with syphilis, it is not only immoral but also probably illegal to withhold the information. Likewise, when failure to disclose information is strictly for the physician's benefit, such as not telling a patient about a dismal prognosis or a medical error, the clinician's behavior suggests serious ethical and legal deficits. Perhaps truth-telling is not universally accepted within the medical profession

because of poor role models, lack of training in interpersonal interactions, and bad experiences, rather than because the value itself has been discounted. The issues become murkier when truth-telling, or lack thereof, involves a third party, such as a sex partner who has been exposed to an infectious disease.[13]

Confidentiality versus Privacy[9]

Stemming at least from the time of Hippocrates, confidentiality is the presumption that what the patient tells the physician will not be revealed to any other person or institution without the patient's permission.[9] Health care workers have an obligation (duty) to maintain patient confidentiality. Occasionally, the law, especially public health statutes, may conflict with this principle, because they require physicians to report specific diseases, injuries and injury mechanisms, and deaths. Drug-seeker lists, long used in EDs, can be seen as violations of patient confidentiality, and especially without firm controls on patient entry and clinician access to these lists, they can directly harm patients.[14] Rarely discussed are similar computer lists of previous ED visits that can be easily generated from most ED computer systems. The Health Insurance Portability and Accountability Act of 1996, a U.S. federal law designed to protect patient information, however, takes the principle of confidentiality to the extreme, resulting, paradoxically, in greater difficulty in obtaining crucial information needed to treat ED patients.

Privacy, which often is confused with confidentiality, is a patient's right to sufficient physical and auditory isolation that they cannot be seen or heard by others during interactions with medical personnel.[9] ED overcrowding, patient and staff safety issues, and ED design limit patient privacy in many cases.

The increasing use of telemedicine to render advice and guide procedures at remote sites also places a strain on both patient privacy and confidentiality. Suggested ethical guidelines for such practice can facilitate the use of these new technologies without sacrificing either patient rights or physician duties.[15]

Another recent development has been filming ED patients for public viewing. Such filming, whether for medical records, education, peer review, or "reality television," encroaches on ED patients' reasonable expectation of privacy and confidentiality, because the recording can easily be distributed or misused. Although good reasons exist to allow such filming with patient acquiescence,[16] the standard is now to abstain from such filming for commercial purposes and to require patient or surrogate consent for educational purposes.[17]

MEDICAL AND MORAL IMPERATIVES IN EMERGENCY MEDICINE[9]

Professional Values

Emergency clinicians, in both the out-of-hospital care and ED environments, operate with four imperatives: to save lives when possible, to relieve pain and suffering, to comfort patients and families, and to protect staff and patients from injury. All but the last of these also are the imperatives of most other clinicians, although saving lives may occur more often and more dramatically in emergency medicine settings.

Clinical Competency

Although it is tempting to use the latest instruments or medications, physicians have a duty to obtain competency in new technologies, and to be informed of new medications, to decrease any risks to patients. Because there is little oversight of individual practitioners in this area, it remains a substantial matter for personal ethics.[9]

Emergency Medical Services Personnel Values

Emergency medical services (EMS) personnel are required to attempt resuscitation except when there is no chance that life exists (e.g., with decapitation, rigor mortis, charring of a body beyond recognition, decomposition). They usually have little leeway in whom to resuscitate, resulting in prolonged dying for some patients. The real answer is for primary physicians to educate the families of homebound, hospice-type patients to call their clinician to pronounce death, rather than 911.

Safety: A Unique Value

The last imperative, safety, is nearly unique to emergency medical clinicians. Both in the out-of-hospital and ED settings, clinicians often encounter dangerous situations in which the environment (e.g., fires, wilderness, floods), the patient, or a family member poses a threat. Although most try to accommodate basic patient rights, clinicians' priority must be their own safety and the safety of their coworkers. This priority does not imply that clinicians should ignore patient safety, but only that they should first ensure their own safety if they or their colleagues are at risk.

CODIFYING PROFESSIONAL VALUES: ETHICAL OATHS AND CODES

Conflicting Principles

In the abstract, bioethical principles often appear simple. However, clinicians adhere not only to basic bioethical principles but also, at least tacitly, to a number of professional, religious, and social organizations' ethical oaths, codes, and statements.[9] This complexity can make for a confusing array of potentially conflicting bioethical imperatives. Because bioethical principles seem to be neither universal nor universally applied, the principles that are most patient-centered normally hold sway.

Organizational and Institutional Values

Institutions, including health care facilities and professional organizations, have their own value systems. Health care facilities, although relatively well standardized under the requirements of regulatory bodies and government agencies, often have specific value-related missions. Religiously oriented or affiliated institutions may be the most obvious of these, but charitable, for-profit, and academic institutions also have specific role-related values. The values of professional organizations often are set forth in their ethical codes.

Professional Codes

Through the years, the medical profession has codified its ethics more rigorously than any other professional group, incorporating many standard bioethics principles into its ethical codes and oaths. For generations, the existing part of the Hippocratic Oath set the ethical standard for the medical profession.[18] Yet its precepts clash with modern bioethical thinking, and many subsequent professional codes have included what may best be termed economic guidelines and

Table 200-2 Comparison of Six Ethical Codes for Physicians

PRINCIPLE/CONCEPT	SAEM	ACEP	EMRA	AMA	AOA	HIPPOCRATIC OATH
Protect patient confidentiality		×	×	×	×	×
Maintain professional expertise	×	×	×	×	×	×
Committed to serve humanity	×	×	×	×	×	
Patient welfare primary concern	×	×	×	×		×
Considerate to patients, colleagues	×	×	×	×		×
Respect human dignity	×	×	×	×		×
Safeguard public health	×	×	×	×		×
Protect vulnerable populations	×	×		×	×	×
Advance professional ideals	×	×	×	×		×
Honesty		×		×	×	
Report incompetent, dishonest, impaired physicians		×	×	×		
Moral sensitivity	×	×		×		
Obtain necessary consultation				×	×	×
Altruism in teaching	×					
Fairness to students, colleagues				×		×
Obey, respect the law			×	×	×	
Prudent resource use	×	×				
Work to change laws for patient benefit				×	×	
Not abuse privileges	×					×
Respect for students	×					×
Choose whom to serve except in emergencies				×	×	
Ensure beneficial research by employing competence, impartiality, compassion	×					
No abortions						×
No euthanasia						×
Do not compromise clinical judgment for money			×			
Universal access to health care				×		
Preserve human life						×

ACEP, American College of Emergency Physicians; AOA, American Osteopathic Association; AMA, American Medical Association; EMRA, Emergency Medicine Residents' Association; SAEM, Society for Academic Emergency Medicine.
Adapted from Iserson KV: Ethical principles—emergency medicine. In Schears RM, Marco CA (eds): Ethical Issues in Emergency Medicine. Emerg Med Clin North A 24:531, 2006.

professional etiquette, along with ethical precepts.[19] EP professional values have been incorporated into organization codes, such as the American College of Emergency Physicians' *Code of Ethics*, and into a more personal oath developed by the Society for Academic Emergency Medicine.[20,21]

Most modern ethical codes prescribe only the same basic moral behavior for members to follow that is expected by the society at large and do not require any higher level of duty or commitment. In fact, many of the ethical issues that would seem to be important to medical specialties usually are not addressed in their codes. Even when topics of interprofessional interactions are excluded, existing medical professional codes differ markedly (Table 200-2). All, however, try to give a "bottom line"—that is, minimally acceptable—course of action.

APPLYING BIOETHICS

Emergency Physician–Patient Relationship

The EP has a markedly different relationship with patients from that typical for other practitioners, especially those providing primary care[22-24] (Table 200-3). EPs care for patients who are unfamiliar to them and to the institution. Practitioners who either know their patients or who care for them in less acute settings often have the time and the mechanisms for making sound ethical decisions, but EPs have more limited options. A suggested method for rapid, ethical decision-making in the ED setting is outlined in Box 200-3 and discussed in a later section.[25]

Recognizing Ethical Problems

Although physicians like to reduce all clinical situations to "medical problems," today's increasingly complex medical environment often produces problems that are inexorably intertwined with fundamental bioethical dilemmas. Some are obvious, but many are more difficult to recognize.

Prioritizing Conflicting Principles

Once such dilemmas are recognized, applying bioethical principles to clinical situations can be confusing. When two or more seemingly equivalent principles or values seem to compel different actions, a bioethical dilemma exists. This situation is often described as being "damned if you do and damned if you don't," in which any potential action appears, on first reflection, to be an option between two seemingly equivalent goods or evils. In the following real case, taken from the book *Ethics in Emergency Medicine*, the attending physician can be said to be on the horns of a dilemma (involving two prickly but seemingly equal choices): Although only two options for

Table 200-3 Relative Differences between Emergency Practice and Primary Care Practice

ED SETTING	PRIMARY CARE SETTING
Patient often is brought in by ambulance, police, or family.	Patient chooses to enter medical care system.
Patient does not choose physician.	Patient chooses physician.
ED personnel must gain patient's trust.	Physicians and nurses already enjoy patient's confidence and trust.
ED personnel do not know patient, family, values.	Physicians and nurses often already know patient, family, values.
Patient experiences an acute change in health status.	Patient has chronic medical problems.
Anxiety, pain, alcohol, and altered mental status are common.	Anxiety, pain, alcohol, and altered mental status are less common.
Decisions are made quickly.	There is usually time for reflection and deliberation.
Physician makes decisions independently.	Physician has greater opportunity to consult with patient, family, other physicians, ethics committees, lawyers, courts, ethicists.
Physician represents institution and medical staff.	Physician represents self or medical group.
Work environment is open and less controlled.	Work environment is private and controlled.
ED personnel frequently have a stressful work schedule.	Work schedule often is set or canceled by physician.

ED, emergency department.
Modified from Sanders AB: Unique aspects of ethics in emergency medicine. In Iserson KV, Sanders AB, Mathieu D (eds): Ethics in Emergency Medicine, 2nd ed. Tucson, Ariz, Galen Press, 1995.

BOX 200-3 A Rapid Approach to Ethical Problems in the ED

Is this a type of ethical problem for which you have already worked out a rule, or is it at least similar enough that the rule could reasonably be extended to cover it?

- YES → Follow the rule.
- NO → Is there an option that will buy you time for deliberation without excessive risk to the patient?
  - YES → Take that option.
  - NO →
    1. Apply Impartiality Test.
    2. Apply Universalizability Test.
    3. Apply Interpersonal Justifiability Test.

ED, emergency department.
Modified from Iserson KV: An approach to ethical problems in emergency medicine. In Iserson KV, Sanders AB, Mathieu D (eds): Ethics in Emergency Medicine, 2nd ed. Tucson, Ariz, Galen Press, 1995.

action may be available, both options involve a number of conflicting bioethical principles.

Case Example: Conflicting Bioethical Principles

A 60-year-old man stabbed himself in the abdomen because of intractable pain from terminal pancreatic cancer, unrelieved by any medical therapy. A well-meaning friend, who happened to be in the house when the event occurred, called the paramedics, who brought him to the ED. Although the man will obviously bleed to death if not given aggressive care, neither the patient, who is still alert and oriented, nor his wife, who is present, wants any treatment other than pain control. A review of his chart confirms that his physicians are at a loss as to how to alleviate his pain and that he is expected to die within the next several weeks.[26] The physician believes in respecting a patient's autonomy, yet usually questions patients' decision-making capacity when they attempt suicide. Such patients' actions seem to raise the question of whether, in fact, they have a right or an ability to be autonomous. This physician also believes strongly in beneficence: helping those in need, relieving pain, and saving lives when possible. Beneficence suggests two alternative courses of action: palliative care or aggressive therapeutic intervention. Merely using analgesics and other comfort measures will abet a suicide; initiating aggressive medical and surgical interventions will prolong a dying process that the physician's colleagues have found to be unresponsive to even palliative treatment. Which value takes precedence: patient autonomy or beneficence? And if beneficence predominates, should it be aimed toward relieving suffering, prolonging life, or a third option that could include both? Bioethics deals with problems that are neither black nor white—only gray.[27]

MEDICAL IMPERATIVES AND BIOETHICAL DILEMMAS

Clinicians have their own ethical values, as do professional organizations and health care institutions. Conscience clauses permit clinicians to "opt out" when they feel that they have a moral conflict with professionally, institutionally, or legally required actions. These conflicts, which may have a religious, philosophical, or practical basis, pose a barrier to use of the normal ethical decision-making algorithm. When such conflicts exist, it is morally and legally acceptable, within certain constraints, for the physician to follow a course of action based on his or her own value system. The constraint generally requires that timely and adequate medical care be provided for the patient—which may be particularly difficult to achieve in emergency medicine. When conflicts over values exist, however, it is essential for the practitioner to recognize the patient's identity, dignity, and autonomy, to avoid the error of blindly imposing personal values on another.[9]

Professional Value Conflicts

The imperative to save lives causes the most conflict between EPs and intensive care unit (ICU) clinicians. EPs recognize that some of the intubations and resuscitations they perform will be unwanted by patients or surrogates. Nearly all EPs have on occasion been berated by an irate intensivist or private practitioner for resuscitating a patient "who should not have been resuscitated." Many families have heard these physicians criticize the ED and ambulance staffs for overaggressive resuscitative efforts. Nevertheless, the lifesaving imperative begins when the ambulance is called.

One classic dilemma is that posed by the exsanguinating adult patient, awake and still with medical decision-making

capacity, who explicitly states a refusal to accept any blood or blood products based on religious beliefs. The physician, with a professional duty and moral commitment to preserve life, does not agree with the patient's decision. Yet society (through the benchmark of court decisions) has repeatedly sided with the patient. In this case the patient's autonomy and right to practice his or her religion are recognized as the overriding values. The case becomes less clear when the patient does not have decision-making capacity, is a minor, or appears to be under external pressure to make a life-threatening decision.

Other examples of ethical problems and conflicts in emergency medical care are uncertainty regarding resuscitation efforts, especially when patients and families may not want such efforts; teaching, particularly in critical situations or using procedures performed on the newly deceased; EMS control, when administrative rules and good patient care conflict; helping others when one's own life may be placed at risk; and patient access, such as limited financial and personnel resources in the face of obvious patient need. Even if these problems do not fit into the classic form of a dilemma, they may be recognized as bioethical problems because they require the clinician to make a choice between two (or more) accepted values.

Rapid Ethical Decision-Making Model

The rapid ethical decision-making method of ethical case analysis, described in Box 200-3, is designed as a way of avoiding an ethically incorrect course of action for the EP in need of a fast answer to an ethical dilemma. A decision based on a known precedent—the first step—is the most productive way to use this method. However, such decision making requires advance planning, in-depth reading, and thought regarding ethical problems. Just as with the indications for any emergency procedure, EPs should at the very least be prepared with a course of action for the most common ethical dilemmas they may face in the ED.

Even the prepared clinician, however, can encounter cases without relevant known precedents. With no precedent to rely on and no way to "buy time," the practitioner must select a possible course of action and test it for ethical validity. In such instances, three tests—the Impartiality Test, the Universalizability Test, and the Interpersonal Justifiability Test—can be used. The *Impartiality Test* asks whether the practitioner would accept this action if he or she were in the patient's place. In essence, this is a form of the golden rule. The *Universalizability Test* asks whether the practitioner would feel comfortable having all practitioners perform this action in all relevantly similar circumstances. This involves generalizing the action to all colleagues and then asking whether a rule for the contemplated behavior is reasonable. The *Interpersonal Justifiability Test* asks whether the practitioner can supply good reasons to others for the action. Will peers, superiors, or the public be satisfied with the answers? If the answer to the question posed in each of the three tests is affirmative, then the practitioner has identified a reasonable probability that the proposed action falls within the scope of ethically acceptable actions.[25]

Advance Directives

The term *advance directive* describes several types of legal and quasilegal documents. These documents indicate what is to be done for a patient *in extremis* who is no longer able to give or withhold permission for medical treatment. Advance directives usually are written to avoid prolonging an inevitable, often painful or nonsentient dying process. However, they also can be used to instruct surrogates and the patient's medical team to "do everything," whenever possible. Advance directives include the living will, durable power of attorney for health care (DPAH), prehospital advance directive (PHAD), and mental health advance directive (MHAD). Although do-not-attempt-resuscitation (DNAR), do-not-hospitalize, and out-of-hospital DNAR orders also are discussed in this section, they are not considered to be advance directives but rather are physician orders, because they are not patient- or surrogate-initiated. All play a role in emergency medicine.[28,29]

Do-Not-Attempt-Resuscitation Orders

DNAR orders, also known as allow-natural-death (AND) and do-not-initiate-resuscitation (DNIR) orders (still somewhat naively called do-not-resuscitate [DNR] orders in many locales), are physician orders informing other medical personnel that they should not institute cardiopulmonary resuscitation (CPR) in the event of cardiopulmonary arrest. (The DNAR order is not strictly an advance directive but does serve to transmit a conditional order to other health care personnel and is operative only if the patient's condition follows a certain pattern.) Ideally, this order is written only after consultation with the patient (who possesses decisional capacity) or with the patient's family or surrogate decision maker. It usually is written only for patients for whom CPR will not achieve the patient's goals of therapy. These orders usually work well within a specific institution, but if patients are transferred to the ED from another facility, the act of transfer or the activation of the EMS system usually negates the order. This outcome can be directly contrary to a patient's wishes regarding terminal care. However, if a patient arriving in the ED still has the capacity to make a decision concerning resuscitation, part of the EP's duty is to document such a decision in the patient's chart, including the specific actions to be limited, the circumstances of the discussion, and the people present during the discussion.[30,31] Many institutions have now recognized that simple DNAR forms are inadequate descriptions for other health care personnel to interpret and thus have changed to or added a limitation-of-treatment form specifying exactly what is not to be done for a patient (e.g., antibiotics, blood products, mechanical ventilation, surgery).

Do-Not-Hospitalize Orders

One type of physician order that has been used successfully in many locales is the do-not-hospitalize order. Normally used for hospice and nursing home patients, it prevents many unwanted ED resuscitation attempts and procedure-laden hospitalizations. Do-not-hospitalize orders instruct nurses not to send the patient to the hospital if further medical interventions are not desired either by the patient or the surrogate decision maker. Compliance with this physician order allows people to die peacefully, rather than having the "last rights of CPR" performed when such interventions would be futile or unwanted. The only caveat to applying do-not-hospitalize orders is that staff members must understand that patients should still be sent to a hospital if they need palliative care not available in the nursing facility.

Out-of-Hospital Advance Directives

As of 2003, 43 U.S. jurisdictions had enacted methods whereby patients outside of health care facilities can avoid unwanted resuscitation attempts. These methods usually take the form of preparing either an out-of-hospital DNAR order or a prehospital advance directive (PHAD).[32] Although often confused, the two forms differ greatly in their philosophies. The out-of-hospital DNAR order is a physician-originated document.[33]

The PHAD is generated by a patient or legal surrogate, with little or no involvement by health care personnel. Both instruct EMS personnel who have been erroneously called at the time of death not to attempt to resuscitate the patient, or to stop resuscitation efforts if they have already begun when such a form is found. Both types of form have proved effective.[32-34] The most common reason for having physician-initiated forms is the fear that murders and suicides could be aided by patient-initiated documents. In practice, this has not occurred.

Of the existing protocols, 34 were specifically authorized by statute, usually supplemented by regulation or guidelines. Eight states implemented protocols solely through regulations or guidelines, without a change in their legal code. Eight states have no statewide protocol in place. In an affront to patient autonomy, 39 are physician orders requiring a physician's signature (7 states require only a physician's signature; 33 states require signatures of both a physician and the patient).[33] Three protocols are patient-initiated advance directives that are valid with a witnessed patient signature, with no physician involvement required.[35] These instruments are of variable complexity; some include liability protection for EMS personnel and base station providers, and some may be usable for pediatric patients.[32-37] Table 200-4 contains a list of the elements ideally included in a PHAD/DNAR policy.

Out-of-hospital DNAR orders or directives must be understandable to all involved, including EMS personnel, physicians, patients, family members, and police, who also may respond to a 911 call. These documents can take many forms, such as a uniform system of state forms, physician orders, standard wallet identification cards or identification bracelets, and other mechanisms approved by the local EMS system. The ideal out-of-hospital directive should continue to be effective if the patient is transferred to a health care institution, at least in the ED.[32]

Living Will

The *living will* is a relatively standardized form adopted in most states and the District of Columbia. (Michigan and Massachusetts do not have authorizing statutes.) This document usually requests that health care workers not perform future resuscitative measures, but on occasion it requests the opposite—that all measures be taken to keep the patient alive. It goes into effect only if the patient lacks decision-making capacity; until that point, the patient continues to determine the medical course, despite anything said in a living will. Living wills normally require both that a physician certify a person as terminally ill and that the patient have the mental capacity to understand its provisions at the time it is signed. (Arizona, in a break with tradition, does not use "terminally ill," because all extant definitions are unclear. No ill effects have resulted.[37]) States allow various levels of specificity in the document, including, in some cases, the ability to refuse artificial nutrition and hydration.

Table 200-4 Guidelines for Developing an Out-of-Hospital Advance Directive Policy

Policy Scope

To ensure maximum coherence and compliance, a comprehensive out-of-hospital DNAR policy should be endorsed by the widest possible jurisdiction, comprising local, regional, state, and the medical community, including the EMS governing body. Whenever feasible, legislative support for such a policy should be sought.

Policy Guidelines

1. Note the established fact that current basic and advanced life support interventions may not be appropriate or beneficial in certain clinical settings.
   - Develop a means to educate the public about the appropriate use of 911 after expected deaths.
   - Establish the fact that comfort care and palliative care are affirmative actions for patients with DNAR orders. These appropriate interventions, including hospice and respite care, do not require EMS activation and often can be arranged by calling the patient's physician in anticipation of death.
   - Develop a means to educate health care workers on topics of advance directives, including information on local out-of-hospital DNARs, community hospice alternatives, and bereavement services.
2. Establish consensus on the ideal identification device for DNAR directives to ensure continuity of care across settings.
3. Reiterate that initial resuscitative attempts usually are indicated when the patient's wishes are not known.
4. Define the conditions under which an out-of-hospital DNAR order can be considered, including its use in long-term care settings and in the emergency department.
5. Define which patients have the decisional capacity to agree to a DNAR order and whether surrogates can sign such orders.
6. Establish a mechanism for determining the precedence of various directives, including living will, durable power of attorney for health care, and out-of-hospital advance directive (i.e., DNAR order).
7. Develop a statutory prioritized list of surrogates to use when there are no advance directives and the patient's decisional capacity is impaired.
8. Consider language acknowledging the growing home hospice movement as it concerns children, and incorporate provisions for document use in minors.
9. Establish that the decision not to attempt resuscitation must be an informed decision made by the patient or the surrogate.
10. Identify the information that should be contained in the DNAR order and the authority that will be responsible for developing such a mechanism.
11. Identify the clinical procedures that are to be provided and those withheld in the adherence to the DNAR order, or specify the authority that will verify adherence.
12. Define the exact manner in which the DNAR order is to be followed, including the role of online medical direction. Each system should ensure that a communication path to access online medical direction is immediately available, when necessary.
13. Establish legal immunity provisions for those who implement DNAR orders in good faith.
14. Establish data collection and protocol evaluation to perform periodic operational assessments.
15. Identify permissible exceptions to compliance with DNAR out-of-hospital directives. For example:
    - The patient is able to revoke a written directive at any time.
    - The EMS personnel can cancel the out-of-hospital DNAR order if there are doubts about the document's validity.

DNAR, do-not-attempt-resuscitation; EMS, emergency medical services.
Modified from Schears RM, Marco CA, Iserson KV: 'Do-not-attempt-resuscitation' (DNAR) policy in the out-of-hospital setting. Ann Emerg Med 44:68, 2004.

Most living wills specify that the patient's physician must have seen and accepted the document's provisions in advance. This requirement establishes a physician who will act on the patient's behalf. For physicians, it protects those whose value systems will not allow them to abide by the document's provisions. It also encourages families and physicians to discuss the circumstances surrounding the time of death and the actions they can take.[38] The EP will rarely, if ever, be in the position of having accepted a living will's provisions. In the setting of an ED resuscitation, the best that a living will can do, assuming that the patient is correctly identified, is to suggest what the patient's wishes were. It does not in any way restrict the EP's actions.[39]

The limitation of living wills is that they list specific actions—either to take or to eschew—in a particular set of circumstances. This specificity reduces the usefulness of such documents and has led to a more flexible and powerful advance directive that names a trusted surrogate decision maker, the DPAH.

Durable Power of Attorney for Health Care

A more commonly used advance directive that specifies a surrogate decision maker is the *durable power of attorney for health care* (DPAH). It goes by many other names, including *durable power of attorney with medical provisions* and *medical directive*. All states and the District of Columbia have statutes authorizing such directives. In its usual form, a durable power of attorney (other than for health care) takes effect immediately. However, a DPAH takes effect only when the individual no longer has the capacity to make his or her own medical decisions.

Typically, a relative or close friend is named as a surrogate, because such persons should know something about the patient's values related to medical treatment. More than one surrogate may be named; they generally are listed in preferential order, with the first being someone who is able to be contacted and is willing and able to act as surrogate in making the decisions.[38]

The DPAH allows more flexibility than a living will, because the surrogate is able to make any health care decisions that the patient would ordinarily make, including gathering new information and choosing among multiple treatment options as the medical situation changes. Optimally, the surrogate's decisions are guided by other written or oral directions the patient has left, including those in a living will. In reality, surrogates often consider many factors when making decisions.[40]

Mental Health Advance Directives

Mental health advance directives (MHADs), also known as *psychiatric advance directives* (PADs), were introduced in the 1980s so that psychiatric patients could specify their preferences regarding future mental health treatment during acute psychiatric illnesses.[41] MHADs allow psychiatric patients to document in advance their acceptance or refusal of particular types of mental health treatment and intervention. Some of these laws also incorporate authorization of proxy decision makers specifically for mental health treatment. Most MHADs can be revoked only if the patient regains decision-making capacity.[42] In practice, civil commitment laws usually override MHADs, as do clinicians who, acting in good faith, consider the instructions to be inconsistent with accepted clinical standards of care.[43]

Nonstandard Advance Directives

EPs occasionally encounter medallions, tattoos, or other indications that seem to be advance directives.[44,45] To be useful, advance directives must be available to the treating clinicians when they are needed, be a product of the patient's (or sometimes the surrogate's) deliberations, and be understandable, and must be applicable in the patient's current medical situation. Nonstandard directives, usually abbreviated or abstract (such as a tattooed symbol for "do not defibrillate"), fail to meet these requirements. Of special concern is whether the patient or the surrogate understood how this "directive" might be interpreted or whether it still communicates the patient's wishes. In general, EPs should not rely on these indicators to make critical patient decisions.

CONSENT, DECISION-MAKING CAPACITY, AND SURROGATE DECISION MAKERS

Respect for patients, the basis for patient autonomy, requires that adults consent before undergoing medical interventions. To give consent, they must retain decision-making capacity. When patients cannot make their own health care decisions, others must make such decisions for them. In such situations, three questions arise: What does "consent" mean in the ED? How can clinicians determine when patients lack such capability? Who then makes the decision?

Consent

Patients can provide three forms of consent: presumed, implied, and informed. Many patients may provide all three types of consent at different times during a single ED visit. Because clinicians use all three types of consent in EDs, and all are ethically and legally valid, clarifying the differences between them is in order.[46]

The concept of *presumed consent* most commonly applies when patients are informed of what will occur and they do not refuse treatment. They allow themselves to be rolled on a gurney to the radiology suite to have a urethral catheter placed, and they remain still while being sutured. The more dramatic ED scenario involving presumed consent is the arrival of moribund patients with grave, often unstable conditions for which a reasonable person would be expected to want treatment. In those cases, clinicians "presume" that rational patients would want treatment. A question that must be raised, however, is whether those patients would want interventions even in the absence of a reasonable chance for meaningful (from the patient's standpoint) survival. Futility often is discussed from the clinician's perspective; whether patients would give consent in these circumstances raises the question from the more valid patient's perspective.[46]

Implied consent is operative when patients actively cooperate with the procedure, such as when they extend the arm for phlebotomy or lift the blouse so ECG leads can be placed.[46] Working under presumed or implied consent does not signify absence of patients' concern regarding the procedure or its complications. Rather, patients may (1) believe they know enough about the procedure to permit it or to cooperate with it without further questioning, (2) be in a condition (e.g., unconscious) in which they are unable to communicate, or (3) feel too afraid (e.g, of the clinician or hospital authority) or uncomfortable (e.g., because of a language barrier) to ask.[46]

Informed consent assumes that a patient who has decision-making capacity has been given all pertinent facts regarding the risks and benefits of a particular procedure, understands them, and voluntarily agrees to undergo the procedure.[46] Even if a patient with decisional capacity does not ask about a complex or potentially dangerous procedure, the clinician is obligated to provide information about the associated risks and benefits, unless the patient specifically asks not to be told. In

those cases, the patient should be asked if he or she would like a relative or friend present in the ED to be told. This person need not be the patient's surrogate but may later help to explain what occurred to the patient.[46]

Informed consent relates to both law and ethics. Respect for persons is the requirement's ethical bulwark; statute and common law provide the legal rationale. Physicians have a professional and moral obligation to provide their patients with the information necessary to make informed decisions. Communicating honestly with patients so that they may participate in decision-making is a recent, rather than historical, imperative. Based on a respect for patients, this cooperative physician-patient relationship reverses the paternalism that, since Hippocratic times, has guided physician interactions with patients.[46,47]

Virtually all states, either in statute or by common law, now require physicians to inform patients about treatment choices and the associated risks and benefits. The legal standard for the information provided is either the "community standard" (also known as the "professional community standard" or the "reasonable physician standard") or the "materiality standard" (also known as the "reasonable or prudent or subjective patient standard"). The former asks: "What would a prudent physician in the same community, with the same background, training, and experience have disclosed to a patient in the same or similar situation?" The latter asks: "What would a reasonable patient in the same or similar situation need to know to make an appropriate decision?"[46,47]

Of interest, great variability exists in the legal requirements. For example, although most of the nation's EDs require informed consent for many regional anesthetic blocks, closed fracture reductions, abscess incision and drainage, lumbar punctures ("spinal taps"), injection of radiocontrast agents and radionuclides for radiography, and nonemergency thoracostomy (chest tube placement), Texas statutes eliminate any requirement to disclose the specific risks or hazards before these procedures are performed.[46,48]

Decision-Making Capacity

Many ethical dilemmas in emergency medical care dissolve on ascertaining the patient's decision-making capacity, often linked with consent to (or, more commonly, refusal of) a medical procedure. A basic canon of both ethics and law, as stated by Justice Benjamin Cardozo, is that "[e]very human being of adult years and sound mind has a right to determine what shall be done with his own body … ."[49] These situations often can be clarified by an appreciation of what is meant by decision-making capacity and how it relates to consent.

EPs must be prepared to decide quickly whether patients lack decision-making capacity—the ability to make their own health care decisions. Although a lack of capacity is obvious in the unconscious or delirious patient, it often is less apparent when the patient remains verbal and at least somewhat coherent. Because such decisions in emergency situations often are time sensitive, unlike in other medical venues, bioethics consultations may not be readily available.

In clinical practice, the word *competence* often is used to mean *capacity*. *Competence* is a legal term and can be determined only by the court. *Capacity* refers to a patient's ability to make decisions about accepting health care recommendations. Capacity is always decision-relative rather than global. Although an inebriated person can have the capacity to refuse to have a small laceration sutured, especially if there is evidence of prior refusal without remorse, the same person may not have the capacity to agree to an elective operation or to refuse to have an emergent lifesaving procedure or operation. To have adequate decision-making capacity in any particular circumstance, the person must understand the options, the consequences of acting on those options, and the costs and benefits of the consequences in relation to a relatively stable framework of personal values and priorities[50,51] (Box 200-4). Disagreement with the physician's recommendation is not in itself grounds for determining that the patient is incapable of making a decision. In fact, even refusing lifesaving medical care may not prove the person incapable of making valid decisions if it is done on the basis of firmly held religious beliefs, as in the case of a Jehovah's Witness patient who refuses a blood transfusion.

BOX 200-4 COMPONENTS OF DECISION-MAKING CAPACITY

1. Knowledge of the options
2. Awareness of consequences of each option
3. Appreciation of personal costs and benefits of options in relation to relatively stable values and preferences*

*As part of the assessment for capacity, the patient should be asked about why he or she made a specific choice.

Modified from Buchanan AE: The question of competence. In Iserson KV, Sanders AB, Mathieu D (eds): Ethics in Emergency Medicine, 2nd ed. Tucson, Ariz, Galen Press, 1995.

Surrogates

If patients lack capacity to participate in some decisions about their care, surrogate decision makers must become involved. In most locales, the patient's advance directive may designate surrogates, or such persons or agencies may be detailed in institutional policy or law. Surrogates often include spouses, adult children, parents (of adults), and others, including the attending physician. On occasion, bioethics committees or the courts will need to intervene to help determine the decision maker.

Children represent a special case. Persons younger than the age of majority (or unemancipated) usually are deemed incapable of making independent medical decisions, although they often are asked to give their assent to the decision, allowing them to "buy in" to their medical treatment plan. In many cases, when determining whether a child has decision-making capacity, the same rules as those that apply to adult capacity are used. The more serious the consequences, the more the capacity to understand the options, consequences, and values involved is required of children to make a decision.[9]

In the relatively rare case in which a patient has a court-appointed guardian for health care decisions, the guardian's decisions supersede those of both the patient and any other surrogates. Even if a parent is present, it is not always clear that the adult is acting in the best interest of the child. In such cases, child protective services may need to become involved. Disagreements between parents may, in extreme cases, require the involvement of bioethics committees or the courts.

Family

Traditionally, and usually in practice, the family, in particular the spouse, acts as a surrogate decision maker when the patient does not have the capacity to make medical decisions. Yet even when there is a strong family tie, emotional or fiscal costs may sway the surrogate decision maker from certain courses of action the patient would wish taken.

Surrogates make decisions based on two distinct patterns: substituted judgment and best interests. *Substituted judgment* is used when there is an assumption that the surrogate knows enough about the patient's values to make a decision similar to that which the patient would make. It is not clear that anyone knows that much about a person to make decisions in every situation.[52,53] Surrogates use the *best interest* standard when they do not know what the patient would want done in a particular situation but, as in the case of Karen Ann Quinlan, they can use earlier statements and behavior to document the patient's values and then make a decision.[54] Some states may require explicit written directives for surrogates to follow.[55,56] The best interest standard also applies, as in the Saikewicz case, when the patient has never had adequate decision-making capacity.[57] Unless there is already a court-appointed guardian, these situations often end up in court.

Surrogate Lists

If a patient lacks decision-making capacity and has no advance directive, many states provide that another person may automatically become the person's surrogate. In practice, this almost always means that the patient's spouse may act in that capacity. Some states now have a statutory surrogate list to simplify the process. The most extensive of such lists, which has worked well for nearly 2 decades, specifies surrogates in the following order: spouse (not divorced or legally separated), a majority of the adult children who can be reasonably contacted, parents (of an adult), domestic partner, sibling, close friend, and attending physician in consultation with a bioethics committee.[37]

Bioethics Committees and Consultants

Multidisciplinary committees have been developed in most large hospitals to consult on cases with bioethical dilemmas and also may participate in surrogate decision making.[37] These committees usually have four main functions. First, they coordinate education on bioethical issues involving clinical care for the committee members, hospital physicians and staff, patients, families, and the local community. Second, they help institute mandatory or suggested policies or guidelines for health care professionals regarding decision-making processes in problematic cases and resource allocation. Third, they consult prospectively and retrospectively on clinical cases and offer advice and conclusions to those directly involved, most often concerning the treatment or nontreatment of patients who lack decision-making capacity. Ethics committees usually do not act as the primary decision makers. Rather, its members serve as consultants, providing information, advising, and supporting the primary decision-making role of the patient-family-physician triad. A common consultation relates to urgent decisions about withholding, withdrawing, or continuing life-sustaining medical care. A large part of ethics committee work consists of clarifying the facts and fostering communication.[58] Some smaller hospitals have bioethics consultants rather than committees to perform many of the same functions. In 1995, The Joint Commission (formerly the Joint Commission for the Accreditation of Healthcare Organizations [JCAHO]) began requiring that hospitals ensure that ethics committees' functions are accomplished.[59]

Physicians

In the past, physicians made unilateral decisions for their patients, regardless of whether the patients had the capacity to decide for themselves. This still occurs, of course—especially for the acute illnesses and unexpected injuries seen in EDs. There is a tendency for physicians to determine that a patient does not have the capacity to make medical decisions simply because the patient disagrees with the clinician. If the patient's decision-making capacity is questioned in the ED, the clinician often is forced to make a decision without assistance. But when it is possible to "buy time," clinicians should consult with colleagues and, if possible, the hospital's bioethics committee (see Box 200-3). When making unilateral decisions, physicians should recognize that they are not omniscient. Prognoses often are incorrect and medical knowledge is finite.

Courts

The courts often act as the final adjudicators of disagreements over medical care. They appoint legal guardians and, in a few select cases, set precedent that is followed as health law. The courts, however, usually are neither expeditious nor necessarily cognizant of bioethical principles. They are instructed only to follow the societal values codified in the law. Many courts have suggested that, whenever possible, health care decisions should remain at the bedside rather than in legal chambers.[54-56]

RESUSCITATION ETHICS

The most time-dependent of all activities and arguably the best training periods in the ED occur during resuscitations. The patients who require this care have implicitly been guaranteed that all appropriate medical knowledge and skill will be brought to bear to attempt to save their lives. This implied promise leads to a dilemma. If the most proficient ED professional always leads the resuscitations and performs procedures, the patient will receive the maximum beneficence, as well as nonmaleficence, as expected. Yet restricting ED practice in this manner also deprives future patients of trained clinicians who could bestow the same beneficence.

This controversy has raged for many years. The appropriate balance seems to be that training in EDs can ethically proceed, as it does in other areas of medicine, if safeguards are provided in the form of on-site supervision by experienced clinicians to ascertain that the patients do receive the best possible and appropriate care. It also has been suggested that medical students and residents could be certified for cognitive and procedural skills in a manner similar to that for other hospital physicians. This certification would enable faculty to know when trainees are capable of performing resuscitations, as well as other medical procedures, on their own.[60]

Rarely discussed, but a common practice in some teaching hospitals, has been the custom of allowing trainees with little skill or knowledge to learn and practice procedures on those undergoing resuscitation only when a patient is deemed "unsalvageable."[61] This practice does a disservice to the patient, because prolonging resuscitative attempts solely for this purpose may lead to a clinical state that prolongs dying. It also harms the family and society by making them pay for unnecessary procedures.

Futility[46]

Emergency physicians, nurses, and emergency medical system (EMS) personnel may, in some circumstances, feel that further medical interventions are "futile." Yet only three situations meet the most commonly accepted definition.[62] The first such situation, which clinicians can identify only in a very limited set of circumstances, is that in which the intervention is effec-

tive in less than 1% of identical cases, based on the medical literature. ED thoracotomy for blunt trauma is a well-documented example. Another common scenario with survival rates approaching zero is that of the out-of-hospital cardiac arrest, either unwitnessed or in a patient who arrives from a long-term care facility.[63] Individual clinicians should not rely on their own experiences to make such decisions, however, because they often are skewed owing to selective memory, limited numbers of similar cases, and other biases.

The second futile situation is physiologic futility, in which known anatomic or biochemical abnormalities will not permit successful medical interventions. Examples of such abnormalities generally accepted by EMS systems as reasons not to intervene or provide transport to hospitals are rigor mortis, algor mortis, burns so severe that the victim is beyond recognition, and injuries incompatible with life (e.g., decapitation). These, along with prolonged normothermic resuscitative attempts without success or prolonged "down time" with an isoelectric ECG, and pulseless electrical activity (PEA) are the criteria often used to help determine whether EMS personnel can pronounce death on the scene. In these instances, EMS need not expend valuable resources in a futile resuscitative effort.

The third situation is that in which the proposed intervention will not achieve the patient's goals for medical therapy in accordance with the patient's values. Recognizing this instance, the American College of Emergency Physicians asserted, "Physicians are under no ethical obligation to render treatments that they judge have no realistic likelihood of medical benefit to the patient."[64] Because this course of action is based on knowing the patient's values related to medical treatment, it is necessary to have talked with the patient in advance (rare in the ED setting), to have received surrogate-supplied information or decisions, or to have access to the medical record. The danger is that differences in values between caregivers and patients may lead to over- or undertreatment. Communication, if necessary using a third party, may help to resolve these issues.

The futility concept should never be used to deny care to dying patients. Even terminal patients experience medical emergencies that require intervention. The goal is to ease pain and suffering. How that is accomplished depends on the patient, the medical condition causing discomfort, and their value system.

Withholding versus Withdrawing Treatments[38]

In emergency medicine, a significant difference *rightfully* exists between the withholding and the withdrawal of life-sustaining medical treatment. The justification for this distinction stems, in part, from the nature of the practice of emergency medicine and the unique manner in which emergency medicine clinicians apply many ethical principles. Because EPs often lack vital information about their patients' identities, medical conditions, and goals for medical treatment, withholding emergency medical treatment is more problematic than is later withdrawing unwanted or useless interventions. Owing to the nature of emergency medicine, in both out-of-hospital and ED settings, higher standards are required to withhold medical treatment than to withdraw it.[65]

Physicians should begin or continue resuscitation on those patients who arrive at the ED without sufficient evidence to determine that the resuscitation effort will be unsuccessful. The only reason to *withhold* CPR is the availability of clear evidence, such as a standard advance directive, that the patient did not wish to have this done, or of clinical evidence that further efforts would be futile.[38] Without such information, the presumption must be to intervene.

Once the EP obtains information confirming a patient's wish not to be resuscitated or indicating a medical condition not amenable to resuscitation, resuscitative efforts and other medical treatment may appropriately be withdrawn. This information may be obtained from an advance directive, a patient surrogate, recent documentation in the medical chart, or EMS communication detailing the failed results of the ongoing resuscitative effort. With rare exceptions, such as after failed suicide attempts, resuscitative efforts should be withdrawn when information is provided either that the patient did not want such efforts or that the patient's medical condition precludes success.[66,67]

Many factors influence the potential success of resuscitative efforts, including time to CPR; time to defibrillation, placement of an intravenous line, and first epinephrine dose; time to insertion of first advanced airway device; presence of comorbid illness; prearrest clinical status; and initial arrest rhythm. No combination of these factors, however, clearly predicts the outcome.[68,69] The most important factor associated with poor outcomes is the *duration* of unsuccessful resuscitative efforts.

The possibility of a successful resuscitation becomes clearer as time progresses: A patient's chance of being discharged from the hospital alive and neurologically intact diminishes if spontaneous circulation does not return after 10 minutes of intensive resuscitative efforts.[30,70-72] Malpractice concerns have led some physicians to prolong all resuscitation attempts until they reach the point at which there have been no survivors.[68] In reality, cardiac resuscitation with properly executed advanced cardiac life support (ACLS) interventions and documented asystole should not last more than 30 minutes and usually should end much sooner, except in unusual circumstances such as with prearrest hypothermia, after some drug-induced events, following lightning or electrical shocks, or in infants or children with refractory ventricular fibrillation or tachycardia.[68,72-77] Without these mitigating factors, prolonged resuscitative efforts are unlikely to be successful.[46]

Three special situations should be noted: (1) Cardiac arrest from blunt trauma is nearly uniformly fatal, so little benefit derives from doing chest compressions for any extended period after the airway is secured.[78] (2) When health care resources are limited, such as during disasters, available resources, such as time, personnel, and equipment, should be devoted to treating those patients with the greatest chance of benefiting. This principle may lead to withholding or more rapid discontinuation of resuscitative efforts than is standard in normal practice. (3) It is unethical to prolong resuscitative efforts to practice or teach procedures or to complete research protocols.[67]

Palliative Care

Although lifesaving medical interventions may not be appropriate in all cases, EPs, whenever possible, should provide patients with palliative care. Terminally ill and fatally injured patients have the right to receive state-of-the-art palliative care.[79] Palliation often includes analgesics and may include diuretics, sedation, oxygen, paracentesis or thoracentesis, and other medications or procedures to alleviate suffering. Medical personnel should never withdraw or withhold care; only treatment should be withheld when appropriate. Although medical practitioners, surrogate decision makers, and sometimes patients find it emotionally easier to forgo new interventions than to withdraw ongoing treatment, no orders, policies, or directives should ever prevent EPs from alleviating discomfort.[1]

The purpose of palliative interventions is not to prolong the dying process but rather, when death is inevitable, to make it as comfortable as possible for the patient. As patient advocates, EPs may need to "push" to have the patient admitted to a hospital, hospice, or nursing home, or to get ancillary personnel (e.g., social workers, home health nurses) to intervene for the patient.[1]

Notifying Survivors

Death, especially when it is sudden and unexpected, shocks and devastates family and friends. For them, it is a life-changing event, with every nuance burned into their memories. Moreover, although they may not consciously acknowledge it, such losses also may deeply affect ED personnel, despite their almost constant exposure to life's disasters. This makes death notifications and dealing with the survivors both vitally important and extremely difficult. EPs, who deal with sudden death on a daily basis, are in a position to gain considerable knowledge of and to hone their skills in how to care for the survivors, their newest patients.[80]

Even though notifying survivors of a sudden, unexpected death is one of the most difficult parts of the EP's job, they and other professionals whose job includes delivering news about sudden, unexpected deaths rarely are taught the skills necessary to perform this task. Notifying survivors is emotionally draining—70% of EPs find death notifications to be personally difficult. Perhaps this is because only one half received any type of death-notification education in medical school and only one third received any such training during residency.[81] Moreover, most medical "short courses" dealing with resuscitation, such as those on ACLS, advanced trauma life support (ATLS), and pediatric advanced life support (PALS), have not incorporated death notification into their training programs or manuals. This serious omission continues despite the occurrence of approximately 325,000 cardiac disease–related deaths annually in out-of-hospital settings and EDs in the United States.[80,82]

Occasionally, physicians give the job of death notification to residents, medical students, or nurses. Although all three groups should be present to learn the techniques involved, to have an opportunity to hear what is said, and to observe an attending physician showing sensitivity, they should not be left to do death notifications on their own. That is a form of professional abandonment and, in a teaching hospital, the worst form of student abuse.[83]

Viewing Resuscitations

Traditionally, survivors have not been permitted to view resuscitation attempts.[80] That attitude, however, is gradually giving way to a more enlightened view based, in part, on recognizing that families gain enormous psychosocial benefits from being present and that they are also patients in need of appropriate support.

The argument against allowing survivor onlookers has been that resuscitations often involve large teams, unclear communications, and team leaders who are unwilling or unable to make firm, timely, and rational decisions.[84] Having family members present, the argument goes, introduces the possibility of an onlooker's fainting or otherwise becoming another patient. Survivors also frequently misinterpret the team's discussions or actions. Team members may also feel uncomfortable having family members judging their actions.

Yet studies in both the United States and Britain have shown that nearly all survivors who witnessed ED resuscitative efforts found the experience helpful. Seventy-six percent of survivors responded that their grieving was facilitated by having witnessed the resuscitation, and 64% felt that their presence was helpful to their dying family member.[85] Psychological tests of survivors who witness resuscitation attempts, performed at 3 and 9 months after the event, showed that this group experienced fewer episodes of "intrusive imagery," such as flashbacks of the events leading to the death, compared with survivors not present at the resuscitation (relatives in the control group). They also had lower levels of anxiety, depression, post-traumatic avoidance behavior, and grief.[86]

The American Heart Association now endorses giving family members the opportunity to be present so long as the patient has not previously objected. This position stems from the benefit families can derive from their presence during resuscitation attempts, the lack of harmful effects on them from viewing these resuscitations, and their quasi-right to be there based on the nature of their relationship to the patient.[68,87]

The presence of these survivors does not hinder the resuscitative efforts and often leads to quieter, more effective team efforts. Experience has shown that survivors who witness ED resuscitative attempts never question whether the team "tried hard enough," do not ask whether the person is *really* dead, and spend less time in the ED trying to come to terms with the death. In addition, survivors may actually thank the ED team for their efforts, a situation that rarely occurs under other circumstances, and the ED staff never has to "notify" survivors of the death.

The general procedure is as follows:

1. Ask survivors if they want to view resuscitative efforts.
2. If they do, give them a quick briefing about what they will see, and have a knowledgeable staff member, usually a chaplain, social worker, or ED nurse who can answer their questions, accompany them.
3. Provide a chair for any elderly persons and allow survivors to leave and reenter as they wish.
4. Staff should attempt to cover as much of the patient as is compatible with effective resuscitative efforts.
5. Team members should be advised that family is in the room.
6. The survivors should be encouraged to talk to and touch the patient.
7. Decisions to pronounce the patient dead, although often discussed with the family, generally are communicated in the format of advising them that "we must stop now." They should never be asked whether to stop the resuscitative effort; this is a medical decision.

Experience shows that the process of having key survivors view resuscitations often works best if EMS personnel notify the receiving hospital in advance of this request. This allows the ED staff to decide whether they will permit it (if it is not policy), to advise team members, and to be ready to provide an escort for the relative to the resuscitation room at the appropriate time.

If the family is present when it is clear that resuscitative efforts should cease, this should be explained to the family before supportive measures are discontinued. This provides them with a chance to "say good-bye" before death is pronounced. Dedicated pediatric EDs and pediatric resuscitation units in general EDs have adopted these procedures more often than others.

Postmortem Teaching

A less commonly discussed aspect of emergency medicine education programs is the use of recently deceased patients to

teach or practice emergency techniques, such as intubations and central line placement. Although whether this practice is ethical is a matter of controversy, a reasonable argument might be that if medical treatment could not save the patient, then the EP's responsibility is to hone skills for the next patient in need of expertise in resuscitative techniques. This is not to condone the desecration of a body. Rather, it suggests that because clinicians learned the techniques used during the attempted resuscitation on other dead or living patients, this (now dead) patient owes the next patient the same courtesy. No one would advocate practicing unneeded procedures on living patients, and many people argue against using experimental animals. The religious or ethical beliefs of some ED personnel may make practicing or teaching these procedures in such circumstances problematic.[88-91]

Resuscitation Research

Physicians in a new and advancing specialty have an obligation to advance the knowledge base from which they practice. This can be done only through research, a significant component of which must necessarily be clinically based. In the United States, federally mandated institutional review boards (IRBs) must approve any research involving human subjects, including research in EDs and, possibly, in prehospital care.[92] Increasingly, research ethics committees are being used to approve human-subject research throughout the world. The IRBs try to guarantee that patients who are asked to participate in research review and sign an adequate informed-consent document. Yet even if the patient is conscious, it is unclear whether truly free and informed consent can be given in the midst of a medical emergency.[93] In both trauma and cardiac resuscitation research, informed consent is, of course, not feasible. It usually is difficult, if not impossible, to obtain retrospective patient or, if appropriate, prospective surrogate consent. So as not to deny critically ill and injured patients the opportunity to participate in possibly beneficial research trials, the U.S. Food and Drug Administration and the Department of Health and Human Services issued regulations, which became effective in 1996, that allow "emergency research" without informed consent. These regulations contain extensive patient safeguards, including community consultation, public disclosure, and intensive oversight.[94]

The ethical and legal basis for these regulations is "presumed consent": If the research is not harmful, and especially if it is potentially helpful, most "reasonable" patients would acquiesce to the research, given the basic values of good and evil (see Box 200-1).[95-97] As routinely occurs in emergency medical practice, persons suffering unexpected adverse events with a high probability of rapid death or serious morbidity generally demand that the physician deliver acute care interventions—immediately and without discourse. If there is a chance that the patient could benefit from a therapeutic course of action in such circumstances, most people would demand that it be used. Similar logic applies with acute care research, especially when accepted or standard therapy is futile, and possibly when the investigators believe that equipoise (therapeutic equality) exists between the two tested forms of therapy. Protection for the patient in these cases rests with IRBs, which among other considerations must guard against the possibility of organ-specific success but failure to benefit the entire person, such as producing a patient in a persistent vegetative state after "successful" CPR.

Beyond IRB authorization for research is a moral responsibility for the individual researcher to ensure that the research protocol and its execution are ethical. This responsibility extends to the journals in which the research is published.[98] In the main, emergency medicine has an excellent record of ethical research.[99]

PUBLIC POLICY AND BIOETHICS

Restricted Access to Emergency Medical Care

Society has acknowledged its moral obligation to ensure that everyone has reasonable access to adequate health care.[100] People's need for health care is unequally distributed and highly unpredictable. Few could afford this care if left to their own devices, so mechanisms are in place to share the risk.[101]

The ethical dilemma for EPs comes in basically two forms: one precipitated by the institution in which the ED is housed and one by outside third-party payers. Some institutions have refused care to patients coming to the ED, sending some away for clinic appointments at a later time.[102] Institutions also have pressured EPs to limit treatment, ancillary tests, or hospital admission for patients without the ability to pay. Although such limitation may seem patently immoral, another question must be asked: Is there a moral obligation to the community to keep the health care institution financially viable? Hospitals have closed their doors because of financial losses, and many hospitals, especially in inner-city areas, are on the verge of bankruptcy.

Some prepaid health maintenance organizations (HMOs) use "gatekeepers" to keep patients in need of emergency medical care away from immediate assistance at institutions other than the HMO parent hospital. Moreover, the HMO's income may depend on *not* hospitalizing patients, *not* using ancillary tests, and *not* permitting ED visits. Nevertheless, it is prudent and ethical for EPs to err on the side of providing for the patient's needs.

Morality of Triage Decisions

In the aftermath of a massive natural or man-made disaster, triage officers face difficult decisions about who will receive scarce life-saving treatment and who will be left to die without treatment. Even in "routine" ED triage, decisions about who should receive treatment priority and who can wait for treatment may, at least occasionally, have life-and-death consequences.[103,104]

Triage provides a method to distribute health care resources when patient needs exceed available resources. Triage operates along a continuum of decreasing resources, social order, and the resource-to-patient ratio. Arrival patterns, triage methods, and the applicable ethical basis for triage vary along this continuum.

Most triage systems are designed to serve the values of human life, human health, efficient use of resources, and fairness. Nevertheless, because of the variety of specific triage settings and goals, no single "correct" way to perform or to justify triage can be identified. Routine triage in the relatively resource-rich setting of the modern hospital ED, for example, focuses appropriately on maximizing benefits for each individual patient, giving treatment priority to patients whose needs are most urgent. In triage following a massive disaster, when not all individual needs for lifesaving care can be met, the focus may shift from an individual to a group perspective, and triage officers may seek to save as many lives as possible with the limited resources at their disposal. In special circumstances such as times of war, military commanders may direct that triage systems devote scarce medical resources to achieving a nonmedical goal—namely, military victory. In situations

of complete devastation, the lack of social order and minimal resources may make triage impossible.

Whether the choice of a triage system is justifiable will depend on an evaluation of the specific system itself, its underlying values and principles, and the setting in which it is applied.

Physician Response to Risky Situations

Over the millennia, personal values have dictated whether a physician would remain with his or her patients during extreme or catastrophic circumstances.[105] Physicians, even legends of medicine such as Galen, often fled to save their own lives. In the era of modern epidemics of unknown virulence and etiology, it remains a personal moral decision, especially for EPs who are on the frontline of these medical assaults.

How will physicians respond when a catastrophe involving personal risk strikes? The moral backbone of medical professionals may be tested as health care providers weigh multiple factors to determine whether to stay and carry out their professional roles or to step back and decrease their personal risk.

With incomplete information, providers may make decisions based on heated emotions and panic, rather than an accurate perception of risk. The decision to stay or leave will ultimately depend on the individual practitioner's risk assessment and value system. Professional ethical statements about expected conduct establish important professional standards and norms, but each practitioner will interpret and apply them based on his or her own situation and values. Recent historical precedent suggests that many physicians and other health care providers will dutifully care for the sick and needy, even at great risk to themselves. Although some EPs have worked in dangerous situations, most have not: Nothing in day-to-day emergency medical practice prepares EPs for the great opportunities and challenges that will accompany a pandemic. EPs can, however, reflect on their professional and personal responsibilities in crisis situations, and public and private institutions can create plans for effective communication and care when a disaster strikes. If this can be achieved before the next pandemic or disaster that includes personal risk to clinicians, EPs, who are inevitably among those at highest risk, can be encouraged to "stay and fight."[105]

"Proactive Ethics": How Can Emergency Physicians Change the Rules?

In every medical system, practitioners find that they repeatedly face identical ethical dilemmas. The normal outcome is an incomplete and often unsatisfactory solution made by administrators, lawyers, bioethics committees, or others. "Proactive ethics" involves changing the rules under which we operate. Easier done in some settings than in others, the process requires that all "stakeholders," those with a vested interest in an equitable solution, first come to the table and reach a compromise. Such groups often will include physicians, nurses, EMS personnel, lawyers, religious authorities, and representatives of affected groups (e.g., an organization of elderly persons in the case of issues about the aged). Armed with this agreement or even sample legislation that they can present to politicians, it becomes easier to change laws or administrative rules to address recurrent ethical dilemmas. One such process led to a landmark out-of-hospital advance directive law, which markedly lessened unwanted EMS resuscitation attempts.[37] It also led to an extensive statutory surrogate list and a simplified set of advance directives. Proactive ethics lies in the role of public policy—an arena in which EPs are well suited to play a large role.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 201 End of Life

Jean T. Abbott and Susan Stone

PERSPECTIVE

The emergency department (ED) frequently is the site of critical turns in people's health. It is the place where sudden, unexpected deaths occur and bad news must be delivered to survivors. The ED also is increasingly a source of care for patients struggling with chronic diseases, persons in the late stages of life-limited illness, and people actively dying. Palliative care is the medical specialty that is focused on end-of-life care, and some of its principles are being incorporated into the model of the clinical practice of emergency medicine.[1] The integration of quality management of the dying patient into emergency medicine practice presents challenges but also offers communication and negotiation skills that can be used by emergency physicians in many aspects of their practice.

Death in the ED differs from death in other areas of the hospital in several ways: (1) deaths often are unexpected; (2) the patient and family and their values often are unknown to ED staff; (3) trust needs to be established rapidly; and (4) management decisions often must be based on limited medical information.[2] These factors contribute to stress for the emergency care team in managing the first few minutes of a critical illness. The initial response to life-threatening presentations in the ED must be to treat aggressively and resuscitate persons in extremis in the absence of knowledge that this is counter to patient wishes. Much of the core of emergency medicine is devoted to preventing untimely death in people with severe trauma, a "heart too young to die," or another sudden, unexpected life threat. However, when resuscitative and rescue efforts fail, when patient wishes to forgo further interventions become clear, or when the natural end to life comes, the emergency specialist should be prepared to withdraw unwanted treatments, to make the patient comfortable, and to lead the staff and the patient's loved ones in giving the patient's death the meaning and respect it deserves.

PRINCIPLES OF DISEASE

Epidemiology of Death and Dying

One hundred years ago, the predominant pattern of dying was a rapid, precipitous death from infectious diseases and accidents. With modern medical advances, chronic diseases have become part of the last years of life for most people. Three diseases—heart disease, cancer, and stroke—accounted for 60% of deaths in the United States in 2000, whereas unintentional injury accounted for only 4% of deaths.[3] Most people live with some limitation in their ability for self-care for 2 to 4 years before they die. Four common trajectories of dying have been described (Fig. 201-1). Sudden death (due to cardiac arrest, trauma, or other sudden event) occurs in only 15% of people. The other trajectories are more common and occur with roughly equal frequency. The predictable decline in patients with "terminal illness" over 6 months or less provided the basis for the hospice concept of managing the dying process for patients with cancer and terminal AIDS. In cases of organ failure (e.g., chronic obstructive pulmonary disease [COPD], heart failure, renal failure, and other progressive serious medical diseases), gradual decline is punctuated by intermittent exacerbations (entry-reentry decline). The time of death for people with these progressive and ultimately fatal diseases is not very predictable, and it often happens rather unexpectedly during an acute deterioration. These patients frequently are treated for acute deterioration in EDs. The fourth trajectory of gradual decline, or "frailty," is associated with some form of dementia in 50% of affected persons and a lingering course that can extend over many years, stressing and wearing out caregivers and other support systems as decline in functional abilities progresses.[4]

Several end-of-life skills are important in the practice of emergency medicine. One of these is to rapidly determine, when possible, the patient's wishes for interventions at a time of crisis. Wishes may be transmitted through written advance directives or direct conversation with a patient or proxy about general values or specific management choices that should guide ED management. Invasive interventions may carry greater risk and be less beneficial near the end of life, and patient choices may include spiritual, economic, and community factors that the emergency physician cannot know without clear, rapid communication and establishment of treatment goals.[5] Likewise, the patient or the surrogate needs the best information possible about the medical and technical aspects of a critical turn.

Studies have shown that physicians may be overly optimistic regarding prognosis, particularly if they know the patient well. Patients and families need to understand prognosis in order to make decisions about what treatments they want and to plan priorities for their remaining life. Functional status is a strong indicator of a patient's prognosis; decline is associated with increasing likelihood of death, particularly in patients with terminal cancer, for which the dying trajectory tends to be most predictable. For other end-stage diseases, however, validated scales to predict survival are commonly used in palliative care

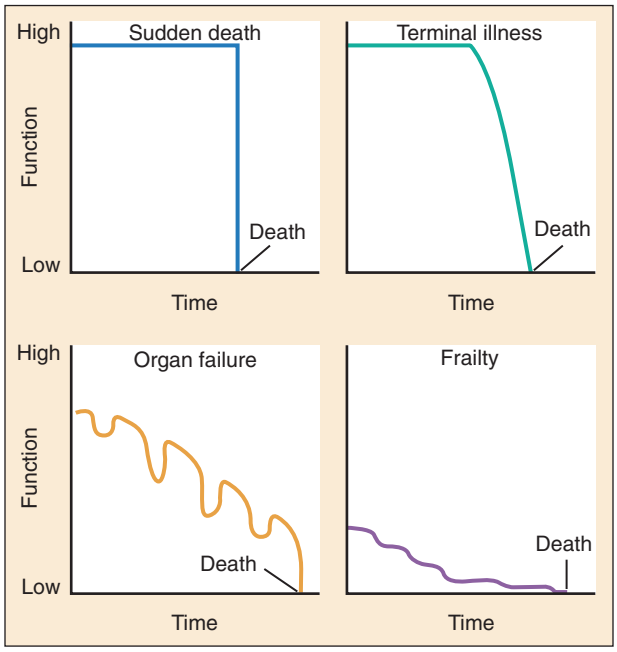


Figure 201-1. Theoretical trajectories of dying. (From Lunney JR, Lynn J, Hogan C: Profiles of older Medicare decedents. J Am Geriatr Soc 50:1108, 2002.)

assessments. In the ED setting, rapid assessment of the likely prognosis in a particular case can be accomplished by eliciting information about the patient's ability to perform activities of daily living (ADLs) (i.e., "performance status"). When a patient is not able to spend time out of bed, has reduced appetite, and cannot dress or bathe without assistance, he or she is likely in the last months of life. Such a patient should be eligible for the Medicare hospice benefit. This is the time to involve hospice or palliative care consultants in the ED or during hospital admission. If a patient has already "enrolled" in hospice, it is important to contact the relevant hospice program (accessible around the clock) from the ED before making treatment and disposition decisions.[1,4,6]

In Western culture, death has become "medicalized" over the last 50 years.[7] Modern technology often has allowed human control over the timing, site, and pace of dying. Death occurs in an institution for approximately two thirds of people.[8] Frequently, the dying process is accompanied by invasive diagnostics and medical interventions, even when death is expected and these interventions may increase suffering at the end of life. Death often is seen in modern society as the failure of scientific know-how to keep people alive, rather than the natural end to a life. When death is approached with less fear by both patients and physicians, it is possible to help patients and families make the best of the time remaining to them and to deal with death as the natural ending of life.

Definitions of Death

Biologic definitions of death are currently the subject of considerable debate. Twenty years ago, cardiorespiratory failure defined death, because this was rapidly followed by brain death (which could not be directly measured) caused by failure of oxygenation and perfusion. Death was a distinct biologic event, because all vital systems stopped when one of them failed.

Currently, cardiopulmonary "death" is not necessarily inevitable or irreversible. Ventilation can be maintained externally, and even circulatory support through pharmacologic means or pump assist can sometimes buttress an inadequate heart. Because of this, a second pathway called "brain death" has been conceptualized. The brain-based determination of death is derived from the irreversible failure of clinical function of the whole brain, manifested by apnea, profound coma with unresponsiveness, and absence of brainstem reflexes.[9] The most common causes of brain death in adults are traumatic brain injury and subarachnoid hemorrhage. In children, the primary causes are accidental or nonaccidental trauma and asphyxia.[10] Although the consequences of these events are seen with some frequency in the ED, the criteria and irreversibility standards for brain death are seldom met in the first hours after the resuscitative effort. One additional impetus for development of a concept of brain death was the need to define a biologic and ethical boundary to life for procuring organs for transplantation. Declaration of brain death allows harvesting of organs while continuing cardiopulmonary support and organ perfusion and currently accounts for more than 90% of organs harvested from deceased donors.[11]

In addition, a new protocol designed to increase the pool of organ donors and acknowledge the rarity of complete brain death defines "non-heart-beating" organ donors. Such patients have a dismal prognosis for meaningful survival but will not sustain complete brain death until the time of cardiopulmonary arrest. Pulmonary and cardiac support is withdrawn, death is declared after an interval of several minutes, and organs can be harvested with a minimum of warm-ischemic time.[10,11] The issues surrounding society's definitions of death are complex, and the struggle with attempts to balance respect for persons and their bodies with the need for transplantable organs is expected to continue.

It is important for physicians to be clear about medical language relating to death. The patient is allowed to "die naturally" when the ventilator and cardiac support are removed. A patient who is declared "brain dead" is dead even though the person may appear to be alive, with pulse and chest rise, to the family. A patient in whom "higher" brain function or cognition is lacking is not considered to be "dead" since "whole brain" death requires failure of the brainstem in addition to cortical function. The confusion over medical definitions of death is made greater by cultural and religious variations in conceptions of death. The different criteria also can lead to suspicion among the public that these definitions are "malleable" and serve physician agendas, rather than respecting the patient. In the ED, cardiopulmonary death is the only death that can be recognized. Use of the term *brain dead* is to be avoided.[12] Brain death requires time and strict criteria to diagnose. However, the emergency physician has an important preparatory role in delineating the status of the patient who is breathing and who has a pulse (perhaps from a successful resuscitation effort) but may ultimately die a brain death. It is very helpful to introduce the family to concepts of prognosis, brain injury, and the further steps that will occur over the succeeding hours that will give physicians and family a clearer picture of whether an injury or insult is fatal or not.

Related Issues

Futility

Physicians are not required to offer treatments that are not beneficial.[13,14] Unfortunately, information available in the out-of-hospital setting or the ED often is insufficient to make the judgment that a particular patient's condition is "terminal" or that treatment efforts would be "futile." In the case of cardiopulmonary resuscitation (CPR), the emergency physician proceeds with full resuscitative measures unless there is a clear

understanding that this is contrary to the patient's wishes. Although the term "futility" can be a nontechnical expression of a physician's assessment that a proposed intervention is nonbeneficial, the definition is unclear and the term is best avoided in medical discussions of critically ill patients. *Futility* may mean treatment for which no survivors have been reported in similar circumstances in well-designed studies. Other definitions attempt to quantify futility as a less than 1% chance of meaningful survival.[14] Rarely does the emergency physician have information about the patient's overall condition that would allow such a determination, even if the physician were to accept the quantitative definition, which continues to be debated. The term *futility* also can be used qualitatively, implying that "meaningful" life will not result from the proposed intervention. This use of the term is likewise problematic because it is a unilateral judgment about values that a patient and family may or may not hold about what constitutes "life."[14]

Quality of Life and a "Good" Death

As technology gives physicians the ability to stabilize patients with serious and noncurable diseases and to manipulate the timing of death, and as people are increasingly exercising their autonomy in deciding how to control their dying, more conversations are occurring about what constitutes a "good death." There is evidence that the quality of life for persons who live into their 80s is better than it was 20 years ago.[15] For that, medicine can be proud. But there are also serious deficiencies in end-of-life care. A majority of people wish to die at home, although nearly 70% die in an institution.[8] In the famous Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments (SUPPORT) of more than 9000 patients with life-threatening diseases and a 6-month mortality rate of approximately 50%, only one half of the physicians knew when patients did not want CPR. In addition, families in that study reported that one half of the conscious patients were experiencing significant pain at the time of death.[16]

In the ED, resuscitation is performed unless patients' wishes to the contrary are clearly known. Information that CPR, intubation, or other invasive treatments are not desired can be conveyed in the form of written advance directives, a state-authorized "no-CPR" or do-not-attempt-resuscitation (DNAR) directive, clear indications from the person assigned the patient's durable power of attorney for medical affairs, or communication with the patient's physician. Unfortunately, fewer than one fourth of people have prepared advance directives of any type.[17] Evidence of wishes from prior conversations between patients and family or physicians also are uncommon and are rarely available in an emergency situation. The lack of knowledge regarding patients' wishes is particularly worrisome because most people—both patients and surrogates—do not understand what "do everything" means. Family and other surrogates also are poor at predicting care that their loved one would want or not want. In one study comparing patient and surrogate choices about life support, surrogates guessed patient wishes only 59% of the time, little better than chance. The best predictor of accurate knowledge of patient wishes in that study and others was a specific discussion between the patient and surrogates about values and wishes.[18]

In patients with severe disabilities, physicians and other health care providers likewise have a difficult time judging quality of life and patient wishes at the end of life. Gerhart and colleagues[19] surveyed emergency care providers' hypothetical attitudes toward quality of life after spinal cord injuries and compared their responses with those of high-level spinal cord injury survivors. Only 18% of providers (e.g., emergency medical technicians, nurses, and physicians) imagined they would be glad to be alive after a severe spinal cord injury, whereas 92% of survivors were glad to be alive. Eighty-six percent of the quadriplegics felt that their quality of life was average or better, whereas only 17% of emergency care providers predicted they would have a similar view of their quality of life in the same condition. It is important to remember that people's assessment of what is a "good life" changes with time, age, and the realities of illness.

What priorities most commonly occupy patients at the end of life? When death is near, patients have both medical and nonmedical concerns about their dying. Singer and associates[20] suggest that five topics predominate in people who are dying: having pain and other symptoms adequately relieved, avoiding inappropriate prolongation of dying, achieving control, relieving others of the burden of their dying, and strengthening personal relationships. The only way to know what is important and what brings joy to patients' lives, particularly in the face of chronic or disabling disease, is by asking patients and those close to them.[21] Most patients want to know prognostic information, although this preference should be ascertained before such information is given. Realistic hope in the dying patient usually centers on desires for dignity, management of symptoms, and resolution of key relationships.[5]

The Goals of Medicine

Medical authorities and philosophers have long debated the proper goals of medicine. Physicians are most familiar with the goal of "curing" diseases. Ellen Fox reminds us of the complexity of our task in medicine: "Although cure is unquestionably an appropriate goal of medicine, other goals are important as well: promoting health, preventing illness and injury, restoring functional capacity, avoiding premature death, relieving suffering, and caring for those who cannot be cured."[22] In Western society, the curative model predominates, and physicians are rewarded for being analytic and rational. The disease, not the person, becomes the object of analysis. Symptoms are clues to diagnosis rather than problems to be treated in and of themselves.[22] Fox points out that the palliative care emphasis on "relief of suffering, control of symptoms, and restoration of functional capacity" is really just one end of a spectrum of care that a physician provides. Most patients with life-limiting conditions have reversible elements to their disease process; likewise, even the patient with streptococcal pharyngitis wants symptom relief in addition to cure. So the goal of medicine may be to discern where to place the emphasis for the patient: The curative and the palliative models need to be balanced in varying proportions to optimize care for the individual patient.[22]

If the physician is to achieve the goal of relieving suffering, he or she needs to understand the difference between *pain* and *suffering*. Eric Cassell first introduced the idea that a primary goal of medicine was the relief of suffering in a landmark article in the *New England Journal of Medicine* in 1982.[23] Cassell emphasizes that pain happens to bodies, but that suffering happens to persons. Suffering derives from the meaning behind the pain or other symptom. It is unique to each person and can only be understood from the patient's perspective. Suffering is "the state of severe distress associated with events that threaten the intactness of the person."[23] Patients may be in severe distress without any physical pain; others may experience their pain with very little distress. Patients suffer, as Cassell points out, "when they feel out of control, when the pain is overwhelming, when the source of the pain is unknown, when the meaning of the pain is dire, or when the pain is chronic."[23]

The World Health Organization defines *palliative care* as "an approach that improves quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial, and spiritual." Palliative care usually consists of an interdisciplinary team of experts that offers various support systems for patients and their physicians near the end of life and can provide inpatient care or consultation, as well as patient management in hospice, in long-term care facilities, and in homes.[24] Examples of some acute palliative care interventions that can be applied in the ED are described at the end of this chapter.

Hospice care is the aspect of palliative care for patients who are likely to be within 6 months of death. The hospice movement, which started in England in the 1950s, initially sought to provide a haven of medical care for persons dying of cancer. Home and inpatient hospice programs now exist throughout the United States and are funded through Medicare. If a clinician would "not be surprised if a patient died within six months if the disease ran its natural course," a hospice evaluation would be appropriate. The patient is "hospice eligible" if hospice judges that the patient's lifespan is likely to be less than 6 months and Medicare will certify a patient for hospice. Currently, hospice care is provided for an expanded spectrum of end-stage illness, including cancer, organ failure (e.g., heart, liver, kidney), neurologic diseases, and terminal AIDS.[1,6]

Confusion about eligibility for hospice care contributes to late referrals. Only approximately 20% of patients die while receiving hospice services, including less than one half of patients with cancer. Referrals occur a median of 20 days before death, leaving insufficient time for many of the services that hospice can offer. Although physicians may have difficulty quantifying a patient's likely lifespan as less than 6 months, prognostic tools exist, and enrollment criteria are based on (1) lack of curative intent as well as (2) progressive decline in function.[1,6]

The palliative care movement has developed as an expansion of end-of-life care to include not only hospice-eligible patients but also patients with incurable, debilitating chronic noncancer illnesses (e.g., COPD, congestive heart failure) that require symptom control but with a less clear course to death.[4] Even though the prognosis at any point in time is uncertain, these diseases are not curable, and goals of care may be better served by switching primarily to enhancing the quality of remaining life for affected patients, keeping them as active as possible, and controlling symptoms. These patients are best cared for by palliative care experts. Palliative care consultation offers patients a mechanism to discuss and review management of symptoms and medical interventions that patients desire or wish to avoid in managing their living and dying with severe chronic diseases, with hospice referral when this is desired and possible.

In 2006, the American Board of Emergency Medicine joined with nine other specialty boards to cosponsor the American Board of Palliative Medicine. This alliance has recognized the real need of emergency physicians to address a wide range of interventions and management decisions that are specific to the end of life. The integration of emergency medicine and palliative medicine has stimulated educational efforts to define the scope of ED-based palliative care and curriculum design.[1]

Emergency Medicine and End-of-Life Care

Emergency physicians encounter death more frequently than physicians in many other specialties. Resuscitation and restoration to functional living will always be a primary goal of practice and research in this field. However, seriously ill patients treated in the ED often present with important but less emergent complaints. The physician often does have time for deliberation about choices of care through conversations with patients or family. Even when a patient has a severe chronic disease that is not curable, interventions are available that can improve the quality of life. Also, at the end of the course of chronic disease, death is not always unwelcome. Addressing the needs of patients and their families at these critical times requires a complex set of skills. The rest of this chapter is devoted to out-of-hospital end-of-life concerns and to the aspects of end-of-life care that should be part of every emergency physician's skill set: delivering bad news, death notification, establishing and honoring patient goals of care and advance directives, symptom control, and palliation.

SPECIFIC DISORDERS AND CONCERNS

Out-of-Hospital Considerations

Historically, out-of-hospital systems were designed to provide immediate resuscitation, stabilization, and transport of seriously ill or injured persons to EDs. Aggressive and early resuscitation, through CPR, airway management, defibrillation, fluid resuscitation, and trauma stabilization, has resulted in significant benefits and reduced mortality in patients with critical illness for whom survival is time-dependent and potentially reversible causes of illness or injury threaten life.

Emergency medical service (EMS) systems also are called to transport patients who have died or to assist patients who are in extremis but whose death is expected. As well, EMS is activated for patients with acute decompensation of chronic medical conditions such as heart failure or COPD, and for symptoms that occur in the context of terminal conditions when caregivers at the scene cannot cope. Patients at the end of life may desire aggressive interventions for acute exacerbations of chronic illnesses, or they may prefer only supportive care or transportation to achieve a nonviolent end to their life. In emergency situations, it may not be possible to determine the patient's underlying medical conditions or where the patient is currently on the arc of living and dying. In some situations, a titrated response is possible, and noninvasive supportive care (such as positioning, suctioning, oxygen, or mask ventilation) during transport can buy time until further evaluation in the ED can clarify the patient's goals of care.

Field Death Pronouncement

Several physiologic circumstances have been identified in which out-of-hospital providers should not initiate or continue CPR because of uniformly poor outcomes and no benefit from intervention. American College of Emergency Physicians (ACEP) and American Heart Association (AHA) guidelines state that CPR should not be initiated in patients with nontraumatic cardiac arrest and signs of irreversible death, such as decapitation, dependent lividity, or rigor mortis.[25,26] ACEP policy recommends discontinuing resuscitation in the out-of-hospital setting if the patient remains in asystole or wide-complex pulseless bradycardia after a trial of adequate resuscitation, including CPR, intubation, medications, defibrillation, and pacing.[25] The National Association of Emergency Medical Services Physicians (NAEMSP) supports this approach. Termination of resuscitation efforts in nontraumatic cardiac arrest patients should be made in agreement with online medical direction and predicated on access to witnesses

or family, provider comfort with death notification and grief counseling, and safety and logistical considerations.[27] If questions arise about resuscitation, CPR and ACLS measures should be initiated and the patient transported. It can be easier and ethically more sound to withdraw care in the ED than to withhold care at the scene.[28,29]

Honoring Advance Directives to Withhold Resuscitation

There is an increasing movement to develop policies that allow EMS providers to honor patient wishes not to receive interventions at the end of life, even when resuscitative measures might succeed. The 1991 Patient Self-Determination Act recognized that health care providers must honor informed decisions by patients who wish not to be resuscitated. Most providers have experienced situations in which attempted resuscitation is later determined to have been against the patient's wishes. In a Seattle review of out-of-hospital cardiac arrests in which all patients received full resuscitative efforts, 7% of patients were ultimately determined to have had "unwanted" resuscitation, and 25% of patients experienced resuscitation in the context of severe chronic disease.[30]

Identifying valid directives to withhold CPR or intubation is problematic for out-of-hospital providers. Information about patient wishes and underlying diseases is frequently confusing, DNAR requests may be difficult to validate, and rapid intervention is frequently required. Many state-based programs have been developed to try to identify patients requesting no CPR through bracelets or official registered forms on their persons, allowing supportive care but no resuscitative efforts if the patient experiences cardiorespiratory arrest.[31,32] The ACEP has recognized the difficulties with respecting patients' desires to forgo resuscitative efforts and issued guidelines for developing out-of-hospital DNAR policies.[33] In some states, statutory authority for EMS personnel to honor DNAR orders has been developed, but provisions vary widely. Written statements or identification bracelets must be consistent, easily recognizable, legally acceptable in that state, and clear about what resuscitative measures the patient would and would not wish to receive.[34] A family member or friend who is present at the scene and has valid medical durable power of attorney for health care documentation also may make decisions to initiate or refuse treatment measures on behalf of the patient. The most widespread initiative to provide out-of-hospital written directives to limit life-sustaining care is the Physician Orders for Life-Sustaining Treatment (POLST) Paradigm program in Oregon, which uses a clearly recognizable pink form posted on the home medicine cabinet to identify a range of patient wishes near the end of life. This program is being adopted in other states.[35]

Several concerns about the validity of written advance directives persist: Patient wishes can change over time, nonstandard forms of DNAR requests (such as "medical alert" bracelets, notes on prescription pads, or tattoos) cannot be recognized, and a theoretical concern is that relatives or bystanders may not be accurately relaying the wishes of the patient.[36] In one survey of emergency medical technicians (EMTs), more than 20% had experienced ethical conflicts over the execution, honoring, or validity of DNAR wishes or orders at the scene.[37] On the other hand, most out-of-hospital providers agree that it is appropriate to withhold resuscitative attempts in terminally ill patients.[38]

Honoring Verbal Requests to Withhold Interventions in the Field

In most EMS systems, verbal requests to limit resuscitation are not accepted, because of the concern that out-of-hospital providers cannot confirm that these represent the patient's current wishes.[38] In view of the incidence of "unwanted" resuscitation, King County in Washington State has introduced a new protocol of allowing EMTs and paramedics to withhold resuscitation in situations in which family or caregivers indicate that no resuscitation is desired and the patient has a terminal condition (i.e., death is expected and the patient is under a physician's care). EMS personnel do not need direct physician approval to forgo resuscitation. The incidence of non-initiation of resuscitation increased from 5.9% to 11.8% in EMS services adopting the expanded standards. Other regions are testing this protocol, which must be accompanied by population buy-in and legal protections against errors. No adverse consequences have resulted so far, although wrongful death suits remain a theoretical concern. EMS provider comfort level with expanded standards has been high.[39,40]

Attempts to honor patients' requests at the end of life should be a goal for both out-of-hospital and ED personnel. Out-of-hospital providers need to be aware of the standards for honoring DNAR requests in their respective states.[32,33] In addition, providers need to be knowledgeable about types of advance directives and surrogate laws for the state in which they practice. In most EMS systems, field pronouncement of death requires physician base-station consultation. Unilateral EMS provider judgment not to start resuscitation has been reported, but snap judgments that patients are "terminal" are not necessarily accurate and should not be the sole criterion for withholding interventions.[40]

Supportive Out-of-Hospital Treatments near the End of Life

Patients at the end of life can benefit from supportive or palliative treatments at the scene and during transport. Positioning, suctioning, and administration of pain medication and oxygen for dyspnea all may be important to maximize patient comfort. Before an intravenous line is established, EMS personnel should ask the patient's permission to do so, because even the pain associated with insertion of the line may be counter to patient wishes. If the patient is being transferred from a long-term care facility to the ED, all care instructions, CPR directives, advance directives, and contact names and numbers are carried with the patient, because these will help guide continuing care in the ED.

Management of Hospice Patients

Although hospice care protocols are written to avoid activating the EMS system, scenarios routinely arise in which the patient is in the dying process and family members panic or cannot handle some terminal situation. There may be anxiety in the last hours of life, a feeling of helplessness, or concern for the patient's perceived or real suffering. There may also be disagreement between family members about the best way to help the dying person. The family may request death pronouncement at home, but out-of-hospital providers should involve medical control to affirm this if necessary. Transport and comfort care should always be offered if the family wishes or if the setting appears uncomfortable for those involved in the dying process.

Special Issues in the Out-of-Hospital Setting

Suicide

Although respect for patient wishes is a core value in today's society, suicidal patients frequently are impaired. Modern belief holds that suicidal depression usually is treatable.[41] Patients near death from suicide should receive full resuscita-

tive efforts unless there is a specific exception, such as physician-assisted suicide in Oregon, with formal documentation and an alternative protocol for out-of-hospital providers to follow. If the patient is dead and meets criteria for not starting resuscitation, the coroner or medical examiner should be notified. The scene needs to be protected to allow an investigation, if needed, because the history is rarely clear or complete during the emergency call. Decisions should be made after consultation with the medical control physician.

Pregnancy

In the case of a pregnant trauma patient, fetal survival is best ensured by aggressive care of the mother. Some unborn babies will die despite major or minor maternal injuries, but field rescue of the baby after the mother is pronounced dead is rarely appropriate and not advised without physician control. A pulseless woman in the third trimester of pregnancy should be transported to the nearest ED capable of performing a perimortem cesarean section for attempted resuscitation of both mother and baby.

Pediatric Deaths: Sudden Infant Death Syndrome

Death of a child is among the most difficult of human experiences. With pediatric deaths, regardless of the cause, a complete resuscitation regimen, including transport, is appropriate. Child abuse should always be considered as a possibility. Transport may be done more for the psychological benefit to the family than in the hope of survival. As sudden infant death syndrome has become more widely recognized and understood by the public, some families wish to avoid "extraordinary measures" of resuscitation once the diagnosis is recognized and the outcome is inevitable. Many desire to be with their infant in his or her last moments. Out-of-hospital personnel should respond to these requests with understanding and compassion; however, the site of pronouncement of death should be in the hospital for almost all pediatric deaths.

Death in the Emergency Department

Delivering Bad News

Every emergency physician will be required to communicate bad news to patients, family members, and caregivers. The manner in which this is done may make a difference in the course of subsequent grief and coping.[42] Compassionate communication can strengthen trust and foster collaboration in planning between the medical team and the patient and family. Emergency physicians have particular challenges in delivering bad news in that they do not have ongoing relationships with their patients and because the bad news may be abrupt and unexpected. However, the newness of relationships in the ED also may allow a more frank and open conversation about a patient's illness, prognosis, and wishes, particularly when the sudden downturn precipitating an ED visit is part of a severe chronic disease.[43,44]

The goal of skillfully breaking bad news is to reduce the severity and the duration of stress and encourage engagement of coping mechanisms, both for physicians and for patients and their caregivers. According to a theoretical construct proposed by Ptacek and Eberhardt, staff and physician stress often peaks just before transmission of the bad news, whereas patient or caregiver stress emerges after delivery of the bad news.[45] Physician stress correlates directly with the severity of the news, as well as any responsibility for the outcome that the medical team may feel, and inversely with the amount of experience delivering bad news. Many providers feel inadequately prepared for death disclosure or delivery of bad news about a new diagnosis or turn in health status for a patient with a life-limiting illness.[46,47] Skilled resuscitation, diagnosis, and treatment of patients are key to keeping the external sources of provider stress manageable. Reduction of the anticipatory stress of delivering bad news may occur with use of a structured protocol, practice, planning the physical and social aspects of the setting, and other methods of enhancing experience.[45] Experience with revealing medical error or other aspects of responsibility for outcomes has not been well studied.

Several initiatives to improve delivery of bad news have been introduced. These encourage training in communication skills, explicit instructional sessions, role playing, use of standardized patients, and observation of colleagues who are comfortable with this aspect of patient care.[2,44,48,49] Little research has examined the best methods of increasing patient and family satisfaction with this important aspect of patient care.[47] Physician coping mechanisms may or may not be helpful to patients, but much still needs to be learned about how to be most helpful in this difficult time for patients. If the physician develops patterns to insulate himself or herself from stress that involve lack of sensitivity to the receiver's needs, he or she may cause greater stress to the receiver by use of vague language, delegation to others, or delaying or rapidly disengaging from the encounter.[43,45]

For the patient and family, the ED typically is the place where bad news is sudden and unexpected. This can certainly make the strain even more severe and overwhelming. Trust between ED caregivers and critically ill patients or their survivors, who were unlinked strangers just a few minutes before, does not come easily. Whereas providers may focus on the content of the information they must convey, patients focus more on the process.[42] Surveys of patients and families have identified the following factors as desirable for receiving bad news: privacy when receiving news, the ability to express emotions safely, information that is free of unclear language or medical jargon, empathic and caring attitude, allowance for hope, and ability to ask for and receive good medical information.[45] One technique for encouraging provider empathy is to structure a conversation according to the NURSE pneumonic: The provider *n*ames the emotions observed, confirms whether this *u*nderstanding of the receivers' feelings is correct, expresses verbal and nonverbal *r*espect for the receivers' feelings, *s*upports them through expressions of concern, understanding and willingness to help, and *e*xplores additional concerns.[43]

The steps listed in Box 201-1 and explained in detail in the following paragraphs are designed to shape the interaction to facilitate the patient's or survivors' work through this stress and movement toward coping. This six-step template was adapted from Buckman's work and adopted also by the Educa-

BOX 201-1 DELIVERING BAD NEWS

The steps listed below can help you think critically about how best to communicate at a time when stress is high. See the text for details about each step.
Step 1: Physician preparation
Step 2: What does the patient know?
Step 3: How much does the patient want to know?
Step 4: Sharing the information
Step 5: Responding to feelings
Step 6: Planning and follow-up

Adapted from Buckman R: How to Break Bad News: A Guide for Health Care Professions. Baltimore, Johns Hopkins University Press, 1992.

tion for Physicians on End-of-Life Care (EPEC) teaching project.[6,43,50] Key to moving through the process of delivering bad news is the "ask-tell-ask" interactional framework in which the physician is guided by the patient and family in regard to the pace, amount of information, and style that will work best to let them feel and hear what they need.[43]

Step 1: Physician Preparation

Before the physician interacts with the family or patient, preparatory steps are important. These include confirming all medical facts of the case, clarifying the name of the patient, being aware of any uncertainty about the patient's identity, and knowing the relationships between the patient and those with whom one will be talking. The physical site for the conversation should be quiet and allow for private exchange of information and safe expression of emotions. Sometimes this is difficult in the ED, but a family room or other quiet area usually is available to use. If the patient can be included, moving the patient to a private area may be possible, or key members of the patient's support group can be gathered around the bedside.

Physicians should identify themselves and their position, directly address the patient (when present) or the key persons receiving the news, and refer to the patient by name. Before beginning the discussion, the physician should sit down close to the patient, make direct eye contact with the patient (or close relatives), and be physically and mentally open to their concerns and needs.

Step 2: What Does the Patient Know?

It is useful to know what the patient or family understands before the delivery of news. An introductory question can be used, such as "What do you understand about your illness?" or "What have you been told happened to [name of spouse/sibling/other]?" This information helps the physician to see the event as the patient and family are seeing it thus far and to adjust the mode of delivering this news to their understanding. In the ED, when patients and families may expect "the worst," this tactic can be perceived as delaying. In a less critical situation, however, asking about previous testing, conversations with physicians, and understanding of the patient's illness can help the subsequently delivered information fit into the patient's perspective and expectations.

Step 3: How Much Does the Patient Want to Know?

Every patient has the right to accept or refuse medical treatments based on informed consent. This also is true for information. Most patients appreciate the direct, simple truth about their condition and prognosis. There will, however, be some patients who do not want to receive the information that the provider is about to deliver. These patients may wish to designate a friend or family member to represent them. This choice should be respected if possible. It is important to remember that people process information and make decisions in many different ways, based on their own cultural and religious views and previous experiences. The Western principles of truth-telling and individual decision-making are cultural values and may be foreign to some families and communities.[43]

Sometimes the family learns of a diagnosis and prognosis before the patient does and requests that the patient not be told. The physician's alliance with both patient and family is important, although responsibility to the patient is primary. Physicians should explore why families do not want the patient told bad news: Is it a cultural tradition? Are they afraid of what harm it will cause the patient? Have they had previous bad experiences? The physician is still required to ask the patient how much he or she would like to know. Sometimes it is helpful for the physician to invite family members to be present for this discussion. This important information should be learned or asked using an independent interpreter (rather than a family member) if the patient does not speak the same language as the physician.

Step 4: Sharing the Information

In general, patients and families want to know bad news in a timely fashion.[45] This is sometimes uncomfortable, particularly when important information may not yet be known—a common occurrence in the ED. At the very least, it is recommended that patients and family be given a preparatory warning after introductions, such as "I am afraid I have some bad news." In delivering the information, it is important to use simple nonmedical language and to make sure that the patient comprehends the information. Space should be allowed for patients and family to absorb the news, to react, and to begin to ask questions. The patient and family stress response will lag behind that of the physician, because the physician has had at least a few minutes to adjust to the current situation, but the family has not.[45]

Although using the phrase "I'm sorry" can be a reflection of empathy, it can be misinterpreted. Some physicians have suggested using expressions such as "I wish things were different" instead, as a sign of solidarity.[51] Providing survival data when the discussion is about a severe or terminal diagnosis may be better reserved for a later time, but it is important to know how to access this information. The physician's message should include some realistic hope and also reassurance that the patient will not be abandoned by the medical care team, even when cure or survival is unlikely.

Step 5: Responding to Feelings

The reaction to bad news often is unpredictable and can range from sadness to rage. It is important for ED clinicians to be aware of the wide varieties of responses that will be seen. The patient and family should be allowed to express their feelings, even if this is uncomfortable. Acute grief is painful but important. The emergency physician must be prepared both for persons who turn inward and those who rage outwardly. Practicing and reflecting on these situations will allow the physician to deliver bad news and support the survivors. In the ED, it often is helpful to invite members of the team into this meeting (e.g., social worker, nurse, or chaplain) who will not be pulled away to other care needs, can provide emotional support, and can help the family navigate through the early stages of grief, as well as the technical details necessary.

Step 6: Planning and Follow-up

The ED is an entry point into the hospital if the patient survives. Family members should be encouraged to stay with the patient, particularly if it is possible that the end of life is near. Prognosticating may be difficult, in view of the limited information that can be obtained in the initial assessment. When initial management has stabilized a patient with an acute, critical turn, it may be appropriate to look ahead to decompensation that could occur later in the hospitalization. Some experts have suggested a "hope for the best and prepare for the worst" kind of conversation.[52] The physician can share the success, however transient, of any ED interventions and the positive news and hope that this provides. At the same time, he or she can prepare the patient or family for the possibility of later setbacks and have them consider what actions may or may not be appropriate if "the worst" happens.[5] If the patient does not have written advance directives, the emergency physician can facilitate the conversation, initiate written wishes, or at least advise the patient that the admitting physician will need to

have an early conversation about future plans and goals for the patient. The physician should assure the patient and family of what the next steps will be, including hospital admission or discharge from the ED, consultation with specialists, support group referral, or chaplain services. It is important to make sure that the patient and family do not feel abandoned. Even when dying is near, providing active care and comfort is a major task for the medical team.

Death Notification

One of the most difficult forms of "bad news" to deliver is death notification. Emergency physicians need to practice this skill specifically (Box 201-2). In general, the format can follow the guidelines for delivering bad news from Box 201-1. With death notification, however, diagnosis is certain, and actions required are more definite. Families do not have time to adjust or think about options, and the message is more stark.

Death notification usually occurs after an unsuccessful resuscitation attempt. Physicians should be sure they are presentable and wear a name badge. If possible, it is recommended to ascertain beforehand the names of the persons who will receive the notification, their relation to the patient, and what they know about the patient's condition. Other members of the medical team may have met them already and can be a source of background information. Sometimes the family initiated the 911 call and recognized that their loved one had died at that time. On the other hand, a family summoned to the ED may have absolutely no idea that they are about to be informed that their loved one has been critically injured or has died. For this reason, it is useful to have a nurse or colleague advise the family briefly about the general nature of the event and the status of resuscitation as soon as possible. When giving the news, physicians should use clear "dead" or "died" language to be sure that there are no misunderstandings about the outcome being conveyed. Survivors should be assured, if at all possible, that their responses to the emergency were appropriate, that the medical care team did all that was possible, and that the victim did not experience unnecessary discomfort. Appreciation of their presence in the ED, or even in the resuscitation room, also is important to emphasize.

Phone Notification

If the first contact with survivors of an ED death is by telephone, it is recommended that the survivor be told to come to the ED if at all possible.[2] Although family members may ask or even demand to know if death has occurred, allowing some time for assimilation of news by delaying information about the final outcome may be more helpful for the grieving process.[53] Nonphysician staff are particularly useful to summon survivors and can inform the relative that the patient has been involved in an accident or is seriously ill and that things are not going well.

When the notification is to somebody who is more than an hour away or otherwise unable to physically come to the ED to receive the bad news, it must be given by phone. The physician should (1) make sure that the relative has someone present in the room if possible, (2) ask the relative to be seated, and (3) name the person involved. It is best to start with brief information about the circumstances and provide a warning that bad news is coming before breaking it to them. Even a few seconds of preparation in these circumstances can serve to partially attenuate the acute psychic pain. As indicated by the perceived response, the physician may need to ask, "Are you able to talk for a few minutes?" Some individuals may be unwilling or unable to continue after they hear the initial news, and they should be given an "out," but a definite time to reconnect must be established (e.g., 10 to 15 minutes).[2,53] Long-distance loved ones cannot view the body to facilitate confirmation and acceptance and inevitably have questions not addressed in the initial conversation. The relative should be given a telephone contact of someone who actually provided care for the patient. Otherwise, if a relative calls back, a lack of information about what transpired on another shift may cause frustration or even feed the person's denial or false hope that this tragedy has not happened.

BOX 201-2 ELEMENTS OF AN EMPATHIC DEATH DISCLOSURE

Introduce self/role.
Sit down.
Assume comfortable communication distance.
Use acceptable tone/rate of speech.
Make eye contact.
Maintain open posture.
Give advance warning of bad news.
Deliver news of death clearly (use "dead"/"died").
Tolerate survivor's reaction.
Explain medical attempts to "save" patient.
Use no medical jargon; use language that is clear and easily understood.
Offer viewing of deceased.
Offer to be available to survivor.
Conclude appropriately.

From Quest TE, et al: The use of standardized patients within a procedural competency model to teach death disclosure. Acad Emerg Med 9:1326, 2002.

Viewing the Body

At some time immediately after death, an opportunity to view the body should be offered to the family. This may be the first exposure to the body for the survivors and can make concrete what has up to now been only abstract and unreal. Although a majority of survivors find viewing the body helpful, no attempt should be made to force this procedure on survivors, and they should not be made to feel that it is wrong not to view the body. If viewing is presented as an alternative and an aid in the mourning process, it is usually considered helpful.

If possible, the body should be moved to a small room, preferably away from the main treatment area. This not only ensures privacy but also makes the family feel more at ease. Family members should be warned of what to expect, such as color and temperature changes, injuries or invasive premortem procedures, and the presence of endotracheal and intravenous tubing. With sufficient preparation, most people are not shocked by the deceased person's appearance.

A staff member should remain in the room or within close range at all times. This contact allows the staff to help make the viewing an important and supportive aspect of the grieving process. At times, it may be necessary to touch the body to assure the family that this is appropriate. Survivors should be allowed to remain with the body for as long as seems appropriate. When gross disfigurement has occurred, the viewers should be warned about this, and the body should be discreetly covered where necessary. Survivors may even find that helping to clean and prepare the body (particularly with a pediatric death), holding a loved one, or preparing for transport may allow a final expression of caring.

Family Presence during Resuscitation

It is increasingly common to invite a close family member to attend resuscitation attempts. Offering this option has been endorsed in the 2005 AHA Emergency Cardiac Care guide-

lines[26] and by the EPEC curriculum.[1] Emerging evidence suggests that presence during procedures and resuscitations may be beneficial to surviving patients and family members who choose to stay. Less consensus exists among providers, and they often express discomfort with the concept.[54] If resuscitation is to be witnessed by a family member, a staff member who is dedicated to supporting that person should always be present.

Sedation for Survivors

Requests for tranquilizers, sedatives, sleeping medications, or just "something for the nerves" are common. The grieving process is important and difficult work. Prescriptions for a light sedative for a few days may be appropriate but usually require direct evaluation of the survivor by the physician. The survivor needs to know that the psychic pain is to be expected and where to turn for help and support during this difficult time.[2]

Autopsy and Closure

The "event" of death notification should be concluded with a physician expression of condolences and concern for the survivors—all physicians can honestly express the wish that they did not need to be the bearer of such life-changing news.[51] In many hospitals, chaplains or social workers or nurses are trained in informing the family about arrangements for the body, including notification of a mortician and interface with a coroner, which is not uncommon in ED deaths. If the ED practitioner desires an autopsy, this is an appropriate time to request permission. Autopsies not only are valuable in contributing to the advancement of knowledge, education, quality assurance, and public education but also can be indispensable in minimizing guilt and blame associated with the death of a loved one. Additionally, findings of unknown pathology may be important for family members if there is a genetic factor.

Consent for Procedures on the Newly Dead

The use of the newly dead to teach procedural skills is currently being debated in the medical community. It is important to educate residents in procedural skills, and emergency physicians often need to review procedures that they perform very rarely. The newly dead have been a silent source of learning in the past. Although some evidence indicates that the public generally supports the practice, serious questions about respect for bodies and the need for informed consent also have been raised.[55] The American Medical Association recently published a policy affirming that consent should be obtained from survivors.[56] In emergency medicine, it has been argued that obtaining consent is not feasible: Finding authorizing survivors is difficult, voluntary consent is questionable in a stressful situation of sudden death, and time pressures require early resumption of other ED activities. Some authorities have tried to distinguish between invasive or major procedures (e.g., thoracotomy, peritoneal lavage, venous cutdown) and minor or less invasive ones, such as intubation. The current ACEP position is that informed consent must be obtained from relatives before any procedures are performed on the newly dead. The performance of involuntary, nontherapeutic invasive procedures, including those performed during CPR, should be regarded as an ethically unacceptable departure from a standard of care that emphasizes the centrality of respect for the patient, the patient's well-being, and the requirement for informed consent.[56-58]

Grieving and Bereavement

Grief is defined as emotional pain induced by sorrow and loss. It is associated with a constellation of symptoms and behaviors that are influenced by cultural and personal issues, other current life stressors, and the relationship of the survivor to the deceased. Survivors are often the "patients" toward whom the emergency physician needs to direct his or her best expertise in the case of an ED death. Giving bad news and sharing in the beginnings of the grief response are among the most difficult situations physicians need to handle. Patients and loved ones also experience grief responses when a sudden medical crisis brings a patient to the ED and is seen as a threat to life and wellness. *Bereavement* is the situation of having experienced the death of a significant person in a survivor's life.[59] It is important to understand the range of what can be expected acutely, and to be able to identify those survivors at risk for complicated grief. Recognition of survivors at higher risk for complicated grief may help stimulate referral and decrease the risk of development of major depression and other stress disorders.[42]

The initial response to any death, whether expected or unexpected, is acute psychic pain that is associated with shock, disbelief, numbness, and inability to process further information.[2] Some persons display anger, loud screaming, crying, and occasionally acute anxiety or syncope. Alternatively, the physician may observe a false calm or no reaction. In addition to the initial emotional shock, other, more cognitive reactions, including denial, guilt, sadness, fear, shame, and anger, may be exhibited. Reactions may be based on the cultural and personal backgrounds of the survivors. This wide range of expressions is normal and expected; there is no "right" way to grieve. In the ED, outward reactions will in many instances be perceived as problematic and disruptive. The goal of the emergency physician is to help as much as survivors allow and to avoid taking personally the survivors' anger, resentment, and other outward emotional expressions, even if directed at ED staff.[2] Likewise, it is important to accept that some survivors will leave the ED still in denial and not emoting; they may need and want to postpone their grieving for what they feel is a more appropriate setting.

A variety of delayed emotional and physical symptoms can emerge as the survivor assimilates the reality that death has occurred. Physical symptoms include fatigue, anorexia, palpitations, hyperventilation, restlessness, headache, irritability, and insomnia. Emotional symptoms, in addition to guilt, anger, depression, and denial, include difficulty in concentrating, lack of organization, fear, and preoccupation with the deceased. These grief responses are to be expected. Special memories can trigger the grief response after the initial grieving period, and the memory and emotional pain of the loss may last a lifetime. Symptoms of grief, including psychic pain, numbness, intrusive thoughts, and disorganization, continue to occur during the recovery of most survivors, gradually becoming attenuated but recurring over months or years without clear "stages."[59,60]

Risk factors for difficulty navigating the work of grieving can sometimes be recognized, even in the ED. Such factors include death of a child or long-term spouse, social isolation of the survivor, and a very dependent or conflicted relationship with the deceased.[2] The physician may be able to alert the survivors' primary physician or support staff, or even the at-risk survivor directly, that ongoing work will be required to see this grief to resolution.

Grief Reactions in Staff

The impact of death in emergency medicine is significant for the staff, including physicians. Stressors that exacerbate grief and the emotional impact of ED work include exposure to premature deaths of young people or to the injuries of victims of random and senseless violence, care for those who may have

caused an accident or injury, and care that must be delivered rapidly on the basis of scant knowledge, but which other professionals can later second-guess. The ED clinician also carries a personal history that may include circumstances that make particular emergencies hit a raw nerve of which colleagues may not be aware, as, for instance, an alcoholic parent, a sibling who committed suicide, or a friend killed by a drunk driver.

Because of the sometimes overwhelming contact with death and dying in the ED, it is important to have intradepartmental mechanisms in place for helping address staff grief responses. At morbidity and mortality conferences, some discussion should be allotted to ethical, sociologic, and emotional sequelae of the cases being presented. The morbidity and mortality analysis process itself helps "make sense" of difficult situations and is part of the grieving process for health care practitioners. Case conferences, including a full range of medical personnel, chaplains, and social workers, are useful to articulate and share sadness, anger toward patients, and other emotional and cognitive work required for healing. This is particularly important to offer staff after major community disasters. Although for some people denial is a positive coping mechanism, for others the opportunity to share and express emotions is needed to begin to move forward and resume the work of caring for patients.[59]

Palliative Care in the Emergency Department

Providing quality palliative end-of-life care is important in the ED. Education in Palliative and End-of-Life Care for Emergency Medicine (EPEC-EM) is a curriculum specifically designed to provide emergency clinicians with the information and skills to practice ED-based palliative care.[1] The evidence that we do not know what others want for themselves or family members at the time of critical illness is discussed in the first part of this chapter. In the case of a cardiopulmonary arrest or major trauma resuscitation, attempts at curative intervention are always indicated unless the emergency physician has clear instructions from the patient or surrogate to the contrary. In less critical situations, however, guidance about the goals and direction of ED care is needed, and management strategies should be "patient-centered."[1] Although some would argue that it is time-consuming and unnecessary for emergency physicians to develop a nuanced approach to end-of-life care, it is no longer appropriate to provide all patients with maximal medical treatment and to "let the admitting doctors sort out the other issues." Comfort and optimal quality of life become a higher priority for many patients with severe chronic diseases, such as cancer, COPD, heart failure, renal insufficiency, or dementia. Some of the procedures that are normal interventions in emergency care may not be appropriate in this subset of patients.

Establishing Goals of Care

The primary skill that emergency physicians must have in managing patients near the end of life is the ability to communicate. In a true emergency, such conversations must take a back seat to resuscitation interventions. In many patients, however, it is not imperative to treat before discussion or diagnosis. In the ED setting, several useful methods can be to establish what treatments patients want near the end of life.

Reviewing and Honoring Advance Directives

Written advance directives can help guide treatment decisions in the ED as well as on hospital admission. Although such documents often do not foresee the particular medical emergency that precipitates an ED visit, their existence indicates that a patient has considered how medical care should or should not look. Advance directives may indicate that aggressive lifesaving interventions are desired, or that a patient is in the dying process and wants to be kept comfortable. People's wishes change over time, and written advance directive requests should be reconfirmed at the time of an acute crisis. The emergency physician should be well versed in the technicalities of the various forms of written legal advance directives that exist.

Processing Verbal Requests

Verbal requests to titrate or limit procedures can be made by the patient or the patient's surrogate. The emergency physician should determine whether the patient has decision-making capacity and, if such capacity is lacking, who will be the spokesperson for the patient. Invasive tests and procedures may not be performed on patients without their consent. In emergency situations, physicians rely on the "emergency exception" to informed consent and act to preserve life, or at least to buy time to consider options. Many situations in the ED, however, do not require immediate intervention, or they allow for a less invasive alternative (such as mask ventilation for respiratory failure) while the patient's goals are discussed.

Initiating a Conversation on Goals of Care

Emergency physicians see many sick patients who do not have written advance directives but are temporarily stable enough to have meaningful conversations about their needs and goals, their perception of where they are in the course of their disease, whether they wish to cure an intercurrent problem, which symptoms require management, and how much effort they wish to have undertaken if resuscitation is needed to preserve their life. Patients with seemingly lethal conditions may be aggressively pursuing curative or at least disease-modifying options, whereas the heavy burden of suffering other patients are experiencing may not be obvious until they are asked specifically about their illness. The only way to determine the patient's needs is to ask.

Questions that can be useful for initiating this conversation are listed in Table 201-1. Pulling up a chair, sitting with the patient and family, and spending a few minutes clarifying the patient's values and view of the present and of the future may make a big difference in designing the patient's care and disposition.

It is useful to start the "goals of care" conversation with a global understanding of the patient's illness, values, fears, and expectations. This makes the "procedures" part of the conversation flow naturally. The physician can then suggest to the patient and family what treatments will be useful (or not) in the context of overall goals and values. Antibiotics may be appropriate for an acute pneumonia, but they may not be indicated in a patient with advanced dementia who has been bedridden and unable to communicate for several years. Intubation will be acceptable to some patients with COPD, whereas others who have struggled on the ventilator before may not wish to experience that discomfort again. Intravenous hydration is useful to correct dehydration but may merely increase secretions in the patient who is actively dying. All of these interventions need to be considered in the context of caring for the patient and enabling them to achieve their goals.

Initiating Advance Directives and DNAR Orders

Several authors have suggested that the ED may be an important link in initiating advance directives because it often is the

Table 201-1 Representative Questions for Initiating the Discussion about End-of-Life Issues

DOMAIN	REPRESENTATIVE QUESTIONS*
Goals	Given the severity of your illness, what is most important for you to achieve? How do you think about balancing quality of life with length of life in terms of your treatment? What are your most important hopes? What are your biggest fears?
Values	What makes life most worth living for you? Would there be any circumstances under which you would find life not worth living? What do you consider your quality of life to be like now? Have you seen or been with someone who had a particularly good death or particularly difficult death?
Advance directives	If with future progression of your illness you are not able to speak for yourself, who would be best able to represent your views and values? (health care proxy) Have you given any thought to what kinds of treatment you would want (and not want) if you become unable to speak for yourself in the future? (living will)
Do-not-attempt-resuscitation order	If you were to die suddenly, that is, if you stopped breathing or your heart stopped, we could try to revive you by using cardiopulmonary resuscitation (CPR). Are you familiar with CPR? Have you given thought as to whether you would want it? Given the severity of your illness, CPR would in all likelihood be ineffective. I would recommend that you choose not to have it, but that we continue all potentially effective treatments. What do you think?
Palliative care: pain and other symptoms	Have you ever heard of hospice (palliative care)? What has been your experience with it? Tell me about your pain. Can you rate it on a scale of 1 to 10? What is your breathing like when you feel at your best? How about when you are having trouble?
Palliative care: "unfinished business"	If you were to die sooner rather than later, what would be left undone? How is your family handling your illness? What are their reactions? Has religion been an important part of your life? Are there any spiritual issues you are concerned about at this point?

*It is important to give the patient an opportunity to respond to each question. Follow-up questions and responses should be based on careful listening to the patient, with use of the patient's own words whenever possible.

From Quill JE: Initiating end-of-life discussions with seriously ill patients: Addressing the "elephant in the room." JAMA 284:2502, 2000.

patient's portal of access to the hospital.[61] Wrenn and Brody described a small series of patients for whom the emergency physician wrote DNAR orders on admission.[62] Balentine and colleagues described another series in which few negative responses were obtained from the families who were approached.[63] Both papers point out that fragmentation in health care may mean that previous wishes are not translated into hospitalized settings, and that the ED may be the best place to establish or renew documentation of the patient's wish to forgo resuscitation at the outset of the hospitalization.[5]

Treating Symptoms Requiring Palliation

When a patient is suffering from a disease that is not curable, he or she may still want a variety of medical interventions as part of care: antibiotics for intercurrent infections, drainage of effusions that cause shortness of breath, wound care for decubitus ulcers, decompression of bowel obstructions, and aggressive pain management. On the other hand, the best way of maximizing patient function and quality of remaining life may require de-emphasizing diagnosis and primarily addressing symptoms. The most common reason that patients with end-stage illness seek emergency care is for control of intolerable symptoms such as nausea, vomiting, dyspnea, severe constipation or diarrhea, and pain (Box 201-3).

The emergency physician may encounter several unfamiliar concepts when attempting to treat symptoms in frail persons near the end of life. One of the more "foreign" concepts to most emergency physicians is the treatment of symptoms without diagnosing the underlying cause, even though this often is the appropriate option. Additionally, concerns regarding "drugging" patients or overtreating them, although common, are mostly unwarranted. Nevertheless, worry about unintended consequences may lead to underdosing medications, leaving patients without desired relief. This problem frequently arises with the use of opioids to control pain. Concerns about respiratory depression arise, leading to inadequate pain control, even though the risk of respiratory depression is minimal when the dose is titrated to the patient's desired endpoint. The EPEC and EPEC-EM curricula are excellent resources for learning about strategies that are unique to palliative care for patients.[1,6] The following "pearls" from those programs may be useful.

BOX 201-3 Palliative Medical Treatment Options to Enhance Quality of Life

- Pain control
- Control of fluid and electrolyte imbalance
- Nausea/vomiting/constipation management
- Radiation therapy for bone pain, cord compression, hemorrhage from tumors
- Drainage tubes for malignant effusions/obstructions
- Treatment of intercurrent infections
- Management of incontinence
- Supplemental oxygen
- Anxiolytics, antidepressants, appetite stimulants when appropriate

Pain

For patients presenting with acute pain or chronic pain of moderate intensity (rated 5/10 or above) opioid use is appropriate (see Chapter 187). A thorough medication history must be obtained to determine tolerance and dose adjustments that may be needed. Pain assessment is different for patients with chronic pain, because they may not show the abnormal vital

signs or outward expressions of discomfort commonly observed with acute pain. Patients with advanced illness and pain may be tolerant to opioids and require high doses to reach comfort. This inevitably causes discomfort on the part of the provider. Patients suffering from malignant pain may need continuous infusions of opioids to obtain relief. These concepts are reviewed in the EPEC curriculum, and many other resources for learning about dosing of analgesics in these situations are available.[1,64]

When available, palliative care consultation should be sought for treatment of malignant pain. However, pain and palliative care consultation is not uniformly available, particularly during the evening and night hours. Therefore, emergency physicians must have the basic knowledge to treat severe pain. Rapid opioid dose escalation is the most important principle in patients with cancer on opioids. Doubling of the dose may be required until successful analgesia is reached.[65] Understanding dosing is key as well. With intravenous administration of morphine, serum levels will be maximal in 6 minutes, which translates to the need to rapidly reassess and redose if the patient is in severe pain. Providing analgesic stability is important, and this is done by providing a long-acting formulation (e.g., MS Contin), with an immediate-release short-acting agent for breakthrough pain. Side effects from opioids must be anticipated as well. Rising serum levels of opioids stimulate the chemotactic trigger zone, causing nausea. Educating the patient that nausea will subside within days is helpful. Minimizing fluctuations by using long-acting agents whenever possible can limit this form of nausea. Constipation is a common effect of opioids, and tolerance will not develop to this very frustrating complication of narcotics. Prevention is far easier than treatment, and a stimulant laxative should be part of all narcotic prescriptions for malignant pain. The use of nonsteroidal anti-inflammatory drugs may be helpful in potentiating the effects of opiates in cancer patients. Recognizing neuropathic pain also is important, because medications such as gabapentin may be added. It is important to clearly explain the proposed treatment plan to the patient and caregivers, to monitor the response to treatment and side effects, and to coordinate changes in treatment regimens with the primary care physician.[1,6]

Nausea and Vomiting

Nausea and vomiting arise from triggers in the gastrointestinal tract, cerebral cortex, vestibular apparatus, or the chemoreceptor trigger zone in the fourth ventricle. The neurotransmitters involved include serotonin, dopamine, acetylcholine, and histamine. Successful treatment of nausea and vomiting involves selecting the drugs that will target the right receptors. In addition to usual antiemetics, dexamethasone, octreotide (which reduces secretions and may be useful in cases of intestinal obstruction), and tetrahydrocannabinol may be important adjuncts for the control of nausea.[1,6,66]

Constipation

Constipation is multifactorial near the end of life; causes include decreased mobility, medications, mechanical obstruction, and dehydration. Stimulant laxatives and then osmotic laxatives should be tried in escalating doses, and combinations may be needed. Opioid-related constipation can be a major problem; tolerance does not develop to this side effect of chronic and high-dose use. Every attempt should be made to prevent rather than treat constipation by anticipating the need for stimulant softener combinations when opioids must be used chronically. In cases of mechanical small bowel obstruction, medical management with clear liquids, loperamide, and octreotide results in resolution in a majority of patients.[1,6]

Anorexia and Cachexia

Anorexia and cachexia develop in patients with advanced diseases and may be more stressful for the family than for the patient. Parenteral nutrition does not necessarily reverse these processes, nor do they affect life expectancy, although infections of the esophagus should be considered. Appetite stimulants are sometimes useful.[6]

Shortness of Breath

Shortness of breath also can be part of the last stages of airway disease or cancer involving the lungs. There are many causes, and several treatments may be helpful. Options include symptomatic treatment with oxygen (which may not work if central triggers are operating), anxiolytics, and low-dose opioids, which may decrease the sensation of breathlessness. Malignant effusions may require drainage. In the actively dying patient, morphine and atropine can be used to dry secretions, slow breathing rates, and decrease the work of breathing.[6]

Depression

Psychosocial distress is exceedingly common in patients suffering with incurable illness. Anxiety and depression have been found to have a negative impact on survival and to decrease quality of life. These issues are best addressed by the primary care provider. Emergency providers can provide empathy and support and recognize that these symptoms are not inevitable components of the dying process and therefore deserve attention.

Special Situations and Diseases

Advanced Dementia

Alzheimer's dementia is a prolonged and relentless chronic disease with a course that can extend up to 20 years. With severe dementia, patients may be combative, incontinent, and unable to ambulate. In the terminal phases of the disease, they are bedridden, mute, and dysphagic and suffer from intercurrent infections.[67] In the demented patient, invasive procedures often require restraints and sedation, and the emotional burden to the patient is high. Even hospitalization, administration of intravenous fluids or antibiotics, and other common interventions are frightening to patients with dementia. As an example, percutaneous gastrostomy or feeding tubes do not prolong life in these patients, and their qualitative benefits are questionable. They do not prevent aspiration, provide palliation, or improve function in a progressive severe disease like dementia.[68,69] For the emergency physician, the increased burden in combination with decreased benefit, even of the simplest procedures such as administration of antibiotics, means that interventions should be thoughtfully chosen and discussed beforehand with surrogates when there is time to do so. Addressing concerns of caregivers also is particularly important in dealing with families of patients with dementia. Depression is common in caregivers; the burden of caring for patients is very heavy, and grieving may occur before death as the person that they knew disappears in front of them.

Renal Failure

Dialysis has been a technical success in prolonging life for patients without kidney function. Because it is now so common,

physicians do not realize that the annual mortality rate is greater than 25% for patients with significant comorbid illness.[70] Understanding that dialysis is a choice and not a mandatory intervention may be a useful attitude to affirm in discussing long-term choices with patients and their families in the ED. In the patient with dementia or cancer, electing not to treat renal failure is an option that should be offered to patients and families.[71]

Heart Failure and Chronic Obstructive Pulmonary Disease

Although the physiologic parameters of terminal heart failure and COPD are well described, death from these diseases is commonly unexpected and may occur as part of a sudden acute deterioration that is not remediable. As a consequence of the entry-reentry pattern of dying associated with CHF and COPD, many patients will not receive good palliative care until the last days of life. However, some guidelines are available to assist the provider in determining prognosis.[72,73] When death occurs, it is important to remind the survivors that the underlying disease is the real cause of mortality.

On the other hand, if the patient presenting with acute decompensation becomes stabilized, the emergency physician may be the best person to have a conversation concerning advance planning with the patient and family to establish what kind of resuscitation measures should be performed if the patient suffers a cardiac or respiratory event in the hospital and who should make decisions on behalf of the patient if he or she should become incapacitated at some time during the admission. In patients with many types of chronic diseases of the entry-reentry type (see Fig. 201-1), the period after an emergency has resolved (at least temporarily) often is the best time to establish what interventions would be appropriate if decompensation occurs again. In terminal stages, an undue focus on diagnostics is more common in these patients than in patients with cancer, particularly if the lethality of these conditions is not acknowledged. Palliative care or hospice referral often is useful in assisting the patient with understanding and acknowledging prognosis and establishing intentional and realistic projects and goals for their remaining life.

KEY CONCEPTS

- In emergency medicine, it is essential to act rapidly, with the presumption of curative goals, and it often is impossible to withhold initial interventions.
- Advance directives and patient wishes should be honored whenever possible, including withdrawal of invasive support if the patient's desire to not receive such treatments is determined after initial ED intervention.
- Suffering is not the same as physical pain: The body experiences pain, whereas persons experience suffering, particularly when physical changes threaten their future.
- Patients have individual perceptions of burdens and benefits when they live with chronic illnesses. The only way to understand a person's quality of life and whether treatment is "right" for a patient is to have a conversation.
- An important aspect of the initial ED evaluation of a patient with a life-limiting illness is to ascertain the patient's general wishes regarding resuscitation and related issues. The conversation with family and patient can begin by asking the following questions: "What kind of resuscitation do you wish to receive if an emergency occurs after admission?" "Whom do you want to make decisions for you if you cannot?"
- A discussion of goals of care is more effective if it starts by clarifying the patient's broad values and goals. From the broad discussion, the clinician can suggest what procedures may or may not be useful in attaining the patient's goals.
- The purposes of hospitalization for persons with severe terminal diseases should be clear and in line with the patient's values.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 202

Medicolegal Issues and Risk Management

Robert A. Bitterman

PERSPECTIVE

Practicing good medicine in the emergency department (ED) may have been enough to avoid legal entanglements historically, but no longer. Federal and state laws now directly govern the practice of emergency medicine. The magnitude and complexity of the controlling legal authority, plus the significant penalties for noncompliance such as criminal sanctions, civil lawsuits, civil monetary penalties, or exclusion from participation in Medicare and Medicaid, dictate that emergency physicians acquire functional knowledge of these laws.

Federal law, the Emergency Medical Treatment and Active Labor Act (EMTALA), (a section of the Consolidated Omnibus Budget Reconciliation Act of 1985 [COBRA]), also known as the "antidumping" statute, governs how emergency physicians must triage, register, examine, provide workup, treat or stabilize, discharge or transfer, utilize hospital resources, and involve medical staff expertise when caring for patients presenting to the ED.[1-3] State laws further control the practice of emergency medicine through such issues as consent, reporting requirements, confidentiality requirements, forensic and police matters, civil commitments, and emergency medical services (EMS) statutes.

EMERGENCY MEDICAL TREATMENT AND ACTIVE LABOR ACT

EMTALA originally was enacted to prevent private hospitals from transferring ("dumping") medically unstable, indigent patients to public hospitals. Subsequent amendments to the law, government regulations, and court decisions greatly expanded the reach of EMTALA, such that the law now sets national standards of care for emergency services.[2-4] Today's practice of emergency medicine requires a firm understanding of EMTALA's statutory requirements and how the regulatory agencies and the courts interpret the three main aspects of the law: screening, stabilizing, and discharging or transferring ED patients.

Medical Screening Examination

Any person who comes to an ED requesting examination or treatment must be provided with an appropriate *medical screening examination* (MSE).[5] The purpose of the MSE is to determine whether the patient has an *emergency medical condition* (EMC).[6,7]

Emergency Medical Condition

The EMTALA defines an EMC as "acute symptoms of sufficient severity (including severe pain) such that the absence of immediate medical attention could reasonably be expected to result in any of the following: (1) placing the health of the individual (or, with respect to a pregnant woman, the health of the woman or her unborn child) in serious jeopardy, (2) serious impairment to bodily functions, or (3) serious dysfunction of any bodily organ or part."[6] In the case of a pregnant woman who is having contractions, an EMC is defined as one in which "[t]here is inadequate time to effect a safe transfer to another hospital before delivery, or the transfer may pose a threat to the health or safety of the woman or the unborn child."[7]

Competent physicians can reasonably disagree whether certain conditions are serious enough to constitute an "emergency." However, the courts hold that the relevant factor is whether the physician *perceived* the patient to have an EMC, not whether the patient actually had an EMC, and not whether the emergency physician or hospital should have known that the EMC existed. The focus is whether the physician or the hospital in fact *actually determines* that the patient has an EMC; the standard is subjective, not objective.[8] If the physician and the hospital perform an appropriate MSE and in good faith determine that no EMC exists, the courts will not retrospectively review that decision; rather, it will be a simple state malpractice issue of whether the examination and diagnosis met the applicable standard of care.

If the MSE does not reveal an EMC, further care of that patient is not controlled by EMTALA, so the law's provisions governing stabilizing treatment, transfer of the patient, or involvement of on-call physicians no longer apply. This interpretation emphasizes the critical importance of documentation of the presence or absence of an EMC during a patient's initial ED evaluation. A checkbox to indicate such should be on every ED medical record.

"Any Individual"

Everyone who presents to the ED requesting care must be screened. Whether the patient is indigent, a member of a managed care plan, or covered by Medicare, Medicaid, or private insurance is irrelevant; the hospital must provide everyone who presents for care with an MSE.[5] This includes all patient populations, such as illegal aliens, minors, and

private patients of the hospital's medical staff but excludes persons who are already patients of the hospital, such as inpatients or outpatients undergoing a scheduled procedure at the hospital who are brought to the ED for emergency care.[2] The screening of minors is discussed later in the section on consent.

Private Patients

In many hospitals, members of the hospital's medical staff often meet their private patients in the ED. These patients are examined and treated by their private physicians, not the emergency physician on duty. Such practice is entirely appropriate to maintain physician-patient relationships and is allowable under EMTALA. However, the hospital should have prearranged procedures for handling private patients that do not unduly delay the patient's MSE; otherwise, the hospital could be liable under EMTALA for failure to provide an "appropriate" MSE. Delay of treatment in such instances also frequently results in hospital liability through state malpractice actions.

All private patients should be triaged according to the hospital's established protocols. If the triage nurse determines that the patient requires immediate care, the emergency physician on duty should provide the necessary treatment until the patient's private physician arrives in the ED to assume the patient's care.

If triage determines that the patient does not require immediate care, the emergency physician should see the patient in the order consistent with the usual practice of the ED, generally in the order of acuity or time of arrival. If the private physician comes to the ED and sees the patient before the emergency physician does, the examination by the private physician constitutes the required MSE by the hospital. In this situation, no undue delay of the MSE for any nonmedical reason has occurred. However, if the patient's private physician has not arrived by the time the emergency physician would normally examine the patient, the emergency physician should perform an MSE. If no EMC is evident, the patient can wait for his or her physician to arrive. If an EMC exists, the emergency physician should undertake appropriate stabilizing treatment until the patient's physician arrives.[9,10]

"Comes to the Emergency Department"

The Centers for Medicare and Medicaid Services (CMS) (formerly the Health Care Financing Administration [HCFA]) deems anyone on hospital property to have "come to the emergency department."[11,12] According to CMS, "hospital property" consists of the entire main hospital campus, including parking lots, sidewalks, and driveways, and any ambulance owned and operated by the hospital, even if the ambulance is not on hospital grounds.[11] CMS then divides hospital property into "dedicated emergency departments" and all other property that is not a dedicated ED.

A *dedicated* ED is defined as any department or facility of the hospital, whether on or off campus, that is licensed by the state as an ED; is held out to the public as a place that provides care for persons with EMCs on an unscheduled basis; or actually does provide care for persons with EMCs a certain percentage of the time.[2] Units qualifying as dedicated EDs include typical hospital EDs, labor and delivery units, and psychiatric intake centers.

CMS also intended EMTALA to apply to urgent care centers. However, urgent care centers do not hold themselves out as able to provide care for EMCs as defined by the statute, nor do they in actuality provide care for a sufficient number of true emergencies to meet the regulatory percentage. Thus, the typical urgent care center is not likely to meet the new regulatory definition of a dedicated ED and therefore will not have to comply with EMTALA. CMS may readdress this issue in the future. Hospitals should examine how their relationship with any urgent care centers is legally structured in conjunction with the new regulations to determine whether EMTALA applies.[2,13]

CMS specifically exempts a number of on-campus areas from compliance with EMTALA—generally, those areas that typically do not provide emergency care, such as physicians' offices, skilled nursing facilities, other entities that participate separately under Medicare, and other nonmedical facilities on campus.[2] CMS also exempts application of the law to off-campus facilities and other "departments of a provider" that were never intended or structured to manage EMCs, such as dialysis centers, rehabilitation units, laboratories and radiology centers, or primary care clinics. These facilities must have, however, written policy and procedures for appraisal of emergencies and arranging transfers when appropriate.[14,15]

Presentations to the hospital's dedicated ED require only a request for examination or treatment of a medical condition; it is not required that the presentation be for a medical condition that constitutes a true emergency to trigger EMTALA's screening duty. Presentations to hospital property other than the dedicated ED do, however, require the request to be for an EMC before EMTALA applies.[2]

"Parking" of Patients Brought by Emergency Medical Services to the ED

Overcrowding led some hospitals to ignore ambulance patients and leave EMS to care for them until the hospital "accepted" the patient, a practice termed "EMS parking." These hospitals erroneously believed that unless they accepted responsibility for the patient, they had no EMTALA duty to provide care or accommodate that patient. CMS issued a memorandum reminding hospitals that their EMTALA obligation begins the moment the patient "comes to the ED" and a request is made on behalf of the patient for examination or treatment of a medical condition, not when the hospital "accepts" the patient.[16] (Of note, the practice of "parking" EMS patients also may violate Medicare regulations, which require hospitals to "meet the emergency needs of patients in accordance with acceptable standards of practice."[17])

Subsequently, EMS organizations cited the CMS memo as requiring hospitals to take instant custody and responsibility of all patients brought in by EMS. In response, CMS issued a clarification to its "parking" memo, stating that its guidance "should not be interpreted to mean that a hospital cannot ever ask EMS personnel to stay with the person they transported to the ED when the hospital does not have the capacity or capability to immediately assume full responsibility for the individual."[18] Also pointed out was that in certain circumstances, such as an influx of multiple trauma victims, it would be reasonable for the hospital to ask the EMS provider to stay with the patient until such time as the ED staff became available to care for that person.

CMS did note, however, that "even if a hospital cannot immediately provide an MSE, it must still triage the individual's condition immediately upon arrival to ensure that an emergent intervention is not required and that the EMS provider staff can appropriately monitor the individual's condition."

CMS will review complaints of this nature on a case-by-case basis to determine if the hospital violated EMTALA's medical screening mandate.[18]

National Emergencies or Disasters

Under certain circumstances, the Secretary of Health and Human Services can exempt hospitals from EMTALA during times of national or local disasters or terrorist acts, bioterrorist events, or pandemic infectious disease.[19,20]

Request for Examination or Treatment of a Medical Condition

Mere presence in the ED or on hospital property is not sufficient to trigger the hospital's duty to provide an MSE; a request for examination or treatment also is necessary. The request can be made by *anyone* on behalf of the patient, including EMS personnel, a police officer, or a babysitter; the request does not have to come from the patient, a family member, or a legal guardian.[5]

Also, if a person is unable to speak to request care, that person's behavior may constitute a request if the hospital's personnel are aware of the behavior and a prudent layperson would believe that the behavior indicated a need for examination or treatment.[2]

Other Emergency Department Functions

Hospital EDs serve many functions other than the evaluation and treatment of patients with true medical emergencies. Physicians on the hospital staff may use the ED in the off-hour periods to provide injections or obtain laboratory tests or radiographs on their patients. Police use the ED to obtain blood alcohol samples on allegedly intoxicated automobile drivers. Some hospitals may use the ED to provide urine drug screens on injured workers, prescription refills, allergy shots, rabies vaccinations, blood transfusions, or other community medical services such as blood pressure screening or flu shots.

Laboratory Tests and Radiography Requests

The test category includes urine or serum drug screening, routine laboratory tests, and imaging studies. In each case, no immediate medical decision making is required. The patient's physician determines the indication for the studies and is responsible for the patient's care, including following up on the test or radiography results. The patient is not requesting "examination or treatment for a medical condition" by the hospital's ED, so the hospital does not need to provide an MSE.

Such patients should not be sent through triage and should not have their vital signs taken, and the hospital should not create the usual ED chart for them. They should not be asked to sign the usual ED "consent for treatment" forms, which could imply they were requesting examination and treatment. Separate paperwork should be used to document the visit, the particular test performed, the patient's informed consent for the testing, any communication with the private physician, and a specific statement that the patient is not requesting an MSE from the ED, with the patient's signature.

Some persons come to the ED on their own, not at the request of their physician, and request a test (e.g., for pregnancy or human immunodeficiency virus serostatus). All such persons should be given an MSE before any test is conducted. If the person declines the MSE, he or she should be referred elsewhere to obtain the requested test: outpatient clinic, personal physician, or public health clinic, or a local drugstore for a pregnancy test. Documentation that the person declined the offered MSE is essential.

Minor Treatments

The minor treatment category includes allergy shots, tetanus shots, rabies vaccines, bloodletting or blood transfusions, chemotherapy infusion for cancer or possible organ transplant rejection, reinsertion of a feeding tube or Foley catheter, prescription refills, suture removals, antibiotic injections, and narcotic injections for chronic pain syndromes. Patients presenting to the ED requesting treatment should be given an MSE. In each instance, the common denominator is the element of medical decision-making.

Antibiotic and narcotic injections require special comment. Physicians, particularly in rural hospitals, send their patients to the ED and then call in phone orders for parenteral medications. The patients are not examined by the emergency physician on duty. This practice should be avoided, and it probably violates EMTALA because the hospital does not provide the patient the same MSE as for any patient with the same complaint. It is irrelevant if the patient's private physician performed an office examination immediately before sending the patient to the ED. This requirement of EMTALA may not be cost-efficient medicine, but both CMS and the courts agree that the hospital must provide an MSE to any person who comes to the ED and requests examination or treatment for a medical condition.[1,21]

All patients presenting for minor treatments should be triaged, registered, and managed as for all other ED patients. The ED evaluation should determine whether the patient's condition meets the definition of an EMC before the hospital administers any medications. CMS and the courts will assume that these patients requested examination or treatment, and the hospital must demonstrate that either (1) these patients did not request that an MSE be performed or (2) the ED evaluation did not reveal an EMC.

CMS recently attempted to eliminate application of EMTALA to persons coming to the ED for reasons other than seeking emergency care. However, the language of the new regulations really did not change anything. The hospital still must perform an MSE of an extent necessary to determine whether an EMC exists, regardless of whether the patient's presenting complaint appears to be for a "nonemergency" condition.[2,13]

Prescriptions

In small communities, local pharmacies frequently are not open continuously. Hospital pharmacies, sometimes through the hospital ED, fill prescriptions for patients in off-hours. Patients presenting to the ED to fill these prescriptions do not need an MSE. If the prescription is filled through the ED, the hospital should have the patients sign a form indicating they are not requesting an MSE, for the same reasons and in the same manner as when tests are done in the ED at the request of physicians.

This situation is different from that in which patients present to the ED for prescription renewals. Patients requesting "refills" on this basis are seeking not pharmacy services but medical decision-making services from a physician by asking for a prescription renewal to treat an underlying medical condition.[2,9] Therefore, patients seeking prescription *renewals* must be provided with an MSE.

Sexual Assault Cases

The ED often assists police in the collection of evidence related to alleged sexual assault cases. If a person comes to the ED solely to provide evidence for the criminal investigation

and is not requesting examination or treatment for a medical condition, no MSE is required. However, if the person complains of pain or injury or wants pregnancy or sexually transmitted disease prophylaxis, that person is requesting examination or treatment for a medical condition and must be provided with an MSE.[22]

Preventive Services

Blood pressure screening and vaccination services do not require an MSE. The patient receiving such services is not requesting examination or treatment for a medical condition. The patient is attempting to prevent illness prophylactically, not seeking treatment of an illness. These vaccinations are distinct from tetanus boosters, because boosters typically are administered in response to injury and represent a component of medical decision-making and treatment.

Police Blood Alcohol Tests

For both medical and legal reasons, an MSE should be offered to all persons presenting to the ED for police-requested blood alcohol samples.[23] This scenario is different from that in which patients present to the ED to have blood tests done as ordered by their physicians. Persons in police custody have not been examined by a physician, and the results of the test will not be returned to a physician to care for the patient. The police officer brought the patient because of aberrant behavior, suspected to be caused by alcohol intoxication. Many diseases mimic alcohol intoxication, including hypoglycemia, cerebral hypoxia, head injury, metabolic abnormalities, and other toxins. Medically, alcohol intoxication should not automatically be presumed as the cause of the patient's condition merely because it is so common. The emergency physician should examine the person in custody to determine if an EMC exists.[9]

The patient may refuse the MSE and request that only the blood be drawn. If the patient appears competent, this can be done. The refusal of the MSE must be documented, as noted for other testing done in the ED, with additional documentation of the risks and benefits of the offered MSE and careful notation of the patient's competence. If the patient is too intoxicated to make medical decisions, release from the ED should be delayed until the patient is competent enough to make rational decisions. Only physicians should assess and document a patient's competence; other ED personnel should not be allowed to make these decisions.[9]

Again, under EMTALA, the "request for examination or treatment" can be made by anyone on behalf of the patient. The police officer's request for blood alcohol sampling may be sufficient to constitute the request for an MSE.

Direct Admissions through the Emergency Department

Direct patient admissions are always problematic. In the three most common scenarios, the patient (1) is sent to the ED after being examined by the primary care physician in the office, (2) is sent in after phone contact with the physician, or (3) is accepted by phone-in transfer from a different hospital ED or inpatient setting. In all three cases, the patient's physician intends to see the patient after admission to the inpatient setting, rather than in the ED. Medically, each presentation may require a different level of acute intervention, but legally all are the same under EMTALA.[2,3,13] CMS does not apply the law to *inpatients* regardless of whether they are directly admitted to the floor, directly admitted by way of the ED, or "boarded" in the ED awaiting bed placement. Even if the inpatient is brought down to the ED, the law does not apply.[2,24]

An *inpatient* is defined as "an individual who is admitted to a hospital for bed occupancy for purposes of receiving inpatient hospital services…with the expectation that he or she will remain at least overnight."[2] It does not matter if the situation changes later and the patient can be discharged or transferred to another hospital and does not actually use the bed overnight. The key element is that the patient must be formally admitted with a documented admission order. A physician's intent to admit or a level of acuity indicating that the patient "obviously will be admitted" is not enough to satisfy the definition. Documentation is critical.[2,24]

CMS does not consider patients admitted to observation status to meet the regulatory definition of admitted patients (not admitted for purposes of receiving inpatient services), so EMTALA still applies to the care of observation patients, such as patients managed in ED chest pain units.[2,24]

Therefore, under existing regulations, persons who were directly admitted and sent through or held in the ED from a physician's office, a nursing home, or in transfer from another ED or another hospital inpatient setting are no longer covered by EMTALA, even though they have "come to the hospital's emergency department."

Health Care Providers Qualified to Do the Medical Screening Examination

EMTALA does not specify whether a physician, a nurse, or another health care provider must perform the MSE. CMS regulations require that the screening examination be done by "qualified medical personnel,"[24] and that the hospital's governing body formally designate, in writing, who is a qualified person to perform medical screening on behalf of the hospital.[25,26] CMS specifies that the hospital cannot allow the medical director of its ED to designate who is qualified to perform screenings on behalf of the hospital.[27]

Triage by a nurse is not considered to constitute an MSE. Neither CMS nor the courts accept triage as adequate to determine whether an EMC exists.[2,9]

It is strongly recommended that hospitals designate physicians to be primarily responsible for MSEs performed in the ED. Either the physician personally performs the screening or is directly responsible for examinations performed by physician assistants or house staff. It is appropriate to use physician assistants and nurse practitioners to screen patients who are determined by nurse triage to have less acute or severe conditions. However, the physician on duty should have a direct supervisory role with the physician assistant and a collaborative arrangement with a nurse practitioner—the difference being that nurse practitioners have an independent state license, whereas the physician assistant functions under the license of the physician.

Ancillary Services as Part of the Medical Screening Exam

The law requires hospitals to provide the screening examination "within the capabilities of the hospital's emergency department, including ancillary services routinely available to the emergency department."[5] According to CMS, this means that the scope of an MSE may "range from a simple process involving only a brief history and physical examination to a complex process that also involves performing ancillary studies and procedures such as (but not limited to) lumbar punctures, clinical laboratory tests, computed tomography scans, diagnostic tests and procedures."[28]

Because the stated purpose of the MSE is to determine whether an EMC exists, CMS and the federal courts hold that the hospital must conduct whatever examination is necessary to make that determination.[3,29] It may take only a visual glance to rule out any EMC in a patient with a rash. However, if it takes a complete neurologic examination, computed tomography scan, and lumbar puncture to decide whether that patient has a serious underlying infection, then those procedures are considered part of the MSE.

Thus, if the ED usually has ultrasonography, computed tomography, ventilation-perfusion scans, and similar tests available, it must use those resources if necessary to determine whether the patient has an EMC. However, the hospital is obligated only to utilize the resources ordinarily available to its ED.[5] Neither the statute nor the regulations mandate that hospitals expand resources or offer additional services to ED patients. An exception may be the use of interpreters for patients not fluent in the English language, which is required by the Medicare conditions of participation.[30,31]

CMS views the ancillary services available to the ED as including the services of on-call physicians if their expertise is required to decide if the patient has an EMC.[2,9,13,28,30,32] If the emergency physician cannot determine whether a patient has an EMC, the physician must use the on-call physician services to help make that determination. For example, if it takes an on-call surgeon to decide whether a patient has an "acute abdomen," the surgical evaluation becomes an integral part of the hospital's MSE.

Policies, Procedures, and Practice Guidelines

The federal courts hold that an appropriate MSE has two components: (1) the examination must be "reasonably calculated to identify critical medical conditions," and (2) the "exact same level of screening must be uniformly provided to all patients who present with substantially similar complaints."[29] In other words, a hospital satisfies the requirements of EMTALA if it conducts standard screening procedures, uniformly, to all patients with similar complaints and circumstances.

Each hospital determines its own standard screening policies and procedures. By necessity, each hospital's standard will be individualized, because each hospital ED has its own capabilities and different ancillary services available. Once a hospital defines its standard screening process, however, it must apply that process uniformly to all patients presenting with similar complaints, and material departure from its standard screening procedure constitutes inappropriate screening under EMTALA. Because motive is not a relevant issue in the federal courts (except the 6th Circuit Court) or during CMS investigations, liability may result from any material deviation of the hospital's screening process, regardless of the hospital's motive and regardless of the reason for the deviation. For example, a Florida hospital's screening policy stated that triage would be conducted within 3 minutes after a patient's arrival at the ED. In one instance, a patient was not triaged until 45 minutes after arrival; this delay constituted a violation of the law because the hospital did not follow its own policy.[9]

Once hospitals define their own standard screening process, they will be held to that standard, by both plaintiffs and the government enforcers. Investigators and plaintiff attorneys will subpoena and closely examine the hospital's policies and procedures, medical staff bylaws, ED rules and regulations, practice guidelines, and other written information on the screening process. They will compare the written process to what actually transpired. These hospital documents must be drafted very carefully to avoid unintended liability.

Practice guidelines or protocols, including managed care manuals, adopted by EDs or hospitals may be treated essentially the same as the hospital's own policies and procedures. They also are routinely used to demonstrate that the hospital "failed to follow its own rules" when hospitals and physicians do not adhere to their adopted parameters. In fact, practice guidelines are used *against* physicians and hospitals much more frequently than they are used to their benefit in malpractice litigation.[33]

Registration Process, Collections or Insurance Information, and Authorization

CMS does allow hospitals to conduct reasonable registration procedures in the ED, including collecting insurance data or cash at the time of registration, as long as the process does not delay the MSE. A reasonable registration process may include obtaining demographic data, the name of the patient's physician, and determining whether the patient is insured and the type of insurance. During the registration process, the patient can sign the hospital's usual "informed consent to be examined" form and a routine form that holds the patient financially accountable for any charges not covered by the patient's insurance carrier.[2]

The key is to create parallel tracks for medical and financial issues and to ensure that the financial track never interferes with the medical care in any way. "Bedside registration" probably is necessary under the existing regulatory scheme to avoid "no-delay" violations, because CMS would consider any delay in access to the MSE due to diversion to the registration area to be against the law. Waiting for examination and treatment because the ED is overwhelmed is not a violation, but waiting for examination because the registration clerks are collecting insurance information may be.[2]

CMS warns hospitals not to coerce patients into leaving before they receive their federally guaranteed MSE, stating "reasonable registration processes may not unduly discourage individuals from remaining for further evaluation."[2]

Collection of copayments, down payments, advanced beneficiary notifications (ABNs), or signatures on managed care financial forms may constitute such "economic coercion" if not done very carefully. Hospitals also must ensure that staff behavior does not create a hostile environment or constructive denial of the MSE.

Furthermore, hospitals should never delay a patient's MSE in order to obtain prior authorization from a managed care organization (MCO). First, managed care authorization is authorization for payment only—it is not authorization for treatment; and second, CMS explicitly bans prior authorization for managed care plans before completion of the MSE and commencement of stabilizing treatment.[2] Hospitals may obtain authorization for payment from insurance entities only "concurrently" with stabilization of the patient.[2,27] Hospitals are legally obligated to provide the MSE, and they will be held to that standard regardless of the financial pressures placed on them by MCOs. (As a related issue, "[m]anaged healthcare plans cannot deny a hospital permission to examine or treat their enrollees. They may only state what they will and will not pay for, and regardless of whether a hospital is to be reimbursed for the treatment, it is obligated to provide the services specified in EMTALA."[27])

Patients often ask questions about their obligation to pay for emergency services, particularly whether their insurance will cover the visit or how much it will cost to receive care at the ED. Regardless of EMTALA, all patient questions should be answered forthrightly, honestly, and completely by the hospital staff. Generally, routine financial questions can be answered

by registration personnel or triage nurses trained to give "stock answers," to not discourage or coerce the patient in any way, and to encourage the patient to stay, with discussions of payment deferred until after an MSE is performed.

After the hospital answers the patient's questions, the patient is responsible for making informed decisions about further aspects of care. If a patient chooses to withdraw a request for examination or treatment and leave the ED, hospitals must carefully handle the interaction related to the patient's "voluntary withdrawal" (see the later section on consent). Whenever the patient intends to leave, the staff should involve the physician on duty.

Regardless of managed care status, "VIP" status, private patient status, or any other classification, all patients should be processed in the same manner.[34,35]

Additionally, the triage team, physician and nursing staff, and all clinical personnel should not know the patient's insurance status throughout the initial screening and stabilizing treatment. This removes insurance status as an issue should the government later claim that the staff was motivated in some way or treated the patient disparately on the basis of financial class. It is easier to prove that actions were not predicated on the patient's financial status when the actor lacks knowledge of that status than to prove that the actions were medically appropriate despite knowledge that the patient had no insurance.

After the MSE and initiation of stabilizing treatment, insurance status and ability to pay can be considered in determining the patient's future care, such as hospital admission, transfer, or discharge and follow-up.

Documentation

EMTALA is a technical law, and compliance with the technicalities requires proper documentation. Furthermore, clinical outcomes are irrelevant under government enforcement, and compliance is not presumed; the hospitals must prove compliance through documentation.

Central Log

Hospitals must maintain a central log of all patients presenting to the ED requesting examination or treatment. The log must contain the name and disposition of the patient, including whether the patient refused treatment, whether the hospital refused to provide an MSE or treatment, and whether the patient was admitted, treated and stabilized, transferred, or discharged.[36] The purpose of the log is to permit CMS and the state surveyors to select and review individual records to investigate whether the hospital is in compliance with the law.[28]

The log must include all persons presenting to the hospital's dedicated EDs, whether on or off campus.[2,36,37] These areas include the typical ED, freestanding emergency centers, labor and delivery suites, ambulatory care or fast track areas contained in the ED, and psychiatric intake centers.[2] The logs are not required to be collated into a single document but must be retrievable at CMS's request.

Medical Record

All areas of the hospital used to conduct the MSE must create a medical record for the patient and keep a log of those presenting for examination and treatment.[38] If members of the hospital medical staff see their patients in the ED, either on a scheduled or an unscheduled basis, the hospital must create a medical record and require the physician to document the care provided in that record. The physician's private office records documenting care provided at the hospital are insufficient.

Most important, the emergency physician should document whether an EMC was determined to exist on *every* patient seen in the ED, even if the initial chief complaint is seemingly trivial. The legal purpose of the required MSE is to determine if an EMC is present. To facilitate documentation, ED charts should include two check boxes: one labeled "EMTALA EMC present" and the other "EMTALA EMC absent." The person performing the MSE should check the appropriate box for each patient, and completion of this documentation should be a prime part of the ED's quality improvement monitoring program.

Stabilization Requirements

Once the hospital determines that an individual has an EMC, EMTALA requires the hospital to either stabilize the EMC or, if it lacks the capability to stabilize the patient, to transfer the patient to another medical facility that can provide the necessary treatment.[39] (A sample form for use in documenting such transfers and patient consent to transfer is shown in Figure 202-1.)

When and if the patient is "stabilized" has significant ramifications for hospitals and physicians, because once patients are stabilized, EMTALA no longer applies.[40] After stabilization, hospitals are free to refuse to provide further treatment or to transfer stabilized patients for purely financial reasons. On-call physicians can refuse to treat or admit stable patients or insist that stable patients be transferred owing to their lack of or type of insurance. An MCO can refuse further payment to the hospital and request that the stabilized patient be transferred to one of its contracting facilities.[41,42]

However, other federal, state, or local standards may govern further treatment or transfer of ED patients. For example, state laws often prohibit hospitals from transferring patients for any reason except that they are incapable of handling the patient's medical problem.

Two elements must be present to trigger EMTALA's stabilization requirement: (1) the patient must have an EMC, as defined by law, and (2) the hospital must determine that an EMC exists. That an EMC exists is not sufficient to invoke the duty to stabilize; the hospital also must have actual knowledge that the EMC is present. *Actual knowledge* is a legal term that means the examining physician subjectively believed that an EMC existed. It is not the commonly understood objective standard used in malpractice cases, wherein liability is predicated on whether the physician knew or reasonably should have known the patient had an emergency condition. Whether the physician's judgment was negligent, or even grossly negligent, is irrelevant under EMTALA. The *subjective perception* of the examining physician controls whether EMTALA's stabilization requirement is triggered.

The appellate courts have uniformly held that if an EMC is not detected, the hospital has no stabilization duty and cannot be charged with failure to stabilize the patient's condition.[9,43,44] Furthermore, consideration or suspicion that an EMC may exist does not rise to the level of actual knowledge. If the hospital fails to detect an EMC through its standard screening procedures, the patient has only a state malpractice claim of "failure to diagnose" and not a federal cause of action for "failure to stabilize" the emergency condition. Once the physician or hospital does diagnose an EMC, however, the courts will allow a failure-to-stabilize claim to be brought in federal or state court under EMTALA.

This aspect of EMTALA is distinctly different from ordinary malpractice. Documentation in the medical record of "no EMC present" eliminates all further liability under EMTALA;

physician

Emergency Medical Condition (EMC) Identified: (*Mark appropriate box(es), then go to Section II)* **[Dr. Bitterman - 2008]**

I. MEDICAL CONDITION: Diagnosis _____

☐ **No Emergency Medical Condition Identified:** This patient has been examined and an EMC has not been identified
☐ **Patient Stable -** The patient has been examined and any medical condition stabilized such that, within reasonable clinical confidence, no material deterioration of this patient's condition is likely to result from or occur during transfer.
☐ **Patient Unstable -** The patient has been examined, an EMC has been identified and patient is not stable, but the transfer is medically indicated and in the best interest of the patient. *I have examined this patient and based upon the reasonable risks and benefits described below and upon the information available to me, I certify that the medical benefits reasonably expected from the provision of appropriate medical treatment at another facility outweigh the increased risk to this patient's medical condition that may result from effecting this transfer.*

II. REASON FOR TRANSFER: ☐ Medically Indicated ☐ Patient Requested _____

☐ On-call physician refused or failed to respond within a reasonable period of time.

Physician Name: _____ Address: _____

III. RISK AND BENEFIT FOR TRANSFER:

Medical Benefits:	**Medical Risks:**
_____ ☐ Obtain level of care/service NA at this facility. Service _____ ☐ Benefits outweigh Risks of Transfer	_____ ☐ Deterioration of condition in route _____ ☐ Worsening of condition or death if you stay here. There is always risk of traffic delay/accident resulting in condition deterioration.

IV. Mode/Support/Treatment During Transfer As Determined by Physician– (Complete Applicable Items):
Mode of transportation for transfer: ☐ BLS ☐ ALS ☐ Helicopter ☐ Neonatal Unit ☐ Private Car ☐ Other_____
Agency:_____ Name/Title accompany hospital employee: _____

Support/Treatment during transfer: ☐ Cardiac Monitor ☐ Oxygen – (Liters): _____ ☐ Pulse Oximeter ☐ IV Pump
☐ IV Fluid: _____ Rate: _____ ☐ Restraints – Type: _____ ☐ Other:_____ ☐ None

Radio on-line medical direction control *(If necessary):* ☐ Transfer Hospital ☐ Destination Hospital ☐ Other

V. Receiving Facility and Individual: ___ The receiving facility has the capability for the treatment of this patient (including adequate equipment and medical personnel) and has agreed to accept the transfer and provide appropriate medical treatment.

Receiving Facility: /Person accepting transfer: _____Time: _____

Receiving MD_____

Transferring Physician Signature_____ Date/Time_____

Per Dr. _____ by _____RN/Qualified Medical Personnel _____ Date/Time

nursing

VI. ACCOMPANYING DOCUMENTATION– sent via: ☐ Patient/Responsible Party ☐ Fax ☐ Transporter
☐ Copy of Pertinent Medical Record ☐ Lab/EKG/X-Ray ☐ Copy of Transfer Form ☐ Court Order
☐ Advanced Directive ☐ Other _____
Report given (Person/title):_____
Time of Transfer: _____Date: _____ Nurse Signature: _____Unit:_____
Vital Signs Just Prior to Transfer: T_____ Pulse _____ R _____ BP _____ Time: _____

patient

VII. PATIENT CONSENT TO "MEDICALLY INDICATED" OR "PATIENT REQUEST" TRANSFER:
☐ I hereby **CONSENT TO TRANSFER** to another facility. I understand that it is the opinion of the physician responsible for my care that the benefits of transfer outweigh the risks of transfer. I have been informed of the risks and benefits upon which this transfer is being made.
☐ I hereby **REQUEST TRANSFER** to _____. I understand and have considered the hospital's responsibilities, the risks and benefits of transfer, and the physician's recommendation. I make this request upon my own suggestion and not that of the hospital, physician, or anyone associated with the hospital.
The reason I request transfer is: _____

Signature of ☐ Patient ☐ Responsible Person_____ Relationship _____
Witness_____ Witness_____

TRANSFER FORM

White: Receiving facility; **Yellow:** Medical Record; **Pink:**-QA

Patient Name:

Date of Birth:

Medical Record Number:

Figure 202-1. Emergency Medical Treatment and Active Labor Act (EMTALA) hospital transfer form.

understanding and utilizing this distinction should be part of every ED's risk management program.

The screening section of EMTALA mandates the hospital to provide only those services within the capability of the *ED*, including ancillary services routinely available to that department.[5] The stabilization section, however, requires the level of services within the capabilities of staff and facilities available at the *hospital*.[45]

The capabilities of the hospital staff include whatever intensity of care the personnel of the hospital can provide within the training and scope of their professional licenses and hospital privileges.[27] To ensure that hospitals can stabilize patients, Congress mandated that Medicare-participating hospitals maintain a list of on-call physicians available to provide treatment necessary to stabilize a patient with an EMC.[46]

Thus, whenever the ED determines that a patient has an EMC, the hospital must utilize the full capabilities of its staff, facilities, and on-call physicians to stabilize the patient.[2,45] If the hospital is unable to stabilize the patient, a physician must certify that a transfer is medically indicated and arrange an "appropriate" transfer to a higher-level facility.

The treating physician should always decide whether a patient's EMC is stable or unstable. If two physicians disagree over whether the patient is stable but only one of the physicians is at the bedside caring for the patient, the on-site physician should make the decision.[2,9] It is *not* appropriate for an on-call physician, a "managed care gatekeeper" physician, a physician at a receiving facility, or even the patient's regular attending physician to disagree with the decision of the on-site physician over the phone. If one of these outside physicians wants to overrule the determination of the on-site physician, he or she must come to the hospital and personally examine the patient.

EMTALA defines the term *stabilized* as follows: "no material deterioration in the condition is likely, within reasonable medical probability, to result from or occur during the transfer of the individual from a facility."[47] For a pregnant woman having contractions who has an EMC, stabilized means that delivery (including the placenta) has occurred.[48]

This is a *legal* definition of stabilization, not a medical definition. The standard of care for any patient diagnosed with an EMC will be judged by this legal definition, not by the usual medical malpractice standards. This is a national standard under federal law, not a local standard under state malpractice law.[9,48]

The "stabilized" question typically arises only when the patient deteriorates during or after the transfer and experiences an adverse medical result. It is likely to appear, particularly in hindsight, that the patient was not completely stabilized before transfer. Health care providers should remember that their compliance usually will be judged by an unsympathetic jury, aided by hindsight, in the context of impairments suffered by the patient in an adverse medical outcome. Unfortunately, the court system, not the health care system, will ultimately determine when a patient with an EMC is legally "stabilized."[9,48]

The U.S. Supreme Court, in the case of *Roberts v. Galen*, ruled that a plaintiff need not show improper motive for a transfer in order to prevail on a failure-to-stabilize claim under EMTALA. The plaintiff merely must prove that the patient was not properly stabilized before the transfer.[49]

It should be noted that all discharges from the ED are legally transfers under EMTALA, which exposes the hospital for claims under EMTALA for failure of its emergency physicians to stabilize patients with known emergency conditions before discharge ("transfer") home.[1,49]

EMTALA's requirement to provide on-call physicians no longer extends to inpatients diagnosed with an EMC.[2] Other Medicare conditions of participation govern inpatient care, and hospitals certainly should implement policies and procedures for providing emergency specialty services to patients in whom an EMC develops after admission to the inpatient setting.[2]

Disposition Issues under EMTALA

Admission

Admitting the patient to the hospital ends the hospital's duty under EMTALA, unless the admission is a ruse to avoid the hospital's EMTALA responsibilities.[2,44] As noted earlier, admission to "observation status" does not meet CMS's regulatory definition of "admitted," so EMTALA still applies to the care of observation patients in the inpatient setting, as well as those in an ED observation or chest pain unit.[2,24]

Once the emergency physician determines that the patient needs to be hospitalized, the patient's physician or the appropriate on-call physician should be contacted. If the admitting or on-call physician disagrees with the emergency physician's judgment, it is incumbent on the admitting or on-call physician to come to the ED to personally examine the patient. This fact should be mutually understood by the entire medical staff and the hospital administration and should be *written* into hospital policy and procedure.

"Discharge" or Transfer to Home

Under EMTALA, any patient movement away from the hospital is legally defined as a "transfer."[50] Thus, from a legal perspective, all patients discharged from an ED are considered to have been transferred. Sending a patient home after treatment in the ED who is retrospectively determined to be unstable is considered to represent a transfer of an unstable patient and, as such, a violation of EMTALA. To avoid such retrospective analyses, emergency physicians should document that no EMC was found or that the patient was stable on discharge. If the patient leaves without permission, the hospital has not legally transferred the patient.[50]

"Discharge" or Transfer from the Emergency Department to an On-Call Physician's Office

Because all discharges from the ED are defined as transfers under EMTALA, so too are discharges from the ED sent directly to an on-call physician's office for acute intervention. CMS looks askance at transferring patients away from the hospital to a physician's office for acute procedures that could have been done in the ED or in the hospital.[21,51] Ophthalmologist services may constitute an exception, because although the ED may have rudimentary eye tools, ophthalmologist typically have much better equipment in their offices for examining patients with eye complaints to determine whether an EMC is present or to treat emergency conditions. In essence, movement to the office in these cases becomes a medically indicated transfer to receive a higher level of services than the hospital can provide. CMS accepts such movement, so long as the ED arranges a formal transfer in compliance with EMTALA, as noted later on.

CMS's view is extremely unsatisfactory, particularly to orthopedic surgeons. It is standard practice in most hospitals for the emergency physician to splint various displaced fractures and send the patient to the on-call orthopedic surgeon's office for reduction of the fracture and further necessary treatment. CMS believes that the orthopedic surgeon should

perform the reduction and treatment at the hospital in each case, because the surgeon's office has no resources that the hospital lacks.

However, EMTALA applies only if the EMC is unstable at the time of transfer.[1,9] If the ED "stabilizes" the fracture, EMTALA's obligations end. Thus, it is reasonable to send patients to the office for further treatment, so long as they meet the legal definition of "stable at the time of discharge" from the ED. The determination of whether the patient is stable for transfer to the orthopedist's office rests solely on the judgment of the examining emergency physician. If the patient has accompanying injuries or is too uncomfortable to be moved, or if the emergency physician believes the injury is such that the patient should not travel, then the orthopedic surgeon should be asked to care for the patient in the ED.[9]

Follow-up Care

Obtaining follow-up care for discharged ED patients, particularly indigent persons and Medicaid recipients, is a significant problem for nearly every hospital. However, EMTALA does not reach the on-call physician's office in this scenario. If the patient does not have an EMC or is stable at the time of discharge, EMTALA does not apply from that point forward, and the on-call physician has no legal duty *under EMTALA* to see the patient in the office.

The real issue in ED follow-up is the level of commitment the hospital and medical staff are willing to make to the community. If the administration, the board, and the medical staff are comfortable with their decision, and if they have acted in the best interests of the patients they serve, they should have no trouble defending their actions to CMS or any other entity.

Whatever decision the hospital and physicians make regarding ED follow-up duties, they should explicitly define those responsibilities in the medical staff bylaws or hospital rules and regulations, so that all personnel understand, in advance, what it means to be "on call" for the ED at that hospital.

ED discharge instruction sheets also should include a *fail-safe clause* advising patients to return to the ED if their condition deteriorates before seeing the referral specialist or if the follow-up arrangements disintegrate for any reason. Such a statement could help the hospital avoid liability when the on-call specialist fails to implement the prescribed follow-up plan.[52]

Transfers to Other Acute Care Hospitals

Before transferring any patient out of the ED, the emergency physician must first determine whether the patient is stable, as defined by law. EMTALA regulates the transfer of unstable patients only; it does not apply to the transfer of stable patients.[2,9] If no EMC is found, the patient is considered stable. The determination of whether a patient is stable must be made at the time of transfer to be valid under the law.[51] Unstable patients can be transferred for only one of two reasons: if the transfer is medically indicated, or if the patient requests the transfer.[9] There is no "managed care transfer of an unstable patient" or even of a stable patient.

Patients usually are transferred out of the ED because the transferring facility lacks the capability or the resources necessary to treat the identified EMC. Examples of patients best served by transfer are the head-injured patient in a hospital without a neurosurgeon on staff, the pregnant woman who needs the services of a high-risk obstetric center, and the multiple-trauma patient treated initially in a rural ED who requires treatment at a level 1 trauma center.

EMTALA defines such transfers as "medically indicated transfers," because the purpose of each transfer is to obtain a higher level of medical care necessary to treat the patient's condition that is not available at the transferring facility. EMTALA governs almost every aspect of medically indicated transfers, including requiring hospitals to adopt and enforce policies to ensure compliance with federal transfer laws and mandating specific actions by the transferring and receiving hospitals (summarized in Boxes 202-1 to Box 202-3).[1-3,9,53-55]

BOX 202-1 Recommended Procedures for the Transferring Facility

1. Stabilize the patient whenever possible.
2. Complete a physician certificate of transfer, including the risks and benefits of transfer.
3. Obtain the patient's informed consent to the transfer.
4. Arrange for another hospital and physician to accept the patient in transfer.
5. Send appropriate data to the accepting facility (e.g., medical records, test results, transfer forms).
6. Arrange the transfer through qualified personnel, with use of appropriate transportation equipment.
7. Maintain records of all transfers for 5 years.

BOX 202-2 Invalid Reasons for Refusing an Appropriate Patient Transfer

- Lack of insurance or out-of-network managed care plan
- Lack of citizenship
- Veteran status
- Patient's physician not on staff
- Transferring hospital is out of network or outside hospital's defined referral area
- "We are not an affiliated hospital"
- "We are not a specialty hospital"
- "We are a specialty hospital, but that's not our specialty"
- "We are not a 'trauma center'
- Transfer originating out of county or out of state (including transfer of out-of-state Medicaid patients)
- EMS skipped over closer hospital
- Another hospital refused the transfer in violation of the law
- Another hospital's on-call physician refused to respond to its ED in violation of the law

ED, emergency department; EMS, emergency medical services.

BOX 202-3 Recommendations for the Facility Asked to Accept the Patient in Transfer

1. Accept all appropriate requests for transfer, regardless of whether the patient is an ED patient or an inpatient of the hospital.
2. Have a formal system for accepting or rejecting transfer requests, and document the reasons for any refusal to accept a patient in transfer.
3. Maintain records of all transfers for 5 years.
4. Report all EMTALA transfer violations to CMS.

CMS, Centers for Medicare and Medicaid Services; ED, emergency department; EMTALA, Emergency Medical Treatment and Active Labor Act.

Some states have enacted their own transfer laws.[56] Most state laws parallel EMTALA, but some are even more restrictive, so physicians responsible for patient transfers should be aware of the controlling laws and regulations in their own state as well as federal law.

Duty to Accept Appropriate Transfers from Other Hospitals

Medicare-participating hospitals that have specialized capabilities or facilities are required by EMTALA to accept appropriate transfers of patients who require such capabilities or facilities, if the hospital has the capacity to treat the patient.[57]

The duty to accept patients in transfer is a problematic issue for many larger, tertiary care, or academic hospitals as a result of the on-call specialty coverage crisis in the United States.[58,59] Numerous hospitals have lost full or partial on-call coverage for specialties such as neurosurgery, orthopedic surgery, maxillofacial surgery, neurology, plastic surgery, and hand surgery.[60,61] CMS's softening of its EMTALA on-call regulations in late 2003 accelerated the trend of physicians' simply taking fewer call nights at many smaller to medium-sized hospitals, forcing still more transfers to access emergency specialty care.[3,62,63] (As confirmed in recent surveys, these changes have accelerated physician and hospital abandonment of on-call services, increased the risk of harm to patients needing specialty care, caused more delay in patient access to specialty care, and increased the number of patient transfers.[62,63])

Specialty hospitals also enticed physicians away from acute care hospitals, in part because the physicians could decrease their on-call burden. However, CMS now requires specialty hospitals to accept appropriate transfers even if the specialty hospital lacks an ED.[64]

When Must a Receiving Hospital Accept a Patient in Transfer?

A Medicare-participating hospital must accept "medically indicated transfers" if it has "specialized capabilities or facilities" and the "capacity" to care for the patient.[1] *Medically indicated transfers* (see definition in the previous section on stabilization) are ones for which a physician determines the patient has an EMC and needs to be transferred to obtain a higher level of medical care necessary to treat the patient's condition that is not available at the transferring facility.[39] *Specialized capabilities or facilities* are essentially any resources, other than a routine admission bed, or physician services available at an accepting hospital but not available at the transferring hospital. *Capacity* is rather generously defined by CMS to include whatever a hospital customarily does to accommodate patients in excess of its occupancy limits. For example, if a hospital customarily moves patients to other units or calls in additional staff, then it has in fact demonstrated the ability to provide services to patients in excess of its occupancy limits.[65]

Who Accepts Patients on Behalf of the Hospital?

The duty to accept appropriate transfers is a hospital duty, not a physician duty, and EMTALA does not require that a physician accept the patient.[1] The hospital must create a formal system designating who is authorized to accept or reject patients on its behalf. It is strongly recommended that hospitals do not use the individual physician on call for each specialty *alone* to accept or reject patients in transfer. Hospitals should involve an administrative person or an emergency physician in addition to or instead of the on-call physician, to avoid inappropriate refusals. Because the duty to accept rests with the hospital, any inappropriate refusal by an uninformed or rogue on-call physician subjects the hospital to termination from Medicare, civil monetary penalties, or civil liability if the patient is harmed because of the refusal to accept the patient in transfer.

The hospital should define the resources and capacity of the institution, and the times during which those resources are available. When necessary resources or capacity are not available, the hospital must in a timely manner inform the persons charged with accepting or rejecting transfers. The hospital also should educate appropriate personnel in its known referral facilities on the proper procedure to transfer patients into its system, including informing them of who is and who is not authorized to accept patients in transfer on behalf of the hospital. The hospital must educate its medical staff, particularly its on-call physicians and emergency physicians, regarding their responsibilities under EMTALA, including the responsibility to accept patients in transfer from other facilities on behalf of the hospital.[66]

Does a Hospital Have to Accept Transfers of Inpatients from Other Hospitals?

CMS says no. In late 2008, CMS issued regulations stating that no hospital has a legal duty under EMTALA to accept an inpatient in transfer from another hospital. Therefore, even if a requested hospital could treat an inpatient's emergency condition that the transferring hospital is unable to treat, it may refuse the transfer for any reason and not be in violation of EMTALA.

However, the issue is certain to be litigated and decided by the courts. It is inevitable that an inpatient will develop an emergency medical condition and proceed to die or suffer severe damages because no other hospital would accept the patient in transfer due to lack of insurance. The patient or family will sue the hospital that refused to accept the patient in transfer, claiming that the hospital had a federal duty under EMTALA to accept appropriate transfers of patients with emergency conditions if the transferring hospital couldn't treat the emergency. The transfer acceptance section of EMTALA was not part of the law when it was originally enacted. Congress later amended the law, calling it the "non-discrimination" section, because tertiary and academic referral hospitals were refusing to accept patients in transfer from other hospitals, leaving the patients to die in community EDs.[67] It remains to be seen if the courts will ultimately interpret EMTALA contrary to Congress's "non-discrimination" intent for patients with life-threatening emergencies.[68]

When Can a Hospital Refuse to Accept a Patient in Transfer?

There are only five reasons a hospital can refuse a request for transfer under EMTALA.

First, if the transfer is not a "medically indicated transfer," a hospital can decline the transfer.[1] Non–medically indicated transfers include patient-requested transfers and lateral transfers for any reason (*lateral* meaning that both hospitals have the same ability to handle the patient's EMC), such as managed care transfers or family- or physician-requested transfers. Any time the sending facility can handle the patient's EMC, a hospital requested to accept the patient in transfer can lawfully decline.

Second, if the hospital does not have the "capacity," as defined by CMS, to accept the patient in transfer, it may and generally should refuse the transfer.[1,2,65]

Third, if the transferring hospital is located outside the boundaries of the United States, the hospital has no legal obligation under EMTALA to accept the transfer.[69] No other territorial limits are imposed on the duty to accept transfers; out of county, out of state, and out of the hospital's designated referral area all are unacceptable reasons to refuse patients in transfer under EMTALA. Moreover, a hospital cannot refuse to accept a transfer just because the sending hospital is "skipping over" other hospitals to send the patient its way.

Fourth, if the transfer is not "appropriate," the hospital may refuse to accept the patient in transfer at that time.[1] This more vague reason takes into account the patient's condition at the time of transfer and the time, distance, and "skipping over" other hospitals necessary to reach a receiving hospital. For example, a trauma patient may need intubation and a chest tube inserted before the transfer is "appropriate," or traveling 100 miles with hypotension from a ruptured abdominal aneurysm may not be "appropriate" if closer hospitals are capable of repairing the aneurysm.

Fifth, the patient has been "admitted" to the hospital as defined by CMS.

There are no other reasons for which a hospital may refuse a request to accept a patient in transfer from another acute care hospital under EMTALA. Furthermore, no "contingencies" are allowed to be placed on the acceptance of a transfer. The receiving hospital may not condition acceptance of the patient on the transferring hospital's agreeing to take the patient back once the emergency condition is resolved, may not require that the transferring hospital have additional consultations completed before the emergency physician transfers the patient, and may not require the transferring hospital to use the receiving hospital's transport ambulance or helicopter service as a condition for accepting the patient.[70]

Also, refusals of appropriate transfers on the basis of the patient's insurance status or delaying appropriate transfers until the transferring hospital obtains authorization for payment from the patient's managed care plan are definitely illegal under EMTALA.[71]

Duty to Report Transfer Violations

Any time a hospital has reason to believe it may have received a patient transferred in an unstable condition from another hospital, in violation of EMTALA, it must report the transferring hospital to CMS.[72] The duty to report rests with the hospital, so emergency physicians who receive unstable patients in transfer should inform the hospital, which then can determine the appropriate action.

CONSENT FOR MEDICAL CARE

Informed Consent

The doctrine of *informed consent* is a fundamental principle of the American legal system: "Every human of adult years with a sound mind has a right to determine what should be done with his own body."[73] Physicians may not examine or treat any person without consent, and that consent must be informed. This means that the patient must be given all pertinent ("material") information concerning the nature, risk, and alternatives of the treatment before that patient can be deemed to have effectively consented to the medical intervention.

Physicians should always endeavor to obtain informed consent yet remain cognizant of the significant limitations on and multiple exceptions to the doctrine, especially in the ED setting. Delaying treatment in an emergency to obtain informed consent is a much more serious and common medicolegal problem than failure to obtain proper informed consent.

The law of informed consent contains a great deal of uncertainty, with many gray areas. Different states have different views, either in their statutory laws (legislation) or in their common law (judge-made law or precedent), on the meaning of "informed consent" in the care of the ED patient. Most cases are unique and depend on the specific circumstances.

Emergency physicians rarely have time to seek legal consultations, let alone wait for a court to render a decision concerning the legal nuances of consent issues. In these situations, it is helpful for emergency physicians to use a "*when-in-doubt*" *rule* to guide their immediate actions. This rule simply states that when emergency physicians are in doubt regarding the legality of a situation, "they should do what they believe to be in the patient's best interest and worry about the legal consequences later." Although emergency physicians risk criminal and civil charges of false imprisonment, battery, and even negligence suits for failure to obtain appropriate informed consent, the courts almost universally rule in favor of physicians who act in good faith on behalf of their patients in emergency situations. Successful civil litigation regarding an issue of consent theory against an emergency physician acting reasonably, and consistent with the appropriate standard of care, is extremely rare.[74] An emergency physician is much more likely to be sued for failure to treat while waiting for consent than for providing reasonable treatment without consent.

Federal versus State Laws

Both federal laws (e.g., EMTALA) and state laws govern consent.[5,39] EMTALA comes into play primarily in the evaluation of minors and with patient refusal of an examination, stabilizing treatment, or transfer. State consent laws vary widely and may be set by statutes or case law, or both. The concepts discussed next are generally applicable to emergency medical care, but all emergency physicians should learn the consent laws specific to their own state.

The law presumes that an adult is mentally competent to make medical decisions and that the competent adult is entitled to sufficient information to make an informed decision concerning the physician's proposed course of examination and treatment.[74] Under the doctrine of informed consent, physicians have the duty to disclose the following information to patients[74-76]:

1. The patient's condition and/or diagnosis
2. The nature and purpose of the proposed treatment, including the likelihood of success in the physician's practice
3. Reasonable alternative measures related to the diagnosis and treatment, including the probable outcome of those alternatives
4. The particular known inherent risks that are material to make an informed decision about whether to accept or reject the proposed treatment, including the consequences of refusing that treatment

"Reasonable Person" versus "Professional Disclosure" Standard

The states are split on the standard used to determine what should be disclosed for patients to make informed decisions, but most require the "reasonable person standard" of disclosure. Under this standard, a physician must disclose all of the

information that a reasonable person would require to make a decision under the facts and circumstances of the case. The less frequent standard, termed "the professional disclosure standard," requires the physician to provide the same information that other physicians in the community would provide to patients in the same or similar circumstances. This is less stringent than the reasonable person standard.[74,76]

Physicians do not need to disclose every remote risk associated with a procedure, or risks that are common knowledge or obvious to the patient, such as the risk of infection after wound repair.[77] The law requires disclosure only of risks that are material, as judged by their seriousness or chance of occurrence. Courts define *material information* as information that "the physician knows or should know would be regarded as significant by a reasonable person in the patient's position when deciding to accept or reject the recommended medical procedure."[78]

Some states legally require physicians to disclose specific risks, such as death.[77] Some states statutorily require a physician to meet both the reasonable person standard and the professional disclosure standard.[79,80]

Physician's Role in the Consent Process

The physician who proposes to undertake the procedure must be the one to obtain the patient's informed consent. The duty to obtain consent cannot be delegated, so physicians cannot ask nurses or other health care providers to obtain patients' consent on their behalf. The physician who will care for the patient is best qualified to discuss the treatment and its risks and benefits with the patient. Nurses, as well as physicians not skilled in performing the procedure, cannot obtain valid informed consent.[81]

The physician should write or dictate into the patient's medical record a summary of the discussion held with the patient and family concerning the elements of informed consent. Particular attention should be made to documenting those material risks discussed with the patient before obtaining the patient's consent.

Consent is a *process*, not a signature. A written, signed, separate consent form is not legally required under the doctrine of informed consent; however, hospitals may require emergency physicians to complete standardized consent forms and obtain the patient's signature. The signed form is not a substitute for the consent process. It cannot replace the exchange of information that occurs between the physician and the patient and family, the answering of questions, and the ultimate agreement of the patient to undergo the medical or surgical intervention.[74]

A signed, written consent form, however, does constitute some evidence of a valid consent. In some states, a signed consent form is presumed to represent valid consent unless that presumption is rebutted by proof that the consent was obtained by fraud, deceit, or misrepresentation of material fact.[82]

Implied Consent in Emergency Situations

If an unconscious or incapacitated patient cannot express consent, the law will assume the patient consented to treatment for the emergency situation. Implied legal consent is premised on two principles: (1) duty to obtain informed consent is excused if death or irreparable harm may result if the physician delays providing treatment, and (2) the law presumes that a reasonable, competent, lucid adult would consent to lifesaving treatment.[83]

The emergency treatment allowed is limited to the circumstances of the emergency, however, and only treatment required to resolve the emergency should be undertaken without consent. Similarly, the emergency condition must require immediate medical attention, with insufficient time to inform the patient or seek consent from another person.

Courts differ on the definition of a "true emergency," and whether the emergency exception applies in a given case depends on the definition accepted by the court and the application of that definition to the particular set of facts. Fortunately, the courts generally will stretch the doctrine to protect physicians who act in good faith in caring for a patient with a perceived emergency condition.[84] This is one situation in which use of the "when-in-doubt rule" and documentation of the physician's concerns will weigh greatly in the court's determination of whether the physician acted appropriately without obtaining informed consent. Physicians can further protect themselves by obtaining a second opinion that a true emergency exists.

Minors

Minors Accompanied by a Parent or Legal Guardian

Parents and legal guardians have the right to consent on behalf of their minor children. However, they must act reasonably and in the best interests of their children. If they do not, their right to consent can be abrogated by the state or the courts. Parents are not allowed to refuse treatment for a child with a life-threatening emergency condition. The management of children with emergency conditions whose parents refuse to give their consent to treatment is discussed later.

Either natural parent of the minor child may provide legally binding consent. If one parent agrees with a proposed treatment and the other does not, consent may be accepted from the agreeing parent. Even if separated or divorced, either parent may give consent unless one parent has been judicially granted sole legal custody of the child, in which case only the custodial parent may consent. The child's biologic father, even if never married to the mother, also may consent for his child.

Unaccompanied Minors

EMTALA mandates that all persons presenting to an ED requesting care be examined to determine whether an emergency condition exists.[5] Because EMTALA is federal law, it takes precedence over all state consent laws regarding the initial evaluation of a minor child. In essence, the child's mere presence at an ED requesting examination or treatment constitutes legal consent to examine the child to determine whether an EMC is present. Furthermore, the hospital should *never* delay this initial screening evaluation in order to wait for consent from a parent or legal guardian (and nurse triage does *not* count as the required medical screening, no matter how nonurgent the child's condition appears to the nurse).

If an EMC is discovered through the initial screening examination,[5,39] the physician may treat the emergency under either state or federal legal theories. First, under state laws the standard emergency exception doctrine applies. State laws allow physicians to proceed with treatment whenever an emergency exists. Although no uniform legal definition of emergency exists among the states, state laws tend to define an emergency very liberally, such as "any threat to the minor's life or health." The courts almost always affirm a physician's judgment regard-

ing an emergency condition and rarely question the treatment given to a minor without parental consent.[85] Preserving life, preventing permanent disability, alleviating pain and suffering, and avoiding eventual harm have been used as guidelines for emergency treatment without consent.[85] Any minor presenting to the ED should be triaged and provided with an MSE to determine whether an EMC exists.

Under EMTALA, if an EMC is present, the hospital and physicians must provide "stabilizing treatment."[39] Federal law also gives the physician broad discretion to decide what treatment should be performed and in what time frame it should be accomplished. The stabilization requirement includes transfer as necessary to an institution capable of handling the minor's emergency condition. Thus, under federal law, a minor could be examined, stabilized, or transferred to another institution without consent ever being obtained from the family; in this instance, the care would be not only in the patient's best interest but also legally mandated.[5,39]

Generally, if the MSE does not reveal an emergency condition, physicians need to obtain proper consent from the minor's parents or legal guardian. However, state laws and the courts have applied a number of exceptions to allow minors to seek treatment on their own without parental consent. These exceptions vary widely from state to state, and most are applied through an analysis of facts and circumstances on a case-by-case basis by the courts. Under the *mature minor* exception, minors who possess an understanding and appreciation of the nature and consequences of the treatment and appear competent to make their own decisions are allowed to consent, despite not having reached the defined age for maturity (usually 18 years).[86] A mature minor usually is 15 to 17 years old.

The *emancipated minor* provides another exception to the need for parental consent. If the minor is living independently, is self-supporting, or is in the U.S. Armed Forces, the courts may recognize the minor as emancipated and able to consent on his or her own behalf. Again, this is determined by the courts on a case-by-case basis.[87] Additionally, most states have statutory reasons, such as sexually transmitted diseases, pregnancy, or domestic violence injuries, that allow minors to seek care without the consent of their parents.[88]

Incompetent or Incapacitated Adults

If a person has been declared legally incompetent by a court, consent must be obtained from the person's court-appointed legal guardian. In addition, people may appoint legal surrogates to make legal decisions for them should they become incompetent. State-sanctioned living wills, advance directives, and durable medical power of attorney documents all transfer consent powers from a person who becomes incompetent to a legally appointed surrogate.[89]

If an incompetent adult has neither a legal guardian nor an appointed surrogate, physicians typically look to the patient's family for consent to treatment. However, consent to treatment by a family member, even the patient's spouse, generally is not acceptable under American law unless the spouse or family member has been appointed legal guardian by a court of proper jurisdiction.[90] Marriage does not confer one spouse the legal capacity to consent to medical treatment for the other spouse, even when the ill or injured spouse is incompetent.

Some states recognized this problem and enacted "family consent statutes," which outline a hierarchy of family members who can legally provide consent when the family member becomes incapacitated.[91] However, even when families have no legal standing to consent for the incompetent relative, it is always wise to involve family in the medical decision-making process. Communication and concern for the family will avoid misunderstandings, surprise, and anger, which are the primary sources of litigation. Fortunately, if an emergency exists, no authorization from family is necessary to provide such reasonable care as is necessary to correct the life-threatening situation. Once the emergency is resolved, consent should be obtained from someone authorized to act on behalf of the incompetent patient. If there is no appointed legal guardian or surrogate and no state statute on family consent, the physician will need to seek consent authorization from the courts. The courts may appoint a guardian at that time, generally a family member, or after judicial review of the issues, the court itself may grant consent on behalf of the incapacitated person.

Other Special Patient Populations

Prisoners

Competent prisoners generally do not surrender the right to consent by virtue of being incarcerated. However, a state or court may compel treatment based on interests perceived as paramount to the prisoner's interests.[92] The elements usually necessary to treat self-inflicted injuries over the objection of the competent prisoner include the following[93]:

1. The injury to the prisoner was willful and intentionally self-inflicted.
2. The proposed treatment is necessary to preserve or restore the health of the prisoner.
3. The prisoner refuses to give consent.
4. The physician documents the medical indications for treatment in writing in the prisoner's medical record.

Alcohol-Intoxicated Patients

Alcohol intoxication itself may not render a patient incompetent to give informed consent.[94] The emergency physician must evaluate each situation individually to determine whether the patient is incapacitated by alcohol to the extent that he or she is no longer able to understand the proposed treatment, risks and benefits, and rational alternatives. In essence, the general rules for determining whether a patient is competent to make informed decisions cannot be disregarded just because the person is intoxicated with alcohol. However, the "when-in-doubt rule" is particularly applicable in these cases because alcohol intoxication often is associated with occult serious illness or injury.

Alcohol intoxication, particularly if documented by a measured blood alcohol concentration (BAC), is strongly suggestive to courts and juries of impaired mental status, even though health care workers recognize that many alcoholics are entirely rational and competent at fairly high BACs.[23,95,96] Conversely, low BACs do not guarantee competence, because other processes (e.g., hypoglycemia, blood loss, impairment from other illicit substances) may cause the patient to be incompetent. Thus, the patient's clinical capacity is more important than the specific level of alcohol in determining competence.

One advantage of obtaining a BAC is that some states allow blood samples drawn solely for medical purposes to be subpoenaed later by the prosecutor for use against the driver in a driving-while-intoxicated prosecution or other criminal charges.[23,97]

It is important to recognize that the state "legal limit" of intoxication is not a measure of a patient's competence. The legal level for driving has little, if anything, to do with the

capacity to make informed medical decisions. However, this distinction is sometimes difficult for judges and juries to understand, and the emergency physician can actually use the level to support a judgment that the patient was not competent to make informed decisions in a particular instance. At other times, it is better not to have a "number," so that the only relevant criterion for determining the patient's competence is the physician's judgment.[95]

Patients Given Pain Medications

Obtaining informed consent from patients treated with pain medications before a procedure is a common issue. As with alcohol intoxication, the mere fact that a patient has been given narcotic analgesia does not render that patient incapable of consenting to surgical procedures. Plaintiff attorneys can always argue "the patient was too snowed with drugs to give consent"; on the other hand, they can equally argue that the patient was "in too much pain to consent and would have agreed to anything to stop the pain." Accordingly, when consent is sought from a patient who has received pain medication, the patient's ability to understand the ramifications pertaining to the procedure should be assessed and taken into consideration, involving the family in the process if possible. The physician should document that the patient's premedicated state was considered when judging the patient's competence to make an informed decision.

REFUSAL OF MEDICAL CARE

Informed Refusal

The corollary to a patient's right to give informed consent is the patient's right to refuse medical care, even if such refusal results in death. In *Cruzan v. Director, Missouri Department of Health*, the U.S. Supreme Court determined that a competent adult has a constitutionally protected right to refuse medical care.[98] However, that right is not absolute. Under particular circumstances, courts will consider countervailing compelling state interests, such as preventing suicide, preserving life, and protecting innocent third parties.

Physicians who honor a competent patient's decision to refuse treatment are not liable for any resulting bad outcome.[99] In fact, physicians are more likely to be successfully sued for treating patients over their objections or without their consent, even when the treatment is lifesaving.

When a competent adult refuses indicated medical intervention, it often is because of fear, anger, misunderstanding, or some other failure in communication in the physician-patient relationship. Before allowing a patient to refuse care, the physician should try to determine and resolve the underlying reasons behind the patient's refusal.

The attending physician must always be involved when a patient refuses medical care or expresses the intent to leave against medical advice.[100,101]

As with consent, refusal of medical care is a process, not a signature. It must be an informed refusal; merely having the patient sign an "informed consent to refuse examination, treatment, or transfer" form or an "against medical advice" form is not sufficient. The four essential components of the process are discussed next.

Determining Competence

The physician must determine that the patient is competent to make decisions. Normal findings on the mental status examination without evidence of diminished mental capacity from closed head injury, severe pain, hypoxia, hypotension, alcohol intoxication, mental retardation, or mind-altering substances constitute good evidence of competency. Noting the patient's rationale for refusing care, even if it is not reasonable, provides additional evidence of competency.[102]

Ensuring an Informed Decision

To be legally binding, a decision to refuse a test or treatment or to sign out against medical advice must be an informed decision. The physician must explain the severity of the patient's condition, the potential complications, and the alternative treatments available. The physician should use terms that the patient can understand and provide the patient an opportunity to ask questions. The patient must understand that the risks of refusing care include the possibility of permanent disability and death. Ideally, a witness should be present when the physician informs the patient and any family members.[103]

Involving Others

The patient's family, friends, and personal physician should be involved whenever possible. These persons should hear the same message as that conveyed to the patient, because they may be able to persuade the patient to accept the recommended therapy. If the patient expressly forbids the emergency physician to speak with others, as is the patient's legal right, this should be explained to them and documented in the medical record.

Documenting Appropriately

Appropriate documentation of the refusal process is necessary to protect the physician and hospital from inappropriate litigation. The patient should be asked to sign the refusal form.[2,9,104] (Fig. 202-2 shows a sample AMA form.)

If the patient refuses to sign the form, that fact should be documented, and the form signed by a hospital representative who witnessed the patient's refusal. The medical record should reflect the patient's mental status examination findings and competency to make informed decisions, the risks and benefits of recommended treatments, the available alternatives, and the participating family or friends. Documenting the patient's rationale for refusing treatment, that the patient was treated to the extent allowed by the patient, and that the patient was invited to return for care at any time offers added protection.[104]

Federal Rules

EMTALA requires hospitals to take and document specific actions when patients refuse medical screening, treatment and stabilization, or transfer. The government and the federal courts presume that the patient requested emergency care and place the burden of proof on the hospital to demonstrate that the patient voluntarily refused care.[2,9,105]

There are essentially two scenarios in which patients leave the ED after refusing examination or treatment. First, some patients simply pick up and leave, without the knowledge of anyone affiliated with the hospital. If the patient's departure is witnessed, the patient does not respond to requests to return for the examination or to discuss the issues with the hospital staff. Hospitals generally refer to these patients as those who "leave without being seen" (LWBS) or "leave before examination." In the second scenario, the hospital personnel are aware that the patient is about to leave and have an opportunity to

INFORMED CONSENT TO REFUSE EXAMINATION, TREATMENT, OR TRANSFER

I understand that the hospital has offered: (Check all that apply).

A. ☐ To examine me (the patient) to determine whether I have an emergency medical condition, or

B. ☐ To provide medical treatment or to provide stabilizing treatment for my emergency condition, or

C. ☐ To provide a medically appropriate transfer to another medical facility.

The hospital and physician have informed me that the ***benefits*** that might reasonably be expected from the offered services are:

_____

_____

_____

and the ***risks*** of the offered services are: _____

_____

Physician Documentation

☐ The patient appears competent and capable of understanding risks and benefits.

☐ Alternative treatments discussed with the patient.

☐ Patient's family involved. ☐ Family not available. ☐ Patient does not want family involved.

Signature of Physician _____

Patient or Legally Responsible Person Documentation.

☐ I have declined to have the physician fully explain to me the risks, benefits, and alternatives to leaving the hospital against medical advice. I knowingly and willingly take and assume the responsibility for all risks incurred.
or
☐ The physician has fully explained to me the risks and benefits but I choose to refuse the offered services. I understand that my refusal is against medical advice, and that my refusal may result in a worsening of my condition and could pose a threat to my life, health, and medical safety. I understand that I am welcome to return at any time.

Signature/Patient or Legally Responsible Person _____

Print Name _____ Address _____

City _____ State/Zip _____ Date _____ Time _____

Witness/Signature _____ Print Name _____

The patient or person legally responsible for the patient was offered but refused to sign form after explanation of their rights and the risks and benefits of the services offered.

Hospital representative who witnessed refusal to sign: _____

Date _____ Time _____

Informed Consent to Refuse Examination Form [Hospital Addressograph or Sticker Goes Here]
White/Patient Record Yellow/Transfer with Patient Pink/Q/A [Robert A. Bitterman, MD JD - 2008]

Figure 202-2. Leaving against medical advice (AMA) form: Informed consent to refuse examination, treatment, or transfer.

interact before the patient leaves. Hospitals generally refer to this as "leaving against medical advice." The Office of the Inspector General (OIG) and CMS refer to both of these scenarios as "voluntary withdrawal" of the patient's request for evaluation or treatment.[2,9,106]

Leaving without Being Seen

If a patient walks out before the MSE and later has an adverse medical result, the burden will be on the hospital to prove that the person left voluntarily and was not denied examination or treatment by the hospital. The OIG and CMS admonish hospitals regarding LWBS patients, stating that "hospitals should be very concerned about patients leaving without being screened. Since every patient that presents seeking emergency services is entitled to a screening examination, a hospital could violate the patient antidumping statute if it routinely keeps patients waiting so long that they leave without being seen, particularly if the hospital does not attempt to determine and document why individual patients are leaving, and reiterate to them that the hospital is prepared to provide a medical screening if they stay."[9,25]

Hospitals need to have a policy and practice for LWBS patients that adequately document pertinent findings and protect the hospital from liability. In most hospitals, the staff calls the patient and checks the waiting area at least three times before declaring that the patient has left the department. These serial checks, with time of day performed, should be documented on the patient's record, and once it is evident that the patient is no longer present, the record should be reviewed on a timely basis by the physician on duty. If the reviewing physician discovers something of concern regarding the patient's chief complaint or triage data, the person can be contacted and encouraged to return to the ED. The registration papers, triage records, nursing documentation at triage, and the physician's review and documentation of that review all should be kept in the patient's permanent record. These records should be retained for a minimum of 5 years to protect the institution should the interaction ever be the subject of a retrospective EMTALA investigation or litigation on behalf of the LWBS patient.[2,9]

Leaving against Medical Advice

If hospital personnel are aware that a patient intends to leave before completion of the MSE or stabilizing treatment for whatever reason (e.g., tired of waiting, changes mind, concerned over cost of care), the hospital must handle and document the interaction carefully to avoid EMTALA or medicolegal liability.[2,9,107-109] (Box 202-4) In each case, the following steps should be taken:

1. *Inform the patient of the hospital's obligation under the law.* The ED staff should inform patients of their rights under the EMTALA to receive medical screening and any necessary stabilizing treatment from the hospital, regardless of their ability to pay for that service.
2. *Determine the patient's competence.* Only legally competent persons can refuse necessary medical care. For example, an alcohol-intoxicated woman who presents to the hospital with a medical complaint cannot be allowed to leave the hospital without examination and treatment until it is determined that she is legally competent to make such a decision.
3. *Explain the risks and the benefits to the patient.* For patients to make an informed consent to voluntarily withdraw their request for services, they must understand the benefits and the risks of withdrawal before refusing examination and treatment. These risks and benefits should be specific to the patient's chief complaint.
4. *Secure the patient's written informed consent to refuse care.* The hospital should take all reasonable steps to secure the patient's written and informed consent (i.e., obtain a signature) to refuse medical care. A standard form should be used that contains space for documenting the patient's competence, the risks and benefits discussed, and whether the patient's family was available to be involved in the discussions. If the patient refuses to sign the form and simply walks out after the interaction with the hospital, the person who discussed the issues with the patient and witnessed the patient's refusal should sign the form and document the interaction.
5. *Offer alternative care within the scope allowed by the patient.* It is outside professional practice standards to respond angrily, act vindictively, or punish patients when they decide to leave against advice by refusing to provide alternative treatments, medications, analgesics, or discharge instructions. Patients always get to define the scope of medical services they are willing to accept. Accordingly, an appropriate strategy is to negotiate and cajole them into allowing the best possible care under the circumstances that they define. For example, if a patient with "fight bite" tenosynovitis refuses hospital admission, operative intervention, and intravenous antibiotics and analgesia, then the next best option can be offered, such as thorough cleansing in the ED, intramuscular antibiotics, and oral narcotics, with recheck in 24 hours. Failing that, cleaning in the home sink, oral antibiotics, acetaminophen, and follow-up with the patient's primary care physician can be recommended.

   Negotiation aims for the best alternative that the patient is willing to accept, even if that means providing

BOX 202-4 Protocol for Managing AMA Cases in the Emergency Department (ED)

1. Always involve the emergency physician.
2. Involve the family and/or the patient's personal physician whenever possible.
3. Explain the risks and benefits specific to the patient's condition; "You could die" alone is too generic.
4. Explain any alternative treatment options to the patient.
5. Ascertain the patient's capacity to make informed medical decisions: "When in doubt, don't let 'em out!"
6. Have the patient and at least one witness sign the AMA form.
7. If the patient refuses to sign the AMA form, a member of the hospital staff should sign the form stating that the patient refused to sign the form.
8. Always still provide the best possible treatment within the scope allowed by the patient, including antibiotics and analgesics when warranted.
9. Provide appropriate discharge instructions, and welcome the patient to return to the ED at any time if he or she reconsiders and decides to accept the recommended care.
10. Document discussions with the patient, the risks explained, and the patient's medical decision-making capacity and understanding of the ramifications of leaving AMA in the medical record (and in real time—not hours after the patient has left the ED).

AMA, against medical advice; ED, emergency department.

less than optimal treatment. Also, pain medications should never be withheld because the patient will not accept the recommended treatment plan. This "strategy" is cruel, further alienates the patient, and serves no useful purpose.

Moreover, patients should *always* be invited to return to the ED (or encouraged to see their private physician) if they change their mind and become willing to accept the recommended treatment. A patient's refusal of the more appropriate treatments, as well as communication of offers to provide treatment within the circumstances proscribed by the patient, should be delineated.

6. *Document the interaction in the patient's hospital record.* The medical record, preferably a dictated and transcribed medical record, should accurately relate the interaction between the hospital and the individual refusing the MSE. The record reflects the hospital's conformity to the law and the patient's leaving of his or her own accord—specifically, the risks of refusing the examination and the reasons for the patient's refusal. Documenting the reasons for refusal provides evidence that the hospital did not economically coerce or in any way financially deter the patient from remaining for the MSE. The chart must clearly indicate that the patient did not leave the department based on a "suggestion" by the hospital concerning any financial issues.

Parent or Guardian Who Refuses Care or Blood Transfusions for a Minor

Generally, state laws support parental control of health issues affecting their children. However, the state will not allow parents to deny children needed emergency medical care under the doctrine of *parens patriae*, the state's paternalistic interest in children.[110] All states empower emergency physicians to intercede under their child abuse and child neglect laws.[111] When a child's injuries are potentially life-threatening, the emergency physician can take custody of the child under the child abuse laws and provide indicated treatment, including blood transfusions. In deciding whether to act, the "when-in-doubt rule" definitely applies, and all jurisdictions statutorily protect physicians from criminal and civil liability for acting in good faith to protect children.[111]

The courts have specifically addressed the issue of Jehovah's Witness parents attempting to refuse emergency blood transfusions for their minor children. All jurisdictions hold that a parent's right to freedom of religion does not include the right to deny life-sustaining medical intervention for that person's children.[112] One judge best summarized the feelings of the courts: "Not even a parent has unbridled discretion to exercise his or her religious beliefs when the state's interest in preserving the health of the children within its borders weighs in the balance."[113]

Some states specifically address the issue of overriding parental refusal of indicated medical intervention by statute.[114] In North Carolina, for example, if the parents refuse to consent to treatment, and the delay to obtain a court order would seriously worsen the child's physical condition or endanger the child's life, and if a second physician agrees that the procedure is necessary to prevent immediate harm, a physician can render treatment without parental consent. If a second physician cannot be contacted before initiating treatment, the physician may still perform the indicated therapeutic intervention without parental consent.[115]

Conversely, courts refuse to rule against the parents' wishes when the child's medical condition is not serious or life-threatening. If there is no life threat or potential for serious impairment, the parents' refusal should be respected. Parental refusal of indicated nonemergency medical treatment is usually statutorily defined as "child neglect," which is not legally sufficient to take custody of the child. Child neglect should still be reported to the appropriate authorities; treatment for the child can then be obtained under a court order.[111]

Jehovah's Witnesses

Adult Blood Transfusions

The approximately 1 million Jehovah's Witnesses in the United States believe that blood transfusion destroys their relationship with God and forfeits their chance for eternal life; accepting transfusion is not a minor infraction of their faith.[116,117] They do not accept whole blood, packed cells, platelets, white cells, or plasma or autotransfusion of stored blood. Most will allow the use of crystalloids, albumin, hemophiliac preparations, immunoglobulins, dialysis, and heart-lung machines.[116-118]

Jehovah's Witnesses and the issue of blood transfusion present difficult medicolegal issues in the ED.[119] State courts may have widely divergent views on the issue, and no clear-cut answers exist. However, the current trend is granting patients greater autonomy to refuse blood, even when the state asserts compelling interests to override a person's refusal.

General principles of consent and the "when-in-doubt rule" apply, but hospitals and medical staff also should (1) develop policies and procedures in advance to resolve potential conflicts with the Jehovah's Witness patients in the community; (2) coordinate the management of each case with hospital legal counsel, in contact with a judge who can issue court orders when appropriate, if time allows; (3) have other physician consultants write notes of agreement regarding the need to give blood; and (4) communicate effectively with patients and family, in advance when possible.

Competent Adult

The courts have found that "the competent adult has the right to refuse a transfusion regardless of whether his refusal to do so arises from fear of adverse reaction, religious belief, recalcitrance, or cost."[120] This applies "even though we may consider a patient's beliefs unwise, foolish, or ridiculous."[121] However, even this right is not absolute. If the patient's refusal conflicts with compelling state interests such as the preservation of life, the prevention of suicide, or the protection of innocent third parties, the courts may order transfusions despite the person's objections.[119] Previously, typical scenarios in which the courts overrode a competent person's refusal included cases involving pregnant women, to protect the life of the fetus; mothers of young children, to promote the general welfare of the children; and a sole supporting father or mother, to prevent offspring from becoming wards of the state.[122] Some courts, however, have significantly restricted the hospital's or state's ability to assert compelling interests challenging a competent person's right of self-determination.[123]

Unconscious or Medically Incompetent Adult

In an emergency, if the Jehovah's Witness's beliefs are unknown, physicians may transfuse the patient because consent will be implied under the emergency doctrine. It is irrelevant if the spouse, mother, or other family members adamantly refuse to allow the transfusion for religious reasons. The state's compelling interest in preserving life outweighs the family's expression of the patient's religious preferences.[118]

In the past, when a Jehovah's Witness's beliefs and transfusion preferences were known in advance, but the patient was

incompetent at the time of the emergency, the courts tended to support transfusion until the patient became competent and could refuse transfusion "contemporaneously."[112,124] The modern trend is to accept objective evidence of the patient's wishes—for example, a signed card carried by the patient that identifies him as a member of the Jehovah's Witnesses and sets out his religious objection to blood transfusion. The card may be accepted as adequate evidence of the patient's intent, like a form of advanced directive, which is binding on hospitals and physicians. In at least six states, if the card is dated and signed before two witnesses, it is statutorily valid.[125] Even if the blood refusal card does not conform to a state's advance directive statute, it should be considered strong evidence, but not necessarily determinative, of the Jehovah's Witness's wishes. Advance directives are merely a means to express an individual's rights and are not the exclusive means to express those rights legally.[118,119] Jehovah's Witnesses increasingly use state statutorily defined advance directive methods to legally express their intentions.[126] Emergency physicians should, however, be certain the card or advance directive actually belongs to the patient.

Of interest, no Jehovah's Witness has successfully sued a health care provider to recover damages in cases in which blood was withheld on the basis of an apparently valid blood refusal card. Also, "criminal, civil, or professional misconduct liability has never been imposed on health care providers for forgoing treatment the patient did not want."[127]

REPORTING REQUIREMENTS

All states require hospital EDs to report certain events or illnesses to local public health authorities.[128] The state's primary intent is to prevent the spread of communicable diseases, protect its citizens from disease and violence, and prosecute criminal acts. In each instance, the state statute overrides patients' rights of confidentiality. The statutes typically also provide physicians with immunity from civil liability or criminal prosecution if the reporting is done in good faith.[129]

All EDs should maintain up-to-date lists of diseases and incidents that must be reported to the state. The process and responsibility for appropriate reporting should be clearly articulated in departmental policy.

Communicable Diseases

Typical communicable diseases that must be reported include those of epidemiologic concern, such as sexually transmitted diseases (including gonorrhea, syphilis, chlamydial infection, nongonococcal urethritis, and human immunodeficiency virus infection) and highly communicable illnesses (such as tuberculosis, hepatitis, pertussis, and recently methacillin-resistant *Staphylococcus aureus* [MRSA] infection). Emergency physicians also have a duty to warn patients with communicable diseases against activities that may spread the disease and should instruct them to inform contacts to seek evaluation and treatment. Physicians should adequately document such instructions in the medical record to prevent liability to third parties for failure to warn appropriately.

Violent Acts

Wounds, injuries, and illness resulting from criminal acts of violence must be reported to state agencies.[130] Bullet wounds, powder burns, stab wounds, intentional poisonings, child abuse or neglect, sexual assaults, spousal abuse, domestic violence, and any suspicious injuries generally must be reported.

Deaths

All deaths must be reported to state or local authorities. Death under certain circumstances also must be reported to the county medical examiner. Typically these include (1) deaths from violence, poisoning, accident, suicide, or homicide; (2) any sudden death in someone in apparently good health or when unattended by a physician; (3) any death occurring in a jail, prison, or correctional institution or in police custody; and (4) any death occurring under suspicious, unusual, or unnatural circumstances.[131] Fetal deaths also may have to be reported, usually if over 20 weeks' gestation or the typical gestational period of possible viability.[132]

When a death requires a report to the medical examiner, the integrity of the scene and the body should be preserved. ED staff should disturb the body as little as possible, secure the patient's belongings and any potential evidentiary materials, and leave in place medical interventions such as endotracheal tubes, nasogastric tubes, and central or peripheral intravenous lines. The medical examiner will determine whether the state will assert authority over the body, order an autopsy, or release the body to the family.[131]

Additionally, any death that occurs while the patient is "restrained or in seclusion for behavior management," when it is reasonable to assume that the death is the result of the restraint or seclusion, must be reported to CMS.[133,134] In the ED setting, this typically would involve use of restraint or seclusion as a last resort to address violent behavior presenting a risk to the patient, hospital staff, or others.

Alcohol-Related Motor Vehicle Crashes

At least six states (Hawaii, Indiana, Illinois, Pennsylvania, Rhode Island, and Utah) have mandatory reporting laws governing alcohol-related motor vehicle crashes.[135] Many other states have laws permitting, but not requiring, EDs to report intoxicated drivers to authorities on the basis of a known BAC.[135,136]

Animal Bites

Most states require the reporting of animal bites, particularly dog and cat bites, to the local public health department. The states also generally require the reporting of bites by any animals known to be potential carriers of rabies, such as bats, raccoons, skunks, foxes, and cattle, to prevent cases of human rabies and control the spread of rabies within the animal community.[137]

Substance Abuse

A few states require reporting of substance abuse to local authorities.[138]

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

CHAPTER 203

Wellness, Stress, and the Impaired Physician

Richard Goldberg and Andrew R. Barnosky

PERSPECTIVE

The maintenance of wellness is critical in achieving a satisfying and productive career as a competent emergency physician. *Wellness* can be defined as the optimal state of health and well-being achieved through the active prevention of illness.[1] Emergency medicine as a specialty was still in its formative years when concerns first surfaced regarding the stressful and potentially unhealthful aspects of practice in this specialty and the impact such stressors could have on wellness and career longevity.[2,3] Although experience has shown that large numbers of emergency physicians enjoy long and fulfilling careers, questions remain about how best to cope with the demands and stresses associated with the practice of emergency medicine.

This chapter presents an overview of wellness issues facing the emergency physician, divided into three main sections: major stressors, physician burnout and impairment, and strategies for promoting wellness in emergency practice.[4]

CAUSATIVE FACTORS: MAJOR STRESSORS IN EMERGENCY MEDICINE

A variety of stressors contribute to the potentially unhealthful aspects of emergency medicine practice, both in practicing physicians and in physicians in training.[5,6] These stressors generally relate to four aspects of emergency practice: (1) difficult patient and professional relationships, (2) diversity of practice elements, (3) diminished resources, and (4) difficult decisions.

Difficult Patient and Professional Relationships

Although the ability to provide care for a variety of acute and complicated patients under significant time constraints is a significant source of gratification for practicing emergency physicians, the challenges imposed on the doctor-patient relationship are unlike those in other specialties in medicine. In clinical practice, most physicians have the opportunity of establishing a sound relationship with their patients over a period of time; in the emergency department (ED), however, patient and physician are thrust together in a relationship that typically is of high intensity, short duration, and based on the circumstances of need. Many patients presenting to the ED often are under high levels of emotional stress, in pain, and suffering from anxiety and apprehension. They may have language barriers, organic brain syndromes, psychiatric illness, personality disorders, or altered behavioral states that make them more difficult to evaluate.[7] They may be frequent users of the ED services well known to the staff, presenting with conditions such as hypochondriasis requiring an inordinate amount of time and resources. Communication and conflict resolution challenges between physician and patient may be considerable. Patients also may present a danger to the physician, manifesting any of a variety of emotional and psychiatric disorders, including chemical dependency disorders, sociopathic behaviors, personality disorders, and psychosis.[8]

Issues of personal safety remain a major concern among ED personnel because practice in this setting is more likely to be associated with exposure to acts of violence, verbal or physical threats, a variety of potentially life-threatening infectious diseases, and acts of bioterrorism.[9,10] Dealing with "difficult patients" can arouse in the emergency physician a variety of emotions that have a negative impact on the doctor-patient relationship, including fear, anger, helplessness, inadequacy, intimidation, vindictiveness, and even hatred. Although such feelings are understandable, they may become a considerable source of stress.[7,11]

Professional relationships may likewise be stressful. Emergency physicians practice "fishbowl medicine," allowing the entire range of their practice habits and decision-making to be in the full view of all members of the medical staff. Disputes can arise regarding patient management and disposition decisions, spheres of practice, referral practices, specialist on-call responsiveness, and care of the uninsured. Moreover, although a less prevalent attitude now than in the early days of the specialty, in some professional circles emergency physicians are not accorded peer respect among colleagues in other specialty areas. Professional status is occasionally an issue in dealings between emergency physicians and hospital administrators, in which the ED may be viewed as a less desirable location for resource allocation compared with other clinical services.[6]

Relationships with other members of the ED staff also may be subject to strain. Because emergency medicine practice often is contractually based for physicians, the physician group often does not have the same degree of workplace "ownership" and supervisory authority as that enjoyed by physicians in a private practice. Nurses and ancillary personnel generally are not hired by the emergency physician group, and disputes may arise over issues of responsibility and control.[6,12]

Diversity of Practice Elements

The "24/7" nature of emergency practice, coupled with the responsibility to treat all persons at all times, fosters a tremendously diverse practice environment. Work schedules typically include a broad mixture of irregularly assigned days, nights, weekends, and holidays. The practice environment often is chaotic. ED patient visits continue to climb in the United States, amidst a diminishing number of hospitals.[13] ED overcrowding and diminished availability of inpatient beds can result in ED holding of admitted patients and long waits for new patients to be assessed and treated. ED overcrowding and capacity issues have worsened to the point of crisis in some communities.[14-21] ED staff are subjected to a barrage of intrusive noises, including alarms, monitors, pagers, and telephones, as patients of all ages, presentations, and acuity arrive for evaluations at unpredictable intervals. This diversity often is cited by medical students and residents embarking on a career in emergency medicine as a challenging, attractive, and often beguiling feature of the specialty. The older practitioner, after years of struggling to maintain some degree of order within the department, amidst a pattern in recent years of increasing volumes and acuity of patients, may tend to view diversity as a major stressor.[5,6,12]

Diminished Resources

In an attempt to maintain financial viability amidst an ever-challenging environment driven by diminished reimbursement, managed care, uninsured patients, and increasing costs, most hospitals have had to implement cost-cutting measures. These measures have resulted in a number of important resource limitations with which the ED must contend. These include (1) diminished staffing of nurses, ancillary personnel, and social services; (2) burdensome cost containment policies and documentation requirements regarding access to diagnostic and treatment modalities and outpatient referrals, specialty consultations, and hospital admissions; (3) inadequate policies providing for the care and disposition of medically indigent patients; and (4) diminished reimbursement for services rendered.[5,6,12,22] Nursing shortages have reduced the ability of some EDs to recruit, retain, and build a solid team of seasoned nursing professionals experienced in emergency medicine.

Difficult Decisions

Emergency physicians often need to make difficult decisions based on ambiguous or incomplete information. Difficulties in the decision-making process, appropriate concerns regarding patient safety, an intense desire to maximize medical outcomes, anxiety over the potential for medical mistakes, the pressure of decisions made under time constraints, and fear of litigation are additional stressors of major importance.[5,6,12]

CONSEQUENCES: THE BURNED-OUT OR IMPAIRED PHYSICIAN

Burnout

The term *burnout* was introduced by Freudenberger in 1975 to refer to feelings of job dissatisfaction caused by work-related stress.[23] It includes long-term physical and emotional exhaustion, resulting in diminished interest in the major activities of the job. Burnout is of special relevance to physicians because it undermines the integrity of the physician-patient relationship, which is the foundation of medical practice and essential to effective service. People in advanced phases of burnout are likely to experience decreased productivity, less satisfaction with work, higher job turnover, lower self-esteem, more physical symptoms, more troubled family relationships, and a variety of affective changes, such as hostility, anxiety, depersonalization, cynicism, and depression. Symptoms of burnout are thought to be potential precursors of more severe manifestations of impairment, including alcoholism, drug abuse, and suicide.[24]

Several studies have documented moderate to high levels of burnout among certain populations of emergency physicians, and few emergency physicians would dispute the particular significance of burnout as an occupational hazard. Of note, however, burnout is not an inevitable consequence for all practicing emergency physicians, and effective strategies are available to avoid it. A randomized survey of 958 physicians conducted by the American Board of Emergency Medicine in 1999 found that most respondents were middle-aged emergency physicians, and most were quite satisfied with their careers; work stressors were graded as only moderate in intensity.[25]

Additional information regarding the burnout process in emergency medicine is available either by accessing the website of the American College of Emergency Physicians (ACEP) (www.acep.org) or by directly contacting the ACEP Practice Management Department (800-798-1822).

Physician Impairment

Physician impairment exists when a physician's professional performance is adversely affected because of mental or physical illness, aging, alcoholism, or chemical dependence.[26,27] The Federation of State Medical Boards defines an impaired physician as one who is unable to practice medicine with reasonable skill and safety because of a mental illness; a physical illness or condition that adversely affects cognitive, motor, or perceptive skills; or substance abuse. It is estimated that 17,000 practicing physicians are afflicted with substance abuse problems in the United States and that 100 deaths annually among physicians are directly attributable to chemical dependency.[28] Several studies suggest that alcohol and substance abuse may be more prevalent among emergency medicine residents and practicing emergency physicians than among other practitioners or specialties.[29,30]

Impairment in a physician colleague often is difficult to detect. The recognition of a pattern of events, rather than a single precipitating incident, may be key to making the diagnosis. Difficulties that arise in the workplace often are preceded by a history of family difficulties, including frequent arguments, periods of separation, extramarital affairs, and divorce. Frequent job changes ("geographic cure") and unexplained time intervals between periods of professional employment also may be signs of impairment. A high value usually is placed on maintaining the source of income, and erosion of hospital duties is one of the last things that may be affected. Patient care responsibilities become neglected, and the impaired physician may exhibit poor medical judgment. The problem may develop over a long period because strong elements of denial are usual among family members and associates, as well as in the impaired physician.[28]

Following the ethical principles of beneficence and nonmaleficence, it is important to deal fairly and honestly with colleagues yet take appropriate actions to protect patients from health care providers who are impaired or incompetent or who engage in fraud or deception.[27,31] The primacy of patient welfare and the role of the physician as patient advocate are critical here. Programs to detect and treat physician impairment have now been established in every state. A few states

have recovery programs that are legislatively mandated, being administered by state medical boards, state medical societies, or independent organizations. A carefully structured program is critical to the recovery process, and the goal is to rehabilitate the physician so that he or she may return to the care of patients. The prognosis for recovery appears to be excellent when long-term monitoring is in place. The ultimate goal is rehabilitation of the affected physician, with an eventual successful return to work.[28,32]

COPING STRATEGIES: WELLNESS STRATEGIES FOR THE EMERGENCY PHYSICIAN

The very qualities that characterize medically successful physicians—perfectionism, the drive to succeed, willingness to work long and irregular hours, and ideals of individual service and sacrifice—also may dispose them to neglect their own physical and emotional needs. The formulation of any comprehensive wellness strategy is based on the concept of lifestyle balance and involves the integration of professional goals and responsibilities with needs for self-care and development.[33-35] Cultivation of lifestyle balance involves four basic elements, summarized in Box 203-1 and discussed next in some detail.

Promoting Wellness in the Workplace

A strong predictor of job satisfaction among professionals with demanding and stressful jobs is the degree to which they have control over the work flow and job responsibilities in their workplace. Emergency physicians can introduce more control over elements of their practice by (1) ensuring adequate physician and support staffing to accommodate patient load, (2) ensuring adequate input in the development of departmental policies and procedures, (3) cultivating relationships among physicians and staff, and (4) mitigating noise, light, space, crowding, wait times, and structural discomforts.[36,37]

The irregularity of scheduled hours is a major workplace issue for emergency physicians. Shift changes often are cited as a major cause of dissatisfaction within the specialty.[12,36] Shift work is associated with a variety of adverse effects on physical and emotional health.[38-40] These include an increased incidence of ulcer disease, depression, mood swings, drug and alcohol abuse, altered immune response, chronic hypertension, cardiovascular mortality, infertility in women, divorce, and work-related accidents and errors.[41] Approximately 25% of persons in the North American population are shift workers, and research has shown that an estimated 20% of people cannot tolerate shift work.[41-43] A variety of shift work strategies have been proposed as a means of mitigating these effects; these are summarized in Box 203-2.[44]

BOX 203-1 LIFESTYLE BALANCE: WELLNESS STRATEGIES FOR THE EMERGENCY PHYSICIAN

1. Promote wellness in the professional environment.
   a. General measures
   b. Strategies for shift work
   c. Strategies for managing difficult and violent patients
   d. Professional support groups
2. Cultivate close family and social relationships.
3. Develop and maintain physical fitness.
4. Cultivate methods of relaxation and renewal.

Professional support groups also can help emergency physicians with issues of coping and control over the stressful aspects of their practice. In the process of sharing relevant information, relating personal experiences, listening to others' experiences, and providing sympathetic understanding, members of support groups can cope in a more effective manner. The ACEP has a Wellness Section devoted to consideration of such issues and has sponsored policies and programs to address them. The ACEP also has a speaker's bureau consisting of members who are available to address a variety of wellness-related issues.

A particularly important form of support group relates to *critical incident stress debriefing*. Critical incidents are witnessed traumatic events that have sufficient emotional power to overcome the usual coping abilities of people exposed to them. Emergency medicine is a field in which situations occur that may cause physicians and other ED personnel, regardless of rank, years of service, or gender, to experience unusually strong emotional reactions that have the potential to interfere with their ability to function. These situations are referred to as *critical incidents*. Emergency physicians are continually being exposed to critical incidents, including serious multiple-casualty incidents, pediatric injuries or deaths, line-of-duty deaths, injuries to ED personnel, events of excessive media interest, and events involving victims known to ED personnel. The impact of a critical incident often goes unrecognized even after common stress reactions appear. Although physical and emotional stress reactions are often considered normal and usually will diminish in time, very intense or prolonged reactions may have adverse effects on physician and staff well-being.

Rescue personnel exposed to such critical incidents can be subject to the cognitive, emotional, and physical sequelae comprising the post-traumatic stress syndrome. Components of this syndrome include a continual reexperiencing of the

BOX 203-2 SHIFT WORK STRATEGIES

1. Work the same shifts as much as possible and keep the same sleep patterns. Compensation should be increased for those willing to work night shifts for extended periods.
2. Work isolated night shifts, with minimal circadian disruptions.
3. Consider the *Thomas schedule* for groups: One physician works extended night schedule for 1 month or longer, with isolated nights off being covered by the other group members.
4. Schedule shift rotations in a clockwise direction, with 1-month minimum time per rotation.
5. Eight-hour shifts are preferable to 12-hour shifts.
6. Sleep in a darkened room; minimize disruptions.
7. For those unable to maintain consistent sleep patterns, use compromise strategies such as anchor sleep, split sleep periods, or napping to mitigate circadian disruptions.
8. Start the awake period with a high-protein meal, switching to complex carbohydrates toward bedtime. Avoid caffeine and high-calorie, high-fat snack food before sleep. Eat meals regularly.
9. Use bright light (>10,000 lux) for 2 hours after arising as an adjunct in adjusting to new shifts.
10. Exercise regularly.
11. Plan regular "quality time" with family and friends.
12. Do not try to live a day shift lifestyle while working night shifts.

BOX 203-3 AMERICAN HEART ASSOCIATION DIETARY GUIDELINES

1. Restrict total fat to ≤30% of total calories.
2. Restrict saturated fat to <10% of total calories.
3. Limit the total intake of cholesterol-raising fatty acids (saturated and trans fats) to ≤10% of calories.
4. Limit cholesterol intake to <300 mg/day.
5. Replace cholesterol-raising fatty acids with whole grains and unsaturated fatty acids from fish, vegetables, legumes, and nuts.
6. Limit sodium intake to ≤2400 mg/day (≤6.0 g/day of salt).
7. If alcohol is consumed, limit intake to two drinks/day for men, one drink/day for women.
8. Eat at least two servings of fish per week.
9. Eat five or more servings of vegetables and fruit per day.
10. Eat six or more servings of grain products per day.
11. Emphasize daily intake of low-fat or nonfat dairy products.

event in thoughts, dreams, or daily life; an avoidance of any stimuli associated with the event; a sense of numbness to one's emotions; and a wide variety of other symptoms, including sleep disturbance, irritability, anxiety, and loss of emotional control.[45]

The concept of critical incident stress debriefing has evolved over the past 30 years from the combined experiences of a variety of emergency services and military personnel. The two main goals of debriefings are to lessen the short-term emotional impact of distressing events and to accelerate recovery from such events before stress reactions occur. As originally described, debriefings are structured group meetings that emphasize venting of emotion and discussion of other reactions to a critical event.[46] Formal critical incident stress debriefing teams are available in many communities through local emergency medical services agencies. Debriefings also can occur on an informal basis in the ED. Such sessions can take the form of impromptu meetings of emergency and rescue personnel involved in specific incidents in which the details of a particular event and its associated emotional content are expressed and shared among members of the team.[44] It is important for those involved in leadership roles to make some form of critical incident debriefing processes available when such events occur.

Family and Social Relationships

Many physicians are overly dedicated to their work and prone to delay sources of emotional gratification outside the work environment. These qualities, which may promote a high degree of professional success and satisfaction, also may interfere with the development of family and social relationships, a problem that may be compounded for emergency physicians by their irregular hours.[47-49] The ability to develop and sustain intimate relationships may be the most critical element in any wellness formula. The simplest and most profound way to maintain mental health while actively absorbed in a demanding career is to establish and cultivate a viable and genuine relationship with a caring, emotionally expressive spouse or significant other. The promotion of a close family relationship involves, at the very least, a willingness to assign and prioritize protected time with spouse and other family members. For many physicians, it also involves a conscious effort to develop communication skills, particularly with respect to active listening and the open expression of feelings.[49]

Physical Fitness

Physical fitness is an important concern for emergency physicians, given the rigors of a typical emergency medicine practice. Unfortunately, the obstacles to developing a comprehensive fitness program may be considerable. Factors such as irregular hours, hectic work pace, and the variable quality of hospital menus complicate the task of establishing and maintaining exercise regimens and healthy dietary habits. The impact of proper diet and exercise on a variety of wellness parameters is clearly established. Documented benefits of an appropriate diet include lower cholesterol levels, weight control, augmented blood pressure control, and a lower incidence of certain cancers. The American Heart Association (AHA) periodically provides dietary guidelines, as summarized in Box 203-3.[50]

The benefits of a regular and vigorous aerobic exercise program include enhanced exercise tolerance, cardiovascular fitness, lower blood pressure, increased high-density lipoproteins, decreased triglyceride levels, augmented weight reduction efforts, lessened anxiety and depression, improved glucose tolerance, and enhanced endurance, flexibility, and strength. According to current AHA guidelines, cardiovascular fitness is best maintained by a program of aerobic exercise (the repetitive use of large muscle groups) three to six times per week for at least 30 minutes per session. Strength-developing activities (resistance training) should be performed at least twice per week, with 8 to 10 exercises that use the major muscle groups of the legs, trunk, arms, and shoulders. A regimen of one or two sets of 8 to 12 repetitions of each exercise is recommended. The exercises should be vigorous, sufficient to raise heart rate to at least 50% of maximum (recommended average maximum heart rate is 220 minus age).[51]

Relaxation and Renewal

In dealing with the innumerable stresses of emergency practice, emergency physicians must be equipped with considerable emotional resources, derived in part from strong peer and personal support systems. Methods of relaxation and renewal are important additional elements.[6,34,36]

Emergency physicians must continually cultivate the ability to remain functional and emotionally resilient when facing the turbulence of the typical ED. Physiologic correlates of stress—increased heart and respiratory rates and increased blood pressure, oxygen consumption, and serum lactate level—can be normalized by a variety of relaxation techniques. These include prayer, Zen, yoga, transcendental meditation, autogenic training, and progressive relaxation. Studies indicate that the regular use of such techniques can allow development of considerable control over the relaxation process.[52-54]

A final element in the promotion of wellness and lifestyle balance is the concept of *renewal*. Physicians typically develop a work ethic that makes it difficult to disengage from medical responsibilities. A single-minded devotion to career ultimately is impoverishing, and by neglecting restorative activities, physicians tend to lose their emotional resilience.[34,55] The concept of renewal involves the ability to prioritize and establish time for rest and revitalization, as well as spiritual, emotional, and intellectual growth. Out of the maelstrom that constitutes a typical day in the ED, emergency physicians should look to sources of renewal as key elements in their formula for lifestyle balance.

SUMMARY

Many aspects of the practice of emergency medicine are potentially unhealthful. Emergency physicians can hope for less stressful, more fulfilling careers by adopting strategies to enhance personal and professional well-being.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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